

# **ADULT ACUTE LEUKEMIAS AND MYELODYSPLASTIC SYNDROMES**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for adults with acute leukemia or myelodysplastic syndrome.
2. Assess the prognostic impact of relevant cancer-related molecular biology testing for an adult with acute leukemia or myelodysplastic syndrome.
3. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions from pharmacotherapy for acute leukemia and myelodysplastic syndrome in an adult, including tumor lysis syndrome, neurotoxicity, differentiation syndrome, and cardiac toxicity from arsenic trioxide, and other agents as appropriate.
4. Determine appropriate pharmacotherapy for acute leukemia or myelodysplastic syndrome in an adult based on genomic test results.

## MYELOYDYSPLASTIC SYNDROMES

### **Patient Case #1:**

CJ is a 69 year-old female with no significant medical history. Despite generally enjoying good health for most of her life, she has noticed an increase in fatigue for the last 2 weeks. When she presented to her primary care provider, her laboratory parameters revealed a white blood cell count (WBC) 2300 cells/mm<sup>3</sup> with 40% neutrophils, hemoglobin 6.1 gm/dL and platelets 138,000 cells/mm<sup>3</sup>. She was given 2 units of packed red blood cells (RBCs) and referred to a hematologist. Bone marrow biopsy was obtained and comes back with a reading of dysplastic changes with ringed sideroblasts and 4% blasts consistent with a *de novo* myelodysplastic neoplasm (MDS). Cytogenetics reveal a normal karyotype and molecular studies are positive for an SF3B1 mutation. Her epoetin level is reported as 150 units/L. Over the past 2 months she has required 2 units of RBCs every other week. Her IPSS-R category is low-risk.

**Based upon this information, which of the following agents is the most appropriate to initiate in CJ?**

- A. Decitabine
- B. Lenalidomide
- C. Epoetin
- D. Luspatercept

### **I. Etiology/Pathogenesis<sup>1</sup>**

- A. Chromosomal abnormalities underlie the molecular pathogenesis of myelodysplastic neoplasm (MDS). Molecular abnormalities may include loss or gain of parts of chromosomes 3, 5, 7, 8, 11, 17 and 20.
  - 1. Abnormalities of chromosome 5 are the most common abnormality in MDS.
- B. Gene mutations have been identified that may contribute to the biological heterogeneity of MDS. Studies have identified approximately 40 recurring genetic mutations with >80% of patients with MDS harboring at least one. Several of these mutations have been associated with adverse clinical features:
  - 1. Complex karyotype (TP53)
  - 2. Excess bone marrow blast proportion (RUNX1, NRAS, and TP53)
  - 3. Severe thrombocytopenia (RUNX1, NRAS, and TP53)
- C. Mutations in TP53, EZH2, ETV6, RUNX1, and ASXL1 hold independent prognostic value and predict decreased OS in multivariate models adjusted for International Prognostic Scoring System (IPSS) and the Revised International Prognostic Scoring System (IPSS-R) risk groups.



## II. Risk Factors<sup>2-4</sup>

- A. Previous exposure to alkylating agents, topoisomerase II inhibitors, and ionizing radiation increase the risk of MDS.
  - 1. Alkylating agents and topoisomerase II inhibitors (individually, or in combination) are the most common causes of treatment-related MDS.
    - a. Alkylating agent-related MDS characteristically causes mutations of chromosomes 5 and 7 or results in a complex karyotype. The median onset after therapy is 5-7 years.
    - b. Topoisomerase inhibitor-related MDS typically causes mutations of chromosome 11q23. The median onset after therapy is 2-3 years.
- B. Risk factors for developing secondary AML from antecedent MDS include number of cytopenias at diagnosis, percentage of blasts in the bone marrow and cytogenetics.

## III. Staging<sup>5-8</sup>

- A. Classification: WHO classification is current standard (2022).
- B. Prognosis based on staging criteria (see tables below)

## IV. Prognosis of MDS based on staging criteria

- A. Two scoring systems are most commonly used: the IPSS and IPSS-R, which superseded the former<sup>9,10</sup>
  - 1. Both scoring systems are based on patients with newly diagnosed MDS who received no therapy to alter the natural course of the disease.
  - 2. Both scoring systems include analysis of peripheral cytopenias, percentage of bone marrow blasts, and cytogenetic characteristics.
    - a. The IPSS-R score includes a cytogenetic risk classification that divides patients into five cytogenetic categories.
      - 1) Has largely replaced IPSS as it is more accurate at predicting prognosis
  - 3. Molecular mutations with independent poor prognostic value (data became available following development of IPSS or IPSS-R): *TP53*, *EZH2*, *ETV6*, *RUNX1*, and *ASXL1* (in practice these mutations may be used to upstage a patient)<sup>4,11-13</sup>
    - a. *SF3B1* mutation has been associated with a more favorable prognosis
  - 4. Refer to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for scoring tool tables for IPSS and IPSS-R (not for testing purposes but rather for your own reference).
- B. Other prognostic scoring systems used include the World Health Organization (WHO) Prognostic Scoring System (WPSS) and Global M.D. Anderson Cancer Center (MDACC). These systems are more dynamic in that they can be applied beyond the point of diagnosis.<sup>14,15</sup>
- C. Current therapy recommendations divide patients into lower-risk and higher-risk groups.<sup>7,8,16-18</sup>

## Summary of MDS Risk Stratification

	Scoring Tool	Prognostic Category
<b>Lower Risk</b>	IPSS	Low or intermediate-1
	IPSS-R	Very low, low, or intermediate ( $\leq 3.5$ score)
	WHO	Very low, low, or intermediate
<b>Higher Risk</b>	IPSS	Intermediate-2 or high risk
	IPSS-R	Intermediate ( $> 3.5$ score), high or very high
	WHO	High or very high

## 1) Treatment

- a) Goals of therapy for patients with MDS include:
  - i) Alteration of the natural history of the disease / delaying disease progression
  - ii) Reducing number of red blood cell transfusions
  - iii) Improving quality of life
  - iv) Prolonging survival
- b) Approximately 50% of patients with newly diagnosed MDS have one or more comorbidities.<sup>8,17</sup>
  - i) The presence of comorbid conditions poses potential challenges in terms of treatment tolerability and outcomes.
  - ii) An evaluation of the presence and extent of comorbid conditions is an important aspect of management of MDS patients.
- c) Allogeneic hematopoietic stem cell transplantation (HCT) is the only curative therapy (see chapter on Hematopoietic Stem Cell Transplantation).
- d) Recommended therapies<sup>8</sup>
  - i) Patients with lower-risk disease benefit from hematopoietic growth factors (ie: erythropoietin stimulating agents and luspatercept), DNA hypomethylating agents, immunosuppressive therapy and immunomodulating agents (ie: lenalidomide).
  - ii) Patients with higher-risk disease are more likely to progress to AML and may benefit from DNA hypomethylating agents, intensive chemotherapy, or allogeneic HCT.
- e) Treatment of lower-risk disease
  - i) Therapy in this subset of patients is based on transfusion needs. Patients that are transfusion independent are typically observed until they become transfusion dependent.<sup>16</sup>
  - ii) Transfusion support with packed RBCs and platelets are employed as indicated.<sup>8</sup>
    - a. RBC transfusions (irradiated and leukocyte-reduced) for symptomatic anemia, and platelet transfusions for thrombocytopenic-related bleeding (reserve for platelets  $< 10,000$  cells/mm<sup>3</sup> for non-bleeding patients).

- b. Aminocaproic acid, tranexamic acid, or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions.
- iii) Antibacterials may be considered, but there is no specific role for prophylaxis based on MDS alone.<sup>8</sup>
- iv) Hematopoietic growth factors<sup>8,16,19-22</sup>
  - (1) Neither granulocyte/macrophage colony stimulating factor (GCSF/GMCSF), thrombopoietin receptor agonists, nor erythropoietic stimulating agents (ESA) change the natural history of the disease.
  - (2) In contrast to some solid tumors, ESA have not been reported to have detrimental effects on overall survival or progression to acute myeloid leukemia (AML) in patients with MDS.
  - (3) GCSF increases circulating neutrophils and may decrease the risk of infections.
    - a. There is a theoretical concern that stimulation of the myeloid stem cell line may hasten the progression to acute leukemia; however, clinical experience has not supported this concern.
    - b. GCSF is not recommended for routine infection prophylaxis. Use can be considered if recurrent or resistant infections occur in a neutropenic patient.
  - (4) ESA increase hematocrit in 30-58% of MDS patients, with most of the benefit occurring in patients with a low serum erythropoietin level at baseline/diagnosis.
    - a. The doses of ESA used are often higher than those used for chemotherapy-induced anemia and/or chronic kidney disease, with epoetin alpha 300 units/kg subcutaneous thrice weekly as a common dose.
    - b. Expert consensus suggests doses should be titrated to achieve a hemoglobin of 10-12 g/dL.
    - c. The best response is seen when a patient's EPO level is < 500 units/L and when the pretreatment RBC transfusion requirement is low (<2 units per month).
    - d. Recommendations for the use of ESA in MDS apply to epoetin alfa and epoetin alfa-epbx.
    - e. In addition to NCCN recommendations the American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) provide recommendations for use of ESAs in patients with cancer. These guidelines provide extensive direction on how to practically use ESAs and are in line with NCCN recommendations<sup>23</sup>
  - (5) The role of thrombopoiesis stimulating agents in MDS is not known at this time.
    - a. There is concern regarding complications related to disease transformation and marrow fibrosis.
    - b. Can consider eltrombopag or romiplostim in patients with severe or refractory thrombocytopenia
- v) Lenalidomide
  - (1) An immunomodulating agent with demonstrated activity in lower-risk MDS.
  - (2) Results are particularly beneficial in patients with del(5q) as the sole chromosomal abnormality. This subtype confers a favorable prognosis.<sup>8,24</sup>
    - a. Patients with complex cytogenetics involving del(5q) do not share the same favorable prognosis. However, they may still respond to lenalidomide.

## Summary of common treatment strategies – lenalidomide

Regimen	Patient Population	Results	Comments
Lenalidomide in various doses (10 mg/day on days 1-21 q28 days or 5 mg/day on days 1-28 q28 days or placebo) <sup>25</sup>  (Phase III trial known as “AZA-004”)	Dose 1 (n = 69) Dose 2 (n = 69) Placebo (n = 67)  Transfusion-dependent patients with IPSS low- or Int-1 and del(5q)	RBC transfusion independence = 56.1% and 42.6% vs 5.9% (p < .001)  Lenalidomide groups combined 3-year OS and AML risk were 56.5% and 25.1%, respectively	No cytogenetic responses occurred in the placebo group (p < 0.001 vs both lenalidomide groups). The most common grade III or IV adverse effects were myelosuppression and deep vein thrombosis. Grade III or IV neutropenia and thrombocytopenia generally occurred within the first 2 cycles and subsequently decreased.
Comparative analysis of AZA-004 and List et. al. trial <sup>26</sup>  Compared to BSC (data from a multicenter registry)	n = 295  Transfusion-dependent patients with IPSS Low- or Int-1 risk and del(5q)	Transformation to AML at 5 years = 23% vs 20%  Median OS = 54% vs 40.5% (p = NS)	Lenalidomide was not a significant factor for AML progression in multivariate analyses, but was associated with a significantly decreased risk of death compared to BSC (HR, 0.597, p = 0.012).
Lenalidomide 10 mg daily or placebo <sup>27,28</sup>  Phase III, double-blind, randomized trial (MDS-005 Study)	Transfusion-dependent patients with IPSS Low- or Int-1 risk and <u>non-del(5q)</u> ; refractory to ESA  n = 160 (len) vs 79 (placebo)	Transfusion independence at 24 weeks: 26.9% vs 2.5%; p < 0.001	Lenalidomide is a reasonable option in non-del(5q) if patients have anemia only; patients with EPO level >500 have lower responses to lenalidomide in non-del(5q) population No disease modifying effects (ie: cytogenetic responses) in non-del(5q) when compared with previous studies of del-5q.

AML = acute myelogenous leukemia; BSC = best supportive care; CR = complete response; HR = hazard ratio; NS = not significant; OR = overall response; OS = overall survival; RBC = red blood cell; RR = response rate.

- vi) Luspatercept – is a first in class recombinant fusion protein that inhibits the transforming growth factor dependent stages of erythroid maturation<sup>29</sup>

(1) Dosing: 1 mg/kg once every 3 weeks by subcutaneous injection

- Increase dose to 1.33 mg/kg if not transfusion independent with 2 doses of 1 mg/kg
- Increase dose to 1.75 mg/kg if not transfusion independent with 2 doses of 1.33 mg/kg
- Similar to ESAs, doses may need to be increased, reduced, or held based on rate of hemoglobin rise

(2) MEDALIST Trial: Randomized, Phase III, double-blind, placebo-controlled trial in patients with lower risk, non-del (5q), MDS (IPSS-R score ≤4.5: very low, low, intermediate risk) who were refractory, intolerant or unlikely to respond to ESAs (EPO >200 U/L) and transfusion dependent

( $\geq 2$  units per 8 weeks). Patients were not allowed to have received prior disease modifying agents (ie: hypomethylating agents). In addition, patients had to have had either  $\geq 15\%$  ring sideroblasts or  $\geq 5\%$  ring sideroblasts if an SF3B1 mutation. Patients were randomized to receive luspatercept 1-1.75 mg/kg subcutaneously every 3 weeks (n=153) or placebo (n=76). The primary endpoint was RBC transfusion independence for  $\geq 8$  weeks (during weeks 1-24).<sup>30</sup>

- (3) The incidence of RBC transfusion independence for  $\geq 8$  weeks (during weeks 1-24) was 38% (luspatercept) versus 13% (placebo),  $p < 0.001$ .
  - a. EPO level did not impact response (thus luspatercept can be used without regard to EPO levels unlike ESAs or lenalidomide in non-del-5q)
- (4) Luspatercept does not provide disease modifying effects, thus is unlikely to reduce the risk of progression to AML (importantly it did not lead to an increased risk of progression to AML)

vii) Immunosuppressive therapy<sup>8,16,31,32</sup>

- (1) Immunosuppression with anti-thymocyte globulin (ATG), steroids, cyclosporine, and eltrombopag can be used to treat the cytopenias associated with MDS.
  - a. These therapies have been modeled after the treatment of aplastic anemia.
  - b. Approximately 30% of MDS patients respond to these agents, with sustained increases in hemoglobin, neutrophil, and platelet production.
- (2) The following pretreatment characteristics are predictive of response to immunosuppressive therapy:
  - a. Younger age ( $\leq 60$  years old)
  - b. Shorter duration of red cell transfusion dependence (RCTD)
  - c. Overrepresentation of the class II histocompatibility antigen DR15 (HLA-DR15)
  - d. Bone marrow hypoplasia ( $< 5\%$  blasts)
  - e. Normal cytogenetics
  - f. Evidence of a paroxysmal nocturnal hemoglobinuria (PNH) clone
  - g. STAT-3 mutant cytotoxic T-cell clones
- (3) Equine or rabbit ATG may be used, although some references state that the equine product is preferred.
- (4) Target cyclosporine level has been suggested as 100-400 ng/mL.

viii) Hypomethylating agents<sup>8,16,17,33-37</sup>

- (1) These agents include azacitidine (administered IV or subQ) and decitabine (administered IV or orally via the combination product decitabine/cedazuridine).<sup>38</sup>
- (2) Both agents have been shown to decrease the risk of leukemic transformation in MDS patients in randomized phase III trials.
  - a. Azacitidine may be preferred over decitabine for MDS patients with progressing or high-risk disease due to improved survival in some trials.
- (3) There are little data in the use of these agents in lower-risk MDS, and neither of them have been shown to modify the natural history of this group of patients. However, they are an appropriate

option for lower-risk patients with symptomatic anemia and elevated epoetin levels who are not expected to respond to other treatment options.

**Patient Case #1 (continued):**

**Correct answer = C (Epoetin).** Given that our patient's EPO level is < 500 units/L, she is likely to respond to an ESA. Therefore, epoetin should be considered as first-line therapy.

A (decitabine) should not be considered in low risk MDS unless they have failed or are unlikely to respond to other agents.

B (lenalidomide) is not correct because she does not have a del 5q thus lenalidomide should not be considered as first-line therapy.

D is incorrect because Luspatercept is indicated for low risk MDS with ringed sideroblasts in patients who have failed or are unlikely to respond to ESAs.

**Patient Case #2**

**According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), which of the following patients is receiving the most appropriate therapy for their MDS?**

- A. A 73-year-old male with newly diagnosed lower risk MDS with a del5q mutation and anemia receiving azacitidine
- B. A 67-year-old female with higher risk MDS with 12% blasts receiving luspatercept
- C. A 58-year-old male with newly diagnosed hypoplastic MDS receiving epoetin
- D. A 61-year-old female with newly diagnosed higher risk MDS undergoing an allogeneic cell transplantation

f) Treatment of **higher-risk** disease<sup>8,16,17</sup>

i) Hypomethylating agents are considered the standard of care in this subgroup.

- (1) Azacitidine and decitabine are therapeutically similar. However, only azacitidine has shown a survival benefit in randomized trials of patients with high-risk MDS. For this reason, azacitidine is preferred by NCCN.
- (2) The minimum number of courses prior to considering the treatment a failure is 4-6 courses.
  - a. Optimal duration is undefined but typically continued until disease progression or intolerance
  - b. Optimal dosing strategy is unknown but several options are available (for reference; various dosing schemas not to be memorized)<sup>39,40</sup>
- (3) Acceptable candidates for these agents are patients with IPSS Intermediate-2 or High-risk disease or IPSS-R Intermediate, High or Very High Risk with any of the following:
  - a. Not a candidate for high-intensity therapy
  - b. Potential candidate for allogeneic HCT, but in which a delay is anticipated. These agents may be used as "bridging therapy" prior to transplant.
  - c. Relapse after allogeneic HCT.

**Summary of common treatment strategies – hypomethylating agents in higher-risk patients**

Regimen	Patient Population	Results	Overall Survival	Comments
Azacitidine vs BSC <sup>36</sup>  (Phase III trial known as “CALGB 9221”)	n = 191  All IPSS risk categories of MDS were included	Hematologic response = 60% in patients receiving azacitidine  Hematologic improvement = 5% in BSC (no responses)	Median time to AML progression or death = 21 months vs 13 months (p = 0.007)	Further improvement was seen in patients who received azacitidine earlier in the course of disease.
Azacitidine (75 mg/m <sup>2</sup> /day) subcutaneously daily x 7 days) vs best supportive care <sup>36,41</sup>  (Phase III cooperative group trial)	306 patients reported from 3 clinical trials  All patients had higher-risk MDS	CR = 10-17% PR = 1-36% OR = 60%  Hematologic improvement (HI) = 23-36%  Median duration of response = 15 months  TTP = 12 month (placebo) vs. 21 months (azacitidine)	Median survival of an additional 18 months for azacitidine vs 11 months for supportive care (p = 0.03)	47% response in patients that crossed over from placebo arm to active treatment. >50% had grade III/IV hematologic toxicity. Less patients in the azacitidine arm transformed to AML (15% vs 38%, p=0.007). Improved QOL reported with azacitidine.
Azacitidine (75 mg/m <sup>2</sup> /day) subcutaneously daily x 7 days vs conventional care <sup>33</sup>  (Phase III study known as “AZA-001”)	Azacitidine (n = 179) vs. conventional care (n = 179)  High-risk MDS patients (IPSS > INT 2)	CR = 10-17% HI = 23-36%  Time to AML/death = 13 months (azacitidine) vs. 7.6 months (conventional care), p = 0.003  RBC transfusion independence = 45% (azacitidine) vs. 11% (conventional care), p < 0.0001.	24.5 months (azacitidine, range 10-not reached) vs. 15 months (conventional care, range 6-24 months), HR 0.58, p = 0.0001	Conventional care included low-dose cytarabine, best supportive care or induction chemotherapy. Toxicity was predominantly hematologic.

AML = acute myelogenous leukemia; BSC = best supportive care; CR = complete response; ECOG = Eastern Cooperative Oncology Group; HI = hematologic improvement; HR = hazard ratio; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndrome; OR = overall response; PFS = progression-free survival; PR = partial response; RR = response rate; QOL = quality of life; TTP = time to progression.

ii) Intensive chemotherapy<sup>8,16,42</sup>

- (1) Regimens that are used for induction therapy in AML may be considered in patients with good performance status and few co-morbidities who are awaiting allogeneic HCT and require a reduction in disease burden.
- (2) Remission rates of 40-60% have been reported, but treatment-related mortality approaches 40%.
  - a. Given the advanced age and potential medical comorbidities of this population, there is high risk of morbidity and mortality from AML-like intensive remission induction therapy with cytotoxic chemotherapy.
- (3) The most important prognostic factor of response to AML-like therapy is karyotype. Patients with unfavorable karyotype [complex karyotype or del(7q)] have a low response rate and short response duration.
- (4) Comparative studies have not shown benefit between different intensive therapy regimens, including regimens that contain anthracyclines, cytarabine, and/or fludarabine.

**Patient Case #2 (continued):**

**Correct answer = D**

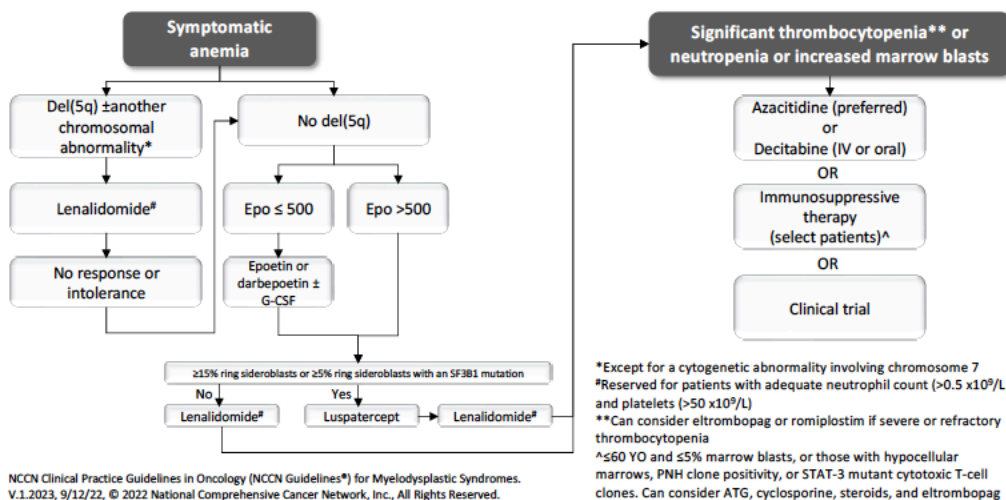
- A) Patients with del5q should receive lenalidomide; azacitidine should be reserved for patients with higher risk MDS or if multi-lineage cytopenias in lower risk MDS.
- B) Patients with higher risk MDS should receive a hypomethylating agent (or go directly to an allo-transplant if eligible and/or after debulking from an HMA), not luspatercept.
- C) Hypoplastic MDS should be treated similar to aplastic anemia: ie IST. Epoetin is not appropriate.
- D) The standard of care for higher risk MDS is an allo-HCT if young/fit/eligible.

## 2) Summary of Preferred Treatment Options<sup>8</sup>



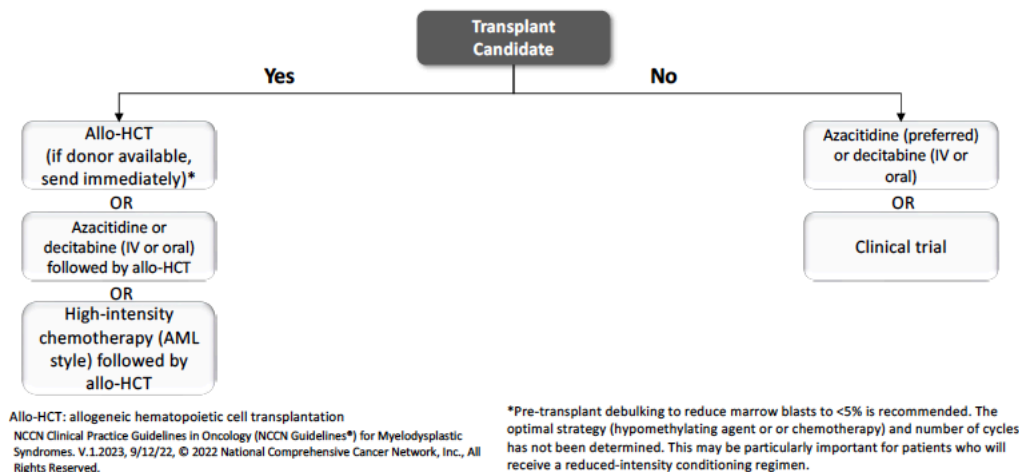
### Myelodysplastic Syndrome (Lower Risk)

Lower risk: IPSS-R (Very low, low, intermediate); IPSS (Low, intermediate-1); WPSS (very low, low, intermediate)



### Myelodysplastic Syndrome (Higher Risk)

Lower risk: IPSS-R (intermediate [score >3.5], high, very high); IPSS (intermediate-2, high); WPSS (high, very high)



### 3) Iron Chelation Therapy (ICT)<sup>8,43-48</sup>

- a) Therapy for MDS may alleviate the patient's RBC transfusion needs, but a substantial proportion of patients may not respond to treatment and may develop iron overload.
  - i) Retrospective and observational studies have shown that chronic iron overload is associated with an increased risk of hepatic, cardiac, and endocrine damage.
    - (1) In one study, each 500 ng/mL increase in serum ferritin above 1000 ng/mL was associated with a 40% increased risk of death.

- ii) A meta-analysis of 8 observational studies revealed that the use of ICT was associated with a greater median survival time than non-use of ICT, especially in low-risk MDS patients.
  - (1) The mean difference in median survival was 61.2 months.
  - (2) However, these studies may be limited by selection bias since the decision to initiate chelation therapy may have been influenced by the patient's clinical status. Improvements in outcomes may reflect a better clinical status and/or the potential benefits of chelation.
- iii) There are no prospective, randomized studies demonstrating an overall survival benefit with iron chelation in patients with MDS.
  - (1) Prospective registry enrolled 600 lower-risk MDS patients with transfusional iron overload.
    - a. At 24 months, chelation was associated with longer median overall survival (104.4 months vs 52.2 months,  $p < 0.001$ ).
    - b. There was also a trend toward longer leukemia-free survival and fewer cardiac events in patients who received chelation therapy.
  - (2) TELESTO Trial<sup>49</sup>
    - a. Multicenter, randomized, double-blind, placebo-controlled trial; initially was a Phase III trial but due to slow enrollment was modified to a phase II trial
    - b. 225 patients with serum ferritin levels greater than 2247 ng/mL; prior receipt of 15 to 75 packed red blood cell units; and no severe cardiac, liver, or renal abnormalities
    - c. Primary endpoint was EFS: 3.9 vs 3 years ([HR = 0.64; 95% CI, 0.42-0.96];  $P = 0.01$ )
    - d. Overall survival: OS: 5.2 vs 4.1 years; ([HR=0.83; 95% CI, 0.54-1.28];  $p = 0.2$ )
- b) If > 20 RBC transfusions have been received and serum ferritin > 2500 ng/mL, consider daily iron chelation to decrease iron overload, particularly for those with >1-year expected lifespan (factoring in co-morbid conditions) and good prognosis (IPSS Low-risk and Intermediate-1 and for potential allogeneic HCT candidates).
  - i) Current guidelines suggest that iron chelation can be achieved with either deferoxamine or deferasirox.
    - (1) Avoid deferoxamine in patients with creatinine clearance < 40 ml/min
  - ii) Data from randomized, controlled clinical trials comparing ICT agents are lacking.
  - iii) Deferasirox is contraindicated in patients with high-risk MDS due to the possibility of liver or kidney impairment and gastrointestinal bleeding.
  - iv) Deferiprone therapy remains a controversial agent in MDS due to its potential for agranulocytosis.
- c) For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to less than 1,000 ng/mL.<sup>46</sup>

#### Summary of available iron chelating agents<sup>8</sup>

	Deferoxamine (Desferal®)	Deferasirox (Exjade®)	Deferasirox (Jadenu®)	Deferiprone (Ferriprox®)
<b>Route</b>	Subcutaneous/IV	Oral	Oral	Oral
<b>Schedule</b>	8-12 hours daily for 5-7 days per week	Daily	Daily (tablet)	Three times a day

		(tablet for oral suspension)		
<b>Major adverse effects</b>	Infusion site reactions Visual changes High-frequency hearing loss	GI upset Renal toxicity Hepatic toxicity GI perforation	GI upset Renal toxicity Hepatic toxicity GI perforation	Agranulocytosis GI upset

GI = gastrointestinal.

- a) Prior to commencing iron chelation therapy, exogenous sources of iron should be discontinued. Oftentimes, vitamin C is used to increase absorption of iron supplements. This too should be discontinued.

## ACUTE MYELOID LEUKEMIA (AML)

### **Patient Case #1:**

RO is a 64-year-old female with a history of diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP eight years ago. She is admitted due to symptoms of newly-diagnosed AML with NPM1, FLT3-ITD, and FLT3-TKD mutation negative and CD33+. Her cytogenetics reveal del7. Prior to her admission, she was biking 15 kilometers per day. Which of the following is the most appropriate to initiate in RO at this time?

- A. 7+3, daunorubicin 45 mg/m<sup>2</sup>/dose
- B. 7+3, daunorubicin 90 mg/m<sup>2</sup>/dose
- C. Liposomal cytarabine and daunorubicin plus gemtuzumab
- D. Liposomal cytarabine and daunorubicin

### **I. Diagnosis of AML<sup>5,6</sup>**

- A. The World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia incorporates information from cytogenetics and evidence of myelodysplasia. The WHO system has replaced the prior classification system for AML defined by the French American British (FAB) system. The WHO system was most recently updated in 2022.
- B. Acute promyelocytic leukemia (APL) is a distinct subtype of AML characterized by accumulation of leukemia blast cells with a 15;17 translocation [t(15;17)]. The translocated fusion protein interferes with factors required for differentiation of myeloid precursors.
- i) Peripheral blasts or bone marrow biopsy findings consistent with AML should be present. Greater than or equal to 20% blasts (or blast equivalents) is required for diagnosis of AML per World Health Organization (WHO). However, **any percentage of myeloid blasts** can be considered AML if the patient displays any of following features:
  - a. t(8;21) or RUNX1::RUNX1T1 fusion
  - b. Inversion (16) or t(16;16) or CBFB::MYH11 fusion
  - c. t(15;17) or PML::RARA fusion
  - d. DEK::NUP214 fusion
  - e. RBM15::MRTFA fusion
  - f. KMT2A rearrangement
  - g. MECOM rearrangement
  - h. NUP98 rearrangement
  - i. NPM1 mutation
  - j. Importantly there was broad agreement within the 5<sup>th</sup> edition of the WHO Classification that MDS-IB2 (10-19% bone marrow or 5–19% PB or Auer rods) may be regarded as AML-equivalent for therapeutic considerations and from a clinical trial design perspective when appropriate

### **II. Prognostic Factors of AML<sup>50-52</sup>**

- A. Patient-specific factors:
  1. Age  $\geq$  60 years and poor performance status are associated with decreased overall survival due to difficulty tolerating therapy (including induction chemotherapy and possible stem cell transplant).
  2. Older age also increases the likelihood of poor risk cytogenetics/molecular characteristics and an antecedent hematological disorder
- B. AML biology-specific factors.<sup>53,54</sup> Risk stratification systems by karyotype and molecular mutations have been proposed by both the National Comprehensive Cancer Network and the European Leukemia Net (ELN).
  1. Karyotype<sup>53-58</sup>
    - a. Karyotype is the strongest prognostic factor for response to induction therapy and survival.
  2. Molecular mutations (see table below).<sup>53,55-60</sup> Prognostic implication of molecular mutation status is an evolving area of AML. In addition to presence of molecular mutation, prognostic impact of some markers is related to the allelic ratio of the mutated allele.
    - a. FMS-like tyrosine kinase (FLT)-3
      - 1) Plays a key role in proliferation, survival and differentiation of early hematopoietic progenitor cells; all mutations lead to uncontrolled proliferation of leukemic blasts
      - 2) FLT3-internal tandem duplication (ITD) – patients have worse outcomes. However, this is related to higher rates of relapse. Prognosis is influenced by co-mutations (ie: nucleophosmin [NPM] 1).
      - 3) FLT3 tyrosine kinase domain (TKD) - encountered less often and less well-studied. Prognostic implication remains controversial. Meta-analysis showed FLT3-TKD exhibited better survival than FLT3-ITD, which was similar to FLT3-wild type in patients with intermediate risk AML<sup>61</sup>
      - 4) FLT3 mutation is both a prognostic and a predictive biomarker. Has an approved FDA companion diagnostic test.
    - b. Nucleophosmin (NPM) 1
      - 1) NPM1 mutation confers high sensitivity toward induction chemotherapy
      - 2) In normal karyotype AML, NPM1 mutations without FLT3-ITD mutation are associated with lower relapse and greater overall survival
      - 3) NPM1 copies are often followed throughout the disease course of AML if positive at baseline to assess minimum residual disease.
    - c. CCAAT enhancer binding protein alpha (CEBPA)
      - 1) Best characterized in normal karyotype.<sup>52</sup> There are two types of CEBPA mutations: a single mutation of the gene or a double mutation of the gene. Only in-frame mutations affecting the bZIP region confer a favorable prognosis (irrespective whether they are monoallelic or biallelic mutations)
      - 2) Confers sensitivity to high-dose cytarabine
    - d. Isocitrate dehydrogenase (IDH) 1 and 2

- 1) Predictive biomarker associated with approved FDA companion diagnostic
- 2) Reports of prognostic value of both IDH 1 and 2 have been inconsistent
- 3) IDH 1 and IDH2 are generally mutually exclusive

C. Response to treatment

1. Lack of complete remission after first induction therapy is associated with a poorer prognosis
2. Duration of remission < 6 months associated with a poor prognosis

### III. Classification of AML<sup>5,53,54</sup>

- A. Risk status and survival with conventional chemotherapy based upon cytogenetics and molecular mutations

#### 2022 European LeukemiaNet (ELN) Risk Stratification<sup>54,59</sup>

Risk	Cytogenetics	Gene Mutations
Favorable	<div> <div> <div>inv (16)</div> <div>t(16;16)</div> <div>t(8;21)</div> <div>t(15;17) - APL</div> </div> <div> <div>“Core binding factor”<sup>a</sup></div> </div> </div>	Mutated NPM1 without FLT3-ITD Mutated bZIP in-frame mutated CEBPα <sup>b</sup>
Intermediate	Cytogenetic abnormalities not classified as favorable or adverse t(9;11)	Mutated NPM1 <sup>c</sup> + FLT3-ITD Wild-type NPM1 + FLT3-ITD
Unfavorable or Adverse	Complex (≥3 clonal chromosomal abnormalities) <sup>d</sup> Monosomal karyotype (ie: -5, -7, 5q-, -17) <sup>e</sup> Abnormalities of 11q23 (MLL gene), excluding t(9;11) Inv(3), t(3;3), t(6;9), t(9;22), t(8;16)	In the absence of favorable-risk subtypes: Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2 Mutated TP53 (variant allele fraction of at least 10%)

NPM1 = Nucleophosmin 1; FLT3-ITD = Fms-like tyrosine kinase 3-internal tandem duplication; CEBPA = CCAAT/enhancer-binding protein alpha; basic leucine (bZIP)

<sup>a</sup>Concurrent KIT and/or FLT3 gene mutation does not alter risk categorization

<sup>b</sup>Only in-frame mutations affecting the bZIP region, irrespective whether they are monoallelic or biallelic mutations

<sup>c</sup>AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk

<sup>d</sup>Presence of two or more monosomies (excluding -X or -Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality

<sup>e</sup>In the absence of other class-defining recurring mutations; excludes hyperdiploid with 3+ trisomies without structural abnormalities

### IV. Treatment of AML

- A. Treatment phases: induction, consolidation, and maintenance
- B. Remission induction chemotherapy should begin soon after a definitive diagnosis is made.<sup>62</sup>
1. Cytogenetic/biomarker/molecular information and patient history (treatment-related AML or prior MDS) is necessary to determine treatment in the remission induction setting
    - a. NCCN Guidelines® recommend expediting molecular and cytogenetic analyses (max 3-5 days) for immediately actionable mutations (eg, CBF, FLT3 [ITD and TKD], NPM1, IDH1, IDH2)

- b. For proliferative cancers, hydroxyurea should be started (and consider leukopheresis) or one dose of intermediate dose cytarabine (1-2 grams) may be considered prior to receiving these results
- C. Modify treatment based upon patient co-morbidities:
  - 1. Cardiac dysfunction may either disqualify patient for intensive remission induction therapy or require using a non-anthracycline containing regimen
- D. Remission induction therapy consists of either an intensive regimen for those who are young/fit or a low-intensity regimen for those who are older/have significant comorbidities<sup>63</sup>
- E. Treat with curative intent for most patients unless significant comorbidities or elderly
- F. General principles of intensive remission induction therapy:
  - 1. The best outcomes are seen in patients < 60 years and with ECOG performance status 0-2<sup>59</sup>
    - a. NCCN Guidelines® recommend reserving intensive remission induction therapy for patients age < 60 years and performance status 0-2
    - b. However, NCCN Guidelines® state that patients ≥ 60 years with performance status 0-2 may also receive intensive remission induction therapy since there is no reliable method to determine who will or will not benefit from intensive remission induction
    - c. The American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults outlines treatment of older patients with AML and are generally consistent with NCCN<sup>64</sup>
  - 2. Goal of intensive remission induction chemotherapy is to induce complete remission (CR)
  - 3. General practice is to obtain bone marrow biopsy on or around day 14-21 counted from the beginning of remission induction chemotherapy for chemotherapy regimens in which this is indicated e.g. 7+3<sup>65,66</sup>
    - a. If evidence of significant AML persists and the patient remains eligible for remission induction chemotherapy, then additional chemotherapy can be considered
    - b. Recent data have called this practice into question, partially due to the insensitivity of bone marrow evaluation around day 14<sup>67,68</sup>
  - 4. Screening lumbar puncture for central nervous system (CNS) involvement and consideration of intrathecal chemotherapy should be considered in patients who present with CNS symptoms consistent with CNS involvement and/or at first remission before first consolidation for patients with monocytic differentiation, mixed phenotype acute leukemia (MPAL), WBC count >40,000/mcL at diagnosis and extramedullary disease
  - 5. Consolidation therapy should begin within 2 weeks following 1) hematologic recovery after induction, and 2) confirmed bone marrow evaluation demonstrating complete remission.
    - a. Patients classified as high risk per ELN are recommended to receive consolidation with an allo-HCT and patients classified as intermediate risk should be considered for an allo-HCT. Patients with favorable risk AML do not require an allo-HCT in first remission (can consider if persistently MRD+)

- 1) Patients who are deemed appropriate for an allo-HCT can be prescribed consolidation chemotherapy as a bridge if logistics lead to a significant delay
6. Maintenance therapy is considered for patients not proceeding to allo-HCT and should begin after consolidation is complete and while patient is still in CR/CRI. It is not intended to replace consolidation therapy nor should it replace allogeneic HCT for fit patients with intermediate and/or adverse-risk cytogenetics.
  - a. Oral azacitidine can be considered for patients with intermediate or adverse cytogenetics who are not candidates for allogeneic HCT.<sup>69</sup>
7. Patient must meet all of the following criteria for CR:<sup>53,66</sup>
  - a. Absolute neutrophil count  $> 1 \times 10^9$
  - b. Platelet count  $> 100 \times 10^9$
  - c. Patient independent of transfusions
  - d. Bone marrow  $< 5\%$  blasts
  - e. Absence of extramedullary disease
  - f. The disappearance of a karyotype abnormality is not required for definition of morphologic complete remission
- G. General principles of low-intensity remission induction therapy:<sup>59</sup>
  1. May be preferential in patients  $\geq 60$  years (although most data support the use in individuals  $\geq 70$  years of age) or relatively unfit patients with comorbidities
  2. Goal is mostly palliative and consists of regaining normal hematopoiesis, minimizing the need for transfusion, improving quality of life, and prolonging life.
  3. Low-intensity therapy generally continues until progression of disease

**V. Intensive remission induction therapy for newly-diagnosed AML age  $<60$  years (or  $<65$  and fit)<sup>50,59,70,71</sup>**

- A. A threshold of division of therapy by age is not clearly delineated in the literature. While some references and guidelines, e.g. NCCN®, denote age 60 years to differentiate between treatment modalities, others suggest 65 years, while others do not use chronologically age as a determinant to decide who is a candidate for intensive chemotherapy.
- B. Standard induction therapy is based on the combination of cytarabine + anthracycline (idarubicin or daunorubicin).
- C. **Daunorubicin Dose:**



Clinical Trial	Trial Details	Take Home Points
<b>ECOG 1900 Trial<sup>71</sup></b>	<p>Daunorubicin 90 mg/m<sup>2</sup>/day x 3 days (270 mg/m<sup>2</sup> total) demonstrates superior overall survival over daunorubicin 45 mg/m<sup>2</sup>/day x 3 days (135 mg/m<sup>2</sup> total) in patients &lt; 60 years (CR 71% vs. 54%, p&lt;0.001, OS 24 months vs. 16 months, p=0.003).</p> <p>Overall survival advantage in:</p> <ol style="list-style-type: none"> <li>1. Patients &lt; age 50 (34 months vs. 19 months, p=0.004)</li> <li>2. Those with favorable or intermediate risk cytogenetics (34 months vs. 21 months, p=0.004).</li> <li>3. Updated analysis<sup>72</sup>: <ol style="list-style-type: none"> <li>a. Those with unfavorable cytogenetics also benefit</li> <li>b. Demonstrated benefit in patients with NPM1 mutation and in patients with FLT3 ITD mutations</li> </ol> </li> </ol>	Daunorubicin 90 mg/m <sup>2</sup> x 3 days should be used for patients < 60 years of age with AML.
<b>HOVON 43 AML / SAKK 30/01 Trial<sup>70</sup></b>	<p>Older patients (&gt;60 years of age) were evaluated to assess use of high doses of daunorubicin. Daunorubicin 90 mg/m<sup>2</sup>/day x 3 days (270 mg/m<sup>2</sup> total) demonstrated superiority over daunorubicin 45 mg/m<sup>2</sup>/day x 3 days (135 mg/m<sup>2</sup> total). In this trial patients also received a second remission induction treatment with cytarabine 1g/m<sup>2</sup> IV twice daily for 6 days.</p> <p>Results:</p> <ol style="list-style-type: none"> <li>1. Patients age 60-65 years had improvement in CR (51% vs 73%, p=0.02), 2-year event free survival (14% vs 29%, p= 0.002), and 2-year overall survival (23% vs 38%, p= &lt;0.001).</li> <li>2. Suggested benefit in those with core binding factor AML but these were not statistically significant.</li> </ol>	Daunorubicin 90 mg/m <sup>2</sup> x 3 days should be used for patients 60-65 years of age with AML.
<b>UK NCRI AML17 Trial<sup>73</sup></b>	<p>Daunorubicin 90mg/m<sup>2</sup>/day x 3 days was compared to 60mg/m<sup>2</sup>/day in the UK NCRI AML17 Trial. However, patients received a double induction where they received an additional 50 mg/m<sup>2</sup>/day for 3 days. The study therefore compared 420 mg/m<sup>2</sup> total (not 270 mg/m<sup>2</sup> total) versus 330 mg/m<sup>2</sup> total (which is higher cumulative dose than daunorubicin 90 mg/m<sup>2</sup>/day x 3 days from the two aforementioned daunorubicin studies).</p> <p>Upon further analysis with additional follow-up, patients with FLT3-ITD mutant had a significant reduction in relapse free survival and overall survival if given the higher cumulative dose of daunorubicin<sup>74</sup></p>	Study is used to justify use of 60 mg/m <sup>2</sup> x3 days as standard practice.

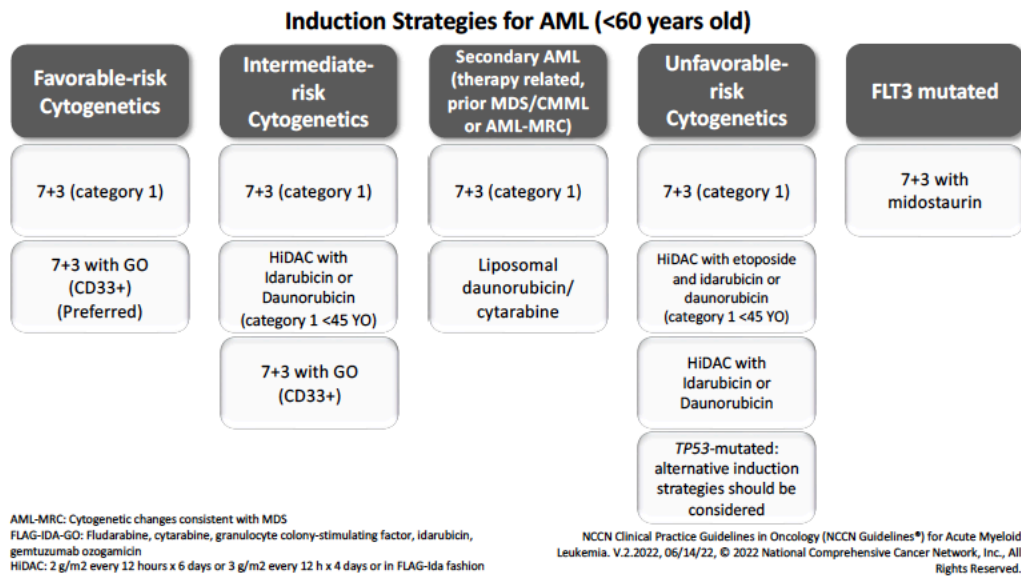
D. For testing purposes, daunorubicin 60-90 mg/m<sup>2</sup>/day x 3 days continues to be an appropriate option.

1. In clinical practice (despite many trials selecting 60 mg/m<sup>2</sup>/day as the *de facto* standard of care), one should consider whether the totality of evidence truly shows benefit for one dose versus the other and should weigh the risks versus potential benefits in each individual patient

2. Daunorubicin 60 mg/m<sup>2</sup> was studied in the ALFA-0701 and the RATIFY Trial, therefore this dose is recommended by NCCN when using 3+7 with gemtuzumab ozogamicin or midostaurin, respectively
- E. Does choice of anthracycline matter?
1. Comparison of idarubicin 12 mg/m<sup>2</sup>/day x 3 days vs. daunorubicin 60-80 mg/m<sup>2</sup>/day x 3 days in patients between 50-65 years demonstrated superior long-term outcomes with idarubicin<sup>75</sup>
    - a. This needs to be confirmed in subsequent studies
    - b. Idarubicin has not been compared with daunorubicin 90mg/m<sup>2</sup>/day x 3 days; daunorubicin 90 mg/m<sup>2</sup>/day x 3 days is considered equivalent to idarubicin 12 mg/m<sup>2</sup>/day x 3 days in clinical practice
- F. High-dose cytarabine used as part of remission induction in younger patients remains controversial.<sup>76</sup>
- G. Midostaurin (Rydapt®) is a multitargeted oral agent that has been shown to inhibit FLT3 kinase.
1. A phase 3 trial (RATIFY) was conducted to determine if midostaurin added to standard chemotherapy would prolong overall survival for AML patients with FLT3 mutations.
    - a. Patients were randomized to receive standard cytarabine + daunorubicin with either midostaurin or placebo.
    - b. Amongst 717 patients randomized, midostaurin was found to improve OS (HR 0.78, p=0.009) and EFS (HR 0.78, p=0.002).
    - c. Midostaurin adverse effects: nausea/vomiting, rash, interstitial lung disease/pneumonitis, anemia.<sup>77</sup>
      - 1) CYP 3A4 substrate: caution with moderate/strong CYP inhibitors
- H. Gemtuzumab ozogamicin (Mylotarg®) and standard 3 + 7. Gemtuzumab ozogamicin is a humanized CD33 targeted monoclonal antibody linked to calicheamicin
1. The drug was voluntarily withdrawn from the market in 2010 after SWOG S0106 was stopped early due to lack of clinical benefit and increased deaths in the experimental arm.
  2. Based on phase I data and results of SWOG S0106, gemtuzumab ozogamicin studies were again pursued but using “fractionated dosing” as a means of minimizing toxicity.
    - a. In the phase 3 ALFA-0701 trial, patients were randomized to receive 3 + 7 daunorubicin 60mg/m<sup>2</sup>/dose +/- gemtuzumab ozogamicin 3mg/m<sup>2</sup> IV on days 1,4,7 during remission induction.
      - 1) This study demonstrated statistically significant results favoring gemtuzumab ozogamicin in EFS (0.58 CI 0.43-0.78, p=0.0003), OS (0.69 CI 0.49-0.98, p=0.0368), and RFS (0.52 CI 0.36-0.75, p=0.0003).
        - a) However, with longer follow-up no longer an OS benefit; OS: HR, 0.81 (95% CI: 0.6-1.09); p=0.16<sup>78</sup>
      - 2) While there were two deaths due to veno-occlusive disease, overall toxicity may be reduced with fractionated dosing.<sup>79</sup>

- 3) Meta-analysis suggests benefit limited primarily to patients with favorable risk cytogenetics; small benefit to patients with intermediate risk cytogenetics; no benefit for those with adverse cytogenetics<sup>80</sup>

### 3. Summary of Preferred Treatment Options<sup>59</sup>



## VI. Intensive remission induction therapy for newly-diagnosed AML age ≥ 60 yrs and fit<sup>59</sup>

- A. Determination of patients who are medically fit versus unfit is not uniformly applied in a standard manner.
- B. For ECOG performance status 0-2:
  1. If favorable or intermediate cytogenetics, choose clinical trial or consider standard “7+3” regimen +/- gemtuzumab ozogamicin
  2. If secondary AML consider liposomal daunorubicin/cytarabine
- C. Daunorubicin and cytarabine liposome for injection (CPX351; Vyxeos®) is a combination product of cytarabine and daunorubicin as an encapsulated liposome at a 5:1 molar ratio.
  1. Administration is via IV infusion over 90 minutes on days 1, 3 and 5 during remission induction (on days 1 and 3 for subsequent cycles).
  2. Liposomal daunorubicin and cytarabine was studied in a phase 3 trial evaluating newly diagnosed AML in patients ages 60-75 years with a history of prior cytotoxic treatment, antecedent MDS or CMML (+/- prior treatment with a hypomethylating agent), or AML with WHO-defined MDS-related cytogenetic abnormalities
    - a. WHO-defined MDS-related cytogenetic abnormalities include complex karyotype without t(8;21), inv16 or t(16;16), t(9;11), t(v;11), t(6;9), inv 3 OR t(3;3); unbalanced abnormalities; balanced abnormalities (refer to WHO for further reference).
  3. Patients in the trial received remission induction treatment with either liposomal daunorubicin and cytarabine or “3 + 7” (daunorubicin 60 mg/m<sup>2</sup>).

- a. Liposomal daunorubicin and cytarabine demonstrated superior OS (HR 0.69,  $p=0.005$ ; median OS 9.56 versus 5.95 months), EFS (HR 0.74,  $p=0.021$ ) and CR + CRi response (47.7% versus 33.3%,  $p=0.016$ ) compared with “3 + 7”.
- b. Due to prolonged thrombocytopenia, higher rates of hemorrhage were observed in the liposomal daunorubicin and cytarabine arm. In addition, prolonged cytopenias were referenced as the cause for discontinuation of liposomal daunorubicin and cytarabine. Monitoring should include hypersensitivity reactions and copper overload [(reconstituted liposomal daunorubicin and cytarabine contains 5mg/ml copper gluconate (maximum total exposure of copper is 106mg/m<sup>2</sup>)).<sup>81</sup>

#### Patient Case #1 Answer

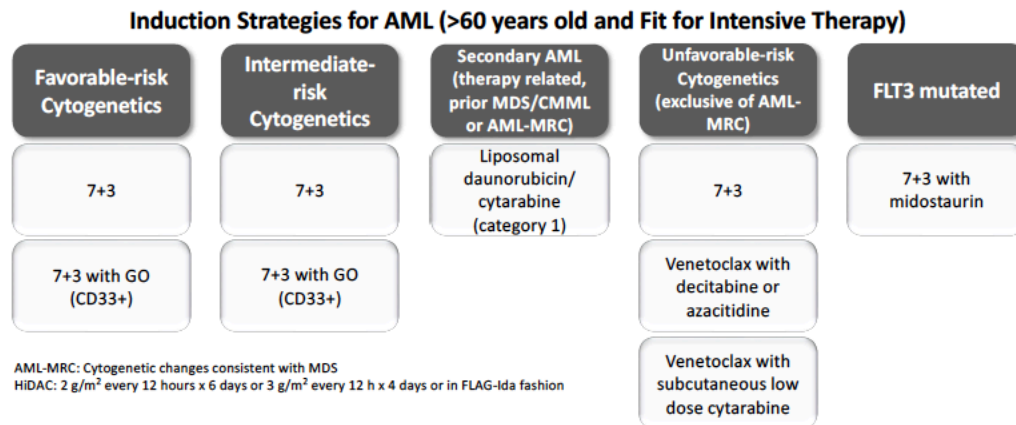
**Correct Answer = D [Liposomal cytarabine and daunorubicin]** – RO has secondary AML (previous exposure to R-CHOP) and is > 60 years of age. The NCCN guidelines recommend liposomal cytarabine and daunorubicin as a Category 1 recommendation in this setting.

A: A Phase III trial compared liposomal cytarabine and daunorubicin to 7+3 (daunorubicin 60 mg/m<sup>2</sup>) in patients >60 years of age who were fit for intensive chemotherapy. The liposomal formulation led to an overall survival benefit compared with 7+3. Additionally, 45 mg/m<sup>2</sup> of daunorubicin is not an acceptable option due to a study by Fernandez, et al demonstrating an overall survival benefit of 90 mg/m<sup>2</sup> versus 45 mg/m<sup>2</sup>.

B: A Phase III trial compared liposomal cytarabine and daunorubicin to 7+3 (daunorubicin 60 mg/m<sup>2</sup>) in patients >60 years of age who were fit for intensive chemotherapy. The liposomal formulation led to an overall survival benefit compared with 7+3.

C: Despite RO being CD33+, there are several reasons to not add gemtuzumab ozogamicin: 1) this regimen has not been adequately studied; 2) there could be significant toxicity related to combined myelosuppression; and, 3) patients with secondary AML do not response well to gemtuzumab ozogamicin / patients with poor risk cytogenetics (del7) do not respond well to gemtuzumab ozogamicin.

#### 4. Summary of Preferred Treatment Options<sup>59</sup>



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#### **Patient Case # 2:**

LJ is a 62 yo female presenting to the ED with a WBC  $0.5 \times 10^9/L$  and platelets  $10 \times 10^9/L$ . She has no past medical history and states she is training for the Boston marathon next month. Unfortunately, she is diagnosed with AML that is found to have a complex karyotype, an IDH1 mutation, and is CD33+.

**Which of the following treatments is most appropriate for LJ at this time?**

- A. Gemtuzumab ozogamicin
- B. Ivosidenib
- C. Azacitidine + venetoclax
- D. Decitabine + enasidenib

#### **VII. Low-intensity remission induction therapy**

##### **A. Advantages:**

1. Benefits EFS and OS versus best supportive care
2. Lower incidence of treatment-related adverse events requiring hospitalization compared with intensive chemotherapy
3. Can be administered in ambulatory setting
4. Benefits derived in both newly-diagnosed and salvage setting
5. Efficacy is seen independent of any cytogenetic findings, adverse or otherwise (except for gemtuzumab ozogamicin which has reduced efficacy in those with adverse cytogenetic findings)

B. Disadvantages:

1. Responses may not be evident for several cycles, thus can have prolonged cytopenias<sup>59</sup>

C. Hypomethylating Agents

1. Azacitidine

- a. Not FDA-approved for treatment of AML; approved in Europe for AML with antecedent MDS
- b. A study evaluated use of azacitidine compared with conventional chemotherapy regimens (e.g. best supportive care, standard induction or subcutaneous cytarabine) in 488 adults with AML who were greater than 65 years of age.
  - 1) The azacitidine arm had a greater number of patients who remained or became RBC/platelet transfusion independent.
  - 2) Overall survival was increased with azacitidine compared with conventional chemotherapy regimens (10.4 months (95% CI 8-12.7) versus 6.5 months (95% CI 5-8.6 months). Respectively, HR was 0.85 (95% CI 0.69-1.03, stratified log rank p = 0.1009).<sup>82</sup>

2. Decitabine

- a. Approved in Europe for AML in adults > 65 yrs, but FDA rejected this indication in March 2012
- b. Studies have investigated multiple doses and schedules; 20 mg/m<sup>2</sup>/day IV x 5-10 days is most commonly cited<sup>83,84</sup>
- c. Multiple studies have shown superiority versus low-dose cytarabine<sup>83,85</sup>
3. For treatment of adult AML, no head-to-head prospective studies between azacitidine and decitabine exist.
4. May require 3-4 cycles to see response if a response will be seen at all. Generally, low-intensity remission induction therapy continues until disease progression, blurring lines between “induction” and “post-remission” therapy (ie: consolidation and maintenance).

D. Gemtuzumab ozogamicin

1. An open label phase 3 trial evaluated gemtuzumab ozogamicin versus best supportive care as remission induction therapy for older patients with newly diagnosed AML who are unsuitable for intensive chemotherapy.
  - a. The AML-19 trial randomized patients stratified by age, performance status, CD33 status, and WBC at diagnosis to receive best supportive care versus gemtuzumab ozogamicin 6mg/m<sup>2</sup> IV on day 1 and 3mg/m<sup>2</sup> IV on day 8.
    - 1) Thereafter, patients who responded favorably to gemtuzumab ozogamicin were eligible to receive 8 monthly infusions of gemtuzumab ozogamicin 2mg/m<sup>2</sup> IV on day 1.
      - a) The median OS was 4.9 months with gemtuzumab ozogamicin versus 3.6 months with best supportive care (HR 0.69, CI 0.53-0.9, p= 0.005).
      - b) Less benefit in those with adverse cytogenetics. Rates of serious adverse events were similar in both groups.<sup>86</sup>

- E. Glasdegib: the BRIGHT AML 1003 study evaluated glasdegib 100mg po daily in combination with low-dose cytarabine i.e. 20mg SC BID x 10 days compared to low dose cytarabine (LDAC) alone in 28-day cycles.<sup>87</sup>
1. Open label, multicenter, phase II report of an ongoing clinical trial. Patients were stratified by cytogenetic risk factor and randomized to treatment arms. Primary objective was OS.
    - a. Median number of cycles was 3 (1-35) for glasdegib + LDAC.
    - b. Complete response rate was 17% vs 2.3% in favor of the glasdegib combination
    - c. Median follow up for glasdegib + LDAC was 21.7 months. Median OS was 8.8 months (6.9-9.9) for glasdegib + LDAC versus 4.9 (3.5-6 months) for LDAC alone (HR, 0.51 [80% CI, 0.39-0.67]; p=0.0004.
    - d. Additional follow-up: median follow up of 48 months demonstrated similar findings as initial publication. In a subgroup analysis within this report, patients with secondary AML seemed to benefit from glasdegib + LDAC compared with LDAC; median OS 9.1 months vs 4.1 months (HR 0.29 [95% CI, 0.15-0.55]; p <0.001).<sup>88</sup> This is hypothesis generating and should be confirmed in a Phase III.
- F. Venetoclax: Venetoclax gained FDA approval via the M14-358 and M14-387 trials. The subsequent Phase III confirmatory studies were VIALE-A (M15-656) and VIALE-C (M16-043) trial, respectively.
1. VIALE-A (M15-656) trial was a phase III, double-blind, placebo-controlled trial which enrolled newly diagnosed patients with AML who are ineligible for intensive chemotherapy (age >75 or comorbidities). Patients received either venetoclax plus azacitidine (VEN+AZA) or placebo plus azacitidine (PBO+VEN). The primary endpoint was overall survival.<sup>89</sup>
    - a. Median OS: 14.7 months in VEN+AZA (n=286) versus 9.6 months in VEN+PBO (n=145) [HR: 0.66, (95% CI: 0.52–0.85); p<0.001].
    - b. CR/CRi rates in VEN+AZA/PBO+AZA were 66%/28% (p< 0.001), respectively
      - 1) CR/CRi rate was significantly improved with VEN+AZA in the following subgroups: De Novo AML, secondary AML, IDH1/2 mutation, FLT3 mutation, NPM1 mutation, and TP53 mutation
    - c. VEN+AZA also improved transfusion independence
  2. VIALE-C (M16-043) trial was a phase III, double-blind, placebo-controlled trial which enrolled newly diagnosed patients with AML who are ineligible for intensive chemotherapy. Patients received either venetoclax plus LDAC (VEN+LDAC) or placebo plus LDAC (PBO+LDAC). The primary endpoint was overall survival.<sup>90</sup>
    - a. Median OS: 7.2 months in VEN+LDAC (n=211) versus 4.1 months in venetoclax plus LDAC versus placebo plus LDAC (n=143) [HR 0.75, (95% CI 0.52–1.07); p=0.11].
      - 1) An unplanned analysis with an additional 6 months of follow up demonstrated a median OS of 8.4 months for the venetoclax arm [HR 0.70, (95% CI 0.50-0.98); p=0.04].
    - b. The CR/CRi rates were 48% and 13% for the Venetoclax plus LDAC arm and LDAC-alone arm, respectively
    - c. VEN+LDAC also improved transfusion independence and patient reported outcomes

3. Venetoclax clinical pearls<sup>91</sup>:
  - a. Compared with HMA alone
    - 1) Responses are faster (CR in 1-2 cycles rather than 3-4+ cycles)
      - a) Obtain a marrow at ~day 21-28
      - b) If no evidence of leukemia give 7-14 day break of therapy
        - i. Significant myelosuppression if no breaks
      - c) Concern for treatment failure if no response after two cycles
  - b. Venetoclax requires significant dose reduction if given with anti-mold azole antifungal
    - 1) Stop antimicrobial prophylaxis when remission attained (and periods of neutropenia becomes shorter)
  - c. Consider shorter course of venetoclax (14-21 days) depending on cytopenias from previous cycles
- G. Ivosidenib: Ivosidenib initially gained FDA approval for the treatment of first-line IDH1 mutated AML as a single agent for patients 75 or older or patients with comorbidities deemed unfit for intensive therapy via the Phase Ib AG120-C-001 Trial.<sup>92,93</sup> The subsequent Phase III combination trial was the AGILE study.
  1. AGILE trial was a phase III, double-blind, placebo-controlled trial which enrolled newly diagnosed patients with AML who are ineligible for intensive chemotherapy. Patients received either Ivosidenib plus azacitidine (IVO+AZA) or placebo plus azacitidine (PBO+AZA). The primary endpoint was initially overall survival but was changed to event free survival.<sup>94</sup>
    - a. Median OS: 24 months in VEN+AZA (n=72) versus 7.9 months in VEN+PBO (n=74) [HR: 0.44, (95% CI 0.27-0.73); p=0.001].
    - b. CR/CRh rates in IVO+AZA/PBO+AZA were 53% vs 18%, respectively
    - c. EFS at 12 months was higher with the IVO+AZA combination (37% vs 12%)
    - d. Differentiation syndrome rate (all grade): 14%

## VIII. Summary of Preferred Treatment Options<sup>59</sup>



### Induction Strategies for AML (>60 years old and Unfit for or Declines Intensive Therapy)

No Actionable Mutations	IDH1 Mutated	IDH2 Mutated	FLT3 mutated
Preferred: Venetoclax with decitabine or azacitidine (category 1 for azacitidine combo)	Preferred: Ivosidenib +/- Azacitidine	Preferred: Enasidenib	Preferred: Venetoclax with decitabine or azacitidine (category 1 for azacitidine combo)
Azacitidine or decitabine			
Venetoclax with subcutaneous low dose cytarabine	Preferred: Venetoclax with decitabine or azacitidine (category 1 for azacitidine combo)	Preferred: Venetoclax with decitabine or azacitidine (category 1 for azacitidine combo)	
Glasdegib with subcutaneous low dose cytarabine			
Gemtuzumab Ozogamicin (CD33+)			
Subcutaneous low dose cytarabine			
Best supportive care (hydroxyurea and transfusions)			

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#### Patient Case # 2 Answer:

**Correct Answer = C Azacitidine + venetoclax** is an NCCN recommended treatment option for patients who are > 60 years of age and fit for intensive therapy but harbor unfavorable cytogenetics (ie: a complex karyotype).

A: Gemtuzumab ozogamicin as a single agent would not be appropriate since it is a therapy recommended for older patients who are unfit. Further, response rates, EFS, and OS would likely be less than azacitidine + venetoclax, especially in patients with unfavorable cytogenetics.

B: Although LJ has an IDH1 mutation, she is relatively young and very fit, thus she should be eligible for a slightly more intense regimen than single agent ivosidenib. Ivosidenib is appropriate for patients with an IDH1 mutation who are elderly and unfit for other therapies. The response rates are significantly lower than azacitidine + venetoclax.

D: Enasidenib is an IDH2 inhibitor. It would not be appropriate for patients with an IDH1 mutation. The combination of decitabine and enasidenib is currently being studied but not yet a recommended combination in the NCCN guidelines.

#### Patient Case # 1 (continued):

Ten days following confirmation of complete remission from induction, RO is to receive post-remission therapy. Renal and hepatic function are normal. Which of the following treatments is most appropriate for RO at this time?

- A. Cytarabine 3,000 mg/m<sup>2</sup>/dose IV Q12 hours on days 1,3,5
- B. Cytarabine 1,000 IV Q12 hours on days 1,3,5 mg/m<sup>2</sup>/dose + gemtuzumab ozogamicin 3 mg/m<sup>2</sup>
- C. Liposomal daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> on days 1 and 3
- D. 5+2 (cytarabine continuous infusion x5 days + daunorubicin IV on days 1,2)

#### IX. Post-remission therapy age < 60 yrs (AKA “consolidation”)

- A. Successfully obtaining CR with remission induction chemotherapy clears the visible signs of leukemia and restores normal hematopoiesis. However, further therapy is required to eliminate minimal disease, which persists. Without post-remission therapy, >95% of patients with AML will eventually relapse.<sup>95</sup>
- B. High-dose cytarabine (HiDAC):
  1. The gold-standard for post-remission therapy for those age < 60 years with favorable or intermediate risk; role in those above 60 years and/or with adverse risk is less clear and these patients should be evaluated for hematopoietic stem cell transplantation<sup>59,96</sup>
    - a. Ideal post-remission therapy in patients age ≥ 60 years unknown, but HiDAC commonly employed, with modified doses<sup>97</sup>
  2. Dosing:
    - a. 3,000 mg/m<sup>2</sup>/dose IV every 12 hours on days 1, 3, 5 (or days 1, 2, 3) for total of 6 doses per cycle every 28 days
      - 1) Reduce dose to 1,000-1,500 mg/m<sup>2</sup>/dose IV for age > 60 years (due to excess neurotoxicity) and renal dysfunction (due to impaired excretion of neurotoxic metabolite [ara-UTP])
      - 2) Add midostaurin the day after chemotherapy has completed if FLT3+
  3. Subsequent analysis demonstrated that patients with core binding factor benefited the most, followed by those with normal karyotype<sup>98</sup>
  4. Controversy surrounds the optimal dose and number of cycles with respect to HiDAC consolidation (generally 2-4 cycles are considered)<sup>99</sup>
  5. Primary non-hematologic toxicities: 1) cerebellar toxicity (see Neurotoxicity below), and 2) chemical conjunctivitis (see Ocular Toxicity below)
- C. Other chemotherapy consolidation strategies
  1. Patients who received dual-drug liposomal encapsulation daunorubicin and cytarabine for induction can receive liposomal daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> over 90 min on days 1 and 3 for 1-2 cycles
  2. Patients who received gemtuzumab ozogamicin in induction may receive HiDAC +/- daunorubicin +/- gemtuzumab ozogamicin for 2 cycles
  3. Patients who are FLT3+ are treated with HiDAC + midostaurin (50 mg every 12 hours on days 8-21) if not a candidate for allo-HCT or as a bridge while awaiting work-up for an allo-HCT
  4. Patients who received a hypomethylating based regimen continue with a hypomethylating based regimen every 4-6 weeks until progression
  5. Truncated anthracycline + cytarabine continuous infusion (e.g.: "5+2" following "7+3") may be an option; head-to-head studies against high-dose cytarabine are lacking.
- D. Allogeneic HCT (if candidate based on cytogenetics/molecular risk and fitness)
  1. Allogeneic HCT can take ~3 months for logistics. A common approach is to bridge patients with 1-2 cycles of the aforementioned consolidation strategies

**X. Post-remission therapy age  $\geq$  60 yrs**

- A. If CR obtained with induction therapy:
1. Clinical trial
  2. High-dose cytarabine (consider dose adjustments)
    - a. If FLT3+ add midostaurin
  3. Consider following consolidation strategies from phase III trials if employing liposomal cytarabine/daunorubicin and gemtuzumab ozogamicin (per tables above)
  4. Patients who received a hypomethylating based regimen continue with a hypomethylating based regimen every 4-6 weeks until progression
  5. Allogeneic HCT (if candidate based on cytogenetics/molecular risk and fitness)

**Patient Case #1 (continued) Answer**

**Correct Answer = C [daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup>].** The phase III trial leading to FDA approval and a Category 1 recommendation in the NCCN employed liposomal daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> as consolidation for those who achieved a CR/CRi following liposomal daunorubicin/cytarabine induction. This regimen demonstrated an overall survival benefit compared with 7+3 induction and 5+2 consolidation.

A: Although this is an NCCN guideline recommended consolidation strategy for AML consolidation and a standard of care, it was not studied with liposomal daunorubicin/cytarabine. It would be appropriate following 7+3 induction.

B: Intermediate dose cytarabine is appropriate for older patients who are deemed unable to tolerate high-dose cytarabine. However, given the induction strategy employed was liposomal daunorubicin/cytarabine, this consolidation regimen would be incorrect.

D: The phase III trial leading to FDA approval and a category 1 recommendation in the NCCN employed liposomal daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> as consolidation for those who achieved a CR/CRi following liposomal daunorubicin/cytarabine induction. This regimen demonstrated an overall survival benefit compared with 7+3 induction and 5+2 consolidation.

**XI. Maintenance Therapy in AML**

- A. Oral azacitidine (CC-486): The QUAZAR AML-001 study evaluated an oral formulation of azacitidine 300 mg orally daily for 14 days of a 28 day cycle continuously compared to placebo for patients with AML who were  $\geq$  55 years of age, in first CR/CRi following intensive chemotherapy, had Intermediate or poor risk cytogenetics and were ineligible for allo-HCT.<sup>69</sup>
1. Multicenter, randomized, placebo-controlled, double-blind, phase III study. The primary endpoint was overall survival.
    - a. Median OS was 24.7 months (oral azacitidine) versus 14.8 months (placebo) (HR, 0.69 [95% CI, 0.55-0.86], p=0.0009).
    - b. Median RFS was 10.2 months (oral azacitidine) versus 4.8 months (placebo) (HR, 0.65 [95% CI, 0.52-0.81], p=0.001).

Oral Azacitidine <sup>100</sup>	
Mechanism of action	Hypomethylating agent (not interchangeable with IV or subQ azacitidine as bioavailability and dosing are different)
Indications for use	Maintenance therapy for adult patients with AML who achieved CR/CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy
Toxicities	<p>Most common adverse reactions (<math>\geq 10\%</math>) are nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity.</p> <p>Patients are instructed to administer an antiemetic before each dose for at least the first 2 cycles</p>
Drug Interactions	Not a substrate for and does not inhibit CYP enzymes or p-glycoprotein.

## XII. Intensive remission induction therapy for relapsed or refractory (R/R) patients<sup>59,101,102</sup>

- A. Relapsed and refractory AML is common in adults. R/R AML is highly associated with adverse cytogenetic features and/or FLT3-ITD positivity. Relapsed AML is considered unfavorable, no matter the cytogenetics.
- B. The goal of salvage intensive remission induction therapy is to produce a CR and take the patient to allogeneic HCT.
  1. Allogeneic HCT is the only known curative therapy for relapsed and refractory AML.
  2. Salvage therapy is still administered, but long-term overall survival and relapse-free survival rates diminishes greatly.
- C. Additional remission induction treatments may be administered either:
  1. Early, upon learning results of day 14 bone marrow biopsy during remission induction therapy. This is called re-induction but is not salvage therapy for R/R disease
  2. Late, upon diagnosing relapsed AML following a period of complete remission (i.e. relapsed AML) or upon incomplete hematopoietic recovery after induction with bone marrow evaluation demonstrating leukemia (i.e. refractory AML)
- D. Clinical outcomes for salvage treatment of R/R AML are driven by the amount of time the patient spent in CR and the amount of post-remission therapy received (e.g. lifetime cumulative dose of anthracycline).
  1. If CR maintained for  $\geq 12$  months, outcomes for salvage treatment are more favorable than if patient maintained  $<12$  month remission
- E. If patient relapses  $> 12$  months from initial remission induction therapy, the same regimen previously used may be re-administered in patients who can tolerate based on performance status and organ function.

### Patient Case #3:

SB is a 55-year old female with relapsed AML following a clinical trial with liposomal

daunorubicin/cytarabine and gemtuzumab ozogamicin. She has a performance status of 0. A bone marrow biopsy is performed revealing a normal karyotype and molecular markers that are negative for FLT-ITD, NPM1, and IDH1. Which of the following would be the most appropriate treatment for SB's relapsed AML?

- A. Midostaurin
- B. FLAG-IDA + ivosidenib
- C. MEC
- D. Gilteritinib

#### Intensive Remission (re)Induction Regimens for Relapsed or Refractory Adult AML<sup>55,103</sup>

Induction Regimen	Dosing and Schedule	Comments
<b>5 + 2 (or 3 + 7)</b> Daunorubicin <b>OR</b> Idarubicin Cytarabine continuous infusion <sup>104</sup>	Daunorubicin 45-60 mg/m <sup>2</sup> /day IV qDay x 2 (or 3) days <b>OR</b> Idarubicin 12 mg/m <sup>2</sup> /day IV qDay x 2 (or 3) days Cytarabine 100 – 200 mg/m <sup>2</sup> /day continuous IV infusion qDay x 5 (or 7) days	Use as reinduction when: (a) results of day 14 bone marrow biopsy demonstrates residual leukemia, (b) residual leukemia is less than prior to initial remission induction therapy and (c) patient tolerates further anthracycline. DFS = 35% Unclear if patients failing first cycle of 7+3 should receive second cycle of 7+3 or 5+2 versus alternative chemo
<b>HiDAC variant</b> High-dose Cytarabine (higher cumulative dose than used for consolidation) <sup>105</sup>	Cytarabine 2,000-3000 mg/m <sup>2</sup> /dose q 12 hrs x 6 days (24,000 mg/m <sup>2</sup> total per cycle)	When employed for re-induction, no data show superiority of high-dose cytarabine versus cytarabine at lower doses. These regimens should be reserved for younger patients without renal dysfunction.
<b>ME(C)</b> Mitoxantrone Etoposide High-dose Cytarabine (with or without cytarabine) <sup>106,107</sup>	Mitoxantrone 8 mg/m <sup>2</sup> IV daily x 5 days Etoposide 100 mg/m <sup>2</sup> IV daily x 5 days Cytarabine 1,000 mg/m <sup>2</sup> IV daily x 5 days	All patients relapsed or refractory. 18-24% CR rates. Median OS 6.7 mo. Those with favorable cytogenetics displayed trend towards greater benefit. <sup>106</sup> Versus CLA, MEC demonstrated inferior OS and CR rates <sup>107</sup> There are several variations of ME and MEC with many different dosing strategies documented within the literature. Standard doses are highlighted here.
<b>FLA (± Ida) (AKA FLAG-Ida)*</b> Fludarabine High-dose Cytarabine ± Idarubicin <sup>108,109</sup>	Fludarabine 30 mg/m <sup>2</sup> /day IV qDay x 5 days Cytarabine 2,000 mg/m <sup>2</sup> /day IV qDay x 5 days ± Idarubicin 10 mg/m <sup>2</sup> /day IV qDay x 3D *Filgrastim 5mcg/kg/day SC days 0-count recovery (or from days 0-5)	CR rates 50-55%. Increased toxicity with idarubicin without clear benefit in outcomes. Both studies conducted in era before current understanding of cytogenetics. There are several dosing variations of the FLAG-Ida regimen available in the literature. Timing of cytarabine relative to fludarabine administration is significant due to a theoretical efficacy advantage based on MOA.
<b>G-CLAC</b> Clofarabine, cytarabine and filgrastim <sup>110</sup>	Clofarabine 25mg/m <sup>2</sup> /day IV days 1-5 Cytarabine 2,000mg/m <sup>2</sup> /day IV days 1-5 Filgrastim 5mcg/kg/day SC day 0 through count recovery	CR rate was 46% for the 46 evaluable patients who received G-CLAC (95% CI 31-60%). Timing of cytarabine relative to clofarabine administration is significant due to a theoretical efficacy advantage based on MOA.
<b>CLA (± M) (AKA CLAG)*</b> Cladribine High-dose Cytarabine ±	Cladribine 5 mg/m <sup>2</sup> /day IV on days 1-5 <sup>111</sup> (alternatively, days 2-6 <sup>107</sup> ) Cytarabine 2,000 mg/m <sup>2</sup> /day IV days 1-5 ± Mitoxantrone 10 mg/m <sup>2</sup> /day IV days 1-3 <sup>112</sup>	CR rates 38-58%. Median OS 7.4-9 months. Favorable cytogenetics improved outcomes slightly. Addition of mitoxantrone increased toxicity without significant improvement in outcomes. Timing of cytarabine relative to cladribine administration is

Mitoxantrone <sup>107,111,112</sup>	*Filgrastim 300 mcg/day SC days 0-5	significant due to a theoretical efficacy advantage based on MOA.
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\*Note: For FLA ( $\pm$  Ida), G-CLAC and CLA ( $\pm$  Mitoxantrone), the addition of filgrastim is controversial being used in this context as “priming.” Some studies suggest benefit to priming with growth factor when used with high dose cytarabine whereas others demonstrate priming only adds to cost and toxicity.<sup>31,113</sup>

F. No head-to-head prospective comparisons of any intensive remission induction therapy for relapsed or refractory adult AML exist.

1. HiDAC based (FLAG+/-Ida, MEC, GCLAC, G-CLAM), gemtuzumab ozogamicin, etc
2. Can consider non-intensive options similar to front line
3. Test (and re-test if previous testing was prior to previous line of therapy) for targetable mutation (ivosidenib, enasidenib, gilteritinib)

G. Enasidenib (Idhifa®)

1. Enasidenib dose is 100mg po daily and should be continued until disease progression or unacceptable toxicity.
2. Overall, enasidenib was well tolerated. It was approved with a companion device to test for IDH2 mutations, the Abbott RealTime™ IDH2 assay.<sup>114</sup>

H. Ivosidenib (Tibsovo®)<sup>115,116</sup>

1. In a phase I dose escalation and expansion study, ivosidenib induced transfusion independence, durable remissions, and molecular remissions in some patients with relapsed/refractory AML. Trial participants had received a median of two prior therapies for their IDH1 mutated AML.

I. Olutasidenib (Rezlidhia™): Study 2102-HEM-101 evaluated the IDH1 inhibitor olutasidenib 150 mg orally twice daily in patients with R/R IDH1 mutated AML (n=147)<sup>117</sup>

1. Phase II open label, single arm, multicenter study
2. CR + CRh: 35%
3. Median duration of response: 25.9 months

Olutasidenib	
Mechanism of action	IDH1 inhibitors
Indications for use	R/R IDH1 mutated AML
Toxicities	<p>The most common (20%) adverse reactions, including laboratory abnormalities, are aspartate aminotransferase increased, alanine aminotransferase increased, potassium decreased, sodium decreased, alkaline phosphatase increased, nausea, creatinine increased, fatigue/malaise, arthralgia, constipation, lymphocytes increased, bilirubin increased, leukocytosis, uric acid increased, dyspnea, pyrexia, rash, lipase increased, mucositis, diarrhea and transaminitis.</p> <p>Differentiation syndrome and hepatotoxicity are a warning/precaution within the prescribing information</p>

Drug Interactions	Avoid strong or moderate CYP3A inducers; olutasidenib induces CYP3A therefore use caution with CYP substrates
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#### Enasidenib, Ivosidenib, and Olutasidenib Comparison<sup>116-118</sup>

Grade $\geq$ III AEs	Enasidenib	Ivosidenib	Olutasidenib
Hyperbilirubinemia	✓ (due to inhibition of UGT1A1)		✓
Diarrhea	✓	✓	✓
Nausea	✓	✓	✓
↓Ca <sup>2+</sup> , K <sup>+</sup> , Phos	✓		✓ (potassium and sodium)
QT prolongation		✓	
Leukocytosis	✓	✓	✓
Differentiation Syndrome	✓	✓	✓

#### J. Gilteritinib (Xospata®)<sup>119</sup>

1. Has an approved FDA companion diagnostic i.e. Leukostrat CDx FLT3 mutation assay
2. The ADMIRAL study was a Phase III, open-label, randomized controlled trial comparing? gilteritinib 120 mg orally daily with physician's choice (low-dose subcutaneous cytarabine, azacitidine, MEC, or FLAG-ida). Patients were 18 years or older with relapsed/refractory FLT3+ AML (ITD or TKD D835/I836 mutation).
  - a. Overall 34% of patients attained a CR/CRh with gilteritinib vs 15.3% with physician's choice. Event free survival (2.8 vs 0.7 months) and overall survival (9.3 vs 5.6 months; p<0.001) were improved with gilteritinib.<sup>119-121</sup>

#### Patient Case #3 Answer: C

A: Midostaurin is only recommended in front line in combination with 3+7.

B: Ivosidenib is recommend in IDH1 mutated AML.

C: MEC is an appropriate salvage option for patients who do not have targetable mutations.

D: OS is improved with gilteritinib in patients with R/R AML and a FLT3 mutation. However, this patient does not have a FLT3 mutation.

#### XIII. Low-intensity therapy for salvage treatment following failure of intensive remission induction therapy in relapsed or refractory AML

- A. Although an option and commonly used, limited data exist that demonstrate utility of low-intensity therapy (ie: venetoclax based regimen with hypomethylating agent or low dose cytarabine; or glasdegib based regimen) following relapse or refractory AML after intensive remission induction therapy except for targeted therapies such as gilteritinib, enasidenib, and ivosidenib
- B. Gemtuzumab ozogamicin was FDA-approved for use in CD33 positive relapsed or refractory AML as monotherapy using fractionated dosing i.e. 3mg/m<sup>2</sup> IV on days 1, 4 and 7.

#### XIV. Selected supportive care for adults with AML

- A. Tumor lysis syndrome addressed in greater detail within this handout.

- B. Patients undergoing remission induction chemotherapy for AML have many risk factors for infectious complications<sup>122,123</sup>. Please see “Cancer-related Infections” chapter for details on prophylaxis and treatment of infectious complications in patients with AML.
- C. White blood cell colony-stimulating factors:<sup>124-131</sup>
1. Primary prophylaxis following remission induction chemotherapy to shorten duration of neutropenia is not recommended in AML patients. Although neutropenia is shortened, not shown to affect overall survival. Theoretical - but unfounded - concern that a myeloid growth factor may stimulate the underlying myeloid malignancy
  2. Primary or secondary prophylaxis following each cycle of post-remission (AKA consolidation) chemotherapy
    - a. Although neutropenia is shortened and neutropenic complications reduced, not shown to affect overall survival or reduce infection-related mortality
    - b. ASCO Guidelines state that myeloid growth factors can be used after consolidation therapy, as they may decrease infection incidence and prevent hospitalizations. The impact on neutropenia duration may also be more profound in consolidation therapy than in induction therapy for AML. Though there is no mortality benefit, decreased rates of infections and prevention of hospitalizations confers a morbidity and potential cost benefit for patients
  3. Administration during remission induction chemotherapy as “priming” is controversial
- D. Neurotoxicity of cytarabine:
1. Cerebellar toxicity manifests as ataxia, nystagmus and dysarthria. Occurs relatively soon upon starting high-dose cytarabine and is most associated with renal dysfunction and inconsistently associated with increased age and alkaline phosphatase<sup>132,133</sup>
    - a. Neurotoxicity associated with high-dose cytarabine can lead to profound morbidity resulting in loss of gross motor ability. Oftentimes, neurotoxicity is reversible but this is not always the case and it can cause irreversible damage
    - b. Doses and/or frequency of cytarabine administration should be adjusted prospectively on a patient-specific basis depending on evaluation of risk factors associated with cytarabine-induced neurotoxicity<sup>134</sup>
  2. Requires periodic evaluation of mental status, proprioception and cerebellar function at a carefully planned frequency typically evaluated prior to each dose of cytarabine
  3. Management of cerebellar toxicity: hold further doses; symptoms often improve to baseline, but permanent neuromotor damage may persist
- E. Ocular toxicity of high-dose cytarabine:<sup>135-139</sup>
1. Cytarabine  $\geq 1,000$  mg/m<sup>2</sup>/dose IV over 1-4 hours for > 2 doses leads to corneal toxicity in over 80% of patients who do not receive eye drops, due to high water solubility and high concentrations achieved in tear glands and aqueous humor
  2. Symptoms of cytarabine-induced ocular toxicity include excessive tearing, pain, photophobia and sensation of foreign body
    - a. Median onset is 2-4 days after first dose of high-dose cytarabine and lasts for up to 2-3 days following final dose, peaking 6 days from first dose of cytarabine



3. Topical deposition of cytarabine contained in tears upon corneal epithelium triggers inflammatory cascade
4. Prevention of cytarabine-induced ocular toxicity:
  - a. Primary mechanism of action for topical eye drops appears to be related to dilution of intraocular concentration of cytarabine but is overall unclear. It may be related to decreased replication rate induced by corticosteroids impacting DNA replication in corneal cells
  - b. Standard of care for prevention remains unclear
    - 1) Artificial tears
      - a) Studies are inconsistent when tears are compared to topical steroids. Many studies demonstrate no difference between the 2 modalities
      - b) May be equally effective to topical prednisolone drops when given on a rigorous schedule
    - 2) Topical corticosteroids
      - a) Dexamethasone may be preferred over prednisolone due to higher potency and greater penetration into corneal epithelium (e.g. dexamethasone 0.1% instill 2 drops into both eyes every six hours)
      - b) Topical prevention therapies are required even if patient receiving systemic corticosteroids
    - 3) Topical corticosteroid + topical non-steroidal anti-inflammatory
      - a) Application of both dexamethasone drops and diclofenac drops proved superior to dexamethasone drops alone, purportedly due to dual mechanism of action
5. Treatment of cytarabine-induced ocular toxicity:
  - a. Discontinuation of cytarabine and frequent administration of topical corticosteroids has proven useful
  - b. Permanent damage is rare, but may occur
  - c. Rechallenge with high-dose cytarabine may be administered without recurrence of ocular toxicity, provided topical prophylaxis is administered

## ACUTE PROMYELOCYTIC LEUKEMIA (APL)

I. The hallmark of acute promyelocytic leukemia (APL) is translocation between promyelocytic leukemia (PML) gene on chromosome 15 and retinoic acid receptor (RAR- $\alpha$ ) on chromosome 17, which produces the PML-RARA fusion gene that can be quantitatively monitored using PCR to document disease burden and ultimately confirm molecular remission.

- A. t(15;17) prevents morphologic differentiation into mature neutrophils.
- B. APL is clinically distinct from other subtypes of AML due to much higher 5-yr overall survival rate and sensitivity to chemotherapy and differentiating agents.
- C. APL can be *de novo* or treatment-related; however, treatment-related APL does not differ prognostically and is treated the same as *de novo* APL.

### II. Staging

- A. Unlike other subtypes of AML, APL is staged into high-risk, intermediate-risk and low-risk based upon WBC and platelet count upon diagnosis and prior to any therapy. Risk stratification is in reference to risk of toxicities and relapse.<sup>140</sup>

#### Risk stratification of APL.

	Low	Intermediate	High
White blood cells	WBC < 10 x 10 <sup>9</sup> /L	WBC < 10 x 10 <sup>9</sup> /L	<u>WBC &gt; 10 x 10<sup>9</sup>/L</u>
Platelets	Platelet > 40 x 10 <sup>9</sup> /L	Platelet $\leq$ 40 x 10 <sup>9</sup> /L	Any

- B. In terms of treatment, risk categories are broken down into only two groups in which high-risk is treated differently than low- or intermediate-risk APL, the latter two of which are treated the same.

### III. Treatment principles of APL<sup>59,141-143</sup>

- A. While high remission rates are observed with APL, the initial clinical presentation may be linked to early death due to APL-associated coagulopathy.
- B. Use of the differentiating agent tretinoin (i.e. ATRA or all-trans-retinoic acid) helps to correct APL-associated coagulopathy and is foundational to treatment as is stratifying treatment according to risk (start ATRA with even the slightest suspicion for APL)
  - 1) Tretinoin causes maturation and terminal differentiation of premature promyelocytes, leading to apoptosis
  - 2) Arsenic trioxide causes degradation of retinoic acid receptor alpha (RARA) oncoprotein leading to differentiation and apoptosis of promyelocytes
    - a. The combination of tretinoin plus arsenic trioxide has been shown to be synergistic with each other and the addition of an anthracycline (e.g. idarubicin as per APM14) to arsenic trioxide + tretinoin is also synergistic
- C. Differentiating agents are used in remission induction, consolidation, and maintenance phases of treatment.
- D. Remission induction therapy:

- 1) Depends on risk stratification
  - 2) For high risk: chemotherapy is added to differentiation agents (ie: tretinoin plus arsenic plus idarubicin (APML4) or tretinoin plus arsenic plus gemtuzumab ozogamicin or other chemotherapy based regimens)<sup>144-147</sup>
  - 3) For low-to-intermediate risk: induction with arsenic trioxide + tretinoin may be employed as per Lo-Coco et al<sup>148,162</sup>
  - 4) Differentiating agents are used until complete remission demonstrated
- E. Consolidation therapy:
- 1) Following similar principle as other AML subtypes, consolidation is employed to eradicate microscopic disease which may lead to early relapse
  - 2) For patients with high risk APL, 4-6 doses of intrathecal chemotherapy should be considered
  - 3) The first assessment by polymerase chain reaction (PCR) of measurable residual disease (MRD) should occur and only after at least one cycle of consolidation treatment has been employed.
- F. Maintenance therapy:<sup>59,149</sup>
- 1) Maintenance therapy is given as part of standard-of-care in all risk groups and differs based on protocol
  - 2) Can consist of 6-mercaptopurine, methotrexate and tretinoin or in the case of the Lo-Coco et al (APL 0406 trial) additional tretinoin and arsenic for low/intermediate risk patients
  - 3) Administered for 1-2 years following completion of consolidation
- G. Patients who are started on a given protocol should remain on said protocol throughout all phases of treatment e.g. remission induction, consolidation, maintenance.

#### **IV. Treatment of newly-diagnosed high-risk APL<sup>143,146,147,150,151</sup>**

- A. Standard-of-care is combination of tretinoin + arsenic coupled with a cytotoxic agent (ie: anthracycline [single agent or in 4+7 fashion] or gemtuzumab ozogamicin.

**V. Treatment of newly-diagnosed low and intermediate risk APL<sup>143,148,149</sup>**

- A. Historical standard-of-care is tretinoin + anthracycline-based therapy
- B. Arsenic trioxide + tretinoin therapy was demonstrated to be non-inferior to tretinoin + idarubicin (AIDA) and is preferred as a “chemotherapy free” regimen

**Treatment Regimens for Newly-diagnosed Adult APL**

Regimen	Dose Regimen	Comments
<b>CALGB 9710<sup>143</sup></b> <u>Induction</u> Tretinoin Daunorubicin Cytarabine  <u>Consolidation</u> Tretinoin Arsenic trioxide Daunorubicin  <u>Maintenance</u> Tretinoin 6-mercaptopurine Methotrexate	<u>Induction</u> Tretinoin 45 mg/m <sup>2</sup> /day PO daily until CR or 90 days Daunorubicin 50 mg/m <sup>2</sup> IV daily on days 3-6 Cytarabine 200 mg/m <sup>2</sup> continuous IV infusion on days 3-9 (“4+7”)  <u>Consolidation x 2 cycles</u> Arsenic trioxide 0.15 mg/kg IV daily 5 days per week x 5 weeks for total of 2 cycles - Followed by - Tretinoin 45 mg/m <sup>2</sup> /day PO daily days 1-7 + Daunorubicin 50 mg/m <sup>2</sup> IV daily on days 1-3 for 2 cycles  <u>Maintenance x 1 year</u> Tretinoin 45 mg/m <sup>2</sup> /day PO daily days 1-7 every 14 days 6-mercaptopurine 60 mg/m <sup>2</sup> /day PO daily Methotrexate 20 mg/m <sup>2</sup> PO weekly	Also enrolled pediatric patients; doses listed are for adults  May be used for low, intermediate or high-risk  Study randomized patients to receive arsenic trioxide or not; those receiving arsenic trioxide demonstrated superior 3-year PFS and 3-year OS
<b>Arsenic trioxide + Tretinoin<sup>148</sup></b> <u>Induction</u> Arsenic trioxide Tretinoin  <u>Consolidation</u> Arsenic trioxide Tretinoin	<u>Induction</u> Arsenic trioxide 0.15 mg/kg IV daily until CR (first bone marrow evaluation around day 28 if appropriate) or 60 days Tretinoin 45 mg/m <sup>2</sup> /day PO daily until CR (first bone marrow evaluation around day 28 if appropriate) or 60 days  <u>Consolidation</u> Arsenic trioxide 0.15 mg/kg IV daily 5 days per week administered 4-weeks on/4-weeks off for total of 4 cycles Tretinoin 45 mg/m <sup>2</sup> /day PO daily for 2-weeks on/2-weeks off for total of 7 cycles	All patients were low-to-intermediate risk  Shown to be non-inferior to AIDA regimen  Maintenance was not employed  Prednisone 0.5mg/kg daily used for differentiation syndrome prophylaxis during the entire treatment period  NCCN preferred regimen for low risk APL
<b>AIDA<sup>152</sup></b> <u>Induction</u> Tretinoin Idarubicin  <u>Consolidation</u> Tretinoin Anthracycline/ Anthracenedione	<u>Induction</u> Tretinoin 25-45 mg/m <sup>2</sup> /day PO daily until CR or 90 days Idarubicin 12 mg/m <sup>2</sup> IV on days 2, 4, 6, ± 8  <u>Consolidation x 3 monthly cycles</u> Tretinoin 45 mg/m <sup>2</sup> /day PO daily on days 1-15 per cycle Idarubicin 5-7 mg/m <sup>2</sup> IV daily days 1-4 (cycle 1)	Treatment differs slightly based upon risk stratification; may be used for low, intermediate and high-risk

<u>Maintenance</u> Tretinoin 6-mercaptopurine Methotrexate	Mitoxantrone 10 mg/m <sup>2</sup> IV daily days 1-5 (cycle 2) Idarubicin 12 mg/m <sup>2</sup> IV daily days 1±2 (cycle 3) For high-risk, add cytarabine 1,000 mg/m <sup>2</sup> daily on days 1-4 <sup>151</sup>  <u>Maintenance x 2 years</u> Tretinoin 45 mg/m <sup>2</sup> /day PO daily days 1-15 every 3 months 6-mercaptopurine 50 mg/m <sup>2</sup> /day PO daily days 1-15 every 3 months Methotrexate 15 mg/m <sup>2</sup> IM weekly	
<b>Tretinoin + daunorubicin + cytarabine<sup>153</sup></b> <u>Induction</u> Tretinoin Daunorubicin Cytarabine  <u>Consolidation</u> Daunorubicin Cytarabine	<u>Induction</u> Tretinoin 45 mg/m <sup>2</sup> /day PO daily until CR Daunorubicin 60 mg/m <sup>2</sup> /day IV daily x 3 days Cytarabine 200 mg/m <sup>2</sup> /day IV daily x 7 days  <u>Consolidation #1</u> Daunorubicin 60 mg/m <sup>2</sup> /day IV daily x 3 days Cytarabine 200 mg/m <sup>2</sup> /day IV daily x 7 days for 1 cycle  <u>Consolidation #2</u> Cytarabine 1,000-2,000 mg/m <sup>2</sup> /dose IV q 12 hrs x 8-10 doses over 4-5 days Daunorubicin 45 mg/m <sup>2</sup> /day IV x 3 days for 1 cycle	Not stratified by currently-accepted principles for risk-stratification  High-dose cytarabine dose attenuated for age >60 yrs  WBC > 10 x 10 <sup>9</sup> administered CNS prophylaxis with intrathecal methotrexate  Prophylaxis with dexamethasone for differentiation syndrome if WBC > 10 x 10 <sup>9</sup>
<b>APML4<sup>154</sup></b> <u>Induction</u> Tretinoin Arsenic trioxide Idarubicin  <u>Consolidation</u> Arsenic trioxide Tretinoin	<u>Induction</u> Tretinoin 45 mg/m <sup>2</sup> /day PO daily on days 1-36 Arsenic trioxide 0.15 mg/kg IV daily on days 9-26 Idarubicin 6-12 mg/m <sup>2</sup> IV daily on days 2, 4, 6, 8  <u>Consolidation #1</u> Arsenic trioxide 0.15 mg/kg IV daily x 4 weeks Tretinoin 45 mg/m <sup>2</sup> /day PO daily x 4 weeks  <u>Consolidation #2</u> Arsenic trioxide 0.15 mg/kg IV daily on days 1-5, 8-12, 15-19, 22-26, 29-33 Tretinoin 45 mg/m <sup>2</sup> /day PO on days 1-7, 15-21, 29-35  <u>Maintenance x 8 cycles</u> Tretinoin 45 mg/m <sup>2</sup> /day PO daily on days 1-14 per cycle Methotrexate 5-15 mg/m <sup>2</sup> /once weekly PO on days 15-90 6-mercaptopurine 50-90 mg/m <sup>2</sup> /day PO on days 15-90	May be used for low, intermediate or high-risk but only recommended for high-risk by NCCN  Dose of idarubicin based upon age: 1-60 yrs: 12 mg/m <sup>2</sup> /day 61-70 yrs: 9 mg/m <sup>2</sup> /day >70 yrs: 6 mg/m <sup>2</sup> /day  Prophylaxis with prednisone 1 mg/kg/day for ≥ 10 days, regardless of WBC at presentation  NCCN preferred regimen for high risk APL
<b>Gemtuzumab ozogamicin (AML17)<sup>146</sup></b>  <u>Induction:</u> Tretinoin Arsenic trioxide	<u>Induction:</u> Tretinoin 45mg/m <sup>2</sup> /day PO in divided doses days 1-60 (cycle 1) Arsenic trioxide 0.3mg/kg/day IV days 1-5 (C1) Arsenic trioxide 0.25mg/kg/day IV twice weekly (weeks 2-8)	In this trial population, 28 of 30 (93%) of high-risk APL patients received gemtuzumab ozogamicin  In the tretinoin and arsenic treatment arm, raised

<p>Gemtuzumab ozogamicin</p> <p><u>Consolidation:</u> Tretinoin Arsenic trioxide</p> <p>No Maintenance.</p>	<p>Gemtuzumab ozogamicin 6mg/m<sup>2</sup> IV one dose (once during days 1-4)</p> <p><u>Consolidation:</u> Tretinoin 45mg/m<sup>2</sup>/day PO in divided doses days 1-14, 29-42 (cycle 2-4) Arsenic trioxide 0.3mg/kg/day IV days 1-5 (C2-C5) Arsenic trioxide 0.25mg/kg/day IV twice weekly (weeks 2-4, cycles 2-5) Tretinoin 45mg/m<sup>2</sup>/day PO in divided doses days 1-14 (cycle 5)</p>	<p>transaminases occurred in 11/108 (10%).</p> <p>Patients in the tretinoin and arsenic trioxide group had significantly less requirement for most aspects of supportive care when compared with the AIDA group.</p> <p>There was no difference in QOL noted. NCCN preferred regimen for high risk APL</p>
<p><b>Gemtuzumab ozogamicin</b> <sup>147</sup></p> <p><u>Induction:</u> Tretinoin Arsenic trioxide Gemtuzumab ozogamicin</p> <p><u>Consolidation:</u> Tretinoin Arsenic trioxide</p> <p>No Maintenance.</p>	<p><u>Induction:</u> Tretinoin 45mg/m<sup>2</sup>/day PO in divided doses until CR Arsenic trioxide 0.15mg/kg/day IV until CR Gemtuzumab ozogamicin 9mg/m<sup>2</sup> IV one dose on day 1</p> <p><u>Consolidation (28 day cycles):</u> Tretinoin 45mg/m<sup>2</sup>/day PO in divided doses days 1-14 Arsenic trioxide 0.15mg/kg/day IV days 1-5 (C1, C3, C5, C7)</p>	<p>Methylpredisolone 50mg IV on days 1-5 followed by a rapid taper beginning day 6 was given as differentiation syndrome prophylaxis</p> <p>CR rate was 96% (52 or 54 high risk APL, 127 of 133 low risk APL)</p> <p>Induction mortality was 4% with only 7 relapses</p> <p>Of low risk patients, 45% required cytorreduction for leukocytosis using gemtuzumab ozogamicin or idarubicin</p> <p>The 5-year event free, disease-free, and overall survival rates are 85%, 96%, and 88%, respectively</p> <p>NCCN preferred regimen for high risk APL</p>

**Patient Case #1:**

LJ received ATRA + arsenic trioxide + gemtuzumab ozogamicin for his high-risk APL. On day 15 of LJ's treatment, his WBC is  $0.1 \times 10^9/\text{L}$  and bilirubin is 4.5 mg/dL. He exhibits fevers, a 10% weight gain, and painful hepatomegaly. An ultrasound is performed revealing ascites and reversal of portal flow. Chest-radiograph is unremarkable.

**Which of the following best describes LJ's symptoms?**

- A. Coagulopathy
- B. Urosepsis
- C. Sinusoidal obstruction syndrome
- D. Differentiation syndrome

**VI. Supportive care specific to treatment of APL**

- A. Coagulopathy is the major cause of early death in patients with newly-diagnosed APL.<sup>155</sup>
  - 1) Patients may present with hypofibrinogenemia and disseminated intravascular coagulation from underlying APL
  - 2) First 7 days of remission induction therapy may trigger and/or worsen coagulation defects
  - 3) Vigilant monitoring of coagulation parameters and replacement of fibrinogen, antithrombin  $\pm$  platelets often needed
- B. Differentiation syndrome<sup>156</sup>
  - 1) Occurs in ~30% of patients during remission induction
    - a. Median onset is 10-12 days following first dose of ATRA and/or arsenic trioxide but may have bimodal incidence occurring around the third week of treatment especially in those patients who did not have anthracycline-based therapy
  - 2) Symptoms: Note these symptoms overlap with infection – especially pneumonia – and may require empiric treatment of pneumonia simultaneously with glucocorticoid (especially given potential of glucocorticoid to worsen infection)
    - a. Dyspnea with interstitial pulmonary infiltrates
    - b. Peripheral and pulmonary edema
    - c. Unexplained fever
    - d. Hypotension
    - e. Acute renal failure
  - 3) Pathophysiology involves cytokine storm unleashed by large number of promyelocytes undergoing differentiation and maturation with migration to organ systems
  - 4) May occur with either tretinoin or arsenic trioxide or combination of both
  - 5) Risk factors for differentiation syndrome
    - a.  $\text{WBC} \geq 10 \times 10^9/\text{L}$

- b. Body mass index (BMI)  $\geq 30$
- 6) Prophylaxis of differentiation syndrome
  - a. Weight-based prednisone 0.5 mg/kg/day or fixed-dose of dexamethasone 10 mg q12h in patients with risk factors (e.g.: WBC  $\geq 10 \times 10^9/L$ )
- 7) Prophylaxis with glucocorticoid not employed consistently within all regimens and not universally done in clinical practice. However, is recommended by NCCN guidelines for high-risk patients (WBC  $\geq 10 \times 10^9/L$ )
- 8) Treatment of differentiation syndrome
  - a. Rapid detection and initiation of steroids is key
  - b. Dexamethasone 10 mg IV q12 hours x 3-5 days, followed by 14-day taper while continuing differentiating agent(s)
  - c. If cardiorespiratory symptoms are severe, temporarily hold tretinoin and/or arsenic trioxide
    - 1. Holding the differentiating agents is not needed if symptoms are mild-to-moderate
  - d. Restart differentiating agent(s) once symptoms improve while continuing corticosteroid
  - e. Can consider cytotoxic chemotherapy in patients with difficult to treat differentiation syndrome (ie: hydroxyurea, anthracycline, gemtuzumab ozogamicin)
- C. Management of non-differentiation syndrome tretinoin-related adverse effects:
  - 1) Topical emollients for cheilitis and dry skin
  - 2) Monitor liver function tests
  - 3) Tretinoin-associated hyperlipidemia generally mild, but may require monitoring in some patients
  - 4) Pseudotumor cerebri may require supportive care with acetazolamide
  - 5) Tretinoin-induced myositis may require supportive care with glucocorticoids
- D. Management of non-differentiation syndrome arsenic trioxide-related adverse effects:<sup>157</sup>
  - 1) Cardiac tachyarrhythmias<sup>158</sup>
    - a. Arsenic can cause QTc prolongation
      - 1. Use Framingham or Fridericia and NOT Bazett when calculating QTc as the latter often overcalls QTc prolongation leading to inappropriate holds, discontinuations, and dose reductions of arsenic
    - b. EKG should be obtained prior to initiating arsenic trioxide and weekly (more frequent if EKG anomalies present) and electrolytes should be monitored twice weekly, especially potassium and magnesium
    - c. Administer intravenous electrolytes to achieve serum potassium  $\geq 4$  mEq/L and serum magnesium  $\geq 1.8$  mEq/L prior to any dose of arsenic trioxide
  - 2) Electrolyte wasting, predominantly potassium and magnesium
- E. Antimicrobial prophylaxis



- 1) Need for antibacterial and antifungal is not same as for other subtypes of AML receiving remission induction chemotherapy<sup>159</sup>
  - a. Neutropenia is generally less severe and less prolonged; use of anthracycline increases risk vs non-anthracycline regimens
  - b. Use of steroid for differentiation syndrome may influence infection risk (consider antibacterial prophylaxis as high dose steroids can mask fever/infection).
- 2) Caution with any QT-prolonging agent (fluoroquinolone, triazole antifungal, 5HT3 antagonist, etc.) used in combination with arsenic trioxide

**Patient Case #1 Answer:**

**Correct answer = C Sinusoidal obstruction syndrome**

LJ is experiencing sinusoidal obstruction syndrome (SOS), formally known as veno-occlusive disease. A well-known side effect of gemtuzumab ozogamicin is SOS. The specific characteristics are discussed in the Hematopoietic Stem Cell Transplant chapter, but it is also important to understand for those using gemtuzumab ozogamicin or inotuzumab ozogamicin in leukemia.

A: No signs or symptoms are present demonstrating bleeding/thrombosis/coagulopathy.

B: There are overlapping signs/symptoms of sepsis and SOS, however, the reversal of portal flow in addition to the other signs/symptoms are consistent with SOS.

D: There are overlapping signs/symptoms of differentiation syndrome and SOS. Both should be on high suspicion in a patient receiving ATRA + arsenic + gemtuzumab ozogamicin. However, the lack of pulmonary infiltrates (generally caused by third spacing in differentiation syndrome), the elevated bilirubin, the painful hepatomegaly, ascites with reversal of portal flow are not common with differentiation syndrome. Additionally, although it is possible for differentiation syndrome symptoms to occur when a white count is nearly undetectable, it is less common.

**VII. Treatment of relapsed APL<sup>59,160</sup>**

- A. Approximately 5-30% of adult patients with APL relapse.
- B. If no antecedent exposure to arsenic trioxide or relapse > 6 month from prior arsenic/anthracycline regimen, may use arsenic trioxide 0.15 mg/kg/day with or without tretinoin 45 mg/m<sup>2</sup>/day PO until CR.
- C. Early relapse (< 6 months) after exposure to tretinoin + arsenic trioxide, may use induction as per APML4 trial.<sup>154</sup>
- D. Majority of studies utilized arsenic trioxide + tretinoin as salvage therapy following failure with tretinoin + anthracycline-based regimen.
- E. With arsenic trioxide + tretinoin used in up-front setting, the best therapy for relapse is unclear.
  - 1) Auto-HCT is considered in patients who achieve measurable residual disease (MRD) negative remission
  - 2) Allo-HCT is considered for patients who achieve CR but remain MRD+

## ADULT ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

### **Patient Case #1:**

DH is a 26 year-old male with complaints of bone pain, early satiety and frequent headaches. His WBC is  $80.4 \times 10^9/L$  with 40% blasts. He is diagnosed with Philadelphia chromosome-positive pre-B cell ALL.

**Which of the following is the optimal remission induction therapy for DH?**

- A. CALGB 10403
- B. CALGB 9511
- C. Mini-CVD + inotuzumab ozogamicin + ponatinib
- D. HyperCVAD + ponatinib

### **I. Classification of adult ALL**

- A. Typically grouped as precursor B-cell ALL, mature B-cell ALL, pro B-cell ALL, and T-cell ALL
  - 1) B-cell lineage accounts for 75-85% of cases and further defined as precursor B-cell ALL and mature B-cell ALL
  - 2) T-cell lineage accounts for 15-25% of cases
- B. Treatment strategies differ by age group
  - 1) Adolescents and young adults (AYA) 15-39 years (some groups include older ages)
  - 2) Adults 40-65 years
  - 3) Older adults >65 years

### **II. Prognostic factors of adult ALL**

- A. Various patient specific and disease specific factors in adult patients with ALL have prognostic significance.
  - 1) Age
  - 2) White blood cell count at diagnosis (note this may lose its independent prognostic influence in the setting of certain phenotypes or cytogenetics)
  - 3) Immunophenotype subtype
  - 4) Cytogenetics
  - 5) The presence of central nervous system (CNS) disease involvement
  - 6) Response to remission induction therapy
    - a. Presence of minimum residual disease (MRD) upon completion of remission induction therapy is a poor prognostic indicator
- B. Molecular genetics with clinical significance
  - 1) Philadelphia chromosome or BCR-ABL mutations: translocation of chromosome [i.e. t(9;22)] or resulting fusion protein present occurs in 25% of adult ALL cases:
    - a. Single-most important poor prognostic cytogenetic finding.
    - b. Referral for hematopoietic stem cell transplantation often recommended in CR1

- 2) Philadelphia-like genotype refers to a gene expression profile similar to Ph+ ALL without the BCR-ABL gene translocation rather it often coincides with mutations in RAS, CRLF2, and JAK/STAT5 pathways mutations i.e. ABL1, EPOR, JAK2, PDGFR-beta, EBF1, FLT2, IL7R, SH2B3.
  - a. This is known to confer poor prognostic influence.
  - b. Additionally, many patients have a concomitant IKZF1 deletion/mutation. IKZF1 mutations are difficult to test for, however can be detected via cytogenetic microarray (may not be routinely available) or next generation sequencing.
  - c. Detecting patients with Ph-like ALL is even more difficult. Multiplex PCRs are available to identify many of the above gene aberrancies.
- C. CD20-positive mature B-cell ALL is often difficult to distinguish from “Burkitt lymphoma.” If a diagnosis of Burkitt lymphoma is made then the disease requires treatment according to principles for Burkitt lymphoma (see Non-Hodgkin Lymphoma materials).

#### Prognostic features of adult ALL<sup>161-164</sup>

Feature	Good Risk	Poor Risk
<b>Cytogenetics/Molecular</b>	Hyperdiploidy (51-65 chromosomes; especially trisomy 4, 10, or 17); t(12;21)(p13;q22): ETV6-RUNX1	Hypodiploidy (<44 chromosomes); KMT2A rearranged (t[4;11] or others); t(v;14q32)/IgH; complex karyotype (5 or more chromosomal abnormalities); iAMP21; BCR-ABL1; Ph-like ALL; IKZF1 mutations; CDKN2A/B mutations
<b>WBC at Diagnosis</b> (may lose prognostic significance when MRD and cytogenetics are considered)	WBC < 30 x 10 <sup>9</sup> /L	B cell: WBC > 30 x 10 <sup>9</sup> /L T cell: WBC > 100 x 10 <sup>9</sup> /L
<b>Induction Response</b>	Complete remission	Primary Refractory (or late > 4 weeks)
<b>CNS/Extramedullary Disease at Diagnosis</b>	Negative	Positive
<b>Age</b>	<35 (<25 in some studies)	>35 years (precipitously declines with age)
<b>MRD</b>	MRD Negative (timing depends on study)	MRD Positive
<b>Immunophenotype</b>	Thymic T-cell	Early T-cell precursor, pro-B cell

#### III. Treatment principles in adult ALL<sup>164</sup>

- A. Goal of treatment is cure. Treatment of ALL is intense and complex. Treatment varies by age and cytogenetics.
  - 1) Age classification: 1) AYA, 2) Adult, and 3) Older adult
  - 2) Philadelphia chromosome: yes/no
    - a. Philadelphia chromosome negative: 1) High risk, 2) Standard risk
  - 3) Immunophenotype

- a. If CD20+, include rituximab
  - b. If CD19+, consider use of blinatumomab (MRD+ or R/R) or tisagenlecleucel (R/R)
  - c. If CD22+, consider use of inotuzumab ozogamicin
- B. Majority of the treatments for ALL are variations that are based off of the Berlin-Frankfurt-Munster group (BFM) or hyper-CVAD regimens.
- C. Dose-intensity is key to obtaining optimal outcomes:
  - 1) Pediatric regimens are reference point for highest dose-intensity (mainly asparaginase, vincristine, and steroids; less myelosuppressive cytotoxic therapy); adult protocols have evolved to become more “pediatric-like” leading to improved outcomes in adults.
- D. For all age groups within adult ALL, CR is achieved in 75-90% of cases, but relapse is common.
- E. Sanctuary sites:
  - 1) CNS: Common sanctuary site in adult ALL
    - a. High risk for CNS relapse in adult ALL with high LDH or WBC at diagnosis, precursor B-cell and T-cell immunophenotypes
    - b. Systemic chemotherapy agents used in adult ALL regimens may not cross blood-brain barrier sufficiently to maintain the required dose-intensity within CNS, leading to untreated CNS disease
  - 2) Testes and/or ocular involvement
- F. Adult ALL treatment protocols are complex and not standardized. Most adult regimens are pediatric regimens that have been “de-intensified” for patient tolerance.
- G. Paradoxically, while ALL is one of most curable cancers in children, long-term prognosis in adults is inadequate due to:
  - 1) Frequency and distribution of genetic mutations
  - 2) Diminished ability to withstand aggressive therapy as a patient ages
- H. Treatment stratified by presence or absence of Philadelphia chromosome mutations. Patients with t(9;22)-positive disease (e.g. Philadelphia chromosome) should receive targeted treatment with a tyrosine kinase inhibitor (targets BCR-ABL) within all phases of treatment.
  - 1) Majority of data in newly-diagnosed adult ALL are with imatinib and dasatinib, but data are emerging with use of nilotinib and ponatinib
    - a. Of available BCR-ABL inhibitors, dasatinib and ponatinib cross blood-brain barrier to greatest extent
    - b. Commonly employed with standard multi-agent chemotherapy regimens
    - c. The optimal duration of BCR-ABL inhibitor is unknown, but may include 3-5 years, even after allogeneic HCT
  - 2) Philadelphia chromosome negative disease is then stratified by high risk or low risk (per table above “Prognostic features of adult ALL”). This may influence long term treatment options i.e. HCT but does not impact remission induction therapy. Influence of cytogenetics/molecular findings outside of the Philadelphia chromosome is a developing area.

I. Treatment phases for adult ALL:<sup>161,164,165</sup>

1) Remission induction

- a. Goal of induction: Eradicate up to 99% of leukemic burden and restore normal hematopoiesis
- b. Treatment plans selected according to age group classification i.e. AYA, adult or older adult.
  1. The CALGB 10403 trial was a phase II study evaluating a pediatric inspired regimen for 17-39 year old patients with newly diagnosed Philadelphia chromosome negative ALL.<sup>166</sup>
    - a) Event free survival was 59% at 3 years (this is an improvement compared with adult based regimens in the AYA population)
  2. Philadelphia chromosome status: For BCR-ABL (Philadelphia)-positive adult: HyperCVAD plus imatinib, dasatinib, or ponatinib is best-studied
    - a) Imatinib 400 mg PO daily on days 1-14 produced CR >90%<sup>167</sup>
    - b) Dasatinib 100mg PO daily on days 1-14 for cycle one followed by 70mg daily and continuous for cycle 2 and beyond. Eighty three percent achieved a cytogenetic CR after one cycle with 93% achieving a major molecular response at a median of four weeks. At two years, OS was 64%<sup>168,169</sup>
    - c) Data also exist with dasatinib 70-140 mg PO daily on days 1-84 which produced CR in 93%, albeit with different combination chemotherapy regimen (e.g. prednisone)<sup>170</sup>
    - d) Ponatinib 45 mg PO daily on days 1-14 of cycle 1 (30 mg starting with cycle 2; reduction to 15 mg if complete molecular remission achieved) produced CR rate of 100% with 99% MRD negative by flow and 83% by PCR (complete molecular response). Event free survival of 70% at 3 years with only 15% of patients going to allogeneic HCT.<sup>171</sup>
    - e) D-ALBA Phase II Study examined induction with dasatinib 140 mg PO daily on days 1-84 with prednisone 60 mg/m<sup>2</sup> (pre-phase, induction, then tapered). Followed by dasatinib plus blinatumomab consolidation. The primary endpoint was sustained molecular response. Median age was 54 and at 18-month follow-up OS was 95% and DFS was 88%. Patients with IKZF1 or IKZF1plus had worse DFS and OS. The primary endpoint demonstrated an MRD- rate of 60% (52% in the intent to treat population). MRD- rate improved with additional cycles of blinatumomab. Thirty-eight percent of patients went on to receive an allo-HCT. Therapy was well tolerated.<sup>172</sup>
- c. Various drugs and combinations constitute the backbone of induction regimens for adult ALL:
  1. Anthracyclines
  2. Vincristine
  3. Corticosteroids

- a) Unclear if prednisone or dexamethasone is drug of choice in adults. Dexamethasone penetrates CNS better and has longer half-life, but associated with more toxicity than prednisone at equipotent dosing

4. Methotrexate, cyclophosphamide and cytarabine often added in various phases, depending upon regimen

5. Asparaginase-Based Products<sup>173-177</sup>

Asparaginase Product	<i>Erwinia</i> -derived (Erwinase)	<i>Erwinia</i> -derived (Rylaze)	Native <i>E. coli</i>	Pegylated <i>E. coli</i>	Calaspargase pegol <i>E. coli</i>
Available in the US	No longer	Yes	No longer	Yes	Yes
Half Life	< 1 day	< 1 day	1.28 days	5.3 days	16.1 days
Dosing Schedule	25,000 IU/M <sup>2</sup> IM or IV 3x per week (ie: M, W, F) (6 doses = 1 cycle)	25 mg/m <sup>2</sup> IM every 48 hours (6 doses = 1 cycle)	Multiple schedules	Adults should have doses capped at 3750 units no more frequently than every 2 weeks	2500 units/m <sup>2</sup> no more frequently than every 3 weeks
Can be used if grade 3+ (severe) hypersensitivity to an <i>E.coli</i> -derived asparaginase	Yes	Yes	No	No	No

- a) Pegylated asparaginase may be preferable due to reduced incidence of clinical hypersensitivity and subclinical hypersensitivity (silent inactivation) compared with native *e.coli*, superior depletion of systemic asparagine, longer half-life requiring less frequent injections, and cost compared with *erwinia*-derived.
- i. Calaspargase pegol can be considered in place of peg-asparaginase in patients ≤ 21 years for more sustained asparaginase activity
- (a) NCCN recommends to consider using calaspargase in regimens that require significant numbers of asparaginase doses (AALL 0434 and DFCl regimens) however it is not FDA approved for adults > 21 years of age
- b) Asparaginase/Pegylated asparaginase toxicities<sup>178-182</sup>:

Toxicity	Management
Hypersensitivity	<ol style="list-style-type: none"> <li>1. Premedications: steroids, diphenhydramine, acetaminophen, slower infusion</li> <li>2. Switch to Erwinia-derived asparaginase product for Grade 3+ allergy (severe hypersensitivity)</li> <li>3. Switch to Erwinia-derived asparaginase product for antibody inactivation - asparaginase activity level &lt;0.1 IU/mL on day 7 and/or undetectable on day 14 with peg-asparaginase<sup>183</sup></li> </ol>
Thrombosis/Bleeding	<ol style="list-style-type: none"> <li>1. Monitor fibrinogen 2x weekly</li> <li>2. Replace per institutional policy [(ie: FFP and Cryoprecipitate when fibrinogen &lt;50-70); others measure and replace antithrombin III however data are poor to support the use of antithrombin III as it is cumbersome to monitor and expensive to replace]</li> <li>3. Prophylactic anticoagulation is considered at some institutions</li> </ol>
Pancreatitis	<ol style="list-style-type: none"> <li>1. If abdominal pain or unexplained nausea/vomiting check amylase/lipase</li> <li>2. Hard stop if develops severe pancreatitis</li> </ol>
Hypertriglyceridemia	<ol style="list-style-type: none"> <li>1. Treatment depends on severity but may include: Fenofibrate, niacin, fish oils, statin, pheresis, insulin, diet modifications/fasting</li> <li>2. Hold asparaginase if &gt; 1000 mg/dL and close monitoring for pancreatitis</li> </ol>
Hyperglycemia	<ol style="list-style-type: none"> <li>1. Educate patients to monitor glucose, when initiating therapy and when therapy will "wear off"</li> </ol>
Hyperammonemia (asparaginase blues)	<ol style="list-style-type: none"> <li>1. Immediate: infusion reactions; delayed: fatigue, somnolence</li> <li>2. Monitor ammonia in patients exhibiting mental status changes</li> <li>3. Lactulose/metronidazole/rifaximin</li> </ol>
Hepatotoxicity	<ol style="list-style-type: none"> <li>1. Prevention: cautious dosing in AYAs/Adults, especially if obese</li> <li>2. Prevention/Treatment: L-carnitine?</li> <li>3. Hold until bilirubin &lt;2 mg/dL</li> </ol>

## 2) CNS prophylaxis<sup>164,184</sup>

- Intrathecal administration of chemotherapy is commonly employed. Intent is to maximize CNS drug concentration in CSF while minimizing systemic toxicity. Volume of distribution in CSF is smaller than plasma and terminal half-life is longer. Corticosteroids should be used as supportive care to assist with cancer cell kill and prevent chemical arachnoiditis
  1. Evaluation of CNS involvement by lumbar puncture should be performed concomitantly with initial intrathecal chemotherapy as dictated by treatment protocol
  2. Must be a drug compatible with administration into the CSF (e.g. methotrexate, cytarabine). Extreme care should be exercised to ensure safety with respect to agent used for injection intrathecally as some drugs are fatal if used in this manner e.g. vinca alkaloids
- Some regimens may also employ high-dose systemic chemotherapy that crosses the blood-brain barrier (e.g.: high-dose methotrexate and high-dose cytarabine) or CNS-directed radiation therapy
  1. A risk with high dose methotrexate is delayed clearance and prolonged exposure to toxic levels leading to life threatening toxicities. Supportive care with rescue agent leucovorin

is recommended. Consensus guidelines are available to provide an algorithm with regard to use of glucarpidase<sup>185</sup>. Please see the Adult Sarcomas handout for more information.

- 3) Post-remission therapy (AKA “Consolidation” and/or “Intensification”)
  - a. Goal of post-remission therapy: eliminate residual disease and eradicate drug-resistant leukemic cells which may lead to relapse
    1. The optimal consolidation/intensification for adult ALL is unknown
  - b. Majority of protocols utilize combination of asparaginase, high-dose cytarabine and high-dose methotrexate (targeting leukemic cells in both systemic and CNS compartments) for 6-8 courses
  - c. Blinatumomab can be considered for consolidation in patients with MRD negative disease/unavailable if induced with inotuzumab ozogamicin + mini-hyperCVD, or in patients for whom multiagent chemotherapy is contraindicated, and for consolidation in patients with persistent/rising MRD.
- 4) Maintenance
  - a. Backbone of oral 6-mercaptopurine plus weekly methotrexate (PO or parenteral administration), with periodic reinforcements with vincristine or prednisone; generally continues for 1-2 years
  - b. Some regimens recommend longer maintenance for males due to testes sanctuary site
  - c. Therapy adapted to immunophenotype of adult ALL
    1. Omission of maintenance in mature B-cell ALL is standard
    2. Omission of maintenance significantly worsens outcomes in other types of B-cell ALL and possibly worsens outcomes in T-cell ALL
- 5) Role of measurable residual disease (MRD) evaluation<sup>164</sup>
  - a. Refers to presence of leukemic cells by molecular testing that is below the threshold of detection using conventional morphologic methods
  - b. Most commonly used is flow cytometry, real-time quantitative PCR (to detect fusion genes), and next-generation sequencing (NGS)-based assays (to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes)
  - c. Prognostically important if MRD is detected post-induction therapy as a predictor of relapsed disease
    1. Additional time points should be guided by the specific regimen used
- 6) Allogeneic HCT is an appropriate treatment for adult ALL in CR1 for “poor risk groups” (although the above tables suggests WBC, immunophenotype, age, etc are considered poor risk, for purposes of deciding transplant, most experts do not use these to commit patients to transplant, rather poor risk cytogenetics/molecular or persistent MRD+ govern the decision to transplant).
  - a. Still the standard of care for patients with Philadelphia positive disease though with use of TKI the role of transplant in Philadelphia positive ALL is less clear



## 7) Summary of Preferred Treatment Options<sup>164</sup>

### Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia

Pediatric	AYA	Adult (<65)	Adults (>65)	
See pediatric BCOP handout	CALGB 10403 (<40)	CALGB 8811/9511 (Larson)	Low Intensity: Vincristine +steroids	Low Intensity: POMP
	COG AALL0232 (<21)	GRAALL-2005 <60	Moderate Intensity: GMALL	Moderate Intensity: PETHEMA ALLOD07
	COG AALL0434 (T-cell)	Hyper-CVAD, USC, Linker (<60)	Moderate Intensity: GRAALL	Moderate Intensity: Modified DFCI 91-01
	DFCI ALL Based <50)	MRC UKALLXII/ ECOG2993	Moderate Intensity: Mini-hyper-CVD + Inotuzumab ozogamicin	
	GRAALL-2005 <60		High Intensity: Hyper-CVAD (dose reduced cytarabine)	High Intensity: CALGB 9111
	PETHEMA ALL-96 <30			
	Single center: Hyper-CVAD, USC, Linker			

Blinatumomab can be considered for consolidation in patients with MRD negative disease/unavailable if induced with inotuzumab ozogamicin + mini-hyper-CVD, or in patients for whom multiagent chemotherapy is contraindicated, and for consolidation in patients with persistent/rising MRD.

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### Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Pediatric	AYA	Adult (<65)	Adult (>65)
See pediatric BCOP handout	EsPhALL (BFM + TKI)	Hyper-CVAD + TKI	Low Intensity: TKI ± steroids
	Hyper-CVAD + TKI	TKI + multiagent chemotherapy	Low Intensity: TKI + vincristine + dexamethasone
	TKI + multiagent chemotherapy	Low Intensity: TKI + steroids ± vincristine	Moderate Intensity: EWALL (TKI + multiagent chemotherapy)
	Low Intensity: TKI + steroids ± vincristine	Moderate Intensity: CALGB 10701 (TKI + multiagent chemotherapy)	Moderate Intensity: CALGB 10701 (TKI + multiagent chemotherapy)
	Moderate Intensity: CALGB 10701 (TKI + multiagent chemotherapy)	Blinatumomab ± TKI	High Intensity: TKI + hyper-CVAD (dose reduced cytarabine)
	Blinatumomab ± TKI		Blinatumomab ± TKI

BFM: Berlin-Frankfurt-Munster (asparaginase based regimen);  
TKI: tyrosine kinase inhibitor  
TKI options include: bosutinib, dasatinib, imatinib, nilotinib, or ponatinib.

Blinatumomab can be considered for consolidation in patients with MRD negative disease/unavailable in patients for whom multiagent chemotherapy is contraindicated, and for consolidation in patients with persistent/rising MRD.

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#### Patient Case #1 Answer:

**Correct Answer = D HyperCVAD + ponatinib** – this is an NCCN recommended regimen based on a single center phase II experience showing exceptionally long event and overall survival.

#### Patient Case #1 (continued)

DH's bone marrow biopsy after hematopoietic recovery from remission induction therapy revealed positive measurable residual disease.

**Which of the following is most appropriate to treat DH with at this time?**

- A. Inotuzumab ozogamicin
- B. Nelarabine
- C. Continue C10403
- D. Blinatumomab

#### **IV. Treatment of patients with MRD+ disease**

- A. In general, MRD positivity at the end of induction predicts high relapse rates (many exceptions to this) and should prompt an evaluation for allogeneic HCT
- B. When possible, therapy aimed at eliminating MRD prior to allogeneic HCT is preferred.
- C. The BLAST trial was a phase II study evaluating blinatumomab for patients aged  $\geq 18$  years in CR1 or CR2+ with persistent MRD ( $\geq 10^{-3}$ ) after  $\geq 3$  intensive chemo blocks.<sup>186</sup>
  - 1) 83% of patients in CR1 and 73% in CR2+ achieved MRD negativity. 67% of patients went on to allogeneic HCT. RFS was 24.6 and 11 months respectively. OS was 36.5 and 19.1 months for patients in CR1 and CR2+, respectively.
- D. Blinatumomab MRD+ clinical pearls<sup>187</sup>
  - 1) When should blinatumomab be added to Adult MRD+ ALL?
    - a. The challenge is various studies employ:
      - 1. Different strategies to detect MRD (Flow vs PCR vs NGS; level of MRD)
      - 2. Different regimens (timing of MRD predicting outcomes will differ)
    - b. BLAST trial: if MRD+ after 3 blocks of intensive therapy
      - 1. This is at  $\sim 3$  months (commonly employed after course II or course III of BFM based regimens [ie: C10403 or ECOG1910])
    - c. Data does not support initiating if MRD+ after induction
      - 1. Many patients can still attain MRD- with more chemo (would overtreat with blinatumomab)<sup>163,187-191</sup>
    - d. MRD+ at  $\sim 3$  months = blinatumomab followed allogeneic HCT (although this approach still lacks randomized control data demonstrating benefit)
      - 1. Allogeneic HCT recommended still regardless if MRD- or MRD+ following blinatumomab
      - 2. Future studies to clarify continuation of blinatumomab vs allogeneic HCT

#### **V. Treatment of relapsed or refractory adult ALL<sup>164</sup>**

- A. CNS relapse occurs in 30% of adult ALL patients surviving for  $> 2$  years from diagnosis.
- B. Due to small number of drugs active in adult ALL (which were already used to treat newly-diagnosed adult ALL), treatment of relapsed adult ALL is associated with dismal outcomes.

- C. For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen
- D. If relapsed BCR-ABL (e.g. Philadelphia) positive adult ALL, test for BCR-ABL kinase mutations and change TKI if appropriate
  - 1) Can consider changing chemotherapy backbone and/or use novel agent (blinatumomab, inotuzumab ozogamicin) with TKI
- E. Agents/regimens which have been studied include:

## Chemotherapy Regimens for relapsed/refractory ALL

Regimen	Agents/Notes
FLAG-IDA	Fludarabine, cytarabine, granulocyte colony-stimulating factor +/- idarubicin <sup>192</sup>
FLAM	Fludarabine, cytarabine, mitoxantrone <sup>193</sup>
MOAD	Methotrexate, vincristine, pegaspargase, dexamethasone <sup>194</sup>
Augmented Hyper-CVAD	Hyper-CVAD backbone with intensification of dexamethasone and vincristine and the addition of asparaginase <sup>195</sup>
Alkylator combination regimens	Ifosfamide, mitoxantrone, etoposide <sup>196</sup>
Clofarabine based	Alone and in combination (CLOVE: clofarabine, cyclophosphamide, etoposide), for B-cell ALL. <sup>197-199</sup> FDA-approved for treatment of pediatric ALL after failing at least 2 prior regimens
Nelarabine based	Alone and in combination (NECTAR: nelarabine, etoposide, cyclophosphamide), for T-cell ALL. <sup>200-202</sup> FDA-approved for treatment of T-cell ALL in patients failing at least 2 prior regimens. Caution with concomitant use of CNS-directed therapy due to neurotoxicity
Inotuzumab ozogamicin + mini-hyperCVD <sup>203-205</sup>	Inotuzumab with dose reduced hyper-CVD (anthracycline omitted) for R/R B-Cell ALL has been reported from a single center institutional report in patients with R/R ALL and first-line therapy in older adults.

### 1) Inotuzumab ozogamicin (Besponsa®)

- a. Inotuzumab ozogamicin was studied in a phase 3 trial evaluating adults with relapsed or refractory ALL in comparison with standard intensive chemotherapy (i.e., HiDAC, FLAG, cytarabine + mitoxantrone).
  1. Inotuzumab ozogamicin was administered as an intermittent infusion at 0.8 mg/m<sup>2</sup> on day 1 and 0.5mg/m<sup>2</sup> on days 8 and 15 during a 21-day cycle.
    - a) Dosing changed once the patient achieved CR.
  2. The rate of complete remission was significantly higher in the inotuzumab ozogamicin group (73.8% versus 30.9%, p < 0.001).
  3. In addition, among those who achieved CR, patients who were treated with inotuzumab ozogamicin had a higher percentage of those who were MRD- (78.4% versus 28.1%, p<0.001).
  4. PFS was significantly longer in the inotuzumab ozogamicin treatment arm (5mos versus 1.8mos, HR 0.45, p<0.001).
  5. OS: 7.7 versus 6.7 months; 0.77 (97.5% CI, 0.58 to 1.03); p=0.04
  6. OS follow-up: 7.7 vs 6.2 months; 0.75 (97.5% CI, 0.57-0.99); p= 0.0105<sup>206</sup>

7. The most frequent severe adverse effects were liver injuries. Veno-occlusive liver disease of any grade occurred in 14% who received inotuzumab ozogamicin and in 1 patient (1%) who received standard chemotherapy.<sup>206,207</sup>
  - a) The number of inotuzumab cycles should be limited to as little as feasible if proceeding to allo-HCT to reduce the risk of VOD/SOS
- 2) Blinatumomab.<sup>208-210</sup> Indicated for relapsed/refractory precursor B-cell. FDA-approved for relapsed or refractory and MRD+ B-cell ALL in adults.
  - a. Phase III TOWER trial was a randomized controlled study comparing blinatumomab with chemotherapy in adult patients with R/R ALL. Demonstrated significantly improved:
    1. CR/CRi rate when compared to standard chemotherapy (44% vs. 25%,  $P < 0.001$ )
    2. OS: 7.7 versus 4 months; HR 0.71 (95% CI 0.55 to 0.93);  $P = 0.01$
  - b. Blinatumomab can be used in Philadelphia-positive disease based on the results of the ALCANTARA trial.<sup>211-215</sup>
  - c. Administered as continuous infusion for 4 weeks without planned interruption, with 2-week break (e.g.; 4 weeks out of 6 weeks) for up to 9 total cycles (induction = 1-2 cycles, consolidation = up to 3 cycles, maintenance/continuation: up to 4 cycles). This will require home infusion to be arranged for the patient
    1. New product formulation includes preservative (benzyl alcohol) allowing for home infusion with a 7-day supply
    2. Due to the preservative seven-day bag option is contraindicated for use in those who weigh  $< 22\text{kg}$ <sup>213</sup>
- 3) Chimeric antigen receptor T cells (CAR-T). Tisagenlecleucel (CTL019; Kymriah®) was the first CAR-T therapy that gained FDA approval. It is a CD19-directed genetically modified autologous T cell immunotherapy indicated for those up to 25 years of age with B-ALL that is refractory or in second or later relapse.
  - a. Tisagenlecleucel is only available at specifically identified treatment centers who are enrolled in a REMS program designed to mitigate toxicities associated with tisagenlecleucel such as cytokine release syndrome and neurological toxicities.
  - b. Leukapheresis is used to collect blood cells from the patient who is to receive tisagenlecleucel. T-cells are separated and transduced with a chimeric antigen receptor (CAR).
    1. The CAR contains four important elements 1) a single chain variable fragment (scFV), which functions as the targeting domain directed against the target of choice, 2) a hinge and transmembrane domain, 3) an intracellular signaling domain to ensure T-cell activation, and 4) one or two costimulatory domains.
    2. CAR-T cells are then cultured.
    3. The patient is treated with chemotherapy for lymphodepletion and the CAR-T cells are reinfused into the patient.
  - c. A phase II, single cohort, multi-center study (ELIANA trial) was conducted evaluating tisagenlecleucel in pediatric and young adult patients with CD19+ r/r B-ALL (n=75). The

overall remission rate at 3 months was 81% with all patients who had a response also found to be negative for MRD by flow cytometry.

- d. At 6 months EFS and OS were 73% (95CI, 35-64) and 90% (95CI, 81-95) and at 12 months 50% (95CI, 35-64) and 76% (95CI, 63-86), respectively.
  - e. CRS occurred in 77% of patients and 48% of these patients received tocilizumab. Neurologic events occurred in 40% of patients and were managed with supportive care. No cerebral edema was reported.<sup>216</sup>
- 4) Brexucabtagene autoleucel is FDA approved for adult patients with relapsed or refractory B-cell precursor ALL
- a. A phase II, single cohort, multi-center study (Zuma-3 trial) was conducted evaluating brexucabtagene autoleucel in adult patients with CD19+ r/r B-ALL (n=55). The CR/CRi rate was 71% with 97% of patients who had a response also found to be MRD negative.
  - b. The median relapse free survival was 11.6 months and the median OS was 18.2 months
  - c. CRS occurred in 89% of patients. Tocilizumab was given to 80%, steroids were given to 75%, and vasopressors were given to 40% of patients. Neurological events occurred in 60% of patients of which 26% were grade 3 or higher.<sup>217</sup>

**Patient Case #1 (continued) Answer:**

**Correct answer = C Continue C10403**

DH has T-cell ALL, not B-cell ALL, therefore blinatumomab and inotuzuman are incorrect. Additionally, based on the BLAST trial, North American MRD guidelines, and other MRD primary literature, blinatumomab should be initiated in patients who are MRD+ following 3 cycles of intensive therapy, NOT after induction. Given that this patient has only received 1 cycle of chemotherapy, he can continue on with the current regimen. Inotuzumab ozogamicin would only be appropriate in fulminant relapsed or refractory B-ALL. Adding nelarabine is not appropriate since DH has only completed induction therapy.

**Patient Case #2:**

JG is a 33 year old female with Philadelphia chromosome negative pre B-cell ALL who has received C10403 (refractory), Part B of hyper-CVAD (refractory), and is now admitted for blinatumomab.

On day 2 of blinatumomab infusion, JG becomes lethargic but awakens when asked questions. She can name 3 objects, follow commands, write her name, and can count backwards but does not know the year or month. Her ICE score is 6 and is experiencing grade 2 immune effector cell–associated neurotoxicity syndrome (ICANS).

**Which of the following strategies should be employed to treat JG’s CRS?**

- A. Supportive care
- B. Permanently stop blinatumomab
- C. Tocilizumab
- D. Dexamethasone

B. Immunotherapy-related toxicities associated with blinatumomab and CAR-T treatment modalities.<sup>218,219</sup>

- 1) Goal is to maximize the benefit of the cellular therapy while minimizing the risk of life-threatening complications
  1. Use of corticosteroids should be avoided for routine use due to risk of interfering with cellular therapy and only used in emergent clinical scenarios when clinically indicated
- 2) Cytokine release syndrome (CRS)<sup>220</sup>
  1. Associated with disease burden but can occur irrespective i.e. higher burden is higher risk for CRS and results from widespread immune activation that results in higher than normal concentrations of systemic cytokines. Potentially fatal, but reversible.
  2. Rarely, CRS can progress to fulminant hemophagocytic lymphohistiocytosis (HLH)
  3. Tocilizumab is an anti-IL-6 antibody that targets a biomarker i.e. IL-6 often upregulated in states of CRS and has been shown to be effective in preventing complications and symptoms of CRS. Maximum dose of tocilizumab is 800mg.
- 3) Neurotoxicity/ CAR-T Related Encephalopathy Syndrome (CRES); now called Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)<sup>221</sup>
  1. Pathophysiology not clearly defined. Pleomorphic presentation; multiple overlapping neurotoxicity symptoms have been reported and appearance of specific neurotoxicity symptom is not predictive of re-appearance of same symptom in subsequent days or cycles
  2. Seizure prophylaxis is indicated for those receiving CAR-T therapies associated with CRES
    - a) Levetiracetam 500-750mg PO/IV Q12h on day of CAR-T infusion and continuing for 30 days
- 4) Grading schemes for CRS and ICANS/CRES have evolved over time and vary with each trial and product<sup>218,219,221-225</sup>
  - a. CTCAE v4.03, CTCAE v5, Lee criteria, Penn criteria, MSKCC criteria, CARTOX criteria

- b. American Society for Transplantation and Cellular Therapy (ASTCT; formerly ABMT) Consensus Grading for CRS and Neurotoxicity
  1. Would utilize this in practice (no need to memorize, just as a reference/FYI)
  2. For CRS: table 2 in Lee et al BBMT 2019 manuscript
  3. For ICANS: table 5 (ICE tool), table 6 (ICANS) in Lee et al BBMT 2019 manuscript

#### CRS and ICANS Management<sup>219,221,226</sup>

CRS Grade	Treatment	Additional Supportive Care
1*	Tocilizumab x1 ONLY IF > 3 days of CRS AND comorbidities/significant symptoms	<ul style="list-style-type: none"> <li>• Empiric antibiotics</li> <li>• Maintenance Fluids</li> </ul>
2	Tocilizumab (max 3 doses in 24 hours; max 4 doses total) Steroids: persistent refractory hypotension	<ul style="list-style-type: none"> <li>• IV fluid bolus as needed</li> <li>• For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors</li> </ul>
3	Tocilizumab (per grade 2) plus dexamethasone	<ul style="list-style-type: none"> <li>• Transfer to ICU</li> </ul>
4	Tocilizumab (per grade 2) plus dexamethasone (if refractory methylprednisolone 1000 mg/day with taper)	<ul style="list-style-type: none"> <li>• ICU care</li> <li>• Mechanical ventilation as needed</li> </ul>

\*For idecabtagene vicleucel and lisocabtagene maraleucel, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS (within 72 hours after infusion)

\*\*other agents for grade 4 CRS refractory to standard therapy include: anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, or extracorporeal cytokine adsorption with continuous renal replacement therapy (experience with these agents are limited).

ICANS Grade	ICANS (without CRS)	Additional Therapy if Concurrent CRS
1*	Supportive care	Tocilizumab
2	1 dose of dexamethasone and reassess in 6 hours	<ul style="list-style-type: none"> <li>• Tocilizumab as per grade 1</li> <li>• Consider ICU if grade <math>\geq 2</math> CRS</li> </ul>
3	<ul style="list-style-type: none"> <li>• ICU care is recommended.</li> <li>• Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours**</li> </ul>	Same as above
4	<ul style="list-style-type: none"> <li>• ICU care, consider mechanical ventilation for airway protection</li> <li>• High-dose steroids</li> </ul>	Same as above

\* For idecabtagene vicleucel and lisocabtagene maraleucel, if ICANS develops within 72 hours after infusion, consider dexamethasone 10 mg IV every 12-24 hours for two doses and reassess; \*\*Axicabtagene ciloleucel and brexucabtagene autoleucel: consider treatment with methylprednisolone 1 gram daily for 3-5 days; \*\*\*Axicabtagene: consider use of prophylactic corticosteroids in patients after weighing risks versus benefits (dexamethasone 10 mg orally once daily for 3 days with the first dose starting pre-CAR T-cell infusion); if dexamethasone is used as prophylaxis there may be an increased risk of grade 4 and prolonged neurotoxicity



### Patient Case #2 Answer:

**Correct answer= D Dexamethasone**

Per the NCCN guidelines and the American Society for Transplantation and Cellular Therapy, grade 2 ICANS should be treated with steroids.

A: Supportive care only would be inappropriate as NCCN recommends steroids in addition to supportive care for grade 2 ICANS.

B: Per the Blincyto® prescribing information, grade 3+ ICANS/neurotoxicity requires interrupting the blinatumomab infusion (not grade 2).

C: Per the NCCN guidelines and the American Society for Transplantation and Cellular Therapy, tocilizumab would be appropriate if JG had several days of grade 1 CRS or if the CRS escalated to 2+ or if concomitant CRS + ICANS otherwise steroids should be employed for ICANS grade  $\geq 2$ .

D: Steroids are the standard of care per the NCCN guidelines for the treatment of grade  $\geq 2$  ICANS.

## II. Supportive care of the adult ALL patient

### A. Tumor lysis syndrome

- 1) ALL is considered high-to-moderate risk for tumor lysis syndrome, depending upon tumor burden.<sup>227</sup>

### B. Antimicrobial prophylaxis<sup>123,228</sup>:

- a. See “Cancer-related Infections” chapter for full overview.

### C. White blood cell colony-stimulating factors<sup>126,128</sup>

- 1) Due to high-risk for febrile neutropenia with induction therapy, white blood cell colony-stimulating factor is indicated
- 2) No concern for stimulating underlying malignancy

## TUMOR LYSIS SYNDROME (TLS)

### Patient Case #1:

DH is diagnosed with Philadelphia chromosome-positive pre-B cell ALL and began HyperCVAD, arm "A" with dasatinib. On day 2 of chemotherapy, his labs are notable for WBC  $42 \times 10^9/L$ , BUN 36 mg/dL, serum creatinine 2.2 mg/dL, potassium 5.7 mEq/L, phosphate 4.9 mg/dL, LDH 2810 IU/L and uric acid 8.6 mg/dL.

**Along with allopurinol, which of the following is most appropriate to manage tumor lysis syndrome in DH?**

- A. Aggressive hydration with normal saline
- B. Rasburicase
- C. Sodium polystyrene sulfonate
- D. Consult for emergent renal dialysis

### I. Tumor Lysis Syndrome (TLS)<sup>229</sup>

- A. Tumor lysis syndrome is a life-threatening oncologic emergency.
  - 1. When tumor cells die/lyse, they release intracellular contents such as potassium, phosphorus (from the phospholipid layer of the cell), and nucleic acids.
  - 2. Nucleic acids are further metabolized into hypoxanthine, xanthine, and finally uric acid, which is poorly soluble. Under normal circumstances the body is able to maintain homeostasis when cancer cells lyse; however, when the volume of cell lysis is high it can overwhelm the body's homeostatic mechanisms leading to accumulation of phosphorus, potassium, uric acid and low calcium levels.
  - 3. The large cytokine release that accompanies this process along with metabolic derangements can lead to life-threatening physiological consequences such as seizure, renal failure, arrhythmias, tetany and death.
  - 4. May occur spontaneously prior to anti-cancer therapy as a tumor effect
  - 5. May occur as a result of anti-cancer therapy
  - 6. Typically observed 12-72 hours after starting chemotherapy and may continue up to 3 days after start of chemotherapy
  - 7. Life-threatening hyperkalemia and permanent renal failure are the most feared complications of tumor lysis syndrome
- B. Historically, classification of tumor lysis syndrome evaluates the clinical scenario as it relates to two definitions. However, this classification is not commonly employed and risk stratification based upon these criteria is the most important aspect of managing TLS.
  - 1. Laboratory tumor lysis syndrome (LTLS): two or more metabolic derangements as listed in below table occurring three days before or seven days after treatment initiation for the malignancy.
  - 2. Clinical tumor lysis syndrome (CTLS):<sup>230</sup> occurs when LTLS is accompanied by dysrhythmias, seizures, increased serum creatinine, or death.

Laboratory and Clinical Signs and Symptoms of Tumor Lysis Syndrome <sup>230</sup>		
Abnormality	Laboratory	Clinical
Hyperuricemia	<ul style="list-style-type: none"> <li>Uric acid &gt;8 mg/dL (adults)</li> <li>Uric acid above upper limit of normal (children)</li> </ul>	Renal failure
Hyperphosphatemia	<ul style="list-style-type: none"> <li>Phosphorus &gt;4.5 mg/dL (adults)</li> <li>Phosphorus &gt;6.5 mg/dL (children)</li> </ul>	Precipitation
Hyperkalemia	Potassium >6 mmol/L	Cardiac dysrhythmia or sudden death
Hypocalcemia	Corrected calcium <7 mg/dL or ionized calcium <1.12 mg/dL	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability, hypotension, tetany, or heart failure
Acute kidney injury	Increase in serum creatinine level >1.5 x upper limit of normal	Presence of oliguria (urine output <0.5 ml/kg/hour for 6 hours)

## II. Risk factors for TLS

- A. All patients receiving anti-cancer therapy should be assessed for TLS risk i.e. low, intermediate or high risk for TLS.<sup>227</sup>
- B. Risk Factors can be patient-related, tumor-related or treatment-related:
  1. Bulky, chemotherapy-sensitive malignancy
    - a. Lymphoproliferative malignancy
    - b. Elevated lactate dehydrogenase (LDH)
    - c. WBC > 25 x 10<sup>9</sup>/L
    - d. Extensive bone marrow involvement
    - e. Extensive extramedullary involvement on imaging
  2. Volume depletion or dehydration at baseline (or on medications known to cause dehydration)
  3. Elevated baseline serum uric acid
  4. Pre-existing renal dysfunction
- C. Despite presence of low-risk, TLS may still occur in rare cases.<sup>231</sup>

### Adult malignancies stratified by TLS risk<sup>227,229,232</sup>

Disease	Low-Risk	Intermediate-Risk	High-Risk
---	Multiple myeloma All solid tumors (except otherwise noted)	Germ cell cancer Small-cell lung cancer	---
Non-Hodgkin Lymphomas (NHL)	Indolent NHL DLBCL with (a) non-bulky disease and (b) LDH < 2 x ULN	Burkitt lymphoma with normal LDH DLBCL with (a) non-bulky disease and (b) LDH > 2 x ULN	Burkitt lymphoma with (a) bulky disease and (b) elevated LDH DLBCL with (a) bulky disease and (b) LDH > 2 x ULN
Hodgkin Lymphoma (HL)	HL with (a) non-bulky disease or (b) normal LDH [most patients]	HL with (a) bulky disease and (b) LDH > 2 x ULN	---
Acute Lymphoblastic Leukemia (ALL)	---	WBC < 100 x 10 <sup>9</sup> /L and LDH normal	WBC > 100 x 10 <sup>9</sup> /L or LDH > 2 x ULN
Chronic Lymphocytic Leukemia (CLL)	All other patients	WBC > 50 x 10 <sup>9</sup> /L Treatment with non-alkylating agent therapies	---
Acute Myeloid Leukemia (AML)	WBC < 25 x 10 <sup>9</sup> /L and LDH < 2 x ULN	WBC 25 - 100 x 10 <sup>9</sup> /L	WBC > 100 x 10 <sup>9</sup> /L
Chronic Myeloid Leukemia (CML)	Chronic and accelerated phases	Blast crisis	---

DLBCL = diffuse large B-cell lymphoma, ULN = upper limit of normal, LDH = lactate dehydrogenase

### III. Principles for prevention of TLS<sup>227,230</sup>

- A. Identify and stratify patients according to TLS risk.
- B. Ideally, TLS prevention would begin 24-48 hours before starting anti-cancer therapy.
- C. Eliminate pharmacotherapy which may contribute to electrolyte anomalies:
  1. Hold thiazide diuretics and/or potassium-sparing diuretics
  2. Discontinue calcium-, potassium- and phosphate-containing supplements
  3. Hold angiotensin-converting enzyme inhibitors
  4. Hold any concurrent nephrotoxic medications
  5. Discontinue enteral or parenteral nutrition
- D. Intravenous fluids are foundational to preventing TLS.
  1. Normal saline-containing intravenous fluids (IVF) serve as the backbone of both prevention and treatment
  2. IVF must be given at aggressive rate; at least 2.5-3 liters/m<sup>2</sup>/24 hours in order to maintain urine output of at least 100 mL/hr
    - a. Typical patient receives a fluid rate of 150-300 ml/hour of normal saline
    - b. Caution should be exercised in patients with pre-existing CHF or underlying renal compromise for fear of fluid overload

3. Addition of bicarbonate to IVF should be avoided
- E. Allopurinol for prophylaxis of TLS
1. Studied as a means of preventing hyperuricemia related to neoplasms as long ago as the 1960s with efficacy demonstrated<sup>233-236</sup>
  2. Staple for prevention in addition to fluids<sup>227,237,238</sup>
  3. Allopurinol 300-800 mg per day is recommended for adults, with higher daily doses given to those with high-risk disease and/or starting uric acid levels
    - a. Children < 15 years: 10-20 mg/kg daily in divided doses, maximum of 400 mg/day
    - b. Usually administered as q24h, q12h or q8h dosing
    - c. Empiric initial dose adjustments of allopurinol based upon renal function for indication of treatment of TLS is debatable (would not recommend reducing dose upfront). Doses may be titrated according to uric acid level if lower doses are tolerated.<sup>239-241</sup>
      - 1) Drug information texts recommend dose decrements for impaired renal function; these tables were developed to guide dosing of allopurinol for gout (where patients often receive allopurinol lifelong)
      - 2) Allopurinol used for prevention of TLS is rarely > 7 days
      - 3) Allopurinol is a relatively weak inhibitor of xanthine oxidase and is relatively slow to onset<sup>232,239</sup>
      - 4) An erratum published in association with the 2008 guidelines for tumor lysis highlights the potential for drug-drug interactions with allopurinol use.<sup>238</sup>
      - 5) In a study of pediatric patients with acute lymphoblastic leukemia, those who received urate oxidase or recombinant urate oxidase had higher clearance of methotrexate than those who received allopurinol for treatment of hyperuricemia (117.1 ml/min/m<sup>2</sup> vs 91.1 ml/min/m<sup>2</sup>, p = 0.019)<sup>242</sup>
      - 6) Degree of xanthine oxidase inhibition by allopurinol is dose-related; higher daily doses decrease production of uric acid more effectively
        - a. Rash may be a sign of toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome.
        - b. Allopurinol does not eliminate uric acid already created, but will reduce continued formation of uric acid.
        - c. Allopurinol dramatically inhibits metabolism of thiopurines; co-administration requires significant (50-90%) reduction in dose of thiopurine (e.g. mercaptopurine).

F. Use of rasburicase in TLS:

1. Recombinant urate oxidase enzyme which catalyzes the degradation of uric acid into allantoin, a compound with far greater solubility than uric acid in physiologic urine pH
2. FDA-approved for both prevention and treatment of TLS in both adults and pediatrics
3. Rapid onset of action
4. Significant, but rare, adverse effects of rasburicase include methemoglobinemia, anaphylaxis, and hemolysis. Patients who are glucose-6-phosphate dehydrogenase (G6PD) deficient should not receive rasburicase
5. Following a dose of rasburicase, specific directions for handling serum samples must be followed:
  - a. Blood must be collected in collection tube containing heparin anticoagulant and immediately plunged into ice bath
  - b. Sample must be delivered to laboratory and assayed within 4 hours of collection to prevent spuriously low serum uric acid result
6. Rasburicase dosing:
  - a. FDA-approved dosing is 0.2 mg/kg IV daily x 5 days for no more than a single course for both adults and pediatrics
    1. Antibodies have been shown to occur 1-6 weeks after administration, leading to higher incidence of hypersensitivity reactions upon repeated exposure
  - b. Numerous case series and small studies have determined the utility of 1 or two fixed-doses of rasburicase, usually 3 - 7.5 mg per dose in adult patients<sup>243,244</sup>
    1. Smaller, single dose strategies are used most commonly in clinical practice
  - c. Majority of rasburicase studies report laboratory findings and short-term outcomes; Few data comparing relevant clinical outcomes (ie: prevention of dialysis or mortality) with alternative uric acid lowering agents<sup>245</sup>
  - d. No adjustment for renal or hepatic dysfunction

G. Febuxostat and pegloticase are two agents with similar mechanisms of action as allopurinol and rasburicase, respectively.<sup>246</sup> A recent phase III study in patients with hematologic malignancies at intermediate to high TLS risk evaluated fixed dose febuxostat versus allopurinol dosed by investigator's choice of 200/300/600mg daily.

1. Statistically significant difference in mean serum uric acid favoring febuxostat (514 +/- 225.71 versus 708 +/- 234.42, P<0.0001).<sup>247</sup>
  - a. Febuxostat can be considered (in addition to fluids) in patients with a uric acid > 7.5 mg/dL in an attempt to prevent the use of the more expensive rasburicase.

**IV. Prevention of low-risk TLS<sup>227</sup>**

- A. Monitor for development of TLS and complications
- B. Normal hydration should be administered, which may mean only oral hydration unless treatment required (see below)

- C. No allopurinol or rasburicase should be administered unless treatment required (see below)

**V. Prevention of intermediate-risk TLS<sup>227</sup>**

- A. Monitor for development of TLS and complications
- B. Obtain a baseline glucose-6-phosphate value. While this is recommended, treatment should not be delayed if results are not available
- C. Administer 2.5-3 liters/m<sup>2</sup>/24 hours of normal saline-containing intravenous fluids unless fluid overload and/or oliguria limit fluids
- D. Allopurinol 300-400 mg/m<sup>2</sup>/day (adults) or 10-20 mg/kg/day (children < 15 years)
- E. As needed use of loop diuretic to allow for aggressive IV hydration

**VI. Prevention of high-risk TLS<sup>227</sup>**

- A. Monitor for development of TLS and complications
- B. Obtain a baseline glucose-6-phosphate value
- C. Administer 2.5-3 liters/m<sup>2</sup>/24 hours of normal saline-containing intravenous fluids unless fluid overload and/or oliguria limit fluids
- D. Allopurinol 300-400 mg/m<sup>2</sup>/day (adults) or 10-20 mg/kg/day (children < 15 years)
- E. Rasburicase 0.1-0.2 mg/kg or fixed-dose once or once daily according to urate concentration response
- F. As needed use of loop diuretic to allow for aggressive IV hydration

**VII. Principles of treatment of TLS<sup>232,248,249</sup>**

- A. Primary goal of treatment is increase urinary excretion of potassium, phosphate and uric acid.
- B. Laboratory values should be monitored every 6-8 hours, then titrated down to once-daily upon resolution of TLS.
- C. Backbone of TLS treatment is aggressive IV fluids:
  - 1. Loop diuretics and rasburicase may be used in select circumstances
  - 2. Allopurinol should be continued or initiated if low risk stratification
- D. Treat each metabolic derangement as it is detected:
  - 1. Treatment of electrolyte derangements use same principles as in non-oncology patients
- E. Treatment of TLS-associated hyperuricemia:
  - 1. Normal saline-containing intravenous fluids administered 150-300 mL/hour (minimum of 2,000-3,000 mL/m<sup>2</sup>/day), titrated to maintain urine output of > 100 mL/hr
  - 2. Allopurinol 300-400 mg/m<sup>2</sup>/day (adults) or 10-20 mg/kg/day (children < 15 years)
  - 3. Rasburicase 0.15-0.2 mg/kg or fixed-dose if not G6PD deficient (though given the urgency of need in TLS if this information was not available typically the dose is not held to await lab data) and serum uric acid > 7-8 mg/dL (adults and pediatrics) and the patient is not on dialysis
    - a. NCCN does not provide recommendations on when to administer rasburicase

F. Treatment of TLS-associated hyperkalemia

1. Often, the earliest and most serious complication of TLS
2. Normal saline-containing intravenous fluids administered 150-300 mL/hour (minimum of 2,000 - 3,000 mL/m<sup>2</sup>/day), titrated to maintain urine output of > 100 mL/hr
3. Loop diuretics should be used to maintain brisk urine output
4. If serum potassium  $\geq$  6 mEq/L and/or ECG changes irrespective of serum potassium, rapid correction of serum potassium and/or stabilization of myocardial tissue is mandated. Treatments are listed in Figure 1.

G. Treatment of TLS-associated hyperphosphatemia

1. Elevated serum phosphate is difficult to control, outside of renal dialysis
  - a. Phosphate binders only bind dietary phosphate in the GI tract, not phosphorus released during TLS
2. Interventions aimed at decreasing oral absorption of exogenous phosphate (Figure 1)

H. Treatment of TLS-associated hypocalcemia

1. Hypocalcemia is a secondary consequence of hyperphosphatemia
2. Asymptomatic hypocalcemia should not be treated
3. To obtain more accurate results, wherever possible, use of ionized calcium is preferable to total serum calcium levels
4. In the presence of cardiac arrhythmias, seizures or tetany, calcium gluconate 1,000 mg (adults) or 20-30 mg/kg (children) under continuous ECG monitoring
  - a. The least amount of calcium should be administered to minimize calcium-phosphate crystal deposition in tissues

I. Treatment of TLS in special circumstances (ex.: elderly, pre-existing cardiac disease, etc.)

1. Elderly
  - a. TLS may occur more frequently in elderly patients
  - b. Elderly patients and cardiac patients may not tolerate the electrolyte derangements as well as younger patients, becoming symptomatic – even critically unstable – under conditions of mild electrolyte anomalies
  - c. IV fluids should be given as aggressively as possible, utilizing loop diuretics to prevent fluid overload
  - d. Rasburicase may need to be used to gain rapid control of hyperuricemia in order to preserve excretory function
2. Decompensated heart failure
  - a. Aggressive hydration may lead to exacerbation of heart failure
  - b. Balance hydration with loop diuretics, keeping keen eye on ins/outs



- J. Renal dialysis is treatment of last resort; efforts to control TLS should be exhausted before instituting renal dialysis

**Treatment of acute TLS<sup>227</sup>**

Sequelae of TLS	Management
First intervention: Hyper-hydration	
Hyperuricemia	Rapid reduction of hyperuricemia is primary goal with treatment of tumor lysis syndrome: <ol style="list-style-type: none"> <li>1. Aggressive hydration</li> <li>2. Allopurinol/Febuxostat</li> <li>3. Rasburicase</li> </ol>
Hyperkalemia	<b>MODERATE AND ASYMPTOMATIC:</b> Avoid exogenous administration. Monitor for EKG changes. Consider sodium polystyrene sulfonate.  <b>SEVERE OR SYMPTOMATIC:</b> As above plus calcium gluconate IV and/or regular insulin 10units plus dextrose or dialysis
Hyperphosphatemia	<b>MODERATE:</b> Avoid exogenous administration. Employ phosphate binders (e.g. aluminum hydroxide, sevelamer, lanthanum) and restrict dietary phosphate intake to 800-1,000 mg/day.  <b>SEVERE:</b> May require dialysis.
Hypocalcemia	Because this electrolyte derangement typically corrects once hyperphosphatemia resolves, reserve treatment for symptomatic patients.  <b>SYMPTOMATIC:</b> parenteral calcium gluconate

**Patient Case #1 Answer:**

**Correct answer = A (Aggressive hydration with normal saline).**

The most important medication for treatment of TLS is intravenous fluid, infused at a rapid rate. This not only dilutes electrolytes, but helps maintain optimal renal function to excrete electrolytes, including potassium and uric acid. The use of rasburicase and sodium polystyrene sulfate is important in the management of TLS, but should occur after intravenous fluids have been maximized.

## RECOMMENDED READINGS

### Myelodysplastic syndromes

1. Sekeres, MA and Bhumika JP. Lowering the Boom on Lower-Risk Myelodysplastic Syndromes. *Hematology Am Soc Hematol Educ Program* . 2019 Dec 6;2019(1):367-372. Available at <https://pubmed.ncbi.nlm.nih.gov/31808873/>

### Acute leukemias

1. Sanz MA, Fenaux P, Tallman MS et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood*. 2019 Apr 11;133(15):1630-1643. Available at <https://www.ncbi.nlm.nih.gov/pubmed/30803991>
2. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel [published online ahead of print, 2022 Jul 7]. *Blood*. 2022;blood.2022016867. doi:10.1182/blood.2022016867 Available at: <https://pubmed.ncbi.nlm.nih.gov/35797463/>
3. Siegel SE, Stock W, Johnson RH, et al. Pediatric-Inspired Treatment Regimens for Adolescents and Young Adults With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Review. *JAMA Oncol*. 2018 May 1;4(5):725-734. Available at <https://www.ncbi.nlm.nih.gov/pubmed/29450465>
4. Saleh K, Fernandez A, Pasquier F. Treatment of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in Adults. *Cancers (Basel)*. 2022;14(7):1805. Published 2022 Apr 1. doi:10.3390/cancers14071805 Available at <https://pubmed.ncbi.nlm.nih.gov/35406576/>

## REFERENCES

1. Kulasekararaj AG, Mohamedali AM, Mufti GJ. Recent advances in understanding the molecular pathogenesis of myelodysplastic syndromes. *British journal of haematology*. Sep 2013;162(5):587-605. doi:10.1111/bjh.12435
2. Felix CA. Secondary leukemias induced by topoisomerase-targeted drugs. *Biochimica et biophysica acta*. Oct 1 1998;1400(1-3):233-55.
3. Czader M, Orazi A. Therapy-related myeloid neoplasms. *American journal of clinical pathology*. Sep 2009;132(3):410-25. doi:10.1309/AJCPD85MCOHHCOMQ
4. Bejar R, Levine R, Ebert BL. Unraveling the molecular pathophysiology of myelodysplastic syndromes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 10 2011;29(5):504-15. doi:10.1200/JCO.2010.31.1175
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. May 19 2016;127(20):2391-405. doi:10.1182/blood-2016-03-643544
6. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. Jun 22 2022;doi:10.1038/s41375-022-01613-1
7. Falantes JF, Garcia-Manero G. Does the concept of lower-risk myelodysplastic syndrome need to be revisited? *Leuk Res*. Oct 2015;39(10):1003-5. doi:10.1016/j.leukres.2015.06.010
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes. V.1.2023, 09/12/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN

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9. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. Mar 15 1997;89(6):2079-88.
10. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. Sep 20 2012;120(12):2454-65. doi:10.1182/blood-2012-03-420489
11. Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood*. Oct 2014;124(18):2793-803. doi:10.1182/blood-2014-04-522136
12. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia*. Feb 2014;28(2):241-7. doi:10.1038/leu.2013.336
13. Hou HA, Tsai CH, Lin CC, et al. Incorporation of mutations in five genes in the revised International Prognostic Scoring System can improve risk stratification in the patients with myelodysplastic syndrome. *Blood Cancer J*. 04 2018;8(4):39. doi:10.1038/s41408-018-0074-7
14. Kantarjian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. *Cancer*. Sep 15 2008;113(6):1351-61. doi:10.1002/cncr.23697
15. Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). *Haematologica*. Oct 2011;96(10):1433-40. doi:10.3324/haematol.2011.044602
16. Garcia-Manero G. Myelodysplastic syndromes: 2015 Update on diagnosis, risk-stratification and management. *Am J Hematol*. Sep 2015;90(9):831-41. doi:10.1002/ajh.24102
17. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 20 2014;32(24):2541-52. doi:10.1200/JCO.2014.55.1564
18. Zeidan AM, Sekeres MA, Wang XF, et al. Comparing the Prognostic Value of Risk stratifying Models for Patients with Lower-Risk Myelodysplastic Syndromes: Is one model better? *Am J Hematol*. Aug 11 2015;doi:10.1002/ajh.24170
19. Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 20 2008;26(21):3607-13. doi:10.1200/JCO.2007.15.4906
20. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet*. May 2 2009;373(9674):1532-42. doi:10.1016/S0140-6736(09)60502-X
21. Ross SD, Allen IE, Probst CA, Sercus B, Crean SM, Ranganathan G. Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis. *The oncologist*. Oct 2007;12(10):1264-73. doi:10.1634/theoncologist.12-10-1264
22. Zarxio [prescribing information]. Princeton NS, Inc. a Novartis Pharmaceuticals Company, 2016.
23. Bohlius J, Bohlke K, Castelli R, et al. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 05 2019;37(15):1336-1351. doi:10.1200/JCO.18.02142
24. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *The New England journal of medicine*. Oct 5 2006;355(14):1456-65. doi:10.1056/NEJMoa061292
25. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. *Blood*. Oct 6 2011;118(14):3765-76. doi:10.1182/blood-2011-01-330126
26. Kuendgen A, Laussek M, List AF, et al. Lenalidomide does not increase AML progression risk in RBC transfusion-dependent patients with Low- or Intermediate-1-risk MDS with del(5q): a comparative analysis. *Leukemia*. Apr 2013;27(5):1072-9. doi:10.1038/leu.2012.369
27. Santini V, Almeida A, Giagounidis A, et al. Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 09 2016;34(25):2988-96. doi:10.1200/JCO.2015.66.0118

28. Santini V, Almeida A, Giagounidis A, et al. Achievement of red blood cell transfusion independence in red blood cell transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes correlates with serum erythropoietin levels. *Leuk Lymphoma*. Jun 2020;61(6):1475-1483. doi:10.1080/10428194.2020.1719088
29. Reblozyl [package insert]. Summit N, USA: Celgene Corporation, 2019.
30. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. *The New England journal of medicine*. 01 2020;382(2):140-151. doi:10.1056/NEJMoa1908892
31. Pabst T, Vellenga E, van Putten W, et al. Favorable effect of priming with granulocyte colony-stimulating factor in remission induction of acute myeloid leukemia restricted to dose escalation of cytarabine. *Blood*. Jun 7 2012;119(23):5367-73. doi:10.1182/blood-2011-11-389841
32. Sauntharajah Y, Nakamura R, Wesley R, Wang QJ, Barrett AJ. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. *Blood*. Oct 15 2003;102(8):3025-7. doi:10.1182/blood-2002-11-3325
33. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *The Lancet Oncology*. Mar 2009;10(3):223-32. doi:10.1016/S1470-2045(09)70003-8
34. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. Apr 15 2006;106(8):1794-803. doi:10.1002/cncr.21792
35. Lubbert M, Suci S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 20 2011;29(15):1987-96. doi:10.1200/JCO.2010.30.9245
36. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 15 2002;20(10):2429-40.
37. Xie M, Jiang Q, Xie Y. Comparison Between Decitabine and Azacitidine for the Treatment of Myelodysplastic Syndrome: A Meta-Analysis With 1392 Participants. *Clinical lymphoma, myeloma & leukemia*. Jun 12 2014;doi:10.1016/j.clml.2014.04.010
38. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine: a phase 2, pharmacokinetic/pharmacodynamic, randomized, crossover study in MDS and CMML. *Blood*. Apr 13 2020;doi:10.1182/blood.2019004143
39. Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 10 2009;27(11):1850-6. doi:10.1200/JCO.2008.17.1058
40. Sasaki K, Jabbour E, Montalban-Bravo G, et al. Low-dose decita-bine versus low-dose azacitidine in lower-risk MDS. *NEJM Evid2022*;1(10). DOI:10.1056/EVIDoa2200034.
41. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 20 2006;24(24):3895-903. doi:10.1200/JCO.2005.05.4346
42. de Witte T, Suci S, Verhoef G, et al. Intensive chemotherapy followed by allogeneic or autologous stem cell transplantation for patients with myelodysplastic syndromes (MDSs) and acute myeloid leukemia following MDS. *Blood*. Oct 15 2001;98(8):2326-31.
43. Steensma DP, Gattermann N. When is iron overload deleterious, and when and how should iron chelation therapy be administered in myelodysplastic syndromes? *Best practice & research Clinical haematology*. Dec 2013;26(4):431-44. doi:10.1016/j.beha.2013.09.009
44. Mainous AG, 3rd, Tanner RJ, Hulihan MM, Amaya M, Coates TD. The impact of chelation therapy on survival in transfusional iron overload: a meta-analysis of myelodysplastic syndrome. *British journal of haematology*. Jul 22 2014;doi:10.1111/bjh.13053
45. Angelucci E, Santini V, Di Tucci AA, et al. Deferasirox for transfusion-dependent patients with myelodysplastic syndromes: safety, efficacy, and beyond (GIMEMA MDS0306 Trial). *European journal of haematology*. Jun 2014;92(6):527-36. doi:10.1111/ejh.12300

46. Meerpohl JJ, Schell LK, Rucker G, et al. Deferasirox for managing iron overload in people with myelodysplastic syndrome. *Cochrane Database Syst Rev*. 2014;10:CD007461. doi:10.1002/14651858.CD007461.pub3
47. Lyons RM, Marek BJ, Paley C, et al. Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry. *Leuk Res*. Feb 2014;38(2):149-54. doi:10.1016/j.leukres.2013.11.004
48. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 20 2005;23(30):7594-603. doi:10.1200/JCO.2005.01.7038
49. Angelucci E, Li J, Greenberg P, et al. Iron Chelation in Transfusion-Dependent Patients With Low- to Intermediate-1-Risk Myelodysplastic Syndromes: A Randomized Trial. *Ann Intern Med*. Apr 2020;172(8):513-522. doi:10.7326/M19-0916
50. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet*. Feb 9 2013;381(9865):484-95. doi:10.1016/S0140-6736(12)61727-9
51. Rowe JM, Tallman MS. How I treat acute myeloid leukemia. *Blood*. Oct 28 2010;116(17):3147-56. doi:10.1182/blood-2010-05-260117
52. Liersch R, Muller-Tidow C, Berdel WE, Krug U. Prognostic factors for acute myeloid leukaemia in adults--biological significance and clinical use. *British journal of haematology*. Apr 2014;165(1):17-38. doi:10.1111/bjh.12750
53. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. Jan 21 2010;115(3):453-74. doi:10.1182/blood-2009-07-235358
54. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood*. Jul 7 2022;doi:10.1182/blood.2022016867
55. Estey EH. Acute myeloid leukemia: 2014 Update on risk-stratification and management. *Am J Hematol*. Nov 2014;89(11):1063-81. doi:10.1002/ajh.23834
56. Chung SS. Genetic mutations in acute myeloid leukemia that influence clinical decisions. *Current opinion in hematology*. Mar 2014;21(2):87-94. doi:10.1097/MOH.000000000000024
57. Martelli MP, Sportoletti P, Tiacci E, Martelli MF, Falini B. Mutational landscape of AML with normal cytogenetics: biological and clinical implications. *Blood reviews*. Jan 2013;27(1):13-22. doi:10.1016/j.blre.2012.11.001
58. Santos FP, Jones D, Qiao W, et al. Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. *Cancer*. May 15 2011;117(10):2145-55. doi:10.1002/cncr.25670
59. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia. V.3.2022, 1/13/23, © 2023 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
60. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *The New England journal of medicine*. May 1 2008;358(18):1909-18. doi:10.1056/NEJMoa074306
61. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *The New England journal of medicine*. Jun 28 2012;366(26):2443-54. doi:10.1056/NEJMoa1200690
62. Bertoli S, Berard E, Hugué F, et al. Time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome of patients with acute myeloid leukemia. *Blood*. Apr 4 2013;121(14):2618-26. doi:10.1182/blood-2012-09-454553
63. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfit to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia*. Apr 2013;27(5):997-9. doi:10.1038/leu.2012.303

64. Sekeres MA, Guyatt G, Abel G, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. *Blood Adv.* Aug 11 2020;4(15):3528-3549. doi:10.1182/bloodadvances.2020001920
65. Arellano M, Pakkala S, Langston A, et al. Early clearance of peripheral blood blasts predicts response to induction chemotherapy in acute myeloid leukemia. *Cancer.* Nov 1 2012;118(21):5278-82. doi:10.1002/cncr.27494
66. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 15 2003;21(24):4642-9. doi:10.1200/JCO.2003.04.036
67. Morris TA, DeCastro CM, Diehl LF, et al. Re-induction therapy decisions based on day 14 bone marrow biopsy in acute myeloid leukemia. *Leuk Res.* Jan 2013;37(1):28-31. doi:10.1016/j.leukres.2012.09.016
68. Mattison RJ, Luger SM, Lazarus HM. New strategies for the evaluation of the nadir bone marrow following induction in acute myeloid leukemia. *Current opinion in hematology.* Mar 2013;20(2):93-9. doi:10.1097/MOH.0b013e32835d8207
69. Wei AH, Döhner H, Pocock C, et al. The QUAZAR AML-001 Maintenance Trial: Results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission [abstract]. *Blood.* 2019;134(suppl 2). Abstract LBA-3.
70. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *The New England journal of medicine.* Sep 24 2009;361(13):1235-48. doi:10.1056/NEJMoa0901409
71. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *The New England journal of medicine.* Sep 24 2009;361(13):1249-59. doi:10.1056/NEJMoa0904544
72. Lusk MR, Lee JW, Fernandez HF, et al. Benefit of high-dose daunorubicin in AML induction extends across cytogenetic and molecular groups. *Blood.* Mar 2016;127(12):1551-8. doi:10.1182/blood-2015-07-657403
73. Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m<sup>2</sup> vs 60 mg/m<sup>2</sup> in AML induction: results from the UK NCRI AML17 trial in 1206 patients. *Blood.* Jun 2015;125(25):3878-85. doi:10.1182/blood-2015-01-623447
74. Burnett AK, Russell NH, Hills RK, Group UKNCRIAMLS. Higher daunorubicin exposure benefits FLT3 mutated acute myeloid leukemia. *Blood.* 07 2016;128(3):449-52. doi:10.1182/blood-2016-04-712091
75. Gardin C, Chevret S, Pautas C, et al. Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jan 20 2013;31(3):321-7. doi:10.1200/JCO.2011.40.3642
76. Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. *The New England journal of medicine.* Mar 17 2011;364(11):1027-36. doi:10.1056/NEJMoa1010222
77. Stone R, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *The New England journal of medicine.* 2017;377:11.
78. Lambert J, Pautas C, Terre C, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. *Haematologica.* Jan 2019;104(1):113-119. doi:10.3324/haematol.2018.188888
79. Castaigne S, Pautas C, Terré C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *The Lancet.* 2012;379(9825):1508-1516. doi:10.1016/s0140-6736(12)60485-1
80. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *The Lancet Oncology.* Aug 2014;15(9):986-96. doi:10.1016/S1470-2045(14)70281-5
81. Vyxeos [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2017.
82. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood.* Jul 16 2015;126(3):291-9. doi:10.1182/blood-2015-01-621664
83. Momparler RL, Cote S, Momparler LF. Epigenetic action of decitabine (5-aza-2'-deoxycytidine) is more effective against acute myeloid leukemia than cytotoxic action of cytarabine (ARA-C). *Leuk Res.* Aug 2013;37(8):980-4. doi:10.1016/j.leukres.2013.04.019

84. Blum W, Garzon R, Klisovic RB, et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proceedings of the National Academy of Sciences of the United States of America*. Apr 20 2010;107(16):7473-8. doi:10.1073/pnas.1002650107
85. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 20 2012;30(21):2670-7. doi:10.1200/JCO.2011.38.9429
86. Amadori S, Suci S, Selleslag D, et al. Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 20 2016;34(9):972-9. doi:10.1200/JCO.2015.64.0060
87. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. Dec 16 2018;doi:10.1038/s41375-018-0312-9
88. Heuser M RT, Montesinos P, et al. Glasdegib (GLAS) plus low-dose cytarabine (LDAC) in AML or MDS: BRIGHT AML 1003 final report and four-year overall survival (OS) follow-up. 10.1200/JCO.2020.38.15\_suppl.7509 *Journal of Clinical Oncology* 38, no. 15\_suppl (May 20, 2020) 7509-7509.
89. DiNardo C JB, Pullarkat V, et al. A randomized, double-blind, placebo-controlled study of venetoclax with azacitidine vs azacitidine in treatment-naïve patients with acute myeloid leukemia ineligible for intensive therapy – VIALE-A. Presented at: Virtual Edition of the 25th European Hematology Association (EHA) Annual Congress, LB2601. JA.
90. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. Jun 2020;135(24):2137-2145. doi:10.1182/blood.2020004856
91. Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. *Leukemia*. Dec 2019;33(12):2795-2804. doi:10.1038/s41375-019-0612-8
92. Roboz G, Dinardo C, Stein E. Ivosidenib (AG-120) Induced Durable Remissions and Transfusion Independence in Patients with IDH1-Mutant Untreated AML: Results from a Phase 1 Dose Escalation and Expansion Study. *Blood*. 2018;132(561)doi:<https://doi.org/10.1182/blood-2018-99-110595>
93. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. Feb 2020;135(7):463-471. doi:10.1182/blood.2019002140
94. Montesinos P, Recher C, Vives S, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. *The New England journal of medicine*. Apr 21 2022;386(16):1519-1531. doi:10.1056/NEJMoa2117344
95. Cassileth PA, Begg CB, Bennett JM, et al. A randomized study of the efficacy of consolidation therapy in adult acute nonlymphocytic leukemia. *Blood*. Apr 1984;63(4):843-7.
96. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *The New England journal of medicine*. Oct 6 1994;331(14):896-903. doi:10.1056/NEJM199410063311402
97. Stone RM. Is it time to revisit standard post-remission therapy? *Best practice & research Clinical haematology*. Dec 2012;25(4):437-41. doi:10.1016/j.beha.2012.10.006
98. Bloomfield CD, Lawrence D, Byrd JC, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. *Cancer research*. Sep 15 1998;58(18):4173-9.
99. Lowenberg B. Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. *Blood*. Jan 3 2013;121(1):26-8. doi:10.1182/blood-2012-07-444851
100. Onureg [prescribed information]. Summit, NJ: Celgene Coporation, 2020.
101. Szer J. The prevalent predicament of relapsed acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program*. 2012;2012:43-48.
102. Thol F, Schlenk RF, Heuser M, Ganser A. How I treat refractory and early relapsed acute myeloid leukemia. *Blood*. Jul 16 2015;126(3):319-27. doi:10.1182/blood-2014-10-551911
103. Kubal T, Lancet JE. The thorny issue of relapsed acute myeloid leukemia. *Current opinion in hematology*. Mar 2013;20(2):100-6. doi:10.1097/MOH.0b013e32835dd99d

104. Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *The New England journal of medicine*. Dec 3 1998;339(23):1649-56. doi:10.1056/NEJM199812033392301
105. Herzig RH, Lazarus HM, Wolff SN, Phillips GL, Herzig GP. High-dose cytosine arabinoside therapy with and without anthracycline antibiotics for remission reinduction of acute nonlymphoblastic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 1985;3(7):992-7.
106. Kohrt HE, Patel S, Ho M, et al. Second-line mitoxantrone, etoposide, and cytarabine for acute myeloid leukemia: a single-center experience. *Am J Hematol*. Nov 2010;85(11):877-81. doi:10.1002/ajh.21857
107. Price SL, Lancet JE, George TJ, et al. Salvage chemotherapy regimens for acute myeloid leukemia: Is one better? Efficacy comparison between CLAG and MEC regimens. *Leuk Res*. Mar 2011;35(3):301-4. doi:10.1016/j.leukres.2010.09.002
108. Montillo M, Mirto S, Petti MC, et al. Fludarabine, cytarabine, and G-CSF (FLAG) for the treatment of poor risk acute myeloid leukemia. *Am J Hematol*. Jun 1998;58(2):105-9.
109. Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia. *British journal of haematology*. Dec 1997;99(4):939-44.
110. Becker PS, Kantarjian HM, Appelbaum FR, et al. Clofarabine with high dose cytarabine and granulocyte colony-stimulating factor (G-CSF) priming for relapsed and refractory acute myeloid leukaemia. *British journal of haematology*. Oct 2011;155(2):182-9. doi:10.1111/j.1365-2141.2011.08831.x
111. Robak T, Wrzesien-Kus A, Lech-Maranda E, Kowal M, Dmoszynska A. Combination regimen of cladribine (2-chlorodeoxyadenosine), cytarabine and G-CSF (CLAG) as induction therapy for patients with relapsed or refractory acute myeloid leukemia. *Leuk Lymphoma*. Sep 2000;39(1-2):121-9. doi:10.3109/10428190009053545
112. Wierzbowska A, Robak T, Pluta A, et al. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group. *European journal of haematology*. Feb 2008;80(2):115-26. doi:10.1111/j.1600-0609.2007.00988.x
113. Uy GL, Rettig MP, Motabi IH, et al. A phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia. *Blood*. Apr 26 2012;119(17):3917-24. doi:10.1182/blood-2011-10-383406
114. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. Aug 10 2017;130(6):722-731. doi:10.1182/blood-2017-04-779405
115. DiNardo CD, Stein EM, de Botton S, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. *The New England journal of medicine*. Jun 21 2018;378(25):2386-2398. doi:10.1056/NEJMoa1716984
116. Tibsovo [prescribing information]. Cambridge MAP, Inc, 2018.
117. REZLIDHIA™ [prescribing information], South San Francisco, CA: Rigel Pharmaceuticals, Inc.
118. Idhifa [prescribed information]. Cambridge MAP, Inc, 2017.
119. Xospata [prescribing information]. Northbrook IAP, 2018.
120. Perl AE eaPaAA, Meeting, March 29 to April 3, Atlanta GAC.
121. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory. *The New England journal of medicine*. 10 2019;381(18):1728-1740. doi:10.1056/NEJMoa1902688
122. Pagano L, Caira M. Risks for infection in patients with myelodysplasia and acute leukemia. *Current opinion in infectious diseases*. Dec 2012;25(6):612-8. doi:10.1097/QCO.0b013e328358b000
123. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. V.1.2021, 7/2/21, © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
124. Harousseau JL, Witz B, Lioure B, et al. Granulocyte colony-stimulating factor after intensive consolidation chemotherapy in acute myeloid leukemia: results of a randomized trial of the Groupe Ouest-Est Leucemies Aigues



- Myeloblastiques. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 2000;18(4):780-7.
125. Heuser M, Zapf A, Morgan M, Krauter J, Ganser A. Myeloid growth factors in acute myeloid leukemia: systematic review of randomized controlled trials. *Annals of hematology*. Mar 2011;90(3):273-81. doi:10.1007/s00277-010-1069-z
  126. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors. V.4.2021, 5/20/21, © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
  127. Wang J, An L, Chen S, et al. Prophylactic use of granulocyte colony-stimulating factor after chemotherapy does not affect survival rate in acute myeloid leukemia: a meta-analysis. *Acta haematologica*. 2009;121(4):223-6. doi:10.1159/000225909
  128. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 1 2015;33(28):3199-212. doi:10.1200/jco.2015.62.3488
  129. Markasz L, Hajas G, Kiss A, et al. Granulocyte colony stimulating factor increases drug resistance of leukaemic blast cells to daunorubicin. *Pathology oncology research : POR*. Sep 2008;14(3):285-92. doi:10.1007/s12253-008-9057-5
  130. Safdar A, Rodriguez G, Zuniga J, Al Akhrass F, Georgescu G, Pande A. Granulocyte macrophage colony-stimulating factor in 66 patients with myeloid or lymphoid neoplasms and recipients of hematopoietic stem cell transplantation with invasive fungal disease. *Acta haematologica*. 2013;129(1):26-34. doi:10.1159/000342121
  131. Bodey GP, Anaissie E, Gutterman J, Vadhan-Raj S. Role of granulocyte-macrophage colony-stimulating factor as adjuvant therapy for fungal infection in patients with cancer. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Oct 1993;17(4):705-7.
  132. Rubin EH, Andersen JW, Berg DT, Schiffer CA, Mayer RJ, Stone RM. Risk factors for high-dose cytarabine neurotoxicity: an analysis of a cancer and leukemia group B trial in patients with acute myeloid leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1992;10(6):948-53.
  133. Jolson HM, Bosco L, Bufton MG, et al. Clustering of adverse drug events: analysis of risk factors for cerebellar toxicity with high-dose cytarabine. *Journal of the National Cancer Institute*. Apr 1 1992;84(7):500-5.
  134. Smith GA, Damon LE, Rugo HS, Ries CA, Linker CA. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 1997;15(2):833-9.
  135. Bubalo J. Prevention and treatment of cytarabine-induced keratoconjunctivitis. *Journal of hematology oncology pharmacy*. 2015;5(1):3.
  136. Higa GM, Gockerman JP, Hunt AL, Jones MR, Horne BJ. The use of prophylactic eye drops during high-dose cytosine arabinoside therapy. *Cancer*. Oct 15 1991;68(8):1691-3.
  137. Lochhead J, Salmon JF, Bron AJ. Cytarabine-induced corneal toxicity. *Eye*. Jul 2003;17(5):677-8. doi:10.1038/sj.eye.6700451
  138. Matteucci P, Carlo-Stella C, Di Nicola M, et al. Topical prophylaxis of conjunctivitis induced by high-dose cytosine arabinoside. *Haematologica*. Feb 2006;91(2):255-7.
  139. Gococo KO, Lazarus HM, Lass JH. The use of prophylactic eye drops during high-dose cytosine arabinoside therapy. *Cancer*. Jun 1 1992;69(11):2866-7.
  140. Sanz MA, Lo Coco F, Martin G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood*. Aug 15 2000;96(4):1247-53.
  141. Shao W, Fanelli M, Ferrara FF, et al. Arsenic trioxide as an inducer of apoptosis and loss of PML/RAR alpha protein in acute promyelocytic leukemia cells. *Journal of the National Cancer Institute*. Jan 21 1998;90(2):124-33.

142. Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 10 2011;29(20):2753-7. doi:10.1200/JCO.2010.32.2107
143. Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. *Blood*. Nov 11 2010;116(19):3751-7. doi:10.1182/blood-2010-02-269621
144. Sanz MA, Grimwade D, Tallman MS, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. Feb 26 2009;113(9):1875-91. doi:10.1182/blood-2008-04-150250
145. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 1 2009;27(4):504-10. doi:10.1200/jco.2008.18.6130
146. Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *The Lancet Oncology*. Oct 2015;16(13):1295-305. doi:10.1016/s1470-2045(15)00193-x
147. Abaza Y, Kantarjian H, Garcia-Manero G, et al. Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. *Blood*. Mar 9 2017;129(10):1275-1283. doi:10.1182/blood-2016-09-736686
148. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *The New England journal of medicine*. Jul 11 2013;369(2):111-21. doi:10.1056/NEJMoa1300874
149. Avvisati G, Lo-Coco F, Paoloni FP, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. *Blood*. May 5 2011;117(18):4716-25. doi:10.1182/blood-2010-08-302950
150. Sanz MA, Montesinos P, Rayon C, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. *Blood*. Jun 24 2010;115(25):5137-46. doi:10.1182/blood-2010-01-266007
151. Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. *Blood*. Oct 28 2010;116(17):3171-9. doi:10.1182/blood-2010-03-276196
152. Sanz MA, Martin G, Gonzalez M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. *Blood*. Feb 15 2004;103(4):1237-43. doi:10.1182/blood-2003-07-2462
153. Ades L, Chevret S, Raffoux E, et al. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 20 2006;24(36):5703-10. doi:10.1200/JCO.2006.08.1596
154. Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). *Blood*. Aug 23 2012;120(8):1570-80; quiz 1752. doi:10.1182/blood-2012-02-410746
155. Breen KA, Grimwade D, Hunt BJ. The pathogenesis and management of the coagulopathy of acute promyelocytic leukaemia. *British journal of haematology*. Jan 2012;156(1):24-36. doi:10.1111/j.1365-2141.2011.08922.x
156. Rogers JE, Yang D. Differentiation syndrome in patients with acute promyelocytic leukemia. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners*. Mar 2012;18(1):109-14. doi:10.1177/1078155211399163
157. Barbey JT, Soignet S. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. *Ann Intern Med*. Nov 6 2001;135(9):842-3.
158. Roboz GJ, Ritchie EK, Carlin RF, et al. Prevalence, management, and clinical consequences of QT interval prolongation during treatment with arsenic trioxide. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 20 2014;32(33):3723-8. doi:10.1200/jco.2013.51.2913
159. Pagano L, Stamouli M, Tumbarello M, et al. Risk of invasive fungal infection in patients affected by acute promyelocytic leukaemia. A report by the SEIFEM-D registry. *British journal of haematology*. Aug 2015;170(3):434-9. doi:10.1111/bjh.13308

160. Tallman MS. Treatment of relapsed or refractory acute promyelocytic leukemia. *Best practice & research Clinical haematology*. Mar 2007;20(1):57-65. doi:10.1016/j.beha.2006.11.002
161. Gokbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. *Seminars in hematology*. Jan 2009;46(1):64-75. doi:10.1053/j.seminhematol.2008.09.003
162. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*. Dec 2005;106(12):3760-7. doi:10.1182/blood-2005-04-1623
163. Stanulla M, Dagdan E, Zaliouva M, et al. IKZF1. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 2018;36(12):1240-1249. doi:10.1200/JCO.2017.74.3617
164. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia. V.1.2021, 4/6/21, © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
165. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 10 2011;29(5):532-43. doi:10.1200/JCO.2010.30.1382
166. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood*. Jan 18 2019;doi:10.1182/blood-2018-10-881961
167. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood*. Jun 15 2004;103(12):4396-407. doi:10.1182/blood-2003-08-2958
168. Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood*. Sep 23 2010;116(12):2070-7. doi:10.1182/blood-2009-12-261586
169. Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. Dec 1 2015;121(23):4158-64. doi:10.1002/cncr.29646
170. Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. Dec 15 2011;118(25):6521-8. doi:10.1182/blood-2011-05-351403
171. Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol*. Dec 2018;5(12):e618-e627. doi:10.1016/s2352-3026(18)30176-5
172. Foà R, Bassan R, Vitale A, et al. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. *The New England journal of medicine*. 10 2020;383(17):1613-1623. doi:10.1056/NEJMoa2016272
173. Erwinaze. (asparaginase Erwinia chrysanthemi) [prescribing information]. Palo Alto CJP, Inc; March 2016. 2016.
174. RYLAZE [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2021.
175. Asselin BL. The three asparaginases. Comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol*. 1999;457:621-9.
176. ASPARLAS [package insert]. Boston, MA: Servier Pharmaceuticals LLC.; 2018.
177. ONCASPAR [package insert]. Lexington, MA: Baxalta US Inc; 2019.
178. Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. *Leuk Lymphoma*. Dec 2011;52(12):2237-53. doi:10.3109/10428194.2011.596963
179. Marini BL, Brown J, Benitez L, et al. A single-center multidisciplinary approach to managing the global Erwinia asparaginase shortage. *Leuk Lymphoma*. May 2019;1-15. doi:10.1080/10428194.2019.1608530
180. Marini BL, Perissinotti AJ, Bixby DL, Brown J, Burke PW. Catalyzing improvements in ALL therapy with asparaginase. *Blood reviews*. Sep 2017;31(5):328-338. doi:10.1016/j.blre.2017.06.002

181. Bade NA, Lu C, Patzke CL, et al. Optimizing pegylated asparaginase use: An institutional guideline for dosing, monitoring, and management. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners*. Mar 2019;1078155219838316. doi:10.1177/1078155219838316
182. Hunault-Berger M, Chevallier P, Delain M, et al. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. *Haematologica*. Oct 2008;93(10):1488-94. doi:10.3324/haematol.12948
183. van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica*. Mar 2016;101(3):279-85. doi:10.3324/haematol.2015.137380
184. Nagpal S, Recht L. Treatment and prophylaxis of hematologic malignancy in the central nervous system. *Current treatment options in neurology*. Aug 2011;13(4):400-12. doi:10.1007/s11940-011-0128-7
185. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. *The oncologist*. Jan 2018;23(1):52-61. doi:10.1634/theoncologist.2017-0243
186. Gökbuğet N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 04 2018;131(14):1522-1531. doi:10.1182/blood-2017-08-798322
187. Short NJ, Jabbour E, Albitar M, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts. *Am J Hematol*. Feb 2019;94(2):257-265. doi:10.1002/ajh.25338
188. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood*. Aug 2015;126(8):964-71. doi:10.1182/blood-2015-03-633685
189. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood*. Apr 2010;115(16):3206-14. doi:10.1182/blood-2009-10-248146
190. Gökbuğet N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood*. Aug 2012;120(9):1868-76. doi:10.1182/blood-2011-09-377713
191. Brüggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood*. Feb 2006;107(3):1116-23. doi:10.1182/blood-2005-07-2708
192. Specchia G, Pastore D, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. *Annals of hematology*. Nov 2005;84(12):792-5. doi:10.1007/s00277-005-1090-9
193. Giebel S, Krawczyk-Kulis M, Adamczyk-Cioch M, et al. Fludarabine, cytarabine, and mitoxantrone (FLAM) for the treatment of relapsed and refractory adult acute lymphoblastic leukemia. A phase study by the Polish Adult Leukemia Group (PALG). *Annals of hematology*. Oct 2006;85(10):717-22. doi:10.1007/s00277-006-0121-5
194. Kadia TM, Kantarjian HM, Thomas DA, et al. Phase II study of methotrexate, vincristine, pegylated-asparaginase, and dexamethasone (MOPAD) in patients with relapsed/refractory acute lymphoblastic leukemia. *Am J Hematol*. Feb 2015;90(2):120-4. doi:10.1002/ajh.23886
195. Faderl S, Thomas DA, O'Brien S, et al. Augmented hyper-CVAD based on dose-intensified vincristine, dexamethasone, and asparaginase in adult acute lymphoblastic leukemia salvage therapy. *Clinical lymphoma, myeloma & leukemia*. Feb 2011;11(1):54-9. doi:10.3816/CLML.2011.n.007
196. Schiller G, Lee M, Territo M, Gajewski J, Nimer S. Phase II study of etoposide, ifosfamide, and mitoxantrone for the treatment of resistant adult acute lymphoblastic leukemia. *Am J Hematol*. Jul 1993;43(3):195-9.
197. Kantarjian H, Gandhi V, Cortes J, et al. Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. *Blood*. Oct 01 2003;102(7):2379-86. doi:10.1182/blood-2003-03-0925
198. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 2006;24(12):1917-23. doi:10.1200/JCO.2005.03.8554

199. Miano M, Pistorio A, Putti MC, et al. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. *Leuk Lymphoma*. Sep 2012;53(9):1693-8. doi:10.3109/10428194.2012.663915
200. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood*. Jun 15 2007;109(12):5136-42. doi:10.1182/blood-2006-11-056754
201. Zwaan CM, Kowalczyk J, Schmitt C, et al. Safety and efficacy of nelarabine in children and young adults with relapsed or refractory T-lineage acute lymphoblastic leukaemia or T-lineage lymphoblastic lymphoma: results of a phase 4 study. *British journal of haematology*. 10 2017;179(2):284-293. doi:10.1111/bjh.14874
202. Commander LA, Seif AE, Insogna IG, Rheingold SR. Salvage therapy with nelarabine, etoposide, and cyclophosphamide in relapsed/refractory paediatric T-cell lymphoblastic leukaemia and lymphoma. *British journal of haematology*. Aug 2010;150(3):345-51. doi:10.1111/j.1365-2141.2010.08236.x
203. Jabbour E, Sasaki K, Ravandi F, et al. Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. *Cancer*. 10 2018;124(20):4044-4055. doi:10.1002/cncr.31720
204. Jabbour E, Ravandi F, Kebriaei P, et al. Salvage Chemoimmunotherapy With Inotuzumab Ozogamicin Combined With Mini-Hyper-CVD for Patients With Relapsed or Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Phase 2 Clinical Trial. *JAMA Oncol*. Feb 2018;4(2):230-234. doi:10.1001/jamaoncol.2017.2380
205. Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *The Lancet Oncology*. 02 2018;19(2):240-248. doi:10.1016/S1470-2045(18)30011-1
206. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. *Cancer*. Jul 2019;125(14):2474-2487. doi:10.1002/cncr.32116
207. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *The New England journal of medicine*. Aug 25 2016;375(8):740-53. doi:10.1056/NEJMoa1509277
208. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *The Lancet Oncology*. Jan 2015;16(1):57-66. doi:10.1016/S1470-2045(14)71170-2
209. Topp MS, Gokbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 20 2014;32(36):4134-40. doi:10.1200/jco.2014.56.3247
210. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 20 2011;29(18):2493-8. doi:10.1200/jco.2010.32.7270
211. Martinelli G, Dombret H, Chevallier P, Ottmann O, Gokbuget N, Topp M. Complete molecular and hematologic response in adult patients with relapsed/refractory (R/R) Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia (ALL) following treatment with blinatumomab: results from a phase 2 single-arm, multicenter study (Alcantara). *Blood*. 2015;126:1.
212. Pulte ED, Vallejo J, Przepiorka D, et al. FDA Supplemental Approval: Blinatumomab for Treatment of Relapsed and Refractory Precursor B-Cell Acute Lymphoblastic Leukemia. *The oncologist*. Jul 17 2018;doi:10.1634/theoncologist.2018-0179
213. Blincyto. Package insert. Amgen ITO, CA. May, 2018.
214. Martinelli G, Boissel N, Chevallier P, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1 2017;35(16):1795-1802. doi:10.1200/jco.2016.69.3531

215. Assi R, Kantarjian H, Short NJ, et al. Safety and Efficacy of Blinatumomab in Combination With a Tyrosine Kinase Inhibitor for the Treatment of Relapsed Philadelphia Chromosome-positive Leukemia. *Clinical lymphoma, myeloma & leukemia*. Dec 2017;17(12):897-901. doi:10.1016/j.clml.2017.08.101
216. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *The New England journal of medicine*. Feb 1 2018;378(5):439-448. doi:10.1056/NEJMoa1709866
217. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet*. Aug 7 2021;398(10299):491-502. doi:10.1016/s0140-6736(21)01222-8
218. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. Jul 10 2014;124(2):188-95. doi:10.1182/blood-2014-05-552729
219. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nature reviews Clinical oncology*. Jan 2018;15(1):47-62. doi:10.1038/nrclinonc.2017.148
220. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer journal*. Mar-Apr 2014;20(2):119-22. doi:10.1097/PPO.000000000000035
221. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. Apr 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758
222. National Cancer Institute. Common terminology criteria for adverse events (CTCAE). Version 4.0. Available at: [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Accessed July 20, 2020.
223. National Cancer Institute. Common terminology criteria for adverse events (CTCAE). Version 5.0. Available at: [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_8.5x11.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). Accessed July 20, 2020.
224. Park JH, Riviere I, Gonen M, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *The New England journal of medicine*. Feb 1 2018;378(5):449-459. doi:10.1056/NEJMoa1709919
225. Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. *J Hematol Oncol*. Mar 2 2018;11(1):35. doi:10.1186/s13045-018-0571-y
226. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities. V.4.2021, 09/27/21 © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
227. Cairo MS, Coiffier B, Reiter A, Younes A, Panel TLSE. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *British journal of haematology*. May 2010;149(4):578-86. doi:10.1111/j.1365-2141.2010.08143.x
228. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb 15 2011;52(4):e56-93. doi:10.1093/cid/cir073
229. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *The New England journal of medicine*. May 12 2011;364(19):1844-54. doi:10.1056/NEJMra0904569
230. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *British journal of haematology*. Oct 2004;127(1):3-11. doi:10.1111/j.1365-2141.2004.05094.x
231. Bose P, Qubaiah O. A review of tumour lysis syndrome with targeted therapies and the role of rasburicase. *Journal of clinical pharmacy and therapeutics*. Jun 2011;36(3):299-326. doi:10.1111/j.1365-2710.2011.01260.x
232. Will A, Tholouli E. The clinical management of tumour lysis syndrome in haematological malignancies. *British journal of haematology*. Jul 2011;154(1):3-13. doi:10.1111/j.1365-2141.2011.08697.x
233. Rundles RW. The development of allopurinol. *Archives of internal medicine*. Aug 1985;145(8):1492-503.

234. Krakoff IH. Use of allopurinol in preventing hyperuricemia in leukemia and lymphoma. *Cancer*. Nov 1966;19(11):1489-96.
235. Krakoff IH, Meyer RL. PREVENTION OF HYPERURICEMIA IN LEUKEMIA AND LYMPHOMA: USE OF ALOPURINOL, A XANTHINE OXIDASE INHIBITOR. *Jama*. Jul 5 1965;193:1-6.
236. DeConti RC, Calabresi P. Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease. *The New England journal of medicine*. Mar 3 1966;274(9):481-6. doi:10.1056/nejm196603032740902
237. Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone--results of a multicenter phase III study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 20 2010;28(27):4207-13. doi:10.1200/JCO.2009.26.8896
238. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1 2008;26(16):2767-78. doi:10.1200/jco.2007.15.0177
239. Graham GG, Kannangara DR, Stocker SL, et al. Understanding the dose-response relationship of allopurinol: predicting the optimal dosage. *British journal of clinical pharmacology*. Dec 2013;76(6):932-8. doi:10.1111/bcp.12126
240. LaRosa C, McMullen L, Bakdash S, et al. Acute renal failure from xanthine nephropathy during management of acute leukemia. *Pediatric nephrology (Berlin, Germany)*. Jan 2007;22(1):132-5. doi:10.1007/s00467-006-0287-z
241. Levin NW, Abrahams OL. Allopurinol in patients with impaired renal function. *Annals of the rheumatic diseases*. Nov 1966;25(6 Suppl):681-7.
242. Crews KR, Zhou Y, Pauley JL, et al. Effect of allopurinol versus urate oxidase on methotrexate pharmacokinetics in children with newly diagnosed acute lymphoblastic leukemia. *Cancer*. Jan 1 2010;116(1):227-32. doi:10.1002/cncr.24681
243. Feng X, Dong K, Pham D, Pence S, Inciardi J, Bhutada NS. Efficacy and cost of single-dose rasburicase in prevention and treatment of adult tumour lysis syndrome: a meta-analysis. *Journal of clinical pharmacy and therapeutics*. Aug 2013;38(4):301-8. doi:10.1111/jcpt.12061
244. Shaikh SA, Marini BL, Hough SM, Perissinotti AJ. Rational use of rasburicase for the treatment and management of tumor lysis syndrome. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners*. Apr 2018;24(3):176-184. doi:10.1177/1078155216687152
245. Lopez-Olivo MA, Pratt G, Palla SL, Salahudeen A. Rasburicase in tumor lysis syndrome of the adult: a systematic review and meta-analysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Sep 2013;62(3):481-92. doi:10.1053/j.ajkd.2013.02.378
246. Takai M, Yamauchi T, Ookura M, et al. Febuxostat for management of tumor lysis syndrome including its effects on levels of purine metabolites in patients with hematological malignancies - a single institution's, pharmacokinetic and pilot prospective study. *Anticancer research*. Dec 2014;34(12):7287-96.
247. Spina M, Nagy Z, Ribera JM, et al. FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. *Ann Oncol*. Oct 2015;26(10):2155-61. doi:10.1093/annonc/mdv317
248. Wetzstein GA. Tumor Lysis Syndrome: A Treatment Guide. *Oncology Special Edition*. 2004;7:125-128.
249. Pession A, Masetti R, Gaidano G, et al. Risk evaluation, prophylaxis, and treatment of tumor lysis syndrome: consensus of an Italian expert panel. *Advances in therapy*. Aug 2011;28(8):684-97. doi:10.1007/s12325-011-0041-1

# **ADULT SARCOMAS**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, management, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for adult patients with sarcoma.
2. Adjust treatment and monitoring plans as needed based on the tumor genetics and pharmacokinetics of anticancer and supportive-care agents (e.g., methotrexate).
3. Develop an appropriate plan for preventing, monitoring, and managing common problems associated with the treatment of adult patients with cancer, including neurotoxicity from ifosfamide and hemorrhagic cystitis.



## BONE CANCER

### **Patient Case #1:**

TB is a 54-year-old male who presented with left knee pain that remained persistent and intermittent after he had fallen during a soccer game. NSAIDs and a lidocaine patch were not beneficial and the pain continued to worsen, leaving TB unable to play soccer. TB's primary care physician orders radiographic imaging after physical therapy. Knee radiograph demonstrates a lytic lesion in the left tibia, approximately 4 cm. MRI showed a defined area of marrow replacement by the lesion. An open biopsy is performed revealing the diagnosis of high-grade osteosarcoma.

The treatment plan for TB is neoadjuvant chemotherapy followed by surgery.

### **Which of the following would be the most appropriate regimen for neoadjuvant therapy for TB?**

- A. Cisplatin and doxorubicin
- B. High dose methotrexate, cisplatin and ifosfamide
- C. Cyclophosphamide and topotecan
- D. Ifosfamide and etoposide

### **I. Osteosarcoma<sup>1</sup>**

- A. Most common primary malignant bone tumor in children and young adults. In adults > 65 years, osteosarcoma can develop as a secondary malignancy related to Paget's disease of the bone.
- B. When osteosarcoma is suspected, the biopsy should always be performed by an experienced surgeon or radiologist to minimize the risk of pathologic fracture.

### **II. Prognosis**

- A. Tumor site and size – larger tumor and axial site of disease worse outcome
- B. Tumor necrosis (>90%) following neoadjuvant chemotherapy: good histologic response
- C. Primary metastasis at diagnosis
- D. Completeness of surgical resection
- E. Age > 40 is worse outcome

### **III. Treatment**

- A. Osteosarcoma<sup>2,3</sup>
  - 1. Surgery – Limb-sparing procedures for extremity lesions are performed when surgically feasible. Amputation is reserved for patients who would gain functional independence from a prosthesis or in whom limb-sparing procedures are not surgically feasible. 15% of patients are cured with surgery as only therapy.
  - 2. Radiation – Osteosarcoma is relatively resistant to radiation, therefore minimizing the role for radiation as an alternate primary therapy to surgery. Role is relegated to combination therapy with chemotherapy in limited circumstances and palliation.
  - 3. Chemotherapy – **preoperative chemotherapy is a Category 1 NCCN recommendation**
    - a. Improves cure rate when given with surgery upwards of 75%.

- 1) Active agents – cisplatin, cyclophosphamide, doxorubicin, ifosfamide, and high-dose methotrexate (leucovorin rescue is required). See selected initial regimens below.
  - a) The addition of ifosfamide and etoposide increases response but does not improve overall survival<sup>4</sup>
- 2) **Two to six cycles of neoadjuvant therapy are recommended prior to surgery for all patients with resectable osteosarcoma.** Response to neoadjuvant therapy should be evaluated from the surgical pathologic specimen.
  - a) With good histologic response (>90% tumor necrosis), adjuvant chemotherapy may be used in sequence following surgery for 2 to 12 cycles.
  - b) The same chemotherapy regimen is used for a good pathologic histologic response
  - c) Patients with poor histological response may require more intensive therapy. Colony stimulating factors are often used to maintain dose and schedule.

B. Selected Initial Regimens<sup>3,5-7</sup>

1. Below are first-line regimens that are utilized in the neoadjuvant and adjuvant setting for patients that are able to have their sarcoma surgically resected.
2. **NCCN® Category 1 recommendations include either cisplatin with doxorubicin or (MAP) cisplatin, doxorubicin and high-dose methotrexate<sup>3</sup>.**
  - a. **Generally, this decision between the two regimens is based on expected tolerance. Typically, patients older than age 40 typically receive cisplatin and doxorubicin alone.**
3. If the tumor is not able to be resected or the patient has metastatic disease at diagnosis, the same regimens are recommended without the surgery component. This is due to cisplatin, doxorubicin, methotrexate, epirubicin and ifosfamide having the most activity for osteosarcoma.

Table 1. Example Schedules of Selected Regimens for Osteosarcomas <sup>3</sup>	
Regimen	Schedule
<b>MAP (M- methotrexate, A- anthracycline (doxorubicin), P – Platinol (cisplatin)</b>  Methotrexate 12 g/m <sup>2</sup> IV (max 20 grams) IV over 4 hours Day 1, Leucovorin 15 mg IV over 15 minutes on Day 2 starting 24 hours from initiation of methotrexate infusion and continuing q6 hours until methotrexate level < 0.05 micromol/L and at least 8 doses. Cisplatin 100 mg/m <sup>2</sup> IV over 2 hours on Day 1 and doxorubicin 75 mg/m <sup>2</sup> IV push on Day 1 or doxorubicin 25 mg/m <sup>2</sup> IV continuous infusion over 24 hours Days 1-3	High-dose methotrexate weeks 4, 5, 9, and 10 (neoadjuvant) followed by weeks 15, 16, 20, 21, 24, 25, 28 and 29 (adjuvant( or on weeks 4, 5, 9, 10, 15, 16, 20, 21, 24, 25, 28, and 29 (metastatic) and doxorubicin/ cisplatin weeks 1 and 6 (neoadjuvant) followed by weeks 12 and 17 (adjuvant) or on weeks 1, 6, 12, and 17 (metastatic), and doxorubicin on weeks 22 and 26 (adjuvant or metastatic) for a duration of 29 weeks.
<b>Cisplatin/Doxorubicin</b>  Cisplatin 100 mg/m <sup>2</sup> IV over 2 hours on Day 1 and doxorubicin 75 mg/m <sup>2</sup> IV push on Day 1 or doxorubicin 25 mg/m <sup>2</sup> IV continuous infusion over 24 hours Days 1-3	*21-day cycle for 2 cycles (neoadjuvant) and 4 cycles (adjuvant) for a total of 6 cycles or 6 cycles total (metastatic)

C. Selected **second line** regimens

1. Osteosarcoma

a. Preferred Regimens:

- 1) **(IE)** Ifosfamide 3 g/m<sup>2</sup> IV daily x 4 days, given with mesna, etoposide 75 mg/m<sup>2</sup> IV daily x 4 days Q 21-28 days. ORR = 48%.<sup>9</sup> (NCCN Category 2A)

a) Other Ifosfamide/Etoposide regimens:

- Ifosfamide 1800 mg/m<sup>2</sup> IV daily x 5 days, given with mesna, etoposide 100 mg/m<sup>2</sup> IV daily x 5 days Q 21 days<sup>10</sup>
- Ifosfamide 3.5 g/m<sup>2</sup> IV daily x 5 days, given with mesna, etoposide 100 mg/m<sup>2</sup> IV daily x 5 days Q 21 days<sup>11</sup>

- 2) Regorafenib 160 mg PO daily x 21 days in a 28 day cycle. **(NCCN Category 1)**

a) A phase 2 trial of regorafenib in specific sarcoma subtypes, including advanced osteosarcoma in a randomized manner versus placebo. (SARC024)<sup>3,12</sup>

- 42 patients enrolled with a median age of 37 yo (range, 18-76 yo)
- Patients received on average 2.3 prior lines of therapy
- Primary endpoint of PFS was 3.6 months for regorafenib and 1.7 months for placebo (P=0.17)
- 20 patients required dose interruption (13 assigned to regorafenib, 7 assigned to placebo). Dose was reduced for 12 patients assigned to regorafenib and 1 assigned to placebo. Median dose at end of blinded treatment was 120 mg (range, 80-160 mg) for regorafenib and 160 mg (range, 40 -160 mg) for placebo.

b) **SARC024 demonstrated a benefit of regorafenib in patients with relapsed metastatic osteosarcoma, with a doubling of median PFS compared to placebo. Additionally, NCCN added regorafenib as a category 1 preferred regimen for second-line relapsed/refractory or metastatic disease.**

- 3) Sorafenib 400 mg PO daily until disease progression

b. Other Recommended Regimens:

- 1) Gemcitabine 675 mg/m<sup>2</sup> IV days 1 and 8, docetaxel 75 – 100 mg/m<sup>2</sup> IV day 8, both Q21 days. ORR = 29%, median response duration was 4.8 months.<sup>13</sup>
- 2) Cyclophosphamide 250 mg/m<sup>2</sup>/day IV plus topotecan 0.75 mg/m<sup>2</sup> IV /day, each daily for 5 days Q21 days. Partial response in 2/18.<sup>14</sup>
- 3) Cabozantinib (Cabometyx<sup>TM</sup>) 60 m PO daily on days 1-28 of a 28 day cycle
  - a) A phase 2 trial of cabozantinib for advanced ewing sarcoma or osteosarcoma in a single-arm study (CABONE)<sup>15</sup>
    - 90 patients (45 with osteosarcoma) were enrolled

- 12% (5 of 42 patients) had an objective response (all partial responses) and 33% (14 of 42 patients) had 6 month non-progression.
  - Median PFS: 6.7 months
  - Median OS: 10.6 months
- 4) Gemcitabine 1200 mg/m<sup>2</sup> IV days 1 and 8 at a fixed dose rate of 10 mg/m<sup>2</sup>/min Q21 days.<sup>44</sup>
  - 5) Sorafenib 400 mg PO BID plus everolimus 5 mg PO daily continuously. 38 patients were enrolled, 17 were free of progression at 6 months.<sup>17</sup>
- c. Useful in Certain Circumstances:
- 1) Cyclophosphamide 4 g/m<sup>2</sup> once on day 1 with mesna plus etoposide 200 mg/m<sup>2</sup> IV /day on days 2,3,4 Q21-28 x 2 cycles. ORR = 19%, 1 year OS = 50%.<sup>18</sup>
  - 2) Ifosfamide 1,800 mg/m<sup>2</sup> IV daily x 5 days, given with mesna, carboplatin 400 mg/m<sup>2</sup> IV/day days 1-2, etoposide 100 mg/m<sup>2</sup> IV daily x 5 days. ORR = 51%, OS at 1 and 2 years was 49% and 28%. Trial included other sarcoma subtypes when reporting OS results.<sup>19</sup>
  - 3) High-dose methotrexate followed by ifosfamide/etoposide<sup>20</sup>
    - a) Weeks 1, 2, 3, 7, 8, 9, 13, 14, 15, 19, 20, and 21: Methotrexate 12 g/m<sup>2</sup> (maximum 20 grams) IV over 4 hours on day 1 with leucovorin 15 mg IV over 15 minutes on day 2 starting 24 hours after methotrexate infusion and continuing every 6 hours until methotrexate level < 0.05 micromol/L and at least 8 total doses
    - b) Weeks 4, 10, 16, and 22: Ifosfamide 3 g/m<sup>2</sup> IV daily x 4 days, given with mesna, etoposide 75 mg/m<sup>2</sup> IV daily x 4 days
  - 4) Sm<sup>153</sup>-EDTMP (high-dose samarium-153 ethylene diamine tetramethylene phosphate) for relapsed or refractory disease beyond second-line therapy<sup>21</sup>

**Patient Case #1, continued:**

**Answer: A.** TB should receive chemotherapy with cisplatin and doxorubicin. Doxorubicin and cisplatin are typical agents, with or without high dose methotrexate. Generally, high dose methotrexate is reserved for patients under 40. Cyclophosphamide + topotecan would be considered options for recurrence based on additional patient characteristics as well as ifosfamide and etoposide would be preferred for relapsed/refractory disease.

**Patient Case #2:**

JS a newly diagnosed 25 year-old-male with metastatic osteosarcoma is inpatient to start his first dose of high dose methotrexate as part of MAP.

**What is the most appropriate treatment recommendation at this time?**

- A. Start premedications to alkalinize the urine to pH < 7 prior to methotrexate initiation
- B. Hold the patient's thiazide diuretic for at least 2 days prior to methotrexate and until after clearance
- C. Reassure team that the patient's pleural effusion will not affect methotrexate clearance
- D. Restrict fluid intake

#### IV. Considerations with High Dose Methotrexate (MTX) Therapy<sup>22</sup>

- A. High dose therapy (500-12,000 mg/m<sup>2</sup>) **requires leucovorin rescue until MTX levels are less than 0.1mM (or  $1 \times 10^{-7}$ M) or 0.05mM (or  $5 \times 10^{-8}$  M)**. Depending on the algorithms followed targets of nmol/L may be listed. (0.1 mM = 100 nmol/L)
1. **High dose MTX is lethal unless reversed by leucovorin rescue initiated within 42 hours.**
  2. Calcium leucovorin is a reduced folate. It can replenish the supply of folate metabolites depleted by MTX. Leucovorin enters cells by passive diffusion, requiring serum concentrations to be much higher than MTX for rescue effect. It allows DNA synthesis to begin again even in the presence of MTX. This process of recovery of DNA synthesis is called "rescue."
  3. Leucovorin is available PO, IM, and IV. Oral bioavailability varies, good at doses less than 35 mg, but above that, ranges from 5-50%. Half-life is about 3 hours, widely distributed, metabolized in tissues.
  4. Levo-leucovorin is an IV isomer of leucovorin and is dosed at 50% of the usual dose of leucovorin.
  5. Leucovorin dose is generally started at 15 mg/m<sup>2</sup> and titrated according to the MTX serum concentration. Generally started 20-24 hours after the end of the infusion of MTX. The rescue (i.e. leucovorin + hydration/alkalinization) can be stopped when the concentration of MTX is less than  $1 \times 10^{-7}$ M (0.1  $\mu$ M), although some algorithms recommend concentrations of less than  $5 \times 10^{-8}$  M (0.05  $\mu$ M).
  6. Dose of leucovorin may need to be increased in the case that methotrexate clearance is delayed.

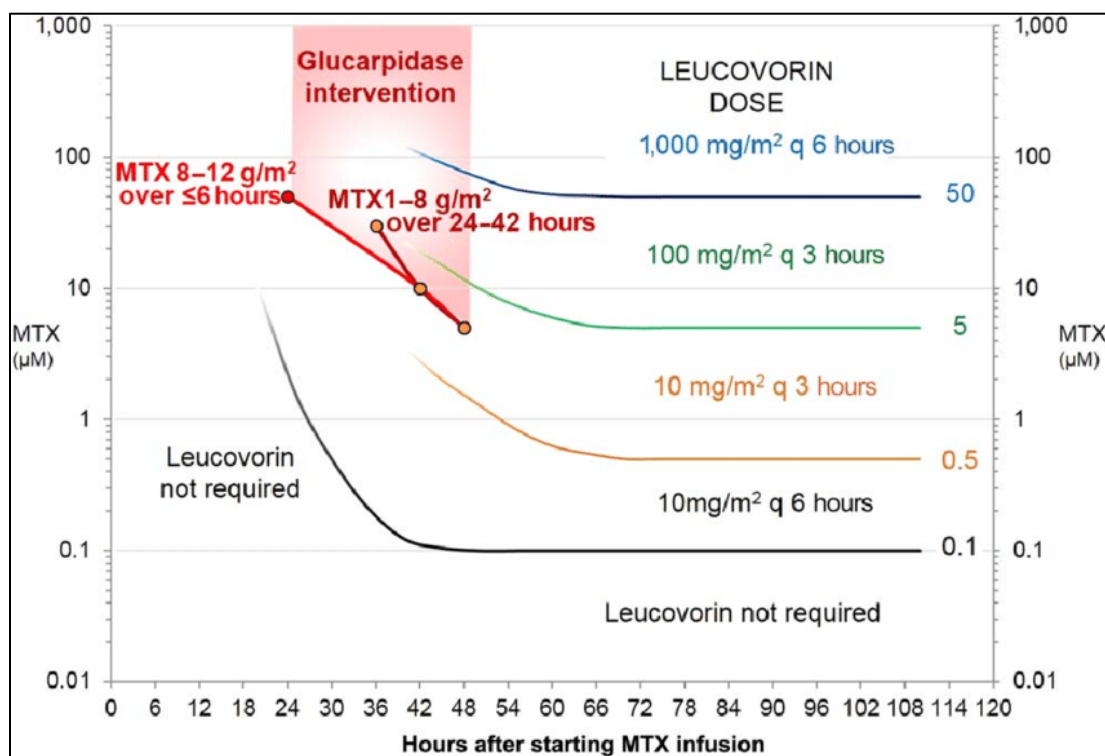


Figure 1. Algorithm for leucovorin rescue for high-dose methotrexate

- B. Precautions:

1. **Third space fluids such as ascites, edema, or pleural effusions can significantly influence the volume of distribution and terminal  $t_{1/2}$ .** High dose methotrexate should not be given in these scenarios. However, if it must be given or third spacing is discovered after drug administration, these patients will usually require prolonged leucovorin rescue until all methotrexate has been cleared.
  2. Renal tubular necrosis is not prevented by leucovorin. **Urine alkalinization and vigorous hydration are required to increase solubility of methotrexate and its metabolites.**
    - a. 2-3 liters/ $m^2$ /day is recommended
    - b. Add sodium bicarbonate to fluids or utilize oral sodium bicarbonate tablets to maintain urine pH
    - c. **Achieve urine pH > 7 prior to the initiation of high dose methotrexate**, and should be maintained until the agent is cleared
    - d. Urine pH checks should occur with each void
- C. Drug Interactions
1. Drugs that are highly protein bound may displace MTX from albumin and increase toxicity (sulfonamides, salicylates, phenytoin, and tetracycline).
  2. Weak organic acids (penicillins) increase toxicity<sup>24</sup>
  3. NSAIDs compete for renal excretion of MTX and increase levels.
  4. Vitamin C will acidify the urine and may increase MTX levels
  5. Proton pump inhibitors may inhibit methotrexate clearance<sup>25</sup>

Table 2. Drug Interactions that Decrease High-dose Methotrexate Clearance*		
Drug/Class	Interaction Details	Recommendation
Bactrim/ Sulfonamides	Synergistic anti-folate effects, protein binding displacement, decreases renal tubular elimination	Avoid within 2 days and until methotrexate has cleared
Ciprofloxacin	Inhibits renal tubular transport of methotrexate	Avoid within 1 day and until methotrexate has cleared
Thiazide Diuretics	Reduces renal excretion of MTX	Avoid within 2 days and until methotrexate has cleared
NSAIDs	Inhibits renal transport proteins and/or decreases renal perfusion	Avoid if possible, but if taken hold day of and until methotrexate has cleared
Penicillins	Inhibits renal tubular transport of methotrexate	Avoid if possible, but if taken hold day of and until methotrexate has cleared
Proton Pump Inhibitors	Inhibits H <sup>+</sup> /K <sup>+</sup> -ATPase in the kidney, which blocks the active secretion of methotrexate	Avoid if possible, but if taken hold day of and until methotrexate has cleared
Salicylates (ASA, sulfasalazine, salsalate)	Competes with MTX for renal tubular secretion and reduce renal perfusion	Avoid within 10 days and until methotrexate has cleared (hold ASA 81 mg day of MTX)
*This table does not include all drug interactions with high dose methotrexate.		

#### Patient Case #2:

B is the correct answer. The patient's thiazide diuretics should be held for at least 2 days prior to methotrexate and until after clearance. Premedications to alkalinize the urine to pH > 7 prior to methotrexate initiation. Pleural effusions can cause third spacing and can significantly influence the volume of distribution and terminal t<sub>1/2</sub>. High dose methotrexate should not be given in these scenarios. However, if it must be given or third spacing is discovered after drug administration, these patients will usually require prolonged leucovorin rescue until all methotrexate has been cleared. Hydration should be encouraged to help with clearance.

#### Patient Case #3:

JS a newly diagnosed 25 year-old-male with metastatic osteosarcoma is inpatient and received his first dose of high dose methotrexate as part of MAP. His methotrexate dose was 12,000 mg/m<sup>2</sup> IV over 4 hours, the 48 hour methotrexate level was 5.1 µM. His baseline serum creatinine was 0.9 mg/dL and currently is 1.2 mg/dL.

**What is the most appropriate treatment recommendation at this time?**

- A. Increase leucovorin
- B. Start glucarpidase
- C. Increase sodium bicarbonate infusion to obtain a urine pH >8
- D. Start dexrazoxane

- D. Consider glucarpidase (also known as carboxypeptidase G2) for toxic methotrexate levels with renal impairment<sup>26, 27</sup>
1. Carboxypeptidase enzyme approved by FDA in 2012 for toxic plasma methotrexate levels in patients with delayed clearance due to renal impairment
  2. MOA: recombinant bacterial enzyme that cleaves methotrexate into inactive metabolites
  3. Not to be used in patients who exhibit the expected clearance of methotrexate (plasma methotrexate concentrations within 2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered); patients with normal or mildly impaired renal function because of the potential risk of subtherapeutic exposure to methotrexate
    - a. Note that glucarpidase use and stock is typically restricted at most hospitals. Hospital sharing and dropship ordering are common practices due to infrequency of use and cost. The current average wholesale price (AWP) of glucarpidase is \$27,000 per 1,000 unit vial. Therefore, one dose of glucarpidase in a 70 kg patient (i.e., four vials needed to supply 3,500 units) may cost >\$100,000 if dosed per the FDA approved dosage
  4. Dose is 50 units/kg IV over 5 minutes
  5. Main efficacy trial included sarcoma patients
  6. **Leucovorin should not be administered within 2 hours before or after a glucarpidase dose because leucovorin is a substrate for glucarpidase.**
  7. Alkalinization/hydration and leucovorin should be continued until methotrexate concentration is maintained below the leucovorin treatment threshold for a minimum of 3 days. For the first 48 hours after glucarpidase administration, administer the same dose of leucovorin dose as given prior to glucarpidase, beyond 48 hours, administer leucovorin based on methotrexate concentration.
    - a. Immunoassay for methotrexate levels is unreliable for 48 hours after glucarpidase administration
  8. A pooled analysis demonstrated in patients with renal toxicity and delayed methotrexate clearance that levels were lowered to < 1 µM in 59% of patients and that 64% of patients with grade 2 renal impairment recovered to grade 0-1 at 12.5 days (median)<sup>28</sup>
  9. No direct comparison with dialysis to date
  10. Recent consensus guideline was published with recommendations for clinical use of glucarpidase based on expert opinions in the field and review of the literature.<sup>29</sup>
    - a. **Glucarpidase administration should optimally occur within 48-60 hours from the start of the methotrexate infusion.**
    - b. NCCN guidelines strongly recommend the use of glucarpidase for patients receiving high-dose methotrexate and experience delayed elimination due to renal impairment.<sup>3</sup>
    - c. Methotrexate infusions over 24-42 hours (1-8 g/m<sup>2</sup>)
      - 1) After a 24 hour infusion, if the plasma methotrexate concentration is > 120 microM/L at the end of the infusion or a ≥ 50% increase in serum creatinine over baseline a level should be drawn at 36 hours.



- a) If the 36-hour level is > 30 microM/L, the 42-hour level > 10 microM/L or 48-hour level > 5 microM/L and the serum creatinine is elevated, glucarpidase may be indicated.
- 2) After a 36-42 hour infusion of methotrexate, if the methotrexate level is > 5 microM/L at 48 hours, glucarpidase may be indicated.
- 3) Methotrexate infusions over  $\leq 6$  hours (8-12 g/m<sup>2</sup>)
  - a) If the 24-hour concentration is > 50 microM/L, 36-hour level > 30 microM/L, 42-hour level > 10 microM/L or 48-hour level > 5 microM/L and serum creatinine is elevated relative to baseline, glucarpidase may be indicated.
- d. Leucovorin should be dosed according to standard guidelines until glucarpidase can be given. Leucovorin should be held 2 hours prior to and 2 hours after glucarpidase administration.
- e. Repeat administration of glucarpidase within 48 hours of the first dose is not recommended due to decreased efficacy.

**Patient Case #3:**

**Answer: A.** Glucarpidase would not be considered yet in this patient as the patient's current serum creatinine compared to baseline has not elevated to a degree where renal toxicity is of concern. Increasing the leucovorin dose is necessary to prevent toxicity as the patient's 48 hour methotrexate level is great than 5  $\mu$ M and would be the most appropriate answer at this time. Increasing sodium bicarbonate is an option but this change alone without increasing the leucovorin dose will not effectively reduce serum methotrexate levels in a timely manner given the patient's current methotrexate level. Dexrazoxane does not have role in improving methotrexate clearance, instead is an agent recommended for extravasation of doxorubicin or to prevent cardiomyopathy as a result of doxorubicin therapy.

**V. Other bone sarcomas<sup>2,3</sup>**

- 1. Chondrosarcoma
  - a. Surgical excision is primary therapy
  - b. High-grade histology can be treated with chemotherapy but poor response; recurrence can be treated with radiation therapy.
  - c. For unresectable or metastatic chondrosarcoma, de-differentiated lesions chondrosarcoma – treat like osteosarcoma; mesenchymal chondrosarcoma – treat like Ewing's Sarcoma (discussed in the Pediatric Oncology Module).
    - 1) Subtypes of chondrosarcoma are treated very differently (i.e. mesenchymal, dedifferentiated, conventional)
  - d. Dasatinib was studied in a phase 2 trial enrolling patients with multiple rare types of sarcoma including chondrosarcoma and chordoma<sup>30</sup>
    - 1) Primary outcome was obtaining at least a 50% 6-month progression free survival rate
      - a) 6-month PFS: 48% with median PFS of 5.8 months (failed to meet primary endpoint)

- b) Subgroup of chondrosarcoma and chordoma patients had 18% objective response rate with more than 10% having stable disease for 1 year.
    - 2) Dasatinib added to NCCN as an option based on subgroup analysis as a potential option for metastatic or systemic recurrence
  - e. Pazopanib was evaluated for metastatic chondrosarcoma in a prospective, phase 2 study.
    - 1) Forty-seven patients were enrolled with conventional chondrosarcoma.<sup>31</sup>
      - a) Disease control rate at 16 weeks: 43%
      - b) Median OS: 17.6 months
      - c) Median PFS: 7.9 months
    - 2) Pazopanib was added to NCCN guidelines as an option for metastatic and widespread disease
  - f. Ivosidenib can be considered for susceptible *IDH1* mutations in chondrosarcoma based on a phase 1 multicenter, open-label, dose-escalation and expansion study. Ivosidenib 500 mg PO daily taken continuously until disease progression.<sup>32</sup>
    - 1) N = 21
      - a) Median PFS was 5.6 months (95% CI: 1.9 – 7.4 months); PFS rate at 6 months was 39.5%
      - b) 52% of patients experienced stable disease.
      - c) Treatment-emergent adverse events were mostly grade 1 or 2.
    - 2) Ivosidenib may be considered for conventional and dedifferentiated chondrosarcoma
2. Chordoma<sup>3</sup>
- a. Surgical excision is primary therapy
  - b. Radiation can be used with surgery for resectable sacral and base of skull tumors
  - c. Radiation is the primary treatment for unresectable tumors; unresponsive to chemotherapy
  - d. Recurrent tumors can be treated with surgery, radiation or selected targeted therapies such as: imatinib, dasatinib and sunitinib as NCCN other recommended regimens followed by imatinib with cisplatin or sirolimus, erlotinib, lapatinib (EGFR-positive), sorafenib as useful in certain circumstances based on pathways thought to be responsible for chordoma development.
  - e. Dedifferentiated should be treated as STS.
3. Undifferentiated Pleomorphic Sarcoma of Bone
- a. Surgery for first-line therapy
  - b. Osteosarcoma-like regimens may be used for both neoadjuvant and adjuvant chemotherapy (NCCN Category 2B recommendation)
4. Giant Cell Tumor of Bone
- a. Surgery for first-line therapy or serial arterial embolizations

- b. Radiation for local recurrence or inoperable lesion
- c. Denosumab (120 mg subcutaneous every 4 weeks with an additional 120 mg on days 8 and 15 of the first month)
- d. Interferon/peginterferon can be treatment options

## SOFT TISSUE SARCOMAS (STS)

### Patient Case #4:

WJ is a 45-year-old man who presented with a gnawing pain in his left thigh. He can feel a “knot,” that he claims has grown over the past several months. Core needle biopsy reveals a high grade, synovial sarcoma. Unfortunately, surgery was incomplete with positive margins and he was treated with adjuvant radiation therapy (RT). He has no significant comorbidities and has an ECOG status of 0. The multidisciplinary team recommends chemotherapy at this time. You are asked to counsel him on his new chemotherapy regimen.

### Which chemotherapeutic agent(s) should be part of WJ’s adjuvant regimen?

- A. Gemcitabine and docetaxel
- B. Regorafenib
- C. Ifosfamide and doxorubicin
- D. Doxorubicin

### I. Etiology and Pathogenesis

- A. The etiology of STS is largely undetermined; however, factors such as genetic predisposition, infectious diseases, occupational chemicals, and radiation therapy are associated with the development of disease.<sup>33</sup>
  - 1. Prior radiation therapy to the affected area is a risk factor for STS<sup>34</sup>
  - 2. Genetic Predisposition to STS

#### Selected Genetic Predisposition to STS<sup>35-37</sup>

Genetic Predisposition to STS	Associated STS Subtype(s)
17q11.2 (NF-1 gene) – neurofibromatosis type I	Malignant peripheral nerve sheath tumor, GIST and rhabdomyosarcoma
13q14.2 (Rb-1 gene) – retinoblastoma	Leiomyosarcoma, rhabdomyosarcoma
17p13.1 (TP53 gene) – Li Fraumeni syndrome	Rhabdomyosarcoma (usually pediatric), fibrosarcoma, Undifferentiated pleomorphic sarcoma
5q21 (APC gene) – Gardner’s syndrome	Desmoid tumors

- 3. Cytogenetic aberrations associated with STS include those listed in the table below:

#### Selected Cytogenetic Aberrations Associated with STS<sup>35,38,39</sup>

Cytogenetic Aberrations Associated with STS
<p><i>Cytogenetic aberration; gene – associated STS</i></p> <p>t(12;16)(q13;p11); TLS-CHOP fusion gene – myxoid or round cell liposarcomas</p> <p>t(X;18)(p11;q11); SS18-SSX1/SSX2 fusion – synovial sarcoma</p> <p>t(12;22)(q13;q12); EWSR1-ATF1 – clear cell sarcoma</p> <p>t(11;22)(p13;q12); EWSR1-WT1 – desmoplastic small round cell tumor</p> <p>Multiple complex karyotypes – Malignant fibrous histiocytoma (MFH)/undifferentiated pleomorphic sarcoma<sup>40</sup></p> <p>t(2,13)(q35;q14); PAX3-FKHR and PAX7-FKHR – alveolar rhabdomyosarcoma</p>

## B. Biopsy for STS

1. Specific subtype STS diagnosis and grade of disease is important to dictate treatment. Determination of histologic grade evaluates tumor cell differentiation, mitotic activity, and extent of necrosis using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) or AJCC/National Cancer Institute (NCI) system.
2. If sarcoma is suspected, the biopsy should be performed by an experienced surgeon (or interventional radiologist) in order to prevent tumor rupture or tumor tracking through the biopsy track.<sup>36</sup>

## C. Pathologic subtypes:

1. Heterogeneous group of tumors arising from mesenchymal cell origin
2. Sarcoma accounts for approximately 1% of adult malignant solid tumors and > 20% of pediatric solid malignant tumors.<sup>34</sup>
3. The three most common subtypes are **undifferentiated pleomorphic sarcoma**, **liposarcoma**, and **leiomyosarcoma**

**Incidence of Soft Tissue Sarcoma Subtypes (1978-2001)<sup>41,42</sup>**

Histologic Subtype	%
Leiomyosarcoma (LMS)	23.9
Undifferentiated pleomorphic sarcoma <sup>40</sup>	17.1
Sarcoma, not otherwise specified (NOS)	12.8
Liposarcoma	11.5
Dermatofibrosarcoma	10.5
Rhabdomyosarcoma	4.6
Angiosarcoma	4.1

## II. Treatment

- A. Surgery – surgical resection is the cornerstone of therapy for STS management. Treatment goals are to achieve cure, avoid local recurrence, maximize function and minimize morbidity. Classic approach is to achieve a 2 cm margin in all directions surrounding the tumor. With this approach alone, local recurrence rates can be as high as 30-50%.<sup>43</sup> Failure to achieve adequate margins may account for a higher local recurrence rate.<sup>44</sup>
  1. Limb-sparing surgery (+ radiation) vs. amputation – higher local recurrence rate in the limb-sparing surgery arm but no difference in overall survival. Most common type of surgery offered.
  2. Amputation – reserved for tumors unable to be resected by any other surgical approach and without metastatic disease; 95% of patients are able to have limb-sparing surgery.
  3. Radical excision – not precisely defined term although the use of a 5 cm wide margin is commonly used if feasible; decreases local recurrence to 25 - 30%. Radical excision is not routinely necessary.
  4. Anatomic compartment excision – local recurrence rate of 10 to 20%. Compartment excision is not routinely necessary.
- B. Radiation Therapy (RT) (See Table: Special Cases Where Radiation Should Be Considered) – can be used as primary therapy, preoperative or post-operative treatment. Most commonly combined with

surgery to decrease the need for a radical excision to maintain functionality and decrease cosmetic deformity or as an alternative to amputation. Typically, tumors have a slow rate of regression following radiation therapy. Notable toxicities include: bone tissue damage/fracture, edema, fibrosis, functional impairment, and impaired wound healing.<sup>45</sup>

1. Newer RT techniques such as brachytherapy, intraoperative RT and intensity-modulated RT (IMRT) have improved outcomes over traditional external beam RT.
2. 2018 meta-analysis of 3958 patients with resectable STS in different anatomic locations evaluated the effects of external beam RT compared to no radiation in both the preoperative and postoperative setting.<sup>46</sup>
  - a. External beam RT reduced local recurrence and improved overall survival for retroperitoneal STS
  - b. External beam RT reduced local recurrence for STS of extremity, head and neck or trunk wall (OR 0.49; p = 0.002)
  - c. Local recurrence rates were lower with preoperative RT than postoperative RT for retroperitoneal STS (OR 0.03; p=0.02)
3. In a comparison of pre- and postoperative external beam radiation in STS of the limbs, preoperative radiation had a small survival advantage (log rank p=0.0481), but significantly more wound complications (35% preoperative vs. 17% postoperative, 95% CI 5-30, p=0.01)<sup>47</sup>
4. A retrospective review evaluated patients receiving preoperative RT compared to preoperative RT with a postoperative boost and showed no difference in rates of local recurrence, distant metastasis or death indicating that a post-operative RT boost is not necessary.<sup>48</sup>

#### Special Cases Where Radiation Should Be Considered<sup>35</sup>

Clinical Scenario	Therapy
Positive margins of resection or close resection margins (less than 1 cm)	Brachytherapy and external beam radiotherapy have been utilized and case series data suggest benefit with radiotherapy following surgery compared to surgery alone. <sup>49</sup>
Small soft tissue sarcomas	Excisions with negative margins do not appear to benefit from adjuvant radiation therapy; positive margins may benefit from adjuvant radiation; studies are inadequate to answer the question definitively.
Soft tissue sarcomas of the hands and feet	The complexity of the surgery in the distal extremities makes wide excision difficult. More conservative surgery with adjuvant radiation is standard of practice.
Definitive radiation	Reserved for patients where surgical resection is not an option. Local control and survival decreases with increasing tumor size.

#### C. Chemotherapy

1. Soft tissue sarcoma comprises greater than 70 histologies. Given the greater number of histologies for this tumor type one should consider the heterogeneity of the data shared to support the below chemotherapy options and the impact on results for all patients, especially those with less common histologies.

2. Preoperative therapy / Neoadjuvant therapy – **Rationale for administering is to decrease tumor size prior to surgery allowing for less extensive surgery, treating micrometastatic disease earlier in disease course prior to development of drug resistance, administering chemotherapy prior to surgery-induced damage to the local vasculature surrounding the tumor site and discerning pathologic tumor response to chemotherapy following resection.**
  - a. Data published consists mainly of single institution retrospective case series with inconsistent results.<sup>50</sup>
  - b. Only one randomized prospective trial in which 150 patients with potentially resectable STS were randomized to definitive local treatment alone versus neoadjuvant chemotherapy with doxorubicin and ifosfamide followed by definitive local treatment.
    - 1) Median follow-up was 7.3 years
    - 2) Estimated 5-year disease-free survival (DFS) was 52% for the no chemotherapy arm and 56% for the chemotherapy arm ( $p = 0.3548$ ) with a corresponding 5-year overall survival was 64% and 65% ( $p=0.2204$ ).<sup>50</sup>
  - c. International, open-label, randomized, phase 3 trial with STS of extremities or trunk wall comparing standard chemotherapy vs. histotype-tailored chemotherapy in the preoperative, neoadjuvant setting<sup>51</sup>
    - 1) 287 patients randomized to standard chemotherapy of 3 cycles of epirubicin + ifosfamide OR histotype-tailored chemotherapy as below prior to definitive therapy
      - a) Myxoid liposarcoma: trabectedin
      - b) Leiomyosarcoma: gemcitabine + dacarbazine
      - c) Synovial sarcoma: ifosfamide
      - d) Malignant peripheral nerve sheath tumors: etoposide + ifosfamide
      - e) Undifferentiated pleomorphic sarcoma: gemcitabine + docetaxel
    - 2) Median follow-up of 12.3 months, projected disease-free survival at 46 months was 62% in standard chemotherapy arm and 38% in histotype-tailored chemotherapy group (HR 2;  $p=0.004$ )
    - 3) Study was closed to recruitment in advance for futility, but potential signal that traditional chemotherapy could have a role in the neoadjuvant setting.
  - d. It is unclear which patients will benefit most from neoadjuvant chemotherapy alone. Outside of a clinical trial, neoadjuvant therapy is reserved for highly selected patients with the goal of avoiding more aggressive surgery or amputation.
3. Postoperative therapy / Adjuvant therapy – The role of adjuvant chemotherapy in STS has been explored by a number of randomized trials since the late 1970's. These studies varied in size from less than 50 patients to the largest single trial with 468 patients, with most enrolling less than 100 patients. Most of these trials found equivocal results.
  - a. Meta-analyses were conducted and published to examine the pooled data.
    - 1) In 1997, the Sarcoma Meta-Analysis Collaboration (SMAC) of Britain conducted a meta-analysis of trials conducted assessing adjuvant therapy for localized, resectable STS by collecting individual patient data and performing an intention-to-treat analysis.

- a) Findings from 14 randomized trials (N=1568 patients) of doxorubicin-containing chemotherapy regimens with a median follow-up of 9.4 years concluded that adjuvant therapy significantly improved local and distant recurrence-free survival, and overall recurrence-free survival.
  - b) There was a trend towards adjuvant chemotherapy improving overall survival, although it was not statistically significant (HR of 0.89 (0.76-1.03),  $p = 0.12$ ).<sup>52</sup>
- 2) In 2008, an updated meta-analysis included four additional trials (N=1953).
- a) The odds ratios (OR) for local recurrence was 0.73 (95% CI 0.56-0.94;  $P = 0.02$ ) in favor of chemotherapy.
  - b) For distant and overall recurrence, the OR was 0.67 (95% CI 0.56-0.82;  $P = 0.0001$ ) in favor of chemotherapy.
  - c) In terms of survival, doxorubicin alone had an OR of 0.84 (95% CI, 0.68-1.03;  $P = 0.09$ ), which was not statistically significant. However, the OR for survival with doxorubicin combined with ifosfamide was 0.56 (95% CI, 0.36-0.85;  $P = 0.01$ ) in favor of chemotherapy. This resulted in an absolute risk reduction in death of 11% with adjuvant doxorubicin and ifosfamide (95% CI, 3%-19%;  $p=0.01$ ).<sup>53</sup>
- b. Summary: There is no “proven” role for adjuvant chemotherapy for adult soft tissue sarcoma due to conflicting data regarding an overall survival benefit. However, it appears that doxorubicin and ifosfamide combination may have the most activity. Toxicity and individual patient factors such as tumor subtype, location and grade, as well as patient age and performance status should be considered.**

**Patient Case #4, continued:**

**Answer: C.** WJ should receive an adjuvant chemotherapy regimen that contains doxorubicin. Additional active chemotherapeutic agents include ifosfamide and dacarbazine, but the most common combination utilized in synovial sarcoma is doxorubicin and ifosfamide. Doxorubicin single-agent did not demonstrate a statistically significant improvement in the 2008 meta-analysis. Additionally combination therapy would be reasonable given the patient’s age, grade of tumor and performance status. Targeted agents do not have a role yet in the adjuvant setting.

4. Metastatic Disease – at initial diagnosis < 10% of patients with STS will have metastatic disease.<sup>54</sup> However, approximately half of patients will relapse with their disease at a distant site, and many patients will require systemic therapy for palliation.
- a. Surgical excision and radiotherapy may benefit select patients to extend DFS.
  - b. STS is poorly responsive to cytotoxic chemotherapy, in general. However, certain histological subtypes have higher response rates to chemotherapy (See Table: Histology Driven Chemotherapy).
    - 1) Doxorubicin has long been considered a drug of choice because of its slightly superior single agent activity relative to other agents (Response Rate (RR) – 20%).
    - 2) Other commonly used drugs include:
      - a) Ifosfamide (RR - 15 to 20%)



- b) Dacarbazine (RR - 15 to 20%)
- c) Epirubicin (RR – 15%)
- d) Gemcitabine (RR – 7%)
- e) Temozolomide (RR – 8%)
- f) Cyclophosphamide (RR – 10%)
- g) Dactinomycin (RR – 15%)

#### First Line Histology Driven Chemotherapy\*<sup>23-25</sup>

Histological Subtype	Chemotherapeutic Agent(s)	Response Rate (%)
Uterine leiomyosarcoma <sup>26</sup>	Gemcitabine and docetaxel	35.8
Myxoid liposarcomas <sup>26</sup>	Doxorubicin	48
	Doxorubicin and dacarbazine	44
Pleomorphic liposarcomas <sup>26</sup>	Doxorubicin	33
Dedifferentiated liposarcomas <sup>26</sup>	Doxorubicin	25
Angiosarcoma <sup>27</sup>	Doxorubicin	33
	Paclitaxel	31
	Doxorubicin liposomal	33
Synovial sarcoma <sup>26</sup>	Doxorubicin and ifosfamide	58

\*small studies, most retrospective analyses

- c. Single agent therapy compared to combination chemotherapy
  - 1) Comparative trials have demonstrated an increase in response rate with multiagent regimens. Most combination regimens have not shown an improvement in overall survival; however, the combination of gemcitabine and docetaxel versus gemcitabine alone improved both PFS (6.2 vs 3 months) and OS (17.9 vs 11.5 months) in a Phase II study.<sup>55</sup>
  - 2) Outcomes with chemotherapy have been evaluated in over 2,000 patients in a meta-analysis. The overall median survival was approximately one year. Factors predicting a favorable response include performance status, lack of hepatic involvement, low-grade histology, long DFS from diagnosis, and age.<sup>56</sup>
  - 3) A phase III trial of 228 patients compared doxorubicin (75 mg/m<sup>2</sup> bolus or 72-hour continuous infusion) to doxorubicin (75 mg/m<sup>2</sup> or 25 mg/m<sup>2</sup> Days 1-3) intensified with ifosfamide (10 gm/m<sup>2</sup> over 4 days with mesna and pegfilgrastim).<sup>57</sup>
    - a) There was no difference in OS. Median overall survival was 12.8 months [95.5% CI 10.5–14.3] in the doxorubicin group vs 14.3 months [12.5–16.5] in the doxorubicin and ifosfamide group; hazard ratio [HR] 0.83 [95.5% CI 0.67–1.03]; stratified log rank test (p=0.076).
    - b) Median PFS was significantly higher for the doxorubicin and ifosfamide group (7.4 months [95% CI 6.6–8.3]) than for the doxorubicin group (4.6 months [2.9–5.6]; HR 0.74 [95% CI 0.60–0.90], stratified log-rank test p=0.003).
    - c) More patients in the doxorubicin and ifosfamide group than in the doxorubicin group had an overall response (60 [26%] of 227 patients vs 31 [14%] of 228; p<0.0006).

- d) There was more toxicity in the ifosfamide/doxorubicin arm.
  - e) Authors concluded intensified doxorubicin and ifosfamide for palliation in the advanced STS is not supported unless the specific goal is tumor shrinkage.
- 4) The GeDDIS phase III trial randomized 257 patients with advanced or metastatic soft tissue sarcoma to either doxorubicin (75 mg/m<sup>2</sup>) day 1 every 3 weeks as monotherapy or gemcitabine (675 mg/m<sup>2</sup>) day 1 and 8 + docetaxel (75 mg/m<sup>2</sup>) day 8 every 3 weeks.<sup>58</sup>
- a) Primary endpoint was the proportion of patients alive and progression-free at 24 weeks after the date of randomization.
    - i. Doxorubicin 46.3% vs. gemcitabine/docetaxel 46.4%
  - b) Median progression-free survival was not statistically different between the groups (23.3 weeks vs. 23.7 weeks; HR 1.28; p = 0.06)
  - c) Overall survival did not differ between groups.
  - d) Side effect profiles were similar between the regimens.
  - e) Doxorubicin remains a viable option as a single agent for the treatment of advanced or metastatic soft tissue sarcoma.

## 5. Selected Regimens

### Selected Chemotherapy Regimens for STS with Non-Specific Histologies<sup>93</sup>

Regimen	Cycle Duration	Response Rate (%)
<b>First-Line Therapy Advanced/Metastatic Preferred Regimens</b>		
Doxorubicin 75 mg/m <sup>2</sup> IV day 1 <sup>59</sup>	21 days	10 – 25 (most PR)
Pegylated liposomal doxorubicin (PLD) 50 mg/m <sup>2</sup> IV day 1 <sup>60</sup>	28 days	10
Epirubicin 75 mg/m <sup>2</sup> IV day 1 <sup>61</sup>	21 days	18
Doxorubicin 25 mg/m <sup>2</sup> IV continuous infusion day 1-3 (total 75 mg/m <sup>2</sup> ) Ifosfamide 2500 mg/m <sup>2</sup> IV over 3 hours daily, days 1-4 Mesna 500 mg/m <sup>2</sup> over 15 minutes before the ifosfamide, then at 4 and 8 hours from the start of each ifosfamide dose on days 1-4 (also known as AI or AIM) <sup>57</sup>	21 days	26
Epirubicin 60 mg/m <sup>2</sup> IV days 1 and 2 <sup>62</sup> Ifosfamide 1,800 mg/m <sup>2</sup> IV over 3 hours daily, days 1-5 Mesna 360 mg/m <sup>2</sup> over 15 minutes before ifosfamide, then at 4 and 8 hours from the start of each ifosfamide dose on days 1-5	21 days	
Doxorubicin 15 mg/m <sup>2</sup> IV continuous infusion day 1-4 (total 60 mg/m <sup>2</sup> ) Dacarbazine 250 mg/m <sup>2</sup> IV continuous infusion day 1-4 (total 1000 mg/m <sup>2</sup> ) <sup>63</sup>	21 days	17
<b>First-Line Therapy Advanced/Metastatic Other Recommended Regimens</b>		
Gemcitabine 675 - 900 mg/m <sup>2</sup> IV over 90 min on days 1, 8 Docetaxel 75 - 100 mg/m <sup>2</sup> IV over 60 minutes on day 8 <sup>55,37</sup>	21 days	53 (LMS)
Gemcitabine 800 mg/m <sup>2</sup> IV over 90 min on days 1, 8 Vinorelbine 25 mg/m <sup>2</sup> IV on days 1, 8 <sup>65</sup> (Schedule could be modified to Days 1 and 15 for toxicity)	21 days 28 days	25 (clinical benefit)*
Gemcitabine 1800 mg/m <sup>2</sup> IV at infusion rate of 10 mg/m <sup>2</sup> /min followed by Dacarbazine 500 mg/m <sup>2</sup> IV Day 1 <sup>66</sup>	14 days	49
Gemcitabine 1000 mg/m <sup>2</sup> IV days 1, 8	21 days	
<b>First-Line Therapy Advanced/Metastatic Useful in Certain Circumstances</b>		
Mesna 2500 mg/m <sup>2</sup> IV continuous infusion days 1 – 4 Doxorubicin 20 mg/m <sup>2</sup> IV continuous infusion days 1 – 3 Ifosfamide 2500 mg/m <sup>2</sup> IV continuous infusion days 1 – 3 Dacarbazine 300 mg/m <sup>2</sup> IV continuous infusion days 1 – 3 (also known as MAID) <sup>67</sup>	21 days	37
Pazopanib 800 mg PO daily (patients ineligible for IV systemic therapy)	Continuous	
<b>Subsequent Lines of Therapy for Advanced/Metastatic Preferred Regimens</b>		
Pazopanib 800 mg PO daily	Continuous	6 (PR) 67 (SD)
Eribulin 1.4 mg/m <sup>2</sup> IV push on day 1 and 8 (Liposarcoma <sup>+</sup> ) <sup>68</sup> ; other subtypes *	21 days	4 (PR) 52 (SD)
Trabectedin 1.5 mg/m <sup>2</sup> as a 24-hour infusion (Liposarcoma <sup>+</sup> , Leiomyosarcoma <sup>+</sup> ) <sup>69</sup> ; other subtypes *	21 days	9.9
<b>Subsequent Lines of Therapy for Advanced/Metastatic Other Recommended Regimens</b>		
Ifosfamide 1800 mg/m <sup>2</sup> /IV days 1-5 <sup>62, 59</sup>	21 days	19

Dacarbazine 1200 mg/m <sup>2</sup> IV day 1 <sup>66</sup>	21 days	49
Temozolomide 200 mg/m <sup>2</sup> PO day 1 followed by 90 mg/m <sup>2</sup> every 12 hours for 9 doses on days 2-6 <sup>49</sup>	28 days	8
Vinorelbine 30 mg/m <sup>2</sup> IV days 1, 8, 15 <sup>50</sup>	21 days	
Regorafenib 160 mg PO daily for 3 weeks followed by 1 week off <sup>62</sup> (for non-adipocytic sarcoma)	28 days	
<b>Subsequent Lines of Therapy for Advanced/Metastatic Disease Useful in Certain Circumstances</b>		
Pembrolizumab 200 mg IV day 1 <sup>71</sup> (for myxofibrosarcoma, undifferentiated pleomorphic sarcoma, cutaneous angiosarcoma, and undifferentiated sarcomas)	21 days	18

<sup>+</sup>Category 1 recommendation per NCCN

<sup>\*</sup> Category 2A recommendation per NCCN

LMS - Leiomyosarcoma

<sup>\*</sup> Clinical Benefit was defined either as objective response or RECIST-defined stable disease for a minimum of 4 months

#### 6. Pegylated liposomal doxorubicin versus conventional doxorubicin<sup>60</sup>

- a. Randomized phase II compared pegylated liposomal doxorubicin (PLD) 50 mg/m<sup>2</sup> IV every 28 days to doxorubicin 75 mg/m<sup>2</sup> IV Q21 days showed no difference in response rate (10% PLD vs 9% doxorubicin), but differences in tolerability.
  - a) Myelosuppression – grade 3/4 neutropenia: PLD 6%, doxorubicin 77%
  - b) Palmar-plantar erythrodysesthesia – PLD 50% vs doxorubicin 0%; PLD grade 3/4 20%
  - c) Additional considerations: PLD showed less cardiotoxicity, alopecia, and requirements for aggressive antiemetics compared to doxorubicin

#### 7. Fixed Dose Rate Gemcitabine<sup>53</sup>

- a) Gemcitabine infused over 10 mg/m<sup>2</sup>/min
- b) Theory: Prolonging the infusion rate increased the amount of active triphosphate metabolite which would then increase efficacy
- c) Increased efficacy has not been proven, but this is the way gemcitabine was administered in the regimens above and, therefore, how it is still commonly administered in clinical practice.

#### 8. Eribulin<sup>68</sup>

- a. Approved for unresectable, metastatic liposarcoma
  - 1) Randomized, phase III, open-label in advanced or metastatic liposarcoma or leiomyosarcoma refractory to a least 2 other regimens (including an anthracycline)
    - a) Eribulin 1.4 mg/m<sup>2</sup> IV on day 1 and 8 q3 weeks (n = 228) vs. Dacarbazine 850-1200 mg/m<sup>2</sup> IV on Day 1 q3 weeks (n = 224)
  - 2) Primary end-point: overall survival
    - a) 13.5 months vs. 11.5 months (HR 0.77; CI 0.62 – 0.95; p=0.0169)
      - i. Results driven by **liposarcoma** results: **FDA only approved in liposarcoma**

- ii. Liposarcoma: 15.6 months vs 8.4 months (HR 0.51; 95 % CI 0.346 – 0.753)
  - iii. Leiomyosarcoma: 12.7 months vs 13 months (HR 0.927; 95 % CI 0.714 – 1.203)
- 3) Eribulin is a category 1 recommendation per NCCN guidelines for liposarcoma, category 2A recommendation for all other subtypes of STS
- 9. Trabectedin<sup>47</sup>
  - a. Phase III, randomized, open-label in advanced or metastatic **liposarcoma** or **leiomyosarcoma** after at least 2 systemic therapy (including an anthracycline)
    - 1) Trabectedin 1.5 mg/m<sup>2</sup> IV over 24 hours q3 weeks (n = 345) vs. dacarbazine 1000 mg/m<sup>2</sup> IV over 20-120 min q3 weeks (n =173)
  - b. Primary end-point: Overall survival
    - 1) The interim analysis of OS (64% censored) demonstrated a 13% reduction in risk of death in the trabectedin arm compared with dacarbazine (median OS for trabectedin vs dacarbazine, 12.4 v 12.9 months; hazard ratio, 0.87; p = 0.37)
  - c. Median Progression Free Survival
    - 1) 4.2 months trabectedin vs. 1.5 months dacarbazine; HR, 0.55; P<0.001
  - d. Conclusions: Although the interim analysis of OS did not show a statistically significant improvement in overall survival, trabectedin did demonstrate a significant improvement in progression-free survival. The authors proposed that a difference in overall survival was not shown due to the use of effective subsequent therapies.
  - e. Trabectedin is a category 1 recommendation per NCCN guidelines for liposarcoma and leiomyosarcoma, and category 2A recommendation for all other subtypes of STS
  - f. **Clinical pearls:**
    - 1) **Trabectedin can cause rhabdomyolysis, so CPK should be monitored prior to each administration. CPK elevations occurred in nearly 1/3 of patients. Patients should be counseled on the signs of rhabdomyolysis.**
      - a) **Creatine phosphokinase >2.5 times ULN: Delay dose for up to 3 weeks**
      - b) **Creatine phosphokinase >5 times ULN during prior cycle: Delay dose for up to 3 weeks and reduce the next dose by one dose level**
    - 2) **Trabectedin is a 24 hour infusion and has vesicant properties. Most health systems administer in the outpatient setting and have support for pump malfunctions and extravasation.**

#### D. Targeted Therapy

- 1. Olaratumab + Doxorubicin<sup>72</sup>
  - a. Based on the phase II results, the FDA granted accelerated approval of olaratumab in combination with doxorubicin with the requirement to complete a phase III larger study to confirm the clinical benefit. January 24<sup>th</sup>, 2019, the FDA received results from the ANNOUNCE phase III clinical trial. **This trial did not confirm the clinical benefit of olaratumab and did not meet the primary endpoint of improvement in overall survival.**

- b. The FDA recommends that patients who are currently receiving olaratumab should consult with their physician about whether to remain on treatment and olaratumab should not be initiated in new patients outside of a clinical study. Olaratumab was officially withdrawn from the market in April of 2019 and only available through the manufacturer for patients who are approved to continue therapy.
  - c. **NCCN Guidelines® have been updated to reflect the removal of olaratumab.**<sup>36,73</sup>
- 2. Pazopanib – Approved by FDA for the treatment of patients with advanced **STS (not liposarcoma)** who have received prior chemotherapy. Pazopanib, a multitargeted tyrosine kinase inhibitor, is an option for palliative therapy for patients with progressive, unresectable, or metastatic non-lipogenic STS.
  - a. Phase III, randomized, multi-center, double-blind placebo-controlled (PALETTE study) trial. Evaluated activity of pazopanib in patients with non-adipocytic soft-tissue sarcoma after failure of standard chemotherapy (containing anthracycline).
    - 1) Patients received pazopanib 800 mg daily or placebo with no subsequent cross-over. Total 369 (246 vs. 123) patients were randomized and majority had high grade STS.<sup>56</sup>
    - 2) Primary end-point of median progression free survival was significantly longer with pazopanib at 4.6 months compared with 1.6 months with placebo.
    - 3) Best overall response was 6% with pazopanib and 0% with placebo (HR 0.31,  $p < 0.0001$ ).
    - 4) Significant improvement in progression free survival did not result in significant improvement in median overall survival (12.5 vs. 10.7 months, HR 0.86,  $p=0.25$ ).

## I. Unique subtypes of STS

### A. Epithelioid sarcoma<sup>57</sup>

- 1. Rare (less than 1% of all STS), aggressive subtype of STS, locally invasive and frequently metastasizes to regional lymph nodes and distant organ sites
- 2. Most prevalent in young adult males
- 3. Commonly presents as a painless small lump in the soft tissue of the hand, lower leg or forearm
- 4. Characterized by inactivation, deletion or mutation of INI-1(SMARCB1)
  - a. Loss of INI-1/SMARCB1 expression opposes the enzymatic function of EZH2, a critical component of epigenetic regulation
- 5. Complete surgical resection is curative in early-stage disease
  - a. High recurrence rate and distant metastatic risk
- 6. Metastatic Disease:
  - a. Tazemetostat demonstrated efficacy in a single-arm cohort (Study EZH-202) in patients with metastatic or locally advanced epithelioid sarcoma. Patients were required to have INI1 loss, ECOG 0-2. Tazemetostat was given as 800 mg orally twice daily until disease progression.<sup>58</sup>
    - 1) N= 62

- a) ORR was 15% (95% CI: 7 – 26%) with 1.6% complete response and 13% partial response

2) Tazemetostat

- a) Mechanism of action: Tazemetostat is a potent, selective, orally available, small molecule inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations (Y646X and A687V). EZH2 is overexpressed or mutated in many cancer types and plays a role in tumor proliferation. Altered EZH2 upregulation and loss-of-function mutations in SWI/SNF are oncogenic in many human cancers.
- b) Indications & Dose:
  - i. Adult and pediatric patients age 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection
  - ii. 800 mg PO twice daily
    - May need to hold or dose reduce for neutropenia, thrombocytopenia, anemia
- c) Toxicities: pain, fatigue, nausea, decreased appetite, vomiting, and constipation
- d) Drug-Drug Interactions: major substrate of CYP3A4, weak inducer of CYP3A4 and weak inhibitor of CYP2C8

B. Tenosynovial giant cell tumor/Pigmented Villonodular Synovitis (PVNS)

1. Rare, locally aggressive, mesenchymal neoplasm arising from the synovium of joints, bursa, or tendon sheaths
2. Tenosynovial giant cell tumors (TGCT) is also known as giant cell tumor of the tendon sheath or pigmented villonodular synovitis (PVNS)
  - a. A minority of TGCT are neoplastic and express colony-stimulating factor 1 (CSF1) as a result of alterations within chromosome 1p13
3. Surgical resection when feasible is standard treatment, however recurrence of the diffuse subtype is common
4. Pexidartinib was approved for adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. (Category 1 NCCN recommendation)<sup>36</sup>
  - a. The ENLIVEN trial was an international, randomized, double-blind, placebo-controlled trial which evaluated pexidartinib or placebo in patients with TGCT. Pexidartinib was given at 1000 mg (400 mg AM and 600 mg PM) as a loading dose for the first 2 weeks, followed by 800 mg (400 mg by mouth twice daily) until disease progression.<sup>74</sup>
    - 1) N = 120
    - 2) ORR = 38% (15% CR and 23% PR) at 25 weeks
    - 3) No patients receiving placebo had a response (p<0.0001)
    - 4) Severe hepatotoxicity was observed with 3 patients having AST/ALT elevations of 3 or more times the upper limit of normal (ULN) with a total bilirubin 2 or more times the ULN. These were later classified as mixed or cholestatic hepatotoxicity and one lasted

for 7 months.

b. Pexidartinib

a) Mechanism of action: Pexidartinib is a selective tyrosine kinase inhibitor with strong inhibitory activity against CSF1 receptor. Additional activity includes inhibition of KIT and FLT3.

b) Indications & Dose:

- i. Adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery
- ii. 400 mg PO twice daily on an empty stomach, at least 1 hour before or 2 hours after a meal or snack
  - May need to hold or dose reduce for hepatotoxicity or renal impairment

c) Black Box Warnings:

- i. **Hepatotoxicity – Pexidartinib can cause serious and potentially fatal liver injury**
  - **REMS Program for Hepatotoxicity Monitoring**
    - **Pexidartinib is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) program with a limited specialty pharmacy distribution model**
- ii. Prescribers, pharmacies and patients must all be enrolled in the REMS program
- d) Toxicities: increased LDH, increased AST/ALT, hair color changes, fatigue, neutropenia, increased cholesterol, lymphopenia, orbital edema, anemia, rash, dysgeusia, and hypophosphatemia
- e) Drug-Drug Interactions: avoid coadministration with other products with known causes of hepatotoxicity; major substrate of CYP3A4, and moderate inducer of CYP3A4
  - i. Avoid concomitant proton pump inhibitors, administer pexidartinib  $\geq 2$  hours before or 10 hours after a H<sub>2</sub>- receptor antagonist

**Patient Case #5:**

PL is a 55-year-old male with synovial sarcoma who is scheduled to start therapy with AIM (doxorubicin, ifosfamide and mesna). **Which of the following counseling points is most appropriate for PL while he receives the AIM regimen?**

A. Samples of your urine will be tested for the presence of red blood cells prior to each dose of ifosfamide.



- B. Report shortness of breath to your healthcare provider because it could represent heart toxicity.
- C. If a dose of oral mesna is vomited after 30 or more minutes have elapsed, there is no need to repeat the dose.
- D. Oral mesna should be taken 12 hours after the last dose of ifosfamide.

### III. Considerations of Ifosfamide Therapy<sup>75,76</sup>

#### A. Toxicities of Ifosfamide

##### 1. Dose-limiting hemorrhagic cystitis due to the formation of metabolite acrolein

###### a. Mesna and hydration are required therapies for prevention

- 1) Must use with mesna (sodium 2-mercaptoethanesulfonate) to prevent hemorrhagic cystitis.
- 2) Intravenous mesna can be dosed by the following schema:
  - a) 20% of ifosfamide dose immediately before and then 20% at 4 hours and 20% at 8 hours after IV boluses of ifosfamide.
  - b) When ifosfamide is given as a continuous infusion the mesna is usually given concurrently (in the same bag in some institutions).
  - c) The dose varies and ranges from the 60% of the ifosfamide dose (as with the bolus infusions) up to 100%. Different schedules (including oral mesna administration) exist.
- d) Patients who vomit within 2 hours of taking oral mesna should repeat the dose or receive intravenous mesna<sup>75</sup>**
  - e) Oral mesna is 50% bioavailable, so the oral dose is twice the intravenous dose.
  - f) Can utilize the IV solution orally and dilute in cola to mask smell.
- 3) The efficacy of mesna for urothelial protecting with doses of ifosfamide  $> 2.5\text{g}/\text{m}^2/\text{day}$  has not been established.<sup>75</sup>
- 4) Vigorous hydration with 1.5 - 2 liters of NS pre- and post-hydration. Encourage patient to increase oral fluid intake to 2-3 liters of fluid per day. Encourage frequent bladder emptying while awake, and first thing in the morning.
- 5) IV fluids such as D5W are not appropriate as the fluid does not stay in the intravascular space and does not promote urinary excretion of acrolein.
- 6) Historically fluids with sodium bicarbonate were utilized in conjunction with ifosfamide, but it hasn't been shown to be more effective than normal saline alone for prevention.
- 7) Patients who develop ifosfamide-induced renal tubular acidosis may be managed with either sodium bicarbonate or sodium acetate-based fluids.

##### 2. Encephalopathy/Neurotoxicity

- a. Presents as confusion, somnolence, hallucinations, myoclonus, coma
- b. Attributed to chloroacetaldehyde metabolite

- c. Risk factors: dose of ifosfamide, drug interactions (CYP2B6 inhibitors), organ dysfunction, hypoalbuminemia, rapid infusion, previous cisplatin use
- d. **Stop ifosfamide infusion – a majority of ifosfamide-induced neurotoxicity cases resolve spontaneously, but require hospital admission for observation**
- 1) **Consider** methylene blue for prophylaxis, treatment<sup>77-79</sup>
    - a) Based on multiple published case reports only
      - 50 mg IV every 6 hours (prophylaxis)
      - 50 mg IV every 3 – 6 hours (treatment)
    - b) Risks with methylene blue: serotonin syndrome, hemolysis
  - 2) Consider changing bolus ifosfamide to continuous infusion
  - 3) Consider re-challenging with ifosfamide if only mild symptoms or a different rate of ifosfamide infusion.
  - 4) If treatment was initiated outpatient, consider admission for future cycles
  - 5) Recent ESMO guidelines describe prophylactic or therapeutic use of methylene blue, thiamine, and/or glucose 5% to be ineffective and not recommended.<sup>80</sup>

**Patient Case #5:**

**Answer: A.**

Daily collection and testing of urine samples is required during treatment with ifosfamide because the presence of red blood cells may indicate hemorrhagic cystitis and warrant a delay in therapy. This should be explained to the patient.

Rationale-Answer Choice #2: Cardiotoxicity is not something that patients need to be advised about, although they should be warned about the possibility of neurotoxicity (e.g., confusion, blurred vision) from ifosfamide.

Rationale-Answer Choice #3: If a dose of mesna is vomited within 2 hours, it should be repeated.

Rationale-Answer Choice #4: Traditional mesna dosing is 0, 4, and 8 hours after ifosfamide either IV or oral.

## GASTROINTESTINAL STROMAL TUMORS (GIST)

### **Patient Case 6:**

JR is a 38-year-old female who undergoes successful resection of her 4 cm gastric gastrointestinal stromal tumor. Pathology indicates that the tumor is cKIT, exon 9 mutation (A502\_Y503dup mutation) positive and 5 mitoses per 50 high power field. What is the best treatment for JR?

- A. Imatinib for 1 year
- B. Imatinib for 3 years
- C. Avapritinib for 1 year
- D. Sunitinib for 3 years

### **I. Gastrointestinal stromal tumors (GIST)<sup>81</sup>**

- A. Most common STS of the gastrointestinal tract resulting from KIT or PDGFRA activating mutations.<sup>82</sup>
  - 1. 60% stomach
  - 2. 30% small intestine
  - 3. 4-5% duodenum
  - 4. 4% rectum
- B. Expression of the KIT (or CD117) tyrosine kinase encoded by the c-KIT gene is activated in about 85% to 90% GIST.
  - 1. Approximately 80% of GIST will have a mutation within KIT
  - 2. KIT mutations most commonly occur in the juxtamembrane domain encoded by KIT exon 11 with a lesser number occurring in the extracellular domain encoded by exon 9.
    - a. KIT exon 11 mutations: most common presentation of GIST of all sites
    - b. KIT exon 9 mutations: more common presentation for intestinal GIST
    - c. KIT exon 13 and exon 17 occur rarely and have been identified in the tyrosine kinase domain
      - 1) Presence of these mutations are most commonly associated with acquired resistance following progression on a KIT inhibitor
- C. PDGFRA mutations have been identified in about 5-10% of patients with GIST with the majority having a genetic mutation in exon 18 in the tyrosine kinase domain 2.
  - a. Most common presentation of PDGFRA exon 18 mutations occur in gastric GISTs.
- D. Only 10-15% of GIST tumors do not have any detectable mutations either within KIT or PDGFRA, but still mostly express KIT (wild-type GIST)
- E. GIST tumors are poorly responsive to cytotoxic chemotherapy and radiation therapy. If resectable, surgery is the primary treatment.
- F. Prognostic factors<sup>82,83</sup>
  - 1. Tumor size
  - 2. Location
  - 3. Mitotic rate (defined as number of mitoses per 50 High Power Field (HPF))
  - 4. KIT mutational status is not used to determine the malignant potential of a primary GIST but can

be used as a predictive response to TKI therapy. For example, patients with wild type GIST do not respond well to TKI therapy.

#### Risk of metastasis for GIST<sup>82</sup>

Risk of Metastasis	Location of GIST, Size, and Mitotic Rate
Low risk for metastasis	<ul style="list-style-type: none"> <li>Gastric GIST <math>\leq 10</math> cm and <math>\leq 5</math> mitoses per 50 HPFs</li> <li>Intestinal GIST <math>\leq 5</math> cm and <math>\leq 5</math> mitosis per 50 HPFs</li> </ul>
Moderate risk for metastasis	<ul style="list-style-type: none"> <li>Intestinal GIST <math>&gt; 5</math> cm independent of mitotic rate (can fall into high if <math>&gt; 5</math> mitoses per 50 HPFs)</li> </ul>
High risk for metastasis	<ul style="list-style-type: none"> <li>Gastric GIST <math>&gt; 5</math> cm and <math>&gt; 5</math> mitosis per 50 HPFs</li> <li>Intestinal GIST independent of size with <math>&gt; 5</math> mitoses per 50 HPFs</li> </ul>

- G. Prior to initiation of therapy, all patients should be evaluated and managed by a multi-disciplinary team with experience and expertise in sarcoma.

## II. Treatment

### A. Neoadjuvant imatinib

- Several small studies have incorporated neoadjuvant imatinib prior to surgery and then continuing post operatively. These studies have demonstrated the safety and efficacy in the neoadjuvant setting, but because all patients received adjuvant imatinib, a survival benefit could not be shown.<sup>84-86</sup>
- NCCN guidelines suggest preoperative imatinib or avapritinib (for PDGFRA exon 18 mutations, including D842V mutation) can be considered to decrease surgical morbidity.
  - Examples include locally advanced GIST located in the rectum, esophageal and esophagogastric junction, duodenum or if a multivisceral resection would be required to resect all gross tumor.
- Preoperative imatinib may prohibit accurate assessment of recurrence risk and should be considered only if surgical morbidity could be reduced by downstaging the tumor preoperatively.
- There is not a definitive role for the use of neoadjuvant imatinib at this time.**

### B. Adjuvant imatinib

- Complete resection is only possible in about 85% of patients with at least 50% of those patients developing recurrence or metastatic disease. This is associated with a 5-year survival of 50%.
- A Phase III, randomized, double-blind, placebo-controlled trial evaluated efficacy of imatinib 400 mg daily in 713 patients with complete resection of a primary GIST at least 3 cm in size and positive for KIT.
  - Imatinib or placebo was given for 1 year after surgery.
  - Recurrence free survival of 98% for patients on imatinib compared with 83% for patients on placebo ( $p < 0.0001$ ).<sup>87</sup>

3. A phase III trial conducted by Scandinavian Sarcoma Group and Sarcoma Group of the AIO suggested that outcome could be further improved with longer adjuvant imatinib therapy.
  - a. 400 patients with high risk for recurrence were randomized to receive either imatinib for 1 year or 3 years following resection of the tumor.
  - b. Median follow-up of 90 months, better 5-year recurrence free survival for patients on 3-year adjuvant imatinib (71.1% vs. 52.3%; HR = 0.6; P < 0.001).
  - c. Five-year overall survival was significantly longer at 93.4% with 3-year vs. 86.8% 1-year adjuvant therapy (HR, 0.53; p = 0.024).
  - d. Higher rate of discontinuation in 3-year arm (13.6% vs. 7.7%).<sup>88,89</sup>
  - e. Median follow-up of 119 months, continued to demonstrate improved recurrence free survival at 10 years for patients on 3-year adjuvant imatinib (52.5% vs. 41.8%; HR = 0.66; P = 0.003).<sup>90</sup>
  - f. Ten-year overall survival was 79% with 3-year vs. 65.5% with 1-year adjuvant treatment (HR, 0.5; P = 0.003).
  - g. **This study established adjuvant imatinib for 36 months as the standard of care for patients who are high risk of relapse.**

**Patient Case #6, continued:**

**Answer: A.** JR should be treated with adjuvant imatinib for a total of 1 year as she is at low risk for recurrence due to the size of her gastric tumor of less than 10 cm at 5 cm and the mitosis rate being ≤ 5 mitoses per 50 HPF. She is also cKIT positive. Sunitinib and avapritinib would not be appropriate to recommend as they are only approved in the metastatic setting.

JR returns 5 years after completion of her adjuvant imatinib therapy. She is found to have recurrent gastric GIST which is deemed unresectable. Pathology was reviewed and she continues to show a cKIT, exon 9 mutation (A502\_Y503dup mutation) positive. She was restarted at an outside cancer center on imatinib 400 mg daily and is tolerating treatment well. She is here for a second opinion as she is found to have progressive disease. Which of the following therapies would be most appropriate to recommend for JR at this time?

- A. Imatinib 400 mg twice daily
- B. Avapritinib 300 mg daily
- C. Regorafenib 160 mg daily for 3 weeks, 1 week off
- D. Ripretinib 150 mg daily

C. Metastatic

1. First-line therapy:

- a. Imatinib – (Preferred, NCCN Category 1 Recommendation)<sup>83</sup>
  - 1) A study investigated relationship between kinase genotype and treatment outcome in 428 patients with advanced GIST in phase III trial of 400 mg or 800 mg daily of imatinib.<sup>91</sup>
    - a) This study suggested favorable outcome in patients with KIT exon 11 mutations compared with patients with KIT exon 9 mutation or wild-type for KIT mutations.

- b) In addition to better response rate and time to tumor progression, patients with exon 11 mutation had 60 months overall survival compared with 38 and 49 months survival for exon 9 mutation and wild-type respectively.
    - c) Patients with exon 9 mutation had better response rate with 800 mg compared with 400 mg dose (67% vs. 17%,  $P = 0.02$ ).<sup>91</sup>
  - 2) Patients should be initiated on imatinib 400 mg daily and monitored for toxicity.
  - 3) Patients who have progressed on imatinib 400 mg daily or those with a KIT exon 9 mutation and ability to tolerate the agent may be increased to a maximum of imatinib 400 mg twice daily.<sup>83</sup>
- b. Avapritinib for GIST with PDGFRA exon 18 mutation (Preferred, NCCN Category 2A Recommendation)
  - 1) A Phase I international trial for patients with unresectable GIST with both dose-escalation and dose expansion. Eligibility for the dose expansion phase included unresectable PDGFRA D842V mutant GIST regardless of prior therapy and GIST with other mutations who progressed on prior imatinib therapy and/or one or more TKI.<sup>92</sup> (NAVIGATOR)
    - a) Initial dosing for avapritinib was 400 mg PO daily, but was later reduced to 300 mg PO daily secondary to toxicity
      - i. 43 patients with GIST harboring PDGFRA exon 18 mutations as well as 38 patients with PDGFRA D842V mutations were enrolled
      - ii. PDGFRA exon 18 – ORR: 84% (95% CI: 69-93%)
      - iii. PDGFRA D842V – ORR: 89% (95% CI: 75-97%)
      - iv. Median response duration was not reached with the duration of follow-up for all patients of 10.6 month (0.3 to 24.9 months)
  - 2) Avapritinib
    - a) Mechanism of action: Avapritinib is a potent tyrosine kinase inhibitor that blocks PDGFRA with targets of PDGFRA, PDGFRA D842V mutants, KIT exon 11, 11/17, and 17 mutants. Inhibition of autophosphorylation of KIT D816V and PDGFRA D842V were observed in mutants associated with resistance with approved kinase inhibitors.
    - b) Indications & Dose:
      - i. Adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including D842V mutations.
      - ii. 300 mg PO daily on an empty stomach, at least one hour before and two hours after a meal
        - May need to hold or dose reduce for CNS effects, and intracranial hemorrhage
    - c) Toxicities: edema, nausea, fatigue/asthenia, cognitive impairment, myelosuppression, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash, and dizziness

- d) Drug-Drug Interactions: major substrate of CYP3A4, minor substrate of CYP2C9
- 3) Imatinib response based on PDGFRA mutation
  - a) International survey of 58 patients with PDGFRA-mutated GIST treated with imatinib<sup>93</sup>
    - i. 69% gastric site of tumor
      - 55% PDGFRA D842V missense mutations (within exon 18)
      - 29% mutations affecting other areas of exon 18
      - 16% mutations outside of exon 18
    - ii. Median PFS 2.8 months with D824V substitution vs. 28.5 months with other PDGFRA mutations (95% CI 5.4-51.6; p = 0.0001)
    - iii. Median OS 14.7 months with D824V mutation vs. not reached for other mutations
    - iv. Most PDGFRA exon 18 mutated GISTs will respond to imatinib with the exception of the D842V substitution that does not respond.
- 2. Second-line therapy:
  - a. Primary resistance to imatinib can develop in 20% of patients.
  - b. Sunitinib (Preferred, NCCN Category 1 Recommendation)
    - 1) A Phase III trial randomized patients with GIST that had failed initial treatment with imatinib to sunitinib 50 mg PO daily x 4 weeks with 2 weeks off, every 6 weeks or placebo. The primary endpoint was time to tumor progression (TTP). Observed TTP for sunitinib was 6.3 months compared to 1.5 months for placebo.<sup>94</sup>
- 3. Third-line therapy:
  - a. Regorafenib (Preferred, NCCN Category 1 Recommendation)
    - 1) GRID Trial, phase III, randomized trial for patients with treatment-refractory metastatic GIST. All patients had received prior imatinib and sunitinib.<sup>95</sup>
      - a) Patients were randomized to receive regorafenib 160 mg daily for 3 weeks, then 1 week off every 4 weeks or placebo.
      - b) In 199 evaluable patients regorafenib improved the median progression free survival to 4.8 months from 0.9 month in placebo (HR 0.27, p < 0.0001).
      - c) 85% of patients on placebo crossed over to regorafenib upon progression.
- 4. Fourth-line therapy:
  - a. Ripretinib (Preferred, NCCN Category 1 Recommendation)
    - 1) INVICTUS Trial, phase III, randomized trial for patients with advanced GIST with progression on at least imatinib, sunitinib, and regorafenib.<sup>96</sup>
      - a) N=129
      - b) Ripretinib 150 mg PO daily vs. Placebo (2:1), crossover was permitted

- c) Median PFS was 6.3 months (ripretinib) vs. 1 month (placebo); median OS was 15.1 months (ripretinib) vs. 6.6 months (placebo)
- 2) Ripretinib
- a) Mechanism of action: Ripretinib is a switch control tyrosine kinase inhibitor and inhibits KIT and PDGFRA kinase signaling pathways. Binding occurs with both wild type as well as mutant forms of both KIT and PDGFRA, preventing the switch from inactive to active conformations of these kinases. Additional inhibition has been identified with PDGFRB, TIE2, VEGFR2, and BRAF kinases.
  - b) Indications & Dose:
    - i. Adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.
    - ii. 150 mg PO daily
      - May need to hold or dose reduce for arthralgia/myalgia, hypertension, LVEF dysfunction, and palmar-plantar erythrodysesthesia syndrome
  - c) Toxicities: alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia, and vomiting.
  - d) Additional risks associated with ripretinib include new primary cutaneous malignancies, hypertension, and cardiac dysfunction.
  - e) Drug-Drug Interactions: major substrate of CYP3A4, and minor substrate of CYP2C8, CYP2D6, CYP2E1, and P-gp/ABCB1
5. Additional options after failure on approved therapies:
- a. Avapritinib (Useful in Certain Circumstances, NCCN Recommendation)
    - 1) A Phase III, open-label, randomized study evaluating avapritinib vs. regorafenib in patients with locally advanced metastatic or unresectable GIST who were previously treated with imatinib and 1 or 2 other tyrosine kinase inhibitors who have experience disease progression. (VOYAGER)
      - a) Avapritinib 300 mg PO daily (n = 240) vs. Regorafenib 160 mg PO daily (3 weeks on, 1 week off) (n = 236). Cross-over was permitted for patients who experience disease progression on regorafenib
      - b) Median PFS of 4.2 months (avapritinib) vs. 5.6 months (regorafenib) which was not statistically significant
        - i. ORR was 17 % (avapritinib) vs. 7 % (regorafenib)
    - 2) The results of this study prevented the addition of 4<sup>th</sup> line indication for avapritinib, however the presence of certain KIT resistance mutations may make it more desirable in select cases.



### Systemic Therapy for Unresectable or Metastatic GIST<sup>3</sup>

Unresectable or Metastatic GISTs	Preferred Regimens
First line	<ul style="list-style-type: none"> <li>• Imatinib<sup>+</sup></li> <li>• Avapritinib (for GIST with PDGFRA exon 18 mutation, including PDGFRA D842V mutations)</li> </ul>
Second line, progressive disease after imatinib	Sunitinib <sup>+</sup>
Third line, progressive disease after imatinib and sunitinib	Regorafenib <sup>+</sup>
Fourth line, progressive disease after imatinib, sunitinib, and regorafenib	Ripretinib <sup>+</sup>
Additional options after failure on approved therapies	<p><u>Useful in Certain Circumstances:</u></p> <ul style="list-style-type: none"> <li>• Avapritinib</li> <li>• Cabozantinib</li> <li>• Dasatinib (for patients with PDGFRA D842V mutations)</li> <li>• Everolimus + TKI</li> <li>• Larotrectinib or entrectinib (for <i>NTRK</i> gene-fusion GISTs)</li> <li>• Nilotinib</li> <li>• Pazopanib</li> <li>• Sorafenib</li> </ul>

<sup>+</sup>Category 1 NCCN Recommendation

#### Patient Case #6, continued:

**Answer: A.** JR was restarted at standard dosing of imatinib 400 mg daily which is appropriate given her mutation status of cKIT, exon 9 mutation positive. Exon 9 mutations in cKIT have demonstrated improved response with increased doses of imatinib at 400 mg twice daily and would be appropriate at this time to try as the patient does not report intolerance at the current dose. Avapritinib in the metastatic setting is only indicated in patients with PDGFRA mutations and would not be appropriate for this patient at this time. Regorafenib is approved for metastatic GIST, however should be reserved for third line therapy following progression on imatinib as well as sunitinib. Ripretinib is approved for fourth line therapy and this patient does not qualify for this therapy at this time.

## RECOMMENDED READINGS AND REFERENCES

### General

1. Skubitz KM, D'Adamo DR. Sarcoma. *Mayo Clin Proc.* 2007; 82:1409-32. (<https://www.ncbi.nlm.nih.gov/pubmed/17976362> )
2. Schaefer I-M, Cote GM, Hornick JL. Contemporary sarcoma diagnosis, genetics and genomics. *J Clin Oncol* 2018; 36: 101-110. (<https://www.ncbi.nlm.nih.gov/pubmed/29220288>)

### Soft-Tissue Sarcoma

1. Haas RL, Gronchi A, van de Sande MA et al. Perioperative management of extremity soft tissue sarcomas. *J Clin Oncol* 2018; 36: 118-124. (<https://www.ncbi.nlm.nih.gov/pubmed/29220299> )
2. Von Mehren M, Joensuu H. Gastrointestinal stromal tumors. *J Clin Oncol* 2018; 36: 136-143. (<https://www.ncbi.nlm.nih.gov/pubmed/29220298> )
3. Smrke A, Wang Y, Simmons C. Update on systemic therapy for advanced soft-tissue sarcoma. *Curr Oncol.* 2020; 27:25-33. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7050046>)

### Sarcomas of Bone

1. Whelan JS, Davis LE. Osteosarcoma, chondrosarcoma, and chordoma. *J Clin Oncol* 2018; 36: 188-193. (<https://www.ncbi.nlm.nih.gov/pubmed/29220289> )
2. Luetke A, Meyers PA, Lewis I et al. Osteosarcoma treatment – where do we stand? *Cancer Treat Rev.* 2014; 40:523-32. (<https://www.ncbi.nlm.nih.gov/pubmed/24345772> )
3. Meyers PA, Heller G, Healy J et al. Chemotherapy for nonmetastatic osteogenic sarcoma: The Memorial Sloan-Kettering experience. *J Clin Oncol.* 1992; 10:5-15. (<https://www.ncbi.nlm.nih.gov/pubmed/1370176> )
4. Pollack S, Ingham M, Spraker, M et al. Emerging targeted and immune-based therapies in sarcoma. *J Clin Oncol* 2018; 36: 125-135. (<https://www.ncbi.nlm.nih.gov/pubmed/29220291> )

### Methotrexate Toxicities

1. Ramsey LB, Balis FM, O'Brien MM et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. *Oncologist.* 2018; 23(1): 52-61. (<https://www.ncbi.nlm.nih.gov/pubmed/29079637>)

## References

1. Whelan JS, Davis LE. Osteosarcoma, Chondrosarcoma, and Chordoma. *Journal of Clinical Oncology*. 2017;36(2):188-193.
2. DeVita V. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bone Cancer. V.2.2023, 09/28/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
4. Gaspar N, Occean BV, Pacquement H, et al. Results of methotrexate-etoposide-ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/sarcome-09 study. *Eur J Cancer*. 2018;88:57-66.
5. Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. *J Natl Cancer Inst*. 2007;99(2):112-128.
6. Meyers PA, Gorlick R, Heller G, et al. Intensification of preoperative chemotherapy for osteogenic sarcoma: results of the Memorial Sloan-Kettering (T12) protocol. *J Clin Oncol*. 1998;16(7):2452-2458.
7. Meyers PA, Schwartz CL, Krailo M, et al. Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. *J Clin Oncol*. 2005;23(9):2004-2011.
8. Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol*. 2016;17(10):1396-1408.
9. Gentet JC, Brunat-Mentigny M, Demaille MC, et al. Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology. *Eur J Cancer*. 1997;33(2):232-237.
10. Miser JS, Kinsella TJ, Triche TJ, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. *J Clin Oncol*. 1987;5(8):1191-1198.
11. Goorin AM, Harris MB, Bernstein M, et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. *J Clin Oncol*. 2002;20(2):426-433.
12. Davis LE, Bolejack V, Ryan CW, et al. Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma. *J Clin Oncol*. 2019;37(16):1424-1431.
13. Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. *Cancer*. 2008;113(2):419-425.
14. Saylor RL, 3rd, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol*. 2001;19(15):3463-3469.
15. Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21(3):446-455.
16. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol*. 2007;25(19):2755-2763.
17. Grignani G, Palmerini E, Ferraresi V, et al. Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. *Lancet Oncol*. 2015;16(1):98-107.
18. Berger M, Grignani G, Ferrari S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. *Cancer*. 2009;115(13):2980-2987.
19. Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. *Pediatr Blood Cancer*. 2005;44(4):338-347.

20. Le Deley MC, Guinebretiere JM, Gentet JC, et al. SFOP OS94: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. *Eur J Cancer*. 2007;43(4):752-761.
21. Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol*. 2002;20(1):189-196.
22. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist*. 2006;11(6):694-703.
23. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance, *Oncologist*. 2017; 23(1): 7, by permission of Oxford University Press.
24. Green MR, Chowdhary S, Lombardi KM, Chalmers LM, Chamberlain M. Clinical utility and pharmacology of high-dose methotrexate in the treatment of primary CNS lymphoma. *Expert Rev Neurother*. 2006;6(5):635-652.
25. Bezabeh S, Mackey AC, Kluetz P, Jappara D, Korvick J. Accumulating evidence for a drug-drug interaction between methotrexate and proton pump inhibitors. *Oncologist*. 2012;17(4):550-554.
26. Fermiano M, Bergsbaken J, Kolesar JM. Glucarpidase for the management of elevated methotrexate levels in patients with impaired renal function. *Am J Health Syst Pharm*. 2014;71(10):793-798.
27. Widemann BC, Balis FM, Kim A, et al. Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. *J Clin Oncol*. 2010;28(25):3979-3986.
28. Widemann BC, Schwartz S, Jayaprakash N, et al. Efficacy of glucarpidase (carboxypeptidase g2) in patients with acute kidney injury after high-dose methotrexate therapy. *Pharmacotherapy*. 2014;34(5):427-439.
29. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. *Oncologist*. 2018;23(1):52-61.
30. Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. *Cancer*. 2017;123(1):90-97.
31. Chow W, Frankel P, Ruel C, et al. Results of a prospective phase 2 study of pazopanib in patients with surgically unresectable or metastatic chondrosarcoma. *Cancer*. 2020;126(1):105-111.
32. Tap WD, Villalobos VM, Cote GM, et al. Phase I Study of the Mutant IDH1 Inhibitor Ivosidenib: Safety and Clinical Activity in Patients With Advanced Chondrosarcoma. *J Clin Oncol*. 2020;38(15):1693-1701.
33. Zahm SH, Fraumeni JF, Jr. The epidemiology of soft tissue sarcoma. *Semin Oncol*. 1997;24(5):504-514.
34. Burningham Z, Hashibe M, Spector L, Schiffman JD. The Epidemiology of Sarcoma. *Clinical Sarcoma Research*. 2012;2(1):14.
35. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma.
36. V.2.2022, 5/17/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
37. Farid M, Ngeow J. Sarcomas Associated With Genetic Cancer Predisposition Syndromes: A Review. *Oncologist*. 2016;21(8):1002-1013.
38. Lazar A, Abruzzo LV, Pollock RE, Lee S, Czerniak B. Molecular diagnosis of sarcomas: chromosomal translocations in sarcomas. *Arch Pathol Lab Med*. 2006;130(8):1199-1207.
39. Schaefer IM, Cote GM, Hornick JL. Contemporary Sarcoma Diagnosis, Genetics, and Genomics. *J Clin Oncol*. 2018;36(2):101-110.
40. Worden FP, Taylor JM, Biermann JS, et al. Randomized phase II evaluation of 6 g/m2 of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (G-CSF) compared with 12 g/m2 of ifosfamide plus doxorubicin and G-CSF in the treatment of poor-prognosis soft tissue sarcoma. *J Clin Oncol*. 2005;23(1):105-112.

41. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: An analysis of 26,758 cases. *Int J Cancer*. 2006;119(12):2922-2930.
42. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30.
43. Crompton JG, Ogura K, Bernthal NM, Kawai A, Eilber FC. Local Control of Soft Tissue and Bone Sarcomas. *Journal of Clinical Oncology*. 2018;36(2):111-117.
44. Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS. Surgical margins and reresection in the management of patients with soft tissue sarcoma using conservative surgery and radiation therapy. *Cancer*. 2003;97(10):2544-2553.
45. Haas RL, Gronchi A, van de Sande MAJ, et al. Perioperative Management of Extremity Soft Tissue Sarcomas. *Journal of Clinical Oncology*. 2017;36(2):118-124.
46. Albertsmeier M, Rauch A, Roeder F, et al. External Beam Radiation Therapy for Resectable Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis. *Ann Surg Oncol*. 2018;25(3):754-767.
47. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*. 2002;359(9325):2235-2241.
48. Alamanda VK, Song Y, Shinohara E, Schwartz HS, Holt GE. Postoperative radiation boost does not improve local recurrence rates in extremity soft tissue sarcomas. *J Med Imaging Radiat Oncol*. 2014;58(5):633-640.
49. Delaney TF, Kepka L, Goldberg SI, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. *Int J Radiat Oncol Biol Phys*. 2007;67(5):1460-1469.
50. Gortzak E, Azzarelli A, Buesa J, et al. A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. *Eur J Cancer*. 2001;37(9):1096-1103.
51. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STs 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18(6):812-822.
52. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. *Lancet*. 1997;350(9092):1647-1654.
53. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer*. 2008;113(3):573-581.
54. Ferguson PC, Deheshi BM, Chung P, et al. Soft tissue sarcoma presenting with metastatic disease: outcome with primary surgical resection. *Cancer*. 2011;117(2):372-379.
55. Stacchiotti S, Van Tine BA. Synovial Sarcoma: Current Concepts and Future Perspectives. *J Clin Oncol*. 2018;36(2):180-187.
56. Lee ATJ, Thway K, Huang PH, Jones RL. Clinical and Molecular Spectrum of Liposarcoma. *Journal of Clinical Oncology*. 2017;36(2):151-159.
57. George S, Serrano C, Hensley ML, Ray-Coquard I. Soft Tissue and Uterine Leiomyosarcoma. *J Clin Oncol*. 2018;36(2):144-150.
58. Scurr M. Histology-driven chemotherapy in soft tissue sarcomas. *Curr Treat Options Oncol*. 2011;12(1):32-45.
59. D'Angelo SP, Munhoz RR, Kuk D, et al. Outcomes of Systemic Therapy for Patients with Metastatic Angiosarcoma. *Oncology*. 2015;89(4):205-214.
60. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15(4):415-423.
61. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol*. 2017;18(10):1397-1410.
62. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol*. 1995;13(7):1537-1545.
63. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer*. 2001;37(7):870-877.

64. Petrioli R, Coratti A, Correale P, et al. Adjuvant epirubicin with or without Ifosfamide for adult soft-tissue sarcoma. *Am J Clin Oncol*. 2002;25(5):468-473.
65. Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol*. 2001;19(5):1238-1247.
66. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol*. 1993;11(7):1276-1285.
67. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol*. 2002;20(12):2824-2831.
68. Dileo P, Morgan JA, Zahrieh D, et al. Gemcitabine and vinorelbine combination chemotherapy for patients with advanced soft tissue sarcomas: results of a phase II trial. *Cancer*. 2007;109(9):1863-1869.
69. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29(18):2528-2533.
70. Elias A, Ryan L, Sulkes A, Collins J, Aisner J, Antman KH. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. *J Clin Oncol*. 1989;7(9):1208-1216.
71. Schoffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016;387(10028):1629-1637.
72. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. *J Clin Oncol*. 2016;34(8):786-793.
73. Patel SR, Vadhan-Raj S, Papadopolous N, et al. High-dose ifosfamide in bone and soft tissue sarcomas: results of phase II and pilot studies--dose-response and schedule dependence. *J Clin Oncol*. 1997;15(6):2378-2384.
74. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet*. 2016;388(10043):488-497.
75. FDA Approved Drugs. Olaratumab (Lartruvo). <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm526087.htm>. Accessed February 10, 2019.
76. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379(9829):1879-1886.
77. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394(10197):478-487.
78. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. 2009;27(1):127-145.
79. Patel PN. Methylene blue for management of Ifosfamide-induced encephalopathy. *Ann Pharmacother*. 2006;40(2):299-303.
80. Kupfer A, Aeschlimann C, Wermuth B, Cerny T. Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. *Lancet*. 1994;343(8900):763-764.
81. Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prove A, Vermorken JB. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer*. 2000;82(2):291-294.
82. Zulian GB, Tullen E, Maton B. Methylene blue for ifosfamide-associated encephalopathy. *N Engl J Med*. 1995;332(18):1239-1240.
83. Jordan B, Margulies A, Cardoso F, et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. *Ann Oncol*. 2020;31(10):1306-1319.
84. von Mehren M, Joensuu H. Gastrointestinal Stromal Tumors. *Journal of Clinical Oncology*. 2017;36(2):136-143.

85. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23(2):70-83.
86. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors (GISTs). V.2.2022, 09/01/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
87. Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
88. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol.* 2009;99(1):42-47.
89. McAuliffe JC, Hunt KK, Lazar AJ, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. *Ann Surg Oncol.* 2009;16(4):910-919.
90. Blesius A, Cassier PA, Bertucci F, et al. Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial. *BMC Cancer.* 2011;11:72.
91. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2009;373(9669):1097-1104.
92. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA.* 2012;307(12):1265-1272.
93. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial. *J Clin Oncol.* 2016;34(3):244-250
94. Joensuu H, Eriksson M, Sundby Hall K, et al. Survival Outcomes Associated With 3 Years vs 1 Year of Adjuvant Imatinib for Patients With High-Risk Gastrointestinal Stromal Tumors: An Analysis of a Randomized Clinical Trial After 10-Year Follow-up. *JAMA Oncol.* 2020;6(8):1241-1246.
95. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol.* 2008;26(33):5360-5367.
96. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. *Lancet Oncol.* 2020;21(7):935-946.
97. Cassier PA, Fumagalli E, Rutkowski P, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Clin Cancer Res.* 2012;18(16):4458-4464.
98. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006;368(9544):1329-1338.
99. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):295-302.
100. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2020;21(7):923-934.

# **BLADDER, RENAL CELL, AND TESTICULAR CANCERS**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with bladder, renal, or testicular carcinomas.
2. Discuss short- and long-term treatment goals, including post-therapy and survivorship, with a patient with bladder, renal, or testicular carcinomas and his or her caregiver
3. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with the treatment with tyrosine kinase inhibitors and mTOR inhibitors.



## BLADDER CANCER

### **Patient Case #1: ARS Question #1**

CT is a 71-year-old man who presented to his primary care doctor with complaints of hematuria and urinary urgency. He was referred to a urologist for cystoscopy, which revealed a lesion in the bladder. Subsequently, he underwent a TURBT (transurethral resection of the bladder tumor) followed by single-dose intravesical chemotherapy. Pathology revealed Tis (in situ), non-muscle invasive urothelial carcinoma (UC).

#### **What is the best treatment option for CT at this time?**

- A. Intravesical Bacillus Calmette-Guerin (BCG)
- B. Intravesical mitomycin
- C. Systemic gemcitabine + cisplatin
- D. Pembrolizumab

### **I. Etiology and Pathogenesis<sup>1-5</sup>**

- A. Environmental exposures are responsible for the majority of bladder cancers, see risk factors below
- B. Initially thought to involve “field cancerization” due to the multifocal occurrences that are seen in bladder cancer. However, majority of cases are monoclonal supporting a single genetically mutated cell which spreads throughout the urothelium.<sup>2,6</sup>
- C. In the United States and Europe, urothelial carcinomas (UC) are the most common histologic subtype. Other histologic subtypes include squamous cell, glandular neoplasms (including adenocarcinoma and villous adenoma), epithelial tumors of the upper urinary tract and the bladder diverticulum.
- D. Molecular mechanisms<sup>7</sup>
  - 1. Altered metabolism/detoxification of carcinogens
  - 2. Inherent or acquired genetic abnormalities
- F. Genetic alterations of chromosome 9, including deletions, are often associated with the development of UC. Noninvasive tumors are also associated with activation of RAS-MAPK pathway. Invasive and noninvasive high-grade tumors are frequently associated with alterations of p53 tumor suppressor gene and retinoblastoma gene.<sup>6,8</sup>
- G. Natural History of Disease<sup>1,5,7,8</sup>
  - 1. Non-muscle invasive (Ta, Tis, T1)
    - a. 70-80% of all newly diagnosed bladder cancers
    - b. 50-80% will recur and 30% will progress to muscle invasive disease
  - 2. Muscle invasive (T2 or greater)
    - a. 20-30% of newly diagnosed bladder cancers

3. Bladder cancer metastasizes by lymphatic or hematogenous routes or direct extension. The most common sites of distant metastases include the lymph nodes beyond common iliacs, liver, lung, and bone.

## II. **Risk Factors**<sup>1,4,5</sup>

### A. Factors associated with increased risk:

1. Cigarette smoking
  - a. Responsible for 50-60% of bladder cancers
  - b. A prospective analysis found a significantly increased risk of bladder cancer for current smokers, male and female (HR 3.89 and 4.65, respectively). The risk in former smokers, male and female, was reduced, but still elevated (HR 2.14 and 2.5, respectively).<sup>4</sup>
2. Chemical exposures (10-20% of bladder cancers)
  - a. Occupations associated with bladder cancer include painters, rubber industry workers, textile and electrical workers, leather industry, and manufacturers of carpet, paint, plastics and industrial chemicals as well as other occupations with exposure to dyes.
  - b. Aromatic amines including 2-naphthylamine and benzidine, 4-aminobiphenyl, methylene dianiline, arsenic, benzidine-derived azo dyes, phenacetin-containing compounds.
3. Chronic bladder inflammation or infections
  - a. Usually develop nonurothelial cancers, such as squamous cell tumors
  - b. Chronic indwelling catheters- 80% of patients with chronic indwelling catheters (bladder) will develop squamous cell metaplasia which can progress to squamous cell cancer of the bladder.<sup>9</sup>
  - c. Schistosomiasis infection
4. Human papillomavirus (HPV)
5. Cyclophosphamide/ifosfamide exposure

### B. Factors associated with decreased risk:

1. Smoking cessation
2. Increase total fluid intake

## III. **Prevention and Screening**<sup>10</sup>

### A. There are no recommended prevention or screening guidelines at this time

## IV. **Treatment and Supportive Care of Non-Muscle Invasive (Ta, Tis or T1; Stage 0 or Stage 1)**<sup>5</sup>

- A. Goal is to manage/reduce recurrences and prevent progression to muscle invasive disease.
- B. TURBT

1. Initial therapy for non-muscle-invasive tumors. With bimanual examination under anesthesia (EUA), it is used to resect visible tumor as well as sample muscle within the area of the tumor. Key to include bladder muscle in TURBT, otherwise repeat resection may be warranted.
2. Repeat TURBT (2-6 weeks after initial TURBT) is recommended for patients with pT1 disease as it improved 3-year recurrence-free survival compared to those without repeat resection.<sup>11</sup>

Risk Stratification of NMIBC Following TURBT<sup>5,12</sup>

Low Risk	Papillary urothelial neoplasm of low malignant potential  Ta (low grade): solitary and $\leq 3$ cm
Intermediate Risk	Ta (low grade): recurrence < 1 year, > 3 cm, or multifocal  Ta (high grade): $\leq 3$ cm  T1 (low grade)
High Risk	Ta (high grade): recurrent, > 3 cm, or multifocal  T1 (high grade)  Tis  Very high risk features: BCG unresponsiveness, variant histologies, lymphovascular invasion, or prostatic urethral invasion

C. Intravesical therapy

1. Intravesical therapy is instilled directly into the bladder, held for up to 2 hours, and then eliminated/drained via urination/catheter.
2. Agents used in this include cytotoxic chemotherapy (mitomycin or gemcitabine) or immunotherapy agents (BCG).
3. Depending on the risk of recurrence, perioperative or adjuvant/prophylactic intravesical therapy may be considered.
4. Rationale for perioperative chemotherapy includes killing residual microscopic malignant cells at the tumor site as well as circulating cells to prevent reimplantation.
5. Intravesical therapy should be avoided in patients with extensive TURBT or if bladder perforation is suspected.
6. Optimal agent, dose and schedule for intravesical therapy are difficult to determine due to heterogeneity of the disease, lack of well-designed studies and lack of control for additional therapies.
7. Immediate Postoperative Intravesical Chemotherapy
  - a. Gemcitabine (preferred, NCCN Guidelines® category 1) and mitomycin (NCCN Guidelines® category 1) are the most common agents used in this setting

- b. A single dose of chemotherapy is instilled within 24 hours of TURBT, ideally within 6 hours
  - c. Reduces 5-year recurrence from 58.8% to 44.8%, but does not reduce risk of progression or cancer mortality HR 0.65; 95% CI, 0.58-0.74;  $p < 0.001$ <sup>13</sup>
  - d. Should not be given to patients with recurrence rate of  $>1$  recurrence per year due to lack of benefit or to those with an EORTC recurrence score  $\geq 5$  due to a possible increased risk of death from bladder cancer.<sup>13</sup>
- 8. Induction/Adjuvant Intravesical Chemotherapy or BCG
  - a. BCG, gemcitabine and mitomycin are most common in this setting
  - b. BCG is superior compared to chemotherapy for Tis disease<sup>14</sup>
  - c. Initiate 3-4 weeks after TURBT with or without maintenance
  - d. Given as weekly instillations for 6 weeks, with a maximum of 2 consecutive induction cycles (12 weekly doses) without complete response
  - e. Avoid if traumatic catheterization, infection (bacteriuria), persistent gross hematuria, severe local symptoms of treatment, or systemic symptoms
- 9. Intravesical BCG Maintenance
  - a. No standard regimen though SWOG regimen is commonly used: Following 6-week induction, 3 weekly instillations can be done at 3, 6, 12, 18, 24, 30 and 36 months, which have been associated with decreased recurrence
  - b. Maintenance should continue for 1 year in intermediate-risk (multifocal or multi-recurrent low-grade Ta tumors) and 3 years in high risk disease (T1 invasive into lamina propria)
  - c. Dose reductions may be considered during the maintenance phase for either substantial local symptoms or in the event of a BCG shortage.<sup>5</sup>
  - d. Avoid if trauma, infection, persistent gross hematuria or severe symptoms of treatment
- 10. Agents used
  - a. BCG (Bacillus Calmette-Guerin)
    - 1) BCG is a live attenuated strain of *Mycobacterium bovis*. Its use in bladder cancer requires an intact immune system and direct contact with bladder cancer cells. It is thought that BCG is internalized by urothelial cells resulting in antigen presentation as well as release of cytokines including IL-2, IL-8, and TNF- $\alpha$ . Immune cells are then recruited leading to local inflammation and cell death.<sup>8,15</sup>
    - 2) BCG is not used perioperatively and is generally delayed for 2-3 weeks after TURBT to allow the urothelium to heal and decrease risk of systemic toxicity

- 3) BCG should be prepared using aseptic techniques in a separate area. Parenteral drugs should not be prepared in areas where BCG has been prepared to prevent cross-contamination. Equipment, supplies, and receptacles in contact with BCG should be handled and disposed of as biohazardous waste. If prepared without a containment device, respiratory protection, gloves and gown should be utilized to avoid inhalation or contact with BCG organisms.
- b. Gemcitabine (NCCN Guidelines® Category 1 recommendation, preferred)<sup>5</sup>
    - 1) Can be used in the perioperative setting (within 24 hours of TURBT) in patients with suspected low-grade non-muscle invasive urothelial cancer
    - 2) Preferred by many providers due to good tolerability
    - 3) May be used as an alternative agent for induction/adjuvant treatment in the setting of a BCG shortage
    - 4) Dose: 2000mg x1 dose
  - c. Mitomycin (NCCN Guidelines® Category 1 recommendation)<sup>5</sup>
    - 1) One of the most common agents utilized in the adjuvant/induction setting
    - 2) Weekly instillations of 40mg intravesical for approximately 6 weeks for a maximum of 2 consecutive induction cycles
    - 3) A new thermosensitive gel pharmaceutical formulation of mitomycin (Jelmyto®) has been approved for low-grade upper urothelial tract cancer, but this formulation has no established role in treatment of urothelial carcinoma of the bladder.

## 11. Summary of Studies Using Intravesical Therapy

- a. Multiple trials have demonstrated the superiority of intravesicular chemotherapy compared to no active treatment in the perioperative setting.<sup>13,16-20</sup>
- b. In the adjuvant setting, BCG has demonstrated superior efficacy to observation and doxorubicin.<sup>21,22</sup> Compared to mitomycin, BCG yielded similar rates of tumor recurrence, while mitomycin was more effective in preventing progression to invasive disease in patients with Ta or T1.<sup>23</sup>

## D. Recurrent or Persistent Ta, T1 or Tis Disease<sup>8</sup>

1. After observation only, repeat TURBT followed single dose intravesical chemotherapy within 24 hours followed by adjuvant intravesical therapy based on stage and grade of recurrent lesion<sup>8</sup>
2. After intravesical therapy

- a. If response to initial induction intravesical therapy: Proceed with second induction course of BCG or mitomycin. No more than 2 consecutive induction courses should be given.
- b. If recurrence after second induction: repeat TURBT should be performed at second week 12. If patient has Tis or Ta after repeat TURBT, consider different intravesical agent or cystectomy.
- c. If no residual disease after 1-2 courses of induction therapy, maintenance BCG is recommended. Optimal regimen not defined, but typically 1-3 years in duration.

#### E. Treatment options for Recurrence or Progression following BCG<sup>24</sup>

##### 1. Valrubicin

- a. Novel, lipid soluble, semisynthetic analogue of doxorubicin
- b. Evaluated in 90 patients with primarily Tis who had received at least 2 previous courses of BCG. Patients received valrubicin 800mg intravesical weekly for 6 doses. Complete response (CR) in 21% of patients.<sup>25</sup>
- c. Adverse events include urinary frequency, dysuria, urinary urgency, urinary tract infections, and asthenia.<sup>25</sup>

##### 2. Gemcitabine

- a. Randomized, phase 3 trial of intravesical gemcitabine 2000mg weekly x 6 weeks versus mitomycin 40mg weekly for 5 weeks in patients with recurrent Ta or T1 UC.
  - 1) Patients had progressed or relapsed after BCG or were ineligible for BCG therapy. Patients who responded received monthly therapy for 10 months.
  - 2) Median time to tumor recurrence was 15 months in the mitomycin versus not reached in the gemcitabine group. The relative risk of recurrence was not significantly different between the two groups.
  - 3) Gemcitabine had significantly less dysuria and chemical cystitis.<sup>24</sup>

##### 3. Pembrolizumab

- a. KEYNOTE-057, a single-arm, phase II trial of pembrolizumab in 101 patients with high-risk, BCG-unresponsive NMIBC evaluated pembrolizumab 200 mg IV every 3 weeks for up to 2 years.<sup>26</sup>
  - 1) 39 patients of 96 in the efficacy cohort (41%) achieved a CR, suggesting pembrolizumab may have a role in BCG-unresponsive patients.
  - 2) However, the toxicity of systemic immunotherapy (13% Grade 3/4 TRAEs) is worrisome given the availability of less toxic intravesicular treatments.

- b. NCCN Guidelines® Category 2A recommendation for patients with BCG-unresponsive high-risk NMIBC with Tis with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy

F. Managing intravesical toxicities<sup>27</sup>

1. Local versus systemic. Local toxicities are generally mild and transient. Systemic toxicities may range from mild to life threatening.
2. BCG
  - a. Dysuria and frequency (may feel like a urinary tract infection): result of immune stimulation. Manage with phenazopyridine.
  - b. Flu-like symptoms: generally, occur after 3<sup>rd</sup> administration. Manage with acetaminophen or non-steroidal anti-inflammatory drugs.
  - c. Bladder spasms can be managed with tolterodine or oxybutynin
  - d. Gross hematuria: Occurs in up to 34% of patients. Usually self-limiting. Generally, hold intravesical therapy until hematuria resolves.
  - e. Allergic reaction: rash has been reported rarely. Prophylaxis with antihistamine.
  - f. BCG sepsis: most serious complication due to systemic absorption of BCG (Should wait 7-14 days after TURBT prior to instilling BCG). Patients may present with high fevers, chills, hypotension, and mental confusion. Cultures are often negative and patient should be treated with antituberculosis therapy on clinical suspicion.
  - g. Exposure precautions: Patients should use caution when voiding for 48 hours after intravesical BCG. Avoid urine splashing or dripping on toilet seat to prevent spread of the vaccine. Take care to avoid urine on hands, and if urine does contact skin, wash with soap and water immediately. Many facilities will instruct patients to put ½ cup of undiluted bleach in toilet bowl for 15 minutes prior to flushing to destroy any live vaccine.
3. Chemotherapy (mitomycin, epirubicin, doxorubicin, valrubicin, gemcitabine)
  - a. Little risk of absorption due to high molecular weight.
  - b. Chemical cystitis: Treatment options include phenazopyridine and anticholinergics.
  - c. Eczema-like desquamation of skin on hands, perineum, chest, face: from direct contact or contact dermatitis due to delayed hypersensitivity. Counsel regarding careful cleansing of hands, genitals and perineum after voiding.
  - d. Patients should use condoms for 48 hours after any intravesical therapy

## Ta, Tis, T1 and Tumor Management<sup>5,28</sup>

Stage	Treatment	Follow up
Ta tumors	<p><b>Low Grade</b></p> <p>Observation</p> <p>Single dose of intravesical therapy within 24 hours of resection</p> <p>Additional 6-week induction course of intravesical therapy based on risk of recurrence (Mitomycin most commonly utilized)</p> <p><b>High Grade</b></p> <p>Intravesical BCG or gemcitabine or mitomycin after TURBT or observation</p> <p>Four meta-analyses confirm BCG + TURBT is superior to TURBT alone or TURBT + chemotherapy.</p> <p>BCG preferred over mitomycin</p>	<p><b>Low Risk</b></p> <p>Observation with cystoscopy at 3 and 12 months then at increasing intervals</p> <p><b>Intermediate risk</b></p> <p>Observation with urine cytology and cystoscopy every 3, 6 and 12 then every 6 months for 2 years, then increasing intervals.</p> <p><b>High Risk</b></p> <p>Observation with cystoscopy and urine cytology every 3 months for two years then at increasing intervals</p>
Tis tumors	<p>TURBT followed by:</p> <p>Induction course of weekly intravesical BCG for 6 weeks</p> <p>Second induction may be repeated after 12 weeks</p> <p>If unable to tolerate BCG, give mitomycin</p> <p>Maintenance BCG or mitomycin given with optimal schedule not established</p>	<p>Observation with urine cytology and cystoscopy every 3-6 months for 2 years, then increasing intervals</p>
T1 tumors	<p>Generally high grade</p> <p>Repeat TURBT followed by:</p> <p>Intravesical therapy with BCG (preferred, category 1) or mitomycin or gemcitabine if no residual disease found</p> <p>BCG (category 1) or cystectomy for residual disease</p>	<p>Observation with urine cytology and cystoscopy every 3-6 months for 2 years, then increasing intervals</p>

### **Patient Case #1, ARS Question #1 Answer:**

CT should receive at least one induction course of weekly intravesical BCG (answer A). If he responds, he may receive an additional induction course or subsequent maintenance BCG with repeat cystoscopy every 3-6 months for 2 years. Mitomycin is inferior to BCG in Tis disease, but may be utilized if patient is unable to tolerate BCG. Systemic chemotherapy is only indicated in muscle-invasive disease. Pembrolizumab is not an option at this time, but may be considered if CT lesions do not respond to BCG and cystectomy is not an option.



V. **Treatment Options and Supportive Care for Muscle Invasive (T2-T4, Stage II or above)**<sup>5,8</sup>

A. The therapeutic goal is the determination of whether cystectomy is needed without compromising survival, and if the primary lesion can be managed independently or if the patient is at high risk for distant spread.

B. Surgery

1. TURBT, including bladder muscle sampling, is initial therapy to determine true pathologic stage
2. Radical cystectomy with pelvic lymph node dissection. Generally, includes cystoprostatectomy in men and cystectomy and hysterectomy in women.
3. Partial cystectomy may be considered in patients who are medically unfit for surgery or those seeking bladder-sparing alternatives to a radical cystectomy. Most frequently utilized for tumors on the dome of the bladder with no Tis component.
4. Partial cystectomy and/or combinations of extensive TURBT, radiation and chemotherapy
5. These approaches are options but they have not been compared prospectively to the standard of radical cystectomy

C. Chemotherapy

1. Neoadjuvant Chemotherapy

- a. Local therapy of muscle-invasive bladder cancer yields only a 5-yr survival rate of 30-50%. The majority of these deaths are due to relapsed bladder cancer. To lower the incidence of recurrent disease, many investigators have studied neoadjuvant chemotherapy<sup>29-31</sup>
- b. Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy is recommended for stage II or IIIA bladder cancers (NCCN Guidelines® Category 1 recommendation)
- c. For patients who are not candidates for cisplatin-based treatment no perioperative chemotherapy should be given
  - 1) No data to support non-cisplatin-based chemotherapy in neoadjuvant setting
  - 2) Carboplatin should not be substituted for cisplatin when giving chemotherapy in a perioperative setting. Split dose cisplatin may be considered for borderline renal function (NCCN Guidelines® Category 2B).<sup>8</sup>
  - 3) Splitting cisplatin in gemcitabine/cisplatin regimen over days 1 and 8 every 21 days resulted in little renal toxicity and can safely be given in patients with CrCl as low as 40mL/min.<sup>32</sup> However, the efficacy of this approach compared to standard neoadjuvant regimens is unknown.
- d. Dose Dense MVAC (ddMVAC)<sup>33</sup> (preferred)

- 1) Methotrexate 30mg/m<sup>2</sup>, vinblastine 3mg/m<sup>2</sup>, doxorubicin 30mg/m<sup>2</sup> and cisplatin 70mg/m<sup>2</sup> with growth factor support given every 14 days for 3-6 cycles.
  - 2) Prospective phase II, multicenter trial. Patients (n=44) had stage III-IV disease. Patients received ddMVAC followed by radical cystectomy.
    - a) Patients received three cycles of ddMVAC with pegfilgrastim followed by radical cystectomy with lymph node dissection
    - b) A CrCl of 50 mL/min was required for enrollment, but patients with CrCl < 60 mL/min were allowed to receive split-dose cisplatin (35 mg/m<sup>2</sup> on days 1 & 2)
    - c) 15 (38%) of the patients evaluable for efficacy were pT0 at cystectomy, 6 downgraded to non-muscle invasive disease
    - d) With the efficacy of preoperative MVAC previously well-established,<sup>30</sup> this trial established the feasibility and activity of ddMVAC in the neoadjuvant setting compared to historic control
- e. ddMVAC vs. Gemcitabine/cisplatin
- 1) Despite ddMVAC's neoadjuvant data, clinicians routinely extrapolated data from the metastatic setting to justify the use of the more tolerable gemcitabine/cisplatin regimen in the neoadjuvant setting.
  - 2) VESPER randomized 500 patients to either ddMVAC x 6 cycles every 2 weeks or gemcitabine/cisplatin x 4 cycles every 3 weeks. The majority (88%) received neoadjuvant therapy.<sup>34</sup>
  - 3) ddMVAC demonstrated improved 3-year PFS (HR 0.70, 95% CI 0.51-0.96; p = 0.025) in patients receiving neoadjuvant chemotherapy.
  - 4) **As a result of this trial, ddMVAC is the preferred neoadjuvant chemotherapy regimen for MIBC.**
- f. Gemcitabine/cisplatin (other recommended regimen)
- 1) Neoadjuvant use historically based on extrapolation of evidence in metastatic patients demonstrating similar efficacy compared to MVAC.
  - 2) Cisplatin 70mg/m<sup>2</sup> on day 2 with Gemcitabine 1000mg/m<sup>2</sup> day 1, 8 and 15 every 28 days for 4 cycles. A 21-day cycle, as used in VESPER, is preferred.<sup>5,34,35</sup>
- g. BA06 30894 Trial<sup>29</sup>
- 1) Phase III, multicenter, randomized controlled trial, n= 976
  - 2) Patients randomized to 3 cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) or observation with cystectomy and/or full-dose external beam radiotherapy.
    - a. Day 1 and 8: methotrexate 30 mg/m<sup>2</sup>, vinblastine 4 mg/m<sup>2</sup>

- b. Day 2: cisplatin 100 mg/m<sup>2</sup>
    - c. Every 21 days for a total of three cycles
  - 3) Long-term follow-up confirms neoadjuvant chemotherapy also decreased the risk of metastases or death (HR, 0.77; 95% CI 0.66-0.90; p=0.01).
  - 4) 3 and 5-year survival in CMV group was 55.5% and 36% respectively
  - 5) Chemotherapy related mortality was 1%
- 2. Adjuvant Chemotherapy following cystectomy
  - a. No well-designed randomized trials have shown a definitive survival benefit (due in large part to low accrual).
  - b. Patients with <T2 disease and no nodal involvement are not recommended to receive adjuvant chemotherapy due to lowered risk.
  - c. Adjuvant chemotherapy has not been compared head-to-head with neoadjuvant chemotherapy.<sup>36</sup>
  - d. If no neoadjuvant chemotherapy was given, adjuvant therapy should be considered based on pathologic risk (positive nodes or T3-4 lesions) (NCCN Guidelines® category 2A).<sup>8</sup>
    - 1) Preferred regimen: ddMVAC (gemcitabine/cisplatin is another recommended regimen)
- 3. Adjuvant Immunotherapy following cystectomy
  - a. Checkmate-274 showed DFS benefit of nivolumab for 1 year following surgery in patients with high-risk muscle-invasive urothelial carcinoma.<sup>37</sup>
    - 1) The greatest benefit in DFS was observed in patients with either PD-L1 positive tumors or those who received neoadjuvant cisplatin-based chemotherapy.<sup>37</sup>
    - 2) Based on the results of Checkmate-274, FDA approved nivolumab as adjuvant treatment in this patient population.
      - a) High-risk disease in Checkmate-274 was defined as follows<sup>37</sup>:
        - i. pT3, pT4a, or pN+ disease and not eligible/declined adjuvant cisplatin-based chemotherapy if these patients had not received neoadjuvant cisplatin-based therapy.
        - ii. ypT2 to ypT4a or ypN+ disease patients who received neoadjuvant cisplatin-based chemotherapy
    - 3) While OS data remains immature, NCCN has listed adjuvant nivolumab as a 2A other recommended regimen for the corresponding trial populations.

4. Combined chemotherapy and radiation following TURBT (category 1 recommendation for non-cystectomy candidates with stage II and stage IIIA)
  - a. Currently, NCCN Guidelines® list the following as preferred regimens in combination with radiation after TURBT for bladder preservation: fluorouracil + mitomycin or cisplatin. Other recommended regimens include cisplatin + fluorouracil, cisplatin + paclitaxel, and low-dose gemcitabine.
    - 1) Characteristics of Optimal Candidates for Bladder Preservation
      - a) Lack of hydronephrosis with presentation
      - b) Lack of concurrent extensive or multifocal Tis disease
      - c) Tumor size < 6 cm
    - 2) A meta-analysis that largely relied on non-randomized cohort studies found no improvement in OS when comparing organ-preserving trimodality therapy (TURBT, chemoradiation) to radical cystectomy. Randomized trials are needed to further delineate the role of organ-preserving approaches.<sup>38</sup>
    - 3) NCCN Guidelines® note bladder-preserving approaches should be used in the context of a clinical trial when possible.
  - b. BC2001 Trial<sup>39</sup>
    - 1) Multicenter, phase 3, randomized controlled trial, n=360
    - 2) Patients randomized to radiation with or without synchronous chemotherapy, fluorouracil and mitomycin. A nonsignificant increase in grade 3 and 4 toxicity was seen with chemoradiation.
    - 3) 2-year DFS 67% in chemoradiation arm versus 54% in radiation alone (p=0.03)
  - c. RTOG 89-03<sup>40</sup>
    - 1) Evaluated concurrent cisplatin and radiation with and without induction methotrexate, cisplatin and vinblastine (MCV) after TURBT in 123 patients with T2-T4a disease.
    - 2) 5-year overall survival was 49% in both arms.
    - 3) There is no benefit of neoadjuvant chemotherapy if bladder-preserving chemotherapy + radiation is planned following TURBT.<sup>5</sup>
  - d. Twice daily radiation with chemotherapy
    - 1) RTOG 95-06<sup>41</sup>
      - a) Evaluated BID radiation with concurrent cisplatin and fluorouracil in 34 patients.
      - b) At 3 years, overall survival was 83%.
    - 2) RTOG 99-06<sup>42</sup>

- a) Evaluated BID radiation with cisplatin and paclitaxel followed by adjuvant cisplatin/gemcitabine in 80 patients.
    - b) Five-year overall survival was 56%.
  - e. Adjuvant radiation with or without chemotherapy
    - 1) Limited data regarding adjuvant radiation or chemoradiation following cystectomy.
    - 2) NCCN Guidelines® recommends consideration of adjuvant radiation in pT3/pT4 pN0-2 disease following radical cystectomy or those with positive margins due to high risk for recurrence (pelvic failure 20-45% and survival 10-50% at 5 years, depending on risk factors). Adjuvant radiation may be given alone or with concurrent cisplatin
- 5. Treatment of Stage IIIB disease
  - a. Both downstaging systemic chemotherapy and concurrent chemoradiotherapy are options (NCCN Guidelines® 2A recommendation)
- 6. Monitoring for muscle invasive disease after initial therapy<sup>5</sup>
  - a. Urine cytology, liver function tests (LFTs), complete blood counts and complete metabolic panel every 3-6 months if received chemotherapy. After the first-year renal function testing, LFTs, and B12 annually for next 4 years then B12 annually
  - b. Chest, abdomen, and pelvis imagining every 3-6 months for 2 years, then annually for next 3 years. After 5 years renal ultrasound annually for next 5 years then as clinically indicated
  - c. If patient had bladder preservation therapy, cystoscopy and urine cytology every 6-12 months for 2 years then as clinically indicated.

**Patient Case #1, ARS Question #2:**

CT did well with maintenance BCG, however he later developed gross hematuria. Repeat TURBT revealed muscle-invasive urothelial carcinoma and staging subsequently showed distant metastases. Further pathologic analysis revealed PD-L1 tumor infiltrating immune cells covering 2% of the tumor area and a CPS = 10%. His ECOG PS = 0 and CrCl is now 40 mL/min. **Which therapy would be most appropriate at this time?**

- A) Atezolizumab
- B) Pembrolizumab
- C) Gemcitabine/carboplatin followed by avelumab maintenance
- D) Neoadjuvant ddMVAC followed by cystectomy

- VI. Treatment options for Advanced or Metastatic Disease (Stage IV) <sup>5</sup>
  - A. Goal in this treatment space is to prolong quantity and maintain quality of life
  - B. NCCN guidelines® recommend molecular testing for stage IIIB, IVA and IVB at diagnosis
    1. Testing should include FGFR2 or FGFR3 alterations
  - C. 1st-Line therapy: Cisplatin-Eligible<sup>43</sup>
    1. **Gemcitabine/cisplatin and dose-dense MVAC are the NCCN guideline® category 1 preferred regimens for patients with good performance status and adequate organ function.<sup>5</sup> Maintenance avelumab should follow either therapy in patients who do not experience disease progression (category 1).**
    2. Dose-Dense MVAC (Methotrexate, vinblastine, doxorubicin, cisplatin; ddMVAC) <sup>8,44</sup>
      - a. Day 1: Methotrexate 30mg/m<sup>2</sup>, Day 2: vinblastine 3mg/m<sup>2</sup>, doxorubicin 30mg/m<sup>2</sup>, cisplatin 70mg/m<sup>2</sup>, Day 3: peg-filgrastim every 14 days
      - b. Randomized, phase 3 trial of patients with locally advanced or metastatic bladder cancer with no prior systemic therapy; n=263
      - c. Patients randomized to ddMVAC every 2 weeks with G-CSF or classic MVAC given every 4 weeks.

#### Results of ddMVAC vs classic MVAC

	Complete Response*	Overall Response	5-yr OS*	Time to Progression	Febrile Neutropenia*
ddMVAC	21%	72%	21.8%	11.1 mo	10%
Classic MVAC	9%	58%	13.5%	9.6 mo	26%

\*p<0.05

- d. 7-year follow-up confirmed superior efficacy of dose-dense MVAC. Median PFS was 9.5 months with ddMVAC vs. 8.1 months with classic MVAC. At the median follow-up of 7.3 years, 24.6% of patients who received ddMVAC were alive vs 13.2% of those who received classic MVAC.
  - e. Significantly less toxicity was seen with the dose-dense regimen.<sup>8</sup>
  - f. **Dose-dense MVAC is the preferred way to administer this combination.**
  - g. Carboplatin may be substituted for cisplatin for unfit (ECOG 2, glomerular filtration rate < 60 mL/min) patients as phase II/III trial found overall response rate of 30%.<sup>7</sup>
3. Gemcitabine/Cisplatin vs. classic MVAC<sup>35,45</sup>
  - a. Randomized, phase 3 trial of patients with locally advanced or metastatic UC and no prior therapy; n=405
  - b. Patients were randomized to gemcitabine/cisplatin or classic MVAC.

#### Results of Gem/Cis versus Classic MVAC

	Median Survival	Response Rate	Toxic Deaths	Neutropenic Sepsis	Grade III/IV Mucositis*
Cisplatin /Gemcitabine	13.8 mos.	49.4%	1%	1%	1%
Classic MVAC	14.8 mos.	45.7%	3%	12%*	22%

\* p<0.05

c. 5-year follow-up showed overall survival was similar between the 2 arms (HR, 1.09; 95% CI, 0.88-1.34; p=0.66).<sup>45</sup>

d. **Gemcitabine/cisplatin has become a standard first-line regimen due to its equivalent outcomes and less toxicity.**

D. 1st-line Therapy: Non-cisplatin eligible (e.g. CrCl < 60 mL/min)<sup>46</sup>

1. Carboplatin/Gemcitabine (category 1) followed by avelumab maintenance<sup>47</sup>

a. Carboplatin (AUC=4.5) day 1 and gemcitabine (1000 mg/m<sup>2</sup>) days 1 and 8 every 21 days<sup>47</sup>

b. ORR 42% in patients with GFR < 60 mL/min. In patients with ECOG performance status of 2 and GFR < 60 mL/min, ORR 26%

2. Pembrolizumab (preferred option by the NCCN guidelines®)<sup>5</sup>

a. Restriction to cisplatin-ineligible patients in the first line setting was based on the data from early review of the KEYNOTE-361 trial which showed decreased survival for patients receiving pembrolizumab compared to patients who received platinum-based chemotherapy. Updated results have now been published.

1) Co-primary endpoint PFS (pembrolizumab + chemotherapy vs. chemotherapy): HR 0.78, 95% CI 0.65 – 0.94; p = 0.0033 which did not meet the alpha threshold of 0.0019 after alpha spent on interim analyses.

2) Co-primary endpoint OS (pembrolizumab + chemotherapy vs. chemotherapy): HR 0.86, 95% CI, 0.72 – 1.02; p = 0.0407 which did not meet the alpha threshold of 0.0142 after alpha spent on interim analyses.

3) The hierarchal design of the trial prohibited hypothesis testing of the pembrolizumab vs chemotherapy groups. Thus, an exploratory analysis of OS was performed on pembrolizumab vs. chemotherapy cohorts.

a) All patients: OS HR 0.92, 95% CI 0.77 – 1.11

i. Pembrolizumab (n = 307) median OS = 15.6 months

ii. Chemotherapy (n = 352) median OS = 14.3 months

b) Patients with CPS ≥ 10%: HR 1.01, 95% CI 0.77 – 1.32

i. Pembrolizumab median OS = 16.1 months

- ii. Chemotherapy median OS = 15.2 months
- b. Restricted for use in first line therapy for patients who are **ineligible for any platinum** based chemotherapy regardless of PD-L1 status (please refer to the Pharmacogenomics module for additional discussion on PD-L1 testing)<sup>48-50</sup>
- 3. Atezolizumab (preferred option by the NCCN guidelines<sup>®</sup>)<sup>5</sup>
  - a. Restricted to use in those patients ineligible for cisplatin and PD-1 positive by PD-L1 stained tumor-infiltrating immune cells [IC] covering  $\geq 5\%$  of the tumor area determined by an FDA approved test (VENTANA PD-L1 (SP142)) or if ineligible for any platinum based chemotherapy regardless of PD-L1 status<sup>48</sup>
  - b. Restriction in the first line setting was based on the early review of the IMvigor-130 trial which showed decreased survival in patients receiving first line atezolizumab compared to patients who received platinum based chemotherapy. <sup>51</sup> IMvigor130 utilized a similar study design as Keynote-361, although with a larger sample size, to randomize subjects 1:1:1 to atezolizumab + chemotherapy vs. chemotherapy vs. atezolizumab. Interim OS results have been published.
    - 1) Atezolizumab vs. chemotherapy
      - a) OS: HR 1.02, 95% CI 0.83 - 1.25
        - i. Atezolizumab (n = 362) median OS 15.7 months
        - ii. Chemotherapy (n = 400) median OS 13.1 months
      - b) OS (PD-L1 IC  $\geq 5\%$  subgroup): HR 0.68, 95% CI 0.43-1.08)
        - i. Atezolizumab (n = 88): median OS not reached
        - ii. Chemotherapy (n = 91): median OS 17.8 months
    - c. Atezolizumab's FDA approval for bladder cancer was voluntarily withdrawn in 12/2022 due to lack of OS benefit in a confirmatory Phase III trial, a component its accelerated approval in this disease state. Publication and presentation of this data (IMvigor 130) has not yet occurred.
- 4. Ifosfamide/doxorubicin/gemcitabine<sup>52</sup>
  - a. Reserved for those with good kidney function and good performance status
  - b. Ifosfamide 1500 mg/m<sup>2</sup> daily with mesna 225mg/m<sup>2</sup> day 1–4, doxorubicin 45 mg/m<sup>2</sup> day 3, and gemcitabine at 150 mg/m<sup>2</sup> on day 2 and day 4, every 14 days with growth factor support
- 5. Paclitaxel/Gemcitabine<sup>53</sup>
  - a. Paclitaxel 200 mg/m<sup>2</sup> on day 1 & gemcitabine 1000 mg/m<sup>2</sup> IV on days 1, 8, & 15 every 21 days.
- 6. Patients with advanced or metastatic disease are generally treated for a maximum of 6 cycles of cytotoxic chemotherapy. Patients are evaluated after 2-3 cycles of chemotherapy, with continuation for 2-3 more cycles if responding or stable disease.



Select patients may be considered for surgery or radiotherapy if a major partial response is seen followed by 2 additional cycles of chemotherapy. If no response is seen after 2 cycles of chemotherapy or significant toxicity is noted, regimen change is indicated.<sup>8</sup>

**Patient Case #1, ARS Question #2 Answer:**

CT should receive platinum-based chemotherapy followed by avelumab maintenance (**answer C**). His CrCl < 50 mL/min makes him cisplatin-ineligible. His distant metastases preclude curative treatment with neoadjuvant cisplatin-based chemotherapy and surgery. The first-line use of immune checkpoint inhibitors continues to evolve. Pembrolizumab is approved and an option only for patients not eligible for any platinum-based regimen. Atezolizumab remains an option for patients who are not candidates for cisplatin if tumors PD-L1 positive (IC  $\geq$  5%) or not candidates for any platinum-based chemo. Thus, had CT's tumor had  $\geq$  5% IC PD-L1 positivity atezolizumab also would be considered correct.

7. Maintenance therapy

a. Avelumab (category 1)

- 1) A Phase III study (JAVELIN Bladder 100) of maintenance avelumab (10 mg/kg q 2 weeks) vs. best supportive care (BSC) in patients who did not progress following initial treatment with platinum-based chemotherapy showed a significant improvement in overall survival.<sup>54</sup> The majority (53.1%) of patients in the BSC subsequently received immunotherapy after progression.<sup>55</sup>

**JAVELIN Bladder 100 Overall Survival Outcomes by Cohort**

Median OS	Avelumab (n = 350)	BSC (n = 350)	HR; 95% CI (p-value)
All Patients	21.4 months	14.3 months	0.69; 0.56-0.86 (p = 0.001)
PD-L1 (+)	Not estimable	17.1 months	0.56; 0.40-0.79 (p < 0.001)
PD-L1 (-)	18.8 months	13.7 months	0.85; 0.62-1.18 (p not reported)

**30-Month Landmark Analysis<sup>55</sup>**

Endpoint	Avelumab	BSC
PFS	19.3%	6.3%
PD-L1 (+) cohort	25.1%	6.7%
OS	43.7%	33.5%
PD-L1(+) cohort	51.3%	38.5%

b. Pembrolizumab

- 1) A Phase II study of maintenance pembrolizumab vs. placebo following initial treatment with platinum-based therapy did not demonstrate a benefit in overall survival. Patients in the placebo arm were readily able to receive pembrolizumab upon progression.<sup>56</sup>

#### 8. Summary of Initial treatment of metastatic disease

- a. Platinum-based chemotherapy followed by avelumab maintenance appears to be the optimal treatment approach at this time. Initial treatment of metastatic disease with concurrent chemotherapy and immunotherapy (i.e. Keynote-361) has not shown benefit at this time and single agent immunotherapy appears inferior to platinum-based chemotherapy.<sup>57</sup>

#### Initial Treatments (advanced or metastatic disease)<sup>5</sup>

NCCN Guidelines®	Cisplatin eligible*	Cisplatin ineligible
<b>Preferred</b>	ddMVAC (Category 1) followed by avelumab maintenance if no progression following chemotherapy  Gemcitabine/cisplatin (Category 1) followed by avelumab maintenance if no progression following chemotherapy	Gemcitabine/carboplatin followed by avelumab maintenance if no progression following chemotherapy  Atezolizumab (only PD-L1+ tumors or patients not eligible for any platinum-based chemotherapy)  Pembrolizumab (only for patients not eligible for any platinum-based chemotherapy)
<b>Alternatives</b>		Gemcitabine +/- paclitaxel
<b>Useful under certain circumstances</b>		Ifosfamide, doxorubicin, gemcitabine**

\*Cisplatin eligibility may vary, but common criteria utilized in clinical trials include adequate renal function, ECOG performance status = 0 or 1, and lack of hearing impairment

\*\*May be useful in certain circumstances in patients with good renal function and performance status

#### E. Second line therapy

#### 2<sup>nd</sup>-line Treatments (advanced or metastatic disease)<sup>5</sup>

	Post-platinum	Post-checkpoint inhibitor
<b>Preferred</b>	Pembrolizumab (Category 1)	<u>Cisplatin eligible, but chemotherapy naïve</u>  Gemcitabine/cisplatin ddMVAC with growth factor support  <u>Cisplatin ineligible, but chemotherapy naïve</u>  Gemcitabine/carboplatin

		Enfortumab vedotin-ejfv
<b>Alternative preferred</b>	<u>Immune Checkpoint inhibitors</u> Avelumab Nivolumab Erdafitinib* Enfortumab vedotin-ejfv	
<b>Other recommended regimens</b>	Docetaxel or paclitaxel Gemcitabine	Erdafitinib* Paclitaxel or docetaxel Gemcitabine
<b>Useful in certain circumstances</b>	Ifosfamide, doxorubicin, & gemcitabine Gemcitabine & paclitaxel Gemcitabine & cisplatin ddMVAC and growth factor support	Ifosfamide, doxorubicin, & gemcitabine Gemcitabine & paclitaxel

\*If susceptible FGFR2 or FGFR3 alterations present

1. Clinical trial recommended
2. Checkpoint inhibitors preferred after first line platinum-based therapy
3. May consider single chemotherapeutic agents or combination regimens.
  - a. Platinum-based chemotherapy regimens may be repeated if the PFS > 12 months from last platinum-based treatment
4. Checkpoint inhibitors
  - a. Indication- Treatment of locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy and have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This is based on data from clinical trials before the currently recommended use of maintenance avelumab.
  - b. For cisplatin-ineligible patients and with PD-L1 expression or those who are not eligible for platinum-containing chemo
    - 1) **Immune checkpoint inhibitor monotherapy in 1<sup>st</sup>-line setting metastatic disease is limited to those who are cisplatin ineligible or PD-L1 (+) for atezolizumab. Inferior survival has been observed patients with low PD-L1 expression compared to platinum-based regimens.<sup>48</sup> Recommendations may evolve as OS data matures.**

- c. Toxicities- please see Melanoma module for in depth discussion of checkpoint inhibitor toxicities and management
  - d. Treat until disease progression or unacceptable toxicity
  - e. In patients without disease progression may treat for up to 24 months
- 5. The role of checkpoint inhibitors in patients who previously received maintenance avelumab remains unknown at this time
  - a. Pembrolizumab NCCN® guideline Category 1 approval in the second line setting regardless of PD-L1 level was based on the results of a randomized, phase III trial<sup>58</sup>:
    - 1) 542 patients with advanced UC with recurrence or progression after platinum-based therapy randomized to pembrolizumab or chemotherapy (that included single agent paclitaxel, docetaxel or vinflunine)
    - 2) Pembrolizumab resulted in an improved mOS of 10.3 months compared with 7.4 months in the chemotherapy group (p=0.002).
    - 3) There were fewer grade  $\geq 3$  adverse effects in the pembrolizumab group as well (15% compared with 49.4% in the chemotherapy group)

## Summary of Anti-PD-1/PD-L1 Therapy Trials

Drug/Trial	PD-L1 Positivity Definitions	Key Findings
<b>Pembrolizumab vs. Chemo</b> Bellmunt et al <sup>58</sup> Keynote-045 N = 542	PD-L1 combined positive score (CPS*) $\geq 10$ *PD-L1 (+) TC: PD-L1 (+) IC	<u><b>Median OS (all patients)</b></u> <ul style="list-style-type: none"> <li>• <b>Pembrolizumab 10.3 months (95% CI 8.0-11.8)</b></li> <li>• <b>Chemo: 7.4 months (95% CI 6.1-8.3)</b>  <b>HR 0.73; 95% CI, 0.59-0.91; p = 0.002</b></li> </ul> <u><b>Median OS (CPS <math>\geq 10</math>)</b></u> <ul style="list-style-type: none"> <li>• Pembrolizumab 8.0 months (95% CI 5.0-12.3)</li> <li>• Chemo: 5.2 months (95% CI 4.0-7.4)                      HR 0.57; 95% CI, 0.37-0.88; p = 0.005</li> </ul>
Avelumab Patel et al <sup>59,60</sup> JAVELIN N = 249	PD-L1 $\geq 5\%$	Entire cohort (2-year follow-up) <ul style="list-style-type: none"> <li>• ORR: 16.5% (95% CI 12.1-21.8)</li> <li>• Median DOR: 20.5 months (95% CI 9.7-NE)</li> <li>• Median OS: 7 months (95% CI 5.9-8.5)</li> <li>• 24-month OS: 20.1% (95% CI 15.2-25.4)</li> </ul> Activity by PD-L1 status (interim analysis) <ul style="list-style-type: none"> <li>• PD-L1 (+) ORR (n = 63): 24% (95% CI 14-36)</li> <li>• PD-L1 (-) ORR (n = 76): 13% (95% CI 7-23)</li> </ul>
Durvalumab Powles et al <sup>61,62</sup> N= 191	PD-L1 high: TC or IC $\geq 25\%$ PD- L1 low/negative: TC or IC < 25%	<u><b>ORR</b></u> <ul style="list-style-type: none"> <li>• All patients: 17.8% (95% CI 12.7-24.0)</li> <li>• PD-L1 high: 27.6% (95% CI 19.0-37.5)</li> <li>• PD- L1 low: 4% (95% CI 1.4- 12.5)</li> </ul> <u><b>Median OS</b></u> <ul style="list-style-type: none"> <li>• All pts: 18.2 months (95% CI 8.1-NE)</li> <li>• PD-L1 high: 20.0 months (95% CI 11.6-NE)</li> <li>• PD- L1 low: 8.1 months (95% CI 3.1-NE)</li> </ul> <u><b>12-month OS</b></u> <ul style="list-style-type: none"> <li>• All pts: 55% (95% CI 44-65)</li> <li>• PD-L1 high: 63% (95% CI 49-74)</li> <li>• PD- L1 low: 41% (95% CI 21-60)</li> </ul>
Atezolizumab vs. chemo Powles et al <sup>63,64</sup> IMvigor211 N=931	IC0 (<1%), IC1 ( $\geq 1\%$ but <5%) IC2/3 ( $\geq 5\%$ )	<u><b>Median OS (IC2/3), n = 234</b></u> <ul style="list-style-type: none"> <li>• Atezolizumab 11.1 months (95% CI 8.6-15.5)</li> <li>• Chemo: 10.6 months (95% CI 8.4-12.2)                      HR 0.87; 95% CI, 0.63-1.21; p = 0.41</li> </ul>

Nivolumab Sharma et al <sup>65,66</sup> N= 265	PD-L1 (+): $\geq 1\%$ TC PD-L1 (-): $< 1\%$	<u>ORR</u> <ul style="list-style-type: none"> <li>All patients: 20.7% (95% CI 16.1-26.1)</li> <li>PD-L1 (+): 25.8% (95% CI 18.4-34.4)</li> <li>PD- L1 (-): 16.4% (95% CI 10.8- 23.5)</li> </ul>
		<u>Median OS</u> <ul style="list-style-type: none"> <li>All patients: 8.6 months (95% CI 6.1-11.3)</li> <li>PD-L1 (+): 11.9 months (95% CI 9.1-19.1)</li> <li>PD- L1 (-): 6.0 months (95% CI 4.4-8.1)</li> </ul>

TC, tumor cell; IC, immune cell

#### 6. Erdafitinib

- Inhibitor of fibroblast growth factor receptors 1-4 (FGFR)
- 2<sup>nd</sup>-line and later line option for metastatic disease in patients with FGFR2 or FGFR3 actionable alterations<sup>5</sup>

#### 7. Enfortumab vedotin

- Nectin-4 targeting antibody-drug conjugate with a MMAE payload.
- Category 1** recommendation for use following progression on platinum-based chemotherapy and PD-1/PD-L1 inhibitor.

##### 1) EV-301<sup>67</sup>

- Phase III randomized-controlled clinical trial in patients with locally advanced or metastatic urothelial carcinoma in patients previously treated with both platinum-based chemotherapy and PD-1/PD-L1 inhibitors

Treatment	Enfortumab vedotin	Investigator's choice of chemotherapy (docetaxel, paclitaxel or vinflunine)	
Median PFS	5.55 months	3.71 months	HR 0.62 (95% CI, 0.51 – 0.75)
Median OS	12.88 months	8.97 months	HR 0.70 (95% CI, 0.56 – 0.89)

- Category 2A option in the second-line setting for cisplatin-ineligible patients.

##### 1) EV-201<sup>68</sup>

- Phase II single-arm study of 89 patients considered cisplatin-ineligible previously treated with PD-1/PD-L1 inhibitors.
  - 75% did not respond to prior immune checkpoint inhibitor treatment
- Enfortumab vedotin produced an ORR = 52% (20% CR)

#### F. Subsequent Lines of Therapy Summary (i.e. 3<sup>rd</sup> line or later)

- Enfortumab vedotin (**category 1**) or erdafitinib (with susceptible FGFR 2 or FGFR 3 alterations) are preferred regimens

2. Other recommended regimens include sacituzumab govitecan-hziy; gemcitabine; paclitaxel or docetaxel; ifosfamide, doxorubicin, and gemcitabine; gemcitabine & paclitaxel; gemcitabine & cisplatin; and ddMVAC with growth factor support

## VII. Survivorship<sup>5,69</sup>

### A. Prognosis

1. Non-muscle invasive disease
  - a. 5-year survival rate is > 70%
  - b. Stage and grade are most important prognostic features
  - c. Follow up includes cystoscopy, imaging and urine studies
2. Muscle invasive disease
  - a. 5-year survival rates range between 30-40%
3. Metastatic disease
  - a. Generally, not curable. 5-year survival is approximately 5%.
  - b. Patients without visceral metastases tend to have better prognosis. In trial by von der Maase et al, 5-year overall survival was 6.8% vs. 20.9% for patients with and without visceral metastases, respectively.<sup>45</sup>

### B. Urinary complications: following radical cystectomy, urinary diversion must be established

1. Incontinent cutaneous diversion
  - a. Conduit created using small or large intestine (commonly ileal conduit)
  - b. Requires cutaneous stoma and external stoma appliances to collect urine
  - c. Early and late complications occur in 18-30%; parastomal hernia, urinary leakage, stromal stenosis, skin irritations
  - d. Significant psychological effects that decrease emotional well-being including decreased body image, sexual dysfunction, difficulties with activities of daily living and social activities.
2. Continent cutaneous diversion
  - a. Creates an intra-abdominal reservoir
  - b. Requires a catheter to drain 4-6 times per day
  - c. Infrequent catheterization may cause acute renal failure, perforation, infection
  - d. Early and late complications occur in 3-30%; stenosis, pouch leakage, incontinence
  - e. Less body image disruption than incontinent cutaneous diversion. However, nighttime catheterization may reduce sleep. Need for regular catheterization may limit social activities or ability to work.

3. Orthotopic diversion
  - a. Creates reservoir from colon or ileum that is connected to native urethra (neobladder)
  - b. Patients learn to void with relaxation of pelvic muscles and increase in intraabdominal pressure
  - c. Intermittent catheterization required for urinary retention or periodic irrigation
  - d. Requires timed voiding as normal bladder sensation is no longer intact
  - e. Good daytime continence achieved; nighttime continence ranges from 45-65%
  - f. Body image is generally maintained. Patients have fewer problems with bathing, sleeping, and sexual function.
4. Patients should be provided explanation of types of urinary diversion and effects on quality of life and functioning during counseling



## RENAL CELL CANCER

### I. Genomics, Etiology, and Pathogenesis

#### A. Pathophysiology<sup>70</sup>

1. The majority (>85%) of renal cell carcinomas arise from the proximal renal tubular epithelium. Histologically, renal cell carcinoma can be of various cell types.
2. Clear cell (ccRCC): most common (75-85%). Exhibits the 3p- cytogenetic abnormality which is where the VHL gene is located
3. Non-clear cell: Includes papillary (15%), chromophobe (5%), oncocytic (2-4%), and collecting-duct (1%). Translocation RCC is seen in pediatrics and young adults. It is characterized by a genetic translocation of Xp11.<sup>71</sup> Sarcomatoid features may be present in any subtype of RCC and is associated with more aggressive behavior. Medullary RCC is a rare tumor seen as a component of nephropathy of sickle cell disease.

#### B. Renal cell carcinoma (RCC) development may be sporadic or associated with familial or hereditary syndromes.

##### 1. Von Hippel-Lindau gene mutations

- a. Up to 90% of sporadic RCC is associated with the loss of function of the VHL tumor suppressor gene, located on short arm of chromosome 3 (3p25).<sup>72</sup>
- b. In the presence of normal oxygen concentrations, von Hippel-Lindau protein (pVHL) inhibits hypoxia-inducible factors (HIFs). HIFs are transcription factors which regulate the expression of many target genes, including vascular endothelial growth factor (VEGF).
- c. In low oxygen concentrations, HIF levels rise leading to increased gene expression including increased VEGF which facilitates angiogenesis and cell proliferation. In the majority of clear cell RCC, pVHL is not functional, leading to continued HIF activity promoting tumor growth and angiogenesis.<sup>71-73</sup>

#### C. The mammalian target of rapamycin (mTOR), specifically the mTOR complex 1, has been found to be activated in 60-80% of clear cell RCC and possibly in many non-clear cell tumors. mTOR promotes protein translation involved with regulation of cell growth and metabolism.<sup>71</sup>

#### D. Other genetic mutations identified include the chromatin remodeling gene polybromo 1 (PBRM1); histone-modifying genes SET domain containing 2 (SETD2), lysine (K)-specific demethylase (KDM5C), and lysine (K)-specific demethylase 6A (KDM6A); and tumor suppressor neurofibromin 2 (NF2). c-Met is noted to be amplified in metastatic RCC as well as implicated in the development of hereditary and sporadic papillary tumors.<sup>72,73</sup>

#### E. Genetic syndromes associated with RCC

##### 1. Von Hippel-Lindau syndrome

- a. Hereditary, autosomal dominant germline mutation of the VHL gene.<sup>73</sup>

- b. Patients are at high risk for RCC, renal cysts, retinal hemangiomas, hemangioblastomas of the cerebellum & spinal cord, pheochromocytomas, and pancreatic carcinomas.
  - c. 40% of patients will develop RCC and usually at a younger age. Often these patients develop multiple tumors in both kidneys.<sup>73</sup>
- 2. Birt-Hogg-Dube syndrome is associated with mutations in the folliculin gene (FLCN) which leads to chromophobe RCC, oncocytomas, and clear cell RCC.<sup>73</sup>
- 3. Hereditary leiomyomatosis and renal cell cancer: Familial syndrome with fumarate hydratase enzyme mutations is associated with leiomyomatosis and RCC. Usually an aggressive disease.<sup>73</sup>
- 4. Hereditary papillary renal cancer

## II. Prevention/Screening<sup>70,74,75</sup>

- A. Currently, there are no established guidelines for screening or prevention in the general population.
- B. Patients at risk for VHL syndrome (family history or showing signs/symptoms) should receive genetic counseling and testing. Patients found to have VHL syndrome may receive CT or MRI of abdomen yearly to screen for neoplasms including RCC. However, this is not an evidence-based recommendation.
- C. Risk Factors<sup>70,72,75</sup>
  - 1. Cigarette smoking. Heavy smoking (> 21 cigarettes per day) was associated with a relative risk of developing RCC of 2.03 and 1.58 in men and women, respectively.<sup>76</sup>
  - 2. Obesity: Estimated that 30-40% of RCC may be due to obesity.
  - 3. Hypertension
  - 4. Acquired polycystic disease of the kidney
  - 5. 2-3% of RCC thought to be secondary to inherited syndromes.<sup>72</sup> RCC in patients < 46 years old may be indicative of a hereditary disorder.<sup>70</sup>
  - 6. Age

## III. Treatment and Symptom Management<sup>70</sup>

- A. Prognosis<sup>74,75</sup>
  - 1. Only surgery is curative. 20-30% of patients with localized disease who undergo a nephrectomy will relapse. The median time from nephrectomy to relapse is one to two years with most recurring in 3 years. Local recurrences are rare with the majority of metastases occurring at distant sites.
  - 2. Overall, 1- and 5- year relative survival rates are 85% and 72%, respectively.<sup>74,75,77</sup>
  - 3. Most important determinants of prognosis are tumor stage, grade, local extent of tumor, presence of regional lymph node metastases, and metastatic disease at presentation.
- B. Memorial Sloan Kettering Cancer Center model (MSKCC): derived from clinical trials using interferon (IFN)
  - 1. Risk factors: low Karnofsky performance status (< 80%), high LDH (> 1.5 times the upper limit of normal [ULN]), low serum hemoglobin (less than lower limit of normal [LLN]), high corrected serum calcium (> ULN), and time from initial diagnosis to systemic therapy of less than 1 year.
    - a. 0 risk factors = good risk

- b. 1-2 risk factors = intermediate risk
  - c. 3-5 risk factors = poor risk
- C. International Metastatic RCC Database Consortium (IMRD) (Heng's model): derived from trials using sunitinib, sorafenib and bevacizumab + IFN
  - 1. Risk factors: low serum hemoglobin (less than lower limit of normal), high corrected serum calcium (> ULN), low Karnofsky performance status (< 80%), time from initial diagnosis to systemic therapy of less than 1-year, absolute neutrophil count > ULN, platelet count > ULN.
    - a. 0 risk factors = favorable risk (2-year OS 75%, 95% CI 65%-82%)
    - b. 1-2 risk factors = intermediate risk (2-year OS 53%, 95% CI 46%-59%)
    - c. 3-6 risk factors = poor risk (2-year OS 7%, 95% CI 2%-16%)
- D. Natural History of Disease<sup>3,70,74</sup>
  - 1. Patients with T1 or T2 lesions confined to the renal parenchyma who undergo radical nephrectomy are cured about 80% of the time.<sup>75</sup>
  - 2. 20% of patients present with lymph node involvement. Lymph node involvement and/or extracapsular spread are associated with a 5-year survival of approximately 60%.
  - 3. 20% present with metastatic disease. The most common sites of metastatic disease are the lungs (50-60%), bone (30-40%), liver (30-40%), and brain (5%). Patients with metastatic disease have a median survival of one year.
  - 4. 1-3% of tumors occur bilaterally, most commonly in patients with hereditary etiology.
  - 5. Up to 3% of patients with advanced disease may undergo a spontaneous regression of the disease. These spontaneous regressions suggest an important role of the immune response in controlling the tumor.
- E. Stage I disease<sup>70</sup>
  - 1. The goal of treatment in stage I disease is curative
  - 2. pT1a
    - a. Confined to kidney
    - b. Partial nephrectomy is preferred therapy. If partial nephrectomy is not feasible, radical nephrectomy should be performed.
    - c. Active surveillance in selected patients (elderly, small renal masses, decreased life expectancy). Involves abdominal imaging with treatment for progression.
    - d. Ablative therapy for non-surgical candidates (cryosurgery, radiofrequency ablation). Increased risk of local recurrence compared to surgical options.
  - 3. pT1b
    - a. Partial or radical nephrectomy
    - b. Active surveillance in select patients
  - 4. No adjuvant immunotherapy, chemotherapy, or radiation therapy indicated
  - 5. Follow-up

- a. H&P, laboratory tests annually, or as clinically indicated. Abdominal imaging within 3-12 months of surgery, 3-6 months after ablative therapy, or within 6 months of surveillance initiation then at least annually based on risk factors

**Patient Case #2: ARS Question #3**

LL is a 51-year-old man who was referred to urology after presenting to his PCP with several months of intermittent hematuria. His past medical history is significant only for hypertension (controlled with amlodipine). Workup revealed a 10 cm tumor of the left kidney (clear cell histology) with regional lymph node involvement (Stage III). Following radical nephrectomy, **what adjuvant therapy is most appropriate for LL?**

- A) Axitinib
- B) Sunitinib
- C) Ipilimumab + nivolumab
- D) Pembrolizumab

F. Stage II and III disease<sup>28</sup>

1. Curative therapy is partial or radical nephrectomy. Radical nephrectomy includes resection of kidney, adrenal gland & perirenal fat. Regional lymph nodes may be resected for staging purposes.
2. No adjuvant chemotherapy or radiation therapy indicated
3. Adjuvant TKIs
  - a. Five trials using either sunitinib, sorafenib, axitinib, or pazopanib failed to show an OS benefit.<sup>78-81</sup>
  - b. One sunitinib trial (S-TRAC) demonstrated an improvement in PFS, and was thus granted an FDA approval. Adjuvant sunitinib x 1 year for stage III clear cell RCC is a Category 3 recommendation, signifying disagreement in this recommendation from the NCCN<sup>®</sup> committee.<sup>82,83</sup>
4. Trials evaluating adjuvant interferon alpha (IFN-alfa) and/or high-dose interleukin (IL-2) after complete resection have not shown a delay in time to relapse nor improvement in survival.
5. Adjuvant immunotherapy
  - a. Keynote-564 demonstrated improved DFS in high risk stage II (grade 4 or sarcomatoid features), stage III patients, and stage IV patients with no evidence of disease (NED) following resection of oligometastatic disease who received pembrolizumab for 1 year compared to placebo.<sup>84</sup>
    - 1) Disease-free survival HR 0.63, 95% CI 0.50 – 0.80<sup>85</sup>
      - a) Estimated 30 month DFS
        - i. Pembrolizumab 75.2%

- ii. Placebo 65.5%
- b) The largest benefit was observed in the subgroup with M1 (resected with no evidence of disease): HR 0.28 (95% CI 0.12-0.66)
- b. Adjuvant pembrolizumab is a Category 2A recommendation for these patients following nephrectomy
  - 1) Stage II ccRCC with grade 4 disease +/- sarcomatoid features
  - 2) Stage III ccRCC
  - 3) Stage IV patients following metastatectomy within one year of nephrectomy
- 6. Surveillance is also a category 2A option following nephrectomy for all patients

**Patient Case #2, ARS Question #3 Answer:**

The correct answer is pembrolizumab (D). LL has a high risk of disease recurrence with Stage III RCC. Both sunitinib and pembrolizumab are FDA-approved options. However, sunitinib has only been shown to improve disease-free survival (DFS) and not overall survival (OS) despite adequate follow-up. Thus, sunitinib's category 3 recommendation. Pembrolizumab (category 2A) has only demonstrated DFS benefit thus far as OS data are not mature. Surveillance is also a category 2A recommendation.

**Patient Case #2, ARS Question #4:**

LL undergoes surveillance instead of adjuvant therapy. At his 6-month follow up, he is noted to have lymphadenopathy on his abdominal CT. A chest CT shows a 2 cm lung lesion. Biopsy of the lung lesion was consistent with metastatic clear cell renal cell carcinoma. His BP is 124/72 (on amlodipine). Pertinent labs: SCr 1 mg/dl, Ca 9.3 mg/dl, Alb 4.2 g/dl, WBC  $7.0 \times 10^9/L$ , ANC  $4.0 \times 10^9/L$ , Hgb 11.1 g/dL, Platelets 250K, Karnofsky performance score is 90%.

**Which of the following is the most appropriate treatment option for LL?**

- A) Axitinib + pembrolizumab
- B) Cabozantinib + ipilimumab
- C) Lenvatinib plus everolimus
- D) Pazopanib

**Summary of NCCN Guidelines\* for Stage IV RCC<sup>®70</sup>**

Clear Cell Histology	Favorable Risk	Poor or Intermediate Risk
Preferred	Cabozantinib + nivolumab (category 1) Lenvatinib + pembrolizumab (category 1) Axitinib + pembrolizumab (category 1)	Ipilimumab + nivolumab (category 1) Axitinib + pembrolizumab (category 1) Cabozantinib + nivolumab (category 1) Lenvatinib + pembrolizumab (category 1) Cabozantinib
Other recommended regimens	Ipilimumab + nivolumab Axitinib + avelumab Sunitinib Pazopanib Cabozantinib (category 2B)	Pazopanib Sunitinib Axitinib + avelumab
Useful in certain circumstances	Active surveillance High-dose IL-2** (category 2B) Axitinib (category 2B)	Axitinib (category 2B) High-dose IL-2 (category 3) Temsirolimus (category 3)^

\*All recommendations 2A unless stated otherwise

\*\* For patients with excellent performance status and normal organ function.

^poor risk model used to direct treatment of temsirolimus included at least 3 of the 6 predictors of short survival: <1 year from time of diagnosis to start of treatment, Karnofsky score 60-70, Hgb < LLN, corrected Ca > 10 mg/dL, LDH > 1.5 x ULN, metastases in multiple organs

Subsequent Therapy (clear cell histology)	
Preferred	Cabozantinib (category 1) Nivolumab (category 1) Lenvatinib + everolimus
Other recommended regimens	Axitinib (category 1) Tivozanib (category 1; for patients who received 2+ prior regimens) Axitinib + pembrolizumab Cabozantinib + nivolumab Ipilimumab + nivolumab Lenvatinib + pembrolizumab Pazopanib

	Sunitinib Axitinib + avelumab (category 3)
Useful in certain circumstances	Everolimus Bevacizumab (category 2B)* High-dose IL-2 (category 2B for patients with excellent performance status and normal organ function) Temsirolimus (category 2B for poor-prognosis risk group)** Belzutifan (category 2B) Sorafenib (category 3)

\*An FDA approved biosimilar is an appropriate substitute for bevacizumab

\*\* poor risk model used to direct treatment of temsirolimus included at least 3 of the 6 predictors of short survival: <1 year from time of diagnosis to start of treatment, Karnofsky score 60-70, Hgb < LLN, corrected Ca > 10 mg/dL, LDH > 1.5 x ULN, metastases in multiple organs

Treatment Non-Clear Cell Histology	
Preferred	Clinical trial Sunitinib Cabozantinib
Other recommended regimens	Nivolumab Nivolumab + cabozantinib Pembrolizumab Lenvatinib + everolimus
Useful in certain circumstances	<b>Temsirolimus (category 1 for poor-prognosis risk group**, category 2A for other risk groups)</b> Bevacizumab*** Bevacizumab + erlotinib (papillary histology)*** Bevacizumab + everolimus*** Axitinib Erlotinib Everolimus Pazopanib Nivolumab + ipilimumab (category 2B)

\*all recommendations category 2A unless noted

\*\* poor risk model used to direct treatment of temsirolimus included at least 3 of the 6 predictors of short survival: <1 year from time of diagnosis to start of treatment, Karnofsky score 60-70, Hgb < LLN, corrected Ca > 10 mg/dL, LDH > 1.5 x ULN, metastases in multiple organs

\*\*\*An FDA approved biosimilar is an appropriate substitute for bevacizumab

#### G. Advanced or Stage IV Disease<sup>70</sup>

##### 1. Surgery

a. Cytoreductive nephrectomy before systemic therapy may be considered in patients with advanced or metastatic disease who have lung-only metastases, good prognostic risk, and good performance status and are considered for immunotherapy or targeted therapies

1) Patients with surgically resectable primary tumor and a solitary site of metastasis should have nephrectomy and surgical metastasectomy, stereotactic body radiation therapy (SBRT) or ablative techniques if not candidates for surgery. Patients who develop solitary site of recurrence after prolonged disease-free survival following nephrectomy may have metastasectomy.

a) If metastasectomy occurs within 1 year of nephrectomy, adjuvant pembrolizumab x 1 year is recommended (Category 2A).

2) Select patients (ECOG < 2, no brain metastases) with surgically resectable primary and lung-only metastases appear most likely to benefit from cytoreductive nephrectomy.<sup>70</sup>

3) Most data supporting cytoreductive nephrectomy hails from the pre-TKI era. The CARMENA study showed sunitinib was non-inferior to cytoreductive nephrectomy followed by sunitinib.<sup>86</sup> The role or potential benefit of cytoreductive nephrectomy is unknown in the immune checkpoint inhibitor era.

4) Traditionally immunotherapy agents like IL-2 and interferon were the primary treatment for advanced RCC until the more recent development of targeted agents like tyrosine kinase inhibitors and checkpoint inhibitors which have significantly altered the treatment approach for these patients.

#### **Patient Case #2, ARS Question #4 Answer:**

Based on the time to recurrence being < 1 year and the presence of anemia, the patient is classified as having intermediate risk disease. The correct choice is A. Axitinib + pembrolizumab is the only option that includes a category 1 preferred medication for intermediate risk disease. Cabozantinib + nivolumab would be an acceptable option, but TKIs + ipilimumab are not recommended. Lenvatinib plus everolimus is not an option in the first line setting, but lenvatinib + pembrolizumab would also have been acceptable choice.



**Patient Case #2, ARS Question #5:**

LL is scheduled to begin therapy with axitinib 5mg po BID + pembrolizumab.

**Throughout therapy with axitinib, LL should be monitored for which of the following?**

- A) Signs of depression
- B) Hypertension
- C) Hyperlipidemia
- D) Hyperglycemia

2. Targeted therapy

a. VEGF-targeting TKIs supplanted cytokines (IL-2, TNF-alpha) as 1<sup>st</sup>-line treatments of metastatic disease.

1) VEGF: angiogenic factor and was first described as an essential growth factor for vascular endothelial cells

a) VEGF-inhibiting TKIs

i. Sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, lenvatinib, tivozanib

2) Tivozanib (newly approved VEGF-inhibiting TKI)

a) MOA: tivozanib is a TKI that inhibits VEGFR-1, VEGFR-2, & VEGFR-3 in addition c-kit and PDGFR-beta.<sup>87</sup>

3) Indications & Dose:

a) Tivozanib was recently FDA-approved for patients with relapsed or refractory RCC after previously receiving at least 2 prior lines of systemic therapy by on the TIVO-3 study.<sup>88</sup>

b) TIVO-3 was a randomized, controlled clinical trial of 350 patients with advanced RCC with relapsed or refractory disease after 2 or more systemic therapies, including a VEGF-targeting agent.

c) Patients were randomized to tivozanib or sorafenib. Tivozanib demonstrated an improved PFS compared to sorafenib. Median PFS was 5.6 months vs. 3.9 months (HR 0.73, 95% CI 0.56-0.94; p = 0.016)

d) The FDA-approved dose of tivozanib is 1.34 mg PO daily without regards to food for 21 days of a 28-day cycle.

4) Toxicities:<sup>87</sup>

a) The most common toxicities reported with tivozanib include fatigue (67%), hypertension (44%), diarrhea (43%), decreased appetite (39%), nausea (30%), dysphonia (27%), hypothyroidism (24%) and stomatitis (21%).

b) Serious toxicity concerns include hypertension/hypertensive crisis, cardiac failure, cardiac ischemia and arterial thrombotic events, venous thrombotic events, hemorrhage, proteinuria, thyroid

dysfunction, impaired wound healing, reversible posterior leukoencephalopathy, and allergic reactions to the excipient tartrazine (FD&C Yellow No. 5)

- 5) Drug-drug interactions: As a CYP 3A4 substrate, tivozanib is susceptible to drug interactions with potent CYP 3A4 inducers (i.e. rifampin), but does not appear to interact with the potent CYP 3A4 inhibitor, ketoconazole. The use of strong 3A4 inducers should be avoided with tivozanib.

b. VEGF-targeting monoclonal antibody: bevacizumab

c. Hypoxia-inducible factor (HIF) inhibitor: belzutifan

a) Mechanism of action<sup>89</sup>

- i. Inhibits the effects of the transcription factor HIF-2-alpha (HIF-2a). In the setting of hypoxia or VHL-gene impairment, HIF-2a translocates to the nucleus and combines with HIF-1-beta to form a complex that results in increased expression of genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2a, preventing the formation of the transcriptional complex with HIF-1b.

b) Indications and Dose

- i. Indicated for adults with VHL-disease associated cancers (RCC, CNS hemangioblastomas, or pancreatic neuroendocrine tumors) not requiring immediate surgery.
- ii. Dose: 120 mg PO daily without regards to meals.
- (a) Patients with CYP2C19 and/or UGT2B17 impaired function are prone to increased drug exposure, but no formal dose recommendations exist for these patients.

c) Toxicities

- i. Serious toxicities include anemia (90%), hypoxia (up to 29%), and embryo-fetal harm. Common toxicities include fatigue, headache, visual impairment, nausea, dizziness, and hyperglycemia.

d) Drug-Drug Interactions

- i. CYP2C19 or UGT2B17 inhibitors increase belzutifan exposure as these are the main metabolic routes
- ii. CYP3A4 substrates: belzutifan is a weak CYP3A4 inducer and can decrease the exposure of 3A4 substrates. This interaction may be most pronounced in patients who are poor metabolizers of CYP2C19 or UGT2B17.
- (a) Avoid belzutifan in patients taking CYP3A4 substrates where therapeutic failure may occur with lower concentrations

- iii. Hormonal contraceptive use with belzutifan can lead to unanticipated pregnancy or breakthrough menstrual bleeding
  - d. Checkpoint inhibitors
    - 1) CTLA-4 monoclonal antibody
      - a) ipilimumab
    - 2) PD-1 monoclonal antibodies
      - a) nivolumab, pembrolizumab
    - 3) PD-L1 monoclonal antibody
      - a) Avelumab
  - e. mTOR: regulates micronutrients, cell growth, apoptosis and angiogenesis by its downstream effects on a variety of proteins
    - 1) mTOR inhibitors: everolimus and temsirolimus
- H. First-line therapy- predominantly clear cell histology<sup>70</sup>
  - 1. Sunitinib
    - a. First targeted agent to demonstrate improved PFS compared to interferon-alpha, the standard of care at the time.<sup>90</sup> Thus, sunitinib has been the comparator for recent clinical trials that have established combination therapies as preferred regimens for initial treatment of advanced RCC.
    - b. Sunitinib is no longer a preferred first-line treatment option for patients with advanced RCC by the NCCN guidelines®, but is a category 2A recommendation.<sup>70</sup>
  - 2. Axitinib + pembrolizumab<sup>91,92</sup>
    - a. This combination is a preferred treatment by the NCCN Guidelines® for both **favorable** and **poor/intermediate** risk disease, and is now a **category 1** recommendation for all levels of disease risk <sup>70</sup>
    - b. This was based off the KEYNOTE-426 trial which was a randomized, multicenter, open-label trial conducted in 861 ccRCC patients without previous treatment to receive either the combination of pembrolizumab and axitinib or single-agent sunitinib
      - 1) Pembrolizumab 200 mg every 3 weeks with axitinib 5 mg orally twice daily
      - 2) Sunitinib 50 mg orally once daily x 4 weeks of each 6-week cycle

### Keynote-426: Results of axitinib + pembrolizumab<sup>92</sup>

	Overall Survival at 24 Months (all patients)	Overall Survival at 24 Months (favorable risk)	Overall Survival at 24 Months (Int./poor risk)
Axitinib + pembrolizumab (n = 432)	74.4%	85.3%	69.2%
Sunitinib (n = 429)	65.5%	87.7%	55.8%
	p = 0.0003* (p < 0.0001)	p = 0.58	p = 0.0001

- c. The benefit of the combination was seen across all IMDC risk groups in preliminary results.<sup>91</sup> However, longer follow-up revealed no apparent benefit of axitinib & pembrolizumab in the favorable risk group.
    - 1) \*Since an improvement in overall survival was found in the intent-to-treat population (all risk patients), the author's state the p-values reported for the favorable and intermediate/poor risk subgroups are nominal.
  - d. Grade 3 or higher AE occurred in 75.8% of patients in the pembrolizumab-axitinib group and 70.6% in the sunitinib group.
3. Ipilimumab and Nivolumab<sup>93</sup>
- a. This combination is a **preferred, category 1** regimen for patients with **poor/intermediate** risk disease and is classified as an "other recommended regimen" for patients with favorable risk disease by the NCCN Guidelines®.<sup>70</sup>
  - b. This was based on the CheckMate 214 trial which was a phase III trial conducted in 1096 patients with previously untreated advanced clear cell RCC (ccRCC) to receive either nivolumab and ipilimumab or sunitinib regardless of PD-L1 expression. The co-primary endpoints were OS, ORR and PFS in patients with intermediate or poor risk disease.
    - 1) Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks
    - 2) Sunitinib 50 mg orally once daily x 4 weeks of each 6-week cycle

### Checkmate 214: Updated results of ipilimumab + nivolumab vs. sunitinib<sup>94</sup>

Intermediate/Poor Risk Patients	Overall Survival at 48 Months	PFS at 48 months	Objective Response Rate
Ipilimumab + nivolumab (n = 425)	50.0%	32.7%	42% (95% CI, 37-47)
Sunitinib (n = 422)	35.8%	12.3%	27% (95% CI, 22-31)
	HR 0.65, 95% CI 0.54-0.78	HR 0.74, 95% CI 0.62-0.88	p < 0.001

- c. Of the 1096 patients, the intent-to-treat population included 249 favorable-risk , 425 intermediate risk and 422 poor risk
  - 1) An exploratory 18-month OS analysis of favorable-risk patients differed from the results in intermediate/poor risk patients. In patients with favorable risk, more sunitinib patients (93%) remained alive at 18 months than ipilimumab + nivolumab patients (88%), though this result was not statistically significant (HR 1.45, 99.8% CI 0.51-4.12, p=0.27).
  - 2) These discordant results explain why NCCN® guidelines list ipilimumab + nivolumab as a category 1 recommendation for intermediate/poor risk patients, while not being a preferred regimen for favorable-risk patients.

#### 4. Lenvatinib + pembrolizumab

- a. Lenvatinib + pembrolizumab is a **preferred, Category 1** recommendation for patients regardless of risk category based on the results of the CLEAR trial.<sup>95</sup>
- b. This recommendation is based on the CLEAR trial which randomized assigned 1,069 newly diagnosed, untreated advanced ccRCC patients to sunitinib, lenvatinib 20 mg PO daily + pembrolizumab, or lenvatinib 18 mg PO daily + everolimus 5 mg PO daily. Randomization was stratified by MSKCC risk, geographic region, and PD-L1 status
- c. A hierarchal statistical analysis plan established PFS as the primary endpoint, followed by OS if PFS statistical significance was met
- d. Both lenvatinib arms showed improved PFS vs. sunitinib, albeit with high rates of drug discontinuation due to adverse events (37.2% of patients receiving lenvatinib + pembrolizumab stopped a drug, while 27% of patients receiving lenvatinib + everolimus stopped a drug compared to 14.4% with sunitinib).
- e. While a PFS benefit favoring lenvatinib + pembrolizumab appeared consistent in all risk sub-groups, the OS benefit in the favorable risk population is less certain – especially as OS data are not fully mature at this time.

Treatment arm	Median PFS	PFS HR (v. sunitinib)
Lenvatinib + pembrolizumab (n = 355)	23.9 months	0.39 (95% CI, 0.32-0.49)
Lenvatinib + everolimus (n = 357)	14.7 months	0.65 (95% CI, 0.53-0.80)
Sunitinib (n = 357)	9.2 months	-

Lenvatinib + Pembrolizumab OS by IMDC Risk Group	OS HR (v. sunitinib)
Favorable	1.15 (95% CI, 0.55-2.40)
Intermediate	0.72 (95% CI, 0.50-1.05)
Poor	0.30 (95% CI, 0.14-0.64)

Note: OS hazard ratios are presented by IMDC risk sub-group for consistency, but randomization was stratified by MSKCC risk group, not IMDC categories.

#### 5. Cabozantinib + nivolumab

- a. Cabozantinib + nivolumab is a **preferred, Category 1** recommendation for patients regardless of risk category based on the results of CheckMate 9ER.<sup>96</sup>
- b. CheckMate 9ER randomized 1651 newly diagnosed, untreated advanced ccRCC patients to sunitinib or cabozantinib 40 mg PO daily + nivolumab. Randomization was stratified by IMDC risk, geographic region, and PD-L1 status
- c. The primary endpoint was PFS, with OS as a key secondary endpoint with an alpha spending function used for analyzing OS.
- d. Cabozantinib + nivolumab improved both PFS and OS compared to sunitinib in the intent-to-treat population
- e. Longer follow-up of CheckMate 9ER shows consistent PFS benefit in all subgroups, with OS benefit demonstrated in poor risk patients with a median follow-up of 32.9 months.<sup>97</sup> The most common subsequent therapy in the sunitinib arm was an immune checkpoint inhibitor.

Treatment arm	Median OS	PFS HR (v. sunitinib)
Cabozantinib + nivolumab (n = 323)	37.7 months	0.7 (95% CI, 0.55-0.90)
Sunitinib (n = 328)	34.3 months	-

Cabozantinib + Nivolumab OS by IMDC Risk Group	OS HR (v. sunitinib)
Favorable	1.03 (95% CI, 0.55-1.92)
Intermediate	0.74 (95% CI, 0.54-1.01)
Poor	0.49 (95% CI, 0.31-0.79)

#### 1. Pazopanib<sup>70</sup>

- a. Pazopanib is an “other recommended option” for any risk disease by the NCCN guidelines®.<sup>70</sup>
- b. The COMPARZ Trial<sup>98</sup> was a non-inferiority trial conducted in 1110 metastatic ccRCC patients without previous treatment to receive either pazopanib or sunitinib.
  - 1) Pazopanib was found to be non-inferior to sunitinib for PFS (HR 1.05, 95% CI, 0.9-1.22). Overall survival was no different between the 2 groups (HR for death with pazopanib, 0.91; 95% CI, 0.76 to 1.08).
  - 2) Patients treated with sunitinib had more fatigue, hand-foot syndrome, taste alterations, lower quality of life scores and thrombocytopenia while pazopanib patients had higher incidence of increased LFTs.<sup>98</sup> Grade 3 and 4 increased AST and ALT occurred in 12% and 17% of pazopanib patients versus 3% and 4% of patients receiving sunitinib, respectively. Concomitant use with simvastatin increased risk of ALT elevations to 27%. It is recommended that pazopanib and simvastatin be used with caution and close monitoring or discontinue simvastatin.<sup>99</sup>

## Results of COMPARZ

	Progression Free Survival	Objective Response Rate*	Overall Survival
Sunitinib 50 mg PO daily x 4 week, then 2 weeks off (n = 557)	9.5 mo	25%	29.3 mo
Pazopanib 800 mg PO daily (n = 553)	8.4 mo	31%	28.4 mo

\*p<0.05

### Subgroup analysis of COMPARZ trial based on risk status

	OS with pazopanib	OS with sunitinib
Favorable Risk*	42.5 mo	43.6 mo
Intermediate Risk*	26.9 mo	26.1 mo
Poor Risk*	9.9 mo	7.7 mo

\*Based on MSKCC and Heng's model found in treatment and symptom management

- c. The PISCES Trial (n = 169) was designed to assess patient preference and health-related quality of life (HRQoL) between pazopanib and sunitinib in a double-blind, cross over design.
  - 1) **Approximately 70% of patients preferred pazopanib versus 22% preferring sunitinib due to better quality of life.** Patients reported less fatigue and taste changes with pazopanib than sunitinib.<sup>100,101</sup>
2. Axitinib + avelumab<sup>102</sup>
  - a. This combination is currently listed as an **“other recommended regimen”** for both favorable and poor/intermediate risk patients by the NCCN guidelines®.<sup>70</sup>
  - b. The JAVELIN Renal 101 trial was a randomized, phase 3 trial conducted in 886 patients without previous treatment to receive either the combination of avelumab and axitinib or single agent sunitinib. The co-primary endpoints were PFS and OS in PD-L1–positive (greater than 1% staining positive) patients, which represented 63% of the study population. PFS was a secondary endpoint in the overall population.
    - 1) Avelumab 10 mg/kg IV every 2 weeks with axitinib 5 mg orally twice daily
    - 2) Sunitinib 50 mg orally once daily x 4 weeks of each 6-week cycle

### Results of axitinib + avelumab vs. sunitinib

PD-L1 Positive			Overall population		
	Median PFS	Objective Response Rate		Median PFS	Objective Response Rate
Axitinib + avelumab (n = 270)	13.8 months	55.2% (95% CI, 49.0-61.2)	Axitinib + avelumab (n = 442)	13.8 months	51.4% (95% CI, 46.6-56.1)
Sunitinib (n = 290)	7.2 months	25.5% (95% CI, 20.6-30.9)	Sunitinib (n = 444)	8.4 months	25.7% (95% CI, 21.7-30.0)
	HR 0.61, 95% CI 0.47-0.79 (p < 0.001)	Stratified OR 3.73 (95% CI, 2.53-5.37)		HR 0.69, 95% CI 0.56-0.84 (p < 0.001)	Stratified OR 3.10 (95% CI, 2.30-4.15)

- c. Benefit in PFS and RR was seen irrespective of PD-L1 status and MSKCC or IMDC risk stratification.
- d. The regimen is not considered preferred as overall survival remain immature.<sup>103</sup>

### 3. Cabozantinib<sup>104</sup>

- a. Cabozantinib is a **preferred (category 2A)** first line option for patients with **poor/intermediate risk** disease and is an **“other recommended regimen”** with category **2B** classified for **favorable** risk disease by the NCCN Guidelines®.<sup>70</sup>
- b. This was based on the CABOSUN trial that was a randomized phase II trial in 157 patients with untreated advanced poor or intermediate risk RCC who were randomized to receive either cabozantinib or sunitinib, with PFS as the primary endpoint.

### Results of CABOSUN by Independent Review<sup>105</sup>

	Median Progression Free Survival	Objective Response Rate	Median Overall Survival
Cabozantinib 60mg daily (n = 79)	8.6 months	20%	26.6 months
Sunitinib 50mg daily 4 wks on, 2 wks off (n = 78)	5.3 months	9%	21.2 months
	HR 0.48, 95% CI, 0.31-0.74		HR 0.80, 95% CI, 0.53-1.21

- c. Toxicity: Grade 3 or 4 adverse events were 67% for cabozantinib and 68% for sunitinib and included diarrhea (cabozantinib, 10% v sunitinib, 11%), fatigue (6% v 15%), hypertension (28% v 22%), palmar-plantar erythrodysesthesia (8% v 4%), and hematologic adverse events (3% v 22%).

### 4. Summary of 1<sup>st</sup>-line treatments of ccRCC<sup>70</sup>

- a. Risk stratification is important in determining initial therapy



b. Favorable Risk

- 1) Three TKI/ICI combinations are preferred, Category 1 recommended regimens: axitinib + pembrolizumab, cabozantinib + nivolumab, and lenvatinib + pembrolizumab
  - a) These three combination regimens demonstrated superior efficacy compared to sunitinib in the RCC population.
  - b) The trial of axitinib + pembrolizumab has the longest published follow-up to date of these 3 regimens. It appears the overall survival benefit over sunitinib to be most pronounced, or even limited to, intermediate/poor risk patients.<sup>92</sup>

c. Intermediate & Poor Risk Patients

- 1) Four combination regimens have demonstrated superior overall survival compared to sunitinib in these patients. Thus, these are NCCN guideline **category 1** recommended regimens.
  - a) Axitinib + pembrolizumab
  - b) Cabozantinib + nivolumab
  - c) Lenvatinib + pembrolizumab
  - d) Ipilimumab + nivolumab (Note, this regimen is only category 1 for intermediate/poor risk patients, while the other 3 are also category 1 for favorable risk patients.)
- 2) A phase II trial (CABOSUN) showed cabozantinib improves surrogate markers of survival (PFS and ORR) compared to sunitinib

**Additional Treatment Options for Advanced ccRCC**

Trial	Patient Population	Therapies	Results	Comments
<b>ARCC<sup>106</sup></b>	N= 626	Temsirolimus 25 mg IV weekly	OS* improved in single agent temsirolimus arm only 10.9 months versus 7.3 and 8.4 months	Studied poor risk patients with 3 or more unfavorable risk factors: <ul style="list-style-type: none"> <li>• &lt; 1 year from diagnosis to systemic treatment</li> <li>• Karnofsky PS &lt; 80</li> <li>• Anemia</li> <li>• cCa &gt; 10 mg/dL</li> <li>• LDH &gt; 1.5x ULN</li> <li>• Metastases to multiple organs</li> </ul>
	Previously untreated RCC	versus  IFN alfa 3 MU titrated to 18MU SQ TIW versus  Temsirolimus 15 mg IV weekly + IFN alfa 6 MU TIW	PFS* temsirolimus 5.5 months vs 3.1 and 4.7 months	

RR= Response Rate, PFS= progression free survival, OS overall survival;\*= statistically significant MU= million units  
IFN=interferon, TIW= three times per week

**Patient Case #2, ARS Question #5 Answer:**

The correct answer is B. Elevated blood pressure is important monitoring parameter in patients receiving VEGF TKIs in general. Although the adverse effect profile is vast, the most likely adverse effect that LL will experience is increased hypertension which can occur in up to 40% of patients. Signs of depression, hyperlipidemia, hyperglycemia are all important monitoring parameters but are not part of the key adverse events associated with that VEGF TKIs. Mood disturbances, hyperlipidemia and hypokalemia were not reported Keynote-426, but not considered necessary monitoring parameters for this regimen.

**B. Cytokine therapy**

1. High-dose Interleukin-2 (IL-2) (aldesleukin)
  - a. Has largely fallen out of use with the advent of checkpoint inhibitors and TKIs.
  - b. Fyfe G et al published a report of 255 patients enrolled on seven different phase II trials of bolus high-dose IL-2 in metastatic renal cell carcinoma<sup>107</sup>
  - c. Overall response rate of 15% (7% CR).<sup>108</sup> Median survival was 16.3 months with 10-20% of patients estimated to be alive at 5-10 years after treatment demonstrating long-lasting remissions in a subset of patients.
  - d. The only predictive factor for response to IL-2 was a good performance status (ECOG 0-1).<sup>107,108</sup>
  - e. The most common Grade III - IV toxicities associated with IL-2 were hypotension (74%), oliguria (46%), altered mental status (28%), N/V (25%), diarrhea (22%), and dyspnea (17%). 4% of patients died of toxicity judged to be possibly or probably related to IL-2.<sup>107,108</sup> Reader is referred to review article from Poust JC et al. for review on toxicity management<sup>109</sup>
  - f. NCCN Guidelines® currently only recommends IL-2 for highly selected patients with relapsed or metastatic RCC (category 2B for favorable risk; category 3 for intermediate/poor risk).<sup>75</sup> Due to the high risk of toxicities, high dose IL-2 is given in an inpatient intensive care setting preferably at a facility experienced with using this therapy.

**Patient Case #2, ARS Question #6:**

LL presents to his oncologist after 15 months of stable disease while on axitinib + pembrolizumab. His treatment course thus far is notable for immune-related hypothyroidism, which is stable on levothyroxine. His ECOG performance status has declined from 0 to 1. His follow-up imaging reveals progressive disease with metastases to 2 bone sites.

**Which of the following is the most appropriate treatment at this time for LL?**

- A) Cabozantinib
- B) Ipilimumab
- C) High dose interleukin-2 (HD IL-2)
- D) Everolimus

**C. Subsequent treatment of metastatic RCC (clear cell)**

1. Two agents (cabozantinib and nivolumab) have demonstrated improved overall survival in patients who progressed on prior TKI therapy. Additionally, the combination of lenvatinib + everolimus also is a preferred recommendation for use following progression after prior therapy.
2. Further studies are needed to clarify the optimal treatment of patients who receive 1<sup>st</sup>-line treatment with a checkpoint inhibitor
  - a. Salvage nivolumab + ipilimumab has been studied retrospectively (n = 45) in heavily treated metastatic RCC patients who received prior checkpoint inhibitor therapy.<sup>110</sup>
    - 1) ORR = 20%
    - 2) irAE = 64% (grade 3+ =13%)
    - 3) The retrospective nature of this analysis and lack of clear dosing descriptions of ipilimumab & nivolumab highlight the need for further studies in RCC patients who progress after checkpoint inhibitors

### Second-line Therapy - Clear Cell Histology Clinical Trials<sup>70</sup>

Trial	Patient Population	Therapies	Notable Results	Comments
<b>CheckMate 025</b> <sup>111</sup>	821 patients	Nivolumab 3 mg/kg IV every 2 weeks or everolimus 10 mg PO daily	<b>Median OS:</b> Nivolumab 25 mos vs everolimus 19.6 mos	FDA approved dosage is a flat dose of 240mg
<b>METEOR</b> <sup>112,113</sup>	658 patients	Cabozantinib 60mg daily versus everolimus 10mg daily	<b>Median OS:</b> cabozantinib 21.4 mos vs everolimus 16.5 mos	
CheckMate 016 <sup>114</sup> (Phase I trial)	<b>N3I1:</b> 47 patients 47% previously treated  <b>N1I3:</b> 47 patients 55% previously treated	<b>N3I1:</b> Nivolumab 3mg/kg IV + Ipilimumab 1 mg/kg Q 3 weeks → Nivolumab 3 mg/kg Q 2 weeks  <b>N1I3:</b> Nivolumab 1mg/kg IV + Ipilimumab 3 mg/kg Q 3 weeks → Nivolumab 3 mg/kg Q 2 weeks	<b>N3I1:</b> ORR = 45.5% in previously treated patients  <b>N1I3:</b> ORR = 38.5% in previously treated patients  <u>Grade 3/4 adverse events</u> <b>N3I1:</b> 38.3% <b>N1I3:</b> 61.7%	Basis of NCCN category 2A preferred recommendation for subsequent treatment of ccRCC
AXIS <sup>77</sup>	723 patients	Axitinib 5mg PO bid versus sorafenib 400mg PO bid	RR: axitinib 19% versus sorafenib 9% PFS axitinib 6.7 mos versus sorafenib 6.7 mos	Increase to 7mg PO bid and 10mg PO bid allowed based on toxicity
Motzer et al <sup>115</sup>	153 patients	Lenvatinib 18mg + everolimus 5mg PO daily vs lenvatinib 24mg PO daily vs everolimus 10mg PO daily	PFS: lenvatinib + everolimus 14.6 mos vs lenvatinib 5.5 mos vs everolimus 7.4 mos	Trend towards OS benefit Median OS (months): Lenvatinib + everolimus: 25.5 Everolimus: 15.4 HR, 0.67; 95% CI (0.42-1.08)
Record 1 <sup>116</sup>	410 patients	Everolimus 10mg PO daily versus placebo	PFS: everolimus 4.9 mos versus placebo 1.9 mos	
TARGET <sup>117</sup>	903 patients	Sorafenib 400mg PO BID versus placebo	PFS: 5.5 mos versus 2.8 mos	

RR= Response Rate, PFS= progression free survival, OS overall survival

**Patient Case #2, ARS Question #6 Answer:**

The correct answer is A. Cabozantinib and nivolumab are both NCCN guideline® category 1 recommendations for subsequent treatment of ccRCC as both have shown improved OS compared to everolimus in patients who progressed on prior TKI therapy. Nivolumab + ipilimumab has demonstrated impressive ORR and duration of response in this patient population, but single agent ipilimumab is not recommended. HD IL-2 is not an ideal option in LL as his performance status has declined since starting treatment.

V. Treatment of Non-Clear Cell Histology

A. mTOR inhibitors<sup>75</sup>

1. ARCC trial: Ph 3 trial comparing temsirolimus vs temsirolimus/IFN vs IFN alone. OS benefit with temsirolimus for those with non-clear cell RCC compared to IFN-containing group (11.6mo vs 4.3mo). Temsirolimus is NCCN Guideline® **category 1 for poor prognosis and 2A for other risk groups non-clear cell RCC**<sup>70,106</sup>
2. REACT trial: Everolimus versus placebo, included non-clear cell histology. The median duration of treatment (12.1 weeks v 14 weeks) was similar between the non-clear cell and overall population. Overall response rate (1.3% v 1.7%) and rate of stable disease (49.3% v 51.6%) were similar between the clear cell and non-clear cell RCC patients as well.<sup>75</sup>
3. Additional phase 2 data supports everolimus for non-clear cell RCC: PFS of 5-7 months<sup>118</sup>. Everolimus is NCCN Guideline® category 2A for non-clear cell RCC.

B. Tyrosine kinase inhibitor (TKI)<sup>75</sup>

1. Sunitinib: treatment-naïve patients based on two phase II studies and data from expanded-access trials. Sunitinib is a **preferred** systemic treatment for non-clear cell RCC outside of a clinical trial
2. Sorafenib: has shown some clinical activity in non-clear cell RCC in phase II, retrospective, and expanded access trials. **Its use is no longer recommended.**
3. Pazopanib and axitinib: Ongoing trials evaluating these agents for non-clear cell histology
4. Erlotinib SWOG S0317: A phase II trial of erlotinib in 52 patients with advanced papillary RCC. Overall response was 11% and median OS was 27 months.<sup>119</sup>
5. Cabozantinib:
  - a. A retrospective analysis of 30 patients with non-clear cell RCC treated with cabozantinib demonstrated benefit. The median PFS was 8.6 months and median OS was 25.4 months<sup>120</sup>
  - b. The phase II SWOG 1500 (Pal SK, et al. ASCO GU 2021) suggested cabozantinib was superior to sunitinib in treatment metastatic papillary RCC (and crizotinib and savolitinib, in which accrual was stopped due to futility) in terms of PFS.
    - 1) Cabozantinib mPFS = 9.2 months vs. sunitinib mPFS (5.6 months) (1-sided p-value = 0.021)

- 2) This was a small study with 44 (cabozantinib) and 46 (sunitinib) patients per arm.

c. A **preferred** systemic treatment for non-clear cell histology.

6. Lenvatinib + everolimus:

- a. A single-arm, phase II trial of lenvatinib + everolimus in 31 patients advanced non-clear cell renal cell carcinoma yielded an objective response rate = 25.8%, a median PFS of 9.23 months, and a median OS of 15.64 months.<sup>121</sup>

7. Nivolumab + cabozantinib

C. VEGF inhibitor<sup>75</sup>

1. Bevacizumab: phase II trial for papillary RCC. The trial closed early for poor accrual; however PFS ranged from 6-25 months with reasonable toxicities.

D. Chemotherapy<sup>70</sup>

1. Generally, chemotherapy is of limited value in treating RCC
2. Sarcomatoid, renal medullary and collecting-duct carcinoma are rare, aggressive, and associated with poor prognosis. Treatment of these histologies may include cytotoxic chemotherapy regimens.
  - a. Renal medullary carcinomas typically do not respond to TKIs or mTOR inhibitors. If clinical trial enrollment is not an option, then platinum-based chemotherapy (carboplatin/gemcitabine, carboplatin/paclitaxel, or cisplatin/gemcitabine) is the preferred treatment.

E. Summary

1. Temezirolimus is the only treatment in this patient population with an NCCN guideline® category 1 recommendation for those with non-clear cell histology who have a poor prognosis.
2. Sunitinib, cabozantinib or clinical trial enrollment are the next preferred options per NCCN Guidelines

## VI. Survivorship and Long Term Follow Up<sup>70</sup>

A. Long term follow-up

1. History and physical Imaging with Chest x-ray or CT scan
2. Bone scan
3. Laboratory evaluations
4. Skeletal metastases: Occur in 30-40% of patients. Generally osteolytic lesions and lead to skeletal related events (SRE) such as pain with need for surgery or radiation, fractures, hypercalcemia, and spinal cord compression
  - a. Zoledronic acid
    - 1) A retrospective analysis of 74 patients found a significant reduction in SRE for those receiving zoledronic acid 4 mg vs placebo every 3 weeks (37% v 74%; p=0.015)<sup>122</sup>

- 2) A randomized trial of 773 patients found zoledronic acid delayed time to first SRE and decreased the number of patients with at least 1 SRE compared to placebo in solid tumor patients with skeletal metastases.<sup>123</sup>
- b. Denosumab
  - 1) A non-inferiority randomized trial evaluated denosumab 120mg or zoledronic acid 4mg every 4 weeks in patients with solid tumors (excluding breast or prostate) or multiple myeloma with skeletal metastases. Denosumab was non-inferior to zoledronic acid in delaying time to first SRE. Hypocalcemia was more commonly seen with denosumab. There was no difference in OS or disease progression between the groups.<sup>74</sup>
5. Brain metastases: Surgery for solitary brain metastases with well controlled extracranial disease is recommended. Stereotactic radiotherapy or whole brain radiation is also recommended depending on the volume of brain metastases.<sup>75</sup>
  - a. Brain metastases from RCC (and melanoma) are more likely to bleed spontaneously than other metastatic brain lesions.<sup>124</sup> However, this does not preclude the use of anticoagulation as this does not appear to further increase the risk of CNS hemorrhage.

## TESTICULAR CANCER

### Patient Case 3 Question 1:

SD, a 26-year-old male, presents to his primary care physician with painless swelling of his left testicle. After a two-week trial of antibiotics with no improvement in symptoms, the patient is referred to a urologist who confirms a solid testicular nodule on ultrasound. The patient then undergoes an inguinal orchiectomy, which reveals embryonal cell carcinoma. Staging CTs of the chest and abdomen reveal bulky retroperitoneal lymphadenopathy and pulmonary nodules. His alpha-fetoprotein is 500 ng/ml (normal range <10 ng/ml), beta-hCG is 3000 units/ml (<15 ng/ml), and lactate dehydrogenase is 290 (100 – 250 IU/ml). **Based upon this information, what is SD's risk classification for his newly diagnosed nonseminoma?**

- A) Good risk
- B) Intermediate risk
- C) Poor risk
- D) Unable to determine

### I. Risk Estimation

#### A. Tumor Markers<sup>125,126,127</sup>

1. Tumor markers are assessed before and after orchiectomy as well as throughout therapy. **Post-orchiectomy levels are important in risk stratification for nonseminoma patients.**
2. Alpha-fetoprotein (AFP)
  - a. AFP is the major serum protein of the fetus that is also elevated in pregnant women and in patients with hepatocellular carcinoma
  - b. Produced by nonseminomatous cells and may be elevated at any stage
  - c. Elevated only in 40-60% of nonseminomatous tumors
  - d. Biologic half-life of 5-7 days
  - e. A histologically "pure" seminoma with an elevated AFP is assumed to have an undetected nonseminoma focus
3.  $\beta$ -human chorionic gonadotropin (HCG)
  - a. HCG elevated in 10-20% of seminomas, and 40-60% of nonseminomatous disease.
  - b. HCG may be elevated in pregnancy, hypogonadism and marijuana use
  - c. Biologic half-life of 1-3 days
4. Patients with nonseminomatous germ cell tumors with slower than predicted improvement of HCG ( $t_{1/2} > 3.5$  days) and AFP ( $t_{1/2} > 7$  days) after treatment have a lower complete response rate and shorter survival.<sup>128</sup>
5. Lactate dehydrogenase (LDH)
  - a. Nonspecific marker that appears related to tumor burden

- b. Elevated in 60% of nonseminomatous tumors, and 80% of patients with seminomas.
- B. Risk Factor-Based Staging System for Metastatic Germ Cell Tumors<sup>125</sup>
  - 1. Seminoma
    - a. "Good Risk" → No non-pulmonary visceral metastasis, normal AFP, any LDH, any betaHCG
    - b. "Intermediate Risk" → Non-pulmonary visceral metastasis (bone, liver, brain), normal AFP, any LDH, any betaHCG
    - c. "Poor Risk" does not exist with seminoma due to sensitivity to chemotherapy ± radiation
  - 2. Nonseminoma
    - a. "Good Risk" → All of the following:
      - 1) Post-orchietomy tumor markers, all must be : HCG < 5,000 IU/ml, AFP < 1,000 ng/ml, LDH < 1.5 x ULN
      - 2) Testicular or retroperitoneal primary tumor
      - 3) No non-pulmonary visceral metastasis
    - b. "Intermediate Risk" → All of the following:
      - 1) Post-orchietomy tumor markers, any of: HCG 5,000 - 50,000 IU/ml, AFP 1,000 - 10,000 ng/ml, or LDH 1.5 - 10 x ULN
      - 2) Testicular or retroperitoneal primary tumor
      - 3) No non-pulmonary visceral metastasis
    - c. "Poor Risk" → Any of the following:
      - 1) Post-orchietomy HCG > 50,000 IU/ml, AFP > 10,000 ng/ml, or LDH > 10x ULN
      - 2) Mediastinal primary site
      - 3) Non-pulmonary visceral metastasis present

**Patient Case #3, Question 1 Answer:**

The correct answer is A. SD has been diagnosed with embryonal cell testicular cancer which is a nonseminoma. He has a testicular primary with retroperitoneal lymphadenopathy and pulmonary metastases only. His HCG, AFP and LDH are 3000 IU/ml, 500ng/ml and 290 IU/ml, respectively. Therefore, SD is classified as good prognosis.



**Patient Case #3, Question 2:**

SD is diagnosed with stage IIIA non-seminoma, good risk testicular cancer. He is scheduled to begin BEP for 3 cycles. He presents to clinic today for chemotherapy education. He has read that chemotherapy may cause neutropenia with fevers and is asking about filgrastim (G-CSF) use. **Which of the following best explains the use of filgrastim with BEP?**

- A) The use of G-CSF with bleomycin has been associated with an increased risk of bleomycin induced pulmonary toxicity in patients receiving BEP and is contraindicated.
- B) BEP is associated with a high (>20%) incidence of FN, so G-CSF for primary prophylaxis is recommended in all patients.
- C) Since SD has metastatic cancer, the goal of therapy is palliative, therefore G-CSF should only be used if SD develops FN during cycle 1 of BEP.
- D) G-CSF may increase one's risk of bleomycin induced pulmonary toxicity, but this risk is not proven and G-CSF may still be used when necessary in patients receiving BEP.

**II. Treatment and Symptom Management<sup>125,126</sup>****A. The initial intervention for testicular cancer is a radical inguinal orchiectomy.**

1. Testicles should not be biopsied as this can increase the risk of disease recurrence

**B. Pathophysiology<sup>125</sup>**

4. Histologically, greater than 95% of testicular tumors are germ cell tumors. Germ cell tumors are classified into two major histological subtypes: seminoma ( $\approx$  45%) and nonseminoma ( $\approx$  50%).
5. Seminoma
  - 1) Most frequent in the 4th decade of life
  - 2) Three subtypes: classic, anaplastic, & spermatocytic
  - 3) Spermatocytic presents in elderly men & rarely metastasizes so only surgery (radical orchiectomy) is recommended.
  - 4) Sensitive to radiation and platinum-based chemotherapy
  - 5) Elevated beta-human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH) may be seen; if alpha-fetoprotein (AFP) is elevated, patient should be treated as nonseminoma
2. Nonseminoma
  - 1) Most frequent in the 3<sup>rd</sup> decade of life
  - 2) Subtypes: embryonal carcinoma, teratoma, choriocarcinoma, & yolk sac carcinoma
  - 3) Sensitive to chemotherapy but not radiation
  - 4) May secrete both HCG and AFP

- 5) When both seminoma and nonseminoma parts are present in the tumor, treatment should be based on the nonseminoma guidelines because these tumors are more aggressive.
- 6) Occasionally, germ cell tumors arise from extragonadal primary sites (ex: mediastinal primary), but their management follows that of testicular primaries.

#### H. Natural History of Disease<sup>125,126</sup>

1. The first site of dissemination of testicular cancer is retroperitoneal lymph nodes. After lymph node involvement, hematogenous dissemination occurs to the lungs & other visceral organs. Pure choriocarcinomas (<1% of testicular tumors) are characterized by early hematogenous spread to lungs, viscera, and brain.
2. Left-sided testicle tumors spread first to the left para-aortic, preaortic, & left common iliac nodes while right-sided testicle tumors spread to right interaortocaval, paracaval, & preaortic and right common iliac lymph nodes.
3. Common sites of metastasis of testicular cancer are lungs, liver, bone, & brain.
4. Risk factors include prior history of germ cell tumor, family history, cryptorchidism, Klinefelter's syndrome and testicular dysgenesis.
5. Genetic alterations have been linked to a portion of germ cell tumors but the genetic basis of the disease remains poorly understood

#### C. Seminoma (exquisitely sensitive to radiation)

1. Stage IA and IB<sup>125</sup>
  - 1) Radical inguinal orchiectomy followed by surveillance (strongly preferred), adjuvant radiation, or adjuvant chemotherapy with 1-2 cycles of carboplatin AUC 7; regardless of treatment option, risk of recurrence is greatest in the first 2 years; most common site for relapse is retroperitoneal nodes.
  - 2) Relapse rate of 15-20% at 5 years
    - a) Despite this relapse rate, the NCCN panel strongly prefers surveillance for patients who can adhere to scheduled surveillance
  - 3) Adjuvant radiation or chemotherapy<sup>125</sup>
    - a) Relapse rate of <0.3% annually at 5 years
    - b) Oliver et al evaluated radiation vs. 1 cycle carboplatin (AUC 7) in 1477 patients with stage 1 seminoma.
      - i. Relapse-free survival at 3 years was 95.9% vs. 94.8% for radiation vs carboplatin, respectively (p=0.32).<sup>129</sup>
      - ii. Carboplatin appears less toxic than radiation as fewer patients in the carboplatin arm reported lethargy or needed time off work.

- iii. Long-term follow-up showed no difference in 5-year relapse free survival, 96% vs 94.7% for radiation vs carboplatin, respectively.<sup>130</sup>
    - iv. Carboplatin x 2 cycles has also been shown to decrease relapse rates. Therefore, carboplatin AUC 7 x 1 or 2 doses is recommended by the NCCN guidelines® as an additional option.<sup>125</sup>
  - c) Radiation 20 Gy in 10 daily fractions of 2 Gy to infradiaphragmatic area
    - i. Radiation therapy in these patients has been associated with secondary malignancies, but this may be due to outdated treatment practices that used higher radiation doses and larger treatment fields.<sup>125</sup>
- 2. Stage IS<sup>125</sup>
  - 1) Persistently elevated serum tumor markers after orchiectomy
  - 2) Imaging studies recommended to evaluate for evidence of disease and possible subsequent systemic therapy.
- 3. Stage IIA and IIB<sup>125</sup>
  - 1) Radiation can be considered although chemotherapy is preferred for stage IIB, with radiation being reserved for non-bulky ( $\leq 3$ cm) disease<sup>131</sup>
  - 2) Chemotherapy: cisplatin/etoposide (EP) chemotherapy x 4 cycles or bleomycin/etoposide/cisplatin (BEP) x 3 cycles as an alternative to radiation. Both are preferred options<sup>132,133</sup>
    - a) EP should be considered over BEP in these patients > 50 years of age, reduced GFR, or pulmonary co-morbidities due to possible increased risks of bleomycin-induced pulmonary toxicity.<sup>125</sup>
  - 3) If recurrence, treat based on extent of disease at time of recurrence
- 4. Stage IIC and III<sup>125</sup>
  - 1) Radical inguinal orchiectomy followed by systemic chemotherapy
  - 2) Good risk patients
    - a) EP x 4 cycles (NCCN guideline® category 1)
    - b) BEP x 3 cycles (NCCN guideline® category 1)
  - 3) Intermediate risk patients
    - a) BEP x 4 cycles (NCCN guideline® category 1)
    - b) VIP (etoposide/ifosfamide/cisplatin) x 4 cycles
      - i. VIP use should be reserved for patients not candidates for bleomycin

5. Immediate follow up therapy after initial chemotherapy for stage IIA, IIB, IIC, and III: obtain chest/abdominal/pelvis CT and serum tumor markers<sup>125</sup>
  - 1) No residual mass or residual mass <3 cm and normal tumor markers: Surveillance
  - 2) Residual mass (>3cm) and normal tumor markers: PET scan >6 weeks post chemo. If PET negative, surveillance. If PET positive, consider resection with retroperitoneal lymph node dissection (RPLND) or second-line cisplatin-based chemotherapy (TIP-paclitaxel/ifosfamide/cisplatin or VeIP-vinblastine/ifosfamide/cisplatin)
  - 3) If complete resection of residual disease, consider 2 cycles (EP or TIP or VIP or VeIP)
  - 4) If incomplete resection, recommend full course of second line therapy
  - 5) Progressive disease: second-line chemotherapy (TIP-paclitaxel/ifosfamide/cisplatin or VeIP-vinblastine/ifosfamide/cisplatin) or high dose chemotherapy with autologous HSCT

D. Nonseminoma<sup>94</sup>

1. Risk factors of relapse (as determined from orchiectomy)
  - 1) Lymphovascular invasion
  - 2) Invasion of spermatic cord
  - 3) Invasion of the scrotum
2. Stage I without relapse risk factors
  - 1) Surveillance (preferred), or
  - 2) Nerve-sparing RPLND, or
  - 3) BEP x 1 cycle (unless pure teratoma histology)
3. Stage I with relapse risk factors
  - 1) Surveillance, or
  - 2) Nerve-sparing RPLND, or
  - 3) BEP x 1 cycle (unless pure teratoma histology)
  - 4) Stage 1 survival rate exceeded 98% (due to excellent outcomes if patients progress, but is identified early due to surveillance). However, high cure rate is dependent on adherence to follow up examinations in the 20-30% of surveillance patients which will relapse.
4. Stage IS<sup>125</sup>
  - 1) EP x 4 cycles or BP x 3 cycles (both category 1)
5. Stage IIA<sup>125</sup>
  - 1) Treatment then depends on tumor marker levels after surgery.

- 2) Normal post-orchietomy tumor markers
    - a) Primary RPLND, or
    - b) EP x 4 cycles or BEP x 3 cycles
  - 3) Elevated post-orchietomy tumor markers – high risk of relapse
    - a) EP x 4 cycles or BEP x 3 cycles
6. Stage IIB<sup>125</sup>
- 1) Treatment dependent on post-orchietomy tumor markers and residual disease
  - 2) If normal tumor markers and residual disease confined to sites within lymphatic drainage in the retroperitoneum, either
    - a) Primary nerve-sparing RPLND in select cases, or
    - b) 4 cycles EP or 3 cycles BEP
  - 3) Relapse free survival with either regimen is near 98%
  - 4) If normal tumor markers and multifocal, symptomatic or lymph node metastases with aberrant lymphatic drainage: Primary chemotherapy with EP x 4 cycle or BEP x 3 cycles
  - 5) Persistently elevated tumor markers: EP x 4 cycles or BEP x 3 cycles
7. Subsequent therapy for Stage IIA or IIB<sup>125</sup>
- 1) After primary chemotherapy
    - a) Negative tumor markers and residual mass > 1cm: nerve-sparing RPLND
    - b) Negative tumor markers, no residual mass or residual mass <1cm
      - i. Surveillance, or
      - ii. Nerve sparing RPLND in select patients (category 2B)
    - c) After primary nerve-sparing RPLND, additional therapy based on lymph node status
      - i. pN0- no adjuvant chemotherapy; surveillance
      - ii. pN1
        - (a) Surveillance (preferred), or
        - (b) Adjuvant chemotherapy: EP x2 cycles or BEP x2 cycles (EP preferred regimen)
      - iii. pN2
        - (a) Adjuvant chemotherapy (preferred): EP x2 cycles, or BEP x2 cycles (EP preferred)

(b) Surveillance

- iv. pN3- adjuvant chemotherapy (BEP x 3 cycles or EP x 4 cycles)  
no preferred regimen

8. Stage IIC and IIIA<sup>125</sup>

- 1) Primary chemotherapy based on risk classification.
- 2) Good Risk: EP x 4 cycles (category 1) or BEP x 3 cycles (category 1)
  - a) Importance of bleomycin
  - b) Loehrer et al conducted a randomized trial of 178 patients with good risk testicular cancer comparing EP for 3 cycles vs BEP for 3 cycles. Both overall survival and relapse-free survival were worse for EP as compared to BEP.<sup>134</sup> More patients receiving EP had persistent carcinoma in post chemotherapy resected disease and relapses from complete remission.<sup>84</sup>

**Results of EP vs BEP**

	<b>Disease-free Survival (3 yrs.)</b>	<b>Overall Survival (3 yrs.)</b>
EP x 3	69%	86%
BEP x 3	89% (p=0.01)	95% (p=0.01)

- c) De Wit et al conducted a randomized trial of 419 patients with good risk testicular cancer comparing 4 cycles of BEP to 4 cycles of EP. Complete response was higher in the BEP group (95% vs 87% in BEP vs EP, respectively; p=0.0075). However, there was no significant difference in time to progression and overall survival between the 2 groups. Acute and late pulmonary toxicity was significantly greater in the BEP group.<sup>135</sup>
- d) To determine the number of cycles, Saxman et al compared 3 vs. 4 cycles of BEP in 118 good risk patients. There was no significant difference between the groups for overall survival or disease-free survival.<sup>136</sup>
- e) To try to eliminate toxicities associated with bleomycin Kondagunta et al evaluated EP x 4 cycles in 289 patients with good risk testicular cancer. Complete response was seen in 98% of patients. 6% experienced a relapse and 3% died from disease progression after median follow up of over 7 years.<sup>137</sup>
- f) A retrospective study evaluated 214 patients enrolled on 2 prospective studies of EP x 4 cycles for good risk GCT. Complete response was achieved by 91% of patients and 9% of those relapsed. At a median of 7.6 months of follow-up, 86% of patients were alive.<sup>138</sup>

- g) **Based on these studies, EP x 4 is an acceptable standard regimen and an alternative to BEP x 3**
- h) Bleomycin pulmonary toxicity (BPT): See Survivorship (below) for additional information.
- i. Bleomycin is deactivated by bleomycin hydrolase. Bleomycin hydrolase is not found in the lungs; therefore, lung toxicity may occur. Most common form of pulmonary toxicity from bleomycin is interstitial pneumonitis. However, this may progress to pulmonary fibrosis.<sup>139</sup>
  - ii. Pulmonary function tests, including DLCO (diffusing capacity of the lung for carbon monoxide) should be followed routinely during bleomycin therapy. Bleomycin should be discontinued for significant changes in pulmonary function, including a decrease in DLCO of 40-60%.<sup>139</sup>
  - iii. Scuba diving and supplemental oxygen may exacerbate BPT. The lowest possible FIO<sub>2</sub> that maintains adequate tissue oxygenation should be provided only when necessary
  - iv. BPT may lead to fibrosis which is irreversible and potentially fatal
  - v. Role of granulocyte colony stimulating factor use
    - (a) Several retrospective reviews evaluating risk of BPT in patients with Hodgkin lymphoma receiving ABVD found use of G-CSF as risk factor for the development of BPT.<sup>140</sup>
    - (b) While G-CSF has been associated with BPT in retrospective studies, randomized clinical trials have not demonstrated an increased risk of BPT in patient receiving G-CSFs.<sup>141</sup>
    - (c) While an increased risk of BPT may exist, G-CSF should still be used as clinically indicated for primary or secondary neutropenic complications.
    - (d) Consequently, do not confuse data recommending avoidance of G-CSF in Hodgkin lymphoma patients with use of G-CSF in testicular cancer patients
      - In testicular cancer, use of G-CSF is acceptable

**Patient Case #3, Question #2 Answer:**

The correct answer is D. Bleomycin pulmonary toxicity (BPT) has been associated with the use of colony stimulating factors in Hodgkin lymphoma. Currently, no increased risk has been seen with the combined use of colony stimulating factors and bleomycin containing regimens for testicular cancer. BEP is associated with an intermediate (10 to 20%) incidence of FN. While an increased risk of BPT may exist, G-CSF may still be used as primary prophylaxis in patients at high-risk for FN or as secondary prophylaxis during BEP treatment.

## i) Carboplatin vs. Cisplatin

- i. Multicenter, randomized trial comparing carboplatin/etoposide (CE) vs EP in 265 patients with good risk testicular cancer.
- ii. Complete response was similar between the 2 groups. However, **more patients receiving carboplatin had an incomplete response or relapse compared to cisplatin patients.**<sup>142</sup>

**Results of Carboplatin / etoposide versus cisplatin/ etoposide**

	CR	Event*	Deaths
Carboplatin + VP-16	88%	32	12
Cisplatin + VP-16	90% (p=0.32)	17(p=0.02)	4

\*Event = incomplete response or relapse

- iii. Randomized trial of 598 patients with good risk nonseminoma were randomized to BEP or carboplatin/etoposide/bleomycin (CEB) for 4 cycles.<sup>143</sup>

**Results of BEP versus CEB**

	CR	Relapses	Deaths
CEB	87.3%	79	27
BEP	94.4% (p=0.009)	30 (p<0.001)	10 (p=0.03)

- iv. Based on above studies, **cisplatin is the platinum of choice for good prognosis nonseminoma germ cell tumors**

- j) If a patient has persistent radiographic disease 4-6 weeks after completing chemotherapy, a surgical resection should be performed.

b. Intermediate Risk IIIB<sup>125</sup>

- 1) BEP x 4 cycles (category 1) cure rate is approximately 70%.
  - a) 3 cycles of BEP (or 4 cycles of EP) may be considered if LDH > 1.5-3 x ULN is the basis for intermediate risk
- 2) VIP x 4 cycles (category 1; for patients that may not tolerate the pulmonary toxicity of bleomycin due to a preexisting pulmonary condition)



- 3) A randomized trial compared 4 cycles of BEP vs 4 cycles of etoposide/ifosfamide/cisplatin (VIP) in 87 patients with intermediate risk nonseminoma. Complete response rates were similar between the 2 groups (79% vs 74% for BEP vs VIP, respectively;  $p=0.62$ ). The 5-year progression free survival was similar as well (83% vs 85%). VIP was associated with more toxicity, primarily bone marrow toxicity, although GCSF was not widely used.<sup>144</sup>
- c. Poor Risk IIIC<sup>125</sup>
- 1) 20-30% of patients with poor risk disease will not be cured with conventional therapy and less than 50% have durable response.
  - 2) Therefore, NCCN Guidelines® recommends BEP or VIP for 4 cycles (both category 1), with VIP being used in select patients such as those unable to tolerate bleomycin.
  - 3) A randomized trial compared high-dose cisplatin (40 mg/m<sup>2</sup> IV x 5 days) plus etoposide & bleomycin to standard dose BEP x 4 cycles in 159 patients with poor risk disease.
    - a) The study found no difference in overall survival or complete response between the two regimens. There was more toxicity in the patients receiving high dose cisplatin (neurotoxicity, ototoxicity, nausea/vomiting, myelosuppression).<sup>145</sup>
  - 4) A randomized trial compared BEP or VIP x 4 cycles in 304 patients with poor risk disease. There was no difference in complete response, failure free survival at 2 years, or 2-year overall survival. Grade 3 toxicities were more common in the VIP arm.<sup>146</sup>
9. Subsequent treatment after primary chemotherapy for good risk (Stage IS, IIA SI, IIB SI, IIC, IIIA), intermediate risk and poor risk<sup>125</sup>
- 1) Complete response and negative tumor markers
    - a) Stage IS: surveillance
    - b) Stage IIA SI, IIB SI, IIC, IIIA: surveillance or RPLND
  - 2) Partial response, residual masses with normal tumor markers: surgical resection of all residual masses, then:
    - a) Teratoma or necrosis: surveillance
    - b) Residual embryonal, yolk sac, choriocarcinoma, or seminoma element: EP or cisplatin, ifosfamide and paclitaxel (TIP) or VIP or cisplatin, ifosfamide and vinblastine (VeIP) x 2 cycles
  - 3) Partial response, residual masses with abnormal tumor markers
    - a) Elevated and rising AFP and  $\beta$ -HCG
      - i. Second line therapy
    - b) Elevated but stable AFP and  $\beta$ -HCG
      - i. Close surveillance

- c) Mildly elevated and normalizing AFP and  $\beta$ -HCG
  - i. Surgical resection of all masses
  - ii. If teratoma or necrosis, then surveillance is recommended
  - iii. If other histology, then 2 cycles of EP or TIP or VIP or VeIP
- 4) Relapse<sup>125</sup>
  - a) Options include conventional dose chemotherapy, high-dose chemotherapy with autologous stem cell transplant, salvage surgery, clinical trial or best supportive care.
  - b) Clinical trial (preferred) in early relapse (< 2 years from completion of primary therapy)
  - c) Surgical salvage if resectable (preferred) in late relapse
  - d) Favorable prognosis: low tumor markers, low volume of disease, complete response on first line therapy and testis primary
  - e) Chemotherapy with VeIP or TIP or high dose chemotherapy with stem cell support
    - i. Retrospective review of VeIP x 4 cycles in 24 patients with recurrent seminoma after cisplatin containing primary chemotherapy showed an 83% complete response rate. 54% of the patients experienced long term survival.<sup>147</sup>
    - ii. A phase II trial of 46 patients with favorable prognosis relapsed testicular GCT evaluated TIP x 4 cycles. Complete response was seen in 70% of patients, with 63% having a durable complete response and a 2-year progression free survival of 65%.<sup>148</sup>
    - iii. A retrospective review was published of 184 patients with progressive, metastatic testicular cancer given high dose carboplatin/etoposide followed by autologous stem cell support. 116 of the 184 patients had complete remission of disease without relapse during the median follow up of 48 months.<sup>149</sup>
    - iv. A retrospective study of 1,435 patients from 38 centers worldwide who relapsed following at least three cycles of cisplatin-based chemotherapy investigated the benefit of conventional cisplatin-based chemotherapy vs. high-dose chemotherapy.<sup>150</sup>
      - (a) 2-year PFS favored high-dose chemotherapy (50% vs. 28%;  $p < 0.001$ )
      - (b) 5-year OS favored high-dose chemotherapy (53% vs. 41%;  $p < 0.001$ )

- (c) TIGER, a prospective clinical trial that randomized patients to either conventional chemo (TIP) or high-dose chemotherapy, is ongoing with OS as its primary endpoint.<sup>28</sup>
  - f) Unfavorable prognosis: incomplete response, high tumor markers, high volume, extratesticular primary
    - i. Clinical trial (preferred) or
    - ii. VeIP or TIP, high-dose chemotherapy, or
    - iii. Surgical salvage if solitary site
  - g) Phase II trial of paclitaxel/ifosfamide followed by high dose carboplatin/etoposide with stem cell support in patients with poor prognosis relapsed/refractory testicular GCT showed a 5 year disease free survival rate of 47% and overall survival of 52%.<sup>151</sup>
  - h) Late relapse: >2 years after completion of primary therapy<sup>125</sup>
    - i. Surgical salvage if resectable (preferred), or
    - ii. Conventional chemotherapy (VeIP or TIP)
    - iii. High dose chemotherapy
10. Palliative therapy: consider in patients with intensively pretreated, cisplatin-resistant or refractory germ cell tumors<sup>125</sup>
- 1) Gemcitabine and oxaliplatin (GEMOX)
  - 2) Gemcitabine and paclitaxel
  - 3) Gemcitabine, oxaliplatin and paclitaxel
  - 4) Oral etoposide

## Common Chemotherapy Regimens for Testicular Cancer Chemotherapy Regimens

Regimen	Drugs and Doses	Frequency
<b>BEP</b>	Etoposide 100mg/m <sup>2</sup> /day IV on days 1-5 Cisplatin 20mg/m <sup>2</sup> /day IV on days 1-5 Bleomycin 30 units IV weekly on days 1, 8, 15 or days 2, 9, 16 Intermediate risk of FN, G-CSF use should be considered	Repeat every 21 days
<b>EP</b>	Etoposide 100mg/m <sup>2</sup> /day IV on days 1-5 Cisplatin 20mg/m <sup>2</sup> /day IV on days 1-5 Intermediate risk of FN, G-CSF use should be considered	Repeat every 21 days
<b>VIP</b>	Etoposide 75mg/m <sup>2</sup> /day IV on days 1-5 Ifosfamide 1200mg/m <sup>2</sup> /day IV on days 1-5 with Mesna support Cisplatin 20mg/m <sup>2</sup> /day IV on days 1-5 High risk of FN, G-CSF should be used	Repeat every 21 days
<b>VeIP</b>	Vinblastine 0.11 mg/kg/day IV push on days 1-2 Ifosfamide 1200mg/m <sup>2</sup> /day IV on days 1-5 with Mesna support Cisplatin 20mg/m <sup>2</sup> /day IV on days 1-5 High risk of FN, G-CSF should be used	Repeat every 21 days
<b>TIP</b>	Paclitaxel 250mg/m <sup>2</sup> IV over 24 hours on day 1 Ifosfamide 1500mg/m <sup>2</sup> /day IV on days 2-5 Mesna support Cisplatin 25mg/m <sup>2</sup> /day IV on days 2-5 High risk of FN, G-CSF should be used	Repeat every 21 days

### Patient Case #3, Question #3:

SD completed 3 cycles of BEP and has no evidence of disease. He is now being followed by his oncologist for recurrence. **Which of the following survivorship issues is SD at risk for?**

- A) Secondary malignancies and cardiovascular disease
- B) Ocular toxicity and cardiovascular disease
- C) Ocular and dermatologic toxicity
- D) Pulmonary toxicity and hepatotoxicity

### III. Survivorship: Long-term and Late Complications of Treatment<sup>152,153</sup>

- A. Due to life expectancy of 40-60 years after the successful treatment of testicular cancer (median age at diagnosis 33 years), long-term and late effects of treatment have become more concerning and offset the high cure rate. The long term effects are generally grouped as life-threatening (secondary malignancies or cardiovascular disease) or quality-of-life conditions (infertility, fatigue, etc.).<sup>153</sup> Secondary malignancies and cardiovascular disease have been identified as causes of premature death in long-term survivors.<sup>154</sup>
- B. Secondary malignancies<sup>152</sup>
  - 1. One of the most severe and serious long-term complications of treatment
  - 2. Observed/expected ratio of secondary solid malignancy was 1.55 (95% CI, 1.48-1.62) in 10-year survivors. These tumors usually develop 10 or more years after therapy for GCT and may be due to radiation or chemotherapy.

3. Observed/expected ratio of leukemia was 2.6 (95% CI, 2.1-3.2) in 10-year survivors. Most of the leukemias were acute myeloid and lymphoblastic leukemias. These malignancies tend to develop within the first 10 years after therapy.
4. Radiation induced cancers generally occur close to initial radiation fields, such as stomach, bladder, pancreas and colon cancers.
5. Much of the increased incidence of solid tumors is based on older cytotoxic chemotherapy and higher radiation doses than used today. Risk of secondary solid tumors is less well established with current risk adapted therapy.

#### C. Cardiovascular disease

1. Vascular complications including myocardial infarction, pulmonary emboli, venous thrombosis, and Raynaud phenomenon are reported<sup>153</sup>
2. Increased incidence of metabolic syndrome noted. Metabolic syndrome includes hypertension, dyslipidemia, obesity and insulin resistance.<sup>153</sup>
  - 1) De Haas et al found that at a median follow up of 5 years after chemotherapy, 25% of survivors developed metabolic syndrome compared with controls (OR 2.2, 95% CI, 1.5-3.3). Those with testosterone levels < 15 nmol/L had an increased risk of developing metabolic syndrome (OR 4.1, 95% CI, 1.8-9.3)<sup>155</sup>
  - 2) Haugnes et al found cisplatin-based chemotherapy more than doubled the odds of metabolic syndrome versus nonchemotherapy controls.<sup>156</sup>
  - 3) Willemse et al found an age-adjusted increased risk for metabolic syndrome of 1.9 for testicular cancer survivors versus controls with the highest risk in those treated with combination chemotherapy and those with the lowest testosterone levels.<sup>157</sup>
3. Increased risk of coronary artery disease (CAD) has been reported in multiple evaluations. Risk of CAD ranges from 1.2-7.1 with chemotherapy alone. Risk increases to ranges of 1.3-4.8 in patients receiving chemotherapy and radiation therapy.<sup>152</sup>
4. Raynaud's phenomenon is experienced during and after treatment and likely a result of direct vascular damage. It is seen in 15%-45% of patients who received chemotherapy. Bleomycin and cumulative cisplatin are thought to contribute.<sup>152</sup>
5. Smoking increases risk of cardiovascular disease and Raynaud phenomenon.<sup>153</sup> Smoking cessation is an important part of survivorship (See Smoking Cessation section in Head and Neck).
6. Low testosterone has been associated with increased risk of metabolic syndrome in several studies. Treatment of low testosterone is a potential area of intervention.

#### D. Pulmonary toxicity

1. A 2.5-fold increased risk of mortality from pulmonary disease has been seen in testicular cancer survivors treated with chemotherapy<sup>152,153</sup>
2. Nonfatal bleomycin pulmonary toxicity (BPT) occurs in 7-21%. Fatal BPT occurs in 1-3%.<sup>152</sup>

3. Risk factors for BPT: lifetime cumulative dose (>300 units), age at diagnosis (> 40 years), smoking, renal dysfunction, mediastinal radiation, Stage IV disease at diagnosis, oxygen administration, granulocyte colony stimulating factor use.
4. Pulmonary toxicity less common with standard 3-4 cycles of BEP. Acute pulmonary toxicities such as bronchiolitis obliterans, interstitial pneumonitis, and eosinophilic hypersensitivity should be treated with drug discontinuation and corticosteroids.<sup>153</sup>

#### E. Nephrotoxicity

1. Acute and long-term effect of radiation and chemotherapy. Persistent dysfunction following cisplatin therapy is estimated to occur in 20-30% of patients, however it is often asymptomatic.<sup>153</sup>
2. Along with hypomagnesemia, hypokalemia and hypocalcemia, cisplatin may cause sodium wasting and proteinuria.<sup>152</sup>
3. Renal artery stenosis has been reported in patients receiving para-aortic radiation and may lead to severe hypertension.<sup>152</sup> Post radiation induced renal dysfunction is gradual and generally detected 3-5 years after therapy.<sup>153</sup>
4. Vigorous hydration and avoidance of other nephrotoxic medications during cisplatin administration may help limit cisplatin nephrotoxicity

#### F. Neurotoxicity

1. Peripheral neuropathy (PN)
  - 1) Persistent PN from cisplatin reported in 20-40% of patients.<sup>152</sup> Risk factors include cisplatin cumulative dose and development of Raynaud phenomenon.<sup>153</sup>
2. Ototoxicity
  - 1) Generally seen as tinnitus and high-frequency hearing loss. Risk factors include cumulative cisplatin dose, high peak cisplatin levels, pre-existing hearing impairment, concomitant vinblastine exposure, hypomagnesemia.<sup>153</sup>
  - 2) Symptoms more than 5 years after cisplatin have been reported in 21-24% of survivors
  - 3) 5-day BEP preferred to 3-day BEP in regards to minimizing ototoxicity
3. Cognitive impairment<sup>158</sup>
  - 1) Amidi A, et al evaluated the prevalence of cognitive impairment in testicular cancer survivors by comparing neuropsychological test scores with normative data 2 to 7 years post treatment. Seventy-two survivors were tested on multiple cognitive domains including attention and working memory, processing speed, verbal fluency, learning and memory, and executive functioning. Survivors exhibited significantly impaired scores on 9 of the 12 neuropsychological outcomes and nearly 63% of patients were classified as having cognitive impairment. No association was found between treatment modality and cognitive impairment.

G. Avascular necrosis

1. Survivors are at increased risk compared to other solid tumor patients for unknown reasons. Incidence is around 1.5% after chemotherapy and generally occurs more than 6 months after therapy. Most commonly seen in femoral head
2. Should be suspected in patients with hip or inguinal pain, decreased hip motion or limp.

H. Hypogonadism

1. Subnormal testosterone levels. Approximately 12%-16% of long-term survivors become hypogonadal.<sup>154</sup>
2. Hypogonadism has been associated with development of osteoporosis, metabolic syndrome, cardiovascular disease, type 2 diabetes, decreased quality of life and premature aging.<sup>154</sup> GCT survivors have been found to have higher luteinizing hormone (LH) levels than controls as well. High LH levels have been associated with higher levels of depression.<sup>153</sup>

I. Infertility<sup>152</sup>

1. **Patients should be offered sperm cryopreservation prior to treatment.**
2. Post-treatment conception and paternity rates range from 50%-82%. Preservation of antegrade ejaculation is most important factor for conception. Therefore nerve-sparing RPLND should be used preferentially.
3. Chemotherapy may lead to azoospermia in 19-47% of patients depending on regimen and number of cycles.<sup>152</sup> Cisplatin-based therapy has been shown to result in azoospermia in the majority of patients, however is reversible in at least 50% of patients given up to 4 cycles of standard dose therapy.<sup>153</sup>

J. Psychosocial Issues<sup>152</sup>

1. Chronic fatigue: higher incidence seen in GCT survivors compared to controls. Anxiety, depression, young age, and comorbidity were associated with the development of chronic fatigue.<sup>153</sup>
2. High prevalence of active smoking and alcohol problems found in survivors.
3. Increased anxiety related to fear of recurrence, younger age at diagnosis, economic concerns, not being married, alcohol abuse, sexual difficulties, and mental health problems have been reported in GCT survivors<sup>153</sup>

K. Currently no evidence-based guidelines on long term follow up of GCT survivors. Prevention of long-term complications includes smoking cessation and non-sedentary lifestyle. Utilizing risk adapted therapy to limit exposure to unnecessary radiation and chemotherapy may also help ameliorate long-term complications of GCT therapy. GCT survivors likely to benefit from long-term health surveillance.

**Patient Case #3, Question #3 Answer:**

The correct answer is A. SD should be monitored for increased risk of secondary malignancies and cardiovascular disease as these long-term complications have been associated with premature mortality in testicular cancer survivors. Although pulmonary toxicity has been seen in testicular cancer survivors, hepatotoxicity, ocular toxicity, and dermatologic toxicity have not been associated as strongly with testicular cancer therapies.

**IV. Drug-Induced QT Prolongation<sup>159-163</sup>**

- A. The QT interval is measured from the beginning of the QRS complex to the end of the T wave as it returns to baseline.
  - 1. The QT interval is a marker for the potential of ventricular tachyarrhythmias such as torsades de pointes and potentially sudden death.
- B. QTc is the duration of the QT interval adjusted for heart rate
  - 1. Definitions of normal QTc range from 400 to 440ms.
  - 2. Risk of sudden cardiac death may exist with borderline prolongation ( 431-450ms in males and 451-470ms in females).
  - 3. Abnormal QTc in males is considered above 450ms and in females is above 470ms.
  - 4. Drug-induced QT prolongation is unpredictable and it appears that additional risk factors play a role in developing torsades de Pointes
- C. Monitoring for QTc prolongation varies widely
  - 1. Some clinicians document QTc before initiation of a medication and then every 8 to 12 hours while inpatient
  - 2. Outpatient monitoring may include EKG pretreatment and again at steady state
  - 3. Consult drug-specific resources (i.e. package inserts) for any recommended monitoring parameters

**Drugs that prolong QT and Risk of Torsades de Pointes (TdP)<sup>164</sup>**

Drugs that Prolong QT	Risk Categorization	General Risk Factors for Torsades de Pointes	General Management of Medications that prolong QT
Arsenic trioxide	<b>Known risk of TdP</b>	Female sex	Avoid QT prolonging drugs in patients with pre-existing heart disease, history of ventricular arrhythmias or with
Bortezomib	Possible risk of TdP	Advanced age	
Bosutinib	Possible risk of TdP		
Capecitabine	Possible risk of TdP		
Ceritinib	Possible risk of TdP		



Crizotinib	Possible risk of TdP	Recent conversion from atrial fibrillation with QT prolonging drugs	metabolic abnormalities
Dabrafenib	Possible risk of TdP		
Dasatinib	Possible risk of TdP		
Degarelix	Possible risk of TdP	Concurrent use of more than one drug that can prolong QT interval	Hospitalized patients are high risk
Dolasetron	Possible risk of TdP		
Encorafenib	Possible risk of TdP		
Entrectinib	Possible risk of TdP	Electrolyte disturbance (hypokalemia, hypomagnesemia, hypocalcemia)	Avoid concomitant drugs that inhibit cytochrome P450 or those that cause electrolyte disturbances
Eribulin	Possible risk of TdP		
Fluorouracil	Possible risk of TdP		
Gilteritinib	Possible risk of TdP	Use of diuretics	
Granisetron	Possible risk of TdP		
Inotuzumab	Possible risk of TdP	Hepatic and renal dysfunction	Recommend surveillance EKGs before and after initiation of QT-prolonging drugs
ozogamicin	Possible risk of TdP		
Ivosidenib	Possible risk of TdP	Bradycardia	
Lapatinib	Possible risk of TdP		
Lenvatinib	Possible risk of TdP		
Leuprolide	Possible risk of TdP	Occult congenital long QT syndrome (LQTS) or silent mutations in LQTS genes	Routine monitoring of electrolytes (particularly potassium) in patients on diuretics and QT-prolonging drugs
Midostaurin	<b>Known risk of TdP</b>		
Mobocertinib	Possible risk of TdP		
Nilotinib	Conditional risk of TdP	Ion-channel polymorphism	
Olanzapine	<b>Known risk of TdP</b>		
Ondansetron	Possible risk of TdP	Underlying heart disease such as heart failure, left ventricular hypertrophy, and myocardial infarction	
Osimertinib	<b>Known risk of TdP</b>		
Oxaliplatin	Possible risk of TdP		
Pazopanib	Possible risk of TdP	Baseline QT prolongation	
Ribociclib	Possible risk of TdP		
Romidepsin	Possible risk of TdP	Rapid rate of intravenous infusion with a QT prolonging drug	
Selpercatinib	Possible risk of TdP		
Sorafenib	Possible risk of TdP		
Sunitinib	Possible risk of TdP	High drug concentration	
Tamoxifen	<b>Known risk of TdP</b>	Digoxin therapy	
Vandetanib	Possible risk of TdP		
Vemurafenib	Possible risk of TdP		

Vorinostat			
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## V. Medication Specific Tyrosine Kinase Inhibitor Toxicity<sup>165</sup>

- A. The use of tyrosine kinase inhibitors continues to be increase year after year. These agents often possess a plethora of possible toxicities that can be challenging to memorize in their entirety. It is helpful to think of the “on-target” toxicities, as these are generally expected as a continuation of the drug’s specific kinase inhibition.
  1. In some cases, toxicities occur within a drug class that are not easily explained by the kinase target. These toxicities are presented as “on target” in the table below for educational purposes.
  2. Some TKIs are only approved for a specific target (e.g. pralsetinib for RET-mutated lung or thyroid cancer), but inhibit a myriad of other kinases. Thus, attributed toxicity to inhibition of a single kinase is not always possible.
- B. Certain agents possess notable “off-target” toxicities, such as QT prolongation mentioned above, that are not expected based on inhibition of the desired target. In some cases, this is due to indiscriminate inhibition of kinases in different cellular pathways.
  1. Agents sometimes referred to as “multi-kinase” inhibitors and therefore have multiple possible therapeutic targets. Thus, some agents are listed more than once in the table below.
- C. There are some toxicities that are quite common across TKI categories. These include diarrhea, rash, fatigue, transaminitis/hepatotoxicity, & embryo-fetal toxicity.

### Targeted and Kinase Inhibitor Toxicity Comparison by Therapeutic Target

Therapeutic Target	Agents	On-Target Toxicities	Other Notable Toxicities
VEGF-R	Sunitinib Sorafenib Pazopanib Axitinib Cabozantinib Lenvatinib Regorafenib Tivozanib Selpercatinib Vandetanib Ripretinib Sepercatinib	Hypertension, hemorrhage, impaired wound healing, proteinuria, thrombotic events	Hypothyroidism, dysphonia

	Pralsetinib		
BRAF	Dabrafenib Vemurafenib Encorafenib Ripretinib Regorafenib	Dermatologic toxicity: Hand-foot syndrome, rash, photosensitivity, non-melanoma skin cancers	
RAF	Sorafenib	Hand-foot syndrome, rash	
MEK	Trametinib Binimetinib Cobimetinib Selumetinib		Cardiomyopathy, fever, eye disorders
CDK 4/6	Abemaciclib Palbociclb Ribociclib	Myelosuppression, alopecia, nausea, mucositis	Pulmonary embolism, interstitial lung disease
EGFR	Erlotinib Gefitinib Afatinib Dacomitinib Osimertinib Mobocertinib	Rash, diarrhea, paronychia	Interstitial lung disease
ALK and/or ROS1	Crizotinib (both) Ceritinib (both) Alectinib (ALK) Lorlatinib (both) Brigatinib (both)	Bradycardia, visual disturbances	Interstitial lung disease, low testosterone (crizotinib), CNS toxicity (lorlatinib), increased CPK (brigatinib, alectinib)
PARP	Olaparib Rucaparib Talazoparib Niraparib	Myelosuppression, secondary leukemias/myelodysplastic syndrome	
FGFR	Erdafitinib Pemigatinib Infigratinib	Hyperphosphatemia	Eye disorders

HER2	Lapatinib Tucatinib Neratinib	LVEF dysfunction, diarrhea	
RET	Selpercatinib Pralsetinib Vandetenib	Hypothyroidism	Hypersensitivity reactions (selpercatinib)
MET	Capmatinib Tepotinib	Hepatotoxicity	
NTRK	Entrectinib Larotrectinib	CNS toxicity (including eye disorders), fractures,	Edema
mTOR	Everolimus Temozolimus	Metabolic (hyperglycemia, hypercholesterolemia, hypertriglyceridemia), impaired wound healing, infection, mucositis	
PI3K- $\alpha$	Alpelisib	Hyperglycemia, hepatotoxicity	Pneumonitis
FLT3	Sunitinib	Myelosuppression	

## RECOMMENDED READINGS AND REFERENCES

### Recommended Readings

1. Kotecha RR, Motzer RJ, & Voss MH. Towards individualized therapy for metastatic renal cell carcinoma. *Nature Rev Clin Oncol*. 2019;16:621-633. <https://www.nature.com/articles/s41571-019-0209-1>
2. Mollica V, Rizzo A, Montironi R, et al. Current strategies and novel therapeutic approaches for metastatic urothelial carcinoma. *Cancers (Basel)*. 2020;12:e1449. <https://pubmed.ncbi.nlm.nih.gov/32498352/>
3. Haugnes HS, Bosl GJ, Boer H et al. Long-term and late effects of germ cell testicular cancer treatment and implications for follow up. *J Clin Oncol* 2012; 30:3752-63. <http://www.ncbi.nlm.nih.gov/pubmed/23008318>
4. Hanna NH, Einhorn LH. Testicular cancer – discoveries and updates. *N Engl J Med*. 2014; 371:2005-16. <http://www.ncbi.nlm.nih.gov/pubmed/25409373>
5. Coppola C, Rienzo A, Piscopo G et al. Management of QT prolongation induced by anti-cancer drugs: target therapy and old agents. Different algorithms for different drugs. *Cancer Treat Rev*. 2018;63:135-143. [https://www.cancertreatmentreviews.com/article/S0305-7372\(17\)30201-3/pdf](https://www.cancertreatmentreviews.com/article/S0305-7372(17)30201-3/pdf)

### References

1. Resnick MJ, Bassett JC, Clark PE. Management of superficial and muscle-invasive urothelial cancers of the bladder. *Current opinion in oncology*. May 2013;25(3):281-8. doi:10.1097/CCO.0b013e32835eb583
2. Jones TD, Wang M, Eble JN, et al. Molecular evidence supporting field effect in urothelial carcinogenesis. *Clin Cancer Res*. Sep 15 2005;11(18):6512-9. doi:10.1158/1078-0432.CCR-05-0891
3. Sidransky D, Frost P, Von Eschenbach A, Oyasu R, Preisinger AC, Vogelstein B. Clonal origin bladder cancer. *N Engl J Med*. Mar 12 1992;326(11):737-40. doi:10.1056/NEJM199203123261104
4. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *Jama*. Aug 17 2011;306(7):737-45. doi:10.1001/jama.2011.1142
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer. V.2.2022, 5/20/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
6. Tsao CK, Gartrell BA, Oh WK, Galsky MD. Emerging personalized approaches for the management of advanced urothelial carcinoma. *Expert review of anticancer therapy*. Dec 2012;12(12):1537-43. doi:10.1586/era.12.141
7. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 20 2009;27(33):5634-9. doi:10.1200/JCO.2008.21.4924
8. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer*. Jan 2006;42(1):50-4. doi:10.1016/j.ejca.2005.08.032
9. Kaufman JM, Fam B, Jacobs SC, et al. Bladder cancer and squamous metaplasia in spinal cord injury patients. *J Urol*. Dec 1977;118(6):967-71. doi:10.1016/s0022-5347(17)58266-x
10. Moyer VA, on behalf of the USPSTF. Screening for bladder cancer: U.S. preventive services task force recommendation statement. *Annals of internal medicine*. 2011;155(4):246-251. doi:10.7326/0003-4819-155-4-201108160-00008

11. Divrik RT, Yildirim Üt, Zorlu F, Özen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *The Journal of urology*. 2006;175(5):1641-1644.
12. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J Urol*. Oct 2016;196(4):1021-9. doi:10.1016/j.juro.2016.06.049
13. Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: which patients benefit from the instillation? *European Urology* 2016. p. 231-244.
14. Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol*. Jul 2005;174(1):86-91; discussion 91-2. doi:10.1097/01.ju.0000162059.64886.1c
15. Patel SG, Cohen A, Weiner AB, Steinberg GD. Intravesical therapy for bladder cancer. *Expert Opin Pharmacother*. Apr 2015;16(6):889-901. doi:10.1517/14656566.2015.1024656
16. Bohle A, Leyh H, Frei C, et al. Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. *European urology*. Sep 2009;56(3):495-503. doi:10.1016/j.eururo.2009.06.010
17. Berrum-Svennung I, Granfors T, Jahnson S, Boman H, Holmang S. A single instillation of epirubicin after transurethral resection of bladder tumors prevents only small recurrences. *The Journal of urology*. Jan 2008;179(1):101-5; discussion 105-6. doi:10.1016/j.juro.2007.08.166
18. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *The Journal of urology*. Jun 2004;171(6 Pt 1):2186-90, quiz 2435.
19. Huncharek M, Geschwind JF, Witherspoon B, McGarry R, Adcock D. Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials. *Journal of clinical epidemiology*. Jul 2000;53(7):676-80.
20. Messing EM, Tangen CM, Lerner SP, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: Swog s0337 randomized clinical trial. *Jama*. 2018;319(18):1880-1888. doi:10.1001/jama.2018.4657
21. Lamm DL, Blumenstein BA, Crawford ED, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guerin for transitional-cell carcinoma of the bladder. *N Engl J Med*. Oct 24 1991;325(17):1205-9. doi:10.1056/NEJM199110243251703
22. Herr HW, Schwalb DM, Zhang ZF, et al. Intravesical bacillus Calmette-Guerin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1995;13(6):1404-8.
23. Witjes JA, v d Meijden AP, Collette L, et al. Long-term follow-up of an EORTC randomized prospective trial comparing intravesical bacille Calmette-Guerin-RIVM and mitomycin C in superficial bladder cancer. EORTC GU Group and the Dutch South East Cooperative Urological Group. European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group. *Urology*. Sep 1998;52(3):403-10.
24. Addeo R, Caraglia M, Bellini S, et al. Randomized phase III trial on gemcitabine versus mitomycin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 1 2010;28(4):543-8. doi:10.1200/JCO.2008.20.8199
25. Steinberg G, Bahnson R, Brosman S, Middleton R, Wajzman Z, Wehle M. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *The Journal of urology*. Mar 2000;163(3):761-7.
26. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol*. May 26 2021;doi:10.1016/s1470-2045(21)00147-9
27. Koya MP, Simon MA, Soloway MS. Complications of intravesical therapy for urothelial cancer of the bladder. *The Journal of urology*. Jun 2006;175(6):2004-10. doi:10.1016/S0022-5347(06)00264-3
28. Ongoing Clinical Trials in Testicular Cancer: The TIGER Trial. *Oncol Res Treat*. 2016;39(9):553-6. doi:10.1159/000448868
29. International Collaboration of T, Medical Research Council Advanced Bladder Cancer Working P, European Organisation for R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine

- chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1 2011;29(16):2171-7. doi:10.1200/JCO.2010.32.3139
30. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. Aug 28 2003;349(9):859-66. doi:10.1056/NEJMoa022148
  31. Advanced Bladder Cancer Meta-analysis C. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *European urology*. Aug 2005;48(2):202-5; discussion 205-6. doi:10.1016/j.eururo.2005.04.006
  32. Hussain S.A. PDH, Lloyd B., Collins S. I., Barton D., Ansari J., and James N.D. A study of split-dose cisplatin-based neo-adjuvant chemotherapy in muscle-invasive bladder cancer. *Oncology Letters*. 2012;3:855-859.
  33. Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Is Safe, Effective, and Efficient Neoadjuvant Treatment for Muscle-Invasive Bladder Cancer: Results of a Multicenter Phase II Study With Molecular Correlates of Response and Toxicity. *Journal of Clinical Oncology*. 2014/06/20 2014;32(18):1895-1901. doi:10.1200/JCO.2013.53.2465
  34. Pfister C, Gravis G, Fléchon A, et al. Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for patients with muscle-invasive bladder cancer (MIBC): Results of the GETUG/AFU VESPER V05 phase III trial. *ESMO Congress 2021*. Sept. 2021 2021;(Abstract 6520)
  35. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 2000;18(17):3068-77.
  36. Sternberg CN, Bellmunt J, Sonpavde G, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Chemotherapy for urothelial carcinoma-neoadjuvant and adjuvant settings. *European urology*. Jan 2013;63(1):58-66. doi:10.1016/j.eururo.2012.08.010
  37. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *N Engl J Med*. Jun 3 2021;384(22):2102-2114. doi:10.1056/NEJMoa2034442
  38. García-Perdomo HA, Montes-Cardona CE, Guacheta M, Castillo DF, Reis LO. Muscle-invasive bladder cancer organ-preserving therapy: systematic review and meta-analysis. *World J Urol*. Dec 2018;36(12):1997-2008. doi:10.1007/s00345-018-2384-6
  39. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med*. Apr 19 2012;366(16):1477-88. doi:10.1056/NEJMoa1106106
  40. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 1998;16(11):3576-83.
  41. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. *Oncologist*. 2000;5(6):471-6.
  42. Kaufman DS, Winter KA, Shipley WU, et al. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology*. Apr 2009;73(4):833-7. doi:10.1016/j.urology.2008.09.036
  43. Abida W, Bajorin DF, Rosenberg JE. First-line treatment and prognostic factors of metastatic bladder cancer for platinum-eligible patients. *Hematol Oncol Clin North Am*. Apr 2015;29(2):319-28, ix-x. doi:10.1016/j.hoc.2014.10.005
  44. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 15 2001;19(10):2638-46.

45. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 20 2005;23(21):4602-8. doi:10.1200/JCO.2005.07.757
46. Cathomas R, De Santis M, Galsky MD. First-line treatment of metastatic disease: cisplatin-ineligible patients. *Hematol Oncol Clin North Am*. Apr 2015;29(2):329-40, x. doi:10.1016/j.hoc.2014.10.006
47. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jan 10 2012;30(2):191-9. doi:10.1200/JCO.2011.37.3571
48. FDA Alerts Health Care Professionals and Oncology Clinical Investigators about an Efficacy Issue Identified in Clinical Trials for Some Patients Taking Keytruda (pembrolizumab) or Tecentriq (atezolizumab) as Monotherapy to Treat Urothelial Cancer with Low Expression of PD-L1. Accessed November 15th, 2018. <https://www.fda.gov/Drugs/DrugSafety/ucm608075.htm>
49. Vuky J, Balar AV, Castellano D, et al. Long-Term Outcomes in KEYNOTE-052: Phase II Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Patients With Locally Advanced or Metastatic Urothelial Cancer. *Journal of Clinical Oncology*. 0(0):JCO.19.01213. doi:10.1200/jco.19.01213
50. Powles T, Csősz T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol*. Jul 2021;22(7):931-945. doi:10.1016/s1470-2045(21)00152-2
51. Galsky MD, Arija JA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. May 16 2020;395(10236):1547-1557. doi:10.1016/s0140-6736(20)30230-0
52. Siefker-Radtke AO, Dinney CP, Shen Y, et al. A Phase II Clinical Trial of Sequential Neoadjuvant Chemotherapy with Ifosfamide, Doxorubicin, and Gemcitabine, followed by Cisplatin, Gemcitabine, and Ifosfamide in Locally Advanced Urothelial Cancer: Final Results. *Cancer*. 08/22 2013;119(3):10.1002/cncr.27751. doi:10.1002/cncr.27751
53. Meluch AA, Greco FA, Burris HA, 3rd, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 15 2001;19(12):3018-24.
54. Powles T, Park SH, Voog E, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *New England Journal of Medicine*. 2020;383(13):1218-1230. doi:10.1056/NEJMoa2002788
55. Powles T, Park SH, Voog E, et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Long-term follow-up results from the JAVELIN Bladder 100 trial. *Journal of Clinical Oncology*. 2022;40(6\_suppl):487-487. doi:10.1200/JCO.2022.40.6\_suppl.487
56. Galsky MD, Pal SK, Mortazavi A, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients (pts) with metastatic urothelial cancer (mUC): HCRN GU14-182. *Journal of Clinical Oncology*. 2019;37(15\_suppl):4504-4504. doi:10.1200/JCO.2019.37.15\_suppl.4504
57. Powles T, Csősz T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol*. May 26 2021;doi:10.1016/s1470-2045(21)00152-2
58. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *New England Journal of Medicine*. 2017;376(11):1015-1026. doi:10.1056/NEJMoa1613683
59. Patel MR, Ellerton JA, Infante JR, et al. Avelumab in patients with metastatic urothelial carcinoma: Pooled results from two cohorts of the phase 1b JAVELIN Solid Tumor trial. *Journal of Clinical Oncology*. 2017;35(6\_suppl):330-330. doi:10.1200/JCO.2017.35.6\_suppl.330
60. Apolo AB, Ellerton JA, Infante JR, et al. Avelumab treatment for metastatic urothelial carcinoma in the phase 1b JAVELIN Solid Tumor Study: Updated safety and efficacy analysis with ≥ two years of follow-up. *Journal of Clinical Oncology*. 2019;37(7\_suppl):425-425. doi:10.1200/JCO.2019.37.7\_suppl.425
61. Powles T, O'Donnell PH, Massard C, et al. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma. *Journal of Clinical Oncology*. 2017;35(6\_suppl):286-286. doi:10.1200/JCO.2017.35.6\_suppl.286



62. Powles T, O'Donnell PH, Massard C, et al. Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. *JAMA Oncology*. 2017;3(9):e172411-e172411. doi:10.1001/jamaoncol.2017.2411
63. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *The Lancet*. 2016;387(10031):1909-1920. doi:10.1016/S0140-6736(16)00561-4
64. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *The Lancet*. 2018/02/24/ 2018;391(10122):748-757. doi:[https://doi.org/10.1016/S0140-6736\(17\)33297-X](https://doi.org/10.1016/S0140-6736(17)33297-X)
65. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *The Lancet Oncology*. 18(3):312-322. doi:10.1016/S1470-2045(17)30065-7
66. Siefker-Radtke AO, Baron AD, Necchi A, et al. Nivolumab monotherapy in patients with advanced platinum-resistant urothelial carcinoma: Efficacy and safety update from CheckMate 275. *Journal of Clinical Oncology*. 2019;37(15\_suppl):4524-4524. doi:10.1200/JCO.2019.37.15\_suppl.4524
67. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *New England Journal of Medicine*. 2021;384(12):1125-1135. doi:10.1056/NEJMoa2035807
68. Yu EY, Petrylak DP, O'Donnell PH, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. Jun 2021;22(6):872-882. doi:10.1016/S1470-2045(21)00094-2
69. Mohamed NE, Diefenbach MA, Goltz HH, et al. Muscle invasive bladder cancer: from diagnosis to survivorship. *Advances in urology*. 2012;2012:142135. doi:10.1155/2012/142135
70. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer. V.2.2023, 8/3/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
71. Keefe SM, Nathanson KL, Rathmell WK. The molecular biology of renal cell carcinoma. *Seminars in oncology*. Aug 2013;40(4):421-8. doi:10.1053/j.seminoncol.2013.05.006
72. Pecuchet N, Fournier LS, Oudard S. New insights into the management of renal cell cancer. *Oncology*. 2013;84(1):22-31. doi:10.1159/000342962
73. Dutcher JP. Recent developments in the treatment of renal cell carcinoma. *Therapeutic advances in urology*. Dec 2013;5(6):338-53. doi:10.1177/1756287213505672
74. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 20 2011;29(9):1125-32. doi:10.1200/JCO.2010.31.3304
75. Blank C, Bono P, Larkin J, et al. Safety and efficacy of everolimus in patients with non-clear cell renal cell carcinoma refractory to VEGF-targeted therapy. Subgroup analysis of REACT [abstract]. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(5\_suppl):Abstract 402.
76. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. *International journal of cancer Journal international du cancer*. Mar 10 2005;114(1):101-8. doi:10.1002/ijc.20618
77. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. Dec 3 2011;378(9807):1931-9. doi:10.1016/S0140-6736(11)61613-9
78. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *The Lancet*. 2016;387(10032):2008-2016. doi:10.1016/S0140-6736(16)00559-6

79. Motzer RJ, Haas NB, Donskov F, et al. Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. *Journal of Clinical Oncology*. 2017;35(35):3916-3923. doi:10.1200/jco.2017.73.5324
80. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. *Ann Oncol*. Dec 1 2018;29(12):2371-2378. doi:10.1093/annonc/mdy454
81. Eisen T, Frangou E, Oza B, et al. Adjuvant Sorafenib for Renal Cell Carcinoma at Intermediate or High Risk of Relapse: Results From the SORCE Randomized Phase III Intergroup Trial. *J Clin Oncol*. Dec 1 2020;38(34):4064-4075. doi:10.1200/jco.20.01800
82. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. *N Engl J Med*. Dec 8 2016;375(23):2246-2254. doi:10.1056/NEJMoa1611406
83. Motzer RJ, Ravaud A, Patard JJ, et al. Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results. *Eur Urol*. Jan 2018;73(1):62-68. doi:10.1016/j.eururo.2017.09.008
84. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. *New England Journal of Medicine*. 2021;385(8):683-694. doi:10.1056/NEJMoa2106391
85. Powles T, Tomczak P, Park SH, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. Sep 2022;23(9):1133-1144. doi:10.1016/s1470-2045(22)00487-9
86. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*. 2018;379(5):417-427. doi:10.1056/NEJMoa1803675
87. Fotivda<sup>®</sup> [package insert]. AVEO Pharmaceuticals IB, MA.
88. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol*. Jan 2020;21(1):95-104. doi:10.1016/s1470-2045(19)30735-1
89. Weligreg<sup>®</sup> [package insert]. Merck & Co. IWS, NJ.
90. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*. 2007;356(2):115-124. doi:10.1056/NEJMoa065044
91. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*. 2019;380(12):1116-1127. doi:10.1056/NEJMoa1816714
92. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol*. Dec 2020;21(12):1563-1573. doi:10.1016/s1470-2045(20)30436-8
93. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*. 2018/04/05 2018;378(14):1277-1290. doi:10.1056/NEJMoa1712126
94. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open*. Nov 2020;5(6):e001079. doi:10.1136/esmoopen-2020-001079
95. Motzer R, Alekseev B, Rha S-Y, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *New England Journal of Medicine*. 2021;384(14):1289-1300. doi:10.1056/NEJMoa2035716
96. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*. 2021;384(9):829-841. doi:10.1056/NEJMoa2026982
97. Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol*. Jun 7 2022;doi:10.1016/s1470-2045(22)00290-x
98. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. Aug 22 2013;369(8):722-31. doi:10.1056/NEJMoa1303989
99. Votrient (R) [package insert]. Novartis Pharmaceuticals Corporation EH, NJ, 2016.
100. Escudier BF PC, Bono P, et al. . Patient preference between pazopanib and sunitinib: results of a randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma-PISCES study. NCT 01064310 [abstract]. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(Abtract CRA4502)

101. Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 10 2014;32(14):1412-8. doi:10.1200/JCO.2013.50.8267
102. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*. 2019;380(12):1103-1115. doi:10.1056/NEJMoa1816047
103. Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol*. Apr 25 2020;doi:10.1016/j.annonc.2020.04.010
104. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *Journal of Clinical Oncology*. 2017/02/20 2016;35(6):591-597. doi:10.1200/JCO.2016.70.7398
105. Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. *European Journal of Cancer*. 2018/05/01/ 2018;94:115-125. doi:<https://doi.org/10.1016/j.ejca.2018.02.012>
106. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. May 31 2007;356(22):2271-81. doi:10.1056/NEJMoa066838
107. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 1995;13(3):688-96.
108. Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Fyfe G. High-dose aldesleukin in renal cell carcinoma: long-term survival update. *The cancer journal from Scientific American*. Dec 1997;3 Suppl 1:S70-2.
109. Poust JC, Woolery JE, Green MR. Management of toxicities associated with high-dose interleukin-2 and biochemotherapy. *Anti-cancer drugs*. Jan 2013;24(1):1-13. doi:10.1097/CAD.0b013e32835a5ca3
110. Gul A, Stewart TF, Mantia CM, et al. Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors. *Journal of Clinical Oncology*. 0(0):JCO.19.03315. doi:10.1200/jco.19.03315
111. Cella D, Grunwald V, Nathan P, et al. Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial. *The Lancet Oncology*. Jul 2016;17(7):994-1003. doi:10.1016/S1470-2045(16)30125-5
112. T.K. Choueiri BE, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373:1814-1823.
113. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. Jul 2016;17(7):917-927. doi:10.1016/s1470-2045(16)30107-3
114. Hammers HJ, Plimack ER, Infante JR, et al. Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. *Journal of Clinical Oncology*. 2017;35(34):3851-3858. doi:10.1200/jco.2016.72.1985
115. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *The Lancet Oncology*. 16(15):1473-1482. doi:10.1016/S1470-2045(15)00290-9
116. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer*. Sep 15 2010;116(18):4256-65. doi:10.1002/cncr.25219
117. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. Jan 11 2007;356(2):125-34. doi:10.1056/NEJMoa060655
118. Koh Y, Kim HY, et al. Phase II trial of RAD001 in renal cell carcinoma patients with non-clear histology [abstract]. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(supp\_15):Abstrat 4544.
119. Gordon MS HM, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27:5788-93.

120. Campbell MT, Bilen MA, Shah AY, et al. Cabozantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: A retrospective analysis. *European Journal of Cancer*. 2018/11/01/ 2018;104:188-194. doi:<https://doi.org/10.1016/j.ejca.2018.08.014>
121. Hutson TE, Michaelson MD, Kuzel TM, et al. A phase II study of lenvatinib plus everolimus in patients with advanced non-clear cell renal cell carcinoma (nccRCC). *Journal of Clinical Oncology*. 2020;38(6\_suppl):685-685. doi:10.1200/JCO.2020.38.6\_suppl.685
122. Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer*. Sep 1 2003;98(5):962-9. doi:10.1002/cncr.11571
123. Rosen LS, Gordon D, Tchekmedyan NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer*. Jun 15 2004;100(12):2613-21. doi:10.1002/cncr.20308
124. Donato J, Campigotto F, Uhlmann EJ, et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. *Blood*. Jul 23 2015;126(4):494-9. doi:10.1182/blood-2015-02-626788
125. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Testicular Cancer. V.2.2022, 1/4/22 , © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
126. Albers P, Albrecht W, Algaba F, et al. EAU guidelines on testicular cancer: 2011 update. *European urology*. Aug 2011;60(2):304-19. doi:10.1016/j.eururo.2011.05.038
127. Gilligan TD, Hayes DF, Seidenfeld J, Temin S. ASCO Clinical Practice Guideline on Uses of Serum Tumor Markers in Adult Males With Germ Cell Tumors. *J Oncol Pract*. Jul 2010;6(4):199-202. doi:10.1200/JOP.777010
128. Mazumdar M, Bajorin DF, Bacik J, Higgins G, Motzer RJ, Bosl GJ. Predicting Outcome to Chemotherapy in Patients With Germ Cell Tumors: The Value of the Rate of Decline of Human Chorionic Gonadotrophin and Alpha-Fetoprotein During Therapy. *Journal of Clinical Oncology*. 2001/05/01 2001;19(9):2534-2541. doi:10.1200/JCO.2001.19.9.2534
129. Oliver RT, Mason MD, Mead GM, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet*. Jul 23-29 2005;366(9482):293-300. doi:10.1016/S0140-6736(05)66984-X
130. Oliver RT, Mead GM, Rustin GJ, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 10 2011;29(8):957-62. doi:10.1200/JCO.2009.26.4655
131. Classen J, Schmidberger H, Meisner C, et al. Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. *Journal of clinical oncology*. 2003;21(6):1101-1106.
132. Detti B, Livi L, Scoccianti S, et al. Management of Stage II testicular seminoma over a period of 40 years. Elsevier; 2009:534-538.
133. Garcia-del-Muro X, Maroto P, Guma J, et al. Chemotherapy as an alternative to radiotherapy in the treatment of stage IIA and IIB testicular seminoma: a Spanish Germ Cell Cancer Group Study. *Journal of Clinical Oncology*. 2008;26(33):5416-5421.
134. Loehrer PJ, Sr., Johnson D, Elson P, Einhorn LH, Trump D. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 1995;13(2):470-6.
135. de Wit R, Stoter G, Kaye SB, et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 1997;15(5):1837-43.
136. Saxman SB, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indian University

- experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 1998;16(2):702-6.
137. Kondagunta GV, Bacik J, Bajorin D, et al. Etoposide and cisplatin chemotherapy for metastatic good-risk germ cell tumors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 20 2005;23(36):9290-4. doi:10.1200/JCO.2005.03.6616
  138. Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 1997;15(7):2553-8.
  139. Shippee BM, Bates JS, Richards KL. The role of screening and monitoring for bleomycin pulmonary toxicity. *J Oncol Pharm Pract*. Mar 2 2015;doi:10.1177/1078155215574294
  140. Ngeow J, Tan IB, Kanesvaran R, et al. Prognostic impact of bleomycin-induced pneumonitis on the outcome of Hodgkin's lymphoma. *Annals of hematology*. Jan 2011;90(1):67-72. doi:10.1007/s00277-010-1032-z
  141. Bleomycin [package insert]. Hospira Inc. LF, IL. 2018.
  142. Bajorin DF, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1993;11(4):598-606.
  143. Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 1997;15(5):1844-52.
  144. de Wit R, Stoter G, Sleijfer DT, et al. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. *Br J Cancer*. Sep 1998;78(6):828-32.
  145. Nichols CR, Williams SD, Loehrer PJ, et al. Randomized study of cisplatin dose intensity in poor-risk germ cell tumors: a Southeastern Cancer Study Group and Southwest Oncology Group protocol. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 1991;9(7):1163-72.
  146. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1998;16(4):1287-93.
  147. Miller KD, Loehrer PJ, Gonin R, Einhorn LH. Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1997;15(4):1427-31.
  148. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 20 2005;23(27):6549-55. doi:10.1200/JCO.2005.19.638
  149. Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med*. Jul 26 2007;357(4):340-8. doi:10.1056/NEJMoa067749
  150. Lorch A, Bascoul-Mollevi C, Kramar A, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. *J Clin Oncol*. Jun 1 2011;29(16):2178-84. doi:10.1200/jco.2010.32.6678
  151. Feldman DR, Sheinfeld J, Bajorin DF, et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1 2010;28(10):1706-13. doi:10.1200/JCO.2009.25.1561
  152. Haugnes HS, Bosl GJ, Boer H, et al. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 20 2012;30(30):3752-63. doi:10.1200/JCO.2012.43.4431
  153. Abouassaly R, Fossa SD, Giwercman A, et al. Sequelae of treatment in long-term survivors of testis cancer. *European urology*. Sep 2011;60(3):516-26. doi:10.1016/j.eururo.2011.05.055

154. Travis LB, Beard C, Allan JM, et al. Testicular cancer survivorship: research strategies and recommendations. *Journal of the National Cancer Institute*. Aug 4 2010;102(15):1114-30. doi:10.1093/jnci/djq216
155. de Haas EC, Altena R, Boezen HM, et al. Early development of the metabolic syndrome after chemotherapy for testicular cancer. *Ann Oncol*. Mar 2013;24(3):749-55. doi:10.1093/annonc/mds527
156. Haugnes HS, Aass N, Fossa SD, et al. Components of the metabolic syndrome in long-term survivors of testicular cancer. *Ann Oncol*. Feb 2007;18(2):241-8. doi:10.1093/annonc/mdl372
157. Willemse PM, Burggraaf J, Hamdy NA, et al. Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. *Br J Cancer*. Jul 9 2013;109(1):60-7. doi:10.1038/bjc.2013.226
158. Amidi A, Wu LM, Pedersen AD, et al. Cognitive impairment in testicular cancer survivors 2 to 7 years after treatment. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. Oct 2015;23(10):2973-9. doi:10.1007/s00520-015-2663-3
159. Nachimuthu S, Assar MD, and Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. *Therapeutic Advances in Drug Safety*. 2012;3(5):241-253.
160. Choy A, Darbar, D., Dell'Orto, S. and Roden, D.M. Exaggerated QT prolongation after cardioversion of atrial fibrillation. *J Am Coll Cardiol*. 1999;34:396-401.
161. Drew B, Ackerman, M., Funk, M., Gibler, W., Kligfield, P., Menon, V. et al. . Prevention of Torsade de Pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121:1047-1060.
162. Makkar R, Fromm, B., Steinman, R., Meissner, M. and Lehmann, M. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *Jama*. 1993;270:2590-2597.
163. Acquired long QT syndrome. Dec 1, 2018. Accessed 2018 Dec 1.
164. Woosley R, Hesie C, Gallo T, Woosley D, Romero K. [www.CredibleMeds.org](http://www.CredibleMeds.org), QTdrugs List, [Accessed Dec. 7, 2022], AZCERT, Inc.
165. Lexi-Comp Online. Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc. Accessed 2022 Dec 7.

# **BREAST CANCER**

## **Cardiotoxicity, Use of Bone Modifying Agents, Survivorship**

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### **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with breast cancer.
2. Discuss short- and long-term treatment goals, including post-therapy and survivorship, with a patient with breast cancer and her or his caregiver.
3. Determine appropriate pharmacotherapy for a patient with breast cancer based on genomic test results.
4. Identify appropriate diagnostic and prognostic tests related to breast cancer.
5. Select relevant information and guidance for the public regarding breast cancer-related issues (e.g., cancer risk factors, prevention, screening).



## OVERVIEW OF DISEASE AND MANAGEMENT

**Patient case #1:** TS is a 36-year-old premenopausal white female who presents with a diagnosis of lobular carcinoma in situ (LCIS). She has a significant family history of breast cancer including her mother, maternal grandmother, and maternal aunt who were all diagnosed prior to 60 years of age. TS had one child at age 31 and no history of oral contraceptive use or estrogen replacement therapy. She was 12 years old at first menarche. What are TS's risk factors for the development of invasive ductal carcinoma?

- A. Premenopausal status, family history, race, and LCIS
- B. LCIS, family history, early age of menarche, age > 30 at birth of first child
- C. Family history, race, early age of menarche, age > 30 at birth of first child
- D. Premenopausal status, age, LCIS, and < 3 pregnancies

### I. GENOMICS AND RISK FACTORS<sup>1</sup>

#### A. Genetics

1. Hereditary breast cancer represents 5-10% of all breast cancer cases
  - a. *BRCA1* and *BRCA2* (tumor suppressor genes)
    - 1) Increased incidence of breast cancer, ovarian cancer, male breast cancer, fallopian tube cancer, and prostate cancer with *BRCA1* and *BRCA2*. Also increased risk of melanoma and pancreatic cancer with *BRCA2*. Patients with *BRCA1* have predisposition to triple negative breast cancer (TNBC) (ER-negative, PR-negative, and HER2-negative) and those with *BRCA2* have predisposition to ER-positive disease.
    - 2) The prevalence of *BRCA1/2* oncologic mutations is very low in the general population (between 0.2 – 0.3%)<sup>2</sup>; however, germline mutations in *BRCA1/2* are found in 3 – 4% of all women with breast cancer, including 10 – 20% with TNBC and 10 – 15% of Jewish women with breast cancer.<sup>3</sup>
    - 3) Lifetime risk of breast cancer for a *BRCA* mutation carrier is ~70% but risk estimates from 50 – 90% have been reported.<sup>3</sup>
    - 4) Management of women who are *BRCA* mutation-positive<sup>4</sup>:
      - a) See table “Screening Recommendations for Breast Cancer” for screening recommendations in high-risk individuals
      - b) Discuss option of risk-reducing mastectomy
      - c) Recommend risk-reducing salpingo-oophorectomy (typically between 35 – 40 y and upon completion of childbearing)
  - b. NCCN Guidelines® are available for Genetic/Familial High-Risk Assessment of Breast, Ovarian, and Pancreatic Cancer including criteria for individuals most likely to derive benefit from testing for high-penetrance breast cancer susceptibility genes (including *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *TP53*)<sup>4</sup>
  - c. The U.S. Preventive Services Task Force (USPSTF) also has recommendations for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women<sup>5</sup>



2. Male patients with breast cancer may carry an identifiable inherited risk factor for breast cancer in > 20% of cases (*BRCA1/2*, *CHEK2*, *PALB2*, *PTEN*). Genetic counseling and consideration of genetic testing is recommended for all male patients with breast cancer. <sup>6</sup>
3. Progression genes
  - a. HER2 (Human Epidermal Growth Factor Receptor-2; erbB-2) proto-oncogene
    - 1) Amplified/overexpressed in approximately 20-25% of all breast cancers
    - 2) Amplification/overexpression generally imparts a poorer prognosis
    - 3) Used primarily to select patients who will benefit from HER2-directed therapy
    - 4) Guidelines for HER2 testing are available from the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP)<sup>7</sup>
      - a) HER2 status should be determined on every primary invasive breast cancer, recurrence, and at presentation of metastatic disease (if stage IV and specimen is available)
      - b) Immunohistochemistry (IHC) measures protein expression on cell surface

#### HER2 Testing by IHC <sup>7</sup>

IHC Score	Invasive Component of Specimen	HER2 Overexpression
0	No staining is observed OR membrane staining that is incomplete and is faint/barely perceptible and in ≤ 10% of tumor cells	Negative
1+	Incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells	Negative
2+	Weak to moderate complete membrane staining observed in >10% of tumor cells	Equivocal – confirm by FISH or other method. If FISH+ and IHC 2+, then HER2 Positive
3+	Circumferential membrane staining that is complete, intense and in >10% of tumor cells	Positive

- c) In-situ hybridization (ISH) measures the presence of gene amplification
  - i. ISH reported as copy number with single probe test or as a ratio of HER2 gene copy number: Chromosome 17 (CEP17) copy number with dual probe test.
    - (a) Fluorescence in situ hybridization (FISH) is a type of ISH which uses fluorescent probes
    - (b) Dual-probe ISH assay preferred over the single-probe
  - ii. Refer to ASCO/CAP guideline for specifics regarding testing
  - iii. Testing by ISH indicated If IHC is equivocal, ISH testing should be performed (if not already completed) from the same tissue sample used for IHC and the slides from both ISH and IHC be reviewed together to guide the selection of areas to score by ISH

## HER2 Testing by ISH using Dual-Probe

HER2/CEP17 Ratio	Average HER2 Copy Number	HER2 Overexpression
≥ 2.0	≥ 4.0 signals/cell	Positive
	< 4.0 signals/cell	Additional work-up is required (see ASCO/CAP guideline for details <sup>7</sup> )
< 2.0	≥ 6.0 signals/cell	Additional work-up is required (see ASCO/CAP guideline for details <sup>7</sup> )
	≥ 4.0 and < 6.0 signals/cell	Additional work-up is required (see ASCO/CAP guideline for details <sup>7</sup> )
	< 4.0 signals/cell	Negative

### d) HER2-Low <sup>8,9</sup>

- i. Defined as IHC 1+ or 2+ but ISH-negative
- ii. Estimated 60% of patients with breast cancer have HER2-low disease
- iii. Heterogenous group, majority are HR-positive (65 – 83%)
- iv. Historically, HER2 targeted therapies have not improved clinical outcomes for this subtype
- v. Predictive of benefit with fam-trastuzumab deruxtecan in the metastatic setting (see addition details in the section on HER2-targeted therapies for metastatic BC)

### B. Risk Factors (>60% of breast cancer patients have no identifiable risk factors beyond female gender and aging)<sup>1</sup>

1. Age – incidence and death rates increase with age until the 7<sup>th</sup> decade<sup>10</sup>
2. Family history of breast cancer - first and second-degree relatives impart an increased risk; early-onset breast cancer in a family member is suggestive of a hereditary predisposition.
3. Reproductive history
  - a. Younger age at menarche (typically defined as ≤ 12 y/o)
  - b. Older age at menopause (typically defined as ≥ 55 y/o)
  - c. Age at birth of first child ≥ 30 y/o or nulliparity/lower parity
4. History of LCIS or atypical hyperplasia (ALH or ADH)
5. Early thoracic irradiation encompassing the chest/breast area before age 30 (e.g., to treat Hodgkin lymphoma)
6. Increased body mass index (BMI)<sup>11</sup>
  - a. In postmenopausal women there is an increased incidence of breast cancer with increasing weight (RR 1.12; 95% CI 1.08–1.16; *P* < 0.0001).
  - 1) Attributed to increase in circulating endogenous estrogen levels from fat tissue
7. Current or prior estrogen and progesterone hormone therapy
  - a. A meta-analysis of 13 prospective cohort studies reported a non-significant increase in breast cancer incidence for patients who used oral contraceptives (OC) compared to those who had never used OC.<sup>12</sup>
  - b. Hormonal IUDs have very low systemic absorption and associated breast cancer risk.<sup>13</sup>

- c. A large prospective cohort study conducted in Denmark found that breast cancer risk was greater among users of hormonal contraception compared to those who had never used hormonal contraception (RR 1.20; 95% CI, 1.14-1.26) and risk increased with longer durations of use. The absolute increases in risk were small (overall absolute increase was 13 per 100,000 person-years or approximately 1 extra breast cancer for every 7,690 women using hormonal contraception for 1 year).<sup>14</sup>
- d. Women's Health Initiative (WHI) - estrogen vs. estrogen + progesterone
  - 1) WHI trial Prempro® (estrogen + progesterone) arm discontinued early; HR=1.3 (1.0-1.6) with 290 breast cancer cases.<sup>15</sup>
- e. Epidemiologic studies indicate an association between the release of WHI results, a decline in use of hormone replacement therapy (HRT) and a decline in the incidence of breast cancer diagnoses.<sup>16,17</sup>
- f. The increased risk of breast cancer in patients who received HRT in the WHI trial declined after discontinuation of estrogen and progesterone.<sup>18</sup>
- 8. Alcohol consumption
  - a. Epidemiological data has shown that risk increases with consumption (relative risk of breast cancer increased by 7% for each additional 10 g of alcohol per day which is  $\leq 1$  drink/day).<sup>19</sup>
  - b. Limit to no more than 1 drink equivalent/day<sup>13</sup>
- 9. Breast density and mammographic patterns - Women with more radiodense breast tissue are at a higher risk compared to women with more radiolucent breast tissue (between 2 and 6 times that of women of the same age with little density).<sup>20</sup>
- 10. Decreased risk: <sup>13</sup>
  - a. Menopause before age 45
  - b. Prior risk-reducing therapy
  - c. Exercise
  - d. Breastfeeding

## II. RISK ESTIMATION

- A. Gail Model risk assessment tool<sup>21</sup>
  - 1. Mathematical model to determine RR of developing breast cancer compared to an age-matched control at 5 years and during lifetime.
    - a. Age (tool is for women age  $\geq 35$  y/o)
    - b. Age at menarche
    - c. Number of female first-degree relatives with invasive breast cancer
    - d. Nulliparity or age at first birth
    - e. Number of previous benign breast biopsies
    - f. Atypical hyperplasia in a previous breast biopsy
    - g. Race

2. May not accurately assess breast cancer risk in non-Caucasian, non-Asian, and non-African American women. It is not appropriate for assessing lifetime risk in women with a strong family history of breast and related cancers.<sup>22</sup>
    - a. Claus, BRCAPRO, and Tyrer-Cuzick, models may be helpful in determining risk for breast cancer in women with a strong family history of breast, ovarian, or other cancers (see below).
  3. Not appropriate for women who received thoracic radiation to treat Hodgkin lymphoma or those with LCIS
  4. Consider risk reduction strategies if  $\geq 1.7\%$  five-year risk for breast cancer using the Gail model<sup>23</sup>
  5. Modified Gail model (also known as Breast Cancer Risk Assessment Tool), as modified by NSABP investigators, is available on the National Cancer Institute website: [www.cancer.gov/bcrisktool/](http://www.cancer.gov/bcrisktool/)
    - a. Provides absolute 5-year and lifetime risk of breast cancer.
- B. Other risk assessment tools also available
1. BRCAPRO
    - a. Computer program for calculating an individual's probability of carrying a deleterious mutation of *BRCA1*, *BRCA2*, neither, or both
  2. Tyrer-Cuzick (IBIS Tool)<sup>24</sup>
    - a. Provides personalized breast cancer risk assessment based on individual risk factors and family history<sup>13</sup>
    - b. Provides 10-year and residual absolute lifetime risk estimate of breast cancer
    - c. Overestimates risk for Hispanic individuals, atypical hyperplasia, LCIS, dense breasts<sup>13</sup>
  3. CanRisk Tool (BOADICEA v5)<sup>13</sup>
    - a. Models risks of breast and ovarian cancer based on family history and genotypes for variants in *BRCA1* and *BRCA2*. Can be used with susceptibility variants high/moderate risk other than *BRCA1/2*.
    - b. Includes personal and lifestyle risk factors, family history of breast/non-breast cancer

**Patient case #1 (continued):** Correct answer is B. TS is at an increased risk for developing invasive breast cancer due to her LCIS, significant family history, early age of menarche, and age > 30 at birth of her first child.

Answer A is incorrect because premenopausal status and race are not risk factors.

Answer C is incorrect because race is not a risk factor.

Answer D is incorrect because her age, premenopausal status, and number of pregnancies (other than nulliparity) are not risk factors.

A decision was made to calculate TS's lifetime risk of breast cancer using the Claus model and the result was > 20% lifetime risk. She declined to undergo genetic testing at this time. She was counseled that bilateral mastectomy +/- bilateral salpingo-oophorectomy is a recommended strategy for breast cancer risk reduction. Given that she is premenopausal, what is another appropriate risk reduction strategy according to NCCN Guidelines®?

- A. Tamoxifen
- B. Goserelin
- C. Anastrozole
- D. Raloxifene

### III. SCREENING & PREVENTION

#### A. Screening

##### 1. Breast self-examination (BSE)

- a. Not generally recommended; little data supporting reduction in mortality when used alone. Meta-analysis of randomized trials of BSE has shown no effect on breast cancer mortality.<sup>25</sup> May lead to high rates of unnecessary biopsies.
- b. NCCN® states that women 25 years and older should have breast awareness.<sup>22</sup> American Cancer Society (ACS) and USPSTF recommend against teaching BSE<sup>26 27</sup>(see table “Screening Recommendations for Breast Cancer”).
- c. If performed, perform monthly; week after menses.
- d. Education is required to ensure careful examination and prompt reporting to a health care professional if any abnormalities are noted.

##### 2. Clinical breast examination (CBE)

- a. Not uniformly recommended. May be most beneficial with mammograms (at the same time).

##### 3. Mammography

- a. Definite evidence that annual screening mammography reduces the mortality from breast cancer in women aged 50 years and older.
- b. Data is lacking in women 75 years or older. The decision to stop screening should be individualized based on the potential benefits and risks of screening and in the context of overall health.
- c. Screening is controversial in women ages 40-49 years:
  - 1) A systematic review conducted by the USPSTF estimated that the “number needed to invite for screening to prevent 1 breast cancer death” (NNI) for women aged 39 to 49 years was 1,904 compared to an estimated NNI of 1,339 for women aged 50 to 59 years and 377 in women aged 60 to 69 years.<sup>28</sup>
  - 2) Still under debate, but should take into account the potential benefits and harms of screening mammography and an individualized assessment of risk for breast cancer to help guide decisions (see table “Screening Recommendations for Breast Cancer”).

##### 4. Breast MRI

- a. American Cancer Society (ACS) guidelines<sup>29</sup> indicate that breast MRI screening is appropriate as an adjunct to mammography in women with the following:
  - 1) *BRCA* mutation carrier<sup>3</sup>
  - 2) First-degree relative (FDR) of a *BRCA* mutation carrier, but untested
  - 3) Lifetime risk ~20-25% or greater, as defined by BRCAPRO or other models largely dependent on family history
- b. Still controversial in other high-risk groups and for women with a personal history of breast cancer

## Screening Recommendations for Breast Cancer

Average risk			
	ACS <sup>27,29,30</sup>	NCCN <sup>®22</sup>	USPSTF <sup>26</sup>
BSE	NA	Age ≥ 25 y: breast awareness	Recommends against teaching
CBE	Not recommended	Clinical Encounter: Age ≥ 25 to 39 y: every 1-3 years Age ≥ 40 y: annually	Insufficient evidence
Mammogram	Age 40 -44 y: option of annual screening Age 45 – 54 y: annually Age ≥ 55: biennial screening (or option of annual) Continue as long as in good health and life expectancy ≥ 10 y	Age ≥ 40 y: annually	Age 40-49 y: decision to start biennial mammography is individualized Age 50-74 y: biennial Age ≥75 y: Insufficient evidence
High risk <sup>a,b</sup>			
BSE	NA	All ages: breast awareness	NA
CBE	NA	- Every 6-12 months to start when identified as increased risk (but not prior to age 21 y) or at diagnosis of LCIS/ALH or ADH - Women with prior RT beginning 8 y after RT: Current age < 25 y: annual Current age ≥ 25 y: every 6-12 months	NA
Mammogram	Age ≥ 30 y: annually w/ MRI	Age ≥ 30: Annual for all categories (Exceptions: (1) if current age ≥25 and prior RT between age 10-30 y: annually beginning 8 y after RT but not before age 30 y (2) if residual lifetime risk ≥20%: begin 10 years prior to youngest family member with breast cancer but not prior to age 30 or begin at age 40 y (whichever comes first) (3) to begin at diagnosis of LCIS/ALH or ADH but not prior to age 30 y (4) to begin when identified as increased risk by Gail Model	NA
Breast MRI	Age ≥ 30 y: annually w/ mammogram <sup>c</sup>	Recommended annually w/ mammogram for women age ≥ 25 y (Exceptions: (1) if current age ≥25 and prior RT between age 10-30 y: begin 8 y after RT but not prior to age 25 y (2) patients with a residual lifetime risk ≥ 20%: begin 10 y prior to youngest family member with breast cancer but not < age 25 y or begin age 40 y (whichever comes first) (3) Begin at diagnosis of LCIS/ALH or ADH but not prior to age 25 y (4) to begin when identified as increased risk by Gail model	NA

**Abbreviations:** ACS = American Cancer Society; BSE = breast self-exam; CBE = clinical breast exam; MRI = magnetic resonance imaging; NA = not applicable; NCCN® = National Comprehensive Cancer Network®; USPSTF = United States Preventive Services Task Force; ADH=atypical ductal hyperplasia; ALH=atypical lobular hyperplasia; RT= radiation therapy

- <sup>a</sup> High risk is defined by the ACS as 1) a known *BRCA1/2* gene mutation; 2) untested women with first-degree relative with a known *BRCA1/2* gene mutation; 3) lifetime risk of breast cancer of 20-25% or greater using a risk assessment tool based largely on family history; 4) radiation therapy (RT) to the chest between the ages of 10 - 30 y; 5) Li-Fraumeni syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome or first-degree relatives with one of these syndromes.
- <sup>b</sup> High risk is defined by the NCCN® as 1) prior thoracic RT between the ages of 10 – 30 y; 2) individuals ≥ 35 y with 5-year Gail model risk of invasive breast cancer ≥ 1.7%; 3) residual lifetime risk of ≥ 20% as defined by models that are largely based on family history (e.g., Claus, BRCAPRO, Tyrer-Cuzick); 4) pedigree suggestive of or known genetic predisposition (see NCCN Guidelines® for Genetic/Familial High-Risk Assessment for specific recommendations); 5) Women with ADH and a ≥ 20% residual lifetime risk; 6) lobular neoplasia (lobular carcinoma in situ [LCIS]/atypical lobular hyperplasia [ALH]) and ≥ 20% residual lifetime risk
- <sup>c</sup> MRI screening is not recommended for women whose lifetime risk of breast cancer is < 15%

## B. Prevention (“risk reduction”)

1. Prophylactic mastectomies
2. Bilateral oophorectomy
3. Primary prevention trials

### a. Tamoxifen vs. placebo

#### 1) NSABP Breast Cancer Prevention Trial (BCPT, P-1)<sup>31</sup>

- a) 13,388 women at high-risk of developing breast cancer with one of the following:
  - i. Age ≥ 60 years
  - ii. Age 35-59 years with a ≥1.66% cumulative 5-year risk of developing breast cancer (by modified Gail model)
  - iii. LCIS
- b) Premenopausal and postmenopausal women randomized to tamoxifen 20 mg PO daily x 5 years or placebo.
- c) Benefits: reduction in risk of invasive (49%) and noninvasive breast cancers (50%); reduction in invasive breast cancers in women with LCIS (56%) and with atypical hyperplasia (86%); reduced incidence of ER-positive tumors, but not ER-negative tumors. Reduction in incidence of invasive and noninvasive breast cancers persisted with 7 years of follow up. Absolute risk reduction was 21.4 cases per 1,000 women over 5 years.<sup>32</sup>
- d) Risks: increased incidence of endometrial cancer in postmenopausal women, thromboembolic events (pulmonary embolism (PE) significantly increased in women ≥ 50 y/o), hot flashes, and cataracts.
- e) No reliable data regarding survival differences (potentially due to crossover).
- f) Subset analyses: Women with *BRCA1* mutations did not have a reduction in breast cancer incidence with tamoxifen. Women with *BRCA2* mutations have a similar reduction in breast cancer incidence compared with the entire study population. Analysis is limited by small numbers of patients in this subset.<sup>33</sup>

- 2) FDA approved tamoxifen for breast cancer risk reduction for women at increased risk based on P-1 study results
  - 3) Overview analysis of all 4 prevention trials with tamoxifen has been published.<sup>34</sup> Included the effects of adjuvant tamoxifen on contralateral breast cancer incidence.
    - a) Overall reduction in breast cancer incidence of 34%-38% with tamoxifen, but no effect on all-cause mortality.
    - b) Isolated to reduction in incidence of ER-positive tumors only; no reduction in ER-negative tumors.
    - c) Rates of endometrial cancer and VTE were significantly increased
- b. Tamoxifen vs. Raloxifene - STAR trial (NSABP P-2)<sup>35</sup>
- 1) 19,747 postmenopausal women  $\geq 35$  y/o; similar eligibility to P-1, but all women were postmenopausal with either:
    - a) Gail model risk  $\geq 1.66\%$
    - b) LCIS
  - 2) Randomized to 5 years of tamoxifen 20 mg daily or raloxifene 60 mg daily.
  - 3) Benefits: similar reduction in incidence of invasive breast cancers; numerically fewer cases of noninvasive breast cancer with tamoxifen; no difference in fractures or total deaths.
  - 4) Risks: statistically greater number of patients with endometrial hyperplasia, VTE [PE + deep vein thrombosis (DVT)], and cataracts with tamoxifen than raloxifene; numerically more endometrial cancers and myocardial infarction (MI) with tamoxifen compared to raloxifene
  - 5) Outcome: FDA-approved raloxifene for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.
  - 6) Update with 81 months of follow-up<sup>36</sup>
    - a) Significant increase in risk of invasive breast cancer in patients who received raloxifene compared to tamoxifen (RR 1.24, 95% CI: 1.05–1.47); thus tamoxifen is superior to raloxifene in reducing invasive breast cancer; however, both remain valid options
    - b) Risk of uterine cancers, VTE, and cataracts/cataract surgery greater with tamoxifen vs. raloxifene
- c. Aromatase inhibitors (AIs)
- 1) NCIC CTG MAP.3 trial<sup>37</sup>
    - a) 4,560 postmenopausal women  $\geq 35$  y/o with one of the following risk factors:
      - i.  $\geq 60$  y/o
      - ii. Gail model risk  $\geq 1.66\%$
      - iii. Diagnosis of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), LCIS, or ductal carcinoma in situ (DCIS) treated with mastectomy
    - b) Randomized to 5 years of exemestane 25 mg PO daily or placebo daily
    - c) 65% relative reduction in invasive breast cancers in the exemestane group



- d) Risks: Arthritis, hot flashes, fatigue, sweating, insomnia, diarrhea, nausea, joint pain, and muscle pain were more common in the exemestane group; fractures, osteoporosis, cardiovascular events and deaths were not statistically different.
- 2) IBIS II<sup>38</sup>
- a) 3,864 postmenopausal women aged 40 - 70 y/o with:
    - i. At least 4x greater risk than general population (aged 40-44 years)
    - ii. At least 2x greater risk than general population (aged 45-60 years)
    - iii. At least 1.5x greater risk than general population (aged 60-70 years)
    - iv. 10-year breast cancer risk of >5% by the Tyrer-Cuzick model
    - v. Diagnosis of ADH, ALH, LCIS, or DCIS treated with mastectomy
  - b) Randomized to 5 years of anastrozole 1 mg PO daily or placebo daily
  - c) Significant reduction in incidence of invasive and non-invasive breast cancers favoring anastrozole (2.8% vs. 5.6%, HR 0.47, 95% CI 0.32-0.68)
  - d) Risks: musculoskeletal events, arthralgias, carpal tunnel syndrome, joint stiffness, vasomotor symptoms, dry eyes, vaginal or uterine prolapse, vaginal dryness, vaginal pruritus, and hypertension were more common in the anastrozole group; fractures, cardiovascular events and deaths were not statistically different.
- d. No primary prevention trials comparing tamoxifen to an AI
- e. NCCN Breast Cancer Risk Reduction Guidelines<sup>®13</sup>
- 1) Risk reduction therapy for individuals with life expectancy  $\geq 10$  years AND any of the following: history of LCIS (strongly recommended), atypical hyperplasia (strongly recommended), breast cancer risk elevated based on validated risk estimation models,  $\geq 20\%$  lifetime risk based on models largely dependent on family history, pedigree suggestive of genetic predisposition, known genetic predisposition, or prior thoracic radiotherapy (RT)  $< 30$  years of age
    - a) Consider risk-reducing agents when 5-year Gail risk is  $\geq 1.7\%$  but strongly recommend when risk is  $\geq 3\%$  or 10-year risk by IBIS (International Breast Intervention Study)/Tyrer-Cuzick is  $\geq 5\%$
  - 2) Utility of risk reducing agents in women age  $< 35$  years is unknown
  - 3) Options for risk reduction include:
    - a) Bilateral total mastectomy  $\pm$  reconstruction
      - i. Consider for select women with a pathogenic/likely pathogenic genetic mutation conferring high risk for breast cancer (e.g., women with a *BRCA1/2*, *p53*, *PTEN* mutation), compelling family history, or prior thoracic RT at age  $< 30$  years<sup>23</sup>
    - b) Bilateral salpingo-oophorectomy (BSO)
    - c) Pharmacologic agents x 5 years:
      - i. Premenopausal – tamoxifen or clinical trial
      - ii. Postmenopausal – tamoxifen, raloxifene (if age  $> 35$  years), AI, or clinical trial

- iii. Low-dose tamoxifen (5 mg/day for 3 years) is an option only if patient is symptomatic on 20 mg dose or if patient is unwilling or unable to take standard-dose (20 mg/day x 5 years).<sup>39</sup>
      - (a) 10 mg every other day is an option since 5- mg dose is not available in the US<sup>13</sup>
  - d) Risk reduction assessment
    - i. Raloxifene and tamoxifen increase risk of VTE and are contraindicated in patients with a history of deep vein thrombosis, pulmonary embolus, thrombotic stroke, transient ischemic attack, or known inherited clotting trait.
    - ii. Tamoxifen is contraindicated during pregnancy or in women planning a pregnancy
    - iii. Baseline gynecologic assessment (for women with intact uterus) to ensure no abnormal bleeding that requires evaluation before beginning treatment
    - iv. Baseline bone density evaluation (for postmenopausal females only)
      - (a) Consider choosing raloxifene over AI for women with low baseline bone density
    - v. Consider raloxifene over tamoxifen in postmenopausal women with an intact uterus
- 4) NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic<sup>4</sup>
  - a) Specifies more detailed criteria for consideration of risk reduction therapy and the type of therapy recommended based on the risk category (see guideline for details).
- f. ASCO Guidelines on the use of endocrine therapy for risk reduction<sup>24</sup>
  - 1) Consider endocrine therapy in those age ≥ 35 with ≥ 1 of the following:
    - a) Diagnosis of atypical (ductal or lobular) hyperplasia or LCIS
    - b) Age 35 – 59 years and estimated 5-year risk National Cancer Institute Breast Cancer Risk Assessment Tool (BCRAT) of at least 3%
    - c) Age 35 – 59 years and 10-year risk (IBIS/Tyrer-Cuzick Risk Calculator) of at least 5%
    - d) Relative risk of at least 4x the population risk for their age group if age 40-44 years or 2x population risk for their age group if they are age 45-69 years
  - 2) Women age ≥ 70 should not be offered endocrine prevention unless short-term risk is ≥ 1% (i.e. atypical hyperplasia plus family history or LCIS), they are active, and have life expectancy ≥ 10 years.
  - 3) Agents for risk reduction (given for 5 years duration)
    - a) Premenopausal: tamoxifen 20 mg/day
    - b) Postmenopausal: anastrozole 1 mg/day, exemestane 25 mg/day, raloxifene 60 mg/day, or tamoxifen 20 mg/day
    - c) Decision regarding choice of endocrine therapy should take into consideration age, baseline comorbidities, and adverse effect profiles
      - i. Use AI with caution in postmenopausal women with moderate bone mineral density. If used, consider use of bone-protective agents
      - ii. History of osteoporosis and/or severe bone loss is a relative contraindication to AIs

- iii. Tamoxifen is not recommended in women with history of DVT, PE, stroke, transient ischemic attack (TIA), or during prolonged immobilization
- g. USPSTF recommendations regarding the use of pharmacologic agents for breast cancer risk reduction.<sup>40</sup>
  - 1) Women at increased risk for breast cancer age  $\geq 35$  y and at low risk for adverse medication effects: recommend risk-reducing medications such as tamoxifen, raloxifene, or Ais

**Patient case #1 (continued):** Correct answer is A. TS's  $>20\%$  lifetime risk of breast cancer and diagnosis of LCIS put her at a high-risk for development of breast cancer. Risk reduction strategies for TS include bilateral total mastectomy, bilateral salpingo-oophorectomy or chemoprevention with tamoxifen given that she is  $\geq$  age 35. Salpingo-oophorectomy is an option if BRCA 1/2 mutation is strongly suspected.

Answer B is incorrect because luteinizing hormone-releasing hormone (LHRH agonists) (including goserelin) are not appropriate as a risk reduction strategy.

Answer C is incorrect because aromatase inhibitors are only indicated in postmenopausal women.

Answer D is incorrect because raloxifene is only indicated in postmenopausal women.

If TS were postmenopausal her options for risk reduction would include bilateral total mastectomy, or chemoprevention with tamoxifen, raloxifene, or an aromatase inhibitor.

TS should receive screening according to high-risk guidelines. NCCN<sup>®</sup> screening recommendation for TS include CBE every 6 – 12 months, annual mammography, and annual breast MRI. ACS recommends annual mammography and breast MRI.

**Patient case #2 (ARS 1):** JH is a 39-year-old premenopausal Caucasian woman who presents to the clinic with a newly diagnosed left breast cancer found on screening mammogram. The breast mass measured 2.8 x 1.3 cm and her axillary LNs were negative by ultrasound. Core biopsy of the breast mass indicates an invasive ductal carcinoma, nuclear grade 1 (well differentiated), ER = 80%, PR = 20%, HER2 IHC = 1+

JH has stage IIA disease (T2, N0, M0) that is ER-positive, PR-positive, HER2-negative and well differentiated. She has several good prognostic features (ER/PR-positive, HER2-negative, low grade).

#### IV. Treatment Decision Making for Early-Stage Breast Cancer

##### Prognostic factors other than staging<sup>1</sup>

Poor prognostic factors
Primary resistance to systemic chemotherapy <ul style="list-style-type: none"><li>Pathologic complete response (pCR, defined as absence of tumor in pathologic specimen of breast tissue and/or lymph node tissue) after primary systemic therapy is associated with a better relapse-free survival compared to patients with less than a pCR.<sup>41</sup> Correlation between pCR and long-term outcome is strongest for triple negative breast cancer, less so for HER2-positive disease, and least for ER-positive disease.<sup>4</sup></li></ul>
Estrogen- and/or progesterone-negative receptor status
Poorly differentiated tumors (grade 3)
High levels of proliferative markers (e.g. Ki-67, mitotic index) <ul style="list-style-type: none"><li>Faster growing, more aggressive, but might be more responsive to chemotherapy</li></ul>
Lymphatic/vascular invasion (LVI)
Aneuploid tumors
Diabetes
Obesity <ul style="list-style-type: none"><li>Poorer outcomes in obese women regardless of menopausal status, although not all studies support this correlation.<sup>42</sup></li></ul>
HER2 amplification/overexpression (predicts response to HER2-directed therapy)

##### A. Gene expression assays

1. Provide prognostic and therapy-predictive information that complements staging and biomarker information
2. Oncotype DX®
  - a. Commercially available gene expression assay – screens for expression of 21 genes (16 cancer-related genes and 5 control genes), resulting in a recurrence score (RS) from 0 – 100.
  - b. Determines a score that estimates the likelihood of distant recurrence of disease in patients with HR-positive, HER2-negative, lymph node (LN) -negative, invasive breast cancer. This score is used to assess the benefit of adjuvant chemotherapy.
    - 1) The higher the score → greater the risk of recurrence and greater the benefit for chemotherapy
  - c. Preferred by NCCN® because it provides prognosis and predicts benefit of chemotherapy. Other gene expression assays can provide prognostic information but ability to predict chemotherapy benefit is unknown.<sup>23</sup>
  - d. TAILORx trial prospectively evaluated Oncotype DX® to predict benefit of adjuvant chemotherapy in women with HR-positive, HER2-negative, LN-negative disease (n= 10,273 patients)
    - 1) Assigned patients into groups based on RS: low (0-10), intermediate (11-25), high (> 25)

- a) Low: endocrine therapy alone (no chemotherapy)
  - b) Intermediate: randomized to either chemotherapy followed by endocrine therapy (chemoendocrine) or endocrine therapy alone
  - c) High: chemoendocrine
- 2) Initial analysis reported on the RS 0-10 subset (16% of participants). At 12 years, 75.9% were free of invasive disease, 93% free of distant relapse, 89.8% were alive. Results support use of Oncotype DX® to identify low-risk subset of women that can be spared adjuvant chemotherapy.<sup>43</sup>
- 3) 69% of participants had an intermediate RS of 11-25. Endocrine therapy was noninferior to chemoendocrine therapy for invasive disease-free survival (HR 1.08; 95% CI, 0.94-1.24; P=0.26) in the intermediate group. These results were sustained at 12 years of follow up, (iDFS 76.8% in endocrine group vs. 77.4% in chemoendocrine group; HR 1.08) and OS (89.8% in both arms; HR 1.06).<sup>44</sup> Some benefit for chemotherapy was found in women age ≤ 50 with recurrence score of 16-25.<sup>43</sup>
  - a) No benefit from chemotherapy for younger women (age ≤ 50 years) with a RS of 16-20 and at **low risk clinically**<sup>45</sup>
- 4) Plan B trial<sup>46</sup> suggests no clinical benefit with chemo for patients with high clinical risk and low RS (≤ 11)
  - a) Enrolled 3,198 patients with clinically high-risk features: LN-positive (41.1%) or high-risk LN-negative. All patients were HER2-negative.
  - b) 15.3% of patients had RS ≤ 11 and received endocrine therapy alone. 3-year DFS was 98% vs. chemotherapy-treated group (92% for RS > 25 and 98% for RS 12 – 25)
- e. Oncotype DX® can predict the benefit of adjuvant chemotherapy in women with HR-positive, HER2-negative, LN-positive breast cancer<sup>47</sup>
  - 1) RxPONDER randomized 5,083 (33.2% premenopausal and 66.8% postmenopausal) patients with 1 – 3 positive axillary LN and an RS ≤ 25 to endocrine therapy alone vs. chemotherapy followed by endocrine therapy. The primary objective was to determine the effect of chemotherapy on invasive disease-free survival (iDFS) and whether the effect depended on RS.<sup>48</sup>
    - a) At 5 years of follow-up, postmenopausal patients (N=3350) had no benefit with the addition of chemotherapy to endocrine therapy (iDFS 91.9% vs. 91.3%; HR 1.02; 95% CI 0.82 – 1.26; P=0.89). Premenopausal patients (N=1665) there was a benefit to the addition of chemotherapy (iDFS 93.9% vs. 89%; HR 0.60; 95% CI 0.43 – 0.83; P=0.002). The relative chemotherapy benefit did not increase as the RS increased.
    - b) A 6-year follow-up, there was continued lack of benefit for the additional of chemotherapy in postmenopausal women; however, premenopausal patients had a 5.9% absolute benefit in iDFS from the addition of chemotherapy.<sup>49</sup>
  - 2) NCCN® lists Oncotype DX® as an option for select patients with 1 – 3 ipsilateral axillary LNs (pN1) to guide the addition of combination chemotherapy to standard hormone therapy.
- 3. Mammprint®

- a. FDA approved gene expression assay – screens for expression of 70 genes, resulting in either a good prognosis or a poor prognosis classification on basis of risk of distant recurrence at 5 and 10 years.
  - b. Prospectively evaluated in the MINDACT trial<sup>50,51</sup>
    - 1) Randomized, phase 3 study that enrolled 6,693 women with early-stage breast cancer. Mammaprint® used to assess genomic risk and Adjuvant!Online used to assess clinical risk.
    - 2) Patients at low clinical and genomic risk did not receive chemotherapy, whereas those at high clinical and genomic risk did receive chemotherapy. Study focused on discordant subgroup that was high clinical risk, low genomic risk. All patients with HR-positive disease received endocrine therapy.
    - 3) 23.2% patients deemed high clinical risk and low genomic risk (48% had LN-positive disease, 93% had grade 2 or 3 disease, and 34% were ≤ 50 y – all features that usually indicate high risk)
    - 4) At 8 years of follow-up, the rate of survival without distant metastasis was 89.4% without chemo and 92% with chemo (HR 0.66; 95% CI 0.48-0.92)
      - a) Only 2.6% absolute improvement in those who received chemo confirms this test as a positive de-escalation strategy
      - b) OS was 94.3% without chemotherapy and 95.7% with chemotherapy
    - 5) 8.8% patients deemed low clinical risk and high genomic risk
      - a) 5-year rate of survival without distant metastasis was 95.8% with chemo vs. 95% without chemo which shows no benefit for use of adjuvant chemo
    - 6) Among patients with 1 – 3 positive nodes, rates of survival without distant metastases at 8 years was 91.2% with chemotherapy vs. 89.9% without chemotherapy.
    - 7) In a subset analyses, benefit of chemotherapy was mostly seen in patients ≤ 50 years of age. Absolute difference in distant metastatic-free survival at 8 years in those receiving chemotherapy and age ≤ 50 was 5% (93.6% with chemo vs. 88.6% without chemo) vs. 0.2% for those > 50 years (90.2% vs. 90%). Benefit of chemo in younger patients may be due to chemotherapy-induced ovarian function suppression.<sup>52</sup>
4. PAM50 (Prosigna®)<sup>23</sup>
    - a. Gene expression assay that screens for expression of 50 genes (+ 5 control genes).
    - b. Identifies intrinsic breast cancer subtypes (luminal A/B, HER2 enriched, basal-like).
    - c. Predicts distant relapse-free survival and likelihood of recurrence at 10 years in ER-positive postmenopausal patients with LN-negative or LN-positive breast cancer treated with endocrine therapy.
  5. Breast Cancer Index (BCI) is predictive of benefit of extended adjuvant endocrine therapy<sup>23</sup>
    - a. In secondary analyses of MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1-T3, pN0 or pN+ who had a BCI (H/I) in the high range (5.1 – 10) demonstrated significant improvements in DFS with extended adjuvant endocrine therapy compared to control arm. BCI (H/I) low patients (range 0 – 5) did not benefit from extended adjuvant therapy.<sup>53</sup>
  6. If considering preoperative therapy, consider use of a gene expression assay during workup for postmenopausal patients with cN0, operable ER-positive, HER2-negative disease.<sup>23, 54, 55</sup>

7. ASCO guideline on the use of biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer<sup>56</sup>
  - a. Oncotype DX, Mammaprint, BCI, and EndoPredict may be used to guide adjuvant endocrine and chemotherapy in patients who are postmenopausal or age > 50 years with early stage ER-positive, HER2-negative breast cancer that is LN negative or 1 – 3 positive nodes
  - b. Prosigna and BCI may be used in postmenopausal patients with LN-negative ER-positive and HER2-negative breast cancer.
  - c. Oncotype DX may be used in patients who are premenopausal or age ≤ 50 years with early stage ER-positive, HER2-negative LN-negative
  - d. BCI may be used to guide decisions about extended endocrine therapy for patients with 0 – 3 positive LN who received 5 years of endocrine therapy without evidence of recurrence.
  - e. Treatment decisions should also consider disease stage, comorbidities, and patient preferences
  - f. Biomarker testing is not recommended for the following:
    - 1) ≥ 4 positive LN
    - 2) Premenopausal patients with 1 – 3 positive LN (benefit from chemotherapy regardless of genomic assay result)
    - 3) HER2-positive breast cancer
    - 4) TNBC

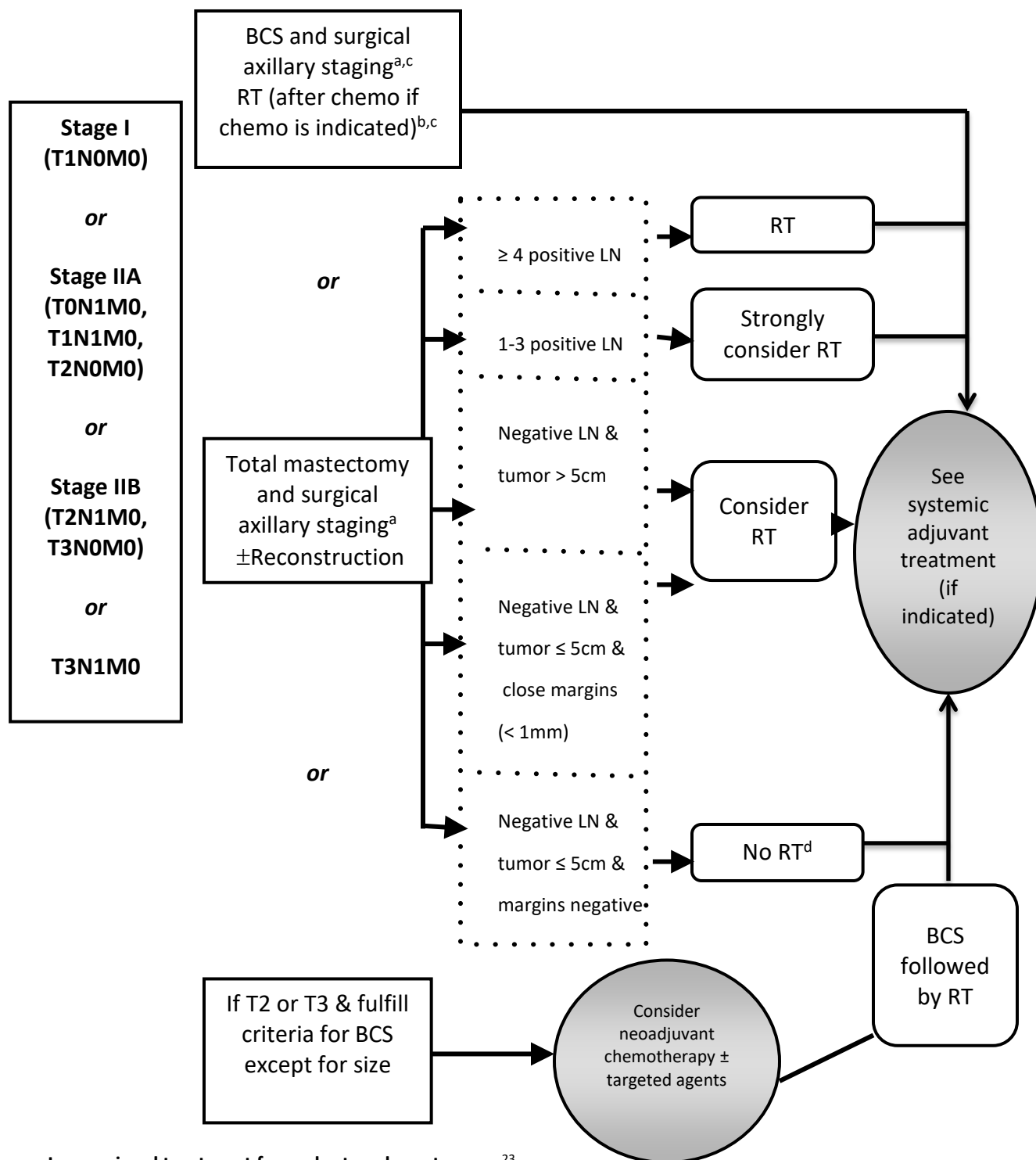
## V. Treatment of Early Stage and Locally Advanced Breast Cancer

### A. DCIS<sup>23</sup>

1. Local management (no survival differences between the 3 approaches)
  - a. Breast conserving surgery (BCS) (aka lumpectomy) + radiation therapy **OR**
  - b. Total mastectomy ± reconstruction **OR**
  - c. BCS without radiation
    - 1) After BCS, radiation reduces recurrence rates of DCIS by about 50%<sup>57</sup>; half of recurrences are invasive and half are DCIS
2. Endocrine therapy
  - a. Following BCS +/- RT, consider endocrine therapy for 5 years to decrease risk of ipsilateral recurrence in patients with ER-positive DCIS:
    - 1) NSABP B-24 found absolute risk reduction of 5% and relative risk reduction of 37% in invasive and non-invasive recurrence with tamoxifen x 5 years after BCS + XRT.<sup>58</sup>
  - b. Consider risk reduction in women treated with total mastectomy (decrease development of contralateral second primary breast cancers)
  - c. Tamoxifen is an option for premenopausal patients
  - d. AIs or tamoxifen for postmenopausal patients
    - 1) Anastrozole compared to tamoxifen x 5 years for DCIS in postmenopausal women in NSABP B-35.<sup>59</sup> At mean follow-up of 9 years, 122 breast cancer-free interval (BCFI) events in tamoxifen group vs. 90 in the anastrozole group (HR, 0.73; p=0.0234)

- 2) Some advantage for AI in postmenopausal women < 60 years old or those with concerns for thromboembolism
  - e. Standard dose of tamoxifen is 20 mg /day x 5 years. Low-dose tamoxifen (5 mg/day x 3 years) is an option only if patient is symptomatic on standard dose or if patient is unwilling or unable to take standard dose.<sup>23</sup>
- B. Stage IA, IB, IIA, IIB Invasive Breast Cancers (Early Stage) or T3 N1 M0<sup>23</sup>
  - 1. Goals of therapy: CURE
    - a. In clinical trials, rates of cure determined by comparisons of DFS and OS.





### Locoregional treatment for early stage breast cancer<sup>23</sup>

Abbreviations: RT = radiation therapy; BCS = breast conserving surgery; LN = lymph nodes.

<sup>a</sup> Surgical axillary staging discussed in text. <sup>b</sup> See relative contraindications to BCS in text. <sup>c</sup> Breast RT may be omitted if patient is ≥ 70 y/o with ER+, node-negative, T1 tumor who receives adjuvant endocrine therapy (category 1). <sup>d</sup> Postmastectomy RT may be considered for patients with multiple high-risk recurrence factors including central/medial tumors or tumors ≥ 2 cm and at least one of the following: grade 3, ER-negative, or LVI

2. Summary - Most patients are eligible for primary surgery ± radiation therapy. However, some patients who otherwise are candidates for BCS except for the size of the tumor (in relationship to the size of the breast) may be better served with neoadjuvant/preoperative chemotherapy to attempt to shrink the tumor and possibly allow for BCS. Neoadjuvant therapy is also preferred for patients with HER2-positive disease and TNBC if T ≥ 1c or N ≥ 1 (see additional information in section “Primary (preoperative, neoadjuvant) systemic chemotherapy”)
3. Locoregional therapy (surgery ± radiation therapy)
  - a. Total mastectomy + surgical axillary staging (if w/ axillary lymph node dissection, then called modified radical mastectomy) ± reconstruction **OR**
  - b. BCS (segmental mastectomy, lumpectomy, etc.) + surgical axillary staging + XRT
    - 1) Meta-analysis of 10,801 patients in 17 RCT of XRT vs. no XRT after BCS showed a reduction in the 10-year risk of first recurrence by 15.7% (95%CI 13.7-17.7, 2p<0.00001) and the 15-year risk of breast cancer death by 3.8% (95%CI 1.6-6.0, 2p<0.00005) favoring radiation.<sup>60</sup>
    - 2) Contraindications include:
      - a) Absolute
        - i. Radiation prohibited during pregnancy
        - ii. Diffuse suspicious or malignant appearing microcalcifications on mammography
        - iii. Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result
        - iv. Diffusely positive pathologic margin
      - b) Relative
        - i. Prior radiation therapy to chest wall or breast
        - ii. Active connective tissue disease involving the skin
        - iii. Positive pathologic margin
        - iv. Women with known or suspected genetic predisposition to breast cancer (consider prophylactic bilateral mastectomy)
          - (a) ASCO guidelines state that *BRCA* status should not preclude a patient eligible for breast-conserving therapy (BCT) from receiving BCT; however, the increased risk of contralateral breast cancer and possible increased risk of ipsilateral new primary breast cancer compared to noncarriers should be discussed. Patients with *BRCA* mutations should be considered for ipsilateral therapeutic and contralateral risk-reducing mastectomy (bilateral mastectomy) based on risk factors (refer to the guidelines for additional details).<sup>3</sup>
          - (b) Women with breast cancer who have a *BRCA1/2* mutation and have been treated with unilateral mastectomy should be offered a contralateral risk-reducing mastectomy.<sup>3</sup>
  - 3) Candidates for this procedure include:
    - a) Willingness to undergo radiation therapy
    - b) Appropriate breast-to-tumor ratio (in terms of size) allowing for a good cosmetic result

- 4) BCS has a slightly higher rate of locoregional recurrences but does not appear to affect survival.
- c. Those with BRCA1/2 mutation and who have been treated or are being treated with unilateral mastectomy, contralateral risk reducing mastectomy should be offered. <sup>61</sup>
- d. Surgical Axillary Staging<sup>23</sup>
  - 1) Axillary lymph node dissection (ALND)
    - a) Required if:
      - i. Clinically LN-positive at diagnosis (pathologically confirmed w/ FNA) **OR**
      - ii. Sentinel LN-positive or not identified
  - 2) Lymphatic mapping with sentinel lymph node biopsy (SLNB) preferred<sup>23</sup>
    - a) Guidelines for SLNB are also available from ASCO<sup>62</sup>
- e. Radiation therapy after mastectomy
  - a) See recommendations for RT in figure “Locoregional treatment of early stage breast cancer”
  - 2) Not recommended for patients with:
    - a) Negative axillary lymph nodes **AND**
    - b) Tumors  $\leq 5$  cm **AND**
    - c) Negative margins
    - d) Radiation of the intact breast is contraindicated in women with breast cancer who are carriers of a germline *TP53* mutation. Mastectomy is the recommended therapeutic option. Postmastectomy RT should only be considered in patients with significant risk for locoregional recurrence due to increased risk of toxicity. <sup>61</sup>
  - 3) If margins are positive following resection, re-excision to negative margins is preferred. If not feasible, then radiation therapy is recommended.
  - 4) Common for radiation therapy to follow chemotherapy when both are indicated

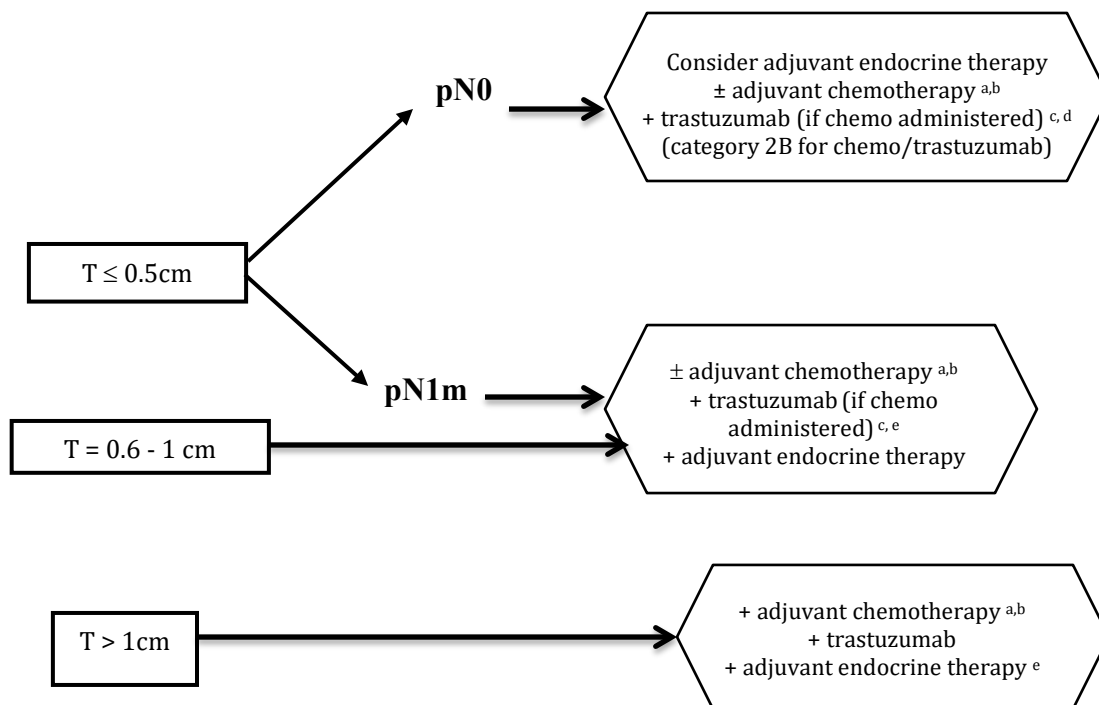
**Patient case #2, continued (ARS 1):** The goal of therapy for JH is cure. She plans to undergo primary surgery. If she were to have a lumpectomy, lymphatic mapping with SLNB would be the most appropriate option. Radiation therapy would be required with a lumpectomy. If this patient underwent a mastectomy, post-mastectomy radiation would only be considered if she were to have positive lymph nodes or close or positive surgical margins. JH elected to have a lumpectomy with surgical axillary staging. She has negative axillary nodes. Her pathologic stage is IIA (pT2, pN0, M0). The Oncotype DX recurrence score on the surgical specimen is 26.

**What is the most appropriate adjuvant therapy for JH according to NCCN Guidelines®?**

- A. Anastrozole
- B. Docetaxel and cyclophosphamide (TC) followed by anastrozole
- C. Tamoxifen
- D. Docetaxel and cyclophosphamide (TC) followed by tamoxifen

4. Systemic adjuvant therapy for early-stage breast cancer
  - a. Goal of therapy is to CURE the patient, prevent recurrences, and eradicate micrometastatic disease.
  - b. Appropriate therapies: endocrine therapy, chemotherapy, HER2-directed therapies, bisphosphonates, select targeted therapies
  - c. Disease characteristics which should be considered when making a decision regarding adjuvant systemic therapy include lymph node status, T stage, ER/PR status, HER2 status, tumor grade, and presence of tumor LVI<sup>63</sup>
  - d. ASCO/Cancer Care Ontario guidelines recommend patients with early-stage (stage I – IIA, T1N0-1, T2N0, T2N1) and at least one of the following tumor characteristics should be considered for adjuvant chemotherapy:<sup>63</sup>
    - 1) LN positive ( $\geq 1$  with a macrometastatic deposit  $> 2\text{mm}$ )
    - 2) ER-negative tumors with  $T > 5\text{ mm}$
    - 3) HER2-positive tumors
    - 4) High-risk LN-negative tumors with  $T > 5\text{mm}$  and  $\geq 1$  other high-risk feature: grade 3, triple negative, LVI positive, Oncotype DX RS associated with an estimated distant relapse rate of  $> 15\%$  at 10 years, or HER2-positive
    - 5) Adjuvant! Online 10-year risk of death from breast cancer  $> 10\%$
  - e. Patients with  $T < 5\text{ mm}$ , LN-negative tumors, and no high-risk features as listed above may not benefit from adjuvant chemotherapy. Additionally, tumors that are well-differentiated, especially luminal-A pathology, should be considered for omission from chemotherapy.<sup>63</sup>
  - f. Gene expressions assays are recommended for patients with HR-positive, HER2-negative, LN-negative or T1 disease ( $< 4$  positive LN) (see previous section on gene expression assays)<sup>23, 56</sup>

T1, T2, T3 and pN0 or N1mi – HORMONE RECEPTOR-POSITIVE, HER2-POSITIVE (PRE- OR POSTMENOPAUSAL)

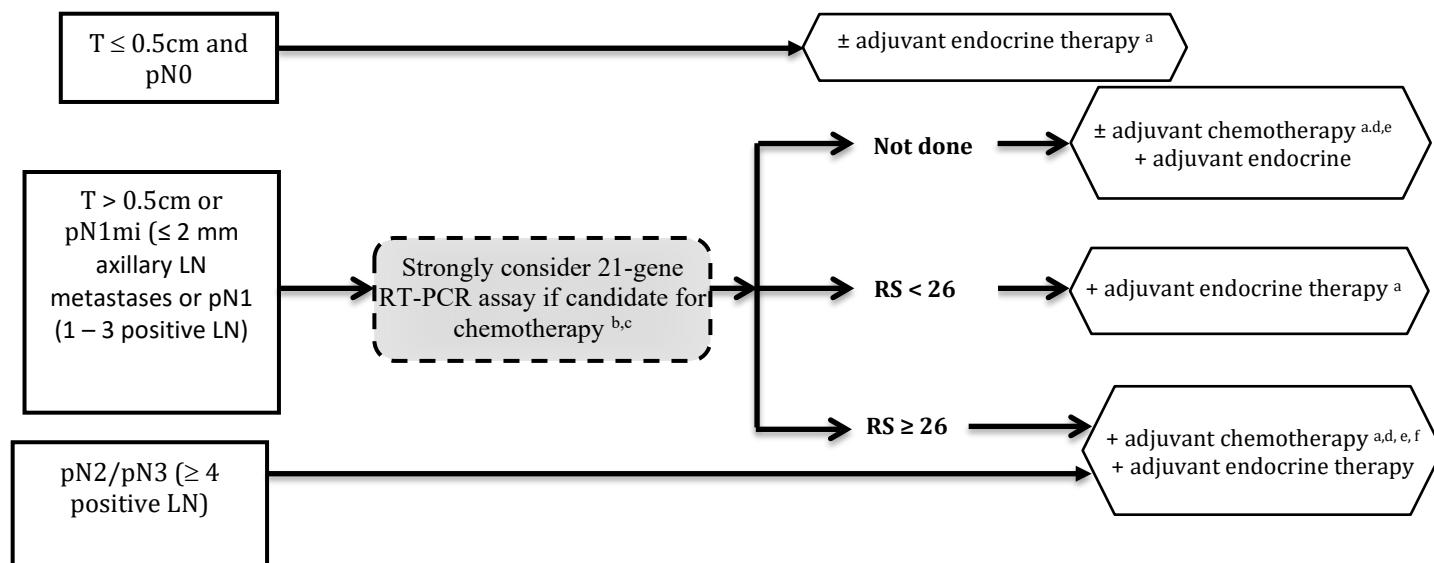


**Systemic Adjuvant Therapy for Node-Negative, HR-Positive, HER2-Positive Breast Cancer <sup>23</sup>**

Abbreviations: T = tumor; HER2 = human epidermal growth factor receptor-2; pN0 = pathologic lymph node negative; pN1m = ≤ 2 mm axillary lymph node metastasis

- <sup>a</sup> Treatment should be individualized for patients > 70 years based on presence or absence of comorbidities.
- <sup>b</sup> Adjuvant chemotherapy and endocrine therapy should be given sequentially with chemotherapy preceding endocrine therapy.
- <sup>c</sup> This is a population of breast cancer patients that was not studied in the available randomized trials. The decision to use trastuzumab must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain absolute benefits that may exist with trastuzumab therapy.
- <sup>d</sup> Consider adjuvant chemo with weekly paclitaxel and trastuzumab for HER2+, T1,N0,M0 cancer, particularly if ER negative<sup>64</sup>
- <sup>e</sup> Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3 – 5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors

## HORMONE RECEPTOR POSTIVE, HER2-NEGATIVE AND POSTMENOPAUSAL

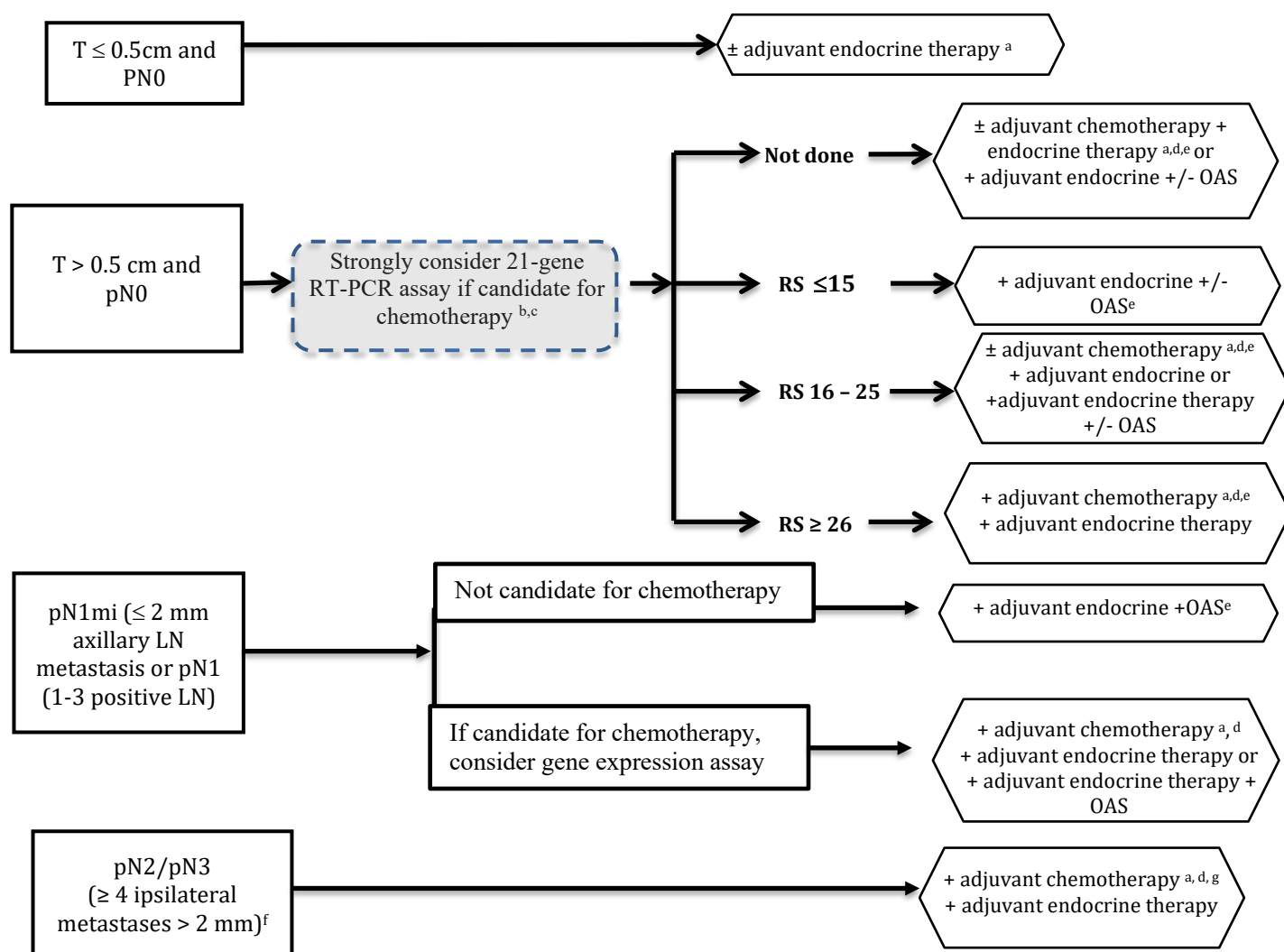


### Systemic Adjuvant Therapy for HR-Positive, HER2-Negative Breast Cancer for Postmenopausal Patients<sup>23</sup>

**Abbreviations:** T = tumor; HER2 = human epidermal growth factor receptor-2; pN0 = pathologic lymph node negative; RS = recurrence score

- <sup>a</sup> Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3 – 5 years in postmenopausal patients (natural or induced) with high-risk LN-negative or LN-positive tumors
- <sup>b</sup> Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy
- <sup>c</sup> Patients with T1b tumors with low-grade histology and no LVI should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors
- <sup>d</sup> Treatment should be individualized for patients > 70 years based on presence or absence of comorbidities
- <sup>e</sup> Adjuvant chemotherapy and endocrine therapy should be given sequentially with chemotherapy preceding endocrine therapy.
- <sup>f</sup> 1 year of adjuvant olaparib is an option for select patients with germline BRCA1/2 mutation after completion of adjuvant chemotherapy.

## HORMONE RECEPTOR POSITIVE, HER2-NEGATIVE AND PREMENOPAUSAL

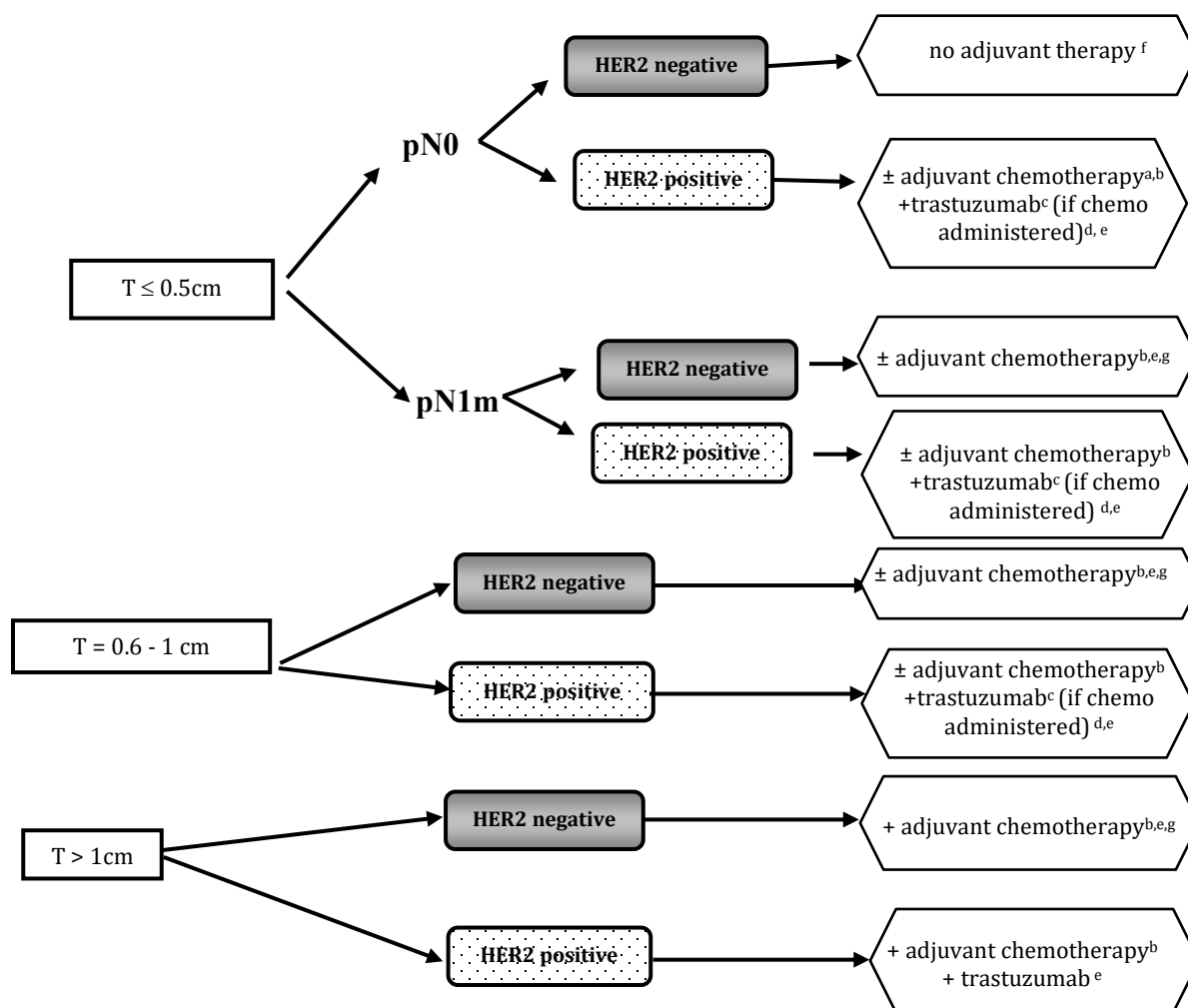


### Systemic Adjuvant Therapy for HR-Positive, HER2-Negative Breast Cancer for Premenopausal Patients<sup>23</sup>

**Abbreviations:** T = tumor; HER2 = human epidermal growth factor receptor-2; LN = lymph node(s); pN0 = pathologic lymph node negative; RS = recurrence score

- <sup>a</sup> Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3 – 5 years in postmenopausal patients (natural or induced) with high-risk LN-negative or LN-positive tumors
- <sup>b</sup> Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy
- <sup>c</sup> Patients with T1b tumors with low-grade histology and no LVI should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors
- <sup>d</sup> Adjuvant chemotherapy and endocrine therapy should be given sequentially with chemotherapy preceding endocrine therapy.
- <sup>e</sup> In premenopausal patients with RS < 26, the addition of chemotherapy to endocrine therapy was associated with a lower risk of distant recurrence compared to endocrine monotherapy but it is unclear if benefit was due to ovarian suppression effects promoted by chemotherapy.
- <sup>f</sup> Few data exist regards the role of gene expression assays in those with ≥ 4 ipsilateral axillary lymph LNs. Decisions to administer adjuvant chemotherapy in this group should be based on clinical factors.
- <sup>g</sup> 1 year of adjuvant olaparib is an option for select patients with germline BRCA1/2 mutation after completion of adjuvant chemotherapy.

T1, T2, T3 and pN0 or pN1mi – HORMONE RECEPTOR NEGATIVE, HER2-POSITIVE AND HER2-NEGATIVE

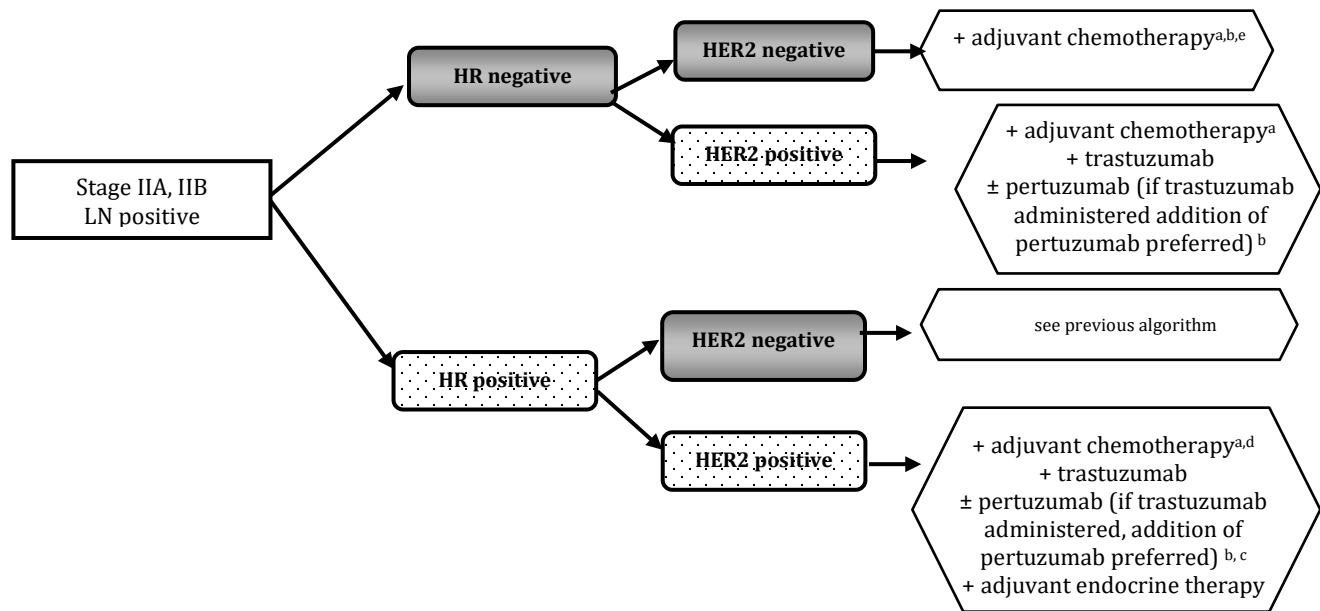


**Systemic Adjuvant Therapy for LN-Negative, HR-Negative, HER2-Positive and HER2-Negative Breast Cancer<sup>23</sup>**

**Abbreviations:** T = tumor; HER2 = human epidermal growth factor receptor-2.

- <sup>a</sup> Adjuvant chemotherapy ± trastuzumab is not routinely recommended (category 2B in NCCN Guidelines®)
- <sup>b</sup> Treatment should be individualized for patients > 70 years based on the presence or absence of comorbid conditions.
- <sup>c</sup> This is a population of breast cancer patients that was not studied in the available randomized trials. The decision to use trastuzumab must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain absolute benefits that may exist with trastuzumab therapy.
- <sup>d</sup> Consider adjuvant chemo with weekly paclitaxel and trastuzumab particularly for ER-, HER2+, stage I cancer<sup>64</sup>
- <sup>e</sup> Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3 – 5 years in postmenopausal patients (natural or induced) with high-risk LN-negative or LN-positive tumors
- <sup>f</sup> In select patients with high-risk features (e.g., very young women with high grade histology), adjuvant chemotherapy may be considered (category 2B in NCCN Guidelines®)
- <sup>g</sup> 1 year of adjuvant olaparib is an option for select patients with germline BRCA1/2 mutation after completion of adjuvant chemotherapy.





### Systemic Adjuvant Therapy for LN-Positive Breast Cancer<sup>23</sup>

**Abbreviations:** T = tumor; HR = hormone receptors; HER2 = human epidermal growth factor receptor-2.

- <sup>a</sup> Treatment should be individualized for patients > 70 years based on the presence or absence of comorbid conditions.
- <sup>b</sup> Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3 – 5 years in postmenopausal patients (natural or induced) with high-risk LN-negative or LN-positive tumors
- <sup>c</sup> Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy in HR-positive, HER2-positive patients with perceived high risk of recurrence
- <sup>d</sup> Adjuvant chemotherapy and endocrine therapy should be given sequentially with chemotherapy preceding endocrine therapy.
- <sup>e</sup> 1 year of adjuvant olaparib is an option for select patients with germline BRCA1/2 mutation after completion of adjuvant chemotherapy.

**Patient Case #3 (ARS 2):** CW is a postmenopausal female with a new diagnosis of ER-positive, PR-positive, HER2-negative breast cancer. Her disease is clinically staged as T2 N2 M0 (with a 3 cm primary tumor and 4 positive LNs). She was treated with neoadjuvant chemotherapy followed by breast conserving surgery and radiation. CW has no major comorbidities and desires to be aggressive with treatment.

**What is the most appropriate adjuvant endocrine therapy for CW?**

- A. Anastrozole + leuprolide
- B. Anastrozole + abemaciclib
- C. Anastrozole
- D. Tamoxifen

g. Endocrine therapy

- 1) Determination of ER and PR positivity- ASCO/CAP Recommendations for Testing of Estrogen and Progesterone Receptors in Breast Cancer.<sup>65</sup>
  - a) ER and PR status should be determined by IHC on all newly diagnosed invasive breast cancers and breast cancer recurrences. Breast cancer samples with 1 – 100% tumor nuclei positive should be interpreted as ER positive.
  - b) Samples with ER 1 – 10% (not PR) should be reported as ER Low Positive
  - c) PR positive that is ER negative is rare. Pathology results with that profile usually require retesting and confirmation.<sup>63</sup>
  - d) Data suggests that patients with greater percentage of ER/PR positivity will have a higher probability of positive outcomes with endocrine therapies (OS, DFS, etc.).
- 2) The NCCN® panel recommends considering endocrine therapy in patients whose breast tumors show at least 1% ER+ and/or PR+ cells and withholding endocrine therapy if less than 1% for both ER and PR. The guidelines state that ER-low-positive cancers (1-10%) often behave similar to ER-negative cancers and this should be considered in decision-making for adjuvant therapy.<sup>4</sup>
- 3) Definition of menopause:<sup>23</sup>
  - a) Prior bilateral oophorectomy
  - b) Age ≥ 60 years
  - c) Age < 60 years and amenorrheic for ≥ 12 months in the absence of prior chemotherapy, tamoxifen, toremifene, or ovarian suppression, and follicle-stimulating hormone (FSH) and estradiol levels in postmenopausal range
  - d) Age < 60 years: chemotherapy-induced amenorrhea for ≥ 12 months with FSH and estradiol in post-menopausal range on serial assessments
  - e) Age < 60 years: on tamoxifen with FSH and estradiol in post-menopausal range
  - f) It is not possible to assign menopausal status to women receiving an LHRH agonist because these agents induce a menopausal state that is reversible upon cessation.
  - g) In women premenopausal at the time of neo/adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status.
- 4) Timing of adjuvant endocrine therapy
  - a) Endocrine therapy given concurrently during chemotherapy has been shown to decrease DFS<sup>66</sup>
  - b) Chemotherapy is typically given first and then endocrine therapy, sequentially. Endocrine therapy may be given sequential or concurrent with radiation.<sup>23</sup>
- 5) Endocrine options for premenopausal women
  - a) ASCO and NCCN® recommendations for initial therapy:<sup>23,67,</sup>
    - i. Tamoxifen for 5 years
      - (a) EBCTCG overview analysis indicates a substantial benefit of tamoxifen in ER positive disease (all patients regardless of age or menopausal status).<sup>68</sup>

- ii. Consider combination of ovarian ablation or suppression (OAS) + tamoxifen x 5 years or OAS + AI x 5 years for patients at higher risk of recurrence
  - (a) OAS = surgical oophorectomy, ovarian irradiation, or administration of LHRH agonists
  - (b) NCCN® recommends consideration of combination therapy for young age, high-grade tumor, LN involvement<sup>23,69</sup>
  - (c) ASCO recommends combination therapy for stage II or III breast cancers that would be eligible to receive adjuvant chemo. Women with stage I disease not warranting chemo or LN-negative disease  $\leq 1$  cm (T1a, T1b) should not be offered combination endocrine therapy.<sup>67</sup>
  - (d) After initial 5 years of tamoxifen +OAS, NCCN® recommends consideration for:
    - Additional tamoxifen x 5 years or no further endocrine therapy for women that remain premenopausal
    - AI x 5 years or tamoxifen x 5 years for women that become postmenopausal
  - (e) After initial 5 years of AI + OAS, NCCN® recommends consideration for:
    - Additional AI x 3 – 5 years
  - (f) Guidelines support OAS x 5 years (standard duration in clinical trials)
- b) After 5 years of tamoxifen alone
  - i. If patient remains premenopausal, consider an additional 5 years of tamoxifen (total of 10 years) or no further therapy.<sup>23</sup> ASCO guidelines state that women who remain premenopausal or perimenopausal should be offered an additional 5 years of tamoxifen.<sup>67</sup>
    - (a) Conflicting data exists regarding the benefit of tamoxifen therapy for greater than 5 years. Three trials have evaluated 10 years of tamoxifen compared to 5 years
    - (b) NSABP B-14 showed no benefit of tamoxifen beyond 5 years<sup>70</sup>
    - (c) Patients in the ATLAS trial (n=6,846 ER+) had a decreased risk of recurrence (RR 0.84; CI 0.76-0.94) and improved survival (639 vs 722 deaths, p=0.01) with 10 years of tamoxifen, but had an increased risk of endometrial cancer, pulmonary embolism, and ischemic heart disease (12,894 patients evaluated for toxicity).<sup>71</sup>
    - (d) Patients in the aTTom trial (n=6,953 ER+ or ER-unknown) had a decreased risk of recurrence (580 vs 672, p=0.003), but not breast cancer mortality (404 vs 456, p=0.06) with 10 years of tamoxifen, and had an increased risk of endometrial cancer and death from endometrial cancer.<sup>72</sup>

- ii. If a patient is initiated on tamoxifen and becomes postmenopausal during therapy or at the completion of 5 years, then an AI (preferred) or tamoxifen for an additional 5 years can be considered.
- 6) Endocrine options for postmenopausal women<sup>23</sup>
  - a) AI for 5-10 years
    - i. ASCO guidelines recommend an AI for 10 years for women with LN-positive breast cancer.<sup>67</sup>
    - ii. NCCN Guidelines® state that the optimal duration of adjuvant AI remains uncertain but states that patients with LN involvement may benefit from an extended AI duration (7.5 – 10 years total).<sup>23</sup>
  - b) Tamoxifen for 2-3 years followed by AI to complete 5 years of endocrine therapy or up to 5 additional years of an AI
  - c) AI for 2-3 years followed by tamoxifen to complete 5 years of endocrine therapy
  - d) Tamoxifen for 4.5-6 years followed by an AI for an additional 5 years or consider additional 5 years of tamoxifen to complete 10 years of tamoxifen
  - e) Women with contraindication to AIs, who decline AIs or who are intolerant of the AIs: tamoxifen for 5 - 10 years.
- 7) Endocrine options for males with breast cancer
  - a) Treat similarly to postmenopausal women except that if AIs are used, they must be combined with an agent to suppress testicular steroidogenesis (such as an LHRH agonist)<sup>6, 23</sup>
  - b) Tamoxifen for 5- 10 years is preferred. If tamoxifen is contraindicated, then consider LHRH agonist + AI<sup>23</sup>
    - i. An additional 5 years of tamoxifen may be offered to men who have completed an initial 5 years of tamoxifen, have tolerated therapy, and still have a high risk of recurrence based on considerations of recurrence risk using established prognostic factors (e.g., nodal status, tumor size, and grade).<sup>6</sup>
- 8) Tamoxifen (pre- and postmenopausal women)
  - a) Tamoxifen has tissue-specific activity; estrogenic - bones, lipids, endometrium; antiestrogenic - breast, vaginal mucosa.
  - b) Potential drug interactions with CYP2D6 inhibitors (see details in Survivorship section)
  - c) Side effects: hot flashes, vaginal discharge or dryness, menstrual irregularities, sexual dysfunction, venous thromboembolism (VTE), cataracts, endometrial cancer and uterine sarcoma (postmenopausal patients), decline in bone mineral density in premenopausal patients (protective effect on bone mineral density in postmenopausal patients), hyperlipidemia
- 9) OAS in combination with tamoxifen or AI (premenopausal women only)
  - a) ABCSG 12- ovarian suppression with goserelin plus anastrozole or tamoxifen +/- zoledronic acid for 3 years. DFS was not significantly changed between endocrine therapies (HR = 1.08, p=0.591).<sup>73</sup>

- b) SOFT trial - phase 3 trial that compared tamoxifen, tamoxifen + OAS, and AI + OAS (included use of triptorelin, oophorectomy, or ovarian irradiation) (n=3,066).<sup>74</sup>
  - i. 8-year DFS rate was 78.9% with tamoxifen alone, 83.2% with tamoxifen + OAS, and 85.9% with exemestane + OAS (p=0.009 for tamoxifen alone vs. tamoxifen + OAS)<sup>75</sup>
  - ii. 8-year OS was 91.5% in tamoxifen alone, 93.3% in tamoxifen + OAS, and 92.1% in exemestane + OAS (p=0.01 for tamoxifen alone vs. tamoxifen + OAS)
  - iii. Tamoxifen + OAS resulted in 24% lower relative risk of recurrence, a second invasive cancer, or death compared to tamoxifen alone (p=0.0009)
- c) Combined analysis of SOFT and TEXT trials – evaluated OAS (triptorelin, oophorectomy, or ovarian irradiation) and tamoxifen or OAS and exemestane for 5 years. Updated analysis after a median follow-up of 8 years for SOFT, and 9 years for TEXT:<sup>75</sup>
  - i. DFS at 8 years was 86.8% with exemestane + OAS and 82.8% with tamoxifen + OAS (HR 0.77, 95% CI 0.67-0.9, p<0.001).
  - ii. 8-year OS rate was not statistically different (93.4% with exemestane + OAS and 93.3% with tamoxifen + OAS; p=0.84)
  - iii. Increased rates of adverse effects in arms who received endocrine therapy + OAS compared to tamoxifen alone.
- d) Combined analysis of SOFT and TEXT after a median follow-up of 12 years: <sup>76</sup>
  - i. DFS 80.5% for exemestane + OAS vs. 75.9% for tamoxifen + OAS (4.6% absolute improvement with the exemestane group; HR 0.79, 95% CI 0.70-0.90)
  - ii. 12-year OS was comparable in both groups (90.1% in exemestane + OAS vs. 89.1% in tamoxifen + OAS; HR 0.93, 95% CI, 0.78-1.11)
- e) Safety data support administration of GnRH agonists before or with chemotherapy especially if patient desires fertility preservation. They can also be initiated after chemotherapy if patient remains premenopausal. <sup>23</sup>

#### 10) Aromatase Inhibitors (postmenopausal women)

- a) Agents:
  - i. Nonsteroidal: anastrozole and letrozole
  - ii. Steroidal: exemestane
- b) Side effects: hot flashes, arthralgias/myalgias, mild headache, diarrhea, bone loss (osteoporosis, fractures), vaginal dryness, cardiovascular events
  - i. Myalgia/arthralgia <sup>77</sup>
    - (a) Up to 50% of postmenopausal women receiving AI. Leads to treatment discontinuation in 20% of women.
    - (b) Onset is approximately 6 weeks following initiation. Severity may worsen further over 1 year.<sup>78</sup>
    - (c) Pre-existing joint-related comorbidity at baseline is associated with worse AI-associated arthralgia.<sup>78</sup>
    - (d) Often not responsive to NSAIDs or acetaminophen

- (e) Duloxetine, acupuncture, and exercise are several treatment strategies that have shown a decrease in AI-associated arthalgias<sup>79,80,81</sup>
  - (f) Approximately 40% who discontinue the drug may tolerate a different AI
- c) First-line adjuvant therapy compared with tamoxifen
- i. Anastrozole – approved for adjuvant therapy for early stage breast cancer (1 mg daily for 5 years); ATAC trial found anastrozole superior to tamoxifen in terms of disease-free survival (DFS). At 68 months of follow-up, 575 events with anastrozole vs. 651 events with tamoxifen, HR 0.87, 95% CI 0.78-0.95, p=0.01)<sup>82</sup>.
  - ii. Letrozole – approved for adjuvant therapy for early stage breast cancer (2.5 mg daily for 5 years); superior to tamoxifen (BIG 1-98 trial found letrozole superior to tamoxifen in terms of DFS. At 51 month follow-up, 352 DFS events vs. 418 events HR 0.82, 95% CI, 0.71 to 0.95, p=0.007).<sup>83</sup>
  - iii. Exemestane – The TEAM trial evaluated exemestane x 5 years vs. sequential tamoxifen x 2.5-3 years followed by anastrozole to complete 5 years. DFS at 10 years was 67% in both arms (HR 0.96; P=0.39)<sup>84, 85</sup>
  - iv. Meta-analysis of AI vs. tamoxifen.<sup>86</sup>
    - (a) Included data from ATAC and BIG 1-98 studies
    - (b) AI x 5 years vs. tamoxifen x 5 years (n=9,856): absolute decrease of 2.9% in breast cancer recurrence at 5 yrs (9.6% vs. 12.6%) and absolute decrease of 3.9% at 8 yrs (15.3% vs. 19.2%) favoring the AI group.
    - (c) Tamoxifen x 5 years vs. tamoxifen → AI (total of 5 years) (n=9,015): absolute decrease of 3.1% in breast cancer recurrence at 5 yrs (5% vs. 8.1%) and absolute decrease of 3.6% at 6 yrs (12.6% vs. 16%) favoring tamoxifen → AI group.
- d) Sequential adjuvant therapy after 2-3 years of tamoxifen (switching strategy)
- i. Anastrozole – 1 mg daily to complete 5 years of adjuvant endocrine therapy; superior to tamoxifen alone for 5 years. At 36-month follow-up, 45 events vs. 17 events (p=0.0002). DFS and local recurrence-free survival also significantly longer in anastrozole group (HR = 0.35 and 0.15 respectively).<sup>87</sup>
  - ii. Exemestane (IES trial) – 25 mg daily to complete 5 years of adjuvant endocrine therapy; superior to tamoxifen alone for 5 years. At 30.6 month follow-up, 449 first events vs. 266 events (unadjusted HR 0.68; 95% CI 0.56 to 0.82; p<0.001).<sup>88</sup>
  - iii. In BIG 1-98, sequential treatment with letrozole and tamoxifen (Tam → Let and Let → Tam) were compared with letrozole for 5 years. With 8.1 years of median follow-up, the sequential arms did not significantly decrease the risk of a DFS event compared to letrozole alone in either comparison.<sup>89</sup>
  - iv. In an evaluation of TEAM trial after results of the IES study were made available, there was no difference in 5 year DFS with sequential tamoxifen x 2.5-3 yrs → exemestane to complete 5 years of treatment compared to exemestane x 5 years (HR 0.97, 5.1 years of follow-up).<sup>84</sup>
  - v. Meta-analysis of tamoxifen → AI for total of 5 years vs. tamoxifen x 5 years.<sup>86</sup>

- (a) Absolute decrease in breast cancer recurrence at 3 years (5.0% vs. 8.1%) and 6 years (12.6% vs. 16.0%) after switching favoring the AI group.
- e) Second adjuvant therapy after 5 years of tamoxifen (extended strategy)
  - i. Letrozole (MA-17 trial) – 2.5 mg daily for another 5 years superior to placebo; DFS (HR 0.52; 95% CI 0.45-0.61) and OS (HR 0.61; 95% CI 0.52-0.71) was superior with letrozole compared to placebo.<sup>90</sup>
    - (a) Delayed treatment with letrozole also improved DFS compared to patients who received placebo (median 2.8 years from stopping Tam; range 1.1-7.1 years).<sup>91</sup>
  - ii. Exemestane (NSABP B-33) – 25 mg daily for another 5 years vs. placebo; stopped when MA-17 results available; recent report of available data (about half of initial accrual goal) indicate non-significant benefit in 4-year DFS (91% vs. 89%; RR = 0.68; p=0.07) with 30 months median follow-up.<sup>92</sup>
- f) Extending duration of AI
  - i. 5 years vs. 10 years
    - (a) MA.17R trial randomized postmenopausal women who previously received 4.5 – 6 years of adjuvant AI to letrozole 2.5 mg daily x additional 5 years or placebo. Primary endpoint was DFS.<sup>93</sup>
      - 68.5% patients also previously received tamoxifen for 4.5 – 5.5 years
    - (b) After median follow-up of 6.3 years, 5-year DFS was 95% (95% CI; 89 to 96) with letrozole and 91% (95% CI; 89 to 93) with placebo (HR=0.66, p=0.01). Annual incidence rate of contralateral breast cancer was reduced in the letrozole group (0.21% vs. 0.49%; HR =0.42; P=0.007). OS did not significantly differ between groups.
    - (c) Bone-related adverse effects (bone pain, fractures, and new-onset osteoporosis) occurred more frequently in patients receiving extended therapy with letrozole
  - ii. 7 years vs. 10 years
    - (a) SALSA was a phase 3 trial that randomized 3484 postmenopausal women who had received 5 years of adjuvant endocrine therapy to AI for additional 2 years (total 7 years) or additional 5 years (total 10 years). PFS was DFS.<sup>94</sup>
    - (b) At 8-year follow-up, disease progression or death occurred in 335 women in each group (HR 0.99; 95% CI, 0.85 – 1.15; P=0.90). No difference in most secondary end points. Risk of clinical bone fracture was higher in 5-year group.
    - (c) Conclusion: Extending hormone therapy by 5 years to total of 10 years provided no benefit over 2-year extension to total of 7 years
- g) All three selective AIs (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles.<sup>23</sup>
- h) Consider concurrent use of bisphosphonate (IV/oral) or denosumab to maintain or to improve bone mineral density (BMD) and reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant AI.
  - i. See Survivorship section for further details on management of bone health

11) CDK4/6 inhibitor + endocrine therapy for adjuvant treatment

- a) MonarchE was an open-label, phase 3 study of 5637 patients with HR-positive, HER2-negative high-risk early-stage breast cancer who had surgery +/- radiation and/or neoadjuvant/adjuvant chemotherapy. Patients were randomized 1:1 to standard-of-care adjuvant endocrine therapy (ET)  $\geq$  5 years +/- abemaciclib 150 mg PO BID x 2 years. Primary endpoint was iDFS.<sup>95, 96</sup>
  - i. High-risk defined as:  $\geq$  4 positive LN OR 1 – 3 positive LN and tumor  $\geq$  5 cm, histologic grade 3, or central Ki-67  $\geq$  20%
  - ii. The 4-year analysis found sustained benefit for abemaciclib + ET. iDFS rate was 85.8% in the abemaciclib +ET arm compared to 79.4% for ET only (HR 0.664; 95% CI 0.578 - 0.762;  $p < 0.0001$ ) and distant relapse-free survival (DRFS) was 88.4% in the abemaciclib + ET arm compared to 82.5% for ET only (HR 0.659; 95% CI 0.567 - 0.767).
  - iii. Higher incidence of diarrhea, fatigue, and neutropenia in the abemaciclib + ET arm
- b) NCCN Guidelines® state to consider 2 years of adjuvant abemaciclib for patients meeting high-risk criteria as defined by MonarchE.<sup>23</sup>
- c) ASCO Guidelines recommend that 2 years of adjuvant abemaciclib + endocrine therapy may be offered to patients with HR-positive, HER2-negative, LN-positive early breast cancer with a high risk of recurrence and a Ki-67 score  $\geq$  20%. The panel also recommends this combination may be offered to the broader ITT population (based on high-risk criteria as defined by MonarchE).<sup>97</sup>

**Patient case #2, continued (ARS 1):**

Correct answer: D docetaxel and cyclophosphamide (TC) followed by tamoxifen. Given her high RS, JH is a candidate for chemotherapy. There are several options including TC or doxorubicin and cyclophosphamide (AC) followed by paclitaxel. Following completion of chemotherapy, JH is scheduled to start radiation to the whole breast with boost to the tumor bed along with endocrine therapy. Tamoxifen is an appropriate adjuvant endocrine therapy to be initiated following chemotherapy. It may be administered concurrently with radiation or following the completion of radiation.

Answer A is incorrect because JH has a high RS and therefore should receive chemotherapy followed by endocrine therapy. Also, anastrozole is not an appropriate adjuvant endocrine therapy for JH, who is premenopausal. Single agent anastrozole for endocrine therapy would only be appropriate for a postmenopausal patient.

Answer B is incorrect because anastrozole is not an appropriate adjuvant endocrine therapy for JH, who is premenopausal.

Answer C is incorrect because chemotherapy is indicated for JH based on her high RS =26. This endocrine only option would be appropriate for a patient with a RS < 26. If JH had a low or intermediate score, tamoxifen +/- OAS (such as goserelin) would be an appropriate option.

**Following a course of chemotherapy, what would be the most appropriate adjuvant endocrine therapy for JH if she were postmenopausal?**

- A. Anastrozole x 5 years
- B. Goserelin + anastrozole x 10 years
- C. Tamoxifen x 10 years
- D. Goserelin + tamoxifen x 5 years



**Patient case # 2 (continued):**

Correct answer is A. NCCN Guidelines® recommend an AI, such as anastrozole, for 5 – 10 years. Other appropriate options include sequential regimens and AI and tamoxifen or tamoxifen x 5-10 years for patients who have a contraindication or intolerance to an AI.

Answer B is incorrect because the combination of an AI and OAS, such as goserelin, is only recommended for premenopausal patients and this combination is only recommended for 5 years. OAS is not needed for postmenopausal patients.

Answer C is incorrect because tamoxifen is considered to be appropriate option for a postmenopausal woman if she has a contradiction or intolerance to AIs.

Answer D is incorrect because the combination of tamoxifen and OAS, such as goserelin, is only recommended for premenopausal patients. OAS is not needed for postmenopausal patients.

**Patient case # 3 (continued) (ARS 2):**

Correct answer is B. ASCO and NCCN Guidelines® recommend the addition of abemaciclib for 2 years to endocrine therapy for patients at a high risk for recurrence. Criteria for high-risk of recurrence includes patients with ≥ 4 positive LN or 1 – 3 positive LN with at least one additional high risk feature. Given that CW has 4 positive lymph nodes, she meets this high-risk criterion. This recommendation is based on the results of the MonarchE trial in which the addition of abemaciclib to endocrine therapy improved iDFS compared to endocrine therapy alone.

Answer A is incorrect because leuprolide is only indicated for premenopausal patients. CW is postmenopausal and therefore, does not need the addition of leuprolide.

Answer C is incorrect because this patient meets high-risk criteria established for the addition of abemaciclib and the patient desires to be aggressive with treatment. If she does not tolerate or declines the addition of abemaciclib, single agent AI (such as anastrozole) would be an appropriate adjuvant treatment option.

Answer D is incorrect because tamoxifen is only recommended for patients who are unable to tolerate an aromatase inhibitor, which is the preferred endocrine therapy for postmenopausal patients, such as CW.

**Patient case #4 (ARS 3):** YC is a 37-year-old premenopausal African American woman who presents to her medical oncologist with a newly diagnosed right breast cancer confirmed with ultrasound and core needle biopsy as invasive ductal carcinoma. The tumor is 1.3 cm x 1.3 cm (T1c,N0,M0; stage 1A), ER negative, PR negative, HER2-negative (triple negative). Pathology also reveals a nuclear grade of 2 (moderately differentiated) and a Ki-67 of 50%. She recently underwent a modified radical mastectomy with negative LN and negative margins (>1 mm). She was found to have a *BRCA2* mutation but otherwise has no other comorbidities.

**According to NCCN Guidelines®, which of the following adjuvant regimens would be the most appropriate for YC?**

- A. Cyclophosphamide + methotrexate + fluorouracil (CMF)
- B. Carboplatin
- C. Dose dense doxorubicin + cyclophosphamide (AC) → paclitaxel
- D. Paclitaxel

## h. Adjuvant Chemotherapy

### 1) Summary

- a) The optimal regimen in any clinical situation has not been determined; no standard regimen; many acceptable, evidence-based regimens demonstrate improvement in reducing the risk of recurrent breast cancer.
- b) LN-negative vs. LN-positive: controversial whether to include a taxane in addition to an anthracycline-based regimen in LN-negative disease (NCCN® and ASCO guidelines do not differentiate regimens based on nodal status, although there are some RCTs that support taxane use in high-risk LN-negative patients).<sup>98,99</sup> ASCO guidelines recommend the use of an anthracycline and taxane regimen for patients with high-risk features (including patients with LN-positive disease).<sup>100</sup>
- c) NCCN® identifies “preferred” chemotherapy regimens.
  - i. The NCCN® panel states that the preferred designation takes efficacy, toxicity, and treatment schedules into consideration.

### 2) Summary of Consensus Guidelines (see table Selected Regimens for Neoadjuvant/Adjuvant Therapy):

- a) In patients who can tolerate it, use of a regimen containing anthracycline-taxane is considered the optimal strategy in patients deemed to be at high risk.<sup>100</sup>
- b) Consider use of taxane-based regimens, such as docetaxel and cyclophosphamide (TC), for patients with lower risk disease features or those who are not candidates for an anthracycline.
- c) Anthracycline-containing regimens
  - i. Use of anthracyclines reduced recurrence by 25% (absolute difference of 8%) and reduced overall mortality by 16% (absolute decrease 5%) compared to no chemotherapy.<sup>101</sup>
  - ii. An optimal-dose anthracycline 3-drug regimen (cumulative doxorubicin  $\geq 240$  mg/m<sup>2</sup> or epirubicin  $\geq 600$  mg/m<sup>2</sup> but no higher than 720 mg/m<sup>2</sup>) should be considered for patients with high-risk disease who will not receive a taxane. Cumulative dose of doxorubicin in two-drug regimens should not exceed 240 mg/m<sup>2</sup>.<sup>100</sup>
- d) Taxane-containing regimens
  - i. EBCTCG update included taxane data<sup>101</sup>
    - (a) Incorporation of a taxane significantly reduced the risk of distant recurrence (RR 0.87), any recurrence (RR 0.86), breast cancer mortality (RR 0.87), and overall mortality (RR 0.89).
  - ii. TC x 4 cycles offers improved DFS and OS compared with AC x 4 cycles.<sup>102</sup>
    - (a) Higher risk of infection with TC
  - iii. A joint efficacy analysis of 3 phase 3 adjuvant trials (the ABC trials) that randomized a total of 2,125 patients with HER2-negative breast cancer to TC x 6 cycles (TC6) or taxane + AC regimens (TaxAC). Median follow-up was 3.3 years. 4-year invasive DFS was improved with TaxAC regimens (90.7%) compared to TC6 (88.2%) (p=0.04).

Benefits appear to be most meaningful in patients with HR-negative tumors or HR-positive, LN-positive.<sup>103</sup>

- iv. NCCN® supports substitution of nab-paclitaxel for paclitaxel or docetaxel due to medical necessity (i.e. hypersensitivity reaction). Weekly dose should not exceed 125 mg/m<sup>2</sup>.<sup>23</sup>

e) CMF

- i. 4 cycles of AC appear to be equivalent to classic CMF (reduction in recurrence, breast cancer mortality, and overall mortality were nearly equivalent).<sup>101</sup>
- ii. ASCO guidelines consider this as an option for patients in whom an anthracycline-taxane is contraindicated. Preference given for the classic CMF regimen (containing oral cyclophosphamide) over all-IV regimens due to absence of randomized controlled trials with all-IV.<sup>100</sup>

3) Other information

- a) Taxane frequency (weekly vs. Q 3 week) and comparison of taxanes (paclitaxel vs. docetaxel) following 4 cycles of AC given every 3 cycles<sup>104</sup>
  - i. No statistically significant differences in DFS or OS were observed when comparing docetaxel weekly vs. paclitaxel every 3 week
  - ii. Improved DFS with weekly paclitaxel and Q 3 week docetaxel compared to Q 3 week paclitaxel
  - iii. Improved OS with weekly paclitaxel compared to Q 3 week paclitaxel
  - iv. Higher incidence of febrile neutropenia with Q 3 week docetaxel and higher incidence of grade 2- 4 neuropathy with weekly paclitaxel compared to paclitaxel every 3 weeks
  - v. Q 3 week paclitaxel is no longer recommended for curative intent breast cancer treatment
  - vi. Data with the taxanes, especially paclitaxel, appear to support a weekly therapy producing optimal outcomes.<sup>93, 94</sup>
- b) Dose-dense (DD) therapy (every 2 weeks)
  - i. LN-positive breast cancer patients in the CALGB 9741 study were randomized after surgery to sequential versus concurrent chemotherapy (AC → Pac vs. A → Pac → C), and standard dose (Q 3 week) versus dose dense (AC → Pac).<sup>105</sup>
    - (a) Patients receiving every-2-week chemotherapy had a significantly prolonged DFS (85% vs. 81%,  $p = 0.01$ ) and OS (92% vs. 90%  $p = 0.013$ ) vs. every 3-week chemotherapy.
    - (b) Based on these results, NCCN Guidelines® preferentially lists dose dense AC regimens (followed by a taxane) over conventional AC every 3 weeks (followed by a taxane)
    - (c) Growth factor support is recommended for all cycles of dose-dense chemotherapy

- 4) All attempts to maintain chemotherapy schedule should be made; dose-reductions should be made only when other measures (e.g., growth factor support) have failed.

**Patient Case #4, continued (ARS 3):** Correct answer is C. YC has a stage Ia (T1c,N0,M0) breast cancer. Given that her primary tumor was > 1 cm, adjuvant chemotherapy is routinely recommended following her modified radical mastectomy. There is not one standard recommended adjuvant regimen. YC and her oncologist have decided to proceed with dose dense doxorubicin + cyclophosphamide followed by paclitaxel (see table for additional appropriate regimens). She would not need radiation therapy since she was LN-negative, primary tumor was < 5 cm, and margins were > 1 mm. She also would not receive adjuvant endocrine therapy since she is ER- and PR-negative.

Answer A is incorrect because cyclophosphamide, methotrexate, fluorouracil (CMF) is an option for adjuvant treatment but it is not listed as a preferred option by NCCN Guidelines®.

Answer B is incorrect because single agent carboplatin is not a recommended option for adjuvant chemotherapy. It is a recommended option for the treatment of metastatic disease in patients with TNBC and *BRCA1/2* mutation, such as YC.

Answer D is incorrect because single agent paclitaxel is not recommended for the adjuvant treatment of early stage breast cancer.

**Patient case #5 (ARS 4):** VT is a 58-year-old postmenopausal Caucasian woman who was diagnosed with stage IIIA (T2N2M0) invasive ductal carcinoma. Pathology revealed a tumor that is ER-negative, PR-negative, HER2-negative (triple negative). She has a germline *BRCA1* mutation. VT was treated with neoadjuvant doxorubicin and cyclophosphamide (AC) every 2 weeks x 4 cycles followed by paclitaxel weekly x 12 cycles. Following neoadjuvant treatment, she underwent breast-conserving surgery. At the time of surgery, she is found to have residual disease in the breast.

**In addition to radiation, which adjuvant treatment is most appropriate for VT?**

- A. Ado trastuzumab emtansine
- B. Docetaxel + cyclophosphamide
- C. Paclitaxel + carboplatin
- D. Olaparib

5) Role of additional adjuvant chemotherapy for patients with residual disease following neoadjuvant chemotherapy

i. Capecitabine

- (a) CREATE-X was a phase 3 open-label trial that randomized 910 patients with HER2-negative stage I – IIIB breast cancer with residual disease following neoadjuvant chemo and surgery to placebo or adjuvant capecitabine 1,250 mg/m<sup>2</sup> BID on days 1 – 14 every 21 days x 6 or 8 cycles (protocol extended to 8 cycles after 1<sup>st</sup> 50 patients were enrolled). Postsurgical XRT could be given before or after randomization.<sup>106</sup>

- At interim analysis (5-year follow-up), the primary endpoint of DFS was 74.1% vs. 67.6% in favor of capecitabine group (HR 0.7; p=0.01). OS was longer in capecitabine group (89.2% vs. 83.6% (HR 0.59; p=0.01).

- Among patients with triple negative disease, DFS was 69.8% in capecitabine group vs 56.1% in control (HR 0.58) and OS was 78.8% vs 70.3% (HR 0.52)
- 73.4% of patients experienced hand-foot syndrome (grade 3 in 11.1%)
- (b) NCCN® and ASCO guidelines recommend considering the use of 6-8 cycles of adjuvant capecitabine in patients with TNBC and pathologic invasive residual disease following standard neoadjuvant treatment with taxane-, alkylator-, and anthracycline-based chemotherapy.<sup>23,100</sup>
  - NCCN® guidelines recommend administering following completion of XRT
- (c) ASCO guidelines state that the capecitabine dose of 1,250 mg/m<sup>2</sup> BID used in the CREATE-X study is associated with higher toxicity in patients ≥ 65 years old.<sup>100</sup>
- ii. Consider adjuvant olaparib x 1 year for patients who have a germline BRCA1/2 mutation and:<sup>107, 61, 108</sup>
  - (a) TNBC if:
    - ≥pT2 or ≥pN1 disease after adjuvant chemotherapy OR
    - residual disease after neoadjuvant chemotherapy
  - (b) HR-positive, HER2-negative tumors if:
    - ≥ 4 positive LN after adjuvant chemotherapy or
    - residual disease following neoadjuvant treatment and a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score ≥ 3
  - (c) OlympiA trial was a phase 3, double-blind, randomized trial of 1836 patients with HER2-negative early breast cancer with *BRCA1/2* germline pathogenic or likely pathogenic variants (aka mutations) and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. Randomized to olaparib 300 mg PO BID x 1 year or placebo. Primary end point was iDFS.
    - 82.2% of patients had TNBC
    - At interim analysis with median follow-up of 2.5 years, 3-year iDFS was 85.9% in olaparib group vs. 77.1% in placebo group (HR 0.58; 99.5% CI, 0.41 – 0.82; P<0.001). 3-year distant DFS was 87.5% in olaparib group vs. 80.4% in placebo group (HR 0.57; 99.5% CI, 0.39 -0.83; P<0.001).
    - OS data is immature at this time.
    - Of note, patients were required to have completed all local therapy including radiation (which interacts with PARP inhibition) at least 2 weeks prior to trial entry and all patients completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy. Post-neoadjuvant capecitabine was not permitted because it was not standard of care at the time of trial design. Olaparib and concurrent endocrine therapy was safe and effective.
    - Only grade 3 effect that occurred in > 5% of patients was anemia (8.7%).

- (d) Olaparib should be given after completion of radiation but may be given concurrently with endocrine therapy.<sup>23</sup>
- iii. Adjuvant ado-trastuzumab emtansine x 14 cycles recommended by NCCN® for patients with HER2-positive breast cancer and residual disease following preoperative therapy based on the results of the KATHERINE trial (see additional information in the HER2-Directed Therapy section below). May be administered concurrent with XRT.
- iv. Adjuvant pembrolizumab for up to 9 cycles of the q21 day regimen (or 400 mg every 6 weeks x 5 cycles) if patient received pembrolizumab + chemotherapy in the neoadjuvant setting (see more information in section below: Choice of Neoadjuvant Regimen)
- v. There is no data on sequencing or combining adjuvant capecitabine, pembrolizumab, and/or olaparib in patients who meet criteria for treatment with one or more of these agents. Sequential/combined use may be considered in certain patients at high risk of recurrence.<sup>23</sup>

**Patient case #5, continued (ARS 4):**

Correct answer is D. Based on the results of the OlympiA trial, iDFS was improved in patients with germline BRCA1/2 mutation and high-risk features (such as residual disease following neoadjuvant chemotherapy in TNBC). NCCN Guidelines® AND ASCO Guidelines recommend considering adjuvant olaparib x 1 year in patients, such as VT, with triple-negative breast cancer and pathologic invasive residual disease following neoadjuvant chemotherapy.

Answer A is incorrect because ado trastuzumab emtansine is only appropriate as adjuvant treatment for patients with HER2-positive breast cancer and residual disease following neoadjuvant treatment.

Answer B is incorrect because docetaxel and cyclophosphamide is an option in the adjuvant setting for patients who have not received neoadjuvant chemotherapy.

Answer C is incorrect because paclitaxel and carboplatin is not recommended in the adjuvant setting.

**Selected Regimens for Neoadjuvant/Adjuvant Therapy for HER2-negative Breast Cancer**

Regimen	Drugs	Doses	Schedule	Frequency	Cycles
<b>Dose-dense AC<sup>b</sup></b>	Doxorubicin	60 mg/m <sup>2</sup> IV	D 1	Q 14 days	4
	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 14 days	4
<b>EC</b>	Epirubicin	100 mg/m <sup>2</sup> IV	D 1	Q 21 days	8
	Cyclophosphamide	830 mg/m <sup>2</sup> IV	D 1	Q 21 days	8
<b>AC ⇒ Paclitaxel<sup>c</sup></b>	Doxorubicin	60 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
	Paclitaxel	80 mg/m <sup>2</sup> IV over 1h	Weekly	Q 7 days	12 wks
<b>AC ⇒ Docetaxel<sup>c</sup></b>	Doxorubicin	60 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
	Docetaxel	100 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
<b>TAC<sup>b,c</sup></b>	Docetaxel	75 mg/m <sup>2</sup> IV	D 1	Q 21 days	6
	Doxorubicin	50 mg/m <sup>2</sup> IV	D 1	Q 21 days	6
	Cyclophosphamide	500 mg/m <sup>2</sup> IV	D 1	Q 21 days	6
<b>TC<sup>*,c</sup></b>	Docetaxel	75 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
<b>Pembrolizumab + chemo<sup>*d</sup></b> Preoperative:	Pembrolizumab	200 mg IV	D 1	Q 21 days	4
	Paclitaxel	80 mg/m <sup>2</sup> IV	D 1, 8, 15	Q 21 days	4
	Carboplatin	AUC 5 IV OR	D 1	Q 21 days	4
		AUC 1.5 IV	D 1, 8, 15	Q 21 days	4
	<b>followed by</b>		D 1	Q 21 days	4
	Pembrolizumab	200 mg IV	D 1	Q 21 days	4
	Doxorubicin <sup>e</sup>	60 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
	Cyclophosphamide	600 mg/m <sup>2</sup> IV			
	Postoperative:	Pembrolizumab	200 mg	D 1	Q 21 days
<b>Dose-Dense<sup>b</sup> AC</b> <b>Followed (or preceded) by:</b>	Doxorubicin	60 mg/m <sup>2</sup> IV	D 1	Q 14 days	4
	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 14 days	4
<b>Dose-Dense<sup>b</sup> Pac<sup>*,f</sup></b> <b>OR</b>	Paclitaxel	175 mg/m <sup>2</sup> IV over 3h	D 1	Q 14 days	4
<b>Weekly Pac<sup>*,f</sup></b>	Paclitaxel	80 mg/m <sup>2</sup> IV over 1h	Weekly	Q 7 days	12 wks
<b>CMF</b>	Cyclophosphamide	100 mg/m <sup>2</sup> PO	D 1-14	Q 28 days	6
	Methotrexate	40 mg/m <sup>2</sup> IV	D 1, 8	Q 28 days	6
	5-Fluorouracil	600 mg/m <sup>2</sup> IV	D 1, 8	Q 28 days	6
<b>CMF</b>	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 21 days	8
	Methotrexate	40 mg/m <sup>2</sup> IV	D 1	Q 21 days	8
	5-Fluorouracil	600 mg/m <sup>2</sup> IV	D 1	Q 21 days	8
<b>Weekly paclitaxel + carboplatin (neoadjuvant only)</b>	Paclitaxel	80 mg/m <sup>2</sup> IV	D 1, 8, 15	Q 21 days	4
	Carboplatin	AUC 5 or 6	D 1	Q 21 days	4
<b>Weekly paclitaxel + weekly carboplatin (neoadjuvant only)</b>	Paclitaxel	80 mg/m <sup>2</sup> IV	D 1, 8, 15	Q 28 days	6
	Carboplatin	AUC 1.5 – 2	D 1, 8, 15	Q 28 days	6
<b>Olaparib<sup>*</sup> (adjuvant only)</b>		300 mg PO BID		Q 28 days	X 1 year

<b>Capecitabine</b> <sup>*g,h</sup>	1,000-1,250 mg/m <sup>2</sup> PO BID	D 1 – 14	Q 21 days	X 6 – 8 cycles
<b>Capecitabine</b> <b>(maintenance)</b>	650 mg/m <sup>2</sup> PO BID	D 1 – 28	Q 28 days	1 year

\* Designated by NCCN® as a preferred regimen

<sup>a</sup> No anthracycline only-based chemotherapy regimens are designated as a preferred regimen. All preferred regimens contain a taxane ± anthracycline

<sup>b</sup> Given with growth factor support

<sup>c</sup> Recommended by ASCO guidelines for higher-risk early-stage breast cancer <sup>109</sup>

<sup>d</sup> Consider for high-risk early stage breast cancer (stage II – III) TNBC

<sup>e</sup> Ok to substitute epirubicin 90 mg/m<sup>2</sup> for doxorubicin

<sup>f</sup> Acceptable to change administration sequence to paclitaxel followed by dose-dense AC

<sup>g</sup> Recommended in adjuvant setting only. Considered a NCCN® preferred regimen for patients with TNBC and residual disease after preoperative therapy. Considered “useful in certain circumstances” as maintenance therapy for TNBC following adjuvant chemotherapy.



**Selected Neoadjuvant/Adjuvant Therapy for HER2-positive Breast Cancer<sup>23</sup>**

Regimen	Drugs	Doses	Schedule	Frequency	Cycles	
TCH*	Docetaxel	75 mg/m <sup>2</sup> IV	D 1	Q 21 days	6	
	Carboplatin	AUC 6 IV	D 1	Q 21 days	6	
	Trastuzumab	4 mg/kg IV → 2 mg/kg IV	D 1,8,15	Q 21 days	18 weeks	
	<b><i>followed by</i></b> Trastuzumab	2 mg/kg IV or 6 mg/kg IV	D 1, 8,15 or D 1	Q 21 days	Complete 1 year	
TCH+P*	Docetaxel	75 mg/m <sup>2</sup> IV	D 1	Q 21 days	6	
	Carboplatin	AUC 6 IV	D 1	Q 21 days	6	
	Trastuzumab	8 mg/kg IV → 6 mg/kg IV	D 1	Q 21 days	1 year	
	Pertuzumab	840 mg → 420 mg	D 1	Q 21 days	1 year	
AC or dose dense AC <sup>a</sup> ⇒ T + H <sup>b,c</sup>	Doxorubicin	60 mg/m <sup>2</sup> IV	D 1	Q 21 days	4	
	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 21 days	4	
	<b><i>followed by</i></b> Paclitaxel	80 mg/m <sup>2</sup> IV over 1h	D 1,8,15	Q 21 days	12 weeks	
	Trastuzumab	4 mg/kg IV → 2 mg/kg IV	D 1,8,15	Q 21 days	12 weeks	
	<b><i>followed by</i></b> Trastuzumab	2 mg/kg IV or 6 mg/kg IV	D 1,8,15 or D 1	Q 21 days	Complete 1 year	
	AC ⇒ T + H + P <sup>b,c</sup>	Doxorubicin	60 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
		Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 21 days	4
		<b><i>followed by</i></b> Paclitaxel	80 mg/m <sup>2</sup> IV over 1h	D 1,8,15	Q 21 days	4
		Pertuzumab	840 mg IV → 420 mg	D 1	Q 21 days	1 year
		Trastuzumab	8 mg/kg IV → 6 mg/kg IV	D 1	Q 21 days	1 year
		AC ⇒ TH <sup>b,c</sup>	Doxorubicin	60 mg/m <sup>2</sup> IV	D 1	Q 21 days
Cyclophosphamide	600 mg/m <sup>2</sup> IV		D 1	Q 21 days	4	
<b><i>followed by</i></b> Docetaxel	100 mg/m <sup>2</sup> IV		D 1	Q 21 days	4	
Trastuzumab	4 mg/kg IV → 2 mg/kg IV		D 1,8,15	Q 21 days	12 weeks	
<b><i>followed by</i></b> Trastuzumab	2 mg/kg IV or 6 mg/kg IV		D 1,8,15 D 1	Q 21 days	Complete 1 year	
Dose dense AC ⇒dose dense T + H <sup>b</sup>	Doxorubicin		60 mg/m <sup>2</sup> IV	D 1	Q 14 days	4
	Cyclophosphamide	600 mg/m <sup>2</sup> IV	D 1	Q 14 days	4	
	<b><i>followed by</i></b> Paclitaxel	175 mg/m <sup>2</sup> IV over 1h	D 1	Q 14 days	4	
	Trastuzumab	4 mg/kg IV → 2 mg/kg IV	D 1, 8	Q 14 days	4	
	<b><i>followed by</i></b> Trastuzumab	2 mg/kg or 6 mg/kg IV	D 1,8,15 D 1	Q 21 days	Complete 1 year	
	Paclitaxel + trastuzumab* <sup>d</sup>	Paclitaxel	80 mg/m <sup>2</sup> IV		Q 7 days	12
Trastuzumab		4 mg/kg IV → 2 mg/kg IV		Q 7 days	12	
<b><i>followed by</i></b> Trastuzumab		2 mg/kg or 6 mg/kg IV	D 1,8,15 D 1	Q 21 days	Complete 1 year	

\* Designated by NCCN® as a preferred regimen

a. Dose dense AC administered at the same doses but given every 14 days x 4 cycles

- b. Acceptable to change administration sequence to taxane (+/- HER2 targeted therapy) followed by AC<sup>c</sup>. Pertuzumab may be incorporated into regimen for patients with  $\geq T2$  or  $\geq N1$ , HER2+, early-stage breast cancer preoperatively. Patients may receive adjuvant pertuzumab if not given in the neoadjuvant setting per NCCN Guidelines<sup>®</sup> breast cancer.<sup>23</sup>
- d. Consider for patients with low-risk T1,N0,M0, HER2+ disease (particularly those not eligible for other standard adjuvant regimens due to comorbidities)
  - i. Adjuvant HER2-Directed Therapy (see table Selected Neoadjuvant/Adjuvant Therapy for HER2-positive Breast Cancer)
    - 1) If no residual disease after preoperative therapy or if no preoperative therapy is given, NCCN Guidelines<sup>®</sup> recommend to complete up to 1 year of HER2 targeted therapy with trastuzumab +/- pertuzumab.<sup>23,110</sup>
    - 2) If residual disease after preoperative therapy, NCCN<sup>®</sup> and ASCO guidelines recommend ado-trastuzumab emtansine alone x 14 cycles. If ado-trastuzumab emtansine is discontinued for toxicity, then it is recommended to complete up to 1 year of HER2-directed therapy with trastuzumab +/- pertuzumab. If LN-positive at initial staging, trastuzumab + pertuzumab.<sup>23</sup>
    - 3) Trastuzumab
      - a) Recommended for all HER2-positive patients with tumors > 1 cm
      - b) According to the NCCN<sup>®</sup> and ASCO guidelines,<sup>23,100</sup> trastuzumab should be considered in HER2-positive patients with tumors < 1 cm due to poor recurrence-free survival in this patient population who did not receive trastuzumab in retrospective analyses. These patients were not included in the prospectively conducted randomized clinical trials of adjuvant trastuzumab.
      - c) Preferentially administered concurrently (not sequentially) with a non-anthracycline chemotherapy regimen
        - i. Typically given concurrent with taxane portion of the regimen
      - d) Can be administered with any acceptable adjuvant chemotherapy regimen
      - e) Should not be given concurrent with an anthracycline due to cardiac toxicity seen in patients with metastatic breast cancer.
      - f) Trastuzumab has been given for a total of 1 year in the majority of clinical trials, and this duration is considered to be the standard of care in the U.S.
        - i. The PHARE trial failed to show that 6 months of treatment with trastuzumab was non-inferior to 12 months of trastuzumab<sup>111</sup>
        - ii. In the HERA trial, no differences in DFS or OS were seen with one year of trastuzumab compared to two years of trastuzumab after adjuvant chemotherapy in patients with HER2-positive breast cancer after 8 years of follow-up.<sup>112</sup>
      - g) Cardiac monitoring should be performed (see Cardiotoxicity section)
      - h) Trastuzumab can be administered either weekly or every 3 weeks
      - i) Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta<sup>™</sup>) is a subcutaneous formulation<sup>113</sup>

- j) Trastuzumab-pkrb, trastuzumab-dkst, trastuzumab-dttb, trastuzumab-anns, and trastuzumab-qyyp are FDA-approved biosimilars to trastuzumab for patients with HER2-positive breast cancer, and NCCN® supports substitution.

#### 4) Pertuzumab

- a) Pertuzumab has a low response rate as a single agent in patients with HER2-positive breast cancer (3.4%), and therefore has been studied in combination with other anti-HER2 agents.<sup>114</sup>
- b) NCCN® and ASCO guidelines include a recommendation to consider the addition of pertuzumab to trastuzumab in the adjuvant setting to complete up to 1 year of HER2 targeted therapy for patients with LN-positive disease<sup>23,100</sup>
  - i. Guidelines cite a clinically insignificant absolute benefit among patients with LN-negative disease.<sup>100</sup>
  - ii. No data to guide duration of pertuzumab in patients who received neoadjuvant pertuzumab and achieved a pathologic complete response.<sup>100</sup>
- c) The APHINITY trial investigated the addition of pertuzumab to adjuvant trastuzumab and chemotherapy.<sup>115</sup>
  - i. Double-blind, placebo-controlled phase 3 trial that included 4,805 patients with LN-positive (63% of patients) or high-risk LN-negative disease who were randomized to chemotherapy and trastuzumab plus either pertuzumab or placebo. Trastuzumab and pertuzumab or placebo were initiated with the first cycle of taxane therapy and continued for a total of 1 year.
  - ii. At 8.4-year follow-up, iDFS was 88.4% vs. 85.8% (HR 0.77; 95% CI 0.66 – 0.91). The LN-positive subgroup derived a clear benefit from the addition of pertuzumab (86.1% vs. 81.2%; HR 0.72 (95% CI 0.60 – 0.87). There was no benefit in the LN-negative subgroup (HR 1.01 with > 92% of patients event-free in both arms at 8 years).
  - iii. No statistically significant difference in OS with the addition of pertuzumab (92.7% vs. 92%; HR 0.83; 95% CI 0.68 – 1.02; p=0.078).
  - iv. There was a greater incidence of ≥ grade 3 diarrhea in the pertuzumab group (9.8% vs. 3.7%).

#### 5) Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use (Phesgo®)

- a) Indications are same as IV trastuzumab and pertuzumab. According to NCCN®, it may be substituted anywhere that the combination of IV pertuzumab and trastuzumab are given as part of systemic therapy.<sup>23</sup>

#### 6) Ado-trastuzumab emtansine

- a) The KATHERINE trial was a phase 3, randomized, open-label trial of patients with HER2-positive early breast cancer (T1-T4, N0-N3, and M0) who had residual disease in the breast or axilla at surgery following neoadjuvant therapy containing a taxane (with or without an anthracycline) and trastuzumab. Patients received adjuvant ado-trastuzumab emtansine 3.6 mg/kg every 21 days or trastuzumab for 14 cycles (N=1,486).

<sup>116</sup>

- i. Primary end point was iDFS

- ii. At interim analysis, 3-year iDFS was significantly higher in the ado-trastuzumab emtansine group compared to the trastuzumab group (88.3% vs. 77%; HR, 0.50; 95% CI 0.39 – 0.64;  $P < 0.001$ ). There were more adverse effects in the ado-trastuzumab emtansine arm.
  - iii. Distance recurrence occurred in 10.5% of patients receiving ado-trastuzumab emtansine vs. 15.9% in patients receiving trastuzumab (HR 0.60; 95% CI, 0.45-0.79). There were less deaths in the ado-trastuzumab emtansine arm (42 vs. 56; HR 0.70; 95% CI, 0.47 – 1.05;  $p = 0.08$ ).
- b) ATEMPT trial randomized 497 patients with stage I HER2+ breast cancer 3:1 to ado-trastuzumab emtansine ( $n = 383$ ) 3.6 mg/kg IV every 3 weeks x 17 cycles or paclitaxel + trastuzumab (TH – paclitaxel weekly x 12 weeks + trastuzumab x 1 year;  $n = 114$ ). Co-primary endpoints were to compare the incidence of clinically relevant toxicities (CRTs) between the two arms and to evaluate iDFS in patients receiving ado-trastuzumab emtansine.<sup>117</sup>
- i. CRTs experienced by 46% in ado-trastuzumab emtansine arm vs. 47% TH arm ( $p = 0.83$ ). There was less neuropathy and alopecia, as well as better work productivity for patients receiving ado-trastuzumab emtansine.
  - ii. 3-year iDFS was 97.8% for ado-trastuzumab emtansine.
  - iii. Added to NCCN Guidelines® as an option in the adjuvant setting (category 2A).

#### 7) Neratinib<sup>118</sup>

- a) NCCN® recommends to consider the use of extended adjuvant neratinib following adjuvant trastuzumab-containing therapy in HR-positive patients with a perceived high risk of recurrence.<sup>23</sup>
- b) ASCO recommends to consider use in patients with early-stage, HER2-positive, HR-positive, LN-positive disease.<sup>100</sup>
- c) Benefit or toxicities of neratinib in patients who have received neoadjuvant/adjuvant pertuzumab or adjuvant ado-trastuzumab emtansine is unknown.<sup>23</sup>
- d) Approval based on ExteNET trial<sup>118</sup>
  - i. Double-blind, placebo-controlled trial that included 2,840 women with stage I – III HER2-positive breast cancer who had completed neoadjuvant and adjuvant trastuzumab up to 2 years before randomization. Inclusion criteria amended after 671 patients were enrolled to only include higher-risk patients with LN-positive disease who had completed trastuzumab therapy up to 1 year previously.
  - ii. Primary endpoint was invasive DFS at 2-years after randomization. DFS events occurred in 70 patients in the neratinib group vs. 109 in the placebo group (HR 0.67;  $p = 0.001$ ). 2-year DFS rate was 93.9% in neratinib group and 91.6% in the placebo group.
  - iii. At a median follow-up of 5.2 years, there were significantly fewer invasive DFS events in the neratinib group vs. placebo group (116 vs 163 events) (HR 0.73; 95% CI 0.57-0.92,  $p = 0.0083$ ). The 5-year DFS was 90.2% in the neratinib group vs. 87.7% in the placebo group. No OS benefit has been observed.<sup>119</sup>

iv. Patients who began neratinib within 1 year of trastuzumab completion, those with LN-positive disease, and those with HR-positive disease appeared to derive the greatest benefit.

(a) Subgroup with HR-positive disease: 59 DFS events in neratinib group and 100 events in placebo group (HR 0.60)

v. 95% of patients on neratinib arm developed diarrhea (grade 3 in 40%). Most patients had diarrhea in the 1<sup>st</sup> month of treatment with median of 8 days to onset of grade  $\geq 3$  diarrhea and median duration of 5 days.

vi. Prophylaxis with loperamide +/- colestipol or budesonide as well as neratinib dose escalation strategies have been shown to reduce the rate, severity, and duration of neratinib-associated grade  $\geq 3$  diarrhea in an interim analysis of the CONTROL trial.

120

(a) Two-week dose escalation is recommended to minimize diarrhea <sup>121</sup>

- Week 1 (days 1 – 7) → 120 mg daily
- Week 2 (days 8 – 14) → 160 mg daily
- Week 3 and beyond → 240 mg daily

(b) If dose escalation is not utilized, antidiarrheal prophylaxis is recommended with 1<sup>st</sup> 2 cycles (56 days) of treatment and should be initiated with the 1<sup>st</sup> dose of neratinib. Recommended loperamide prophylaxis:<sup>121</sup>

- Weeks 1 – 2 → 4 mg TID
- Weeks 3 – 8 → 4 mg BID
- Weeks 9 – 52 → 4 mg as needed (not to exceed 16 mg/day)

j. Adjuvant bone-modifying agents (BMAs)

1) Joint ASCO and CCO (Cancer Care Ontario) guideline recommends to consider the administration of bisphosphonates as adjuvant therapy for postmenopausal patients with breast cancer, irrespective of HR status and HER2 status, who are deemed candidates for adjuvant systemic therapy <sup>122</sup>

a) Postmenopausal defined as natural or induced by LHRH analogs or oophorectomy

b) Decision to recommend should consider patient's risk of recurrence, risk of side effects, financial toxicity, drug availability, patient preference, comorbidities, and life expectancy

c) NHS PREDICT tool provides estimates of benefit of adjuvant bisphosphonate therapy (<https://breast.predict.nhs.uk/>)

d) Options for treatment include clodronate 1600 mg PO daily x 2 – 3 years, oral ibandronate 50 mg PO daily x 3 years, zoledronic acid 4 mg IV every 6 months x 3 years or 4 mg IV every 3 months x 2 years

e) Recommend starting early. Many studies initiated bisphosphonates within 3 months of definitive surgery or within 2 months of completion of adjuvant chemotherapy.

- 2) NCCN Guidelines® recommend to consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3 – 5 years in postmenopausal patients (natural or induced) with high-risk LN-negative or LN-positive disease <sup>23,122</sup>
  - a) EBCTCG meta-analysis was the main source of evidence for these guidelines <sup>123</sup>
    - i. Included data from 18,766 women in 26 trials
    - ii. 66% were LN positive and 83% received systemic chemotherapy
    - iii. Use of bisphosphonates reduced the rate of breast cancer recurrence in the bone in postmenopausal women

**Adjuvant bisphosphonates for treatment of early stage breast cancer <sup>123</sup>**

Outcome (10 year-risk)	Bisphosphonate	Control Arm	Rate Ratio (95% CI)	Log rank 2p
Bone recurrence rate	7.8%	9%	0.83 (0.73 – 0.94)	0.004
• Postmenopausal*	6.6%	8.8%	0.72 (0.60 – 0.86)	0.0002
Distant recurrence	20.4%	21.8%	0.92 (0.85 – 0.99)	0.03
Breast cancer mortality	16.6%	18.4%	0.91 (0.83 – 0.99)	0.04
• Postmenopausal*	14.7%	18%	0.82 (0.73 – 0.93)	0.002
All-cause mortality	20.8%	22.3%	0.92 (0.85 – 1.00)	0.06

\* Postmenopausal subgroup analysis

- iv. Other outcomes that were improved but to a lesser extent were distant recurrence, breast cancer mortality and any death. There was no effect on distant recurrence outside of bone.
  - v. Bisphosphonates had no significant effect on outcomes for premenopausal women.
- 3) Denosumab
  - a) Current guidelines state that data are insufficient to make a recommendation on the use of denosumab in the adjuvant setting except to reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.
  - b) Double-blind, placebo-controlled phase 3 ABCSG-18 trial randomized postmenopausal women to denosumab 60 mg SC every 6 months or placebo during adjuvant AI therapy.
    - i. Denosumab significantly delayed time to first clinical fracture (primary endpoint) (HR 0.5; 95% CI 0.39-0.65; p< 0.001).<sup>124</sup>
    - ii. At median follow-up of 73 months, DFS (secondary endpoint) events occurred in 240 patients in the denosumab group and 287 in the placebo groups (HR 0.82, 95% CI 0.69-0.98; p=0.0260). DFS was 80.6% in the denosumab group at 8 years of follow-up compared to 77.5% in the placebo group.<sup>125</sup>
  - c) D-CARE trial randomized 4,509 patients with EBC to standard loco-regional and neoadjuvant/adjuvant therapy plus denosumab or placebo every 3 – 4 weeks x 6 months then every 12 weeks for a total duration = 5 years.<sup>126</sup>
    - i. Primary endpoint was bone metastasis free survival (BMFS) which was not significantly different at 67 months of follow-up (HR 0.97; 95% CI 0.82-1.14 p=0.7).
    - ii. Osteonecrosis of the jaw (ONJ) was reported in 5% of patients treated with denosumab

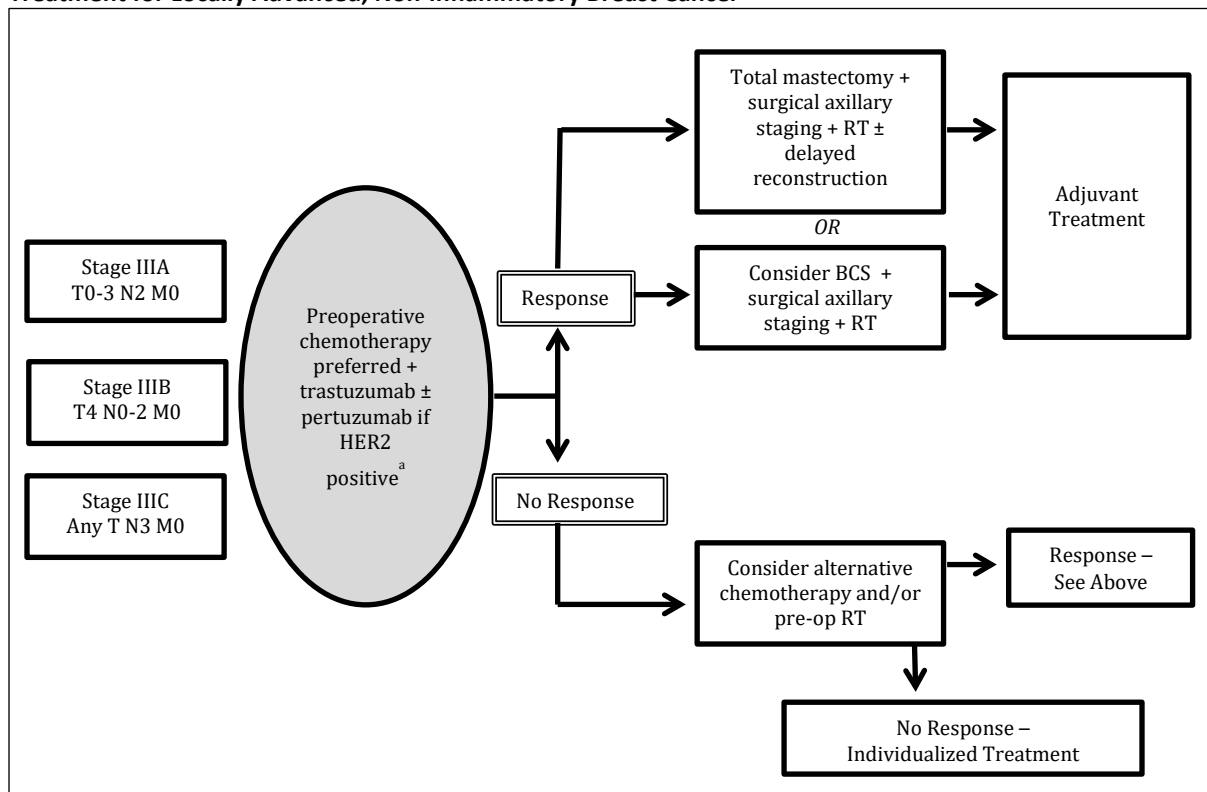
- 4) Adjuvant BMAs are not recommended for men with early-stage breast cancer to prevent recurrence but may be used to prevent or treat osteoporosis. <sup>6</sup>

A. Stage IIIA, IIIB & IIIC Invasive Breast Cancers (locally advanced, non-inflammatory)

1. Summary:

- a. Operable stage IIIA (T3, N1, M0)
  - 1) See guidelines for early stage breast cancer (listed above)
  - 2) Local therapy or neoadjuvant systemic therapy followed by local therapy based on patient and disease factors (see below)
- b. All other stage IIIA, IIIB, IIIC (non-inflammatory)
  - 1) Primary (preoperative, neoadjuvant) systemic chemotherapy; HER2-directed therapy should be incorporated if HER2-positive.
  - 2) If a response is demonstrated and tumor is operable, then local therapy would be performed.
    - a) Mastectomy or BCS +/- RT may be considered, depending on clinical situation.
- c. If no response to preoperative chemotherapy, then proceed to mastectomy or consider additional systemic therapy and/or preoperative radiation.

**Treatment for Locally Advanced, Non-Inflammatory Breast Cancer<sup>23</sup>**



**Abbreviations:** RT = radiation therapy; BCS = breast conserving surgery.

<sup>a</sup> Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology

**Patient case #6 (ARS 5):** HF is a 60-year-old healthy female with minimal comorbidities including hyperlipidemia and hyperthyroidism. She has a newly diagnosed Stage IIIB (T4, N2, M0) left breast cancer that is ER 70%, PR 0%, and HER2 IHC 3+. She would prefer a lumpectomy and radiation; therefore, she must undergo neoadjuvant chemotherapy with the hope of decreasing the size of the primary tumor to allow for adequate surgical resection.

**What neoadjuvant regimen would be most appropriate?**

- A. AC + trastuzumab x 4 cycles
- B. Docetaxel + trastuzumab + pertuzumab x 6 cycles
- C. TCH + pertuzumab x 6 cycles
- D. AC x 4 cycles → paclitaxel weekly x 12

2. Preoperative (neoadjuvant) systemic chemotherapy

- a. Benefits of neoadjuvant therapy: <sup>23</sup>
  - 1) Decrease the size of the tumor to minimize surgery
  - 2) Determine response to chemotherapy (an important prognostic indicator especially for triple-negative disease and HER2+ disease)
  - 3) Allows modification or addition of adjuvant regimens among patients with HER2-positive and TNBC with residual disease
  - 4) Allows time for genetic testing
  - 5) Allows time to plan breast reconstruction in patients electing mastectomy
- b. Neoadjuvant (primary, preoperative) vs. adjuvant systemic therapy
  - 1) Meta-analysis of neoadjuvant vs. adjuvant systemic treatment<sup>127</sup>
    - a) Nine trials included in analysis (n=3,861)
    - b) No significant difference in death, disease progression, or distant recurrence



c. Candidates for neoadjuvant therapy

NCCN Guidelines® <sup>23</sup>	ASCO Guidelines <sup>108</sup>
<ul style="list-style-type: none"> <li>• Preferred for patients with inoperable breast cancer (inflammatory breast cancer, bulky or matted cN2 axillary LNs, cN3 nodal disease, cT4 tumors)</li> <li>• In patients with operable breast cancer, neoadjuvant therapy is preferred for those with: <ul style="list-style-type: none"> <li>○ HER2-positive disease or TNBC, if cT <math>\geq 2</math> or cN <math>\geq 1</math> (consider neoadjuvant therapy for cT1,N0)</li> <li>○ Large primary tumor relative to breast size in a patient that desires breast conservation</li> <li>○ With clinically LN-positive disease likely to become LN-negative with preoperative systemic therapy</li> </ul> </li> <li>• Patients in whom definitive surgery may be delayed</li> </ul>	<ul style="list-style-type: none"> <li>• Inflammatory breast cancer</li> <li>• Unresectable or locally advanced disease at presentation whose disease may be rendered resectable with neoadjuvant treatment</li> <li>• Reduce the extent of surgery</li> <li>• Patients for whom a delay in surgery is preferable (eg, for genetic testing required for surgical decision making, to allow time to consider reconstructive options)</li> <li>• Patients with TNBC who have clinically LN-positive and/or at least T1c disease <ul style="list-style-type: none"> <li>○ cT1a or cT1b N0 should not be routinely offered neoadjuvant therapy</li> </ul> </li> <li>• Consider for patients with HR-positive, HER2-negative disease when a treatment decision can be made without surgical information</li> <li>• Patients with HER2-positive disease that is LN-positive or high-risk LN-negative <ul style="list-style-type: none"> <li>○ T1aN0 and T1bN0 should not be routinely offered neoadjuvant therapy</li> </ul> </li> </ul>

d. Choice of neoadjuvant regimen

1) Chemotherapy

- a) NCCN Guidelines® recommend that in general, those chemotherapy regimens recommended in the adjuvant setting may also be considered in the preoperative setting. This is a consensus recommendation, not an evidence-based one. (See tables Selected Regimens for Neoadjuvant/Adjuvant Therapy)
  - i. Weekly paclitaxel + carboplatin or docetaxel + carboplatin could be considered in the neoadjuvant setting for select patients with TNBC (such as those for whom achieving better local control is necessary). Use of these regimens in the adjuvant setting is not recommended.
- b) Preferred to complete standard regimen prior to surgery. If all intended treatment is not completed prior to surgery, the remainder may be given in the adjuvant setting.
- c) Tumor response should be routinely assessed by clinical exam and imaging studies during delivery of preoperative therapy.

- d) ASCO guidelines state that patients with TNBC should be offered an anthracycline and taxane-containing regimen.<sup>108</sup>
  - i. Carboplatin may be offered to patients with TNBC to increase pathologic CR (pCR) especially in patients at high clinical risk (such as LN-positive disease)
  - ii. Consider a taxane-based regimen, such as docetaxel and cyclophosphamide, for lower-risk patients or those with cardiac risk factors
- e) Addition of platinum to anthracycline- and taxane-based neoadjuvant chemotherapy is not supported by data for patients with germline BRCA-mutations.<sup>61</sup>
- f) Pembrolizumab + chemotherapy is recommended for stage II – III patients with TNBC<sup>128, 23</sup>
  - i. Keynote-522 was a phase 3, double-blind trial that randomized patients to either pembro (pembrolizumab) or placebo in the neoadjuvant and adjuvant phase. Patients receiving either pembrolizumab or placebo plus paclitaxel + carboplatin (every 3 weeks or weekly) x 12 weeks followed by 4 cycles of pembrolizumab or placebo + doxorubicin or epirubicin + cyclophosphamide every 3 weeks in the neoadjuvant setting. Patients underwent definitive surgery then received pembrolizumab or placebo every 3 weeks x up to 9 cycles in the adjuvant setting (+/- radiation).
  - ii. Primary endpoints: pathological complete response (pCR) defined as ypT0/Tis ypN0 at the time of definitive surgery (no residual disease in the complete resected breast specimen and all sampled regional LNs) and event free survival (EFS) in the ITT population.
  - iii. At primary analysis of pCR endpoint (n=602), pCR was 64.8% in the pembro group vs. 51.2% in the placebo group (estimated treatment difference = 13.6%; 95% CI, 5.4 – 21.8; p<0.001)
  - iv. 1174 patients were randomized to pembrolizumab (n=784) or placebo (n=390). The estimated EFS at 36 months was 84.5% in the pembro group vs. 76.8% in the placebo group (HR 0.63; 95% CI, 0.48 – 0.82; p=0.001). Benefit consistent across subgroups (menopausal status, nodal status, stage (II and III), LDH level.<sup>129</sup>
  - v. No data to support pembrolizumab in combination with capecitabine or olaparib<sup>128</sup>
- e. Regimens for HER2-positive disease
  - 1) In general, those chemotherapy regimens recommended in the adjuvant setting may also be considered in the neoadjuvant setting and vice versa<sup>23</sup>
    - a) Patients with LN-positive or high-risk LN-negative disease should be offered neoadjuvant therapy with an anthracycline and taxane or non-anthracycline-based regimen in combination with trastuzumab +/- pertuzumab.<sup>108</sup>
  - 2) Patients with HER2-positive disease should receive preoperative systemic therapy incorporating trastuzumab.<sup>23</sup>
  - 3) Patients with HER2-positive early stage or locally advanced breast cancer should receive trastuzumab-based chemotherapy, but concomitant administration of trastuzumab and anthracycline-based chemotherapy is generally not recommended due to increased cardiotoxicity (see cardiotoxicity section for more details).

4) Pertuzumab

- a) Pertuzumab received accelerated approval from the FDA in combination with docetaxel and trastuzumab for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (ESBC) ( $T \geq 2$  cm or LN-positive) based on results from the NeoSphere and TRYPHAENA studies.<sup>130</sup>
- b) In the Neosphere study<sup>131</sup>, 417 women with HER2-positive, locally advanced, inflammatory, or ESBC were randomized to one of four treatment arms. Three arms included neoadjuvant pertuzumab (docetaxel + trastuzumab + pertuzumab [THP], trastuzumab + pertuzumab, or docetaxel + pertuzumab). The fourth arm included neoadjuvant docetaxel + trastuzumab. All arms received FEC (fluorouracil, epirubicin, cyclophosphamide) x 3 cycles after surgery.
  - i. Addition of pertuzumab to trastuzumab and docetaxel resulted in significant improvement in pCR ( $p=0.0141$ )
- c) In the TRYPHAENA study<sup>132</sup>, 225 women with HER2-positive, locally advanced, inflammatory, or ESBC were randomized to one of three treatment arms:
  - i. Arm A: FEC + trastuzumab + pertuzumab q3wks x 3 cycles followed by THP q3wks x 3 cycles prior to surgery
  - ii. Arm B: FEC q3wks x 3 cycles followed by THP q3wks x 3 cycles prior to surgery
  - iii. Arm C: TCH + pertuzumab (TCHP) every 3 weeks x 6 cycles prior to surgery
  - iv. Primary endpoint of the study was safety and tolerability during neoadjuvant treatment
  - v. pCR rates in the breast and axilla were: Arm A 50.7%, Arm B 45.3%, Arm C 51.9%
  - vi. Study did not evaluate superiority of arms but pCR rates were deemed encouraging in all arms. There were low rates of symptomatic left ventricular systolic dysfunction (LVSD).

f. Preoperative endocrine therapy

- 1) Historically, utilized for locally advanced breast tumors in elderly patients, patients with poor performance status or comorbid conditions precluding the use of chemotherapy, or patients who refuse chemotherapy.
- 2) NCCN® includes option of endocrine therapy alone for patients with ER-positive disease based on comorbidities or low-risk luminal biology based on clinical characteristics and/or genomic signatures.<sup>23</sup>
- 3) ASCO recommends that postmenopausal patients with HR-positive, HER2-negative disease can be offered hormone therapy with an aromatase inhibitor to downstage disease.<sup>108</sup>
  - a) Premenopausal patients should not routinely be offered neoadjuvant endocrine therapy
- 4) AI preferred over tamoxifen in postmenopausal women<sup>23</sup>
  - a) Four randomized phase 3 clinical trials comparing an AI to tamoxifen; overall rates of pCR with endocrine therapy 1-3%.<sup>133, 134, 135, 136</sup>
  - b) Randomized phase 2 study (ACOSOG Z1031) compared 4 months of preoperative anastrozole, letrozole, and exemestane ( $n=377$ ).<sup>137</sup>

- i. Eligibility restricted to high ER expression
  - ii. Primary endpoint was clinical response rate
  - iii. Clinical CR+PR= 69% (A), 75% (L), and 63% (E); low rates of grade 3 to 4 toxicity with all agents.
- 5) Optimal duration of neoadjuvant endocrine therapy is not known
  - a) Most studies administered 3-6 months of treatment
- g. Local therapy following primary/preoperative systemic therapy consists of:
  - 1) Total mastectomy + surgical axillary staging ± reconstruction **OR**  
BCS + surgical axillary staging
  - 2) All patients should receive chest wall/breast and supraclavicular radiation to reduce the risk of local recurrence.
  - 3) Patients with involved internal mammary chain LNs should receive radiation to this LN basin.
- h. Nonresponders to primary/preoperative systemic therapy or less than operable tumors
  - 1) Change to non-cross-resistant chemotherapy **OR**  
Radiation to breast and supraclavicular area
  - 2) If no response to non-cross-resistant chemotherapy, then go to radiation
  - 3) Residual disease following preoperative chemotherapy (see section above “Role of additional adjuvant chemotherapy for patients with residual disease following neoadjuvant chemotherapy “)
- i. Inflammatory breast cancer (IBC) (Any T4d) (separate algorithm in NCCN Guidelines®)<sup>23</sup>
  - 1) Distinct clinical entity; rare (1-6% of all breast cancer cases in US); poor prognosis; extremely aggressive; often ER-negative, HER2-positive
  - 2) Some studies with neoadjuvant taxanes included inflammatory breast cancer patients.
  - 3) No standard of care; clinical trials are most appropriate for these patients.
  - 4) Treat as locally advanced disease (see figure for Treatment for Locally Advanced, Non-Inflammatory Breast Cancer), but they are not candidates for BCS and local radiation is more extensive.
  - 5) Chemotherapy regimens are similar to patients with locally advanced disease and trastuzumab +/- pertuzumab should be considered for HER2-positive disease.
- j. Consider use of adjuvant bisphosphonates (zoledronic acid or clodronate) as recommended by ASCO/CCO guidelines for use in postmenopausal women who were deemed candidates for systemic chemotherapy (see previous section under adjuvant therapy)<sup>138</sup>.

**Patient case #6, continued (ARS 5):** Answer C is correct. It is preferred that HF receives a neoadjuvant chemotherapy regimen with or without pertuzumab. Any regimen listed in table “Selected Neoadjuvant/Adjuvant Therapy for HER2-positive Breast Cancer” would be appropriate according to NCCN Guidelines®. Based on the results of the TRYPHAENA study, HF will receive docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) x 6 cycles.

Answer A is incorrect because trastuzumab should not be given concurrently with an anthracycline-containing regimen due to the increased risk for cardiotoxicity.

Answer B is incorrect because docetaxel + trastuzumab + pertuzumab is recommended for metastatic breast cancer not as neoadjuvant therapy.

Answer D is incorrect because HF should receive a neoadjuvant regimen that contains HER2-directed therapy.

After completion of neoadjuvant TCH + pertuzumab x 6 cycles, HF undergoes a lumpectomy. She does not have residual disease at the time of surgery. HF will receive whole breast radiation and adjuvant HER2-targeting therapy. She should also begin endocrine therapy with an AI following the completion of chemotherapy.

**ARS 6: Which of the following is the most appropriate adjuvant HER2-directed regimen for HF?**

- A. Pertuzumab
- B. Ado-trastuzumab emtansine
- C. Trastuzumab + pertuzumab
- D. Neratinib

The correct answer is C. Trastuzumab + pertuzumab. Since HF does not have residual disease following neoadjuvant TCHP, it is most appropriate for her to continue trastuzumab + pertuzumab in the adjuvant setting to complete 1 year of HER2- targeted therapy. NCCN Guidelines® recommend trastuzumab +/- pertuzumab in this setting. HF received trastuzumab + pertuzumab in the neoadjuvant setting so it is reasonable to continue both agents in the adjuvant setting.

Answer A is incorrect because single agent pertuzumab is not recommended. It should be used in combination with trastuzumab.

Answer B is incorrect because adjuvant ado-trastuzumab emtansine is recommended for patients with residual disease at the time of surgery following neoadjuvant treatment based on the results of the KATHERINE trial.

Answer D is incorrect because neratinib is only indicated in the adjuvant setting as extended adjuvant following 1 year of trastuzumab.

**Patient Case #7:** FR is a 37-year-old premenopausal woman with a history of breast cancer. She was originally diagnosed four years ago with stage IIB (T2, N1, M0), ER/PR-positive, HER2-negative invasive ductal carcinoma. She underwent a modified radical mastectomy and adjuvant chemotherapy with dose dense AC followed by weekly paclitaxel. After completing chemotherapy, she initiated tamoxifen with a planned initial duration of 5 years. Now 2 years after starting tamoxifen, she presents to her oncologist with severe back pain x 3 weeks. A bone scan reveals multiple areas of increased uptake in her thoracic and lumbar spine. Biopsy of T3 confirms metastatic breast cancer that is now ER+, PR+, and HER2-positive (IHC 3+). CT of the chest/abdomen was negative for other sites of metastases.

FR has bone-only metastases, her disease is now ER/PR positive, HER2-positive, and she is relatively asymptomatic (pain controlled with OTC analgesics). Given that she experienced disease progression while receiving endocrine therapy and there is a known survival benefit for chemotherapy + HER2-targeted therapy, her oncologist treated her with docetaxel, trastuzumab, and pertuzumab (THP) x 6 cycles with a good response. She is now planned to continue maintenance trastuzumab and pertuzumab and restart endocrine therapy. FR's estradiol and FSH levels are still in the premenopausal range.

**What is the most appropriate endocrine treatment for FR's metastatic disease?**

- A. Continue tamoxifen
- B. Discontinue tamoxifen; start exemestane
- C. Continue tamoxifen; add fulvestrant
- D. Discontinue tamoxifen; start goserelin and anastrozole

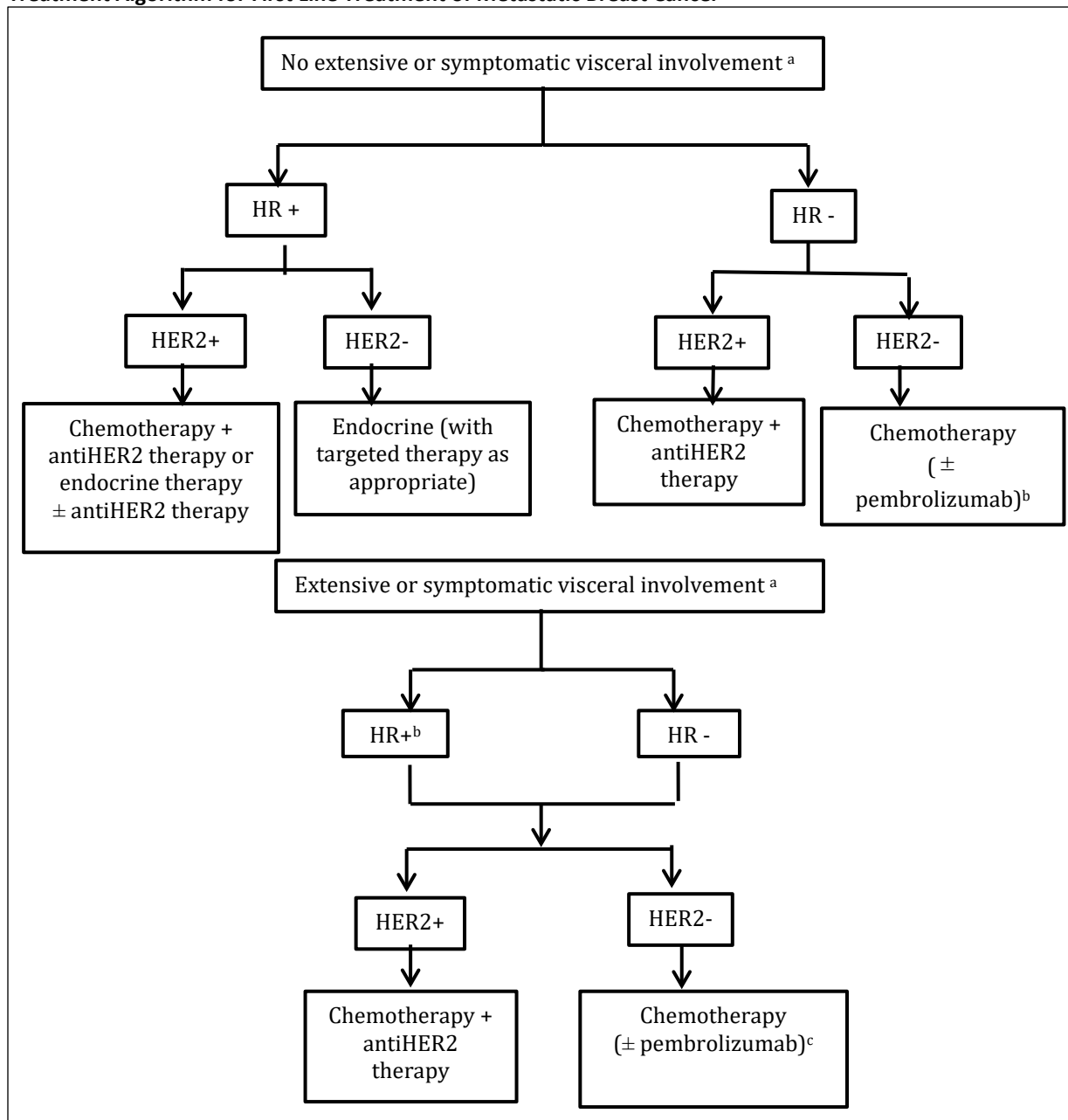
## VI. Treatment of metastatic/recurrent breast cancer<sup>139</sup>

### A. General considerations

1. Goals of therapy: palliation, prolongation of life (if possible) and to maximize quality of life; cure is not likely (< 5% at 10 years); however, in some selected patients, disease may be controlled for many years with good QOL.
2. Bone and soft tissue metastases tend to have a better prognosis and are more likely to respond to endocrine therapy
3. Patients with visceral crisis generally require chemotherapy due to need for rapid response
  - a. Visceral crisis = severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.<sup>140</sup>
4. Brain metastases generally do not respond to the standard chemotherapy regimens given for breast cancer
5. HR receptor-positive breast cancers tend to be more indolent and respond better to endocrine therapy than cancers that are negative for hormone receptors
6. Standard of care is to obtain a biopsy at time of first recurrence of disease to determine ER/PR and HER2 status of metastatic site (consider re-biopsy if progression)
  - a. ER/PR and HER2 status can change with treatment and metastatic progression
  - b. ASCO guidelines recommend using ER, PR, or HER2 status from the metastasis to direct therapy but no strong evidence to guide this recommendation. Recurrent disease should also be biopsied whenever feasible for determination of tumor HR and HER2 status.<sup>141</sup>

7. At time of diagnosis of metastatic disease, all patients should be tested for germline BRCA1/2 mutation (if not previously completed) and PD-L1 CPS score for those with TNBC.<sup>23</sup>
  - a. Additional biomarker testing may be helpful in the second or subsequent lines of treatment (see table below “Additional Targeted Therapies and Associated Biomarker Testing for Recurrent Unresectable or Metastatic Disease” for more details)
8. Tumor markers (CEA, CA 27-29, and CA 15-3) may be used in conjunction with diagnostic imaging, history and physical examination for monitoring patients with metastatic disease during active therapy.<sup>142</sup>

**Treatment Algorithm for First Line Treatment of Metastatic Breast Cancer<sup>23,143</sup>**



HR= hormone receptor (ER/PR)

<sup>a</sup> Consider use of PARP inhibitor for patients with germline *BRCA1/2* mutation

<sup>b</sup> It is acceptable to switch to endocrine-based therapy after disease stabilizes or response is observed

<sup>c</sup> Consider the addition of pembrolizumab for patients with PD-L1 CPS ≥ 10 and TNBC

## B. Endocrine therapy

### 1. General principles

#### a. Targets:

- 1) Inhibit or eliminate the production of estrogen
  - a) Oophorectomy or LHRH agonist (premenopausal women)
  - b) Aromatase inhibitors (postmenopausal women)
- 2) Block the effect of estrogen at the cellular level
  - a) Selective estrogen receptor modulators (SERMs) - pre- and postmenopausal
  - b) Selective estrogen receptor down-regulators (SERDs) - postmenopausal

b. Patients whose tumors express any level of estrogen and/or progesterone receptors should be offered hormone therapy <sup>141</sup>

c. It is generally recommended to continue treatment until disease progression <sup>141</sup>

d. Use of combination chemotherapy and endocrine therapy is not recommended <sup>141</sup>

e. Addition of HER2-targeted therapy to first-line AIs should be offered to patients with HR-positive, HER2-positive MBC who are not considered candidates for chemotherapy <sup>141</sup>

- 1) HER2-targeted therapy in combination with chemotherapy resulted in improvements in OS and is the preferred first-line approach in most cases

f. Situations where chemotherapy may be appropriate as first-line treatment of HR-positive MBC: <sup>141</sup>

- 1) Immediately life-threatening disease
- 2) Extremely low levels of estrogen receptor expression
- 3) HR-positive, HER2 positive MBC where combining chemotherapy with anti-HER2 treatments has a survival advantage

### 2. Agents

#### a. SERMs (pre- and postmenopausal women)

- 1) Tamoxifen - see drug specific details in above section on endocrine therapy in the adjuvant setting
- 2) Toremifene
  - a) No advantage over tamoxifen; less data supporting its use long-term; RR similar in randomized, controlled comparative trials and meta-analyses. <sup>144</sup>

b. AI (anastrozole, letrozole, exemestane) – see drug specific details in above section on endocrine therapy in the adjuvant setting

#### c. Selective Estrogen Receptor Down-regulators (SERDs)

- 1) Fulvestrant



- a) Approved for use in HR-positive, HER2-negative advanced breast cancer in postmenopausal women who have not been previously treated with endocrine therapy and in women with disease progression following endocrine therapy
- b) First-line fulvestrant
  - i. Phase 3 RCT comparing anastrozole to anastrozole plus fulvestrant in postmenopausal women with HR+ MBC (first-line setting)<sup>145</sup>
    - (a) PFS (15 mo vs 13.5 mo, HR=0.80 95% CI 0.68-0.94, p=0.007) was significantly longer for the combination of anastrozole plus fulvestrant than for anastrozole alone.
    - (b) OS was prolonged in the combination-therapy group (49.8 mo vs. 42 mo; HR 0.82; p=0.03).<sup>146</sup>
      - Among women who had received tamoxifen previously, OS was similar in the two groups (median, 48.2 mo vs. 43.5 mo; HR,0.97; p=0.09).
    - (c) Results from the FACT<sup>147</sup> and SoFEA<sup>148</sup> trials of similar study design were negative
    - (d) One limitation of this study was that the fulvestrant 500 mg dosing schedule was not used in this study
  - ii. Fulvestrant 500 mg dose compared with anastrozole as 1<sup>st</sup>-line therapy for postmenopausal, HR-positive locally advanced or MBC in a phase 3, double-blind, RCT (n=524)<sup>149</sup>
    - (a) PFS longer in fulvestrant arm (HR 0.797, 95% CI 0.637 – 0.999, p=0.0486). Median PFS was 16.6 months in fulvestrant group vs. 13.8 months in anastrozole group.
- c) Second-line fulvestrant
  - i. Similar time to progression (TTP), duration of response, and toxicity when compared to exemestane as second-line therapy for metastatic, postmenopausal, hormone-receptor positive breast cancer in women who progressed on a non-steroidal AI.<sup>126</sup>
    - (a) Randomized, double-blind, placebo-controlled phase 3 trial (n=736)
    - (b) PFS (primary endpoint) was improved for patients who received high dose fulvestrant vs standard dosing (6.5 mo vs 5.5 mo, p=0.006). Toxicities were similar between groups.
    - (c) Final OS results with further follow-up show an improvement with high dose fulvestrant (26.4 months vs. 22.3 mo, p=0.02).<sup>150</sup>

## 2) Elacestrant <sup>151</sup>

- a) Mechanism of action: estrogen receptor antagonist that binds to estrogen receptor-alpha (ER $\alpha$ ) resulting in degradation of ER $\alpha$  through proteasomal pathway
- b) Indication: treatment of postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy
- c) Dose: 345 mg PO once daily with food

- d) Toxicities: musculoskeletal pain, nausea, increased cholesterol, increased triglycerides, increased AST/ALT, fatigue, diarrhea, constipation, hot flush, dyspepsia
- e) Drug-drug interactions: avoid use with strong and moderate CYP3A4 inducers and inhibitors
- f) Approval was based on the open-label, phase III EMERALD trial which randomized patients with ER-positive, HER2-negative advanced breast cancer who had 1-2 lines of endocrine therapy to elacestrant 400 mg PO daily (n=239) or standard-of-care endocrine monotherapy (fulvestrant or AI) (n=238) <sup>152</sup>
  - i. All patients were pretreated with a CDK4/6 inhibitor and  $\leq 1$  line of chemotherapy
  - ii. *ESR1*-mutation detected in 47.8% of patients
  - iii. Primary end points were PFS in all patients and patients with detectable *ESR1* mutation. PFS was prolonged in all patients (HR 0.70; 95% CI, 0.55 – 0.88; P=0.002) and patients with *ESR1* mutation (HR 0.55; 95% CI, 0.39 – 0.77; P=0.0005)
  - iv. Any grade nausea occurred in 35% receiving elacestrant and 18.8% receiving SOC (grade 3/4, 2.5% and 0.9%, respectively).
- d. LHRH agonists
  - 1) Leuprolide- Not approved in the US for breast cancer
    - a) Use in premenopausal patients only. Similar to oophorectomy data
  - 2) Goserelin
    - a) Similar efficacy to leuprolide (with more data than with leuprolide). Approved for advanced breast cancer in the U.S.
      - i. Different administration technique; subcutaneous pellet injected.
  - 3) Triptorelin
    - i. Phase 2 trials indicate significant response in HR-positive patients (70%) as first line therapy for metastatic breast cancer.
- e. Additional hormonal agents (mechanism largely unknown and poorly tolerated)
  - 1) Progestins (megestrol acetate and medroxyprogesterone)
  - 2) Estrogens (diethylstilbestrol (DES), ethinyl estradiol)
- 3. Management of advanced breast cancer in males (sex assigned at birth) is similar to that in women; however, it is preferred to concurrently administer LHRH agonist when an AI is used. Available data suggest single-agent fulvestrant has similar efficacy in men as in women. Newer agents (CDK4/6 inhibitors, mTOR inhibitors, and PIK3CA inhibitors) have not been systemically evaluated in clinical trials in men with breast cancer but are considered to be reasonable options. Recommendations for chemotherapy, HER2-targeted therapy, immunotherapy, and PARP inhibitors in men are similar to those in women. <sup>6,23</sup>
- 4. Sequencing of endocrine therapy <sup>141</sup>
  - a. Sequential hormone therapy should be offered to patients with endocrine-responsive disease (except in case of rapid progression with organ dysfunction)
  - b. No specific order of agents is recommended

- c. If a patient responds to an endocrine therapy, it predicts response to another endocrine agent; the number of patients who respond decreases with each subsequent line of therapy.
  - d. NCCN Guidelines® recommend to consider chemotherapy for patients with no clinical benefit after up to 3 sequential endocrine therapy regimens or patients that develop symptomatic visceral disease.<sup>23</sup>
- 5. Combination vs. sequential single agents
  - a. Sequential hormone therapy is preferred for most women with HR-positive MBC except in cases of immediately life-threatening disease or those with rapid visceral recurrence during adjuvant endocrine therapy<sup>141</sup>
  - b. First line treatment with fulvestrant plus a non-steroidal AI may be offered as first-line treatment.<sup>23,141</sup>
    - 1) SWOG 0226 demonstrated that the addition of fulvestrant to anastrozole resulted in prolonged time to progression and OS. Subset analysis suggested that patients without prior adjuvant tamoxifen and > 10 years since diagnosis experienced the greatest benefit.<sup>145,146</sup>
    - 2) Two similarly designed trials (FACT and SoFEA) found no benefit for combination (fulvestrant + anastrozole) compared to single agent AI.<sup>147,148</sup>
  - c. Caveat in ASCO guidelines: Combination of fulvestrant plus a nonsteroidal AI may be offered to patients without prior exposure to adjuvant endocrine therapy based on results of SWOG 0226<sup>145</sup>
- 6. Premenopausal women (see adjuvant endocrine therapy section for definition of menopause)<sup>141</sup>
  - a. ASCO guidelines strongly recommend OAS in combination with treatment options as recommended for postmenopausal women.
    - 1) Tamoxifen or OAS alone can be considered in patients who are naïve to prior hormone therapy
  - b. Premenopausal women who develop metastatic disease while receiving adjuvant tamoxifen or within 12 months of treatment should be treated with OAS + AI.
  - c. Ovarian suppression should be continued during subsequent hormone therapies.
  - d. Estradiol levels performed with a high-sensitivity assay should be monitored in women treated with LHRH agonists and AIs.
    - 1) No data to define optimal level

Systemic Therapy Options for ER+ and/or PR+ Recurrent or Metastatic Breast Cancer<sup>23</sup>

HER2-Negative and Postmenopausal or Premenopausal Receiving OAS	HER2-Positive and Postmenopausal or Premenopausal Receiving OAS <sup>d</sup>
<b>Preferred Regimens: 1<sup>st</sup> Line</b>	AI ± trastuzumab
CDK4/6 inhibitor + AI <sup>a</sup> (ribociclib + AI is category 1)	AI ± lapatinib
CDK4/6 inhibitor + fulvestrant <sup>a</sup> (Fulvestrant + ribociclib or abemaciclib is category 1)	AI ± lapatinib + trastuzumab
<b>Preferred Regimens: 2<sup>nd</sup> and Subsequent Line</b>	Fulvestrant ± trastuzumab
CDK4/6 inhibitor + fulvestrant (if CDK4/6 inhibitor not previously used) (category 1) <sup>a</sup>	Tamoxifen ± trastuzumab
Alpelisib + fulvestrant (for <i>PIK3CA</i> -mutated tumors) (category 1)	
Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen) <sup>a,b</sup>	
<b>Other Recommended Regimens: 1<sup>st</sup> and Subsequent-Line Therapy</b>	
SERD (fulvestrant)	
Fulvestrant + non-steroidal AI (category 1)	
Non-steroidal AI (anastrozole, letrozole)	
Steroidal AI (exemestane)	
Selective ER modulator (tamoxifen)	
<b>Useful in certain circumstances</b>	
Megesterol acetate	
Estradiol	
Abemaciclib <sup>a,c</sup>	

<sup>a</sup> If there is progression while on CDK4/6 inhibitor, there is limited data to support additional line of therapy with another CDK4/6-containing regimen. Same is true for everolimus-containing regimens

<sup>b</sup> Combination of exemestane and everolimus can be considered for patients who have progressed within 12 months or on a non-steroidal AI

<sup>c</sup> Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting

<sup>d</sup> If treatment was initiated with chemo and trastuzumab + pertuzumab, and the chemo was stopped, endocrine therapy may be added to the trastuzumab + pertuzumab

**Patient case #7 (continued):** Correct answer is D. Given that FR's breast cancer recurred while receiving tamoxifen and she is premenopausal, it would be appropriate to discontinue tamoxifen and initiate 2<sup>nd</sup>-line therapy with OAS and endocrine therapy as for postmenopausal women. FR will receive ovarian suppression with goserelin in combination with anastrozole. She should continue to receive endocrine therapies sequentially at time of disease progression unless her disease becomes endocrine-refractory, she progresses through endocrine options, or she develops symptomatic metastatic disease at which time chemotherapy would be indicated.

FR is also prescribed trastuzumab every 3 weeks since her disease now HER2-positive.

Answer A is incorrect because endocrine therapy should be modified since her disease has recurred on tamoxifen.

Answer B is incorrect because she is premenopausal; therefore, she should be treated with an LHRH agonist in addition to an AI.

Answer C is incorrect because the combination of fulvestrant and tamoxifen is not recommended by ASCO or NCCN Guidelines®.

C. NCCN Guidelines® Systemic Therapy Regimens for Recurrent Unresectable or Metastatic: HR-Positive, HER2-Negative with Visceral Crisis or Endocrine Refractory

	Subtype/Biomarker	Regimen
First Line	No germline BRCA1/2 mutation	Systemic chemotherapy
	Germline BRCA1/2 mutation	PARP inhibitor (category 1, preferred) <sup>a</sup>
Second Line	HER2 IHC 1+ or 2+/ISH negative (HER2-low)	Fam-trastuzumab deruxtecan-nxki (category 1, preferred) <sup>b</sup>
	Not HER2-low	Sacituzumab govitecan (category 1, preferred) <sup>c</sup>
		Systemic chemotherapy
Third Line and Beyond	Any	Systemic chemotherapy
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	See targeted therapy options

<sup>a</sup> PARP inhibitor can be considered for a later line of therapy, but evidence suggests it is more effective if used earlier.

<sup>b</sup> Consider in a later line if not used in second line

<sup>c</sup> After prior treatment including endocrine therapy, a CDK4/6 inhibitor, and at least 2 lines of chemotherapy (one of which was a taxane, and at least one of which was in the metastatic setting). May be considered in a later line of therapy if not used in second line

D. NCCN Guidelines® Systemic Therapy Regimens for Recurrent Unresectable or Metastatic: HR-Negative and HER2-Negative (TNBC)

	Subtype/Biomarker	Regimen
First Line	PD-L1 CPS $\geq$ 10 regardless of germline BRCA mutation status	Pembrolizumab + chemotherapy (category 1, preferred) <sup>a</sup>
	PD-L1 CPS < 10 and no germline BRCA1/2 mutation	Systemic chemotherapy
	PD-L1 CPS < 10 and germline BRCA1/2 mutation	PARP inhibitor (category 1, preferred) OR Platinum chemotherapy (category 1, preferred)
Second Line	Germline BRCA1/2 mutation	PARP inhibitor (category 1, preferred)
	Any	Sacituzumab govitecan (category 1, preferred) <sup>b</sup>
		Systemic chemotherapy
	No germline BRCA1/2 mutation and HER2-low	Fam-trastuzumab deruxtecan-nxki (category 1, preferred)
Third Line and Beyond	Any	Systemic chemotherapy
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	See targeted therapy options

<sup>a</sup> Regimen may be considered in the 2<sup>nd</sup> and subsequent lines of therapy if PD-1/PD-L1 inhibitor therapy has not been previously used. If there is disease progression while on a PD-1/PD-L1 inhibitor, there is no data to support an additional line of therapy with another PD-1/PD-L1 inhibitor.

<sup>b</sup> Sacituzumab govitecan-hziy may be used for adult patients with metastatic TNBC who have received at least 2 prior therapies, at least one of which was for metastatic disease. Consider for later line if not used as second line therapy.

E. Chemotherapy

1. Consider first-line chemotherapy for patients with:
  - a. ER/PR negative tumors
  - b. Symptomatic, visceral sites of metastases (visceral crises)
  - c. Faster growing; high ki-67
2. Chemotherapy is continued until progression or unacceptable toxicity. Most patients will be given multiple lines of systemic therapy as palliation. Patients should be continually reassessed for the value of ongoing treatments, risks/benefits of therapy, performance status, and patient preference. <sup>23</sup>
3. Combination vs. sequential single agents
  - a. Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis<sup>20</sup>
  - b. Combination regimens are generally associated with higher response rates compared with single agent chemotherapy.
  - c. Increases in OS have been demonstrated with few regimens; none of which were compared with sequential administration of the same agents.

- 1) Only 1 study prospectively designed to study combination therapy compared to both agents administered sequentially.<sup>153</sup>
  - a)  $A \rightarrow T$  vs  $T \rightarrow A$  vs AT (A = doxorubicin, T = paclitaxel).
  - b) Crossover to other single agent upon progression was part of study design.
  - c) Response rate and TTF (time to treatment failure) were higher with AT vs single agents
  - d) OS and QOL was similar between all groups
- 2) O'Shaughnessy J et al<sup>154</sup>
  - a) Docetaxel vs docetaxel + capecitabine
  - b) Response rates were higher with combination (42% vs 30%,  $p=0.006$ ).
  - c) TTP higher with combination (6.1 v 4.2mo; HR=0.652; 95% CI=0.545-0.78;  $p=0.0001$ ).
  - d) OS higher with combination (14.5 v 11.5mo; HR=0.775; 95% CI=0.634-0.947;  $p=0.0126$ ).
  - e) Did not adequately compare sequential use of these agents to combination.
- 3) Albain K et al.<sup>155</sup>
  - a) Paclitaxel vs paclitaxel + gemcitabine (n=529)
  - b) Response rates were higher with the combination (41.4% vs 26.2%,  $p=0.0002$ ).
  - c) Median TTP = 6.14 mo vs 3.98 mo (HR 0.70; 95% CI=0.59-0.85;  $p=0.0002$ ).
  - d) OS higher with combination (18.6 mo v 15.8 mo; HR=0.82; 95% CI=0.67-1.00;  $p=0.0489$ ).
  - e) Safety: increased toxicity with combination, including anemia (increased RBC transfusions), neutropenia, febrile neutropenia, thrombocytopenia, motor neuropathy, fatigue and elevations in transaminases.
- d. Widely accepted that combination chemotherapy regimens impart greater toxicity
- e. Very complex decision; made on an individual basis. No standard regimen.
4. Treatment Decisions in Metastatic Breast Cancer – Chemotherapy

## Chemotherapy for Metastatic Breast Cancer<sup>23</sup>

<b><u>Preferred</u></b>	<b><u>Other Recommended Regimens</u></b>	<b><u>Combinations: Useful in Certain Circumstances<sup>a</sup></u></b>
Doxorubicin/ liposomal doxorubicin	Epirubicin	AC/EC
Paclitaxel	Docetaxel	CMF
Capecitabine	Cyclophosphamide	Gemcitabine / carboplatin
Vinorelbine	Albumin-bound paclitaxel	Docetaxel / capecitabine
Gemcitabine	Ixabepilone	Gemcitabine / paclitaxel
Eribulin		Carboplatin + paclitaxel or albumin-bound paclitaxel

AC = doxorubicin and cyclophosphamide  
EC = epirubicin and cyclophosphamide  
CMF = cyclophosphamide, methotrexate, and fluorouracil

<sup>a</sup> Sequential single agents preferred but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

### 4. Anthracyclines (doxorubicin, epirubicin, liposomal doxorubicin)

#### a. Liposomal doxorubicin

- 1) Phase 3 trial comparing to conventional doxorubicin.<sup>156</sup>
  - a) MBC patients; no prior chemotherapy for MBC; prior adjuvant anthracyclines were allowed (cumulative doxorubicin equivalents  $\leq 300$  mg/m<sup>2</sup>). Non-inferiority analysis.
  - b) Median PFS and OS were similar between liposomal doxorubicin and conventional doxorubicin.

#### b. Cross-resistance with anthracyclines

- 1) Doxorubicin pretreated patients may respond to liposomal doxorubicin<sup>157</sup>
- 2) Conversions for calculating cumulative doxorubicin dose have not been established for this agent; but it appears to be less cardiotoxic compared with equal bolus doses of conventional doxorubicin (perhaps similar to continuous infusion doxorubicin).<sup>158</sup>

### 5. Taxanes

#### a. Paclitaxel

- 1) Weekly schedules generally preferred (greater efficacy, better toxicity profile, however, also less convenient)
  - a) May take advantage of cell cycle with more frequent smaller doses (80 mg/m<sup>2</sup> over 1 hour weekly without a break is the most commonly used dose)



- b) Side effects differ with weekly administration: less myelosuppression, alopecia (still significant), and myalgias/arthralgias, and peripheral neuropathy is delayed. May see more nail/skin changes and edema with weekly compared with q 3 week.
- b. Docetaxel
  - 1) Q 3 week dose: 60-100 mg/m<sup>2</sup> over 1 hour (FDA-approved dose)
    - a) Dose comparison trial<sup>159</sup>
    - b) 60 vs 75 vs 100 mg/m<sup>2</sup> IV over 1 hour Q 3 weeks
    - c) Increased response rates and TTP with higher doses
    - d) Similar median survival between groups (60=11.3 mo; 75=10.1 mo; 100=14.7 mo; p=NS)
    - e) Dose may be important for patients with symptomatic or bulky disease
    - f) Side effects also significantly increased with higher dose (neutropenia, febrile neutropenia, infection, stomatitis, diarrhea, and neurosensory)
  - 2) Weekly dosing
    - a) 30-35 mg/m<sup>2</sup> weekly most common dose (more toxic compared w/ weekly paclitaxel)
    - b) Compared with Q 3 week<sup>160</sup>
      - i. Q week 35 mg/m<sup>2</sup> (to 40 mg/m<sup>2</sup> if tolerated) vs Q3 week 75 mg/m<sup>2</sup> (to 100 mg/m<sup>2</sup> if tolerated)
      - ii. Increased response rates with Q3 week, but similar PFS and OS
      - iii. Higher overall toxicity rate (grade 3/4 toxicities: 88% vs 56%, p=0.0001) with Q 3 week compared to weekly
  - 3) Incomplete cross-resistance with paclitaxel<sup>161</sup>
    - a) Response rate of 18% in patients progressing while on paclitaxel
    - b) May have to start at a lower dose in patients who are heavily pretreated
- c. Albumin-bound paclitaxel (nab-paclitaxel)
  - 1) Phase 3 clinical trial in MBC:
    - a) Response rates significantly better with albumin-bound paclitaxel every 3 weeks compared to paclitaxel every 3 weeks (33% vs 19%, p<0.001)<sup>162</sup>
    - b) Median TTP 23 weeks vs 16.9 weeks (p=0.006), OS not significantly different
    - c) Safety: more grade 4 neutropenia (but not febrile neutropenia) with paclitaxel (p<0.001); more grade 2 flushing with paclitaxel (p<0.001); more grade 3 sensory neuropathy with nab-paclitaxel (p<0.001).
  - 2) Weekly administration:
    - a) Weekly x 3 doses Q 28 days (days 1, 8, 15)
    - b) MTD in lightly pretreated patients 150 mg/m<sup>2</sup>; DLT neuropathy – sensory (NCCN® recommends max of 125 mg/m<sup>2</sup>)
    - c) MTD in heavily pretreated patients 100 mg/m<sup>2</sup>; DLT neutropenia

- 3) Phase 2 trials in heavily pretreated, taxane-refractory metastatic breast cancer found some benefit.<sup>163</sup>
- 4) Comparative trial – albumin-bound paclitaxel vs. docetaxel randomized phase 2 trial, first-line chemotherapy for MBC.<sup>164</sup>
  - a) Investigator-assessed response: albumin-bound paclitaxel Q week better than Q 3 week and albumin-bound paclitaxel weekly schedule better than docetaxel.
    - i. Docetaxel had significantly more grade 4 neutropenia and grade 3 fatigue but less grade 3 neuropathy
- 5) As with the adjuvant setting, albumin-bound paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (i.e. hypersensitivity reaction).<sup>23</sup>
- d. Consider use of cryotherapy of hands and feet to decrease risk of peripheral neuropathy when receiving taxane therapies.<sup>23</sup>
6. Capecitabine
  - a. Approved as monotherapy for metastatic breast cancer resistant to paclitaxel and an anthracycline and in combination with docetaxel for metastatic breast cancer after failing an anthracycline-containing regimen.
  - b. Dosing:
    - 1) 2,500 mg/m<sup>2</sup>/day PO divided BID x 14 days, then 7 days rest Q 21 days
    - 2) Full dose often not tolerated; starting dose of 2000mg/m<sup>2</sup>/day may be a better starting dose with similar efficacy.<sup>165,166</sup> Another common modification of the regimen is to treat for 7 days on followed by 7 days off.<sup>167</sup>
7. Platinum agents (cisplatin, carboplatin)
  - a. Preferred to taxane therapy for patients with germline *BRCA* mutations<sup>61</sup>
    - 1) The TNT trial was a RCT that compared carboplatin to docetaxel in patients with metastatic TNBC. In subset with a *BRCA1/2* mutation (TNBC n=32, ER-positive n=11), ORR was 68% for carboplatin and 33.3% for docetaxel.<sup>168</sup>
8. Ixabepilone
  - a. FDA-approved indications:
    - 1) Monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane and capecitabine.
    - 2) In combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.
      - a) Of note, the ixabepilone + capecitabine combination regimen has been removed from the NCCN Guidelines®
  - b. Adverse events: neutropenia (grade 3/4 50%); febrile neutropenia (rare); sensory neuropathy (grade 3/4 15-20%); fatigue; myalgias/artralgias; infusion-related hypersensitivity reactions (uncommon with premedications); combination has slightly more neutropenia, but similar capecitabine-related adverse events.
9. Eribulin mesylate

- a. FDA-indicated for the treatment of patients with metastatic breast cancer who have previously received  $\geq 2$  chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and taxane in either the adjuvant or metastatic setting.
  - b. Efficacy data:
    - 1) Phase 3 study - eribulin vs physician's choice single agent therapy<sup>169</sup>
      - a) Open-label, randomized, multicenter trial (n=762)
      - b) Patients had prior anthracycline and/or taxane therapy for adjuvant or metastatic breast cancer
        - i. 1.4 mg/m<sup>2</sup> intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle vs primarily single agent treatment (26% vinorelbine, 19% gemcitabine, 18% capecitabine, 15% taxane, 10% anthracycline, 10% other chemotherapy, 4% endocrine therapy).
      - c) OS (primary endpoint) = 13.1 mo vs 10.6 mo (HR 0.81 95%CI 0.66-0.99, p=0.041)
      - d) Investigator assessed PFS = 3.6 mo vs 2.2 mo (HR=0.76 95%CI 0.64-0.90, p=0.002)
      - e) ORR = 12% vs 5% (p=0.002)
    - 2) Eribulin compared to capecitabine in phase 3 trial of patients with MBC who had received prior anthracycline- and taxane-based therapy. Eribulin was not shown to be superior to capecitabine in regard to OS or PFS<sup>170</sup>
  - c. Adverse events: neutropenia (grade 3/4 57%); febrile neutropenia (5%); sensory neuropathy (grade 3/4 8%); anemia; alopecia; asthenia/fatigue; nausea; constipation; QT prolongation (monitor in patients with CHF, bradyarrhythmias, concomitant drugs that prolong QT interval, and electrolyte abnormalities)
10. Vinorelbine
- a. Not FDA-approved for breast cancer but has demonstrated activity
11. Gemcitabine
- a. Approved in combination with paclitaxel as first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.<sup>155</sup>
  - b. ORR 14-42% as a single agent<sup>171</sup>
12. Also see the ASCO guidelines for Chemotherapy and Targeted Therapy for Women with HER2-negative Advanced Breast Cancer for additional details.<sup>172</sup>
- F. Trop-2-Directed Antibody-Drug Conjugate
1. Sacituzumab govitecan-hziy
    - a. Approved for locally advanced or metastatic TNBC for patients who have received  $\geq 2$  prior systemic therapies, at least 1 of them for metastatic disease. Approval based on IMMU-132-01, a phase 1/2, basket design, open-label, single-group trial that included 108 patients with metastatic TNBC who received  $\geq 2$  previous anticancer therapies for metastatic disease.<sup>173</sup>
      - 1) Patients received a median of 3 previous therapies
      - 2) ORR (primary endpoint) was 33.3% (95% CI, 24.6 to 43.1) (included 3 complete responses and 33 partial responses). Median duration of response = 7.7 months.

- 3) CBR = 45.4%
  - 4) PFS = 5.5 months (95% CI, 4.1 to 6.3) and OS = 13 months (95% CI, 11.2 to 13.7)
- b. A confirmatory trial, ASCENT, randomized 529 patients with advanced TNBC who had received  $\geq 2$  lines of prior therapy in the metastatic setting, to sacituzumab govitecan or physician's choice of chemotherapy (TPC) (eribulin, gemcitabine, vinorelbine, or capecitabine). Primary endpoint was PFS among patients without brain metastases.<sup>174</sup>
- 1) Patients received a median of 4 prior lines of therapy.
  - 2) In the patients without brain metastases (n=468), median PFS as 5.6 months with sacituzumab govitecan (n=235) vs. 1.7 months with TPC (n=233) (HR 0.41; 95% CI, 0.32 – 0.52; P<0.001). PFS also improved in the full population at 4.8 months vs. 1.7 months (HR 0.43; 95% CI, 0.38 – 0.59; P < 0.001).
  - 3) Among patients without brain metastases, median OS was 12.1 months vs. 6.7 months in favor of sacituzumab govitecan. (HR 0.48; P <0.001).
  - 4) Grade  $\geq 3$  adverse effects: neutropenia (51%), leukopenia, diarrhea, anemia, and febrile neutropenia (6%).
- c. Approved for unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer who have received endocrine based therapy and at least 2 additional systemic therapies in the metastatic setting. Approval based on TROPiCS-02, a phase 3 trial that randomized patients with HR-positive, HER2-negative advanced breast cancer to sacituzumab govitecan (n=272) or physician's choice of chemotherapy (TPC) (capecitabine, eribulin, vinorelbine, or gemcitabine) (n=271) until disease progression.<sup>175,176</sup>
- 1) Eligible patients received 2 – 4 prior chemotherapy regimens for metastatic breast cancer or 1 prior therapy for metastatic breast cancer if disease progressed  $\leq 12$  months after (neo)adjuvant therapy. Patients must also have received  $\geq 1$  prior taxane, CDK4/6 inhibitor, and endocrine therapy in any setting.
  - 2) Enrolled patients had received a median of 3 lines of prior chemotherapy in the metastatic setting.
  - 3) Sacituzumab govitecan improved median PFS (5.5 vs. 4 months; HR, 0.66; 95% CI, 0.53-0.83; p=0.0003). Median OS was improved in the sacituzumab govitecan arm (14.4 vs. 11.2 months; HR 0.79; 95% CI, 0.65 – 0.96); p=0.02)
  - 4) 74% of patients in sacituzumab govitecan arm and 60% of patients in TPC experienced grade  $\geq 3$  treatment-emergent AEs [most common were neutropenia (51% vs. 38%), leukopenia (9% vs. 5%), diarrhea (9% vs. 1%)].

#### G. Chemoimmunotherapy

##### 5. Pembrolizumab + chemotherapy

- a. FDA approved the combination of pembrolizumab and chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC who tumors express PD-L1 (CPS  $\geq 10$ ) as determined by an FDA approved test.
- b. Approval based on KEYNOTE-355, a multicenter, double-blind, randomized phase 3 trial in patients with locally recurrent unresectable or metastatic TNBC. Patients were randomized 2:1 to pembrolizumab + chemo (nab-paclitaxel, paclitaxel, or gemcitabine and carboplatin) (n=566) or

placebo + chemo (n=281). Dual primary endpoints were PFS and OS assessed in PD-L1 combined positive score (CPS)  $\geq 10$ , CPS  $\geq 1$ , and ITT populations.<sup>177</sup>

- 1) In patients with CPS  $\geq 10$ , median PFS was statistically significantly prolonged at 9.7 months with pembrolizumab + chemo and 5.6 months with placebo + chemo (HR 0.65; one sided p=0.0012). Median PFS was 7.6 months vs. 5.6 months [HR 0.74; one-sided p=0.0014 (not significant)] in patients with CPS  $\geq 1$  and 7.5 months and 5.6 months (HR 0.82; stats not done due to hierarchical statistical design) in the ITT population
  - 2) At time of final analysis (median follow-up of 44 months), OS in the CPS-1 subgroup was comparable between the pembro and placebo arms (HR 0.86; 95% CI, 0.72 – 1.04; p=0.1125). In the CPS-10 subgroup, median OS was 23 months in the pembro + chemo arm vs. 16.1 months in the placebo + chemo arm (HR 0.73; 95% CI, 0.55 – 0.95; p=0.0185). These results confirmed the benefit of adding pembrolizumab for patients with CPS  $\geq 10$  but not for those with CPS < 10.<sup>178</sup>
  - 3) Adverse events consistent with known safety profile. Grade 3-5 treatment-related AE in 68% in the pembro arm vs. 67% in the placebo arm.
6. Available data is in the first-line setting but these regimens can be used in second or subsequent lines of therapy if immunotherapy has not been previously used.

**Patient case #8 (ARS 12):** GS is a 62-year-old postmenopausal female was diagnosed with stage IIB ER-negative, PR-negative, HER2 positive (IHC 3+) breast cancer 10 years ago and received treatment with lumpectomy, adjuvant chemotherapy with AC x 4 cycles followed by paclitaxel and trastuzumab x 12 weeks. She then received radiation and trastuzumab to complete 1 year of treatment. She presented one year ago with metastatic breast cancer to the bone and lung. A biopsy of her recurrent disease is consistent with the original tumor pathology. She was treated with THP (docetaxel, trastuzumab, pertuzumab) x 6 cycles followed by trastuzumab and pertuzumab maintenance. She now presents with increasing lung metastases after 6 months on maintenance therapy.

**Which of the following regimens is the most appropriate option for GS in the second-line setting?**

- A. Neratinib + capecitabine
- B. Fam-trastuzumab deruxtecan
- C. Trastuzumab + lapatinib
- D. Ado-trastuzumab emtansine

#### H. HER2-Targeted Therapy

1. Overview of treatment options for HER2-positive MBC
  - a. HER2-targeted therapy is recommended for all patients with HER2-positive advanced breast cancer [except for patients with clinical congestive heart failure (CHF) or significantly compromised left ventricular ejection fraction (LVEF)]<sup>179, 23</sup>
    - 1) ASCO and NCCN Guidelines® recommend trastuzumab, pertuzumab and a taxane as the preferred first-line treatment unless patient has a contraindication to taxanes.<sup>179, 23</sup>
      - a) Patients previously treated with chemo + trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both

trastuzumab + pertuzumab in combination with or without cytotoxic chemo (such as vinorelbine or taxane). Further research is needed to determine the ideal sequence for anti-HER2 therapy.<sup>23</sup>

- b) Maintenance trastuzumab/pertuzumab may be administered after response (with concurrent endocrine therapy if ER-positive and HER2-positive metastatic breast cancer).<sup>23</sup>

**NCCN Guidelines® Systemic Therapy Regimens for Recurrent Unresectable or Metastatic: HER2-Positive<sup>23</sup>**

Regimen	Notes
<b>First Line</b>	
Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel)	Preferred regimen Category 1 for docetaxel
<b>Second Line</b>	
Fam-trastuzumab deruxtecan-nxki (T-Dxd)	Preferred regimen Category 1 May be considered in 1 <sup>st</sup> line setting as an option for select patients [ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy (12 months for pertuzumab-containing regimens)] Regular monitoring for ILD/pneumonitis is recommended. No data for using in patients with a history of ILD/pneumonitis.
<b>Third Line</b>	
Tucatinib + trastuzumab + capecitabine	Category 1, preferred in patients with both systemic and CNS progression in the 3 <sup>rd</sup> line setting and beyond (it may be given in the 2 <sup>nd</sup> line setting)
Ado-trastuzumab emtansine (T-DM1)	Consider in second line setting if patient is not a candidate for T-Dxd
<b>Fourth Line and Beyond (Optimal Sequence is Unknown)</b>	
Trastuzumab + docetaxel or vinorelbine	No meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Optimal sequence or true benefit of therapy is not known.  Trastuzumab may be safely given in combination with all non-anthracycline-containing preferred and other single agents.
Trastuzumab + paclitaxel +/- carboplatin	
Capecitabine + trastuzumab or lapatinib	
Trastuzumab + lapatinib	
Trastuzumab + other agents	
Neratinib + capecitabine	
Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)	

<sup>b</sup> Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents as recommended by NCCN Guidelines®

### Select Regimens for HER2-Positive Metastatic Breast Cancer<sup>23</sup>

	Dose	Schedule	Frequency
<b>1<sup>st</sup> Line Regimens</b>			
Pertuzumab	840 mg loading dose followed by 420 mg IV	D 1	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D 1	Q 21 days
Docetaxel	75 – 100 mg/m <sup>2</sup> IV	D 1	Q 21 days
Pertuzumab	840 mg loading dose followed by 420 mg IV	D 1	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D 1	Q 21 days
Paclitaxel	80 mg/m <sup>2</sup> IV OR 175 mg/m <sup>2</sup> IV	D 1, 8, 15 D1	Q 21 days
<b>Other Regimens</b>			
Ado-trastuzumab emtansine	3.6 mg/kg IV	D 1	Q 21 days
Fam-trastuzumab deruxtecan-nxki	5.4 mg/kg IV	D 1	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D 1	Q 21 days
Paclitaxel	175 mg/m <sup>2</sup> <sup>a</sup>	D 1	Q 21 days
+/- Carboplatin	AUC 6 IV <sup>a</sup>	D 1	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D 1	Q 21 days
Docetaxel	80 – 100 mg/m <sup>2</sup> IV	D 1	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D1	Q 21 days
Vinorelbine	25 mg/m <sup>2</sup> IV	D 1, 8, 15	Q 21 days
	20 – 35 mg/m <sup>2</sup> IV	D 1, 8	Q 21 days
	25 – 35 mg/m <sup>2</sup> IV	D 1, 8, 15	Q 28 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D 1	Q 21 days
Capecitabine	1000 – 1250 mg/m <sup>2</sup> PO BID	D 1 – 14	Q 21 days
Lapatinib	1250 mg PO daily	D 1 – 21	Q 21 days
Capecitabine	1000 mg/m <sup>2</sup> PO BID	D 1 – 14	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D 1	Q 21 days
Capecitabine	1000 – 1250 mg/m <sup>2</sup> PO BID	D 1 – 14	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV <sup>a</sup>	D 1	Q 21 days
Lapatinib	1000 mg PO daily	D 1 – 21	Q 21 days
Neratinib <sup>b</sup>	240 mg PO daily	D 1 – 21	Q 21 days
Capecitabine	750 mg/m <sup>2</sup> PO BID	D 1 – 14	Q 21 days
Tucatinib	300 mg PO BID	D 1 – 21	Q 21 days
Trastuzumab	8 mg/kg loading dose followed by 6 mg/kg IV	D1	Q 21 days
Capecitabine	1000 mg/m <sup>2</sup> PO BID	D 1 – 14	Q 21 days
Margetuximab-cmkb	15 mg/kg IV	D 1	Q 21 days
Capecitabine	1000 mg/m <sup>2</sup> PO BID	D 1 – 14	Q 21 days
Margetuximab-cmkb	15 mg/kg IV	D 1	Q 21 days
Gemcitabine	1000 mg/m <sup>2</sup> IV	D 1, 8	Q 21 days

<sup>a</sup> Can also be administered weekly at an alternate dose

<sup>b</sup> Option for dose escalation: 120 mg PO daily days 1 – 7 followed by 160 mg PO daily days 8 – 14 followed by 240 mg PO daily

- 2) Duration of therapy
  - a) ASCO guidelines state that the optimal duration of chemotherapy is at least 4-6 months or until maximum response, progression, or unacceptable toxicities. HER2-targeted therapy can continue until progression or unacceptable toxicities.<sup>180</sup>
  - b) NCCN Guidelines® state to continue treatment until progression or unacceptable toxicity.<sup>23</sup>
- 3) If ER and/or PR-positive and HER2-positive, ASCO guidelines<sup>179</sup> recommend either:
  - a) HER2-targeted therapy plus chemotherapy (strong recommendation)
  - b) Endocrine therapy plus trastuzumab or lapatinib (in selected cases)
  - c) Endocrine therapy alone (in selected cases)
  - d) Abemaciclib + trastuzumab + fulvestrant (after 2 lines of previous treatment)
- 4) If patient has started a HER2-targeted therapy and chemotherapy combination, clinicians may add endocrine therapy to HER2-targeted therapy when chemotherapy ends and/or at time of progression.<sup>179, 23</sup>
- 5) Most patients with HR+ disease should still receive chemotherapy + HER2-targeted therapy. In special circumstances, such as low disease burden, presence of comorbidities (such as CHF), and/or presence of a long disease-free interval, clinicians may offer first-line endocrine therapy alone.<sup>179</sup>
- b. ASCO guidelines recommend T-DXd for second-line treatment if not previously received.<sup>179</sup>
  - 1) May consider tucatinib + trastuzumab + capecitabine for those with progressive brain metastases
- c. ASCO guidelines recommend the following for third-line treatment and greater (who previously received pertuzumab and T-DXd) (insufficient evidence to recommend one regimen over another):
  - 1) Strong recommendation: T-DM1, tucatinib + trastuzumab + capecitabine, T-DXd (if not previously received)
  - 2) Weak recommendation: neratinib + capecitabine, lapatinib + trastuzumab, lapatinib + capecitabine, chemotherapy + trastuzumab, margetuximab + chemotherapy, endocrine options if HR+ (as listed above)
    - a) Presence of CD16A-158F allele may predict benefit of margetuximab over trastuzumab
- d. If patient finished trastuzumab-based adjuvant treatment ≤ 12 months before recurrence, clinicians should follow second line HER2-targeted therapy recommendations. If recurrence is > 12 months after completion of trastuzumab-based adjuvant treatment, clinicians should follow first-line treatment recommendations.<sup>179</sup>
2. Trastuzumab (Herceptin® or biosimilar)
  - a. Activity in HER2-positive MBC as single agent or in combination with chemotherapy.
  - b. Studied in combination with a variety of chemotherapeutic agents: docetaxel, vinorelbine, capecitabine, paclitaxel<sup>181, 182, 183, 184</sup>



- c. May be safely combined with all non-anthracycline regimens and single agents that are recommended for recurrent or metastatic breast cancer.<sup>23</sup>
  - d. Phase 3 trials of endocrine therapy + trastuzumab
    - 1) Anastrozole vs. anastrozole + trastuzumab<sup>185</sup>
      - a) Improved PFS, CBR, and TTP with addition of trastuzumab
        - i. 70% of patients receiving anastrozole alone crossed over to combination upon progression; therefore, OS was numerically higher with trastuzumab (23.9 mo vs 28.5 months), but did not reach statistical significance (p=0.325).
    - 2) Letrozole vs letrozole + trastuzumab in patients with ER-positive, HER2-positive MBC (n=57) showed a numerically improved TTP in patients who received trastuzumab (3.3 mo vs 14.1 mo, HR 0.67, p=0.23); OS was not different.<sup>186</sup>
  - e. Patient selection: IHC 3+ or FISH positive - significant predictors for response to trastuzumab. IHC 0-1+ or FISH negative - no indication for trastuzumab; IHC 2+ must be confirmed by FISH. See previous section on HER2 testing guidelines.
  - f. Re-load if patient has missed a dose of trastuzumab by more than 1 week from their normal dosing schedule
3. Pertuzumab (Perjeta<sup>®</sup>)
- a. Initial FDA approval based on a phase 3 RCT, CLEOPATRA, which evaluated pertuzumab or placebo in combination with docetaxel and trastuzumab as 1st-line therapy for MBC (n=808).<sup>187</sup>
    - 1) Addition of pertuzumab to docetaxel and trastuzumab improved PFS compared to placebo group (18.5 mo vs 12.4 mo; HR 0.68 (0.58-0.80 p<0.001)
    - 2) Median OS was 56.5 months vs. 40.8 months in favor of the pertuzumab group (HR 0.68; 95% CI, 0.56-0.84; P<0.0001).<sup>188</sup>
    - 3) 8-year OS was 37% in pertuzumab group and 23% in the placebo group.<sup>189</sup>
    - 4) Patients in the pertuzumab arm had more diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin
  - b. NCCN<sup>®</sup> recommends the combination of trastuzumab plus pertuzumab in combination with a taxane as a preferred 1<sup>st</sup>-line option for HER2-positive MBC (category 1 for combination with docetaxel and category 2A in combination with paclitaxel).<sup>23,180</sup>
  - c. Paclitaxel once weekly in combination with trastuzumab and pertuzumab is efficacious and well-tolerated<sup>190</sup>
  - d. Two phase 2 trials have also evaluated pertuzumab in combination with trastuzumab after prior progression on trastuzumab-based therapy.
    - 1) ORR 24%, 26% SD, CBR 50%, PFS 5.5 months<sup>191</sup>
    - 2) ORR 18%, 27% SD, CBR 45%, PFS 6 weeks<sup>192</sup>
  - e. Pertuzumab should be discontinued if trastuzumab treatment is discontinued
  - f. Cardiotoxic (see detailed information in cardiotoxicity section)
  - g. Recommended to reload with 840 mg if the patient has not received a dose of pertuzumab for 6 weeks or longer.<sup>130</sup>

4. Margetuximab-cmkb (Margenza®) <sup>193</sup>

- a. HER2/neu receptor antagonist that binds to the extracellular domain of HER2 and inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain, and mediates antibody-dependent cellular cytotoxicity (ADCC).
  - 1) Designed to increase affinity to the CD16A-158F allele compared to trastuzumab
- b. Indication: in combination with chemotherapy for the treatment of adult patients with metastatic HER2-positive breast cancer who have received  $\geq 2$  prior anti-HER2 regimens, at least 1 of which was for metastatic disease
- c. SOPHIA trial was a randomized, open-label phase 3 trial comparing margetuximab-cmkb plus chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) (n=266) to trastuzumab plus chemotherapy (n=270) in patients with HER2-positive metastatic breast cancer who had disease progression on  $\geq 2$  prior HER2-targeted therapies and 1 – 3 lines of therapy for metastatic disease. All patients had previously received trastuzumab and most patients had received pertuzumab and ado-trastuzumab emtansine. Sequential primary end points were PFS and OS.  
<sup>194</sup>
  - 1) Median PFS favored margetuximab plus chemo (5.8 months vs. 4.9 months; HR 0.76; 95% CI 0.59-0.98; P=0.03)
  - 2) PFS benefit was more pronounced in patients with CD16A genotypes containing a 158F allele (median PFS 6.9 vs. 5.1 mo, HR 0.68; 95% CI 0.52-0.90; P=0.005)
  - 3) Median OS was 21.6 months with margetuximab vs. 19.8 months with trastuzumab (HR, 0.89; 95% CI, 0.69 – 1.13; P=0.33).

**Patient case #8, continued (ARS 12):** Correct answer is B. Fam-trastuzumab deruxtecan is the preferred second-line treatment approach by NCCN Guidelines® and ASCO guidelines for patients with metastatic HER2-positive breast cancer following first-line treatment with THP. This recommendation is based on the DESTINY-Breast03 trial which found a PFS and OS benefit with second-line fam-trastuzumab deruxtecan compared to the historical standard of ado-trastuzumab emtansine.

Answers A and C are incorrect because both of these regimens (neratinib + capecitabine and trastuzumab+ lapatinib) are only recommended in the third-line setting and beyond.

Answer D is incorrect because fam-trastuzumab deruxtecan is preferred over ado-trastuzumab emtansine in the second-line setting based on the DESTINY-Breast03 trial.

5. Ado-trastuzumab emtansine (Kadcyla®) (T-DM1)

- a. FDA approval based on a Phase 3 RCT, EMILIA, which compared T-DM1 to the combination of capecitabine and lapatinib for MBC in patients who failed trastuzumab and a taxane.<sup>195</sup>
  - 1) T-DM1 significantly improved PFS (9.6 mo vs 6.4 mo, HR 0.65, 95% CI 0.55-0.77) and OS (30.9 mo vs 25.1 mo, HR 0.68, 95% CI 0.55-0.85) compared to capecitabine and lapatinib.
  - 2) Patients in the capecitabine/lapatinib arm had more diarrhea, hand-foot syndrome, nausea, vomiting, and neutropenia; patients in the T-DM1 arm had more peripheral neuropathy, fatigue, anemia, elevated AST/ALT, and thrombocytopenia.
- b. NCCN Guidelines® recommends as an option for HER2-positive MBC.<sup>23</sup>

- c. T-DM1 has also been evaluated as monotherapy vs physician's choice therapy<sup>196</sup>
  - 1) Open-label, randomized, multicenter trial (n=602)
  - 2) Patients had progressed on 2 or more anti-HER2 therapies, including trastuzumab and lapatinib for MBC and prior taxane in any setting.
    - a) Physician's choice included: trastuzumab + chemotherapy (68%), trastuzumab + lapatinib (10%), trastuzumab + endocrine therapy (2%), lapatinib + chemotherapy (3%), single agent chemotherapy (17%).
      - i. PFS = 6.2 mo vs 3.3 mo (HR=0.53 95%CI 0.42-0.66, p<0.0001)
  - d. Cardiotoxic (see detailed information in cardiotoxicity section)
- 6. Fam-trastuzumab deruxtecan-nxki (T-Dxd)
  - a. FDA indication: unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting
  - b. Approval based on a two-part, open-label, single-group, phase 2 DESTINY-Breast01 trial in 184 patients with HER2+ metastatic breast cancer who had received previous treatment with trastuzumab emtansine. Primary endpoint was the ORR.<sup>197,198</sup>
    - 1) Patients had received a median of 6 previous treatments
    - 2) At 20.5 months of follow-up, ORR = 61.4%. Median duration of response was 20.8 months and a median PFS of 19.4 months.
    - 3) Most common AEs grade 3-5 were decreased neutrophil count, anemia, nausea.
    - 4) 15.2% of patients developed ILD [the majority of cases were grade 1 – 2 although there were 5 fatalities (2.7%) attributed to ILD].
  - c. DESTINY-Breast03 was a phase 3 open-label, randomized trial comparing the efficacy and safety of ado-trastuzumab emtansine and fam-trastuzumab deruxtecan-nxki in 524 patients with HER2+ metastatic breast cancer previously treated with trastuzumab and taxane. Primary endpoint was PFS.<sup>199, 200</sup>
    - 1) Median PFS not reached for fam-trastuzumab deruxtecan-nxki vs. 6.8 months for ado-trastuzumab emtansine (HR 0.28; P= <0.001). Benefit for fam-trastuzumab deruxtecan-nxki seen across all subgroups.
    - 2) 12-month OS improved with fam-trastuzumab deruxtecan (94.1% vs. 85.9%; HR 0.55; p=0.007 which did not cross pre-specified boundary for significance)
    - 3) Updated results confirm the superiority of fam-trastuzumab deruxtecan for PFS and OS. Median PFS was 28.8 months with fam-trastuzumab deruxtecan vs. 6.8 months for ado-trastuzumab emtansine (HR 0.33; p < 0.0001). 24-month OS rate was improved in the fam-trastuzumab deruxtecan arm (77.4% vs. 69.9%; HR 0.64: p=0.0037).
    - 4) Standard of care in the 2<sup>nd</sup> line setting following trastuzumab + taxane in the 1<sup>st</sup>-line
    - 5) Drug-related ILD occurred in 15% of patients receiving fam-trastuzumab deruxtecan-nxki (most grade 1/2; no grade 4/5) vs. 3% with ado-trastuzumab emtansine (all grade 1/2).
  - d. Use in HER2-Low

- 1) FDA approved for unresectable or metastatic HER2-low (IHC 1+ or 2+ and ISH negative) breast cancer who received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
  - 2) NCCN® guidelines and ASCO guidelines recommend for patients with tumors that are HER2-low (who have received at least 1 prior line of chemotherapy for metastatic disease and, if tumor is HR+, are refractory to endocrine therapy<sup>23,201</sup>
- e. DESTINY-Breast04 trial was a phase 3 trial that randomized patients with metastatic breast cancer and HER2-low expression (defined as a IHC score of 1+ or an IHC score of 2+ and negative results of ISH) in a 2:1 ratio to trastuzumab deruxtecan or physician's choice of chemotherapy. Primary endpoint was PFS in HR-positive cohort (n=494) and among all patients (n=557).<sup>9</sup>
- 1) In HR-positive cohort, median PFS was 10.1 months in trastuzumab deruxtecan group and 5.4 months in physician's choice group (HR, 0.51; P<0.001). OS was 23.9 months vs. 17.5 months respectively (HR, 0.64; P=0.003).
  - 2) Among all patients, median PFS was 9.9 months in trastuzumab deruxtecan group and 5.1 months in physician's choice group (HR, 0.50; P<0.001). OS was 23.4 months and 16.8 months respectively (HR, 0.64; P=0.001).
  - 3) Grade ≥ 3 AE occurred in 52.6% within trastuzumab deruxtecan group and 67.4% within the physician's choice of chemotherapy group. Drug-related ILD or pneumonitis occurred in 12.1% of patients receiving trastuzumab deruxtecan (0.8% had fatal events).
7. Tucatinib
- a. Approval based on HER2CLIMB, a double-blind, phase 3 trial that randomized patients to capecitabine and trastuzumab plus either tucatinib (N=410) or placebo (N=202). Patients had HER2-positive metastatic breast cancer that was previously treated with trastuzumab, pertuzumab, and ado-trastuzumab emtansine and an ECOG of 0 or 1. Brain metastases were present in 47.5% of patients (40.2% treated, stable brain mets, 37.1% with treated, progressing brain mets, and 22.7% with untreated brain mets).<sup>202,203</sup>
- 1) Primary endpoint was PFS among the first 480 randomized patients. PFS at 1 year was 33.1% in the tucatinib-combo group and 12.3% in the placebo-combo group (HR, 0.54; 95% CI, 0.42 to 0.71; P< 0.001). Median duration of PFS was 7.8 months and 5.6 months, respectively.
  - 2) OS at 2 years was 44.9% in the tucatinib-combo group and 26.6% in the placebo-combo group (HR, 0.66; 95% CI, 0.50 to 0.88; P=0.005) and median OS was 21.9 months and 17.4 months, respectively.
  - 3) In the sub-group of patients with brain metastases, PFS at 1 year was 24.9% in the tucatinib-combo group and 0% in the placebo-combo group (HR, 0.48; 95% CI, 0.34 to 0.69; P<0.001), and the median PFS was 7.6 months and 5.4 months, respectively. At 29.6 months of follow-up, median OS was 9.1 months longer in the tucatinib arm (21.6 vs. 12.5 months). Risk of developing new brain lesions as the site of first progression or death was reduced by 45.1% (HR 0.55; 95% CI, 0.36 – 0.85).
  - 4) Common adverse events in the tucatinib group included diarrhea, palmar-plantar erythrodysesthesia, nausea/vomiting, and fatigue. Grade 3 diarrhea and elevated AST/ALT levels were more common in the tucatinib-combo group compared to placebo.
8. Neratinib + capecitabine

- a. NALA is a randomized, open-label, phase 3 trial of neratinib 240 mg PO daily with food plus capecitabine 750 mg/m<sup>2</sup> PO BID (N=307) vs. lapatinib 1,250 mg PO daily plus capecitabine 1,000 mg/m<sup>2</sup> PO BID (N=314) until progression in patients with heavily pretreated HER2-positive metastatic breast cancer. Approximately 16% of patients in each arm had brain metastases.<sup>204</sup>
  - 1) Received  $\geq 2$  prior HER2-directed regimens for metastatic disease
  - 2) Co-primary endpoints were PFS and OS by central review
  - 3) Mean PFS was 8.8 months vs. 6.6 months in favor of the neratinib group (HR 0.76; 95% CI 0.63-0.93; P=0.0059)
  - 4) Mean OS was 24 months vs. 22.2 months in favor of the neratinib group numerically, yet not statistically significant (HR 0.88; 95% CI 0.72-1.07; P=0.2086)
  - 5) Time to intervention for symptomatic CNS disease was delayed in the neratinib group (overall cumulative incidence of intervention 22.8% vs. 29.2%; p=0.043)
  - 6) Among patients with CNS metastases at baseline, outcomes were improved with neratinib + capecitabine (median PFS 7.8 mo. vs. 5.5 mo.; HR 0.66; P=0.0741 and median OS 16.4 mo. vs. 15.4 mo.; HR 0.90; P=0.6352).<sup>205</sup>
9. Lapatinib
  - a. May also cross the blood-brain barrier, although results in patients with brain metastases have been disappointing.<sup>206</sup>
  - b. Daily oral medication (with or without food)
    - 1) Lapatinib 1,250 mg PO daily (no break in therapy) in combination with capecitabine 2,000 mg/m<sup>2</sup>/day PO divided BID x 14 days every 21 days.
    - 2) In combination with trastuzumab: 1,000 mg PO daily
    - 3) In combination with letrozole: 1,500 mg PO daily
  - c. Combination trial (lap + cape vs cape alone)<sup>207</sup>
    - 1) Studied in patients previously treated with an anthracycline, taxane and trastuzumab.
    - 2) Median TTP and RR was superior with combination. No difference in OS.
  - d. Other efficacy information
    - 1) Single agent efficacy modest with RR = 24% for first line treatment and 8% for trastuzumab-pretreated patients.
    - 2) Longer PFS (8.2 mo vs 3 mo, HR = 0.71, p=0.019) in ER-positive, HER2-positive patients (n=219) that received letrozole + lapatinib compared to letrozole alone.<sup>208</sup>
    - 3) Longer PFS (11.1 weeks vs 8.1 weeks, HR 0.74, p=0.011) and OS (14 mo. vs 9.5 mo, HR 0.74, p=0.026) in HER2-positive patients that received trastuzumab + lapatinib compared to lapatinib alone.<sup>209</sup>
    - 4) Did not improve PFS or OS when added to fulvestrant in patients with ER-positive MBC (regardless of HER2 status) and increased toxicity.<sup>210</sup>
10. Recommendations on management of patients with advanced HER2-positive breast cancer and brain metastases<sup>211</sup>
  - a. Treatment typically consists of appropriate local therapy and systemic therapy.

- b. Local therapies include surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS).
  - 1) Most patients who undergo surgical resection should receive postoperative radiotherapy
    - a) Memantine should be given concurrently and x 6 months following WBRT to delay time to cognitive decline.
- c. Treatment depends on patient prognosis, presence of symptoms, resectability, number and size of metastases, prior therapy, and whether metastases are diffuse.
- d. Tucatinib + trastuzumab + capecitabine may be offered to patients with HER2-positive metastatic breast cancer who have brain metastases without symptomatic mass effect and whose disease has progressed on at least one previous HER2-directed therapy for metastatic disease. If these agents are used, local therapy may be delayed until evidence of intracranial progression.
- e. For patients whose systemic disease is not progressive at time of brain metastasis diagnosis, systemic therapy should not be switched. For patients with progressive systemic disease, clinicians should offer targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer<sup>212</sup>
- f. Routine MRI to screen for brain metastases is not recommended but clinicians should have a low threshold for MRI of the brain because of the high incidence of brain metastases among patients with HER2-positive advanced disease.

**Patient case # 9 (ARS 9):** DS is a 45-year-old premenopausal female who presents with a 2.5 cm right breast mass detected on routine screening mammogram. Biopsy reveals invasive ductal carcinoma, ER 60%, PR 0%, HER2 2+ IHC and negative ISH. During her workup, she admits to back pain x 2 months. Bone scan confirms metastatic breast cancer in her spine and pelvis. Additional biomarker testing reveals a *PIK3CA* mutation.

**What first-line treatment is most appropriate for DS?**

- A. Alpelisib + anastrozole
- B. Alpelisib + anastrozole + goserelin
- C. Abemaciclib + letrozole
- D. Abemaciclib + letrozole + goserelin

**I. Other Targeted Therapies**

- 1. CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib)
  - a. Primary use in patients with HR+, HER2- advanced or metastatic breast cancer
  - b. Choice of CDK4/6 inhibitor is controversial; however, NCCN Guidelines® lists AI + ribociclib, fulvestrant + ribociclib, and fulvestrant + abemaciclib as category 1 recommendations. This is based on OS benefit with these combinations in their respective clinical trials (see details below).<sup>23</sup>
    - 1) ASCO and NCCN Guidelines® state that any AI could be substituted in the front-line setting depending on individual tolerance although no data exists at present.<sup>23,141</sup>
  - c. NCCN Guidelines® recommend fulvestrant + any of the CDK4/6 inhibitors as preferred 2<sup>nd</sup> – and subsequent-line therapy (for patients that have not previously received a CDK4/6 inhibitor).<sup>23</sup>

d. Palbociclib (Ibrance®)<sup>213</sup>

- 1) PALOMA-2 was a double-blind, placebo-controlled, phase 3 study that randomized, in a 2:1 ratio, 666 postmenopausal women with ER+, HER2-, advanced breast cancer to palbociclib + letrozole or placebo + letrozole.<sup>214</sup>
  - a) The primary endpoint of median PFS was 24.8 months for palbociclib-letrozole vs. 14.5 months for placebo-letrozole (HR 0.58, 95% CI 0.46 – 0.72; p<0.001)
  - b) Most common grade 3 – 4 adverse events were neutropenia (66.4% in palbociclib-letrozole arm vs. 1.4% in placebo-letrozole arm), leukopenia (24.8% vs. 0%), anemia, and fatigue. Febrile neutropenia was reported in 1.8% of patients in palbociclib-letrozole arm.
  - c) Median OS was not significantly different with a median follow-up of 90 months (53.9 months in the palbociclib-letrozole arm vs. 51.2 months in the placebo-letrozole arm; HR, 0.956; p=0.3378).<sup>215</sup>
- 2) PALOMA-3 was a double-blind, placebo-controlled, phase 3 study that randomized 521 patients to palbociclib alone or in combination with fulvestrant in premenopausal and postmenopausal women with advanced breast cancer that progressed during prior endocrine therapy.<sup>216,217</sup> Premenopausal women also received goserelin.
  - a) PFS was 9.5 months for palbociclib + fulvestrant vs. 4.6 months for fulvestrant alone (HR 0.46; 95% CI, 0.36-0.59; p<0.0001)
  - b) Median OS was longer in the palbociclib + fulvestrant arm vs. placebo + fulvestrant arm (34.9 months vs. 28 months respectively; HR 0.81; 95% CI, 0.64 to 1.03; p=0.09).
  - c) At 6-year follow-up, OS benefit was maintained (median OS 34.8 months vs. 28 months; HR 0.81; 95% 0.65 to 0.99; p=0.0221)<sup>218</sup>

e. Ribociclib (Kisqali®)<sup>219</sup>

- 1) MONALEESA-2 was a phase 3, double-blind trial that randomized 668 postmenopausal women with HR-positive, HER2-negative; recurrent or metastatic breast cancer that had not received previous therapy for advanced disease to ribociclib and letrozole or placebo and letrozole.<sup>220</sup>
  - a) 58.8% patients had visceral disease
  - b) Primary endpoint of PFS was not reached in the ribociclib group vs. 14.7 months in placebo group (HR 0.56; 95% CI 0.43-0.72; P = 3.29 x 10<sup>-6</sup> for superiority) at pre-planned interim analysis. At the time of the second interim analysis (median follow-up of 26.4 months) PFS was 25.3 months in ribociclib group (95% CI, 23.0 to 30.3) vs. 16 months in placebo group (95% CI, 13.4 to 18.2) (HR 0.568; CI 0.457-0.704; P=9.63 x 10<sup>-8</sup>).<sup>221</sup>
  - c) At median follow-up of 6.6 years, median OS was significantly longer in the ribociclib arm (63.9 months vs. 51.4 months; HR 0.76; 95% CI 0.63-0.93; p=0.008).<sup>222</sup>
  - d) Incidence of neutropenia was greater in the ribociclib group (76.9% vs. 5.8%). There was 62% grade 3 or 4 neutropenia in the ribociclib group. Incidence of all-grade LFT abnormality was 20.1% in the ribociclib group (10.2% grade 3 or 4).<sup>221</sup>
- 2) MONALEESA-3 was a phase 3, double-blind study that evaluated ribociclib plus fulvestrant or placebo plus fulvestrant in postmenopausal patients with HR-positive, HER2-negative

advanced breast cancer (n=726) who were either treatment naïve or had received up to 1 line of prior endocrine therapy in the advanced setting.<sup>223,224</sup>

- a) Median PFS was significantly improved with ribociclib plus fulvestrant (20.5 months) vs. placebo plus fulvestrant (12.8 months) (HR 0.593; 95% CI 0.48-0.732; P<.001).
- b) Significant OS benefit for ribociclib plus fulvestrant. Median OS at 42 months was not reached for ribociclib + fulvestrant compared to 40 months for fulvestrant + placebo (HR, 0.72; 95% CI, 0.57 to 0.92; P=0.00455). Benefit was consistent across most subgroups.
- c) Grade 3-4 neutropenia 57.1% in ribociclib-containing arm vs. 0.8% in placebo plus fulvestrant arm.
- d) At 56.3 months of follow-up, OS benefit for ribociclib was maintained (median OS 53.7 months vs. 41.5 months; HR, 0.73; 95% CI, 0.59-0.90). OS benefit was observed in first-line and second-line subgroups.<sup>225</sup>

3) MONALEESA-7 was a phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of ribociclib plus endocrine therapy in premenopausal or perimenopausal women with advanced, HR-positive, HER2-negative breast cancer (n= 672). Previous endocrine therapy for advanced disease was not permitted but patients could have received one previous line of chemotherapy for advanced disease.<sup>226,227</sup>

- a) Randomized to ribociclib or placebo with endocrine therapy (tamoxifen or AI) in combination with ovarian suppression with goserelin. Goserelin could be initiated on same day as other study drugs.
- b) Visceral disease was present in 57% of patients
- c) Primary endpoint was investigator-assessed PFS (23.8 months in ribociclib group vs 13 months in endocrine therapy alone; HR 0.55, 95% CI 0.44-0.69; p<0.0001).
- d) OS (secondary endpoint) was significantly longer in the ribociclib-containing arm. OS at 42 months was 70.2% in the ribociclib group and 46% in the placebo group. Median OS not reached for ribociclib group vs. 40.9 months for placebo group (HR for death, 0.71; 95% CI, 0.54 to 0.95; p=0.00973).
- e) Grade 3-4 neutropenia occurred in 61% of patients in ribociclib group vs. 4% in placebo group (FN 2% of ribociclib group vs. 1% of placebo group)

f. Abemaciclib (Verzenio®)<sup>228</sup>

1) Approval based on MONARCH 1, MONARCH 2, and MONARCH 3 trials

- a) MONARCH 1 was a phase 2 open-label study of abemaciclib monotherapy (200 mg PO BID continuous) in 132 women with HR-positive, HER2-negative metastatic breast cancer who had progressed on or after prior endocrine therapy and had 1 – 2 chemotherapy regimens in the metastatic setting.<sup>229</sup>
  - i. Patients had a median of 3 lines of prior systemic therapy in the metastatic setting and 90.2% had visceral disease
  - ii. Primary endpoint of ORR was 19.7%
  - iii. Secondary endpoints included clinical benefit rate = 42.4%, PFS = 6 months, and median OS was 17.7 months



- b) MONARCH 2 was a double-blind, phase 3 study of 669 women with HR-positive, HER2-negative advanced breast cancer who progressed while receiving neoadjuvant or adjuvant endocrine therapy, ≤12 months from end of adjuvant endocrine therapy, or while receiving 1<sup>st</sup> line endocrine therapy for metastatic disease. Patients were randomized 2:1 to abemaciclib (150 mg PO BID continuous) plus fulvestrant or placebo plus fulvestrant.<sup>230,231,176</sup>
    - i. Included pre- and post-menopausal patients. Pre- or peri-menopausal patients received a LHRH agonist.
    - ii. PFS was significantly extended in abemaciclib + fulvestrant vs. fulvestrant alone (16.4 vs 9.3 months, HR 0.553; P< 0.001). ORR was 48.1% vs. 21.3% in abemaciclib and placebo arms, respectively.
    - iii. Most common adverse events in the abemaciclib arm included diarrhea (87.1% all grade and 14.5% grade 3) neutropenia (49.7% all grade and 29.7% grade 3-4), nausea (49.2% all grade), and fatigue (42.9% all grade).
    - iv. ALT increase occurred in 15.9% of patients (4.5% grade 3-4) and AST increase occurred in 15.6% of patients (2.7% grade 3).
    - v. Final OS analysis at 6.5 years: median OS of 45.8 months for abemaciclib plus fulvestrant and 37.2 months for placebo plus fulvestrant (HR, 0.784; 95% CI, 0.644-0.955). Abemaciclib delayed receipt of subsequent chemotherapy.
  - c) MONARCH 3 was a double-blind, randomized phase 3 study of abemaciclib or placebo plus a non-steroidal aromatase inhibitor in 493 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting.<sup>232,233</sup>
    - ii. Primary objective was investigator-assessed PFS. Median PFS was significantly prolonged in the abemaciclib arm (28.18 months vs. 14.76 months; HR, 0.540; CI 0.418-0.698; p=0.000002).
    - iii. Secondary objectives included response evaluation and safety; ORR = 61% in the abemaciclib arm and 45.5% in the placebo arm (P = .003).
    - iv. Diarrhea was typically low grade (72.8% was grade 1-2) and often occurred early (69.5% of patients experienced in cycle 1). Incidence dropped below 10% (grade 2) by cycle 4.
    - v. 6.1% incidence of VTE in the abemaciclib group compared to 0.6% in the placebo group.
  - g. FDA issued a safety announcement in September 2019 warning about rare but serious cases of interstitial lung disease (ILD) and pneumonitis with all three CDK 4/6 inhibitors.<sup>234</sup>
    - 1) Healthcare providers should monitor patients regularly for pulmonary symptoms. It is recommended to interrupt CDK 4/6 inhibitor treatment in patients who have new or worsening respiratory symptoms and permanently discontinue treatment in patients with severe ILD and/or pneumonitis.
2. Everolimus (Afinitor®)
- a. FDA approval in combination with exemestane based on the Phase 3 RCT BOLERO-2<sup>235</sup>

- 1) 724 patients with ER-positive, HER2-negative MBC after failure of a nonsteroidal AI (anastrozole or letrozole) were randomized to exemestane 25 mg PO daily + everolimus 10 mg PO daily vs exemestane 25 mg PO daily + placebo daily
  - 2) Nonsteroidal AI resistance was defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease.
  - 3) PFS based on centrally assessed radiographic studies (primary endpoint) was significantly longer in the everolimus group compared to the placebo group (10.6 mo vs 4.1 mo), HR 0.36 (0.27-0.47;  $p < 0.001$ )
  - 4) OS was not significantly different in a subsequent analysis at 31 months of follow up.<sup>236</sup>
  - 5) Serious adverse events occurred in 33% of everolimus group compared to 16% in the placebo group.<sup>236</sup>
  - 6) Any grade of stomatitis, rash, diarrhea, and hyperglycemia were increased with the everolimus group compared to the placebo group
- b. Everolimus + fulvestrant considered a preferred regimen in second and subsequent lines of therapy based on the results of the randomized, double-blind, placebo-controlled phase 2 PrE0102 trial, which included 131 postmenopausal women with ER-positive, HER2-negative, AI-resistant metastatic breast cancer.<sup>237</sup>
- 1) Addition of everolimus to fulvestrant improved median PFS from 5.1 months to 10.3 months (HR, 0.61; 95% CI, 0.40-0.92); stratified log-rank  $P = 0.02$ ). Clinical benefit rate was higher in the everolimus arm (63.6% vs. 41.5%;  $p = 0.01$ ).
  - 2) Adverse events occurred more often in the everolimus arm including oral mucositis (53% vs. 12%), fatigue (42% vs. 22%), rash (38% vs. 5%), anemia (31% vs. 6%), diarrhea (23% vs. 8%), hyperglycemia (19% vs. 5%), hypertriglyceridemia (17% vs. 3%), and pneumonitis (17% vs. 0%).
- c. Also phase 2 data with the combination of tamoxifen and everolimus<sup>238</sup>
- 1) Tamoxifen + everolimus improved CBR, TTP (8.6 mo vs 4.5 mo, exploratory  $p = 0.002$ ) and OS (not reached vs 32.9 mo exploratory  $p = 0.007$ ) compared to tam alone. Toxicity increased in the combination arm.
- d. Stomatitis is a common adverse effect with everolimus. Prophylactic dexamethasone oral solution may be beneficial to reduce the incidence of stomatitis.
- 1) SWISH trial evaluated prophylactic dexamethasone mouth rinse 10 mL of 0.5mg/5 mL oral solution (swish for 2 minutes and spit 4 times daily) starting on day 1 of everolimus/exemestane. Incidence of grade  $\geq 2$  stomatitis at 8 weeks was 2.4% compared with 33% in BOLERO-2 (historical control).<sup>239</sup>

**Patient Case #9, continued (ARS 9):** Correct answer is D. DS is a candidate to receive a combination of CDK4/6 inhibitor + endocrine therapy, such as abemaciclib + anastrozole + goserelin, for her HR-positive, HER2 negative metastatic breast cancer. Other acceptable options include fulvestrant + AI, fulvestrant + CDK 4/6 inhibitor, fulvestrant, AI, or tamoxifen. DS would also need to receive ovarian suppression or ablation, such as goserelin, with the aforementioned therapies (with the exception of tamoxifen) in order to eliminate ovarian production of estrogen.

Answers A and B are incorrect because alpelisib + anastrozole is not recommended as a treatment option for metastatic breast cancer. Alpelisib is only recommended in combination with fulvestrant after progression on a prior line of endocrine therapy in the metastatic setting. Given that DS has a PIK3CA mutation, alpelisib + fulvestrant (with the additional of goserelin due to her premenopausal state) could be considered in the second-line setting.

Answer C is incorrect because DS should receive OAS, such as goserelin, because she is premenopausal.

DS is treated with abemaciclib + letrozole + goserelin for 2.5 years after which, a repeat CT scan reveals increasing bone metastases. Repeat pathologic review is consistent with the original pathology: ER 60%, PR 0%, HER2 2+ by IHC, negative by ISH, *PIK3CA* mutation positive.

**ARS 10: Which of the following is the most appropriate second-line endocrine treatment for DS?**

- A. Palbociclib + fulvestrant + goserelin
- B. Palbociclib + tamoxifen
- C. Alpelisib + fulvestrant + goserelin
- D. Alpelisib + tamoxifen

The correct answer is C. Alpelisib + fulvestrant is a recommended 2<sup>nd</sup> and subsequent line of therapy option by NCCN Guidelines® based on the SOLAR-1 trial. Goserelin should be added to her regimen because she is premenopausal.

Answer A is incorrect because there is limited data to support use of a CDK4/6 inhibitor (palbociclib) in patients who progressed on a previous line of therapy including a CDK4/6 inhibitor (abemaciclib).

Answer B is incorrect because of the rationale included above for answer A. In addition, palbociclib is not recommended in combination with tamoxifen.

Answer D is incorrect because alpelisib is not recommended in combination with tamoxifen.

**Patient Case #10 (ARS 11):** BZ is a 50-year-old postmenopausal woman who presents with jaundice, dyspnea on exertion, and fatigue. Workup reveals a left breast cancer that has metastasized to the liver and lung, which is the cause of her symptoms. The pathology is ER=0%, PR=0%, HER2-negative, PD-L1 negative, and germline *BRCA1/2* positive. **Which of the following first-line regimens is the most appropriate for BZ at this time?**

- A. Rucaparib
- B. Talazoparib
- C. Gemcitabine
- D. Docetaxel

### 3. PARP Inhibitors

- a. NCCN® includes as an option to treat recurrent or metastatic breast cancer for patients with germline *BRCA1/2* mutation. Of note, olaparib and talazoparib approvals are for patients with HER2-negative metastatic breast cancer; however, NCCN® guidelines supports use in any breast cancer subtype associated with a germline *BRCA1/2* mutation.<sup>23</sup>
  - 1) Patients with HER2-negative disease eligible for single-agent therapy are eligible for germline *BRCA1/2* testing
- b. ASCO recommends olaparib or talazoparib as preferred over taxanes in the 1<sup>st</sup> to 3<sup>rd</sup> line settings for patients with germline *BRCA1/2* mutation and metastatic HER2-negative breast cancer. There is no data to directly compare PARP inhibitors to platinum chemotherapy<sup>61</sup>
- c. NCCN® states that PARP inhibitors may be considered for patients with somatic *BRCA1/2* mutations or germline *PALB2*; however, data is limited.<sup>23</sup>
- d. Olaparib
  - 1) OlympiAD was an open-label phase 3 trial that randomized 2:1 to olaparib or physician's choice of capecitabine, eribulin, or vinorelbine in patients with germline *BRCA* mutation and HER2-negative metastatic breast cancer who received ≤ 2 previous chemotherapy regimens for metastatic disease (n=302).<sup>240</sup>
    - a) Median PFS was significantly longer in the olaparib arm (7 mo vs. 4.2 mo; HR = 0.58; 95% CI, 0.43 – 0.8; p<0.001)
    - b) Grade ≥ 3 adverse events were 36.6% in olaparib arm and 50.5% in standard-therapy arm. Anemia, N/V, fatigue, headache, and cough were more frequent in the olaparib arm.
    - c) No statistically significant difference in median OS between the two arms [19.3 months with olaparib vs. 17.1 months with TPC (HR 0.90; P=0.513)]; however, the subgroup of patients who had not received prior chemotherapy for metastatic breast cancer appeared to have greater benefit with olaparib (22.6 vs. 14.7 months; HR=0.51).<sup>241</sup>
- e. Talazoparib<sup>242</sup>
  - 1) Indication: treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic
  - 2) Approval based on the phase 3 open-label EMBRACA trial. Patients with germline *BRCA*-mutated, HER2-negative locally advanced or metastatic breast cancer who had previously received ≤ 3 prior chemotherapy regimens were randomized 2:1 to receive talazoparib 1 mg PO daily (n=287) or physician's choice of chemotherapy (n=144) including capecitabine, gemcitabine, eribulin, and vinorelbine. Primary endpoint was PFS.<sup>243</sup>
    - a) At median follow-up of 11.2 months, median PFS was 8.6 months in talazoparib arm vs. 5.6 month in chemo arm (HR 0.52; P<0.0001). ORR was 62.6% in talazoparib arm vs. 27.2% in chemo arm (P<0.0001).
    - b) Final OS analysis found no statistically significant difference. Median OS was 19.3 months in the talazoparib arm vs. 19.5 months in the chemo arm (HR 0.848; 95% CI, 0.670-1.073; P=0.17).<sup>244</sup>

### 4. Alpelisib<sup>245</sup>

- a. PIK3CA mutations occur in approximately 40% of HR+, HER2- breast cancer.
  - 1) Mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.<sup>23</sup>
- b. Approval based on the randomized, double-blind, placebo-controlled, phase 3 SOLAR-1 trial in 572 patients with HR+, HER2-, advanced or metastatic breast cancer enrolled into two cohorts, with (n= 341) or without PIK3CA mutation. Primary endpoint was PFS in cohort with PIK3CA mutation.<sup>246</sup>
  - 1) At a median follow-up of 20 months, PFS in cohort with PIK3CA-mutation was 11 months in the alpelisib and fulvestrant arm (n=169) vs. 5.7 months in the placebo and fulvestrant arm (HR for progression or death, 0.65; 95% CI, 0.50-0.85, P<0.001) (n=172). In the cohort without PIK3CA mutation, HR was 0.85; 95% CI, 0.58 – 1.25.
  - 2) Among those in the PIK3CA cohort, median OS was 39.3 months in the alpelisib and fulvestrant arm and 31.4 months in the fulvestrant arm (HR 0.86, CI 0.64-1.15; P=0.15). OS results did not cross the prespecified efficacy boundary.<sup>247</sup>
  - 3) Most frequent grade 3-4 adverse reactions were hyperglycemia (36.6% in alpelisib arm and 0.7% in placebo arm) and rash (9.9% in alpelisib arm and 0.3% in placebo arm).
    - a) Safety in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.<sup>23</sup>

J. Additional Targeted Therapies and Associated Biomarker Testing for Recurrent Unresectable or Metastatic Disease<sup>23,248, 249</sup>

Breast Cancer Subtype	Biomarker	Method of Detection	Potential Therapies
HR-positive/HER2-negative	<i>PIK3CA</i> activating mutation	PCR (blood or tissue if blood negative)	Alpelisib + fulvestrant
Any	<i>NTRK</i> fusion	FISH, NGS, PCR (tissue)	Larotrectinib, entrectinib
	MSI-H/dMMR	IHC, NGS, PCR (tissue)	Pembrolizumab Dostarlimab-gxly
	Tumor Mutational Burden-High (TMB-H) defined as $\geq 10$ muts/mb	NGS	Pembrolizumab Dostarlimab-gxly
	<i>RET</i> -fusion	NGS	Selpercatinib

K. Monitoring of metastatic disease

1. Carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA 15-3), and cancer antigen 27-29 (CA 27-29) may be used as adjunctive assessments, but not alone, to guide decisions regarding therapy modification or discontinuation.<sup>142</sup>

**Patient case #10, continued (ARS 11):** Correct answer is B. Talazoparib. The EMBRACA trial, which compared talazoparib with physician's choice of chemotherapy for patients with germline *BRCA1/2* mutation, found an improved median PFS and response rate in the talazoparib group. As a result, olaparib or talazoparib are preferred treatment options for patients with germline *BRCA1/2* mutations in the NCCN Guidelines®.

Answer A is incorrect because the PARP inhibitor rucaparib has not been adequately studied for use in breast cancer at this time.

Answer C and D are incorrect because the PARP inhibitors olaparib and talazoparib have shown an improved median PFS and response rate compared to chemotherapy. Chemotherapy, such as gemcitabine or docetaxel, could be considered for this patient as second-line therapy after a PARP inhibitor.

**Patient case #6, continued (ARS 7):** HF is planned to receive docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) x 6 cycles followed by surgery for her diagnosis of HER2-positive, stage IIIB breast cancer.

**According to pertuzumab's prescribing information, what is an appropriate frequency for monitoring HF's LVEF during neoadjuvant therapy following baseline assessment?**

- A. Every 12 weeks
- B. Every 6 months
- C. Every 6 weeks
- D. Every 2 months

## VII. Cardiotoxicity<sup>250-253</sup>

### A. ASCO Guidelines risk factors for developing cardiotoxicity<sup>254</sup>

1. High-dose anthracycline (i.e., cumulative doxorubicin dose  $\geq 250$  mg/m<sup>2</sup>, epirubicin  $\geq 600$  mg/m<sup>2</sup>)
2. High-dose radiotherapy (RT;  $\geq 30$  Gy) where the heart is in the treatment field
3. Lower-dose anthracycline (i.e., doxorubicin  $< 250$  mg/m<sup>2</sup>, epirubicin  $< 600$  mg/m<sup>2</sup>) in combination with lower-dose RT ( $< 30$  Gy) where the heart is in the treatment field
4. Treatment with lower-dose anthracycline or trastuzumab alone, and presence of any of the following risk factors:
  - a. Multiple CV risk factors ( $\geq$  two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - b. Older age ( $\geq 60$  years) at cancer treatment
  - c. Compromised cardiac function (i.e., borderline low LVEF (50 – 55%), history of myocardial infarction (MI),  $\geq$  moderate valvular heart disease) at any time before or during treatment
5. Treatment with lower-dose anthracycline followed by trastuzumab (sequential therapy)

### B. Anthracyclines

1. The anthracycline antibiotics (daunorubicin, doxorubicin, idarubicin, epirubicin) can cause a dose-related, cumulative cardiomyopathy.
2. NCCN Guidelines® risk factors for cardiotoxicity with anthracyclines<sup>255</sup>
  - a. Hypertension

- b. Dyslipidemia
  - c. Diabetes mellitus
  - d. Age > 65 years
  - e. Family history of cardiomyopathy
  - f. High cumulative anthracycline dose (i.e., cumulative doxorubicin dose  $\geq 250 \text{ mg/m}^2$  or equivalent)
  - g. Low-normal LVEF (50-54%) at baseline
  - h. History of other cardiovascular (CV) comorbidities (i.e., atrial fibrillation, known coronary artery disease (CAD), baseline evidence of structural heart disease)
  - i. Smoking
  - j. Obesity
3. Acute
- a. Occurs immediately after a single dose or course of therapy with an anthracycline
  - b. Uncommon and transient
  - c. May involve abnormal ECG findings, including QT-interval prolongation, ST-T wave changes, and arrhythmias
  - d. Rarely, CHF and/or pericarditis are observed
  - e. May be caused by an inflammatory response
  - f. Not related to cumulative dose
4. Chronic
- a. Onset usually within a year of receiving anthracycline therapy
  - b. Rapid onset and progression
  - c. More common and life threatening
  - d. Related to cumulative dose patient received<sup>256</sup> - estimated incidences of developing CHF are:
    - 1) 0.2% with a cumulative doxorubicin dose of  $150 \text{ mg/m}^2$
    - 2) 1.6% incidence with a cumulative doxorubicin dose of  $300 \text{ mg/m}^2$
    - 3) 3.3% incidence with a cumulative doxorubicin dose of  $450 \text{ mg/m}^2$
    - 4) 8.7% incidence with a cumulative doxorubicin dose of  $600 \text{ mg/m}^2$
  - e. Can be resistant to treatment
  - f. Symptoms include tachycardia, tachypnea, exercise intolerance, pulmonary and venous congestion, ventricular dilatation, poor perfusion and pleural effusion.
  - g. Exact mechanism is unknown; but is likely to be multifactorial including DNA damage due to reactive oxygen species production and topoisomerase 2.<sup>257</sup>
    - 1) Onset may be masked at first as the initial loss of function is compensated by remaining myocytes.

- 2) Will become apparent eventually, usually as a decreased left ventricular ejection fraction (LVEF) and CHF, as patient receives increasing cumulative doses of anthracyclines.
5. Late-onset
  - a. Develops several years or even decades after therapy
  - b. Manifests as ventricular dysfunction, CHF, conductile disturbances and arrhythmias
6. Occurs more often in childhood / adolescence cancer survivors who received anthracyclines
7. Dexrazoxane (Zinecard<sup>®</sup>) for secondary prevention<sup>258-261</sup>
  - a. Approved for use in metastatic breast cancer patients who are responding to and intend to stay on doxorubicin-containing chemotherapy and have received a cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin
  - b. Dosing is based on a ratio of 10: 1 (dexrazoxane-to-doxorubicin, i.e. 500 mg/m<sup>2</sup> dexrazoxane and 50 mg/m<sup>2</sup> doxorubicin).
    - 1) Must administer doxorubicin within 15 to 30 minutes of completion of dexrazoxane injection, due to a short half-life of approximately 2 hours.
    - 2) Administer 15 – 30 minutes prior to doxorubicin or epirubicin
    - 3) A dose ratio of 10:1 may be reasonable with epirubicin; however, the optimal dose ratio has not been determined.
    - 4) No evidence currently exists regarding use with liposomal anthracyclines, idarubicin, or mitoxantrone
  - c. In a meta-analysis of 6 RCTs, dexrazoxane given with doxorubicin or epirubicin significantly reduced the risk of clinical cardiotoxicity (OR 0.21), subclinical cardiotoxicity (RR 0.33), and any cardiotoxic event (RR 0.34) compared to no cardioprotective agent.<sup>262</sup>
  - d. Difficult to determine side effects of dexrazoxane versus the chemotherapy agent it is co-administered with, but generally well tolerated and lacks additive toxicity with anthracycline-based chemotherapy except for a small, but significant increase in leukopenia and/or thrombocytopenia seen in some trials.
  - e. ASCO guidelines on use of dexrazoxane as cardioprotectant<sup>258</sup>
    - 1) Use in breast cancer
      - a) Consider use of dexrazoxane for patients with MBC who have received  $\geq 300$  mg/m<sup>2</sup> of doxorubicin in the metastatic setting and who may benefit from continued doxorubicin-containing therapy
    - 2) Do not use routinely in women who are receiving initial doxorubicin therapy for metastatic disease
      - i. Consider for patients who received  $\geq 300$  mg/m<sup>2</sup> in the adjuvant setting and are now initiating doxorubicin-based chemo in the metastatic setting
      - b) Not recommended for use in the adjuvant setting (outside of a clinical trial)
    - 3) Other malignancies besides breast cancer
      - a) Consider for adult patients who received  $\geq 300$  mg/m<sup>2</sup> of doxorubicin-based therapy



- b) Caution use in settings in which doxorubicin-based therapy has been shown to improve survival given the potential for dexrazoxane to decrease response rates
  - 4) Not beneficial with continuous infusions of anthracyclines
- 8. Options for monitoring<sup>251,263,</sup>
  - a. Methods to determine cardiac function include:
    - 1) Left ventricular (LVEF) systolic function can be evaluated via either echocardiography (ECHO) or multigated acquisition scans (MUGA), but neither are sensitive enough to detect early preclinical cardiac dysfunction.
    - 2) Monitoring diastolic function may be useful in detecting early anthracycline-induced cardiac dysfunction.
    - 3) Exercise or dobutamine echocardiography have also been used to assess early anthracycline cardiotoxicity.
    - 4) Measurement of myocardial strain and strain rate by speckle-tracking imaging.
  - b. Troponin T and troponin I may also be useful in early detection of cardiotoxicity before changes develop in LV ejection fraction<sup>264</sup>
    - 1) Natriuretic peptides (ANP, BNP, NT-proBNP) have also been studied in early detection of cardiotoxicity, but the results have been less consistent than troponins.
    - 2) None of these serological markers of cardiotoxicity are routinely recommended.
  - c. ASCO guideline on the prevention and monitoring of cardiac dysfunction in survivors of adult cancers<sup>254</sup>
    - 1) Clinicians should perform a comprehensive assessment in patients with cancer that includes a history and physical exam, screening for cardiovascular disease risk factors, and an echocardiogram before initiation of potentially cardiotoxic therapies.
    - 2) In individuals with clinical signs or symptoms concerning for cardiac dysfunction during routine clinical assessment, the following is recommended:
      - a) ECHO for diagnostic workup
      - b) Cardiac MRI or MUGA scan if ECHO is not available or technically feasible (preference for cardiac MRI)
      - c) Serum cardiac biomarkers (troponins, natriuretic peptides) or ECHO-derived strain imaging in conjunction with routine diagnostic imaging
      - d) Referral to a cardiologist based on findings
    - 3) Routine surveillance imaging may be offered during treatment in asymptomatic patients considered to be at increased risk (see guideline for description of patients at increased risk). ECHO is the preferred imaging modality of choice. Frequency of surveillance should be determined by health care providers based on clinical judgment.
    - 4) An ECHO may be performed between 6 – 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk of cardiac dysfunction.
      - a) No recommendation is made for frequency and duration of surveillance in patients at increased risk who are asymptomatic and have no evidence of cardiac dysfunction on post-treatment ECHO.

- 5) NCCN Guidelines® recommend ECHO with doppler flow study within 1 year after completion of anthracycline therapy for survivors with high cumulative anthracycline dose or low cumulative anthracycline dose and 1 or more heart failure risk factors. Refer to cardiologist/cardio-oncologist if there are echocardiographic abnormalities.<sup>255</sup>
9. Recommendations<sup>251</sup>
    - a. Any patient with a risk factor for cardiotoxicity should have a baseline evaluation of cardiac function by ECHO or MUGA scanning.
    - b. For patients with a LVEF >50% at baseline:
    - c. Consider repeating after reaching 250-300 mg/m<sup>2</sup> doxorubicin, or equivalent
      - 1) Repeat after reaching 400 mg/m<sup>2</sup> in patients with known risk factors of cardiac failure or after 450 mg/m<sup>2</sup> in the absence of risk factors
      - 2) Discontinue doxorubicin if:
        - a) Functional signs of cardiotoxicity and/or
        - b) Absolute decrease in LVEF ≥ 10% associated with a decline to a level of < 50%.
      - 3) If receiving anthracyclines and dexrazoxane, ASCO guideline on the use of chemoprotectants recommend cardiac monitoring for patients who have received a cumulative dose of 400 mg/m<sup>2</sup>, repeat monitoring when reaching a cumulative dose of 500 mg/m<sup>2</sup> and then repeat monitoring after every 50 mg/m<sup>2</sup> thereafter<sup>258</sup>
- C. Trastuzumab (including trastuzumab and hyaluronidase-oysk and trastuzumab biosimilars)
    1. Cardiotoxicity is not dose-related, no direct myocardial damage has been found, appears to be reversible and short-lived once trastuzumab is discontinued
    2. Cardiomyopathy leading to CHF; clinically similar to anthracycline-induced CHF, but reversible with medication despite continuing trastuzumab therapy.
    3. Rate of cardiotoxicity ~5% with single agent therapy
    4. Acceptable rate of cardiotoxicity with most regimens tested in the adjuvant setting (see table “Cardiotoxicity Associated With Adjuvant Trastuzumab Clinical Trials”).
    5. Black box warning for left ventricular dysfunction
    6. Appears to be responsive to heart failure medical therapy; however, few patients recover their LVEF to baseline; may recover to a normal LVEF (> 50%), but some residual damage evident and may not have reserve to adequately respond to subsequent stressors; need to follow for longer to determine long-term risks.<sup>265</sup>
    7. Serial prospective cardiac monitoring with MUGA scans or echocardiograms was performed in all studies, but definitions for cardiac events differ.
    8. Cardiac function should be assessed every 3 months during trastuzumab-based therapy according to the PI.<sup>266</sup> NCCN® notes that optimal frequency of monitoring during adjuvant therapy is not known.<sup>23</sup>
    9. If trastuzumab is given concurrently with an anthracycline the rate of cardiac toxicity increases substantially to 27% (16% NYHA class III/IV)<sup>267</sup>
    10. Monitoring<sup>266</sup>
      - a. Assess LVEF prior to initiation, every 3 months during, and upon completion of trastuzumab

- b. Repeat LVEF measurement at 4 week intervals if trastuzumab is held (according to criteria below)
  - c. LVEF measurement every 6 months for at least 2 years following completion of adjuvant trastuzumab
  - d. Clinicians may use routine ECHO surveillance in patients with metastatic breast cancer continuing to receive trastuzumab indefinitely. Frequency of cardiac imaging should be determined based on clinical judgment and patient circumstances.<sup>254</sup>
11. Recommendations for management<sup>266</sup>
- a. Withhold trastuzumab for at least 4 weeks for any of the following
    - 1)  $\geq 16\%$  absolute decrease in LVEF from baseline
    - 2) LVEF below institutional limit of normal and  $\geq 10\%$  absolute decrease from baseline
  - b. Resume if LVEF returns to normal limits and absolute decrease from baseline is  $\leq 15\%$  (within 4 – 8 weeks)
  - c. Permanently discontinue if persistent ( $> 8$  weeks) LVEF decline or if suspended  $\geq 3$  occasions for cardiomyopathy

#### Cardiotoxicity Associated with Adjuvant Trastuzumab Clinical Trials

Endpoint	B-31 <sup>268</sup> N=1964	N9831 <sup>269</sup> N=1610	HERA <sup>270</sup> N=3401	BCIRG 006 <sup>271</sup> N=3222			FinHer <sup>272</sup> N=232
	AC $\rightarrow$ TH vs. AC $\rightarrow$ T		H vs. no H	AC $\rightarrow$ T	AC $\rightarrow$ TH	TCH	DH/VH $\rightarrow$ FEC vs D/V $\rightarrow$ FEC
Cardiotoxicity	4.0% vs. 1.3%	3.3% vs. 0.3%	0.8% vs. 0.1%	0.7%	2.0%	0.4%	0.9% vs. 1.7%
Median F/U	7 years	3 years	8 years	5.4 years			5.2 years

Definition of cardiotoxicity differs:

B-31/N9831: NYHA Class III/IV CHF or cardiac death.

HERA: Symptomatic CHF, including severe.

BCIRG: Cardiac death, symptomatic CHF, and asymptomatic decreases in LVEF.

FinHer: Symptomatic HF.

- D. Pertuzumab
1. Asymptomatic left ventricular systolic dysfunction (LVSD) was 3.4% and 6.5% and symptomatic heart failure was 1.1% with pertuzumab/non-anthracycline based chemotherapy and pertuzumab/trastuzumab, respectively.<sup>273</sup>
  2. Black box warning for left ventricular dysfunction
  3. Monitoring<sup>130</sup>
    - a. Assess LVEF prior to initiation and at regular intervals during treatment. Prescribing information recommends every 12 weeks in metastatic and neoadjuvant/adjuvant settings (at least once during neoadjuvant therapy)
  4. Recommendations for Management
    - a. Withhold pertuzumab (and trastuzumab) for at least 3 weeks for:

- 1) MBC: LVEF < 40% or 40 – 45% with a fall of ≥ 10% points below pre-treatment value
- 2) Neoadjuvant/adjuvant: LVEF < 50% with a fall of ≥ 10% points below pre-treatment value
- b. Treatment with pertuzumab and trastuzumab can be resumed if LVEF recovered to:
  - 1) MBC: > 45% or 40 – 45% with a fall of < 10% points below pre-treatment value
  - 2) Neoadjuvant/adjuvant: ≥ 50% or < 10% points below pre-treatment value
  - 3) Repeat LVEF assessment within approximately 3 weeks. Discontinue if LVEF has not improved or has declined further at repeat assessment
- E. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use (Phesgo™) <sup>274</sup>
  1. Incidence of NYHA class II heart failure= 1.2% and NYHA class III/IV heart failure= 0.8%
  2. Monitoring and recommendations for management are the same as listed above for pertuzumab
- F. Ado-trastuzumab emtansine (T-DM1)
  1. LVSD occurred in 1.8% of patients who received T-DM1 and 3.3% in patients who received capecitabine/lapatinib.<sup>195</sup>
  2. Black box warning for left ventricular dysfunction
  3. Monitoring<sup>275</sup>
    - a. LVEF should be monitored at baseline and regular intervals (e.g. every 3 months) during therapy.
  4. Recommendations for management
    - a. Metastatic breast cancer
      - 1) LVEF > 45% then continue treatment
      - 2) T-DM1 should be withheld for at least 3 weeks and LVEF repeated within 3 weeks if:
        - a) LVEF decreases to < 40% or
        - b) LVEF decreases to 40-45% with at least a 10% absolute decrease from baseline
      - 3) Treatment can be resumed if LVEF recovers to > 45% or to 40-45% with < 10% absolute decrease from baseline value within 3 weeks.
      - 4) Discontinue for symptomatic heart failure.
    - b. Early stage breast cancer
      - 1) LVEF ≥ 50%: continue treatment
      - 2) LVEF < 45%: hold and repeat LVEF within 3 weeks. If LVEF < 45% is confirmed, discontinue
      - 3) LVEF 45 to < 50% and decrease is ≥ 10% points from baseline: hold and repeat LVEF within 3 weeks. If LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue.
      - 4) LVEF 45 to < 50% and decrease is < 10% points from baseline: continue treatment and repeat LVEF within 3 weeks
- G. Fam-trastuzumab deruxtecan-nxki <sup>276</sup>
  1. Two cases (0.9%) of asymptomatic LVEF decrease were reported in the DESTINY-Breast01 trial<sup>197</sup>
  2. Monitoring

- a. Assess LVEF prior to initiation and at regular intervals during treatment as clinically indicated
3. Management
  - a. LVEF > 45% and absolute decrease from baseline is 10 – 20%: continue treatment
  - b. LVEF 40 – 45% and:
    - 1) Absolute decrease from baseline < 10%: continue treatment and repeat LVEF assessment within 3 weeks
    - 2) Absolute decrease from baseline is 10 – 20%: interrupt treatment and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue. If LVEF recovers to within 10% from baseline, resume treatment at the same dose.
  - c. LVEF < 40% or absolute decrease from baseline is > 20%: interrupt treatment and repeat LVEF assessment within 3 weeks. If LVEF of < 40% or absolute decrease from baseline of  $\geq 20\%$  is confirmed, permanently discontinue
  - d. Symptomatic CHF: permanently discontinue
- H. Margetuximab
  1. Left ventricular dysfunction occurred in 1.9% of patients treated with margetuximab in the SOPHIA trial
  2. Monitoring
    - a. Monitor LVEF within 4 weeks prior to and every 3 months during and upon completion of treatment
    - b. Monitor LVEF every 4 weeks if margetuximab is withheld for significant left ventricular cardiac dysfunction
  3. Management
- I. Taxanes
  1. Paclitaxel (conventional)
    - a. Cardiotoxicity (usually asymptomatic) present as bradyarrhythmias, tachyarrhythmias, atrioventricular and bundle branch blocks, cardiac ischemia, and hypotension (possibly secondary to hypersensitivity reaction to the solubilizing agent)
    - b. CHF can develop in patients treated with doxorubicin and paclitaxel
      - 1) Appears to be related to doxorubicin total cumulative dose ( $> 380 \text{ mg/m}^2$ )
      - 2) Pharmacokinetic interaction between paclitaxel and doxorubicin leads to decreased hepatic elimination of doxorubicin - depends on interval, sequence of drug administration, and duration of paclitaxel infusion
      - 3) Similar interaction occurs with epirubicin at cumulative dose of  $990 \text{ mg/m}^2$ ; 12% cumulative risk for heart failure develops - risk factors include older age, co-existing HTN or diabetes, and prior radiotherapy to the chest wall
    - c. Risk factors: unstable angina, severe coronary artery disease, CHF, and atrial fibrillation

- d. Patients with cardiac histories were excluded in most clinical trials - one study administered paclitaxel as either a single-agent or in combination with carboplatin/cisplatin in patients with major cardiac risk factors; found to be safe in patients with major cardiac risk factors
- 2. Albumin-bound paclitaxel has similar cardiotoxicity as paclitaxel
  - a. Asymptomatic ECG changes including sinus bradycardia and tachycardia, chest pain (rare), supraventricular tachycardia, and cardiac arrest have all been reported
- 3. Docetaxel
  - a. Conduction abnormalities, angina, and cardiovascular collapse have been reported, however no direct link between docetaxel and these events has been found
- J. Patients who develop heart failure should be treated according to standard heart failure guidelines.
- K. Helpful review on cardiovascular toxic effects of targeted cancer therapies has been published <sup>277</sup>

**Patient case #6, continued (ARS 7):** The correct answer is A. Monitoring of LVEF with an ECHO or MUGA is recommended by pertuzumab's prescribing information at baseline and every 12 weeks during neoadjuvant treatment (at least once during neoadjuvant therapy).

**ARS 8: While receiving adjuvant trastuzumab and pertuzumab HF's LVEF decreased from a baseline of 60% to 49% via MUGA scan prior to cycle 12. What is the most appropriate action at this time?**

- A. Continue trastuzumab and pertuzumab
- B. Hold trastuzumab and pertuzumab
- C. Restart trastuzumab but discontinue pertuzumab
- D. Restart pertuzumab but discontinue trastuzumab

**Patient case #6, continued (ARS 8):**

The correct answer is B. It is recommended to hold trastuzumab and pertuzumab if the LVEF is < 50% with a fall of ≥ 10% points below pre-treatment value in patients receiving neoadjuvant or adjuvant treatment with trastuzumab and pertuzumab. This patient had an absolute decrease in 11 and an LVEF < 50%.

Answer A, C, and D, are incorrect because this patient meets the criteria above to hold trastuzumab and pertuzumab.

## VIII. Breast Cancer Survivorship

- A. ASCO and ACS published a joint guideline on breast cancer survivorship. <sup>77</sup>
  - 1. Women should have a detailed cancer-related history and physical examination every 3 to 6 months for the first 3 years after primary therapy, then every 6 to 12 months for the next 2 years, then annually.
    - a. Should be performed by the treating oncology team
  - 2. Patients should be educated regarding the symptoms associated with breast cancer recurrence (new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headache).
  - 3. Women at high risk of familial breast cancer should be referred for genetic counseling.
  - 4. Women should be referred for annual mammography

- a. Intact breast for women who received a unilateral mastectomy
- b. Both breasts for women who received breast conserving surgery
- 5. Primary care clinicians should counsel patients to adhere to adjuvant endocrine therapy
- 6. Primary care clinicians should consult with the cancer treatment team and obtain a treatment summary and survivorship care plan.
- 7. Regular gynecologic exams are recommended.
  - a. Postmenopausal women who receive tamoxifen are at increased risk for endometrial cancer and should report any abnormal vaginal bleeding to their provider immediately.
- 8. The following are not recommended:
  - a. Routine CBC
  - b. Routine chest x-rays, ultrasound of the liver, bone scans, CT scans, PET scans, breast MRI (exception is breast MRI for patients who meet high-risk criteria for increased breast cancer surveillance as per ACS guidelines<sup>29</sup>).
  - c. Tumor markers (CA 15-3, CA 27.29, CEA)

**Patient Case #11 (ARS 14):** AH is a 50-year-old postmenopausal female who is receiving adjuvant treatment with letrozole x 5 years for the treatment of an ER-positive, PR-positive, HER2-negative stage IA breast cancer. Her baseline dual-energy X-ray absorptiometry (DXA) scan reveals a T-score of -2.7. She is taking calcium 1,500 mg PO divided twice daily and vitamin D3 800 international units PO daily. In addition to encouraging physical activity and continued calcium and vitamin D supplementation, **which of the following is the most appropriate action based on her DXA scan?**

- A. Initiate denosumab every 6 months
- B. Observation
- C. Increase calcium and vitamin D supplementation
- D. Initiate zoledronic acid every 4 weeks

- B. NCCN® has published a survivorship guideline that addresses many survivorship issues (including cardiac toxicity, fatigue, sexual dysfunction, cognitive function). It is not specific to breast cancer.<sup>255</sup>
- C. Bone health
  - 1. Increased bone resorption can result from:
    - a. Chemotherapy-induced ovarian failure
    - b. Tamoxifen in premenopausal women
    - c. LHRH agonists or oophorectomy in premenopausal women
    - d. Aromatase inhibitors in postmenopausal women
  - 2. Several guidelines are available for monitoring and treatment of cancer treatment-induced bone loss (CTIBL) including from NCCN®<sup>278</sup>, and ESMO<sup>279</sup>, primarily focusing on bone loss from aromatase inhibitors.
  - 3. Screening and monitoring
    - a. Screen for osteoporotic risk factors

- b. Consider use of FRAX algorithm<sup>278</sup>
  - c. Baseline and periodic bone mineral density (every 1 to 2 years) in patients on an AI, premenopausal women taking tamoxifen and/or a LHRH agonist, and women who experience ovarian failure due to treatment.<sup>77</sup>
- 4. Treatment algorithm from NCCN® Task Force<sup>278</sup>
  - a. Physical activity (all women)
  - b. Adequate calcium + vitamin D intake (all women)
    - 1) IOM report in 2010<sup>280</sup>
      - a) Recommended 1,000 mg of calcium and 600 IU of vitamin D per day in healthy adults
        - i. No more than 600 mg calcium at one time
      - b) Recommended 1,200 mg of calcium for women > 50 y/o
      - c) Recommended 800 IU of vitamin D per day in adults > 70 y/o
      - d) Defined 25-OH vitamin D levels of 20 ng/mL (50 nmol/L) as adequate, corresponding to 600 IU/day of vitamin D.
    - 2) NCCN® Task Force recommends 1,200 mg of calcium and 800-1,000 IU of vitamin D for all patients at risk for cancer treatment-associated bone loss.<sup>278</sup>
  - c. T-score > -1
    - 1) Repeat DXA scan every 2 years
  - d. T-score between -1 and -1.5
    - 1) Consider checking a 25(OH) vitamin D level
    - 2) Repeat DXA scan every 2 years
  - e. T-score between -1.5 and -2.0
    - 1) Consider checking a 25(OH) vitamin D level
    - 2) Consider pharmacologic therapy
    - 3) Repeat DXA scan every 2 years
  - f. T-score < -2.0 OR FRAX 10 year risk >20% for major fracture or > 3% for hip fracture
    - 1) Consider checking a 25(OH) vitamin D level
    - 2) Strongly consider pharmacologic therapy
    - 3) Repeat DXA scan every 2 years
- 5. NCCN Guidelines® for Breast Cancer notes the option of a bisphosphonate (oral/IV) or denosumab to maintain or to improve bone mineral density (BMD) and reduce risk fractures in postmenopausal (natural or induced) patients receiving adjuvant AI therapy.
- 6. Treatment options
  - a. Optimal duration of therapy has not been established. Duration beyond 3 years is not known. Factors to consider for duration of therapy include BMD, response to therapy, and risk factors for continued bone loss or fracture.



- b. Dental exam with preventive dentistry is recommended prior to initiation of a bisphosphonate or denosumab.
- c. Bisphosphonates
  - 1) Both oral and IV bisphosphonates are valid options
    - a) No clinical trials have directly compared oral and IV
    - b) Oral bisphosphonates include alendronate, ibandronate, and risedronate
  - 2) Most studies in patients with cancer evaluated zoledronic acid 4 mg IV every 3 to 6 months.
  - 3) Use of zoledronic acid 5 mg IV yearly (marketed as Reclast®) may be necessary for reimbursement purposes.
- d. Denosumab (Prolia®) 60 mg SQ every 6 months also an option for patients with bone loss
  - 1) FDA-approved to treat bone loss in women at high risk of fracture receiving adjuvant AI therapy for breast cancer.
  - 2) Can be considered for the prevention of AI-induced bone loss based on the recent results of ABSCG-18 that showed a reduction in the risk of clinical fractures in postmenopausal women receiving an AI without added toxicity <sup>124</sup>.
  - 3) Case reports of spontaneous fractures after denosumab discontinuation.<sup>23</sup>
- e. The use of estrogen, progesterone, or SERMs to treat osteoporosis or osteopenia in women with breast cancer is not recommended.

**Patient Case #11, continued (ARS 14):** The correct answer is A. Initiate denosumab every 6 months. Given that AH has osteoporosis at baseline and is taking an AI (letrozole) which is well-known to cause bone loss, NCCN® task force and guidelines recommend initiating a bone modifying agent. Other acceptable options include zoledronic acid 4 mg every 6 months or zoledronic acid (Reclast®) 5 mg every year. Oral bisphosphonates could also be considered for this patient. A DXA scan should be repeated every 2 years. Answer B is incorrect because the patient is a candidate for a bone modifying agent (for reasons listed above). Answer C is incorrect because AH is already taking appropriate amounts of supplemental calcium and vitamin D. Answer D is incorrect because zoledronic acid is typically dosed every 6 months or annually for treatment of bone loss

D. Lymphedema<sup>23,77,</sup>

- 1. Common complication after treatment for breast cancer, occurring on the same side of the body as the cancer treatment, because of dysfunction of the lymphatic system
- 2. Most often diagnosed within 18 months of treatment; however it can develop anytime in the life of the survivor (can be an acute or chronic condition)
- 3. Factors associated with increased risk for development of lymphedema include extent of axillary surgery, axillary radiation, infection, obesity, and higher initial extent of disease
- 4. Recommend patient education, weight loss, monitoring for lymphedema, and referring to a specialist for lymphedema management as needed (compression garments, resistance training, manual lymphatic drainage)
- 5. Early detection/diagnosis is key for optimal management (stages 0 and 1 are reversible)

6. Medical procedures such as venipuncture and blood pressure measurement is recommended to be done on the non-at-risk limb if possible, If necessary, procedures may be done using the at-risk limb.
- E. Cardiotoxicity
1. Primary care clinicians should monitor lipid levels and provide cardiovascular monitoring as indicated, educate survivors on health lifestyle modifications, and when to report relevant symptoms (shortness of breath or fatigue)
- F. Fatigue<sup>77</sup>
1. Estimated prevalence of 28 – 91%
  2. Screen for anemia, thyroid dysfunction, and cardiac dysfunction
  3. Mood disorders, sleep disturbance, and pain should be addressed
  4. Treatment strategies may include regular exercise regimen and cognitive behavioral therapy. Minimal data to support use of pharmacologic agents in this population.
  5. If treating concomitant depression or anxiety, consider less-sedating antidepressants such as bupropion.<sup>255</sup>
  6. See ASCO guideline for more details on management of fatigue for cancer survivors<sup>281</sup>
- G. Cognitive Impairment
1. Can be a result of cancer and cancer treatments<sup>77</sup>
  2. Limited evidence to guide management
  3. Imaging studies may not be helpful, except to rule out structural abnormalities as indicated by high-risk disease, or focal neurologic deficits or comorbidities<sup>255</sup>
  4. Assess for contributing factors: medications, emotional distress (depression/anxiety), symptom burden (pain, fatigue, sleep disturbance, nutritional issues), comorbidities (i.e., endocrine dysfunction, cardiac dysfunction, infection, anemia, etc.), and use of alcohol or other agents that alter cognition<sup>255</sup>
  5. No effective screening tool has been identified
  6. Interventions (see NCCN Survivorship Guidelines® for specific behavioral recommendations)<sup>255</sup>
    - a. First line
      - 1) Neuropsychologic evaluation and recommendations (including group cognitive training)<sup>77</sup>
      - 2) Cognitive rehabilitation (occupational therapy, speech therapy, and neuropsychology)
      - 3) Psychotherapy
      - 4) Routine physical activity
    - b. Second line
      - 1) Consider use of psychostimulants (methylphenidate, modafinil, or donepezil)
- H. Hot flashes<sup>282</sup>
1. Hot flashes affect 65 – 85% of breast cancer survivors as a result of therapy.
  2. Chemotherapy and tamoxifen can cause more frequent and severe hot flashes than natural menopause, which often results in decreased quality of life and may affect adherence.

### 3. Treatment

a. Hormonal therapies are a relative contraindication in survivors of hormonally mediated cancers.  
255

#### b. Antidepressants

- 1) Venlafaxine - Considered preferred option by NCCN Guidelines® – recommend to start at lowest dose possible (25 mg or 37.5mg and increase as tolerated). Commonly used daily dose = 75 mg.
- 2) Also evidence to support the use of desvenlafaxine, escitalopram, paroxetine, fluoxetine, sertraline, and citalopram
- 3) Note of caution with antidepressants
  - a) Some SSRIs and SNRIs have been shown to alter the PK of tamoxifen and its active metabolites (decrease concentrations of active metabolite endoxifen through inhibition of CYP 2D6).
  - b) Strong to moderate inhibitors should be avoided during tamoxifen therapy if possible (sertraline, paroxetine, fluoxetine, bupropion, duloxetine)
  - c) NCCN Guidelines® recommend that weak CYP2D6 inhibitors (listed as citalopram, escitalopram, and venlafaxine) appear to have no or only minimal effect on tamoxifen metabolism<sup>23</sup>

#### Effects of Selected Antidepressants on CYP 2D6<sup>283</sup>

Antidepressant							
Fluoxetine	Paroxetine	Sertraline	Duloxetine	Citalopram	Bupropion	Venlafaxine	Escitalopram
+++	+++	++	++	+	+++	(-)	+
(-) = no inhibition; + (weak inhibitor)= > 1.25-fold but < 2-fold x increase in AUC or 20-50% decrease in clearance; ++ (moderate inhibitor)= > 2-fold increase in AUC or 50-80% decrease in clearance; +++ (strong inhibitor)= > 5-fold increase in AUC or > 80% decrease in clearance; ± = all other inhibition.							

- c. Gabapentin – Considered preferred option by NCCN Guidelines® - recommend to start at lowest possible dose (100 – 300 mg) and increase as tolerated. Consider starting at night time.  
Recommended daily dose = 900 mg (typically 300 mg TID)
- d. Pregabalin – start at lowest dose possible (25 mg) and increase as tolerated to daily dose = 150 – 300 mg
- e. Clonidine – caution with hypotension; recommended daily dose = 0.1 mg (oral or transdermal).  
Transdermal preparations may have fewer side effects.
- f. Oxybutynin – start with 2.5 - 5 mg BID and titrate to recommended daily dose = 5 – 10 mg; may cause urinary retention along with other anticholinergic side effects
- g. Non-pharmacologic treatments: weight loss if overweight or obese, acupuncture, exercise/physical activity, lifestyle modifications, integrative therapies including yoga and hypnosis.<sup>255</sup>

#### I. Vaginal dryness

1. Use lubricants for sexual activity

2. Local estrogen treatment (ie, rings, suppositories, creams) – limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories; therefore, they are preferred over creams for survivors of hormonally sensitive tumors.

**Patient case #4 (continued):** YC is a 37-year-old premenopausal female who was diagnosed with triple negative stage IA breast cancer. She had a modified radical mastectomy and is planned to receive adjuvant treatment in 3 weeks with dose dense doxorubicin + cyclophosphamide (AC) x 4 cycles followed by weekly paclitaxel. She is interested in fertility preservation options.

**Based on the ASCO guideline on fertility preservation, which option is most appropriate for YC at this time?**

- A. Ovarian transposition
- B. Embryo cryopreservation
- C. Ovarian tissue cryopreservation
- D. Leuprolide

L. Fertility preservation for females with breast cancer

1. Primary care clinicians should refer survivors of childbearing age who experience infertility to a specialist in reproductive endocrinology and infertility<sup>77</sup>
2. Few randomized trials exist to guide practice
3. ASCO guidelines on fertility preservation for patients with cancer were updated in 2018.<sup>284</sup>
  - a. Fertility preservation approaches should be discussed as early as possible, before treatment starts.
  - b. Patients should be referred to reproductive specialists.
  - c. Options for fertility preservation
    - 1) Embryo cryopreservation
    - 2) Cryopreservation of unfertilized oocytes – option particularly for patients who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing
    - 3) Ovarian transposition – can be offered when pelvic irradiation is performed as cancer treatment. Should be performed as close to time of radiation as possible
    - 4) Ovarian suppression with LHRH agonists – conflicting evidence as a means of fertility preservation. It can be recommended when proven fertility preservation methods (above) are not feasible and in the setting of young women with breast cancer.
    - 5) Ovarian tissue cryopreservation and transplantation (considered experimental)– does not require ovarian stimulation or sexual maturity and hence may be only method available in children.
  - d. Other considerations
    - 1) Concern that fertility preservation interventions (e.g., ovarian stimulation regimens that increase estrogen levels)
      - a) Ovarian stimulation protocols using letrozole have been developed that may ameliorate this concern

- 2) Studies do not indicate increased cancer recurrence risk as a result of subsequent pregnancy
4. American Society of Reproductive Medicine (ASRM) published guidelines on fertility preservation and reproduction in patients facing gonadotoxic therapies<sup>285</sup>
  - a. Recommend embryo and oocyte cryopreservation as viable options
    - 1) Embryo cryopreservation is available only if there is time before treatment to undergo a cycle of stimulation to obtain eggs; a safe method of ovarian stimulation exists; and requires use of donor sperm.
    - 2) Oocyte cryopreservation should be offered when embryo cryopreservation is not feasible or desired.
    - 3) Recommend that other fertility preservation options be offered in addition to LHRH agonist therapy.
5. LHRH agonists
  - a. NCCN Guidelines<sup>®</sup> state that GnRH agonist therapy (aka LHRH agonists) administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of HR status) may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.<sup>23</sup>
  - b. POEMS trial compared the rate of ovarian failure with goserelin + chemotherapy vs. chemotherapy alone<sup>286,287</sup>
    - 1) Goserelin 3.6 mg SQ every 4 weeks beginning 1 week before initial chemo dose and continued to within 2 weeks before or after the final chemo dose.
    - 2) Ovarian failure defined as absence of menses in the preceding 6 months and levels of FSH in the postmenopausal range
    - 3) Only included patients with HR-negative breast cancer
    - 4) Ovarian failure rate was 8% in goserelin + chemo group vs. 22% in the chemo-alone group (p=0.04)
    - 5) Pregnancy occurred in more women in the goserelin group compared to chemo-alone group (five-year cumulative incidence was 23.1% vs. 12.2%; p=0.04)
    - 6) Nonstatistically significant improvement in DFS (HR=0.55, p=0.09) and OS (HR=0.45, p=0.06)
  - c. PROMISE-GIM6 trial was an open-label, phase 3 study comparing triptorelin + chemotherapy vs. chemotherapy alone in reducing the incidence of early menopause in 282 premenopausal patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy.<sup>288</sup>
    - 1) Triptorelin 3.75 mg IM at least 1 week before starting chemo then every 4 weeks for the duration of treatment
    - 2) Triptorelin every 4 weeks (in addition to tamoxifen) was continued for all patients with hormone-sensitive tumors whose ovarian function had returned during the 12-month period of observation after the end of chemo until ovarian function had been suppressed for at least 2 years.
    - 3) Rate of early menopause (defined as no resumption of menstrual activity and postmenopausal levels of FSH and estradiol for 1 year after the end of chemotherapy) 25.9% in chemo-alone group vs. 8.9% in chemo + triptorelin group (9% CI, -26% to -7.9%; P<.001). Number needed to treat was 6.

- 4) At median follow-up of 7.3 years, no difference in 5-year DFS between treatment arms was observed (83.7% chemo arm vs. 80.5% chemo + triptorelin arm: HR=1.17; 95%CI 0.72-1.92, p=0.519).<sup>289,247</sup>
- 5) There were 3 pregnancies in the chemo arm vs. 8 pregnancies in the control arm. Five-year cumulative incidence estimate of pregnancy was 2.1% in the triptorelin arm and 1.6% in the control arm (p=0.14).<sup>289</sup>
- d. A systematic review and meta-analysis of individual patient-level data found GnRH agonists to be efficacious and safe as temporary ovarian suppression during chemotherapy to reduce the likelihood of chemotherapy-induced premature ovarian insufficiency (POI) and potentially improve future fertility.<sup>290</sup>
  - 1) Included 873 patients from 5 trials. POI rate was 14.1% in GnRH agonist group and 30.9% in control group (adjusted odds ratio, 0.38; 95% CI 0.26-0.57; p<0.001). 10.3% patients in GnRH agonist group had at least one post-treatment pregnancy compared to 5.5% in the control group (p=0.30).
  - 2) There was no significant difference in DFS and OS observed between the groups

**Patient case #4 (continued):** The correct answer is B. YC should be referred to a fertility specialist as soon as possible (prior to the initiation of chemotherapy). According to the ASCO guideline, embryo cryopreservation and cryopreservation of unfertilized oocytes are considered viable options for this patient. Based on the results of the POEMS trial, the use of LHRH agonists, such as goserelin 3.6 mg SQ monthly starting 1 week prior to chemotherapy and continuing until the completion of chemotherapy, is an option for this patient; however, the ASCO guideline considers the use of LHRH agonists to be investigational

Answer A is incorrect because ovarian transposition would only be recommended for patients undergoing irradiation as part of their cancer treatment.

Answer C is not the most appropriate option because ovarian tissue cryopreservation is considered an investigational procedure at this time and therefore, should not be routinely recommended.

Answer D is not the most appropriate answer because LHRH agonists are considered an investigational option according to the ASCO guidelines. Based on the recent results of the POEMS and PROMISE-GIM6 studies, this option could be considered in select patients; however, this is not currently supported by the ASCO or ASRM guidelines.

## BONE METASTASES

**Patient Case #7, continued (ARS 13):** FR is a 37-year-old premenopausal woman who is receiving endocrine therapy for newly diagnosed bone metastases. Since FR has metastatic breast cancer to the bone, the addition of a supportive therapy for bone metastasis would also be discussed with the patient. Her CrCl is within normal limits.

**According to ASCO and NCCN Guidelines®, which of the following is the most appropriate regimen to prevent skeletal-related events (SREs)?**

- A. Denosumab 60 mg SQ every 6 months
- B. Pamidronate 90 mg IV every 6 months
- C. Zoledronic acid 4 mg IV every 12 weeks
- D. Denosumab 120 mg SQ every 12 weeks

### I. Epidemiology<sup>291</sup>

- A. Incidence is high in patients with advanced cancer
  - 1. 50% of breast cancer patients each year develop metastases and 65-75% of these patients develop bone metastases.
- B. Skeletal-related events include:
  - 1. Pathologic fracture
  - 2. Spinal cord compression
  - 3. Surgery to bone
  - 4. Radiotherapy to bone
  - 5. +/- Hypercalcemia

### II. Etiology & Pathophysiology<sup>291</sup>

- A. Adult bones undergo continuous bone remodeling by osteoclasts and osteoblasts. Osteoclasts first break down bone to form a resorption cavity, then this resorption stimulates osteoblasts to form new bone over the resorption cavity.
- B. Radiographically, lesions are described as osteolytic, osteoblastic or mixed.
  - 1. Osteolytic lesions (appear less dense on radiographs)
    - a. Tumor cells activate osteoclast activity without any stimulation of osteoblastic activity.
    - b. Parathyroid hormone related protein (PTHrP; secreted by tumor cells) thought to be important factor in breast cancer bone metastases.
  - 2. Osteoblastic lesions (appear more dense on radiographs)
    - a. Tumor cells stimulate osteoclasts and osteoblasts with the new bone formation being deposited in sites unrelated to the resorption cavities.
    - b. Factors related to osteoblast activation are largely unknown; may be related to similar mechanisms as seen with PTHrP.
  - 3. Mixed lesions (appear to have features of both osteolytic and osteoblastic lesions).

- a. Most common for patients with breast cancer
- 4. Regardless of appearance, excess bone resorption is the hallmark of all malignant bone lesions and compromises the integrity of the bone matrix, resulting in skeletal complications of malignancy.
  - a. Tumor cells secrete factors (autocrine and paracrine) that cause an imbalance in bone resorption and formation.
  - b. Many of these factors are being investigated as potential therapeutic targets.
- C. Biochemical markers:
  - 1. Bone resorption - urinary calcium, acid phosphatase, hydroxyproline, n-telopeptide, and c-telopeptide (useful as study endpoints, but not clinically relevant at this time).
  - 2. Bone formation - bone-specific isoform of alkaline phosphatase (BAP) and procollagen peptide fragments formed during the conversion to mature collagen (investigational only).

### III. Management

- A. ASCO Update on bone modifying agents (BMA) in MBC<sup>292</sup>
  - 1. Patients with evidence of bone metastases should be treated with BMA with concurrent anticancer treatment.
  - 2. One BMA is not recommended over another. Options include:
    - a. Pamidronate 90 mg IV over at least 2 hours Q 3 – 4 weeks OR
    - b. Zoledronic acid (ZA) 4 mg IV over at least 15 minutes Q 12 weeks or Q 3 – 4 weeks OR
    - c. Denosumab 120 mg SQ Q 4 weeks
  - 3. BMA should be continued until evidence of a substantial decline in a patient's general performance status.
  - 4. Analgesic effects of BMAs are modest and they should not be used alone for bone pain.
  - 5. Monitor SCr level with each bisphosphonate dose
  - 6. All patients should have a dental examination and preventative dentistry before using a BMA
- B. NCCN Guidelines® recommend to administer denosumab, ZA, or pamidronate (with calcium and vitamin D supplementation) in addition to chemotherapy or endocrine therapy for stage IV disease if patients meet the following criteria: bone metastasis is present, expected survival is  $\geq 3$  months, and renal function is adequate.<sup>23</sup>
  - 1. Patients should undergo a dental examination with preventative dentistry prior to initiation of therapy
- C. Bisphosphonates<sup>293</sup>
  - 1. Inhibits osteoclast maturation and function – pamidronate and ZA approved for this indication in U.S; others being investigated (e.g., clodronate, ibandronate).
  - 2. Affinity for bone with exposed minerals (areas of osteolysis).
  - 3. Efficacy
    - a. Cochrane review of bisphosphonates and other agents for breast cancer<sup>294</sup>



- 1) For patients with MBC to bone (n=2806), the use of bisphosphonates (ZA IV, pamidronate IV, ibandronate IV, clodronate PO) reduced the risk of SREs by 15% vs. placebo or no bisphosphonates (RR 0.85; 95% CI 0.77 to 0.94).
- b. Optimal duration of therapy unknown
  - 1) Patients generally on these therapies indefinitely; however, with growing concern over longer-term toxicities (especially ONJ; see next section), multiple studies are ongoing to better determine optimal duration of therapy (with ZA).
- c. ZOOM was a noninferiority trial that compared ZA 4 mg IV every 4 weeks vs. every 12 weeks for one year in 425 patients with MBC to bone.<sup>295</sup>
  - 1) Patients were enrolled after completing 12-15 months of monthly ZA.
  - 2) ZA every 12 weeks was noninferior to ZA every 4 weeks
- d. The OPTIMIZE-2 trial was a prospective, randomized, double-blind, phase 3, non-inferiority trial that randomized 416 patients to ZA 4 mg IV either every 4 weeks or every 12 weeks after receiving 9 or more doses of ZA for MBC to bone.<sup>296</sup>
  - 1) Rates of SREs were similar between the two arms and met the criteria for non-inferiority.
  - 2) The incidence of treatment-emergent adverse events was similar between the two arms.
- e. CALGB 70604 (ALLIANCE) was a prospective, randomized, non-inferiority phase 3 study that compared standard dosing (monthly) with longer interval dosing (q 12 weeks) for a total duration of 24 months in bisphosphonate-naïve patients with metastatic breast carcinoma, metastatic prostate carcinoma, or multiple myeloma.<sup>297</sup>
  - 1) 855 patients of a total 1,822 patients had breast cancer
  - 2) Rates of SRE within 2 years after randomization were similar between the two arms, and met the criteria for non-inferiority
  - 3) Dose delays were more common with monthly
  - 4) Authors concluded that use of ZA every 12 weeks is an acceptable treatment option.
  - 5) NCCN Guidelines® recommend ZA every 12 weeks as the optimal schedule

#### Zoledronic Acid Dosing Interval Noninferiority Trials<sup>292</sup>

Study and Interval	Prior IV BMA	Median Time to 1 <sup>st</sup> SRE (months)	Skeletal Morbidity Rate	SRE Rate (%)
CALGB 70604 (ALLIANCE) <sup>297</sup>	No			
• Every 4 weeks		15.7*	0.4*	29.5*
• Every 12 weeks		16.8*	0.4*	28.6*
ZOOM <sup>295</sup>	Yes			
• Every 4 weeks		NR	0.22	15
• Every 12 weeks		NR	0.26	15
OPTIMIZE-2 <sup>296</sup>	Yes			
• Every 4 weeks		NR	0.46	22
• Every 12 weeks		NR	0.50	23.2

\* Entire study population; NR = not reported;

- f. The BISMARCK trial (BISphosphonate therapy directed by bone resorption MARKers) evaluated the biomarker of bone turnover N-telopeptide to guide the administration of ZA either every 4 weeks or as needed based on a marker-directed schedule.<sup>298</sup>
  - 1) Study closed early due to poor accrual and was underpowered for primary outcome but results suggested that adjusted the dosing schedule based on N-telopeptide may be a suboptimal strategy.
- 4. Safety considerations
  - a. Renal dysfunction
    - 1) Patients with impaired renal function should receive reduced doses of ZA when being administered for bone metastases as detailed in the prescribing information<sup>299</sup>
      - a) In patients with CrCl > 60 mL/min, no change in dosage, infusion time, or interval is required
    - 2) Consider dose reductions for pamidronate; but specific recommendations are not available.
    - 3) Lengthening the duration of the infusion has also been noted to help the renal clearance and minimize renal dysfunction related to these compounds.
    - 4) Patients with more severe renal dysfunction (SCr > 3) have not been sufficiently studied.
    - 5) Generally do not dose reduce when treating hypercalcemia of malignancy (HCM).
    - 6) Monitoring
      - a) ASCO recommends checking serum SCr prior to each dose.
      - b) Electrolytes, calcium, phosphorus, magnesium, Hg/HCT should be monitored periodically (interval not suggested).
  - b. Hypocalcemia, hypophosphatemia, hypomagnesemia
    - 1) Guidelines for zoledronic acid (product information) indicate calcium supplementation should be given to all patients (500mg + 400 IU vitamin D daily); would not supplement in a patient with a history of hypercalcemia or extensive bone metastases.
    - 2) No other guidelines for supplementation – close monitoring recommended.
  - c. Myalgias/arthralgias (flu-like symptoms including fever)
    - 1) Usually occurs within 48 hours of infusion with the first and possibly the second dose of bisphosphonate therapy.
    - 2) Usually managed with OTC NSAIDs or acetaminophen and/or transient increases in the patients' current pain medication regimen.
  - d. Osteonecrosis of jaw (ONJ)<sup>300</sup>
    - 1) More than 600 cases now reported with long-term use of pamidronate and ZA; cases have also been reported with oral bisphosphonates, alendronate and risedronate.
    - 2) Common terminology to describe death of bone cells (osteocytes in the cortical bone and cells of the bone marrow organ residing in the hematopoietic compartment of trabecular bone); also destroys bone endothelial cells and vasculature leading to impaired blood flow within the bone; lesions exposing bone in the mouth (e.g., mandible, maxilla) do not heal due to lack of blood flow.

- 3) Usually present as painful, soft tissue swelling and infection, loosening teeth, drainage, exposed bone, or it may be asymptomatic.
- 4) Most cases were diagnosed after dental procedures such as tooth extractions, though a few cases occurred spontaneously.
- 5) Additional risk factors for development of ONJ include concurrent use of chemotherapy, steroids, advanced breast cancer, multiple myeloma, periodontal disease, local trauma including poorly fitting dentures
- 6) Causality is still questionable; many reviews into this phenomenon and whether it is related to bisphosphonate therapy or not (may be related to radiotherapy, chemotherapy, glucocorticoids, other factors).
- 7) Recommendations in product information include:
  - a) Baseline dental examination prior to initiating a bisphosphonate.
  - b) Periodic oral examination during bisphosphonate therapy, limiting invasive dental procedures if at all possible.
- 8) If ONJ does occur, a minimalistic approach appears to be the best course of action. Aggressive surgical debridement delays healing and worsens the condition.
- 9) Refer to MASCC/ISOO/ASCO clinical practice guideline on medication-related osteonecrosis of the jaw for additional details.<sup>301</sup>

D. Denosumab (Xgeva®)<sup>302</sup>

1. FDA approved to prevent SREs in patients with bone metastases from solid tumors and multiple myeloma at a dose of 120 mg SQ every 28 days
2. Denosumab can cause severe symptomatic hypocalcemia. Correct pre-existing hypocalcemia prior to treatment. Monitor levels throughout therapy especially in the first several weeks of initiation. Calcium, magnesium, and vitamin D should be administered as necessary.
3. Denosumab is also marketed as Prolia™ and indicated for postmenopausal osteoporosis at a dose of 60 mg SQ every 6 months.
4. A randomized phase 3 trial compared denosumab to ZA in delaying or preventing SREs in patients with MBC to bone.<sup>303</sup>
  - a. SREs were defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression.
  - b. The primary endpoint of time to first on-study SRE (noninferiority comparison) was met (HR, 0.82; 95% CI, 0.71 to 0.95).
  - c. Secondary endpoints:
    - 1) Time to first on-study SRE was longer with denosumab vs. ZA (superiority comparison, HR, 0.82; 95% CI, 0.71 to 0.95) and the risk of multiple SREs was reduced with denosumab vs. ZA (RR 0.77; 95% CI, 0.66 to 0.89.)
  - d. OS and PFS were similar between the two groups.
  - e. The risk of ONJ, hypocalcemia, and hypophosphatemia with denosumab was similar to ZA.
5. Combined analysis of 3-identically designed phase 3 trials patients comparing ZA and denosumab in patients with breast cancer, prostate cancer, other solid tumors, and multiple myeloma<sup>304</sup>

- a. Denosumab was superior to ZA in delaying time to first on-study SRE by median of 8.21 months, reducing risk of first SRE by 17% (HR 0.83 [95% CI: 0.76 – 0.90];  $p < 0.001$ )
  - b. Disease progression and OS similar between arms
6. Denosumab is administered subcutaneously and there are no major concerns about renal dysfunction as seen with the bisphosphonates however, severe hypocalcemia and hypophosphatemia may occur in patients with renal insufficiency.
- 1) In patients with CrCl < 30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.
- E. A comparison of the cost-effectiveness of monthly ZA, ZA every 3 months, and monthly denosumab in women with breast cancer and skeletal metastases found that the mean costs of denosumab are 9-fold higher than generic ZA every 3 months. Quality-adjusted life-years were nearly identical in all 3 treatment areas. The authors concluded that the optimal treatment would be ZA every 3 months because it is the least costly treatment.<sup>305</sup>

**Patient case #7, continued (ARS 13):**

The correct answer is C. Zoledronic acid 4 mg IV every 12 weeks.

Answer A is incorrect because denosumab 60 mg SQ every 6 months is indicated for osteopenia and osteoporosis and would not be appropriate for a patient with bone metastases.

Answer B is incorrect because pamidronate should be given every 3 – 4 weeks.

Answer D is incorrect because denosumab should be given every 4 weeks.

Baseline renal function should be evaluated for all BMAs and prior to each dose of bisphosphonates. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should be monitored regularly with bisphosphonates. She would continue on a BMA for at least 2 years, or until there is a significant deterioration in her performance status.

## RECOMMENDED READING AND REFERENCES

### Recommended Reading

#### Risk Reduction

Visvanathan K, Fabrian C. J., Bantug E, et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol* 2019;37: published online September 3, 2019. <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/9816>

#### Management of Breast Cancer

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#### Adjuvant Endocrine Therapy

Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2018;37(5):423-38. <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/9326>

#### Adjuvant/Neoadjuvant Chemotherapy

Korde LA, Somerfield MR, Carey LA et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer. *J Clin Oncol* 2021;39:1485-1505. <https://www.asco.org/research/guidelines/quality-guidelines/breast-cancer#/150037>

Denduluri N, Somerfield MR, Eisen A et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update. *J Clin Oncol*. 2021;39:685-693. <https://www.asco.org/research-guidelines/quality-guidelines/guidelines/breast-cancer#/11081>

#### Anti-HER2 Therapy

Giordano SH, Franzoi MAB, Temin S, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2022; published online 5/31/22. <https://ascopubs.org/doi/pdf/10.1200/JCO.22.00519>

#### Therapy for Metastatic Disease

McAndrew NP, Finn, RS. Clinical Review on the Management of Hormone Receptor-Positive Metastatic Breast Cancer. *JCO Oncology Practice* 2022;18(5):319-27. <https://ascopubs.org/doi/pdf/10.1200/OP.21.00384>

#### Fertility Preservation

Donnez J, Dolmans MM. Fertility Preservation in Women. *N Eng J Med* 2017; 377(17):1657-65.

Oktay K, Harvey BE, Partridge AH, et al. Fertility Preservation in Patients with Cancer. *J Clin Oncol* 2018;36(19):1994-2001.

## REFERENCES

1. Burstein HJ HJ, Morrow M. . Malignant Tumors of the Breast, Chapter 106. In: DeVita VT Jr, Lawrence TS, Rosenberg SA et al., eds. *Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011:1401-1446.
2. Lippi G, Mattiuzzi C, Montagnana M. BRCA population screening for predicting breast cancer: for or against? *Annals of Translational Medicine*. 2017;5(13):275-275. doi:10.21037/atm.2017.06.71
3. Tung NM, Boughey JC, Pierce LJ, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society of Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol*. 2019;38(18):2080-2106.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V.2.2022, 03/09/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™* *Surveys & Data, Powered by NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
5. Moyer VA. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Annals of internal medicine*. Feb 18 2014;160(4):271-81. doi:10.7326/m13-2747
6. Hassett MJ, Somerfield MR, Baker ER, et al. Management of Male Breast Cancer: ASCO Guideline. *J Clin Oncol*. 2019;38(16):1849-1863.
7. Wolff AC, Hammond EH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2018;36(20):2105-2122. doi:<https://doi.org/10.1200/JCO.2018.77.8738>
8. Eiger D, Agostinetti E, Saude-Conde R, de Azambuja E. The Exciting New Field of HER2-Low Breast Cancer Treatment. *Cancers (Basel)*. Mar 1 2021;13(5)doi:10.3390/cancers13051015
9. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med*. Jul 7 2022;387(1):9-20. doi:10.1056/NEJMoa2203690
10. American Cancer Society. Breast Cancer Facts & Figures 2019-2020. Atlanta: American Cancer Society I. 2019;
11. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. Feb 16 2008;371(9612):569-78. doi:10.1016/s0140-6736(08)60269-x
12. Zhu H, Lei X, Feng J, Wang Y. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. *The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception*. Dec 2012;17(6):402-14. doi:10.3109/13625187.2012.715357
13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Risk Reduction V.1.2022, 01/31/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™* *Surveys & Data, Powered by NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
14. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. *N Engl J Med*. Dec 7 2017;377(23):2228-2239. doi:10.1056/NEJMoa1700732
15. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. Jul 17 2002;288(3):321-33.
16. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. Apr 19 2007;356(16):1670-4. doi:10.1056/NEJMSr070105
17. Farhat GN, Walker R, Buist DS, Onega T, Kerlikowske K. Changes in invasive breast cancer and ductal carcinoma in situ rates in relation to the decline in hormone therapy use. *J Clin Oncol*. Dec 10 2010;28(35):5140-6. doi:10.1200/jco.2010.29.5121
18. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med*. Feb 5 2009;360(6):573-87. doi:10.1056/NEJMoa0807684

19. McDonald JA, Goyal A, Terry MB. Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. *Current breast cancer reports*. Sep 2013;5(3)doi:10.1007/s12609-013-0114-z
20. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Jun 2006;15(6):1159-69. doi:10.1158/1055-9965.epi-06-0034
21. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. Dec 20 1989;81(24):1879-86.
22. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis Guidelines Version 1.2022, 06/02/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
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24. Visvanathan K, Fabian CJ, Bantug E, et al. Use of Endocrine Therapy for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2019;37doi:10.1200/JCO.19.01472
25. Kusters JP, Gotzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. *The Cochrane database of systematic reviews*. 2003;(2):CD003373. doi:10.1002/14651858.cd003373
26. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of internal medicine*. Nov 17 2009;151(10):716-26, W-236. doi:10.7326/0003-4819-151-10-200911170-00008
27. Oeffinger KC, Fontham ETH, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk. *Jama*. 2015;314(15):1599. doi:10.1001/jama.2015.12783
28. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Annals of internal medicine*. Nov 17 2009;151(10):727-37, W237-42. doi:10.7326/0003-4819-151-10-200911170-00009
29. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. Mar-Apr 2007;57(2):75-89.
30. Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2014: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. Jan-Feb 2014;64(1):30-51. doi:10.3322/caac.21212
31. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. Sep 16 1998;90(18):1371-88.
32. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. Nov 16 2005;97(22):1652-62. doi:10.1093/jnci/dji372
33. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA*. Nov 14 2001;286(18):2251-6.
34. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet*. Jan 25 2003;361(9354):296-300. doi:10.1016/s0140-6736(03)12342-2
35. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *Jama*. Jun 21 2006;295(23):2727-41.
36. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. *Cancer prevention research (Philadelphia, Pa)*. Jun 2010;3(6):696-706. doi:10.1158/1940-6207.capr-10-0076
37. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med*. Jun 23 2011;364(25):2381-91. doi:10.1056/NEJMoa1103507

38. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet*. Mar 22 2014;383(9922):1041-8. doi:10.1016/s0140-6736(13)62292-8
39. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. *J Clin Oncol*. 2019;37(19):1629-1637.
40. Force USPST, Owens DK, Davidson KW, et al. Medication Use to Reduce Risk of Breast Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. Sep 3 2019;322(9):857-867. doi:10.1001/jama.2019.11885
41. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*. Aug 1998;16(8):2672-85.
42. McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. *J Clin Oncol*. Sep 10 2010;28(26):4074-80. doi:10.1200/jco.2010.27.9752
43. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med*. Jul 12 2018;379(2):111-121. doi:10.1056/NEJMoa1804710
44. Sparano JA, Gray RJ, Makower DF, et al. GS1-05 Trial Assigning Individualized Options for Treatment (TAILORx): An Update Including 12-Year Event Rates. Abstract. 12/6/2022 2022;
45. Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. *N Engl J Med*. Jun 20 2019;380(25):2395-2405. doi:10.1056/NEJMoa1904819
46. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. *J Clin Oncol*. Jul 10 2016;34(20):2341-9. doi:10.1200/JCO.2015.63.5383
47. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol*. Jan 2010;11(1):55-65. doi:10.1016/s1470-2045(09)70314-6
48. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. GS3-00. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS)  $\leq$  25: SWOG S1007 (RxPonder). *San Antonio Breast Cancer Symposium*. 2020;Presented December 10, 2020
49. Kalinsky K, Barlow WE, Gralow J, et al. GS2-07. Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes (LN), hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS)  $<$  25 randomized to endocrine therapy (ET) +/- chemotherapy (CT): SWOG S1007 (RxPONDER). *San Antonio Breast Cancer Symposium*. 2021;
50. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med*. Aug 25 2016;375(8):717-29. doi:10.1056/NEJMoa1602253
51. Cardoso F, van't Veer LJ, Poncet C, Lopes Cardoso J, Delaloge S, Pierga JY. MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients. *J Clin Oncol*. 2020;38(15\_suppl):506-506.
52. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *The Lancet Oncology*. 2021;22(4):476-488. doi:10.1016/s1470-2045(21)00007-3
53. Noordhoek I, Treuner K, Putter H, et al. Breast Cancer Index Predicts Extended Endocrine Benefit to Individualize Selection of Patients with HR+ Early-stage Breast Cancer for 10 Years of Endocrine Therapy. *Clinical Cancer Research*. 2021;27(1):311-319. doi:10.1158/1078-0432.ccr-20-2737
54. Bartlett JMS, Sgroi DC, Treuner K, et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen—To Offer More? (aTTom) trial. *Annals of Oncology*. 2019;30(11):1776-1783. doi:10.1093/annonc/mdz289
55. Sgroi DC, Carney E, Zarrella E, et al. Prediction of Late Disease Recurrence and Extended Adjuvant Letrozole Benefit by the HOXB13/IL17BR Biomarker. *JNCI: Journal of the National Cancer Institute*. 2013;105(14):1036-1042. doi:10.1093/jnci/djt146
56. Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. *J Clin Oncol*. 2022;doi:10.1200/JCO.22.00069
57. Donker M, Litiere S, Werutsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma In Situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. *J Clin Oncol*. Nov 10 2013;31(32):4054-9. doi:10.1200/jco.2013.49.5077
58. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet*. Jun 12 1999;353(9169):1993-2000.



59. Margolese RG CR, Julian TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *The Lancet*. 2016;387(10021):849-856. doi:10.1016/S0140-6736(15)01168-X
60. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. Nov 12 2011;378(9804):1707-16. doi:10.1016/s0140-6736(11)61629-2
61. Tung NM, Boughey JC, Pierce LJ, Robson M, Bedrosian I, Dietz JR. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society of Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol*. 2020;38:2080-2106.
62. Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. May 1 2014;32(13):1365-83. doi:10.1200/jco.2013.54.1177
63. Henry NL, Somerfield MR, Abramson VG, et al. Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: American Society of Clinical Oncology Endorsement of Cancer Care Ontario Guideline Recommendations. *J Clin Oncol*. Jul 1 2016;34(19):2303-11. doi:10.1200/JCO.2015.65.8609
64. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med*. Jan 8 2015;372(2):134-41. doi:10.1056/NEJMoa1406281
65. Allison KH, Hammond EH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol*. 2020;38(12):1346-1366.
66. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet*. Dec 9 2009;doi:S0140-6736(09)61523-3 [pii] 10.1016/S0140-6736(09)61523-3
67. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: ASCO Clinical Practice Guideline Update on Ovarian Suppression. *J Clin Oncol*. May 10 2018;37(5):423-438. doi:10.1200/JCO.2015.65.9573
68. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. Aug 27 2011;378(9793):771-84. doi:10.1016/s0140-6736(11)60993-8
69. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. Jul 10 2014;371(2):107-18. doi:10.1056/NEJMoa1404037
70. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. May 2 2001;93(9):684-90.
71. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. Mar 9 2013;381(9869):805-16. doi:10.1016/s0140-6736(12)61963-1
72. Gray RG RD, Handley K et al. . aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *J Clin Oncol*. 2013;31(abstr 5)
73. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol*. Jul 2011;12(7):631-41. doi:10.1016/s1470-2045(11)70122-x
74. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. Jan 29 2015;372(5):436-46. doi:10.1056/NEJMoa1412379
75. Francis PA, Pagani O, Fleming GF, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. *New England Journal of Medicine*. 2018;379(2):122-137. doi:10.1056/NEJMoa1803164
76. Regan MM, Walley BA, Fleming GF, et al. GS2-05. Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): update of the combined TEXT and SOFT trials. 2021;
77. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol*. Feb 20 2016;34(6):611-35. doi:10.1200/JCO.2015.64.3809
78. Castel LD, Hartmann KE, Mayer IA, et al. Time course of arthralgia among women initiating aromatase inhibitor therapy and a postmenopausal comparison group in a prospective cohort. *Cancer*. Jul 1 2013;119(13):2375-82. doi:10.1002/cncr.28016

79. Henry NL, Unger JM, Schott AF, et al. Randomized, Multicenter, Placebo-Controlled Clinical Trial of Duloxetine Versus Placebo for Aromatase Inhibitor- Associated Arthralgias in Early-Stage Breast Cancer: SWOG S1202. *J Clin Oncol*. February 1, 2018 2018;36(4):326 - 332.
80. Hershman DL, Unger JM, Greenlee H, et al. Effect of Acupuncture vs Sham Acupuncture or Waitline Control on Joint Pain Related to Aromatase Inhibitors Among Women with Early-Stage Breast Cancer. *JAMA*. 2018;320(2):167 - 176.
81. Irwin ML, Cartmel B, Gross CP, et al. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J Clin Oncol*. Apr 1 2015;33(10):1104-11. doi:10.1200/JCO.2014.57.1547
82. Howell A CJ, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *The Lancet*. 2005;365(9453):60-62. doi:10.1016/s0140-6736(04)17666-6
83. Group TBIGB-C. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer. *N Engl J Med*. 2005;353(26):2747-2757.
84. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet*. Jan 22 2011;377(9762):321-31. doi:10.1016/s0140-6736(10)62312-4
85. Derks MGM, Blok EJ, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*. 2017;18(9):1211-1220. doi:10.1016/s1470-2045(17)30419-9
86. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. Jan 20 2010;28(3):509-18. doi:10.1200/jco.2009.23.1274
87. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol*. Aug 1 2005;23(22):5138-47. doi:10.1200/JCO.2005.04.120
88. Bliss JM, Kilburn LS, Coleman RE, et al. Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study. *J Clin Oncol*. Mar 1 2012;30(7):709-17. doi:10.1200/jco.2010.33.7899
89. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol*. Nov 2011;12(12):1101-8. doi:10.1016/s1470-2045(11)70270-4
90. Jin H, Tu D, Zhao N, Shepherd LE, Goss PE. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol*. Mar 1 2012;30(7):718-21. doi:10.1200/jco.2010.34.4010
91. Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol*. Apr 20 2008;26(12):1948-55. doi:10.1200/jco.2007.11.6798
92. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol*. Apr 20 2008;26(12):1965-71. doi:10.1200/jco.2007.14.0228
93. Goss PE, Ingle JN, Pritchard KI, et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. *N Engl J Med*. Jul 21 2016;375(3):209-19. doi:10.1056/NEJMoa1604700
94. Gnant M, Fitzal F, Rinnerthaler G, et al. Duration of Adjuvant Aromatase-Inhibitor Therapy in Postmenopausal Breast Cancer. *New England Journal of Medicine*. 2021;385(5):395-405. doi:10.1056/NEJMoa2104162
95. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*. Dec 1 2020;38(34):3987-3998. doi:10.1200/JCO.20.02514
96. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. Dec 5 2022;doi:10.1016/S1470-2045(22)00694-5
97. Giordano SH, Freedman RA, Somerfield MR, Optimal Adjuvant C, Targeted Therapy Guideline Expert P. Abemaciclib With Endocrine Therapy in the Treatment of High-Risk Early Breast Cancer: ASCO Optimal Adjuvant Chemotherapy and Targeted Therapy Guideline Rapid Recommendation Update. *J Clin Oncol*. Dec 8 2021;JCO2102677. doi:10.1200/JCO.21.02677
98. Martin M, Segui MA, Anton A, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. *N Engl J Med*. Dec 2 2010;363(23):2200-10. doi:10.1056/NEJMoa0910320
99. Martin M, Ruiz A, Ruiz Borrego M, et al. Fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus FAC followed by weekly paclitaxel as adjuvant therapy for high-risk, node-negative breast cancer: results from the GEICAM/2003-02 study. *J Clin Oncol*. Jul 10 2013;31(20):2593-9. doi:10.1200/jco.2012.46.9841

100. Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2018;36(23):2433-2443. doi:<https://doi.org/10.1200/JCO.2018.78.8604>
101. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. Feb 4 2012;379(9814):432-44. doi:10.1016/s0140-6736(11)61625-5
102. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. *J Clin Oncol*. Mar 10 2009;27(8):1177-83. doi:10.1200/JCO.2008.18.4028
103. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: the aBC trials - USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol*. August 10, 2017 2017;35(23):2647-2655.
104. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med*. Apr 17 2008;358(16):1663-71. doi:10.1056/NEJMoa0707056
105. Citron ML, Berry DA, Cirincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. Apr 15 2003;21(8):1431-9. doi:10.1200/jco.2003.09.081
106. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med*. Jun 01 2017;376(22):2147-2159. doi:10.1056/NEJMoa1612645
107. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *New England Journal of Medicine*. 2021;384(25):2394-2405. doi:10.1056/NEJMoa2105215
108. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *J Clin Oncol*. 2021;39:1485-1505.
109. Denduluri N, Somerfield MR, Eisen A, et al. Selection of Optimal Adjuvant Chemotherapy Regimens for Human Epidermal Growth Factor Receptor 2 (HER2) -Negative and Adjuvant Targeted Therapy for HER2-Positive Breast Cancers: An American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline. *J Clin Oncol*. Jul 10 2016;34(20):2416-27. doi:10.1200/JCO.2016.67.0182
110. Denduluri N, Somerfield MR, Chavez-MacGregor M, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update. *J Clin Oncol*. 2020;38doi:10.1200/JCO.20.111
111. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol*. Jul 2013;14(8):741-8. doi:10.1016/s1470-2045(13)70225-0
112. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. Sep 21 2013;382(9897):1021-8. doi:10.1016/s0140-6736(13)61094-6
113. Herceptin Hylecta™ package insert. South San Francisco, CA: Genentech, Inc; 2019 February.
114. Cortes J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. May 10 2012;30(14):1594-600. doi:10.1200/jco.2011.37.4207
115. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. Jul 13 2017;377(2):122-131. doi:10.1056/NEJMoa1703643
116. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med*. Dec 5 2018;doi:10.1056/NEJMoa1814017
117. Tolaney SM, Tayob N, Dang C, et al. Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial. *J Clin Oncol*. Jul 20 2021;39(21):2375-2385. doi:10.1200/JCO.20.03398
118. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2016;17(3):367-377. doi:10.1016/s1470-2045(15)00551-3
119. Martin M, Holmes FA, Eljertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncology*. 2017;18:1688-1700. doi:10.1016/S1470-2045(17)30717-9
120. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Annals of Oncology*. 2020;31(9):1223-1230. doi:10.1016/j.annonc.2020.05.012
121. Nerlynx® package insert. Los Angeles, CA: Puma Biotechnology, Inc; 2021 June.

122. Eisen A, Somerfield MR, Accordino MK, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: ASCO-OH (CCO) Guideline Update. *J Clin Oncol*. Mar 1 2022;40(7):787-800. doi:10.1200/JCO.21.02647
123. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *The Lancet*. 2015;386(10001):1353-1361. doi:10.1016/s0140-6736(15)60908-4
124. Gnant M, Pfeiler G, Dubsy PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet*. 2015;386(9992):433-443. doi:10.1016/s0140-6736(15)60995-3
125. Gnant M, Pfeiler G, Steger GG, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2019;20(3):339-351. doi:10.1016/s1470-2045(18)30862-3
126. Coleman R, Finkelstein DM, Barrios C, et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. *The Lancet Oncology*. 2020;21(1):60-72. doi:10.1016/s1470-2045(19)30687-4
127. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*. Feb 2 2005;97(3):188-94. doi:10.1093/jnci/dji021
128. Korde LA, Somerfield MR, Hershman DL, Neoadjuvant Chemotherapy ET, Targeted Therapy for Breast Cancer Guideline Expert P. Use of Immune Checkpoint Inhibitor Pembrolizumab in the Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol*. Apr 13 2022;JCO2200503. doi:10.1200/JCO.22.00503
129. Schmid P, Cortes J, Dent R, et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. *N Engl J Med*. Feb 10 2022;386(6):556-567. doi:10.1056/NEJMoa2112651
130. Perjeta® package insert. South San Francisco, CA: Genentech, Inc; 2020 January.
131. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. Jan 2012;13(1):25-32. doi:10.1016/s1470-2045(11)70336-9
132. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. Sep 2013;24(9):2278-84. doi:10.1093/annonc/mdt182
133. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol*. Aug 1 2005;23(22):5108-16. doi:10.1200/jco.2005.04.005
134. Cataliotti L, Buzdar AU, Noguchi S, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. *Cancer*. May 15 2006;106(10):2095-103. doi:10.1002/cncr.21872
135. Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. *Ann Oncol*. Nov 2001;12(11):1527-32.
136. Semiglazov V KA, Zhiltzova E et al. Exemestane (E) vs tamoxifen (T) as neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer (T2N1-2, T3N0-1, T4N0M0). *J Clin Oncol*. 2005; 23: 530. Abstract.
137. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. *J Clin Oncol*. Jun 10 2011;29(17):2342-9. doi:10.1200/jco.2010.31.6950
138. Dhesy-Thind S, Fletcher GG, Blanchette S, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. June 20 2017;35(18):2062-2081. doi:10.1200/JCO.2016.67.1487
139. Barnett CM ML, Esteva FJ. . Breast Cancer, Chapter 136. In: DiPiro JT, Talbert RL, Yee GC et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 9th ed. New York: McGraw-Hill Professional; 2014.
140. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. Dec 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
141. Rugo HS, Rumble RB, Macrae E, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. *J Clin Oncol*. Sep 1 2016;34(25):3069-103. doi:10.1200/JCO.2016.67.1487

142. Van Poznak C, Somerfield MR, Bast RC, et al. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. Aug 20 2015;33(24):2695-704. doi:10.1200/JCO.2015.61.1459
143. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Oct 2012;23 Suppl 7:viii11-9. doi:10.1093/annonc/mds232
144. Zhou WB, Ding Q, Chen L, Liu XA, Wang S. Toremifene is an effective and safe alternative to tamoxifen in adjuvant endocrine therapy for breast cancer: results of four randomized trials. *Breast Cancer Res Treat*. Aug 2011;128(3):625-31. doi:10.1007/s10549-011-1556-5
145. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med*. Aug 2 2012;367(5):435-44. doi:10.1056/NEJMoa1201622
146. Mehta RS, Barlow WE, Albain KS, et al. Overall Survival with Fulvestrant plus Anastrozole in Metastatic Breast Cancer. *N Engl J Med*. Mar 28 2019;380(13):1226-1234. doi:10.1056/NEJMoa1811714
147. Bergh J, Jonsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol*. Jun 1 2012;30(16):1919-25. doi:10.1200/jco.2011.38.1095
148. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol*. Sep 2013;14(10):989-98. doi:10.1016/s1470-2045(13)70322-x
149. Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *The Lancet*. 2016;388(10063):2997-3005. doi:10.1016/s0140-6736(16)32389-3
150. Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst*. Jan 2014;106(1):djt337. doi:10.1093/jnci/djt337
151. Orserdu package insert. New York, NY: Stemline Therapeutics, Inc; 2023 January.
152. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol*. Oct 1 2022;40(28):3246-3256. doi:10.1200/JCO.22.00338
153. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol*. Feb 15 2003;21(4):588-92.
154. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. Jun 15 2002;20(12):2812-23.
155. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*. Aug 20 2008;26(24):3950-7. doi:10.1200/jco.2007.11.9362
156. O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol*. Mar 2004;15(3):440-9.
157. Trudeau ME, Clemons MJ, Provencher L, et al. Phase II multicenter trial of anthracycline rechallenge with pegylated liposomal doxorubicin plus cyclophosphamide for first-line therapy of metastatic breast cancer previously treated with adjuvant anthracyclines. *J Clin Oncol*. Dec 10 2009;27(35):5906-10. doi:10.1200/jco.2009.22.7504
158. Ewer MS, Martin FJ, Henderson C, Shapiro CL, Benjamin RS, Gabizon AA. Cardiac safety of liposomal anthracyclines. *Semin Oncol*. Dec 2004;31(6 Suppl 13):161-81.
159. Harvey V, Mouridsen H, Semiglazov V, et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. *J Clin Oncol*. Nov 1 2006;24(31):4963-70. doi:10.1200/jco.2005.05.0294
160. Rivera E, Mejia JA, Arun BK, et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer*. Apr 1 2008;112(7):1455-61. doi:10.1002/cncr.23321
161. Valero V, Jones SE, Von Hoff DD, et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol*. Oct 1998;16(10):3362-8.
162. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. Nov 1 2005;23(31):7794-803.

163. Blum JL, Savin MA, Edelman G, et al. Phase II study of weekly albumin-bound paclitaxel for patients with metastatic breast cancer heavily pretreated with taxanes. *Clin Breast Cancer*. Dec 2007;7(11):850-6. doi:10.3816/CBC.2007.n.049
164. Gradishar WJ KD, Cheporov SV et al. . Albumin-bound paclitaxel (ab-pac) versus docetaxel for first-line treatment of metastatic breast cancer (MBC): Final overall survival (OS) analysis of a randomized phase II trial. *J Clin Oncol*. 2011; 29: 275. Abstract.
165. Hennessy BT, Gauthier AM, Michaud LB, Hortobagyi G, Valero V. Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: retrospective analysis of patients treated at M. D. Anderson Cancer Center and a review of capecitabine toxicity in the literature. *Ann Oncol*. Aug 2005;16(8):1289-96. doi:10.1093/annonc/mdi253
166. Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J Clin Oncol*. Apr 01 2005;23(10):2155-61. doi:10.1200/JCO.2005.02.167
167. Cadoo KA, Gajria D, Suh E, et al. Decreased gastrointestinal toxicity associated with a novel capecitabine schedule (7 days on and 7 days off): a systematic review. *NPJ Breast Cancer*. 2016;2:16006. doi:10.1038/nnpjbcancer.2016.6
168. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med*. May 2018;24(5):628-637. doi:10.1038/s41591-018-0009-7
169. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. Mar 12 2011;377(9769):914-23. doi:10.1016/s0140-6736(11)60070-6
170. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol*. Feb 20 2015;33(6):594-601. doi:10.1200/JCO.2013.52.4892
171. Modi S, Seidman AD. Single-Agent Gemcitabine in the Treatment of Advanced Breast Cancer. *Clinical Breast Cancer*. 2004;4:S101-S106. doi:10.3816/CBC.2004.s.002
172. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. Oct 10 2014;32(29):3307-29. doi:10.1200/jco.2014.56.7479
173. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. *N Engl J Med*. Feb 21 2019;380(8):741-751. doi:10.1056/NEJMoa1814213
174. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *New England Journal of Medicine*. 2021;384(16):1529-1541. doi:10.1056/NEJMoa2028485
175. Rugo HS, Bardia A, Marme F, et al. Sacituzumab Govitecan in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2 - Negative Metastatic Breast Cancer. *J Clin Oncol*. 2022;doi:<https://doi.org/10.1200/JCO.22.01002>
176. Llombart-Cussac A, Sledge G, Toi M, et al. PD13-11 Final Overall Survival Analysis of Monarch 2: A Phase 3 trial of Abemaciclib plus Fulvestrant in Patients with Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer. *San Antonio Breast Cancer Symposium*. 2022;
177. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *The Lancet*. 2020;396(10265):1817-1828. doi:10.1016/s0140-6736(20)32531-9
178. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. Jul 21 2022;387(3):217-226. doi:10.1056/NEJMoa2202809
179. Giordano SH, Franzoi MAB, Temin S, et al. Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Guideline Update. *J Clin Oncol*. May 31 2022;JCO2200519. doi:10.1200/JCO.22.00519
180. Giordano SH, Temin S, Chandarlapaty S, et al. Systemic Therapy for Patients with Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(26):2736-2740. doi:<https://doi.org/10.1200/JCO.2018.79.2697>
181. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol*. Jul 1 2005;23(19):4265-74. doi:10.1200/jco.2005.04.173
182. Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. *Cancer*. Sep 1 2007;110(5):965-72. doi:10.1002/cncr.22885



183. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. *J Clin Oncol*. Apr 20 2009;27(12):1999-2006. doi:JCO.2008.19.6618 [pii] 10.1200/JCO.2008.19.6618
184. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*. Jun 20 2006;24(18):2786-92. doi:10.1200/jco.2005.04.1764
185. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol*. Nov 20 2009;27(33):5529-37. doi:JCO.2008.20.6847 [pii] 10.1200/JCO.2008.20.6847
186. Huober J, Fasching PA, Barsoum M, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial. *Breast (Edinburgh, Scotland)*. Feb 2012;21(1):27-33. doi:10.1016/j.breast.2011.07.006
187. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. Jan 12 2012;366(2):109-19. doi:10.1056/NEJMoa1113216
188. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. Feb 19 2015;372(8):724-34. doi:10.1056/NEJMoa1413513
189. Swain SM, Miles D, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *The Lancet Oncology*. 2020;21(4):519-530. doi:10.1016/s1470-2045(19)30863-0
190. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. Feb 10 2015;33(5):442-7. doi:10.1200/JCO.2014.57.1745
191. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol*. Mar 1 2010;28(7):1138-44. doi:10.1200/jco.2009.24.2024
192. Portera CC, Walshe JM, Rosing DR, et al. Cardiac toxicity and efficacy of trastuzumab combined with pertuzumab in patients with [corrected] human epidermal growth factor receptor 2-positive metastatic breast cancer. *Clin Cancer Res*. May 1 2008;14(9):2710-6. doi:10.1158/1078-0432.ccr-07-4636
193. Margenza™ package insert. Rockville, MD: MacroGenics, Inc.; 2020 Dec.
194. Rugo HS, Im S-A, Cardoso F, et al. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer. *JAMA Oncology*. 2021;7(4):573. doi:10.1001/jamaoncol.2020.7932
195. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. Nov 8 2012;367(19):1783-91. doi:10.1056/NEJMoa1209124
196. Krop IE, Kim SB, Gonzalez-Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol*. Jun 2014;15(7):689-99. doi:10.1016/s1470-2045(14)70178-0
197. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med*. Feb 13 2020;382(7):610-621. doi:10.1056/NEJMoa1914510
198. Modi S, Saura C, Yamashita T, et al. PD3-06. Updated results from DESTINY-breast01, a phase 2 trial of trastuzumab deruxtecan (T-DXd) in HER2 positive metastatic breast cancer. *San Antonio Breast Cancer Symposium*. 2020;Presented on December 9, 2020
199. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *New England Journal of Medicine*. 2022;386(12):1143-1154. doi:10.1056/NEJMoa2115022
200. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet*. Dec 6 2022;doi:10.1016/S0140-6736(22)02420-5
201. Moy B, Rumble RB, Come SE, Davidson N, Di Leo A, Gralow J. Chemo- and Targeted Therapy for Patients With HER2-Negative Metastatic Breast Cancer That is Either Endocrine-Pretreated or Hormone Receptor-Negative. *J Clin Oncol*. 2022;40(26):3088-3090.
202. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. Feb 13 2020;382(7):597-609. doi:10.1056/NEJMoa1914609
203. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. *JAMA Oncol*. Dec 1 2022;doi:10.1001/jamaoncol.2022.5610

204. Saura C, Oliveira M, Feng Y-H, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With  $\geq 2$  HER2-Directed Regimens: Phase III NALA Trial. *J Clin Oncol*. 2020;38(27):3138-3149.
205. Saura C, Ryvo L, Hurvitz S, et al. PD13-09 Impact of neratinib on outcomes in HER2-positive metastatic breast cancer patients with central nervous system disease at baseline: Findings from the phase 3 NALA trial. . *San Antonio Breast Cancer Symposium*. 2020;Presented on December 11, 2020
206. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. Apr 20 2008;26(12):1993-9. doi:10.1200/jco.2007.12.3588
207. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat*. Dec 2008;112(3):533-43. doi:10.1007/s10549-007-9885-0
208. Johnston S, Pippen J, Jr., Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. Nov 20 2009;27(33):5538-46. doi:10.1200/jco.2009.23.3734
209. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol*. Jul 20 2012;30(21):2585-92. doi:10.1200/jco.2011.35.6725
210. Burstein HJ, Cirincione CT, Barry WT, et al. Endocrine Therapy With or Without Inhibition of Epidermal Growth Factor Receptor and Human Epidermal Growth Factor Receptor 2: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Fulvestrant With or Without Lapatinib for Postmenopausal Women With Hormone Receptor-Positive Advanced Breast Cancer-CALGB 40302 (Alliance). *J Clin Oncol*. Oct 27 2014;32(35):3959-3966. doi:10.1200/jco.2014.56.7941
211. Ramakrishna N, Anders CK, Lin NU, et al. Management of Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases: ASCO Guideline Update. *J Clin Oncol*. May 31 2022;JCO2200520. doi:10.1200/JCO.22.00520
212. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on Disease Management for Patients with Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(27):2804-2807. doi:<https://doi.org/10.1200/JCO.2018.79.2713>
213. Ibrance® package insert. New York, NY: Pfizer Labs Division of Pfizer Inc; 2019 September.
214. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. Nov 17 2016;375(20):1925-1936. doi:10.1056/NEJMoa1607303
215. Finn RS, Rugo HS, Dieras VC, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer (ER+/HER2- ABC): Analyses from PALOMA-2. *J Clin Oncol*. 2022;40(17)
216. Cristofanilli M TN, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17(4):425-439. doi:10.1016/S1470-2045(15)00613-0
217. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. *N Engl J Med*. Nov 15 2018;379(20):1926-1936. doi:10.1056/NEJMoa1810527
218. Cristofanilli M, Rugo HS, Im S, DJ S. Overall Survival (OS) with Palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): Updated analyses from PALOMA-3. *J Clin Oncol*. 2021;39(suppl 15)
219. Kisqali® package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018 July.
220. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. Nov 03 2016;375(18):1738-1748. doi:10.1056/NEJMoa1609709
221. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol*. Jul 1 2018;29(7):1541-1547. doi:10.1093/annonc/mdy155
222. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *N Engl J Med*. Mar 10 2022;386(10):942-950. doi:10.1056/NEJMoa2114663
223. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. *J Clin Oncol*. 2018;36(24):2465-2472. doi:<https://doi.org/10.1200/JSCO2018.78.9909>



224. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. *N Engl J Med*. Dec 11 2019;doi:10.1056/NEJMoa1911149
225. Slamon DJ, Neven P, Chia SKL, G H. Updated overall survival (OS) results from the phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2- advanced breast cancer (ABC) treated with fulvestrant (FUL) +/- ribociclib (RIB). *J Clin Oncol*. 2021;39(suppl 15)
226. Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *The Lancet Oncology*. 2018;19(7):904-915. doi:10.1016/s1470-2045(18)30292-4
227. Im SA, Lu YS, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. *N Engl J Med*. Jul 25 2019;381(4):307-316. doi:10.1056/NEJMoa1903765
228. Verzenio® package insert. Indianapolis, IN: Eli Lilly and Company; 2020 March.
229. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer. *Clin Cancer Res*. Sep 01 2017;23(17):5218-5224. doi:10.1158/1078-0432.CCR-17-0754
230. Sledge J, G.W., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol*. September 1, 2017 2017;35(25):2875-2884. doi:10.1200/JCO.2017.10.1200/JCO.2017
231. Sledge GW, Jr., Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. *JAMA Oncol*. 2020;6(1):116-124.
232. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. 2017;35:3638 - 3646.
233. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer*. 2019;5:5. doi:10.1038/s41523-018-0097-z
234. Administration USFaD. FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer. Accessed September 15, 2019, 2019. <https://www.fda.gov/media/130787/download>
235. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. Feb 9 2012;366(6):520-9. doi:10.1056/NEJMoa1109653
236. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2daggr. *Ann Oncol*. Dec 2014;25(12):2357-62. doi:10.1093/annonc/mdu456
237. Kornblum N, Zhao F, Manola J, et al. Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. *J Clin Oncol*. 2018;36(16):1556-1563.
238. Bachelot T, Bourcier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol*. Aug 1 2012;30(22):2718-24. doi:10.1200/jco.2011.39.0708
239. Rugo H SL, Beck J, et al. . Prevention of everolimus/exemestane stomatitis in postmenopausal women with hormone receptor-positive metastatic breast cancer using a dexamethasone-based mouthwash: Results of the SWISH trial. . *MASCC/ISOO International Symposium on Supportive Care in Cancer* 2016;Abstract MASCC-0638(Presented June 23, 2016)
240. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med*. Aug 10 2017;377(6):523-533. doi:10.1056/NEJMoa1706450
241. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Annals of Oncology*. 2019;30(4):558-566. doi:10.1093/annonc/mdz012
242. Talzena® package insert. New York, NY: Pfizer Labs Div of Pfizer Inc; 2020 March.
243. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med*. Aug 23 2018;379(8):753-763. doi:10.1056/NEJMoa1802905
244. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. *Annals of Oncology*. 2020;31(11):1526-1535. doi:10.1016/j.annonc.2020.08.2098
245. Piqray® package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation. 2019 May.
246. Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. May 16 2019;380(20):1929-1940. doi:10.1056/NEJMoa1813904

247. Andre F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. *Ann Oncol*. Feb 2021;32(2):208-217. doi:10.1016/j.annonc.2020.11.011
248. Keytruda® package insert. Whitehouse Station, NJ. Merck & Co, Inc; 2020 June.
249. Henry NL, Somerfield MR, Dayao Z, et al. Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update. *J Clin Oncol*. Jun 27 2022;JCO2201063. doi:10.1200/JCO.22.01063
250. Albin A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst*. Jan 6 2010;102(1):14-25. doi:10.1093/jnci/djp440
251. Geiger S, Lange V, Suhl P, Heinemann V, Stemmler HJ. Anticancer therapy induced cardiotoxicity: review of the literature. *Anti-cancer drugs*. Jul 2010;21(6):578-90. doi:10.1097/CAD.0b013e3283394624
252. Stortecky S, Suter TM. Insights into cardiovascular side-effects of modern anticancer therapeutics. *Current opinion in oncology*. Jul 2010;22(4):312-7. doi:10.1097/CCO.0b013e32833ab6f1
253. Senkus E, Jassem J. Cardiovascular effects of systemic cancer treatment. *Cancer treatment reviews*. Jun 2011;37(4):300-11. doi:10.1016/j.ctrv.2010.11.001
254. Armenian SH, Lacchetti C, Barac A, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. Mar 10 2017;35(8):893-911. doi:10.1200/JCO.2016.70.5400
255. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Survivorship. V.1.2022 , 03/30/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
256. Volkova M, Russell III R. Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment. *Current Cardiology Reviews*. 2011;7(4):214 - 220.
257. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline Chemotherapy and Cardiotoxicity. *Cardiovasc Drugs Ther*. Feb 2017;31(1):63-75. doi:10.1007/s10557-016-6711-0
258. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. Jan 1 2009;27(1):127-45. doi:10.1200/jco.2008.17.2627
259. Zinecard package insert. New York, NY: Pfizer Division of Pfizer Inc; 2016 October.
260. Cvetkovic RS, Scott LJ. Dexrazoxane : a review of its use for cardioprotection during anthracycline chemotherapy. *Drugs*. 2005;65(7):1005-24.
261. van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. *The Cochrane database of systematic reviews*. 2011;(6):CD003917. doi:10.1002/14651858.CD003917.pub4
262. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer*. Jun 29 2010;10:337. doi:10.1186/1471-2407-10-337
263. Altena R, Perik PJ, van Veldhuisen DJ, de Vries EG, Gietema JA. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol*. Apr 2009;10(4):391-9. doi:10.1016/s1470-2045(09)70042-7
264. Sheppard RJ, Berger J, Sebag IA. Cardiotoxicity of cancer therapeutics: current issues in screening, prevention, and therapy. *Frontiers in pharmacology*. 2013;4:19. doi:10.3389/fphar.2013.00019
265. Telli ML, Witteles RM. Trastuzumab-related cardiac dysfunction. *Journal of the National Comprehensive Cancer Network : JNCCN*. Feb 2011;9(2):243-9.
266. Herceptin® package insert. South San Francisco, CA: Genentech; 2018 November.
267. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. Mar 15 2001;344(11):783-92.
268. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. Nov 1 2012;30(31):3792-9. doi:10.1200/jco.2011.40.0010
269. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol*. Mar 10 2008;26(8):1231-8. doi:10.1200/jco.2007.13.5467

270. de Azambuja E, Procter MJ, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01). *J Clin Oncol*. Jul 10 2014;32(20):2159-65. doi:10.1200/jco.2013.53.9288
271. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. Oct 6 2011;365(14):1273-83. doi:10.1056/NEJMoa0910383
272. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol*. Dec 1 2009;27(34):5685-92. doi:10.1200/jco.2008.21.4577
273. Lenihan D, Suter T, Brammer M, Neate C, Ross G, Baselga J. Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol*. Mar 2012;23(3):791-800. doi:10.1093/annonc/mdr294
274. Phesgo™ package insert. South San Francisco, CA: Genentech Inc.; 2020 June.
275. Kadcyla® package insert. South San Francisco, CA: Genentech, Inc; 2019 May.
276. Enhertu® package insert. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2019 December.
277. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. *N Engl J Med*. Oct 13 2016;375(15):1457-1467. doi:10.1056/NEJMr1100265
278. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health In Cancer Care. *Journal of the National Comprehensive Cancer Network : JNCCN*. Aug 2013;11 Suppl 3:S1-50; quiz S51.
279. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J. Bone health in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. Sep 2014;25 Suppl 3:iii124-37. doi:10.1093/annonc/mdu103
280. Medicine. IriIo.
281. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*. Jun 10 2014;32(17):1840-50. doi:10.1200/JCO.2013.53.4495
282. Kontos M, Agbaje OF, Rymer J, Fentiman IS. What can be done about hot flushes after treatment for breast cancer? *Climacteric*. Feb 2010;13(1):4-21. doi:10.3109/13697130903291058
283. DA. F. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. Accessed 1/20/2014.
284. Oktay K, Harvey BE, Partridge AH, et al. Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(19):1994-2001. doi:<https://doi.org/10.1200/JCO.2018.78.1914>
285. Ethics Committee of American Society for Reproductive M. Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion. *Fertil Steril*. Nov 2013;100(5):1224-31. doi:10.1016/j.fertnstert.2013.08.041
286. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med*. Mar 5 2015;372(10):923-32. doi:10.1056/NEJMoa1413204
287. Moore HCF, Unger JM, Phillips KA, et al. Final Analysis of the Prevention of Early Menopause Study (POEMS)/SWOG Intergroup S0230. *J Natl Cancer Inst*. Feb 1 2019;111(2):210-213. doi:10.1093/jnci/djy185
288. Del Mastro LB, L; Michelotti, A; et al. Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast Cancer A Randomized Trial. *JAMA*. 2011;306(3):269-276.
289. Lambertini MB, L; Michelotti, A; et al. Long-term results of the phase III PROMISE-GIM6 study evaluating the role of LHRH analog (LHRHa) during chemotherapy (CT) as a strategy to reduce ovarian failure in early breast cancer (BC) patients. *J Clin Oncol*. 2014;32(suppl 26; abstr 105)
290. Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. *J Clin Oncol*. 2018;36(19):1981-1990. doi:<https://doi.org/10.1200/JCO.2018.78.0858>
291. Rizzoli R, Body JJ, Brandi ML, et al. Cancer-associated bone disease. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. Dec 2013;24(12):2929-53. doi:10.1007/s00198-013-2530-3
292. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology - Cancer Care Ontario Focused Guideline Update. *J Clin Oncol*. 2017;35(35):3978 - 3986.
293. Krempien R, Niethammer A, Harms W, Debus J. Bisphosphonates and bone metastases: current status and future directions. *Expert review of anticancer therapy*. Apr 2005;5(2):295-305. doi:10.1586/14737140.5.2.295
294. Wong MH, Stockler MR, Pavlakakis N. Bisphosphonates and other bone agents for breast cancer. *The Cochrane database of systematic reviews*. 2012;2:CD003474. doi:10.1002/14651858.CD003474.pub3
295. Amadori D, Aglietta M, Alessi B, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. *Lancet Oncol*. Jun 2013;14(7):663-70. doi:10.1016/s1470-2045(13)70174-8

296. Hortobagyi GN LA, Chew HK, et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. *J Clin Oncol*. 2014; LBA9500. Abstract.
297. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. *JAMA*. Jan 3 2017;317(1):48-58. doi:10.1001/jama.2016.19425
298. Coleman RE, Wright J, Houston S, et al. Randomized trial of marker-directed versus standard schedule zoledronic acid for bone metastases from breast cancer. *J Clin Oncol*. 2012;30(15 suppl ):511.
299. Zometa® package insert. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017 February.
300. Sarin J, DeRossi SS, Akintoye SO. Updates on bisphosphonates and potential pathobiology of bisphosphonate-induced jaw osteonecrosis. *Oral diseases*. Apr 2008;14(3):277-85. doi:10.1111/j.1601-0825.2007.01381.x
301. Yarom N, Shapiro CL, Peterson DE, et al. Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. *J Clin Oncol*. 2019;37(25):2270-2290.
302. Xgeva® package insert. Thousand Oaks, CA: Amgen, Inc; 2020 June.
303. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. Dec 10 2010;28(35):5132-9. doi:10.1200/jco.2010.29.7101
304. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer*. Nov 2012;48(16):3082-92. doi:10.1016/j.ejca.2012.08.002
305. Shapiro CL, Moriarty JP, Dusetzina S, et al. Cost-Effectiveness Analysis of Monthly Zoledronic Acid, Zoledronic Acid Every 3 Months, and Monthly Denosumab in Women With Breast Cancer and Skeletal Metastases: CALGB 70604 (Alliance). *J Clin Oncol*. December 10, 2017 2017;35(35):3949 - 3955.

# **CANCER-RELATED INFECTIOUS DISEASES**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific management and monitoring plan to address potential infection-related problems that may arise during and following cancer treatment based on current guidelines for treating cancer-related infectious diseases.
2. Discuss short- and long-term treatment goals, including post-therapy, with a patient with cancer-related infectious disease and his or her caregiver.

## FEBRILE NEUTROPENIA

### **Patient Case #1:**

BB is a 55 year-old male with acute myeloid leukemia (AML) s/p CLAG (cladribine and cytarabine) salvage re-induction chemotherapy. On day 9 of hospitalization, he reports chills, shortness of breath, and dizziness to his bedside nurse. Vital signs are obtained and he has a fever of 39.5°C, blood pressure of 82/54 mm Hg (baseline 120/80 mm Hg), heart rate of 124 BPM, and respiratory rate of 26 breaths per minute. Of note, he has an absolute neutrophil count of  $0.1 \times 10^9$  cells/L. A chest X-ray is significant for a right lower lung opacification concerning for pneumonia, and blood and urine culture results are pending. His creatinine clearance is approximately 80 mL/min. He has no allergies and no other past medical history except that his AML induction course was complicated by an extended-spectrum  $\beta$ -lactamase (ESBL) producing *Escherichia coli* bloodstream infection.

**Which of the following is the most appropriate treatment for BB at this time?**

- A. Cefepime + daptomycin
- B. Levofloxacin + linezolid
- C. Aztreonam + vancomycin
- D. Meropenem + vancomycin

### **I. Principles of Febrile Neutropenia (FN)<sup>1-3</sup>**

- A. Neutropenia occurs frequently in patients receiving chemotherapy
- B. Neutropenic patients are at an increased risk of developing serious infections
  - 1. Patients with prolonged, profound neutropenia are at a greater risk for infection
  - 2. Disruption of mucosal barriers following chemotherapy, microbial flora shifts due to severe illness, and antimicrobial use also predispose neutropenic patients to infection
  - 3. Other host factors such as immunodeficiencies associated with the primary malignancy, splenectomy and functional asplenia, and the use of corticosteroids or other immunosuppressive agents play a role in a patient's risk for infection
- C. Signs and symptoms of infection are often absent, but fever remains an early but nonspecific sign
- D. Prevention and management of FN is critical as it is a common source of morbidity and mortality in cancer patients (considered an oncologic emergency)<sup>4,5</sup>
  - 1. Rate of major complications (hypotension, renal/respiratory/heart failure) ~ 25-30%
  - 2. Mortality rate ranges up to 11%
- E. FN occurs in 10-50% of patients with solid tumors, and > 80% of those with a hematologic malignancy
- F. Primary sites of infection are the alimentary tract (mouth, pharynx, esophagus, large and small bowel, and rectum), urinary tract, lungs, sinuses, skin, intravascular device, and bloodstream
  - 1. Only ~ 30% of FN episodes will have a clinically documented infection (defined as either positive culture or clinical sign/symptom such as radiographic evidence)
  - 2. Other common causes of fever: malignancy, medications, blood products, thromboembolic events, engraftment syndrome/neutrophil recovery, cytokine release syndrome

## II. Definition of FN<sup>1,2</sup>

### A. Neutropenia

1. Absolute neutrophil count (ANC)  $< 0.5 \times 10^9$  cells/L, or an ANC  $< 1 \times 10^9$  cells/L with a predicted decrease to  $< 0.5 \times 10^9$  cells/L over the next 48 hours
  - a. Profound neutropenia =  $< 0.1 \times 10^9$  cells/L
  - b. Prolonged neutropenia =  $\geq 7$  days

- B. FN is defined as neutropenia (as above) and a single oral temperature  $\geq 101^\circ\text{F}$  ( $\geq 38.3^\circ\text{C}$ ) or  $\geq 100.4^\circ\text{F}$  ( $\geq 38^\circ\text{C}$ ) sustained over 1 hour

## III. Workup of FN<sup>1-3</sup>

- A. In the absence of an alternative explanation, clinicians should assume that fever in a patient with neutropenia from cancer chemotherapy is the result of an infection
- B. Initial diagnostic approach should maximize the chances of establishing clinical and microbiological diagnoses that may affect antibacterial choice; recommendations are outlined in the table below

### Work-up for FN

Recommendation	ASCO/IDSA <sup>2,3</sup>	NCCN <sup>1</sup>
Complete H&P	✓	✓
CBC with differential	✓	✓
Serum electrolytes	✓	✓
Serum creatinine/BUN	✓	✓
Serum lactate	✓	X
Liver function tests	✓	✓
Blood cultures	At least two sets from different sites (including a peripheral site and one lumen of a CVAD)*	Two sets (one peripheral and one from a CVAD preferred, or two peripheral sets, or two from CVAD if unable to obtain peripheral blood)
Cultures from other sites	Urine, lower respiratory tract, CSF, stool, wounds as clinically indicated	Urine culture (if symptoms or abnormal UA); stool, skin, CVAD site as clinically indicated
Imaging	Chest imaging if signs/symptoms of lower respiratory tract infection	Consider CXR
Viral testing	Nasopharyngeal swab for influenza if sudden onset of signs/symptoms during influenza season	Vesicular/ulcerated lesions on skin/mucosa; nasopharyngeal swab for respiratory viruses if symptoms
Comments	Assessment should occur within 15 minutes after triage for patients presenting with FN within 6 weeks of receiving chemotherapy	Consider UA

✓ = Recommended; X = NOT recommended

\*The Panel recognizes some centers' preference for obtaining both sets peripherally due to the potential for false-positive results

H&P = history and physical; CBC = complete blood count; BUN = blood urea nitrogen; CVAD = central venous access device; CSF = cerebrospinal fluid; CXR = chest X-ray; UA = urinalysis

## IV. Treatment of FN

### A. Treatment Overview<sup>1-3</sup>

1. The goal of initial antibiotic therapy is to prevent morbidity and mortality due to bacterial infections until more data is available to guide subsequent treatment decisions
  - a. The first dose of empiric antibiotic therapy should be administered within 1 hour after triage from initial presentation
  - b. Cultures are usually negative, but broad-spectrum antibacterial therapy is still warranted to cover possible occult infection
2. Most common source of infection is a patient's own flora (gram-negative or gram-positive; fungal pathogens play more of a role in prolonged neutropenia)
  - a. Incidence of gram-positive and gram-negative infections are similar when antibacterial prophylaxis is NOT administered<sup>6</sup>
3. Choice of Empiric Agent
  - a. No single agent or regimen has clearly emerged as superior
    - 1) Effective regimens are bactericidal, cost-effective, and well-tolerated
  - b. Choice of empiric antibiotic should be based on:
    - 1) Patient's risk assessment (see section below)
    - 2) Potential infecting organism (history of resistant pathogens, local susceptibility patterns)
    - 3) Potential sites of infection
    - 4) Need for antipseudomonal coverage
    - 5) Clinical instability (hypotension, organ dysfunction)
    - 6) Drug allergies
    - 7) Recent antibiotic use (including prophylaxis)

#### Common Site-Specific Pathogens<sup>2</sup>

Pulmonary	Oral	Central Catheter
<i>P. aeruginosa</i> <i>S. aureus</i> <i>S. pneumoniae</i> <i>Aspergillus</i> spp. PJP	Gram-Positive Anaerobes HSV <i>Candida</i> spp. <i>Streptococcus</i> spp.	<i>Staphylococcus</i> spp. <i>Streptococcus</i> spp. Gram-Negatives
Skin	Abdominal/Perianal	Diarrhea
<i>Staphylococcus</i> spp. <i>Streptococcus</i> spp. Fungal VZV	Enterobacteriaceae Anaerobes <i>Enterococcus</i> spp.	<i>C. Difficile</i>

PJP = *Pneumocystis jirovecii* pneumonia; HSV = herpes simplex virus; VZV = varicella zoster virus

#### B. Risk Stratification – Low-Risk vs. High-Risk<sup>2, 3</sup>

1. Patients presenting with FN should have a risk assessment for complications of severe infection
  - a. Risk assessment may determine type of empiric antibiotic regimen (PO vs. IV), venue of treatment (outpatient vs. inpatient), and duration of treatment



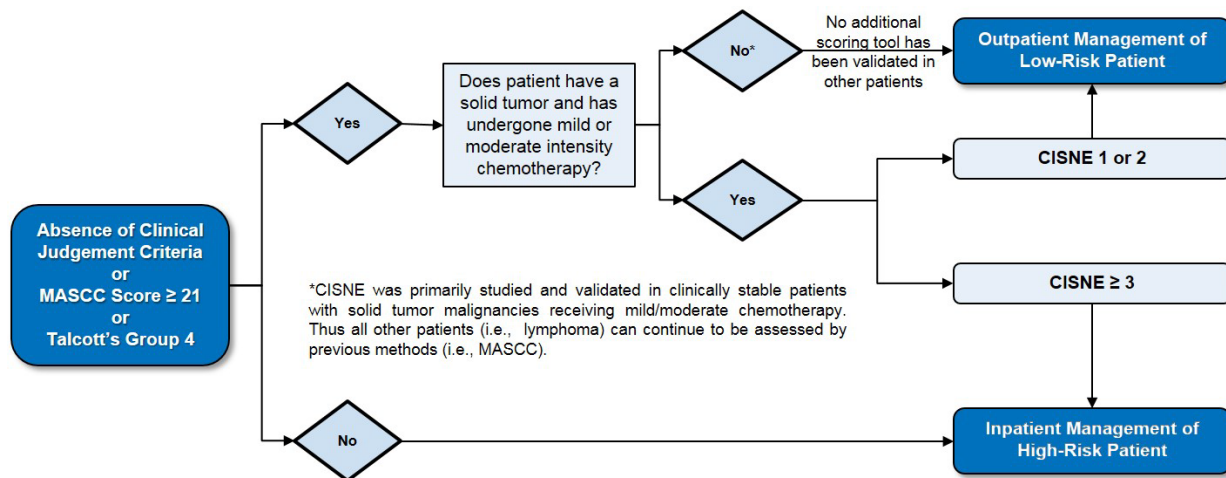
- b. The Multinational Association for Supportive Care in Cancer (MASCC) index or Talcott's rules are guideline-recommended tools for identifying patients who may be candidates for outpatient management<sup>3</sup>
  - 1) MASCC score and Talcott's rules have been found to misclassify some patients as being at low risk (these classifications were derived and validated in heterogeneous samples)<sup>7</sup>; thus, the 2018 update of the ASCO/IDSA guidelines identified a more recently validated tool, the Clinical Index of Stable Febrile Neutropenia (CISNE)<sup>3</sup>
    - a) CISNE may be used to further determine risk of complications among clinically stable solid tumor patients who have received mild/moderate-intensity chemotherapy
  - 2) Refer to individual guidelines for specific criteria for each risk tool
2. Definition of Low-Risk FN<sup>1, 3</sup>
  - a. ASCO/IDSA and NCCN define low-risk patients as anyone who has a MASCC score  $\geq 21$  or CISNE score  $< 3$ , Talcott's group 4, or if the patient has none of the high-risk factors listed below and most of the following (note, this is a summation of the two guidelines combined):
    - 1) Patient is ambulatory/outpatient at time of fever onset
    - 2) No associated acute comorbid illness requiring inpatient therapy or close observation
    - 3) Short duration of severe neutropenia defined as  $ANC \leq 0.1 \times 10^9$  cells/L for  $< 7$  days
    - 4) ECOG performance status of 0 or 1
    - 5) No hepatic or renal insufficiency
3. Definition of High-Risk FN<sup>1, 3</sup>
  - a. ASCO/IDSA and NCCN define high-risk patients as anyone who has a MASCC score  $< 21$  or CISNE score  $\geq 3$ , Talcott's groups 1-3, or if the patient has any of the high-risk factors listed below (note, this is a summation of the two guidelines combined):
    - 1) Patient is hospitalized at time of fever onset
    - 2) Clinically unstable or significant comorbid conditions including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes
    - 3) Prolonged duration of severe neutropenia defined as  $ANC \leq 0.1 \times 10^9$  cells/L for  $\geq 7$  days
    - 4) Hepatic or renal insufficiency (liver function tests  $> 5 \times$  ULN or  $CrCl < 30$  mL/min)
    - 5) Progressive or uncontrolled cancer (leukemia patient not in complete remission or non-leukemia patient with disease progression after  $\geq 2$  cycles of chemotherapy)
    - 6) Patient received alemtuzumab or allogeneic HCT; use of immune and/or targeted treatments
    - 7) Grade 3-4 mucositis

#### C. Treatment of Low-Risk FN<sup>1-3</sup>

1. Low-risk patients may be considered for outpatient management (see figure below)
  - a. ASCO/IDSA recommends the first dose of empiric antibiotics should be administered in the clinic, emergency department or hospital and observed for  $\geq 4$  hours before discharge<sup>3</sup>

- b. NCCN recommends to consider an observation period (2-12 hours) to administer first dose of antibiotics and monitor for reaction, as well as to confirm low-risk status and clinical stability<sup>1</sup>
2. Patients eligible for outpatient management should also meet the following psychosocial and logistic requirements:
  - a. Close proximity (within 1 hour) to clinic or 24-hour hospital facility
  - b. Caregiver at home 24 hours/day
  - c. Adequate home environment including access to a telephone and transportation 24 hours/day
3. Close monitoring and follow-up are also recommended
  - a. Daily monitoring (clinic or home visit) x 72 hours to assess response
4. Antimicrobial regimens recommended for outpatient treatment of FN are outlined in the table below

### Identification of Candidates for Outpatient Management of FN<sup>3</sup>



Taplitz RA et al. *J Clin Oncol.* 2018;36(14):1443-1453.

### Treatment Options for Low-Risk FN Eligible for Outpatient Management

Recommendation	ASCO/IDSA <sup>2, 3</sup>	NCCN <sup>1</sup>
Ciprofloxacin + amoxicillin/clavulanate (or clindamycin if PCN allergic)	✓	✓ (category 1)
Levofloxacin + amoxicillin/clavulanate (or clindamycin if PCN allergic)	✓	X
Levofloxacin	X	✓
Moxifloxacin	X	✓ (category 1)*

✓ = Recommended; X = NOT recommended

\*Insufficient activity against *pseudomonas* spp.; recommended for low-risk patients who may not require pseudomonal coverage

PCN = penicillin

#### D. Treatment of High-Risk FN<sup>1, 2</sup>

1. High-risk patients should be hospitalized to receive empiric IV antibiotic therapy
2. Treatment typically consists of monotherapy with an antipseudomonal beta lactam

- a. Other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to initial therapy for complicated infections or suspected/proven antimicrobial resistance
3. Double coverage of gram-negatives with an aminoglycoside is not routinely recommended based on data from a meta-analysis demonstrating similar survival outcomes with less adverse events in patients receiving beta-lactam monotherapy as compared to double coverage<sup>8</sup>
  - a. Double coverage with a beta-lactam and aminoglycosides should be reserved for patients who are seriously ill/hemodynamically unstable or those with a history or risk factors for resistant gram-negative infections
4. Empiric vancomycin is not a routine component of initial therapy
  - a. Fever is not an indication for vancomycin
  - b. Randomized studies comparing empiric regimens with and without vancomycin have not demonstrated a reduction in duration of fever or mortality<sup>9, 10</sup>
  - c. Linezolid, tedizolid, quinupristin-dalfopristin, tigecycline, televancin, dalbavancin, oritavancin, ceftaroline, and daptomycin also have no proven role in routine empirical coverage
  - d. If empiric vancomycin is initiated, it should be discontinued within 48-72 hours if susceptible bacteria are not identified
  - e. Indications for addition of antibiotics active against resistant gram-positive organisms to the initial regimen are listed in the table below
5. Consider addition of atypical coverage (e.g., azithromycin, doxycycline, or fluoroquinolone) if concerned for community-acquired source
6. Insufficient experience with ceftazidime/avibactam and ceftolozane/tazobactam in treatment of FN

### Empiric Treatment Options for High-Risk FN

Recommendation	IDSA <sup>2</sup>	NCCN <sup>1</sup>
Cefepime	✓	✓ (category 1)
Imipenem/cilastatin	✓	✓ (category 1)
Meropenem	✓	✓ (category 1)
Piperacillin/tazobactam	✓	✓ (category 1)
Ceftazidime*	✓	✓ (category 2B)
Aztreonam (+ vancomycin)**	✓ (for severe PCN allergy)	✓ (for severe PCN allergy)
Indications for Vancomycin		
Hemodynamic instability	✓	✓
Pneumonia	✓	✓ (if MRSA suspected)
Skin and soft tissue infection	✓	✓ (particularly in regions where MRSA is common)
Blood cultures with gram-positive organisms (pending susceptibility)	✓	✓
CVAD entry or site infection	✓ (if clinically serious e.g., rigors with infusion through catheter and cellulitis around catheter entry/exit site)	✓ (clinically apparent, serious infections)
Colonization with MRSA, PCN/CEPH-resistant pneumococci	✓	✓
Severe mucositis (if FQ prophylaxis used and ceftazidime employed as empiric therapy)	✓	X

✓ = Recommended; X = NOT recommended

\*Weak gram-positive coverage and increased breakthrough infections (including pseudomonal resistance) limit use

\*\*Vancomycin must be used in combination with aztreonam for initial therapy due to lack of gram-positive coverage with aztreonam

PCN = penicillin; MRSA = methicillin-resistant *Staphylococcus aureus*; CVAD = central vascular access device; CEPH = cephalosporin;

FQ = fluoroquinolone

# Antibacterial Agent Spectrum and Dosing for Treatment of Low- and High-Risk FN with Normal Organ Function<sup>1</sup>

Agent and Dose	MSSA	MRSA	E. faecalis	E. faecium	S. viridans	Entero-bacteriaceae	P. aeruginosa	Anaerobes
Amoxicillin/clavulanate 500-875 mg PO Q8-12H	+	-	+	-	+	+	-	+
Clindamycin 300-600 mg PO Q6-8H	+	+/-	-	-	+	+/-	-	+/-
Aztreonam 2 g IV Q8H	-	-	-	-	-	+	+	-
Cefepime 2 g IV Q8H	+	-	-	-	+	+	+	-
Ceftazidime 2 g IV Q8H	+/-	-	-	-	+/-	+	+/-	-
Ciprofloxacin 500-750 mg PO Q12H; 400 mg IV Q8-12H	-	-	-	-	-	+	+	-
Levofloxacin 500-750 mg PO/IV Q24H	-	-	-	-	+/-	+	+	-
Imipenem/cilastatin 500 mg IV Q6H	+	-	+	-	+	+	+	+
Meropenem 1-2g IV Q8H or 500 mg IV Q6H	+	-	+	-	+	+	+	+
Piperacillin/tazobactam 4.5 g IV Q6H*	+	-	+	-	+	+	+	+
Vancomycin 15-20 mg/kg IV Q8-12H	+	+	+	-	+	-	-	-
Daptomycin 6-10 mg/kg IV Q24H**	+	+	+	+	+	-	-	-
Linezolid 600 mg IV/PO Q12H	+	+	+	+	+	-	-	-

\* Some institutions use extended infusion strategies

\*\* Lung surfactant inactivates daptomycin and should not be used for pulmonary indications

## **Patient Case #1 (Answer):**

### **Correct Answer = D (meropenem + vancomycin)**

Rationale for correct answer: BB has high-risk febrile neutropenia (e.g., hospitalized at time of fever, clinically unstable with hypotension and new pneumonia, anticipated long duration of profound neutropenia, and acute leukemia not in remission). Antipseudomonal beta-lactam monotherapy is recommended by the ASCO/IDSA and NCCN guidelines for the treatment of high-risk febrile neutropenia. Although cefepime is an appropriate choice, the ASCO/IDSA and NCCN guidelines recommend the addition of empiric vancomycin for patients with febrile neutropenia and hemodynamic instability, pneumonia, skin soft tissue infection, blood cultures with gram-positive organisms, concern for central venous access device infection, or colonization with MRSA or beta-lactam-resistant pneumococci. BB does have an indication for use of vancomycin (pneumonia, hemodynamic instability), so vancomycin should be added to his empiric regimen. Daptomycin is not appropriate given lack of lung penetration in the setting of a pneumonia. Aztreonam + vancomycin should only be reserved for those with a severe penicillin allergy. Lastly, given the history of ESBL *E. Coli*, meropenem is the most appropriate option to cover resistant gram-negative pathogens.

## V. Follow-up of FN<sup>2</sup>

- A. Modifications to empiric regimen should be guided by clinical/microbiological data (see table below)
1. Patients who become/remain hemodynamically unstable after receiving initial doses of standard agents should have their regimen broadened to include coverage for resistant gram-negative, gram-positive and anaerobic bacteria, as well as fungi
- B. Patients with unexplained, persistent fever who are clinically stable rarely require a change to the initial antibiotic regimen
1. Time to defervescence typically 2-7 days (median = 5 days) in patients who have received appropriate empiric antibiotic therapy
  2. No proven advantage to adding vancomycin for persistent or recurrent fever
  3. If an infection is identified, modify antibiotics to target appropriate coverage for the site and the susceptibilities of any isolated organisms
    - a. If vancomycin or other coverage for gram-positive organisms was part of the initial regimen, it can be discontinued after 48-72 hours if no evidence of gram-positive infection

### Recommendations for Modification to Initial Empiric Regimen in FN<sup>1, 2</sup>

Clinical Scenario	Recommendation
Antimicrobial resistance (suspected or confirmed)	Broaden regimen to cover suspected resistant pathogen (e.g., MRSA, ESBLs, VRE, CRE)
Pneumonia	Consider vancomycin or linezolid
Cellulitis	Consider vancomycin, linezolid, or daptomycin
Abdominal symptoms, imaging consistent with neutropenic enterocolitis (typhlitis)	Consider metronidazole or switch to antipseudomonal $\beta$ -lactam with anaerobic coverage
Suspected or identified <i>C. difficile</i>	Add PO vancomycin or fidaxomicin
Esophagitis	Addition of appropriate antifungal/antiviral according to potential/identified pathogen
Sinus/nasal symptoms	Sinus/orbit imaging as indicated, consider ENT evaluation; add vancomycin for periorbital cellulitis, amphotericin B product if suspicious for IFI
Persistent fever $\geq$ 4 days	Evaluation for IFI (empirical vs. preemptive approach)

MRSA = methicillin-resistant *Staphylococcus aureus*; ESBL = extended-spectrum  $\beta$ -lactamase producing enterobacteriaceae; VRE = vancomycin-resistant enterococcus; CRE = carbapenem-resistant enterobacteriaceae; ENT = ear, nose and throat; IFI = invasive fungal infection

- C. Low-risk patients who initiated treatment with either IV or PO antibiotics in a hospital setting and are clinically stable may have their treatment simplified
1. If GI absorption is adequate and the patient is stable, IV antibiotics may be converted to PO
  2. Select patients who have adequate daily follow-up may be transitioned to the outpatient setting for continued antibiotic therapy
    - a. If fever persists or recurs within 48 hours of being an outpatient, readmission is recommended
- D. High-risk patients with persistent fever after 4-7 days despite appropriate coverage (and no other source of infection identified) should be considered for anti-mold coverage (two clinical approaches):
1. Empirical Approach:

- a. Initiation of an antifungal agent at the first possible clinical evidence of fungal infection (persistent fever  $\geq$  4 days of empirical antibiotic therapy)
2. Preemptive Approach:
  - a. More-targeted, less broad treatment of only those patients with additional findings suggestive of IFI (e.g., serologic tests or chest CT findings)
3. Preemptive therapy was associated with increased incidence of invasive fungal disease (without increasing mortality) compared to empirical antifungal therapy, but less exposure to antifungals and decreased costs of antifungals<sup>11</sup>
  - a. IDSA guidelines recommend empiric approach after 4-7 days of persistent fever, but note that a preemptive approach is an acceptable alternative in a subset of patients (clinically stable, negative workup including imaging, serologic markers, etc.)<sup>2</sup>
  - b. NCCN guidelines recommend empiric approach after 4-7 days of persistent fever unless the patient is receiving anti-mold prophylaxis<sup>1</sup>
4. Choice of antifungal agent depends on likely fungal pathogen, toxicities, drug interactions, and cost
  - a. If antifungal prophylaxis has not been given, *Candida* infections are the greatest concern
  - b. If antifungal prophylaxis has been given, azole-resistant *Candida* infections or invasive mold infections are more likely
  - c. Amphotericin B, voriconazole, and caspofungin have been studied in the empirical setting<sup>12, 13</sup>
5. No data to guide empirical/preemptive antifungal in patients receiving anti-mold prophylaxis
  - a. Typical approach involves use of serologic markers and CT findings to guide therapy
    - 1) Example: Patient on posaconazole prophylaxis with persistent or recurrent fever following 4-7 days of antibiotics may continue posaconazole prophylaxis if a full diagnostic workup does not reveal an IFI (assuming serum levels are adequate)
    - 2) Patients who develop bIFIs on anti-mold prophylaxis require an individualized approach similar to salvage treatment (see section below on management of fungal infections); switching to a different class of anti-mold antifungal should be considered

**Patient Case #2:**

BL is a 55-year-old female with breast cancer who is day 10 s/p dose dense AC (doxorubicin and cyclophosphamide). Her chemotherapy cycle has been complicated by culture-negative febrile neutropenia (high-risk due to MASCC score < 21, CISNE score = 3) with chest x-ray findings suggestive of pneumonia. She required hospitalization and received empiric treatment with cefepime for a total of 3 days. She has been afebrile for 48 hours and has now recovered her neutrophil count. Your team would like to know when it would be appropriate to discontinue BL's antibacterials.

**Which of the following is the most appropriate response at this time?**

- A. Discontinue cefepime since neutropenia has resolved
- B. Continue cefepime since BL has not received an adequate course for FN
- C. Continue cefepime since BL has not received an adequate course for pneumonia
- D. De-escalate to oral step-down therapy to complete an adequate course for pneumonia

**VI. Duration of Treatment<sup>1-3</sup>**

- A. In patients with clinically or microbiologically documented infections, duration of treatment is dictated by the site of infection and the identified organism (see table below for minimum suggested treatment; refer to organism or site-specific guidelines for more details)
  - 1. Per IDSA guidelines, antibiotics should continue for the duration of neutropenia<sup>2</sup>
    - a. Alternatively, if appropriate course has completed and signs/symptoms have resolved, patients who remain neutropenic may resume oral fluoroquinolone prophylaxis until ANC recovery
  - 2. In the setting of a documented infection, NCCN guidelines recommend to consider reassessment of empiric gram-negative therapy; de-escalation and duration may be individualized based on<sup>1</sup>:
    - a. Neutrophil recovery
    - b. Rapidity of defervescence
    - c. Specific site of infection and infecting pathogen
    - d. Patient's underlying illness
- B. Although evidence is limited, the traditional approach to duration of antibiotic therapy for fever of unknown etiology in a neutropenic patient is to continue broad-spectrum antibiotics until the patient has been afebrile and ANC is recovered
  - 1. Based on the principle that return of adequate effector cells are necessary to protect the patient
- C. Several small European studies have recently evaluated the safety of de-escalating broad-spectrum antibiotics in patients who become afebrile but remain neutropenic with success<sup>14, 15</sup>
  - 1. These studies are not without limitations and lack generalizability to many centers (i.e., patients did not receive antibacterial prophylaxis)
- D. Data are insufficient to definitively recommend one approach in patients who are clinically stable and afebrile but without neutrophil recovery; the NCCN guidelines recommend the following options with the choice to depend on particular patient details<sup>1</sup>:
  - 1. Discontinue therapy



2. De-escalate to prophylaxis
3. Continue current regimen until neutropenia resolves

#### Suggested Duration of Therapy for Documented Infection

Infection	Recommendation (NCCN) <sup>1</sup>
Skin/soft tissue	5-14 days
Bloodstream infection	
Gram-negative	7-14 days
Gram-positive	7-14 days
<i>S. aureus</i>	≥ 4 weeks after clear cultures (longer if complicated)*
Bacterial sinusitis	7-14 days
Bacterial pneumonia	5-14 days
Fungal infections	
Candida	≥ 2 weeks after clear cultures
Mold (e.g., aspergillus)	≥ 12 weeks
Viral infections	
HSV/VZV	7-10 days (uncomplicated, localized to skin)
Influenza	≥ 5 days (some centers consider longer courses)

\*Encourage ID consult

HSV = herpes simplex virus; VZV = varicella zoster virus

#### **Patient Case #2 (Answer):**

**Correct Answer = D (de-escalate to oral step-down therapy to complete an adequate course for pneumonia)**

Rationale for correct answer: Since the patient has neutrophil recovery, she can be considered similar to a general patient with pneumonia. Thus, it would be appropriate to de-escalate to oral antibiotics to facilitate discharge where she can complete a course at home.

## PREVENTION OF INFECTION

### **Patient Case #3:**

KP is preparing to initiate therapy with rituximab for diffuse large B-cell lymphoma. Her pre-treatment workup included a hepatitis B panel, which revealed a positive surface antibody (HBsAb), a negative surface antigen (HBsAg), and a positive core antibody (HBcAb). All of her liver function test results are within normal limits.

**Which of the following is the most appropriate course of action for KP at this time?**

- A. Initiate entecavir and proceed with rituximab
- B. Initiate lamivudine and proceed with rituximab
- C. Eliminate rituximab therapy and initiate entecavir
- D. Eliminate rituximab therapy and obtain HBV DNA

### **I. Principles of Prevention<sup>1, 2, 16</sup>**

- A. Prevention measures include antimicrobial prophylaxis, use of granulocyte-colony stimulating factors (G-CSFs; see section below), vaccination, handwashing, and minimization of potential exposures to opportunistic pathogens
- B. Risk Assessment<sup>16</sup>
  - 1. Risk of FN should be systematically assessed in patients undergoing cytotoxic chemotherapy for treatment of cancer. Considerations include:
    - a. Patient-related factors such as advanced age, performance status, nutritional status, prior FN episodes, and comorbidities
    - b. Cancer-related factors such as diagnosis (risk greatest with AML/MDS and high-grade lymphomas), cancer stage, remission status, and treatment response
    - c. Treatment-related factors such as type of cytotoxic regimen, dose intensity, degree and duration of GI and/or oral mucositis, and degree and duration of cytopenias
      - 1) Refer to tables below for an overview of infection concerns with select targeted therapies used in the treatment of blood cancers and solid tumors

## Infection Concerns with Select Targeted Therapies in the Treatment of Blood Cancers<sup>1</sup>

Drug Class	Select Agents	Infection Concerns	Recommendations/Comments
Proteasome Inhibitors	Bortezomib Carfilzomib Ixazomib	Respiratory tract infection, VZV, HBV, PML, neutropenia	<ul style="list-style-type: none"> <li>VZV PPx</li> </ul>
BTK Inhibitors	Acalabrutinib Ibrutinib Zanubrutinib	Fungal infection, PJP, VZV, HBV, neutropenia	<ul style="list-style-type: none"> <li>Consider PJP and VZV PPx if additional risk factors</li> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
BCR-ABL TKIs	Bosutinib Dasatinib Imatinib Nilotinib Ponatinib	CMV, VZV, HBV, neutropenia	<ul style="list-style-type: none"> <li>No clear benefit from PPx</li> </ul>
PI3K Inhibitors	Copanlisib Idelalisib	Fungal infection, PJP, CMV, PML, neutropenia	<ul style="list-style-type: none"> <li>Consider PJP PPx</li> <li>Consider monitoring for CMV reactivation</li> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
JAK Inhibitors	Ruxolitinib	HBV, PJP, HSV, VZV, CMV, TB, PML, neutropenia, fungal infection	<ul style="list-style-type: none"> <li>Consider PJP and HSV/VZV PPx</li> <li>Screen/treat HBV &amp; TB</li> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
IDH1 & IDH2 Inhibitors	Enasidenib Ivosidenib	No clear increased infection risk beyond AML	<ul style="list-style-type: none"> <li>Differentiation syndrome may be difficult to distinguish from infection</li> <li>CYP3A4 inhibitors increase drug levels (ivosidenib)*</li> </ul>
BCL2 Inhibitors	Venetoclax	Neutropenia, lymphocytopenia	<ul style="list-style-type: none"> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
FLT3 Inhibitors	Gilteritinib Midostaurin	Neutropenia	<ul style="list-style-type: none"> <li>Differentiation syndrome may be difficult to distinguish from infection</li> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
CD19/CD3 mAb	Blinatumomab	CMV, PJP, HSV, VZV, PML, fungal infection, neutropenia	<ul style="list-style-type: none"> <li>Consider PJP and HSV/VZV PPx</li> </ul>
CD20 mAb	Obinutuzumab Ofatumumab Rituximab	HBV, HCV, HSV, VZV, PML, neutropenia, low IgG, lymphocytopenia	<ul style="list-style-type: none"> <li>Consider HSV/VZV PPx</li> <li>Screen/treat HBV</li> <li>Consider PJP PPx if additional risk factors</li> </ul>
CD30 mAb	Brentuximab vedotin	PML, CMV, VZV, neutropenia, PJP, HSV	<ul style="list-style-type: none"> <li>Consider monitoring for CMV reactivation</li> <li>Consider PJP and HSV/VZV PPx</li> </ul>
CD38 mAb	Daratumumab	<i>Listeria</i> , HBV, HSV, VZV, CMV, PJP, neutropenia,	<ul style="list-style-type: none"> <li>HSV/VZV PPx</li> <li>Consider PJP PPx</li> </ul>
CD52 mAb	Alemtuzumab	HSV, VZV, CMV, PML, <i>Listeria</i> , <i>Nocardia</i> , BK, fungal infection, TB	<ul style="list-style-type: none"> <li>PJP PPx if CD4 &lt; 200</li> <li>HSV/VZV PPx</li> <li>Consider monitoring for CMV reactivation</li> <li>Screen/treat HBV &amp; TB</li> </ul>

\*Drug-drug interaction information obtained from Product Information

PNA = pneumonia; VZV = varicella zoster virus; HBV = hepatitis B virus; PML = progressive multifocal leukoencephalopathy; PPx = prophylaxis; BTK = bruton tyrosine kinase; PJP = pneumocystis jirovecii pneumonia; TKIs = tyrosine kinase inhibitors; CMV = cytomegalovirus; PI3K = phosphatidylinositol-3-kinase; JAK = janus kinase; IDH = isocitrate dehydrogenase; AML = acute myeloid leukemia; BCL2 = B-cell lymphoma-2; FLT3 = FMS-like tyrosine kinase; TB = tuberculosis; mAb = monoclonal antibody; HSV = herpes simplex virus

## Infection Concerns with Select Targeted Therapies in the Treatment of Solid Tumors<sup>1</sup>

Drug Class	Select Agents	Infection Concerns	Recommendations/Comments
BRAF kinase inhibitors	Dabrafenib Encorafenib Vemurafenib	Neutropenia, lymphocytopenia	<ul style="list-style-type: none"> <li>May develop drug fever</li> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
MEK kinase inhibitors	Cobimetinib Trametinib	Neutropenia, lymphocytopenia	<ul style="list-style-type: none"> <li>May develop drug fever</li> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
Multi-target protein kinase inhibitors	Sorafenib	Neutropenia, lymphocytopenia, delayed wound healing	<ul style="list-style-type: none"> <li>CYP3A4 inhibitors increase drug levels*</li> </ul>
VEGF inhibitors/ receptor inhibitor	Bevacizumab Aflibercept Ramucirumab	Neutropenia, increased risk of bowel perforation, poor wound healing	<ul style="list-style-type: none"> <li>No clear benefit from PPx</li> </ul>

\*Drug-drug interaction information obtained from Product Information

MEK = mitogen-activated extracellular signal-regulated kinase; VEGF = vascular endothelial growth factor; PPx = prophylaxis

## II. Bacterial Prophylaxis<sup>1, 2, 16</sup>

### A. Antibacterial prophylaxis with fluoroquinolones is well-studied

#### 1. GIMEMA Infection Program Study – Bucaneve et al<sup>17</sup>

- Study Design: Prospective, multicenter, double-blind, randomized, placebo-controlled
- Participants: Patients (N=760) at risk for chemotherapy-induced neutropenia (during hospitalization) lasting > 7 days (49% with acute leukemia, 51% lymphoma/solid tumors)
- Interventions: Levofloxacin 500 mg PO daily vs. placebo until resolution of neutropenia
- Results:
  - Primary endpoint of incidence of fever in 65% vs. 85% (p=0.001)
  - Lower rate of microbiologically documented infections, bacteremias, and single agent gram-negative bacteremias in favor of levofloxacin group
  - No difference in mortality (though underpowered for this outcome) or tolerability
- Significance: Guidelines recommend considering antibacterial prophylaxis in high-risk patients (neutropenia > 7 days) citing this data as supporting evidence

#### 2. SIGNIFICANT Trial – Cullen et al<sup>18</sup>

- Study Design: Prospective, multicenter, double-blind, randomized, placebo-controlled
- Participants: Patients (N=1565) receiving cytotoxic chemotherapy as an outpatient for solid tumors (87%) or lymphoma (13%) and at risk for bacterial infections
- Interventions: Levofloxacin 500 mg PO daily vs. placebo x 7 days during the expected neutropenic period
- Results:
  - Primary endpoint of incidence of fever in 10.8% vs. 15.2% (p=0.01)

- 2) Lower rate of probable infections (34.2% vs. 41.5%;  $p=0.004$ ) and hospitalization (15.7% vs. 21.6%;  $p=0.004$ )
- 3) No difference in severe infection or infection-related deaths; more patients had minor GI symptoms and rash with levofloxacin compared with placebo
- e. Significance: Number of patients needed to treat = 70 (per chemotherapy cycle) to prevent one febrile episode<sup>19</sup>; these findings, along with the concerns below, have factored into guideline recommendations against antibacterial prophylaxis in low-risk patients with expected duration of neutropenia < 7 days
3. Several meta-analyses have produced conflicting results with some evaluations demonstrating an infection-related mortality benefit while others have not produced similar results<sup>20-22</sup>
- B. Role for antibacterial prophylaxis remains controversial due to inconclusive benefit in the reduction of incidence/severity of FN episodes and mortality, as well as concerns for increased bacterial resistance and new FDA warnings (for fluoroquinolones) related to potential adverse events<sup>23</sup>
  1. Although randomized, controlled trials have not demonstrated a mortality benefit, NCCN, the Infectious Diseases Society of America (IDSA), and the American Society of Clinical Oncology (ASCO)/IDSA guidelines support consideration of prophylaxis if anticipated duration of neutropenia is > 7 days<sup>1, 2, 16</sup>

### III. Fungal Prophylaxis<sup>1, 2, 16</sup>

- A. Primary prophylaxis of fungal infections should only be considered in “high-risk” patients with neutropenia, such as those with:
  1. Profound, prolonged neutropenia ( $ANC < 0.1 \times 10^9$  cells/L for at least 7 days)
  2. Acute leukemia patients receiving intensive remission induction therapy
- B. Agent Selection
  1. Clinicians should differentiate the risk of invasive candidiasis from invasive mold infections
  2. Selection of agent determined by the cancer diagnosis and/or chemotherapy plan, with options including azoles, amphotericin B products, and echinocandins
    - a. Drug interactions and toxicity profiles are also important considerations (see section below regarding practical use of antifungal agents in oncology patients)
- C. Reduction in all-cause mortality observed with mold-active prophylaxis in AML/MDS induction
  1. PO1899 Study – Cornely et al<sup>24</sup>
    - a. Study Design: Prospective, multicenter, randomized, open-label, non-inferiority
    - b. Participants: Patients (N=602) expected to have  $ANC < 0.5 \times 10^9$  cells/L for  $\geq 7$  days resulting from induction chemotherapy for newly diagnosed or 1<sup>st</sup> relapse of AML/MDS
    - c. Intervention: Randomized to receive posaconazole suspension 200 mg PO TID or either fluconazole suspension 400 mg PO daily or itraconazole solution 200 mg PO BID beginning 24 hours after the last anthracycline dose and continuing until neutropenia recovery and complete remission (CR); patients followed for 100 days
    - d. Results:
      - 1) Primary endpoint of incidence of proven/probable invasive fungal infection (IFI) 2% with posaconazole vs. 8% with fluconazole/itraconazole ( $p<0.001$ )

- a) Number needed to treat in order to prevent 1 IFI = 16
- 2) Kaplan–Meier analysis of the time to death from any cause at the end of the 100-day period demonstrated a survival benefit for patients treated with posaconazole over fluconazole or itraconazole (p=0.04)
  - a) Number needed to treat in order to prevent 1 death = 14
- 3) Treatment-related adverse events similar between groups
- e. Significance: Posaconazole was more effective at preventing IFIs than fluconazole or itraconazole in patients with AML/MDS receiving induction chemotherapy and improved overall survival
- D. Isavuconazole is an attractive candidate for mold prophylaxis given tolerability and drug interaction profile (less CYP3A4 inhibition than posaconazole), but a high rate of breakthrough invasive fungal infections (bIFIs) was observed in a recent retrospective comparison of isavuconazole with voriconazole/posaconazole in patients with hematologic malignancies or HCT<sup>25</sup>
  - 1. Additional investigation is warranted for isavuconazole in the primary prophylaxis setting and is currently an off-label indication
- E. ASCO/IDSA guidelines recommend an oral triazole or parenteral echinocandin in populations when the risk of candida infections is > 10% and a mold-active triazole when the risk of invasive aspergillosis is > 6%<sup>16</sup>; NCCN recommends posaconazole specifically for AML/MDS induction/reinduction (category 1), and fluconazole, an echinocandin, or amphotericin B products for acute lymphoblastic leukemia (ALL) patients<sup>1</sup>
- F. Secondary prophylaxis of fungal infections in adult oncology patients<sup>1, 2</sup>
  - 1. IDSA guidelines recommend antifungal prophylaxis in patients with prior IFI who are expected to be neutropenic for ≥ 14 days
  - 2. NCCN guidelines recommend antifungal prophylaxis in patients with prior IFI during subsequent cycles of chemotherapy or hematopoietic cell transplantation (HCT)
  - 3. Antifungal should be given for duration of immunosuppression (even if neutropenia resolved)

#### IV. Viral Prophylaxis<sup>1, 16</sup>

- A. Herpes Simplex Virus (HSV)
  - 1. Seropositivity is an important consideration in patients receiving chemotherapy who may develop neutropenia and mucositis
    - a. HSV infections primarily occur as a result of reactivation of latent virus
    - b. Disseminated disease is uncommon, but reactivation may be associated with mucosal damage, increased pain, decreased oral intake, and increased risk of superinfection
  - 2. NCCN and ASCO/IDSA guidelines recommend antiviral prophylaxis against HSV in patients undergoing leukemia induction
    - a. Acyclovir, famciclovir, or valacyclovir are appropriate choices
    - b. Prophylaxis may also be considered in other patients with hematologic malignancies (depending on degree of immunosuppression; treatment modalities and type of malignancy affect risk level)
- B. Varicella Zoster Virus (VZV)<sup>1</sup>
  - 1. Highest reactivation risk among those with impaired cellular immunity (e.g., allogeneic HCT)

2. NCCN guidelines recommend consideration of VZV prophylaxis in other patients at intermediate risk for viral reactivation, such as those with prolonged neutropenia, those receiving T-cell depleting agents (e.g., fludarabine, alemtuzumab), or those receiving proteasome inhibitors
  - a. Agents listed above for HSV prophylaxis are also appropriate for VZV prophylaxis

#### V. **Antipneumocystis Prophylaxis**<sup>1, 16</sup>

- A. ASCO/IDSA guidelines recommend prophylaxis of *Pneumocystis jirovecii* pneumonia (PJP) in patients receiving chemotherapy regimens with > 3.5% risk for developing PJP (e.g., ≥ 20 mg prednisone equivalents daily for ≥ 1 month or purine analog-based therapy)<sup>16</sup>
- B. NCCN guidelines recommend PJP prophylaxis in patients with ALL (category 1) throughout anti-leukemic therapy, as well as those who have received alemtuzumab, phosphoinositide 3-kinase (PI3K) inhibitors, ≥ 20 mg prednisone equivalents daily for ≥ 4 weeks, or concomitant temozolomide with radiation.
  1. Prophylaxis in those receiving purine analogs or other T-cell depleting agents should be considered<sup>1</sup>
- C. Trimethoprim/sulfamethoxazole (TMP/SMX) preferred agent by both NCCN and ASCO/IDSA<sup>1, 16</sup>
  1. Alternatives such as dapsone, aerosolized or IV pentamidine, and atovaquone are also options

#### VI. **Hepatitis B Virus (HBV) Screening and Management**<sup>1, 26-28</sup>

- A. Reactivation
  1. Patients with cancer are at an increased risk for hepatitis B reactivation due to immunosuppressive treatment regimens (e.g., anti-CD20 monoclonal antibodies) and the underlying malignancy. Complications may range from asymptomatic reactivation and self-limited hepatitis to fulminant liver failure and death.
  2. A substantial portion of patients with newly diagnosed cancer and concurrent HBV are unaware of their viral infection at the time of cancer diagnosis, and many have no identifiable risk factors<sup>29</sup>
  3. Recent meta-analysis reported that HBcAb positivity was correlated with an increased incidence of rituximab-associated HBV reactivation<sup>30</sup>
  4. NCCN guidelines recommend HBsAg and HBcAb testing in all cancer patients expected to receive immunosuppressive therapy (IST) or chemotherapy. If one of these screening tests is positive, quantitative viral load by PCR should be performed.<sup>1, 26</sup>
    - a. HBsAb positivity is of limited value due to the widespread use of the HBV vaccine
    - b. HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression
    - c. Patients receiving intravenous immunoglobulin (IVIG) may be HBcAb+ following IVIG therapy
  5. ASCO Provisional Clinical Opinion Update from 2020 also recommends screening all patients anticipating systemic anticancer therapy<sup>28</sup>
  6. Anticancer therapy should not be delayed if screening is not complete at time of therapy initiation<sup>28</sup>
- B. Prophylaxis
  1. Prophylactic antiviral therapy should be considered for any patient who is HBsAg or HBcAb positive and receiving anticancer therapy<sup>1, 26, 28</sup>
    - a. ASCO Provisional Clinical Opinion Update recommends antiviral therapy in the following cases<sup>28</sup>:

- 1) Patients with chronic HBV (HBsAg+) receiving any systemic anticancer therapy should receive antiviral prophylactic therapy during and for a minimum 12 months following anticancer therapy
  - 2) Patients with past HBV infection (HBcAb+) undergoing anticancer therapies associated with a high risk of HBV reactivation (e.g., anti-CD20 monoclonal antibodies or HCT), should receive antiviral prophylaxis during and for a minimum 12 months following anticancer therapy
  - 3) Patients with past HBV undergoing other systemic anticancer therapies not clearly associated with a high risk of HBV reactivation should be monitored with HBsAg and alanine aminotransferase (ALT) during cancer treatment; antiviral therapy should commence if HBV reactivation occurs
- b. NCCN Guidelines for B-Cell Lymphomas recommends prophylactic antiviral therapy (for cases of HBsAg+; also preferred for HBsAg-/HBcAb+ cases) or preemptive antivirals upon detection of an increasing viral load (an option for HBsAg-/HBcAb+ cases with concurrent high levels of HBsAb)<sup>26</sup>
  - c. Entecavir and tenofovir are the preferred agents according to the NCCN Guidelines and the ASCO Provisional Clinical Opinion Update<sup>1, 28</sup>
    - 1) The choice of agent is dependent upon renal function, type of chemotherapy planned and clinical status of the patient
- C. Monitoring
1. Monitor hepatitis B viral load with PCR monthly through treatment and every 3-6 months thereafter. If the viral load is undetectable, then continue the prophylactic treatment. If the viral load increases or fails to decrease, consult an expert in hepatitis treatment.<sup>26</sup>
- D. Vaccination against HBV should be strongly considered in HBV-naïve patients

## **VII. Hepatitis C Virus (HCV) Screening and Management<sup>1</sup>**

- A. NCCN guidelines recommend HCV testing in all cancer patients expected to receive immunosuppressive IST or chemotherapy
- B. Data are limited regarding the treatment of HCV in patients with cancer. However, it is generally not recommended to administer HCV treatment and cancer treatment concurrently.
  1. Infectious diseases consult is necessary to evaluate the use of concomitant or sequential anti-HCV and cancer therapy
  2. Monitoring of ALT levels and HCV viral load monthly, or as clinically indicated, should be initiated as part of surveillance

**For information regarding prophylaxis in HCT as well as CMV monitoring and management, please refer to the “Hematopoietic Stem Cell Transplantation” chapter.**



## Summary of Guideline Recommendations for Antimicrobial Prophylaxis in Non-HCT Patients\*

	ASCO/IDSA <sup>16</sup>	NCCN <sup>1</sup>
<b>ANTIBACTERIAL PROPHYLAXIS</b>		
Population	<i>Consider</i> for high-risk (ANC $\leq 0.1 \times 10^9$ cells/L for > 7 days)	<i>Consider</i> for intermediate to high-risk (ANC $\leq 1 \times 10^9$ cells/L for > 7 days)
Preferred Agent	Fluoroquinolone	Fluoroquinolone
Alternative	Cefpodoxime	TMP/SMX or 3 <sup>rd</sup> generation CEPH
Duration	During periods of expected neutropenia	During periods of expected neutropenia
Comments	---	Use of fluoroquinolone prophylaxis precludes use as empiric treatment for FN
<b>ANTIFUNGAL PROPHYLAXIS</b>		
Population	Populations with a risk of candidiasis > 10% or risk of invasive aspergillosis > 6%	<i>Consider</i> for ALL, MDS/AML (neutropenic)
Preferred Agent	Oral triazole or parenteral echinocandin; depending on level of risk	Posaconazole (category 1) for AML/MDS; fluconazole, echinocandin, or AmB for ALL
Alternative	---	Voriconazole, fluconazole, echinocandin, or AmB (for AML/MDS)
Duration	During periods of neutropenia	During periods of neutropenia
Comments	---	Role of antifungal prophylaxis in consolidation chemotherapy has not been adequately evaluated; consider drug interactions and toxicity profiles
<b>ANTIVIRAL PROPHYLAXIS</b>		
Population	Acute leukemia (HSV)	Acute leukemia (HSV); alemtuzumab (HSV/VZV); proteasome inhibitors (VZV)
Preferred Agent	Acyclovir, famciclovir, or valacyclovir	Acyclovir or equivalent
Alternative	---	---
Duration	During active therapy	During active therapy
Comments	---	<i>Consider</i> HSV prophylaxis in lymphoma, myeloma, and CLL (treatment modalities and type of malignancy affect risk level), purine analog therapy
<b>ANTIPNEUMOCYSTIS PROPHYLAXIS</b>		
Population	Chemotherapy regimens with > 3.5% risk for developing PJP (e.g., $\geq 20$ mg prednisone equivalents daily for $\geq 1$ month or purine analog-based therapy)	ALL patients; receipt of alemtuzumab, select PI3K inhibitors $\pm$ rituximab, $\geq 20$ mg prednisone equivalents daily $\geq 4$ weeks, or concomitant temozolomide with XRT
Preferred Agent	TMP/SMX	TMP/SMX
Alternative	Dapsone <sup>†</sup> , aerosolized pentamidine, atovaquone	Dapsone <sup>†</sup> , aerosolized/IV pentamidine, atovaquone
Duration	During active therapy	During active therapy; until CD4 > 200 if receiving alemtuzumab
Comments	---	<i>Consider</i> in those receiving purine analogs or other T-cell depleting agents

\*Information regarding infection risk with emerging immune-targeted therapies is continuously evolving. Refer to the FDA-approved labeling for individual agents for further information on infectious risk and prophylactic/monitoring strategies.

<sup>†</sup>Assess G6PD levels prior to initiation

TMP/SMX = trimethoprim/sulfamethoxazole; CEPH = cephalosporin; AmB = amphotericin B; CLL = chronic lymphocytic leukemia; PI3K = phosphoinositide 3-kinase; XRT = radiation

**Patient Case #3 (Answer):**

**Correct Answer = A (Initiate entecavir and proceed with rituximab)**

Rationale for correct answer: Prophylactic antiviral therapy should be considered in patients who are HBsAg or HBcAb positive and receiving anticancer therapy. Although prophylaxis is warranted, treatment with rituximab can begin as planned. Entecavir is preferred over lamivudine due to concerns of resistance. An HBV DNA should be obtained for monitoring purposes, but there is no indication to eliminate rituximab at this time.

## CLOSTRIDIODES DIFFICILE INFECTION

### **Patient Case #4:**

AP is a 68-year-old female with multiple myeloma who is receiving treatment with lenalidomide, bortezomib, and dexamethasone (RVD). She presents to the infusion clinic today for her bortezomib injection and reports diarrhea with 12 bowel movements in the last 24 hours. WBC =  $25 \times 10^9$  cells/L. She has a temperature of 39.1°C, BP 80/43, and SCr 1.65 mg/dL (baseline 0.5 mg/dL). An ileus was detected on CT abdomen/pelvis. She has a history of receiving levofloxacin for pneumonia two weeks ago. Workup includes testing for *C. difficile* toxin and antigen, which were positive.

**Which of the following is the most appropriate treatment for AP at this time?**

- C. Vancomycin 500 mg PO and rectally Q6H + metronidazole 500 mg IV Q8H
- D. Vancomycin 125 mg PO and rectally Q6H + metronidazole 500 mg PO Q8H
- E. Metronidazole 500 mg PO Q8H
- F. Fidaxomicin 200 mg PO BID

### **I. *Clostridioides Difficile* Infection (CDI) – Overview<sup>31</sup>**

- A. *C. difficile* is a multidrug resistant bacteria; surpassed MRSA as leading cause of nosocomial infections<sup>32</sup>
- B. Immunocompromised patients experience a high incidence of CDI, ranging from 6-33% in the hematology/oncology population<sup>33</sup>
  - 1. Hematology/oncology population frequently experiences diarrhea not only related to CDI, but also due to antibiotic prophylaxis, chemotherapy, mucositis, etc.
  - 2. High rate of asymptomatic colonization of *C. difficile* in this population may lead to over-diagnosis if overly sensitive tests are used for diagnosis
- C. CDI characterized by secretory diarrhea caused by toxin produced by the *C. difficile* anaerobic organism
  - 1. Can be life threatening (pseudomembranous colitis)
  - 2. Rate and severity of CDI in the United States may be increasing, partly because of the emergence of a more virulent strain of *C. difficile*<sup>34, 35</sup>
- D. Risk factors for CDI include advanced age, prolonged hospitalization, disruption of intestinal microbiota by antibiotics, chemotherapy, GI surgery/manipulation of the GI tract, and proton pump inhibitors (PPIs)

### **II. Diagnosis of CDI<sup>31</sup>**

- A. Perform testing in patients with unexplained and new-onset diarrhea ( $\geq 3$  unformed stools in 24 hours)
- B. Various diagnostic methods are outlined in the IDSA/Society for Healthcare Epidemiology of America (SHEA) guidelines<sup>31</sup>
- C. Do not perform repeat testing (within 7 days) during the same episode of diarrhea
  - 1. Do not test stool from asymptomatic patients, or those who have received laxatives recently

### **III. Prevention of CDI<sup>31</sup>**

- A. Patients with CDI should be housed in a private room with a dedicated toilet to decrease transmission
  - 1. Continue contact precautions for at least 48 hours after diarrhea has resolved

- B. Healthcare providers should wear gloves and gowns on entry to a room of a patient with CDI and while caring for patients with CDI
- C. Perform hand hygiene with soap and water before and after contact of a patient with CDI (alcohol-based hand washes not sufficient)
- D. Antimicrobial Stewardship
  - 1. Minimize frequency and duration of high-risk antibiotics and the number of antibiotic agents prescribed
  - 2. High-risk antibiotics are based on local epidemiology and *C. difficile* strains present, but the most common high-risk antibiotics include fluoroquinolones, clindamycin, and cephalosporins
- E. There is an epidemiologic association between PPIs and CDI, but insufficient evidence for discontinuation of PPIs as a measure to prevent CDI
  - 1. Discontinue unnecessary PPIs
- F. There is insufficient data to recommend administration of probiotics for primary prevention of CDI

#### IV. Treatment of CDI<sup>1, 31, 36</sup>

- A. Discontinue therapy with the inciting antibiotic agent as soon as possible (may influence risk of CDI recurrence)
- B. Initial CDI Episode
  - 1. Fidaxomicin or oral vancomycin are recommended for treatment of an initial CDI episode per IDSA/SHEA<sup>36</sup> and NCCN guidelines<sup>1</sup>
    - a. The 2021 IDSA/SHEA focused update of the CDI guidelines now recommends fidaxomicin rather than vancomycin (preferred, conditional recommendation), but vancomycin remains an acceptable alternative if fidaxomicin is unavailable<sup>36</sup>; NCCN guidelines continue to recommend fidaxomicin or vancomycin.<sup>1</sup>
  - 2. Fidaxomicin has been compared with vancomycin in 4 large randomized controlled trials<sup>37-40</sup>
    - a. Initial clinical responses are similar for both agents, whereas CDI recurrences are fewer following fidaxomicin
    - b. The pooled analysis of the 4 randomized controlled trials demonstrated that fidaxomicin increased sustained response at 4 weeks after the end of therapy compared with standard vancomycin (RR 1.15, 95% CI 1.09-1.24) with comparable cure rate (RR 1.00, 95% CI 0.96-1.04) and no difference in mortality (RR 0.90, 95% CI 0.96-1.23)<sup>36</sup>
- C. Fulminant CDI
  - 1. Oral vancomycin 500 mg Q6H rather than fidaxomicin is recommended by both IDSA/SHEA and NCCN guidelines for the treatment of fulminant CDI<sup>1, 36</sup>
    - a. This recommendation remains unchanged in the 2021 IDSA/SHEA focused update as fulminant CDI is not common and studies comparing vancomycin and fidaxomicin generally excluded patients with fulminant disease; thus, there are no available data supporting the use of fidaxomicin for treatment of fulminant CDI<sup>36</sup>

#### D. Recurrent CDI

1. The 2021 IDSA/SHEA focused update of the CDI guidelines now recommends fidaxomicin as the preferred therapy rather than vancomycin for recurrent CDI, but vancomycin in a tapered and pulsed regimen or as a standard course are acceptable alternatives<sup>36</sup>; NCCN guidelines recommend fidaxomicin if not previously received, or vancomycin in a tapered and pulsed regimen.<sup>1</sup>
  - a. The 2021 IDSA/SHEA focused update also recommends bezlotoxumab as a co-intervention along with standard antibiotics for patients with a recurrent CDI episode within the last 6 months<sup>36</sup>
    - 1) The guidelines acknowledge that implementation depends upon available resources and logistics for intravenous administration

#### Guideline Recommendations for the Treatment of CDI

Setting	IDSA/SHEA <sup>36</sup>	NCCN <sup>1</sup>
Initial episode	FDX 200 mg PO BID x 10 days (preferred); or VAN 125 mg PO Q6H x 10 days	VAN 125 mg PO Q6H x 10 days; or FDX 200 mg PO BID x 10 days
Initial episode, fulminant	VAN 500 mg PO Q6H + MTZ 500 mg IV Q8H (consider +VAN 500 mg rectally Q6H if ileus)	VAN 500 mg PO Q6H + MTZ 500 mg IV Q8H (consider +VAN 500 mg rectally Q6H if ileus)
First recurrence	FDX 200 mg PO BID x 10 days, OR BID x 5 days then every other day x 20 days (preferred); or VAN taper*; or VAN 125 mg PO Q6H x 10 days  Adjunctive bezlotoxumab 10 mg/kg IV x 1 <sup>†</sup>	FDX if not previously received; or VAN taper; consider fecal microbiota transplant (avoid if neutropenic) or bezlotoxumab**
Second or subsequent recurrence	FDX 200 mg PO BID x 10 days, OR BID x 5 days then every other day x 20 days; or VAN in a tapered regimen*; or VAN 125 mg PO Q6H x 10 days followed by rifaximin 400 mg PO TID x 20 days; or fecal microbiota transplant  Adjunctive bezlotoxumab 10 mg/kg IV x 1 <sup>†</sup>	

\*e.g., VAN 125 mg PO Q6H x 10-14 days, then BID x 7 days, then daily x 7 days, then every 2-3 days x 2-8 weeks

<sup>†</sup>Implementation depends upon available resources and logistics

\*\*With appropriate consultation

VAN = vancomycin; FDX = fidaxomicin; MTZ = metronidazole

#### **Patient Case #4 (Answer):**

**Correct Answer = A (Vancomycin 500 mg PO and rectally Q6H + metronidazole 500 mg IV Q8H)**

Rationale for correct answer: Concomitant vancomycin and metronidazole would be indicated for fulminant infection (hypotension or shock, ileus, megacolon) per IDSA/SHEA guidelines, and only patients with an ileus should receive vancomycin rectally as well. As this patient does have fulminant CDI, vancomycin 500 mg PO and rectally Q6H plus metronidazole 500 mg IV Q8H is the most appropriate choice from the listed options.

## MANAGEMENT OF FUNGAL INFECTIONS IN NON-HEMATOPOEITIC CELL TRANSPLANT (HCT) PATIENTS

### **Patient Case #5:**

JD is a 33-year-old male with relapsed ALL currently receiving blinatumomab salvage therapy. JD's antimicrobial prophylaxis regimen includes levofloxacin 500 mg PO daily, fluconazole 400 mg PO daily, valacyclovir 500 mg PO daily, and dapsone 100 mg PO daily. On day 15, JD develops FN (ANC =  $0.1 \times 10^9$  cells/L) with a temperature to 39°C. A chest CT obtained after four consecutive days of fever demonstrates large and numerous nodules with a halo sign. A bronchoscopy is performed and reveals a positive galactomannan antigen assay.

**Which of the following is the most appropriate treatment for JD at this time?**

- A. Increase fluconazole to 800 mg PO daily
- B. Switch fluconazole from PO to IV
- C. Switch fluconazole to micafungin
- D. Switch fluconazole to voriconazole

### **I. Invasive Fungal Infections (IFI) in Oncology Patients – Overview<sup>2, 41</sup>**

- A. Invasive fungal infections occur as a result of significant systemic immunocompromise (e.g., myelosuppressive chemotherapy, underlying hematologic malignancy, or high-dose corticosteroids)
  - 1. Most common examples in oncology patients include candidiasis, aspergillosis, and mucormycosis
- B. Risk Factors for IFIs<sup>42</sup>
  - 1. Disease-specific factors: Prolonged/profound neutropenia, high-dose prolonged corticosteroids, graft-versus-host disease, absence of prophylaxis in at-risk patients, and significant mucositis
    - a. Invasive mold infections more frequent in AML ( $> 20 \times$  greater than myeloma/lymphoma)<sup>43</sup>
  - 2. Environmental factors: Fungal colonization/prior exposure, climate, high-risk outdoor activities during at-risk periods (e.g., gardening, spelunking), home renovation/construction prior to chemotherapy, lack of HEPA filtration in hospital
  - 3. Other host factors: Underlying lung disease, older age, tobacco or cannabis use

### **II. Diagnosis of Fungal Infections<sup>41</sup>**

- A. Diagnosis of IFIs can be difficult, particularly due to challenges with specimen acquisition
- B. The European Organization for Research and Treatment of Cancer (EORTC) guidelines from 2008 provide criteria for defining IFIs and categorize infections as “proven”, “probable”, or “possible”<sup>44</sup>
  - 1. Proven: Requires microbiological (culture) and/or histopathologic diagnosis
  - 2. Probable: Requires the presence of one from each of the following:
    - a. Host factor: Prolonged neutropenia (ANC  $< 0.5 \times 10^9$  cells/L for  $> 10$  days), allogeneic HCT, prolonged steroid use ( $\geq 0.3$  mg/kg/day prednisone equivalents for  $> 3$  weeks), or T-cell immunosuppression (e.g., calcineurin inhibitors, alemtuzumab)
    - b. Clinical criteria: Clinical/imaging findings consistent with lower respiratory fungal disease (chest CT), tracheobronchitis, sinonasal infection, CNS infection, or signs of disseminated candidiasis

- c. Mycological criteria: Positive serologic markers (galactomannan assay, (1→3)-β-D-glucan assay)
3. Possible: Requires the presence of one host factor plus one clinical criteria
- C. Serologic Markers<sup>41, 45</sup>
  1. Galactomannan Assay (Platelia™ *Aspergillus* Ag)
    - a. Immunoenzymatic assay that detects the presence of the galactomannan antigen in serum or bronchoalveolar lavage (BAL) fluid
      - 1) Galactomannan is a polysaccharide component of *Aspergillus* cell walls
        - a) Not present in *Candida* spp.
      - 2) *Aspergillus* sheds the polysaccharide in serum/BAL fluid
    - b. The galactomannan assay is neither specific nor sensitive to *Aspergillus* spp. and is susceptible to numerous interfering substances (see table below)
  2. (1→3)-β-D-glucan Assay (Fungitell®)
    - a. (1→3)-β-D-glucan is a polysaccharide molecule found on the outer cell wall of numerous fungi, including *Aspergillus* spp., *Candida* spp., *Pneumocystis jirovecii*, and others
      - 1) Does not detect *Cryptococcus* or *Mucorales* spp. (produce low levels of (1→3)-β-D-glucan)
    - b. Many substances/conditions interfere with results, potentially limiting utility (see table below)
  3. Both serologic tests unable to discriminate between infection and colonization

#### Causes of Inaccurate Results with Galactomannan and β-D-Glucan Assays

GALACTOMANNAN ASSAY <sup>45, 46</sup>		
Pharmacologic Agents	Medical Conditions	Miscellaneous
β-lactams and carbapenems* Plasmalyte® Soybean protein (EN) Mold-active antifungal agents**	GI colonization with <i>Bifidobacterium</i> spp.; <i>Histoplasma</i> spp.	Cotton Cardboard Very young children† Flavored ice pop <sup>47</sup>
β-D-GLUCAN ASSAY <sup>45, 48, 49</sup>		
False-Positives		False-Negatives
Cellulose membranes used in HD Glucan-containing gauze Blood products (through glucan-containing filters)‡ Heat stroke GI fungal colonization (especially if mucositis) Semisynthetic β-lactams		Hypertriglyceridemia (lipemic blood) Hyperbilirubinemia Mold- and yeast-active antifungal agents Hemolysis in blood samples

\*Recent data suggest concomitant use of piperacillin/tazobactam does not interfere with galactomannan assay, but use caution when interpreting results<sup>50, 51</sup>

\*\*Concomitant use of mold-active antifungals may cause false negatives due to inhibition of growth and shedding of galactomannan polymers

†High rate of false-positive results in very young children

‡Examples include albumin and immunoglobulins filtered through glucan-containing filters

EN = enteral nutrition; HD = hemodialysis

### III. Treatment of *Candida* Infections<sup>52</sup>

#### A. Non-Neutropenic Patients

##### 1. Candidemia and Invasive Candidiasis:

- a. Echinocandin is gold-standard for treatment of candidemia or invasive candidiasis
  - 1) Fluconazole is preferred alternative to echinocandin in select patients
- b. Fluconazole is recommended as step-down therapy following 5-7 days of an echinocandin contingent the patient is clinically stable, has susceptible isolates, and has cleared their blood cultures

#### B. Neutropenic Patients

##### 1. Candidemia:

- a. Echinocandin is gold-standard for treatment of candidemia
  - 1) Fluconazole (in those not critically ill who have had no prior azole exposure), lipid/liposomal amphotericin (less attractive due to toxicities) or voriconazole (in cases where additional mold coverage is desired) are acceptable alternatives
- b. Fluconazole is recommended as step-down therapy if the patient is clinically stable, has susceptible isolates, and has cleared their blood cultures
  - 1) Voriconazole is an alternative in similar cases that are appropriate to use fluconazole, but additional mold coverage is desired

##### 2. Invasive Candidiasis (i.e., hepatosplenic):

- a. Liposomal amphotericin B or an echinocandin is preferred for treatment of invasive candidiasis
- b. Step-down therapy with fluconazole is recommended in those unlikely to have resistant isolate
- c. Therapy should continue until lesions resolve on imaging, usually several months

#### C. Duration of Therapy

1. For candidemia without metastatic complications, minimum duration should be 2 weeks from clearance of *Candida* from bloodstream and resolution of symptoms (provided neutropenia resolved)

#### D. Additional Workup

1. Funduscopic exam (within first week after neutrophil recovery) to identify choroidal and vitreal infection
2. Central venous catheter removal should be considered early
3. Echocardiogram should be considered

### IV. Treatment of *Aspergillus* Infections<sup>41</sup>

#### A. Triazoles are preferred for the treatment of *Aspergillus* spp. infections

1. Voriconazole is the gold-standard treatment of *Aspergillus* spp. infections based on results from the Global Comparative Aspergillosis Study (307/602) by Herbrecht et al<sup>53</sup>
  - a. Due to non-linear PK and intra/inter patient variability, therapeutic drug monitoring (TDM) targeting a trough of > 1-1.5 mg/L with an upper limit of < 5-6 mg/L should be employed
2. Amphotericin lipid/liposomal formulations and isavuconazole are appropriate treatment options for invasive aspergillosis (IA) when voriconazole is contraindicated



- a. SECURE Study – Maertens et al<sup>54</sup>
  - 1) Study Design: Prospective, multicenter, randomized, double-blind, non-inferiority
  - 2) Participants: Patients (N=527) with proven/probable/possible IA (74% with hematologic cancer)
  - 3) Interventions: Randomized to isavuconazole (as isavuconazonium sulfate 372 mg IV TID x 2 days, then IV/PO daily thereafter) or voriconazole (6 mg/kg IV BID x 1 day, then 4 mg/kg IV BID beginning on day 2 with the option to change to 200 mg PO BID on day 3)
    - a) No TDM allowed to maintain blinding
  - 4) Results:
    - a) Primary endpoint of all-cause mortality at day 42 in 19% with isavuconazole vs. 20% with voriconazole with an adjusted treatment difference -1.0% (95% CI, -7.8 to 5.7; p=0.744)
    - b) No difference in success at the end of treatment between groups (35% vs. 36.4%)
    - c) Treatment-related adverse events higher with voriconazole than isavuconazole (less skin, eye, and hepatobiliary disorders with isavuconazole)
  - 5) Significance: Isavuconazole non-inferior to voriconazole for the treatment of IA
- B. Echinocandins are not recommended as initial treatment (may be used in salvage therapy)
- C. Combination antifungals lack sufficient data to routinely recommend
  1. Consider combination voriconazole with an echinocandin in select patients with severe disease, especially if profound and prolonged neutropenia anticipated
    - a. A8851009 Study – Marr et al<sup>55</sup>
      - 1) Study Design: Prospective, multicenter, randomized, double-blind, placebo-controlled
      - 2) Participants: Patients (N=277) with proven/probable IA and hematologic cancer or HCT
      - 3) Interventions: All patients received voriconazole (6 mg/kg BID x 1 day, then 4 mg/kg BID x 1 week with the option to change to 300 mg BID) for 6 weeks plus either anidulafungin (200 mg IV x 1 day, then 100 mg IV daily) or placebo for the first 2-4 weeks
        - a) TDM of voriconazole allowed
      - 4) Results:
        - a) Primary endpoint of all-cause mortality at 6 weeks trended toward improvement with 19.3% for combination therapy vs. 27.5% with monotherapy (p=0.087)
          - i. Underpowered to show a difference given the higher than expected mortality at 6 and 12 weeks with lower than expected difference in mortality between the two groups
        - b) Patients with probable IA had a statistically significant 6-week mortality benefit with combination therapy (15.7% vs. 27.3%, p=0.037)
        - c) Adverse events requiring discontinuation of treatment similar between groups
          - i. More patients in combination group had hepatobiliary adverse events
      - 5) Significance: Combination therapy with voriconazole and an echinocandin led to high survival rates in a subgroup of patients with probable IA; limitations in power preclude definitive conclusions about superiority

- D. Other considerations for treatment:
  - 1. Reduce immunosuppressive agents when possible
  - 2. Consider granulocyte-colony stimulating factors or granulocyte macrophage colony-stimulating factors in neutropenic patients
- E. Duration is not well defined; generally, 6-12 weeks to several months, even years depending upon recovery of counts and restoration of immune competence
  - 1. Patients who remain immunocompromised should have secondary prophylaxis against aspergillus
- F. Treatment of refractory IA (salvage therapy)
  - 1. Individualized based on rapidity, severity, comorbidities, and potential pathogen
    - a. Consider changing class of antifungal, reducing immunosuppression if able, and/or surgical resection if amenable to surgery
  - 2. Add a second agent (from a different antifungal class) or switch to a different single agent
    - a. Amphotericin lipid formulation, micafungin, caspofungin, posaconazole, or itraconazole
  - 3. If utilizing a triazole as salvage therapy, consider prior antifungal therapy, host factors, potential resistance or non-aspergillus mold, and pharmacokinetics
  - 4. For presumptive triazole failure, consider if subtherapeutic serum concentrations (i.e., posaconazole < 700 ng/mL) contributed before switching to an amphotericin lipid formulation ± echinocandin

**Patient Case #5 (Answer):**

**Correct Answer = D (switch fluconazole to voriconazole)**

Rationale for correct answer: Voriconazole is the gold-standard treatment of *Aspergillus* spp. infections. This patient has imaging and serologic markers consistent with aspergillosis, thus voriconazole is warranted. Fluconazole would not cover *Aspergillus* spp., and echinocandins are not recommended as initial treatment per the IDSA Practice Guidelines for the Diagnosis and Management of Aspergillosis.

**V. Practical Use of Antifungal Agents in Oncology<sup>41</sup>**

- A. CYP450 Drug-Drug Interactions
  - 1. All triazole antifungals inhibit CYP450 3A4, but fluconazole and isavuconazole much less than others
  - 2. The drug of choice when anti-mold therapy is required in the setting of significant drug interactions is an amphotericin lipid formulation
  - 3. Although echinocandins do not interact with CYP450 metabolized drugs, they are not the most optimal agent for the treatment of invasive mold infections
  - 4. Use caution when triazole antifungals are co-administered with other CYP450 3A4 agents, especially:
    - a. Vinca alkaloids (generally considered contraindicated with strong CYP3A4 inhibitors)
    - b. High-dose cyclophosphamide
    - c. Thiotepa<sup>56</sup>

d. Oral small molecule anticancer agents (e.g., dasatinib, venetoclax, midostaurin)

B. IV Triazoles in Renal Dysfunction

1. IV formulations of voriconazole and posaconazole contain cyclodextrin, which may accumulate and lead to further renal damage when creatinine clearance < 30 mL/min
2. Recent data have not demonstrated increased harm or adverse events when IV voriconazole was used in patients with creatinine clearance < 30mL/min<sup>57</sup>

C. TDM of Triazole Antifungals

1. Several agents exhibit narrow therapeutic window and variable serum concentrations
2. TDM is necessary for itraconazole, voriconazole and posaconazole suspension
  - a. Due to unreliable absorption, effect of meals on absorption, etc
3. Role of TDM for posaconazole tablets, IV posaconazole, and PO/IV isavuconazole unclear
  - a. Consider in cases of non-adherence
  - b. All of the triazole antifungals are CYP3A4 substrates (as well as inhibitors); drug-drug interactions can also cause increase/decrease in triazole serum levels

## Summary of Antifungal Agents<sup>1, 41</sup>

Agent	Dose*	Spectrum	Comments
Azoles <sup>†,‡</sup>			
Fluconazole	400-800 mg IV/PO daily	<i>Candida spp.</i> , coccidioidomycosis, <i>C. neoformans</i>	<ul style="list-style-type: none"><li>• <i>C. glabrata</i> with variable resistance</li><li>• <i>C. krusei</i> intrinsically resistant</li></ul>
Isavuconazole	372 mg IV/PO Q8H x 48H, then 372 mg IV/PO daily	<i>Candida spp.</i> , <i>Aspergillus spp.</i> , <i>Mucorales spp.</i>	<ul style="list-style-type: none"><li>• May shorten QT interval</li><li>• Moderate CYP3A4 inhibitor (may be less clinically significant than voriconazole or Posaconazole)</li></ul>
Itraconazole	200 mg PO TID x 3 days, then 200 mg PO BID	<i>Candida spp.</i> , <i>Aspergillus spp.</i> , dimorphic fungi, <i>C. neoformans</i>	<ul style="list-style-type: none"><li>• Contraindicated in patients with cardiac systolic dysfunction</li><li>• H2RAs/PPIs may inhibit absorption (oral solution preferred)</li><li>• TDM recommended</li></ul>
Posaconazole	300 mg IV/PO (tablet) BID x 1 day, then 300 mg IV/PO (tablet) daily	<i>Candida spp.</i> , <i>Aspergillus spp.</i> , <i>Mucorales spp.</i> , some rarer molds, dimorphic fungi, <i>C. neoformans</i>	<ul style="list-style-type: none"><li>• Suspension dosing different than tablets (200 mg TID-QID)</li><li>• Suspension must be administered with a full meal/liquid nutritional supplement/or acidic carbonated beverage; no concomitant PPIs</li><li>• Tablets better absorbed</li><li>• TDM recommended for suspension</li></ul>
Voriconazole	6 mg/kg IV/PO BID x 1 day, then 4 mg/kg IV/PO BID	<i>Candida spp.</i> , <i>Aspergillus spp.</i> , some rarer molds, dimorphic fungi, <i>C. neoformans</i>	<ul style="list-style-type: none"><li>• Visual disturbances/hallucinations may occur</li><li>• Administer on empty stomach</li><li>• TDM recommended</li><li>• Standard of care for invasive aspergillosis</li></ul>
Amphotericin B Formulations			
Conventional Amphotericin B (AmB-D)	Varies by indication, 0.5-1.5 mg/kg IV daily	<i>Candida spp.</i> , <i>Aspergillus spp.</i> , <i>Mucorales spp.</i> , rarer molds, dimorphic fungi, <i>C. neoformans</i>	<ul style="list-style-type: none"><li>• Significant infusional and renal toxicity including electrolyte wasting</li></ul>
Amphotericin B Lipid Complex (ABLC)	3-5 mg/kg IV daily		<ul style="list-style-type: none"><li>• Reduced infusional and renal toxicity compared to AmB-D</li></ul>
Liposomal Amphotericin B (L-AMB)			
Echinocandins			
Anidulafungin	200 mg IV x 1 dose, then 100 mg IV daily	<i>Candida spp.</i> , <i>fungistatic against Aspergillus spp.</i>	<ul style="list-style-type: none"><li>• Standard of care for candidemia and invasive candidiasis</li><li>• Poor CNS, urine, and eye penetration</li><li>• Well-tolerated</li></ul>
Caspofungin	70 mg x 1 dose, then 50 mg IV daily; 70 mg IV daily used at some centers for <i>Aspergillus spp.</i> 2 <sup>nd</sup> line		
Micafungin	100 mg IV daily for candidemia; 150 mg IV daily used at some centers for <i>Aspergillus spp.</i> 2 <sup>nd</sup> line		

\* In the setting of normal organ function

<sup>†</sup>Azoles inhibit CYP3A4; drug-drug interactions are common and need to be closely monitored

<sup>‡</sup>QT prolongation is a concern with all azoles with the exception of isavuconazole (causes shortening)

H2RAs = histamine-2 receptor antagonists; PPIs = proton pump inhibitors; TDM = therapeutic drug monitoring; CNS = central nervous systemic

## MYELOID COLONY-STIMULATING FACTORS

### I. Colony-Stimulating Factors – Overview<sup>58, 59</sup>

- A. Recombinant myeloid colony-stimulating factors (CSFs) are hematopoietic growth factors that stimulate the production, maturation, and activation of neutrophils to increase their migration and cytotoxicity
  - 1. Granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF) are available
- B. Primarily used to reduce incidence of febrile neutropenia in patients with solid tumors receiving myelosuppressive chemotherapy

### II. Recommendations for the Use of CSFs<sup>58, 59</sup>

- A. Myelosuppressive chemotherapy
  - 1. Studies with prophylactic use following myelosuppressive chemotherapy support reduction in:
    - a. Incidence of FN
    - b. Length of hospitalization
    - c. Confirmed infections
    - d. Duration of antibiotics
  - 2. No effect on infection-related mortality, tumor response rate, or overall survival
- B. Acute Leukemias/MDS
  - 1. Acute Lymphoblastic Leukemia (ALL)<sup>60</sup>
    - a. CSF use is recommended for myelosuppressive blocks of therapy or as directed by protocol
    - b. May overlap CSF with asparaginase and/or vincristine as these are not myelosuppressive
    - c. Do not overlap with myelosuppressive chemotherapy (see same day administration below)
  - 2. Acute Myeloid Leukemia (AML)<sup>61</sup>
    - a. ASCO guidelines do not provide recommendations regarding use of CSFs in adults with AML<sup>59</sup>
    - b. NCCN suggests CSFs may be considered as part of supportive care for post-remission therapy
      - 1) Discontinue CSFs  $\geq 7$  days before obtaining remission bone marrow
  - 3. Myelodysplastic Syndromes (MDS)<sup>62</sup>
    - a. Consider CSFs for neutropenic patients with MDS with recurrent or resistant bacterial infections
- C. See table below for a summary of ASCO and NCCN recommendations on the use of CSFs

### III. CSF Biosimilars<sup>58</sup>

- A. Studies comparing filgrastim and pegfilgrastim to their respective biosimilar formulations (see table below) have not demonstrated significant differences in efficacy/safety
- B. Per NCCN, filgrastim, tbo-filgrastim, and FDA-approved filgrastim biosimilars can be used for the prevention of chemotherapy-induced FN<sup>58</sup>
  - 1. Daily dose of 5 mcg/kg (rounded to nearest vial/syringe size) beginning the next day or up to 3-4 days after chemotherapy completion and continued through post-nadir recovery

- C. Per NCCN, pegfilgrastim and FDA-approved pegfilgrastim biosimilars can be used for the prevention of chemotherapy-induced FN<sup>58</sup>
  1. Single dose of 6 mg administered the day after chemotherapy (up to 3-4 days after is also reasonable)
    - a. There are data for and against same day dosing but the FDA-approved dosing schedule is still recommended
  2. There should be at least 12 days between the dose of pegfilgrastim and the next chemotherapy cycle

#### IV. Same day administration of CSFs<sup>58</sup>

- A. Concern that bone marrow stimulation by CSFs when administered concurrently with chemotherapy will cause release of early myeloid progenitor cells when chemotherapy is still circulating, leading to worsened neutropenia than if the CSF was not administered
- B. Current recommendations are to administer filgrastim 24 to 72 hours after chemotherapy and to administer pegfilgrastim 24 hours after chemotherapy (and at least 12 days prior to next cycle)
  1. An alternative to same-day administration is now available with the FDA approval of a pegfilgrastim on-body injector (Neulasta Onpro®) which can be applied the same day as chemotherapy but administered approximately 27 hours later on the following day<sup>63</sup>

#### V. Pediatric Use of CSFs – Refer to “Pediatrics” chapter

#### Overview of Commercially Available CSFs<sup>64-74</sup>

Agent	Biosimilar	FDA Approval	Primary PPx (non-myeloid)	Primary PPx (AML)	Primary PPx (HCT)	XRT Injury Syndrome	Mobilization (HCT)	Chronic Neutropenia
Sargramostim	X	1991	X	✓	✓	✓	✓	X
Filgrastim	X	1998	✓	✓	✓	✓	✓	✓
Pegfilgrastim	X	2002	✓	X	X	✓	X	X
Tbo-filgrastim	X	2012	✓	X	X	X	X	X
Filgrastim-sndz	✓	2015	✓	✓	✓	X	✓	✓
Pegfilgrastim-jmdb	✓	2018	✓	X	X	X	X	X
Filgrastim-aafi	✓	2018	✓	✓	✓	X	✓	✓
Pegfilgrastim-cbqv	✓	2018	✓	X	X	X	X	X
Pegfilgrastim-bmez	✓	2019	✓	X	X	X	X	X
Pegfilgrastim-agpf	✓	2020	✓	X	X	X	X	X
Filgrastim-ayow	✓	2022	✓	✓	✓	X	✓	✓
Pegfilgrastim-pbbk	✓	2022	✓	X	X	X	X	X

✓ = Approved indication; X = Unapproved indication

PPx = prophylaxis; AML = acute myeloid leukemia induction/consolidation; XRT = radiation

## Summary of Guideline Recommendations for CSFs

	ASCO <sup>59</sup>	NCCN <sup>58</sup>
<b>PRIMARY PROPHYLAXIS</b>		
Chemotherapy regimen with ≥ 20% incidence of FN	✓	✓
Chemotherapy regimen with 10-20% incidence of FN	X	✓ (if risk factors present)
Chemotherapy regimen with < 10% incidence of FN	X	X
High-risk for complications of FN irrespective of FN risk	✓	---
Dose-dense chemotherapy regimen	✓	According to incidence of FN
Neutropenia in afebrile patients	X	---
<b>SECONDARY PROPHYLAXIS</b>		
Prior FN or dose-limiting neutropenic event (CSF not used)	Consider CSF; dose reduction or delay is a reasonable alternative	Consider CSF; consider dose reduction or change in regimen
<b>THERAPEUTIC USE*</b>		
Expected neutropenia > 10 days	Consider	Consider
Profound neutropenia (ANC < 0.1 x 10 <sup>9</sup> cells/L)	Consider	Consider
Patients > 65 years	Consider	Consider
Pneumonia	Consider	Consider (or other clinically documented infection)
Hypotension	Consider	---
Sepsis syndrome	Consider	Consider
Uncontrolled primary disease	Consider	---
Invasive fungal infection	Consider	Consider
Hospitalized at onset of fever	Consider	Consider
Prior FN episode	---	Consider
If patient received prophylactic CSF	---	Continue (pegylated CSFs should not be re-dosed)

✓ = Recommended; X = NOT recommended; --- = No recommendation provided

\*Assumes prophylactic CSFs not administered; “---” denotes no recommendation provided

FN = febrile neutropenia; HCT = hematopoietic cell transplantation; DLBCL = diffuse large B-cell lymphoma; XRT = radiation

## VACCINATIONS IN CANCER PATIENTS

### **Patient Case #6:**

TS is a 19-year-old female with relapsed ALL who was just discharged from the hospital after having received CD19-directed CAR-T therapy. She presents to clinic today and has questions regarding COVID-19 vaccinations following therapy.

**Which of the following is correct regarding COVID-19 vaccination for TS?**

- A. TS may receive any of the COVID-19 vaccines at any time after CAR-T.
- B. TS may receive any of the COVID-19 vaccines  $\geq 3$  months after CAR-T.
- C. TS may receive any of the mRNA COVID-19 vaccines  $\geq 3$  months after CAR-T.
- D. COVID-19 vaccines are contraindicated in patients who have received CAR-T.

### **I. Overview<sup>75</sup>**

- A. IDSA guidelines developed in 2013 to provide primary care and specialty clinicians with evidence-based guidelines for active immunization of patients with altered immunocompetence
  - 1. **Refer to the IDSA guideline by Rubin LG et al.** (available at: <https://pubmed.ncbi.nlm.nih.gov/24311479/>)
    - a. See Table 3 in reference above entitled, “Vaccinations for Patients with Cancer”
    - b. Guideline provides specific recommendations for active immunization of patients with altered immunocompetence both prior to the start of chemotherapy and following chemotherapy
- B. Goal to decrease morbidity/mortality from vaccine-preventable infections in immunocompromised patients
- C. This section will focus on patients  $\geq 18$  years of age with cancer
  - 1. For vaccinations in pediatric patients, please refer to the “Pediatrics” chapter
  - 2. For vaccinations in HCT, please refer to the “Hematopoietic Stem Cell Transplantation” chapter

### **II. Timing of Vaccinations<sup>1, 75</sup>**

- A. Vaccines should be administered prior to planned immunosuppression, if feasible
- B. Live vaccines should be administered  $\geq 4$  weeks prior to immunosuppression and should be avoided within 2 weeks of initiation of immunosuppression to prevent risk of infection
- C. Inactivated vaccines should be administered  $\geq 2$  weeks prior to immunosuppression
  - 1. This is often not feasible in patients with cancer
  - 2. Those who are vaccinated  $< 2$  weeks before receiving cytotoxic chemotherapy may have limited response and should be revaccinated once immune competent<sup>76</sup>

### **III. Recommendations for Vaccination in Patients with Cancer<sup>1, 75, 77</sup>**

- A. Inactivated vaccines administered during cancer chemotherapy should **NOT** be considered valid doses unless there is documentation of a protective antibody level
- B. Live viral vaccines should **NOT** be administered during chemotherapy due to risk of infection



- C. Three months after the completion of chemotherapy, patients should be vaccinated with inactivated and live vaccines per the CDC annual schedule for immunocompetent individuals
1. In regimens that include anti-B-cell antibodies, vaccinations should be delayed at least 6 months (antibody formation to antigens will be diminished with B-cell depleting agents)
- D. Influenza Vaccine
1. Patients with hematologic or solid tumor malignancies should receive the inactivated influenza vaccine (IIV) or recombinant influenza vaccine (RIV) annually; age-appropriate vaccines are recommended (i.e., high-dose influenza recommended if > 65 years of age)
  2. Insufficient data to recommend high-dose influenza over standard-dose specifically in cancer patients
  3. The following patients **SHOULD NOT** receive IIV or RIV (these patients are unlikely to be harmed but are unlikely to derive any benefit):
    - a. Those receiving anti-B-cell antibodies (within 6 months)
    - b. Intensive chemotherapy such as induction or consolidation chemotherapy for acute leukemia (within 3 months)
    - c. Patients receiving blinatumomab or chimeric antigen receptor T-cell (CAR-T) therapy
      - 1) Likely > 1 year before mounting a humoral response
      - 2) Immunoglobulin levels suppressed for ~1 year<sup>78</sup>
- E. Pneumococcal Conjugate Vaccine (PCV15 and PCV20) and Pneumococcal Polysaccharide Vaccine (PPSV23)<sup>79</sup>
1. Pneumococcal vaccine-naïve patients with newly diagnosed hematological or solid malignancies should receive PCV15 or PCV20 prior to or during chemotherapy
  2. PPSV23 should be administered at least 8 weeks after the indicated dose of PCV15; if PCV20 is used, a dose of PPSV23 is NOT indicated.
  3. If previously received PPSV23, PCV15 or PCV20 should be given at least 1 year later
- F. Herpes Zoster Vaccine<sup>80</sup>
1. Zoster Vaccine Live (ZVL; Zostavax<sup>®</sup>) is discussed in 2013 IDSA guidelines but is no longer available for use in the United States, as of November 18, 2020
  2. Zoster Vaccine Recombinant (RZV; Shingrix<sup>®</sup>) is a more recently FDA-approved biologically inactive adjuvanted recombinant subunit vaccine<sup>81</sup>; RZV was not discussed in the 2013 IDSA guidelines, but the use of RZV in immunocompromised adults was addressed by the CDC in October 2021
  3. Recommendations for immunocompetent adults:
    - a. For adults aged ≥ 50 years, the CDC recommends 2 doses of RZV separated by 2-6 months
    - b. In those who previously received ZVL, the CDC recommends administering RZV
  4. Recommendations for immunocompromised adults:
    - a. For adults ≥ 19 years, the CDC recommends 2 doses of RZV separated by 2-6 months
    - b. For individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule, the second dose can be administered 1–2 months after the first

- c. When possible, patients should be vaccinated before becoming immunosuppressed; otherwise, providers should consider timing vaccination when the immune response is likely to be most robust (i.e., during periods of lower immunosuppression and stable disease)

G. Patients with asplenia or sickle cell diseases should receive:

1. PCV15 and PPSV23 or PCV20 according to the CDC schedule
2. Hib vaccine according to the CDC schedule
3. Meningococcal vaccine according to the CDC schedule
4. Live attenuated influenza vaccine is contraindicated

#### **IV. Recommendations for Caregivers/Household Members<sup>75</sup>**

A. Caregivers/household members should receive IIV

1. Live attenuated influenza vaccine is not recommended

B. Certain live viral vaccines can be safely administered to household members of severely immunocompromised patients (e.g., MMR), whereas others cannot (e.g., polio) based on the risk for transmission

#### **V. Immunotherapy and Vaccination<sup>82</sup>**

A. Patients receiving immune therapies/checkpoint inhibitors may receive vaccines that are inactivated or killed, or mRNA (e.g., COVID vaccines) preparations per NCCN

B. Live vaccinations were generally excluded from clinical trials<sup>83-85</sup>

1. Not given ~1 month prior to randomization in some studies, and at least 90 days following last dose
2. Due to lack of clarity regarding the risk/benefits of live vaccines, NCCN does not recommend use of live vaccines during immune-checkpoint inhibitor therapy

C. No data to suggest inactivated viruses cause harm (e.g., no increase in immune toxicity)

D. Some data to suggest humoral responses<sup>86</sup>

#### **VI. COVID-19 Vaccination<sup>87</sup>**

A. Recommendations provided by the NCCN COVID-19 Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis:

1. The committee endorses vaccination for all eligible persons based on FDA-approved indications or emergency use authorization (EUA)
2. The committee prefers the use of mRNA vaccines for the primary series and boosters
  - a. Pfizer/BioNTech [BNT162b2 mRNA vaccine]
  - b. Moderna [mRNA-1273 SARS-CoV-2 vaccine]
3. Specified immunocompromised individuals are recommended to receive 3 doses for their primary series, plus approved boosting (follow CDC recommendations for detailed timing schedule):
  - a. Receiving active cancer treatment for tumors or cancers of the blood
  - b. Received an organ transplant and are taking medicine to suppress the immune system

- c. Received chimeric antigen receptor (CAR)-T-cell therapy (a treatment to help your immune system attach to and kill cancer cells) or received a stem cell transplant (within the last 2 years)
- d. Moderate or severe primary immunodeficiency
- e. Advanced or untreated HIV infection
- f. Treatment with high-dose corticosteroids or other drugs that may suppress their immune response
- 4. Most cancer patients can receive COVID-19 vaccinations as soon as possible with a few exceptions; reasons for delay are similar to those in the general public (e.g., recent exposure to COVID-19)
- 5. COVID-19 vaccines and other vaccines may be administered without regard to timing
- 6. COVID-19 vaccination does not need to be delayed following receipt of monoclonal antibodies, including prophylactic tixagevimab plus cilgavimab
- B. Recommendations regarding the timing of COVID-19 vaccination in patients with cancer:
  - 1. HCT/Cellular Therapy:  $\geq 3$  months post-HCT/CAR-T
    - a. Revaccination (of the 3-dose primary series and booster) is recommended 3 months following HCT or CAR T-cell therapy, if a patient was vaccinated before such therapy
  - 2. Hematologic malignancies:
    - a. Receiving intensive cytotoxic chemotherapy (e.g., “induction”): delay until ANC recovery
    - b. For those not expected to have ANC recovery: as soon as possible
  - 3. Solid tumor malignancies:
    - a. Receiving cytotoxic chemotherapy, targeted therapy, checkpoint inhibitors and other immunotherapy, or radiation: when vaccine available
    - b. Major surgery: separate date of surgery from vaccination by at least a few days
- C. Notes on timing of COVID-19 vaccination administration:
  - 1. Concerns for attenuated response/optimal timing with cancer treatment:
    - a. Given variability of regimens and intervals between cycles, it is not possible to predict optimal timing of vaccination in relation to chemotherapy; thus, vaccination recommended when available
    - b. Neutropenia itself does not significantly affect immunologic response to vaccination; in the setting of profound immunosuppression, it is used as a surrogate for recovery of adequate immunocompetence to respond to vaccines
      - 1) Due to short periods of neutropenia among solid tumors, this is not used for vaccine timing
    - c. The primary reason to avoid COVID-19 vaccination in the perioperative period is so that symptoms (e.g., fever) can be correctly attributed to surgery vs. vaccination

## **VII. Pre-exposure prophylaxis**

- A. COVID-19 vaccination is a form of pre-exposure prophylaxis; vaccination is designed to induce immune responses to prevent or diminish the severity of COVID-19 following exposure<sup>87</sup>
  - 1. Major gap in vaccination with immunocompromised persons who develop inadequate immune response

- B. The NCCN Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis recommends pre-exposure prevention with tixagevimab plus cilgavimab for specified individuals (including all persons undergoing active cancer therapy)<sup>87</sup>
  1. Tixagevimab plus cilgavimab is NOT a substitute for COVID-19 vaccination
  2. To avoid interference with vaccine-induced immunity, tixagevimab and cilgavimab should be administered at least 2 weeks *after* COVID-19 vaccination
- C. Tixagevimab co-packaged with cilgavimab (Evusheld™)<sup>88</sup>
  1. Mechanism of action:
    - a. A long-acting monoclonal antibody combination; tixagevimab and cilgavimab simultaneously bind to non-overlapping regions of the receptor binding domain of the SARS-CoV-2 spike protein, blocking its interaction with human ACE2, the SARS-CoV-2 receptor, which is required for virus attachment
  2. Indications & dose:
    - a. EUA-approved for the pre-exposure prophylaxis of COVID-19 in adults and children (≥ 12 years weighing at least 40 kg) who have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination
      - 1) Per the EUA, medical conditions or treatments that may result in moderate to severe immune compromise include (but are not limited to):
        - a) Active treatment for solid tumor and hematologic malignancies
        - b) Receipt of solid-organ transplant and taking immunosuppressive therapy
        - c) Receipt of CAR T-cell or HCT (within 2 years or taking immunosuppression therapy)
        - d) Moderate or severe primary immunodeficiency
        - e) Advanced or untreated HIV infection
        - f) Active treatment with high-dose corticosteroids and other agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)
      - 2) Individuals must not be currently infected with SARS-CoV-2 and should not have a known recent exposure to an individual infected with SARS-CoV-2
    - b. The initial dosage is 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular (IM) injections; the repeat dosage is 300 mg of tixagevimab and 300 mg of cilgavimab administered every 6 months
      - 1) Note, the previous dosage regimen in the initial EUA of 150 mg each of tixagevimab and cilgavimab was increased based on data on the *in vitro* neutralizing activity against the Omicron BA.1 and BA.1.1 subvariants<sup>87</sup>
  3. Toxicities: Headache, fatigue, cough, allergic reactions, cardiac events (rare; causal relationship has not been established – see EUA Fact Sheet for more details)
  4. Drug-drug interactions: None known (not renally excreted or metabolized by CYP enzymes)
- D. PROVENT Trial - Levin et al<sup>89</sup>
  1. Study design: Multicenter, double-blind, parallel-group, randomized, placebo-controlled trial

2. Participants: Adults who had an increased risk of an inadequate response to COVID-19 vaccination, an increased risk of exposure to SARS-CoV-2, or both (N=5197)
    - a. 77.5% had baseline comorbidities or characteristics associated with an increased risk for severe COVID-19; however, only 7.4% had cancer and only 3.3% received immunosuppressive medications
  3. Interventions: Randomized in a 2:1 ratio to receive a single 300-mg dose of AZD7442 (one 1.5-ml intramuscular injection of each antibody administered consecutively) or saline placebo (two 1.5-ml intramuscular injections administered consecutively) on day 1
  4. Results:
    - a. Primary endpoint of symptomatic COVID-19 occurred in 8 of 3441 participants (0.2%) in the AZD7442 group and in 17 of 1731 participants (1.0%) in the placebo group (relative risk reduction, 76.7%; 95% confidence interval [CI], 46.0 to 90.0;  $P < 0.001$ )
    - b. Five cases of severe or critical COVID-19 and two COVID-19–related deaths occurred, all in the placebo group
    - c. Adverse events similar between groups and most mild to moderate in severity
  5. Significance: A single dose of AZD7442 had efficacy for the prevention of COVID-19, without evidence of safety concerns; this data led to the EUA for the use of AZD7442 (tixagevimab and cilgavimab) for pre-exposure prophylaxis in patients with moderate to severe immune compromise
- E. **UPDATE (January 2023): Due to the emergence of new variants, Evusheld may not be as effective in neutralizing circulating strains. Refer to the FDA and CDC website for the most current information.**
- F. Information continues to evolve rapidly regarding COVID-19 vaccinations and pre-exposure prophylaxis, particularly in immunocompromised individuals. Refer to the NCCN Cancer and COVID-19 Vaccination Clinical Recommendations for the most current recommendations.
1. [https://www.nccn.org/docs/default-source/covid-19/2021\\_covid-19\\_vaccination\\_guidance\\_v4-0.pdf?sfvrsn=b483da2b\\_70](https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v4-0.pdf?sfvrsn=b483da2b_70)

**Patient Case #6 (Answer):**

**Correct Answer = C (TS may receive any of the mRNA COVID-19 vaccines  $\geq$  3 months after CAR-T)**

Rationale for correct answer: The NCCN COVID-19 Vaccination Advisory Committee recommends COVID-19 vaccination with any mRNA COVID-19 vaccine  $\geq$  3 months after CAR-T. Thus, answer choice C is correct.

# MANAGEMENT OF COVID-19 IN CANCER PATIENTS

## I. COVID-19 in Cancer Patients

- A. Scientific understanding of COVID-19 disease is rapidly evolving
- B. Most information about COVID-19 in cancer patients is based on observational data and extrapolation from studies that may have included patients with cancer
- C. Patients with cancer are at increased risk for severe disease and increased mortality
  - 1. All-cause mortality and likelihood of ICU admission are higher in cancer patients, even after adjustment for other common risk factors
  - 2. Patients with hematologic malignancies have a high mortality rate nearly twice that of patients with solid tumor malignancies (50% vs. 26.1%)<sup>90</sup>

## II. Treatment Recommendations

- A. NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections Version 2.2022 now includes recommendations on the management of concurrent COVID-19 and cancer in patients<sup>1</sup>
  - 1. Guideline addresses SARS-CoV-2 testing in oncology patients, considerations for cancer-directed therapy in patients with positive SARS-CoV-2, COVID-19 treatment in patients with cancer, and co- and secondary infections associated with COVID-19
- B. Refer to the NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines website for the most up-to-date recommendations on the general and therapeutic management of hospitalized and non-hospitalized patients, available at <https://www.covid19treatmentguidelines.nih.gov>
- C. COVID-19 Treatment Approach<sup>91</sup>
  - 1. Treatment/management recommendations can be divided into two categories:
    - a. Nonhospitalized adults
    - b. Hospitalized adults
- D. COVID-19 Therapeutics<sup>91</sup>
  - 1. Several therapeutic options are now available (antivirals, anti-SARS-CoV-2 antibody products, and immunomodulators)
  - 2. Considerations in the selection of the best treatment option for a specific patient:
    - a. Clinical efficacy and availability of the treatment option
    - b. Feasibility of administering parenteral medications (i.e., remdesivir)
    - c. The potential for significant drug-drug interactions (e.g., those associated with the use of ritonavir-boosted nirmatrelvir [Paxlovid™])
    - d. Regional prevalence of variants of concern (e.g., the regional prevalence of the Omicron BA.2 subvariant may affect which anti-SARS-CoV-2 mAbs can be used for treatment)

## RECOMMENDED READINGS:

1. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. *J Clin Oncol*. 2018 May 10;36(14):1443-1453. Available at <https://www.ncbi.nlm.nih.gov/pubmed/29461916>
2. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. *J Clin Oncol*. 2018 Sep 4;JCO1800374. Available at <https://www.ncbi.nlm.nih.gov/pubmed/30179565>
3. Johnson S, Laverne V, Skinner AM et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridoides difficile* Infection in Adults. *Clin Infect Dis*. 2021; 73(5): 755-57. Available at <https://www.ncbi.nlm.nih.gov/pubmed/34164674>
4. Patterson TF, Thompson GR 3rd, Denning DW et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; Aug 15;63(4):e1-e60. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27365388>
5. Pappas PG, Kauffman CA, Andes DR et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; Feb 15;62(4):e1-50. Available at <https://www.ncbi.nlm.nih.gov/pubmed/26679628>

## REFERENCES:

- 1 NCCN clinical practice guidelines in oncology (nccn guidelines®) for prevention and treatment of cancer-related infections. V.3.2022, 10/28/22, © 2022 national comprehensive cancer network, inc., all rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 2 Freifeld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clinical Infectious Diseases*. 2011; 52(4): e56-e93.
- 3 Taplitz RA, Kennedy EB, Bow EJ et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American society of clinical oncology and infectious diseases society of america clinical practice guideline update. *Journal of Clinical Oncology*. 2018; 36(14): 1443-53.
- 4 Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela Echaburu J et al. Prediction of serious complications in patients with seemingly stable febrile neutropenia: Validation of the clinical index of stable febrile neutropenia in a prospective cohort of patients from the finite study. *Journal of Clinical Oncology*. 2015; 33(5): 465-71.
- 5 Kuderer NM, Dale DC, Crawford J et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer*. 2006; 106(10): 2258-66.
- 6 Ganti BR, Marini BL, Nagel J et al. Impact of antibacterial prophylaxis during reinduction chemotherapy for relapse/refractory acute myeloid leukemia. *Support Care Cancer*. 2017; 25(2): 541-47.
- 7 Carmona-Bayonas A, Gomez J, Gonzalez-Billalabeitia E et al. Prognostic evaluation of febrile neutropenia in apparently stable adult cancer patients. *Br J Cancer*. 2011; 105(5): 612-7.
- 8 Paul M, Soares-Weiser K, Grozinsky S et al. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. *Cochrane Database Syst Rev*. 2003; (3): CD003038.
- 9 EORTC. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. European organization for research and treatment of cancer (eortc) international antimicrobial therapy cooperative group and the national cancer institute of canada-clinical trials group. *J Infect Dis*. 1991; 163(5): 951-8.

- 10 Paul M, Borok S, Fraser A et al. Empirical antibiotics against gram-positive infections for febrile neutropenia: Systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2005; 55(4): 436-44.
- 11 Cordonnier C, Pautas C, Maury S et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: A randomized, controlled trial. *Clin Infect Dis.* 2009; 48(8): 1042-51.
- 12 Walsh TJ, Pappas P, Winston DJ et al. Voriconazole compared with liposomal amphotericin b for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med.* 2002; 346(4): 225-34.
- 13 Walsh TJ, Teppler H, Donowitz GR et al. Caspofungin versus liposomal amphotericin b for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med.* 2004; 351(14): 1391-402.
- 14 Aguilar-Guisado M, Espigado I, Martin-Pena A et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (how long study): An open-label, randomised, controlled phase 4 trial. *Lancet Haematol.* 2017; 4(12): e573-e83.
- 15 Le Clech L, Talarmin JP, Couturier MA et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: The antibiostop study. *Infect Dis (Lond).* 2018; 50(7): 539-49.
- 16 Taplitz RA, Kennedy EB, Bow EJ et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: Asco and idsa clinical practice guideline update. *Journal of Clinical Oncology.* 2018; 36(30): 3043-54.
- 17 Bucaneve G, Micozzi A, Menichetti F et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *New England Journal of Medicine.* 2005; 353(10): 977-87.
- 18 Cullen M, Steven N, Billingham L et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med.* 2005; 353(10): 988-98.
- 19 Baden LR. Prophylactic antimicrobial agents and the importance of fitness. *New England Journal of Medicine.* 2005; 353(10): 1052-54.
- 20 Engels EA, Lau J and Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: A meta-analysis. *Journal of Clinical Oncology.* 1998; 16(3): 1179-87.
- 21 Gafter-Gvili A, Fraser A, Paul M et al. Meta-analysis: Antibiotic prophylaxis reduces mortality in neutropenic patients. *Annals of Internal Medicine.* 2005; 142(12\_Part\_1): 979.
- 22 Gafter-Gvili A, Fraser A, Paul M et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev.* 2012; 1: CD004386.
- 23 Communication FDS. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics> 07/08/19).
- 24 Cornely OA, Maertens J, Winston DJ et al. Posaconazole vs. Fluconazole or itraconazole prophylaxis in patients with neutropenia. *New England Journal of Medicine.* 2007; 356(4): 348-59.
- 25 Fontana L, Perlin DS, Zhao Y et al. Isavuconazole prophylaxis in patients with hematologic malignancies and hematopoietic-cell transplant recipients. *Clin Infect Dis.* 2019.
- 26 NCCN clinical practice guidelines in oncology (nccn guidelines®) for b-cell lymphomas. V.5.2022, 7/12/22, © 2022 national comprehensive cancer network, inc., all rights reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 27 Kusumoto S, Arcaini L, Hong X et al. Risk of hbv reactivation in patients with b-cell lymphomas receiving obinutuzumab or rituximab immunochemotherapy. *Blood.* 2019; 133(2): 137-46.
- 28 Hwang JP, Feld JJ, Hammond SP et al. Hepatitis b virus screening and management for patients with cancer prior to therapy: Asco provisional clinical opinion update. *J Clin Oncol.* 2020; 38(31): 3698-715.
- 29 Ramsey SD, Unger JM, Baker LH et al. Prevalence of hepatitis b virus, hepatitis c virus, and hiv infection among patients with newly diagnosed cancer from academic and community oncology practices. *JAMA Oncol.* 2019; 5(4): 497-505.
- 30 Evens AM, Jovanovic BD, Su YC et al. Rituximab-associated hepatitis b virus (hbv) reactivation in lymphoproliferative diseases: Meta-analysis and examination of fda safety reports. *Ann Oncol.* 2011; 22(5): 1170-80.



- 31 McDonald LC, Gerding DN, Johnson S et al. Clinical practice guidelines for clostridium *difficile* infection in adults and children: 2017 update by the infectious diseases society of america (idsa) and society for healthcare epidemiology of america (shea). *Clin Infect Dis*. 2018; 66(7): 987-94.
- 32 Miller BA, Chen LF, Sexton DJ et al. Comparison of the burdens of hospital-onset, healthcare facility-associated clostridium *difficile* infection and of healthcare-associated infection due to methicillin-resistant staphylococcus aureus in community hospitals. *Infect Control Hosp Epidemiol*. 2011; 32(4): 387-90.
- 33 Revolinski SL and Munoz-Price LS. Clostridium *difficile* in immunocompromised hosts: A review of epidemiology, risk factors, treatment, and prevention. *Clin Infect Dis*. 2019; 68(12): 2144-53.
- 34 Loo VG, Poirier L, Miller MA et al. A predominantly clonal multi-institutional outbreak of clostridium *difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med*. 2005; 353(23): 2442-9.
- 35 McDonald LC, Killgore GE, Thompson A et al. An epidemic, toxin gene-variant strain of clostridium *difficile*. *N Engl J Med*. 2005; 353(23): 2433-41.
- 36 Johnson S, Laverigne V, Skinner AM et al. Clinical practice guideline by the infectious diseases society of america (idsa) and society for healthcare epidemiology of america (shea): 2021 focused update guidelines on management of clostridioides *difficile* infection in adults. *Clin Infect Dis*. 2021; 73(5): 755-57.
- 37 Cornely OA, Crook DW, Esposito R et al. Fidaxomicin versus vancomycin for infection with clostridium *difficile* in europe, canada, and the USA: A double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012; 12(4): 281-9.
- 38 Louie TJ, Miller MA, Mullane KM et al. Fidaxomicin versus vancomycin for clostridium *difficile* infection. *N Engl J Med*. 2011; 364(5): 422-31.
- 39 Guery B, Menichetti F, Anttila VJ et al. Extended-pulsed fidaxomicin versus vancomycin for clostridium *difficile* infection in patients 60 years and older (extend): A randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis*. 2018; 18(3): 296-307.
- 40 Mikamo H, Tateda K, Yanagihara K et al. Efficacy and safety of fidaxomicin for the treatment of clostridioides (clostridium) *difficile* infection in a randomized, double-blind, comparative phase iii study in japan. *J Infect Chemother*. 2018; 24(9): 744-52.
- 41 Patterson TF, Thompson GR, 3rd, Denning DW et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of america. *Clin Infect Dis*. 2016; 63(4): e1-e60.
- 42 Herbrecht R, Bories P, Moulin JC et al. Risk stratification for invasive aspergillosis in immunocompromised patients. *Ann N Y Acad Sci*. 2012; 1272: 23-30.
- 43 Pagano L, Cairra M, Candoni A et al. The epidemiology of fungal infections in patients with hematologic malignancies: The seifem-2004 study. *Haematologica*. 2006; 91(8): 1068-75.
- 44 De Pauw B, Walsh TJ, Donnelly JP et al. Revised definitions of invasive fungal disease from the european organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (eortc/msg) consensus group. *Clin Infect Dis*. 2008; 46(12): 1813-21.
- 45 Wheat LJ and Walsh TJ. Diagnosis of invasive aspergillosis by galactomannan antigenemia detection using an enzyme immunoassay. *Eur J Clin Microbiol Infect Dis*. 2008; 27(4): 245-51.
- 46 Boonsarngsuk V, Niyompattama A, Teosirimongkol C et al. False-positive serum and bronchoalveolar lavage aspergillus galactomannan assays caused by different antibiotics. *Scand J Infect Dis*. 2010; 42(6-7): 461-8.
- 47 Guigue N, Menotti J and Ribaud P. False positive galactomannan test after ice-pop ingestion. *N Engl J Med*. 2013; 369(1): 97-8.
- 48 Pickering JW, Sant HW, Bowles CA et al. Evaluation of a (1->3)-beta-d-glucan assay for diagnosis of invasive fungal infections. *J Clin Microbiol*. 2005; 43(12): 5957-62.
- 49 Tran T and Beal SG. Application of the 1,3-beta-d-glucan (fungitell) assay in the diagnosis of invasive fungal infections. *Arch Pathol Lab Med*. 2016; 140(2): 181-5.
- 50 Metan G. The interaction between piperacillin-tazobactam and aspergillus galactomannan antigenemia assay: Is the story over? *Infection*. 2013; 41(1): 293-4.
- 51 Mikulska M, Furfaro E, Del Bono V et al. Piperacillin/tazobactam (tazocin) seems to be no longer responsible for false-positive results of the galactomannan assay. *J Antimicrob Chemother*. 2012; 67(7): 1746-8.

- 52 Pappas PG, Kauffman CA, Andes DR et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of america. *Clin Infect Dis*. 2016; 62(4): e1-50.
- 53 Herbrecht R, Denning DW, Patterson TF et al. Voriconazole versus amphotericin b for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002; 347(6): 408-15.
- 54 Maertens JA, Raad, II, Marr KA et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by aspergillus and other filamentous fungi (secure): A phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016; 387(10020): 760-9.
- 55 Marr KA, Schlamm HT, Herbrecht R et al. Combination antifungal therapy for invasive aspergillosis: A randomized trial. *Ann Intern Med*. 2015; 162(2): 81-9.
- 56 Tepadina (thiotepa) [package insert]. Lugano, switzerland: Adienne sa; 2021.
- 57 Neofytos D, Lombardi LR, Shields RK et al. Administration of voriconazole in patients with renal dysfunction. *Clin Infect Dis*. 2012; 54(7): 913-21.
- 58 NCCN clinical practice guidelines in oncology (nccn guidelines®) for hematopoietic growth factors. V.1.2022, 12/22/21, © 2022 national comprehensive cancer network, inc., all rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 59 Smith TJ, Bohlke K, Lyman GH et al. Recommendations for the use of wbc growth factors: American society of clinical oncology clinical practice guideline update. *J Clin Oncol*. 2015; 33(28): 3199-212.
- 60 NCCN clinical practice guidelines in oncology (nccn guidelines®) for acute lymphoblastic leukemia. V.1.2022, 4/2/22, © 2022 national comprehensive cancer network, inc., all rights reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
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- 63 Yang BB, Morrow PK, Wu X et al. Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: On-body injector and manual injection with a prefilled syringe. *Cancer Chemother Pharmacol*. 2015; 75(6): 1199-206.
- 64 Leukine (sargramostim) [package insert]. Bridgewater, nj: Sanofi-aventis us llc; 2017.
- 65 Neupogen (filgrastim) [package insert]. Thousand oaks, ca: Amgen inc; 2013.
- 66 Neulasta (pegfilgrastim) [package insert]. Thousand oaks, ca: Amgen inc; 2015.
- 67 Granix (tbo-filgrastim) [package insert]. North wales, pa: Teva pharmaceuticals USA, inc; 2014.
- 68 Zarxio (filgrastim-sndz) [package insert]. Princeton, nj: Sandoz inc; 2015.

- 69 Fulphila (pegfilgrastim-jmdb) [package insert]. Zurich, switzerland: Mylan gmbh; 2018.
- 70 Nivestym (filgrastim-aafi) [package insert]. Lake forest, il: Hospira inc; 2018.
- 71 Udenyca (pegfilgrastim-cbqv) [package insert]. Redwood city, ca: Coherus biosciences inc; 2018.
- 72 Nyvepria (pegfilgrastim-apgf) [package insert]. Lake forest, il: Hospira inc; 2020.
- 73 Releuko (filgrastim-ayow) [package insert]. Piscataway, nj: Kashiv biosciences, llc; 2022.
- 74 Fylnetra (pegfilgrastim-pbbk) [package insert]. Piscataway, nj: Kashiv biosciences, llc; 2022.
- 75 Rubin LG, Levin MJ, Ljungman P et al. 2013 idsa clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014; 58(3): 309-18.
- 76 Kroger AT, Atkinson WL, Marcuse EK et al. General recommendations on immunization: Recommendations of the advisory committee on immunization practices (acip). *MMWR Recomm Rep*. 2006; 55(RR-15): 1-48.
- 77 Centers for disease control and prevention. Recommended adult immunization schedule for ages 19 years or older, united states, 2021. Available from: <https://www.Cdc.Gov/vaccines/schedules/hcp/imz/adult.Html> [accessed 7/14/21].
- 78 Zugmaier G, Topp MS, Alekar S et al. Long-term follow-up of serum immunoglobulin levels in blinatumomab-treated patients with minimal residual disease-positive b-precursor acute lymphoblastic leukemia. *Blood Cancer J*. 2014; 4: 244.
- 79 Kobayashi M, Farrar JL, Gierke R et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among u.s. Adults: Updated recommendations of the advisory committee on immunization practices - united states, 2022. *MMWR Morb Mortal Wkly Rep*. 2022; 71(4): 109-17.
- 80 Anderson TC, Masters NB, Guo A et al. Use of recombinant zoster vaccine in immunocompromised adults aged >=19 years: Recommendations of the advisory committee on immunization practices - united states, 2022. *MMWR Morb Mortal Wkly Rep*. 2022; 71(3): 80-84.
- 81 Dooling KL, Guo A, Patel M et al. Recommendations of the advisory committee on immunization practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018; 67(3): 103-08.
- 82 NCCN clinical practice guidelines in oncology (nccn guidelines®) for management of immunotherapy-related toxicities. V.1.2022, 2/28/22, © 2022 national comprehensive cancer network, inc., all rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 83 Rittmeyer A, Barlesi F, Waterkamp D et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (oak): A phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017; 389(10066): 255-65.
- 84 Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-pd-1 antibody in cancer. *N Engl J Med*. 2012; 366(26): 2443-54.
- 85 Wolchok JD, Kluger H, Callahan MK et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013; 369(2): 122-33.
- 86 Weber JS, Hamid O, Chasalow SD et al. Ipilimumab increases activated t cells and enhances humoral immunity in patients with advanced melanoma. *J Immunother*. 2012; 35(1): 89-97.
- 87 NCCN clinical practice guidelines in oncology (nccn guidelines®) for cancer and covid-19 vaccination. V.7.0, 9/22/22, © 2022 national comprehensive cancer network, inc., all rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 88 (evusheld) tixagevimab co-packaged with cilgavimab [eua fact sheet]. Wilmington, de: Astrazeneca pharmaceuticals lp; 2022.).

- 89 Levin MJ, Ustianowski A, De Wit S et al. Intramuscular azd7442 (tixagevimab-cilgavimab) for prevention of covid-19. *N Engl J Med*. 2022; 386(23): 2188-200.
- 90 Meng Y, Lu W, Guo E et al. Cancer history is an independent risk factor for mortality in hospitalized covid-19 patients: A propensity score-matched analysis. *J Hematol Oncol*. 2020; 13(1): 75.
- 91 Covid-19 treatment guidelines panel. Coronavirus disease 2019 (covid-19) treatment guidelines. National institutes of health. Available at <https://www.Covid19treatmentguidelines.Nih.Gov/>. Accessed [7/14/2022].).

## **CHRONIC LEUKEMIAS**

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### **LEARNING OBJECTIVES:**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration relevant molecular biology testing, genomic information, efficacy and safety outcomes from clinical trials, and current treatment guidelines for patients with chronic leukemia.
2. Develop an appropriate plan for preventing, monitoring, and treating infusion-related reactions from monoclonal antibodies used in the treatment of hematologic malignancies.
3. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with pharmacotherapy for the treatment of cancers, including toxicities from tyrosine kinase inhibitors used to treat hematologic cancers.

## CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

### **Patient Case #1:**

JF is a retired 68-year-old male with a history of chronic kidney disease, hypertension and hypercholesterolemia. He was in his usual state of health until approximately 6 months ago, when he noted significant and painful lymph node swelling in his neck and groin. His family medical doctor prescribed an antibiotic, but his symptoms did not resolve. He returned to his family doctor, where his CBC revealed marked lymphocytosis (lymphocytes = 27,000 B cells/mm<sup>3</sup>). Flow cytometry confirmed the diagnosis of CLL.

### **I. Natural history of disease**

- A. CLL is considered an indolent disease.
  - 1. However, transformation to an aggressive non-Hodgkin lymphoma may occur (see “Richter transformation” or “Richter syndrome” below).
- B. Survival following diagnosis ranges from 1-20 years.<sup>1,2</sup>
  - 1. Some CLL patients survive for many years without therapy and succumb to unrelated causes, whereas others have a rapidly fatal disease despite aggressive therapy.<sup>3</sup>
  - 2. Survival is correlated with stage at diagnosis.

### **II. Prognostic factors and genomics<sup>1,2,4-13</sup>**

- A. Comorbidity has been identified as an independent adverse prognostic factor in CLL.<sup>14</sup>
  - 1. Disease control was less likely in patients with increased comorbidities (see section III, part D below for further discussion of comorbidity indices). This was likely due to more dose reductions and treatment discontinuations as compared to healthier patients.
  - 2. In this study, toxicity rates in patients with increased comorbidity were equivalent to healthier patients, likely due to pre-emptive dosage reductions of chemoimmunotherapy.<sup>14</sup> However, some studies suggest that patients with increased comorbid conditions have higher rates of discontinuation of novel agents due to adverse effects.<sup>15</sup>
- B. Genetic markers<sup>2,16-18</sup>
  - 1. Immunoglobulin heavy-chain variable (IGHV) region gene mutation status is an important predictor of survival outcomes.
    - a. All cases of CLL contain clonal rearrangements of the immunoglobulin heavy and light chain genes, consistent with their malignant nature.
    - b. Recent data show there are two subtypes of CLL, as determined by the presence or absence of somatic hypermutations in the immunoglobulin gene.
    - c. Unmutated IGHV ( $\leq 2\%$  mutated, also reported as  $\geq 98\%$  homology with germline sequence) is associated with a poor prognosis and significantly decreased survival compared to cases of mutated IGHV. This difference is independent of the stage of disease.

2. CD38 expression in  $\geq 30\%$  of B lymphocytes is associated with shorter progression-free survival and overall survival.
3. ZAP-70 is an intracellular protein that transmits activation signals to T lymphocytes. It is rarely present in normal B cells, but has been found in patients with CLL.
  - a. Expression of ZAP-70 in  $\geq 20\%$  of B lymphocytes is associated with shorter progression-free survival (PFS) and overall survival (OS).
  - b. Standardization and reproducibility of ZAP-70 flow cytometry methods remains a challenge. In clinical practice, evaluation of ZAP-70 expression is not recommended outside the context of a clinical trial.
4. Expression of CD49d in  $\geq 30\%$  of B lymphocytes is associated with lymphadenopathy, progressive disease and aggressive disease biology.
  - a. Among the prognostic factors that are based on flow cytometry (CD38, CD49d and ZAP-70), CD49d appears to be the strongest predictor of OS and treatment-free survival.
5. Both CD38 and ZAP-70 positivity correlate with unmutated IGHV and have been suggested as surrogate markers for IGHV mutational status. However, results are inconclusive, and the evaluation of CD38, CD49d and ZAP-70 are not currently recommended outside of clinical trials.

**Outcomes associated with IGHV gene mutations and surrogate markers in CLL.**<sup>2,16</sup>

	Outcome Association	
	Favorable	Unfavorable
<b><u>Flow cytometry</u></b>		
<b>ZAP-70</b>	<20%	$\geq 20\%$
<b>CD38</b>	<30%	$\geq 30\%$
<b>CD49d</b>	<30%	$\geq 30\%$
<b><u>DNA sequencing</u></b>		
<b>IGHV mutation</b>	>2%	$\leq 2\%$
<b>TP53 status</b>	Wild-type	Mutated

6. Cytogenetic mutations can be detected by fluorescence *in situ* hybridization (FISH) and provide prognostic information.<sup>19-25</sup>
  - a. 80% of previously untreated CLL have at least one cytogenetic mutation.

**Frequency of occurrence of the most commonly observed cytogenetic abnormalities in CLL.** <sup>2,16,20,26,27</sup>

Cytogenetic Abnormality	Frequency at Diagnosis
Deletion 13q	55%
Deletion 11q	10-25%
Trisomy 12	10-20%
Deletion 17p	5-8%
Deletion 6q	7%

**b. Specific deletions and prognosis**

- 1) Del(13q) as the sole abnormality is associated with a favorable prognosis and the longest median survival.
- 2) Del(11q) is associated with bulky lymphadenopathy, rapid disease progression, and shorter median survival when treated with conventional chemoimmunotherapy.
  - a) Del(11q) involves the loss of the ATM gene, which plays a role in regulation of the cell cycle.<sup>25</sup>
  - b) Patients with this mutation may have an impaired response to radiation or cytotoxic drugs, resulting in a poor outcome.
  - c) Previously untreated patients with del(11q) respond well to the combination of fludarabine and an alkylating agent.
  - d) When patients with del(11q) were treated with ibrutinib in the first-line setting, progression-free survival was comparable to patients who did not have del(11q).<sup>28</sup> Similar results were noted with venetoclax in patients with and without del(11q).<sup>29</sup>
- 3) Del(17p) is the single most important prognostic factor in CLL.
  - a) This mutation reflects the loss of the key tumor suppressor TP53 gene and is frequently associated with mutations in the remaining TP53 allele (80% of cases).<sup>17,25,30,31</sup>
  - b) Patients with this mutation progress more often and more rapidly to symptomatic disease.
  - c) The mutation may be acquired during the disease course. Reassessing mutational status by DNA sequencing at the time of disease progression is warranted.<sup>32</sup>
  - d) The presence of TP53 mutations is associated with the worst outcomes, including short treatment-free intervals, poor response to chemotherapy, and short median survival (median < 3 years) with standard chemoimmunotherapy and/or rituximab.
  - e) Patients with this mutation are considered to have “ultra-high risk” CLL and should be treated with novel therapies.
- 4) Complex karyotype ( $\geq 3$  unrelated chromosomal abnormalities) is associated with an unfavorable prognosis.<sup>12</sup>
- 5) Favorable prognosis refers to deletion 13q as the sole abnormality, while neutral prognosis includes normal cytogenetics and trisomy 12. Unfavorable prognosis includes del(11q) and



del(17p). When multiple abnormalities exist, the impact on prognosis is ordered as **del(17p)** > **del(11q)** > **trisomy 12** > **del(13q)**.<sup>33</sup>

**Prognosis associated with cytogenetics in CLL.**<sup>2,16,27,34</sup>

Chromosomal Abnormality	Median Overall Survival (months)	Median Treatment-Free Survival (months)
Deletion 13q	133	92
Normal karyotype	111	49
Trisomy 12	114	33
Deletion 11q	79	13
Deletion 17p/TP53 mutation	32	9

- c. The survival estimates for these markers were derived prior to the widespread use of small molecule inhibitor-based therapies. As such, estimates of survival outcomes may not reflect current expectations.<sup>2</sup>
- d. In the general clinical practice setting, prognostic factors should not determine treatment choices, with the exception of del(17p).<sup>2</sup>

**C. International Prognostic Index for CLL (CLL-IPI)**<sup>17,21,23,24,31,33,35-39</sup>

1. Using data from 3472 previously untreated patients with CLL who participated in prospective, randomized controlled clinical trials, five independent prognostic factors were identified:
  - a. TP53 deletion or mutation, or both
  - b. IGHV mutational status
  - c. Serum  $\beta_2$ -microglobulin concentration
  - d. Clinical stage of disease
  - e. Age
2. Patients were classified into one of four risk groups based on a weighted grading of the independent factors: low, intermediate, high and very high risk. Five year OS was low risk = 93%, intermediate risk = 79%, high risk = 63% and very high risk = 23%.<sup>31</sup>
3. The CLL-IPI findings have been validated by several other groups, but its use is not yet recommended in treatment guidelines as only applies at the time of first treatment. Likewise, it was developed prior to the use of novel small molecule inhibitors. However, it is expected to improve both clinical trial design and patient counseling.

**Patient Case #1, continued:**

After further workup, JF is diagnosed with Binet stage B disease. His cytogenetic analysis reveals that he has a del(13q) mutation and unmutated IGHV. He is considered medically fit to receive treatment.

**Which of the following treatment regimens is the most appropriate first-line therapy for FB?**

- A. Acalabrutinib +/- obinutuzumab
- B. Chlorambucil + ofatumumab
- C. Fludarabine, cyclophosphamide and rituximab (FCR)
- D. Alemtuzumab + rituximab

**III. Treatment**

- A. The clinical course of CLL varies greatly.<sup>2,22,24,40</sup>
  - 1. A significant portion of CLL patients never require treatment, or can be effectively managed with supportive care.
  - 2. In contrast, other patients have a very aggressive clinical course and suffer early disease progression and death.
- B. For all patients with CLL, the goal of frontline therapy is to palliate symptoms and extend survival.<sup>16,41</sup>
- C. Initiating treatment<sup>2,8,24,31,33,38,39,42-47</sup>
  - 1. An “active surveillance” approach may be appropriate for asymptomatic patients with early-stage, low-risk disease (Rai stage 0 or Binet stage A).
    - a. Two phase III studies and a meta-analysis revealed that there is no statistically significant difference in survival between patients who were treated early versus those who were deferred until there was a clinical indication for treatment.<sup>44,48</sup>
    - b. The potential benefit of early-intervention therapy with the currently available treatment agents remains to be proven.<sup>38</sup>
  - 2. Patients with intermediate-risk disease (Rai stage I or II or Binet stage B) may benefit from therapy if they show evidence of progressive disease or become symptomatic.
    - a. Absolute lymphocyte count (ALC) or symptoms related to leukostasis should not be the sole indicator to begin treatment. The symptoms of leukostasis that develop in patients with acute leukemia rarely occur in patients with CLL.
    - b. Indications for initiating treatment include:
      - 1) Disease-related constitutional symptoms: severe fatigue, unintended weight loss ( $\geq 10\%$  in previous 6 months, drenching night sweats and/or fever without infection
      - 2) Threatened end-organ function
      - 3) Progressive bulky disease: massive or symptomatic splenomegaly or lymphadenopathy
      - 4) Progressive bone marrow failure, as evidenced by worsening anemia and/or thrombocytopenia

- 5) Autoimmune anemia or thrombocytopenia that is unresponsive to treatment with corticosteroids or other standard therapies
  - 6) An increase in absolute lymphocyte count (ALC) of  $\geq 50\%$  over a 2-month period, or lymphocyte doubling time (LDT) of  $< 6$  months
  - 7) Symptomatic extranodal involvement (skin, kidney, lung, spine, etc)
3. Patients with advanced stage or high-risk CLL (Rai stage III or IV or Binet stage C) typically present with symptomatic disease and require immediate treatment.
- D. Patient evaluation / goals of therapy<sup>2,17,23,25,42,46,49-56</sup>
1. CLL is primarily a disease of the elderly. The median age at diagnosis is 72 years, with 40% of patients being  $> 75$  years and  $\sim 30\%$  being  $> 80$  years old.
  2. Up to 90% of patients with CLL have one or more comorbidities.<sup>53,54</sup>
  3. A decline in organ function and/or co-existing disease(s) may impact the choice of therapy. A higher burden of comorbidities is known to impact the outcome of patients with CLL.<sup>56</sup>
  4. It is critical to assess each individual patient's comorbidities, age and performance status to evaluate the patient's "fitness" for therapy.<sup>57-59</sup>
    - a. Younger or physiologically fit patients are called "go-go" patients. In these patients, achieving a durable response is the goal of treatment.
    - b. Older patients who cannot tolerate aggressive regimens, but may still benefit from active therapy, are called "slow-go" patients.
    - c. Frail patients with significant comorbidities, called "no-go" patients, should be treated with palliative therapy. In these patients, controlling symptoms is the essential treatment goal. A regimen with a more favorable toxicity profile should be applied in this setting.
  5. At this time, there is no standard tool to assess a patient's fitness for therapy.<sup>56</sup>
    - a. Patients were traditionally classified based on age alone, but it is now recognized that chronological age is not a reliable surrogate marker of fitness.<sup>41,54,60,61</sup>
    - b. Creatinine clearance (CrCl), rather than age, has been noted as the primary predictor of higher toxicity with fludarabine-based regimens. References suggest reducing the dose of fludarabine when  $\text{CrCl} < 80 \text{ mL/min}$ .<sup>62</sup>
    - c. Suggested tools to assess comorbidity that have been validated include the Charlson Comorbidity Index (CCI), the Cumulative Illness Rating Scale (CIRS), the National Cancer Institute (NCI) comorbidity index and the Comprehensive Geriatric Assessment (CGA).<sup>2,12,54,56,57,59,63-65</sup>
    - d. The presence of a reliable caregiver for elderly and/or unfit patients is also important for the patient's candidacy for various treatments and effective adherence to treatment.<sup>56</sup> Continuous therapy may be a more viable option compared to fixed-duration therapy in terms of toxicity, number of clinic visits, and amount of laboratory monitoring.
  6. A detailed medication review should be performed to assess potential drug interactions with therapy. It has been reported that most older adults with blood cancers take  $\geq 5$  medications, and that polypharmacy (defined as taking  $\geq 8$  medications) is associated with frailty in older adults with blood cancers.<sup>66</sup>

7. An emerging goal of treatment is “minimal residual disease” or “measurable residual disease” (MRD).<sup>67-69</sup>
  - a. MRD describe the inability to detect measurable disease at a specified reporting threshold.
  - b. Unlike adult and childhood acute leukemias, where the assessment of response to therapy by MRD monitoring drives therapeutic choices, MRD analysis in CLL has only recently been introduced.
  - c. Undetectable MRD (U-MRD) at the end of treatment has demonstrated independent prognostic significance in CLL, correlating with favorable progression-free survival and overall survival with chemoimmunotherapy and small molecule inhibitors in both the first and second-line settings.<sup>2,68,70,71</sup>
  - d. Decisions made by MRD assessments are not currently applied in clinical practice guidelines.<sup>68</sup>
  - e. MRD may not be the treatment goal for every patient. This may be particularly relevant for elderly patients with multiple comorbidities or patients in the relapsed/refractory setting, in which achieving durable disease control while minimizing adverse effects may be a more desirable goal.<sup>67,71,72</sup>
  - f. If used, MRD evaluation should be performed using an assay with a sensitivity of  $10^{-4}$ . Validated assay methods include allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and flow cytometry (MRD flow). Next generation sequencing (NGS) is also used with a greater level of sensitivity ( $10^{-6}$ ).
- E. Choice of first-line therapy<sup>2,17,23,42,73-79</sup>
  1. The current standard of care has evolved from single-agent alkylating agents, through the introduction of purine analogs, to chemoimmunotherapy combinations and small molecule inhibitors.
  2. Choice of therapy can be subdivided based on genetic mutation:
    - a. Presence or absence of del (17p)/TP53 mutation
    - b. Mutated IGHV
  3. **First-line therapy in patients without del (17p)/TP53 mutation**
    - a. Acalabrutinib +/- obinutuzumab is an NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Category 1 preferred regimen in this setting.<sup>2</sup>
      - 1) The “ELEVATE-TN” study was a phase III trial of 535 patients with previously untreated CLL who were 65 years of age or older, or under 65 years of age with comorbidities (considered as a Cumulative Illness Ratings Scale score > 6 or CrCl < 70 mL/min). The results of this trial have been extrapolated to young, medically fit patients with CLL.<sup>80-82</sup>
        - a) Patients were randomized to acalabrutinib alone, acalabrutinib + obinutuzumab or chlorambucil + obinutuzumab. Note that patients who received chlorambucil + obinutuzumab received treatment for 6 cycles, and patients who received acalabrutinib + obinutuzumab received obinutuzumab for 6 cycles, but acalabrutinib was continued until disease progression in both of the acalabrutinib-containing arms.
        - b) The primary endpoint was PFS of acalabrutinib + obinutuzumab compared to chlorambucil + obinutuzumab as assessed by an independent review committee.

- c) At a median follow-up of 28 months, both acalabrutinib monotherapy and acalabrutinib + obinutuzumab had significantly longer PFS compared to chlorambucil + obinutuzumab, reducing the risk of progression or death by 80% with acalabrutinib monotherapy and by 90% with acalabrutinib + obinutuzumab. Improvements in PFS were consistent in the five-year follow-up report.
- d) Improvement in PFS with acalabrutinib monotherapy or acalabrutinib + obinutuzumab was consistent across subgroups, including del(17p).

**Results of the ELEVATE-TN study, which randomized previously untreated, elderly patients with CLL to acalabrutinib monotherapy, acalabrutinib + obinutuzumab or chlorambucil + obinutuzumab.**<sup>80-82</sup>

Selected Results of the ELEVATE-TN Study				
	Acalabrutinib	Acalabrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Statistics
Median PFS	---	Not reached	27.8 months	p < 0.0001
	Not reached	---	27.8 months	p < 0.0001
PFS at 60 months	72%	84%	21%	NR
OS at 60 months	84%	90%	82%	NR

NR = not reported; OS = overall survival; PFS = progression-free survival.

- b. Venetoclax + obinutuzumab is an NCCN Guidelines® Category 1 preferred regimen in this setting.<sup>2</sup>
  - 1) The “CLL14” study was a phase III trial of 432 patients with previously untreated CLL who had co-existing conditions (considered as a CIRS score > 6 or CrCl < 70 mL/min). The median age of trial participants was 72 years of age.<sup>83-86</sup> The results of this trial have been extrapolated to young, medically fit patients with CLL.
    - a) Patients were randomized to venetoclax + obinutuzumab or chlorambucil + obinutuzumab. The total duration of therapy with venetoclax + obinutuzumab was 1 year, while the total duration of therapy with chlorambucil + obinutuzumab was 6 months. The primary endpoint was investigator-assessed PFS.
    - b) At a median of 65.4 months, PFS was superior for venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab (median not reached vs 36.4 months; HR 0.35, p<0.0001). At 5 years, the estimated PFS was 62.6% with venetoclax + obinutuzumab compared to 27.1% with chlorambucil + obinutuzumab.
    - c) The benefit in PFS was observed in patients with TP53 mutation, patients with unmutated IGHV, and other prespecified subgroups. A multivariable analysis indicated del(17p) and high disease burden as independent prognostic factors for PFS in patients treated with venetoclax + obinutuzumab.
    - d) At 5 years, the time to next treatment was significantly longer after venetoclax + obinutuzumab.
    - e) A notable portion of both treatment groups required growth factor support.

**Results of the CLL14 study, which randomized previously untreated patients with CLL and comorbidities to venetoclax + obinutuzumab or chlorambucil + obinutuzumab.<sup>83-86</sup>**

Selected Results of the CLL14 Study			
	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	<i>p</i> value
PFS at 36 months, investigator-assessed	81.9%	49.5%	NR
PFS at 60 months	62.6%	27%	NR
Median OS	Not reached	Not reached	NR
Complete response to treatment	49.5%	23.1%	< 0.001
Negative for minimal residual disease in peripheral blood 18 months after completion of treatment	47.2%	7.4%	NR
Time to next treatment at 60 months	72.1%	42.8%	< 0.0001
Required treatment with growth factor	43.5%	45.8%	NR

NR = not reported; OS = overall survival; PFS = progression-free survival.

- c. Zanubrutinib is a Category 1 preferred regimen in this setting per the NCCN Guidelines<sup>®</sup>.<sup>2</sup>
  - 1) Zanubrutinib is a next-generation irreversible BTK inhibitor with high specificity for BTK. Its off-target activity with structurally related kinases such as EGFR, ITK and SRC is comparatively lower than ibrutinib.<sup>87</sup>
  - 2) This recommendation is based on the phase 3 trial “SEQUOIA” trial, an ongoing phase III trial with multiple cohorts. Cohort 1 compared zanubrutinib with bendamustine + rituximab in 479 patients with treatment-naïve CLL, with PFS as assessed by an independent review committee as the primary endpoint.<sup>88,89</sup>
    - a) At 24 months, PFS was prolonged with zanubrutinib vs BR (85.5% vs 69.5%; HR 0.42, *p* < 0.0001).
    - b) PFS was also superior with zanubrutinib across high-risk subgroups; however, patients with del(17p) were not included in this cohort of the SEQUOIA study.
- d. Ibrutinib is an NCCN Guidelines<sup>®</sup> Category 1 recommendation in the first-line setting. However, this recommendation is categorized as an “Other recommended regimen” as of August 2022.<sup>2</sup>
  - 1) The change in designation from a “preferred regimen” to an “other recommended regimen” was implemented due to concerns about the toxicity profile of this agent.<sup>2</sup> Please see the “Toxicities of small molecule inhibitors and management” section below for further details.
  - 2) The “ECOG-E1912” study was a randomized phase III trial that compared ibrutinib + rituximab (IR) to fludarabine, cyclophosphamide and rituximab (FCR) in 529 treatment-naïve patients with CLL who were ≤ 70 years of age and required therapy. The primary endpoint was PFS, with a secondary endpoint of OS.<sup>79,90-93</sup>

- a) Patients with del(17p)/TP53 mutation were excluded from trial participation.
  - b) The hazard ratio for PFS at 45 months favored IR over FCR (HR = 0.39, 95% CI = 0.26 – 0.57; p < 0.0001).
  - c) The improvement in PFS was seen across subgroups, including in patients with both IGHV-mutated and IGHV-unmutated disease.
  - d) Improvement in OS was also observed for patients in the IR arm (HR, 0.47; p = 0.018).
- 3) The “RESONATE-2” study was an open-label, randomized phase III trial that compared ibrutinib and chlorambucil in 269 previously untreated older patients with CLL or small lymphocytic leukemia (SLL).<sup>94-99</sup>
- a) The primary endpoint was PFS as assessed by an independent review committee.
  - b) Patients who received ibrutinib had a statistically significantly longer PFS. This benefit was consistent in higher-risk subgroups (TP53 mutation, 11q deletion, and/or unmutated IGHV).
  - c) OS and ORR were also statistically significantly improved with ibrutinib.
  - d) Rates of sustained increases in both hemoglobin and platelet levels were higher with ibrutinib. In addition, greater improvements in quality of life occurred in the ibrutinib arm.
  - e) Patients who progressed during the study were allowed to cross over to the alternate therapy; ultimately, more than half of the chlorambucil patients crossed over to ibrutinib, which may have influenced OS.

**Results of the RESONATE-2 study, which randomized previously untreated, elderly patients with CLL to ibrutinib or chlorambucil.**<sup>94-99</sup>

Selected Results of the RESONATE-2 Study			
	Ibrutinib	Chlorambucil	Statistics
ORR	92%	36%	p < 0.0001
PFS at 7 years	59%	9%	HR = 0.154 (95% CI, 0.108 – 0.22)
OS at 5 years	83%	68%	HR = 0.45 (95% CI, 0.266-0.761)

CI = confidence interval; HR = hazard ratio; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

- 4) The phase III Alliance North American Intergroup Study (“A041202”) compared ibrutinib monotherapy, ibrutinib + rituximab and bendamustine + rituximab in 547 patients with untreated CLL who were ≥ 65 years old. The primary endpoint was PFS.<sup>100-102</sup>
- a) The results of the trial were released on the results of protocol-defined interim analyses.
  - b) Median PFS was reached only with bendamustine + rituximab. The estimated percentage of patients with PFS at two years was statistically significantly higher with ibrutinib alone and with ibrutinib + rituximab than with bendamustine + rituximab.

There was no significant difference between ibrutinib and ibrutinib + rituximab with regard to PFS.

- c) In the subgroup analyses, PFS was longer with ibrutinib-containing regimens in all risk factor-related subgroups. There was no significant difference in OS between the groups.
- d) The rate of grades 3-5 hematologic adverse events was greater in the bendamustine + rituximab arm, while the rates of grades 3-5 non-hematologic adverse events was greater in the ibrutinib-containing regimens.

**Results of the ALLIANCE A041202 study, which randomized previously untreated, elderly patients with CLL to ibrutinib monotherapy, ibrutinib + rituximab or bendamustine + rituximab.**<sup>100-102</sup>

Selected Results of the ALLIANCE A041202 Study				
	Ibrutinib	Ibrutinib + rituximab	Bendamustine + rituximab	Statistics
PFS at 2 years	87%	---	74%	p < 0.001
	---	88%	74%	p < 0.001
	87%	88%	---	p = 0.49
Median PFS	Not reached	Not reached	44 months	p < 0.0001
PFS at 4 years	76%	76%	47%	---
OS at 2 years	90%	94%	95%	p ≥ 0.65 for all pairwise comparisons
OS at 4 years	85%	86%	84%	0.49

PFS = progression-free survival; OS = overall survival.

- 5) The results of these trials and others call the benefit of adding an anti-CD20 monoclonal antibody to ibrutinib into question.<sup>79,93,100</sup> Therefore, the NCCN Guidelines® recommend ibrutinib alone in this setting.<sup>2</sup>
- e. Bendamustine and anti-CD20 monoclonal antibody combinations are “other recommended regimens” in the first-line setting.<sup>2</sup>
  - 1. NCCN Guidelines® recommend initiating bendamustine 70 mg/m<sup>2</sup> in cycle 1, with dose escalation to 90 mg/m<sup>2</sup> in subsequent cycles if tolerated, in patients age ≥ 65 and in younger patients with significant comorbidities (specifically, creatinine clearance < 70 mL/min).<sup>2</sup>
  - 1) The final results of the phase III “CLL10 study” have been reported.<sup>49,103-107</sup>
    - a) This trial randomized 564 previously untreated, medically fit CLL patients without del(17p) to FCR or bendamustine + rituximab (BR). The primary endpoint was non-inferiority of PFS.
    - b) The FCR arm had significantly improved PFS, but OS was not different between the groups.
    - c) The benefit of improved PFS with FCR was not seen in patients > 65 years of age.
    - d) Patients who received FCR experienced more grade 3-4 neutropenia and grade 3-4 infections. The use of prophylactic growth factor support was not permitted in this trial.



- e) The updated results of the study confirmed that the rates of secondary AML or MDS were greater in the FCR arm (7% vs 1% in patients > 65 years and  $\leq$  3% vs 1% in patients  $\leq$  65 years).

**Results of the CLL10 study, which randomized previously untreated, medically fit patients with CLL to FCR or BR therapy.**<sup>103,105-107</sup>

Selected Results of the CLL10 Study			
	FCR	BR	p value
CRR	40.7%	31.5%	0.026
ORR	97.8%	97.8%	1.0
Median PFS	57.6 months	42.3 months	0.001
PFS of pts $\leq$ 65 years	57.6 months	38.2 months	< 0.0001
PFS of pts > 65 years	57.9 months	48.5 months	0.134
OS of pts $\leq$ 65 years at 5 years	85.6%	81.1%	0.119
OS of pts > 65 years at 5 years	70.9%	78.8%	0.238
Grade 3/4 neutropenia	84%	59%	< 0.001
Grade 3/4 infections	39%	25%	0.001

BR = bendamustine and rituximab; CRR = complete response rate; FCR = fludarabine, cyclophosphamide and rituximab; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

- f. Chlorambucil + obinutuzumab is an “other recommended regimen” in the NCCN Guidelines<sup>®</sup>.<sup>2</sup>
- 1) The “CLL11 study” randomized nearly 800 previously untreated CLL patients with co-existing conditions (CRS >6 and/or CrCl 30-69 mL/min) to single-agent chlorambucil, rituximab + chlorambucil, or obinutuzumab + chlorambucil.<sup>77,108-111</sup>
    - a) The direct comparison of obinutuzumab + chlorambucil to chlorambucil revealed statistically superior PFS and OS, as well as improved ORR, with the combination.
    - b) PFS, ORR and OS were statistically superior with obinutuzumab + chlorambucil compared to rituximab + chlorambucil.
    - c) Infusion reactions were common, and severe in some cases. They can be managed in a manner similar to rituximab-related reactions – see separate section on Infusion-Related Reactions from Monoclonal Antibodies Used in Hematologic Malignancies.

Results of the CLL11 study, which randomized previously untreated patients with co-existing conditions to chlorambucil, rituximab + chlorambucil or obinutuzumab + chlorambucil.<sup>77,108,110,111</sup>

Selected Results of the CLL11 Study				
	Chlorambucil	Rituximab + chlorambucil	Obinutuzumab + chlorambucil	P value
CRR	---	7%	20.7%	< 0.001
ORR	---	65.1%	78.4%	< 0.001
Median PFS	---	15.7 months	28.9 months	< 0.0001
	11.1 months	---	31.1 months	< 0.0001
	11.1 months	15.7 months	---	< 0.001
Time to next treatment	---	34.9 months	56.4 months	< 0.0001
Median OS	---	73.1 months	Not reached	p = 0.0245
OS at 24 months	---	84%	91%	NR
OS at 60 months	---	57%	66%	NR

CRR = complete response rate; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

- g. FCR is listed as a regimen that may be “useful in certain circumstances” in the first-line setting as per the NCCN Guidelines®.<sup>2</sup>
  - 1) This regimen may be considered for patients with **mutated IGHV** who are < 65 years of age and without significant comorbidities.
  - 2) This recommendation is based on the CLL10 study (discussed above), the “CLL8 study” and others.<sup>2,107,112</sup>
- h. Subcutaneous rituximab (Rituxan Hycela®) in CLL<sup>113</sup>
  - 1) A combination of rituximab and the endoglycosidase hyaluronidase human.
  - 2) The prescribing information explicitly states that the product should only be initiated after patients have received at least one full dose of a rituximab product by intravenous infusion. Current NCCN Guidelines® reiterate this concept.<sup>2</sup>
  - 3) For CLL, the dose is 1600 mg/26,800 units (13.4 mL of product) subcutaneously according to the recommended schedule. The product is supplied in single dose vials. Note that the doses and vial sizes differ between CLL and lymphoma.
  - 4) The product should be injected into the subcutaneous tissue of the abdomen over approximately 7 minutes. Note that this administration time is different than that which is recommended for lymphoma.
- i. Biosimilar rituximab products in CLL<sup>2,114-116</sup>
  - 1) Rituximab-abbs (Truxima®), rituximab-arxx (Riabni®) and rituximab-pvvr (Ruxience®) have all been approved by the FDA. See the Lymphomas handout for specifics of approved indications and uses.
  - 2) NCCN Guidelines® state that an FDA-approved biosimilar is an appropriate substitution for rituximab for all rituximab indications.

#### 4. First-line therapy in patients with del (17p)/TP53 mutations

- a. Preferred regimens for first-line therapy in this setting include acalabrutinib +/- obinutuzumab, venetoclax + obinutuzumab, and zanubrutinib.<sup>2</sup>
- b. Other recommended options in this setting include alemtuzumab +/- rituximab, high-dose methylprednisolone + rituximab, ibrutinib, and obinutuzumab.<sup>2</sup>
- c. Chemoimmunotherapy is not recommended, as del(17p)/TP53 mutation is associated with low response rates.<sup>2</sup>
- d. First-line therapy options historically included alemtuzumab.
  - 1) Although it was initially approved as first-line treatment for CLL, adverse effects such as infusion-related events, cytomegalovirus infections, and neutropenia limited its use. With the introduction of other novel agents, it currently has a very limited role in the management of CLL.<sup>43</sup>
  - 2) Alemtuzumab is no longer commercially available for the treatment of CLL, although it may be available from the manufacturer if necessary via the Campath® Distribution Program.

#### 5. Duration of first-line therapy<sup>2</sup>

- a. For patients who are treated with BTKi in the first-line setting and have disease response, the same BTKi should be continued until disease progression.
- b. In patients who receive venetoclax fixed-duration regimens in the first-line setting, observation until relapse with indications for treatment is appropriate.

#### F. Response criteria<sup>2,69,117</sup>

1. The National Cancer Institute-sponsored Working Group (NCI-WG) revised its guidelines in 2018 to provide the most recent recommendations for general clinical practice.
2. In clinical practice, response assessment requires both a physical examination and evaluation of blood parameters.
3. Response should be evaluated at least 2 months after the completion of therapy.
4. Response definitions

#### Definitions of response to therapy in CLL.<sup>2,45</sup>

Response	Definition
Complete response (CR)	At ≥2 months post-therapy: <ul style="list-style-type: none"><li>• Absence of hepatomegaly, splenomegaly and constitutional symptoms</li><li>• No lymph nodes ≥ 1.5 cm in longest dimension</li><li>• Normalization of CBC (neutrophils ≥ 1500/mm<sup>3</sup>, platelets ≥100,000/mm<sup>3</sup>, hemoglobin ≥11 g/dL)</li><li>• Lymphocytes &lt;4000/mm<sup>3</sup></li><li>• Marrow is normocellular, no CLL cells and no B-lymphoid nodules</li></ul>
Partial response (PR)	At ≥2 months post-therapy: <ul style="list-style-type: none"><li>• A decrease in the number of peripheral blood lymphocytes by ≥50% from baseline</li></ul>

	<ul style="list-style-type: none"> <li>• Reduction in lymphadenopathy (by CT scan in clinical trials, or by palpation in clinical practice) as defined by: <ul style="list-style-type: none"> <li>○ Decreased lymph node size by <math>\geq 50\%</math></li> <li>○ Spleen and/or liver size has decreased by <math>\geq 50\%</math> from baseline</li> <li>○ No increase in any lymph node, and no new node(s) detected</li> </ul> </li> <li>• Normalization of CBC (neutrophils <math>\geq 1500/\text{mm}^3</math> or 50% improvement over baseline; platelets <math>\geq 100,000/\text{mm}^3</math> or 50% improvement over baseline; hemoglobin <math>\geq 11</math> g/dL or 50% improvement over baseline)</li> <li>• Marrow has presence of CLL cells or of B-lymphoid nodules (bone marrow biopsy was not performed)</li> </ul>
Stable disease (SD) / Nonresponse	No CR or PR, no progressive disease
Progressive disease (PD)	<p>At least 1 of the following:</p> <ul style="list-style-type: none"> <li>• Lymphadenopathy (<math>\geq 50\%</math> increase from baseline or from response)</li> <li>• <math>\geq 50\%</math> increase in hepatomegaly or splenomegaly from baseline or from response</li> <li>• Transformation to a more aggressive histology (Richter's transformation)</li> <li>• Occurrence of cytopenias (neutropenia, anemia or thrombocytopenia) attributable to CLL</li> <li>• Marrow has increase of CLL cells by <math>\geq 50\%</math> on successive biopsies</li> </ul>
Treatment failure	<p>Includes the following responses:</p> <ul style="list-style-type: none"> <li>• Stable disease</li> <li>• Nonresponse</li> <li>• Progressive disease</li> </ul>
Relapse	Patient achieved CR or PR but at $\geq 6$ months shows evidence of disease progression
Refractory	Treatment failure or disease progression within 6 months of the last treatment

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**Patient Case #1, continued:**

**Correct answer = A (Acalabrutinib +/- obinutuzumab).**

This patient is over 65 years of age and has chronic kidney disease, making him ineligible for fludarabine-based chemoimmunotherapy regimens in the first-line setting. Acalabrutinib +/- obinutuzumab has an NCCN Guidelines® Category 1 preferred regimen recommendation in this setting based on the results of the ELEVATE-TN trial. Treatment with ofatumumab is no longer recommended for the treatment of CLL. Alemtuzumab is not recommended in the first-line setting in patients without del(17p).

**Patient Case #2:**

DG is a 63-year old male with CLL with del(11q). His past medical history is significant for hypothyroidism, well-controlled atrial fibrillation, and gastroesophageal reflux disease. He received treatment with FCR three years ago and achieved a complete response. After experiencing a recurrence of painful cervical lymphadenopathy, he has recently been diagnosed with relapsed CLL.

**Which of the following regimens is most appropriate for DG at this point in his course?**

- A. Repeat FCR**
- B. Chlorambucil + obinutuzumab**
- C. Venetoclax + rituximab**
- D. Bendamustine, rituximab + idelalisib**

**G. Treatment of relapsed / refractory disease<sup>2,17,23,25,40,118-134</sup>**

1. Although newer agents have improved the results of first-line therapy, CLL remains incurable. Patients will universally relapse after primary treatment.<sup>135</sup>
2. The management of relapsed disease depends on patient age, performance status, previous therapy, response and duration of response to therapy, tolerance of previous therapy, time from last therapy, adverse effect profile and cost.<sup>134</sup>
3. Genetic abnormalities may change during a patient's course of CLL. Therefore, genetic analysis should be repeated before any second-line or subsequent treatment, with specific interest in del(17p)/TP53 mutation status.<sup>2,25</sup>
4. Early relapse (within 24-36 months) or a poor response to chemoimmunotherapy suggests aggressive disease and is associated with a short OS.<sup>47</sup>
5. Sequence of therapy in relapsed / refractory disease
  - a. At this time, there are no formal recommendations for the sequencing of agents in the relapsed / refractory setting.<sup>24,134-137</sup>
  - b. Following BTKi discontinuation for toxicity, an alternative BTKi may be considered.<sup>133,137</sup>
  - c. Selections are often made based on the unique toxicities of each agent, as well as patient and physician preference.<sup>23,138</sup> BTKi may be preferred due to convenient dosing, while venetoclax may be preferred if the patient has significant cardiac co-morbidities.
6. **Second- or third-line therapy in patients without del (17p)/TP53 mutation**
  - a. Acalabrutinib is an NCCN Guidelines® Category 1 preferred regimen in this setting.<sup>2</sup>
    - 1) The phase III "ASCEND" trial evaluated the efficacy and safety of acalabrutinib monotherapy vs investigators' choice of therapy (either idelalisib + rituximab or bendamustine + rituximab) in 310 patients with relapsed or refractory CLL. The primary endpoint was PFS as assessed by an independent review committee.<sup>139-141</sup>
      - a) At a median follow-up of 36 months, acalabrutinib significantly prolonged independently-assessed PFS compared to both other therapies (median not reached vs

16.8 months; HR 0.29, 95% CI 0.21-0.41,  $p < 0.0001$ ). This represents a 71% reduction in risk of progression or death in patients who received acalabrutinib.

- b) PFS improvement with acalabrutinib were seen across subgroups including del(17p), TP53 mutation and higher Rai stage.
  - c) Overall survival rates at 12 months were not different between the treatment groups; however, 23% of patients randomized to either idelalisib + rituximab or bendamustine + rituximab crossed over to receive subsequent acalabrutinib monotherapy.
- 2) The “ELEVATE-RR” trial was the first head-to-head trial comparing ibrutinib to acalabrutinib in patients with previously treated CLL and del(17p) or del(11q).<sup>142,143</sup>
- a) After a median follow-up of 40.9 months, acalabrutinib was determined to be noninferior to ibrutinib with a median PFS of 38.4 months in both arms (HR 1.00; 95% CI, 0.79 to 1.27).
  - b) Additional details of this trial can be found below under “Toxicities of small molecule inhibitors and management.
- b. Zanubrutinib is a preferred regimen in this setting as per NCCN Guidelines®.<sup>2</sup>
- 1) The phase III “ALPINE” trial compared zanubrutinib to ibrutinib in patients with relapsed/refractory CLL who were previously treated with  $\geq 1$  systemic therapies but no prior BTKi.<sup>144-146</sup>
  - 2) In the interim analysis after 415 patients were enrolled, the investigator-assessed ORR at 15 months was statistically greater with zanubrutinib. The 12-month PFS was also statistically higher with zanubrutinib.
  - 3) The rate of atrial fibrillation was statistically significantly lower in the zanubrutinib arm. Rates of major hemorrhage and cardiac events were lower in the zanubrutinib arm, while grade  $\geq 3$  neutropenia occurred more frequently in the zanubrutinib arm.

**Results of the ALPINE study, which compared zanubrutinib to ibrutinib in patients with relapsed or refractory CLL.<sup>146</sup>**

Selected Results of the ALPINE Study			
	Zanubrutinib	Ibrutinib	p value
ORR at 15 months	78.3%	62.5%	$< 0.001$
ORR in patients with del(17p)/TP53 mutation	80.5%	50%	NR
PFS at 12 months	94.9%	84%	NR
Incidence of any grade of atrial fibrillation	2.5%	10.1%	0.001
Incidence of grade $\geq 3$ neutropenia	18.6%	15%	NR
Adverse events leading to treatment discontinuation	7.8%	13%	NR

- c. Venetoclax + rituximab is an NCCN Guidelines® Category 1 preferred recommendation in this setting.
  - 1) The phase III “MURANO” trial was the basis for FDA approval of venetoclax in combination with rituximab in relapsed or refractory CLL.<sup>70,147-150</sup>
    - a) 389 patients with relapsed or refractory CLL were randomized to receive venetoclax for up to 2 years plus rituximab for the first 6 months or bendamustine + rituximab for 6 months. The primary endpoint was investigator-assessed PFS.
    - b) Note that ibrutinib was not widely available at the time of study design and patient recruitment. Therefore, bendamustine + rituximab was considered an appropriate control arm.
    - c) Median PFS and OS were both statistically significantly higher in the venetoclax + rituximab group. This benefit was maintained across all clinical and biologic subgroups, including patients with del(17p).

**Results of the MURANO study, which compared venetoclax and rituximab to bendamustine and rituximab in patients with previously treated CLL.**<sup>70,147,149,150</sup>

Selected Results of the MURANO Study			
	Venetoclax + rituximab	Bendamustine + rituximab	p value
PFS at 48 months	57.3%	4.6%	< 0.0001
PFS at 24 months in patients with del(17p)	81.5%	27.8%	NR
Median PFS	53.6 months	17.0 months	< 0.0001
OS at 60 months	82.1%	62.2%	< 0.0001
Undetectable MRD at end of therapy	62.4%	13.3%	< 0.001

MRD = minimal residual disease; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

- d. Ibrutinib is an NCCN Guidelines® Category 1 recommendation in this setting; however, it was moved to an “other recommended regimen” in August 2022 based on concerns of toxicity.<sup>2</sup>
  - 1) A phase III randomized trial comparing ibrutinib to ofatumumab in relapsed / refractory CLL patients (“RESONATE”) was stopped at the interim analysis due to statistically significant improvements in PFS and OS.<sup>127,151,152</sup>
    - a) 391 patients with CLL or SLL who had received at least one prior therapy were included.
    - b) The primary endpoint was investigator-assessed PFS. The endpoint was significantly improved in patients receiving ibrutinib.
    - c) OS was significantly better in patients who received ibrutinib, despite a large number of patients who were assigned to ofatumumab and crossed over to ibrutinib at disease progression.
    - d) Patient-reported outcomes were significantly greater in patients receiving ibrutinib.

**Results of the RESONATE study, which compared ibrutinib to ofatumumab in patients with previously treated CLL.**<sup>127,152-154</sup>

Selected Results of the RESONATE Study			
	Ibrutinib	Ofatumumab	Statistics
ORR	90%	25%	p < 0.001
Median PFS	44.1 months	8.1 months	p < 0.0001
PFS at 60 months	40%	3%	NR
Median OS	67.7 months	65.1 months	HR = 0.81 (95% CI, 0.602 – 1.091)
OS at 60 months	40%	3%	NR

CI = confidence interval; HR = hazard ratio; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

2) Outcomes after ibrutinib discontinuation<sup>2,155-164</sup>

- a) Patients with disease progression on ibrutinib may develop Richter's transformation (RT, see below) or progressive CLL. Richter's transformation tends to occur earlier than progressive CLL, with RT typically occurring in the first 1-2 years of treatment and progressive CLL occurring later.<sup>164,165</sup>
- b) Patients with RT or progressive CLL tend to have rapid disease progression following discontinuation of ibrutinib, with some sources estimating survival at 3 months or less. Patients require rapid initiation of additional therapy (within 2 weeks of discontinuing ibrutinib) to achieve disease control. It is recommended to transition to the next therapy as soon as possible after stopping ibrutinib.
- c) In single institution studies, the median survival after ibrutinib discontinuation was 3-12 months.

e. Venetoclax as a single agent is also an "Other recommended regimen" in this setting.<sup>2</sup>

f. Retreatment with venetoclax + obinutuzumab may be considered for the treatment of relapse in the second- or third-line setting if the regimen was previously used as first-line therapy and a period of remission was achieved.<sup>2</sup>

**7. Therapy for relapsed or refractory disease in patients without del (17p)/TP53 mutation after prior BTKi- and venetoclax-based regimens**

a. Duvelisib<sup>166-168</sup>

- 1) An inhibitor of PI3K, with predominant activity against PI3K-δ and PI3K-γ isoforms that are expressed in normal and malignant B cells.
- 2) Approved for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.
  - a) Approval was based on a randomized, open-label trial comparing duvelisib ("DUO") to ofatumumab in 319 patients with relapsed or refractory CLL or SLL. The estimated median PFS, as assessed by an independent review committee, was 13.3 months in the duvelisib arm and 9.1 months in the ofatumumab arm.
  - b) Benefit was also seen in patients with del(17p) and/or TP53 mutations.



- 3) Fatal and/or serious reactions occurred in 31% of patients. Black Box Warnings for infection, diarrhea or colitis, cutaneous reactions and pneumonitis are included in the prescribing information.
  - 4) Note the FDA released a warning regarding a possible increased risk of death with duvelisib in July 2022. These concerns were raised during extended follow-up of the “DUO” trial. There are also concerns regarding an association with a higher risk of serious side effects, including infections, diarrhea, inflammation of the intestines and lungs, skin reactions, and elevated liver enzyme levels. The FDA anticipates providing updates to this warning as more information becomes available.<sup>169</sup>
- b. Idelalisib (per NCCN Guidelines®, an “other recommended regimen” both as a single agent and in combination with rituximab)
- 1) An oral inhibitor of phosphoinositide 3-kinase (PI3K) delta.
  - 2) FDA approval for the treatment of relapsed CLL was based on a phase III randomized clinical trial (“Study 116”) comparing idelalisib + rituximab to placebo + rituximab. The trial was stopped after the first interim analysis revealed a significant improvement in RR, PFS and OS in favor of idelalisib and rituximab.<sup>128,170</sup>
    - a) 220 patients with relapsed CLL and who were unable to receive cytotoxic chemotherapy due to co-existing illnesses were included.
    - b) Patients in the placebo group could cross over to receive idelalisib at the time of disease progression, and patients receiving idelalisib could receive a dosage increase at the time of disease progression.
    - c) The primary endpoint was investigator-assessed PFS.
    - d) The treatment effect of idelalisib and rituximab was favorable in all treatment subgroups, including those with del(17p) and other poor prognostic markers.

**Results of Study 116, which compared idelalisib + rituximab to placebo + rituximab in patients with previously treated CLL.**<sup>128,170,171</sup>

Selected Results of Study 116			
	Idelalisib + rituximab	Placebo + rituximab	Statistics
ORR	77%	15%	OR = 19.6 (95% CI, 9.6-39.9)
PFS at 12 months	66%	13%	NR
Median PFS	19.4 months	6.5 months	NR
Median OS	40.6 months	34.6 months	HR = 0.8 (95% CI, 0.5-1.1)

HR = hazard ratio; NR = not reported; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

- e) Patients in either arm of Study 116 could receive idelalisib monotherapy after study termination as part of an extension study.<sup>171</sup>
  - i. Final results of this study showed a median PFS of 19.4 months in patients who received idelalisib + rituximab followed by idelalisib.

- ii. Median OS was 40.6 months and 34.6 months for patients assigned to the idelalisib + rituximab and placebo + rituximab groups, respectively.
- c. Chemoimmunotherapy or immunotherapy may also be considered in this setting. Suggested regimens include:<sup>2</sup>
  - 1) Bendamustine + rituximab (only for patients < 65 years of age and without significant comorbidities)
  - 2) FCR (only for patients < 65 years of age without co-morbidities)
  - 3) Lenalidomide +/- rituximab
  - 4) Obinutuzumab
- 8. **Second-line and subsequent therapy in patients with del (17p)/TP53 mutation<sup>2</sup>**
  - a. Acalabrutinib is an NCCN Guidelines® Category 1 preferred regimen in this setting.
  - b. Venetoclax + rituximab is also an NCCN Guidelines® Category 1 preferred regimen in this setting.
  - c. Other preferred regimens in this setting include single-agent venetoclax and zanubrutinib.
  - d. Other recommended regimens in this setting include:
    - 1) Ibrutinib (Category 1)
    - 2) Alemtuzumab +/- rituximab
    - 3) Duvelisib
    - 4) High-dose methylprednisolone + rituximab
    - 5) Idelalisib +/- rituximab
    - 6) Lenalidomide +/- rituximab
- 9. Patients with relapsed or refractory disease after prior therapy with BTKi- and venetoclax-based regimens may be considered for allogeneic hematopoietic stem cell transplantation, if eligible.<sup>2</sup> Note that most patients will not be considered candidates due to advanced age and/or comorbidities.<sup>31,172,173</sup> Please see Hematopoietic Stem Cell Transplantation section for details.

**Patient Case #2, continued:**

**Correct answer = C (Venetoclax + rituximab).**

Of the proposed choices, venetoclax + rituximab is the most appropriate. This regimen has an NCCN Guidelines® Category 1 recommendation for use in the second-line setting based on the results of the MURANO study. Chlorambucil + obinutuzumab is not currently recommended in the second-line setting. Repeating FCR would not be the most appropriate as there are more effective choices for second-line treatment. The combination of bendamustine, rituximab and idelalisib is a Category 2B recommendation at this time and therefore is not the most appropriate choice of the proposed options.

**Patient Case #1, continued:**

JF is a 68-year-old male with newly diagnosed CLL who will be initiating therapy with acalabrutinib.

**Which of the following adverse effects are frequently seen with acalabrutinib and should be discussed during your counseling session with JF?**

- A. Hypotension
- B. Tumor lysis syndrome
- C. Headache
- D. Periorbital edema

**Patient Case #2, continued:**

DG is a 63-year old male with relapsed CLL who will be initiating treatment with venetoclax + rituximab.

**Which of the following statements about venetoclax is correct?**

- A. Pancreatitis is common.
- B. Tumor lysis syndrome prophylaxis is required.
- C. Lower extremity edema often occurs.
- D. Visual changes are frequent.

H. Toxicities of small molecule inhibitors and management<sup>2,24,138,174</sup>

1. Ibrutinib

- a. The recommendation for use of ibrutinib in the treatment of CLL was changed from an NCCN Guidelines® Category 1 “preferred regimen” to Category 1 “other recommended regimen” in the August 2022.<sup>2</sup>
  - 1) The reason for this change was a concern regarding toxicities, specifically cardiac toxicities. A baseline assessment of cardiac function should be completed prior to initiation of ibrutinib.<sup>2</sup>
  - 2) If a patient has been receiving ibrutinib and has no issues with tolerance, ibrutinib can be continued until disease progression.
- b. Atrial fibrillation is observed in up to 16% of patients.

- 1) Ibrutinib may exacerbate atrial fibrillation by inhibiting cardiac BTK proteins, thus silencing a critical regulator of cardiac protection against stressors. However, other unidentified off-target effects may also play a role, and the exact mechanism remains unknown.<sup>175,176</sup>
- 2) The risk of atrial fibrillation is intrinsically higher in this patient population, given the advanced age and comorbid conditions of most patients with CLL.<sup>177</sup> Conditions that have been associated with increased risk of atrial fibrillation on ibrutinib therapy include older age, male sex, history of hypertension, history of coronary artery disease, and history of valvular heart disease.<sup>178</sup>
- 3) Most references suggest that atrial fibrillation typically occurs early after ibrutinib initiation and decreases over time.<sup>15,98,179</sup> Other references suggest that there are higher incidences of atrial fibrillation in the treatment-naïve population as opposed to the relapsed or refractory setting.<sup>15</sup>
- 4) Modifiable risk factors for atrial fibrillation should be identified and treated, if possible. Such factors include obesity, hypertension, heart failure, diabetes, and thyroid function.<sup>179</sup>
- 5) Atrial fibrillation that develops during BTKi treatment should be treated according to standard practice. However, drug-drug interactions with the non-dihydropyridine calcium channel blockers and amiodarone must be considered; rate control may be preferred over rhythm control in this scenario. Consultation with cardiology services is encouraged.<sup>175,179,180</sup>
- 6) A validated tool to estimate the patient's risk of stroke, such as the CHA2DS2-VASc risk stratification, should be used to determine the patient's need for concomitant anticoagulation.<sup>175,177,179,180</sup>
  - a) Clinical trials of ibrutinib excluded patients on concurrent warfarin. Non-warfarin alternatives should be considered, if possible, in patients who have pre-existing atrial fibrillation requiring anticoagulation.<sup>165,176</sup>
  - b) Low molecular weight heparins may be used in this setting.<sup>176</sup> However, emerging data suggests that direct oral anticoagulants are appropriate and possibly preferred in this setting.<sup>181</sup>
  - c) If treatment with a direct oral anticoagulant is appropriate, some references suggest apixaban due to minimal drug interactions with ibrutinib.<sup>177,182,183</sup>
- 7) Pre-existing atrial fibrillation is not an absolute contraindication to the use of ibrutinib.<sup>175</sup> However, patients with recurrent atrial fibrillation that is not medically controllable should be changed to other CLL therapy.<sup>2,184</sup>
- 8) If atrial fibrillation occurs during ibrutinib therapy, it is not recommended to hold or reduce the dose of ibrutinib while treatment is initiated unless the arrhythmia is grade  $\geq 3$ .<sup>185</sup> Withholding ibrutinib does not result in higher resolution rates of atrial fibrillation, but may compromise PFS and OS.<sup>183</sup>
- c. Hypertension is an important adverse effect of ibrutinib.<sup>98,174,186,187</sup>
  - 1) Early trials reported that approximately 25% of patients taking ibrutinib developed new or worsened hypertension. Follow-up data suggests a potential continual rise in the incidence of hypertension over time.

- 2) In a retrospective study of 562 patients who received ibrutinib, more than 75% of patients developed new or worsened hypertension over a median of 30 months.<sup>174</sup>
  - a) The increase in hypertension remained after adjustment for ibrutinib dose.
  - b) No single anti-hypertensive agent or class was associated with prevention or control of ibrutinib-related hypertension.
  - c) The risk of major adverse cardiovascular events, such as atrial fibrillation and ventricular arrhythmias, disproportionately elevated in patients who developed hypertension during ibrutinib therapy. However, the initiation of an anti-hypertensive agent was associated with a lower risk of a subsequent major adverse cardiovascular event (HR 0.40, 95% CI, 0.24-0.66).<sup>187</sup>
- 3) Hypertension that occurs during ibrutinib therapy should be managed according to local/national hypertension management guidelines.<sup>177</sup> However, caution should be used when prescribing non-dihydropyridine calcium channel blockers due to drug-drug interactions.<sup>188</sup>
- d. Minor bleeding has been reported in up to 66% of patients. Serious bleeding events are observed in up to 9% of patients on ibrutinib.<sup>165,176,177</sup>
  - 1) It is postulated that ibrutinib selectively inhibits platelet signaling and strongly affects platelet adhesion on von Willebrand factor.<sup>24,176,189-191</sup>
  - 2) The risk of ibrutinib-related bleeding is highest during the first 3-6 months of treatment, and then decreases with continued therapy.<sup>98,175</sup>
  - 3) Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies (see below).<sup>132,175,176,190</sup>
  - 4) Patients should be advised to discontinue vitamin E, fish oils and NSAIDs while on ibrutinib, as these agents were prohibited in the ibrutinib trials.
  - 5) For planned surgical procedures considered as high risk for bleeding, ibrutinib should be held for 3 days prior to and after minor surgical procedures, and for 7 days prior to and after major surgical procedures.<sup>176,191,192</sup>
- e. Diarrhea frequently occurs early in the treatment course, but can be managed with standard supportive care and is self-limiting.<sup>176</sup>
- f. There are several reports of invasive fungal infections and other atypical infections in patients who received ibrutinib. However, it is unclear to what extent these infections are attributable solely to ibrutinib, and therefore routine prophylaxis is not recommended at this time. Consideration may be given to patient at high risk of fungal infections, including concomitant corticosteroid therapy or patients with diabetes.<sup>24,193</sup>
2. Acalabrutinib<sup>2,194,195</sup>
  - a. Headache is commonly reported, occurring in up to 40% of patients early in the treatment course and usually resolving in 4-8 weeks. Management includes hydration, analgesics and caffeine supplementation.

- b. Grade 3 or 4 bleeding events are rare. The risks and benefits of withholding acalabrutinib before and after surgery depends on the type of surgery and risk of bleeding.
  - c. Grade 3 or 4 hypertension is reported in ~3% of patients, and atrial fibrillation is reported in ~4% of patients.<sup>194</sup> Ventricular arrhythmias have also been reported.<sup>195</sup>
  - d. When the capsule formulation of acalabrutinib is prescribed, co-administration with proton pump inhibitors (PPI) must be avoided. If histamine 2 receptor antagonists or antacids are necessary, the doses should be staggered to allow for maximum absorption of acalabrutinib; the prescribing information recommends giving acalabrutinib 2 hours before or after a histamine 2 receptor antagonist or antacid.<sup>194</sup>
  - e. Such a drug interaction does not occur with the tablet formulation; concomitant use of acalabrutinib tablets with any acid-reducing agent, including PPIs, antacids, and histamine 2-receptor antagonists does not require adjustment of administration times.<sup>194</sup>
3. Zanubrutinib<sup>2,87,196</sup>
    - a. Myelosuppression (specifically neutropenia), upper respiratory infection and pneumonia are the most frequently reported adverse effects.
    - b. Grade 3 or 4 bleeding events are reported in ~ 5% of patients. The risks and benefits of withholding zanubrutinib before and after surgery depends on the type of surgery and risk of bleeding.
    - c. Atrial fibrillation and hypertension have been reported, but follow-up has been short compared to other studies of BTKis.
  4. Comparison of BTKi toxicities

**Reported incidence of toxicities across trials of BTKi inhibitors used for the treatment of CLL.**<sup>87,142,146,176,177,180,185,194,197</sup>

	Acalabrutinib	Ibrutinib	Zanubrutinib
Arthralgias	+	++	+
Atrial fibrillation	+	+++	+
Bleeding events	++	+++	++
Diarrhea	++	+++	+
Headache	+++	--	--
Hypertension	+	+++	++
Infections	++	++	++
Lymphocytosis	+	++	+
Myelosuppression	++	++	+++
Rash	+	+	++

- a. The “ELEVATE-RR” trial compared ibrutinib to acalabrutinib in patients with previously treated CLL and del(17p) or del(11q). Key secondary endpoints included the incidence of any grade atrial fibrillation / flutter and grade ≥ 3 infections.<sup>142,143</sup>

- 1) Patients who received acalabrutinib had statistically significantly less atrial fibrillation / flutter of any grade (9.4% vs 16.0%,  $p = 0.02$ ). The incidence of grade  $\geq 3$  atrial fibrillation / flutter and incidence among patients without a prior history of atrial fibrillation / flutter were both less in the acalabrutinib arm.
- 2) The incidence of grade  $\geq 3$  infections was not different between the two treatment arms.
- 3) Bleeding events were not a key secondary endpoint, but there were significantly more events of all grades of bleeding as well as numerically more grade  $\geq 3$  bleeding events in the ibrutinib arm.
- 4) The incidence of grade  $\geq 3$  adverse events, serious adverse events, and treatment discontinuations due to adverse events all tended to be lower in the acalabrutinib arm.

#### 5. Venetoclax

- a. Neutropenia is the most commonly reported adverse effect of venetoclax, occurring in approximately 60% of patients (53% grade 3 or higher). Neutropenia can be managed with neutrophil growth factor or dose reduction.<sup>198</sup>
- b. Dosing of venetoclax requires a stepwise “ramp-up” schedule over 5 weeks to minimize the risk of tumor lysis syndrome (TLS). The suggested “ramp-up” dosing schedule as per the prescribing information is listed below.<sup>199,200</sup>
- c. If treatment is interrupted for longer than one week during dose escalation, consider re-initiating therapy at a lower dose and continuing dose escalation as appropriate.
- d. The prescribing information’s recommended TLS prophylaxis and monitoring are detailed below. All patient comorbidities should be considered before the final determination of prophylaxis and monitoring schedule.
- e. Further information regarding TLS risk with venetoclax can be found at <http://www.venclextahcp.com/venclexta-dosing-regimen/tumor-lysis-syndrome-risk-assessment.html>. Please see the Acute Leukemias handout for more detailed information on TLS prevention and management in other malignancies.

#### **Suggested “ramp-up” dosing schedule of venetoclax to minimize risk of tumor lysis syndrome.<sup>199</sup>**

Week	Daily dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

Venetoclax [package insert]. North Chicago, IL; Abbvie Inc.: 2017. Used with permission.

**Recommended tumor lysis prophylaxis for patients receiving venetoclax. Recommendations are based on tumor burden and are derived from clinical trial data.<sup>199</sup>**

<b>Tumor Burden</b>	<b>Prophylaxis*</b>	<b>Blood Chemistry Monitoring^</b>
<b><u>Low</u></b> All lymph nodes < 5 cm <b>AND</b> Absolute lymphocyte count (ALC) < 25 x 10 <sup>9</sup> /L	<ul style="list-style-type: none"> <li>Oral hydration (1.5-2 L)</li> <li>Allopurinol<sup>#</sup></li> </ul>	<b><u>Outpatient</u></b> <ul style="list-style-type: none"> <li>Pre-dose, 6-8 hours and 24 hours at first dose of 20 mg and 50 mg</li> <li>Pre-dose at subsequent ramp-up doses</li> </ul>
<b><u>Medium</u></b> Any lymph node 5 cm to < 10 cm <b>OR</b> ALC ≥ 25 x 10 <sup>9</sup> /L	<ul style="list-style-type: none"> <li>Oral hydration (1.5-2 L) and consider additional intravenous hydration</li> <li>Allopurinol</li> </ul>	<b><u>Outpatient</u></b> <ul style="list-style-type: none"> <li>Pre-dose, 6-8 hours and 24 hours at first dose of 20 mg and 50 mg</li> <li>Pre-dose at subsequent ramp-up doses</li> <li>Consider hospitalization for patients with CrCl &lt; 80 mL/min at first dose of 20 mg and 50 mg; see below for inpatient monitoring</li> </ul>
<b><u>High</u></b> Any lymph node ≥ 10 cm <b>OR</b> ALC ≥ 25 x 10 <sup>9</sup> /L <b>AND</b> any lymph node ≥ 5 cm	<ul style="list-style-type: none"> <li>Oral hydration (1.5-2 L) and intravenous hydration (150-200 mL/hr as tolerated)</li> <li>Allopurinol</li> <li>Consider rasburicase if baseline uric acid is elevated</li> </ul>	<b><u>Inpatient for first dose of 20 mg and 50 mg</u></b> <ul style="list-style-type: none"> <li>Pre-dose, 4, 8, 12 and 24 hours</li> </ul> <b><u>Outpatient at subsequent ramp-up doses</u></b> <ul style="list-style-type: none"> <li>Pre-dose, 6-8 hours and 24 hours</li> </ul>

\*Administer intravenous hydration for any patient who cannot tolerate oral hydration.

<sup>#</sup>Start allopurinol or xanthine oxidase inhibitor 2-3 days prior to initiation of venetoclax.

<sup>^</sup>Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium and creatinine) and review in real time. Venetoclax [package insert]. North Chicago, IL; Abbvie Inc.: 2017. Used with permission.

6. Idelalisib is associated with immune-mediated adverse effects, including elevated liver function tests, rash, pneumonitis and severe diarrhea / colitis. Recent reports have also noted a potential increase in infections.<sup>2,135,192,201-203</sup>
  - a. Diarrhea is common and has 2 peaks of occurrence. A lower-grade diarrhea occurs in 30% of patients in the first weeks of therapy. The median time to onset of severe diarrhea / colitis is 9.5 months and occurs in ~10% of patients. Colitis should be managed promptly with steroids (either budesonide or intravenous products).<sup>135,183,203-205</sup>
  - b. Grade 3 or higher transaminitis occurs in ~14% of patients receiving idelalisib in the second-line setting. In a small phase II study using idelalisib in patients with previously untreated CLL, the incidence of hepatotoxicity was much higher (54%) and occurred rapidly after treatment



initiation.<sup>206,207</sup> This hepatotoxicity was felt to be autoimmune mediated and occurred more often in younger patients.

- c. Due to these findings and a potential increased risk of infections (see below), many trials of idelalisib in the first-line setting have closed.
  - d. The FDA alerted healthcare professionals of reports of an increased rate of adverse events, including deaths, in clinical trials with idelalisib in combination chemotherapy, generally due to an increased risk of infections.<sup>208</sup> The majority of these infections occurred within the first 6 months of treatment. Some sources advise that *Pneumocystis jiroveci* prophylaxis be administered with this agent.<sup>2,183,193,203,209,210</sup>
  - e. Anti-infective prophylaxis for herpes virus and cytomegalovirus should be considered. See Supportive Care section below.
  - f. Monitoring for hepatitis B reactivation is recommended.<sup>2,203</sup> See Supportive Care section below.
7. Duvelisib has Black Box Warnings for infection, diarrhea or colitis, cutaneous reactions and pneumonitis, and further action by the FDA may be forthcoming as of July 2022 (see duvelisib information above).<sup>169</sup>
8. Redistribution lymphocytosis
- a. A transient increase in ALC occurs in many patients due to the inhibition of the CXCR4/5 chemokine receptors, which results in trafficking of CLL cells from the lymph nodes and other sites into the peripheral blood.<sup>2,30,192,211-213 24,165,214</sup>
    - 1) This “redistribution lymphocytosis” does not signify disease progression. A new category of disease response (partial response with lymphocytosis) is used in these cases.
    - 2) The onset of isolated lymphocytosis occurs during the first few weeks and persists for several weeks on treatment.
    - 3) This phenomenon is not associated with tumor lysis syndrome or leukostasis. Clinical consequences are extremely rare and therapy should be continued.
    - 4) Lymphocytosis is more pronounced in patients with mutated IGHV and those with del(13q).
    - 5) This phenomenon can occur with all of the kinase inhibitors used to treat CLL.
    - 6) Slow or incomplete resolution of lymphocytosis does not appear to impact outcomes.
  - b. In “Study 116,” the addition of rituximab to idelalisib blunted and shortened the duration of lymphocytosis. The onset of isolated lymphocytosis peaked at week 2 and resolved by week 12 in the idelalisib group.<sup>128,170</sup>

**Patient Case #1, continued:**

**Correct answer = C (Headache).**

Headache is the most commonly reported adverse effect of acalabrutinib treatment, occurring in up to 40% of patients. This effect is usually transient and can be mitigated with fluids, caffeine, and treatment with NSAIDs or other agents. Acalabrutinib is associated with hypertension, but hypotension has not been reported. Tumor lysis syndrome is associated with venetoclax, not acalabrutinib. Periorbital edema is commonly seen with imatinib therapy, but not acalabrutinib.

**Patient Case #2, continued:**

**Correct answer = B (Tumor lysis syndrome prophylaxis is required).**

Tumor lysis syndrome is a potentially deadly adverse effect of venetoclax. Estimation of individual patient risk and suggested mitigation strategies are available from the manufacturer as well as in NCCN Guidelines.<sup>®</sup> Pancreatitis, lower extremity edema and visual changes are not common adverse effects with this agent.

A. Summary of treatment recommendations

**Suggested treatment regimens for treatment of CLL in patients without del(17p)/TP53 mutation per the NCCN Guidelines®.<sup>2</sup>**

First-line therapy	<p><b>Preferred regimens:</b></p> <ul style="list-style-type: none"> <li>• Acalabrutinib +/- obinutuzumab (Category 1)</li> <li>• Venetoclax + obinutuzumab (Category 1)</li> <li>• Zanubrutinib (Category 1)</li> </ul> <p><b>Other recommended regimens:</b></p> <ul style="list-style-type: none"> <li>• Ibrutinib (Category 1)</li> <li>• Bendamustine + anti-CD20 monoclonal antibody</li> <li>• Chlorambucil + obinutuzumab</li> <li>• Obinutuzumab</li> </ul> <p><b>Useful in certain circumstances:</b></p> <ul style="list-style-type: none"> <li>• FCR (consider in patients &lt; 65 years of age without significant co-morbidities <u>and</u> with mutated IGHV)</li> </ul>
Second- and third-line therapy	<p><b>Preferred regimens:</b></p> <ul style="list-style-type: none"> <li>• BTKi <ul style="list-style-type: none"> <li>○ Acalabrutinib (Category 1)</li> <li>○ Zanubrutinib</li> </ul> </li> <li>• BCL-2 inhibitor <ul style="list-style-type: none"> <li>○ Venetoclax + rituximab (Category 1)</li> </ul> </li> </ul> <p><b>Other recommended regimens:</b></p> <ul style="list-style-type: none"> <li>• Ibrutinib (Category 1)</li> <li>• Venetoclax</li> </ul> <p><b>Useful in certain circumstances:</b></p> <ul style="list-style-type: none"> <li>• Retreatment with venetoclax + obinutuzumab (for relapse after a period of remission if previously used for first-line therapy)</li> </ul>
Therapy for relapsed or refractory disease after prior BTKi- and venetoclax-based regimens	<p><b>Other recommended regimens:</b></p> <ul style="list-style-type: none"> <li>• PI3K inhibitors (in alphabetical order) <ul style="list-style-type: none"> <li>○ Duvelisib</li> <li>○ Idelalisib +/- rituximab</li> </ul> </li> <li>• CIT or immunotherapy <ul style="list-style-type: none"> <li>○ Bendamustine + rituximab (only for patients &lt; 65 years of age without co-morbidities)</li> <li>○ FCR (only for patients &lt; 65 years of age without co-morbidities)</li> <li>○ Lenalidomide +/- rituximab</li> <li>○ Obinutuzumab</li> </ul> </li> </ul>

BTKi = Bruton's tyrosine kinase inhibitor; CIT = chemoimmunotherapy; FCR = fludarabine, cyclophosphamide + rituximab; PI3K = phosphoinositide 3-kinase.

**Suggested treatment regimens for treatment of CLL in patients with del(17p)/TP53 mutation per the NCCN Guidelines.<sup>2</sup>**

First-line therapy	<p><b>Preferred regimens:</b></p> <ul style="list-style-type: none"> <li>• Acalabrutinib +/- obinutuzumab</li> <li>• Venetoclax + obinutuzumab</li> <li>• Zanubrutinib</li> </ul> <p><b>Other recommended regimens:</b></p> <ul style="list-style-type: none"> <li>• Alemtuzumab +/- rituximab</li> <li>• HDMP + rituximab</li> <li>• Ibrutinib</li> <li>• Obinutuzumab</li> </ul>
Second-line and subsequent regimens	<p><b>Preferred regimens:</b></p> <ul style="list-style-type: none"> <li>• Acalabrutinib (Category 1)</li> <li>• Venetoclax + rituximab (Category 1)</li> <li>• Venetoclax</li> <li>• Zanubrutinib</li> </ul> <p><b>Other recommended regimens:</b></p> <ul style="list-style-type: none"> <li>• Ibrutinib (Category 1)</li> <li>• Alemtuzumab +/- rituximab</li> <li>• Duvelisib</li> <li>• HDMP + rituximab</li> <li>• Idelalisib +/- rituximab</li> <li>• Lenalidomide +/- rituximab</li> </ul>

BTKi = Bruton's tyrosine kinase inhibitor; HDMP = high-dose methylprednisolone.

**Patient Case #1, continued:**

JF has now been receiving ibrutinib for 18 months. Over the past two weeks, he has noted rapidly enlarging cervical, axillary and inguinal lymphadenopathy. He also reports new fevers, splenomegaly and unintentional weight loss.

**Which of the following is the most likely the cause of JF's new complaints?**

- A. Richter's transformation
- B. Ibrutinib resistance
- C. Redistribution lymphocytosis
- D. Tuberculosis infection

B. Richter's transformation / histologic transformation<sup>2,9,17,24,30,31,40,53,133,138,162,163,214-219</sup>

1. Approximately 2-16% of CLL patients will develop Richter's transformation (RT), a transformation into diffuse large B-cell non-Hodgkin lymphoma (DLBCL) (up to 90% of these patients) or Hodgkin lymphoma (up to 10% of these patients). However, the exact incidence is unknown and likely under-reported, due to the aggressiveness of the disease and absence of adequate biopsy samples.<sup>219</sup>
2. The incidence of transformation increases with the presence of complex cytogenetics, del(17p), inactivation of TP53, unmutated IGHV status, NOTCH1 mutation, increased age and with number of prior regimens received.
3. In contrast to progression of CLL, RT is histologically more aggressive and occurs early in the course of treatment.<sup>133</sup>
4. RT is typically suspected in a patient with known CLL who develops inappropriate weight loss, rapidly growing and/or asymmetrical lymphadenopathy, new constitutional symptoms, a rapidly rising lactate dehydrogenase level, new onset cytopenias, and/or new hypercalcemia. Biopsy is recommended to confirm RT.<sup>2</sup>
5. The clinical outcome of RT is generally poor. The disease is typically resistant to chemotherapy, has an aggressive course and a median survival of only 8-12 months from transformation.
6. There are no randomized trials comparing treatment approaches for RT. Treatment should be promptly initiated and directed at aggressive non-Hodgkin lymphoma or Hodgkin lymphoma (see Hodgkin Lymphoma and Non-Hodgkin Lymphoma). Continuation of BTKi or other "bridging" therapies until initiation of the next line of treatment should be considered.<sup>133</sup>
7. Allogeneic hematopoietic stem cell transplantation has shown promising results in this patient population (see Hematopoietic Stem Cell Transplantation).

**Patient Case #1, continued:**

**Correct answer = A (Richter's transformation).**

The rapid onset, nature and severity of JF's symptoms suggests a transformation to a more aggressive malignancy, commonly known as histologic transformation or Richter's transformation (RT). While ibrutinib resistance does occur, the onset is often insidious. Redistribution lymphocytosis occurs early in a patient's treatment course and would not occur after 18 months of therapy. Tuberculosis infection is not associated with ibrutinib.

**Patient Case #3:**

PV is a 71-year-old female with newly diagnosed CLL. She has no known drug allergies and will be initiating therapy with zanubrutinib.

**What supportive care measure should PV receive to prevent complications from her underlying disease and/or treatment regimen?**

- A. Zoster vaccine recombinant, adjuvanted**
- B. Dapsone**
- C. Valganciclovir**
- D. IVIG**

**IV. Supportive Care of Patients with CLL****A. Adherence**

1. A real-world analysis revealed that discontinuation of ibrutinib occurred in approximately 41% of patients after a median of only 7 months of treatment. Intolerance (as opposed to progression of CLL) was the most common reason for discontinuation in all settings.<sup>15</sup>
2. Studies have noted that patients with higher dose intensity of ibrutinib is associated with longer PFS.
  - a. In one study, a shorter median PFS was observed in patients who missed more than 8 days of ibrutinib.<sup>220</sup>
  - b. In a second study, patients on ibrutinib who had dose adherence < 80% had decreased PFS, and inferior OS was related to early dose reduction.<sup>221</sup>
3. “Financial toxicity” is an important consideration for patients with CLL.
4. Oncology pharmacists are well positioned to partner with the multidisciplinary team in the management of patients with CLL, including identification and management of adverse effects, medication adherence strategies, improved cost effectiveness and increased patient satisfaction.<sup>222,223</sup>

**B. Infections<sup>2,31,40,43,53,59,224-233</sup>**

1. Infections are a major cause of morbidity and mortality in patients with CLL. Patients with CLL are more susceptible to infections than the general population due to their underlying disease, as well as the immunosuppressive properties of chemotherapy and monoclonal antibody treatments.<sup>232</sup>
2. The use of corticosteroids and other immunosuppressive agents should be minimized, if possible.<sup>233</sup>
3. The development of infections is influenced by the reduction of immunoglobulin levels. Hypogammaglobulinemia increases with the duration of disease.
4. Intravenous immunoglobulin (IVIG)
  - a. Use of IVIG is associated with a significant decrease in the occurrence of sinopulmonary infections, but does not improve survival outcomes.

- b. IVIG may be considered in patients with serum IgG < 500 mg/dL and who have recurrent sinopulmonary infections ( $\geq 2$  in 6 months) requiring intravenous antibiotics or hospitalization.
  - c. In appropriate candidates, IVIG or subcutaneous immunoglobulin (SCIG) 0.3-0.5 mg/kg should be given to maintain IgG nadir levels of approximately 500 mg/dL.
  - d. In patients who do not qualify or cannot tolerate IVIG, antibacterial prophylaxis may be useful.
5. Anti-infective prophylaxis
- a. Antiviral prophylaxis
    - 1) For the prevention of herpes virus infections in patients receiving purine analog-based treatment, bendamustine-based treatment, and/or alemtuzumab, acyclovir or an equivalent is recommended during treatment and thereafter.
    - 2) Cytomegalovirus (CMV) reactivation may occur in patients receiving PI3K inhibitors or alemtuzumab.
      - a) The optimal approach to CMV monitoring and management has not yet been defined.
      - b) Regular monitoring for the presence of CMV antigens with quantitative polymerase chain reactions (PCR) every 4 weeks has been suggested.
      - c) If CMV viremia is present prior to therapy, prophylactic ganciclovir or valganciclovir may be considered.
      - d) Consultation with an infectious diseases expert may be necessary.
  - b. *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis with sulfamethoxazole-trimethoprim or an equivalent is recommended for patients receiving purine analog-based treatment, bendamustine-based treatment, PI3K inhibitors, and/or alemtuzumab.
    - 1) The risk of developing PJP is directly proportional to prior treatment status and corticosteroid exposure.
    - 2) The majority of patients with CLL diagnosed with PJP are older than 65 years of age.
    - 3) For patients receiving alemtuzumab, prophylaxis should continue for a minimum of 2 months after the completion of therapy and until the CD4 count is > 200 cells/mcL.
    - 4) For patients receiving purine analogs, consider continuing prophylaxis until the CD4 count is >200 cells/mcL.
  - c. Hepatitis B virus (HBV) reaction may occur in patients treated for CLL. All patients receiving therapy should be screened for hepatitis B; screening is necessary prior to starting therapy and prophylaxis may be required (see Cancer-Related Infectious Disease handout for further details). Screening recommendations for hepatitis C in patients with CLL is currently controversial.<sup>2</sup>
  - d. Vaccinations
    - 1) Vaccination efficacy is suboptimal in patients with CLL. If possible, routine vaccinations should be performed prior to the initiation of treatment.
    - 2) Annual influenza vaccination is recommended for all patients with CLL.

- a) Patients with CLL tend to have poor response to this vaccination, and should be counseled to use caution during influenza season even if they have been vaccinated.
    - b) In patients who have received rituximab, B-cell recovery occurs by approximately 9 months after completion of therapy. Prior to B-cell recovery, patients generally do not respond to influenza vaccine. If administered during this timeframe, patients should not be considered as vaccinated.
  - 3) COVID-19 vaccination is recommended in all CLL patients.
    - a) There is some evidence that the protective response rate to COVID-19 vaccination may be lower in patients with CLL, regardless of treatment status. Appropriate precautions should be taken.
    - b) The utility of antibody testing in this population is unknown at this time.
    - c) Patients with CLL may be candidates for COVID-19 prophylaxis with monoclonal antibodies. Data is emerging and the preferred product, dosing and schedule is being updated frequently.
    - d) Please see the Cancer-Related Infectious Disease handout for more information.
  - 4) Pneumococcal vaccination
    - a) Vaccination with Pneumococcal polysaccharide vaccine (PPSV23) is recommended every 5 years or to maintain protective serologic antibody levels based on serologic testing.
    - b) For newly diagnosed patients who are pneumococcal vaccine-naïve, the pneumococcal conjugate vaccine (PCV20) should be administered, followed by PPSV23 at least 8 weeks later. Subsequent doses of PPSV23 should be administered according to current PPSV23 recommendations for high-risk adult patients.
  - 5) Zoster vaccine recombinant, adjuvanted is recommended in treatment-naïve patients or those treated with a BTK inhibitor.
  - 6) All live vaccines should be avoided, including the live herpes zoster vaccine.
- B. Autoimmune cytopenias are associated with CLL and may precede the diagnosis of CLL in up to 10% of patients.<sup>2,31,38-40,43,53,234-246</sup>
- 1. Patients with CLL have a 10-25% lifetime risk of hematologic autoimmune complications.
  - 2. Treatment of CLL may trigger autoimmune cytopenias, and these complications may occur at any time during the course of the disease.
  - 3. Loss of immune self-tolerance causes non-malignant B cells to produce high-affinity polyclonal IgG antibodies directed against blood cell antigens.
  - 4. Autoimmune hemolytic anemia (AIHA) is the most common form of autoimmune cytopenia.
    - a. Patients with advanced disease, unmutated IGHV, increased serum  $\beta$ -2 microglobulin, and high expression of ZAP-70 are at a higher risk of developing AIHA.
    - b. Purine analog-based therapy has been associated with AIHA. If AIHA develops in the setting of treatment with fludarabine, fludarabine should be stopped and avoided in subsequent therapies.



- c. Management is directed against the autoimmune phenomenon and typically begins with corticosteroids. Cyclosporine, IVIG, splenectomy, anti-CD20 antibodies such as rituximab, and/or BTK inhibitor-based therapies may be considered in recurrent or steroid-refractory cases.
4. Immune thrombocytopenic purpura (ITP) occurs in 2-5% of patients with CLL.
  - a. The presence of ITP is associated with poorer survival, independent of other common clinical prognostic factors.
  - b. Management typically begins with corticosteroids. Synthetic thrombopoietin-like agents such as romiplostim, eltrombopag and avatrombopag are now viable options. Treatments including IVIG, cyclosporine, fostamatinib, splenectomy and/or rituximab may be considered in refractory cases. In the absence of specific guidelines, the therapeutic approach is generally based on physician or treatment center experience.
5. Pure red cell aplasia (PRCA) occurs in approximately 1% of patients with CLL.
  - a. Consider bone marrow evaluation and testing for parvovirus B12, herpes virus, and drug effects.
  - b. Management includes corticosteroids, cyclophosphamide, cyclosporine, methotrexate, or anti-thymocyte globulin.
  - c. Corticosteroids tend to be less effective in PRCA than in ITP or AIHA.
- B. Tumor lysis syndrome (TLS)<sup>2,247,248</sup>
  1. Patients with CLL that have a high white blood cell counts may experience TLS. This is especially true in cases of bulky lymph nodes, high circulating lymphocyte count, the use of bendamustine-based therapy or venetoclax, and progressive disease after small molecule inhibitor therapy (see Acute Leukemias for further discussion).
- C. Non-melanomatous skin cancer<sup>2,38,43,59</sup>
  1. Patients with CLL have a markedly increased risk of non-melanomatous skin malignancies. Squamous cell and basal cell carcinoma rates are increased by 5-14 fold. These malignancies are more likely to be locally aggressive or metastatic and are more likely to be fatal than in patients without CLL.
  2. Risk factors include Caucasian ethnicity and history of invasive sun exposure at a young age.
  3. Patients should be educated on avoidance of ultraviolet radiation, and should be evaluated by a dermatologist annually.
- D. Other age-appropriate cancer screenings, such as colonoscopy, mammograms and prostate cancer screening, are also recommended.

**Patient Case #2, continued:**

**Correct answer = A (Zoster vaccine recombinant, adjuvanted).**

Zoster vaccine recombinant, adjuvanted is recommended for treatment-naïve patients with CLL and for those treated with BTKi, such as zanubrutinib. Sulfamethoxazole - trimethoprim (or an equivalent such as dapsone) is recommended as *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis in patients receiving purine analogs, bendamustine, PI3K inhibitors, or alemtuzumab, but PV is receiving zanubrutinib, which does not require PJP prophylaxis. Routine prophylaxis with azole antifungal agents is not required in patients with CLL, and voriconazole would have a drug-drug interaction with zanubrutinib requiring dosage adjustment. Finally, IVIG would only be appropriate if PV had suffered recurrent infections and had an IgG level <500 mg/dL.

## HAIRY CELL LEUKEMIA (HCL)

### I. Natural history of disease<sup>249,250</sup>

- A. HCL is an indolent mature B-cell leukemia.
- B. It is an incurable disease, but durable remissions are often achieved and patients may live many years without requiring retreatment. In some reports, the median PFS is 9-27 years after first-line therapy.<sup>251-253</sup>

### II. Genomics<sup>250,251,254-260</sup>

- A. The BRAF V600E mutation is recognized as the causal event in classic HCL. Nearly all patients with HCL have a BRAF-V600E gain of function mutation.
  - 1. Presence of this mutation can predict benefit from the BRAF inhibitor, vemurafenib.
  - 2. The primary role of vemurafenib at this time is an option in the relapsed setting, either alone or in combination with rituximab.
- B. Unmutated BRAF (known as hairy cell leukemia variant, or HCL-v) may be associated with poorer outcomes, more rapid disease progression and resistance to primary therapy.<sup>260,261</sup>

### III. Treatment

- A. The decision to initiate therapy is often one of clinical judgment. In approximately 10% of patients, a “watch and wait” approach can be considered in asymptomatic patients.<sup>253</sup> Reasons to initiate treatment may include:<sup>250,253,254,256,258,259,262</sup>
  - 1. Recurrent infections
  - 2. Splenic discomfort or other symptomatic organomegaly
  - 3. Hemoglobin < 11 gm/dL
  - 4. Platelets < 100,000 cells/mm<sup>3</sup>
  - 5. ANC < 1000 cells/mm<sup>3</sup>
  - 6. Progressive lymphocytosis or lymphadenopathy
  - 7. Unexplained weight loss, defined as > 10% within the previous 6 months
  - 8. Excessive fatigue
- B. If treatment is warranted, the preferred first line treatment is a purine analogue.<sup>249,250,253,254,256-259,263-265</sup>
  - 1. The most commonly used agents are pentostatin and cladribine. These agents have not been directly compared in randomized controlled trials, but both agents can produce durable remissions when given as first-line therapy.
  - 2. Different routes of administration and schedules of both agents have been evaluated in small studies. However, no route or schedule is preferred. The choice of agent is usually based on physician preference and/or patient convenience.

3. Purine analogs may be combined with rituximab in the first-line setting. In a phase 2 study, the combination of cladribine and rituximab resulted in a deeper response as compared to cladribine monotherapy.<sup>264</sup>
  4. Previous studies suggest that treatment with interferon alfa can produce durable remissions. However, given the adverse effect profile of this agent, purine analogues are preferred.
  5. Caution is advised when initiating treatment during concomitant severe infection, since purine analogs will initially worsen immunosuppression.
- C. If treatment is warranted and the patient is unable to tolerate a purine analog (such as a patient with an active infection or a frail patient), vemurafenib + obinutuzumab may be considered.<sup>258</sup>
- D. Treatment of relapsed or refractory disease<sup>249,250,253,254,257-259,265,266</sup>
2. Nearly all patients eventually relapse after a median follow-up of 15 years, and up to 25% of patients require retreatment within 5 years.<sup>265</sup>
  3. If relapse occurs  $\geq 2$  years after the completion of initial therapy, re-initiation of a purine analog (pentostatin or cladribine) may be considered. Retreatment with the same agent can produce a second remission of reasonable duration.
    - a. If a purine analog is selected in this setting, rituximab should be combined with either pentostatin or cladribine.
    - b. Rituximab as a single agent may be considered in patients who are no longer candidates for purine analogue therapy.
  2. If relapse occurs  $< 2$  years after completion of initial therapy, treatment options include:
    - a. Alternative purine analogue + rituximab (preferred)
    - b. Vemurafenib +/- rituximab (preferred)
    - c. Alternative purine analogue
    - d. Peginterferon alfa 2a
    - e. Rituximab as a single agent (in patients who are not candidates for purine analogue therapy)
  3. Treatment options for second or greater relapse include:
    - a) Vemurafenib +/- rituximab (preferred, if not previously given)<sup>265,267</sup>
      - 1) A phase 2 trial of 30 patients with relapsed or refractory HCL who received vemurafenib plus concurrent and sequential rituximab has been reported. A complete response was achieved in 87% of patients, and progression-free survival was 78% at a median of 37 months.
    - b) Moxetumomab pasudotox-tdfk (HA-22, Lumoxiti®)<sup>258,259,262,268-272</sup>
      - 1) FDA approval was based on "Study 1053," which included 80 patients with HCL who had received at least 2 prior therapies, including one purine analogue. All patients received moxetumomab pasudotox-tdfk.

- a) The primary endpoint was blinded independent review committee (IRC)-assessed durable complete response (CR). Durable complete response CR was defined as maintenance of hematologic response for more than 180 days after IRC-assessed CR.
  - b) At a median follow-up of 24.6 months, the IRC-assessed durable CR was 36.3% (95% CI, 25.8-47.8%). The median duration of CR was 62.8 months. The objective response rate was 75%, and the median duration of response was 66.7 months.
- 2) Premedication
- a) Hydration: one liter of isotonic solution should be administered over 2-4 hours before and after each infusion of moxetumomab pasudotox-tdfk. If the patients weighs less than 50 kg, administer 500 mL of isotonic solution.
  - b) Infusion reactions: prior to each dose, patients should receive acetaminophen, a histamine-1 receptor antagonist and a histamine-2 receptor antagonist 30-90 minutes prior to each infusion.
  - c) Thromboprophylaxis: consider low-dose aspirin on days 1-8 of each 28-day cycle.
- 3) Postmedication
- a) Hydration: Advise all patients to hydrate with up to 3 liters of oral fluids every 24 hours on days 1-8 of each 28 day cycle. For patients who weigh less than 50 kg, up to 2 liters should be recommended. Fluid balance and serum electrolytes should be monitored as appropriate.
  - b) Infusion reactions: stop infusion and administer appropriate management. Administer an oral or IV corticosteroid 30 minutes prior to resuming the infusion. For future infusions, consider adding a corticosteroid 30 minutes prior to the infusion and consider administering an oral anti-histamines and anti-pyretics for up to 24 hours after each infusion.
- 4) Adverse reactions
- a) Serious and life-threatening AE included capillary leak syndrome and hemolytic uremic syndrome (HUS).
  - b) Assessment and management of adverse reactions
    - i. Capillary leak syndrome (CLS)
      1. Most instances of CLS occurred within the first 8 days of treatment. Median time to resolution was 12 days.
      2. Before every infusion, check weight and blood pressure.
      3. If weight has increased by 2.5 kg or  $\geq 5\%$  from Day 1 of the cycle and the patient is hypotensive, initiate a physical exam to assess for peripheral edema and respiratory symptoms. Oxygen saturations and imaging studies may be warranted.
      4. Patients with  $\geq$  Grade 2 CLS should receive oral or intravenous corticosteroids and other supportive care measures as appropriate. Moxetumomab pasudotox should be discontinued for grade 3 or 4 CLS.

ii. Hemolytic uremic syndrome (HUS)

1. The majority of cases of HUS manifested in the first 9 days of treatment, and resolved within a median of 11 days.
  2. Before each infusion, assess hemoglobin levels, platelet count and serum creatinine.
  3. If HUS is suspected, promptly evaluate for evidence of hemolysis (LDH, indirect bilirubin, reticulocyte count, haptoglobin and blood smear for schistocytes).
  4. If HUS is present, discontinue moxetumomab pasudotox. Fluid replacement and other supportive care measures should be initiated.
- 5) Preparation instructions: the product is provided with a separate IV solution stabilizer. The stabilizer must be added to the infusion bag prior to adding moxetumomab pasudotox-tdfk solution to the infusion bag.
- 6) In November 2022, the manufacturer announced its decision to withdraw this product from the US market starting in July 2023 due to low clinical use, presumably from availability of other treatment options and complex monitoring procedures.<sup>268</sup>
- c. Ibrutinib may also be considered for progressive disease after other treatment for relapsed or refractory disease. In a phase 2 study, the estimated 36-month PFS was 73% in patients with previously treated HCL.<sup>273</sup>

E. Supportive care of patients with HCL<sup>232,254,256,258,262</sup>

1. Infections

- a. Due to the underlying disease and treatment with purine analogues, patients with HCL are markedly susceptible to infections.
  - 1) Acyclovir or equivalent is recommended for HSV prevention .
  - 2) Sulfamethoxazole/trimethoprim or an equivalent is recommended for PJP prophylaxis.
  - 3) Broad-spectrum anti-microbial therapy should be considered in patients with prolonged neutropenia.
  - 4) Anti-infective prophylaxis should continue for a minimum of 3 months after the completion of therapy and until the CD4 count is  $\geq 200$  cells/mm<sup>3</sup>.
  - 5) Hepatitis B reactivation – see Hepatitis B section of Cancer-Related Infectious Diseases handout.
2. The use of myeloid growth factors may be considered on a case-by-case basis.
3. HCL patients appear to have an increased risk of other malignancies, with some references citing an incidence of up to 23%. It is unclear whether this is due to the immunosuppression from the underlying disease or treatment with purine analogs.<sup>256,257,266</sup>

## INFUSION-RELATED REACTIONS TO MONOCLONAL ANTIBODIES USED TO TREAT HEMATOLOGIC MALIGNANCIES

### I. Overview<sup>274-277</sup>

- A. Many oncology therapeutic agents, including cytotoxic agents and biologics, have the potential to cause infusion-related reactions (IRRs). Several of these agents are monoclonal antibodies used in the treatment of hematologic malignancies.
- B. The incidence of acute infusion reactions are increasing as more patients with cancer are exposed to multiple agents and multiple cycles of agents.

**Monoclonal antibodies used in the treatment of hematologic malignancies that are associated with infusion-related reactions.**<sup>62,274,278-283 284,285</sup>

Alemtuzumab
Belantamab mafodotin-blmf
Blinatumomab
Brentuximab vedotin
Daratumumab
Elotuzumab
Gemtuzumab ozogamicin
Inotuzumab ozogamicin
Isatuximab-irfc
Mogamulizumab
Moxetumomab pasudotox-tdfk
Obinutuzumab
Polatuzumab vedotin-piiq
Rituximab
Tafasitamab-cxix

- C. These reactions may range in severity from mild flushing to potentially life-threatening events.
  1. Most infusion reactions are mild to moderate in intensity, and develop during the infusion or shortly thereafter. These reactions may manifest in many different organ systems:
    - a. Cutaneous – erythema, flushing, pruritis, urticarial, angioedema, or itching
    - b. Cardiovascular – chest pain, tachycardia, presyncope, syncope, or hypotension
    - c. Respiratory – dyspnea, wheezing, or throat tightness
    - d. Gastrointestinal – nausea, vomiting, diarrhea, or abdominal pain
    - e. Neurological – mental confusion, visual disturbances, numbness, or weakness
  2. A small but significant percentage ( $\leq 5\%$ ) of patients will develop severe infusion reactions, including an acute onset of bronchospasm, hypotension, urticaria and/or cardiac arrest.

- D. The vague and inconsistent terminology used to describe these reactions likely reflects the poor understanding of the cause of these reactions.
  - 1. Although the term “hypersensitivity” is widely used, no common definition has been adopted. Likewise, the requirement of an immunological basis for a true hypersensitivity is sometimes overlooked. Consequently, some IRRs are sometimes incorrectly described as “hypersensitivities” while others that should be described as such are not.<sup>286,287</sup>
  - 2. It is suspected that the incidence of mild and moderate infusion reactions is underestimated in the oncology community.
- E. Mechanism of infusion-related reactions<sup>274,277,288-290</sup>
  - 1. The exact mechanism by which hypersensitivity reactions occur is unclear, and may vary between agents.
    - a. Infusion reactions caused by monoclonal antibodies is unlikely to be due to true, type I IgE-mediated hypersensitivity reactions.
    - b. These reactions are also unlikely to be caused by the same mechanism as hypersensitivity to small molecule agents.
    - c. The most widely accepted explanation is the release of inflammatory cytokines by the binding of the monoclonal antibody to its target cell. When released into the peripheral circulation, cytokines produce a variety of symptoms that are characteristic of infusion reactions.
      - 1) Cytokine-dependent infusion reactions should not be confused with tumor lysis syndrome, as this is a separate clinical entity (see Tumor Lysis Syndrome section).

## **II. Identification of an infusion-related reaction**<sup>274,275,290,291</sup>

- A. Infusion reactions to monoclonal antibodies occur predominantly during the first infusion. However, 10-30% of reactions to monoclonal antibodies are delayed and may occur in later infusions.
- B. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) distinguish between hypersensitivity reactions and acute infusion reactions induced by cytokine release.<sup>292</sup>
  - 1. Allergic reaction is defined as “a disorder characterized by an adverse local or general response from exposure to an allergen.”
  - 2. Infusion-related reaction is defined as “a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.”
  - 3. The clinical signs and symptoms associated with these reactions overlap.



**National Cancer Institute Common Terminology Criteria for Adverse Events definitions of allergic reactions and infusion-related reactions.<sup>292</sup>**

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	<ul style="list-style-type: none"> <li>• Systemic intervention not indicated</li> </ul>	<ul style="list-style-type: none"> <li>• Oral intervention indicated</li> </ul>	<ul style="list-style-type: none"> <li>• Bronchospasm</li> <li>• Intravenous intervention indicated</li> <li>• Hospitalization indicated for clinical sequelae</li> </ul>	<ul style="list-style-type: none"> <li>• Urgent intervention indicated</li> <li>• Life-threatening consequences</li> </ul>	<ul style="list-style-type: none"> <li>• Death</li> </ul>
Infusion-related reaction	<ul style="list-style-type: none"> <li>• Mild transient reaction</li> <li>• Infusion interruption not indicated</li> <li>• Intervention not indicated</li> </ul>	<ul style="list-style-type: none"> <li>• Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids)</li> <li>• Prophylactic medications indicated for ≤ 24 hrs</li> </ul>	<ul style="list-style-type: none"> <li>• Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion)</li> <li>• Recurrence of symptoms following initial improvement</li> <li>• Hospitalization indicated for clinical sequelae</li> </ul>	<ul style="list-style-type: none"> <li>• Life-threatening consequences</li> <li>• Urgent intervention indicated</li> </ul>	<ul style="list-style-type: none"> <li>• Death</li> </ul>

**C. Identification of patients at high risk**

1. The degree of antibody humanization influences the frequency of monoclonal antibody-associated IRRs. Mouse and chimeric antibodies elicit the highest frequency of immunogenic responses, while the majority of fully humanized antibodies have a relatively low immunogenicity by comparison.<sup>293</sup>
2. Studies have attempted to identify patient characteristics that may predict for an IRR. At present, no formal criteria to predict IRR incidence or severity for all monoclonal antibodies are available.

**Incidence and potential predictive factors for infusion-related reactions from monoclonal antibodies used to treat hematologic malignancies.** 62,108,268,274,277-280,282-287,291,294-296

Agent	Mild to moderate IRR incidence	Severe IRR incidence	Predictive factors
Alemtuzumab	89%	NR	
Belantamab mafodotin-blmf	16%	2%	
Blinatumomab	30%	NR	
Brentuximab vedotin	12%	NR	
Daratumumab	63%	6%	<ul style="list-style-type: none"> <li>• Infusion rate</li> </ul>
Elotuzumab	10%	1%	
Gemtuzumab ozogamicin	66-82%	8%	
Inotuzumab ozogamicin	2%	NR	
Isatuximab-irfc	38%	2.6%	<ul style="list-style-type: none"> <li>• All infusion-related reactions started during the first infusion and resolved on the same day in 98% of the cases</li> </ul>
Mogamulizumab	35%	8%	
Moxetumomab pasudotox-tdfk	50%	4%	
Obinutuzumab	66%	20%	
Polatuzumab vedotin-piiq	25-67%	8%	
Rituximab	77%	<10%	<ul style="list-style-type: none"> <li>• High circulating malignant cell counts</li> <li>• Pulmonary infiltrates</li> <li>• Elderly patients</li> <li>• Female gender</li> <li>• Diagnosis of chronic lymphocytic leukemia or mantle cell lymphoma</li> </ul>
Tafasitamab-cxix	6%	NR	<ul style="list-style-type: none"> <li>• 80% of infusion-related reactions occurred during cycle 1 or 2</li> </ul>

NR = not reported.

### III. Prevention of infusion-related reactions<sup>275,276,278,289,290,296</sup>

- A. Prophylaxis with antihistamines, corticosteroids, or both is generally recommended to reduce both the frequency and severity of infusion reactions. Acetaminophen may also be given. In addition, montelukast has been used prior to daratumumab.
- B. In some cases, the first dose may be “split” over two days to reduce the amount of antibody given at one time.
  - 1. In February 2019, the FDA approved a split-dosing regimen of daratumumab for patients with multiple myeloma. The first prescribed 16 mg/kg dose given during week 1 may be split over two consecutive days (8 mg/kg on day 1 and day 2 respectively). The approval was based on data from a phase 1b study which demonstrated that splitting the first dose over 2 consecutive days reduced the duration of the first infusion and resulted in a similar rate and pattern of infusion reactions.<sup>281,297</sup>
  - 2. Split-dosing administration is also recommended for obinutuzumab when it is used in CLL.
  - 3. An alternative strategy is to give sequentially increasing doses of the agent over time.
- C. Patients should be closely monitored during and immediately after all infusions.
  - 1. Vital signs should be monitored before, during and after each infusion. Some protocols may also include post-infusion monitoring parameters.
  - 2. Patients should be strongly encouraged to notify a healthcare provider immediately if they notice any symptoms or discomfort during the infusion.

### IV. Management of infusion-related reactions<sup>275,291</sup>

- 1. When an infusion reaction occurs, the infusion should be interrupted and supportive care should be administered until all symptoms resolve.
  - 1. In most cases, mild to moderate reactions will resolve after a brief interruption of the infusion and the administration of supportive care.
    - a. Most patients can be safely re-challenged with the same agent following complete resolution of symptoms using a reduced infusion rate and premedication administration.
    - b. A desensitization protocol may be considered in cases of moderate and severe reactions.
  - 2. For severe reactions, the infusion should be stopped and supportive care should be provided.
    - a. Treatment should be discontinued in these cases.
    - b. However, even repeated severe IRRs to a particular monoclonal antibody may not necessarily preclude the administration of another appropriately targeted antibody (i.e., the use of obinutuzumab after repeated IRRs to rituximab).<sup>286</sup>
  - 3. Supportive care medications may include epinephrine, corticosteroids, antihistamines, bronchodilators, isotonic crystalloid solutions, and/or oxygen. All of these agents should be readily available where monoclonal antibodies are infused.

## RECOMMENDED READINGS AND REFERENCES - CHRONIC LYMPHOCYTIC LEUKEMIA

### RECOMMENDED READINGS

1. Hallek M and Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. *Am J Hematol*. 2021;96:1679-1705. Available at <https://pubmed.ncbi.nlm.nih.gov/34625994/> .
2. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32:23-33. Available at <https://pubmed.ncbi.nlm.nih.gov/33091559/> .
3. Fresa A, Autore F, Galli E, et al. Treatment options for elderly/unfit patients with chronic lymphocytic leukemia in the era of targeted drugs: a comprehensive review. *J Clin Med*. 2021;10:5104. Available at <https://pubmed.ncbi.nlm.nih.gov/34768624/> .
4. Wierda WG, Rawstron A, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. *Leukemia*. 2021; 35:3059-72. Available at <https://pubmed.ncbi.nlm.nih.gov/34168283/> .
5. Pula A and Robak T. Hairy cell leukemia: a brief update on current knowledge and treatment prospects. *Curr Opin Oncol*. 2021;33:412-419. Available at <https://pubmed.ncbi.nlm.nih.gov/34264896/> .

### REFERENCES

1. Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. *The New England journal of medicine*. Feb 24 2005;352(8):804-15. doi:10.1056/NEJMra041720
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma. V.1.2023, 8/30/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
3. Scheffold A, Stilgenbauer S. Revolution of Chronic Lymphocytic Leukemia Therapy: the Chemo-Free Treatment Paradigm. *Curr Oncol Rep*. Feb 5 2020;22(2):16. doi:10.1007/s11912-020-0881-4
4. Wierda WG, O'Brien S, Wang X, et al. Characteristics associated with important clinical end points in patients with chronic lymphocytic leukemia at initial treatment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1 2009;27(10):1637-43. doi:10.1200/JCO.2008.18.1701
5. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood*. Sep 15 1999;94(6):1848-54.
6. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood*. Sep 15 1999;94(6):1840-7.
7. Tsimberidou AM TC, Wierda W, et al. Beta-2 microglobulin (B2M) is an independent prognostic factor for clinical outcomes in patients with CLL treated with frontline fludarabine, cyclophosphamide, and rituximab (FCR) regardless of age, creatinine clearance (CrCl). *Journal of Clinical Oncology*. 2007;109:4679-4685.
8. Chung C, Lee R. Ibrutinib, obinutuzumab, idelalisib, and beyond: review of novel and evolving therapies for chronic lymphocytic leukemia. *Pharmacotherapy*. Dec 2014;34(12):1298-316. doi:10.1002/phar.1509
9. Dreger P, Schetelig J, Andersen N, et al. Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents? *Blood*. Dec 18 2014;124(26):3841-9. doi:10.1182/blood-2014-07-586826

10. Tam CS, Stilgenbauer S. How best to manage patients with chronic lymphocytic leukemia with 17p deletion and/or TP53 mutation? *Leukemia & lymphoma*. Mar 2015;56(3):587-93. doi:10.3109/10428194.2015.1011641
11. Innis-Shelton RD, Davis RS, Lamb L, Mineishi S. Paradigm shifts in the management of poor-risk chronic lymphocytic leukemia. *Leukemia & lymphoma*. Jun 2015;56(6):1626-35. doi:10.3109/10428194.2014.974041
12. Zelenetz AD, Gordon LI, Wierda WG, et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2015. *J Natl Compr Canc Netw*. Mar 2015;13(3):326-62.
13. Kittai AS, Lunning M, Danilov AV. Relevance of Prognostic Factors in the Era of Targeted Therapies in CLL. *Curr Hematol Malig Rep*. Aug 2019;14(4):302-309. doi:10.1007/s11899-019-00511-1
14. Goede V, Cramer P, Busch R, et al. Interactions between comorbidity and treatment of chronic lymphocytic leukemia: results of German Chronic Lymphocytic Leukemia Study Group trials. *Haematologica*. Jun 2014;99(6):1095-100. doi:10.3324/haematol.2013.096792
15. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica*. May 2018;103(5):874-879. doi:10.3324/haematol.2017.182907
16. Kurtin S, McBride A. Risk Assessment and Risk-Adapted Treatment Selection: A Case-Based Approach for Chronic Lymphocytic Leukemia. *J Adv Pract Oncol*. Jul-Aug 2017;8(5):502-520.
17. Bosch F, Dalla-Favera R. Chronic lymphocytic leukaemia: from genetics to treatment. *Nat Rev Clin Oncol*. Jul 5 2019;doi:10.1038/s41571-019-0239-8
18. Uhm J. Recent advances in chronic lymphocytic leukemia therapy. *Blood Res*. Jul 31 2020;55(S1):S72-S82. doi:10.5045/br.2020.S012
19. Parikh SA, Strati P, Tsang M, West CP, Shanafelt TD. Should IGHV status and FISH testing be performed in all CLL patients at diagnosis? A systematic review and meta-analysis. *Blood*. Apr 7 2016;127(14):1752-60. doi:10.1182/blood-2015-10-620864
20. Ghamlouch H, Nguyen-Khac F, Bernard OA. Chronic lymphocytic leukaemia genomics and the precision medicine era. *British journal of haematology*. Apr 25 2017;doi:10.1111/bjh.14719
21. Iovino L, Shadman M. Novel Therapies in Chronic Lymphocytic Leukemia: A Rapidly Changing Landscape. *Curr Treat Options Oncol*. Mar 13 2020;21(4):24. doi:10.1007/s11864-020-0715-5
22. Hanna KS. Updates in the management of chronic lymphocytic leukemia/small lymphocytic leukemia. *J Oncol Pharm Pract*. Jan 2020;26(1):146-155. doi:10.1177/1078155219853030
23. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *American journal of hematology*. Nov 2019;94(11):1266-1287. doi:10.1002/ajh.25595
24. Burger JA. Treatment of Chronic Lymphocytic Leukemia. *The New England journal of medicine*. Jul 30 2020;383(5):460-473. doi:10.1056/NEJMra1908213
25. Hanna KS, Fijalka A, Watson I, Brown O, Ojulu A. Long-term follow-up and future direction on the management of chronic lymphocytic leukemia/small lymphocytic leukemia. *J Oncol Pharm Pract*. May 30 2022;10781552221103820. doi:10.1177/10781552221103820
26. Bertilaccio MT, Scielzo C, Muzio M, Caligaris-Cappio F. An overview of chronic lymphocytic leukaemia biology. *Best practice & research Clinical haematology*. Mar 2010;23(1):21-32. doi:10.1016/j.beha.2009.12.005
27. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *The New England journal of medicine*. Dec 28 2000;343(26):1910-6. doi:10.1056/NEJM200012283432602
28. Kipps TJ, Fraser G, Coutre SE, et al. Long-Term Studies Assessing Outcomes of Ibrutinib Therapy in Patients With Del(11q) Chronic Lymphocytic Leukemia. *Clinical lymphoma, myeloma & leukemia*. Nov 2019;19(11):715-722 e6. doi:10.1016/j.clml.2019.07.004
29. Tausch E, Schneider C, Robrecht S, et al. Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax. *Blood*. Jun 25 2020;135(26):2402-2412. doi:10.1182/blood.2019004492
30. Rai KR, Jain P. Chronic lymphocytic leukemia (CLL)-Then and now. *American journal of hematology*. Mar 2016;91(3):330-40. doi:10.1002/ajh.24282
31. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. *Lancet*. Apr 14 2018;391(10129):1524-1537. doi:10.1016/S0140-6736(18)30422-7

32. Ladetto M, Buske C, Hutchings M, et al. ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia. *Ann Oncol*. Mar 27 2017;doi:10.1093/annonc/mdx061
33. Woyach JA. Treatment-naïve CLL: lessons from phase 2 and phase 3 clinical trials. *Hematology Am Soc Hematol Educ Program*. Dec 6 2019;2019(1):476-481. doi:10.1182/hematology.2019001321
34. Van Bockstaele F, Verhasselt B, Philippe J. Prognostic markers in chronic lymphocytic leukemia: a comprehensive review. *Blood reviews*. Jan 2009;23(1):25-47. doi:10.1016/j.blre.2008.05.003
35. Molica S, Giannarelli D, Mirabelli R, Levato L, Kay NE, Shanafelt TD. Chronic lymphocytic leukemia international prognostic index: a systematic review and meta-analysis. *Blood*. Jan 18 2018;131(3):365-368. doi:10.1182/blood-2017-09-806034
36. Molica S, Giannarelli D, Mirabelli R, Levato L, Shanafelt TD. Chronic lymphocytic leukemia international prognostic index (CLL-IPI) in patients receiving chemoimmuno or targeted therapy: a systematic review and meta-analysis. *Ann Hematol*. May 8 2018;doi:10.1007/s00277-018-3350-5
37. Molica S, Shanafelt TD, Giannarelli D, et al. The chronic lymphocytic leukemia international prognostic index predicts time to first treatment in early CLL: Independent validation in a prospective cohort of early stage patients. *American journal of hematology*. Nov 2016;91(11):1090-1095. doi:10.1002/ajh.24493
38. Strati P, Jain N, O'Brien S. Chronic Lymphocytic Leukemia: Diagnosis and Treatment. *Mayo Clin Proc*. May 2018;93(5):651-664. doi:10.1016/j.mayocp.2018.03.002
39. Parikh SA. Chronic lymphocytic leukemia treatment algorithm 2018. *Blood Cancer J*. Oct 3 2018;8(10):93. doi:10.1038/s41408-018-0131-2
40. Gribben JG, O'Brien S. Update on therapy of chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 10 2011;29(5):544-50. doi:10.1200/JCO.2010.32.3865
41. Samples LS, Graf SA. On the front line: first choice pharmacotherapeutics for chronic lymphocytic leukemia. *Expert opinion on pharmacotherapy*. Oct 2018;19(15):1675-1684. doi:10.1080/14656566.2018.1524874
42. Foon KA, Hallek MJ. Changing paradigms in the treatment of chronic lymphocytic leukemia. *Leukemia*. Mar 2010;24(3):500-11. doi:10.1038/leu.2009.266
43. Stilgenbauer S, Furman RR, Zent CS. Management of chronic lymphocytic leukemia. *Am Soc Clin Oncol Educ Book*. 2015:164-75. doi:10.14694/EdBook\_AM.2015.35.164
44. Ma S, Platanias LC. Can early intervention with pharmacotherapy reduce the morbidity and mortality of chronic lymphocytic leukemia? *Expert opinion on pharmacotherapy*. Jul 18 2018:1-5. doi:10.1080/14656566.2018.1498844
45. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. Jun 21 2018;131(25):2745-2760. doi:10.1182/blood-2017-09-806398
46. Eichhorst B, Hallek M, Goede V. Management of unfit elderly patients with chronic lymphocytic leukemia. *Eur J Intern Med*. Dec 2018;58:7-13. doi:10.1016/j.ejim.2018.02.001
47. Sharma S, Rai KR. Chronic lymphocytic leukemia (CLL) treatment: So many choices, such great options. *Cancer*. May 1 2019;125(9):1432-1440. doi:10.1002/cncr.31931
48. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group. *J Natl Cancer Inst*. May 19 1999;91(10):861-8.
49. Jain N, O'Brien S. Initial treatment of CLL: integrating biology and functional status. *Blood*. Jul 23 2015;126(4):463-70. doi:10.1182/blood-2015-04-585067
50. Ysebaert L, Feugier P, Michallet AS. Management of elderly patients with chronic lymphocytic leukemia in the era of targeted therapies. *Curr Opin Oncol*. Sep 2015;27(5):365-70. doi:10.1097/CCO.0000000000000213
51. Merli F, Mammi C, Ilariucci F. Integrating oncogeriatric tools into the management of chronic lymphocytic leukemia: current state of the art and challenges for the future. *Curr Oncol Rep*. Jul 2015;17(7):31. doi:10.1007/s11912-015-0454-0
52. Balducci L. ESH-SIOG International Conference on Haematological Malignancies in the Elderly. *Expert Rev Hematol*. Dec 2010;3(6):675-7. doi:10.1586/ehm.10.72
53. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. *British journal of haematology*. Jul 15 2018;doi:10.1111/bjh.15460

54. Strati P, Ferrajoli A. Treating Older Patients with Chronic Lymphocytic Leukemia: A Personalized Approach. *Drugs Aging*. May 4 2019;doi:10.1007/s40266-019-00678-5
55. Rogers A, Woyach JA. BTK inhibitors and anti-CD20 monoclonal antibodies for treatment-naïve elderly patients with CLL. *Ther Adv Hematol*. 2020;11:2040620720912990. doi:10.1177/2040620720912990
56. Fresa A, Autore F, Galli E, et al. Treatment Options for Elderly/Unfit Patients with Chronic Lymphocytic Leukemia in the Era of Targeted Drugs: A Comprehensive Review. *J Clin Med*. Oct 30 2021;10(21)doi:10.3390/jcm10215104
57. Eichhorst B, Hallek M, Goede V. New treatment approaches in CLL: Challenges and opportunities in the elderly. *J Geriatr Oncol*. Aug 1 2016;doi:10.1016/j.jgo.2016.07.007
58. Eichhorst B, Goede V, Hallek M. Treatment of elderly patients with chronic lymphocytic leukemia. *Leukemia & lymphoma*. Feb 2009;50(2):171-8. doi:10.1080/10428190802688517
59. Woyach JA. What is the optimal management of older CLL patients? *Best practice & research Clinical haematology*. Mar 2018;31(1):83-89. doi:10.1016/j.beha.2017.10.007
60. Thibaud V, Deneve L, Dubruielle S, et al. Identifying frailty in clinically fit patients diagnosed with hematological malignancies using a simple clinico-biological screening tool: The HEMA-4 study. *J Geriatr Oncol*. Jul 2021;12(6):902-908. doi:10.1016/j.jgo.2021.02.019
61. Goede V, Bahlo J, Chataline V, et al. Evaluation of geriatric assessment in patients with chronic lymphocytic leukemia: Results of the CLL9 trial of the German CLL study group. *Leukemia & lymphoma*. 2016;57(4):789-96. doi:10.3109/10428194.2015.1091933
62. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: <http://www.micromedexsolutions.com>. Accessed November 28, 2017.
63. Hamaker ME, Prins MC, Stauder R. The relevance of a geriatric assessment for elderly patients with a haematological malignancy--a systematic review. *Leuk Res*. Mar 2014;38(3):275-83. doi:10.1016/j.leukres.2013.12.018
64. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. Nov 1994;47(11):1245-51.
65. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. May 1968;16(5):622-6.
66. Hsieh TT, DuMontier C, Jaung T, et al. Association of Polypharmacy and Potentially Inappropriate Medications With Frailty Among Older Adults With Blood Cancers. *J Natl Compr Canc Netw*. Aug 2022;20(8):915-923 e5. doi:10.6004/jnccn.2022.7033
67. Del Giudice I, Raponi S, Della Starza I, et al. Minimal Residual Disease in Chronic Lymphocytic Leukemia: A New Goal? *Front Oncol*. 2019;9:689. doi:10.3389/fonc.2019.00689
68. Wierda WG, Rawstron A, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. *Leukemia*. Jun 24 2021;doi:10.1038/s41375-021-01241-1
69. Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. *American journal of hematology*. Dec 1 2021;96(12):1679-1705. doi:10.1002/ajh.26367
70. Kater AP, Kipps TJ, Eichhorst B, et al. Five-year analysis of Murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx). *ASH Annual Meeting and Exposition 2020*:Abstract 125.
71. Thompson M, Brander D, Nabhan C, Mato A. Minimal Residual Disease in Chronic Lymphocytic Leukemia in the Era of Novel Agents: A Review. *JAMA Oncol*. Jul 27 2017;doi:10.1001/jamaoncol.2017.2009
72. Parikh SA, Gale RP, Kay NE. Chronic lymphocytic leukemia in 2020: a surfeit of riches? *Leukemia*. Aug 2020;34(8):1979-1983. doi:10.1038/s41375-020-0852-7
73. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *The New England journal of medicine*. Dec 14 2000;343(24):1750-7. doi:10.1056/NEJM200012143432402
74. Lepage M, Chevret S, Cazin B, et al. Randomized comparison of fludarabine, CAP, and ChOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. *Blood*. Oct 15 2001;98(8):2319-25.
75. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. Oct 2 2010;376(9747):1164-74. doi:10.1016/S0140-6736(10)61381-5

76. Mossner E, Brunker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood*. Jun 3 2010;115(22):4393-402. doi:10.1182/blood-2009-06-225979
77. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *The New England journal of medicine*. Mar 20 2014;370(12):1101-10. doi:10.1056/NEJMoa1313984
78. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 10 2012;30(26):3209-16. doi:10.1200/JCO.2011.39.2688
79. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. *The New England journal of medicine*. Aug 1 2019;381(5):432-443. doi:10.1056/NEJMoa1817073
80. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet*. Apr 18 2020;395(10232):1278-1291. doi:10.1016/S0140-6736(20)30262-2
81. Sharman JP, Egyed M, Jurczak W, al. e. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: ELEVATE-TN four-year follow up. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2021;39:Abstract 7059.
82. Sharman JP, Egyed M, Jurczak W, al. e. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2022;40:7539.
83. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *The New England journal of medicine*. Jun 6 2019;380(23):2225-2236. doi:10.1056/NEJMoa1815281
84. Al-Sawaf O, Zhang C, Tandon M, al. e. Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: Follow-up of efficacy and safety results from the multicenter, open-label, randomized, phase III CLL14 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020;38(15):Abstract 8027.
85. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*. Sep 2020;21(9):1188-1200. doi:10.1016/S1470-2045(20)30443-5
86. Al-Sawaf O, Zhang C, Robrecht S, al. e. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study. *EHA Library* 2022;357012:S148.
87. Brukinsa [package insert]. San Mateo, CA: Beigene USA, Inc., 2019.
88. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *The Lancet Oncology*. Jul 7 2022;doi:10.1016/S1470-2045(22)00293-5
89. Tam CS, Giannopoulos K, Jurczak W, al. e. SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab (BR) in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL). *American Society of Hematology Annual Meeting*. 2021:Abstract 396.
90. Shanafelt T, Wang V, Kay NE, al. e. A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912). *Blood* 2018;132:LBA-4.
91. ASH Clinical News. Ibrutinib Versus FCR: A “Paradigm Shift” for Younger Patients With Treatment-Naïve CLL. Available at <https://www.ashclinicalnews.org/on-location/ibrutinib-paradigm-shift-younger-cll/>. Accessed July 3, 2019.
92. Shanafelt TD, Wang V, Kay NE, et al. Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia (CLL): Extended Follow-up from the E1912 Trial. *Blood*. Nov 13 2019;134(Supplement\_1):33. doi:10.1182/blood-2019-126824



93. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood*. Jul 14 2022;140(2):112-120. doi:10.1182/blood.2021014960
94. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. *The New England journal of medicine*. Dec 17 2015;373(25):2425-37. doi:10.1056/NEJMoa1509388
95. Barr PM, Robak T, Owen C, al. e. Updated Efficacy and Safety from the Phase 3 Resonate-2 Study: Ibrutinib As First-Line Treatment Option in Patients 65 Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. *Blood* 2016:Abstract 642.
96. Barr PM, Robak T, Owen C, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. *Haematologica*. Jun 7 2018;doi:10.3324/haematol.2018.192328
97. Burger J, Tedeschi A, Barr P, al. e. Five-Year Follow-Up After Ibrutinib Therapy for First-Line Treatment of Chronic Lymphocytic Leukemia. *Clinical lymphoma, myeloma & leukemia*. 2019;19 Supplement 1:S274.
98. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. Mar 2020;34(3):787-798. doi:10.1038/s41375-019-0602-x
99. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. Jun 14 2022;6(11):3440-3450. doi:10.1182/bloodadvances.2021006434
100. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *The New England journal of medicine*. Dec 27 2018;379(26):2517-2528. doi:10.1056/NEJMoa1812836
101. Woyach JA, Ruppert AS, Mandrekar SJ. Ibrutinib Regimens in Older Patients with Untreated CLL. Reply. *The New England journal of medicine*. Apr 25 2019;380(17):1680-1681. doi:10.1056/NEJMc1901284
102. Woyach JA, Ruppert AS, Heerema NA, al. e. Long-term results of Alliance A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab (BR) chemoimmunotherapy. *Blood*. 2021;138(1):639.
103. Eichhorst B, Fink AM, Busch R, al. e. Chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus bendamustine and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): results of a planned interim analysis of the CLL10 trial, an international, randomized study of the German CLL Study Group (GCLLSG) [abstract]. *Blood* 2014;124:Abstract 526.
104. O'Brien SM. VIII. Treatment of chronic lymphocytic leukaemia, where are we heading? *Hematol Oncol*. Jun 2015;33 Suppl 1:46-9. doi:10.1002/hon.2216
105. Eichhorst B, Fink AM, Busch R, al. e. Frontline Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Shows Superior Efficacy in Comparison to Bendamustine (B) and Rituximab (BR) in Previously Untreated and Physically Fit Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Final Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10 Study) [abstract]. *Blood* 2014;124:Abstract 19.
106. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *The Lancet Oncology*. Jul 2016;17(7):928-42. doi:10.1016/S1470-2045(16)30051-1
107. Eichhorst B, Bahlo J, Maurer C, al. e. Favorable Toxicity Profile and Long Term Outcome of Elderly, but Physically Fit CLL Patients (pts) Receiving First Line Bendamustine and Rituximab (BR) Frontline Chemoimmunotherapy in Comparison to Fludarabine, Cyclophosphamide, and Rituximab (FCR) in Advanced Chronic Lymphocytic Leukemia (CLL): Update Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10 Study). . *Blood*. 2016;128:Abstract 4382.
108. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. Jul 2015;29(7):1602-4. doi:10.1038/leu.2015.14
109. Owen CJ, Stewart DA. Obinutuzumab for the treatment of patients with previously untreated chronic lymphocytic leukemia: overview and perspective. *Ther Adv Hematol*. Aug 2015;6(4):161-70. doi:10.1177/2040620715586528

110. Goede V, Fischer K, Bosch F, et al. Updated survival analysis from the CLL11 study: obinutuzumab versus rituximab in chemoimmunotherapy-treated patients with chronic lymphocytic leukemia. *Blood*. 2015;126:Abstract 1733.
111. Goede V, Fischer K, Dyer MJ, et al. Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: final survival analysis of the CLL11 study. Presented at: 2018 EHA Congress; June 14-17, 2018; Stockholm, Sweden. Abstract S151. 2018;
112. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. Jan 21 2016;127(3):303-9. doi:10.1182/blood-2015-09-667675
113. Rituxan Hycela [package insert]. South San Francisco, CA: Genentech, Inc., 2017.
114. Truxima [package insert]. Yeonsu-gu, Incheon, Republic of Korea: Celltreon, Inc., 2018.
115. Ruxience [package insert]. New York, NY: Pfizer Labs, 2019.
116. Riabni [package insert]. Thousand Oaks, CA; Amgen, Inc.: 2020.
117. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. Jun 15 2008;111(12):5446-56. doi:10.1182/blood-2007-06-093906
118. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. *Blood*. Jun 1 2008;111(11):5291-7. doi:10.1182/blood-2007-12-130120
119. Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 1 2006;24(34):5343-9. doi:10.1200/JCO.2005.05.0401
120. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 10 2013;31(5):584-91. doi:10.1200/JCO.2012.42.8623
121. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood*. May 15 2002;99(10):3554-61.
122. Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. *Blood*. May 1 2004;103(9):3278-81. doi:10.1182/blood-2003-10-3729
123. Osuji NC, Del Giudice I, Matutes E, Wotherspoon AC, Dearden C, Catovsky D. The efficacy of alemtuzumab for refractory chronic lymphocytic leukemia in relation to cytogenetic abnormalities of p53. *Haematologica*. Oct 2005;90(10):1435-6.
124. Stilgenbauer S, Dohner H. Campath-1H-induced complete remission of chronic lymphocytic leukemia despite p53 gene mutation and resistance to chemotherapy. *The New England journal of medicine*. Aug 8 2002;347(6):452-3. doi:10.1056/NEJM200208083470619
125. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 20 2009;27(24):3994-4001. doi:10.1200/JCO.2008.21.1128
126. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *The Lancet Oncology*. Jan 2014;15(1):48-58. doi:10.1016/S1470-2045(13)70513-8
127. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *The New England journal of medicine*. Jul 17 2014;371(3):213-23. doi:10.1056/NEJMoa1400376
128. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *The New England journal of medicine*. Mar 13 2014;370(11):997-1007. doi:10.1056/NEJMoa1315226
129. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *The New England journal of medicine*. Mar 13 2014;370(11):1008-18. doi:10.1056/NEJMoa1314583
130. Varghese AM SH, Moreton P, et al. Long term survival report of the UKCLL02 trial: a phase II study of subcutaneous alemtuzumab in patients with fludarabine refractory CLL (on behalf of the NCRI CLL trials sub-group). *Blood*. 2010;116:922.

131. Badoux XC KM, O'Brien S, et al. . Final analysis of a phase 2 study of lenalidomide and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). *Blood*. 2011;118:980.
132. Stephens DM, Spurgeon SE. Ibrutinib in mantle cell lymphoma patients: glass half full? Evidence and opinion. *Ther Adv Hematol*. Oct 2015;6(5):242-52. doi:10.1177/2040620715592569
133. Thompson MC, Mato AR. Treatment of Chronic Lymphocytic Leukemia After Discontinuation of Bruton's Tyrosine Kinase Inhibitors. *Hematology/oncology clinics of North America*. Aug 2021;35(4):793-806. doi:10.1016/j.hoc.2021.03.008
134. Smolewski P, Robak T. Current Treatment of Refractory/Relapsed Chronic Lymphocytic Leukemia: A Focus on Novel Drugs. *Acta Haematol*. Nov 25 2020;1-15. doi:10.1159/000510768
135. Patel K, Pagel JM. Exploring a Future for PI3K Inhibitors in Chronic Lymphocytic Leukemia. *Curr Hematol Malig Rep*. Aug 2019;14(4):292-301. doi:10.1007/s11899-019-00525-9
136. Mato AR, Thompson M, Allan JN, et al. Real world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States. *Haematologica*. Jun 7 2018;doi:10.3324/haematol.2018.193615
137. Roeker LE, Thompson M, Mato AR. Current Treatment of Chronic Lymphocytic Leukemia: The Diminishing Role of Chemoimmunotherapy. *Drugs*. Feb 2022;82(2):133-143. doi:10.1007/s40265-021-01657-0
138. Mato AR, Nabhan C, Barr PM, et al. Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. *Blood*. Nov 03 2016;128(18):2199-2205. doi:10.1182/blood-2016-05-716977
139. Ghia P, Pluta A, Wach Mea. ASCEND Phase 3 Study of Acalabrutinib vs Investigator's Choice of Rituximab Plus Idelalisib or Bendamustine in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia. *European Hematology Association* 2019;Available at [https://library.ehaweb.org/eha/2019/24th/273259/paolo.ghia.ascend.phase.3.study.of.acalabrutinib.vs.investigators.choice.of.html?f=menu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Ace\\_id%3D1550%2Aces\\_id%3D22585%2Amarker%3D533](https://library.ehaweb.org/eha/2019/24th/273259/paolo.ghia.ascend.phase.3.study.of.acalabrutinib.vs.investigators.choice.of.html?f=menu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Ace_id%3D1550%2Aces_id%3D22585%2Amarker%3D533). Accessed December 10, 2019.
140. Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 27 2020;JCO1903355. doi:10.1200/JCO.19.03355
141. Jurczak W, Pluta A, Wach M, al. e. Three-Year Follow-up of the Ascend Trial: Acalabrutinib Vs Rituximab Plus Idelalisib or Bendamustine in Relapsed/Refractory Chronic Lymphocytic Leukemia. *american Society of Hematology Annual Meeting*. 2021:Abstract 393.
142. Byrd JC, Hillmen P, Ghia P, al. e. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2021;39:Abstract 7500.
143. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 26 2021;JCO2101210. doi:10.1200/JCO.21.01210
144. Hillmen P, Eichhorst B, Brown JR, al. e. First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *European Hematology Association*. Available at <https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/330170/peter.hillmen.first.interim.analysis.of.alpine.study.results.of.a.phase.3.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dalpine>. Accessed December 12, 2021. . 2021;
145. Onclive. Final Response Analysis of ALPINE Trial Shows Superior ORR With Zanubrutinib Vs Ibrutinib in CLL. Available at <https://www.onclive.com/view/final-response-analysis-of-alpine-trial-shows-superior-orr-with-zanubrutinib-vs-ibrutinib-in-cll> . Accessed June 20, 2022.
146. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 17 2022;JCO2200510. doi:10.1200/JCO.22.00510
147. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *The New England journal of medicine*. Mar 22 2018;378(12):1107-1120. doi:10.1056/NEJMoa1713976

148. D'Rozario J, Bennett SK. Update on the role of venetoclax and rituximab in the treatment of relapsed or refractory CLL. *Ther Adv Hematol*. 2019;10:2040620719844697. doi:10.1177/2040620719844697
149. Kater AP, Seymour JF, Hillmen P, et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 1 2019;37(4):269-277. doi:10.1200/JCO.18.01580
150. Seymour JF, Kipps TJ, Eichhorst BF, al. e. Four-Year Analysis of Murano Study Confirms Sustained Benefit of Time-Limited Venetoclax-Rituximab (VenR) in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL). *Blood*. 2019;134:335.
151. Barrientos JC, O'Brien S, Brown JR, al. e. Hematologic and immunologic function and patient well-being for the phase III RESONATE study of ibrutinib vs ofatumumab in relapsed/refractory chronic leukemia/small lymphocytic leukemia [abstract]. *Blood* 2014;124:Abstract 4696.
152. Brown JR, Hillmen P, O'Brien S, al. e. Updated efficacy including genetic and clinical subgroup analysis and overall safety in the phase 3 RESONATE trial of ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. *Blood* 2014;124:Abstract 3331.
153. Byrd J, Hillmen P, O'Brien SM, al. e. Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia (CLL): Up to four years follow-up of the RESONATE study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35:Abstract 7510.
154. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *American journal of hematology*. Dec 2019;94(12):1353-1363. doi:10.1002/ajh.25638
155. Woyach JA, Johnson AJ. Targeted therapies in CLL: mechanisms of resistance and strategies for management. *Blood*. Jul 23 2015;126(4):471-7. doi:10.1182/blood-2015-03-585075
156. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. *JAMA Oncol*. Apr 2015;1(1):80-7. doi:10.1001/jamaoncol.2014.218
157. Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood*. Mar 26 2015;125(13):2062-7. doi:10.1182/blood-2014-09-603670
158. Brown JR. Optimal First-Line Therapy for Previously Untreated Chronic Lymphocytic Leukemia: The Case for Chemotherapy. *Oncology (Williston Park)*. Jun 2015;29(6):442, 444.
159. Byrd JC, Jones JJ, Woyach JA, Johnson AJ, Flynn JM. Entering the era of targeted therapy for chronic lymphocytic leukemia: impact on the practicing clinician. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 20 2014;32(27):3039-47. doi:10.1200/JCO.2014.55.8262
160. Sandoval-Sus JD, Chavez JC, Dalia S, al. e. Outcomes of patients with relapsed/refractory chronic lymphocytic leukemia after ibrutinib discontinuation outside clinical trials: a single institution experience. . *American Society of Hematology*. 2015:Abstract 2945.
161. Parikh SA, Chaffee KR, Call TG, al. e. Ibrutinib therapy for chronic lymphocytic leukemia (CLL): an analysis of a large cohort of patients treated in routine clinical practice. *American Society of Hematology*. 2015:Abstract 2935.
162. Woyach JA. How I manage ibrutinib-refractory chronic lymphocytic leukemia. *Blood*. Mar 09 2017;129(10):1270-1274. doi:10.1182/blood-2016-09-693598
163. Davids MS, Huang Y, Rogers KA, al. e. Richter's syndrome (RS) in patients with chronic lymphocytic leukemia (CLL) on novel agent therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35:Abstract 7505.
164. Innocenti I, Rossi D, Trape G, et al. Clinical, pathological, and biological characterization of Richter syndrome developing after ibrutinib treatment for relapsed chronic lymphocytic leukemia. *Hematol Oncol*. Feb 27 2018;doi:10.1002/hon.2502
165. Brown JR. How I treat CLL patients with ibrutinib. *Blood*. Jan 25 2018;131(4):379-386. doi:10.1182/blood-2017-08-764712
166. US Food and Drug Administration. Duvelisib (COPIKTRA, Verastem, Inc.) for adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Available at <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm621503.htm> . Accessed September 24, 2018.
167. Copiktra [package insert]. Needham, MA: Verastem, Inc., 2018.

168. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. Dec 6 2018;132(23):2446-2455. doi:10.1182/blood-2018-05-850461
169. U.S. Food and Drug Administration. FDA warns about possible increased risk of death and serious side effects with cancer drug Copiktra (duvelisib). Available at <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-possible-increased-risk-death-and-serious-side-effects-cancer-drug-copiktra> . Accessed July 6, 2022.
170. Sharman JP, Coutre S, Furman RR, al. e. Second interim analysis of a phase 3 study of idelalisib (Zydelig) plus rituximab (R) for relapsed chronic lymphocytic leukemia (CLL): efficacy analysis in patient subpopulations with del(17p) and other adverse prognostic factors [abstract]. *Blood* 2014;124:Abstract 330.
171. Sharman JP, Coutre SE, Furman RR, et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1 2019;37(16):1391-1402. doi:10.1200/JCO.18.01460
172. Stephens DM. Allogeneic Stem Cell Transplantation in Chronic Lymphocytic Leukemia: An Archaic Intervention or a Necessary Evil? *Oncology (Williston Park)*. Jun 2016;30(6):539-40.
173. Gribben JG. How and when I do allogeneic transplant in CLL. *Blood*. Jul 5 2018;132(1):31-39. doi:10.1182/blood-2018-01-785998
174. Dickerson T, Wiczter T, Waller A, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood*. Nov 28 2019;134(22):1919-1928. doi:10.1182/blood.2019000840
175. Boriani G, Corradini P, Cuneo A, et al. Practical management of ibrutinib in the real life: Focus on atrial fibrillation and bleeding. *Hematol Oncol*. Mar 7 2018;doi:10.1002/hon.2503
176. Stephens DM, Byrd JC. How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia. *Blood*. Mar 21 2019;133(12):1298-1307. doi:10.1182/blood-2018-11-846808
177. Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematology Am Soc Hematol Educ Program*. Dec 4 2020;2020(1):336-345. doi:10.1182/hematology.2020000118
178. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). *Leukemia & lymphoma*. Jul 2017;58(7):1630-1639. doi:10.1080/10428194.2016.1257795
179. Stuhlinger MC, Weltermann A, Staber P, Heintel D, Nosslinger T, Steurer M. Recommendations for ibrutinib treatment in patients with atrial fibrillation and/or elevated cardiovascular risk. *Wien Klin Wochenschr*. Feb 2020;132(3-4):97-109. Empfehlungen für die Behandlung mit Ibrutinib bei Patienten mit Vorhofflimmern und/oder erhöhtem kardiovaskulärem Risiko. doi:10.1007/s00508-019-1534-1
180. Pineda-Gayoso R, Alomar M, Lee DH, Fradley MG. Cardiovascular Toxicities of Bruton's Tyrosine Kinase Inhibitors. *Curr Treat Options Oncol*. Jun 30 2020;21(8):67. doi:10.1007/s11864-020-00764-6
181. Essa H, Lodhi T, Dobson R, Wright D, Lip GYH. How to Manage Atrial Fibrillation Secondary to Ibrutinib. *JACC CardioOncol*. Mar 2021;3(1):140-144. doi:10.1016/j.jaccao.2020.11.016
182. Chai KL, Rowan G, Seymour JF, Burbury K, Carney D, Tam CS. Practical recommendations for the choice of anticoagulants in the management of patients with atrial fibrillation on ibrutinib. *Leukemia & lymphoma*. Dec 2017;58(12):2811-2814. doi:10.1080/10428194.2017.1315115
183. de Weerd I, Koopmans SM, Kater AP, van Gelder M. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. *Haematologica*. Oct 2017;102(10):1629-1639. doi:10.3324/haematol.2017.164103
184. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. *The New England journal of medicine*. Oct 13 2016;375(15):1457-1467. doi:10.1056/NEJMr1100265
185. Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics LLC, 2020.
186. Chen KY, Brunk KM, Patel BA, et al. Pharmacists' Role in Managing Patients with Chronic Lymphocytic Leukemia. *Pharmacy (Basel)*. Mar 27 2020;8(2)doi:10.3390/pharmacy8020052
187. Estupinan HY, Berglof A, Zain R, Smith CIE. Comparative Analysis of BTK Inhibitors and Mechanisms Underlying Adverse Effects. *Front Cell Dev Biol*. 2021;9:630942. doi:10.3389/fcell.2021.630942
188. Coutre SE, Byrd JC, Hillmen P, et al. Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. *Blood Adv*. Jun 25 2019;3(12):1799-1807. doi:10.1182/bloodadvances.2018028761
189. Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. *Blood*. Dec 18 2014;124(26):3991-5. doi:10.1182/blood-2014-06-583294

190. Jones JA, Hillmen P, Coutre S, et al. Use of anticoagulants and antiplatelet in patients with chronic lymphocytic leukaemia treated with single-agent ibrutinib. *British journal of haematology*. Jul 2017;178(2):286-291. doi:10.1111/bjh.14660
191. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. *J Thromb Haemost*. May 2017;15(5):835-847. doi:10.1111/jth.13651
192. Jain N, O'Brien S. Targeted therapies for CLL: Practical issues with the changing treatment paradigm. *Blood reviews*. May 2016;30(3):233-44. doi:10.1016/j.blre.2015.12.002
193. Kin A, Schiffer CA. Infectious Complications of Tyrosine Kinase Inhibitors in Hematological Malignancies. *Infect Dis Clin North Am*. Jun 2020;34(2):245-256. doi:10.1016/j.idc.2020.02.008
194. Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2019.
195. Bhat SA, Gambriel JA, Azali L, al. e. Ventricular arrhythmias and sudden death events following acalabrutinib initiation. *Blood*. 2022:2022016953.
196. Syed YY. Zanubrutinib: First Approval. *Drugs*. Jan 2020;80(1):91-97. doi:10.1007/s40265-019-01252-4
197. Rhodes JM, Barrientos JC. Chemotherapy-free frontline therapy for CLL: is it worth it? *Hematology Am Soc Hematol Educ Program*. Dec 4 2020;2020(1):24-32. doi:10.1182/hematology.2020000085
198. Wierda WG, Tambaro FP. How I manage CLL with venetoclax-based treatments. *Blood*. Apr 23 2020;135(17):1421-1427. doi:10.1182/blood.2019002841
199. Venclexta [package insert]. North Chicago, IL; AbbVie Inc.: 2016.
200. Gribben JG. Practical management of tumor lysis syndrome in venetoclax-treated patients with chronic lymphocytic leukaemia. *British journal of haematology*. 2019;188:844-851.
201. Barrientos JC, Kaur M, Mark A, al. e. Outcomes of patients with chronic lymphocytic leukemia (CLL) after idelalisib therapy discontinuation. *American Society of Hematology*. 2015;(Abstract 4155.)
202. Coutre SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leukemia & lymphoma*. 2015;56(10):2779-86. doi:10.3109/10428194.2015.1022770
203. Cuneo A, Barosi G, Danesi R, et al. Management of adverse events associated with idelalisib treatment in chronic lymphocytic leukemia and follicular lymphoma: A multidisciplinary position paper. *Hematol Oncol*. Feb 2019;37(1):3-14. doi:10.1002/hon.2540
204. O'Brien S, Lamanna N, Kipps TJ, al. e. Update on a phase 2 study of idelalisib in combination with rituximab in treatment-naïve patients >65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) [abstract]. *Blood*. 2014;124:Abstract 1994.
205. Nair KS, Cheson B. The role of idelalisib in the treatment of relapsed and refractory chronic lymphocytic leukemia. *Ther Adv Hematol*. Apr 2016;7(2):69-84. doi:10.1177/2040620715625966
206. Lampson BL, Kasar SN, Matos TR, et al. Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood*. Jul 14 2016;128(2):195-203. doi:10.1182/blood-2016-03-707133
207. Thompson PA, Stingo F, Keating MJ, et al. Outcomes of patients with chronic lymphocytic leukemia treated with first-line idelalisib plus rituximab after cessation of treatment for toxicity. *Cancer*. Aug 15 2016;122(16):2505-11. doi:10.1002/cncr.30069
208. FDA alerts healthcare professionals about clinical trials with Zydelig (idelalisib) in combination with other cancer medicines. U. S. Food and Drug Administration. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm490618.htm>. Accessed September 26, 2016.
209. Commentary on idelalisib by Dr. Richard Furman. CLL Society. Available at <http://cllsociety.org/2016/03/commentary-idelalisib-dr-richard-furman/>. Accessed September 26, 2016.
210. The Lancet H. Straying from the target. *Lancet Haematol*. May 2016;3(5):e205. doi:10.1016/S2352-3026(16)30025-4
211. Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. *Blood*. Mar 20 2014;123(12):1810-7. doi:10.1182/blood-2013-09-527853
212. Wiestner A. The role of B-cell receptor inhibitors in the treatment of patients with chronic lymphocytic leukemia. *Haematologica*. Dec 2015;100(12):1495-507. doi:10.3324/haematol.2014.119123



213. Coutre SE, Furman RR, Flinn IW, et al. Extended Treatment with Single-Agent Ibrutinib at the 420 mg Dose Leads to Durable Responses in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *Clin Cancer Res*. Mar 01 2017;23(5):1149-1155. doi:10.1158/1078-0432.CCR-16-1431
214. Burger JA, O'Brien S. Evolution of CLL treatment - from chemoimmunotherapy to targeted and individualized therapy. *Nat Rev Clin Oncol*. Aug 2018;15(8):510-527. doi:10.1038/s41571-018-0037-8
215. Gaidano G, Foa R, Dalla-Favera R. Molecular pathogenesis of chronic lymphocytic leukemia. *The Journal of clinical investigation*. Oct 1 2012;122(10):3432-8. doi:10.1172/JCI64101
216. Jamrozik K, Tadmor T, Robak T, Polliack A. Richter syndrome in chronic lymphocytic leukemia: updates on biology, clinical features and therapy. *Leukemia & lymphoma*. Jul 2015;56(7):1949-58. doi:10.3109/10428194.2014.979411
217. Eyre TA, Schuh A. An update for Richter syndrome - new directions and developments. *British journal of haematology*. Aug 2017;178(4):508-520. doi:10.1111/bjh.14700
218. Wang Y, Tschautscher MA, Rabe KG, et al. Clinical characteristics and outcomes of Richter transformation: Experience of 204 patients from a single center. *Haematologica*. Jun 13 2019;doi:10.3324/haematol.2019.224121
219. Tadmor T, Levy I. Richter Transformation in Chronic Lymphocytic Leukemia: Update in the Era of Novel Agents. *Cancers (Basel)*. Oct 14 2021;13(20)doi:10.3390/cancers13205141
220. Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. *Blood*. May 11 2017;129(19):2612-2615. doi:10.1182/blood-2016-12-737346
221. Williams AM, Baran AM, Casulo C, et al. Ibrutinib Dose Adherence and Therapeutic Efficacy in Non-Hodgkin Lymphoma: A Single-Center Experience. *Clinical lymphoma, myeloma & leukemia*. Jan 2019;19(1):41-47. doi:10.1016/j.clml.2018.10.005
222. Mackler E, Segal EM, Muluneh B, Jeffers K, Carmichael J. 2018 Hematology/Oncology Pharmacist Association Best Practices for the Management of Oral Oncolytic Therapy: Pharmacy Practice Standard. *J Oncol Pract*. Apr 2019;15(4):e346-e355. doi:10.1200/JOP.18.00581
223. Durr P, Schlichtig K, Kelz C, et al. The Randomized AMBORA Trial: Impact of Pharmacological/Pharmaceutical Care on Medication Safety and Patient-Reported Outcomes During Treatment With New Oral Anticancer Agents. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 20 2021;39(18):1983-1994. doi:10.1200/JCO.20.03088
224. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. *British journal of haematology*. Sep 1994;88(1):209-12.
225. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. *The New England journal of medicine*. Oct 6 1988;319(14):902-7. doi:10.1056/NEJM198810063191403
226. Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. *Clinical and laboratory haematology*. Mar 1995;17(1):75-80.
227. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIg) in chronic lymphocytic leukemia. Results of a crossover study. *Haematologica*. Mar-Apr 1996;81(2):121-6.
228. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. *Leukemia & lymphoma*. May 2009;50(5):764-72. doi:10.1080/10428190902856824
229. O'Brien S, Ravandi F, Riehl T, et al. Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. *Blood*. Feb 15 2008;111(4):1816-9. doi:10.1182/blood-2007-03-080010
230. O'Brien SM, Keating MJ, Mocarski ES. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Clinical lymphoma & myeloma*. Sep 2006;7(2):125-30. doi:10.3816/CLM.2006.n.049
231. Shah N, Tam C, Seymour JF, Rule S. How applicable is fludarabine, cyclophosphamide and rituximab to the elderly? *Leukemia & lymphoma*. Jun 2015;56(6):1599-610. doi:10.3109/10428194.2014.963083
232. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-related Infections. V.1.2021, 07/02/21, © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN

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233. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Jan 2021;32(1):23-33. doi:10.1016/j.annonc.2020.09.019
234. Borthakur G, O'Brien S, Wierda WG, et al. Immune anaemias in patients with chronic lymphocytic leukaemia treated with fludarabine, cyclophosphamide and rituximab--incidence and predictors. *British journal of haematology*. Mar 2007;136(6):800-5. doi:10.1111/j.1365-2141.2007.06513.x
235. Zanotti R, Frattini F, Ghia P, et al. ZAP-70 expression is associated with increased risk of autoimmune cytopenias in CLL patients. *American journal of hematology*. Jul 2010;85(7):494-8. doi:10.1002/ajh.21737
236. Moreno C, Hodgson K, Ferrer G, et al. Autoimmune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. *Blood*. Dec 2 2010;116(23):4771-6. doi:10.1182/blood-2010-05-286500
237. Cortes J, O'Brien S, Loscertales J, et al. Cyclosporin A for the treatment of cytopenia associated with chronic lymphocytic leukemia. *Cancer*. Oct 15 2001;92(8):2016-22.
238. D'Arena G, Laurenti L, Capalbo S, et al. Rituximab therapy for chronic lymphocytic leukemia-associated autoimmune hemolytic anemia. *American journal of hematology*. Aug 2006;81(8):598-602. doi:10.1002/ajh.20665
239. Berentsen S. Rituximab for the treatment of autoimmune cytopenias. *Haematologica*. Dec 2007;92(12):1589-96. doi:10.3324/haematol.11312
240. Visco C, Ruggeri M, Laura Evangelista M, et al. Impact of immune thrombocytopenia on the clinical course of chronic lymphocytic leukemia. *Blood*. Feb 1 2008;111(3):1110-6. doi:10.1182/blood-2007-09-111492
241. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet*. Feb 2 2008;371(9610):395-403. doi:10.1016/S0140-6736(08)60203-2
242. Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood*. Mar 5 2009;113(10):2161-71. doi:10.1182/blood-2008-04-150078
243. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *The New England journal of medicine*. Nov 29 2007;357(22):2237-47. doi:10.1056/NEJMoa073275
244. Zent CS, Kay NE. Autoimmune complications in chronic lymphocytic leukaemia (CLL). *Best practice & research Clinical haematology*. Mar 2010;23(1):47-59. doi:10.1016/j.beha.2010.01.004
245. Vitale C, Montalbano MC, Salvetti C, et al. Autoimmune Complications in Chronic Lymphocytic Leukemia in the Era of Targeted Drugs. *Cancers (Basel)*. Jan 23 2020;12(2)doi:10.3390/cancers12020282
246. Moreno C. Autoimmune cytopenia and CLL ride together. *Blood*. Jun 24 2021;137(25):3464-3465. doi:10.1182/blood.2021010944
247. Leong H, Bonk ME. Bendamustine (treanda) for chronic lymphocytic leukemia: a brief overview. *P T*. Feb 2009;34(2):73-6.
248. Huhn D, von Schilling C, Wilhelm M, et al. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. *Blood*. Sep 1 2001;98(5):1326-31.
249. Getta BM, Park JH, Tallman MS. Hairy cell leukemia: Past, present and future. *Best practice & research Clinical haematology*. Dec 2015;28(4):269-72. doi:10.1016/j.beha.2015.10.015
250. Roider T, Falini B, Dietrich S. Recent advances in understanding and managing hairy cell leukemia. *F1000Res*. 2018;7doi:10.12688/f1000research.13265.1
251. Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *British journal of haematology*. Jun 2009;145(6):733-40. doi:10.1111/j.1365-2141.2009.07668.x
252. Goodman GR, Burian C, Koziol JA, Saven A. Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 1 2003;21(5):891-6. doi:10.1200/JCO.2003.05.093



253. Pula A, Robak T. Hairy cell leukemia: a brief update on current knowledge and treatment prospects. *Curr Opin Oncol*. Sep 1 2021;33(5):412-419. doi:10.1097/CCO.0000000000000771
254. Grever MR, Abdel-Wahab O, Andritsos LA, et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. *Blood*. Feb 2 2017;129(5):553-560. doi:10.1182/blood-2016-01-689422
255. Falini B, Martelli MP, Tiacci E. BRAF V600E mutation in hairy cell leukemia: from bench to bedside. *Blood*. Oct 13 2016;128(15):1918-1927. doi:10.1182/blood-2016-07-418434
256. Cross M, Dearden C. Hairy Cell Leukaemia. *Curr Oncol Rep*. Apr 16 2020;22(5):42. doi:10.1007/s11912-020-00911-0
257. Maitre E, Cornet E, Troussard X. Hairy cell leukemia: 2020 update on diagnosis, risk stratification, and treatment. *American journal of hematology*. Dec 2019;94(12):1413-1422. doi:10.1002/ajh.25653
258. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hairy Cell Leukemia. V.1.2023, 8/30/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™* Surveys & Data, Powered by *NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
259. Ramos Perez J, Ravandi-Kashani F. The pharmacological management of hairy cell leukemia. *Expert opinion on pharmacotherapy*. Aug 2020;21(11):1337-1344. doi:10.1080/14656566.2020.1754397
260. Liu Q, Harris N, Epperla N, Andritsos LA. Current and Emerging Therapeutic Options for Hairy Cell Leukemia Variant. *Onco Targets Ther*. 2021;14:1797-1805. doi:10.2147/OTT.S242247
261. Tran J, Gaulin C, Tallman MS. Advances in the Treatment of Hairy Cell Leukemia Variant. *Curr Treat Options Oncol*. Jan 2022;23(1):99-116. doi:10.1007/s11864-021-00927-z
262. King AC, Kabel CC, Pappacena JJ, Stump SE, Daley RJ. No Loose Ends: A Review of the Pharmacotherapy of Hairy Cell and Hairy Cell Leukemia Variant. *Ann Pharmacother*. Sep 2019;53(9):922-932. doi:10.1177/1060028019836775
263. Andrasiak I, Rybka J, Wrobel T. Response to the Therapy in Hairy Cell Leukemia: Systematic Review and Meta-Analysis. *Clinical lymphoma, myeloma & leukemia*. Jun 2018;18(6):392-399 e3. doi:10.1016/j.clml.2018.03.011
264. Chihara D, Arons E, Stetler-Stevenson M, et al. Randomized Phase II Study of First-Line Cladribine With Concurrent or Delayed Rituximab in Patients With Hairy Cell Leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 10 2020;38(14):1527-1538. doi:10.1200/JCO.19.02250
265. Bohn JP, Dietrich S. Treatment of Classic Hairy Cell Leukemia: Targeting Minimal Residual Disease beyond Cladribine. *Cancers (Basel)*. Feb 15 2022;14(4)doi:10.3390/cancers14040956
266. Paillassa J, Troussard X. Biology and Treatment of Hairy Cell Leukemia. *Curr Treat Options Oncol*. Apr 30 2020;21(6):44. doi:10.1007/s11864-020-00732-0
267. Tiacci E, De Carolis L, Simonetti E, et al. Vemurafenib plus Rituximab in Refractory or Relapsed Hairy-Cell Leukemia. *The New England journal of medicine*. May 13 2021;384(19):1810-1823. doi:10.1056/NEJMoa2031298
268. Lumoxiti [package insert]. Wilmington, DE: Astrazeneca Pharmaceuticals LP, 2022.
269. US Food and Drug Administration. FDA approves moxetumomab pasudotox-tdfk for hairy cell leukemia. Available at <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm620473.htm>. Accessed September 15, 2018.
270. Kreitman RJ, Dearden C, Zinzani PL, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. *Leukemia*. Aug 2018;32(8):1768-1777. doi:10.1038/s41375-018-0210-1
271. Fancher KM, Lally-Montgomery ZC. Moxetumomab pasudotox: A first-in-class treatment for hairy cell leukemia. *J Oncol Pharm Pract*. Mar 27 2019;1078155219838041. doi:10.1177/1078155219838041
272. Kreitman RJ, Dearden CE, Zinzani PL, al. e. Moxetumomab pasudotox-tdfk in heavily pretreated patients with relapsed/refractory hairy cell Leukemia (HCL): long-term follow-up from the pivotal phase 3 trial. *Blood* 2019;134:2808.
273. Rogers KA, Andritsos LA, Wei L, al. e. Phase 2 study of ibrutinib in classic and variant hairy cell leukemia. *Blood*. 2021;137(25):3473-83.

274. Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. *The oncologist*. Jun 2008;13(6):725-32. doi:10.1634/theoncologist.2008-0012
275. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *The oncologist*. May 2007;12(5):601-9. doi:10.1634/theoncologist.12-5-601
276. Hsu Blatman KS, Castells MC. Desensitizations for chemotherapy and monoclonal antibodies: indications and outcomes. *Curr Allergy Asthma Rep*. Aug 2014;14(8):453. doi:10.1007/s11882-014-0453-5
277. Laudati C, Clark C, Knezevic A, Zhang Z, Barton-Burke M. Hypersensitivity Reactions: Priming Practice Change to Reduce Incidence in First-Dose Rituximab Treatment. *Clin J Oncol Nurs*. Aug 1 2018;22(4):407-414. doi:10.1188/18.CJON.407-414
278. Moreau P, van de Donk NW, San Miguel J, et al. Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma. *Drugs*. May 2016;76(8):853-67. doi:10.1007/s40265-016-0573-4
279. Mylotarg [package insert]. Philadelphia, pa; wyeth pharmaceuticals inc: 2017.
280. Comer H, Cardwell K. Brentuximab Vedotin Infusion Reaction Management: A Case Study. *J Adv Pract Oncol*. Sep-Oct 2017;8(6):626-629.
281. Darzalex [package insert]. Horsham, PA: Janssen Biotech, Inc., 2019.
282. Polivy [package insert]. South San Francisco, CA: Genentech, Inc., 2019.
283. Monjuvi [package insert]. Boston, MA: Morphosys US Inc., 2020.
284. Blenrep [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2020.
285. Sarclisa [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC, 2020.
286. Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses. *Oncoimmunology*. Oct 1 2013;2(10):e26333. doi:10.4161/onci.26333
287. Fouda GE, Bavbek S. Rituximab Hypersensitivity: From Clinical Presentation to Management. *Front Pharmacol*. 2020;11:572863. doi:10.3389/fphar.2020.572863
288. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol*. Dec 2009;124(6):1259-66. doi:10.1016/j.jaci.2009.09.009
289. Dawson K, Moran M, Guindon K, Wan H. Managing Infusion-Related Reactions for Patients With Chronic Lymphocytic Leukemia Receiving Obinutuzumab. *Clin J Oncol Nurs*. Apr 2016;20(2):E41-8. doi:10.1188/16.CJON.E41-E48
290. Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. *Clin Transl Immunology*. Jul 2015;4(7):e39. doi:10.1038/cti.2015.14
291. Galvao VR, Castells MC. Hypersensitivity to biological agents-updated diagnosis, management, and treatment. *J Allergy Clin Immunol Pract*. Mar-Apr 2015;3(2):175-85; quiz 186. doi:10.1016/j.jaip.2014.12.006
292. National Cancer Institute Common Terminology for Adverse Events v5. (CTCAE). Available at [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). Accessed June 17, 2019.
293. Thompson LM, Eckmann K, Boster BL, et al. Incidence, risk factors, and management of infusion-related reactions in breast cancer patients receiving trastuzumab. *The oncologist*. Mar 2014;19(3):228-34. doi:10.1634/theoncologist.2013-0286
294. Jean GW, Comeau JM. Role of obinutuzumab in the treatment of chronic lymphocytic leukemia. *Am J Health Syst Pharm*. Jun 1 2015;72(11):933-42. doi:10.2146/ajhp140282
295. Patel J, Ho M, Ho V, et al. Rapid infusion rituximab for maintenance therapy: is it feasible? *Leuk Res Treatment*. 2013;2013:629283. doi:10.1155/2013/629283
296. Poteligeo [package insert]. Bedminster, NJ: Kyowa Kirin, Inc., 2017.
297. The ASCO Post. FDA Approves Daratumumab Split-Dosing Regimen. Available at <https://www.ascopost.com/News/59736>. Accessed June 18, 2019.

# LOWER GASTROINTESTINAL AND PANCREATIC CANCERS

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## LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with lower gastrointestinal (GI) or pancreatic cancers.
2. Discuss short- and long-term treatment goals, including post-therapy and survivorship, with a patient with lower GI or pancreatic cancers and his or her caregiver.
3. Select relevant information and guidance for the public regarding lower GI and pancreatic cancer-related issues (e.g., risk factors, prevention, screening).
4. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with pharmacotherapy for lower GI or pancreatic cancers, including chemotherapy-induced diarrhea, hand-foot syndrome, hand foot skin reaction, neurotoxicity from oxaliplatin, and dermatologic toxicities from epidermal growth factor receptor inhibitors.

## COLON AND RECTAL CANCER

### Patient Case #1 (ARS Question 1):

LS is a 73-year old female who presents her PCP with complaints of abdominal cramping, dark stools, and feeling excessively fatigued. Laboratory results reveal a hemoglobin of 6.2 g/dL. A colonoscopy reveals a large, circumferential mass, mostly obstructing and unable to be traversed. CT scans of the chest, abdomen, and pelvis reveal no evidence of metastatic disease. LS therefore underwent a laparoscopic right colectomy. Pathology revealed a moderately differentiated adenocarcinoma, negative margins, 0/29 lymph nodes positive for disease, evidence of perineural invasion but no lymphovascular invasion, and microsatellite low. LS was staged with T4a N0 M0 disease with high-risk features. She presents to the medical oncologist today about 6 weeks from surgery and confirms she feels back to “normal” and is open to discussing adjuvant treatment.

**Which of the following is the most appropriate adjuvant therapy for LS’s stage high-risk IIB colon cancer?**

- A. Observation
- B. Capecitabine
- C. FOLFOX
- D. FOLFIRI

### I. Genomics<sup>1</sup>

#### A. Genetic alterations<sup>1-3</sup>

1. 5-10% of all colorectal cancer cases can be attributed to well-defined hereditary syndromes
2. Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch Syndrome
  - a. Not characterized by excessive polyps
  - b. Accounts for 2-4% of all colorectal cancers
  - c. Autosomal dominant trait caused by germline mutations in DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*
    - 1) Lifetime risk of colon cancer ranges from 46-61%, compared to 4.2% in the general population
    - 2) Women have 34-54% risk of endometrial cancer, compared to 3.1% in the general population
    - 3) Increased risk for a variety of other malignancies, including ovarian and gastric
  - d. Onset of colon cancer occurs earlier than in the general population, and initiation of screening depends on the MMR gene variant(s) affected
3. Familial adenomatous polyposis (FAP)
  - a. Manifested by hundreds to thousands of adenomatous polyps throughout the colon and rectum
    - 1) Classical FAP starts to develop adenomas in early adolescence

- 2) Attenuated FAP (AFAP) is variant of FAP in which there is a later onset of disease and fewer cumulative lifetime adenomas than classical FAP
  - b. Accounts for about 1% of all colorectal cancers
  - c. Autosomal dominant disorders caused by mutation in *APC* (adenomatous polyposis coli) gene
    - 1) About 20-30% of patients have a de novo *APC* germline mutation (no prior family history)
    - 2) If risk-reducing surgery is not performed, 100% of patients will progress to colorectal cancer by the age of 50
  4. Other well-defined colorectal cancer syndromes include *MUTYH*-associated polyposis and hamartomatous polyposis syndromes (Juvenile Polyposis Syndrome, Peutz-Jeghers, *PTEN* hamartoma tumor syndromes)
- B. Defective DNA mismatch repair (dMMR)<sup>2</sup>
1. Defective function of the DNA mismatch repair system has been reported in up to 19% of colorectal cancers
    - a. Patients with dMMR status are biologically the same as those with high level microsatellite instability (MSI-H) status, though dMMR is determined by immunohistochemistry (IHC) testing and microsatellite status is determined by next generation sequencing (NGS). (See Pharmacogenomics module for more information).
  2. dMMR/MSI-H status predicts decreased benefit from adjuvant therapy with a fluoropyrimidine in patients with stage II disease
    - a. dMMR/MSI-H has been reported in about 22% of stage II patients
    - b. Multiple retrospective reviews have investigated the benefit of using fluorouracil (5-FU)-based adjuvant chemotherapy versus observation in MSI-H/dMMR patients after curative resection of stage II or stage III colon cancer
      - 1) Patients with MSI-H/dMMR tumors have significantly increased overall survival (OS), increased disease-free survival (DFS), and lower rates of tumor recurrence than patients with MSI-L, MSS, or pMMR who were observed after surgery (IE, no adjuvant therapy)<sup>4-6</sup>
      - 2) In patients with MSI-H/dMMR stage II disease, adjuvant therapy was associated with decreased OS and higher risk of death compared to observation<sup>4,5</sup>; however patients with MSI-H/dMMR stage III disease still experienced benefit from adjuvant therapy over observation<sup>6</sup>
    - c. Patients with stage II MSI-H/dMMR tumors seem to have a good prognosis and do not benefit from adjuvant 5-FU therapy<sup>2</sup>
    - d. Patients with stage III MSI-H/dMMR tumors can still benefit from 5-FU-based adjuvant therapy and therefore should be considered for treatment over observation alone<sup>6</sup>
  3. dMMR/MSI-H status also predicts increased benefit from checkpoint inhibitors in patients with metastatic disease (further discussed in “Treatment of metastatic colon and rectal cancer” section below)
    - a. Approximately 3.5% of stage IV colorectal tumors are dMMR/MSI-H<sup>2</sup>

- 1) Since dMMR/MSI-H tumors generally have a better prognosis, these tumors tend to metastasize less frequently
  - b. Both pembrolizumab and nivolumab with or without ipilimumab have shown encouraging response rates, progression-free survival, and overall survival in heavily pretreated metastatic colorectal cancer that is dMMR/MSI-H<sup>7-10</sup>, as well as treatment-naïve patients<sup>11-13</sup>
    - 1) See “Treatment of metastatic colon and rectal cancer (stage IV)” section for detailed discussion of these regimens
  - c. Dostarlimab was shown to be effective in a phase I study (GARNET) in dMMR solid tumors<sup>14</sup>
    - 1) Included patients in cohort F had dMMR or POLE mutated solid tumors, with the majority (93.4%) having a GI cancer
    - 2) Confirmed ORR was 38.7%
- C. Enzymatic deficiencies
1. Dihydropyridine dehydrogenase (DPD) deficiency and fluoropyrimidines<sup>15-17</sup>
    - a. 5-FU is metabolized by 2 routes:
      - 1) 20% anabolic
      - 2) 80% catabolic (mainly occurs in liver)
    - b. DPD is an enzyme that is involved in the initial and rate-limiting step of fluoropyrimidine catabolism
      - 1) Varying concentrations of DPD in humans may affect 5-FU and capecitabine bioavailability and account for varying patient response
    - c. DPD deficiency occurs due to genetic abnormality in the *DPYD* gene
      - 1) Partial and complete deficiency occurs in 3-5% and 0.2% of general population, respectively
      - 2) High concentration of DPD = decreased fluoropyrimidine activity
      - 3) Low concentration of DPD = increased levels of fluoropyrimidine that may result in severe GI toxicities (mucositis, diarrhea), myelosuppression, neurologic toxicity, and possibly death
      - 4) Routine screening for *DPYD* variants prior to fluoropyrimidine exposure is controversial and not supported by the NCCN panel<sup>2</sup> at this time
        - a) There are numerous *DPYD* variants, and only a few have clearly established relationships to DPD function
        - b) In addition, there is no universally used test for DPD deficiency
          - i. Testing options range from targeted analysis of specific variants to full coding regions
      - 5) The Clinical Pharmacogenetics Implementation Consortium (CPIC®) provides dose modification recommendations for fluoropyrimidines based on an assigned activity score<sup>17</sup>:
        - a) Activity Score 2
          - i. *DPYD* normal metabolizer: an individual carrying 2 normal function alleles

- ii. No dose modifications recommended
- b) Activity Score 1 or 1.5
  - i. DPYD intermediate metabolizer: an individual carrying 1 normal function allele and 1 no function allele, or 2 decreased function alleles
  - ii. Reduce starting dose by 50%
- c) Activity Score 0 or 0.5
  - i. DPYD poor metabolizer: an individual carrying 2 no function alleles, or 1 no function allele and 1 decreased function allele
  - ii. Avoid the use of fluoropyrimidines; if these agents are required, the starting dose should be significantly decreased and early drug monitoring should be implemented
- 6) An antidote, uridine triacetate, is available commercially for patients who experience fluoropyrimidine overdose or overexposure, and has shown efficacy in patients with DPD deficiencies experiencing severe toxicity<sup>18</sup>
  - a) Uridine triacetate is given orally every 6 hours for 20 doses and is most effective if started within 96 hours following the end of fluorouracil or capecitabine administration<sup>19</sup>
- 2. Uridine diphosphate glycosyltransferase 1 family polypeptide A1 (UGT1A1) and irinotecan<sup>20,21</sup>
  - a. Metabolism and pharmacokinetics of irinotecan
    - 1) Irinotecan has a dipiperidino side-chain linked to the camptothecin base molecule
    - 2) Carboxylesterases in the liver and gastrointestinal (GI) tract cleave the side chain to form the metabolite SN-38
      - a) SN-38 is about 1000-fold more potent inhibitor of topoisomerase I than irinotecan
    - 3) SN-38 is then glucuronidated by UGT1A1 in the liver, creating the inactive metabolite SN-38G which is eliminated via biliary excretion into the GI tract
    - 4) SN-38G can be “reactivated” back to SN-38 via bacterial  $\beta$ -glucuronidase enzymes that remove the glucuronide group
  - b. Reduced activity of UGT1A1 can lead to significant toxicities<sup>22</sup>
    - 1) Patients with a UGT1A1\*28 polymorphism, especially a homozygous mutation, are at much higher risk to develop significant neutropenia
    - 2) Approximately 10% of the US population is homozygous for UGT1A1\*28 allele
    - 3) Irinotecan dose reductions are recommended for patients who are UGT1A1\*28 homozygous in the prescribing information<sup>23</sup>
      - a) A reduction of at least one level from the starting dose is recommended, however modifications should also consider the specific dosing regimen and individual patient characteristics

- 4) FDA-approved test is available to evaluate for UGT1A1 polymorphisms, however there are no official guidelines for the use of this test in clinical practice, and testing prior to irinotecan exposure is not routinely performed

D. Predictive biomarkers<sup>24-28</sup>

1. RAS (KRAS, NRAS, and HRAS)

- a. Activating RAS mutations predict lack of response to anti-EGFR MABs
  - 1) Several trials have demonstrated these agents only work in RAS-wild type (WT) disease
- b. NCCN Guidelines<sup>®2,29</sup> and ASCO guidelines recommend testing all patients with metastatic disease prior to starting an anti-EGFR MAB for treatment
- c. ASCO Guideline on Molecular Biomarkers for the Evaluation of Colorectal Cancer<sup>28</sup>
  - 1) All patients with metastatic colorectal cancer who are candidates for anti-EGFR MAB therapy should have their tumor tested for the following:
    - a) KRAS and NRAS
      - i. Exon 2, codons 12 and 13
      - ii. Exon 3, codons 59 and 61
      - iii. Exon 4, codons 117, and 146
      - iv. RAS mutations in exons 2, 3, or 4 are associated with lack of benefit from anti-EGFR MAB therapy and may be associated with worse outcomes when added to chemotherapy
    - b) Treatment with anti-EGFR MAB therapy should only be considered in patients whose tumor does not have one of the above mutations (IE, these agents are only appropriate for wild-type disease)

2. BRAF<sup>27</sup>

- a. BRAF V600E mutation occurs in 5-15% of colorectal cancers and results in poorer prognosis
  - 1) The presence of BRAF V600E mutation in a tumor that also harbors MLH1 promoter methylation is consistent with a sporadic dMMR tumor (vs hereditary) and further germline testing is not required
- b. RAS and BRAF V600E mutations are typically mutually exclusive at diagnosis
- c. Data suggest lack of activity for anti-EGFR MAB therapy in the presence of V600E mutations
  - 1) The NCCN<sup>®</sup> panel recommends all patients at diagnosis of stage IV disease undergo tumor genetic testing for BRAF<sup>2,29</sup>
  - 2) ASCO recommends BRAF mutational analysis be performed for prognostic stratification<sup>28</sup>
- d. Unlike other disease states with BRAF V600E mutations responsive to BRAF +/- MEK inhibition, colorectal cancers with these mutations show limited, if any, response to these inhibitors alone<sup>30</sup>
  - 1) Response rates for single-agent BRAF inhibitors in BRAF V600E-mutated melanomas have been reported up to 80%, vs <5% seen in BRAF-mutated colorectal cancers



- 2) The lack of response is hypothesized to be due to feedback activation of EGFR, which leads to MAPK signaling pathway reactivation, which could in turn result in further progression of the tumor rather than control
  - a) Colorectal cancer cells are of epithelial origin and express EGFR; melanoma cells do not
- 3) In order to overcome this reactivation of the MAPK pathway, BRAF inhibition therapies have been evaluated with the addition of anti-EGFR MAB therapies
- 4) This dual inhibition has led to improved response rates and promising survival outcomes
- e. Various regimens containing anti-EGFR MABs and BRAF ± MEK inhibitors have been evaluated for use in patients with BRAF V600E-mutated metastatic colorectal cancer (See “Treatment of metastatic colon and rectal cancer (stage IV)” section for detailed discussion)
  - 1) Colorectal cancer patients with BRAF V600E mutations should not be treated with either an anti-EGFR MAB alone or a BRAF inhibitor alone due to lack of effectiveness and/or potential for exacerbation of disease

## II. Prevention and screening

### A. Chemoprevention

#### 1. Diet

##### a. Vitamin supplementation

##### 1) Vitamin D

- a) The Women’s Health Initiative<sup>31</sup> randomly assigned 18,176 participants to receive supplemental calcium and vitamin D, and 18,106 received placebo
  - i. After 7 years of follow-up, calcium and vitamin D had no effect on the risk of colorectal cancer (HR 1.08, 95% CI, 0.86 – 1.34)
- b) Multiple randomized trials have investigated vitamin D supplementation in patients with colorectal adenomas and colorectal cancer
  - i. No trial to date has shown vitamin D supplementation improves survival outcomes in patients with colorectal cancer, and the NCCN® panel currently does not recommend routine screening for vitamin D deficiency nor superfluous supplementation of vitamin D in colorectal cancer patients<sup>2,29</sup>

##### 2) Selenium supplementation has shown mixed results in observational studies

##### b. High fiber<sup>32</sup>

- 1) High fiber diet thought to dilute carcinogens in stool, decrease colon transit time and create favorable environment in colon
- 2) Increased fiber intake does not significantly reduce colon cancer risk

##### c. Other modifiable dietary factors linked to increased incidence of colon cancer include high-caloric diet, high red meat consumption, overcooked red meats, high saturated fats, excess alcohol consumption, and cigarette smoking<sup>1</sup>

#### 2. Cyclooxygenase inhibition<sup>33</sup>

- a. Cyclooxygenase-2 (COX-2) expression is enhanced in up to 90% of colorectal carcinomas
    - 1) Data have shown the efficacy of using COX-2 inhibitors to decrease the incidence of colorectal adenomas,<sup>34,35</sup> however due to the risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for prevention of sporadic adenomas<sup>36</sup>
  - b. NSAIDs
    - 1) In April 2022, the U.S. Preventive Services Task Force (USPSTF) officially rescinded the recommendation for low-dose aspirin use to prevent colorectal cancer<sup>37</sup>
      - a) In a review of 11 randomized controlled trials (N = 134,470), there were limited and variable data that low-dose aspirin reduced colorectal cancer incidence and mortality
    - 2) Chemoprevention in familial adenomatous polyposis (FAP)
      - a) COX-2 inhibition in FAP resulted in reduction of the number of colorectal polyps, decreases risk of developing colorectal adenocarcinoma, and may also delay need for a prophylactic colectomy<sup>38</sup>
        - i. Due to lack of phase IV data however, the FDA indication for use of celecoxib in FAP was removed in 2011<sup>36</sup>
      - b) The use of sulindac or aspirin has not been shown to significantly decrease the development of colorectal adenomatous polyps in patients with FAP<sup>39</sup>
        - i. There are some data that the use of sulindac in combination with erlotinib can decrease duodenal polyp burden compared to placebo<sup>40</sup>
      - c) Currently, there are no FDA-approved medications for chemoprevention of colorectal cancer in patients with FAP and the NCCN® Panel acknowledges the limited data available<sup>36</sup>
  3. Bisphosphonate use may result in decrease incidence of colorectal cancer, however at this time there are insufficient data to recommend use as chemoprevention<sup>1</sup>
- B. Screening
1. The NCCN Guidelines<sup>®36,39</sup>, American Cancer Society (ACS)<sup>41,42</sup>, USPSTF<sup>43</sup>, and the U.S. Multi-Society Task Force on Colorectal Cancer (USMSTF)<sup>44-46</sup> all have published recommendations for colorectal cancer screening in average risk patients. NCCN Guidelines<sup>®</sup> and USMSTF have screening recommendations specifically for patients at increased or high risk.

## Colorectal Cancer Screening Recommendations<sup>36,39,41-46</sup>

	NCCN Guidelines®, ACS, USPSTF, & USMSTF	
<b>Average Risk</b>	<b>Any one of the following options is appropriate</b>	
Age 45 to 75 years	Colonoscopy every 10 years	
The decision to screen patients age 76-85 years should be individualized	Fecal occult blood test OR Fecal immunohistochemical test (FIT) every 1 year	
Screening is not recommended >85 years	FIT-DNA test every 1 or 3 years <sup>#</sup>	
	CT Colonography every 5 years	
	Flexible sigmoidoscopy every 5-10 years <sup>†</sup>	
	NCCN Guidelines®	USMSTF
<b>Increased Risk</b>		
IBS (ulcerative colitis, Crohn's disease)	Colonoscopy beginning 8 years after onset of symptoms, then every 1-3 years based on findings	
Personal history of adenomatous polyp, SSP, TSA, or large hyperplastic polyps	Colonoscopy Low-risk findings: every 5-10 years High-risk findings: every 3 years	
≥1 1 <sup>st</sup> -degree relative with CRC* or confirmed advanced adenoma or SSP	Colonoscopy CRC: initiate at age 40 or 10 years before earliest diagnosis, then every 5 years  Advanced adenoma or SSP: initiate at age 40 or at age of onset, whichever is first, then every 5-10 years	
2 <sup>nd</sup> - or 3 <sup>rd</sup> -degree relative with CRC*	Colonoscopy beginning at age 45-50 years, then every 10 years	
<b>High Risk</b>		
Positive family history of CRC*		Two 1 <sup>st</sup> -degree relatives diagnosed at any age OR 1 1 <sup>st</sup> -degree relative diagnosed at <60 years: initiate colonoscopy 10 years before age of earliest diagnosis or age 40 (whichever is earlier)  One 1 <sup>st</sup> -degree relative diagnosed at ≥60 years: initiate tests and intervals per average-risk at age 40
Lynch syndrome	Colonoscopy beginning at age 20-25 or 2-5 years before earliest colon cancer diagnosis if ≤25, then every 1-2 years	

IBS = inflammatory bowel disease; SSP = serrated sessile polyp; TSA = traditional sessile adenoma; CRC = colorectal cancer

<sup>#</sup>NCCN®, ACS, & USMSTF recommend every 3 years, USPSTF recommends every 1 or 3 years

<sup>†</sup>NCCN® and USMSTF allow a range of 5-10 years, ACS & USPSTF recommend every 5 years

\*Positive family history is considered increased-risk by NCCN® and high-risk by USMSTF

2. Refer to the NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Colorectal<sup>36</sup> for screening recommendations for patients with other high-risk conditions (IE, classical and attenuated FAP, Li-Fraumeni syndrome, *MUTYH*-associated polyposis, Peutz-Jeghers syndrome, etc)

# Screening modalities for colorectal cancer<sup>39,43,47</sup>

Method	Procedure	Advantages	Disadvantages
<b>Fecal occult blood test (FOBT)</b>	Checks for occult (hidden) blood in stool	<ul style="list-style-type: none"> <li>• No bowel preparation</li> <li>• Inexpensive</li> <li>• Easy to use; test can be performed at home</li> <li>• Noninvasive and no sedation needed</li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy needed if abnormal results</li> <li>• 50% of colorectal cancers go undetected due to no bleeding at the time of examination</li> <li>• Certain foods and medications may alter results</li> </ul>
<b>Fecal immunochemical test (FIT)</b>	Uses antibodies to detect hemoglobin in stool	<ul style="list-style-type: none"> <li>• No bowel preparation</li> <li>• No drug or food interactions</li> <li>• Improved accuracy compared with FOBT</li> <li>• Easy to use; test can be performed at home</li> <li>• Noninvasive and no sedation needed</li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy needed if abnormal results</li> </ul>
<b>FIT-DNA test (Cologuard®; aka stool DNA test)</b>	Screens stool samples for presence of red blood cells and DNA mutations that may indicate presence of cancer	<ul style="list-style-type: none"> <li>• No bowel preparation</li> <li>• No pre-test dietary restrictions</li> <li>• Easy to use; test can be performed at home</li> <li>• Noninvasive and no sedation needed</li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy needed if abnormal results</li> <li>• May miss diagnosis of polyps</li> <li>• May produce false positive results</li> <li>• Limited data on optimal interval between screening</li> <li>• Insufficient evidence regarding follow-up after abnormal tests</li> </ul>
<b>Flexible sigmoidoscopy</b>	Visualizes distal portion of the colon (lower 35-60%) and rectum via a sigmoidoscope	<ul style="list-style-type: none"> <li>• Can be used for biopsy or excision of polyps</li> <li>• Minimal bowel preparation</li> <li>• Does not require a specialist</li> </ul>	<ul style="list-style-type: none"> <li>• Views only lower 1/3 of colon and can miss ~50% of lesions if not done past the sigmoid colon</li> <li>• Test availability has declined in the United States</li> </ul>
<b>Colonoscopy</b> <i>Preferred due to its superior ability to detect lesions in proximal or right side of the colon</i>	Visualizes the entire colon using a colonoscope	<ul style="list-style-type: none"> <li>• Provides information on the mucosa of the entire colon</li> <li>• Can be used for biopsy or excision of polyps</li> <li>• Highly sensitive diagnostic tool</li> <li>• Best method for screening high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>• Inability to detect small lesions because of mucosa folds, blind corners, and cecum may not be reached</li> <li>• Full bowel preparation, expensive, sedation needed</li> <li>• Risk of bowel tears or infection</li> </ul>
<b>CT colonography (aka virtual colonoscopy)</b>	Examines the entire colon via series of X-rays used to produce 2-D and 3-D images	<ul style="list-style-type: none"> <li>• Views entire colon</li> <li>• Does not require sedation</li> </ul>	<ul style="list-style-type: none"> <li>• Requires full bowel preparation</li> <li>• If polyps or other suspicious lesions are detected, a colonoscopy is needed for biopsy and/or excision</li> <li>• Can miss small polyps, some false positive results</li> <li>• Expensive</li> <li>• Unclear follow up for potential of extracolonic findings</li> </ul>

### III. Treatment and symptom management

#### A. Principles of Surgery <sup>1,2,29</sup>

1. Treatment of choice in patients with potentially curable disease
2. Palliation or symptom management in metastatic disease
  - a. Bleeding, obstruction, localized abdominal pain caused by bulky tumor mass
3. Removal of isolated pulmonary or hepatic metastases
  - a. Curative in about 20% of patients if primary tumor and all metastatic disease can be resected
4. A minimum of 12 lymph nodes necessary for adequate sampling to determine node positive or negative disease
5. Surgical approach for colon cancer<sup>2</sup>
  - a. Generally involves partial colectomy
    - 1) Complete resection of tumor and adjacent mesentery and regional lymph nodes
6. Surgical approach for rectal cancer<sup>29</sup>
  - a. The rectum is located 12-15 cm from the anal verge
  - b. Transanal excision
    - 1) May be performed for certain superficial rectal tumors
  - c. Transabdominal resection
    - 1) Abdominoperineal resection (APR) – performed for tumors located in the lower one-third of the rectum involving the anal sphincter or the levator muscles
      - a) APR generally removes distal sigmoid colon, rectum, and anus. To achieve negative margins, usually results in loss of anal sphincter function leading to incontinence thus requiring creation of a permanent colostomy
    - 2) Low anterior resection (LAR) – used for tumors located in the mid to upper rectum, leaves the anal sphincter intact
      - a) Generally removes primary tumor and 4-5 cm below distal edge of the tumor using TME (see below) and creation of colorectal anastomosis
    - 3) Total mesorectal excision (TME) – removal of the mesorectum including vascular and lymphatic structures, fatty tissue, and mesorectal fascia, sparing autonomic nerves
      - a) TME is designed to remove surrounding lymphatic structures, which reduces positive radial margin and local recurrence rates

#### B. Principles of radiation therapy <sup>1,2,29</sup>

1. Colon cancer - minimal role as rates of distant recurrences are higher than local recurrences
  - a. May use radiation for a T4 lesion, perforation, obstruction, bleeding tumor, incomplete resection or palliative therapy if unresectable or inoperable

2. Rectal cancer<sup>29</sup>
  - a. Larger role than in colon cancer and used throughout all stages of disease
  - b. Neoadjuvant for stage II and III disease
    - 1) Utilized to improve resectability of primary tumor (higher chance of negative margins, sphincter-sparing) and to decrease risk of local recurrence
    - 2) Short-course radiation vs long-course chemoradiation
      - a) Multiple trials have investigated the differences between short-course radiation (25 Gy in 5 fractions) vs long-course chemoradiation (45-50 Gy in 25-28 fractions with fluoropyrimidine chemotherapy)
      - b) The decision for short-course vs long-course should be made in a multidisciplinary setting
  - c. Adjuvant for stage II and III disease
    - 1) May decrease risk of rectal cancer death compared to preoperative radiation, however radiation alone after surgery has been found to be inferior to concurrent radiation and chemotherapy
  - d. Metastatic disease
    - 1) Utilized for symptom reduction (pain, bleeding)
3. Complications of radiation to the rectum
  - a. Acute toxicity
    - 1) Thrombocytopenia/leukopenia, dysuria, diarrhea, abdominal cramping, proctitis, vaginal stenosis and/or dryness, dyspareunia
  - b. Chronic toxicity (can persist for months following discontinuation of XRT)
    - 1) Diarrhea, small bowel disease, proctitis, enteritis, pelvic fractures/decreased bone density, infertility, sexual dysfunction, erectile dysfunction, urinary incontinence/frequency/urgency
- C. Principles of systemic therapy<sup>2,29</sup>
  1. Select regimens/targeted agents and dosing (For the most up-to-date information on dosing and schedules of systemic therapy regimens, please refer to the NCCN Guidelines® for Colon Cancer and NCCN Guidelines® for Rectal Cancer<sup>2,29</sup>)
    - a. Chemotherapy regimens act as the backbone of treatment, with the ability to add on targeted agents to most regimens
      - 1) Toxicity profile differs between infusional and bolus 5-FU/leucovorin
        - a) Infusional 5-FU more commonly associated with hand-foot syndrome and GI toxicity
          - i. Also requires a central venous access device for administration
        - b) Bolus 5-FU/leucovorin more commonly associated with hematologic toxicity
      - 2) There are also various regimens administering 5-FU/leucovorin or irinotecan as single agents

Regimen / agent	Dosing	Frequency
<b>mFOLFOX6*</b>	5-FU IV 400 mg/m <sup>2</sup> Leucovorin IV 400 mg/m <sup>2</sup> Oxaliplatin IV 85 mg/m <sup>2</sup> 5-FU continuous IV infusion (CIVI) 1200 mg/m <sup>2</sup> /day x 2 days (over 46-48 hours)	Every 14 days
<b>mFOLFOX7*</b>	Leucovorin IV 400 mg/m <sup>2</sup> Oxaliplatin IV 85 mg/m <sup>2</sup> 5-FU CIVI 1200 mg/m <sup>2</sup> /day x 2 days (over 46-48 hours)	Every 14 days
<b>CAPEOX (aka XELOX)</b>	Day 1: Oxaliplatin IV 130 mg/m <sup>2</sup> Days 1-14: Capecitabine PO 1000 mg/m <sup>2</sup> /dose BID <sup>#</sup>	Every 21 days
<b>FOLFIRI</b>	5-FU IV 400 mg/m <sup>2</sup> Leucovorin IV 400 mg/m <sup>2</sup> Irinotecan IV 180 mg/m <sup>2</sup> 5-FU CIVI 1200 mg/m <sup>2</sup> /day x 2 days (over 46-48 hours)	Every 14 days
<b>FOLFIRINOX<sup>&amp;</sup></b>	5-FU IV 400 mg/m <sup>2</sup> Leucovorin IV 400 mg/m <sup>2</sup> Irinotecan IV 180 mg/m <sup>2</sup> Oxaliplatin IV 85 mg/m <sup>2</sup> 5-FU CIVI 1200 mg/m <sup>2</sup> /day x 2 days (over 46-48 hours)	Every 14 days
<b>mFOLFIRINOX<sup>&amp;</sup></b>	Leucovorin IV 400 mg/m <sup>2</sup> Irinotecan IV 150 mg/m <sup>2</sup> Oxaliplatin IV 85 mg/m <sup>2</sup> 5-FU CIVI 1200 mg/m <sup>2</sup> /day x 2 days (over 46-48 hours)	Every 14 days
<b>IROX</b>	Oxaliplatin IV 85 mg/m <sup>2</sup> Irinotecan IV 200 mg/m <sup>2</sup>	Every 21 days
<b>Bevacizumab</b> (only indicated in combination with a chemotherapy backbone)	5 mg/kg IV	Every 14 days
	7.5 mg/kg IV	Every 21 days
<b>Panitumumab</b>	6 mg/kg IV	Every 14 days
<b>Cetuximab</b>	400 mg/m <sup>2</sup> for first infusion, then 250 mg/m <sup>2</sup> IV	Every 7 days
	500 mg/m <sup>2</sup> IV	Every 14 days

\*There are multiple iterations of FOLFOX. The current standards are mFOLFOX6 and mFOLFOX7, but the term "FOLFOX" may be used interchangeably for either regimen

<sup>#</sup>North American patients may require lower doses of capecitabine based on tolerance/toxicities

<sup>&</sup>NCCN<sup>®</sup> now recommends FOLFIRINOX over FOLFOXIRI due to poor tolerance in U.S. patients of the higher dose of CIVI 5-FU used in the FOLFOXIRI regimen (3200 mg/m<sup>2</sup> total dose)<sup>2,29</sup>

## 2. Neoadjuvant

### a. Colon cancer

#### 1) Not commonly used for localized disease

- Regimen should be based on expected patient tolerability, and prior chemotherapy if applicable

#### 2) Can be used for metastatic patients for conversion to resectability

- Optimal sequencing of neoadjuvant/adjvant chemotherapy unknown

- b) Multiple trials have shown successful conversion with fluoropyrimidine-based regimens<sup>48</sup>, adding bevacizumab<sup>49-51</sup> or cetuximab<sup>52-54</sup>
  - b. Rectal cancer
    - 1) Used in combination with radiation to increase radiation sensitization and improve systemic control of disease
    - 2) Fluoropyrimidine-based chemotherapy is recommended, and should be delivered concurrently with radiation
    - 3) Neoadjuvant FOLFIRINOX may also be considered as part of a total neoadjuvant therapy approach
- 3. Adjuvant
  - a. Decreases risk of disease recurrence by eradicating micrometastatic disease and improving disease-free survival (DFS) after surgical resection for curative intent
  - b. Colon cancer
    - 1) Stage I patients have no benefit, stage II patients have minimal to moderate benefit, and stage III patients have definite benefit from adjuvant therapy in terms of survival outcomes when compared to surgery alone
    - 2) Adjuvant therapy ideally begins 4 to 8 weeks after surgery and continues for up to 6 months
      - a) Certain patients with stage III disease may be eligible for 3 months of therapy (see section detailing Stage III disease below)
    - 3) Fluoropyrimidine-based regimens are standard of care
      - a) Capecitabine is clinically equivalent to bolus 5-FU/leucovorin in terms of disease-free survival<sup>55</sup>
        - i. Capecitabine associated with significantly lower incidence of grade 3/4 neutropenia and stomatitis; however also associated with significantly higher incidence of grade 3/4 hand-foot syndrome
      - b) Addition of oxaliplatin increases benefit for stage III patients
        - i. The MOSAIC trial compared 5-FU/leucovorin to FOLFOX4 in patients with resected stage II and stage III colon cancer<sup>56,57</sup>
          - (a) FOLFOX4 was superior in overall survival (OS) to 5-FU/leucovorin at 6 years (72.9% vs. 68.7%; p=0.023) for stage III colon cancer
          - (b) There was no difference in disease-free survival (DFS) or OS for stage II disease: DFS HR 0.84 (95% CI, 0.62-1.14) and OS HR 1.00 (95% CI, 0.7-1.41)
          - (c) Patients over 70 years may not derive the same benefit from addition of oxaliplatin to adjuvant therapy, and therefore should be carefully evaluated for risk vs benefit
        - ii. CAPEOX is considered an acceptable alternative to FOLFOX<sup>58,59</sup>



- 4) Neither irinotecan nor targeted agents have shown survival benefits, and therefore are not recommended in the adjuvant setting for early stage patients
- c. Rectal cancer
  - 1) Adjuvant chemotherapy is typically part of a perioperative treatment regimen, of which total treatment is up to 6 months
  - 2) May be combined with radiation
  - 3) Many of the same principles from adjuvant therapy in colon cancer apply to rectal cancer
4. Metastatic disease
  - a. Used for palliation of symptoms and to prolong life in patients with unresectable, incurable disease
  - b. Can be used in some patients for conversion to resectability
  - c. Includes either a combination of systemic therapies or single agents in sequential, continuous fashion (see "Treatment of metastatic colon and rectal cancer" section for detailed discussion)
- D. Treatment of early stage colon cancer (stages I, II, III)<sup>2</sup>
  1. Goal of treatment is cure
  2. Stage I
    - a. Surgical excision of primary tumor and removal of regional lymph nodes followed by observation
  3. Stage II<sup>60</sup>
    - a. Surgical excision of primary tumor and removal of regional lymph nodes
    - b. Considerations for adjuvant chemotherapy:
      - 1) May only provide a 2% increase in overall survival vs surgery alone<sup>1</sup>
      - 2) Evaluation of MSI/MMR status
      - 3) High-risk factors for recurrence (exclusive of MSI-H cancers) per NCCN Guidelines<sup>®2</sup>:
        - a) Inadequate (<12) lymph nodes surgically examined
        - b) Poorly differentiated/undifferentiated histology
        - c) Lymphatic/vascular invasion
        - d) Bowel obstruction
        - e) Perineural invasion
        - f) Localized perforation
        - g) Close, indeterminate, positive margins
    - c. Stage II, MSI-H/dMMR
      - 1) Observation
    - d. Stage II, no high-risk factors

- 1) Observation
- 2) Consider adjuvant capecitabine or 5-FU/leucovorin (either for 6 months)
- e. Stage II at high-risk for recurrence
  - 1) Adjuvant capecitabine (6 months), 5-FU/leucovorin (6 months), FOLFOX (6 months) or CAPEOX (3 months)
  - 2) Observation
4. Stage III
  - a. Surgical excision of primary tumor and removal of regional lymph nodes
  - b. Adjuvant chemotherapy with FOLFOX or CAPEOX is recommended
  - c. Can consider capecitabine or 5-FU/leucovorin for patients in whom oxaliplatin may not be a suitable option (i.e. patients over 70 years of age, baseline severe neuropathy)
  - d. Duration of adjuvant therapy in stage III disease<sup>61</sup>
    - 1) The IDEA consortium of trials showed that for patients with low-risk stage III disease (T1-3, N1), 3 months of CAPEOX is non-inferior to 6 months of CAPEOX in terms of disease-free survival
      - a) Although noninferiority of CAPEOX for 3 months has not been proven in the overall population of stage III patients, the 5-year overall survival was numerically similar to 6 months of CAPEOX with considerably less neurotoxicity<sup>62</sup>
      - b) Non-inferiority of 3 vs 6 months of FOLFOX has not been shown, however 3 months is inferior to 6 months for high-risk patients
    - 2) NCCN® recommendations<sup>2</sup>:
      - a) Stage III, low-risk
        - i. Preferred: CAPEOX (3 months) or FOLFOX (3-6 months)
        - ii. Other options: capecitabine or 5-FU/LV (either for 6 months)
      - b) Stage III, high-risk
        - i. Preferred: CAPEOX (3-6 months) or FOLFOX (6 months)
        - ii. Other options: capecitabine or 5-FU/LV (either for 6 months)
    - 3) ASCO has published similar recommendations<sup>63</sup>:
      - a) For patients with low-risk (T1, T2, T3, and N1) stage III disease: oxaliplatin-containing regimen for 3 or 6 months after a discussion with the patient of risks and benefits
      - b) For patients with high-risk (T4 and/or N2) stage III disease: oxaliplatin-containing regimen for 6 months

**Patient Case #1 (ARS Question 1):**

**Correct answer is B.** Patients with stage II disease with high-risk features are recommended to receive adjuvant chemotherapy with a single agent fluoropyrimidine. Patients with stage II disease with no high-risk features or with MSI-high disease would be eligible for observation.<sup>2</sup>

Answer A is incorrect because LS has stage II disease with high-risk features with no contraindications to chemotherapy.

Answer C is not the most appropriate adjuvant therapy at this time, as oxaliplatin in addition to a fluoropyrimidine has not been shown to improve survival benefit for stage II patients. Furthermore, oxaliplatin may not provide the same benefit in adjuvant therapy for patients over 70 years of age and is currently cautioned against.

Answer D is incorrect as irinotecan-containing regimens have not been shown to provide survival benefit in the adjuvant setting for early stage disease

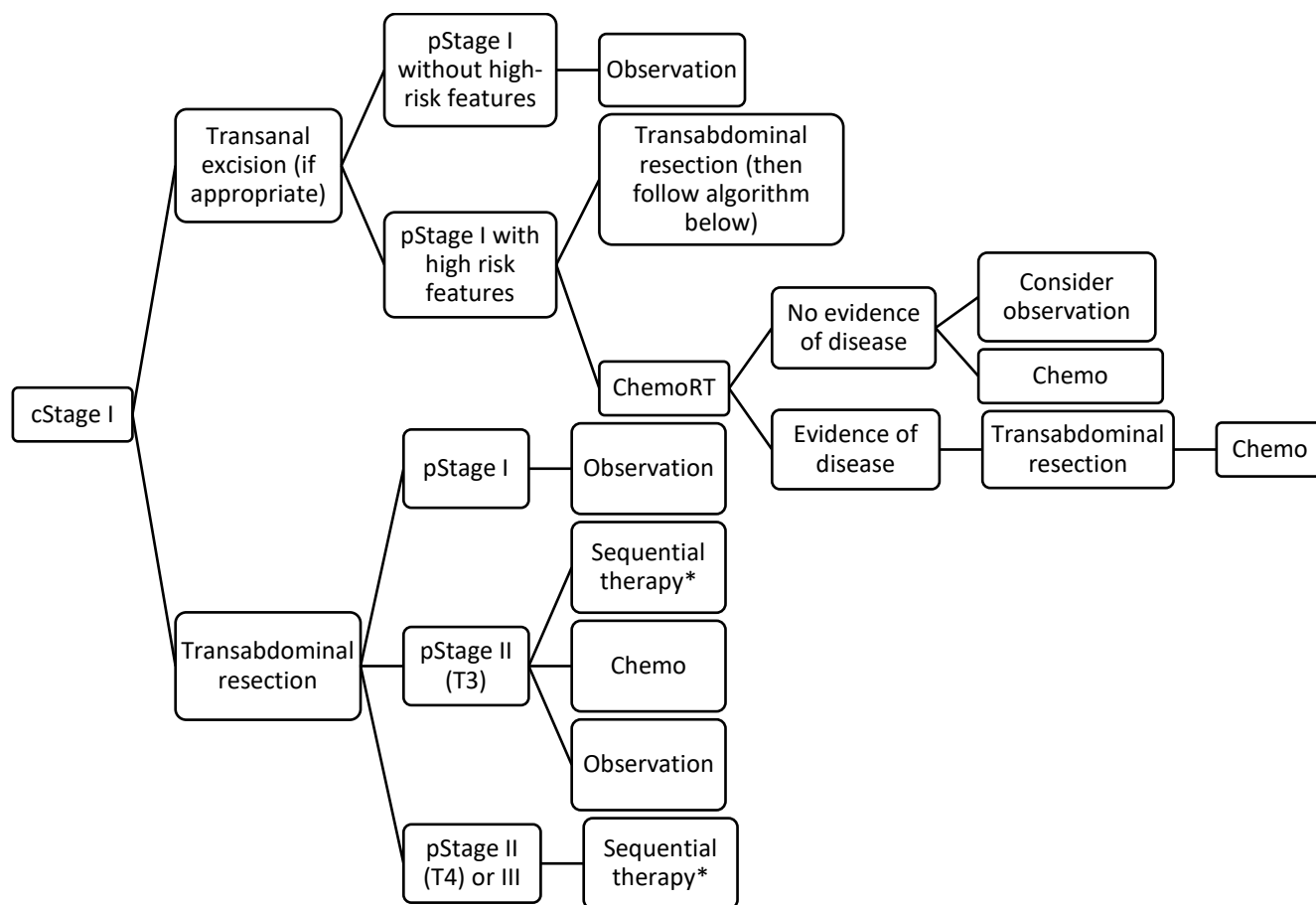
E. Treatment of early stage rectal cancer (stages I, II, III)<sup>29</sup>

1. Treatment goal is **cure**
2. Clinical stage
  - a. Upon diagnosis, patients are staged clinically by endorectal ultrasound (EUS) or MRI of pelvis to determine whether patients should receive neoadjuvant therapy or proceed with surgery first
3. Pathologic stage / restaging
  - a. Findings after resection determine the patient's pathologic stage, which determines appropriate post-operative therapy
4. Adjuvant chemotherapy is indicated in all patients who receive neoadjuvant chemoradiation, unless chemotherapy was given neoadjuvantly, regardless of surgical pathology results
  - a. Because the optimal duration of adjuvant therapy for rectal cancer is unclear, 6 months of adjuvant chemotherapy is considered adequate based on data from colon cancer. If patients received neoadjuvant chemoradiation, a duration of 4 months is considered adequate.<sup>29</sup>
5. Radiation<sup>29</sup>
  - a. Plays a much larger role in the treatment of rectal cancer than colon cancer
  - b. Short-course radiation: 25 Gy in 5 fractions (~1 week of treatment)
  - c. Long-course chemoradiation: 45-50 Gy in 25-28 fractions plus chemotherapy (~5.5 weeks of treatment)
6. Chemoradiation (chemoRT)<sup>64-66</sup>
  - a. The addition of chemotherapy to radiation either pre- or postoperatively improves local radiation sensitization and systemic control of disease
  - b. Preoperative chemoRT also has increased rates of pathologic complete response, leading to sphincter preservation
  - c. Despite improvements in local control, most trials have not shown improvements in DFS or OS

- d. If a patient is medically fit to receive chemotherapy concurrently with radiation, it is preferred over radiation alone
  - e. The addition of oxaliplatin to fluoropyrimidine-based chemoRT did not improve surgical or survival outcomes and resulted in patients experiencing more diarrhea<sup>67,68</sup>, therefore is not supported or recommended
  - f. Regimens include:
    - 1) Capecitabine/RT or infusional 5-FU/RT
      - a) Bolus 5-FU/RT is an option for patients not able to tolerate infusional 5-FU or capecitabine
    - 2) Refer to the NCCN Guidelines® for Rectal Cancer for dosing and schedules of chemoradiation regimens<sup>29</sup>
7. Chemotherapy
- a. FOLFOX or CAPEOX
    - 1) 5-FU/LV or capecitabine can be considered for patients unable to tolerate oxaliplatin
  - b. FOLFIRINOX<sup>69</sup>
    - 1) Investigators compared adding 6 cycles of neoadjuvant FOLFIRINOX to a “standard” regimen of chemoRT → surgery → adjuvant chemotherapy
      - a) Adjuvant chemotherapy consisted of either FOLFOX or CAPEOX, chosen by the treating physician. Patients in the experimental group received 3 months adjuvant chemotherapy, and the standard group received 6 months adjuvant chemotherapy
    - 2) 3-year disease-free survival was 76% in the FOLFIRINOX group, and 69% in the standard group (HR 0.69, 95% CI 0.49 – 0.97; p=0.034)
    - 3) 3-year overall survival was 91% in the FOLFIRINOX group, and 88% in the standard group (HR 0.64, 95% CI 0.40 – 1.05; p=0.0773)
    - 4) When this study was designed, the “standard” neoadjuvant approach did not include chemotherapy. However, recent data support using chemotherapy, specifically FOLFOX or CAPEOX, in the neoadjuvant setting.
      - a) The NCCN Guidelines® support consideration of using FOLFIRINOX in the neoadjuvant setting for T4 N+ tumors
8. Total neoadjuvant therapy (TNT)
- a. In the TNT approach to rectal cancer, patients receive both neoadjuvant chemotherapy and chemoradiation or radiation prior to surgery, with no adjuvant therapy
    - 1) Chemotherapy is given for 12-16 weeks, and is typically FOLFOX or CAPEOX
    - 2) Can give in either order:
      - a) Chemotherapy followed by long-course chemoRT or short-course radiation
      - b) Long-course chemoRT or short-course radiation followed by chemotherapy

- b. Some studies have reported fewer toxicities, higher rates of pathologic complete responses, and shorter length of time for ileostomy
- 9. Emerging data on immunotherapy
  - a. The multimodal, total neoadjuvant approach, albeit successful, can be associated with significant complications and toxicities
  - b. Investigators at a single institution evaluated the use of neoadjuvant dostarlimab-gxly in stage II and III rectal cancer patients with MSI-H/dMMR disease<sup>70</sup>
    - 1) This phase II study was designed to administer dostarlimab first for 6 months, then long-course chemoRT followed by resection
    - 2) 16 patients were enrolled and treated; 15 with clinical stage III disease and 1 with clinical stage II disease
    - 3) In the 12 patients who completed 6 months of dostarlimab therapy at time of publication, the complete response rate was 100% (95% CI 74 – 100)
      - a) Due to the 100% response rate, none of the 12 patients needed to receive chemoRT, nor surgery, and proceeded directly to surveillance (4 of whom had 1 year of sustained clinical complete response after completion of dostarlimab)
    - 4) No adverse events of grade 3 or higher were reported
  - c. This treatment approach is not currently incorporated in the NCCN Guidelines<sup>@29</sup>

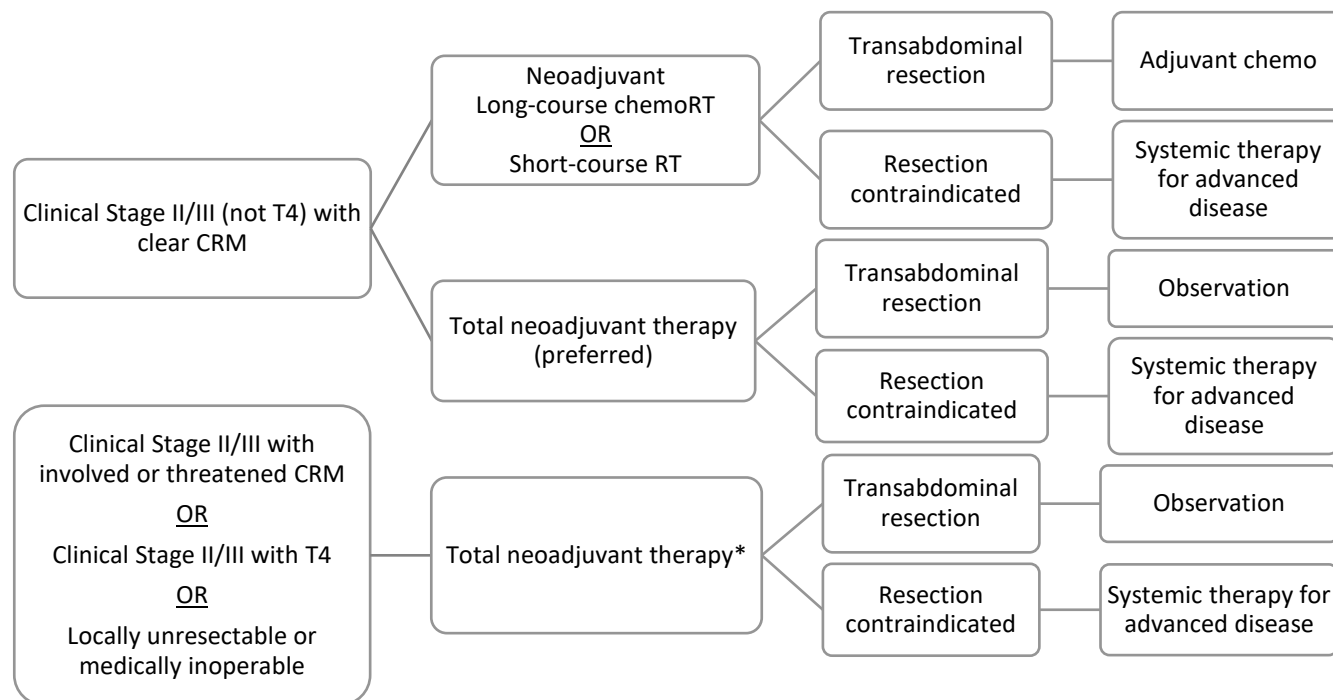
**NCCN Guidelines® Treatment Pathway for Early Stage Rectal Cancer: Clinical Stage I<sup>29</sup>**



c = clinical; p = pathologic

\*Sequential therapy is either: chemoradiation followed by chemotherapy OR chemotherapy followed by chemoradiation

**NCCN Guidelines® Treatment Pathways for Early Stage Rectal Cancer: Clinical Stages II and III<sup>29</sup>**



CRM = circumferential margin (by MRI)

\*Can consider FOLFIRINOX for T4 N+ tumors; otherwise chemotherapy regimens are FOLFOX or CAPEOX

**Patient Case #2 (ARS Question 2):**

EH is a 65-year old male who presents to his PCP with complaints of bleeding with bowel movements. A colonoscopy demonstrated an obstructing and circumferential mass in the rectum. CT abdomen/pelvis revealed bilobular liver lesions. Biopsy of a liver lesion displayed moderately differentiated adenocarcinoma consistent with colorectal primary. The tissue was sent for next generation sequencing which showed KRAS G12C and TP53 Y107\* mutations and was microsatellite stable. He presents to the medical oncologist today to discuss systemic therapy. His ECOG performance status is 1 and he has controlled hypertension on amlodipine.

**Which of the following is the most appropriate initial therapy for EH's metastatic colorectal cancer?**

- A. Capecitabine
- B. FOLFOX + cetuximab
- C. FOLFIRI + bevacizumab
- D. FOLFIRINOX + panitumumab

F. Treatment of metastatic colon and rectal cancer (stage IV)<sup>2,29</sup>

1. Treatment goal is **palliation**, although select patients can still be treated for cure
2. Principles
  - a. Systemic therapy is used for palliation of symptoms and to prolong life
  - b. Radiation may be used for palliation and/or symptom control
  - c. Liver-directed therapy may also be considered for solitary or limited liver metastases (refer to “Locoregional Therapy” section in the Upper Gastrointestinal and Hepatocellular Carcinomas module for more detailed information)
  - d. Surgical resection of the primary tumor may be performed for palliation or symptom management in patients with bleeding, obstruction, or localized abdominal pain due to large or bulky primary tumor
    - 1) Removal of isolated pulmonary or hepatic metastases may be performed in select patients (refer to “Resectable liver and/or lung only metastases” section below)
    - 2) Cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) can be considered for patients with peritoneal carcinomatosis
      - a) The high morbidity and mortality, as well as conflicting efficacy, make this intervention a controversial issue. If considered, CRS with HIPEC should be performed in an experienced center.
3. First-line systemic treatment options
  - a. Fluoropyrimidine-based regimens are the standard of care
    - 1) Capecitabine is considered equivalent to 5-FU/LV in terms of clinical outcomes
      - a) Capecitabine is associated with less stomatitis, alopecia, and neutropenia, and higher incidence of hand-foot syndrome and grade 3/4 hyperbilirubinemia<sup>71</sup>
    - 2) The addition of oxaliplatin or irinotecan to 5-FU (FOLFOX or FOLFIRI, respectively) was shown to increase PFS and TTP, and OS for irinotecan, vs 5-FU alone
      - a) Oxaliplatin associated with more neutropenia, mucositis, diarrhea, and peripheral neuropathy
      - b) Irinotecan associated with significantly more diarrhea, neutropenia, and asthenia<sup>72,73</sup>
    - 3) CAPEOX is non-inferior to FOLFOX for PFS, OS, and ORR<sup>74,75</sup>
      - a) FOLFOX associated with more neutropenia and febrile neutropenia
      - b) CAPEOX associated with more diarrhea and hand-foot syndrome
      - c) Neurotoxicity similar between regimens
    - 4) Combining oxaliplatin and irinotecan with 5-FU (FOLFOXIRI) significantly improved RR ( $p<0.0001$ ), PFS ( $p=0.0006$ ), and OS (0.032) over FOLFIRI, while associated with significantly more neurotoxicity and neutropenia<sup>76</sup>



- a) NCCN® now recommends FOLFIRINOX over FOLFOXIRI due to poor tolerance in U.S. patients of the higher dose of CIVI 5-FU used in the FOLFOXIRI regimen (3200 mg/m<sup>2</sup> total dose)<sup>2,29</sup>
  - b) FOLFIRINOX should be strongly considered for patients with excellent performance status
- 5) Either FOLFOX or FOLFIRI may be used 1<sup>st</sup> line, followed by the other regimen in 2<sup>nd</sup> line, as PFS has not been shown to be significantly different; toxicities associated with each regimen may help determine the sequence<sup>77</sup>
  - a) FOLFOX associated with significantly more neurotoxicity, grade 3/4 neutropenia and thrombocytopenia
  - b) FOLFIRI associated with significantly more grade 3/4 febrile neutropenia, nausea/vomiting, mucositis, fatigue
- b. Bevacizumab
  - 1) Bevacizumab has demonstrated improved response rates and survival outcomes when added to fluoropyrimidine-based regimens
  - 2) Bevacizumab is recommended in combination with 5-FU, capecitabine, FOLFOX, CAPEOX<sup>75,78,79</sup>, FOLFIRI<sup>80,81</sup>, and FOLFIRINOX<sup>82,83</sup> for 1<sup>st</sup> line therapy of metastatic colon and rectal cancer
  - 3) Associated with grade 3/4 toxicities of thromboembolic events, hypertension, bleeding
  - 4) The NCCN panel states that an FDA-approved biosimilar is an appropriate substitute for bevacizumab<sup>2,29</sup>
- c. Anti-EGFR MABs
  - 1) Cetuximab and panitumumab have demonstrated improved response rates and PFS when added to FOLFOX<sup>84-86</sup> or FOLFIRI<sup>87</sup>, however the addition has not shown to significantly increase OS
  - 2) The addition of cetuximab or panitumumab to FOLFOX and FOLFIRI for 1<sup>st</sup> line therapy of metastatic colon and rectal cancer with RAS wild-type tumors is supported in the NCCN Guidelines<sup>2,29</sup>
    - a) FOLFIRI + panitumumab is listed as an option for first-line therapy in the NCCN Guidelines® based on extrapolation from data in second-line treatment<sup>2,29</sup>
    - b) Cetuximab + CAPEOX was associated with significant diarrhea and dermatologic toxicities, therefore is not recommended<sup>84</sup>
  - 3) Cetuximab is associated with infusion reactions, and panitumumab is associated with paronychia and mucositis; both are associated with rash, diarrhea, and low magnesium
  - 4) Primary tumor sidedness<sup>2</sup>
    - a) Right-sided tumors occur from cecum to hepatic flexure, and left-sided tumors occur from splenic flexure to rectum

- b) A growing body of evidence<sup>88-91</sup> has shown that patients with right-sided, RAS wild-type primary tumors confer little to no benefit from cetuximab or panitumumab
    - c) The NCCN<sup>®</sup> panel recommends that only patients whose primary tumors originate on the **left side** of the colon that are RAS/RAF wild-type be offered an anti-EGFR monoclonal antibody for treatment of metastatic disease<sup>2,29</sup>
      - i. Response to the EGFR MABs of RAS/RAF wild-type tumors that originate in the transverse colon (hepatic flexure to splenic flexure) is unclear at this point as data are lacking
  - 5) For patients with RAS wild-type, left-sided tumors, they are more likely to benefit from addition of an EGFR MAB rather than bevacizumab to front-line chemotherapy<sup>92</sup>
- d. Checkpoint inhibitors
  - 1) Pembrolizumab (KEYNOTE-177)<sup>12</sup>
    - a) Previously untreated patients with dMMR/MSI-H metastatic colorectal cancer were randomized to receive pembrolizumab or investigator's choice of FOLFOX or FOLFIRI, with or without bevacizumab or cetuximab (if indicated)
    - b) Patients in the pembrolizumab group did not reach median overall survival (95% CI 49.2 months to not reached), compared to 36.7 months in the chemotherapy group (95% CI 27.6 to not reached)
      - i. The hazard ratio was 0.74 with a 95% CI of 0.53 – 1.03, p=0.036. Statistically, superiority of pembrolizumab was not able to be confirmed due to the prespecified  $\alpha$  of 0.025 needed for statistical significance.
    - c) Pembrolizumab was shown to significantly improve median PFS at the second interim analysis, and numerically stayed consistent in the final analysis (16.5 vs 8.2 months, HR 0.59; 95 % CI 0.45 – 0.79)
    - d) The FDA granted approval for pembrolizumab for up to 2 years in the first-line setting for patients with dMMR/MSI-H metastatic colorectal cancer
  - 2) Nivolumab + ipilimumab (CheckMate 142)<sup>13</sup>
    - a) The Phase 2 CheckMate 142 trial consisted of multiple cohorts, including 1 investigating nivolumab + ipilimumab in the first-line setting for metastatic, dMMR/MSI-H colorectal cancer patients
    - b) The dosing used was nivolumab 3 mg/kg every 2 weeks and low-dose ipilimumab 1 mg/kg every 6 weeks continuously
    - c) Median PFS and OS were still not reached at 24.2 months of follow-up
- e. Summary of first-line treatment options per NCCN Guidelines<sup>®2,29</sup>
  - 1) Intensive therapy recommended
    - a) FOLFOX or CAPEOX ± bevacizumab
    - b) FOLFIRI ± bevacizumab
    - c) FOLFIRINOX/mFOLFIRINOX ± bevacizumab

- d) FOLFOX or FOLFIRI + cetuximab or panitumumab (KRAS/NRAS/BRAF wild-type and left-sided tumors only)
  - e) Pembrolizumab (preferred) or nivolumab ± ipilimumab (dMMR/MSI-H only)
- 2) Intensive therapy NOT recommended
- a) 5-FU/LV or capecitabine ± bevacizumab
  - b) Cetuximab or panitumumab (KRAS/NRAS/BRAF wild-type and left-sided tumors only) [Category 2B]
  - c) Pembrolizumab (preferred) or nivolumab ± ipilimumab [Category 2B for combination] (dMMR/MSI-H only)
  - d) Trastuzumab + pertuzumab OR lapatinib (HER2-amplified and RAS/BRAF wild-type only)

**Patient Case #2 (ARS Question 2):**

**Correct answer is C.** FOLFIRI ± bevacizumab is an acceptable option for first-line treatment of metastatic colorectal cancer in patients who are eligible to receive intensive therapy. Controlled hypertension is not a contraindication to receive bevacizumab.

Answers B and D are incorrect because EH has a KRAS G12C activating mutation, which confers resistance to EGFR monoclonal antibodies.

Answer A is not the most appropriate at this time. If EH was not eligible for intensive therapy, single agent capecitabine would be an appropriate choice.

4. Subsequent-line systemic treatment options
- a. Principles<sup>2,29</sup>
    - 1) In general, metastatic colorectal cancers are treated continuously with systemic therapy in a sequential fashion upon progression
      - a) Systemic therapy may be modified to a “maintenance” type regimen, where only a fluoropyrimidine with/without a targeted agent is continued
      - b) Therapy is stopped either upon change in level of care (i.e, hospice) or patient preference/oncologist support for a treatment “holiday”
    - 2) Choice of subsequent-line therapy is based on previous therapies received, presence of predictive biomarkers, patient comorbidities, and adverse effects/tolerance from previous treatments
      - a) Patients should at least receive a fluoropyrimidine, oxaliplatin, irinotecan, an anti-vascular agent, and an anti-EGFR MAB (if KRAS/NRAS/BRAF wild-type and left-sided tumor) at some point in their continuum of systemic therapy treatment, if no contraindications or comorbidities preclude these therapies
    - 3) Please refer to the NCCN Guidelines<sup>®</sup> for Colon Cancer<sup>2</sup> and NCCN Guidelines<sup>®</sup> for Rectal Cancer<sup>29</sup> sections on Continuum of Care – Systemic Therapy for Advanced or Metastatic Disease for full algorithm on specific recommendations for sequencing therapy
  - b. Anti-vascular agents

- 1) Continuation of bevacizumab with 2<sup>nd</sup>-line chemotherapy significantly improved PFS and OS over chemotherapy alone in patients who had bevacizumab with their 1<sup>st</sup> line of treatment<sup>93</sup>
  - 2) Ziv-aflibercept<sup>94</sup> and ramucirumab<sup>95</sup>, each in combination with FOLFIRI, have shown improved PFS and OS over FOLFIRI alone in patients with metastatic colorectal cancer that have progressed following an oxaliplatin-based regimen with and without bevacizumab
    - a) NCCN Guidelines<sup>®</sup> also support the use of single agent irinotecan with ziv-aflibercept or ramucirumab<sup>2,29</sup>
  - 3) Bevacizumab is the preferred anti-angiogenic agent based on toxicity and cost<sup>2,29</sup>
- c. Anti-EGFR MABs
- 1) Cetuximab or panitumumab may be given in combination with irinotecan, FOLFOX, or FOLFIRI in RAS/RAF wild-type metastatic colorectal cancer in the 2<sup>nd</sup> line setting as this has been shown to improve PFS over chemotherapy alone<sup>96,97</sup>
    - a) The strongest evidence for predictive value of primary tumor sidedness is in the first-line setting. Although evidence suggests this to apply in the subsequent-line setting as well, more definitive studies are needed. Therefore, it is still acceptable to use anti-EGFR MABs in the subsequent-line setting for any sided tumor.<sup>2,29</sup>
  - 2) Either agent may also be given alone as monotherapy, as this has shown to improve PFS and OS compared to best supportive care<sup>98,99</sup>
  - 3) If cetuximab or panitumumab is used with initial therapy, the NCCN<sup>®</sup> panel recommends against use of the other agent in subsequent lines of therapy.<sup>2,29</sup>
- d. BRAF-targeted regimens
- 1) Patients with BRAF V600E mutation positive disease have worse outcomes compared to those without the mutation<sup>2,29</sup>
    - a) Blockade with BRAF inhibitors with or without MEK inhibitors has resulted in feedback upregulation of EGFR via the MAPK pathway, and therefore these agents are utilized with anti-EGFR therapies
  - 2) Encorafenib + cetuximab OR panitumumab
    - a) The BEACON CRC<sup>100</sup> trial investigated the efficacy and safety of 3 different regimens in patients with BRAF V600E mutation positive colorectal cancer who had progressed on one or two previous regimens
      - i. Encorafenib, binimetinib, cetuximab (triplet therapy)
      - ii. Encorafenib, cetuximab (doublet therapy)
      - iii. Investigator's choice of irinotecan or FOLFIRI with cetuximab (control)
    - b) The triplet and doublet therapy arms were only compared statistically to the control arm, and not to each other
      - i. The median overall survival for the triplet, doublet, and control arms were 9.0 months (95% CI 8.0-11.4), 8.4 months (95% CI 7.5-11.0), and 5.4 months (95% CI 4.8-6.6) respectively

- ii. Both the triplet and doublet were significantly better than the control arm
- c) Grade 3 or higher adverse events occurred in 58% of patients in the triplet arm, 50% of patients in the doublet arm, and 61% of patients in the control arm
- d) Although the authors of the article supported use of the triplet therapy, the FDA approved the doublet therapy for use in colorectal patients with BRAF V600E mutation
  - i. This is due to superiority of survival outcomes over the control arm, and numerically lower adverse effects than triplet therapy
- e) The NCCN Guidelines® support the use of encorafenib with cetuximab or panitumumab for these patients<sup>2,29</sup>
  - i. This regimen is only appropriate in patients with a BRAF V600E mutation and who have not previously received an anti-EGFR MAB + BRAF inhibitor combination
- e. HER2-targeted regimens
  - 1) Only about 2-3% of metastatic colorectal cancers harbor HER2 amplification, although incidence may be up to 14% in RAS/BRAF wild-type tumors<sup>2</sup>
  - 2) Trastuzumab + lapatinib
    - a) The HERACLES trial<sup>101</sup> included patients with HER2-positive metastatic colorectal cancer who had progressed on at least one prior standard of care regimen
    - b) Of the 27 patients included, 8 (30%) achieved an objective response
      - i. 74% of patients had received four or more prior treatment regimens
    - c) Median PFS was 21 weeks (95% CI 16-32) and OS was 46 weeks (95% CI 33-68)
    - d) Toxicities were as expected, including diarrhea (78%), rash (48%), fatigue (48%), paronychia (33%), and conjunctivitis (19%)
  - 3) Trastuzumab + pertuzumab
    - a) The phase II basket trial MyPathway<sup>102</sup> reported on patients with HER2-amplified metastatic colorectal cancer who were treated with trastuzumab and pertuzumab
      - i. Patients were included who had received at least 1 standard regimen, and no previous HER2-directed therapy
    - b) Of the 57 patients included, 18 (32%) achieved an objective response
      - i. The majority of patients were heavily pretreated, with the median number of prior treatments being 4
    - c) Estimated PFS was 2.9 months (95% CI 1.4-5.3) and OS was 11.5 months (95% CI 7.7 months to not reached)
  - 4) Fam-trastuzumab deruxtecan-nxki (T-DXd)<sup>103,104</sup>
    - a) The phase II DESTINY-CRC01 evaluated T-DXd in HER2-expressing metastatic colorectal cancers that had progressed on two or more previous regimens, including other HER2-targeted therapies

- i. Patients were treated with 6.4 mg/kg T-DXd every 3 weeks, which is equivalent to the dose used in gastric and upper GI cancers, but lower than the dose used in breast cancer
  - b) Patients were allocated to one of three cohorts based on HER2 expression:
    - i. Cohort A: IHC3+ OR IHC2+ and ISH+ (HER2 positive)
    - ii. Cohort B: HER2 IHC2+ and ISH-
    - iii. Cohort C: HER2 IHC1+ (HER2 negative)
  - c) The primary endpoint of ORR was 45.3% in Cohort A (95% CI 31.6 to 59.6%), and 0 in cohorts B and C
  - d) Median PFS for Cohort A was 6.9 months (95% CI 4.1 – 8.7), and median overall survival was 15.5 months (95% CI 8.8 – 20.8); median PFS for Cohorts B and C was 2.1 and 1.4 months, respectively.
  - e) The most common adverse effects were hematologic and gastrointestinal
- 5) These regimens are supported by the NCCN Guidelines® for HER2-amplified and RAS/BRAF wild-type<sup>2,29</sup>
- a) T-DXd can be used in patients who have previously received HER2-directed therapies; other HER2-directed therapies are not indicated after patients have already failed a HER2-directed regimen
- f. Regorafenib (CORRECT<sup>105</sup>)
- 1) Regorafenib significantly increased OS (6.4 vs 5.0 months; p=0.0052) and PFS (1.9 vs 1.7 months; p<0.0001) compared to best supportive care in patients who had received fluoropyrimidine-based therapy, irinotecan, oxaliplatin, and bevacizumab, and an anti-EGFR MAB if RAS wild-type
  - 2) Dose modifications required in 76% of patients, of which 70% required more than 1 dose interruption due to adverse events
    - a) Adverse events requiring dose modifications included dermatological, gastrointestinal, constitutional, and metabolic/laboratory events
  - 3) Original dose studied was 160 mg PO daily days 1-21 of 28-day cycle
    - a) Can titrate dose during 1<sup>st</sup> cycle to attenuate toxicities per the ReDOS trial<sup>106</sup>:
      - i. First cycle: 80 mg PO daily days 1-7, then 120 mg PO daily days 8-14, then 160 mg PO daily on days 15-21 as tolerated
      - ii. Subsequent cycles: 160 mg, or highest tolerated dose, PO daily days 1-21 of 28-day cycle
- g. Trifluridine/tipiracil (aka TAS-102)
- 1) TAS-102 is a combination of a cytotoxic thymidine analog (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil)

- a) Dose is 35 mg/m<sup>2</sup>/dose (based on trifluridine, max 80 mg) PO twice daily days 1-5 and 8-12 of 28-day cycle
- 2) RECOURSE<sup>107</sup>
  - a) TAS-102 significantly increased OS (7.1 vs 5.3 months; p<0.001), PFS (p<0.001), and disease control rate (44% vs 16%; p<0.001) compared to best supportive care in patients who had received ≥2 prior regimens, including fluoropyrimidine-based therapy, irinotecan, oxaliplatin, and bevacizumab, and an anti-EGFR MAB if RAS wild-type
  - b) In TAS-102 group, 53% of patients had a delay in beginning of next cycle by ≥4 days due to toxicity
  - c) Dose reductions due to toxicity were required in 14% of patients
    - i. Grade 3/4 adverse events included neutropenia (38%), anemia (18%), and thrombocytopenia (5%)
- 3) C-TASK FORCE<sup>108</sup>
  - a) TAS-102 alone was compared to TAS-102 with bevacizumab in a similar patient population studied in the RECOURSE trial, except previous therapy with an anti-angiogenic agent was allowed but not mandated
  - b) TAS-102 was given per standard dosing and bevacizumab was given as 5 mg/kg IV days 1 and 15 of the 28-day cycle
  - c) Median PFS was 2.6 months in the monotherapy group and 4.6 months in the combination group (HR 0.45, 95% CI 0.29 to 0.72; p=0.0010)
  - d) Disease control was not significantly different between the 2 groups (51% vs 67%, p=0.14)
  - e) Dose modifications of TAS-102 were required in 26% of the monotherapy group and 37% of the combination group, with the main reason being hematological toxicity
    - i. Serious adverse events were reported similarly in both groups (45% in monotherapy group vs 41% in combination group)
- h. Checkpoint Inhibitors
  - 1) Pembrolizumab<sup>7</sup>
    - a) Before being approved for first-line use, pembrolizumab showed efficacy in dMMR/MSI-H patients with treatment refractory progressive metastatic cancer (97.5% patients had ≥2 previous lines of therapy)
  - 2) Nivolumab ± ipilimumab<sup>8,10</sup>
    - a) Nivolumab ± ipilimumab was evaluated in patients with MSI-H and non-MSI-H metastatic colorectal cancer
    - b) Patients had progressed or were intolerant to ≥1 previous line of therapy
    - c) Responses were observed in the MSI-H group regardless of PD-L1 expression or BRAF or KRAS mutation status

- 3) Dostarlimab-gxly has shown efficacy in dMMR and POLE mutated GI cancers<sup>14</sup>, and is an appropriate option for dMMR/MSI-H tumors in the subsequent line<sup>2,29</sup>
- 4) Patients progressing on any of these immunotherapy regimens should not be offered a subsequent immunotherapy agent, unless on clinical trial<sup>12,29</sup>
- i. Larotrectinib or entrectinib are treatment options for patients with cancers that are NTRK gene fusion positive, although these are extremely rare in colorectal carcinomas<sup>109</sup>
- j. Selpercatinib is a treatment option for patients with cancers that are RET gene fusion-positive
5. Resectable liver and/or lung only metastases<sup>2,29</sup>
  - a. Patients with a primary tumor and metastatic disease amenable to surgical resection can be treated with curative intent
  - b. For colon cancer patients who present with resectable synchronous liver or lung metastases, options are:
    - 1) Synchronous or staged colectomy with liver or lung resection and/or local therapy, followed by adjuvant chemotherapy
    - 2) Neoadjuvant chemotherapy for 2-3 months, followed by synchronous or staged colectomy with liver or lung resection and/or local therapy, followed by adjuvant chemotherapy
    - 3) Colectomy followed by adjuvant chemotherapy and a staged resection and/or local therapy of metastatic disease, then adjuvant chemotherapy
    - 4) Nivolumab ± ipilimumab or pembrolizumab (preferred) for dMMR/MSI-H patients, followed by synchronous or stage colectomy and resection and/or local therapy of metastatic disease
    - 5) Neoadjuvant and adjuvant treatments should not exceed a combined total of 6 months
      - a) Neoadjuvant options: FOLFOX or CAPEOX preferred; FOLFIRI or FOLFIRINOX [both category 2B]
      - b) Adjuvant options: FOLFOX or CAPEOX preferred; 5-FU/LV or capecitabine
  - c. Rectal cancer patients who present with resectable synchronous liver or lung metastases will receive a TNT approach similar to early stage disease, although exact treatment is dependent on the predicted status of the CRM by MRI
    - 1) Patients with a predicted clear CRM can receive chemotherapy followed by short-course RT or long-course chemoRT
    - 2) For patients with a predicted involved CRM, options are:
      - a) Chemotherapy followed by long-course chemoRT
      - b) Short-course RT or long-course chemoRT followed by chemotherapy
    - 3) Perioperative therapy should not exceed 6 months
      - a) Nivolumab ± ipilimumab or pembrolizumab (preferred) can be considered for dMMR/MSI-H patients
    - 4) Resection can be done in a simultaneous or staged approach and should be performed 5 to 12 weeks following completion of treatment



- a) If a patient is treated with short-course RT, surgery can occur within 1 week, or delayed 6 to 8 weeks
- d. Notes on regimens used in resectable patients
  - 1) Irinotecan is associated with increased risk of steatohepatitis (20.2%, P=0.00001) and oxaliplatin is associated with increased risk of sinusoidal injury (18.9%, P=0.0001). Pre-operative chemotherapy has also been associated with steatosis and portal hypertension. These adverse effects may affect outcomes after liver resection.<sup>110</sup>
  - 2) The NCCN Guidelines® consider it acceptable to add bevacizumab to chemotherapy to convert patients to resectability.<sup>2,29</sup> Bevacizumab should be discontinued at least 6 weeks prior to surgery, and re-initiation should be delayed until 6-8 weeks after surgery.<sup>2,29,49-51</sup>
  - 3) It is acceptable practice to add an anti-EGFR MAB (cetuximab or panitumumab) to planned chemotherapy for conversion to resectability in patients with KRAS WT disease based on improvement in RR and R0 resection rates<sup>52,54,111,112</sup>, however there are conflicting data regarding the use of FOLFOX + cetuximab in patients with potentially resectable liver metastases<sup>2</sup>

**Patient Case #2, continued (ARS question 3):**

EH agreed to receive FOLFIRI + bevacizumab and presents today to begin treatment. He requests further education about the diarrhea he might experience.

**What is the most appropriate counseling information regarding irinotecan-induced diarrhea?**

- A. EH will be pre-medicated with loperamide to prevent acute diarrhea
- B. Acute diarrhea may be accompanied by sweating which is treated with atropine
- C. EH will be given octreotide injections to prevent delayed diarrhea from the start
- D. Delayed diarrhea will only occur if EH experiences acute diarrhea

**IV. Supportive care**

- A. Chemotherapy-Induced Diarrhea (CID)<sup>113,114</sup>
  1. Any chemotherapeutic agent may cause diarrhea, but higher rates of diarrhea are reported with irinotecan, 5-FU, methotrexate, cytarabine, tyrosine kinase inhibitors, immune checkpoint inhibitors and stem cell transplant conditioning
    - a. 50 - 80% of patients receiving modulated 5-FU regimens, single-agent irinotecan, and combination regimens of irinotecan and 5-FU experience diarrhea and greater than 30% of these patients may experience grade 3 to 5 diarrhea
    - b. If diarrhea is suspected to be caused by an immune checkpoint inhibitor, management differs from “typical” chemotherapy-induced diarrhea. Refer to the Melanoma and Non-melanoma Skin Cancers module for management of immune therapy-related diarrhea/colitis.
  2. Possible contributing factors include<sup>113,114</sup>:

- a. Underlying malignancy
  - b. Infection
  - c. Radiation
  - d. Diet (high fiber, dairy products)
  - e. Medications other than chemotherapy (antibiotics, opiate withdrawal, SSRIs)
  - f. Inflammatory disorders
  - g. Malabsorption
  - h. Neuroendocrine factors
  - i. Psychological factors
3. Assessment
- a. Duration and timing of symptoms
  - b. Constellation of signs and symptoms
  - c. Severity of symptoms

1) Grading based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0<sup>115</sup>

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

- d. Patient's constellation of symptoms should be classified as either uncomplicated or complicated
    - 1) Uncomplicated: Grade 1 or 2 diarrhea with no other complicating signs or symptoms
    - 2) Complicated
      - a) Grade 1 or 2, but has any of the following risk factors:
        - i. Moderate to severe cramping
        - ii. Grade 2 or higher nausea and/or vomiting
        - iii. Decreased performance status
        - iv. Fever, sepsis, neutropenia
        - v. Frank bleeding or dehydration
      - b) Grade 3 or 4 diarrhea
4. Management (Of note, official CID management guidelines were last updated in 2010. Clinical practice may differ.)<sup>113,116</sup>
- a. Uncomplicated CID

- 1) For grade 2, hold chemotherapy until resolution
  - 2) Recommend elimination of all lactose-containing products and alcohol
  - 3) Frequent small meals and oral hydration (e.g., 8-10 glasses of clear fluids such as water, sport drinks, broth)
  - 4) Instruct patients to record number of stools and report any symptoms described above
  - 5) Initiate loperamide 4 mg x 1 followed by 2 mg every 4 hours or after every loose stool (not to exceed 16 mg/day; 24 mg/day for irinotecan-induced diarrhea)
  - 6) If diarrhea resolves:
    - a) Continue dietary modifications and gradually add solid foods to diet
    - b) Patients with chemotherapy-induced diarrhea can discontinue loperamide when diarrhea-free for at least 12 hours
    - c) Patients with radiation-induced diarrhea should continue taking loperamide for the duration of radiation therapy
  - 7) If mild to moderate diarrhea persists >24 hours on loperamide, increase dose of loperamide to 2 mg every 2 hours and consider starting oral antibiotics as prophylaxis for infection
  - 8) If mild to moderate diarrhea persists for more than 48 hours on loperamide (24 hours after starting high-dose loperamide):
    - a) Discontinue loperamide
    - b) Start a second-line antidiarrheal, such as octreotide 100 to 150 mcg subcutaneously or other agent (tincture of opium 10 to 15 drops in water every 3-4 hours or budesonide)
    - c) Patients with chemotherapy-induced diarrhea should undergo complete stool and blood work-up and replace fluids and electrolytes as needed
    - d) Patients with radiation-induced diarrhea may continue on high-dose loperamide with frequent evaluation
- b. Complicated CID
- 1) Admit to hospital and start intravenous hydration and electrolyte replacement
  - 2) Octreotide 100 to 150 mcg subcutaneously TID or continuous infusion (25 to 50 mcg/hour) if patient severely dehydrated, with dose escalation up to 500 mcg subcutaneously TID until diarrhea is controlled
    - a) Upon improvement, titrate off; do not abruptly discontinue
  - 3) Administration of IV antibiotics as indicated
  - 4) Complete stool and blood work-up
  - 5) Discontinue any cytotoxic chemotherapy until all symptoms resolve and consider dose reductions for future cycles
- c. Patients who progress to grade 3 or 4 diarrhea while on loperamide therapy for 24 to 48 hours should be treated as described above

5. Irinotecan-induced diarrhea<sup>20,21,113,117</sup>

- a. Refer above to “Metabolism and Pharmacokinetics of Irinotecan in the Genomics” section for background on irinotecan
- b. Two phases of diarrhea:
  - 1) Acute phase
    - a) Occurs during or immediately after irinotecan infusion (within 24 hours)
    - b) Accompanied with cholinergic symptoms such as cramps, diaphoresis, flushing, salivation, visual disturbances, and lacrimation
    - c) Mechanism: Direct inhibition of acetylcholinesterase by irinotecan
  - 2) Delayed phase
    - a) Dose-limiting toxicity
    - b) Occurs after 24 hours after irinotecan infusion
      - i. Median onset reported is day 6 (range 2 to 12)
    - c) Mechanism: primarily a secretory process with exudative properties, thought to be due to the reactivated form of SN-38
      - i. SN-38 may directly cause mucosal damage to intestinal lumen
      - ii. Luminal environment altered by irinotecan, allowing proliferation of bacteria that produce  $\beta$ -glucuronidase
      - iii. Irinotecan itself can cause severe colonic damage or an increase in mucin secretion
- c. Management
  - 1) Acute: atropine
    - a) Suppresses cholinergic effects of irinotecan
    - b) Start with 0.25 mg IV or subcutaneous to a maximum cumulative dose of 1.2 mg
    - c) Monitor blood pressure and heart rate
    - d) May also be given as secondary prophylaxis in a patient with prior acute diarrhea
  - 2) Delayed
    - a) Atropine has no role in management of delayed diarrhea
    - b) Loperamide<sup>118,119</sup>
      - i. 4 mg at first sign of diarrhea, followed by 2 mg every 2 hours (4 mg every 4 hours at night) until 12 hours following last bowel movement up to 24 mg/day
        - (a) Exceeding the daily limit of 16 mg/day is accepted for treatment of irinotecan-associated diarrhea in adults
      - ii. Change to as-needed dosing after 12-hour bowel movement-free period
    - c) Supportive management

- i. Fluids and electrolytes
  - (a) Dehydration is common with persistent and/or severe diarrhea
  - (b) Goal: drink 3 or more liters of clear liquids/day, which should consist of electrolyte-containing fluids (sport drinks, broth, decaffeinated tea, etc.)
  - (c) Route of rehydration (IV or PO) is dependent upon severity of dehydration and electrolyte abnormalities
- ii. Nutrition
  - (a) Avoid dairy, caffeine, alcohol and concentrated fruit juices
  - (b) "BRAT" diet (bananas, rice, applesauce, and toast)
  - (c) Bulk-forming agents
  - (d) Severe diarrhea may require bowel rest with parenteral nutrition

**Patient Case #2, continued (ARS question 3):**

**Correct answer is B.** Acute irinotecan-associated diarrhea is a cholinergic reaction, often accompanied by cholinergic symptoms such as diaphoresis and significant abdominal cramping. Atropine, or other anticholinergic agents, is the most appropriate treatment to alleviate acute irinotecan-induced diarrhea.

Answer A is incorrect because loperamide will not alleviate the cholinergic reaction of acute irinotecan diarrhea. Loperamide can be considered for delayed diarrhea.

Answer C is incorrect because octreotide should only be considered for complicated delayed diarrhea or diarrhea that is refractory to loperamide, not as a pre-emptive treatment.

Answer D is incorrect because there is no association between the occurrence of acute and delayed irinotecan-induced diarrhea, as they are caused by different mechanisms.

# Agents for chemotherapy-induced diarrhea (CID)<sup>113,114,116</sup>

Agent	Mechanism	Dose	Place in Therapy	Comments
<b>Loperamide</b>	Decreases intestinal motility via direct action on the smooth muscle of the intestine	4 mg PO initial dose, followed by 2 mg every 2-4 hours or with every loose stool (maximum daily dose of 16mg; 24mg if irinotecan-induced)	First-line for uncomplicated	Reduces fecal incontinence, frequency of bowel movements and stool weight
<b>Tincture of opium</b>	Contains various opioid alkaloids including morphine, which is primary agent for mechanism. Decreases digestive secretions and increases gastrointestinal muscle tone, resulting in reduction in intestinal transit time.	Deodorized formulation (10 mg/mL)  10-15 drops in water every 3 to 4 hours	Alternative second choice for persistent, uncomplicated	Recommended, despite lack of literature in CID  Pay close attention to formulation being used, as concentrations and dosing differs  Ensure patients dilute in water or other liquids due to very unpleasant taste if not diluted
		Camphorated formulation AKA paregoric* (0.4 mg/mL)  5-10 mL in water 1 to 4 times daily		
<b>Octreotide</b>	Decreases secretion of various hormones, such as vasoactive intestinal peptide  Prolongation of intestinal transit time  Reduced secretion and increased absorption of fluid and electrolytes	100 to 150 mcg subcutaneous three times daily initially, then up titrate to symptom control	Persistent uncomplicated or first-line for complicated	Patients may also be transitioned to octreotide LAR  May be more beneficial for radiation-induced diarrhea vs oral opioids  Optimal dosage not well defined
<b>Budesonide</b>	Inhibitory effect on mucosal prostaglandins	9 mg PO once daily	Second-line for persistent, uncomplicated	Effective in loperamide-refractory diarrhea
<b>Diphenoxylate/atropine</b>	Decreases intestinal motility via direct action on the smooth muscle of the intestine	1-2 tablets PO every 6-8 hours	In combination with loperamide for uncomplicated	Little published data for CID
<b>Absorbents (psyllium, methylcellulose)</b>	Absorbs excess fluid to form a gelatinous mass to increase density of fecal matter	7.5-30 g PO daily	Alternative	Large volume and abdominal bloating limit use
<b>Probiotics</b>	Counteracts disturbances in normal gut flora	Not defined	In conjunction with other agents	Patients with severely weakened immune system should avoid

\*Paregoric tincture has been discontinued in the U.S.

B. Hypersensitivity to monoclonal antibodies used in solid tumors<sup>120-123</sup>

1. Presentation<sup>120,124</sup>

- a. Accompanied by flushing, rash, fever, pruritus, dyspnea, bronchospasm, rigors, nausea/vomiting, and/or hypotension
- b. Type I hypersensitivity reaction
  - 1) IgE-mediated drug-immunoglobulin complex binds to mast cells, causing release of mediators of reaction
  - 2) Usually occurs within the first few minutes of the 1<sup>st</sup> or 2<sup>nd</sup> infusion, however 10 to 30% of reaction are delayed
- c. Occurs in up to 20% of patients
  - 1) Severe hypersensitivity reactions are rare with an estimated incidence of  $\leq 5\%$

2. Geographic influences on cetuximab reactions<sup>125,126</sup>

- a. The Southeastern United States has consistently reported higher incidence of cetuximab-related infusion reactions (up to 27%), vs the rest of the country (1-3%)
- b. O'Neil and colleagues quantified the rates of hypersensitivity reactions at 3 Southeastern institutions
  - 1) Out of 88 assessable patients, 22% experienced first infusion grade 3 to 5 hypersensitivity reaction
  - 2) All patients were pretreated with H1 antagonist, and 65% were given a steroid as an anti-emetic
  - 3) They reported no significant association between reactions and age, sex, or race
  - 4) There was an association of increase hypersensitivity reactions in lung cancer patients (43%;  $P=0.03$ ) and prior significant allergy history (36%;  $P=0.009$ )
  - 5) The authors theorized that the increased incidence may be a result of increased exposure to mouse antigens or other antigens that mimic cetuximab that are regionally based, such as a particular plant or tree pollen
- c. There is currently no way to test patients for hypersensitivity risk
  - 1) Patients with head & neck cancers may be at higher risk
- d. As the reaction typically occurs within 30 minutes of infusion, the use of a test dose has been proposed but is not standard of care
- e. Patients who experience a hypersensitivity reaction may be successfully treated with panitumumab, as it is a fully humanized monoclonal antibody

3. Prevention of hypersensitivity reactions (HSR) and infusion reactions<sup>120,124</sup>

- a. Recognition of high-risk patients
  - 1) Type of antibody (IE, chimeric, murine, humanized)
  - 2) Ensure appropriate premedication regimen, if indicated, is given

- b. Premedication
  - 1) There is no established standard premedication regimen
    - a) Use prescribing information or guidelines to guide choice of regimen
  - 2) Usually includes acetaminophen, H<sub>1</sub> antagonist, H<sub>2</sub> antagonist, and/or corticosteroids
  - 3) Premedication with corticosteroids may prevent or dampen non-IgE mediated infusion reactions
    - a) Dexamethasone 8-20 mg (commonly used antiemetic doses)
  - 4) Generally given with first dose and continued throughout treatment
- 4. For detailed management of HSR and infusion reactions, refer to the Gynecologic Malignancies module
- C. Oxaliplatin-induced neurotoxicity<sup>127-131</sup>
  - 1. Dose-limiting toxicity that is a persistent sensory peripheral neuropathy which has been reported with all dose levels and schedules of administration
  - 2. Development is primarily related to total cumulative dose
  - 3. Up to 97% of patients receiving oxaliplatin will have neurologic symptoms and abnormalities during treatment
  - 4. Patients can develop delayed onset or worsening of the persistent form of neuropathy even after treatment discontinuation
  - 5. Two distinct clinical forms of neuropathy: acute and chronic
    - a. Acute neurotoxicity
      - 1) Transient, sensory disturbance in 85% to 95% of patients
      - 2) Rapid onset of hours to days following treatment
      - 3) May regress between treatment cycles, but frequently reoccurs with further treatment
      - 4) Presents as paresthesia, dysesthesia, and hypoesthesia in the hands, feet, perioral area, or throat
      - 5) Paresthesias without pain occur in about 65% patients and paresthesias with pain occur in approximately 11% of patients
      - 6) Dysesthesias occur in approximately 68% patients and are exacerbated by cold exposure
      - 7) Pharyngolaryngeal dysesthesias are also reported in approximately 38% and are characterized by subjective sensations of dysphagia or dyspnea and/or jaw spasm without associated laryngospasm, bronchospasm, or stridor
        - a) Disturbing to patients and can be described as a loss of breathing sensation
      - 8) May be exacerbated by exposure to cold ambient temperature, drinking cold liquids, or handling cold objects



- 9) 13% to 28% of patients receiving doses of 85 to 130 mg/m<sup>2</sup> experience severe neurosensory adverse effects with functional impairment
- 10) Symptoms resolve in about a week, but can recur with subsequent infusions
- b. Chronic neurotoxicity
  - 1) Persistent sensory chemotherapy-induced peripheral neuropathy that is gradually progressive in onset
  - 2) Related to cumulative dose and similar to other forms of platinum- and taxane-induced neuropathies
    - a) Incidence is 16% to 21% patients
    - b) Onset >14 days after oxaliplatin dose and can become persistent between treatment cycles with progression in symptom severity
    - c) Pain and paresthesias can completely resolve in some cases and may only be partially reversible or permanent in others
      - i. Numbness and tingling can worsen during the first 3 months after discontinuing therapy (sometimes called “coasting”), and then begin to resolve<sup>132</sup>
    - d) Associated with cumulative doses between  $\geq 540$  to 850 mg/m<sup>2</sup>. It is estimated that 10-15% of patients have moderate neuropathy after a cumulative dose of 780 to 850 mg/m<sup>2</sup><sup>128</sup>
    - e) Clinical presentation is subjective, usually progresses gradually, and manifests as pure sensory symptoms including numbness, paresthesia, and pain in the hands and feet with symptoms usually appearing in the toes followed by the fingers
      - i. Sensory findings, such as diminished or absent proprioception, sharp/dull discrimination, temperature, touch, touch/pain two-point discrimination, and vibration are typically diminished in the stocking and glove distribution in patients with symptoms
      - ii. Longest nerves in extremities are usually the first affected leading to a symmetric, length-dependent peripheral neuropathy that spreads from distal to proximal (stocking / glove) distribution
      - iii. Distribution is usually symmetrical and has a disproportionate degree of sensory symptoms reported in comparison to the motor symptoms and findings on exam
      - iv. Paresthesias occur in the lower distal extremities in a stocking-glove distribution with the most severe symptoms occurring on plantar surfaces
      - v. Motor weakness symptoms are less commonly reported, and if present are observed in up to 50% of patients with more persistent and severe sensory findings
6. Pathophysiology<sup>127-130</sup>
  - a. Acute toxicity
    - 1) Oxalate metabolite of oxaliplatin chelates calcium and magnesium and interferes with voltage-gated sodium channels and electrical current

- 2) Oxaliplatin causes prolonged opening of the sodium channels in sensory nerves that results in a hyperexcitable state
- b. Chronic toxicity
  - 1) Exact mechanism unknown
  - 2) Damage to peripheral nerves by harming microtubules and interfering with microtubule-based axonal transport
  - 3) Oxaliplatin binds to mitochondrial DNA resulting in oxidative stress
  - 4) Drug accumulation in dorsal root ganglion and sensory nerves
7. Prevention of acute oxaliplatin-induced neuropathy<sup>127</sup>
  - a. Prolonging infusion from 2 hours up to 6 hours may decrease acute neuropathy
  - b. Dose reduction
  - c. Calcium and magnesium (Ca/Mg) infusion
    - 1) Retrospective review that evaluated Ca/Mg infusions reported less frequent and severe distal and lingual paresthesias and no reports of pseudolaryngospasm<sup>133</sup>, however prospective trials found no benefit (see below)
8. Prevention of chronic oxaliplatin-induced neuropathy
  - a. Stop-and-Go Approach (OPTIMOX1)<sup>134</sup>
    - 1) Patients undergoing treatment for metastatic disease were randomized to 1 of 2 arms
      - a) Arm A = FOLFOX4 every 14 days until disease progression or toxicity
      - b) Arm B = FOLFOX7 for 6 cycles, followed by 12 cycles of maintenance 5-FU and leucovorin, and reintroduction of FOLFOX7 for an additional 6 cycles
    - 2) Outcomes
      - a) Median PFS for Arm A was 9 months versus 8.7 months for Arm B (p=0.47)
      - b) Median OS for Arm A was 19.3 months versus 21.2 months for Arm B (p=0.49)
      - c) Grade 3 sensory neuropathy in 18% of patients in Arm A and 13% in Arm B (p=0.12)
    - 3) Discontinuing oxaliplatin after 6 cycles followed by 5-FU maintenance achieved similar PFS, OS, and response rates compared to continuing oxaliplatin until disease progression or toxicity. Patients who received maintenance therapy experienced less grade 3 and 4 toxicities compared to those that received continuous therapy with FOLFOX, including less neuropathy.
    - 4) This approach may be considered for preventing and/or delaying the development of sensory neuropathy in patients receiving oxaliplatin-based chemotherapy
  - b. Ca/Mg infusions<sup>127,128,130</sup>
    - 1) Rationale: Increasing extracellular calcium facilitates sodium channel closing, decreasing oxaliplatin-induced hyperexcitability of peripheral neurons, which is the mechanism proposed for acute oxaliplatin neurotoxicity. Repeated episodes of hyperexcitability may

lead to structural damage of neurons, which may lead to the development of chronic neurotoxicity.

- 2) Because there were mixed results and incomplete data from previous studies, the definitive N08CB/Alliance<sup>135</sup> trial was performed. This trial showed no significant evidence that Ca/Mg infusions prevent oxaliplatin-induced neurotoxicity, therefore this strategy is not recommended by NCCN Guidelines<sup>®2</sup> nor ASCO.
- c. The American Society of Clinical Oncology (ASCO) guideline for prevention and management of chemotherapy-induced neuropathy does support a moderate recommendation for the use of duloxetine for the treatment of chemotherapy-induced peripheral neuropathy.<sup>136</sup>

**Patient Case #3 (ARS question 4):**

RL is a 64-year-old female with metastatic, KRAS-wild-type colorectal cancer to her liver and lungs. She recently started FOLFOX + panitumumab and presents today for Cycle 3. She reports a new rash that is pruritic, occasionally weeps pus, and extends over her face and chest mainly, and partially covers her back. She states she has been compliant taking her doxycycline since she started treatment.

**What is the most appropriate intervention for RL's grade 2 papulopustular rash at this time?**

- A. Continue panitumumab at same dose and change the doxycycline to minocycline
- B. Continue panitumumab at same dose and initiate topical hydrocortisone
- C. Dose reduce panitumumab and initiate topical salicylic acid
- D. Dose reduce panitumumab and initiate oral prednisone

**D. Dermatologic toxicities**

1. Hand-foot syndrome (HFS) vs hand foot skin reaction (HFSR)
  - a. Dose dependency, pain, and a palmoplantar distribution can be seen with both HFS and HFSR, however they differ in both histopathological and clinical features<sup>137-140</sup>
  - b. HFSR is seen with multi-kinase inhibitors, such as sorafenib, sunitinib, and regorafenib<sup>138-141</sup>
    - 1) HFSR can be seen within the first 2 to 4 weeks after therapy is initiated
      - a) Presents with dysesthesias, erythema or paresthesias involving the palms and soles with blisters which are followed by thick hyperkeratotic, tender lesions
      - b) Lesions arise in areas of friction and/or trauma including the flexural surface of interphalangeal joints, distal phalanges or heels and may significantly impact weight-bearing ability and mobility of patients
    - 2) Loss of repair mechanisms by endothelial cells and fibroblasts, when combined with daily trauma may result in the characteristic palmoplantar symptoms
    - 3) May manifest as loss of fingerprints
    - 4) Preemptive strategies are crucial in the management of HFSR<sup>142</sup>:
      - a) Perform full body exam to locate hyperkeratotic regions on palms / soles and removal of all calluses

- b) Wear thick cotton gloves and/or slippers or socks
- c) Avoid:
  - i. Exposing skin to hot water
  - ii. Friction, trauma, or rigorous exercise (especially during first 4 weeks of therapy)
  - iii. Tight fitting shoes
  - iv. Excessive pressure when applying lotions
- d) Data to support topical urea prior to and during treatment
  - i. Randomized, open-label trial of 871 patients with hepatocellular cancer receiving sorafenib received 10% urea-based cream versus placebo<sup>143</sup>
    - (a) 12-week incidence of any grade HFSR was 56% vs. 73.6% with significantly longer time to first occurrence of HFSR (84 days vs 34 days)
- c. HFS can be seen with cytotoxic chemotherapies, such as capecitabine and 5-FU<sup>137,139,144</sup>
  - 1) Also known as palmar-plantar erythrodysesthesia
  - 2) More diffuse regions of edema and erythema than seen with HFSR
  - 3) Longer exposure to drug appears to increase incidence; e.g. continuous infusion 5-FU has higher incidence versus bolus administration
  - 4) Symptom onset is quite variable and may range from a few days to up to 10 months after therapy initiation
  - 5) Initial symptom is paresthesias followed by symmetrical painful erythema and edema of the palms and soles after 3 to 4 days; if not managed the lesions may blister, desquamate, form crusts, ulcerate or progress to epidermal necrosis
  - 6) Conflicting data regarding use of pyridoxine (vitamin B6) for prevention and/or treatment of HFS. A randomized controlled trial to prevent capecitabine-induced HFS was negative, so not recommended.
  - 7) Use of corticosteroids is also conflicting and cannot be recommended
  - 8) Regional cooling strategies also lack adequate evidence to support its use
- d. Management of HFS and HFSR<sup>141,145</sup>
  - 1) Grading based on CTCAE Version 5.0<sup>115</sup>

Grade 1	Grade 2	Grade 3
Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care ADL

- 2) Prophylaxis recommended with ammonium lactate 12% cream BID or heavy moisturizer (petroleum- or lanolin-based ointments) BID
- 3) Grade 1

- a) Continue antineoplastic treatment at current dose and monitor for change in severity
  - b) Urea 20% cream BID AND clobetasol 0.05% cream daily
  - c) Reassess in 2 weeks; if reaction is worse or not improved proceed to treatment of next grade
- 4) Grade 2
  - a) Continue antineoplastic treatment at current dose and monitor for change in severity
  - b) Urea 20% cream BID AND clobetasol 0.05% cream daily to BID AND pain control (with NSAIDs or GABA agonists or opioids)
  - c) Reassess in 2 weeks; if reaction is worse or not improved proceed to treatment of next grade
- 5) Grade 3
  - a) Hold antineoplastic therapy until severity decreases to grade 0 or 1
  - b) Clobetasol 0.05% cream BID AND pain control (with NSAIDs or GABA agonists or opioids)
  - c) Reassess in 2 weeks and if reaction is worse or not improved then dose interruption or discontinuation per PI may be necessary
- 2. EGFR inhibitor papulopustular (acneiform) rash <sup>138,139,146</sup>
  - a. Most common adverse effect seen with these agents
    - 1) Incidence is 75 to 90% of patients receiving these medications
    - 2) Most cases are mild to moderate in nature; however, up to 32% of providers will discontinue therapy and up to 76% hold therapy
    - 3) Rash onset is early, within the first two weeks of treatment
    - 4) Rash more frequent with monoclonal antibodies than TKIs
  - b. EGFRs play an important role in the development, integrity and physiology of normal skin via the regulation of keratinocyte proliferation, differentiation and survival
    - 1) The direct inhibition of EGFRs is thought to be the underlying cause of the rash: exposure of epithelial cells to medication leads to an increased synthesis of a variety of chemokines that recruit inflammatory cells, including leukocytes and neutrophils, leading to an inflammatory response
    - 2) Pathophysiology does not appear to involve underlying bacterial infection, however there does appear to be some benefit from oral semisynthetic tetracycline antibiotics due to anti-inflammatory effects<sup>147</sup>
  - c. Rash is characterized by papules and pustules coupled with pruritus and pain
    - 1) Distributed in seborrheic areas, such as the face and scalp, but is not acne as no comedones are seen and histopathology differs
    - 2) Changes in the appearance of the skin lesions, oozing of fluid, yellow and/or brown crusting may be symptoms of superinfection and should be treated promptly

- a) Superinfection has been reported in up to 38% of patients
  - d. Positive correlation between rash severity and occurrence with overall survival and tumor response has been proven, therefore it is important to manage the rash so therapy can continue<sup>146</sup>
  - e. Management primarily based on Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group clinical practice guidelines for prevention and treatment of EGFR inhibitor-associated dermatologic toxicities<sup>139</sup>
- 1) Grading based on CTCAE Version 5.0<sup>115</sup>

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering >30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; IV antibiotics indicated	Life-threatening consequences	Death

2) Pre-emptive management

- a) Should be used in all patients due to the high frequency of rash and the fact that it consistently presents in the first 2 to 4 weeks of therapy
- b) STEPP: A phase II, open-label randomized trial evaluating a pre-emptive skin regimen in patients receiving panitumumab<sup>148</sup>
  - i. Patients were assigned 1:1 to pre-emptive (n=48) or reactive (n=47) treatment
  - ii. Pre-emptive treatment was started 1 day prior to 1<sup>st</sup> dose of panitumumab and continued through weeks 1 to 6
  - iii. Incidence of grade  $\geq 2$  skin toxicities was 29% and 62% for pre-emptive and reactive groups, respectively. Patients in the pre-emptive group also reported less QOL impairment than patients in the reactive arm.
- c) Hydrocortisone 1% combined with a moisturizer, sunscreen and doxycycline 100 mg BID for the 1<sup>st</sup> 6 weeks is recommended; prophylactic minocycline 100 mg QD is also effective.
  - i. Doxycycline seems to be better tolerated than minocycline, especially in patients with renal dysfunction. Minocycline is less photosensitizing; therefore, preferred in areas with a high UV index.
- 3) Reactive management consists of the use of medium- to high-potency topical corticosteroids (alclometasone 0.05% cream or fluocinonide 0.05% cream BID), topical clindamycin 1%, and/or oral antibiotics (doxycycline or minocycline)
- 4) Other guidelines and recommendations exist, all espousing a similar approach<sup>149,150</sup>
- 5) Standard acne therapies should be avoided as they will worsen rash

- f. Summary of recommendations for treatment
  - 1) Pre-emptive management (for at least first 6 weeks of treatment)
    - a) Hydrocortisone 1% with a moisturizer, sunscreen, and doxycycline 100 mg BID
  - 2) Reactive management (initiate any therapies not already in use)
    - a) Grade 1: Continue dose, topical hydrocortisone, and topical clindamycin
    - b) Grade 2: Continue dose, topical hydrocortisone, oral doxycycline or minocycline
    - c) Grade 3/4: Modify dose per PI; topical hydrocortisone, oral doxycycline or minocycline, oral prednisone

**Patient Case #3 (ARS question 4):**

**Correct answer is B.** Since RL's rash is categorized as a Grade 2 rash, the most appropriate therapy would be to continue panitumumab at the same dose and initiate therapy with topical steroids in addition to the doxycycline.

Answer A is incorrect because there is currently no evidence minocycline is more effective than doxycycline for EGFR inhibitor-associated papulopustular rash. The panitumumab however can be continued at the same dose.

Answer C is incorrect. Dose reduction would be appropriate for a grade 3 or 4 rash, however salicylic acid should never be used for EGFR inhibitor-associated papulopustular rash

Answer D is incorrect. This intervention would be appropriate for a grade 3 or 4 rash

**V. Survivorship issues and long-term follow-up**

**A. Survivorship**

1. Management of late sequelae of disease and/or treatment<sup>2,132,151,152</sup>
  - a. Fatigue can last for years after completion of treatment and interventions
    - 1) Physical activity should be encouraged
    - 2) Patients may require other behavioral interventions including psychosocial interventions, nutrition consultation, or behavioral therapy for sleep
    - 3) Consider psychostimulants such as methylphenidate after ruling out other causes of fatigue and failure of other interventions
  - b. Higher prevalence of chronic diarrhea in patients who have received radiation or an ostomy
    - 1) Anti-diarrhea agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments should be considered alone or in combination for management
  - c. Oxaliplatin-induced neuropathy
    - 1) May worsen over the first 3 months after discontinuation of therapy (called the "coasting" effect)
    - 2) Some patients may have long-lasting or permanent neuropathy

- 3) Duloxetine can be considered for painful neuropathy, however it is not effective for numbness, tingling, or cold sensitivity
2. Healthy lifestyle and wellness<sup>152</sup>
  - a. Patients should be encouraged to achieve and maintain healthy body weight through appropriate diet and physical activity
    - 1) Active lifestyle should be appropriately modified for any disease or treatment sequelae (IE, ostomy, neuropathy)
    - 2) Multiple large observational studies have shown that increased activity in non-metastatic colorectal cancer survivors decreases mortality<sup>2</sup>
  - b. Aspirin
    - 1) Numerous trials have shown the benefit of colorectal cancer survivors taking a low-dose aspirin<sup>2</sup>
    - 2) A large, population-based study with 23,162 patients with colorectal cancer showed that low-dose aspirin therapy after diagnosis improved colorectal cancer-specific survival and overall survival<sup>153</sup>
    - 3) The NCCN® panel recommends survivors consider taking aspirin 325mg daily to reduce their risk of recurrence and death, if the potential risks of aspirin are discussed and considered<sup>2,29</sup>
3. Disease-preventive measures
  - a. Follow immunization recommendations
  - b. Age and gender appropriate cancer screenings (e.g., breast, cervical, prostate)
- B. Long-term follow-up recommendations
  1. Carcinoembryonic antigen (CEA) level
    - a. May be useful in monitoring colorectal cancer response to treatment
    - b. Monitoring CEA is not recommended for colorectal cancer screening
    - c. Normal < 3 ng/mL; in smokers 0-6 ng/mL
    - d. CEA can be higher with elevated serum creatinine, hepatic dysfunction or chemo (5-FU) so may see an increase in CEA and then a decrease after a few months of treatment
    - e. T  $\frac{1}{2}$  is ~ 7 days
  2. NCCN Guidelines®<sup>2,29</sup>
    - a. Stage I colon and rectal cancer
      - 1) Colonoscopy at 1 year after surgery, if normal repeat in 3 years, then every 5 years
    - b. Stage II, III, and IV (with no evidence of disease [NED]) colon and rectal cancer
      - 1) History and physical exam and CEA every 3-6 months for 2 years, then every 6 months for a total of 5 years



- 2) CT of the chest, abdomen, and pelvis every 6-12 months (Category 2B for <12 months) for a total of 5 years
  - a) For stage IV NED: CT scans every 3-6 months (Category 2B for <6 months) for 2 years, then every 6-12 months for a total of 5 years
- 3) Colonoscopy at 1 year after surgery, if normal repeat in 3 years, then every 5 years
  - a) If no preoperative colonoscopy due to obstructing tumor, colonoscopy should be in 3-6 months after surgery
- 3. ASCO guidelines<sup>154</sup>
  - a. Colonoscopy 1 year after initial surgery and then every 5 years, dictated by the findings of the previous one. If not performed before diagnosis, a colonoscopy should be performed after completion of adjuvant therapy before 1 year
  - b. History and physical examination and CEA every 3-6 months for 5 years
  - c. Annual CT of the chest, abdomen, pelvis for 3 years after primary therapy

## PANCREATIC CANCER

### Patient Case #4 (ARS question #5):

ZT is a 78-year-old female who underwent a Whipple procedure for resectable pancreatic cancer 11 weeks ago. She now presents to the medical oncologist to begin adjuvant therapy. She did not receive neoadjuvant therapy. She has recovered moderately from the surgery with an ECOG performance status of 1. Her medical history is pertinent for diabetic neuropathy in her feet, causing her to use a walker.

**Which of the following is the most appropriate adjuvant treatment for ZT?**

- A. Observation
- B. Gemcitabine + capecitabine
- C. Gemcitabine + nab-paclitaxel
- D. mFOLFIRINOX

### I. Genomics<sup>155,156</sup>

- A. There are various genetic syndromes associated with increased risk of pancreatic cancer, thought to be associated with about 10% of cases
  - 1. These include Peutz-Jeghers syndrome, familial pancreatitis, melanoma-pancreatic cancer syndrome, Lynch syndrome, hereditary breast-ovarian cancer syndrome, and familial pancreatic cancer
- B. Lynch syndrome
  - 1. Patients are at a 9- to 11-fold increase risk for pancreatic cancer
  - 2. Because these patients have germline mutations in DNA mismatch repair genes (IE, MSI-H or dMMR), these tumors may be susceptible to immunotherapy
- C. Hereditary breast-ovarian cancer syndrome (refer to the Breast Cancer and Gynecologic Malignancies modules for more information)
  - 1. Patients are at a 2.4- to 6-fold increase risk for pancreatic cancer
  - 2. Reported *BRCA* mutation rates have varied greatly in the literature (primarily due to under testing), ranging from 1-11% for *BRCA1* and 0-17% for *BRCA2*
  - 3. The risk for pancreatic cancer is better established with mutations in *BRCA2* (absolute risk 5-10%) vs *BRCA1* (absolute risk  $\leq 5\%$ )
  - 4. Any patient that tests positive for a pathogenic mutation should be referred to genetic counseling
  - 5. The NCCN® Guidelines<sup>155</sup> for pancreatic cancer recommend systemic therapies specifically for patients with mutations in *BRCA1/2* (as well as *PALB2* mutations), discussed further below
- D. Genetic counseling/testing is recommended for any patient with confirmed pancreatic cancer to assess for inherited mutations

### II. Screening

- A. Routine screening for pancreatic cancer is not recommended for patients who are asymptomatic and have no family history of pancreatic cancer<sup>155</sup>

- B. Limited data exist for screening in patients with strong family history of pancreatic cancer and/or presence of a known pathogenic/likely pathogenic germline variant in a pancreatic cancer susceptibility gene<sup>156</sup>
1. These genes include *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PALB2*, *STK11*, and *TP53*
  2. The discussion to screen should be at a high-volume center due to the lack of definitive data regarding risks and benefits
  3. If screening is performed, the NCCN panel<sup>®</sup> recommends annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS)<sup>156</sup>
    - a. For patients with a family history, screening can begin at age 50 or 10 years younger than the earliest pancreatic cancer diagnosis (whichever is earlier)
    - b. For patients with a *CDKN2A* or *STK11* pathogenic variant, no additional family history is necessary to screen. Screening can start at age 40 for those with *CDKN2A* and at age 30-35 for those with *STK11*, or if family history is present, 10 years younger than the earliest pancreatic cancer diagnosis (whichever is earlier)

### III. Treatment and symptom management<sup>155,157</sup>

#### A. Treatment modalities

1. Nearly all patients with pancreatic cancer should be evaluated for a clinical trial
2. Principles of surgery
  - a. Only potential cure for pancreatic cancer
  - b. Less than 20% patients are eligible for complete surgical resection
  - c. The primary curative surgical procedure involves a radical pancreatic resection
    - 1) Whipple procedure (pancreatoduodenectomy) for tumors in the head or uncinate of pancreas
    - 2) Distal pancreatectomy with en-bloc splenectomy for tumors in the body or tail of pancreas
  - d. May be used in the palliative setting for duodenal bypass (gastrojejunostomy) or bypass of biliary obstruction or biliary stent placement
3. Principles of radiation<sup>158,159</sup>
  - a. Post-surgery, radiation alone does not improve survival
    - 1) When combined with 5-FU, radiation offers significantly longer median survival (20.9 months vs. 11 months) in patients who have had curative resection and no adjuvant therapy<sup>159</sup>
  - b. Neoadjuvant therapy with 5-FU and radiation has been shown to improve tumor resectability rates with no change in OS
  - c. Palliative radiotherapy can be used to control pain, bleeding, and/or obstruction
4. Principles of systemic therapy
  - a. Systemic therapy is used in all stages of pancreatic cancer

- b. 5-FU and gemcitabine are the most studied single agents available for the treatment of pancreatic cancer, and the backbones of many regimens
- c. Combination chemotherapy improves response rates with minimal improvement in median survival (Refer to the NCCN Guidelines® for Pancreatic Adenocarcinoma for most up-to-date dosing recommendations)<sup>155</sup>

Regimen	Dosing	Frequency
<b>FOLFIRINOX*</b>	5-FU IV 400 mg/m <sup>2</sup> Leucovorin IV 400 mg/m <sup>2</sup> Irinotecan IV 180 mg/m <sup>2</sup> Oxaliplatin IV 85 mg/m <sup>2</sup> 5-FU CIVI 1200 mg/m <sup>2</sup> /day x 2 days (over 46-48 hours)	Every 14 days
<b>mFOLFIRINOX*</b>	Leucovorin IV 400 mg/m <sup>2</sup> Irinotecan IV 150 mg/m <sup>2</sup> Oxaliplatin IV 85 mg/m <sup>2</sup> 5-FU CIVI 1200 mg/m <sup>2</sup> /day x 2 days (over 46-48 hours)	Every 14 days
<b>Gemcitabine + nab-paclitaxel</b>	Days 1, 8, & 15: Gemcitabine IV 1000 mg/m <sup>2</sup> Nab-paclitaxel IV 125 mg/m <sup>2</sup>	Every 28 days
<b>Gemcitabine + capecitabine</b>	Days 1, 8 & 15: Gemcitabine IV 1000 mg/m <sup>2</sup> Days 1-21: Capecitabine PO 830 mg/m <sup>2</sup> /dose BID	Every 28 days
<b>Gemcitabine + cisplatin</b>	Days 1 & 15: Gemcitabine IV 1000 mg/m <sup>2</sup> Cisplatin IV 50 mg/m <sup>2</sup>	Every 28 days
	Gemcitabine 750 mg/m <sup>2</sup> Cisplatin 25-30 mg/m <sup>2</sup>	Every 14 days
<b>Gemcitabine + nab-paclitaxel + cisplatin</b>	Days 1 & 8: Nab-paclitaxel 100-125 mg/m <sup>2</sup> Cisplatin 25 mg/m <sup>2</sup> Gemcitabine 800-1000 mg/m <sup>2</sup>	Every 21 days

\*Should be limited to ECOG performance status 0-1

- B. Pancreatic cancer is treated based on clinical stage rather than TNM stage
- C. Resectable disease<sup>160</sup>
  1. Surgical resection remains the primary treatment modality and may occasionally lead to long-term survival
  2. In select patients with resectable disease with high-risk features, neoadjuvant therapy may be considered (see “Borderline Resectable” section for neoadjuvant therapy options)
    - a. High-risk features include: concerning imaging findings, highly elevated CA 19-9, large primary tumor, large regional lymph nodes, excessive weight loss, and/or extreme pain
    - b. For patients who receive neoadjuvant therapy, adjuvant chemotherapy after surgery may be considered
  3. Adjuvant therapy
    - a. Radical pancreatic resection plus adjuvant chemotherapy is standard for resectable disease
      - 1) Even with an R0 resection, recurrence rates remain very high

- 2) The addition of chemoradiation to adjuvant chemotherapy in a sequential fashion may be considered for patients with positive margins and/or positive nodes<sup>155,161</sup>
- b. Treatment should be initiated within 8-12 weeks after surgery and continued for 6 months
- c. There is no definitive standard regimen
- d. Gemcitabine (CONKO-001<sup>162</sup>)
  - 1) Showed that adjuvant chemotherapy with gemcitabine had significantly better median DFS and OS versus observation after surgery (13.4 vs 6.7 months and 22.8 vs 20.2 months, respectively)
- e. 5-FU/leucovorin (ESPAC-3<sup>163</sup>)
  - 1) No significant difference in survival between adjuvant 5-FU / leucovorin and adjuvant gemcitabine (23.0 vs. 23.6 months)
  - 2) Treatment-related serious adverse events were significantly higher in the 5-FU / leucovorin group (14% vs 7.5%; p<0.001)
- f. Gemcitabine + capecitabine (ESPAC-4<sup>164</sup>)
  - 1) The addition of capecitabine to gemcitabine significantly extended median OS compared to gemcitabine alone (28.0 vs. 25.5 months; HR=0.82, 95% CI 0.68 – 0.98, p=0.032)
  - 2) Rates of adverse events between the two groups were not significantly different
- g. mFOLFIRINOX (PRODIGE 24/CCTG PA.6<sup>165</sup>)
  - 1) Phase III trial comparing mFOLFIRINOX vs gemcitabine following surgery
  - 2) Dosing of mFOLFIRINOX was oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup>, irinotecan 180 mg/m<sup>2</sup>; 5-FU 2,400 mg/m<sup>2</sup> CIVI over 46 hours
    - a) Irinotecan dose was further lowered to 150 mg/m<sup>2</sup> per an interim safety analysis
  - 3) Median disease-free survival (primary endpoint) was significantly extended in the mFOLFIRINOX group at 21.6 months, vs 12.8 months in the gemcitabine group (HR 0.58, 95% CI 0.46 - 0.73, p<0.001)
  - 4) Median OS was significantly better in the mFOLFIRINOX group than the gemcitabine group: 54.4 vs 35.0 months (HR 0.64, 95% CI 0.48 – 0.86, p=0.003)
  - 5) Grade 3/4 adverse events were reported in 75.9% patients in the mFOLFIRINOX group and 52.9% patients in the gemcitabine group
- h. Gemcitabine + nab-paclitaxel (APACT<sup>166,167</sup>)
  - 1) Phase III trial comparing gemcitabine + nab-paclitaxel vs gemcitabine following surgery
  - 2) Median independent reviewer-assessed disease-free survival (primary endpoint) was not statistically significant between the 2 groups (combination 19.4 months vs gemcitabine 18.8 months; HR 0.88, 95% CI 0.729 - 1.063, p = 0.1824)
  - 3) Median OS was in favor of gemcitabine + nab-paclitaxel group: 41.8 months vs 37.7 months in gemcitabine group (HR 0.80, 95% CI 0.678 – 0.947, p=0.0091)

- 4) Although authors suggest adjuvant gemcitabine + nab-paclitaxel may be an option for patients not eligible for FOLFIRINOX, the NCCN Guidelines® do not include this regimen as an option for adjuvant therapy at this time
- i. NCCN Guidelines® recommendations for post-operative adjuvant therapy<sup>155</sup>
  - 1) Preferred
    - a) Gemcitabine + capecitabine (category 1)
    - b) mFOLFIRINOX (category 1)
  - 2) Other
    - a) Gemcitabine (category 1)
    - b) 5-FU/leucovorin (category 1)
    - c) Continuous infusion 5-FU
    - d) Capecitabine (category 2B)
    - e) Induction chemotherapy (gemcitabine, 5-FU/leucovorin, or continuous infusion 5-FU) followed by chemoradiation
      - i. This option can also be followed by subsequent chemotherapy, which would be the same regimen as induction chemotherapy
- j. ASCO Guidelines for Potentially Curable Pancreatic Cancer<sup>161,168</sup>
  - 1) Preferred regimen is mFOLFIRINOX
  - 2) Alternate regimens include:
    - a) Gemcitabine + capecitabine
    - b) Gemcitabine
    - c) Bolus 5-FU/leucovorin

**Patient Case #4 (ARS question #5):**

**Correct answer is B.** Based on results from the ESPAC-4 trial, both the NCCN Guidelines®<sup>155</sup> and ASCO guidelines support gemcitabine + capecitabine as a regimen for adjuvant treatment of resected pancreatic cancer. Due to this patient's baseline neuropathy, avoidance of agents that could worsen her neuropathy would be prudent.

Answer A is incorrect because observation has shown inferior results to chemotherapy in the adjuvant setting

Answer C is incorrect because at this time there are insufficient data to recommend gemcitabine + nab-paclitaxel for adjuvant treatment

Answer D is not most appropriate for this patient due to her baseline neuropathy and the potential for worsening neuropathy with oxaliplatin. However, mFOLFIRINOX is a preferred option for adjuvant treatment for patients with good performance status.

**D. Borderline resectable disease**

1. Typically treated with neoadjuvant therapy first to optimize resection

- a. Rates of conversion to resectability have been reported in a variety of trials from 15% up to 53%
  - b. If deemed resectable, surgical resection to be attempted 4-8 weeks after completion of neoadjuvant therapy
  - c. For patients who receive neoadjuvant therapy, additional adjuvant chemotherapy after surgery may be considered
2. Patients may undergo neoadjuvant therapy but never become resectable, in which case they are treated as locally advanced unresectable, or metastatic if distant disease is discovered
3. Chemoradiation can be considered for neoadjuvant treatment. Although this has been shown to improve local control over chemotherapy alone, there are no differences in survival outcomes.
4. Preferred neoadjuvant chemotherapy regimens (typically given for 2-6 cycles)
  - a. FOLFIRINOX/mFOLFIRINOX (option for *BRCA1/2* or *PALB2* mutations)
  - b. Gemcitabine + nab-paclitaxel
  - c. Gemcitabine + cisplatin (only for *BRCA1/2* or *PALB2* mutations)
  - d. Any of these regimens can be followed by fluoropyrimidine- or gemcitabine-based chemoradiation
- E. Locally advanced unresectable disease<sup>155,158,169,170</sup>
  1. At the time of diagnosis, over 85% of tumors have extended beyond the pancreas
  2. Some patients are surgically unresectable, but may benefit from chemoradiation
    - a. Chemoradiation improved median survival (10.5 vs. 5.5 months,  $p<0.05$ )<sup>171</sup> and 1-year survival (41% vs. 19%,  $p<0.05$ )<sup>172</sup> over chemotherapy alone in unresectable disease
    - b. There is no strong evidence to suggest that gemcitabine-based chemoradiation is better than 5-FU- based chemoradiation<sup>173</sup>
      - 1) CALGB 80003 analyzed 5-FU plus gemcitabine with radiation<sup>174</sup> and demonstrated acceptable toxicity and a median survival of 12.2 months with a median time to progression of 10 months
  3. Chemotherapy alone may be used for management of locally advanced, unresectable pancreatic cancer
    - a. Recent trials have examined gemcitabine alone or different chemotherapy combinations in mixed populations of patients with locally advanced, unresectable and metastatic disease
    - b. Median survival values have been similar to those demonstrated in trials utilizing chemoradiotherapy for unresectable patients
  4. NCCN Guidelines® supported regimens<sup>155</sup> are recommended based on performance status (refer to Metastatic disease section for expanded information on regimens)
    - a. Good performance status (ECOG performance status 0-1, good pain management, patent biliary stent, and adequate nutritional intake)
      - 1) Preferred:

- a) FOLFIRINOX/mFOLFIRINOX (option for *BRCA1/2* or *PALB2* mutations)
  - b) Gemcitabine + nab-paclitaxel
  - c) Gemcitabine + cisplatin (only for *BRCA1/2* or *PALB2* mutations)
- 2) Other:
  - a) Gemcitabine
  - b) Gemcitabine + erlotinib
  - c) Gemcitabine + capecitabine
  - d) Gemcitabine + nab-bound paclitaxel + cisplatin (category 2B)
  - e) Capecitabine or continuous infusion 5-FU (both category 2B)
  - f) Fixed dose rate (FDR) gemcitabine, docetaxel, capecitabine (GTX; category 2B)
  - g) Fluoropyrimidine + oxaliplatin (category 2B)
- 3) Useful in certain circumstances:
  - a) Induction chemotherapy with any of the above regimens ( $\geq 4$ -6 cycles) followed by chemoradiation or radiation alone may be an option for patients with advanced, unresectable disease with no metastases
  - b) Chemoradiation or radiation alone may be an option for patients unable to tolerate combination therapy
- b. Preferred for poor performance status
  - 1) Gemcitabine (category 1)
  - 2) FDR gemcitabine (category 2B)
  - 3) Capecitabine or continuous infusion 5-FU (both category 2B)
- 5. ASCO Guidelines for locally advanced, unresectable pancreatic cancer<sup>175</sup>
  - a. Goals of care, patient preferences, psychological status, patient support systems, and symptoms should guide treatment decisions
  - b. ECOG PS 0-1 and favorable comorbidity profile
    - 1) Clinical trial
    - 2) FOLFIRINOX
    - 3) Gemcitabine + nab-paclitaxel
  - c. Borderline ECOG PS or patient preference for less toxic regimen
    - 1) Gemcitabine
    - 2) Gemcitabine + capecitabine
  - d. Patients who have local progression on first-line therapy may be offered radiation therapy
  - e. Patients who have systemic progression on first-line therapy should be treated per the metastatic disease recommendations



**Patient Case #5 (ARS question #6):**

TS is a 60-year-old male who presented to his primary care physician with painless jaundice. Further workup reveals a mass in the pancreatic head compressing the bile ducts. A CT of his chest, abdomen, and pelvis reveals suspicious lesions in his liver, which is found to be adenocarcinoma, consistent with a pancreatic primary. TS states he “wants to fight this cancer” for his family. His ECOG performance status is 0. He mentions both of his sisters have had breast cancer, and he believes his mother had ovarian cancer. A genetic workup reveals a deleterious germline mutation in *BRCA2*.

**Which of the following is the most appropriate initial treatment for TS’s metastatic pancreatic cancer?**

- A. Gemcitabine
- B. Gemcitabine + erlotinib
- C. Gemcitabine + nab-paclitaxel
- D. mFOLFIRINOX

F. Metastatic disease<sup>155,176</sup>

1. Systemic therapy is offered to patients for palliation and to extend survival
  - a. A majority of patients will also require palliative and supportive care interventions throughout their treatment
  - b. ASCO guidelines endorse early testing for germline and somatic actionable alterations<sup>176</sup>
2. Gemcitabine as a single agent
  - a. Gemcitabine improved median OS (5.65 vs 4.41 months;  $P=0.0025$ ), 1-year survival (18% vs 2%), and clinical benefit response (23.8% vs 4.8%;  $P=0.0022$ ) when compared against 5-FU<sup>177</sup>
    - 1) Clinical benefit is defined as an improvement in pain, lean body mass, and Karnofsky performance status
    - 2) Gemcitabine received FDA approval for metastatic pancreatic cancer based on the significant improvement in clinical benefit
  - b. Fixed-dose rate (FDR) infusions of gemcitabine<sup>178</sup>
    - 1) Longer infusion increases pharmacokinetic benefit
      - a) Intracellular activation of gemcitabine to the active triphosphate form by deoxycytidine kinase is saturated at infusion rates of approximately 10 mg/m<sup>2</sup>/min (FDR infusion)
        - i. “Standard” gemcitabine given over 30 minutes
      - b) Theoretically, this allows for higher concentrations of the active form of gemcitabine which may correlate with improved cytotoxicity and enhanced clinical effectiveness
    - 2) FDR improved median OS (8.0 vs 5.0 months;  $p=0.013$ ), 1-year survival (29% vs 9%;  $P=0.014$ ), and 2-year survival (18.3% vs 2.2%;  $P=0.007$ ) against standard gemcitabine<sup>179</sup>

- a) Patients in the FDR arm experienced more grade 3 and 4 anemia, thrombocytopenia, and neutropenia
- b) Despite these promising results, preliminary data from a phase III combination therapy trial was not able to confirm a benefit with FDR gemcitabine<sup>180</sup>

### 3. Combination chemotherapy

- a. Several randomized trials have compared gemcitabine monotherapy to gemcitabine with another agent such as 5-FU<sup>181</sup>, cisplatin<sup>182</sup>, irinotecan<sup>183</sup>, oxaliplatin<sup>184</sup>, and capecitabine<sup>185</sup>
  - 1) Although the results of these combination therapy trials indicate favorable response rates and time to tumor progression, median OS was still not statistically significant when compared to gemcitabine alone
- b. Gemcitabine + erlotinib<sup>186</sup>
  - 1) The erlotinib combination improved median OS (6.24 vs 5.9 months;  $P=0.038$ ), 1-year survival (23% vs 17%;  $P>0.023$ ), and overall response rate (57% vs 49%;  $P>0.07$ ) over gemcitabine alone
  - 2) Severity of rash directly correlated with improved OS in combination arm (10.5 months with grade 2 rash vs. 5.2 months with no rash,  $p=0.0001$ ) and 1 year survival (43% vs. 16%), but no correlation with EGFR expression
  - 3) Although erlotinib in combination with gemcitabine has a NCCN Guidelines® category 1 recommendation for first-line treatment, it is not considered a preferred regimen due to minimal improvement in survival and increased toxicities<sup>155</sup>
- c. FOLFIRINOX<sup>187</sup>
  - 1) Phase II/III study that included patients less than or equal to 75 years old with newly diagnosed metastatic pancreatic adenocarcinoma (no prior systemic therapy) and ECOG performance status 0 or 1
  - 2) FOLFIRINOX improved median OS (11 vs 6.8 months;  $P<0.001$ ), PFS (6.4 vs 3.3 months;  $P<0.001$ ), and ORR (31.6% vs 9.4%;  $P<0.001$ ) over gemcitabine alone
  - 3) QOL was similar for the first 8 cycles except for diarrhea, which was worse with FOLFIRINOX
  - 4) Patients in FOLFIRINOX group experienced significantly more neutropenia (45.7%), febrile neutropenia (5.4%), thrombocytopenia (9.1%), diarrhea (12.7%), and neuropathy (9%). Patients in FOLFIRINOX group also had more grade 2 alopecia.
- d. Gemcitabine + nab-paclitaxel<sup>188</sup>
  - 1) Phase III trial including patients over the age of 18 (no maximum age) with newly diagnosed metastatic pancreatic adenocarcinoma (no prior systemic therapy) and Karnofsky performance status  $> 70$
  - 2) Nab-paclitaxel with gemcitabine improved median OS (8.5 vs 6.7 months;  $P<0.001$ ), PFS (5.5 vs 3.7 months;  $P<0.001$ ), and ORR (23% vs 7%;  $P<0.001$ ) over gemcitabine alone
  - 3) Most frequent adverse events in nab-paclitaxel group were fatigue, alopecia, and nausea

- a) Nab-paclitaxel group had more grade 3, 4 adverse events of neutropenia, fatigue, and peripheral neuropathy
- e. Gemcitabine + nab-paclitaxel + cisplatin<sup>189</sup>
  - 1) Many pancreatic cancers thought to harbor DNA repair deficiencies, so this phase 1b/2 trial hypothesized addition of cisplatin to gemcitabine and nab-paclitaxel may increase survival outcomes and response rates
  - 2) All patients received growth factor
  - 3) The ORR was 71% with complete response in 8% (n=2) patients
  - 4) The median OS was 16.4 months and median PFS was 10.1 months
  - 5) Most frequent grade 3 or higher adverse events were thrombocytopenia, anemia, and neutropenia

#### First-line recommendations for metastatic pancreatic cancer

Good Performance Status*	Poor Performance Status
NCCN Guidelines <sup>155</sup>	
<b>Preferred Regimens</b> <ul style="list-style-type: none"> <li>FOLFIRINOX (category 1) or mFOLFIRINOX (options for <i>BRCA 1/2</i> or <i>PALB2</i> mutations)</li> <li>Gemcitabine + nab-paclitaxel (category 1)</li> <li>Gemcitabine + cisplatin (only for <i>BRCA 1/2</i> or <i>PALB2</i> mutations)</li> </ul> <b>Other Regimens</b> <ul style="list-style-type: none"> <li>Gemcitabine (category 1)</li> <li>Gemcitabine + erlotinib (category 1)</li> <li>Gemcitabine + capecitabine</li> <li>Gemcitabine + nab-paclitaxel + cisplatin</li> <li>FDR gemcitabine, docetaxel, capecitabine (GTX; category 2B)</li> <li>Fluoropyrimidine + oxaliplatin (category 2B)</li> <li>Dabrafenib + trametinib (<i>BRAF V600E</i> mutation; category 2B)</li> </ul> <b>Useful in certain circumstances</b> <ul style="list-style-type: none"> <li>Pembrolizumab (MSI-H/dMMR or TMB-high tumors)</li> </ul>	<b>Preferred Regimens</b> <ul style="list-style-type: none"> <li>Gemcitabine (category 1)</li> <li>FDR gemcitabine (category 2B)</li> <li>Capecitabine or continuous infusion 5-FU (both category 2B)</li> </ul> <b>Useful in certain circumstances</b> <ul style="list-style-type: none"> <li>Pembrolizumab (MSI-H/dMMR or TMB-high tumors)</li> <li>Larotrectinib (<i>NTRK</i> gene fusion positive tumors)</li> <li>Entrectinib (<i>NTRK</i> gene fusion positive tumors; category 2B)</li> <li>Dabrafenib + trametinib (<i>BRAF V600E</i> mutation; category 2B)</li> </ul>
ASCO Guidelines <sup>176</sup>	
<ul style="list-style-type: none"> <li>FOLFIRINOX</li> <li>Gemcitabine + nab-paclitaxel</li> </ul>	<ul style="list-style-type: none"> <li>Gemcitabine</li> <li>Gemcitabine + erlotinib†</li> <li>Gemcitabine + capecitabine†</li> <li>Gemcitabine + nab-paclitaxel†</li> </ul>

\*Per NCCN Guidelines<sup>®</sup> defined as ECOG PS of 0-1, good pain management, patent biliary stent, and adequate nutritional intake. Per ASCO Guidelines defined as favorable comorbidity profile, patient preference, support for aggressive therapy, and access to port and infusion pump management services.

†These regimens may be offered, but with proactive dose and schedule adjustments to minimize toxicities

**Patient Case #5 (ARS question #6):**

**The correct answer is D.** TS has a PS ECOG score of 0, no pertinent comorbidities, minimal symptoms, good family support, and his goal is to treat; therefore, he is a good candidate for aggressive chemotherapy with FOLFIRINOX. In addition, due to his *BRCA2* mutation, he should receive platinum-based chemotherapy with either FOLFIRINOX or gemcitabine + cisplatin.

Answer A is not appropriate because TS is eligible and willing to receive more aggressive chemotherapy. Gemcitabine alone would be appropriate if his ECOG PS was 2-3.

Answer B is not the most appropriate option because gemcitabine + erlotinib is not considered a preferred regimen by NCCN Guidelines® despite a category 1 recommendation.<sup>155</sup>

Answer C is not the most appropriate option because TS is *BRCA2* and should receive platinum-based chemotherapy.

**4. Maintenance treatment**

- a. Patients who have response or stable disease after 4-6 months of systemic therapy are eligible for maintenance therapy<sup>155</sup>
- b. Olaparib emerged as the first option for maintenance therapy in metastatic pancreatic cancer patients with deleterious or suspected deleterious germline *BRCA1/2* mutations
  - 1) The POLO trial<sup>190</sup> evaluated olaparib 300 mg PO twice daily vs placebo in patients who had not progressed during at least 16 weeks of first-line platinum-based chemotherapy
    - a) The primary endpoint of PFS was significantly longer in the olaparib group (7.4 vs 3.8 months; HR 0.53, 95% CI 0.35-0.82, P=0.004)
    - b) The adverse effects experienced by the olaparib group were similar to those previously documented, including fatigue, nausea, anemia, abdominal pain, and diarrhea
    - c) Of note, the authors state the POLO trial was initiated when FOLFIRINOX chemotherapy was recommended for only 6 months for metastatic patients; it does not take into account patients who may continue chemotherapy past 6 months
  - 2) The NCCN Guidelines® and ASCO guidelines both support the use of olaparib as maintenance for patients with germline deleterious or likely deleterious *BRCA1/2* mutations, good performance status, metastatic disease, and no disease progression during the first 16 weeks of first-line, platinum-based chemotherapy<sup>155,176</sup>
    - a) ASCO guidelines encourage discussion between patients with germline *BRCA1/2* mutations who are considered platinum-sensitive and their oncologists on whether to continue treatment with chemotherapy or switch to olaparib maintenance<sup>176</sup>
- c. Maintenance options include<sup>155</sup>:
  - 1) Previous platinum-based chemotherapy
    - a) Preferred: olaparib (germline *BRCA1/2* mutations)

- b) Useful in certain circumstances: rucaparib (germline or somatic *BRCA1/2* or *PALB2* mutations)
- 2) Other:
  - a) Clinical trial
  - b) If first-line treatment with FOLFIRINOX/mFOLFIRINOX:
    - i. Capecitabine
    - ii. 5-FU ± irinotecan (consider if oxaliplatin-induced neuropathy or allergy to oxaliplatin)
    - iii. FOLFOX (category 2B; consider if patient cannot tolerate irinotecan)
  - c) If first-line treatment with nab-paclitaxel/gemcitabine:
    - i. Modified schedule of nab-paclitaxel/gemcitabine (category 2B)
    - ii. Gemcitabine alone (category 2B)
  - d) Rucaparib (germline or somatic *BRCA1/2* mutations)
- 3) Can also consider a treatment holiday

**Patient Case #5, continued (ARS question #7):**

TS received 6 cycles of mFOLFIRINOX, complicated by grade 2 neuropathy, so the oxaliplatin was dropped. He eventually switched to olaparib maintenance therapy. TS returns today to review a recent CT scan. Unfortunately, his CT of the chest shows new lung lesions and CT of the abdomen shows enlarged liver lesions. All labs are within normal limits, his neuropathy has resolved to grade 1, and his ECOG is now 1.

**What would be most appropriate subsequent therapy for TS?**

- A. Gemcitabine
- B. 5-FU + radiation
- C. Gemcitabine + cisplatin
- D. Best supportive care

- 5. Subsequent systemic therapy
  - a. Therapy for patients who have progressed in the front-line setting has been poorly studied and therefore there is no preferred regimen
    - 1) Subsequent chemotherapy is highly dependent on the type of chemotherapy received previously
  - b. 5-FU + liposomal irinotecan (NAPOLI-1)<sup>191</sup>
    - 1) Phase III trial including patients with metastatic pancreatic adenocarcinoma who progressed on previous gemcitabine-based therapy

- 1) Liposomal irinotecan, folinic acid, 5-FU infusion every 2 weeks vs folinic acid + 5-FU infusion weekly x 4 weeks repeated every 6 weeks
    - a) *UGT1A1* genotype testing was performed for all patients. Dose modification of liposomal irinotecan from 70 mg/m<sup>2</sup> to 50 mg/m<sup>2</sup> is recommended in the label for patients who are homozygous for *UGT1A1*\*28.<sup>192</sup>
  - 2) Addition of liposomal irinotecan to 5-FU improved median OS (6.1 vs 4.22 months; P=0.012), median PFS (3.1 vs 1.5 months; P=0.0001), median time to treatment failure (2.3 vs 1.4 months; P=0.0002), and ORR (16% vs 1%)
    - a) A third arm included patients receiving liposomal irinotecan alone, which was compared only to the 5-FU + folinic acid arm and showed no significant difference in survival benefits
  - 3) Liposomal irinotecan was associated with more diarrhea, nausea/vomiting, fatigue, neutropenia, and anemia
- c. Oxaliplatin + 5-FU<sup>193</sup>
- 1) Phase III study including patients with metastatic pancreatic adenocarcinoma who progressed while receiving first-line gemcitabine therapy
  - 2) 5-FU and oxaliplatin plus best supportive care (BSC) VS BSC alone
  - 3) Study was stopped early due to low recruitment due to decreased acceptance of BSC alone, however the addition of chemotherapy to BSC improved median survival (4.82 vs 2.3 months; P=0.008) and OS (9.9 vs 7.9 months)
    - a) Best response was stable disease
  - 4) Most frequent adverse events in the treatment group were neuropathy, diarrhea, nausea/vomiting
- d. NCCN Guidelines® recommendations for subsequent treatment in metastatic disease<sup>155</sup>
- 1) Good performance status
    - a) Preferred
      - i. Pembrolizumab for tumors with MSI-H/dMMR or TMB-high
      - ii. Larotrectinib or entrectinib for *NTRK* gene fusions
    - b) Other recommended regimens
      - i. Dabrafenib + trametinib (*BRAF V600E* mutation)
      - ii. Selpercatinib (*RET* gene fusion-positive)
      - iii. Prior gemcitabine-based therapy
        - (a) 5-FU/leucovorin + liposomal irinotecan (category 1)
        - (b) FOLFIRI
        - (c) FOLFIRINOX/mFOLFIRINOX
        - (d) Fluoropyrimidine + oxaliplatin (OFF, FOLFOX, or CAPEOX)

- (e) Capecitabine or continuous infusion 5-FU
- iv. Prior fluoropyrimidine-based therapy
  - (a) Gemcitabine
  - (b) Gemcitabine + nab-paclitaxel
  - (c) Gemcitabine + cisplatin (only for *BRCA 1/2* or *PALB2* mutations)
  - (d) Gemcitabine + erlotinib
  - (e) 5-FU + liposomal irinotecan (if no previous irinotecan)
  - (f) Gemcitabine + nab-paclitaxel + cisplatin (category 2B)
- c) Chemoradiation if not given previously, and only if patients have locally advanced disease that progressed in the primary site, or for select patients with recurrent disease in combination with systemic therapy
- 2) Poor performance status
  - a) Preferred
    - i. Pembrolizumab for tumors with MSI-H/dMMR or TMB-high
    - ii. Larotrectinib or entrectinib for *NTRK* gene fusions
  - b) Other
    - i. Gemcitabine (category 1)
    - ii. FDR gemcitabine (category 2B)
    - iii. Capecitabine or continuous infusion 5-FU (both category 2B)
    - iv. Dabrafenib + trametinib (*BRAF V600E* mutation)
- e. ASCO Guidelines recommendations for subsequent treatment of metastatic disease<sup>176</sup>
  - 1) Targeted treatments
    - a) Pembrolizumab for MSI-H/dMMR only
    - b) Larotrectinib or entrectinib for *NTRK* fusions only
  - 2) Good performance status (ECOG 0-1), relatively favorable comorbidity profile, patient preference, support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services
    - a) First-line gemcitabine + nab-paclitaxel, then:
      - i. 5-FU + liposomal irinotecan OR FOLFIRI (either preferred)
      - ii. 5-FU + oxaliplatin may be considered
    - b) First-line FOLFIRINOX/mFOLFIRINOX, then:
      - i. Gemcitabine + nab-paclitaxel can be offered
  - 3) ECOG PS 2 or comorbidity profile that precludes more aggressive treatment

- a) Gemcitabine
  - i. Can consider adding nab-paclitaxel with proactive dose and schedule adjustments to minimize toxicities
- b) 5-FU
  - i. Can consider adding liposomal irinotecan with proactive dose and schedule adjustments to minimize toxicities
- 4) Clinical trial is encouraged for third-line or greater

**Patient Case #5, continued (ARS question #7):**

**The correct answer is C.** Due to his *BRCA2* mutation and good performance status, TS should be offered gemcitabine + cisplatin.

Answer A would be considered if TS had a poor performance status and was otherwise ineligible for cisplatin

Answer B is incorrect due to TS's extra-pancreatic sites of disease. Radiation could be considered for TS if he was experiencing pain or obstruction from his tumor.

Answer D would not be considered at this time due to TS's good performance status and ability to receive further treatment

**IV. Supportive care<sup>155,176</sup>**

- A. Palliative care focusing on symptom relief and quality of life is an important adjunct in the management of pancreatic cancer
  - 1. Even patients with resectable disease who undergo appropriate treatment only have median survivals of 20.1 to 23.6 months
- B. Biliary obstruction
  - 1. Approximately 65-75% of patients will develop symptomatic biliary obstruction
  - 2. Biliary decompression (should be resolved prior to initiation of chemotherapy or chemoradiation)
    - a. Endoscopic biliary stent (preferred)
    - b. Percutaneous biliary drainage catheter
    - c. Surgical biliary bypass
- C. Gastric outlet obstruction
  - 1. Symptomatic gastric outlet obstruction occurs in 10-25% of patients
  - 2. Good performance status
    - a. Surgical intervention (gastrojejunostomy)
    - b. Consider enteral stent
  - 3. Poor performance status or short life expectancy
    - a. Enteral sent



- b. Venting percutaneous endoscopic gastrostomy (PEG) tube for gastric decompression
- D. Pain<sup>176</sup>
  - 1. Most patients with pancreatic cancer develop cancer-related pain
    - a. Advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen
  - 2. Pharmacologic approaches
    - a. Systemic narcotics
      - 1) Long- and short-acting formulations often used together
      - 2) Oral, sublingual, buccal, rectal, subcutaneous, IV, and/or topical administration forms should all be considered options
    - b. Adjunctive therapies (non-steroidal agents, neuropathic agents, steroids)
    - c. Topical analgesics
  - 3. Invasive techniques should be considered for patients who may be unresponsive to narcotics or those who develop undesirable side effects<sup>194</sup>
    - a. Intrathecal pumps
    - b. Nerve blocks (celiac plexus neurolysis)
    - c. Epidural pumps
    - d. Palliative radiation with or without chemotherapy
- E. Depression and anxiety
  - 1. Screen and evaluate all patients and refer to specialists if needed
    - a. Suicide rates in male pancreatic cancer patients are 11 times higher than in the general population
  - 2. Encourage discussion about the natural history of the disease and provide support through the primary oncology team and specialists
  - 3. Pharmacologic interventions may be necessary and can be helpful
- F. Pancreatic enzyme insufficiency<sup>195,196</sup>
  - 1. Patients with pancreatic cancer will have some degree of fat malabsorption due to pancreatic exocrine insufficiency
  - 2. Up to 94% of patients undergoing pancreatic surgery may experience enzyme insufficiency
  - 3. Develops due to loss of pancreatic parenchyma, obstruction of main pancreatic duct, decreased pancreatic stimulation, or acid mediated inactivation of pancreatic enzymes
  - 4. Signs and symptoms
    - a. Weight loss (malnutrition)
    - b. Epigastric discomfort, abdominal distention
    - c. Flatulence, steatorrhea, malodorous stools

## 5. Management

### a. Diet<sup>195</sup>

- 1) Fat restriction should not be considered, as it may lead to insufficient intake of fat-soluble vitamins
- 2) Frequent, low volume meals
- 3) Avoidance of foods difficult to digest
- 4) Consider addition of fat-soluble vitamin supplementation

### b. Exogenous pancreatic enzymes<sup>155,195</sup>

- 1) Goal is to relieve symptoms and achieve normal nutritional status
  - a) Insufficiency has been reported in up to 94% patients who underwent pancreatic surgery
- 2) Dose is based on lipase units and titrated based on clinical symptoms, degree of steatorrhea and the fat content of the diet
  - a) Starting dose can be weight-based (500 lipase units/kg/meal or 1,000 units lipase/kg/day, rounded to the closest dosage form) or flat dose (25,000–75,000 units of lipase for a main meal). Half of the prescribed dose should be given with each snack.
  - b) The maximum recommended dose is 10,000 lipase units/kg/day
- 3) Efficacy appears to be higher when enzymes are administered either portioned along with meals or after completion of meals compared to before meals
  - a) NCCN Guidelines® recommends administering half the dose at the beginning of the meal, and half the dose in the middle of the meal<sup>155</sup>
- 4) Several pancrelipase products are commercially available; however, products are not interchangeable
  - a) All products contain a combination of lipase, protease, and amylase in various ratios
- 5) Insufficient response
  - a) Confirm compliance and proper use
  - b) Increase enzyme dose
  - c) H2-antagonists or proton pump inhibitors (PPI) may improve efficacy of enzymes by increasing gastric pH and decreasing acid in duodenum where enzymes are absorbed
  - d) Assess for bacterial overgrowth
  - e) Consider a more thorough nutritional evaluation

## G. Thromboembolic disease

### 1. Prophylaxis

- a. Pancreatic cancer patients are at a substantial risk for venous thromboembolic disease
- b. Avoid medications known to increase thromboembolic events, if possible

- c. The International Initiative on Thrombosis and Cancer (ITAC) updated their guidelines in 2022 to include new recommendations for prophylaxis in pancreatic cancer patients<sup>197</sup>
  - 1) The guidelines recommend primary pharmacological VTE prophylaxis in ambulatory patients with locally advanced or metastatic pancreatic cancer undergoing treatment with systemic anticancer therapy and who have a low risk of bleeding
  - 2) Preference is for subcutaneous low-molecular weight heparins, but direct oral anticoagulants are acceptable
- d. The NCCN® panel does not yet recommend prophylactic anticoagulation<sup>155</sup>
- 2. Treatment
  - a. Based on results of the CLOT and CONKO-004 trials, low-molecular weight heparins are the preferred therapy over warfarin<sup>198,199</sup>
  - b. The NCCN® panel does not address the use of direct-acting oral anticoagulants at this time<sup>155</sup>
- H. GI bleeding
  - 1. Although rare, GI bleeding or bleeding from the primary tumor site carries a serious prognosis
  - 2. Management is based on cause/location of bleeding and patient-specific characteristics
    - a. Options include:
      - 1) Endoscopic techniques
      - 2) Radiation
      - 3) Angiography with embolization for upper GI sources

## **V. Survivorship issues and long-term follow-up**<sup>155</sup>

- A. Surveillance following curative intent therapy
  - 1. Local recurrence after surgery alone for non-metastatic disease occurs in 85% of patients
    - a. Liver metastases are most common, occurring in 50-70% of the patients after potentially curative resection followed by adjuvant chemo-radiotherapy
  - 2. History and physical exam, CA 19-9 (category 2B), and CT scan of chest, abdomen, and pelvis (MRI of abdomen and pelvis alternative option) should be performed every 3-6 months for 2 years, then every 6-12 months as clinically indicated
- B. CA 19-9<sup>155</sup>
  - 1. Tumor associated antigen
  - 2. Not specific for pancreatic cancer; levels can be elevated in other GI cancers
    - a. Can help differentiate between benign disease and pancreatic cancer
    - b. May also be elevated in the presence of biliary inflammation, obstruction, or infection, thus accurate levels may only be obtained after total bilirubin has returned to normal limits
  - 3. Frequently normal in the early stages of pancreatic cancer so it is not suitable for screening

4. Useful in patients with suspected pancreatic cancer when accompanied by other tests and in follow-up during and after treatment
- C. Extremely poor prognosis overall<sup>176,200</sup>
1. Only 11.5% of all patients are alive at five years after diagnosis
  2. Supportive care (see above) should be incorporated into survivorship care

## ANAL CANCER

### Patient Case #6:

VP is a 64-year-old female with HIV since 1996 on HAART therapy who presents with increasing discomfort with defecation over the past two months. A sigmoidoscopy demonstrated a firm, fixed obstructing rectal mass 3 cm from the anal verge. This was biopsied and found to be consistent with a squamous cell carcinoma. She has no evidence of metastatic disease.

**Which of the following treatment options is most appropriate for VP's localized anal cancer?**

- A. Abdominoperineal resection with permanent colostomy
- B. Radiation alone
- C. Chemoradiation with 5-FU and mitomycin
- D. Chemoradiation with 5-FU and cisplatin

### I. Prevention and screening<sup>201-204</sup>

#### A. Risk Factors

1. Human papilloma virus (HPV) infection
  - a. Estimates are that 84-97% of anal cancer cases can be attributed to HPV<sup>201</sup>
  - b. Persistent infection with high-risk subtypes or infection with multiple HPV genotypes increases risks
    - 1) Over 80 different HPV subtypes, at least 23 of which infect the anogenital mucosa
    - 2) HPV-16 and -18 associated with approximately 72-73% of HPV-positive cases
2. HIV infection
  - a. Difficult to fully separate from confounders (anoreceptive intercourse, men who have sex with men)
  - b. Population-based study demonstrated that incidence relatively similar before the introduction of HAART therapy (0.8 per 100,000) versus after the introduction of HAART therapy (1.0 per 100,000)
    - 1) Reflects the lack of impact of HAART on anal cancer precursors
3. Immunosuppression
  - a. After solid organ transplantation, patients at higher risk for any squamous cell carcinoma
  - b. Corticosteroid use shown to increase risk in both men (OR, 3.2) and women (OR, 2.3)
4. Cigarette smoking
  - a. Risk increases for current smokers vs former smokers for both men (OR, 3.9; 95% CI 1.9-8.0 vs OR, 0.9; 95% CI 0.4-1.9) and women (OR, 3.8; 95% CI 2.3-6.2 vs OR, 1.5; 95% CI 0.9-2.6) regardless of age and other risk factors
  - b. Current smoking appears to have a promotional effect at late stages of disease progression

5. History of receptive anal intercourse
  - a. Men who are not exclusively heterosexual have increased risk vs men who are (OR, 17.3; 95% CI, 8.2 – 36.1)
  - b. Women who reported anoreceptive intercourse at higher risk (overall adjusted OR, 2.2; 95% CI 1.4 – 3.3)
- B. Routine screening for anal cancer not recommended, even in high-risk individuals
- C. Prevention: HPV immunization
  1. The quadrivalent vaccine (active against HPV-6, -11, -16, -18) has been shown to reduce the occurrence of anal intraepithelial neoplasia (AIN) vs placebo in men who have sex with men (16 to 26 years of age) with an observed efficacy of 77.5% (95% CI, 39.6 – 93.3)<sup>205</sup>
    - a. The vaccine also reduced persistent infection with HPV-6,- 11, -16, or -18 with an observed efficacy of 59.4%
    - b. High-grade AIN believed to be precursor to anal cancer
      - 1) Although no anal cancers developed in either group during the 3-year observation period, it is believed that the reduction in the rates of AIN could lead to a reduction in the rates of anal cancer in this population
    - c. The quadrivalent vaccine is no longer available in the United States
  2. The 9-valent vaccine (active against HPV-6, -11, -16, -18, -31, -33, -45, -52, -58) is the only HPV vaccine available in the United States
    - a. Although the 9-valent vaccine has no published data regarding prevention of AIN and/or anal cancer, it is predicted to prevent 464 cases of anal cancer annually<sup>201</sup>
  3. The Advisory Committee on Immunization Practices (ACIP)<sup>206</sup> and the American Cancer Society (ACS)<sup>207</sup> both support HPV vaccination for males and females aged 9 through 26 years
    - a. Although the 9-valent vaccine is FDA-approved for adults aged up to 45 years, the ACIP does not recommend “catch-up” vaccination for adults aged 27 to 45, but rather recommends shared clinical decision making with those who are not adequately vaccinated
    - b. ACS does not recommend vaccination for adults over 26 years of age

## II. Treatment and symptom management

- A. Treatment modalities focus on radiation and chemotherapy<sup>201</sup>
  1. Historically, primary treatment was abdominoperineal resection (APR)
    - a. High local recurrence rates (40-70%)
    - b. High morbidity (requires removal of anorectum, necessitating a permanent colostomy)
  2. Refer to the NCCN Guidelines® for Anal Carcinoma for the most up-to-date recommendations on dosing and schedules of chemoradiation and chemotherapy regimens<sup>201</sup>
- B. TNM staging does exist, but treatment decisions are made based on clinical staging and do not usually involve surgery

C. Treatment of localized anal carcinoma<sup>201</sup>

1. Chemoradiation with 5-FU + mitomycin (aka Nigro protocol<sup>208</sup>)

- a. Nigro and colleagues were the first to show complete tumor regression in some patients treated with neoadjuvant chemoradiation
  - 1) Of the 28 patients included in trial, 24 patients had no gross tumor in the anal canal following treatment and were able to avoid APR
- b. Further trials have compared 5-FU plus mitomycin with concurrent radiotherapy vs radiotherapy alone<sup>209-211</sup>
  - 1) The addition of chemotherapy to radiation improved complete remission rates, reduced locoregional recurrence, and decreased risk of having a colostomy, however have not shown statistically significant increase in OS
- c. These trials affirmed that the standard of care for non-metastatic anal cancer should be chemotherapy regimen of 5-FU and mitomycin concurrent with radiotherapy
  - 1) 5-FU CIVI 1000 mg/m<sup>2</sup>/day Days 1-4 & 29-32
  - 2) Mitomycin 10 mg/m<sup>2</sup> IV Days 1 & 29 **OR** 12 mg/m<sup>2</sup> Day 1
    - a) Capped at 20 mg

2. Chemoradiation with capecitabine + mitomycin

- a. Capecitabine known to be an acceptable alternative to 5-FU in colon and rectal cancer data
- b. EXTRA (prospective, phase II)<sup>212</sup>
  - 1) Capecitabine 825 mg/m<sup>2</sup> BID on days of radiation only (Monday through Friday), with mitomycin on day 1, had expected toxicities of severe moist skin desquamation, diarrhea, and myelosuppression
  - 2) Local control at the timing endpoint of 6 months was seen in 28 patients (90%)
- c. Retrospective data have found lower toxicities with capecitabine-based chemoradiation<sup>213</sup> and no significant differences in clinical complete response or longer term outcomes when compared with 5-FU-based chemoradiation<sup>214</sup>
- d. The NCCN Guidelines® consider capecitabine an acceptable substitute for 5-FU<sup>201</sup>

3. Chemoradiation with 5-FU + cisplatin

- a. Intergroup RTOG 98-11<sup>215</sup> compared 5-FU + mitomycin against 5-FU + cisplatin both with concurrent radiotherapy
- b. Although not statistically significant, trends favored the mitomycin group in local-regional relapse, disease-free survival, and OS
- c. Colostomy rates were significantly increased in the cisplatin group at 3 and 5 years (p=0.02)
- d. Authors concluded cisplatin-based chemoradiation should generally be avoided for patients with localized anal cancer unless they are unable to tolerate mitomycin

4. Summary<sup>201</sup>

- a. Surgery plays a minimal role in localized disease; the preferred primary treatment is chemotherapy with radiation
  - 1) Depending on size of tumor, radiation given in 28-30 fractions
- b. Preferred regimens
  - 1) 5-FU + mitomycin + radiation
  - 2) Capecitabine + mitomycin + radiation
- c. Other regimen
  - 1) 5-FU + cisplatin + radiation (category 2B)

**Patient Case #6:**

**The correct answer is C.** Chemoradiation with 5-FU and mitomycin (or capecitabine in place of 5-FU) is the preferred first-line treatment for localized anal cancer

Answer A is not appropriate because APR is not recommended for first-line therapy of anal cancer due to long-term morbidity complications and high local recurrence rates

Answer B is not appropriate because the addition of chemotherapy to radiation has been shown to improve complete remission rates, reduce locoregional recurrence, and decrease risk of having a colostomy compared to radiation alone

Answer D is not appropriate because chemoradiation with 5-FU and cisplatin has been shown to have non-superior outcomes and increased colostomies compared to 5-FU and mitomycin. In addition, it is only a Category 2B recommendation from NCCN®.<sup>201</sup>

- D. Treatment of locally progressive or recurrent anal cancer<sup>201</sup>
  - 1. Locoregional failure rates are 10-30%
  - 2. Higher recurrence rates associated with tumor size >5cm, male sex, and positive local lymph nodes
  - 3. Patients who develop locally progressive disease should undergo APR
  - 4. Depending on site of recurrence and previous treatment, patients may have to undergo APR or be eligible for further radiation and/or chemotherapy
- E. Treatment of metastatic anal cancer<sup>201,216</sup>
  - 1. Because of the rarity of metastatic anal cancer, there are limited data on treatment
    - a. Extrapelvic, metastatic disease only seen in 10-20% of patients
  - 2. Enrollment on a clinical trial is encouraged
  - 3. First-line treatment
    - a. InterAACT trial randomized patients to receive 5-FU + cisplatin or carboplatin + paclitaxel<sup>217</sup>
      - 1) Response rates were similar between the two regimens (57.1% with cisplatin + 5-FU compared to 59% with carboplatin + paclitaxel)



- 2) Median PFS was numerically longer for carboplatin + paclitaxel at 8.1 months compared to 5.7 months for cisplatin + 5-FU, although not significant ( $p = 0.375$ ). However median OS was significantly higher with carboplatin + paclitaxel at 20 months vs 12.3 months with cisplatin + 5-FU (HR 2.0;  $p = 0.014$ ).
- 3) In addition, serious adverse events were significantly lower in the carboplatin + paclitaxel group vs the cisplatin + 5-FU group (36% vs 62%,  $p=0.016$ )
- 4) The NCCN Panel<sup>®</sup> acknowledges carboplatin + paclitaxel as the preferred first-line regimen, but also accepts cisplatin + 5-FU as a first-line regimen based on this trial<sup>201</sup>
- b. FOLFOX can be considered for patients, although inclusion in the guidelines is based on a case report and panel consensus<sup>201</sup>
- c. The FOLFICIS regimen utilizes 5-FU/leucovorin and cisplatin, and was shown to be safe and effective at a single institution
  - 1) A response rate of 48% (95% CI, 32.6%-63%) was documented, with PFS of 7.1 months (95% CI, 4.4-8.6 months) and OS of 22.1 months (95% CI, 16.9-28.1 months)<sup>218</sup>
- d. NCCN Guidelines<sup>®</sup> recommendations for metastatic disease<sup>201</sup>
  - 1) Preferred: Carboplatin + paclitaxel (various dosing strategies)
  - 2) Other regimens
    - a) 5-FU + cisplatin (various dosing strategies)
    - b) FOLFICIS
    - c) FOLFOX
    - d) Modified docetaxel, cisplatin, 5-FU (DCF)
4. Subsequent treatment<sup>201</sup>
  - a. Nivolumab or pembrolizumab are preferred options, if not previously received
    - 1) MSI and/or PD-L1 testing is not required
    - 2) Nivolumab was studied in patients regardless of PD -L1 status<sup>219</sup>, however pembrolizumab was studied only in patients who were PD-L1 positive (PD-L1  $\geq 1\%$ )<sup>220</sup>
  - b. If patients progress on a platinum-based regimen in the first-line, they should not be given a platinum-based regimen in the second-line setting

### III. Supportive care

- A. Toxicity from chemoradiation<sup>201,221</sup>
  1. Acute toxicities include anoproctitis, perineal dermatitis, moist desquamation, pain, fatigue, genitourinary complications, and diarrhea
    - a. Grade 3/4 skin toxicity reported in >80% patients
  2. Long-term toxicities include increased frequency and urgency of defecation, chronic perineal dermatitis, dyspareunia, impotence, infertility, and bone injury
  3. If relevant, patients should discuss fertility issues with their oncologist

- B. Skin toxicity from radiation<sup>222</sup>
  - 1. Radiation dermatitis can appear as red, irritated, swollen, blistered, or sunburned
  - 2. Patients should be advised to care for the area by avoiding tight clothes that may rub or irritate the area
  - 3. Cleaning the area may be difficult; patients should use lukewarm water and mild soap without perfumes or dyes
- C. Diarrhea management (see diarrhea management in Colon and Rectal Cancer Supportive Care)

#### **IV. Survivorship issues and long-term follow-up**

- A. Development of metastatic disease seems to be highest within first 2 years after treatment for locally advanced disease<sup>216</sup>
- B. Follow-up after treatment for non-metastatic disease<sup>201</sup>
  - 1. Patients should be re-evaluated by digital rectal exam (DRE) between 8 to 12 weeks after completion of chemoradiation
    - a. About 1/3 of patients who do not show a complete response by this time may take up to 26 weeks or longer to achieve a complete clinical response
  - 2. If clinical evidence of disease is absent, patients are recommended to undergo:
    - a. DRE and inguinal node palpation every 3 – 6 months for 5 years
    - b. Anoscopic evaluation every 6 – 12 months for 3 years
    - c. CT scan of chest, abdomen, and pelvis (MRI of abdomen and pelvis alternative) annually for 3 years
  - 3. For patients with persistent disease, it is recommended to re-evaluate in 4 weeks. For tumor regression or no progression, patients can be re-evaluated every 3 months. If they achieve remission, patients can undergo surveillance as above for absence of disease. If patients ever show progression at any point, a biopsy should be obtained and the patient treated accordingly.
- C. Long-term side effects from treatment affects quality of life<sup>221,223,224</sup>
  - 1. Long-term effects can persist for years after treatment
  - 2. Avoidance of APR and permanent colostomy is the main reason for definitive chemoradiation
  - 3. Bowel dysfunction (diarrhea, fecal incontinence, flatulence) and sexual dysfunction (impotence, dyspareunia) are the most commonly reported issues after chemoradiation in quality of life literature
  - 4. Sexual dysfunction<sup>152</sup>
    - a. Patients should be referred to a sexual health specialist if interested
    - b. Patients with global symptoms of distress may benefit from anxiolytics or antidepressants
    - c. Females with vaginal dryness or other issues may benefit from topical therapies (vaginal moisturizers/lubricants, topical hormones, topical anesthetics)
    - d. Males with impotence may benefit from oral phosphodiesterase type 5 inhibitors

## RECOMMENDED READINGS

### Colon and Rectal Cancer

1. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;68(4):250-281. (<https://pubmed.ncbi.nlm.nih.gov/29846947/>)
2. Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal Cancer. *Lancet*. 2019; 394: 1467–80. (<https://pubmed.ncbi.nlm.nih.gov/31631858/>)
3. Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduct Target Ther*. 2020;5(1):22. (<https://pubmed.ncbi.nlm.nih.gov/32296018/>)
4. Schlechter BL. Management of Rectal Cancer. *Hematol Oncol Clin N Am*. 2022;36:521–537. (<https://pubmed.ncbi.nlm.nih.gov/35577705/>)

### Pancreatic Cancer

1. Khorana AA, McKernin SE, Berlin J, et al. Potentially Curable Pancreatic Adenocarcinoma: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2019;37:DOI <https://doi.org/10.1200/JCO.2019.00946>.
2. Sohal DPS, Kennedy EB, Cinar P. Metastatic Pancreatic Cancer: ASCO Guideline Update. *J Clin Oncol*. 2020;38:DOI: 10.1200/JCO.20.01364.
3. Conroy T, Hammel P, Hebbar M et al. Folfirinox or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018; 379: 2395-406. (<https://www.ncbi.nlm.nih.gov/pubmed/30575490>)

### Anal Cancer

1. Eng C, Ciombor KK, Cho M, et al. Anal Cancer: Emerging Standards in a Rare Disease. *J Clin Oncol*. 2022;40(24):2774-2788. (<https://pubmed.ncbi.nlm.nih.gov/35649196/>)
2. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA*. 2008;299(16):1914-21. (<https://www.ncbi.nlm.nih.gov/pubmed/18430910>)

## REFERENCES

1. Libutti SK, Saltz L, Willett C, Levine RA. Cancer of the Colon. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2019:chap 62.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer. V.2.2022, 10/27/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
3. Calvert PM, Frucht H. The genetics of colorectal cancer. *Ann Intern Med*. 2002;137:603-612.
4. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor Microsatellite-Instability Status as a Predictor of Benefit from Fluorouracil-Based Adjuvant Chemotherapy for Colon Cancer. *N Engl J Med*. 2003;349(3):247-257. doi:10.1056/NEJMoa022289
5. Sargent DJ, Marsoni S, Monges G, et al. Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer. *J Clin Oncol*. 2010;28(20):3219-3226. doi:10.1200/jco.2009.27.1825

6. Sinicrope FA, Foster NR, Thibodeau SN, et al. DNA Mismatch Repair Status and Colon Cancer Recurrence and Survival in Clinical Trials of 5-Fluorouracil-Based Adjuvant Therapy. *J Natl Cancer Inst.* June 8, 2011 2011;103(11):863-875. doi:10.1093/jnci/djr153
7. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 2015;372:2509-20.
8. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer. *J Clin Oncol.* 2018;36(8):773-779.
9. Overman MJ, Lonardi S, Leone F, et al. Nivolumab in patients with DNA mismatch repair deficient/microsatellite instability high metastatic colorectal cancer: Update from CheckMate 142. *J Clin Oncol.* 2017;35(no. 4\_suppl (February 2017)):519.
10. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol.* 2017;18:1182-91.
11. André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med.* 12 2020;383(23):2207-2218. doi:10.1056/NEJMoa2017699
12. Diaz LA, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol.* 05 2022;23(5):659-670. doi:10.1016/S1470-2045(22)00197-8
13. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. *J Clin Oncol.* 01 10 2022;40(2):161-170. doi:10.1200/JCO.21.01015
14. André T, Berton D, Curigliano G, et al. Safety and efficacy of anti-PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Results from GARNET study. *J Clin Oncol.* 2021;DOI: 10.1200/JCO.2021.39.3\_suppl.9
15. Morel A, Boisdron-Celle M, Fey L, et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. *Mol Cancer Ther.* 2006;5(11):2895-904.
16. van Kuilenburg ABP. Dihydropyrimidine dehydrogenase and the efficacy and toxicity of 5-fluorouracil. *Eur J Cancer.* 2004;40:939-950.
17. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther.* 2017;00
18. Ma WW, Saif MW, El-Rayes BF, et al. Emergency Use of Uridine Triacetate for the Prevention and Treatment of Life-Threatening 5-Fluorouracil and Capecitabine Toxicity. *Cancer.* 2017;123:345-56.
19. Vistogard® (uridine triacetate) oral granules. Prescribing Information. Wellstat Therapeutics Corporation, Rockville, MD. Revised:2/2017.
20. Pizzolato JF, Saltz LB. The camptothecins. *Lancet.* 2003;361:2235-42.
21. Wallace BD, Wang H, Lane KT, et al. Alleviating Cancer Drug Toxicity by Inhibiting a Bacterial Enzyme. *Science.* 2010;330(6005):831-835.
22. Hoskins J, Goldberg R, Qu P, Ibrahim J, McLeod H. UGT1A1\*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst.* 2017;99(17):1290-5.
23. Irinotecan hydrochloride. Prescribing Information. Cipla Ltd., Verna Goa, India. Revised:11/2015.
24. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer. *N Engl J Med.* 2008;359(17):1757-1765. doi:doi:10.1056/NEJMoa0804385
25. Amado RG, Wolf M, Peeters M, et al. Wild-Type KRAS Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer. *J Clin Oncol.* April 1, 2008 2008;26(10):1626-1634. doi:10.1200/jco.2007.14.7116
26. Jimeno A, Messersmith WA, Hirsch FR, Franklin WA, Eckhardt SG. KRAS Mutations and Sensitivity to Epidermal Growth Factor Receptor Inhibitors in Colorectal Cancer: Practical Application of Patient Selection. *J Clin Oncol.* March 1, 2009 2009;27(7):1130-1136. doi:10.1200/jco.2008.19.8168
27. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-Type BRAF Is Required for Response to Panitumumab or Cetuximab in Metastatic Colorectal Cancer. *J Clin Oncol.* December 10, 2008 2008;26(35):5705-5712. doi:10.1200/jco.2008.18.0786

28. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. *J Clin Oncol*. 2017;35(13):1453-86.
29. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer. V.3.2022, 10/27/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™ Surveys & Data, Powered by NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
30. Ursem C, Atreya CE, Loon KV. Emerging treatment options for BRAF-mutant colorectal cancer. *Gastrointest Cancer Res*. 2018;8:13-23.
31. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus Vitamin D Supplementation and the Risk of Colorectal Cancer. *N Engl J Med*. 2006;354(7):684-696. doi:doi:10.1056/NEJMoa055222
32. Park Y, Hunter DJ, Spiegelman D, Bergkvist L, Berrino F. Dietary fiber intake and risk of colorectal cancer. *JAMA*. 2005;294(22):2849-2857.
33. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs C. Long-term Use of Aspirin and Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Cancer. *JAMA*. 2005;294:914-23.
34. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the Prevention of Colorectal Adenomatous Polyps. *N Engl J Med*. 2006;355:885-95.
35. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the Prevention of Sporadic Colorectal Adenomas. *N Engl J Med*. 2006;355:873-84.
36. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.1.2022, 06/08/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™ Surveys & Data, Powered by NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
37. Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, Senger CA. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: An Evidence Update for the U.S. Preventive Services Task Force. 2022.
38. Steinbach G, Lynch PM, Phillips RKS, et al. The Effect of Celecoxib, a Cyclooxygenase-2 Inhibitor, in Familial Adenomatous Polyposis. *N Engl J Med*. 2000;342(26):1946-1952. doi:doi:10.1056/NEJM200006293422603
39. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colorectal Cancer Screening. V.3.2022, 09/30/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™ Surveys & Data, Powered by NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
40. Samadder NJ, Neklason DW, Boucher KM, et al. Effect of Sulindac and Erlotinib vs Placebo on Duodenal Neoplasia in Familial Adenomatous Polyposis A Randomized Clinical Trial. *JAMA*. 2016;315(12):1266-75.
41. American Cancer Society. American Cancer Society recommendations for colorectal cancer early detection. Updated 11/17/20. Accessed July 14, 2022. Available from: <http://www.cancer.org/cancer/colonandrectumcancer/moreinformation/colonandrectumcancerearlydetection/colorectal-cancer-early-detection-ac-s-recommendations>
42. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update From the American Cancer Society. *CA Cancer J Clin*. 2018;000:000-000.
43. U.S. Preventive Services Task Force. Final Recommendation Statement: Colorectal Cancer: Screening. Updated 5/18/21. Accessed July 14, 2022. Available from: <https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening>

44. Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol*. 2017;112:1016-30.
45. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2014;147:502-26.
46. Patel SG, May FP, Anderson JC, et al. Updates on Age to Start and Stop Colorectal Cancer Screening: Recommendations From the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol*. 01 01 2022;117(1):57-69. doi:10.14309/ajg.0000000000001548
47. Rockey DC, Paulson E, Niedzwiecki D, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. *Lancet*. 2005;365:305-11.
48. Delaunoy T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol*. March 1, 2005 2005;16(3):425-429. doi:10.1093/annonc/mdi092
49. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, Capecitabine, and Oxaliplatin As Neoadjuvant Therapy for Patients With Potentially Curable Metastatic Colorectal Cancer. *J Clin Oncol*. April 10, 2008 2008;26(11):1830-1835. doi:10.1200/jco.2007.13.7679
50. Wong R, Cunningham D, Barbachano Y, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. *Ann Oncol*. September 1, 2011 2011;22(9):2042-2048. doi:10.1093/annonc/mdq714
51. Nasti G, Piccirillo MC, Izzo F, et al. Neoadjuvant FOLFIRI+bevacizumab in patients with resectable liver metastases from colorectal cancer: a phase 2 trial. *Br J Cancer*. Apr 30 2013;108(8):1566-70. doi:10.1038/bjc.2013.140
52. Ye L-C, Liu T-S, Ren L, et al. Randomized Controlled Trial of Cetuximab Plus Chemotherapy for Patients With KRAS Wild-Type Unresectable Colorectal Liver-Limited Metastases. *J Clin Oncol*. June 1, 2013 2013;31(16):1931-1938. doi:10.1200/jco.2012.44.8308
53. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol*. May 2014;15(6):601-11. doi:10.1016/s1470-2045(14)70105-6
54. Folprecht G, Gruenberger T, Bechstein W, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann Oncol*. May 1, 2014 2014;25(5):1018-1025. doi:10.1093/annonc/mdu088
55. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as Adjuvant Treatment for Stage III Colon Cancer. *N Engl J Med*. 2005;352(26):2696-2704. doi:doi:10.1056/NEJMoa043116
56. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350:2343-51.
57. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. Jul 1 2009;27(19):3109-16. doi:10.1200/JCO.2008.20.6771
58. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*. Apr 10 2011;29(11):1465-71. doi:10.1200/JCO.2010.33.6297
59. Schmoll H-J, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial. *J Clin Oncol*. November 10, 2015 2015;33(32):3733-3740. doi:10.1200/jco.2015.60.9107
60. Benson AB, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol*. Aug 15 2004;22(16):3408-19. doi:10.1200/JCO.2004.05.063
61. Grothey A, Sobrero AF, Shields AF, et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. *N Engl J Med*. 2018;378(13):1177-88.
62. André T, Meyerhardt J, Iveson T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. *Lancet Oncol*. 12 2020;21(12):1620-1629. doi:10.1016/S1470-2045(20)30527-1
63. Lieu C, Kennedy EB, Bergsland E, et al. Duration of Oxaliplatin-Containing Adjuvant Therapy for Stage III Colon Cancer: ASCO Clinical Practice Guideline. *J Clin Oncol*. 2019;37:1436-47.
64. Bosset J-F, Calais G, Mineur L, et al. Enhanced Tumorocidal Effect of Chemotherapy With Preoperative Radiotherapy for Rectal Cancer: Preliminary Results—EORTC 22921. *J Clin Oncol*. 2005;23:5620-7.

65. Bosset J-Fo, Collette L, Calais G, et al. Chemotherapy with Preoperative Radiotherapy in Rectal Cancer. *N Engl J Med*. 2006;355:1114-23.
66. Hofheinz R-D, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol*. 2012;13:579-88.
67. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and Oxaliplatin in the Preoperative Multimodality Treatment of Rectal Cancer: Surgical End Points From National Surgical Adjuvant Breast and Bowel Project Trial R-04. *J Clin Oncol*. June 20, 2014 2014;32(18):1927-1934. doi:10.1200/jco.2013.53.7753
68. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or Capecitabine Plus Radiation With or Without Oxaliplatin in Rectal Cancer Patients: A Phase III Randomized Clinical Trial. *J Natl Cancer Inst*. 2015;107(11):djv248.
69. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 05 2021;22(5):702-715. doi:10.1016/S1470-2045(21)00079-6
70. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N Engl J Med*. 06 23 2022;386(25):2363-2376. doi:10.1056/NEJMoa2201445
71. Van Cutsem E, Twelves C, Cassidy J, et al. Oral Capecitabine Compared With Intravenous Fluorouracil Plus Leucovorin in Patients With Metastatic Colorectal Cancer: Results of a Large Phase III Study. *J Clin Oncol*. 2001;19(21):4097-4106.
72. de Gramont A, Figer A, Seymour M, et al. Leucovorin and Fluorouracil With or Without Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer. *J Clin Oncol*. August 16, 2000 2000;18(16):2938-2947.
73. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*. 2000;355:1041-47.
74. Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid Plus Oxaliplatin As First-Line Therapy for Metastatic Colorectal Cancer. *J Clin Oncol*. 2008;26(12):2006-2012. doi:10.1200/jco.2007.14.9898
75. Cassidy J, Clarke S, Diaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer*. 2011;105(1):58-64. doi:10.1038/bjc.2011.201
76. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25(13):1670-6. doi:10.1200/JCO.2006.09.0928
77. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22(2):229-37. doi:10.1200/JCO.2004.05.113
78. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. *J Clin Oncol*. April 20, 2008 2008;26(12):2013-2019. doi:10.1200/jco.2007.14.9930
79. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol*. 2008;26(21):3523-9. doi:10.1200/JCO.2007.15.4138
80. Fuchs CS, Marshall J, Barrueco J. Randomized, Controlled Trial of Irinotecan Plus Infusional, Bolus, or Oral Fluoropyrimidines in First-Line Treatment of Metastatic Colorectal Cancer: Updated Results From the BICC-C Study. *J Clin Oncol*. 2008;26(4):689-90.
81. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, Controlled Trial of Irinotecan Plus Infusional, Bolus, or Oral Fluoropyrimidines in First-Line Treatment of Metastatic Colorectal Cancer: Results From the BICC-C Study. *J Clin Oncol*. 2007;25(30):4779-4786. doi:10.1200/jco.2007.11.3357
82. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med*. Oct 23 2014;371(17):1609-18. doi:10.1056/NEJMoa1403108
83. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16:1306-15.
84. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet*. 2011;377:2103-14.

85. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol*. 2014;25(7):1346-1355. doi:10.1093/annonc/mdu141
86. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-705. doi:10.1200/JCO.2009.27.4860
87. Van Cutsem E, Köhne C-H, Hitre E, et al. Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. *N Engl J Med*. 2009;360(14):1408-1417. doi:doi:10.1056/NEJMoa0805019
88. Moretto R, Cremolini C, Rossini D, et al. Location of Primary Tumor and Benefit From Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies in Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer. *The Oncologist*. 2016;21:988-994.
89. Brulé SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer*. 2015;51:1405-1414.
90. Lee MS, Advani SM, Morris Jr, et al. Association of primary (1°) site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (αEGFR) therapy. *J Clin Oncol*. 2016;34(no. 15\_suppl (May 2016)):3506.
91. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1o) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol*. 2016;34(no. 15\_suppl (May 2016)):3504.
92. Yoshino T, Watanabe J, Shitara K, et al. Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. *J Clin Oncol*. 2022;DOI: 10.1200/JCO.2022.40.17\_suppl.LBA1 Journal of Clinical Oncology 40, no. 17\_suppl (June 10, 2022) LBA1-LBA1.
93. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2013;14:29-37.
94. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen. *J Clin Oncol*. 2012;30(28):3499-3506. doi:10.1200/jco.2012.42.8201
95. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16(5):499-508.
96. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: Phase III Trial of Cetuximab Plus Irinotecan After Fluoropyrimidine and Oxaliplatin Failure in Patients With Metastatic Colorectal Cancer. *J Clin Oncol*. 2008;26(14):2311-2319. doi:10.1200/jco.2007.13.1193
97. Peeters M, Price TJ, Cervantes A, et al. Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second-Line Treatment in Patients With Metastatic Colorectal Cancer. *J Clin Oncol*. 2010;28(31):4706-4713. doi:10.1200/jco.2009.27.6055
98. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the Treatment of Colorectal Cancer. *N Engl J Med*. 2007;357(20):2040-2048. doi:doi:10.1056/NEJMoa071834
99. Van Cutsem E, Peeters M, Siena S, et al. Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer. *J Clin Oncol*. 2007;25(13):1658-1664. doi:10.1200/jco.2006.08.1620
100. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer. *N Engl J Med*. 2019;381:1632-43.
101. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:738-46.
102. Meric-Bernstam F, Hurwitz H, Raghav KPS, McWilliams RR, Fakih M, VanderWalde A. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2019;20:518-30.



103. Siena S, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2021;22(6):779-789. doi:10.1016/S1470-2045(21)00086-3
104. Yoshino T, Bartolomeo MD, Raghav KPS, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): Final results from a phase 2, multicenter, open-label study (DESTINY-CRC01). *J Clin Oncol.* 2022;DOI: 10.1200/JCO.2022.40.4\_suppl.119 Journal of Clinical Oncology 40, no. 4\_suppl (February 01, 2022) 119-119.
105. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381:303-12.
106. Bekaii-Saab TS, Ou F-S, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): Randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC) An ACCRU Network study. *J Clin Oncol.* 2018;36:DOI: 10.1200/JCO.2018.36.4\_suppl.611
107. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.* 2015;372(20):1909-19. doi:10.1056/NEJMoa1414325
108. Pfeiffer P, Yilmaz M, Möller S, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2020;21(3):412-420. doi:10.1016/S1470-2045(19)30827-7
109. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD. Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. *N Engl J Med.* 2018;378:731-9.
110. Vauthey J-N, Pawlik TM, Ribero D, et al. Chemotherapy Regimen Predicts Steatohepatitis and an Increase in 90-Day Mortality After Surgery for Hepatic Colorectal Metastases. *J Clin Oncol.* 2006;24(13):2065-2072. doi:10.1200/jco.2005.05.3074
111. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol.* 2010;11:38-47.
112. Petrelli F, Barni S. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. *Int J Colorectal Dis.* 2012;27:997-1004.
113. Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. *Ther Adv Med Oncol.* 2010;2(1):51-63.
114. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Pract.* 2007;13:181-198.
115. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. National Institutes of Health, National Cancer Institute. Updated 11/27/17. Accessed July 14, 2022. Available from: [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_8.5x11.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)
116. Benson AB, Ajani JA, Catalano RB, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea. *J Clin Oncol.* 2004;22(14):2918-2926.
117. Saliba F, Hagipantelli R, Misset J-L, et al. Pathophysiology and Therapy of Irinotecan-Induced Delayed-Onset Diarrhea in Patients With Advanced Colorectal Cancer: A Prospective Assessment. *J Clin Oncol.* 1998;16:2745-2751.
118. Abigeres D, Armand J-P, Chabot GG, et al. Irinotecan (CPT-11) High-Dose Escalation Using Intensive High-Dose Loperamide to Control Diarrhea. *J Natl Cancer Inst.* 1994;86(6):446-9.
119. Rothenberg ML, Eckardt JR, Kuhn JG, et al. Phase II Trial of Irinotecan in Patients With Progressive or Rapidly Recurrent Colorectal Cancer. *J Clin Oncol.* 1996;14:1128-35.
120. Gobel BH. Hypersensitivity Reactions to Biological Drugs. *Semin Oncol Nurs.* 2007;23(3):191-200.
121. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist.* 2007;12(5):601-9. doi:10.1634/theoncologist.12-5-601
122. Syrigou EA, Makrilla NA, Koti LA, Saif MW, Syrigos K. Hypersensitivity reactions to antineoplastic agents: an overview. *Anticancer Drugs.* 2009;20(1):1-6.
123. Kang S, Saif MW. Infusion-related and hypersensitivity reactions of monoclonal antibodies used to treat colorectal cancer—identification, prevention, and management. *J Support Oncol.* 2007;5(9):451-7.
124. Kingsley CD. Hypersensitivity Reactions. In: Perry MC, Doll DC, Freter CE, eds. *Perry's The Chemotherapy Source Book*. 5th ed. Lippincott Williams & Wilkins; 2012:chap Chapter 15.

125. O'Neil BH, Allen R, Spigel DR, et al. High Incidence of Cetuximab-Related Infusion Reactions in Tennessee and North Carolina and the Association With Atopic History. *J Clin Oncol*. 2007;25(24):3644-3648.
126. George TJ, LaPlant KD, Walden EO, et al. Managing Cetuximab Hypersensitivity-Infusion Reactions: Incidence, Risk Factors, Prevention, and Retreatment. *J Support Oncol*. 2010;8:72-77.
127. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-Induced Peripheral Neuropathy: Prevention and Treatment. *Clin Pharmacol Ther*. 2011;90(3):377-387. doi:10.1038/clpt.2011.115
128. Cersosimo RJ. Oxaliplatin-associated neuropathy: A review. *Ann Pharmacother*. 2005;39(Jan):128-135.
129. Cavaletti G, Zanna C. Current status and future prospects for the treatment of chemotherapy-induced peripheral neurotoxicity. *Eur J Cancer*. 2002;38(14):1832-1837.
130. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): An update. *Crit Rev Oncol Hematol*. 2012;82(1):51-77. doi:10.1016/j.critrevonc.2011.04.012
131. Hoff P, Saad E, Costa F, et al. Literature review and practical aspects on the management of oxaliplatin-associated toxicity. *Clin Colorectal Cancer*. 2012;11(2):93-100.
132. Pachman DR, Qin R, Seisler DK, et al. Clinical Course of Oxaliplatin-Induced Neuropathy: Results From the Randomized Phase III Trial N08CB (Alliance). *J Clin Oncol*. 2015;33(30):3416-3422.
133. Gamelin L, Boisdron-Celle M, Delva R, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: A retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res*. 2004;10(12):4055-4061.
134. Tournigand C, Cervantes A, Figuer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer--a GERCOR study. *J Clin Oncol*. 2006;24(3):394-400. doi:10.1200/JCO.2005.03.0106
135. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity (N08CB/Alliance). *J Clin Oncol*. 2014;32(10):997-1005. doi:10.1200/jco.2013.52.0536
136. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2014;32(18):1941-1967. doi:10.1200/jco.2013.54.0914
137. Payne AS, James WD, Weiss RB. Dermatologic toxicity of chemotherapeutic agents. *Semin Oncol*. 2006;33(1):86-97.
138. Balagula Y, Lacouture ME, Cotliar JA. Dermatologic toxicities of targeted anticancer therapies. *J Support Oncol*. 2010;8(4):149-61.
139. Balagula E, Lacouture ME. Dermatologic Toxicities. In: Olver IN, ed. *The MASCC Textbook of Cancer Supportive Care and Survivorship*. Springer; 2011:361-380:chap 34.
140. Wood LS, Lemont H, Jatoi A, et al. Practical considerations in the management of hand-foot skin reaction caused by multikinase inhibitors. *Community Oncol*. 2010;7(1):23-9.
141. Urban C, Anadkat MJ. A review of cutaneous toxicities from targeted therapies in the treatment of colorectal cancers. *J Gastrointest Oncol*. 2013;4(3):319-327. doi:10.3978/j.issn.2078-6891.2013.033
142. Macedo LT, Lima JP, dos Santos LV, Sasse AD. Prevention strategies for chemotherapy-induced hand-foot syndrome: a systematic review and meta-analysis of prospective randomised trials. *Support Care Cancer*. 2014;22(6):1585-93. doi:10.1007/s00520-014-2129-z
143. Ren Z, Zhu K, Kang H, et al. Randomized Controlled Trial of the Prophylactic Effect of Urea-Based Cream on Sorafenib-Associated Hand-Foot Skin Reactions in Patients With Advanced Hepatocellular Carcinoma. *J Clin Oncol*. 2015;33(8):894-900. doi:10.1200/jco.2013.52.9651
144. Ailor SK, Miles SC. Dermatologic Toxicity. In: Perry MC, ed. *The Chemotherapy Source Book*. 4th ed. Lippincott Williams & Wilkins; 2008:1136-147:chap 15.
145. Lacouture ME, Reilly LM, Gerami P, Guitart J. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. *Ann Oncol*. 2008;19(11):1955-1961. doi:10.1093/annonc/mdn389
146. Lacouture ME. Management of dermatologic toxicities. *J Natl Compr Canc Netw*. 2015;13:686-9.
147. Bachet J, Peuvrel L, Bachmeyer C, et al. Folliculitis induced by EGFR inhibitors, preventive and curative efficacy of tetracyclines in the management and incidence rates according to the type of EGFR inhibitor administered: a systematic literature review. *Oncologist*. 2012;17(4):555-68.
148. Lacouture M, Mitchell E, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;28(8):1351-7.

149. Regui Z, Bachet J, Bachmeyer C, et al. Management of cutaneous adverse events induced by anti-EGFR (epidermal growth factor receptor): a French interdisciplinary therapeutic algorithm. *Support Care Cancer*. 2012;20(7):1395-404.
150. Baas J, Krens L, Guchelaar H, et al. Recommendations on management of EGFR inhibitor-induced skin toxicity: a systematic review. *Cancer Treat Rev*. 2012;38(5):505-14.
151. Schneider EC, Malin JL, Kahn KL, Ko CY, Adams J, Epstein AM. Surviving Colorectal Cancer. *Cancer*. 2007;110:2075-82.
152. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Survivorship. V.1.2022, 03/30/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™* *Surveys & Data, Powered by NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
153. Bains SJ, Mahic M, Myklebust TA, et al. Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study. *J Clin Oncol*. 2016;34:2501-8.
154. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol*. 2013;31(35):4465-70. doi:10.1200/JCO.2013.50.7442
155. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma. V.2.2022, 12/06/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™* *Surveys & Data, Powered by NCCN™*, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
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157. Winter JM, Brody JR, Abrams RA, Lewis NL, Yeo CJ. Cancer of the pancreas. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles & Practices of Oncology*. 10th ed. Lippincott Williams & Wilkins; 2015:chap 49.
158. Yang G, Wagner T, Fuss M, Thomas CJ. Multimodality approaches for pancreatic cancer. *CA Cancer J Clin*. 2005;55(6):352-67.
159. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. *Cancer*. 1987;59(12):2006-10.
160. Chua YJ, Cunningham D. Adjuvant treatment for resectable pancreatic cancer. *J Clin Oncol*. 2005;23(20):4532-7.
161. Khorana AA, McKernin SE, Berlin J, et al. Potentially Curable Pancreatic Adenocarcinoma: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2019;37:2082-2088.
162. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297(3):267-77. doi:10.1001/jama.297.3.267
163. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA*. 2010;304(10):1073-81. doi:10.1001/jama.2010.1275

164. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011-24.
165. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N Engl J Med*. 2018;379:2395-406.
166. Tempero MA, Reni M, Riess H, et al. APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. *J Clin Oncol*. 2019;37:DOI: 10.1200/JCO.2019.37.15\_suppl.4000.
167. Tempero M, O'Reilly E, Cutsem EV, et al. LBA-1 Phase 3 APACT trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P + Gem) vs gemcitabine (Gem) alone in patients with resected pancreatic cancer (PC): Updated 5-year overall survival. *Ann Oncol*. 2021;32(3, S226):DOI:<https://doi.org/10.1016/j.annonc.2021.06.009>.
168. Khorana AA, Mangu PB, Berlin J, et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. Jul 20 2016;34(21):2541-56. doi:10.1200/JCO.2016.67.5553
169. Willett CG, Czito BG, Bendell JC, Ryan DP. Locally advanced pancreatic cancer. *J Clin Oncol*. 2005;23(20):4538-44. doi:10.1200/jco.2005.23.911
170. Czito BG, Willett CG, Clark JW, Fernandez Del Castillo C. Current perspectives on locally advanced pancreatic cancer. *Oncology (Williston Park)*. 2000;14(11):1535-45; discussion 1546, 1549-52.
171. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer*. 1981;48(8):1705-10.
172. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst*. 1988;80(10):751-5.
173. Crane CH, Abbruzzese JL, Evans DB, et al. Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? *Int J Radiat Oncol Biol Phys*. 2002;52(5):1293-302.
174. Mamon HJ, Niedzwiecki D, Hollis D, et al. A Phase 2 Trial of Gemcitabine, 5-Fluorouracil, and Radiation Therapy in Locally Advanced Nonmetastatic Pancreatic Adenocarcinoma. *Cancer*. 2011;117:2620-8.
175. Balaban EP, Mangu PB, Khorana AA, et al. Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34(22):2654-68. doi:10.1200/JCO.2016.67.5561
176. Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic Pancreatic Cancer: ASCO Guideline Update. *J Clin Oncol*. 2020;38:DOI: 10.1200/JCO.20.01364.
177. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403-13.
178. Grunewald R, Kantarjian H, Keating MJ, Abbruzzese J, Tarassoff P, Plunkett W. Pharmacologically directed design of the dose rate and schedule of 2',2'-difluorodeoxycytidine (Gemcitabine) administration in leukemia. *Cancer Res*. 1990;50(21):6823-6.
179. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol*. 2003;21(18):3402-8. doi:10.1200/jco.2003.09.140
180. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009;27(23):3778-85. doi:10.1200/JCO.2008.20.9007
181. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol*. 2002;20(15):3270-5.
182. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol*. 2006;24(24):3946-52. doi:10.1200/jco.2005.05.1490
183. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol*. 2004;22(18):3776-83. doi:10.1200/jco.2004.12.082

184. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol*. May 20 2005;23(15):3509-16. doi:10.1200/jco.2005.06.023
185. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009;27(33):5513-8. doi:10.1200/jco.2009.24.2446
186. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(15):1960-6. doi:10.1200/jco.2006.07.9525
187. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-25. doi:10.1056/NEJMoa1011923
188. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-703. doi:10.1056/NEJMoa1304369
189. Jameson GS, Borazanci E, Babiker HM, et al. Response Rate Following Albumin-Bound Paclitaxel Plus Gemcitabine Plus Cisplatin Treatment Among Patients With Advanced Pancreatic Cancer: A Phase 1b/2 Pilot Clinical Trial. *JAMA Oncol*. Oct 03 2019;doi:10.1001/jamaoncol.2019.3394
190. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer. *N Engl J Med*. 2019;381(4):317-327. doi:10.1056/NEJMoa1903387
191. Wang-Gillam A, Li C-P, Bodoky Gr, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet*. 2016;387:545-57.
192. Onivyde (irinotecan liposome injection). Prescribing Information. Merrimack Pharmaceuticals, Inc., Cambridge, MA. Revised:6/2017.
193. Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer*. 2011;47(11):1676-81. doi:10.1016/j.ejca.2011.04.011
194. Sindt JE, Brogan SE. Interventional Treatments of Cancer Pain. *Anesthesiol Clin*. 2016;34:317-39.
195. Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: Diagnosis and treatment. *J Gastroenterol Hepatol*. 2011;26(Suppl 2):12-16.
196. Berry AJ. Pancreatic enzyme replacement therapy during pancreatic insufficiency. *Nutr Clin Pract*. 2014;29(3):312-21. doi:10.1177/0884533614527773
197. Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol*. 07 2022;23(7):e334-e347. doi:10.1016/S1470-2045(22)00160-7
198. Lee AYY, Levine MN, Baker RI, et al. Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer. *N Engl J Med*. 2003;349:146-53.
199. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial. *J Clin Oncol*. 2015;33:2028-34.
200. SEER Stat Fact Sheets. Pancreas Cancer. National Cancer Institute, Bethesda, MD. Accessed July 14, 2022. Available from: <http://seer.cancer.gov/statfacts/html/pancreas.html>
201. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Anal Carcinoma. V.2.2022, 09/02/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
202. Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. *ANZ J Surg*. 2006;76(8):715-7. doi:10.1111/j.1445-2197.2006.03837.x
203. Uronis HE, Bendell JC. Anal cancer: an overview. *Oncologist*. 2007;12(5):524-34. doi:10.1634/theoncologist.12-5-524
204. Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer*. 2004;101(2):270-80. doi:10.1002/cncr.20365

205. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011;365:1576-85.
206. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. Aug 2019;68(32):698-702. doi:10.15585/mmwr.mm6832a3
207. American Cancer Society. American Cancer Society Recommendations for Human Papillomavirus (HPV) Vaccine Use. Updated 7/9/20. Accessed July 14, 2022. Available from: <https://www.cancer.org/cancer/cancer-causes/infectious-agents/hpv/acs-recommendations-for-hpv-vaccine-use.html>
208. Nigro ND, Seydel G, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer*. 1983;51:1826-1829.
209. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant Radiotherapy and Chemotherapy Is Superior to Radiotherapy Alone in the Treatment of Locally Advanced Anal Cancer: Results of a Phase III Randomized Trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol*. 1997;15:2040-2049.
210. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR anal cancer trial (ACT I). *Br J Cancer*. 2010;102:1123-1128.
211. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet*. 1996;348:1049-54.
212. Glynne-Jones R, Meadows H, Wan S, et al. EXTRA—A multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. *Int J Radiat Oncol Biol Phys*. 2008;72(1):119-126.
213. Goodman KA, Rothenstein D, Lajhem C, Wu A, Cercek A, Saltz L. Capecitabine plus mitomycin in patients undergoing definitive chemoradiation for anal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2014;90:S32-S33.
214. Meulendijks D, Dewit L, Tomaso NB, et al. Chemoradiotherapy with capecitabine for locally advanced anal carcinoma: an alternative treatment option. *Br J Cancer*. 2014;111:1726-1733.
215. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized controlled trial. *J Am Med Assoc*. 2008;299(16):1914-1921.
216. Eng C, Chang GJ, You YN, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. *Oncotarget*. 2014;5(22):11133-42.
217. Rao S, Scalfani F, Eng C, et al. InterAACT: A multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease - An International Rare Cancers Initiative (IRCI) trial. *Ann Oncol*. 2018;29:Abstract LBA21.
218. Mondaca S, Chatila WK, Bates D, et al. FOLFACIS Treatment and Genomic Correlates of Response in Advanced Anal Squamous Cell Cancer. *Clin Colorectal Cancer*. 2019;18(1):e39-e52. doi:10.1016/j.clcc.2018.09.005
219. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(4):446-453. doi:10.1016/S1470-2045(17)30104-3
220. Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. *Ann Oncol*. 2017;28(5):1036-1041. doi:10.1093/annonc/mdx029
221. Sodergren SC, Vassiliou V, Dennis K, et al. Systematic review of the quality of life issues associated with anal cancer and its treatment with radiochemotherapy. *Support Care Cancer*. 2015;23:3613-3623.
222. American Cancer Society. A Guide to Radiation Therapy. Updated 12/10/20. Accessed July 14, 2022. Available from: <http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/radiation/understandingradiationtherapyaguideforpatientsandfamilies/understanding-radiation-therapy-common-side-effects>
223. Bentzen AG, Balteskard L, Wanderas EH, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: Late effects in a national cohort of 128 survivors. *Acta Oncol*. 2013;52(4):736-44.

224. Knowles G, Haigh R, McLean C, Phillips H. Late effects and quality of life after chemo-radiation for the treatment of anal cancer. *Eur J Oncol Nurs*. 2015;19:479-85.



# UPPER GASTROINTESTINAL AND HEPATOCELLULAR CARCINOMAS

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## LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, management, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with esophageal, gastric, or hepatic malignancies.
2. Assess the impact of pharmacogenomics on the efficacy and toxicity of relevant anticancer agents used for gastrointestinal malignancies.
3. Develop an appropriate plan for preventing, monitoring, and treating radiation recall and other complications of radiation therapy.



## GASTRIC AND ESOPHAGEAL CANCERS

### I. Genomics<sup>1,4</sup>

A. Roughly 5-10% of gastric cancers are thought to have a familial component, with 3-5% associated with an inherited cancer predisposition syndrome

1. Patients who meet criteria for high-risk syndromes should be referred for cancer genetics evaluation. This includes a gastric cancer diagnosis<sup>2</sup>:

- a. Before age 40
- b. Before age 50 and in one first- or second-degree relative
- c. At any age and in two or more first- or second-degree relatives
- d. And breast cancer diagnosis, with one of those diagnoses before age 50
- e. At any age and a breast cancer diagnosis before age 50 in one first- or second-degree relative
- f. At any age with a family history of juvenile polyps or gastrointestinal polyps, or cancers associated with Lynch syndrome

2. Autosomal dominant syndromes

a. Increased risk of gastric cancer

- 1) Hereditary diffuse gastric cancer (CDH1 germline mutations in 30-50% of cases)
  - a) Characterized by development of signet ring cell gastric cancer at young age
  - b) Average age at diagnosis is 37
  - c) Women carry higher risk of developing lobular breast cancer
  - d) Lifetime risk for developing gastric cancer by age 80 is 67% for men and 83% for women
- 2) Peutz-Jeghers syndrome (STK11 germline mutations in 30-80% of cases) – lifetime risk 29%
- 3) Juvenile Polyposis syndrome (SMAD4 or BMPR1A germline mutations) – lifetime risk 21%
- 4) Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, and/or *PMS2* or more rarely *EPCAM* germline mutations) – lifetime risk 1-13%
- 5) Familial Adenomatous Polyposis (FAP) (*APC* germline mutations) – lifetime risk 1-2%
- 6) Hereditary breast and ovarian cancer syndrome (*BRCA1*, *BRCA2* germline mutations)
- 7) Li-Fraumeni syndrome (*TP53* germline mutations)
- 8) Cowden syndrome (*PTEN* germline mutation)

b. Increased risk of esophageal and esophagogastric junction (EGJ) cancers

- 1) Tylosis with non-epidermolytic palmoplantar keratoderma (PPK) and Howel-Evans syndrome
  - a) Caused by germline mutations in *RHBDF2* gene
  - b) Increases risk of squamous cell carcinoma of the esophagus
  - c) Individuals present with diffuse, punctate, or focal patterns of skin thickening on palms and soles

- 2) Familial Barrett's esophagus
  - a) Increases risk of adenocarcinoma of the esophagus and EGI
  - b) Strongly associated with gastroesophageal reflux disease
  - c) It is unvalidated which genes are at fault
3. Autosomal recessive syndromes
  - a. Ataxia-telangiectasia (ATM mutations), Bloom syndrome (*BLM/RECQL3*), xeroderma pigmentosum (7 different genes involved), Fanconi anemia (*FANCD1, BRCA2, FANCN [PALB2]*)
- B. Molecular alterations for esophageal and gastric cancer<sup>3</sup>
  1. Tumor suppressor genes – CDKN2A *P16<sup>INK4a</sup>*, *TP53*, *CDH1*, *CTNNB1*
    - a. Genomic alterations may vary across histologic subtypes of esophageal and gastric cancers<sup>5</sup>
  2. Defective DNA mismatch repair (dMMR)<sup>6</sup>
    - a. Patients with dMMR status are biologically the same as those with high level microsatellite instability (MSI-H) status
    - b. All patients with metastatic gastric or esophageal cancer should undergo dMMR/MSI testing<sup>1,2</sup>, although rates of MSI-high may only be around 3%<sup>7</sup>
- C. HER2-neu<sup>2,8,9</sup>
  1. Human epidermal growth factor receptor two (HER2) is involved in transmembrane signaling that is necessary for cell replication, proliferation, and survival
  2. HER2 amplification occurs in 12-23% of patients with gastric cancer
    - a. Occurs more commonly with
      - 1) Intestinal vs. diffuse histology
      - 2) Gastrointestinal junction tumors vs. gastric tumors
    - b. High variability in positivity rates due to differences in tumor location and histologies
    - c. Conflicting opinions on whether HER2 positivity is a poor or favorable prognostic indicator
  3. In esophageal cancers, HER2 amplification is more common in adenocarcinomas (15-30%) than squamous cell carcinomas (5-13%)
  4. All patients with advanced gastric, gastroesophageal junction, or esophageal adenocarcinoma tumors should be tested for HER2 expression<sup>1,2</sup>
  5. Immunohistochemistry (IHC) testing is preferred for determining HER2 positivity
    - a. The same concepts and techniques for testing HER2 in breast cancer also apply to upper GI cancers (refer to the Breast Cancer module for more information)
    - b. Gastric tumors demonstrate variability of staining intensity within tissues and positivity rates may vary between tissue obtained via biopsy vs. surgery
    - c. Greatest treatment effect occurs in tumors that express IHC 2+/FISH-positive and IHC 3+
  6. Patients with HER2 positive/amplified tumors are eligible to receive HER2-directed therapies

D. Programmed death 1 ligand (PD-L1)<sup>10</sup>

1. Expression of PD-L1 has emerged as a biomarker to predict response to PD-1 and PD-L1 inhibitors (refer to the Pharmacogenomic module for more information)
2. PD-L1 expression has been detected in over 40% of gastric cancer patients, and may be increased in those infected with *H pylori*
3. PD-L1 testing should be performed for all patients with metastatic gastric or esophageal adenocarcinoma and is reported as combined positive score (CPS)<sup>1,2</sup>

E. Refer to the Lower GI Cancers module for more information on DPD and UGT1A1 deficiencies that may affect toxicities from 5-FU and irinotecan, respectively

II. **Prevention and Screening**

A. Prevention

1. Diet appears to play a significant role in the pathogenesis of stomach and esophageal cancer<sup>11,12</sup>
  - a. Increased intake of fresh fruits and vegetables is associated with lower risk
  - b. Vitamin C rich diets, as well as diets high in whole grains, carotenoids, and green tea have been associated with a reduced risk of stomach cancer
  - c. In addition, low salt diets may be partially responsible for the decrease in gastric cancer incidence
  - d. Processed meat intake as well as alcohol intake were associated with increased risk
2. Chemoprevention
  - a. Beta-carotene, vitamin E, and selenium were shown to decrease mortality from stomach cancer in a Chinese trial.<sup>13</sup>
  - b. Ascorbic acid, B-carotene, or triple-drug *H. pylori* treatment shown to decrease the incidence of precursor lesions in a high-risk population.<sup>14</sup>
  - c. Despite being well known risk factors, eradication of *H. pylori* or treatment/prevention of gastroesophageal reflux has not been shown to prevent stomach cancer in randomized trials; however one study showed a decreased incidence of gastric cancer in a subpopulation of *H. pylori* carriers without precancerous lesions.<sup>15</sup>
3. In patients with hereditary diffuse gastric cancer, prophylactic total gastrectomy is recommended between ages 18 and 40

B. There are currently no screening recommendations for the general population for gastric or esophageal cancers in the U.S.<sup>1,2</sup>

1. High risk populations who may benefit from screening include:
  - a. Gastric cancer – hereditary diffuse gastric cancer, Lynch Syndrome, juvenile polyposis syndrome, Peutz-Jeghers syndrome, familial adenomatous polyposis
  - b. Esophageal cancer – tylosis with non-epidermolytic palmoplantar keratosis and Howel-Evans syndrome, familial Barrett esophagus, Bloom syndrome, fanconi anemia

**Patient Case #1: (ARS Question #1)**

KW is a 56-year-old female who presents to the emergency room with syncope and hematemesis. She underwent an endoscopy (EGD) which showed an ulcerated mass in the antrum of the stomach. Pathology from the biopsy was consistent with poorly differentiated adenocarcinoma, diffuse type with signet ring cells. PET scan was negative for metastases. An exploratory laparotomy did not show any peritoneal disease. After discussion with a multi-disciplinary team, KW will undergo perioperative chemotherapy with surgery.

**Which of the following perioperative regimens is most appropriate for KW's localized gastric cancer?**

- A. EOX (epirubicin, oxaliplatin, capecitabine)
- B. 5-FU + oxaliplatin + radiation
- C. FLOT (5-FU, leucovorin, oxaliplatin, docetaxel)
- D. Carboplatin + paclitaxel + radiation

**III. Treatment and Symptom Management****A. Gastric Cancer Treatment Modalities<sup>2</sup>**

1. The primary goal for localized gastric cancer is cure with surgery; otherwise the goal shifts to palliative treatment.
2. Principles of Surgery<sup>16,17</sup>
  - a. Treatment of choice since it can be palliative or curative. Most patients (except those with documented metastasis) should undergo exploratory surgery to determine if palliative resection or complete resection of the primary tumor for cure can be done.
  - b. Defining surgical candidates
    - 1) Medically fit defined as patients who are able to tolerate major surgery
    - 2) Non-surgical candidates include medically fit patients who decline surgery and those who are medically unfit for surgery
  - c. Surgical resection is classified as:
    - 1) R0 = no cancer at resection margins (primary goal)
    - 2) R1 = microscopic residual tumor
    - 3) R2 = macroscopic residual tumor in the absence of distant metastasis
  - d. The type of surgery (distal vs subtotal vs. total gastrectomy) is dependent on size and location of tumor. Regional lymph nodes should be resected during gastrectomy, although the extent of lymph node dissection remains a controversy.
  - e. Lymph node dissection is classified based on the extent of removal with gastrectomy
    - 1) A minimum of 16 lymph nodes should be evaluated for accurate staging
    - 2) D0 = incomplete resection of N1 lymph nodes
    - 3) D1 = removal of greater and lesser omental lymph nodes

- 4) D2 = D1 plus the removal of all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery
  - a) D2 resection requires significant training and expertise. Gastrectomy with D2 lymph node dissection more commonly performed in eastern Asia for curable disease. D2 resection is associated with increased postoperative morbidity and mortality. Extended lymph node dissection has been associated with lower recurrence rates, but not translated into improved overall survival benefit.<sup>17</sup>
3. Principles of Radiation<sup>2</sup>
  - a. Radiation in combination with chemotherapy may be used in the preoperative or postoperative settings for resectable gastric cancer
  - b. Radiation also may help palliate symptoms of localized obstructions
  - c. Preoperative chemoradiation regimens all are 2B recommendations<sup>2</sup>
    - 1) Fluoropyrimidine + oxaliplatin OR cisplatin
    - 2) Fluoropyrimidine
    - 3) Paclitaxel + carboplatin
  - d. Postoperative chemoradiation
    - 1) Only for patients who received less than a D2 lymph node dissection
    - 2) Fluoropyrimidine before and after fluoropyrimidine-based chemoradiation
      - a) The NCCN Panel® recommends dose modifications from the original regimen used in the Intergroup 0116 trial<sup>18,19</sup>
  - e. Chemoradiation for unresectable disease
    - 1) Fluoropyrimidine + oxaliplatin OR cisplatin (both preferred)
    - 2) Fluoropyrimidine + paclitaxel (category 2B)
4. Principles of systemic therapy<sup>2</sup>
  - a. Systemic therapy may be used in all settings of treatment, including postoperative, perioperative, and advanced or metastatic disease
  - b. Category 1 regimens may not always be preferred over a lower category regimen that may have a more favorable toxicity profile without compromising efficacy
  - c. Postoperative chemotherapy for patients who have undergone D2 lymph node dissection
    - 1) Capecitabine + oxaliplatin (category 1)
    - 2) 5-FU + oxaliplatin
  - d. Perioperative chemotherapy
    - 1) The MAGIC trial established the initial standard of care of perioperative chemotherapy vs surgery alone,<sup>20</sup> showing improved PFS, OS, and 5-year survival with perioperative chemotherapy

- a) The perioperative chemotherapy consisted of three preoperative and three post-operative cycles (21 days) of epirubicin, cisplatin, and continuous infusion 5-FU (ECF)
  - i. Acceptable modifications of ECF:
    - (a) Epirubicin, cisplatin, capecitabine (ECX)
    - (b) Epirubicin, oxaliplatin, 5-FU (EOF)
    - (c) Epirubicin, oxaliplatin, capecitabine (EOX)
- 2) The FLOT4-AIO trial updated the new standard of care for perioperative chemotherapy<sup>21,22</sup>
  - a) Patients were randomized 1:1 to FLOT (5-FU, leucovorin, oxaliplatin, docetaxel) or ECF/ECX
  - b) Due to the schedule of FLOT being every 14 days, patients in the FLOT arm received four pre- and post-operative cycles vs patients in the ECF/ECX arm received three pre- and post-operative cycles on a 21-day schedule
  - c) FLOT significantly improved OS to 50 months compared to 35 months with ECF/ECX (HR 0.77; 95% CI 0.63 to 0.94; p=0.012), as well as improved PFS (HR 0.75; 95% CI 0.62 to 0.91; p=0.004)
  - d) Perioperative complications, as well as 30- and 90-day mortality, were similar between the two groups. In addition, similar rates of patients proceeded to surgery in both groups.
  - e) Patients receiving ECF/ECX experienced more grade 3/4 nausea and vomiting (16% and 8% vs 7% and 2%, respectively), thromboembolic events (6% vs 3%), and anemia (6% vs 3%), while patients receiving FLOT experienced more grade 3/4 neutropenia (51% vs 39%), infections (18% vs 9%), diarrhea (10% vs 4%), and neuropathy (7% vs 2%)
  - f) Based on this trial, the NCCN Panel replaced ECF and its modifications with FLOT as the preferred, category 1 regimen
    - i. FLOT is recommended for patients with good performance status; for patients with good to moderate performance status, FOLFOX (5-FU, leucovorin, oxaliplatin) is an acceptable alternative
- 3) Perioperative chemotherapy regimen summary
  - a) Preferred
    - i. 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) (category 1)
    - ii. Fluoropyrimidine + oxaliplatin
  - b) Other: Fluoropyrimidine + cisplatin (category 1)
- e. Chemotherapy in the setting of unresectable locally advanced, recurrent, or metastatic disease<sup>2</sup>
  - 1) Chemotherapy regimens utilized in the locally advanced and metastatic settings are similar for gastric and esophageal cancer. See “Chemotherapy for treatment of locally advanced, recurrent, or metastatic gastric and esophageal cancers” section for detailed chemotherapy review

- 2) Goal of chemotherapy for advanced and metastatic disease is palliation
  - 3) Systemic therapy should only be offered to patients with a Karnofsky performance score  $\geq 60\%$  or ECOG performance score  $\leq 2$
5. Treatment of gastric cancer by clinical stage<sup>2</sup>
- a. Gastric cancer patients are typically divided into clinical stages based on their eligibility for surgery
  - b. Medically fit, resectable
    - 1) Endoscopic resection (for cTis or T1a tumors only) followed by surveillance
    - 2) Surgical resection, followed by either
      - a) Surveillance
      - b) Chemotherapy  $\pm$  radiation, based on extent of resection and tumor classification
  - c. Medically fit, potentially resectable
    - 1) Surgical resection (appropriate for  $\geq T1b$ , actively bleeding, or when postoperative therapy may be preferred), followed by either
      - a) Surveillance
      - b) Chemotherapy  $\pm$  radiation, based on extent of resection and tumor classification
    - 2) Perioperative chemotherapy and surgical resection if resectable (category 1, preferred)
    - 3) Preoperative chemoradiation followed by surgical resection if resectable (category 2B)
    - 4) If patients are deemed unresectable or develop metastatic disease at any point, they are treated as unresectable locally advanced or metastatic
  - d. Medically fit, surgically unresectable
    - 1) Chemoradiation
    - 2) Systemic therapy
  - e. Non-surgical candidate
    - 1) Chemoradiation (for locally unresectable and not previously received only)
    - 2) Systemic therapy
    - 3) Best supportive care
- B. Esophageal cancer treatment modalities<sup>1,23</sup>
1. Esophageal cancers are classified into squamous cell carcinoma (SCC) or adenocarcinoma histologies. Incidence, risk factors, and prognoses differ, as do recommendations for certain treatment modalities.
  2. The primary goal for localized esophageal cancer is cure with surgery; otherwise the goal shifts to palliative treatment
  3. Principles of Surgery

- a. Surgical resection for esophageal cancer (esophagectomy) is usually performed with a curative intent but may also be used in the palliative setting
  - b. Patients should be “medically fit” in order to undergo resection
  - c. Adenocarcinomas of the esophagogastric junction (EGJ) should be further classified according to the Siewart Classification<sup>1</sup>
    - 1) Type I: adenocarcinoma of the lower esophagus with the center located within 1 - 5 cm above the anatomic EGJ
    - 2) Type II: true carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below EGJ
    - 3) Type III: subcardial carcinoma with the tumor center between 2 and 5 cm below EGJ, which infiltrates the EGJ and lower esophagus below
    - 4) Types I and II are treated per the NCCN Guidelines® for Esophageal and Esophagogastric Junction Cancers<sup>1</sup>, and Type III is treated per the NCCN Guidelines® for Gastric Cancer<sup>2</sup>
  - d. There are many types of resection which are dictated by the size, stage and location of the primary tumor, as well as the surgeon’s experience and preference and the patient’s preference
    - 1) Patients who undergo surgery without preoperative chemoradiation should have at least 15 lymph nodes resected for proper staging
    - 2) The optimum number of lymph nodes is unknown for patients who have undergone preoperative chemoradiation
4. Principles of Radiation<sup>1</sup>
- a. Radiation is used concurrently with chemotherapy in the preoperative and postoperative settings, as well as for definitive treatment
    - 1) Patients with locally advanced esophageal cancer could potentially be cured with definitive chemoradiation alone
    - 2) Radiation is generally not recommended alone, unless used for palliation or for patients medically unfit to receive chemotherapy
  - b. Preoperative chemoradiation
    - 1) Preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ
    - 2) The CROSS trial established the benefits of preoperative chemoradiation therapy<sup>24,25</sup>
      - a) Patients were randomized 1:1 to preoperative chemoradiation with carboplatin and paclitaxel vs surgery alone
      - b) Preoperative chemoradiation doubled OS over surgery alone (48.6 vs 24 months; HR 0.68; 95% CI 0.53-0.88; p=0.003)
      - c) The 5-year survival for patients in the chemoradiation group was 47% and in the surgery group was 33%
      - d) Overall and progression-free survival benefits were seen for both adenocarcinoma and SCC histologies



- 3) Regimens:
  - a) Preferred
    - i. Paclitaxel + carboplatin (category 1)
    - ii. Fluoropyrimidine + oxaliplatin (category 1)
  - b) Other
    - i. 5-FU + cisplatin (category 1)
    - ii. Cisplatin + irinotecan (category 2B)
    - iii. Fluoropyrimidine + paclitaxel (category 2B)
- c. Postoperative Chemoradiation
  - 1) Fluoropyrimidine before and after fluoropyrimidine-based chemoradiation
- d. Definitive chemoradiation
  - 1) Preferred
    - a) Paclitaxel + carboplatin
    - b) Fluoropyrimidine + cisplatin OR oxaliplatin (both category 1)
  - 2) Other
    - a) Cisplatin + docetaxel OR paclitaxel
    - b) Irinotecan + cisplatin (category 2B)
    - c) Fluoropyrimidine + paclitaxel (category 2B)
5. Principles of chemotherapy<sup>1</sup>
  - a. Regimens are typically chosen based on performance status, comorbidities, and toxicity profile
  - b. Category 1 regimens may not always be preferred over a lower category regimen that may have a more favorable toxicity profile without compromising efficacy
  - c. Perioperative Chemotherapy (only recommended for adenocarcinoma of the thoracic esophagus or EGJ)
    - 1) FLOT (category 1, preferred)
    - 2) Fluoropyrimidine + oxaliplatin (preferred)
    - 3) Fluoropyrimidine + cisplatin (category 1)
  - d. Preoperative chemotherapy (only recommended for adenocarcinoma of the thoracic esophagus or EGJ)
    - 1) Cisplatin + 5-FU (category 2B)
  - e. Postoperative systemic therapy
    - 1) Nivolumab - only after preoperative chemoradiation with R0 resection and residual disease
      - a) Adjuvant nivolumab was studied in the phase III CheckMate 577 trial<sup>26</sup>

- i. The trial included patients with stage II or III esophageal or EGJ cancers that had undergone preoperative chemoradiation and had residual pathologic disease after an R0 resection
      - ii. Because adjuvant treatment was not standard of care, nivolumab was compared against placebo
        - (a) Nivolumab was administered at 240 mg every 2 weeks for 16 weeks, followed by 480 mg every 4 weeks for 1 year of therapy
      - iii. Median disease-free survival (DFS) was 22.4 months (95% CI, 16.6-34.0) in the nivolumab group and 11.0 months (95% CI, 8.3-14.3) in the placebo group (HR 0.69; 96.4% CI, 0.56-0.86;  $p < 0.001$ )
      - iv. Patients with either histology benefited from nivolumab shown in a post-hoc analysis:
        - (a) Adenocarcinoma DFS was 19.4 vs 11.1 months (HR 0.75; 95% CI, 0.59-0.96)
        - (b) SCC DFS was 29.7 vs 11.0 months (HR 0.61; 95% CI, 0.42-0.88)
      - v. Common adverse events of any grade from nivolumab were fatigue (17%), diarrhea (17%), pruritis (10%), and rash (10%)
      - vi. Based on this trial, nivolumab gained an FDA indication for adjuvant treatment of esophageal and EGJ patients<sup>27</sup>
    - b) Preferred, Category 1 recommendation from NCCN<sup>®1</sup>, and supported by ASCO for patients with ECOG 0-1<sup>28</sup>
  - 2) Other: fluoropyrimidine + oxaliplatin
- f. Chemotherapy in the unresectable locally advanced, recurrent or metastatic setting
- 1) Chemotherapy regimens utilized in the locally advanced and metastatic settings are similar for gastric and esophageal cancer. See “Chemotherapy for treatment of locally advanced, recurrent, or metastatic gastric and esophageal cancers” section for detailed chemotherapy review.
6. Treatment of esophageal cancer by stage<sup>1</sup>
- a. Patients with esophageal cancer are preliminarily staged based on clinical staging which takes the results from CT and PET scans as well as other diagnostic procedures into consideration. Pathologic staging is determined after surgical resection and will determine whether additional postoperative therapy is necessary.
  - b. Patients are categorized into two clinical groups: locoregional or metastatic cancer
    - 1) Patients in the locoregional group are then categorized into medically fit or non-surgical candidates
  - c. Locoregional disease
    - 1) Medically fit
      - a) Endoscopic resection and/or ablation for superficial tumors

- b) Surgical resection (esophagectomy), followed by surveillance or chemoradiation based on extent of resection
  - c) Preoperative chemoradiation (for non-cervical esophagus) followed by surgical resection, then surveillance
  - d) Definitive chemoradiation (for cervical esophagus) followed by surveillance or surgical resection based on response
  - e) For tumors that invade the trachea, great vessels, or heart, can consider chemotherapy alone then resection or surveillance based on response
  - f) In addition to the above options, medically fit patients with adenocarcinoma are also eligible for:
    - i. Surgical resection, followed by chemotherapy
    - ii. Perioperative or preoperative chemotherapy followed by surgical resection
- 2) Non-surgical candidates
- a) Endoscopic resection and/or ablation for superficial tumors
  - b) Definitive chemoradiation followed by surveillance
  - c) Palliative radiation or best supportive care for those not able to tolerate chemoradiation
- d. Locally advanced, recurrent, or metastatic cancer
- 1) Concurrent chemoradiation (locally advanced or recurrent only)
  - 2) Systemic therapy
  - 3) Best supportive care

**Patient Case #1 Answer: (ARS Question #1)**

**Correct answer is C.** The FLOT4-AIO trial showed significant improvement in overall survival with perioperative FLOT over the ECF/ECX regimen. FLOT has now replaced ECF and its modifications as the category 1 perioperative regimen for localized gastric cancer.<sup>2</sup>

Answer A is not most appropriate due to the removal of ECF and its modifications, including EOX, from the perioperative regimen recommendations.

Answers B and D are not appropriate perioperative regimens for localized gastric cancer due to the inclusion of radiation. These regimens would be more appropriate for preoperative or definitive treatment of localized or locally advanced esophageal cancer, respectively.

- C. Systemic therapy for the treatment of locally advanced, recurrent, or metastatic gastric and esophageal cancers<sup>1,2</sup>
- 1. Used in the metastatic setting as palliative therapy with limited improvement in PFS or OS
  - 2. Regimens containing two cytotoxic drugs are preferred over regimens containing three cytotoxic drugs due to lower toxicity without compromising efficacy

- a. A platinum-based doublet of cisplatin and fluorouracil is utilized as the standard of care in clinical trials, however oxaliplatin is generally preferred over cisplatin in clinical practice due to lower toxicity
- b. Three cytotoxic drug regimens should be reserved for patients who are medically fit with a good performance status and access to frequent toxicity evaluation
3. Modifications of regimens are allowed to attenuate toxicities, as long as efficacy is not compromised
4. First-line therapy<sup>1,2</sup>
  - a. Fluoropyrimidine (5-FU or capecitabine) + cisplatin
    - 1) 5-FU or capecitabine may be combined with cisplatin based on the results of a noninferiority trial of capecitabine and cisplatin (XP) compared to 5-FU and cisplatin (FP)<sup>29</sup>
      - a) Median overall survival for XP was 10.5 months vs. 9.3 months for FP, meeting the noninferiority criteria, and median PFS was significantly increased in the XP group (5.6 vs 5.0 months,  $p < 0.001$ )
      - b) The XP regimen was associated with more hand-foot syndrome (22%) and anemia (17%), whereas the FP regimen had more vomiting (59%) and stomatitis (26%)
      - c) The XP group required more frequent modifications for anemia, nausea/vomiting, diarrhea, and hand-foot syndrome
  - b. Fluoropyrimidine (5-FU or capecitabine) + oxaliplatin
    - 1) Oxaliplatin has a more favorable toxicity profile compared to cisplatin, so Al-Batran, et al.<sup>30</sup> evaluated safety and efficacy of 5-FU combined with either oxaliplatin or cisplatin
    - 2) Oxaliplatin was associated with significantly less anemia, nausea, vomiting, alopecia, fatigue, and renal toxicity
    - 3) Incidence of peripheral neuropathy and elevations of AST and ALT were significantly higher with oxaliplatin
    - 4) This trial provided support for using oxaliplatin in place of cisplatin for front-line regimens

**Patient Case #2: (ARS Question #2)**

FT is a 55-year-old female with a newly diagnosed metastatic intestinal type gastroesophageal junction adenocarcinoma. Molecular testing of her tumor reveals HER2 IHC 3+ and PD-L1 CPS 10. Her ECOG is 0.

**Which of the following regimens is most appropriate for first-line therapy for FT?**

- A. FOLFOX + nivolumab
- B. FOLFOX + trastuzumab + pembrolizumab
- C. Trastuzumab + pembrolizumab
- D. Fam-trastuzumab deruxtecan-nxki

- c. Trastuzumab<sup>1,2</sup>

- 1) The ToGA trial<sup>31</sup> was a phase III study of trastuzumab added to first line standard chemotherapy consisting of 5-FU or capecitabine plus cisplatin in HER2 positive advanced gastric adenocarcinoma patients versus standard chemotherapy alone
    - a) HER2 positive defined as IHC 3+ or FISH-positive
    - b) Median PFS was 6.7 months in the trastuzumab arm versus 5.2 months in the chemotherapy arm (p=0.002) and median OS was 13.8 months in the trastuzumab arm versus 11.1 months in the chemotherapy arm (p=0.0046)
    - c) The addition of trastuzumab to chemotherapy did not significantly increase toxicity
  - 2) HER2 testing is not typically performed in SCC of the esophagus, and trastuzumab is not currently recommended for use in SCC histology
  - 3) NCCN® supports using an FDA-approved biosimilar product in place of trastuzumab<sup>1,2</sup>
- d. Immunotherapy
- 1) Nivolumab
    - a) CheckMate 649<sup>32,33</sup>
      - i. Phase 3 trial assessed the addition of nivolumab to first-line chemotherapy or ipilimumab for HER2-negative patients with advanced or metastatic gastric, EGJ, or esophageal adenocarcinomas
      - ii. Patients were randomized to one of three arms:
        - (a) Nivolumab + investigator's choice of chemotherapy
          - Capecitabine + oxaliplatin (CAPEOX) + nivolumab 360 mg Q3 weeks **OR** 5-FU + oxaliplatin (FOLFOX) + nivolumab 240 Q2 weeks
        - (b) Ipilimumab 3 mg/kg + nivolumab 1 mg/kg Q3 weeks x4 doses, followed by nivolumab 240mg Q2 weeks
        - (c) Investigator's choice of chemotherapy alone
      - iii. Nivo + chemo vs chemo alone<sup>32</sup>
        - (a) Both primary endpoints of OS and PFS in patients with PD-L1 CPS ≥5 were statistically in favor of nivo + chemo vs chemo alone
          - OS in the combination group was 14.4 vs 11.1 months (HR 0.71; 95% CI, 0.59-0.86; p<0.0001)
          - PFS in the combination group was 7.7 vs 6.05 months (HR 0.68; 95% CI, 0.56-0.81; p<0.0001)
        - (b) There was also a statistically significant improvement in OS for all patients, regardless of PD-L1 status (13.8 vs 11.6 months; HR 0.80; 95% CI, 0.68-0.94; p=0.0002). PFS was numerically improved (7.7 vs 6.9 months), but statistical analysis was not performed.
        - (c) No new or unexpected side effects were noted

- (d) The FDA approved nivolumab in combination with chemotherapy regardless of PD-L1 status<sup>34</sup>, however NCCN® considers these regimens category 1 for PD-L1 CPS  $\geq 5$  and category 2B for PD-L1 CPS  $< 5$ <sup>1,2</sup>
- iv. Ipi + nivo vs chemo alone<sup>33</sup>
  - (a) Updated results from the nivo + chemo vs chemo alone analysis supported original conclusions
  - (b) Secondary endpoint of OS in patients with PD-L1 CPS  $\geq 5$  in the ipi + nivo vs chemo alone populations did not meet prespecified boundary for significance
    - OS in ipi + nivo vs chemo was 11.2 vs 11.6 months, respectively
  - (c) Neither PFS nor ORR were statistically improved either
    - Authors state the duration of response were more durable with ipi + nivo, at 13.2 months vs 6.9 months in the chemotherapy group
  - (d) The ipi + nivo regimen is not currently supported for use in patients with adenocarcinoma
- b) CheckMate 648<sup>35</sup>
  - i. Phase 3 trial investigated addition of nivolumab to first-line chemotherapy for patients with advanced or metastatic squamous cell or adenosquamous cell esophageal carcinomas
  - ii. Patients were randomized to one of three arms:
    - (a) Nivolumab 240 mg Q2 weeks + 5-FU 800 mg/m<sup>2</sup> weekly D1-5 + cisplatin 80 mg/m<sup>2</sup> Q4 weeks
    - (b) Nivolumab 3 mg/kg Q2 weeks + ipilimumab 1 mg/kg Q6 weeks
    - (c) 5-FU 800 mg/m<sup>2</sup> weekly D1-5 + cisplatin 80 mg/m<sup>2</sup> Q4 weeks
  - iii. Nivo + chemo vs chemo alone
    - (a) The primary endpoint of OS in patients with PD-L1  $\geq 1\%$  was significantly longer for the combination: 15.4 vs 9.1 months (HR 0.54; 95% CI 0.37-0.80,  $p < 0.001$ )
      - The overall population also saw OS benefit from the combination: 13.2 vs 10.7 months (HR 0.74; 99.1% CI 0.58-0.96,  $p = 0.002$ )
    - (b) The combination also significantly improved PFS in the PD-L1  $\geq 1\%$  population (6.9 vs 4.4 months [HR 0.65; 98.5% CI 0.46-0.92,  $p = 0.002$ ]), but not in the overall population (5.8 vs 5.6 months)
  - iv. Ipi + nivo vs chemo alone
    - (a) Ipi + nivo significantly improved OS in patients with PD-L1  $\geq 1\%$  and the overall population compared to chemo alone:
      - PD-L1  $\geq 1\%$ : 13.7 vs 9.1 months (HR 0.64; 98.6% CI 0.46-0.90,  $p = 0.001$ )
      - Overall: 12.7 vs 10.7 months (HR 0.78; 98.2% CI 0.62-0.98,  $p = 0.01$ )

- (b) Ipi + nivo did not significantly improve PFS in the PD-L1  $\geq 1\%$  population (4.0 vs 4.4 months with chemo alone) and therefore was not analyzed in the overall population
- v. Grade 3/4 treatment-related ADRs were 47% in the nivo + chemo arm, 32% in the ipi + nivo arm, and 36% in the chemo alone arm
- vi. Both the nivo + chemo and ipi + nivo regimens received FDA approval<sup>36</sup>, as well as support from NCCN<sup>®1</sup>
  - (a) NCCN<sup>®</sup> supports using oxaliplatin in place of cisplatin in the chemotherapy regimen

## 2) Pembrolizumab

- a) The phase 3 KEYNOTE-590<sup>37</sup> compared the addition of pembrolizumab to chemotherapy vs chemotherapy alone in patients with advanced esophageal or EGJ cancers
  - i. Patients were randomized to either pembrolizumab + chemotherapy (5-FU + cisplatin Q3 weeks) or chemotherapy alone
  - ii. The primary endpoint of OS was found to be significantly higher in various groups of patients:
    - (a) Esophageal squamous cell with PD-L1 CPS  $\geq 10$ : 13.9 vs 8.8 months (HR 0.57; 95% CI, 0.43-0.75;  $p < 0.0001$ )
    - (b) Esophageal squamous cell: 12.6 vs 9.8 months (HR 0.72; 95% CI, 0.60-0.88;  $p = 0.0006$ )
    - (c) PD-L1 CPS  $\geq 10$ : 13.5 vs 9.4 months (HR 0.62; 95% CI, 0.49-0.78;  $p < 0.0001$ )
    - (d) All patients: 12.4 vs 9.8 months (HR 0.73, 95% CI, 0.62-0.86;  $p < 0.0001$ )
  - iii. PFS was also significantly higher in the combination arm:
    - (a) PD-L1 CPS  $\geq 10$ : 7.5 vs 5.5 months (HR 0.51, 95% CI 0.41-0.65;  $p < 0.0001$ )
    - (b) All patients: 6.3 vs 5.8 months (HR 0.65, 95% CI 0.55-0.76;  $p < 0.0001$ )
  - iv. Safety results were as expected
  - v. The FDA approved pembrolizumab “in combination with platinum and fluoropyrimidine-based chemotherapy” regardless of PD-L1 status and supports dosing of pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks<sup>38</sup>
  - vi. NCCN Guidelines<sup>®</sup> for Esophageal and Esophagogastric Junction Cancers support the use of pembrolizumab in combination with a fluoropyrimidine and cisplatin OR oxaliplatin, with PD-L1 specifications:
    - (a) PD-L1 CPS  $\geq 10$ :
      - Fluoropyrimidine + cisplatin + pembrolizumab is category 1
      - Fluoropyrimidine + oxaliplatin + pembrolizumab is category 2A
    - (b) PD-L1 CPS  $< 10$ :

- Either chemo regimen + pembrolizumab is category 2B
- b) The phase 3 KEYNOTE-811<sup>39</sup> assessed the addition of pembrolizumab to chemotherapy with trastuzumab for HER2-positive gastric and EGJ cancers
- i. The chemotherapy used in this trial was either 5-FU + cisplatin or capecitabine + oxaliplatin. All regimens were given every 3 weeks.
  - ii. Results from the first interim analysis showed ORR of 74.4% (95% CI, 66.2-81.6%) for the pembro group, and 51.9% (95% CI, 43.0-60.7%) for the standard of care group
  - iii. No new or concerning adverse effects were noted
  - iv. Although survival data are still maturing, the FDA granted this regimen accelerated approval<sup>40</sup>
  - v. This regimen is listed as an “other recommended” regimen in the NCCN Guidelines<sup>®</sup> for Gastric Cancer<sup>2</sup> and the NCCN Guidelines<sup>®</sup> for Esophageal and Esophagogastric Junction Cancers<sup>1</sup>

**Patient Case #2 Answer: (ARS Question #2)**

**Correct answer is B.** Because FT is HER2-positive, trastuzumab should be added to first-line chemotherapy. Based on KEYNOTE 811, pembrolizumab in addition to trastuzumab and chemotherapy showed promising results, and is an appropriate regimen for FT.

Answer A is incorrect because it does not contain trastuzumab. If FT was HER2 negative, this would be an appropriate regimen.

Answer C is incorrect because it does not contain chemotherapy, and FT should be able to tolerate chemotherapy. In addition, trastuzumab + pembrolizumab is not an appropriate front-line regimen.

Answer D is not appropriate at this time because fam-trastuzumab deruxtecan-nxki is only indicated after progression on a trastuzumab-containing regimen

- e. Summary of NCCN recommendations for first-line systemic therapy<sup>1,2</sup>
- 1) The criteria to consider when choosing a regimen are: site of disease (esophageal, EGJ, or gastric), histology, PD-L1 status, and HER2 status for adenocarcinomas
  - 2) HER2-positive adenocarcinoma
    - a) Preferred regimens
      - i. Fluoropyrimidine + cisplatin + trastuzumab (category 1)
      - ii. Fluoropyrimidine + oxaliplatin + trastuzumab
    - b) Other: Fluoropyrimidine + cisplatin OR oxaliplatin + trastuzumab + pembrolizumab
      - i. Guidelines also support adding trastuzumab to any recommended chemotherapy regimen in the Other recommended chemotherapy regimens listed below
  - 3) HER2 negative adenocarcinoma



- a) Fluoropyrimidine + oxaliplatin + nivolumab, preferred
  - i. PD-L1 CPS  $\geq 5$ : category 1
  - ii. PD-L1 CPS  $< 5$ : category 2B
- 4) Squamous cell carcinoma only (all are preferred)
  - a) Fluoropyrimidine + oxaliplatin OR cisplatin + nivolumab
  - b) Ipilimumab + nivolumab
- 5) Esophageal or EGJ only, regardless of histology
  - a) Fluoropyrimidine + oxaliplatin OR cisplatin + pembrolizumab, preferred
    - i. PD-L1 CPS  $\geq 10$ : category 1 for cisplatin, 2A for oxaliplatin
    - ii. PD-L1 CPS  $< 10$ : category 2B for either platinum
- 6) Any site or histology
  - a) Fluoropyrimidine + oxaliplatin OR cisplatin, preferred
  - b) Other recommended chemotherapy regimens:
    - i. 5-FU + irinotecan
    - ii. Paclitaxel + cisplatin OR carboplatin
    - iii. Docetaxel + cisplatin
    - iv. Fluoropyrimidine
    - v. Docetaxel OR paclitaxel
    - vi. Docetaxel + 5-FU + cisplatin OR oxaliplatin
    - vii. Docetaxel + carboplatin + 5-FU (category 2B)

**Patient Case #3: (ARS Question #3)**

GM is a 60-year-old male with metastatic esophageal squamous cell carcinoma and a PD-L1 CPS of 25. He has been receiving first-line chemotherapy with FOLFOX (5-FU, leucovorin, and oxaliplatin) + nivolumab for 10 cycles. GM has handled treatment well. Recent CT scans of the chest and abdomen reveal that the primary tumor and liver metastases have increased in size. GM would like to continue to receive treatment.

**Which of the following regimens is most appropriate for second-line treatment of GM's metastatic esophageal squamous cell carcinoma?**

- A. ECF (epirubicin, cisplatin, 5-FU)
- B. Pembrolizumab
- C. Ramucirumab + paclitaxel
- D. Paclitaxel

- 5. Subsequent-line therapy<sup>1,2</sup>
  - a. Principles

- 1) Subsequent-line therapy for gastric and esophageal cancers may be considered in select patients
  - 2) The decision to give subsequent-line therapy will depend on the patient's performance status and what agents the patient was exposed to previously
  - 3) Single agent or two-drug combinations are utilized in this setting due to tolerability; three-drug regimens are not recommended after first-line
- b. Ramucirumab ± paclitaxel
- 1) In the phase III trials REGARD and RAINBOW, investigators evaluated the efficacy of ramucirumab for the treatment of advanced gastric or EGJ adenocarcinomas

**Summary of data from REGARD and RAINBOW trials**

Trial	REGARD <sup>41</sup>		RAINBOW <sup>42</sup>	
Treatment arms	Ramucirumab	Best supportive care	Ramucirumab with paclitaxel	Paclitaxel with placebo
Median OS	5.2 months [p=0.047]	3.8 months	9.6 months [p=0.017]	7.4 months
Median PFS	2.1 months [p <0.0001]	1.3 months	4.4 months [p <0.0001]	2.9 months
ORR	3% [p=0.76]	3%	28% [p=0.0001]	16%

OS=overall survival; PFS=progression-free survival; ORR=objective response rate

- 2) Adverse effects<sup>43</sup>
    - a) Ramucirumab as a single agent is commonly associated with hypertension and diarrhea
    - b) Ramucirumab plus paclitaxel is commonly associated with fatigue, neutropenia, diarrhea, and epistaxis
  - 3) Ramucirumab is FDA-approved as a single agent or in combination with paclitaxel for patients with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy<sup>43</sup>
- c. Pembrolizumab
- 1) Evidence for use in patients with MSI-H or dMMR tumors is based on multiple trials by Le and colleagues<sup>7,44,45</sup>
  - 2) KEYNOTE-181<sup>46</sup> demonstrated pembrolizumab as second-line therapy improved OS in patients with esophageal cancer of any histology with PD-L1 CPS ≥10 compared to investigator-choice chemotherapy (9.3 vs 6.7 months; HR 0.69, 95% CI, 0.52-0.93; p=0.0074)
    - a) Pembrolizumab did not improve OS in the overall population (regardless of PD-L1 status), although OS was significantly improved in those with SCC
- d. Nivolumab
- 1) Nivolumab was compared against investigator's choice of chemotherapy in patients with unresectable or metastatic esophageal SCC who were refractory or intolerant to one

previous fluoropyrimidine-based and platinum-based chemotherapy in the ATTRACTION-3 trial<sup>47</sup>

- a) Median OS was significantly improved with nivolumab at 10.9 months vs 8.4 months with chemotherapy (HR 0.77, 95% CI 0.62 – 0.96; p=0.019)
- b) Common adverse events with nivolumab were rash, diarrhea, and decreased appetite

e. Fam-trastuzumab deruxtecan-nxki (T-DXd)

- 1) The DESTINY-Gastric01<sup>48</sup> trial established the first HER2-directed therapy for subsequent-line treatment of HER2-positive gastric cancers
  - a) Prior to this trial, no HER2-targeted agents other than trastuzumab had shown significant benefit in HER2-positive gastric cancers
- 2) Patients with HER2-positive gastric or EGJ cancer who had received at least 2 prior lines of therapy were randomized to either T-DXd or physician's choice of chemotherapy
- 3) T-DXd improved response rates (51% vs 14%, p<0.001), OS (12.5 vs 8.4 months, p=0.01), and PFS (5.6 vs 3.5 months, p not reported) over physician's choice of chemotherapy
- 4) No new or concerning adverse events were noted
  - a) 10% of patients developed interstitial lung disease or pneumonitis, with a median time to onset of 84.5 days (range 36-638 days)
- 5) Of note, the dose used in 6.4 mg/kg, which is higher than the dose used in breast cancer

f. Trifluridine/tipiracil

- 1) The TAGS trial<sup>49</sup> compared trifluridine/tipiracil against placebo in patients with metastatic gastric or EGJ adenocarcinoma who had progressed on two or more standard-of-care regimens
- 2) Previous regimens had to have included a fluoropyrimidine, a platinum agent, and a taxane or irinotecan
- 3) Trifluridine/tipiracil significantly increased OS (5.7 vs 3.6 months; HR 0.69 95% CI 0.56-0.85, p=0.00058) and PFS (2.0 vs 1.8 months; HR 0.57 95% CI 0.47-0.70, p<0.0001)
- 4) All patients, regardless of performance status, number of previous regimens, or HER2 status had significant survival benefit from trifluridine/tipiracil
- 5) Trifluridine/tipiracil was associated with grade 3 or worse adverse events of neutropenia (34%), anemia (19%), and leukopenia (9%)
  - a) Dose modifications were required for 58% of patients in the trifluridine/tipiracil group
- 6) Trifluridine/tipiracil garnered FDA approval for use in patients with metastatic gastric or EGJ adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2 -targeted therapy. The NCCN panel<sup>®</sup> recommendation follows this approval.

g. Summary of subsequent-line regimens<sup>1,2</sup>

- 1) Preferred
  - a) Nivolumab for esophageal SCC only (category 1, if no prior tumor progression on checkpoint inhibitor)

- b) Pembrolizumab for esophageal SCC with PD-L1 CPS  $\geq 10$  only (category 1, if no prior tumor progression on checkpoint inhibitor)
  - c) Ramucirumab + paclitaxel for adenocarcinoma only (category 1 for gastric & EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)
  - d) Fam-trastuzumab deruxtecan-nxki for HER2+ adenocarcinoma
  - e) Docetaxel OR paclitaxel (category 1)
  - f) Irinotecan (category 1)
  - g) 5-FU + irinotecan
  - h) Trifluridine/tipiracil for gastric & EGJ adenocarcinoma only (category 1 for third-line or greater)
- 2) Other
- a) Ramucirumab for adenocarcinoma only (category 1 for gastric & EGJ, category 2A for esophageal adenocarcinoma)
  - b) Irinotecan + cisplatin
  - c) Irinotecan + ramucirumab  $\pm$  5-FU for adenocarcinoma only
  - d) Docetaxel + irinotecan (category 2B)
  - e) Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors
  - f) Dostarlimab-gxly or pembrolizumab for MSI-H/dMMR gastric tumors that have not progressed on checkpoint inhibitor therapy
    - i. Pembrolizumab can also be used in TMB-high ( $\geq 10$  mutations/Mb) tumors

**Patient Case #3 Answer: (ARS Question #3)**

**Correct answer is D.** Because GM received immune therapy in the front-line, it is not appropriate to continue immune therapy in the subsequent-line setting. A single agent taxane, such as paclitaxel, is an appropriate subsequent-line therapy.

Answer A is incorrect because three-drug chemotherapy regimens are not used in the subsequent-line setting.

Answer B is not appropriate because GM already progressed on immune therapy in the front-line setting.

Answer C is incorrect because ramucirumab-based regimens are only indicated for adenocarcinoma histologies.

**IV. Long Term Follow-up and Survivorship<sup>1,2,50</sup>**

**A. Gastric cancer<sup>2</sup>**

**1. Long-term follow-up**

- a. The majority of gastric cancer recurrences occur within two years; routine gastric cancer-specific surveillance is not recommended past 5 years
- b. Stage I or superficial tumor

- 1) History and physical exam every 3-6 months for 1-2 years, then every 6-12 months for 3-5 years, then annually
- 2) Chemistry profile with CBC, as well as monitoring for nutritional deficiency as clinically indicated
- 3) Upper GI endoscopy every 6 months for 1 year, then annually for up to 3 years for superficial tumors and up to 5 years for stage I
- 4) CT chest, abdomen, pelvis as clinically indicated
- c. Stage II-III or Stage I-III treated with neoadjuvant  $\pm$  adjuvant therapy
  - 1) History and physical exam every 3-6 months for 1-2 years, then every 6-12 months for 3-5 years, then annually
  - 2) Chemistry profile, CBC, as well as monitoring for nutritional deficiency as clinically indicated
  - 3) Upper GI endoscopy as clinically indicated for patients who had partial or subtotal gastrectomy
  - 4) CT chest, abdomen, pelvis every 6-12 months for 2 years, then annually up to 5 years
  - 5) PET/CT can be considered as clinically indicated
2. Survivorship
  - a. Patients who have undergone a total gastrectomy have greater restrictions and have been shown to have a lower quality of life than those who have undergone a partial gastrectomy
  - b. Monitor for weight loss and consider referral to dietician/nutrition services
  - c. Manage diarrhea with anti-diarrheal and/or bulk-forming agents and diet
  - d. Chemotherapy induced neuropathy – consider duloxetine for painful neuropathy
  - e. Bone health
    - 1) Consider vitamin D testing and replacement
    - 2) Monitor bone density per established national guidelines
  - f. Specific issues in subtotal gastrectomy survivors
    - 1) Indigestion
      - a) Avoid foods that increase acid production
      - b) Consider proton pump inhibitor
    - 2) B<sub>12</sub> and iron deficiency (distal gastrectomy only)
      - a) Monitor CBC and B<sub>12</sub> every 3 months for up to 3 years, then every 6 months up to 5 years, then annually
      - b) Iron levels annually
      - c) Supplementation as indicated
  - g. Specific issues in total gastrectomy survivors

- 1) Post-prandial fullness/eating dysfunction
  - a) Encourage small meals and avoiding fluid intake with meals
- 2) Dumping syndrome
  - a) Can occur early (within 30 minutes) or late (within 2-3 hours) of meals
  - b) Encourage diet high in protein and fiber and low in simple carbohydrates
- 3) B<sub>12</sub> and iron deficiency (see above)
  - a) If supplementation with iron is indicated, avoid sustained release or enteric-coated products
- 4) Small intestine bacterial overgrowth (blind loop)
  - a) Consider antibiotic treatment (rifaximin 550 mg TID x7-10 days)
  - b) Diet high in protein and low in carbohydrates

#### C. Esophageal Cancer<sup>1</sup>

1. Long-term follow-up
  - a. Majority of relapses occur within the first 2 years; routine esophageal/EGJ cancer-specific surveillance not recommended past 5 years
  - b. Surveillance after successful localized therapy remains controversial as there are currently no high-level data to guide development of algorithms
  - c. Stage 0-I
    - 1) Guidelines have not been established and recommendations vary according to the depth of invasion and treatment modality
  - d. Stage II-III treated with definitive chemoradiation
    - 1) CT chest, abdomen every 6 months for 2 years
    - 2) EGD every 3-6 months for 2 years, then every 6 months for 1 year, then as clinically indicated
  - e. Stage II-III treated with chemoradiation and surgery
    - 1) CT chest, abdomen every 6 months for 2 years
    - 2) EGD as clinically indicated
2. Survivorship
  - a. Patients who have undergone esophagectomy are at higher risk for long-term issues
  - b. Malnutrition/malabsorption
    - 1) Monitor weight with the expectation of weight loss within the first 6 months
    - 2) Consider monitoring vitamin B, folic acid, vitamin D, and calcium levels
  - c. Delayed gastric emptying
    - 1) Encourage small meals throughout the day, as well as a diet low in fat and fiber

- d. Radiation-induced cardiotoxicity
  - 1) Patients who receive radiation as part of their treatment are at increased risk for cardiac-related death than those who did not
  - 2) Coordinate with primary care provider for age-specific cardiac risk factor management
  - 3) Refer to a cardiologist as indicated
- e. Reflux
  - 1) Consider proton pump inhibitors, although biliary reflux typically exacerbates symptoms
- f. Dumping syndrome (see above)
- g. Dysphagia
- h. Chemotherapy induced neuropathy (see above)

## LIVER CANCER (HEPATOCELLULAR CARCINOMA OR HCC)

### I. Genomics<sup>51,52</sup>

- A. Molecular pathways known to be abnormal in HCC include cell-cycle dysregulation (TP53, CDKN2A, RB1, CCND1), increased angiogenesis (VEGF, PDGF, ANGPT2), and evasion of apoptosis (NF-κB)
- B. Fibrolamellar hepatocellular carcinoma (FLHC) is a very rare variant of HCC that can be identified by the DNAJB1-PRKACA chimera<sup>53</sup> (This module does not cover management of FLHC)

### II. Prevention and Screening

- A. Chronic liver disease is the basis for the development of HCC, with more than 80% of cases due to preexisting liver cirrhosis, regardless of etiology.
- B. Prevention
  - 1. Hepatitis B infection (HBV)<sup>53,54</sup>
    - a. HBV appears to be the most significant risk factor for the development of HCC. The long-term risk of developing HCC may be as high as 40% in these patients.
    - b. Control of HBV infection includes sanitation and living condition improvements, antiviral treatment, and vaccination
    - c. The American Association for the Study of Liver Disease (AASLD) recommends treatment of HBV with antiviral therapy, such as peg-interferon, entecavir, or tenofovir, to decrease the risk of liver-related complications<sup>55</sup>
    - d. With approximately 70-80% of HCC in developing countries attributed to HBV, vaccination seems to be the most effective route to lower HCC incidence
      - 1) Data from Taiwan showed universal hepatitis B vaccination from birth significantly decreased incidence of HCC<sup>54</sup>
  - 2. Hepatitis C infection (HCV)<sup>53</sup>
    - a. Development of cirrhosis typically occurs 20-50 years after the initial infection with HCV<sup>56</sup>
    - b. HCV is an independent risk factor for HCC, but risk may be increased in patients with concurrent HBV or cirrhosis. A recent large meta-analysis in China demonstrated a synergistic increased risk of HCC in patients with both HBV & HCV<sup>57,58</sup>
    - c. HCC from hepatitis C is best avoided with preventative strategies avoiding exposure through blood transfusions, unprotected sex, and sharing contaminated needles in IV drug abusers
    - d. AASLD in conjunction with the Infectious Diseases Society of America (IDSA) recommend antiviral treatment for patients infected with HCV based on history of treatment and genotype<sup>59</sup>
      - 1) Antiviral treatment may in turn lead to decreased incidence of HCV-related HCC, however due to the extended period for HCC to develop, this may take years to come to fruition
  - 3. Alcoholic cirrhosis is an independent risk factor for HCC, but also may be synergistic with viral hepatitis infections<sup>53</sup>
- C. Screening



1. Alpha-fetoprotein (AFP)
  - a. A study in over 18,000 patients age 35-59 and hepatitis B surface antigen- (HBsAg) positive or with chronic hepatitis were screened with AFP and ultrasound every 6 months vs no screening<sup>60</sup>
    - 1) Ultrasound was found to have a higher detection rate (84% vs. 69%), lower false positive rate (2.9% vs. 5.0%), and higher positive predictive value (6.6% vs. 3.3%) compared to AFP
    - 2) Detection rate for combination of ultrasound and AFP was 92%, but was associated with a higher false positive rate (7.5%)
  - b. AFP is not specific for HCC and is often not elevated in patients with early-stage HCC, thus making it an unreliable biomarker for screening on its own
2. The AASLD organizes their surveillance recommendations into high-risk groups that have clear benefit from surveillance, and those that have unclear benefit

**AASLD Surveillance Recommendations for Patients at High Risk to Develop HCC<sup>61</sup>**

<b>Surveillance Benefit</b>
Hepatitis B carriers
Asian males ≥40 years of age
Asian females ≥50 years of age
All cirrhotic patients
Family history of HCC
Africans/North American Blacks
Non-hepatitis B cirrhosis
Hepatitis C
Other cirrhosis
Genetic hemochromatosis
Primary biliary cirrhosis, stage 4
Alpha-1 antitrypsin deficiency
<b>Unclear Surveillance Benefit</b>
Male hepatitis B carriers <40 years of age
Female hepatitis B carriers >50 years of age
Non-alcoholic fatty liver disease without cirrhosis
Hepatitis C and stage 3 fibrosis

- a. AASLD recommends ultrasonography every 6 months, with or without AFP
  - b. Patients with cirrhosis and Child-Pugh class C (see below) should be excluded from surveillance unless they are on the transplant waiting list
3. NCCN® recommends the following patients undergo screening for HCC:<sup>53</sup>
  - a. Patients with cirrhosis caused by any of the following:
    - 1) Hepatitis B, C
    - 2) Alcohol
    - 3) Genetic hemochromatosis
    - 4) Non-alcoholic fatty liver disease
    - 5) Stage 4 primary biliary cholangitis

- 6) Alpha-1 antitrypsin deficiency
- 7) Other causes of cirrhosis
- b. Hepatitis B carriers without cirrhosis
- c. Screening is recommended with ultrasound and AFP every 3-6 months
  - 1) Additional imaging (abdominal multiphasic CT scan or MRI) is recommended in the setting of a rising AFP or upon identification of a liver nodule on ultrasound

**Patient Case #4: (ARS Question #4)**

JP is a 53-year-old male who presents to his physician because he has been experiencing night sweats that wake him up and is feeling more tired. He has a history of hepatitis B infection. His physician performs diagnostic testing and an alpha fetoprotein (AFP) level is 1,405 ng/mL. A CT scan of the abdomen and pelvis reveals a liver mass involving the right lobe of the liver measuring 5.5 x 5.3 cm and is consistent with a locally advanced, unresectable HCC. He is Child-Pugh class A6.

**Which treatment option will offer JP the best overall survival for his unresectable HCC?**

1. Liver transplantation
2. FOLFOX
3. Atezolizumab + bevacizumab
4. Sorafenib

### III. Treatment and Symptom Management

#### A. Treatment modalities

1. Surgery<sup>53,62</sup>
  - a. Hepatic resection is the backbone of curative therapy for localized HCC, but only approximately 30% of patients are candidates for surgery
  - b. Surgical resection can range from segmental resection to tri-segmental resection where up to 80% of the liver is removed
  - c. The Child-Pugh score was originally developed to predict mortality from surgery, but is now also used to determine hepatic functional reserve in patients with cirrhosis<sup>53,63,64</sup>

**Child-Pugh Score<sup>53</sup>**

Parameters	Score for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)	None	1-2	3-4
Ascites	None	Slight	Moderate
Albumin (g/dL)	>3.5	2.8 – 3.5	< 2.8
Prothrombin time prolonged (seconds)	< 4	4-6	> 6
INR	< 1.7	1.7-2.3	> 2.3
Bilirubin (mg/dL)	< 2	2-3	> 3
*for primary biliary cirrhosis	<4	4-10	>10
<div> <div>Class A = 5-6 points Good operative risk</div> <div>Class B = 7-9 points Moderate operative risk</div> <div>Class C = 10-15 points Poor operative risk</div> </div>			

- d. Surgical resection indicated if the following criteria are met:
  - 1) Patient is medically fit for major operation
  - 2) Adequate liver function
  - 3) Solitary mass of any size without major vascular involvement
  - 4) Adequate future liver remnant
  - 5) Suitable tumor location amenable to resection
- e. 5-year risk of recurrence after resection as high as 70% due to the further decline of underlying chronic liver disease<sup>65,66</sup>
- f. 5-year survival rates range from 30-40% with a median survival of approximately 3 years<sup>65,66</sup>
- 2. Transplant<sup>53,67</sup>
  - a. Liver transplantation is potentially curative therapy for patients with early HCC and moderate-to-severe cirrhosis
  - b. 5-year survival rates have been reported most commonly between 60-75%<sup>67</sup>, and in some reports up to 90%<sup>66</sup>
  - c. Selection for transplant is based on the UNOS criteria, which were developed from the Milan criteria<sup>53</sup>:
    - 1) AFP  $\leq$ 1000 ng/mL
    - 2) Single tumor 2-5 cm in diameter OR 2-3 tumors 1-3 cm in diameter
  - d. Model for End-Stage Liver Disease (MELD) score is used by UNOS to assess severity of disease and prioritize transplant recipients
  - e. Bridge therapy<sup>53</sup>
    - 1) Typically locoregional therapy used to decrease tumor progression and dropout rate from the transplant list, although sorafenib has been used as well
    - 2) Due to the heterogenous nature of trials, the NCCN® panel does not provide specific recommendations for bridge therapy at this time<sup>53</sup>
  - f. Downstaging therapy<sup>53</sup>
    - 1) Similar to neoadjuvant therapy, downstaging therapy is used to reduce tumor burden in patients who are marginally beyond the acceptable criteria for transplant
    - 2) Candidates may be eligible for the MELD exception if they meet specific tumor size criteria *before* downstaging therapy
- 3. Locoregional Therapy<sup>68,69 51</sup>
  - a. Preferred for patients who are not transplant candidates, inoperable due to performance status, comorbidities, local disease or local disease with minimal extrahepatic disease
  - b. Exert effects by causing tumor necrosis

## Locoregional Therapies Used in HCC<sup>53,65,66</sup>

Procedure	Mechanism	Place in therapy
<b>Ablation</b>		
Chemical	Direct instillation of ethanol or acetic acid results in tumor necrosis. Requires multiple applications, so used less frequently.	Tumors must be in a location accessible for percutaneous, laparoscopic, or open approaches.
Thermal - Radiofrequency ablation (RFA) - Microwave ablation (MWA)	RFA: Electrical current heats the tumor leading to tumor cell death causing tissue necrosis  MWA: Electromagnetic waves produce heat at higher frequency than RFA, creating a larger area of tumor necrosis	Best alternative for early-stage HCC not suitable for surgical resection or transplant. May be curative for tumors $\leq 3$ cm and may prolong survival for tumors 3-5 cm.
Cryoablation <sup>70</sup>	Direct cellular injury via ice crystal formation in extracellular and intracellular spaces, as well as vascular-related injury via cold-induced tissue ischemia or necrosis	RFA most frequently used form of local ablation therapy, likely due to excellent short-term outcomes (2-year OS reported to be 98%), but 5-year recurrence rate up to 70% <sup>65</sup>
<b>Arterially-directed techniques</b>		
Transarterial bland embolization (TAE)	Uses gelatin sponge or polyvinyl alcohol particles to result in tumor ischemia/necrosis, reducing blood flow to the tumor site	Tumors irrespective of location are amenable, as long as tumor blood supply can be isolated.
Transarterial chemoembolization (TACE)	Local delivery of chemotherapy via a catheter (doxorubicin, cisplatin, and/or mitomycin c) to the tumor causing occlusion of arterial vessels which induces tumor ischemia.	Typically used in patients with intermediate-stage HCC; the intent is for palliation. May be used for unresectable tumors >5 cm. Contraindicated in patients with bilirubin >3 mg/dL, portal vein thrombosis, Child-Pugh Class C.
Drug-eluting bead (DEB) TACE	The use of DEB allows the controlled release of drug, which reduces both hepatic and systemic side effects.	
Transarterial radioembolization (TARE) with yttrium-90 (Y-90) microspheres	Internal delivery of radiation to the tumor bed through catheter administration of microspheres embedded with Y-90 microspheres, which emit beta radiation	TAE and TACE are highly associated with postembolization syndrome and systemic complications (abdominal pain, nausea, fever, ileus).
<b>Radiotherapy</b>		
External beam radiation therapy (EBRT)	Focal administration of high-dose radiation, usually sparing surrounding tissue	For patients with unresectable or inoperable HCC, for which curative therapies are not an option. All tumors irrespective of location may be amenable to radiation therapy.
Stereotactic body radiation therapy (SBRT)	Advanced technique of EBRT that delivers large ablative doses of radiation. Typically reserved for patients with 1-3 tumors with minimal extrahepatic disease.	Consider for patients if other locoregional therapies are contraindicated or have failed

OS=overall survival

### 4. Systemic therapy

- a. There are insufficient data at this time to support using neoadjuvant or adjuvant therapy<sup>66</sup>, therefore systemic therapy is reserved for the advanced/metastatic setting outside of a clinical trial.<sup>53</sup>

- b. Historically, cytotoxic chemotherapy regimens including doxorubicin, fluorouracil, gemcitabine, oxaliplatin, or irinotecan provided no survival benefit compared with best supportive care, with response rates ranging from 0-40%<sup>66</sup>
- c. First-line options
  - 1) Sorafenib
    - a) SHARP<sup>71</sup> trial
      - i. Included treatment-naïve patients from North America, South America, and Europe
      - ii. The majority of patients were Child-Pugh class A (95% in sorafenib group, 98% in placebo group), with the remainder being Child-Pugh class B
      - iii. Response rates were similar for sorafenib (2%) vs placebo (1%)
      - iv. Patients in the sorafenib group experienced significantly more weight loss (9%), alopecia (14%), hand-foot skin reaction (21%), anorexia (14%), diarrhea (39%), and voice changes (6%) of any grade
    - b) Asia-Pacific<sup>72</sup> trial
      - i. Parallel study to SHARP that included patients from the Asia-Pacific region (China, Taiwan, South Korea)
      - ii. Again, the majority of patients were Child-Pugh class A (97.3% in sorafenib group, 97.4% in placebo group), with the remainder being Child-Pugh class B
      - iii. Response rates were 3.3% for sorafenib and 1.3% for placebo
      - iv. Patients in the sorafenib group experienced significantly more hand-foot skin reaction (45%), diarrhea (25.5%), alopecia (24.8%), fatigue (20.1%), rash/desquamation (20.1%), hypertension (18.8%), and anorexia (12.8%)
    - c) The Asia-Pacific trial included more patients with HBV (73%) than the SHARP trial (6.1%), but this is likely due to regional differences in infection rates

#### Sorafenib vs placebo for advanced HCC

Outcomes	SHARP trial <sup>71</sup>	Asia-Pacific trial <sup>72</sup>
<b>OS (months)</b>	10.7 vs 7.9 P<0.001	6.5 vs 4.2 P=0.014
<b>PFS (months)</b>	5.5 vs 2.8 P=0.001	5.5 vs 2.8 P=0.001
<b>Disease control rate</b>	43% vs 32% P=0.002	53% vs 12% P=0.0019
<b>Time to symptomatic progression (months)</b>	4.9 vs 4.1 NS	3.5 vs 3.4 NS

OS=overall survival; PFS=progression-free survival; NS=not significant

- d) Sorafenib was the first systemic therapy to significantly prolong survival in HCC patients
- e) Sorafenib dosing in hepatic impairment
  - i. Results from a phase I study evaluated the use of sorafenib in patients with hepatic or renal dysfunction has been published<sup>73</sup>

### Sorafenib dose adjustments for hepatic or renal dysfunction<sup>73</sup>

Study Group	Lab Parameter(s)	Recommended Starting Dose
Cohort 1	Bilirubin < ULN AST < 1.5 x ULN, and CrCl > 60 mL/min	400 mg BID (standard dose)
Cohort 2	Bilirubin > ULN, but < 1.5 x ULN and/or AST > ULN	400 mg BID
Cohort 3	CrCl between 40-59 mL/min	400 mg BID
Cohort 4	Bilirubin > 1.5 x ULN to < 3 x ULN with any AST value	200 mg BID
Cohort 5	CrCl between 20-39 mL/min	200 mg BID
Cohort 6	Bilirubin > 3 x ULN to 10 x ULN with any AST value	200 mg every 3 <sup>rd</sup> day was not tolerated
Cohort 7	CrCl < 20 mL/min	Recommended starting dose was not defined in the study. Four patients received 200 mg every other day and 1 patient experienced dose limiting toxicity.
Cohort 8	Albumin < 2.5 mg/dL with any bilirubin or AST value	200 mg daily
Cohort 9	Hemodialysis, any CrCl	200 mg daily

ULN = upper limit of normal

- ii. Pinter and colleagues retrospectively evaluated sorafenib in patients with mild to advanced stage cirrhosis of the liver<sup>74</sup>
  - (a) 59 patients with Child-Pugh class A (n=26) / B (n=23) / C (n=10) were treated with sorafenib
  - (b) All patients received an initial dose of 400 mg BID which was adjusted based on tolerance
    - 46% Child-Pugh class A patients, 48% Child-Pugh class B and 20% Child-Pugh class C patients had to reduce their daily dose
    - The lower discontinuation rate in the Child-Pugh C patients was likely due to their shorter OS
    - Diarrhea was the most common side effect overall; GI bleeding, nausea, emesis, and epistaxis were only seen in the Child-Pugh class B and C patients
  - (c) Median OS was 8.3, 4.3, and 1.5 months for Child-Pugh class A, B, and C patients, respectively
  - (d) Authors concluded that sorafenib may not provide any benefit for Child-Pugh class C patients due to their poor prognosis overall
    - The NCCN Guidelines® reflect this notion, and only recommend sorafenib for Child-Pugh class A and B7 patients<sup>53</sup>

### 2) Lenvatinib (REFLECT<sup>75</sup>)

- a) Non-inferiority trial to assess lenvatinib against sorafenib as a first-line therapy for HCC

- b) Lenvatinib dosing based on body weight
  - i. 12 mg/day for weight  $\geq 60$  kg
  - ii. 8 mg/day for weight  $< 60$  kg

**Summary of the REFLECT<sup>75</sup> trial**

<b>Lenvatinib versus Sorafenib for First-line Advanced Hepatocellular Carcinoma</b>		
	Lenvatinib (n=478)	Sorafenib (n=476)
Median OS [HR 0.92; 95% CI 0.79-1.06]	13.6 months	12.3 months
PFS [ <b>p &lt;0.0001</b> ]	<b>7.4 months</b>	3.7 months
ORR [ <b>p &lt;0.0001</b> ]	<b>24.1%</b>	9.2%
Adverse events (any grade occurring in $\geq 20\%$ of patients in either group)		
<b>Palmar-plantar erythrodysesthesia</b>	27%	<b>52%</b>
Diarrhea	39%	46%
<b>Hypertension</b>	<b>42%</b>	30%
Decreased appetite	34%	27%
Decreased weight	31%	22%
Fatigue	30%	25%
<b>Alopecia</b>	3%	<b>25%</b>
<b>Proteinuria</b>	<b>25%</b>	11%
<b>Dysphonia</b>	<b>24%</b>	12%
<b>Nausea</b>	<b>20%</b>	14%

OS=overall survival; PFS=progression-free survival; ORR=objective response rate

- c) Majority of patients were Child-Pugh class A (99% in both groups), with the remainder being Child-Pugh class B
  - d) Non-inferiority for OS of lenvatinib was shown, and superiority of sorafenib was not achieved
  - e) Treatment-related adverse events that led to drug interruption were similar between the lenvatinib (40%) and sorafenib (32%) groups
- 3) Atezolizumab + bevacizumab (IMbrave150<sup>76,77</sup>)
- a) Phase III trial compared atezolizumab + bevacizumab against sorafenib in previously untreated patients with unresectable HCC
  - b) All patients were Child-Pugh class A
  - c) Median OS was 19.2 months in the atezolizumab + bevacizumab group and 13.2 months in the sorafenib group (HR 0.66, 95% CI, 0.52-0.85; p <0.001)
  - d) Median PFS was significantly longer in the atezolizumab + bevacizumab group at 6.9 months vs 4.3 months in the sorafenib group (HR 0.65, 95% CI, 0.53-0.81; p<0.001)
  - e) Serious adverse events occurred more frequently in the atezolizumab + bevacizumab group (38%) than the sorafenib group (30.8%), with the most common grade 3/4 event in the combination group being hypertension (15.2%)
  - f) Results from the IMbrave trial led to FDA approval for this combination in the first-line setting for unresectable or metastatic HCC, as well as support in the NCCN Guidelines<sup>53</sup>

- 4) Durvalumab + tremelimumab-actl (HIMALAYA<sup>78</sup>)
  - a) Phase 3 trial investigated various immunotherapy regimens against standard sorafenib in the front-line setting for metastatic HCC patients:
    - i. Tremelimumab x1 300 mg dose + durvalumab 1500 mg Q4 weeks (aka STRIDE regimen)
      - (a) A single priming dose of the CTLA-4 inhibitor tremelimumab was shown to synergize with ongoing PD-L1 inhibitor durvalumab, while not increasing toxicities
    - ii. Durvalumab 1500 mg Q4 weeks
    - iii. Tremelimumab 75 mg Q4 weeks x4 doses + durvalumab 1500 mg Q4 weeks
      - (a) Enrollment to this arm ceased after interim analysis showed no efficacy difference from durvalumab alone
    - iv. Sorafenib 400 mg BID
  - b) The primary objective of OS for STRIDE vs sorafenib was significantly improved at data presentation: 16.4 vs 13.8 months (HR 0.78, 96% CI, 0.65–0.92; p=0.0035)
    - i. The secondary objective of noninferiority of median OS for durvalumab vs sorafenib was also met: 16.6 vs 13.8 months (HR 0.86; 96% CI, 0.73–1.03), noninferiority margin was 1.08
    - ii. Superiority of durvalumab vs sorafenib was not shown
  - c) Grade 3/4 adverse events occurred in 25.8% STRIDE group, 12.9% durvalumab group, and 36.9% sorafenib group
  - d) Tremelimumab-actl (Imjudo<sup>®</sup>)<sup>79</sup>
    - i. Mechanism of action
      - (a) Binds to CTLA-4 and blocks interaction with ligands CD80 and CD86, preventing CTLA-4-mediated inhibition of T-cell activation
    - ii. Indications & dosing
      - (a) Unresectable hepatocellular carcinoma
        - 300 mg (weight ≥30 kg) or 4 mg/kg (weight <30 kg) as a single dose in combination with durvalumab
      - (b) Metastatic non-small cell lung cancer (NSCLC)
        - 75 mg (weight ≥30 kg) or 1 mg/kg (weight <30 kg) every 3 weeks for 4 cycles in combination with durvalumab and platinum-based chemotherapy, then a fifth dose (with durvalumab dose #6) at week 16
    - iii. Toxicities
      - (a) Most common adverse reactions include rash, diarrhea, fatigue, pruritus, musculoskeletal pain, abdominal pain, AST/ALT/alk phos/bilirubin increases,



hemoglobin decrease, sodium decrease, and lymphocyte decrease in HCC patients

(b) Most common adverse reactions include nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea in NSCLC patients

(c) Can also cause immune-related adverse events similar to other checkpoint inhibitors

iv. Direct drug-drug interactions are not expected

5) Pembrolizumab (KEYNOTE 224<sup>80</sup>)

a) Cohort 2 of the phase 2 trial that investigated ORR of pembrolizumab in treatment-naïve patients

b) All patients had Child-Pugh A disease

c) ORR was 16%, with best response of 18% PR

d) Median PFS was 4 months with median OS of 17 months

e) No new safety signals were identified, and treatment-related adverse effects were predictable

6) Nivolumab (CheckMate 459<sup>81</sup>)

a) Phase 3 trial compared nivolumab to sorafenib for first line treatment of HCC

b) The median OS did not meet the prespecified threshold for statistical significance: 15.2 months for nivolumab and 13.4 months for sorafenib, HR 0.85, 95% CI 0.72–1.02;  $p=0.075$

c) Median PFS was 3.8 months for nivolumab and 3.9 months for sorafenib

d) Serious adverse events occurred in 12% of patients in nivolumab group and 11% of patients in sorafenib group

i. Adverse events accounted for 57% of dose delays in nivolumab group and 89% of dose delays in sorafenib group

e) The authors concluded that although the statistical endpoints were not met, nivolumab still showed clinically meaningful improvements in OS with a favorable safety profile

d. Subsequent-line options

1) Regorafenib (RESORCE<sup>82</sup>)

a) Evaluated regorafenib in HCC patients with disease progression on sorafenib

i. Patients had to tolerate  $\geq 400$  mg/day of sorafenib for at least 20 of the last 28 days before discontinuation of treatment and have Child Pugh class A liver function

b) Regorafenib significantly improved OS (10.6 vs 7.8 months,  $p<0.0001$ ), PFS (3.1 vs 1.5 months,  $p<0.0001$ ), and ORR (11% vs 4%,  $p=0.0047$ ) compared to placebo

c) Of the patients in the regorafenib group, 68% had dose interruptions or reductions due to adverse events

- i. Most common adverse events leading to discontinuation were increase in ALT and AST increase and hand-foot skin reaction
- 2) Cabozantinib (CELESTIAL<sup>83</sup>)
  - a) Evaluated cabozantinib in HCC patients who had previous treatment with sorafenib and had disease progression after at least one systemic treatment
    - i. Patients had to be Child-Pugh class A
    - ii. Cabozantinib was dosed as 60 mg orally once daily
  - b) Cabozantinib improved median OS (10.2 vs 8.0 months,  $p=0.005$ ), PFS (5.2 vs 1.9 months,  $p<0.001$ ), and ORR (4% vs <1%,  $p=0.009$ ) over placebo
  - c) Most common adverse events in more than 20% of patients taking cabozantinib were diarrhea (54%), decreased appetite (48%), palmar-plantar erythrodysesthesia (46%), fatigue (45%), nausea (31%), hypertension (29%), vomiting (26%), increased AST (22%), and asthenia (22%)
    - i. 62% of patients required a dose adjustment leading to a median average daily dose of 35.8 mg
  - d) Cabozantinib is supported by the NCCN<sup>®</sup> panel and FDA approved for use in HCC patients who have failed or progressed on sorafenib
    - i. Cabozantinib is commercially available as two distinct formulations, and Cabometyx<sup>®</sup> tablets is the product approved for HCC
- 3) Ramucirumab (REACH-2<sup>84</sup>)
  - a) Randomized patients who had progressed after sorafenib to ramucirumab or placebo
    - i. Key inclusion criteria were Child-Pugh class A disease only, serum AFP  $\geq 400$  ng/mL, and sorafenib as the only prior systemic treatment
    - ii. The authors state the AFP threshold of 400 ng/mL does not have a clear significance, however concentrations above this have been associated with worse outcomes and aggressive tumor features
  - b) Ramucirumab significantly improved OS (8.5 vs 7.3 months; HR 0.71 95% CI 0.531-0.949,  $p=0.0199$ ) and PFS (2.8 vs 1.6 months; HR 0.452 95% CI 0.339-0.603,  $p<0.0001$ ), but did not significantly change ORR compared to placebo (5% vs 1%)
  - c) Frequent adverse events of any grade in the ramucirumab group were fatigue (27%), peripheral edema (25%), hypertension (25%), and decreased appetite (23%)
    - i. Serious adverse events of grade  $\geq 3$  occurring in >5% patients were hypertension and hyponatremia
  - d) Ramucirumab is FDA-indicated for the treatment of patients with HCC who have an AFP of  $\geq 400$  ng/mL and have been treated with sorafenib
- 4) Nivolumab  $\pm$  ipilimumab

- a) CheckMate-040<sup>85</sup> was a phase 1/2, multicenter, single arm, open label dose escalation/expansion trial in patients with advanced HCC that investigated nivolumab with and without ipilimumab in multiple cohorts
    - i. Patients had disease progression on at least 1 prior line of systemic therapy or intolerant or refused sorafenib, and had Child-Pugh class A liver function in most cohorts
    - ii. Single-agent nivolumab cohort<sup>85</sup>:
      - (a) Tumor response rate (20% overall) and durability of response (9 months) lead to accelerated approval of nivolumab for treatment of HCC
      - (b) Any grade adverse events were reported in 83% of patients, with 25% grade 3/4
    - iii. Nivolumab + ipilimumab cohort<sup>86</sup>:
      - (a) Three dosing schema were investigated:
        - Arm A: Ipi 3 mg/kg + nivo 1 mg/kg Q3 weeks x4 doses, then nivo 240 mg Q2 weeks
        - Arm B: Ipi 1 mg/kg + nivo 3 mg/kg Q3 weeks x4 doses, then nivo 240 mg Q2 weeks
        - Arm C: Ipi 1 mg/kg Q6 weeks + nivo 3 mg/kg Q2 weeks
      - (b) Arm A had numerically the highest response rates (32%) and median OS (22.8 months), however also the highest grade 3/4 treatment-related adverse events (53%)
    - iv. Single-agent nivolumab in Child-Pugh class B cohort<sup>87</sup>:
      - (a) Patients had Child-Pugh B7 or B8 disease
      - (b) 25 patients were sorafenib-naïve, and 24 were sorafenib-treated
      - (c) ORR was 12%, with a disease control rate of 55%
      - (d) Median OS for all patients was 7.6 months; 9.8 months for sorafenib-naïve and 7.4 months for sorafenib-treated patients
- 5) Pembrolizumab
- a) KEYNOTE-224 was a phase II trial that enrolled patients with HCC who were either intolerant to or had progression on sorafenib<sup>88</sup>
    - i. ORR of 18.3% was seen in the 104 patients, with a median PFS of 4.8 months
    - ii. 97% of patients experienced at least one adverse event of any grade, and 40% of these events were deemed serious
  - b) KEYNOTE-240 was the phase III confirmatory trial that randomized patients for pembrolizumab or best supportive care<sup>89</sup>

- i. This trial failed to meet statistical significance for median OS: 13.9 months (95% CI, 11.6 to 16.0 months) for pembrolizumab vs 10.6 months (95% CI, 8.3 to 13.5 months) for placebo (HR, 0.781; 95% CI, 0.611 to 0.998;  $p = .0238$ )
  - c) Pembrolizumab has an FDA indication for HCC in patients who have previously progressed on sorafenib<sup>90</sup>, however based on the negative results of KEYNOTE-240, the NCCN Guidelines<sup>®</sup> downgraded the recommendation for pembrolizumab to category 2B
- e. NCCN Guidelines recommendations for systemic therapy<sup>53</sup>
  - 1) First-line options
    - a) Preferred, category 1
      - i. Atezolizumab + bevacizumab (Child-Pugh A only)
      - ii. Tremelimumab-actl + durvalumab
    - b) Other
      - i. Sorafenib (Child-Pugh A [category 1] or B7)
      - ii. Lenvatinib (Child-Pugh A only; category 1)
      - iii. Durvalumab
      - iv. Pembrolizumab (category 2B)
    - c) Useful in certain circumstances
      - i. Nivolumab if ineligible for TKIs or anti-angiogenic agents (Child-Pugh A or B, category 2B)
  - 2) Subsequent-line options
    - a) Category 1
      - i. Regorafenib (Child-Pugh A only)
      - ii. Cabozantinib (Child-Pugh A only)
      - iii. Ramucirumab (AFP  $\geq 400$  ng/mL and Child-Pugh A only)
    - b) Lenvatinib (Child-Pugh A only), if not used in first-line setting
    - c) Sorafenib (Child-Pugh A or B7), if not used in first-line setting
    - d) Other recommended regimens
      - i. Nivolumab + ipilimumab (Child-Pugh A only)
      - ii. Pembrolizumab (Child-Pugh A only; category 2B)
    - e) Useful in certain circumstances
      - i. Nivolumab (Child-Pugh B only, category 2B)
      - ii. Dostarlimab-gxly for MSI-H/dMMR tumors (category 2B)
      - iii. Selpercatinib for *RET* gene fusion-positive tumors (category 2B)
- B. Treatment of potentially resectable or transplantable, operable by performance status or comorbidity<sup>53</sup>

1. Primary goal is cure with surgery or liver transplant; otherwise the goal shifts to palliative treatment
    - a. Severity of underlying cirrhosis often limits treatment options since residual liver must be able to tolerate toxicity from treatment to regenerate
  2. Surgery
  3. Transplant
  4. Locoregional therapy
- C. Treatment of unresectable disease due to tumor location or inadequate hepatic reserve<sup>53</sup>
1. Transplant
  2. If not eligible for transplant:
    - a. Locoregional therapy (preferred)
    - b. Systemic Therapy
    - c. Clinical trial
    - d. Best supportive care
- D. Treatment of inoperable disease due to performance status or comorbidity with local disease or local disease with minimal extrahepatic disease only<sup>53</sup>
1. Locoregional therapy (preferred)
  2. Systemic therapy
  3. Clinical trial
  4. Best supportive care
- E. Treatment of metastatic disease or extensive liver tumor burden<sup>53</sup>
1. Systemic therapy
  2. Clinical trial
  3. Best supportive care

**Patient Case #4 Answer: (ARS Question #4)**

**Correct answer is C.** In the IMbrave 150 trial, atezolizumab + bevacizumab was compared against sorafenib in previously untreated patients with unresectable HCC. Median OS had not been reached in the combination group, vs only 13.2 months in the sorafenib group. The combination did significantly improve PFS as well.

Answer A is incorrect because this patient's tumor is >5 cm so he is not eligible for liver transplantation

Answer B is incorrect because cytotoxic chemotherapy has not been shown to improve OS in patients with HCC. FOLFOX is an option for patients with unresectable or metastatic HCC if they cannot otherwise tolerate a TKI or anti-angiogenic agent.

Answer D is incorrect, although up until recently would have been the correct choice. But with the results of the IMbrave150 trial, atezolizumab + bevacizumab provides an OS survival advantage over sorafenib in the first-line setting for unresectable or metastatic HCC.

**IV. Survivorship and Long-term Follow-up**

**A. Survivorship<sup>53</sup>**

1. Transplant recipients should be managed according to transplant guidelines
2. Serious toxicities from locoregional therapies are rare, however patients should be monitored and appropriately managed
  - a. TAE or TACE
    - 1) Liver failure, pancreatitis, cholecystitis
    - 2) Acute portal vein thrombosis, hepatic necrosis, liver abscess
    - 3) Bone marrow suppression
  - b. TARE
    - 1) Cholecystitis/bilirubin toxicity
    - 2) GI ulceration
    - 3) Radiation-induced liver disease, liver abscess

**B. Surveillance following curative intent therapy<sup>53</sup>**

1. Imaging with CT or MRI every 3-6 months for 2 years, then every 6 months thereafter
2. AFP every 3-6 months for 2 years, then every 6 months
3. Refer hepatitis carriers to hepatologist for discussion about antiviral therapy

## RADIATION RECALL

### Patient Case #5: (ARS Question #5)

HT is a 58-year-old female with a locally advanced adenocarcinoma of the esophagus. She received preoperative chemoradiation with carboplatin and paclitaxel which was followed by esophagectomy. She has been observed for the past year for disease progression and was found to have new liver metastases on the most recent restaging evaluation. HT received cycle 1 of chemotherapy with fluorouracil and irinotecan (FOLFIRI) and presents to the infusion center today for chemotherapy pump disconnection. She reports that the skin on her chest is red and painful to touch. The physician is concerned HT may be experiencing mild radiation recall.

**Which of the following management strategies is most appropriate for HT's mild radiation recall?**

- A. Observation and continue therapy with no modifications
- B. Supportive care and continue therapy with dose reduction
- C. Steroid premedication and continue therapy with dose reduction
- D. High-dose steroids and discontinue therapy

### I. Radiation Recall<sup>91-97</sup>

- A. Radiation recall is an inflammatory reaction that occurs in a previously irradiated area and is precipitated by administration of a causative agent
  - 1. Offending chemotherapy agents include alkylating agents, taxanes, anthracyclines, antitumor antibiotics, antimetabolites, vinca alkaloids, EGFR inhibitors, and BRAF inhibitors
  - 2. Other non-chemotherapeutic agents include antibacterial agents, NSAIDs, lipid-lowering agents, and antitubercular drugs

### Chemotherapy Agents Associated with Radiation Recall and Radiation Sensitization<sup>91-93</sup>

Radiation Recall			
Actinomycin Bleomycin Capecitabine Carboplatin Cisplatin Cyclophosphamide Cytarabine Dacarbazine Dactinomycin	Daunorubicin Docetaxel Doxorubicin Doxorubicin, Liposomal Epirubicin Etoposide Fluorouracil Gefitinib Gemcitabine	Hydroxyurea Idarubicin Interferon Ixabepilone Lomustine Melphalan Methotrexate Oxaliplatin Paclitaxel	Paclitaxel, Protein bound Pemetrexed Sorafenib Sunitinib Tamoxifen Trastuzumab Vinblastine Vincristine Vinorelbine
Radiation Sensitizers			
Actinomycin Bleomycin Capecitabine Carboplatin Chlorambucil Cisplatin Dactinomycin	Daunorubicin Doxorubicin Doxorubicin, liposomal Etoposide Fluorouracil	Gemcitabine Hydroxyurea Interferon 6-Mercaptopurine Methotrexate	Paclitaxel Pemetrexed Thiotepa Trastuzumab Vorinostat

- A. Pathophysiology of radiation recall remains unclear, but several hypotheses have been generated
  - 1. Changes to stem cell function or sensitivity due to radiation
  - 2. Radiation induces secretion of cytokines and presence of a chemotherapy agent causes cytokine upregulation, resulting in radiation recall
  - 3. Cumulative DNA damage and stress causes keratinocyte necrosis (radiation recall dermatitis)
  - 4. Idiosyncratic drug hypersensitivity reaction also a possibility due the potential for rapid onset after drug exposure
- B. Incidence difficult to determine as mostly case reports (6-8%)
- C. Radiation recall can be confused with radiosensitization
  - 1. Occurs >7 days after completion of radiation therapy
  - 2. Can occur weeks to years after radiation exposure
    - a. Radiation recall reported to occur 6-37 days between completion of radiation therapy and chemotherapy exposure <sup>95</sup>
      - 1) Although radiation recall has been reported up to 15 years post-completion of radiation, recall tends to be more severe when the period of time between radiation and chemotherapy is short
- D. Characterized by acute inflammatory reaction that is confined to an area previously irradiated
  - 1. Reaction affects normal skin and/or organs, but affects a previously irradiated area
  - 2. Skin reaction most commonly reported (2/3rd of cases)
  - 3. Can also affect lungs, oral mucosa, GI system, GU system, nervous system
    - a. Mucositis, ulcerative stomatitis, gastritis, colitis, myositis, panniculitis, pneumonitis
  - 4. Pathology demonstrates mixed, nonspecific inflammatory infiltrate <sup>93</sup>
- E. Symptoms typically occur within days to few weeks after exposure to precipitating chemotherapy agent
  - 1. Can occur during or immediately after intravenous infusion to after multiple chemotherapy cycles
  - 2. May take months to appear with oral agents
- F. Management
  - 1. Biopsy typically not necessary
  - 2. Most cases resolve with symptom management
  - 3. Stop the suspected agent to allow skin to heal
  - 4. Topical and/or systemic corticosteroids or anti-inflammatory agents may be used to decrease inflammation
  - 5. Antihistamines may also be used
  - 6. Reactions typically resolve within days to two weeks



## Radiation Recall Management<sup>96</sup>

Radiation Recall Reaction			
Skin Reaction		Internal Organs	
Mild to Moderate	Severe	Mild to Moderate	Severe
<ul style="list-style-type: none"> <li>• Close observation</li> <li>• As needed               <ul style="list-style-type: none"> <li>○ Topical steroids</li> <li>○ Nonsteroidal anti-inflammatories</li> <li>○ Anti-histamines</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue agent or reduce dose</li> <li>• High-dose systemic steroids</li> <li>• Topical steroids</li> <li>• Nonsteroidal anti-inflammatories</li> <li>• Anti-histamines</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue agent or reduce dose</li> <li>• High-dose systemic steroids</li> <li>• Supportive care</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue agent</li> <li>• High-dose systemic steroids</li> <li>• Supportive care</li> <li>• Surgical consult as necessary</li> </ul>

G. Rechallenge with a precipitating agent does not always elicit a subsequent reaction

1. Rechallenging with an agent suspected to cause a reaction will depend on the extent, severity, and location of the reaction, as well as the patient's preference
2. Patients may tolerate further treatment with dose reduction or premedication with corticosteroids

## II. Radiation Dermatitis<sup>92,98</sup>

- A. One of the most common adverse effects associated with radiation therapy
- B. Typically presents within the first several weeks but can manifest up to 6 months after treatment
- C. Presentation ranges from erythema and dry desquamation and/or pruritus to moist desquamation and ulceration
- D. Consensus guideline for the management of radiation dermatitis and coexisting acne-like rash in patients who are receiving EGFR inhibitors plus radiotherapy have been published<sup>99</sup>
  1. EGFR inhibitor-induced rash may actually be lacking in the areas of previous irradiation possibly because of a lack of cells that express EGFRs as a result of prior treatment
  2. However, EGFR inhibitors can act as sensitizers causing a more severe skin reaction when radiation treatment is given concurrently
- E. General management:
  1. Establish a proper technique to minimize epidermis exposure
  2. Verify skin reaction is not due to any other concomitant medication other than the EGFR-inhibitor
- F. Prevention:
  1. Key step is to keep the irritated area clean and dry even when ulcerated. Gentle washing and drying of the skin within the radiation portal prior to treatment is recommended
    - a. Use a gentle cleaner and dry the area with a soft, clean towel – use of a pH-neutral synthetic detergent is preferable to soap which is irritating to the skin
  2. Numerous topical high-potency corticosteroid creams (beclomethasone, betamethasone, methylprednisolone, mometasone) can be considered for use to treat this condition
  3. Avoid sun exposure and tanning beds, use sunscreen and wear loose clothing<sup>91</sup>
- G. Treatment principles:

1. Topical treatment approaches can provide symptomatic relief and may facilitate skin healing
2. Drying pastes can be used in areas within skin folds where skin reactions remain moist
3. Gels can be used in seborrheic areas
4. Creams can be used in areas outside skin folds and seborrheic areas
5. Hydrophilic dressings can also be used in moist areas and should be placed over the cleaned, dried wound and some even absorb wound exudate
6. Avoid greasy topical products
7. Topical moisturizers, gels, emulsions and dressings should not be applied shortly before radiation treatment as they may cause a bolus effect and artificially increase the radiation dose to the epidermis

H. Treatment by toxicity grade criteria<sup>92,100</sup>

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

1. Grade 1
  - a. Requires no specific treatment, but the area should be kept clean between treatments
  - b. Use of a non-perfumed moisturizer is an option
  - c. Moisturizers containing anti-bacterials may be used occasionally if infective measures are considered appropriate
  - d. Overtreatment and/or excessive rubbing can irritate the skin and should be avoided
2. Grades 2 and 3
  - a. Keep area clean and dry, even when ulcerated
  - b. Topical applications can be considered
    - 1) Drying gels with the addition of antiseptics, if considered appropriate
    - 2) Hydrophilic dressings
    - 3) Anti-inflammatory emulsion
    - 4) Zinc oxide paste – if considered easy to remove prior to radiation
    - 5) Silver sulfadiazine or beta-glucan cream may also be useful but should only be applied after radiation, in the evening, after cleaning the irradiated area

- c. If infection is suspected, use best clinical judgment for management including culturing the area for possible infectious cause
    - 1) Check CBC as may be associated with a risk of sepsis in patients with severe desquamation
    - 2) Topical antibiotics should be reserved for superinfection and should not be used prophylactically
    - 3) Doxycycline is not recommended at this stage
  - d. Assess skin reactions weekly
- 3. Grade 4
  - a. Rare complication, occurring in <5% of patients receiving radiotherapy for squamous cell carcinoma of the head and neck
  - b. Requires specialized wound care and should be treated on a case-by-case basis and managed primarily by a wound specialist in conjunction with the radiation oncologist and medical oncologist, dermatologist, and nurse as needed
- I. Management of coexisting radiation dermatitis and EGFR inhibitor-related acne-like rash within irradiated fields <sup>98,99</sup>
  - 1. Grade 1 radiation dermatitis (or no radiation dermatitis) – follow general guidelines on the management of EGFR inhibitor-related acne-like rash outside of the irradiated fields
  - 2. For ≥grade 2 – preferred to adhere to the management recommendations for radiation dermatitis as outlined above

**Patient Case #5 Answer: (ARS Question #5)**

**Correct answer is A.** Fluorouracil is a chemotherapy agent known to be associated with radiation recall. Symptoms can occur during or immediately after intravenous infusions, which is consistent with timing of the fluorouracil infusion and onset of symptoms. The area should be kept clean and dry and avoid excessive rubbing which may further irritate the skin. Supportive care with moisturizers, nonsteroidal anti-inflammatories, anti-histamines, or topical steroids may be considered if needed. Given that the patient is experiencing mild symptoms, it would be reasonable for her to continue receiving chemotherapy with close monitoring for worsening of symptoms.

Answer B: Supportive care with moisturizers, nonsteroidal anti-inflammatories, anti-histamines, or topical steroids may be considered if needed. Dose reduction of therapy is indicated for severe skin reactions.

Answer C: Steroid premedication can be considered, but dose reduction of therapy is indicated for severe skin reactions.

Answer D: High-dose steroids are indicated for severe skin reactions or reactions affecting internal organs. Discontinuation of therapy is indicated for severe skin reactions.

## SUGGESTED READINGS

### Gastric/Esophageal Cancer

1. Joshi SS, Badgwell BD. Current Treatment and Recent Progress in Gastric Cancer. *CA Cancer J Clin*. 2021;71:264-79. (<https://pubmed.ncbi.nlm.nih.gov/33592120/>)
2. Kelly RJ, Ajani JA, Kuzdzal J. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. 2021;384:1191-1203. (<https://pubmed.ncbi.nlm.nih.gov/33789008>)
3. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol*. 2016;17:1697-708. (<https://www.ncbi.nlm.nih.gov/pubmed/27776843>)

### Liver Cancer

1. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular Carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. (<https://pubmed.ncbi.nlm.nih.gov/33479224/>)
2. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382:1894-1905. (<https://pubmed.ncbi.nlm.nih.gov/33556230/>)
3. Cheng AL, Hsu C, Chan SL, et al. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. 2020;72:307-39. (<https://pubmed.ncbi.nlm.nih.gov/31954494/>)

### Radiation Recall

1. Burris HA, Hurtig J. Radiation recall with anticancer agents. *Oncologist*. 2010;15:1227-37. (<https://pubmed.ncbi.nlm.nih.gov/21045191/>)
2. Purkayastha A, Sharma N, Taneja S, et al. Sociodemographic, clinical profile, and treatment characteristics of oncology patients developing radiation recall phenomenon: Two tertiary care center's experience of an eternal unpredictable phenomenon of cancer treatment. *Tzu Chi Med J*. 2021;34(3):337-47. (<https://pubmed.ncbi.nlm.nih.gov/35912053/>)

## REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers. V.5.2022, 12/05/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
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3. Rustgi AK. Molecular Biology of the Esophagus and Stomach. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 10th ed. Lippincott Williams & Wilkins; 2015:chap 44.

4. Avital I S, A, Pisters PWT, Kelsen DP, Willett CG. *Cancer of the Stomach. In: Cancer: principles and practice of oncology*. 10th ed. JB Lippincott Company; 2015.
5. Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. Sep 2014;513(7517):202-9. doi:10.1038/nature13480
6. Libutti SK, Saltz L, Willett C, Levine RA. Cancer of the Colon. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2019:chap 62.
7. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357:409-13.
8. Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer*. Jul 2015;18(3):476-84. doi:10.1007/s10120-014-0402-y
9. Ruschoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. *Virchows Arch*. Sep 2010;457(3):299-307. doi:10.1007/s00428-010-0952-2
10. Muro K, Chung HC, Shankaran V, Geva R, Daniel Catenacci SG, Joseph Paul Eder, Talia Golan, Dung T Le, Barbara Burtness, Autumn J McRee, Chia-Chi Lin, Kumudu Pathiraja, Jared Lunceford, Kenneth Emancipator, Jonathan Juco, Minori Koshiji, Yung-Jue Bang. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol*. 2016;17:717-26.
11. Vingeliene S, Chan DSM, Vieira AR, et al. An update of the WCRF/AICR systematic literature review and meta-analysis on dietary and anthropometric factors and esophageal cancer risk. *Ann Oncol*. 2017;28:2409-19.
12. Fang X, Wei J, He X, et al. Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. *Eur J Cancer*. 2015;51:2820-32.
13. Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst*. Sep 15 1993;85(18):1483-92.
14. Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *J Natl Cancer Inst*. Dec 6 2000;92(23):1881-8.
15. Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA*. Jan 14 2004;291(2):187-94. doi:10.1001/jama.291.2.187
16. Brennan MF, Karpeh MS, Jr. Surgery for gastric cancer: the American view. *Semin Oncol*. Jun 1996;23(3):352-9.
17. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol*. Jun 1 2004;22(11):2069-77. doi:10.1200/jco.2004.08.026
18. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. Sep 6 2001;345(10):725-30. doi:10.1056/NEJMoa010187
19. Smalley SR, Benedetti JK, Haller DG, et al. Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection. *J Clin Oncol*. 2012;30(19):2327-33.
20. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. Jul 6 2006;355(1):11-20. doi:10.1056/NEJMoa055531
21. Al-Batran S-E, einz RDH, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol*. 2016;17:1697-708.
22. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 05 2019;393(10184):1948-1957. doi:10.1016/S0140-6736(18)32557-1
23. Posner MD MB, Ilson DH. *Cancer of the esophagus. In: Cancer: principles and practice of oncology*. 10th ed. JB Lippincott Company; 2015.

24. Shapiro J, van Lanschot J, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol.* 2015;16:1090-98.
25. van Hagen P, Hulshof M, van Lanschot J, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med.* 2012;366:2074-84.
26. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med.* 04 2021;384(13):1191-1203. doi:10.1056/NEJMoa2032125
27. Opdivo (nivolumab) injection. Prescribing Information. Bristol-Myers Squibb Company, Princeton, NJ. Revised::8/2018.
28. Shah MA, Hofstetter WL, Kennedy EB. Immunotherapy in Patients With Locally Advanced Esophageal Carcinoma: ASCO Treatment of Locally Advanced Esophageal Carcinoma Guideline Rapid Recommendation Update. *J Clin Oncol.* 2021;DOI: 10.1200/JCO.21.01831
29. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol.* Apr 2009;20(4):666-73. doi:10.1093/annonc/mdn717
30. Al-Batran S-E, Hartmann JT, Probst S, Schmalenberg H, Stephan Hollerbach RH, Volker Rethwisch, Gernot Seipelt, Nils Homann, Gerhard Wilhelm, Gunter Schuch,, Jan Stoehlmacher HGnD, Susanna Hegewisch-Becker, Johannes Grossmann, Claudia Pauligk, Akin Atmaca, Carsten Bokemeyer, Alexander Knuth, and Elke Jäger. Phase III Trial in Metastatic Gastroesophageal Adenocarcinoma with Fluorouracil, Leucovorin Plus Either Oxaliplatin or Cisplatin: A Study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol.* 2008;26(9):1435-42.
31. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* Aug 28 2010;376(9742):687-97. doi:10.1016/s0140-6736(10)61121-x
32. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet.* 07 03 2021;398(10294):27-40. doi:10.1016/S0140-6736(21)00797-2
33. Shitara K, Ajani JA, Moehler M, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature.* 03 2022;603(7903):942-948. doi:10.1038/s41586-022-04508-4
34. U.S. Food and Drug Administration. FDA approves nivolumab in combination with chemotherapy for metastatic gastric cancer and esophageal adenocarcinoma. Updated 04/16/2021. Accessed July 14, 2021. Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal>
35. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med.* 02 03 2022;386(5):449-462. doi:10.1056/NEJMoa2111380
36. Administration USFaD. FDA approves Opdivo in combination with chemotherapy and Opdivo in combination with Yervoy for first-line esophageal squamous cell carcinoma indications. Updated 5/27/2022. Accessed August 31, 2022. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-opdivo-combination-chemotherapy-and-opdivo-combination-yervoy-first-line-esophageal>
37. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet.* 08 28 2021;398(10302):759-771. doi:10.1016/S0140-6736(21)01234-4
38. U.S. Food and Drug Administration. FDA approves pembrolizumab for esophageal or GEJ carcinoma. Updated 03/22/2021. Accessed July 14, 2021. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma>
39. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature.* 12 2021;600(7890):727-730. doi:10.1038/s41586-021-04161-3
40. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for HER2-positive gastric cancer. Updated 05/05/2021. Accessed July 14, 2021. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-her2-positive-gastric-cancer>
41. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* Jan 4 2014;383(9911):31-9. doi:10.1016/s0140-6736(13)61719-5

42. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* Oct 2014;15(11):1224-35. doi:10.1016/s1470-2045(14)70420-6
43. Cyramza (ramucirumab) injection. Prescribing Information. Eli Lilly and Company, Indianapolis, IN. Revised:8/2018.
44. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 2015;372:2509-20.
45. Le DT, Uram JN, Wang H, Kemberling H, Aleksandra Eyring BB, Richard M. Goldberg, Todd S. Crocenzi, George A. Fisher, James J. Lee, Tim F. Greten, Dan Laheru, Nilofer Saba Azad, Ross C. Donehower, Brandon Luber, Minoru Koshiji, James R. Eshleman, Robert A Anders, Bert Vogelstein, Luis A. Diaz PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers. *J Clin Oncol.* 2016;34, no. 4\_suppl(February 1 2016):195.
46. Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. *J Clin Oncol.* 12 2020;38(35):4138-4148. doi:10.1200/JCO.20.01888
47. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20:1506-17.
48. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med.* 06 2020;382(25):2419-2430. doi:10.1056/NEJMoa2004413
49. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 11 2018;19(11):1437-1448. doi:10.1016/S1470-2045(18)30739-3
50. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Survivorship. V.1.2022, 03/30/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
51. Fong Y DD, Feng M, Abou-Alfa G. Cancer of the liver. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: principles and practice of oncology.* 10th ed. Lippincott Williams & Wilkins; 2015:chap 52.
52. Marquardt JU, Thorgeirsson SS. Molecular Biology of Liver Cancer. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* Lippincott Williams & Wilkins; 2015:chap 51.
53. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers. V.5.2022, 01/13/2023, © 2023 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
54. Kao J-H. Hepatitis B vaccination and prevention of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol.* 2015;29:907-17.
55. Terrault NA, Lok ASF, McMahon BJ, Chang K-M, Jessica P. Hwang MMJ, 6 Robert S. Brown Jr., 7 Natalie H. Bzowej, 8 and John B. Wong. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. *Hepatology.* 2018;67(4):1560-99.
56. Clark T, Maximin S, Meier J, Pokharel S, Bhargava P. Hepatocellular Carcinoma: Review of Epidemiology, Screening, Imaging Diagnosis, Response Assessment, and Treatment. *Curr Probl Diagn Radiol.* 2015;44:479-86.
57. Shi J, Zhu L, Liu S, Xie WF. A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. *Br J Cancer.* Feb 14 2005;92(3):607-12. doi:10.1038/sj.bjc.6602333

58. Tagger A, Donato F, Ribero ML, et al. Case-control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with hepatitis B virus and alcohol. Brescia HCC Study. *Int J Cancer*. May 31 1999;81(5):695-9.
59. AASLD and IDSA. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America Present HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated May 24, 2018. Accessed September 20, 2018. Available from: [https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance\\_May\\_24\\_2018b.pdf](https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_May_24_2018b.pdf)
60. Zhang B, Yang B. Combined alpha fetoprotein testing and ultrasonography as a screening test for primary liver cancer. *J Med Screen*. 1999;6(2):108-10.
61. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 08 2018;68(2):723-750. doi:10.1002/hep.29913
62. Poon RT-P, Fan S-T. Hepatectomy for Hepatocellular Carcinoma: Patient Selection and Postoperative Outcome. *Liver Transpl*. 2004;10(2)(1 (February)):539-45.
63. Child C, Turcotte J. Surgery and portal hypertension. *Major Probl Clin Surg*. 1964;1:1-85.
64. Pugh R, Murray-Lyon I, Dawson J, Pietroni M, Williams R. Transection of the Oesophagus for Bleeding Oesophageal Varices. *Br J Surg*. 1973;60(8):646-9.
65. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. Sep 22 2011;365(12):1118-27. doi:10.1056/NEJMra1001683
66. Rich NE, Yopp AC, Singal AG. Medical Management of Hepatocellular Carcinoma. *J Oncol Pract*. 2017;13(6):356-64.
67. Yoo HY, Patt CH, Geschwind JF, Thuluvath PJ. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. *J Clin Oncol*. Dec 1 2003;21(23):4329-35. doi:10.1200/jco.2003.11.137
68. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology*. Feb 2003;37(2):429-42. doi:10.1053/jhep.2003.50047
69. Nakakura EK, Choti MA. Management of hepatocellular carcinoma. *Oncology (Williston Park)*. Jul 2000;14(7):1085-98; discussion 1098-102.
70. Song KD. Percutaneous cryoablation for hepatocellular carcinoma. *Clinical and Molecular Hepatology*. 2016;22:509-15.
71. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. Jul 24 2008;359(4):378-90. doi:10.1056/NEJMoa0708857
72. Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Jun Suk Kim RL, Jifeng Feng, Shenglong Ye, Tsai-Sheng Yang, Jianming Xu, Yan Sun, Houjie Liang, Jiwei Liu, Jiejun Wang, Won Young Tak, Hongming Pan, Karin Burock, Jessie Zou, Dimitris Voliotis, Zhongzhen Guan. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:25-34.
73. Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *J Clin Oncol*. Apr 10 2009;27(11):1800-5. doi:10.1200/jco.2008.20.0931
74. Pinter M, Sieghart W, Graziadei I, et al. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. *Oncologist*. Jan 2009;14(1):70-6. doi:10.1634/theoncologist.2008-0191
75. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391:1163-73.
76. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 05 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745
77. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. Apr 2022;76(4):862-873. doi:10.1016/j.jhep.2021.11.030
78. Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *J Clin Oncol*. 2022;40, no. 4\_suppl:379. doi:DOI: 10.1200/JCO.2022.40.4\_suppl.379
79. Imjudo (tremelimumab-actl) injection. Prescribing Information. AstraZeneca Pharmaceuticals LP, Wilmington, DE. Revised:11/2022.



80. Laethem J-LV, Borbath I, Karwal M, et al. Pembrolizumab (pembro) monotherapy for previously untreated advanced hepatocellular carcinoma (HCC): Phase II KEYNOTE-224 study. *J Clin Oncol*. 2021;39(no. 3\_suppl):297. doi:DOI: 10.1200/JCO.2021.39.3\_suppl.297
81. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 01 2022;23(1):77-90. doi:10.1016/S1470-2045(21)00604-5
82. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. Jan 07 2017;389(10064):56-66. doi:10.1016/s0140-6736(16)32453-9
83. Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med*. 2018;379:54-63.
84. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased  $\alpha$ -fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. Feb 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9
85. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. Jun 24 2017;389(10088):2492-2502. doi:10.1016/s0140-6736(17)31046-2
86. Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol*. Nov 01 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564
87. Kudo M, Matilla A, Santoro A, et al. CheckMate 040 cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. *J Hepatol*. 09 2021;75(3):600-609. doi:10.1016/j.jhep.2021.04.047
88. Kudo M, Finn RS, Edeline J, et al. Updated efficacy and safety of KEYNOTE-224: a phase II study of pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. *Eur J Cancer*. 05 2022;167:1-12. doi:10.1016/j.ejca.2022.02.009
89. Finn RS, Ryoo B-Y, Merle P, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). *J Clin Oncol*. 2019;37:no. 15\_suppl (May 20, 2019) 4004-4004.
90. Keytruda (pembrolizumab) for injection. Prescribing Information,. Merck & Co., Inc., Whitehouse Station, NJ. Revised:7/2019.
91. Burris HA, 3rd, Hurlig J. Radiation recall with anticancer agents. *Oncologist*. 2010;15(11):1227-37. doi:10.1634/theoncologist.2009-0090
92. Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. *Radiother Oncol*. Jun 2001;59(3):237-45.
93. Azria D, Magne N, Zouhair A, et al. Radiation recall: a well recognized but neglected phenomenon. *Cancer Treat Rev*. Nov 2005;31(7):555-70. doi:10.1016/j.ctrv.2005.07.008
94. Yeo W, Johnson PJ. Radiation-recall skin disorders associated with the use of antineoplastic drugs. Pathogenesis, prevalence, and management. *Am J Clin Dermatol*. Mar-Apr 2000;1(2):113-6.
95. Kodym E, Kalinska R, Ehringfeld C, Sterbik-Lamina A, Kodym R, Hohenberg G. Frequency of radiation recall dermatitis in adult cancer patients. *Onkologie*. Jan 2005;28(1):18-21. doi:10.1159/000082175
96. Caloglu M, Yurut-Caloglu V, Cosar-Alas R, Saynak M, Karagol H, Uzal C. An ambiguous phenomenon of radiation and drugs: recall reactions. *Onkologie*. Apr 2007;30(4):209-14. doi:10.1159/000099632
97. Bennardo L, Passante M, Cameli N, et al. Skin Manifestations after Ionizing Radiation Exposure: A Systematic Review. *Bioengineering (Basel)*. Oct 22 2021;8(11)doi:10.3390/bioengineering8110153
98. Balagula Y, Lacouture ME, Cotliar JA. Dermatologic toxicities of targeted anticancer therapies. *J Support Oncol*. 2010;8(4):149-61.
99. Bernier J, Bonner J, Vermorken JB, et al. Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck. *Ann Oncol*. Jan 2008;19(1):142-9. doi:10.1093/annonc/mdm400
100. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. National Institutes of Health, National Cancer Institute. Updated 11/27/17. Accessed July 14, 2022. Available from:

[https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_8.5x11.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

# **GYNECOLOGIC MALIGNANCIES**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, management, and monitoring plan taking into consideration efficacy and safety outcomes of clinical trials and current treatment guidelines for a patient with a gynecologic malignancy.
2. Discuss short and long-term goals, including post-therapy and survivorship, with a patient with a gynecologic malignancy and her caregiver.
3. Select relevant information and provide guidance for the public regarding gynecologic malignancy-related issues (e.g., risk factors, prevention, and screening).

## EPITHELIAL OVARIAN CANCER (Including Fallopian Tube and Primary Peritoneal Cancer)

*NOTE: Ovarian, fallopian tube and primary peritoneal cancers are distinct pathologic entities. However, they are diagnosed and managed in the same way. For the purposes of this handout, these three entities will collectively be referred to as “ovarian cancer”.*

### I. Pathogenesis<sup>1-4</sup>

- A. The exact cause of sporadic ovarian cancer is unknown; development is likely a combination of endocrine and environmental factors.
  - 1. Sporadic, or non-hereditary ovarian cancer, is the most common type, accounting for 85-90% of all ovarian cancers in the United States.
  - 2. Familial and hereditary syndromes are less common and account for 10-15% of all ovarian cancers.
    - a. Familial ovarian cancer: The lifetime risk of a woman developing ovarian cancer increases by 50% if she has two or more first degree relatives with ovarian cancer.
    - b. Ovarian cancer occurs in 5-10% of women known to have hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, or other rare genetic syndromes.
    - c. Germline mutations in tumor suppressor genes such as *BRCA1*, *BRCA2*, and *TP53* are thought to play a role in approximately 5-10% of ovarian cancer cases. Mutations of these genes result in unregulated production of mutant proteins and progression toward malignancy.
    - d. Germline deleterious *BRCA1* mutations are associated with a 39-58% absolute risk of developing ovarian cancer. Germline deleterious *BRCA2* mutations are associated with a 13-29% absolute risk. Survival appears to be better in patients with ovarian cancer with *BRCA1* or *BRCA2* mutations compared to women with sporadic ovarian cancer.
      - 1) Germline and somatic *BRCA 1/2* testing are recommended as part of initial workup for newly diagnosed ovarian cancer. Assessment of homologous recombination deficiency (HRD) may provide additional guidance for PARP inhibitor-based maintenance strategies.<sup>4</sup>
      - 2) It is recommended to first test for germline *BRCA 1/2*. If the germline testing results in *BRCA* wildtype (*BRCAwt*) it is then recommended to pursue somatic *BRCA 1/2* testing. While HRD may be important to guide treatment decisions it is not currently recommended at this time given the inconsistency with this test.<sup>5</sup>

### II. Pathophysiology/Pathology<sup>3, 4, 6, 7</sup>

- A. Diverse pathologic entities
  - 1. Epithelial adenocarcinoma makes up approximately 90% of all cases of ovarian cancer
    - a. Four primary histopathology subtypes
      - 1) Serous (70%) – most common
      - 2) Endometrioid (10%)

- 3) Clear-cell (10%) – associated with poor prognosis
- 4) Mucinous (3%)
- b. Grading
  - 1) Grade 1 – well differentiated
  - 2) Grade 2 – moderately differentiated
  - 3) Grade 3 – poorly differentiated; most virulent
  - 4) Serous: grade 1 = low-grade, grade 2-3 = high-grade
- c. Low malignant potential or borderline malignancies (good prognosis) (**\*Not covered in this handout**)
- 2. Germ-cell tumors: highly aggressive and rare (**\*Not covered in this handout**)
  - a. Includes dysgerminoma, endodermal sinus tumor, malignant teratoma, embryonal carcinoma and primary choriocarcinoma of the ovary
- 3. Sex-cord stromal tumors: often hormone producing (**\*Not covered in this handout**)
  - a. Includes granulosa cell tumors, Sertoli-Leydig tumor, and others
- 4. Carcinosarcoma or carcinoma of Mullerian origin: components of both malignant epithelial and sarcomatous portions
- 5. Metastatic from other malignancies (breast and colon are most common). A mucinous histology found on/in the ovaries is more likely to be metastatic gastrointestinal cancer than primary ovarian cancer.

### III. Screening and Prevention

#### A. Screening<sup>3, 4, 8-11</sup>

- 1. There is currently no effective method of screening for ovarian cancer and routine screening in the general population is not recommended.
- 2. Studies looking at transvaginal ultrasound, pelvic examination and/or CA-125 have not been sensitive or specific enough to warrant implementation of large-scale screening programs. The cancer antigen-125 (CA-125) is a non-specific indicator of pelvic inflammation and may be elevated by other conditions including pelvic inflammatory disease or benign fibroids.
- 3. Current recommendation for low-risk women (no history of hereditary ovarian cancer, *BRCA1* and *BRCA2* wild-type).
  - a. **Routine screening is not recommended for asymptomatic, low-risk patients**
  - b. The U.S. Preventive Services Task Force (USPSTF) updated their recommendations in 2018, which remain consistent with the 2012 iteration, stating that routine screening should not be undertaken in asymptomatic low-risk patients. This is based on data from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) Trial which demonstrated no benefit, and substantial risks, for routine screening in the general population:
    - 1) Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) Trial

- a) 78,216 women were randomized to screening with annual transvaginal ultrasound and CA-125 measurements, or usual care with no additional screening. There was no reported difference in ovarian cancer mortality between the two groups. False positives led to unnecessary surgeries in over 1,000 women and serious complications occurred in 163 women.
  - 2) The USPSTF and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend women with symptoms suggestive of ovarian cancer be referred to a gynecologic oncologist for evaluation.
    - a) Symptoms suggestive of ovarian cancer include early satiety, abdominal bloating, abdominal pain, pelvic pain, and changes in urinary habits.
    - b) Women experiencing symptoms, particularly if occurring > 12 days per month should be evaluated by a gynecologic oncologist.<sup>12</sup>
  - 3) Further screening trials continue in women with positive symptoms, trends in CA-125 levels, and patients at risk for hereditary ovarian cancer.
  4. Current recommendations for high-risk women (hereditary ovarian cancer, *BRCA1* or *BRCA2* mutated).<sup>13</sup>
    - a. Consideration of risk-reducing salpingo-oophorectomy (RRSO) between age 35-40 years and upon completion of childbearing. May consider delaying until age 40-45 years in patients with *BRCA2* mutations due to a later onset as compared to *BRCA1* mutation carriers.<sup>13</sup>
    - b. Counsel regarding use of birth control pills and/or prophylactic oophorectomy on a case-by-case basis.
    - c. Women who defer RRSO may be considered for dual modality monitoring with transvaginal ultrasounds and CA-125, beginning at age 30-35 years.
  5. Biomarker panel tests, including OVA1 (evaluates transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, CA-125) and OVASURE (evaluates leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor CA-125), are not currently recommended as screening tools for ovarian cancer.
- B. Prevention<sup>14, 15</sup>
1. Oral contraceptives
    - a. Use of oral contraceptives for five or more years may decrease risk of ovarian cancer by up to 50%.
      - 1) The longer the use, the greater the protection.
      - 2) Protection may persist for up to 30 years following cessation.
    - b. Many women at risk of ovarian cancer may also be at risk for breast cancer (e.g., *BRCA1* mutation positive). These women should carefully consider the risk of oral contraceptive pills as they may increase the risk of developing breast cancer.<sup>16</sup>
  2. Surgery
    - a. Prophylactic risk-reducing salpingo-oophorectomy (RRSO) decreases the risk of ovarian cancer in high-risk patients including those with *BRCA* mutations, hereditary breast ovarian

cancer (HBOC) syndrome, or moderate penetrance gene variations (e.g., BRIP1, RAD51C, RAD51D).

- 1) Not recommended for low-risk patients because of cardiovascular benefit of maintaining ovaries.
- 2) Not protective against risk of developing primary peritoneal carcinoma.
- 3) Perform laparoscopy with a survey of upper abdominal cavity, bowel surface, omentum, appendix, and pelvic organs.
  - a) Biopsy any abnormal peritoneal findings, obtain pelvic washings for cytology, perform bilateral salpingo-oophorectomy (BSO).
- 4) Controversial if a hysterectomy should be performed after RRSO.

**Patient Case #1 (ARS Question #1):** JJ is a 57-year-old female who presented to the emergency department with 17 days of abdominal distension and 3 days of abdominal pain. Physical exam revealed a mass in her right lower abdomen. Laboratory results were notable for Hgb 7.1 g/dL and CA-125 of 212 U/mL. Ultrasound confirmed the mass and imaging ruled out distant metastases. The patient is clinically staged with IB, high-grade serous ovarian cancer and underwent adequate surgical cytoreduction and staging. **Which of the following is the most appropriate management for JJ at this time?**

- a. Carboplatin/paclitaxel for 3 cycles
- b. Observation
- c. Carboplatin/paclitaxel for 6 cycles
- d. Carboplatin/paclitaxel/bevacizumab for 6 cycles

#### IV. Treatment of Early Stage Ovarian Cancer (stage I and II)<sup>3,4</sup>

- A. The goal is to cure the patient
- B. Initial surgical management (comprehensive surgical staging for all patients)
  1. Stage I (fertility desired)
    - a. Stage IA: Unilateral salpingo-oophorectomy (preserving the uterus and contralateral ovary) and comprehensive surgical staging.
    - b. Stage IB: BSO (preserving the uterus) and comprehensive surgical staging.
  2. Stage I-II (no fertility desired): total abdominal hysterectomy (TAH)/BSO, omentectomy, pelvic and para-aortic lymph node sampling, appendectomy, peritoneal biopsies, cytologic washings, complete abdominal exploration and intact tumor removal if possible.
  3. Surgical management by specially trained gynecologic oncologist is important for accurate staging as this determines post-operative therapy (NCCN Guidelines® category 1).
- C. Early stage disease<sup>17-20</sup>
  1. Comprehensive cytoreductive (debulking) surgery and staging followed by adjuvant treatment based on stage and histology

2. Stage I disease

- a. Stage IA or stage IB (grade 1 and 2 endometrioid or low-grade serous)
  - a) Grade 1 endometrioid or low-grade serous: surgical staging followed by observation. Survival for these patients is > 90% with surgery alone.
  - b) Grade 2 (endometrioid): surgical staging followed by observation *or* platinum-based chemotherapy for 3-6 cycles.
- b. Stage IA or IB (grade 3 endometrioid or high-grade serous) and stage IC (grade 2, or 3 endometrioid)
  - 1) Platinum-based chemotherapy consisting of a taxane (paclitaxel or docetaxel) or liposomal doxorubicin plus carboplatin administered intravenously for 3-6 cycles (6 cycles are recommended for high-grade serous).
  - 2) 3 versus 6 cycles for early stage ovarian cancer
    - a) GOG-157: early stage ovarian cancer, adjuvant platinum-based chemotherapy
      1. Following comprehensive surgery, 457 women with high-risk early stage ovarian cancer were randomized to paclitaxel 175 mg/m<sup>2</sup> over 3 hrs + carboplatin (AUC 7.5) for 3 or 6 cycles.
      2. Adjusted for stage and grade, recurrence rate was 24% lower in patients treated with 6 cycles (HR 0.761; 95% CI, 0.51-1.13, p=0.18).
      3. No difference in OS (HR 1.02; 95% CI, 0.662-1.57).
      4. Toxicity was greater in patients treated with 6 cycles.<sup>17</sup>
      5. Subgroup analysis demonstrated that patients with **early stage ovarian cancer and serous histology had significantly lower risk of recurrence when treated with 6 cycles** (HR 0.33; 95% CI, 0.14-0.77, p=0.04). 5-year recurrence-free survival was 83% and 60% for patients receiving 6 and 3 cycles, respectively.<sup>18</sup>
  - 3) For patients ≤ 70 years of age and no major medical comorbidities, the following are NCCN Guidelines® recommended chemotherapy regimens for stage I ovarian cancer (3-6 cycles, depending on histology):
    - a) Paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours followed by carboplatin AUC 5-6 IV over 1 hour on day 1 every 3 weeks (preferred)
    - b) Docetaxel 60-75 mg/m<sup>2</sup> IV over 1 hour followed by carboplatin AUC 5-6 IV over 1 hour on day 1 every 3 weeks
    - c) Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m<sup>2</sup> IV on day 1 every 4 weeks
  - 4) For patients > 70 years of age and/or with major medical comorbidities, the following are NCCN Guidelines® recommended chemotherapy regimens for **stage I-IV** ovarian cancer (3-6 cycles for stage I, depending on histology; 6 cycles for stage II-IV):
    - a) Paclitaxel 135 mg/m<sup>2</sup> IV over 3 hours followed by carboplatin AUC 5 IV over 1 hour on day 1 every 3 weeks



- b) Paclitaxel 60 mg/m<sup>2</sup> IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes on day 1, 8, 15 every 3 weeks

3. Large European studies support adjuvant treatment in patients with early stage, high-grade, or surgically un-staged tumors

### Selected trials of adjuvant treatment in early stage ovarian cancer

Trial	Patients	Regimen	Outcome	Comments
<b>ICON-1</b> <sup>20</sup>	477 newly diagnosed patients	Surgery followed by randomization to observation versus 6 cycles of platinum-based chemotherapy (single agent carboplatin, cyclophosphamide + doxorubicin + cisplatin or other combinations)	Relapse free survival (RFS) and 5-year survival statistically improved with chemotherapy	Included patients with grade 1 tumors (typically observed in the United States)
<b>ACTION</b> <sup>19</sup>	448 newly diagnosed patients with early stage high-grade (grade 2 or 3) tumors	Surgery followed by randomization to observation versus 4-6 cycles of platinum-based chemotherapy (single agent carboplatin or cisplatin + cyclophosphamide)	No significant improvement in OS  RFS significantly improved: 70% vs 62% (HR 0.64; 95% CI, 0.46-0.89)  Incomplete surgical staging: RFS and cancer specific survival significantly improved	Patients with stage IA or IB well-differentiated tumors were excluded

- a. Results of these trials support adjuvant treatment of early stage ovarian cancer, including patients with grade 1 tumors who have undergone incomplete surgical staging.
- b. Many patients in both European studies received single agent carboplatin as primary therapy.
- 1) This is widely used throughout Europe for adjuvant treatment of early stage ovarian cancer.
  - 2) If treatment is recommended in the United States, combination therapy with a taxane and platinum is considered the standard of care.
4. Stage II disease<sup>4</sup>
- a. **Platinum-based chemotherapy for 6 cycles as is recommended in stage III-IV disease** (see table: Acceptable regimens for the primary systemic treatment of stage II-IV ovarian cancer).
- 1) There is no randomized data supporting the use of intraperitoneal (IP) therapy in patients with stage II disease. This NCCN Guidelines® category 2A recommendation in optimally debulked stage II disease is extrapolated from the data of Armstrong et al. (GOG-172) in advanced stage ovarian cancer discussed below.<sup>21</sup>

**Patient Case # 1, continued (ARS Question #1)-Answer:**

**The correct answer is C.** Six cycles of platinum-based combination chemotherapy are recommended as adjuvant therapy for patients with early stage, high-grade serous ovarian cancer.

Answer A is incorrect based on the subgroup analysis of GOG-157 exhibiting favorable recurrence free survival with six over three cycles for high-grade serous histology.

Answer B is incorrect because observation is only appropriate for stage IA/IB, low-grade serous or grade 1 of other histology.

Answer D is incorrect because bevacizumab-based combination therapies are not currently recommended for stage I disease; these may be utilized for stage II-IV disease.

**Patient Case #2 (ARS Question #2):**

SM presents for a pelvic ultrasound that confirms a left adnexa mass 3 x 2.6 x 2.3 cm and subsequent biopsy reveals high-grade serous carcinoma. Additional staging confirms SM has clinical stage IVB (pleural effusions and liver lesions) ovarian cancer and is deemed upon imaging and in consultation with surgery to be unlikely to be optimally cytoreduced. **Which of the following is the most appropriate initial therapy for SM?**

- a. Staging TAH/BSO followed by carboplatin + paclitaxel
- b. IP/IV carboplatin + paclitaxel followed by interval debulking surgery
- c. Carboplatin + paclitaxel followed by interval debulking surgery
- d. Carboplatin + gemcitabine + bevacizumab

**V. Treatment of Advanced Stage Ovarian Cancer (stage III and IV)<sup>2,3,7</sup>**

- A. The goal of therapy is to cure the patient, although the probability of cure decreases in stage IV or unresectable disease.
  - 1. Overall 5-year relative survival is 48.6% (< 30% for distant metastatic disease)
- B. Comprehensive surgical staging for all patients as in early-stage disease (includes TAH/BSO, omentectomy, lymph node sampling if no bulky disease, peritoneal biopsies, cytologic washings, complete abdominal exploration and cytologic debulking). Goal of surgery is optimal cytoreduction, which has been associated with improved survival in stage III-IV disease (NCCN Guidelines® category 1).<sup>22, 23</sup>
  - 1. Optimal cytoreduction: < 1 cm residual disease following surgery (historically defined as < 2 cm, relevant with respect to historical literature)
  - 2. Suboptimal cytoreduction: > 1 cm residual disease following surgery
- C. Intraperitoneal chemotherapy should be discussed with appropriately selected patients (e.g., optimally debulked stage II-III)
- D. Choice of adjuvant chemotherapy
  - 1. Platinum-based chemotherapy with a taxane (paclitaxel or docetaxel) and carboplatin IV, liposomal doxorubicin and carboplatin IV, or paclitaxel and cisplatin administered IV/IP for a total of 6 cycles.

#### Acceptable regimens for the primary systemic treatment of stage II-IV ovarian cancer<sup>4</sup>

Regimen	Comments
Paclitaxel 175 mg/m <sup>2</sup> IV over 3 hr + carboplatin AUC 5-6 IV every 21 days for 6 cycles <sup>24, a, b</sup>	Consider for patients who are not candidates for IP therapy
Docetaxel 60-75 mg/m <sup>2</sup> IV + carboplatin AUC 5-6 IV every 21 days for 6 cycles <sup>25</sup>	Consider in patients at risk for peripheral neuropathy
Paclitaxel 135 mg/m <sup>2</sup> IV over 3 or 24 hours (day 1) + cisplatin 75-100 mg/m <sup>2</sup> IP (day 2) + paclitaxel 60 mg/m <sup>2</sup> IP (day 8); repeat every 21 days for 6 cycles <sup>21, 26</sup>	For optimally debulked stage II-III disease; appropriate patient selection necessary.
Dose-dense paclitaxel: Paclitaxel 80 mg/m <sup>2</sup> IV over 1 hour days 1, 8, 15 + carboplatin AUC 5-6 IV day 1; repeat every 21 days for 6 cycles <sup>27</sup>	Increased myelosuppression; controversial benefit on PFS and OS
Paclitaxel 60 mg/m <sup>2</sup> IV + carboplatin AUC 2 IV once weekly for 18 weeks. <sup>28</sup>	Consider for elderly patients or those with poor performance status
Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m <sup>2</sup> IV every 28 days for 6 cycles <sup>29</sup>	Consider in patients at risk for neurotoxicity or to avoid alopecia
<sup>a</sup> regimen given alone or in combination with bevacizumab <sup>^</sup> as either: (1) 7.5 mg/kg IV over 30-90 minutes day 1 x 5-6 cycles then continue bevacizumab maintenance up to 12 additional cycles <u>OR</u> (2) 15 mg/kg IV over 30-90 minutes day 1 (starting day 1 cycle 2) for up to 22 cycles. (carboplatin preferred at AUC 6) <sup>b</sup> preferred regimen	
<b>Elderly (&gt; 70 years) and/or significant comorbidities</b>	
Paclitaxel <u>135 mg/m<sup>2</sup></u> IV over 3 hours + carboplatin AUC 5 IV every 21 days for 6 cycles	Reduced dose paclitaxel
Paclitaxel 60 mg/m <sup>2</sup> IV over 1 hour + carboplatin AUC 2 both days 1, 8, 15 every 21 days for 6 cycles	Reduced dose paclitaxel and carboplatin, both administered weekly

<sup>^</sup> = Per NCCN, an FDA-approved biosimilar may be substituted for bevacizumab

#### Selected trials of adjuvant treatment in advanced stage ovarian cancer

Trial	Patients	Regimen	Outcomes	Comments
<b>GOG-158<sup>24</sup></b> (Paclitaxel, carboplatin)	792 patients with optimally debulked (< 1 cm) advanced stage ovarian cancer	Paclitaxel 175 mg/m <sup>2</sup> IV over 3 hr followed by carboplatin (AUC 7.5) IV over 1 hour vs Cisplatin 75 mg/m <sup>2</sup> IV + paclitaxel 135 mg/m <sup>2</sup> IV over 24 hr Repeat every 21 days for 6 cycles	Median PFS and OS similar between arms.  Hematologic toxicity greater with carboplatin.  Non-hematologic toxicity greater with cisplatin.	<b>Paclitaxel + carboplatin preferred over paclitaxel + cisplatin due to equal efficacy and reduced toxicity.</b>
<b>SCOTROC<sup>25</sup></b> (Docetaxel, carboplatin)	1077 patients with advanced stage ovarian cancer following surgery	Docetaxel 75 mg/m <sup>2</sup> IV over 1 hour infusion + carboplatin (AUC 5) IV vs	No difference in PFS at 23 months.  Docetaxel associated with significantly more	Docetaxel is equally efficacious and less neurotoxic than paclitaxel when given in combination with carboplatin.

Trial	Patients	Regimen	Outcomes	Comments
		<p>Paclitaxel 175 mg/m<sup>2</sup> IV over 3 hr + carboplatin (AUC 5) IV</p> <p>Repeat every 21 days for 6 cycles</p>	<p>grade <math>\geq</math> 3 neutropenia and fever.</p> <p>Paclitaxel associated with significantly more grade <math>\geq</math> 2 neurotoxicity.</p> <p>Global quality of life (QOL) not significantly different between groups, but QOL significantly different when rating muscle weakness, pain and neurotoxicity.</p>	
<p><b>GOG-172 (Armstrong et al<sup>21</sup>)</b></p> <p>(IV/IP therapy)</p>	<p>429 patients with stage IIIC ovarian and primary peritoneal cancer following optimal cytoreduction</p>	<p>Paclitaxel 135 mg/m<sup>2</sup> IV over 24 hours on day 1 + cisplatin 75 mg/m<sup>2</sup> IV on day 2</p> <p>vs</p> <p>Paclitaxel 135 mg/m<sup>2</sup> IV over 24 hrs on day 1 + cisplatin 100 mg/m<sup>2</sup> IP on day 2 + paclitaxel 60 mg/m<sup>2</sup> IP on day 8</p> <p>Repeat every 3 weeks for 6 cycles</p>	<p>Median PFS significantly improved (23.8 vs 18.3 months; p=0.05)</p> <p>Median OS significantly improved (65.6 vs 49.7 months; p=0.03)</p> <p>Grade 3-4 toxicities significantly worse in IP arm.</p> <p>QOL significantly worse for patients in the IP arm while on treatment; however, no longer a difference at 12 months.</p>	<p>Only 42% of patients randomized to IP therapy completed six cycles of treatment (median 3 cycles).</p> <p>Patients unable to tolerate IP therapy were switched to IV treatment arm.</p> <p>Data extrapolated to include stage II patients following optimal cytoreduction.</p>
<p><b>MITO-7 (Pignata et al<sup>28</sup>)</b></p> <p>(Weekly, elderly/frail)</p>	<p>822 patients with stage IC-IV ovarian and primary peritoneal cancer following optimal cytoreduction</p>	<p>Paclitaxel 175 mg/m<sup>2</sup> IV + carboplatin (AUC 6) IV every 3 weeks for 6 cycles</p> <p>vs</p> <p>Paclitaxel 60 mg/m<sup>2</sup> IV + carboplatin (AUC 2) IV once weekly for 18 weeks</p>	<p>No significant difference in PFS (17.3 [3-week] vs 18.3 months [weekly]; p=0.66)</p> <p>Grade 3-4 toxicities worse with every 3 week regimen.</p> <p>QOL worse for patients treated with every 3 week regimen.</p>	<p>Consider weekly regimen for elderly (&gt; 70), those with comorbidities, or poor ECOG performance status.</p>
<p><b>JGOG-3016 (Katsumata et al<sup>27</sup>)</b></p>	<p>637 patients with stage II-IV ovarian cancer</p>	<p>Paclitaxel 180 mg/m<sup>2</sup> IV + carboplatin (AUC 6) IV every 3 weeks for 6 cycles</p> <p>vs</p>	<p>Median PFS 28.2 months in dose-dense arm vs 17.5 months in conventional</p>	<p>Increased anemia and decreased QOL with dose-dense regimen.</p>

Trial	Patients	Regimen	Outcomes	Comments
(Dose-dense paclitaxel)		Dose-dense paclitaxel 80 mg/m <sup>2</sup> IV days 1, 8, 15 + carboplatin (AUC 6) IV day 1 every 3 weeks for 6 cycles	chemotherapy arm (p=0.0037).  Median OS 100.5 months in dose-dense arm vs 62.2 months in conventional chemotherapy arm (p=0.039).	Concern regarding ability to extrapolate beyond Asian ethnicity.
<b>ICON-8<sup>30</sup></b> (Dose-dense paclitaxel)	1566 patients with stage IC-IV ovarian cancer	<u>A:</u> Paclitaxel 175 mg/m <sup>2</sup> IV + carboplatin (AUC 5-6) IV every 3 weeks <u>B:</u> Dose-dense paclitaxel 80 mg/m <sup>2</sup> IV days 1, 8, 15 + carboplatin (AUC 5-6) IV day 1 every 3 weeks <u>C:</u> Dose-dense paclitaxel 80 mg/m <sup>2</sup> IV + carboplatin (AUC 2) both on days 1, 8, 15 every 3 weeks	Median PFS not significantly different (17.7 months (A); 20.8 months (B); 21.0 months (C)). OS data is immature.  Increased ≥ grade 3 toxicities with weekly dosing.	Dose-dense paclitaxel can be safely administered; however, results conflict with prior published PFS and OS benefit in JGOG-3016.
<b>MITO-2 (Pignata et al<sup>31</sup>)</b> (Liposomal doxorubicin, carboplatin)	820 patients with stage IC-IV ovarian cancer	Paclitaxel 175 mg/m <sup>2</sup> IV + carboplatin (AUC 5) IV every 3 weeks for 6 cycles vs Pegylated liposomal doxorubicin 30 mg/m <sup>2</sup> IV + carboplatin (AUC 5) IV every 3 weeks for 6 cycles	Median PFS not significantly different (19 months with liposomal doxorubicin vs 16.8 months with paclitaxel; p=0.58)  No relevant difference in global QOL.	Less neurotoxicity and alopecia with liposomal doxorubicin.  Increased hematologic toxicity with liposomal doxorubicin.
<b>EWOC-1<sup>32</sup></b> (First-Line Treatment in Elderly)	120 patients with stage III-IV, ≥ 70 years with GVS (geriatric vulnerability score) ≥ 3	<u>A:</u> Carboplatin (AUC 5-6) IV + paclitaxel 175 mg/m <sup>2</sup> IV every 3 weeks <u>B:</u> Carboplatin (AUC 5-6) IV every 3 weeks <u>C:</u> Carboplatin (AUC 2) IV + paclitaxel 60 mg/m <sup>2</sup> IV days 1, 8, 15 every 4 weeks	Median PFS improved with combination regimens: 12.5 months (A); 4.8 months (B); 8.3 months (C).  Median OS: NR (A); 7.4 months (B); 17.3 months (C).	Trial prematurely terminated because carboplatin monotherapy arm less active with worse survival outcome.

#### E. Considerations for intraperitoneal therapy<sup>21, 26, 33, 34</sup>

- Based on the results of GOG-172 (Armstrong et al.) and previously published trials with IP therapy, the National Cancer Institute (NCI), NCCN Guidelines®, and the Society of Gynecologic Oncology (SGO) recommend that **all appropriate patients be counseled about the clinical benefit and associated risks with IV and IP treatment before undergoing surgery.**
- A meta-analysis published by the Cochrane Collaboration of 8 high quality trials in 2,026 women confirmed the above recommendation. The authors concluded that women were less likely to die if they received an IP component of therapy (HR 0.81; 95% CI, 0.72-0.90). This analysis also

confirmed that there is greater toxicity associated with IP therapy (gastrointestinal, pain, fever, and infection).<sup>34</sup>

3. Appropriate candidates for adjuvant IP therapy include:
    - a. Optimally cytoreduced stage II-III disease.
    - b. Good performance status
    - c. Normal renal function at baseline
    - d. No relevant pre-existing comorbidities (e.g., peripheral neuropathy)
    - e. No history of prior bowel surgery or resectosigmoid bowel resection at time of primary therapy
  4. Patients with poor performance status, stage IV disease, or age > 65 may not tolerate IP therapy
  5. Significant toxicities of IP therapy include infection, leukopenia, fatigue, nausea, renal toxicity, neurotoxicity, dehydration, electrolyte abnormalities, catheter malfunction, and abdominal pain.
  6. Strategies to reduce toxicity and improve patient outcomes with IP chemotherapy:
    - a. Heat peritoneal fluid to body temperature to improve patient comfort.
    - b. Use aggressive oral and IV hydration pre- and post-IP therapy to reduce renal toxicity (may require return visits to clinic for IV hydration and electrolyte replacement).
    - c. Antiemetic regimen suitable for highly emetogenic chemotherapy prior to IP cisplatin on day 2 and provide additional antiemetics to prevent delayed nausea and vomiting (please see Nausea and Vomiting section in the Lung Cancer module).
  7. Modifications to dosage and delivery of intraperitoneal therapy
    - a. Paclitaxel: administration over 3 hours (instead of 24 hours, as studied) to reduce myelosuppression and facilitate outpatient administration.
    - b. Cisplatin: reduce dose to 75 mg/m<sup>2</sup> (instead of 100 mg/m<sup>2</sup>, as studied) to reduce likelihood of severe renal/metabolic abnormalities.<sup>35</sup>
- F. Dose-dense paclitaxel<sup>27</sup>
1. The JGOG-3016 study by Katsumata et al. evaluated weekly, dose-dense paclitaxel plus carboplatin given every three weeks compared to conventional paclitaxel plus carboplatin every three weeks.
    - a. Phase III, multicenter, randomized trial including 631 newly diagnosed patients with stage II-IV ovarian cancer.
    - b. Following surgery, patients were randomized to six cycles of either paclitaxel 180 mg/m<sup>2</sup> IV over 3 hours + carboplatin (AUC 6) repeated every 21 days or paclitaxel 80 mg/m<sup>2</sup> IV on days 1, 8, 15 + carboplatin (AUC 6) on day 1 repeated every 21 days.
    - c. After median follow-up of 76.8 months, median PFS was significantly longer in the dose-dense arm compared to conventional treatment (28.2 months vs 17.5 months [HR 0.76; 95% CI, 0.62-0.91, p=0.0037]). However, the increase in PFS was not observed in the subgroups of patients with clear cell or mucinous tumors.
    - d. Median OS was significantly improved for dose-dense arm compared to conventional treatment (100.5 months vs 62.2 months [HR 0.79; 95%, CI 0.63-0.99, p=0.039]).

- e. The frequency of grade 3 anemia was significantly higher in the dose-dense arm (69% vs 44%,  $p < 0.0001$ ).
  - f. Results of this trial remain controversial as to whether they can be extrapolated to a non-Asian patient population. Racial disparities exist in the natural history of ovarian cancer, with Asian women experiencing superior survival independent of treatment.
2. The Gynecologic Oncology Group has completed a similar study evaluating dose-dense therapy (GOG-262) to clarify its role in a non-Asian patient population. This study also included the addition of bevacizumab to both treatment arms.<sup>36</sup>
    - a. Phase III, randomized trial including 692 patients with stage III-IV ovarian cancer
      - 1) Following surgery, patients were randomized to paclitaxel 175 mg/m<sup>2</sup> IV and carboplatin (AUC 6) on day 1 every 21 days for 6 cycles vs paclitaxel 80 mg/m<sup>2</sup> IV on days 1, 8, 15 and carboplatin (AUC 6) on day 1 every 21 days for 6 cycles.
        - b) Patients who underwent interval cytoreduction received 3 cycles of neoadjuvant chemotherapy followed by surgery and 3 additional cycles of chemotherapy for a total of 6 cycles.
        - c) 84% of patients received bevacizumab, which administered as 15 mg/kg IV every 21 days starting cycle 2. If undergoing neoadjuvant chemotherapy followed by interval cytoreduction, bevacizumab was omitted during cycles 1, 3, 4.
      - b. No significant difference in median PFS for overall population (14.7 months (dose-dense) vs 14 months;  $p = 0.18$ ).
        - 1) Among patients who **did not** receive bevacizumab, weekly paclitaxel was associated with an increase in PFS (14.2 months vs 10.3 months;  $p = 0.03$ ); however, this benefit was not present in those who received bevacizumab.
  3. The Gynecologic Cancer Intergroup (GCIg) completed an additional study to assess the potential benefit of dose-dense paclitaxel in a predominantly European patient population (ICON-8)<sup>30</sup>
    - a. Phase III, randomized trial including 1,566 patients with stage IC-IV ovarian cancer
      - 1) Patients were randomized to one of three arms:
        - a) A: carboplatin (AUC 5-6) and paclitaxel 175 mg/m<sup>2</sup> every 3 weeks
        - b) B: carboplatin (AUC 5-6) every 3 weeks and dose-dense paclitaxel 80 mg/m<sup>2</sup> weekly
        - c) C: carboplatin (AUC 2) and dose-dense paclitaxel 80 mg/m<sup>2</sup>, both given weekly
      - 2) No significant improvement in PFS (17.7 months [A], 20.8 months [B], 21.0 months [C])
      - 3) Increased grade  $\geq 3$  toxicities with weekly dosing.
- G. Role of dose intensity<sup>27, 37-41</sup>
1. There is no data to support the concept of dose intensity in ovarian cancer.
  2. The paper by Katsumata et al. suggests that *dose density* is more important than *dose intensity*; however, data is mixed.
- H. Neoadjuvant chemotherapy (NACT) followed by surgery or secondary cytoreduction<sup>42</sup>

1. The benefit of neoadjuvant chemotherapy has historically been controversial.
  - a. The Society of Gynecologic Oncology (SGO) and the American Society of Clinical Oncology (ASCO) have published guidelines on neoadjuvant chemotherapy for newly diagnosed advanced ovarian cancer.<sup>43</sup>
  - b. Appropriate for patients with bulky stage III-IV disease who are not surgical candidates, or those assessed by a gynecologic oncologist and deemed unlikely to be optimally cytoreduced.
    - 1) Requires histologic confirmation of diagnosis (biopsy, paracentesis).
    - 2) NACT is not appropriate for patients with disease confined to the ovary.
  - c. For select women with stage III-IV disease, NACT with interval cytoreduction is non-inferior to primary cytoreduction and adjuvant chemotherapy with respect to OS and PFS and is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations, but primary cytoreductive surgery may offer superior survival in select patients (SGO and ASCO).<sup>43</sup>
2. One of the strongest predictors of overall survival (other than stage) is the extent of primary surgery. Patients with microscopic residual disease live longer than those with gross residual disease.
3. NACT is a treatment option for patients with advanced stage ovarian cancer who are not initial surgical candidates.
  - a. Consideration of interval debulking surgery (IDS) after 3 cycles; surgery preferred after 3-4 cycles if possible. Post IDS adjuvant therapy should be continued for a minimum of 6 total cycles ( $\geq 3$  cycles post IDS).
  - b. Any recommended primary regimen (IV) for stage II-IV disease may be used as NACT prior to IDS. Following IDS, adjuvant therapy may include any of the recommended primary regimens (IV or IP/IV), although there is limited data on the use of IP regimens after NACT. For stage II-IV disease, carboplatin/paclitaxel represents an additional IP option.<sup>44</sup>
  - c. HIPEC (hyperthermic intraperitoneal chemotherapy; cisplatin 100 mg/m<sup>2</sup>) may be considered for patients with stage III disease at time of IDS.<sup>45</sup>
  - d. Caution is warranted if bevacizumab-based combination therapy is utilized for NACT; it is recommended to hold bevacizumab for at least 6 weeks prior to IDS to reduce risk of postoperative complications.
4. **NCCN® recommends considering NACT and IDS for patients with bulk stage III-IV disease that is unlikely to be optimally cytoreduced (< 1 cm) or patients who are deemed poor surgical candidates.**
  - I. Results of phase III trials have demonstrated that adding a third drug to the taxane plus platinum doublet does not improve survival but may improve PFS while also adding toxicity.<sup>46</sup>
  - J. Bevacizumab in the adjuvant management of ovarian cancer<sup>7</sup>
    1. FDA approved June 13, 2018 for primary treatment of stage III-IV ovarian cancer in combination with carboplatin + paclitaxel following initial surgical resection. Approved dosing schedule as per GOG-218 (see table below).



2. There is a well-established association between vascular endothelial growth factor (VEGF) overexpression, increased angiogenesis, and the development and progression of ovarian cancer.
3. Per NCCN, an FDA-approved biosimilar may be substituted for bevacizumab.
4. Two primary phase III trials of bevacizumab in the frontline adjuvant setting
  - a. GOG-218 and ICON-7 both exhibited minor improvement in PFS over standard chemotherapy. Both studies found no improvement in OS and small but significant differences in patient-reported QOL (worse in bevacizumab-treated patients).
  - b. Improvement in PFS only exhibited in patients who received bevacizumab maintenance.
  - c. Analysis of GOG-218 suggests that patients with ascites have a significantly improved PFS and OS with the addition of bevacizumab to carboplatin and paclitaxel.<sup>47</sup>
  - d. Patients should be counseled regarding efficacy, toxicity, and cost prior to use in adjuvant setting.

**Selected trials of bevacizumab in the first-line treatment of advanced stage ovarian cancer**

<b>Trial</b>	<b>Patients</b>	<b>Regimen</b>	<b>Outcomes</b>	<b>Comments</b>
<b>GOG-218</b> <sup>48, 49,50</sup>	1873 patients with stage III-IV following surgery, any gross residual disease allowed	Standard chemotherapy (paclitaxel + carboplatin) cycles 1-6 and <b>either</b> Placebo (cycle 2-5) followed by placebo (cycle 7-22) <b>or</b> Bevacizumab 15 mg/kg (cycle 2-5) followed by placebo (cycle 7-22) <b>or</b> Bevacizumab 15 mg/kg (cycle 2-5) followed by bevacizumab 15 mg/kg (cycle 7-22)	Median PFS statistically significantly improved by 3.8 months for patients treated with chemotherapy + bevacizumab + bevacizumab maintenance vs chemotherapy + bevacizumab + placebo maintenance or chemotherapy alone.  OS not different between groups.  OS improved in subgroup of patients with stage IV disease (42.8 vs 32.6 months; HR 0.75; 95% CI, 0.59-0.95).  Small but significant decrease in QOL for bevacizumab compared to placebo	Hypertension and gastrointestinal perforation were significantly higher in bevacizumab-treated patients.
<b>ICON-7</b> <sup>51-53</sup>	1528 patients with high-risk stage I-IV  (optimal or suboptimal disease allowed)	Standard chemotherapy (paclitaxel + carboplatin) for 6 cycles <b>or</b> Standard chemotherapy + bevacizumab 7.5 mg/kg (cycles 2-6) followed by bevacizumab 7.5 mg/kg maintenance (12 additional cycles)	At 48.9 months, no difference in PFS or OS.  Median OS was improved in patients with poor prognosis disease (39.3 vs 34.5 months; p=0.03).  Worse QOL in patients treated with bevacizumab.	Incidence of hypertension and gastrointestinal events were significantly higher in bevacizumab-treated patients.

**Patient Case #2, continued (ARS Question #2)-Answer:**

**The correct answer is C.** SM has stage IVB ovarian cancer and was unfortunately deemed to be unlikely to attain optimal cytoreduction. Neoadjuvant chemotherapy followed by interval debulking surgery is most appropriate.

Answer A is not appropriate as patients who are unfit for surgery or unlikely to be optimally debulked should be considered for neoadjuvant chemotherapy prior to surgical cytoreduction.

Answer B is not appropriate as intraperitoneal therapy should not be used as neoadjuvant treatment; these therapies may, however, be used following interval debulking surgery.

Answer D is not appropriate as carboplatin + gemcitabine + bevacizumab is a preferred regimen in the setting of platinum-sensitive recurrence but not frontline therapy.

**Patient Case #2, continued (ARS Question #3):**

SM completed 3 cycles of neoadjuvant chemotherapy, underwent interval debulking surgery attaining optimal cytoreduction, and subsequently completed 3 more cycles of adjuvant chemotherapy with paclitaxel, carboplatin, and bevacizumab. Her response to therapy was a partial response (PR) and following germline genetic testing, she was found to be BRCA-wt. SM underwent additional tumor next generation sequencing and was found to be HRD negative. SM would like to pursue maintenance therapy. Which of the following would you recommend?

- a. Niraparib 300 mg once daily
- b. Rucaparib 600 mg twice daily
- c. Olaparib 300 mg twice daily
- d. Olaparib 300 mg twice daily plus bevacizumab 15 mg/kg every 3 weeks

2. Bevacizumab toxicities<sup>39, 41, 54-58</sup>

a. Bleeding and impaired wound healing

- 1) Grade 1 mucocutaneous bleeding occurred in 36% of patients treated with bevacizumab in the ICON-7 trial. However, the incidence of severe bleeding was not different between bevacizumab and placebo treated patients in the GOG-218 trial.
- 2) When bevacizumab is used with chemotherapy in the adjuvant setting following surgery, it is often initiated beginning with cycle 2 to reduce potential impact on wound healing.

b. GI events including bowel perforation

- 1) Patients with ovarian cancer are predisposed to bowel perforation or obstruction due to their disease, surgery at the site of the bowel, and the presence of high circulating levels of VEGF in many ovarian tumors.
- 2) While the overall incidence of severe GI events was low in both the GOG-218 and ICON-7 trials, these events were increased in patients treated with bevacizumab compared to placebo.
- 3) In general, the risk of bowel perforation with bevacizumab is thought to be higher in patients with recurrent ovarian cancer and those who have been treated with multiple lines of therapy.

- a) Follow-up studies of the GOG-218 trial suggested that additional risk factors may include a history of treatment for irritable bowel disease (IBD) and bowel resection at time of primary surgery.

**Significant bevacizumab toxicities in ovarian cancer patients<sup>48, 52</sup>**

Toxicity	GOG-218		ICON-7	
	Placebo (%) n=601	BEV 15 mg/kg/dose (cycle 2-22) (%) n=608	Placebo (%) n=753	BEV 7.5 mg/kg/dose (cycle 2-18) (%) n=745
Hypertension (grade $\geq 2$ )	7	23	2	18
GI Events (grade $\geq 2$ )	1.2	2.6	<1	1
Bleeding (grade 1-2)	NR	NR	11	38
Thrombosis	6.6	7.4	3	7
Fatal events	6 deaths	14 deaths	1 death	4 deaths

**Patient Case #2, continued (ARS Question #3)-Answer:**

**Correct answer is A.**

Based on the PRIMA data niraparib was found to have a progression free survival benefit in all patients with a CR/PR to platinum-based therapy in the frontline setting. In the NCCN guidelines this is a category 2A recommendation as the progression free survival is minimal and would be a risk benefit discussion with the patient but given that she is interested in maintenance therapy it is an option for the patient.

Answer B is not appropriate because rucaparib is not currently recommended for primary maintenance therapy; however, it may be used as recurrent platinum-sensitive maintenance therapy or for treatment of recurrent disease after at least 2 prior lines of therapy.

Answer C is not correct because olaparib for frontline maintenance therapy requires that the patient have a germline or somatic deleterious BRCA mutation.

Answer D is incorrect because olaparib plus bevacizumab is only recommended in patients with BRCA mutated or HRD positive ovarian cancer in the frontline. This patient is BRCAwt and HRD negative.

**VI. Post-Remission Therapy<sup>4</sup>**

- A. Imaging if clinically indicated (chest/abdominal/pelvic CT, MRI, PET, or PET-CT).
  1. Complete (CR) or partial (PR) clinical remission
    - a. Clinical trial
    - b. Observation
    - c. Continuation, consolidation, or maintenance therapy<sup>4, 59-62</sup>
      - 1) Maintenance therapy following partial or complete response to primary platinum-based therapy
        - a) Bevacizumab

- ii. May continue as per GOG-218 or ICON-7 if utilized as primary therapy (and at least stable disease) but there is no data to support introducing bevacizumab maintenance if not included in primary therapy.
  - iii. May be continued for up to 12 or 22 cycles depending on original regimen.
- b) Olaparib
- i. Recommended indication: PR/CR to 1<sup>st</sup> line platinum-based chemotherapy and germline or somatic deleterious or suspected deleterious *BRCA1/2* alteration (NCCN Guidelines® category 1).
  - ii. SOLO-1: phase III, randomized, double-blind, placebo-controlled trial (n=391).<sup>63</sup>
    - (a) Olaparib 300 mg twice daily (n=260) vs placebo (n=131)
    - (b) 70% lower risk of progression or death with olaparib maintenance (95% CI=0.23-0.41; p<0.001)
    - (c) At five-year follow-up, median PFS significantly prolonged with olaparib (56.0 vs 13.8 months; HR 0.33).<sup>64</sup>
- c) Olaparib + bevacizumab<sup>65</sup>
- i. Recommended indication: PR/CR to 1<sup>st</sup> line platinum-based (including bevacizumab) chemotherapy and germline or somatic deleterious or suspected deleterious *BRCA1/2* mutation (NCCN Guidelines® category 1) *and/or* genomic instability (*BRCA1/2* wild-type and homologous recombination deficiency (HRD)-positive)) (NCCN Guidelines® category 2A).<sup>4</sup>
  - ii. PAOLA-1: phase III, randomized, double-blind, placebo-controlled trial (n=806)
    - (a) Bevacizumab 15 mg/kg every 3 weeks for up to 15 months + *either* olaparib 300 mg twice daily (n=537) *or* placebo (n=269) for up to 24 months
    - (b) Median PFS (BRCA wild-type + HRD): 28.1 vs 16.6 months (HR 0.43; 95% CI, 0.28-0.66)
      - 1. Homologous recombination deficiency (HRD) was defined in this study as a score of  $\geq 42$  on the Myriad myChoice CDx, reflective of genomic instability.
    - (c) Median PFS (HRD+, including BRCA mutated): 37.2 vs 17.7 months (HR 0.33; 95% CI, 0.25-0.45)
- d) Niraparib
- i. Recommended indication: PR/CR to 1<sup>st</sup> line platinum-based chemotherapy and germline or somatic deleterious or likely deleterious *BRCA1/2* alteration (NCCN Guidelines® category 1) *or* *BRCA* wild-type (NCCN Guidelines® category 2A).<sup>4</sup>
  - ii. PRIMA: phase III, randomized, double-blind, placebo-controlled trial (n=733)<sup>66</sup>

(a) Niraparib 300 mg once daily (n=484) vs placebo (n=244)

1. Protocol amended due to thrombocytopenia. If weight < 170 lbs or platelets < 150,000/ $\mu$ L then starting dose is 200 mg once daily otherwise 300 mg once daily

(b) Median PFS (all patients): 13.8 vs 8.2 months (p<0.001)

(c) Median PFS (HRD): 21.9 vs 10.4 months (p<0.001)

1. Homologous recombination deficiency (HRD) was defined in this study as tumors with deleterious *BRCA 1/2* mutations (germline or somatic) or an HRD score of  $\geq 42$  on the Myriad myChoice CDx, reflective of genomic instability.
2. The HRD score assesses 3 biomarkers of genomic instability: loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions. A score of  $\geq 42$  is reported as “positive”.

e) Following primary treatment with bevacizumab, data are limited regarding use of single agent PARP inhibitor maintenance.

2. Role of secondary cytoreduction

- a. Approximately 85% of patients with optimal first surgery are expected to achieve a clinical complete remission after first-line therapy. Of these, 25-75% have pathologic evidence of disease at time of second-look surgery.
- b. Second-look surgery does not improve survival.<sup>67</sup>

B. Surveillance<sup>4, 68</sup>

1. Following completion of six cycles of treatment, NCCN® and the Society of Gynecologic Oncology recommend:
  - a. Complete physical and pelvic examination every 2-4 months for two years, then every 3-6 months for three years, then annually after five years.
  - b. CA-125 monitoring if initially elevated; however, should be discussed with the patient as CA-125 elevations usually pre-date clinical symptoms by several months.
  - c. CBC and chemistry as indicated.
  - d. Chest X-ray, CT, MRI, PET, or PET-CT as clinically indicated.
  - e. Patient education regarding symptoms of recurrence, including bloating, weight gain, abdominal pain, early satiety.
  - f. Refer for genetic counseling if not previously done.

**Patient Case #2, continued (ARS Question #4):**

SM presents to clinic after 3 months of niraparib maintenance therapy. Her adjuvant chemotherapy was complicated by grade 2 peripheral neuropathy. She presents today with worsening abdominal distension. A CT scan was completed revealing new lymphadenopathy and confirmed disease recurrence. **Which of the following regimens is most appropriate for SM?**

- a. Carboplatin + gemcitabine
- b. Pegylated liposomal doxorubicin
- c. Niraparib PO + bevacizumab IV
- d. Pembrolizumab

**VII. Treatment of recurrent, refractory and resistant ovarian cancer**

**A. General principles<sup>3, 4, 69</sup>**

1. 60-80% of all patients with ovarian cancer ultimately relapse from their disease.
2. Length of subsequent remissions is shorter than the initial remission (i.e., length of first remission > length of second remission > length of third remission, etc).
3. Goal of treatment is no longer curative. Goal is to improve/eliminate symptoms, achieve an objective response, improve QOL, delay time to symptomatic disease, and prolong survival if possible.
4. Decisions regarding therapy should include patient and family member convenience, prior toxicities, insurance coverage/financial implications, and overall QOL.
5. When to initiate therapy: biochemical recurrence (elevated CA-125 only and no clinical evidence of disease or symptoms) versus measurable or symptomatic disease
  - a. A European study randomized 1442 women in complete clinical remission following primary therapy to blinded measurement of CA-125 every 3 months. Patients were randomized to undergo treatment at first chemical recurrence or initiate chemotherapy when symptoms or measurable disease were documented. There was no difference in survival between the two groups.<sup>70</sup>
  - b. Immediate re-treatment for a biochemical recurrence is not beneficial (NCCN Guidelines® category 2B). It is recommended for these patients to enroll in a clinical trial or delay treatment until symptoms arise or imaging indicates recurrence.

**B. Prognosis and treatment are defined by response to initial chemotherapy.**

1. Platinum-sensitive disease: duration of initial response > 6 months.
  - a. The longer the initial remission, the greater the likelihood of responding to second and third-line agents.
  - b. Combination chemotherapy is recommended for patients in first relapse with platinum-sensitive disease as the probability of response to chemotherapy is  $\geq 30\%$ .
2. Platinum-resistant disease: duration of initial response < 6 months.
  - a. Probability of response to additional treatment is 10-15%.

3. Primary progressive (platinum-refractory) disease: no response and/or progression of disease during primary therapy with platinum.
  - a. Carries the worst prognosis. Probability of response to additional chemotherapy  $\leq 10\%$ .
- C. Tumor molecular testing of the most recently available tissue is recommended prior to initiation of therapy for recurrent/persistent disease.
  1. Testing *should* include at least *BRCA* 1/2 and microsatellite instability or DNA mismatch repair.
  2. Testing *may* also include homologous recombination pathway genes and loss of heterozygosity (LOH).
  3. Pembrolizumab is FDA approved for treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options (MSI-H, dMMR, and TMB-H are discussed in more detail in the Pharmacogenomics module).<sup>71</sup>
- D. Treatment options<sup>3, 55, 56</sup>
  1. Platinum-sensitive recurrent disease:
 

**The NCCN Guidelines® consider combination platinum-based chemotherapy to be the therapy of choice for ovarian cancer in first relapse (disease-free interval > 6 months), unless there are clinical reasons why the patient cannot tolerate combination therapy.** The table below lists preferred regimens for platinum-sensitive first recurrence.

    - a. Chemotherapy sparing - AVANOVA2: Randomized, open-label phase 2 study investigating niraparib monotherapy vs niraparib plus bevacizumab in platinum-sensitive recurrence.<sup>72</sup>
      - 1) Niraparib 300 mg PO once daily +/- bevacizumab 15 mg/kg IV every 3 weeks until disease progression or intolerance
      - 2) Median PFS improved with combination therapy (11.9 vs 5.5 months; HR 0.35, 95% CI 0.21-0.57;  $p < 0.0001$ )
      - 3) Increased grade  $\geq 3$  hypertension (21 vs 0%) and neutropenia (8.3 vs 2.0%) with combination therapy.



#### Preferred regimens for platinum-sensitive ovarian cancer in first relapse<sup>4</sup>

Regimen	Comments
Paclitaxel 175 mg/m <sup>2</sup> IV + carboplatin (AUC 5-6) IV every 21 days <sup>73, 74</sup>	Survival benefit, particularly in patients with platinum free-interval > 12 months (ICON-4 trial). 60% of patients had not received prior paclitaxel.
Paclitaxel 175 mg/m <sup>2</sup> IV + carboplatin (AUC 5) IV + bevacizumab <sup>^</sup> 15 mg/kg every 21 days. Bevacizumab continued as maintenance therapy until PD or unacceptable toxicity. <sup>75</sup>	Patients who received bevacizumab as part of primary therapy may be re-challenged with bevacizumab + platinum-based therapy in platinum-sensitive recurrence. If response, bevacizumab maintenance can be continued until PD or unacceptable toxicity.
Gemcitabine 1000 mg/m <sup>2</sup> IV days 1, 8 + carboplatin (AUC 4) day 1 every 21 days <sup>76</sup>	Gemcitabine may reverse platinum resistance. Recommended for patients with pre-existing peripheral neuropathy.
Gemcitabine 600-750 mg/m <sup>2</sup> IV days 1,8 + cisplatin 30 mg/m <sup>2</sup> IV days 1, 8; repeat every 21 days <sup>77, 78</sup>	Gemcitabine may reverse platinum resistance.
Liposomal doxorubicin 30 mg/m <sup>2</sup> + carboplatin (AUC 5) both on day 1; repeat every 28 days <sup>79, 80</sup>	Non-inferior to carboplatin + paclitaxel (CALYPSO, phase III trial); more tolerable toxicity profile.
Liposomal doxorubicin 30 mg/m <sup>2</sup> + carboplatin (AUC 5) + bevacizumab <sup>^</sup> 15 mg/kg IV on day 1; repeat every 21 days <sup>81</sup>	Based on the AGO-OVAR 2.21 trial (phase III vs carboplatin plus gemcitabine plus bevacizumab); improved PFS with carboplatin plus liposomal doxorubicin.
Carboplatin (AUC 4) IV day 1 + gemcitabine 1000 mg/m <sup>2</sup> IV day 1, 8 + bevacizumab <sup>^</sup> 15 mg/kg on day 1 every 21 days for 6 cycles. Bevacizumab maintenance was continued beyond 6 cycles. <sup>55, 82</sup>	Patients who received bevacizumab as part of primary therapy may be re-challenged with bevacizumab + platinum-based therapy in platinum-sensitive recurrence. If response, bevacizumab maintenance can be continued until PD or unacceptable toxicity.

<sup>^</sup> = Per NCCN, an FDA-approved biosimilar may be substituted for bevacizumab.

2. Secondary cytoreduction may be considered in patients with platinum-sensitive recurrence (> 6 months) following primary therapy who have disease presumed to be amenable to resection, and do not have ascites.
3. Role of bevacizumab in platinum-sensitive recurrent disease
  - a. MITO16B-MaNGO evaluated patients with platinum-sensitive recurrent ovarian cancer who received bevacizumab as part of primary therapy. Patients were randomized to 6 cycles of platinum-based therapy +/- bevacizumab.<sup>83</sup> Median PFS was improved in patients receiving bevacizumab (11.8 months vs 8.8 months; HR 0.51, 95% CI 0.41-0.64; p<0.001) suggesting that patients may be re-challenged with bevacizumab in the recurrent platinum-sensitive setting.
  - b. GOG-213 evaluated patients with platinum-sensitive recurrent ovarian cancer who received paclitaxel/carboplatin with or without bevacizumab. Chemotherapy plus bevacizumab numerically improved overall survival (42.2 months vs 37.3 months; HR 0.829; 95% CI 0.683-1.005; p=0.056).<sup>69</sup>
  - c. The OCEANS trial demonstrated an improvement in PFS when bevacizumab is added to gemcitabine plus carboplatin (12.4 months vs 8.4 months, p<0.0001) in bevacizumab-naïve platinum-sensitive patients. However, overall survival was not increased.<sup>55, 82</sup>

### Comparison of combination regimen trials for platinum-sensitive first relapse

Trial	Patients	Regimen	Outcome	Comments
<b>ICON-4/ AGO-OVAR 2.2</b> <sup>73</sup>	802 patients with first relapse and treatment-free interval (TFI) > 6-12 months	Platinum vs Paclitaxel + platinum	PFS and OS statistically better in combination chemo arm.	Only 40% of patients received paclitaxel as first-line therapy, potentially biasing results in favor of paclitaxel arm.  Outcomes favor patients with longer TFI (> 12 and > 22 months).
<b>AGO/OVAR/ EORTC</b> <sup>76</sup>	356 patients with first relapse	Carboplatin vs Gemcitabine + carboplatin	Overall response and PFS significantly better in the combination arm.  No difference in OS.	Significantly more bone marrow toxicity in combination arm.  No difference in QOL scores.  Consider for patients with pre-existing neuropathy.
<b>CALYPSO</b> <sup>79, 80, 84</sup>	976 patients with platinum-sensitive first relapse	Liposomal doxorubicin + carboplatin vs Paclitaxel + carboplatin	PFS significantly improved in the liposomal doxorubicin arm.  No difference in OS.	Toxicity profile favored liposomal doxorubicin + carboplatin.  Decreased incidence of $\geq$ grade 2 hypersensitivity reactions in patients treated with liposomal doxorubicin (15 vs 33%).
<b>OCEANS</b> <sup>82</sup>	484 patients in first relapse with measurable disease	Gemcitabine + carboplatin <i>with either</i> Bevacizumab <i>or</i> Placebo	PFS significantly improved in bevacizumab treated patients.  No difference in OS with addition of bevacizumab.	Hypertension, proteinuria, and GI events greater in bevacizumab treated patients.
<b>GOG-213</b> <sup>75</sup>	714 patients with recurrent platinum-sensitive ovarian cancer	Paclitaxel + carboplatin +/- Bevacizumab	Numerically improved the overall survival difference (42.2 months vs 37.3 months; HR 0.829; 95% CI 0.683-1.005; p=0.056).	
<b>MITO16B- MaNGO</b> <sup>83</sup>	405 patients with recurrent platinum-sensitive disease following bevacizumab based primary therapy	Platinum-based doublet +/- Bevacizumab	Improved PFS with bevacizumab (11.8 months vs 8.8 months; HR 0.51; 95% CI 0.41-0.64; p<0.001).  No difference in OS with addition of bevacizumab.	Patients may be re-challenged with bevacizumab in the platinum-sensitive recurrent setting.

<b>AGO-OVAR 2.21<sup>81</sup></b>	682 patients with recurrent platinum-sensitive recurrent ovarian cancer	Carboplatin + liposomal doxorubicin + bevacizumab vs Carboplatin + gemcitabine + bevacizumab	Improved PFS in liposomal doxorubicin arm (13.3 months vs 11.7 months; HR 0.80; 95% CI 0.68-0.96, p=0.0128).	41.5% of patients had been pretreated with bevacizumab as part of primary therapy.
<b>NSGO-AVANOVA2/ENGOT-ov24<sup>72</sup></b>	97 patients with recurrent platinum-sensitive ovarian cancer	Niraparib vs Niraparib + bevacizumab	Improved PFS with combination therapy (12.5 vs 5.5 months; p<0.0001)	Chemotherapy sparing treatment option  Not compared to standard Pt-based combination therapy in Pt-sensitive recurrent setting

4. Maintenance therapy if partial or complete response to platinum-based chemotherapy for recurrent disease (**irrespective of germline or somatic *BRCA* status**)

a. Bevacizumab

- 1) Continuation as single agent maintenance therapy if bevacizumab received as part of chemotherapy for recurrent disease.

b. Niraparib<sup>85</sup>

1) Mechanism of Action

- 1) Inhibits poly(ADP-ribose) polymerase enzymes PARP-1 and PARP-2.

2) Indication and Dosing

- a) Recurrent maintenance: FDA approved for maintenance therapy in adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in in a PR/CR to platinum-based chemotherapy following platinum-sensitive relapse (independent of *BRCA* status).
- b) 300 mg by mouth once daily with or without food. Bedtime administration may help manage nausea.
- c) **Consider initial dose adjustment (200 mg daily) for patients with baseline weight < 77 kg and/or baseline platelets < 150,000/mm<sup>3</sup>.** However, this weight and platelet adjustment is only FDA indicated for first-line maintenance niraparib, not recurrent maintenance or treatment. **If started a reduced dose as above,** may increase to 300 mg daily after 2-3 months in the absence of worsening thrombocytopenia.<sup>86</sup>
  - i. Retrospective analysis of NOVA trial: “weights and plates”
  - ii. 68.9% of patients experienced dose reduction, 14.7% of patients discontinued therapy
  - iii. Baseline body weight and platelet count identified as risk factors for thrombocytopenia and dose reduction

3) ENGOT-OV16/NOVA trial<sup>85</sup>

- a) Evaluated 553 patients with platinum-sensitive recurrent ovarian cancer; patients were randomized 2:1 to receive niraparib 300 mg orally or placebo once daily.
  - b) PFS was improved with niraparib maintenance irrespective of most recent response to platinum-based treatment.<sup>87</sup>
    - a. Improved PFS in patients with PR
      - i. Germline BRCA (gBRCA) mutated: HR 0.24 (95% CI, 0.131-0.441;  $p < 0.0001$ )
      - ii. Non-gBRCA mutated: HR 0.35 (95% CI, 0.230-0.532;  $p < 0.0001$ )
    - b. Improved PFS in patients with CR
      - i. gBRCA mutated: HR 0.30 (95% CI, 0.160-0.546;  $p < 0.0001$ )
      - ii. Non-gBRCA mutated: HR 0.58 (95% CI, 0.383-0.868;  $p = 0.0082$ )
  - c) Patient reported QOL outcomes similar between groups.
  - d) Final analysis of OS demonstrate lack of benefit other than germline BRCA mutated patients therefore niraparib is only FDA approved in recurrent maintenance for gBRCAm patients.
    - a. gBRCAm (n=203) OS 40.9 m vs 38.1 m (HR = 0.85 [95% CI 0.61, 1.2])
    - b. non-gBRCAm (n=350) OS 31.0 m vs 34.8m (HR = 1.06 [95% CI 0.81, 1.37])
    - c. non-gBRCAm/HRD+ (n=162) OS 35.6 m vs 41.4 m (HR = 1.29 [95% CI 0.85, 1.95])
- c. Olaparib
- 1) Olaparib capsules were FDA approved in 2014; however, in 2017 the FDA approved olaparib tablets based on the SOLO-2 study. Olaparib capsules and tablets are not interchangeable and the capsules are mostly phased out of the US market.
  - 2) Indication and Dosing
    - a) Recurrent maintenance: FDA approved for maintenance therapy in patients with recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer in a PR/CR to platinum-based chemotherapy following platinum-sensitive relapse (independent of germline or somatic BRCA status).
    - b) 300 mg by mouth twice daily with or without food
      - i. First dose reduction: 250 mg twice daily
      - ii. Second dose reduction: 200 mg twice daily
  - 3) SOLO-2<sup>88</sup>
    - a) Randomized 295 patients with platinum-sensitive recurrent ovarian, fallopian tube or primary peritoneal cancer *with germline BRCA mutation* 2:1 to receive olaparib *tablets* 300 mg orally twice daily or placebo.
    - b) Median PFS in the olaparib arm was significantly longer than those in the placebo arm, 19.1 vs 5.5 months (HR 0.3; 95% CI, 0.22 to 0.41;  $p < 0.0001$ ).

- c) Long-term analysis exhibited trend toward OS benefit; however, not statistically significant [51.7 vs 38.8 months ( $p=0.054$ )].
  - d) Patient reported QOL outcomes similar between groups.
- 3) Study 19<sup>89, 90, 91</sup>
  - a) Randomized 265 patients with platinum-sensitive recurrent ovarian, fallopian tube or primary peritoneal cancer 1:1 to receive olaparib *capsules* 400 mg orally twice daily or placebo regardless of *BRCA* status.
  - b) Median PFS in the olaparib arm was significantly longer than those in the placebo arm, 8.4 months vs 4.8 months (HR 0.35; 95% CI 0.25 to 0.49;  $p<0.0001$ ).
  - c) Long-term analysis exhibited improved OS regardless of *BRCA* status: HR 0.73 (95% CI, 0.55-0.95;  $p=0.02$ ). The predefined threshold for statistical significance was not met.
- c. Rucaparib
  - 1) Indication and dosing
    - a) Recurrent maintenance: FDA approved for maintenance therapy in patients with recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer in a PR/CR to platinum-based chemotherapy following platinum-sensitive relapse (independent of germline or somatic *BRCA* status).
    - b) 600 mg by mouth twice daily with or without food
      - ii. First dose reduction: 500 mg twice daily
      - iii. Second dose reduction: 400 mg twice daily
      - iv. Third dose reduction: 300 mg twice daily
  - 2) ARIEL3<sup>92</sup>
    - a) Patients with platinum-sensitive recurrent high-grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer ( $n=564$ ) were randomized 2:1 to receive rucaparib 600 mg twice daily or placebo.
    - b) Median PFS in the intention to treat population was 10.8 months in rucaparib arm vs 5.4 months in the placebo arm (HR 0.36; 95% CI, 0.3 to 0.45;  $p<0.0001$ ).

**Patient Case #2, continued (ARS Question #4)-Answer:**

**Correct answer is B.** SM experienced progression of disease 3 months following completion of initial platinum-based adjuvant chemotherapy, indicating a platinum-resistant recurrence. Pegylated liposomal doxorubicin monotherapy is a category 2A, preferred therapy for platinum-resistant recurrence.

Answer A is inappropriate as this a platinum-resistant recurrence, as such platinum-based regimens are no longer preferred.

Answer C is inappropriate as combination niraparib/bevacizumab should be reserved for platinum-sensitive recurrence, as a conventional chemotherapy sparing treatment option based on the AVANOVA2 trial.

Answer D is inappropriate as pembrolizumab is currently only approved for advanced solid tumors, including ovarian cancer, with dMMR, MSI, or TMB-h. This tumor was not determined to be dMMR by immunohistochemistry testing based on the information provided.

**Patient Case #2, continued (ARS Question #5):**

SM has now received 5 lines of chemotherapy, most recently topotecan monotherapy. She unfortunately complains of worsening abdominal pain and is confirmed to have progressive disease. She inquires about immunotherapy for treatment of ovarian cancer. **Which of the following is true?**

- A. Nivolumab is FDA approved for microsatellite instability-high (MSI-H) solid tumors
- B. Pembrolizumab is only appropriate if MSI-H, dMMR, or TMB-H when there is no satisfactory alternative
- C. Pembrolizumab may be given as maintenance therapy following a PR/CR to platinum-based therapy for recurrent disease
- D. Checkpoint blockade may be given in platinum-sensitive relapse

5. Platinum-resistant recurrent disease <sup>93-95</sup>

- a. No standard therapy, response rates similar.
- b. In the absence of significant disease or drug related toxicity, it is common for patients with recurrent ovarian cancer to receive multiple lines of therapy (e.g. 5 or more regimens for recurrent disease).
- c. Consider enrollment in clinical trials.
- d. Mirvetuximab Soravtansine-gynx
  - 1) Mechanism of action:
    - Antibody-drug conjugate (ADC) that targets folate receptor alpha (FR $\alpha$ ) for delivery of maytansinoid DM4, a potent tubulin-targeting agent.
  - 2) Indication & Dose
    - Treatment of FR $\alpha$  positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults who have received 1 to 3 prior systemic therapies. FR $\alpha$  positive defined as  $\geq 75\%$  of cells with PS2+ staining.
    - 6 mg/kg (adjusted body weight) IV every 21 days
  - 3) Toxicities: ocular, constipation, diarrhea, nausea, vomiting, anemia, neutropenia, LFT elevation, neuropathy
    - Ocular toxicity management: Baseline eye exam and every other cycle for at least 8 cycles. Prophylactic artificial tears and ophthalmic topical steroids. Advise patients not to wear contact lenses throughout therapy.
  - 4) DDI: Strong CYP3A4 inhibitors as DM4 is a CYP3A4 substrate.

- 5) The SORAYA trial is a phase III single-arm study evaluating mirvetuximab soravtansine-gynx in patients with FR $\alpha$  high platinum-resistant ovarian cancer. 106 patients were enrolled with approximately half receiving 1-2 prior lines of therapy and the remaining half receiving 3 prior lines. The ORR was 32.4%, including 5 complete responses. Median duration of response was 5.9 months.<sup>96</sup>
- e. Randomized trial of topotecan vs pegylated liposomal doxorubicin demonstrated non-significant survival advantage for topotecan.
  - 1) Weekly topotecan may be less toxic than daily topotecan.<sup>97</sup>
- f. The AURELIA trial was a randomized, phase III trial comparing chemotherapy to chemotherapy plus bevacizumab in platinum-resistant ovarian cancer.<sup>94</sup>
  - 1) Chemotherapy regimens included pegylated liposomal doxorubicin, weekly paclitaxel or topotecan (NCCN Guidelines® category 2A).
  - 2) Median PFS (6.7 months vs 3.4 months,  $p < 0.001$ ) and ORR (27.3% vs 11.8%) were statistically significantly improved in the chemotherapy + bevacizumab arm when compared to chemotherapy alone.
  - 3) OS was not significantly different between arms.
  - 4) Strict exclusion criteria were implemented to reduce the risk of GI perforation. Patients with refractory disease, history of bowel obstruction or > 2 prior chemotherapy regimens were ineligible to participate.
  - 5) Grade  $\geq 2$  hypertension and proteinuria were more common in the bevacizumab containing arm. GI perforation occurred 2.2% of patients in the bevacizumab arm.
  - 6) Bevacizumab increased the proportion of patients achieving a 15% improvement in patient-reported abdominal/GI symptoms.
- g. Olaparib was evaluated in a multi-center, non-randomized, phase II study in patients with **deleterious germline BRCA 1/2 mutated** advanced ovarian cancer who had received 3 or more prior lines of chemotherapy (n=154).<sup>98</sup>
  - 1) Patients received olaparib 400 mg (capsules) twice a day.
  - 2) The overall response rate (ORR) in the study population was 34%, and 30% in patients with platinum-resistant disease.
  - 3) Median duration of response was 7.9 months.<sup>99</sup>
  - 4) Olaparib was FDA approved for the **treatment** of recurrent, advanced ovarian cancer with germline BRCA mutation following  $\geq 3$  prior lines of therapy, but after results of SOLO-3, a phase 3 study of olaparib treatment, demonstrated potential inferior outcomes compared to chemotherapy this indication was voluntarily removed.<sup>100</sup> NCCN still lists the use of olaparib monotherapy treatment for germline BRCA mutation following  $\geq 2$  prior lines of therapy as a category 3 recommendation.
- h. Rucaparib
  - 1) Clinical studies
    - a) ARIEL2 part 1 – phase II study evaluated 192 patients with either germline or somatic deleterious BRCA mutation, non-BRCA mutated loss of heterozygosity

(LOH) high, or non-*BRCA* mutated LOH low. Median PFS was 12.8 months (*BRCA* mutated), 5.8 months (non-*BRCA* mutated, LOH high), and 5.2 months (non-*BRCA* mutated, LOH low), respectively. The median duration of treatment was 5.7 months.<sup>101</sup>

- i. Loss of heterozygosity (LOH) is a biomarker included in commercial assays for ovarian cancer which may predict response to PARP inhibitors, including rucaparib. LOH results from the loss of one copy of a gene or chromosome region leading to homologous recombination deficiency. LOH may be reported as negative (< 16) or positive (≥ 16).
  - ii. While higher response rates were seen in patients with higher LOH scores, it was not incorporated into the product labeling as patients with low LOH scores still experienced benefit.
- b) Two single arm, open label trials of 106 patients with advanced ovarian cancer who had received at least 2 prior lines of chemotherapy. All patients had a deleterious germline and/or somatic *BRCA* mutation as detected by the FDA approved Foundation Focus CDxBRCA test.<sup>102</sup> The ORR was 54% with a median duration of response of 9.2 months. Within the platinum-resistant patient population, ORR was 25%.
- 2) Rucaparib was FDA approved for the **treatment** of recurrent, advanced ovarian cancer with deleterious germline and/or somatic *BRCA* (g/sBRCA) mutation following ≥ 2 prior lines of therapy. A phase 3 study, ARIEL4, compared chemotherapy to rucaparib monotherapy in patients with a deleterious germline or somatic *BRCA* mutation and found inferior outcomes therefore this indication has subsequently been removed.<sup>103</sup> NCCN still lists the use of rucaparib monotherapy treatment for germline *BRCA* mutation following ≥ 2 prior lines of therapy as a category 3 recommendation.
- i. Niraparib
    - 1) Niraparib treatment was studied in the QUADRA trial, in which 463 patients with recurrent high-grade ovarian cancer received niraparib 300 mg once daily.<sup>104</sup>
      - a) With a median of four prior lines of therapy (IQR 3-5), 26% of patients had platinum-sensitive, 33% had platinum-resistant, and 35% had platinum-refractory disease (7% unknown).
      - b) ORR was highest in patients with platinum-sensitive relapse and *BRCA* mutation (39%), followed by platinum-resistant/refractory and *BRCA* mutation (27%), and platinum-sensitive with HRD-positivity (26%).
    - 2) Niraparib was FDA approved for the **treatment** of recurrent, advanced ovarian cancer associated with homologous recombination deficiency (HRD) positive status, following ≥ 3 prior lines of therapy. Given the concerning evidence with other PARP inhibitors for treatment niraparib has withdrawn the treatment indication. NCCN still lists the use of niraparib monotherapy treatment for HRD positive following ≥ 3 prior lines of therapy as a category 3 recommendation.



Comparison of PARP inhibitors for ovarian cancer<sup>105-107</sup>

	Olaparib	Rucaparib	Niraparib
<b>Frontline Maintenance</b>	<b>Yes</b> -Monotherapy: PR/CR with g/s BRCA mutation (category 1 if no prior bevacizumab)  -With bevacizumab: PR/CR in HRD-positive (BRCA mutation or genomic instability) [category 1 for g/s BRCA mutation]	<b>No</b>	<b>Yes</b> -Monotherapy: PR/CR with g/s BRCA mutation (category 1 if no prior bevacizumab) or BRCA wild-type
<b>Advanced Disease (Not recurrent disease)</b>			
<b>Recurrent Pt-Sensitive Maintenance</b>	<b>Yes</b> -PR/CR to $\geq 2^{\text{nd}}$ line Pt-based recurrent therapy (category 1 if BRCA mutation)	<b>Yes</b> -PR/CR to $\geq 2^{\text{nd}}$ line Pt-based recurrent therapy (category 1 if BRCA mutation)	<b>Yes</b> -PR/CR to $\geq 2^{\text{nd}}$ line Pt-based recurrent therapy (category 1 if BRCA mutation)
<b>Recurrent Treatment</b>	<b>No</b> -No longer FDA approved but listed as category 3 for f BRCA mutated after $\geq 2$ prior lines	<b>No</b> -No longer FDA approved but listed as category 3 for g/s BRCA mutated after $\geq 2$ prior lines	<b>Yes</b> -No longer FDA approved but listed as category 3 after $\geq 3$ prior lines and HRD-positive (BRCA mutated or genomic instability)  -With bevacizumab: for platinum-sensitive recurrence
<b>Typical Dosing</b>	300 mg twice daily	600 mg twice daily	300 mg once daily (consider 200 mg once daily in patients with baseline weight < 77 kg and/or platelets < 150K)
<b>Common Adverse Effects</b>	Myelosuppression (neutropenia, thrombocytopenia, anemia) Fatigue GI (nausea, changes in bowel habits)		
<b>Notable Adverse Effects</b>	Pneumonitis (< 1%) Increased SCr ( $\leq 45\%$ )	Hypercholesterolemia (40-84%) Elevated AST/ALT (60-70%) Increased SCr (98%)	Hypertension (20%) Palpitations (10%)
<b>MDS/AML</b>	< 1.5%	1.1%	0.9%
<b>Metabolism</b>	-Major substrate: CYP3A4 -P-glycoprotein	-Minor substrate: CYP1A2, 2D6, 3A4 -P-glycoprotein -Moderate inhibitor: CYP1A2 -Weak inhibitor: CYP2C19, 2C9, 3A4	-P-glycoprotein -Carboxylesterases to inactive metabolite

**Patient Case #2, continued (ARS Question #5)-Answer:**

**The correct answer is B.** Pembrolizumab should be reserved for treatment of relapsed ovarian cancer that is MSI-H, dMMR, or TMB-H in which there are “no satisfactory alternatives”.

Answer A is incorrect as nivolumab is only approved for colorectal cancer with MSI-H status.

Answer C is incorrect as pembrolizumab is not appropriate for maintenance therapy. The recommended agents for maintenance following platinum-based therapy in recurrent disease are olaparib, rucaparib, and niraparib.

Answer D is incorrect because patients with platinum-sensitive relapse should continue to receive platinum-based therapy as they are able. Platinum-sensitive relapse would not qualify as having “no satisfactory alternative”.

**Additional salvage agents for platinum-resistant recurrent ovarian cancer OR second and subsequent relapse (agents listed alphabetically)<sup>4</sup>**

Agent(s)	Platinum-Status	Dose/Schedule
Anastrozole <sup>108</sup>	Pt-resistant <i>or</i> Pt-sensitive	1 mg PO daily
Bevacizumab <sup>^, 109, 110</sup>	Pt-resistant <i>or</i> Pt-sensitive	15 mg/kg IV every 3 weeks
Capecitabine <sup>111, 112</sup>	Pt-resistant <i>or</i> Pt-sensitive	1000-1250 mg/m <sup>2</sup> PO BID for 14 days every 3 or 4 weeks
Carboplatin <sup>76</sup>	Pt-sensitive	AUC 5-6 IV every 21 days for 6 cycles. Patients who are platinum-sensitive but cannot tolerate combination chemotherapy
Carboplatin + paclitaxel <sup>27</sup>	Pt-sensitive	Paclitaxel 80 mg/m <sup>2</sup> IV over 1 hour days 1, 8, 15 + carboplatin (AUC 5-6) IV day 1. Patients who are platinum-sensitive and do not have pre-existing neuropathy
Carboplatin + docetaxel <sup>25</sup>	Pt-sensitive	Docetaxel 75 mg/m <sup>2</sup> IV + carboplatin (AUC 5) IV every 21 days. Patients who are platinum-sensitive and have pre-existing neuropathy.
Cisplatin <sup>73</sup>	Pt-sensitive	Cisplatin 75 mg/m <sup>2</sup> IV every 28 days for 6 cycles. Patients who are platinum-sensitive but cannot tolerate combination chemotherapy
Cyclophosphamide (oral) <sup>113, 114</sup>	Pt-resistant <i>or</i> Pt-sensitive	50 mg PO daily, 50 mg PO BID, or 150 mg days 1-14 every 21 days
*Cyclophosphamide (oral) + bevacizumab <sup>^, 115</sup>	Pt-resistant	Cyclophosphamide 50 mg PO daily and bevacizumab 10 mg/kg IV every 14 days
*Docetaxel <sup>116</sup>	Pt resistant	75-100 mg/m <sup>2</sup> IV every 21 days
Doxorubicin <sup>117</sup>	Pt-resistant <i>or</i> Pt-sensitive	50-60 mg/m <sup>2</sup> IV every 21 days
*Etoposide (oral) <sup>118</sup>	Pt-resistant	50 mg/m <sup>2</sup> /day PO days 1-21; repeat every 28 days
Exemestane <sup>119</sup>	Pt-resistant <i>or</i> Pt-sensitive	25 mg PO daily
*Gemcitabine <sup>120, 121</sup>	Pt-resistant	800-1000 mg/m <sup>2</sup> days 1, 8, 15; repeat every 28 days
Ifosfamide <sup>122</sup>	Pt-resistant <i>or</i> Pt-sensitive	1-1.2 g/m <sup>2</sup> /day x 5 days; repeat every 28 days
Irinotecan <sup>123</sup>	Pt-resistant <i>or</i> Pt-sensitive	100 mg/m <sup>2</sup> IV days 1, 8, 15; repeat every 28 days
Letrozole <sup>124</sup>	Pt-resistant <i>or</i> Pt-sensitive	2.5 mg PO daily
Leuprolide acetate <sup>125</sup>	Pt-resistant <i>or</i> Pt-sensitive	3.75 mg IM depot every 28 days
Megestrol acetate <sup>126</sup>	Pt-resistant <i>or</i> Pt-sensitive	400-800 mg PO daily
Melphalan <sup>127</sup>	Pt-resistant <i>or</i> Pt-sensitive	10 mg PO daily x5 days; repeat every 6 weeks
Nanoparticle albumin-bound paclitaxel <sup>128</sup>	Pt-resistant <i>or</i> Pt-sensitive	100 mg/m <sup>2</sup> IV days 1, 8, 15 every 28 days or 260 mg/m <sup>2</sup> IV every 3 weeks
Oxaliplatin <sup>129</sup>	Pt-resistant <i>or</i> Pt-sensitive	130 mg/m <sup>2</sup> IV every 3 weeks
*Paclitaxel <sup>130</sup>	Pt-resistant <i>or</i> Pt-sensitive	80 mg/m <sup>2</sup> days 1, 8, 15; repeat every 28 days
*Paclitaxel + bevacizumab <sup>^, 94</sup>	Pt-resistant	Paclitaxel 80 mg/m <sup>2</sup> days 1, 8, 15 and bevacizumab 10 mg/kg day 1, 15 every 28 days
*Pegylated liposomal doxorubicin (PLD) <sup>93, 131</sup>	Pt-resistant	40-50 mg/m <sup>2</sup> every 28 days
*PLD + bevacizumab <sup>^, 94</sup>	Pt-resistant	PLD 40 mg/m <sup>2</sup> day 1 and bevacizumab 10 mg/kg day 1, 15 every 28 days
Pemetrexed <sup>132, 133</sup>	Pt-resistant <i>or</i> Pt-sensitive	500 mg/m <sup>2</sup> IV every 3 weeks
Tamoxifen <sup>134</sup>	Pt-resistant <i>or</i> Pt-sensitive	20 mg PO BID

*Topotecan <sup>93, 135, 136</sup>	Pt-resistant	1.25 mg/m <sup>2</sup> /day x 5 days; repeat every 21 days <u>or</u> 3-4 mg/m <sup>2</sup> /week days 1, 8, 15; repeat every 28 days
*Topotecan + bevacizumab <sup>^, 94</sup>	Pt-resistant	Topotecan 1.25 mg/m <sup>2</sup> /day x 5 days and bevacizumab 15 mg/kg day 1 every 21 days or 4 mg/m <sup>2</sup> days 1, 8, 15 and bevacizumab 10 mg/kg day 1 and 15 every 28 days
Topotecan + sorafenib <sup>137</sup>	Pt-resistant	Topotecan 1.25 mg/m <sup>2</sup> /day x 5 days and sorafenib 400 mg PO twice daily days 6-15; repeat every 21 days
Vinorelbine <sup>138</sup>	Pt-resistant <i>or</i> Pt-sensitive	30 mg/m <sup>2</sup> days 1, 8; repeat every 21 days

\* NCCN Guidelines® preferred regimen for platinum-resistant recurrence

<sup>^</sup> = Per NCCN, an FDA-approved biosimilar may be substituted for bevacizumab

**Patient Case #2, continued (ARS Question #6):**

During SM's initial adjuvant chemotherapy with paclitaxel and carboplatin following interval debulking surgery, she experienced a severe hypersensitivity reaction on cycle 6 of carboplatin, characterized by cough and shortness of breath.

**Which of the following is the proper management of a severe platinum hypersensitivity reaction?**

- A. Stop infusion, give corticosteroid, monitor for 30 minutes and resume at a slower rate
- B. Stop infusion, start oxygen and observe
- C. Administer IM epinephrine
- D. Stop infusion, start oxygen, administer H1 and H2 blocker and corticosteroid

E. Symptom management

1. Hypersensitivity reactions (taxanes/platinum compounds)<sup>139-141</sup>

- a. Patients and families should be counseled on the signs and symptoms of hypersensitivity reactions.
  - 1) Signs and symptoms: flushing, dizziness, itching, change in vital signs from baseline, shortness of breath, back pain, nausea/vomiting, diarrhea, abdominal cramping, throat tightening, hypoxia, seizures, or anaphylaxis.
- b. Platinum agents
  - 1) Carboplatin
    - a) The incidence of carboplatin hypersensitivity reactions is between 1-44%.
    - b) Risk is markedly higher after 6-8 exposures, irrespective of individual doses.
    - c) When determining a patient's risk, total lifetime exposure to platinum agent must be assessed – even if many years between exposure. Increased time between doses may increase a patient's risk of developing a reaction.
    - d) Skin testing may be helpful but not always predictive.
    - e) Patients who experience low to moderate hypersensitivity reactions or patients with more severe hypersensitivity reactions who successfully undergo inpatient

desensitization can be evaluated for carboplatin desensitization in an ambulatory clinic.<sup>142, 143</sup>

- f) Data suggests that an extended infusion schedule and use of premedications may decrease the number of hypersensitivity reactions to carboplatin.<sup>144</sup>

2) Oxaliplatin<sup>145, 146</sup>

- a) The incidence of acute reactions is between 12-25% of patients receiving oxaliplatin with 1/3 of those being severe infusion reactions.
- b) Reactions may occur within minutes of drug administration and with any cycle of therapy; however, like carboplatin, the risk is markedly higher following multiple cycles of therapy.
- c) Patients with mild reactions may be re-challenged and can be expected to tolerate infusions.
- d) Severe reactions are typically anaphylactic and despite reducing infusion rates or additional premedications, patients typically cannot be successfully re-challenged.

c. Taxanes

1) Conventional paclitaxel

- a) The incidence of paclitaxel infusion reactions is 8-45% and occurs most frequently within the first few minutes of the first or second administration, irrespective of dose infused.
- b) Majority of reactions are minor
  - i. Upon stopping infusion, symptoms rapidly resolve spontaneously.
  - ii. Once patient recovers from mild reaction, remainder of infusion may be restarted at a lower infusion rate and titrated to tolerance.
- c) Standard premedications (dexamethasone oral 20 mg given 12 and 6 hours prior to paclitaxel OR dexamethasone IV 20 mg 30 minutes prior to paclitaxel, diphenhydramine 50 mg, and H<sub>2</sub>-antagonist) reduce reaction rate to: severe reactions = 2% and mild-to-moderate reactions = 40%.
  - i. If patients tolerate the first two doses of paclitaxel without an infusion reaction, clinicians may consider reducing or discontinuing the dexamethasone premedication.<sup>147, 148</sup>
- d) Cremophor EL® may be contributory source of hypersensitivity reactions with paclitaxel.

2) Docetaxel

- a) Hypersensitivity reactions occur at approximately the same frequency as paclitaxel.
- b) Onset with first or second administration.
- c) Premedication with dexamethasone 8 mg oral twice daily x 3 days, beginning day prior to chemotherapy greatly reduces frequency and severity of reactions.

- d) Retrospective study employing single dose of dexamethasone 20 mg IV prior to docetaxel resulted in 7.8% (7 of 90 patients) rate of HSR requiring emergency treatment.
  - e) Polysorbate 80 may be contributory source of hypersensitivity reactions with docetaxel.
- d. Acute management of hypersensitivity reactions
- 1) Emergency supplies should be readily available: antihistamines, epinephrine, intravenous fluids, corticosteroid, aerosolized bronchodilators, oxygen, tracheostomy equipment, and defibrillator.
  - 2) Mild infusion reaction
    - a) Symptoms may include pruritus, rash, or flushing
    - b) Stop infusion of suspected medication
    - c) Administer H1 antagonist antihistamines
    - d) If vitals are stable and patient is a candidate to re-challenge, restart infusion at a slower rate
    - e) Administer premedication with H1 antagonist antihistamine (if not previously given), corticosteroid, H2 antagonist
  - 3) Severe reaction: follow the management of mild reaction and add the following interventions as necessary:
    - a) Symptoms may include nausea/vomiting, dyspnea, shortness of breath, hypo- or hypertension necessitating intervention.
    - b) Stop infusion of suspected medication
    - c) Administer oxygen
    - d) Nebulized bronchodilators if short of breath
    - e) Give both H1 and H2 antagonists
    - f) Corticosteroid
    - g) Do not re-challenge until evaluated by allergist or specialist with desensitization
  - 4) Life-threatening (anaphylaxis)
    - a) Symptoms may include hives, severe hypotension, nausea/vomiting, respiratory distress; symptoms typically develop rapidly.
    - b) Stop infusion of suspected medication
    - c) Place patient in recumbent position to maintain blood flow and oxygen (maintain airway)
    - d) Administer epinephrine 0.3 mg intramuscularly mid-outer thigh
    - e) Give 8 to 10 L per minute via facemask or up to 100% O<sub>2</sub> based on O<sub>2</sub> saturation
    - f) Give 1-2 L IV normal saline as a rapid bolus for hypotension

- g) Administer both H1 and H2 antagonists
- h) Administer corticosteroid to prevent a delayed reaction
- i) Acute cardiopulmonary arrest: standard advanced cardiac life support measures should be followed
- j) Do not re-challenge until evaluated by allergist or specialist with desensitization

2. Chemotherapy Desensitization<sup>139, 143, 149-151</sup>

- a. For severe or true drug allergies, the patient should have a discussion with their oncologist reviewing the risks involved with future doses of the chemotherapy agent and determine if the benefits of ongoing treatment outweigh the risks.
- b. In a patient who previously had a severe reaction to an agent and it is determined they will resume treatment, then desensitization would be recommended. Most patients can be desensitized (90%).
- c. There are many different desensitization protocols for taxane and platinum that have been published. Mild reactions can be treated with outpatient desensitization protocol while more severe are usually treated inpatient.

**Patient Case #2, continued (ARS Question #6)-Answer:**

**Correct answer is D.** Stopping the offending agent in any hypersensitivity reaction is the first step along with appropriate pharmacologic intervention which includes both H1 and H2 antagonists to stop the acute hypersensitivity reaction and steroid to prevent a delayed or rebound reaction.

Answer A is not correct as steroids alone do not provide immediate benefit in management of an acute hypersensitivity reaction; rather corticosteroids prevent rebound or delayed reactions.

Answer B is inappropriate as a pharmacologic intervention is needed to stop the hypersensitivity reaction.

Answer C is missing the most important step of stopping the offending agent as well as providing oxygen. Additionally, this is not reported to be a life threatening or anaphylactic reaction and other interventions should be considered first.

3. Alopecia<sup>152</sup>

- a. Patients may develop frontal alopecia (e.g., male-pattern baldness), particularly associated with taxanes and anthracyclines; no effective treatment exists.
- b. Hair growth on scalp slows down
  - 1) Chemotherapy does not differentiate between tumor cell and non-tumor cell growth process.
    - a) In the anagen phase, keratinocytes of the hair follicle bulb rapidly proliferate, which makes them susceptible to chemotherapy effects causing weakened hair shaft or complete failure to produce hair.

- b) Approximately 85% of hair is actively growing, which is why patients may not lose all hair at once, but progressively over several cycles.
  - c) Scalp hair affected greater than facial or body hair
    - i. Eyebrows, eyelashes, beard, axillary hair, and pubic hair are affected differently based on drug, dose, and rate of hair matrix mitoses.
  - d) Hair loss is noticeable 1 to 2 weeks after chemotherapy administration but becomes most apparent 1 to 2 months after administration.
- 2) After chemotherapy is discontinued, hair regrowth will usually reoccur
  - a) Stem cells of the hair follicle spared from chemotherapy and generate new follicles
  - b) Hair grows about ½" per month; however, growth rate slows with aging
  - c) May be associated with a change in color or texture
- 3) Hair loss can have a major impact on patient lives; women more than men
- 4) Management of chemotherapy-induced alopecia
  - a) A three-step strategy for dealing with hair loss has been suggested:
    - i. Anticipation and education of hair loss
    - ii. Coping with alopecia
      - (a) Loss of hair seen as an outward sign of courage in the journey against cancer
      - (b) Use of hats, scarves, cranial prosthetics
      - (c) Reminder for use of sunscreen SPF 15+ on scalp
    - iii. Regrowth of hair
  - b) The Dignicap Cooling System<sup>153</sup>
    - i. FDA approved in 2015 to reduce the frequency and severity of alopecia during chemotherapy in patients with breast cancer receiving alopecia-inducing chemotherapy agents and doses.
      - (a) Indication was expanded in 2017 to include patients with solid tumors.
    - ii. Studied in 122 women with Stage I and II breast cancer who were undergoing chemotherapy known to cause hair loss.
      - (a) More than 66 percent of patients treated with the DigniCap reported losing less than half their hair.
    - iii. Contraindicated in pediatric patients and patients with cold sensitivity or susceptibility to cold-related injuries.
    - iv. Mechanism: A computer-controlled system circulates liquid to a cap to cool the scalp during treatment, constricting blood vessels in the scalp, thereby reducing the amount of chemotherapy reaching the hair follicle and slowing down cell division. The cold temperature also decreases the activity of the hair follicles and slows down cell division, making them less affected by chemotherapy. This cap



is covered by a second cap made from neoprene, a type of rubber that holds the cooling cap in place and acts as an insulation cover to prevent loss of cooling.

- v. Side effects: cold-induced headaches, neck and shoulder discomfort, chills, and pain. Long-term effects of scalp-cooling and risk of scalp metastasis have not been fully studied.

#### **Prognostic Factors and Prognosis<sup>4, 8, 154</sup>**

- A. Initial extent of disease is the single most important prognostic factor.

<b>Extent of disease</b>	<b>5-year survival for invasive epithelial ovarian cancer</b>
Localized	92.7%
Regional	73.3%
Distant	28.5%
Unstaged	28.2%

- B. Volume of residual disease at time of surgery

- 1. Patients with initial optimal surgical cytoreduction have a significant survival advantage compared to patients with suboptimal status (39 months vs 17 months).

- C. Histologic subtype and grade

- 1. High-grade tumors are more aggressive than low-grade tumors.
- 2. Clear cell and carcinosarcoma histologies considered poor prognosis.
- 3. Histology is especially important in assessing prognosis and management for patients with early stage disease.

- D. CA-125<sup>155</sup>

- 1. Grossly correlated with volume of disease.
- 2. Prognosis and response to chemotherapy predicted by rate of decline. Better prognosis/survival if CA-125 is normal (0-35 IU/mL) following three cycles of therapy. Slow response or failure to normalize after 6 cycles of chemotherapy associated with worse prognosis.
- 3. An indicator of progression following complete remission in patients that CA125 is a good marker (elevated at time of diagnosis and normalizes with treatment).
- 4. Significant laboratory variation. For interpretation of CA-125 trends to be meaningful in any given patient, all levels should be drawn at the same laboratory.

- E. Obesity and dose intensity<sup>156</sup>

- 1. A recent Australian study of 333 women with advanced stage (FIGO stage III or IV) serous ovarian cancer evaluated the relationship between body mass index (BMI), dose intensity of chemotherapy received, OS and PFS.
- 2. Obese women are statistically significantly more likely to have received <85% relative dose intensity compared to normal weight women.

3. Women who had <85% relative dose intensity of carboplatin had a significantly statistically worse PFS, but there was no difference in OS.

#### **VIII. Supportive Care for End-Stage Ovarian Cancer<sup>157, 158</sup>**

- A. Bowel obstruction (intermittent or complete).
- B. Low residue diet with frequent, small meals.
- C. Avoid agents that slow GI motility; use prokinetic agents cautiously (e.g. low dose metoclopramide).
- D. Paracentesis/thoracentesis for accumulating ascites/pleural effusions.
- E. Cancer-related anemia is common, occurring in approximately 50% of cases.
  1. Preemptive therapy with IV iron may reduce the need for transfusions when compared to oral iron in this patient population.
- F. Parenteral/enteral feeding is of limited value.
- G. Palliative care and pain management.
- H. Psychosocial support of patient and family.

#### **IX. Toxicity and Survivorship Issues<sup>159</sup>**

- A. Treatment with surgery, radiation, and chemotherapy are associated with both acute and chronic toxicities. In general, surgery for early stage disease is associated with less long-term toxicity than pelvic radiation.
- B. Treatment with surgery and chemotherapy is associated with both acute and chronic toxicities:
  1. Acute toxicities include low-grade nausea, vomiting, fatigue, anemia, mild bone marrow suppression and diarrhea.
  2. Premature menopause is a potential complication of therapy after surgery. Hot flashes can be managed with various supportive care including: <sup>160, 161</sup>
    - a. Simple behavior measures such as adjusting room temperature or using fans.
    - b. Non-hormonal therapy utilizing anticonvulsants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.
    - c. Hormonal therapy: estrogen with progestin if use is longer than 6 months.
  3. Sexuality is an issue for women with ovarian cancer irrespective of treatment modality.
    - a. Loss of fertility
    - b. Significant decrease in sexual pleasure in women with ovarian germ cell cancer survivors when compared to age-race-education matched control.<sup>162</sup>
  4. Psychological effects: depression, anxiety, guilt, poor body image

# CERVICAL CANCER

*Note: This section does not cover the diagnosis or treatment of cervical sarcomas or other unusual histologic subtypes.*

## I. Pathogenesis<sup>163-166</sup>

- A. Cervical cancer is causally related to infection with oncogenic human papillomavirus (HPV) strains. In sexually active adults it has been estimated that 75 to 80 percent will acquire genital tract HPV before the age of 50.
  - 1. Oncogenic HPV strains infect epithelium of lower anogenital tract, including the cervical squamo-columnar junction.
    - a. More than 100 subtypes of HPV identified. **HPV-16 and HPV-18** are responsible for more than 70% of invasive cervical cancers. Other less common oncogenic strains include HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.
    - b. HPV-6 and HPV-11 are associated with the development of genital warts.
    - c. Infection with HPV is associated with the development of other cancers including oropharyngeal, anal, vaginal, vulvar, penile, and non-melanoma skin cancers.
  - 2. Circular, double-stranded HPV DNA can open and insert into host cell's DNA, which exploits host cell mitotic activity and subverts protective mechanisms. This inactivates E1 and E2 open reading frames, allowing overproduction of E6 and E7 gene products, which bind to, and partially inactivate, the cell regulatory proteins, retinoblastoma (Rb) and p53 respectively.
    - a. This cascade results in dysregulation of the cell cycle, increase in mutational events, aneuploidy and possibly neoplasia.
  - 3. HPV can remain dormant within cervical cells for years as persistent HPV infection.
  - 4. The presence of concurrent immunosuppression (e.g., transplantation, HIV) and/or carcinogenic cofactors such as nicotine accelerate the progression from persistent infection to invasive carcinoma.
- B. Cervical dysplasia is a precursor to cervical cancer
  - 1. Risk of progression to invasive cancer increases with grade of dysplasia.
  - 2. Most infections with HPV regress spontaneously.
  - 3. Persistent HPV infection with an oncogenic subtype can result in progression to pre-cancerous lesions known as high-grade cervical dysplasia (often referred to as cervical intra-epithelial neoplasm (CIN) III. CIN III is a precursor lesion for cervical cancer. The time lag from infection with oncogenic HPV to the development of invasive cervical cancer is usually measured in years (often 10 or more). However, the carcinogenic process can be accelerated in patients with underlying immunodeficiency (e.g., HIV).
  - 4. Early detection and appropriate treatment of cervical dysplasia can stop progression to cervical cancer.

## II. Histology

**Common cervical cancer histologies<sup>164, 167, 168</sup>**

Histology	Prevalence	Comment
Squamous cell	72.1%	Highly associated with HPV.
Adenocarcinoma	19%	Incidence is increasing over past 3 decades; traditional screening may be less effective; screening using HPV testing may increase detection. HPV vaccination effective against this sub-type as well. Associated with worse prognosis.
Adenosquamous	<5%	Mixed glandular and squamous features; poor prognosis.
Other subtypes (neuroendocrine small cell, glassy cell, primary sarcoma)	Rare	Associated with poor prognosis; unlikely to be associated with HPV infection.

**III. Screening and Prevention<sup>168-173</sup>****A. Screening**

1. The U.S. Preventive Services Task Force (USPSTF) updated its recommendations for cervical cancer screening in August 2018.
  - a. Age < 21: no screening recommended.
  - b. Age 21-29: screening with cervical cytology alone every 3 years.
  - c. Age 30-65: screening with cervical cytology alone every 3 years and HPV testing every 5 years, OR co-testing with both cervical cytology and HPV every 5 years.
  - d. Age > 65: no screening recommended if patient has had proper prior screening and not considered high-risk of cervical cancer.
2. The Papanicolaou (PAP) test is an effective screening tool for reducing the incidence and mortality from cervical cancer. There are two types of PAP tests available.
  - a. The traditional PAP test scrapes the cervix for cells that are smeared on a slide and viewed under a microscope. Many sampling errors can occur with this test.
  - b. The liquid-based PAP tests obtain cervical cells with a brush and suspend them into a liquid that is then viewed under a microscope. The liquid method is most widely used because it reduces errors in sampling and HPV DNA testing can be performed on one sample.
3. HPV DNA testing: There is more than one approved test for HPV DNA. Some assays test for the presence of high-risk (oncogenic) HPV strains but do not detail specific strains. Other tests specifically test for the presence of HPV-16 and HPV-18.
4. The frequency of screening will increase based on one or more of the following clinical scenarios:
  - a. Results demonstrating abnormal PAP results or positive HPV tests.
  - b. Presence of underlying immunodeficiency syndrome (e.g., HIV, transplantation, long-term steroid use).
  - c. Personal history of cervical cancer or surveillance following surgery for cervical cancer.

5. Results of either a positive screening cytology and/or positive screening HPV DNA test require additional work-up.
6. Additional recommendations for cervical cancer screening by age. *Note that the NCCN Guidelines® for Cervical Cancer Screening endorse the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical pathology Screening Guidelines for the prevention and early detection of cervical cancer.*<sup>169</sup>
  - a. Age < 25: no screening due to very low risk of developing invasive cancer and screening may lead to increased incidence of cervical procedures.
  - b. Age 25-65: primary HPV testing every 5 years (preferred). HPV and cytology co-testing every 5 years or cytology alone every 3 years (acceptable).
  - c. Age > 65: no screening necessary if adequate negative prior screenings.
  - d. Special populations
    - 1) After total hysterectomy (removal of uterus and cervix): no screening if hysterectomy due to benign disease; however, if hysterectomy was for treatment of cervical cancer or dysplasia then follow age specific recommendations.
    - 2) HPV vaccinated females: follow age specific recommendations.

B. Prevention<sup>169, 174-178</sup>

1. Prevention is aimed at avoiding risk factors (e.g., delay onset of sexual activity, minimize number of sexual partners, avoid smoking, etc.). The long pre-invasive phase between infection with HPV and development of invasive disease makes cervical cancer ideal for effective screening.
2. HPV vaccination<sup>179</sup>
  - a. There is only one HPV vaccination being distributed in the United States, Human Papillomavirus 9-valent Vaccine, which was originally FDA approved in 2014. This vaccine does not contain thimerosal or mercury as a preservative.
  - b. The HPV vaccine does not contain DNA and is non-infectious. Capsid proteins (L1) assemble into virus-like particle (VLP). VLPs resemble native HPV particles, which elicit HPV neutralizing antibodies.
  - c. Human Papillomavirus 9-valent Vaccine, Recombinant against HPV strains 6, 11, 16, 18, 31, 33, 45, 52, 58 (Gardasil®9)
    - 1) This vaccine is FDA approved for use in **females age 9-45** for the prevention of cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers, genital warts, and the following precancerous or dysplastic lesions caused by HPV: cervical intraepithelial neoplasia (CIN) grade 1, 2, 3; cervical adenocarcinoma *in situ* (AIS); vulvar intraepithelial neoplasia (VIN) grade 2, 3; vaginal intraepithelial neoplasia (VaIN) grade 2, 3; and anal intraepithelial neoplasia (AIN) grade 1, 2, 3.
    - 2) It is also approved for use in **males age 9-45** for the prevention of anal and oropharyngeal and other head and neck cancers, genital warts, and anal precancerous dysplastic lesions AIN grades 1, 2, 3 caused by HPV.

- 3) Based on newer clinical data the FDA approved new dosing for Gardasil-9 with an expansion of the upper age range to include adults between 27-45 years of age.
    - a) Age 9-14: 2 dose schedule (0, 6-12 months) however if the second dose was administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose and 3 dose schedule (0, 2, 6 months).
    - b) Age 15-45: 3 dose schedule (0, 1-2, 6 months)
  - d. HPV vaccines are preventative and not therapeutic (i.e., are not effective in treating patients with HPV).
  - e. Guidelines from the American Congress of Obstetricians and Gynecologist (ACOG), the American Cancer Society (ACS), the Society of Gynecologic Oncology (SGO) and the Advisory Committee on Immunization Practices (ACIP) recommend that vaccination should begin between 11-12 years of age for both male and female patients. The vaccine series can be started as young as 9 years of age in cases of sexual abuse. It is also recommended for girls and women ages 13-26 to complete the vaccination series if they have not yet been vaccinated.<sup>180-183</sup> These guidelines pre-date the FDA expanded age range which included individuals between 27-45 years of age.
  - f. Vaccines are associated with injection site reactions, including pain, which is generally self-limiting.
3. For a more in-depth review of the clinical data supporting the use of these vaccines, the reader is referred elsewhere.<sup>175, 177</sup>

**Patient Case #1:**

DD is a 55 year-old-female, ECOG status 0 who presents with complaints of severe fatigue, 6 months of post-menopausal bleeding and lab work revealing a Hgb of 7.8 g/dL. A pelvic ultrasound and endometrial biopsy reveal non-keratinizing squamous cell carcinoma, invasive, moderately to poorly differentiated, consistent with cervical origin. Surgical staging reveals a cervical lesion ~2 cm in diameter and firm with the uterus and cervix deviated left. On rectovaginal exam, there is left parametrium tethering and there is thickening of the parametrium, consistent with parametrial invasion. Cystoscopy and vaginal exam are normal. Unfortunately, imaging reveals rectal involvement not appreciated on exam; therefore, she has stage IVA cervical cancer.

**What management options are available for this patient?**

- A. Surgery
- B. Radiation
- C. Chemoradiation
- D. Chemotherapy

**IV. Primary Treatment<sup>168, 184, 185</sup>**

- A. The goal of primary treatment is to cure the patient. This is an achievable goal for early-stage disease. It is also possible to cure patients who present with advanced stage disease, although less likely. Metastatic disease is rarely curable.

1. A multidisciplinary, multinational panel incorporating cancer control, medical and radiation oncology, health economic, obstetric and gynecologic, and palliative care experts convened to produce recommendations reflecting resource tiered settings (basic, limited, enhanced and maximal resource settings).<sup>186</sup> Women in the US have access to maximal tiered care therefore the treatment options within this chapter will reflect the recommendations based on the highest tiered setting.
  - a. If a woman cannot access the most effective evidence-based care within her country or a neighboring country she may need to be treated with a lower-tier modality.
- B. Vaccine therapies currently have no established role in the treatment of cervical cancer.<sup>187</sup>
- C. Cervical cancer can be treated with surgery, radiation, and/or chemotherapy.
  1. Surgery
    - a. The extent of surgery varies with the stage of disease (stage I-IIA) and the patient's desire for future fertility.
    - b. Fertility-sparing approaches may be considered for select patients who have been counseled regarding disease risk as well as prenatal and perinatal issues. Fertility sparing approaches include cone biopsy or radical vaginal trachelectomy with laparoscopic lymphadenectomy.
      - 1) Due to lack of data, fertility-sparing approaches should not be considered in small cell neuroendocrine tumors, gastric type adenocarcinoma, or adenoma malignum.
    - c. Non-fertility-sparing approaches
      - 1) Simple/extrafascial hysterectomy (Type A), modified radical hysterectomy (Type B), and radical hysterectomy (Type C).
    - d. Pelvic lymph node dissection with or without para-aortic lymph node sampling usually accompanies the surgery of choice above.
      - 1) Consideration of sentinel lymph node (SLN) mapping and dissection to decrease the need for pelvic lymphadenectomy.
  2. Radiation
    - a. Radiation therapy (RT) plays a major role in the management of cervical cancer.
    - b. Therapies include pelvic external beam radiation therapy (EBRT) and vaginal brachytherapy, along with stereotactic body radiotherapy which is applied to isolated metastases.
    - c. The combination of EBRT and brachytherapy are the mainstay of primary treatment for advanced stage disease (stage IIB-IVA).
    - d. Radiation can also be used following surgery to reduce the risk of recurrence in patients with high-risk features (adjuvant therapy).
  3. Chemotherapy
    - a. In general, chemotherapy alone plays a limited role in the frontline management of localized cervical cancer.
    - b. Chemotherapy is most commonly used in conjunction with radiation to enhance its effectiveness (chemosensitization). Cisplatin is the most commonly used agent for this purpose.

- c. Platinum-based combination chemotherapy is used in the management of advanced stage (IVB) or recurrent cervical cancer. The number of active agents used in the treatment of metastatic disease is limited.
- D. Treatment is based upon stage and individual patient characteristics.
  - 1. CIN-III (Carcinoma in situ; high-grade dysplasia) (Stage 0)
    - a. Patients with persistent high-grade intra-epithelial neoplasia (Stage 0) are at higher risk of developing invasive cervical cancer. Persistent CIN-III can be treated with either excision or ablation procedures.
    - b. Excision procedures include a CKC (cold knife cone) or LEEP (loop electrosurgical excision procedure) to negative margins or a total hysterectomy.
    - c. Ablative procedures include cryotherapy or laser ablation.
    - d. Excessive use of ablative cervical procedures is associated with a higher risk of miscarriage.
  - 2. Early stage disease (Stage I – IIA)
    - a. See table below (Summary of primary treatment for cervical cancer by stage).
    - b. Fertility preservation may be considered for subset of patients, including stage IA1, IA2, IB1, and IB2.
  - 3. Advanced Stage Disease (Bulky Stage IIB, III and IVA)
    - a. Surgery no longer plays a primary role in the treatment of advanced stage disease. The primary treatment is focused on radiation.
      - 1) Pelvic or extended-field EBRT plus concurrent platinum containing chemosensitization and brachytherapy are NCCN Guidelines® category 1 recommendations for the management of advanced stage cervical cancer.<sup>168</sup>
  - 2. Local/Regional recurrence after prior RT or stage IVB metastatic disease not amenable to local treatment
    - a. Systemic therapy or best supportive care
  - 4. Chemosensitization<sup>168, 188-191</sup>
    - a. Use of platinum-containing chemotherapy concurrent with radiation improves response rates and survival.
      - 1) Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent or carboplatin if patient is cisplatin intolerant.
    - b. Five large, randomized trials accruing patients in the 1980s and 1990s compared radiation to radiation plus concurrent cisplatin-based chemotherapy.
    - c. Although old, these seminal trials demonstrated that the risk of death from cervical cancer is decreased by 30-50% with the addition of concurrent cisplatin to pelvic radiation.<sup>189, 192-197</sup>
      - 2) The control arms contained radiation therapy compared with various experimental arms consisting of cisplatin-containing regimens dosed at 40-50 mg/m<sup>2</sup> IV weekly or 70-75 mg/m<sup>2</sup> every 3 weeks with or without 5-fluorouracil 1 gram/m<sup>2</sup>/day x 4 days.



- d. These five trials were not uniform in their study inclusion criteria, or in the control groups. Due to this, some have questioned the magnitude of benefit previously reported.
- 1) To address these concerns, a meta-analysis of 18 randomized trials using concurrent chemotherapy and radiation (chemoradiation) was conducted using trials with clean control groups. The original five trials were not included in this analysis.
  - 2) Results of this analysis endorse chemoradiation as the standard of care, but with less magnitude than originally suggested in the NIH consensus paper (6% improvement in five-year overall survival for concurrent chemoradiation; HR 0.81;  $p < 0.001$ ).
  - 3) In addition, a benefit was noted for non-cisplatin-containing chemotherapy.
  - 4) The paper concludes that cisplatin is still the standard, but that other agents may be considered in patients unable to tolerate this agent.
  - 5) Alternative agents to cisplatin include carboplatin or hydroxyurea; however, these are not frequently used in clinical practice.

**Patient Case #1 - Answer:**

**Correct answer is C.** Given the locally metastatic disease, the therapy of choice would be primary chemoradiation. Therefore, the treatment will include external beam whole pelvic radiation therapy plus chemosensitization with weekly cisplatin 40 mg/m<sup>2</sup> IV followed by high-dose rate brachytherapy.

Answer A is not the most appropriate treatment option as DD has stage IVA disease and therefore is not a surgical candidate.

Answers B and D are incorrect as single modality therapy would not be the most appropriate treatment options. Multiple trials have demonstrated the risk of death from cervical cancer is decreased by 30% to 50% by the addition of concurrent cisplatin to pelvic radiation.

- e. Clinical issues related to radiation plus chemosensitization
- 1) Survival is related to the dose intensity of radiation. Radiation oncologists prefer to complete the entire treatment within eight weeks. There is some evidence that patients who receive less than five doses of cisplatin have inferior outcomes. Therefore, the goal is to administer at least five, and preferably six weekly cisplatin doses. It is common to initiate chemotherapy within 24-48 hours of starting radiation.
  - 2) Cisplatin 40 mg/m<sup>2</sup> weekly for 5-6 weeks is considered the standard. Many institutions empirically cap the **dose at 70 mg** based on data supported in Gynecologic Oncology Group (GOG) and Radiation Therapy Oncology Group (RTOG) trials.<sup>198</sup>
  - 3) Pain assessment: if patients present with pain due to a large tumor burden (common in stage IIIB patients), pain scores may transiently increase during first 1-2 weeks of radiation due to an inflammatory response. Pain usually improves dramatically once tumor shrinkage occurs.

- 4) Weight loss may occur while receiving pelvic radiation due to low-grade nausea, vomiting, and diarrhea.

**Summary of primary treatment for cervical cancer by stage<sup>168</sup>**

Stage	Treatment
IA1	<p><b>Fertility Sparing</b>  <u>No LVSI</u>: Cone biopsy with negative margins  <u>LVSI</u>: Radical trachelectomy + pelvic lymphadenectomy (consider SLN mapping) <u>OR</u> cone biopsy with negative margins + pelvic lymphadenectomy (consider SLN mapping)</p> <p><b>Non-fertility Sparing</b>  <u>No LVSI</u>: Extrafascial (simple) or modified radical hysterectomy (if inoperable, may observe) + pelvic lymphadenectomy if positive margins (consider SLN mapping)  <u>LVSI</u>: Modified radical hysterectomy + pelvic lymphadenectomy (consider SLN mapping) <u>OR</u> pelvic EBRT + brachytherapy</p>
IA2	<p><b>Fertility Sparing</b>  Radical trachelectomy + pelvic lymphadenectomy (consider SLN mapping) <u>OR</u> cone biopsy with negative margins + pelvic lymphadenectomy (consider SLN mapping)</p> <p><b>Non-fertility Sparing</b>  Modified radical hysterectomy + pelvic lymphadenectomy (consider SLN mapping) <u>OR</u> pelvic EBRT + brachytherapy</p>
IB1, IB2, IIA1	<p><b>Fertility Sparing (IB1 and IB2 only)</b>  Radical trachelectomy + pelvic lymphadenectomy +/- PALN sampling (consider SLN mapping)</p> <p><b>Non-fertility Sparing</b>  Radical hysterectomy + pelvic lymphadenectomy [NCCN Guidelines<sup>®</sup> category 1] ± para-aortic lymphadenectomy (category 2B) (consider SLN mapping)  <u>OR</u>  Pelvic EBRT + brachytherapy +/- platinum-containing chemotherapy</p>
IB3, IIA2	<p>Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy (NCCN Guidelines<sup>®</sup> category 1)  <u>OR</u>  Radical hysterectomy + pelvic lymphadenectomy <u>OR</u>  Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy + selective complete hysterectomy (category 3)</p>
IIB, III, and IVA	<p><b>Without nodal disease or disease limited to pelvis</b>  Pelvic EBRT + brachytherapy + platinum-containing chemotherapy (NCCN Guidelines<sup>®</sup> category 1)</p> <p><b>Positive pelvic lymph nodes but negative para-aortic lymph nodes by surgical staging</b>  Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy (NCCN Guidelines<sup>®</sup> category 1)</p> <p><b>Positive para-aortic lymph nodes by surgical staging</b>  <u>Negative for distant metastasis</u>: Extended-field EBRT + concurrent platinum-containing chemotherapy + brachytherapy  <u>Positive for distant metastasis</u>: Biopsy suspicious areas, if negative then extended-field EBRT + concurrent platinum-containing chemotherapy + brachytherapy; if positive then systemic therapy +/- individualized radiation therapy</p>
IVB	<p><b>Amenable to local treatment</b>  Resection +/- individualized EBRT <u>OR</u> local ablative therapies +/- individualized EBRT <u>OR</u> individualized EBRT +/- systemic therapy  Consider adjuvant systemic therapy</p> <p><b>Not amenable to local treatment</b>  Systemic therapy <u>OR</u> best supportive care</p>

PALN: para-aortic lymph node; SLN: *sentinel lymph node*

**Patient Case #1, continued:**

DD completed successful chemoradiation and has been under active surveillance. DD presents to her 2-year follow-up feeling great and her only complaint is a new onset of a persistent dry cough. A CT of her chest is notable for diffuse pulmonary nodules, consistent with metastatic cervical cancer. PD-L1 testing was attempted on a prior tissue sample but failed. **Which of the following every 3 week treatment options would be most appropriate for DD according to the NCCN Guidelines®?**

- A. Cisplatin 50 mg/m<sup>2</sup> + paclitaxel 175 mg/m<sup>2</sup> + bevacizumab 15 mg/kg
- B. Cisplatin 50 mg/m<sup>2</sup>
- C. Topotecan 1.5 mg/m<sup>2</sup> days 1-5
- D. Pembrolizumab 200 mg

**V. Treatment of Relapsed Disease<sup>168</sup>**

- A. Defined as appearance of a new lesion after achieving a complete response to primary therapy
- B. Locoregional therapy: retreatment for localized recurrence
  - 1. Radiation therapy and/or chemotherapy
  - 2. Surgery
- C. Locoregional recurrence without prior radiation therapy or relapse outside previous radiation field
  - 1. Tumor directed EBRT with or without chemotherapy and/or brachytherapy; surgical resection can be considered
  - 2. Consider alternative non-cisplatin containing chemotherapy for patients who relapse soon after completing initial chemoradiation.
- D. Central pelvic recurrence after prior radiation therapy
  - 1. Pelvic exenteration may be performed in highly selected patients with persistent or recurrent cervical cancer confined to the central pelvis following radiation therapy. This offers the potential for long-term cure, although few patients qualify based on pattern of recurrence.
  - 2. Radical hysterectomy or brachytherapy may be an option in patients with small lesions (<2 cm)
- E. Noncentral recurrent disease
  - 1. EBRT with or without chemotherapy, resection, chemotherapy, best supportive care, or clinical trial

**VI. Primary Treatment of Stage IVB Disease<sup>168</sup>**

- A. The most common distant metastatic sites are the lungs, mediastinal and supraclavicular lymph nodes, bones, and liver.
- B. Curative therapy is unlikely. Treatment should be focused on palliation of symptoms and pain management. Disease that recurs within a previously radiated field responds poorly to chemotherapy.
- C. Survival has been reported in patients with isolated distant metastases amenable to local treatment with surgical resection with or without EBRT, local ablative therapies with or without EBRT, or EBRT with or without chemotherapy.

- D. If the lesion occurs outside a previously radiated field, tumor-directed radiation plus platinum-based chemotherapy may be used.
- E. Palliative chemotherapy for patients who are not candidates for either radiation or surgery. <sup>199-205</sup>
- F. All patients should be considered for enrollment in clinical trials.
- G. Platinum-containing doublets (combination chemotherapy) are considered the standard for first recurrence if the patient already received cisplatin as a radiation sensitizer.
  - 1. Combination chemotherapy incorporates the most active agents (platinum) with newer agents to enhance response rates; combination therapy is thought to be better than single agent therapy if the patient has already received concurrent chemoradiation with a platinum.
  - 2. Combination chemotherapy increases response rates, although only one phase III trial demonstrated a survival benefit compared to single agent therapy.
  - 3. GOG-204 was a phase III trial in patients (n=513) with advanced metastatic or recurrent cervical cancer; patients were randomized to one of four arms comparing cisplatin plus paclitaxel to cisplatin plus either vinorelbine, gemcitabine or topotecan.
    - a. No difference in overall survival was seen between any of these regimens when compared to paclitaxel plus cisplatin (see table below comparing regimens); however, the trends for response rate, progression-free survival and overall survival in favor of cisplatin-paclitaxel compared to the other regimens should be noted.
    - b. Leukopenia, neutropenia, anemia, and infection with fever were significantly lower in patients treated with gemcitabine plus cisplatin. Cisplatin-paclitaxel combination had less thrombocytopenia and anemia compared to the other regimens; however, it led to increased nausea, vomiting, and infections as well as a statistically significant increase in grade 2 alopecia.
- H. Carboplatin-based doublets are a category 1 recommendation from the NCCN Guidelines® in patients who have received prior cisplatin therapy and a category 2A recommendation for patients who have not received prior platinum-based therapy.
  - 1. JCOG0505, a phase III trial in patients with metastatic or recurrent cervical cancer (n=253) randomized patients to cisplatin plus paclitaxel (TP) vs carboplatin plus paclitaxel (TC).
    - a. No difference in overall survival was seen between the two arms; however, subgroup analysis did show that of those patients who had not previously received cisplatin-based chemotherapy, the median OS was shorter with TC (13 months) compared to TP (23.3 months) (HR 1.571; 95% CI, 1.062-2.324).
    - b. Incidence of grade 4 neutropenia (42.5% vs 75%; p=0.001) and grade 3/4 febrile neutropenia (7.1% vs 16%; p=0.031) were significantly lower in patients treated with TC compared to TP. Additionally, the incidence of nausea/vomiting (3.2% vs 6.4%; p=0.254) and elevated creatinine (0% vs 2.4%; p=0.122) were lower with TC compared to TP.
- I. The addition of bevacizumab to platinum-based doublet chemotherapy has been shown to improve overall survival in primary advanced or recurrent cervical cancer.
  - 1. GOG-240 was a four-arm randomized trial comparing cisplatin plus paclitaxel with or without bevacizumab to a non-platinum doublet (paclitaxel plus topotecan) with or without bevacizumab.

- a. The non-platinum doublet (paclitaxel + topotecan) was not superior to paclitaxel plus cisplatin and may be considered an alternative in patients who are not a candidate for platinum-based therapy.
  - b. When the chemotherapy only arms were compared to the chemotherapy plus bevacizumab regimens, overall survival was statistically significantly longer in the patients treated with bevacizumab (16.8 vs 13.3 months; HR 0.77, 95% CI 0.62-0.95; p=0.007).<sup>204,206</sup>
  - c. Based on these results, paclitaxel + cisplatin + bevacizumab and topotecan + paclitaxel + bevacizumab are NCCN Guideline® category 1 recommendations for persistent, recurrent, or metastatic cervical cancer.<sup>168</sup>
  - d. Patients treated with bevacizumab experienced more side effects than patients treated with chemotherapy alone; however, this did not diminish their quality of life.
  - e. Based on the results from both GOG-240 and JGOG0505, the NCCN Guidelines® include carboplatin/paclitaxel/bevacizumab as an additional treatment option for recurrent or metastatic cervical cancer.
2. An FDA-approved biosimilar may be substituted for bevacizumab.
- J. The addition of pembrolizumab to a platinum-based (cisplatin or carboplatin) regimen in combination with paclitaxel ± bevacizumab demonstrated improved progression free survival and overall survival in PD-L1 positive tumors.
1. KEYNOTE-826 was a double-blind, phase 3 trial which patients were assigned to platinum-based chemotherapy (carboplatin or cisplatin) plus paclitaxel plus or minus bevacizumab at physicians discretion either with pembrolizumab or placebo.
    - a. For patients with a PD-L1 combine positive score (CPS) of 1 or more the median progression free survival was 10.4 months in the pembrolizumab arm compared to 8.2 months in the placebo arm.
    - b. Overall survival at 24 months in the pembrolizumab arm was 53.0% compared to 41.7% in the placebo arm.
    - c. The pembrolizumab arm experienced immune-mediated adverse events in 33.9% compared to 15.2% in the placebo arm. Grade 3 to 5 immune-mediated adverse events occurred in 11.4% in the pembrolizumab arm and 2.3% in the placebo arm.<sup>207</sup>
    - d. Based on these results, for PD-L1 positive tumors (PD-L1 CPS ≥ 1) pembrolizumab + cisplatin + paclitaxel ± bevacizumab, pembrolizumab + carboplatin + paclitaxel ± bevacizumab are now NCCN Guideline® Category 1, preferred recommendations for persistent, recurrent, or metastatic cervical cancer.<sup>168</sup>

**Phase III trials evaluating combination chemotherapy for advanced stage or recurrent cervical cancer\***

Protocol	ORR	% Patients with Prior Cisplatin	Survival (months)	Statistics
<b>GOG-169<sup>208</sup></b>				
Cisplatin 50 mg/m <sup>2</sup>	19%	30	8.8	ORR (p=0.002) Survival (no diff)
Cisplatin 50 mg/m <sup>2</sup> + Paclitaxel 135 mg/m <sup>2</sup> /24 hours	36%	24	9.7	
<b>GOG-179<sup>199</sup></b>				
Cisplatin 50 mg/m <sup>2</sup>	13%	56	6.5	p=0.017
Cisplatin 50 mg/m <sup>2</sup> + Topotecan 0.75 mg/m <sup>2</sup> (Day 1-3)	27%	58	9.4	
<b>GOG-204<sup>200</sup></b>				
Cisplatin 50 mg/m <sup>2</sup> + Paclitaxel 135 mg/m <sup>2</sup>	29%	70	12.9	No difference
Cisplatin 50 mg/m <sup>2</sup> + Vinorelbine 30 mg/m <sup>2</sup> (Day 1, 8)	26%	79	10	
Cisplatin 50 mg/m <sup>2</sup> + Gemcitabine 1000 mg/m <sup>2</sup> (Day 1, 8)	22%	72	10	
Cisplatin 50 mg/m <sup>2</sup> + Topotecan 0.75 mg/m <sup>2</sup> (Day 1-3)	23%	81	10	
<b>GOG-240<sup>204</sup></b>				
<i>Chemotherapy arms</i> Paclitaxel 135-175 mg/m <sup>2</sup> + Cisplatin 50 mg/m <sup>2</sup> OR Topotecan 0.75 mg/m <sup>2</sup> Day 1-3	36%	>70%	13.3	HR 0.71 for addition of bevacizumab (0.54-0.95; p=0.004)
<i>Bevacizumab 15 mg/kg +</i> Paclitaxel 135-175 mg/m <sup>2</sup> + Cisplatin 50 mg/m <sup>2</sup> OR Topotecan 0.75 mg/m <sup>2</sup> Day 1-3	48%	>70%	17	
<b>JCOG0505<sup>209</sup></b>				
Paclitaxel 135 mg/m <sup>2</sup> /24 hours day 1 + Cisplatin 50 mg/m <sup>2</sup> on day 2	58.8%	43%	18.3	HR 0.994 (0.79-1.25; p=0.032)
Paclitaxel 175 mg/m <sup>2</sup> /3 hours + Carboplatin AUC 5 on day 1	62.6%	48%	17.5	

\*All regimens repeat every 21 days to progression or toxicity

2. Non-taxane combination chemotherapy is a reasonable alternative for patients who are not candidates for taxane-based treatment.
3. Single agent chemotherapy
  - 1) Sequential, salvage single agent chemotherapy is reasonable for patients who progress following combination chemotherapy or are unable to tolerate combination chemotherapy.

- 2) Cisplatin, paclitaxel, and carboplatin have the most activity as single agents in recurrent disease.
  - 3) Response rates for single agent therapy range from 10-20% and median survival is approximately one year.
  - 4) Patients whose disease recurs within a radiation field respond poorly to chemotherapy (<10%). Conversely, patients who recur outside the radiated field are more likely to respond.
- a. Patients with recurrent cervical cancer who have received prior cisplatin-based chemoradiation are at risk of developing hypersensitivity reactions to platinum when cisplatin or carboplatin is reinitiated.
  - b. For all patients with recurrent disease, treatment is continued for as long as the patient responds. Therapy is stopped or changed due to progression or toxicity.
  - c. For recurrent/metastatic cervical cancer, single-agent pembrolizumab may be considered especially for patients that have not already received pembrolizumab in combination with platinum and taxane.
- 1) Pembrolizumab was FDA approved June 12, 2018 for recurrent or metastatic cervical cancer in patients whose tumors express PD-L1 with a CPS  $\geq 1$  and with disease progression on or after chemotherapy.
    - a) The KEYNOTE-158 study was a phase II basket study which investigated pembrolizumab 200 mg every 3 weeks (cervical cancer n=98) in patients having progressed on  $\geq 1$  prior line of therapy for metastatic disease.<sup>210</sup>
    - b) 84% of patients had PD-L1 positive tumors, defined as a Combined Positive Score (CPS) of  $\geq 1$
    - c) ORR was 12.2% (95% CI, 6.5-20.4); 9 patients with PR and 3 patients with CR.
    - d) All responding patients had PD-L1 positive tumors. Median duration of response has not yet been reached (range 3.7-18.6 months)
  - 2) Tumor agnostic approvals of pembrolizumab for MSI-H (microsatellite instability-high) and TMB-H (tumor mutational burden-high;  $\geq 10$  mutations/megabase) solid tumors. Both indications reserved for patients with no satisfactory treatment alternatives.
  - 3) Tisotumab-vedotin-tfty
    - a) Tissue factor (TF)-directed antibody drug conjugate (ADC). The small molecule, MMAE, is a microtubule-disrupting agent. The anticancer activity of tisotumab vedotin is due to the binding of the ADC to TF expressing cells followed by internalization of the ADC-TF complex, and release of MMAE. MMAE then disrupts the microtubule network leading to cell cycle arrest.
  - 4) Indications & Dose:
    - a) Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.
    - b) 2 mg/kg (maximum 200 mg) IV every 3 weeks

- 5) Toxicities: ocular toxicity, peripheral neuropathy, fatigue, nausea, epistaxis, alopecia, hemorrhage
- 6) Drug-drug interactions: strong CYP3A4 inhibitors
- 7) Granted accelerated approval
  - a) Single-arm, phase 2 study in recurrent or metastatic cervical cancer with disease progression on or after doublet chemotherapy with bevacizumab. The confirmed objective response rate was 24% with 7% complete response.<sup>211</sup>



# Chemotherapy for advanced or recurrent cervical cancer <sup>168</sup>

Regimen	Comments
<b>First Line</b>	
Cisplatin 50 mg/m <sup>2</sup> + paclitaxel 175 mg/m <sup>2</sup> + bevacizumab <sup>^</sup> 15 mg/kg <sup>204</sup>	Preferred regimen. <b>NCCN® category 1 recommendation</b> based on phase III data demonstrating improved survival for patients treated with bevacizumab.
Carboplatin (AUC 5) + paclitaxel 175 mg/m <sup>2</sup> + bevacizumab <sup>^</sup> 15 mg/kg	Preferred regimen. NCCN® category 2A recommendation based on data from GOG-240 and JCOG0505.
Pembrolizumab 200 mg + Cisplatin 50 mg/m <sup>2</sup> + paclitaxel 175 mg/m <sup>2</sup> ± bevacizumab <sup>^</sup> 15 mg/kg <sup>207</sup>	Preferred regimen for PD-L1 positive tumors. <b>NCCN® category 1 recommendation</b> based on phase III data demonstrating improved survival for patient's receiving pembrolizumab
Pembrolizumab 200 mg + Carboplatin AUC 5 + paclitaxel 175 mg/m <sup>2</sup> ± bevacizumab <sup>^</sup> 15 mg/kg <sup>207</sup>	Preferred regimen for PD-L1 positive tumors. <b>NCCN® category 1 recommendation</b> based on phase III data demonstrating improved survival for patient's receiving pembrolizumab
Topotecan 0.75 mg/m <sup>2</sup> (Day 1-3) + paclitaxel 175 mg/m <sup>2</sup> + bevacizumab <sup>^</sup> 15 mg/kg <sup>204</sup>	<b>NCCN® category 1 recommendation</b> based on phase III data demonstrating improved survival for patients treated with bevacizumab.
Cisplatin 50 mg/m <sup>2</sup> + paclitaxel 135-175 mg/m <sup>2</sup> <sup>200, 208</sup>	<b>NCCN® category 1 recommendation.</b>
Cisplatin 50 mg/m <sup>2</sup> + Topotecan 0.75 mg/m <sup>2</sup> (Day 1-3) <sup>199</sup>	NCCN® category 2A recommendation. Recommended for patients who cannot tolerate taxanes.
Topotecan 0.75 mg/m <sup>2</sup> (Day 1-3) + paclitaxel 175 mg/m <sup>2</sup> <sup>204</sup>	NCCN® category 2A recommendation for patients who are not candidates for cisplatin.
Carboplatin (AUC 5) + paclitaxel 175 mg/m <sup>2</sup> <sup>203, 209</sup>	<b>NCCN® category 1 recommendation</b> for patients who have received prior cisplatin therapy and 2A for those who have not.
Cisplatin 50 mg/m <sup>2</sup> single agent <sup>199</sup>	Preferred first line agent if single agent to be used (in patients deemed unable to tolerate combination therapy). NCCN® category 2A recommendation.
Paclitaxel 135-175 mg/m <sup>2</sup> <sup>212</sup>	Acceptable alternative first line treatment in patients unable to tolerate combination chemotherapy or cisplatin. NCCN® category 2A recommendation.
Carboplatin (AUC 5-7.5) <sup>213</sup>	Acceptable alternative first line treatment in patients unable to tolerate combination chemotherapy or cisplatin. NCCN® category 2A recommendation.
<b>Second Line or later</b>	
Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks <sup>210, 214</sup>	NCCN® category 2A preferred recommendation for ≥ second line recurrent/metastatic cervical cancer; PD-L1 positive (CPS ≥ 1), or MSI-H/dMMR tumors. NCCN® category 2A recommendation for TMB-H tumors.
Nivolumab 240 mg IV every 2 weeks or 480 mg every 4 weeks <sup>215</sup>	NCCN® category 2A preferred regimen for ≥ second line recurrent/metastatic cervical cancer; PD-L1 positive tumors
<sup>215</sup> Tisotumab vedotin-tftv 2 mg/kg IV every 3 weeks <sup>211</sup>	NCCN® category 2A

\* All regimens repeat until progression or toxicity unless otherwise noted.

Note: These agents can be used for second-line therapy if not previously used

<sup>^</sup> = FDA-approved biosimilar may be substituted for bevacizumab.

**Patient Case #1 - Answer:**

**Correct answer is A.** The most appropriate treatment for DD is combination chemotherapy with cisplatin, paclitaxel and bevacizumab as GOG-240 showed an improved overall survival with the addition of bevacizumab to combination chemotherapy.

Answers B and C are not the most appropriate treatment options as multiple trials have demonstrated patients receiving 2-drug combinations for relapsed metastatic cervical cancer had higher response rates and improved progression-free survival compared to single agent therapy.

Answer D is not the most appropriate treatment option as we do not know if DD's malignancy expresses PD-L1 or is MSI-H/dMMR.

**VII. Monitoring and Follow-up<sup>68</sup>**

- A. Recommendations for surveillance of recurrent disease in women treated for cervical cancer is evolving.
- B. The Society of Gynecologic Oncology (SGO) has reviewed data supporting various methods used to detect early recurrence. Based on this review, the guidelines have changed, and the frequency and type of tests used for surveillance have changed.
  - 1. Patient education regarding signs or symptoms of recurrence is the most important recommendation as most recurrences present with symptoms.
    - a. Clear or bloody vaginal discharge
    - b. Post-coital bleeding
    - c. Pelvic pain
    - d. Unexplained weight loss
    - e. Cough
  - 2. Follow-up physical examination with complete review of systems every 6 months for the first two years for low-risk patients (early stage disease, surgery alone, no adjuvant therapy); followed by annually thereafter. For higher risk patients, follow-up and examination every 3 months for two years, then every 6 months from 2-5 years, then yearly after five years.<sup>216</sup>
  - 3. PAP test (cytologic examination) of the cervix or vagina to identify vaginal dysplasia yearly (optional). There is limited evidence that many recurrences are detected with this method.
  - 4. Routine imaging or laboratory assessment is not recommended for surveillance. There is insufficient evidence to warrant routine use. Imaging should be done at time of detection of recurrence by physical exam or patient symptoms.
  - 5. Patient education regarding sexual health, vaginal dilator use, and vaginal lubricants/moisturizers.
- C. Patients who do not achieve a complete remission should be followed per physician preference based on current therapy and extent of disease.

**VIII. Prognosis (with treatment)<sup>168, 170</sup>**

- A. Factors associated with a poor prognosis
  - 1. Large primary tumor
  - 2. Positive lymph nodes

3. Adenocarcinoma or adenosquamous carcinoma
  4. Lymphovascular space invasion
- B. The five-year survival by extent of disease is listed below.<sup>217</sup>

Extent of Disease	5-year Survival
Localized	91.4%
Regional	57.6%
Distant	16.9%
Unstaged	55.6%

#### IX. Toxicity and Survivorship Issues<sup>168</sup>

- A. Treatment with surgery, radiation, and chemotherapy is associated with both acute and chronic toxicities. In general, surgery for early stage disease is associated with less long-term toxicity than pelvic radiation.
- B. Treatment with pelvic radiation with or without chemosensitization is associated with both acute and chronic toxicities:
  1. Acute toxicities include low-grade nausea, vomiting, fatigue, anemia, mild bone marrow suppression and diarrhea. These side effects can be caused by pelvic radiation alone and are generally made worse by the concurrent use of chemotherapy. Anemia has been identified as a predictor of poor local control and reduced overall survival in patients with radiation or concurrent chemoradiation.<sup>218, 219</sup>
  2. Vaginal stenosis and dryness are the most common long-term effects following completion of pelvic radiation. Patients should be counseled on the use of vaginal dilators and vaginal moisturizers/lubricants, which can be used beginning 2 to 4 weeks following radiation and can be performed indefinitely. Other late effects include secondary cancers in the bowel or bladder.
  3. Future fertility is a concern for many young women facing cervical cancer. If fertility sparing surgery is used, future pregnancies will require some form of reproductive assistance such as embryo transplantation. If radiation is used for treatment, moving the ovaries out of the radiation field (known as ovarian transposition) can be used to prevent premature menopause.
  4. Premature menopause is a potential complication of therapy. If a woman is undergoing a radical hysterectomy, the ovaries can be transposed and retained to avoid abrupt surgical menopause. Pelvic radiation usually results in premature menopause. Patients should receive post-treatment hormone replacement therapy (with estrogen alone if the uterus has been removed surgically) and have careful follow-up regarding bone health.
  5. Radiation damage to surrounding pelvic tissue and/or fibrosis can result in bowel obstructions, rectal or vaginal fistula formation, or secondary cancers. Patients need to be screened accordingly.
  6. Bladder dysfunction is a common long-term complication especially in patients treated with chemoradiation compared to surgical intervention.

7. Mood disorders, specifically anxiety, confusion, dysphoria, and anger have been reported compared to healthy controls.<sup>220</sup>
8. Body image issues such as lower self-esteem and poor body image can be particularly challenging for women who were of reproductive age at the time of diagnosis.<sup>221</sup>
9. Sexuality is an issue for women with cervical cancer irrespective of treatment modality.

## ENDOMETRIAL CANCER

*Note: This section does not cover the diagnosis or treatment of uterine sarcomas.*

### I. Pathogenesis<sup>222-224</sup>

- A. The primary etiology for the development of endometrial cancer is excess exposure to estrogen stimulation on the uterine lining. However, two primary mechanisms of carcinogenesis have been proposed:
  - 1. Type I or classic pathway
    - a. Proposes that endometrial cancer arises from a precursor lesion (atypical endometrial hyperplasia with atypia) in an estrogen-rich environment.
    - b. Body weight and high-estrogen risk factors contribute to pathogenesis.
    - c. Often well differentiated, associated with endometrioid histology and lower nuclear grade.
    - d. The estrogen-dependent pathway is the most common pathway and is thought to be responsible for about 80% of all endometrial cancers.
  - 2. Type II or alternative pathway
    - a. Not dependent on estrogen and is not linked to body weight or fat intake.
    - b. Generally, poorly differentiated, associated with serous and clear cell histology, and high nuclear grade.
    - c. This pathway is thought to account for about 20% of all endometrial cancers, although this incidence may be on the rise (for unknown reasons).
- B. Genetic mutations
  - 1. Approximately 5% of endometrial cancers are caused by inherited genetic susceptibility.
    - a. Defective DNA mismatch repair (e.g., MSH2, MLH1, MSH6, PMS2) is associated with Lynch Syndrome. Women that carry this mutation have a 40-60% lifetime risk of developing endometrial cancer.
    - b. Universal testing for mismatch repair (MMR) gene abnormalities is recommended in endometrial carcinomas on final hysterectomy specimen using immunohistochemistry and/or genetic testing for microsatellite instability (MSI).
    - c. Genetic counseling and testing are recommended for patients with MMR abnormalities and for women without MMR abnormalities but who have a significant family history of endometrial and/or colorectal cancer.
- C. Tamoxifen
  - 1. The effects of tamoxifen on the uterus are complex. Its effects can range from benign endometrial proliferation to the development of invasive endometrial adenocarcinoma or sarcoma.
  - 2. The risk of endometrial cancer in pre-menopausal women has not been well established; in premenopausal women tamoxifen has an antiestrogenic effect however in postmenopausal women it has a weak estrogenic effect due to the upregulation of estrogen receptors.

3. Phase III data from the long-term follow-up of the NSABP- P-1 study demonstrate that the risk of developing endometrial cancer was 29% higher in patients treated with tamoxifen for 5 years or more compared to placebo treated post-menopausal patients. However, this was not statistically significant.<sup>225</sup>
4. In addition, a meta-analysis of 32 trials using tamoxifen therapy demonstrated that use of tamoxifen was significantly associated with the development of endometrial cancer (RR=2.7; 95% CI, 1.94 to 3.75).<sup>226</sup>
5. The ATLAS trial in breast cancer evaluated 10 years vs 5 years of tamoxifen and found the cumulative risk of endometrial cancer during years 5-14 was 3.1% (mortality 0.4%) for women randomized to 10 years vs 1.6% (mortality 0.2%) for controls. Despite the increased risk of endometrial cancer, the reduction of breast cancer recurrence and mortality outweighed this risk.<sup>227</sup>
6. When this data is analyzed for menopausal status, however, the effects of tamoxifen vary. Premenopausal women taking tamoxifen are not at risk for the development of invasive cancer while post-menopausal women are. Because this issue is complex, and the information is changing, the reader is referred elsewhere for a more comprehensive review of this topic.

## **II. Histology<sup>223, 228</sup>**

- A. There are several subtypes of endometrial cancer.
- B. The majority are epithelial adenocarcinomas, which account for 75-80% of all endometrial cancers. Examples of adenocarcinomas include endometrioid, serous, clear cell, mucinous and carcinosarcoma (also known as malignant mixed mullerian tumor or MMMT). Other histologies (rare and not covered in this text) include stromal/mesenchymal tumors (low-grade endometrial stromal sarcomas), high-grade undifferentiated sarcoma and leiomyosarcomas.
- C. Prognostic and treatment significance
  1. Endometrioid adenocarcinomas are the most common and are often well-differentiated with low-grade.
    - a. These cancers are often cured with surgery and tumor-directed therapy if detected early.
    - b. This histology is often associated with hormone-receptor positive disease and responds well to hormonal therapy.
  2. Clear cell and serous adenocarcinomas are often poorly differentiated with high-grade.
    - a. These histologies often spread and behave like ovarian cancer.
    - b. Women with endometrial cancer and one of these histologies are treated very aggressively and often have a poor prognosis.
    - c. Clear cell and serous cancers are most often hormone-receptor negative; thus, hormonal therapy is not indicated in the treatment of serous endometrial carcinomas.

## **III. Screening and Prevention<sup>222, 223, 228-231</sup>**

- A. Screening: currently no effective non-invasive screening test to identify precursor lesions exists.
  1. Healthy women: No screening recommended.
  2. Women on tamoxifen: The American College of Obstetricians and Gynecologists does not recommend routine screening for endometrial carcinoma for women taking tamoxifen.

- a. Premenopausal women: have no known increased risk of endometrial cancer with tamoxifen and do not require additional monitoring beyond routine gynecologic care.
- b. Postmenopausal women: annual pelvic examination and education on monitoring for symptoms. Routine screening endometrial biopsies are not recommended. The American College of Obstetricians and Gynecologists recommends that women on tamoxifen should undergo endometrial sampling only if they become symptomatic (i.e., develop abnormal bleeding).
3. For women with known Lynch syndrome who are asymptomatic, The American College of Obstetricians and Gynecologists recommends endometrial biopsy every one to two years starting at age 30-35. An annual endometrial biopsy, without mention to starting age, followed by hysterectomy and bilateral salpingo-oophorectomy (BSO) immediately after completion of childbearing or sooner, depending on patient's preference is recommended by the NCCN Guidelines®.

#### B. Prevention

1. Hysterectomy in women with complex atypical hyperplasia (CAH).
2. Progesterone challenge in women with CAH.
3. Hysterectomy with BSO in women with Lynch syndrome after childbearing is completed, or sooner based on patient preference.

#### **Patient Case #1:**

SK is a 64-year-old morbidly obese woman who presents to the emergency department complaining of one month of post-menopausal vaginal bleeding. Her last menstrual period was in 2005 and she has a history of estrogen therapy for 6 months in 1990s following heavy menstrual bleeding. She has never had children. The emergency department obtains a pelvic ultrasound which demonstrated endometrial thickening at 4.5 mm. She is referred to OB/GYN who performs a colposcopy with endometrial biopsies at 10 and 2 which reveal FIGO grade 1 endometrioid adenocarcinoma as well as cervical intraepithelial neoplasia grade 1 at 10.

SK undergoes primary surgical management with a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy and biopsies. Her final pathology reveals a grade 1 endometrioid adenocarcinoma of the endometrium with tumor diameter 2.6x2.1x1.1 cm, depth of invasion 1.1 cm, into a 1.7 cm myometrium (> 50% invasion), negative cervix, adnexa, and pelvic washing. There is no lymphovascular space invasion and negative lymph nodes.

**What further therapy, if any, should SK receive?**

- a. Paclitaxel 175 mg/m<sup>2</sup> + carboplatin (AUC 6) every 21 days for 6-8 cycles
- b. Observation or vaginal brachytherapy
- c. Doxorubicin 45 mg/m<sup>2</sup> + cisplatin 50 mg/m<sup>2</sup> every 21 days for 6 cycles
- d. Tamoxifen 20 mg daily

#### **IV. Treatment**<sup>25, 222, 223, 228, 232-247</sup>

##### A. General principles

1. The goal of initial therapy is to cure the patient.
  - a. Cure is a realistic goal for patients with early-stage disease.
  - b. Five-year survival for patients with localized endometrial cancer is approximately 95%.
2. Endometrial cancer is treated with multi-modality therapy which includes surgery, radiation, and chemotherapy.
  - a. In general, surgery alone, or surgery plus adjuvant radiation is used for the management of early stage (I) disease.
  - b. Surgery plus chemotherapy, with or without radiation, is used in the management of advanced stage (II, III, IV) disease.
3. Surgery – general information
  - a. The primary surgical procedure is a total hysterectomy plus bilateral salpingo-oophorectomy (TH/BSO) and pelvic lymph node dissection +/- para-aortic lymph node dissection for select high-risk tumors (deep invasion, high-grade histology, or serous carcinoma, clear cell carcinoma, undifferentiated/dedifferentiated, or carcinosarcomas). Sentinel lymph node mapping may be considered in select patients.
    - 1) The surgery can be performed by an open, laparoscopic or robotic approach with similar outcomes. Laparoscopic and robotic surgery decrease length of stay and other complications.
    - 2) Some patients with advanced bulky disease (stage III and IV) are treated with more radical surgery like ovarian cancer patients and undergo debulking, omentectomy, and intra-abdominal tumor stripping.
4. Radiation – general information
  - a. Radiation is an integral part of the management of endometrial cancer. Historically, whole pelvic radiation therapy was used as a primary treatment or adjuvant to surgery.
  - b. Whole pelvic radiation causes tremendous toxicity to other pelvic organs and significantly reduces quality of life; therefore, is no longer recommended.
  - c. Currently, radiation is delivered as pelvic external beam radiation therapy (EBRT) and/or vaginal brachytherapy.
    - 1) Adjuvant radiation after surgery for patients deemed to be at high risk for recurrence reduces the risk of local pelvic recurrences but does not improve overall survival.
    - 2) More extensive radiation (i.e., to the pelvic lymph nodes and/or para-aortic lymph nodes) can be used in the management of stage III disease although it is no longer standard for all advanced stage patients.
      - a) Para-aortic radiation is difficult for patients to tolerate and can result in significant fatigue, nausea, and vomiting.
      - b) Pelvic radiation can also be used as primary treatment of early stage endometrial cancer in patients who are not suitable for primary surgery.
    - 3) Tumor-directed radiation may be used in the metastatic setting to treat isolated recurrences.



5. Chemotherapy – general information
    - a. Chemotherapy plays a larger role in the management of endometrial cancer than it did in the past.
    - b. Chemotherapy is used for the treatment of stage II and III as well as advanced and recurrent disease.
    - c. Compared to ovarian cancer, there are fewer agents with activity in endometrial cancer.
  6. Hormonal therapy – general information
    - a. Many endometrial cancers express estrogen or progesterone receptors (ER/PR positive).
    - b. Hormonal agents are most useful in well-differentiated adenocarcinomas such as endometrioid tumors. They are not useful in the management of serous or clear cell tumors, which typically do not express ER/PR receptors.
    - c. Hormones make excellent treatments for elderly or debilitated patients who cannot tolerate chemotherapy or surgery.
- B. Early-Stage Disease (Stage I and II)
1. Surgery and radiation:
    - a. Primary therapy usually includes comprehensive surgical staging followed by either observation, vaginal brachytherapy, and/or external beam radiation therapy (EBRT).
    - b. Medically Operable:
      - 1) Non-fertility sparing: TH/BSO with surgical staging and collection of peritoneal cytology. Enlarged or suspicious lymph nodes should be excised and in the absence of lymphadenopathy, retroperitoneal lymph node dissection.
      - 2) Fertility sparing: select patients may forego surgery and consider continuous progestin-based therapy with megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.
        - a) Must have biopsy proven grade 1, endometrioid histology, and disease limited to the endometrium
        - b) Requires close monitoring every 3 to 6 months (endometrial biopsy or dilation and curettage) and TH/BSO with staging is recommended once childbearing complete or progression of disease.
        - c) Patients must be counseled that fertility preservation is not standard of care.
    - c. Not Suitable for primary surgery: EBRT and brachytherapy (preferred) or may consider hormone therapy in select patients who are not candidates for RT or surgery.
    - d. Stage IA (low grade) without LVSI: observation
    - e. Stage IA (high grade) or stage IB (low grade): vaginal brachytherapy preferred
    - f. Stage IB (high grade) or stage II: EBRT and/or vaginal brachytherapy with consideration for systemic therapy
    - g. Stage III, IV: Systemic therapy with consideration for EBRT and/or vaginal brachytherapy

2. A multi-institutional retrospective review evaluated the impact of adjuvant therapy in patients with stage 1A uterine serous carcinoma (vaginal brachytherapy, n=103, pelvic radiation or chemotherapy, n=115). Patients who underwent surgical staging/lymphadenectomy had greater PFS and OS than un-staged patients in both arms. Vaginal brachytherapy reduced vaginal recurrence rates but did not impact PFS or OS. In patients who were not staged, chemotherapy and pelvic radiation were associated with improved PFS and OS; however, this did not translate into survival benefit in patients who were surgically staged. Chemotherapy has no role in early stage disease.<sup>247</sup>

**Patient Case #1, continued - Answer**

**Correct answer is B.** SK has early stage IB, grade 1 endometrial cancer (tumor invades more than one-half the myometrium). Given her low-risk, early-stage disease, and no known adverse risk factors, observation or vaginal brachytherapy is recommended.

Answer A, C and D are inappropriate as the patient has low-risk, early-stage disease and chemotherapy and anti-hormonal therapy would only be appropriate for advanced endometrial cancer.

**C. Management of Advanced Stage/Extra-uterine Disease (Stage III-IVA)**

1. Surgery
  - a. Total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, omentectomy, pelvic washings and peritoneal biopsies.
  - b. The surgical management of these patients is comparable to the management of patients with ovarian cancer.
2. Adjuvant Therapy
  - a. Chemotherapy is the foundation of adjuvant therapy for advanced disease and almost all patients require adjuvant chemotherapy. Adjuvant therapy usually includes EBRT with or without vaginal brachytherapy as well.
  - b. Significant disagreement among experts regarding optimal post-operative adjuvant therapy, and sequencing.
    - 1) There is general agreement that advanced stage, high-grade tumors should include chemotherapy as adjuvant therapy +/- EBRT (+/- vaginal brachytherapy).
    - 2) When both chemotherapy and radiation are used for adjuvant therapy, chemotherapy may be given first, followed by radiation. If the sequence is reversed, there can be greater bone marrow suppression from chemotherapy. An alternative sequencing method called "sandwich" therapy may be administered which consists of adjuvant chemotherapy, followed by radiation, then sequential chemotherapy (for example: carboplatin/paclitaxel x 3 cycles, break for pelvic EBRT +/- vaginal brachytherapy, then finish chemotherapy with 3 more cycles of carboplatin/paclitaxel).
  - c. When chemotherapy is used in the adjuvant setting for stage III or IV disease, combination chemotherapy is preferred. Platinum-based combination chemotherapy with carboplatin and paclitaxel is the standard for adjuvant treatment of advanced stage disease.
    - 1) Although no longer preferred, doxorubicin plus cisplatin (AP) is the historical standard.

- a) GOG-184 compared AP to TAP (paclitaxel plus doxorubicin plus cisplatin); showed no difference in efficacy but more toxicity with TAP when used for the adjuvant treatment of advanced stage disease.<sup>240</sup>
- b) GOG-209, a phase III trial, compared TAP to paclitaxel plus carboplatin in the advanced or recurrent setting. Interim results showed no difference in efficacy and less toxicity in the paclitaxel/carboplatin treatment arm.<sup>244</sup>
  - i. Due to improved tolerability, paclitaxel plus carboplatin is widely considered to be the preferred regimen.
- 2) NCCN® recommends the same systemic therapy for recurrent/metastatic disease, except bevacizumab, which can be considered for use in patients who have progressed on prior cytotoxic chemotherapy. Carboplatin and paclitaxel is the preferred adjuvant therapy for uterine-confined disease.
- 3) When patient has HER2-positive uterine serous carcinoma can consider the addition of trastuzumab to carboplatin and paclitaxel.
  - a) A phase II trial compared carboplatin plus paclitaxel to carboplatin plus paclitaxel plus trastuzumab in uterine serous carcinoma that overexpress HER2/neu.<sup>248</sup>
    - i. Overexpression of HER2/neu is defined as IHC score of 3+ or 2+ with gene amplification confirmed by fluorescence in situ hybridization (FISH).
    - ii. Overall median PFS was 8.0 months in the control group versus 12.6 months in the experimental arm.
    - iii. For those undergoing primary treatment median PFS was 9.3 months in control versus 17.9 months experimental.
    - iv. Toxicity was not different between treatment arms.

**Patient Case #1, continued:**

SK has been appropriately undergoing active surveillance with visits every three to six months for the past 2 years. She is generally feeling well, but she does report intermittent bleeding. Upon further work-up SK is found to have local recurrence confined to the vagina. **Which of the following is the most appropriate treatment for SK at this time?**

- a. Surgical resection and intraoperative radiation therapy
- b. Chemotherapy
- c. Pelvic EBRT and brachytherapy
- d. Hormone therapy

**D. Treatment of Recurrent Disease or Disseminated Metastases**

1. Most recurrences are symptomatic and recur within 3 years of initial diagnosis and treatment. Prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.
2. All patients should be considered for enrollment in clinical trials. If the patient declines, or they are not eligible, then consideration of surgery, radiation, and or chemotherapy.

3. No prior radiation therapy at recurrence site (confined to the vagina or pelvis alone): pelvic EBRT plus brachytherapy or surgery.
  - a. Radiation provides good local control for isolated vaginal recurrences with 5-year survival rates 50-70%
4. Prior radiation therapy at recurrence site (isolated relapse):
  - a. Surgery
5. If surgical exploration, may consider resection followed by EBRT with (or without) brachytherapy and with (or without) chemotherapy.
6. For disseminated metastases, consider endocrine therapy if low-grade, asymptomatic, and/or ER/PR-positive; otherwise systemic chemotherapy +/- palliative EBRT if grade 2/3, large volume, or symptomatic disease.
7. Endocrine based therapy (see table below)
  - a. These agents are for lower grade endometroid histologies only (not useful in the management of women with grade 3 endometrioid, serous carcinoma, clear cell carcinoma, or carcinosarcoma).
  - b. Progestins and tamoxifen act as anti-estrogens.
    - 1) Due to their tolerable side effect profile, these are the agents of choice for treatment of first recurrence in patients with long disease-free intervals, well differentiated, and estrogen and/or progesterone-receptor positive tumors.
      - a) Monitor for thromboembolic events with the combination of tamoxifen and progestational agents.
    - 2) No specific drug, dose, or schedule has been found to be superior.
    - 3) The overall response rates are approximately 10-25%.
    - 4) The median duration of remission is approximately 4 months and overall survival 12 months.
    - 5) Aromatase inhibitors or fulvestrant may be exchanged for tamoxifen or progestational agents.

### Endocrine therapy for endometrial cancer

Agent	Dose	Comments
Medroxyprogesterone acetate <sup>242</sup>	200 mg orally daily; doses may vary	Breast tenderness, irregular bleeding, abnormal glucose control.
Medroxyprogesterone acetate (MPA) alternating with tamoxifen (T)	T 40 mg orally daily + alternating weekly cycles of MPA 200 mg orally daily	See respective agents.
Megestrol acetate alternating with tamoxifen <sup>249</sup>	Megestrol acetate 80 mg PO BID x 3 weeks alternating with tamoxifen 20 mg PO BID x 3 weeks	See respective agents.
Megestrol acetate <sup>223</sup>	160 mg orally daily (in divided doses)	Weight gain, appetite stimulation, nausea, abnormal glucose control, venous thromboembolism.
Everolimus (E) + letrozole (L) <sup>250</sup>	E 10 mg orally daily + L 2.5 mg orally daily	For endometrioid histology only. See respective agents.
Tamoxifen <sup>243, 251</sup>	20 mg BID or 40 mg orally once daily	Hot flashes, nausea, irregular bleeding, weight gain, cataracts.
Anastrozole <sup>252, 253</sup>	1 mg daily	Hot flashes, asthenia, nausea, depression, osteoporosis, peripheral edema, arthralgia.
Letrozole <sup>254</sup>	2.5 mg PO daily	Hot flashes, asthenia, nausea, depression, osteoporosis, peripheral edema, arthralgia.
Exemestane	25 mg PO daily	Hot flashes, asthenia, nausea, depression, osteoporosis, peripheral edema, arthralgia.
Fulvestrant	500 mg IM days 1, 15, 29, followed by 500 mg every 28 days thereafter	Injection-site pain, arthralgia, hot flashes, increased hepatic enzymes.
Levonorgestrel intrauterine device (IUD)	--Kyleena 19.5 mg; Liletta 52 mg; Mirena 52 mg; Skyla 13.5 mg	For select fertility-sparing cases

#### **Patient Case #1, continued - Answer**

**Correct answer is C.** SK has local recurrence confined to the vagina. Since she has not had prior radiation or brachytherapy to the site of recurrence, SK is eligible for pelvic EBRT plus brachytherapy or surgical exploration + resection. Isolated vaginal recurrences treated with radiation therapy alone have good local control with 5-year survival rates of 50 to 70%.

Answer A would not be most appropriate as intraoperative radiation therapy is a NCCN Guidelines® category 3 recommendation.

Answer B and D would not be appropriate as chemotherapy and hormone therapy are considered for patients with local recurrence who have previously undergone previous external beam radiation therapy.

**Patient Case #1, continued:**

SK received EBRT and brachytherapy followed by active surveillance. At her follow-up she reports feeling well other than shortness of breath she contributes to an ongoing cold. Unfortunately, laboratory tests show an elevated CA-125 and prompting imaging which reveals lung, pelvic and para-aortic metastases. **Which of the following is the most appropriate treatment for SK at this time?**

- a. Chemotherapy
- b. Hormone therapy
- c. Surgical resection
- d. Radiation therapy

E. Chemotherapy for metastatic disease (IVB) or recurrent endometrial cancer

1. The main predictors of response in the treatment of metastatic disease are:
  - a. Well-differentiated tumors, expression of ER/PR receptors, long disease-free interval, location and extent of extra pelvic metastases.
2. Combination Chemotherapy
  - a. Combination chemotherapy regimens are preferred if tolerated.
  - b. Platinum-based combination chemotherapy is used in the management of patients with recurrent and advanced endometrial cancer.
    - 1) Doxorubicin plus cisplatin with or without paclitaxel (AP or TAP) are the most widely studied. In a phase III comparison between these two regimens in 273 patients, overall response rate, PFS, and overall survival were all statistically improved in the TAP arm (15 vs 12 months,  $p=0.037$  for survival).<sup>244</sup> However, neurotoxicity was significantly worse in the three-drug combination. In addition, TAP requires the use of hematopoietic growth factors to reduce toxicity.
      - a) Many elderly patients or patients with significant comorbidities are unable to tolerate TAP.
    - 2) A phase III trial comparing paclitaxel plus carboplatin to TAP plus filgrastim has been completed. Paclitaxel plus carboplatin showed similar outcomes but a favorable toxicity profile compared to TAP, although final results of this trial are still pending.<sup>241</sup>
      - a) Due to improved tolerability, paclitaxel plus carboplatin is widely considered to be the preferred regimen.
      - b) For patients in whom paclitaxel is contraindicated, docetaxel may be considered in combination with carboplatin.
  - c. Lenvatinib and pembrolizumab
    - 1) For patients who are not candidates for surgery/radiation and tumor is not MSI-H or dMMR (single agent pembrolizumab may still be used for MSI-H or dMMR solid tumors).
    - 2) For patients whose tumor is microsatellite stable consider the combination Lenvatinib + pembrolizumab.

- a) Phase III, multicenter, randomized controlled trial including 827 patients with advanced endometrial cancer<sup>255</sup>
- Lenvatinib 20 mg by mouth daily plus pembrolizumab 200 mg IV every 21 days
  - Chemotherapy was the treating physician's choice (doxorubicin 60 mg/m<sup>2</sup> IV every 3 weeks or paclitaxel 80 mg/m<sup>2</sup> IV weekly (3 weeks on and 1 week off))
  - Median PFS was 6.6 months in Lenvatinib plus pembrolizumab versus 3.8 months chemotherapy (HR 0.6; 95% CI, 0.5-0.72; p<0.001). Median overall survival 17.4 months Lenvatinib plus pembrolizumab versus 12.0 months chemotherapy (HR 0.68; 95% CI, 0.56-0.84; P <0.001)
  - Adverse events of grade 3 or higher occurred in 88.9% of patients in the Lenvatinib plus pembrolizumab arm compared to 72.7% chemotherapy arm.

#### Combination chemotherapy for endometrial cancer

Regimen	Comments
Paclitaxel 175 mg/m <sup>2</sup> plus carboplatin (AUC 6); repeat every 21 days <sup>241</sup>	<b>Preferred regimen.</b> Commonly used due to reduced toxicity.
<sup>^</sup> Paclitaxel 175 mg/m <sup>2</sup> plus carboplatin (AUC 5) and trastuzumab 8 mg/kg loading dose cycle 1 followed by trastuzumab 6 mg/kg IV every 21 days for future cycles <sup>248</sup>	<b>Preferred regimen.</b> For stage III/IV or recurrent <b>HER2-positive uterine serous carcinoma.</b>
Lenvatinib 20 mg PO daily + pembrolizumab 200 mg IV every 21 days <sup>255</sup>	<b>Preferred regimen (category 1)</b> For advanced or recurrent disease that is <b>not MSI-H or dMMR.</b> Patients who are not candidates for surgery/radiation and have progressed on prior systemic therapy.
Doxorubicin 60 mg/m <sup>2</sup> plus cisplatin 50 mg/m <sup>2</sup> (AP) repeated every 21 days <sup>244</sup>	Reduce doxorubicin to 45 mg/m <sup>2</sup> in patients previously treated with pelvic radiation to reduce hematologic toxicity.
Doxorubicin 45 mg/m <sup>2</sup> (Day 1) plus cisplatin 50 mg/m <sup>2</sup> (Day 1) plus paclitaxel 160 mg/m <sup>2</sup> over 3 hr (Day 2) (TAP); plus G-CSF; repeat every 21 days <sup>240, 244</sup>	Not widely used due to increased toxicity, difficult to tolerate in elderly patients or patients with comorbidities.
Docetaxel 75 mg/m <sup>2</sup> IV + carboplatin (AUC 5) IV every 21 days for 6 cycles <sup>256</sup>	May be considered for patients in whom paclitaxel is contraindicated (e.g., severe neuropathy)
Paclitaxel 135 mg/m <sup>2</sup> /3 hr Day 1 + ifosfamide 1.6 g/m <sup>2</sup> /d (Day 1-3) + mesna + filgrastim (or equivalent) or pegfilgrastim	Used for carcinosarcoma histologies only. Reduce ifosfamide dose 25% for any history of prior pelvic radiation.
Cisplatin 20 mg/m <sup>2</sup> /day days 1-4 + ifosfamide 1500 mg/m <sup>2</sup> /day days 1-4 + mesna <sup>257</sup>	Used for carcinosarcoma histologies only.
<sup>^</sup> Paclitaxel 175 mg/m <sup>2</sup> plus carboplatin (AUC 5) and bevacizumab 15 mg/kg IV; repeat every 21 days <sup>258</sup>	For advanced or recurrent disease only.

<sup>^</sup> = FDA-approved biosimilar may be substituted for trastuzumab or bevacizumab.

#### 3. Single agent chemotherapy (see table below)

- a. Cisplatin, carboplatin, doxorubicin, and paclitaxel are the most active, well-studied chemotherapeutic agents in the treatment of recurrent endometrial cancer.
- b. Single agent therapy is used in the management of women who have failed prior primary treatment, hormonal therapy, and/or who are unable to tolerate combination chemotherapy.
- c. Response rates for single-agent chemotherapy range from 21-36% when used as first line treatment or from 4-27% when used as second-line treatment; paclitaxel is the most used in this setting.
- d. Liposomal doxorubicin may be used due to decreased toxicity; the response rate is 9.5%.
- e. Duration of therapy is until clinical complete remission (rare), development of intolerable side effects, or disease progression.
- f. The median life expectancy for a patient with advanced stage recurrent endometrial cancer is approximately 12 months.
- g. In a phase II study, bevacizumab was shown to have a 13.5% response rate and 10.5 month overall survival rate.
- h. Temsirolimus has been used for recurrent or metastatic endometrial cancer in both first and second-line.
- i. For recurrent endometrial carcinoma, biomarker-directed checkpoint blockade may be considered
  - 1) Pembrolizumab may be considered for MSI-H/dMMR tumors that have progressed on prior chemotherapy.
  - 2) Nivolumab may be considered for dMMR metastatic, recurrent, or high risk disease.
  - 3) Dostarlimab-gxly may be considered for dMMR tumors that have progressed on prior chemotherapy.

#### Single agent therapy for recurrent, metastatic, or high risk endometrial cancer

Agent	Dose	Overall Response	Comments
<sup>259</sup> Bevacizumab	15 mg/kg IV q 21 days	13%	For those that have progressed on prior cytotoxic chemotherapy. ADRs: hypertension, bowel perforation, thrombosis, bleeding, and proteinuria.
<sup>260-262</sup> Cisplatin	50-60 mg/m <sup>2</sup> IV q 21 days	25-40%	Withhold for CrCl < 40-50 mL/min.
<sup>263-265</sup> Carboplatin	360-400 mg/m <sup>2</sup> IV q 21-28 days	25-30%	Doses from historical references; most clinicians use AUC-based dosing of 5-6.
<sup>266</sup> Doxorubicin	45-60 mg/m <sup>2</sup> IV q 21 days	25-35%	Reduce dose in patients who have received whole abdominal radiation.
<sup>267</sup> Paclitaxel	110-200 mg/m <sup>2</sup> IV over 3 hours; q 21 days	25-35%	Higher doses cause more neurotoxicity. No evidence that higher doses improve survival. A dose of 135-175 mg/m <sup>2</sup> is recommended.
<sup>268</sup> Pegylated liposomal doxorubicin	40-50 mg/m <sup>2</sup> IV q 28 days	10%	40 mg/m <sup>2</sup> recommended to reduce toxicity.
<sup>269, 270</sup> Temsirolimus	25 mg IV weekly	4%	Responses were higher in chemotherapy-naïve patients



			compared to chemotherapy-treated patients.
Topotecan <sup>271</sup>	0.5-1.5 mg/m <sup>2</sup> /day (days 1-5) q 21 days	9%	Patients received a median of 4 cycles.
Pembrolizumab <sup>272</sup>	200 mg IV every 21 days or 400 mg IV every 42 days	52%	For MSI-H/dMMR or TMB-H tumors that have progressed following prior cytotoxic chemotherapy only.
Nivolumab	3 mg/kg IV every 2 weeks (28 day cycles). After cycle 4, could switch to 480 mg IV every 4 weeks.	36%	For dMMR metastatic, recurrent, or high-risk disease.
Dostarlimab-gxly	500 mg IV every 3 weeks for 4 doses, then 1,000 mg every 6 weeks thereafter	42%	For dMMR tumors that have progressed following prior cytotoxic chemotherapy only.
Albumin-bound paclitaxel	Dosing not standardized 100 mg/m <sup>2</sup> IV days 1, 8, 15 q 28 days		Suitable for those with a hypersensitivity to paclitaxel and negative skin test to paclitaxel.
Ifosfamide <sup>245</sup>	1.6-2.0 g/m <sup>2</sup> /day x 3 days every 21 days	29%	Carcinosarcoma only.
Cabozantinib <sup>273</sup>	60 mg oral daily	14%	Serous or endometrioid who progressed on chemotherapy
Avelumab <sup>274</sup>	10 mg/kg IV every 2 weeks	26.7%	For dMMR/MSI-H tumors

^ = FDA-approved biosimilar may be substituted for bevacizumab.

#### F. Summary of treatment for recurrent disease

1. Clinical trial should be considered for all patients.
2. For patients who decline and are appropriate candidates (ER+ and/or PR+), first-line treatment with progestins provides the best quality of life.
3. Combination chemotherapy provides higher response rates and more toxicity than single-agent chemotherapy.
4. Irrespective of the regimen chosen, responses are short and median survival is approximately 12 months.

#### G. Surveillance / Monitoring / Follow-up<sup>228</sup>

1. For low risk history and physical every 6 months for the first 2 years then annually. For high risk every 3 months for the first 2 years then every 6 months for years 2-5 followed by annual.<sup>216</sup>
2. CA-125 at each visit if initially elevated (optional).
3. Chest X-ray annually (optional).
4. CT/MRI if clinically indicated.
5. Consider genetic counseling for patients < 50 and/or those with a significant family history of endometrial and/or colon cancer and/or selected pathologic risk features.
6. Education regarding symptoms of potential recurrence, lifestyle, nutrition, obesity, exercise, and smoking cessation. Additionally, education regarding sexual health, vaginal dilator use, and vaginal lubricants/moisturizers.

## V. Prognosis<sup>223, 228, 229</sup>

- A. Early stage endometrial carcinoma is the most curable gynecologic cancer; however, advanced stage endometrial cancer has a poor prognosis. The following is five-year survival data based on extent of disease at diagnosis.<sup>275</sup>

Extent of Disease	5-year Survival
Localized	95.2%
Regional	68.0%
Distant	17.1%
Unstaged	53.4%

### Patient Case #1, continued - Answer

**Correct answer is A**, SK has symptomatic disseminated metastases; therefore, chemotherapy would be most appropriate at this time.

Answer B would not be most appropriate as hormone therapy would only be considered in a patient with asymptomatic disseminated metastases or poor performance status.

Answer C and D would not be appropriate as SK has disseminated metastases and according to the **NCCN Guidelines®** pharmacologic intervention is most appropriate.

## VI. Toxicity and Survivorship Issues<sup>159, 220, 228, 276, 277</sup>

- A. Treatment with surgery, radiation, and chemotherapy are associated with both acute and chronic toxicities. In general, surgery for early stage disease is associated with less long-term toxicity than pelvic radiation.
- B. After BSO, hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis and an increased risk of cardiovascular disease.
1. Estrogen replacement therapy is a reasonable option for patients who are at low risk of tumor recurrence but initiating this therapy should be individualized.
- C. Vaginal stenosis and dryness are the most common long-term effects following completion of pelvic radiation. Patient education regarding sexual health including use of vaginal lubricants/moisturizers and vaginal dilators.
- D. Psychotherapy may be helpful for women experiencing sexual dysfunction. Referrals for psychotherapy, sexual/couples counseling, and ongoing communication should be encouraged.
- E. Radiation damage to surrounding pelvic tissue and/or fibrosis can result in bowel obstructions, rectal or vaginal fistula formation, or secondary cancers. Patients need to be screened accordingly.
- F. Mood disorders have been reported compared to healthy controls.

## RECOMMENDED READINGS AND REFERENCES

1. Tew WP, Lacchetti C, Ellis A et al. PARP inhibitors in the management of ovarian cancer: ASCO guideline. *J Clin Oncol*. 2020; 38(30):3468-93. Available at: <https://ascopubs.org/doi/full/10.1200/JCO.20.01924>.
2. Mirza MR, Lundqvist EA, Birrer MJ et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOV2/ENGOT-ov24): a randomised, phase 2, superiority trial. *Lancet Oncol*. 2019; 20: 1409-19. Available at: <https://pubmed.ncbi.nlm.nih.gov/31474354/>
3. Ray-Coquard I, Pautier P, Pignata S et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med*. 2019;381:2416-28. Available at: <https://www.nejm.org/doi/full/10.1056/nejmoa1911361>
4. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med*. 2021;385(20):1856-1867. Available at: <https://pubmed.ncbi.nlm.nih.gov/34534429/> [Makker V](#), Colombo N, Herraes AC, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. *N Engl J Med*. 2022;386(5):437-448. Available at: <https://pubmed.ncbi.nlm.nih.gov/35045221/>

## References

- 1 Seidman JD, Zhao P and Yemelyanova A. "Primary peritoneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: Assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. *Gynecol Oncol*. 2011; 120(3): 470-3.
- 2 Kurman RJ and Shih Ie M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. *Hum Pathol*. 2011; 42(7): 918-31.
- 3 Berek js. Epithelial ovarian cancer. In: Berek, js and hacker nf, eds. Practical gynecologic oncology, 4th edition. Baltimore: Lippincott williams & wilkins, 2005. Pp 443-510.
- 4 Nccn clinical practice guidelines in oncology (nccn guidelines<sup>(r)</sup>) for ovarian cancer including fallopian tube cancer and primary peritoneal cancer. V.5.2022, 09/16/2022, (c) 2022 national comprehensive cancer network, inc., all rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK(R), NCCN(R), NCCN GUIDELINES(R), NCCN IMAGING AUC<sup>TM</sup>, NCCN COMPENDIUM(R), NCCN BIOMARKERS COMPENDIUM(R), NCCN RADIATION THERAPY COMPENDIUM<sup>TM</sup>, NCCN IMAGING AUC COMPENDIUM<sup>TM</sup>, NCCN TEMPLATES(R), NCCN EVIDENCE BLOCKS<sup>TM</sup>, NCCN FRAMEWORK<sup>TM</sup>, NCCN HARMONIZED GUIDELINES<sup>TM</sup>, NCCN FLASH UPDATES<sup>TM</sup>, NCCN TRENDS<sup>TM</sup> Surveys & Data, Powered by NCCN<sup>TM</sup>, NCCN ONCOLOGY INSIGHTS REPORTS<sup>TM</sup>, and NCCN GUIDELINES FOR PATIENTS(R) are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc. .
- 5 Konstantinopoulos PA, Norquist B, Lacchetti C et al. Germline and somatic tumor testing in epithelial ovarian cancer: Asco guideline. *J Clin Oncol*. 2020; 38(11): 1222-45.
- 6 Prat J and Oncology FCoG. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet*. 2014; 124(1): 1-5.
- 7 Aravantinos G and Pectasides D. Bevacizumab in combination with chemotherapy for the treatment of advanced ovarian cancer: A systematic review. *J Ovarian Res*. 2014; 7: 57.
- 8 Ovarian cancer. American cancer society. Available at [www.Cancer.Org](http://www.Cancer.Org). Accessed september 24, 2018.
- 9 Buys SS, Partridge E, Black A et al. Effect of screening on ovarian cancer mortality: The prostate, lung, colorectal and ovarian (plco) cancer screening randomized controlled trial. *JAMA*. 2011; 305(22): 2295-303.
- 10 Prostate, lung, colorectal, and ovarian cancer screening trial. National cancer institute. Available at [www.Prevention.Cancer.Gov/plco](http://www.Prevention.Cancer.Gov/plco). Accessed september 24, 2018.
- 11 Buys SS, Partridge E, Greene MH et al. Ovarian cancer screening in the prostate, lung, colorectal and ovarian (plco) cancer screening trial: Findings from the initial screen of a randomized trial. *Am J Obstet Gynecol*. 2005; 193(5): 1630-9.

- 12 Goff BA, Mandel LS, Drescher CW et al. Development of an ovarian cancer symptom index: Possibilities for earlier detection. *Cancer*. 2007; 109(2): 221-7.
- 13 Nccn clinical practice guidelines in oncology (nccn guidelines<sup>(r)</sup>) for genetic/familial high-risk assessment: Breast, ovarian, and pancreatic. V.1.2023, 09/07/2022, (c) national comprehensive cancer network, inc., all rights reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK(R), NCCN(R), NCCN GUIDELINES(R), NCCN IMAGING AUCTION(R), NCCN COMPENDIUM(R), NCCN BIOMARKERS COMPENDIUM(R), NCCN RADIATION THERAPY COMPENDIUM<sup>TM</sup>, NCCN IMAGING AUC COMPENDIUM<sup>TM</sup>, NCCN TEMPLATES(R), NCCN EVIDENCE BLOCKS<sup>TM</sup>, NCCN FRAMEWORK<sup>TM</sup>, NCCN HARMONIZED GUIDELINES<sup>TM</sup>, NCCN FLASH UPDATES<sup>TM</sup>, NCCN TRENDS<sup>TM</sup> Surveys & Data, Powered by NCCN<sup>TM</sup>, NCCN ONCOLOGY INSIGHTS REPORTS<sup>TM</sup>, and NCCN GUIDELINES FOR PATIENTS(R) are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
- 14 Gross TP and Schlesselman JJ. The estimated effect of oral contraceptive use on the cumulative risk of epithelial ovarian cancer. *Obstet Gynecol*. 1994; 83(3): 419-24.
- 15 Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R et al. Ovarian cancer and oral contraceptives: Collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet*. 2008; 371(9609): 303-14.
- 16 Narod SA DM, Kligg J et al. Oral contraceptives and risk of brca breast cancer. *Journal of the National Cancer Institute*. 2002; 94(23): 1773-79.
- 17 Bell J, Brady MF, Young RC et al. Randomized phase iii trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2006; 102(3): 432-9.
- 18 Chan JK, Tian C, Fleming GF et al. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: An exploratory analysis of a gynecologic oncology group study. *Gynecol Oncol*. 2010; 116(3): 301-6.
- 19 Trimbos JB, Vergote I, Bolis G et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European organisation for research and treatment of cancer-adjuvant chemotherapy in ovarian neoplasm trial. *J Natl Cancer Inst*. 2003; 95(2): 113-25.
- 20 Colombo N, Guthrie D, Chiari S et al. International collaborative ovarian neoplasm trial 1: A randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer Inst*. 2003; 95(2): 125-32.
- 21 Armstrong DK, Bundy B, Wenzel L et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006; 354(1): 34-43.
- 22 Curtin JP, Malik R, Venkatraman ES et al. Stage iv ovarian cancer: Impact of surgical debulking. *Gynecol Oncol*. 1997; 64(1): 9-12.
- 23 Bristow RE, Montz FJ, Lagasse LD et al. Survival impact of surgical cytoreduction in stage iv epithelial ovarian cancer. *Gynecol Oncol*. 1999; 72(3): 278-87.
- 24 Ozols RF, Bundy BN, Greer BE et al. Phase iii trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage iii ovarian cancer: A gynecologic oncology group study. *J Clin Oncol*. 2003; 21(17): 3194-200.
- 25 Vasey PA, Jayson GC, Gordon A et al. Phase iii randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004; 96(22): 1682-91.
- 26 Barlin JN, Dao F, Bou Zgheib N et al. Progression-free and overall survival of a modified outpatient regimen of primary intravenous/intraperitoneal paclitaxel and intraperitoneal cisplatin in ovarian, fallopian tube, and primary peritoneal cancer. *Gynecol Oncol*. 2012; 125(3): 621-4.
- 27 Katsumata N, Yasuda M, Isonishi S et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (jgog 3016): A randomised, controlled, open-label trial. *Lancet Oncol*. 2013; 14(10): 1020-6.
- 28 Pignata S, Scambia G, Katsaros D et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (mito-7): A randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2014; 15(4): 396-405.

- 29 Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol.* 2010; 28(20): 3323-9.
- 30 Clamp AR, James EC, McNeish IA et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (icon8): Primary progression free survival analysis results from a gcig phase 3 randomised controlled trial. *The Lancet.* 2019; 394(10214): 2084-95.
- 31 Pignata S, Scambia G, Ferrandina G et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: The mito-2 randomized phase iii trial. *J Clin Oncol.* 2011; 29(27): 3628-35.
- 32 Falandry C, Rousseau F, Mouret-Reynier MA et al. Efficacy and safety of first-line single-agent carboplatin vs carboplatin plus paclitaxel for vulnerable older adult women with ovarian cancer: A gineco/gcig randomized clinical trial. *JAMA Oncol.* 2021; 7(6): 853-61.
- 33 Alberts DS, Liu PY, Hannigan EV et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage iii ovarian cancer. *N Engl J Med.* 1996; 335(26): 1950-5.
- 34 Jaaback K, Johnson N and Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev.* 2011; (11): CD005340.
- 35 Battelli C, Campo M, Buss MK et al. Safety and outcome of patients treated with a modified outpatient intraperitoneal regimen for epithelial ovarian, primary peritoneal or fallopian tube cancer. *Chemotherapy.* 2013; 59(4): 251-9.
- 36 Chan JK, Brady MF, Penson RT et al. Weekly vs. Every-3-week paclitaxel and carboplatin for ovarian cancer. *N Engl J Med.* 2016; 374(8): 738-48.
- 37 McGuire WP, Hoskins WJ, Brady MF et al. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: A gynecologic oncology group study. *J Clin Oncol.* 1995; 13(7): 1589-99.
- 38 Conte PF, Bruzzone M, Carnino F et al. High-dose versus low-dose cisplatin in combination with cyclophosphamide and epidoxorubicin in suboptimal ovarian cancer: A randomized study of the gruppo oncologico nord-ovest. *J Clin Oncol.* 1996; 14(2): 351-6.
- 39 Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD et al. European-canadian randomized trial of paclitaxel in relapsed ovarian cancer: High-dose versus low-dose and long versus short infusion. *J Clin Oncol.* 1994; 12(12): 2654-66.
- 40 Stiff PJ, Bayer R, Kerger C et al. High-dose chemotherapy with autologous transplantation for persistent/relapsed ovarian cancer: A multivariate analysis of survival for 100 consecutively treated patients. *J Clin Oncol.* 1997; 15(4): 1309-17.
- 41 Legros M, Dauplat J, Fleury J et al. High-dose chemotherapy with hematopoietic rescue in patients with stage iii to iv ovarian cancer: Long-term results. *J Clin Oncol.* 1997; 15(4): 1302-8.
- 42 Vergote I, Trope CG, Amant F et al. Neoadjuvant chemotherapy or primary surgery in stage iiic or iv ovarian cancer. *N Engl J Med.* 2010; 363(10): 943-53.
- 43 Wright AA, Bohlke K, Armstrong DK et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of gynecologic oncology and american society of clinical oncology clinical practice guideline. *J Clin Oncol.* 2016; 34(28): 3460-73.
- 44 Provencher DM, Gallagher CJ, Parulekar WR et al. Ov21/petroc: A randomized gynecologic cancer intergroup phase ii study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer. *Ann Oncol.* 2018; 29(2): 431-38.
- 45 van Driel WJ, Koole SN, Sikorska K et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med.* 2018; 378(3): 230-40.
- 46 Bookman MA, Brady MF, McGuire WP et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: A phase iii trial of the gynecologic cancer intergroup. *J Clin Oncol.* 2009; 27(9): 1419-25.
- 47 Ferriss JS, Java JJ, Bookman MA et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: An nrg oncology/gog study. *Gynecol Oncol.* 2015; 139(1): 17-22.
- 48 Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011; 365(26): 2473-83.

- 49 Monk BJ, Huang HQ, Burger RA et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: A gynecologic oncology group study. *Gynecol Oncol.* 2013; 128(3): 573-8.
- 50 Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. *Journ Clin Oncol.* 37(26): 2317-29.
- 51 Oza AM, Cook AD, Pfisterer J et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (icon7): Overall survival results of a phase 3 randomised trial. *Lancet Oncol.* 2015; 16(8): 928-36.
- 52 Perren TJ, Swart AM, Pfisterer J et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011; 365(26): 2484-96.
- 53 Stark D, Nankivell M, Pujade-Lauraine E et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: Quality-of-life outcomes from the international collaboration on ovarian neoplasms (icon7) phase 3 randomised trial. *Lancet Oncol.* 2013; 14(3): 236-43.
- 54 Stone RL, Sood AK and Coleman RL. Collateral damage: Toxic effects of targeted antiangiogenic therapies in ovarian cancer. *Lancet Oncol.* 2010; 11(5): 465-75.
- 55 Aghajanian C, Blank SV, Goff BA et al. Oceans: A randomized, double-blind, placebo-controlled phase iii trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012; 30(17): 2039-45.
- 56 Cannistra SA, Matulonis UA, Penson RT et al. Phase ii study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol.* 2007; 25(33): 5180-6.
- 57 Burger RA, Brady MF, Bookman MA et al. Risk factors for gi adverse events in a phase iii randomized trial of bevacizumab in first-line therapy of advanced ovarian cancer: A gynecologic oncology group study. *J Clin Oncol.* 2014; 32(12): 1210-7.
- 58 An MM, Zou Z, Shen H et al. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: An updated meta-analysis. *Eur J Clin Pharmacol.* 2010; 66(8): 813-21.
- 59 Markman M, Liu PY, Wilczynski S et al. Phase iii randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: A southwest oncology group and gynecologic oncology group trial. *J Clin Oncol.* 2003; 21(13): 2460-5.
- 60 Hess LM, Rong N, Monahan PO et al. Continued chemotherapy after complete response to primary therapy among women with advanced ovarian cancer: A meta-analysis. *Cancer.* 2010; 116(22): 5251-60.
- 61 Mei L, Chen H, Wei DM et al. Maintenance chemotherapy for ovarian cancer. *Cochrane Database Syst Rev.* 2010; (9): CD007414.
- 62 du Bois A, Floquet A, Kim JW et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol.* 2014; 32(30): 3374-82.
- 63 Moore K, Colombo N, Scambia G et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2018; 379(26): 2495-505.
- 64 Banerjee S MK, Colombo N et al. Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (oc) and a brca mutation (brcam): 5-year (y) follow-up (f/u) from solo1. *Ann Oncol.* 2020; 31.
- 65 Ray-Coquard I, Pautier P, Pignata S et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med.* 2019; 381(25): 2416-28.
- 66 Gonzalez-Martin A, Pothuri B, Vergote I et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2019; 381(25): 2391-402.
- 67 Nicoletto MO, Tumolo S, Talamini R et al. Surgical second look in ovarian cancer: A randomized study in patients with laparoscopic complete remission--a northeastern oncology cooperative group-ovarian cancer cooperative group study. *J Clin Oncol.* 1997; 15(3): 994-9.
- 68 Salani R, Backes FJ, Fung MF et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of gynecologic oncologists recommendations. *Am J Obstet Gynecol.* 2011; 204(6): 466-78.
- 69 Rustin GJ, van der Burg ME, Griffin CL et al. Early versus delayed treatment of relapsed ovarian cancer (mrc ov05/eortc 55955): A randomised trial. *Lancet.* 2010; 376(9747): 1155-63.
- 70 Miller RE and Rustin GJ. How to follow-up patients with epithelial ovarian cancer. *Curr Opin Oncol.* 2010; 22(5): 498-502.

- 71 Keytruda (pembrolizumab) [prescribing information]. Whitehouse station, nj: Merck, august 2018.
- 72 Mirza MR, Åvall Lundqvist E, Birrer MJ et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (nsgo-avanova2/engot-ov24): A randomised, phase 2, superiority trial. *The Lancet Oncology*. 2019; 20(10): 1409-19.
- 73 Parmar MK, Ledermann JA, Colombo N et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: The icon4/ago-ovar-2.2 trial. *Lancet*. 2003; 361(9375): 2099-106.
- 74 Gronlund B, Hogdall C, Hansen HH et al. Results of reinduction therapy with paclitaxel and carboplatin in recurrent epithelial ovarian cancer. *Gynecol Oncol*. 2001; 83(1): 128-34.
- 75 Coleman RL, Brady MF, Herzog TJ et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (nrg oncology/gynecologic oncology group study gog-0213): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017; 18(6): 779-91.
- 76 Pfisterer J, Plante M, Vergote I et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: An intergroup trial of the ago-ovar, the ncic ctg, and the eortc gcg. *J Clin Oncol*. 2006; 24(29): 4699-707.
- 77 Nagourney RA, Brewer CA, Radecki S et al. Phase ii trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol*. 2003; 88(1): 35-9.
- 78 Rose PG, Mossbruger K, Fusco N et al. Gemcitabine reverses cisplatin resistance: Demonstration of activity in platinum- and multidrug-resistant ovarian and peritoneal carcinoma. *Gynecol Oncol*. 2003; 88(1): 17-21.
- 79 Wagner U, Marth C, Largillier R et al. Final overall survival results of phase iii gcig calypso trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. *Br J Cancer*. 2012; 107(4): 588-91.
- 80 Mahner S, Meier W, du Bois A et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in very platinum-sensitive ovarian cancer patients: Results from a subset analysis of the calypso phase iii trial. *Eur J Cancer*. 2015; 51(3): 352-8.
- 81 Pfisterer J DA, Baumann K, Rau J, Harter P, Joly F, Sehouli J, Canzler U, Schmalfeldt B, Shannon C, Hein A, Reimer DU, Hanker LC, Petit T, Marme F, El-Balat A, Glasspool R, DeGregorio N, Mahner S, Kurtz J. Carboplatin/pegylated liposomal doxorubicin/bevacizumab (cd-bev) vs. Carboplatin/gemcitabine/bevacizumab (cg-bev) in patients with recurrent ovarian cancer. *Annals of Oncology*. 2018; 29: viii332-viii58.
- 82 Aghajanian C, Goff B, Nycum LR et al. Final overall survival and safety analysis of oceans, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol*. 2015; 139(1): 10-6.
- 83 Pignata S LD, Joly F, Gallo C, Colombo N, Sessa C, Bamias A, Pisano C, Selle F, Zaccarelli E, Scambia G, Pautier P, Nicoletto MO, Giorgi UD, Dubot C, Bologna A, Orditura M, Ray-Coquard IL, Perrone F, Daniele G. Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: The randomized phase 3 trial mito16b-mango ov2b-engot ov17. *American Society of Clinical Oncology*. 2018.
- 84 Joly F, Ray-Coquard I, Fabbro M et al. Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin compared to carboplatin-paclitaxel combination: Analysis from the gcig calypso relapsing ovarian cancer trial. *Gynecol Oncol*. 2011; 122(2): 226-32.
- 85 Mirza MR, Monk BJ, Herrstedt J et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016; 375(22): 2154-64.
- 86 Berek JS, Matulonis UA, Peen U et al. Safety and dose modification for patients receiving niraparib. *Ann Oncol*. 2018; 29(8): 1784-92.
- 87 Del Campo JM MU, Malander S, Provencher Diane, Mahner S, Follana P, Waters J, Berek JS, Woie K, Oza AM, Canzler U, Gil-Martin M, Lesoin A, Monk BJ, Lund B, Gilbert L, Wenham R, Benigno B, Arora S, Hazard SJ, Mirza MR. Niraparib maintenance therapy in patients with recurrent ovarian cancer after a partial response to the last platinum-based chemotherapy in the engot-ov16/nova trial. *Journ Clin Oncol*. 2019; 37: 2968-73.
- 88 Pujade-Lauraine E, Ledermann JA, Selle F et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a brca1/2 mutation (solo2/engot-ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017; 18(9): 1274-84.

- 89 Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012; 366(15): 1382-92.
- 90 Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by brca status in a randomised phase 2 trial. *Lancet Oncol*. 2014; 15(8): 852-61.
- 91 Friedlander M, Matulonis U, Gourley C et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer*. 2018; 119(9): 1075-85.
- 92 Coleman RL, Oza AM, Lorusso D et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ariel3): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017; 390(10106): 1949-61.
- 93 Gordon AN, Fleagle JT, Guthrie D et al. Recurrent epithelial ovarian carcinoma: A randomized phase iii study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001; 19(14): 3312-22.
- 94 Pujade-Lauraine E, Hilpert F, Weber B et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The aurelia open-label randomized phase iii trial. *J Clin Oncol*. 2014; 32(13): 1302-8.
- 95 Stockler MR, Hilpert F, Friedlander M et al. Patient-reported outcome results from the open-label phase iii aurelia trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. *J Clin Oncol*. 2014; 32(13): 1309-16.
- 96 Matulonis UA, Oaknin A, Pignata S et al. Mirvetuximab soravtansine (mirv) in patients with platinum-resistant ovarian cancer with high folate receptor alpha (frα) expression: Characterization of antitumor activity in the soraya study. *J Clin Oncol*. 2022; 40(16\_suppl): 5512-12.
- 97 Sehouli J, Stengel D, Harter P et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: A randomized multicenter phase ii trial of the north-eastern german society of gynecological oncology ovarian cancer study group. *J Clin Oncol*. 2011; 29(2): 242-8.
- 98 Kaufman B, Shapira-Frommer R, Schmutzler RK et al. Olaparib monotherapy in patients with advanced cancer and a germline brca1/2 mutation. *J Clin Oncol*. 2015; 33(3): 244-50.
- 99 Domchek SM, Aghajanian C, Shapira-Frommer R et al. Efficacy and safety of olaparib monotherapy in germline brca1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. *Gynecol Oncol*. 2016; 140(2): 199-203.
- 100 Penson RT, Valencia RV, Cibula D et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline brca1/2 mutation (solo3): A randomized phase iii trial. *J Clin Oncol*. 2020; 38(11): 1164-74.
- 101 Swisher EM, Lin KK, Oza AM et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ariel2 part 1): An international, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2017; 18(1): 75-87.
- 102 Balasubramaniam S, Beaver JA, Horton S et al. Fda approval summary: Rucaparib for the treatment of patients with deleterious brca mutation-associated advanced ovarian cancer. *Clin Cancer Res*. 2017.
- 103 Kristeleit R, Lisyanskaya A, Fedenko A et al. Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious brca1 or brca2 mutation (ariel4): An international, open-label, randomised, phase 3 trial. *The Lancet Oncology*. 2022; 23(4): 465-78.
- 104 Moore KN, Secord AA, Geller MA et al. Niraparib monotherapy for late-line treatment of ovarian cancer (quadra): A multicentre, open-label, single-arm, phase 2 trial. *The Lancet Oncology*. 2019; 20(5): 636-48.
- 105 Lynparza (olaparib) [prescribing information]. Wilmington, de: Astra zeneca, august 2017.
- 106 Rubraca™ (rucaparib) [prescribing information]. Boulder, co: Clovis oncology, april 2018. .
- 107 Zejula™ (niraparib) [prescribing information]. Waltham, ma: Tesaro, march 2017. .
- 108 del Carmen MG, Fuller AF, Matulonis U et al. Phase ii trial of anastrozole in women with asymptomatic mullerian cancer. *Gynecol Oncol*. 2003; 91(3): 596-602.
- 109 Burger RA, Sill MW, Monk BJ et al. Phase ii trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A gynecologic oncology group study. *J Clin Oncol*. 2007; 25(33): 5165-71.
- 110 Monk BJ, Choi DC, Pugmire G et al. Activity of bevacizumab (rhumb vegf) in advanced refractory epithelial ovarian cancer. *Gynecol Oncol*. 2005; 96(3): 902-5.
- 111 Boehmer C and Jaeger W. Capecitabine in treatment of platinum-resistant recurrent ovarian cancer. *Anticancer Res*. 2002; 22(1A): 439-43.



- 112 Vasey PA, McMahon L, Paul J et al. A phase ii trial of capecitabine (xeloda) in recurrent ovarian cancer. *Br J Cancer*. 2003; 89(10): 1843-8.
- 113 Handolias D, Quinn M, Foo S et al. Oral cyclophosphamide in recurrent ovarian cancer. *Asia Pac J Clin Oncol*. 2016; 12(1): e154-60.
- 114 Watanabe Y, Etoh T, Koike E et al. Feasibility study of oral cyclophosphamide salvage therapy for the treatment of heavily pretreated patients with recurrent epithelial ovarian cancer. *Int J Clin Oncol*. 2010; 15(5): 468-71.
- 115 Barber EL, Zsiros E, Lurain JR et al. The combination of intravenous bevacizumab and metronomic oral cyclophosphamide is an effective regimen for platinum-resistant recurrent ovarian cancer. *J Gynecol Oncol*. 2013; 24(3): 258-64.
- 116 Kaye SB, Piccart M, Aapro M et al. Phase ii trials of docetaxel (taxotere) in advanced ovarian cancer--an updated overview. *Eur J Cancer*. 1997; 33(13): 2167-70.
- 117 Cantu MG, Buda A, Parma G et al. Randomized controlled trial of single-agent paclitaxel versus cyclophosphamide, doxorubicin, and cisplatin in patients with recurrent ovarian cancer who responded to first-line platinum-based regimens. *J Clin Oncol*. 2002; 20(5): 1232-7.
- 118 Rose PG, Blessing JA, Mayer AR et al. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: A gynecologic oncology group study. *J Clin Oncol*. 1998; 16(2): 405-10.
- 119 Makar AP. Hormone therapy in epithelial ovarian cancer. *Endocr Relat Cancer*. 2000; 7(2): 85-93.
- 120 Markman M, Webster K, Zanotti K et al. Phase 2 trial of single-agent gemcitabine in platinum-paclitaxel refractory ovarian cancer. *Gynecol Oncol*. 2003; 90(3): 593-6.
- 121 D'Agostino G, Amant F, Berteloot P et al. Phase ii study of gemcitabine in recurrent platinum-and paclitaxel-resistant ovarian cancer. *Gynecol Oncol*. 2003; 88(3): 266-9.
- 122 Markman M HT, Reichman B, Lewis JL, Rubin S, Jones W, Almadrones L, Pizzuto F, Hoskins W. Ifosfamide and mesna in previously treated advanced epithelial ovarian cancer: Activity in platinum-resistant disease. *Journ Clin Oncol*. 1992; 10: 243-48.
- 123 Matsumoto K, Katsumata N, Yamanaka Y et al. The safety and efficacy of the weekly dosing of irinotecan for platinum- and taxanes-resistant epithelial ovarian cancer. *Gynecol Oncol*. 2006; 100(2): 412-6.
- 124 Smyth JF, Gourley C, Walker G et al. Antiestrogen therapy is active in selected ovarian cancer cases: The use of letrozole in estrogen receptor-positive patients. *Clin Cancer Res*. 2007; 13(12): 3617-22.
- 125 Marinaccio M DA, Seratti A, Pinto V, Cagnazzo G. Leuprolide acetate as a salvage-therapy in relapsed epithelial ovarian cancer. *Eur J Gynaecol Oncol*. 1996; 17(4): 286-88.
- 126 Veenhof CH, van der Burg ME, Nooy M et al. Phase ii study of high-dose megestrol acetate in patients with advanced ovarian carcinoma. *Eur J Cancer*. 1994; 30A(5): 697-8.
- 127 Hasan J JG. Oral melphalan as a treatment for platinum-resistant ovarian cancer. *Br J Cancer*. 2003; 88: 1828-30.
- 128 Teneriello MG, Tseng PC, Crozier M et al. Phase ii evaluation of nanoparticle albumin-bound paclitaxel in platinum-sensitive patients with recurrent ovarian, peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2009; 27(9): 1426-31.
- 129 Fracasso PM, Blessing JA, Morgan MA et al. Phase ii study of oxaliplatin in platinum-resistant and refractory ovarian cancer: A gynecologic group study. *J Clin Oncol*. 2003; 21(15): 2856-9.
- 130 Gynecologic Oncology G, Markman M, Blessing J et al. Phase ii trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: A gynecologic oncology group study. *Gynecol Oncol*. 2006; 101(3): 436-40.
- 131 Muggia FM, Hainsworth JD, Jeffers S et al. Phase ii study of liposomal doxorubicin in refractory ovarian cancer: Antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol*. 1997; 15(3): 987-93.
- 132 Miller DS, Blessing JA, Krasner CN et al. Phase ii evaluation of pemetrexed in the treatment of recurrent or persistent platinum-resistant ovarian or primary peritoneal carcinoma: A study of the gynecologic oncology group. *J Clin Oncol*. 2009; 27(16): 2686-91.
- 133 Vergote I, Calvert H, Kania M et al. A randomised, double-blind, phase ii study of two doses of pemetrexed in the treatment of platinum-resistant, epithelial ovarian or primary peritoneal cancer. *Eur J Cancer*. 2009; 45(8): 1415-23.

- 134 Markman M, Iseminger KA, Hatch KD et al. Tamoxifen in platinum-refractory ovarian cancer: A gynecologic oncology group ancillary report. *Gynecol Oncol*. 1996; 62(1): 4-6.
- 135 ten Bokkel Huinink W, Gore M, Carmichael J et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*. 1997; 15(6): 2183-93.
- 136 McGuire WP, Blessing JA, Bookman MA et al. Topotecan has substantial antitumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: A gynecologic oncology group study. *J Clin Oncol*. 2000; 18(5): 1062-7.
- 137 Chekerov R, Hilpert F, Mahner S et al. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (trias): A multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Oncology*. 2018; 19(9): 1247-58.
- 138 Burger RA, DiSaia PJ, Roberts JA et al. Phase ii trial of vinorelbine in recurrent and progressive epithelial ovarian cancer. *Gynecol Oncol*. 1999; 72(2): 148-53.
- 139 Markman M, Kennedy A, Webster K et al. Paclitaxel-associated hypersensitivity reactions: Experience of the gynecologic oncology program of the cleveland clinic cancer center. *J Clin Oncol*. 2000; 18(1): 102-5.
- 140 Chouhan JD and Herrington JD. Single premedication dose of dexamethasone 20 mg iv before docetaxel administration. *J Oncol Pharm Pract*. 2011; 17(3): 155-9.
- 141 Boulanger J, Boursiquot JN, Cournoyer G et al. Management of hypersensitivity to platinum- and taxane-based chemotherapy: Cepo review and clinical recommendations. *Curr Oncol*. 2014; 21(4): e630-41.
- 142 Li Q, Cohn D, Waller A et al. Outpatient rapid 4-step desensitization for gynecologic oncology patients with mild to low-risk, moderate hypersensitivity reactions to carboplatin/cisplatin. *Gynecol Oncol*. 2014; 135(1): 90-4.
- 143 Lee CW, Matulonis UA and Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: Standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol*. 2005; 99(2): 393-9.
- 144 O'Cearbhaill R, Zhou Q, Iasonos A et al. The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin retreatment. *Gynecol Oncol*. 2010; 116(3): 326-31.
- 145 Polyzos A, Tsavaris N, Gogas H et al. Clinical features of hypersensitivity reactions to oxaliplatin: A 10-year experience. *Oncology*. 2009; 76(1): 36-41.
- 146 Suenaga M, Mizunuma N, Shinozaki E et al. Management of allergic reactions to oxaliplatin in colorectal cancer patients. *J Support Oncol*. 2008; 6(8): 373-8.
- 147 Berger MJ, Vargo C, Vincent M et al. Stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. *Support Care Cancer*. 2015; 23(7): 2019-24.
- 148 Braverman AS, Rao S, Salvatti ME et al. Tapering and discontinuation of glucocorticoid prophylaxis during prolonged weekly to biweekly paclitaxel administration. *Chemotherapy*. 2005; 51(2-3): 116-9.
- 149 Castells MC, Tennant NM, Sloane DE et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008; 122(3): 574-80.
- 150 Lee CW, Matulonis UA and Castells MC. Carboplatin hypersensitivity: A 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/ige-mediated reactions. *Gynecol Oncol*. 2004; 95(2): 370-6.
- 151 Markman M, Hsieh F, Zanotti K et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: Carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol*. 2004; 130(1): 25-8.
- 152 Ailor sk and miles sc. In: M. C. Perry ed. The chemotherapy source book. 4th ed. Philadelphia: Lippincott williams & wilkins; 2008:1136-147.
- 153 Scalp cooling system from dignitana | cold caps | chemotherapy hair loss. Available at: <https://dignicap.Com/> accessed september 24, 2018.
- 154 Seer stat fact sheet: Ovarian cancer. Available at: <http://seer.Cancer.Gov/statfacts/html/ovary.Html> accessed june 24, 2020.
- 155 Fayers PM, Rustin G, Wood R et al. The prognostic value of serum ca 125 in patients with advanced ovarian carcinoma: An analysis of 573 patients by the medical research council working party on gynaecological cancer. *Int J Gynecol Cancer*. 1993; 3(5): 285-92.

- 156 Au-Yeung G, Webb PM, DeFazio A et al. Impact of obesity on chemotherapy dosing for women with advanced stage serous ovarian cancer in the australian ovarian cancer study (aocs). *Gynecol Oncol*. 2014; 133(1): 16-22.
- 157 Philip J and Depczynski B. The role of total parenteral nutrition for patients with irreversible bowel obstruction secondary to gynecological malignancy. *J Pain Symptom Manage*. 1997; 13(2): 104-11.
- 158 Athibovonsuk P, Manchana T and Sirisabya N. Prevention of blood transfusion with intravenous iron in gynecologic cancer patients receiving platinum-based chemotherapy. *Gynecol Oncol*. 2013; 131(3): 679-82.
- 159 Nccn clinical practice guidelines in oncology (nccn guidelines<sup>(r)</sup>) for survivorship. V.1.2022, 03/30/2022, (c) national comprehensive cancer network, inc., all rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK(R), NCCN(R), NCCN GUIDELINES(R), NCCN IMAGING AUCTM, NCCN COMPENDIUM(R), NCCN BIOMARKERS COMPENDIUM(R), NCCN RADIATION THERAPY COMPENDIUM<sup>TM</sup>, NCCN IMAGING AUC COMPENDIUM<sup>TM</sup>, NCCN TEMPLATES(R), NCCN EVIDENCE BLOCKS<sup>TM</sup>, NCCN FRAMEWORK<sup>TM</sup>, NCCN HARMONIZED GUIDELINES<sup>TM</sup>, NCCN FLASH UPDATES<sup>TM</sup>, NCCN TRENDS<sup>TM</sup> Surveys & Data, Powered by NCCN<sup>TM</sup>, NCCN ONCOLOGY INSIGHTS REPORTS<sup>TM</sup>, and NCCN GUIDELINES FOR PATIENTS(R) are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 160 Jenkins MR and Sikin AL. Update on nonhormonal approaches to menopausal management. *Cleve Clin J Med*. 2008; 75 Suppl 4: S17-24.
- 161 Barton DL, Loprinzi C and Gostout B. Current management of menopausal symptoms in cancer patients. *Oncology (Williston Park)*. 2002; 16(1): 67-72, 74; discussion 75-6, 79-80.
- 162 Gershenson DM, Miller AM, Champion VL et al. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: A gynecologic oncology group study. *J Clin Oncol*. 2007; 25(19): 2792-7.
- 163 Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999; 189(1): 12-9.
- 164 Schiffman M and Wentzensen N. Human papillomavirus infection and the multistage carcinogenesis of cervical cancer. *Cancer Epidemiol Biomarkers Prev*. 2013; 22(4): 553-60.
- 165 Melnikow J, Nuovo J, Willan AR et al. Natural history of cervical squamous intraepithelial lesions: A meta-analysis. *Obstet Gynecol*. 1998; 92(4 Pt 2): 727-35.
- 166 Manhart LE, Holmes KK, Koutsky LA et al. Human papillomavirus infection among sexually active young women in the united states: Implications for developing a vaccination strategy. *Sex Transm Dis*. 2006; 33(8): 502-8.
- 167 Watson M, Saraiya M, Benard V et al. Burden of cervical cancer in the united states, 1998-2003. *Cancer*. 2008; 113(10 Suppl): 2855-64.
- 168 Nccn clinical practice guidelines in oncology (nccn guidelines<sup>(r)</sup>) for cervical cancer. V.1.2022, 10/26/2021, (c) national comprehensive cancer network, inc., all rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK(R), NCCN(R), NCCN GUIDELINES(R), NCCN IMAGING AUCTM, NCCN COMPENDIUM(R), NCCN BIOMARKERS COMPENDIUM(R), NCCN RADIATION THERAPY COMPENDIUM<sup>TM</sup>, NCCN IMAGING AUC COMPENDIUM<sup>TM</sup>, NCCN TEMPLATES(R), NCCN EVIDENCE BLOCKS<sup>TM</sup>, NCCN FRAMEWORK<sup>TM</sup>, NCCN HARMONIZED GUIDELINES<sup>TM</sup>, NCCN FLASH UPDATES<sup>TM</sup>, NCCN TRENDS<sup>TM</sup> Surveys & Data, Powered by NCCN<sup>TM</sup>, NCCN ONCOLOGY INSIGHTS REPORTS<sup>TM</sup>, and NCCN GUIDELINES FOR PATIENTS(R) are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 169 Fontham ETH, Wolf AMD, Church TR et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the american cancer society. *CA Cancer J Clin*. 2020; 70(5): 321-46.
- 170 Cervical cancer. American cancer society cancer facts & figures 2020. Available at [www.Cancer.Org](http://www.Cancer.Org). Accessed june 24, 2020.
- 171 Moyer VA and Force USPST. Screening for cervical cancer: U.S. Preventive services task force recommendation statement. *Ann Intern Med*. 2012; 156(12): 880-91, W312.
- 172 Committee on Practice B-G. Acog practice bulletin number 131: Screening for cervical cancer. *Obstet Gynecol*. 2012; 120(5): 1222-38.
- 173 Force USPST, Curry SJ, Krist AH et al. Screening for cervical cancer: Us preventive services task force recommendation statement. *JAMA*. 2018; 320(7): 674-86.

- 174 Dobson SR, McNeil S, Dionne M et al. Immunogenicity of 2 doses of hpv vaccine in younger adolescents vs 3 doses in young women: A randomized clinical trial. *JAMA*. 2013; 309(17): 1793-802.
- 175 Julius JM, Ramondeta L, Tipton KA et al. Clinical perspectives on the role of the human papillomavirus vaccine in the prevention of cancer. *Pharmacotherapy*. 2011; 31(3): 280-97.
- 176 Macartney KK, Chiu C, Georgousakis M et al. Safety of human papillomavirus vaccines: A review. *Drug Saf*. 2013; 36(6): 393-412.
- 177 McKeage K RB. As04-adjuvanted human papillomavirus (hpv) types 16 and 18 vaccine (cervarix®): A review of its use in the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic hpv types. *Drugs*. 2011; 71: 465-88.
- 178 Human Papillomavirus 9-valent Vaccine RpiWS, NJ: Merck; 2015.
- 179 Gardasil 9 (human papillomavirus 9-valent vaccine, recombinant) [prescribing information]. Whitehouse station, nj: Merck, october 2018.
- 180 Committee on Adolescent Health Care of the American College of O, Gynecologists, Immunization Expert Work Group of the American College of O et al. Committee opinion no. 588: Human papillomavirus vaccination. *Obstet Gynecol*. 2014; 123(3): 712-8.
- 181 Cervical cancer. Hpv vaccines. Available at [www.Cancer.Org](http://www.Cancer.Org). Accessed september 24, 2018.
- 182 Herzog TJ, Huh WK and Einstein MH. How does public policy impact cervical screening and vaccination strategies? *Gynecol Oncol*. 2010; 119(2): 175-80.
- 183 Markowitz LE, Dunne EF, Saraiya M et al. Human papillomavirus vaccination: Recommendations of the advisory committee on immunization practices (acip). *MMWR Recomm Rep*. 2014; 63(RR-05): 1-30.
- 184 Cormier B, Diaz JP, Shih K et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. *Gynecol Oncol*. 2011; 122(2): 275-80.
- 185 Massad LS, Einstein MH, Huh WK et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol*. 2013; 121(4): 829-46.
- 186 Chuang LT, Temin S and Berek JS. Management and care of women with invasive cervical cancer: American society of clinical oncology resource-stratified clinical practice guideline summary. *J Oncol Pract*. 2016; 12(7): 693-6.
- 187 Hung CF, Ma B, Monie A et al. Therapeutic human papillomavirus vaccines: Current clinical trials and future directions. *Expert Opin Biol Ther*. 2008; 8(4): 421-39.
- 188 Chemoradiotherapy for Cervical Cancer Meta-Analysis C. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol*. 2008; 26(35): 5802-12.
- 189 National cancer institute: Nci clinical announcement. Concurrent chemoradiation for cervical cancer. United states department of health and human services, public health service, national institutes of health. 1999.
- 190 Cervical cancer. Nih consensus statement. 1996 april 1-3; 14(1): 1-38.
- 191 Rose PG. Concurrent chemoradiation for locally advanced carcinoma of the cervix: Where are we in 2006? *Ann Oncol*. 2006; 17 Suppl 10: x224-9.
- 192 Nci issues clinical announcement on cervical cancer: Chemotherapy plus radiation improves survival - 02/22/1999. Nation institutes of health (u.S national library of medicine) available at <http://www.Nih.Gov/news/pr/feb99/nci-22.Htm> accessed september 24, 2018.
- 193 Keys HM, Bundy BN, Stehman FB et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage ib cervical carcinoma. *N Engl J Med*. 1999; 340(15): 1154-61.
- 194 Rose PG, Bundy BN, Watkins EB et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999; 340(15): 1144-53.
- 195 Whitney CW, Sause W, Bundy BN et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage iib-iva carcinoma of the cervix with negative para-aortic lymph nodes: A gynecologic oncology group and southwest oncology group study. *J Clin Oncol*. 1999; 17(5): 1339-48.
- 196 Morris M, Eifel PJ, Lu J et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999; 340(15): 1137-43.

- 197 Peters WA, 3rd, Liu PY, Barrett RJ, 2nd et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol.* 2000; 18(8): 1606-13.
- 198 Stehman FB, Ali S, Keys HM et al. Radiation therapy with or without weekly cisplatin for bulky stage 1b cervical carcinoma: Follow-up of a gynecologic oncology group trial. *Am J Obstet Gynecol.* 2007; 197(5): 503 e1-6.
- 199 Long HJ, 3rd, Bundy BN, Grendys EC, Jr. et al. Randomized phase iii trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A gynecologic oncology group study. *J Clin Oncol.* 2005; 23(21): 4626-33.
- 200 Monk BJ, Sill MW, McMeekin DS et al. Phase iii trial of four cisplatin-containing doublet combinations in stage ivb, recurrent, or persistent cervical carcinoma: A gynecologic oncology group study. *J Clin Oncol.* 2009; 27(28): 4649-55.
- 201 Saito I, Kitagawa R, Fukuda H et al. A phase iii trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage ivb, persistent or recurrent cervical cancer: Gynecologic cancer study group/japan clinical oncology group study (jcog0505). *Jpn J Clin Oncol.* 2010; 40(1): 90-3.
- 202 Moore KN, Herzog TJ, Lewin S et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage ivb, recurrent or persistent cervical cancer. *Gynecol Oncol.* 2007; 105(2): 299-303.
- 203 Kitagawa R KN, Shibata T, et al. A randomized, phase iii trial of paclitaxel plus carboplatin (tc) versus paclitaxel plus cisplatin (tp) in stage ivb, persistent or recurrent cervical cancer: Japan clinical oncology group study (jcog0505). *J Clin Oncol.* 2012; 30: 5006.
- 204 Tewari KS, Sill MW, Long HJ, 3rd et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med.* 2014; 370(8): 734-43.
- 205 Bevacizumab significantly improves survival for patients with recurrent and metastatic cervical cancer. National cancer institute. Available at [www.Cancer.Gov](http://www.Cancer.Gov). Accessed september 25, 2017.
- 206 Tewari KS, Sill MW, Penson RT et al. Bevacizumab for advanced cervical cancer: Final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (gynecologic oncology group 240). *The Lancet.* 2017; 390(10103): 1654-63.
- 207 Colombo N, Dubot C, Lorusso D et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med.* 2021; 385(20): 1856-67.
- 208 Moore DH, Blessing JA, McQuellon RP et al. Phase iii study of cisplatin with or without paclitaxel in stage ivb, recurrent, or persistent squamous cell carcinoma of the cervix: A gynecologic oncology group study. *J Clin Oncol.* 2004; 22(15): 3113-9.
- 209 Kitagawa R, Katsumata N, Shibata T et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: The open-label randomized phase iii trial jcog0505. *J Clin Oncol.* 2015; 33(19): 2129-35.
- 210 Chung H, Ross W, Delord J et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the phase ii keynote-158 study. *J Clin Oncol.* 2019; 37(17): 1470-78.
- 211 Coleman RL, Lorusso D, Gennigens C et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovatv 204/gog-3023/engot-cx6): A multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol.* 2021; 22(5): 609-19.
- 212 Kudelka AP, Winn R, Edwards CL et al. An update of a phase ii study of paclitaxel in advanced or recurrent squamous cell cancer of the cervix. *Anticancer Drugs.* 1997; 8(7): 657-61.
- 213 Weiss GR, Green S, Hannigan EV et al. A phase ii trial of carboplatin for recurrent or metastatic squamous carcinoma of the uterine cervix: A southwest oncology group study. *Gynecol Oncol.* 1990; 39(3): 332-6.
- 214 Frenel JS, Le Tourneau C, O'Neil B et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: Results from the phase ib keynote-028 trial. *J Clin Oncol.* 2017; 35(36): 4035-41.
- 215 Naumann RW, Hollebecque A, Meyer T et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: Results from the phase i/ii checkmate 358 trial. *J Clin Oncol.* 2019; 37(31): 2825-34.
- 216 Salani R, Khanna N, Frimer M et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of gynecologic oncology (sgo) recommendations. *Gynecol Oncol.* 2017; 146(1): 3-10.



- 217 Seer stat fact sheet: Cervical cancer. Available at: <http://seer.Cancer.Gov/statfacts/html/cervix.Html>  
accessed june 24, 2020.
- 218 Look KY, Blessing JA, Gallup DG et al. A phase ii trial of 5-fluorouracil and high-dose leucovorin in patients  
with recurrent squamous cell carcinoma of the cervix: A gynecologic oncology group study. *Am J Clin*  
*Oncol.* 1996; 19(5): 439-41.
- 219 Cetina L, Garcia-Arias A, Uribe Mde J et al. Concurrent chemoradiation with carboplatin for elderly,  
diabetic and hypertensive patients with locally advanced cervical cancer. *Eur J Gynaecol Oncol.* 2008;  
29(6): 608-12.
- 220 Bradley S, Rose S, Lutgendorf S et al. Quality of life and mental health in cervical and endometrial cancer  
survivors. *Gynecol Oncol.* 2006; 100(3): 479-86.
- 221 Kullmer U, Stenger K, Milch W et al. Self-concept, body image, and use of unconventional therapies in  
patients with gynaecological malignancies in the state of complete remission and recurrence. *Eur J Obstet*  
*Gynecol Reprod Biol.* 1999; 82(1): 101-6.
- 222 Irvin WP, Rice LW and Berkowitz RS. Advances in the management of endometrial adenocarcinoma. A  
review. *J Reprod Med.* 2002; 47(3): 173-89; discussion 89-90.
- 223 Berek js, hacker nf. Uterine cancer. In: Hacker nf, ed. Practical gynecologic oncology, 4th edition.  
Baltimore: Lippincott williams & wilkins, 2005. Pp 397-442.
- 224 Bonadona V, Bonaiti B, Olschwang S et al. Cancer risks associated with germline mutations in mlh1, msh2,  
and msh6 genes in lynch syndrome. *JAMA.* 2011; 305(22): 2304-10.
- 225 Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for the prevention of breast cancer: Current status  
of the national surgical adjuvant breast and bowel project p-1 study. *J Natl Cancer Inst.* 2005; 97(22):  
1652-62.
- 226 Braithwaite RS, Chlebowski RT, Lau J et al. Meta-analysis of vascular and neoplastic events associated with  
tamoxifen. *J Gen Intern Med.* 2003; 18(11): 937-47.
- 227 Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus  
stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: Atlas, a randomised trial.  
*Lancet.* 2013; 381(9869): 805-16.
- 228 Nccn clinical practice guidelines in oncology (nccn guidelines <sup>(r)</sup>) for uterine neoplasms. V.1.2021  
11/04/2021, (c) national comprehensive cancer network, inc., all rights reserved. *NATIONAL*  
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- 229 Endometrial (uterine) cancer. American cancer society cancer facts & figures 2016. Available at  
[www.Cancer.Org](http://www.Cancer.Org). Accessed september 24, 2018.
- 230 Tamoxifen and uterine cancer. The american college of obstetricians and gynecologists. Available at  
[www.Acog.Org](http://www.Acog.Org). Accessed september 24, 2018.
- 231 Committee on Practice B-G and Society of Gynecologic O. Acog practice bulletin no. 147: Lynch syndrome.  
*Obstet Gynecol.* 2014; 124(5): 1042-54.
- 232 Walker JL, Piedmonte MR, Spirtos NM et al. Laparoscopy compared with laparotomy for comprehensive  
surgical staging of uterine cancer: Gynecologic oncology group study lap2. *J Clin Oncol.* 2009; 27(32):  
5331-6.
- 233 Mourits MJ, Bijen CB, Arts HJ et al. Safety of laparoscopy versus laparotomy in early-stage endometrial  
cancer: A randomised trial. *Lancet Oncol.* 2010; 11(8): 763-71.
- 234 Boggess JF, Gehrig PA, Cantrell L et al. A comparative study of 3 surgical methods for hysterectomy with  
staging for endometrial cancer: Robotic assistance, laparoscopy, laparotomy. *Am J Obstet Gynecol.* 2008;  
199(4): 360 e1-9.
- 235 Kornblith AB, Huang HQ, Walker JL et al. Quality of life of patients with endometrial cancer undergoing  
laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: A  
gynecologic oncology group study. *J Clin Oncol.* 2009; 27(32): 5337-42.

- 236 Group AES, Blake P, Swart AM et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (mrc astec and ncic ctg en.5 randomised trials): Pooled trial results, systematic review, and meta-analysis. *Lancet*. 2009; 373(9658): 137-46.
- 237 Morrow CP, Bundy BN, Homesley HD et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage i and occult stage ii: A gynecologic oncology group study. *Gynecol Oncol*. 1990; 36(2): 166-71.
- 238 Hogberg T, Signorelli M, de Oliveira CF et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. *Eur J Cancer*. 2010; 46(13): 2422-31.
- 239 Randall ME, Filiaci VL, Muss H et al. Randomized phase iii trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A gynecologic oncology group study. *J Clin Oncol*. 2006; 24(1): 36-44.
- 240 Homesley HD, Filiaci V, Gibbons SK et al. A randomized phase iii trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A gynecologic oncology group study. *Gynecol Oncol*. 2009; 112(3): 543-52.
- 241 Miller D FV, Fleming G, et al. Randomized phase iii noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2012; 125: 771 [Abstract].
- 242 Thigpen JT, Brady MF, Alvarez RD et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: A dose-response study by the gynecologic oncology group. *J Clin Oncol*. 1999; 17(6): 1736-44.
- 243 Thigpen T, Brady MF, Homesley HD et al. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: A gynecologic oncology group study. *J Clin Oncol*. 2001; 19(2): 364-7.
- 244 Fleming GF, Brunetto VL, Cella D et al. Phase iii trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A gynecologic oncology group study. *J Clin Oncol*. 2004; 22(11): 2159-66.
- 245 Homesley HD, Filiaci V, Markman M et al. Phase iii trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: A gynecologic oncology group study. *J Clin Oncol*. 2007; 25(5): 526-31.
- 246 Creutzberg CL, van Putten WL, Koper PC et al. Survival after relapse in patients with endometrial cancer: Results from a randomized trial. *Gynecol Oncol*. 2003; 89(2): 201-9.
- 247 Mahdi H, Elshaikh MA, DeBenardo R et al. Impact of adjuvant chemotherapy and pelvic radiation on pattern of recurrence and outcome in stage i non-invasive uterine papillary serous carcinoma. A multi-institution study. *Gynecol Oncol*. 2015; 137(2): 239-44.
- 248 Fader AN, Roque DM, Siegel E et al. Randomized phase ii trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. *J Clin Oncol*. 2018; 36(20): 2044-51.
- 249 Fiorica JV, Brunetto VL, Hanjani P et al. Phase ii trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2004; 92(1): 10-4.
- 250 Slomovitz BM, Jiang Y, Yates MS et al. Phase ii study of everolimus and letrozole in patients with recurrent endometrial carcinoma. *J Clin Oncol*. 2015; 33(8): 930-6.
- 251 Whitney CW, Brunetto VL, Zaino RJ et al. Phase ii study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2004; 92(1): 4-9.
- 252 Rose PG, Brunetto VL, VanLe L et al. A phase ii trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2000; 78(2): 212-6.
- 253 Decruze SB and Green JA. Hormone therapy in advanced and recurrent endometrial cancer: A systematic review. *Int J Gynecol Cancer*. 2007; 17(5): 964-78.
- 254 George S, Feng Y, Manola J et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. *Cancer*. 2014; 120(5): 738-43.
- 255 Makker V CN, Herraes AC, Santin AD, Colomba E, Miller DS, Fujiwara K, Pignata S, Baron-Hay S, Ray-Coquard I, Shapira-Frommer R, Ushijima K, Sakata J, Yonemori K, Kim YM, Guerra EM, Sanli UA, McCormack MM, Smith AD, Keefe S, Bird S, Dutta L, Orlowski RJ, Lorusso D. Lenvatinib + pembrolizumab in patients with advanced endometrial cancer. *N Engl J Med*. 2022; 386(5): 437-48.

- 256 Nomura H, Aoki D, Takahashi F et al. Randomized phase ii study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: A japanese gynecologic oncology group study (jgog2041). *Ann Oncol*. 2011; 22(3): 636-42.
- 257 Wolfson AH, Brady MF, Rocereto T et al. A gynecologic oncology group randomized phase iii trial of whole abdominal irradiation (wai) vs. Cisplatin-ifosfamide and mesna (cim) as post-surgical therapy in stage i-iv carcinosarcoma (cs) of the uterus. *Gynecol Oncol*. 2007; 107(2): 177-85.
- 258 Rose PG, Ali S, Moslemi-Kebria M et al. Paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma. *Int J Gynecol Cancer*. 2017; 27(3): 452-58.
- 259 Aghajanian C, Sill MW, Darcy KM et al. Phase ii trial of bevacizumab in recurrent or persistent endometrial cancer: A gynecologic oncology group study. *J Clin Oncol*. 2011; 29(16): 2259-65.
- 260 Deppe G, Cohen CJ and Bruckner HW. Treatment of advanced endometrial adenocarcinoma with cis-dichlorodiammine platinum (ii) after intensive prior therapy. *Gynecol Oncol*. 1980; 10(1): 51-4.
- 261 Seski JC, Edwards CL, Herson J et al. Cisplatin chemotherapy for disseminated endometrial cancer. *Obstet Gynecol*. 1982; 59(2): 225-8.
- 262 Thigpen JT, Blessing JA, Homesley H et al. Phase ii trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 1989; 33(1): 68-70.
- 263 Burke TW, Munkarah A, Kavanagh JJ et al. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. *Gynecol Oncol*. 1993; 51(3): 397-400.
- 264 Green JB, 3rd, Green S, Alberts DS et al. Carboplatin therapy in advanced endometrial cancer. *Obstet Gynecol*. 1990; 75(4): 696-700.
- 265 van Wijk FH, Lhomme C, Bolis G et al. Phase ii study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the eortc gynaecological cancer group. *Eur J Cancer*. 2003; 39(1): 78-85.
- 266 Thigpen JT, Buchsbaum HJ, Mangan C et al. Phase ii trial of adriamycin in the treatment of advanced or recurrent endometrial carcinoma: A gynecologic oncology group study. *Cancer Treat Rep*. 1979; 63(1): 21-7.
- 267 Lincoln S, Blessing JA, Lee RB et al. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2003; 88(3): 277-81.
- 268 Muggia FM, Blessing JA, Sorosky J et al. Phase ii trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: A gynecologic oncology group study. *J Clin Oncol*. 2002; 20(9): 2360-4.
- 269 Oza AM, Elit L, Tsao MS et al. Phase ii study of temsirolimus in women with recurrent or metastatic endometrial cancer: A trial of the nci clinical trials group. *J Clin Oncol*. 2011; 29(24): 3278-85.
- 270 Alvarez EA, Brady WE, Walker JL et al. Phase ii trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2013; 129(1): 22-7.
- 271 Miller DS, Blessing JA, Lentz SS et al. A phase ii trial of topotecan in patients with advanced, persistent, or recurrent endometrial carcinoma: A gynecologic oncology group study. *Gynecol Oncol*. 2002; 87(3): 247-51.
- 272 Le DT, Durham JN, Smith KN et al. Mismatch repair deficiency predicts response of solid tumors to pd-1 blockade. *Science*. 2017; 357(6349): 409-13.
- 273 Dhani NC, Hirte HW, Wang L et al. Phase ii trial of cabozantinib in recurrent/metastatic endometrial cancer: A study of the princess margaret, chicago, and california consortia (nci9322/phl86). *Clin Cancer Res*. 2020; 26(11): 2477-86.
- 274 Konstantinopoulos PA, Luo W, Liu JF et al. Phase ii study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/persistent endometrial cancer. *J Clin Oncol*. 2019; 37(30): 2786-94.
- 275 Seer stat fact sheet: Endometrial cancer. Available at: <http://seer.Cancer.Gov/statfacts/html/corp.html>. Accessed june 24, 2020.
- 276 Pachman DR, Jones JM and Loprinzi CL. Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. *Int J Womens Health*. 2010; 2: 123-35.
- 277 Morrow PK, Mattair DN and Hortobagyi GN. Hot flashes: A review of pathophysiology and treatment modalities. *Oncologist*. 2011; 16(11): 1658-64.



# HEMATOPOIETIC CELL TRANSPLANTATION

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## LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current guidelines for patients undergoing hematopoietic cell transplantation (HCT).
2. Apply appropriate strategies to prevent and treat toxicity from chemotherapy agents employed in HCT conditioning regimens.
3. Create a plan for prevention and management of acute and chronic graft-versus-host disease (GVHD) using appropriate systemic and ancillary therapies.
4. Discuss short- and long-term treatment goals, including post-therapy and survivorship, with the patient undergoing HCT and his or her caregiver.

**Learner tip:** Information in **bold** and information contained in tables is considered more testable for the BCOP examination. Information in regular font is either background information or not supported by rigorous clinical trials or guidelines.

**Patient Case:** LC is a 56-year-old African American female with acute myeloid leukemia (AML) referred for transplantation evaluation in first remission after induction therapy. At diagnosis she had a complex karyotype and mutated FLT3-ITD. She has no siblings, and a donor registry search did not identify any matched unrelated donors. She has a good performance status and two biological children with no medical issues who are willing to donate stem cells.

**Question #1: What is the most appropriate post-remission therapy plan for LC?**

- A. High dose cytarabine
- B. Myeloablative autologous HCT
- C. Non-myeloablative umbilical cord blood allogeneic HCT
- D. Myeloablative haploidentical allogeneic HCT

**I. Background: rationale and indications for transplant<sup>1</sup>**

- A. Blood and marrow transplant or hematopoietic cell transplant (BMT/HCT): process by which normal hematopoiesis and/or lymphopoiesis is established by the infusion of an *ex vivo* pluripotent hematopoietic stem cell product from one individual to a different individual (allogeneic) or the same individual (autologous). Infusion of stem cells typically occurs following administration of chemotherapy and/or radiation to the recipient (conditioning or preparative regimen).
- B. Rationale for use of autologous HCT
  - 1. To allow dose escalation (intensification) of chemotherapy to overcome drug resistance by bridging hematopoietic failure with infusion of own cells. This only applies to malignancies with a dose intensity response.
    - a. Infusion of autologous stem cells serves to rescue the patient from myelosuppressive effects of high-dose chemotherapy
    - b. Other organ toxicities relating to high-dose therapy become dose-limiting
- C. Rationale for uses of allogeneic HCT
  - 1. To replace a missing or abnormal hematopoietic or lymphoid component in non-malignant disorders (i.e., aplastic anemia or immune disorders)
  - 2. To rescue the recipient from myeloablative therapy given for treatment of malignant disease (i.e., acute leukemias)
  - 3. To establish a graft-versus-leukemia (tumor) effect mediated by donor cell recognition and destruction or inhibition of residual host malignant cells (i.e., reduced intensity conditioning and chronic lymphocytic leukemia)
- D. Indications for transplant
  - 1. **American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT) published guidelines to describe the level of evidence for use of HCT for treatment of different diseases<sup>2</sup>**
    - a. Indications for transplant categorized as: standard of care (indication supported by high-quality clinical trial or observational study), standard of care

clinical evidence available, standard of care rare indication, developmental, or not generally recommended

2. Additional guidelines and evidence regarding the role of HCT exist for various malignancies, including multiple myeloma<sup>3,4</sup>, Hodgkin lymphoma<sup>5</sup>, and others, and can be found in many disease-specific National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

#### Standard of Care Indications and Other Guideline Recommendations for HCT in Adults<sup>2</sup>

Disease	Autologous	Allogeneic
Multiple myeloma <sup>3,4</sup>  Plasma cell disorders	<ul style="list-style-type: none"> <li>Initial response <ul style="list-style-type: none"> <li>Single, upfront transplant should be offered to transplant-eligible patients; delayed HCT may be considered in select patients</li> </ul> </li> <li>Sensitive relapse</li> <li>Amyloid light-chain amyloidosis</li> </ul>	<ul style="list-style-type: none"> <li>Sensitive relapse</li> <li>Plasma cell leukemia</li> </ul>
Hodgkin lymphoma <sup>5</sup>	<ul style="list-style-type: none"> <li>Sensitive primary refractory</li> <li>Sensitive first relapse</li> <li>Sensitive second or greater relapse</li> </ul>	<ul style="list-style-type: none"> <li>Sensitive first relapse</li> <li>Second or greater relapse</li> <li>Relapse after autologous transplant</li> </ul>
Diffuse large B-cell lymphoma <sup>6</sup>	<ul style="list-style-type: none"> <li>Sensitive primary refractory <ul style="list-style-type: none"> <li>Per NCCN® Guidelines, only for R/R &gt;12 months<sup>7</sup></li> </ul> </li> <li>Sensitive first relapse</li> <li>Sensitive second or greater relapse</li> </ul>	<ul style="list-style-type: none"> <li>Primary refractory (sensitive or refractory)</li> <li>First relapse (sensitive or refractory)</li> <li>Second or greater relapse</li> <li>Relapse after autologous transplant</li> </ul>
Follicular lymphoma <sup>8</sup>	<ul style="list-style-type: none"> <li>Sensitive primary refractory</li> <li>Sensitive first relapse</li> <li>Sensitive second or greater relapse</li> <li>Transformation to high grade lymphoma</li> </ul>	<ul style="list-style-type: none"> <li>Resistant primary refractory</li> <li>Resistant first relapse</li> <li>Second or greater relapse</li> <li>Relapse after autologous transplant</li> </ul>
Mantle cell lymphoma	<ul style="list-style-type: none"> <li>CR1 and PR1</li> <li>Sensitive primary refractory</li> <li>Sensitive first relapse</li> <li>Sensitive second or greater relapse</li> </ul>	<ul style="list-style-type: none"> <li>Sensitive primary refractory</li> <li>Sensitive first relapse</li> <li>Second or greater relapse</li> <li>Relapse after autologous transplant</li> </ul>
T cell lymphoma	<ul style="list-style-type: none"> <li>CR1 and PR1</li> <li>Sensitive primary refractory</li> <li>Sensitive first relapse</li> </ul>	<ul style="list-style-type: none"> <li>CR1 and PR1</li> <li>Sensitive primary refractory</li> <li>Sensitive first relapse</li> <li>Second or greater relapse</li> <li>Relapse after autologous transplant</li> <li>Relapsed cutaneous T cell lymphoma</li> </ul>
Chronic lymphocytic leukemia	<ul style="list-style-type: none"> <li>Transformation to high-grade lymphoma</li> </ul>	<ul style="list-style-type: none"> <li>T cell prolymphocytic leukemia</li> </ul>
Germ cell tumor	<ul style="list-style-type: none"> <li>Relapse / refractory</li> </ul>	N/A

Disease	Autologous	Allogeneic
Acute myeloid leukemia <sup>9</sup>	N/A	<ul style="list-style-type: none"> <li>• CR1, intermediate and high risk</li> <li>• CR2 and higher</li> <li>• CR1, therapy-related</li> <li>• Remission not achieved (preferably in clinical trial)</li> </ul>
Acute promyelocytic leukemia	<ul style="list-style-type: none"> <li>• CR2, in molecular remission</li> </ul>	<ul style="list-style-type: none"> <li>• CR2, not in molecular remission</li> </ul>
Acute lymphoblastic leukemia <sup>10</sup>	N/A	<ul style="list-style-type: none"> <li>• CR1, standard and high risk <ul style="list-style-type: none"> <li>• Per NCCN® Guidelines, greater consideration for transplant in those with high risk features<sup>11</sup></li> </ul> </li> <li>• Persistent or rising measurable residual disease<sup>11</sup></li> <li>• CR2 and higher</li> <li>• Remission not achieved (exploration of other options recommended as transplant has demonstrated high failure rates)</li> </ul>
Myelodysplastic syndrome <sup>12</sup>	N/A	<ul style="list-style-type: none"> <li>• Intermediate-2/high risk</li> <li>• CR1, therapy-related</li> </ul>
Chronic myeloid leukemia	N/A	<ul style="list-style-type: none"> <li>• Chronic phase 2+ (not as common in current era of TKI therapy)</li> <li>• Accelerated and blast phase</li> </ul>
Nonmalignant diseases	<ul style="list-style-type: none"> <li>• Systemic sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Severe aplastic anemia, new diagnosis</li> <li>• Severe aplastic anemia, relapse/refractory</li> <li>• Sickle cell disease</li> <li>• Hemophagocytic syndromes, refractory</li> </ul>

CR1 = first complete response, CR2 = second complete response, PR1 = first partial response, R/R = relapsed/refractory

## II. Pre-HCT Process

### A. Initial referral/consult to establish appropriateness of HCT

1. Guidelines for recommended timeline for HCT referral are jointly published by the National Marrow Donor Program and ASTCT: 2022 Referral Guidelines on Recommended Timing for Transplant Consultation, and are available at: <https://bethematchclinical.org/transplant-indications-and-outcomes/referral-timing-guidelines> (accessed July 1, 2022)
2. Transplant evaluation includes patient and disease factors such as: disease status/stage, chemosensitivity (especially for autologous HCT), age, performance status, organ

function, comorbidities, psychosocial fitness, and insurance evaluation. Several tools are available to assess risk/comorbidities.<sup>13,14</sup>

- B. Central line placement for: apheresis (if needed), administration of chemotherapy and other intravenous medications (i.e. supportive care medications), infusion of stem cells, and other blood products
- C. Donor search, evaluation, and selection (allogeneic HCT only)
  - 1. Multiple factors evaluated including but not limited to human leukocyte antigen (HLA) match, age (younger age preferred), sex (male donor preferred), parity of female donors (multiparous may increase risk for chronic GVHD), blood type and ABO compatibility, and cytomegalovirus serologic status
  - 2. HLA-matching and clinical implications for pharmacists<sup>15</sup>
    - a. Matching of donor and recipient based on HLA system which determines compatibility; matches are based on gene expression of alleles (variant copies of the same gene) for HLA -A, -B, -C, -DRB1, -DP and -DQ
    - b. **Preferred donor is a 10/10 matched related donor (MRD)**
    - c. **Contemporary matched unrelated donor (MUD) outcomes have shown improved overall survival (OS) and reduction in treatment related mortality (TRM), making it a suitable option when an MRD is not available**
      - 1) Improved outcomes attributed to better patient selection (transplant earlier in disease course or lower risk disease), better donor selection (allele level molecular typing), and improved transplant practices<sup>16</sup>
      - 2) Grade II – IV acute graft-versus-host disease (GVHD) remains higher in MUD vs. MRD<sup>17-20</sup>
    - d. **Alternative immunologic donor sources when MRD or MUD is not available include umbilical cord blood (UCB), haploidentical (haplo), and mismatched unrelated donor (MMUD)**
    - e. **Increased experience shows haploidentical transplant with post-transplant cyclophosphamide may be considered as first alternative option, even above an unrelated donor (URD), in absence of MRD<sup>21</sup>**
      - 1) The BMT CTN 1101 trial randomized 368 patients to UCB or haplo. Although the primary endpoint of 2-year PFS was not significantly different between groups, 2-year OS was improved with haplo transplant vs. UCB (57% vs. 46%, P=0.04) as well as 2-year non-relapse mortality (11% vs. 18%, P=0.04). There were no differences in rates of GVHD or relapse between groups.<sup>22</sup>
      - 2) In a 2019 systematic review/meta-analysis (all retrospective data), there was no difference in overall survival or relapse when comparing haplo vs. URD, and improved rates of non-relapse mortality and all types and grades of GVHD with haplo<sup>21</sup>

- 3) Another 2019 systematic review/meta-analysis comparing haplo with post-transplant cyclophosphamide vs. other donor types (MRD, MUD, MMUD) showed similar results<sup>23</sup>
- a) All-cause mortality: haplo had higher rates than MRD, similar rates to MUD, and lower rates than MMUD
  - b) Non-relapse mortality: haplo had higher rates than MRD, but improved rates compared to MUD and MMUD
  - c) Relapse: haplo had similar rates to MRD and MMUD, but higher rates than MUD
  - d) GVHD: haplo had lower rates of acute GVHD compared to MUD and MMUD, and lower rates of chronic GVHD compared to MRD and MUD, demonstrating the effectiveness of post-transplant cyclophosphamide for prevention of GVHD

# Alternative Donor Sources Compared to MRD/MUD<sup>14,21-26</sup>

	UCB	Haplo	MMUD
<b>Degree of match</b>	Match at least 4 of 6 HLA antigens at -A, -B, and -DRB1  If using 2 UCB units to achieve sufficient cell dose, they do not need to match each other	Match at half of HLA markers	One or more HLA markers do not match at -A, -B, -C, or -DRB1
<b>Advantages</b>	Lower risk of GVHD, including severe  Rapid time to acquisition  Less stringent HLA-matching requirements	Readily available donor and donor lymphocytes (most have parent, sibling, or child willing to donate)  Lower acquisition costs  Lower acute and chronic GVHD risk with post-transplant cyclophosphamide  Lower NRM than MUD, MMUD and UCB	Potentially increased availability of grafts, particularly for minorities  Lower risk of relapse seen in some studies  Similar engraftment time
<b>Disadvantages</b>	Delayed neutrophil and platelet engraftment and higher rate of graft failure  High risk of infection, particularly viral  Increased acquisition costs  Units for minorities may be difficult to find  No additional donor lymphocytes available  Higher NRM than MRD and haplo	High risk of infection  GVHD may be severe, especially without T cell depletion/post-transplant cyclophosphamide  Higher risk of graft rejection, particularly with T-cell depletion  Higher NRM than MRD	Higher risk of GVHD, which may be severe  Greater risk of graft failure  Additional donor lymphocytes may be difficult to obtain  Higher NRM than MRD

GVHD = graft-versus-host disease, Haplo = haploidentical donor, MMUD = mismatched unrelated donor, MRD = matched related donor, MUD = matched unrelated donor, NRM = non-relapse mortality, UCB = umbilical cord blood donor

**Patient Case, Question #1:**

**Answer: D. Myeloablative haploidentical allogeneic HCT.**

LC has poor risk AML based on her unfavorable cytogenetics and molecular abnormality and a good performance status. A myeloablative matched sibling or alternative donor allogeneic HCT in first remission is the preferred post-remission strategy for physiologically younger, poor risk AML patients per the NCCN Guidelines<sup>®</sup>.<sup>27</sup> Allogeneic HCT has demonstrated improved survival over autologous HCT and chemotherapy alone for poor risk AML. Although LC does not have a matched sibling or unrelated donor, a haploidentical donor from a child is an acceptable alternative. A recent randomized trial demonstrated improved overall survival with haploidentical transplant compared to umbilical cord blood transplant.

3. Comparison of anatomic stem cell source in allogeneic HCT
  - a. **Peripheral blood (PB) grafts have largely replaced bone marrow due to ease of collection, faster engraftment times, and lower risk of graft failure, but do carry a higher risk of chronic GVHD compared to bone marrow (BM)**<sup>14</sup>

**Comparison of peripheral blood (PB) vs. bone marrow (BM) in allogeneic transplant types**

	<b>MRD</b> Meta-analysis of 1,111 patients from 9 randomized trials <sup>28</sup>	<b>MUD</b> N= 551 at 48 centers, prospective, randomized trial <sup>29</sup>
<b>Engraftment</b>	<b>Faster with PB</b> <ul style="list-style-type: none"> <li>Median time to ANC &gt; 0.5 x 10<sup>9</sup>/L was 14 (PB) vs. 21 (BM) days, P &lt; 0.00001</li> <li>Median time to platelets &gt; 20 x 10<sup>9</sup>/L was 14 (PB) vs. 22 (BM) days, P &lt; 0.00001</li> </ul>	<b>Faster with PB</b> <ul style="list-style-type: none"> <li>Median time to neutrophil engraftment 5 days shorter with PB (P &lt; 0.001)</li> <li>Median time to platelet engraftment 7 days shorter with PB (P &lt; 0.001)</li> </ul>
<b>aGVHD</b>	<b>No difference in overall incidence of aGVHD grades I – IV between groups</b> <ul style="list-style-type: none"> <li>54% PB vs. 53% BM, P = 0.49</li> </ul>	<b>No difference in overall incidence of aGVHD grades II – IV between groups</b> <ul style="list-style-type: none"> <li>Grade II-IV: 47% PB vs. 56% BM</li> <li>Grade III-IV: 16% PB vs. 14% BM</li> </ul>
<b>cGVHD</b>	<b>Significant increase in the odds of developing both extensive stage (OR = 1.89) and overall cGVHD (any stage; OR 1.92) in PB recipients</b> <ul style="list-style-type: none"> <li>At 5 years 51% PB vs. 35% BM recipients developed extensive cGVHD</li> <li>73% PB vs. 56% BM developed any stage cGVHD (P = 0.001)</li> </ul>	<b>Less cGVHD in BM</b> <ul style="list-style-type: none"> <li><b>At 2 years 53% PB vs. 41% BM, p=0.01</b></li> <li>Among patients alive at 2 years, 57% of PB remained on immunosuppression vs. 37% of BM patients, P = 0.03</li> </ul>
<b>Relapse and non-relapse mortality (NRM)</b>	<b>PB associated with a reduction in relapse</b> <ul style="list-style-type: none"> <li>At 5 years 23% vs. 32%, P = 0.01</li> </ul> <b>NRM was not different between PB and BM with 30% in both arms</b>	28% relapse rate in both groups  2-year NRM no difference, rate 26% PB vs. 27% BM
<b>Survival</b>	<b>No significant differences in OS between PB and BM in all patients.</b> <b>PB was associated with a higher 5-year OS in the subgroup with late stage disease, but not in patients with early stage disease</b>	<b>2-year OS no difference, rate 51% PB vs. 46% BM, P = 0.29</b>
<b>Graft failure</b>	<b>NR</b>	<b>3% PB vs. 9% BM, P = 0.002</b>



D. Collection of stem cells

1. Stem cell targets and doses<sup>14,30</sup>

- a. **Minimum recommended dose is  $2 \times 10^6$  CD34<sup>+</sup> cells/kg of recipient body weight per transplant**
- b. **Ideal recommended target is between  $2-5 \times 10^6$  CD34<sup>+</sup> cells/kg, although consideration should be given to balance the number of apheresis sessions needed to attain the target collection and number of transplants planned.**  
Compared with doses  $< 3 \times 10^6$  CD34<sup>+</sup> cells/kg, CD34<sup>+</sup> cell doses of  $5 \times 10^6$  CD34<sup>+</sup>/kg are associated with improved platelet and neutrophil recovery and less resource utilization if the higher target can be collected in a few apheresis sessions.

2. Stem cell collection methods

**Comparison of Different Anatomic Stem Cell Collection Processes<sup>31</sup>**

<b>Bone marrow (BM)</b>	<ul style="list-style-type: none"><li>• Procured through bone marrow harvest through multiple needle aspirations into the posterior iliac crest</li><li>• Obtained under general or regional anesthesia</li><li>• Volume typically = 10 - 20 mL/kg of recipient weight to achieve final total nucleated cell (TNC) dose of at least <math>2 - 4 \times 10^8</math>/kg (maximum volume 1500 mL)</li><li>• Risks minimal; serious adverse events reported in <math>&lt;0.3\%</math></li><li>• Has largely been replaced by peripheral blood collection in adults (see comment above)</li></ul>
<b>Umbilical cord blood (UCB)</b>	<ul style="list-style-type: none"><li>• Pregnant women are recruited as potential cord blood donors prior to delivery</li><li>• Consent of the mother is obtained for the collection of the cord blood sample, processing and freezing the cord unit, maternal infectious disease testing, and for the storage of both maternal and cord blood samples for possible future genetic and infectious disease testing</li></ul>
<b>Peripheral blood stem cell (PBSC)</b>	<ul style="list-style-type: none"><li>• Collected via one or multiple apheresis procedures; usually requires adequate central line for autologous collections and venous access for allogeneic donors</li><li>• Has largely replaced BM harvest in adults due to ease of collection, lack of anesthesia requirement, more rapid engraftment rates and lower graft failure</li><li>• Volume processed typically 3 - 5 times the blood volume (10 - 30 L)</li><li>• Minimal risks: complications include hypocalcemia, fatigue, nausea/vomiting, post procedure anemia, thrombocytopenia, hypotension due to fluid shifts, thrombosis of central line, bleeding; growth factors used may rarely lead to splenic enlargement and/or rupture</li><li>• Typically, a relatively low number of stem cells exist in the peripheral blood; thus, mobilization of stem cells from bone marrow to peripheral blood is required (see Mobilization strategies below)</li><li>• Goal of mobilization is to collect adequate numbers of stem cells cost-effectively with minimization of apheresis sessions and avoidance of mobilization-related complications</li></ul>

3. Mobilization strategies for PBSC collection

### Comparison of Mobilization Strategies for PBSC collection<sup>30</sup>

<b>Cytokine mobilization</b>	<ul style="list-style-type: none"> <li>Utilizes granulocyte-colony-stimulating-factor (GCSF) alone such as filgrastim, tbo-filgrastim, or approved biosimilar<sup>32</sup></li> <li>Cost-effective with predictable collection scheduling</li> <li>5-38% failure rate of minimum number of CD34<sup>+</sup> cells to proceed</li> <li>Appropriate strategy for healthy donors for allogeneic collection</li> <li>GCSF preferred over GM-CSF as use of GM-CSF has demonstrated decreased number of stem cells collected in addition to longer post-transplant recovery and increased resources such as transfusion and antibiotic support</li> </ul>
<b>Chemo-mobilization</b>	<ul style="list-style-type: none"> <li>Utilizes chemotherapy followed by GCSF administration</li> <li>May be stand-alone or part of induction or salvage therapy for autologous patients</li> <li>Shown to generally produce greater CD34<sup>+</sup> cell yield than GCSF alone</li> <li>Similar failure rates of GCSF alone, but can have increased costs and toxicity and less predictable scheduling</li> </ul>
<b>Plerixafor plus GCSF</b>	<ul style="list-style-type: none"> <li>Upfront plerixafor has confirmed higher CD34<sup>+</sup> cell yields, lower mobilization failure rates (0-15%), and fewer days of apheresis compared with GCSF alone, but has increased drug acquisition costs</li> <li>Preemptive plerixafor is a commonly employed strategy to optimize costs and resources that involves the addition of plerixafor only in patients identified as poor mobilizers after initiation of GCSF, but before starting apheresis based on circulating peripheral blood CD34<sup>+</sup> cell count; this has similarly shown low mobilization failure rates of &lt;10%</li> <li>Well-tolerated, most common side effect is diarrhea (30-40%)</li> <li>Dose adjustment recommended for estimated creatinine clearance ≤50 mL/min</li> <li>Hazardous agent per NIOSH (group 3)</li> <li>Long-term observational follow-up study of two phase III plerixafor trials showed no difference in 5-year OS or PFS for MM and NHL patients who received plerixafor compared to placebo<sup>33</sup></li> </ul>

#### E. Stem cell mobilization regimens in autologous HCT patients<sup>34,35</sup>

1. Goal is to increase the number of circulating stem cells to facilitate peripheral blood stem cell harvesting, thus enabling patients to undergo autologous HCT
2. Factors that negatively influence patient's ability to mobilize:<sup>30,34,36</sup>
  - a. Tumor infiltration in bone marrow
  - b. Fibrotic bone marrow
  - c. History of pelvic or abdominal irradiation
  - d. Bone marrow hypocellularity
  - e. Diagnosis of non-Hodgkin lymphoma
  - f. Prior exposure to chemotherapy including alkylating agents (melphalan, chlorambucil, busulfan)<sup>37</sup>, nitrosoureas (carmustine), fludarabine, imatinib, and lenalidomide (especially >4-6 cycles)
  - g. Older age (>60-70) and low baseline platelet count (i.e., < 150 x 10<sup>9</sup>/L)

- h. Number of prior regimens (>6), duration of exposure to chemotherapy (> 12 months), short interval since last chemotherapy (<2-6 months)
  - i. Infection or fever during mobilization process, iron overload, diabetes
3. **Mobilization guideline recommendations for autologous peripheral blood stem cell transplant (PBSCT)<sup>30,32,38</sup>**
- a. **Multiple myeloma<sup>30</sup>**
    - 1) Single agent GCSF 10-16 mcg/kg/day, but limited to patients with no more than 1 previous line of chemotherapy, no prior melphalan, and no more than 4 cycles of lenalidomide
    - 2) Preemptive plerixafor for patients with low peripheral blood CD34<sup>+</sup> counts following 4-5 days of filgrastim
    - 3) Prior therapy with lenalidomide (or other novel agents known to impair mobilization)
      - a) Collect PBSC after 2-4 cycles of lenalidomide when possible
      - b) Wait 2-4 weeks after last lenalidomide dose before start of apheresis
      - c) Mobilization with GCSF alone after 4-6 cycles of lenalidomide is associated with a higher failure rate and should be avoided
      - d) Insufficient data on whether to recommend GCSF + plerixafor vs. GCSF + chemotherapy- both have been shown to be effective
  - b. **Non-Hodgkin lymphoma<sup>30</sup>**
    - 1) Single agent GCSF 10-16 mcg/kg/day but limited to patients with low risk for mobilization failure. It may be associated with a higher failure than other disease states, but it has low toxicity and is easier to schedule than chemotherapy-based mobilization.
    - 2) Preemptive plerixafor for patients with low peripheral blood CD34<sup>+</sup> counts following 4-5 days of filgrastim grants successful collection in majority of cases.
    - 3) Chemotherapy based mobilization, either incorporated into the initial 3-6 cycles of planned chemotherapy or as part of a salvage regimen is appropriate and effective (consider in those patients with residual disease)
  - c. **General recommendations for all autologous patients<sup>14,14,30</sup>**
    - 1) **Chemotherapy + GCSF**
      - a) If given as stand-alone therapy and not needed for disease control, it is associated with higher costs (hospitalization, transfusions, and antibiotics) and toxicities than GCSF alone

- b) **Consider limiting stand-alone chemotherapy to those who have not responded optimally to salvage therapy or failed other mobilization strategies**
  - c) **Cyclophosphamide typically dosed 1.5 – 3 gm/m<sup>2</sup>; data to support cyclophosphamide doses above 4 gm/m<sup>2</sup> is limited**
- 2) **Upfront plerixafor + GCSF is a suitable initial therapy option for all patients; however, product cost has limited its universal implementation for all patients at all centers**
  - a) **Consider if:**
    - i. **The goal is the highest possible CD34<sup>+</sup> yield**
    - ii. **Real-time CD34<sup>+</sup> cell counts are not available**
    - iii. **Fewer apheresis days is the top priority**
  - b) **Preemptive use of plerixafor based on peripheral blood CD34<sup>+</sup> measure is reasonable in other cases**
  - c) Plerixafor may be cost effective in patients with DLBCL because it enables more patients to undergo PBSCT
- 3) NCCN Guidelines<sup>®</sup> also list GCSF + disease-target chemotherapy ± plerixafor, GM-CSF + cyclophosphamide ± plerixafor and pegfilgrastim + plerixafor as options for mobilization regimens<sup>1414</sup>
- d. **Prevention of stem cell mobilization failure<sup>30</sup>**
  - 1) Monitoring pre-apheresis peripheral blood CD34<sup>+</sup> cell count is recommended to identify poor mobilizers prior to failure
  - 2) No phase III trials support the recommendation, but preemptive plerixafor use based on peripheral blood CD34<sup>+</sup> cell count may balance mobilization failure and resource utilization
  - 3) Upfront plerixafor + GCSF is a reliable method to prevent mobilization failure and need for remobilization
- e. **Recommendations for remobilization<sup>30</sup>**
  - 1) **Avoid regimens with only CSFs**
  - 2) **Plerixafor should be added if it was not used in the initial mobilization regimen. This has shown successful remobilization in ~70% of patients with a previous failed mobilization attempt. It may also be effective in patients who previously failed a plerixafor-containing regimen. Plerixafor + chemotherapy + GCSF may be effective, although data is limited.**
  - 3) **Chemotherapy + GCSF is an acceptable remobilization strategy for patients who failed a GCSF monotherapy regimen.**

- 4) Bone marrow harvest is a third line option for patients ineligible for mobilization clinical trials and for whom the benefits of autologous HCT outweigh the drawbacks of a bone marrow graft source.

F. Mobilization of healthy donors for allogeneic PBSCT<sup>35 1414</sup>

1. **GCSF (10 mcg/kg/day for 4 - 5 days)** with apheresis to begin on fifth day of GCSF; effective in 95% of healthy donors
2. GCSF preferred over GM-CSF as the latter mobilizes fewer CD34<sup>+</sup> cells and donors require more leukapheresis sessions for adequate PBSC collection
3. Typically requires 1-2 apheresis procedures; target CD34<sup>+</sup> cell dose ranges from 2 - 3 x 10<sup>6</sup>/kg of the recipient body weight to 8 x 10<sup>6</sup>/kg; doses above 8 x 10<sup>6</sup>/kg may increase risk for chronic GVHD
4. Generally well-tolerated by donor; reported adverse effects including bone pain, fever, headaches, myalgia, fatigue, transient thrombocytopenia
5. Serious adverse events occur in 0.6% of healthy donors with filgrastim for PBSC collection<sup>39</sup>

G. Processing and storage of stem cells

1. In autologous setting, processed then cryopreserved (frozen) in dimethylsulfoxide (DMSO)
2. In allogeneic setting, may be infused fresh or cryopreserved in DMSO and then thawed for infusion
3. Red cell depletion for ABO incompatibility between donor and recipient (allogeneic HCT only)
4. May be frozen for years and maintain viability

**Patient Case (continued):** LC is a 56-year-old African American female with AML in first remission who is planning to undergo a haploidentical allogeneic HCT. She is scheduled to receive myeloablative fludarabine and total body irradiation (1200 cGy) as conditioning prior to HCT.

**Question #2: Which of the following should LC receive to prevent toxicity from her conditioning regimen?**

- A. Palifermin
- B. Levetiracetam
- C. Ursodiol
- D. Twice daily skin cleaning

H. Conditioning regimen (preparative regimen)

1. **Myeloablative, nonmyeloablative, and reduced-intensity conditioning definitions<sup>14,40</sup>**
  - a. See example regimens of each intensity in tables below

### Comparison of Different Conditioning Regimen Intensities

Conditioning Regimen Intensity	Cytopenia Risk	Stem Cell Support	Transplant Type	Comments
Myeloablative (MA)	Irreversible	Mandatory	All autologous Some allogeneic	<ul style="list-style-type: none"> <li>Generally includes high doses of one or more alkylating agents or high dose total body irradiation (TBI)</li> </ul>
Reduced intensity (RI)	Variable duration	“Required”	Some allogeneic	<ul style="list-style-type: none"> <li>Includes regimens that do not fit the criteria for MA or NMA</li> <li>Generally accepted criteria for RI regimens include<sup>40</sup>: <ul style="list-style-type: none"> <li>&lt; 500 cGy TBI as single fraction or &lt; 800 cGy fractionated</li> <li>&lt; 9 mg/kg oral busulfan or intravenous equivalent</li> <li>&lt; 140 mg/m<sup>2</sup> melphalan (CIBMTR uses 150 mg/m<sup>2</sup>)</li> <li>&lt; 10 mg/kg thiotepa</li> </ul> </li> </ul>
Nonmyeloablative (NMA)	Minimal	Not required	Some allogeneic	<ul style="list-style-type: none"> <li>Rely on pre- and post-HCT immunosuppression to allow donor engraftment</li> <li>Generally contains low dose TBI (≤200 cGy) or total lymphoid irradiation and immunosuppressive chemotherapy (fludarabine, cyclophosphamide)</li> </ul>

## 2. Selection of conditioning regimen for HCT<sup>14,41</sup>

- a. **Regimen selection guided by several factors: type of transplant, disease state, disease status at time of transplant (e.g., measurable residual disease), patient comorbidities, chronologic and physiologic age of patient, performance status**
- b. **Multiple regimens under investigation and use; limited data to support one standard of care regimen**
- c. **General selection principles for allogeneic HCT**
  - 1) **Myeloablative regimens should be selected for patients thought able to tolerate (younger age, low comorbidities) with AML, MDS, ALL, CML**
  - 2) **Total body irradiation-based regimens preferred for ALL**
  - 3) **Reduced intensity/nonmyeloablative regimens may be selected for older age or patients with significant comorbidities**

- 4) **Reduced intensity/nonmyeloablative regimens may be preferred for CLL, NHL, HL, plasma cell disorders, or those with history of prior transplant**
3. Role of nonmyeloablative (NMA) and reduced intensity (RI) conditioning in allogeneic HCT<sup>41</sup>
    - a. Designed as an alternative to MA allogeneic HCT in patients who do not qualify for conventional allogeneic HCT due to age or co-morbidity<sup>42</sup>
    - b. Based on the premise that a main therapeutic component of allogeneic HCT may be due to T-cell mediated graft-versus-tumor effects rather than the physical eradication of tumor cells by high-dose myeloablative preparative regimens prior to stem cell infusion
    - c. NMA involves minimization of anti-tumor intensity and maximization of immunosuppression
    - d. Engraftment of donor hematopoietic cells is achieved by suppression of host immunity rather than myeloablation. NMA is associated with a higher risk of graft rejection compared with MA conditioning regimens.<sup>42</sup>
    - e. A successful outcome may only require partial or mixed, but stable, lympho- or hematopoietic engraftment (chimerism)
    - f. Post-transplant immune manipulation may be used to optimize immune recovery and create a mixed chimeric state. This induces tolerance to prevent graft rejection and GVHD. An example of post-transplant immune manipulation is donor lymphocyte infusion (DLI). Full donor T-cell chimerism is strongly correlated with a reduced risk of disease progression or relapse.<sup>43</sup>
    - g. NMA/RI aim to exploit graft-versus-leukemia or graft-versus-tumor (GVT) potential of HCT while reducing toxicity
      - 1) GVT sensitivity based on disease response to DLI<sup>44</sup>
        - a) Sensitive: chronic lymphocytic leukemia (CLL), low-grade lymphoma, chronic myeloid leukemia (CML), and mantle cell lymphoma
        - b) Intermediate: AML, intermediate grade lymphoma, multiple myeloma (MM), Hodgkin lymphoma
        - c) Insensitive: acute lymphoblastic leukemia (ALL), high-grade lymphoma
      - 2) GVT sensitivity based on correlation of increased GVHD with improved relapse free survival:<sup>45</sup>
        - a) Sensitive: CML, myeloproliferative neoplasms, ALL
        - b) Intermediate: MDS and lymphoproliferative disorders
        - c) Insensitive: AML and plasma cell disorders

4. MA vs. RI/NMA allogeneic HCT

- a. There are several comparisons of different intensities published with some discordant findings, therefore selection remains a patient-specific decision based on factors listed above.

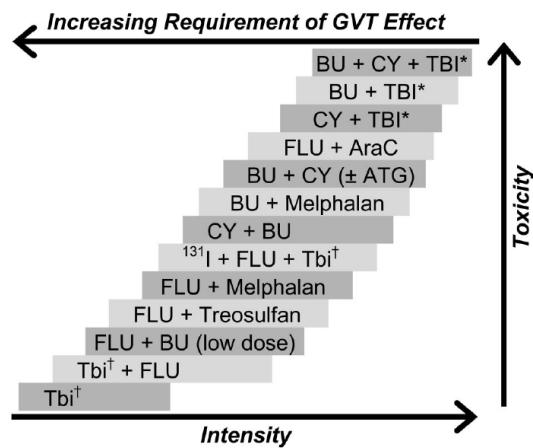
**Key Comparisons of MA vs. RI Regimens**

Study design	Population	Survival	Relapse	Comments
Randomized, phase III trial (BMT CTN 0901 Scott BL et al.) <sup>46,47</sup> [MAvRIC trial]	N = 272  AML or MDS with MRD or MUD donors	<b>4-year OS:</b> <b>65% in MA vs. 49% in RI</b>  <b>P = 0.02</b>	<b>4-year RFS:</b> <b>58% in MA vs. 34% in RI</b>  <b>P &lt; 0.001</b>	Closed early due to high relapse incidence in RI. <b>OS and RFS benefit in MA; MA conditioning remains the standard of care for AML patients eligible to receive.</b>
Randomized, phase III trial (Kroger N et al.) <sup>48</sup>	N = 129  MDS or secondary AML	<b>2-year OS:</b> <b>63% in MA vs. 76% in RI</b>  <b>P = 0.08</b>	<b>2-year RFS:</b> <b>58% in MA vs. 62% in RI</b>  <b>P = 0.58</b>	Toxicity was similar except more infections in MA arm. <b>RI may be reasonable alternative in MDS.</b>
Observational retrospective CIBMTR study (Bejanyan N et al.) <sup>49</sup>	N = 4387  AML or MDS, further classified as low/intermediate or high/very high risk groups	<b>3-year DFS:</b> <b>Low/intermediate risk:</b> <b>48% in MA vs. 42% in RI</b> <b>P &lt; .001</b>  High/very high risk: 27% in MA vs. 26% in RI P = 0.24	<b>3-year relapse probability:</b> <b>Low/intermediate risk:</b> <b>28% in MA vs. 40% in RI</b> <b>P &lt; .001</b>  High/very high risk: 47% in MA vs. 52% in RI P = 0.002	<b>For low/intermediate risk disease, RI was associated with lower NRM but higher relapse and overall poorer DFS, supporting MA for this population if clinically appropriate.</b>  <b>For high/very high risk disease, there was no difference in DFS with RI vs. MA regimens.</b>

*CIBMTR = Center for International Blood and Marrow Transplant Research; DFS = disease-free survival; NRM = non-relapse mortality; RFS = relapse-free survival*



# Selected Conditioning Regimens of Differing Dose Intensities<sup>50</sup>



BU = busulfan; CY = cyclophosphamide; TBI = total body irradiation; FLU= fludarabine; AraC=cytarabine; ATG=anti-thymocyte globulin; <sup>131</sup>I= Tositumomab

\*"High-dose" TBI (800-1320 cGy) †"Low-dose" TBI (200-400 cGy)

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### Selected Myeloablative Conditioning Regimens

MYELOABLATIVE (MA) CONDITIONING			
PREPARATIVE REGIMEN	REGIMEN	DAYS	HCT TYPE/DISEASE
<b>BEAM</b> <sup>51</sup> BCNU (carmustine) Etoposide Ara-C (cytarabine) Melphalan	300 mg/m <sup>2</sup> IV x 1 dose 200 mg/m <sup>2</sup> IV daily x 4 days 200 mg/m <sup>2</sup> IV Q12h x 4 days 140 mg/m <sup>2</sup> IV x 1 dose	-6 -5, -4, -3, -2 -5, -4, -3, -2 -1	Autologous or allogeneic NHL/HD
<b>BuCy (BUCY 2)</b> <sup>52</sup> Busulfan Cyclophosphamide	3.2 mg/kg IV daily x 4 days 60 mg/kg IV daily x 2 days	-7 to -4 -3, -2	Allogeneic > autologous Hematologic malignancies
<b>BuFlu</b> <sup>53</sup> Busulfan Fludarabine	130 mg/m <sup>2</sup> IV daily x 4 days 40 mg/m <sup>2</sup> IV daily x 4 days	-6, -5, -4, -3 -6, -5, -4, -3	Allogeneic Hematological malignancies
<b>Carmustine/thiotepa</b> <sup>54</sup> Carmustine Thiotepa	400mg/m <sup>2</sup> IV x 1 dose 5 mg/kg IV daily or twice daily x 2 days	-6 -5, -4	Autologous Lymphoma with CNS disease
<b>CE</b> <sup>55</sup> Carboplatin Etoposide	700 mg/m <sup>2</sup> IV daily x 3 days 750 mg/m <sup>2</sup> IV daily x 3 days	-5, -4, -3 -5, -4, -3	Autologous Germ cell tumor
<b>Cy/TBI</b> <sup>56</sup> Cyclophosphamide TBI	60 mg/kg IV daily x 3 days 200-220 cGy BID	-5, -4 -3, -2, -1	Allogeneic Hematological malignancies
<b>Flu/TBI</b> <sup>57</sup> Fludarabine TBI	30 mg/m <sup>2</sup> IV daily x 3 days 150 cGy BID	-7, -6, -5 -4, -3, -2, -1	Allogeneic Haploidentical
<b>Flu/Cy/TBI</b> <sup>58</sup> Cyclophosphamide Fludarabine TBI	60 mg/kg IV daily x 2 days 25 mg/m <sup>2</sup> IV daily x 3 days 220 cGy BID	-5, -4 -6, -5, -4 -3, -2, -1	Allogeneic Cord Blood
<b>Melphalan</b> <sup>59</sup> Melphalan	140 - 200 mg/m <sup>2</sup> IV x 1 dose	Day -2 or -1 or split between both in 2 doses	Autologous Multiple Myeloma Amyloid

*NOTE: the accuracy of the doses listed in this table cannot be guaranteed. Always check drug and doses against the primary reference before prescribing chemotherapy.*

### Selected Nonmyeloablative and Reduced Intensity Conditioning Regimens

REDUCED INTENSITY (RI) CONDITIONING			
PREPARATIVE REGIMEN	REGIMEN	DAYS	HCT TYPE/DISEASE
<b>Flu/Bu<sup>60</sup></b> Fludarabine Busulfan	30 mg/m <sup>2</sup> IV daily x 6 days 3.2 mg/kg IV daily x 2 days	-10 to -5 -6, -5	Allogeneic Hematological malignancies
<b>Flu/Cy<sup>61</sup></b> Cyclophosphamide Fludarabine	60 mg/kg IV daily x 2 days 25 mg/m <sup>2</sup> IV daily x 5 days	-7, -6 -5, -4, -3, -2, -1	Allogeneic Hematological malignancies Aplastic anemia
<b>Flu/Cy/TBI<sup>62</sup></b> Cyclophosphamide Fludarabine ± TBI	50 mg/kg IV x 1 dose 40 mg/m <sup>2</sup> IV daily x 5 days 200 cGy	-6 -6, -5, -4, -3, -2 -1	Allogeneic Cord Blood
<b>Flu/Cy/Thiotepa/TBI<sup>63</sup></b> Cyclophosphamide Fludarabine Thiotepa TBI	50 mg/kg IV x 1 dose 30 mg/m <sup>2</sup> IV daily x 5 days 5 mg/kg/day IV daily x 2 days 200 cGy x 2 days	-6 -6, -5, -4, -3, -2 -5, -4 -2, -1	Allogeneic Cord Blood
<b>Flu/Mel<sup>64</sup></b> Fludarabine Melphalan	25 – 30 mg/m <sup>2</sup> IV daily x 4 - 5 days 100 – 180 mg/m <sup>2</sup> IV daily x 1 day	-6 to -2 (or -1) -2	Allogeneic Hematological malignancies
NONMYELOABLATIVE (NMA)			
PREPARATIVE REGIMEN	REGIMEN	DAYS	HCT TYPE/DISEASE
<b>Flu/TBI<sup>65</sup></b> TBI ± Fludarabine	200 cGy x 1 dose 25-30 mg/m <sup>2</sup> IV daily x 3 days	0 -4, -3, -2	Allogeneic CLL, Hematological malignancies

*NOTE: the accuracy of the doses listed in this table cannot be guaranteed. Always check drug and doses against the primary reference before prescribing chemotherapy.*

5. **Toxicities of chemotherapy agents used in conditioning regimens**
  - a. **The most severe toxicity of chemotherapy used in myeloablative regimens is myelosuppression (which is overcome by re-infusion of stem cells); the next most severe toxicity is the dose limiting toxicity.** HCT allows dose intensification of chemotherapy by 3-10-fold over standard doses.
  - b. Overlapping toxicities in a drug regimen should be avoided
6. Dosing in hepatic impairment<sup>66</sup>
  - a. Standards or dosing guidelines are unable to be made because evidence is unavailable
  - b. Current published literature reviewed in publication by Bodge et al.<sup>66</sup>
7. Dosing in chronic kidney disease<sup>66</sup>

- a. Standards or dosing guidelines are unable to be made because evidence is unavailable
  - b. Current published literature reviewed in publication by Bodge et al.<sup>66</sup>
- 8. Dosing in obesity<sup>67</sup>
  - a. Standards or dosing guidelines are unable to be made because evidence is unavailable, but several publications available to guide dose modification<sup>67,68</sup>
- I. Chemotherapy used for HCT conditioning<sup>69</sup> (*\*note this is not all inclusive and is intended to highlight aspects of chemotherapy that are noteworthy in HCT*)
  - 1. Busulfan
    - a. **Dose limiting toxicities are hepatotoxicity, mucositis, and pulmonary fibrosis.** Doses used in transplant can be up to 7 fold dose increase over standard doses.<sup>70</sup>
    - b. **Toxicity is dose related. Many centers perform pharmacokinetic dosing based on area under the curve (AUC), especially with myeloablative doses**
      - 1) **Validated pharmacokinetic modeling tools are recommended to personalize doses following the initial high dose of busulfan; test dose strategies not currently recommended<sup>71</sup>**
      - 2) **To promote safe clinical use, accurate interpretation of busulfan pharmacokinetics, and facilitation of future research efforts, 10 professional societies endorsed the use of a single, harmonized busulfan plasma exposure unit to be expressed in AUC (mg x h/L) to be utilized beginning 2021.<sup>72</sup>**
      - 3) **Study in CML with every 6 hour IV busulfan found the relapse rate increased with an AUC below 3.9 mg x h/L (950  $\mu$ Molar x min) and the incidence of veno-occlusive disease of the liver, gastrointestinal toxicity, and acute GVHD increased above 6.2 mg x h/L (1500  $\mu$ Molar x min).<sup>73</sup> Other studies confirm every 6 hour oral busulfan AUC > 6.2 mg x h/L (1500  $\mu$ Molar x min) increases the risk of veno-occlusive disease (VOD).<sup>74-76</sup>**
      - 4) **Intravenous busulfan has led to a significant decrease in VOD and pharmacokinetic (PK) variability – even in the absence of therapeutic drug monitoring.<sup>52,77</sup> Although no reported differences in overall survival between formulations, intravenous is commonly preferred due to convenience and concerns for inpatient variability.<sup>71</sup>**
      - 5) **Once daily intravenous busulfan is a commonly used dosing strategy, with a daily goal AUC of approximately 14.8 – 24.6 mg x h/L (3600-6000  $\mu$ Molar x min).<sup>78</sup> PK study comparing AUC of 24.6 mg x h/L (6000  $\mu$ Molar x min) x 4 days vs. 130 mg/m<sup>2</sup>/day x 4 days combined with fludarabine 40 mg/m<sup>2</sup>/day x 4 days showed improvement in progression free survival (primary endpoint), overall survival, and a trend for reduced non-relapse mortality in patients with AML/MDS.<sup>79</sup>**

- 6) **The need for therapeutic drug monitoring (TDM) in reduced intensity regimens (total busulfan dose < 9 mg/kg/PO or IV equivalent) is less well established<sup>71</sup>**
- c. **Busulfan causes seizures in up to 10% of patients if given no pharmacologic prophylaxis, therefore seizure prophylaxis is routinely provided<sup>80</sup>**
  - 1) Phenytoin was historically the standard of care and was studied in most of the studies of busulfan pharmacokinetics
  - 2) Many centers utilize alternatives such as levetiracetam or benzodiazepines in an attempt to avoid phenytoin induction of chemotherapy metabolism<sup>80</sup>
- d. **Use with caution in patients with significant pulmonary dysfunction<sup>14</sup>**
- e. Hepatic elimination- enzymatic conjugation with glutathione<sup>70</sup>
- f. Drug interactions<sup>81</sup>
  - 1) Avoid acetaminophen and metronidazole 72 hours before and after busulfan, since use leads to increased busulfan levels
  - 2) Itraconazole, voriconazole, and posaconazole may increase busulfan levels (note PK studies were typically done with fluconazole)
  - 3) Induces phenytoin metabolism & vice versa
2. Carboplatin
  - a. **Dose limiting toxicities are hepatic and renal toxicity, ototoxicity, mucositis, and peripheral neuropathy; 4-6 fold dose increase over standard dose<sup>70</sup>**
  - b. Typically dosed using mg/m<sup>2</sup> strategy in HCT conditioning regimens
3. Carmustine
  - a. **Dose limiting toxicity is pulmonary toxicity<sup>82-84</sup>; 5.3 fold dose increase over standard dose<sup>70</sup>**
    - 1) 5 to 60% Incidence, with a higher incidence with higher doses of carmustine (**> 450 mg/m<sup>2</sup>=15% incidence**)
    - 2) Acute lung injury – cough, dyspnea, fever, minimal radiographic changes
    - 3) Risk factors: prior chest radiation, smoking, prior bleomycin, concomitant cyclophosphamide
    - 4) Treatment with early corticosteroids - prednisone 1 mg/kg/day
  - b. High dose carmustine (>150 mg/m<sup>2</sup>) is associated with headaches, perioral paresthesia, and flushing within 2 hours of the infusion due to the alcohol diluent used in drug reconstitution. Supportive care with acetaminophen, morphine, hydromorphone, or benzodiazepines diminishes the severity of the reaction.<sup>85</sup>

- c. Hydrolysis, renal elimination
  - d. Drug interactions: avoid aldehyde dehydrogenase-2 inhibitors and drugs that induce disulfiram reaction due to the alcohol diluent. Most other interactions are not clinically significant.
4. Cyclophosphamide<sup>86</sup>
- a. **Dose limiting toxicity is cardiac<sup>87-89</sup>; 8-10-fold dose increase over standard dose**
    - 1) **Occurs most often at doses above 150 mg/kg. Causes myocardial necrosis and acute congestive heart failure; typically occurs in the first 10 days following administration. Pericarditis has also been reported.**
    - 2) **Monitoring with electrocardiogram may be appropriate for high dose therapy**
  - b. **Hemorrhagic cystitis<sup>90</sup>**
    - 1) Incidence ranges from 0.5% to 40%, mortality rates of 2% to 4% reported
    - 2) **Caused by the metabolite acrolein**
    - 3) **Mesna plus saline diuresis or forced saline diuresis is recommended to decrease the incidence of urothelial toxicity associated with high-dose cyclophosphamide; IV hydration with saline > 3 L/m<sup>2</sup>/d plus IV furosemide after each dose of cyclophosphamide to maintain urine output at greater than 100 mL/h**
  - c. May also cause syndrome of inappropriate antidiuretic hormone (SIADH), pulmonary toxicity
  - d. Hepatic toxicity
    - 1) In a prospective study using a conditioning regimen of cyclophosphamide 120 mg/kg and TBI 900-1440 cGy for allogeneic transplant, elevated cyclophosphamide metabolite concentrations were associated with increased risk of hepatic toxicity and NRM.<sup>91</sup> In a subsequent study, pharmacokinetic dosing was not been shown to mitigate toxicity risk for the CyTBI regimen<sup>92</sup>
    - 2) For patients receiving a conditioning regimen of cyclophosphamide with targeted oral busulfan, elevated cyclophosphamide metabolite concentrations were NOT associated with increased risk of hepatic toxicity, non-relapse mortality, relapse or survival<sup>93</sup>
    - 3) Administration of Cy before targeted IV busulfan does reduce VOD (0% vs. 30% in historical control) and day 100 TRM (2% vs. 12%) in patients with myelofibrosis; no difference in AML/MDS patients (who have an inherently lower risk for VOD)<sup>94</sup>
  - e. Hepatic metabolism; 5-25% renal elimination

- f. Drug interactions
  - 1) Prodrug, metabolized to active and inactive metabolites by CYP3A4, CYP2B6, CYP2A6, CYP2C8, CYP2C9, and CYP2C19
  - 2) Busulfan or phenytoin increases cyclophosphamide metabolism to toxic metabolites, therefore some experts suggest administering cyclophosphamide before busulfan or 12-18 hours after completion of busulfan<sup>93</sup>
5. Cytarabine<sup>95</sup>
  - a. **Dose limiting toxicity is neurotoxicity, but most of the transplant regimens that include cytarabine are not “high dose” (< 1 gm/m<sup>2</sup>/dose)**
    - 1) Presents with slurred speech, confusion, unsteady gait, coma
    - 2) Risk factors for neurotoxicity include renal dysfunction and inconsistently: age over 40 years and elevated alkaline phosphatase
    - 3) See the Acute Leukemia handout for management of cytarabine-induced neurotoxicity
  - b. Contributes to mucositis; high dose is associated with pulmonary toxicity (non-cardiogenic pulmonary toxicity), and hepatic toxicity; conjunctivitis with high-dose therapy (see Acute Leukemias section); skin rash
  - c. **Deamination in liver, plasma and peripheral tissues**
6. Etoposide<sup>86</sup>
  - a. **Dose limiting toxicity is mucositis; 3-6-fold dose increase over standard dose**
  - b. Infusion can cause hypotension; associated with metabolic acidosis possibly due to large dose of ethanol used as excipient
  - c. **Metabolized in liver to glucuronide metabolite and then renally eliminated; one-third is excreted by kidney unchanged. Renal elimination increased in patients with hepatic dysfunction. Consider dose reduction in renal dysfunction.**
  - d. Drug interactions: CYP3A4 substrate- any CYP3A4 inducers or inhibitors have potential for a pharmacokinetic interaction, and caution should be used when these medications are administered concurrently with etoposide.<sup>81</sup>
7. Fludarabine
  - a. **Dose limiting toxicity is neurotoxicity**
    - 1) The incidence of fludarabine-related neurotoxicity in HCT conditioning regimens doses is 2.4%. **Fludarabine dosing of 40-100 mg/m<sup>2</sup>/day or a total dose of 200 mg/m<sup>2</sup> is associated with an increased risk of neurotoxicity.** The onset of neurotoxicity is approximately 2 months after receiving fludarabine and it develops with progressively increasing severity. Neurotoxicity associated with fludarabine was

associated with poor median overall survival (estimated one year survival of 43%).<sup>96</sup>

- 2) Potential risk factors for fludarabine neurotoxicity include: age over 60 years, renal dysfunction contributing to elevated fludarabine concentrations in the central nervous system (CNS)<sup>97</sup>, prior high dose cytarabine, intrathecal therapy, or cranial irradiation and prior HCT with fludarabine conditioning<sup>96</sup>
- 3) Fludarabine-induced neurotoxicity may present as cognitive dysfunction, decreased levels of consciousness, vision changes, confusion, somnolence, seizure, severe persistent headache, and blurred vision<sup>96</sup>
- b. Renal elimination: consider dose reduction, especially for regimens with higher doses of fludarabine (40 mg/m<sup>2</sup>/day or 200 mg/m<sup>2</sup> total dose) for patients with renal dysfunction<sup>97</sup>
8. Ifosfamide<sup>70</sup>
  - a. **Dose limiting toxicity is renal toxicity and neurotoxicity; 2.7-fold dose increase over standard dose. See Sarcoma materials for thorough discussion of neurotoxicity.**
  - b. **Renal tubular damage may cause Fanconi-like syndrome (elevated Scr, BUN, electrolyte wasting)<sup>90</sup>**
  - c. **Hemorrhagic cystitis (HC)**
    - 1) **Caused by the metabolite acrolein. Administer mesna to prevent HC**
    - 2) **Toxicity is usually within 4-6 weeks of administration (if it occurs later suspect viral cystitis)**
    - 3) May present as mild cystitis to massive hemorrhage; patients may complain of urinary retention, pain with urination; micro or macroscopic hematuria may be present
  - d. Hepatic metabolism to active metabolite, renal elimination
  - e. Drug interactions
    - 1) Concomitant administration of ifosfamide and CYP3A4 inducers may increase the metabolism of ifosfamide to its active alkylating metabolites and may increase the formation of neurotoxic and nephrotoxic metabolites
    - 2) Concomitant use of CYP3A4 inhibitors and ifosfamide may decrease the metabolism of ifosfamide to its active alkylating metabolites, possibly reducing the effectiveness of ifosfamide
9. Melphalan<sup>70</sup>
  - a. **Dose limiting toxicity is mucositis; 5.6-fold dose increase over standard dose**



- 1) Cryotherapy (ice chips) is effective for prevention of mucositis in patients with multiple myeloma receiving single agent melphalan<sup>98,99</sup>
  - b. May cause SIADH, pulmonary toxicity, hepatic toxicity, and delayed emesis
  - c. **Primary method of elimination is hydrolysis; renal elimination accounts for 13%**
  - d. **Renal dose adjustment has conflicting data. Some reports indicate safe to use full dose with renal dysfunction and some describe increased toxicity<sup>100-102</sup>**
  - e. **No consensus for reduction of melphalan in the setting of renal dysfunction**
10. Thiotepa<sup>86</sup>
- a. **Dose limiting toxicity is mucositis and neurotoxicity; 8-12-fold dose increase over standard dose**
  - b. Neurotoxicity presents as confusion, somnolence, and coma. May cause significant elevations in hepatic enzymes, acute erythroderma with maculopapular dissemination and desquamation, interstitial pneumonitis, and cardiac toxicity. **Skin hyperpigmentation can occur as metabolites can accumulate in skin folds & dressings.**
    - 1) **Due to skin excretion at high doses, avoid occlusive dressings and clean skin at least twice daily during therapy and for 48 hours after. Change linens daily during therapy<sup>103</sup>**
  - c. Oxidative metabolism by CYP2B1, CYP2C11, CYP3A4, and minor by CYP2B6; metabolized to active metabolite TEPA
  - d. Drug interactions: inhibitor of CYP2B6. Cyclophosphamide may not be activated, therefore administer cyclophosphamide before thiotepa.
- J. Immunosuppression (allogeneic HCT only)
1. Prevention of graft (i.e., allogeneic stem cell) rejection
    - a. Achieved with immunosuppressive therapy in conditioning regimen (e.g., cyclophosphamide, fludarabine, anti-thymocyte globulin)
    - b. Required to eradicate host immune system (T-lymphocytes) and thus allow acceptance of donor cells; prevents “host-versus-graft” reaction
  2. **Prevention of GVHD**
    - a. **Achieved with longer-term immunosuppressive medications initiated prior to infusion and continued typically until at least three to six months after HCT or until resolution of GVHD. Combination regimens of calcineurin inhibitors with short course methotrexate (day + 1, 3, 6, +/- 11) are standard of care for myeloablative MRD and MUD transplant; the addition of post-transplant cyclophosphamide is standard of care for haploidentical transplant. See GVHD section below.**
    - b. Required to suppress donor immune system (T-lymphocytes) and minimize recognition of host cells as foreign

- K. Infusion of stem cells
  - 1. Day of infusion of stem cells referred to as Day 0. Days leading up to transplant are counted as negative numbers (e.g., Day -1) and post infusion is counted as positive (e.g., Day +100).
  - 2. Infused as fresh (manipulated or unmanipulated) allogeneic stem cells or thawed cryopreserved (manipulated or unmanipulated) allogeneic or autologous stem cells; infused via central line; thawed stem cells must be infused rapidly due to limited time of viability post thawing
  - 3. If cryopreserved, infusion may be associated with DMSO toxicity including nausea, bradycardia, and garlic-like odor from recipient (lasts approximately 24 hours). Other adverse effects can include vomiting, diarrhea, flushing, headache, and rarely, anaphylactic reaction. If multiple bags of CD34<sup>+</sup> cells, may separate over several days into different aliquots to avoid DMSO toxicity.
  - 4. Generally well tolerated; hydration often given to minimize hematuria. Premedication generally given to prevent infusion reactions (e.g., acetaminophen +/- corticosteroid +/- diphenhydramine)<sup>104</sup>
- L. Engraftment: sustained ANC >0.5 x 10<sup>9</sup>/L for three consecutive days and platelet count > 20 x 10<sup>9</sup>/L without transfusion for seven days

### III. Post-HCT Complications

- A. Mucositis
  - 1. HCT-specific risk factors: myeloablative conditioning, regimens containing total body irradiation, high dose etoposide or melphalan, and use of methotrexate to prevent GVHD
  - 2. Follow Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines<sup>105</sup> for prevention and treatment of mucositis (refer to Head, Neck, Thyroid and Adult Central Nervous System Malignancies handout for full guideline information)
  - 3. **Key HCT-specific prevention guideline recommendations<sup>105</sup>**
    - a. **Multiagent oral care protocols suggested for all patients**
    - b. **Cryotherapy (ice chips) recommended for patients undergoing autologous HCT who receive high dose melphalan**
    - c. **Palifermin 60 mcg/kg/day x 3 days prior to conditioning treatment and for 3 days post-transplant recommended for patients with hematological malignancies receiving high-dose chemotherapy therapy + TBI with autologous HCT**
      - 1) Palifermin did not benefit multiple myeloma patients receiving melphalan 200 mg/m<sup>2</sup> when given both pre- and post-transplant or pre-transplant only<sup>106</sup>.

- 2) Palifermin has been studied in multiple studies of allogeneic HCT patients and did not reduce GVHD.<sup>107-111</sup>
- 3) The impact on mucositis has not been shown to be significant in most studies and subgroups of patients and is not recommended in the MASCC guidelines.

**d. Low level laser therapy recommended for patients receiving HCT conditioned with high-dose chemotherapy, with or without TBI**

**B. Nausea and Vomiting**

1. **Follow ASCO guidelines for high-dose chemotherapy with stem cell transplant, radiation, and multiday regimens.**<sup>112</sup> Refer to the Lung Cancer handout for more details on these guidelines. Most conditioning regimens are considered moderate or high emetic risk.
2. **ASCO guidelines recommend adult patients treated with high-dose chemotherapy with stem cell transplantation should receive a three-drug combination of a neurokinin 1 (NK<sub>1</sub>) receptor antagonist, a 5HT<sub>3</sub> receptor antagonist, and dexamethasone based on randomized controlled trials showing a benefit in no emesis rates with the addition of NK<sub>1</sub> therapy**<sup>112</sup>
  - a. **Aprepitant may elevate levels of calcineurin inhibitors and sirolimus through CYP3A4 inhibition**<sup>113,114</sup>
3. **2020 ASCO guideline update states a 4-drug combination of an NK<sub>1</sub> antagonist, a 5HT<sub>3</sub> receptor antagonist, dexamethasone and olanzapine can be considered in the setting of high-dose chemotherapy and stem cell transplant (evidence quality: low, strength of recommendation: weak)**<sup>112</sup>
  - a. Evidence for olanzapine-based prophylactic regimens in HCT is currently limited to a single placebo-controlled phase III trial<sup>115</sup>, a small retrospective report<sup>116</sup>, or use as a break-through agent<sup>117</sup>
4. **ASCO guidelines recommend patients treated with high-emetic-risk radiation (i.e. total body irradiation) should be offered a two-drug combination of a 5HT<sub>3</sub> receptor antagonist and dexamethasone before each fraction and for one day after the planned radiation ends**<sup>112</sup>

**C. Sinusoidal Obstruction Syndrome (SOS) / Veno-Occlusive Disease (VOD)**

1. **Potentially life-threatening complication characterized by damage to liver endothelium, most commonly associated with high-dose chemotherapies/radiation used with HCT. Severe disease with multi-organ failure associated with high mortality (>80%).**<sup>118,119</sup>
2. **Risk factors**<sup>119-121</sup>
  - a. **Identification of highest risk patients is critical for efficient diagnosis and management, and to reduce modifiable risk factors**

### Reported Risk Factors for Development of SOS/VOD<sup>118,119,121</sup>

Type	Risk Factor
Patient-related	<ul style="list-style-type: none"> <li>• <b>Preexisting liver disease (including elevated transaminases, hepatitis, or cirrhosis)</b></li> <li>• <b>Iron overload</b></li> <li>• <b>Lower performance status (e.g., KPS &lt; 90% or ECOG 2-4)</b></li> <li>• Younger age in pediatric patients</li> <li>• Older age in adult patients</li> <li>• Platelet refractoriness</li> <li>• Elevated international normalized ratio (INR)</li> <li>• Impaired pulmonary function</li> <li>• Acute kidney injury</li> <li>• Primary diagnosis of osteopetrosis, primary hemophagocytic lymphocytosis or adrenoleukodystrophy, neuroblastoma, Wilms tumor, or leukemia</li> <li>• Advanced disease (beyond second CR or relapse/refractory)</li> <li>• Metabolic syndrome</li> <li>• Genetic factors (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype)</li> </ul>
Transplant-related	<ul style="list-style-type: none"> <li>• <b>Allogeneic HCT (especially unrelated/HLA mismatch) &gt; autologous HCT</b></li> <li>• <b>Myeloablative / high intensity condition regimen</b> <ul style="list-style-type: none"> <li>○ Busulfan based (oral &gt; intravenous)</li> <li>○ Busulfan-thiotepa</li> <li>○ Busulfan and cyclophosphamide</li> <li>○ TBI-based (especially doses &gt;12 Gy)</li> </ul> </li> <li>• <b>GVHD prophylaxis / treatment</b> <ul style="list-style-type: none"> <li>○ Sirolimus</li> <li>○ Horse ATG</li> <li>○ Cyclosporine &gt; tacrolimus</li> <li>○ Tacrolimus trough levels above range of 5 – 10 ng/mL</li> </ul> </li> </ul>
Prior therapy	<ul style="list-style-type: none"> <li>• <b>Previous HCT (especially myeloablative)</b></li> <li>• <b>Gemtuzumab ozogamicin</b></li> <li>• <b>Inotuzumab ozogamicin</b></li> <li>• <b>Abdominal irradiation</b></li> <li>• <b>Hepatic irradiation</b></li> <li>• <b>Norethisterone use</b></li> </ul>

### 3. Diagnosis

- a. Can occur at any time after HCT, but most commonly occurs during first 3 weeks post-transplant
- b. Multiple different diagnostic criteria are used in clinical practice, however the revised criteria from the European Society for Blood and Marrow Transplantation (ESBMT) provide criteria for both classic and late onset disease (see table below) as well as criteria for severity of disease<sup>121</sup>
  - 1) More severe disease is characterized by features such as: bilirubin  $\geq 5$  mg/dL, bilirubin doubling time <48 hours, renal function  $\geq 1.5$  times baseline, hepatic transaminases  $\geq 5$  times upper limit of normal<sup>121</sup>

# ESBMT Revised Diagnostic Criteria for SOS<sup>121</sup>

Classical SOS (Within 21 days after HCT)	Late Onset SOS (>21 days after HCT)
Bilirubin $\geq 2$ mg/dL plus at least 2 of the following: <ul style="list-style-type: none"> <li>Painful hepatomegaly</li> <li>Ascites</li> <li>Weight gain &gt;5% from pre-HCT weight</li> </ul>	<ul style="list-style-type: none"> <li>Classical SOS after day 21</li> </ul> OR <ul style="list-style-type: none"> <li>Histologically proven SOS</li> </ul> OR <ul style="list-style-type: none"> <li>At least 2 of the following: <ul style="list-style-type: none"> <li>Bilirubin <math>\geq 2</math> mg/dL</li> <li>Painful hepatomegaly</li> <li>Weight gain &gt;5% from pre-HCT weight</li> <li>Ascites</li> </ul> </li> </ul> AND <ul style="list-style-type: none"> <li>Hemodynamic and/or ultrasound evidence</li> </ul>

## 4. Prevention<sup>122,123</sup>

- a. **Conditioning regimen modification: reduced intensity conditioning regimen, targeted dosing of IV busulfan to an AUC below 6.2 mg x h/L (1500 Mol-min) for myeloablative conditioning regimens using every 6-hour busulfan dosing, fractionation of TBI**
- b. Risk-adjust preparative regimen intensity according to HCT comorbidity index
- c. **Identify drug-drug interactions in preparative regimen and modify as appropriate**
- d. **Avoid use of hepatotoxins before and during conditioning if possible (e.g., azoles, acetaminophen)**
- e. **Avoid use of progesterone, estrogen if possible**
- f. **Ursodiol: systematic review of ursodiol to prevent VOD – pooled results of 3 randomized clinical trials demonstrated a reduction in VOD with an RR= 0.34 (CI 0.17 – 0.66); TRM was also reduced RR 0.58 (CI 0.35-0.95).<sup>124</sup> There was no effect on acute GVHD, relapse, or overall survival.**
  - 1) Generally given as 12 mg/kg/day in 2-3 divided doses through at least day + 30, although some report benefits through day + 80 to 90. **Suggested for use by BCSH/BSBMT Guideline.<sup>120</sup>**
  - 2) 10 year follow-up of the largest study shows the overall survival benefit for ursodiol compared with a control group found at 1 year was maintained long-term (1 yr. = 71% vs. 55%; 10 yr. 48% vs. 38%)<sup>125</sup>
- g. Defibrotide: 4 small, retrospective trials reported VOD in 0 to 11% of patients receiving defibrotide as prophylaxis. Defibrotide is recommended for use by BCSH/BSBMT Guideline for prevention in patients with selected risk factors.<sup>120</sup>

- h. Other prevention strategies not suggested for use by BCSH/BSBMT Guideline<sup>120</sup>, including pentoxifylline, antithrombin, prostaglandin E1, and low molecular weight heparin and heparin

5. **Treatment**<sup>120,122</sup>

- a. Early intervention associated with improved overall survival<sup>118</sup>
- b. Mild to moderate cases may be able to be treated with supportive care alone
  - 1) Sodium and fluid restriction, diuresis, dialysis if needed
  - 2) Avoid further renal and hepatic insults
  - 3) Pain management
- c. **Defibrotide**<sup>126</sup>
  - 1) **Should be utilized in severe cases, and can be considered in mild/moderate cases to prevent progression**
  - 2) **Historically controlled, open label, phase III study of adult and pediatric patients with severe VOD/SOS and advanced multi-organ failure (i.e., renal and/or pulmonary dysfunction by day + 28 post HCT) enrolled 101 patients and compared with 32 matched historical controls**
  - 3) **Primary endpoint: day 100 OS was 38.2% in the defibrotide group and 25% in the historical control group (P = 0.01); CR rate was 25.5% in defibrotide group vs. 12.5% in historical control group (P = 0.16)**
  - 4) **FDA approved dosing is 6.25 mg/kg IV every 6 hours for at least 21 days and a maximum of 60 days (until resolution or hospital discharge)**
- d. Limited data for treatment options if refractory to defibrotide
  - 1) Methylprednisolone may be considered with caution regarding infection
  - 2) Transjugular intrahepatic portosystemic shunt (TIPS) or hepatic transplantation
- e. Treatment not recommended due to lack of efficacy<sup>120</sup>
  - 1) Tissue plasminogen activator
  - 2) N-acetylcysteine

**Patient Case, Question #2:**

**Answer: C. Ursodiol**

LC is at risk for development of sinusoidal obstruction syndrome due to planned allogeneic haploidentical transplant with myeloablative and high dose TBI conditioning. She should receive ursodiol for prevention of sinusoidal obstruction syndrome. Palifermin is not recommended in the setting of allogeneic HCT per the MASCC/ISOO guidelines as it has not been consistently beneficial in the allogeneic setting. Levetiracetam or other antiepileptic medication is required with busulfan therapy and twice daily skin cleaning is recommended for thiotepea use, neither of which LC is receiving.

**Patient Case, continued:** LC is a 56-year-old African American female with AML in first remission who is planning to undergo a haploidentical allogeneic HCT. She is scheduled to receive myeloablative fludarabine and total body irradiation (1200 cGy) as conditioning prior to HCT.

**Question #3: What is the most appropriate graft-versus-host disease prophylaxis regimen for LC?**

- A. Cyclosporine + methotrexate
- B. Post-transplant cyclophosphamide
- C. Tacrolimus + mycophenolate + anti-thymocyte globulin
- D. Tacrolimus + mycophenolate + post-transplant cyclophosphamide

D. Graft-versus-host disease (GVHD)

1. **An immunological disorder affecting multiple organ systems resulting from donor T cells responding to foreign recipient antigens, resulting in injury of host organs<sup>127,128</sup>**
2. A leading cause of morbidity and non-relapse mortality after allogeneic HCT, with significant detrimental impact on quality of life, health status, and return to social roles for HCT recipients<sup>14,129</sup>
3. **Clinical features and presentation determine the classification of acute (aGVHD) or chronic (cGVHD), not solely the time since transplant<sup>127</sup>**
  - a. aGVHD occurs primarily in 3 organs: skin, gastrointestinal tract, and liver, with specific manifestations in each organ (see aGVHD section below)
  - b. cGVHD can occur in a multitude of organs, often characterized by fibrosis or autoimmune-like syndromes<sup>130</sup> (see cGVHD section below)
  - c. Overlap syndrome: presence of 1 or more aGVHD manifestation(s) in a patient with a diagnosis of cGVHD

## Types of GVHD<sup>127</sup>

Category	Time of symptoms post HCT or DLI	Presence of Acute GVHD Features	Presence of Chronic GVHD Features
Acute GVHD (aGVHD) <ul style="list-style-type: none"> <li>Classic acute GVHD</li> <li>Persistent, recurrent, or late-onset acute GVHD</li> </ul>			
	≤ 100 days	Yes	No
	> 100 days	Yes	No
Chronic GVHD (cGVHD) <ul style="list-style-type: none"> <li>Classic chronic GVHD</li> <li>Overlap syndrome</li> </ul>			
	No time limit	No	Yes
	No time limit	Yes	Yes

DLI = donor lymphocyte infusion

### 4. Prevention of GVHD

a. **Non-pharmacologic: donor selection based on best histocompatible match**

b. **Pharmacologic: combination immunosuppression**

- 1) See table below for recommended pharmacologic GVHD prophylaxis regimens for various transplant types. These recommendations are based on available literature and expert opinion due to a lack of large-scale, well-designed comparative studies. Considerable variation in practice may exist amongst different institutions and countries.

## Summary of Pharmacologic GVHD Prophylaxis Regimen Recommendations<sup>131</sup>

Transplant type	Recommended GVHD prophylaxis regimen(s)
<b>Myeloablative matched related or unrelated donor (BM/PBSC)</b>	<p><b>Calcineurin inhibitor (CNI) + methotrexate ± anti-T-lymphocyte globulin (ATG)<sup>131</sup></b></p> <ul style="list-style-type: none"> <li>Consider cyclosporine as CNI of choice in related donors due to potential survival benefit<sup>132,133</sup></li> <li>Consider tacrolimus as CNI of choice in unrelated donors due to potential survival benefit<sup>133,134</sup></li> <li>ATG recommended for matched unrelated donors and matched related donors at high risk for GVHD<sup>131</sup></li> </ul> <p>CNI + sirolimus</p> <ul style="list-style-type: none"> <li>Acceptable alternative in non-busulfan based, myeloablative conditioning regimens with related donors<sup>135</sup></li> </ul>
<b>Reduced intensity/nonmyeloablative matched related or unrelated donor (BM/PBSC)</b>	<p><b>CNI + mycophenolate ± ATG<sup>131</sup></b></p> <ul style="list-style-type: none"> <li>Mycophenolate is an alternative to methotrexate with reduced toxicity (decreased mucositis and faster engraftment)<sup>136,137</sup>. Although not comparatively studied against methotrexate in this setting, it is commonly used in clinical practice.</li> <li>ATG recommended for matched unrelated donors and matched related donors at high risk for GVHD</li> </ul> <p>CNI + MTX ± ATG CNI + mycophenolate + sirolimus<sup>138</sup></p>



Transplant type	Recommended GVHD prophylaxis regimen(s)
Mismatched unrelated donor (BM/PBSC)	<b>CNI + MTX + abatacept<sup>139</sup></b> <ul style="list-style-type: none"> <li>Consider addition of abatacept in this setting due to lower rate of severe aGVHD in a phase II study</li> </ul> CNI + MTX + ATG CNI + MTX + post-transplant cyclophosphamide (PTCy)
Haploidentical (BM/PBSC)	<b>Post-transplant cyclophosphamide (PTCy) + tacrolimus + mycophenolate<sup>140,141</sup></b>
Umbilical cord blood	<b>CNI + MMF<sup>142</sup></b> <ul style="list-style-type: none"> <li>MTX is generally avoided in this setting due to its effect on hematopoietic function</li> <li>ATG is not recommended in this setting due to findings of increased infection, transplantation-related mortality, and slowed immune reconstitution.</li> </ul>

## 2) Abatacept: 1<sup>st</sup> FDA-approved agent for acute GVHD prophylaxis<sup>139</sup>

- a) Mechanism of action:
  - i. Selective costimulation blockade agent; inhibits T-lymphocyte activation by binding to CD80 and CD86 on antigen presenting cells
- b) Indications & Dose:
  - i. Acute GVHD prophylaxis
  - ii. 10 mg/kg (1000 mg maximum dose) on days -1, +5, +14 and +28
- c) Toxicities:
  - i. Common: hypertension, hypermagnesemia, CMV, infection
  - ii. Severe: lymphoproliferative disorder, hypoxia
- d) Drug-drug interactions: none significant

## 3) Post-transplant cyclophosphamide (PTCy) 50 mg/kg IV on days +3 and +4 in haploidentical transplants<sup>140,141</sup>

- a) Use in haploidentical transplants, in addition to standard prophylaxis (typically tacrolimus and mycophenolate), has demonstrated acceptable low rates of GVHD, especially chronic
- b) A randomized, phase 2 trial in reduced intensity MRD and MUD HCT showed an improved rate of GVHD-free, relapse-free survival in a tacrolimus, methotrexate, and post-transplant cyclophosphamide arm compared to a contemporary control group that received only tacrolimus and methotrexate (HR 0.72, 90% CI 0.54 – 0.94, P = 0.044).<sup>143</sup>

A prospective phase 3 trial is currently being conducted further examining the role of PTCy in the non-haploidentical setting.

- 4) **T-cell depletion *in vivo* or *ex vivo*: randomized trials have demonstrated inconsistent survival outcomes<sup>144</sup>**
- a) Anti-T-lymphocyte immune globulin (ATG)
- i. Several prospective studies in MRD and MUD have used Fresenius ATG in addition to cyclosporine and methotrexate in patients receiving myeloablative conditioning regimens and have shown reduced incidence of acute and chronic GVHD without statistically significant decrease in relapse free or overall survival<sup>145-147</sup>
  - ii. In contrast, a randomized, placebo-controlled trial of Fresenius ATG in combination with tacrolimus and methotrexate in myeloablative MUD showed decreased rates of acute and chronic GVHD, but lower rates of progression-free and overall survival at 2 years in the ATG arm<sup>148</sup>
  - iii. **Although ATG use remains controversial and is not implemented universally, guidelines recommend ATG for matched unrelated donors and matched related donors at high risk of GVHD due to evidence of decreased cGVHD. Additional studies are needed to elucidate its place in therapy as well as optimal dosing and timing.<sup>131</sup>**

### Select Pivotal Randomized Studies of GVHD Prophylaxis Regimens

Study	Prophylaxis Regimen	Patients (n)	Grade II – IV Acute GVHD (%)	Chronic GVHD (%)	Overall Survival	Comments
Calcineurin Inhibitor Trials						
Ratanatharthorn et al. <sup>132</sup> 1998	CSA + MTX	164 MRD	44%	56%	57%	Myeloablative conditioning
	TAC + MTX	165 MRD	32% P = 0.01	49% P = NS at 2 years	47% P = 0.02 at 2 years	
Nash et al. <sup>134</sup> 2000	CSA + MTX	63 MUD	74%	70%	54%	Myeloablative conditioning
	TAC + MTX	46 MUD	56% P = 0.002	76% P = NS at 2 years	50% P = NS at 2 years	
Huang et al. 2020 <sup>133</sup>  Systematic review and meta-analysis	CSA + MTX	9850	OR = 0.42 (95% CI 0.28-0.61) favoring TAC + MTX  P < .00001  [when including RCT only]	OR = 0.79 (95% CI 0.62-1.00) favoring TAC + MTX  P = 0.05  [when including RCT only]	Improved in MRD: OR = 0.77 (95% CI 0.64-0.94)  P = 0.008	MRD and MUD
	TAC + MTX	5214		Improved in MUD: OR = 1.30 (95% CI 1.15-1.48)  P < .0001		
Mycophenolate Trials						
Bolwell et al. <sup>136</sup> 2004	CSA + MMF	21 MRD	48%	63%	52%	Myeloablative conditioning MMF associated with shorter time to neutrophil engraftment (11 vs. 18 days) and less severe mucositis
	CSA + MTX	19 MRD	37% P = 0.49	64% P = NS	68% P = NS at 6 months	

Study	Prophylaxis Regimen	Patients (n)	Grade II – IV Acute GVHD (%)	Chronic GVHD (%)	Overall Survival	Comments
Perkins et al. <sup>137</sup> 2010	TAC + MMF	42 MRD MUD MMUD	78%	38%	54%	Mostly myeloablative conditioning MMF associated with less severe mucositis; duration of neutropenia similar in both arms.
	TAC + MTX	47 MRD MUD MMUD	P = 0.8	P = 0.71 (moderate or severe at 1 year)	P = 0.58 at 3 years	
Sirolimus Trials						
Cutler et al. <sup>135</sup> 2014	TAC (trough 5-10 ng/mL) + sirolimus (trough 3-12 ng/mL)	151 MRD	26%	53%	59%	Myeloablative conditioning with TBI (busulfan arm closed early due to toxicity/VOD). Trend for more VOD and thrombotic microangiopathy with sirolimus
	TAC (trough 5-10 ng/mL) and MTX	153 MRD	P = 0.48	P = 0.06	P = 0.36	
Sandmaier et al. <sup>138</sup> 2019	CSA + MMF + sirolimus	90 MUD	26%	49%	64%	Non-myeloablative conditioning with fludarabine and TBI
	CSA + MMF	77 MUD	P = 0.0013	P = 0.74	P = 0.035 at 4 years	
Post-transplant cyclophosphamide (PTCy) trials						
Luznik et al. 2008 <sup>140</sup>	TAC + MMF + PTCy 50 mg/kg days +3, ±4	68 Haplo	34%	25% (day +3 PTCy)  5% (days +3, +4 PTCy)  P = 0.05	36%  at 2 years	Non-myeloablative conditioning  Bone marrow  Lower rates of extensive cGVHD inpatients who received 2 doses of PTCy

Study	Prophylaxis Regimen	Patients (n)	Grade II – IV Acute GVHD (%)	Chronic GVHD (%)	Overall Survival	Comments
Brunstein et al. 2011 <sup>141</sup>	TAC + MMF + PTCy	50 Haplo	32%	13%	62%	Comparison of 2 separate prospective cohorts conducted in parallel
Luznik et al. 2021 <sup>149</sup>  BMT CTN 1301	Ex vivo CD34-selected T-cell-depleted	114 (PBSC)	NR	8.9%  P < 0.001	60.1%  P = 0.02	Myeloablative conditioning  Primary composite endpoint of moderate to severe cGVHD, relapse and survival was not different between the groups
Prospective, randomized phase III	PTCy	114 (BM)	NR	27%  P = 0.342	76.2%  P = 0.95	
	TAC + MTX [control arm]	118 (BM)	NR	33.7%	76.1%  At 2 years	
Broers et al. 2022 <sup>150</sup>  HOVON-96 trial	PTCy + CSA	99  MRD/ MUD	30%	16%	71%	Non-myeloablative conditioning  Primary endpoint of non-severe GVHD within 180 days was not significantly different between groups
Prospective, randomized phase III	CSA + MMF	52  MRD/ MUD	48%  P = 0.007	48%  P < 0.001	65%  At 3 years	
Anti-thymocyte Globulin (ATG) Trials						
Kroger et al. <sup>145</sup> 2016	CSA + MTX + ATG- Fresenius 10 mg/kg IV on days -3, -2, -1	83 MRD	10.8%	32.2%	74.1%	Myeloablative conditioning Peripheral blood stem cells
	CSA + MTX	72 MRD	18.1%  P = 0.013	68.7%  P < 0.001 at 2 years	77.9%  P = 0.46 at 2 years	
Finke et al. <sup>147</sup> 2009 Socie et al. <sup>146</sup> 2011	CSA + MTX + ATG- Fresenius 20 mg/kg IV on days -3, -2, -1	103 MUD	33%	12.2%	55.2%	Myeloablative conditioning ~80% peripheral blood stem cells

Study	Prophylaxis Regimen	Patients (n)	Grade II – IV Acute GVHD (%)	Chronic GVHD (%)	Overall Survival	Comments
	CSA + MTX	98 MUD	51%  P = 0.011	45%  P < 0.001 at 3 years	43.3%  P = 0.39 at 3 years	
Soiffer et al. <sup>148</sup> 2017	TAC + MTX + ATG-Fresenius 20 mg/kg IV on days -3, -2, -1	126 MUD	23%	12%	59%	Myeloablative conditioning  No difference in moderate to severe cGVHD-free survival between arms (P = 0.47)  Lower 2-year PFS and OS in ATG arm
	TAC + MTX + placebo	128 MUD	40%  P = 0.004	33%  P < 0.001	74%  P = 0.034 at 2 years	
Walker et al. 2020 <sup>151</sup>	Standard + ATG-4.5 mg/kg	99 MUD	-	26.3%	70.6%	Myeloablative & non-myeloablative conditioning No difference in relapse between arms
	Standard (TAC/CSA + MTX/MMF)	97 MUD	-	41.3%  P = 0.032 at 2 years	53.3%  P = 0.017 at 2 years	
Abatacept trial						
Watkins et al. <sup>139</sup> 2021	CNI + MTX + abatacept	73 MUD	6.8%	51.9%	74.3%	2 strata: RCT in MUD  Historical control for MMUD  Primary endpoint: severe aGVHD (grade III-IV)
	CNI + MTX + placebo	69 MUD	14.8%  P = 0.013 HR = 0.45 (95% CI 0.22-0.9)	45.3%  P = 0.55	64%  P = 0.15 at 2 years	
	CNI + MTX + abatacept	38 MMUD	2.3%	62%	73.6%	

Study	Prophylaxis Regimen	Patients (n)	Grade II – IV Acute GVHD (%)	Chronic GVHD (%)	Overall Survival	Comments
	CNI + MTX (historical control)	127 MMUD	30.2%  severe aGVHD (grade III-IV)  P < 0.001	45.9%  P = 0.74	45.3%  P = 0.002 at 2 years	
<b>Dipeptidyl Peptidase 4 (DPP-4) trial</b>						
Farag et al. 2021 <sup>152</sup>	TAC + sirolimus + sitagliptin 600 mg BID x 16 days	36	5%	37%	94% at 1 year	Myeloablative conditioning  Peripheral blood stem cells

CSA = cyclosporine, Haplo = haploidentical transplant, MMF = mycophenolate, MMUD = mismatched unrelated donor, MRD = matched related donor, MTX = methotrexate, MUD = matched unrelated donor, NR = not reported, OR = odds ratio, PTCy = post-transplant cyclophosphamide, RCT = randomized controlled trial, TAC = tacrolimus, UCB = umbilical cord blood

#### **Patient Case, Question #3:**

**Answer: D. Tacrolimus + mycophenolate + post-transplant cyclophosphamide**

Post-transplant cyclophosphamide in combination with tacrolimus and mycophenolate is the most appropriate standard of care combination immunosuppression for a haploidentical transplant based on multiple clinical trials demonstrating acceptable rates of acute and chronic graft-versus-host disease in this population.

5. Drug monitoring for medications used to prevent GVHD
  - a. Cyclosporine and tacrolimus
    - 1) **Cyclosporine = 150 - 450 ng/mL; 200 – 300 ng/mL most used in clinical practice especially early post-transplant. There is data to suggest lower levels (< 200 -300 ng/ml) are associated with increased risk of acute GVHD; less data correlates levels with toxicity including nephrotoxicity<sup>131,132,153</sup>**
    - 2) **Tacrolimus = 5 - 20 ng/mL; 5 - 15 ng/mL most used in clinical practice; levels > 20 ng/mL associated with increased toxicity, primarily nephrotoxicity. Dose reduction strategies based on levels and/or serum creatinine.<sup>132,154,155</sup>**
      - a) **Target tacrolimus trough levels of 5-10 ng/mL with concomitant sirolimus<sup>156</sup>**

- 3) Dose adjustments for either drug based on nephrotoxicity as recommended in randomized trials<sup>132</sup>
  - a) If creatinine 2 - 2.9 X baseline = at least 25% dose reduction
  - b) If creatinine  $\geq 3$  X baseline = at least 50% dose reduction
- 4) Dose adjustments may be considered in moderate to severe hepatic dysfunction, which can affect metabolism
- 5) Close monitoring and dose adjustments (including empiric therapy modifications in some cases) should occur with concomitant moderate to strong CYP3A4 inducers and inhibitors. See Immunosuppressive Therapies table below.
- 6) Tapering either medication in patients who do not develop acute GVHD may be started from day 50-100 depending on the risk of relapse. The dose should be reduced by approximately 10% per week
- 7) Cyclosporine or tacrolimus conversion factors (IV:PO)
  - a) IV cyclosporine to PO cyclosporine (Sandimmune) = 1:4
  - b) IV cyclosporine to PO modified cyclosporine (Neoral or Gengraf) = 1:2-3
  - c) IV tacrolimus to PO tacrolimus = 1:3-4
- b. Sirolimus
  - 1) **Target trough levels of 3 – 14 ng/mL**<sup>135,157,158</sup>
  - 2) **Higher levels associated with thrombotic microangiopathy and veno-occlusive disease as well as myelosuppression in some studies**<sup>135,159,160</sup>
  - 3) Long half-life (approximately 46 to 78 hours), therefore loading dose may be considered when starting therapy<sup>157</sup>
- c. Mycophenolate: therapeutic drug monitoring not well established in HCT
- d. Methotrexate (MTX)
  - 1) Standard of care in addition to calcineurin inhibitor<sup>156</sup>
    - a) May increase risk for mucositis and pulmonary toxicity
    - b) May delay time to neutrophil and platelet engraftment (not as significant with PBSC vs. bone marrow)
  - 2) Dosing
    - a) **15 mg/m<sup>2</sup> IV day 1, 10 mg/m<sup>2</sup> IV days 3, 6, 11 established as standard methotrexate regimen based on randomized trial (often referred to as “short course methotrexate”)**<sup>161</sup>
    - b) 5 mg/m<sup>2</sup> IV days 1, 3, 6,  $\pm$  11 has been evaluated in non-randomized studies (often referred to as “mini-



methotrexate")<sup>162,163</sup>; overall appears similar to standard dose methotrexate with less systemic toxicity

c) **Assess for dose reduction or elimination on the day each dose is administered**

- i. **If creatinine > 2 x baseline, transaminases > 200 IU/L, or bilirubin > 5 mg/dL = 50% dose reduction<sup>132</sup>**
- ii. **If more severe renal or hepatic dysfunction, fluid third spacing (pleural effusions or ascites), severe mucositis with threatening airway obstruction – omit dose<sup>132</sup>**
- iii. Leucovorin rescue may be given (not standard of care) beginning 12 - 24 hrs after MTX x 2-8 doses; may ameliorate MTX-associated toxicities including delayed engraftment, mucositis; no negative impact on GVHD or event-free survival.<sup>164,165</sup> There are no data to support that leucovorin is helpful in patients at increased risk for methotrexate toxicity.

**Patient Case, continued:** LC is a 56-year-old African American female with AML in first remission who underwent a haploidentical allogeneic HCT. She received tacrolimus, mycophenolate and post-transplant cyclophosphamide to prevent GVHD. The transplant team began tapering her tacrolimus at day +100. One month later, she presents with a maculopapular skin rash on 45% of her body and had 1200 mL of diarrhea in the past 24 hours. She is diagnosed with grade III acute GVHD.

**Question #4: What is the most appropriate GVHD treatment for LC at this time?**

- A. Ruxolitinib 5 mg twice daily and therapeutic tacrolimus
- B. Methylprednisolone 2 mg/kg/day and therapeutic tacrolimus
- C. Prednisone 0.5 mg/kg/day and beclomethasone
- D. Methylprednisolone 2 mg/kg/day and discontinue tacrolimus

6. Manifestations and grading of acute GVHD (aGVHD)<sup>14,166</sup>
  - a. 20-80% of patients will develop aGVHD despite prophylaxis
  - b. **Clinical manifestations seen in primarily 3 organs**
    - 1) **Skin: maculopapular rash, pruritus**
    - 2) **Gastrointestinal tract: secretory diarrhea, abdominal cramping, vomiting, nausea, anorexia, dyspepsia, severe abdominal pain with or without ileus**
    - 3) **Liver: cholestatic hyperbilirubinemia, increased alkaline phosphatase**
  - c. Each organ involved is individually staged from Stage 1 – 4 based on degree and severity of involvement

- d. Staging of each organ is combined to give an overall acute GVHD grade from I (mild) to IV (life-threatening)
- e. Rule out other potential causes (i.e., infection, drug toxicity, etc.) with additional testing as indicated
- f. Organ-directed biopsy can be considered to confirm diagnosis, but is not required and is not absolutely sensitive
- g. Multiple scoring tools (e.g., Minnesota GVHD Risk Score<sup>167</sup>, Ann Arbor score<sup>168</sup>, etc.) have been developed to stratify severity of disease and mortality risk and may guide more treatment decisions in the future

7. **Initial treatment of acute GVHD**<sup>138,169-171</sup>

- a. **First line treatment based on organ involvement and grade (see table)**

**Comparison of First Line Acute GVHD Treatment Guideline Recommendations**

	NCCN Guidelines <sup>®14</sup>	ASTCT (ASBMT) Guidelines <sup>170</sup>
<b>Grade I (Skin only)</b>	<ul style="list-style-type: none"> <li>Continue or consider reinitiating original immunosuppressive agent</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Topical skin-directed steroids (medium to high potency except to face and intertriginous areas) and/or topical tacrolimus</li> <li>Antihistamines as needed for itching</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Observe if asymptomatic / stable</li> </ul>	N/A
<b>Grade II - IV</b>	<ul style="list-style-type: none"> <li>Continue, consider reinitiating, or increase to therapeutic levels if tapering original immunosuppressive agent</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Enroll in clinical trial</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Systemic corticosteroids ± topical steroids <ul style="list-style-type: none"> <li>Skin/lower GI/liver: methylprednisolone* 1-2 mg/kg/day</li> <li>Grade II: consider 1 mg/kg/day</li> <li>Upper GI involvement only: methylprednisolone* 0.5-1 mg/kg/day + GI topical steroids (beclomethasone, budesonide)</li> </ul> </li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Consider sirolimus for standard-risk aGVHD (see BMT CTN 1501 trial below)<sup>158</sup></li> </ul>	<ul style="list-style-type: none"> <li>Methylprednisolone* 2 mg/kg/day</li> <li>Upper GI involvement only: methylprednisolone* 1 mg/kg/day + GI topical steroids</li> </ul>

*\*Or equivalent dose of prednisone*

- b. **No benefit to a higher corticosteroid dose** (10 mg/kg/day vs. 2 mg/kg/day methylprednisolone) in randomized trial in grade II – IV acute GVHD<sup>172</sup>
- c. **No additional systemic agent combined in initial therapy with methylprednisolone has shown benefit**, thus first line combination therapy should only be done in the setting of a clinical trial<sup>14,170</sup>
- d. **Sirolimus is an alternative first-line option instead of corticosteroids for standard-risk acute GVHD based on the randomized, phase II BMT CTN 1501 trial**<sup>158</sup>
  - 1) **Complete and partial response rates at day 28 were similar between patients randomized to sirolimus compared to prednisone, 64.8% vs. 73%**
  - 2) **Sirolimus group had decreased steroid exposure and hyperglycemia as well as improved patient-reported quality of life, but increased thrombotic microangiopathy**
- e. Complete response rates with durable remission range from 25 to 40%, overall response rate 50 to 65%<sup>170</sup>
- f. If response occurs, corticosteroids should be tapered as feasible. An optimal steroid taper schedule has not been defined but factors to be considered include response, toxicity, and risk for relapse. ASTCT recommendations suggest tapering by 0.2 mg/kg/day every 3-5 days once GVHD symptoms are under good control; taper should be slowed after the prednisone dose has been decreased to less than 20-30 mg/day.<sup>170</sup>
- g. **‘Nonabsorbable’ steroids (e.g., beclomethasone or budesonide extended release) have a role in decreasing systemic steroids and improving clinical outcomes in mild (grade II) disease**
  - 1) **A randomized, phase III study demonstrated benefit of nonabsorbable steroids with prednisone 0.5 mg/kg/day for mild grade II acute GVHD**<sup>173</sup>
  - 2) **Budesonide 9 mg orally daily**
    - a) Prospective cohort of patients treated with budesonide + systemic corticosteroid in stage 2 or higher gut acute GVHD compared with retrospective cohort<sup>174</sup>
    - b) Acute GVHD resolved/no relapse in 77% budesonide group vs. 32% control (P < 0.01)
  - 3) **Beclomethasone 8 mg PO daily**
    - a) Multicenter, randomized trial in stage 1 isolated gut GVHD patients given prednisone 1 – 2 mg/kg/day and randomized to beclomethasone or placebo<sup>175</sup>

- b) **Treatment failure rate at day 50 was primary endpoint and was not statistically different, but day 80 treatment failure rate was improved (HR =0.55; P = 0.02)**
- c) **Overall survival at 1 year was 71% in the beclomethasone group and 58% in the placebo group (HR 0.54; P = 0.04)**
- d) Drug is not available commercially but is commonly compounded as 1-2 mg/mL in corn oil and given as 2 mg PO four times daily<sup>176</sup>

**Patient Case, Question #4:**

**Answer: B. Methylprednisolone 2 mg/kg/day + therapeutic tacrolimus**

LC's acute GVHD developed during a taper of her original immunosuppressive regimen (tacrolimus), therefore the NCCN Guidelines® recommend increasing the original agent back to therapeutic levels for first-line treatment. In addition to therapeutic tacrolimus, the most appropriate initial therapy per the NCCN® and ASTCT guidelines is methylprednisolone 2 mg/kg/day<sup>14,170</sup> for grade III acute GVHD. Ruxolitinib is approved for steroid-refractory acute graft-versus-host disease and should not be utilized first-line. Beclomethasone + prednisone may be appropriate for patients with upper gastrointestinal GVHD alone but is not recommended therapy for lower gastrointestinal GVHD.

- 8. Steroid-refractory acute GVHD
  - a. Various criteria are utilized in clinical trials and practice to describe steroid-refractory aGVHD and guide the need for new or additional therapy (see table below)
  - b. Secondary systemic therapy may be indicated sooner in patients who do not tolerate high-dose glucocorticoids

**aGVHD Response Criteria and Definitions of Steroid-refractory aGVHD<sup>14,170</sup>**

Response Category	Response Criteria
Steroid refractoriness/resistance	<ul style="list-style-type: none"> <li>Progression within 3-5 days of <math>\geq 2</math> mg/kg/day methylprednisolone</li> <li>No improvement within 5-7 days of treatment initiation</li> <li>Incomplete response after more than 28 days of immunosuppressive treatment</li> </ul>
Steroid dependence	<ul style="list-style-type: none"> <li>Inability to taper prednisone <math>&lt; 2</math> mg/kg/day</li> <li>Recurrence of acute GVHD during steroid taper</li> </ul>
Steroid intolerance	<ul style="list-style-type: none"> <li>Unacceptable toxicity attributed to corticosteroid therapy</li> </ul>

- c. **ASTCT and NCCN Guidelines® do not recommend any specific agent for second line therapy, citing insufficient evidence/lack of comparative studies<sup>14,170</sup>**
- d. **The choice of a second-line regimen should be guided by the effects of previous treatment(s), considerations of potential toxicity, interactions with**

other agents including those used for prophylaxis, convenience, expense, and prior experience of the transplant physician/team. Clinical trials should be pursued if available. See table below for agents with evidence for use.

- e. **Additional agents may be added to the original immunosuppressant agent and steroid therapy. If steroids are determined to be ineffective, slow tapering is recommended.<sup>14</sup>**
- f. **Ruxolitinib: only FDA-approved medication for steroid-refractory acute GVHD**
  - 1) **FDA-approved May 24, 2019 for treatment of steroid-refractory aGVHD in adult and pediatric patients  $\geq 12$  years of age**
  - 2) **Approval based on the open-label, single-arm, multicenter REACH1 study with 71 steroid-refractory aGVHD grades II-IV patients, which showed a 55% overall response rate at day 28, including 27% complete response<sup>177</sup>**
  - 3) **REACH2 was a randomized, open-label phase III clinical trial comparing ruxolitinib 10 mg twice daily (N=154) to investigator's choice of 9 control options(N=155) in patients with steroid-refractory aGVHD<sup>178</sup>**
    - a) **Overall response at day 28 was higher in ruxolitinib group vs. control (62% vs. 39%, OR 2.64 [1.65-4.22];  $P < 0.001$ )**
    - b) **Median OS was longer in ruxolitinib group vs. control (11 months vs. 6.5 months, HR 0.83; 95% CI 0.60-1.15)**
    - c) **Doses should be adjusted for neutropenia, clinically significant thrombocytopenia, renal, and liver dysfunction**
    - d) **Dose may be tapered slowly after 6 months in patients who have successfully discontinued therapeutic doses of corticosteroids**

### Systemic Therapies for Steroid-Refractory aGVHD\*

Agent	Regimen	Response Rate	Organ most likely to respond
$\alpha_1$ -antitrypsin <sup>179</sup>	60 mg/kg/day IV twice weekly for up to 4 consecutive weeks/8 doses	CR 35% PR 30%	Skin/GI/liver
Alemtuzumab <sup>180-182</sup>	10 mg/day x 5 days – higher and lower doses have been used	50-94%	GI/liver
Anti-thymocyte globulin <sup>183-189</sup>	10 – 15 mg/kg (equine) QOD x 7-14 days (if using the rabbit preparation use a dose of 1 – 1.5 mg/kg/dose)	19-57%	Skin
Basiliximab <sup>190,191</sup>	20 mg IV daily x 1-2 consecutive days, repeated weekly in cases of persistent GVHD or 20 mg IV on days 1, 4	70-83%	Skin/GI
Etanercept <sup>192</sup>	25 mg SQ twice weekly for 4 weeks, then weekly x 4 weeks	46%	GI
Extracorporeal photopheresis (ECP) <sup>193-195</sup>	ECP on 2 consecutive days at 1-2 week intervals until improvement, then every 2-4 weeks; other schedules utilized based on response	67-75% CR 52-60%	Skin/liver/GI
Infliximab <sup>196-199</sup>	10 mg/kg IV weekly x 3- 4 doses (minimum)	40-67%	Skin/GI
Mycophenolate mofetil <sup>200-203</sup>	1.5 g – 3 g/day	31-60%	Skin/liver/GI
Pentostatin <sup>204-206</sup>	1-1.5 mg/m <sup>2</sup> on days 1 to 3	38-63%	Skin/GI [Not effective in liver]
<b>Ruxolitinib<sup>177,178,207</sup></b> <b>(Only FDA-approved agent for steroid-refractory aGVHD, NCCN® category 1)</b>	5-10 mg PO twice daily	ORR 50-70% CR 25-55%	Skin/GI
Sirolimus <sup>208-210</sup>	Loading dose followed by maintenance dose (1-4 mg/day) adjusted to target levels of 4-12 ng/mL	57%-91%	Liver/GI
Tocilizumab <sup>211-213</sup>	8 mg/kg IV q 2-4 weeks	CR 22-63% PR 22-38%	Skin/GI

CR = complete response, GI = gastrointestinal, ORR = overall response rate, PR = partial response, QOD = every other day

\* No standard salvage therapy has been defined, as few comparative clinical trials or prospective case series are available. The available studies often have small numbers of patients and variable definitions of steroid refractory and response to therapy. Some reports are of initial therapy after steroids, while others are after multiple lines of therapy. Use caution when comparing regimens.

9. **Manifestations and grading of chronic GVHD<sup>14,128,129</sup>**
  - a. Leading cause of non-relapse mortality post-transplant and can significantly decrease quality of life. Multidisciplinary care is recommended to recognize signs and symptoms early and mitigate organ damage.
  - b. **Time frame: can occur at any point after allogeneic HCT but typically after 100 days post HCT (generally between 3 months to 2 years after HCT, with two-thirds of cases in the first 12 months)<sup>214</sup>**
  - c. **Can present in a multitude of organ systems: skin, nails, mouth, eyes, genitalia, gastrointestinal tract, liver, lungs, musculoskeletal, hematologic/immune (see table below)<sup>215</sup>**
  - d. **Often characterized by fibrosis in involved organ(s)**
  - e. **National Institutes of Health (NIH) Consensus Development Project established diagnostic and distinctive signs to assist diagnosis and classification<sup>127</sup>**

**Organ Specific Signs and Symptoms of cGVHD<sup>127,128,215</sup>**

Organ	Signs / Symptoms	
Skin	Sclerosis Poikiloderma Lichen-like features	Erythema Hypo- or hyperpigmentation Maculopapular rash
Eyes	Dry eyes Photophobia	Keratoconjunctivitis
Mouth	Xerostomia Ulcers	Gingivitis Erythema
Gastrointestinal	Difficulty swallowing Esophageal strictures	Anorexia
Liver	Elevated total bilirubin Elevated alkaline phosphatase	Fibrosis
Lungs	Shortness of breath Bronchiolitis obliterans	Cryptogenic organizing pneumonia
Musculoskeletal	Joint stiffness Muscle cramps	Decreased range of motion
Hematologic/immune	Thrombocytopenia	Hypo- or hypergammaglobulinemia

- g. Clinical and Global Scoring System for cGVHD<sup>127</sup>
  - 1) A clinical scoring system (0 – 3) proposed by the NIH Consensus Development Project enables grading of each individual organ system and considers the effect of cGVHD on the patient’s functional status

- 2) The Global Score considers the number of organs/sites involved and the severity of clinical scores within those organs/sites to give an overall rating of mild, moderate, or severe.

10. Initial treatment of chronic GVHD<sup>14,216</sup>

- a. First line therapy based on organ involvement, severity, presence/absence of high-risk features and risk of corticosteroid toxicity (see table)

Comparison of First Line Chronic GVHD Treatment Guideline Recommendations

NCCN Guidelines <sup>14</sup>	ASTCT (ASBMT) Guidelines <sup>216</sup>
<ul style="list-style-type: none"> <li>Enroll in clinical trial if available</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>Restart, continue, or escalate original immunosuppressive agent</li> </ul> <p>AND/OR</p> <ul style="list-style-type: none"> <li>Systemic corticosteroids <ul style="list-style-type: none"> <li>Methylprednisolone* 0.5-1 mg/kg/day</li> <li>Initial dose influenced by: organs involved, severity, comorbidities</li> </ul> </li> <li>Topical steroids/treatments as clinically indicated (e.g., triamcinolone, tacrolimus, clobetasol, dexamethasone oral rinse, estrogen cream)</li> </ul>	<p><u>Mild cGVHD</u></p> <ul style="list-style-type: none"> <li>Topical immunosuppressants alone with close follow-up and screening <ul style="list-style-type: none"> <li>Consider relapse risk when deciding between topical and systemic</li> </ul> </li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>Systemic corticosteroids <ul style="list-style-type: none"> <li>Consider prednisone 1 mg/kg/day</li> </ul> </li> </ul>
<p><u>Lung (BOS) involvement</u></p> <ul style="list-style-type: none"> <li>Inhaled corticosteroid ± azithromycin (for treatment of BOS only) <ul style="list-style-type: none"> <li>Example: FAM regimen</li> <li>Fluticasone (or other inhaled steroid)</li> <li>Azithromycin</li> <li>Montelukast</li> </ul> </li> </ul> <p>Lung transplant evaluation with progressive disease after multiple lines of therapy</p>	<p><u>Moderate or severe cGVHD</u></p> <ul style="list-style-type: none"> <li>Systemic corticosteroids ± topical treatments <ul style="list-style-type: none"> <li>Prednisone 1 mg/kg/day or equivalent dose of methylprednisolone</li> </ul> </li> <li>Consider restarting or adding calcineurin inhibitor in those at high risk for corticosteroid toxicity or high-risk features (e.g. thrombocytopenia, progressive onset from acute GVHD)</li> </ul>

\*Or equivalent dose of prednisone. BOS = bronchiolitis obliterans syndrome

- b. Consider the presence or absence of high-risk features (e.g. thrombocytopenia, progressive onset from acute GVHD, bilirubin > 2 mg/dL) in decision for systemic vs. local therapy as well as the underlying disease indication for transplant (malignant vs. non-malignant disease)<sup>217</sup>
- c. Consideration of prednisone + calcineurin inhibitor
- 1) May benefit patients with platelet count < 100,000/L<sup>218</sup>



- a) Complete response in 33% of patients receiving initial therapy
  - b) 53% of patients receiving initial therapy survived; higher than historical control in the azathioprine vs. prednisone study<sup>219</sup>; supports combination therapy for patients with thrombocytopenia
- 2) Not more effective if platelets are > 100,000/L<sup>220</sup>
  - a) TRM was 17% in cyclosporine + prednisone vs. 13% in prednisone at 5 years, P = 0.11. No difference in the cumulative incidence of survival, relapse, need for secondary GVHD treatment, or discontinuation of immunosuppression.
  - b) Survival without recurrent malignancy lower in combination arm 61% vs. 71%, P = 0.03
  - c) Avascular necrosis less in combination 12% vs. 23%, P = 0.04
- d. **FAM regimen for bronchiolitis obliterans syndrome (BOS) - lung cGVHD<sup>138,221</sup>**
  - 1) In addition to systemic corticosteroids, the FAM regimen of inhaled fluticasone twice daily (or other inhaled corticosteroid), azithromycin 250 mg 3 times weekly, and montelukast 10 mg daily was shown to slow progression of pulmonary function decline in an open label, phase 2 study<sup>222</sup>
- e. **Other combinations have not been shown to be beneficial as initial therapy<sup>216</sup>**
- f. Response should be reevaluated according to the NIH Response Criteria<sup>223</sup> every 3 months or whenever a major change in treatment is made.
- g. Patients with moderate to severe GVHD will generally require systemic therapy for at least 1 year<sup>217</sup>
- h. If a response is achieved, steroids should be tapered as possible to lessen side effects and infection risk.<sup>14,216</sup> Systemic treatment typically should continue for at least 4-8 weeks to avoid frequent relapses of symptoms.<sup>216</sup> The ASTCT guidelines recommend tapering prednisone to an every other day regimen as able to potentially reduce toxicity.<sup>216</sup>
- i. Ancillary and supportive care therapies<sup>224</sup>
  - 1) Due to the refractory nature of cGVHD and the use of prolonged and high dose immunosuppressant treatments, ancillary and supportive therapies are paramount to prevent morbidity from cGVHD itself and treatments of cGVHD<sup>14</sup>
  - 2) **Review the NIH Ancillary Therapy and Supportive Care Working Group Report by Carpenter S et al.<sup>224</sup> (one of recommended readings for module available at: <http://www.ncbi.nlm.nih.gov/pubmed/25838185>), in particular Table 1**

- a) Provides organ-specific recommendations for topical treatments, infection prevention recommendations, and other protective measures

11. Steroid-refractory chronic GVHD

- a. Approximately 40-50% of patients will develop steroid-refractory chronic GVHD and be evaluated for additional or alternative therapy. In clinical practice, second-line therapy is generally considered when one of the criteria in the table below is met.<sup>138,214,225,226</sup>

**cGVHD Response Criteria and Definitions of Steroid-refractory cGVHD<sup>14,216</sup>**

Response Category	Response Criteria
Steroid refractoriness/resistance	<ul style="list-style-type: none"> <li>Progression or development of new clinical manifestations on prednisone <math>\geq 1</math> mg/kg/day for 1-2 weeks</li> <li>No improvement despite treatment for 4-8 weeks on prednisone <math>\geq 0.5</math> mg/kg/day</li> </ul>
Steroid dependence	<ul style="list-style-type: none"> <li>Inability to taper prednisone below 1 mg/kg/day within 3 months</li> <li>Inability to taper prednisone below 0.25 mg/kg/day for at least 2 attempts separated by 8 weeks</li> <li>Worsening of symptoms during a taper below 0.5 mg/kg/day</li> </ul>
Steroid intolerance	<ul style="list-style-type: none"> <li>Unacceptable toxicity attributed to corticosteroid therapy</li> </ul>

- b. **ASTCT and NCCN Guidelines<sup>®</sup> do not recommend any specific agent for second line therapy, citing insufficient evidence/lack of comparative studies<sup>14,226</sup>.** There is no standard of care (minimal randomized trials have been done, see table below). Clinical trials should be pursued if available and appropriate. General considerations for selection of additional systemic agents include<sup>14,130</sup>
  - 1) History/response with prior therapies
  - 2) Agents with non-overlapping toxicities
  - 3) Likelihood of response to organ involved
  - 4) History of infectious complications
  - 5) Drug-drug interactions
  - 6) Patient preference
  - 7) Provider experience
  - 8) Cost
- c. Additional systemic therapies can be added to steroid therapy for steroid-refractory cGVHD. NCCN Guidelines<sup>®</sup> recommend tapering steroids as able after addition of additional systemic agent(s), although some patients may require life-long steroid therapy.

- d. **Belumosudil: FDA-approved medication for steroid-refractory chronic GVHD after failure of at least 2 prior lines of systemic therapy<sup>227</sup>**
- 1) Mechanism of action:
    - a) Selective kinase inhibitor of rho-associated, coiled-coil-containing protein kinase-2 (ROCK2). ROCK2 inhibition leads to downregulation of signal transducer and activator of transcription 3 (STAT3) and upregulation of STAT5, which shifts the type 17 helper T-cell and regulatory T-cell balance. Overall, ROCK2 inhibition decreases abnormal profibrotic signaling and proinflammatory pathways.
  - 2) Indications & Dose:
    - a) FDA-approved July 2021 for treatment of chronic graft-versus-host disease in adult and pediatric patients at least 12 years of age after failure of at least 2 prior lines of systemic therapy
    - b) 200 mg orally once daily
  - 3) Toxicities:
    - a) Common: infection, increased liver function tests, edema, asthenia
    - b) Severe (grade 3 or 4): hypertension, hyperglycemia, lymphocytopenia, hemorrhage
  - 4) Drug-Drug Interactions:
    - a) Substrate of CYP3A4 (major), P-glycoprotein/ABCB1 (minor), CYP2C8 (minor) and CYP2D6 (minor)
    - b) A dose adjustment of belumosudil to 200 mg orally twice daily is recommended when used with strong CYP3A4 inducers
    - c) Antacids may decrease the serum concentration of belumosudil and should be separated by 2 hours if used concomitantly
    - d) A dose adjustment of belumosudil to 200 mg orally twice daily is recommended when used with proton pump inhibitors
  - 5) Clinical Evidence:

## Belumosudil Clinical Trials

Reference/Trial	Trial Design/Population	Outcomes
ROCKstar Study Cutler et al. 2021 <sup>227</sup>	<ul style="list-style-type: none"> <li>Randomized, phase II, open-label trial evaluating 2 doses of belumosudil</li> <li>N=132 with chronic GVHD after 2-5 prior lines of therapy</li> </ul>	<ul style="list-style-type: none"> <li>ORR for 200 mg daily = 74% (62-84%)</li> <li>Median duration of response 54 weeks</li> <li>21% discontinued corticosteroid treatment during study</li> <li>Approximately 60% reported significant improvement in symptoms</li> </ul>
Jagasia et al. 2021 <sup>228</sup>	<ul style="list-style-type: none"> <li>Phase IIa, open-label, dose-finding trial</li> <li>N=54 with chronic GVHD after 1-3 prior lines of therapy</li> </ul>	<ul style="list-style-type: none"> <li>ORR for 200 mg daily = 65% (38-86%)</li> <li>Median duration of response 35 weeks</li> <li>19% discontinued corticosteroid treatment during study</li> <li>Significant improvements in quality-of-life scores achieved in 50%</li> </ul>

ORR = overall response rate

- e. **Ruxolitinib: FDA-approved in September 2021 for chronic GVHD in adult and pediatric patients  $\geq 12$  years after failure of one or two lines of systemic therapy**
- 1) **REACH3 was a randomized, open-label phase III clinical trial comparing ruxolitinib 10 mg twice daily (N=165) to investigator's choice of 10 control options (N=164) in patients with glucocorticoid-refractory or glucocorticoid-dependent cGVHD<sup>229</sup>**
  - 2) **Overall response rate at week 24 was higher in the ruxolitinib group vs. control (49.7% vs. 25.6%, OR 2.99; P<0.001)**
  - 3) **The ruxolitinib group had greater response of symptoms compared to the control group (24.2% vs. 11%, OR 2.62; P=0.001)**
  - 4) **Most common grade 3 or greater adverse events in ruxolitinib arm were primarily hematologic, including thrombocytopenia (15.2%), anemia (12.7%), and neutropenia (8.5%)**
  - 5) **Infections rates, including viral, bacterial, and fungal, appeared to be similar between ruxolitinib and control arms**

**Systemic Therapies for Steroid-Refractory cGVHD\***

Agent	Regimen	Response Rate	Organ(s) most likely to respond
Abatacept <sup>230</sup>	10 mg/kg every 2-4 weeks	PR 44%	Mouth, GI, joints, skin, eyes, lung
Alemtuzumab <sup>231,232</sup>	3 mg once, then 10 mg x 5 doses over 4 weeks	PR 40% CR 30%	GI, liver
<b>Belumosudil (FDA-approved for cGVHD after failure of at least 2 lines of therapy)<sup>227</sup></b>	200 mg orally once daily	60-80%	Joints/fascia, GI, eyes, mouth, liver, skin, lungs
Etanercept <sup>192,233</sup>	25 mg twice weekly x 4 weeks, then 25 mg weekly x 4 weeks	62%	Lung
Extracorporeal photopheresis <sup>195,234-252</sup> (randomized study in second line therapy for chronic GVHD) <sup>253</sup>	Various schedules- three times per week in week 1, followed by two consecutive days per week in weeks 2-12, then twice every month during weeks 12-24 is common.	60-70%, CR as high as 80% reported.	Skin is most responsive organ, GI, liver, eyes, oral mucosa
Hydroxychloroquine <sup>254</sup>	800 mg PO daily	53%	Skin, oral, liver
<b>Ibrutinib<sup>255,256</sup> (FDA-approved agent for cGVHD after failure of 1 or more lines of systemic therapy based on multicenter, open-label study)<sup>222</sup></b>	420 mg PO daily	60-70% CR ~30%	Skin, oral, GI
Imatinib <sup>257-261</sup>	100 mg PO daily, increase to 400 mg daily if tolerated	50-79%	Skin, eyes, GI Mild pulmonary GVHD may respond, but moderate and severe are not likely to respond
Interleukin-2 <sup>262</sup>	1x10 <sup>6</sup> IU/m <sup>2</sup> /day	52%	Skin, muscle/joints, GI, lungs, liver
Ixazomib <sup>263</sup>	4 mg PO day 1, 8, 15 every 28 days	40-50%	Skin, eyes, joint, oral
Methotrexate <sup>264</sup>	7.5 mg/m <sup>2</sup> /week	75%	Skin, oral
Mycophenolate mofetil <sup>200,202,203,265-271</sup>	500 mg - 1g PO BID increasing up to 1.5g BID if no initial response or in some cases based on therapeutic drug monitoring	40-57%	Skin, oral, GI
Pentostatin <sup>272-275</sup>	4 mg/m <sup>2</sup> IV every other week x 24 weeks	53-55%	Skin, oral *Avoid in pulmonary GVHD because of high infection risk
Rituximab <sup>276-287</sup> (or biosimilar)	50- 375 mg/m <sup>2</sup> weekly x 4 – 8 weeks	50-80% (meta-analysis 66%)	Skin, oral, musculoskeletal, autoimmune cytopenias
<b>Ruxolitinib<sup>207,229,288</sup> (FDA-approved after failure of 1 or 2 lines of systemic therapy, NCCN® category 1)</b>	5-10 mg PO twice daily	78%	Skin, oral, liver, lung, gastrointestinal, musculoskeletal
Sirolimus <sup>289-291</sup>	0.25-0.5 mg PO daily, titrate to trough level of 4-8 ng/mL. Loading dose (6-12 mg) may be omitted	56-81%	Skin, oral, eyes, and lower GI

12. Vaginal cGVHD – Clinical Guidelines for Gynecologic Care after HCT<sup>292</sup>
  - a. Clinical assessment
    - 1) **Symptomatic women should be referred to a gynecologist with experience in GVHD**
    - 2) **Asymptomatic women should be offered a gynecological exam yearly**
    - 3) **Yearly gynecological exam should include cervical cytology to assess for secondary malignancy**
    - 4) **If treatment of suspected genital chronic GVHD is not successful in 6 – 8 weeks, biopsy should be obtained to avoid incorrect diagnosis**
  - b. Treatment
    - 1) **Water only is recommended for genital hygiene**
    - 2) **Tight clothing and perfumed products should be avoided**
    - 3) **Topical estrogen can be used for genital atrophy**
    - 4) **Topical corticosteroids can be used for rapid control of inflammation in the setting of genital chronic GVHD**
    - 5) Regular intercourse, dilators, and surgery can improve vaginal narrowing

E. Immunosuppressive Agent Toxicity and Drug Monitoring

**Immunosuppressive Therapies**<sup>157,226,293-295</sup>

<b>α<sub>1</sub>-antitrypsin</b>	
Toxicity	Generally well-tolerated
Drug Interactions	No known significant interactions
Convenience	IV formulation only; dosed at 60 mg/kg twice weekly for 4 weeks
<b>Abatacept</b>	
Toxicity	Pulmonary infections, diarrhea, fatigue, CMV, EBV
Drug Interactions	Not usually clinically significant
Convenience	30-minute infusion every 2-4 weeks
<b>Alemtuzumab</b>	
Toxicity	Serious and, in rare instances, fatal cytopenia and marrow hypoplasia. Autoimmune thrombocytopenia and hemolytic anemia have occurred. Higher incidence of pancytopenia if exceeds single doses >30 mg or cumulative doses >90 mg per week, which are not recommended, and such doses are unnecessary to induce profound lymphopenia in GVHD. Prolonged CD4 lymphopenia means that prophylaxis against <i>Pneumocystis jiroveci</i> pneumonia and herpes virus infections is advised. Very high risk for viral infections. Weekly PCR monitoring for EBV, adenovirus, and CMV PCR for at least 6 months after last dose of alemtuzumab or until absolute lymphocyte count >300 per microliter.
Drug Interactions	Not usually clinically significant

Convenience	Infusion therapy is given over 2 hours and should not begin at doses >3 mg. If tolerated, daily doses may increase to 10 mg, but higher doses are not likely to be necessary for GVHD therapy. The schedule and number of doses for GVHD therapy is unclear. The overall average half-life (t <sub>1/2</sub> ) is about 12 days. No longer commercially available, provided through the Campath Distribution Program free of charge with patient-specific drug supply.
<b>Horse Anti-thymocyte Globulin</b>	
Toxicity	Intradermal skin testing advised before the first infusion. Fever 51% and chills 16% (due to release of endogenous leukocyte pyrogens), thrombocytopenia 30%, leukopenia 14%, and rash 27%. Five to 10 percent of patients experience serum sickness (lower if premedicated with steroids), dyspnea/apnea, arthralgia, chest, back, or flank pain, diarrhea, nausea and/or vomiting. Very high risk for viral infections. Weekly PCR monitoring for EBV, adenovirus, and CMV PCR for at least 6 months after last dose of horse ATG or until absolute lymphocyte count >300 per microliter.
Drug Interactions	Not usually clinically significant
Convenience	Intense clinical and vital sign monitoring required during infusion; IV infusion only. Regimens vary for GVHD: 15 mg/kg every other day × 6 doses to 15 mg per kg twice daily × 5 days
<b>Rabbit Anti-thymocyte Globulin</b>	
Toxicity	Skin testing is not considered necessary but must be monitored closely for anaphylaxis or cytokine release syndrome. Premedication includes methylprednisolone. Thrombocytopenia and opportunistic infections are common. Very high risk for viral infections. Weekly PCR monitoring for EBV, adenovirus, and CMV PCR for at least 6 months after last dose of rabbit ATG or until absolute lymphocyte count >300 per microliter.
Drug Interactions	Not usually clinically significant
Convenience	Intense clinical and vital sign monitoring required; IV infusion only. Variable 4- to 7-dose course with complex schedule for GVHD. It is advisable to start with 0.5 mg/kg for the first infusion and increase to 1-1.5 mg/kg for subsequent doses (maximum is 1.5 mg/kg in a given day); total cumulative dose is 6-7.5 mg/kg.
<b>Basiliximab</b>	
Toxicity	Hypersensitivity reactions possible although not reported in patients receiving it for chronic GVHD; bacterial, viral and fungal infections reported
Drug Interactions	May increase trough level and toxicity of tacrolimus
Convenience	IV formulation only
<b>Belumosudil<sup>227</sup></b>	
Toxicity	Generally well-tolerated, edema, hypertension, increased liver function tests, infection
Drug Interactions	Substrate for CYP3A4 and P-glycoprotein so careful attention to concomitant therapies that interact with CYP3A or P-glycoprotein is necessary. Separation from antacids by 2 hours recommended. Dose adjustment with proton pump inhibitors recommended.
Convenience	Oral formulation only
<b>Cyclosporine</b>	

Toxicity	Nephrotoxicity, hypertension (generally controlled with dihydropyridine calcium channel blockers or dose reduction), hypomagnesemia (common; may be difficult to replete with oral magnesium), tremors of extremities (common, particularly hands; may limit activity), neurotoxicity (headaches, seizures, peripheral neuropathy, cortical blindness, posterior reversible encephalopathy syndrome [PRES]), hyperkalemia; hyperglycemia, hirsutism, thrombotic microangiopathy (TMA), allergic reactions (with intravenous products; related to the diluents)
Drug Interactions	Cyclosporine is a substrate for CYP3A4 and P-glycoprotein so careful attention to concomitant therapies that interact with CYP3A or P-glycoprotein is necessary, including voriconazole and posaconazole.
Convenience	Oral and IV formulations available; use modified cyclosporine for oral dosing Pharmacokinetic monitoring required
<b>Etanercept</b>	
Toxicity	Risk of infection (viral, fungal, bacterial). Subcutaneous injections are generally well tolerated.
Drug Interactions	Not usually clinically significant
Convenience	Subcutaneous administration given twice weekly for 8 weeks at a dose of 0.4 mg/kg per dose (maximum dose, 25 mg)
<b>Extracorporeal Photopheresis (ECP)</b>	
Toxicity	Generally well-tolerated. Blood loss from the extracorporeal circuit, hypocalcemia due to anticoagulant, mild cytopenia, and catheter-associated bacteremia, but overall infection risks do not seem to be increased beyond standard therapy.
Drug Interactions	None
Convenience	Requires travel to ECP centers for up to many months. Complex schedule typically 3 per week (week 1), 2 per week (weeks 2-12), and 2 per 4 weeks thereafter.
<b>Glucocorticoids</b>	
Toxicity	Hyperglycemia, hypertension, insomnia, labile mood, gastritis, osteopenia, avascular bone necrosis, myopathy, impaired wound healing and secondary adrenal insufficiency.
Drug Interactions	Not usually clinically significant
Convenience	Easy to prescribe
<b>Ibrutinib<sup>255</sup></b>	
Toxicity	Nausea, vomiting, diarrhea, fatigue, rash, bleeding, hypertension, edema, myelosuppression, second cancers, musculoskeletal pain, infection, atrial fibrillation, nephrotoxicity
Drug Interactions	Ibrutinib is a substrate of CYP3A4 so careful attention to concomitant therapies that inhibit CYP3A4 is necessary, including azoles. Dose adjustments recommended for concomitant voriconazole and posaconazole
Convenience	Oral formulation only
<b>Imatinib</b>	
Toxicity	Nausea, vomiting, diarrhea, arthralgia, myalgia, edema, fluid retention, myelosuppression, rash, hepatotoxicity
Drug Interactions	Imatinib is a substrate and inhibitor of CYP3A4 so careful attention to concomitant therapies that interact with CYP3A4 is necessary, including cyclosporine, tacrolimus, voriconazole, and posaconazole
Convenience	Oral formulation only
<b>Infliximab</b>	



Toxicity	Generally well tolerated. Anaphylaxis is uncommon. High risk for infections. Very high risk for viral infections; weekly PCR monitoring for EBV, adenovirus, and CMV PCR for at least 6 months after last dose of infliximab or until absolute lymphocyte count >300 per microliter.
Drug Interactions	Not usually clinically significant
Convenience	IV formulation only; dosed at 10 mg/kg/week for at least 4 doses
<b>Interleukin-2</b>	
Toxicity	Constitutional symptoms (fever, malaise, fatigue), renal dysfunction, thrombocytopenia
Drug Interactions	Not usually clinically significant
Convenience	Daily subcutaneous administration of $1 \times 10^6$ IU/m <sup>2</sup>
<b>Ixazomib<sup>263</sup></b>	
Toxicity	Thrombocytopenia, fatigue, nausea, diarrhea, infection
Drug Interactions	CYP3A4 substrate
Convenience	Oral formulation only; once weekly administration
<b>Methotrexate</b>	
Toxicity	<b>Mucositis</b> , delayed engraftment, hepatotoxicity, pulmonary toxicity and VOD, myelosuppression
Drug Interactions	Penicillin, salicylate, phenytoin, sulfonamides, probenecid, tetracycline, chloramphenicol (may not be relevant at dosing used for GVHD)
Convenience	Oral and IV formulations available
<b>Mycophenolate</b>	
Toxicity	Dose-related cytopenia and gastrointestinal toxicity, consider risk: benefit carefully when treating gastrointestinal GVHD. Enteric-coated mycophenolic acid (Myfortic®) may be better tolerated.
Drug Interactions	May compound cytopenia when used with other myelosuppressive drugs
Convenience	Smallest pill formulations are 250 mg or 180 mg (Myfortic®). IV formulation and oral suspension are available
<b>Pentostatin</b>	
Toxicity	Myelosuppression, reversible elevation of liver function test results may occur. Dose reduction to 0.75 mg/m <sup>2</sup> is recommended if creatinine clearance reduced to between 30 mL/min and 50 mL/min and discontinued if <30 mL/min/1.73 m <sup>2</sup> . Stop or withhold therapy for neurotoxicity. Very high risk for viral infections. Weekly PCR monitoring for EBV, adenovirus and CMV PCR for at least 6 months after last dose of pentostatin or until absolute lymphocyte count >300 per microliter.
Drug Interactions	Not usually clinically significant
Convenience	IV formulation only and complex schedule: 1.5 mg/m <sup>2</sup> on days 1 to 3 and 15 to 17
<b>Rituximab</b>	
Toxicity	Infection, infusion related reaction, late neutropenia/thrombocytopenia
Drug Interactions	Not usually clinically significant
Convenience	IV formulation, typically given as 375 mg/m <sup>2</sup> IV weekly x 4 weeks
<b>Ruxolitinib<sup>159</sup></b>	
Toxicity	<b>Myelosuppression (anemia, neutropenia, thrombocytopenia), hemorrhage, hypercholesterolemia, hypertriglyceridemia, hepatotoxicity, edema, infection including bacterial, mycobacterial, fungal and viral</b>
Drug Interactions	<b>Substrate of CYP3A4 (primary) and minimally CYP2C9</b> <b>No dose adjustment per package insert for CYP3A4 inhibitors when treating steroid-refractory aGVHD except ketoconazole (5 mg daily)</b>
Convenience	Oral formulation only; may administer through nasogastric tube
<b>Sirolimus</b>	

Toxicity	Reversible, dose-related myelosuppression, hypertriglyceridemia, nephrotoxicity, TMA and neurotoxicity when combined with calcineurin inhibitors. Less common clinically relevant toxicities are transaminase elevations, edema, arthralgia, and noninfectious pneumonitis.
Drug Interactions	Sirolimus is a substrate for CYP3A4 and P-glycoprotein. Initial 90% dose reduction in sirolimus when combining with voriconazole (75% reduction for posaconazole, 25% reduction for fluconazole). Sirolimus may increase the risk for rhabdomyolysis if used with HMG-CoA reductase inhibitors. In patients who develop HUS, calcineurin inhibitor therapy should be stopped, and the dose of sirolimus should be adjusted to ensure that the trough level <10 ng/mL. In patients with a serum total bilirubin >2 mg/dL, the sirolimus dose should be reduced by 30%.
Convenience	Oral formulations only: 0.5-mg, 1-mg, and 2-mg tablets as well as a 1-mg/mL oral solution. Pharmacokinetic monitoring required.
<b>Tacrolimus</b>	
Toxicity	Nephrotoxicity, hypertension (generally controlled with dihydropyridine calcium channel blockers or dose reduction), hypomagnesemia (common; may be difficult to replete with oral magnesium), tremors of extremities (common, particularly hands; may limit activity), neurotoxicity (headaches, seizures, peripheral neuropathy, cortical blindness, posterior reversible encephalopathy syndrome [PRES]), hyperkalemia; hyperglycemia, hyperlipidemia, alopecia, TMA, allergic reactions (with intravenous products-related to the diluents).
Drug Interactions	Tacrolimus is a substrate for CYP3A4 - reductions are needed, including with voriconazole and posaconazole
Convenience	Oral (0.5 mg, 1 mg, and 5 mg capsules) and IV formulations available Pharmacokinetic monitoring required
<b>Tocilizumab</b>	
Toxicity	Hepatotoxicity, hyperlipidemia, infusion related hypersensitivity reactions, infection, neutropenia, thrombocytopenia, GI perforation
Drug Interactions	Not usually clinically significant
Convenience	IV formulations only

**Patient Case (continued):** LC is a 56-year-old African American female with AML in first remission who underwent a haploidentical allogeneic HCT. She was diagnosed with grade III acute GVHD at day +130 and is currently treated with tacrolimus and methylprednisolone 2 mg/kg/day. She has no known drug allergies.

**Question #5: What is the most appropriate infection prophylaxis regimen for LC at this time?**

- A. Sulfamethoxazole/trimethoprim, acyclovir, posaconazole
- B. Levofloxacin, acyclovir, letermovir, fluconazole
- C. Penicillin, acyclovir, posaconazole, pentamidine
- D. Sulfamethoxazole/trimethoprim, letermovir, voriconazole

F. Infection

1. Hematopoietic colony stimulating factors (CSFs)<sup>32</sup>

a. **Autologous**

1) **Administration of CSFs after autologous HCT is standard of care to reduce the duration of severe neutropenia.<sup>32</sup> Filgrastim (G-CSF) or**

**biosimilar dosing is 5 mcg/kg SQ daily starting between day + 1 and day +5 and continued until ANC is greater than  $2-3 \times 10^9/L$ <sup>32</sup>**

- 2) Post-transplant GCSF is associated with savings in the duration of hospitalization and overall medical costs<sup>296</sup>
- 3) Note most of the data supporting use after autologous HCT is with bone marrow, not GCSF-mobilized peripheral blood stem cells, which are the current standard stem cell source

**b. Allogeneic**

- 1) **CSF may be used after allogeneic HCT to reduce the duration of severe neutropenia.<sup>32</sup> Benefit was shown in patients receiving bone marrow stem cells, however there are limited data for benefit with peripheral blood stem cells.<sup>297</sup> CSF use is standard of care with cord blood transplant, but not consistently used for other allogeneic HCT patients.**

**2. Risk of infection mainly related to time since transplant and presence/absence of GVHD<sup>298</sup>**

**Risk Factors for Infection Based on Impairment of Host Defenses<sup>201,298</sup>**

<b>Phase of HCT</b>	<b>Impaired host defense as a result of:</b>
Early recovery (Pre-engraftment, or conditioning start to around Day 30)	Neutropenia and lymphopenia Breakdown in oral and gastrointestinal mucosa from chemotherapy Breakdown in skin barrier (rash, central venous catheter) Underlying malignancy Changes in normal microbial flora (due to antibiotic prophylaxis)
Mid recovery (2-3 months post HCT)	Breakdown in mucosal and/or skin barriers due to GVHD Depressed cellular and humoral immune responses due to recovery of donor-related immune system, immunosuppressive therapy, or aGVHD Skin barrier compromised by central venous catheter
Late recovery (> 3 months post HCT)	Depressed reticuloendothelial function, functional asplenia due to cGVHD Persistent depressed cellular and humoral immunity with cGVHD Immunoglobulin subclass deficiencies Non-specific suppressor cells with cGVHD

3. **Multiple guidelines exist providing recommendations to prevent infection in HCT patients<sup>298-300</sup>**
  - a. **Key summary points are listed below for prevention of the most common types of infections, as well as comparison prophylaxis tables from various guidelines for antibacterial, *Pneumocystis*, antifungal, and antiviral pathogens**
4. **The Global Guidelines<sup>298</sup> are the most specific to prevent infection in HCT patients but are over 10 years old and therefore do not incorporate newer medications, testing methods, etc.**
5. **In 2021, ASTCT began publishing updated guidelines for individual infections, which serve to update the previous Global Guidelines in a more concise and practical format**

- a. **Topics published thus far: Enterobacterales<sup>301</sup>, Aspergillosis<sup>302</sup>, and Cytomegalovirus<sup>303,304</sup>, *Clostridioides difficile*<sup>305</sup>**
6. **The ASCO/IDSA<sup>300</sup> and NCCN<sup>299</sup> guidelines have also been published/updated more recently**
7. **Antibacterial prophylaxis summary**
  - a. **Early (peri-transplant, pre-engraftment): fluoroquinolone recommended during period of neutropenia**
  - b. **Late (> day 100): for those with cGVHD on immunosuppression, risk of *Streptococcus pneumoniae* warrants prophylaxis with penicillin or other appropriate agent while on immunosuppression or low IgG levels**
  - c. **Routine IVIG prophylaxis not recommended irrespective of IgG level in the absence of recurrent infection<sup>306</sup>**
8. ***Pneumocystis* prophylaxis summary**
  - a. **Prophylaxis is recommended for all allogeneic patients for at least 6 months and autologous patients with risk factors for 3-6 months**
  - b. **Corticosteroid therapy with prednisone  $\geq 20$  mg or equivalent for  $\geq 4$  weeks warrants prophylaxis (e.g., GVHD treatment)**
  - c. **Sulfamethoxazole/trimethoprim is the preferred first-line agent**
    - 1) Sulfamethoxazole/trimethoprim also provides protection against additional pathogens such as *Nocardia*, *Toxoplasma*, enteric pathogens, urinary pathogens, and some respiratory pathogens
    - 2) Prophylaxis is usually started after sustained engraftment achieved due to potential concerns for delayed engraftment with use
9. **Antifungal prophylaxis summary**
  - a. **Autologous HCT: consider fluconazole for those with risk factors (e.g., mucositis) during duration of neutropenia associated with conditioning regimen**
  - b. **Allogeneic HCT at low risk of mold infection: fluconazole through at least Day +75**
  - c. **Allogeneic HCT at high risk of mold infection: triazole or echinocandin through duration of prolonged neutropenia or immunosuppressive treatment**
  - d. **Allogeneic HCT with GVHD on treatment: posaconazole through duration of immunosuppressive treatment**
    - 1) In a randomized, double-blind trial, posaconazole was superior to fluconazole for preventing invasive aspergillosis (2.3% vs. 7%, OR 0.31; 95% CI 0.13-0.75, P = 0.006) and deaths from invasive fungal infections (1% vs. 4%, P = 0.046) in patients with GVHD on immunosuppression<sup>307</sup>

10. **Antiviral prophylaxis summary**

- a. **HSV prophylaxis: recommended for all allogeneic HSV-seropositive patients and considered in autologous HSV-seropositive patients (especially with mucositis) through the duration of neutropenia or resolution of mucositis**
- b. **VZV prophylaxis: recommended for all HCT patients typically for at least one year post transplant**
- c. **Acyclovir or valacyclovir preferred agents for HSV and VZV**
- d. **Influenza A and B prevention: life-long seasonal influenza vaccination recommended for all HCT candidates and recipients (see vaccination section for timing)**
  - 1) Prophylaxis or preemptive treatment recommended for exposure or during outbreaks <24 months post-HCT or during significant immunosuppression
  - 2) Oseltamivir 75 mg PO twice daily x 5 days (treatment) or 75 mg PO daily x 10-14 days (postexposure prophylaxis)
- e. **CMV prevention: either a prophylaxis strategy or preemptive strategy is recommended for allogeneic patients**
  - 1) **Preemptive: historically more commonly used strategy to minimize toxicity, especially before the availability of letermovir and in CMV seronegative HCT**
    - a) **Preemptive therapy is initiated for asymptomatic patients with evidence of CMV on laboratory markers (e.g., polymerase chain reaction [PCR])**
    - b) **Most common initial agent is valganciclovir 900 mg PO BID x 7-14 days (induction dosing), then 900 mg PO daily x 1 – 2 weeks or until indicator test is negative (maintenance dosing); alternatives include ganciclovir, foscarnet, cidofovir**
    - c) **Minimum treatment course is 14 days regardless of medication used**
  - 2) **Prophylaxis: letermovir 480 mg IV/PO once daily beginning between day 0 and day 28 post-HCT and continuing through day 100 for CMV prophylaxis in CMV-seropositive adult allogeneic HCT patients (\*FDA-approved in 2017, therefore not included in global guidelines)<sup>308</sup>**
    - a) **Spectrum of activity limited to CMV**
    - b) **Adjust dose to 240 mg daily with concomitant cyclosporine**
    - c) **Similar rates of adverse effects compared to placebo**
    - d) **Limited data regarding efficacy for treatment of CMV**

- 3) **Primary prophylaxis with ganciclovir, valganciclovir, or foscarnet is not generally recommended due to toxicity profile<sup>303</sup>**
- f. **Hepatitis B prevention<sup>299</sup>: screening recommended prior to start of immunosuppressive therapy and chemotherapy**
- 1) **Allogeneic HCT patients at high risk of reactivation (HBsAg+, HBcAb+, or increasing viral load) should be considered for prophylaxis with entecavir or tenofovir in consultation with hepatology specialist**
  - 2) **Surveillance should occur for 6 to 12 months post allogeneic HCT or through duration of GVHD**

#### Antibacterial Prophylaxis Guideline Comparisons and Recommendations

Guideline	Patient population	Timeline and Duration	Agent(s)
<b>Global Guidelines<sup>298</sup></b>  <b>Early bacterial prophylaxis</b>	Allogeneic & autologous HCT (adult)	From stem cell infusion until recovery from neutropenia or start of empiric antibacterial therapy for febrile neutropenia	Antipseudomonal fluoroquinolone (levofloxacin, ciprofloxacin)  Alternative: azithromycin
<b>Global Guidelines<sup>298</sup></b>  <b>Late bacterial (<i>Streptococcus pneumoniae</i>) prophylaxis</b>	Allogeneic with cGVHD	While on cGVHD immunosuppressive therapy or IgG levels remain low	Penicillin  Alternative: based on local resistance patterns
<b>ASTCT Enterobacterales<sup>301</sup></b>	Adult HCST	During neutropenia following HCT	Levofloxacin
<b>ASCO/IDSA<sup>300</sup></b>	Patients at high risk of febrile neutropenia or profound, protracted neutropenia (e.g., HCT patients with myeloablative regimens)	During anticipated time of neutropenia	Fluoroquinolone  Alternative: cefpodoxime
<b>NCCN<sup>299</sup></b>	Autologous & allogeneic HCT  Moderate to severe GVHD	During period of neutropenia	Consider fluoroquinolone  Alternatives: SMX/TMP, oral 3 <sup>rd</sup> generation cephalosporin

SMX/TMP = sulfamethoxazole/trimethoprim

### Pneumocystis Prophylaxis Guideline Comparisons and Recommendations

Guideline	Patient population	Timeline and Duration	Agent(s)
Global Guidelines <sup>298</sup>	Allogeneic HCT	From engraftment until at least 6 months post HCT  Continue longer if patients continue to receive immunosuppressive drugs or have cGVHD	SMX/TMP single strength or double strength daily or double strength three times per week  Alternatives: dapsone, aerosolized pentamidine, atovaquone
	Consider in autologous HCT with certain risk factors: <ul style="list-style-type: none"> <li>• Underlying hematologic malignancies</li> <li>• Intense conditioning regimens</li> <li>• Graft manipulation</li> <li>• High-dose corticosteroids</li> <li>• Recent purine analog therapy</li> </ul>	From engraftment until 3 to 6 months post HCT, or longer in patients with ongoing immunomodulatory therapy	
ASCO/IDSA <sup>300</sup>	Chemotherapy regimens with >3.5% risk of <i>Pneumocystis</i> pneumonia (e.g., ≥20 mg prednisone for ≥1 month, purine analog use)	Begin after engraftment, continue through period of augmented immunosuppression	SMX/TMP  Alternatives: dapsone, aerosolized pentamidine, atovaquone
NCCN <sup>®299</sup>	Allogeneic HCT (category 1)	Continue at least 6 months and while receiving immunosuppressive therapy	SMX/TMP (category 1)  Alternatives: dapsone, pentamidine (aerosolized or IV), atovaquone
	Consider autologous HCT (category 2B)	Continue 3-6 months post HCT	
	Prolonged corticosteroid use (prednisone equivalent ≥20 mg for ≥4 weeks)	Continue through duration of therapy	

SMX/TMP = sulfamethoxazole/trimethoprim

### Antifungal Prophylaxis Guideline Comparisons and Recommendations

Guideline	Patient population	Timeline and Duration	Agent(s)
<b>Global Guidelines<sup>298</sup></b>  <b><u>Yeast</u> Prophylaxis</b>	Allogeneic HCT	Start at beginning or end of conditioning regimen and continue for at least 75 days	Fluconazole  Alternatives: itraconazole, micafungin, voriconazole, posaconazole
	Consider in autologous HCT with certain risk factors: <ul style="list-style-type: none"> <li>• Underlying hematologic malignancies</li> <li>• Intense conditioning regimens or graft manipulation leading to prolonged neutropenia or mucosal damage</li> <li>• Recent purine analog therapy</li> </ul>	Start with conditioning regimen and continue through engraftment or 7 days after ANC >1000 cells/mm <sup>3</sup>	
<b>Global Guidelines<sup>298</sup></b>  <b><u>Mold</u> Prophylaxis</b>	Consider in allogeneic HCT at high risk: <ul style="list-style-type: none"> <li>• Prolonged neutropenia (higher risk includes UCB, BM, and neutropenia prior to HCT [e.g., aplastic anemia])</li> <li>• Presence of GVHD and treatment for GVHD</li> </ul>	Through duration of neutropenia or duration of treatment for GVHD	Posaconazole  Alternative: voriconazole
<b>ASTCT</b> <b>Aspergillosis<sup>302</sup></b>	Allogeneic HCT at high risk for Aspergillosis <ul style="list-style-type: none"> <li>• Prior Aspergillosis infection</li> <li>• Active hematologic malignancy</li> <li>• Mismatched unrelated, haploidentical, or UCB donor</li> <li>• Prolonged neutropenia</li> <li>• Presence of GVHD and treatment for GVHD</li> </ul>	Until day 75 or longer if risk factors for Aspergillosis continue or GVHD therapy continues	Posaconazole or voriconazole  Alternative: echinocandin if needed based on hepatic function or drug-drug interactions  Posaconazole preferred in those with GVHD



	<ul style="list-style-type: none"> <li>Significant environmental exposure</li> </ul>		
<b>ASCO/IDSA<sup>300</sup></b>	Patients at high risk of febrile neutropenia or profound, protracted neutropenia, especially with mucositis (e.g., HCT patients)	During anticipated time of neutropenia	<p>Oral triazole or parenteral echinocandin</p> <p>Mold-active azole recommended when risk of invasive aspergillosis is &gt;6% (e.g., treatment of GVHD): posaconazole, voriconazole, isavuconazole</p>
	Allogeneic HCT with GVHD	During treatment of GVHD	Mold-active azole (posaconazole, voriconazole, isavuconazole)
<b>NCCN<sup>®299</sup></b>	Allogeneic HCT (neutropenic)	During neutropenia	<p>Fluconazole or echinocandin (category 1)</p> <p>Alternatives (category 2B): voriconazole, posaconazole, amphotericin B</p>
	Allogeneic HCT with GVHD on significant immunosuppression	Until resolution of GVHD	<p>Posaconazole (category 1)</p> <p>Alternatives (category 2B): voriconazole, echinocandins, amphotericin B</p>
	Autologous HCT with mucositis	During neutropenia	Fluconazole or echinocandin (category 1)
	Autologous HCT without mucositis	N/A	Consider no prophylaxis (category 2B)
<b>IDSA<sup>309</sup></b>	<p>Allogeneic HCT at high risk of invasive Aspergillosis</p> <ul style="list-style-type: none"> <li>Hematologic disorders with dysfunctional neutrophils</li> </ul>	During prolonged neutropenia	<p>Posaconazole</p> <p>Alternatives: voriconazole, micafungin</p>

	<ul style="list-style-type: none"> <li>• Acute leukemia with repeated or prolonged neutropenia</li> <li>• History of invasive <i>Aspergillosis</i> prior to transplant</li> </ul>		
	Allogeneic HCT with GVHD	Through duration of immunosuppression	Posaconazole  Alternative: voriconazole

**Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) Antiviral Prophylaxis Guideline Comparisons and Recommendations**

Guideline	Patient population	Timeline and Duration	Agent(s)
<b>Global Guidelines<sup>298</sup></b>  <u>HSV</u>	HSV-seropositive allogeneic HCT	From start of conditioning regimen through engraftment or resolution of mucositis (approximately day +30)	Acyclovir  Alternative: valacyclovir
	Consider in HSV-seropositive autologous HCT who are likely to experience substantial mucositis		
<b>Global Guidelines<sup>298</sup></b>  <u>VZV</u>	Allogeneic and autologous HCT	Continue for at least one-year post-HCT  May consider longer duration in allogeneic patients with GVHD or on immunosuppression, including up to 6 months after discontinuation of immunosuppression	Acyclovir  Alternatives: valacyclovir
<b>ASCO/IDSA<sup>300</sup></b>	HSV-seropositive allogeneic and autologous HCT	Through duration of neutropenia or resolution of mucositis, whichever is longer  Duration can be continued for frequent recurrent HSV infections, GVHD, or as VZV prophylaxis for up to one year	Nucleoside analog (e.g., acyclovir)
<b>NCCN<sup>@299</sup></b>  <u>HSV</u>	Consider for autologous HCT	During active therapy or longer depending on degree of immunosuppression	Options include acyclovir, valacyclovir, famciclovir
	Allogeneic HCT	During active therapy including through neutropenia periods	
<b>NCCN<sup>@299</sup></b>  <u>VZV</u>	Consider for autologous HCT	6 – 12 months post-HCT	
	Allogeneic HCT, especially with GVHD	Consider for at least one-year post-HCT	

**Cytomegalovirus (CMV) Antiviral Prophylaxis Guideline Comparisons and Recommendations**

Guideline	Patient population	Timeline and Duration	Agent(s)
<b>Global Guidelines</b> <sup>298</sup>	Allogeneic HCT – prophylaxis strategy	From engraftment through day 100	Ganciclovir  Alternatives: foscarnet, acyclovir, valganciclovir
	Allogeneic HCT – preemptive strategy*  *The historical approach (especially before letermovir availability and in CMV-seronegative patients) to minimize toxicity	From engraftment through day 100 or continued longer for those on GVHD treatment or who received CMV therapy during first 100 days	Ganciclovir or valganciclovir  Alternatives: foscarnet, cidofovir  Begin preemptive therapy if CMV viremia, antigenemia, or DNA is detected and continue for a minimum of two weeks
	Consider preemptive strategy for certain CMV-seropositive autologous patients <ul style="list-style-type: none"> <li>• Conditioning regimen includes TBI</li> <li>• Graft manipulation</li> <li>• Recent purine analogs</li> </ul>	From engraftment through day 60	Ganciclovir  Alternatives: foscarnet, valganciclovir, cidofovir  Begin preemptive therapy if CMV viremia, antigenemia, or DNA is detected and continue for a minimum of two weeks
<b>ASTCT Cytomegalovirus</b> <sup>303</sup>	Adult CMV seropositive allogeneic HCT	No later than day 28 and continued through day 100	Letermovir  If unavailable due to cost, access, etc., preemptive approach recommended
<b>NCCN</b> <sup>299</sup>	Allogeneic HCT with CMV seropositivity or GVHD on therapy – preemptive strategy	Continue for at least one to six months post-HCT or duration of GVHD therapy	Valganciclovir (usually preferred), ganciclovir, foscarnet  Begin therapy if CMV reactivation detected
	CMV seropositive allogeneic HCT recipient – prophylaxis strategy	Start between day 0 and 28 and continue through day 100	Letermovir

**Patient Case, Question #5:**

**Answer: A. Sulfamethoxazole/trimethoprim, acyclovir, posaconazole**

Due to the high dose of corticosteroids and expected prolonged duration, *Pneumocystis* prophylaxis is warranted. Bactrim is the agent of choice unless contraindications exist.

Acyclovir is a recommended agent for HSV/VZV prophylaxis, which should continue in the setting of ongoing immunosuppression.

Posaconazole is the guideline preferred mold active azole for patients with graft-versus-host disease on immunosuppression due to efficacy in preventing invasive fungal infections and related mortality.

Antibacterial coverage is not warranted for LC at this time as she has engrafted (non-neutropenic) and does not have a diagnosis of chronic graft-versus-host disease.

Letermovir is FDA-approved for prevention of CMV through Day +100 post-transplant. Therapy beyond Day +100 is not currently recommended in clinical guidelines.

**11. Treatment of Selected Infections Post HCT**

**a. Cytomegalovirus**

- 1) CMV pneumonia: ganciclovir 5 mg/kg IV every 12 hours (assuming normal renal function)
  - a) Consider IVIG 500 mg/kg IV QOD x 21 days, followed by maintenance<sup>310</sup>
  - b) CMV-IVIG 150 mg/kg twice weekly may be used, although no apparent clinical advantage has been shown<sup>311,312</sup>
- 2) CMV disease (esophagitis, bone marrow infection with secondary cytopenias, colitis): ganciclovir 5 mg/kg IV every 12 hours x 14 -21 days or until evidence of resolution of the process.
  - a) Maintenance may be given for several weeks or longer until immunosuppression can be reduced.<sup>311</sup>
  - b) Two studies demonstrated similar bioavailability in patients with mild to moderate gut GVHD for oral valganciclovir so experts suggest it can be used for maintenance if there is no severe gut GVHD, symptoms are improved, there is good oral intake, and systemic CMV viral load is suppressed.
- 3) Refractory or resistant CMV treatment: maribavir FDA-approved 11/23/2021 for ages 12 and older with post-transplant refractory CMV<sup>313</sup>
  - a) Mechanism of action:

- a. riboside antiviral that inhibits the protein kinase activity of human CMV enzyme pUL97 leading to inhibition of protein phosphorylation
- b) Indications and dose:
  - a. 400 mg orally twice daily
  - b. Treatment of post-transplant CMV infection/disease that is refractory to treatment with ganciclovir, valganciclovir, cidofovir, or foscarnet
- c) Toxicities:
  - a. Common: taste disturbance (46%), nausea (21%), diarrhea (19%), vomiting (14%), fatigue (12%),
  - b. Severe: increased serum creatinine (7-33%), decreased platelet count (5-18%)
- d) Drug-drug interactions:
  - a. Substrate of CYP3A4
  - b. May reduce antiviral activity if co-administered with ganciclovir/valganciclovir
- 4) Secondary prophylaxis: one retrospective study demonstrated low rates of CMV disease and infection (5.5%) when letermovir was used as secondary prophylaxis after an episode of CMV infection or disease<sup>314</sup>
- b. Varicella zoster virus
  - 1) **Acyclovir 10 mg/kg IV every 8 hours for 7 - 14 days, or 2 days after cessation of new lesion formation, whichever is longer**
  - 2) **Can change to oral valacyclovir 1 g TID (if normal renal function) once no new vesicles are appearing, and all existing lesions have crusted**
- c. Adenovirus
  - 1) **Rapid tapering or withdrawal of immunosuppression (AII) (not always feasible)**
  - 2) **Cidofovir 5 mg/kg IV once weekly or 1 mg/kg 3 times weekly for 2-4 weeks or until immune recovery if tolerated and effective (BII) or ribavirin 15 mg/kg PO TID for 4 days, followed by 8 mg/kg TID for up to 10 days (CIII)<sup>298</sup>**
- d. Human herpes virus 6
  - 1) **Ganciclovir, foscarnet, and cidofovir have demonstrated in-vitro activity with limited clinical data<sup>298</sup>**
- e. BK Virus

- 1) **Hyperhydration, reduce immunosuppression if possible**
- 2) Insufficient evidence to support preemptive fluoroquinolone or cidofovir therapy in asymptomatic patients with BK viruria or viremia (DIII)<sup>298</sup>
- 3) Leflunomide was not addressed by the guideline- also insufficient evidence
- 4) **Cidofovir 1 mg/kg IV 3 times weekly or 5 mg/kg/week with or without probenecid may be used for patients with BK viruria and hemorrhagic cystitis (CIII)<sup>298</sup>**

f. Respiratory Syncytial Virus (RSV)

- 1) **Aerosolized ribavirin 6 g over 18 hours per day or intermittent 2 g over 2 to 3 hours every 8 hours x 7 to 10 days – course may be prolonged in severe lower respiratory infection (LRI) (CIII)<sup>298</sup>.** Inhaled ribavirin is now prohibitively expensive.
- 2) IVIG may decrease rate of progression to LRI and reduce mortality associated with LRI
- 3) Limited retrospective data supports the use of oral ribavirin, though many centers use it because of cost of inhaled ribavirin<sup>315-317</sup>
- 4) There is limited data on the use of palivizumab

g. Influenza

- 1) **Anti-influenza antiviral agents have not been studied in randomized trials in patients undergoing HCT and antiviral susceptibilities of circulating influenza strains must be continually evaluated**
- 2) **Oral or inhaled neuraminidase inhibitors are recommended for asymptomatic viral shedding and URI depending on susceptibility patterns. Oseltamivir 75 – 150 mg PO BID x at least 10 days for LRI**
- 3) IVIG may be utilized in critically ill patients with LRI and acute lung injury<sup>318</sup>

G. Transplant Associated Thrombotic Microangiopathy (TA-TMA)

1. Potentially life-threatening complication (median survival around 40%) with varied reported incidence from 2.5 – 25%<sup>319</sup>
2. Presentation: hallmark feature is endothelial injury<sup>319</sup>
  - a. Typically presents within 20 – 100 days of HCT
  - b. Various diagnostic criteria exist but common diagnostic features include thrombocytopenia, microangiopathic hemolysis (as evidenced by presence of schistocytes, elevated lactose dehydrogenase, elevated indirect bilirubin,

decreased haptoglobin), renal dysfunction, proteinuria, and neurologic complications

3. Treatment<sup>320</sup>

- a. No consensus regarding definitive treatment due to lack of controlled trials. There are no FDA-approved therapies for treatment of TA-TMA; best supportive care is a foundation of treatment.
- b. Manipulation of GVHD regimen: reducing trough levels of calcineurin inhibitors or substituting calcineurin inhibitors and mTOR inhibitors for another agent is a common first-line intervention in clinical practice<sup>321</sup>
- c. Therapeutic plasma exchange: response rates range from 0 to 80% with most recent studies in the 40- 60% range. The only prospective study had a response rate of 64% with cyclosporine withdrawal and plasma exchange. Some experts consider it to be ineffective and not recommended.<sup>322</sup>
- d. Rituximab, defibrotide, and eculizumab have been reported in case series as salvage therapy with response rates of 69-80%.<sup>323</sup> A small retrospective study showed overall survival was significantly higher in subjects treated with eculizumab compared with untreated patients (56% versus 9%, P = 0.003).<sup>319</sup>

H. Pulmonary Complications

1. Types of pulmonary toxicities

- a. Interstitial pneumonitis (IP) due to infection, including bacterial, fungal, CMV, and *Pneumocystis* pathogens
- b. Idiopathic pneumonia syndrome (IPS)<sup>324</sup>
  - 1) Treatment
    - a) **Methylprednisolone (or equivalent corticosteroid) 2 mg/kg/day x 7 days, then taper per clinical indication**
    - b) Etanercept 0.4 mg/kg (maximum 25 mg) twice weekly for a maximum of 8 doses may be considered.<sup>325</sup> Study closed early due to slow enrollment and subsequently showed no difference in 28 day response. Overall survival was not statistically significantly different (170 vs. 64 days).
  - c. Diffuse alveolar hemorrhage (considered a subtype of IPS)<sup>324,326</sup>
    - 1) Treatment
      - a) **Prompt initiation of high dose corticosteroids (2 mg/kg/day to 1 g/m<sup>2</sup>/day)<sup>324</sup>; lower doses (<250 mg/day) may be associated with improved outcomes<sup>327</sup>**
      - b) Limited evidence to support use of recombinant factor VIIa<sup>328</sup>
  - d. Peri-engraftment respiratory distress syndrome (PERDS) (considered a subtype of IPS)<sup>324,326</sup>



- 1) **Treatment: mild cases are managed with supportive care. Strongly consider discontinuing filgrastim. Severe cases may be managed with corticosteroids, often 1 mg/kg/day followed by a rapid taper.**
- e. Bronchiolitis obliterans organizing pneumonia (BOOP) (AKA cryptogenic organizing pneumonia [COP])<sup>324</sup>
  - 1) **Treatment: prednisone 1 mg/kg/day, tapered over 3-6 months**
- f. **Bronchiolitis obliterans syndrome (BOS) (note this is considered a diagnostic feature for chronic GVHD)**<sup>127,221,324</sup>
  - 1) **Screening: baseline PFTs within 2 weeks prior to initiating conditioning chemotherapy, then every 3 months for the first 2 years, then every 6 months thereafter**<sup>329</sup>
  - 2) **Treatment**<sup>221,329</sup>
    - a) **Prednisone 1-1.5 mg/kg/day, taper gradually over 6-12 months**
    - b) Consider additional immunosuppression (e.g., calcineurin inhibitor, imatinib, mycophenolate, MTOR inhibitors)
    - c) **Consider FAM therapy**
      - i. **Azithromycin 250 mg PO three times per week as maintenance anti-inflammatory**<sup>330</sup>
      - ii. **High-dose inhaled corticosteroids (fluticasone 500-940 mcg inhaled BID) +/- a bronchodilator (based on improved FEV<sub>1</sub> with budesonide/ formoterol)**<sup>331</sup>
      - iii. **Montelukast 10 mg daily**
    - d) Anti-reflux measures (proton-pump inhibitor)
    - e) Consider extracorporeal photopheresis
    - f) Initiate appropriate antimicrobial prophylaxis for chronic GVHD including vaccinations for influenza and pneumococcus
    - g) Advanced cases may require oxygen, pulmonary rehabilitation, and/or lung transplantation
- I. Renal Complications<sup>332</sup>
  1. Acute kidney injury (AKI)
    - a. Etiology: conditioning chemotherapy, TBI, nephrotoxic drugs, infection/sepsis, dehydration, obstruction, tumor lysis syndrome, hepatorenal syndrome from VOD, TMA/HUS, GVHD
    - b. Treatment: depending on the etiology may involve appropriate use of fluids, antimicrobial therapy, discontinuation of offending agents, and management of the underlying problem leading to AKI<sup>333</sup>

2. Chronic Kidney Disease (CKD)
  - a. **Treatment: angiotensin converting enzyme inhibitors and angiotensin receptor blockers can help reduce inflammation and inflammatory markers and are the treatment of choice for hypertension and chronic kidney disease<sup>333,334</sup>**

**Patient Case, continued:** LC is a 56-year-old African American female with AML in first remission who underwent a haploidentical allogeneic HCT. At diagnosis she had a complex karyotype and mutated FLT3-ITD. At 2 months post-transplant, LC has no evidence of GVHD and is interested in strategies to prevent relapse of her disease. Which maintenance agent is most likely to decrease LC's risk of relapse?

**Question #6: Which maintenance agent is most likely to decrease LC's risk of relapse?**

- A. Midostaurin
- B. Sorafenib
- C. Venetoclax
- D. Lenalidomide

#### IV. Post-HCT Relapse Prevention

- A. Relapse prevention<sup>335,336</sup>
  1. Relapse is the major cause of death for patients after HCT
  2. Strategies to prevent relapse
    - a. Improve the conditioning regimen (novel drugs, monoclonal antibodies)
    - b. Graft engineering (graft depletion of T cells, NK cell enrichment, cytotoxic T lymphocyte enrichment)
    - c. Monitor for measurable residual disease and use pre-emptive therapy
      - 1) Immunologic (investigational agents e.g., tumor vaccine, genetically modified T cells)
      - 2) Cellular therapy (e.g., donor lymphocyte infusion)
      - 3) Pharmacologic (e.g., imatinib for Philadelphia chromosome-positive acute lymphoblastic leukemia)
    - d. Early withdrawal of immunosuppression to promote graft vs. tumor effect
    - e. Consolidation therapy post-HCT (e.g., brentuximab for R/R Hodgkin lymphoma)
    - f. Maintenance therapy post-HCT
      - 1) Cellular therapy (e.g., donor lymphocyte infusion)
      - 2) Pharmacologic (e.g., lenalidomide for multiple myeloma)
        - a) Active in the disease
        - b) Acceptable non-hematologic toxicity
        - c) Acceptable myelotoxicity

- d) Minimal drug interactions
- e) Will not inhibit graft vs. tumor effect or will enhance graft vs. tumor effect
- f) Will not worsen GVHD
- g) Other factors: cost, convenience, quality of life impact
- h) Doses often lower than in treatment

B. Autologous HCT maintenance therapies for relapse prevention

1. **Lymphoma**<sup>337</sup>

- a. Relapse of disease is the primary cause of death in lymphoma patients following autologous HCT, with most relapses occurring within 1 – 3 years. Several pharmacologic maintenance strategies have been studied to lessen this complication.
- b. Joint expert panel from ASTCT, Center for International Blood and Marrow Transplant Registry (CIBMTR), and European Society for Blood and Marrow Transplantation (EBMT) provided recommendations based on existing prospective data and consensus statements when limited data is available.

**Joint Consensus Maintenance/Consolidation Therapy Recommendations from ASTCT, CIBMTR, and EBMT for Hodgkin and non-Hodgkin Lymphoma post-HCT**<sup>337-340</sup>

Disease	Agent	Consensus Statement	Grade of recommendation
Classical Hodgkin lymphoma	Brentuximab vedotin	<b>Recommended if brentuximab vedotin-naïve with at least 1 or more high-risk features based on AETHERA trial<sup>338</sup> (see below)</b> <ul style="list-style-type: none"> <li>Refractory to initial therapy</li> <li>Relapse &lt;12 months after initial therapy</li> <li>Extranodal disease at start of pre-transplant salvage therapy</li> </ul>	A
		<b>Recommended regimen is every 3 weeks for 16 cycles or until unacceptable toxicity, disease relapse, or disease progression (whichever comes first)</b>	A
		Recommended if limited prior exposure to brentuximab vedotin (approximately 4 – 6 cycles) with at least 1 or more high-risk features, and no evidence of brentuximab vedotin-refractory disease	C
		Not recommended if prior evidence of disease refractory to brentuximab vedotin	C
Diffuse large B-cell lymphoma	Rituximab	<b>Not recommended, even if disease is sensitive to rituximab-based salvage approaches, based on CORAL trial<sup>339</sup> (see below)</b>	A

	Agents other than rituximab	Not recommended outside of clinical trial	C
<b>Mantle cell lymphoma</b>	<b>Rituximab</b>	<b>Recommended following upfront autologous HCT if chemosensitive after 1 line of prior rituximab and cytarabine-containing therapy</b>	<b>A</b>
		<b>Recommended regimen is every 2 months for 3 years as in LYSA trial<sup>340</sup> (see below), or until unacceptable toxicity, disease relapse, or disease progression (whichever comes first)</b>	<b>A</b>
		<b>Recommended following upfront autologous HCT if chemosensitive regardless of pretransplant induction</b>	<b>B</b>
		Not recommended if prior evidence of rituximab resistance (relapse or progression while on or within 6 months of rituximab-containing regimen)	C
		Recommended following delayed autologous HCT, regardless of history of rituximab maintenance, if no evidence of rituximab resistance	C
	Agents other than rituximab	Not recommended outside of clinical trial	C
<b>Follicular lymphoma</b>	<b>Rituximab</b>	<b>Recommended every 2 months for 4 doses if chemosensitive, rituximab-naïve disease</b>	<b>A</b>
		<b>Recommended if chemosensitive, previously rituximab- (or other CD20 antibody) treated disease without evidence of rituximab resistance</b>	<b>B (lack of prospective data)</b>
		Not recommended if prior evidence of rituximab resistance (relapse or progression while on or within 6 months of rituximab-containing regimen)	C
	Agents other than rituximab	Not recommended outside of clinical trial	C

*Agency of Healthcare Research and Quality grading of recommendations based on level of evidence:*

*A, there is good research-based evidence to support the recommendation;*

*B, there is fair research-based evidence to support the recommendation;*

*C, the recommendation is based on expert opinion and panel consensus;*

*X, there is evidence of harm from this intervention.*

### Select Studies on Maintenance/Consolidation Therapy post-HCT in Hodgkin and non-Hodgkin Lymphoma

Disease	Study	N	Regimen	Median PFS / event free survival (EFS)	OS	Comments
Hodgkin lymphoma	AETHERA, 2015 <sup>338</sup>  Randomized, double-blind, placebo-controlled, phase III study of brentuximab vedotin in high risk patients	329	Brentuximab vedotin 1.8 mg/kg (maximum dose 180 mg) IV every 21 days up to 16 cycles starting 30-45 days after HCT	42.9 brentuximab vs. 24.1 months placebo  P = 0.0013 for PFS	No difference 88% at 2 years	85% of placebo patients who received therapy for progression received brentuximab
Diffuse large B-cell lymphoma	CORAL, 2012 <sup>339</sup>  Randomized, multicenter, phase III study of rituximab maintenance vs. observation	242	Rituximab 375 mg/m <sup>2</sup> every 2 months for 1 year	52% rituximab vs. 53% observation  P = 0.7 for EFS at 4 years	No difference at 4 years	Increased serious adverse effects, including infection, in the rituximab arm
Mantle cell lymphoma	LYSA, 2017 <sup>340</sup>  Randomized, unblinded, phase III study of rituximab vs. placebo	240	Rituximab 375 mg/m <sup>2</sup> every 2 months for 3 years	79% rituximab vs. 61% placebo  P < 0.001 for EFS at 4 years	89% rituximab vs. 80% placebo  P = 0.04	All patients received R-DHAP induction regimen, therefore unknown applicability to other induction strategies

R-DHAP = rituximab, dexamethasone, cytarabine, platinum derivative

## 2. Multiple myeloma

### a. ASCO guidelines for treatment of multiple myeloma include post-HCT maintenance recommendations<sup>4</sup>

- 1) **Lenalidomide maintenance should be routinely offered to standard-risk patients starting approximately 3 months post-transplant based on improved progression free and overall survival. The recommended dose is 10 – 15 mg daily until progression or for a minimum of 2 years, which is associated with improved overall survival.**
  - a) **Recent meta-analysis confirmed overall survival benefit of lenalidomide maintenance compared to observation (HR 0.75, 95% CI 0.63 – 0.90, P = 0.001)<sup>341</sup> – see table below**
  - b) **Lenalidomide 10 mg daily approved by US Food and Drug Administration for maintenance after HCT in 2017**

- 2) For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks can be considered.
- 3) In high-risk patients (decreased creatinine clearance, adverse chromosome changes, or elevated lactate dehydrogenase), proteasome inhibitor therapy with or without lenalidomide may be considered.

#### Select Studies on Maintenance Therapy post-HCT in Multiple Myeloma

Study	N	Maintenance Regimen	EFS or PFS	OS	Comments
<b>Lenalidomide (LEN)</b>					
CALGB 100104 <sup>342,343</sup>  IMiDs or bortezomib in induction regimen in 94% of patients followed by single autologous PBSCT	460	LEN 10 mg daily vs. placebo (PBO)	3-year PFS 66% LEN 39% PBO  P < 0.001	5-year OS 76% LEN 64% PBO  P = 0.0004	Discontinuation due to adverse events: 12% LEN vs. 2% PBO  Higher rate of second primary cancers: 7.8% LEN vs. 2.6% PBO
IFM 2005-02 <sup>344</sup>  Bortezomib in induction in 44-46% of patients Single PBSCT in 79%; tandem PBSCT in 21%	614	LEN 10-15 mg daily until PD or intolerance vs. PBO  Maintenance stopped early because of high rate of second primary cancers	4-year PFS 43% LEN 22% PBO  P < 0.001	4-year OS 73% LEN 75% PBO  P = NS	Discontinuation due to adverse events 27% LEN vs. 15% PBO  Higher rate of second primary cancers: 7.5% LEN vs. 2.9% PBO
GIMEMA RV-209 <sup>345</sup>  Lenalidomide + dex induction x 4 cycles, tandem autologous PBSCT vs. MPR (melphalan, prednisone, Revlimid), then second randomization to lenalidomide or no therapy	273 for first  253 for second	LEN 10 mg daily days 1-21, repeat q 28 days until PD or intolerance vs. none	PFS 42 mos LEN 22 mos none  P < 0.001	3-year OS 88% LEN 79% none  P = 0.14	5.2% of LEN patients discontinued maintenance because of adverse effects.  4.3% had second primary cancers in both LEN maintenance and no maintenance groups.

Study	N	Maintenance Regimen	EFS or PFS	OS	Comments
Meta-analysis <sup>341</sup>  Patient-level data of LEN maintenance vs. control post-HCT (included 3 trials listed above) powered for primary endpoint of OS	1208	LEN 10-15 mg vs. placebo or observation (control)	PFS 52.8 mos LEN 23.5 mos control  HR = 0.48 (95% CI 0.41 – 0.55)	79.5 mos follow-up: NR LEN 86 mos control  P = 0.001	<b>Higher rate of second primary malignancy in LEN arm vs. control</b>  <b>Confirmed OS benefit of LEN maintenance</b>
DETERMINATION <sup>346</sup>  RVD alone or RVD + autologous HCT followed by lenalidomide maintenance until progression	722	LEN 10-15 mg until disease progression, toxicity, or withdrawal	PFS 46.2 mos RVD alone 67.5 mos RVD + auto HCT  HR 1.53 (95% CI 1.23 – 1.91) P < 0.001	5-year OS 79.2% RVD alone 80.7% RVD + auto HCT  HR 1.10 (95% CI 0.73-1.65)	<b>Confirmed benefit of front-line autologous HCT in combination with RVD</b>  <b>Supports LEN maintenance until disease progression if tolerated</b>
<b>Bortezomib</b>					
HOVON-65/GMMG-HD4 <sup>347</sup>  VAD induction vs. PAD induction followed by autologous PBSCT (~1/3 of patients had 2 PBSCT)	827	VAD arm: Thalidomide 50 mg daily or  PAD arm: bortezomib 1.3 mg/m <sup>2</sup> q 2 weeks  Maintenance x 2 years	Median PFS 28 mos VAD 35 mos PAD  P = 0.002	5-year OS 55% VAD 61% PAD  P = 0.07	30% of thalidomide and 11% of bortezomib patients discontinued early due to peripheral neuropathy. Note- design does not allow firm conclusion about benefit of maintenance.
PETHEMA/GEM <sup>348</sup>  Induction with 1 of 3 regimens (all had thalidomide, bortezomib or both) followed by single autologous PBSCT	386	Interferon alfa-2b (3 MU SQ 3 times per week) vs. thalidomide 100 mg PO daily vs. thalidomide 100 mg PO daily + bortezomib on days 1, 4, 8, and 11 every 3 months. Planned for 3 years	2-year PFS thalidomide/ bortezomib 78% thalidomide 63% Interferon alfa-2b 49%  P = 0.01	No difference	No maintenance specific adverse effects reported

Study	N	Maintenance Regimen	EFS or PFS	OS	Comments
Nordic <sup>349</sup>  Bortezomib naïve patients (almost all had not received novel therapies), received induction and autologous PBSCT; < 10% had 2 PBSCT	370	Bortezomib twice weekly on days 1, 4, 8, and 11 in a 3-week schedule x 2 cycles, followed by once weekly on days 1, 8, and 15 in a 4-week schedule x 4 cycles	27 mos vs. 20 mos P = 0.05	No difference	Median number of bortezomib injections received was 19, and median given dose was 90%

NR = not reached; PAD = bortezomib, doxorubicin, dexamethasone ; RVD = lenalidomide, bortezomib, dexamethasone; VAD = vincristine, doxorubicin, dexamethasone.

C. Allogeneic HCT maintenance therapies for relapse prevention

1. Acute myeloid leukemia/myelodysplastic syndrome

a. **Currently insufficient data to recommend for or against routine universal maintenance therapy<sup>350</sup>**

- 1) Several agents studied but available data is heterogenous in terms of trial design, patient population, intervention, and outcomes (see table below), making a consensus recommendation difficult
- 2) **Sorafenib maintenance therapy may reduce relapse rates and improve survival in FLT3-ITD AML and can be considered for appropriate patients. Additional data is needed for midostaurin and gilteritinib to determine benefit.**<sup>351,352</sup>

b. Lenalidomide is not recommended as it may promote development of severe GVHD<sup>353</sup>



### Select Studies on Maintenance Therapy post-HCT in AML/MDS

Study	N	Maintenance Regimen	Relapse endpoint	OS	Comments
<b>Tyrosine kinase inhibitors</b>					
SORMAIN, 2020 <sup>354</sup>  Randomized, double-blind, placebo-controlled, phase II of sorafenib post-transplant to prevent relapse for FLT3-ITD-positive AML	83	Sorafenib to maximum dose of 800 mg daily starting 60-100 days after HCT and continued for 24 months	85% sorafenib vs. 53.3% placebo  P = 0.002 for relapse-free survival at 2 years	90.5% sorafenib vs. 66.2% placebo  P = 0.007 at 2 years	Patients with undetectable measurable residual disease before HCT and detectable measurable residual disease after HCT benefited most from sorafenib
Xuan et al., 2020 <sup>355</sup>  Randomized, open-label, phase III trial of sorafenib vs. no maintenance	202	Sorafenib 400 mg orally twice daily starting 30-60 days after HCT and continued until day 180	7% sorafenib vs. 24.5% no maintenance  P = 0.0010 for 1-year cumulative incidence of relapse	82% sorafenib vs. 68% no maintenance  P = 0.012 at 2 years	
RADIUS, 2021 <sup>356</sup>  Randomized, open-label, phase II study of midostaurin maintenance vs. standard of care	60	Midostaurin 50 mg twice daily in twelve 4-week cycles starting 28-60 days after HCT  Standard of care by physician choice but excluded alternative tyrosine kinase inhibitor therapy	89% midostaurin vs. 76% standard of care  P = 0.027 for 18-month relapse-free survival	85% midostaurin vs. 76% standard of care  P = 0.34 at 2 years	Patients who experienced higher levels of FLT3 inhibition had significantly decreased relapse rates and improved RFS and OS compared to the standard of care arm, indicating that a subset of patients may benefit from FLT3 inhibition post-transplant
Gagelmann et al., 2021 <sup>352</sup>  Systematic review and meta-analysis of TKI maintenance compared to control	680	Sorafenib (N=504)  Midostaurin (N=176)	RFS pooled RR = 0.48 (95% CI 0.37-0.61)  P < 0.001	OS pooled RR = 0.48 (95% CI 0.36-0.64)  P < 0.001	
Bewersdorf et al., 2021 <sup>351</sup>  Systematic review and meta-analysis	366	Sorafenib (N=323)  Midostaurin (N=30)  Quizartinib (N=13)	HR for relapse = 0.35 (95% CI 0.23-0.52) for FLT3 inhibitor compared to control	HR for death = 0.41 (95% CI 0.26-0.62) for FLT3 inhibitor compared to control	

Study	N	Maintenance Regimen	Relapse endpoint	OS	Comments
<b>Hypomethylating agents</b>					
RICAZA, 2016 <sup>357</sup>  Single center study of azacitidine maintenance	37	Azacitidine 36 mg/m <sup>2</sup> x 5 days, every 28 days for up to 12 cycles starting approximately day 42	1-year RFS: 57% 2-year RFS: 49%	1-year OS: 81% 2-year OS: 49%	
de Lima et al., 2010 <sup>358</sup>  Single center, dose finding study of azacitidine maintenance	47	Azacitidine 32 mg/m <sup>2</sup> x 5 days, every 30 days for at least 4 cycles starting approximately day 40	1-year event-free survival: 58%	1-year OS: 77%	
Oran et al., 2020 <sup>359</sup>  Phase III, randomized controlled trial	187	Azacitidine 32 mg/m <sup>2</sup> x 5 days, every 28 days for up to 12 cycles starting approximately day 60	Median RFS (years): 2.07 AZA vs. 1.28 control P = 0.43	Median OS (years): 2.52 AZA vs. 2.56 control P = 0.85	
Gao et al., 2020 <sup>360</sup>  Phase II, multi-center, open-label, randomized trial	202	G-CSF 100 µg/m <sup>2</sup> + 5 mg/m <sup>2</sup> decitabine x 5 days, every 6-8 weeks for 6 cycles (G-Dec) vs. no intervention	15% G-Dec vs. 38.3% no intervention  P < 0.01 for 2-year cumulative incidence of relapse	85.8% G-Dec vs. 69.7% no intervention  P = 0.01 at 2 years	Combination of G-CSF with minimal dose decitabine hypothesized to promote the graft-versus-tumor effect
Bewersdorf et al., 2021 <sup>351</sup>  Systematic review and meta-analysis	443	Various	HR for relapse = 0.45 (95% CI 0.30-0.65) for HMA compared to control	HR for death = 0.45 (95% CI 0.31-0.66) for HMA compared to control	

HR = hazard ratio; RFS = relapse-free survival; RR = risk ratio

2. Acute lymphoblastic leukemia, Philadelphia chromosome-positive<sup>10</sup>
  - a. **Maintenance or preemptive MRD-guided TKI therapy should be considered post-transplant**
    - 1) Limited evidence suggests TKI therapies (imatinib, dasatinib, nilotinib) improve outcomes, including overall survival compared to no therapy/historical data<sup>361-371</sup>
3. Chronic myeloid leukemia<sup>372,373</sup>

- a. Currently published data includes patients who did not receive a TKI pre-transplant or had received imatinib and were not considered resistant or intolerant to it. This is no longer typical of the patient population currently undergoing allogeneic HCT.
- b. It is not known if all patients should receive a TKI after allogeneic HCT for CML or at what level of molecular relapse a TKI should be initiated
- c. The optimal agent, dose, or duration of TKI therapy after allogeneic HCT for CML has not been determined. Current data suggests it is safe and well tolerated to administer a TKI post HCT. Post HCT TKI therapy has been associated with a lower incidence of extensive, chronic GVHD.

**Patient Case, Question #6:**

**Answer: B. Sorafenib**

Sorafenib is the preferred post-transplant maintenance agent for FLT3-ITD AML due to multiple randomized trials demonstrating decreased incidence of relapse compared to no maintenance. Midostaurin is not preferred over sorafenib due to conflicting evidence and inconsistent relapse benefit in clinical trials. Venetoclax has only preliminary data for post-transplant maintenance, and primarily combined with other agents. Lenalidomide is not recommended for post-transplant maintenance due to an increase in graft-versus-host disease.

**Patient Case, continued:** LC is now 6 months post-transplant and the transplant team would like to start revaccination. Her current medications include tacrolimus 1 mg twice daily, prednisone 10 mg daily, acyclovir 800 mg twice daily, posaconazole 300 mg daily, and sulfamethoxazole/trimethoprim 800/160 mg three times weekly.

**Question #7: Which of the following vaccines should LC receive at this time?**

- A. Measles, mumps, and rubella
- B. Pneumococcal polysaccharide (PPSV23)
- C. Hepatitis B
- D. Vaccines are not appropriate at this time

**V. Long-term complications / Survivorship**

**A. Late Complications – Screening Recommendations<sup>332</sup>**

1. The Center for International Blood and Marrow Transplant Research, American Society of Blood and Marrow Transplantation, European Group for Blood and Marrow Transplantation, Asia-Pacific Blood and Marrow Transplantation Group, Bone Marrow Transplant of Australia and New Zealand, East Mediterranean Blood and Marrow Transplantation, and Sociedade Brasileira de Transplante de Medula Ossea have developed recommended screening and preventative practices for long-term survivors after HCT

- a. **Review Table 1 in Majhail et al.<sup>332</sup> for recommended long-term monitoring and frequency by organ (one of recommended readings for module available at: <http://www.ncbi.nlm.nih.gov/pubmed/22178693>)**
- B. Ocular<sup>332</sup>
  1. Monitoring: ophthalmologic exam 1 year after HCT and continued annually, with prompt assessment of any acute changes/symptoms
  2. Sicca syndrome (usually part of GVHD; refer to GVHD section for management)
  3. Cataracts
    - a. Surgical management is recommended even if patients have sicca syndrome
- C. Oral<sup>332</sup>
  1. Monitoring: dental assessment 1 year after HCT and continued annually
  2. Salivary gland hypofunction may persist, especially in patients with local irradiation
    - a. Discontinue medications that cause oral dryness (antidepressants, antihistamines, diuretics, muscle relaxants, some analgesics, anticholinergics/antiemetics)
    - b. Manage symptomatically with artificial saliva and oral rinses, sugar-free candies or gum, sialagogues (pilocarpine or cevimeline), frequent sips of water, and good oral hygiene
- D. Cardiac and vascular complications<sup>332</sup>
  1. Monitoring: assessment of cardiovascular risk factors 1 year after HCT and continued annually
    - a. Echocardiogram, electrocardiogram only indicated in at risk or symptomatic patients
  2. Hypertension: manage per national guidelines<sup>334,374</sup>
    - a. Screen with blood pressure assessment at every clinic visit and at least every year<sup>375</sup>
    - b. Choice of antihypertensive agent is based on comorbidities, medication side effect profile, drug interactions. Nonpharmacological treatments may be tried for mild hypertension
    - c. Patients on cyclosporine or tacrolimus respond well to treatment with a dihydropyridine calcium channel blocker (e.g., amlodipine or nifedipine)
    - d. Angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors are generally preferred in CKD and diabetes
  3. Hyperlipidemia: manage per national guidelines<sup>334,376,377</sup>
    - a. Assess lipids at 3 months after HCT. For patients with ongoing risk factors (including those on corticosteroids) reassess every 3-6 months. For standard

risk patients, reassess every 5 years in males above 35 years and females over 45 years.<sup>375</sup>

- b. Primary goal: reduction in LDL via lifestyle modifications and lipid lowering therapy<sup>375</sup>
- c. Sirolimus, tacrolimus, cyclosporine, and corticosteroids increase risk
- d. Chronic liver GVHD, nephrotic syndrome, hypothyroidism, and hypogonadism may contribute to dyslipidemia
- e. Most statins (except for pravastatin, rosuvastatin and pitavastatin) are substrates of CYP3A4 and patients on inhibitors of CYP3A4 (e.g., cyclosporine and azole antifungals) are at increased risk for toxicity (e.g., myopathy, elevated LFTs). Consider using a statin not metabolized by CYP3A4 in those patients. Note all statins are substrates of hepatic transporter proteins (OATP1B1) which is inhibited by cyclosporine (but not tacrolimus).
- f. High intensity statin not metabolized by CYP3A4
  - 1) Rosuvastatin 20-40 mg daily
- g. Moderate intensity statins not metabolized by CYP3A4
  - 1) Rosuvastatin 5-10 mg daily
  - 2) Pravastatin 40-80 mg daily
  - 3) Pitavastatin 2-4 mg daily
- h. If triglycerides > 500 mg/dL, initiate fibrate or nicotinic acid<sup>375</sup>
- 4. Diabetes (no established treatment guidelines in HCT)
  - a. Monitoring: screen with oral plasma glucose, 2-hour plasma glucose during an oral glucose tolerance test or HBA1c every 3 years in adults > 45 years or with sustained hypertension in standard risk patients. For high-risk patients (e.g., on corticosteroids) screen every 3-6 months<sup>375</sup>
  - b. Goal: HBA1c <7%
  - c. Lifestyle modifications include weight reduction and increased physical activity
  - d. Insulin recommended for short-term use or medically unstable patients
  - e. Sulfonylureas, metformin, and sitagliptin can be used if there are no major contraindications or drug interactions<sup>334</sup>
- E. Thyroid dysfunction<sup>332</sup>
  - 1. Monitoring: thyroid function testing annually after HCT or if symptoms occur
  - 2. Manage with thyroid hormone replacement and reassess approximately 6 weeks after start of therapy<sup>334</sup>
- F. Male hypogonadism
  - 1. Monitoring: gonadal function if symptoms present

2. Management: if low testosterone confirmed on 2 measurements and the patient has symptoms of low libido, erectile dysfunction, fatigue, or bone loss, may initiate testosterone replacement titrated to a testosterone level within normal range and symptom improvement<sup>334</sup>
- G. Primary ovarian insufficiency or failure<sup>292</sup>
1. Monitoring: gonadal assessment within 1 year of HCT
  2. Management: hormone replacement until the age of normal menopause
  3. Estradiol 100 mcg/day by transdermal patch + cyclic medroxyprogesterone 10 mg/day x 12 days/month in women with an intact uterus or a combination oral contraceptive may be used<sup>334</sup>
- H. Osteoporosis/osteopenia<sup>332,378</sup>
1. Monitoring: dual photon densitometry 1 year after HCT for all adult women recipients, all allogeneic recipients, and patients at high risk of bone loss (e.g., prolonged high dose corticosteroids, total body irradiation)
  2. Prevention<sup>378,379</sup>
    - a. Calcium 1000-1200 mg daily
    - b. Vitamin D 800-2000 IU daily with titration to 25 hydroxyvitamin D level between 20-50 ng/mL
    - c. Weight-bearing or resistance physical activity
    - d. Smoking cessation
    - e. Limit alcohol intake
    - f. Fall prevention
    - g. Prophylactic bisphosphonate therapy in patients receiving corticosteroids is optional as there is no long-term data to support that it prevents fractures in HCT patients.
  3. Treatment<sup>378-380</sup>: recommended for patients with T scores  $\leq$  -1.5 or fractures
    - a. Calcium and vitamin D recommended as for prevention
    - b. Bisphosphonate therapy is recommended first-line although the optimal agent, dose, route, and duration are undefined
    - c. Hormone replacement may be considered in deficient states
    - d. Available alternatives have no data for use in HCT patients and are thus considered experimental in this setting: teriparatide, raloxifene, denosumab
- I. Avascular necrosis<sup>378,379</sup>
1. Monitoring: MRI is best for diagnosis of avascular necrosis to evaluate patients with joint symptoms<sup>381</sup>

2. Symptom control with analgesics is recommended. Managed with core decompression for mild to moderate symptoms and joint replacement surgery for severe symptoms<sup>334</sup>

J. Secondary Cancers

1. Standardized incidence ratio (ratio of observed cancer cases in a HCT cohort compared to expected cancer cases in the general population of similar age and gender) for cancers with a statistically significantly increased risk of cancer<sup>382</sup>

**Standardized Incidence Ratio (SIR) for Secondary Cancers after HCT<sup>382</sup>**

Site	SIR
Any skin	7.2
Melanoma	1.4-8.3
Thyroid	5.8-6.6
Mouth/pharynx	7-16
Lip	19-27
Tongue	9.3-20
Oral cavity	7.3-17
Salivary gland	14-23
Gum	5.1-13
Esophagus	8.5-11
Liver	6.3-28
Brain/nervous system	3.8-9.5
Bone	8.5-13
Connective tissue	6.5-8

2. Screening Guidelines: follow cancer screening guidelines for the general population except for the following<sup>382</sup>
  - a. **Skin: annual routine skin and physical exam**
  - b. **Thyroid: annual physical exam**
  - c. **Oropharyngeal: oral exam every 12 months (6 months if risk factors)**
  - d. **Esophagus: upper GI endoscopy for patients with persistent GERD or dysphagia, especially in those with immunosuppressive therapy  $\geq$  24 months**
  - e. **Breast: for patients with prior chest radiation or TBI, start screening at age 25 or 8 years after radiation (whichever comes first), but no later than age 40; annual clinical breast exam, annual mammogram, and annual breast MRI**
  - f. **Cervix: annual Pap test and HPV DNA test**

K. Vaccination of HCT recipients<sup>299,383</sup>

1. Antibody titers to vaccine-preventable diseases decline in the 1-10 years after HCT
2. Studies demonstrate allogeneic HCT patients develop immunogenicity to vaccines and they are safe to use, but there is limited data regarding efficacy against disease development
3. While there is variability in immunodeficiency, immune recovery, and vaccine immunogenicity among autologous, allogeneic, umbilical cord blood, reduced intensity

conditioning, patients with T-cell depleted grafts and chronic GVHD, **the same vaccination schedule (with a few exceptions – see table below) for all HCT patients is recommended until additional data are available**

4. **Patients with active GVHD or ongoing immunosuppression should not receive live vaccines;** it may be prudent to measure vaccine antibody titers after vaccination to determine level of protection and need for booster immunization
5. Pre-transplant vaccination<sup>384</sup>
  - a. HCT donor
    - 1) Should be current with vaccines based on CDC annual schedule
    - 2) Avoid administration of live MMR, MMRV, VAR and ZOS vaccines within 4 weeks of stem cell harvest
    - 3) Vaccination of the donor for the benefit of the recipient is not recommended
  - b. HCT recipient
    - 1) Vaccinate based on CDC annual schedule if the patient is not already immunosuppressed and when the interval to the start of the conditioning regimen is  $\geq 4$  weeks for live and  $\geq 2$  weeks for inactivated vaccines. This is based on persistent immunity for several months after HCT if titers were adequate.
6. Post-transplant vaccination<sup>383-385</sup>
  - a. In general, treat a post-transplant patient as one who has never received vaccination
  - b. **No difference in autologous and allogeneic HCT patients except where noted related to immunosuppression or GVHD**
  - c. **Follow post-transplant vaccination schedule recommendations from the 2009<sup>383</sup> and 2013<sup>384</sup> IDSA guidelines, NCCN Guidelines®, and expert opinion when limited data is available (see table below)**

**Patient Case, Question #7:**

**Answer: C. Hepatitis B**

Vaccines can be safely administered at this time according to the IDSA and NCCN Guidelines<sup>299,384</sup>. Hepatitis B revaccination is recommended for all patients post-transplant beginning at 6 months. The measles, mumps, and rubella vaccine is live and is contraindicated in LC because of her ongoing immunosuppression and time since transplant of less than 2 years. The pneumococcal polysaccharide vaccine is not recommended until after completion of the pneumococcal conjugate series.



**Summary of Post-transplant Vaccination Schedule Recommendations**<sup>299,383-385</sup>

Inactivated Vaccine	Recommended Number of Doses	Earliest Post-transplant Initiation	Comment
COVID-19 <sup>386</sup>	5 (3 primary series + 2 boosters)	3 months	<b>Refer to national guidelines for most up-to-date recommendations given evolving situation</b>
DTaP, DT, Td, Tdap	3	6 months	DTaP preferred for all ages (although only approved for age <7 years), with others as alternatives if dictated by insurance
<i>Haemophilus influenzae</i> b conjugate	3	3 months	
Hepatitis A	2	6 months	
Hepatitis B	2-3 (depending on product used)	6 months	Consider high dose vaccine unless ≥ 6 months without immunosuppression
Human papillomavirus	3	6 months	For patients aged 11 – 26 years, consider up to age 45
Influenza (inactivated)	1 dose annually	4 months	2 doses one month apart should be given to children 6 months – 8 years who are receiving the vaccine for the first time
Meningococcal conjugate	2 for patients aged 11 – 18 years	6 months	Consider in asplenia and complement deficiency  Consider vaccinating all HCT recipients regardless of age, as chronic GVHD is a functionally immunodeficient state
Pneumococcal conjugate 13-Valent (PCV13)	3	3 months	A fourth dose can be given to patients with chronic GVHD 12 months after HCT instead of PPSV23
Pneumococcal conjugate 15-Valent (PCV15)	Unknown	Unknown	Limited data currently
Pneumococcal conjugate 20-Valent (PCV20)	Unknown	Unknown	Limited data currently
Pneumococcal polysaccharide (PPSV23)	1	12 months	
Polio	3	3 months	

Zoster (inactivated)	2	50 – 70 days after autologous HCT Consider in allogeneic HCT	A randomized phase III trial demonstrated efficacy and safety in <u>autologous patients only</u> <sup>387</sup> and a prospective observational study demonstrated safety in allogeneic patients. <sup>388</sup>
<b>Live Vaccine</b>	<b>Recommended Number of Doses</b>	<b>Earliest Post-transplant Initiation</b>	<b>Comment</b>
Influenza (live attenuated)	Contraindicated	NA	
Measles, mumps & rubella	1-2*	24 months	*Administer only if measles seronegative, ≥24 months since HCT, no GVHD, and no current immunosuppression. Consider waiting until ≥8 months since last IVIG dose.
Measles, mumps, rubella, varicella	Contraindicated	NA	
Rabies	May be given for potential exposure	Any time	
Rotavirus	Contraindicated	NA	
Varicella	1-2*	24 months	*Administer only if varicella seronegative, ≥24 months since HCT, no GVHD, and no current immunosuppression. Consider waiting until ≥8 months since last IVIG dose.
Yellow fever	May be used for patients residing or traveling to endemic areas.	Unknown	Limited safety and efficacy data.

*DTaP = diphtheria toxoid, tetanus toxoid, acellular pertussis; DT = diphtheria toxoid, tetanus toxoid; Td = tetanus toxoid, reduced diphtheria toxoid; Tdap = tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis*

## RECOMMENDED READINGS AND RESOURCES

1. <https://bethematchclinical.org/resources-and-education/education-courses-and-events/curriculum/curriculum-modules-and-videos> [BMT Curriculum by the National Marrow Donor Program that is free after you register - these are videos that teach the basics of HCT designed for physicians to use to teach medical students doing a BMT elective. They are well done and helpful if you are new to BMT.]
2. Carpenter PA, Kitko CL, Elad S et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant* 2015; 21:1167-1187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25838185>
3. Tomblyn M, Chiller T, Einsele H et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Bone Marrow Transplant*. 2009; 15:1143-238. Available at: <https://pubmed.ncbi.nlm.nih.gov/20095071>
4. Majhail NS, Rizzo JD, Lee SJ et al. Recommended Screening and Preventive Practices for Long-Term Survivors after Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2012; 18:348-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22178693>

## REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-1826.
2. Kanate AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2020;26(7):1247-1256.
3. Shah N, Callander N, Ganguly S, et al. Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2015;21(7):1155-1166.
4. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. *J Clin Oncol*. 2019;37(14):1228-1263.
5. Perales MA, Ceberio I, Armand P, et al. Role of cytotoxic therapy with hematopoietic cell transplantation in the treatment of Hodgkin lymphoma: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21(6):971-983.
6. Oliansky DM, Czuczman M, Fisher RI, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: update of the 2001 evidence-based review. *Biol Blood Marrow Transplant*. 2011;17(1):20-47 e30.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas. V.5.2022. 07/12/22. © 2022 National Comprehensive Cancer Network, Inc., All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
8. Oliansky DM, Gordon LI, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2010;16(4):443-468.
9. Heidrich K, Thiede C, Schafer-Eckart K, et al. Allogeneic hematopoietic cell transplantation in intermediate risk acute myeloid leukemia negative for FLT3-ITD, NPM1- or biallelic CEBPA mutations. *Ann Oncol*. 2017;28(11):2793-2798.

10. DeFilipp Z, Advani AS, Bachanova V, et al. Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2019;25(11):2113-2123.
11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia. V.1.2022. 04/04/22. © 2022 National Comprehensive Cancer Network, Inc., All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
12. Oliansky DM, Antin JH, Bennett JM, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. *Biol Blood Marrow Transplant*. 2009;15(2):137-172.
13. Elsayw M, Sorror ML. Up-to-date tools for risk assessment before allogeneic hematopoietic cell transplantation. *Bone marrow transplantation*. 2016;51(10):1283-1300.
14. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Cell Transplantation (HCT). V.1.2022. 04/01/22. © 2022 National Comprehensive Cancer Network, Inc., All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
15. Bray RA, Hurley CK, Kamani NR, et al. National marrow donor program HLA matching guidelines for unrelated adult donor hematopoietic cell transplants. *Biol Blood Marrow Transplant*. 2008;14(9 Suppl):45-53.
16. Majhail NS, Chitphakdithai P, Logan B, et al. Significant improvement in survival after unrelated donor hematopoietic cell transplantation in the recent era. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2015;21(1):142-150.
17. Yakoub-Agha I, Mesnil F, Kuentz M, et al. Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. *J Clin Oncol*. 2006;24(36):5695-5702.
18. Ringden O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood*. 2009;113(13):3110-3118.
19. Saber W, Opie S, Rizzo JD, Zhang MJ, Horowitz MM, Schriber J. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. *Blood*. 2012;119(17):3908-3916.
20. Saber W, Cutler CS, Nakamura R, et al. Impact of donor source on hematopoietic cell transplantation outcomes for patients with myelodysplastic syndromes (MDS). *Blood*. 2013;122(11):1974-1982.
21. Arcuri LJ, Aguiar MTM, Ribeiro AAF, Pacheco AGF. Haploidentical Transplantation with Post-Transplant Cyclophosphamide versus Unrelated Donor Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis. *Biol Blood Marrow Transplant*. 2019;25(12):2422-2430.
22. Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. *Blood*. 2021;137(3):420-428.
23. Gagekmann N, Bacigalupo A, Rambaldi A, et al. Haploidentical Stem Cell Transplantation With Posttransplant Cyclophosphamide Therapy vs Other Donor Transplantations in Adults With Hematologic Cancers: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2019.
24. Ballen KK, Koreth J, Chen YB, Dey BR, Spitzer TR. Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. *Blood*. 2012;119(9):1972-1980.

25. Kekre N, Antin JH. Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match does not exist. *Blood*. 2014;124(3):334-343.
26. Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood*. 2019;134(12):924-934.
27. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia. V.2.2022. 06/14/22. © 2022 National Comprehensive Cancer Network, Inc., All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
28. Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol*. 2005;23(22):5074-5087.
29. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367(16):1487-1496.
30. Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. *Biol Blood Marrow Transplant*. 2014;20(3):295-308.
31. Panch SR, Szymanski J, Savani BN, Stroncek DF. Sources of Hematopoietic Stem and Progenitor Cells and Methods to Optimize Yields for Clinical Cell Therapy. *Biol Blood Marrow Transplant*. 2017;23(8):1241-1249.
32. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(28):3199-3212.
33. Micallef IN, Stiff PJ, Nademanee AP, et al. Plerixafor Plus Granulocyte Colony-Stimulating Factor for Patients with Non-Hodgkin Lymphoma and Multiple Myeloma: Long-Term Follow-Up Report. *Biol Blood Marrow Transplant*. 2018;24(6):1187-1195.
34. Gertz MA. Current status of stem cell mobilization. *Br J Haematol*. 2010;150(6):647-662.
35. Motabi IH, DiPersio JF. Advances in stem cell mobilization. *Blood reviews*. 2012;26(6):267-278.
36. Kurnaz F, Kaynar L. Peripheral blood stem cell mobilization failure. *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis*. 2015;53(1):3-7.
37. Ford CD, Green W, Warenski S, Petersen FB. Effect of prior chemotherapy on hematopoietic stem cell mobilization. *Bone marrow transplantation*. 2004;33(9):901-905.
38. Sheppard D, Bredeson C, Allan D, Tay J. Systematic review of randomized controlled trials of hematopoietic stem cell mobilization strategies for autologous transplantation for hematologic malignancies. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2012(0).
39. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2009;113(15):3604-3611.
40. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15(12):1628-1633.
41. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. *Blood*. 2014;124(3):344-353.
42. Servais S, Baron F, Beguin Y. Allogeneic hematopoietic stem cell transplantation (HCT) after reduced intensity conditioning. *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis*. 2011;44(2):205-210.
43. Kharfan-Dabaja MA, Kumar A, Ayala E, et al. Standardizing Definitions of Hematopoietic Recovery, Graft Rejection, Graft Failure, Poor Graft Function, and Donor Chimerism in Allogeneic Hematopoietic Cell

- Transplantation: A Report on Behalf of the American Society for Transplantation and Cellular Therapy. *Transplant Cell Ther.* 2021;27(8):642-649.
44. Kolb HJ. Graft-versus-leukemia effects of transplantation and donor lymphocytes. *Blood.* 2008;112(12):4371-4383.
  45. Stern M, de Wreede LC, Brand R, et al. Sensitivity of hematological malignancies to graft-versus-host effects: an EBMT megafile analysis. *Leukemia.* 2014;28(11):2235-2240.
  46. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. *J Clin Oncol.* 2017;35(11):1154-1161.
  47. Scott BL. Long-Term Follow up of BMT CTN 0901, a Randomized Phase III Trial Comparing Myeloablative (MAC) to Reduced Intensity Conditioning (RIC) Prior to Hematopoietic Cell Transplantation (HCT) for Acute Myeloid Leukemia (AML) or Myelodysplasia (MDS) (MAvRIC Trial). *Biol Blood Marrow Transplant.* 2020;26(3):S11.
  48. Kroger N, Iacobelli S, Franke GN, et al. Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial). *J Clin Oncol.* 2017;35(19):2157-2164.
  49. Bejanyan N, Zhang M, Bo-Subait K, et al. Myeloablative Conditioning for Allogeneic Transplantation Results in Superior Disease-Free Survival for Acute Myelogenous Leukemia and Myelodysplastic Syndromes with Low/Intermediate but not High Disease Risk Index: A Center for International Blood and Marrow Transplant Research Study. *Transplant Cell Ther.* 2021;27(1):68 e61-68 e69.
  50. Deeg HJ, Sandmaier BM. Who is fit for allogeneic transplantation? *Blood.* 2010;116(23):4762-4770.
  51. Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol.* 1995;13(3):588-595.
  52. Andersson BS, Kashyap A, Gian V, et al. Conditioning therapy with intravenous busulfan and cyclophosphamide (IV BuCy2) for hematologic malignancies prior to allogeneic stem cell transplantation: a phase II study. *Biol Blood Marrow Transplant.* 2002;8(3):145-154.
  53. de Lima M, Couriel D, Thall PF, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. *Blood.* 2004;104(3):857-864.
  54. Ferreri AJ, Donadoni G, Cabras MG, et al. High Doses of Antimetabolites Followed by High-Dose Sequential Chemoimmunotherapy and Autologous Stem-Cell Transplantation in Patients With Systemic B-Cell Lymphoma and Secondary CNS Involvement: Final Results of a Multicenter Phase II Trial. *J Clin Oncol.* 2015;33(33):3903-3910.
  55. Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med.* 2007;357(4):340-348.
  56. Blaise D, Maraninchi D, Archimbaud E, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytosan versus Cytosan-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. *Blood.* 1992;79(10):2578-2582.
  57. Solomon SR, Sizemore CA, Sanacore M, et al. Total Body Irradiation-Based Myeloablative Haploidentical Stem Cell Transplantation Is a Safe and Effective Alternative to Unrelated Donor Transplantation in Patients Without Matched Sibling Donors. *Biol Blood Marrow Transplant.* 2015;21(7):1299-1307.
  58. Brunstein CG, Gutman JA, Weisdorf DJ, et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. *Blood.* 2010;116(22):4693-4699.
  59. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med.* 2003;348(19):1875-1883.
  60. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood.* 1998;91(3):756-763.

61. Srinivasan R, Takahashi Y, McCoy JP, et al. Overcoming graft rejection in heavily transfused and allo-immunised patients with bone marrow failure syndromes using fludarabine-based haematopoietic cell transplantation. *Br J Haematol*. 2006;133(3):305-314.
62. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood*. 2003;102(5):1915-1919.
63. Sharma P, Pollyea DA, Smith CA, et al. Thiotepa-Based Intensified Reduced-Intensity Conditioning Adult Double-Unit Cord Blood Hematopoietic Stem Cell Transplantation Results in Decreased Relapse Rate and Improved Survival Compared with Transplantation Following Standard Reduced-Intensity Conditioning: A Retrospective Cohort Comparison. *Biol Blood Marrow Transplant*. 2018;24(8):1671-1677.
64. Ciurea SO, Kongtim P, Varma A, et al. Is there an optimal conditioning for older patients with AML receiving allogeneic hematopoietic cell transplantation? *Blood*. 2020;135(6):449-452.
65. Kornblit B, Maloney DG, Storb R, et al. Fludarabine and 2-Gy TBI is superior to 2 Gy TBI as conditioning for HLA-matched related hematopoietic cell transplantation: a phase III randomized trial. *Biol Blood Marrow Transplant*. 2013;19(9):1340-1347.
66. Bodge MN, Reddy S, Thompson MS, Savani BN. Preparative regimen dosing for hematopoietic stem cell transplantation in patients with chronic kidney disease: analysis of the literature and recommendations. *Biol Blood Marrow Transplant*. 2014;20(7):908-919.
67. Bubalo J, Carpenter PA, Majhail N, et al. Conditioning chemotherapy dose adjustment in obese patients: a review and position statement by the American Society for Blood and Marrow Transplantation practice guideline committee. *Biol Blood Marrow Transplant*. 2014;20(5):600-616.
68. Brunstein CG, Pasquini MC, Kim S, et al. Effect of Conditioning Regimen Dose Reduction in Obese Patients Undergoing Autologous Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2019;25(3):480-487.
69. Bensinger WL. High-dose Preparatory Regimens. In: Appelbaum FR FS, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. Hoboken: Wiley-Blackwell; 2009: 316-332.
70. Tew KD CM, Jones RB. Clinical and high-dose alkylating agents. In: Chabner BA, Longo DL, eds. *Cancer Chemotherapy and Biotherapy: Principles and Practice*, 4th ed. Philadelphia: Lippincott Williams and Wilkins. 2006:283-309. In.
71. Palmer J, McCune JS, Perales MA, et al. Personalizing Busulfan-Based Conditioning: Considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee. *Biol Blood Marrow Transplant*. 2016;22(11):1915-1925.
72. McCune JS, Quinones CM, Ritchie J, et al. Harmonization of Busulfan Plasma Exposure Unit (BPEU): A Community-Initiated Consensus Statement. *Biol Blood Marrow Transplant*. 2019;25(9):1890-1897.
73. Andersson BS, Thall PF, Madden T, et al. Busulfan systemic exposure relative to regimen-related toxicity and acute graft-versus-host disease: defining a therapeutic window for i.v. BuCy2 in chronic myelogenous leukemia. *Biol Blood Marrow Transplant*. 2002;8(9):477-485.
74. Slattery JT, Clift RA, Buckner CD, et al. Marrow transplantation for chronic myeloid leukemia: the influence of plasma busulfan levels on the outcome of transplantation. *Blood*. 1997;89(8):3055-3060.
75. Slattery JT, Risler LJ. Therapeutic monitoring of busulfan in hematopoietic stem cell transplantation. *Therapeutic drug monitoring*. 1998;20(5):543-549.
76. Slattery JT, Sanders JE, Buckner CD, et al. Graft-rejection and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics. *Bone marrow transplantation*. 1995;16(1):31-42.
77. Grochow LB. Parenteral busulfan: is therapeutic monitoring still warranted? *Biol Blood Marrow Transplant*. 2002;8(9):465-467.
78. Kanakry CG, O'Donnell PV, Furlong T, et al. Multi-institutional study of post-transplantation cyclophosphamide as single-agent graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation using myeloablative busulfan and fludarabine conditioning. *J Clin Oncol*. 2014;32(31):3497-3505.
79. Andersson BS, Thall PF, Valdez BC, et al. Fludarabine with pharmacokinetically guided IV busulfan is superior to fixed-dose delivery in pretransplant conditioning of AML/MDS patients. *Bone marrow transplantation*. 2016.

80. Eberly AL, Anderson GD, Bubalo JS, McCune JS. Optimal prevention of seizures induced by high-dose busulfan. *Pharmacotherapy*. 2008;28(12):1502-1510.
81. Glotzbecker B, Duncan C, Alyea E, 3rd, Campbell B, Soiffer R. Important drug interactions in hematopoietic stem cell transplantation: what every physician should know. *Biol Blood Marrow Transplant*. 2012;18(7):989-1006.
82. Bhalla KS, Wilczynski SW, Abushamaa AM, et al. Pulmonary toxicity of induction chemotherapy prior to standard or high-dose chemotherapy with autologous hematopoietic support. *American journal of respiratory and critical care medicine*. 2000;161(1):17-25.
83. Cao TM, Negrin RS, Stockerl-Goldstein KE, et al. Pulmonary toxicity syndrome in breast cancer patients undergoing BCNU-containing high-dose chemotherapy and autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2000;6(4):387-394.
84. Todd NW, Peters WP, Ost AH, Roggli VL, Piantadosi CA. Pulmonary drug toxicity in patients with primary breast cancer treated with high-dose combination chemotherapy and autologous bone marrow transplantation. *The American review of respiratory disease*. 1993;147(5):1264-1270.
85. Woo MH, Ippoliti C, Bruton J, Mehra R, Champlin R, Przepiorka D. Headache, circumoral paresthesia, and facial flushing associated with high-dose carmustine infusion. *Bone marrow transplantation*. 1997;19(8):845-847.
86. Doroshow J.H. and Synold T.W. Pharmacologic basis for high-dose chemotherapy. In: Appelbaum FR FS, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. Hoboken: Wiley-Blackwell; 2009: 289-315.
87. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. *J Clin Oncol*. 1991;9(7):1215-1223.
88. Goldberg MA, Antin JH, Guinan EC, Rapoport JM. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood*. 1986;68(5):1114-1118.
89. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. *Arch Intern Med*. 1981;141(6):758-763.
90. Hensley ML, Schuchter LM, Lindley C, et al. American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol*. 1999;17(10):3333-3355.
91. McDonald GB, Slattery JT, Bouvier ME, et al. Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. *Blood*. 2003;101(5):2043-2048.
92. McCune JS, Batchelder A, Guthrie KA, et al. Personalized dosing of cyclophosphamide in the total body irradiation-cyclophosphamide conditioning regimen: a phase II trial in patients with hematologic malignancy. *Clin Pharmacol Ther*. 2009;85(6):615-622.
93. McCune JS, Batchelder A, Deeg HJ, et al. Cyclophosphamide following targeted oral busulfan as conditioning for hematopoietic cell transplantation: pharmacokinetics, liver toxicity, and mortality. *Biol Blood Marrow Transplant*. 2007;13(7):853-862.
94. Rezvani AR, McCune JS, Storer BE, et al. Cyclophosphamide followed by intravenous targeted busulfan for allogeneic hematopoietic cell transplantation: pharmacokinetics and clinical outcomes. *Biol Blood Marrow Transplant*. 2013;19(7):1033-1039.
95. Ryan DP, Garcia-Carboner R., Chabner, B.A. Cytidine Analogs. In: *Chabner BA, Longo DL, eds Cancer Chemotherapy and Biotherapy: Principles and Practice, 4th ed Philadelphia: Lippincott Williams & Wilkins, 2006:183-211.*
96. Beitinjaneh A, McKinney AM, Cao Q, Weisdorf DJ. Toxic leukoencephalopathy following fludarabine-associated hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2011;17(3):300-308.
97. Long-Boyle JR, Green KG, Brunstein CG, et al. High fludarabine exposure and relationship with treatment-related mortality after nonmyeloablative hematopoietic cell transplantation. *Bone marrow transplantation*. 2011;46(1):20-26.
98. Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2014;120(10):1453-1461.
99. Wang L, Gu Z, Zhai R, et al. Efficacy of oral cryotherapy on oral mucositis prevention in patients with hematological malignancies undergoing hematopoietic stem cell transplantation: a meta-analysis of randomized controlled trials. *PloS one*. 2015;10(5):e0128763.



100. Tricot G, Alberts DS, Johnson C, et al. Safety of autotransplants with high-dose melphalan in renal failure: a pharmacokinetic and toxicity study. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 1996;2(6):947-952.
101. Sirohi B, Powles R, Kulkarni S, et al. Glomerular filtration rate prior to high-dose melphalan 200 mg/m<sup>2</sup> as a surrogate marker of outcome in patients with myeloma. *British journal of cancer*. 2001;85(3):325-332.
102. Carlson K. Melphalan 200 mg/m<sup>2</sup> with blood stem cell support as first-line myeloma therapy: impact of glomerular filtration rate on engraftment, transplantation-related toxicity and survival. *Bone marrow transplantation*. 2005;35(10):985-990.
103. Alimohamed N, Daly A, Owen C, Duggan P, Stewart DA. Upfront thiotepa, busulfan, cyclophosphamide, and autologous stem cell transplantation for primary CNS lymphoma: a single centre experience. *Leuk Lymphoma*. 2012;53(5):862-867.
104. Alessandrino P, Bernasconi P, Caldera D, et al. Adverse events occurring during bone marrow or peripheral blood progenitor cell infusion: analysis of 126 cases. *Bone marrow transplantation*. 1999;23(6):533-537.
105. Elad S, Cheng KKF, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126(19):4423-4431.
106. Blijlevens N, de Chateau M, Krivan G, et al. In a high-dose melphalan setting, palifermin compared with placebo had no effect on oral mucositis or related patient's burden. *Bone marrow transplantation*. 2013;48(7):966-971.
107. Blazar BR, Weisdorf DJ, DeFor T, et al. Phase 1/2 randomized, placebo-control trial of palifermin to prevent graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HCT). *Blood*. 2006;108(9):3216-3222.
108. Levine JE, Blazar BR, DeFor T, Ferrara JL, Weisdorf DJ. Long-term follow-up of a phase I/II randomized, placebo-controlled trial of palifermin to prevent graft-versus-host disease (GVHD) after related donor allogeneic hematopoietic cell transplantation (HCT). *Biol Blood Marrow Transplant*. 2008;14(9):1017-1021.
109. Nasilowska-Adamska B, Rzepecki P, Manko J, et al. The influence of palifermin (Kepivance) on oral mucositis and acute graft versus host disease in patients with hematological diseases undergoing hematopoietic stem cell transplant. *Bone marrow transplantation*. 2007;40(10):983-988.
110. Langner S, Staber P, Schub N, et al. Palifermin reduces incidence and severity of oral mucositis in allogeneic stem-cell transplant recipients. *Bone marrow transplantation*. 2008;42(4):275-279.
111. Schmidt V, Niederwieser D, Schenk T, et al. Efficacy and safety of keratinocyte growth factor (palifermin) for prevention of oral mucositis in TBI-based allogeneic hematopoietic stem cell transplantation. *Bone marrow transplantation*. 2018;53(9):1188-1192.
112. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. *J Clin Oncol*. 2020;38(24):2782-2797.
113. Ibrahim RB, Abidi MH, Ayash LJ, et al. Effect of aprepitant on intravenous tacrolimus disposition in reduced intensity hematopoietic stem cell transplantation. *J Oncol Pharm Pract*. 2008;14(3):113-121.
114. Stiff P, Fox-Geiman M, Kiley K, et al. Aprepitant Vs. Placebo Plus Oral Ondansetron and Dexamethasone for the Prevention of Nausea and Vomiting Associated with Highly Emetogenic Preparative Regimens Prior to Hematopoietic Stem Cell Transplantation: A Prospective, Randomized Double-Blind Phase III Trial. *ASH Annual Meeting Abstracts*. 2009;114(22):2267-.
115. Clemmons AB, Orr J, Andrick B, Gandhi A, Sportes C, DeRemer D. Randomized, Placebo-Controlled, Phase III Trial of Fosaprepitant, Ondansetron, Dexamethasone (FOND) Versus FOND Plus Olanzapine (FOND-O) for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients with Hematologic Malignancies Receiving Highly Emetogenic Chemotherapy and Hematopoietic Cell Transplantation Regimens: The FOND-O Trial. *Biol Blood Marrow Transplant*. 2018;24(10):2065-2071.
116. Trifilio S, Welles C, Seeger K, et al. Olanzapine Reduces Chemotherapy-induced Nausea and Vomiting Compared With Aprepitant in Myeloma Patients Receiving High-dose Melphalan Before Stem Cell Transplantation: A Retrospective Study. *Clin Lymphoma Myeloma Leuk*. 2017;17(9):584-589.
117. Nakagaki M, Barras M, Curley C, Butler JP, Kennedy GA. A randomized trial of olanzapine versus palonosetron versus infused ondansetron for the treatment of breakthrough chemotherapy-induced

- nausea and vomiting in patients undergoing hematopoietic stem cell transplantation. *Support Care Cancer*. 2017;25(2):607-613.
118. Corbacioglu S, Jabbour EJ, Mohty M. Risk Factors for Development of and Progression of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome. *Biol Blood Marrow Transplant*. 2019;25(7):1271-1280.
  119. Cairo MS, Cooke KR, Lazarus HM, Chao N. Modified diagnostic criteria, grading classification and newly elucidated pathophysiology of hepatic SOS/VOD after haematopoietic cell transplantation. *Br J Haematol*. 2020;190(6):822-836.
  120. Dignan FL, Wynn RF, Hadzic N, et al. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. *Br J Haematol*. 2013;163(4):444-457.
  121. Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone marrow transplantation*. 2016;51(7):906-912.
  122. Dalle JH, Giralt SA. Hepatic Veno-Occlusive Disease after Hematopoietic Stem Cell Transplantation: Risk Factors and Stratification, Prophylaxis, and Treatment. *Biol Blood Marrow Transplant*. 2016;22(3):400-409.
  123. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone marrow transplantation*. 2015;50(6):781-789.
  124. Tay J, Tinmouth A, Fergusson D, Huebsch L, Allan DS. Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007;13(2):206-217.
  125. Ruutu T, Juvonen E, Remberger M, et al. Improved survival with ursodeoxycholic Acid prophylaxis in allogeneic stem cell transplantation: long-term follow-up of a randomized study. *Biol Blood Marrow Transplant*. 2014;20(1):135-138.
  126. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127(13):1656-1665.
  127. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant*. 2015;21(3):389-401 e381.
  128. Zeiser R, Blazar BR. Pathophysiology of Chronic Graft-versus-Host Disease and Therapeutic Targets. *N Engl J Med*. 2017;377(26):2565-2579.
  129. Kitko CL, Pidala J, Schoemans HM, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IIa. The 2020 Clinical Implementation and Early Diagnosis Working Group Report. *Transplant Cell Ther*. 2021;27(7):545-557.
  130. Sarantopoulos S, Cardones AR, Sullivan KM. How I treat refractory chronic graft-versus-host disease. *Blood*. 2019;133(11):1191-1200.
  131. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol*. 2020;7(2):e157-e167.
  132. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. *Blood*. 1998;92(7):2303-2314.
  133. Huang B, Lin X, Zhang Z, et al. Comparison of Tacrolimus and Cyclosporine Combined With Methotrexate for Graft Versus Host Disease Prophylaxis After Allogeneic Hematopoietic Cell Transplantation. *Transplantation*. 2020;104(2):428-436.
  134. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Blood*. 2000;96(6):2062-2068.
  135. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood*. 2014;124(8):1372-1377.

136. Bolwell B, Sobecks R, Pohlman B, et al. A prospective randomized trial comparing cyclosporine and short course methotrexate with cyclosporine and mycophenolate mofetil for GVHD prophylaxis in myeloablative allogeneic bone marrow transplantation. *Bone marrow transplantation*. 2004;34(7):621-625.
137. Perkins J, Field T, Kim J, et al. A randomized phase II trial comparing tacrolimus and mycophenolate mofetil to tacrolimus and methotrexate for acute graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant*. 2010;16(7):937-947.
138. Sandmaier BM, Kornblit B, Storer BE, et al. Addition of sirolimus to standard cyclosporine plus mycophenolate mofetil-based graft-versus-host disease prophylaxis for patients after unrelated non-myeloablative haemopoietic stem cell transplantation: a multicentre, randomised, phase 3 trial. *Lancet Haematol*. 2019;6(8):e409-e418.
139. Watkins B, Qayed M, McCracken C, et al. Phase II Trial of Costimulation Blockade With Abatacept for Prevention of Acute GVHD. *J Clin Oncol*. 2021;39(17):1865-1877.
140. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14(6):641-650.
141. Brunstein CG, Fuchs EJ, Carter SL, et al. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011;118(2):282-288.
142. Ponce DM, Politikos I, Alousi A, et al. Guidelines for the Prevention and Management of Graft-versus-Host Disease after Cord Blood Transplantation. *Transplant Cell Ther*. 2021;27(7):540-544.
143. Bolanos-Meade J, Reshef R, Fraser R, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). *Lancet Haematol*. 2019;6(3):e132-e143.
144. Nishihori T, Al-Kadhimi Z, Hamadani M, Kharfan-Dabaja MA. Antithymocyte globulin in allogeneic hematopoietic cell transplantation: benefits and limitations. *Immunotherapy*. 2016;8(4):435-447.
145. Kroger N, Solano C, Wolschke C, et al. Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease. *N Engl J Med*. 2016;374(1):43-53.
146. Socie G, Schmoor C, Bethge WA, et al. Chronic graft-versus-host disease: long-term results from a randomized trial on graft-versus-host disease prophylaxis with or without anti-T-cell globulin ATG-Fresenius. *Blood*. 2011;117(23):6375-6382.
147. Finke J, Bethge WA, Schmoor C, et al. Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial. *Lancet Oncol*. 2009;10(9):855-864.
148. Soiffer RJ, Kim HT, McGuirk J, et al. Prospective, Randomized, Double-Blind, Phase III Clinical Trial of Anti-T-Lymphocyte Globulin to Assess Impact on Chronic Graft-Versus-Host Disease-Free Survival in Patients Undergoing HLA-Matched Unrelated Myeloablative Hematopoietic Cell Transplantation. *J Clin Oncol*. 2017;35(36):4003-4011.
149. Luznik L, Pasquini MC, Logan B, et al. Randomized Phase III BMT CTN Trial of Calcineurin Inhibitor-Free Chronic Graft-Versus-Host Disease Interventions in Myeloablative Hematopoietic Cell Transplantation for Hematologic Malignancies. *J Clin Oncol*. 2022;40(4):356-368.
150. Broers AEC, de Jong CN, Bakunina K, et al. Posttransplant cyclophosphamide for prevention of graft-versus-host disease: results of the prospective randomized HOVON-96 trial. *Blood Adv*. 2022;6(11):3378-3385.
151. Walker I, Panzarella T, Couban S, et al. Addition of anti-thymocyte globulin to standard graft-versus-host disease prophylaxis versus standard treatment alone in patients with haematological malignancies undergoing transplantation from unrelated donors: final analysis of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. 2020;7(2):e100-e111.
152. Farag SS, Abu Zaid M, Schwartz JE, et al. Dipeptidyl Peptidase 4 Inhibition for Prophylaxis of Acute Graft-versus-Host Disease. *N Engl J Med*. 2021;384(1):11-19.

153. Yee GC, Self SG, McGuire TR, Carlin J, Sanders JE, Deeg HJ. Serum cyclosporine concentration and risk of acute graft-versus-host disease after allogeneic marrow transplantation. *N Engl J Med*. 1988;319(2):65-70.
154. Przepiorka D, Devine S, Fay J, Uberti J, Wingard J. Practical considerations in the use of tacrolimus for allogeneic marrow transplantation. *Bone marrow transplantation*. 1999;24(10):1053-1056.
155. Przepiorka D, Nash RA, Wingard JR, et al. Relationship of tacrolimus whole blood levels to efficacy and safety outcomes after unrelated donor marrow transplantation. *Biol Blood Marrow Transplant*. 1999;5(2):94-97.
156. Storb R, Antin JH, Cutler C. Should methotrexate plus calcineurin inhibitors be considered standard of care for prophylaxis of acute graft-versus-host disease? *Biol Blood Marrow Transplant*. 2010;16(1 Suppl):S18-27.
157. McCune JS, Bemer MJ, Long-Boyle J. Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics of Immunosuppressants in Allogeneic Hematopoietic Cell Transplantation: Part II. *Clin Pharmacokinet*. 2016;55(5):551-593.
158. Pidala J, Hamadani M, Dawson P, et al. Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. *Blood*. 2020;135(2):97-107.
159. Shayani S, Palmer J, Stiller T, et al. Thrombotic microangiopathy associated with sirolimus level after allogeneic hematopoietic cell transplantation with tacrolimus/sirolimus-based graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant*. 2013;19(2):298-304.
160. Kiel PJ, Vargo CA, Patel GP, Rosenbeck LL, Srivastava S. Possible correlation of sirolimus plasma concentration with sinusoidal obstructive syndrome of the liver in patients undergoing myeloablative allogeneic hematopoietic cell transplantation. *Pharmacotherapy*. 2012;32(5):441-445.
161. Sullivan KM, Storb R, Buckner CD, et al. Graft-versus-host disease as adoptive immunotherapy in patients with advanced hematologic neoplasms. *N Engl J Med*. 1989;320(13):828-834.
162. Przepiorka D, Ippoliti C, Khouri I, et al. Tacrolimus and minidose methotrexate for prevention of acute graft-versus-host disease after matched unrelated donor marrow transplantation. *Blood*. 1996;88(11):4383-4389.
163. Devine SM, Geller RB, Lin LB, et al. The outcome of unrelated donor bone marrow transplantation in patients with hematologic malignancies using tacrolimus (FK506) and low dose methotrexate for graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant*. 1997;3(1):25-33.
164. Nevill TJ, Tirgan MH, Deeg HJ, et al. Influence of post-methotrexate folinic acid rescue on regimen-related toxicity and graft-versus-host disease after allogeneic bone marrow transplantation. *Bone marrow transplantation*. 1992;9(5):349-354.
165. Russell JA, Woodman RC, Poon MC, Jones AR, Ruether BA. Addition of low-dose folinic acid to a methotrexate/cyclosporin A regimen for prevention of acute graft-versus-host disease. *Bone marrow transplantation*. 1994;14(3):397-401.
166. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18(4):295-304.
167. MacMillan ML, DeFor TE, Holtan SG, Rashidi A, Blazar BR, Weisdorf DJ. Validation of Minnesota acute graft-versus-host disease Risk Score. *Haematologica*. 2020;105(2):519-524.
168. Levine JE, Braun TM, Harris AC, et al. A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study. *Lancet Haematol*. 2015;2(1):e21-29.
169. Custer C and Antin JH. Manifestations and treatment of acute graft-versus-host disease. In: Appelbaum FR, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. Hoboken: Wiley-Blackwell; 2009: 1287-1303.
170. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2012;18(8):1150-1163.
171. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol*. 2012;158(1):30-45.
172. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high- or low-dose 6-methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. *Blood*. 1998;92(7):2288-2293.

173. Mielcarek M, Furlong T, Storer BE, et al. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. *Haematologica*. 2015;100(6):842-848.
174. Bertz H, Afting M, Kreisel W, Duffner U, Greinwald R, Finke J. Feasibility and response to budesonide as topical corticosteroid therapy for acute intestinal GVHD. *Bone marrow transplantation*. 1999;24(11):1185-1189.
175. Hockenbery DM, Cruickshank S, Rodell TC, et al. A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. *Blood*. 2007;109(10):4557-4563.
176. Castilla C, Perez-Simon JA, Sanchez-Guijo FM, et al. Oral beclomethasone dipropionate for the treatment of gastrointestinal acute graft-versus-host disease (GVHD). *Biol Blood Marrow Transplant*. 2006;12(9):936-941.
177. Jagasia MA, Schroeder MA, et al. Ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute graft-vs-host disease: results from the phase 2 REACH1 trial. *Biology Blood Marrow Transplant*. 2019;25(3):S52.
178. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. *N Engl J Med*. 2020;382(19):1800-1810.
179. Magenau JM, Goldstein SC, Peltier D, et al. alpha1-Antitrypsin infusion for treatment of steroid-resistant acute graft-versus-host disease. *Blood*. 2018;131(12):1372-1379.
180. Martinez C, Solano C, Ferra C, Sampol A, Valcarcel D, Perez-Simon JA. Alemtuzumab as treatment of steroid-refractory acute graft-versus-host disease: results of a phase II study. *Biol Blood Marrow Transplant*. 2009;15(5):639-642.
181. Gomez-Almaguer D, Ruiz-Arguelles GJ, del Carmen Tarin-Arzaga L, et al. Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2008;14(1):10-15.
182. Schub N, Gunther A, Schrauder A, et al. Therapy of steroid-refractory acute GVHD with CD52 antibody alemtuzumab is effective. *Bone marrow transplantation*. 2011;46(1):143-147.
183. Van Lint MT, Milone G, Leotta S, et al. Treatment of acute graft-versus-host disease with prednisolone: significant survival advantage for day +5 responders and no advantage for nonresponders receiving anti-thymocyte globulin. *Blood*. 2006;107(10):4177-4181.
184. Roy J, McGlave PB, Filipovich AH, et al. Acute graft-versus-host disease following unrelated donor marrow transplantation: failure of conventional therapy. *Bone marrow transplantation*. 1992;10(1):77-82.
185. MacMillan ML, Weisdorf DJ, Davies SM, et al. Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8(1):40-46.
186. Arai S, Margolis J, Zahurak M, Anders V, Vogelsang GB. Poor outcome in steroid-refractory graft-versus-host disease with antithymocyte globulin treatment. *Biol Blood Marrow Transplant*. 2002;8(3):155-160.
187. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: secondary treatment. *Blood*. 1991;77(8):1821-1828.
188. Khoury H, Kashyap A, Adkins DR, et al. Treatment of steroid-resistant acute graft-versus-host disease with anti-thymocyte globulin. *Bone marrow transplantation*. 2001;27(10):1059-1064.
189. Macmillan ML, Couriel D, Weisdorf DJ, et al. A phase 2/3 multicenter randomized clinical trial of ABX-CBL versus ATG as secondary therapy for steroid-resistant acute graft-versus-host disease. *Blood*. 2007;109(6):2657-2662.
190. Massenkeil G, Rackwitz S, Genvresse I, Rosen O, Dorken B, Arnold R. Basiliximab is well tolerated and effective in the treatment of steroid-refractory acute graft-versus-host disease after allogeneic stem cell transplantation. *Bone marrow transplantation*. 2002;30(12):899-903.
191. Schmidt-Hieber M, Fietz T, Knauf W, et al. Efficacy of the interleukin-2 receptor antagonist basiliximab in steroid-refractory acute graft-versus-host disease. *Br J Haematol*. 2005;130(4):568-574.
192. Busca A, Locatelli F, Marmont F, Ceretto C, Falda M. Recombinant human soluble tumor necrosis factor receptor fusion protein as treatment for steroid refractory graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. *American journal of hematology*. 2007;82(1):45-52.
193. Perfetti P, Carlier P, Strada P, et al. Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. *Bone marrow transplantation*. 2008;42(9):609-617.

194. Greinix HT, Volc-Platzer B, Kalhs P, et al. Extracorporeal photochemotherapy in the treatment of severe steroid-refractory acute graft-versus-host disease: a pilot study. *Blood*. 2000;96(7):2426-2431.
195. Oarbeascoa G, Lozano ML, Guerra LM, et al. Retrospective Multicenter Study of Extracorporeal Photopheresis in Steroid-Refractory Acute and Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2020;26(4):651-658.
196. Pidala J, Kim J, Field T, et al. Infliximab for managing steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2009;15(9):1116-1121.
197. Patriarca F, Sperotto A, Damiani D, et al. Infliximab treatment for steroid-refractory acute graft-versus-host disease. *Haematologica*. 2004;89(11):1352-1359.
198. Couriel D, Saliba R, Hicks K, et al. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. *Blood*. 2004;104(3):649-654.
199. Yalniz FF, Hefazi M, McCullough K, et al. Safety and Efficacy of Infliximab Therapy in the Setting of Steroid-Refractory Acute Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2017;23(9):1478-1484.
200. Furlong T, Martin P, Flowers ME, et al. Therapy with mycophenolate mofetil for refractory acute and chronic GVHD. *Bone marrow transplantation*. 2009;44(11):739-748.
201. Pidala J, Kim J, Perkins J, et al. Mycophenolate mofetil for the management of steroid-refractory acute graft vs host disease. *Bone marrow transplantation*. 2010;45(5):919-924.
202. Kim JG, Sohn SK, Kim DH, et al. Different efficacy of mycophenolate mofetil as salvage treatment for acute and chronic GVHD after allogeneic stem cell transplant. *European journal of haematology*. 2004;73(1):56-61.
203. Krejci M, Doubek M, Buchler T, Brychtova Y, Vorlicek J, Mayer J. Mycophenolate mofetil for the treatment of acute and chronic steroid-refractory graft-versus-host disease. *Annals of hematology*. 2005;84(10):681-685.
204. Schmitt T, Luft T, Hegenbart U, Tran TH, Ho AD, Dreger P. Pentostatin for treatment of steroid-refractory acute GVHD: a retrospective single-center analysis. *Bone marrow transplantation*. 2011;46(4):580-585.
205. Bolanos-Meade J, Jacobsohn DA, Margolis J, et al. Pentostatin in steroid-refractory acute graft-versus-host disease. *J Clin Oncol*. 2005;23(12):2661-2668.
206. Klein SA, Bug G, Mousset S, Hofmann WK, Hoelzer D, Martin H. Long term outcome of patients with steroid-refractory acute intestinal graft versus host disease after treatment with pentostatin. *Br J Haematol*. 2011;154(1):143-146.
207. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29(10):2062-2068.
208. Hoda D, Pidala J, Salgado-Vila N, et al. Sirolimus for treatment of steroid-refractory acute graft-versus-host disease. *Bone marrow transplantation*. 2010;45(8):1347-1351.
209. Benito AI, Furlong T, Martin PJ, et al. Sirolimus (rapamycin) for the treatment of steroid-refractory acute graft-versus-host disease. *Transplantation*. 2001;72(12):1924-1929.
210. Ghez D, Rubio MT, Maillard N, et al. Rapamycin for refractory acute graft-versus-host disease. *Transplantation*. 2009;88(9):1081-1087.
211. Roddy JV, Haverkos BM, McBride A, et al. Tocilizumab for steroid refractory acute graft-versus-host disease. *Leuk Lymphoma*. 2016;57(1):81-85.
212. Drobyski WR, Pasquini M, Kovatovic K, et al. Tocilizumab for the treatment of steroid refractory graft-versus-host disease. *Biol Blood Marrow Transplant*. 2011;17(12):1862-1868.
213. Ganetsky A, Frey NV, Hexner EO, et al. Tocilizumab for the treatment of severe steroid-refractory acute graft-versus-host disease of the lower gastrointestinal tract. *Bone marrow transplantation*. 2018.
214. Pavletic SZ and Vogelsang GB. Chronic graft-versus-host disease: clinical manifestations and therapy. In: Appelbaum FR FS, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. Hoboken: Wiley-Blackwell; 2009: 1304-1324.
215. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet*. 2009;373(9674):1550-1561.
216. Wolff D, Gerbitz A, Ayuk F, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. *Biol Blood Marrow Transplant*. 2010;16(12):1611-1628.
217. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125(4):606-615.

218. Sullivan KM, Witherspoon RP, Storb R, et al. Alternating-day cyclosporine and prednisone for treatment of high-risk chronic graft-v-host disease. *Blood*. 1988;72(2):555-561.
219. Sullivan KM, Witherspoon RP, Storb R, et al. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-v-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. *Blood*. 1988;72(2):546-554.
220. Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood*. 2002;100(1):48-51.
221. Williams KM. How I treat bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Blood*. 2017;129(4):448-455.
222. Williams KM, Cheng GS, Pusic I, et al. Fluticasone, Azithromycin, and Montelukast Treatment for New-Onset Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2016;22(4):710-716.
223. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2015;21(6):984-999.
224. Carpenter PA, Kitko CL, Elad S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2015;21(7):1167-1187.
225. Inamoto Y, Flowers ME. Treatment of chronic graft-versus-host disease in 2011. *Current opinion in hematology*. 2011;18(6):414-420.
226. Wolff D, Schleuning M, von Harsdorf S, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2011;17(1):1-17.
227. Cutler CS, Lee SJ, Arai S, et al. Belumosudil for Chronic Graft-versus-Host Disease (cGVHD) After 2 or More Prior Lines of Therapy: The ROCKstar Study. *Blood*. 2021.
228. Jagasia M, Lazaryan A, Bachier CR, et al. ROCK2 Inhibition With Belumosudil (KD025) for the Treatment of Chronic Graft-Versus-Host Disease. *J Clin Oncol*. 2021;39(17):1888-1898.
229. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *N Engl J Med*. 2021;385(3):228-238.
230. Nahas MR, Soiffer RJ, Kim HT, et al. Phase 1 clinical trial evaluating abatacept in patients with steroid-refractory chronic graft-versus-host disease. *Blood*. 2018;131(25):2836-2845.
231. Nikiforow S, Kim HT, Bindra B, et al. Phase I study of alemtuzumab for therapy of steroid-refractory chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2013;19(5):804-811.
232. Gutierrez-Aguirre CH, Cantu-Rodriguez OG, Borjas-Almaguer OD, et al. Effectiveness of subcutaneous low-dose alemtuzumab and rituximab combination therapy for steroid-resistant chronic graft-versus-host disease. *Haematologica*. 2012;97(5):717-722.
233. Yanik GA, Mineishi S, Levine JE, et al. Soluble tumor necrosis factor receptor: enbrel (etanercept) for subacute pulmonary dysfunction following allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(7):1044-1054.
234. Apisarnthanarax N, Donato M, Korbling M, et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone marrow transplantation*. 2003;31(6):459-465.
235. Bisaccia E, Palangio M, Gonzalez J, Adler KR, Rowley SD, Goldberg SL. Treating refractory chronic graft-versus-host disease with extracorporeal photochemotherapy. *Bone marrow transplantation*. 2003;31(4):291-294.
236. Child FJ, Ratnavel R, Watkins P, et al. Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus-host disease (GVHD). *Bone marrow transplantation*. 1999;23(9):881-887.
237. Foss FM, DiVenuti GM, Chin K, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone marrow transplantation*. 2005;35(12):1187-1193.

238. Gorgun G, Miller KB, Foss FM. Immunologic mechanisms of extracorporeal photochemotherapy in chronic graft-versus-host disease. *Blood*. 2002;100(3):941-947.
239. Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood*. 1998;92(9):3098-3104.
240. Perseghin P, Galimberti S, Balduzzi A, et al. Extracorporeal photochemotherapy for the treatment of chronic graft-versus-host disease: trend for a possible cell dose-related effect? *Ther Apher Dial*. 2007;11(2):85-93.
241. Gatz E, Rogers CE, Clouthier SG, et al. Extracorporeal photopheresis reverses experimental graft-versus-host disease through regulatory T cells. *Blood*. 2008;112(4):1515-1521.
242. Couriel DR, Hosing C, Saliba R, et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. *Blood*. 2006;107(8):3074-3080.
243. Salvaneschi L, Perotti C, Zecca M, et al. Extracorporeal photochemotherapy for treatment of acute and chronic GVHD in childhood. *Transfusion*. 2001;41(10):1299-1305.
244. Dall'Amico R, Messina C. Extracorporeal photochemotherapy for the treatment of graft-versus-host disease. *Ther Apher*. 2002;6(4):296-304.
245. Kanold J, Messina C, Halle P, et al. Update on extracorporeal photochemotherapy for graft-versus-host disease treatment. *Bone marrow transplantation*. 2005;35 Suppl 1:S69-71.
246. Owsianowski M, Gollnick H, Siegert W, Schwerdtfeger R, Orfanos CE. Successful treatment of chronic graft-versus-host disease with extracorporeal photopheresis. *Bone marrow transplantation*. 1994;14(5):845-848.
247. Seaton ED, Szydlo RM, Kanfer E, Apperley JF, Russell-Jones R. Influence of extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response. *Blood*. 2003;102(4):1217-1223.
248. Perotti C, Del Fante C, Tinelli C, et al. Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. *Transfusion*. 2010;50(6):1359-1369.
249. Jagasia MH, Savani BN, Stricklin G, et al. Classic and overlap chronic graft-versus-host disease (cGVHD) is associated with superior outcome after extracorporeal photopheresis (ECP). *Biol Blood Marrow Transplant*. 2009;15(10):1288-1295.
250. Lucid CE, Savani BN, Engelhardt BG, et al. Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT. *Bone marrow transplantation*. 2011;46(3):426-429.
251. Greinix HT, van Besien K, Elmaagacli AH, et al. Progressive improvement in cutaneous and extracutaneous chronic graft-versus-host disease after a 24-week course of extracorporeal photopheresis--results of a crossover randomized study. *Biol Blood Marrow Transplant*. 2011;17(12):1775-1782.
252. Gandelman JS, Song DJ, Chen H, et al. A Prospective Trial of Extracorporeal Photopheresis for Chronic Graft-versus-Host Disease Reveals Significant Disease Response and No Association with Frequency of Regulatory T Cells. *Biol Blood Marrow Transplant*. 2018;24(12):2373-2380.
253. Flowers ME, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*. 2008;112(7):2667-2674.
254. Gilman AL, Chan KW, Mogul A, et al. Hydroxychloroquine for the treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2000;6(3A):327-334.
255. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood*. 2017.
256. Waller EK, Miklos D, Cutler C, et al. Ibrutinib for Chronic Graft-versus-Host Disease After Failure of Prior Therapy: 1-Year Update of a Phase 1b/2 Study. *Biol Blood Marrow Transplant*. 2019;25(10):2002-2007.
257. Moreno-Romero JA, Fernandez-Aviles F, Carreras E, Rovira M, Martinez C, Mascaro JM, Jr. Imatinib as a potential treatment for sclerodermatous chronic graft-vs-host disease. *Archives of dermatology*. 2008;144(9):1106-1109.
258. Chen GL, Arai S, Flowers ME, et al. A phase 1 study of imatinib for corticosteroid-dependent/refractory chronic graft-versus-host disease: response does not correlate with anti-PDGFRα antibodies. *Blood*. 2011;118(15):4070-4078.



259. Magro L, Mohty M, Catteau B, et al. Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. *Blood*. 2009;114(3):719-722.
260. Olivieri A, Locatelli F, Zecca M, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. *Blood*. 2009;114(3):709-718.
261. Stadler M, Ahlborn R, Kamal H, et al. Limited efficacy of imatinib in severe pulmonary chronic graft-versus-host disease. *Blood*. 2009;114(17):3718-3719; author reply 3719-3720.
262. Koreth J, Matsuoka K, Kim HT, et al. Interleukin-2 and regulatory T cells in graft-versus-host disease. *N Engl J Med*. 2011;365(22):2055-2066.
263. Pidala J, Bhatt VR, Hamilton B, et al. Ixazomib for Treatment of Refractory Chronic Graft-versus-Host Disease: A Chronic GVHD Consortium Phase II Trial. *Biol Blood Marrow Transplant*. 2020;26(9):1612-1619.
264. Huang XJ, Jiang Q, Chen H, et al. Low-dose methotrexate for the treatment of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Bone marrow transplantation*. 2005;36(4):343-348.
265. Takami A, Mochizuki K, Okumura H, et al. Mycophenolate mofetil is effective and well tolerated in the treatment of refractory acute and chronic graft-versus-host disease. *Int J Hematol*. 2006;83(1):80-85.
266. Busca A, Locatelli F, Marmont F, Audisio E, Falda M. Response to mycophenolate mofetil therapy in refractory chronic graft-versus-host disease. *Haematologica*. 2003;88(7):837-839.
267. Busca A, Saroglia EM, Lanino E, et al. Mycophenolate mofetil (MMF) as therapy for refractory chronic GVHD (cGVHD) in children receiving bone marrow transplantation. *Bone marrow transplantation*. 2000;25(10):1067-1071.
268. Basara N, Blau WL, Kiehl MG, et al. Efficacy and safety of mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant recipient. *Transplant Proc*. 1998;30(8):4087-4089.
269. Mookerjee B, Altomonte V, Vogelsang G. Salvage therapy for refractory chronic graft-versus-host disease with mycophenolate mofetil and tacrolimus. *Bone marrow transplantation*. 1999;24(5):517-520.
270. Baudard M, Vincent A, Moreau P, Kergueris MF, Harousseau JL, Milpied N. Mycophenolate mofetil for the treatment of acute and chronic GVHD is effective and well tolerated but induces a high risk of infectious complications: a series of 21 BM or PBSC transplant patients. *Bone marrow transplantation*. 2002;30(5):287-295.
271. Lopez F, Parker P, Nademanee A, et al. Efficacy of mycophenolate mofetil in the treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11(4):307-313.
272. Jacobsohn DA, Chen AR, Zahurak M, et al. Phase II study of pentostatin in patients with corticosteroid-refractory chronic graft-versus-host disease. *J Clin Oncol*. 2007;25(27):4255-4261.
273. Pidala J, Kim J, Roman-Diaz J, et al. Pentostatin as rescue therapy for glucocorticoid-refractory acute and chronic graft-versus-host disease. *Ann Transplant*. 2010;15(4):21-29.
274. Jacobsohn DA, Gilman AL, Rademaker A, et al. Evaluation of pentostatin in corticosteroid-refractory chronic graft-versus-host disease in children: a Pediatric Blood and Marrow Transplant Consortium study. *Blood*. 2009;114(20):4354-4360.
275. Goldberg JD, Jacobsohn DA, Margolis J, et al. Pentostatin for the treatment of chronic graft-versus-host disease in children. *Journal of pediatric hematology/oncology*. 2003;25(7):584-588.
276. Carella AM, Biasco S, Nati S, Congiu A, Lerma E. Rituximab is effective for extensive steroid-refractory chronic graft-vs.-host-disease. *Leuk Lymphoma*. 2007;48(3):623-624.
277. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood*. 2006;108(2):756-762.
278. Okamoto M, Okano A, Akamatsu S, et al. Rituximab is effective for steroid-refractory sclerodermatous chronic graft-versus-host disease. *Leukemia*. 2006;20(1):172-173.
279. Teshima T, Nagafuji K, Henzan H, et al. Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. *Int J Hematol*. 2009;90(2):253-260.
280. von Bonin M, Oelschlagel U, Radke J, et al. Treatment of chronic steroid-refractory graft-versus-host disease with low-dose rituximab. *Transplantation*. 2008;86(6):875-879.
281. Mohty M, Marchetti N, El-Cheikh J, Faucher C, Furst S, Blaise D. Rituximab as salvage therapy for refractory chronic GVHD. *Bone marrow transplantation*. 2008;41(10):909-911.
282. Zaja F, Bacigalupo A, Patriarca F, et al. Treatment of refractory chronic GVHD with rituximab: a GITMO study. *Bone marrow transplantation*. 2007;40(3):273-277.

283. Canninga-van Dijk MR, van der Straaten HM, Fijnheer R, Sanders CJ, van den Tweel JG, Verdonck LF. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus-host disease. *Blood*. 2004;104(8):2603-2606.
284. Ratanatharathorn V, Ayash L, Reynolds C, et al. Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody. *Biol Blood Marrow Transplant*. 2003;9(8):505-511.
285. Ratanatharathorn V, Carson E, Reynolds C, et al. Anti-CD20 chimeric monoclonal antibody treatment of refractory immune-mediated thrombocytopenia in a patient with chronic graft-versus-host disease. *Annals of internal medicine*. 2000;133(4):275-279.
286. Szabolcs P, Reese M, Yancey KB, Hall RP, Kurtzberg J. Combination treatment of bullous pemphigoid with anti-CD20 and anti-CD25 antibodies in a patient with chronic graft-versus-host disease. *Bone marrow transplantation*. 2002;30(5):327-329.
287. Kharfan-Dabaja MA, Mhaskar AR, Djulbegovic B, Cutler C, Mohty M, Kumar A. Efficacy of rituximab in the setting of steroid-refractory chronic graft-versus-host disease: a systematic review and meta-analysis. *Biol Blood Marrow Transplant*. 2009;15(9):1005-1013.
288. Spoerl S, Mathew NR, Bscheider M, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. *Blood*. 2014;123(24):3832-3842.
289. Couriel DR, Saliba R, Escalon MP, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. *Br J Haematol*. 2005;130(3):409-417.
290. Johnston LJ, Brown J, Shizuru JA, et al. Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11(1):47-55.
291. Jurado M, Vallejo C, Perez-Simon JA, et al. Sirolimus as part of immunosuppressive therapy for refractory chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2007;13(6):701-706.
292. Frey Tirri B, Hausermann P, Bertz H, et al. Clinical guidelines for gynecologic care after hematopoietic SCT. Report from the international consensus project on clinical practice in chronic GVHD. *Bone marrow transplantation*. 2015;50(1):3-9.
293. Pidala J, Anasetti C. Glucocorticoid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2010;16(11):1504-1518.
294. Hill L, Alousi A, Kebriaei P, Mehta R, Rezvani K, Shpall E. New and emerging therapies for acute and chronic graft versus host disease. *Ther Adv Hematol*. 2018;9(1):21-46.
295. McCune JS, Bemer MJ. Pharmacokinetics, Pharmacodynamics and Pharmacogenomics of Immunosuppressants in Allogeneic Haematopoietic Cell Transplantation: Part I. *Clin Pharmacokinet*. 2016;55(5):525-550.
296. McQuaker IG, Hunter AE, Pacey S, Haynes AP, Iqbal A, Russell NH. Low-dose filgrastim significantly enhances neutrophil recovery following autologous peripheral-blood stem-cell transplantation in patients with lymphoproliferative disorders: evidence for clinical and economic benefit. *J Clin Oncol*. 1997;15(2):451-457.
297. Dekker A, Bulley S, Beyene J, Dupuis LL, Doyle JJ, Sung L. Meta-analysis of randomized controlled trials of prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor after autologous and allogeneic stem cell transplantation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(33):5207-5215.
298. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Preface. *Biol Blood Marrow Transplant*. 2009(15):1143-1238.
299. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. V.1.2022. 06/02/22. © 2022 National Comprehensive Cancer Network, Inc., All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.

300. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(30):3043-3054.
301. Satlin MJ, Weissman SJ, Carpenter PA, Seo SK, Shelburne SA. American Society of Transplantation and Cellular Therapy Series, 1: Enterobacterales Infection Prevention and Management after Hematopoietic Cell Transplantation. *Transplant Cell Ther*. 2021;27(2):108-114.
302. Dadwal SS, Hohl TM, Fisher CE, et al. American Society of Transplantation and Cellular Therapy Series, 2: Management and Prevention of Aspergillosis in Hematopoietic Cell Transplantation Recipients. *Transplant Cell Ther*. 2021;27(3):201-211.
303. Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3-Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation. *Transplant Cell Ther*. 2021;27(9):707-719.
304. Yong MK, Shigle TL, Kim YJ, Carpenter PA, Chemaly RF, Papanicolaou GA. American Society for Transplantation and Cellular Therapy Series: #4 - Cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation. *Transplant Cell Ther*. 2021.
305. Alonso CD, Maron G, Kamboj M, et al. American Society for Transplantation and Cellular Therapy Series: #5-Management of Clostridioides difficile Infection in Hematopoietic Cell Transplant Recipients. *Transplant Cell Ther*. 2022;28(5):225-232.
306. Bhella S, Majhail NS, Betcher J, et al. Choosing Wisely BMT: American Society for Blood and Marrow Transplantation and Canadian Blood and Marrow Transplant Group's List of 5 Tests and Treatments to Question in Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2018;24(5):909-913.
307. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356(4):335-347.
308. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med*. 2017;377(25):2433-2444.
309. Patterson TF, Thompson GR, 3rd, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1-e60.
310. Schmidt GM, Kovacs A, Zaia JA, et al. Ganciclovir/immunoglobulin combination therapy for the treatment of human cytomegalovirus-associated interstitial pneumonia in bone marrow allograft recipients. *Transplantation*. 1988;46(6):905-907.
311. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood*. 2009;113(23):5711-5719.
312. Alexander BT, Hladnik LM, Augustin KM, et al. Use of cytomegalovirus intravenous immune globulin for the adjunctive treatment of cytomegalovirus in hematopoietic stem cell transplant recipients. *Pharmacotherapy*. 2010;30(6):554-561.
313. Avery RK, Alain S, Alexander BD, et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial. *Clin Infect Dis*. 2021.
314. Robin C, Thiebaut A, Alain S, et al. Letermovir for Secondary Prophylaxis of Cytomegalovirus Infection and Disease after Allogeneic Hematopoietic Cell Transplantation: Results from the French Compassionate Program. *Biol Blood Marrow Transplant*. 2020;26(5):978-984.
315. Beaird OE, Freifeld A, Ison MG, et al. Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative. *Transplant infectious disease : an official journal of the Transplantation Society*. 2016;18(2):210-215.
316. Marcelin JR, Wilson JW, Razonable RR. Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients. *Transplant infectious disease : an official journal of the Transplantation Society*. 2014;16(2):242-250.
317. Foolad F, Aitken SL, Shigle TL, et al. Oral Versus Aerosolized Ribavirin for the Treatment of Respiratory Syncytial Virus Infections in Hematopoietic Cell Transplant Recipients. *Clin Infect Dis*. 2019;68(10):1641-1649.

318. Casper C, Englund J, Boeckh M. How I treat influenza in patients with hematologic malignancies. *Blood*. 2010;115(7):1331-1342.
319. Jodele S, Fukuda T, Mizuno K, et al. Variable Eculizumab Clearance Requires Pharmacodynamic Monitoring to Optimize Therapy for Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2016;22(2):307-315.
320. Laskin BL, Goebel J, Davies SM, Jodele S. Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation-associated thrombotic microangiopathy. *Blood*. 2011;118(6):1452-1462.
321. Kojouri K, George JN. Thrombotic microangiopathy following allogeneic hematopoietic stem cell transplantation. *Curr Opin Oncol*. 2007;19(2):148-154.
322. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood*. 2010;116(20):4060-4069.
323. Kim SS, Patel M, Yum K, Keyzner A. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. *Transfusion*. 2015;55(2):452-458.
324. Panoskaltis-Mortari A, Griesse M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *American journal of respiratory and critical care medicine*. 2011;183(9):1262-1279.
325. Yanik GA, Horowitz MM, Weisdorf DJ, et al. Randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor: enbrel (etanercept) for the treatment of idiopathic pneumonia syndrome after allogeneic stem cell transplantation: blood and marrow transplant clinical trials network protocol. *Biol Blood Marrow Transplant*. 2014;20(6):858-864.
326. Diab M, ZazaDitYafawi J, Soubani AO. Major Pulmonary Complications After Hematopoietic Stem Cell Transplant. *Exp Clin Transplant*. 2016;14(3):259-270.
327. Rathin NK, Tanner AR, Dinh A, et al. Low-, medium- and high-dose steroids with or without aminocaproic acid in adult hematopoietic SCT patients with diffuse alveolar hemorrhage. *Bone marrow transplantation*. 2015;50(3):420-426.
328. Elinoff JM, Bagci U, Moriyama B, et al. Recombinant human factor VIIa for alveolar hemorrhage following allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(7):969-978.
329. Hildebrandt GC, Fazekas T, Lawitschka A, et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. *Bone marrow transplantation*. 2011;46(10):1283-1295.
330. Yadav H, Peters SG, Keogh KA, et al. Azithromycin for the Treatment of Obliterative Bronchiolitis after Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis. *Biol Blood Marrow Transplant*. 2016.
331. Bergeron A, Chevret S, Chagnon K, et al. Budesonide/Formoterol for bronchiolitis obliterans after hematopoietic stem cell transplantation. *American journal of respiratory and critical care medicine*. 2015;191(11):1242-1249.
332. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended Screening and Preventive Practices for Long-Term Survivors after Hematopoietic Cell Transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2012;18( ):348-371.
333. Hingorani S. Renal Complications of Hematopoietic-Cell Transplantation. *N Engl J Med*. 2016;374(23):2256-2267.
334. Savani BN, Griffith ML, Jagasia S, Lee SJ. How I treat late effects in adults after allogeneic stem cell transplantation. *Blood*. 2010;117(11):3002-3009.
335. de Lima M, Porter DL, Battistella M, et al. Proceedings from the National Cancer Institute's Second International Workshop on the Biology, Prevention, and Treatment of Relapse after Hematopoietic Stem Cell Transplantation: Part III. Prevention and Treatment of Relapse after Allogeneic Transplantation. *Biol Blood Marrow Transplant*. 2014;20(1):4-13.
336. Porter DL, Alyea EP, Antin JH, et al. NCI First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: Report from the Committee on Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2010;16(11):1467-1503.

337. Kanate AS, Kumar A, Dreger P, et al. Maintenance Therapies for Hodgkin and Non-Hodgkin Lymphomas After Autologous Transplantation: A Consensus Project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT. *JAMA Oncol.* 2019;5(5):715-722.
338. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;385(9980):1853-1862.
339. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol.* 2012;30(36):4462-4469.
340. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. *N Engl J Med.* 2017;377(13):1250-1260.
341. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. *J Clin Oncol.* 2017;35(29):3279-3289.
342. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366(19):1770-1781.
343. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol.* 2017;4(9):e431-e442.
344. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366(19):1782-1791.
345. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med.* 2014;371(10):895-905.
346. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *N Engl J Med.* 2022.
347. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol.* 2012;30(24):2946-2955.
348. Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood.* 2012;120(8):1589-1596.
349. Mellqvist UH, Gimsing P, Hjertner O, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood.* 2013;121(23):4647-4654.
350. Rashidi A, Walter RB, Tallman MS, Appelbaum FR, DiPersio JF. Maintenance therapy in acute myeloid leukemia: an evidence-based review of randomized trials. *Blood.* 2016;128(6):763-773.
351. Bewersdorf JP, Allen C, Mirza AS, et al. Hypomethylating Agents and FLT3 Inhibitors As Maintenance Treatment for Acute Myeloid Leukemia and Myelodysplastic Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation-A Systematic Review and Meta-Analysis. *Transplant Cell Ther.* 2021;27(12):997 e991-997 e911.
352. Gagelmann N, Wolschke C, Klyuchnikov E, Christopeit M, Ayuk F, Kroger N. TKI Maintenance After Stem-Cell Transplantation for FLT3-ITD Positive Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis. *Front Immunol.* 2021;12:630429.
353. Sockel K, Bornhaeuser M, Mischak-Weissinger E, et al. Lenalidomide maintenance after allogeneic HCT seems to trigger acute graft-versus-host disease in patients with high-risk myelodysplastic syndromes or acute myeloid leukemia and del(5q): results of the LENAMAIN trial. *Haematologica.* 2012;97(9):e34-35.
354. Burchert A, Bug G, Fritz LV, et al. Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3-Internal Tandem Duplication Mutation (SORMAIN). *J Clin Oncol.* 2020;38(26):2993-3002.
355. Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. *Lancet Oncol.* 2020;21(9):1201-1212.

356. Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. *Bone marrow transplantation*. 2021;56(5):1180-1189.
357. Craddock C, Jilani N, Siddique S, et al. Tolerability and Clinical Activity of Post-Transplantation Azacitidine in Patients Allografted for Acute Myeloid Leukemia Treated on the RICAZA Trial. *Biol Blood Marrow Transplant*. 2016;22(2):385-390.
358. de Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. *Cancer*. 2010;116(23):5420-5431.
359. Oran B, de Lima M, Garcia-Manero G, et al. A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients. *Blood Adv*. 2020;4(21):5580-5588.
360. Gao L, Zhang Y, Wang S, et al. Effect of rhG-CSF Combined With Decitabine Prophylaxis on Relapse of Patients With High-Risk MRD-Negative AML After HCT: An Open-Label, Multicenter, Randomized Controlled Trial. *J Clin Oncol*. 2020;38(36):4249-4259.
361. Carpenter PA, Snyder DS, Flowers ME, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood*. 2007;109(7):2791-2793.
362. Kebriaei P, Saliba R, Rondon G, et al. Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact of tyrosine kinase inhibitors on treatment outcomes. *Biol Blood Marrow Transplant*. 2012;18(4):584-592.
363. Pfeifer H, Wassmann B, Bethge W, et al. Randomized comparison of prophylactic and minimal residual disease-triggered imatinib after allogeneic stem cell transplantation for BCR-ABL1-positive acute lymphoblastic leukemia. *Leukemia*. 2013;27(6):1254-1262.
364. Caocci G, Vacca A, Ledda A, et al. Prophylactic and preemptive therapy with dasatinib after hematopoietic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2012;18(4):652-654.
365. Teng CL, Yu JT, Chen HC, Hwang WL. Maintenance therapy with dasatinib after allogeneic hematopoietic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia. *Annals of hematology*. 2013;92(8):1137-1139.
366. Shimoni A, Volchek Y, Koren-Michowitz M, et al. Phase 1/2 study of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 2015;121(6):863-871.
367. DeFilipp Z, Langston AA, Chen Z, et al. Does Post-Transplant Maintenance Therapy With Tyrosine Kinase Inhibitors Improve Outcomes of Patients With High-Risk Philadelphia Chromosome-Positive Leukemia? *Clin Lymphoma Myeloma Leuk*. 2016;16(8):466-471.e461.
368. Brissot E, Labopin M, Beckers MM, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Haematologica*. 2015;100(3):392-399.
369. Carpenter PA, Johnston L, Fernandez HF, et al. Posttransplant feasibility study of nilotinib prophylaxis for high-risk Philadelphia chromosome positive leukemia. *Blood*. 2017;130(9):1170-1172.
370. Chen H, Liu KY, Xu LP, et al. Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *J Hematol Oncol*. 2012;5:29.
371. Ravandi F, Othus M, O'Brien SM, et al. US Intergroup Study of Chemotherapy Plus Dasatinib and Allogeneic Stem Cell Transplant in Philadelphia Chromosome Positive ALL. *Blood Adv*. 2016;1(3):250-259.
372. Bar M, Radich J. Maintenance therapy with tyrosine kinase inhibitors after transplant in patients with chronic myeloid leukemia. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2013;11(3):308-315.
373. Barrett AJ, Ito S. The role of stem cell transplantation for chronic myelogenous leukemia in the 21st century. *Blood*. 2015;125(21):3230-3235.
374. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA : the journal of the American Medical Association*. 2014;311(5):507-520.

375. DeFilipp Z, Duarte RF, Snowden JA, et al. Metabolic Syndrome and Cardiovascular Disease after Hematopoietic Cell Transplantation: Screening and Preventive Practice Recommendations from the CIBMTR and EBMT. *Biol Blood Marrow Transplant*. 2016;22(8):1493-1503.
376. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1-45.
377. Marini BL, Choi SW, Byersdorfer CA, Cronin S, Frame DG. Treatment of dyslipidemia in allogeneic hematopoietic stem cell transplant patients. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2015;21(5):809-820.
378. Bar M, Ott SM, Lewiecki EM, et al. Bone Health Management After Hematopoietic Cell Transplantation: An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2020;26(10):1784-1802.
379. Hautmann AH, Elad S, Lawitschka A, et al. Metabolic bone diseases in patients after allogeneic hematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease. *Transpl Int*. 2011;24(9):867-879.
380. McClune BL, Polgreen LE, Burmeister LA, et al. Screening, prevention and management of osteoporosis and bone loss in adult and pediatric hematopoietic cell transplant recipients. *Bone marrow transplantation*. 2011;46(1):1-9.
381. McClune B, Majhail NS, Flowers ME. Bone loss and avascular necrosis of bone after hematopoietic cell transplantation. *Seminars in hematology*. 2012;49(1):59-65.
382. Inamoto Y, Shah NN, Savani BN, et al. Secondary solid cancer screening following hematopoietic cell transplantation. *Bone marrow transplantation*. 2015;50(8):1013-1023.
383. Ljungman P, Cordonnier C, Einsele H, et al. Vaccination of hematopoietic cell transplant recipients. *Bone marrow transplantation*. 2009;44(8):521-526.
384. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44-100.
385. Carpenter PA, Englund JA. How I vaccinate blood and marrow transplant recipients. *Blood*. 2016;127(23):2824-2832.
386. Ali H, Ngo D, Aribi A, et al. Safety and Tolerability of SARS-CoV2 Emergency-Use Authorized Vaccines for Allogeneic Hematopoietic Stem Cell Transplant Recipients. *Transplant Cell Ther*. 2021;27(11):938 e931-938 e936.
387. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association*. 2019;322(2):123-133.
388. Baumrin E, Izaguirre NE, Bausk B, et al. Safety and reactogenicity of the recombinant zoster vaccine after allogeneic hematopoietic cell transplantation. *Blood Adv*. 2021;5(6):1585-1593.

## **HEAD, NECK, THYROID AND ADULT CENTRAL NERVOUS SYSTEM (CNS) MALIGNANCIES**

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### **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, management, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with head, neck, adult central nervous system (CNS), or thyroid cancers.
2. Select relevant information and guidance for the public regarding head and neck cancer-related issues (e.g., risk factors, prevention, screening).
3. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with the treatment of cancers including cancer cachexia, mucositis, and xerostomia.



## HEAD AND NECK TUMORS

### **Patient Case #1 (ARS Question #1):**

CS is a 60-year-old gentleman with a new diagnosis of locally advanced squamous cell carcinoma of the oral cavity. He has a 20-pack year smoking history, and only has occasional alcohol use. Staging scans revealed no distant disease, but multiple positive lymph nodes so he underwent resection of the tumor. Pathology after surgery showed positive margins. **Which of the following is most appropriate first line treatment for this patient at this time?**

- A) Pembrolizumab/fluorouracil/cisplatin
- B) Concurrent radiation and weekly cetuximab
- C) Concurrent radiation and every-3-week cisplatin
- D) Concurrent radiation with weekly carboplatin

### **I. Risk Factors and Prevention<sup>1</sup>**

- A. Screening for head and neck cancers by health-care professionals is feasible given accessible location.
  - 1. Screening includes oral inspections for premalignant lesions (leukoplakia and erythroblastic lesions).
  - 2. Although extensively studied, screening has not been proven to decrease mortality associated with head and neck cancer.
    - a. Reasons include a high noncompliance rate and high false-positive rate.
  - 3. As a result, there is no consensus for screening. The U.S. Preventive Services Task Force concludes that the evidence is insufficient to recommend for or against routine screening while the American Cancer Society are in favor of routine screening, though acknowledge that there is no official routine screening test or plan.<sup>2,3</sup>
  - 4. Primary chemoprevention: No chemopreventive agents have been found to decrease the incidence of squamous cell carcinoma of the head and neck (HNSCC) in adequately designed clinical trials
  - 5. Secondary chemoprevention
    - a. Isotretinoin (50–100 mg/m<sup>2</sup> PO daily for 12 months) was compared to placebo for the prevention of second primary tumors.<sup>4</sup>
      - 1) At 32 months follow-up, 4% of patients receiving isotretinoin and 24% of patients receiving placebo developed second primary tumors.
      - 2) Toxicity, however, was significant and prohibits its use for long-term chemoprevention.
      - 3) Randomized trials using lower dose isotretinoin have not proven to be beneficial.<sup>5</sup>
    - b. Alpha-tocopherol supplementation was associated with higher rates of tumor recurrence and second primary cancers.<sup>6</sup>

B. Tobacco and alcohol abuse account for 75% of head and neck cancer cases

1. Tobacco (cigarettes, pipe, snuff, chewing): amount of usage directly correlates with severity of disease
2. Alcohol (alone, and is synergistic with tobacco): The combined effect of heavy alcohol and tobacco use increases risk 200-fold over non-users.
3. Cessation of smoking and alcohol use has been associated with a decreased risk of second primary malignancies including secondary H&N, lung, and esophagus.
4. Smoking cessation:
  - a. Reduces rates of oral cancer among former smokers compared with current smokers were seen within 4 years after smoking cessation (35% reduction). The risk of oral cancer approached that of never-smokers after  $\geq 20$  years of cessation (OR 0.19, 95% CI, 0.15-0.24).<sup>7</sup>
  - b. Following HNSCC diagnosis, risk of progression or death increased by 2% per year of smoking (HR 1.02; 95% CI, 1.01 to 1.03;  $P$ .001). Risk of death more than doubled for those who smoked during radiation (HR, 2.19; 95% CI, 1.46 to 3.28).<sup>8</sup>

C. Viral Causes

1. Human papillomavirus (HPV) is associated with oropharynx tumors<sup>9</sup>
  - a. Case control studies confirm the relationship between HPV and oropharyngeal tumors independent of tobacco and alcohol exposure but correlated with p16 tumor status
  - b. The use of **immunohistochemistry to detect p16** can be used as surrogate for HPV tumor infection and **is now required at diagnosis for oropharyngeal cancers**.
    - 1) In tumors infected by HPV, the E6 and E7 oncoprotein causes degradation of the retinoblastoma (RB1) tumor-suppressor protein. Loss of RB1 results in overexpression of p16 and other cell senescence pathways, however other methods of RB1 inactivation (including mutations) can also result in elevated p16 levels.
    - 2) The true-positive rate of the p16 detection predicting HPV infection is associated with pretest probability factors associated with HPV including age and smoking status<sup>9</sup>.
  - c. Incidence of HPV-associated cases are increasing relative to tobacco- and alcohol-related cases that are decreasing in incidence
  - d. HPV-associated disease is associated with improved survival (OS/PFS) as compared with non-HPV cases<sup>10</sup>. The staging for oropharyngeal cancers with the same initial tumor size and nodal status but disparate HPV status is now different taking into consideration the outcomes.
  - e. Unknown what impact HPV vaccination will have on incidence in the future
    - 1) HPV type 16 is commonly implicated and covered by all commercially available HPV vaccines. Less common subtypes associated with incidence include HPV type 18, 31 and 33, also included in the 9-valent (Gardasil®9) vaccine.

- f. HPV vaccination is associated with reduced oral HPV prevalence based on analysis from the National Health and Nutrition Examination Survey (2011-2014), however controlled trials evaluating the effectiveness of the HPV vaccine in specific prevention of HNSCC have not been completed and this practice cannot be routinely recommended at this time.
- 2. Epstein Barr virus (EBV) is associated with nasopharyngeal carcinoma
  - a. EBV Screening<sup>11</sup>
    - a. Prospective trial of 20,174 participants in China underwent EBV DNA assessment from plasma. Those with a positive result were retested approximately 4 weeks later.
    - b. Of the 309 participants with persistently positive results, 34 were ultimately found to have nasopharyngeal carcinoma. These patients were more likely to have stage I or II disease and had improved 3-year overall survival (97% vs. 70%), compared with historical controls.
    - c. The sensitivity was 97.1% and the specificity was 98.6%
    - d. This population was at high risk for nasopharyngeal carcinoma given the location in an endemic area. The value of this screening universally is unknown and not currently recommended as routine care.
- D. Radiation exposure
- E. Occupational (formaldehyde, asbestos, metal processing, leather and wood working).

## II. Treatment Options<sup>1</sup>

### A. General

- a. The primary goal is cure with a secondary goal being the preservation of organ form and function as well as prevention of second primaries.
- b. Recommended treatment options are similar for most types of head and neck cancer, but may have variations based on anatomic tumor location, nodal status, stage, and other factors. The National Comprehensive Cancer Network (NCCN®) panel advocates for management at a high-volume treatment center if possible.

### B. Surgery<sup>1</sup>

- a. Treatment of choice when it can be curative, except in cases such as laryngeal cancer where chemotherapy combined with radiation gives equivalent results with preservation of the organ resulting in normal speech or in some localized oropharyngeal tumors.
- b. Resection may be done simultaneously with free flap and other reconstructive efforts, skin grafting, or prosthetic interventions to decrease cumulative time in the operating room and improve cosmetic results. Tracheostomy is often performed as part of surgery as a means of avoiding airway compromise or difficulties intubating post-operatively.
- c. Prophylactic feeding tube placement may be considered at the time of surgery. This and other nutritional considerations are discussed in symptom management section.
- d. When considering surgery, two terms are commonly used:
  - a. Unresectable: refers to a tumor

- b. Inoperable: refers to a patient (and their comorbid conditions, etc.)
  - e. Type of surgery and whether neck dissection (lymphadenectomy) is included (and on what side and at which levels) depends on the nodal status, tumor anatomy, and risk of developing metastatic disease. Neck dissections are now referred to as comprehensive vs selective rather than radical vs modified radical.
- C. Radiation<sup>1</sup>
  - a. Nearly all patients with advanced-stage disease require adjuvant radiotherapy. Indications for postoperative radiotherapy relating to the primary tumor include: pT3 or pT4 primary tumor, extranodal extension, multiple positive nodes, histologically positive margins or close margins, and perineural or perivascular infiltration by tumor.
  - b. Acute complications include mucositis, dysphagia (potentially leading to enteral feeding tube placement), dermatitis, xerostomia, and weight loss. Long-term sequelae include taste loss, permanent xerostomia, hypothyroidism, neck fibrosis, chronic feeding tube dependency, risk to the dentition and mandible (including osteoradionecrosis), and secondary malignancies.
    - a. Severity of acute complications is related to daily fraction size
    - b. Long-term sequelae are determined by the total dose delivered.
    - c. It is recommended to commence radiation therapy within 6 weeks of surgery if done in an adjuvant manner.
  - c. Intensity, type, schedule, and duration of radiation is dictated by stage, histology, and surgical pathology
- D. Systemic Therapy<sup>1</sup>
  - 1. Chemotherapy
    - a. Utilized in the neoadjuvant (induction) setting, adjuvant setting, concomitantly with radiation therapy, and in the metastatic or recurrent setting.
    - b. Combined chemoradiotherapy is more effective than radiation alone in the post-operative and inoperable settings.
    - c. Commonly used cytotoxic chemotherapy agents include cisplatin, carboplatin, fluorouracil, paclitaxel, docetaxel, capecitabine, and etoposide. See NCCN Guidelines for comprehensive list of all single agents utilized.
  - 2. Targeted Agents
    - a. EGFR inhibitors: cetuximab, afatinib
      - a. Cetuximab has been evaluated in combination with radiation therapy and chemotherapy in first- line as well as single agent in refractory settings
      - b. Afatinib has been evaluated for non-nasopharyngeal cancer following progression on or after a platinum-based regimen

- b. Salivary ductal carcinomas can overexpress androgen receptors (AR), HER2, and NTRK. Antiandrogen, HER2-directed, and NTRK inhibitors are recommended for corresponding overexpressing tumors.
    - a. Other targeted agents for salivary gland tumors include lenvatinib, axitinib, and sorafenib (NCCN Category 2B recommendations)
- 3. Immunotherapy
  - a. Pembrolizumab has been studied and approved for 1<sup>st</sup>-line metastatic or unresectable alone or in combination with chemotherapy
  - b. Pembrolizumab and nivolumab have been studied in recurrent or progressive disease on or after platinum-based therapy

### III. Treatment by Stage/Type

#### A. Early-Stage Disease (Stage I or II, T1 or T2)<sup>1</sup>

- a. Treatment is administered with a curative intent and generally consists of surgery or radiation therapy. Between 60-90% of patients can achieve a cure, with a 5-year relative survival of 75-93%.
- b. For select cases, (i.e. based on anatomic tumor location in the oral cavity, oropharynx, larynx, hypopharynx) adjuvant chemotherapy and radiation is recommended if adverse pathological findings of extracapsular nodal extension and/or positive mucosal margins are present
- c. This is based on the pooled analysis of the RTOG 9501 and EORTC 22931 trials which randomized high-risk patients to radiation alone or radiation with cisplatin 100 mg/m<sup>2</sup> IV q3 weeks for 3 cycles<sup>12</sup>
  - a. This analysis demonstrated the significance of these two adverse features in predicting outcome and benefits of post-operative chemoradiation
  - b. These trials found statistically improved locoregional control and disease-free survival (DFS) at 3- and 5-years for high-risk patients that received concurrent chemotherapy and radiation
    - 1) Locoregional failure rate (chemoradiotherapy vs RT alone): 5-year: 18% vs 31% (p=0.007); 3-year: 22% vs 33% (p=0.01)
    - 2) Disease-free survival (chemoradiotherapy vs RT alone): 5-year: 47% vs 36% (p=0.04); 3-year: 47% vs 36% (p=0.04)
  - c. Additionally, the EORTC 22931 trial also showed a statistically significant improvement in 5-year OS for these patients (53% vs 40%, p=0.02)<sup>13</sup>

#### B. Locally Advanced Disease (T3-T4, N1-N3)<sup>1</sup>

- a. This is the most common initial presentation diagnosed in approximately 60% of patients

- b. Long-term remission occurs in 30% of patients with the most common cause of failure being local or regional tumor recurrence. The 5-year relative survival is 38-48%.
- c. Treatment consists of surgery followed by radiation or concurrent radiation and chemotherapy for patients with unresectable disease (or for patients who decline surgical intervention). Chemotherapy may be given as induction therapy or concomitantly with radiation therapy.
  - a. Induction therapy
    - 1) The theoretical benefits of **induction chemotherapy** are the possibility of tumor shrinkage, improved organ preservation and the prevention of distant metastases
    - 2) Several trials demonstrated the benefit of the addition of a taxane to standard induction therapy with cisplatin and fluorouracil. The addition of docetaxel to cisplatin and fluorouracil (TPF) has shown improved overall survival compared to cisplatin and fluorouracil without docetaxel when either regimen is followed by chemoradiation.<sup>14</sup>
      - i. Estimated 3-year OS for the triplet was 62% vs 48% in the cisplatin and fluorouracil arm
      - ii. Although these trials demonstrated the superiority of a three- drug combination over the two- drug combination, they were not designed to compare induction chemotherapy vs concurrent chemoradiation
      - iii. These trials also demonstrated increased toxicities in the three- drug regimens including grade 3-4 neutropenia (83% vs 56%), febrile neutropenia (12% vs 7%), and neutropenic infection (12% vs 8%)
      - iv. Long-term follow-up of these trials confirm the overall survival advantage of the inclusion of docetaxel with an estimated 5-year survival of 52% in patients treated with the three-drug regimen vs 42% in those only treated with cisplatin/fluorouracil<sup>15</sup>
    - 3) The role of induction therapy is still one of debate and categories of evidence and consensus vary depending on site NCCN Guidelines®.<sup>1</sup>
      - i. NCCN Guidelines® Category 3 recommendation for locoregionally advanced p16 negative and p16 positive oropharyngeal cancer.
      - ii. NCCN Guidelines® Category 2A recommendation as part of a larynx preservation strategy for selected patients with hypopharyngeal and laryngeal cancers with < T4a disease in whom total laryngectomy is indicated.
      - iii. Both the PARADIGM<sup>16</sup> and DeCIDE<sup>17</sup> trials assessed the role of TPF induction followed by chemoradiotherapy compared with chemoradiotherapy alone in non-nasopharyngeal tumors. Different comparative arms were used in the trials as was the chemoradiotherapy treatment, but neither study demonstrated an improvement in overall survival.

- (a) Toxicity rates were also higher in each induction therapy arm. Of note, both trials were also halted early due to poor accrual.
- iv. If induction therapy is chosen, the recommended regimen is TPF (NCCN Category 1) followed by concurrent chemoradiation with weekly carboplatin (weekly cisplatin is category 2B) as the preferred regimens. Weekly cetuximab is also an option, though not preferred.
- v. For **nasopharyngeal tumors**, induction therapy with gemcitabine + cisplatin or TPF is an NCCN Guidelines® Category 1 recommendation for EBV-positive disease (category 2A for EBV-negative)<sup>1</sup>
  - (a) Gemcitabine + Cisplatin induction therapy<sup>18</sup>
    - i) Phase III multicenter, randomized, controlled trial. Primary endpoint was recurrence-free survival.
    - ii) 480 patients with locally advanced nasopharyngeal HNSCC were randomized 1:1 to either gemcitabine + cisplatin (1000 mg/m<sup>2</sup> days 1 and 8 plus 80 mg/m<sup>2</sup> day 1) every 3 weeks for 3 cycles followed by chemoradiotherapy (cisplatin 100 mg/m<sup>2</sup> with standard radiotherapy) or chemoradiotherapy alone.
    - iii) 3 year recurrence-free survival was 85.3% in the induction group compared to 76.5% in the control group (HR 0.51; p=0.001).
    - iv) Overall survival at 3 years was 94.6% in the induction group and 90.3% in the control group (HR 0.43; 95% CI 0.24-0.77).
    - v) 96.7% of patient completed all 3 cycles of induction therapy. Acute effects of cisplatin were greater with higher cumulative dose in the induction group, however, the trial found similar rates of severe late complications in both groups (except for peripheral neuropathy) suggesting that induction therapy had similar long-term safety regardless of increased cumulative cisplatin dose.
  - b. Concomitant radiation and chemotherapy<sup>1</sup>
    - 1) Goal is to increase the cytotoxicity of radiation therapy since the majority of patients fail locally or regionally. Therefore, chemotherapy agents with radiosensitizing ability are preferred.
    - 2) **Cisplatin (100 mg/m<sup>2</sup> IV every 3 weeks for 2-3 doses) – NCCN Category 1 Recommendation.**
      - i. Phase III trial of 300 patients with locally advanced HNSCC was conducted to assess the non-inferiority of cisplatin 100 mg/m<sup>2</sup> IV every 3 weeks compared with cisplatin 30 mg/m<sup>2</sup> IV weekly, both given with curative intent radiation.<sup>19</sup>

- (a) 93% of patients received chemoradiation in the adjuvant setting.
  - (b) After a median follow up of 22 months, the 2- year locoregional control rate was 58.5% in the weekly group and 73.1% in the q 3 weekly group (HR 1.76; 95% CI 1.11-2.79, p=0.014).
  - (c) Median OS was 39.5 months in the weekly group and not reached in the q 3 weekly group (HR 1.14; 95% CI 0.79-1.65, p=0.48).
  - (d) Grade 3 or higher acute toxicities were higher in the q 3 weekly arm (84.6%) compared with weekly arm (71.6%), p=0.006.
- ii. A meta-analysis completed by Mohamed and colleagues compared cisplatin 100 mg/m<sup>2</sup> q 3 weeks vs 40 mg/m<sup>2</sup> weekly<sup>20</sup>

- (a) 39 prospective studies including 3668 patients qualified for inclusion

	<b>Cisplatin 100 mg/m<sup>2</sup> every 3 weeks</b>	<b>Cisplatin 40 mg/m<sup>2</sup> weekly</b>	<b>P value</b>
<b>2- year locoregional control</b>	61%	58%	0.7
<b>2- year PFS</b>	62%	69%	0.9
<b>2- year OS</b>	67%	74%	0.67
<b>5- year OS</b>	51%	48%	0.6

- (b) Adverse events

	<b>Cisplatin 100 mg/m<sup>2</sup> every 3 weeks</b>	<b>Cisplatin 40 mg/m<sup>2</sup> weekly</b>	<b>P value</b>
<b>Grade 3-5 toxicities (all)</b>	40%	36%	0.37

- iii. Although the results of the meta-analysis show lack of inferiority of the weekly 40 mg/m<sup>2</sup> regimen, rates of toxicities are also similar. Every 3 week cisplatin remains the NCCN Category 1 recommendation, whereas 40 mg/m<sup>2</sup> weekly remains an NCCN Category 2B recommendation, even though there is considerable controversy in practice. There is documented OS benefit when cumulative cisplatin doses reach at least 200 mg/m<sup>2</sup> during radiation.<sup>1,19</sup>

### 3) Carboplatin + Infusional Fluorouracil – NCCN Category 1 Recommendation<sup>1</sup>



i. GORTEC 99-02 – open label phase III trial<sup>21</sup>

(a) 840 patients with locally advanced, stage III, and stage IV (non-metastatic) HNSCC. Patients randomized 1:1:1 to:

- i) Conventional chemoradiotherapy (70 Gy in 7 weeks + 4 days of carboplatin 70 mg/m<sup>2</sup> + fluorouracil 600 mg/m<sup>2</sup>/day days 1-4, 22-25, and 43-46).
- ii) Accelerated radiotherapy-chemotherapy (70 Gy in 6 weeks + 5 days of carboplatin 70 mg/m<sup>2</sup> + fluorouracil 600 mg/m<sup>2</sup>/day days 1-5, and 29-33).
- iii) Very accelerated radiotherapy alone (64.8 Gy in 3.5 weeks).

(b) 3-year PFS: 37.6% in conventional chemotherapy, 34.1% in accelerated, and 32.2% in very accelerated.

(c) Increased incidence of grade 3-4 mucosal toxicity in the very accelerated group (84%), compared to the accelerated group (76%) and conventional group (69%).

(d) This trial concluded that chemotherapy in conjunction with radiation should remain a preferred regimen, and that an accelerated regimen is likely not beneficial.

4) Alternative regimens include carboplatin + paclitaxel and weekly cisplatin.

5) In general, radiation toxicities including mucositis and dermatitis are increased when given concurrently with chemotherapy.

6) An absolute survival advantage of 4% at 2 and 5 years in favor of chemotherapy has been reported using based on a meta-analysis of 63 trials including more than 10,700 patients.<sup>22</sup> Patients with good performance status are the optimal candidates for combined chemoradiotherapy.

d. Cetuximab with radiation

a. Cetuximab + radiation vs radiation alone<sup>23,24</sup>

- 1) 400 mg/m<sup>2</sup> 1 week prior to radiation, then 250 mg/m<sup>2</sup> weekly during radiation
- 2) Improvement in progression-free (17.1 vs. 12.4 months, p=0.006) and overall survival (49 vs. 29 months, p=0.03) compared to radiation alone.<sup>23</sup>
- 3) 5-year OS was 45.6% in the cetuximab plus radiation arm and 36.4% in the radiotherapy alone arm (p=0.018).<sup>24</sup>

b. Cetuximab + radiation vs cisplatin + radiation

- 1) Original thought was that those who could not tolerate cisplatin or a poor performance status should receive cetuximab, or that HPV(+) tumors could have less-intense treatment.
- 2) De-ESCALATE HPV<sup>25</sup>
  - i. HPV(+) patients randomized to weekly cetuximab/RT or cisplatin/RT
  - ii. Decreased OS in cetuximab/RT (89% vs 98 % at 2 years, HR 5.0, 95% CI 1.7-14.7). Increased recurrence in cetuximab/RT (16 vs 6% at 2 years, HR 3.4, 95% CI 1.6-7.2). Overall similar mean numbers of grade 3-5 toxicity events in both arms cetuximab/RT (4.8 vs 4.8; p=0.98).
  - iii. In HPV(+) tumors, cetuximab/RT showed no benefit in toxicity reduction, and had worse OS compared to cisplatin/RT.
- 3) RTOG 1016<sup>26</sup>
  - i. Noninferiority phase II trial. Every 3 week cisplatin/RT vs cetuximab/RT in HPV(+) HNSCC
  - ii. Median follow up of 4.5 years. Decreased OS in cetuximab/RT arm (78 vs 85%, HR 1.45, one-sided 95% CI 1.94) along with inferior PFS (67 vs 78%, HR 1.72, 95% CI 1.29-2.29).
  - iii. Cetuximab/RT showed inferior OS and PFS compared to cisplatin/RT. Cisplatin/RT should remain standard of care.
- 4) ARTSCAN III<sup>27</sup>
  - i. Open label, randomized, controlled, phase III study. Cetuximab 400 mg/m<sup>2</sup> once, then 250 mg/m<sup>2</sup> weekly during radiation, or cisplatin 40 mg/m<sup>2</sup> weekly during radiation in locally advanced HNSCC.
    - (a) Patients with oropharyngeal HNSCC could be HPV(-) or HPV(+). The majority (88% in the RT+cisplatin and 90% in RT+cetuximab) were HPV(+)
  - ii. Trial was prematurely closed at and unplanned interim analysis after a clear increase in locoregional events in the RT+cetuximab group compared to the RT+cisplatin group.
    - (a) 3- year OS: 78% vs 88% (HR 1.63, 95% CI, 0.93-2.86; p=0.86)
    - (b) Cumulative incidence of locoregional failure at 3 years: 23% vs 9% (p=0.0036)

- (c) Subgroup analysis of HPV(-) and non-oro-pharyngeal tumors was too small to make a definite comment regarding cetuximab/RT vs cisplatin/RT
- 5) Although there are no large trials comparing cetuximab/RT with cisplatin/RT in HPV(-) HNSCC, cetuximab/RT should not be used in patients with poor performance status over cisplatin.
- c. Acneiform rash and infusion reactions were the most common adverse reactions seen with cetuximab. Patients with rash of at least grade 2 severity had superior OS (HR 0.49,  $p=0.002$ ) compared to those with grade 1 or less rash.<sup>24</sup>
- d. Cetuximab with concurrent radiation is a category 2B option for oropharyngeal, hypopharyngeal or laryngeal cancers, and is not recommended for nasopharyngeal cancers. If patients are deemed cisplatin ineligible and have high-risk features, NCCN Guidelines recommends cetuximab in combination with docetaxel (NCCN Category 2B Recommendation).<sup>1</sup>
- e. Immunotherapy in locally advanced HNSCC
  - a. Immunotherapy has not yet achieved approval for **adjuvant** treatment in locally advanced HNSCC and should not be used outside of a clinical trial setting.
  - b. KEYNOTE-412 is a phase III trial investigating pembrolizumab vs placebo concurrently with chemoradiotherapy followed by maintenance pembrolizumab vs. placebo that did not meet the primary endpoint of event-free survival.<sup>28</sup>
  - c. JAVELIN Head and Neck 100 Trial<sup>29</sup>
    - 1) 697 patients with previously untreated locally advanced HNSCC. Primary objective was progression-free survival
    - 2) Randomized to avelumab 10 mg/kg every 2 weeks plus chemoradiotherapy (100 mg/m<sup>2</sup> cisplatin every 3 weeks plus standard radiotherapy) or placebo plus chemoradiotherapy
    - 3) Median PFS: NR (95% CI 16.9 mo - not estimable) in avelumab group vs NR (95% CI 23 mo – not estimable) favoring the placebo group (HR 1.21, one-sided  $p=0.92$ ).
    - 4) The primary objective of prolonged progression- free survival in the avelumab group was not met, and avelumab is not recommended upfront in locally advanced HNSCC based on these data.

**Patient Case #1 (continued) (ARS question #2):**

Since CS had positive margins after surgery, re-resection is an option, however, pembrolizumab/fluorouracil/cisplatin is not a recommended induction regimen. There are several different regimens for chemoradiation, but cisplatin 100 mg/m<sup>2</sup> every 3 weeks (answer c) for 2-3 doses is the NCCN Guidelines preferred chemotherapy combination with radiation. Weekly cetuximab is a category 2B recommendation. Weekly carboplatin is not a preferred therapy option for primary systemic therapy.

CS comes in for surveillance scans 6 months later and is found to have a new right lung lesion. Biopsy of the lesion proves recurrent HNSCC, and genetic testing reveals PD-L1 CPS of 10. **What is the most appropriate therapy for CS at this time?**

- A) Pembrolizumab/Fluorouracil/Docetaxel
- B) Pembrolizumab/Fluorouracil/Carboplatin
- C) Cisplatin/Paclitaxel
- D) Nivolumab/Fluorouracil/Cisplatin

C. Very advanced, Recurrent, or Metastatic Disease<sup>1</sup>

1. Treatment goal is usually palliation and may involve surgery, radiation or chemotherapy.

- a. No randomized trial has shown combination chemotherapy to be superior to single-agent therapy in patients with metastatic squamous cell carcinoma of the head and neck for overall survival.
- b. Choice of therapy should be based on patient characteristics, especially performance status (PS).
  - 1) PS ≥ 2 should strongly consider single-agent therapy or best supportive care
- c. Most deaths from head and neck cancer are from uncontrolled locoregional disease.

b. First-Line Regimens

a. **Pembrolizumab plus fluorouracil and a platinum (NCCN Guidelines® Category 1, preferred regimen for non-nasopharyngeal)<sup>1</sup>**

1) KEYNOTE-048 Trial<sup>30</sup>: patients were randomized to 3 treatment arms:

- i. Pembrolizumab 200 mg + Cisplatin 100 mg/m<sup>2</sup> or Carboplatin AUC 5 day 1 + Fluorouracil 1,000 mg/m<sup>2</sup>/day x 4 days every 3 weeks for 6 cycles
- ii. Cisplatin 100 mg/m<sup>2</sup> or Carboplatin AUC 5 day 1 + Fluorouracil 1,000 mg/m<sup>2</sup>/day x 4 days + cetuximab 400 mg/m<sup>2</sup> on week 1 then 250 mg/m<sup>2</sup> weekly every 3 weeks for 6 cycles (EXTREME arm)
- iii. Single-agent pembrolizumab 200 mg every 3 weeks

- 2) Pembrolizumab arms were compared to the control arm of cetuximab + chemotherapy (not pembrolizumab +/- chemotherapy)
- 3) Pembrolizumab + chemotherapy had significantly prolonged OS compared to cetuximab + chemotherapy in the CPS  $\geq 20$ , CPS  $\geq 1$ , and total populations.
- 4) Progression-free survival was not improved in the pembrolizumab nor the pembrolizumab + chemotherapy groups versus cetuximab + chemotherapy
- 5) Due to increased OS benefit despite lack of progression-free survival benefit, both **pembrolizumab regimens were added as first- line therapy options for patients with non-nasopharyngeal head and neck cancer.**
  - i. Pembrolizumab + fluorouracil + platinum does not require PD-L1 status

**Outcomes of KEYNOTE-048 trial – Pembrolizumab + Chemo versus Cetuximab + Chemo<sup>30</sup>**

	<b>Pembrolizumab Cisplatin/carboplatin 5FU</b>	<b>Cetuximab Cisplatin/carboplatin 5FU</b>	<b>HR; 95% CI</b>	<b>P value</b>
<b>Median OS, CPS <math>\geq 20</math></b>	14.7 months	11 months	0.60; 0.45-0.82	0.0004
<b>Median OS, CPS <math>\geq 1</math></b>	13.6 months	10.4 months	0.65; 0.53-0.80	<0.0001
<b>All - Median OS</b>	13.0 months	10.7 months	0.77; 0.63-0.93	0.0034
<b>Median PFS, CPS <math>\geq 20</math></b>	5.8 months	5.2 months	NR	NR
<b>Median PFS, CPS <math>\geq 1</math></b>	5.0 months	5.0 months	NR	NR
<b>All - Median PFS</b>	4.9 months	5.1 months	NR	NR

OS = overall survival, CPS = PD-L1 combined positive score, PFS = progression-free survival, NR = not reported

- b. **Pembrolizumab alone if PD-L1 CPS  $\geq 1$  (NCCN Guidelines® category 1 preferred if CPS  $\geq 20$ )**
  - 1) Pembrolizumab alone had significantly prolonged OS compared to cetuximab + chemotherapy in the PD-L1 combined positive score (CPS)  $\geq 20$  and CPS  $\geq 1$  groups but had non-inferior OS in the total population.

### Outcomes of KEYNOTE-048 trial – Pembrolizumab alone versus Cetuximab + Chemo<sup>30,31</sup>

	Pembrolizumab	Cetuximab Cisplatin/carboplatin 5FU	HR; 95% CI	P value
Median OS, CPS ≥ 20	14.9 months	10.7 months	0.61; 0.45-0.83	0.0007
Median OS, CPS ≥ 1	12.3 months	10.3 months	0.78; 0.64-0.96	0.0086
All - Median OS	11.5 months	10.7 months	0.83; 0.70-0.99	0.0199

OS = overall survival, CPS = PD-L1 combined positive score

#### c. Cetuximab plus fluorouracil and a platinum (NCCN Guidelines® Category 1, regimen for non-nasopharyngeal)<sup>1,32</sup>

- 1) The combination of cetuximab plus combined chemotherapy (platinum/fluorouracil) demonstrated median survival benefits over combined chemotherapy alone in 442 patients with previously untreated recurrent or metastatic (non-nasopharyngeal) head and neck cancer (though patients may have had prior therapy for localized disease).
- 2) The most common adverse effect was myelosuppression, however sepsis occurred in 9 patients receiving the cetuximab combination therapy compared to 1 patient in the chemotherapy alone arm.<sup>32</sup>
- 3) Although an NCCN category 1 recommendation, this regimen is not a preferred first line option after publication of the positive results of KEYNOTE-048.

### Outcomes of EXTREME trial<sup>32</sup>

	Cisplatin 100 mg/m <sup>2</sup> or Carboplatin AUC 5 day 1 + Fluorouracil 1,000 mg/m <sup>2</sup> /day x 4 days + cetuximab 400 mg/m <sup>2</sup> on week 1 then 250 mg/m <sup>2</sup>	Cisplatin 100 mg/m <sup>2</sup> or Carboplatin AUC 5 day 1 + Fluorouracil 1,000 mg/m <sup>2</sup> /day x 4 days	HR; 95% CI	P value
Median OS	10.1 months	7.4 months	0.80; 0.64-0.99	0.04
Median PFS	5.6 months	3.3 months	0.54; 0.43-0.67	<0.001
Disease control rate	81%	60%	2.88; 1.87-4.44	<0.001

OS = overall survival; PFS = progression-free survival

#### d. Gemcitabine and cisplatin (NCCN Guidelines® category 1, preferred regimen for nasopharyngeal)<sup>1,18</sup>

- 1) 362 Chinese patients with metastatic or recurrent nasopharyngeal carcinoma were randomized to either gemcitabine or fluorouracil, both given in combination with cisplatin
- 2) Median PFS was higher in the gemcitabine group compared with the fluorouracil group (7 months vs. 5.6 months, HR 0.55, 95% confidence interval 0.44-0.68;  $p < 0.0001$ ).
- 3) Discontinuation due to adverse effects was higher in the fluorouracil group (3% v 8%).

c. Second-Line Preferred Regimens

a. **Nivolumab (NCCN Guidelines® category 1, preferred regimen following progression on or after a platinum therapy, if not previously used; non-nasopharyngeal)<sup>1</sup>**

- i. The CheckMate-141 trial<sup>33</sup> was a phase 3, randomized, open-label trial that randomized 361 patients (2:1) with recurrent HNSCC who had progressed within 6 months following platinum-based chemotherapy.
- ii. Overall survival benefit from nivolumab appeared to occur primarily in patients with tumor membrane PD-L1 expression  $\geq 1\%$  (8.7 months vs 4.6 months, 0.55; 95% CI 0.36-0.83) compared with standard chemotherapy. Treatment-related grade 3 or 4 toxicity was lower in the nivolumab treated patients compared with standard chemotherapy (13.1% versus 35.1%, respectively). Quality of life measures also favored the nivolumab treated patients.
- iii. Nivolumab is dosed per the flat dosing schedule of 240 mg IV every 2 weeks, or 480 mg IV every 4-weeks, rather than the weight-based dosing used in the trial

**Outcomes of CheckMate-141 trial<sup>33</sup>**

	<b>Nivolumab 3 mg/kg every 2 weeks (n= 240)</b>	<b>Standard single agent chemotherapy: methotrexate (n = 46), docetaxel (n= 52) or cetuximab (n = 13)</b>	<b>HR; 95% CI</b>	<b>P value</b>
Median OS	7.5 months	5.1 months	0.70; 0.51-0.96*	0.01
Median PFS	2.0 months	2.3 months	0.89; 0.70-1.13	0.32
6- month PFS	19.7%	9.9%	NR	NR
Response rate	13.3% (6 CR, 26 PR)	5.8% (1 CR, 6 PR)	NR	NR

\* The confidence interval for median overall survival was 97.73%

CR = complete response, PR = partial response, NR = not reported

b. **Pembrolizumab (NCCN Guidelines® category 1, preferred regimen following progression on or after a platinum therapy, if not previously used; non-nasopharyngeal)<sup>1</sup>**

- 1) KEYNOTE-012 trial initial cohort<sup>34</sup>
    - i. Open-label, phase Ib trial for patients with any level of PD-L1 expression (defined as  $\geq 1\%$  by immunohistochemistry).
    - ii. 60 patients with PD-L1 positive disease received pembrolizumab dosed at 10 mg/kg every 2 weeks.
    - iii. Overall response rates by central imaging were 18% (25% in HPV-positive disease, 14% in HPV-negative).
    - iv. Median OS was 13 months (with a 95% CI, of 5 – not reached).
  - 2) KEYNOTE-012 trial expanded cohort<sup>35</sup>
    - i. 132 patients received **fixed-dose** pembrolizumab 200 mg IV every 3 weeks, irrespective of PD-L1 status.
    - ii. The overall response rate was identical to the PD-L1 positive group discussed above at 18% despite the profound difference in total doses received (200 mg every 3 weeks vs 10 mg/kg every 2 weeks).
    - iii. Median duration of response was not reached and 6-month PFS and OS were 23% and 59%, respectively.
    - iv. Patients with PD-L1-positive tumors had higher response rates (22% in positive patients and vs 4% in negative,  $p=0.021$ ).
  - 3) KEYNOTE-040<sup>36</sup>
    - i. 247 patients with metastatic/recurrent HNSCC following progression on a platinum-based therapy were randomized 1:1 to receive either pembrolizumab or standard of care therapy (methotrexate, docetaxel or cetuximab)
    - ii. Median OS was 8.4 months versus 6.9 months ( $p=0.0161$ ) favoring pembrolizumab which also had a lower rate of  $\geq$  grade 3 toxicity (13% v 36%).
  - 4) Pembrolizumab 200 mg IV every 3 weeks is now FDA approved for patients with recurrent or metastatic HNSCC following disease progression on or after a platinum-containing chemotherapy regimen.
  - 5) Patients with recurrent or metastatic **nasopharyngeal** cancer may be considered for pembrolizumab if the PD-L1 status is positive (category 2B).<sup>1</sup>
- d. **Single-agent therapy options (preferred for performance status  $\geq 2$ )**
- a. Non-nasopharyngeal: pembrolizumab, cisplatin, carboplatin, paclitaxel, docetaxel, fluorouracil, methotrexate, capecitabine, cetuximab, afatinib (category 2B)



- b. Nasopharyngeal: cisplatin, carboplatin, paclitaxel, docetaxel, fluorouracil, methotrexate, gemcitabine, capecitabine

D. Locally Recurrent Disease<sup>1</sup>

- a. Ideally treated with surgery though some patients have extensive unresectable disease that is best treated with chemotherapy.
- b. Re-irradiation may be effective salvage therapy in patients who were previously treated with radiation, provided maximum doses have not been reached. Responses may be further improved if combined with chemotherapy.

**IV. Follow-up<sup>1,37</sup>**

- A. American Society of Clinical Oncology (ASCO) released a 2017 Head and Neck Cancer Survivorship Care Guideline that reviews in detail recommendations regarding surveillance and screening for recurrence and second primary cancers as well as management of long term and late side effects.<sup>37</sup>
- B. Locoregional recurrence usually occurs in the first two to three years following initial treatment. Follow-up for recurrence should be done on a routine basis as recommended below. Follow-up involves routine physical exam of the head and neck.
  - 1. Every 1-3 months for the first year
  - 2. Every 2-6 months for the second year
  - 3. Every 4-8 months for years 3-5
  - 4. Every 12 months after year 5
- C. Post-treatment imaging is generally pursued within 6 months of therapy to establish a new baseline. If chosen for follow-up imaging, PET-CT should be done at least 12 weeks after treatment to lessen the rate of false-positives.
- D. Follow-up with dental, nutrition, speech/swallow, hearing, psychiatry, and other professional specialists may be appropriate
- E. TSH should be evaluated every 6-12 months if neck was irradiated (or sooner if thyroid involved in surgical field)
- F. Consider EBV DNA monitoring for nasopharyngeal cancer
- G. As appropriate, counseling on smoking cessation and alcohol use. Previous and continuous smoking is associated with increased risk of death and PFS in oropharyngeal cancer<sup>8</sup>
  - 1. Risk of progression or death increased by 2% per year of smoking
  - 2. Risk of progression or death more than doubled for those who smoked during radiation

**Patient Case #1 (continued):**

**Pembrolizumab/Fluorouracil/Cisplatin (answer B)** would be the most appropriate choice due to PD-L1 CPS of 20 based on the KEYNOTE-048 trial. Pembrolizumab/Fluorouracil/Docetaxel is not an NCCN regimen. Because CPS is 20, a PD-1 agent should be added to chemotherapy (however pembrolizumab has not been compared with or without chemotherapy). Nivolumab + chemotherapy is also not an NCCN regimen.

**Patient Case #2 (ARS Question #3):**

HK is a 63-year-old woman who comes into clinic complaining of terrible mucositis. She can swallow water, but food has been hard for her the past few days. She is currently receiving cisplatin and radiation for locally advanced oropharyngeal cancer, HPV(-). She is a current smoker. **Based on recommendations from MASCC Guidelines, in addition to salt and soda swishes, what would you counsel her on regarding mucositis treatment?**

- A) Add amifostine prior to each cisplatin
- B) Add morphine swishes for pain
- C) Add doxepin swishes for pain
- D) Add dexamethasone swish and spit

**V. Symptom Management and Survivorship**

**A. Cancer Anorexia-Cachexia Syndrome (CACS)<sup>38,39</sup>**

1. CACS is a syndrome in which a persistently elevated basal metabolic rate is not compensated for by adequate calorie/protein intake
  - a. Characterized by anorexia, loss of adipose tissue and loss of skeletal muscle mass<sup>40</sup>
2. Cachexia contributes to depression and is a predictor of poor outcomes and quality of life and impacts quality of life, symptomatic burden, and ability to tolerate cancer therapy
3. Diagnosis and phases of cachexia

Phase	Consensus Criteria
Pre-cachexia	Weight loss $\leq$ 5% <b>AND</b> Early clinical and metabolic changes (anorexia and impaired glucose tolerance)
Cachexia	Weight loss > 5% <b>OR</b> BMI < 20 and weight loss > 2% <b>OR</b> Sarcopenia and weight loss > 2% Reduced food intake and systemic inflammation
Refractory cachexia	Clinically refractory cachexia secondary to advanced cancer Active catabolism Low performance status

4. Assessment of cachexia
  - a. Each patient in the phases of pre-cachexia or cachexia should be evaluated to determine reversible causes
  - b. Anorexia
    - a. Assess underlying factors: taste/smell disturbances, upper gastrointestinal dysmotility, lower gastrointestinal dysmotility (constipation), stomatitis, pain, poor dietary habits
    - b. Quantify protein and calorie consumption and reassess frequently
  - c. Catabolic drivers
    - a. Hypercatabolism secondary to tumor metabolism, i.e. systemic inflammation
      - 1) Surrogate marker: C-reactive protein (CRP)
      - 2) Could also be rapidly progressing cancer
    - b. No consensus on clinical practicality of monitoring CRP
  - d. Muscle mass and strength
    - a. No consensus on type of assessment or frequency
      - 1) Options include: MRI, DEXA, anthropometry
  - e. Functional and psychosocial effects
    - a. ECOG or EORTC (European Organisation for Research and Treatment of Cancer) patient reported quality of life questionnaires
5. Treatment of CACS<sup>38-40</sup>
  - a. Non-pharmacologic methods
    - 1) Fraction food intake, select foods per patient preference and ability to swallow
    - 2) Nutrition supplements to increase calorie and protein intake
    - 3) Enteral feeding (EN) or parenteral nutrition (PN)
      - i. Systemic review of PN use in patients with cancer
        - (a) Weak evidence, but no evidence for improved survival
        - (b) May improve health-related quality of life and physical function
    - 4) Dietary counseling and intervention has no proven benefit in CACS but this may be the result of lack of high quality studies assessing this as nutrition is clearly important in the management of CACS. Data indicate that while nutritional intervention does not significantly affect weight gain or energy intake, it can improve quality of life including emotional functioning, dyspnea and hunger.<sup>40,41</sup>
  - b. Management of pancreatic insufficiency with pancreatic enzyme therapy (refer to 'Pancreatic Cancer' materials for further details)
  - c. Pharmacologic interventions<sup>38,42</sup>
    - 1) Agents with confirmed efficacy

- i. Corticosteroids – Prednisone 10 - 20 mg BID or dexamethasone 3-8 mg/day
  - ii. Megestrol acetate 200-600 mg/day
    - (a) Approximately 1 in 4 patients will have improvement in appetite and 1 in 8 will have improvements in weight compared to placebo patients after a mean follow up of 4-12 weeks. Higher doses were associated with more weight improvement.<sup>43</sup>
    - (b) Risk of venous thromboembolism and edema may outweigh benefit of use with 1 in 6 patients developing thromboembolic events and 1 in 23 patients dying<sup>43,44</sup>
  - iii. Mirtazapine 7.5-30 mg/day (with overlapping depression/insomnia)
- 2) Agents with conflicting results<sup>38,39</sup>
- i. Metoclopramide
  - ii. Methylphenidate: Increased energy and mental stimulation offset by suppression of appetite
  - iii. Dronabinol<sup>44</sup>
  - iv. Medical marijuana<sup>45</sup>
- 3) Agents with proven lack of efficacy
- i. Melatonin<sup>46</sup>
- 4) Agents currently investigational
- i. Anamorelin (ghrelin agonist) – not commercially available
  - ii. Thalidomide
  - iii. Omega-3 fatty acids
  - iv. Anabolic steroids (commonly, oxandrolone)
  - v. Interleukin-6 antagonists
  - vi. Selective androgen receptor modulator (SARMs)
  - vii. Bortezomib
  - viii. NSAIDs
  - ix. Cyproheptadine
  - x. Hydrazine sulfate
  - xi. Pentoxifylline
  - xii. Melanocortin antagonists
  - xiii. Beta-2 agonists (formoterol)

## B. Mucositis<sup>47-49</sup>

1. Oral Mucositis may range from mild inflammation to frank bleeding ulcerations

- a. Usually affects the non-keratinized oral mucosa; most often affects labial, buccal and soft-palate mucosa, the floor of the mouth, and the ventral aspect of the tongue
- b. Mucositis normally progresses in a step-wise fashion:
  - 1) **Asymptomatic redness/erythema** occurring 0 to 5 days after therapy
  - 2) **Desquamation**, characterized by white patches, occurring 0 to 7 days after therapy. This is sometimes mistaken for candidiasis due to white patchy appearance
  - 3) **Contiguous pseudomembranes** occurring 6 to 12 days after therapy
  - 4) **Painful lesions with or without ulceration** occurring 7 to 16 days after therapy

#### Risk Factors for Mucositis<sup>47,48</sup>

Patient Risk Factors	Disease Risk Factors
Tobacco and/or alcohol use Poor baseline oral hygiene Age (younger with increased cell turnover and older patients due to delayed wound healing) Female sex Pre-treatment nutritional status (specifically low BMI)	Head and neck cancer Treatment plan: chemotherapy vs radiation vs combined therapy Frequency, dose, and type of chemotherapy Previous history of radiation and/or chemotherapy

1. Incidence and Outcomes of Mucositis<sup>50,51</sup>
  - a. Standard-dose chemotherapy:
    - 1) Severe mucositis may occur in 90% of patients treated for oropharyngeal cancer and can result in the increased cost of treatment in part due to about 62% of patients requiring hospitalization
    - 2) Approximately 35% of patients who develop grade 3 or 4 mucositis have a subsequent cycle of chemotherapy delayed
    - 3) Approximately 60% of patients require dose reductions of chemotherapy secondary to mucositis and 30% have their chemotherapy regimen discontinued
    - 4) 70% of patients with grade 3 or 4 mucositis require feeding tubes to maintain adequate nutrition
    - 5) Solid tumor patients receiving myelosuppressive chemotherapy who develop mucositis have an infection in 73% of their cycles versus 36% in patients without mucositis

Chemotherapy Agents Associated with Mucosal Toxicity <sup>38,48,51,52</sup>			
Actinomycin Alemtuzumab Bevacizumab Bleomycin Bortezomib Busulfan (high-doses) Capecitabine Cetuximab Chlorambucil Cisplatin Cyclophosphamide Cytarabine	Daunorubicin Docetaxel Doxorubicin Epirubicin Erlotinib Etoposide Everolimus Fluorouracil Gefitinib Hydroxyurea Idarubicin Imatinib	Interferon Irinotecan Ixabepilone Lapatinib Melphalan (high-doses) Mercaptopurine Mechlorethamine Methotrexate Mitomycin Mitoxantrone Oxaliplatin Paclitaxel Panitumumab	Procarbazine Rituximab Sunitinib Temsirolimus Thioguanine Thiotepa Topotecan Trastuzumab Vinblastine Vincristine Vinorelbine

## 2. Prevention and Treatment:

### Summary of Evidence-Based Clinical Practice Guidelines for Management of Mucositis secondary to cancer treatment<sup>48,49,53</sup>

Gastrointestinal mucositis (not including the oral cavity)
<ul style="list-style-type: none"> <li><b>RECOMMENDATIONS FOR USE:</b> <ul style="list-style-type: none"> <li>Amifostine <math>\geq 340</math> mg/m<sup>2</sup> to prevent radiation proctitis in patients receiving standard-dose radiation for treatment of rectal cancer</li> <li>Octreotide <math>\geq 100</math> mcg SQ BID to treat diarrhea unresponsive to loperamide</li> </ul> </li> <li><b>SUGGESTIONS FOR USE:</b> <ul style="list-style-type: none"> <li>Amifostine to reduce incidence of esophagitis in patients with non-small cell lung cancer receiving chemoradiation</li> <li>Sucralfate enemas to treat chronic radiation-induced proctitis in patients who have rectal bleeding</li> <li>Sulfasalazine 500 mg orally BID to prevent radiation-induced enteropathy in patients receiving external beam radiation for pelvic malignancy</li> <li><i>Lactobacillus</i>-containing probiotics to prevent chemotherapy and/or radiation-induced diarrhea in patients with pelvic malignancies</li> <li>Hyperbaric oxygen to treat radiation-induced proctitis in patients receiving radiation therapy for a solid tumor</li> </ul> </li> <li><b>RECOMMENDATIONS AGAINST USE:</b> <ul style="list-style-type: none"> <li>Systemic sucralfate, administered orally, should not be used to treat gastrointestinal mucositis in patients receiving radiation for solid tumor</li> <li>Aspirin, mesalamine and olsalazine, administered orally, should not be used to prevent radiation-induced diarrhea in patients receiving radiation for pelvic malignancy</li> <li>Misoprostol suppositories should not be used to prevent radiation-induced proctitis in patients receiving radiation therapy for prostate cancer</li> </ul> </li> </ul>
Oral mucositis
<ul style="list-style-type: none"> <li><b>RECOMMENDATIONS FOR USE:</b> <ul style="list-style-type: none"> <li>Oral cryotherapy for 30 minutes to prevent oral mucositis in patients receiving bolus fluorouracil</li> </ul> </li> </ul>

- Oral cryotherapy to prevent oral mucositis in patients undergoing HSCT receiving high-dose melphalan with or without TBI
- *Benzydamine mouthwash (not available in the US) for prevention or oral mucositis in patients with head and neck cancer receiving a moderate dose radiation*
- Palifermin 60 mcg/kg/day x 3 days prior to conditioning treatment and for 3 days post-transplant to prevent oral mucositis in patients with hematological malignancies receiving high-dose chemotherapy and total body irradiation (TBI) + autologous HSCT (Refer to 'Hematopoietic Stem Cell Transplantation' chapter for more details)
- Low-level laser therapy may be used to prevent oral mucositis in patients receiving HSCT conditioning with high-dose chemotherapy with or without TBI
- Low-level laser therapy to prevent oral mucositis in patients receiving radiation without chemotherapy for head and neck cancer
- Patient-controlled analgesia with morphine may be used to treat oral mucositis pain in patients undergoing HSCT
- **SUGGESTIONS FOR USE:**
  - Honey for the prevention of oral mucositis in patients with HNSCC receiving RT-CT
  - Multi-agent oral care protocols to prevent oral mucositis in all age groups across all cancer treatment modalities
  - Morphine mouthwash (0.2%) to treat oral mucositis-associated pain in patients receiving chemoradiation for head and neck cancer
  - Oral glutamine to prevent oral mucositis pain in patients receiving chemoradiation for head and neck cancer
  - *Benzydamine mouthwash (not available in the US) for prevention or oral mucositis in patients receiving chemoradiation for head and neck cancer*
- **RECOMMENDATIONS AGAINST USE:**
  - Polymyxin/tobramycin/amphotericin B and bacitracin/clotrimazole/gentamicin for prevention of oral mucositis in patients with head and neck cancer receiving radiation
  - Sucralfate mouthwash to prevent oral mucositis in patients receiving chemotherapy or radiation
  - Sucralfate mouthwash to treat oral mucositis in patients receiving chemotherapy or radiation
  - Intravenous glutamine to prevent oral mucositis in patients receiving high-dose chemotherapy
  - Amifostine to prevent oral mucositis associated with radiation therapy for head and neck cancer
- **SUGGESTIONS AGAINST USE:**
  - Chewing gum for the prevention of oral mucositis in pediatric patients with hematological or solid cancer who receive chemotherapy
  - Chlorhexidine mouthwash to prevent oral mucositis in patients with head and neck cancer receiving radiation
  - GM-CSF mouthwash to prevent oral mucositis in patients undergoing allogeneic or autologous HSCT
  - Misoprostol mouthwash to prevent oral mucositis in patients with head and neck cancer receiving radiation
  - Pentoxifylline to prevent oral mucositis in patients undergoing HSCT
  - Pilocarpine to prevent oral mucositis in patients with head and neck cancer or undergoing HSCT

a. Prevention strategies: Practical management<sup>54</sup>

- 1) Basic oral care (BOC) protocols should be used in all cancer patients irrespective of treatment modality and includes:
  - a. Tooth brushing and flossing

- b. Bland saline and/or sodium bicarbonate mouth rinses
  - c. Hydration and lubrication agents to mucosal surfaces
- 2) Formal dental assessment
- 3) Cryotherapy
- 4) Dietary modifications
  - a. Limited to no: sharp foods (chips), starchy, spicy or acidic foods, alcohol
- 5) Prophylactic placement of percutaneous gastrostomy tube
- b. Treatment strategies: Practical management

**Summary of practical management of oral mucositis<sup>47</sup>**

	<b>Chemotherapy- induced</b>	<b>Radiation- induced</b>	<b>Targeted agents (often called stomatitis)</b>
<b>Mild symptoms</b>	Saline based rinses, 2% viscous lidocaine rinse, diet modifications	Saline based rinses, 2% viscous lidocaine rinse, diet modifications, gabapentin, low-level laser therapy	Saline based rinses
<b>Moderate symptoms</b>	0.2% morphine rinse	0.2% morphine rinse, doxepin rinse	Dexamethasone rinse for everolimus (possibly better for prevention)
<b>Severe symptoms</b>	Systemic opiates (patient-controlled analgesia)	Systemic opiates (patient-controlled analgesia)	Systemic corticosteroids (for refractory mTOR inhibitor mucositis)

- a. Doxepin rinse<sup>55</sup>
  - i. Phase III, randomized, placebo controlled, cross-over design trial in 155 total patients
  - ii. Composite pain scores for doxepin arm approximately 50% of that of placebo
  - iii. More patients chose to use doxepin rinse upon unblinding of study despite more adverse effects including stinging/burning, unpleasant taste and drowsiness
  - iv. MASCC guidelines updated doxepin rinse to “no guideline possible” due to mixed study populations, however, may still be used in practice for certain patients
- b. Low-dose morphine rinse (0.2%)<sup>47</sup>
  - i. Single center, randomized, controlled, parallel comparison in 26 patients undergoing chemoradiation treatment for HNSCC with WHO Grade 2 mucositis or higher
  - ii. Morphine group: 15 mL of 0.2% morphine oral rinse every 3 hours (up to 6 times per day) compared to magic mouthwash group: 15 mL of a



1:1:1 mixture of magnesium aluminum hydroxide + 2% viscous lidocaine + diphenhydramine every 3 hours (up to 6 times per day)

- (i) Mean duration of severe pain: 5.07 vs 8.58 days;  $p=0.032$
- (ii) Mean duration of severe functional impairment: 1.85 vs 7.67 days;  $p=0.017$
- (iii) Need for supplemental analgesia: 21% vs 67%,  $p = 0.019$

c. Dexamethasone rinse (TKI-induced)<sup>56</sup>

- i. Multi-center, single arm, phase 2 study in 85 women with breast cancer receiving everolimus + exemestane (SWISH trial)
- ii. Dexamethasone 0.5 mg/5mL oral solution four times daily for 8 weeks was started with cycle 1 day 1 of treatment
  - (i) Used historical comparison from BOLERO-2 trial
  - (ii) Incidence of grade 2 or higher stomatitis: 2% vs 33%
- iii. Grade 3 or 4 adverse effects of dexamethasone hyperglycemia (8%), rash (4%), dyspnea (3%).

C. Xerostomia

1. Clinical Presentation<sup>57,58</sup>

- a. Impaired ability to chew, taste or swallow food and alters the normal oral microbial flora leading to development of dental caries
- b. Oral mucosa and lips will appear dry, cracked, and painful on examination
- c. Alterations in speech and the inability to communicate occur
- d. Patients awaken frequently to moisten mucosa or to relieve the polyuria that occurs as result of polydipsia
- e. Primarily caused by radiation but problems may be exacerbated in patients who have also had surgery for head and neck cancer
- f. Secondary infections can occur with *Candida* species
- g.

Summary of ISOO/MASCC/ASCO Evidence-Based Clinical Practice Guidelines for Patients with Xerostomia<sup>59</sup>

Xerostomia
<b>PREVENTION OF XEROSTOMIA</b> <ul style="list-style-type: none"><li>● <b>RECOMMENDATIONS FOR USE:</b><ul style="list-style-type: none"><li>• Adjustments to radiation therapy to spare major and minor salivary glands with high doses of radiation or to limit cumulative doses</li></ul></li><li>● <b>SUGGESTIONS FOR USE:</b><ul style="list-style-type: none"><li>• Acupuncture</li><li>• Bethanechol</li></ul></li></ul>

• **INSUFFICIENT EVIDENCE FOR USE:**

- Submandibular gland transfer prior to treatment start
- Oral pilocarpine, amifostine, or low-level laser therapy

• **RECOMMENDATIONS AGAINST USE:**

- Vitamin E (or other antioxidants)

**TREATMENT OF XEROSTOMIA**

• **RECOMMENDATIONS FOR USE:**

- None

• **SUGGESTIONS FOR USE:**

- Topical mucosal lubricants or saliva substitutes
- Salivary reflex stimulation with sugar-free lozenges or chewing gum to temporarily increase saliva flow rate
- Oral pilocarpine to temporarily improve xerostomia
- Acupuncture
- Transcutaneous electrostimulation of salivary glands

• **INSUFFICIENT EVIDENCE FOR USE:**

- Ginger extract
- Mesenchymal stem cell therapy

D. Depression, psychiatric and psychosocial issues

1. ASCO recommends that all patients with cancer and cancer survivors be evaluated periodically for symptoms of depression and anxiety using validated measurements<sup>60</sup>
  - 1) Failure to identify and treat these issues can result in decreased quality of life and potentially increased disease-related mortality and morbidity
  - 2) Coordination with institution and community resources is recommended
2. NCCN Guidelines® on Survivorship<sup>61</sup>
  - 1) Anxiety / Nervousness can include general anxiety disorder, adjustment disorder with anxious mood, panic disorder, post-traumatic stress disorder, and obsessive-compulsive disorder.
  - 2) Depression / Sadness can include major depressive disorder, depression not otherwise specified, and adjustment disorder with anxious mood or with mixed depressed mood with anxiety.
  - 3) Guideline includes non-pharmacologic and pharmacologic treatments.
3. 2015 Psychiatric Considerations in the Oncology Setting<sup>62</sup> discusses in detail the following:
  - 1) Interventions for cancer patients such as behavioral training, education, group and / or individual intervention have all shown significant improvements in anxiety, distress and quality of life.
  - 2) Specific disorders presented include adjustment, anxiety, depression, and delirium.

- 3) This publication contains several tables of useful pharmacotherapy agents for these disorders.
  - a. Antidepressants, benzodiazepines and antipsychotics, are useful for adjustment and anxiety disorders.
  - b. Antipsychotics can be used to treat delirium.
- 4) Other disorders presented are cancer-related cognitive dysfunction, fatigue, psychiatric impact of pain in cancer patients, sleep disturbances, and sexual dysfunction.

#### E. Smoking Cessation<sup>63</sup>

1. Cigarette smoking is estimated to cause 1 in every 5 deaths and 30% of all cancer- related deaths.
2. Even after a cancer diagnosis, smoking cessation has been associated with improved cancer treatment outcomes, recurrence rate and secondary cancer occurrence. This is regardless of stage or prognosis.<sup>64</sup>
  - 1) Smoking increases the rates of pulmonary complications, surgical site infection and poor wound healing following surgery
  - 2) Smoking can impact the metabolism of certain chemotherapy agents and targeted therapies including erlotinib, irinotecan, and bendamustine
  - 3) Smoking increases the risk of radiation therapy- associated treatment complications and may also decrease response to radiation
3. Evaluation of smoking behavior should occur for all cancer patients and should assess whether the patient is currently smoking and/or has ever smoked.
  - 1) Details on duration of smoking history and number of packs per day smoked will allow calculation of a total pack year history: (packs per day x number of years of smoking)
4. If the patient is ready to quit within 4 weeks or has quit within the prior 30 days, then smoking cessation treatment is appropriate.<sup>63</sup>
5. Behavioral therapy<sup>63</sup>
  - 1) Therapy should be targeted to the patient's history of nicotine dependence and previous quit attempts.
  - 2) Motivational counseling is beneficial for all smokers, regardless of their current willingness to quit, and involves expressing empathy while attempting to build confidence for quitting or continuing smoking cessation. Problem-solving skills, support, and encouragement are provided addressing:
    - a. Coping with nicotine withdrawal that typically peaks 1-2 weeks after quitting smoking
    - b. Identifying triggers that cause the desire for smoking

- c. Coping with stressful situations and avoiding high-risk situations that may trigger desire for smoking
  - d. Addressing other patient-specific barriers to behavior changes
- 3) Patients with cancer who are trying to quit smoking have unique needs compared with the general population and may benefit from specific programs targeted specifically for cancer patients
- 4) Frequency/type of therapy recommendations
  - a. Four or more sessions of at least 3 minutes. Longer (10-30 minutes) with a trained health care provider in smoking cessation is associated with higher abstinence rates
  - b. Can be individual or group
  - c. In-person or telehealth visits are appropriate
- 6. Pharmacologic therapy<sup>63</sup>
  - 1) Pharmacotherapy methods have more than 3-fold greater effectiveness when combined with behavioral therapy and can further assist with supporting medication adherence<sup>65</sup>
  - 2) Preferred primary therapy options
    - a. Combination nicotine replacement therapy (NRT) with a nicotine patch and short- acting NRT (lozenge, gum, inhaler, or nasal spray) + behavior therapy x 12 weeks (**NCCN Guidelines category 1 recommendation**)
      - i. Start with a 21 mg patch and short-acting NRT
      - ii. If not effective, then increase to 35 or 42 mg patch
    - b. Varenicline + behavior therapy x 12 weeks (**NCCN Guidelines category 1 recommendation**)
      - i. Should be started 1-6 weeks prior to the actual quit date
      - ii. Nausea is a common side effect, seen in about 28% of otherwise healthy patients taking varenicline. This should be considered in the context of the cancer population who may be experiencing concurrent chemotherapy-induced nausea and vomiting.<sup>66</sup>
      - iii. Due to increased seizure risk, varenicline should be avoided in patients with brain metastases or prior seizure history.
      - iv. Patients should be monitored for neuropsychiatric effects including depression and suicidal behavior.
        - (i) A clinical trial of 8144 patients receiving NRT, varenicline, or bupropion was divided into two cohorts based on whether they had a history of psychiatric disorders or not.<sup>67</sup>

- Moderate or severe neuropsychiatric events occurred to a greater extent (in both varenicline and bupropion arms) in patients with a history of psychiatric disorders:
- Varenicline: 1.25% of non-psychiatric cohort and 6.42% of the psychiatric cohort.
- Bupropion: 2.44% of non-psychiatric cohort and 6.62% of the psychiatric cohort.

(ii) Varenicline treated patients had higher rates of smoking abstinence at weeks 9-12.

- A minimum of 12 weeks is recommended for the initial quit attempt and may be extended for as long as it is beneficial though shorter durations are preferred
- Follow-up is recommended within 2-3 weeks followed by periodic visits at least every 12 weeks following completion of cessation therapy
- The contaminant NDMA caused mass recalls of varenicline, leading to shortages, however the FDA considers the health benefits of stopping smoking to outweigh the cancer risk from NDMA and encourages patients not to abruptly stop taking their medication.

### 3) Other recommended therapy options<sup>63</sup>

- NRT and varenicline
- Bupropion (long-acting) ± NRT (specifically for patients with overlapping depression and fatigue)
- Varenicline and bupropion (long-acting)
  - Should be avoided in patients with brain metastases due to lowering of the seizure threshold, those taking MAO inhibitors, tamoxifen or in patients with closed-angle glaucoma.

### 7. Alternative approaches<sup>63</sup>

- E-cigarettes or vaping
  - Not FDA- approved smoking cessation devices
  - Insufficient evidence to support use in smoking cessation either alone or in combination with other evidence-based methods
- Hypnosis, acupuncture, nutritional supplements
  - Insufficient evidence to support their use either alone or in combination with other evidence-based methods.

#### **Patient Case #2:**

**Salt and soda swishes and add morphine swishes for pain (answer B)** is the only “suggested for use” option for treatment of mucositis based on MASCC guidelines.

## THYROID CANCER

### Patient Case #3 (ARS Question #4):

LH is a 52-year-old woman who initially developed a large goiter. Imaging showed a thyroid mass and she underwent total thyroidectomy. Pathology confirmed an 8 cm predominantly thyroid mass with 8 of 33 positive lymph nodes consistent with a follicular thyroid carcinoma. Next generation sequencing was performed on the specimen and showed an NRAS Q61R alteration. Additional staging does not show any evidence of distant metastatic disease.

### What is the most appropriate therapy for LH at this time?

- A. Observation
- B. Radioactive iodine
- C. Dabrafenib/trametinib
- D. Lenvatinib

## I. Genomics<sup>68,69</sup>

### A. Histologic subtypes

#### 1. Differentiated thyroid carcinoma (DTC)

- a. Arise from primarily follicular cells from the endocrine compartment of the thyroid gland<sup>69</sup>
- b. There are 3 subtypes of DTC

##### 1) Papillary thyroid cancer (PTC)

- a) Most common subtype, representing about 89% of thyroid cancer diagnoses
- b) BRAF V600E mutations and activating RET fusions are most common genetic abnormalities – see table below for specific percentages

##### 2) Follicular thyroid cancer (FTC)

- a) Accounts for about 4.6% of thyroid cancers and has a slightly worse prognosis than PTC
- b) Typically more well-differentiated than PTC, have higher thyroglobulin (Tg) levels, and greater radioactive iodine (RAI) avidity

##### 3) Hürthle cell

- a) Represents 2% of thyroid cancer diagnoses
- b) Considered a variant of FTC, however Hürthle cell has a distinct histologic appearance, unique genetic signature and is not responsive to RAI unlike typical FTC<sup>69</sup>

#### 2. Medullary thyroid cancer (MTC)<sup>70,71</sup>

- a. Accounts for 3% of thyroid cancers
- b. Arises from the parafollicular C cells of the thyroid, which produce calcitonin and CEA

- 1) Calcitonin and CEA can be used as tumor markers in patients treated for MTC or as a screening tool in family members
- c. Sporadic vs hereditary
  - 1) About 75% of MTC are sporadic, while 25% are hereditary
  - 2) Hereditary MTC is often a component of multiple endocrine neoplasia (MEN) type 2 syndromes
    - a) MEN2A accounts for 95% of cases, MEN2B and familial medullary thyroid carcinoma (FMTC) account for the remainder
    - b) Each of the syndromes have variable clinical features, however MTC is present in nearly all cases
    - c) About 6-7% of patients with sporadic MTC will have a **germline** RET mutation, and should be evaluated for an underlying MEN2 defect
  - 3) RET mutations play a large role
    - a) Of the sporadic MTC, about 65% have **somatic** RET mutations with 80% of these being the **RET M918T** and is associated with a poor prognosis but is amenable to RET-targeted therapy
    - b) The majority of hereditary cases are associated with mutations in RET on chromosome 10q11.2
3. Anaplastic thyroid cancer (ATC)<sup>68</sup>
  - a. Least common type of thyroid cancer representing about 1.5% of thyroid cancers
  - b. Associated with an aggressive, undifferentiated histology and the poorest prognosis with disease-specific mortality nearly 100%
  - c. Tumors traditionally do not respond to RAI and have poor responses chemotherapy
  - d. Prior or coexistent DTC is seen in about half of patients with ATC
    - 1) This occurs through an acquisition of additional mutations including inactivation in TP53 and PTEN along with activation of the oncogene ALK<sup>69</sup>

### Genetic abnormalities seen in thyroid cancer<sup>69</sup>

Mutation	PTC	FTC	Hürthle cell	MTC	ATC
RET	-	-	-	>60%	-
RET-PTC fusions	13-43%	-	-	-	-
BRAF (V600E/K)	29-69%	-	-	-	10-35%
PAX8-PParg fusions	-	25-63%	-	-	-
RAS	0-10%	25-63%	-	10-45%	22-55%
TERT	20-30%	-	20-30%	-	45-55%
PTEN	-	-	-	-	12%
EGFR	15%	-	-	35%	80%
PI3K	-	-	-	-	17%
AXIN1	-	-	-	-	82%
CTNNB1	-	-	-	-	66%
APC	-	-	-	-	9%
ALK	0.8-1.6%*			-	4%

\*Reported as differentiated thyroid cancer

## II. Prevention and screening

### A. Risk Factors<sup>68</sup>

#### 1. Ionizing radiation

- a. Either therapeutic (e.g. from a prior cancer) or environmental (e.g. radioactive fallout from a nuclear disaster)
  - 1) PTC most common subtype of radiation-induced thyroid cancer
- b. Children are most at risk
  - 1) A child's thyroid gland has one of the highest risks of developing cancer of any organ
  - 2) Thyroid cancer risk following therapeutic radiation for other malignancies is related to dose of radiation. A 7 to 15-fold increase in the relative risk of developing thyroid cancer following 2-30 Gy of radiation has been reported.
- c. Nuclear disasters, such as Fukushima and Chernobyl
  - 1) Can release a combination of radioactive materials including iodine-131 (I-131), which concentrates in the thyroid
  - 2) Stable iodine can be administered prior to radioactive iodine exposure
    - a) This would prevent the low-dose, internal exposure of the I-131 and reduce the secondary risk of thyroid cancer
    - b) The efficacy of this is currently being assessed in Fukushima children, especially those younger than 10 years of age who are at the highest risk<sup>72</sup>

#### 2. Hereditary germline alterations

- a. MEN2<sup>71,73</sup>
  - 1) Autosomal dominant, multi-tumor syndrome



- 2) Associated with early onset MTC. If a family member is positive for the RET mutation, a prophylactic thyroidectomy is indicated.

#### Subtypes of MEN2

Subtype	Characteristics
<b>MEN2A</b>	Associated with pheochromocytoma, parathyroid hyperplasia or adenoma, and/or skin condition lichen planus amyloidosis
<b>MEN2B</b>	Most severe form of disease Poorest prognosis Associated with pheochromocytoma and other developmental abnormalities
<b>FMTC</b>	MTC without other features Generally more indolent in nature May be a phenotypic continuum of MEN2A

- b. Familial non-medullary thyroid cancer syndrome (FNMTTC): present in about 5-9% of PTC and may either occur independently or be linked to the presence of another cancer predisposition syndrome like Cowden's, Carney complex or familial adenomatous polyposis.<sup>71</sup>
  3. Iodine deficiency: uncommon in the United States where salt is typically fortified with iodine
- B. Screening
1. There are no formal screening guidelines from the American Cancer Society
  2. The U.S. Preventive Services Task Force recommends against screening in asymptomatic adults<sup>74</sup>

### III. Treatment

- A. Differentiated thyroid cancer
1. Surgery<sup>68</sup>
    - a. Ipsilateral lobectomy vs total thyroidectomy
      - 1) The appropriate extent of thyroid resection is controversial for lower-risk PTC
      - 2) Decisions about the extent of thyroidectomy should be individualized and done in consultation with each patient
    - b. Following total thyroidectomy, thyroid replacement therapy will be required and is discussed below in the Survivorship section
    - c. If recurrent disease is deemed resectable, surgery is the preferred therapy
  2. Radioactive iodine (RAI)<sup>68</sup>
    - a. RAI takes advantage of the thyroid's follicular cells' ability to transport and incorporate iodide into Tg
      - 1) BRAF-mutated cancers are often refractory to RAI
      - 2) This may be overcome by administering RAF or MEK inhibitors
    - b. Hürthle cell tumors are less likely to concentrate I-131

c. Goals of therapy:

- 1) Ablation of the normal thyroid tissue, which can make surveillance with Tg more accurate
- 2) Eliminate any micrometastatic disease in the adjuvant setting
- 3) Treatment of known persistent disease

**Radioactive iodine (RAI) recommendations<sup>68</sup>**

Typically recommended*	Selectively recommended*	Not recommended <sup>†</sup>
<ul style="list-style-type: none"> <li>Gross extrathyroidal extension</li> <li>Primary tumor &gt; 4 cm</li> <li>Postoperative unstimulated Tg &gt; 10 ng/mL (6-12 weeks after total thyroidectomy) <ul style="list-style-type: none"> <li>Can indicate biochemical residual disease</li> <li>Bulky or &gt; 5 positive lymph nodes</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Detectable anti-Tg antibodies</li> <li>Primary tumor 2-4 cm</li> <li>High risk histology including poorly differentiated tumors or those with other known high risk pathologic features</li> <li>Lymphatic invasion and/or cervical lymph node involvement</li> <li>Vascular invasion</li> <li>Cervical lymph node metastases</li> <li>Macroscopic multifocality (one focus &gt;1 cm)</li> <li>Postoperative unstimulated Tg &lt;10 ng/mL (6-12 weeks after total thyroidectomy)</li> <li>Microscopic positive margins</li> </ul>	<ul style="list-style-type: none"> <li>Classic papillary thyroid carcinoma</li> <li>Largest primary tumor &lt; 2 cm</li> <li>Intrathyroidal</li> <li>Unifocal or multifocal primary papillary tumor ≤1 cm</li> <li>No detectable anti-Tg antibodies</li> <li>Post-operative unstimulated Tg &lt; 1 ng/mL (6-12 weeks after total thyroidectomy)</li> <li>Negative postoperative ultrasound, if done</li> </ul>

\*For patients with at least one of the characteristics

<sup>†</sup>Only if ALL characteristics are present

- d. Prior to dosing, pretreatment diagnostic imaging with TSH stimulation is performed to confirm RAI-avidity
  - e. Dosing methods include empiric, fixed dosing (most common), quantitative dosimetry, and upper-bound limits set by blood dosimetry
  - f. Following administration, whole-body I-131 imaging should be performed to ensure uptake by the tumor as well as assess for any additional lesions not initially detected that have also taken up the RAI
3. Systemic therapy for RAI-refractory DTC<sup>68</sup>
- a. The NCCN Guidelines<sup>®</sup> recommends that treatment with systemic therapy should be individualized based on likelihood of response and comorbidities, and the decision to start therapy may be delayed for patients with stable or slowly progressive indolent disease
    - 1) Active surveillance is an appropriate choice for asymptomatic patients with no brain metastases
  - b. First-line therapy options
    - 1) Lenvatinib (**NCCN guidelines category 1, preferred regimen**)<sup>68</sup>
    - 2) Sorafenib (NCCN guidelines category 1, other recommended regimen)<sup>68</sup>

**Tyrosine kinase inhibitors approved for use in RAI-refractory DTC<sup>68,75,76</sup>**

	<b>Sorafenib</b>	<b>Lenvatinib</b>
Dose	400 mg twice daily on an empty stomach <i>200 mg tablets</i>	24 mg once daily (with/without food) <i>4 mg &amp; 10 mg capsules</i>
Common ADRs	≥20%: Diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage	≥30%: Hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, hand-foot skin reaction, abdominal pain, and dysphonia
Efficacy vs placebo	DECISION trial <sup>75</sup> PFS 10.8 months vs. 5.8 months (p<0.0001), ORR 12.2% vs. 0.5% (p<0.0001)	SELECT trial <sup>76</sup> PFS 18.3 months vs. 3.6 months (p<0.001) ORR 64.8% vs. 1.5% (p<0.001)

ADR = adverse drug reaction; PFS = progression-free survival; ORR = objective response rate

*\* Both sorafenib and lenvatinib are options for patients with advanced thyroid cancer who are refractory to RAI. Though the drugs have not been compared directly, the NCCN Guidelines® prefers lenvatinib due to higher response rates seen with lenvatinib (64.8%) than sorafenib (12%)*

- c. Selpercatinib or pralsetinib (RET-fusion positive tumors)
  - 1) See MTC section below for full discussion
- d. Subsequent line therapy options<sup>68</sup>
  - 1) Cabozantinib
    - a) COSMIC-311 trial<sup>77</sup>
      - i. Randomized, double-blind, placebo-controlled, phase 3 trial evaluating cabozantinib (Cabometyx® tablets) or matching placebo in patients with RAI-refractory DTC who previously received lenvatinib or sorafenib
      - ii. 187 patients were randomized 2:1 to receive cabozantinib 60 mg tablets once daily or placebo
        - (a) Primary endpoint was objective response rate for the first 100 randomly assigned patients (objective response rate intent to treat population; OITT) and progression free survival in all patients (intent-to-treat population; ITT).

## COSMIC-311: Clinical Results <sup>77</sup>

	Objective response rate intent to treat population		Intent-to-treat population	
	Cabozantinib (n=67)	Placebo (n=33)	Cabozantinib (n=125)	Placebo (n=62)
<b><u>Best overall response:</u></b>				
Complete response	0	0	0	0
Partial response	15%	0	9%	0
Stable disease	69%	42%	61%	34%
Progression free survival, median (months)	NA	NA	NR (95% CI 5.4-NE) HR 0.22 (95% CI 0.13- 0.36; p<0.0001)	1.9 (95% CI 1.8-3.6)
6-month Overall survival			85% (95% CI 75-91)	73% (95% CI 58.4-83.7)

NR = not reached, NA = not applicable, NE = not evaluable

iii. Due to the significant prolongation of PFS, **cabozantinib is recommended by the NCCN guidelines as category 1 recommendation in patients who have progressed after lenvatinib and/or sorafenib.**<sup>68</sup>

- 2) The NCCN Guidelines<sup>® 68</sup> note that if a clinical trial is not available, other commercially available small molecule TKIs that are not currently FDA approved for differentiated thyroid cancer may also be considered including:
  - a) Axitinib, pazopanib, sunitinib, vandetanib, cabozantinib or everolimus or
  - b) Selpercatinib or pralsetinib (for RET-fusion positive tumors) or
  - c) Larotrectinib or entrectinib (for NTRK-fusion positive tumors) or
  - d) Vemurafenib or dabrafenib (for BRAF V600E- positive disease, notably the combination of dabrafenib and trametinib is now FDA approved for advanced BRAF V600E- mutated solid tumors) or
  - e) Pembrolizumab (tumors with high mutational burden as defined by  $\geq 10$  mutations/Mb)<sup>68</sup>
- 3) Choice of therapy should be dependent on potential adverse effects and patient tolerance
- 4) Traditional cytotoxic chemotherapy may also be considered if a trial is not available, however chemotherapy is typically not effective for non-RAI avid tumors. There are no recommendations on regimens.

**Patient Case #3, continued (ARS question #4):**

**Correct answer is B:** Radioactive iodine (RAI) is preferred since the primary tumor was > 4 cm (at 8 cm) and there were > 5 lymph nodes involved. Lenvatinib is approved for FTC after progression of RAI. The combination of dabrafenib and trametinib can be considered for advanced thyroid cancers with BRAF V600E mutations following therapy with RAI but this is not the case for NRAS activating alterations.

**Patient Case #4 (ARS question #5):**

JA is a 67-year-old man who noted an enlarging mass in the right side of his neck. A total thyroidectomy was performed and pathology confirmed medullary thyroid carcinoma. The primary lesion was 2.9 cm along with multiple positive lymph nodes of the bilateral neck. He underwent surveillance for 3 years, but after continued elevation of calcitonin, he had imaging to suggest metastatic disease in the lungs. He was started on vandetanib.

**According to the main trial supporting vandetanib use in MTC, what was the most concerning side effect that brought about required REMS program for its use?**

- A. Fetal harm
- B. Prolonged QTc
- C. GI perforation
- D. Stevens-Johnson syndrome

**B. Medullary Thyroid Cancer**

1. Surgery<sup>68</sup>
  - a. Main treatment for MTC is total thyroidectomy
    - 1) Patients should be assessed for co-existing hyperparathyroidism and pheochromocytoma pre-operatively
  - b. Radiation can be used in the adjuvant setting for cases where residual disease is present
  - c. Followed post-operatively by ongoing assessment of calcitonin and CEA
    - 1) In the setting of calcitonin  $\geq 150$  pg/mL or elevated CEA above normal then further work up is indicated
2. RAI
  - a. Not used in the treatment of MTC as these cells do not concentrate RAI
3. Systemic therapy<sup>68</sup>
  - a. The NCCN Guidelines® recommends that treatment with systemic therapy should be individualized based on likelihood of response and comorbidities, and the decision to start therapy may be delayed for patients with stable or slowly progressive indolent disease.

Adjunctive therapies may also be considered depending on whether tumors secrete specific proteins the results of which may be responsive to counteracting therapies (e.g. somatostatin analogs).

b. First-line therapy options

- 1) Vandetanib (NCCN Guidelines® Category 1)
- 2) Cabozantinib capsules (NCCN Guidelines® Category 1)

**Non-Selective tyrosine kinase inhibitors approved for use in metastatic/unresectable MTC<sup>68,78,79</sup>**

	<b>Vandetanib* (Caprelsa®)</b>	<b>Cabozantinib (Cometriq®)</b>
Common ADRs	>20%: diarrhea/colitis, rash, acneiform dermatitis, hypertension, nausea, headache, upper respiratory tract infections, decreased appetite and abdominal pain	≥25%: diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, and constipation, increased AST, increased ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia
<b>Black box warning</b>	QTc prolongation, Torsades de pointes, and sudden death	Perforations and fistulas Hemorrhage
Efficacy vs placebo	ZETA trial <sup>78</sup> PFS 30.5 (estimated) vs 19.3 (months) p<0.001 ORR 45% vs. 13% (p<0.001) Patients with RET M918T had improved RR with vandetanib vs. RET negative patients	EXAM trial <sup>79</sup> PFS 11.2 vs. 4 months (p<0.001) ORR 28% vs. 0% Responses to cabozantinib seen regardless of mutation status

ADR = adverse drug reaction; PFS = progression-free survival; ORR = objective response rate

*\*Only prescribers and pharmacies certified through the vandetanib REMS education program are able to prescribe and dispense vandetanib. It is recommended to obtain baseline potassium, calcium, magnesium, TSH, and ECG before initiation and regularly throughout treatment.*

*\*Selection between cabozantinib and vandetanib should be based on patient characteristics and side effect profiles*

3) Selpercatinib (RET positive tumors)

- a) Refer to Lung Cancer materials for mechanism of action, toxicities, drug-drug interactions, and administration
- b) LIBRETTO-001<sup>80</sup>
  - i. Multi-center, open-label, multi-cohort trial in patients with RET alterations (including 143 patients with RET-mutant MTC and 19 patients with RET fusion-positive thyroid cancers)
  - ii. This was a dose escalation trial that included a phase 1 dose escalation from 20 mg once daily to 240 mg twice daily with intra-patient escalation to higher doses

determined to be safe after at least one cycle of therapy. In phase 2, all patients received 160 mg twice daily.

iii. RET-mutated MTC

- (a) In the patients 55 previously treated with cabozantinib, vandetanib or both, the ORR was 69% (95% CI: 55%, 81%) with 76% of the responses lasting  $\geq 6$  months. The 1-year PFS was 82%.
- (b) In the 88 patients who were treatment-naïve, the ORR was 73% (95% CI: 62%, 82%) with 61% of the responses lasting  $\geq 6$  months. The 1-year PFS was 92%.

iv. RET fusion-positive thyroid cancer

- (a) In the 19 previously treated patients (RAI-refractory) the ORR was 79% (95% CI: 54%, 94%) with 87% of the responses lasting  $\geq 6$  months.
- (b) In the 8 patients who were treatment-naïve but RAI-refractory, the ORR was 100% with 75% of the responses lasting  $\geq 6$  months.

v. Selpercatinib is now included as an NCCN Category 2A recommendation for RET-altered thyroid cancer based on these data.<sup>68</sup>

4) Pralsetinib (RET- positive tumors)

- a) Refer to Lung Cancer materials for mechanism of action, toxicities, drug-drug interactions, and administration

b) ARROW trial<sup>81</sup>

- i. Multicenter open label, phase 1 and 2 study in patients with RET-altered metastatic solid tumors (including 122 patients with RET-mutant MTC and 20 patients with RET fusion-positive thyroid cancers)
- ii. All patients received pralsetinib 400 mg once daily
- iii. RET-mutated MTC
  - (a) In the 55 patients previously treated with cabozantinib, vandetanib or both, the ORR was 60% (95% CI 52-100%). The 1-year PFS was 92%.
  - (b) In the 21 patients who were treatment-naïve, the ORR was 71% (95% CI 48-89%). The 1-yr PFS was 84%.
- iv. RET-fusion positive thyroid cancer
  - (a) All 20 patients were RAI-refractory and previously treated, mostly with lenvatinib and/or sorafenib
  - (b) The ORR was 89% (95% CI 52-100). The 1-year PFS was 86%.
- v. These are interim analysis results. Full survival data to be published at a later date, however, pralsetinib is now included as an NCCN Category 2A recommendation for RET-altered thyroid cancer based on these data.<sup>68</sup>

c. Subsequent line therapy options

- 1) Selpercatinib or pralsetinib (RET-mutated or RET-fusion positive) if not already used

- 2) Clinical Trial
  - 3) If clinical trials are not available, options include other off-label small-molecule kinase inhibitors as discussed above for DTC, and dacarbazine (NCCN level 2A recommendation)<sup>68</sup>
  - b. Radiation and other regional therapies such as embolization or radiofrequency ablation are also options for appropriate patients
- C. Anaplastic Thyroid Cancer<sup>68</sup>
1. ATC responds poorly to conventional therapy, therefore the main goal of treatment is palliation and supportive care
    - a. Patients should also be considered for clinical trials
  2. Surgery
    - a. Most patients have unresectable or metastatic disease, but for those that are deemed surgical candidates, a total thyroidectomy should be attempted
    - b. Tracheostomy is often performed to ensure patency of upper airways from invading and/or obstructing tumors, however this is often a temporary effort as the disease progresses rapidly
  3. Radiation therapy
    - a. ATC cells do not concentrate RAI
    - b. External beam radiation (EBRT) or intensity-modulated radiation therapy (IMRT) can be used for local control and palliation
  4. Targeted therapy (currently NCCN Guidelines® Category 2A)<sup>68</sup>
    - a. BRAF and MEK combination therapy
      - 1) Dabrafenib and trametinib were FDA approved in May 2018 for patients with locally advanced or metastatic anaplastic thyroid cancer with the BRAF V600E mutation and no satisfactory locoregional treatment options
      - 2) Subset of phase II, open-label trial in patients with BRAF-V600E mutated malignancies<sup>82</sup>
        - a) Sixteen patients with BRAF V600E-mutated anaplastic thyroid cancer were evaluable with a median follow up of 47 weeks. (All patients had progressed on prior radiation and/or surgery and 6 had prior systemic therapy)
        - b) The confirmed overall response rate was 69% (95% CI, 41-89%) with 7 responses ongoing
        - c) Median duration of response, PFS and OS were not reached
        - d) The most common adverse effects were consistent with the drug combination profile including fatigue (38%), pyrexia (37%) and nausea (35%)
    - b. Selpercatinib or pralsetinib (RET-fusion positive)
    - c. Pembrolizumab (TMB-H only)
  5. Cytotoxic therapy (all regimens are NCCN Guidelines® Category 2A)<sup>68</sup>
    - a. Paclitaxel and carboplatin either weekly or every 3-4 weeks



- b. Docetaxel and doxorubicin either weekly or every 3-4 weeks
- c. Single- agent paclitaxel or doxorubicin either weekly or every 3-4 weeks
  - 1) Single agent doxorubicin is the only FDA-approved agent for ATC
- d. Chemotherapy generally produces response rates of about 10-20% so referral to clinical trials is the preferential treatment option when available

**Patient Case #4, Continued:**

**Correct answer is B.** In the ZETA trial, 19 patients (8%) experienced prolongation of QTc. Because of this prolongation and risk for Torsades de pointes as well as sudden death, vandetanib is only available from certified REMS providers.

- D. Symptom management and supportive care<sup>68</sup>
  - 1. Bone metastases
    - a. Intravenous bisphosphonates or subcutaneous denosumab are recommended to prevent skeletal-related events
    - b. EBRT, stereotactic body radiation therapy (SBRT), or other local therapies are also acceptable for symptomatic or asymptomatic tumors in weight-bearing extremities
  - 2. RAI toxicities
    - a. Short-term toxicities: neck tenderness/swelling, nausea, vomiting, salivary gland tenderness/swelling, dry mouth, taste changes, and dry eyes
    - b. Long-term/rare toxicities: lower sperm counts in men, irregular menstruation in women, leukemia, gastric cancer, and HNSCC (salivary gland).
  - 3. TKI toxicities<sup>83</sup>
    - a. TKIs are associated with a multitude of adverse events, most commonly including diarrhea, anorexia, weight loss, fatigue, hypertension, hypothyroidism, hand-foot skin reaction (HFSR), and skin rash
    - b. Appropriate supportive care should be initiated for adverse effects in order to prevent patients from suddenly stopping these medications
    - c. Dose reductions or modifications are often necessary
      - 1) In almost all the phase III studies for thyroid cancer TKIs, the median dose used by patients was lower than the starting dose
    - d. Patients should be counseled to report intolerable side effects immediately to their care team

**IV. Survivorship issues & Long-term Follow up<sup>68</sup>**

- A. More than two-thirds of patients are diagnosed with localized disease, which results in 5-year overall survival rate of 98.2%
- B. Surgical complications

1. Most common complications of a total thyroidectomy are hypoparathyroidism (2.6%) and recurrent laryngeal nerve injury (3%)
2. Hypocalcemia is present in about 5.4% of patients immediately after total thyroidectomy, but only persists in 0.5% after 1 year

C. TSH suppression

1. In patients with PTC, FTC and Hürthle cell carcinoma, use of levothyroxine to maintain low TSH levels is recommended because TSH can stimulate the growth of thyroid-derived cells, including cancer cells
2. No specific goal level has been established. However, NCCN Guidelines® recommendations are as follows based on risk of recurrence:<sup>68</sup>
  - a. Patients with known residual carcinoma or at a high risk for recurrence should have a TSH below 0.1 mU/L.
  - b. Patients with clear margins, no evidence of residual disease and at low risk should have TSH levels maintained near the lower limit of the reference range.
  - c. For low risk patients with biochemical (e.g. Tg positive) disease, but no evidence of disease on imaging, TSH levels should be maintained at 0.1-0.5 mU/L
  - d. Patients on chronic TSH-suppression therapy should be counseled to take calcium 1,200 mg/day and vitamin D 1,000 units/day if not obtained through diet
3. Long- term administration of supraphysiological doses of levothyroxine are known to cause adverse effects. The most concerning are atrial fibrillation and accelerated bone loss. Studies have shown just below the normal ranges is relatively safe and effective.

D. Thyroglobulin (Tg)<sup>68,84</sup>

1. Secreted by normal (non-neoplastic follicular) thyroid cells and differentiated thyroid cancer cells so it can be helpful for use as a tumor marker
  - 1) Since normal thyroid cells can secrete it, it is only useful in the post-thyroidectomy setting
  - 2) Tg and anti-Tg antibodies can be assessed 6-12 weeks following total thyroidectomy, then every 6 and 12 months and then annually if disease free. Typically, patients with measurable Tg levels during TSH suppression and those with stimulated Tg (using rh TSH) levels > 2 ng/mL are likely to have residual or recurrent disease either at present or in the next 3-5 years.
2. One limitation for use is that patients can develop antibodies to Tg so assessment of both Tg and Tg antibodies is most accurate
3. Tg is not secreted by anaplastic or medullary thyroid cancers so can be used to distinguish these subtypes from DTC

## ADULT CNS TUMORS

### **Patient Case #5 (ARS question #6):**

L.M. is a 62-year-old woman who initially experienced a tonic-clonic seizure which led to a brain MRI that showed a left parietal lobe lesion. She underwent maximum safe resection and pathology showed a glioblastoma, IDH-wild type, WHO grade 4, MGMT promoter methylated, negative for co-deletion of 1p/19q and positive for both EGFR amplification and EGFR VIII. She recovered well from surgery and her ECOG performance status is 0.

### **What is the most appropriate therapy for LM at this time?**

- A. Observation
- B. Temozolomide with concurrent radiation followed by temozolomide maintenance
- C. Osimertinib with concurrent radiation followed by osimertinib maintenance
- D. Radiation followed by procarbazine, lomustine (CCNU), and vincristine

### **I. Classification<sup>85,86</sup>**

- A. Primary tumors of the CNS arise from neurons, astrocytes, oligodendrocytes, ependymal cells, and microglial cells. Tumors that develop from neuroglial tissues (astrocytes, oligodendrocytes, and ependymal cells) are gliomas.
- B. Brain tumors are classified on the basis of tumor cell type and histologic grade. Most neuro-oncologists use the World Health Organization (WHO) classification as discussed below.
  - 1. Current central nervous system nomenclature was recently updated (WHO 2021) and the NCCN Guidelines for CNS Cancers v.1.2022 now incorporates this nomenclature.
- C. The CNS lacks a lymphatic system, so histologically malignant tumors, although locally invasive, almost never metastasize systemically. Designations such as “benign” or “malignant” are only relative distinctions for CNS neoplasms.

### **II. Benign Brain Tumors**

- A. Meningiomas<sup>87</sup>
  - 1. General
    - a. Most common benign brain tumor that accounts for 20% of all primary brain tumors (peak occurrence in the sixth decade). They are twice as common in women as men.
    - b. Originate in the arachnoid matter of the brain (intradural, also described as extra- vs intra-medullary) so technically speaking, they are not brain tumors
    - c. Rarely invasive, but can cause significant morbidity (and occasionally death) from compression of adjacent brain parenchyma, cranial, and spinal nerves
    - d. Anaplastic meningiomas are rare (~2% of all meningiomas), difficult to treat, and diffusely invade the dura and surface of the brain
  - 2. Pathology/Biology - slow growing

- a. Contain abnormalities in chromosome 22 and mutations of the NF2 gene located on chromosome 22.
    - 1) Neurofibromatosis type 2 (NF2) is a hereditary condition most commonly associated with bilateral vestibular schwannomas but 50-75% of patients with NF2 also develop meningiomas.
    - 2) Allelic losses of chromosome 22, including NF2, also occur in more than 50% of sporadic meningiomas.
  - b. May be single lesions or in multiple sites occurring primarily at the base of the skull
3. Treatment<sup>85,87</sup>
- a. Dependent upon symptoms, patient age, and site/size ( $\leq/\geq$  30 mm) of tumor.
  - b. Surgical resection is curable if completely resected with 75% 10-year PFS but recurrence rates are high for subtotal resection (39% 10-year PFS).
  - c. Adjuvant radiation therapy decreases the rate of recurrence from 60% to 32% and extends the length of time to tumor recurrence and should be considered for all patients with anaplastic meningiomas. Stereotactic radiosurgery may also be considered.
  - d. Systemic therapy is usually considered for patients with progression following surgery and radiation or patients with anaplastic meningioma.
    - 1) There are limited data supporting systemic therapies, but bevacizumab alone is an NCCN Guidelines® category 2A recommendation. Sunitinib and bevacizumab with everolimus are NCCN Guidelines® category 2B recommendations. See below regarding low-grade glioma subtypes for more information regarding targeted therapies.
    - 2) If an octreotide scan is positive, then somatostatin analogues can also be considered (NCCN Guidelines® category 2B).
    - 3) Clinical trials are also assessing bevacizumab and other small-molecule tyrosine kinase inhibitors including those directed against NF2 such as the ALK inhibitor brigatinib and novel HDAC inhibitors.

#### B. Schwannoma (acoustic neuroma)

- 1. Benign tumors that originate from the nerve sheath of the vestibular nerve
- 2. Patients present with sensorineural hearing loss and vertigo, followed by facial palsy, dysphagia, facial numbness, and hydrocephalus
- 3. Surgery is treatment of choice with maximal safe resection pursued especially for symptomatic patients, adjuvant treatment is not necessary.

#### C. Pituitary Adenomas

- 1. Patients present with a syndrome of hypersecretion of hormones, hypopituitarism, bitemporal visual-field loss, or headache
- 2. Prolactinomas are the most common hypersecretory tumors of the pituitary (bromocriptine is the preferred initial treatment)

3. Cushing's disease results in many patients from hypersecretion of corticotropin by a pituitary adenoma
4. Pituitary carcinomas are treated as aggressive neuroendocrine tumors

### III. Malignant Glial Brain Tumors (Gliomas)

#### A. Astrocytoma and oligodendroglioma<sup>85</sup>

1. Molecular pathology and prognosis
  - a. Co-deletion of 1p and 19q
    - 1) The combined loss of one copy of the short arm of chromosome 1 and the long arm of chromosome 19 is associated with oligodendroglial histology
    - 2) Associated with a favorable prognosis
    - 3) Predictive of response to alkylating chemotherapy alone or in combination with radiation<sup>88</sup>
  - b. Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations
    - 1) IDH1 and IDH2 encode for metabolic enzymes involved in oxidative decarboxylation of L-isocitrate and ultimately lead to the production of alpha-ketoglutarate ( $\alpha$ KG) and nicotinamide adenine dinucleotide phosphate (NADPH).
      - a) Approximately 90% of IDH1 mutations occur as a somatic, heterozygous R132H missense mutation in the isocitrate binding zone.
      - b) R132H mutated IDH1 utilizes NADPH to reduce  $\alpha$ KG to R(-)-2-hydroxyglutarate (2HG). Increased production of 2HG serves as an oncometabolite resulting in significantly increased DNA hypermethylation and prevention of cellular differentiation.
      - c) The same applies to IDH2, however they are less common than IDH1 and typically occur at the R172 location.<sup>89</sup>
    - 2) IDH1 R132H mutations are common in grade 2 and 3 gliomas and occur in > 90% of gliomas overall but only 10% of primary glioblastomas. These mutations can be helpful in identifying a primary from a secondary glioblastoma that evolved from a lower grade glioma
    - 3) IDH mutations are associated with co-deletion of 1p and 19q and with MGMT promoter methylation. They have a favorable prognosis in general while wild-type IDH in grade II or III gliomas is associated with more aggressive disease.
    - 4) IDH mutations are associated with survival benefits following alkylating chemotherapy or radiation but not in untreated patients<sup>90</sup>
    - 5) In patients with IDH-mutated gliomas, the presence of homozygous CDKN2A/B loss is associated with inferior overall survival compared with tumors lacking this alteration<sup>91</sup>
  - c. O<sup>6</sup>-methylguanine-DNA-methyltransferase (MGMT) promoter methylation
    - 1) MGMT is an enzyme involved in DNA repair that corrects the damage caused by alkylating agents like temozolomide. Promoter methylation of MGMT results in epigenetic silencing of MGMT and the inability of the enzyme to repair damage due to temozolomide, ultimately resulting in improved tumor response to temozolomide.<sup>92</sup>

- 2) MGMT promoter methylation is a positive predictive marker associated with improved progression free and overall survival.
  - a) The 18-month overall survival for patients with MGMT promoter methylation treated with temozolomide and radiation was 62% compared with 8% in those with an unmethylated MGMT ( $p=0.002$ ).<sup>93</sup>
- 3) Patients with unmethylated MGMT promoters achieve less benefit from temozolomide, though it is still used as the standard management for these patients. Ongoing trials are assessing the value of non-temozolomide based regimens.
- d. Epidermal growth factor receptor (EGFR)<sup>94</sup>
  - 1) EGFR amplification is seen in 44% of GBM. EGFR vIII alteration is found in 24-57% of GBM with 50-60% of those that overexpress EGFR also having this vIII alteration.
  - 2) The EGFR vIII mutation results in a deletion of exons 2-7 in the extracellular domain of EGFR.
    - a) This results in the loss of the domain II loop that causes a shift favoring the active, open conformation of EGFR rather than the closed, inactive conformation.
    - b) This mutated EGFR cannot bind EGFR-family ligands but is constitutively active.<sup>95</sup>
  - 3) Use of the reversible EGFR inhibitors erlotinib, gefitinib and lapatinib has shown minimal responses, typically in 10-20% of patients with short response durations.
  - 4) The third generation EGFR-TKI osimertinib has been shown to inhibit EGFR vIII with high potency and is > 10 more efficient at crossing the blood-brain-barrier than first-generation inhibitors like erlotinib.<sup>96</sup>
    - a) A retrospective trial assessed 15 patients with glioblastoma harboring both EGFR amplification and EGFR vIII mutations who had previously received prior standard therapy with radiation and temozolomide.
    - b) Patients were treated with osimertinib 80 mg PO daily and bevacizumab 15 mg/kg every 3 weeks at the time of recurrence.
    - c) Median PFS was 5.1 months (95% CI 2.8-7.3) with OS of 9 months (95% CI 3.9 – 14).
    - d) The 6 months PFS was 46.7% and the overall response rate was 13.3%
  - 5) Concurrent deletion of PTEN (seen in about 50% of GBM) has been shown to be one mechanism of resistance.<sup>97</sup>
  - 6) **Currently the NCCN Guidelines® do not discuss EGFR-directed therapy for EGFR mutated or amplified gliomas.**<sup>85</sup> Numerous clinical trials assessing monoclonal antibodies and immunoconjugates, as well as irreversible EGFR-directed tyrosine kinase inhibitors are ongoing.

## 2. Treatment<sup>85</sup>

- a. Grade 2 astrocytoma or oligodendroglioma
  - 1) Surgery: the goal is maximum safe resection and acquisition of tissue for diagnosis
  - 2) Radiation

- a) No consensus regarding the proper timing of postoperative radiation for low-grade gliomas and may be done either immediately after surgery or at the time of tumor progression.
- b) EORTC 22845 showed improved mPFS with early radiation (5.3 vs 3.4 years,  $p < 0.0001$ ) but there was no difference in overall survival (7.4 vs 7.2 years, respectively). Seizure control was better in the early radiation group, however.<sup>88</sup>

3) Chemotherapy:

- a) PCV: Procarbazine, lomustine (CCNU) and vincristine<sup>98</sup>

Drug	Dose	Route	Days Administered
Procarbazine	60 mg/m <sup>2</sup>	PO	Days 8-21
CCNU	110 mg/m <sup>2</sup>	PO	Day 1
Vincristine	1.4 mg/m <sup>2</sup> (maximum 2 mg)	IV	Days 8 and 29
Regimen is repeated every 8 weeks x 6 cycles			

- i. 251 patients with grade 2 gliomas who were < 40 years old and had subtotal resection or just biopsy and patients  $\geq$  40 years old who had undergone biopsy or resection of any tumor were randomized to radiation alone or radiation followed by 6 cycles of PCV.
  - ii. After 11.9 years of follow up, the patients who received radiation with chemotherapy had a longer median OS compared to the radiation alone group (13.3 vs 7.8 years, HR 0.59,  $p = 0.003$ ).
  - iii. 10-year PFS was 51% in the PCV group and 21% in the radiation alone group and 10-year OS was 60% and 40%, respectively as well.
  - iv. Patients with oligodendroglioma appeared to have the longest PFS and OS.
- b) Radiation followed by adjuvant PCV is an NCCN Guidelines® category 1 recommendation for patients with high risk disease (> 40 years of age or subtotal resection) or any patient in whom maximal safe resection is not feasible.<sup>85</sup>**
- 4) Low grade glioma subtypes (pilocytic astrocytoma, pilocytic xanthoastrocytoma, ganglioglioma)<sup>85</sup>
- a) There are specific subtypes of WHO Grade 1 gliomas that are more susceptible to targeted therapy
  - b) Pilocytic astrocytoma (PA), pilocytic xanthoastrocytoma (PXA), and gangliogliomas often have BRAF V600E mutation
    - i. Dabrafenib/trametinib or vemurafenib/cobimetinib are NCCN Guidelines® Category 2A recommendations

- ii. Patients with a BRAF fusion should NOT receive combination BRAF/MEK therapy, but are susceptible to the MEK inhibitor selumetinib, especially in the recurrent setting. Clinical trials are also assessing novel agents, including RAF inhibitors, for BRAF fusions.
    - iii. Subependymal giant cell astrocytoma (SEGA) are susceptible to mTOR inhibitors (specifically everolimus) and are used to decrease seizure frequency
- 5) Follow-up: MRI every 3-6 months x 5 years, then annually
- b. Grade 3 IDH-mutated Astrocytoma and Oligodendroglioma
  - 1) Surgery
    - a. Goals are to obtain tissue for a diagnosis, alleviate symptoms, improve overall survival and decrease the need for corticosteroids
    - b. Aggressive surgery with gross total resection improves overall survival, though grade 3 astrocytomas often diffusely infiltrate surrounding tissue and cross the midline, making gross total resection challenging
  - 2) Radiation: Fractionated external beam radiation after surgery is the standard of care for anaplastic astrocytomas (NCCN Guidelines® Category 1 recommendation).
  - 3) Chemotherapy
    - a. **For grade 3 oligodendrogliomas with co-deletion of 1p/19q, radiation and neoadjuvant or adjuvant PCV is the standard of care (NCCN Guidelines® Category 1 recommendation)<sup>85</sup>**
    - b. For grade 3 astrocytomas adjuvant temozolomide with radiation can be considered. Additionally, in patients with deferred radiation, temozolomide or PCV can also be considered. The optimal temozolomide duration of treatment for anaplastic astrocytomas is unknown.
  - 4) Salvage Treatment
    - a. Temozolomide is approved for the treatment of adults with anaplastic astrocytoma who have relapsed following treatment with a nitrosourea and procarbazine.
      - i. Dose is 150 mg/m<sup>2</sup>/day for 5 days for the first cycle and if tolerated, increased to 200 mg/m<sup>2</sup>/day for 5 days for subsequent cycles (28-day cycles).
      - ii. In a phase II study of 162 patients with anaplastic astrocytoma who had failed radiation therapy, patients received 200 mg/m<sup>2</sup>/day for the first 5 days of a 28-day cycle. PFS was 46% at 6 months and 24% had no disease progression at 12 months. The median PFS was 5.4 months. The median OS was 13.6 months (75% 6-month, 56% 12-month).<sup>99</sup>
    - b. Other chemotherapy options include lomustine or carmustine given alone or in combination as part of the PCV regimen, bevacizumab alone or with other chemotherapy agents, regorafenib, or carboplatin or etoposide alone.



- 5) Follow-up: MRI every 3-6 weeks after radiation, every 2-4 months x 2-3 years, then less frequently as indicated

B. Grade 4 Glioblastoma Multiforme (GBM), or IDH-wildtype Astrocytoma<sup>85</sup>

1. General

- i. GBM is the most common primary malignant brain tumor in adults and comprises 54% of all gliomas with peak incidence from age 45 to 65.
  - 1) Primary GBM occurs in older patients (mean age, 55 years)
  - 2) Secondary GBM occurs in younger patients (45 years of age or less)
- ii. IDH-wildtype grade 4 astrocytoma is known as a “molecular GBM” and has similar prognosis to GBM.
- iii. Primary and secondary GBM arise through different molecular pathways.
  - 2) Primary GBM is associated with a high rate of overexpression or mutation of EGFR, *p16* deletions, and PTEN mutations.
  - 3) Secondary GBM have genetic alterations involving the *p53* gene and overexpression of PDGFRA.

2. Treatment

a. Surgery

- 1) Goal is to obtain tissue for diagnosis and alleviate symptoms
- 2) Should be as extensive as possible while balancing quality of function and life.
- 3) Aggressive surgery is a favorable prognostic factor vs biopsy alone.
- 4) Placement of a carmustine (BCNU) wafer intra-operatively can be considered if frozen section diagnosis supports a high-grade glioma though it may impact enrollment in some clinical trials (NCCN Guidelines® Category 2B recommendation).<sup>85</sup> These biodegradable polymers containing BCNU placed at the time of initial surgical debulking have demonstrated a median survival of 13.8 months for the BCNU wafer-treated group and 11.6 months for the placebo-treated group (pP -value = 0.017).<sup>100</sup>

b. Radiation

- 1) Improves overall survival as compared with best supportive care alone
- 2) Standard adjuvant therapy is 60 Gy in 30 fractions; interstitial brachytherapy has been shown to be beneficial. No benefit to whole brain radiotherapy. Proton radiation can also be used if available mainly to spare critical structures. Typically used in spinal radiation.

c. Chemotherapy

- 1) The Blood Brain Barrier (BBB) is a significant obstacle to effective chemotherapy and restricts access to most chemotherapy. Therefore, agents which cross the BBB (nitrosoureas) have the highest activity in GBM.

- 2) There is no clear evidence of improved survival with altered routes (intra-arterial, disruption of BBB) of administration for patients with malignant glial tumors.
- 3) Temozolomide
  - a. Concurrent temozolomide with radiation followed by 6-monthly cycles of adjuvant temozolomide post-radiation has been shown to prolong survival in GBM.
    - i. Treatment with 75 mg/m<sup>2</sup> PO daily during radiation followed by a 4- week break, then 150-200 mg/m<sup>2</sup> PO daily x 5 every 28 days for 6 cycles improves 2- year survival from 10% (XRT alone) to 26% (XRT + temozolomide).
    - ii. Treatment with maintenance temozolomide after radiation beyond 6 cycles does not improve OS even for patients with MGMT promoter methylation.
      - (a) Concurrent temozolomide daily with radiation has been shown to cause lymphocytopenia with a risk for opportunistic infections. Routine prophylaxis of *Pneumocystis jiroveci* is recommended with oral trimethoprim-sulfamethoxazole, pentamidine, atovaquone or dapsone.<sup>101</sup>
  - b. Special circumstances:
    - i. MGMT-methylated tumors with age > 70 and/or Karnofsky performance score (KPS) < 60: Temozolomide alone
    - ii. MGMT-methylated tumors with age ≤ 70 and KPS ≥ 60: radiation with concurrent lomustine and temozolomide (NCCN Guidelines® Category 2B recommendation)
- 4) Alternating Electric Field Therapy
  - a) Also known as TTFields or tumor treating fields
  - b) In 2015, FDA approved a portable medical device that generates low-intensity (200 kHz) alternating electric fields to stop mitosis/cell division
  - c) EF-14 Trial<sup>102</sup>
    - a. Phase III trial of TTFields plus temozolomide (after chemoradiation) vs temozolomide alone
      - i. 210 patients included in TTFields vs 105 in temozolomide only
    - b. Patients in TTFields plus temozolomide arm had continuous treatment (>18 hours/day) via 4 transducer arrays placed on shaved scalp and connected to a portable medical device
    - c. Primary endpoint was progression- free survival
    - d. Median PFS was 7.1 months in TTFields vs 4.0 months in temozolomide only group (HR 0.62 [98.7% CI, 0.43-0.89], p = 0.001)
    - e. Median OS was 20.5 months in TTFields vs 15.6 months in temozolomide only group (HR 0.64 [99.4% CI, 0.42-0.98]; p = 0.004)
    - f. Addition of TTFields to temozolomide was not associated with any significant increase in systemic toxic effects compared with temozolomide only. The

exception was higher incidence of localized skin toxicity (due to transducer array reaction with skin). This was observed in 43% of patients, and grade 3 severe skin reaction in 2%. The incidence of seizures was almost identical between the two groups (7% vs 8%).

**Patient Case #5 (ARS question #6)**

**Correct answer is B.** Temozolomide with concurrent radiation followed by temozolomide maintenance. The standard of care for glioblastoma is adjuvant temozolomide 75 mg/m<sup>2</sup> PO daily during radiation followed by maintenance temozolomide 150-200 mg/m<sup>2</sup> PO daily x 5 days every 28 days for 6 cycles. This improves the 2-year overall survival rate by 16%. Patients with MGMT promoter methylation have improved outcomes compared with unmethylated MGMT promoter status. NCCN Guidelines® recommend the same regimen regardless of promoter status because these patients still derive benefit, albeit a smaller one. The patient does have EGFR amplification and the vIII mutation, however the presence of this alteration is not currently recommended as a biomarker to direct therapy given the lower responses with anti-EGFR therapies though clinical trials are enrolling. The PCV regimen may be used for low grade astrocytomas and oligoastrocytomas, but the patient has a glioblastoma and so this would not be recommended

- C. Recurrent Disease for grade 3 or 4 oligodendroglioma, astrocytoma and glioblastoma<sup>85</sup>
1. Pseudo-progression: radiation can cause additional BBB dysfunction and an increase in corticosteroid requirements. During the first 3 months following completion of radiation, scans may look worse when there is no actual tumor progression.
  2. There is currently no established second-line therapy for recurrent gliomas
  3. Local recurrence
    - a. Resectable Disease
      - 1) Surgical resection
      - 2) Systemic chemotherapy: Options include bevacizumab +/- chemotherapy, temozolomide, nitrosourea (lomustine and carmustine), PCV, regorafenib
      - 3) Re-irradiation: especially if there has been a long interval since the initial radiation and/or if there was a good prior response (NCCN Guidelines® category 2B recommendation)
      - 4) Consider alternating electric field therapy for glioblastoma (NCCN Guidelines® category 2B recommendation)
    - b. Unresectable Disease: palliative and best supportive therapy
  4. Diffuse or multi-site recurrence
    - a. Options include bevacizumab +/- chemotherapy, temozolomide, nitrosourea, PCV, regorafenib
    - b. In a non-comparative, 2-arm trial, the combination of every 2 week irinotecan (340 mg/m<sup>2</sup> IV with enzyme-inducing antiepileptic drugs (EIAEDs) or 125 mg/m<sup>2</sup> without EIAEDs) and bevacizumab (10mg/kg) demonstrated a 50.3% 6-month PFS while every 2 week bevacizumab

(10mg/kg) alone demonstrated a 42.6% 6-month PFS ( $p < 0.0001$ ).<sup>103</sup> Median overall survival was 8.7 months and 9.2 months respectively.

- 1) Although there was no demonstrated OS benefit, there was a symptomatic benefit (mainly due to decreased cerebral edema) and allows patients to decrease systemic steroids.
- 2) Irinotecan is no longer included in the guidelines, however, bevacizumab may be combined with other chemotherapeutic agents to decrease overall steroid use.

c. REGOMA phase II trial<sup>104</sup>

- 1) 114 patients with relapsed GBM were randomized 1:1 to regorafenib 160 mg (3 weeks on, 1 week off) or lomustine 110 mg/m<sup>2</sup> (every 6 weeks)
- 2) mOS was 7.4 months for regorafenib vs 5.6 months for lomustine (HR 0.5, 95% CI 0.33-0.75,  $p = 0.0009$ )
- 3) 6-month PFS trended longer for regorafenib but was not statistically significant: 15.5% vs 8.3 % (HR 0.69, 95% CI 0.47-1.01,  $p = 0.051$ )
- 4) Grade 3-4 AE: 56% with regorafenib vs 40% with lomustine
  - a) Regorafenib common AEs: hand-foot skin reaction, increased lipase and increased bilirubin
  - b) Lomustine common AEs: decreased platelet count, decreased lymphocyte count, and neutropenia

D. Follow-up: MRI every 3-6 weeks after radiation, every 2-4 months x 2-3 years, then less frequently as indicated

## II. Primary Central Nervous System Lymphomas (PCNSL)<sup>85</sup>

### A. Biology/Pathology<sup>105</sup>

1. Pathologically, PCNSL is an aggressive B-cell non-Hodgkin's lymphoma arising without systemic disease in 95% of cases. The majority of cases are BCL-2 and BCL-6 positive and CD138 negative.
2. It involves the brain parenchyma in > 90%, leptomeninges in up to 30% and ocular involvement in 10-20% of cases. More than half of the cases have multi-focal disease.
3. Virtually all PCNSL seen in immunocompromised patients have evidence of Epstein-Barr virus infection

### B. Treatment<sup>85</sup>

1. Immunocompetent
  - a. Surgery: The role of surgery is limited to biopsy to confirm diagnosis.
  - b. Radiotherapy
    - 1) Whole brain radiotherapy (WBRT) is insufficient for tumor control and is associated with a high rate of neurotoxicity, particularly in those > 60 years.

- 2) Methotrexate-based chemotherapy plus WBRT improves response rates and survival over WBRT alone, but controlled trials comparing the combination to chemotherapy alone are lacking.
- c. Induction Chemotherapy
- 1) Should be considered for every patient with good performance status ( $KPS \geq 40$ ) and adequate renal function (Creatinine Clearance  $> 50$  mL/min).
  - 2) Corticosteroids should be avoided prior to confirming diagnosis. Dexamethasone induces an objective response in up to 40% of patients; however the effectiveness diminishes as the disease progresses and is usually short-lived.
  - 3) High dose methotrexate (HD-MTX)  $\geq 3.5$  g/m<sup>2</sup> is the single most active drug in PCNSL. The two NCCN® preferred regimens for first line therapy include RMPV and RMT (see below). They have not been compared head-to-head.
    - a. Methotrexate + rituximab, procarbazine, and vincristine (RMPV)<sup>106</sup>
      - i.) RMPV + consolidation therapy (cytarabine) followed by ASCT
      - ii.) MTX dose was 3.5 mg/m<sup>2</sup>
      - iii.) 2-year OS was 81%, and 2 year PFS was (79%).
    - b. Methotrexate + rituximab and temozolomide (RMT) – CALGB 50202<sup>107</sup>
      - i.) RMT + consolidation therapy (etoposide + cytarabine) with or without whole brain radiation
      - ii.) MTX dose was 8 g/m<sup>2</sup>
      - iii.) CR rate with RMT was 66%, 2-year PFS was 57%; 2-year OS was 70%
  - 4) The addition of rituximab to combination chemotherapy has been shown to improve response rates and long-term disease control while causing minimal neurotoxicity. Rituximab 500 mg/m<sup>2</sup> with each cycle of methotrexate, procarbazine and vincristine (R-MPV) followed by radiation and cytarabine resulted in a 60% complete response rate, 2-year PFS of 77% and 3-year OS of 87%.<sup>108</sup>
- d. Consolidation therapy
- a. High-dose chemotherapy with stem cell rescue
  - b. High-dose cytarabine with or without etoposide
- e. Relapsed or refractory disease (no preferred regimen)
- a. Intrathecal methotrexate, rituximab, or cytarabine
  - b. Lenalidomide +/- rituximab
  - c. Ibrutinib (560 mg or 840 mg daily)<sup>109-111</sup>
  - d. Re-treat with high-dose methotrexate (+/- rituximab and ibrutinib)
  - e. High-dose cytarabine
  - f. Temozolomide +/- rituximab

- g. Pemetrexed<sup>112</sup>
- h. Pomalidomide<sup>113</sup>
- i. High-dose chemotherapy with stem cell rescue

2. Treatment Considerations in immunosuppressed Patients

- a. Solid organ transplant - an occasional spontaneous remission can occur when the immunosuppressive medications are reduced or discontinued. Therefore, tapering of immunosuppressants should be attempted when feasible in collaboration with solid organ transplant service.
- b. HIV/AIDS patients - disease occurs at a late stage and have a very poor prognosis. Initiation of highly active antiretroviral therapy is highly encouraged. Modification of therapy or growth factor support is recommended for treatment.

## SUGGESTED READINGS

1. Chow LQM. Head and Neck Cancer. N Engl J Med 2020;382:60-72.  
<https://www.nejm.org/doi/full/10.1056/NEJMra1715715>
2. Brown TJ and Gupta A. Management of Cancer Therapy – Associated oral mucositis. JCO Oncol Pract. 2020;16(3):103-109. <https://ascopubs.org/doi/pdf/10.1200/JOP.19.00652>
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma. V.2.2022, 5/5/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved.
4. Bible KC and Ryder M. Evolving molecular targeted therapies for advanced-stage thyroid cancers. Nat Rev Clin Oncol. 2016;13:403-416. <https://www.nature.com/articles/nrclinonc.2016.19.pdf> (**Note: this was paper was published prior to the approval of the RET inhibitors seliparitinib and pralsetinib, however provides an excellent discussion of each of the subtypes of thyroid cancer and the other approved therapies. The updated NCCN guidelines cited as #3 are a good supplement to this review for these updated therapies.**)
5. Lapointe S, Perry A, Butowski NA. Primary Brain Tumors in Adults. Lancet. 2018;392(10145):432-446. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(18\)30990-5/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30990-5/fulltext) (**Note: this paper was published before the updated 2021 WHO Classification for CNS Tumors, however continues to provide a concise and accurate review of treatment options**)

## REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancer, v.2.2022, 4/26/2022 © 2022 National Comprehensive Cancer Network, Inc 2020. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancer, v.2.2022, 4/26/2022 © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
2. U. S. Preventative Services Task Force (USPST): Final Recommendation Statement Oral Cancer: Screening. 2013
3. American Cancer Society: Oral Cavity and Oropharyngeal Cancer: Detection. 2018
4. Hong WK, Lippman SM, Itri LM, et al: Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 323:795-801, 1990
5. Khuri FR, Shin DM: Head and neck cancer chemoprevention gets a shot in the arm. J Clin Oncol 26:345-7, 2008
6. Bairati I, Meyer F, Gelinas M, et al: A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. J Natl Cancer Inst 97:481-8, 2005
7. Marron M, Boffetta P, Zhang ZF, et al: Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. Int J Epidemiol 39:182-96, 2010
8. Gillison ML, Zhang Q, Jordan R, et al: Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol 30:2102-11, 2012
9. Hayes DN, Van Waes C, Seiwert TY: Genetic Landscape of Human Papillomavirus-Associated Head and Neck Cancer and Comparison to Tobacco-Related Tumors. J Clin Oncol 33:3227-34, 2015
10. Ang KK, Harris J, Wheeler R, et al: Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24-35, 2010
11. Chan KCA, Woo JKS, King A, et al: Analysis of Plasma Epstein-Barr Virus DNA to Screen for Nasopharyngeal Cancer. N Engl J Med 377:513-522, 2017

12. Bernier J, Cooper JS, Pajak TF, et al: Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 27:843-50, 2005
13. Bernier J, Dommenege C, Ozsahin M, et al: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 350:1945-52, 2004
14. Posner MR, Herschock DM, Blajman CR, et al: Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 357:1705-15, 2007
15. Lorch JH, Goloubeva O, Haddad RI, et al: Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. *Lancet Oncol* 12:153-9, 2011
16. Haddad R, O'Neill A, Rabinowits G, et al: Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol* 14:257-64, 2013
17. Cohen EE, Karrison TG, Kocherginsky M, et al: Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol* 32:2735-43, 2014
18. Zhang L, Huang Y, Hong S, et al: Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet* 388:1883-1892, 2016
19. Noronha V, Joshi A, Patil VM, et al: Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. *J Clin Oncol* 36:1064-1072, 2018
20. Mohamed A, Twardy B, Zordok MA, et al: Concurrent chemoradiotherapy with weekly versus triweekly cisplatin in locally advanced squamous cell carcinoma of the head and neck: Comparative analysis. *Head Neck* 41:1490-1498, 2019
21. Bourhis J, Sire C, Graff P, et al: Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol* 13:145-53, 2012
22. Pignon JP, Bourhis J, Dommenege C, et al: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 355:949-55, 2000
23. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 354:567-78, 2006
24. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 11:21-8, 2010
25. Mehanna H, Robinson M, Hartley A, et al: Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet* 393:51-60, 2019
26. Gillison ML, Trotti AM, Harris J, et al: Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 393:40-50, 2019
27. Gebre-Medhin M, Brun E, Engström P, et al: ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer. *J Clin Oncol* 39:38-47, 2021
28. J M: LBA5 - Primary results of the phase III KEYNOTE-412 study: Pembrolizumab (pembro) with chemoradiation therapy (CRT) vs. placebo plus CRT for locally advanced head and neck squamous cell carcinoma (HNSCC). *Ann Oncol* 33:S808-S869, 2022
29. Lee NY, Ferris RL, Psyrri A, et al: Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 22:450-462, 2021
30. Burtneess B, Harrington KJ, Greil R, et al: Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 394:1915-1928, 2019



31. Rischin DH, Greil R, et al. : Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma. *J Clin Oncol* 37:abstr 6000, 2019
32. Vermorken JB, Mesia R, Rivera F, et al: Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 359:1116-27, 2008
33. Ferris RL, Blumenschein G, Jr., Fayette J, et al: Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*, 2016
34. Seiwert TY, Burtneß B, Mehra R, et al: Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 17:956-65, 2016
35. Chow LQ, Haddad R, Gupta S, et al: Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. *J Clin Oncol*, 2016
36. Cohen EEW, Soulières D, Le Tourneau C, et al: Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* 393:156-167, 2019
37. Nekhlyudov L, Lacchetti C, Davis NB, et al: Head and Neck Cancer Survivorship Care Guideline: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Cancer Society Guideline. *J Clin Oncol* 35:1606-1621, 2017
38. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care, v.1.2022, 3/8/2022 © 2022 National Comprehensive Cancer Network, Inc 2020. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care, v.1.2022, 3/8/2022© 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
39. Tuca A, Jimenez-Fonseca P, Gascon P: Clinical evaluation and optimal management of cancer cachexia. *Crit Rev Oncol Hematol* 88:625-36, 2013
40. Fearon K, Arends J, Baracos V: Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol* 10:90-9, 2013
41. Balstad TR, Solheim TS, Strasser F, et al: Dietary treatment of weight loss in patients with advanced cancer and cachexia: a systematic literature review. *Crit Rev Oncol Hematol* 91:210-21, 2014
42. Mantovani G, Madeddu C: Cancer cachexia: medical management. *Support Care Cancer* 18:1-9, 2010
43. Ruiz Garcia V, Lopez-Briz E, Carbonell Sanchis R, et al: Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev*:Cd004310, 2013
44. Jatoi A, Windschitl HE, Loprinzi CL, et al: Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 20:567-73, 2002
45. Strasser F, Luftner D, Possinger K, et al: Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol* 24:3394-400, 2006
46. Del Fabbro E, Dev R, Hui D, et al: Effects of melatonin on appetite and other symptoms in patients with advanced cancer and cachexia: a double-blind placebo-controlled trial. *J Clin Oncol* 31:1271-6, 2013
47. Brown TJ, Gupta A: Management of Cancer Therapy-Associated Oral Mucositis. *JCO Oncol Pract* 16:103-109, 2020
48. Elad S, Cheng KKF, Lalla RV, et al: MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 126:4423-4431, 2020
49. Lalla RV, Bowen J, Barasch A, et al: MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 120:1453-61, 2014

50. Sonis ST, Elting LS, Keefe D, et al: Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 100:1995-2025, 2004
51. Clarkson JE, Worthington HV, Furness S, et al: Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev*:Cd001973, 2010
52. Keefe DM, Gibson RJ: Mucosal injury from targeted anti-cancer therapy. *Support Care Cancer* 15:483-90, 2007
53. Hensley ML, Hagerty KL, Kewalramani T, et al: American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 27:127-45, 2009
54. Lalla RV, Saunders DP, Peterson DE: Chemotherapy or radiation-induced oral mucositis. *Dent Clin North Am* 58:341-9, 2014
55. Leenstra JL, Miller RC, Qin R, et al: Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). *J Clin Oncol* 32:1571-7, 2014
56. Rugo HS, Seneviratne L, Beck JT, et al: Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncol* 18:654-662, 2017
57. Jensen SB, Pedersen AM, Vissink A, et al: A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. *Support Care Cancer* 18:1061-79, 2010
58. Bhide SA, Miah AB, Harrington KJ, et al: Radiation-induced xerostomia: pathophysiology, prevention and treatment. *Clin Oncol (R Coll Radiol)* 21:737-44, 2009
59. Mercadante V, Jensen SB, Smith DK, et al: Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies: ISOO/MASCC/ASCO Guideline. *J Clin Oncol* 39:2825-2843, 2021
60. Andersen BL, Rowland JH, Somerfield MR: Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an american society of clinical oncology guideline adaptation. *J Oncol Pract* 11:133-4, 2015
61. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Survivorship, v.1.2022, 3/30/2022 © 2022 National Comprehensive Cancer Network, Inc 2020. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Survivorship, v.1.2022, 3/30/2022© 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
62. Mehta RD, Roth AJ: Psychiatric considerations in the oncology setting. *CA Cancer J Clin* 65:300-14, 2015
63. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Smoking Cessation, v.1.2022, 4/4/2022 © 2022 National Comprehensive Cancer Network, Inc 2020. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Smoking Cessation, v.1.2022, 4/4/2022 © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
64. Borges S, Desta Z, Jin Y, et al: Composite functional genetic and comedication CYP2D6 activity score in predicting tamoxifen drug exposure among breast cancer patients. *J Clin Pharmacol* 50:450-8, 2010
65. National Center for Chronic Disease P, Health Promotion Office on S, Health: Reports of the Surgeon General, The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Atlanta (GA), Centers for Disease Control and Prevention (US), 2014
66. Ebbert JO, Hughes JR, West RJ, et al: Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *Jama* 313:687-94, 2015

67. Anthenelli RM, Benowitz NL, West R, et al: Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 387:2507-20, 2016
68. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Cancer, v.3.2022, 11/1/2022 © 2022 National Comprehensive Cancer Network, Inc 2020. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Cancer, v.2.2022, 5/5/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
69. Bible KC, Ryder M: Evolving molecularly targeted therapies for advanced-stage thyroid cancers. *Nat Rev Clin Oncol* 13:403-16, 2016
70. Fagin JA, Wells SA, Jr.: Biologic and Clinical Perspectives on Thyroid Cancer. *N Engl J Med* 375:1054-67, 2016
71. Rowland KJ, Moley JF: Hereditary thyroid cancer syndromes and genetic testing. *J Surg Oncol* 111:51-60, 2015
72. Yamashita S, Suzuki S: Risk of thyroid cancer after the Fukushima nuclear power plant accident. *Respir Investig* 51:128-33, 2013
73. Mulligan LM: RET revisited: expanding the oncogenic portfolio. *Nat Rev Cancer* 14:173-86, 2014
74. Bibbins-Domingo K, Grossman DC, Curry SJ, et al: Screening for Thyroid Cancer: US Preventive Services Task Force Recommendation Statement. *Jama* 317:1882-1887, 2017
75. Brose MS, Nutting CM, Jarzab B, et al: Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 384:319-28, 2014
76. Schlumberger M, Tahara M, Wirth LJ, et al: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 372:621-30, 2015
77. Brose MS, Robinson B, Sherman SI, et al: Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 22:1126-1138, 2021
78. Wells SA, Jr., Robinson BG, Gagel RF, et al: Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 30:134-41, 2012
79. Elisei R, Schlumberger MJ, Muller SP, et al: Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 31:3639-46, 2013
80. Wirth LJ, Sherman E, Robinson B, et al: Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. *N Engl J Med* 383:825-835, 2020
81. Subbiah V, Hu MI, Wirth LJ, et al: Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. *Lancet Diabetes Endocrinol* 9:491-501, 2021
82. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600–Mutant Anaplastic Thyroid Cancer. *Journal of Clinical Oncology* 36:7-13, 2018
83. Viola D, Valerio L, Molinaro E, et al: Treatment of advanced thyroid cancer with targeted therapies: ten years of experience. *Endocr Relat Cancer* 23:R185-205, 2016
84. Groen AH, Klein Hesselink MS, Plukker JT, et al: Additional value of a high sensitive thyroglobulin assay in the follow-up of patients with differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)*, 2016
85. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers, v.2.2022, 9/29/2022 © 2022 National Comprehensive Cancer Network, Inc 2020. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers, v.2.2022, 9/29/2022 © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN

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86. Louis DN, Perry A, Wesseling P, et al: The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 23:1231-1251, 2021
87. Mawrin C, Chung C, Preusser M: Biology and clinical management challenges in meningioma. *Am Soc Clin Oncol Educ Book*:e106-15, 2015
88. van den Bent MJ, Afra D, de Witte O, et al: Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 366:985-90, 2005
89. Kloosterhof NK, Bralten LB, Dubbink HJ, et al: Isocitrate dehydrogenase-1 mutations: a fundamentally new understanding of diffuse glioma? *Lancet Oncol* 12:83-91, 2011
90. Houillier C, Wang X, Kaloshi G, et al: IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. *Neurology* 75:1560-6, 2010
91. Shirahata M, Ono T, Stichel D, et al: Novel, improved grading system(s) for IDH-mutant astrocytic gliomas. *Acta Neuropathol* 136:153-166, 2018
92. Hegi ME, Diserens AC, Gorlia T, et al: MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 352:997-1003, 2005
93. Hegi ME, Diserens AC, Godard S, et al: Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin Cancer Res* 10:1871-4, 2004
94. Eskilsson E, Røsland GV, Solecki G, et al: EGFR heterogeneity and implications for therapeutic intervention in glioblastoma. *Neuro Oncol* 20:743-752, 2018
95. Huang PH, Xu AM, White FM: Oncogenic EGFR signaling networks in glioma. *Sci Signal* 2:re6, 2009
96. Cardona AF, Jaramillo-Velásquez D, Ruiz-Patiño A, et al: Efficacy of osimertinib plus bevacizumab in glioblastoma patients with simultaneous EGFR amplification and EGFRvIII mutation. *J Neurooncol* 154:353-364, 2021
97. Mellinghoff IK, Wang MY, Vivanco I, et al: Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. *N Engl J Med* 353:2012-24, 2005
98. Buckner JC, Shaw EG, Pugh SL, et al: Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. *N Engl J Med* 374:1344-55, 2016
99. Yung WK, Prados MD, Yaya-Tur R, et al: Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. *J Clin Oncol* 17:2762-71, 1999
100. Westphal M, Ram Z, Riddle V, et al: Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 148:269-75; discussion 275, 2006
101. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352:987-96, 2005
102. Stupp R, Taillibert S, Kanner AA, et al: Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. *Jama* 314:2535-43, 2015
103. Friedman HS, Prados MD, Wen PY, et al: Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 27:4733-40, 2009
104. Lombardi G, De Salvo GL, Brandes AA, et al: Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet Oncol* 20:110-119, 2019
105. Batchelor T, Loeffler JS: Primary CNS lymphoma. *J Clin Oncol* 24:1281-8, 2006
106. Omuro A, Correa DD, DeAngelis LM, et al: R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. *Blood* 125:1403-10, 2015
107. Rubenstein JL, Hsi ED, Johnson JL, et al: Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol* 31:3061-8, 2013
108. Morris PG, Correa DD, Yahalom J, et al: Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol* 31:3971-9, 2013

109. Chamoun K, Choquet S, Boyle E, et al: Ibrutinib monotherapy in relapsed/refractory CNS lymphoma: A retrospective case series. *Neurology* 88:101-102, 2017
110. Grommes C, Pastore A, Palaskas N, et al: Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma. *Cancer Discov* 7:1018-1029, 2017
111. Grommes C, Tang SS, Wolfe J, et al: Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. *Blood* 133:436-445, 2019
112. Raizer JJ, Rademaker A, Evens AM, et al: Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer* 118:3743-8, 2012
113. Tun HW, Johnston PB, DeAngelis LM, et al: Phase 1 study of pomalidomide and dexamethasone for relapsed/refractory primary CNS or vitreoretinal lymphoma. *Blood* 132:2240-2248, 2018

## **LUNG CANCER**

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### **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with lung cancer.
2. Select relevant information and guidance for the public regarding lung cancer-related issues (e.g., risk factors, prevention, screening).
3. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with pharmacotherapy for lung cancer.

**Patient Case #1:**

MD is a 69-year-old retired nurse who is at her annual wellness visit with her primary care provider. Her provider discusses lung cancer screening options with MD.

MD started smoking at age 20 and quit smoking at age 42. She smoked 1 pack per day at the time when she quit.

**Is MD a candidate for lung cancer screening based on the NCCN® Lung Cancer Screening Guidelines?**

- A. Yes, she is a candidate for an annual chest X-ray
- B. Yes, she is a candidate for an annual chest CT
- C. No, she stopped smoking
- D. D. No, because she smoked < 2 packs per day

**1. Molecular Etiology/Pathogenesis of Non-Small Cell Lung Cancer/Testing Methodologies<sup>1-4</sup>**

- A. KRAS and epidermal growth factor receptor (EGFR) (HER-1, erb-B1)
  - 1. KRAS mutations in adenocarcinoma are strongly associated with smokers<sup>5</sup>
    - a. Overall frequency in NSCLC = 10-30%
    - b. KRAS is a G-protein with intrinsic GTPase activity, and activating mutations result in unregulated signaling through the MAP/ERK pathway.
    - c. Mutations in KRAS (proto-oncogene) are most commonly at codon 12, although other mutations can be seen in NSCLC.
    - d. Presence of a KRAS point mutation G12C is associated with responsiveness to the oral KRAS G12C inhibitor, sotorasib, which is specific for this mutation and can be used for subsequent therapy. Responsiveness to this inhibitor has not been prospectively evaluated with mutations other than KRAS G12C.
    - e. Predicts primary resistance to EGFR tyrosine kinase inhibitors (TKIs)<sup>6</sup>
    - f. Overlapping targetable alterations is low thus the presence of a known activating mutation in KRAS predicts for patients who are unlikely to benefit from further molecular testing.
  - 2. EGFR mutations activate the MAPK (RAS-RAF-MEK-ERK) pathway, as well as other oncogenic pathways, leading to increased cell proliferation, motility, and invasion.
    - a. Overall frequency in NSCLC = 10-15%
    - b. Generally occurs in females > males, Asian ethnicity and light or never smokers. However, these characteristics should not take the place of molecular testing.
    - c. The most common mutations in EGFR (exon 19 deletions, and L858R point mutation in exon 21) are associated with responsiveness to oral EGFR tyrosine kinase inhibitor (TKI) therapy.
      - 1) Less commonly observed alterations in EGFR include exon 19 insertions, L861Q, G719X, S768I are also associated with responsiveness to EGFR TKI therapy, although the number of patients studied is low.

- d. EGFR exon 20 mutations are a heterogeneous group and response to targeted therapy require knowledge of the specific alteration.
    - 1) The T790M mutation has been found in approximately 60% of patients that develop resistance to erlotinib, gefitinib or afatinib<sup>7</sup> and it may also occur without TKI-based therapy.<sup>8,9</sup>
      - a) Most common EGFR resistance mechanism (50-60%)
      - b) Can be present at diagnosis, if found genetic counseling and possible germline genetic testing is warranted
    - 2) EGFR exon 20 alterations are made of both in-frame duplication or insertion mutations and typically occur between amino acids 763-774.
      - a) Generally associated with lack of response to EGFR TKI therapy with the following exceptions:
        1. A763\_Y764insFQEA is associated with TKI therapy sensitivity
        2. A763\_Y764insLQEA may be associated with TKI therapy sensitivity
      - b) It is best to further clarify EGFR exon 20 insertions found on some assays as the sequence found may have additional therapy options. Some evidence suggests that insertions closer to the amino acid 763 position could be more sensitive to EGFR TKIs while those closer to 770 are less responsive.
      - c) Presence of EGFR exon 20 insertions/duplications is associated with responsiveness to specific targeted therapy agents (ie. amivantamab, mobocertinib).
  - e. Real-time PCR, Sanger sequencing, and next generation sequencing (NGS) are the most commonly used methods for examining EGFR mutation status.
  - f. Testing for EGFR gene mutations is recommended with patients on diagnostic biopsy or surgical resection so results are available for adjuvant treatment decisions with stage IIB-IIIa or high-risk stage IB-IIa as well as metastatic nonsquamous NSCLC. (NCCN® Category 1)
  - g. Testing for EGFR gene mutations should be considered in squamous cell NSCLC.<sup>10</sup>
  3. KRAS and EGFR mutations are mutually exclusive outside of the setting of acquired resistance.<sup>11</sup>
- B. Anaplastic Lymphoma Kinase (ALK) Rearrangement
1. Overall frequency in NSCLC of 4 – 8%
  2. Inversion in chromosome 2 that links the 5' end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3' end of the anaplastic lymphoma kinase<sup>12,13</sup>
  3. Results in fusion oncogene EML4-ALK, which is an independent driver of cancer cell proliferation
  4. This leads to activation of downstream signaling pathways (through the RAS pathway) and inhibition of apoptosis.
  5. Clinical features include adenocarcinoma histology (97%), no/light smoking history, younger age (median age of ALK + patients = 52 years)<sup>14</sup>



6. FISH testing for ALK rearrangement was the first testing method used. IHC can be used and has an FDA-approved IHC test (ALK [D5F3] CDx Assay) to detect ALK without requiring confirmation by FISH.<sup>15</sup> Next generation sequencing methods can be used to detect ALK fusions, real-time PCR can be used however it is unlikely to detect fusions with novel partners.
  7. Testing for ALK rearrangements is recommended with patients found to have metastatic nonsquamous NSCLC. (NCCN<sup>®</sup> Category 1)
- C. *ROS1* Rearrangement
1. Overall frequency in NSCLC = 1-2%
  2. The *ROS1* oncogene encodes a tyrosine kinase related to ALK.<sup>16</sup>
  3. Rearrangement leads to fusion of the portion of *ROS1* that includes the tyrosine kinase domain with 1 of 12 different partner proteins. Fusion kinases are constitutively active which drives cellular transformation.<sup>17</sup>
  4. Clinical features include adenocarcinoma histology and no/light smoking history.<sup>18</sup>
  5. Numerous NGS methods can detect *ROS1* fusions, although DNA-based NGS may under-detect *ROS1* fusions and RNA-based testing is preferred over DNA.
  6. NCCN<sup>®</sup> guidelines recommend testing for *ROS1* gene rearrangements prior to first line therapy in the metastatic setting for NSCLC
- D. *BRAF V600E*<sup>19,20</sup>
1. *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) *V600E*: most common of the *BRAF* mutations
    - a. Other mutations in *BRAF* are observed in NSCLC, the impact of those mutations on therapy selection is not well understood at this time. These include *BRAF* class II and class III mutations for which clinical trials with novel RAF and/or ERK1/2 inhibitors are enrolling.
  2. Occurs in 1-2% of patients with lung adenocarcinoma who are typically current or former smokers.<sup>21</sup>
  3. Does not generally overlap with *EGFR* mutations or *ALK* rearrangements.
  4. Real-time PCR, Sanger sequencing, and NGS are most commonly used for examining *BRAF* mutation status.
  5. Testing for *BRAF* mutations prior to first line therapy in the metastatic setting for NSCLC is recommended (NCCN Category 2A), but no testing is recommended for SCLC.<sup>4,22</sup>
- E. *NTRK* (neurotrophic tyrosine receptor kinase) gene fusions<sup>4</sup>
1. Numerous fusion partners have been identified
  2. Presence of an oncogenic fusion is associated with responsiveness to NTRK-directed therapy (i.e. entrectinib or larotrectinib). (Please see the pharmacogenomics module for a more detailed discussion).
  3. No specific clinicopathologic features identified

4. Point mutations outside of the acquired resistance setting are generally non-activating and have not been studied in association with targeted therapy.
  5. FISH, IHC, PCR and NGS are used to detect NTRK1/2/3 gene fusions however false negatives may occur
  6. Testing for this rearrangement would be suggested for advanced/metastatic non-squamous cell carcinoma and considered for squamous cell carcinoma
- F. Mesenchymal-epithelial transition (MET) exon 14 skipping variants<sup>4</sup>
1. Presence of MET exon 14 skipping mutation is associated with responsiveness to oral MET targeted therapy
  2. More frequently observed in older women who are nonsmokers<sup>23</sup>
  3. A broad range of molecular alterations lead to MET exon 14 skipping
  4. NGS is the primary method of detection; RNA-based NGS is demonstrating improvement in detection. IHC is not a method for detection of MET exon 14 skipping mutations.
  5. NCCN<sup>®</sup> guidelines recommend testing for MET exon 14 skipping mutation in the advanced/metastatic NSCLC patient population.
- G. Rearranged during transfection (RET) gene rearrangements<sup>4</sup>
1. RET is a receptor tyrosine kinase which can be rearranged in NSCLC. Common fusion partners include KIF5B, NCOA4, and CCDC6; however many other partners have been identified.
  2. Presence of pathogenic RET rearrangement is associated with responsiveness of oral RET targeted therapy, regardless of the fusion partner.
  3. Identified in 1-2% of patients with NSCLC and greater prevalence in adenocarcinoma. European studies demonstrated both smokers and nonsmokers may have RET rearrangements.<sup>24</sup>
  4. NGS testing has high specificity and RNA-based NGS is preferred compared to DNA-based NGS for fusion detection.
  5. NCCN<sup>®</sup> guidelines recommend testing for RET rearrangements in the advanced/metastatic NSCLC patient population.
- H. ERBB2 (HER2) mutations
1. ERBB2 (HER2) exon 20 mutations occur in approximately 3% of patients (median age of 62 years) with advanced nonsquamous NSCLC.
  2. Patients tend to be never smokers and female.
  3. There seems to be a higher incidence of brain metastases than those with other actionable mutations.
  4. NCCN<sup>®</sup> guidelines recommend all patients with metastatic nonsquamous NSCLC are tested for ERBB2 (HER2) mutations, and testing should be considered in patients with metastatic squamous NSCLC.<sup>4</sup>
- I. PD-L1 (program cell death-ligand 1) Expression Levels<sup>25</sup>
1. PD-L1 binds to the PD-1 receptors found on activated cytotoxic T-cells

2. IHC testing for PD-L1 expression is recommended before first-line treatment in patients with metastatic NSCLC. (NCCN® Category 1)
    - a. Testing for PD-L1 expression is not recommended for SCLC at this time.
  3. Patients with oncogenic drivers can have elevated PD-L1 expression; however, treatment with targeted therapy takes precedence over treatment with an immune checkpoint inhibitor.
  4. Positivity of PD-L1 expression is variable and unique IHC assays have been developed for each of the PD-1 and PD-L1 inhibitors currently on the market.
- J. Emerging Biomarkers
1. High-level MET amplification may have available therapies with activity against the driver.

#### Molecular Targets for Analysis in NSCLC

	Recommended	Consider
Nonsquamous histology	EGFR*, ALK*, ROS1, BRAF, KRAS, NTRK1/2/3, MET exon 14 skipping, RET  PD-L1*	
Squamous cell carcinoma	PD-L1*	EGFR, ALK, ROS1, BRAF, KRAS, NTRK1/2/3, MET exon 14 skipping, RET
Testing should be conducted as part of a broad molecular profiling		

**\*NCCN Category 1 Recommendation**

- K. Other genetic mutations:

#### Other Genetic Mutations in Lung Cancer<sup>6-8,11,15</sup>

	Small Cell Lung Cancer (SCLC)	Non-Small Cell Lung Cancer (NSCLC)
<b>Oncogenes</b>		
	MYC family overexpression	<i>c-myc</i>
	BCL2	<i>c-met</i>
	<i>c-kit</i>	<i>BCL2</i> (12 – 25%)
		<i>HER2 (ERBB2)</i>
<b>Tumor Suppressor Genes (inactivated)</b>		
	<i>p53</i> (75-90%)	<i>p53</i>
	<i>RB</i> (100%)	<i>RB</i>
	<i>PTEN</i>	<i>p16<sup>INK4a</sup></i>
<b>Other Genetic Changes</b>		
Deletion of 3p	> 90%	50%
Telomerase activation	90%	80%
DNA repair genes		High ERCC1 expression: ↑ survival
Hypermethylation	Present	Present

## 2. Prevention and Screening<sup>26-28</sup>

### A. Prevention

1. No known effective method of chemoprevention at this time.<sup>29</sup>
  - a. None of the phase 3 trials with  $\beta$ -carotene, retinol, 13-cis-retinoic acid,  $\alpha$ -tocopherol, N-acetylcysteine, acetylsalicylic acid, or selenium have demonstrated beneficial and reproducible results.
2. Smoking cessation – decreases risk of second primary cancer, improves tolerance and possible response to treatment (Please see the Head/neck, Thyroid and CNS module for more detailed discussion on smoking cessation)

### B. Screening

1. Prevention (smoking cessation) is preferred over screening.
2. Patients with NSCLC have a 1-2% risk per year of developing a second primary lung cancer. Patients with SCLC have a 2-14% risk per year of developing a second primary lung cancer.<sup>30</sup>
3. Chest X-ray (CXR) and spiral CT are not recommended for routine screening of the general population.
4. PET
  - a. Following up positive CT scan findings with a PET scan appears to be useful and may minimize unnecessary invasive procedures for benign lesions.<sup>31</sup>
5. National Lung Screening Trial (NLST)<sup>32</sup>
  - a. 2002 to 2004 – randomized 53,454 patients ages 55-74 at high risk ( $\geq 30$  pack year smoking history, and if a former smoker, had quit within the last 15 years) to CXR versus low dose helical CT annually through the end of 2009.
    - 1) Primary endpoint was lung cancer mortality between the two screening groups
    - 2) Results: deaths due to lung cancer - CT 247/100,000 person- years versus CXR 309/100,000 person-years. (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23)
      - a) Achieved primary outcome of 20% fewer lung cancer deaths in those screened with CT (CI 6.8 to 26.7; P=0.004); All-cause mortality reduced by 6.7% with CT (CI 1.2 – 13.6 ; P=0.02); Positive screens – 24.2% with CT versus 6.9% with CXR.
    - 3) Challenges of applying this data to practice:
      - a) False positives – 96.4% with CT, 94.5% with CXR
      - b) Evaluations of cost effectiveness are ongoing
    - 4) Number needed to screen to prevent one death = 320 in CT arm
  - b. Median follow-up of 11.3 years for incidence and 12.3 years for mortality confirmed the primary endpoint was maintained at with similar number needed to screen at 303 in the CT

arm. There was no overall increase in lung cancer incidence in the CT arm compared to the CXR arm.<sup>33</sup>

6. The Dutch-Belgian lung-cancer screening trials (Netherlands-Leuvens Longkanker Screenings Onderzoek (NELSON Trial))<sup>34</sup>
  - a. Randomized 15,789 patients at high risk of lung cancer based on age and smoking history
  - b. 85% Male, age 50-74 years, and currently smoked or quit smoking within the last 10 years
  - c. Evaluated 4 rounds of low-dose CT compared to no screening
  - d. At 10 years of follow-up, NELSON demonstrated a reduction in lung cancer mortality in males of 24%, reduction in females was 33%.
  - e. Number needed to screen to prevent one lung cancer death was 130 over 10 years of follow-up.

#### Summary of Guidelines for Lung Cancer Screening

	Patient Criteria	Screening Recommendation
U.S. Preventive Services Task Force (Grade B) <sup>28,35</sup>	Adults aged 50-80 years and ≥ 20 pack-year smoking history and currently smoke or have quit within the past 15 years	Annual low dose CT <sup>a</sup>
NCCN <sup>®</sup> Lung Cancer Screening Recommendations <sup>27</sup>	High Risk <sup>b</sup> <ul style="list-style-type: none"> <li>Age ≥ 50 years and ≥ 20 pack-year history of smoking</li> </ul>	Annual low dose CT <sup>c,d</sup> (NCCN Category 1)
	Low risk <sup>b</sup> <ul style="list-style-type: none"> <li>Age &lt; 50 years and/or &lt; 20 pack-year history of smoking</li> </ul>	Not recommended

<sup>a</sup> Discontinue screening if a patient has not smoked for 15 years, develops a life-limiting health issue, or does not have ability/willingness to have curative lung surgery

<sup>b</sup> Risk Assessment: Complete a risk assessment including smoking history, radon and occupational exposure, cancer history, family history of lung cancer in first-degree relatives, disease history (COPD or pulmonary fibrosis) and smoking exposure (second-hand smoke).

<sup>c</sup> In candidates for screening, shared patient/provider decision-making is recommended, including a discussion of benefits/risks.

<sup>d</sup> Patients not eligible for lung screening would include patients with symptoms of lung cancer, previous lung cancer, or functional status and/or comorbidity that would prohibit curative intent treatment. Curative intent treatment includes surgery, stereotactic body radiation therapy or ablation.

7. Summary
  - a. Screening impacts lung cancer survival, and to date CXR, regular spiral CT, and PET scans have not consistently improved mortality. Annual low dose CT scans in patients similar to those evaluated in the NLST data may be employed at qualified centers in patients where cost is not an issue.<sup>36</sup>

**Follow Up Patient Case #1**

The correct answer is B.

MD quit smoking and she should be commended for her decision to stop smoking and continue smoking cessation. The risk of lung cancer decreases over time after smoking cessation.

MD is also a candidate for annual screening for lung cancer with CT based on the NCCN<sup>®</sup> guideline criteria. She is greater than 50 years of age and has a greater than 20 pack year history of smoking at 22 pack-year history. Chest X-rays are not recommended as screening strategies and she would meet NCCN<sup>®</sup> guideline screening recommendations.

**Patient Case #2:**

SJ is a 72-year-old man in the emergency room.

**HPI:** SJ's family brings him to the ED because he is disoriented. His family reports he received azithromycin for bronchitis 2 weeks ago, hasn't been eating, and has experienced a 15-pound unintentional weight loss in the last 3 weeks.

**PMH:** Hypertension

**FH/SH:** Smoked two packs a day for 20 years, recently decreased to ½ a pack per day in the last month. Social alcohol use.

**Physical Exam:** Wt: 72 kg Ht: 165 cm ECOG performance status 1

Normal except for:

General: Confused

Neck: Extensive lymphadenopathy

Lung: Normal respiratory effort, speaking in full sentences.  
(+) Rhonchi with expiratory wheezes.

Neuro: Alert and oriented x 2

<b>Laboratory:</b>	Na 126	Cl 104	WBC 6.5
	K 4.6	BUN 28	ANC 3.4
	SCr 1.5	Bilirubin 1.2	Platelets 238
	ALT 68	AST 45	
	CrCL (using C-G) 45 mL/min		

CT abdomen/pelvis/chest further reveals 3.3 x 3.2 x 4.6 cm right lower lobe mass, extensive lymphadenopathy throughout the neck and chest as well as innumerable liver metastases. He undergoes a brain MRI which is negative for metastatic lesions. Based on the CT findings, a lung biopsy was performed and pathology results were conclusive for small cell lung cancer. He has **extensive stage SCLC** due to the presence of extensive lymphadenopathy within the neck as well as innumerable liver metastases.

**Which treatment option is most appropriate for HN at this time?**

- A. Cisplatin 75 mg/m<sup>2</sup> IV Day 1 and etoposide 120 mg/m<sup>2</sup> IV Days 1-3 Q 21 days x 4 cycles with radiation (70 Gy)
- B. Cisplatin 75 mg/m<sup>2</sup> IV Day 1 and etoposide 100 mg/m<sup>2</sup> IV Days 1-3 Q 21 days x 4-6 cycles
- C. Carboplatin AUC 5 IV Day 1, etoposide 100 mg/m<sup>2</sup> IV Days 1-3 and durvalumab 1500 mg IV Day 1 Q 28 days x 4 cycles followed by durvalumab 1500 mg IV Day 1 Q 28 days
- D. Carboplatin AUC 5 IV Day 1 and etoposide 75 mg/m<sup>2</sup> IV Days 1-3 and atezolizumab 1200 mg IV Day 1 Q 21 days x 4 cycles followed by atezolizumab 1200 mg IV Day 1 Q 21 days

### 3. Treatment

#### A. Small cell lung cancer<sup>37,38</sup>

##### 1. General points

- a. Very sensitive to radiation and chemotherapy
- b. Systemic chemotherapy is the backbone of treatment at all stages in eligible patients.
- c. Surgery only has a limited role
  - 1) Option in T1-2 (stage I-IIA) disease without mediastinal pathology (<5% of patients)
    - a) Select patients with T3 (based on size), NO SCLC may also be considered for surgery
  - 2) Preferred operation: Lobectomy with mediastinal lymph node dissection
- d. Staging via the Veterans Administration (VA) stage as well as AJCC TNM staging is adopted by the NCCN SCLC Panel.
  - 1) Limited stage – disease confined to the ipsilateral hemithorax (safely encompassed within a radiation field)
  - 2) Extensive stage – disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases
- e. Overall 5 year survival: ~5%
  - 1) Limited Stage: 10-13%
  - 2) Extensive Stage: 1-2%

##### 2. Limited stage

- a. Treatment: concurrent chemoradiotherapy
  - 1) Cisplatin-etoposide with concurrent radiation has the best supporting clinical data (NCCN<sup>®</sup> category 1).<sup>38</sup> If a patient is not able to tolerate cisplatin-based therapy (e.g. poor renal function, inability to tolerate fluids, SIADH) carboplatin may be substituted for cisplatin.
    - a) Preferred, NCCN Category 1 Recommendations:
      1. Cisplatin 60 mg/m<sup>2</sup> IV D1, etoposide 120 mg/m<sup>2</sup> IV D1-3 Q21-28 days x 4 cycles or cisplatin 75 mg/m<sup>2</sup> IV D1, etoposide 100 mg/m<sup>2</sup> IV D1-3 Q21-28 days x 4 cycles **WITH radiation** <sup>38,39</sup>
    - b) Other Recommended Regimens, NCCN Recommendations:
      1. Cisplatin 25 mg/m<sup>2</sup> IV D1-3, etoposide 100 mg/m<sup>2</sup> D1-3 Q21-28 days x 4 cycles **WITH radiation**
    - c) Caution with low sodium (SIADH paraneoplastic syndrome). Cisplatin requires aggressive hydration to prevent nephrotoxicity. SIADH necessitates fluid restriction to prevent further reduction in sodium.<sup>40</sup>
      1. Can utilize carboplatin in this situation, and other situations when cisplatin is contraindicated



- i. Carboplatin AUC 5-6 IV D1, etoposide 100 mg/m<sup>2</sup> IV D1-3 Q21-28 days x 4 cycles **WITH radiation** (Other Recommended Regimen, NCCN Recommendation)
  - 2) Four cycles of chemotherapy are recommended. Maintenance therapy has not shown any improvement in disease-free survival or overall survival (OS).
  - 3) Thoracic radiotherapy
    - a) Should begin early in the course of treatment, preferably with cycle 1 or 2.
    - b) Radiation schedule:
      1. Randomized, phase III European CONVERT trial as well as CALGB 30610/RTOG 0538 did not demonstrate superiority of 66 Gy (Once daily) in 6.5 weeks or 70 Gy (Once daily) in 7 weeks over 45 Gy (BID) in 3 weeks, but overall survival and toxicity were comparable.<sup>41</sup>
      2. Randomized, phase II trials suggest that higher dose accelerated radiation therapy of 60-65 Gy in 4-5 weeks given BID or daily fractionation may increase overall and progression-free survival compared to 45 Gy in 3 weeks in BID fractionation.<sup>42</sup>
  - 4) Prophylactic cranial irradiation (PCI) should be offered for patients attaining a CR or PR. (NCCN<sup>®</sup> Category 2A recommendation).
    1. A meta-analysis showed improved 3 year survival (15% vs 21%).<sup>43</sup>
    - b) PCI is not recommended for patients with a poor performance status or baseline impaired neurocognitive function
    - c) The benefit of PCI is unknown in patients who undergo complete resection for pathologic stage I-IIA SCLC. Consider PCI or brain MRI surveillance for NO.
    - d) Patients ≥ 60 years old have demonstrated increased cognitive decline after PCI. The risks and benefits should be discussed with older adults.
3. Extensive stage<sup>38,44</sup>
  - a. Median survival without treatment: 5 weeks
  - b. Rarely curable
  - c. Treatment: Cisplatin- or carboplatin-based combination chemotherapy for 4 cycles, additional 2 cycles may be given based on response and tolerability after 4 cycles of therapy<sup>38</sup>
    - 1) Option for cisplatin or carboplatin is based on a meta-analysis of 663 patients with 32% limited-stage and 68% extensive stage that demonstrated no significant difference in response rate (67% with cisplatin and 66% with carboplatin), progression-free survival (PFS) (5.5 months vs. 5.3 months) or OS (9.6 months vs. 9.4 months).<sup>45</sup>
    - 2) Cisplatin or carboplatin can be combined with either etoposide or irinotecan

- a) Two large phase 3 trials have compared irinotecan plus cisplatin to etoposide plus cisplatin and demonstrated no difference in response rate (RR) or OS.<sup>46,47</sup>
- b) A phase 3 trial of 220 patients demonstrated a slight improvement in median OS with irinotecan and carboplatin over etoposide and carboplatin in patients with extensive stage disease (8.5 months vs. 7.1 months,  $p = 0.04$ ).<sup>48</sup>

3) Role of immunotherapy with chemotherapy

	<b>IMpower 133<sup>49</sup></b>	<b>CASPIAN<sup>50,51</sup></b>
Eligibility	Untreated, extensive stage SCLC ECOG: 0-1 Treated, asymptomatic CNS metastases	Untreated, extensive stage SCLC WHO performance status score: 0-1 Treated, asymptomatic CNS metastases (stable off steroids and anticonvulsants for at least 1 month)
Treatment	Double-Blind, Placebo Controlled (1:1) <ul style="list-style-type: none"> <li>Carboplatin AUC 5 IV Day 1 and etoposide 100 mg/m<sup>2</sup> IV Days 1-3 and atezolizumab/placebo 1200 mg IV Day 1 every 21 days x 4 cycles, followed by atezolizumab/placebo 1200 mg IV day 1 every 21 days</li> </ul>	Randomized, open label (1:1:1) <p>Platinum-etoposide and durvalumab</p> <ul style="list-style-type: none"> <li>Carboplatin AUC 5-6 OR Cisplatin 75 – 80 mg/m<sup>2</sup> IV day 1 and etoposide 80 – 100 mg/m<sup>2</sup> IV days 1-3 and durvalumab 1500 mg IV day 1 every 21 days x 4 cycles, followed by Durvalumab 1500 mg IV day 1 every 28 days</li> </ul> <p>Platinum-etoposide</p> <ul style="list-style-type: none"> <li>Carboplatin AUC 5-6 OR Cisplatin 75 – 80 mg/m<sup>2</sup> IV day 1 and etoposide 80 – 100 mg/m<sup>2</sup> IV days 1-3 every 21 days x 6 cycles<sup>+</sup></li> </ul> <p><sup>+</sup> Patients could receive an additional 2 cycles (up to 6 cycles total) as well as PCI post chemotherapy at the investigators discretion</p> <p>Platinum-etoposide, durvalumab and tremelimumab</p> <ul style="list-style-type: none"> <li>Carboplatin AUC 5-6 OR Cisplatin 75 – 80 mg/m<sup>2</sup> IV day 1 and etoposide 80 – 100 mg/m<sup>2</sup> IV days 1-3 and durvalumab 1500 mg IV day 1 and tremelimumab 75 mg IV day 1 every 21 days x 4 cycles, followed by durvalumab 1500 mg IV day 1 and tremelimumab 75 mg IV day 1 every 28 days x 1, then durvalumab 1500 mg IV day 1 every 28 days (up to 5 doses of tremelimumab)</li> </ul>
Enrollment	N = 403	N = 805

		<ul style="list-style-type: none"> <li>• Durvalumab/Tremelimumab + Platinum-etoposide: 268</li> <li>• Durvalumab + Platinum-etoposide: 268</li> <li>• Platinum-Etoposide: 269</li> </ul>
Median PFS	5.2 months (atezolizumab) vs. 4.3 months (placebo) (HR: 0.77, p=0.02)	5.1 months (durvalumab) vs. 5.4 months (platinum-etoposide) (HR: 0.78, 95% CI: 0.65 – 0.94)
Median OS	<p>Intention to treat population: 12.3 months (atezolizumab) vs. 10.3 months (placebo) (HR: 0.7, p = 0.007)</p> <p>Median follow-up of 22.9 months<sup>52</sup>:</p> <ul style="list-style-type: none"> <li>• 18 month OS: 34% (atezolizumab) vs. 21% (placebo) patient were alive</li> </ul>	<p>Median follow-up of 25.1 months:</p> <p>Durvalumab + Platinum-etoposide compared to Platinum-etoposide: 12.9 months (durvalumab) vs. 10.5 months (platinum-etoposide) (HR: 0.75, p = 0.0032)</p> <p>Durvalumab/Tremelimumab + Platinum – etoposide compared to Platinum-etoposide: 10.4 months (durvalumab/tremelimumab) vs. 10.3 months (platinum-etoposide) (HR: 0.82, p = 0.045)</p> <p>Median follow-up of 39.4 months<sup>53</sup>:</p> <p>86% maturity</p> <p>Durvalumab + platinum-etoposide 36 month OS rate was 17.6% compared to 5.8% with platinum-etoposide</p> <p>Durvalumab/tremelimumab + platinum-etoposide demonstrated a 36 month OS rate of 15.3%</p>
Adverse Events	<p>Most common grade 3 or 4 adverse events: neutropenia, anemia, and decreased neutrophil count</p> <p>Deaths related to the trial regimen occurred in 3 (1.5%) of patients in the atezolizumab group and 3 (1.5%) in the placebo group</p>	<p>Most common grade 3 or 4 adverse events: Neutropenia and anemia</p> <p>Deaths related to the trial regimen occurred in 13 (5%) of patients in the durvalumab group and 15 (6%) in the platinum-etoposide group</p>
NCCN <sup>®</sup> Recommendation	Both atezolizumab 1200 mg and durvalumab 1500 mg containing regimens are Preferred, Category 1, NCCN <sup>®</sup> recommendation for first line treatment for extensive stage SCLC 4 Cycles of Carboplatin/Etoposide therapy is recommended, but some patients can receive up to 6 cycles depending on response/tolerability after 4 cycles	

d. Chest radiation therapy may have a role in the consolidation phase in patients with residual thoracic disease after a systemic therapy response.<sup>54</sup>

e. Cranial radiation:

- 1) **Brain metastases present:** Brain radiation should be given prior to chemotherapy in **symptomatic** patients and may initiate systemic therapy before brain radiation in **asymptomatic** patients.
  - a) Brain MRI / CT should be repeated every 2 cycles of systemic therapy until brain radiation therapy is initiated or systemic therapy is completed, whichever if first.
  - b) If brain metastases progress while on systemic therapy, brain radiation therapy should be initiated before completion of systemic therapy.
- 2) **Brain metastases absent:** prophylactic cranial irradiation (PCI) should be considered if a response is achieved in the chest (Category 2A recommendation) for limited stage.
  - a) EORTC randomized trial with extensive-stage SCLC with initial response demonstrated increased one year survival from 13% to 27% with PCI. However, no required imaging prior and no dose standardization or fractionization.<sup>55</sup>
  - b) Randomized, phase 3 trial in patients with no presence of brain metastases after response to initial chemotherapy. PCI was delivered as 25 Gy in 10 fractions or observation.<sup>56</sup>
    1. Median OS 11.6 months in PCI group vs. 13.7 months in observation group (HR 1.27, p = 0.094)
  - c) With conflicting data, NCCN recommendations are now for consideration for extensive stage disease.<sup>38</sup>
- 3) When administering PCI, consider adding memantine during and after radiation therapy
  - a) Found to decrease neurocognitive impairment following WBRT for brain metastasis
  - b) Dose used in RTOG 0614: week 1 (starting day 1 of WBRT), 5 mg each morning; week 2, 5 mg each morning and evening; week 3, 10 mg each morning and 5 mg each evening; and weeks 4-24, 10 mg each morning and evening<sup>57</sup>
- f. Prolonged chemotherapy (after 4-6 cycles) has not been associated with improved results
- g. Patients who have response to therapy with atezolizumab or durvalumab and chemotherapy should continue maintenance atezolizumab or durvalumab therapy after completion of 4 cycles of combination chemotherapy.
  - 1) Some patients may receive up to 6 cycles of immunotherapy and chemotherapy based on response and tolerability after 4 cycles before moving to maintenance immunotherapy.
- h. Commonly used chemotherapy regimens
  - 1) Three cytotoxic chemotherapy agents in a regimen is NOT superior to two<sup>58,59</sup>
  - 2) Each regimen delivered every 3-4 weeks, depending on counts and recovery

**Patient Case #2, Continued:**

The correct answer is D.

SJ does not have limited stage SCLC, where concurrent chemotherapy with radiation therapy would be the treatment of choice, so option A is incorrect. He should receive chemotherapy with immunotherapy followed by

immunotherapy maintenance because this is considered to be a category 1, preferred regimen in the NCCN Guidelines®, making options B incorrect. HN also has impaired kidney function with an estimated CrCL of 45 mL/min making cisplatin a less than optimal option in the extensive stage setting. Option C contains combination chemotherapy with immunotherapy, however the dose of etoposide should be adjusted for the patient's current kidney function of less than 50 mL/min warranting a 25% dose reduction, as well as the schedule is incorrect for the combination with chemotherapy and should be every 21 days followed by durvalumab 1500 mg IV day 1 every 28 days.

A carboplatin-based regimen was preferred due to the SIADH diagnosis and current kidney function. HN tolerated chemotherapy well after receiving appropriate antiemetics. No G-CSF was used. His SIADH improved with chemotherapy.

**Patient Case #2: continued**

SJ completed 4 cycles of chemoimmunotherapy and was restaged with a PET/CT, which showed stable disease. He proceeded with immunotherapy maintenance with atezolizumab every 21 days. He developed pneumonitis following his 6<sup>th</sup> cycle of atezolizumab and immunotherapy was stopped while continuing with regular CT scans for evaluation of disease progression.

4 months after stopping his immunotherapy treatment a routine CT scan shows stable disease in the lungs and liver but SJ shares in the office his balance is altered and has daily headaches. A brain MRI was obtained and found to have 4 lesions in his brain with localized edema surrounding the lesions.

**Given his most recent CT and Brain MRI, what is the most appropriate treatment for SJ at this time?**

- A. Refer to Radiation Oncology for possible stereotactic brain radiation and start etoposide
- B. Refer to Radiation Oncology for possible stereotactic brain radiation
- C. Lurbinectedin
- D. Carboplatin, etoposide, and durvalumab

**Selected Chemotherapy Regimens for the Treatment of Extensive Stage SCLC<sup>37,38,49</sup>**

Regimen	Agents and Duration
<b>NCCN® Recommendation: Preferred Regimens (Category 1 for all, unless otherwise specified)</b>	
Carboplatin + Etoposide + Atezolizumab	Carboplatin AUC 5 IV Day 1 plus Etoposide 100 mg/m <sup>2</sup> IV Day 1-3 plus Atezolizumab 1200 mg IV Day 1 Every 21 days x 4 cycles followed by Atezolizumab 1200 mg IV Day 1 Every 21 days Or Atezolizumab 1680 mg IV Day 1 (category 2A) Every 28 days
Carboplatin + Etoposide + Durvalumab	Carboplatin AUC 5-6 IV day 1 plus Etoposide 80 - 100 mg/m <sup>2</sup> IV Day 1-3 plus Durvalumab 1500 mg IV Day 1 Every 21 days x 4 cycles

	followed by Durvalumab 1500 mg IV Day 1 Every 28 days
Cisplatin + Etoposide + Durvalumab	Cisplatin 75 – 80 mg/m <sup>2</sup> IV Day 1 plus Etoposide 80 – 100 mg/m <sup>2</sup> IV Day 1-3 plus Durvalumab 1500 mg IV Day 1 Every 21 days x 4 cycles followed by Durvalumab 1500 mg IV Day 1 Every 28 days
<b>NCCN<sup>®</sup> Recommendation: Other Recommended Regimens</b>	
Cisplatin + Etoposide (EP)	Cisplatin 75 mg/m <sup>2</sup> IV Day 1 plus Etoposide 100 mg/m <sup>2</sup> IV Day 1-3 <sup>60</sup>  Cisplatin 80 mg/m <sup>2</sup> IV Day 1 plus Etoposide 80 mg/m <sup>2</sup> IV Day 1-3 <sup>61</sup>  Cisplatin 25 mg/m <sup>2</sup> IV Day 1-3 plus Etoposide 100 mg/m <sup>2</sup> IV Day 1-3 <sup>62</sup>  Every 21 days
Carboplatin + Etoposide	Carboplatin AUC 5-6 IV Day 1 plus Etoposide 100 mg/m <sup>2</sup> IV Day 1-3 <sup>63</sup> Every 21 days
<b>NCCN<sup>®</sup> Recommendation: Useful in Certain Circumstances</b>	
Carboplatin + Irinotecan	Carboplatin AUC 5 IV Day 1 plus Irinotecan 50 mg/m <sup>2</sup> IV Day 1, 8, 15 <sup>64</sup>
Cisplatin + Irinotecan	Cisplatin 60 mg/m <sup>2</sup> IV Day 1 plus Irinotecan 60 mg/m <sup>2</sup> IV Day 1, 8, 15 <sup>47,60</sup> Every 28 days <ul style="list-style-type: none"> <li>Japanese study showed superiority to EP – confirmatory study in the US found no difference versus EP</li> </ul>
	Cisplatin 30 mg/m <sup>2</sup> IV Day 1, 8 plus Irinotecan 65 mg/m <sup>2</sup> IV Day 1, 8 <sup>47</sup> Every 21 days

**Patient Case #2, Continued:**

The correct answer is B.

Now SJ has recurrent extensive stage SCLC. SJ has symptomatic brain metastasis with stable systemic disease. The most appropriate treatment at this time would be to refer SJ to radiation oncology for evaluation for stereotactic radiation treatment and following with routine CT scans. The addition of etoposide chemotherapy at this time would not be recommended as his progression is localized at this time to the brain. The role of lurbinectedin is in patients with disease relapse less than or equal to 6 months and SJ has continued to have stable disease 6 months after immunotherapy discontinuation. Additionally, lurbinectedin was studied in patients without brain metastasis and given this patient has disease progression exclusively in the brain this therapy would not be appropriate. Restarting chemoimmunotherapy at this time would not be recommended given the only site of disease progression is in the brain.

**Patient Case #2, Continued:**

He returns 3 months after completing his stereotactic radiation to his 4 brain lesions and shares new complaints of cough, blood-tinged sputum, dyspnea, and chest pain. Upon work-up, it is determined that SJ has disease progression within the chest and liver. His ECOG performance status remains 1.

**What is the most appropriate treatment option for HN's recurrent extensive stage SCLC?**

- A. Pembrolizumab 400 mg IV Day 1 Q 28 days
- B. Carboplatin AUC 5 IV Day 1 and Etoposide 80 mg/m<sup>2</sup> IV Days 1-3 Q 21 days x 4 cycles
- C. Lurbinectedin 3.2 mg/m<sup>2</sup> IV Day 1 Q 21 days
- D. Topotecan 1.5 mg/m<sup>2</sup> PO Days 1-5 Q 21 days

4. Subsequent therapy<sup>38</sup>

- a. If disease-free interval is > 6 months recommend rechallenge with the initial treatment or similar platinum-based regimen
- b. If disease –free interval of at least 3 to 6 months may consider rechallenge with initial treatment or similar platinum-based regimen
- c. Clinical trial preferred

**SCLC Subsequent Systemic Therapy Options (PS 0-2)**

Preferred Regimens
Original regimen recommended if there has been a disease free interval of > 6 months, may consider rechallenge for patients with disease free interval of at least 3 to 6 months <i>- Use of immune checkpoint inhibitors is discouraged if there is progression on maintenance atezolizumab or durvalumab at time of relapse</i>
Other Recommended Regimens

Lurbinectedin
Topotecan PO or IV
Paclitaxel
Docetaxel
Irinotecan
Temozolomide
Cyclophosphamide / Doxorubicin / Vincristine (CAV)
Oral Etoposide
Vinorelbine
Gemcitabine
Nivolumab
Pembrolizumab
Bendamustine (Category 2B)

#### Examples of Single Agent Therapy for SCLC<sup>38,65-76</sup>

Agent	Dosing	Response Rates
Lurbinectedin <sup>77</sup>	3.2 mg/m <sup>2</sup> IV Day 1 every 21 days	35.2%
Topotecan <sup>65-67</sup>	1.5 mg/m <sup>2</sup> IV Days 1-5 or 2.3 mg/m <sup>2</sup> PO Days 1-5 every 21 days	17 to 23%
Irinotecan <sup>68</sup>	100 mg/m <sup>2</sup> IV weekly	16 to 24%
Gemcitabine <sup>69,70</sup>	1000 mg/m <sup>2</sup> IV Days 1, 8, and 15 every 28 days	14%
Docetaxel <sup>71</sup>	100 mg/m <sup>2</sup> IV every 21 days	25%
Paclitaxel <sup>78,79</sup>	175 mg/m <sup>2</sup> IV every 21 days 80 mg/m <sup>2</sup> IV weekly for 6 weeks followed by 2 week break	29% 24%
Vinorelbine <sup>72,73</sup>	25-30 mg/m <sup>2</sup> IV weekly	12.5 to 16%
Temozolomide <sup>+74,75</sup>	200 mg/m <sup>2</sup> PO daily for days 1- 5 every 28 days OR 75 mg/m <sup>2</sup> PO daily for 21 days every 28 days	12%  16%
Nivolumab <sup>80</sup>	240 mg IV Day 1 every 14 days 480 mg IV Day 1 every 28 days	11.6%
Pembrolizumab <sup>76</sup>	200 mg IV Day 1 every 21 days 400 mg IV Day 1 every 42 days	19.3%
Bendamustine <sup>81</sup> (NCCN <sup>®</sup> Category 2B)	120 mg/m <sup>2</sup> IV Day 1 and 2 every 21 days for 6 cycles	26%

<sup>+</sup> Beneficial specifically in patients with brain metastases and methylated O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT)

#### d. Topotecan vs CAV<sup>65</sup>



- 1) Second-line therapy for recurrent SCLC (N=211) identified topotecan IV had similar time to progression (13.3 weeks vs. 12.3 weeks) and median survival (25 vs. 24.7 weeks) as CAV (Cyclophosphamide 100 mg/m<sup>2</sup> IV, doxorubicin 45 mg/m<sup>2</sup> and vincristine 2 mg IV day 1 every 21 days).
  - 2) Topotecan produced palliative response more often for dyspnea, anorexia, hoarseness, and fatigue compared to CAV. Topotecan produced greater thrombocytopenia and anemia, while CAV had greater neutropenia.
- e. Oral topotecan<sup>66</sup>
- 1) Regimen of 2.3 mg/m<sup>2</sup> PO daily x 5 days Q21 days superior to best supportive care
  - 2) Median survival 26 vs. 13 weeks
  - 3) Median dose intensity achieved: 3.77 mg/m<sup>2</sup>/week
  - 4) Grade IV neutropenia = 32%
- f. Lurbinectedin<sup>77</sup>
- 1) A phase 2 basket trial, open-label, single-arm study of 105 patients with extensive stage SCLC, ECOG 0-2 with **absence of brain metastasis** and on or after platinum-based chemotherapy were treated with lurbinectedin
    - a) Lurbinectedin 3.2 mg/m<sup>2</sup> IV every 21 days until disease progression
    - b) Median follow-up 17.1 months
    - c) Primary endpoint: overall response by investigator assessment of 35.2% (37 patients)
    - d) Median duration of response was 5.3 months
    - e) Chemotherapy-free interval (≥ 90 days vs < 90 days)
      1. Response rate: 22% (95% CI, 11.2% - 37.1%) if the chemotherapy-free interval was < 90 days.
      2. Response rate: 45% (95%CI, 32.1% - 58.4%) if the chemotherapy-free interval was ≥ 90 days
    - f) Treatment-related adverse events (TRAEs): neutropenia (12% resulted in dose delays, and 16% resulted in dose reductions)
  - 2) Mechanism of Action:<sup>82</sup>
    - a) An alkylating agent and selective inhibitor of oncogenic transcription which preferentially binds to guanine residues in the minor groove of DNA. This leads to bends in the DNA helix and affects the activities of DNA binding proteins, including some transcription factors and DNA repair pathways.
  - 3) Indication & Dose:
    - a) Patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy
    - b) 3.2 mg/m<sup>2</sup> IV every 21 days, until disease progression

- 4) Toxicities:
  - a) Common: myelosuppression, fatigue, increased creatinine, increased alanine transferase, increased glucose, nausea, decreased appetite, musculoskeletal pain, decreased albumin, constipation, dyspnea, decreased sodium, increased aspartate aminotransferase, vomiting, cough, decreased magnesium, and diarrhea
- 5) Drug-Drug Interactions: Minor substrate of CYP3A4, avoid coadministration with strong or moderate CYP3A inducers and inhibitors
- 6) Chemotherapy-induced nausea/vomiting risk: Moderate
- g. Combined analysis of phase Ib (KEYNOTE-028) and phase 2 (KEYNOTE-158) reviewed activity of pembrolizumab in SCLC<sup>83</sup>
  - 1) N = 83 evaluable patients
  - 2) Response rate of = 19.3%, median OS = 7.7 months (95% CI, 5.2 – 10.1)
    - a) Response rates were higher in PD-L1 positive patients
  - 3) NCCN panel recommends pembrolizumab for patients with SCLC regardless of PD-L1 level as a category 2A recommendation.
- h. Combination regimens: should contain non-cross resistant agents (e.g., CAV if initially treated with EP)
  - 1) Nivolumab ± ipilimumab (Checkmate 032)<sup>80,84,85</sup>
    - a) Phase I/II open-label trial evaluating several cohorts. Based on results of the Phase 1 portion a randomized cohort was added to confirm activity of nivolumab vs. nivolumab/ipilimumab<sup>86</sup>
      1. Randomization was 3:2 to receive nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks.
        - i. Patients had to have disease progression after 1-2 prior chemotherapy regimens. 147 patients received nivolumab and 96 patients received nivolumab plus ipilimumab.
        - ii. Primary endpoint: ORR 11.6% in the nivolumab group vs. 21.9 % in the nivolumab/ipilimumab group (p=0.03)
        - iii. Median OS: 5.7 months with nivolumab vs. 4.7 months with nivolumab/ipilimumab
        - iv. TRAEs: 53.7% with nivolumab vs. 68.8% nivolumab/ipilimumab
          - a. Grade 3/4 TRAE: 12.9% nivolumab vs. 37.5% nivolumab/ipilimumab
    - b) ***Nivolumab provided a response in a subset of patients who had received prior therapy for recurrent SCLC. Nivolumab as a single agent is not FDA approved, however carries a NCCN Category 2A recommendation.***

- c) ***Nivolumab/ipilimumab significantly improved ORR however, the combination was associated with increased toxicity and the high response rate did NOT translate into longer PFS or OS.***
  - 1. ***Bristol Myers Squibb announcement shared that in consultation with the FDA, they have decided to withdraw the indication of nivolumab for treatment in patients with small cell lung cancer whose disease has progressed after platinum-based chemotherapy and at least one other line of therapy. Additional phase 3 trials failed to prove overall survival benefit. The regimen is not included in the current NCCN guidelines.***

**B. Other considerations**

- a. Trilaciclib or hematopoietic growth factors (CSFs) may be used as prophylactic options to decrease the incidence of chemotherapy-induced myelosuppression when administering platinum/etoposide +/- immunotherapy containing regimens or a topotecan-containing regimen for extensive stage SCLC.
- 1) Trilaciclib was evaluated in three randomized, double-blind, placebo-controlled studies in patients with extensive stage SCLC. (N=245 patients)
  - a) Patients who received trilaciclib prior to chemotherapy and atezolizumab demonstrated a statistically significant decrease in the mean duration of severe neutropenia in Cycle 1 (0 vs. 4 days;  $P < 0.0001$ ) and occurrence of severe neutropenia (1.9 % vs. 49.1 %;  $P < 0.0001$ )<sup>87</sup>
  - b) Patients who received trilaciclib prior to topotecan demonstrated a decrease in duration of severe neutropenia in cycle 1 (2 vs. 7 day; adjusted one-sided  $P < 0.0001$ ) and occurrence of severe neutropenia (40.6 % vs. 75.9 %); adjusted one-sided  $P = 0.016$ )<sup>88</sup>
  - c) Adverse effect profile:
    - 1. Grade 3 or 4 hematologic adverse events in patients receiving trilaciclib vs. placebo included neutropenia (32% vs. %), febrile neutropenia (3% vs. 9%), anemia (16% vs. 34%), thrombocytopenia (18% vs. 33%)
    - 2. Grade 3 or 4 non-hematologic adverse events in patients receiving trilaciclib vs. placebo included pneumonia (7% vs. 7%), hypophosphatemia (7% vs. 2%), and hypokalemia (6% vs. 3%).
  - d) Trilaciclib<sup>89</sup>
    - 1. Mechanism of Action: Highly-potent, selective, and reversible cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6). Through CDK4/6 inhibition, trilaciclib transiently induces hematopoietic stem and progenitor cell G1 cell cycle arrest, preventing the cells from proliferating in the presence of cytotoxic chemotherapy and resulting in myelosuppression
    - 2. Indication & Dose:
      - i. Kinase inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when given prior to

platinum/etoposide-containing regimen or toptotecan-containing regimen for extensive-stage SCLC

- ii. 240 mg/m<sup>2</sup> IV over 30 minutes completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered

3. Toxicities:

- i. Common: fatigue, hypocalcemia, hypokalemia, hypophosphatemia, AST elevations, headache, and pneumonia
- ii. Warnings/Precautions: Injection site reactions (including phlebitis and thrombophlebitis), hypersensitivity reaction, interstitial lung disease/pneumonitis, embryo-fetal toxicity

4. Drug-Drug Interactions: inhibitor of OCT2, MATE1 and MATE-2K

- b. CSFs are not recommended in patients receiving thoracic RT with chemotherapy. (NCCN Category 1 recommendation)<sup>90</sup>
  - c. Dose intensity: does not improve treatment outcomes.<sup>91</sup>
  - d. Management of elderly or severely debilitated patients
    - 1) These patients have a worse prognosis, which can be attributed to attenuated chemotherapy doses or increased rates of comorbid disease.
    - 2) Oral etoposide is not recommended as initial therapy: produces greater toxicity, poorer quality of life and shorter survival than traditional regimens.<sup>92</sup>
  - e. To date, no molecularly targeted agent has proven efficacious in SCLC.<sup>38</sup>
- C. Poorly differentiated Neuroendocrine tumors: Most treated similar to SCLC (with the exception of low grade pancreatic neuroendocrine tumors (PNET)). Can consider treatment with other agents in addition to cisplatin/etoposide including temozolomide, sunitinib, and everolimus.<sup>38</sup>

**Patient Case #2, Follow Up:**

The correct answer is B.

Pembrolizumab is incorrect as the dose/schedule is incorrect and should be either 200 mg every 21 days or 400 mg every 42 days. Additionally caution should be taken with resuming immunotherapy following a prior discontinuation of treatment secondary to pneumonitis with the initial treatment. Lurbinectedin is a treatment option for patients who relapse following initial treatment as another recommended regimen per the NCCN<sup>®</sup> guidelines. Given the patient's good performance status and length of response with initial platinum doublet therapy and no contraindications for use at this time it would be preferred to rechallenge with Carboplatin and Etoposide. Topotecan, both oral and intravenous formulations, is recommended as an other recommended regimen by NCCN guidelines for single agent therapy for relapsed disease that is platinum resistant and relapses less than or equal to 6 months following treatment, however the dose provided is for the IV route rather than the oral route and this patient's disease would be classified as platinum sensitive.

**Patient Case #3:**

EM is a 58-year-old woman with complaints of a persistent dry cough that has not improved with antibiotics and cough suppressants.

**HPI:** EM presented to her family practice physician 1 month ago with same complaints, treated for bronchitis with levofloxacin for 7 days.

**PMH:** Hypothyroidism

**FH/SH:** 10 pack-year smoking history, quit 20 years ago. Social alcohol use.

**Drug History:** NKDA, levothyroxine 88 mcg PO daily

**ECOG:** 0

**Laboratory:** Serum creatinine (SCr) 0.55

**Patient work-up:**

CXR: Left lower lobe mass

CT scan – chest 1.4 cm x 2.2 cm left lower lobe density

CT scan of abdomen, pelvis: negative

Brain MRI: negative

Bone scan: negative

CT guided biopsy of left lower lobe lung nodule revealed poorly differentiated non-small cell carcinoma, adenocarcinoma histology. Tumor tissue was negative for ALK rearrangements, EGFR pathogenic alterations and PD-L1 was 50%.

**Staging:**

T1bN1M0 (one positive ipsilateral hilar lymph node); **Stage IIA**

**Treatment:**

Curative intent resection

**Based on the data, which adjuvant treatment regimen would be most appropriate for FS?**

- A. Osimertinib for 3 years
- B. Nivolumab, Cisplatin and pemetrexed for 3 cycles
- C. Cisplatin and pemetrexed for 4 cycles, followed by atezolizumab for 1 year
- D. Carboplatin and paclitaxel for 4 cycles

D. Non-small cell lung cancer (NSCLC)<sup>4</sup>

1. Resectable (stages I, II, IIIA, IIIB)

- a. Surgery is the initial treatment of choice
- b. Radiation

- 1) Routine postoperative adjuvant radiation should be avoided in patients with stage I or II tumors with negative margins – the PORT meta-analysis demonstrated 21% higher relative risk of death.<sup>93</sup>

2) Adjuvant radiation in stage IIIA may confer a modest benefit.

c. Chemotherapy

1) Adjuvant cisplatin-based chemotherapy is the standard in resected stage II and IIIA and improves 5-year OS.<sup>94-97</sup>

2) Stage IB and IIA disease - chemotherapy can be considered as adjuvant therapy for high-risk patients including poorly differentiated tumors, vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement and unknown lymph node status.<sup>4</sup>

3) Carboplatin/paclitaxel, carboplatin/gemcitabine or carboplatin/pemetrexed can be considered for patients unable to tolerate cisplatin-based therapy.<sup>98-100</sup>

a) Pemetrexed only used for nonsquamous histology

4) EGFR mutation positive NSCLC (Stage IB – IIIA)

a) Osimertinib may be considered for patients with completely resected early-stage disease (Stage IB-IIIa) who received previous adjuvant chemotherapy or are ineligible for platinum-based chemotherapy. (NCCN® Category 2A Recommendation)

1. A phase 3 double-blind randomized trial evaluated osimertinib 80 mg PO daily vs. placebo for 3 years in patients who had complete resection of their early stage (Stage IB – IIIA) EGFR mutated NSCLC. (ADAURA Trial)<sup>101</sup>

i. N = 682 patients

ii. Osimertinib or placebo was continued for 3 years or until disease recurrence or until treatment discontinuation criterion was met.

iii. Median duration of total treatment exposure was 22.5 months (0-38 months) for osimertinib and 18.7 months (0-36 months) for placebo at time of analysis

iv. Primary endpoint: Disease free survival (DFS) (Stage II – IIIA)

a. Median DFS: Osimertinib arm was not reached at time of interim analysis vs. placebo was 20.4 months ( $p < 0.0001$ )

b. Maturity: 33% (osimertinib 11%, placebo 55%)

v. Secondary endpoint: DFS (Stage IB – IIIA), OS and safety

a. Median DFS: Osimertinib arm was not reached at time of interim analysis vs. 28.1 months ( $p < 0.0001$ )

b. Maturity: 29% (osimertinib 12%, placebo 46%)

### Adjuvant Chemotherapy Trials for Non-Small Cell Lung Cancer<sup>4</sup>

All regimens can be used for sequential chemotherapy-radiation.

Trial	# Patients	Stage	Adjuvant therapy	5 Year OS
NCCN® Preferred				
TREAT <sup>102,103</sup>	132	IB, IIA, IIB, pT3pN1 (5% only)	Cisplatin 75 mg/m <sup>2</sup> IV Day 1 Pemetrexed 500mg/m <sup>2</sup> IV Day 1 Q 21 days x 4 cycles <b>(NCCN® Recommended, Preferred (nonsquamous))</b>	3-year 75%
Perol <sup>104</sup>	Data extrapolated from Stage IIB/IV data		Cisplatin 75 mg/m <sup>2</sup> IV Day 1 Gemcitabine 1250 mg/m <sup>2</sup> IV Day 1, 8 Q 21 days x 4 cycles <b>(NCCN® Recommended, Preferred (squamous))</b>	
TAX 326 <sup>105</sup>	Data extrapolated from Stage IIB/IV data		Cisplatin 75 mg/m <sup>2</sup> IV Day 1 Docetaxel 75 mg/m <sup>2</sup> IV Day 1 Q 21 days x 4 cycles <b>(NCCN® Recommended, Preferred (squamous))</b>	
NCCN® Other Recommended				
IALT <sup>106</sup>	1867	I, II, III	Cisplatin-based (vindesine, vinblastine, etoposide, or vinorelbine partner)	44.5%
ANITA <sup>107</sup>	840	IB, II, IIIA	Cisplatin 100 mg/m <sup>2</sup> IV Day 1 Vinorelbine 30 mg/m <sup>2</sup> IV weekly Q 28 days x 4 cycles	51%
NCIC (JBR.10) <sup>108</sup>	482	IB, II	Cisplatin 50 mg/m <sup>2</sup> IV Days 1, 8 Vinorelbine 25 mg/m <sup>2</sup> IV weekly Q 28 days x 4 cycles	69%
NCCN® Useful in Certain Circumstances				
For patients with comorbidities or patients not able to tolerate cisplatin				
CALGB 9633 <sup>98</sup>	344	IB	Carboplatin AUC 6 IV Day 1 Paclitaxel 200 mg/m <sup>2</sup> IV Day 1 Q 21 x 4 cycles	60%
CJLSG 0503 <sup>99</sup>	20	IB, IIA, IIB, IIIA	Carboplatin AUC 5 IV Day 1 Gemcitabine 1000 mg/m <sup>2</sup> IV Day 1, 8 Q 21 days x 4 cycles	Not reported
Zhang <sup>100</sup>	82	II, IIIA	Carboplatin AUC 5 IV Day 1 Pemetrexed mg/m <sup>2</sup> IV Day 1 Q 21 days x 4 cycles (non-squamous histologies)	Not reported

IALT, International Adjuvant Lung Trial; LPI, Adjuvant Lung Project Italy ; ANITA, Adjuvant Navelbine International Trialist Association ; CALGB, Cancer and Leukemia Group B; NCIC, National Cancer Institute of Canada; CJLSG, Central Japan Lung Study Group

### **Patient Case #3 Continued**

The correct answer is C.

Adjuvant chemotherapy for stage II should be cisplatin-based. A carboplatin-based doublet would be appropriate in the palliative setting or in patients that are unable to tolerate cisplatin. Option D is incorrect based on the use of carboplatin, rather than cisplatin. Option B is incorrect as nivolumab in combination with chemotherapy is only approved for neoadjuvant treatment, not adjuvant treatment. Option A is also incorrect as osimertinib is only approved in the adjuvant setting for patients with EGFR (exon 19del, L858R) positive disease, EM is not EGFR positive. EM is a candidate for adjuvant chemotherapy and the use of cisplatin in combination with pemetrexed followed by atezolizumab would be most appropriate as the patient has PD-L1 of 50% which is  $\geq 1\%$ . Based on IMpower010 the addition of atezolizumab following adjuvant chemotherapy improved disease free survival.

- d. Initial and overall management of IIIA disease is controversial<sup>96,109</sup>
  - 1) Surgery, radiation, and chemotherapy have a potential role, sequence is debatable
  - 2) Minimal N2 disease may be resectable
  - 3) Unresectable stage IIIA should be treated according to the unresectable (stage IIIB, IV) section below.
  - 4) Neoadjuvant/induction chemotherapy and/or adjuvant chemotherapy with or without radiation.
    - a) Cisplatin-based therapy should be used as induction
    - b) Surgery is questionable in patients with persistent N2 disease after induction therapy
  - 5) Patients with resectable (tumors  $\geq 4$  cm or node positive disease) NSCLC can be considered for nivolumab plus platinum-doublet chemotherapy as neoadjuvant treatment based on preliminary clinical trial data and FDA approval.
    - a) A phase 3 randomized trial assessed neoadjuvant therapy with nivolumab plus platinum-doublet chemotherapy versus chemotherapy alone in resectable (tumors  $\geq 4$  cm or node positive) NSCLC. (CheckMate 816)<sup>110</sup>
      - 1. N=358 patients
      - 2. Nivolumab 360 mg IV and platinum-doublet every 3 weeks for 3 cycles
        - i. Platinum-doublet:
          - a. Any histology: Carboplatin AUC 5 or AUC 6 IV day 1 and paclitaxel 175 mg/m<sup>2</sup> or 200 mg/m<sup>2</sup> IV day 1
          - b. Non-squamous: Cisplatin 75 mg/m<sup>2</sup> IV and pemetrexed 500 mg/m<sup>2</sup> IV day 1
          - c. Squamous: Cisplatin 75 mg/m<sup>2</sup> IV and gemcitabine 1000 mg/m<sup>2</sup> or 1250 mg/m<sup>2</sup> IV days 1 and 8
      - 3. Median event free survival was 31.6 months with nivolumab/chemotherapy and 20.8 months with chemotherapy alone



4. Pathologic complete response occurred in 24% (95%CI, 18-31%) with nivolumab/chemotherapy compared to 2.2% (95%CI, 0.6 – 5.6%) with chemotherapy alone
  5. Treatment related adverse events were similar at 33.5% in the nivolumab/chemotherapy arm compared to 36.9% in the chemotherapy arm alone.
- b) Per NCCN guidelines, nivolumab in combination with platinum-doublet chemotherapy can be used for patients with resectable NSCLC in the neoadjuvant setting. If immunotherapy is used in the pre-operative setting, immunotherapy should not be used in the adjuvant setting.

**Summary of Cancer Care Ontario and ASCO Recommendations for Adjuvant Treatment<sup>111</sup>**

Stage	Chemotherapy	Radiotherapy (Only for patients with positive margins after resection)
IA	Not recommended	Not recommended
IB	Not recommended	Not recommended
IIA	Cisplatin-based regimen	Not recommended
IIB	Cisplatin-based regimen	Not recommended
IIIA	Cisplatin-based regimen	Not recommended – clinical trials ongoing

- 6) Immunotherapy: PD-L1  $\geq$  1% (Stage IIA – IIIA)
- a) Atezolizumab may be considered for patients with completely resected early-stage disease (Stage IIB-IIIa) who received previous adjuvant chemotherapy or are ineligible for platinum-based chemotherapy. Additionally, the guidelines recommend atezolizumab in high-risk stage IIA who received prior adjuvant chemotherapy with PD-L1  $>$  1% (NCCN<sup>®</sup> Category 2A Recommendation)
1. A phase 3 open-label randomized trial evaluated atezolizumab versus best supportive care (BSC) for 1 year (16 cycles) in patients who had complete resection of their early stage (Stage IB – IIIA) NSCLC. (IMpower010)<sup>112</sup>
    - i. N = 1280 patients
    - ii. Atezolizumab 1200 mg IV every 21 days for up to 1 year (16 cycles) was given following adjuvant chemotherapy with cisplatin and pemetrexed, docetaxel, or vinorelbine for 1-4 cycles.
    - iii. Median duration of follow-up was 32.8 months
    - iv. Primary endpoint: Investigator-assessed disease-free survival (DFS) in 3 populations
      - a. Stage II/IIIA with PD-L1 TC  $\geq$  1%: Atezolizumab arm was not reached at time of analysis compared to BSC of 35.3 months (HR: 0.66 (95%CI: 0.5 – 0.88; p = 0.004)

- b. All randomized Stage II – IIIA: Atezolizumab arm was 42.3 months compared to BSC of 35.3 months (HR: 0.79 (95%CI: 0.64 – 0.96; p = 0.02)
      - c. ITT population Stage IB-IIIA: Atezolizumab arm was not reached at time of analysis compared to BSC of 37.2 months (HR: 0.81 (95%CI: 0.67-0.99; p = 0.04)
    - v. Secondary endpoint:
      - a. OS in ITT population: OS data was immature with only 19% in the atezolizumab and 18% in the BSC group.
- 2. Unresectable (stage IIIB, IV)
  - a. Stage IIIB
    - 1) Combined modality<sup>4,94,96</sup>
      - a) Platinum-based chemotherapy + radiation, with goal of down staging for resection (category 1)
      - b) Duration of therapy unclear, but should not exceed 8 cycles
      - c) Concurrent versus sequential chemoradiation improved survival, but it is more toxic than sequential therapy
      - d) Radiation therapy can be used with curative intent in those that are medically inoperable with stage I-III

#### Chemoradiation Regimens for NSCLC<sup>4</sup>

Select NCCN <sup>®</sup> Chemotherapy Regimens
<b>NCCN<sup>®</sup> Preferred</b> <b>(Nonsquamous histologies)</b>
Carboplatin AUC 5 IV Day 1 Pemetrexed 500 mg/m <sup>2</sup> IV Day 1 every 21 days x 4 cycles radiation – 70 Gy +/- additional 4 cycles of pemetrexed 500 mg/m <sup>2</sup> IV Day 1 <sup>113</sup>
Cisplatin 75 mg/m <sup>2</sup> IV Day 1 Pemetrexed 500 mg/m <sup>2</sup> IV Day 1 every 21 days x 3 cycles radiation +/- additional 4 cycles of pemetrexed 500 mg/m <sup>2</sup> IV Day 1 every 21 days <sup>114</sup>
<b>NCCN<sup>®</sup> Preferred</b> <b>(All histologies)</b>
Paclitaxel 45-50 mg/m <sup>2</sup> IV weekly Carboplatin AUC 2 IV weekly radiation ± additional 2 cycles of Paclitaxel 200 mg/m <sup>2</sup> IV Day 1 and Carboplatin AUC 6 IV Day 1 every 21 days <sup>115</sup>
Cisplatin 50 mg/m <sup>2</sup> IV Days 1,8,29,36 Etoposide 50 mg/m <sup>2</sup> IV Days 1-5, 29-33 radiation – total 61 Gy <sup>116</sup>

#### 2) Consolidation therapy

##### a) PACIFIC Trial<sup>117,118</sup>

1. Randomized phase III trial comparing consolidation therapy with durvalumab 10 mg/kg IV every 2 weeks x 12 months vs. placebo in patients with unresectable stage III NSCLC (PS 0-1) who had not progressed after 2 or more cycles of definitive concurrent platinum-based chemoradiation.
2. Durvalumab started 1-42 days following concurrent chemoradiation.
3. 22.3% of patients had PD-L1 expression of ≥ 25%, 41% with < 25% expression and 36.7% had unknown PD-L1 status.
4. PFS was 17.2 months for durvalumab vs. 5.6 months for placebo (HR 0.52; 95% CI, 0.42-0.65, p < 0.001).
5. PFS benefit with durvalumab occurred irrespective of PD-L1 expression (HR 0.59 for PD-L1 < 25% and HR 0.41 for PD-L1 expression ≥ 25%)
6. Median time to death or distant metastasis was 28.3 months with durvalumab vs. 16.2 months with placebo (p < 0.001).
7. 24-month overall survival rate: 66.3% with durvalumab vs. 55.3% with placebo (p=0.005)
8. 4.8% of patients in the durvalumab group and 2.6% in the placebo group had trial discontinuation due to pneumonitis.

9. 3-year OS rates remained consistent with previously reported outcomes<sup>119</sup>

- i. Median OS was not reached with durvalumab vs. 29.1 months with placebo
- ii. 36-month OS rate: 57% with durvalumab vs. 43.5% with placebo

10. 5-year OS rates demonstrate a robust and sustained OS benefit<sup>120</sup>

- i. Median OS 47.5 months with durvalumab vs. 29.1 months with placebo
- ii. 60-month OS rate: 42.9% with durvalumab vs. 33.4% with placebo

**b) Durvalumab consolidation therapy for up to 12 months in patients with unresectable stage II / III, performance status 0-1 and no disease progression after 2 or more cycles of definitive chemoradiation is considered a NCCN® Category 1 recommendation for stage III disease and 2A recommendation for stage II disease.<sup>4</sup>**

- 1. If patients are receiving carboplatin/paclitaxel weekly with radiation and are using durvalumab, an additional 2 cycles of chemotherapy is NOT recommended

**Patient Case #4:**

DG is 73-year-old female (never smoker) that presents to the ED with a chronic cough and progressive shortness of breath.

**HPI:** Chest X-ray shows large spiculated mass in the right upper lobe suspicious for lung cancer

**Pathology:** consistent with NSCLC (adenocarcinoma)

**Based on the data given, which of the following mutations is most likely associated with DG's cancer and has the most appropriate first-line treatment for said mutation according to NCCN® guidelines?**

- A. EGFR : Afatinib
- B. ROS-1 : Alectinib
- C. ROS-1 : Capmatinib
- D. EGFR : Osimertinib

3. Stage IV 1<sup>st</sup> line Treatment Guiding Principles

- a. **Targeted therapy is preferred first line treatment for patients who are found to have targetable mutations, such as EGFR, ROS-1, and ALK. If no actionable mutations are found, then evaluate PD-L1 status for consideration of immunotherapy single-agent or in combination with systemic chemotherapy. Patients who have contraindications to immunotherapy should receive chemotherapy without immunotherapy in the first-line setting.**
- b. Principles of care: early supportive care with a formal palliative care team (N=151) has been shown to improve quality of life (QOL) (assessed by FACT-L (scale 0-136): 98 vs. 91.5, P=0.3), depression frequency (fewer depressive symptoms, 16% vs. 38%, P=0.01), and fewer

aggressive therapies at end of life (33% vs. 54%,  $P=0.05$ ), and was associated with a 2.7 month increase (11.6 vs. 8.9) in OS.<sup>121</sup>

- c. Meta-analyses demonstrate survival advantage for chemotherapy compared to best supportive care (6-8 week gain).<sup>122</sup>
  - d. One year survival increased by a mean of 16% (up to 40%) with use of chemotherapy.<sup>123</sup>
  - e. Treatment of stage IV NSCLC is cost-effective.<sup>124</sup>
  - f. PS 3-4: No benefit from therapy if no actionable mutation is present. Patients with actionable mutations, which include EGFR, ALK rearrangement, ROS1, NTRK, etc. may benefit from targeted mutation therapy.
  - g. Overall, optimal platinum-based regimen is unclear in most scenarios; optimal duration of therapy is 4-6 cycles. A randomized clinical trial of 1155 patients compared cisplatin + paclitaxel, gemcitabine + cisplatin, docetaxel + cisplatin and carboplatin + paclitaxel. Overall response rates (ORR) and OS were not statistically different between the arms indicating that carboplatin is not inferior to cisplatin and does have less toxicities.<sup>125</sup>
  - h. Patients with resected solitary brain metastases followed by brain radiation live longer and have an improved QOL compared to radiation alone.<sup>126</sup>
4. 1<sup>st</sup> line therapy options for stage IV metastatic NSCLC<sup>4,127</sup>
- a. Evaluate the patient's histology
    - 1) Non-squamous histology
      - a) Molecular testing is recommended
        - 1. NCCN<sup>®</sup> Category 1 testing: EGFR mutation, *ALK*
        - 2. Additional testing: *ROS1*, *KRAS*, *BRAF*, *MET* exon 14 skipping, *RET*, *NTRK1/2/3*
          - i. Broad molecular profiling
      - b) PD-L1 testing (NCCN<sup>®</sup> Category 1 recommendation)
    - 2) Squamous histology
      - a) PD-L1 testing (NCCN<sup>®</sup> Category 1 recommendation)
      - b) Molecular testing recommended
        - 1. Consider testing: *ALK*, *KRAS*, EGFR mutation, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET* exon 14 skipping, and *RET*
  - b. If a driver mutation is identified, initiation of targeted therapy is recommended. It is recommended to exhaust targeted therapy for the driver mutation before switching to cytotoxic chemotherapy options.
  - c. If a driver mutation is identified after initiation of cytotoxic chemotherapy, it is recommended to either complete the planned systemic therapy, (including maintenance therapy) or interruption of therapy to start targeted therapy can be considered. (NCCN<sup>®</sup> Category 2A)

**Patient Case #5:**

DM is a 37-year-old female (never smoker) that presents to the ED with progressive shortness of breath and overall feeling unwell. Two weeks ago she completed a half marathon with no issues. An infectious workup was completed and all results were negative. A CT scan was obtained and shows innumerable lung lesions and pleural effusion concerning for metastatic disease.

Pathology was obtained and she is found to have NSCLC, adenocarcinoma (EGFR mutation negative, ALK rearrangement positive, RET rearrangement negative, MET 14 skipping mutation negative, PD-L1 55%)

**Based on the data given, which of the following is the most appropriate first line treatment for DM and is matched with the appropriate adverse effect?**

- A. Lorlatinib : Acneiform Rash
- B. Crizotinib : Bradycardia
- C. Alectinib : Myalgias
- D. Brigatinib : Mood disorder

## EGFR Target-Driven Therapy for NSCLC

REGIMEN(S)	COMMENTS
<b>Preferred Recommendation (EGFR exon 19 del and L858R mutations)</b>	
1. Osimertinib 80 mg PO daily <sup>128,129</sup> (NCCN <sup>®</sup> category 1) <sup>4</sup>	<p>Osimertinib 80 mg daily vs. standard EGFR-TKI (gefitinib 250 mg daily or erlotinib 150 mg daily) (FLAURA)<sup>130</sup></p> <ul style="list-style-type: none"> <li>• Double-blind phase 3 trial of 556 patients with previously untreated EGFR mutation positive (exon 19 deletion or L858R) advanced NSCLC</li> <li>• Median PFS for osimertinib was 18.9 months vs. 10.2 months with standard EGFR therapy; HR 0.46, p = &lt; 0.001</li> <li>• ORR: 80% vs 76% (p=0.24)</li> <li>• Median duration of response: 17.2 months vs. 8.5 months</li> <li>• Median OS was 38.6 months (95% CI: 34.5 – 41.8) vs. 31.8 months with standard EGFR therapy (95% CI: 26.6 – 36) [HR for death, 0.8; 95% CI: 0.64 – 1; p = 0.046]<sup>131</sup></li> </ul>
<b>Other Recommended</b>	
2. Erlotinib 150 mg PO daily <sup>132</sup> (NCCN <sup>®</sup> category 1) <sup>4</sup>	<p>Erlotinib vs. chemotherapy in the first line treatment of advanced EGFR mutation-positive NSCLC (OPTIMAL): a multicenter, open-label, randomized, phase 3 study:</p> <ul style="list-style-type: none"> <li>• Median PFS was significantly longer in erlotinib-treated patients than in those on chemotherapy (13.1 [95% CI 10.58-16.53] vs 4.6 [4.21-5.42] months; HR 0.16, 95% CI 0.10-0.26; p&lt;0.0001).</li> </ul>
	<p>Erlotinib 150 mg daily vs. erlotinib 150 mg daily and carboplatin/paclitaxel<sup>133</sup></p> <ul style="list-style-type: none"> <li>• CALGB 30406 randomized patients to EGFR therapy vs combination EGFR therapy and chemotherapy</li> <li>• Median PFS erlotinib 5 months vs erlotinib with chemo 6.6 months; p = 0.1988</li> <li>• Addition of erlotinib to chemotherapy is not recommended</li> </ul>
3. Afatinib 40 mg PO daily <sup>134</sup> (NCCN <sup>®</sup> category 1) <sup>4</sup>	<p>Afatinib vs. cisplatin and pemetrexed in the first line setting for EGFR positive NSCLC</p> <ul style="list-style-type: none"> <li>• Median PFS on afatinib 11.1 months vs. 6.9 months on chemo (p = 0.001)</li> <li>• ORR = 55% (CR + PR) at 8 weeks.</li> <li>• Duration = 42-48 weeks</li> <li>• 1, 2 year survival = 74 and 54%</li> </ul>
	<p>Afatinib 40 mg PO daily vs. gefitinib 250 mg PO daily<sup>135</sup></p> <ul style="list-style-type: none"> <li>• Phase 2B trial</li> <li>• Median PFS for afatinib was 11 months vs. 10.9 months with gefitinib (HR 0.73, p= 0.017)</li> <li>• Deemed not clinically significant per NCCN</li> <li>• Serious treatment-related side effects afatinib 11% vs 4% gefitinib</li> </ul>

4. Gefitinib 250 mg PO daily <sup>136</sup> (NCCN <sup>®</sup> category 1) <sup>4</sup>	Phase IV study in Caucasian patients with EGFR-positive NSCLC <ul style="list-style-type: none"> <li>• ORR 69.8%</li> <li>• PFS 9.7 months</li> <li>• Median OS 19.2 Months</li> </ul>
	Gefitinib 250 mg PO daily vs. erlotinib 150 mg daily <sup>137</sup> <ul style="list-style-type: none"> <li>• Patients had previously been treated with chemotherapy.</li> <li>• Median PFS for gefitinib was 8.3 months and 10.0 months for erlotinib (HR 1.093; p = 0.424).</li> <li>• Grade 3/4 rash (gefitinib 2.2% vs erlotinib 18.1%)</li> </ul>
5. Dacomitinib 45 mg PO daily <sup>138,139</sup> (NCCN <sup>®</sup> Category 1) <sup>4</sup>	ARCHER 1050: Phase 3, open label trial of newly diagnosed NSCLC with EGFR mutation (exon 19 deletion or Leu858Arg substitution) Dacomitinib 45 mg PO daily vs. gefitinib 250 mg PO daily <ul style="list-style-type: none"> <li>• Median PFS for dacomitinib was 14.7 months vs. 9.2 months with gefitinib (HR 0.59, p &lt; 0.0001)</li> <li>• Median OS 34.1 months with dacomitinib vs. 26.8 months with gefitinib (HR 0.76, p = 0.044)</li> </ul>
6. Erlotinib 150 mg PO daily + Bevacizumab 15 mg/kg IV day 1 every 21 days (NCCN <sup>®</sup> Category 2A)	NEJ026: Phase 3 trial open-label of bevacizumab in combination with erlotinib vs. erlotinib alone in patients with advanced NSCLC and activating EGFR alteration across Japan <sup>140</sup> <ul style="list-style-type: none"> <li>• Median PFS for the combination was 16.9 months vs. 13.3 months with erlotinib alone (HR: 0.605, P = 0.016)</li> </ul>
7. Erlotinib 150 mg PO daily + Ramucirumab 10 mg/kg IV day 1 every 21 days(NCCN <sup>®</sup> Category 2A)	RELAY: Phase 3 evaluated ramucirumab in combination with erlotinib vs. erlotinib alone in patients with advanced NSCLC and sensitizing EGFR mutations <sup>141</sup> <ul style="list-style-type: none"> <li>• Median PFS for the combination was 19.4 months vs. 12.4 months with erlotinib alone (HR: 0.59, p &lt; 0.0001)</li> </ul>

REGIMEN(S)	COMMENTS
<b>Preferred Recommendation (EGFR S786I, L861Q, and/or G719X mutations)</b>	
1. Osimertinib 80 mg PO daily	KCSG-LU15-09: Phase 2 trial, assessing first-line therapy with osimertinib for patients with metastatic NSCLC and less common EGFR mutations, including S768I, L861Q, and G719X (N=37) <sup>142</sup> <ul style="list-style-type: none"> <li>• Median PFS for osimertinib was 8.2 months (95% CI, 5.9-10.5 months)</li> <li>• ORR 50% (18/36; 95% CI, 33 – 67%)</li> </ul>
2. Afatinib 40 mg PO daily	Post-hoc analysis of several LUX-Lung Trials (LUX-Lung 2, 3, and 6) assessed efficacy of afatinib for first line therapy with metastatic NSCLC found to have EGFR L861Q, G719X, and S768I mutations. <sup>143,144</sup> <ul style="list-style-type: none"> <li>• Median OS was 19.4 months (95% CI, 16.4 – 26.9)</li> <li>• ORR for patients with EGFR: <ul style="list-style-type: none"> <li>○ G719X: 77.8% (95% CI, 52.4 – 93.6%)</li> <li>○ S768I: 100% (95% CI, 63.1 – 100%)</li> <li>○ L861Q: 56% (95% CI, 29.9 – 80.2%)</li> </ul> </li> </ul>
<b>Other Recommended</b>	



3. Erlotinib 150 mg PO daily
4. Gefitinib 250 mg PO daily
5. Dacomitinib 45 mg PO daily

- 1) Subsequent Therapy targeted toward EGFR- positive NSCLC<sup>4</sup>
  - a) Continuation of erlotinib, gefitinib, osimertinib, dacomitinib, or afatinib and consider local therapy for patients with asymptomatic progression.
  - b) For patients who did not receive osimertinib in the first-line setting, recommend testing for T790M mutation at time of progression. If positive, osimertinib therapy is indicated. (Category 1 NCCN<sup>®</sup> Recommendation)
  - c) For patients with symptomatic progression, options include: continuing with an EGFR inhibitor, definitive local radiation therapy, switching to osimertinib if T790M mutation positive or switching to initial systemic chemotherapy option for patients with symptomatic progression with multiple lesions.
  - d) Use caution in patients who discontinue EGFR-based therapy as a flare phenomenon may occur indicating that continuation of an EGFR-based therapy is necessary
  - e) Afatinib with/Cetuximab<sup>145</sup>
    1. Phase Ib study of 126 patients resistant to erlotinib or/ gefitinib
      - i. ORR of 29%, 32% in T790M+ patients
      - ii. Median PFS – 4.7 months
  - f) Osimertinib<sup>146</sup>
    1. FDA-approved in T790M mutation positive for subsequent therapy
      - i. ORR of 61% for T790M positive and 21% for T790M negative
      - ii. Median PFS 9.6 months for T790M positive and 2.8 months in T790M negative
    2. Only indicated if osimertinib was not used in the first line setting
    3. AURA3 clinical trial randomized 419 patients with *EGFR T790M* positive disease to osimertinib vs. platinum-pemetrexed chemotherapy after progression on erlotinib, gefitinib, or afatinib<sup>128</sup>
    4. Median PFS 10.1 months with osimertinib vs. 4.4 months with chemotherapy (HR 0.30, p < 0.001)
    5. PFS increased in patients with CNS metastases indicating that osimertinib crosses the blood brain barrier.
  - g) Leptomeningeal Disease Considerations
    1. Phase 1 study (BLOOM) evaluated osimertinib in patients with leptomeningeal metastases from EGFR-mutated advanced NSCLC with disease progression on previous EGFR-TKI therapy. Patients received osimertinib 160 mg PO daily.
      - i. N = 41

- ii. Blinded central independent review ORR: 62% ; duration of response: 15.2 months
  - iii. Investigator-assessed median PFS: 8.6 months, median OS: 11 months
2. Osimertinib 160 mg had therapeutic efficacy in the CNS and is an effective option for EGFR-mutated, NSCLC patients with leptomeningeal disease (NCCN® Category 2A Recommendation)
- h) After progression EGFR targeted therapy, recommendations would be to move to systemic first-line chemotherapy.
- 1. Chemotherapy is preferred over immunotherapy in patients with EGFR mutations.
    - i. A meta-analysis assessed the role of immunotherapy as second-line therapy in EGFR-positive advanced NSCLC. In the EGFR mutant subgroup (n=186), the pooled HR was 1.05, p < 0.81 compared to docetaxel therapy.<sup>147</sup>
    - ii. Data in the second-line setting suggests that immunotherapy monotherapy is less effective, irrespective of PD-L1 expression

#### ALK Target-Driven Therapy for NSCLC

REGIMEN(S)	COMMENTS
<b>Preferred Recommendation</b>	
1. Alectinib 600 mg PO twice daily <sup>148</sup> (NCCN® Category 1) <sup>4</sup>	<p>Phase 3 trial <sup>149</sup> (ALEX) randomized 303 patients to upfront alectinib or crizotinib</p> <ul style="list-style-type: none"> <li>Median PFS 25.7 months with alectinib vs. 10.4 months with crizotinib p &lt; 0.001</li> <li>CNS progression was 12% with alectinib vs. 45% with crizotinib.</li> </ul> <p>5 year follow-up:<sup>150</sup></p> <ul style="list-style-type: none"> <li>Mature PFS – median PFS 34.8 months with alectinib vs. 10.9 months with crizotinib</li> <li>Median OS (immature) not reached for alectinib vs. 57.4 months with crizotinib</li> <li>5-year OS rate: 62.5% with alectinib vs. 45.5% with crizotinib</li> </ul> <p>Phase 3 trial randomized 207 patients to alectinib 300 mg twice daily or crizotinib 250 mg twice daily in Japan (J-ALEX)<sup>151</sup></p> <ul style="list-style-type: none"> <li>Median PFS not reached for alectinib vs. 10.2 months with crizotinib p &lt; 0.0001</li> </ul> <p>2nd pre-planned interim analysis of OS and safety follow-up:<sup>150,152</sup></p> <ul style="list-style-type: none"> <li>Independent review facility-assessed PFS 34.1 months for alectinib vs. 10.2 months with crizotinib</li> <li>Median OS for alectinib was not reached vs. 43.7 months with crizotinib</li> </ul>

2. Brigatinib 90 mg PO daily x 7 days followed by 180 mg PO daily (NCCN® Category 1) <sup>4</sup>	<p>Phase 3 trial comparing brigatinib to crizotinib therapy in untreated patients with ALK-rearrangement positive, metastatic non-small cell lung cancer (n=275). ALTA-1L</p> <ul style="list-style-type: none"> <li>Estimated 12-month PFS 67% brigatinib vs. 43% crizotinib (HR 0.49, p &lt; 0.001)<sup>153</sup></li> <li>ORR: 71% brigatinib vs. 60% crizotinib</li> </ul> <p>Intracranial response: 78% brigatinib vs. 29% crizotinib</p>
3. Lorlatinib 100 mg PO daily (NCCN® Category 1) <sup>4</sup>	<p>Phase 3 trial comparing lorlatinib 100 mg PO daily vs. crizotinib 250 mg PO twice daily for first-line treatment of ALK-rearranged metastatic non-small cell lung cancer: CROWN<sup>154</sup></p> <ul style="list-style-type: none"> <li>Interim analysis – median PFS was not reached with lorlatinib compared to 9.3 months with crizotinib, PFS at 12 months was 78% in the lorlatinib group compared to 39% in the crizotinib group (HR: 0.28, P &lt; 0.001)</li> <li>Intracranial response was improved with lorlatinib at 82% compared to 23% for crizotinib patients</li> <li>Lorlatinib was associated with greater grade 3 and 4 adverse events (mainly altered lipid levels) compared to crizotinib</li> </ul>
Other Recommended	
2. Ceritinib 450 mg PO daily with food (NCCN® Category 1) <sup>4</sup>	<p>Phase 3 trial comparing ceritinib 750 mg PO daily to chemotherapy for first-line treatment of ALK-rearranged metastatic non-small cell lung cancer: ASCEND-4</p> <ul style="list-style-type: none"> <li>Median PFS with ceritinib was 16.6 months vs. 8.1 months for chemotherapy (HR 0.55, p &lt; 0.00001)</li> </ul> <p>ASCEND-8 was a phase I open-label trial comparing ceritinib 750 mg fasting vs 450 mg or 600 mg with a low-fat meal in patients previously treated with crizotinib.<sup>155,156</sup></p> <ul style="list-style-type: none"> <li>450 mg ceritinib with food had comparable PKs to 750 mg fasting. 600 mg with food had 25% higher PK and is not recommended. <b>The package labeling has been updated to reflect 450 mg PO daily dosing with food to be preferable.</b></li> </ul>
Useful in Certain Circumstances	
4. Crizotinib 250 mg PO twice daily <sup>157</sup> (NCCN® Category 1) <sup>4</sup>	<p>Phase 3 open-label study of crizotinib vs. chemo after platinum-doublet<sup>157</sup></p> <ul style="list-style-type: none"> <li>PFS was 7.7 months in the crizotinib group and 3 months in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; P&lt;0.001)</li> <li>RR was 65% (95% CI, 58 to 72) with crizotinib vs. 20% (95% CI, 14 to 26) with chemotherapy (P&lt;0.001)</li> </ul>

- 2) Subsequent Therapy targeted toward ALK rearrangement positive NSCLC
  - a) Consider continuation of current therapy and definitive local therapy for asymptomatic progression or symptomatic progression but an isolated lesion or progression in the brain.<sup>4</sup>
  - b) For patients with symptomatic progression, options include:

1. If progression on crizotinib → switch to any of the FDA approved ALK inhibitors, except lorlatinib
  2. If progression on alectinib, brigatinib, or ceritinib → switch to lorlatinib or initial systemic chemotherapy options
- c) Use caution in patients who discontinue ALK-based therapy as a flare phenomenon may occur indicating that continuation of an ALK-based therapy is necessary
- d) Alectinib, brigatinib, and ceritinib are recommended for patients with ALK positive NSCLC after failure on crizotinib
1. Phase II trial of 138 patients (122 evaluable) demonstrated ORR of 50% and median duration of response 11.2 months with alectinib. Median PFS 8.9 months. May have added benefit in CNS metastasis.<sup>158</sup>
  2. Phase II trial of 222 patients were given brigatinib following crizotinib progression. Brigatinib was dosed in the traditional dosing with a 7-day lead-in of 90 mg followed by 180 mg once daily compared to 180 mg once daily. The investigator-assessed ORR was 45% and 54% for the two dosing options with brigatinib. Median PFS 9.2 month and 12.9 months.<sup>159</sup>
  3. ASCEND-5 trial (Phase 3) randomized 231 patients to either ceritinib 750 mg daily or chemotherapy with pemetrexed or docetaxel. Patients had progressed on crizotinib and previous chemotherapy.<sup>160</sup>
    - i. Median PFS was 5.4 months with ceritinib vs. 1.6 months with chemotherapy (HR 0.49; p < 0.0001)
    - ii. Ceritinib 450 mg PO daily with food is recommended for patients with ALK positive NSCLC after failure (or intolerance to) on crizotinib
- e) Lorlatinib is recommended as an option after progression on crizotinib plus one other ALK inhibitor, or alectinib, or ceritinib, or brigatinib.
1. Phase II, open-label, single arm trial in 276 patients with metastatic NSCLC that has either an ALK or ROS1 gene rearrangement. Patients were included that were treatment naïve, previous crizotinib treatment or previous crizotinib and another ALK inhibitor treatment with or without chemotherapy<sup>161</sup>
    - i. Patients with ≥ 1 previous ALK therapies had a confirmed objective response of 93% and patients with ≥ 2 previous ALK therapies had a confirmed objective response rate of 43%.
    - ii. In patients with ≥ 2 previous ALK therapies and intracranial disease, 26% of patients had a confirmed intracranial objective response
    - iii. NCCN<sup>®</sup> recommends lorlatinib as option after progression on crizotinib and alectinib, brigatinib or ceritinib if crizotinib was used in the first line setting. If Alectinib, brigatinib or ceritinib were used in the first line setting, lorlatinib may be used.
- f) After further progression on ALK inhibitors, would move to systemic first-line chemotherapy (with or without immunotherapy).

1. Data in the second-line setting suggests that PD-1/PD-L1 inhibitors monotherapy is less effective, irrespective of PD-L1 expression

#### ROS1 Rearrangement Target-Driven Therapy for NSCLC

REGIMEN(S)	COMMENTS
<b>Preferred Recommendation</b>	
Crizotinib 250 mg PO twice daily (NCCN <sup>®</sup> Category 2A) <sup>4</sup>	Phase 1 expansion cohort (n = 50) <ul style="list-style-type: none"> <li>• Objective RR 72%, (95% CI 58-84), 3 complete responses, 33 partial responses<sup>162,163</sup></li> <li>• Median DOR: 17.6 months</li> </ul>
Entrectinib 600 mg PO daily (NCCN <sup>®</sup> Category 2A) <sup>4</sup>	Three multicenter, single-arm, open-label clinical trials (ALKA, STARTRK-1, and STARTRK-2) evaluated efficacy of entrectinib. <sup>164</sup> <ul style="list-style-type: none"> <li>• A pooled subgroup analysis of patients with ROS1-positive metastatic NSCLC (N=51) observed an ORR of 78% (95% CI, 65,89)</li> <li>• DOR: 1.8 months – 36.8+ months (55% DOR ≥ 12 months)</li> </ul> Additional information on entrectinib is located in the Pharmacogenomics module. <ul style="list-style-type: none"> <li>• NCCN<sup>®</sup> guidelines suggests that entrectinib may be better for patients with brain metastases given improved CNS penetration</li> </ul>
<b>Other Recommended:</b>	
Ceritinib 450 mg PO daily with food <sup>165</sup> (NCCN <sup>®</sup> Category 2A) <sup>4</sup>	<ul style="list-style-type: none"> <li>• Objective RR 62% (95% CI, 45-77); 1 complete response</li> <li>• Median PFS 19.3 months for crizotinib-naïve patients</li> <li>• Median OS was 24 months</li> </ul>

- 3) Subsequent Therapy targeted toward ROS1 positive NSCLC
  - a) Patients who progress on crizotinib, ceritinib or entrectinib therapy for ROS1 disease may consider lorlatinib as subsequent therapy. (NCCN<sup>®</sup> Category 2A)<sup>166</sup>
  - b) Entrectinib can be considered for patients with CNS progression after crizotinib
  - c) Initial systemic therapy options that are used for adenocarcinoma or squamous NSCLC may be considered at the time of progression from targeted therapy.
  - d) Use caution in patients who discontinue ROS1-based therapy as a flare phenomenon may occur

### Other Target-Driven Therapy for NSCLC

HISTOLOGY <i>Non-squamous (adenocarcinoma, large cell or NSCLC no otherwise known)</i>	REGIMEN(S)	COMMENTS
<b>NTRK gene fusion positive</b>	Larotrectinib or Entrectinib (NCCN® <b>Preferred</b> Recommendation)	See Pharmacogenomics module
<b>MET exon 14 skipping mutation</b>	Capmatinib 400 mg PO twice daily (NCCN® <b>Preferred</b> Recommendation)	<p>GEOMETRY, a phase 2 study, evaluated capmatinib in different cohorts of MET genomic alterations, including MET exon 14 skipping mutations.<sup>167</sup></p> <ul style="list-style-type: none"> <li>• ORR: 41% in the previously treated patient population and 68% in the previously untreated group</li> <li>• DOR: 9.7 months (previously treated) and 12.6 months (previously untreated)</li> <li>• Median PFS: 5.4 months (previously treated) and 12.4 months (previously untreated)</li> <li>• 12/13 patients with brain metastasis responded to capmatinib, 4 patients with complete response in the brain</li> </ul>
	Tepotinib 450 mg PO daily (NCCN® <b>Preferred</b> Recommendation)	<p>VISION, a phase 2, open-label study, evaluating tepotinib 500 mg PO daily for advanced/metastatic NSCLC with confirmed MET exon 14 skipping mutation.<sup>168</sup></p> <ul style="list-style-type: none"> <li>• Overall ORR: 46%</li> <li>• Median PFS: 8.5 months</li> <li>• Active patients with brain metastases (N=11) – intracranial ORR 55%, median PFS of 10.9 months</li> </ul>
	Useful in Certain Circumstances	
	Crizotinib 250 mg PO twice daily	<p>Crizotinib activity was evaluated for NSCLC harboring MET exon 14 alterations. 69 patients with advanced NSCLC harboring MET exon 14 alterations were given crizotinib therapy.<sup>169</sup></p> <ul style="list-style-type: none"> <li>• Median DOR was 9.1 months</li> <li>• Median PFS was 7.3 months</li> </ul>
<b>RET rearrangement positive</b>	Selpercatinib ≥ 50 kg: 160 mg PO twice daily < 50 kg: 120 mg PO twice daily (NCCN® <b>Preferred</b> Recommendation)	<p>Libretto-001, a phase 1/2 study evaluated selpercatinib in patients with metastatic NSCLC and RET rearrangements<sup>170</sup></p> <ul style="list-style-type: none"> <li>• First line therapy with selpercatinib: ORR 85% independent review (n = 39)</li> </ul>

		<ul style="list-style-type: none"> <li>• Second line therapy with seliperatinib: ORR 64% independent review (n = 105)</li> <li>• Median PFS: 16.5 months in the independent review for previously treated patients</li> <li>• Median PFS: not evaluated for previously untreated patients</li> <li>• 91% of patients with brain metastases responded to seliperatinib</li> </ul>
	Pralsetinib 400 mg PO daily (NCCN® <b>Preferred Recommendation</b> )	ARROW, a phase 1/2 study assessing pralsetinib in patients with metastatic NSCLC and <i>RET</i> rearrangements. <sup>171</sup> <ul style="list-style-type: none"> <li>• First line therapy with pralsetinib: ORR 73% (n = 26)</li> <li>• Second line therapy with pralsetinib: ORR 61% (n = 80)</li> </ul>
	Useful in Certain Circumstances	
	Cabozantinib 60 mg PO daily	A phase 2 study of 26 patients assessed cabozantinib for <i>RET</i> rearranged patients which demonstrated an ORR of 28% <ul style="list-style-type: none"> <li>• 73% (19 patients) needed a dose reduction secondary to adverse events</li> </ul>
Non-small cell (Squamous or non-squamous) – <b><i>BRAF</i> V600E mutation positive</b>	Dabrafenib 150 mg PO twice daily plus trametinib 2 mg PO once daily <sup>22</sup> (NCCN® <b>Preferred Category 2A</b> ) <sup>4</sup>	Phase 2 open-label study previously untreated patients, 36 patients with <i>BRAF</i> V600E mutation positive disease <sup>172</sup> <ul style="list-style-type: none"> <li>• RR = 64%</li> <li>• Median duration of response = 10.4 months</li> <li>• Median PFS = 14.6 months</li> </ul>
	Useful in Certain Circumstances	
	Vemurafenib 960 mg PO twice daily	Single-agent vemurafenib or dabrafenib is a treatment option if combination dabrafenib/trametinib is not tolerated. <sup>4</sup>
	Dabrafenib 150 mg PO twice daily	

#### 4) MET exon 14 skipping mutation positive NSCLC

##### 1. Capmatinib<sup>173</sup>

###### i. Mechanism of Action:

- Potent, highly-selective inhibitor of MET, including the mutant variant produced by exon 14 skipping. Capmatinib inhibits MET phosphorylation triggered by binding of c-MET or by MET amplification as well as MET-mediated phosphorylation of downstream signaling proteins.

###### ii. Indication & Dose:

- a. Metastatic NSCLC harboring a mutation that leads to MET exon 14 skipping (as detected by FDA approved test)
    - b. 400 mg PO twice daily until disease progression with or without food
  - iii. Toxicities:
    - a. Common: peripheral edema, nausea, fatigue, vomiting, dyspnea, decreased appetite
    - b. Rare: interstitial lung disease, hepatotoxicity, and photosensitivity
  - iv. Drug-Drug Interactions: Major substrate of CYP3A4, minor substrate of P-gp as well as an inhibitor of BCRP/ABCG2, P-gp, and moderate inhibitor of CYP1A2
- 2. Tepotinib<sup>174</sup>
  - i. Mechanism of Action:
    - a. Selective inhibitor of MET, including the mutant variant produced by exon 14 skipping. Tepotinib inhibits hepatocyte growth factor-dependent and –independent MET phosphorylation as well as MET-dependent downstream signaling pathways.
  - ii. Indication & Dose:
    - a. Metastatic NSCLC harboring MET exon 14 skipping alterations
    - b. 450 mg PO daily until disease progression **with food**
  - iii. Toxicities:
    - a. Common: peripheral edema, nausea, fatigue, vomiting, diarrhea, musculoskeletal pain, and dyspnea
    - b. Rare: interstitial lung disease, hepatotoxicity, and embryo-fetal toxicity
  - iv. Drug-Drug Interactions: Minor substrate of CYP3A4, minor substrate of P-gp as well as an inhibitor of P-gp/ABCB1
- b) Subsequent Therapy targeted toward MET exon 14 skipping mutation positive NSCLC
  - 1. Patients who progress on capmatinib or tepotinib may consider switching to systemic first-line chemotherapy (with or without immunotherapy)
  - 2. Use caution in patients who discontinue MET-based therapy as a flare phenomenon may occur
- 5) *RET* rearrangement positive NSCLC
  - a) Selpercatinib<sup>175</sup>
    - i. Mechanism of Action:



- a. Highly selective anti-RET kinase inhibitor. Selpercatinib inhibits wild-type RET as well as multiple mutated RET isoforms, VEGFR1 and VEGFR3, as well as FGFR1, 2, and 3.
- ii. Indication & Dose:
  - a. Adult patients with metastatic *RET* fusion positive NSCLC
  - b. Refer to Thyroid Module
  - c. Dosing is driven off of weight:
    - ≥ 50 kg: 160 mg PO twice daily, with or without food
    - < 50 kg: 120 mg PO twice daily, with or without food
  - d. Recommend administration with food if patient is taking concurrent proton pump inhibitor
- iii. Toxicities:
  - a. Common: increased aspartate aminotransferase, increased alanine transferase, increased glucose, decreased leukocytes, decreased albumin, decrease calcium, dry mouth, diarrhea, prolonged QT interval, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.
  - b. Rare: impaired wound healing, hypersensitivity (4.3%), hemorrhagic events
- iv. Drug-Drug Interactions: Major substrate of CYP3A4, as well as a weak inhibitor of CYP3A4, and moderate inhibitor of CYP2C8

b) Pralsetinib<sup>176</sup>

- i. Mechanism of Action:
  - a. Pralsetinib inhibits wild-type RET, oncogenic RET fusions, and RET mutations. In enzyme assays it was observed that pralsetinib inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRb, and FGFR1.
- ii. Indication & Dose:
  - a. Adult patients with metastatic *RET* fusion positive NSCLC as detected by an FDA approved test
  - b. Refer to Thyroid Module
  - c. 400 mg PO daily on an empty stomach at least 1 hour before or at least 2 hours after a meal or food
- iii. Toxicities:

- a. Common: increased aspartate aminotransferase, decreased hemoglobin, decreased lymphocytes, decreased neutrophils, increased alanine transferase, increased creatinine, increased alkaline phosphatase, fatigue, constipation, musculoskeletal pain, decreased calcium, hypertension, decreased sodium, decreased phosphate, and decreased platelets
    - b. Rare: impaired wound healing, hemorrhagic events, interstitial lung disease
  - iv. Drug-Drug Interactions: Major substrate of CYP3A4, minor substrate of CYP1A2, CYP2D6 and P-gp
- 6) Subsequent Therapy targeted toward *RET* rearrangement positive NSCLC
  - a) Patients who progress on selpercatinib or pralsetinib may consider switching to systemic first-line chemotherapy (with or without immunotherapy)
  - b) Use caution in patients who discontinue RET-based therapy as a flare phenomenon may occur
- 7) Subsequent Therapy targeted toward BRAF V600E mutation positive NSCLC
  - a) Patients who progress on dabrafenib/trametinib therapy for BRAF V600E disease may consider switching to systemic first-line chemotherapy (with or without immunotherapy)
  - b) Patients who progress on initial systemic therapy can consider switching to dabrafenib plus trametinib, or single-agent vemurafenib if combination therapy is not tolerated

**Patient Case #4 Follow Up**

The correct answer is D (EGFR:Osimertinib).

Patient is a female, never smoker which are common patient characteristics of the EGFR mutation. Non-smokers are associated with the development of ALK and ROS1 gene rearrangements as well, but since this patient is 73-years old, the likelihood of these mutations is decreased. ROS1 can be managed in the first line setting with either crizotinib or entrectinib, alectinib is used for ALK positive mutation patients. Capmatinib is approved for patients with MET exon 14 skipping mutations. EGFR first line preferred therapy is osimertinib, and afatinib is listed as “other recommended”.

**Patient Case #5 Follow Up**

The correct answer is C (Alectinib:Myalgias).

The most appropriate first line treatment for ALK positive metastatic NSCLC would be lorlatinib, alectinib, or brigatinib as preferred, category 1 NCCN guideline recommendations. Crizotinib is an option as other recommended first line treatment for ALK positive NSCLC however this patient has not contraindications to preferred first line treatment. Lorlatinib is inappropriately associated with acneiform rash which is a common adverse effect of EGFR therapy and not ALK therapy. Crizotinib does have a warning/precaution for bradycardia, however would not be preferred treatment for this patient. Brigatinib has not been associated with mood disorders, rather lorlatinib has a warning/precaution for CNS effects. Alectinib has an overall incidence of > 29% and myalgias. Option C is the most appropriate answer.

**Patient Case #6:**

SW is a 65-year-old male with newly diagnosed Stage IV NSCLC. He presents to the medical oncologist for discussion of treatment options and final results from his pathology. A year ago his PCP recommended he obtain a LD-CT as part of lung cancer screening where he was found to have a suspicious lesion. He was lost to follow-up and returned to his PCP 3 weeks ago with worsening cough and shortness of breath and new hip pain. A CT was obtained and found to have continued growth in the previously identified lung lesion as well as several lytic bone lesions and liver metastasis. He has completed palliative radiation to the hip lesion given his reports of severe pain.

Pathology: Squamous NSCLC (EGFR negative, ALK negative, EGFR exon 20 mutation negative, KRAS G12C positive, RET rearrangement negative, MET skipping mutation negative, PD-L1 88%)

**What is the most appropriate treatment for SW at this time?**

- A. Cemiplimab
- B. Carboplatin, pemetrexed, pembrolizumab, and bevacizumab
- C. Carboplatin, nab-paclitaxel, atezolizumab
- D. Sotorasib

d. Treatment recommendations for based on PD-L1 expression (all histologies)

- 1) Treatment options below are broken down based on PD-L1  $\geq 50\%$ , 1-49%, and all others.

- 2) PD-L1 options include single agent immunotherapy, combination chemotherapy with immunotherapy as well as combination immunotherapy
- 3) Patients with PD-L1 expression  $\geq 1\%$  with a PS: 0-2 can be considered for single-agent immunotherapy, combination chemotherapy and immunotherapy

**First-Line Single-Agent Immunotherapy (High PD-L1 Expression  $\geq 50\%$ )<sup>4</sup> for Advanced or Metastatic NSCLC**

	<b>KEYNOTE 024<sup>177</sup></b>	<b>IMpower 110<sup>178</sup></b>	<b>EMPOWER-Lung 1<sup>179</sup></b>
<b>Eligibility</b>	Untreated metastatic NSCLC with at least 50% expression PD-L1	Untreated metastatic NSCLC with at least $\geq 1\%$ tumor cells (TC) expressing PD-L1 or tumor-infiltrating immune cells (IC) $\geq 1\%$	Untreated stage IIIB, IIIC, and IV NSCLC with PD-L1 expressed in at least 50% of tumor cells
<b>Treatment</b>	Pembrolizumab 200 mg IV every 3 weeks versus investigator's choice of platinum based chemotherapy	Atezolizumab 1200 mg IV every 3 weeks versus either cisplatin/carboplatin + pemetrexed (non-squamous histologies) or gemcitabine (squamous histologies) x every 21 days x 4-6 cycles	Cemiplimab 350 mg IV every 3 weeks (up to 108 weeks or 36 treatments) versus investigator's choice of platinum based chemotherapy for 4-6 cycles
<b>Participants</b>	N= 305	N = 205 (High PD-L1 expression)	N = 710
<b>Outcomes</b>	<p>Improved PFS and OS vs. platinum-based chemotherapy</p> <p>3 year follow-up <sup>180</sup></p> <ul style="list-style-type: none"> <li>Median OS: 30 months (pembrolizumab) vs. 14.2 months (chemotherapy arm) (HR: 0.63, p=0.002)</li> <li>36 month OS rate was 43.7% in the pembrolizumab arm vs. 24.9% in the chemotherapy arm</li> <li>Median DOR: NR (4.2 – 46.7+ months)</li> </ul>	<p><u>High PD-L1 expression (TC <math>\geq 50\%</math> or IC <math>\geq 10\%</math>)</u></p> <ul style="list-style-type: none"> <li>Median OS: 20.2 months (atezolizumab) vs. 13.1 months (platinum-doublet) (HR: 0.59, p=0.0106)</li> <li>Investigator-assessed PFS: 8.1 months (atezolizumab) vs. 5 months (platinum-doublet) (HR: 0.63)</li> </ul>	<p>Improved OS and PFS in the cemiplimab arm vs. chemotherapy</p> <ul style="list-style-type: none"> <li>Median OS: not reached (cemiplimab) vs. 14.2 months (platinum-doublet) (HR: 0.57, p = 0.0002)</li> <li>Blinded independent review median PFS: 8.2 months (cemiplimab) vs. 5.7 months (platinum-doublet) (HR: 0.54, p &lt; 0.0001)</li> </ul>

<b>FDA Approval</b>	First-line treatment for metastatic NSCLC with PD-L1 (Tumor Proportion Test (TPS) $\geq 1\%$ ) as determined by an FDA-approved test, with no EGFR or ALK genomic aberrations	First-line treatment for metastatic NSCLC with high PD-L1 expression (PD-L1 stained $\geq 50\%$ TC or PD-L1 stained IC $\geq 10\%$ as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations	First-line treatment for advanced NSCLC (locally advanced who are not candidates for surgical resection or definitive chemoradiation) with PD-L1 expression (TPS $\geq 50\%$ ) by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations
<b>NCCN Recommendation</b>	<b>Preferred, Category 1 for <math>\geq 50\%</math> PD-L1 expression positive</b>		

1. ASCO recommendations for patients with high PD-L1 expression  $\geq 50\%$ , for non-squamous and squamous cell, PS: 0-1, single-agent pembrolizumab should be offered.<sup>181</sup>
- 4) First-Line Combination immunotherapy with chemotherapy (PD-L1  $\geq 1\%$  and irrespective of PD-L1 status)
  - a) Select regimens are options may be recommended for PD-L1  $\geq 50\%$  see specific regimen comments for consideration.

#### Immunotherapy-Driven First-Line Therapy for Advanced or Metastatic NSCLC

HISTOLOGY	REGIMEN(S)	COMMENTS
Assess for driver mutations, if identified, refer to Target-Driven First-Line Therapy for NSCLC		
Regardless of histology and no contraindications to immunotherapy	Nivolumab 3mg/kg IV q 2 weeks, Ipilimumab 1 mg/kg IV q 6 week <sup>182</sup> (NCCN®, Category 1 Useful in Certain Circumstances for PD-L1 $\geq 50\%$ , Category 1 Other Recommended for PD-L1 1-49%) (NCCN® Category 2A Recommendation for PD-L1 $< 1\%$ )	CheckMate 227
<b>Irrespective of PD-L1 expression and no contraindications</b> to immunotherapy consider the following histology based regimens		
<b>Non-squamous – EGFR mutation negative or unknown</b>  <b>PS 0-2</b>	Pembrolizumab 200 mg IV Day 1, carboplatin AUC 5 IV Day 1, pemetrexed 500 mg/m <sup>2</sup> IV Day 1, q 3 weeks x 4 cycles followed by, pembrolizumab 200 mg IV Day 1 q 3 weeks for 24 months +/- pemetrexed 500 mg/m <sup>2</sup> IV Day 1 q 3 weeks indefinitely <sup>10</sup> (NCCN® Category 1, Preferred for PD-L1 $\geq 50\%$ , PD-L1 $\geq 1-49\%$ , and irrespective of PD-L1 expression)	KEYNOTE-021
	Pembrolizumab 200 mg IV Day 1, Cisplatin 75 mg/m <sup>2</sup> IV Day 1, pemetrexed 500 mg/m <sup>2</sup> IV Day 1, q 3 weeks x 4 cycles	KEYNOTE-189

	<p>followed by,  pembrolizumab 200 mg IV Day 1 q 3 weeks for 24 months +/-  pemetrexed 500 mg/m<sup>2</sup> IV Day 1 q 3 weeks indefinitely<sup>110</sup>  (NCCN<sup>®</sup> Category 1, Preferred for PD-L1 ≥ 50%, PD-L1 ≥ 1-49%,  and irrespective of PD-L1 expression)</p>	
	<p>Nivolumab 360 mg IV Day 1 and 22,  Ipilimumab 1 mg/kg IV Day 1  Carboplatin AUC 6 IV / Cisplatin 75 mg/m<sup>2</sup> IV Day 1 and 22  Pemetrexed 500 mg/m<sup>2</sup> IV Day 1 and 22  42 day cycle  Followed by,  Nivolumab 360 mg IV q 3 weeks,  Ipilimumab 1 mg/kg IV q 6 weeks<sup>84</sup>  (NCCN<sup>®</sup> Category 1, other recommended for PD-L1 ≥ 50%, and  PD-L1 1-49%, and irrespective of PD-L1 expression)</p>	CheckMate 9LA
	<p>Atezolizumab 1200 mg IV Day 1,  Bevacizumab 15 mg/kg IV Day 1, carboplatin AUC 6 IV Day 1,  Paclitaxel 200 mg/m<sup>2</sup> IV Day 1,  q 3 weeks x 4-6 cycles  followed by,  Atezolizumab 1200 mg IV Day 1 +/-  bevacizumab 15 mg/kg IV Day 1  q 3 weeks until disease progression or intolerable toxicities  (NCCN<sup>®</sup> Category 1, Other recommended for PD-L1 ≥ 50%, PD-  L1 ≥ 1-49%, and irrespective of PD-L1 expression)</p>	IMpower150
	<p>Atezolizumab 1200 mg IV Day 1,  carboplatin AUC 6 IV Day 1,  nab-paclitaxel 100 mg/m<sup>2</sup> IV Day 1, 8, and 15  q 3 weeks x 4-6 cycles  followed by,  Atezolizumab 1200 mg IV Day 1  q 3 weeks until disease progression or intolerable toxicities<sup>183</sup>  (NCCN<sup>®</sup>, Other recommended for PD-L1 ≥ 50%, PD-L1 ≥ 1-49%,  and irrespective of PD-L1 expression)</p>	IMpower130
	<p>Cemiplimab 350 mg IV Day 1,  carboplatin AUC 5 or 6 / cisplatin 75 mg/m<sup>2</sup> IV Day 1,  pemetrexed 500 mg/m<sup>2</sup> IV Day 1  q 3 weeks x 4-6 cycles  followed by,  cemiplimab 350 mg IV Day 1 q 3 weeks +/-  pemetrexed 500 mg/m<sup>2</sup> IV Day 1 q 3 weeks until disease  progression or intolerable toxicities<sup>184</sup> (NCCN<sup>®</sup> Category 1,  other recommended for PD-L1 ≥ 50%, and PD-L1 1-49%, and  irrespective of PD-L1 expression)</p>	EMPOWER-Lung 3
	Cemiplimab 350 mg IV Day 1,	

	carboplatin AUC 5 or 6 / cisplatin 75 mg/m <sup>2</sup> IV Day 1, paclitaxel 200 mg/m <sup>2</sup> IV Day 1 q 3 weeks x 4-6 cycles followed by, cemiplimab 350 mg IV Day 1 q 3 weeks until disease progression or intolerable toxicities <sup>184</sup> (NCCN <sup>®</sup> Category 1, other recommended for PD-L1 ≥ 50%, and PD-L1 1-49%, and irrespective of PD-L1 expression)	
	Tremelimumab 75 mg IV Day 1 durvalumab 1500 mg IV Day 1 carboplatin AUC 5 or 6 IV Day 1 nab-paclitaxel 100 mg/m <sup>2</sup> IV Days 1, 8, and 15 q 3 weeks x 4 cycles followed by, tremelimumab 75 mg IV on week 16 only durvalumab 1500 mg IV Day 1 q 4 weeks until disease progression or intolerable toxicities <sup>185</sup> (NCCN <sup>®</sup> Category 2B, other recommended for PD-L1 ≥ 50%, and (Category 1) for PD-L1 1-49% and irrespective of PD-L1 expression)	POSEIDON
	Tremelimumab 75 mg IV Day 1 durvalumab 1500 mg IV Day 1 carboplatin AUC 5 or 6 IV Day 1 / Cisplatin 75 mg/m <sup>2</sup> IV Day 1 pemetrexed 500 mg/m <sup>2</sup> IV Day 1 q 3 weeks x 4 cycles followed by, tremelimumab 75 mg IV on week 16 only durvalumab 1500 mg IV Day 1 q 4 weeks +/- pemetrexed 500 mg/m <sup>2</sup> IV Day 1 q 3-4 weeks until disease progression or intolerable toxicities <sup>185</sup> (NCCN <sup>®</sup> Category 2B, other recommended for PD-L1 ≥ 50%, and (Category 1) for PD-L1 1-49% and irrespective of PD-L1 expression)	
<b>Squamous histology</b>  <b>PS 0-2</b>	Pembrolizumab 200 mg IV Day 1, carboplatin AUC 6 IV Day 1, paclitaxel 200 mg/m <sup>2</sup> IV Day 1, q 3 weeks x 4 cycles followed by, pembrolizumab 200 mg IV Day 1 q 3 weeks for 24 months <sup>111,112</sup> (NCCN <sup>®</sup> Category 1, Preferred for PD-L1 ≥ 50%, PD-L1 ≥ 1-49%, and irrespective of PD-L1 expression)	KEYNOTE-407
	Pembrolizumab 200 mg IV Day 1, carboplatin AUC 6 IV Day 1, nab-paclitaxel 100 mg/m <sup>2</sup> IV Day 1, 8, 15 q 3 weeks x 4 cycles followed by,	

	<p>pembrolizumab 200 mg IV Day 1 q 3 weeks for 24 months<sup>111,112</sup> (NCCN<sup>®</sup> Category 1, Preferred for PD-L1 <math>\geq</math> 50%, PD-L1 <math>\geq</math> 1-49%, and irrespective of PD-L1 expression)</p>	
	<p>Nivolumab 360 mg IV day 1 and 22, Ipilimumab 1 mg/kg IV Day 1 Carboplatin AUC 6 IV day 1 and 22 Paclitaxel 200 mg/m<sup>2</sup> IV day 1 and 22 42 day cycle Followed by, Nivolumab 360 mg IV q 3 weeks, Ipilimumab 1 mg/kg IV q 6 weeks<sup>84</sup> (NCCN<sup>®</sup> Category 1, other recommended for PD-L1 <math>\geq</math> 50%, and PD-L1 1-49%, and irrespective of PD-L1 expression)</p>	CheckMate 9LA
	<p>Cemiplimab 350 mg IV Day 1, carboplatin AUC 5 or 6 / cisplatin 75 mg/m<sup>2</sup> IV Day 1, paclitaxel 200 mg/m<sup>2</sup> IV Day 1 q 3 weeks x 4-6 cycles followed by, cemiplimab 350 mg IV Day 1 q 3 weeks until disease progression or intolerable toxicities<sup>184</sup> (NCCN<sup>®</sup> Category 1, other recommended for PD-L1 <math>\geq</math> 50%, and PD-L1 1-49%, and irrespective of PD-L1 expression)</p>	EMPOWER-Lung 3
	<p>Tremelimumab 75 mg IV Day 1 durvalumab 1500 mg IV Day 1 carboplatin AUC 5 or 6 IV Day 1 nab-paclitaxel 100 mg/m<sup>2</sup> IV Days 1, 8, and 15 q 3 weeks x 4 cycles followed by, tremelimumab 75 mg IV on week 16 only durvalumab 1500 mg IV Day 1 q 4 weeks until disease progression or intolerable toxicities<sup>185</sup> (NCCN<sup>®</sup> Category 2B, other recommended for PD-L1 <math>\geq</math> 50%, and (Category 2A) for PD-L1 1-49% and irrespective of PD-L1 expression)</p>	POSEIDON
	<p>Tremelimumab 75 mg IV Day 1 Durvalumab 1500 mg IV Day 1 Carboplatin AUC 5 or 6 / Cisplatin 75 mg/m<sup>2</sup> IV Day 1 Gemcitabine 1250 or 1000 mg/m<sup>2</sup> IV Days 1 and 8 q 3 weeks x 4 cycles followed by, tremelimumab 75 mg IV on week 16 only durvalumab 1500 mg IV Day 1 q 4 weeks until disease progression or intolerable toxicities<sup>185</sup></p>	



	(NCCN® Category 2B, other recommended for PD-L1 ≥ 50%, and (Category 2A) for PD-L1 1-49% and irrespective of PD-L1 expression)	
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1. Pembrolizumab in combination with chemotherapy

- i. KEYNOTE-021: phase II open-label trial randomizing patients with non-squamous NSCLC to either pembrolizumab 200 mg, carboplatin AUC 5, and pemetrexed 500 mg/m<sup>2</sup> IV day 1 every 3 weeks for 4 cycles followed by pembrolizumab for 24 months and optional indefinite pemetrexed maintenance therapy compared to carboplatin AUC 5 and pemetrexed 500 mg/m<sup>2</sup> IV day 1 every 3 weeks for 4 cycles followed by optional indefinite pemetrexed maintenance therapy.<sup>12</sup>
  - a. Stratified by PD-L1 < 1% positive or ≥ 1% positive
  - b. Primary endpoint: objective response rate (ORR)
  - c. Pembrolizumab plus chemotherapy (n=60): ORR 55%
  - d. Chemotherapy (n=63): ORR 29%; p = 0.0016
  - e. PD-L1 ≥ 50%: ORR 80% pembro + chemo vs 35% chemo alone
  - f. Median PFS 13 months with pembrolizumab + chemo vs. 8.9 months with chemo alone
- ii. KEYNOTE-021 24 Month OS update<sup>186</sup>
  - a. Median PFS 24 months with pembrolizumab + chemo vs. 9.3 months with chemo alone (HR: 0.53 p = 0.0049)
  - b. Median OS was not reached with pembrolizumab + chemo vs. 21.1 months with chemo alone (HR: 0.56 P = 0.0151)
- iii. KEYNOTE-189: phase III trial randomizing patients with non-squamous NSCLC to either pembrolizumab 200 mg or placebo plus platinum-pemetrexed based chemotherapy followed by either pembrolizumab or placebo maintenance therapy in addition to pemetrexed maintenance therapy<sup>187</sup>
  - a. 72.2% patients received carboplatin and 27.8% received cisplatin
  - b. Estimated 1-year OS: 69.2% pembrolizumab + chemotherapy vs. 49.4% chemotherapy alone; p < 0.01
  - c. Median PFS 8.8 months pembrolizumab + chemotherapy vs. 4.9 months for chemotherapy alone ; p < 0.001
  - d. PD-L1 expression ≥ 50%: 80% response rate with pembrolizumab + chemotherapy vs. 35% chemotherapy alone
  - e. FDA approved and NCCN® Category 1 recommendation for pembrolizumab in combination with either carboplatin or cisplatin

and pemetrexed for non-squamous histologies irrespective of PD-L1 status

iv. Updated Analysis of KEYNOTE-189<sup>188</sup>

- a. 24 month OS: 45.7% pembrolizumab + chemotherapy vs. 27.3% chemotherapy alone
- b. Median OS: 22 months with pembrolizumab + chemotherapy vs. 10.6 months for chemotherapy alone (HR: 0.56; 95% CI: 0.46 – 0.69)
- c. Median PFS: 9 months pembrolizumab + chemotherapy vs. 4.9 months for chemotherapy alone (HR: 0.49; 95% CI: 0.41-0.59)

v. KEYNOTE-407: phase III trial randomizing patients to carboplatin/taxane (paclitaxel or nab-paclitaxel)/pembrolizumab or carboplatin/taxane/placebo followed by pembrolizumab/placebo maintenance in patients with squamous cell histology regardless of PD-L1 expression <sup>189,190</sup>

- a. Carboplatin AUC 6 + paclitaxel 200 mg/m<sup>2</sup> IV D1 OR nab-paclitaxel 100 mg/m<sup>2</sup> weekly + pembrolizumab 200 mg IV D1 OR placebo x 4 cycles → pembrolizumab 200 mg IV D1 or placebo maintenance
- b. Median OS: 15.9 months with pembrolizumab vs. 11.3 months with placebo (HR 0.64, p < 0.001)
- c. Median PFS: 6.4 months with pembrolizumab vs. 4.8 months with placebo (HR 0.56, p < 0.001)
- d. FDA approved and NCCN® Category 1 recommendation for pembrolizumab in combination with carboplatin/taxane chemotherapy in squamous histology

2. Atezolizumab in combination with chemotherapy

- i. IMpower150: phase III trial randomizing 356 patients to atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP) or atezolizumab plus BCP (ABCP) for 4-6 cycles followed by maintenance therapy of atezolizumab, bevacizumab or both in patients with non-squamous NSCLC .<sup>191</sup>
  - a. Median PFS: 8.3 months ABCP vs. 6.8 months BCP (HR 0.62, p < 0.001)
  - b. Median OS: 19.2 months ABCP vs. 14.7 months BCP (HR 0.78, p = 0.02)
- ii. FDA approved and NCCN® Category 1 recommendation for atezolizumab in combination with carboplatin, paclitaxel and bevacizumab in non-squamous histologies with no contraindications to PD-L1 or VEGF based-therapy

- iii. IMpower130: phase III trial randomizing 724 patients to atezolizumab plus carboplatin, and nab-paclitaxel or chemotherapy alone for 4-6 cycles followed by maintenance therapy of atezolizumab in patients with non-squamous non-small cell lung cancer<sup>183</sup>
    - a. Median PFS: 7 months atezolizumab group vs. 5.5 months chemotherapy group (HR: 0.64;  $p < 0.0001$ )
    - b. Median OS: 18.2 months atezolizumab group vs. 13.9 months in the chemotherapy group (HR: 0.79,  $p = 0.033$ )
  - iv. FDA approved and NCCN<sup>®</sup> Category 2A, other recommended regimen for atezolizumab with carboplatin, nab-paclitaxel in non-squamous histologies.
3. Combination Immunotherapy with chemotherapy
- i. CheckMate 9LA: phase III trial, randomized to nivolumab + ipilimumab + chemotherapy x 2 cycles followed with nivolumab + ipilimumab maintenance or chemotherapy based on histology x 4 cycles followed with optional pemetrexed maintenance (dependent on histology) in stage IV/recurrent first-line NSCLC.<sup>84</sup>
    - a. Interim analysis
    - b. Patients were enrolled regardless of PD-L1 status
    - c. Median OS: 15.6 months ipilimumab/nivolumab + chemotherapy vs. 10.9 months chemotherapy based on histology (HR: 0.66,  $p = 0.0006$ )
  - ii. FDA approved and NCCN<sup>®</sup> Category 1, other recommended, for all histologies with combination nivolumab and ipilimumab and 2 cycles of platinum-doublet chemotherapy (based on histology), followed by nivolumab and ipilimumab until disease progression for first line treatment with NSCLC with no EGFR or ALK tumor aberrations.
  - iii. EMPOWER-Lung 3: phase 3 trial, randomized cemiplimab + platinum-based chemotherapy vs platinum-based chemotherapy alone (N=466)<sup>184</sup>
    - a. Cemiplimab / paclitaxel / (carboplatin or cisplatin) for either nonsquamous or squamous histology
    - b. Cemiplimab / pemetrexed / (carboplatin or cisplatin) for nonsquamous histology
    - c. Median OS: 21.9 months with cemiplimab/chemotherapy vs. 13 months with chemotherapy alone (HR: 0.71,  $p = 0.01$ )
  - iv. FDA approved and NCCN<sup>®</sup> Category 1, other recommended for all histologies with combination cemiplimab and histology based platinum-doublet as first line options for patients with metastatic NSCLC, regardless of histology or PD-L1 level and with negative actionable driver mutations.

- v. POSEIDON: phase 3 trial, randomized three different treatment arms in the first line setting for patients with metastatic NSCLC who did not have EGFR or ALK mutations. (N=1013)<sup>185</sup>
    - a. Tremelimumab + Durvalumab + platinum-based chemotherapy vs. durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy
    - b. Chemotherapy regimens included tremelimumab/durvalumab/albumin-bound paclitaxel/carboplatin for either nonsquamous or squamous histologies; tremelimumab/durvalumab/pemetrexed/(carboplatin or cisplatin) for nonsquamous NSCLC or tremelimumab/durvalumab/(carboplatin or cisplatin)/gemcitabine for squamous histologies
    - c. Median OS: 14 months (95% CI, 11.7-16.1) for tremelimumab/durvalumab + platinum-based chemotherapy vs. 11.7 months (95% CI, 10.5 – 13.1) for chemotherapy alone (HR: 0.77, p=0.003)
  - vi. FDA approved and NCCN panel recommends tremelimumab + durvalumab + platinum-based chemotherapy regimens as first line treatment for metastatic NSCLC patients regardless of histology of PD-L1 levels, and with negative test results for actionable driver mutations. The category recommendation by NCCN is dependent on histology, chemotherapy and PD-L1 levels.
4. Combination Immunotherapy
- i. CheckMate227: phase III, open-label, randomized to ipilimumab + nivolumab or chemotherapy alone in patients who had PD-L1 expression ≥ 1% with stage IV or recurrent NSCLC
    - a. Median OS: 17.1 months with nivolumab + ipilimumab vs. 14.9 months with chemotherapy (p=0.007)
    - b. Median DOR: 23. 2 months with nivolumab + ipilimumab vs. 6.2 months with chemotherapy
  - ii. FDA approved and NCCN® category 1, other recommended, for all histologies, with metastatic NSCLC irrespective of PD-L1 status, with no EGFR or ALK tumor aberrations.
  - iii. ASCO guidelines reviewed this clinical trial and determined the combination of ipilimumab and nivolumab had insufficient data to recommend for patients in the first line setting.<sup>181</sup>

### Histology-Driven (Non-Immunotherapy) First-Line Therapy for Advanced or Metastatic NSCLC

HISTOLOGY	REGIMEN(S)	COMMENTS
Treatment Strategies for patients <b>without</b> driver mutations and <b>contraindications</b> to immunotherapy based therapy		
<b>Non-squamous – EGFR mutation negative or unknown</b>  <b>PS 0-1</b>	1. Platinum-based doublet (see next table). <sup>125</sup> (NCCN® Category 1)	Efficacy of cisplatin/paclitaxel = carboplatin/paclitaxel= cisplatin/docetaxel= cisplatin/gemcitabine; however, carboplatin/paclitaxel was less toxic. No doublet is clearly superior
	2. Carboplatin AUC 6 day 1, paclitaxel 200 mg/m <sup>2</sup> day 1, bevacizumab 15 mg/kg day 1, q 3 weeks <sup>192</sup> (NCCN® Category 1)	Bevacizumab continued Q3 weeks after 6 cycles of the combination. Key exclusion criteria: <b>squamous cell carcinoma, brain metastases, ECOG &gt; 1, inadequate organ function, and clinically significant hemoptysis</b> (N=858) Response rate: 35% for PCB vs. 15% for PC (P<0.001)  Median OS: 12.3 mo PCB vs. 10.3 mo PC (HR 0.79, P=0.003)  Median PFS: 6.2 mo PCB vs. 4.5 mo PC (HR 0.66, P < 0.001)  Clinically significant bleeding: 4.4% PCB vs. 0.7% PC (P<0.001)
	3. Cisplatin 75 mg/m <sup>2</sup> IV day 1, pemetrexed 500 mg/m <sup>2</sup> IV day 1, q 3 weeks <sup>193</sup> (NCCN® Category 1)	Superior to cisplatin + gemcitabine in non-squamous histology. Cisplatin + gemcitabine improved survival in squamous histology.
	4. Cisplatin 75 mg/m <sup>2</sup> IV day 1, pemetrexed 500 mg/m <sup>2</sup> IV day 1, bevacizumab 7.5 mg/kg IV day 1, q 3 weeks <sup>194</sup> (NCCN® Category 1)	Comparison after 4 cycles of continuing maintenance pemetrexed and bevacizumab to bevacizumab maintenance alone. Combination maintenance increased PFS (7.4 vs 3.7 months, HR 0.48; 95% CI 0.35 to 0.66; P <0.001)
	5. Carboplatin AUC 6 IV day 1, pemetrexed 500 mg/m <sup>2</sup> IV day 1, bevacizumab 15 mg/kg IV day 1 q 3 weeks <sup>195</sup>	Continued maintenance pemetrexed and bevacizumab.  Comparator arm was carboplatin AUC 6 IV day 1, paclitaxel 200 mg/m <sup>2</sup> IV day 1

		<p>and bevacizumab 15 mg/kg IV day 1 q 3 weeks with maintenance bevacizumab.</p> <p>No difference OS, but increased PFS (HR 0.83, 6 vs 5.6 months, P=0.012) in the pemetrexed/bevacizumab arm.</p> <p>More anemia, thrombocytopenia, and fatigue in pemetrexed arm versus more neutropenia, febrile neutropenia, neuropathy, and alopecia with paclitaxel arm</p>
	6. Gemcitabine 1000 mg/m <sup>2</sup> IV days 1, and 8, docetaxel 85 mg/m <sup>2</sup> IV day 8, q 3 weeks <sup>196</sup> (NCCN® Category 1)	No advantage observed with PFS for gemcitabine/docetaxel compared to cisplatin/vinorelbine; however, cisplatin/vinorelbine attributed to higher adverse events, mainly myelosuppression.
	7. Gemcitabine 1000 mg/m <sup>2</sup> IV days 1 and 8, vinorelbine 25 mg/m <sup>2</sup> IV days 1 and 8, q 3 weeks <sup>197</sup> (NCCN® Category 1)	Vinorelbine/gemcitabine was compared to vinorelbine/carboplatin in the metastatic setting. Similar overall response rate was found with favorable median survival and improved toxicity profile with vinorelbine/gemcitabine.
<b>Squamous histology</b>  <b>PS 0-1</b>	Platinum-based doublet (see next table). <sup>125,198</sup>	
	Gemcitabine 1000 mg/m <sup>2</sup> IV days 1, and 8, docetaxel 85 mg/m <sup>2</sup> IV day 8, q 3 weeks <sup>196</sup> (NCCN® Category 1)	
	Gemcitabine 1000 mg/m <sup>2</sup> IV days 1 and 8, vinorelbine 25 mg/m <sup>2</sup> IV days 1 and 8, q 3 weeks <sup>197</sup> (NCCN® Category 1)	

### Examples of Platinum-Based Doublets

(All regimens listed below are NCCN® Category 1, unless noted otherwise)

REGIMEN	DOSES/FREQUENCY	ORR for 1 <sup>st</sup> Line Setting
Cisplatin / Pemetrexed <sup>193</sup> <b>Non-squamous histology</b>	Cisplatin 75 mg/m <sup>2</sup> IV day 1, Pemetrexed 500 mg/m <sup>2</sup> IV day 1 Q 3 weeks	30%
Cisplatin / Docetaxel <sup>125</sup>	Cisplatin 75 mg/m <sup>2</sup> IV day 1, Docetaxel 75 mg/m <sup>2</sup> IV day 1, Q 3 weeks	17%
Cisplatin / Paclitaxel <sup>125</sup>	Paclitaxel 135 mg/m <sup>2</sup> IV over 24 hours, followed by Cisplatin 75 mg/m <sup>2</sup> IV day 2, Q 3 weeks	21%
Cisplatin / Gemcitabine <sup>125</sup>	Gemcitabine 1000 mg/m <sup>2</sup> days 1, 8, and 15 Cisplatin 100 mg/m <sup>2</sup> day 1 Q 4 weeks	22%
Carboplatin / Docetaxel <sup>199</sup>	Carboplatin AUC 6 IV day 1, Docetaxel 75 mg/m <sup>2</sup> IV day 1, Q 3 weeks	24%
Carboplatin / nab- paclitaxel <sup>198</sup>	Carboplatin AUC 6 IV day 1, nab-paclitaxel 100 mg/m <sup>2</sup> IV weekly days 1, 8, 15 Q 3 weeks	33% 41% in squamous subset
Carboplatin / Paclitaxel <sup>125</sup>	Carboplatin AUC 6 IV day 1, Paclitaxel 200-225 mg/m <sup>2</sup> IV day 1 over 3 hours, Q 3 weeks	17-25%
Carboplatin / Paclitaxel <sup>200</sup>	Carboplatin AUC 6 IV day 1, paclitaxel 90 mg/m <sup>2</sup> IV days 1, 8, 15 Q 4 weeks	27%
Carboplatin/ Gemcitabine <sup>201</sup>	Carboplatin AUC 5 IV day 1, Gemcitabine 1000 mg/m <sup>2</sup> IV days 1, 8 and 15 Q 3 weeks	30%
Carboplatin/ Pemetrexed <sup>202</sup> <b>Non-squamous histology</b>	Carboplatin AUC 6 IV day 1, Pemetrexed 500 mg/m <sup>2</sup> IV day 1 Q 3 weeks	32%

#### b) Albumin bound- (or nab-) paclitaxel with carboplatin<sup>198</sup>

1. nab-paclitaxel versus standard paclitaxel. Carboplatin AUC 6 on day 1 in both arms was paired with nab-paclitaxel 100 mg/m<sup>2</sup> days 1, 8, 15 versus paclitaxel 200 mg/m<sup>2</sup> on day 1.
2. ORR was 33% nab-paclitaxel versus 25% conventional paclitaxel, and in squamous histology subgroup, ORR was 41% versus 24%.
3. No difference in PFS (6.3 versus 5.8 months) or OS (12.1 versus 11.2 months).

4. A survival difference was seen in the subset of patients  $\geq 70$  years of age (n=156): 19.9 months in nab-paclitaxel arm versus 10.4 months standard paclitaxel arm.
- c) PointBreak trial randomized patients to pemetrexed/carboplatin/bevacizumab → maintenance pemetrexed/bevacizumab vs. paclitaxel/carboplatin/bevacizumab → maintenance bevacizumab<sup>195</sup>
  1. Stage IIIB or IV non-squamous NSCLC
  2. Median OS 12.6 months pemetrexed/carboplatin/bevacizumab vs. 13.4 months paclitaxel/carboplatin/bevacizumab; p = 0.949
  3. More anemia, thrombocytopenia and fatigue with pemetrexed/carboplatin/bevacizumab, but more neutropenia, febrile neutropenia and neuropathy with paclitaxel/carboplatin/bevacizumab
- d) Cisplatin/pemetrexed vs. cisplatin/gemcitabine<sup>193</sup>
  1. 1725 stage IIIB/IV patients enrolled with NSCLC (all histologies)
  2. Randomized to cisplatin/pemetrexed vs. cisplatin/gemcitabine
    - i. Adenocarcinoma: median OS 11.8 with cis/pem vs. 10.4 months for cis/gem HR 0.81, p = 0.03
    - ii. Squamous cell carcinoma: median OS 9.4 months cis/pem vs. 10.8 months cis/gem HR 1.3, p = 0.05
  3. Significantly less myelosuppression in the cisplatin/pemetrexed arm
  4. Pemetrexed-based therapy is only indicated in non-squamous lung cancer
- 5) Maintenance Therapy<sup>4</sup>
  - a) Delivered following 4-6 cycles of chemotherapy in patients with **response or stable disease.**
  - b) *Continuation maintenance* = continuing at least one of the agents used first-line, e.g., continued bevacizumab<sup>192,194,195</sup>, pemetrexed<sup>194,195,203</sup>, pemetrexed and bevacizumab<sup>195</sup>, pembrolizumab<sup>12,177,189</sup>, atezolizumab<sup>204</sup>, atezolizumab and bevacizumab<sup>113</sup>, pemetrexed and pembrolizumab<sup>110</sup>, pemetrexed and cemiplimab<sup>184</sup>, cemiplimab<sup>184</sup>, durvalumab<sup>185</sup>, durvalumab and pemetrexed<sup>185</sup> (until progression or poor tolerability)
    1. Pembrolizumab maintenance until progression or max of 2 years
    2. Ipilimumab/Nivolumab maintenance until progression or max of 2 years
    3. Pemetrexed continuation compared to placebo **following 4 cycles of cisplatin/pemetrexed in non-squamous, non-progressive disease.**<sup>203</sup>
      - i. Drug-related grade  $\geq 3$  events with pemetrexed = fatigue (4.5%), neutropenia (3.9%), anemia (4.8%)



### Results of Continuation Therapy Trials with Pemetrexed<sup>203</sup>

Population	N	PFS*	OS*
Pemetrexed	359	4.1 months (3.2-4.6)	13.9 months
Placebo	180	2.8 months (2.6 – 3.1)	11.0 months
Hazard Ratio		0.62 (0.49-0.79) p < 0.0001	0.78 (0.64-0.96) p = 0.02

- c) Continuing maintenance pemetrexed and bevacizumab after 4 cycles of platinum-based doublet with pemetrexed and bevacizumab increased PFS. Median PFS was 6 months for bevacizumab and pemetrexed with median OS of 17.7 months.<sup>194,195</sup>
- d) Bevacizumab continuation after induction with carboplatin, paclitaxel and bevacizumab (PCB) versus carboplatin and paclitaxel resulted in an increase in PFS (6.2 months PCB vs 4.5 (P<0.001) months PC only) and OS (12.3 months PCB vs 10.3 (P=0.003) months PC only).<sup>192</sup>
- 6) *Switch maintenance* = initiation of a different agent that is not part of the original induction therapy, such as pemetrexed for *non-squamous* histology (2A)
  - a) Pemetrexed 500 mg/m<sup>2</sup> IV day 1 Q21 days in non-squamous cell histology only<sup>4,205</sup>
  - b) Compared to best supportive care **following 4 cycles** of platinum-based doublet therapy (cisplatin/carboplatin with paclitaxel, docetaxel, or gemcitabine) in stage IIIB/IV non-progressive disease (CR, PR or SD)<sup>205</sup>

### Results of Switch Maintenance Therapy Trials in *Non-Squamous* Patients<sup>205</sup>

Non-Squamous	N	PFS*	OS*
Pemetrexed	326	4.5 months	15.5 months
Supportive care	156	2.6 months	10.3 months

\* P < 0.05 for hazard ratio between groups

### Histology Driven Maintenance Therapy for Advanced or Metastatic NSCLC

HISTOLOGY	Continuation	Switch
	<i>Continuing at least one of the agents used first-line</i>	<i>Initiation of a different agent after completion of first-line therapy</i>
<b>Non-squamous – EGFR, ALK, ROS1 mutation negative or unknown</b>  <b>PS 0-2</b>	Atezolizumab <sup>142</sup> Atezolizumab/Bevacizumab <sup>+ 113</sup> Bevacizumab <sup>+ 103</sup> Bevacizumab/Pemetrexed <sup>103</sup> Nivolumab/Ipilimumab Pemetrexed <sup>+ 103, 136, 137</sup> Pembrolizumab/Pemetrexed <sup>+ 110</sup> Gemcitabine	Pemetrexed <sup>21,145</sup>
<b>Squamous histology</b>  <b>PS 0-1</b>	Pembrolizumab <sup>111</sup> Nivolumab/Ipilimumab Gemcitabine	

\*NCCN Category 1 Recommendation

**Patient Case #6:**

Answer A is the best answer.

He is negative for first line targetable mutations. The next best option is treatment with PD-1 directed therapy as his biopsy was evaluated for PD-L1 expression and found to be greater than 50% at 88%. Based on EMPOWER-Lung 1, single-agent cemiplimab is appropriate to administer for this patient. Option B is incorrect since the patient has squamous cell histology and would not benefit from pemetrexed based chemotherapy additionally the use of bevacizumab is contraindicated in a squamous cell lung cancer patient given the observed increased rates of bleeding complications. Carboplatin, nab-paclitaxel and atezolizumab is not an approved combination and would not be appropriate. While this patient is found to have a KRAS G12C mutation, sotorasib use in the first line setting is not recommended.

**Patient Case #6 Continued:**

He returns to clinic after receiving 9 months of single-agent cemiplimab. His routine CT scan demonstrated increased size in his lung lesion as well as worsening liver metastasis. Given his pathology results at diagnosis, he was started on sotorasib treatment.

**Which of the following is true regarding sotorasib treatment?**

- A. More than 50% of patients observed an objective response while taking sotorasib on the CodeBreak 100 trial.
- B. Sotorasib is effective for several KRAS mutations given its broad binding effect with the RAS pathway
- C. Sotorasib can cause QTc prolongation and should be monitored closely if taking with other QT prolonging medications.
- D. Concomitant use of proton pump inhibitors with sotorasib should be avoided.

**Patient Case #7:**

JR is a previously treated, stage IV, NSCLC patient who was recently found to have disease progression. On repeat review of his pathology, next generation sequencing (NGS) performed on the diagnostic tissue showed an EGFR exon 20 insertion mutation. He is starting amivantamab treatment today in the treatment room.

**A new infusion nurse comes to the pharmacy as she is about to start JR on amivantamab treatment. He is starting cycle 1 day 1 and she would like to verify what would be most appropriate premedication for her patient at this time?**

- A. No premedication is required for amivantamab
- B. Dexamethasone, famotidine, diphenhydramine, and montelukast
- C. Dexamethasone, diphenhydramine, and acetaminophen
- D. Acetaminophen and diphenhydramine

b. Subsequent Therapy after **Chemotherapy**: Targeted Therapy options

5) EGFR exon 20 insertion mutation positive

- a) Following initial systemic therapy and progression is observed targeting EGFR exon 20 insertion mutation with amivantamab-vmjw or mobocertinib may be considered
- b) Amivantamab had an improved ORR in a multicenter, non-randomized, open label multi-cohort trial (CHRYSALIS).<sup>206</sup>

1. Locally advanced or metastatic NSCLC patients with EGFR exon 20 insertion were treated with amivantamab once weekly for 4 weeks followed by every 2-week therapy thereafter until disease progression or unacceptable toxicity.

- i. N = 81
- ii. ORR was 40% with a median response duration of 11.1 months
- iii. Median PFS of 8.3 months and OS of 22.8 months

2. Amivantamab-vmjw<sup>207</sup>

- i. Mechanism of Action:
  - a. Amivantamab is a bispecific antibody targeting EGFR and MET. Through binding of EGFR and MET on the extracellular domain it disrupts EGFR and MET signaling by blocking ligand bind.
- ii. Indication & Dose:
  - a. Adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations as detected by an FDA-approved test whose disease has progressed on or after platinum-based chemotherapy.
  - b. Administer amivantamab week 1 and 2 via a peripheral line due to the high incidence of infusion-related reactions during initial treatment), then subsequent infusions (after week 2) may be administered via central line.

Weight at baseline	Dose
< 80 kg	Week 1: 350 mg IV day 1 and 700 IV mg day 2 Week 2 – 4: 1050 mg IV weekly Subsequent infusions: 1050 mg IV every 2 weeks
≥ 80 kg	Week 1: 350 mg IV day 1 and 1050 mg IV mg day 2 Week 2 – 4: 1400 mg IV weekly Subsequent infusions: 1400 mg IV every 2 weeks

c. Premedication recommendations:

Medication	Dose	Route	Window (Prior to amivantamab)
Antihistamine (Prior to ALL amivantamab doses)	Diphenhydramine 25 – 50 mg	IV	15 to 30 minutes
		PO	30 – 60 minutes
Antipyretic (Prior to ALL amivantamab doses)	Acetaminophen 650 – 1000 mg	PO	30 to 60 minutes
Glucocorticoid (Prior to week 1, days 1 and 2; optional for subsequent doses)	Dexamethasone 10 mg or methylprednisolone 40 mg	IV	45 to 60 minutes

iii. Toxicities:

- a. Common: rash, infusion related reactions, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation and vomiting
- b. Rare: interstitial lung disease, toxic epidermal necrolysis, ocular toxicity, headache

iv. Drug-Drug Interactions: None known

3. NCCN recommends amivantamab as a subsequent therapy option for patients with EGFR exon 20 insertion mutations who have progressed on or after platinum-based chemotherapy with/without immunotherapy.<sup>4</sup> (NCCN Category 2A Recommendation)

c) Mobocertinib demonstrated an improved ORR in Study 101, an international, non-randomized, open-label, multicohort trial of locally advanced or metastatic NSCLC patients with EGFR exon 20 insertion mutations. (N=114)<sup>208</sup>

1. Patients had to have progressed on or after platinum-based chemotherapy
  - i. Mobocertinib was given as 160 mg by mouth daily until disease progression
  - ii. ORR evaluated by blinded independent central review was 28% with a median response duration of 17.5 months
2. Mobocertinib
  - i. Mechanism of Action:

- a. Mobocertinib is an irreversible EGFR kinase inhibitor which binds to EGFR exon 20 insertion mutations
  - ii. Indication & Dose:
    - a. Adult patients with locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation detected by an FDA-approved test whose disease has progressed on or after platinum-based chemotherapy
    - b. 160 mg PO daily with or without food
  - iii. Toxicities:
    - a. Common: diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, musculoskeletal pain, increased amylase, increase lipase, hypokalemia, anemia, increased creatinine and hypomagnesemia
    - b. Warnings/Precautions: QTc prolongation and torsades de pointes, interstitial lung disease/pneumonitis, cardiac toxicity, embryo-fetal toxicity
  - iv. Drug-Drug Interactions: QTc prolongation as well as major substrate of CYP3A4
- 6) ERBB2 (HER2) mutation positive
  - a) Targeting ERBB2 (HER2) mutation should be considered following first-line therapy with platinum-based chemotherapy with or without immunotherapy.
  - b) The response rates for ERBB2 (HER2) mutation positive patients to immunotherapy ranges from 7-27%
  - c) Fam-Trastuzumab Deruxtecan-nxki was approved based on the results of the DESTINY-Lung01, DESTINY-Lung02 trial, a phase 2, multicenter, randomized, blinded, dose-optimized trial for advanced/metastatic nonsquamous NSCLC who progressed on prior platinum-based chemotherapy and HER2 mutant positive.<sup>209</sup>
    - 1. Efficacy was evaluated in 52 patients and dosing of fam-trastuzumab deruxtecan was 5.4 mg/kg IV every 3 weeks until disease progression.
      - i. ORR: 58%
      - ii. Median DOR: 8.7 months
    - 2. NCCN recommends fam-trastuzumab deruxtecan as a preferred subsequent therapy option for patients with ERBB2 (HER2) mutations who have progressed on or after platinum-based chemotherapy with/without immunotherapy.
  - d) Ado-trastuzumab emtansine
    - 1. A Phase 2 basket trial evaluated ado-trastuzumab emtansine in patients with metastatic NSCLC and ERBB2 (HER2) mutations<sup>210</sup>.
      - i. Partial response rate was 44% (95% CI, 22-69%)

- ii. Median PFS: 5 months (95% CI, 3-9)
  - 2. NCCN recommends ado-trastuzumab emtansine as an other recommended subsequent therapy option for patients with ERBB2 (HER2) mutation positive NSCLC.
- 7) KRAS G12C mutation positive
- a) Targeting the KRAS G12C mutation with sotorasib may be considered following initial systemic therapy and progression.
  - b) Sotorasib was approved based on the results of the CodeBreak 100 trial, a multi-center, single-arm, open label trial for locally advanced or metastatic NSCLC with KRAS G12C mutations.
    - 1. Efficacy was evaluated in 124 patients who progressed on or after at least one prior systemic therapy. Sotorasib 960mg PO daily until disease progression.<sup>211</sup>
      - i. ORR: 37.1% (95% CI: 28.6-46.2)
      - ii. Median DOR: 11.1 months
      - iii. Median PFS of 6.8 months and median OS of 12.5 months
    - 2. Sotorasib<sup>212</sup>
      - i. Mechanism of Action:
        - a. Sotorasib is a RAS inhibitor which irreversibly and covalently binds to KRAS G12C. In the inactive state of mutant KRAS G12C, the mutant cysteine resides next to a narrow surface pocket, the P2 pocket. Sotorasib binds with the unique cysteine of KRAS G12C through an interaction with the P2 pocket, locking the protein in an inactive state which prevents downstream signaling leading to inhibition of cell growth and promoting apoptosis only in KRAS G12C tumor cell lines.
      - ii. Indication & Dose:
        - a. Adult patients with locally advanced or metastatic NSCLC with KRAS G12C-mutated as detected by an FDA-approved test who have received at least one prior systemic therapy.
        - b. 960 mg PO daily with or without food
      - iii. Toxicities:
        - a. Common: diarrhea, hepatotoxicity, musculoskeletal pain, nausea, fatigue, and cough
        - b. Rare: interstitial lung disease
      - iv. Drug-Drug Interactions: Avoid coadministration with proton pump inhibitors and H2 receptor antagonists, major substrate of CYP3A4, moderate inhibitor of CYP3A4, and P-gp inhibitor

3. NCCN recommends sotorasib as a subsequent therapy option for patients with NSCLC harboring a KRAS G12C mutation who have progressed on or after platinum-based chemotherapy with/without immunotherapy. (NCCN Category 2A Recommendation). This includes both patients with adenocarcinoma and squamous cell carcinoma.

**Patient Case #6 Continued:**

SW returns to clinic after two months of sotorasib therapy. He reports in the last month having severe diarrhea and has held treatment twice with two dose reductions but continues to have intolerance to the treatment. He requests stopping treatment.

He returns 3 months later with a repeat CT scan and is found to have continued disease progression.

**Based on SWs continued disease progression, what treatment would be most appropriate to recommend at this time?**

- A. Pembrolizumab
- B. Nivolumab and ipilimumab
- C. Docetaxel and ramucirumab
- D. Carboplatin and etoposide

- c. Subsequent Therapy after **Chemotherapy ONLY (no prior immunotherapy in the first line setting)**: Immunotherapy

5) Nivolumab

- a) Nivolumab may be used regardless of the PD-L1 expression of the tumor
- b) Nivolumab improves median OS by 3 months compared to docetaxel in nonsquamous and squamous histologies
  1. Median OS in nivolumab arm for non-squamous histologies (n=292) was 12.2 months versus docetaxel (n=290) was 9.4 months. HR 0.73, 95% CI, 0.59 to 0.89, p=0.002<sup>213</sup>
  2. Median OS in nivolumab arm for squamous histologies (n=135) was 9.2 months versus docetaxel (n=137) was 6 months. HR 0.59, 95% CI, 0.44 to 0.79, p<0.001<sup>214</sup>

6) Pembrolizumab

- a) Guidelines recommend consideration of single-agent pembrolizumab for patients with  $\geq 1\%$  PD-L1 expression
- b) Phase 2/3 trial enrolled 1034 patients with PD-L1 expression of at least 1% and randomized to pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg or docetaxel 75 mg/m<sup>2</sup>

- c) Median overall survival was 10.4 months with 2 mg/mg pembrolizumab, 12.7 months for 10 mg/kg pembrolizumab and 8.5 months with docetaxel HR 0.71, p=0.0008
  - d) OS and PFS was significantly longer in patients with PD-L1 expression  $\geq 50\%$  (HR 0.54 OS, HR 0.59 PFS).<sup>215,216</sup>
  - e) FDA approved dosing for lung cancer is 200 mg flat dose every 3 weeks
- 7) Atezolizumab
- a) Atezolizumab may be used regardless of PD-L1 expression
  - b) POPLAR: Phase II trial of 287 patients demonstrated an OS benefit (intent-to-treat population) of 12.6 months vs 9.7 months in the docetaxel arm (HR 0.73 95% CI 0.53 – 0.99, p=0.04). Higher levels of PD-L1 expression were associated with better OS.<sup>217</sup>
  - c) OAK: Phase III trial of 850 patients randomized to atezolizumab or docetaxel therapy.<sup>204</sup>
    - 1. Median OS: 13.8 months with atezolizumab vs. 9.6 months with docetaxel p < 0.01
- 8) Subsequent immunotherapy after progression on immunotherapy is not recommended.
- d. Subsequent Therapy after **Chemotherapy**: Chemotherapy Options
- 5) Evaluation of PS is appropriate as consideration of additional chemotherapy at the time of progression is based on patients have a PS of 0-2 and selection of chemotherapy is based on prior treatment.
  - 6) Docetaxel improves one-year survival ( $\geq 30\%$ ) in relapsing or progressive disease compared to best supportive care, vinorelbine, or ifosfamide.<sup>199,218</sup>
  - 7) Second- line pemetrexed produces equal response rates as docetaxel and is less toxic when administered with B12 and folate.<sup>219</sup>
    - a) Only recommended for adenocarcinoma
    - b) Median survival time in the pemetrexed arm (N=283) was 8.3 months versus docetaxel (N=288) was 7.9 months.
    - c) One year OS was 29.7% in the pemetrexed arm versus 29.7% in the docetaxel arm (HR 0.99, 95% CI 0.82-1.2)
    - d) Neutropenia, febrile neutropenia, infection with grade 3-4 neutropenia, hospitalizations due to febrile neutropenia, alopecia, and use of growth factors all statistically significantly (P<0.001) favored the pemetrexed arm. More ALT elevation was seen with pemetrexed.
  - 8) Gemcitabine 1000 mg/m<sup>2</sup> IV on days 1, 8 and 15 in a 28-day cycle in the second-line setting has demonstrated a response rate of 13% with a 1-year survival of 22%.<sup>220</sup>
- e. Subsequent Therapy after **Chemotherapy**: VEGF Inhibition
- 5) Ramucirumab + Docetaxel



- a) The addition of ramucirumab 10 mg/kg to docetaxel 75 mg/m<sup>2</sup> every 3 weeks significantly improved median OS (10.5 vs 9.1 months (HR 0.86, 95% CI 0.75-0.98; p=0.023) and median PFS (4.5 months compared with 3.0 months for the control group (0.76, 0.68-0.86; p<0.0001). This study included non-squamous and squamous cell histology.<sup>149</sup>
- b) Single agent ramucirumab is not recommended.

**Patient Case #6:**

Answer D is the best answer.

CodeBreak100 trial demonstrated for the first time that KRAS targeting with sotorasib improved ORR. While an improvement in ORR was observed it was only 37.1% (95% CI: 28.6 – 46.2) which makes option A incorrect as it was not more than 50% ORR. Sotorasib has a very unique mechanism of action and at this time is only active against KRAS G12C. While it is a RAS inhibitor it only irreversibly and covalently binds with KRAS G12C making other KRAS mutations unlikely to respond to sotorasib therapy. Sotorasib has not been reported to effect QTc and/or prolong the QT interval, which makes C incorrect. Sotorasib and proton pump inhibitors should be avoided together based on package labeling and is the most appropriate answer at this time.

**Patient Case #7:**

Answer C is the best answer.

Amivantamab commonly causes an infusion-related reaction. IRRs occurred in approximately two-thirds of patients treated with amivantamab, particularly with the first infusion. The proposed mechanism is non-dose-related, immunologic the overall onset is rapid with a median time to onset of 1 hours after the start of the infusion. Per package labeling acetaminophen and diphenhydramine are to be administered prior to all amivantamab infusions. Glucocorticoids should be administered prior to week 1, days 1 and 2 doses, and are option for subsequent doses. Montelukast and famotidine are not required premedications for patients starting amivantamab.

**Patient Case #6 Continued:**

Answer C is the best answer.

SW received immunotherapy for first line treatment and returning to immunotherapy as third line would not be recommended making options A and B incorrect. Carboplatin and etoposide are options for small cell lung cancer not recurrent NSCLC. Option C would be most appropriate at this time based on the fact that VEGF inhibition was avoided in the first line setting and Ramucirumab was studied in both squamous and nonsquamous histologies. The combination of ramucirumab with docetaxel significantly improved the median overall survival and PFS.

**III. Malignant Pleural Mesothelioma<sup>221,222</sup>**

**A. Risk Factors**

**1. Asbestos**

2. Smoking not an independent risk factor for mesothelioma, but patients that smoke and exposed to asbestos are at increased risk of lung cancer
- B. Prevention and Screening
1. Routine screening has not been shown to decrease mortality in patients who are at high risk of mesothelioma (asbestos exposure)
- C. Molecular Tumor Profiling
1. Broad molecular tumor profiling is recommended with the goal of identifying rare driver alterations for which effective drugs may be available (both FDA approved therapies as well as clinical trial options)<sup>223</sup>
    - a. *ALK* rearrangements by IHC are rare but can be found in patients with peritoneal mesothelioma. These patients have shown dramatic response with *ALK* inhibitor therapies.
    - b. *NTRK* has been reported in a small subset of malignant pleural mesothelioma through evaluation of archival tissue where IHC was performed
- D. Treatment
1. Mesothelioma should be divided into the following histologic subtypes: epithelioid, sarcomatoid or biphasic
    - a. Sarcomatoid histology is associated with shorter survival, failure to benefit from surgery and less likely to respond to systemic therapy.
    - b. Biphasic histology has an intermediate prognosis between epithelioid and sarcomatoid
    - c. Epithelioid histology has the best prognosis
  2. Treatment options for stage I-IIIa and epithelioid or biphasic histology
    - a. Chemotherapy improves survival and QOL
    - b. Induction chemotherapy → surgery (pleurectomy/decortication) → observation
    - c. Induction chemotherapy → surgery (extrapleural pneumonectomy) → radiation
    - d. Surgery (pleurectomy/decortication) → chemotherapy
    - e. Surgery (extrapleural pneumonectomy) → chemotherapy → radiation
    - f. Median survival of 20-29 months for those patients that complete trimodality therapy
  3. Advanced (stage IIIB, IV), sarcomatoid, or medically inoperable, or not a surgical candidate
    - a. Chemotherapy for ECOG PS 0 – 2
      - 1) Pemetrexed/cisplatin vs. cisplatin in phase III trial<sup>224</sup>
        - a) Median OS 12.1 months in pemetrexed/cisplatin vs 9.3 months with cisplatin alone (p=0.02).
      - 2) Pemetrexed/cisplatin/bevacizumab vs. pemetrexed/cisplatin phase III trial<sup>225</sup>
        - a) **Unresectable** disease and PS 0-2

- b) OS 18.8 months with bevacizumab arm vs. 16.1 months with chemotherapy alone (HR 0.77;  $p = 0.0167$ )
  - c) More grade 3 hypertension, proteinuria and thrombotic events in the bevacizumab arm
- 3) Nivolumab/Ipilimumab (CheckMate 743)<sup>226</sup>
  - a) Randomized, open-label phase 3 trial with unresectable malignant pleural mesothelioma as first line treatment. Patients receive nivolumab/ipilimumab for up to 2 years or 6 cycles of combination chemotherapy (cisplatin or carboplatin and pemetrexed).<sup>226</sup>
  - b) N=605
  - c) Median OS: 18.1 months with nivolumab/ipilimumab vs. 14.1 months with chemotherapy (HR: 0.74,  $p = 0.002$ )
  - d) Median PFS: 6.8 months with nivolumab/ipilimumab vs. 7.2 months with chemotherapy (HR: 1; 95% CI: 0.82-1.21)
  - e) Outcomes in the chemotherapy arm were better with epithelioid histology
- b. If ECOG PS 3 – 4 → best supportive care

### Select Chemotherapy Regimens for Mesothelioma

First - Line Chemotherapy Regimens
Preferred, NCCN <sup>®</sup> Recommendation
Pemetrexed 500 mg/m <sup>2</sup> IV day 1 Cisplatin 75 mg/m <sup>2</sup> IV day 1 <sup>224</sup> q 3 weeks (NCCN <sup>®</sup> , category 1)
Pemetrexed 500 mg/m <sup>2</sup> IV day 1 Cisplatin 75 mg/m <sup>2</sup> IV day 1 Bevacizumab 15 mg/kg IV day 1 <sup>**225</sup> q 3 weeks x 6 cycles, then Bevacizumab 15 mg/kg IV day 1 q 3 weeks maintenance until disease progression (NCCN <sup>®</sup> , category 1)
Nivolumab 360 mg IV day 1 q 3 weeks (or 3 mg/kg every 2 weeks) Ipilimumab 1 mg/kg q 6 weeks Continue until disease progression, unacceptable toxicity or up to 2 years (NCCN <sup>®</sup> , category 1) Preferred for non-epithelioid histology
Pemetrexed 500 mg/m <sup>2</sup> IV day 1 Carboplatin AUC 5 IV day 1 <sup>227-229</sup> +/- bevacizumab 15 mg/kg IV day 1 <sup>**</sup> q 3 weeks x 6 cycles, ± maintenance bevacizumab q 3 weeks if given with initial therapy (NCCN <sup>®</sup> , category 2A)
Useful in Certain Circumstances, NCCN <sup>®</sup> Recommendation
Gemcitabine 1000 – 1250 mg/m <sup>2</sup> IV days 1, 8, 15 Cisplatin 80-100 mg/m <sup>2</sup> IV day 1 <sup>230,231</sup> q 3-4 weeks
Pemetrexed 500 mg/m <sup>2</sup> IV day 1 <sup>232</sup> q 3 weeks
Vinorelbine 25-30 mg/m <sup>2</sup> IV day 1 <sup>233</sup> q week

<sup>\*\*</sup>Should only be used if surgery is not an option

#### 4. Subsequent therapy

- a. Pemetrexed combination regimens used in the first line setting are options for subsequent systemic treatment if immunotherapy is administered as first-line treatment
- b. Pemetrexed (if not administered as first-line); can consider re-challenge if good sustained response at time initial chemotherapy was interrupted.<sup>234,235</sup>
  - 1) Preferred, NCCN<sup>®</sup> Category 1 Recommendation
- c. Nivolumab +/- Ipilimumab
  - 1) Phase 2 randomized trial (IFCT-1501 MAPS2) of 125 patients evaluated nivolumab +/- with (or without ipilimumab)
  - 2) Median OS 15.9 months in ipilimumab/nivolumab arm, and 11.9 months in nivolumab arm
  - 3) ORR 28% in ipilimumab/nivolumab arm, and 19% in nivolumab arm

- 4) Preferred, NCCN<sup>®</sup> Recommendation if not administered in first-line
- d. Vinorelbine<sup>236,237</sup>
  - 1) Other recommended, NCCN<sup>®</sup> recommendation
- e. Gemcitabine<sup>237-239</sup>
  - 1) Other recommended, NCCN<sup>®</sup> recommendation

#### IV. Supportive Care Therapy with Cisplatin

##### A. Nephrotoxicity<sup>240</sup>

1. Risk factors include:
  - a. Hyperuricemia
  - b. Hypoalbuminemia
  - c. Dehydration
  - d. Renal irradiation
  - e. Advanced age
  - f. Concomitant nephrotoxins
2. GFR can decrease by 20 - 40% after treatment with cisplatin; older patients have decreased clearance of both unbound and total platinum which results in an increased severity of cisplatin-induced nephrotoxicity
3. Electrolyte abnormalities can occur acutely and may be quite prolonged, even lasting years after completion of therapy
  - a. Hypomagnesemia is the most common electrolyte abnormality with cisplatin
    - 1) Related to cumulative dose, but can occur after a single treatment
    - 2) Incidence may increase with longer therapy duration (cycle 1 - 41%, cycle 5 - 86% and 6<sup>th</sup> cycle - 100%)
    - 3) Supplementation with oral magnesium is often required
  - b. Hypokalemia
  - c. Hypocalcemia may also develop in patients with severe hypomagnesemia
  - d. Hyponatremia may occur due to a defect in sodium and water handling by the kidneys in 4% to 10% of patients.<sup>241</sup>
4. Manifests as lower GFR, higher SCr, and reduced serum potassium and magnesium levels<sup>242</sup>
5. Acute presentation— hypomagnesemia, urinary enzyme excretion, acute reduction in GFR, and in some cases a transient rise in BUN and SCr; usually due to inadequate hydration during therapy
6. Chronic presentation – stable, reduced renal function with or without elevations in SCr; may still have electrolyte abnormalities

7. Mechanism of toxicity<sup>242</sup>
  - a. Exposure of tubular cells to cisplatin activates complex signaling pathways which lead to tubular cell injury and death
  - b. In conjunction with the above, an inflammatory response is also stimulated which further exacerbates renal tissue damage
  - c. Induces renal vasculature injury resulting in decreased blood flow and ischemic injury of the kidneys leading to a decrease in GFR
8. Caution should be used when administering platinum agents in patients at risk for renal dysfunction
  - a. For example with cisplatin, (recommendations vary depending disease, and intent)<sup>243</sup>
    - 1) CrCl 30-60 ml/min: 50% dose reduction
    - 2) Do not give if CrCl < 30 ml/min
    - 3) Repeat courses should not be given until SCr < 1.5 mg/dL
9. Small study of 60 patients with solitary kidneys who successfully received cisplatin therapy<sup>244</sup>
10. Prevention
  - a. Saline based hydration and diuresis are the most frequently utilized technique to prevent nephrotoxicity
    - 1) Range from 1 to 4 liters, but usually consists of 2 to 3 liters of NS
    - 2) Use of hypertonic saline has resulted in inconsistent results and an increased risk of adverse events<sup>245-247</sup>
  - b. Electrolytes should be replaced and many centers add potassium and magnesium to the pre- and/or post-hydration IV fluids
  - c. Furosemide and mannitol reduce the concentration of platinum in the urine and some sources suggest the use of these agent to attenuate cisplatin nephrotoxicity<sup>248</sup>
    - 1) Interestingly, neither platinum content in the kidney or plasma nor degree of cellular necrosis it produces is positively influenced by either diuretic
    - 2) Conflicting results in the literature as some studies show protection and others show that the use of the agents may aggravate nephrotoxicity and currently there is no reason to advocate use of diuretics in prevention of cisplatin-induced nephrotoxicity.
    - 3) Hydration + cisplatin versus hydration + cisplatin + mannitol was studied in the early 1980s<sup>249</sup> - found protection of kidney function after the first cycle in patients receiving mannitol; however, no convincing effect observed during subsequent cycles
    - 4) Study investigated various hydration prevention methods in women with gynecological cancers<sup>250</sup>
      - a) Patients randomized to:
        1. Saline: 500 mL NS over 2 hours, followed by cisplatin mixed in 1000 mL NS followed by 500 mL NS over 2 hours post-cisplatin (n = 15)

2. Saline plus mannitol: 500 mL NS over 2 hours, followed by cisplatin mixed in 1000 mL NS with 50 grams mannitol followed by 500 mL NS over 2 hours post-cisplatin (n = 17)
  3. Saline plus furosemide: 500 mL NS over 2 hours with 40 mg furosemide 30 minutes prior to cisplatin, followed by cisplatin mixed in 1000 mL NS followed by 500 mL NS over 2 hours post-cisplatin (n = 17)
- b) Study was closed early when interim analysis revealed significant more nephrotoxicity in the saline plus mannitol arm
  - c) No difference between saline vs. saline and furosemide, however decrease significantly different for saline vs. saline + mannitol (p=0.02), and saline + furosemide vs. saline + mannitol (p=0.02)
  - d) The decrease in CrCl continued in subsequent cycles with saline + mannitol
  - e) Results need to be confirmed in a large trial
- d. European Society of Clinical Pharmacy Special Interest Group on Cancer Care (ESCP SIG) recommendations<sup>248</sup>
    - a) Assess patient's renal function before each administration, which should consist of an estimation of the GFR or CrCl
    - b) Administer platinum slowly in conjunction with saline solution to produce a brisk diuresis
    - c) Maintain urine flow at 3 to 4 liters / day for the next 2 to 3 days
    - d) Suggest a regimen of:
      1. Prehydration of NS 100 mL/hr for the 12 hours prior to cisplatin administration and continuous infusion of saline during and at least 1 day after cisplatin treatment
    - e) Recommend hydration be continued for at least 3 days after the course via oral or IV route
    - f) Do not use diuretics, either mannitol or furosemide
    - g) Provide appropriate antiemetics therapy to prevent dehydration
    - h) Check SCr 3 to 5 days after completion of cycle
    - i) Monitor magnesium levels and supplement when needed
    - j) Avoid co-administration of other nephrotoxic drugs
  - e. Literature review was conducted in 2011 searching for all studies which mannitol was used for forced diuresis with cisplatin therapy and the authors concluded a lack of compelling evidence for mannitol<sup>251</sup>
11. Amifostine<sup>252</sup>
    - a. Amifostine is a thiol, acting to scavenge oxygen-free radicals

- 1) Prodrug for WR 1065, converted to the active moiety by membrane bound alkaline phosphatase (enzyme is active as a neutral or slightly alkaline pH); sulfhydryl sulfur binds with electrophiles to inactivate
  - 2) Normal cells preferentially take up the drug over tumor cells (acidic pH; less blood supply)
- b. Amifostine is indicated to:
- 1) Decrease cumulative nephrotoxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer
  - 2) Decrease the incidence of moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer
- c. ASCO Guidelines on use of amifostine<sup>252,253</sup>
- 1) Nephrotoxicity
    - a) Dose-limiting toxicity of cisplatin
    - b) Amifostine may be considered to prevent nephrotoxicity from cisplatin
    - c) Should not be administered in patients where chemotherapy can produce a significant survival advantage or cure (2002 guidelines, 2008 guideline update stated no change from 2002 guideline)<sup>253</sup>
    - d) Other acceptable measures are cisplatin dose reduction, switching to carboplatin
  - 2) Dosing
    - a) For use with cisplatin the approved dose of amifostine is 910 mg/m<sup>2</sup>, but most studies utilize 740 mg/m<sup>2</sup> due to better tolerability and similar efficacy; give over ≤ 15 minutes (longer infusion cause greater hypotension)
    - b) Premedications for amifostine:
      - i. NS 1 liter prehydration (no mannitol); ≥ 2 liters if patient dehydrated
      - ii. 5HT<sub>3</sub> antagonist antiemetic (p.r.n. before may be helpful also)
      - iii. Dexamethasone 20 mg IV at least 1 hour before
    - c) Administer IV over 15 minutes with the patient in a reclined position
    - d) Within 30 minutes of completing the infusion, chemotherapy should begin as the drug has a very short half-life (approximately 1 minute)
- d. Adverse effects include:
- 1) Sneezing, allergic reactions, warm or flushed feeling, metallic taste in mouth during infusion, mild somnolence, nausea/vomiting, dermatologic reactions, and hypotension
  - 2) Hypotension is the most clinically significant toxicity
    - a) Patients must have blood pressure medications and diuretics held for 24 hours prior to amifostine administration



- b) BP must be monitored during hydration and at 0, 5, 10, and 15 minutes and again at 10 minutes after infusion completion

<u>Systolic BP</u>		
$\leq 100$	→	Stop infusion if systolic BP decreases by 20 mmHg
100-119	→	Stop infusion if systolic BP decreases by 25 mmHg
120-139	→	Stop infusion if systolic BP decreases by 30 mmHg
140-179	→	Stop infusion if systolic BP decreases by 40 mmHg
$\geq 180$	→	Stop infusion if systolic BP decreases by 50 mmHg

- e. *Due to amifostine's inconsistent efficacy data, and poor tolerability (especially in the elderly patient population), amifostine is not routinely used in clinical practice and is not recommended in recent guidelines*

## V. Common Complications of Lung Cancer

### A. Malignant Effusions<sup>254-257</sup>

#### 1. Incidence

##### a. Types:

- 1) Pleural effusion
- 2) Pericardial effusion
- 3) Malignant ascites/peritoneal effusion (not discussed here due to lack of pharmacologic intervention – best to treat underlying disease)

- b. 15% of all patients with cancer will be affected by malignant pleural effusions. (150,000 new cases of malignant pleural effusions annually)

##### c. Tumor types most likely to cause malignant effusions

- 1) Pleural effusions: lung cancer (35%), breast cancer (20%), leukemia/lymphoma (20%)
- 2) Pericardial effusions: lung cancer, breast cancer, leukemia/lymphoma, GI malignancies, sarcomas, melanoma (essentially all tumors that spread hematogenously)

### **Patient Case # 6 Continued**

SW returns to the office following initiation of immunotherapy. He reports increased symptoms of shortness of breath as well as rib pain. A chest x-ray is obtained to rule out pneumonia, immune-mediated pneumonitis as well as potential pleural effusion. The radiologist calls the clinic to let the team know that her x-ray shows a new pleural effusion.

### **What plan would you recommend for SW?**

- A. Drain the fluid
- B. Placement of chest tube on wall suction
- C. Place a small pigtail catheter in the chest wall
- D. Pleurodesis with doxycycline

d. Diagnostic tests<sup>254-257</sup>

- 1) Pleural effusions: chest x-ray (CXR), thoracentesis for fluid examination
- 2) Pericardial effusions: echocardiography, ECG, cardiocentesis for fluid examination for cytology.<sup>256</sup>
- 3) Examination of fluid for pleural effusion
  - a) Fluid should be sent for culture, gram stain, acid fast stains, cell counts, LDH, protein (a two test rule: if fluid cholesterol > 0.45 mg/dL or fluid LDH > 0.45 x lab upper limit of normal then exudates – many still use Lights criteria see below)
  - b) Malignant effusions are exudative, usually have high number of tissue cells, are often bloody (33% of pleural effusions)

2. Treatment<sup>254-257</sup>

a. General

- 1) Treat underlying cause (best method to prevent fluid re-accumulation)
- 2) Initial management for all types of effusions is a diagnostic “tap” to determine etiology of fluid accumulation. A therapeutic “tap” (removal of the majority of fluid) is typically done at the same time to minimize symptoms.
- 3) The need for additional procedures is determined by the rate of fluid re-accumulation and by severity of clinical symptoms.
- 4) Avoid drugs which “third space”, forming a depot of drug which leaches out slowly over time and prolongs drug exposure, which can increase toxicity (e.g., methotrexate).
- 5) Evaluate pain management and hold NSAIDS before, during and soon after procedures to avoid complications

b. Pleural effusions

- 1) Thoracentesis
  - a) Uses: diagnosis, acute symptom relief, temporary measure
  - b) Complications: pain, pneumothorax, hypotension, pulmonary edema, infection, fluid loculation.
- 2) Pleurodesis/Sclerotherapy
  - a) Indication: rapid re-accumulation of fluid after thoracentesis in refractory tumors. The best predictor of success is lung expansion, which indicates that the visceral and parietal pleura are in contact with each other (may seek radiologic evidence prior to treatment).
  - b) MOA: obliteration of the pleural space (between visceral and parietal pleura)
  - c) Complications: pain, fever, empyema, fluid loculation

### Agents Utilized for Pleurodesis

Agents			
	Talc <sup>258</sup>	Bleomycin <sup>259</sup>	Doxycycline <sup>260</sup>
<b>Dose</b>	5-10 grams	60 units	0.5 – 1 gram
<b>Route</b>	Intrapleural		
<b>Success rate</b>	90-100%	63-85%	60-88%
<b>Adverse effects</b>	Pain, hypotension, infection	Pain, fever, dyspnea	Pain, fever
<b>Comments</b>	Unclear if response rates from slurry equal VATS  Reports of abscesses from incompletely sterilized talc  Product used should be asbestos-free	May be less painful than other agents  Premedicate with acetaminophen to prevent fever	May require multiple instillations to achieve response rates above  Most studies done with tetracycline, which is no longer marketed

VATS: Video-Assisted Thoroscopic Surgery

- d) Medical pleurodesis (solution/slurry infusion through chest tube) has been compared to talc insufflation during a VATS procedure. No difference in efficacy (recurrence at 30 days) was reported; however, a subgroup analysis showed that primary lung cancer and breast cancer patients have more benefit from an aerosol canister. Additionally a meta-analysis comparing the two techniques found a decreased recurrence with thorascopic administration, but no difference in mortality.<sup>261,262</sup>
- 3) Surgery
    - a) Pleurectomy
    - b) Pleuroperitoneal shunt
    - c) External small bore pleural shunt which can be drained at home, a.k.a. Denver drain (Pleurx Pleural Catheter, Denver Biomaterials, Golden, Colorado)
    - d) The TIME2 unblinded, randomized control trial demonstrated no difference in patient-reported dyspnea and QOL in patients with malignant pleural effusion and no prior pleurodesis when comparing indwelling pleural catheters and chest tube with talc slurry pleurodesis.<sup>263</sup>
  - 2) Radiation: For lymphomatous pleural effusions only

**Patient Case #6 Follow Up:**

Answer A is correct.

Thoracentesis is appropriate for initial management of the effusion. The need for a chest tube or pleurodesis with doxycycline would be determined by the rate and volume of further fluid re-accumulation.

A therapeutic tap was performed and fluid was sent for gram stain, cytology, hematology, and chemistry. The results showed the fluid to be exudative in nature (LDH 240) and the cytology was consistent with lung cancer. 1 liter total is drained and SW experiences good symptomatic relief.

SW is discharged to continue receiving immunotherapy in the outpatient setting.

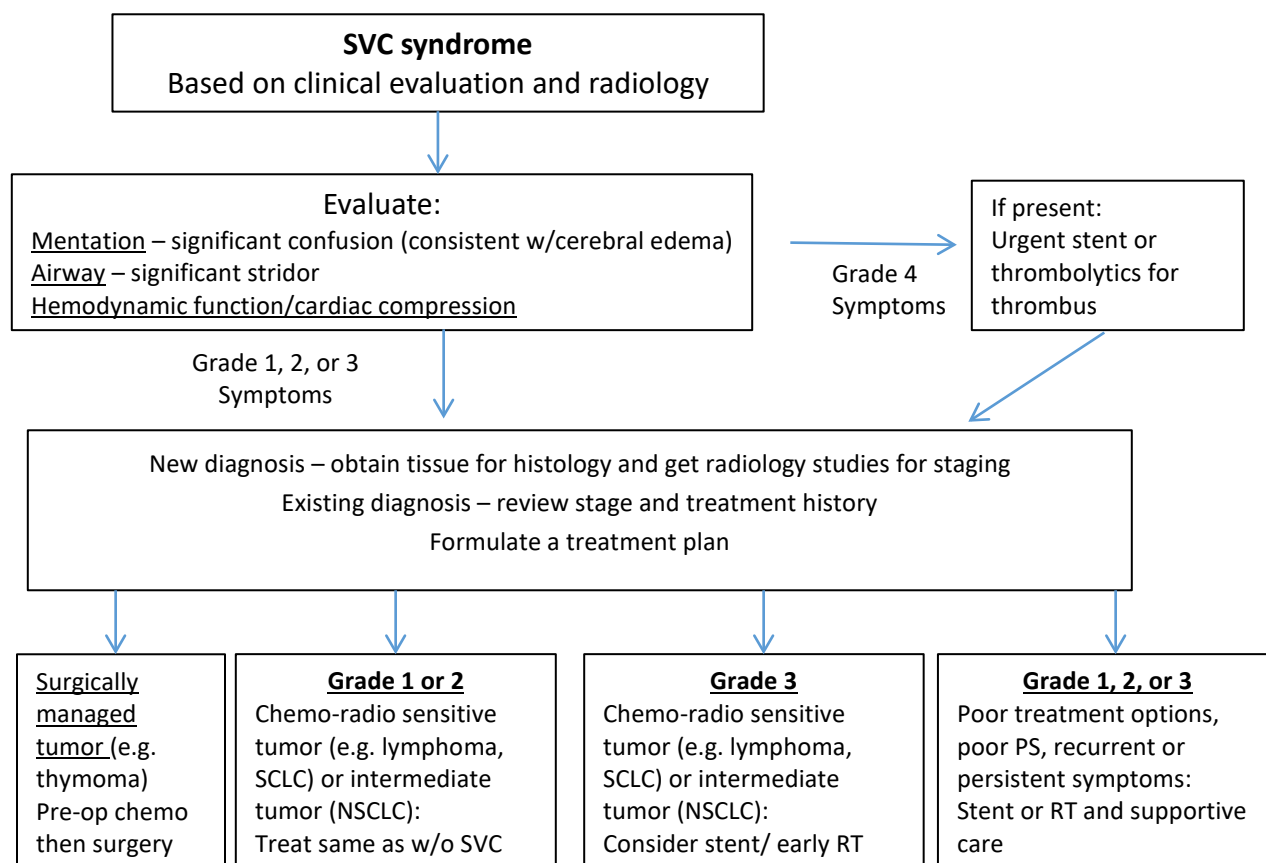
c. Pericardial effusions<sup>256</sup>

- 3) Pericardiocentesis – chronic drain reduces risk of recurrence +/- sclerotherapy
- 4) Surgery: pericardial window, subxiphoid pericardotomy
- 5) Hypotension/clinically unstable – emergent placement of a pericardial drainage catheter. Once stable additional treatment (pericardial window) or prolonged drainage usually required.
- 6) Sclerotherapy – reserved for recurrent effusions

B. Superior Vena Cava (SVC) Syndrome<sup>264-266</sup>

1. SVC syndrome is a constellation of symptoms and signs that result from compression of the superior vena cava with or without development of collaterals.
  - a. Symptoms include face swelling or head fullness which may be exacerbated by bending forward or arm swelling, dyspnea, stridor, cough, hoarseness, and dysphagia.
2. Causes of SVC Syndrome
  - a. Oncologic (60-80%)
    - 1) Lung cancer (75-80%) – 2-4 % of all lung cancer patients (10% of SCLC)
    - 2) Lymphoma with mediastinal mass (10-15%) – 2-4% of all NHL pts (rare in HD)
    - 3) Others: head and neck cancer, thymoma, germ cell tumors, breast cancer
2. Treatment
  - a. Goal is to remove compression, relieve symptoms, and prevent complications.
  - b. Below is a proposed treatment guideline

## Proposed Treatment Guideline for SVC<sup>266</sup>



Grade	Category	Definition
0	Asymptomatic	Radiographic SVC obstruction, (-) symptoms
1	Mild	Edema in the head or neck, cyanosis, plethora
2	Moderate	Edema in head or neck with functional impairment
3	Severe	Mild or moderate cerebral edema or mild/moderate laryngeal edema or diminished cardiac reserve
4	Life-threatening	Significant cerebral edema or significant laryngeal edema (stridor) or significant hemodynamic compromise
5	Fatal	Death

### 3. Supportive measures

- a. Bed rest, with head of bed elevated
- b. Oxygen for dyspnea and tachypnea, if needed
- c. Corticosteroids have been used to decrease inflammation associated with the tumor or radiation; however, clinical benefit has never been evaluated.
- d. Diuretics and low salt diet to reduce edema

**Patient Case #8**

JS is a 60-year-old woman who was recently diagnosed with early stage (stage II) NSCLC. She is a social drinker who stopped smoking 15 years ago. Her past medical history is significant for morning sickness with her 2 pregnancies, and motion sickness. JS has been treated for early stage breast cancer at age 29 with dose-dense AC and reports significant nausea with this regimen. Following surgical resection, her oncologist wishes to use cisplatin 75 mg/m<sup>2</sup> IV and pemetrexed 500 mg/m<sup>2</sup> IV on day 1 every 21 days as her chemotherapy regimen.

**1. Besides being female and having a past medical history of motion and morning sickness, what other risk factor does JS have for increased risk of nausea and vomiting?**

- A. Social drinker
- B. Non-smoker
- C. Poor nausea control with prior chemotherapy
- D. Patient age

**2. In addition to aprepitant 130 mg IV on day 1, she should receive which of the following medications for the prevention of acute nausea and vomiting according to ASCO, MASCC and NCCN®?**

- A. Palonosetron 0.25 mg IV plus dexamethasone 12 mg PO plus olanzapine 5 mg PO
- B. Palonosetron 0.25 mg IV plus dexamethasone 12 mg PO
- C. Ondansetron 8 mg IV plus dexamethasone 20 mg PO plus olanzapine 5 mg PO
- D. Ondansetron 4 mg IV plus dexamethasone 20 mg PO

**3. For the prevention of delayed nausea and vomiting, she should receive:**

- A. Dexamethasone 8 mg PO daily on day 2 to 4
- B. Dexamethasone 8 mg PO daily on days 2 to 4 plus olanzapine 5 mg PO daily on days 2 to 4
- C. Aprepitant 80 mg PO daily on days 2 and 3 plus dexamethasone 8 mg PO daily on days 2 to 4
- D. Aprepitant 80 mg PO daily on days 2 and 3 plus dexamethasone 8 mg PO daily on days 2 to 4 plus ondansetron 8 mg PO daily days 2 to 4

On day 5 she calls the clinic to complain of nausea and vomiting. She has been using prochlorperazine 10 mg PO Q6H without significant improvement. She is worried that her prior intolerance with chemotherapy is making her symptoms worse.

**4. What would be an acceptable addition to her antiemetic regimen in lieu of prochlorperazine?**

- A. Lorazepam 0.5 mg PO every 6 hours
- B. Haloperidol 5 mg PO every 6 hours
- C. Dronabinol 5 mg PO at bedtime
- D. Aprepitant 80 mg PO daily

**5. What would you add to her next cycle of chemotherapy to prevent delayed nausea and vomiting?**

- A. Metoclopramide 10 mg PO daily
- B. Dexamethasone 8 mg PO daily days 5 and 6
- C. Dronabinol 5 mg PO at bedtime
- D. Aprepitant 80 mg PO daily

## VI. Chemotherapy Induced Nausea and Vomiting (CINV)

### A. Antiemetic Guidelines

1. ASCO (American Society of Clinical Oncology)<sup>267</sup>, National Comprehensive Cancer Network (NCCN)<sup>®</sup> Antiemetic Guidelines<sup>®268</sup>, MASCC (Multinational Association of Supportive Care in Cancer) antiemetic guidelines<sup>269</sup>

### B. Important Definitions for Nausea and Vomiting (N/V)<sup>267,268</sup>

1. **Nausea** is described as the inclination to vomit or as a feeling in the throat/epigastric region alerting an individual that vomiting is imminent
  - a. It involves the loss of gastric tone and motility, with duodenal contractions and reflux of contents back into stomach (reverse peristalsis)
  - b. Concurrent tachycardia and hypersalivation occur
  - c. Nausea is the subjective urge to vomit; and therefore, it is difficult to quantify - usually measured with a patient-scored description (0 to 10) or visual analog scale <sup>31</sup>
  - d. Variable response to drug therapy
    - 1) Difficult to achieve complete control even with appropriately chosen/scheduled antiemetics
2. **Vomiting** is the ejection or expulsion of gastric contents through the mouth
  - a. Occurs via contraction of diaphragm and abdominal muscles, with opening of lower esophageal sphincter and forceful expulsion of gastric contents
  - b. Objectively quantified as number of episodes in 24 hours
  - c. Responsive to medication
  - d. Does not require nausea as precursor; e.g.: vomiting may come on by surprise without warning
3. **Retching** is the labored movement of abdominal and thoracic muscles before vomiting
  - a. Spasmodic and abortive respiratory movements, which are distinct from vomiting
  - b. Objectively quantified as number of episodes in 24 hours
  - c. Variable response to drug therapy
4. **Acute emesis** is vomiting that occurs during the first 24 hours after chemotherapy administration; peak occurs at 4 - 6 hours depending on the agent given and is responsive to drug therapy
5. **Delayed emesis** is vomiting occurring > 18-24 hours after chemotherapy administration, but may occur up to 5 days after chemotherapy with the peak in 2 to 3 days
  - a. Mechanism involves stimulation of neuroreceptors other than serotonin
  - b. Classic causative agent is cisplatin<sup>270,271</sup>
    - 1) Prior to the introduction of effective antiemetics, studies revealed a biphasic pattern consisting of emesis occurring within 2 hours of administration followed by a second

peak starting around 16 to 18 hours post dose. The 2<sup>nd</sup> peak reached is maximum intensity approximately 48 hours after administration.

- a) Concept of acute and delayed emesis created based on these observations and a demarcation between < 24 hours = 'acute' and > 24 hours = 'delayed'
- 2) Current data analysis suggests a differential time course for different antiemetics, i.e. serotonin (5-HT<sub>3</sub>)- and neurokinin (NK<sub>1</sub>)-dependent mechanisms for emesis secondary to cisplatin administration.
- c. Delayed nausea/vomiting has also been described for moderately emetogenic chemotherapy, including cyclophosphamide, carboplatin, doxorubicin, epirubicin, and ifosfamide which have a monophasic pattern of emesis.<sup>270,271</sup>
  - 1) Unknown if the mechanisms of 'delayed' nausea/vomiting is similar between cisplatin and other agents.
- d. Hesketh and colleagues summarized the existing data regarding the enhanced control of emesis with the use of aprepitant between cisplatin and AC-based chemotherapy as:<sup>270</sup>
  - 1) Time of aprepitant onset: 15 hours versus 3 hours with cisplatin and AC respectively.
  - 2) Time course of aprepitant: 15 to 60 hours versus 3 to 12 hours
  - 3) This data suggests that for cisplatin 5-HT<sub>3</sub>-dependent mechanisms appear most important during the first 12 hours after cisplatin administration and that NK<sub>1</sub>-dependent mechanisms become important thereafter up to 60 hours post administration.
  - 4) For AC-regimens, both 5-HT<sub>3</sub> and NK<sub>1</sub>-sensitive mechanisms appear to be important in the initial phase; prophylactic administration of NK<sub>1</sub>-inhibitor demonstrates greatest impact within the first 12 hours after chemotherapy.
- e. Patients who experience delayed emesis are at higher risk to develop anticipatory nausea/vomiting.
6. **Anticipatory emesis** is triggered by sights, smells, or sounds; due to poor control of nausea/vomiting in the past
  - a. Occurs before chemotherapy administration
  - b. Mechanism of action is a conditioned reflex not associated with stimulation of neuroreceptors.
  - c. Predisposing factors include: treatment for more than >6 months or with highly emetogenic agents, history of anxiety or depressive disorders, and history of poor antiemetic control
  - d. Prevention of nausea/vomiting with initial cycles of chemotherapy is the best treatment
  - e. Variable response to drug therapy
7. **Breakthrough emesis** occurs on the day of chemotherapy administration or during the delayed period despite appropriate antiemetic prophylaxis and requires the use of rescue therapy.



8. **Refractory emesis** can be seen in patients who have experienced severe nausea/vomiting on previous cycles of chemotherapy and occurs in spite of optimal antiemetic prophylaxis and treatment in previous cycles.

C. Causes

**Differential Diagnosis of Nausea/Vomiting in Cancer Patients**<sup>267,268</sup>

Therapy-Related	Chemotherapy Post-surgical	Radiation Therapy
Gastrointestinal	Gastric outlet obstruction Gastroparesis Partial or complete bowel obstruction Excessive secretions Malignant ascites	Constipation Hepatic metastases Pancreatitis
Neurologic	Severe or chronic pain Vestibular dysfunction	Increased intracranial pressure due to brain metastases
Metabolic	Hypercalcemia Hyperglycemia Hypoadrenalism	Hyponatremia Uremia
Non-Antineoplastic Drugs	Opioids Digitalis glycosides Antibacterials	Anesthetics Ethanol
Psychophysiologic	Anxiety	Anticipatory nausea and vomiting
Other	Cannabinoid hyperemesis syndrome Rapid opioid withdrawal	

**Patient-Related Risk Factors for Chemotherapy-Induced Nausea and Vomiting**<sup>272,273</sup>

Prior experiences with chemotherapy	Children have more N/V than adults
Poor control in previous treatments increases the risk of N/V in subsequent cycles, especially anticipatory N/V	History of morning sickness with previous pregnancies
Psychosocial factors (anxiety, distress, etc.)	Gender (women > men)
History of depression predisposes patients to increased N/V	History of motion sickness
Decreased amount of sleep night before treatment (correlates better with delayed N/V than acute N/V)	Age (< 50 years old))
<b>PROTECTIVE:</b> alcohol use (defined as $\geq 5$ alcoholic drinks / week)	

**Patient Case #8: Answer to question #1**

**Correct answer is C.**

The female gender is more predisposed to nausea and vomiting. Patients with a history of morning sickness or motion sickness seem to also be predisposed to increased nausea and vomiting. Her prior challenges with nausea/vomiting during treatment for her breast cancer increases her risk of CINV this time. Smoking history or current smoking has not been found to be either a positive or negative risk factor. Ethanol abuse has been associated with a decreased risk of nausea and vomiting, but casual drinking is not likely to have an impact.<sup>267-269</sup>

D. Predicting acute and delayed CINV

1. Models have been developed to predict patients at risk for  $\geq$  grade 2 acute and/or delayed CINV.<sup>274</sup>
2. Acute CINV:<sup>274</sup>
  - a. Predictors for  $\geq$  grade 2 acute CINV include:
    - 1) Age  $\leq$  40 years
    - 2) Disease stage I or II
    - 3) Anthracycline- or platinum-based chemotherapy
    - 4) Use of non-prescription drugs at home for N/V
  - b. Factors associated with lesser risk for  $\geq$  grade 2 acute CINV include:
    - 1) Age > 40 years
    - 2) Gynecologic and gastrointestinal disease sites
    - 3) Comorbidity (cardiovascular, diabetes, gastrointestinal, musculoskeletal or thyroid condition)
    - 4) Daily alcohol consumption
    - 5) Cycle 3 or greater in treatment course
3. Delayed CINV<sup>274</sup>
  - a. Predictors for  $\geq$  grade 2 delayed CINV include:
    - 1) Age  $\leq$  40 years
    - 2) Dexamethasone  $\pm$  ondansetron after chemotherapy (might be due to more emetogenic chemotherapy being used in the regimen)
    - 3) CINV with prior cycles
    - 4) Morning sickness with pregnancy
    - 5) Acute CINV episodes with current cycle
  - b. Factors associated with lesser risk for  $\geq$  grade 2 delayed CINV include:
    - 1) Hours of sleep night before chemotherapy (greater hours = more protection)
    - 2) Cycle 3 or greater in treatment course

E. Emetogenicity of chemotherapy regimens

1. Based on the percentage of patients who have emesis without premedication
2. Various ratings have been proposed through the years
  - a. Hesketh and colleagues published a proposal for classifying the acute emetogenicity of cancer chemotherapy based on 5 levels with level 1 being minimal and level 5 being highly emetogenic.<sup>275</sup>
  - b. Recommendations vary between the guidelines, but have been simplified from five levels to

four levels by combining the original level 3 (30-60% of patients with emesis) and level 4 (60-90% of patients with emesis) into a single, moderately emetogenic category encompassing 30-90% emesis incidence.<sup>276</sup>

- 1) High (level 4): > 90% incidence of emesis in both the acute and delayed setting
  - 2) Moderate (level 3): 30-90% incidence of emesis in both the acute and delayed setting
  - 3) Low (level 2): 10-30% incidence of emesis in the acute setting
  - 4) Minimal (level 1): < 10% incidence of emesis in the acute setting
- c. Given the lack of objective data, current recommendations are based on opinions of authors and open to critique.
- d. At the 2009 MASCC / ESMO Consensus Conference, an expert panel used best available data to establish rankings of emetogenicity for chemotherapy agents. In addition, oral chemotherapy agents are now ranked separately from IV agents as there are intrinsic differences in emetogenicity as well as different schedules of administration.<sup>269</sup>
3. Combination chemotherapy is usually more emetogenic than single agent regimens.
4. Emetogenicity is dose-related, with high-dose chemotherapy regimens (i.e., stem cell transplant conditioning regimens) being more emetogenic.
5. This handout summarizes the guidelines from ASCO, MASCC and NCCN® and has added published data where appropriate.<sup>267-269</sup> For a complete list of emetogenic risk for each oncology agent, please reference the specific guideline.
- F. Agents available for prevention and/or treatment of CINV<sup>267-269</sup>
1. Single-agent serotonin (5-HT<sub>3</sub>) antagonists (dolasetron (manufacturer discontinued), granisetron, ondansetron, palonosetron)
    - a. Mechanism of action: selective antagonism of serotonin receptor subtype 3.
    - b. Blocks serotonin in two ways: peripheral antagonism by blocking release from enterochromaffin cells in the GI tract and central antagonism of receptors in the medulla.
      - 1) Palonosetron is only 5-HT<sub>3</sub> antagonist with allosteric and facilitative binding to receptor. Although the clinical significance is unknown, it may explain why palonosetron— and none of the other agents/formulations in this class - has efficacy in delayed CINV.<sup>277</sup>
  - c. Adverse effects include:
    - 1) Headache
    - 2) Asymptomatic/transient ECG abnormalities seen with all 5-HT<sub>3</sub> antagonists (PR, QT, and ST prolongation and QRS widening)
      - a) Two exceptions:
        1. Palonosetron, which appears to be devoid of cardiac ADR, despite information within FDA-approved package insert.<sup>278,279</sup>
        2. Granisetron transdermal and subcutaneous extended release (but not intravenous or oral)<sup>280</sup>

- b) Ondansetron 32 mg dose given “black-box” warning in June 2012 due to clinically significant tachyarrhythmias, including QTc prolongation and torsades de pointes
  - c) Maximum dose of ondansetron per 24 hours = 24 mg orally or 16 mg IV
- 3) Somnolence/sedation/dizziness
- 4) Constipation/diarrhea
- d. All agents, when administered at equipotent doses (IV or oral) and schedule, seem to have similar efficacy and safety. Choice should be based on cost, reimbursement, and your organizational formulary.
- e. Meta-analysis<sup>281</sup> found that neither clinical evidence nor consideration of cost-effectiveness justify using 5-HT<sub>3</sub> antagonists beyond 24 hours to prevent delayed nausea/vomiting.
- f. Palonosetron
  - 1) Study compared palonosetron 0.25 mg IV with dexamethasone 8 mg IV on Day 1 with the same followed by dexamethasone 8 mg PO daily on days 2 and 3 in patients receiving moderately emetogenic chemotherapy<sup>282</sup>
    - a) Overall CR rates were 67.5% for patients receiving day 1 dexamethasone and 71.1% for those receiving dexamethasone on days 1, 2 and 3 (difference -3.6%; 95% CI, -13.5 to 6.3).
    - b) Conclusion: palonosetron plus a single dose of dexamethasone is non-inferior to three days of dexamethasone, however the major benefit was seen in patients receiving non-AC moderately emetogenic regimens.
  - 2) Systematic review and meta-analysis comparing palonosetron to other 5-HT<sub>3</sub> antagonists<sup>283</sup>
    - a) 5 studies were included with a total of 2,057 patients
    - b) Palonosetron vs. other 5-HT<sub>3</sub> antagonists (dolasetron, granisetron (IV and PO, not transdermal) and ondansetron)
    - c) Patients who received palonosetron had less nausea, acute (RR=0.86; 95% CI, 0.76 - 0.96; p=0.007) and delayed (RR=0.82; 95% CI, 0.75 - 0.89; p<0.00001).
    - d) Patients who received palonosetron also had less vomiting, acute (RR=0.76; 95% CI, 0.66 - 0.88; p=0.0002) and delayed (RR=0.76; 95% CI, 0.68 - 0.85; p<0.00001).
    - e) No statistically-significant differences in adverse effects were seen, including constipation (RR=1.29; 95% CI, 0.77 - 2.17; p=0.33); diarrhea (RR=0.67; 95% CI, 2.04 - 1.85; p=0.44); dizziness (RR=0.4; 95% CI, 0.13 - 1.27; p=0.12) and headache (RR=0.84; 95% CI, 0.61 - 1.17; p=0.30).
    - f) Conclusion: palonosetron was more effective than other 5-HT<sub>3</sub> antagonists in preventing both acute and delayed CINV when receiving moderately or highly emetogenic chemotherapy regardless of whether corticosteroids were used concomitantly.
    - g) NCCN does not preferentially recommend palonosetron over other 5-HT<sub>3</sub> antagonists with the exception of when moderately emetogenic chemotherapy is

given without a neurokinin-1 receptor antagonist or in combination with olanzapine and dexamethasone. If palonosetron is given on day 1 of therapy for antiemesis prophylaxis, no further 5-HT<sub>3</sub> therapy is required.

- g. Granisetron transdermal patch<sup>284-286</sup>
    - 1) Contains 34.3 mg of granisetron and releases 3.6 mg / day
    - 2) Should be applied 24 to 48 hours prior to chemotherapy
    - 3) Found to be non-inferior to PO granisetron 2 mg daily for 3 to 5 days in the setting of highly and moderately emetogenic chemotherapy
  - h. Granisetron subcutaneous extended release injection<sup>287</sup>
    - 1) Contains 10 mg of granisetron designed to release up to 7 days, given at least 30 minutes prior to chemotherapy on day 1
    - 2) FDA approved for moderately emetogenic chemotherapy or anthracycline/cyclophosphamide chemotherapy in combination with dexamethasone.
    - 3) Evaluated in a phase 3 trial randomizing patients receiving a single-day moderately or highly-emetogenic chemotherapy to either palonosetron 0.25 mg IV or granisetron subcutaneous (5 mg or 10 mg). All patients received dexamethasone, but no neurokinin-1 antagonist.<sup>82</sup>
      - a) Highly-emetic chemotherapy: acute complete response was 77.7% for 5 mg granisetron, 81.3% for 10 mg granisetron and 80.7% for palonosetron
        - 1. Granisetron subcutaneous was deemed to be not inferior to palonosetron.
      - b) Moderately-emetic chemotherapy: acute complete response was 74.8% for 5 mg granisetron, 76.9% for 10 mg granisetron and 75% for palonosetron.
    - 4) NCCN does not preferentially recommend granisetron subcutaneous extended release injection over other 5-HT<sub>3</sub> antagonists with the exception of when moderately emetogenic chemotherapy is given without a neurokinin-1 receptor antagonist.
2. Neurokinin-1 (NK-1) Receptor Antagonists
- a. Aprepitant, fosaprepitant (prodrug of aprepitant)
    - 1) Highly protein-bound (95%) and crosses both the blood-brain barrier and placenta
    - 2) A single dose of 150 mg of IV fosaprepitant was compared to the three-day oral regimen of aprepitant 125 mg on Day 1 followed by 80 mg on Days 2 & 3<sup>288</sup>
      - a) Antiemetic protection was equivalent between aprepitant and fosaprepitant; therefore, efficacious irrespective of route
    - 3) Aprepitant injectable emulsion was compared to intravenous fosaprepitant<sup>289</sup>
      - a) Aprepitant IV (130 mg) deemed bioequivalent to intravenous fosaprepitant (150 mg)
      - b) Fewer treatment-emergent adverse events compared to fosaprepitant

- 4) Review<sup>290</sup> and pooled analysis<sup>291</sup> have further shown the efficacy of aprepitant as part of combination antiemetic regimen in various tumor types and chemotherapy regimens
- 5) Aprepitant has complex metabolism<sup>292-296</sup>
  - a) Substrate of CYP3A4, but length of administration complicates this
    1. Administered for 3 days per cycle of chemotherapy, it is an inhibitor of CYP3A4
    2. Administered > 14 days it a potent inducer of both CYP3A4 and 2C9
- 6) Review of aprepitant and drug-drug interactions<sup>297</sup>
  - a) Authors concluded that there is either no interaction or no clinically relevant interaction between chemotherapy agents (cyclophosphamide, docetaxel, vinorelbine) or serotonin antagonists (granisetron, ondansetron, palonosetron) and aprepitant.
  - b) Relevant interactions, such as with corticosteroids are managed by dose modifications and/or monitoring of patients can effectively manage these.
  - c) Caution should be used when administering aprepitant with any drug metabolized by CYP3A4 including:
    1. Oral contraceptives – decreases efficacy, therefore women of child-bearing years should use another form of birth control when using aprepitant
    2. Warfarin – patients being treated with therapeutic warfarin will need to have their INR checked 7-10 days after the completion of their 3-day regimen as there may be clinically significant decrease in INR.
    3. Dexamethasone / Methylprednisolone – increased AUCs of dexamethasone were seen in clinical trials; reduced doses should be used.<sup>298</sup> Most significant for PO administration.
- b. Rolapitant (Varubi®)
  - 1) NK-1 antagonist with several key differences from aprepitant:
    - a) Half-life = 180 hours (vs. 9-13 hours with aprepitant); allowing for single dose for most chemotherapy regimens
    - b) Do not administer at less than 2-week intervals.
    - c) Neither inhibitor nor inducer of CYP 3A4 (does not inhibit dexamethasone metabolism)
    - d) Moderate inhibitor of CYP 2D6 and p-glycoprotein
    - e) Inhibits breast cancer resistance protein (BCRP); caution in combination with gefitinib, methotrexate, lapatinib, mitoxantrone, imatinib, topotecan, and irinotecan
    - f) Drug-drug interaction with other agents: cyclosporine, HMG-CoA reductase inhibitors. There is no drug-drug interaction with rolapitant and dexamethasone.
  - 2) Dosing of rolapitant:

- a) 180 mg *PO* once prior to first dose of highly- or moderately-emetogenic chemotherapy (in combination with dexamethasone and 5-HT<sub>3</sub> antagonist)
  - b) IV rolapitant voluntarily removed from the market due to hypersensitivity reactions.
- 3) Prevention of cisplatin-associated CINV<sup>299</sup>
  - a) Report of 2 similar studies pooled together in total of 1,070 patients; primary difference between studies was location
  - b) Rolapitant 180 mg *PO* once on day 1 vs placebo + granisetron 10 µg/kg IV once on day 1 + dexamethasone 20 mg *PO* once on day 1 with 8 mg *PO* BID on days 2-4
  - c) Results from study 1 demonstrate 72.7% complete response rate (no rescue medication or emetic episode) with rolapitant vs. 58.4% complete response rate with placebo (p<0.001) and results from study 2 demonstrate 70.1% complete response rate with rolapitant vs. 61.9% complete response rate with placebo (p<0.043)
- 4) Prevention of anthracycline plus cyclophosphamide or moderately emetogenic CINV<sup>300</sup>
  - a) 1,369 patients randomized to rolapitant 180 mg *PO* once on day 1 or placebo + granisetron 2 mg *PO* daily on days 1-3 + dexamethasone 20 mg *PO* once on day 1
  - b) Results demonstrate 71.3% complete response rate (no emetic episodes or rescue medication) with rolapitant vs. 61.6% complete response rate with placebo (p<0.001)
- 5) Most common treatment-emergent adverse effects were headache, constipation, and fatigue
- 3. Combination 5-HT<sub>3</sub> plus NK-1 antagonist (netupitant / palonosetron (oral) and fosnetupitant/palonosetron (IV))<sup>301,302</sup>
  - a. Fixed dose combination of netupitant 300 mg and palonosetron 0.5 mg orally administered on day 1 of highly-emetogenic (e.g.; cisplatin-based or anthracycline plus cyclophosphamide-based) regimen
    - 1) Dexamethasone dosing differs by regimen:
      - a) Cisplatin-based: dexamethasone 12 mg orally on day 1 and 8 mg orally once-daily on days 2, 3 and 4
      - b) Anthracycline plus cyclophosphamide-based: dexamethasone 12 mg orally on day 1 only
    - 2) Netupitant is a CYP3A4 inhibitor; inhibition may last 4 days following administration
  - b. Aapro et al<sup>302</sup> conducted a phase 3 randomized trial comparing netupitant/palonosetron to palonosetron 0.5 mg orally in 1455 patients receiving moderately emetogenic chemotherapy (anthracycline-cyclophosphamide). All patients received oral dexamethasone. The combination netupitant/palonosetron resulted in a CR during the delayed phase of 76.9% vs. 69.5% with palonosetron alone (p=0.001). Netupitant/palonosetron was superior in all phases of CINV.

- c. Zhang et al<sup>303</sup> conducted a non-inferiority trial in 828 patients receiving highly-emetogenic chemotherapy who were randomized to either netupitant/palonosetron or aprepitant/granisetron. All patients received dexamethasone on days 1-4. The non-inferiority criteria was set at 10%. Netupitant/palonosetron demonstrated non-inferiority to aprepitant/granisetron with CR rates of 73.8% and 72.4%, respectively.
- d. IV fosnetupitant and palonosetron combination
  - 1) 404 patients were randomized to receive oral netupitant/palonosetron or IV fosnetupitant/palonosetron with oral dexamethasone on days 1-4, results demonstrated similar incidence and adverse events in both group.<sup>304</sup>
4. Corticosteroids (dexamethasone, methylprednisolone)<sup>268</sup>
  - a. Exact mechanism is unknown<sup>305</sup>:
    - 1) Inhibition of prostaglandin synthesis in the cortex
    - 2) Decreased serotonin turnover in the CNS
    - 3) Modulation of higher cortical pathways that lead to the emetic center
    - 4) NCCN guidelines note that dexamethasone doses may be individualized based on patient characteristics or intolerance to steroids.
      - a) For patients receiving MEC or non-cisplatin HEC, with few identifiable CINV risk factors or who are intolerant to corticosteroids can limit administration of dexamethasone to day 1 only<sup>306,307</sup>
      - b) If patients cannot tolerate dexamethasone, consider replacing with olanzapine.
    - 5) Data exists about the concern with use of corticosteroids in patients receiving cellular therapies as dexamethasone may interfere.<sup>268</sup>
      - a) Corticosteroid premedication for antiemesis should be avoided for 3-5 days prior to and 90 days after CAR T-cell therapies.
      - b) NCCN® panel removed language previously advising avoidance with dexamethasone and lymphodepleting chemotherapy regimens as well as language describing use of corticosteroids as not recommended with immunotherapies and cellular therapies
      - c) There is no clinical evidence to warrant omission of dexamethasone from guideline-compliant prophylactic antiemetic regimens when checkpoint inhibitors are administered to adults in combination with chemotherapy. Checkpoint inhibitors administered alone or in combination with another checkpoint inhibitors do not require the routine use of a prophylactic antiemetic.
5. Benzamide analogs (metoclopramide, trimethobenzamide)
  - a. Metoclopramide possesses three mechanisms of action contributing to its antiemetic properties.
    - 1) Blocks dopamine at the chemoreceptor trigger zone (CTZ)
    - 2) Stimulates cholinergic activity in the gut, causing increased gut motility
    - 3) Blocks peripheral serotonin receptors in enterochromaffin cells (high-dose only)



- b. Adverse effects include mild sedation, explosive diarrhea, edema, HTN secondary to sodium retention, and, extrapyramidal symptoms (EPS), reversible impotence caused by elevation of prolactin concentration.
    - 1) EPS occur more commonly at higher concentrations ( $\geq 0.5$  mg/kg per dose) and are also age-dependent with an incidence of 27% in patients 15-30 years old and 1.8% of patients 30-72 years old; males have higher incidence than females.<sup>308</sup>
  - c. Use in patients with CINV
    - 1) Only high-dose (0.5 - 2 mg/kg per dose) is effective for highly emetogenic agents and was the therapy of choice prior to approval of serotonin antagonists
    - 2) High-dose therapy requires concomitant anticholinergic agent, such as diphenhydramine, to prevent EPS
    - 3) Doses  $< 0.5$  mg/kg (often, 10 - 40 mg/dose) are effective for moderately and mildly emetogenic agents or for delayed nausea/vomiting<sup>309</sup>
  - d. Main use is for breakthrough nausea/vomiting
- 6. Phenothiazine derivatives (prochlorperazine, promethazine, chlorpromazine)
  - a. The phenothiazine derivatives all work by blocking dopamine receptors
    - 1) Promethazine is a potent histamine<sub>1</sub> antagonist which crosses blood-brain barrier easily
  - b. Common adverse effects of this class include sedation, hypotension, akathisia, and dystonia
  - c. Role for prochlorperazine use in cancer patients
    - 1) Effective with moderately and mildly emetogenic agents
    - 2) Most flexible routes of administration (PO, IV, IM, PR)
      - a) IV formulation is not recommended
  - d. Promethazine is a weak antiemetic and not preferred in adult cancer patients
  - e. Main use is for breakthrough nausea/vomiting
- 7. Butyrophenones (haloperidol, droperidol)
  - a. The mechanism of action of these two agents are similar to the phenothiazines (i.e., blocks dopamine receptors in the CTZ)
  - b. Offer a different chemical structure that has different allosteric binding to the dopamine receptor; an suitable alternative when a phenothiazine fails
  - c. The most common adverse effect is sedation and anticholinergic effects. Hypotension is less frequent than with the phenothiazines and EPS is also uncommon
  - d. Role in patients with CINV<sup>310</sup>
    - 1) Effective with highly, moderately, and mildly emetogenic agents
    - 2) Often administered as a breakthrough antiemetic
    - 3) Routine prophylaxis with anticholinergic agent to prevent EPS is generally not required

- 4) Haloperidol is less sedating than other dopamine-blocking antiemetics (except droperidol)
8. Benzodiazepines (lorazepam)
    - a. Lorazepam is useful to prevent anticipatory N/V by causing anterograde amnesia.
      - 1) In addition, it decreases associated anxiety that may contribute to vomiting.
      - 2) Causes global CNS depression, reducing CNS signaling pathway in dose-dependent manner
    - b. For breakthrough CINV, benzodiazepines work via global CNS depression, including CTZ depression.
    - c. Adverse effects include amnesia, sedation, hypotension, perceptual disturbances (hallucinations), urinary incontinence, disinhibition, and motor incoordination
    - d. Role for use in patients with CINV<sup>268</sup>
      - 1) Best used in combination with other antiemetics or for breakthrough N/V
      - 2) The most effective agents for anticipatory vomiting
    - e. Lorazepam exhibits significant drug-drug interaction with posaconazole in acute leukemia and/or allogeneic HSCT patients.<sup>311</sup>
  9. Cannabinoids (dronabinol, nabilone)
    - a. Target cannabinoid receptor CB<sub>1</sub> in both the central and peripheral nervous systems<sup>312,313</sup>
    - b. Pharmacokinetics of dronabinol and nabilone are quite similar with the major exception being nabilone has fewer metabolites and a longer duration of action
      - 1) Both agents are metabolized by the 2C9 isoenzyme of the CYP P450 system
      - 2) Dronabinol can inhibit CYP 450 3A4 isoenzyme
    - c. Nabilone is a synthetic delta-9-tetrahydrocannabinol analog; used in other countries for many years
      - 1) Meta-analysis on nabilone for the treatment of CINV and pain has been published.<sup>314</sup>
        - a) Nabilone is superior to placebo, domperidone and prochlorperazine
        - b) Nabilone is equivalent to metoclopramide or chlorpromazine
        - c) Combinations of nabilone with prochlorperazine or metoclopramide are better than either drug alone, however dexamethasone plus metoclopramide combinations are more effective than a cannabinoid plus prochlorperazine
    - d. Adverse effects include drowsiness, dizziness, euphoria, dysphoria, mood changes, orthostatic hypotension, ataxia, hallucinations, time disorientation and increased appetite
      - 1) Dysphoric effects tend to be less in patients who use or have used marijuana.
    - e. Role for use in patients with breakthrough CINV
      - 1) Effective with low and moderate emetogenic agents

- 2) Tolerance usually develops to the adverse effects
- f. Meta-analysis of the use of the natural product, *Cannabis sativa*, and derivatives on CINV<sup>315</sup>
  - 1) Out of 12,749 identified papers, 30 met the criteria to be included in the review
  - 2) Dronabinol had superior anti-emetic efficacy versus neuroleptics (e.g. prochlorperazine, metoclopramide, chlorpromazine) for patients receiving chemotherapy
  - 3) No statistical significant difference between dronabinol and placebo for CINV; however, there was a clinically significant difference favoring dronabinol
  - 4) No statistical significant difference between nabilone and neuroleptic for CINV; however, there was a clinically significant difference favoring nabilone
10. Belladonna alkaloid (scopolamine patch)<sup>316</sup>
  - a. May work by blocking acetylcholine receptors in the vestibular apparatus
  - b. Adverse effects include dry mouth, sedation, and impaired eye accommodation
  - c. Useful in patients whose nausea and vomiting is positional or due to motion
  - d. Patients should be instructed not to touch the patch then touch their eye without washing hands due to risk of unilateral mydriasis
11. Miscellaneous Agents / Treatments
  - a. Olanzapine
    - 1) Potently blocks many subtypes of dopaminergic, serotonergic, histaminergic and muscarinic receptors, some of which play roles in CINV, albeit to a lesser extent than well-known subtypes dopamine<sub>2</sub> and 5-HT<sub>3</sub>.<sup>317</sup>
    - 2) Phase III trial comparing olanzapine versus aprepitant for the prevention of CINV<sup>318</sup>
      - a) Chemotherapy-naïve patients receiving cisplatin  $\geq 70$  mg/m<sup>2</sup> or cyclophosphamide  $\geq 500$  mg/m<sup>2</sup> plus doxorubicin  $\geq 50$  mg/m<sup>2</sup> were enrolled
      - b) A total of 251 patients were randomized to OPD (palonosetron 0.25 mg IV, dexamethasone 20 mg IV and olanzapine 10 mg on day 1 and olanzapine 10 mg on days 2 to 4) or APD (palonosetron 0.25 mg IV, dexamethasone 12 mg PO and aprepitant 125 mg day 1 followed by aprepitant 80 mg PO on days 2 & 3 with dexamethasone BID on days 2 to 4)
      - c) For the OPD regimen: CR was 97% for the acute period, 77% for delayed period (days 2 to 5) and 77% for overall period (0 - 120 hrs)
      - d) For the APD regimen CR was 87% for the acute period, 73% for the delayed period and 73% for the overall period
      - e) Patients without nausea were 87% for acute, 69% delayed and 69% for the OPD regimen versus 87% acute, 38% delayed and 38% overall for the APD regimen
      - f) Authors concluded that OPD was comparable to APD in control of CINV with OPD being better at controlling nausea; OPD antiemetic regimen is NCCN® category 1 and recommended in ASCO guidelines.<sup>267,268</sup>

- 3) Olanzapine 10 mg orally daily x 3 days versus metoclopramide 10 mg orally TID x 3 days for treatment of breakthrough CINV in 80 patients receiving highly-emetogenic chemotherapy.<sup>319</sup>
  - a) All patients received palonosetron, fosaprepitant and dexamethasone pre-chemotherapy, with dexamethasone on days 2-4 at appropriate doses per ASCO and NCCN Guidelines®
  - b) Patients with breakthrough CINV received either olanzapine or metoclopramide
  - c) During 72-hour observation period, 67% of olanzapine and 24% of metoclopramide patients experienced no nausea ( $p < 0.01$ ); 71% of olanzapine and 32% of metoclopramide patients experienced no emesis ( $p < 0.01$ )
  - d) Authors conclude that olanzapine was significantly better than metoclopramide for treatment of breakthrough CINV following highly-emetogenic chemotherapy.
  - e) Major flaw of study is comparator arm of metoclopramide 10 mg/dose, which is an insufficient dose of metoclopramide for highly-emetogenic chemotherapy.
- 4) Phase III randomized, placebo controlled trial<sup>320</sup>
  - a) High-emetic risk chemotherapy (cisplatin-based or AC)
  - b) Olanzapine 10 mg on days 1-4 or placebo on days 1-4
  - c) All patients received NK1 antagonist, serotonin antagonist, and dexamethasone
  - d) Rates of no nausea
    1. 0-24 hours: 74% olanzapine vs 45% placebo
    2. 24-120 hours: 42% olanzapine vs 25% placebo
    3. 0-120 hours: 37% olanzapine vs 22% placebo
  - e) Driving clinical trial that prompted adding olanzapine to the ASCO and NCCN® guidelines.<sup>267</sup>
- 5) A dose of 5 mg of olanzapine can be considered efficacious instead of 10 mg. Consider 5 mg dosing especially for elderly, debilitate, frail patients or patients that are overly-sedated, or at risk for orthostatic hypotension. Olanzapine 5 mg was found to have similar improvement in delayed nausea vomiting as compared to 10 mg with less sedation.<sup>321</sup>
  - a) Phase 3, multicenter, double-blind, placebo-controlled trial evaluated olanzapine 5 mg plus standard antiemetic therapy for prevention of CINV (J-FORCE)<sup>322</sup>
    1. High-emetic risk chemotherapy (cisplatin  $\geq 50$  mg/m<sup>2</sup>)
    2. Olanzapine 5 mg on days 1-4 or placebo on days 1-4
    3. All patients received NK1 antagonist, palonosetron, and dexamethasone
    4. In the delayed phase (24 – 120 hr) the proportion of patients who achieved a complete response was 79% in the olanzapine group compared to 66% in the placebo group ( $P < 0.0001$ )

- 6) Consider 2.5 mg of olanzapine if patients report excessive sedation with 5 mg dose.<sup>268</sup>
- 7) If dexamethasone is eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg, olanzapine)<sup>268</sup>
- 8) Adverse effects include extrapyramidal symptoms, weight gain, dyslipidemia, CNS depression, orthostatic hypotension, QTc prolongation
- 9) Use caution with concomitant use of olanzapine with haloperidol or metoclopramide due to increased risk of EPS. Avoid intravenous use of both olanzapine and benzodiazepines. For olanzapine-containing regimens, use only oral lorazepam if needed.<sup>268</sup>

#### G. Important Principles for the Prevention and Management of CINV

1. Basic principles and clinical pearls<sup>268,269</sup>
  - a. Evaluate each patient individually:
    - 1) Review history, diagnosis, prior use and success/failure of antiemetics, and concurrent medications
    - 2) Butyrophenones, corticosteroids, and serotonin antagonists are the least sedating
    - 3) EPS is a risk with phenothiazines, butyrophenones, and metoclopramide
  - b. Evaluate the emetogenic potential and pattern of the chemotherapeutic regimen to be given.<sup>272</sup>
    - 1) Emetogenic potential may be different on different days of treatment (e.g., highly on day 1 and moderately on days 2 and 3); antiemetics should be tailored accordingly.
  - c. Antiemetics are most effective when given prophylactically.
    - 1) Begin therapy at least 30 minutes prior to chemotherapy
    - 2) Administer around-the-clock until chemotherapy is complete and provide PRN agents for breakthrough N/V
    - 3) Provide patients with additional PRN anti-emetics to take home after chemotherapy. Generally an agent with a different mechanism of action should be provided. Some patients may require multiple mechanisms of action for control.<sup>268</sup>
    - 4) Nausea is more challenging to control than emesis
  - d. Health literacy should be taken into consideration with planning an anti-emetic regimen. Clinicians need to identify language and literacy barriers and provide resources (e.g., printed materials, medication calendars, interpreter services) to help whenever possible.

#### H. Current guideline recommendations for adult patients

1. Highly emetogenic chemotherapy<sup>267-269</sup>
  - a. ASCO<sup>267</sup>
    - 1) Highly emetogenic chemotherapy: cisplatin and other agents
      - a) To prevent ACUTE CINV: all patients should be offered a four-drug combination of a NK1 antagonist plus serotonin antagonist plus dexamethasone and olanzapine.

- b) To prevent DELAYED CINV: olanzapine should be continued on days 2-4 along with dexamethasone.
- 2) Highly emetogenic chemotherapy: anthracycline combined with cyclophosphamide
  - a) To prevent ACUTE CINV: all patients should be offered a four-drug combination of a NK1 antagonist plus serotonin antagonist plus dexamethasone and olanzapine.
  - b) To prevent DELAYED CINV: olanzapine should be continued on days 2-4 alone.

b. NCCN<sup>268</sup>

- 1) Highly emetogenic chemotherapy: multiple options available

Highly emetogenic Chemotherapy (acute and delayed emesis prevention (All options are Category 1)		
	Day 1	Days 2, 3, 4
Option A (NCCN <b>Preferred</b> Recommendation)	Olanzapine 5-10 mg PO once One NK1 RA listed below: <ul style="list-style-type: none"> <li>• Aprepitant 125 mg PO once</li> <li>• Aprepitant 130 mg IV once</li> <li>• Fosaprepitant 150 mg IV once</li> <li>• Netupitant 300 mg / palonosetron 0.5 mg PO once</li> <li>• Fosnetupitant 235 mg / palonosetron 0.25 mg IV once</li> <li>• Rolapitant 180 mg PO once</li> </ul> One 5-HT3 RA listed below, unless combination product selected above: <ul style="list-style-type: none"> <li>• Dolasetron<sup>a</sup> 100 mg PO once</li> <li>• Granisetron 10 mg SQ or 2 mg PO or 0.01 mg/kg (Max 1 mg) IV once or 3.1 mg/24 hr transdermal patch applied 24-48 hours prior to first dose of chemotherapy</li> <li>• Ondansetron 16-24 mg PO once, or 8-16 mg IV once</li> <li>• Palonosetron 0.25 mg IV once</li> </ul> Dexamethasone 12 mg PO/IV once	Olanzapine 5-10 mg PO daily on days 2, 3, 4 Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1)  Dexamethasone 8 mg PO/IV daily on days 2, 3, 4
Option B	Olanzapine 5-10 mg PO once Palonosetron 0.25 mg IV once Dexamethasone 12 mg PO/IV once	Olanzapine 5-10 mg PO daily on days 2, 3, 4
Option C	One NK1 RA listed below: <ul style="list-style-type: none"> <li>• Aprepitant 125 mg PO once</li> <li>• Aprepitant 130 mg IV once</li> <li>• Fosaprepitant 150 mg IV once</li> <li>• Netupitant 300 mg / palonosetron 0.5 mg PO once</li> <li>• Fosnetupitant 235 mg / palonosetron 0.25 mg IV once</li> <li>• Rolapitant 180 mg PO once</li> </ul> One 5-HT3 RA listed below, unless combination product selected above: <ul style="list-style-type: none"> <li>• Dolasetron<sup>a</sup> 100 mg PO once</li> <li>• Granisetron 10 mg SQ or 2 mg PO or 0.01 mg/kg (Max 1 mg) IV once or 3.1 mg/24 hr transdermal patch applied 24-48 hours prior to first dose of chemotherapy</li> <li>• Ondansetron 16-24 mg PO once, or 8-16 mg IV once</li> <li>• Palonosetron 0.25 mg IV once</li> </ul> Dexamethasone 12 mg PO/IV once	Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1)  Dexamethasone 8 mg PO/IV daily on days 2, 3, 4

<sup>a</sup> Manufacturer discontinued dolasetron

c. MASCC:<sup>269</sup>

- 1) To prevent ACUTE CINV: NK1 antagonist plus serotonin antagonist plus corticosteroid OR olanzapine, palonosetron (do not substitute) and dexamethasone
- 2) To prevent DELAYED CINV: aprepitant (only if oral aprepitant given day 1) and dexamethasone

**Patient Case #8:**

**Question 2 Answer:**

**For the prevention of acute nausea and vomiting, she would receive:** Correct answer is A.

All three current guidelines recommend a regimen consisting of a four drug regimen (olanzapine, NK-1 antagonist, 5HT3 agonist & dexamethasone) for the prevention of acute emesis due to highly emetogenic chemotherapy. Single dose aprepitant 130 mg IV is supported by all 3 guideline-making bodies. The correct dose per guidelines of dexamethasone is 12 mg prior to chemotherapy. The correct dose for 5HT3 therapy include IV ondansetron is 8-16 mg and palonosetron 0.25 mg IV.<sup>267 268 269</sup> The updated NCCN and ASCO guidelines recommend the addition of olanzapine to the three drug regiment for all highly emetogenic regimens.<sup>267</sup>

**Question 3 Answer:**

**For the prevention of delayed nausea and vomiting, she would receive:** Correct answer is B.

Since JS received fosaprepitant 150 mg on day 1, no additional aprepitant is necessary for this cycle. Therefore, dexamethasone 8 mg PO daily days 2-4 in addition to olanzapine 5 mg PO daily days 2-4 is recommended. There is no data to support the use of serotonin antagonists for delayed nausea & vomiting and the ASCO / MASCC guidelines do not recommend the use of a serotonin antagonist for the prevention of delayed nausea and vomiting due to highly emetogenic chemotherapy.<sup>267,269</sup>

2. Moderately-emetogenic chemotherapy<sup>267-269</sup>

a. ASCO guidelines<sup>267</sup>

- 1) Patients treated with carboplatin AUC  $\geq 4$  should be offered a three-drug combination of a NK1 antagonist, serotonin antagonist and dexamethasone.
- 2) Moderate-emetic risk agents should be offered a two-drug combination of serotonin antagonist and dexamethasone.
- 3) Patients treated with cyclophosphamide, doxorubicin, oxaliplatin and other moderate-emetic risk agents that are known to cause delayed nausea and vomiting may be offered dexamethasone on days 2-3.

b. MASCC guidelines<sup>269</sup>

- 1) Patients receiving highly emetogenic chemotherapy (outside of AC) should receive a three-drug regimen including a NK1 antagonist, serotonin antagonist and dexamethasone. Dexamethasone should be given on days 2-4. If aprepitant 125 mg was given on day 1, either aprepitant and dexamethasone or metoclopramide and dexamethasone should be given in the delayed setting.
- 2) AC for breast cancer was reclassified as a special category within highly emetogenic due to a differing delayed phase. Panel recommends a 3-drug regimen for any

chemotherapy regimen that includes cyclophosphamide in combination with any anthracycline:

- a) Acute: NK1 antagonist plus a serotonin antagonist plus a corticosteroid
  - 1. DO NOT reduce dose or change schedules of any corticosteroids that are part of the treatment regimen (such as prednisone in CHOP)
- b) Delayed: aprepitant alone (if given aprepitant 125 mg on day 1)
- 3) Patients receiving moderately emetogenic chemotherapy (other than carboplatin):
  - a) Acute: serotonin antagonist plus dexamethasone. MASCC no longer has a preferred serotonin antagonist.
  - b) Patients who receive chemotherapy associated with delayed nausea and vomiting should receive antiemetic prophylaxis.
- 4) Olanzapine may be considered in combination with a serotonin antagonist plus dexamethasone in patients particularly where nausea is an issue.
- c. NCCN Guideline<sup>@268</sup>
  - 1) Carboplatin AUC  $\geq 4$  was reclassified as high emetic risk. Carboplatin AUC  $< 4$  remains as moderate emetic risk



Moderately emetogenic Chemotherapy (acute and delayed emesis prevention (All options are Category 1)		
	Day 1	Days 2, 3
Option D	One 5-HT <sub>3</sub> RA listed below: <ul style="list-style-type: none"> <li>• Dolasetron<sup>a</sup> 100 mg PO once</li> <li>• Granisetron 10 mg SQ (preferred) or 2 mg PO or 0.01 mg/kg (Max 1 mg) IV once or 3.1 mg/24 hr transdermal patch applied 24-48 hours prior to first dose of chemotherapy</li> <li>• Ondansetron 16-24 mg PO once, or 8-16 mg IV once</li> <li>• Palonosetron 0.25 mg IV once (preferred)</li> </ul> Dexamethasone 12 mg PO/IV once	Dexamethasone 8 mg PO/IV daily on days 2, 3  OR  5-HT <sub>3</sub> RA monotherapy: <ul style="list-style-type: none"> <li>• Granisetron 1-2 mg (total dose) PO daily or 0.01 mg/kg (max 1 mg) IV daily on days 2 and 3</li> <li>• Ondansetron 8 mg PO twice daily or 16 mg PO daily or 8-16 mg IV daily on days 2, 3</li> <li>• Dolasetron<sup>a</sup> 100 mg PO daily on days 2,3</li> </ul>
Option E	Olanzapine 5-10 mg PO once Palonosetron 0.25 mg IV once Dexamethasone 12 mg PO/IV once	Olanzapine 5-10 mg PO daily on days 2, 3
Option F	One NK1 RA listed below: <ul style="list-style-type: none"> <li>• Aprepitant 125 mg PO once</li> <li>• Aprepitant 130 mg IV once</li> <li>• Fosaprepitant 150 mg IV once</li> <li>• Netupitant 300 mg / palonosetron 0.5 mg PO once</li> <li>• Fosnetupitant 235 mg / palonosetron 0.25 mg IV once</li> <li>• Rolapitant 180 mg PO once</li> </ul> One 5-HT <sub>3</sub> RA listed below, unless combination product selected above: <ul style="list-style-type: none"> <li>• Dolasetron<sup>a</sup> 100 mg PO once</li> <li>• Granisetron 10 mg SQ or 2 mg PO or 0.01 mg/kg (Max 1 mg) IV once or 3.1 mg/24 hr transdermal patch applied 24-48 hours prior to first dose of chemotherapy</li> <li>• Ondansetron 16-24 mg PO once, or 8-16 mg IV once</li> <li>• Palonosetron 0.25 mg IV once</li> </ul> Dexamethasone 12 mg PO/IV once	Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1)  ± Dexamethasone 8 mg PO/IV daily on days 2, 3

<sup>a</sup> Manufacturer discontinued dolasetron

3. Low emetogenic chemotherapy<sup>267-269</sup>

- a. Single agent is suggested for patients receiving low risk chemotherapy

## Guideline Dosing Recommendations for Low Emetogenic Chemotherapy<sup>267-269</sup>

Agent	Dose
Ondansetron	PO: 8 – 16 mg day 1 (NCCN)
Granisetron	PO: 1-2 mg day 1 (NCCN) IV: 1 mg day 1 <sup>267</sup> Patch: 34.3 mg applied 24 to 48 hours prior to first dose of chemotherapy <sup>267</sup> SQ: 10 mg on day 1 <sup>267</sup>
Dolasetron <sup>a</sup>	PO: 100 mg day 1 (NCCN)
Palonosetron	PO: 0.5 mg day 1 <sup>267</sup> IV: 0.25 mg day 1 <sup>267</sup>
Dexamethasone	IV or PO: 8 mg day 1 <sup>267</sup> PO: 4 – 8 mg day 1(MASCC) PO or IV: 8-12 mg day 1 (NCCN®)
Metoclopramide	PO or IV: 10-20 mg IV/PO once (NCCN)
Prochlorperazine	PO or IV: 10 mg once (NCCN®)

Antiemetic agents listed in alphabetical order

Adapted and summarized from<sup>267-269</sup>

<sup>a</sup> Manufacturer discontinued dolasetron

4. Minimally emetogenic chemotherapy<sup>267-269</sup>
  - a. No antiemetic should be routinely administered before chemotherapy in patients without a history of nausea and vomiting
5. Oral chemotherapy<sup>267-269</sup>
  - a. High to Moderate:
    - 1) Recommend serotonin antagonist before the start of chemotherapy and continue daily (dolasetron 100 mg PO daily (manufacturer discontinued), granisetron 1-2 mg PO daily or transdermal patch, ondansetron 8-16 mg PO daily) and may add another agent as breakthrough N/V.
  - b. Low to Minimal: Routine prophylaxis not recommended (see guideline for medication listing)
    - 1) If patient develops N/V, start one of the following and continue daily: metoclopramide 10-20 mg PO then PRN Q6H, prochlorperazine 10 mg PO prior to and then PRN Q6H, or serotonin antagonist (dolasetron (manufacturer discontinued), granisetron or ondansetron) daily prn.

**Table 22: Oral Serotonin Antagonist Dosing**

Prophylaxis Recommended	
Dolasetron (Anzemet®) <sup>a</sup>	PO: 100 mg daily
Granisetron (Kytril®)	PO: 1-2 mg daily
Ondansetron (Zofran®)	PO: 8-16 mg daily (NCCN®)

<sup>a</sup> Manufacturer discontinued dolasetron

6. Multi-Day chemotherapy regimens

- a. Patients receiving multiple days of chemotherapy are at risk for both acute and delayed emesis depending on the chemotherapy they are receiving,
- b. ASCO Guideline<sup>267</sup>
  - 1) Antiemetics appropriate for the emetogenic risk of the chemotherapy should be administered each day of the chemotherapy and for 2 days afterward, if appropriate.
  - 2) Patients receiving 5-day cisplatin regimens should receive a NK1 antagonist plus a serotonin antagonist plus dexamethasone (recommendation based on limited data) on the days of chemotherapy.
- c. MASCC Guidelines<sup>269</sup>
  - 1) Acute: Serotonin antagonist administered on each day of moderate- or highly-emetogenic chemotherapy and dexamethasone 20 mg PO x 1 dose on days 1 and 2
    - a) Palonosetron 0.25 mg IV on days 1, 3, and 5 is an option
  - 2) Delayed (assuming palonosetron on day 1):
    - a) Dexamethasone 8 mg PO BID on days 6 and 7
    - b) Dexamethasone 4 mg PO BID on day 8
- d. NCCN Guideline<sup>268</sup>
  - 1) Depends on the regimen, but need to determine what each day of therapy is – i.e., moderately- or highly-emetogenic as well as risk for delayed emesis
  - 2) Acute:
    - a) Serotonin antagonist plus dexamethasone prior to first daily dose of moderate or highly emetogenic chemotherapy (see previous tables for dosing) and then daily for each day of moderate to highly emetic chemotherapy.
      - 1. Granisetron extended-release subcutaneous can be utilized prior to the first chemotherapy day for a multi-day regimen.
      - 2. Palonosetron may be used prior to the start of a three-day chemotherapy regimen instead of multiple daily doses of oral or IV serotonin antagonist
        - i. Repeat dosing of palonosetron 0.25 mg is likely safe, however the need for repeat dosing with palonosetron, for multiday chemotherapy is not known
  - 3) Delayed: Dexamethasone should be administered 2 to 3 days after chemotherapy for regimens with significant delayed CINV
    - a) Aprepitant may be used for multiday chemotherapy regimens likely to be highly-emetogenic and associated with significant risk for delayed nausea and emesis
    - b) Administer 125 mg on day one with serotonin antagonist and dexamethasone and 80 mg on days 2 and 3 with dexamethasone

- c) Limited data has shown aprepitant 80 mg may be safely administered on days 4 and 5 after chemotherapy, but the efficacy is not known
- d) Studies investigating repeat doses of fosaprepitant, netupitant, or rolapitant are not available.

7. Modifying antiemetics for next cycle of chemotherapy due to breakthrough nausea and vomiting<sup>267-269</sup>

**NCCN Guideline® Dosing Recommendations Breakthrough Nausea and Vomiting<sup>268</sup>**

Agent	Dose
<b><i>Benzodiazepines</i></b>	
Lorazepam	PO/SL/IV: 0.5 to 2 mg every 6 hours
<b><i>Cannabinoids</i></b>	
Dronabinol	PO: 5 to 10 mg every 6 to 8 hours Oral solution: 2.1 – 4.2 mg/m <sup>2</sup> 3-4 times daily.
Nabilone	PO: 1 to 2 mg every 12 hours
<b><i>Corticosteroids</i></b>	
Dexamethasone	PO or IV: 12 mg daily
<b><i>Other</i></b>	
Haloperidol	IV/PO: 0.5-2 mg every 4 to 6 hours
Metoclopramide	PO or IV: 10 to 20 mg every 4 to 6 hours
Olanzapine	PO: 5- 10 mg daily (preferred, category 1)
Scopolamine	Transdermal: 1 patch (1.5 mg) every 72 hours
<b><i>Phenothiazines</i></b>	
Prochlorperazine	PO or IV: 10 mg every 6 hours PR: 25 mg suppository every 12 hours
Promethazine	PO or IV: 12.5 to 25 mg every 4 – 6 hours PR: 25 mg suppository every 6 hours
<b><i>Serotonin Antagonists</i></b>	
Dolasetron <sup>a</sup>	PO: 100 mg daily
Granisetron	PO: 1 to 2 mg daily or 1 mg BID IV: 0.01 mg/kg or 1 mg (maximum dose) Transdermal patch: 3.1 mg/24 hours every 7 days
Ondansetron	IV: 8- 16 mg daily PO: 16-24 mg daily (8 mg PO every 8 – 12 hours)

*Adapted and summarized from<sup>268</sup> Antiemetic agents listed in alphabetical order.*

<sup>a</sup> Manufacturer discontinued dolasetron

a. ASCO Guideline<sup>267</sup>

- 1) Reevaluate emetogenic risk and, if current antiemetic regimen is correct, concurrent illnesses, disease status and other medications requires investigation
- 2) Consider adding:

- a) Olanzapine to existing regimen for those who did not receive it prophylactically
  - b) A drug from a different class (if already received olanzapine) such as NK1 antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol or nabilone
- b. NCCN Guideline<sup>@268</sup>
- 1) If no nausea or emesis, no change in antiemetic regimen
  - 2) If patient has any nausea or emesis, pick from a different drug class than the patient is already receiving and add to current regimen
  - 3) Consider changing antiemetic therapy to higher level for next cycle
  - 4) If nausea and emesis are not controlled: Consider changing antiemetic therapy to an alternative such as:
    - a) Add a NK1 antagonist if not previously included
    - b) Consider changing from a NK1 antagonist containing regimen to an olanzapine containing regimen or vice versa
    - c) Consider combining olanzapine with a NK1 receptor antagonist containing regimen
    - d) Add other concomitant antiemetics such as metoclopramide or haloperidol
    - e) Adjusting the dose (intensity or frequency) of serotonin antagonist
    - f) Changing to a different serotonin antagonist may be efficacious in some patients (not necessarily likely to be effective – limited, anecdotal information)
    - g) Changing chemotherapy regimen in the palliative setting
    - h) Adding an anxiolytic agent in combination with the antiemetics
    - i) Patients with dyspepsia may benefit from antacid therapy with a H2 blocker or proton pump inhibitor

**Patient Case #8:**

**Answer to Question 4:**

**What would be an acceptable addition to her antiemetic regimen?** Correct answer is A.

Studies have not shown one agent to be superior to another for the treatment of breakthrough nausea and vomiting. Re-starting aprepitant in patients with breakthrough nausea and vomiting has not been studied and cannot be recommended at this time. Haloperidol and dronabinol may all be used in this case. Both the dose of haloperidol (1 to 4 mg Q6H) and dronabinol (5-20 mg Q3-4H) are incorrect, which excludes answers b and c. The patient is reporting that she is worried about how she is tolerating treatment given her past intolerance from a CINV standpoint. Lorazepam would be an appropriate recommendation to try given her reported worry as well as lack of improvement with scheduled prochlorperazine.

**Answer to Question 5:**

**What would you add to her next cycle of chemotherapy to prevent delayed nausea and vomiting?** Correct answer is B.

Since JS had to have lorazepam added to control delayed emesis it would be appropriate to re-evaluate her CINV plan. The schedule of metoclopramide is not appropriate for her next cycle, it would require every 6 hour administration for adequate effect. Given her nausea started after completion of her dexamethasone, extended the duration of dexamethasone would be most appropriate at this time by 2 additional days. No data exists to support the use of aprepitant after 3 days for breakthrough nausea and vomiting. Dronabinol may be useful, however the frequency is inappropriate for the indication of prevention of delayed emesis.

8. Anticipatory nausea/vomiting in patients receiving chemotherapy or radiation therapy
  - a. Best approach is to achieve best possible control of acute and delayed emesis
  - b. ASCO Guideline - behavioral therapy with desensitization is effective and suggested.<sup>267</sup>
  - c. MASCC Guideline<sup>269</sup>
    - 1) Behavioral therapies in particular progressive muscle relaxation training, systematic desensitization and hypnosis, can be used to treat anticipatory nausea and vomiting
      - a) MASCC level of confidence / level of consensus: High
    - 2) An alternative to or addition to psychological techniques is the use of benzodiazepines however their efficacy tends to decrease as chemotherapy treatments continue
      - a) MASCC level of confidence / level of consensus: Moderate
  - d. NCCN Guideline® <sup>268</sup>
    - 1) Prevention: use optimal antiemetic therapy during every cycle of treatment.
    - 2) Behavioral:
      - a) Relaxation / systematic desensitization
      - b) Hypnosis /guided imagery

- c) Music therapy
  - 3) Acupuncture / acupressure
  - 4) Lorazepam 0.5 to 2 mg PO starting night before treatment and 1-2 hours before chemotherapy begins.
- I. Radiation-Induced Nausea and Vomiting (RINV)<sup>267-269</sup>
- 1. Most patients will not require antiemetics during radiation therapy
  - 2. Current guidelines recommend evaluating both patient specific risk factors for N/V, simultaneous administration of chemotherapy, and radiation-specific risk factors.
    - a. Prevention of RINV ASCO<sup>267</sup>
      - 1) High risk: serotonin antagonist and dexamethasone before radiation and for at least 24 hours after completion of radiation
      - 2) Moderate risk: serotonin antagonist before each fraction for the entire course of radiation and patients may be offered a short course of dexamethasone during the first 5 fractions
      - 3) Low risk: patients receiving radiation to the brain should be offered rescue dexamethasone therapy. Patients receiving treatment to the head and neck, thorax or pelvis should be offered rescue therapy with a serotonin antagonist, dexamethasone or a dopamine receptor antagonist.
      - 4) Minimal risk: rescue therapy with a serotonin antagonist, dexamethasone or dopamine receptor antagonist
      - 5) Combined chemotherapy and radiation therapy: base antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the radiation is higher
    - b. MASCC Guideline<sup>269</sup>
      - 1) High risk (total body and total nodal irradiation): prophylaxis with serotonin antagonist plus dexamethasone
      - 2) Moderate risk (upper abdomen, upper body, and half body irradiation): prophylaxis with serotonin antagonist and optional short course of dexamethasone
      - 3) Low risk (lower thorax region, pelvis; cranium (radiosurgery), craniospinal and head and neck irradiation): prophylaxis or rescue with a serotonin antagonist
      - 4) Minimal risk (extremities and breast): rescue with dopamine antagonist or serotonin antagonist
      - 5) Treatment of RINV:
        - a) Agents recommended in adults include metoclopramide or prochlorperazine. May use serotonin antagonists
    - c. NCCN Guideline<sup>268</sup>
      - 1) RT of upper abdomen: start pretreatment for each day of RT treatment

- a) Granisetron 2 mg PO daily or
    - b) Ondansetron 8 mg PO BID
    - c) ± Dexamethasone 4 mg PO daily
  - 2) Total body irradiation: start pretreatment for each day of RT treatment
    - a) Granisetron 2 mg PO daily or
    - b) Ondansetron 8 mg PO every 8 to 12 hours or
    - c) ± Dexamethasone 4 mg PO daily
  - 3) Chemotherapy and radiation: refer to the previous chemotherapy guidelines
- J. Hematopoietic stem cell transplant myeloablative conditioning<sup>267,269</sup>
- 1. No guideline is appropriate for rescue antiemesis for high-dose chemotherapy
    - a. Most regimens are considered very highly emetogenic, and patients should receive appropriate antiemetic prophylaxis
    - b. Clinical trials in stem cell transplant are few and far-between
    - c. Both ondansetron and granisetron have been evaluated and found to be at least partially effective; however, the most effective dosing regimen has yet to be determined
    - d. Please refer to handout on 'Hematopoietic Stem Cell Transplantation'
  - 2. ASCO recommends that adult patients receiving high-dose chemotherapy and stem cell or bone marrow transplant should be offered antiemetics<sup>267</sup>
    - 1) Patients receiving stem cell or bone marrow transplantation should be offered a three-drug regimen of NK1 antagonist, serotonin antagonist and dexamethasone.
    - 2) A 4-drug combination with an NK1 antagonist, a 5-HT3 RA, dexamethasone and olanzapine may be offered to adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation.
- K. Agency for Healthcare Research and Quality published a technology assessment on the consideration of evidence on antiemetic drugs for CINV or RINV therapy in adults.<sup>323</sup>
- 1. Excellent summary of antiemetic data to date; expands on the information contained in this handout



## RECOMMENDED READINGS

### Small-Cell Lung Cancer:

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer. V.2.2023, 10/28/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved.  
[https://www.nccn.org/professionals/physician\\_gls/pdf/sclcl.pdf](https://www.nccn.org/professionals/physician_gls/pdf/sclcl.pdf)

### Non-Small Cell Lung Cancer:

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.6.2022, 12/02/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved.  
[https://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf)
2. Hanna N, Schneider B, Temin S et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guidelines Update. *J Clin Oncol*. 2020; 38(14): 1608-632.  
<https://pubmed.ncbi.nlm.nih.gov/31990617/>
3. Singh N, Temin S, Baker S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline. *J Clin Oncol*. 2022; Jul 11. JCO.22.00824. Online ahead of print.  
<https://pubmed.ncbi.nlm.nih.gov/35816666/>
4. US Preventive Services Task Force; Krist AH, Davidson KW, Mangione CM et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325:962-970.  
<https://pubmed.ncbi.nlm.nih.gov/33687470/>

### Mesothelioma:

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Malignant Pleural Mesothelioma. V.2.2022, 10/18/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved..  
[https://www.nccn.org/professionals/physician\\_gls/pdf/mpm.pdf](https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf)

### Chemotherapy Induced Nausea & Vomiting:

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis. V.2.2022, 03/23/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved.  
[https://www.nccn.org/professionals/physician\\_gls/pdf/antiemesis.pdf](https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf)
2. Hesketh PJ, Kris MG, Basch E et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2020; 38: 2782-97. <https://pubmed.ncbi.nlm.nih.gov/28759346/>
3. Roila F, Molassiotis A, Herrstedt J et al. 2016 mascc and esmo guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016; 27(suppl 5): v119-v33. <http://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/MASCC-and-ESMO-Consensus-Guidelines-for-the-Prevention-of-Chemotherapy-and-Radiotherapy-Induced-Nausea-and-Vomiting>

## References

1. Zhu QG, Zhang SM, Ding XX, He B, Zhang HQ. Driver genes in non-small cell lung cancer: Characteristics, detection methods, and targeted therapies. *Oncotarget*. 2017;8(34):57680-57692.
2. Salgia R, Skarin AT. Molecular abnormalities in lung cancer. *J Clin Oncol*. 1998;16(3):1207-1217.
3. Rosell R, Felip E, Garcia-Campelo R, Balana C. The biology of non-small-cell lung cancer: identifying new targets for rational therapy. *Lung Cancer*. 2004;46(2):135-148.
4. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.6.2022, 12/02/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
5. Ahrendt SA, Decker PA, Alawi EA, et al. Cigarette smoking is strongly associated with mutation of the K-ras gene in patients with primary adenocarcinoma of the lung. *Cancer*. 2001;92(6):1525-1530.
6. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol*. 2005;23(25):5900-5909.
7. Gainor JF, Shaw AT. Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *J Clin Oncol*. 2013;31(31):3987-3996.
8. Rosell R, Molina MA, Costa C, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res*. 2011;17(5):1160-1168.
9. Oxnard GR, Arcila ME, Sima CS, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res*. 2011;17(6):1616-1622.
10. Lam VK, Tran HT, Banks KC, et al. Targeted Tissue and Cell-Free Tumor DNA Sequencing of Advanced Lung Squamous-Cell Carcinoma Reveals Clinically Significant Prevalence of Actionable Alterations. *Clin Lung Cancer*. 2019;20(1):30-36 e33.
11. Massarelli E, Varella-Garcia M, Tang X, et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *Clin Cancer Res*. 2007;13(10):2890-2896.
12. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17(11):1497-1508.
13. Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. *Clin Cancer Res*. 2011;17(8):2081-2086.
14. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol*. 2009;27(26):4247-4253.
15. Martelli MP, Sozzi G, Hernandez L, et al. EML4-ALK rearrangement in non-small cell lung cancer and non-tumor lung tissues. *Am J Pathol*. 2009;174(2):661-670.
16. Acquaviva J, Wong R, Charest A. The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. *Biochim Biophys Acta*. 2009;1795(1):37-52.
17. Davies KD, Doebele RC. Molecular pathways: ROS1 fusion proteins in cancer. *Clin Cancer Res*. 2013;19(15):4040-4045.
18. Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. *Oncologist*. 2013;18(7):865-875.
19. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17(7):984-993.

20. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949-954.
21. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol*. 2011;29(15):2046-2051.
22. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18(10):1307-1316.
23. Vuong HG, Ho ATN, Altibi AMA, Nakazawa T, Katoh R, Kondo T. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer - A systematic review and meta-analysis. *Lung Cancer*. 2018;123:76-82.
24. Michels S, Scheel AH, Scheffler M, et al. Clinicopathological Characteristics of RET Rearranged Lung Cancer in European Patients. *J Thorac Oncol*. 2016;11(1):122-127.
25. Kerr KM, Nicolson MC. Non-Small Cell Lung Cancer, PD-L1, and the Pathologist. *Arch Pathol Lab Med*. 2016;140(3):249-254.
26. Bach PB, Kelley MJ, Tate RC, McCrory DC. Screening for lung cancer: a review of the current literature. *Chest*. 2003;123(1 Suppl):72S-82S.
27. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Lung Cancer Screening. V.1.2023, 10/26/2022 © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
28. Force USPST, Krist AH, Davidson KW, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(10):962-970.
29. Szabo E, Mao JT, Lam S, Reid ME, Keith RL. Chemoprevention of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e40S-e60S.
30. Johnson BE, Cortazar P, Chute JP. Second lung cancers in patients successfully treated for lung cancer. *Semin Oncol*. 1997;24(4):492-499.
31. Bastarrika G, Garcia-Velloso MJ, Lozano MD, et al. Early lung cancer detection using spiral computed tomography and positron emission tomography. *Am J Respir Crit Care Med*. 2005;171(12):1378-1383.
32. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.
33. National Lung Screening Trial Research T. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. *J Thorac Oncol*. 2019;14(10):1732-1742.
34. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *N Engl J Med*. 2020;382(6):503-513.
35. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338.
36. Li Y, Sheu CC, Ye Y, et al. Genetic variants and risk of lung cancer in never smokers: a genome-wide association study. *Lancet Oncol*. 2010;11(4):321-330.
37. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e400S-e419S.
38. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer V.2.2023, 10/28/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys &

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39. Turrisi AT, 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340(4):265-271.
40. Tai P, Yu E, Jones K, Sadikov E, Mahmood S, Tonita J. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in patients with limited stage small cell lung cancer. *Lung Cancer*. 2006;53(2):211-215.
41. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18(8):1116-1125.
42. Gronberg BH, Killingberg KT, Flotten O, et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. *Lancet Oncol*. 2021;22(3):321-331.
43. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol*. 2009;10(5):467-474.
44. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30.
45. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol*. 2012;30(14):1692-1698.
46. Lara PN, Jr., Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol*. 2009;27(15):2530-2535.
47. Hanna N, Bunn PA, Jr., Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol*. 2006;24(13):2038-2043.
48. Hermes A, Bergman B, Bremnes R, et al. Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. *J Clin Oncol*. 2008;26(26):4261-4267.
49. Horn L, Mansfield AS, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med*. 2018.
50. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929-1939.
51. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(1):51-65.
52. Liu SV, Reck M, Mansfield AS, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). *J Clin Oncol*. 2021;39(6):619-630.
53. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. *ESMO Open*. 2022;7(2):100408.
54. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *J Clin Oncol*. 1999;17(7):2092-2099.
55. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664-672.
56. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(5):663-671.

57. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* 2013;15(10):1429-1437.
58. Loehrer PJ, Sr., Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. *J Clin Oncol.* 1995;13(10):2594-2599.
59. Pujol JL, Daures JP, Riviere A, et al. Etoposide plus cisplatin with or without the combination of 4'-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes multicenter phase III randomized study. *J Natl Cancer Inst.* 2001;93(4):300-308.
60. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med.* 2002;346(2):85-91.
61. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol.* 1994;12(10):2022-2034.
62. Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol.* 1985;3(11):1471-1477.
63. Skarlos DV, Samantas E, Briassoulis E, et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol.* 2001;12(9):1231-1238.
64. Schmittl A, Fischer von Weikersthal L, Sebastian M, et al. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. *Ann Oncol.* 2006;17(4):663-667.
65. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol.* 1999;17(2):658-667.
66. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol.* 2006;24(34):5441-5447.
67. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol.* 2007;25(15):2086-2092.
68. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol.* 1992;10(8):1225-1229.
69. van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. *Ann Oncol.* 2001;12(4):557-561.
70. Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. *J Clin Oncol.* 2003;21(8):1550-1555.
71. Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. *Eur J Cancer.* 1994;30A(8):1058-1060.
72. Jassem J, Karnicka-Mlodkowska H, van Pottelsberghe C, et al. Phase II study of vinorelbine (Navelbine) in previously treated small cell lung cancer patients. EORTC Lung Cancer Cooperative Group. *Eur J Cancer.* 1993;29A(12):1720-1722.
73. Furuse K, Kubota K, Kawahara M, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Japan Lung Cancer Vinorelbine Study Group. *Oncology.* 1996;53(2):169-172.
74. Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. *Clin Cancer Res.* 2012;18(4):1138-1145.
75. Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. *Lung Cancer.* 2014;86(2):237-240.
76. Chung HC, Ros W, Delord JP, et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol.* 2019;37(17):1470-1478.
77. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol.* 2020;21(5):645-654.

78. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. *Br J Cancer*. 1998;77(2):347-351.
79. Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. *Anticancer Res*. 2006;26(1B):777-781.
80. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17(7):883-895.
81. Lammers PE, Shyr Y, Li CI, et al. Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. *J Thorac Oncol*. 2014;9(4):559-562.
82. Raftopoulos H, Cooper W, O'Boyle E, Gabrail N, Boccia R, Gralla RJ. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. *Support Care Cancer*. 2015;23(3):723-732.
83. Ott PA, Elez E, Hirt S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. *J Clin Oncol*. 2017;35(34):3823-3829.
84. Hellmann MD, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032. *Journal of Clinical Oncology*. 2017;35(15\_suppl):8503-8503.
85. Hellmann M, Antonia S, Ponce S, et al. MA09.05 Nivolumab Alone or with Ipilimumab in Recurrent Small Cell Lung Cancer (SCLC): 2-Year Survival and Updated Analyses from the Checkmate 032 Trial. *Journal of Thoracic Oncology*. 2017;12(1):S393-S394.
86. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. *J Thorac Oncol*. 2020;15(3):426-435.
87. Daniel D, Kuchava V, Bondarenko I, et al. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled Phase II trial. *Int J Cancer*. 2020.
88. Hart LL, Ferrarotto R, Andric ZG, et al. Myelopreservation with Trilaciclib in Patients Receiving Topotecan for Small Cell Lung Cancer: Results from a Randomized, Double-Blind, Placebo-Controlled Phase II Study. *Adv Ther*. 2021;38(1):350-365.
89. Cosela™ package insert. Durham, NC: G1 Therapeutics, Inc.;2021 Feb.
90. Bunn PA, Jr., Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. *J Clin Oncol*. 1995;13(7):1632-1641.
91. Elias A, Ibrahim J, Skarin AT, et al. Dose-intensive therapy for limited-stage small-cell lung cancer: long-term outcome. *J Clin Oncol*. 1999;17(4):1175.
92. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. *Lancet*. 1996;348(9027):563-566.
93. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet*. 1998;352(9124):257-263.
94. Edge S, Byrd D, Compton C. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
95. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e278S-e313S.
96. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e314S-e340S.
97. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559.

98. Strauss GM, Herndon JE, 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26(31):5043-5051.
99. Usami N, Yokoi K, Hasegawa Y, et al. Phase II study of carboplatin and gemcitabine as adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: a report from the Central Japan Lung Study Group, CJLSG 0503 trial. *Int J Clin Oncol*. 2010;15(6):583-587.
100. Zhang L, Ou W, Liu Q, Li N, Liu L, Wang S. Pemetrexed plus carboplatin as adjuvant chemotherapy in patients with curative resected non-squamous non-small cell lung cancer. *Thorac Cancer*. 2014;5(1):50-56.
101. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020;383(18):1711-1723.
102. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol*. 2013;24(4):986-992.
103. Kreuter M, Vansteenkiste J, Fischer JR, et al. Three-Year Follow-Up of a Randomized Phase II Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy with Cisplatin and Pemetrexed versus Cisplatin and Vinorelbine (the TREAT Study). *J Thorac Oncol*. 2016;11(1):85-93.
104. Perol M, Chouaid C, Perol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol*. 2012;30(28):3516-3524.
105. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003;21(16):3016-3024.
106. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004;350(4):351-360.
107. Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys*. 2008;72(3):695-701.
108. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol*. 2010;28(1):29-34.
109. D'Addario G, Felip E. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol*. 2008;19 Suppl 2:ii39-40.
110. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022;386(21):1973-1985.
111. Pisters KM, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIa resectable non small-cell lung cancer guideline. *J Clin Oncol*. 2007;25(34):5506-5518.
112. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIa non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398(10308):1344-1357.
113. Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol*. 2011;29(23):3120-3125.
114. Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. *Lung Cancer*. 2015;87(3):232-240.
115. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol*. 2005;23(25):5883-5891.

116. Albain KS, Crowley JJ, Turrisi AT, 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol*. 2002;20(16):3454-3460.
117. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(20):1919-1929.
118. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.
119. Gray JE, Villegas A, Daniel D, et al. Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. *J Thorac Oncol*. 2020;15(2):288-293.
120. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. *Journal of Clinical Oncology*. 2021;39(15\_suppl):8511-8511.
121. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363(8):733-742.
122. Souquet PJ, Chauvin F, Boissel JP, Bernard JP. Meta-analysis of randomised trials of systemic chemotherapy versus supportive treatment in non-resectable non-small cell lung cancer. *Lung Cancer*. 1995;12 Suppl 1:S147-154.
123. Shanafelt TD, Loprinzi C, Marks R, Novotny P, Sloan J. Are chemotherapy response rates related to treatment-induced survival prolongations in patients with advanced cancer? *J Clin Oncol*. 2004;22(10):1966-1974.
124. Clegg A, Scott DA, Hewitson P, Sidhu M, Waugh N. Clinical and cost effectiveness of paclitaxel, docetaxel, gemcitabine, and vinorelbine in non-small cell lung cancer: a systematic review. *Thorax*. 2002;57(1):20-28.
125. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346(2):92-98.
126. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. 1990;322(8):494-500.
127. Hanna N, Johnson D, Temin S, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2017;35(30):3484-3515.
128. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med*. 2017;376(7):629-640.
129. Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2017;JCO2017747576.
130. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017.
131. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50.
132. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735-742.
133. Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol*. 2012;30(17):2063-2069.
134. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31(27):3327-3334.
135. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol*. 2016;17(5):577-589.
136. Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. *Br J Cancer*. 2014;110(1):55-62.
137. Urata Y, Katakami N, Morita S, et al. Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L. *J Clin Oncol*. 2016;34(27):3248-3257.



138. Mok TS, Cheng Y, Zhou X, et al. Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. *J Clin Oncol*. 2018;36(22):2244-2250.
139. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(11):1454-1466.
140. Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2019;20(5):625-635.
141. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(12):1655-1669.
142. Cho JH, Lim SH, An HJ, et al. Osimertinib for Patients With Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial (KCSG-LU15-09). *J Clin Oncol*. 2020;38(5):488-495.
143. Tu HY, Ke EE, Yang JJ, et al. A comprehensive review of uncommon EGFR mutations in patients with non-small cell lung cancer. *Lung Cancer*. 2017;114:96-102.
144. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16(7):830-838.
145. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov*. 2014;4(9):1036-1045.
146. Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1689-1699.
147. Lee CK, Man J, Lord S, et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. *J Thorac Oncol*. 2017;12(2):403-407.
148. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(9):829-838.
149. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673.
150. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020;31(8):1056-1064.
151. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet*. 2017;390(10089):29-39.
152. Nakagawa K, Hida T, Nokihara H, et al. Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer*. 2020;139:195-199.
153. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;379(21):2027-2039.
154. Shaw AT, Bauer TM, de Marinis F, et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. *N Engl J Med*. 2020;383(21):2018-2029.
155. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017;389(10072):917-929.
156. Cho BC, Kim DW, Bearz A, et al. ASCEND-8: A Randomized Phase 1 Study of Ceritinib, 450 mg or 600 mg, Taken with a Low-Fat Meal versus 750 mg in Fasted State in Patients with Anaplastic Lymphoma Kinase (ALK)-Rearranged Metastatic Non-Small Cell Lung Cancer (NSCLC). *J Thorac Oncol*. 2017;12(9):1357-1367.
157. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.
158. Ou SH, Ahn JS, De Petris L, et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. *J Clin Oncol*. 2016;34(7):661-668.

159. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. *J Clin Oncol*. 2017;35(22):2490-2498.
160. Shaw AT, Kim TM, Crino L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(7):874-886.
161. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654-1667.
162. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol*. 2012;13(10):1011-1019.
163. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971.
164. Drilon A, Siena S, Ou SI, et al. Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). *Cancer Discov*. 2017;7(4):400-409.
165. Lim SM, Kim HR, Lee JS, et al. Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. *J Clin Oncol*. 2017;35(23):2613-2618.
166. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654-1667.
167. Wolf J, Seto T, Han JY, et al. Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020;383(10):944-957.
168. Paik PK, Felip E, Veillon R, et al. Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. *N Engl J Med*. 2020;383(10):931-943.
169. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med*. 2020;26(1):47-51.
170. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020;383(9):813-824.
171. Gainor JF, Curigliano G, Kim D-W, et al. Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion+ non-small cell lung cancer (NSCLC). 2020;38(15\_suppl):9515-9515.
172. Drilon A, Rekhman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016;17(12):1653-1660.
173. Tabrecta™ package insert. East Hannover, NJ: Novartis Pharmaceuticals Corporation;2020 May.
174. Tepmetko® package insert. Rockland, MA: EMD Serono, Inc.;2021 February.
175. Retevmo™ package insert. Indianapolis, IN: Lilly USA, LLC;2021 January.
176. Gavreto™ package insert. Gambridge, MA: Blueprint Medicines Corporation;2020 September.
177. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2016;375(19):1823-1833.
178. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N Engl J Med*. 2020;383(14):1328-1339.
179. Sezer A, Kilickap S, Gumus M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. 2021;397(10274):592-604.
180. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol*. 2019;37(7):537-546.
181. Hanna NH, Schneider BJ, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. *J Clin Oncol*. 2020;38(14):1608-1632.
182. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2019;381(21):2020-2031.
183. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous

- non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(7):924-937.
184. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. *Nat Med.* 2022;28(11):2374-2380.
  185. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J Clin Oncol.* 2022:JCO2200975.
  186. Borghaei H, Langer CJ, Gadgeel S, et al. 24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer. *J Thorac Oncol.* 2019;14(1):124-129.
  187. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018;378(22):2078-2092.
  188. Gadgeel S, Rodriguez-Abreu D, Speranza G, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2020;38(14):1505-1517.
  189. Paz-Ares LG, Luft A, Tafreshi A, et al. Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology.* 2018;36(15\_suppl):105-105.
  190. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *New England Journal of Medicine.* 0(0):null.
  191. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med.* 2018;378(24):2288-2301.
  192. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006;355(24):2542-2550.
  193. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26(21):3543-3551.
  194. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol.* 2013;31(24):3004-3011.
  195. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol.* 2013;31(34):4349-4357.
  196. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. *Ann Oncol.* 2005;16(4):602-610.
  197. Tan EH, Szczesna A, Krzakowski M, et al. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer.* 2005;49(2):233-240.
  198. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol.* 2012;30(17):2055-2062.
  199. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol.* 2000;18(12):2354-2362.
  200. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet.* 2011;378(9796):1079-1088.

201. Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. *Cancer*. 2003;98(3):542-553.
202. Scagliotti GV, Kortsik C, Dark GG, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. *Clin Cancer Res*. 2005;11(2 Pt 1):690-696.
203. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012;13(3):247-255.
204. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255-265.
205. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet*. 2009;374(9699):1432-1440.
206. Syed YY. Amivantamab: First Approval. *Drugs*. 2021.
207. Rybrevant™ package insert. Horsham, PA: Janssen Biotech, Inc.;2021 May.
208. Exkivity™ package insert. Lexington, MA: Takeda Pharmaceuticals America, Inc.;2021 September.
209. Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med*. 2022;386(3):241-251.
210. Li BT, Shen R, Buonocore D, et al. Ado-Trastuzumab Emtansine for Patients With HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial. *J Clin Oncol*. 2018;36(24):2532-2537.
211. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *N Engl J Med*. 2021;384(25):2371-2381.
212. Lumakras™ package insert. Thousand Oaks, CA: Amgen Inc.; 2021 May.
213. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(17):1627-1639.
214. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(2):123-135.
215. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028.
216. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550.
217. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387(10030):1837-1846.
218. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18(10):2095-2103.
219. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22(9):1589-1597.
220. van Putten JW, Baas P, Codrington H, et al. Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. *Lung Cancer*. 2001;33(2-3):289-298.
221. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Malignant Pleural Mesothelioma. V.2.2022, 10/18/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™

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222. Kindler HL, Ismaila N, III SGA, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*. 2018;36(13):1343-1373.
223. Leal JL, Peters G, Szaumkessel M, et al. NTRK and ALK rearrangements in malignant pleural mesothelioma, pulmonary neuroendocrine tumours and non-small cell lung cancer. *Lung Cancer*. 2020;146:154-159.
224. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21(14):2636-2644.
225. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;387(10026):1405-1414.
226. P. Baas AS, A. Nowak, N. Fujimoto, S. Peters, A. Tsao, A. Mansfield, S. Popat, T. Jahan, S. Antonia, Y. Oulkhouri, Y. Bautista, R. Cornelissen, L. Greillier, F. Grossi, D.M. Kowalski, J. Rodriguez-Cid, P. Aanur, C. Baudalet, G. Zalcman,. First-Line Nivolumab + Ipilimumab vs Chemotherapy in Unresectable Malignant Pleural Mesothelioma: CheckMate 743. *Journal of Thoracic Oncology*.15(10):e42.
227. Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). *Ann Oncol*. 2008;19(2):370-373.
228. Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol*. 2006;24(9):1443-1448.
229. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol*. 2008;3(7):756-763.
230. Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer*. 2002;87(5):491-496.
231. van Haarst JM, Baas P, Manegold C, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer*. 2002;86(3):342-345.
232. Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemo-naïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. *J Thorac Oncol*. 2008;3(7):764-771.
233. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet*. 2008;371(9625):1685-1694.
234. Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol*. 2008;26(10):1698-1704.
235. Zucali PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. *Lung Cancer*. 2012;75(3):360-367.
236. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer*. 2009;63(1):94-97.
237. Zauderer MG, Kass SL, Woo K, Sima CS, Ginsberg MS, Krug LM. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. *Lung Cancer*. 2014;84(3):271-274.
238. Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol*. 2005;16(6):923-927.
239. van Meerbeeck JP, Baas P, Debruyne C, et al. A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *Cancer*. 1999;85(12):2577-2582.
240. Kintzel PE. Anticancer drug-induced kidney disorders. *Drug Saf*. 2001;24(1):19-38.
241. Abdelghani L, Modha K, Albaddawi E, Subramanian S. Sodium-wasting nephropathy caused by cisplatin in esophageal cancer. *J Support Oncol*. 2008;6(7):305-306.
242. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. *Kidney Int*. 2008;73(9):994-1007.

243. Bennis Y, Savry A, Rocca M, Gauthier-Villano L, Pisano P, Pourroy B. Cisplatin dose adjustment in patients with renal impairment, which recommendations should we follow? *Int J Clin Pharm*. 2014;36(2):420-429.
244. Cho KS, Joung JY, Seo HK, et al. Renal safety and efficacy of cisplatin-based chemotherapy in patients with a solitary kidney after nephroureterectomy for urothelial carcinoma of the upper urinary tract. *Cancer Chemother Pharmacol*. 2011;67(4):769-774.
245. Bajorin D, Bosl GJ, Fein R. Phase I trial of escalating doses of cisplatin in hypertonic saline. *J Clin Oncol*. 1987;5(10):1589-1593.
246. Fuks JZ, Wadler S, Wiernik PH. Phase I and II agents in cancer therapy: two cisplatin analogues and high-dose cisplatin in hypertonic saline or with thiosulfate protection. *J Clin Pharmacol*. 1987;27(5):357-365.
247. Dimery IW, Legha SS. Sequential methotrexate, 5-fluorouracil, and cisplatin in the treatment of recurrent squamous-cell carcinoma of the head and neck: failure of hypertonic saline to reduce the nephrotoxicity of cisplatin. *J Clin Oncol*. 1986;4(11):1670-1676.
248. Launay-Vacher V, Rey JB, Isnard-Bagnis C, Deray G, Daouphars M. Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. *Cancer Chemother Pharmacol*. 2008;61(6):903-909.
249. Al-Sarraf M, Fletcher W, Oishi N, et al. Cisplatin hydration with and without mannitol diuresis in refractory disseminated malignant melanoma: a southwest oncology group study. *Cancer Treat Rep*. 1982;66(1):31-35.
250. Santoso JT, Lucci JA, 3rd, Coleman RL, Schafer I, Hannigan EV. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. *Cancer Chemother Pharmacol*. 2003;52(1):13-18.
251. Morgan KP, Buie LW, Savage SW. The role of mannitol as a nephroprotectant in patients receiving cisplatin therapy. *Ann Pharmacother*. 2012;46(2):276-281.
252. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. 2009;27(1):127-145.
253. Schuchter LM, Hensley ML, Meropol NJ, Winer EP. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2002;20(12):2895-2903.
254. Marchi E, Teixeira LR, Vargas FS. Management of malignancy-associated pleural effusion: current and future treatment strategies. *Am J Respir Med*. 2003;2(3):261-273.
255. Lee YC, Baumann MH, Maskell NA, et al. Pleurodesis practice for malignant pleural effusions in five English-speaking countries: survey of pulmonologists. *Chest*. 2003;124(6):2229-2238.
256. Maisch B, Ristic A, Pankuweit S. Evaluation and management of pericardial effusion in patients with neoplastic disease. *Prog Cardiovasc Dis*. 2010;53(2):157-163.
257. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(7):839-849.
258. Rintoul RC, Ritchie AJ, Edwards JG, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. *Lancet*. 2014;384(9948):1118-1127.
259. Nikbakhsh N, Pourhasan Amiri A, Hoseinzadeh D. Bleomycin in the treatment of 50 cases with malignant pleural effusion. *Caspian J Intern Med*. 2011;2(3):274-278.
260. Kuzdzal J, Sladek K, Wasowski D, et al. Talc powder vs doxycycline in the control of malignant pleural effusion: a prospective, randomized trial. *Med Sci Monit*. 2003;9(6):PI54-59.
261. Dresler CM, Olak J, Herndon JE, 2nd, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest*. 2005;127(3):909-915.
262. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst Rev*. 2004(1):CD002916.
263. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. 2012;307(22):2383-2389.
264. Cheng S. Superior vena cava syndrome: a contemporary review of a historic disease. *Cardiol Rev*. 2009;17(1):16-23.

265. Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. *N Engl J Med*. 2007;356(18):1862-1869.
266. Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome--a proposed classification system and algorithm for management. *J Thorac Oncol*. 2008;3(8):811-814.
267. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2017;35(28):3240-3261.
268. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis. V.2.2022, 03/23/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
269. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27(suppl 5):v119-v133.
270. Hesketh PJ, Warr DG, Street JC, Carides AD. Differential time course of action of 5-HT<sub>3</sub> and NK1 receptor antagonists when used with highly and moderately emetogenic chemotherapy (HEC and MEC). *Support Care Cancer*. 2011;19(9):1297-1302.
271. Martin M. The severity and pattern of emesis following different cytotoxic agents. *Oncology*. 1996;53 Suppl 1:26-31.
272. Hesketh PJ, Aapro M, Street JC, Carides AD. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. *Support Care Cancer*. 2010;18(9):1171-1177.
273. Warr DG, Street JC, Carides AD. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of phase 3 trial of aprepitant in patients receiving adriamycin-cyclophosphamide-based chemotherapy. *Support Care Cancer*. 2011;19(6):807-813.
274. Dranitsaris G, Bouganim N, Milano C, et al. Prospective validation of a prediction tool for identifying patients at high risk for chemotherapy-induced nausea and vomiting. *J Support Oncol*. 2013;11(1):14-21.
275. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol*. 1997;15(1):103-109.
276. Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. *Support Care Cancer*. 2011;19 Suppl 1:S43-47.
277. Rojas C, Li Y, Zhang J, et al. The antiemetic 5-HT<sub>3</sub> receptor antagonist Palonosetron inhibits substance P-mediated responses in vitro and in vivo. *J Pharmacol Exp Ther*. 2010;335(2):362-368.
278. Gonullu G, Demircan S, Demirag MK, Erdem D, Yucel I. Electrocardiographic findings of palonosetron in cancer patients. *Support Care Cancer*. 2012;20(7):1435-1439.
279. Yavas C, Dogan U, Yavas G, Araz M, Ata OY. Acute effect of palonosetron on electrocardiographic parameters in cancer patients: a prospective study. *Support Care Cancer*. 2012;20(10):2343-2347.
280. Mason JW, Selness DS, Moon TE, O'Mahony B, Donachie P, Howell J. Pharmacokinetics and repolarization effects of intravenous and transdermal granisetron. *Clin Cancer Res*. 2012;18(10):2913-2921.
281. Geling O, Eichler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. *J Clin Oncol*. 2005;23(6):1289-1294.
282. Celio L, Frustaci S, Denaro A, et al. Palonosetron in combination with 1-day versus 3-day dexamethasone for prevention of nausea and vomiting following moderately emetogenic chemotherapy: a randomized, multicenter, phase III trial. *Support Care Cancer*. 2011;19(8):1217-1225.
283. Botrel TE, Clark OA, Clark L, Paladini L, Faleiros E, Pegoretti B. Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT<sub>3</sub>R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. *Support Care Cancer*. 2011;19(6):823-832.

284. Boccia RV, Gordan LN, Clark G, Howell JD, Grunberg SM. Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study. *Support Care Cancer*. 2011;19(10):1609-1617.
285. Howell J, Smeets J, Drenth HJ, Gill D. Pharmacokinetics of a granisetron transdermal system for the treatment of chemotherapy-induced nausea and vomiting. *J Oncol Pharm Pract*. 2009;15(4):223-231.
286. Duggan ST, Curran MP. Transdermal granisetron. *Drugs*. 2009;69(18):2597-2605.
287. Deeks ED. Granisetron Extended-Release Injection: A Review in Chemotherapy-Induced Nausea and Vomiting. *Drugs*. 2016;76(18):1779-1786.
288. Grunberg S, Chua D, Maru A, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol--EASE. *J Clin Oncol*. 2011;29(11):1495-1501.
289. Ottoboni T, Keller MR, Cravets M, Clendeninn N, Quart B. Bioequivalence of HTX-019 (aprepitant IV) and fosaprepitant in healthy subjects: a Phase I, open-label, randomized, two-way crossover evaluation. *Drug Des Devel Ther*. 2018;12:429-435.
290. Aapro MS, Schmoll HJ, Jahn F, Carides AD, Webb RT. Review of the efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in a range of tumor types. *Cancer Treat Rev*. 2013;39(1):113-117.
291. Jin Y, Wu X, Guan Y, et al. Efficacy and safety of aprepitant in the prevention of chemotherapy-induced nausea and vomiting: a pooled analysis. *Support Care Cancer*. 2012;20(8):1815-1822.
292. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Ann Pharmacother*. 2005;39(1):77-85.
293. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs*. 2004;64(7):777-794.
294. Shadle CR, Lee Y, Majumdar AK, et al. Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity. *J Clin Pharmacol*. 2004;44(3):215-223.
295. de Jonge ME, Huitema AD, Holtkamp MJ, van Dam SM, Beijnen JH, Rodenhuis S. Aprepitant inhibits cyclophosphamide bioactivation and thiotepa metabolism. *Cancer Chemother Pharmacol*. 2005;56(4):370-378.
296. Nygren P, Hande K, Petty KJ, et al. Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. *Cancer Chemother Pharmacol*. 2005;55(6):609-616.
297. Aapro MS, Walko CM. Aprepitant: drug-drug interactions in perspective. *Ann Oncol*. 2010;21(12):2316-2323.
298. Marbury TC, Ngo PL, Shadle CR, et al. Pharmacokinetics of oral dexamethasone and midazolam when administered with single-dose intravenous 150 mg fosaprepitant in healthy adult subjects. *J Clin Pharmacol*. 2011;51(12):1712-1720.
299. Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. *Lancet Oncol*. 2015;16(9):1079-1089.
300. Schwartzberg LS, Modiano MR, Rapoport BL, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16(9):1071-1078.
301. Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol*. 2014;25(7):1333-1339.
302. Aapro M, Rugo H, Rossi G, et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol*. 2014;25(7):1328-1333.
303. Zhang L, Lu S, Feng J, et al. A Randomized Phase 3 Study Evaluating the Efficacy of Single-dose NEPA, a Fixed Antiemetic Combination of Netupitant and Palonosetron, Versus an Aprepitant Regimen for



- Prevention of Chemotherapy-induced Nausea and Vomiting (CINV) in Patients Receiving Highly Emetogenic Chemotherapy (HEC). *Ann Oncol*. 2017.
304. Schwartzberg L, Roeland E, Andric Z, et al. Phase III safety study of intravenous NEPA: a novel fixed antiemetic combination of fosnetupitant and palonosetron in patients receiving highly emetogenic chemotherapy. *Ann Oncol*. 2018;29(7):1535-1540.
  305. Barbour SY. Corticosteroids in the treatment of chemotherapy-induced nausea and vomiting. *J Natl Compr Canc Netw*. 2012;10(4):493-499.
  306. Aapro M, Fabi A, Nole F, et al. Double-blind, randomised, controlled study of the efficacy and tolerability of palonosetron plus dexamethasone for 1 day with or without dexamethasone on days 2 and 3 in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy. *Ann Oncol*. 2010;21(5):1083-1088.
  307. Celio L, Bonizzoni E, Bajetta E, Sebastiani S, Perrone T, Aapro MS. Palonosetron plus single-dose dexamethasone for the prevention of nausea and vomiting in women receiving anthracycline/cyclophosphamide-containing chemotherapy: meta-analysis of individual patient data examining the effect of age on outcome in two phase III trials. *Support Care Cancer*. 2013;21(2):565-573.
  308. Robinson D, Omar SJ, Dangel C, Fenn H, Tinklenberg J. Metoclopramide-induced extra pyramidal symptoms in a diabetic patient. *J Am Geriatr Soc*. 1994;42(12):1307-1308.
  309. Roscoe JA, Heckler CE, Morrow GR, et al. Prevention of delayed nausea: a University of Rochester Cancer Center Community Clinical Oncology Program study of patients receiving chemotherapy. *J Clin Oncol*. 2012;30(27):3389-3395.
  310. Hardy JR, O'Shea A, White C, Gilshenan K, Welch L, Douglas C. The efficacy of haloperidol in the management of nausea and vomiting in patients with cancer. *J Pain Symptom Manage*. 2010;40(1):111-116.
  311. Heinz WJ, Grau A, Ulrich A, et al. Impact of benzodiazepines on posaconazole serum concentrations. A population-based pharmacokinetic study on drug interaction. *Curr Med Res Opin*. 2012;28(4):551-557.
  312. Davis M, Maida V, Daeninck P, Pergolizzi J. The emerging role of cannabinoid neuromodulators in symptom management. *Support Care Cancer*. 2007;15(1):63-71.
  313. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. *Br J Pharmacol*. 2011;163(7):1411-1422.
  314. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Investig Drugs*. 2008;17(1):85-95.
  315. Machado Rocha FC, Stefano SC, De Cassia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care (Engl)*. 2008;17(5):431-443.
  316. LeGrand SB, Walsh D. Scopolamine for cancer-related nausea and vomiting. *J Pain Symptom Manage*. 2010;40(1):136-141.
  317. Passik SD, Navari RM, Jung SH, et al. A phase I trial of olanzapine (Zyprexa) for the prevention of delayed emesis in cancer patients: a Hoosier Oncology Group study. *Cancer Invest*. 2004;22(3):383-388.
  318. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *J Support Oncol*. 2011;9(5):188-195.
  319. Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. *Support Care Cancer*. 2013;21(6):1655-1663.
  320. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. *N Engl J Med*. 2016;375(2):134-142.
  321. Yanai T, Iwasa S, Hashimoto H, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. *Int J Clin Oncol*. 2018;23(2):382-388.
  322. Hashimoto H, Abe M, Tokuyama O, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(2):242-249.
  323. McDonagh M, Peterson K, Thakurta S. *Consideration of Evidence on Antiemetic Drugs for Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy in Adults*. Rockville MD2010.

# **NON-HODGKIN AND HODGKIN LYMPHOMAS**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan to include effectiveness, toxicities and outcomes, based on the most current guidelines for patients with lymphoma.
2. Assess the prognostic impact of relevant cancer-related molecular biology testing.
3. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with pharmacotherapy for lymphoma and other cancers, including chemotherapy-induced pulmonary toxicities and extravasation.

## NON-HODGKIN LYMPHOMA

### **Patient Case #1:**

OG is a 67-year-old male who presented to his primary care physician complaining of bloating, drenching night sweats, fever and unintended weight loss over the past 3 months. On physical exam, right inguinal and axillary lymphadenopathy was found. An excisional biopsy revealed a follicular B-cell lymphoma, grade II. CT scans of chest, abdomen, and pelvis revealed retroperitoneal axillary lymphadenopathy, and a bone marrow biopsy was negative for disease. He was ultimately diagnosed with Stage III, grade 2 disease. He has no significant comorbid conditions and desires therapy for his disease.

**Which of the following is the most appropriate treatment for OG at this time?**

- A. Radiotherapy
- B. BR x 6 cycles
- C. Obinutuzumab x 12 cycles
- D. CHOP x 8 cycles

### **I. Classification<sup>1,2</sup>**

- A. Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. Lymphomas arise either in the lymph nodes or mucosal associated lymphoid tissue (MALT).
  - 1. In the United States, B-cell lymphomas represent 85% and T-cell lymphomas represent 15% of NHL cases. NK-cell lymphomas are very rare.
- B. The World Health Organization (WHO) updated the classification of lymphoid neoplasms in 2022. After consideration of cell of origin (B, T or NK), this classification further subdivides lymphomas into those derived from precursor lymphocytes versus those derived from mature lymphocytes.
  - 1. The classification is further refined based on immunophenotype, genetic and clinical features.
  - 2. Treatment and expected outcomes are defined based on the specific subtype.

**Common subtypes of B-cell non-Hodgkin lymphoma according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and World Health Organization (WHO) criteria.<sup>2,3</sup>**

Subtype	Untreated Survival	Curable with Chemotherapy
<b>Indolent</b> 1. Follicular Lymphoma (FL) 2. Marginal Zone Lymphoma a. Extranodal b. Nodal c. Splenic	Years	No
<b>Aggressive</b> 1. *Mantle Cell Lymphoma (MCL) 2. Diffuse Large B-cell Lymphoma (DLBCL) a. AIDS-related DLBCL 3. Primary Mediastinal Large B-cell Lymphoma 4. ^Gray Zone Lymphoma (GZL)	Months	Potentially
<b>Very Aggressive</b> 1. Burkitt Lymphoma (BL) a. AIDS-related BL 2. Burkitt-like Lymphoma	Weeks	Potentially

\*MCL has both features of indolent and aggressive subtypes; its classification is controversial. MCL is typically considered to be incurable.

^GZL refers to various lymphomas that have histologic similarities that are intermediate between them (example: DLBCL and classical Hodgkin lymphoma).

**Common subtypes of T-cell non-Hodgkin lymphoma according to the NCCN Guidelines® and WHO criteria.<sup>2,3</sup>**

Subtype	Untreated Survival	Curable with Chemotherapy
<b>Indolent</b> 1. Cutaneous T-cell lymphoma (CTCL) a. Mycosis fungoides b. Sezary syndrome	Years	No
<b>Aggressive</b> 1. Peripheral T-cell lymphoma (PTCL) a. Anaplastic large cell lymphoma (ALCL), ALK (+) b. Anaplastic large cell lymphoma, ALK (-) c. Angioimmunoblastic lymphoma (AITL) d. PTCL – not otherwise specified (PTCL-NOS) 2. Extranodal NK/T-cell lymphoma	Months	Potentially, particularly in ALK+ ALCL

ALK = anaplastic lymphoma kinase

## II. Genomics

- A. Cytogenetic abnormalities occur in all subtypes of NHL. They most frequently involve translocations of antigen receptor genes: immunoglobulin genes in B-lineage lymphomas and T-cell receptor genes in T-cell lymphomas.
- B. Specific cytogenetic abnormalities are discussed within each subtype of NHL below.

## III. Treatment

- A. Indolent or low-grade lymphomas—Follicular Lymphoma (FL)<sup>3-6</sup>
  1. Natural history and treatment options
    - a. The median age at diagnosis is 60 years. Treatment options may be limited by the patient's comorbidities.
    - b. Despite therapeutic advances that have improved outcomes, FL is generally considered to be a chronic disease characterized by multiple recurrences when standard therapy is used. However, some patients may go years without ever needing treatment.
  2. Since most cases of indolent NHL are incurable, the goal of treatment is **palliation**.
  3. Prognosis for indolent NHL (low-grade lymphomas)
    - a. There are three tools that are frequently used to provide prognostic information that may be used to guide therapeutic decisions. Even if the patient's disease contains components of the different criteria listed below, it does not imply that treatment will be initiated.
      - 1) Group d'Etude des Lymphomas Folliculaires (GELF) criteria, which evaluate therapeutic strategies for FL.<sup>7,8</sup>
      - 2) Follicular Lymphoma International Prognostic Index (FLIPI) criteria<sup>9</sup>
      - 3) Follicular Lymphoma International Prognostic Index 2 (FLIPI-2) criteria<sup>8,10-12</sup>
        - a) FLIPI did not take into account patients treated with rituximab. FLIPI-2 was developed to take patients with FL who were treated with rituximab into consideration.
        - b) Both FLIPI and FLIPI-2 predict for prognosis, but have not been established as a means for selecting treatment options. FLIPI is oriented towards OS, while FLIPI-2 is oriented towards PFS.<sup>13</sup>
        - c) FLIPI remains more widely used because of its validation in prospective trials and observational settings.

### The GELF criteria for prognosis of indolent NHL.<sup>7</sup>

- Involvement of  $\geq 3$  nodal sites, each with a diameter of  $\geq 3$  cm
- Any nodal or extranodal tumor mass with a diameter of  $\geq 7$  cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal effusions
- Cytopenias (leukocytes  $< 1 \times 10^9/L$  and/or platelets  $< 100 \times 10^9/L$ )
- Leukemia ( $> 5 \times 10^9/L$  malignant cells)

**Comparison of the FLIPI and FLIPI-2 criteria for prognosis of indolent NHL.**<sup>8-11</sup>

<b>FLIPI</b>		<b>FLIPI-2</b>	
1 point is assigned for each for each of the following adverse prognostic factors:		1 point is assigned for each for each of the following adverse prognostic factors:	
Age	≥ 60 years	Age	> 60 years
Ann Arbor stage	III – IV	β-2 microglobulin	> Upper limit of normal
Hemoglobin level	< 12 g/dl	Hemoglobin level	< 12 g/dl
Serum LDH level	> Upper limit of normal	Bone marrow	Positive for disease
Number of nodal sites	≥ 5	Largest involved lymph node	> 6 cm
<u>Risk group according to FLIPI</u> Number of Factors Low 0 to 1 Intermediate 2 High ≥3		<u>Risk group according to FLIPI-2</u> Number of Factors Low 0 to 1 Intermediate 2 High ≥3	
The sum of the points allotted correlates with the following risk groups: • Low risk (0-1 point): 5-year OS = 88% • Low-intermediate risk (2 points): 5-year OS = 71% • High-intermediate risk (3 points): 5-year OS = 57% • High risk (4-5 points): 5-year OS = 44%		The sum of the points allotted correlates with the following risk groups: • Low risk (0 point): 5-year PFS = 79% • Low-intermediate risk (1-2 points): 5-year PFS = 51% • High-intermediate risk (3-5 points): 5-year PFS = 19%	

- b. Despite these predictive scales, the strongest predictor of long-term outcomes is the length of first remission after first-line treatment.<sup>14</sup>

4. Grading<sup>3,4,6,13,15,16</sup>

- FL is graded according to the number of centroblasts in 10 neoplastic follicles per high-power microscopic field. The clinical aggressiveness of the disease increases with increasing number of centroblasts.
- The WHO classification utilizes a 1-3 grading system. The large majority of FL cases are grade 1 or 2 (low-grade), and these two grades are typically grouped together due to similar clinical outcomes.
- Some references consider grade 3A as low-grade FL, while others consider it to be more aggressive. However, Grade 3B is biologically distinct from other grades and behaves like an aggressive NHL. Cases of grade 3B are typically treated like diffuse large B cell lymphoma (see Aggressive Lymphoma section below).

5. Selection of initial therapy

### Initial Treatment Overview of Follicular Lymphoma per the NCCN Guidelines®.<sup>3</sup>

Tumor Type	Standard of Care	Comments	Alternative Chemotherapy Regimens
Stage I or contiguous Stage II (Grade 1 – 2)	ISRT (preferred) or ISRT + anti-CD20 monoclonal antibody +/- chemotherapy or Anti-CD20 monoclonal antibody +/- chemotherapy	Observation may be appropriate in selected cases	
Stage II non-contiguous (Grade 1 – 2)	Anti-CD20 monoclonal antibody +/- chemotherapy +/- ISRT for local palliation	Observation may be appropriate in selected cases	
Stage III or IV (Grade 1 – 2)	When patient has indications for treatment:  <u>Preferred regimens (in alphabetical order)</u> Bendamustine + obinutuzumab or rituximab CHOP + obinutuzumab or rituximab CVP + obinutuzumab or rituximab Lenalidomide + rituximab	See indications for treatment with chemotherapy below  Bendamustine not recommended for patients with CrCl < 40 ml/min	Rituximab 375 mg/m <sup>2</sup> x 4 weekly doses (in patients with low tumor burden or if elderly / infirm)
Stage I – IV (Grade 3A)	Controversial – treatment should be individualized	The distinction for FL grade 3A and 3B has not been shown to have clinical significance to date	
Stage I – IV (Grade 3B)	Treat per DLBCL guidelines	The distinction for FL grade 3A and 3B has not been shown to have clinical significance to date	

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CrCl = creatinine clearance; CVP = cyclophosphamide, vincristine and prednisone; ISRT = involved-site radiotherapy.

#### 5. Localized disease (Stage I and Stage II contiguous, grade 1 and 2)

- a. Involved-site radiotherapy (ISRT) is still considered the **standard of care**.<sup>4,5,13,17-19</sup>
- b. The results of radiotherapy were retrospectively evaluated in 177 patients with stage I and II FL.<sup>20</sup>
  - a. Overall survival rates at 5, 10, 15, and 20 years were 82%, 64%, 44%, and 35%, respectively. The median overall survival time was 13.8 years. At 5, 10, 15, and 20 years, 55%, 44%, 40%, and 37% of patients, respectively, were relapse-free.

- c. If a patient is symptomatic from localized disease and radiation is not an option, other options include immunotherapy +/- chemotherapy.<sup>3</sup> See treatment of advanced disease below for preferred regimens.
- d. A “watch and wait” approach may be acceptable in select patients.<sup>21-23</sup>
  - 1) 83 patients with advanced indolent NHL initially managed with no therapy were followed for long-term outcome.
    - a) The median time until any therapy was needed was 3 years.
    - b) Median OS was 11 years. OS was 82% at 5 years and 73% at 10 years.
    - c) Spontaneous regression occurred in 19% of patients during the study period. However, 20% of patients experienced a transformation into DLBCL (histologic transformation) during the study period.
  - 2) A multicenter retrospective analysis evaluated outcomes in 145 patients with newly diagnosed stage I or II FL. Patients received one of six different first-line treatment options: watch and wait, chemotherapy alone, radiotherapy alone, chemotherapy + radiation therapy, rituximab monotherapy and chemotherapy + rituximab.<sup>24</sup>
    - a) PFS at 7.5 years was highest with chemotherapy + rituximab.
    - b) OS at 7.5 years was not different between groups.

**Retrospective study of first-line treatment options for newly diagnosed stage I or II FL.<sup>24</sup>**

Regimen	CR	PFS at 7.5 years	OS at 7.5 years
Observation	---	26%	72%
Chemotherapy alone	69%	23%	74%
Radiation alone	81%	19%	66%
Chemotherapy + radiation	95%	26%	67%
Rituximab monotherapy	57%	---	---
Chemotherapy + rituximab	75%	60%	74%
p value	NS	0.00135	NS

CR = complete response; NS = not significant; OS = overall survival; PFS = progression-free survival.

6. Advanced disease (Stage II non-contiguous; Stages III and IV, grade 1 and 2)<sup>3-6,11,15,19,25</sup>
  - a. Indications for treatment include symptomatic disease, threatened end-organ function, cytopenia due to lymphoma, massive bulk or splenomegaly at presentation, steady progression over at least 6 months, autoimmune cytopenias, recurrent infections and/or patient preference.<sup>26</sup>
  - b. In asymptomatic patients, observation is a recommendation according to NCCN Guidelines®.<sup>3</sup>
  - c. Some patients prefer observation, and several randomized trials have failed to demonstrate a survival advantage with immediate treatment.<sup>26-29</sup>



- d. If treatment is desired, the selection of treatment should be individualized according to the patient's age, extent of disease, presence of comorbid conditions and goals of therapy.
- e. Frontline treatment for advanced disease
  - 1) Addition of rituximab<sup>3,11</sup>
    - a) The addition of rituximab to chemotherapy regimens has consistently increased overall response rate, response duration and progression-free survival. In addition, some studies have shown a benefit in overall survival, and thus the addition of rituximab has become a widely accepted standard of care for first-line therapy for patients with FL.
    - b) However, no head-to-head randomized studies have shown superiority of one chemoimmunotherapy regimen over another.
  - 2) Bendamustine + rituximab (BR)
    - a) A multicenter phase III trial of the Study Group Indolent Lymphomas ("StiL NHL1") randomized 549 patients with indolent or mantle cell NHL to either BR (bendamustine 90 mg/m<sup>2</sup> on day 1 and 2 + rituximab 375 mg/m<sup>2</sup> on day 1 every 28 days) x 6 cycles or R-CHOP x 6 cycles. The primary endpoint was progression-free survival.<sup>30,31</sup>
      - i. Median PFS was significantly longer with BR than R-CHOP (69.5 months vs 31.2 months).
      - ii. Median time to next treatment (TTNT) was significantly prolonged with BR compared to R-CHOP (not reached vs 56 months), and patients treated with BR needed fewer second-line treatments due to disease progression than patients who received R-CHOP.
      - iii. Median survival was not reached in either group; OS did not differ between the groups.
      - iv. The BR regimen was associated with a lower incidence of serious adverse effects, and a similar incidence of secondary malignancies as compared to R-CHOP.
      - v.

**Results of the randomized phase III "StiL NHL1" study comparing BR to R-CHOP in previously untreated patients with indolent or mantle cell NHL.<sup>30,31</sup>**

Regimen	PFS	Time to Next Anti-lymphoma Treatment	10-year OS	Grade 3 – 4 Neutropenia
BR	69.5 months	Not reached	71%	30%
R-CHOP	31.2 months	56 months	66%	68%
p value	< 0.001	< 0.001	NR	< 0.001

BR = bendamustine and rituximab; NR = not reported; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; OS = overall survival.

- b) The phase III “BRIGHT” study compared BR to the investigator’s choice of R-CHOP or R-CVP in newly diagnosed indolent or mantle cell lymphoma. Five-year results showed that patients who received BR had statistically significantly greater PFS and duration of response than those who received R-CHOP or R-CVP. However, there was no difference in OS.<sup>32</sup>

### 3) R-CHOP<sup>33</sup>

- a) A prospective phase III study included 428 patients with untreated FL stage III & IV (grade 1 & 2) with bulky disease, B-symptoms or disruption of hematopoiesis.
  - i. Patients were randomized to either CHOP or R-CHOP x 6 to 8 cycles every 3 weeks.
  - ii. R-CHOP was associated with a 60% reduction in relative risk of treatment failure, significantly prolonged time to treatment failure, higher overall response rate and prolonged duration of remission.
  - iii. OS analysis was complicated by a second randomization of the same study since patients who achieved a CR or PR were offered a second randomization to either autologous HSCT or maintenance interferon alfa.
  - iv. This study confirmed the superiority of R-CHOP to CHOP as first-line therapy in advanced FL.

**Results of a phase III study of CHOP vs. R-CHOP in untreated, advanced FL.<sup>33</sup>**

Regimen	Patients Experiencing Treatment Failure	CR
CHOP	30%	17%
CHOP + Rituximab	13%	20%
p value	< 0.001	No difference

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CR = complete response.

- b) There are several scenarios in which R-CHOP may be preferred over BR for first-line treatment of FL despite a lack of strong evidence. These situations include grade 3 FL, high uptake on PET scan, aggressive disease (such as solid organ invasion), destructive bony lesions, or other markers of aggressive biology.<sup>12</sup>

### 4) R-CVP<sup>34,35</sup>

- a) A randomized, phase III study of newly diagnosed FL patients examined the addition of rituximab to cyclophosphamide, vincristine and prednisone (CVP).
- b) Patients who received rituximab had significantly improved outcomes with no significant increases in toxicity.

**Results of a phase III study of R-CVP compared to CVP in previously untreated FL.<sup>34,35</sup>**

Regimen	ORR	CR	TTF	Received 8 cycles	OS at 4 years
CVP	57%	10%	7 months	68%	77%
CVP + Rituximab	81%	41%	27 months	85%	83%
p value	< 0.001	NR	< 0.0001	NR	< 0.05

CR = complete response; CVP = cyclophosphamide, vincristine and prednisone; NR = not reported; ORR = overall response rate; OS = overall survival; TTF = time to treatment failure.

**5) Lenalidomide + rituximab (R<sup>2</sup>)<sup>3,36</sup>**

- The phase III “RELEVANCE” study randomized 1,030 patients with untreated, advanced stage FL to R<sup>2</sup> or chemotherapy + rituximab, followed by maintenance rituximab in both arms. The chemotherapy regimen was the investigator’s choice of R-CHOP, R-CVP or BR.
- This was a superiority trial, with dual primary endpoints of CR at 120 weeks and PFS.
- The rate of CR at 120 weeks was similar between the groups. Likewise, the interim 3-year rate of PFS was not different between the groups.
- R<sup>2</sup> was associated with lower rate of grade 3 or 4 neutropenia and febrile neutropenia of any grade, but with higher rates of grade 3 or 4 cutaneous reactions.
- Although the trial did not meet the primary endpoints showing superiority of the R<sup>2</sup> regimen, this “chemotherapy-free” regimen may be an effective alternative and is now considered a Category 2A recommendation in the NCCN Guidelines.<sup>3</sup>

**Results of the phase III “RELEVANCE” study, which compared lenalidomide + rituximab to chemotherapy + rituximab in previously untreated FL.<sup>36</sup>**

Regimen	CR at 120 weeks (confirmed or unconfirmed)	3-year PFS	3-year OS
R <sup>2</sup>	48%	77%	94%
R + chemo	53%	78%	94%
p value	0.13	0.48	NR

CR = complete response; NR = not reported; OS = overall survival; PFS = progression-free survival; R = rituximab; R<sup>2</sup> = lenalidomide + rituximab.

**6) Rituximab alone<sup>37,38</sup>**

- FL patients with Stage II to IV disease or early stage FL patients (Stage I to II) who failed radiotherapy were included in a phase II study.
  - All patients were treated with rituximab (375mg/m<sup>2</sup>) x 4 weekly doses.
  - Patients with objective response or stable disease were treated at 6 month intervals for a maximum of 4 courses (2 years of treatment).

- iii. At 1 year, PFS was 77%. Acceptable responses were seen, with 15% of patients achieving a CR and 49% achieving PR.
  - iv. This study, along with other studies, confirmed the activity of rituximab in early stage FL.
  - b) In patients with low tumor burden, single-agent rituximab (375 mg/m<sup>2</sup> weekly for 4 doses) is now preferred.<sup>3</sup>
- 7) Obinutuzumab in the first-line setting
- a) The phase III “GALLIUM” study evaluated rituximab-based chemotherapy vs obinutuzumab-based chemotherapy in patients with newly diagnosed FL. Investigators could select CHOP, CVP or bendamustine as the chemotherapy backbone. The primary endpoint was investigator-assessed PFS.<sup>39-41</sup>
    - i. At a median follow-up of 34.5 months, PFS was significantly longer in the obinutuzumab arm compared to the rituximab arm. The study was unblinded after a planned interim analysis that reported these results.
    - ii. There was a slight numerical benefit in OS in the obinutuzumab arm, but this difference was not statistically significant.
    - iii. Obinutuzumab was associated with a greater incidence of infusion-related reactions and hematologic toxicity.
    - iv. In both arms, there were more deaths in patients who received bendamustine-based induction regimens than in CHOP or CVP. These fatal toxicities were mainly infections, but also included cardiac, neurologic and respiratory toxicities that were fatal.<sup>42</sup> Based on the observed infectious complications, prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP) and herpes simplex virus (HSV) may be considered with bendamustine-containing regimens.<sup>3,43</sup>

**Results of the GALLIUM study, which compared rituximab-based chemotherapy to obinutuzumab-based chemotherapy in newly diagnosed FL.<sup>39,40</sup>**

	R-chemo	G-chemo	p value
Investigator-assessed PFS at 3 years	73.3%	80%	0.001
OS at 3 years	92.1%	94%	0.21
3-year rate of new anti-lymphoma treatment	81.2%	87.1%	0.009
Grade ≥ 3 AE	67.8%	74.6%	NR
Grade ≥ 3 infusion-related reactions	6.7%	12.4%	NR
Grade ≥ 3 infections	15.6%	20%	NR

AE = adverse event; G = obinutuzumab; NR = not reported; OS = overall survival; PFS = progression-free survival; R = rituximab.

**Patient Case #1, Continued:**

**Correct answer = B (BR x 6 cycles).**

Radiotherapy alone is only indicated for stage I & II non-bulky disease; OG's Stage III disease requires systemic therapy. BR is an appropriate and recommended first-line option. Since the patient has a B cell malignancy, his treatment should include rituximab; there are currently no recommendations for single-agent obinutuzumab in the first-line treatment of FL.

**OG completed 6 cycles of BR and achieved a complete response. Which of the following would be the most appropriate option for OG at this time?**

- A. Ofatumumab monthly x 1 year**
- B. Lenalidomide daily**
- C. Rituximab monthly x 1 year**
- D. Rituximab every 2 months x 2 years**

7. First-line consolidation / extended therapy for advanced disease after frontline therapy (optional)
  - a. Rituximab maintenance
    - 1) Several studies have reported that the prolonged administration of rituximab as maintenance therapy significantly improved event-free and/or progression-free survival in previously untreated patients who responded to initial rituximab induction therapy. This benefit has not consistently translated into an OS advantage, however.<sup>44,45</sup>
    - 2) The use of rituximab maintenance therapy (375 mg/m<sup>2</sup> every 8 weeks for 12 doses) is currently recommended for patients who initially presented with high tumor burden (Category 1 recommendation).<sup>3</sup>
    - 3) Rituximab maintenance after CVP chemotherapy: patients with Stage III/IV disease that was stable or responding following CVP chemotherapy were randomized to rituximab 375 mg/m<sup>2</sup> IV once per week for 4 consecutive weeks every 6 months for 2 years or observation.<sup>46</sup>
      - a) This study demonstrated a PFS benefit with rituximab maintenance in patients with advanced indolent lymphoma who responded to first-line chemotherapy with CVP.

**Results of a randomized, phase III study of maintenance rituximab or placebo in patients with indolent lymphoma who had a response to CVP.<sup>46</sup>**

Regimen	Best response improved	3-year PFS	3-year OS
CVP	7%	33%	86%
CVP + R maintenance	22%	68%	92%
p value	0.00006	< 0.001	0.08

CVP = cyclophosphamide, vincristine and prednisone; R = rituximab; OS = overall survival; PFS = progression-free survival.

- b) In the phase III Primary Rituximab and Maintenance (“PRIMA”) trial, 1,202 patients with follicular NHL were randomized to receive rituximab plus one of three chemotherapy regimens (CVP, CHOP or FCM – fludarabine, cyclophosphamide and mitoxantrone). The 1,018 patients who attained a partial or complete response were randomized to maintenance rituximab 375 mg/m<sup>2</sup> every 8 weeks for 2 years (12 total doses) or observation.<sup>47-49</sup>
  - i. The primary endpoint of the trial was progression-free survival.
  - ii. PFS was statistically significantly longer in the rituximab maintenance arm at the time of primary analysis, and ten-year follow-up data have recently been reported that confirm this finding. The benefit of rituximab maintenance for PFS was significant in all predefined patient strata.
  - iii. There was no difference in 10-year OS (80.1% with rituximab and 79.9% with observation, p = 0.7948). Likewise, there was no difference in the rate of histologic transformation to a more aggressive lymphoma.

**Results of the phase III “PRIMA” trial, which randomized FL patients to maintenance rituximab or observation after response to chemotherapy.**<sup>47-49</sup>

Regimen	Median PFS	10-year PFS	Time to Next Treatment	Adverse events leading to discontinuation
Observation	4.1 years	35%	6.1 years	2%
Rituximab maintenance	10.5 years	51.1%	Not reached	4%
p value	< 0.001	< 0.001	< 0.001	NS

NS = not significant; PFS = progression-free survival.

- c) Other studies have demonstrated that the use of maintenance rituximab in FL is safe. Studies have shown that the “rapid” infusion protocol and subcutaneous product are safe in this setting, and both are recommended in the current NCCN Guidelines<sup>®</sup>.<sup>3,50,51</sup>
- 4) Maintenance obinutuzumab (1,000 mg every 8 weeks for 12 doses) is recommended in patients who received obinutuzumab as part of their initial chemotherapy (as in the “GALLIUM” study and others).<sup>3,39</sup>
- 5) In patients initially treated with single-agent rituximab, consolidation with rituximab (375 mg/m<sup>2</sup> every 8 weeks for 4 doses) is recommended.<sup>3,52</sup>

**Patient Case #1, Continued:**

**Correct answer = D (Rituximab every 2 months x 2 years).**

Based on the results of the “PRIMA” trial and others, the use of rituximab maintenance therapy is an NCCN Guidelines<sup>®</sup> Category 1 recommendation in patients who initially responded to first-line chemoimmunotherapy. Several administration schedules have been studied and may be used in clinical practice; however, regardless of the schedule, the duration of maintenance therapy should be 2 years.

**8. Relapsed/Refractory FL**

- a. Progressive disease should be histologically documented to exclude transformation to an aggressive NHL, such as DLBCL or Burkitt lymphoma.<sup>5,53</sup> Histologic transformation occurs in 2-3% of patients per year. Transformation should be suspected in the presence of rising LDH levels, disproportional growth in one area, development of extranodal disease, hypercalcemia, new symptoms, non-response to initial therapy, or early relapse.<sup>3,4,11,13,17,53,54</sup>
- b. Early relapse has been broadly defined as recurrence or progression of disease within 2 years of the initiation of frontline chemoimmunotherapy (POD24).<sup>6,12,13,25,55-59</sup>
  - 1) Approximately 20% of patients will experience POD24, but there is not an established method of identifying patients at risk for this event.
  - 2) POD24 is now established as a marker of poor OS, with an estimated 5-year OS of only 50%.
  - 3) It should be noted that POD24 is not a baseline measurement; it can only be determined after treatment has been initiated.<sup>59</sup> Further, preferred treatment strategies for patients with POD24 are not currently well defined.<sup>60</sup>
- c. Second-line and subsequent treatment
  - 1) After progressing from first line therapy, some patients will still benefit from observation.
    - a) Indications for treatment include symptomatic disease, threatened end-organ function, cytopenia secondary to lymphoma, massive bulk or splenomegaly at presentation, steady progression over at least 6 months, and/or patient preference.<sup>3,15,61</sup>
    - b) As in first-line therapy, the GELF criteria help guide the decision to initiate treatment.
  - 2) The ideal sequencing of therapy in this setting is unknown. The treatment approach should be personalized and balance patient-specific factors such as comorbidities and treatment goals with known response rates and toxicity profiles.<sup>11,15,17-19,61</sup>
  - 3) Preferred treatment options for second-line and subsequent therapy include:<sup>3</sup>
    - a) Bendamustine + obinutuzumab or rituximab (if not previously treated with bendamustine)
    - b) CHOP + obinutuzumab or rituximab
    - c) CVP + obinutuzumab or rituximab
    - d) Lenalidomide + rituximab
  - 4) Other recommended regimens for second-line and subsequent therapy include:<sup>3</sup>
    - a) Ibritumomab tiuxetan
    - b) Lenalidomide, if not a candidate for anti-CD20 monoclonal antibody therapy
    - c) Lenalidomide + obinutuzumab
    - d) Obinutuzumab
    - e) Rituximab

- 5) In the elderly or infirm patient, recommended therapies in the second-line and subsequent setting include:<sup>3</sup>
  - a) Rituximab 375 mg/m<sup>2</sup> weekly for 4 doses (preferred)
  - b) Chlorambucil +/- rituximab
  - c) Cyclophosphamide +/- rituximab
  - d) Tazemetostat, in patients who are EZH2 wild type or unknown and if no satisfactory alternative options are available (see below)
- d. Second line consolidation for FL
  - 1) Rituximab maintenance 375 mg/m<sup>2</sup> one dose every 12 weeks for 2 years is a Category 1 recommendation by the NCCN Guidelines®.<sup>3</sup>
  - 2) Obinutuzumab has received FDA approval for use in combination with bendamustine, followed by obinutuzumab maintenance in patients with relapsed or refractory FL who have failed a rituximab-containing regimen.
    - a) The phase III “GADOLIN” trial demonstrated an improvement in progression-free survival using this strategy compared to bendamustine alone. This regimen is considered a Category 2A recommendation at this time.<sup>3,62,63</sup>
  - 3) High dose chemotherapy with autologous or allogeneic stem cell rescue may be considered in select patients (see Hematopoietic Stem Cell Transplantation section).
- e. Third-line and subsequent therapy<sup>3</sup>
  - 1) Phosphatidylinositol-3-kinase (PI3K) inhibitors
    - a) Copanlisib is recommended in this setting.
    - b) Note that the FDA approval for idelalisib for the treatment of FL was voluntarily withdrawn in January 2022 after the confirmatory trials required as part of the initial approval in 2014 were not completed.<sup>64</sup>
    - c) The FDA withdrew its approval of duvelisib for relapsed or refractory FL in April 2022 due to the inability to conduct a confirmatory trial to verify clinical benefit.<sup>65</sup>
    - d) The FDA approval for umbralisib for the treatment of FL was voluntarily withdrawn in June 2022 after updated findings from a trial of this agent in patients with chronic lymphocytic leukemia showed a possible increased risk of death in patients who received umbralisib.<sup>66</sup>
  - 2) Tazemetostat
    - a) If EZH2 mutation positive
    - b) If EZH2 wild type or unknown and if no satisfactory alternative options are available (see below)
  - 3) Anti-CD-19 CAR T-cell therapy
    - a) Axicabtagene ciloleucel
    - b) Tisagenlecleucel



f. Tazemetostat (Tazverik®) received accelerated FDA approval in June 2020 for the treatment of adult patients with relapsed or refractory FL whose tumors are positive for an EZH2 mutation and have received at least two prior systemic therapies. It was also approved for adult patients with relapsed and refractory FL who have no satisfactory alternative treatment options under the accelerated approval pathway.<sup>67-71</sup>

- 1) Approximately 25% of patients with FL have a mutation in EZH2.<sup>25</sup>
- 2) This approval represents the first epigenetic therapy approval for FL.
- 3) Approval was based on two open-label, single-arm cohorts of a multi-center trial that included 95 patients with relapsed or refractory FL who received tazemetostat 800 mg PO twice daily. The primary endpoint was ORR.
- 4) The ORR in patients with EZH2 mutations was 69% (95% CI, 53-82%), and median duration of response in these patients was 10.9 months. The ORR in patients with EZH2 wild-type was 34% (95% CI, 22-48%) and the median duration of response was 13 months.
- 5) Median OS was not reached in either cohort.
- 6) Please refer to the Adult Sarcomas materials for more information on this agent.

9. Treatment summary of FL

**Overview of Treatment Recommendations for FL per the NCCN Guidelines®.<sup>3</sup>**

<b>Follicular Lymphoma (Grades 1 and 2) Suggested Regimens*</b>	
First-line therapy	<p><u>Preferred, in alphabetical order:</u></p> <p>Bendamustine + obinutuzumab or rituximab  CHOP + obinutuzumab or rituximab  CVP + obinutuzumab or rituximab  Lenalidomide + rituximab</p> <p><u>Other recommended regimens:</u></p> <p>Rituximab 375 mg/m<sup>2</sup> weekly x 4 doses (if low tumor burden)</p>
First-line therapy for elderly or infirm	<p>Rituximab (preferred)  Chlorambucil +/- rituximab  Cyclophosphamide +/- rituximab</p>
First-line consolidation or extended dosing	<p>Rituximab 375 mg/m<sup>2</sup> every 8 weeks up to 2 years for patients presenting initially with a high tumor burden (Category 1)  Obinutuzumab 1,000 mg every 8 weeks for 12 doses  If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m<sup>2</sup> every 8 weeks for 4 doses</p>
Second-line and subsequent therapy	<p><u>Preferred regimens:</u></p> <p>Bendamustine + obinutuzumab or rituximab  CHOP + obinutuzumab or rituximab  CVP + obinutuzumab or rituximab  Lenalidomide + rituximab</p> <p><u>Other recommended regimens:</u></p> <p>Ibritumomab tiuxetan  Lenalidomide (if not a candidate for anti-CD20 monoclonal antibodies)</p>

	<p>Obinutuzumab +/- lenalidomide Rituximab</p> <p><u>In elderly or infirm:</u> Rituximab 375 mg/m<sup>2</sup> weekly for 4 doses (preferred) Chlorambucil +/- rituximab Cyclophosphamide +/- rituximab Tazemetostat (in patients who are EZH2 wild type or unknown and if no satisfactory alternative options are available)</p>
Second-line consolidation or extended dosing	<p><u>Preferred regimens:</u> Rituximab 375 mg/m<sup>2</sup> every 12 weeks for 2 years (Category 1) Obinutuzumab 1,000 mg every 8 weeks for 12 doses</p> <p><u>Other recommended regimens:</u> High dose therapy with autologous stem cell transplant Allogeneic stem cell transplant (for highly selected patients only)</p>
Third-line and subsequent therapy	<p><u>PI3K inhibitor</u> Copanlisib</p> <p><u>Tazemetostat</u> After 2 prior therapies if EZH2 mutation positive In patients who are EZH2 wild type or unknown if no satisfactory alternative options are available</p> <p><u>Anti CD-19 CAR T-cell therapy</u> Axicabtagene ciloleucel Tisagenlecleucel</p>

\* This table does not include Stage I and II non-bulky disease that may be treated with ISRT alone. If systemic therapy is required for Stage I or II non-bulky disease, the recommended regimens are included here.

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CVP = cyclophosphamide, vincristine and prednisone.

**Patient Case #2:**

DM is a 63-year-old male with ECOG performance status 0 who presented to the Lymphoma Clinic with a recent history of lymphadenopathy in his cervical and inguinal lymph nodes. He also complains of drenching night sweats. An excisional lymph node biopsy of a cervical node revealed diffuse large B-cell lymphoma without BCL2, BCL6 or MYC rearrangement. Bone marrow biopsy was positive for malignant lymphoma cells. A CT scan of the chest was remarkable for 3 discrete areas of lymphadenopathy in the cervical lymph nodes, and a CT scan of the pelvis revealed 2 lymph nodes measuring 6.8 and 5.4 cm, respectively. All laboratory values were within normal limits. He was thus diagnosed with Stage IVB disease.

**Based upon this information, what is the goal of therapy for DM?**

- A. Disease cure
- B. Improve disease-free survival
- C. Symptom palliation
- D. Decrease disease burden prior to autologous stem cell transplantation

**What would be most appropriate treatment regimen for DM at this time?**

- A. R-CHOP x 3 cycles + RT
- B. R-ICE x 3 cycles
- C. R-CHOP x 6 cycles
- D. G-CHOP x 6 cycles

**B. Aggressive Lymphoma – Diffuse Large B Cell Lymphoma (DLBCL)**

**1. Common cytogenetic abnormalities**

- a. Gene expression profiling is becoming more common with DLBCL to stratify DLBCL into biologically meaningful and relevant prognostic groups. Although not standard of care at this time, translocations targeting MYC, BCL2 and BCL6 may help alter treatment options in the future since 40% of patients experience early treatment failure with standard therapy.
  - 1) DLBCL can also be stratified morphologically based on cell of origin (COO) as activated B-cell (ABC) DLBCL or germinal center B-cell (GCB) DLBCL.<sup>1,3,23,72-82</sup>
  - 2) These subtypes have distinctly different biologies as a result of different signaling pathways.
  - 3) The prevalence of ABC DLBCL increases continuously with age, reaching 40-50% after age 60 years.
  - 4) Outcomes in GCB DLBCL are better than in ABC DLBCL when conventional immunochemotherapy regimens are used. This may be due to different drug sensitivities between the two subtypes.
  - 5) Ongoing trials are exploring whether the addition of novel agents will selectively improve the outcomes in ABC DLBCL, but the standard of care remains the same for both subtypes at this time.
- b. MYC rearrangement has been reported in 9-17% of DLBCL patients, and often correlates with GCB phenotype.<sup>80,81</sup>

- 1) DLBCL with MYC rearrangement in addition to BCL2 and/or BCL6 rearrangements are known as “double-hit” lymphomas. If all three are rearranged, they are referred to as “triple-hit” lymphomas.<sup>3,83-87</sup>
  - 2) In the 2022 WHO revision of lymphoma, this subtype has been designated in a unique category called “high grade B-cell lymphomas (HGBLs) with MYC and BCL2 and/or BCL6 rearrangements.”<sup>2,72,87-89</sup>
  - 3) MYC gene rearrangement promotes tumor proliferation, while BCL2 protein expression inhibits cell apoptosis. The combination provides a distinct survival advantage to malignant cells.<sup>80,84,87</sup>
  - 4) These lymphomas are characterized by highly aggressive clinical behavior and pathophysiologic features that overlap with Burkitt lymphoma. An increased incidence of CNS involvement has been reported.<sup>83,86,87,90</sup>
  - 5) These patients have very poor clinical outcomes, even with rituximab-containing chemoimmunotherapy regimens or intensive therapy with stem cell transplantation. Progression-free survival and overall survival rates are significantly lower in patients with the “double-hit” than in those with other translocations.<sup>80,83,85,86,91</sup>
  - 6) The co-expression of MYC and BCL2 proteins without underlying rearrangements is known as “double expressor lymphoma (DEL).” While not considered to be a unique entity of DLBCL, it is considered to be a new adverse prognostic indicator.<sup>80,81,87,92,93</sup>
2. DLBCL is further subdivided into the following categories:
    - a. Newly diagnosed
      - 1) Stage I & Stage II non-bulky disease
      - 2) Stage I & Stage II bulky disease
      - 3) Stage II with extensive mesenteric disease or Stage III & IV disease
  3. The goal is to **CURE** the patient.<sup>75</sup>
  4. Prognosis for aggressive (intermediate) lymphomas
    - a. A recent Danish population-based study of 1,621 patients with DLBCL reported that the estimated loss of residual lifetime was low for patients who remained in complete remission 2 years after ending treatment.<sup>94</sup>
    - b. The International Non-Hodgkin's Lymphoma Prognostic Factors project designed the International Prognostic Index (IPI) based upon 5 independent prognostic variables for intermediate-grade or high-grade (aggressive) NHL.<sup>95,96</sup>
    - c. Independent risk factors – negative prognostic variables include:<sup>95,96</sup>
      - 1) Age > 60 years
      - 2) Stage III/IV disease
      - 3) Extranodal disease > 1 site
      - 4) ECOG performance status ≥ 2
      - 5) Serum LDH > 1 x normal limit

### Application of International Prognostic Index (IPI) to aggressive lymphomas.<sup>96</sup>

# of Negative Prognostic Variables	5-year OS
0-1	91%
2-3	65-81%
4-5	59%

OS = overall survival.

### 5. Initial choice of therapy

### Initial Treatment Overview of Diffuse Large B-Cell Lymphoma per the NCCN Guidelines®.<sup>3</sup>

Tumor Type	Standard of Care	Interim Restaging	Alternative Chemotherapy Regimens
Stage I or II, non-bulky disease	R-CHOP x 3 cycles followed by interim restaging	At restaging: <ul style="list-style-type: none"> <li>• If complete response, R-CHOP x1 additional cycle or ISRT</li> <li>• If partial response, R-CHOP x1-3 additional cycles +/- ISRT</li> <li>• If progressive disease, repeat biopsy</li> </ul>	DA-R-EPOCH  <u>Poor LVEF:</u> 1. DA-R-EPOCH- (doxorubicin maintained at base dose) 2. R-CDOP 3. R-CEPP 4. R-CEOP 5. R-GCVP
Stage I or II, bulky disease	R-CHOP x 6 cycles +/- ISRT	Perform after 3-4 cycles	
Stage II with extensive mesenteric disease or Stage III or IV	R-CHOP (Category 1)	Perform after 2-4 cycles, then continue R-CHOP for a total of 6 cycles (Category 1) or repeat biopsy	<u>Patients &gt;80 years of age with co-morbidities:</u> 1. R-CEPP 2. R-CDOP 3. R-mini-CHOP^ 4. R-GCVP

^Rituximab 375 mg/m<sup>2</sup>, cyclophosphamide 400 mg/m<sup>2</sup>, doxorubicin 25 mg/m<sup>2</sup>, and vincristine 1 mg on day 1 and prednisone 40 mg/m<sup>2</sup> on days 1–5.

D = day; DA-R-EPOCH = rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; ISRT = involved site radiation therapy; LVEF = left ventricular ejection fraction; R-CDOP = rituximab, cyclophosphamide, liposomal doxorubicin, vincristine and prednisone; R = rituximab; R-CEPP = rituximab, cyclophosphamide, etoposide, procarbazine and prednisone; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine and prednisone; R-GCVP = rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone.

### 6. Treatment of localized disease (stage I & II, non-bulky disease)<sup>3,97</sup>

- a. Rationale for R-CHOP and involved field radiation therapy (IFRT) (\*please note that NCCN Guidelines® now recommend involved site radiation therapy [ISRT] over IFRT).

- 1) The SWOG 0014 study evaluated the addition of rituximab to CHOP for 3 cycles followed by IFRT in newly diagnosed DLBCL patients.<sup>98</sup>

- i. This trial included patients > 18 years of age with limited stage disease and at least one adverse risk factor as defined by the stage-modified International Prognostic

Index (nonbulky stage II disease, age > 60 years, WHO performance status of 2, or elevated serum lactate dehydrogenase).

- ii. The primary objective was to estimate 2-year progression free survival (PFS).
- 2) A historical comparison using SWOG 8736 was performed to assess adding rituximab to CHOP x 3 cycles plus IFRT.<sup>99,100</sup>
  - i. The SWOG 8736 trial had compared CHOP x 8 cycles with CHOP x 3 cycles with IFRT and concluded that CHOP + IFRT was superior to CHOP alone in this patient population up to 10 years after treatment completion. However, this difference was not sustained with longer follow-up.
- 3) The SWOG 0014 investigators identified 68 patients from SWOG 8736 treated with CHOP x 3 cycles plus IFRT using the same eligibility criteria as for SWOG 0014.
  - i. The results of SWOG 0014 revealed that the addition of rituximab was associated with favorable survival rates.

**Results of the SWOG 0014 study, which evaluated the addition of rituximab to CHOP x 3 cycles + IFRT.<sup>98,99</sup>**

Historical Comparison	2-year PFS	4-year PFS	4-year OS
SWOG 8736: CHOP + IFRT	85%	78%	88%
SWOG 0014: R-CHOP + IFRT	93%	88%	92%

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; IFRT = involved field radiation therapy; OS = overall survival; PFS = progression-free survival; R = rituximab.

- b. The use of four instead of six cycles of R-CHOP in patients with stage I or II DLBCL with favorable prognosis was assessed in the “FLYER” trial.<sup>101</sup>
  - 1) Four cycles of CHOP plus six applications of rituximab was compared to six cycles of R-CHOP in an open-label, prospective, randomized phase 3 non-inferiority study of 592 patients with DLBCL with favorable prognosis. No radiotherapy was planned, except for testicular involvement of lymphoma.
    - a) “Favorable prognosis” was considered to be no risk factors according to age-adjusted IPI (serum lactate dehydrogenase less than the upper limit of normal, ECOG performance status of 0 or 1, Ann Arbor stage I or II disease, and no bulky disease [diameter of a single or conglomerate tumor < 7.5 cm]).
    - b) All patients were age 18-60 years of age.
  - 2) After a median follow-up of 66 months, 3-year progression-free survival of patients who received four cycles of CHOP plus six applications of rituximab was non-inferior to six cycles of R-CHOP.
  - 3) Likewise, no difference in event-free survival or overall survival was noted at 3 and 5 years of follow-up.
  - 4) Fewer total and non-hematologic adverse events occurred during therapy in the four-cycles group.

Results of the “FLYER” study, a non-inferiority trial which compared CHOP x 4 cycles plus 6 applications of rituximab to R-CHOP x 6 cycles in patients with DLBCL with favorable prognosis.<sup>101</sup>

	R-CHOP x 4 cycles plus 2 additional doses of rituximab (n = 293)	R-CHOP x 6 cycles (n = 295)
3-year progression-free survival	96%	94%
3-year event-free survival	89%	89%
3-year overall survival	99%	98%
5-year progression free-survival	94%	94%
5-year event-free survival	87%	88%
5-year overall survival	97%	98%
Hematologic adverse events	294 events	426 events
Non-hematologic adverse events	1036 events	1280 events

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; R = rituximab.

- 5) Based on these findings, R-CHOP x 4 cycles followed by rituximab x 2 cycles is a recommended regimen in patients with Stage I or II, non-bulky DLBCL with IPI = 0.<sup>3</sup>
- c. Several long-term analyses have revealed a pattern of late relapse in patients with limited-stage disease. A continuous risk of treatment failure and lack of PFS plateaus have been observed up to 17 years after treatment completion.<sup>94,100</sup>
7. Treatment of advanced disease (stage I & II, bulky disease, stage II with extensive mesenteric involvement, and stage III & IV disease)
  - a. Approximately 70% of patients present with advanced stage disease.<sup>81</sup>
  - b. Rationale for R-CHOP (**the current standard of care**): Groupe d’Etude des Lymphomes de l’Adulte (GELA) compared CHOP to CHOP + rituximab in newly diagnosed DLBCL patients. All patients were between 60 – 80 years of age.<sup>102,103</sup>
    - 1) Rituximab was added to CHOP because it sensitizes lymphoma cells to chemotherapeutic agents *in vitro* and demonstrated a high response rate (94%) in a phase II trial in aggressive lymphoma.<sup>104</sup>
    - 2) Patients were randomized to CHOP x 8 cycles or rituximab + CHOP x 8 cycles.
    - 3) The study demonstrated that the addition of rituximab to CHOP improved PFS and OS in elderly patients with advanced DLBCL.
    - 4) The authors noted that the death rate during the study was likely due to age of patients at study entry.

**Results of the GELA study, which compared CHOP to R-CHOP in newly diagnosed elderly patients with DLBCL.**<sup>102,105,106</sup>

Regimen	CR Rate	2-year Event Free Survival	2-year Overall Survival
CHOP	63%	38%	57%
CHOP + Rituximab	76%	57%	70%
p value	0.005	< 0.001	0.007
5 year Follow-up Data			
		5-year Event Free Survival	5-year Overall Survival
CHOP	---	28%	45%
CHOP + Rituximab	---	48%	58%
p value	---	< 0.001	0.007
10 year Follow-up Data			
		10-year Event Free Survival	10-year Overall Survival
CHOP	---	19.8%	27.6%
CHOP + Rituximab	---	35.1%	43.5%
p value	---	< 0.001	0.007

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone.

8. Role of dose-intensity

- a. Although **R-CHOP is the current standard of care in the treatment of DLBCL**, many philosophies exist on how to improve response and survival rates in this patient population, and treatment pathways may change in the future based upon tumor subtype. The main strategy is modifying dose-intensity, which can be done in multiple ways:
  - 1) Maintaining dose-intensity of certain chemotherapy agents: Maintaining dose-intensity of doxorubicin >75% was associated with superior survival compared to those with <75% dose-intensity of doxorubicin in regimens such as CHOP and R-CHOP.<sup>107,108</sup>
  - 2) Increase dose-intensity by dose-escalation and infusional schedules of the chemotherapy regimen (i.e. DA-R-EPOCH).<sup>109-112</sup>
    - a) This regimen was developed when it was noted that less resistance to chemotherapy developed in tumor cells with prolonged low-concentration exposure to vincristine and doxorubicin than with short-duration bolus administration, and etoposide was found to be synergistic with CHOP.<sup>112</sup>
    - b) Two phase II trials included previously untreated DLBCL patients stage II to IV (one trial also included stage I bulky thymic lymphomas<sup>109</sup>) treated with dose-adjusted (DA)-R-EPOCH. PFS and OS appeared to be improved when compared historically to R-CHOP.
    - c) The phase III CALGB/Alliance 50303 compared R-CHOP vs DA-R-EPOCH in 524 patients with previously untreated DLBCL. The primary endpoint was EFS, with secondary endpoints of response rates, OS and safety.<sup>113,114</sup>
      - i. After a median follow-up of 5 years, there were no significant differences in EFS or OS between the treatment arms in the overall study population. Subgroup



analysis did not reveal a difference in 5-year EFS for any subgroup; however, the subgroup analysis did not include patients with MYC rearrangements.

- ii. DA-R-EPOCH was associated with significantly higher rates of febrile neutropenia, thrombocytopenia and peripheral neuropathy. In addition, the 96-hour infusion schedule may be a deterrent.

**Results of the CALGB/Alliance 50303 trial, which randomized patients with newly diagnosed DLBCL to R-CHOP or DA-R-EPOCH.**<sup>111,113</sup>

	R-CHOP	DA-R-EPOCH	p value
ORR	89%	86.7%	0.67
PFS at 5 years	66%	68%	0.6519
OS at 5 years	77.5%	78.5%	0.6414
Treatment discontinuation due to AE	2%	6.3%	NR
Incidence of grade 3 or 4 febrile neutropenia	17.7%	35%	< 0.001
Incidence of grade 3 motor neuropathy	3.3%	18.6%	< 0.001

AE = adverse event; NR = not reported; OS = overall survival; PFS = progression-free survival.

- d) Based on these findings, DA-R-EPOCH is a Category 2A recommendation in the NCCN Guidelines® and **cannot be considered as standard of care** for **all** newly diagnosed DLBCL.<sup>3</sup>
- e) In the future, this regimen may become the frontline regimen for specific subtypes of DLBCL, such as double-hit DLBCL (see below).<sup>81,83-85,91</sup>
- 3) Increase dose-intensity by decreasing the interval between cycles (dose-density), i.e. CHOP 14 vs. 21 days.
  - a) Previous trials have compared CHOP-14 vs CHOP-21 to determine if response and survival rates were improved with dose-dense regimens of CHOP in DLBCL patients.<sup>114-116</sup>
  - b) CHOP-14 did show an OS advantage in elderly patients (61 – 75 years of age) when compared to CHOP-21.<sup>115</sup>
  - c) In patients 18 – 60 years of age, response rates and event free survival were improved when etoposide was incorporated into the CHOEP-14 and CHOEP-21 regimens.<sup>116</sup>
  - d) However, these dose-dense trials did not incorporate rituximab in any of the regimens.
    - i. A phase III trial examined the addition of rituximab to both CHOP-14 and CHOP-21 in DLBCL patients > 18 years of age with Stage 1A bulky or Stage 1B – IV disease to attempt to detect an OS difference between the groups.<sup>117</sup>
      - a) The 2-year OS in the R-CHOP-21 group was 80.8% vs. 82.8% in the R-CHOP-14 group (p = 0.5907).
      - b) Therefore, R-CHOP-14 was not superior to R-CHOP-21 for previously untreated DLBCL patients of all ages.

- e) Given the disparity in these results, R-CHOP-14 is currently a Category 3 recommendation in the NCCN Guidelines®.<sup>3</sup>
9. Initially, there is no need for prophylactic neutrophil growth factors (pegfilgrastim, G-CSF or GM-CSF) with R-CHOP when given every 21 days unless patient has specific risk factors, such as age  $\geq$  65 years of age.<sup>77</sup> The incidence of febrile neutropenia and infection were 11% and 23%, respectively.<sup>117,118</sup>
10. Use of obinutuzumab in DLBCL<sup>119</sup>
  - a. The phase III “GOYA” trial evaluated 1,418 patients with newly diagnosed DLBCL. Patients were randomly assigned to open-label treatment with either obinutuzumab or rituximab in combination with standard CHOP (G-CHOP vs R-CHOP). The primary endpoint was investigator-assessed PFS between the treatment arms.
  - b. There was no difference in investigator-assessed PFS between the treatment arms.
  - c. In the safety analysis, G-CHOP was associated with an increased risk of grade  $\geq$  3 adverse effects compared with R-CHOP. Dose reductions, dose interruptions and treatment discontinuation due to adverse events were all more common in the G-CHOP group.
  - d. Given these results, G-CHOP is not currently recommended for DLBCL.
11. Use of polatuzumab vedotin in the first-line treatment of DLBCL
  - a. The phase III, double-blind, placebo-controlled “POLARIX” trial modified the R-CHOP regimen by replacing vincristine with polatuzumab vedotin (pola-R-CHP). Pola-R-CHP was then compared to R-CHOP in 879 patients with previously untreated intermediate- or high-risk DLBCL.<sup>120</sup>
    - 1) All patients received six cycles of either R-CHOP or pola-R-CHP, followed by two cycles of rituximab alone.
    - 2) The primary endpoint was investigator assessed PFS.
    - 3) After a median follow-up of 28.2 months, PFS was statistically significantly greater in the pola-R-CHP group than the R-CHOP group at 2 years (76.7% vs 70.2%; HR 0.73, 95% CI 0.57 – 0.95, p = 0.02).
    - 4) Overall survival at 2 years did not significantly differ between the treatment groups, and safety profiles were similar.
    - 5) Despite positive findings, the pola-R-CHP regimen is not recommended as first-line treatment of DLBCL in the current NCCN Guidelines®.<sup>3</sup> Potential reasons for not recommending this regimen include short follow-up, no difference in overall survival, and increased cost. Likewise, the study was not powered to detect difference in patient subgroups.<sup>120</sup>
12. Treatment of double-hit or triple-hit lymphomas (also known as high-grade B-cell lymphomas or HGBL)<sup>3,23,72,81,83-87,89,91,121-125</sup>
  - a. The standard of care for this subtype has not been established. However, R-CHOP has been associated with inferior outcomes.
  - b. In rare cases of localized disease, consolidative ISRT is preferred.<sup>3</sup>

- c. Data from retrospective studies suggest that more intensive chemotherapy regimens may result in better outcomes, but a meta-analysis reported that overall survival did not differ between various dose-escalated regimens.<sup>126</sup>
- d. Depending on the individual patient's comorbidities and performance status, the following regimens may be considered:
  - 1) DA-R-EPOCH
  - 2) R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with rituximab, high-dose methotrexate and cytarabine)
  - 3) R-CODOX-M/R-IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin and methotrexate alternating with rituximab, ifosfamide, etoposide and cytarabine)
  - 4) R-mini-CHOP (elderly or frail patients only)
- e. Consolidation with high-dose chemotherapy and autologous stem cell rescue may be considered (refer to the Hematopoietic Stem Cell Transplantation materials).
- f. This subtype of disease is associated with higher rates of CNS involvement; prophylaxis should be considered (see CNS Disease section below).<sup>87,89,125,127,128</sup>

### 13. CNS disease

- a. The risk of CNS involvement can be estimated using the CNS IPI score.<sup>3,75,129</sup>
  - 1) The score combines established IPI risk factors (age > 60 years, stage III or IV disease, more than 1 extranodal site, ECOG PS > 1 and LDH above the upper limit of normal) with kidney and adrenal involvement into a six-point scale.
  - 2) High-risk patients are defined by a total score of  $\geq 4$ . The 2-year risk of CNS relapse in these patients is approximately 10%.
- b. Other risk factors that have been identified include high-grade lymphoma, HIV-associated lymphoma, ABC cell of origin, and site-specific disease such as the testes, primary cutaneous DLBCL - leg type, breast, uterine (but not ovarian), paranasal or parameningeal, orbital, and/or bone marrow involvement.<sup>3,90,114,127,129-131</sup>
- c. Despite the establishment of the CNS IPI score, the subsequent utility of prophylaxis in DLBCL is not well established. As a result, there is no standard of care in this scenario and decisions should be individualized.<sup>3,75,81,128,130,131</sup>
- d. If CNS prophylaxis is given, 4-8 doses of IT methotrexate and/or cytarabine are recommended. Alternatively, systemic methotrexate may be administered.<sup>3,90,127,128,131</sup>
- e. Patients who present with parenchymal disease should be treated with systemic high-dose methotrexate ( $\geq 3 \text{ gm/m}^2$ ). Different dosing schedules are used when this agent is administered concurrently with R-CHOP. Growth factor support is necessary with this regimen.<sup>3</sup>
- f. Patients who present with leptomeningeal disease should be given intrathecal methotrexate or cytarabine (consider placement of an Ommaya reservoir to facilitate delivery). Systemic methotrexate may also be considered.<sup>3</sup>
- g. Relapses within the CNS generally occur early in the treatment course, often presenting prior to the completion of initial therapy or shortly thereafter. The outcome is universally poor,

with the median survival following diagnosis of CNS involvement reported at 2-5 months.<sup>75,90,128,131</sup>

- h. Please refer to the Head, Neck, Thyroid and Adult CNS Malignancies materials for discussion of primary CNS lymphoma.

**Patient Case #2 Continued:**

**Correct answers = A (Disease cure) and C (R-CHOP x 6 cycles)**

The goal of treatment in DLBCL is **disease cure**. DM should receive R-CHOP based on the long-term data for survival benefit compared to other regimens. Given his advanced disease, 6 cycles of chemotherapy would be recommended. Since DM does not have BCL2, BCL6 or MYC rearrangements that would suggest “double-hit” lymphoma, more aggressive regimens are not recommended. G-CHOP has been compared to R-CHOP, but no difference in PFS was observed and grade 3 toxicities were greater with G-CHOP; therefore, this regimen is not recommended.

DM completed this therapy and achieved a complete response. Approximately 18 months after completing treatment, DM returns to clinic complaining of recurrent fevers and drenching night sweats. Repeat CT scans reveal retroperitoneal lymphadenopathy. A biopsy reveals diffuse large B-cell lymphoma, Stage IVB. His ECOG performance status is still 0.

**What treatment option is most appropriate for DM at this time?**

- A. R-CHOP x 6 cycles
- B. R-ICE followed by maintenance rituximab
- C. R-DHAP followed by maintenance lenalidomide
- D. R-ESHAP followed by autologous stem cell transplant

**14. Relapsed/Refractory DLBCL<sup>3,81,96,132,133</sup>**

- a. Approximately 20-25% of patients will have a relapse after an initial response, typically within the first 2 years. Further, approximately 10-15% of patients treated with R-CHOP have primary refractory disease.<sup>81,134</sup>
- b. Risk factors for relapse after 2 years of event-free survival include age > 60 years, advanced stage and IPI score > 2.<sup>94,135</sup>
- c. The goal is still considered to be to **CURE** the patient.
- d. Relapsed/refractory disease is further divided into the following categories: relapsed disease >12 months after completion of first-line therapy **or** relapsed disease < 12 months after the completion of first-line therapy or primary refractory disease.
  - 1) Relapsed disease > 12 months after completion of first-line therapy with intention to proceed to high-dose chemotherapy followed by SCT
    - a) Chemotherapy regimens include any of the following, with each regimen having unique toxicities:<sup>3,135-137</sup>
      - i. DHAP (dexamethasone, cytarabine and platinum) +/- rituximab (preferred)
      - ii. ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) +/- rituximab

- iii. GDP (gemcitabine, dexamethasone and cisplatin or carboplatin) +/- rituximab (preferred)
  - iv. GemOx (gemcitabine and oxaliplatin) +/- rituximab
  - v. ICE (ifosfamide, carboplatin and etoposide) +/- rituximab (preferred)
  - vi. MINE (mesna, ifosfamide, mitoxantrone and etoposide) +/- rituximab
  - b) If complete response to second-line chemotherapy is achieved, high-dose chemotherapy followed by autologous stem cell transplant (ASCT) +/- ISRT is an NCCN Guidelines® Category 1 recommendation in this setting.<sup>3</sup>
    - i. The large majority disease relapses after ASCT occur early after ASCT. Nearly 75% of relapses are seen within the first 9 months following ASCT.<sup>138</sup>
    - ii. Allogeneic SCT +/- ISRT may be considered in selected cases.<sup>3</sup>
  - c) If partial response to second-line chemotherapy is achieved, considerations include:
    - i. Anti-CD19 CAR T-cell therapy with axicabtagene ciloleucel, lisocabtagene maraleucel or tisagenlecleucel
    - ii. High-dose chemotherapy followed by ASCT +/- ISRT
    - iii. Allogeneic SCT +/- ISRT in selected cases.
- 2) Relapsed disease > 12 months after completion of first-line therapy in patients who are **not** candidates for high-dose therapy and ASCT. These patients will receive second-line chemotherapy only, palliative ISRT or best supportive care.<sup>3,79,137,139</sup>
- a) Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (> 6 months). Rituximab may be omitted in the setting of primary refractory disease.
  - b) Chemotherapy regimens include any of the following:
    - i. Brentuximab vedotin (if CD30+)
    - ii. CEOP (cyclophosphamide, etoposide, vincristine and prednisone) +/- rituximab
    - iii. DA-EPOCH +/- rituximab
    - iv. GDP (rituximab, gemcitabine, dexamethasone and cisplatin or carboplatin) +/- rituximab
    - v. GemOx (gemcitabine and oxaliplatin) +/- rituximab (preferred)
    - vi. Ibrutinib (non-GCB disease only)
    - vii. Lenalidomide +/- rituximab (non-GCB disease only)
    - viii. Polatuzumab vedotin +/- bendamustine +/- rituximab (preferred)
    - ix. Rituximab
    - x. Tafasitamab + lenalidomide (preferred; see below)
- 3) Relapsed disease < 12 months after completion of first-line therapy or primary refractory disease

- a) For patients who will proceed to CAR T-cell therapy, axicabtagene ciloleucel (with bridging therapy as clinically appropriate) is an NCCN Guidelines® Category 1 recommendation.<sup>3</sup>
  - i. The phase 3 “ZUMA-7” study included 364 patients with relapse < 12 months after completion of first-line therapy or refractory DLBCL who were randomized to second-line conditioning chemotherapy followed by axicabtagene ciloleucel or to platinum-based chemotherapy followed by high dose chemotherapy and ASCT.<sup>140</sup>
    - a) The primary endpoint was event-free survival according to blinded central review. At a median follow-up of 24.9 months, median event-free survival was 8.3 months in the axicabtagene ciloleucel group and 2.0 months in the standard chemotherapy group. The 24-month event-free survival was 41% and 16%, respectively (HR 0.40, 95% CI 0.31 – 0.51,  $p < 0.001$ ).
    - b) In the interim analysis, OS at 2 years was 61% vs 52%.
    - c) Response rates were 33% higher in the axicabtagene ciloleucel group, and rate of CR was doubled compared to the standard chemotherapy group.
- b) Lisocabtagene maraleucel (Breyanzi®) is also recommended in this setting.<sup>3,141-143</sup>
  - i. Mechanism of action: a CD19-directed CAR-T cell immunotherapy.
  - ii. Approved in February 2021 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Approved in June 2022 for adult patients with large B-cell lymphoma (LBCL) who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age.
  - iii. Approval in this setting was based “TRANSFORM,” a randomized, open-label trial in 184 adult patients with primary refractory DLBCL or relapse within 12 months of achieving CR to first-line therapy. Patients were randomized to receive lisocabtagene maraleucel following fludarabine and cyclophosphamide lymphodepleting chemotherapy or to second-line standard therapy (3 cycles of chemoimmunotherapy followed by high-dose therapy and ASCT in patients who attained CR or PR).
    - a) The primary endpoint was EFS as determined by an independent review committee.
    - b) EFS was significantly longer in the lisocabtagene maraleucel arm (HR 0.34, 95% CI 0.22 - 0.52;  $p < 0.0001$ ). The estimated 1-year EFS was 45% in the lisocabtagene maraleucel arm and 24% in the standard therapy arm. The estimated median EFS was 10.1 months and 2.3 months, respectively.

- c) The IRC-assessed PFS was also significantly longer in the lisocabtagene maraleucl arm (HR 0.41, 95% CI 0.25 - 0.66; p = 0.0001).
  - iv. The recommended regimen is a single dose containing 50 to 110 x 10<sup>6</sup> CAR-positive viable T cells with a 1:1 ratio of CD4 and CD8 components, administered by intravenous infusion and preceded by fludarabine and cyclophosphamide for lymphodepletion.
  - v. Common adverse effects included cytokine release syndrome (CRS, 46%), neurologic toxicity (35%), infections (36%) and prolonged cytopenias (36%).
- c) If bridging therapy is required, recommended regimens include DHAP +/- rituximab, GDP +/- rituximab, GemOx +/- rituximab, ICE +/- rituximab, or polatuzumab vedotin +/- bendamustine +/- rituximab (bendamustine should be considered or added only after leukapheresis is completed).<sup>3</sup>
- d) For patients who will not proceed to CAR T-cell therapy, second-line chemotherapy (as listed above), palliative ISRT or best supportive care should be utilized.
- 4) Tafasitamab-cxix (Monjuvi®)<sup>144-147</sup>
  - a) Mechanism of action: a CD19-directed cytolytic antibody. CD19 is widely expressed across the B-cell malignancies; tafasitamab is an Fc-enhanced, humanized, anti-CD19 monoclonal antibody that mediates antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, as well as exerts direct cytotoxicity.
  - b) Approved in July 2020 via accelerated approval in combination with lenalidomide for adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant.
    - i. Approval was based on the “L-MIND” study, an open label, multicenter single-arm trial in 81 patients. Patients received tafasitamab with lenalidomide for up to 12 cycles, followed by tafasitamab-cxix as monotherapy.
    - ii. The primary endpoint was ORR as assessed by an independent review committee. The best ORR in 71 patients with a diagnosis of DLBCL was 55% (95% CI, 43 – 67%), with CR in 37% and PR in 18% of patients.
    - iii. Median response duration was 21.7 months (range, 0 – 24).
  - c) The recommended dose is 12 mg/kg as an intravenous infusion. In cycle 1, it is administered on days 1, 4, 8, 15 and 22 of the 28-day cycle. In cycles, 2 and 3, it is given on days 1, 8, 15 and 22 of each 28-day cycle. In cycles 4 and beyond, it is given on days 1 and 15 of each 28-day cycle. Lenalidomide is given as 25 mg PO daily on days 1-21 of each cycle.
  - d) Adverse reactions that occurred in ≥20% of patients were myelosuppression, fatigue, diarrhea, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.
- 5) Third-line and subsequent therapy<sup>3,81</sup>
  - a) Options include:

- i. Anti-CD19 CAR-T therapy: axicabtagene ciloleucel, lisocabtagene maraleucel (see below) or tisagenlecleucel <sup>148-150</sup>
  - ii. Loncastuximab tesirine (see below)
  - iii. Selinexor (only after at least two lines of systemic therapy, including patients with disease progression after transplant or CAR-T cell therapy; see below)
- 7) Loncastuximab tesirine-lpyl (Zynlonta<sup>®</sup>)<sup>141,151</sup>
  - a) Mechanism of action: a CD19-directed antibody and alkylating agent conjugate. The product consists of a pyrrolobenzodiazepine DNA-alkylating warhead covalently attached via a cleavable linker to a humanized anti-CD19 monoclonal antibody.
  - b) Approved in April 2021 for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.
    - i. Approval was based on “LOTIS-2,” an open-label, phase 2, single arm trial in 145 adult patients with relapsed or refractory DLBCL or high-grade B-cell lymphoma after at least two prior systemic regimens. The main efficacy outcome was overall response rate as assessed by an independent review committee.
    - ii. After a median follow-up of 7.3 months, the overall response rate was 48.3%, with a complete response rate of 24.1%.
    - iii. Median duration of response was 10.3 months.
  - c) The agent is dosed every three weeks, with 0.15 mg/kg given for the first two cycles and then 0.75 mg/kg in subsequent cycles. Administered via intravenous infusion over 30 minutes on day 1 of each cycle.
    - i. Patients should be premedicated with dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before loncastuximab tesirine.
  - d) Adverse reactions that occurred in ≥ 20% of patients were elevated liver function tests, myelosuppression, hyperglycemia, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.
- 9) Selinexor (Xpovio<sup>®</sup>)<sup>3,152,153</sup>
  - a) Approved for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.
    - i. Approval was based on multicenter, single-arm, open-label trial in 134 patients with DLBCL after 2 to 5 systemic regimens. Patients received selinexor 60 mg orally on days 1 and 3 of each week.
    - ii. ORR, as assessed by an independent review committee, was 29% (95% CI, 22-38%) with CR in 13%. Of the 39 patients who achieved a PR or CR, 38% had response durations of at least 6 months and 15% had response durations of at least 12 months.



- b) Please refer to the Multiple Myeloma materials for more information about this agent.

**Patient Case #2, Continued:**

**Correct answer = D (R-ESHAP followed by autologous stem cell transplant)**

Chemotherapy options for DM include R-ICE, R-ESHAP and R-DHAP followed by autologous stem cell transplant since he experienced relapsed disease > 12 months after the completion of first-line therapy and he still has a good performance status. Repeating R-CHOP would not be the best option since he has already received this regimen, and cumulative doses of anthracyclines may limit the feasibility of this choice. There are currently no recommendations for maintenance therapy in the treatment of DLBCL.

15. Administration of rituximab

- a. Patients receiving rituximab may develop an infusion-related reaction, especially during the first infusion. Patients with a high tumor burden or with a high number of circulating tumor cells ( $> 25,000$  cells/mm<sup>3</sup>) are particularly at high risk for these severe reactions to rituximab. These types of reactions are less likely to occur after the first or second doses of rituximab.
- 1) The management of severe infusion reactions is to discontinue the rituximab infusion and institute supportive care (e.g. oxygen, IV fluids, bronchodilators, antihistamines and steroids) as indicated. Refer to Infusion-Related Reactions to Monoclonal Antibodies Used in Hematologic Malignancies in the Chronic Leukemias materials for an in-depth discussion on symptom management of hypersensitivity reactions.
- b. A “rapid” infusion rituximab protocol has been approved for previously untreated follicular NHL and DLBCL patients based on the results of several studies, including the phase IIIb “MAXIMA” study. The protocol is as follows.<sup>50,154</sup>
  - 1) If the patient did not experience a Grade 3 or 4 infusion related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.
  - 2) Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes.
  - 3) If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).
  - 4) Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count  $\geq 5000$  cells/mm<sup>3</sup> before Cycle 2 should not be administered the 90-minute infusion.
  - 5) For mild to moderate infusion reactions, interrupt the infusion or slow the infusion rate for infusion reactions. Continue the infusion at one-half the previous rate upon improvement of symptoms.<sup>155,156</sup>
  - 6) The use of the rapid infusion protocol as stated above is now endorsed by NCCN Guidelines®.<sup>3</sup>
- c. Subcutaneous rituximab (Rituxan Hycela®)<sup>4,157,158</sup>

- 1) A combination of rituximab and the endoglycosidase hyaluronidase human. The addition of hyaluronidase allows increased permeability into subcutaneous tissue and facilitates rapid absorption of a large volume of drug.
- 2) Approved in 2017 for 5 indications (see table below).
- 3) The prescribing information explicitly states that the product should only be initiated after patients have received and tolerated at least one full dose of a rituximab product by intravenous infusion. The NCCN Guidelines® reiterate this concept.<sup>3</sup>
- 4) Patients should receive premedication with acetaminophen and an antihistamine before each dose. Glucocorticoids may also be considered. Patients should be monitored for 15 minutes after each dose.
- 5) For FL and DLBCL, the dose is 1,400 mg rituximab/23,400 units hyaluronidase (11.7 mL of product) subcutaneously according to the recommended schedule. The product is supplied in single dose vials. Note that the doses and vial sizes differ between CLL and lymphoma.
- 6) The product should be injected into the subcutaneous tissue of the abdomen over approximately 5 minutes in a single administration site. Note that this administration time is different than that which is recommended for CLL.

**FDA-approved indications for Rituxan Hycela®.<sup>157</sup>**

Indication	Place in therapy	Single agent or in combination
Follicular lymphoma	Relapsed or refractory	As a single agent
	Previously untreated	In combination with first line therapy, and in patients receiving a complete or partial response, as single-agent maintenance therapy
	Non-progressing (including stable disease) after first-line CVP therapy	As a single agent
Diffuse large B cell lymphoma	Previously untreated	In combination with CHOP or other anthracycline-based regimens
Chronic lymphocytic leukemia	Previously treated or untreated	In combination with fludarabine and cyclophosphamide

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CVP = cyclophosphamide, vincristine and prednisone.

d. Rituximab biosimilars

- 1) Three currently available products: rituximab-abbs (Truxima®), Rituximab-pvvr (Ruxience®) and rituximab-arxx (Riabni®)<sup>3,159-161</sup>
- 2) These approvals were granted without extrapolation to all of the indications for rituximab, including indications for CLL and others.
- 3) These products were approved as biosimilars, **not** interchangeable products. However, NCCN Guidelines® state that an FDA-approved rituximab biosimilar is an appropriate substitute for rituximab.<sup>3</sup>

- e. Viral reactivation – Hepatitis B and C virus<sup>3,43,162,163</sup>
  - 1) Patients with lymphoma are at increased risk for hepatitis B reactivation due to immunosuppressive treatment regimens, the use of anti-CD20 monoclonal antibodies, and the underlying malignancy. Complications may range from asymptomatic and self-limited hepatitis to fulminant liver failure and death.
  - 2) Please refer to the Cancer-Related Infectious Diseases handout for more information.
- 16. Bone health in patients who have received steroid-containing regimens<sup>3</sup>
  - a. The greatest risk is in women with chemotherapy-induced menopause and in older patients receiving chemotherapy. The condition may worsen during treatment with steroid-based systemic therapy.
  - b. Calcium intake from food, and with supplements if necessary, should be initiated along with corticosteroid-containing regimens as per the Institute of Medicine recommendations.<sup>164</sup>
  - c. Patients should be evaluated one year after completing therapy.
  - d. Evaluation should include a vitamin D, 25-OH level. If the patient is vitamin D 25-OH deficient, replacement therapy should be initiated.
  - e. Evaluation should include bone mineral density (BMD evaluation).
    - 1. If osteopenic on BMD evaluation (T score between -1.1 and -2.4), use the Fracture Risk Assessment Tool (FRAX) to determine if drug therapy is necessary. The FRAX Tool is available at [www.sheffield.ac.uk/FRAX/](http://www.sheffield.ac.uk/FRAX/)
    - 2. Patients with osteoporotic BMD, with a history of hip or vertebral fractures, or with asymptomatic vertebral compression deformity should initiate therapy as per National Osteoporosis Foundation guidelines.<sup>165</sup>
      - a) Referral to an endocrinologist with expertise in bone health is recommended.
      - b) Pharmacologic agents may include hormone replacement therapy, bisphosphonates or denosumab. Teriparatide is contraindicated in patients who have received XRT, along with theoretical concerns of using this agent in patients with a recent history of cancer.
- 17. Some references suggest that survivors of DLBCL are at greater risk of immune-related conditions including autoimmune diseases, immune deficiencies and infections. This may be the result of persistent immune dysregulation from the disease and/or treatment.<sup>166</sup>
  - a. There are no specific guidelines for vaccinations of survivors of DLBCL; however, existing general vaccinations recommendations should be followed and encouraged.

18. Treatment summary of DLBCL

**Overview of Treatment Recommendations for DLBCL per the NCCN Guidelines®.<sup>3</sup>**

Diffuse Large B-cell Lymphoma	
First-line therapy	R-CHOP (Category 1) DA-R-EPOCH
First-line therapy for patients with poor left ventricular function	DA-R-EPOCH R-CDOP R-CEOP R-CEPP R-GCVP
Patients > 80 years of age with comorbidities	R-CEPP R-CDOP R-mini-CHOP R-GCVP
Second-line and subsequent therapy – patients intending to proceed to stem cell transplant	<u>Preferred</u> (in alphabetical order): DHAP +/- rituximab GDP +/- rituximab ICE +/- rituximab  <u>Other recommended regimens</u> (in alphabetical order): ESHAP +/- rituximab GemOx +/- rituximab MINE +/- rituximab
Second-line therapy – not candidates for high-dose therapy	<u>Preferred</u> : GemOx +/- rituximab Polatuzumab vedotin +/- bendamustine +/- rituximab Tafasitamab + lenalidomide  <u>Other recommended regimens</u> (in alphabetical order): CEOP +/- rituximab DA-EPOCH +/- rituximab GDP +/- rituximab Rituximab  <u>Useful in certain circumstances</u> : Brentuximab vedotin (if CD30+) Ibrutinib (non-GCB disease only) Lenalidomide +/- rituximab (non-GCB disease only)
Second-line therapy – relapsed disease <12 months after completing treatment or primary refractory disease	Axicabtagene ciloleucel (Category 1) Lisocabtagene maraleucel
Third-line and subsequent therapy	Anti-CD19 CAR-T therapy Axicabtagene ciloleucel Lisocabtagene maraleucel Tisagenlecleucel  Loncastuximab tesirine  Selinexor (only after at least 2 prior lines of systemic therapy, including patients with disease progression after transplant or CAR-T cell therapy)

Bridging chemotherapy as clinically necessary for CAR T-cell therapy	DHAP +/- rituximab GDP +/- rituximab GemOx +/- rituximab ICE +/- rituximab Polatuzumab vedotin +/- bendamustine +/- rituximab
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CAR = chimeric antigen receptor; CD = cluster of differentiation; DA-R-EPOCH = rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; DHAP = dexamethasone, cytarabine and cisplatin; ESHAP = etoposide, methylprednisolone, cytarabine and cisplatin; GCB = germinal B-cell; GDP = gemcitabine, dexamethasone and cisplatin or carboplatin; GemOx = gemcitabine and oxaliplatin; ICE = ifosfamide, carboplatin and etoposide; MINE = mesna, ifosfamide, mitoxantrone and etoposide; R-CDOP = rituximab, cyclophosphamide, liposomal doxorubicin, vincristine and prednisone; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine and prednisone; R-CEPP = rituximab, cyclophosphamide, etoposide, procarbazine and prednisone; R-GCVP = rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

### **Patient Case #3:**

TR is a 72 year old male with mantle cell lymphoma. He was initially treated with VR-CAP and achieved a remission for approximately 15 months. Unfortunately, his most recent surveillance scan demonstrated new lymphadenopathy, and a biopsy of one of the involved lymph nodes confirmed the presence of relapsed disease.

TR is a candidate for treatment for his relapsed disease, but still has residual peripheral neuropathies from his previous chemotherapy regimen that inhibit his activities of daily living.

**Based on this information, which of the following is the most appropriate treatment for TR at this time?**

- A. Acalabrutinib + rituximab
- B. Bortezomib + rituximab
- C. Brexucabtagene autoleucel
- D. Zanubrutinib

### C. Mantle cell lymphomas (MCL)

1. Characterized by the chromosomal translocation t(11;14)(q13;q32), which results in the overexpression of cyclin D1 and deregulation of the cell cycle.<sup>167-169</sup>
2. Generally thought to possess the worst characteristics of both indolent and aggressive NHL subtypes. This is due to the aggressive disease course and incurability with conventional chemotherapy.<sup>3,170,171</sup>
3. Prognosis of MCL
  - a. The International Prognostic Index lacks discriminatory power in MCL. Thus, the Mantle Cell Lymphoma International Prognostic Index (MIPI) is used in this disease subtype.
    - 1) MIPI is based on age, LDH, WBC, and ECOG performance status. Other important prognostic factors include blastoid or pleomorphic features, SOX-11 negativity, higher proliferation Ki-67 indices (>20-40%), complex karyotype, higher levels of  $\beta_2$  microglobulin, and central nervous system involvement.<sup>168,169,172-178</sup>

- 2) MIPI divides patients into 3 risk groups: low, intermediate and high.
- 3) A web-based calculator is available at [www.european-mcl.net/de/clinical\\_mipi.php](http://www.european-mcl.net/de/clinical_mipi.php)

**Survival rates according to the Mantle Cell Lymphoma International Prognostic Index (MIPI).<sup>173</sup>**

Risk Group	Number of Patients	Median Overall Survival
Low	44%	Not reached
Intermediate	35%	51 months
High	21%	30 months

- b. Ki-67 index has also been shown to be a predictive biomarker, independent of MIPI, when stratified into 3 groups (<10%, 10-29% and ≥30%).<sup>179-181</sup>
  - c. Mutations of TP53 occur in 10-25% of patients, and are associated with both a more aggressive histology and shorter survival.<sup>181,182</sup>
  - d. Blastoid and pleomorphic variants typically have a more aggressive disease course.<sup>180</sup>
4. Treatment
- a. A subset of patients will have a more indolent course and can be safely observed for a period of time. However, the large majority of patients will require treatment at some point during the course of their disease.<sup>180-184</sup>
  - b. At present, there is no standard of care for the first-line treatment of MCL. Selection should be based on age, performance status, comorbid conditions, presence of symptoms, and prognostic scoring. The majority of patients are elderly and thus ineligible for high intensity therapy.<sup>170,175,176,180,185-188</sup>
  - c. Using treatment with doxorubicin-based chemotherapy regimens, the median survival was only 36 months with a 10-year overall survival rate of only 8%.<sup>189</sup>
  - d. Based on poor results with doxorubicin-based therapies (e.g., CHOP), regimens such as R-Hyper-CVAD alternating with R-methotrexate/cytarabine +/- subsequent transplantation have been evaluated.<sup>190</sup>
    - 1) If the patient has a good performance status, aggressive induction therapy would be selected (such as R-HyperCVAD). The addition of cytarabine to intensive induction regimens has been shown to improve outcomes in young, fit patients with MCL.<sup>178,183,191</sup>
    - 2) If the patient is older and/or poor performance status, less aggressive induction would be selected (such as BR).<sup>172,191,192</sup>

## Initial Treatment Overview of Mantle Cell Lymphoma per the NCCN Guidelines®.<sup>3</sup>

Tumor Type	Treatment Options
Stage I or contiguous Stage II, non-bulky	ISRT alone Chemoimmunotherapy +/- ISRT
Non-contiguous Stage II, non-bulky	Chemoimmunotherapy Observation (in highly selected cases only)
Stage II bulky, III and IV	<p><u>The standard treatment regimen has not been established.</u></p> <p><u>Aggressive induction</u> (preferred regimens):*</p> <ol style="list-style-type: none"> <li>1. R-DHA + platinum (carboplatin, cisplatin or oxaliplatin)</li> <li>2. Alternating R-CHOP / R-DHAP</li> <li>3. NORDIC regimen (R-maxi-CHOP alternating with R-high-dose cytarabine)</li> <li>4. R-HyperCVAD</li> <li>5. BR followed by R + high-dose cytarabine</li> </ol> <p><u>Less aggressive induction</u> (preferred regimens):</p> <ol style="list-style-type: none"> <li>1. BR</li> <li>2. VR-CAP</li> <li>3. R-CHOP</li> <li>4. Lenalidomide + R</li> </ol> <p><u>Less aggressive induction</u> (other recommended regimens):</p> <ol style="list-style-type: none"> <li>1. Modified R-HyperCVAD in patients &gt; 65 years</li> <li>2. RBAC500</li> </ol>

\* These regimens include first-line consolidation with high dose therapy and autologous stem cell rescue.

BR = bendamustine and rituximab; NORDIC regimen = rituximab + cyclophosphamide, vincristine, doxorubicin and prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine; ISRT = involved-site radiation therapy; R = rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHA + platinum = rituximab, dexamethasone, cytarabine and platinum; RBAC500 = rituximab, bendamustine and cytarabine; R-HyperCVAD = rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with rituximab, methotrexate and cytarabine; VR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

### 5. Less aggressive first-line therapy

#### a. Bendamustine + rituximab

- 1) A multicenter phase III trial of the Study Group Indolent Lymphomas ("StiL NHL1") randomized 549 patients with indolent or mantle cell NHL to either BR (bendamustine 90 mg/m<sup>2</sup> on day 1 and 2 + rituximab 375 mg/m<sup>2</sup> on day 1 every 28 days) x 6 cycles or R-CHOP x 6 cycles. Refer to the FL section of this handout for further details.<sup>30,31</sup>
- 2) The phase III "BRIGHT" study compared BR to the investigator's choice of R-CHOP or R-CVP in newly diagnosed indolent or mantle cell lymphoma. Five-year results showed that BR was non-inferior to R-CHOP or R-CVP in event-free survival, progression-free survival and duration of response.<sup>193,194</sup>

#### b. Bortezomib-based regimens

- a) A phase III randomized study (the “LYM-3002” study) compared bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) vs R-CHOP in 487 patients with newly diagnosed MCL who were not candidates for stem cell transplantation.<sup>167,195,196</sup>
  - a) The primary endpoint was progression-free survival as assessed by independent radiologic review.
  - b) Median PFS, CR rate and median time to progression were all statistically significantly improved in the VR-CAP arm.
  - c) There was a higher incidence of grade 3 or 4 adverse events in the VR-CAP arm, but these were felt to be manageable. Specifically, rates of thrombocytopenia, neutropenia and infections were higher with VR-CAP.
  - d) Based on these results, the FDA approved the use of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone.

**Results of the phase III LYM-3002 study, which compared VR-CAP to R-CHOP in patients with newly diagnosed MCL.**<sup>195,196</sup>

Regimen	Median PFS	Median TTP	Median duration of response	Median OS
VR-CAP	24.7 months	30.5 months	36.5 months	90.7 months
R-CHOP	14.4 months	16.1 months	15.1 months	55.7 months
p value	< 0.001	0.001	NS	0.001

NS = not significant; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; PFS = progression-free survival; OS = overall survival; TTP = time to progression; VR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

6. First-line consolidation followed by maintenance rituximab<sup>3,23,187,197,198</sup>
  - a. High-dose chemotherapy followed by ASCT + maintenance rituximab has demonstrated promising outcomes in a number of studies (refer to Hematopoietic Stem Cell Transplantation materials).
    1. The phase III “LyMa” trial randomly assigned patients < 66 years of age to receive rituximab maintenance or observation after autologous HSCT for MCL. The primary endpoint was event-free survival. Investigators concluded that rituximab maintenance prolonged event-free survival, PFS and OS in this patient population.<sup>199</sup>
    2. The results of the “LyMa” trial also indicated that a cytarabine-based induction regimen (without anthracyclines or alkylating agents) may be considered.<sup>199</sup>
  - b. Maintenance rituximab every 8 weeks for 3 years after ASCT is an NCCN Guidelines® Category 1 recommendation in this setting.<sup>3</sup>
7. Maintenance rituximab after less aggressive therapy<sup>3,23,169,172,174,181,183,188,200</sup>
  - a. Maintenance rituximab may provide extended disease control for patients who are not candidates for aggressive first-line treatment regimens and stem cell transplantation.



This strategy is a Category 1 recommendation in the NCCN Guidelines® when given after R-CHOP.

- b. NCCN Guidelines® suggest that maintenance rituximab should be administered for 2-5 years following modified R-HyperCVAD.
  - c. Prospective trial data suggest no benefit of maintenance rituximab if BR was used in the first-line setting.<sup>3,175,186</sup>
  - d. The use of this strategy after regimens such as VR-CAP and RBAC500 is untested.<sup>3,192,196,201</sup>
  - e. It is unknown whether first-line consolidation with stem cell transplantation provides an advantage over rituximab maintenance in patients of any age or performance status.
8. Relapsed MCL<sup>3,169-171,176,178,180,191,202-204</sup>
- a. Disease relapse is nearly universal, and most patients will require multiple lines of therapy throughout their lifetime.
  - b. Treatment of relapsed MCL is a major challenge, with the currently available regimens producing a generally low response rate and duration. The optimal approach to relapsed or refractory disease remains to be defined, as there are no randomized trials comparing therapies in this setting.<sup>172,201-207</sup>
  - c. Radiotherapy should be considered in the rare case of localized relapse. MCL is one of the most radiosensitive of all NHLs, and response rates may be meaningful even in the relapsed setting. Symptom relief is achieved in > 90% of patients, and CR is achieved in up to 70% of patients.<sup>180</sup>
  - d. Preferred regimens for second-line and subsequent therapy include:<sup>3</sup>
    - 1) Acalabrutinib
    - 2) Ibrutinib +/- rituximab
    - 3) Zanubrutinib
    - 4) Lenalidomide + rituximab (if BTKi therapy is contraindicated)
  - d. Other recommended regimens for second-line and subsequent therapy include:<sup>3</sup>
    - 1) Bendamustine + rituximab, if not previously given
    - 2) Bendamustine + rituximab + cytarabine (RBAC500), if not previously given
    - 3) Bortezomib +/- rituximab
    - 4) DHAP + rituximab
    - 5) GemOx + rituximab
    - 6) Ibrutinib + venetoclax
    - 7) Venetoclax +/- rituximab
  - f. Second-line consolidation
    - 1) Allogeneic stem cell transplant may be considered. Refer to the Hematopoietic Stem Cell Transplantation materials for more information.

- g. Brexucabtagene autoleucel (KTE-X19, Tecartus®) may be considered only if given after both chemoimmunotherapy and a Bruton tyrosine kinase (BTK) inhibitor.<sup>201,208-210</sup>
- 1) Mechanism of action: a CD19-directed genetically modified autologous T cell immunotherapy
  - 2) Indication & dose:
    - i. Approved in July 2020 for the treatment of for the treatment of adult patients with relapsed or refractory MCL. FDA granted orphan drug designation, breakthrough therapy designation, and priority review for this indication.
      - a. Approval was based on the “ZUMA-2” study, an open-label, multicenter, single-arm trial of 74 patients with relapsed or refractory MCL who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTKi.
      - b. The primary efficacy outcome measure was ORR as assessed by an independent review committee. Of the 60 patients evaluable for efficacy based on a minimum duration of follow-up for response of six months, the ORR was 87%, with 62% of patients achieving a CR.
      - c. The estimated median duration of response was not reached (range, 0 – >29 months) after a median follow-up time for duration of response of 8.6 months.
    - 3) The recommended dose is a single infusion of  $2 \times 10^6$  CAR-positive viable T cells per kg body weight (maximum  $2 \times 10^8$  CAR-positive viable T cells), after the receipt of fludarabine and cyclophosphamide lymphodepleting chemotherapy.
    - 4) The most common ( $\geq 10\%$ ) Grade 3 or higher reactions were myelosuppression, hypotension, hypophosphatemia, encephalopathy, hypoxia, pyrexia, hyponatremia, hypertension, infection (pathogen unspecified), pneumonia, and hypocalcemia.
    - 5) Approval includes a mandatory REMS program because of the risk of cytokine release syndrome (CRS) and neurologic toxicities. Please refer to the Acute Leukemias materials for more information.
  - k. Treatment summary of MCL

## Overview of Treatment Recommendations for MCL per the NCCN Guidelines®.<sup>3</sup>

Mantle Cell Lymphoma	
Induction Therapy – Aggressive Therapy	<u>Preferred regimens:</u> R-DHA + platinum (carboplatin, cisplatin or oxaliplatin) Alternating R-CHOP / R-DHAP NORDIC regimen R-HyperCVAD BR followed by R + high-dose cytarabine
Induction Therapy – Less Aggressive Therapy	<u>Preferred regimens:</u> BR VR-CAP R-CHOP Lenalidomide + R  <u>Other recommended regimens:</u> Modified R-HyperCVAD in patients > 65 years RBAC500
First-line Consolidation after Aggressive Therapy	High dose therapy with autologous stem cell transplant followed by rituximab maintenance every 8 weeks for 3 years (Category 1)
First-line Consolidation after Less Aggressive Therapy	Rituximab every 8 weeks until progression or intolerance (Category 1 for R-CHOP, unknown for other regimens)
Second-line and Subsequent Therapy	<u>Preferred regimens:</u> Acalabrutinib Ibrutinib +/- rituximab Zanubrutinib Lenalidomide +/- rituximab (if BTK inhibitor is contraindicated)  <u>Useful in certain circumstances (in alphabetical order):</u> Bendamustine + rituximab, if not previously given Bendamustine + rituximab + cytarabine (RBAC500), if not previously given Bortezomib +/- rituximab DHAP + rituximab GemOx + rituximab Ibrutinib + venetoclax Venetoclax +/- rituximab
Second-line Consolidation	Allogeneic stem cell transplant (myeloablative or non-myeloablative) in selected cases
Third-line Therapy	Brexucabtagene autoleucel (only given after chemoimmunotherapy and a BTK inhibitor)

BTK = Bruton tyrosine kinase; DHAP = dexamethasone, cytarabine and cisplatin; DHAX = dexamethasone, cytarabine and oxaliplatin; NORDIC regimen = rituximab + cyclophosphamide, vincristine, doxorubicin and prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHA + platinum = rituximab, dexamethasone, cytarabine and platinum; R-HyperCVAD = rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with rituximab, methotrexate and cytarabine; R-ICE = rituximab, ifosfamide, carboplatin and etoposide; VR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

**Patient Case #3, Continued:**

**Correct answer = D (Zanubrutinib).**

TR still has residual peripheral neuropathies from his previous treatment with VR-CAP. Therefore, it would be most appropriate to avoid re-administering agents that are associated with peripheral neuropathies such as bortezomib. Zanubrutinib and acalabrutinib are both recommended for the treatment of relapsed MCL, but acalabrutinib is used as a single agent in this setting and there is no evidence to support combining acalabrutinib with rituximab in this setting. At this time, brexucabtagene autoleucel is only recommended after the receipt of both chemoimmunotherapy and a BTK inhibitor.

**D. Burkitt lymphoma (BL)**

1. Some references refer to this disease as the most rapidly proliferating human malignancy.<sup>23,211,212</sup>
2. There are three clinical variants of BL: endemic, sporadic and immunodeficiency-associated. Sporadic BL is most often encountered in developed countries.<sup>211-215</sup>
3. Treatment (the handout will only focus on the treatment of sporadic BL)
  - a. The goal is to **CURE** the patient. Durable remission is possible in 60-90% of patients.<sup>3,212</sup>
  - b. Cure is achieved in a significant subset of patients when treated with dose-intensive, multi-agent chemotherapy regimens that include central nervous system prophylaxis. CHOP or R-CHOP chemotherapy is NOT ADEQUATE TREATMENT.<sup>212,214</sup>
  - c. Prompt initiation of therapy is critical to achieve optimal outcomes.
  - d. Tumor lysis syndrome (TLS) is common in patients with BL.<sup>211,212</sup> NCCN Guidelines® state that prophylaxis is mandatory in this subtype of NHL (see Acute Leukemias section).<sup>3</sup> Some references suggest a “pre-phase” induction treatment with low doses of steroids +/- chemotherapy to reduce the risk of fatal TLS.<sup>89,211,215</sup>
  - e. Participation in clinical trials is recommended for all patients.
  - f. The treatment regimens used in adult patients are extrapolated from pediatric protocols, and there are no randomized controlled trials in this setting. Regimens include intensive multi-agent chemotherapy and CNS prophylaxis with either systemic or intrathecal chemotherapy due to the tendency of the disease to disseminate into the CNS. Recommended intrathecal agents include methotrexate and/or cytarabine.<sup>3,23,74,211,214,216-218</sup>
  - g. In high-risk patients who present with symptomatic CNS disease, the portion of regimen that contains agents that penetrate the CNS should be initiated first.<sup>3</sup>
  - h. The recommended induction regimens are listed below. Some references suggest that the relatively low toxicity and high efficacy of DA-R-EPOCH make it the preferred regimen in patients without CNS involvement, but the optimal treatment regimen remains undefined.<sup>212,219</sup>

### Initial treatment overview of BL per the NCCN Guidelines®.<sup>3</sup>

Tumor Type	Standard of Care	Comments
Low risk disease for age < 60	<u>Preferred induction therapy :</u> <ul style="list-style-type: none"> <li>CODOX-M + rituximab (3 cycles)</li> <li>DA-R-EPOCH (minimum 3 cycles with 1 additional cycle beyond CR), including intrathecal methotrexate</li> <li>R-HyperCVAD alternating with R-Methotrexate/Ara-C, including intrathecal methotrexate</li> </ul>	The difference between low-risk disease and high-risk disease is the number of chemotherapy cycles that can be given.
High risk disease for age < 60	<u>Preferred induction therapy:</u> <ul style="list-style-type: none"> <li>CODOX-M alternating with IVAC +rituximab</li> <li>R-HyperCVAD alternating with R-Methotrexate/Ara-C, including intrathecal methotrexate</li> </ul> <u>Other recommended regimen:</u> <ul style="list-style-type: none"> <li>DA-R-EPOCH (for high-risk patients not able to tolerate aggressive treatment)</li> </ul>	With high-risk disease, R-CODOX-M alternates with R-IVAC, for a total of 4 cycles. In low-risk disease, the patient would not receive R-IVAC.
All patients of age ≥ 60	<u>Preferred regimen:</u> <ul style="list-style-type: none"> <li>DA-R-EPOCH (minimum 3 cycles with 1 additional cycle beyond CR), including intrathecal methotrexate</li> </ul>	

CODOX-M = cyclophosphamide, doxorubicin, vincristine, with intrathecal methotrexate and cytarabine and systemic high-dose methotrexate; DA-R-EPOCH = rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; R-HyperCVAD = rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone; R-IVAC = rituximab, ifosfamide, cytarabine and etoposide.

#### 4. Relapsed disease<sup>3,89,215</sup>

- a. Second-line therapy is only considered in select patients with a reasonable duration of first remission. Patients with relapsed disease have a very poor prognosis, and salvage treatment is generally unsuccessful.<sup>211,212</sup>
- b. No definitive second-line regimens exist. Clinical trials are preferred. Chemotherapy with rituximab-containing regimens followed by high-dose therapy and autologous or allogeneic stem cell transplantation may be considered in selected patients (refer to Hematopoietic Stem Cell Transplantation materials), and CAR-T therapy may also be considered.<sup>3,212,214,216</sup>
- c. There are limited data with the following regimens:<sup>3,214,215</sup>
  - 1) DA-R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) with intrathecal methotrexate
  - 2) R-ICE (rituximab, ifosfamide, carboplatin and etoposide) with intrathecal methotrexate, if not used previously
  - 3) R-IVAC (rituximab, ifosfamide, etoposide and cytarabine) with intrathecal methotrexate, if not used previously
  - 4) R-GDP (rituximab, gemcitabine, dexamethasone and cisplatin)
  - 5) High-dose cytarabine + rituximab

#### 5. Treatment summary for BL

**Overview of treatment recommendations for BL per the NCCN Guidelines®.<sup>3</sup>**

<b>Burkitt Lymphoma</b> (CHOP or R-CHOP is <b>not</b> adequate therapy)	
Induction therapy – low risk combination regimens	CODOX-M + rituximab DA-R-EPOCH, including intrathecal methotrexate R-HyperCVAD alternating with high-dose methotrexate and cytarabine + rituximab, including intrathecal methotrexate
Induction therapy – high risk combination regimens	CODOX-M alternating with IVAC + rituximab DA-R-EPOCH (for high risk patients not able to tolerate aggressive treatment) R-HyperCVAD alternating with high-dose methotrexate and cytarabine + rituximab
Second-line therapy	DA-R-EPOCH R-ICE R-IVAC R-GDP High-dose cytarabine + rituximab

CODOX-M = cyclophosphamide, doxorubicin, vincristine, with intrathecal methotrexate and cytarabine and systemic high-dose methotrexate; DA-R-EPOCH = rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; R-HyperCVAD = rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone; R-ICE = rituximab, ifosfamide, carboplatin and etoposide; R-IVAC = rituximab, ifosfamide, cytarabine and etoposide; R-GDP = rituximab, gemcitabine, dexamethasone and cisplatin.

**Patient Case #4:**

PG is a 67-year-old female with refractory cutaneous T-cell lymphoma. She has tried numerous topical and systemic therapies over the past six years.

**Which of the following supportive care issues is a frequent consideration in the treatment of patients with cutaneous T-cell lymphoma?**

- A. Bleomycin-induced pulmonary toxicity
- B. Hepatitis B reactivation
- C. Pruritus
- D. Mucositis

**E. T-cell lymphoma**

1. Cutaneous T-cell lymphoma (CTCL)<sup>220-232</sup>
  - a. The most common subtypes are mycosis fungoides (MF) and Sezary syndrome (SS).
  - b. Due to the rarity of this condition, an individualized approach must be used. Referral to a multidisciplinary academic specialty center with expertise in this area is recommended.
  - c. Goals of therapy should be individualized. Therapy is rarely given with curative intent; therefore, reduction of symptoms and minimization of disease progression are paramount.
  - d. Skin-directed therapies are reserved for early stage CTCL (Stage I – IIA).
    - 1) The initial goal of therapy is to improve symptoms and quality of life while avoiding treatment-related systemic toxicities. Factors such as route of administration, potential adverse effects and goals of therapy should be carefully considered.

- 2) Treatments for localized skin involvement (Stage IA) include topical corticosteroids, topical chemotherapy (such as mechlorethamine), topical retinoids (bexarotene or tazarotene), topical imiquimod, phototherapy or local radiation therapy.
  - 3) Treatment for generalized skin involvement (Stage IB-IIA) includes phototherapy (such as PUVA) and total skin electron beam therapy (TSEBT). Generalized therapy can be given with any of the localized treatments listed above.
- e. Systemic therapies are reserved for CTCL stage IIB – IV or in early-stage patients who have failed multiple topical therapies.
- 1) Various combinations of skin-directed therapies, radiation therapy, biologic response modifiers and systemic chemotherapy can be used. Therapeutic decisions should be individualized, based on factors such as:
    - a) Patient age
    - b) Performance status
    - c) Extent of disease burden
    - d) Rate of disease progression
    - e) Previous therapies
  - 2) When chemotherapy is required, single agents are preferred over combination therapy. Multi-agent regimens are associated with higher toxicity profiles without an increase in duration of response.<sup>230</sup>
    - a) Recommended agents according to NCCN Guidelines® include extracorporeal photopheresis (ECP), systemic retinoids, interferons, HDAC inhibitors, methotrexate, brentuximab vedotin, and mogamulizumab-kpkc, among others.<sup>220</sup>
  - 3) Conventional cytotoxic systemic chemotherapy is used as a primary treatment only for patients with very aggressive, extracutaneous or relapsed disease.
    - a) Combination regimens are generally reserved for patients who do not respond to multiple prior therapies or those patients with bulky lymph node or solid organ disease. Decisions regarding regimen selection should be made using clinical judgement.
  - 4) Mogamulizumab-kpkc (KW-0761, Poteligeo®)<sup>222,233,234</sup>
    - a) A defucosylated, humanized IgG kappa monoclonal antibody that selectively binds to CC chemokine receptor type 4 (CCR4). CCR4 is consistently expressed on the surface of tumor cells in T-cell malignancies, and is a receptor for chemokines involved in the trafficking of lymphocytes to skin.
    - b) FDA-approved for the treatment of adult patients with relapsed or refractory MF or SS after at least one prior systemic therapy.
    - c) Approval was based on the “MAVORIC” trial, a phase III randomized trial of 372 patients with relapsed or refractory MF or SS who had failed at least one prior systemic therapy. Patients were randomized to mogamulizumab-kpkc or vorinostat. The primary endpoint was PFS as assessed by study investigators.
      - i. Mogamulizumab-kpkc therapy resulted in superior PFS compared to vorinostat.

- ii. The preplanned QOL analyses revealed that patients treated with mogamulizumab-kpkc had a statistically significantly greater improvement in patient-reported outcomes at the 6-month assessment.
- iii. The results were most robust in patients with blood and/or skin involvement, as opposed to patients with nodal or visceral disease.

**Results of the phase III “MAVORIC” study, which compared mogamulizumab-kpkc or vorinostat in patients with relapsed or refractory MF or SS.**<sup>222,233</sup>

Regimen	Median PFS	ORR	Median OS
Mogamulizumab	7.7 months	28%	NR
Vorinostat	3.1 months	5%	43.9 months
p value	< 0.0001	< 0.0001	0.9439

ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

- d) Treatment with mogamulizumab may increase the risk of autoimmune-mediated adverse effects in patients with autoimmune disorders, as well as the risk of graft-versus-host disease (GVHD) after allogeneic stem cell transplantation. Caution should be applied when choosing this agent for patients with pre-existing autoimmune conditions or who are candidates for allogeneic HSCT.<sup>234</sup>

**Selected systemic treatment options for CTCL.**<sup>223,225-231</sup>

Drug	Class	Dose	Response	Toxicities
Alemtuzumab <sup>235</sup>	Anti-CD52 monoclonal antibody	Escalate to 30 mg IV or subq 3 times per week for up to 12 weeks (usually start with 3 mg for dose 1, 10 mg for dose 2, 30 mg for dose 3).	ORR 55% CR 32%	Cytopenias, infusion reactions, infections (CMV), nausea, emesis, fatigue. *No longer commercially available. Need to order through manufacturer on a per-patient basis. *All patients receive pneumocystis and herpes simplex prophylaxis and CMV surveillance or prophylaxis. <sup>43</sup>
Bexarotene <sup>236</sup>	Retinoid analogue (RAR X receptor subtype)	300-400 mg/m <sup>2</sup> PO daily	RR 50%	Hyperlipidemia and hypothyroidism (consider baseline lipid and thyroid panels prior to initiating and during therapy). <sup>227</sup>
Brentuximab vedotin <sup>237,238</sup>	Anti-CD30 monoclonal antibody	1.8 mg/kg IV every 3 weeks for up to 16 cycles	ORR 54.7% CR 17.2% PFS 16.7 months	Peripheral neuropathy, neutropenia.



Gemcitabine <sup>239</sup>	Antimetabolite	1200 mg/m <sup>2</sup> IV days 1, 8, 15 of 28-day cycle	RR 70% CR 12%	Myelosuppression, pulmonary, fever, rash, edema.
Interferon alfa <sup>240,241</sup>  *Specific product used in these studies is no longer available. Peginterferon alfa-2a may be substituted. <sup>242</sup>	Immuno-modulator	3-10 million units subq daily or three times weekly	RR 67-80% CR 41%	Myelosuppression, transaminitis, flu-like adverse effects, depression.
Mogamulizumab-kpkc <sup>222,234</sup>	Monoclonal antibody against CC chemokine receptor type 4 (CCR4)	1 mg/kg IV on days 1,8, 15 and 22 of the first 28-day cycle, then on days 1 and 15 of subsequent cycles	ORR 28% PFS 7.7 months	Rash, cellulitis, infusion reactions
Pegylated liposomal doxorubicin <sup>243,244</sup>	Anthracycline	20 or 40 mg/m <sup>2</sup> IV every 28 days	ORR 56-84% CR 20-42%	Hand-foot syndrome, gastrointestinal toxicities, infection.
Pralatrexate <sup>245</sup>	Folate analogue	15 mg/m <sup>2</sup> IV days 1, 8, 15 of 28-day cycle	ORR 41% CR 6%	Edema, fever, hypokalemia, mucositis, myelosuppression, increased liver function tests.
Romidepsin <sup>246</sup>	Histone deacetylase inhibitor	14 mg/m <sup>2</sup> IV on days 1, 8, 15 of 28 day cycle	RR 34% CR 6%	Gastrointestinal toxicities (nausea, vomiting, diarrhea), anemia, thrombocytopenia, QTc prolongation.
Vorinostat <sup>247</sup>	Histone deacetylase inhibitor	400 mg PO daily	RR 30%	Gastrointestinal toxicities (nausea, vomiting, diarrhea), anemia, thrombocytopenia.

CMV = cytomegalovirus; CR = complete response; ORR = overall response rate; PFS = progression-free survival; RR = response rate; TSH = thyroid stimulating hormone.

f. Supportive care of patients with MF or SS<sup>221,227,228,231,248-251</sup>

- 1) CTCL can greatly impact a patient's health-related quality of life (QOL). QOL reductions are more frequent and pronounced in patients with MF or SS compared to control populations with general dermatology conditions, with the largest decreases in social functioning and physical / emotional health.<sup>231</sup>
- 2) Non-physical factors such as insomnia, anxiety, depression and suicidal ideation may be more prevalent due to the visibility of the disease on the patient's skin and the associated psychological distress.
- 3) Use of supportive care measures to treat pruritus and minimize the risk of skin infections are a critical part of the treatment plan.
- 4) Pruritus

- a) Referral to a dermatologist with expertise in CTCL is recommended.
  - b) Daily use of moisturizers and emollients to protect the skin barrier. Use of mild, unscented soaps for bathing are optimal to prevent skin dryness.
  - c) Topical steroids (with or without occlusion) may be effective in early-stage disease.
  - d) First-line systemic therapies include antihistamines (either a single agent or a combination of antihistamines from different classes), gabapentin or pregabalin.
  - e) Second-line therapies may include aprepitant, mirtazapine, or selective serotonin reuptake inhibitors. Naltrexone and/or systemic steroids may be considered in the third-line setting.
- 5) Prevention and treatment of infections, as infections are a major cause of morbidity and mortality in patients with CTCL.
- a) The use of central lines should be avoided or minimized, if possible.
  - b) Maintain and protect the skin barrier (see above).
  - c) For limited areas, diluted bleach baths or soaks performed two to three times per week may be considered. The recommended preparations are 1 teaspoonful of bleach in 1 gallon of water or ½ cup of regular-strength bleach (5-6%) in a bathtub full of water. A moisturizer should be put on immediately following the bath or soak.
  - d) Prophylaxis with mupirocin (in cases of *Staphylococcus aureus* colonization) may be considered. Oral dicloxacillin or cephalexin may also be used. Vancomycin may be considered if there is no improvement or if bacteremia is documented.
  - e) Patients are at high risk for skin dissemination of localized viral infections, including HSV and VZV (see Cancer-Related Infectious Disease section). HSV prophylaxis should be considered for patients who have frequent recurrence of HSV infection.
  - f) Gram-negative rods are common in necrotic tumors. If there is high suspicion for an infection, empirical therapy for both Gram-negative rods and Gram-positive cocci should be initiated even in the absence of fever.

#### B. Treatment summary of CTCL

Overview of treatment recommendations for CTCL per the NCCN Guidelines<sup>®</sup>.<sup>220</sup>

**\*\*Please note that skin directed therapies are specified in NCCN Guidelines<sup>®</sup> but are NOT included here.**

Stage	Suggested Regimens	Preferred Regimens	Useful in Certain Circumstances
Stage IA MF (Limited skin involvement only, < 10% BSA)	<p>Skin directed therapies:</p> <ul style="list-style-type: none"> <li>• Alone</li> <li>• In combination with other skin-directed therapies</li> <li>• In combination with systemic therapy in selected cases</li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Bexarotene</li> <li>○ Interferon alfa</li> <li>○ Methotrexate</li> </ul> </li> <li>• Combination therapy <ul style="list-style-type: none"> <li>○ Phototherapy + interferon</li> <li>○ Phototherapy + retinoid</li> </ul> </li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Acitretin</li> <li>○ ECP</li> <li>○ Interferon γ-1b</li> <li>○ Isotretinoin</li> </ul> </li> <li>• Combination therapy <ul style="list-style-type: none"> <li>○ Phototherapy + ECP</li> </ul> </li> </ul>
<p>Stage IB MF (Limited skin involvement only, ≥ 10% BSA)</p> <p>or</p> <p>Stage IIA MF</p>	<p>Skin directed therapies:</p> <ul style="list-style-type: none"> <li>• Alone</li> <li>• In combination with other skin-directed therapies</li> <li>• In combination with systemic therapy in selected cases</li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Bexarotene</li> <li>○ Brentuximab vedotin</li> <li>○ Interferon alfa</li> <li>○ Methotrexate</li> <li>○ Mogamulizumab</li> <li>○ Romidepsin</li> <li>○ Vorinostat</li> </ul> </li> <li>• Combination therapy <ul style="list-style-type: none"> <li>○ Phototherapy + interferon</li> <li>○ Phototherapy + retinoid</li> </ul> </li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Acitretin</li> <li>○ ECP</li> <li>○ Interferon γ-1b</li> <li>○ Isotretinoin</li> </ul> </li> <li>• Combination therapy <ul style="list-style-type: none"> <li>○ Phototherapy + ECP</li> </ul> </li> </ul>
Stage IIB MF (Limited tumor disease)	<ul style="list-style-type: none"> <li>• Local RT</li> <li>• Skin-directed therapy</li> <li>• Local RT + skin-directed therapy</li> <li>• Systemic therapy +/- local RT</li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Bexarotene</li> <li>• Brentuximab vedotin</li> <li>• Interferon alfa</li> <li>• Methotrexate</li> <li>• Mogamulizumab</li> <li>• Romidepsin</li> </ul> <p>Other recommended regimen:</p> <ul style="list-style-type: none"> <li>• Vorinostat</li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Acitretin</li> <li>• ECP</li> <li>• Interferon γ-1b</li> <li>• Isotretinoin</li> </ul>
Stage IIB MF (Generalized tumor disease)	<ul style="list-style-type: none"> <li>○ Total skin electron beam therapy</li> <li>○ Systemic therapy + skin-directed therapy</li> <li>○ Combination therapies</li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Bexarotene</li> <li>○ Brentuximab vedotin</li> <li>○ Gemcitabine</li> <li>○ Interferon alfa</li> <li>○ Liposomal doxorubicin</li> </ul> </li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Acitretin</li> <li>○ ECP</li> <li>○ Interferon γ-1b</li> <li>○ Isotretinoin</li> </ul> </li> <li>• Combination therapy <ul style="list-style-type: none"> <li>○ ECP + interferon</li> <li>○ ECP + retinoid</li> </ul> </li> </ul>

		<ul style="list-style-type: none"> <li>○ Methotrexate</li> <li>○ Mogamulizumab</li> <li>○ Pralatrexate</li> <li>○ Romidepsin</li> <li>● Combination therapy <ul style="list-style-type: none"> <li>○ Phototherapy + interferon</li> <li>○ Phototherapy + retinoid</li> <li>○ Retinoid + interferon</li> </ul> </li> </ul> <p>Other recommended regimen:</p> <ul style="list-style-type: none"> <li>● Vorinostat</li> </ul>	<ul style="list-style-type: none"> <li>○ ECP + interferon + retinoid</li> <li>○ Phototherapy + ECP</li> </ul>
Stage III MF (erythrodermic disease)	---	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>● Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Bexarotene</li> <li>○ Brentuximab vedotin</li> <li>○ ECP</li> <li>○ Interferon alfa</li> <li>○ Methotrexate</li> <li>○ Mogamulizumab</li> <li>○ Romidepsin</li> </ul> </li> <li>● Combination therapy <ul style="list-style-type: none"> <li>○ ECP + interferon</li> <li>○ ECP + retinoid</li> <li>○ ECP + interferon + retinoid</li> <li>○ Phototherapy + ECP</li> <li>○ Phototherapy + interferon</li> <li>○ Phototherapy + retinoid</li> <li>○ Retinoid + interferon</li> </ul> </li> </ul> <p>Other recommended regimen:</p> <ul style="list-style-type: none"> <li>● Vorinostat</li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>● Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Acitretin</li> <li>○ Alemtuzumab</li> <li>○ Gemcitabine</li> <li>○ Interferon γ-1b</li> <li>○ Isotretinoin</li> <li>○ Liposomal doxorubicin</li> <li>○ Pembrolizumab</li> <li>○ Pralatrexate</li> </ul> </li> <li>● Skin-directed therapy <ul style="list-style-type: none"> <li>○ Phototherapy</li> </ul> </li> </ul>
Sezary Syndrome (Stage IVA1 or IVA2), low-intermediate burden	----	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>● Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Bexarotene</li> <li>○ ECP</li> <li>○ Interferon alfa</li> <li>○ Methotrexate</li> <li>○ Mogamulizumab</li> <li>○ Romidepsin</li> <li>○ Vorinostat</li> </ul> </li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>● Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Acitretin</li> <li>○ Interferon γ-1b</li> <li>○ Isotretinoin</li> </ul> </li> </ul>

		<ul style="list-style-type: none"> <li>• Combination therapy <ul style="list-style-type: none"> <li>○ ECP + interferon</li> <li>○ ECP + retinoid</li> <li>○ ECP + interferon + retinoids</li> <li>○ Phototherapy + ECP</li> <li>○ Phototherapy + interferon</li> <li>○ Phototherapy + retinoid</li> <li>○ Retinoid + interferon</li> </ul> </li> </ul> <p>Other recommended regimens, in alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Alemtuzumab</li> <li>○ Brentuximab vedotin</li> <li>○ Gemcitabine</li> <li>○ Liposomal doxorubicin</li> <li>○ Pembrolizumab</li> <li>○ Pralatrexate</li> </ul> </li> </ul>	
Sezary Syndrome (Stage IVA1 or IVA2), high burden	----	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Mogamulizumab</li> <li>○ Romidepsin</li> </ul> </li> <li>• Combination therapy <ul style="list-style-type: none"> <li>○ ECP + interferon</li> <li>○ ECP + retinoid</li> <li>○ ECP + interferon + retinoids</li> <li>○ Phototherapy + ECP</li> <li>○ Phototherapy + interferon</li> <li>○ Phototherapy + retinoid</li> <li>○ Retinoid + interferon</li> </ul> </li> </ul> <p>Other recommended regimens, in alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Alemtuzumab</li> </ul> </li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Systemic therapy + skin directed therapy <ul style="list-style-type: none"> <li>○ Acitretin</li> <li>○ Interferon <math>\gamma</math>-1b</li> <li>○ Isotretinoin</li> </ul> </li> </ul>

		<ul style="list-style-type: none"> <li>○ Bexarotene</li> <li>○ Brentuximab vedotin</li> <li>○ ECP</li> <li>○ Gemcitabine</li> <li>○ Interferon alfa</li> <li>○ Liposomal doxorubicin</li> <li>○ Methotrexate</li> <li>○ Pembrolizumab</li> <li>○ Pralatrexate</li> <li>○ Vorinostat</li> </ul>	
Stage IV MF (non-Sezary [stage IVA2] or visceral/solid organ disease [stage IVB])	<ul style="list-style-type: none"> <li>• Systemic therapy +/- RT for local control</li> </ul>	<p>In alphabetical order:</p> <ul style="list-style-type: none"> <li>• Brentuximab vedotin</li> <li>• Gemcitabine</li> <li>• Liposomal doxorubicin</li> <li>• Pralatrexate</li> <li>• Romidepsin</li> </ul> <p>Other recommended regimens:</p> <ul style="list-style-type: none"> <li>• Mogamulizumab</li> <li>• Multiagent chemotherapy regimens (listed under PTCL-NOS below)</li> </ul>	---
Relapsed or disease refractory to multiple prior therapies	---	---	<p>Alphabetical order by category:</p> <ul style="list-style-type: none"> <li>• Alemtuzumab</li> <li>• Chlorambucil</li> <li>• Cyclophosphamide</li> <li>• Etoposide</li> <li>• Pembrolizumab</li> <li>• Pentostatin</li> <li>• Temozolomide (for CNS involvement)</li> </ul>

## II. Peripheral T-cell lymphoma (PTCL)<sup>23,248,252-262</sup>

- a. A heterogeneous group of lymphoproliferative disorders arising from mature T-cells of post-thymic origin. More than 25 different variations of PTCL have been defined by the World Health Organization.<sup>2,260</sup>
- b. The most common subtype is PTCL-not otherwise specified (PTCL-NOS), comprising up to 30% of PTCL.
- c. The prognosis is poor compared to B-cell NHL, with 5-year overall survival of 10-30% for the most common subtypes.

- 1) This is largely due to lower response rates and less durable responses to standard combination chemotherapy such as CHOP, as well as the lack of targeted agents such as monoclonal antibodies for this subtype of lymphoma
  - 2) However, chemotherapy regimens that are more intensive than CHOP have not shown any significant improvement in overall survival in this patient population (with the exception of anaplastic large cell lymphoma [ALCL]).
- d. Anthracycline-based chemotherapy is an essential component of treatment regimens, extrapolating the results from B-cell NHL despite a different biology and natural history.<sup>263</sup>
- e. ISRT may be included in the treatment plan in select cases.
- f. The phase III “ECHELON-2” trial compared CHOP to brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone (A+CHP) in 452 patients with previously untreated CD30-positive PTCL. The primary endpoint was PFS according to blinded independent central review.<sup>255,264,265</sup>
- 1) Median PFS was 48.2 months in the A+CHP group and 20.8 months in the CHOP group (HR, 0.71 [95% CI, 0.54 – 0.93],  $p = 0.011$ ).
  - 2) The benefit of A+CHP over CHOP was particularly pronounced for those with ALCL, but was less impressive in those with other forms of PTCL; however, the analysis was underpowered for specific histologies other than ALCL.
  - 3) Adverse events, including febrile neutropenia and peripheral neuropathy, were similar between groups.
  - 4) In the 6-year update, PFS rates were 51.4% vs 43% (HR 0.70 [95% CI, 0.53 – 0.91]) and OS rates were 70.1% vs 61.0% (HR 0.72 [95% CI, 0.53 – 0.99]). Both PFS and OS were generally consistent across subgroups.
- g. The final analysis of the phase III “RoCHOP” trial comparing romidepsin + CHOP with CHOP failed to demonstrate an improvement in PFS, response rates or OS with the addition of romidepsin in the front-line setting. Additionally, grade  $\geq 3$  adverse events occurred more frequently in the romidepsin-containing treatment arm.<sup>262,266</sup>
- h. Treatment overview

**Initial treatment overview of peripheral T-cell lymphoma per the NCCN Guidelines®.<sup>248</sup>**

<b>Tumor Type</b>	<b>Suggested Regimens*</b>	<b>Comments</b>
ALCL	<u>Preferred regimen:</u> Brentuximab vedotin + CHP (Category 1)  <u>Other recommended regimens:</u> CHOP CHOEP DA-EPOCH	Rituximab is not given since T-cell lymphomas are typically not CD20+.
PTCL-NOS, AITL, other histologies	<u>Preferred regimens (in alphabetical order):</u> Brentuximab vedotin + CHP for CD30+ histologies CHOEP CHOP DA-EPOCH  <u>Other recommended regimen:</u> CHOP followed by IVE alternating with intermediate-dose methotrexate (only studied in patients with EATL)	
PTCL-NOS and other histologies <u>if initial intent is palliative</u>	<u>Preferred regimens (in alphabetical order):</u> Belinostat Brentuximab vedotin + CHP for CD30+ histologies Pralatrexate Romidepsin  <u>Other recommended regimens (in alphabetical order):</u> Alectinib (ALK+ ACL only) Alemtuzumab Bendamustine Crizotinib (ALK+ ACL only) Cyclophosphamide +/- etoposide (IV or PO) Duvelisib Gemcitabine Lenalidomide Radiation therapy	

\*ISRT may be added in select cases.

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CHP = cyclophosphamide, doxorubicin and prednisone; DA-EPOCH = dose-adjusted etoposide, cyclophosphamide, doxorubicin, vincristine and prednisone; ISRT = involved site radiation therapy; IVE = ifosfamide, etoposide and epirubicin; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified.

- i. First-line consolidation with high-dose chemotherapy and autologous stem cell rescue may be considered.<sup>248,257,267</sup>
- j. Relapsed PTCL<sup>23,248,254,257,259,263,267,268</sup>
  - 1) No comparative studies have been conducted in this setting.
  - 2) Treatment choice is based on whether the patient will be proceeding to high-dose therapy and stem cell rescue.
  - 3) Patients who are candidates for transplant can be treated with second-line chemotherapy, followed by an autologous or allogeneic stem cell transplant if a



complete or partial response is obtained. However, there have been no randomized controlled trials to identify patients who will benefit from stem cell transplantation (refer to Hematopoietic Stem Cell Transplantation materials).

- 4) The selection of second-line chemotherapy should be based on patient-specific factors, such as age, performance status, availability of a stem cell donor, adverse effect profile and goals of therapy.

#### Selected single-agent treatment options for relapsed PTCL.

Drug	Class	Dose	Response	Toxicity
Belinostat <sup>269,270</sup> (BELIEF trial)	Histone deacetylase inhibitor	1000 mg/m <sup>2</sup> IV daily on days 1 – 5 every 21 days	ORR 26% CR 11% PFS 1.6 months OS 7.9 months	Anemia, thrombocytopenia, neutropenia, hepatotoxicity (reduce starting dose to 750 mg/m <sup>2</sup> in patients known to be homozygous for the UGT1A1*28 allele to minimize dose-limiting toxicities), nausea, fatigue, pyrexia.
Brentuximab vedotin <sup>271,272</sup>	MMAE conjugate	1.8 mg/kg IV every 21 days  *Trial only included relapsed or refractory anaplastic large cell lymphoma patients	ORR 86% CR 57% 5-year PFS 39% 5-year OS 60%	Neutropenia, thrombocytopenia, neuropathy.
Duvelisib <sup>273</sup> (PRIMO trial)	Dual PI3K- $\delta,\gamma$ inhibitor	75 mg BID for 2 cycles, then 25 mg BID	ORR 50% CR 32.1%	Neutropenia, transaminitis, rash, lymphopenia.
Pralatrexate <sup>274</sup> (PROPEL trial)	Antimetabolite	30 mg/m <sup>2</sup> IV weekly for 6 weeks of a 7-week treatment cycle (continue until disease progression)  *Supplementation with vitamin B12 1000 mcg IM within 10 weeks of treatment and Q8 – 10 weeks thereafter and folate 1-1.25 mg/day is required	ORR 29% CR 11% PFS 3.5 months OS 14.5 months	Edema, fatigue, fever, rash, hypokalemia, mucositis, nausea/vomiting, myelosuppression, increased liver function tests.  *Pralatrexate competes for renal tubular secretion similar to methotrexate. Monitor accordingly for drug interactions.
Romidepsin <sup>275</sup>	Histone deacetylase inhibitor	14 mg/m <sup>2</sup> IV on days 1, 8, 15 of 28 day cycle	ORR 25% CR/CRu 15% PFS 4 months DOR 17 months	ST-T wave changes, QTc prolongation, hypotension, rash, nausea/vomiting, myelosuppression, fatigue, electrolyte abnormalities.

CR = complete response; CR/CRu = complete response/complete response unconfirmed; MMAE = monomethyl auristatin E; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

- k. Based on the results of the “RoCHOP” trial discussed above, the manufacturer chose to voluntarily withdraw romidepsin from the US market for the PTCL indication in August 2021.<sup>276</sup> However, the drug is still available for treatment of CTCL as discussed above and is still listed as a treatment option for PTCL in the NCCN Guidelines.<sup>248</sup>
- l. Brentuximab vedotin should be the preferred choice in relapsed/refractory CD30+ ALCL. There is not enough data to support a particular regimen in the second-line setting for other types of PTCL.
- m. Treatment summary of PTCL

**Overview of treatment recommendations for PTCL per the NCCN Guidelines<sup>248</sup>**

Peripheral T-cell Lymphoma	
First-line therapy	<p><u>Preferred regimens (in alphabetical order):</u></p> <p>Brentuximab vedotin + CHP for CD30+ histologies (Category 1 for ALCL)</p> <p>CHOEP</p> <p>CHOP</p> <p>DA-EPOCH</p> <p><u>Other recommended regimen:</u></p> <p>CHOP followed by IVE alternating with intermediate-dose methotrexate</p>
First-line consolidation	Consider high dose chemotherapy and autologous stem cell transplant
First-line therapy if initial intent is palliative	<p><u>Preferred regimens (in alphabetical order):</u></p> <p>Belinostat</p> <p>Brentuximab vedotin + CHP for CD30+ histologies</p> <p>Pralatrexate</p> <p>Romidepsin</p> <p><u>Other recommended regimens (in alphabetical order):</u></p> <p>Alectinib (ALK+ ALCL only)</p> <p>Alemtuzumab</p> <p>Bendamustine</p> <p>Crizotinib (ALK+ ALCL only)</p> <p>Cyclophosphamide +/- etoposide (IV or PO)</p> <p>Duvelisib</p> <p>Gemcitabine</p> <p>Lenalidomide</p> <p>Radiation therapy</p>

Peripheral T-cell Lymphoma	
Second-line therapy – if candidate for hematopoietic stem cell transplant	<p><u>Preferred single agents (in alphabetical order):</u></p> <ul style="list-style-type: none"> <li>Belinostat</li> <li>Brentuximab vedotin (for CD30+ PTCL only)</li> <li>Pralatrexate</li> <li>Romidepsin</li> </ul> <p><u>Preferred combination regimens (in alphabetical order):</u></p> <ul style="list-style-type: none"> <li>DHAP</li> <li>DHAX</li> <li>ESHAP</li> <li>GDP</li> <li>GemOx</li> <li>ICE</li> </ul> <p><u>Alternative regimens (in alphabetical order):</u></p> <ul style="list-style-type: none"> <li>Alectinib (ALK+ ALCL only)</li> <li>Bendamustine</li> <li>Crizotinib (ALK+ ALCL only)</li> <li>Duvelisib</li> <li>Gemcitabine</li> <li>Lenalidomide</li> <li>GVD</li> </ul>
Second-line therapy – not a candidate for hematopoietic stem cell transplant	<p><u>Preferred single agents (in alphabetical order):</u></p> <ul style="list-style-type: none"> <li>Belinostat</li> <li>Brentuximab vedotin (for CD30+ PTCL only)</li> <li>Pralatrexate</li> <li>Romidepsin</li> </ul> <p><u>Alternative agents or regimens (in alphabetical order):</u></p> <ul style="list-style-type: none"> <li>Alectinib (ALK+ ALCL only)</li> <li>Alemtuzumab</li> <li>Bendamustine</li> <li>Crizotinib (ALK+ ALCL only)</li> <li>Cyclophosphamide and/or etoposide (IV or PO)</li> <li>Duvelisib</li> <li>Gemcitabine</li> <li>Lenalidomide</li> <li>Radiation therapy</li> </ul>

ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; DA-EPOCH = dose-adjusted etoposide, cyclophosphamide, doxorubicin, vincristine and prednisone; DHAP = dexamethasone, cytarabine and cisplatin; DHAX = dexamethasone, cytarabine and oxaliplatin; ESHAP = etoposide, methylprednisolone, cytarabine and platinum (cisplatin or oxaliplatin); GDP = gemcitabine, dexamethasone and cisplatin; GemOx = gemcitabine and oxaliplatin; GVD = gemcitabine, vinorelbine and liposomal doxorubicin; ICE = ifosfamide, carboplatin and etoposide.

**Patient Case #4, Continued:**

**Correct answer = C (Pruritus).**

Pruritus is a frequent and debilitating symptom in patients with cutaneous T-cell lymphoma, especially in patients with widespread and/or refractory disease. Bleomycin is not frequently used in the treatment of CTCL, nor are anti-CD20 monoclonal antibodies that would increase hepatitis B reactivation risk. Mucositis could occur based on the systemic treatment selected, but is not a common symptom in all patients with CTCL.

## HODGKIN LYMPHOMA

### **Patient Case #1:**

KU is a non-smoking 31-year old female who presented to her primary care provider with complaints of fatigue, low-grade fevers, 10 pound weight loss, pruritus, and mild dyspnea on exertion that had been increasing over the last few months. She has a past medical history of type 1 diabetes mellitus, iron deficiency anemia and dysmenorrhea. PET/CT scans of the chest, abdomen, and pelvis revealed left supraclavicular adenopathy contiguous with a bulky, 11 cm mediastinal mass and retroperitoneal lymphadenopathy. An excisional biopsy of a supraclavicular lymph node is positive for Reed-Sternberg cells, and she is diagnosed with Stage IIB classical Hodgkin lymphoma (CHL).

**Based on this information, which of the following is the most appropriate initial treatment option for KU?**

- A. ISRT
- B. ABVD
- C. Brentuximab vedotin
- D. Stanford V

### **I. Pathogenesis and genomics**

#### **A. Pathogenesis<sup>277,278</sup>**

1. The malignant cell is the Reed-Sternberg cell. The Reed-Sternberg cell is characterized by its large size, classic binucleated structure, and expression of CD30 and CD15. The cellular origin of the Reed-Sternberg is the monoclonal pre-apoptotic germinal center derived B-lymphocyte.
2. Classical Hodgkin lymphoma (CHL) is characterized by the presence of Reed-Sternberg cells in an inflammatory background.
3. Nodular lymphocyte-predominant Hodgkin Lymphoma (NLPHL) lacks Reed-Sternberg cells, but is characterized by the presence of lymphocyte predominant cells, sometimes called “popcorn cells.” It is also usually CD20 positive and CD30 negative. This subtype is characterized by an indolent course and late relapse, with a different natural history and response to therapy compared with CHL.

#### **B. Genomics**

1. Epstein-Barr Virus (EBV): 20-40% of Reed-Sternberg cells contain the EBV genome. The human leukocyte antigen (HLA) region HLA-A\*01 is associated with an increased risk of developing EBV(+) HL.<sup>279,280</sup>

#### **C. The WHO classification divides HL into 2 main types: CHL and NLPHL. CHL is divided further into 4 subtypes.<sup>2,281,282</sup>**

1. The histologic subtype is not an independent prognostic factor.

## WHO classification for HL.<sup>2,281,282</sup>

Hodgkin Lymphoma Classification	
Classical Hodgkin Lymphoma	Prevalence Rate
1. Nodular sclerosing	75%
2. Mixed cellularity	13% (the most frequent subtype in HIV+ patients)
3. Lymphocyte-rich	6%
4. Lymphocyte-depleted	1%
Lymphocyte-predominant*	5%

\*Considered a low-grade monoclonal B-cell malignancy distinct from classic Hodgkin lymphoma histopathologic subtypes.

## II. Staging and risk estimation<sup>282</sup>

- A. Staging for CHL is based on the Ann Arbor staging system. Patients with HL are classified into 3 groups:
1. Early-stage favorable (stage I – II with no unfavorable factors)
    - a. Unfavorable factors include any of the following:
      - 1) Erythrocyte sedimentation rate (ESR)  $\geq 50$
      - 2) The presence of constitutional symptoms (“B” symptoms)
      - 3) Mediastinal mass ratio (MMR)  $> 0.33$
      - 4)  $> 3$  nodal sites of involvement
      - 5) Bulky disease (any node  $> 10$  cm in diameter)
  2. Early-stage unfavorable (stage I – II)
  3. Advanced stage disease (stage III – IV)
- B. The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis. The more negative prognostic factors present at diagnosis, the worse the prognosis. This scoring system is intended to help in clinical management and predict prognosis for patients with stage III – IV disease. Currently, patients are divided into scores of 0-2 or  $\geq 3$  prognostic factors.<sup>283</sup>

## The International Prognostic Score (IPS) for CHL.<sup>283</sup>

Score	% of Patients with Advanced Disease	5-year PFS	5-year OS
0-2	58%	74%	86%
$\geq 3$	42%	55%	70%

OS = overall survival; PFS = progression-free survival.

## III. Treatment

- A. The treatment goal is **cure for ALL patients**. HL is now curable in up to 90% of patients.<sup>277,282,284-290</sup>
1. The 5-year survival rates of HL are unmatched by any other cancer over the past 4 decades.

2. Every patient with newly diagnosed HL has an overwhelming likelihood of being cured with appropriate treatment.
  3. Cure rates of HL have increased so profoundly that treatment considerations often relate to long-term toxicity, especially for patients in early stages of disease.
- B. Risk-adapted treatment per the Deauville PET criteria<sup>277,282,286,288,291,292</sup>
1. One approach to minimize long-term toxicities is to identify patients who can have a reduction in their therapy early in their treatment course, without compromising the high cure rate of CHL.
  2. The Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of FDG uptake by the radiologist in the involved sites. The criteria use a five-point scale.
    - a. Recent reports suggest that interim response assessment with PET/CT after 2-3 cycles of chemotherapy based on the Deauville criteria is a good prognostic indicator in patients with early-stage disease.<sup>293</sup>
    - b. PET positivity at the end of treatment has been identified as a significant adverse risk factor in patients with early-stage as well as advanced-stage disease.<sup>294</sup>
    - c. A Deauville score of 1, 2, or 3 on interim PET/CT scans may result in the elimination of bleomycin or other de-escalation of therapy in the remaining cycles. The results of the “RATHL” trial suggested that dropping bleomycin and continuing with AVD in those who are responding well is safer than continuing with ABVD but no less effective.<sup>295</sup>
    - d. A Deauville score of 4 or 5 on interim PET/CT scans may result in the intensification of treatment, while a score of 4 or 5 at the end of treatment may result in a biopsy and the addition of consolidative radiation to the positive sites.<sup>277,287</sup>
  3. NCCN Guidelines® recommend incorporating the Deauville criteria for interim response assessment with PET scans in the following scenarios:<sup>282</sup>
    - a. In patients who receive ABVD or BEACOPP (escalated), perform PET/CT after 2 cycles of treatment
    - b. In patients who receive brentuximab + AVD, perform PET/CT after 6 cycles of AVD

**Treatment overview of CHL per the NCCN® Guidelines.<sup>282</sup>**

Tumor Type	Initial Therapy	Subsequent Therapy Based on Results of Restaging PET/CT Scans	Alternative Chemotherapy Regimens^
Stage IA or IIA Favorable (non-bulky)	ABVD x 2 cycles (Category 1)	Any of the following may be added:• <ul style="list-style-type: none"> <li>• ABVD x 1-2 additional cycles</li> <li>• ISRT</li> <li>• AVD x 4 cycles</li> <li>• ABVD x 1-2 additional cycles + ISRT</li> </ul>	
Stage I or II Unfavorable (bulky lymphadenopathy or constitutional symptoms)	ABVD x 2 cycles	Any of the following may be added:• <ul style="list-style-type: none"> <li>• ABVD x 2 additional cycles + ISRT</li> <li>• AVD x 4 cycles</li> <li>• BEACOPP (escalated) x 2-4 cycles +/- ISRT</li> </ul>	
Stage III – IV	ABVD x 2 cycles (preferred, Category 1)	Any of the following may be added:• <ul style="list-style-type: none"> <li>• AVD x 4 cycles</li> <li>• BEACOPP (escalated) x 3-4 cycles +/- ISRT</li> </ul>	• BEACOPP (escalated) in selected patients with IPS ≥ 4 and age < 60 years
	Brentuximab vedotin + AVD (Category 1)  Use with caution in patients age > 60 years; contraindicated in pre-existing neuropathy		

\*See NCCN Guidelines® for more detail regarding restaging PET/CT scans.

ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; AVD = doxorubicin, vinblastine and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CHL = classical Hodgkin lymphoma; IPS = International Prognostic Score; ISRT = involved site radiation therapy; PET/CT = positron emission tomography / computed tomography.

**C. Stage IA – IIA favorable (non-bulky) CHL**

1. Combined modality therapy (chemotherapy + ISRT) has replaced ISRT alone, which for many decades was the standard of care in this patient population. ISRT alone is no longer the standard of care due to the potential long-term toxicity of high-dose, large-field irradiation increasing risks for heart disease, pulmonary dysfunction and secondary malignancies.<sup>277,287,291,296</sup>
  - a. The German Hodgkin Study Group conducted the HD10 multicenter trial to evaluate the relative intensity of chemotherapy and radiation therapy in early stage CHL with a favorable prognosis.<sup>297,298</sup>
    - 1) The HD10 study confirmed that 2 cycles of ABVD + 20 Gy IFRT is an effective primary treatment for patients with a favorable presentation. No significant differences were



seen in OS, PFS or freedom from treatment failure (FFTF), and the risk of late effects is minimized.

- 2) Note that NCCN Guidelines® now recommend ISRT over IFRT. ISRT is preferred due to the radiation fields being smaller than with IFRT. This minimizes the radiation exposure to uninvolved organs and potential long-term toxicities.<sup>282</sup>
- 3) Acute toxicity was more pronounced in the patients receiving 4 cycles of ABVD with 51.7% of patients experiencing Grade III/IV toxicity compared to 33.2% with 2 cycles ( $p < 0.001$ ). There was no difference in secondary neoplasia or death between the treatment arms.

**Results of the HD10 trial, which examined chemotherapy intensity and XRT in early-stage, favorable CHL.**<sup>297,298</sup>

Regimen	FFTF at 8 years	OS at 10 years	PFS at 10 years
ABVD x 4 with 30 Gy XRT	87.2%	94%	87%
ABVD x 4 with 20 Gy XRT	89.9%	--	--
ABVD x 2 with 30 Gy XRT	85.5%	--	--
ABVD x 2 with 20 Gy XRT	85.9%	94%	87%

ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; FFTF = freedom from treatment failure; PFS = progression-free survival; OS = overall survival; XRT = radiation therapy.

2. The National Cancer Institute of Canada (NCIC) Clinical Trial Groups compared ABVD alone vs treatment that include radiation therapy in patients with non-bulky stage IA – IIA disease, both favorable and unfavorable, in the HD.6 trial.<sup>299</sup>
  - a. Unfavorable characteristics in this trial included age  $\geq 40$  years, ESR  $\geq 50$ mm/hour, mixed cellularity or lymphocyte depleted and  $> 3$  sites of disease.
  - b. Patients were randomized into 2 cohorts:
    - 1) Chemotherapy alone (ABVD)—included favorable and unfavorable subtypes. Patients received 4 to 6 cycles of chemotherapy based upon response.
    - 2) Radiation therapy
      - a) Patients with favorable characteristics received radiation therapy alone.
      - b) Patients with unfavorable characteristics received 2 cycles of chemotherapy (ABVD) followed by radiation therapy.
  - c. At a median follow-up of 12 years, OS was higher among patients treated with ABVD alone than those treated with radiation with or without ABVD. However, ABVD alone was also associated with a lower rate of freedom from progression.

**Results of the HD.6 study, which compared ABVD alone to ABVD + radiation in non-bulky stage IA – IIA disease.<sup>299</sup>**

Patient group	ABVD Alone	Radiation Therapy, with or without ABVD	P value
<b>All patients</b>			
Patients in cohort (no.)	196	203	
Rate of outcome (%)			
OS	94	87	0.04
FFP	87	92	0.05
EFS	85	80	0.6
<b>Favorable cohort</b>			
Patients in cohort (no.)	59	64	
Rate of outcome (%)			
OS	98	98	0.95
FFP	89	87	0.82
EFS	89	86	0.64
<b>Unfavorable cohort</b>			
Patients in cohort (no.)	137	139	
Rate of outcome (%)			
OS	92	81	0.04
FFP	86	94	0.006
EFS	83	78	0.74

ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; EFS = event-free survival; FFP=freedom from disease progression; OS = overall survival.

3. The results of an exploratory subset analysis of patients in the HD10 and HD.6 trials confirmed that combined modality therapy provides better disease control than ABVD alone in patients with stage IA-IIA disease who do not achieve complete response after 2 cycles of ABVD.<sup>300</sup>

**D. Stage I – II unfavorable CHL (bulky lymphadenopathy or constitutional symptoms)**

1. The HD8 trial investigated whether radiotherapy can be reduced without loss of efficacy from extended field (EF) to involved field (IF) after four cycles of chemotherapy.<sup>298,301</sup>
  - a. The EF includes the IF as well as the adjacent lymph node regions.
  - b. 1,204 patients were randomized to 4 cycles of chemotherapy (2 cycles of COPP – cyclophosphamide, vincristine, procarbazine and prednisone + 2 cycles of ABVD) followed by EFRT or IFRT (30 Gy plus 10 Gy to bulky sites in both arms).
2. The HD8 trial confirmed that IFRT was equivalent to EFRT.
  - a. Acute adverse events including thrombocytopenia, leukopenia and gastrointestinal toxicity, were more frequent in the EFRT group at 5-year follow-up.
  - b. After 10 years of follow-up, IFRT was associated with less acute toxicity and secondary malignancies than EFRT.

**Results of the HD8 trial, which studied extended field vs involved field radiotherapy after chemotherapy.<sup>301,302</sup>**

Regimen	FFTF at 5 years	OS at 5 years	FFTF at 10 years	OS at 10 years
Chemotherapy + EFRT	85.8%	90.8%	79.8%	86.4%
Chemotherapy + IFRT	84.2%	92.4%	79.7%	87.3%

EFRT = extended field radiation therapy; FFTF = freedom from treatment failure; IFRT = involved field radiation therapy; OS = overall survival.

3. The German Hodgkin Study Group's HD11 trial randomized 1,395 patients with stage I-II unfavorable disease to either ABVD x 4 cycles followed by IFRT or standard-dose BEACOPP x 4 cycles followed by IFRT.<sup>298,303</sup>
  - a. BEACOPP did not improve PFS or OS compared to ABVD, regardless of the dose of IFRT that was administered.
  - b. BEACOPP was also associated with more toxicity than ABVD.
4. These results and the results of other trials suggest that ABVD x 4 cycles + IFRT remains the standard of care for patients with early-stage unfavorable disease.

**E. Stages III – IV CHL**

1. The Cancer and Leukemia Group B (CALGB) performed a landmark randomized trial in patients with stage III – IV CHL, comparing MOPP (mechlorethamine, vincristine, procarbazine and prednisone, 6-8 cycles) vs. ABVD (6-8 cycles) vs. MOPP alternating each cycle with ABVD (6 cycles each for a total of 12 cycles).<sup>304</sup>
  - a. This trial demonstrated that ABVD alone or alternating with MOPP was superior to MOPP alone.
  - b. Patients receiving MOPP exhibited more hematologic toxicity, loss of fertility, infections and peripheral neuropathy ( $p < 0.001$ ).
  - c. The 14-year follow-up of this study found patients who received ABVD exhibited a superior failure-free survival over MOPP alone ( $p < 0.03$ ), but similar to MOPP/ABVD. There was no difference in overall survival between the 3 groups, probably due to effective salvage treatments for relapsed disease.<sup>305</sup>

**Results of the CALGB randomized trial that compared MOPP vs. ABVD vs. MOPP/ABVD in patients with stage III-IV CHL.<sup>304</sup>**

Regimen	CR	5-year OS
MOPP (n=123)	67%	66%
ABVD (n=123)	82%	73%
MOPP/ABVD (n=115)	83% ( $p=0.006$ )	75% ( $p=0.28$ )

ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; CR = complete response; MOPP = mechlorethamine, vincristine, procarbazine and prednisone; OS = overall survival.

2. The results of the trial by the CALGB were confirmed in a large US Inter-group study. This trial compared ABVD with a MOPP/ABV hybrid regimen in 856 patients with advanced CHL.<sup>306</sup>

- a. The trial showed that CR, FFS and OS were similar between the regimens.
- b. MOPP/ABV was associated with increased risk of hematologic toxicity, including life-threatening or lethal neutropenia, anemia, thrombocytopenia, or infection ( $p < 0.001$ ).
- c. MOPP/ABV was also associated with significantly increased incidence of severe malaise, fatigue, anorexia, and hypotension ( $p < 0.01$ ).
- d. There were 11 cases of AML/MDS in the hybrid arm vs 2 cases in the ABVD arm ( $p = 0.011$ ).

**Results of the US Intergroup Study, which compared ABVD vs MOPP/ABV hybrid in advanced CHL.<sup>306</sup>**

Regimen	CR	FFS at 5 years	OS at 5 years	Secondary Malignancies
MOPP/ABV Hybrid	80%	66%	81%	28
ABVD	76%	63%	82%	18
p-value	0.16	0.42	0.82	0.13

ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; CR = complete response; FFS = failure-free survival; MOPP/ABV hybrid = mechlorethamine, vincristine, procarbazine and prednisone alternating with doxorubicin, bleomycin and vinblastine; OS = overall survival.

3. It should be noted that the FDA announced the discontinuation of manufacture, distribution and sale of intravenous mechlorethamine in October 2018 due to extremely low demand.<sup>307</sup>
4. Other oncology groups have tried to improve response rates with other chemotherapy regimens besides ABVD. Other regimens that are included in the NCCN Guidelines® as options for CHL include BEACOPP (escalated).<sup>282</sup>
  - a. A Cochrane Library systematic review reported that there is moderate to high-quality evidence that BEACOPP (escalated) provides a PFS and OS benefit in early unfavorable and advanced stage CHL compared to ABVD. However, the study also concluded that “it is clear that BEACOPP (escalated) may be more toxic than ABVD, and the very important long-term side effects of second malignancies and infertility have not been sufficiently analyzed yet.”<sup>288,308</sup>
  - b. Using these regimens as front-line treatment is still considered controversial in the United States, and ABVD is still preferred by NCCN Guidelines®. Dose-intense regimens such as BEACOPP (escalated) may be considered in selected patients who are  $< 60$  years old and with  $IPI \geq 4$ .<sup>282</sup>

**Other selected initial chemotherapy options for patients with advanced CHL.**<sup>281,282</sup>

Chemotherapy Regimen	Drug	Dose (mg/m <sup>2</sup> )	Days	Route	Frequency
BEACOPP (escalated)	Bleomycin	10 unit/m <sup>2</sup>	8	IV	Every 21 days
	Etoposide	200	1 – 3	IV	
	Doxorubicin	35	1	IV	
	Cyclophosphamide	1250	1	IV	
	Vincristine	1.4 (*capped at 2 mg)	8	IV	
	Procarbazine	100	1 – 7	PO	
	Prednisone	40	1 – 14	PO	

5. Use of brentuximab vedotin in first-line therapy<sup>282,289,309-314</sup>

- a. An open-label, randomized phase III trial (“ECHELON-1”) compared brentuximab vedotin, doxorubicin, vinblastine and dacarbazine (A+AVD) to ABVD in 1,334 patients with previously untreated stage III or IV CHL.<sup>310,313,315</sup>
  - 1) The primary endpoint was “modified” PFS, defined as time to progression, death or noncomplete response and use of subsequent anti-cancer therapy, as assessed by an independent review committee. Patients who received A+AVD had statistically significantly increased modified PFS at 2 years (82.1% vs 77.2% [HR 0.77, 95% CI, 0.60 to 0.98; p = 0.04]). Modified PFS at 5 years was also significantly increased (82.2% with A+AVD and 75.3% with ABVD [HR 0.68, 95% CI 0.53-0.87; p=0.0017]).<sup>311,313</sup>
  - 2) The key secondary endpoint was OS. At 6-year follow-up, OS significantly favored A+AVD vs ABVD (HR 0.59, 95% CI, 0.396-0.879; p = 0.009). Estimated 6-year OS rates were 93.9% vs 89.4%, respectively. There was consistent OS benefit for A+AVD across subgroups.<sup>315</sup>
  - 3) Patients in the A+AVD arm had higher rates of febrile neutropenia, such that primary prophylaxis with GCSF was instituted in this arm after 76% of enrollment was complete. After this change, the incidence of febrile neutropenia in the A+AVD arm was mitigated; an additional study reported that the addition of GCSF may have decreased the risk of a modified progression-free survival event.<sup>312</sup>
  - 4) Based on these results, A+AVD is now a Category 1 recommendation for the first-line treatment for advanced CHL in the NCCN Guidelines®. The guidelines specify that this regimen should be used with caution in patients > 60 years of age, and is contraindicated in patients with neuropathy at baseline.<sup>282</sup>
  - 5) Other considerations would include the use of an atypical primary endpoint, cost of therapy, the use of a comparator arm that is no longer recommended (given data for bleomycin dose-escalation discussed above), an increase in neurotoxic effects and myelosuppression, and the unknown implications of using of brentuximab vedotin in the salvage or maintenance setting after A+AVD.<sup>288,316,317</sup>
  - 6) Fewer secondary cancers and more live births were reported in the A+AVD group than the ABVD group at 6 years of follow-up.<sup>315,317</sup>

**Results of the “ECHELON-1” study, which compared A+AVD vs ABVD in previously untreated advanced CHL.**<sup>310,313-315</sup>

Parameter	A+AVD	ABVD	P value
2-year modified PFS per independent review	82.1%	77.2%	0.04
5-year modified PFS per investigator review	82.2%	75.3%	0.0017
6-year OS	93.9%	89.4%	NR
Receipt of ≥ 1 subsequent anti-cancer treatment	20%	24%	NR
Febrile neutropenia	19%	8%	NR
Peripheral neuropathy	67%	43%	NR
Ongoing peripheral neuropathy at 5 years	18%	9%	NR
Pulmonary toxicity	2%	7%	NR

ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; A+AVD = brentuximab vedotin, doxorubicin, vinblastine and dacarbazine; NR = not reported; OS = overall survival; PFS = progression-free survival.

6. Dose intensity with BEACOPP

- a. The HD15 study included 2182 patients with newly diagnosed, advanced stage CHL. Patients were randomized to escalated BEACOPP x 8 cycles or escalated BEACOPP x 6 cycles or BEACOPP<sub>14</sub> x 8 cycles in a non-inferiority study design.<sup>318</sup> Patients with a persistent mass of 2.5cm or larger following completion of chemotherapy and positive PET scan received additional local radiotherapy of 30Gy.<sup>318</sup>
  - 1) The trial concluded that treatment with 6 cycles of BEACOPP (escalated) followed by PET-guided radiotherapy was more effective in terms of freedom from treatment failure and less toxic than 8 cycles of the same chemotherapy regimen. Thus, six cycles of BEACOPP (escalated) could be the treatment of choice for advanced stage Hodgkin lymphoma.
  - 2) A meta-analysis of several studies has suggested that the 5-year survival rate may be 5-10 percentage points higher with BEACOPP (escalated) than with ABVD.<sup>295,319</sup>
  - 3) However, this is still controversial and not recognized as standard of care in the United States due to the short- and long-term toxicities associated with BEACOPP (escalated) and due the ability to salvage many patients who relapse or are refractory to ABVD.
  - 4) There is a high incidence of myelosuppression and subsequent infection, and administration of growth factor is necessary with each cycle. In addition, a small number of patients develop secondary malignancies, including myelodysplastic syndromes and acute myeloid leukemias.<sup>289,291,308,320,321</sup>
  - 5) HD-18 and AHL-2011 are PET-adapted BEACOPP (escalated) protocols that can reduce the incidence of BEACOPP associated toxicities. Therefore, when BEACOPP is deemed appropriate, the NCCN Guidelines recommend either HD-18 or AHL2011.<sup>282,322,323</sup>
  - 6) BEACOPP (escalated) is generally considered to be too toxic to administer to patients who are > 60 years old.<sup>287,291</sup>

**Results of the HD15 study, which compared BEACOPP (escalated) x 8 cycles vs. BEACOPP (escalated) x 6 cycles vs. BEACOPP<sub>14</sub> x 8 cycles in advanced CHL.<sup>318</sup>**

Parameter	BEACOPP <sub>escalated</sub> x 8	BEACOPP <sub>escalated</sub> x 6	BEACOPP <sub>14</sub> x 8
CR	90.1%	94.2%	92.4%
PR	2.6%	1.3%	2%
5 year freedom from treatment failure	84.4%	89.3%	85.4%
5 year PFS	85.6%	90.3%	85.8%
5 year OS	91.9%	95.3%	94.5%
Secondary cancer	4.7%	2.4%	3.1%
Treatment-related mortality	2.1%	0.8%	0.8%

BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CR = complete response; OS = overall response; PFS = progression-free survival; PR = partial response.

**F. Management of CHL in patients > 60 years of age<sup>282,284-287,324</sup>**

1. CHL in older patients is characterized by aggressive disease, unfavorable prognostic factors and a predominance of advanced stages.
2. CHL is associated with poorer outcomes in older adult patients, likely due to a combination of more aggressive disease and poor performance status. Further, administration of bleomycin and/or anthracyclines may be limited or prohibited based on cardiopulmonary comorbidities.
3. The use of standard chemotherapy regimens is associated with dose reductions, treatment toxicity and treatment-related mortality in these patients.
  - a. Prospective data evaluating alternative regimens are limited.
  - b. Selection of first-line therapy should be individualized, with the goal of minimizing toxicity while maximizing efficacy.
4. Suggested treatment regimens
  - a. ISRT alone is an option if systemic therapy is not considered to be feasible or safe.
  - b. Stage I or II Favorable disease (in alphabetical order):
    - 1) ABVD or AVD x 2 cycles +/- AVD x 2 cycles + ISRT 20-30 Gy (preferred)
    - 2) CHOP x 4 cycles + ISRT
  - c. Stage I or II Unfavorable or Stage III or IV disease (in alphabetical order):
    - 1) ABVD or AVD x 2 cycles followed by AVD x 4 cycles
    - 2) Brentuximab vedotin followed by AVD; for patients who achieve CR or PR, brentuximab vedotin may be continued
    - 3) Brentuximab vedotin + dacarbazine
    - 4) CHOP x 6 cycles +/- ISRT

**Patient Case #1, Continued:**

**Correct answer = B (ABVD).**

ISRT alone was a historical treatment for early-stage CHL, but is no longer recommended. Brentuximab vedotin as a single agent is not currently recommended for the first-line treatment of CHL. The Stanford V regimen was recently removed as a recommended regimen in NCCN Guidelines®, while ABVD x 2 cycles is the current recommendation for initial treatment of Stage IIB disease.

G. Relapsed / refractory CHL<sup>282,287,325-328</sup>

1. The majority of relapses following a CR in patients with CHL occur within 3 years of the completion of therapy.
2. The goal is still to **CURE** the patient
3. Options for treatment of relapsed/refractory disease include:
  - a. Second-line chemotherapy, with intention to proceed to high-dose chemotherapy followed by autologous stem cell transplant +/- ISRT (refer to Hematopoietic Stem Cell Transplantation materials). This is a Category 1 recommendation per NCCN Guidelines®.<sup>282</sup>
    - 1) Autologous HSCT can provide a cure in approximately 50% of patients.<sup>329</sup>
    - 2) In randomized studies, autologous HSCT used as salvage therapy improved event-free survival and progression-free survival compared to non-transplant approaches.<sup>330-332</sup>
    - 3) The quality of response at time of transplantation is the most relevant prognostic criterion, with patients in CR having improved outcomes.<sup>333</sup>
  - b. Radiotherapy is recommended when the sites of relapse have not been previously irradiated.<sup>282,330</sup>
  - c. Chemotherapy regimens include any of the following, which are listed in alphabetical order. No regimen has emerged as the clear choice, but platinum-based regimens with non-cross-resistant agents are preferred.<sup>282,287,326,328,330,333-335</sup>
    - 1) BeGEV (bendamustine, gemcitabine, vinorelbine, and prednisone)
    - 2) Bendamustine
    - 3) Bendamustine + carboplatin + etoposide
    - 4) Brentuximab vedotin
    - 5) Brentuximab vedotin + bendamustine
    - 6) Brentuximab vedotin + nivolumab
    - 7) C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisone)
    - 8) DHAP (dexamethasone, cisplatin and high-dose cytarabine)
    - 9) ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)
    - 10) Everolimus
    - 11) GCD (gemcitabine, cisplatin and dexamethasone)



- 12) Gemcitabine, bendamustine and vinorelbine
  - 13) GemOx (gemcitabine and oxaliplatin)
  - 14) GVD (gemcitabine, vinorelbine and liposomal doxorubicin)
  - 15) GVD + pembrolizumab
  - 16) ICE (ifosfamide, carboplatin and etoposide)
  - 17) ICE + brentuximab vedotin
  - 18) ICE + nivolumab
  - 19) IGEV (ifosfamide, gemcitabine, and vinorelbine)
  - 20) Lenalidomide
  - 21) MINE (etoposide, ifosfamide, Mesna and mitoxantrone)
  - 22) Mini-BEAM (carmustine, etoposide, cytarabine and melphalan)
  - 23) Nivolumab – see further explanation below
  - 24) Pembrolizumab – see further explanation below
  - 25) Vinblastine
4. The outcomes of relapsed / refractory disease in older adults are universally poor. Individualized treatment is necessary, with consideration given to single-agent palliative treatment. Palliative therapy options include (in alphabetical order):<sup>282</sup>
    - a. Bendamustine
    - b. Brentuximab vedotin
    - c. ISRT
    - d. Nivolumab
    - e. Pembrolizumab
    - f. Additional therapies as listed above
  5. Brentuximab vedotin in relapsed CHL<sup>336</sup>
    - a. A meta-analysis reported that the median overall survival for patients with relapsed / refractory CHL was longer with brentuximab than other therapies, including chemotherapy, allogeneic HSCT and other therapies.<sup>337</sup>
    - b. A randomized, double-blind, phase III trial (“AETHERA”) included 329 patients with unfavorable risk factors who had relapsed or primary refractory CHL and had undergone autologous HSCT. Brentuximab vedotin was given as planned consolidation therapy consisting of 16 doses starting 30-45 days after HSCT.<sup>329,338</sup>
      - 1) The primary endpoint was progression-free survival as assessed by an independent committee. PFS was significantly improved in patients who received brentuximab compared to placebo (HR 0.57, 95% CI 0.40-0.81, p = 0.0013).
      - 2) Consistent benefit of brentuximab was seen across subgroups.
      - 3) OS was not different between groups at the interim analysis.

- 4) In a quality of life analysis, there were no significant differences between patients with and without peripheral neuropathy within the brentuximab vedotin arm at any time point.<sup>339,340</sup>

**Results of the AETHERA trial, which compared brentuximab to placebo given as planned consolidation after autologous HSCT in patients with relapsed or refractory CHL.<sup>329</sup>**

Parameter	Brentuximab	Placebo
Progression-free survival, median	42.9 months (95% CI, 30.4 – 42.9)	24.1 months (95% CI, 11.5 – not estimable)
2-year progression-free survival	63% (95% CI, 55-70)	51% (95% CI, 43-59)

CI = confidence interval.

- 5) Based on the results of the AETHERA trial, the American Society for Blood and Marrow Transplantation now recommends post-ASCT maintenance with brentuximab in high-risk patients.<sup>330</sup> Likewise, the NCCN Guidelines® have included maintenance therapy with brentuximab for one year following ASCT for patients with high risk of disease relapse as per the AETHERA trial (primary refractory disease, duration of first CR < 1 year, or relapse with extranodal or advanced stage disease).<sup>282</sup>
6. Immune checkpoint inhibitors for relapsed CHL<sup>277,282,289,326,334,341-345</sup>
  - a. Reed-Sternberg cells overexpress PDL-1 ligands in 65-100% of cases through amplification of chromosome 9p24.1. In addition, Epstein-Barr virus, which is prevalent in CHL, also increases the expression of PD-L1. Thus, CHL may be genetically susceptible to blockade of the PD-1 pathway.
  - b. These agents are recommended for CHL patients with relapsed or refractory disease who are not eligible for HSCT or for any patient who has relapsed after autologous HSCT +/- brentuximab vedotin maintenance therapy.<sup>282</sup>
  - c. Nivolumab
    - 1) A multi-cohort phase II study (“CHECKMATE 205”) examined the use of nivolumab in patients with relapsed or refractory CHL who had failed both autologous HSCT and brentuximab vedotin. Objective response was observed in 66% of patients, with 9% of patients achieving CR. Across all cohorts, >90% of patients had a decrease in tumor burden.<sup>346</sup>
    - 2) Currently FDA approved for adult patients with CHL who have relapsed or progressed after autologous HSCT and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT.
    - 3) In a phase 1/2 study, nivolumab was combined with brentuximab vedotin as initial salvage therapy in 62 patients with relapsed or refractory CHL. The objective response rate was 82%, and the complete response rate was 61%. At a median follow-up of 34.3 months, estimated 3-year PFS was 77% for all patients and 91% for patients undergoing ASCT immediately after the completion of study treatment. OS at 3 years was 93%.<sup>347,348</sup>
  - d. Pembrolizumab<sup>345</sup>

- 1) The “KEYNOTE-204” phase III trial compared pembrolizumab to brentuximab vedotin in 304 patients with relapsed or refractory CHL.<sup>349</sup>
  - a) Eligible patients were post autologous HSCT or ineligible for autologous HSCT. Patients who had previously received brentuximab vedotin were eligible to participate.
  - b) Statistically significant improvement was observed with pembrolizumab compared to brentuximab vedotin for primary PFS as per an independent review committee (HR 0.65 [95% CI 0.48-0.88; p = 0.00271]; median 13.2 vs 8.3 months). The 12-month PFS rates were 53.9% vs 35.6%, respectively. The benefit of pembrolizumab was observed in all subgroups.
- 2) Currently FDA approved for the treatment of adult patients with relapsed or refractory CHL. Also FDA approved for the treatment of pediatric patients with refractory CHL, or CHL that has relapsed after ≥2 lines of therapy.
- e. Severe and fatal transplant-related complications have been reported in patients who received anti-PD1 agents both prior to and after allogeneic HSCT. Deaths were reported from acute GVHD exacerbations and veno-occlusive disease, among other causes.<sup>321,328,333,345,350</sup>

H. Nodular lymphocyte-predominant HL (NLP HL)<sup>277,278,282,287,351,352</sup>

1. NLP HL has a different behavior and response to therapy than CHL, especially in early-stage disease. The clinical course is usually indolent, but there is a tendency towards late and multiple relapses.<sup>352</sup>
2. There is an absence of randomized clinical trials comparing different chemotherapy regimens in this patient population.
3. No preferred chemotherapy regimen exists; ABVD is often used based on data with CHL.
4. Because NLP HL cells consistently express the CD20 antigen, rituximab can be considered as single-agent therapy or in combination with multidrug chemotherapy regimens.
5. Since malignant NLP HL lack the CD30 antigen, brentuximab vedotin is not a treatment option.

**Overview of treatment recommendations for NPLHL per the NCCN Guidelines®.<sup>282</sup>**

<b>Nodular Lymphocyte Predominate Hodgkin Lymphoma</b>	
Stage IA or IIA non-bulky disease	ISRT (preferred) Observation
Stage IB or IIB Stage IA or IIA bulky disease	Chemotherapy + rituximab + ISRT  The most common regimens used include: ABVD + rituximab CHOP + rituximab CVbP + rituximab Single agent rituximab
Stage III or IV	Chemotherapy + rituximab +/- ISRT Rituximab alone Local RT (palliation of symptomatic disease) Observation (if asymptomatic)

ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CVbP = cyclophosphamide, vinblastine and prednisolone; ISRT = involved site radiation therapy; RT = radiation therapy.

6. Treatment of relapsed NPLHL is based on CHL experience. Therapy is usually combination systemic therapy, with the choices of specific regimen based on recommendations for CHL. Recommended regimens include:
  - a. R-bendamustine
  - b. R-DHAP
  - c. R-ICE
  - d. R-IGEV
  - e. If not previously used, regimens such as R-CHOP, R-ABVD or R-CVbP could also be considered

**Patient Case #1, Continued:**

KU returns to the Lymphoma Clinic for cycle 2 of ABVD. All of her labs were within normal limits, except her ANC = 0.5. The attending physician asks the clinical pharmacist if KU's chemotherapy doses should be reduced.

**Which of the following is appropriate for KU at this time?**

- A. Hold chemotherapy and add growth factor support**
- B. Reduce all chemotherapy doses by 25%**
- C. Reduce the dose of doxorubicin by 25%**
- D. Proceed with chemotherapy at full doses**

- I. Supportive Care for HL
  1. Bleomycin pulmonary toxicity (BPT)
    - a. BPT can cause fibrosis, which is irreversible and potentially fatal.

- b. This toxicity is more common in patients of older age, with up to one-third of patients >60 years old developing BPT (compared to <3% of young patients).<sup>286</sup>
  - c. Other risk factors may include receiving pulmonary irradiation, prior history of lung disease, smoking, when cumulative doses are greater than 400 units, and in patients with renal dysfunction.<sup>353-355</sup>
  - d. There is no reliable predictive test for bleomycin-related lung toxicity in those with normal baseline pulmonary function tests (PFTs).<sup>309</sup> PFTs, including DLCO (diffusing capacity of the lung for carbon monoxide) should be followed routinely (e.g. before treatment and periodically during bleomycin therapy).<sup>291</sup> In general, a DLCO threshold of  $\geq 60\%$  is acceptable to administer bleomycin.<sup>282</sup>
  - e. Bleomycin should be discontinued for significant changes in pulmonary function.
  - f. Supplemental oxygen exacerbates BPT.<sup>356</sup>
  - g. Treatment often includes high-dose corticosteroids, although there is no standard of care.<sup>355</sup>
2. Prophylactic neutrophil growth factors (G-CSF or GM-CSF) are not recommended during initial therapy, except with BEACOPP (escalated).<sup>282,357</sup>
    - a. A retrospective analysis was performed by the Mayo Clinic of 141 patients who received bleomycin-containing regimens to delineate outcomes in these patients. A high rate of BPT was associated with use of G-CSF compared with patients who did not receive G-CSF (26% vs 9%,  $p = 0.014$ ).<sup>353</sup> However, small studies have suggested that pegfilgrastim can safely be administered during ABVD.<sup>358,359</sup>
    - b. Leukopenia is not a risk factor for reduction of dose intensity and therefore the NCCN Guidelines<sup>®</sup> do not recommend the routine use of growth factors during bleomycin therapy.<sup>282</sup>
    - c. Several studies have confirmed that ABVD can be safely administered at the full-dose intensity and density without the support of growth factor.<sup>360-363</sup>
    - d. Further, five-year EFS (87.4% vs. 80%) and OS (94.1% vs. 91.3%) rates were comparable in patients who received ABVD with no growth factors compared to those who received prophylactic growth support.<sup>361, 363</sup>
  3. Extravasation – see section on Extravasation at the end of this chapter.

## **XII. Late treatment effects and survivorship issues<sup>282,286,287,289,298,364,365</sup>**

- A. Cure rates of HL have increased so profoundly that treatment considerations often relate to long-term toxicity, especially for patients in early stages of disease. Some reports estimate that compared to the general population patients with CHL have a 5-fold higher risk of death from causes other than CHL.
- B. Further, the young age of most patients at diagnosis (median age = 15-24 years) makes the development of long-term toxicities a serious consideration.
- C. The incidence of late effects increases with longer follow-up time.
- D. The risk of late effects may be less with current treatment options compared to those used more than 10 years ago. However, most HL survivors experience at least one physical and/or psychosocial effect.<sup>364</sup>

- E. Patients are strongly encouraged to follow up with an oncologist who is aware of these risks and complications, especially during the first 5 years after treatment and then annually. Care should be coordinated with the patient's primary care provider as well.
- F. It is also recommended that the patient be provided with a treatment summary at the completion of his or her therapy, including details of radiation therapy, organs at risk and cumulative anthracycline dose received.
- G. The frequency and types of tests may vary based on the patient's clinical scenario, such as age and stage at diagnosis, social habits, treatment modalities used, and so forth.
- H. Specific late adverse effects include:
  - 1. Secondary cancers<sup>282,289,290,365-368</sup>
    - a. Most secondary cancers are solid tumors that develop >10 years after the completion of treatment. Lung cancer and breast cancer are the most common secondary cancers in patients with CHL.
    - b. The risk of developing secondary cancers is highest when radiation therapy is used as a component of first-line treatment.<sup>368</sup>
    - c. Appropriate screenings should be performed as indicated.
      - 1) Annual breast screening (mammography or MRI) beginning 8 years after completion of therapy or at age 40, whichever comes first, is recommended for women who received chest or axillary irradiation. Referral to a breast specialist should be considered. Both NCCN and the American Cancer Society Guidelines also recommend breast MRI in addition to mammography for women who received chest irradiation between 10 and 30 years of age.<sup>282,369</sup>
      - 2) Routine surveillance tests for cervical, colorectal, endometrial, lung and prostate cancer should be performed according to the appropriate NCCN Guidelines® for Detection, Prevention and Risk Reduction as well as the appropriate American Cancer Society Guidelines.
  - 2. Cardiovascular disease<sup>282,289,365,367,370,371</sup>
    - a. The greatest risk factors for cardiovascular disease are mediastinal radiation and anthracycline-based chemotherapy.<sup>372</sup>
    - b. Radiation- and anthracycline-induced cardiovascular toxicity is usually observed > 5-10 years after treatment and often manifests as congestive heart failure that is considered irreversible.
    - c. The development of cardiac disease may be asymptomatic. Annual blood pressure monitoring, even in asymptomatic individuals is recommended.<sup>373</sup>
    - d. Aggressive management of other cardiac risk factors, including serum cholesterol, smoking status, hypertension, diabetes, pre-existing heart failure and/or coronary atherosclerotic disease should be optimally managed.<sup>370</sup>
    - e. A stress test or echocardiogram should be considered at 10-year intervals after the completion of treatment. A carotid ultrasound should also be considered at 10-year intervals in patients who received radiation to the neck.

3. Hypothyroidism<sup>282,287</sup>
  - a. Hypothyroidism is reported in approximately 50% of long-term survivors who received neck or upper mediastinal irradiation.
  - b. A thyroid examination and thyroid function tests should be performed annually, particularly in patients who received radiation therapy to the neck.
4. Infections – this may be related to splenectomy and/or splenic radiation as part of treatment.<sup>365</sup>
5. Fertility issues – refer to sections in Bladder, Renal and Testicular Cancers and Breast Cancer materials.
6. Vaccines – refer to section in Cancer-Related Infections Diseases.
7. Other general survivorship strategies include:
  - a. Counseling on health habits
  - b. Psychosocial counseling, including an assessment for emotional distress, depression and/or anxiety<sup>290</sup>
  - c. Skin cancer risk counseling
  - d. End-of-treatment discussion
  - e. Consider referral to a survivorship clinic, if available
  - f. Annual influenza vaccine and other vaccines as clinically appropriate

**Patient Case #1, Continued:**

**Correct answer = D (Proceed with chemotherapy at full doses).**

According to the NCCN Guidelines®, leukopenia is not a risk factor for reduction of dose intensity. Likewise, the routine use of growth factors is not recommended for patients with CHL, except in patients receiving BEACOPP (escalated).

## EXTRAVASATIONS

### **Patient Case #1:**

KU has just completed her ABVD infusions and comments that she feels some warmth and burning around her central line site. Since KU's infusions are completed, it is unclear which agent(s) may have extravasated.

**How should extravasation antidotes be directed in this case?**

- A. Treat the anthracycline extravasation**
- B. Treat the vinca alkaloid extravasation**
- C. Treat both the anthracycline and vinca alkaloid extravasations**
- D. Treatment is not necessary since extravasation has not been definitively confirmed**

### **I. Definitions<sup>374-376</sup>**

- A. Extravasation: the inadvertent instillation or leakage of a cytotoxic drug into the perivascular space during infusion.
- B. Irritant
  - 1. Short-term injury; does not lead to tissue injury / necrosis.
  - 2. May induce a local inflammatory reaction.
  - 3. Vein may be tender and have burning and erythema.
  - 4. Blood return remains intact.
- C. Vesicant
  - 1. Severe local or extensive tissue necrosis – joints and tendons may also be involved.
  - 2. Symptoms may not appear for up to 6 to 12 hours after extravasation.
  - 3. Patients may initially complain of pruritus without pain.
  - 4. Erythema and blistering of tissue surrounding area of extravasation.
  - 5. Damage depends on the drug, volume extravasated, concentration of solution, site of infiltration, length of drug exposure, and measures taken to treat once infiltration occurs
  - 6. Blood return is absent.
  - 7. Can be classified as DNA binding and DNA non-binding vesicants.<sup>377-380</sup>
    - a. DNA binding vesicants have the ability to bind to the nucleic acids in DNA, as well as to the DNA in the cells of healthy adjacent tissue. This leads to prompt cell death and may result in a continuing cycle of tissue damage as the drug is retained in the tissue and recirculated into the surrounding area.
      - 1) If left untreated, extravasation of these agents can lead to injuries that become larger in size, deeper in depth and more painful.



- 2) Agents in this category include dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mechlorethamine, mitomycin and mitoxantrone. Anthracyclines have the greatest vesicant potential when compared to other chemotherapy agents.<sup>376,380</sup>
- b. DNA non-binding vesicants have an indirect effect on the cells in the healthy tissue. These compounds are eventually metabolized by the tissue and are more easily neutralized than those agents that bind to DNA.
- 1) Any injury remains localized and is mild to moderately painful, but improves over time.
  - 2) Agents include the plant alkaloids: amsacrine, docetaxel, paclitaxel, trabectedin, vinblastine, vincristine, vindesine and vinorelbine.
- D. The distinction between a vesicant and an irritant is not absolute; a chemotherapeutic drug can exhibit characteristics of both. It has been suggested that irritants can display vesicant-like properties with increasing amounts of extravasation.<sup>381</sup>

**Irritant and vesicant properties of anticancer agents.**<sup>374-378,382-386</sup>

***\*Agents not listed in this table have no documented irritant/vesicant properties.***

Drug	Irritant	Vesicant	Other Information
Ado-trastuzumab	Yes	?	Case reports of skin necrosis after extravasation <sup>387</sup>
Arsenic trioxide	?	No	Conflicting data on being an irritant
Bendamustine	Yes	No	Co-administration of D5W decreases infusion pain <sup>388</sup>
Bevacizumab	Yes	?	
Bleomycin	?	No	Conflicting data on being an irritant
Brentuximab vedotin	?	Yes	Conflicting data on being an irritant
Busulfan	?	No	Conflicting data on being an irritant
Cabazitaxel	Yes	No	
Carboplatin	Yes	No	≥ 10 mg/mL
Carfilzomib	Yes	No	Venous irritation rare
Carmustine	Yes	Yes	
Cisplatin	Yes	Yes/No	Vesicant if >20 mL of a 0.5 mg/mL solution infiltrates
Cyclophosphamide	?	No	Conflicting data on being an irritant
Cytarabine-daunorubicin, liposomal (CPX-351)	Yes	?	Conflicting data on being a vesicant <sup>381</sup>
Dacarbazine	Yes	No	
Dactinomycin	No	Yes	
Daunorubicin	No	Yes	
Daunorubicin, liposomal	?	No	Conflicting data on being an irritant
Denileukin diftitox	Yes	No	
Dexrazoxane	Yes	No	
Docetaxel	?	?	Conflicting data on being an irritant Has been reported as a vesicant
Doxorubicin	Yes	Yes	
Doxorubicin, liposomal	?	No	Conflicting data on being an irritant
Epirubicin	No	Yes	
Etoposide	Yes	No	Vesicant treatment required if a large volume infiltrates
Etoposide phosphate	Yes	No	

Drug	Irritant	Vesicant	Other Information
Floxuridine	?	No	Conflicting data on being an irritant
Fluorouracil	?	No	Conflicting data on being an irritant
Gemcitabine	Yes	No	Co-administration of D5W decreases infusion pain <sup>389</sup>
Idarubicin	No	Yes	
Ifosfamide	?	No	Conflicting data on being an irritant
Ipilimumab	No	No	
Irinotecan	?	No	Conflicting data on being an irritant
Ixabepilone	Yes	No	
Mechlorethamine	No	Yes	
Melphalan	Yes	No	
Mitomycin	No	Yes	
Mitoxantrone	Yes	Yes	Higher concentrations can cause ulcerations
Nelarabine	Yes	No	
Oxaliplatin	Yes	?	Has been reported as a vesicant
Paclitaxel, conventional	No	Yes	Weak vesicant
Paclitaxel, albumin-bound	Yes	No	
Streptozocin	Yes	Yes	
Temsirolimus	No	No	
Teniposide	Yes	Yes	Vesicant treatment required if a large volume infiltrates
Thiotepa	?	No	Conflicting data on being an irritant
Topotecan	?	No	Conflicting data on being an irritant
Trabectedin	No	Yes	
Trastuzumab emtansine	Yes	No	
Triptorelin	Yes	No	
Vinblastine	No	Yes	
Vincristine	No	Yes	
Vincristine, Liposomal	Yes	No	
Vindesine	No	Yes	
Vinorelbine	Yes	Yes	Flush line with $\geq 75$ to 124 mL of IV fluid <sup>390</sup>

## II. Prevention<sup>376,380,384,391</sup>

- A. Use of central catheters has decreased the incidence of extravasation injuries, however extravasation can still occur if the line is not positioned appropriately.
- B. Patient education is a crucial step in prevention, since the patient is the first to feel any symptoms and is relied upon to report them.
- C. Careful administration with required checking of blood return frequently throughout administration period is necessary.
- D. IV site(s) should be started as distant from the hand, dorsum of the foot, and any joint space as possible (order of preference: forearm → dorsum of hand → wrist → antecubital fossa).
  1. Do not administer chemotherapy distal to a recent venipuncture site as extravasation may occur where vein was previously punctured.

2. Consider using hot compress to dilate vein prior to drug administration.
3. Bolus doses of irritant / vesicant chemotherapy should be given over 5-10 minutes through a free-flowing IV line. Administration of vinca alkaloids using a mini-bag did not show increased risk of extravasation versus syringe administration and prevents inadvertent intrathecal administration.<sup>392</sup>
4. Educate the patient to report any pain, burning, edema, swelling, tingling, or itching (all of which could be signs of extravasation).
5. Monitor IV site frequently during infusion and flush line between bolus injections and at end of chemotherapy administration.

### III. Treatment / Management<sup>375-377,380,382,384,386,391,393,394</sup>

- A. No studies have compared the various methods for treating extravasation. There is no universal or evidence-based data regarding course of action, antidotes or surgical intervention.
- B. General management protocol
  1. Stop the infusion immediately.
  2. Leave the venous access device in place.
  3. Elevate and immobilize the affected limb, if possible.
  4. Aspirate any drug via the intravenous cannula using a sterile syringe.
  5. Do not flush the line.
  6. Remove the catheter / needle.
  7. Apply cold or warm packs as recommended.
    - a. Heat is indicated for non-DNA binding agents such as vinca alkaloids and epipodophyllotoxins, but there is conflicting data on taxanes. Local warming increases blood flow to the area, which helps to distribute the extravasated vesicant and prompts its absorption.
    - b. For DNA binding agents, cooling may be effective. Constriction of blood vessels helps to prevent the vesicant from spreading to adjacent tissues. One report showed that 89% of extravasations treated with topical cold required no further treatment.<sup>395</sup>
  8. If antidote is available, instill through a different intravenous access site.
  9. Photograph the site with the extravasation area marked with a permanent marker.
  10. Inform and instruct the patient and caregivers.
  11. Administer pain relief if indicated.
  12. Monitor site closely for 24 hours, at 1 and 2 weeks and then as necessary for redness, swelling, pain, ulceration and/or necrosis.
  13. Consult plastic surgery and other supportive care services as appropriate. Soft-tissue reconstruction following extravasation of chemotherapeutic agents may be required.
  14. Assess and document the incident in healthcare records as appropriate.
- C. Patient and caregiver instructions<sup>394</sup>
  1. Monitor the affected area for any changes.

2. Avoid touching the affected area or touch the area as little as possible. Wear loose clothing around the area when possible.
3. Protect the area from sunlight.
4. Raise the injured area, if possible and if this helps with comfort.
5. Move and exercise the area gently.
6. Do not use any creams or other topical treatments on the area other than those prescribed.

#### D. Antidotes

##### 1. Dexrazoxane (Totect®)

- a. Dosing: 1000 mg/m<sup>2</sup> (maximum 2000 mg/dose) IV within 6 hours of extravasation followed by 1000 mg/m<sup>2</sup> (maximum 2000 mg/dose) on day 2 and 500 mg/m<sup>2</sup> (maximum 1000 mg/dose) on day 3 has been beneficial for anthracycline extravasation.<sup>383</sup>
- b. Must start no more than 6 hours after the extravasation occurs; ideally, administer as soon as possible.
- c. Clinical studies<sup>396</sup>
  - 1) Patients with fluorescence-positive tissue biopsies received IV dexrazoxane using a different venous access point. In 98.2% of patients (53/54) who were evaluable for efficacy, the treatment successfully prevented surgery for necrosis. 71% (38) patients were able to continue their chemotherapy on schedule.
  - 2) FDA-approved for the treatment of extravasations due to anthracyclines.
  - 3) In patients with CrCl < 40 mL/minute, decrease the dose by 50%.
  - 4) Cool packs should be removed for at least 15 minutes prior to and during treatment.

##### 2. Dimethyl sulfoxide (DMSO)

- a. Topical applied solvent that increases permeability of skin, promoting the absorption of extravasated vesicants, in addition to being a free radical scavenger.
- b. 99% DMSO (15 ml) was given every 6 hours for 14 days, and ulceration did not develop in any of the 16 patients.<sup>397</sup>
- c. 99% DMSO every 8 hours for 7 days plus cold packs for one hour three times a day were used in 52 patients. Ulceration was prevented in 51 patients.<sup>398</sup>
- d. The optimal dose and schedule of administration is not known. However, based on the two studies above, DMSO does seem effective (efficacy rate of 98 to 100% versus historical reports of cooling alone at 72%). A literature review recommended two applications of DMSO 99% to be applied four times daily for at least 7 days.
- e. Toxicities are generally mild, reversible and include burning sensation, blistering, followed by itch, erythema and superficial scaling.
- f. DMSO > 50% is not available for human use in the United States for this indication, but may be available at centers processing stem cells for HSCT.
- g. DO NOT use concurrently with dexrazoxane.

##### 3. Hyaluronidase is an adjuvant to cause dispersion and absorption of injected drugs.<sup>375,391</sup>

- a. Accelerates local connective tissue breakdown and absorption of the extravasated alkaloid.
  - b. Can be used as an antidote for plant alkaloid (vinca and taxane) extravasations.
  - c. Dilute 150 units with 1 mL 0.9% NS and inject 1 mL of resultant solution into cannula for each 1 mL of estimated infiltrated drug (maximum of 6 mL total) or administer as 5 separate 0.2 mL injections via a 24-gauge or smaller needle in infiltration site.
  - d. Change the needle with each injection.
4. Sodium thiosulfate
- a. Injected directly into area of extravasation caused by alkylating agents (see table below).
  - b. Thiosulfate treated lesions healed in 5 days versus 21 days for steroid treatment.
  - c. Suggested antidote for mechlorethamine, although there is very scant clinical evidence to support this practice. The recommended administration is to subcutaneously inject 2 mL of solution for each mg of mechlorethamine extravasated.
- C. Early surgery for minimizing the injury followed by skin grafting has reduced the extent of later injury; however, residual damage may still be evident.

**Recommended extravasation antidotes.**<sup>376,382,383,391</sup>

Drug	Local Antidote Recommendations
Anthracyclines (doxorubicin, daunorubicin)	Dexrazoxane (preferred) and <b>cold</b> compress or DMSO 50-99% (w/v) topical solution  Local <b>cold</b> compresses (such as dry cold packs) should be applied topically for the first hour and then in cycles of 15-20 minutes 3-4 daily for 2-3 days
Cisplatin	1/6 or 1/3 molar sodium thiosulfate
Etoposide, teniposide	<b>Warm</b> compress
Bendamustine, mechlorethamine	DMSO 50-99% (w/v) topical solution or 1/6 molar sodium thiosulfate solution
Mitomycin	DMSO 50-99% (w/v) topical solution
Oxaliplatin	<b>Warm</b> compress as cold may precipitate or worsen the cold neuropathy
Taxanes (docetaxel, paclitaxel)	Hyaluronidase (mouse study) and cold compress
Vinca alkaloids (vinblastine, vincristine, vinorelbine)	Hyaluronidase, normal saline, and <b>warm</b> compress  Local dry heat compresses (such as dry heat packs or electric pads should be topically applied for 15-20 minutes 3-4 times per day for 2 days

**Patient Case #1, Continued:**

**Correct answer = A (treat the anthracycline extravasation).**

ABVD contains both an anthracycline and a vinca alkaloid. In this case, it is impossible to determine which agent has extravasated; treatment should be aimed at the anthracycline since this is more severe of the two. It would not be possible to treat both an anthracycline and vinca alkaloid extravasation simultaneously, since both cold and warm compresses would be needed. Withholding treatment for a suspected extravasation would not be appropriate.

## **RECOMMENDED READINGS AND REFERENCES**

### **RECOMMENDED READINGS – NON-HODGKIN LYMPHOMA**

1. Dada R. Diagnosis and management of follicular lymphoma: a comprehensive review. *Eur J Hematol*. 2019; 103: 152-63. Available at <https://pubmed.ncbi.nlm.nih.gov/31270855/>.
2. Sehn LH and Salles G. Diffuse large B-cell lymphoma. *N Eng J Med*. 2021; 384: 9. Available at <https://pubmed.ncbi.nlm.nih.gov/33657296/>.
3. Armitage JO and Longo DL. Mantle-cell lymphoma. *N Eng J Med*. 2022;386:2495-506. Available at <https://pubmed.ncbi.nlm.nih.gov/35767440/>.
4. Roschewski M, Staudt LM, Wilson WH. Burkitt's lymphoma. *N Eng J Med*. 2022;12:1111-22. Available at <https://pubmed.ncbi.nlm.nih.gov/36129999/>.
5. Sethi TK, Montanari F, Foss F, Reddy N. How we treat advanced stage cutaneous T-cell lymphoma - mycosis fungoides and Sezary syndrome. *Br J Haematol*. 2021;195:352-64. Available at <https://pubmed.ncbi.nlm.nih.gov/33987825/>.
6. Wudhikarn K and Bennani NN. How to sequence therapies in peripheral T cell lymphoma. *Curr Treat Options in Oncology*. 2021; 22: 74. Available at <https://pubmed.ncbi.nlm.nih.gov/34213653/>.

### **RECOMMENDED READINGS – HODGKIN LYMPHOMA**

1. Brice P, de Kerviler E, Friedberg JW. Classical Hodgkin lymphoma. *Lancet*. 2021;S0140-6736(20)32207-8. Available at <https://pubmed.ncbi.nlm.nih.gov/33493434/>.
2. Eichenauer DA and Engert A. Current treatment options for nodular lymphocyte-predominant Hodgkin lymphoma. *Curr Opin Oncol*. 2021;33:395-9. Available at <https://pubmed.ncbi.nlm.nih.gov/34224482/>.

### **RECOMMENDED READINGS – EXTRAVASATIONS**

1. Doolittle D. Closing the knowledge gap on extravasation. *Pharmacy Practice News*. 2022. Available at <https://www.pharmacypracticenews.com/Clinical/Article/04-22/Closing-the-Knowledge-Gap-On-Extravasation-/66553>.

## **REFERENCES**

1. Ladetto M, Buske C, Hutchings M, et al. ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Mar 27 2017;doi:10.1093/annonc/mdx061
2. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. Jul 2022;36(7):1720-1748. doi:10.1038/s41375-022-01620-2
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas. V.5.2022, 7/12/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
4. Freedman A, Jacobsen E. Follicular lymphoma: 2020 update on diagnosis and management. *Am J Hematol*. Mar 2020;95(3):316-327. doi:10.1002/ajh.25696

5. Lumish M, Falchi L, Imber BS, Scordo M, von Keudell G, Joffe E. How we treat mature B-cell neoplasms (indolent B-cell lymphomas). *J Hematol Oncol*. Jan 6 2021;14(1):5. doi:10.1186/s13045-020-01018-6
6. Cartron G, Trotman J. Time for an individualized approach to first-line management of follicular lymphoma. *Haematologica*. Jan 1 2022;107(1):7-18. doi:10.3324/haematol.2021.278766
7. Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin-containing regimen with or without interferon alfa-2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 1998;16(7):2332-8.
8. Boughan KM, Caimi PF. Follicular Lymphoma: Diagnostic and Prognostic Considerations in Initial Treatment Approach. *Curr Oncol Rep*. May 23 2019;21(7):63. doi:10.1007/s11912-019-0808-0
9. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. Sep 1 2004;104(5):1258-65. doi:10.1182/blood-2003-12-4434
10. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 20 2009;27(27):4555-62. doi:10.1200/JCO.2008.21.3991
11. Casulo C. How I manage patients with follicular lymphoma. *British journal of haematology*. Jun 7 2019;doi:10.1111/bjh.16011
12. Sutamtewagul G, Link BK. Novel treatment approaches and future perspectives in follicular lymphoma. *Ther Adv Hematol*. 2019;10:2040620718820510. doi:10.1177/2040620718820510
13. Dada R. Diagnosis and management of follicular lymphoma: A comprehensive review. *European journal of haematology*. Sep 2019;103(3):152-163. doi:10.1111/ejh.13271
14. Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. *Blood*. Apr 28 2016;127(17):2055-63. doi:10.1182/blood-2015-11-624288
15. Matasar MJ, Luminari S, Barr PM, et al. Follicular Lymphoma: Recent and Emerging Therapies, Treatment Strategies, and Remaining Unmet Needs. *Oncologist*. Nov 2019;24(11):e1236-e1250. doi:10.1634/theoncologist.2019-0138
16. Apostolidis J, Mokhtar N, Al Omari R, Darweesh M, Al Hashmi H. Follicular lymphoma: Update on management and emerging therapies at the dawn of the new decade. *Hematol Oncol*. Aug 2020;38(3):213-222. doi:10.1002/hon.2711
17. Becnel MR, Nastoupil LJ. Follicular Lymphoma: Past, Present, and Future. *Curr Treat Options Oncol*. May 24 2018;19(7):32. doi:10.1007/s11864-018-0550-0
18. Sorigue M, Sancho JM. Recent landmark studies in follicular lymphoma. *Blood Rev*. May 2019;35:68-80. doi:10.1016/j.blre.2019.03.006
19. Northend M, Townsend W. Novel Therapy Approaches to Follicular Lymphoma. *Drugs*. Mar 2021;81(4):453-469. doi:10.1007/s40265-020-01446-1
20. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1996;14(4):1282-90.
21. Seng JE, Peterson BA. Indolent B-cell non-Hodgkin's lymphomas. *Oncology*. Dec 1997;11(12):1883-94, 1987; discussion 1901-2, 1.
22. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 15 2004;22(8):1454-9. doi:10.1200/JCO.2004.10.086
23. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. *Lancet*. Jul 15 2017;390(10091):298-310. doi:10.1016/S0140-6736(16)32407-2
24. Michallet AS, Lebras LL, Bauwens DD, et al. Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? *J Hematol Oncol*. 2013;6:45. doi:10.1186/1756-8722-6-45
25. Cahill KE, Smith SM. Follicular Lymphoma: a Focus on Current and Emerging Therapies. *Oncology*. Feb 8 2022;36(2):97-106. doi:10.46883/2022.25920946  
10.46883.2022.25920946
26. El-Galaly TC, Bilgrau AE, de Nully Brown P, et al. A population-based study of prognosis in advanced stage follicular lymphoma managed by watch and wait. *British journal of haematology*. May 2015;169(3):435-44. doi:10.1111/bjh.13316

27. Young RC, Longo DL, Glatstein E, Ihde DC, Jaffe ES, DeVita VT, Jr. The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. *Seminars in hematology*. Apr 1988;25(2 Suppl 2):11-6.
28. Ardeschna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*. Aug 16 2003;362(9383):516-22.
29. Solal-Celigny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 1 2012;30(31):3848-53. doi:10.1200/JCO.2010.33.4474
30. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. Apr 6 2013;381(9873):1203-10. doi:10.1016/S0140-6736(12)61763-2
31. Rummel MJ, Maschmeyer G, Ganser A, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: nine-year updated results from the StiL NHL1 study. *American Society of Clinical Oncology Annual Meeting*. 2017;
32. Flinn IW, van der Jagt R, Kahl B, et al. First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 20 2019;37(12):984-991. doi:10.1200/JCO.18.00605
33. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. Dec 1 2005;106(12):3725-32. doi:10.1182/blood-2005-01-0016
34. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. Feb 15 2005;105(4):1417-23. doi:10.1182/blood-2004-08-3175
35. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 1 2008;26(28):4579-86. doi:10.1200/JCO.2007.13.5376
36. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. *The New England journal of medicine*. Sep 6 2018;379(10):934-947. doi:10.1056/NEJMoa1805104
37. Hainsworth JD, Burris HA, 3rd, Morrissey LH, et al. Rituximab monoclonal antibody as initial systemic therapy for patients with low-grade non-Hodgkin lymphoma. *Blood*. May 15 2000;95(10):3052-6.
38. Ardeschna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol*. Apr 2014;15(4):424-35. doi:10.1016/S1470-2045(14)70027-0
39. Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study. *American Society of Hematology Annual Meeting & Exposition*. 2016:Session 6.
40. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *The New England journal of medicine*. Oct 5 2017;377(14):1331-1344. doi:10.1056/NEJMoa1614598
41. Armitage JO, Longo DL. Which Anti-CD20 Antibody Is Better in Follicular Lymphoma? *The New England journal of medicine*. Oct 5 2017;377(14):1389-1390. doi:10.1056/NEJMe1706154
42. Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 10 2018;36(23):2395-2404. doi:10.1200/JCO.2017.76.8960
43. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections. V.1.2022, 06/2/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN



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44. Zhang L, Ghielmini M, Cheson BD, Ujjani C. Pros and cons of rituximab maintenance in follicular lymphoma. *Cancer treatment reviews*. Jul 2017;58:34-40. doi:10.1016/j.ctrv.2017.05.007
45. Golfier C, Salles G. Antibody Therapy Maintenance in Follicular Lymphoma. *Hematol Oncol Clin North Am*. Aug 2020;34(4):689-699. doi:10.1016/j.hoc.2020.02.005
46. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1 2009;27(10):1607-14. doi:10.1200/JCO.2008.17.1561
47. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. Jan 1 2011;377(9759):42-51. doi:10.1016/S0140-6736(10)62175-7
48. Salles GA, Seymour JF, Feugier P, al. e. Long-term follow-up of the PRIMA study: half of patients receiving rituximab maintenance remain progression free at 10 years. *Blood* 2017;130:486.
49. Bachy E, Seymour JF, Feugier P, et al. Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 1 2019;37(31):2815-2824. doi:10.1200/JCO.19.01073
50. Witzens-Harig M, Foa R, Di Rocco A, et al. Maintenance with rituximab is safe and not associated with severe or uncommon infections in patients with follicular lymphoma: results from the phase IIIb MAXIMA study. *Ann Hematol*. Oct 2014;93(10):1717-24. doi:10.1007/s00277-014-2103-3
51. Patel J, Ho M, Ho V, et al. Rapid infusion rituximab for maintenance therapy: is it feasible? *Leuk Res Treatment*. 2013;2013:629283. doi:10.1155/2013/629283
52. Kahl B, Hong F, Peterson C, al. e. Long Term Follow up of the Resort Study (E4402): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Follicular Lymphoma. *Blood*. 2021;138:815.
53. Casulo C. Treatment of Histologic Transformation. *Hematol Oncol Clin North Am*. Aug 2020;34(4):785-794. doi:10.1016/j.hoc.2020.03.001
54. Smith S. Transformed lymphoma: what should I do now? *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. Dec 4 2020;2020(1):306-311. doi:10.1182/hematology.2020000115
55. Casulo C, Barr PM. How I treat early-relapsing follicular lymphoma. *Blood*. Apr 4 2019;133(14):1540-1547. doi:10.1182/blood-2018-08-822148
56. Welaya K, Casulo C. Follicular Lymphoma: Redefining Prognosis, Current Treatment Options, and Unmet Needs. *Hematol Oncol Clin North Am*. Aug 2019;33(4):627-638. doi:10.1016/j.hoc.2019.03.003
57. Lipof JJ, Barr PM. Early Progression of Follicular Lymphoma: Biology and Treatment. *Hematol Oncol Clin North Am*. Aug 2020;34(4):757-769. doi:10.1016/j.hoc.2020.02.009
58. Bachy E, Rufibach K, Parreira J, Launonen A, Nielsen T, Hackshaw A. Phase III Clinical Trials in First-Line Follicular Lymphoma: A Review of Their Design and Interpretation. *Adv Ther*. Jul 2021;38(7):3489-3505. doi:10.1007/s12325-021-01738-2
59. Nogueira DS, Lage L, Culler HF, Pereira J. Follicular Lymphoma: Refining Prognostic Models and Impact of Pod-24 in Clinical Outcomes. *Clinical lymphoma, myeloma & leukemia*. Feb 2022;22(2):67-75. doi:10.1016/j.clml.2021.08.004
60. Rodgers TD, Casulo C, Boissard F, Launonen A, Parreira J, Cartron G. Early Relapse in First-Line Follicular Lymphoma: A Review of the Clinical Implications and Available Mitigation and Management Strategies. *Oncol Ther*. Dec 2021;9(2):329-346. doi:10.1007/s40487-021-00161-5
61. Salles G. How do I sequence therapy for follicular lymphoma? *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. Dec 4 2020;2020(1):287-294. doi:10.1182/hematology.2020000156
62. Gabellier L, Cartron G. Obinutuzumab for relapsed or refractory indolent non-Hodgkin's lymphomas. *Ther Adv Hematol*. Apr 2016;7(2):85-93. doi:10.1177/2040620715622613

63. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol*. Aug 2016;17(8):1081-93. doi:10.1016/S1470-2045(16)30097-3
64. ASH Clinical News. Gilead Withdraws Idelalisib to Treat FL. Available at <https://ashpublications.org/ashclinicalnews/news/6128/Gilead-Withdraws-Idelalisib-to-Treat-FL?searchresult=1>. Accessed June 29, 2022.
65. Federal Register. Secura Bio, Inc.; Withdrawal of Approval of Relapsed or Refractory Follicular Lymphoma Indication for COPIKTRA. Available at <https://www.federalregister.gov/documents/2022/04/13/2022-07931/secura-bio-inc-withdrawal-of-approval-of-relapsed-or-refractory-follicular-lymphoma-indication-for>. Accessed June 14, 2022.
66. U.S. Food and Drug Administration. FDA approval of lymphoma medicine Ukonig (umbralisib) is withdrawn due to safety concerns. Available at [https://www.fda.gov/drugs/drug-safety-and-availability/fda-approval-lymphoma-medicine-ukonig-umbralisib-withdrawn-due-safety-concerns#:~:text=6%2D1%2D2022%20FDA%20Drug,and%20follicular%20lymphoma%20\(FL\)](https://www.fda.gov/drugs/drug-safety-and-availability/fda-approval-lymphoma-medicine-ukonig-umbralisib-withdrawn-due-safety-concerns#:~:text=6%2D1%2D2022%20FDA%20Drug,and%20follicular%20lymphoma%20(FL)). Accessed June 29, 2022.
67. U.S. Food and Drug Administration. FDA granted accelerated approval to tazemetostat for follicular lymphoma. Available at <https://www.fda.gov/drugs/fda-granted-accelerated-approval-tazemetostat-follicular-lymphoma#:~:text=On%20June%2018%2C%202020%2C%20the,approved%20test%20and%20who%20have>. Accessed July 2, 2020.
68. Lymphoma Hub. Phase II study update of tazemetostat in patients with relapsed/refractory follicular lymphoma. Available at <https://lymphomahub.com/medical-information/phase-ii-study-update-of-tazemetostat-in-patients-with-relapsedrefractory-follicular-lymphoma>. Accessed July 2, 2020.
69. Tazverik [prescribing information]. Cambridge, MA: Epizyme, Inc., 2020.
70. von Keudell G, Salles G. The role of tazemetostat in relapsed/refractory follicular lymphoma. *Ther Adv Hematol*. 2021;12:20406207211015882. doi:10.1177/20406207211015882
71. Morin RD, Arthur SE, Assouline S. Treating lymphoma is now a bit EZ-er. *Blood Adv*. Apr 27 2021;5(8):2256-2263. doi:10.1182/bloodadvances.2020002773
72. Lynch RC, Gratzinger D, Advani RH. Clinical Impact of the 2016 Update to the WHO Lymphoma Classification. *Curr Treat Options Oncol*. Jul 2017;18(7):45. doi:10.1007/s11864-017-0483-z
73. Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *The New England journal of medicine*. Apr 12 2018;378(15):1396-1407. doi:10.1056/NEJMoa1801445
74. Dunleavy K, Gross TG. Management of aggressive B-cell NHLs in the AYA population: an adult vs pediatric perspective. *Blood*. Jul 26 2018;132(4):369-375. doi:10.1182/blood-2018-02-778480
75. Thieblemont C, Bernard S, Meignan M, Molina T. Optimizing initial therapy in DLBCL. *Best Pract Res Clin Haematol*. Sep 2018;31(3):199-208. doi:10.1016/j.beha.2018.08.001
76. Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. *Am J Hematol*. May 2019;94(5):604-616. doi:10.1002/ajh.25460
77. Kesavan M, Eyre TA, Collins GP. Front-Line Treatment of High Grade B Cell Non-Hodgkin Lymphoma. *Curr Hematol Malig Rep*. Aug 2019;14(4):207-218. doi:10.1007/s11899-019-00518-8
78. Di M, Huntington SF, Olszewski AJ. Challenges and Opportunities in the Management of Diffuse Large B-Cell Lymphoma in Older Patients. *Oncologist*. Feb 2021;26(2):120-132. doi:10.1002/onco.13610
79. Allen P. Diffuse Large B-Cell Lymphoma in the Elderly: Current Approaches. *Curr Oncol Rep*. Aug 22 2020;22(11):114. doi:10.1007/s11912-020-00976-x
80. Lodhi N, Tun M, Nagpal P, et al. Biomarkers and novel therapeutic approaches for diffuse large B-cell lymphoma in the era of precision medicine. *Oncotarget*. Nov 3 2020;11(44):4045-4073. doi:10.18632/oncotarget.27785
81. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. *The New England journal of medicine*. Mar 4 2021;384(9):842-858. doi:10.1056/NEJMra2027612
82. Alduaij W, Collinge BJ, Ben-Neriah S, et al. Molecular Determinants of Clinical Outcomes In a Real-World Diffuse Large B-cell Lymphoma Population. *Blood*. Oct 27 2022;doi:10.1182/blood.2022018248
83. Stephens DM, Sweetenham JW. Clinical controversies of double-hit lymphoma. *American Journal of Hematology / Oncology*. 2015;11:10-16.
84. Goyal G, Caponetti GC, Silberstein PT. Double-Hit Lymphoma. *J Clin Exp Hematop*. 2015;55(1):51-3. doi:10.3960/jslrt.55.51

85. Dunleavy K. Double-hit lymphomas: current paradigms and novel treatment approaches. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. Dec 05 2014;2014(1):107-12. doi:10.1182/asheducation-2014.1.107
86. Friedberg JW. How I treat double-hit lymphoma. *Blood*. Aug 3 2017;130(5):590-596. doi:10.1182/blood-2017-04-737320
87. Gordon MJ, Westin JR. Fitting double-hit lymphoma into the aggressive lymphoma spectrum: a square peg in a round hole? *Leukemia & lymphoma*. May 2022;63(5):1034-1044. doi:10.1080/10428194.2021.2008383
88. Ok CY, Medeiros LJ. High-grade B-cell lymphoma: a term re-purposed in the revised WHO classification. *Pathology*. Jan 2020;52(1):68-77. doi:10.1016/j.pathol.2019.09.008
89. Lap CJ, Nassereldine S, Dunleavy K. Novel Biological Insights and New Developments in Management of Burkitt Lymphoma and High-Grade B-Cell Lymphoma. *Curr Treat Options Oncol*. Jun 7 2021;22(7):60. doi:10.1007/s11864-021-00857-w
90. Puckrin R, El Darsa H, Ghosh S, Peters A, Owen C, Stewart D. Ineffectiveness of high-dose methotrexate for prevention of CNS relapse in diffuse large B-cell lymphoma. *Am J Hematol*. Jul 1 2021;96(7):764-771. doi:10.1002/ajh.26181
91. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 10 2017;35(20):2260-2267. doi:10.1200/JCO.2017.72.2157
92. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: Definition and treatment. *Cancer*. Dec 15 2018;124(24):4622-4632. doi:10.1002/cncr.31646
93. Davies A. Double-hit lymphoma: So what? *Hematol Oncol*. Jun 2019;37 Suppl 1:19-23. doi:10.1002/hon.2581
94. Jakobsen LH, Bogsted M, Brown PN, et al. Minimal Loss of Lifetime for Patients With Diffuse Large B-Cell Lymphoma in Remission and Event Free 24 Months After Treatment: A Danish Population-Based Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 2017;35(7):778-784. doi:10.1200/JCO.2016.70.0765
95. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *The New England journal of medicine*. Sep 30 1993;329(14):987-94. doi:10.1056/NEJM199309303291402
96. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 10 2010;28(14):2373-80. doi:10.1200/JCO.2009.26.2493
97. Zhang XY, Collins GP, Cutter DJ, Eyre TA. Limited-stage diffuse large B-cell lymphoma: current management and challenges. *British journal of haematology*. Aug 2021;194(3):508-517. doi:10.1111/bjh.17359
98. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 10 2008;26(14):2258-63. doi:10.1200/JCO.2007.13.6929
99. Miller TP, Dahlberg S, Cassady JR, et al. *Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma*. vol 339. The New England journal of medicine. 1998:21-6.
100. Stephens DM, Li H, LeBlanc ML, et al. Continued Risk of Relapse Independent of Treatment Modality in Limited-Stage Diffuse Large B-Cell Lymphoma: Final and Long-Term Analysis of Southwest Oncology Group Study S8736. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 01 2016;34(25):2997-3004. doi:10.1200/JCO.2015.65.4582
101. Poeschel V, Held G, Ziepert M, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. *Lancet*. Dec 21 2019;394(10216):2271-2281. doi:10.1016/S0140-6736(19)33008-9
102. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *The New England journal of medicine*. Jan 24 2002;346(4):235-42. doi:10.1056/NEJMoa011795

103. Vose JM, Link BK, Grossbard ML, et al. Phase II study of rituximab in combination with chop chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jan 15 2001;19(2):389-97.
104. Alas S, Bonavida B. Rituximab inactivates signal transducer and activation of transcription 3 (STAT3) activity in B-non-Hodgkin's lymphoma through inhibition of the interleukin 10 autocrine/paracrine loop and results in down-regulation of Bcl-2 and sensitization to cytotoxic drugs. *Cancer research*. Jul 1 2001;61(13):5137-44.
105. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 20 2005;23(18):4117-26. doi:10.1200/JCO.2005.09.131
106. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. Sep 23 2010;116(12):2040-5. doi:10.1182/blood-2010-03-276246
107. Kwak LW, Halpern J, Olshen RA, Horning SJ. Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1990;8(6):963-77.
108. Dlugosz-Danecka M, Szmit S, Ogorka T, Skotnicki AB, Jurczak W. The average relative dose intensity of R-CHOP is an independent factor determining favorable overall survival in diffuse large B-cell lymphoma patients. *Cancer Med*. Mar 2019;8(3):1103-1109. doi:10.1002/cam4.2008
109. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood*. Apr 15 2002;99(8):2685-93.
110. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 1 2008;26(16):2717-24. doi:10.1200/JCO.2007.13.1391
111. Bartlett NL, Wilson WH, Jung SH, et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 20 2019;37(21):1790-1799. doi:10.1200/JCO.18.01994
112. Major A, Smith SM. DA-R-EPOCH vs R-CHOP in DLBCL: How do we choose? *Clin Adv Hematol Oncol*. Nov 2021;19(11):698-709.
113. Wilson WH, sin-Ho J, Pitcher BN, al. e. Phase III Randomized Study of R-CHOP Versus DA-EPOCH-R and Molecular Analysis of Untreated Diffuse Large B-Cell Lymphoma: CALGB/Alliance 50303. *Blood* 2016;128:469.
114. Mondello P, Mian M. Frontline treatment of diffuse large B-cell lymphoma: Beyond R-CHOP. *Hematol Oncol*. Oct 2019;37(4):333-344. doi:10.1002/hon.2613
115. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood*. Aug 1 2004;104(3):634-41. doi:10.1182/blood-2003-06-2095
116. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. *Blood*. Aug 1 2004;104(3):626-33. doi:10.1182/blood-2003-06-2094
117. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*. May 25 2013;381(9880):1817-26. doi:10.1016/S0140-6736(13)60313-X
118. Morrison VA, Weller EA, Habermann TM, et al. Patterns of growth factor usage and febrile neutropenia among older patients with diffuse large B-cell non-Hodgkin lymphoma treated with CHOP or R-CHOP: the Intergroup experience (CALGB 9793; ECOG-SWOG 4494). *Leukemia & lymphoma*. Aug 2017;58(8):1814-1822. doi:10.1080/10428194.2016.1265111
119. Vitolo U, Trneny M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 1 2017;35(31):3529-3537. doi:10.1200/JCO.2017.73.3402

120. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *The New England journal of medicine*. Jan 27 2022;386(4):351-363. doi:10.1056/NEJMoa2115304
121. Sun H, Savage KJ, Karsan A, et al. Outcome of Patients With Non-Hodgkin Lymphomas With Concurrent MYC and BCL2 Rearrangements Treated With CODOX-M/IVAC With Rituximab Followed by Hematopoietic Stem Cell Transplantation. *Clinical lymphoma, myeloma & leukemia*. Jun 2015;15(6):341-8. doi:10.1016/j.clml.2014.12.015
122. Nabhan C, Mato AR. Emerging Strategies in Treating Double Hit Lymphomas. *Clinical lymphoma, myeloma & leukemia*. Sep 2017;17(9):563-568. doi:10.1016/j.clml.2017.06.017
123. Villa D, Sehn LH. Double hit lymphoma: do we need a 'double hit' of intensive therapy? *Leukemia & lymphoma*. Aug 2018;59(8):1767-1768. doi:10.1080/10428194.2018.1429606
124. Merron B, Davies A. Double hit lymphoma: How do we define it and how do we treat it? *Best Pract Res Clin Haematol*. Sep 2018;31(3):233-240. doi:10.1016/j.beha.2018.07.012
125. Dunleavy K. Double-hit lymphoma: optimizing therapy. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. Dec 10 2021;2021(1):157-163. doi:10.1182/hematology.2021000247
126. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. *British journal of haematology*. Aug 2015;170(4):504-14. doi:10.1111/bjh.13463
127. Hall KH, Panjic EH, Valla K, Flowers CR, Cohen JB. How to Decide Which DLBCL Patients Should Receive CNS Prophylaxis. *Oncology*. Jun 2018;32(6):303-9.
128. Qualls D, Abramson JS. Advances in risk assessment and prophylaxis for central nervous system relapse in diffuse large B-cell lymphoma. *Haematologica*. Jan 2019;104(1):25-34. doi:10.3324/haematol.2018.195834
129. Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 10 2016;34(26):3150-6. doi:10.1200/JCO.2015.65.6520
130. Siegal T, Goldschmidt N. CNS prophylaxis in diffuse large B-cell lymphoma: if, when, how and for whom? *Blood Rev*. May 2012;26(3):97-106. doi:10.1016/j.blre.2011.12.001
131. Wilson MR, Eyre TA, Martinez-Calle N, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: an analysis of toxicity and impact on R-CHOP delivery. *Blood Adv*. Aug 11 2020;4(15):3586-3593. doi:10.1182/bloodadvances.2020002421
132. Harris LJ, Patel K, Martin M. Novel Therapies for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Int J Mol Sci*. Nov 13 2020;21(22)doi:10.3390/ijms21228553
133. Roschewski M, Longo DL, Wilson WH. CAR T-Cell Therapy for Large B-Cell Lymphoma - Who, When, and How? *The New England journal of medicine*. Feb 17 2022;386(7):692-696. doi:10.1056/NEJMe2118899
134. Kesireddy M, Lunning M. Relapsed or Refractory Diffuse Large B-Cell Lymphoma: "Dazed and Confused". *Oncology*. Jun 10 2022;36(6):366-375. doi:10.46883/2022.25920963
135. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. Oct 19 2017;130(16):1800-1808. doi:10.1182/blood-2017-03-769620
136. Davison K, Chen BE, Kukreti V, et al. Treatment outcomes for older patients with relapsed/refractory aggressive lymphoma receiving salvage chemotherapy and autologous stem cell transplantation are similar to younger patients: a subgroup analysis from the phase III CCTG LY.12 trial. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Mar 01 2017;28(3):622-627. doi:10.1093/annonc/mdw653
137. Gisselbrecht C, Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. *British journal of haematology*. May 29 2018;doi:10.1111/bjh.15412
138. Epperla N, Fenske TS, Lazarus HM, Hamadani M. Post-autologous transplant maintenance therapies in lymphoid malignancies: are we there yet? *Bone Marrow Transplant*. Aug 17 2015;doi:10.1038/bmt.2015.184
139. Moccia AA, Schaff K, Freeman C, et al. Long-term outcomes of R-CEOP show curative potential in patients with DLBCL and a contraindication to anthracyclines. *Blood Adv*. Mar 9 2021;5(5):1483-1489. doi:10.1182/bloodadvances.2020002982
140. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *The New England journal of medicine*. Feb 17 2022;386(7):640-654. doi:10.1056/NEJMoa2116133
141. Breyanzi [package insert]. Bothell, WA; Juno Therapeutics Inc., 2021.

142. Kersten MJ, Spanjaart AM, Thieblemont C. CD19-directed CAR T-cell therapy in B-cell NHL. *Curr Opin Oncol*. Sep 2020;32(5):408-417. doi:10.1097/CCO.0000000000000668
143. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet*. Jun 18 2022;399(10343):2294-2308. doi:10.1016/S0140-6736(22)00662-6
144. Monjuvi [package insert]. Boston, MA: Morphosys US Inc., 2020.
145. U.S. Food and Drug Administration. FDA grants accelerated approval to tafasitamab-cxix for diffuse large B-cell lymphoma. Available at <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-tafasitamab-cxix-diffuse-large-b-cell-lymphoma>. Accessed August 4, 2020.
146. Salles G, Duell J, Gonzalez Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. Jul 2020;21(7):978-988. doi:10.1016/S1470-2045(20)30225-4
147. Hoy SM. Tafasitamab: First Approval. *Drugs*. Nov 2020;80(16):1731-1737. doi:10.1007/s40265-020-01405-w
148. Sermer D, Batlevi C, Palomba ML, et al. Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies. *Blood Adv*. Oct 13 2020;4(19):4669-4678. doi:10.1182/bloodadvances.2020002118
149. Cappell KM, Sherry RM, Yang JC, et al. Long-Term Follow-Up of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 10 2020;38(32):3805-3815. doi:10.1200/JCO.20.01467
150. Johnson PC, Abramson JS. Patient selection for chimeric antigen receptor (CAR) T-cell therapy for aggressive B-cell non-Hodgkin lymphomas. *Leukemia & lymphoma*. Nov 2020;61(11):2561-2567. doi:10.1080/10428194.2020.1786563
151. Lee A. Loncastuximab Tesirine: First Approval. *Drugs*. Jun 18 2021;doi:10.1007/s40265-021-01550-w
152. U.S. Food and Drug Administration. FDA approves selinexor for relapsed/refractory diffuse large B-cell lymphoma. Available at <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selinexor-relapsedrefractory-diffuse-large-b-cell-lymphoma>. Accessed July 6, 2020.
153. Xpovio [prescribing information]. Newton, MA: Karyopharm Therapeutics Inc., 2020.
154. Dakhil S, Hermann R, Schreeder MT, et al. Phase III safety study of rituximab administered as a 90-minute infusion in patients with previously untreated diffuse large B-cell and follicular lymphoma. *Leukemia & lymphoma*. Oct 2014;55(10):2335-40. doi:10.3109/10428194.2013.877135
155. Sehn LH, Donaldson J, Filewich A, et al. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood*. May 15 2007;109(10):4171-3. doi:10.1182/blood-2006-11-059469
156. Salar A, Casao D, Cervera M, et al. Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. *European journal of haematology*. Oct 2006;77(4):338-40. doi:10.1111/j.1600-0609.2006.00713.x
157. Riabni [package insert]. Thousand Oaks, CA: Amgen, Inc., 2020.
158. Yelvington BJ. Subcutaneous Rituximab in Follicular Lymphoma, Chronic Lymphocytic Leukemia, and Diffuse Large B-Cell Lymphoma. *J Adv Pract Oncol*. Jul-Aug 2018;9(5):530-534.
159. U.S Food and Drug administration. FDA approves first biosimilar for treatment of adult patients with non-Hodgkin's lymphoma. Available at <https://www.fda.gov/news-events/press-announcements/fda-approves-first-biosimilar-treatment-adult-patients-non-hodgkins-lymphoma>. Accessed June 25, 2019.
160. Truxima [package insert]. Yeonsu-gu, Incheon, Republic of Korea: Celltreon, Inc., 2018.
161. Ruxience [package insert]. New York, NY: Pfizer Labs, 2019.
162. Kusumoto S, Arcaini L, Hong X, et al. Risk of HBV reactivation in patients with B-cell lymphomas receiving obinutuzumab or rituximab immunochemotherapy. *Blood*. Jan 10 2019;133(2):137-146. doi:10.1182/blood-2018-04-848044
163. Hwang JP, Feld JJ, Hammond SP, et al. Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 27 2020;JCO2001757. doi:10.1200/JCO.20.01757
164. Ross AC. The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutr*. May 2011;14(5):938-9. doi:10.1017/S1368980011000565

165. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. Oct 2014;25(10):2359-81. doi:10.1007/s00198-014-2794-2
166. Shree T, Li Q, Glaser SL, et al. Impaired Immune Health in Survivors of Diffuse Large B-Cell Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 20 2020;38(15):1664-1675. doi:10.1200/JCO.19.01937
167. McCormack PL. Bortezomib: A Review in Mantle Cell Lymphoma in Previously Untreated Patients Unsuitable for Stem-Cell Transplantation. *BioDrugs*. Jun 2015;29(3):207-14. doi:10.1007/s40259-015-0131-8
168. Chen Y, Wang M, Romaguera J. Current regimens and novel agents for mantle cell lymphoma. *British journal of haematology*. Oct 2014;167(1):3-18. doi:10.1111/bjh.13000
169. Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol*. Aug 2017;92(8):806-813. doi:10.1002/ajh.24797
170. Jain P, Wang M. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. *Am J Hematol*. Jun 2019;94(6):710-725. doi:10.1002/ajh.25487
171. Silkenstedt E, Dreyling M. Mantle cell lymphoma-Advances in molecular biology, prognostication and treatment approaches. *Hematol Oncol*. Jun 2021;39 Suppl 1:31-38. doi:10.1002/hon.2860
172. Cheah CY, Seymour JF, Wang ML. Mantle Cell Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 10 2016;34(11):1256-69. doi:10.1200/JCO.2015.63.5904
173. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. Jan 15 2008;111(2):558-65. doi:10.1182/blood-2007-06-095331
174. Smolewski P, Witkowska M, Robak T. Treatment options for mantle cell lymphoma. *Expert Opin Pharmacother*. 2015;16(16):2497-507. doi:10.1517/14656566.2015.1087507
175. Pease DF, Morrison VA. Treatment of mantle cell lymphoma in older adults. *J Geriatr Oncol*. Jul 2018;9(4):308-314. doi:10.1016/j.jgo.2017.12.001
176. Maddocks K. Update on mantle cell lymphoma. *Blood*. Oct 18 2018;132(16):1647-1656. doi:10.1182/blood-2018-03-791392
177. Ladha A, Zhao J, Epner EM, Pu JJ. Mantle cell lymphoma and its management: where are we now? *Exp Hematol Oncol*. 2019;8:2. doi:10.1186/s40164-019-0126-0
178. Hanel W, Epperla N. Emerging therapies in mantle cell lymphoma. *J Hematol Oncol*. Jun 17 2020;13(1):79. doi:10.1186/s13045-020-00914-1
179. Ruan J, Yamshon S, van Besien K, Martin P. An update on options of therapy for aggressive mantle cell lymphoma. *Leukemia & lymphoma*. Sep 2020;61(9):2036-2049. doi:10.1080/10428194.2020.1755860
180. Armitage JO, Longo DL. Mantle-Cell Lymphoma. *The New England journal of medicine*. Jun 30 2022;386(26):2495-2506. doi:10.1056/NEJMra2202672
181. Silkenstedt E, Linton K, Dreyling M. Mantle cell lymphoma - advances in molecular biology, prognostication and treatment approaches. *British journal of haematology*. Oct 2021;195(2):162-173. doi:10.1111/bjh.17419
182. Cortelazzo S, Ponzoni M, Ferreri AJM, Dreyling M. Mantle cell lymphoma. *Crit Rev Oncol Hematol*. Sep 2020;153:103038. doi:10.1016/j.critrevonc.2020.103038
183. Romancik JT, Cohen JB. Management of Older Adults with Mantle Cell Lymphoma. *Drugs Aging*. Jul 2020;37(7):469-481. doi:10.1007/s40266-020-00765-y
184. Romancik JT, Cohen JB. Is Limited-Stage Mantle Cell Lymphoma Curable and How Is It Best Managed? *Hematol Oncol Clin North Am*. Oct 2020;34(5):849-859. doi:10.1016/j.hoc.2020.06.003
185. McCulloch R, Rule S. What is the optimal initial management of the younger mantle cell lymphoma patient? *Best Pract Res Clin Haematol*. Mar 2018;31(1):90-98. doi:10.1016/j.beha.2017.10.008
186. Robak T, Smolewski P, Robak P, Dreyling M. Mantle cell lymphoma: therapeutic options in transplant-ineligible patients. *Leukemia & lymphoma*. Apr 25 2019;1-13. doi:10.1080/10428194.2019.1605511
187. Gerson JN, Barta SK. Mantle Cell Lymphoma: Which Patients Should We Transplant? *Curr Hematol Malig Rep*. Aug 2019;14(4):239-246. doi:10.1007/s11899-019-00520-0
188. Chen R, Sanchez J, Rosen ST. Clinical Management Updates in Mantle Cell Lymphoma. *Oncology*. Apr 2016;30(4):353-60.
189. Fisher RI, Dahlborg S, Nathwani BN, Banks PM, Miller TP, Grogan TM. A clinical analysis of two indolent lymphoma entities: mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): a Southwest Oncology Group study. *Blood*. Feb 15 1995;85(4):1075-82.



190. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 1998;16(12):3803-9.
191. Dreyling M, Campo E, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Jul 1 2017;28(suppl\_4):iv62-iv71. doi:10.1093/annonc/mdx223
192. Ruan J. Approach to the Initial Treatment of Older Patients with Mantle Cell Lymphoma. *Hematol Oncol Clin North Am*. Oct 2020;34(5):871-885. doi:10.1016/j.hoc.2020.06.005
193. Flinn I, Van der Jagt R, Chang JE, al. e. First-line treatment of iNHL or MCL patients with BR or R-CHOP/R-CVP: Results of the BRIGHT 5-year follow-up study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35:Abstract 7500.
194. Flinn IW, van der Jagt R, Kahl BS, et al. *Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study*. vol 123. Blood. 2014:2944-52.
195. Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *The New England journal of medicine*. Mar 5 2015;372(10):944-53. doi:10.1056/NEJMoa1412096
196. Robak T, Jin J, Pylypenko H, et al. Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study. *Lancet Oncol*. Nov 2018;19(11):1449-1458. doi:10.1016/S1470-2045(18)30685-5
197. Gordon LI. Counterpoint: The Role of Stem Cell Transplantation in Mantle Cell Lymphoma. *Oncology*. Dec 15 2016;30(12):1055, 1060-2.
198. Goy A. Point: The Role of Stem Cell Transplantation in Mantle Cell Lymphoma. *Oncology*. Dec 15 2016;30(12):1055-8, 1060.
199. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. *The New England journal of medicine*. Sep 28 2017;377(13):1250-1260. doi:10.1056/NEJMoa1701769
200. Tallarico M, Smith SM. From Minimal Residual Disease to Maintenance Therapy: Optimizing Tools for Treatment of Mantle Cell Lymphoma. *Oncology*. Apr 2016;30(4):361-2.
201. Wallace D, Reagan PM. Novel Treatments for Mantle Cell Lymphoma: From Targeted Therapies to CAR T Cells. *Drugs*. Apr 2021;81(6):669-684. doi:10.1007/s40265-021-01497-y
202. Kumar A, Sha F, Toure A, et al. Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. *Blood Cancer J*. May 20 2019;9(6):50. doi:10.1038/s41408-019-0209-5
203. Witzig TE, Inwards D. Acalabrutinib for Mantle Cell Lymphoma. *Blood*. Apr 9 2019;doi:10.1182/blood.2019852368
204. Eyre TA, Cheah CY, Wang ML. Therapeutic options for relapsed/refractory mantle cell lymphoma. *Blood*. Feb 3 2022;139(5):666-677. doi:10.1182/blood.2021013326
205. Parrott M, Rule S, Kelleher M, Wilson J. A Systematic Review of Treatments of Relapsed/Refractory Mantle Cell Lymphoma. *Clinical lymphoma, myeloma & leukemia*. Jan 2018;18(1):13-25 e6. doi:10.1016/j.clml.2017.10.004
206. Owen C, Berinstein NL, Christofides A, Sehn LH. Review of Bruton tyrosine kinase inhibitors for the treatment of relapsed or refractory mantle cell lymphoma. *Curr Oncol*. Apr 2019;26(2):e233-e240. doi:10.3747/co.26.4345
207. Bond DA, Martin P, Maddocks KJ. Relapsed Mantle Cell Lymphoma: Current Management, Recent Progress, and Future Directions. *J Clin Med*. Mar 14 2021;10(6)doi:10.3390/jcm10061207
208. U.S. Food and Drug Administration. FDA approves brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma. Available at <https://www.fda.gov/drugs/fda-approves-brexucabtagene-autoleucel-relapsed-or-refractory-mantle-cell-lymphoma>. Accessed August 3, 2020.
209. Tecartus [package insert]. Santa Monica, CA; Kite Pharma, Inc., 2020.
210. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *The New England journal of medicine*. Apr 2 2020;382(14):1331-1342. doi:10.1056/NEJMoa1914347
211. Saleh K, Michot JM, Camara-Clayette V, Vassetsky Y, Ribrag V. Burkitt and Burkitt-Like Lymphomas: a Systematic Review. *Curr Oncol Rep*. Mar 6 2020;22(4):33. doi:10.1007/s11912-020-0898-8



212. Roschewski M, Staudt LM, Wilson WH. Burkitt's Lymphoma. *The New England journal of medicine*. Sep 22 2022;387(12):1111-1122. doi:10.1056/NEJMra2025746
213. Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. *Lancet*. Mar 31 2012;379(9822):1234-44. doi:10.1016/S0140-6736(11)61177-X
214. Jacobson C, LaCasce A. How I treat Burkitt lymphoma in adults. *Blood*. Nov 6 2014;124(19):2913-20. doi:10.1182/blood-2014-06-538504
215. Zayac AS, Olszewski AJ. Burkitt lymphoma: bridging the gap between advances in molecular biology and therapy. *Leukemia & lymphoma*. Aug 2020;61(8):1784-1796. doi:10.1080/10428194.2020.1747068
216. Casulo C, Friedberg JW. Burkitt lymphoma- a rare but challenging lymphoma. *Best Pract Res Clin Haematol*. Sep 2018;31(3):279-284. doi:10.1016/j.beha.2018.07.013
217. Alderuccio JP, Lossos IS. DA-EPOCH-R for Adult Burkitt's Lymphoma: Pros and Cons. *J Oncol Pract*. Nov 2018;14(11):676-678. doi:10.1200/JOP.18.00624
218. Lacasce A, Howard O, Lib S, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. *Leukemia & lymphoma*. Apr 2004;45(4):761-7. doi:10.1080/1042819031000141301
219. Chamuleau M, Stenner F, Chitu D, al. e. R-CODOX-M/R-IVAC versus DA-EPOCH-R in patients with newly diagnosed high-risk Burkitt lymphoma: first results of a multi-center randomized HOVON/SAKK trial. *Presented at the 27th Congress of the European Hematology Association*. 2022;
220. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Primary Cutaneous Lymphomas. V.2.2022, 6/8/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . *NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*
221. Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sezary syndrome from 1982 to 2009. *Clin Cancer Res*. Sep 15 2012;18(18):5051-60. doi:10.1158/1078-0432.CCR-12-0604
222. Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. Aug 9 2018;doi:10.1016/S1470-2045(18)30379-6
223. Larocca C, Kupper T. Mycosis Fungoides and Sezary Syndrome: An Update. *Hematol Oncol Clin North Am*. Feb 2019;33(1):103-120. doi:10.1016/j.hoc.2018.09.001
224. Tarabackar ES, Shinohara MM. Skin Directed Therapy in Cutaneous T-Cell Lymphoma. *Front Oncol*. 2019;9:260. doi:10.3389/fonc.2019.00260
225. Wilcox RA. Cutaneous T-cell lymphoma: 2016 update on diagnosis, risk-stratification, and management. *Am J Hematol*. Jan 2016;91(1):151-65. doi:10.1002/ajh.24233
226. Larocca CA, LeBoeuf NR. Overview of Cutaneous T-Cell Lymphomas. *Hematol Oncol Clin North Am*. Aug 2019;33(4):669-686. doi:10.1016/j.hoc.2019.04.004
227. Zic JA. Diagnosis and Management of Cutaneous Lymphomas Including Cutaneous T-cell Lymphoma. *Med Clin North Am*. Jul 2021;105(4):737-755. doi:10.1016/j.mcna.2021.04.010
228. Scarisbrick JJ, Bagot M, Ortiz-Romero PL. The changing therapeutic landscape, burden of disease, and unmet needs in patients with cutaneous T-cell lymphoma. *British journal of haematology*. Feb 2021;192(4):683-696. doi:10.1111/bjh.17117
229. Sethi TK, Montanari F, Foss F, Reddy N. How we treat advanced stage cutaneous T-cell lymphoma - mycosis fungoides and Sezary syndrome. *British journal of haematology*. Nov 2021;195(3):352-364. doi:10.1111/bjh.17458
230. Brumfiel CM, Patel MH, Puri P, et al. How to Sequence Therapies in Mycosis Fungoides. *Curr Treat Options Oncol*. Sep 27 2021;22(11):101. doi:10.1007/s11864-021-00899-0
231. Dummer R, Vermeer MH, Scarisbrick JJ, et al. Cutaneous T cell lymphoma. *Nat Rev Dis Primers*. Aug 26 2021;7(1):61. doi:10.1038/s41572-021-00296-9
232. Kempf W, Mitteldorf C. Cutaneous T-cell lymphomas-An update 2021. *Hematol Oncol*. Jun 2021;39 Suppl 1:46-51. doi:10.1002/hon.2850
233. Poteligeo [package insert]. Bedminster, NJ: Kyowa Kirin, Inc., 2017.

234. Blackmon AL, Pinter-Brown L. Spotlight on Mogamulizumab-Kpkc for Use in Adults with Relapsed or Refractory Mycosis Fungoides or Sezary Syndrome: Efficacy, Safety, and Patient Selection. *Drug Des Devel Ther*. 2020;14:3747-3754. doi:10.2147/DDDT.S185896
235. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. *Blood*. Jun 1 2003;101(11):4267-72. doi:10.1182/blood-2002-09-2802
236. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 1 2001;19(9):2456-71.
237. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. Aug 05 2017;390(10094):555-566. doi:10.1016/S0140-6736(17)31266-7
238. Horwitz SM, Scarisbrick JJ, Dummer R, et al. Randomized phase 3 ALCANZA study of brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma: final data. *Blood Adv*. Dec 14 2021;5(23):5098-5106. doi:10.1182/bloodadvances.2021004710
239. Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 2000;18(13):2603-6.
240. Suchin KR, Cucchiara AJ, Gottlieb SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. *Arch Dermatol*. Aug 2002;138(8):1054-60.
241. Jumbou O, N'Guyen JM, Tessier MH, Legoux B, Dreno B. Long-term follow-up in 51 patients with mycosis fungoides and Sezary syndrome treated by interferon-alfa. *Br J Dermatol*. Mar 1999;140(3):427-31.
242. Schiller M, Tsianakas A, Sterry W, et al. Dose-escalation study evaluating pegylated interferon alpha-2a in patients with cutaneous T-cell lymphoma. *J Eur Acad Dermatol Venereol*. Nov 2017;31(11):1841-1847. doi:10.1111/jdv.14366
243. Pulini S, Rupoli S, Goteri G, et al. Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. *Haematologica*. May 2007;92(5):686-9.
244. Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. *Arch Dermatol*. Jun 2008;144(6):727-33. doi:10.1001/archderm.144.6.727
245. Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. *Blood*. May 3 2012;119(18):4115-22. doi:10.1182/blood-2011-11-390211
246. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 10 2009;27(32):5410-7. doi:10.1200/JCO.2008.21.6150
247. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 20 2007;25(21):3109-15. doi:10.1200/JCO.2006.10.2434
248. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-cell Lymphomas. V.2.2022, 3/7/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
249. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol*. Jul 2003;139(7):857-66. doi:10.1001/archderm.139.7.857
250. Zhou T, Zhang Y, Ma Y, et al. Comparison of aprepitant versus desloratadine for EGFR-TKI-induced pruritus: A randomized phase 2 clinical trial. *Cancer*. Nov 15 2022;128(22):3969-3976. doi:10.1002/cncr.34474

251. Zic JA, Straka BT, McGirt LY, Nian H, Yu C, Brown NJ. Aprepitant for the Treatment of Pruritus in Sezary Syndrome: A Randomized Crossover Clinical Trial. *JAMA Dermatol*. Oct 1 2018;154(10):1221-1222. doi:10.1001/jamadermatol.2018.2510
252. Lunning MA. Treatment of Peripheral T-Cell Lymphoma: Many Shades of Gray. *Oncology*. Aug 2015;29(8):545-50.
253. Mehta-Shah N, Horwitz S. Therapy for Peripheral T-Cell Lymphomas: Where We Are and Where We Hope to Be. *Oncology*. Aug 2015;29(8):558-9.
254. Zhang Y, Xu W, Liu H, Li J. Therapeutic options in peripheral T cell lymphoma. *J Hematol Oncol*. 2016;9:37. doi:10.1186/s13045-016-0267-0
255. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. Jan 19 2019;393(10168):229-240. doi:10.1016/S0140-6736(18)32984-2
256. Ng SY, Jacobsen ED. Peripheral T-Cell Lymphoma: Moving Toward Targeted Therapies. *Hematol Oncol Clin North Am*. Aug 2019;33(4):657-668. doi:10.1016/j.hoc.2019.04.002
257. Marchi E, O'Connor OA. The rapidly changing landscape in mature T-cell lymphoma (MTCL) biology and management. *CA: a cancer journal for clinicians*. Jan 2020;70(1):47-70. doi:10.3322/caac.21589
258. Barta SK, Gong JZ, Porcu P. Brentuximab vedotin in the treatment of CD30+ PTCL. *Blood*. Dec 26 2019;134(26):2339-2345. doi:10.1182/blood.2019001821
259. Bachy E, Broccoli A, Dearden C, et al. Controversies in the Treatment of Peripheral T-cell Lymphoma. *Hemasphere*. Oct 2020;4(5):e461. doi:10.1097/HS9.0000000000000461
260. Angelos MG, Ballard HJ, Barta SK. Advances and Personalized Approaches in the Frontline Treatment of T-Cell Lymphomas. *J Pers Med*. Feb 11 2022;12(2)doi:10.3390/jpm12020267
261. Mina A, Pro B. T time: Emerging and new therapies for peripheral T-cell lymphoma. *Blood Rev*. Mar 2022;52:100889. doi:10.1016/j.blre.2021.100889
262. Abeyakoon C, van der Weyden C, Harrop S, et al. Advances in Frontline Management of Peripheral T-cell Lymphoma. *Clinical lymphoma, myeloma & leukemia*. Jun 2021;21(6):368-378. doi:10.1016/j.clml.2021.01.012
263. Wudhikarn K, Bennani NN. How to Sequence Therapies in Peripheral T Cell Lymphoma. *Curr Treat Options Oncol*. Jul 2 2021;22(9):74. doi:10.1007/s11864-021-00873-w
264. Shea L, Mehta-Shah N. Brentuximab Vedotin in the Treatment of Peripheral T Cell Lymphoma and Cutaneous T Cell Lymphoma. *Curr Hematol Malig Rep*. Feb 2020;15(1):9-19. doi:10.1007/s11899-020-00561-w
265. Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Mar 2022;33(3):288-298. doi:10.1016/j.annonc.2021.12.002
266. Bachy E, Camus V, Thieblemont C, et al. Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jan 20 2022;40(3):242-251. doi:10.1200/JCO.21.01815
267. Zain JM. Aggressive T-cell lymphomas: 2019 updates on diagnosis, risk stratification, and management. *Am J Hematol*. Aug 2019;94(8):929-946. doi:10.1002/ajh.25513
268. Foster C, Kuruvilla J. Treatment approaches in relapsed or refractory peripheral T-cell lymphomas. *F1000Res*. 2020;9doi:10.12688/f1000research.22257.1
269. Lee HZ, Kwitkowski VE, Del Valle PL, et al. FDA Approval: Belinostat for the Treatment of Patients with Relapsed or Refractory Peripheral T-cell Lymphoma. *Clin Cancer Res*. Jun 15 2015;21(12):2666-70. doi:10.1158/1078-0432.CCR-14-3119
270. O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 10 2015;33(23):2492-9. doi:10.1200/JCO.2014.59.2782
271. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 20 2012;30(18):2190-6. doi:10.1200/JCO.2011.38.0402
272. Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. *Blood*. Oct 3 2017;doi:10.1182/blood-2017-05-780049

273. Brammer JE, Zinzani PL, Zain J, et al. Duvelisib in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma from the Phase 2 Primo Trial: Results of an Interim Analysis. *Blood*. 2021;138:Abstract 2456.
274. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 20 2011;29(9):1182-9. doi:10.1200/JCO.2010.29.9024
275. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 20 2012;30(6):631-6. doi:10.1200/JCO.2011.37.4223
276. Cancer Network. Bristol Myers Squibb Withdraws Romidepsin R/R Peripheral T-Cell Lymphoma Indication For Lack of Clinical Benefit. Available at <https://www.cancernetwork.com/view/bristol-myers-squibb-withdraws-romidepsin-r-r-peripheral-t-cell-lymphoma-indication-for-lack-of-clinical-benefit> . Accessed June 16, 2022.
277. Ansell SM. Hodgkin lymphoma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematol*. May 2018;93(5):704-715. doi:10.1002/ajh.25071
278. Pugliese N, Picardi M, Della Pepa R, et al. Rituximab-Containing Risk-Adapted Treatment Strategy in Nodular Lymphocyte Predominant Hodgkin Lymphoma: 7-Years Follow-Up. *Cancers (Basel)*. Apr 7 2021;13(8)doi:10.3390/cancers13081760
279. Caporaso NE, Goldin LR, Anderson WF, Landgren O. Current insight on trends, causes, and mechanisms of Hodgkin's lymphoma. *Cancer journal*. Mar-Apr 2009;15(2):117-23. doi:10.1097/PPO.0b013e3181a39585
280. Niens M, Jarrett RF, Hepkema B, et al. HLA-A\*02 is associated with a reduced risk and HLA-A\*01 with an increased risk of developing EBV+ Hodgkin lymphoma. *Blood*. Nov 1 2007;110(9):3310-5. doi:10.1182/blood-2007-05-086934
281. Gobbi PG, Ferreri AJ, Ponzoni M, Levis A. Hodgkin lymphoma. *Critical reviews in oncology/hematology*. Feb 2013;85(2):216-37. doi:10.1016/j.critrevonc.2012.07.002
282. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin Lymphoma. V.2.2023, 11/8/22, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. . NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
283. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *The New England journal of medicine*. Nov 19 1998;339(21):1506-14. doi:10.1056/NEJM199811193392104
284. Longley J, Johnson PWM. Current treatment paradigms for advanced stage Hodgkin lymphoma. *British journal of haematology*. Jan 2019;184(1):60-71. doi:10.1111/bjh.15622
285. Boll B, Gorgen H. The treatment of older Hodgkin lymphoma patients. *British journal of haematology*. Jan 2019;184(1):82-92. doi:10.1111/bjh.15652
286. Allen PB, Winter JN. Controversies in the Approach to Initial Therapy of Hodgkin Lymphoma. *Curr Oncol Rep*. Mar 27 2019;21(5):39. doi:10.1007/s11912-019-0788-0
287. Eichenauer DA, Aleman BMP, Andre M, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Oct 1 2018;29(Supplement\_4):iv19-iv29. doi:10.1093/annonc/mdy080
288. Reid JH, Marini BL, Nachar VR, Brown AM, Devata S, Perissinotti AJ. Contemporary treatment options for a classical disease: Advanced Hodgkin lymphoma. *Critical reviews in oncology/hematology*. Apr 2020;148:102897. doi:10.1016/j.critrevonc.2020.102897
289. Brice P, de Kerviler E, Friedberg JW. Classical Hodgkin lymphoma. *Lancet*. Jan 22 2021;doi:10.1016/S0140-6736(20)32207-8
290. Connors JM, Cozen W, Steidl C, et al. Hodgkin lymphoma. *Nat Rev Dis Primers*. Jul 23 2020;6(1):61. doi:10.1038/s41572-020-0189-6
291. Johnson P, McKenzie H. How I treat advanced classical Hodgkin lymphoma. *Blood*. Mar 12 2015;125(11):1717-23. doi:10.1182/blood-2014-09-551556

292. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *European journal of nuclear medicine and molecular imaging*. Oct 2010;37(10):1824-33. doi:10.1007/s00259-010-1490-5
293. Oki Y, Chuang H, Chasen B, et al. The prognostic value of interim positron emission tomography scan in patients with classical Hodgkin lymphoma. *British journal of haematology*. Apr 2014;165(1):112-6. doi:10.1111/bjh.12715
294. de Wit M, Bohuslavizki KH, Buchert R, Bumann D, Clausen M, Hossfeld DK. 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Jan 2001;12(1):29-37.
295. Johnson P, Federico M, Kirkwood A, et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. *The New England journal of medicine*. Jun 23 2016;374(25):2419-29. doi:10.1056/NEJMoa1510093
296. Gustavsson A, Osterman B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. *Acta oncologica*. 2003;42(5-6):589-604.
297. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *The New England journal of medicine*. Aug 12 2010;363(7):640-52. doi:10.1056/NEJMoa1000067
298. Sasse S, Brockelmann PJ, Goergen H, et al. Long-Term Follow-Up of Contemporary Treatment in Early-Stage Hodgkin Lymphoma: Updated Analyses of the German Hodgkin Study Group HD7, HD8, HD10, and HD11 Trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 20 2017;35(18):1999-2007. doi:10.1200/JCO.2016.70.9410
299. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 20 2005;23(21):4634-42. doi:10.1200/JCO.2005.09.085
300. Hay AE, Klimm B, Chen BE, et al. An individual patient-data comparison of combined modality therapy and ABVD alone for patients with limited-stage Hodgkin lymphoma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Dec 2013;24(12):3065-9. doi:10.1093/annonc/mdt389
301. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 1 2003;21(19):3601-8. doi:10.1200/JCO.2003.03.023
302. Sasse S, Klimm B, Gorgen H, et al. Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Nov 2012;23(11):2953-9. doi:10.1093/annonc/mds110
303. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 20 2010;28(27):4199-206. doi:10.1200/JCO.2010.29.8018
304. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *The New England journal of medicine*. Nov 19 1992;327(21):1478-84. doi:10.1056/NEJM199211193272102
305. Canellos GP, Niedzwiecki D. Long-term follow-up of Hodgkin's disease trial. *The New England journal of medicine*. May 2 2002;346(18):1417-8. doi:10.1056/NEJM200205023461821
306. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 15 2003;21(4):607-14.
307. OptumRx. Mustargen® (mechlorethamine) – Product discontinuation. Available at [https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal\\_mustargen\\_2018-1005.pdf](https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal_mustargen_2018-1005.pdf). Accessed December 1, 2019.
308. Skoetz N, Will A, Monsef I, Brillant C, Engert A, von Tresckow B. Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or

- advanced stage Hodgkin lymphoma. *Cochrane Database Syst Rev*. May 25 2017;5:CD007941. doi:10.1002/14651858.CD007941.pub3
309. Longo DL, DeVita VT, Jr. Progress in the Treatment of Hodgkin's Lymphoma. *The New England journal of medicine*. Dec 10 2017;doi:10.1056/NEJMe1715141
310. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. *The New England journal of medicine*. Jan 25 2018;378(4):331-344. doi:10.1056/NEJMoa1708984
311. Ramchandren R, Advani RH, Ansell SM, et al. Brentuximab Vedotin plus Chemotherapy in North American Subjects with Newly Diagnosed Stage III or IV Hodgkin Lymphoma. *Clin Cancer Res*. Mar 15 2019;25(6):1718-1726. doi:10.1158/1078-0432.CCR-18-2435
312. Straus D, Collins G, Walewski J, et al. Primary prophylaxis with G-CSF may improve outcomes in patients with newly diagnosed stage III/IV Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy. *Leukemia & Lymphoma*. Aug 25 2020;1-8. doi:10.1080/10428194.2020.1791846
313. Straus DJ, Dlugosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. Jun 2021;8(6):e410-e421. doi:10.1016/S2352-3026(21)00102-2
314. Ansell SM, Radford J, Connors JM, et al. Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma. *The New England journal of medicine*. Jul 13 2022;doi:10.1056/NEJMoa2206125
315. Ansell S, Connors JM, Radford JA, et al. First-line brentuximab vedotin plus chemotherapy to improve overall survival in patients with stage III/IV classical Hodgkin lymphoma: An updated analysis of ECHELON-1. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2022;40:Abstract 7503.
316. Huntington SF, von Keudell G, Davidoff AJ, Gross CP, Prasad SA. Cost-Effectiveness Analysis of Brentuximab Vedotin With Chemotherapy in Newly Diagnosed Stage III and IV Hodgkin Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 4 2018;JCO1800122. doi:10.1200/JCO.18.00122
317. Longo DL, Armitage JO. A Better Treatment for Advanced-Stage Hodgkin's Lymphoma? *The New England journal of medicine*. Jul 28 2022;378(4):370-372. doi:10.1056/NEJMe2207639
318. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. May 12 2012;379(9828):1791-9. doi:10.1016/S0140-6736(11)61940-5
319. Skoetz N, Trelle S, Rancea M, et al. Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: a systematic review and network meta-analysis. *Lancet Oncol*. Sep 2013;14(10):943-52. doi:10.1016/S1470-2045(13)70341-3
320. Ansell SM. Hodgkin lymphoma: MOPP chemotherapy to PD-1 blockade and beyond. *Am J Hematol*. Jan 2016;91(1):109-12. doi:10.1002/ajh.24226
321. Carella AM, Corradini P, Mussetti A, Ricardi U, Vitolo U, Viviani S. Treatment of classical Hodgkin lymphoma in the era of brentuximab vedotin and immune checkpoint inhibitors. *Ann Hematol*. Aug 2018;97(8):1301-1315. doi:10.1007/s00277-018-3366-x
322. Kreissl S, Goergen H, Buehnen I, et al. PET-guided eBEACOPP treatment of advanced-stage Hodgkin lymphoma (HD18): follow-up analysis of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. Jun 2021;8(6):e398-e409. doi:10.1016/S2352-3026(21)00101-0
323. Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol*. Feb 2019;20(2):202-215. doi:10.1016/S1470-2045(18)30784-8
324. Lim SH, Johnson PWM. Optimizing therapy in advanced-stage Hodgkin lymphoma. *Blood*. Apr 12 2018;131(15):1679-1688. doi:10.1182/blood-2017-09-772640
325. Winkfield KM, Advani RH, Ballas LK, et al. ACR Appropriateness Criteria(R) Recurrent Hodgkin Lymphoma. *Oncology*. Dec 15 2016;30(12):1099-103, 1106-8.
326. Alinari L, Blum KA. How I treat relapsed classical Hodgkin lymphoma after autologous stem cell transplant. *Blood*. Jan 21 2016;127(3):287-95. doi:10.1182/blood-2015-10-671826
327. Castagna L, Santoro A, Carlo-Stella C. Salvage Therapy for Hodgkin's Lymphoma: A Review of Current Regimens and Outcomes. *J Blood Med*. 2020;11:389-403. doi:10.2147/JBM.S250581
328. Voorhees TJ, Beaven AW. Therapeutic Updates for Relapsed and Refractory Classical Hodgkin Lymphoma. *Cancers (Basel)*. Oct 8 2020;12(10)doi:10.3390/cancers12102887

329. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. May 9 2015;385(9980):1853-62. doi:10.1016/S0140-6736(15)60165-9
330. Perales MA, Ceberio I, Armand P, et al. Role of cytotoxic therapy with hematopoietic cell transplantation in the treatment of Hodgkin lymphoma: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. Jun 2015;21(6):971-83. doi:10.1016/j.bbmt.2015.02.022
331. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. Apr 24 1993;341(8852):1051-4.
332. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. Jun 15 2002;359(9323):2065-71. doi:10.1016/S0140-6736(02)08938-9
333. Broccoli A, Zinzani PL. The role of transplantation in Hodgkin lymphoma. *British journal of haematology*. Jan 2019;184(1):93-104. doi:10.1111/bjh.15639
334. Khan N, Moskowitz AJ. Where Do the New Drugs Fit in for Relapsed/Refractory Hodgkin Lymphoma? *Curr Hematol Malig Rep*. Jun 2017;12(3):227-233. doi:10.1007/s11899-017-0384-z
335. Shah GL, Moskowitz CH. Transplant strategies in relapsed/refractory Hodgkin lymphoma. *Blood*. Apr 12 2018;131(15):1689-1697. doi:10.1182/blood-2017-09-772673
336. Scott LJ. Brentuximab Vedotin: A Review in CD30-Positive Hodgkin Lymphoma. *Drugs*. Mar 2017;77(4):435-445. doi:10.1007/s40265-017-0705-5
337. Bonthapally V, Yang H, Ayyagari R, et al. Brentuximab vedotin compared with other therapies in relapsed/refractory Hodgkin lymphoma post autologous stem cell transplant: median overall survival meta-analysis. *Curr Med Res Opin*. 2015;31(7):1377-89. doi:10.1185/03007995.2015.1048208
338. Gautam A, Zhu Y, Ma E, et al. Brentuximab vedotin consolidation post-autologous stem cell transplant in Hodgkin lymphoma patients at risk of residual disease: number needed to treat. *Leukemia & lymphoma*. Jan 2018;59(1):69-76. doi:10.1080/10428194.2017.1324160
339. Ramsey SD, Nademanee A, Masszi T, et al. Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma. *British journal of haematology*. Dec 2016;175(5):860-867. doi:10.1111/bjh.14316
340. Sureda A, Andre M, Borchmann P, et al. Improving outcomes after autologous transplantation in relapsed/refractory Hodgkin lymphoma: a European expert perspective. *BMC Cancer*. Nov 10 2020;20(1):1088. doi:10.1186/s12885-020-07561-2
341. Jelinek T, Mihalyova J, Kascak M, Duras J, Hajek R. PD-1/PD-L1 inhibitors in haematological malignancies: update 2017. *Immunology*. Jul 06 2017;doi:10.1111/imm.12788
342. Chen R, Zinzani PL, Fanale MA, et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 01 2017;35(19):2125-2132. doi:10.1200/JCO.2016.72.1316
343. Meti N, Esfahani K, Johnson NA. The Role of Immune Checkpoint Inhibitors in Classical Hodgkin Lymphoma. *Cancers (Basel)*. Jun 15 2018;10(6)doi:10.3390/cancers10060204
344. De Re V, Caggiari L, Repetto O, Mussolin L, Mascarini M. Classical Hodgkin's Lymphoma in the Era of Immune Checkpoint Inhibition. *J Clin Med*. Oct 2 2019;8(10)doi:10.3390/jcm8101596
345. Al Hadidi SA, Lee HJ. Pembrolizumab for the treatment of Hodgkin Lymphoma. *Expert Opin Biol Ther*. Nov 2020;20(11):1275-1282. doi:10.1080/14712598.2020.1830056
346. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol*. Sep 2016;17(9):1283-94. doi:10.1016/S1470-2045(16)30167-X
347. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. Mar 15 2018;131(11):1183-1194. doi:10.1182/blood-2017-10-811224
348. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. *Blood*. Aug 12 2021;138(6):427-438. doi:10.1182/blood.2020009178



349. Kuruvilla J, Ramchandren R, Santoro A, et al. Randomized, open-label, phase III study of pembrolizumab (pembro) versus brentuximab vedotin (BV) in relapsed or refractory classic Hodgkin lymphoma (R/R cHL). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020;38:8005.
350. Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood*. Jul 13 2017;130(2):221-228. doi:10.1182/blood-2017-01-761346
351. Borchmann S, Joffe E, Moskowitz CH, et al. Active surveillance for nodular lymphocyte-predominant Hodgkin lymphoma. *Blood*. May 16 2019;133(20):2121-2129. doi:10.1182/blood-2018-10-877761
352. Eichenauer DA, Engert A. Current treatment options for nodular lymphocyte-predominant Hodgkin lymphoma. *Curr Opin Oncol*. Sep 1 2021;33(5):395-399. doi:10.1097/CCO.0000000000000774
353. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE, Ansell SM. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 20 2005;23(30):7614-20. doi:10.1200/JCO.2005.02.7243
354. O'Sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Jan 2003;14(1):91-6.
355. Banakh I, Lam A, Tiruvoipati R, Carney I, Botha J. Imatinib for bleomycin induced pulmonary toxicity: a case report and evidence-base review. *Clin Case Rep*. May 2016;4(5):486-90. doi:10.1002/ccr3.549
356. Ge V, Banakh I, Tiruvoipati R, Haji K. Bleomycin-induced pulmonary toxicity and treatment with infliximab: A case report. *Clin Case Rep*. Oct 2018;6(10):2011-2014. doi:10.1002/ccr3.1790
357. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 1 2015;33(28):3199-212. doi:10.1200/JCO.2015.62.3488
358. Younes A, Fayad L, Romaguera J, Pro B, Goy A, Wang M. Safety and efficacy of once-per-cycle pegfilgrastim in support of ABVD chemotherapy in patients with Hodgkin lymphoma. *Eur J Cancer*. Nov 2006;42(17):2976-81. doi:10.1016/j.ejca.2006.07.012
359. Janakiraman N, O'Brien TE. Pegfilgrastim use and risk of bleomycin induced pulmonary toxicity in hodgkin lymphoma. *Blood*. 2008;112:4950.
360. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Feb 2007;18(2):376-80. doi:10.1093/annonc/mdl397
361. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. *British journal of haematology*. Jun 2007;137(6):545-52. doi:10.1111/j.1365-2141.2007.06598.x
362. Minuk LA, Monkman K, Chin-Yee IH, et al. Treatment of Hodgkin lymphoma with adriamycin, bleomycin, vinblastine and dacarbazine without routine granulocyte-colony stimulating factor support does not increase the risk of febrile neutropenia: a prospective cohort study. *Leukemia & lymphoma*. Jan 2012;53(1):57-63. doi:10.3109/10428194.2011.602771
363. Graczyk J, Cheung MC, Buckstein R, Chan K. Granulocyte colony-stimulating factor as secondary prophylaxis of febrile neutropenia in the management of advanced-stage Hodgkin lymphoma treated with adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy: a decision analysis. *Leukemia & lymphoma*. Jan 2014;55(1):56-62. doi:10.3109/10428194.2013.796046
364. Nijdam A, Dekker N, Aleman BMP, et al. Setting up a national infrastructure for survivorship care after treatment for Hodgkin lymphoma. *British journal of haematology*. May 15 2019;doi:10.1111/bjh.15936
365. de Vries S, Schaapveld M, Janus CPM, et al. Long-Term Cause-Specific Mortality in Hodgkin Lymphoma Patients. *Journal of the National Cancer Institute*. Jun 1 2021;113(6):760-769. doi:10.1093/jnci/djaa194
366. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Dec 2006;17(12):1749-60. doi:10.1093/annonc/mdl302
367. Depaus J, Delcourt A, Andre M. Therapeutic recommendations for early stage Hodgkin lymphomas. *British journal of haematology*. Jan 2019;184(1):9-16. doi:10.1111/bjh.15623
368. Nassi L, De Sanctis V, Loseto G, et al. Second Cancers in Classical Hodgkin Lymphoma and Diffuse Large B-Cell Lymphoma: A Systematic Review by the Fondazione Italiana Linfomi. *Cancers (Basel)*. Jan 20 2022;14(3)doi:10.3390/cancers14030519



369. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA: a cancer journal for clinicians*. Mar-Apr 2007;57(2):75-89.
370. Jacob A, Thyagarajan B, Kumar MP, Shaikh N, Sharon D. Cardiovascular effects of Hodgkin's lymphoma: a review of literature. *J Cancer Res Clin Oncol*. Jan 2018;144(1):99-107. doi:10.1007/s00432-017-2560-x
371. Oliva S, Puzzovivo A, Gerardi C, et al. Late Cardiologic Sequelae and Long-Term Monitoring in Classical Hodgkin Lymphoma and Diffuse Large B-Cell Lymphoma Survivors: A Systematic Review by the Fondazione Italiana Linfomi. *Cancers (Basel)*. Dec 23 2021;14(1)doi:10.3390/cancers14010061
372. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood*. Mar 1 2007;109(5):1878-86. doi:10.1182/blood-2006-07-034405
373. Ng A, Constine LS, Advani R, et al. ACR Appropriateness Criteria: follow-up of Hodgkin's lymphoma. *Curr Probl Cancer*. May-Jun 2010;34(3):211-27. doi:10.1016/j.crrprobcancer.2010.04.007
374. Chu E, DeVita VT, Jr., Copur MS, et al. *Physicians' Cancer Chemotherapy Drug Manual 2008*. Jones and Bartlett; 2008:552.
375. Pluschnig U, Haslik W, Bartsch R, Mader RM. Extravasation emergencies: state-of-the-art management and progress in clinical research. *Memo*. 2016;9(4):226-230. doi:10.1007/s12254-016-0304-2
376. Doolittle D. Closing the Knowledge Gap On Extravasation. *Pharmacy Practice News*. 2022;
377. Boulanger J, Ducharme A, Dufour A, et al. Management of the extravasation of anti-neoplastic agents. *Support Care Cancer*. May 2015;23(5):1459-71. doi:10.1007/s00520-015-2635-7
378. Schulmeister L. Extravasation. In: Oliver IN, ed. *The MASCC Textbook of Cancer Supportive Care and Survivorship*. Springer; 2011:351-359:chap 34.
379. Schulmeister L. Extravasation management. *Semin Oncol Nurs*. Aug 2007;23(3):184-90. doi:10.1016/j.soncn.2007.05.003
380. Kreidieh FY, Moukadem HA, El Saghir NS. Overview, prevention and management of chemotherapy extravasation. *World J Clin Oncol*. Feb 10 2016;7(1):87-97. doi:10.5306/wjco.v7.i1.87
381. Howell G, Oliai C, Schiller G. Liposomal Cytarabine-Daunorubicin (CPX-351) Extravasation: Case Report and Literature Review. *Anticancer Res*. Dec 2018;38(12):6927-6930. doi:10.21873/anticancer.13070
382. Dorr RT, Von Hoff DD. Pharmacologic management of vesicant chemotherapy extravasations. In: Dorr RT, Von Hoff DD, eds. *Cancer Chemotherapy Handbook*. 2 ed. Appleton & Lange; 1994:109-118.
383. Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: Prevention and treatment. *Seminars in Oncology*. 2006;33(1):139-143.
384. Clamon GH. Extravasation. In: Perry MC, ed. *The Chemotherapy Source Book*. 4th ed. Lippincott Williams & Wilkins; 2008:148-151:chap 16.
385. Jackson-Rose J, Del Monte J, Groman A, et al. Chemotherapy Extravasation: Establishing a National Benchmark for Incidence Among Cancer Centers. *Clin J Oncol Nurs*. Aug 01 2017;21(4):438-445. doi:10.1188/17.CJON.438-445
386. Rodriguez-Alarcon A, Conde-Estevez D. Monoclonal antibody extravasations: Two case reports and literature review. *J Oncol Pharm Pract*. Apr 2021;27(3):761-763. doi:10.1177/1078155220950005
387. Shafae MN, Salahudeen AA, Valero V. Skin Necrosis After Adu-Trastuzumab Emtansine Extravasation. *J Oncol Pract*. Aug 2017;13(8):555-556. doi:10.1200/JOP.2016.020198
388. Nakashima T, Ogawa Y, Kimura A, et al. Coadministration of 5% glucose solution has a decrease in bendamustine-related vascular pain grade. *Journal of Oncology Pharmacy Practice*. Dec 2012;18(4):445-7. doi:10.1177/1078155212442560
389. Hosokawa A, Nakashima T, Ogawa Y, Kozawa K, Kiba T. Coadministration of 5% glucose solution relieves vascular pain in the patients administered gemcitabine immediately. *Journal of Oncology Pharmacy Practice*. Jun 25 2012;doi:10.1177/1078155212449679
390. de Lemos MrL. Vinorelbine and venous irritation: optimal parenteral administration. *Journal of Oncology Pharmacy Practice*. 06 2005;11(2):79-81.
391. Schulmeister L. Extravasation management: Clinical update. *Seminars in Oncology Nursing*. 2011;27(1):82-90. doi:DOI: 10.1016/j.soncn.2010.11.010
392. Gilbar PJ, Carrington CV. The incidence of extravasation of vinca alkaloids supplied in syringes or mini-bags. *Journal of Oncology Pharmacy Practice*. 2006;12:113-118.
393. Neuss MN, Polovich M, McNiff K, et al. 2013 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. *Oncol Nurs Forum*. May 01 2013;40(3):225-33. doi:10.1188/13.ONF.40-03AP2

- 394. ISOPP Standards for the Safe Handling of Cytotoxics. *J Oncol Pharm Pract.* 2022;28:1-126.
- 395. Lexi-Comp. Lexi-Comp Clinical Reference Library OnLine. Lexi-Comp, Inc. Accessed November 1, 2014, 2014.
- 396. Mouridsen HT, Langer SW, Buter J, et al. Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. *Annals of Oncology.* March 1, 2007 2007;18(3):546-550. doi:10.1093/annonc/mdl413
- 397. Olver IN, Aisner J, Hament A, Buchanan L, Bishop JF, Kaplan RS. A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. *Journal of Clinical Oncology.* November 1, 1988 1988;6(11):1732-1735.
- 398. Bertelli G, Gozza A, Forno GB, et al. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: A prospective clinical study. *Journal of Clinical Oncology.* 1995;13(11):2851-2855.

# **CUTANEOUS MELANOMA and NON-MELANOMA SKIN CANCERS**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with melanoma or non-melanoma skin cancer.
2. Discuss short- and long-term goals, including post-therapy and survivorship, with a patient with melanoma or non-melanoma skin cancer and his or her caregiver.
3. Select relevant information and guidance for the public regarding melanoma and non-melanoma skin cancer-related issues (e.g., risk factors, prevention, screening).
4. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with the treatment of melanoma and non-melanoma skin cancers, including thyroid level monitoring for chemotherapy agents, immune-mediated toxicities, and toxicity from BRAF inhibitors.

# MELANOMA

## I. Etiology and Risk Factors<sup>1</sup>

- A. Melanoma can occur regardless of ethnicity and in areas that are not associated with exposure to substantial sunlight; however, skin type, history of atypical moles, dysplastic nevi or a prior melanoma can increase the risk in addition to the following:
  - 1. Light skin with fair hair (red or blond) and light-colored eyes (blue or green)
  - 2. Latitude nearer the equator with high intensity of solar exposure
  - 3. Experiencing blistering sunburns (especially during youth)
  - 4. Immunocompromised conditions
- B. Intermittent, intense sun exposure is more closely correlated with melanoma than chronic, occupational exposure.<sup>2</sup>
- C. Exposure to sunbeds or sunlamps increases the risk of cutaneous melanoma, especially when exposed as a young adult<sup>3</sup>
- D. Family history including certain genetic mutations

## II. Pathophysiology<sup>4, 5</sup>

- A. Histologic subtypes of melanoma
  - 1. Superficial spreading melanoma
    - a. Most common morphologic type of cutaneous melanoma (70% of all melanoma) and usually evolves from a preexisting nevus
    - b. Early in the lesion development the melanoma is flat, but as the lesion develops the surface becomes irregular and asymmetrical
    - c. Common pathogenic mutations include BRAF V600E/K in 41%, NRAS in 22%, and TP53 in 17%<sup>6</sup>
  - 2. Nodular melanoma
    - a. Second most common melanoma (15% to 30% of cutaneous melanoma)
    - b. Nodular melanoma is a “pure” vertical growth-phase disease and is more aggressive, and develop more rapidly than superficial spreading melanoma
    - c. Typically, lesions are dark blue-black and often uniform in color, although about 5% are amelanotic and have a fleshy appearance. They typically occur on the trunk, head and neck.
    - d. Common pathogenic mutations are similar to superficial spreading melanoma including mutations in BRAF (29%) and NRAS (27%).<sup>7</sup>
  - 3. Lentigo maligna melanoma
    - a. Rare form of melanoma that is unique from other histologic subtypes because it does not have the same propensity to metastasize.
    - b. Most commonly seen in elderly patients with sun-exposed or damaged skin.

4. Acral lentiginous melanoma
  - a. Characteristically seen on the palms of the hands, soles of the feet, and beneath the nailbeds.
  - b. Most common type of melanoma in Blacks, Asians, and Hispanics
  - c. Pathogenic alterations in KIT are seen in 11% of acral melanomas along with mutations in NRAS (24%) and BRAF V600E/K (19%)<sup>6</sup>
5. Mucosal melanoma
  - a. 1% of all melanomas
  - b. Arises from the melanocytes located in mucous membranes and is most commonly seen in the head and neck region with the gastrointestinal and genital tracks also being possible sources.
  - c. Common pathogenic mutations include mutations in NRAS (21%), KIT (16%), TP53 (9%), and BRAF V600E/K (7%).<sup>6</sup>
6. Uveal melanoma is the most common primary intraocular malignancy seen in adults, but only accounts for about 3% of all melanomas (NCCN now has a separate guideline focused on the management of uveal melanoma and it will not be discussed in detail as part of this module)<sup>8</sup>
  - a. Uveal melanoma arises from the melanocytes of the choroid plexus, ciliary body, and iris.
  - b. The liver is the most common site of uveal melanoma metastases
  - c. Common pathogenic mutations
    - 1) Unlike cutaneous melanoma, uveal melanoma is not typically BRAF mutated
    - 2) GNA11 were seen in 32% of primary uveal melanomas and 57% of metastatic lesions.
    - 3) GNAQ mutations were seen in 45% of primary and 22% of metastatic lesions.
    - 4) Occurrence of alterations in these genes was mutually exclusive and most commonly occur at Q209 in both genes.<sup>9</sup>
    - 5) GNA11 and GNAQ are G-protein-coupled receptors and mutations in uveal melanoma have been shown to activate downstream signaling targets including MAPK, PI3K, and others though the optimal method of targeting is less clear with clinical trials assessing inhibitors of MEK and protein kinase C.

### III. Prevention/Screening <sup>10-12</sup>

- A. Prevention is aimed at minimizing exposure to UV radiation. The American Cancer Society (ACS) and Centers for Disease Control and Prevention (CDC) recommend the following measures to minimize sun exposure:
  1. Avoid direct exposure to the sun between the hours of 10 a.m. to 4 p.m. (Daylight Savings Time), when UV rays are the most intense.
  2. Wear hats with a brim wide enough to shade face, ears, and neck, as well as clothing that covers as much as possible of the arms, legs, and torso.
    - a. Covering up does not block all UV rays and in general, if you can see light through a fabric, UV rays can also get through it

- b. Clothing with UV protection factor (UPF) can also provide protection from UV radiation. The UPF indicates the level of protection the clothing provides from the sun on a scale of 15 to 50+
- 3. Avoid tanning beds and sun lamps, which provide an additional source of UV radiation.
  - a. Based on a meta-analysis of 27 studies, using tanning beds before the age of 35 can increase the risk of developing melanoma by 59% with increasing usage correlated with increased risk. There was a 1.8% increased risk of melanoma for each additional session of tanning bed use per year.<sup>13</sup>
  - b. Women who are younger than 30 are 6 times more likely to develop melanoma if they tan indoors.<sup>14</sup>
- 4. The CDC recommends covering exposed skin with a sunscreen lotion with a Sun Protection Factor (**SPF**) of **15** or higher even on cloudy and cool days.<sup>11</sup>
  - a. SPF indicates the level of protection against UVB rays, which are the main cause of sunburn. "Broad spectrum" sunscreen has been tested and shown to prevent exposure to both UVB and UVA rays.
  - b. SPF 15 filters out about 93% of UVB rays, SPF 30 filters out about 97% and SPF 50 filters out about 98%. Only broad spectrum sunscreen with SPF of  $\geq 15$  can state it helps to protect against skin cancer and early skin aging if used as directed. SPF < 15 must include a warning indicating that it has been shown to help only with sunburn and not skin cancer or early skin aging.
  - c. Counseling about the appropriate use of sunscreens to optimize benefits including use of about 1 ounce of sunscreen (about a shotglass or palmful) with reapplication every 2 hours (more frequently after swimming or sweating)
  - d. Sun protection beyond sunscreen may be beneficial for those individuals in the sun for prolonged periods of time or who are at high risk of burning
  - e. Sunscreen without an expiration date will have a shelf life of no more than 3 years and will be less if stored in high temperatures.

## B. Screening

- 1. The clinical features used to describe or evaluate a questionable lesion are called the ABCDEs of melanoma – approximately 50% of melanomas evolve from pre-existing nevi, while the remaining are new lesions.<sup>10</sup>
  - a. Asymmetric
  - b. Irregular Borders
  - c. Color of melanoma lesions are often variegated, ranging in color from tan to blue-black, and at times the lesion is intermingled with colors of red, purple, and white.
  - d. Diameter of a melanoma lesion is frequently 6 mm or greater
  - e. Evolving characteristics of a lesion
- 2. A similar 7 point check list (3 major, 4 minor) was designed in England for early detection<sup>15</sup>
  - a. Major criteria: Change in **size, color, shape**

- b. Minor features: **Inflammation, bleeding/crusting, sensory change, diameter** greater than 6 mm
- 3. The American Academy of Dermatology recommends monthly self-examination of skin to serve as a mechanism of recognizing moles or marks on the skin that may be melanoma (derived from publications of the American Academy of Dermatology).<sup>16</sup>
- C. Suspicious lesions should be excised or biopsied by a professional

**Patient Case #1:**

LB is a 42-year-old female with newly diagnosed stage IIC melanoma involving her upper back. LB underwent a complete wide excision and next generation sequencing which confirmed the presence of a BRAF V600E mutation. After discussion, LB wishes to pursue adjuvant therapy.

**Which of the following is the most appropriate adjuvant treatment for LB at this time?**

- A. ipilimumab
- B. nivolumab
- C. encorafenib and binimetinib
- D. pembrolizumab

#### IV. Treatment<sup>1</sup>

- A. The treatment and management of a patient with cutaneous melanoma is based on the stage of disease.
- B. Surgery
  - 1. Complete surgical excision provides best chance for cure. May be used as single modality in localized and regional disease.
  - 2. Defining a clear surgical margin around lesion depends on the thickness but is generally 1-2 cm
    - a. Margins may need to accommodate anatomical or cosmetic considerations (i.e., Moh's surgery)
  - 3. Sentinel lymph node (SLN) mapping and evaluation:
    - a. Consider for patients with clinical stage IB, T1b disease (Breslow depth < 0.8 mm with ulceration or 0.8-1 mm with or without ulceration) or T1a with Breslow depth < 0.8 mm but with other adverse features (very high mitotic index especially with young age and/or lymphovascular invasion).
    - b. SLN biopsy should be offered to patients with stage IB melanoma or greater. If the sentinel node is found to have micrometastatic melanoma, regional dissection of the involved nodal basin can be considered.<sup>1</sup>
- C. Radiation therapy
  - 1. Limited role in melanoma
  - 2. Adjuvant therapy for prevention of nodal relapse in high-risk patients.
  - 3. More commonly confined to palliation of metastatic disease sites that are unresectable
  - 4. Stereotactic radio surgery can be useful for isolated brain metastasis
- D. Adjuvant therapy<sup>1</sup>

## 1. Treatment by extent of tumor

- a. For patients with node negative early stage (stage I - IIA), observation is recommended unless a clinical trial is being considered.
- b. For patients with stage IIB - IIID, adjuvant treatment options following wide excision of the primary tumor and sentinel lymph node (SLN) dissection include:
  - 1) Observation
    - a) This a consideration for patients with very low risk stage IIIA disease (non-ulcerated primary,  $\leq 2$ mm in thickness, SLN metastasis  $< 1$  mm)
    - b) The toxicity of therapy should be weighed against the patient's risk of relapse
  - 2) Pembrolizumab (NCCN Guidelines® category 1 option for patients with AJCC 7<sup>th</sup> Edition stage IIB/C – IIIC disease (IIIA-IIIC with SLN metastasis  $> 1$  mm)<sup>1</sup>
  - 3) Nivolumab (NCCN Guidelines® category 1 option for patients with AJCC 7<sup>th</sup> Edition stage IIIB-IIIC disease)<sup>1</sup>
  - 4) Dabrafenib/trametinib for tumors found to harbor a BRAF V600E/K mutation
  - 5) NCCN Guidelines® category 1 option for patients with AJCC 7<sup>th</sup> Edition stage IIIA with SLN metastasis  $> 1$  mm or stage IIIB/C disease<sup>1</sup>
  - 6) Other BRAF/MEK inhibitor combinations may be considered in the context of unacceptable toxicities to dabrafenib/trametinib
- c. For stage III melanoma not completely resected with satellite (visible cutaneous and/or subcutaneous metastases occurring within 2 cm of the primary melanoma) or in-transit lesions (regional cutaneous and/or subcutaneous metastases at a distance  $> 2$  cm from the primary melanoma):
  - 1) Talimogene laherparepvec (T-VEC) (NCCN Guidelines® category 1 recommendation)<sup>1</sup>
  - 2) NCCN Guidelines category 2B recommendations include BCG, interferon, interleukin-2, local ablation therapy or topical imiquimod.<sup>1</sup>
  - 3) Regional therapy with isolated limb infusion/perfusion with melphalan (NCCN Guidelines category 2A)<sup>1</sup>

## 2. Treatment options in the adjuvant setting

- a. Nivolumab
  - 1) CheckMate 238 was a randomized, double-blind, phase III trial comparing nivolumab to ipilimumab in 906 patients who underwent complete resection of stage IIIB, IIIC or IV melanoma<sup>17, 18</sup>
  - b) Nivolumab was dosed at 3 mg/kg every 2 weeks for up to one year. Ipilimumab was dosed at 10 mg/kg every 3 weeks x 4 doses then every 12 weeks for up to one year.
  - c) The primary endpoint was recurrence-free survival (RFS) which after 4 years was 51.7% in the nivolumab patients and 41.2% in the ipilimumab patients (HR 0.71; 95% CI 0.60-0.86;  $p = 0.0003$ ). 4-year OS was 77.9% in the nivolumab patients and 76.6% in the ipilimumab patients ( $p=0.31$ )<sup>18</sup>



- d) Adverse events were higher in the ipilimumab-treated patients compared with those who received nivolumab
  - i. Grade 3 or 4 adverse effects were seen in 14.4% of nivolumab patients and 45.9% of ipilimumab patients
  - ii. Treatment discontinuation due to adverse effects occurred in 9.7% and 42.6% of patients receiving nivolumab or ipilimumab, respectively
- 2) Based on the results of this trial, nivolumab is now an NCCN Guidelines® category 1 option for patients with AJCC 7<sup>th</sup> Edition stage IIIB/C melanoma following complete resection.<sup>1</sup>
- b. Pembrolizumab
  - 1) EORTC 1325/KEYNOTE-054 was a randomized, double-blind, phase III trial comparing pembrolizumab with placebo in 1019 patients with completely resected stage III melanoma.<sup>19, 20</sup>
    - a) Pembrolizumab was dosed at 200 mg IV every 3 weeks for a total of 18 doses (1 year) or until disease progression.
    - b) The primary endpoints were RFS in both the intent-to-treat (ITT) population and subgroup who were PD-L1 positive
      - i. For the ITT patients: 1-year RFS was 75.4% in the pembrolizumab patients and 61% in those receiving placebo (HR 0.57; 98.4% CI 0.43-0.74; p<0.0001). After 3.5-years, RFS was 59.8% in the pembrolizumab patients and 41.1% in those receiving placebo (HR 0.59; 95% CI 0.49-0.70).
      - ii. PD-L1 positive patients (n=853): 1-year RFS was 77.1% in the pembrolizumab patients and 62.6% in those receiving placebo (HR 0.54; 95% CI 0.42-0.69; p<0.0001). After 3.5-years, RFS was 61.4% in the pembrolizumab patients and 44.1% in those receiving placebo (HR 0.59; 95% CI 0.49-0.73).
      - iii. This benefit was seen across subtypes including patients with BRAF-mutated melanoma
    - c) Grade  $\geq$  3 adverse effects were seen in 14.7% of pembrolizumab patients and 3.4% of those who received placebo. There was one death in the pembrolizumab group due to myositis.
  - 2) KEYNOTE-716 was a randomized, double-blind, phase III trial comparing pembrolizumab with placebo in 976 patients ( $\geq$  12 years old) with completely resected stage IIB or IIC melanoma<sup>21</sup>
    - a) Pembrolizumab was dosed at 200 mg IV every 3 weeks for a total of 17 doses (1 year) or until disease progression.
    - b) The primary endpoint was RFS in the ITT population
      - i. For the ITT population: 1-year RFS was 90% in the pembrolizumab patients and 83% in the those receiving placebo
      - ii. Longer follow-up needed to evaluate impact on overall survival.

- 3) Based on the results of these trials, pembrolizumab is now an NCCN Guidelines® category 1 option for patients with AJCC 7<sup>th</sup> Edition stage III disease following complete resection and a listed option for stage IIB/C disease.<sup>1</sup>

**Patient Case #1, Discussion:**

**Pembrolizumab (answer D):** Pembrolizumab is now approved for adjuvant therapy in resected stage IIB to IIID melanoma. Nivolumab is approved for adjuvant treatment in stage IIIB to IIID. Encorafenib and binimetinib are only approved in BRAF mutated metastatic melanoma. Ipilimumab is no longer recommended for adjuvant treatment in melanoma.

**Patient Case #2**

HB is a 57-year-old man with recently diagnosed stage IIIC BRAF wild-type melanoma involving his scalp. He underwent a wide excision with negative margins and his treatment plan is for adjuvant pembrolizumab. You are asked to provide patient education to HB prior to starting therapy.

Which of the following immune-related toxicities is most likely to occur during the first 4 weeks of treatment with pembrolizumab?

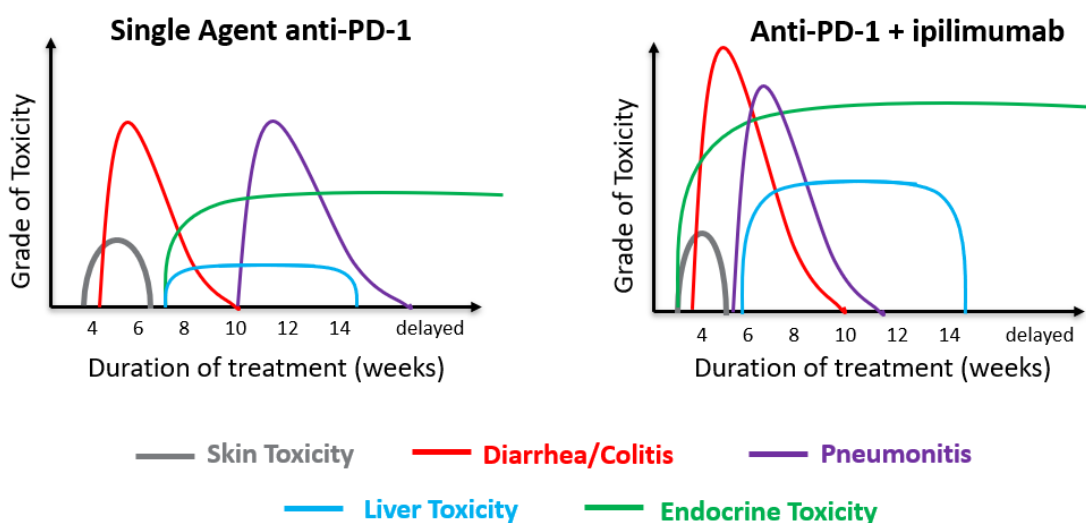
- A. Skin rash
- B. Hypothyroidism
- C. Flu-like symptoms
- D. Elevated liver enzymes

c. Anti-CTLA4 and anti-PD1 Toxicity: <sup>22-24</sup>

- 1) The American Society of Clinical Oncology (**ASCO**) and **NCCN Guidelines**® published a joint guideline focused on the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors initially in June 2018 with subsequent updates by NCCN. These guidelines provide recommendations for the management of toxicities associated with these treatments.
  - a) The importance of patient education is emphasized including mechanism of action of the treatment and the clinical profile of the possible adverse effects prior to starting treatment, throughout treatment, and survivorship.
  - b) When a new side effect occurs, there should be a high suspicion for it being treatment-related
  - c) Though treatment interruption may be needed for some toxicities depending on severity, dose adjustments are not recommended after restarting therapy following toxicity

- 2) Most common immune-related adverse events are seen in the skin and GI tract (similar to graft-versus-host-disease), which are treated with steroids and have a median time to resolution of about 2 weeks with treatment.
  - a) Systemic steroids should be initiated for higher grade toxicity and persistence of low grade toxicity.
  - b) Oral steroids are preferred; however, in cases where absorption may be compromised (i.e. colitis), IV methylprednisolone or equivalent should be used

#### Timeline of anti-PD-1 and anti-PD-L1 Immune Related Toxicities<sup>25</sup>



#### General Management of Immune-Related Adverse Effects<sup>24</sup>

Grade (G)	Management
<b>G1</b>	<ul style="list-style-type: none"> <li>Continue ICPI therapy with close monitoring</li> <li>Exceptions: neurologic, hematologic, and cardiac toxicities</li> </ul>
<b>G2</b>	<ul style="list-style-type: none"> <li>Hold ICPI for most toxicities, resume when resolved to <math>\leq</math> grade 1</li> <li>Prednisone 0.5-1 mg/kg/day or equivalent may be administered</li> </ul>
<b>G3</b>	<ul style="list-style-type: none"> <li>Hold ICPI</li> <li>Start prednisone 1-2 mg/kg/day or methylprednisolone IV 1-2 mg/kg/day with taper over <math>\geq</math> 4-6 weeks</li> <li>If no improvement after 48-72 hours, then consider alternative immunosuppression</li> </ul>
<b>G4</b>	<ul style="list-style-type: none"> <li>Generally warrant permanent ICPI discontinuation (except for endocrine therapy controlled by hormonal replacement)</li> </ul>

ICPI: Immune checkpoint inhibitor

- 3) Skin
  - a) One of the most common immune-related adverse effects seen in about 45% of ipilimumab patients and 34% of patients receiving PD-1 inhibitors. Skin effects commonly occur within the first few weeks after starting therapy.

- b) Common presentations include rash and pruritis. Vitiligo has also been reported in about 8% of melanoma patients receiving either anti-PD-1 therapy alone or in combination with ipilimumab and was positively associated with clinical response.

#### Management of Rash and Inflammatory Dermatitis Immune-Related Adverse Effects<sup>24</sup>

Grading	Management
<b>G1:</b> Rash covering < 10 % BSA, which may or may not be associated with symptoms of pruritis or tenderness	<ul style="list-style-type: none"> <li>Continue ICPI</li> <li>Topical emollients and/or mild/moderate topical corticosteroids</li> <li>Avoid irritants and sun exposure</li> </ul>
<b>G2:</b> Rash covering 10-30% BSA with/without symptoms; limiting instrumental ADL; rash covering >30% with/without mild symptoms	<ul style="list-style-type: none"> <li>Consider holding ICPI, monitor weekly for improvement. If not improved after 4 weeks, regrade as grade 3</li> <li>Treat with Topical emollients, oral antihistamines, and moderate/high topical corticosteroids</li> <li>Consider prednisone 0.5-1 mg/kg, taper over at least 4 weeks. In patients with pruritis without rash, topical anti-itch remedies</li> </ul>
<b>G3:</b> Rash covering >30% BSA with moderate or severe symptoms; limiting self-care ADL	<ul style="list-style-type: none"> <li>Hold ICPI and consult dermatology</li> <li>Treat with Topical emollients, oral antihistamines, and high potency topical corticosteroids. May consider phototherapy for severe pruritis</li> <li>Oral prednisone or equivalent (1 mg/kg/day) tapering over at least 4 weeks</li> <li>Once downgraded to ≤ G1 and prednisone &lt;10 mg/day, may resume ICPI with close monitoring and follow up with dermatology</li> <li>In patients with pruritis without rash, may treat with gabapentin, pregabalin, aprepitant, dupilumab</li> </ul>
<b>G4:</b> Severe consequences requiring hospitalization/urgent intervention or life-threatening consequences	<ul style="list-style-type: none"> <li>Hold ICPI, consult dermatology, admit patient</li> <li>Methylprednisolone 1-2 mg/kg, slow taper when toxicity resolves</li> <li>Monitor closely for progression</li> <li>Consider alternative future therapy or restart ICPI when resolved to G1 with close follow-up</li> </ul>

#### 4) Gastrointestinal<sup>26,27</sup>

- a) Diarrhea is more common with ipilimumab compared with the PD-1 inhibitors with the more severe colitis being seen in around 8-22% of ipilimumab-treated patients.
- b) One of the most common grade 3 or higher toxicities seen with ipilimumab and is often the first immune-related toxicity that leads to treatment discontinuation.

#### Management of Colitis Immune-Related Adverse Effects<sup>24</sup>

Grading	Management
<b>G1:</b> Increase of < 4 stools /day or mild increase in ostomy output	<ul style="list-style-type: none"> <li>• May continue ICPI or hold until &lt; G1</li> <li>• Monitor dehydration, rule out infection, may include loperamide</li> </ul>
<b>G2:</b> Increase in 4-6 stools/day, moderate increase in ostomy output	<ul style="list-style-type: none"> <li>• Hold ICPI until <math>\leq</math> G1 (may permanently d/c CTLA-4 inhibitors)</li> <li>• Consult with gastroenterology, consider EGD/colonoscopy to stratify for infliximab or vedolizumab</li> <li>• Initiate prednisone 1 mg/kg/day, taper over 4-6 weeks when <math>\leq</math> G1</li> </ul>
<b>G3:</b> Increase in $\geq$ 7 stools/day, incontinence, severe ostomy output, hospitalization indicated; limiting self-care ADL	<ul style="list-style-type: none"> <li>• As above for G3, with hospitalization for electrolyte replacement initiate prednisone 1-2 mg/kg/day, consider methylprednisolone</li> <li>• If symptoms <math>\geq</math> 3 days or recur after improvement, consider infliximab or vedolizumab</li> <li>• Consider permanent discontinuation of CTLA-4 agent</li> </ul>
<b>G4:</b> Life threatening consequences	<ul style="list-style-type: none"> <li>• Follow G2-G3 recommendations</li> <li>• Permanently discontinue ICPI</li> <li>• Methylprednisolone 1-2 mg/kg/day</li> <li>• Infliximab or vedolizumab if inadequate response to steroids</li> </ul>

#### 5) Hepatic<sup>24</sup>

- a) Typically occurs in about 5-10% of patients receiving either single agent ipilimumab or PD-1 inhibitors with less than 2% of cases being grade 3 or higher. Combination therapy results in about 15% grade 3 hepatitis.
- b) Liver enzymes (LFT) and bilirubin should be assessed prior to each cycle of immunotherapy
- c) Therapy should be withheld for grade 2 elevations and systemic corticosteroids (e.g. prednisone 1-2 mg/kg/day) should be started for persistent grade 2 or more severe toxicity.
- d) If grade 3 or 4, LFT monitoring should be done daily or every other day. For LFT and/or bilirubin elevations, immunotherapy should be permanently discontinued and systemic corticosteroids started. If no response after 2-3 days, then mycophenolate mofetil or azathioprine can be added. Infliximab not recommended due to risk of hepatitis.

#### 6) Endocrine

- a) Typically appear later in therapy and are the last to reverse, though in some cases may not be completely reversible.
- b) Monitoring of ACTH, thyroid function (TSH and T4), blood glucose, testosterone and other endocrine markers as appropriate at baseline and during the course of therapy is recommended.
- c) Treatment includes correcting the endocrine abnormality with steroids and/or hormonal replacement (i.e. levothyroxine, testosterone, etc.)

- d) A meta-analysis comparing incidence of endocrine dysfunction across the different immunotherapies assessed 7551 patients who received either a PD-1 inhibitor, CTLA-4 inhibitor, or the combination of the two.<sup>28</sup>
- Patients receiving combination therapy had the higher rates of hypothyroidism (OR 3.81;  $p < 0.01$ ) and hyperthyroidism (OR 4.27;  $p = 0.001$ ) compared to ipilimumab monotherapy.
  - Patients receiving PD-1 inhibitor monotherapy had a higher rate of hypothyroidism (OR 1.89;  $p = 0.03$ ) though were less likely to experience hypophysitis (OR 0.29;  $p < 0.001$ ) compared with ipilimumab monotherapy

#### Management of Hypothyroid Immune-Related Adverse Effects<sup>24</sup>

Grading	Management
<b>G1:</b> TSH > 4.5 and < 10 mIU/L and asymptomatic	<ul style="list-style-type: none"> <li>Continue ICPI with monitoring of TSH (option for free T4) every 4-6 weeks as part of routine care</li> </ul>
<b>G2:</b> Moderate symptoms, TSH persistently > 10 mIU/L	<ul style="list-style-type: none"> <li>May continue or hold ICPI until symptoms resolve to baseline</li> <li>Consider endocrine consult</li> <li>Thyroid supplementation in symptomatic patients with TSH levels &gt; 10 mIU/L, monitor every 6-8 weeks while titrating</li> </ul>
<b>G3-4:</b> Severe symptoms, life threatening consequences	<ul style="list-style-type: none"> <li>Hold ICPI until symptoms resolve to baseline with appropriate supplementation</li> <li>Endocrine consultation</li> <li>May admit for IV therapy such as steroids if bradycardia and/or hyperthermia is present, depending on the underlying endocrinopathy</li> <li>All the above from G2</li> </ul>

#### 7) Lung toxicity

- Reported incidence is variable from 0% to 10%. In a combined analysis of 915 patients treated with anti-PD-1/PD-L1 therapy, pneumonitis developed in 5% of patients with a time of onset ranging from 9 days to 19.2 months.<sup>29</sup> Earlier occurrences have been reported with combination therapy compared with single agent.
- The incidence appears higher in patients receiving combined anti-PD-1 and anti-CTLA-4 therapy than monotherapy. Patients treated with single agent ipilimumab appear to have lower rates of pneumonitis than patients receiving single agent anti-PD-1 inhibitors.
- It is unclear whether tumor type is associated with occurrence of pneumonitis with some studies showing higher rates in patients with lung and renal cell cancer compared with melanoma but this has not been consistent.

## Management of Lung Immune-Related Adverse Effects <sup>24</sup>

Grading	Management
<b>G1:</b> Asymptomatic, confined to one lung lobe or < 25% of lung parenchyma	<ul style="list-style-type: none"> <li>• Hold ICPI with radiographic evidence of pneumonitis progression</li> <li>• May resume ICPI with radiographic evidence of improvement or resolution. If no improvement, treat as a grade 2.</li> <li>• Monitor weekly</li> </ul>
<b>G2:</b> Symptomatic, involves more than one lung lobe or 25-50% of lung parenchyma, medical intervention indicated	<ul style="list-style-type: none"> <li>• Hold ICPI until resolution to <math>\leq</math> grade 1</li> <li>• Prednisone 1-2 mg/kg/day with taper by 5-10 mg/week over 4-6 weeks</li> <li>• Consider empirical antibiotics</li> <li>• Monitor every 3 days, if no improvement after 48-72 hours of prednisone, treat as grade 3.</li> </ul>
<b>G3:</b> Severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, oxygen indicated	<ul style="list-style-type: none"> <li>• Permanently discontinue ICPI</li> <li>• Empirical antibiotics and methylprednisolone IV 1-2 mg/kg/day, if no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil or IVIG for 5 days or cyclophosphamide. Steroids should be tapered over 4-6 weeks</li> </ul>
<b>G4:</b> Life threatening respiratory compromise, urgent intervention (intubation) required	<ul style="list-style-type: none"> <li>• Pulmonary and infectious disease consults if necessary</li> <li>• Hospitalize for further management</li> </ul>

### 8) Less common immune-related toxicities:

- a) These include musculoskeletal, renal, nervous system, hematologic, cardiovascular and ocular.
- b) Detailed guidelines regarding management are available in the ASCO Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors document<sup>24</sup> and the NCCN Guidelines® on Management of Immunotherapy -Related Toxicities.<sup>30</sup>

### 9) Immunosuppression considerations:<sup>24</sup>

- a) Some patients may require longer steroid tapers of > 4 weeks and even up to 6-8 weeks or longer, especially for pneumonitis and hepatitis
- b) Prophylaxis considerations:
  - i) Herpes zoster prophylaxis may be considered in patients with prior zoster infection.
  - ii) For patients with a higher risk of gastritis, proton pump inhibitors or H2 blockers can be considered
  - iii) Patients receiving prednisone 20 mg (or equivalent) daily **for  $\geq$  4 weeks** or >30 mg **for 3 weeks or more** may require pneumocystis jirovecii pneumonia (PJP) prophylaxis
  - iv) Patients receiving prednisone 20 mg (or equivalent) daily **for > 12 weeks** may require **antifungal** prophylaxis
- c) Vitamin D and calcium should be used to prevent osteoporosis

- d) Inactivated vaccines may be used during immunotherapy but live vaccines should be avoided due to lack of data currently
- 10) Immunotherapy should be used with caution in patients with pre-existing autoimmune disorders, organ transplantation or prior stem cell transplantation though successful use has been reported.<sup>31</sup>
- 11) An observational, cross-sectional pharmacovigilance cohort study assessed the rate of recurrence of irAE after rechallenge with an immune checkpoint inhibitor using the WHO VigiBase database<sup>32</sup>
  - a) A total of 24,079 irAE cases were identified with 452 of 6,123 irAEs being associated with immune checkpoint rechallenge and included for analysis
  - b) The recurrence rate of the initial irAE was 28.8% with colitis, hepatitis and pneumonitis having the highest rates of recurrence following re-challenge with immune checkpoint inhibitor therapy.

**Patient Case #2, Discussion:**

**Skin rash (answer A)** is usually seen after 2-3 weeks of immunotherapy treatment with an agent like pembrolizumab. Gastrointestinal side effects, including diarrhea and colitis, as well as elevations in liver enzymes generally occur after 6-7 weeks. Endocrine toxicity, including hypophysitis and hypothyroidism, are typically seen after several doses, around 9 weeks or later but can be prolonged. Pembrolizumab does not typically cause flu-like symptoms like those seen traditionally with interferon.

- d. Dabrafenib and Trametinib<sup>33</sup>
  - 1) The combination of the BRAF-inhibitor dabrafenib and MEK-inhibitor trametinib was assessed in a double-blind, placebo controlled trial of 870 patients with completely resected, stage III melanoma with either a BRAF V600E or V600K mutation.
    - i. Patients were randomized 1:1 to receive either dabrafenib 150 mg PO BID and trametinib 2 mg PO daily or matched placebo for a duration of 12 months
    - ii. The primary endpoint was RFS and the estimated 3-year RFS rate was 58% in the combination therapy arm and 39% in the placebo arm (HR 0.47; 95% CI 0.39-0.58; p<0.001).
    - iii. The 3-year OS rate was 86% and 77% in the combination and placebo arms, respectively (HR 0.57; p=0.0006)
    - iv. An updated 5-year analysis showed a RFS of 52% in patients treated with dabrafenib and trametinib and 36% in patients treated with placebo (HR 0.51; 95% 0.42-0.61)<sup>34</sup>
    - v. The most common toxicities in the combination arm were pyrexia, fatigue and nausea, (see additional details in the metastatic treatment setting below). In this trial, 26% of combination-treated patients discontinued therapy due to toxicity and 38% of patients required a dose reduction.
  - 2) The combination of dabrafenib and trametinib is a NCCN Guidelines® category 1 option for patients with AJCC 8<sup>th</sup> Edition stage IIIA with sentinel lymph node metastasis > 1 mm or stage IIIB/C disease<sup>1</sup>



- 3) It remains unclear whether patients with BRAF mutations derive the most benefit from adjuvant BRAF/MEK inhibitors or immunotherapy. This is the focus of ongoing clinical trials.
  - 4) See additional information the section below on the use of this combination in the metastatic setting
- e. Intralesional vaccine therapy: Talimogene laherparepvec (T-VEC)
- 1) First therapeutic vaccine for melanoma, approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.<sup>35</sup>
    - a) T-VEC is an HSV-1 derived oncolytic virus that exerts its mechanism of action by selectively replicating in tumor cells, which results in cell lysis. The virus is modified through deletion of ICP34.5 to decrease viral pathogenicity and increase tumor-selective replication and deletion of ICP47 to decrease virally mediated antigen presentation suppression and increase HSV US11 gene expression<sup>36</sup>
    - b) It is also engineered to express granulocyte-macrophage colony stimulating factor (GM-CSF) to further enhance cancer immunity.<sup>36</sup>
  - 2) NCCN Guidelines® list it as a category 1 recommendation for patients with unresectable stage III melanoma with in-transit or satellite lesions<sup>1</sup>.
  - 3) Dosing is based on the size of the lesion with a max of 4 mL total given intralesionally across all treated lesions.<sup>37</sup>
  - 4) Approval was based on a randomized, open-label, phase III trial of 436 patients with unresected stage IIIB or IV melanoma suitable for direct or ultrasound-guided injection of at least 1 cutaneous, subcutaneous, or nodal lesion or aggregation of lesions  $\geq 10$  mm in diameter.<sup>35</sup>
    - a) Patients were randomized 2:1 to either T-VEC administered at  $10^6$  plaque forming units(pfu)/mL to seroconvert HSV-seronegative patients followed 3 weeks later by treatment doses of  $10^8$  pfu/mL every 2 weeks or GM-CSF 125 mcg/m<sup>2</sup> once daily for 14 days of every 28 day cycle.
    - b) The primary endpoint was durable response rate (DRR), defined as an objective response lasting continuously for at least 6 months by independent review. The DRR was 19% with T-VEC and 1.4% with GM-CSF ( $p < 0.0001$ ). The overall RR was 31.5% in those treated with T-VEC with a 16.9% complete response rate compared with 1.4% and less than 0.7% in the GM-CSF group, respectively. Among the patients who achieved a CR, 88.5% were alive at 5 years<sup>38</sup>
    - c) The final updated analysis showed a median OS of 23.3 months with T-VEC and 18.9 months with GM-CSF (unstratified HR 0.79;  $p = 0.0494$ )<sup>38</sup>
    - d) T-VEC was well tolerated with the most common adverse effects being fatigue, chills, and pyrexia. No premedication was required. The only grade 3 or higher toxicity was cellulitis, seen in 2.1% of patients.
    - e) The greatest response benefits were seen in treatment-naïve patients and those with stage IIIB, IIIC and IV M1a disease. Responses were seen in both injected and uninjected lesions<sup>35</sup>

- f) Viral shedding occurs at the injection site and can pass through the dressing placed following injection<sup>37</sup>.
- g) Blood should be considered infectious and viral DNA was found in the urine on the day of the injection but cleared afterwards.
- h) Acyclovir and other antiherpetic viral agents should be avoided as they may interfere with the effectiveness of T-VEC
- i) Patient recommendations include educating the importance of avoiding direct contact with treatment sites, dressings or body fluids. Gloves should be worn when dressings are changed and the injection site should be covered for at least 1 week following the injection. All used dressings and cleaning materials should be disposed of in a sealed plastic bag before disposing in the garbage.<sup>37</sup>

**Patient Case #3:**

KL is a 48-year-old woman with newly diagnosed cutaneous melanoma of her right upper arm. Additional imaging shows 2 suspicious lesions in her lung which are biopsied and consistent with metastatic melanoma. Next generation sequencing is performed on the lung specimen and is negative for any pathogenic BRAF alterations. She is asymptomatic with no significant past medical history and has extensive family support. She wishes to be as aggressive as possible treatment.

**Which of the following treatment options is most appropriate for KL at this time?**

- A. Pembrolizumab
- B. Vemurafenib, cobimetinib and atezolizumab
- C. Ipilimumab and nivolumab
- D. Pembrolizumab and low-dose ipilimumab

**E. Metastatic disease**

**1. First line systemic therapy options:<sup>1</sup>**

- a. Nivolumab (NCCN Guidelines category 1, preferred)
- b. Pembrolizumab (NCCN Guidelines category 1, preferred)
- c. Combination nivolumab plus ipilimumab (NCCN Guidelines category 1, preferred)
  - 1) Useful in certain circumstances with relative indications for combination therapy over single agent including the patient's willingness to take on the high risk of treatment-related toxicities, the absence of comorbidities or autoimmune processes that would elevate the risk of irAE, presence of social support and anticipated compliance with medical team to handle toxicities and/or the absence/low tissue PD-L1.
- d. Nivolumab/Relatlimab (NCCN Guidelines category 2A, preferred)
- e. Pembrolizumab and low-dose ipilimumab (NCCN Guidelines category 2B, other recommended regimen)

- f. For patients with BRAF V600-activating mutations (all doublet combinations are NCCN Guidelines category 1. They are preferred over immune checkpoint inhibitor therapy if clinically needed for an early response):
  - 1) Dabrafenib and trametinib (preferred)
  - 2) Vemurafenib and cobimetinib (preferred)
  - 3) Encorafenib and binimetinib (preferred)
  - 4) Combination of vemurafenib, cobimetinib and atezolizumab is a NCCN category 2A, other recommended regimen

## **2. Second or Subsequent Systemic Therapy Options for Metastatic Melanoma<sup>1</sup>**

- a. For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and if from a different class.
- b. For patients who progressed on single-agent anti-PD-1 checkpoint immunotherapy, nivolumab/ipilimumab combination therapy or ipilimumab monotherapy is a reasonable treatment option.
- c. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered

## Second or Subsequent Systemic Therapy Options for Metastatic Melanoma<sup>1</sup>

Preferred Regimens	Useful in Certain Circumstances
Nivolumab	Ipilimumab and intralesional T-VEC (category 2B)
Pembrolizumab	Imatinib (for tumors with KIT-activating mutations)
Nivolumab and ipilimumab	Binimetinib for NRAS-mutated tumors after progression on prior immune checkpoint inhibitor therapy (category 2B)
Nivolumab/Relatlimab	
Pembrolizumab and low-dose ipilimumab (following progression on prior anti-PD-1 therapy)	Larotrectinib or entrectinib for activating NTRK gene fusions
Dabrafenib and trametinib (BRAF-mutated)	Cytotoxic agents*
Vemurafenib and cobimetinib (BRAF-mutated)	Pembrolizumab/lenvatinib (Category 2B) for patients who have progressed after treatment with anti-PD-1/PD-L1 therapy including with ipilimumab for $\geq 2$ doses
Encorafenib and binimetinib (BRAF-mutated)	
Other Regimens	
Ipilimumab	
High-dose interleukin-2: should not be used for patients with inadequate organ reserve, poor performance status or untreated or active brain metastases. Therapy should be restricted to an institution with medical staff experienced in the administration of the drug.	

\* Case-by-case basis for patients who are unable to receive immunotherapy and/or targeted therapy, which are preferred options. Cytotoxic agents that have been used alone or in combination include (but are not limited to): dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin/paclitaxel, and cisplatin/vinblastine/dacarbazine (CVD) (category 2B for CVD)

**\*\*All recommendations are category 2A unless otherwise indicated**

### Patient Case #3, Discussion:

#### Answer C: Ipilimumab and nivolumab

Ipilimumab and nivolumab is most appropriate. All of the answers are options for first-line metastatic melanoma; however, she is young, healthy with strong family support and can likely tolerate the combination of ipilimumab and nivolumab. This combination is most useful over single agent when the patient is willing to take on the high risk of treatment-related toxicities, the absence of comorbidities or autoimmune processes that would elevate the risk of irAE, and the presence of social support. This would make it preferred over single agent pembrolizumab and the combination with low-dose ipilimumab (category 2A). She does not have a BRAF V600 mutation and so BRAF/MEK therapy is not indicated.

KL starts on combined ipilimumab and nivolumab x 4 doses and then continues on single agent nivolumab. Three months following the start of therapy, KL is tolerating therapy well but having low grade fatigue. Her disease is responding to therapy. While at a routine monitoring visit, her TSH level is 12 mIU/L

#### Based on this finding, what is the most appropriate management strategy at this time?

- A. Continue nivolumab and monitor TSH
- B. Hold nivolumab until TSH normalizes
- C. Continue nivolumab and start levothyroxine
- D. Continue nivolumab and start levothyroxine and prednisone 1 mg/kg

3. BRAF V600 should be assessed in all stage III and metastatic melanomas.<sup>1, 5</sup>
  - a. BRAF V600 mutations are found in 40-50% of cutaneous melanomas. The V600E mutation is the most common, representing about 80-90% of the BRAF mutations while 5-12% are V600K. In V600E or V600K mutated tumors, the initial selection between BRAF inhibitors and immunotherapy is commonly done based on the aggressive nature of the tumor. While patients with BRAF V600K mutations still benefit from BRAF +/- MEK inhibitor therapy, responses may be slightly lower.
  - b. BRAF non-V600 mutations near V600E such as BRAF L597 and K601 have derived some clinical benefit to inhibitors of BRAF and MEK while mutations in other codons like exon 11 or exon 15 have not shown responses.<sup>39</sup>
  - c. Rapidly growing tumors that are symptomatic are preferentially treated with BRAF-directed therapy because it generates a higher response rate and quicker response, while asymptomatic or more indolent tumors may be treated with immunotherapy.
  - d. Effects on the biology or best sequence from a large randomized trial are unclear but trials are underway to better assess.<sup>1</sup>
4. Surgery: metastasectomy of isolated lesions may result in prolonged survival in patients where resection is anatomically possible<sup>1</sup>
5. Immunotherapy (anti-PD1 and anti-CTLA4 therapy) in the metastatic setting
  - a. Patient responses have been described to fall into 1 of four categories:<sup>40</sup>
    - 1) **A:** response in baseline lesions
    - 2) **B:** “stable disease” with slow, steady decline in total tumor volume
    - 3) **C:** response after initial increase in total tumor volume
    - 4) **D:** reduction in total tumor burden after the appearance of new lesions.
    - 5) Both C and D above are traditionally considered progression of disease, but this is not necessarily the case with immunotherapy. Consequently, there has been discussion and proposed response criteria developed for immunotherapy (immune related Response Criteria; irRC).<sup>40</sup>
  - ii. Pseudoprogression<sup>1</sup>
    - 1) Describes when there is radiographic or clinically evident increase in tumor size early in the treatment course followed by regression
    - 2) Average time to response can vary between 6 to 12 weeks
    - 3) NCCN Guidelines recommend continuing immune checkpoint inhibitor therapy for an additional 6 to 10 weeks even in the presence of tumor growth
    - 4) Continued growth at 16 weeks after starting therapy can be considered true progression

### Comparison of Response Criteria for Immunotherapy <sup>40</sup>

	WHO	irRC
New, measurable lesions (i.e., $\geq 5 \times 5$ mm)	<u>Always represent PD</u>	<u>Incorporated into tumor burden</u>
New, nonmeasurable lesions (i.e., $< 5 \times 5$ mm)	<u>Always represent PD</u>	<u>Do not define progression (but preclude irCR)</u>
Non-index lesions	Changes contribute to defining CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR (complete response)	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR (partial response)	$\geq 50\%$ decrease in all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	$\geq 50\%$ decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD (stable disease)	50% decrease in the sum of the product of the diameters (SPD) compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD (progressive disease)	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

#### **Patient Case #3, Continued:**

##### **Answer C:**

KL has grade 2 hypothyroidism as evidenced by increasing low grade fatigue and TSH 12mIU/L. Thyroid supplementation is recommended in symptomatic patients with TSH  $> 10$  mIU/L with monitoring every 6-8 weeks while the dose is titrated. Nivolumab can be held, but this is clinical judgment based on the severity of side effects. This patient is only having low grade fatigue; therefore, immunotherapy can be continued. Steroids are not typically utilized for immune-related hypothyroid like other immune-related toxicities.

#### **Patient Case #4**

MT is a 51-year-old man with newly diagnosed metastatic melanoma involving the scalp, liver, lungs and numerous lymph nodes. Biopsy of the liver confirms the diagnosis and next generation sequencing performed on the specimen shows a BRAF V600E mutation. He has moderate to severe shortness of breath requiring oxygen and moderate abdominal pain requiring daily opioids for management.

##### **Which of the following options is most appropriate first-line therapy for MT at this time?**

- A. Talimogene laherparepvec (T-VEC)
- B. Pembrolizumab + low-dose ipilimumab
- C. Vemurafenib
- D. Encorafenib and binimetinib

iii. Pembrolizumab.<sup>41-43</sup>

- 1) First line therapy: The KEYNOTE-006 trial<sup>42</sup> compared 2 dosing regimens of pembrolizumab with ipilimumab in 834 patients with unresectable, stage III or IV melanoma who had received no more than 1 previous therapy for advanced disease. Approximately 66% of patients were untreated and >95% had metastatic disease.
  - a) It is important to note that this dose of pembrolizumab in this study (10 mg/kg) is different than the 200mg every 3 week dose that is currently FDA-approved for metastatic melanoma.
  - b) For the long-term outcome analysis, the 2 pembrolizumab groups were combined due to similarity in results

**5-Year Outcomes from KEYNOTE-006<sup>43</sup>**

	Pembrolizumab 10 mg/kg q 2 or 3 weeks*	Ipilimumab 3 mg/kg q 3 weeks x 4 doses	
Median PFS	8.4 months	3.4 months	HR 0.55, 95% CI 0.48-0.67, p < 0.0001
Median OS	32.7 months	15.9 months	HR 0.73, 95% CI 0.61-0.88, p < 0.00049

\*Pembrolizumab was continued until disease progression in each arm while ipilimumab was only give for a total of 4 doses.

- c) The estimated 24-month PFS in patients with complete and partial responses was 85.4% and 82.3%, supporting the durable nature of these responses.<sup>43</sup>
  - d) Treatment toxicities were lower in the pembrolizumab arms with grade ≥ 3 toxicities in 17% of the combined pembrolizumab-treated patients compared to 20% of the ipilimumab-treated patients. The most common treatment-related effects were colitis, diarrhea and fatigue.<sup>43</sup>
  - e) Single agent pembrolizumab is a NCCN category 1 preferred regimen option for first line therapy<sup>1</sup>
- 2) Pembrolizumab and low-dose ipilimumab<sup>44, 45</sup>
  - a) KEYNOTE-029 assessed the combination of pembrolizumab (initially 2 mg/kg amended to 200 mg) every 3 weeks plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by pembrolizumab alone for up to 2 years in 153 patients with advanced melanoma who had not received prior immune checkpoint inhibitor therapy
  - b) Safety was the primary endpoint with secondary endpoints of ORR, PFS and OS (median follow-up of 36.8 months)
    - i. ORR was 62.1% with 27.5% complete responses and 34.6% partial responses
    - ii. Median PFS and OS were not reached
    - iii. 36-month PFS was 59.1% and OS was 73.4%

- c) This combination is an NCCN category 2B option for first line therapy
- 3) Second line therapy<sup>41, 46</sup>
  - a) 70 patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody therapy were enrolled with the median length of prior treatment being 4.8 months
    - i. Treatment was pembrolizumab 200 mg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by pembrolizumab monotherapy
    - ii. Primary endpoint was response rate by irRECIST: 29% with 5 complete and 15 partial responses
    - iii. Median PFS was 5 months
    - iv. Median OS was 24.7 months
    - v. Response was not associated with median time on prior anti-PD-1/L1 antibody therapy or time to starting pembrolizumab/ipilimumab

This combination is an NCCN category 2A option (along with other options) for second line therapy

- 4) Pembrolizumab and Lenvatinib
  - a) LEAP-004: 103 patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody therapy or combination immunotherapy<sup>47</sup>
    - i. Treatment was pembrolizumab 200 mg every 3 weeks with lenvatinib 20 mg once daily
    - ii. Primary endpoint was overall response rate: 21.4 % with 3 complete and 19 partial responses
    - iii. Median PFS was 4.2 months
    - iv. Median OS was 14 months
    - v. Grade 3-5 treatment related AEs: 45.6 %, most commonly hypertension (21.4%), with one death from decreased platelet count
- iv. Nivolumab +/- ipilimumab
  - 1) First-line therapy: CheckMate 067<sup>48</sup> study compared single agent nivolumab with single agent ipilimumab or the combination of nivolumab and ipilimumab in this placebo-controlled trial of 945 patients with previously untreated, unresectable stage III or IV melanoma.



## 6.5-Year Outcomes from CheckMate 067<sup>49,50</sup>

	Nivolumab 3 mg/kg q 2 weeks*	Ipilimumab 3 mg/kg q 3 weeks x 4 doses	Nivolumab and Ipilimumab**	P value
Median PFS	6.9 months	2.9 months	11.5 months	<0.001 for both nivolumab and the combination vs. ipilimumab
Median OS	36.9 months	19.9 months	72.1 months	<0.001 for both nivolumab and the combination vs. ipilimumab

\*Nivolumab was continued until disease progression in each arm while ipilimumab was only give for a total of 4 doses

\*\* Nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks x 4 doses followed by nivolumab 3 mg/kg every 2 weeks for cycle 3 and beyond until toxicity or progression. Note that the FDA approved dosing recommends the flat dose of nivolumab 240 mg every 2 weeks after the initial 4 doses of ipilimumab.

- a) Notably, the median OS and PFS in patients who discontinued ipilimumab and nivolumab due to treatment-related toxicities were similar to patients who did not discontinue due to toxicity
- b) Patients with PD-L1 positive tumors had similar benefits from the 2 nivolumab arms with a median PFS of about 14 months for single agents and combination. The PD-L1 negative patients had a higher median PFS with the combination (11.2 months) compared with nivolumab alone (5.3 months).
- c) Grade 3 or higher treatment-related toxicities were highest in the combination group (55%) compared with the single agent nivolumab (16.3%) or ipilimumab (27.3%) patients. Drug discontinuation due to toxicity occurred in 36.4% of the patients treated in the combination group compared to 7.7% with nivolumab monotherapy and 14.8% of ipilimumab monotherapy arms<sup>48</sup>
- d) Both **single agent nivolumab** and the combination of **ipilimumab and nivolumab** are NCCN Category 1 preferred options for first line therapy<sup>1</sup>

Combination therapy is associated with higher clinical response rates, PFS and OS but needs to be balanced with the increase risk of toxicity so may be preferred in patients with good performance status who have appropriate supportive resources

**CheckMate 067: Toxicity comparison between nivolumab, ipilimumab and the combination<sup>48</sup>**

Toxicity (%)	Nivolumab		Ipilimumab		Nivolumab and Ipilimumab	
	All grade	Grade 3 - 4	All grade	Grade 3 - 4	All grade	Grade 3 - 4
Diarrhea	19.2	2.2	33.1	6.1	44.1	9.3
Fatigue	34.2	1.3	28	1	35	4.2
Rash	25.9	0.6	32.8	1.9	40.3	4.8
Increased ALT	3.8	1.3	3.9	1.6	17.6	8.3
Increased AST	3.8	1.0	3.5	0.6	15.3	6.1
Hypothyroidism	8.6	0	4.2	0	15	0.3
Colitis	1.3	0.6	11.6	8.7	11.8	7.7
Arthralgia	7.7	0	6.1	0	10.5	0.3
Dyspnea	4.5	0.3	4.2	0	10.2	0.6

**2) Nivolumab/Relatlimab-rmbw<sup>51</sup>**

- a) Mechanism of action: Combination of nivolumab (PD-1 inhibitor) and relatlimab-rmbw (LAG-3 inhibitor)
  - i. Lymphocyte-activation gene-3 (LAG-3) inhibitor blocks the interaction between LAG-3 and its ligands (including MHC II) to reduce LAG-3 pathway-mediated immune response inhibition. Antagonism of this pathway promotes T cell proliferation and cytokine secretion.
- b) RELATIVITY-047 evaluated the combination versus nivolumab alone in 714 patients with previously untreated metastatic or unresectable melanoma. <sup>51</sup>
- c) Nivolumab 480 mg/relatlimab-rmbw 160 mg every 4 weeks versus nivolumab 480 mg every 4 weeks until disease recurrence
- d) Primary endpoint was progression-free survival
  - i. Median PFS 10.1 months versus 4.6 months
  - ii. 12-month PFS: 47.7% versus 36%
- e) Grade 3 or 4 irAEs: 18.9% versus 9.7%

Toxicity (%)	Nivolumab		Nivolumab/relatlimab-rmbw	
	All grade	Grade 3 and 4	All grade	Grade 3 and 4
Puritis	15.9	0.6	23.4	0
Fatigue	12.8	0.3	23.1	1.1
Rash	12	0.6	15.5	0.8
Arthralgia	7.2	0.3	14.4	0.8
Hypothyroidism	12	0	14.4	0
Diarrhea	9.2	0.6	13.5	0.8
Vitiligo	9.7	0	10.4	0
<b>Hepatitis</b>	<b>2.5</b>	<b>1.1</b>	<b>5.6</b>	<b>3.9</b>

f) This combination is a NCCN preferred, category 2A option for first line therapy

### 3) Second line therapy<sup>52</sup>

- a) Patients with advanced melanoma who had received at least one prior line of therapy, including prior immunotherapy, were treated with escalating doses of nivolumab every 2 weeks until disease progression or toxicity.
  - i. Median OS was 16.8 months with 1-year and 2-year survival of 62% and 43%, respectively.
  - ii. Most common toxicities of any grade were fatigue (32%), rash (23%) and diarrhea (18%).

#### **Patient Case #4, Continued:**

##### **Answer D: Encorafenib and binimetinib**

MT has symptomatic BRAF V600E mutated metastatic melanoma. Other first line therapy options include inhibitors of BRAF (including dabrafenib and vemurafenib) and MEK (including trametinib and cobimetinib.) The combination of a BRAF and MEK inhibitor has resulted in improved outcomes compared with the BRAF inhibitor alone and BRAF-targeted therapy is preferred over immunotherapy when patients are symptomatic and/or have rapidly growing tumors. T-VEC is currently only approved for unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (not metastatic disease).

**MT is beginning treatment with encorafenib and binimetinib. What baseline labs or other monitoring should be ordered?**

- A. Mg, Phos
- B. CBC, CMP, CPK, EKG, echocardiogram, routine eye exams
- C. PFTs, Chest x-ray, CMP
- D. INR, PT/PTT

4. BRAF / MEK targeted therapies in the metastatic setting
  - a. Dabrafenib, encorafenib and vemurafenib are all BRAF inhibitors. Trametinib, binimetinib and cobimetinib are all MEK inhibitors.<sup>53-56</sup>
  - b. BRAF and MEK inhibitor toxicities:<sup>53, 54</sup>
    - 1) The most common BRAF inhibitor all grade toxicities include: rash, photosensitivity, hair loss, and joint pain though the incidence differs slightly between the 3 agents.
    - 2) Grade 3 toxicities included dermatologic effects (rash, keratoacanthoma and cutaneous squamous cell cancer), gastrointestinal, fatigue, and joint pain.
    - 3) Cutaneous squamous cell cancers and keratoacanthomas are the result of compensatory RAF signaling and are decreased with the addition of a MEK inhibitor.
      - i. In the phase III trial with vemurafenib alone, the rate of grade 3 cutaneous squamous cell cancer was 12% but was higher in the phase I and II trials at 26%.
      - ii. These cancers are typically localized and easily treated with surgical excision or topical fluorouracil cream.
      - iii. Regular skin assessments should be done throughout therapy with BRAF inhibitors.<sup>54</sup>
    - 4) Pyrexia (defined as a temperature of  $\geq 38.5$  C) is seen in about 55% of patients receiving BRAF and MEK inhibitor combination therapy<sup>53, 54</sup>
      - i. Usual onset of 2-4 weeks following the start of therapy and lasting a median duration of 9 days.
      - ii. Holding the BRAF and MEK inhibitor therapy at the onset of pyrexia will typically lead to resolution and therapy can be restarted at full dose upon cessation.
      - iii. For prolonged or severe pyrexia that does not resolve with holding of therapy, prednisone 10 mg PO daily can be used
      - iv. Patients should be educated to use antipyretics and increase fluid intake
    - 5) It is recommended to hold BRAF and/or MEK inhibitors 1 day before and after stereotactic radiosurgery (SRS) and at least 3 days before and after fractionated radiation therapy
  - c. Though initially evaluated as single agents, combination therapy is now the recommended treatment regimen. This is secondary to the development of resistance to the single agent BRAF inhibitors typically after 6-7 months. Combination therapy with both BRAF and MEK inhibitors may suppress the downstream resistance mechanism.
    - 1) The combination of vemurafenib and cobimetinib was compared with vemurafenib and placebo in 495 patients with previously untreated, unresectable, advanced melanoma that was BRAF V600-positive (coBRIM trial).<sup>56, 57</sup>
      - a) After median follow-up of 14.2 months, the primary endpoint of PFS was 12.3 months in the combination group and 7.2 months in the vemurafenib and placebo group (HR 0.58, 95% CI 0.46 – 0.72,  $p < 0.001$ ).
      - b) Median OS was 22.3 months in the combination group and 17.4 months in the vemurafenib and placebo group (HR 0.70, 95% CI 0.55-0.90;  $p < 0.005$ )

- c) Though the combination was associated with a higher incidence of grade 3 or higher toxicities, the discontinuation rate was 14% and 7% in the combination and single arm groups, respectively. Toxicities were more common in the combination group including gastrointestinal effects, central serous retinopathy, photosensitivity, renal and hepatic effects.<sup>56</sup>
- 2) The combination of dabrafenib and trametinib was compared with dabrafenib alone in the phase III COMBI-d trial. Dabrafenib 150 mg PO BID was alone or in combination with trametinib 2 mg PO daily. The trial included 423 previously untreated patients with unresectable stage IIIC or IV melanoma that had either a BRAF V600E or V600K mutation.<sup>58, 59</sup>
- a) Median PFS was 11 months in the combination arm compared with 8.8 months in the monotherapy arm (HR 0.67, 95% CI 0.53-0.84; p=0.0004.
  - b) Median OS was 25.1 months in the combination arm compared with 18.7 months in the monotherapy arm (HR 0.71; 95% CI 0.55-0.92; p=0.0107)
  - c) Toxicity was similar between the two arms with except for more pyrexia (51% v 28%) and less cutaneous toxicity including squamous cell carcinomas (2% v 9%) seen in the combination arm. Discontinuation due to toxicity occurred in 11% of the combination and 7% of the monotherapy groups.<sup>59</sup>
- 3) The combination of dabrafenib and trametinib was also compared with single agent vemurafenib in an open-label phase III trial. Dabrafenib and trametinib were dosed as above and compared with vemurafenib 960 mg PO BID in 704 advanced melanoma patients with either a BRAF V600E or V600K mutation.<sup>60</sup>
- a) OS at 12 months was longer in the combination arm (72% v 65%, 95% CI 0.53-0.89, p = 0.005).
  - b) Median PFS was 11.4 months in the combination arm compared with 7.3 months in the vemurafenib arm (HR 0.56 (95% CI 0.46-0.69), p < 0.001)
  - c) Toxicity was similar between the two arms with less cutaneous squamous cell carcinomas and keratoacanthomas seen in the combination group (1% v 18%).
  - d) Long-term follow-up of dabrafenib and trametinib treated patients showed a median overall survival (mOS) of more than 2 years with about 20% of patients remaining free of disease progression at 3 years.<sup>60</sup>

**Comparison of toxicity between single agent vemurafenib compared with dabrafenib and trametinib<sup>61</sup>**

Toxicity	Vemurafenib		Dabrafenib + Trametinib	
	All grade	Grade 3 and 4	All grade	Grade 3 and 4
Pyrexia	21%	1%	53%	4%
Rash	43%	9%	22%	1%
Diarrhea	38%	< 1%	32%	1%
Hand Foot Syndrome	25%	< 1%	4%	0%
Hyperkeratosis	25%	1%	4%	0%
Cutaneous Squamous cell carcinoma (SqCC)	18%	17%	1%	1%
Decreased ejection fraction	0%	0%	8%	4%

- 4) The BRAF inhibitor encorafenib and MEK inhibitor binimetinib were compared with encorafenib alone and with vemurafenib alone in the COLUMBUS trial (n=577 patients). **Encorafenib was dosed at 300 mg PO daily which is lower than the FDA approved dose of 450 mg PO daily.** This was due to subsequent studies that showed the maximum tolerated dose of encorafenib was higher when it was dosed with binimetinib compared to when it was dosed alone. Binimetinib was dosed at the FDA approved 45 mg PO BID dose.<sup>62, 63</sup>
  - a) The primary endpoint was median PFS by blinded independent review and was higher for the combination at 14.9 months compared to 7.3 months with vemurafenib [HR 0.54 (95% CI 0.41-0.71), two sided p<0.0001].
  - b) Median OS was also higher with the combination at 33.6 months compared to 16.9 months with vemurafenib [HR 0.61 (95% CI 0.47 – 0.79), two sided p<0.0001].
  - c) The combination arm had a higher median PFS compared to single agent encorafenib (14.9 months vs 9.6 months, HR 0.75 (95% CI 0.56-1.00) though the p value was 0.051. Median OS was also improved with the combination with a 33.6 month mOS with encorafenib and binimetinib compared with 16.9 months with vemurafenib alone (HR 0.61, 95% CI 0.47-0.79; p<0.001) and 23.5 months with encorafenib alone (HR 0.76, 95% CI 0.58-0.98; two sided p=0.033)
  - d) The toxicity associated with encorafenib and binimetinib had some differences compared with other approved BRAF and MEK inhibitors including less pyrexia (seen with dabrafenib and trametinib) and photosensitivity (seen with vemurafenib and cobimetinib).
  - e) Grade 3 or 4 toxicities reported included increased gamma-glutamyltransferase (9%), increased creatinine phosphokinase (7%), and hypertension (6%). Rates of discontinuation due to toxicity were similar, being seen in 15% of patients in the encorafenib and binimetinib group compared with 16% in the encorafenib alone group<sup>63</sup>
- 5) The combination of vemurafenib, cobimetinib and atezolizumab became the first BRAF/MEK targeted therapy combined with an immune checkpoint inhibitor to be approved for advanced BRAF V600-mutated melanoma

- a) The IMSPiRE150 trial was a phase 3 trial that randomized 514 patients 1:1 with unresectable stage IIIC-IV BRAF V600-mutated melanoma to receive either the combination of vemurafenib, cobimetinib and atezolizumab (atezolizumab group) or vemurafenib, cobimetinib and placebo (placebo group)<sup>64</sup>
    - i. The primary endpoint of median PFS assessed by study investigator was 15.1 vs. 10.6 months in the atezolizumab and placebo groups, respectively (HR 0.78; 95% CI 0.63-0.97; p=0.025)
    - ii. The most common toxicities reported in more than 30% of patients in the atezolizumab group were increased creatinine phosphokinase, diarrhea, rash, arthralgia, pyrexia, AST and lipase increases.
  - b) The NCCN Guidelines include this triplet combination as another first-line recommended regimen for BRAF V600-mutated metastatic or unresectable melanoma with a category 2A. It is noted that currently it is not preferred over the double combinations as mature overall survival data has not yet been reported.<sup>1</sup>
5. Management of brain metastases<sup>1</sup>
- a. Treatment modalities include surgery, radiation and systemic therapies and depend on the burden of intracranial disease and associated symptoms.
    - 1) Higher volume intracranial disease associated with symptoms will often require local brain-directed therapies like radiation
    - 2) Lower volume, asymptomatic brain metastases and/or patients with a high burden of extracranial disease may benefit most from systemic therapy
    - 3) Patients commonly require both brain-directed and systemic therapies
  - b. Systemic therapy<sup>1</sup>
    - 1) Sole systemic therapy as the initial treatment option may be considered in patients with < 3 cm asymptomatic brain metastases who do not require corticosteroids and who have not received prior systemic therapy
    - 2) Ipilimumab and nivolumab<sup>65</sup>
      - a) Assessed in 94 patients with metastatic melanoma and at least one measurable, nonirradiated brain metastasis (0.5 to 3 cm in diameter) and no neurologic symptoms
      - b) Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks x 4 doses followed by nivolumab 3 mg/kg every 2 weeks until progression
      - c) Primary endpoint: 57% of patients had stable disease for  $\geq 6$  months including 26% with complete response and 30% with partial response
      - d) Safety was similar to patients with melanoma who did not have brain metastases
    - 3) In patients for whom ipilimumab and nivolumab is not preferred, single agent anti-PD-1 therapy has had more limited benefits and is not preferred as the initial treatment options. Brain-directed therapy should be considered as first line therapy, if appropriate.
    - 4) For BRAF V600-mutated patients, BRAF/MEK inhibitor combination therapy can be considered for select symptomatic patients who have not received prior BRAF/MEK therapy. PFS is typically shorter than reported for extracranial disease.

- c. Corticosteroids are often required for symptom management. The lowest dose possible to control symptoms is recommended with plan for taper if intracranial disease responds to therapy.
- d. Patients who undergo brain metastases resection can be considered for adjuvant radiation and, in the event of no evidence of disease, can be considered for systemic adjuvant therapy

**Patient Case #2, continued:**

**Answer B: CBC, CMP, CK, EKG, echocardiogram, routine eye exams**

Baseline and routine labs should include a CBC, CMP, and CPK level. While rare, BRAF/MEK inhibitor combinations can cause anemia, thrombocytopenia, and leukopenia. Monitoring of LFTs and renal function are also recommended due to potential elevations of LFTs and changes in renal function. Binimetinib can cause increases in creatinine phosphokinase. BRAF/MEK inhibitor combinations have warnings for QTc prolongation. Baseline EKG is recommended and routine monitoring should be done as well. Baseline echocardiogram is also recommended and repeated regularly in patients with a history of low ejection fraction or show signs of cardiac dysfunction while on therapy. BRAF/MEK inhibitor combinations can cause visual impairment, eye irritation, and more severe toxicities such as retinal detachment and macular edema.

6. Aldesleukin (IL-2)

- a. Clinical trials report response rates from 15% to 25% with 2% to 5% of patients achieving complete responses. Durable responses can be seen in 5-10% of patients and can last for decades.<sup>66</sup>
- b. The doses used in the initial clinical trials and recommended in the labeling of the drug are associated with significant toxicities and may limit the practicality of therapy for individual patients. Treatment-related mortality was as high as 2.2% in clinical trials.<sup>67</sup> The high dose (600,000 international units (IU)/kg/dose q8h x 14 doses) is FDA-approved for treatment of metastatic melanoma.
- c. Administration of high-dose IL-2 requires careful attention to management of toxicities, adherence to patient-eligibility criteria and well-trained staff.<sup>68</sup> Toxicities include:
  - 1) Cytokine-induced capillary leak syndrome (hypotension sometimes requiring vasopressor support, visceral edema sometimes requiring diuresis, dyspnea sometimes requiring artificial ventilator support, tachycardia, and arrhythmia)
  - 2) Visceral edema can result in pulmonary congestion, pleural effusions, and edema
  - 3) Constitutional symptoms
  - 4) Pruritis
  - 5) Eosinophilia
  - 6) Bone marrow suppression
  - 7) Increase in liver function test
  - 8) Renal insufficiency/failure
  - 9) Nausea/vomiting
- d. Majority of toxicities will reverse following discontinuation



- e. Should not be used in patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases
7. Chemotherapy now has a limited role in the treatment of metastatic melanoma. The benefits of novel immunotherapy agents have moved chemotherapy agents to the salvage setting. None of the chemotherapy agents/regimens have been shown to improve OS in a randomized phase III setting.
- a. Dacarbazine (DTIC)<sup>1</sup>
    - 1) DTIC is the only FDA-approved chemotherapeutic agent for the treatment of metastatic melanoma in the United States. The optimal dose and schedule has never been determined.
    - 2) Response rates: 20% to 25% with an average duration of response of 5 to 7 months, complete responses are uncommon<sup>1</sup>
  - b. Temozolomide was developed as a potential alternative to dacarbazine and can be administered orally.
    - 1) Temozolomide appears to cross into the central nervous system (CNS) and therefore may be beneficial for patients with CNS metastases
    - 2) One phase III randomized trial demonstrated equivalent efficacy vs. dacarbazine<sup>69</sup>
  - c. Taxanes – paclitaxel is listed as an option in the NCCN Guidelines®; however, the response rates to paclitaxel and docetaxel are relatively low (6-18%).<sup>1</sup>
  - d. Combination Chemotherapy

Paclitaxel/carboplatin – although suggested as an alternative in the NCCN Guidelines®, when compared to weekly paclitaxel monotherapy, the combination only increases toxicity, with no improvement in response or OS. Some evidence of benefit as second line therapy after temozolomide or dacarbazine.<sup>70</sup>

## **II. Survivorship and Long-Term Follow-up<sup>1</sup>**

- A. Scheduled screening in addition to routine surgical follow-up is required for any patient with a history of melanoma. The frequency and duration recommended is dependent on the stage of melanoma and the pre-existing risk factors of the patient. The optimal duration of follow-up is controversial; however, the period of greatest risk is the first 2 years after initial diagnosis. Guidelines for follow-up are present in the NCCN Guidelines®<sup>1</sup>
- B. All melanoma patients should have a skin examination and surveillance at least once per year for the rest of their life, regardless of stage at diagnosis
- C. Patients should also be educated about self skin and lymph node checks
- D. Continued use of sunscreen and skin care is also recommended

**NON-MELANOMA SKIN CANCERS (NMSC)  
BASAL CELL CARCINOMA (BCC), SQUAMOUS CELL CANCER (SCC) AND MERKEL CELL  
CARCINOMA (MCC)**

**I. Risk Factors (within a common ancestry – cumulative sun exposure [UV light] and age are most important)<sup>71-73</sup>**

- A. UV light exposure – additional risk in individuals with a susceptibility for sunburn
  - 1. Fair complexion including those with skin freckling
  - 2. Skin freckling
  - 3. Individuals treated with psoralens and PUVA for psoriasis
  - 4. Inhabitants of areas closer to the equator
  - 5. Total skin exposure (prolonged sun exposure appears to be most closely linked to SCC)
    - a. Correlation with age
  - 6. BCC closely correlates with tendency to sunburn and intermittent childhood & adolescent exposure
  - 7. MCC that is Merkel cell polyomavirus negative is more likely to have a UV genetic signature which is associated with a high tumor mutation burden
- B. Approximately 60% of SCC lesions came from actinic keratosis. Sun avoidance and sunscreen can decrease incidence of actinic keratosis.
  - 1. Treatment depends on size, number of lesions, and location. Therapy ranges from liquid nitrogen, surgical excision, topical fluorouracil, topical diclofenac, topical imiquimod, topical retinoids, dermabrasion, chemical peels, and photodynamic therapy.
- C. Ionizing radiation – 3-5 fold increase with therapeutic radiation
- D. Chronic immunosuppression
  - 1. Immunosuppressive diseases (HIV infection, chronic lymphocytic leukemia, severe combined immunodeficiency (SCID)) significantly increase the risk of skin cancer (basal cell, melanoma, and especially SCC).
  - 2. Solid organ transplant patients on long-term immunosuppression are also at an increased risk of skin cancer, particularly SCC. The type of transplant also seems to differentiate risk; highest with heart transplant, followed by renal, then liver. Immunosuppression with tacrolimus, mycophenolate, or rapamycin seems to convey a lower risk than cyclosporine, glucocorticoids, or azathioprine in organ transplant.
- E. Viruses
  - 1. Human papilloma virus (HPV) infection types 16 and 18 increase risk of anogenital SCC
  - 2. Merkel cell polyomavirus (MCPyV) is found in 43-100% of MCC<sup>73</sup>
- F. Chronic arsenic exposure
- G. Chronic skin inflammation

H. Genetic conditions affecting skin pigmentation only account for a relatively small portion of skin cancers, but at an individual level predict a very high risk. They include: xeroderma pigmentosum, epidermolysis bullosa, albinism, epidermodysplasia verruciformis

I. Risk factors for **recurrence**

1. Increased size
2. Poorly defined borders
3. Recurrent disease
4. Site of prior radiotherapy (RT)
5. Immunosuppression
6. Aggressive growth pattern
7. Perineural involvement

II. **Prevention**<sup>71, 72</sup>

- A. Minimize UV radiation exposure
- B. Use of sunscreen decreases incidence of SCC, but not BCC
- C. Actinic keratosis (premalignant SCC lesion) can be treated with retinoids to prevent SCC formation
- D. Nicotinamide may help reduce development of SCC

III. **Screening:** see melanoma section for details

**Patient Case #3:**

TC is a 78-year-old male with a 2 cm lesion on his scalp that he has noticed is bleeding more frequently and does not appear to be healing. His PMH is significant for multiple severe sunburns during his childhood. He has had several small BCCs removed from his face, arms and back. An excisional biopsy of the lesion reveals a sclerosing BCC. TC is treated with Moh's surgery and then radiation for extensive positive margins. Eight months following local therapy, he develops a recurrence with numerous satellite lesions.

**What is the most appropriate systemic therapy for TC's recurrent BCC?**

- A. Fluorouracil
- B. Cisplatin
- C. Ipilimumab
- D. Vismodigib

IV. **Treatment**<sup>71, 72</sup>

- A. The goal of primary treatment in non-melanoma skin cancer is cure and maximal preservation of function.
- B. Surgery:
  1. Moh's micrographic surgery
  2. Curettage and electrodesiccation

3. Surgical excision
- C. Radiation (RT)
1. Radiation is used for lesions that are not surgically resectable
  2. Radiation is fractionated to maximize cosmesis
  3. Contraindicated in patients with genetic conditions predisposing to skin cancer and in connective tissue diseases (SLE, XP)
  4. Adjuvant RT may be considered in non-melanoma skin cancers with significant perineural involvement
  5. Adverse effects:
    - a. Erythema
    - b. Radiation to eyelids: loss of eyelashes
    - c. RT to nose: mucositis
    - d. Long-term complications: radiation dermatitis
- D. Photodynamic therapy (PDT): involves application of a photosensitizing agent (such as methyl aminolevulinate or 5-aminolevulinic acid) to the skin followed by irradiation.

#### Local Management Options

Management of BCC and SCC	
Low risk BCC	Curettage and electrodesiccation <i>or</i> Excision with postoperative margin assessment <i>or</i> Radiation
High risk BCC	Excision with postoperative margin assessment <i>or</i> Moh's or resection with complete circumferential peripheral and deep margin assessment with frozen or permanent section <i>or</i> Radiation
Low risk SCC	Curettage and electrodesiccation <i>or</i> Excision with postoperative margin assessment <i>or</i> Radiation
High risk SCC	Excision with postoperative margin assessment <i>or</i> Moh's or resection with complete circumferential peripheral and deep margin assessment with frozen or permanent section <i>or</i> Radiation
SCC with palpable LN	Biopsy – if LN is positive regional LN dissection

- E. Chemotherapy is not routinely used for BCC or SCC
1. Topical imiquimod or fluorouracil (5-FU) for select patients when surgery or radiation are not appropriate.
  2. For MCC, adjuvant therapy with cisplatin or carboplatin with or without etoposide may be considered in select cases, however no survival benefit has been reported with the use of adjuvant therapy..<sup>73</sup>
  3. For locally advanced SCC in patients who are not surgical candidates, concurrent chemoradiation may be a consideration after multidisciplinary discussion for select patients. If indicated, cisplatin is the preferred agent..<sup>72</sup>

F. Targeted therapy and immune checkpoint inhibition for BCC<sup>71</sup>:

1. Considered for locally advanced or metastatic BCC when topical therapy, surgery or radiation is unlikely to be curative.
2. Side effects with vismodegib and sonidegib can be intolerable. Based on this, drug holidays or alternatives to daily dosing can be used to improve adherence, reduce toxicity and improve quality of life.
3. Vismodegib<sup>74, 75</sup>
  - a. Approved for the treatment of adults with metastatic or locally advanced BCC that has recurred following surgery or who are not candidates for surgery or radiation (NCCN Guideline® Category 2A for this indication).<sup>71</sup>
  - b. The registry trial evaluated 96 patients (33 with metastatic disease, 63 with locally advanced disease)<sup>75, 76</sup>.
    - 1) After 9 months, ORR of 30% in those with metastatic disease and 43% in locally advanced disease; 21% and 22% had a complete remission, respectively.
    - 2) After 39 months, the final efficacy results showed investigator assessed ORR of 48.5% in those with metastatic disease (all partial responses) and 60.3% in those with locally advanced disease (including 20 complete responses). Median OS was 33.4 months and not reached, respectively.<sup>76</sup>
    - 3) Toxicity: grade 3 toxicities in > 1% of patients included weight loss, fatigue, muscle spasms, and decreased appetite. Adverse reactions occurred in more than 10% of patients: muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia<sup>75</sup>
4. Sonidegib
  - a. This is the second hedgehog pathway inhibitor to gain FDA approval and is approved for the treatment of adults with locally advanced BCC that has recurred following surgery or who are not candidates for surgery or radiation (NCCN Guideline® Category 2A for locally advanced disease and Category 2B for metastatic disease).<sup>71</sup>
  - b. The approval was based on the BOLT trial that enrolled 230 patients with locally advanced or metastatic basal cell carcinoma not amenable to curative surgery or radiation. This 2 arm trial randomized patients in a 1:2 ratio to either 200 mg (FDA approved dose) or 800 mg of sonidegib daily.<sup>77</sup>
    - 1) The primary endpoint was objective response rate (ORR). After a follow-up of 13.9 months, ORR was seen in 36% of patients receiving 200 mg and 39% receiving 800 mg.<sup>77</sup>
    - 2) After 30 months, the centrally assessed ORR was 56.1% in those with locally advanced disease and 7.7% in those with metastatic disease receiving 200 mg daily. Median duration of response was 26.1 months and 24 months, respectively with median OS not reached in either population.<sup>78</sup>
    - 3) The most common grade 3 or higher toxicities were increased creatinine kinase and lipase concentration. The most common adverse effects of any grade were muscle spasms, dysgeusia, alopecia, nausea, increase creatinine kinase, decreased weight and fatigue which were less common in the 200 mg group.<sup>77</sup>

**Patient Case #3: continued**

**Answer D: Vismodegib**

Hedgehog inhibitors are the most active against BCC so vismodegib is recommended in this setting. Chemotherapy has shown limited response and ipilimumab is not currently recommended for the treatment of BCC.

**Which of the following toxicities with vismodegib is most appropriate to discussed with TC prior to starting therapy?**

- A. Changes in taste
- B. Secondary skin cancers
- C. Hypothyroidism
- D. Weight gain

5. Cemiplimab-rwlc

- a. FDA approved for patients with locally advanced basal cell carcinoma followed treatment with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. It is also an NCCN Guideline® Category 2A recommendation for this indication.
- b. The approval was based on a phase 2 trial of patients with either metastatic or locally advanced BCC who had progressed on prior or were intolerant to previous hedgehog inhibitor therapy. The primary analysis was only reported for the 84 locally advanced patients as the metastatic patient analysis was still ongoing.<sup>79</sup>
  - 1) The ORR by independent review was 31% with best ORR of 5 complete responses and 21 partial responses.
  - 2) The most common grade 3 or higher toxicities were hypertension and colitis.

**Patient Case #3: continued**

**Answer A: Changes in taste**

Vismodegib is associated with taste changes (dysgeusia) in about 55% of patients; making it one of the most common all grade toxicities. Secondary skin cancers are not seen with the hedgehog inhibitors, weight loss (rather than weight gain) is seen in about 45% of patients and hypothyroidism is also not a common side effect with the drug.

G. Therapy for disseminated MCC<sup>73</sup>

- 1. Clinical trial (preferred)
- 2. Immunotherapy: non-randomized trials indicate rates of durable response are improved with PD-1/PD-L1 inhibitors compared with chemotherapy (All NCCN category 2A level recommendations)
  - a. Avelumab
    - 3) JAVELIN Merkel 200 trial<sup>80, 81</sup>
      - a) 88 patients with metastatic MCC who had not received prior therapy were treated with avelumab 10 mg/kg over 1 hour every 2 weeks

- b) The ORR was 33% including 10 patients (11.4%) with a complete response. The median duration of response was 40.5 months with a 42-month OS of 31%.
      - iii. Avelumab was granted FDA accelerated approval for adults and pediatric patients 12 years of age or older with metastatic MCC. Approval was granted based on tumor response and duration of response.
    - b. Pembrolizumab
      - 1) Multicenter, phase 2, single arm trial<sup>82, 83</sup>
        - a) 50 patients with advanced MCC who had not received prior therapy were enrolled to receive pembrolizumab 2 mg/kg IV every 3 weeks for a maximum of 2 years
        - b) The ORR was 56% in patients with Merkel cell polyomavirus (MCPyV)-positive tumors (n=32) and 53% in MCPyV-negative tumors (n=18).
        - c) The median PFS in the whole population was 16.8 months and the 24-month OS was 68.7%.
      - 2) Pembrolizumab has been granted FDA accelerated approval for adults and pediatric patients with recurrent locally advanced or metastatic MCC. Approval was granted based on tumor response rate and duration of response.
    - c. Nivolumab
      - 1) CheckMate 358 phase I/II trial<sup>84</sup>
        - a) 25 patients with MCPyV-positive MCC who had received  $\leq 2$  prior therapies were enrolled to receive nivolumab 240 mg IV every 2 weeks
        - b) The overall response rate was 68% with 3 patients have complete responses and 12 having partial responses.
        - c) A separate cohort of 29 patients with resectable stage IIA to IV were also enrolled at the same dose and demonstrated a 40% radiographic regression of more than 30% and the pathologic complete response rate was 47%.
      - 2) Has not received FDA-approval for this indication yet
  - 3. Chemotherapy
    - a. Considered in patients who are not candidates for immune checkpoint inhibitors
    - b. Options include cisplatin or carboplatin alone or with etoposide, topotecan, or the combination of cyclophosphamide, doxorubicin/epirubicin, and vincristine (CAV)
- H. Therapy for metastatic or locally advanced SCC<sup>72</sup>
- 1. Cemiplimab-rwlc<sup>85</sup>
    - a. Approved for patients with metastatic or locally advanced cutaneous SCC who are not candidates for curative surgery or curative radiation and recommended by the NCCN guidelines as a preferred regimen
    - b. Approval based on R-2810-ONC-1423 and R2810-ONC-1540 which included 75 patients with metastatic and 33 patients with locally advanced disease

- 1) The ORR was 47% with 4% complete responses and 44% partial responses in the overall population
  - 2) For the 75 patients with metastatic disease, the ORR was 47%
  - 3) For the 33 patients with locally advanced disease, the ORR was 49%
  - 4) The median duration of response was not reached and 61% of responses were durable for 6 months or longer
2. Pembrolizumab
- a. Approved for patients with metastatic, recurrent or locally advanced SCC who are not candidates for curative surgery or curative radiation and recommended by the NCCN guidelines as a preferred regimen
  - b. Approval based on KEYNOTE-629 which included 105 patients with relapsed/metastatic disease<sup>86</sup>
    - 1) The ORR was 34.3% with 4 complete responses and 32 partial responses
    - 2) Disease control rate: 52.4%
    - 3) Median PFS was 6.9 months and median OS was not reached
  - c. Additional data published separately included 54 patients with locally advanced SCC<sup>87</sup>
    - 1) The ORR was 50%, including 16.7% CR and 33.3% PR
3. Additional options in the NCCN guidelines for patients who are ineligible or who have progressed on immune checkpoint inhibition and clinical trials
- a. Carboplatin and paclitaxel is another recommended regimen
  - b. Cetuximab, capecitabine, cisplatin +/- fluorouracil and carboplatin may be useful in certain circumstances
  - c.

## **V. Survivorship and Long-Term Follow-up<sup>71-73</sup>**

- A. Nonmelanoma skin cancers generally have a favorable prognosis. There are only ~ 2000 deaths out of 1-2 million new diagnoses each year.
- B. Local recurrence is the most common problem; however, the rare patient who has metastatic disease has < 50% chance of being alive at 5 years.
- C. Close follow-up is extremely important with prevention counseling
  1. BCC – every 6-12 months for the first 5 years then at least annually for life
  2. SCC – every 2-3 months for 1 year, then every 2-4 months for 1 year, then every 4-6 months for 3 years, then every 6-12 months for life
  3. MCC – every 3-6 months for 3 years and then every 6-12 months thereafter



## RECOMMENDED READING AND REFERENCES

### Recommended Reading

1. Curti BD and Faries MB. Recent advances in the treatment of melanoma. *N Eng J Med*. 2021;384(23):2229-40. <https://www.nejm.org/doi/full/10.1056/NEJMra2034861>
2. B Schneider BJ, Naidoo J, Santomasso B, et al. Management of immune-related adverse effects in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2021; 36: 4073-4126. <https://ascopubs.org/doi/full/10.1200/JCO.21.01440>
3. Proietti I, Skroza N, Michelini S, et al. BRAF Inhibitors: Molecular Targeting and Immunomodulatory Actions. *Cancers (Basel)*. 2020 Jul 7;12(7):1823. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7408709/pdf/cancers-12-01823.pdf>

### REFERENCES

- 1 NCCN clinical practice guidelines in oncology (nccn guidelines®) for cutaneous melanoma, v.3.2022 4/11/2022, © 2022 national comprehensive cancer network, inc 2020. All rights reserved. . *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cutaneous Melanoma*. V.3.2022 4/11/2022, © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 2 Gandini S, Sera F, Cattaruzza MS et al. Meta-analysis of risk factors for cutaneous melanoma: li. Sun exposure. *Eur J Cancer*. 2005; 41(1): 45-60.
- 3 Gallagher RP, Spinelli JJ and Lee TK. Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(3): 562-6.
- 4 Rabbie R, Ferguson P, Molina-Aguilar C et al. Melanoma subtypes: Genomic profiles, prognostic molecular markers and therapeutic possibilities. *J Pathol*. 2018.
- 5 Hayward NK, Wilmott JS, Waddell N et al. Whole-genome landscapes of major melanoma subtypes. *Nature*. 2017; 545(7653): 175-80.
- 6 Siroy AE, Boland GM, Milton DR et al. Beyond braf(v600): Clinical mutation panel testing by next-generation sequencing in advanced melanoma. *J Invest Dermatol*. 2015; 135(2): 508-15.
- 7 Akslen LA, Angelini S, Straume O et al. Braf and nras mutations are frequent in nodular melanoma but are not associated with tumor cell proliferation or patient survival. *J Invest Dermatol*. 2005; 125(2): 312-7.
- 8 NCCN clinical practice guidelines in oncology (nccn guidelines®) for uveal melanoma, v.3.2022, 4/05/2022 © 2022 national comprehensive cancer network, inc 2022 all rights reserved. . *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uveal Melanoma*. V.3.2022, 4/05/2022 , © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 9 Van Raamsdonk CD, Griewank KG, Crosby MB et al. Mutations in gna11 in uveal melanoma. *N Engl J Med*. 2010; 363(23): 2191-9.
- 10 Rigel DS, Russak J and Friedman R. The evolution of melanoma diagnosis: 25 years beyond the abcds. *CA Cancer J Clin*. 2010; 60(5): 301-16.
- 11 Centers for Disease Control and Prevention (CDC). Basic skin cancer information and prevention. [https://www.Cdc.Gov/cancer/skin/basic\\_info/prevention.htm](https://www.Cdc.Gov/cancer/skin/basic_info/prevention.htm). Accessed 09/17/2022. 2018.

- 12 American Cancer Society skin cancer prevention and early detection.  
<https://www.Cancer.Org/cancer/skin-cancer/prevention-and-early-detection/uv-protection.html>  
accessed 07/17/2022. 2017.
- 13 Boniol M, Autier P, Boyle P et al. Cutaneous melanoma attributable to sunbed use: Systematic review and meta-analysis. *BMJ : British Medical Journal*. 2012; 345: e4757.
- 14 Lazovich D, Isaksson Vogel R, Weinstock MA et al. Association between indoor tanning and melanoma in younger men and women. *JAMA Dermatol*. 2016; 152(3): 268-75.
- 15 Healsmith MF, Bourke JF, Osborne JE et al. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. *Br J Dermatol*. 1994; 130(1): 48-50.
- 16 Bibbins-Domingo K, Grossman DC, Curry SJ et al. Screening for skin cancer: Us preventive services task force recommendation statement. *Jama*. 2016; 316(4): 429-35.
- 17 Weber J, Mandala M, Del Vecchio M et al. Adjuvant nivolumab versus ipilimumab in resected stage iii or iv melanoma. *N Engl J Med*. 2017.
- 18 Ascierto PA, Del Vecchio M, Mandalá M et al. Adjuvant nivolumab versus ipilimumab in resected stage iiib-c and stage iv melanoma (checkmate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020; 21(11): 1465-77.
- 19 Eggermont AMM, Blank CU, Mandala M et al. Adjuvant pembrolizumab versus placebo in resected stage iii melanoma. *New England Journal of Medicine*. 2018; 378(19): 1789-801.
- 20 Eggermont AMM, Blank CU, Mandalà M et al. Adjuvant pembrolizumab versus placebo in resected stage iii melanoma (eortc 1325-mg/keynote-054): Distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021; 22(5): 643-54.
- 21 Luke JJ, Rutkowski P, Queirolo P et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage iib or iic melanoma (keynote-716): A randomised, double-blind, phase 3 trial. *Lancet*. 2022; 399(10336): 1718-29.
- 22 Haanen J, Carbone F, Robert C et al. Management of toxicities from immunotherapy: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017; 28(suppl\_4): iv119-iv42.
- 23 Boutros C, Tarhini A, Routier E et al. Safety profiles of anti-ctla-4 and anti-pd-1 antibodies alone and in combination. *Nature Reviews Clinical Oncology*. 2016; 13: 473.
- 24 Schneider BJ, Naidoo J, Santomasso BD et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: Asco guideline update. *Journal of Clinical Oncology*. 2021; 39(36): 4073-126.
- 25 Martins F, Sofiya L, Sykietis GP et al. Adverse effects of immune-checkpoint inhibitors: Epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019; 16(9): 563-80.
- 26 Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010; 363(8): 711-23.
- 27 O'Day SJ, Hamid O and Urba WJ. Targeting cytotoxic t-lymphocyte antigen-4 (ctla-4): A novel strategy for the treatment of melanoma and other malignancies. *Cancer*. 2007; 110(12): 2614-27.
- 28 Barroso-Sousa R, Barry WT, Garrido-Castro AC et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. *JAMA Oncol*. 2017.
- 29 Naidoo J, Wang X, Woo KM et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol*. 2017; 35(7): 709-17.
- 30 NCCN clinical practice guidelines in oncology (nccn guidelines®) for management of immunotherapy-related toxicities, v.1.2022, 2/28/2022 © 2022 national comprehensive cancer network, inc 2020. All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 31 Leonardi GC, Gainor JF, Altan M et al. Safety of programmed death–1 pathway inhibitors among patients with non–small-cell lung cancer and preexisting autoimmune disorders. *Journal of Clinical Oncology*. 2018; 36(19): 1905-12.

- 32 Dolladille C, Ederhy S, Sassier M et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. *JAMA Oncology*. 2020; 6(6): 865-71.
- 33 Long GV, Hauschild A, Santinami M et al. Adjuvant dabrafenib plus trametinib in stage iii braf-mutated melanoma. *New England Journal of Medicine*. 2017; 377(19): 1813-23.
- 34 Dummer R, Hauschild A, Santinami M et al. Five-year analysis of adjuvant dabrafenib plus trametinib in stage iii melanoma. *New England Journal of Medicine*. 2020; 383(12): 1139-48.
- 35 Andtbacka RH, Kaufman HL, Collichio F et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol*. 2015; 33(25): 2780-8.
- 36 Lawler SE and Chiocca EA. Oncolytic virus-mediated immunotherapy: A combinatorial approach for cancer treatment. *J Clin Oncol*. 2015; 33(25): 2812-4.
- 37 Hoffner B, Iodice GM and Gasal E. Administration and handling of talimogene laherparepvec: An intralesional oncolytic immunotherapy for melanoma. *Oncol Nurs Forum*. 2016; 43(2): 219-26.
- 38 Andtbacka RHI, Collichio F, Harrington KJ et al. Final analyses of optim: A randomized phase iii trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage iii–iv melanoma. *Journal for ImmunoTherapy of Cancer*. 2019; 7(1): 145.
- 39 Menzer C, Menzies AM, Carlino MS et al. Targeted therapy in advanced melanoma with rare braf mutations. *J Clin Oncol*. 2019; 37(33): 3142-51.
- 40 Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. *Clin Cancer Res*. 2009; 15(23): 7412-20.
- 41 Robert C, Ribas A, Wolchok JD et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: A randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014; 384(9948): 1109-17.
- 42 Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015; 372(26): 2521-32.
- 43 Robert C, Ribas A, Schachter J et al. Pembrolizumab versus ipilimumab in advanced melanoma (keynote-006): Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol*. 2019; 20(9): 1239-51.
- 44 Long GV, Atkinson V, Cebon JS et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (keynote-029): An open-label, phase 1b trial. *Lancet Oncol*. 2017; 18(9): 1202-10.
- 45 Carlino MS, Menzies AM, Atkinson V et al. Long-term follow-up of standard-dose pembrolizumab plus reduced-dose ipilimumab in patients with advanced melanoma: Keynote-029 part 1b. *Clin Cancer Res*. 2020; 26(19): 5086-91.
- 46 Olson DJ, Eroglu Z, Brockstein B et al. Pembrolizumab plus ipilimumab following anti-pd-1/l1 failure in melanoma. *J Clin Oncol*. 2021; 39(24): 2647-55.
- 47 Arance A, Cruz-Merino Ldl, Petrella TM et al. Phase ii leap-004 study of lenvatinib plus pembrolizumab for melanoma with confirmed progression on a programmed cell death protein-1 or programmed death ligand 1 inhibitor given as monotherapy or in combination. *Journal of Clinical Oncology*. 0(0): JCO.22.00221.
- 48 Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015; 373(1): 23-34.
- 49 Larkin J, Chiarion-Sileni V, Gonzalez R et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *New England Journal of Medicine*. 2019; 381(16): 1535-46.
- 50 Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *Journal of Clinical Oncology*. 2022; 40(2): 127-37.
- 51 Tawbi HA, Schadendorf D, Lipson EJ et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022; 386(1): 24-34.
- 52 Topalian SL, Sznol M, McDermott DF et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014; 32(10): 1020-30.
- 53 Hauschild A, Grob JJ, Demidov LV et al. Dabrafenib in braf-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012; 380(9839): 358-65.
- 54 Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with braf v600e mutation. *N Engl J Med*. 2011; 364(26): 2507-16.

- 55 Flaherty KT, Robert C, Hersey P et al. Improved survival with mek inhibition in braf-mutated melanoma. *N Engl J Med*. 2012; 367(2): 107-14.
- 56 Larkin J, Ascierto PA, Dreno B et al. Combined vemurafenib and cobimetinib in braf-mutated melanoma. *N Engl J Med*. 2014; 371(20): 1867-76.
- 57 Ascierto PA, McArthur GA, Dréno B et al. Cobimetinib combined with vemurafenib in advanced braf(v600)-mutant melanoma (cobrim): Updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016; 17(9): 1248-60.
- 58 Long GV, Flaherty KT, Stroyakovskiy D et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic braf v600e/k-mutant melanoma: Long-term survival and safety analysis of a phase 3 study. *Ann Oncol*. 2017; 28(7): 1631-39.
- 59 Long GV, Stroyakovskiy D, Gogas H et al. Combined braf and mek inhibition versus braf inhibition alone in melanoma. *N Engl J Med*. 2014; 371(20): 1877-88.
- 60 Long GV, Weber JS, Infante JR et al. Overall survival and durable responses in patients with braf v600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. *J Clin Oncol*. 2016; 34(8): 871-8.
- 61 Robert C, Karaszewska B, Schachter J et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015; 372(1): 30-9.
- 62 Dummer R, Ascierto PA, Gogas HJ et al. Overall survival in patients with braf-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (columbus): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018.
- 63 Dummer R, Ascierto PA, Gogas HJ et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with braf-mutant melanoma (columbus): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018; 19(5): 603-15.
- 64 Gutzmer R, Stroyakovskiy D, Gogas H et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced braf(v600) mutation-positive melanoma (imspire150): Primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020; 395(10240): 1835-44.
- 65 Tawbi HA, Forsyth PA, Algazi A et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *New England Journal of Medicine*. 2018; 379(8): 722-30.
- 66 Atkins MB, Lotze MT, Dutcher JP et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999; 17(7): 2105-16.
- 67 Mouawad R, Seibert M, Michels J et al. Treatment for metastatic malignant melanoma: Old drugs and new strategies. *Crit Rev Oncol Hematol*. 2010; 74(1): 27-39.
- 68 Schwartz RN, Stover L and Dutcher J. Managing toxicities of high-dose interleukin-2. *Oncology (Williston Park)*. 2002; 16(11 Suppl 13): 11-20.
- 69 Middleton MR, Grob JJ, Aaronson N et al. Randomized phase iii study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol*. 2000; 18(1): 158-66.
- 70 Rao RD, Holtan SG, Ingle JN et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. *Cancer*. 2006; 106(2): 375-82.
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- 74 Sekulic A, Migden MR, Lewis K et al. Pivotal erivance basal cell carcinoma (bcc) study: 12-month update of efficacy and safety of vismodegib in advanced bcc. *J Am Acad Dermatol*. 2015; 72(6): 1021-6.e8.
- 75 Sekulic A, Migden MR, Oro AE et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012; 366(23): 2171-9.
- 76 Sekulic A, Migden MR, Basset-Seguín N et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: Final update of the pivotal erivance bcc study. *BMC Cancer*. 2017; 17(1): 332.
- 77 Migden MR, Guminski A, Gutzmer R et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (bolt): A multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol*. 2015; 16(6): 716-28.
- 78 Lear JT, Migden MR, Lewis KD et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 bolt study. *J Eur Acad Dermatol Venereol*. 2018; 32(3): 372-81.
- 79 Stratigos AJ, Sekulic A, Peris K et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: An open-label, multi-centre, single-arm, phase 2 trial. *Lancet Oncol*. 2021; 22(6): 848-57.
- 80 D'Angelo SP, Russell J, Lebbé C et al. Efficacy and safety of first-line avelumab treatment in patients with stage iv metastatic merkel cell carcinoma: A preplanned interim analysis of a clinical trial. *JAMA Oncology*. 2018; 4(9): e180077.
- 81 D'Angelo SP, Bhatia S, Brohl AS et al. Avelumab in patients with previously treated metastatic merkel cell carcinoma: Long-term data and biomarker analyses from the single-arm phase 2 javelin merkel 200 trial. *J Immunother Cancer*. 2020; 8(1).
- 82 Nghiem PT, Bhatia S, Lipson EJ et al. Pd-1 blockade with pembrolizumab in advanced merkel-cell carcinoma. *New England Journal of Medicine*. 2016; 374(26): 2542-52.
- 83 Nghiem P, Bhatia S, Lipson EJ et al. Durable tumor regression and overall survival in patients with advanced merkel cell carcinoma receiving pembrolizumab as first-line therapy. *Journal of Clinical Oncology*. 2019; 37(9): 693-702.
- 84 Topalian SL, Bhatia S, Hollebecque A et al. Abstract ct074: Non-comparative, open-label, multiple cohort, phase 1/2 study to evaluate nivolumab (nivo) in patients with virus-associated tumors (checkmate 358): Efficacy and safety in merkel cell carcinoma (mcc). *Cancer Research*. 2017; 77(13 Supplement): CT074-CT74.
- 85 Soura E, Gagari E and Stratigos A. Advanced cutaneous squamous cell carcinoma: How is it defined and what new therapeutic approaches are available? *Curr Opin Oncol*. 2019; 31(5): 461-68.
- 86 Grob JJ, Gonzalez R, Basset-Seguín N et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: A single-arm phase ii trial (keynote-629). *J Clin Oncol*. 2020; 38(25): 2916-25.

- 87 Hughes BGM, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial [published correction appears in *Ann Oncol*. 2022 Aug;33(8):853]. *Ann Oncol*. 2021;32(10):1276-1285. doi:10.1016/j.annonc.2021.07.008

# **MULTIPLE MYELOMA**

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## **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current guidelines for patients with multiple myeloma.
2. Evaluate oncology pharmacy services for compliance with established REMS regulations and standards.
3. Develop an appropriate plan for preventing, monitoring, and managing common problems associated with the treatment of cancers, including bone metastases in multiple myeloma, thromboembolism, hypercalcemia of malignancy, and spinal cord compression.

## MULTIPLE MYELOMA

### **Patient Case #1, (ARS Question #1):**

SB is a 62-year-old female with newly diagnosed low risk smoldering myeloma with a serum monoclonal protein of 3.5 g/dL and 15% plasma cells in the bone marrow. Her baseline labs include SCr 0.60 mg/dL, calcium 9.2 mg/dL, Hgb 12.7 g/dL. **According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), which of the following would be the most appropriate therapy for SB?**

- A. Observation
- B. Lenalidomide, dexamethasone
- C. Daratumumab, lenalidomide, dexamethasone
- D. Bortezomib, lenalidomide, dexamethasone

### **I. Background and Natural History<sup>1,2</sup>**

- A. Multiple myeloma (MM) is a plasma cell disorder characterized by the accumulation of malignant clonal plasma cells in the bone marrow
- B. The natural history of MM is typically characterized by different disease phase including an initial presentation of symptomatic/active MM and initial treatment that leads to response and remission, followed by relapsing MM that may encompass multiple periods of response and remission with treatment, and eventually the development of MM refractory to treatment
- C. Other plasma cell disorders that also have abnormal plasma cells, but do not meet criteria for active MM: monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, solitary plasmacytoma, light chain amyloidosis

### **II. Metaphase cytogenetics on bone marrow<sup>3-5</sup>**

- A. Major cytogenetic abnormalities in MM include:
  - 1. Deletion 13q – monoallelic loss of chromosome 13 or its long arm is an adverse prognostic factor
  - 2. Immunoglobulin heavy chain translocations – approximately 65% of patients present with translocations that involve chromosome 14. Multiple translocations exist with differing prognosis:
    - a. t(4;14) – poor prognosis
    - b. t(14;16) – poor prognosis
    - c. t(11;14) – intermediate risk
  - d. Deletion 17p13 – present in 10% of patients, confers poor survival
  - e. Hyperdiploid myeloma – standard prognosis, has been associated with trisomy of chromosomes 3,5,7,9,11,15,17,19 and 21. However, data suggest that not all trisomies are equivalent.<sup>6</sup>
    - 1) Improved overall survival (OS) with trisomies 3 and 5. These have also been shown to overcome the poor prognosis associated with patient with t(4;14).
    - 2) Decreased OS with trisomy 21.



- f. Mutations involving Ras are found in approximately 39% of newly diagnosed MM and more prevalent following disease progression
- 3. Gene Expression Profiling (GEP)<sup>7-9</sup>
  - a. GEP is a technology that extracts RNA from CD138 positive plasma cells obtained from bone marrow aspirate. GEP may provide additional prognostic value to further define risk.
  - b. There are several groups who have developed gene (15, 70, or 92 genes) models based on GEP signatures of MM cells.
  - c. Although GEP is not routinely used in clinical practice, the National Comprehensive Cancer Network® (NCCN®) panel agree that GEP is a useful tool that may be helpful determine the aggressiveness of the MM and to tailor treatment decisions.<sup>10</sup>

### III. Screening

- A. Currently there are no established guidelines for the prevention and screening of MM. Careful monitoring for patients at risk (ie; MGUS)

### IV. Signs and Symptoms<sup>11-17</sup>

- A. The major symptoms can be described using the acronym “CRAB”: Calcium, Renal dysfunction, Anemia, and Bone disease (see below for descriptions)
- B. Calcium
  - 1. Hypercalcemia (corrected for hypoalbuminemia; calcium of > 11 mg/dL) or > 1 mg/dL above the upper limit of normal (ULN); ionized calcium is a much better assessment (normal range: 4.4-5.4 mg/dL)
  - 2. Symptoms may include constipation and confusion
- C. Renal dysfunction
  - 1. Serum creatinine (SCr) > 2 mg/dL or creatinine clearance < 40 mL/min
  - 2. Nephropathy occurs in 15% to 40% of cases
    - a. The most common cause is tubular damage by monoclonal light chain proteins leading to light chain tubular casts and interstitial nephritis.
    - b. Other causes: hypercalcemia due to osmotic diuresis, volume depletion, hyperuricemia, use of nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs, bisphosphonate therapy, contrast media), and hyperviscosity.
- D. Anemia
  - 1. Typically, normochromic normocytic anemia <10 g/dL or 2 g/dL below lower limit of normal due to myeloma involvement in the bone marrow as well as inadequate erythropoietin responsiveness
  - 2. Symptoms may include fatigue, weakness, and shortness of breath
- E. Bone
  - 1. Lytic lesions, severe osteopenia, pathologic fractures

2. Approximately 80% of MM patients present with bone disease and 30% present with a pathologic fracture
  3. Myeloma cells secrete IL-6, IL-1, and soluble IL-6 receptor that increase osteoclast and decrease osteoblast function leading to hypercalcemia, bone weakening, pain, and potentially pathologic fractures and/or spinal cord compression
- F. Extramedullary plasmacytomas (EMPs)
1. EMPs are plasma cell tumors that arise outside the bone marrow (present in 7% of MM patients)
  2. The upper respiratory tract is the most common site but may appear in any organ
  3. Solitary plasmacytomas are characterized by a mass of plasma cells confined to a single area of the body (either bone or soft tissue); however, there is absence of myeloma cells in the bone marrow or elsewhere in the body.
- G. Increased susceptibility to infections
1. Decreased normal/functional IgG concentrations
  2. Decreased T-lymphocyte function
- H. Hyperviscosity (rare) may present with headache, blurred vision, epistaxis, oral bleeding, altered mental status, or confusion
1. Most common with IgA disease because of the dimeric forms of IgA and managed with plasmapheresis
- I. Neurologic disease
1. Peripheral neuropathy
  2. Cord compression
  3. Intracranial plasmacytomas
  4. Rare cases of encephalopathy due to hyperviscosity

**V. Staging and Risk Stratification<sup>8,18-25</sup>**

- A. International Staging System (ISS)
1. Should only be used in patients with symptomatic MM
- B. Revised ISS (R-ISS)
1. Published in 2015, accounts for ISS in addition to cytogenetic abnormalities and LDH
  2. More effective as it is a corrected approach to include genetic factors

### Multiple Myeloma Staging Systems<sup>10</sup>

Stage	International Staging System (ISS)	Revised International Staging System (R-ISS)	5-year PFS	5-year OS
I	Serum beta-2 microglobulin < 3.5 mg/L AND serum albumin ≥ 3.5 g/dL	ISS Stage I AND no high-risk cytogenetic abnormalities by iFISH <sup>a</sup> AND normal serum LDH	55%	82%
II	Neither stage I nor III	Neither R-ISS stage I nor III	36%	62%
III	Serum beta-2 microglobulin ≥ 5.5 mg/L	ISS Stage III AND EITHER high-risk chromosomal abnormalities (del17p, t4;14, t14;16) by iFISH <sup>a</sup> OR elevated LDH	24%	40%

<sup>a</sup> iFISH: interphase fluorescent *in situ* hybridization

## VI. Treatment<sup>12,25-40</sup>

### A. Management of MGUS

- Diagnosis
  - Serum monoclonal protein < 3 g/dL *and* bone marrow plasma cells (BMPC) < 10%
  - If light chain MGUS:
    - Free light chain ratio < 0.26 or > 1.65 with no Ig heavy chain on serum immunofixation
  - And* absence of myeloma defining events or amyloidosis
- Median age at diagnosis: 72 years old
- Overall progression of MGUS toward a plasma cell malignancy is at a rate of 1% per year
- Cumulative probability of progression from MGUS to MM is 12% at 10 years, 25% at 20 years, and 30% at 25 years
- Management: observation

### B. Management of smoldering myeloma<sup>41</sup>

- Diagnosis
  - Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL, *or* urinary monoclonal protein ≥ 500 mg per 24 hours *and/or* BMPC 10%-59%
  - Absence of myeloma defining events or amyloidosis
- Overall progression from smoldering myeloma to active myeloma is 10% per year in the first 5 years following diagnosis, and decreases to 3% over the subsequent 5 years, and eventually declines to 1%.
  - Heterogeneous population in which some have low risk of progression similar to MGUS, while others are at high risk for progression (criteria for high risk smoldering myeloma exist but are beyond the scope of this educational activity)

3. Management: observation (both low and high risk patients should consider enrollment in clinical trial)

**Patient Case #1, (ARS Question #1)- Answer:**

**Correct answer is A (observation).** Smoldering myeloma requires observation as it is a plasma cell proliferative disorder with a risk of progressing into active MM; however, chemotherapy is reserved for the management of patients with active MM.

Answers B, C, and D are all treatment regimens reserved for patients with active MM and are not appropriate for a patient with smoldering myeloma.

**Patient Case #2, (ARS Question #2):**

TL is a 62-year-old male with newly diagnosed multiple myeloma. His corrected calcium is 11.8 mg/dL, 55% plasma cells on bone marrow pathology, R-ISS stage III ( $\beta$ 2M of 7.5 mg/L; high risk cytogenetics including t(14;16)), and SCr 0.91. ECOG status 0. He is eligible for autologous stem cell transplant and will be starting primary induction therapy. **Which of the following is the most appropriate first-line treatment option for TL according to the NCCN Guidelines®?**

- A. Daratumumab, bortezomib, dexamethasone
- B. Daratumumab, lenalidomide, dexamethasone
- C. Elotuzumab, lenalidomide, dexamethasone
- D. Bortezomib, lenalidomide, dexamethasone

C. Diagnosis of active MM<sup>42</sup>

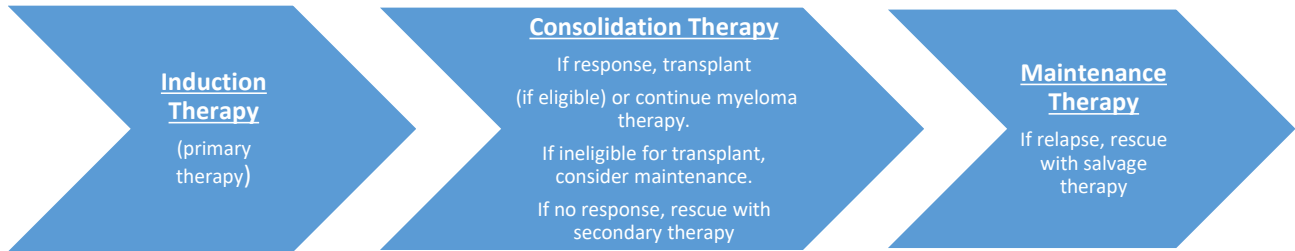
1. BMPC  $\geq$  10% or biopsy-proven bony or extramedullary plasmacytoma; and any of the following:
  - a. CRAB:
    - 1) Corrected calcium  $> 11$  mg/dL or  $> 1$  mg/dL above ULN
    - 2) SCr  $> 2$  mg/dL or CrCl  $< 40$  mL/min
    - 3) Hgb  $< 10$  g/dL or 2 g/dL below lower limit of normal
    - 4)  $\geq 1$  bone lesion on imaging (whole-body low-dose CT or FDG PET/CT preferred)
  - b. Or any of the following (SLiM):
    - 1) BMPC  $\geq 60\%$
    - 2) Involved:uninvolved free light chain ratio  $\geq 100$
    - 3)  $> 1$  focal marrow lesion  $\geq 5$  mm on MRI
2. Despite recent advances, MM remains incurable
3. Goals of therapy: disease control, improved quality of life, and prolonged survival
4. NCCN Guidelines® recommend 3-drug regimens over 2-drug regimens as the standard-of-care for primary treatment of MM based on improved response rates (RR), depth of response, progression free survival (PFS) and overall survival (OS).

- a. Doublet therapy may be considered in patients who are elderly and/or frail or who may not tolerate a 3-drug regimen.

- 1) Can consider adding a third drug if performance status improves

D. Induction therapy for transplant candidates

**Multiple myeloma treatment algorithm<sup>12,25</sup>**



1. Goal of induction therapy is to reduce tumor burden prior to autologous stem cell transplant (ASCT)
  - 1) Avoid alkylating agents and nitrosoureas that are toxic to progenitor cells (e.g., melphalan) and avoid prolonged lenalidomide and/or daratumumab exposure before collecting stem cells
2. Depth of response pre- and post- ASCT predict PFS and OS<sup>26,31</sup>
3. NCCN Guidelines® recommend harvesting peripheral blood early during primary treatment (preferably after 3 to 4 cycles of induction)

**NCCN Guidelines® primary therapy for transplant-eligible patients<sup>10</sup>**

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> <li>Bortezomib/lenalidomide/dex (VRd) (1)<sup>43</sup></li> <li>Carfilzomib/lenalidomide/ dex (KRd)<sup>44</sup></li> </ul>	<ul style="list-style-type: none"> <li>Daratumumab<sup>^</sup>/bortezomib /lenalidomide/dex<sup>45</sup></li> </ul>	<ul style="list-style-type: none"> <li>Bortezomib/cyclophos/dex (CyBorD) *<sup>46,47</sup></li> <li>Bortezomib/doxorubicin/ dex<sup>27,48</sup></li> <li>Bortezomib/thalidomide/ dex (VTd) (1)<sup>28</sup></li> <li>Carfilzomib/cyclophos/dex</li> <li>Ixazomib/cyclophos/dex</li> <li>Cyclophos/lenalidomide/dex</li> <li>Daratumumab<sup>^</sup>/bortezomib /thalidomide/dex<sup>49</sup></li> <li>Daratumumab/carfilzomib/ lenalidomide/dexamethasone<sup>50</sup></li> <li>Daratumumab<sup>^</sup>/cyclophos /bortezomib/dex<sup>51</sup></li> <li>Dex/thalidomide/cisplatin/ doxorubicin/cyclophos/ etoposide/bortezomib (VTD-PACE)<sup>52</sup></li> </ul>

(1)=Category 1 recommendation by NCCN Guidelines®. Category 2A if category is not listed.

Dex = dexamethasone; cyclophos = cyclophosphamide

\* Preferred in patients with acute renal insufficiency

<sup>^</sup> May substitute daratumumab and hyaluronidase-fihj subcutaneous

**Patient Case #2, Continued (ARS Question #2)- Answer:**

**Correct answer is D (Bortezomib, lenalidomide, dexamethasone).** The combination of bortezomib, lenalidomide, dexamethasone is a recommended induction regimen for patients with newly diagnosed multiple myeloma who are transplant eligible. All the remaining answer choices include monoclonal antibodies, and the only monoclonal antibody-based induction therapies currently recommended by the NCCN Guidelines® for transplant candidates are daratumumab + VRd (bortezomib, lenalidomide, dexamethasone) as per the GRIFFIN trial, daratumumab + VTd (bortezomib, thalidomide, dexamethasone) as per the CASSIOPEIA trial, and daratumumab + CyBorD (cyclophosphamide, bortezomib, dexamethasone) as per the LYRA trial.

Answer A: daratumumab, bortezomib, dexamethasone would be a suitable therapy for a patient with relapsed/refractory multiple myeloma. This triplet regimen is not currently indicated for the treatment of patients with newly diagnosed multiple myeloma who are transplant eligible.

Answer B: daratumumab, lenalidomide, dexamethasone may be utilized in non-transplant eligible patients as per the MAIA trial; however, it is not currently recommended for transplant eligible patients.

Answer C: elotuzumab, lenalidomide, dexamethasone may be utilized in patients with relapsed or refractory multiple myeloma; however, it is not recommended for newly diagnosed patients.

**Patient Case #2, Continued (ARS Question #3):**

TL is a guitarist and concerned about developing peripheral neuropathy (PN) from his treatment. Following a discussion of potential options for induction therapy, TL inquires which of following bortezomib-based regimens is least likely to cause PN?

- A. 1.3 mg/m<sup>2</sup> SubQ days 1, 4, 8, 11
- B. 1.3 mg/m<sup>2</sup> IV days 1, 8, 15, 22
- C. 1.3 mg/m<sup>2</sup> IV days 1, 4, 8, 11
- D. 1.5 mg/m<sup>2</sup> IV days 1, 8, 15, 22

4. Proteasome inhibitors

- a. All patients receiving proteasome inhibitors (bortezomib, carfilzomib, or ixazomib) should receive antiviral prophylaxis for prevention of herpes zoster reactivation (acyclovir, valacyclovir or famciclovir).
- b. Bortezomib-based regimens for induction in transplant-eligible patients
  - 1) Bortezomib works on both the intrinsic and extrinsic signaling pathways and is often combined with dexamethasone which works on the intrinsic pathway only
  - 2) Bortezomib/lenalidomide/dexamethasone (VRd)<sup>43</sup> (NCCN Guidelines® preferred regimen for both transplant eligible and ineligible patients)
    - a) Bortezomib 1.3 mg/m<sup>2</sup> IV/SC d1,4,8,11, lenalidomide 25 mg daily day 1-14, dexamethasone 20 mg 1,2,4,5,8,9,11,12
    - b) SWOG-S0777, a phase III trial (n=525) with previously untreated MM patients who were not planned for immediate autologous stem cell transplant; patients were randomized to lenalidomide/dexamethasone or

bortezomib/lenalidomide/dexamethasone each followed by maintenance therapy with lenalidomide/dexamethasone until progression or unacceptable toxicity.<sup>53</sup>

- i. Toxicities: Grade 3 neuropathy more frequent in bortezomib arm (24% vs 5%;  $p < 0.0001$ ). AE  $\geq$  grade 3 greater in bortezomib arm (82% vs 75%)

#### Results of trial SWOG-S0777

Regimen	ORR	CR	Median PFS	Median OS
Lenalidomide/ dexamethasone	72%	8%	29 months	69 months
Bortezomib/lenalidomide/ dexamethasone	82%	16%	41 months	Not reached
HR	-	-	0.74;95% CI 0.59-0.93	0.71;95% CI 0.54-0.93
p-value			0.003	0.0114

- c) IFM-2009, phase III trial (n=700) of previously untreated patients randomized to VRd induction followed by either melphalan autologous stem cell transplantation (ASCT) or VRd consolidation, followed by maintenance lenalidomide for 1 year in both arms.<sup>54</sup>
  - i. Patients received 3 cycles of VRd, followed by cyclophosphamide mobilization and stem cell collection. Following collection, patients then received either: VRd for 5 more cycles and subsequent lenalidomide maintenance or ASCT followed by 2 more cycles of VRd and subsequent lenalidomide maintenance.
  - ii. Median PFS (50 vs 36 months,  $p < 0.001$ ) and CR rates (59% vs 48%,  $p < 0.03$ ) significantly improved with ASCT. Overall survival at 4 years was not different between groups (82% vs 81%,  $p = 0.87$ ).
  - iii. PFS benefit of transplant independent of ISS stage and cytogenetic risk.
  - iv. Minimal residual disease (MRD) negativity was significantly improved with transplant (79% vs 65%,  $p < 0.001$ ).
- d) DETERMINATION, phase III trial (n=722) of previously untreated patients who received VRd induction and were randomized to either melphalan ASCT or VRd consolidation, followed by maintenance lenalidomide until progression in both arms.<sup>55</sup>
  - i. Patients received 3 cycles of VRd, followed by stem cell collection. Following collection, patients received either: VRd for 5 more cycles and subsequent lenalidomide maintenance or ASCT followed by 2 more cycles of VRd and subsequent lenalidomide maintenance.
  - ii. Lenalidomide maintenance was given until disease progression in both arms of trial
  - iii. Median PFS improved with ASCT (67.5 vs. 46.2 months)

- iv. No statistically significant difference in  $\geq$ CR with ASCT (46.8% vs. 42%, p=0.99)
  - v. No overall survival benefit found with ASCT over no ASCT at median follow-up of 76 months
- c. Impact of bortezomib dosing schedule and administration route on toxicity
- 1) Twice weekly versus once weekly bortezomib
    - a) Either weekly or twice weekly may be utilized; however, weekly is preferred as per NCCN Guidelines®.
    - b) Peripheral neuropathy is a significant toxicity associated with bortezomib which may lead to delays or discontinuation of therapy
    - c) Reeder et al, modified the CyBorD regimen with the goal to improve outcomes and reduce toxicity (see table: results of twice weekly versus once weekly bortezomib)<sup>37,38</sup>
      - i. Original CyBorD phase II trial induction therapy (cohort 1, n=33)
        - (a) Cyclophosphamide 300 mg/m<sup>2</sup> PO D 1, 8, 15 & 22 plus bortezomib **1.3 mg/m<sup>2</sup> IV** D 1, 4, 8 and 11 plus **pulse dexamethasone** 40 mg PO D 1-4, 9-12, 17-20 given every 28 days x 4 cycles
        - (b) Mild to moderate peripheral neuropathy in 66% of patients; grade 1 = 46%, grade 2 = 13%, grade 3 = 7% and no grade 4 peripheral neuropathy
      - ii. Modified CyBorD by Reeder et al (cohort 2, n=30).
        - (a) Cyclophosphamide the same as the original, bortezomib **1.5 mg/m<sup>2</sup> IV** D 1, 8, 15 and 22 and dexamethasone 40 mg was given in the same pulsed fashion for cycles 1 and 2, then weekly for cycles 3 and 4
        - (b) ORR were similar; however, the weekly group had fewer bortezomib and dexamethasone dose reductions.
        - (c) Peripheral neuropathy rates were the same, however the total bortezomib dose per cycle was higher in the weekly versus the twice weekly schedule (6 mg/m<sup>2</sup> vs 5.2 mg/m<sup>2</sup>)
        - (d) Take home message: bortezomib may be given once weekly

**Results of twice weekly versus once weekly bortezomib<sup>38</sup>**

Regimen	ORR	CR/nCR	VGPR	Bortezomib dose reductions	Grade 3 events	Grade 4 events
Original CyBorD (biweekly)	88%	39%	61%	21%	48%	12%
Modified CyBorD (weekly)	93%	43%	60%	13%	37%	3%



- 2) Subcutaneous (SubQ) versus intravenous bortezomib: SubQ bortezomib offers non-inferior efficacy to standard IV, with an improved safety profile
  - a) A non-inferiority phase III trial by Moreau et al. in relapsed MM (n=222) after 1 - 3 previous lines of therapy, evaluated bortezomib 1.3 mg/m<sup>2</sup> on D 1, 4, 8, and 11 every 21 days up to 8 cycles given IV or SubQ. Patients were randomized 2:1 (SubQ:IV)<sup>26,33,56</sup>
    - i. Non-inferior ORR and no difference in time to progression between SubQ and IV bortezomib
    - ii. Overall grade 3/4 toxicity was lower in SubQ vs IV groups (57% vs 70%)
      - (a) Hematologic toxicities (SubQ vs IV): thrombocytopenia (13% vs 19%), neutropenia (18% both groups), and anemia (12% vs 8%).
      - (b) Peripheral neuropathy was significantly less common with SubQ vs IV administration; all grade 38% vs 53% (p=0.044), grade 2 or worse 24% vs 41% (p=0.012), and grade 3 or worse 6% vs 16% (p=0.026)
  - b) Bortezomib is FDA approved for SubQ or IV administration in the frontline setting despite the SubQ route only being studied in the relapsed setting
- d. Carfilzomib-based regimens for induction in transplant-eligible patients
  - 1) Carfilzomib/lenalidomide/dexamethasone (KRd):
    - a) UNITO-MM-01/FORTE, phase II trial (n=474) evaluated KRd x4 cycles plus ASCT vs. carfilzomib, cyclophosphamide, dexamethasone (KCyd) x4 cycles plus ASCT vs. KRd x12 cycles, followed by maintenance therapy with carfilzomib/lenalidomide or lenalidomide<sup>57</sup>
      - i. KRd and KCyd given in 28-day cycles: Carfilzomib 36 mg/m<sup>2</sup> IV d1,2,8,9,15,16 (20 mg/m<sup>2</sup> d1,2 of cycle 1), lenalidomide 25 mg daily days 1-21, cyclophosphamide 300 mg/m<sup>2</sup> po d1,8,15, dexamethasone 20 mg IV/PO 1,2,8,9,15,16,22,23
      - ii. After 4 cycles of induction, patients underwent stem cell mobilization. ASCT arms proceeded to transplant and then received additional 4 cycles as consolidation between days 90-120 post ASCT
      - iii. Primary endpoint of very good partial response (VGPR) or better after induction improved with KRd over KCyd (70% vs. 53%, p=0.0002)
      - iv. KRd plus ASCT had significant reduction in risk of progression compared to KCyd plus ASCT (HR 0.54, 95% CI 0.38-0.78, p=0.0008)
      - v. 3-year PFS rates improved with KR maintenance vs. lenalidomide maintenance (75% vs. 65%, p=0.023)
    - b) Take home message: KRd induction may be considered for primary treatment of transplant-eligible patients.
  - e. Selection of upfront triplet therapy (i.e., VRd vs KRd)

- 1) ENDURANCE: phase III trial including 1087 patients with newly diagnosed MM, randomized to VRd or KRd induction, independent of transplant eligibility.<sup>58,59</sup>
  - a) VRd: bortezomib 1.3 mg/m<sup>2</sup> SQ d1,4,8,11; lenalidomide 25 mg PO d1-14; dexamethasone 40 mg d1,2,4,5,8,9,11,12 (21 day cycle).
  - b) KRd: carfilzomib 36 mg/m<sup>2</sup> IV d1,2,8,9,15,16; lenalidomide 25 mg d1-21, dexamethasone 40 mg weekly (28 day cycle).
  - c) Eligible patients could undergo ASCT following induction therapy. Both arms followed by maintenance lenalidomide 15 mg daily for 21 out of 28 days per cycle.
  - d) Results
    - i. No significant difference in median PFS (34.4 months VRd vs 34.6 months KRd)
    - ii. No significant difference in 3 year OS (84% VRd vs 86% KRd)
    - iii.  $\geq$  CR in 10% with VRd compared to 14% with KRd
    - iv. More peripheral neuropathy with VRd (8% vs 1%) and more cardiac/pulmonary/renal composite toxicities with KRd (16% vs 5%)

**Patient Case #2, Continued (ARS Question #3)- Answer:**

**Correct answer is A (1.3 mg/m<sup>2</sup> SubQ days 1, 4, 8, 11).** SubQ administration of bortezomib has exhibited reduced all-grade peripheral neuropathy when compared to IV bortezomib.

Answers B, C, and D are all administered intravenously, which has exhibited increased peripheral neuropathy when compared to SubQ administration. Patients who received weekly bortezomib vs administration on days 1,4, 8, and 11 experienced similar incidence of peripheral neuropathy; however, the total bortezomib dose per cycle was higher in the weekly group and they required fewer dose reductions.

5. Daratumumab-based regimen for induction in transplant-eligible patients
  - a. Daratumumab-based induction therapies for transplant-eligible patients may be in combination with: bortezomib, lenalidomide, dexamethasone (VRd), carfilzomib, lenalidomide, dexamethasone (KRd), bortezomib, thalidomide, dexamethasone (VTd), or cyclophosphamide, bortezomib, dexamethasone (CyBorD).
  - b. CASSIOPEIA, phase III trial comparing VTd (n=542) to VTd + daratumumab (n=543) in transplant eligible patients
    - 1) Primary endpoint was stringent CR at day 100 post ASCT: achieved by 29% of patients in the daratumumab arm, compared to 20% with VTd (p=0.001)<sup>49</sup>
    - 2) Secondary endpoints
      - a)  $\geq$  CR: 39% with daratumumab versus 26% with VTd
      - b) MRD negativity (10<sup>-5</sup>): 64% (daratumumab) vs 44% (VTd) [p<0.0001]
  - c. GRIFFIN, phase II trial comparing VRd (n=103) to VRd + daratumumab (n=104) in transplant eligible patients.<sup>45</sup>

- 1) Primary endpoint was stringent CR at day 100 post ASCT: achieved by 42.4% of patients in the daratumumab arm, compared to 32% with VRd ( $p=0.068$ ). This result met the prespecified 1 side alpha of 0.10.
- 2) Secondary endpoints
  - a) Responses deepened with continued therapy;  $\geq$  stringent CR after a median of 22.1 months follow up: 62.6% (daratumumab) vs 45.4% (VRd) [ $p=0.0177$ ].
  - b) MRD negativity ( $10^{-5}$ ): 51.0% (daratumumab) vs 20.4% (VRd) [ $p<0.0001$ ].
- d. LYRA, phase II single-arm trial including 101 patients with both newly diagnosed ( $n=87$ ) and relapsed myeloma ( $n=14$ ), independent of transplant eligibility.<sup>51</sup> Evaluated the addition of daratumumab to CyBorD (cyclophosphamide, bortezomib, dexamethasone).
  - 1) Eligible newly diagnosed patients ( $n=28$ ) underwent ASCT.
  - 2) Overall response rate at completion of induction therapy was 81.4% and 71.4% in newly diagnosed and relapsed patients, respectively. PFS at 12 months was 87% in newly diagnosed and 66.2% in relapsed patients.
- e. MASTER, multicenter, single arm phase II trial of daratumumab plus KRd in newly diagnosed patients with high-risk cytogenetic abnormalities ( $n=123$ ) followed by melphalan ASCT and then MRD testing to guide further treatment. Patients with two consecutive MRD negative  $< 10^{-5}$  assessments transitioned to a treatment-free<sup>50</sup> observation
  - 1) MRD negativity achieved in 80%; 71% had two consecutive MRD-negative assessments and entered a treatment-free observation period
  - 2) Two-year PFS rate was 87%
6. Lenalidomide-based regimens for induction in transplant-eligible patients
  - a. Collect stem cells within first 4 cycles of lenalidomide and dexamethasone if deemed transplant eligible<sup>10</sup>
    - 1) A decrease in CD34-positive cells collection has been reported after prolonged lenalidomide exposure.<sup>30,34</sup>
  - b. Secondary malignancies
    - 1) The increased use of lenalidomide as induction and maintenance therapy in MM has led to an increase in second primary malignancies.<sup>60</sup> This has not been seen with the use of thalidomide. Pomalidomide is the newest IMiD and experience is lacking to determine if an increased risk of secondary malignancies exists with this agent.

#### Risk of secondary malignancy with lenalidomide use

Study	Study Design	Total Patients	Hematologic Malignancy, n	Solid Tumor Malignancy, n
Attal <sup>61</sup>	Randomized, phase III, maintenance lenalidomide post auto-transplant	614	13-lenalidomide 5-placebo	10-lenalidomide 4-placebo
Holstein <sup>62</sup>	Randomized, phase III, maintenance lenalidomide post auto-transplant	460	18-lenalidomide 3-placebo	14-lenalidomide 9-placebo
Palumbo <sup>40</sup>	*Randomized, phase III, maintenance lenalidomide post MPR induction only (MPR-R)	459	7-MPR-R 5-MPR 1-MP	5-MPR-R 4-MPR 3-MP

\*Patients were randomized to induction with MPR (melphalan, prednisone, lenalidomide) followed by lenalidomide maintenance, MPR followed by placebo, or MP (melphalan, prednisone) followed by placebo

#### E. Induction therapy for non-transplant candidates<sup>10</sup>

1. Primary goal is to reduce tumor burden and prolong survival.

#### NCCN Guidelines® induction regimens for non-transplant candidates (assess for response after each cycle)<sup>10</sup>

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide/dex (VRd) (1)<sup>43</sup></li> <li>• Daratumumab^/lenalidomide/dex (1)<sup>63</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Carfilzomib/lenalidomide/dex (KRd)<sup>44,64</sup></li> <li>• Ixazomib/lenalidomide/dex</li> <li>• Daratumumab^/bortezomib/melphalan/prednisone (1)<sup>65</sup></li> <li>• Daratumumab^/cyclophosphamide/bortezomib/dex<sup>51</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Bortezomib/dex<sup>66</sup></li> <li>• Bortezomib/cyclophosphamide/dex (CyBorD)<sup>46,67</sup></li> <li>• Bortezomib/lenalidomide/dex (VRD-lite) for frail patients<sup>68</sup></li> <li>• Cyclophosphamide/lenalidomide/dex</li> <li>• Carfilzomib/cyclophosphamide/dex (KCyd)<sup>69</sup></li> <li>• Lenalidomide/low-dose dex (1)<sup>70,71*</sup></li> </ul>

(1)=Category 1 recommendation by NCCN Guidelines®. Category 2A if category is not listed.

Dex = dexamethasone

\* NCCN Guidelines® recommend considering doublet therapy for frail or elderly patients

^ May substitute daratumumab and hyaluronidase-fihj subcutaneous

## 2. Daratumumab

- a. Interferes with cross-matching and red blood cell antibody screening; therefore, providers should type and screen patients prior to starting therapy. Once on therapy, blood banks should be informed that the patient has received daratumumab.
- b. Initiate antiviral prophylaxis within 1 week of starting daratumumab and continue for 3 months after completion of treatment to prevent herpes zoster reactivation.
- c. Pre-medicate with corticosteroids, antipyretics, and antihistamines; consider corticosteroids as take home for 2 days following treatment.
  - 1) The addition of montelukast 10 mg to standard pre-medications has been shown to further reduce the risk of infusion-related reactions (38.0% vs 58.5%).<sup>72</sup>
- d. Rapid administration (over 90 minutes) of daratumumab may be considered following at least 2 tolerated doses<sup>73</sup>
- e. Daratumumab and hyaluronidase-fihj subcutaneous formulation may be substituted for intravenous administration as part of any NCCN® recommended daratumumab-based regimen<sup>74</sup>
  - 1) Flat dose: 1,800 mg daratumumab + 30,000 units hyaluronidase (in 15 mL)
    - c) Subcutaneous administration in abdomen over 3-5 minutes
  - 2) Infusion-related reactions
    - c) Significantly lower rate of infusion-related reactions with subcutaneous administration compared to intravenous (13% vs 34%; odds ratio 0.28, 95% CI 0.18-0.44;  $p < 0.0001$ ).<sup>75</sup>
    - d) Local: median onset approximately 5 minutes
    - e) Systemic: median onset approximately 3 hours
- f. Daratumumab-containing regimens for non-transplant candidates
  - 1) Daratumumab + VMP (bortezomib, melphalan, prednisone) – category 1 for non-transplant eligible patients based on ALCYONE trial<sup>65,76</sup>
    - a) Phase III study in which newly diagnosed non-transplant eligible patients (n=706) were randomized to receive nine cycles of VMP (bortezomib, melphalan and prednisone) with or without daratumumab.
    - b) The primary endpoint was PFS
      - i. Median PFS was 36.4 months (95% CI 32.1-45.9) in the daratumumab group versus 19.3 months (18-20.4) in the non-daratumumab group.
      - ii. At a median follow-up of 40.1 months, disease progression or death occurred in 50% in the daratumumab group compared to 74% in the non-daratumumab group.
    - c) The secondary endpoints included ORR, very good partial response (VGPR) rates, MRD negativity, and OS

- i. ORR 90.9% in the daratumumab group compared to 73.9% in the non-daratumumab arm ( $p < 0.001$ ).
      - ii. VGPR 71.1% in the daratumumab group compared to 49.7% in the non-daratumumab arm ( $p < 0.001$ ).
      - iii. MRD negativity (1 cell per  $10^5$ ) attained in 22.3% of patients in daratumumab arm vs 6.2% in VMP arm ( $p < 0.001$ ).
      - iv. 36-month OS was 78.0% in the daratumumab containing group and 67.9% in the non-daratumumab group (HR=0.60; 95% CI 0.46-0.80;  $p = 0.0003$ ).<sup>76</sup>
    - d) Adverse effects: similar rates of hematologic toxicities but increased grade  $\geq 3$  infections with daratumumab (23.1% vs 14.7%).
  - 2) Daratumumab + CyBorD (cyclophosphamide, bortezomib, dexamethasone) – category 2A for non-transplant eligible patients based on LYRA trial (see details above).
  - 3) Daratumumab, lenalidomide, dexamethasone<sup>63</sup>
    - c) FDA approved in June 2019 for non-transplant eligible patients, NCCN Guidelines® category 1 recommendation.
      - i. Phase III study (MAIA;  $n = 737$ ) of non-transplant eligible, newly diagnosed patients who were randomized to lenalidomide, dexamethasone +/- daratumumab<sup>77</sup>
        - (a) ORR of 92.9% with daratumumab vs 81.3% for non-daratumumab group ( $p < 0.001$ ).
        - (b) Median PFS not reached in the daratumumab group vs 31.9 months in non-daratumumab ( $p < 0.001$ ). Estimated 5-year OS was 66.3% with daratumumab vs 53.1% for non-daratumumab group.
        - (c) MRD negativity (1 cell per  $10^5$ ) attained in 31% of patients in daratumumab arm vs 10% in lenalidomide/dexamethasone arm ( $p < 0.001$ ).
        - (d) Adverse effects (grade  $\geq 3$ ): myelosuppression increased with daratumumab; neutropenia (54% vs 37%) and lymphopenia (16% vs 11%). Rates of infection increased with daratumumab (41% vs 29%) and increased complaints of fatigue (9% vs 5%).
3. Proteasome Inhibitors
- a. Bortezomib-based regimens for non-transplant candidates<sup>46,67</sup>
    - 1) VRd
    - 2) VRd-lite<sup>63 68</sup>
      - a) Dose modified version of standard VRd for frail patients
        - ii. 35-day cycle: lenalidomide 15 mg daily days 1-21, bortezomib 1.3 mg/m<sup>2</sup> SC d1,8,15,22, dexamethasone 20 mg d1,2,8,9,15,16,22,23 for 9 cycles followed by 6 cycles of consolidation lenalidomide and bortezomib

- 3) CyBorD
  - 4) Bortezomib/dexamethasone (see the UPFRONT trial in maintenance therapy section)
- b. Carfilzomib-based regimens for non-transplant candidates
- 1) Patients with newly diagnosed multiple myeloma age  $\geq 65$  or non-transplant eligible (n=58) were enrolled in a phase II trial evaluating carfilzomib/cyclophosphamide/dexamethasone (KCyd)<sup>64 69</sup> for up to nine 28-day cycles followed by carfilzomib maintenance therapy.
    - a) The primary endpoints included evaluation of toxicity and efficacy (a pre-planned definition of PR in  $\geq 35\%$  of patients) at the end of cycle 3.
      - i. 95% of patients achieved PR, 71% achieved VGPR, 49% nCR, and 20% CR.
    - b) Secondary endpoints included response rates, PFS, time to progression (TTP), duration of response, OS, time to next therapy, rates of peripheral neuropathy, subgroup analysis of prognostic factors, the effect of maintenance on PFS and OS and the relationship between responses and PFS in patients who responded compared to those who did not respond.
    - c) Toxicity: most common  $\geq$  grade 3 toxicities included neutropenia (20%), cardiopulmonary events (7%), anemia (11%), and grade 1/2 peripheral neuropathy (9%).
- c. Ixazomib-containing regimens for non-transplant candidates
- 1) The phase III, double-blind TOURMALINE-MM2 trial randomized patients to lenalidomide 25 mg D 1-21, dexamethasone 40 mg weekly + ixazomib 4 mg days 1, 8, 15 or placebo<sup>78</sup>
    - a) An increase in the primary endpoint of PFS was demonstrated in the ixazomib arm (35.3 vs. 21.8 months, HR 0.830; 95% confidence interval, 0.676-1.018; P = 0.073), although not statistically significant
    - b) Grade 3 or greater toxicities that were more common in the ixazomib group included thrombocytopenia, rash, and diarrhea

#### F. Maintenance therapy<sup>79</sup>

1. Key take-home points include:
  - a. For patients unable to tolerate intensive therapy after induction treatment, less aggressive strategies should be considered
  - b. Maintenance therapy may be considered following induction therapy in lieu of autologous transplant (for non-transplant candidates) or following autologous transplant.
  - c. Maintenance therapy should maintain or increase response after induction therapy
  - d. Maintenance therapy should be easily administered (preferably oral) with minimal toxicity

### Maintenance therapy for MM per the NCCN Guidelines<sup>®10</sup>

Preferred Regimen	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> <li>• Lenalidomide <ul style="list-style-type: none"> <li>○ (1, transplant eligible and ineligible)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Bortezomib <ul style="list-style-type: none"> <li>○ (transplant eligible and ineligible)</li> </ul> </li> <li>• Daratumumab <ul style="list-style-type: none"> <li>○ (transplant eligible)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Bortezomib and lenalidomide <ul style="list-style-type: none"> <li>○ (transplant eligible and ineligible)</li> </ul> </li> <li>• Carfilzomib and lenalidomide <ul style="list-style-type: none"> <li>○ (transplant eligible)</li> </ul> </li> </ul>

(1)=Category 1 recommendation by NCCN Guidelines<sup>®</sup>. Category 2A if category is not listed.

#### d. Lenalidomide maintenance

- 1) CALGB 100104 trial, evaluated lenalidomide (n=231) vs placebo (n=229) maintenance after ASCT. Therapy was initiated at day 100 post ASCT.<sup>62,80</sup>
  - a) More patients who received placebo had disease progression at 34 months compared to those who received lenalidomide (58% vs 37%)
  - b) Median time to progression (TTP) in the lenalidomide arm was 57.3 months vs 28.9 months in the placebo arm (p<0.0001)
  - c) Median PFS in the lenalidomide arm was 5.7 years vs 1.9 years in the placebo arm (HR=0.38; 95% CI=0.28-0.5)
  - d) Median OS in the lenalidomide arm was 113.8 months vs. 84.1 months in the placebo arm (HR=0.61, 95% CI 0.46-0.80, p=0.0004)
  - e) Second primary cancers (hematologic) occurred in 7.8% of patients receiving lenalidomide vs 1.3% in placebo; second primary cancers (solid tumor) occurred in 6.1% of patients receiving lenalidomide vs 3.9% in placebo.
- 2) MM-015 trial was a double-blind, multicenter, randomized study of melphalan/prednisone/lenalidomide induction followed by lenalidomide maintenance (10 mg on days 1-21 of 28 day cycles) [MPR-R] vs melphalan/prednisone/lenalidomide (MPR) or melphalan/prednisone (MP) followed by placebo.<sup>40</sup>
  - a) In transplant ineligible patients ≥ 65 with newly diagnosed MM, lenalidomide maintenance after induction with MPR reduced the risk of disease progression.

#### Results of MM-015 trial

Regimen	Median PFS	3-Year OS
MPR-R	31 months	70%
MPR	14 months	62%
MP	13 months	66%
p-value	<0.001	Not reported

#### e. Bortezomib maintenance<sup>66</sup>



- 1) In the UPFRONT trial, non-transplant candidates (n=502) were randomly assigned 1:1:1 to receive eight 21-day cycles of induction chemotherapy followed by maintenance bortezomib 1.6 mg/m<sup>2</sup> D 1,8,15,22 for five 35-day cycles.
  - a) The induction regimens included:
    - i. All induction regimens included bortezomib 1.3 mg/m<sup>2</sup> IV D 1,4,8,11
    - ii. VD [dexamethasone 20 mg D 1,2,4,5,8,9,11,12 (cycles 1 to 4) followed by dexamethasone 20 mg D 1-5 (cycles 5 to 8)]
    - iii. VTD (thalidomide 100 mg D 1-21 plus dexamethasone 20 mg D 1,2,4,5,8,9,11,12)
    - iv. VMP (melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> D 1-4 every other cycle)
  - b) Results from UPFRONT trial (see table below): no difference in PFS (primary endpoint) or OS
  - c) Adverse events were more common with VTD than VD or VMP. Authors also state that bortezomib maintenance was feasible without producing cumulative toxicity.

**Results of UPFRONT trial**

Regimen	Median PFS	ORR
VD	14.7 months	73%
VTD	15.4 months	80%
VMP	17.3 months	70%
p-value	0.46	Not Reported

- 2) In the HOVON-65 trial, patients (n=827) received induction therapy with doxorubicin, dexamethasone and either vincristine or bortezomib followed by autologous transplant. Patients then randomized to either thalidomide or bortezomib maintenance (every 2 weeks) for 2 years.<sup>81</sup>
  - a) Median PFS prolonged with bortezomib maintenance (34 vs 28 months; p=0.001).

**G. Evaluating response to therapy**

1. Response criteria (see table: response criteria in multiple myeloma)
  - a. Response to treatment remains a key determinant in treatment decisions
2. Relapse criteria (see table: relapse criteria in multiple myeloma)

**Response criteria in multiple myeloma** <sup>82-85</sup>

Response Criteria	International Myeloma Working Group (IMWG)
Stringent complete response* (sCR)	CR defined as below plus: Normal free light chain (FLC) ratio Absence of clonal cells in bone marrow biopsy by immunohistochemistry or immunofluorescence
Complete response* (CR)	Negative serum and urine immunofixation and disappearance of soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates Normal FLC ratio if light chain restricted disease
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg per 24-hour
Partial response (PR)	≥ 50% reduction in serum M-protein plus ≥ 90% reduction in 24-hour urine M-protein or to < 200 mg per 24-hour If serum/urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC is required. If serum/urine M-protein, and free light chain assay is also unmeasurable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30%  If present at baseline, a >50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response (MR)	≥ 25% but ≤49% reduction of serum M-protein and reduction of 24-hour urine M-protein by 50-89% If present at baseline, 25-49% reduction in soft tissue plasmacytomas
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or progressive disease (PD)

*\*sCR and CR criteria must be met on 2 separate assessments. Confirmation with repeat bone marrow biopsy is not needed.*

# Relapse criteria in multiple myeloma<sup>82,83,85</sup>

Relapse Category	IMWG
Progressive Disease	<p>Requires at least one of the following:</p> <ul style="list-style-type: none"> <li>• Increase of 25% from lowest value in at least one of the following criteria: <ul style="list-style-type: none"> <li>○ Serum M-protein (absolute increase of <math>\geq 0.5</math> g/dL)</li> <li>○ Serum M-protein increase <math>\geq 1</math> g/dL, if lowest M component was <math>\geq 5</math> g/dL</li> <li>○ Urine M-protein (absolute increase <math>\geq 200</math> mg/24 hours)</li> <li>○ Patients without measurable serum/urine M-protein: difference between involved and uninvolved FLC levels (absolute increase must be <math>&gt;10</math> mg/dL)</li> <li>○ Patients without measurable serum/urine M-protein and without measurable involved FLC: bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be <math>\geq 10\%</math>)</li> <li>○ Appearance of new lesion(s)</li> <li>○ <math>\geq 50\%</math> increase in circulating plasma cells (minimum of 200 cells per <math>\mu\text{L}</math>) if this is only measurable disease</li> </ul> </li> </ul>
Clinical Relapse	<p>Requires at least one of the following:</p> <ul style="list-style-type: none"> <li>• Development of new bone lesions or soft tissue plasmacytoma</li> <li>• Increase in size of existing plasmacytomas or bone lesions (50% increase or <math>\geq 1</math> cm)</li> <li>• <b>Any of the following attributable to myeloma:</b> <ul style="list-style-type: none"> <li>○ Development of hypercalcemia (<math>&gt; 11</math> mg/dL)</li> <li>○ Development of anemia (drop in Hb <math>\geq 2</math> g/dL)</li> <li>○ Rise in SCr (by <math>\geq 2</math> mg/dL)</li> </ul> </li> <li>• Hyperviscosity related to serum protein</li> </ul>
Relapse from CR	<p>Requires at least one of the following:</p> <ul style="list-style-type: none"> <li>• Reappearance of serum or urine M-protein by immunofixation or electrophoresis</li> <li>• <math>\geq 5\%</math> plasma cells in the bone marrow</li> </ul> <p>Appearance of any other sign of progression (e.g., new plasmacytoma, new lytic bone lesion, or hypercalcemia)</p>

Abbreviation: CR, complete response; FLC, free light chain

## Patient Case #2, Continued (ARS Question #4):

TL was treated with 4 cycles of induction VRd (bortezomib, lenalidomide, dexamethasone), ASCT, and 2 cycles of VRd consolidation and achieved a complete response. He then continued lenalidomide maintenance until presenting 4 years later with progressive disease, now requiring further therapy.

**Which of the following is the most appropriate therapy for TL at this time according to the NCCN Guidelines®?**

- Bendamustine, lenalidomide, dexamethasone
- Selinexor, dexamethasone
- Isatuximab, carfilzomib, dexamethasone
- Ciltacabtagene autoleucel

H. Treatment—Relapsed/Refractory Disease<sup>10</sup>

**Therapy for early relapses (1-3 prior therapies) of previously treated MM per the NCCN Guidelines® (assess response after each cycle) \*<sup>10</sup>**

<b>Preferred Regimens</b>	
<ul style="list-style-type: none"> <li>Patients who are still sensitive to bortezomib and/or lenalidomide, any of the regimens below can be considered</li> <li>Ixazomib/lenalidomide/dex (1)</li> <li>Bortezomib/lenalidomide/dex</li> </ul>	
<b><i>Bortezomib-Refractory</i></b>	<b><i>Lenalidomide-Refractory</i></b>
<ul style="list-style-type: none"> <li>Carfilzomib/lenalidomide/dex (1)</li> <li>Daratumumab<sup>^</sup>/carfilzomib/dex (1)</li> <li>Daratumumab<sup>^</sup>/lenalidomide/dex (1)</li> <li>Isatuximab/carfilzomib/dex (1)</li> <li>Carfilzomib/pomalidomide/dex</li> </ul>	<ul style="list-style-type: none"> <li>Daratumumab<sup>^</sup>/bortezomib/dex (1)</li> <li>Daratumumab<sup>^</sup>/carfilzomib/dex (1)</li> <li>Isatuximab/carfilzomib/dex (1)</li> <li>Carfilzomib/pomalidomide/dex</li> </ul>
After 1 prior therapy including lenalidomide and PI • Daratumumab <sup>^</sup> /pomalidomide/dex (1)	After 1 prior therapy including lenalidomide and PI • Daratumumab <sup>^</sup> /pomalidomide/dex (1)
After 2 prior therapies including lenalidomide and PI • Isatuximab/pomalidomide/dex (1)	• After 2 prior therapies including lenalidomide and PI Isatuximab/pomalidomide/dex (1)
After 2 prior therapies including an IMiD and PI and with disease progression within 60 days of completing last therapy • Ixazomib/pomalidomide/dex	After 2 prior therapies including an IMiD and PI and with disease progression within 60 days of completing last therapy • Bortezomib/pomalidomide/dex (1) • Ixazomib/pomalidomide/dex
<b>Other Recommended Regimens</b>	<b>Useful in Certain Circumstances</b>
<ul style="list-style-type: none"> <li>Bortezomib/liposomal doxorubicin/dex (1)</li> <li>Carfilzomib (twice weekly)/dex (1)</li> <li>Elotuzumab/lenalidomide/dex (1)</li> <li>Selinexor/bortezomib/dex (1)</li> <li>Bortezomib/cyclophos/dex</li> <li>Carfilzomib/cyclophos/dex</li> <li>Daratumumab/cyclophos/bortezomib/dex</li> <li>Elotuzumab/bortezomib/dex</li> <li>Ixazomib/cyclophosphamide/dex</li> <li>Lenalidomide/cyclophosphamide/dex</li> </ul>	<ul style="list-style-type: none"> <li>Bortezomib/dex (1)</li> <li>Lenalidomide/dex (1)</li> <li>Carfilzomib (weekly)/dex</li> <li>Carfilzomib/cyclophos/thalidomide/dex</li> <li>Selinexor/daratumumab<sup>^</sup>/dex</li> <li>Selinexor/carfilzomib/dex</li> <li>Venetoclax/dex [only for pts with t(11;14)]</li> </ul>
After 2 prior therapies including an IMiD and PI and disease progression ≤ 60 days of completion of last therapy • Pomalidomide/cyclophosphamide/dex	After 2 prior therapies including an IMiD and PI and disease progression ≤ 60 days of completion of last therapy • Pomalidomide/cyclophosphamide/dex (1) • Pomalidomide/selinexor/dex
After 2 prior therapies including lenalidomide and PI • Elotuzumab/pomalidomide/dex	Treatment of aggressive MM • DCEP: Dex/cyclophosphamide/etoposide/cisplatin • VTD-PACE: Dex/thalidomide/cisplatin/doxorubicin/cyclophos/etoposide (DT-PACE) ± bortezomib (VTD-PACE) After at least 3 prior therapies including PI and IMiD or double-refractory to PI and IMiD • Daratumumab

(1) = Category 1 recommendation by NCCN Guidelines®. Category 2A if category is not listed.

Dex = dexamethasone; cyclophos = cyclophosphamide.

\* if a regimen listed above was used as primary induction therapy and relapse is > 6 months, the regimen may be repeated

<sup>^</sup> May substitute daratumumab and hyaluronidase-fihj subcutaneous

**Therapy for late relapses (>3 prior therapies) of previously treated MM per the NCCN Guidelines® (assess response after each cycle) \*<sup>10</sup>**

Regimens for Late Relapses (>3 prior therapies)	
<ul style="list-style-type: none"> <li>• Bendamustine</li> <li>• Bendamustine/bortezomib/dexamethasone</li> <li>• Bendamustine/carfilzomib/dexamethasone</li> <li>• Bendamustine/lenalidomide/dexamethasone</li> </ul> Fractionated or high-dose cyclophosphamide	
After at least 4 therapies, including an anti-CD38 monoclonal antibody, a PI, and IMiD	After at least 4 therapies and disease is refractory to at least 2 PIs, 2 IMiDs, and an anti-CD38 monoclonal antibody
<ul style="list-style-type: none"> <li>• Idecabtagene vicleucel</li> <li>• Ciltacabtagene autoleucel</li> <li>• Teclistamab-cqyv</li> </ul>	<ul style="list-style-type: none"> <li>• Selinexor/dexamethasone</li> </ul>

\* Regimens listed above for early relapses may also be used later in disease course with an attempt to utilize drugs and or classes not previously seen or more than 1 line before. Autologous transplant should be considered if eligible if not previously received or if prolonged response to first transplant.

1. Proteasome inhibitors

a. Bortezomib

1) DT-PACE ± bortezomib <sup>86-88</sup>

- a) Salvage chemotherapy regimen that uses conventional chemotherapy with thalidomide +/- bortezomib.
  - i. DT-PACE consisted of high-dose dexamethasone 40 mg orally daily for 4 days; thalidomide 400 mg PO at night continuous; 4-day continuous infusion of cisplatin 10 mg/m<sup>2</sup>/day (total dose per cycle 40 mg/m<sup>2</sup>), doxorubicin 10 mg/m<sup>2</sup>/day (total dose per cycle 40 mg/m<sup>2</sup>), cyclophosphamide 400 mg/m<sup>2</sup>/day (total dose per cycle 1,600 mg/m<sup>2</sup>), and etoposide 40 mg/m<sup>2</sup>/day (total dose per cycle 160 mg/m<sup>2</sup>). If bortezomib is added it is dosed at 1 mg/m<sup>2</sup> on D 1, 4, 8, 11.
  - ii. All patients received a prophylactic regimen of fluconazole, levofloxacin, and acyclovir from the first day of chemotherapy, which was continued until the ANC reached more than 1,000/μL for 2 consecutive days. Bactrim prophylaxis was continued throughout treatment for PJP prevention.
  - iii. Regimen is extremely myelosuppressive and requires colony stimulating factor due to high rates of febrile neutropenia

b. Carfilzomib <sup>89</sup>

- 1) Approved in combination with dexamethasone or dexamethasone and lenalidomide in patients who have received 1 – 3 prior lines of therapy or as single agent therapy in patients who received ≥ 1 line of therapy for patients with relapsed/refractory disease
- 2) Carfilzomib/lenalidomide/dexamethasone

- a) Phase III study (ASPIRE; n=792) evaluated Rd +/- carfilzomib.<sup>90</sup>
  - i. Dosing: lenalidomide 25 mg D 1-21 and dexamethasone 40 mg weekly +/- carfilzomib 1,2,8,9,15,16 (20 mg/m<sup>2</sup> on D 1,2 of cycle 1; 27 mg/m<sup>2</sup> thereafter) IV over 10 minutes during cycles 1-12 and on D 1,2,15, and 16 with cycles 13-18.
  - ii. ORR improved with addition of carfilzomib (87.1% vs 66.7%; p<0.001)
  - iii. PFS 26.3 months in carfilzomib arm vs 17.6 months Rd (p<0.001)
  - iv. Updated OS data indicates significant improvement in survival; median OS 48.3 months with carfilzomib vs 40.4 months with lenalidomide/dexamethasone (p=0.0045).<sup>91</sup>
  - v. Toxicities:
    - (a) Peripheral neuropathy similar in each arm
    - (b) Non-hematologic toxicities ( $\geq$  grade 3) were higher in carfilzomib arm: dyspnea (2.8% vs 1.8%), cardiac failure (3.8% vs 1.8%), and hypertension 4.3% vs 1.8%).

### 3) Carfilzomib/dexamethasone

- a) Phase III study (ENDEAVOR; n=929) evaluated carfilzomib on D 1,2,8,9,15,16 (20 mg/m<sup>2</sup> on D 1,2 of cycle 1; 56 mg/m<sup>2</sup> thereafter) IV over 30 minutes and dexamethasone 20 mg twice weekly (1,2,8,9,15,16,22,23) on a 28 day cycle vs bortezomib 1.3 mg/m<sup>2</sup> IV or SubQ on D 1,4,8,11 in combination with dexamethasone 20 mg (1,2,4,5,8,9,11,12) on a 21 day cycle.<sup>92</sup>
  - i. PFS was 18.7 months in the carfilzomib containing arm vs 9.4 months in the bortezomib/dexamethasone arm (HR 0.52; p=0.0001)
  - ii. ORR were 76.9% in the carfilzomib containing arm and 62.5% in the bortezomib/dexamethasone arm (p=0.001)
  - iii. Toxicities: grade 3/4 adverse events that were increased in the carfilzomib arm compared to bortezomib include hypertension (8.9% vs 2.6%), dyspnea (5.6% vs 2.2%), cardiac failure (4.8 % vs 1.8%), and renal failure (4.1% vs 2.6%).
- b) Phase III study (ARROW; n=578) evaluated carfilzomib in patients with relapsed/refractory myeloma on a once weekly schedule (20 mg/m<sup>2</sup> IV Day 1, cycle 1; 70 mg/m<sup>2</sup> IV Days 8, 15, cycle 1; Days 1, 8, 15, cycle 2+) with dexamethasone vs twice weekly schedule (20 mg/m<sup>2</sup> IV Days 1, 2, cycle 1; 27 mg/m<sup>2</sup> IV Days 8, 9, 15, 16, cycle 1; Days 1, 2, 8, 9, 15, 16, cycle 2+) with dexamethasone.<sup>93</sup>
  - i. PFS was 11.2 months vs 7.6 months [HR 0.69 (CI 0.51-0.83; p=0.0029)] in favor of once weekly carfilzomib
  - ii. ORR was 62.9% vs 40.8% [OR 2.49(CI 1.72-3.6; p=0.0001)] in favor of once weekly carfilzomib. CR or better was attained in 7% and 2% of patients in the once and twice weekly arms, respectively.

- iii. Toxicities: increased  $\geq$  grade 3 adverse effects with once weekly dosing (68% vs 62%). Similar rates of  $\geq$  grade 3 cardiac failure (3% and 4%, respectively). No new safety signals occurred.
- c. Ixazomib<sup>94</sup>
  - 1) Phase III study (TOURMALINE-MM1; n=722) randomized patients with relapsed or refractory MM to receive ixazomib/lenalidomide/dexamethasone or placebo/lenalidomide/dexamethasone.<sup>95</sup>
    - a) Patients received lenalidomide 25 mg D 1-21 plus dexamethasone 40 mg D 1,8,15,22 (28-day cycles) with or without ixazomib 4 mg D 1, 8, 15.
    - b) Adverse effects: all grade toxicities occurring more frequently with ixazomib included thrombocytopenia (31% vs 16%), rash (36% vs 23%), and diarrhea (45% vs 39%).

#### Results of TOURMALINE-MM1

Regimen	ORR	CR	Median PFS	Median OS
Ixazomib/lenalidomide/dex	78%	11.7%	20.6 months	53.6 months
Placebo/lenalidomide/dex	72%	6.6%	14.7 months	51.6 months
p-value	0.035	0.019	0.01	0.495

- 2. Daratumumab<sup>96</sup>
  - 1) Phase II study (MMY2002/SIRIUS; n=106), previously treated patients following at least 3 lines of therapy (including proteasome inhibitors and immunomodulatory agents or refractory to both) received daratumumab 8 mg/kg IV every 4 weeks, or 16 mg/kg IV every week for 8 weeks (cycles 1 and 2), then every 2 weeks for 16 weeks (cycles 3-6), and then every 4 weeks thereafter (cycle 7 and higher).<sup>97</sup>
    - a) Median duration of response was 7.4 months and median PFS was 3.7 months.
    - b) Estimated 1-year OS was 65%
    - c) ORR= 29.2%
    - d) Adverse effects (all grade): fatigue (40%), anemia (33%), thrombocytopenia (25%), neutropenia (23%), and infusion-related reactions (42%).
  - 2) Phase III study (CASTOR; n=498) evaluated patients with relapsed/refractory MM who were randomized to receive bortezomib/dexamethasone +/- daratumumab.<sup>98,99</sup>
    - a) Patients received bortezomib 1.3 mg/m<sup>2</sup> SubQ D 1,4,8,11 plus dexamethasone 20 mg D 1,2,4,5,8,9,11,12 (21 day cycles) for up to 8 cycles
      - i. With or without daratumumab 16 mg/kg IV D 1,8,15 for 3 cycles, D 1 cycles 4-8, then every 4 weeks thereafter.
    - b) Grade 3/4 toxicities increased in the daratumumab arm vs control arm included thrombocytopenia (45.3% vs 32.9%), anemia (14.4% vs 16%), and neutropenia

(12.8% vs 4.2%). Grade 1/2 infusion reactions occurred in 45.3% and grade 3 in 8.6% of patients who received daratumumab.

#### Results of CASTOR

Regimen	ORR	VGPR	CR	PFS
Daratumumab/bortezomib/dex	85%	62.1%	30%	16.7 months
Bortezomib/dex	63%	29.1%	10%	7.1 months
p-value	<0.0001	<0.0001	<0.0001	0.01

- 3) Phase III trial (POLLUX; n=569) randomized previously treated patients to receive lenalidomide/dexamethasone +/- daratumumab.<sup>100,101</sup>
  - a) Grade 3/4 toxicities increased in the daratumumab arm vs control arm included thrombocytopenia (12.7% vs 13.5%), anemia (12.4% vs 19.6%), and neutropenia (51.9% vs 37%).
  - b) MRD negativity (1 cell per 10<sup>5</sup>) was attained in 30.4% of patients in the daratumumab arm vs 5.3% in the lenalidomide/dexamethasone arm (p<0.0001).

#### Results of POLLUX<sup>102</sup>

Regimen	ORR	≥CR	PFS
Daratumumab/lenalidomide/dex	92.9%	56.6%	44.5 months
Lenalidomide/dex	76.4%	23.2%	17.5 months
p-value	<0.0001	<0.0001	<0.0001

- 4) Phase III trial (APOLLO; n=304) randomized previously treated patients to receive pomalidomide/dexamethasone +/- daratumumab.<sup>103</sup>
  - a) Median PFS was 12.4 months in the daratumumab arm vs. 6.9 months in the pomalidomide/dexamethasone arm (p=0.0018).
  - b) Grade 3/4 toxicities increased in the daratumumab arm vs control arm included neutropenia (68% vs. 51%), lymphopenia (12% vs. 3%), febrile neutropenia (9% vs. 3%), pneumonia (11% vs. 6%)
- 5) Phase III trial (CANDOR; n=466) randomized previously treated patients to receive carfilzomib/dexamethasone +/- daratumumab.<sup>104</sup>
  - a) Median PFS was not reached in the daratumumab arm vs. 15.8 months in the carfilzomib/dexamethasone arm (p=0.0027).
  - b) Grade 3/4 toxicities increased in the daratumumab arm vs control arm included thrombocytopenia (24% vs. 18%), hypertension (18% vs. 13%).
3. Isatuximab-irfc (Sarclisa®)<sup>105</sup>
  - a. Mechanism of action: IgG monoclonal antibody targeting CD38; induces antibody-dependent, complement-dependent, and cell-mediated cytotoxicity.



- b. Indication & dosing:
  - 1) FDA approved in combination with pomalidomide and dexamethasone *or* with carfilzomib and dexamethasone
    - a) Isatuximab, pomalidomide, dexamethasone: following  $\geq 2$  prior therapies, including a proteasome inhibitor and lenalidomide.
    - b) Isatuximab, carfilzomib, dexamethasone: following 1-3 prior therapies.
  - 2) Dosing: 10 mg/kg IV on days 1, 8, 15, 22 of cycle 1 (28 days), then 10 mg/kg IV on days 1 and 15 for cycles 2+ (28 days). Routine pre-medications (dexamethasone, acetaminophen, and H1 + H2 antagonists) should be given prior to each dose to reduce the risk of infusion reactions.
- c. Interferes with cross-matching and red blood cell antibody screening; therefore, providers should type and screen patients prior to starting therapy. Once on therapy, blood banks should be informed that the patient has received isatuximab.
- d. Adverse reactions (all grade, in combination with pomalidomide)
  - 1) GI: nausea (15%), vomiting (12%), diarrhea (26%)
  - 2) Hematologic: neutropenia (96%, including 12% febrile neutropenia), anemia (99%), thrombocytopenia (84%)
  - 3) Respiratory: upper respiratory tract infection (57%), pneumonia (31%), dyspnea (17%)
  - 4) Miscellaneous: infusion reactions (38%)
- e. ICARIA-MM<sup>106</sup>, phase III, randomized trial including 307 patients with relapsed MM, following at least 2 prior lines
  - 1) Pomalidomide and dexamethasone +/- isatuximab
    - a) Isatuximab 10 mg/kg IV on d1,8,15,22 of cycle 1, then d1,15 thereafter (28-day cycles)
  - 2) Median PFS improved with addition of isatuximab, 11.5 vs 6.5 months ( $p=0.001$ )
  - 3) Median OS improved with addition of isatuximab 24.6 vs. 17.7 months ( $p=0.028$ )<sup>107</sup>
  - 4) Most common adverse effects (all grade) included infusion reactions (38%), upper respiratory infections (28 vs 17%), and diarrhea (26 vs 20%).
- f. IKEMA, phase III, randomized trial including 302 patients with relapsed MM, following 1-3 prior lines<sup>108</sup>
  - 1) Carfilzomib and dexamethasone +/- isatuximab-irfc
    - a) Isatuximab-irfc 10 mg/kg IV on d1,8,15,22 of cycle 1, then d1,15 thereafter (28-day cycles)
  - 2) Median PFS improved with addition of isatuximab, NR vs 19.15 months (HR 0.531; 95% CI, 0.318-0.889,  $p=0.0007$ )
  - 3) Adverse effects: grade  $\geq 3$  respiratory infections (32.2% vs 23.8%), grade  $\geq 3$  neutropenia (19.2% vs 7.4%)

4. Elotuzumab<sup>109,110</sup>

- a. Phase III open-label study (ELOQUENT-2; n=646) evaluated patients with relapsed or refractory MM who had received between 1-3 prior lines of therapy. Randomized to receive lenalidomide/dexamethasone +/- elotuzumab.<sup>111</sup>

- 1) Patients received lenalidomide/dexamethasone with or without elotuzumab 10 mg/kg per week for 8 doses, then every 2 weeks thereafter.

**Results of ELOQUENT-2**

Regimen	ORR	Median PFS (months)	PFS at 12 months	PFS at 24 months	PFS at 48 months
Elotuzumab/lenalidomide/dex	79%	19.4	69%	41%	21%
Lenalidomide/dex	66%	14.9	57%	28%	14%
p-value	<0.001	<0.001			

- 2) Median OS was 48 months in the elotuzumab group vs. 40 months in control group. 4-year OS rate: 50% in the elotuzumab group vs. 43% in control group (HR 0.78, 95% CI 0.63-0.96).

- 3) The most common grade 3/4 adverse events in elotuzumab group vs control group included: lymphocytopenia (79% vs 49%), neutropenia (36% vs 45%), fatigue (10% vs 8%), and pneumonia (14% vs 10%). Infusion reactions occurred in 10% of patients in the elotuzumab group.

- b. Phase II open label study (ELOQUENT-3; n=117) evaluated patients with MM that was relapsed or refractory to lenalidomide and a proteasome inhibitor. Randomized to receive pomalidomide/dexamethasone +/- elotuzumab.<sup>112,113</sup>

- 1) Patients received pomalidomide/dexamethasone with or without elotuzumab 10 mg/kg per week for 8 doses, then 20 mg/kg every 4 weeks thereafter.

- 2) Adverse effects: overall similar  $\geq$  grade 3 between groups (57% and 60%, respectively).

**Results of ELOQUENT-3**

Regimen	ORR	Median PFS (months)	Median OS (months)
Elotuzumab/pomalidomide/dex	53%	10.3	29.8
Pomalidomide/dex	26%	4.7	17.4
p-value	0.0029	0.008	0.0217

5. Pomalidomide

- a. A multicenter, phase II randomized study was designed to assess two different dosing regimens of pomalidomide and dexamethasone in advanced MM (n=84).<sup>114</sup> Pomalidomide (4 mg) was given PO on D 1-21 (arm 21/28) or continuously (arm 28/28) over a 28-day cycle, plus dexamethasone 40 mg PO weekly. The median number of prior lines of therapy was 5.

- 1) ORR was 35% (arm 21/28) and 34% (arm 28/28), independent of the number of prior lines and level of refractoriness. Median duration of response, time to disease progression, and PFS was 7.3, 5.4, and 4.6 months, respectively, which were similar across cohorts. At 23 months follow-up, median OS was 14.9 months, with 44% of the patients alive at 18 months.
- 2) Toxicity consisted primarily of myelosuppression.

**Toxicities among IMiD's<sup>115,116,117</sup>**

	Thalidomide	Lenalidomide	Pomalidomide
Neuropathies	+++	+	++
Myelosuppression	+	+++	+++
Renal Toxicity	+	+++	+
Secondary Malignancies	+	+++	unknown
Drowsiness	+++	+	+

**5. Selinexor (KPT-330, Xpovio®)<sup>118</sup>**

- a. BOSTON: phase III, randomized trial including 402 patients with relapsed/refractory MM, following 1-3 prior lines of therapy.
  - a) Bortezomib + dexamethasone +/- Selinexor 100 mg once weekly
  - b) ORR: 76.4% vs 62.3%
  - c) Median PFS: 13.9 months vs 9.5 months (p=0.0075)
  - d) All-grade toxicities (selinexor arm): thrombocytopenia (60%), anemia (36%), neutropenia (15%), nausea (50%)
- b. STORM Part 2: Single arm, 122 patients with penta-refractory (refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and a CD38 monoclonal antibody) MM received selinexor and dexamethasone.<sup>119</sup> Patients had been previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.
  - a) Selinexor 80 mg twice weekly + dexamethasone 20 mg twice weekly, continuous
  - b) Primary endpoint ORR: 26.2%
    - i. 6.5% with  $\geq$  VGPR and 2 patients attained sCR
  - c) Median duration of response of 4.4 months
  - d) Median PFS 3.7 months and median OS 8.6 months
  - e) Adverse effects (all grade) included thrombocytopenia (73%), anemia (67%), neutropenia (40%), nausea (72%), anorexia (56%), weight loss (50%), and fatigue (73%).

- f) 80% of patients experienced an adverse event leading to interruption or dose modification.

**Patient Case #2, Continued (ARS Question #4)- Answer:**

**Correct Answer is C (Isatuximab, carfilzomib, dexamethasone).** Isatuximab, carfilzomib, dexamethasone is a category 1 recommendation from the NCCN Guidelines® for relapsed multiple myeloma with early relapse. Answer A, B, and C are all therapies recommended to be used in late relapse (>3 prior lines of therapy) by the NCCN Guidelines® and there are other treatment options that would be more preferred and appropriate for TL at this time.

**Patient Case #2, Continued (ARS Question #5):**

TL is treated with isatuximab, carfilzomib, and dexamethasone for 1 year, and then progresses. He is then treated with third line elotuzumab, pomalidomide, dexamethasone and then also fourth line selinexor, bortezomib, dexamethasone. He presents to your clinic with a rising free light chain ratio, increase in his M-spike, and a new osteolytic lesion, all indicative of disease relapse. TL is to start fifth line treatment with teclistamab. The patient mentions his concern for the cytokine release syndrome with teclistamab that he had read on an online myeloma patient forum. **Which of the following is the most appropriate premedication regimen to recommend upon initiation of teclistamab to reduce the risk of cytokine release syndrome?**

- A. Dexamethasone, acetaminophen
- B. Dexamethasone, acetaminophen, diphenhydramine
- C. Acetaminophen, diphenhydramine
- D. Tocilizumab, acetaminophen, diphenhydramine

7. Idecabtagene vicleucel (ide-cel, bb2121, Abecma®)<sup>120</sup>
- a. Mechanism of action: genetically modified autologous chimeric antigen receptor (CAR) T-cell; includes CD3 T-cell activating domain, 4-1BB costimulatory domain, and single BCMA targeting domain.
  - b. Indication & dosing:
    - A. FDA approved for relapsed/refractory MM in patients who have received  $\geq 4$  prior lines of therapy, including an immunomodulatory agent, proteasome inhibitor, and CD-38 monoclonal antibody.
    - B. Lymphodepletion with cyclophosphamide and fludarabine for 3 days, then 2 days later infusion of idecabtagene vicleucel  $300-460 \times 10^6$  CAR+ T-cells
    - C. Premedicate with acetaminophen and diphenhydramine 30-60 minutes prior to ide-cel infusion. Avoid corticosteroid premedication due to potential impact on efficacy.
  - c. Adverse reactions
    - A. All-grade hematologic toxicities included neutropenia (91%), anemia (70%), and thrombocytopenia (63%)
    - B. Cytokine release syndrome: all-grade (84%), grade  $\geq 3$  (5%)

- C. Neurotoxicity: all-grade (18%), grade  $\geq 3$  (3%)
- d. REMS program
  - A. Healthcare facilities must be enrolled and comply with REMS requirements.
  - B. Certified healthcare facilities must have on-site and immediate access to tocilizumab. A minimum of 2 doses of tocilizumab must be available for each patient for infusion within 2 hours after ide-cel infusion, if needed for treatment of cytokine release syndrome.
- e. KarMMa: phase II, multicenter trial including 128 patients with relapsed multiple myeloma, median 6 prior lines of therapy.<sup>121</sup>
  - A. Overall response achieved in 73% of patients, median PFS 8.6 months
  - B. CAR+ T-cell persistence was noted in 59% of patients at 6 months and 36% of patients at 12 months
- 8. Ciltacabtagene autoleucel (cilta-cel, Carvykti®)<sup>122</sup>
  - a. Mechanism of action: genetically modified autologous CAR T-cells; includes two BCMA-targeting single-domain antibodies, a 4-1BB costimulatory domain, and a CD3-zeta signaling cytoplasmic domain.
  - b. Indication & dosing:
    - A. FDA approved for relapsed/refractory multiple myeloma in patients who have received  $\geq 4$  prior lines of therapy, including an immunomodulatory agent, proteasome inhibitor, and CD-38 monoclonal antibody.
    - B. Lymphodepletion with cyclophosphamide and fludarabine for 3 days, then 2-4 days later infusion of ciltacabtagene autoleucel  $0.5-1 \times 10^6$  CAR+ T-cells per kg of body weight. Maximum of  $1 \times 10^8$  CAR+ T-cells per single infusion.
    - C. Premedicate with acetaminophen and diphenhydramine 30-60 minutes prior to cilta-cel infusion. Avoid corticosteroid premedication due to potential impact on efficacy.
  - c. Adverse reactions
    - A. All-grade hematologic toxicities included neutropenia (96%), anemia (81%), and thrombocytopenia (79%)
    - B. Cytokine release syndrome: all-grade (95%), grade  $\geq 3$  (4%)
    - C. Neurotoxicity: all-grade (21%), grade  $\geq 3$  (9%)
      - a) Parkinsonism with symptoms including tremor, bradykinesia, involuntary movements, stereotypy, loss of spontaneous movements, and masked facies has been observed with cilta-cel
  - d. REMS program: due to risk of cytokine release syndrome and neurologic toxicities
    - A. Healthcare facilities must be enrolled and comply with REMS requirements.
    - B. Certified healthcare facilities must have on-site and immediate access to tocilizumab. A minimum of 2 doses of tocilizumab must be available for each patient for infusion within 2 hours after cilta-cel infusion, if needed for treatment of cytokine release syndrome.

- e. CARTITUDE-1: phase II, multicenter trial included 97 patients that received CAR T-cells, median 6 prior lines of therapy<sup>123</sup>
  - A. Overall response achieved in 97% of patients, stringent CR in 67% of patients
  - B. Median PFS not reached after median follow-up of 12.4 months; 12-month PFS rate 77%
- 9. Teclistamab (Tecvayli®)<sup>124</sup>
  - a. Mechanism of action: bispecific BCMA-directed CD3 T-cell engager. Teclistamab activates T-cells via the release of proinflammatory cytokines and results in the lysis of MM cells.
  - b. Indication & Dosing
    - A. FDA approved for relapsed/refractory MM in patients who have received  $\geq 4$  prior lines of therapy, including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody
    - B. Dosing & Administration: Step-up dosing schedule required to mitigate risk of CRS; administered subcutaneously
      - a) Step-up Dosing Schedule: Day 1 – 0.06 mg/kg, Day 4 – 0.3 mg/kg, Day 7 – 1.5 mg/kg
      - b) Subsequent Dosing: 1.5 mg/kg SubQ once weekly thereafter
    - C. Premedicate 1 to 3 hours before each dose of the step-up dosing schedule (Cycle 1 Day 1, 4, and 7) to reduce risk of CRS. Premedicate with corticosteroid (oral or IV dexamethasone 16 mg), antipyretic (oral or IV acetaminophen 650-1000 mg or equivalent), and histamine-1 receptor antagonist (oral or IV diphenhydramine 50 mg or equivalent)
      - a) Premedication may also be required with subsequent teclistamab doses if patients experience CRS following the prior dose of teclistamab or those who repeat doses within the step-up dosing schedule following a dose delay.
  - c. Adverse reactions<sup>125</sup>
    - A. Hematologic toxicity (grade 3/4): neutropenia (64%), lymphopenia (33%), thrombocytopenia (21%)
    - B. Infections: all -grade (76.4%), grade 3/4 (44.8%)
    - C. Cytokine release syndrome: all-grade (72%), grade 3 (0.6%)
    - D. Neurotoxicity: all-grade (14.5%), grade 3/4 (0.6%)
  - d. REMS program: due to risk of CRS and neurologic toxicities
    - A. Prescribers must be certified with program by enrolling and completing training
    - B. Prescribers must counsel patients receiving teclistamab on risk of CRS and neurologic toxicities, and provide patients with patient wallet card
    - C. Pharmacies and healthcare facilities that dispense teclistamab must be certified with REMS program
  - e. MajesTEC-1: Phase I/II multicenter trial included 165 patients with relapsed/refractory MM, median 5 prior lines of therapy<sup>125</sup>

- A. Overall response rate achieved in 63% of patients;  $\geq$ CR in 39.4%
- B. Median PFS was 11.3 months

10. Recently withdrawn medications for MM

- a. Belantamab mafodotin<sup>126</sup>
  - A. Previously approved under accelerated approval for relapsed/refractory MM in patients who have had  $\geq 4$  prior lines of therapy including a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 monoclonal antibody
  - B. Voluntarily withdrawn from market due to failure of confirmatory phase III DREAMM-3 trial to demonstrate PFS benefit of belantamab mafodotin vs. pomalidomide-dexamethasone
- b. Panobinostat<sup>127</sup>
  - A. Previously approved under accelerated approval in combination with bortezomib and dexamethasone for relapsed/refractory MM in patients who have had  $\geq 2$  prior lines of therapy
  - B. Withdrawn from market as confirmatory studies to demonstrate clinical benefit have been deemed not feasible, therefore post-approval benefit has not been confirmed to support continued approval

VI. Restrictions on prescribing IMiD's (thalidomide, lenalidomide, or pomalidomide):

- A. The FDA was granted authority to require REMS programs to ensure that the benefits of a drug or biologic outweighs its risks according to the Food and Drug Administration Act of 2007.<sup>128</sup>
  - 1. The requirements for REMS programs vary based on the class of medications. Some REMS programs require enrollment to prescribe and/or dispense the medication while other programs may only require safety information to be sent to the healthcare team at regular intervals or a medication guide to be given to patients.
- B. The IMiD's REMS program has a restricted distribution program for prescribing and dispensing these agents due to the risk of embryo-fetal toxicity. Each medication has the risk of causing limb abnormalities to the fetus; therefore, women of childbearing potential need to meet the following requirements:
  - 1. Effective contraception (use of two reliable methods of contraception or continuously abstain from heterosexual sex) must be used by female patients for at least 4 weeks prior to starting therapy, during therapy, and for at least 4 weeks after discontinuing therapy.<sup>115-117</sup>
    - a. Pregnancy screening:
      - 1) Prior to initiating therapy pregnancy must be excluded by 2 negative pregnancy tests. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing the IMiD.
      - 2) During the first month of therapy patients are required to undergo weekly pregnancy tests and then monthly thereafter in women with regular menstrual cycles or every 2 weeks for women with irregular menstrual cycles while they remain on treatment.
        - i. If pregnancy does occur, IMiD therapy must be discontinued.

2. Male patients are required to use latex or synthetic condoms during any sexual contact with females of childbearing potential while on treatment, during dose delays, and for up to 28 days after therapy as the drug is present in semen. This includes males who have undergone a vasectomy. Male patients taking an IMiD must not donate sperm.
3. Obtaining IMiD therapy<sup>115-117</sup>
  - a. Providers must be registered with each IMiD-associated REMS program
  - b. Provider certification confirms that providers will
    - 1) Counsel patients on the risks and benefits of the drug
    - 2) Provide counseling on contraception and emergency contraception
    - 3) Confirm negative pregnancy tests prior to initiating therapy and then as required while on treatment for females of child-bearing potential
    - 4) Complete a Patient-Physician Agreement form for each patient and keep a copy on file with the manufacturer
    - 5) Complete applicable, mandatory survey
    - 6) Obtain authorization number and write it on the prescription (each prescription is allowed a max 28-day supply) along with the patient's risk category
    - 7) Send prescription to certified pharmacy
  - c. Patients must enroll in the respective IMiD program and comply with the requirements of the program.
  - d. Pharmacy REMS Requirements
    - 1) Pharmacy confirmation
    - 2) Obtains confirmation number from the manufacturer prior to dispensing
    - 3) Counsels the patient and completes the Education and Counseling Checklist
    - 4) Dispenses the IMiD along with the corresponding medication guide

**Patient Case #2, Continued (ARS Question #5)- Answer:**

**Correct Answer is B (Dexamethasone, acetaminophen, diphenhydramine).** Patients receiving teclistamab should receive dexamethasone, an antipyretic (i.e. acetaminophen), and a histamine-1 receptor antagonist (i.e. diphenhydramine) prior to at least the 0.06 mg/kg, 0.3 mg/kg, and 1.5 mg/kg step-up doses when initiating teclistamab in order to reduce the risk of cytokine release syndrome.

Answer A is incorrect as patients should also receive diphenhydramine (or equivalent histamine-1 receptor antagonist) prior to teclistamab initiation along with dexamethasone and acetaminophen. Answer C is incorrect as dexamethasone is missing from the premedication regimen and should be administered along with acetaminophen and diphenhydramine. Answer D is incorrect as the premedication regimen is missing dexamethasone and also because tocilizumab is not a recommended premedication to be given prior to teclistamab.



## VII. Supportive Care

### **Patient Case #2, ARS Question #6:**

With his most recent relapse of his myeloma, TL also has an osteolytic lesion. His oncologist would like to resume a bone modifying therapy at this time. His CrCl is 70 mL/min. **Which of the following is the most appropriate to recommend for TL at this time?**

- A. Zoledronic acid 5 mg IV push over 15 min every 12 months
- B. Pamidronate 90 mg IV over 15 min every 4 weeks
- C. Denosumab 120 mg SubQ every 4 weeks
- D. Denosumab 60 mg SubQ every 6 months

- A. Transplant-related supportive care is covered in another chapter (see transplant chapter)
- B. Bone Disease in MM
  1. Diffuse osteopenia and/or osteolytic lesions are a major complication and develop in over 85% of MM patients. Approximately 30% of MM patients have a pathological fracture at diagnosis and 60% experience this complication during the course of the disease.<sup>129</sup>
  2. Bone destruction is frequently associated with pain and leads to skeletal-related events (SREs) such as pathologic fracture or spinal cord compression which may lead to surgery or radiation.
  3. Bone destruction is mainly due to increased osteoclastic activity and accompanying decreased osteoblastic function.<sup>130</sup>
  4. There are four main modalities used for the management of bone disease in MM which include pharmacotherapy, radiotherapy, balloon kyphoplasty, and surgery.
  5. Bone-modifying agents in MM<sup>131</sup>
    - a. Bisphosphonates in MM<sup>132</sup>
      - 1) Bisphosphonate or denosumab therapy is recommended as an NCCN Guidelines® category 1 recommendation for all patients receiving primary myeloma therapy
      - 2) Bisphosphonate or denosumab therapy is not recommended for prevention of skeletal related events in patients with a single plasmacytoma, smoldering myeloma, or MGUS.
      - 3) Bisphosphonates may be used as adjunctive therapy in patients with pain secondary to osteolytic lesions in conjunction with standard interventions such analgesics, radiation, and surgery.
      - 4) Monitor renal function and dose adjust per manufacturer recommendations
      - 5) Continue the bisphosphonate for up to 2 years. The frequency and dosing (monthly vs. every 3 months) would be dependent on individual patients and response to therapy, Decision to continue thereafter should be made on an individualized basis. Upon relapse, it is recommended to restart bisphosphonate therapy as per ASCO supportive care guidelines.<sup>10,131</sup>
      - 6) Osteonecrosis of the jaw (ONJ): Patients should receive comprehensive dental exams and appropriate dentistry PRIOR to starting bisphosphonate therapy. Active oral infections should be treated and areas at risk for infection should be addressed.

Invasive dental procedures should be avoided while patients are receiving bisphosphonates. Temporary suspension of bisphosphonate therapy should be considered if invasive dental procedures are necessary.<sup>132</sup>

- 7) Long-term follow-up (25 months) of a randomized trial comparing zoledronic acid to pamidronate in multiple myeloma or breast cancer patients with osteolytic disease found that zoledronic acid decreases the risk of developing skeletal complications by an additional 16%. This effect was most dramatic in patients with breast cancer.<sup>133</sup>
- 8) Bisphosphonates are known to cause hypocalcemia; therefore, it is recommended that all patients receiving pamidronate or zoledronic acid to prevent SREs take at least 500 mg/day of elemental calcium and 400–500 international units/day of vitamin D. Do not start calcium or vitamin D supplementation during an episode of hypercalcemia.
- 9) Common acute adverse effects that may develop within 24 to 48 hours following bisphosphonate administration include: fevers, flu-like malaise, arthralgias, nausea, fatigue, and electrolyte abnormalities.
- 10) Randomized trials have shown that monthly infusions of pamidronate or zoledronic acid can decrease pain and bone-related complications, improve performance status, and preserve quality of life.<sup>134,135</sup>

b. Receptor activator of nuclear factor kappa-B ligand (RANK-L)

- 1) Denosumab received FDA approval in 2018 for prevention of SREs in patients with MM.
- 2) Denosumab is preferred over bisphosphonates in patients with renal dysfunction.
- 3) Similar considerations as with bisphosphonates regarding indication, duration, ONJ, and hypocalcemia. In addition, since denosumab does not incorporate into the bone matrix as bisphosphonates do, its effects are reversible with therapy discontinuation. Close monitoring for skeletal related events is warranted when stopping denosumab.
- 4) In a phase III randomized study ('482 Study'), denosumab demonstrated non-inferiority to zoledronic acid at delaying time to first SRE in patients with multiple myeloma (HR=0.98; 95% CI 0.85-1.14; p=0.01)<sup>136</sup>

**Bisphosphonate and denosumab dosing/administration**

	<b>Zoledronic Acid</b>	<b>Pamidronate</b>	<b>Denosumab</b>
<b>Typical Dose and Schedule</b>	4 mg IV over 15-30 minutes every 4 weeks	60-90 mg IV over 2-6 hours every 4 weeks	120 mg SubQ every 4 weeks
<b>Clearance</b>	Renal  *Dose adjust when used for prevention of skeletal related events	Renal  *Dose adjust when used for prevention of skeletal related events	No renal adjustment  *Not studied in CrCl < 30 mL/min  *Monitor patients with renal dysfunction closely for hypocalcemia and hypophosphatemia

**ARS Question #6- Answer:**

Correct answer is **C (Denosumab 120 mg SubQ every 4 weeks)**. As per the NCCN Guidelines®, all patients with active multiple myeloma, regardless of presence of lytic bone lesions, should receive bone modifying therapy with a bisphosphonate or denosumab. Denosumab 120 mg SubQ is a recommended option as per both the ASCO and NCCN Guidelines®.

Answer A is incorrect as the correct dose zoledronic acid in the setting of multiple myeloma with osteolytic bone lesions and normal renal function would be 4 mg IV over 15 minutes. Zoledronic acid 5 mg IV every 12 months is the FDA approved dose marketed as Reclast® for osteoporosis. Answer B is incorrect as pamidronate needs to be administered over a period of 2-6 hours. Answer D is incorrect as denosumab 60 mg is not indicated for multiple myeloma; denosumab 60 mg is the FDA approved dose marketed as Prolia® for osteoporosis.

**C. Malignant Spinal Cord Compression (MSCC)<sup>137-139</sup>**

1. Compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumor mass.
2. Minimum radiographic evidence for cord compression is indentation of the theca at the level of clinical features. Subclinical cord compression: presence of radiographic features in the absence of clinical features. Magnetic resonance imaging (MRI) is the gold standard for imaging due to its high sensitivity and specificity.
3. Considered an oncologic emergency - delay in treatment may result in irreversible paralysis and loss of sphincter control. Estimated new cases in US annually are > 20,000; MSCC occurs in 5-10% of patient with malignancies. May be the first symptom of cancer diagnosis in 20-34% of patients.
4. Most commonly arises in the thoracic spine (70%) with fewer cases in the cervical (10%) and lumbar (20%) spine.
5. Breast, prostate, and myeloma may involve more than one site of epidural involvement (second site occurs in 8-37% of patients).
6. Clinical presentation
  - a. Back pain most common complaint (80-95%)
  - b. Other common signs of MSCC
    - 1) Radiculopathy, motor weakness, sensory deficits, sphincter incontinence, and autonomic dysfunction (e.g., urinary hesitancy, retention).
7. Predictive factors for MSCC
  - a. Inability to walk
  - b. Increased deep tendon reflexes
  - c. Compression fractures on radiographs of spine
  - d. Bone metastases present
  - e. Bone metastases diagnosed more than 1 year earlier
  - f. Age less than 60 years

8. No risk factors (4% risk of MSCC) vs more than 6 risk factors (87% risk of MSCC).
9. Approximately 70% of patients have loss of neurologic function between the onset of symptoms and the start of treatment.
  - a. Majority of delays caused by lack of symptom recognition by the patient and diagnostic delay at the general practitioner or general hospital level.
10. Sensory loss usually begins distally and ascends proximally to the level of the involved spinal cord
11. Autonomic dysfunction – urinary retention, constipation; or a palpable bladder, a large post-void urinary residual, or decreased anal tone.
12. Progression to irreversible paraplegia can be complete within hours to days.
13. Management
  - a. Goals: relieve pain, preserve or improve neurologic function, provide local tumor control, and stabilize the spine.
  - b. Most important factor determining neurologic status after treatment is the neurologic status prior to treatment.
  - c. Most ambulatory patients (40-60%) will remain ambulatory following radiation or surgery.
  - d. Steroids followed by surgery in patients with a solitary epidural spinal cord compression by a tumor not known to be radiosensitive who are willing to undergo surgery (NCCN Guidelines® category 1 recommendation).<sup>140</sup>
  - e. Primary radiation therapy may be considered
  - f. Chemotherapy in the absence of clinical myopathy in chemosensitive tumors (e.g., lymphoma, germ cell, multiple myeloma).
  - g. Corticosteroids: immediate administration of corticosteroids is important for symptomatic patients and can increase the number of patients that are ambulatory after radiation therapy.
    - 1) Mechanism: reduces vasogenic edema by decreasing production of prostaglandin E2 and vascular endothelial growth factor.
    - 2) Dexamethasone is most often utilized; methylprednisolone, more commonly used in trauma, offers an alternative (although less data is available in malignant spinal cord injury).
    - 3) The dose of dexamethasone is variable; no clear evidence that “high-dose” is better than “moderate-dose”.
    - 4) Appropriate doses range from 16 mg/day (moderate-dose) to 96 mg/day (high-dose) divided QID; due to side effects, most clinicians use a minimum of 4 mg (range of 4-10 mg) PO or IV every 6 hours.
    - 5) Clinically, the higher doses in this range (10 mg) are usually reserved for those patients that have profound or rapidly progressive neurologic demise.
    - 6) Asymptomatic patients with incidental SCC may not require steroids with radiation therapy. (Small case series indicate this may be safe; level of evidence is not strong;

most clinicians prefer to err on the side of caution and administer steroids due to risk of inflammation with radiation therapy which could cause initial symptoms).

- 7) Steroids may also temporarily treat the cancer (e.g., multiple myeloma, lymphoma).
- h. Surgery: several different techniques have been employed with differing results; surgical consult should be sent immediately to evaluate potential surgical approaches. Generally considered if at least 3-month life expectancy and less than 24 hours of paraplegia.
  - 1) Posterior decompressive laminectomy not favored due to high rate of spinal instability and inferior ambulatory outcomes compared with radiation alone.
  - 2) Vertebroplasty/kyphoplasty – injection of cement percutaneously into a vertebral compression fracture; typically used for painful compression fractures within a few weeks of onset.
  - 3) Circumferential decompression – randomized clinical trial compared this surgery + radiation to radiation alone in 101 patients.<sup>141</sup>
    - a) Goal of surgery was to remove as much tumor as possible, provide immediate decompression and stabilize the spine followed by adjuvant radiation therapy vs radiation therapy alone.
    - b) Ability to walk after treatment better with surgery 42/50 (84%) vs radiation 29/51 (57%); OR = 6.2 (95% CI 2.0-19.8), p=0.001.
    - c) Meta-analysis confirmed that patients with symptomatic MSCC who underwent surgery (with or without preoperative or postoperative radiation therapy) were 1.3 times more likely (p< 0.001) to be ambulatory than patients treated primarily with radiation.<sup>142</sup>
  - i. NCCN Guidelines® recommend this as a category 1 recommendation
  - d) Surgery is indicated for the following patients who have an anticipated life expectancy of at least 3 months:
    - i. Spinal instability
    - ii. No prior history of cancer
    - iii. Radioresistant malignancies (renal cell carcinoma, melanoma, sarcoma)
    - iv. Rapid neurologic deterioration
    - v. Previous radiation
    - vi. High cervical location
    - vii. No diagnosis of lymphoma/myeloma/leukemia (unless spinal instability present)
    - viii. Single site epidural/spinal cord compression
    - ix. Treatment of choice if patient is willing to undergo surgery
  - e) Consider surgery *after* radiation if intractable pain or radiographic and/or clinical progression while on radiation.

- i. **Radiation therapy:** remains therapy most frequently offered to patients.
  - 1) Candidates for radiation therapy include those with radiosensitive tumors (lymphoma, breast, multiple myeloma, SCLC, seminoma of the testes, neuroblastoma, Ewing sarcoma); expected survival of less than 3 months; those unable to tolerate surgery; those with total neurological deficit below the level of the compression for more than 24 hours; those with multilevel or diffuse spinal involvement.
  - 2) Standard radiation field includes the level of disease with a 5 cm margin that effectively includes 2 vertebral bodies above and below.
  - 3) Doses range from 2000-4000 cGy with an average dose of 3000 cGy; administered over 10-14 days with higher doses delivered in the first few days and then tapered down; other dosing schedules (e.g., 7 days, 5 days, 2 days one week apart, one day) have been investigated; no regimen has been shown to be superior. Generally advised to wait 1-3 weeks after surgery if radiation used after decompression.<sup>143</sup>
  - 4) In patients with disease isolated to the spine without epidural compression, a single dose of 8 Gy provides good pain relief and is as effective as various fractionated regimens.<sup>144</sup> Retreatment rates may be higher with single fractions.<sup>145</sup>
  - 5) Consider chemotherapy after radiotherapy if chemosensitive tumor

**Most common malignancies associated with MSCC<sup>137</sup>**

Malignancy	Percent of Patients
Lung	23-24
Breast	21
Prostate	18-20

**Patient Case #3, Continued (ARS Question #7):**

NK is a 63-year-old male who presents to the emergency department with significant confusion and lethargy. He also reports not having a bowel movement for several days. His labs are notable for a serum calcium of 15.6 mg/dL, SCr 3.1 mg/dL, and albumin of 3.4 g/dL. **Along with aggressive intravenous hydration, which of the following initial interventions would be the most appropriate for NK?**

- A. Zoledronic acid 4 mg IV once + calcitonin 4 IU/kg SubQ every 12 hours
- B. Zoledronic acid 3 mg IV once + calcitonin 4 IU/kg SubQ every 12 hours
- C. Calcitonin 4 IU/kg SubQ every 12 hours only, a bisphosphonate is contraindicated with his renal function
- D. Denosumab 120 mg IV once

**D. Hypercalcemia of Malignancy<sup>146-148</sup>**

1. Incidence:
  - a. Hypercalcemia of malignancy occurs at some time during the course of disease in 10-30% of patients with cancer. However, this incidence has been in decline with increased use of bisphosphonates.

- b. Hypercalcemia may be a presenting feature, but it more commonly occurs in patients with an established diagnosis.
  - c. The severity of symptoms is related to the level of calcium as well as how quickly the rise in calcium occurs.
    - 1) Symptoms are typically non-specific but can include lethargy, weakness, confusion, anorexia, nausea, constipation, acute renal failure, polyuria, and polydipsia. Cardiovascular effects may include hypertension, arrhythmias, shortened QT interval, and vascular calcification.
    - 2) Hypercalcemia may lead to progressive decline including renal failure and coma.
  - d. Hypercalcemia is a poor prognostic factor. Historically, 50% of patients die within 30 days; however, survival rates have improved with the use of bisphosphonates.
2. Pathophysiology
- a. Can be divided into four categories
    - 1) Humoral hypercalcemia is often mediated by the systemic secretion of parathyroid hormone-related protein (PTHrP) by tumors and accounts for more than 80% of all cases of hypercalcemia of malignancy.
      - a) Associated malignancies include squamous-cell cancers (head and neck, lung, cervical, esophageal), ovarian, endometrial, renal, breast, and Human T-cell leukemia/lymphoma virus type 1 (HTLV-1)-associated lymphoma.
    - 2) Osteolytic hypercalcemia, which results from increased osteoclastic bone resorption, occurs in 20% of all cases.
      - a) Associated malignancies include multiple myeloma, breast cancer, and lymphoma
    - 3) 1,25(OH)<sub>2</sub>D-secreting lymphomas result from a combination of enhanced osteoclastic bone resorption and enhanced intestinal absorption of calcium; only accounts for <1% of all cases of hypercalcemia of malignancy.
    - 4) Ectopic secretion of authentic PTH is rare and only accounts for <1% of all cases of hypercalcemia of malignancy.
3. Diagnosis
- a. Measure total serum calcium and correct for albumin level
    - 1) Corrected calcium = measured calcium + [0.8 x (4-albumin level)]
      - a) Mild hypercalcemia = corrected calcium 10.5-12 mg/dL
      - b) Moderate hypercalcemia = corrected calcium 12-14 mg/dL
      - c) Severe hypercalcemia = corrected calcium >14 mg/dL
  - b. Ionized serum calcium
    - a) Mild hypercalcemia = calcium 5.6-8 mg/dL
    - b) Moderate hypercalcemia = calcium 8-10 mg/dL

- c) Severe hypercalcemia = calcium >10 mg/dL
- c. A low serum chloride level (<100 mEq/L) may be suggestive of hypercalcemia
- d. Intact PTH is typically low in patients with hypercalcemia. Measuring PTHrP is not needed for diagnosis; however, can clarify the mechanism of hypercalcemia.
- 4. Treatment
  - a. Symptomatic hypercalcemia is classified as an oncologic emergency
  - b. Hydration is one of the first steps in managing hypercalcemia as patients typically are hypovolemic on presentation.
    - 1) Bolus IV fluids 500-1000 mL/hr for the first hour then reduced to maintain a urine output 100-150 mL/hr until euvolemia is reached. Caution is warranted in patients with congestive heart failure.
    - 2) Hydration may not be needed in patients with mild non-symptomatic hypercalcemia.
  - c. May resolve with definitive treatment related to the malignancy
  - d. Loop diuretics may be considered; however, should be avoided until euvolemia has been reached as hypovolemia resulting from reduced renal perfusion may further reduce the renal excretion of calcium.
    - 1) Furosemide 20-40 mg IV x 1 if loop diuretic naive; may be repeated every 1 to 4 hours
  - e. Discontinue offending agents that may contribute to increased calcium such as calcium supplements, thiazide diuretics, and vitamin D.
  - f. Adjunctive Therapy
    - 1) Bisphosphonates
      - a) Bisphosphonates reduce osteoclastic bone resorption
      - b) Preferred: zoledronic acid 4 mg IV over 15 minutes (renal dose adjustment not necessary in hypercalcemia of malignancy when SCr < 4.5 mg/dL).
      - c) Pamidronate 60-90 mg IV over 2-24 hours
      - d) Onset of action 2-4 days, nadir days 4-7. Retreatment may be considered after 7 days.
      - e) Once calcium is within normal limits and stable, consider supplementation with calcium 500 mg and vitamin D 400 IU to prevent hypocalcemia
    - 2) RANK-L inhibitor
      - a) Denosumab 120 mg SubQ weekly x 3 doses during the first month then every 4 weeks thereafter
      - b) Indicated in hypercalcemia of malignancy refractory to bisphosphonates
      - c) Onset 2-4 days
      - d) Once calcium is within normal limits and stable, consider supplementation with calcium 500 mg and vitamin D 400 IU to prevent hypocalcemia



g. Additional adjunct medications

- 1) Glucocorticoids inhibit vitamin D conversion to calcitriol
  - a) May have a role in patients with lymphoma and elevated levels of vitamin D
  - b) Prednisone 20-60 mg/day x 10 days may reduce serum calcium concentration within 2-5 days or intravenous hydrocortisone 200 mg daily x 3 days
- 2) Calcitonin 4-8 IU/kg SubQ or IM (NOT intranasal) every 6-12 hours. May be considered as an alternate or adjunct to aggressive hydration and bisphosphonates in symptomatic hypercalcemia.
  - a) Can reduce calcium concentrations 1-2 mg/dL within 4 to 6 hours with maximum response within 12-24 hours. Efficacy is limited to the first 48 hours with repeated dosing due to development of tachyphylaxis.
- 3) Calcimimetic (e.g., cinacalcet) may be effective for parathyroid carcinoma or primary/secondary hyperparathyroidism.
- 4) Dialysis may be considered in the setting of severe hypercalcemia and renal insufficiency if unable to hydrate the patient.

**Patient Case #3, Continued (ARS Question #7)- Answer:**

**Correct answer is A (Zoledronic acid 4 mg IV + calcitonin 4 IU/kg SubQ).** Bisphosphonate therapy has been proven to reduce hypercalcemia of malignancy. The patient is symptomatic, so consideration should be given to calcitonin SubQ or IM to provide more rapid reduction in his calcium before the effect of bisphosphonate therapy in 48-96 hours.

Answer B is incorrect as the zoledronic acid dose does not need to be reduced in this setting as it is recommended to give the full dose of zoledronic acid when used for hypercalcemia of malignancy with a SCr up to 4.5 mg/dL.

Answer C is incorrect as bisphosphonate therapy is not contraindicated in this example and should be given for the treatment of hypercalcemia of malignancy.

Answer D is incorrect as denosumab should be reserved for patients with hypercalcemia of malignancy that is refractory to a bisphosphonate. Also, the route of administration of denosumab is SubQ and not IV.

## VIII. Cancer Associated Coagulopathy<sup>149-153</sup>

### **Patient Case #3, Continued (ARS Question #8):**

NK receives appropriate treatment for his hypercalcemia of malignancy, undergoes a bone marrow biopsy, and is stabilized and discharged home with a follow visit in your clinic. His bone marrow biopsy reveals 50% involvement by plasma cells and he is ultimately diagnosed with IgG kappa multiple myeloma. He is to start induction therapy with bortezomib, lenalidomide, and dexamethasone. While counseling the patient on his new regimen, you also assess his risk of venous thromboembolism (VTE). He is African American, no recent history of surgery, no history of VTE, and will receive 120 mg of dexamethasone per cycle. You calculate his SAVED score to be 1. **According to the SAVED criteria, which of the following is most appropriate for NK?**

- A. Aspirin 81 mg once daily
- B. Apixaban 2.5 mg twice daily
- C. Enoxaparin 40 mg once daily
- D. No thromboprophylaxis required

A. Arterial and venous thrombosis is a common complication in cancer patients. First described in 1868 by Armand Trousseau; thrombosis in cancer patients is commonly referred to as “Trousseau’s syndrome”.

1. The type and frequency of thrombosis varies but has been reported to occur in ~15% of all cancer patients.
2. Most thrombotic complications occur in cancer patients with known risk factors
3. Patients with cancer have up to a 6X increased risk of venous thromboembolism (VTE) and represent ~20% of all new VTEs.
4. Rarely, thrombosis may be the first symptom of an otherwise occult malignancy
  - a. Development of VTE in cancer patients may have a fatal outcome more often than in non-cancer patients.
  - b. The presence of VTE is an independent predictor of worse survival in patients with cancer.
    - 1) Rates of cancer-associated VTE appear to be steadily increasing, particularly in the past 2 decades.
5. An analysis of over 17,000 patients demonstrated that 80% of VTE in cancer occurred in outpatients.<sup>154</sup> A retrospective analysis of 932 patients receiving cisplatin-based chemotherapy for any type of malignancy demonstrated that 18.1% of patients experienced a venous or arterial thrombosis during treatment or within 4 weeks of the last dose.<sup>155</sup>

B. Etiology/Pathogenesis<sup>156-160</sup>

1. The causes of most thrombi are multifactorial, including one or more general high-risk features as listed below and/or tumor-specific causes. Risk factors are generally felt to be additive.
2. Malignant cells can secrete pro-coagulants or stimulate the immune system to secrete cytokines that increase coagulopathy. Additionally, solid tumors can cause turbulent blood flow which increases the risk of coagulation.

3. Patients with cancer undergoing surgical procedures have 2X the risk of VTE and 3X the risk of fatal PE compared to non-cancer patients undergoing similar procedures.
4. Pathophysiology<sup>157,158,161</sup>
  - a. General clotting pathways are activated when associated with non-cancer specific causes of thrombosis
    - 1) Cancer-related factors
      - a) Direct
        - i. Tissue factor
        - ii. Cancer pro-coagulant (cysteine protease that directly activates factor X) – exact role in thrombosis is unclear but may explain why patients with cancer exhibit a high rate of resistance to warfarin
        - iii. Tumor compressing vessels creating turbulent blood flow
      - b) Indirect
        - i. Tumor necrosis factor
        - ii. Interleukin-1

C. Risk Factors<sup>156-161</sup>

**VTE risk factors in patients with cancer (NCCN Guidelines®)<sup>161</sup>**

General Patient Risk Factors	Treatment-Related Risk Factors	Modifiable Risk Factors
Active cancer	Major surgery	Smoking, tobacco
Advanced stage of cancer	Central venous catheter/IV catheter	Obesity
Cancer types at higher risk*	Chemotherapy (e.g., thalidomide/lenalidomide/pomalidomide plus high-dose dexamethasone, or proteasome inhibitors)	Activity level/exercise
Regional bulky lymphadenopathy with extrinsic vascular compression	Exogenous hormonal therapies (e.g., hormone replacement therapy, contraceptives, tamoxifen/raloxifene, or diethylstilbestrol)	
Familial and/or acquired hypercoagulability (including pregnancy)		
Medical comorbidities**		
Poor performance status		
Older age		

\*High-risk cancers: brain, pancreas, stomach, bladder, gynecologic, lung, lymphoma, myeloproliferative neoplasms, kidney, and “metastatic cancers”

\*\*Medical comorbidities: infection, renal disease, pulmonary disease, congestive heart failure, arterial thromboembolism

Note: Listed risk factors are limited to cancer populations included in recent, prospective observational studies of solid tumor/lymphoma outpatients receiving chemo. Additional prospective randomized data are needed to assess benefit and safety of routine VTE prophylaxis in outpatients with a favorable risk-benefit ratio.

1. Predictive models have been published – a relatively easy, externally validated, model with 5 baseline variables in ambulatory patients (median follow-up 2.5 months) is outlined below.<sup>162</sup>

**Predictive model for chemotherapy-associated VTE (Khorana Score)<sup>161,162</sup>**

Patient Characteristic	Score
Site of primary cancer*	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Pre-chemotherapy platelet count $\geq 350,000/\text{mm}^3$	1
Hgb $< 10 \text{ g/dL}$ or use of erythropoietin stimulating agent (ESA)	1
Pre-chemotherapy WBC $> 11,000/\text{mm}^3$	1
BMI $\geq 35 \text{ kg/m}^2$	1

*Sum the score: 0 = low risk (0.3-1.5% incidence); 1-2 = intermediate risk (1.8-4.8% incidence);  $\geq 3$  = high risk (6.7%-12.9% incidence)<sup>128</sup>*

*\*Scoring system is not used in patients with multiple myeloma, acute leukemia, myeloproliferative neoplasms, and patients with primary/metastatic brain tumors*

**D. Primary Prevention<sup>157,158, 163</sup>**

1. Prophylaxis:
  - a. NCCN Guidelines® recommend prophylaxis for outpatient medical oncology patients with a Khorana score  $\geq 2$ 
    - 1) May consider oral anticoagulation for up to 6 months, may consider longer course if persistent risk.
    - 2) Apixaban 2.5 mg twice daily
    - 3) Rivaroxaban 10 mg once daily
    - 4) LMWH
      - a) Data supports LMWH use in patients with advanced unresectable or metastatic pancreatic cancer
      - b) Dalteparin 200 units/kg SubQ daily x1 month, then 150 units/kg SubQ daily x2 months
      - c) Enoxaparin 1 mg/kg SubQ daily x3 months, then 40 mg SubQ daily
  - b. Patients with multiple myeloma receiving thalidomide, lenalidomide, or pomalidomide-based regimens with chemotherapy and/or dexamethasone should be considered for thromboprophylaxis with either aspirin (low-risk patients) or oral/parenteral anticoagulant (high-risk patients) (**see tables below: SAVED and IMPEDE venous thromboembolism risk assessments**).
  - c. Post-surgical thromboprophylaxis for patients undergoing major surgery for cancer should be continued at least 7-10 days. Extended LMWH prophylaxis up to 4 weeks postoperatively

should be considered for major abdominal or pelvic surgery patients who have high risk features such as:

- 1) Restricted mobility
- 2) Obesity
- 3) History of VTE
- 4) Additional high-risk factors
  - a) Surgery for gastrointestinal malignancies
  - b) Patients with a history of VTE
  - c) Anesthesia time > 2 hours
  - d) Bed rest  $\geq$  4 days
  - e) Advanced-stage disease
  - f) Age > 60 years

**SAVED VTE score for patients receiving IMiDs<sup>164</sup>**

Risk Factors	Points
Surgery within 90 days	+2
Asian race	-3
VTE history	+3
Age $\geq 80$	+1
Dexamethasone dosing	
Standard (120-160 mg/cycle)	+1
High (> 160 mg/cycle)	+2
<b>High Risk</b> ( $\geq 2$ points)	<b>Low Risk</b> (< 2 points)
Enoxaparin 40 SubQ mg daily	Aspirin 81-325 POmg daily
Fondaparinux 2.5 mg SubQ once daily	
Warfarin (INR 2-3)	
Apixaban 2.5 mg PO twice daily	
Rivaroxaban 10 mg PO once daily	

**IMPEDE VTE score for patients with multiple myeloma<sup>165</sup>**

Risk Factors	Points
IMiD therapy	+4
BMI $\geq 25$ kg/m <sup>2</sup>	+1
Pelvic, hip, or femur fracture	+4
Erythropoiesis-stimulating agent	+1
Dexamethasone dosing	
Standard ( $\leq 160$ mg/cycle)	+2
High (> 160 mg/cycle)	+4
Doxorubicin or multi-agent chemotherapy	+3
Asian/Pacific Islander race	-3
VTE history before diagnosis	+5
Tunneled line or CVC	+2
VTE prophylaxis (treatment dose LMWH or warfarin)	-4
VTE prophylaxis (prophylactic dose LMWH or aspirin)	-3
<b>High Risk</b> (> 3 points)	<b>Low Risk</b> ( $\leq 3$ points)
Enoxaparin 40 mg SubQ daily	Aspirin 81-325 PO mg daily
Fondaparinux 2.5 mg SubQ once daily	
Warfarin (INR 2-3)	
Apixaban 2.5 mg PO twice daily	
Rivaroxaban 10 mg PO once daily	

d. Clinical trials

- 1) Anticoagulation in cancer patients without other risk factors is not recommended; Fragmin Advanced Malignancy Outcome Study (FAMOUS) treated 382 patients with dalteparin 5000 units SubQ daily or placebo for ~9 months. No difference in survival or VTE (3.4% vs 2.4%, respectively).<sup>166</sup>
- 2) The CONKO-004 study in pancreatic cancer patients demonstrated a VTE rate of 5% in those receiving enoxaparin (1 mg/kg daily X 3 months, then 40 mg daily) vs 14.5% in the observation alone arm (p<0.01)<sup>167</sup>
- 3) The FRAGEM study in patients with pancreatic cancer demonstrated a VTE rate of 3.4% for those on full dose dalteparin vs 23% on observation alone (p=0.02), a risk reduction of 85% (risk ratio = 0.145, 95% CI 0.035-0.612)<sup>168</sup>
- 4) The AVERT trial in patients receiving active chemotherapy with Khorana score  $\geq 2$  demonstrated lower rates of VTE with apixaban 2.5 mg twice daily (4.2%) vs. placebo (10.2%) (HR 0.41, 95% CI 0.26-0.65; p<0.001)<sup>169</sup>
- 5) The CASSINI trial in patients with Khorana score  $\geq 2$  demonstrated a lower rate of VTE with rivaroxaban 10 mg once daily compared to placebo in the prespecified intervention-period analysis which was first receipt of trial agent to last dose plus 2 days (2.6% vs. 6.4%; HR 0.40, 95% CI 0.20-0.80), but not in the 180-day trial period (6% vs. 8.8%; HR 0.66, 95% CI 0.40-1.09; p=0.10)<sup>170</sup>

**NCCN Guidelines® recommendations for medical oncology inpatient prophylactic anticoagulation<sup>161</sup>**

Agent	Standard Dosing	Obesity Dosing (BMI $\geq 40$ kg/m <sup>2</sup> ) [limited data]
Low molecular weight heparin (LMWH)	Dalteparin 5000 units SubQ daily*	Consider dalteparin 7500 units SubQ daily OR 5000 units SubQ every 12 hours OR 40-75 units/kg SubQ daily
	Enoxaparin 40 mg SubQ daily*	Consider enoxaparin 40 mg SubQ q 12 hours OR 0.5 mg/kg SubQ daily
Unfractionated heparin	UFH 5000 units SubQ q 8-12 hours*	UFH 7500 units SubQ q 8 hours
Fondaparinux	Fondaparinux 2.5 mg SubQ daily* (avoid in patients < 50 kg)	Consider fondaparinux 5 mg SubQ daily

\* NCCN Guidelines® category 1 for medical oncology inpatients

**NCCN Guidelines® recommendations for ambulatory medical oncology prophylactic anticoagulation<sup>161</sup>**

Agent	Standard Dosing	Dose modifications
LMWH	Dalteparin 200 units/kg SubQ daily x 1 month, then 150 units/kg SubQ daily x 2 months	<ul style="list-style-type: none"> <li>• Avoid if CrCl &lt;30 mL/min</li> <li>• Avoid if platelets &lt; 50,000/mm<sup>3</sup></li> <li>• Avoid if weight &lt;40 kg</li> </ul>
	Enoxaparin 1 mg/kg SubQ daily x 3 months, then 40 mg SubQ daily	<ul style="list-style-type: none"> <li>• Avoid if CrCl &lt;30 mL/min</li> <li>• Reduce to 0.5 mg/kg SubQ daily for platelet count 50,000-70,000/mm<sup>3</sup></li> <li>• Avoid if platelets &lt; 50,000/mm<sup>3</sup></li> </ul>
Direct oral anticoagulant (DOAC)	Apixaban 2.5 mg PO twice daily	<ul style="list-style-type: none"> <li>• Avoid if CrCl &lt;30 mL/min</li> <li>• Avoid if platelets &lt; 50,000/mm<sup>3</sup></li> <li>• Avoid if weight &lt;40 kg</li> </ul>
	Rivaroxaban 10 mg PO once daily	<ul style="list-style-type: none"> <li>• Avoid if CrCl &lt;30 mL/min</li> <li>• Avoid if platelets &lt; 50,000/mm<sup>3</sup></li> </ul>

- E. The International Society on Thrombosis and Haemostasis guidelines recommend the use of prophylaxis in:<sup>171</sup>
1. Locally advanced/metastatic pancreatic cancer patients on chemotherapy with a low bleeding risk
  2. Locally advanced/metastatic lung cancer patients on chemotherapy with a low bleeding risk
- F. Indwelling catheters
1. Chest guidelines suggest **against** routine prophylaxis with LMWH or low dose unfractionated heparin (LDUH) (Grade 2B) and against prophylactic use of VKAs (Grade 2C)<sup>172</sup>
  2. Prophylactic use of warfarin or LMWH has not been shown to decrease central venous catheter (CVC)-related thrombosis, and therefore are not recommended by ASCO<sup>173</sup>

**Patient Case #3, Continued (ARS Question #8)- Answer:**

**Correct answer is A (Aspirin 81 mg once daily).** NK is deemed to be at a low risk of VTE based on the SAVED scoring system, as therefore aspirin 81 mg once daily would be appropriate.

Answer B and C are incorrect due to the patient having a SAVED score <2. If his SAVED score was ≥2 and he was considered high risk for VTE, then either of these would be appropriate options. Answer D is incorrect as thromboprophylaxis is indicated in this patient who is to receive an immunomodulatory drug (lenalidomide) and dexamethasone.



**Patient Case #3, Continued (ARS Question #9):**

Upon presenting to the clinic for Cycle 2 Day 1 of bortezomib, lenalidomide, and dexamethasone, NK reports lower extremity swelling in his right leg. Ultrasound doppler reveals a deep vein thrombosis (DVT) despite NK having taken adequate thromboprophylaxis. Pertinent labs and findings: 63 kg, SCr 1.1 mg/dL, platelets 130,000/mm<sup>3</sup>. **According to the NCCN Guidelines®, which of the following is the most appropriate treatment of NK's DVT?**

- A. Edoxaban 60 mg once daily
- B. Rivaroxaban 20 mg once daily
- C. Enoxaparin 30 mg SubQ q12h
- D. Enoxaparin 60 mg SubQ q12h

G. Treatment<sup>156-160,174</sup>

1. An objective diagnosis is required to provide successful therapy
2. An understanding of the goals of therapy is necessary for successful treatment of all thrombotic complications; the goal of therapy should be precisely stated prior to beginning therapy in any individual with thrombosis
3. Anticoagulation combined with specific antineoplastic therapy is the cornerstone of treatment of most thrombotic complications
4. Generally, all patients with VTE require anticoagulation therapy.<sup>151,161</sup>
  - a. In a small subset of patients, anticoagulation therapy may be contraindicated.
    - 1) These contraindications may be absolute or relative.
    - 2) Consideration of the degree of contraindication and its duration in each individual patient is an essential component of care.
    - 3) Patients with relative contraindications should be frequently reassessed to determine whether the contraindication still exists.

**Contraindications to therapeutic anticoagulation in patients with cancer**<sup>151,160,161</sup>

Absolute	Relative
<ul style="list-style-type: none"><li>• Active major bleeding (&gt;2 units transfused in 24 hours, decrease in Hb by <math>\geq 2</math> g/dL, or intracranial / intraspinal bleeding)</li><li>• Indwelling neuraxial catheters</li><li>• Interventional spine and pain procedures</li><li>• Neuraxial anesthesia or lumbar puncture</li></ul>	<ul style="list-style-type: none"><li>• Chronic, clinically significant measurable bleeding for &gt;48 hours</li><li>• Thrombocytopenia (platelets &lt;50,000/mm<sup>3</sup>)</li><li>• Severe platelet dysfunction</li><li>• Hemorrhagic coagulopathy or known bleeding disorder in the absence of replacement therapy</li><li>• Recent major surgery at high risk for bleeding</li><li>• High risk for falls/head trauma</li><li>• Primary and metastatic brain tumors</li><li>• Long-term antiplatelet therapy*</li></ul>

\* Reassess need for antiplatelet therapy and discontinue/reduce dose of antiplatelet therapy if possible

- b. Data suggests that in selected low-risk patients with pulmonary embolism (PE), outpatient care can be safely and effectively utilized.<sup>175</sup> Patients excluded from this study for any of the following:
    - 1) O<sub>2</sub> saturation <90% on pulse oximetry or PO<sub>2</sub> <60 mmHg on arterial blood gas
    - 2) SBP <100 mmHg
    - 3) Chest pain requiring parenteral opioids
    - 4) Active bleeding
    - 5) High risk of bleeding defined by stroke in the preceding 10 days, gastrointestinal bleeding in the preceding 14 days, or platelets <75,000/mm<sup>3</sup>
    - 6) CrCl <30 mL/min
    - 7) Obesity (weight >150 kg)
    - 8) History of heparin induced thrombocytopenia (HIT) or heparin allergy
    - 9) Therapeutic oral anticoagulation at time of PE
    - 10) Barriers to adherence or follow up
    - 11) Pregnancy
    - 12) Imprisonment
    - 13) Diagnosis of PE >23 hours before screening for the trial/previous trial enrollment
5. Thrombolytic treatment may be administered in acute PE associated with hypotension in patients not prone to bleeding, per the Chest guidelines, so these patients should also be hospitalized for treatment<sup>174</sup>
  - a. Antithrombotic therapy with warfarin is associated with higher rates of bleeding complications and recurrent thrombosis in patients with cancer compared to patients without cancer.
6. NCCN Guidelines<sup>®</sup>, ASCO, and Chest guidelines recommend **indefinite** anticoagulation with *active cancer*, those receiving *chemotherapy* (ASCO), or *persistent risk factors* (NCCN Guidelines<sup>®</sup>)
7. ASCO states that LMWH is preferred over unfractionated heparin (UFH) for the initial 5-10 days of anticoagulation in cancer patients with newly diagnosed VTE who do not have CrCl <30 mL/min
8. Thrombocytopenia
  - a. Use full doses of anticoagulants for platelet count >50,000/mm<sup>3</sup> and no evidence of bleeding
    - 1) DOAC's are not recommended for platelet count <50,000/mm<sup>3</sup> due to currently limited experience.
  - b. Assess on a case by case basis for platelets <50,000/mm<sup>3</sup>
  - c. NCCN Guidelines<sup>®</sup> recommend the following for enoxaparin when platelets <50,000/mm<sup>3</sup><sup>176</sup>.

- 1) Platelet count 25,000-50,000/mm<sup>3</sup>: reduce to half-dose enoxaparin (0.5 mg/kg twice daily)
  - 2) Platelet count <25,000/mm<sup>3</sup>: hold enoxaparin
  - 3) Patients at high risk for recurrent VTE and anticipated prolonged thrombocytopenia: consider transfusing platelets to maintain platelet count >50,000/mm<sup>3</sup> to allow for continuation of enoxaparin
  - 4) These recommendations have only been validated for enoxaparin
- d. The International Society on Thrombosis and Haemostasis (ISTH) offers additional recommendations for challenging cases <sup>177</sup>
- 1) For acute thrombosis and platelet count <50,000/mm<sup>3</sup>, use full dose anticoagulation and platelet transfusions to maintain >50,000/mm<sup>3</sup>; suggest filter if transfusions are not an option
  - 2) For subacute/chronic thrombosis, reduce LMWH to 50% of the therapeutic dose or use a prophylactic dose for platelet count of 25-50,000/mm<sup>3</sup>; discontinue anticoagulation in patients with platelets <25,000/mm<sup>3</sup>.
9. Brain tumors are not an absolute contraindication to anticoagulation
10. Standard treatment with LMWH for pregnant patients with cancer
11. It is noteworthy that the FDA has approved long-term use of dalteparin for cancer patients. <sup>156,158</sup>
12. Although warfarin is inferior to LMWH for long-term use, it is an option for some patients; bridge therapy with UFH, LMWH, or fondaparinux for 5-7 days is recommended. <sup>156,158</sup>
- a. The CLOT TRIAL <sup>178</sup> provides the primary evidence for this recommendation. It evaluated thrombosis recurrence in cancer patients receiving warfarin or dalteparin for 6 months.
- 1) N = 336 continued dalteparin 200 units/kg/day SubQ X 1 month then dalteparin SubQ 150 units/kg/day X 5 months
  - 2) N = 336 received dalteparin 200 units/kg/day SubQ X 5-7 days then a coumarin derivative orally X 6 months with target INR = 2.5
  - 3) Primary outcome: VTE recurrence rates at 6 months: 9% in dalteparin group vs 17% in the warfarin group (p=0.002).
  - 4) Secondary outcomes: no significant difference in the rate of major bleeding (6% in the dalteparin group vs 4% in the oral anticoagulant group), or any bleeding (14% vs 19%). Mortality rate at 6 months was 39% vs 41% in each arm, respectively.
13. Direct oral anticoagulants (DOACs) are now recommended as monotherapy (apixaban or rivaroxaban) or used when bridged with a parenteral anticoagulant (edoxaban) for patients with malignancies. These are preferred by the NCCN Guidelines<sup>®</sup> in patients who do not have gastric or gastroesophageal lesions. <sup>160,161,171,174</sup>
- a. If a direct oral anticoagulant is used, the NCCN Guidelines<sup>®</sup> prefer apixaban, edoxaban, or rivaroxaban. Consideration may be given to dabigatran if the 3 preferred agents are unavailable.

- b. Caravaggio trial: multinational, open-label trial randomizing 1170 patients with cancer-associated VTE to dalteparin or apixaban<sup>179</sup>
  - 1) Apixaban arm received 10 mg PO twice daily for 7 days, followed by 5 mg twice daily for a total of 6 months
  - 2) Dalteparin arm received 200 units/kg/d SubQ x1 month, followed by 150 units/kg/d months 2 through 6
  - 3) Recurrent VTE with apixaban was non-inferior to dalteparin (5.6% vs. 7.9%,  $p < 0.001$  for non-inferiority)
  - 4) Similar rates of major bleeding in the apixaban group compared to the dalteparin group (3.8% vs. 4%;  $p = 0.60$ )
- c. ADAM-VTE trial: multicenter, open-label trial randomizing 300 patients with cancer-associated VTE to dalteparin or apixaban.<sup>180</sup>
  - 1) Apixaban arm received 10 mg PO twice daily for 7 days, followed by 5 mg twice daily for a total of 6 months
  - 2) Dalteparin arm received 200 units/kg/d SubQ x1 month, followed by 150 units/kg/d months 2 through 6
  - 3) Recurrent VTE occurred less frequently with apixaban (0.7% vs 6.3%); HR 0.099, 95% CI 0.013-0.780;  $p = 0.0281$
  - 4) Low rates of major bleeding in both arms, with 0% in apixaban arm compared to 1.4% in dalteparin arm ( $p = 0.138$ )
- d. HOKUSAI-VTE trial: non-inferiority trial randomizing 1,050 patients with cancer-associated VTE to dalteparin or edoxaban.<sup>181</sup>
  - 1) Edoxaban arm received LMWH x 5 days, then edoxaban 60 mg PO daily
  - 2) Dalteparin arm received 200 units/kg/d SubQ x1 month, then 150 units/kg/d thereafter
    - i. Treatment in both arms was given for at least 6 months and for up to 12 months
  - 3) No significant difference in recurrent VTE (7.9% edoxaban vs 11.3% dalteparin;  $p = 0.09$ )
  - 4) Combined endpoint of recurrent VTE or major bleed: 12.8% with edoxaban vs 13.5% with dalteparin ( $p = 0.006$  for noninferiority).
  - 5) Major bleeding increased with edoxaban (6.9% vs 4.0%) and more GI bleeding events in the edoxaban arm
- e. SELECT-D trial: multicenter, open-label trial randomizing 406 patients with cancer-associated VTE to dalteparin or rivaroxaban.<sup>182</sup>
  - 1) Rivaroxaban arm received 15 mg PO twice daily for 21 days, then 20 mg once daily for a total of 6 months
  - 2) Dalteparin arm received 200 units/kg/d SubQ x1 month, then 150 units/kg/d for months 2 through 6

- 3) Lower 6-month cumulative VTE recurrence rate with rivaroxaban (4% vs 11%); HR 0.43, 95% CI 0.19-0.99
- 4) Higher rates of clinically relevant non-major bleeding with rivaroxaban (13% vs 4%); HR 3.76, 95% CI 1.63-8.69
- 5) Higher rates of major bleeding with rivaroxaban compared to dalteparin in patients with esophageal and gastroesophageal cancer, 4 of 11 (36%) vs. 1 of 19 (11%)

14. Treatment of acute VTE in patients **who are not candidates for anticoagulation**<sup>151,161,183</sup>

- a. Treatment options may include placement of an inferior vena cava (IVC) filter, thrombolysis, and/or thrombo-embolectomy.
  - 1) IVC filter placement
  - 2) Guidelines generally recommend IVC filter placement in patients presenting with an acute proximal lower extremity DVT or PE and who are not candidates for anticoagulation.
  - 3) The benefit of placing an IVC filter in other types of VTE is not clear at the present time.
  - 4) IVC filter should be considered in patients who:
    - a) Develop PE while on adequate anticoagulation for DVT (anticoagulation failure)
    - b) Are non-adherent with prescribed anticoagulation
    - c) Have baseline cardiac or pulmonary dysfunction severe enough to make any new or recurrent PE life-threatening
    - d) Have documented multiple PE and chronic thromboembolic pulmonary hypertension
- b. A retrievable IVC filter is preferred in most clinical situations.
  - 1) Permanent filters should only be considered in rare situations when patients have permanent contraindications to anticoagulation.
- c. Thrombolysis
  - 1) Anticoagulation prevents clot extension and recurrence but does not actively dissolve clot. In contrast, thrombolytics promote clot dissolution, which may limit long-term complications.
  - 2) Available agents include alteplase (tPA), reteplase, and tenecteplase.
  - 3) The Chest Guidelines state that patients who are most likely to benefit from catheter-directed thrombolysis include<sup>174</sup>:
    - a) Iliofemoral DVT
    - b) Symptom duration <14 days
    - c) Good functional status
    - d) Life expectancy of at least 1 year
    - e) Low risk of bleeding

- 4) Contraindications to thrombolysis include intracranial tumor, history of hemorrhagic stroke, stroke within 3 months, recent head trauma, low platelet count ( $< 100,000/\text{mm}^3$ ), or active bleeding.

#### H. Recurrent thrombosis

1. Addressed in the NCCN Guidelines<sup>®</sup>, international guidelines, and management of challenging cases from the ISTH<sup>161,171,177</sup>
  - a. If therapeutic on VKA, transition to LMWH (NCCN<sup>®</sup> preferred, also lists fondaparinux as an alternative)
  - b. If on LMWH at time of symptomatic recurrence, verify therapeutic anti-Xa; increase dose of LMWH (~25% or increase back to weight-based therapeutic dose if the patient has been on non-therapeutic dosing)
  - c. Re-assess 5-7 days after a dose escalation. If symptomatic improvement from thrombosis, continue the current dose; if not, use peak anti-Xa level to estimate next dose escalation.
  - d. Per NCCN<sup>®</sup>, if on LMWH, change to q12 hour schedule, or increase dose (again 25% recommended with limited data) or switch to fondaparinux
  - e. If on heparin, increase dose of heparin or switch to LMWH or fondaparinux
  - f. If on fondaparinux, switch to heparin or increase dose (25%, limited data)
  - g. Evaluate for HIT on heparin products, consider IVC filter

#### I. Bleeding on anticoagulation as per ISTH<sup>177</sup>

1. Identify source, severity, and reversibility
2. Supportive care with transfusions and surgical intervention to stop the bleeding
3. Withhold anticoagulation for life-threatening bleeding
4. Insert IVC filter for acute or sub-acute (not chronic) thrombosis for major/life-threatening bleeding

#### J. Reversal of anticoagulation

1. NCCN Guidelines<sup>®</sup> have recommendations for reversal of anticoagulation and all reversal protocols are associated with risk of thromboembolism.<sup>161</sup>

**Therapeutic anticoagulation for VTE (NCCN Guidelines®)<sup>161</sup>**

Agent		Notes
<b>Parenteral Anticoagulants</b>		
LMWH (Preferred in patients <i>with</i> gastric or gastroesophageal lesions)	Dalteparin 200 units/kg SubQ daily X 1 month then 150 units/kg SubQ daily <b>(category 1)</b>	<ul style="list-style-type: none"> <li>• Use with caution with renal dysfunction.</li> <li>• Only FDA approved agent for the indication.</li> <li>• Monitoring anti-Xa is recommended for patients with severe renal dysfunction.</li> <li>• Contraindicated in patients with recent/acute HIT.</li> </ul>
	Enoxaparin 1 mg/kg SubQ q12 hours (may consider 1.5 mg/kg SubQ daily after 1 month)	<ul style="list-style-type: none"> <li>• Use based on dalteparin data.</li> <li>• Monitoring anti-Xa is recommended for patients with severe renal dysfunction.</li> </ul>
Fondaparinux	Fondaparinux SubQ daily <50 kg: 5 mg daily 50-100 kg: 7.5 mg daily >100 kg: 10 mg daily	<ul style="list-style-type: none"> <li>• Weight based dosing</li> <li>• Contraindicated in CrCl &lt;30 mL/min</li> <li>• Use caution with CrCl 30-50 mL/min, weight &lt;50 kg, or age &gt;75 years</li> </ul>
Unfractionated heparin (UFH)	IV: 80 units/kg load, then 18 units/kg/hr to target aPTT 2-2.5 X control  SubQ: 333 units/kg load, then 250 units/kg every 12 hours	Contraindicated in patients with recent/acute HIT.
<b>Direct Oral Anticoagulants (DOACs)</b> <b>(Preferred in patients <i>without</i> gastric or gastroesophageal lesions)</b>		
Apixaban (category 1)	10 mg BID for 7 days, then 5 mg BID	<ul style="list-style-type: none"> <li>• Contraindicated CrCl &lt;30 mL/min.</li> <li>• Contraindicated in active/clinically significant liver disease.</li> </ul>
Edoxaban (category 1)	Bridge with LMWH or UFH for ≥ 5 days, then edoxaban 60 mg daily	<ul style="list-style-type: none"> <li>• Contraindicated in active/clinically significant liver disease.</li> <li>• 30 mg once daily if CrCl 15-30 mL/min, weight ≤60 kg, or concomitant potent P-gp inhibitors).</li> </ul>
Rivaroxaban	15 mg BID x 21 days, then 20 mg daily	<ul style="list-style-type: none"> <li>• Contraindicated CrCl &lt;30 mL/min. Contraindicated in active/clinically significant liver disease.</li> <li>• Contraindicated with dual inhibitors/inducers of CYP3A4, P-gp.</li> </ul>

		<ul style="list-style-type: none"> <li>Avoid in patients with urinary or gastrointestinal tract lesions due to risk of urinary and intestinal tract bleeding.</li> </ul>
Dabigatran	Bridge with LMWH or UFH $\geq$ 5 days, then dabigatran 150 mg BID	<ul style="list-style-type: none"> <li>Contraindicated CrCl &lt;30 mL/min</li> <li>Contraindicated in active/clinically significant liver disease.</li> <li>Consider if other 3 DOACs (above) are unavailable or inappropriate</li> </ul>
Bridging from parenteral anticoagulant to warfarin		
Warfarin	Dalteparin, enoxaparin, or fondaparinux can all be used to bridge to warfarin. Give LMWH for at least 5 days until INR is $\geq$ 2 for 24 hours.	<ul style="list-style-type: none"> <li>Initiate warfarin at 2.5-5 mg daily initially and adjust to target INR 2-3.</li> <li>Monitor INR twice weekly while bridging therapy.</li> <li>Once stable and on warfarin monotherapy, INR testing can be gradually decreased.</li> </ul>
	UFH IV: 80 units/kg IV load followed by 18 units/kg/hr to target aPTT 2-2.5 x control or SubQ 333 units/kg load then 250 units/kg every 12 hours.	

## 2. Contraindications and precautions for DOAC therapy

### a. Contraindications

- 1) Chronic kidney disease (stage IV/V)
- 2) Active liver disease

### b. Relative contraindications (use caution in patients with):

- 1) Urinary or gastrointestinal tract lesions, pathology, or instrumentation due to risk of bleeding
- 2) Compromised renal or liver function

### c. Monitor closely if patient is receiving nephrotoxic or hepatotoxic chemotherapy

### d. Monitor for drug-drug interactions with CYP3A4 and/or P-glycoprotein inhibitors or inducers



**ARS Question #9- Answer**

**Correct answer is D (Enoxaparin 60 mg SubQ q12hr).** Enoxaparin 1 mg/kg every 12 hours is the most appropriate agent to initiate at this time.

Option A is incorrect because edoxaban when used treatment for an acute DVT in the setting of cancer should be first preceded by at least 5 days of parenteral anticoagulation.

Option B is incorrect because rivaroxaban must be first administered as a loading dose of 15 mg twice daily for 21 days before continuing on the 20 mg once daily maintenance dose.

Option C is not appropriate at this time because the patient is not thrombocytopenic (platelets are  $>50,000/\text{mm}^3$ ). Adjusting the dose of LMWH to 0.5 mg/kg every 12 hours would be appropriate in the setting of platelets being 25,000-50,000/ $\text{mm}^3$ ; however, with the patient's platelets being 130,000/ $\text{mm}^3$ , this would be underdosing the patient.

## RECOMMENDED READINGS AND REFERENCES

### Recommended Readings

1. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. *The New England journal of medicine*. 2022; online ahead of print. Available at: <https://www.nejm.org/doi/pdf/10.1056/NEJMoa2204925>
2. Isatuximab , carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet*. 2021; 397(10292):2361-2371. Available at: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00592-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00592-4/fulltext)
3. NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *The New England journal of medicine*. 2021; 384:705-716. Available at: <http://www.nejm.org/doi/full/10.1056/nejmoa2024850>
4. Pozzi S, Bari A, Pecherstorfer M, Vallet S. Management of adverse events and supportive therapy in relapsed/refractory multiple myeloma. *Cancers (Basel)*. 2021; 13(19):4978.
5. Bossaer JB, Covert KL. Direct oral anticoagulants in patients with cancer. *Am J Health Syst Pharm*. 2019; 76(14):1019-1027.

### References

1. Multiple Myeloma. American Cancer Society. <https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html>. Accessed 2 September 2022.
2. International Myeloma Foundation Concise Review. Available at: <https://imf-d8-prod.s3.us-west-1.amazonaws.com/resource/ConciseReview.pdf>. Accessed 2 September 2022.
3. Fonseca R, Blood E, Rue M, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood*. Jun 1 2003;101(11):4569-75. doi:10.1182/blood-2002-10-3017
4. Chng WJ, Santana-Davila R, Van Wier SA, et al. Prognostic factors for hyperdiploid-myeloma: effects of chromosome 13 deletions and IgH translocations. *Leukemia*. May 2006;20(5):807-13. doi:10.1038/sj.leu.2404172
5. Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia*. Dec 2009;23(12):2210-21. doi:10.1038/leu.2009.174
6. Chretien ML, Corre J, Lauwers-Cances V, et al. Understanding the role of hyperdiploidy in myeloma prognosis: which trisomies really matter? *Blood*. Dec 17 2015;126(25):2713-9. doi:10.1182/blood-2015-06-650242
7. Decaux O, Lode L, Magrangeas F, et al. Prediction of survival in multiple myeloma based on gene expression profiles reveals cell cycle and chromosomal instability signatures in high-risk patients and hyperdiploid signatures in low-risk patients: a study of the Intergroupe Francophone du Myelome. *J Clin Oncol*. Oct 10 2008;26(29):4798-805. doi:10.1200/JCO.2007.13.8545
8. Kuiper R, Broyl A, de Knecht Y, et al. A gene expression signature for high-risk multiple myeloma. *Leukemia*. Nov 2012;26(11):2406-13. doi:10.1038/leu.2012.127
9. Shaughnessy JD, Jr., Zhan F, Burington BE, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood*. Mar 15 2007;109(6):2276-84. doi:10.1182/blood-2006-07-038430
10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma. V2.2023, 10/31/2022. © National Comprehensive Cancer Network, Inc 2022. All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
11. Bird JM, Owen RG, D'Sa S, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. *British journal of haematology*. Jul 2011;154(1):32-75. doi:10.1111/j.1365-2141.2011.08573.x

12. Cavo M, Rajkumar SV, Palumbo A, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood*. Jun 9 2011;117(23):6063-73. doi:10.1182/blood-2011-02-297325
13. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. Jan 2003;78(1):21-33. doi:10.4065/78.1.21
14. Dimopoulos M, Kyle R, Fermand JP, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. *Blood*. May 5 2011;117(18):4701-5. doi:10.1182/blood-2010-10-299529
15. Eleutherakis-Papaiakevou V, Bamias A, Gika D, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. *Leukemia & lymphoma*. Feb 2007;48(2):337-41. doi:10.1080/10428190601126602
16. Palumbo A, Anderson K. Multiple myeloma. *The New England journal of medicine*. Mar 17 2011;364(11):1046-60. doi:10.1056/NEJMra1011442
17. Varettoni M, Corso A, Pica G, Mangiacavalli S, Pascutto C, Lazzarino M. Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Feb 2010;21(2):325-30. doi:10.1093/annonc/mdp329
18. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. Sep 1975;36(3):842-54.
19. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. May 20 2005;23(15):3412-20. doi:10.1200/JCO.2005.04.242
20. Munshi NC, Anderson KC, Bergsagel PL, et al. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood*. May 5 2011;117(18):4696-700. doi:10.1182/blood-2010-10-300970
21. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol*. Sep 10 2015;33(26):2863-9. doi:10.1200/JCO.2015.61.2267
22. Kapoor P, Fonseca R, Rajkumar SV, et al. Evidence for cytogenetic and fluorescence in situ hybridization risk stratification of newly diagnosed multiple myeloma in the era of novel therapies. *Mayo Clin Proc*. Jun 2010;85(6):532-7. doi:10.4065/mcp.2009.0677
23. Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. *American journal of hematology*. Jan 2012;87(1):78-88. doi:10.1002/ajh.22237
24. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. Apr 2013;88(4):360-76. doi:10.1016/j.mayocp.2013.01.019
25. Sidiqi MH, Al Saleh AS, Leung N, et al. Venetoclax for the treatment of translocation (11;14) AL amyloidosis. *Blood Cancer Journal*. 2020/05/11 2020;10(5):55. doi:10.1038/s41408-020-0321-6
26. Arnulf B, Pylypenko H, Grosicki S, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. *Haematologica*. Dec 2012;97(12):1925-8. doi:10.3324/haematol.2012.067793
27. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). *J Clin Oncol*. Oct 20 2010;28(30):4630-4. doi:10.1200/JCO.2010.28.3945
28. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. Dec 18 2010;376(9758):2075-85. doi:10.1016/S0140-6736(10)61424-9
29. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. Oct 20 2010;28(30):4621-9. doi:10.1200/JCO.2009.27.9158

30. Kumar S, Dispenzieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. *Leukemia*. Sep 2007;21(9):2035-42. doi:10.1038/sj.leu.2404801
31. Martiniani R, Di Loreto V, Di Sano C, Lombardo A, Liberati AM. Biological activity of lenalidomide and its underlying therapeutic effects in multiple myeloma. *Advances in hematology*. 2012;2012:842945. doi:10.1155/2012/842945
32. Moreau P, Coiteux V, Hulin C, et al. Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. *Haematologica*. Dec 2008;93(12):1908-11. doi:10.3324/haematol.13285
33. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *The lancet oncology*. May 2011;12(5):431-40. doi:10.1016/S1470-2045(11)70081-X
34. Paripati H, Stewart AK, Cabou S, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. *Leukemia*. Jun 2008;22(6):1282-4. doi:10.1038/sj.leu.2405100
35. Quach H, Ritchie D, Stewart AK, et al. Mechanism of action of immunomodulatory drugs (IMiDs) in multiple myeloma. *Leukemia*. Jan 2010;24(1):22-32. doi:10.1038/leu.2009.236
36. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *The lancet oncology*. Jan 2010;11(1):29-37. doi:10.1016/S1470-2045(09)70284-0
37. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia*. Jul 2009;23(7):1337-41. doi:10.1038/leu.2009.26
38. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood*. Apr 22 2010;115(16):3416-7. doi:10.1182/blood-2010-02-271676
39. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood*. Oct 15 2008;112(8):3107-14. doi:10.1182/blood-2008-04-149427
40. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *The New England journal of medicine*. May 10 2012;366(19):1759-69. doi:10.1056/NEJMoa1112704
41. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *The New England journal of medicine*. Jun 21 2007;356(25):2582-90. doi:10.1056/NEJMoa070389
42. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The lancet oncology*. 2014;15(12):e538-e548. doi:10.1016/s1470-2045(14)70442-5
43. Durie B, Hoering A, Rajkumar SV, et al. Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777. *Blood*. 2015;126(23):25-25.
44. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood*. Aug 30 2012;120(9):1801-9. doi:10.1182/blood-2012-04-422683
45. Voorhees P, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, Chari A, Silbermann R, Costa LJ et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood*. 2020;136(8):936-45.
46. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood*. May 10 2012;119(19):4375-82. doi:10.1182/blood-2011-11-395749
47. Einsele H, Engelhardt M, Tappich C, et al. Phase II study of bortezomib, cyclophosphamide and dexamethasone as induction therapy in multiple myeloma: DSMM XI trial. *British journal of haematology*. Sep 29 2017;doi:10.1111/bjh.14920

48. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol*. Aug 20 2012;30(24):2946-55. doi:10.1200/JCO.2011.39.6820
49. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *The Lancet*. 2019;394(10192):29-38. doi:10.1016/s0140-6736(19)31240-1
50. Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol*. Sep 1 2022;40(25):2901-2912. doi:10.1200/JCO.21.01935
51. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. *British journal of haematology*. May 2019;185(3):492-502. doi:10.1111/bjh.15806
52. Griffin PT, Ho VQ, Fulp W, et al. A comparison of salvage infusional chemotherapy regimens for recurrent/refractory multiple myeloma. *Cancer*. Oct 15 2015;121(20):3622-30. doi:10.1002/cncr.29533
53. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J*. May 11 2020;10(5):53. doi:10.1038/s41408-020-0311-8
54. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *The New England journal of medicine*. Apr 6 2017;376(14):1311-1320. doi:10.1056/NEJMoa1611750
55. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *The New England journal of medicine*. Jun 5 2022;doi:10.1056/NEJMoa2204925
56. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma: subanalysis of patients with renal impairment in the phase III MMY-3021 study. *Haematologica*. May 2015;100(5):e207-10. doi:10.3324/haematol.2014.118182
57. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *The lancet oncology*. Dec 2021;22(12):1705-1720. doi:10.1016/S1470-2045(21)00535-0
58. Kumar S JS, Cohen AD, Weiss M, Callander NS, Singh AA. Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM): Results of the ENDURANCE (E1A11) phase III trial. *J Clin Oncol*. 2020;38:abstr LBA3.
59. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *The lancet oncology*. 2020;21(10):1317-1330. doi:10.1016/s1470-2045(20)30452-6
60. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *The lancet oncology*. Mar 2014;15(3):333-42. doi:10.1016/S1470-2045(13)70609-0
61. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *The New England journal of medicine*. May 10 2012;366(19):1782-91. doi:10.1056/NEJMoa1114138
62. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol*. Sep 2017;4(9):e431-e442. doi:10.1016/S2352-3026(17)30140-0
63. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. *The New England journal of medicine*. May 30 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249

64. Korde N, Roschewski M, Zingone A, et al. Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma. *JAMA Oncol.* Sep 2015;1(6):746-54. doi:10.1001/jamaoncol.2015.2010
65. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *The New England journal of medicine.* Feb 8 2018;378(6):518-528. doi:10.1056/NEJMoa1714678
66. Niesvizky R, Flinn IW, Rifkin R, et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. *J Clin Oncol.* Jun 8 2015;doi:10.1200/JCO.2014.58.7618
67. J Z, P D, P N, N B. Cyclophosphamide, Bortezomib and Dexamethasone (CyBORD) Is a Feasible and Active Regimen for Non-Transplant Eligible Multiple Myeloma Patients. *Blood.* 2014;124(21):5751.
68. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *British journal of haematology.* Jul 2018;182(2):222-230. doi:10.1111/bjh.15261
69. Brinthen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. *Blood.* Jul 03 2014;124(1):63-9. doi:10.1182/blood-2014-03-563759
70. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *The New England journal of medicine.* Sep 4 2014;371(10):906-17. doi:10.1056/NEJMoa1402551
71. Rajkumar SV, Jacobus S, Callander N, et al. A Randomized Trial of Lenalidomide Plus High-Dose Dexamethasone (RD) Versus Lenalidomide Plus Low-Dose Dexamethasone (Rd) in Newly Diagnosed Multiple Myeloma (E4A03): A Trial Coordinated by the Eastern Cooperative Oncology Group. *Blood.* 2007;110(11):74-74.
72. Chari A TM, Krishnan A et al. Use of montelukast to reduce infusion reactions in an early access treatment protocol of daratumumab in United States patients with relapsed or refractory multiple myeloma. *Blood.* 2016;128(22):2142.
73. Barr H, Dempsey J, Waller A, et al. Ninety-minute daratumumab infusion is safe in multiple myeloma. *Leukemia.* Nov 2018;32(11):2495-2518. doi:10.1038/s41375-018-0120-2
74. Darzalex Faspro® (Daratumumab and hyaluronidase-fihj) [prescribing information]. Horsham, PA. Janssen; 5/2020
75. Mateos M-V, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *The Lancet Haematology.* 2020;7(5):e370-e380. doi:10.1016/s2352-3026(20)30070-3
76. Mateos M-V, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *The Lancet.* 2020;395(10218):132-141. doi:10.1016/s0140-6736(19)32956-3
77. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *The lancet oncology.* Nov 2021;22(11):1582-1596. doi:10.1016/S1470-2045(21)00466-6
78. Facon T, Venner CP, Bahlis NJ, et al. Oral ixazomib, lenalidomide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood.* Jul 1 2021;137(26):3616-3628. doi:10.1182/blood.2020008787
79. McCarthy PL, Palumbo A. Maintenance therapy for multiple myeloma. *Hematology/oncology clinics of North America.* Oct 2014;28(5):839-59. doi:10.1016/j.hoc.2014.06.006
80. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *The New England journal of medicine.* May 10 2012;366(19):1770-81. doi:10.1056/NEJMoa1114083
81. Sonneveld P, Salwender H, Van der Holt B, et al. Bortezomib induction and maintenance in patients with newly diagnosed multiple myeloma: long-term follow-up of the HOVON-65/GMMG-HD4 trial. *Blood.* 2015;126:27.
82. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia.* Sep 2006;20(9):1467-73. doi:10.1038/sj.leu.2404284
83. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood.* May 5 2011;117(18):4691-5. doi:10.1182/blood-2010-10-299487

84. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*. Feb 20 2014;32(6):587-600. doi:10.1200/JCO.2013.48.7934
85. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The lancet oncology*. Aug 2016;17(8):e328-46. doi:10.1016/S1470-2045(16)30206-6
86. Lee CK, Barlogie B, Munshi N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. *J Clin Oncol*. Jul 15 2003;21(14):2732-9. doi:10.1200/JCO.2003.01.055
87. Nair B, van Rhee F, Shaughnessy JD, Jr., et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. *Blood*. May 27 2010;115(21):4168-73. doi:10.1182/blood-2009-11-255620
88. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *British journal of haematology*. Jul 2007;138(2):176-85. doi:10.1111/j.1365-2141.2007.06639.x
89. Khan ML, Stewart AK. Carfilzomib: a novel second-generation proteasome inhibitor. *Future oncology*. May 2011;7(5):607-12. doi:10.2217/fon.11.42
90. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *The New England journal of medicine*. Jan 8 2015;372(2):142-52. doi:10.1056/NEJMoa1411321
91. Siegel D, Dimopoulos A, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *Journal of Clinical Oncology*. 2018 36(8):728-34. doi:10.1200/JCO.2017.10.1200/JCO.2017
92. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *The lancet oncology*. Jan 2016;17(1):27-38. doi:10.1016/S1470-2045(15)00464-7
93. Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. *The lancet oncology*. Jul 2018;19(7):953-964. doi:10.1016/S1470-2045(18)30354-1
94. Ninlaro® (Ixazomib) [prescribing information]. Cambridge MTD.
95. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *The New England journal of medicine*. Apr 28 2016;374(17):1621-34. doi:10.1056/NEJMoa1516282
96. Darzalex® (Daratumumab) [prescribing information]. Horsham PJA.
97. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*. Apr 9 2016;387(10027):1551-60. doi:10.1016/S0140-6736(15)01120-4
98. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *The New England journal of medicine*. Aug 25 2016;375(8):754-66. doi:10.1056/NEJMoa1606038
99. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. *Haematologica*. 2018;doi:10.3324/haematol.2018.194118
100. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *The New England journal of medicine*. Oct 06 2016;375(14):1319-1331. doi:10.1056/NEJMoa1607751
101. Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. *Haematologica*. 2018;doi:10.3324/haematol.2018.194282
102. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia*. Jul 2020;34(7):1875-1884. doi:10.1038/s41375-020-0711-6
103. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *The lancet oncology*. Jun 2021;22(6):801-812. doi:10.1016/S1470-2045(21)00128-5

104. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet*. Jul 18 2020;396(10245):186-197. doi:10.1016/S0140-6736(20)30734-0
105. Sarclisa® (Isatuximab-irfc) [prescribing information]. Bridgewater NS-AM.
106. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *The Lancet*. 2019;394(10214):2096-2107. doi:10.1016/s0140-6736(19)32556-5
107. Richardson PG, Perrot A, San-Miguel J, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. *The lancet oncology*. Mar 2022;23(3):416-427. doi:10.1016/S1470-2045(22)00019-5
108. Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet*. Jun 19 2021;397(10292):2361-2371. doi:10.1016/S0140-6736(21)00592-4
109. Empliciti™ (Elotuzumab) [prescribing information]. Princeton NB-MSO.
110. Dimopoulos MA, Lonial S, Betts KA, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. *Cancer*. Oct 15 2018;124(20):4032-4043. doi:10.1002/cncr.31680
111. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *The New England journal of medicine*. Aug 13 2015;373(7):621-31. doi:10.1056/NEJMoa1505654
112. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. *The New England journal of medicine*. Nov 8 2018;379(19):1811-1822. doi:10.1056/NEJMoa1805762
113. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab Plus Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Final Overall Survival Analysis From the Randomized Phase II ELOQUENT-3 Trial. *J Clin Oncol*. Aug 12 2022;JCO2102815. doi:10.1200/JCO.21.02815
114. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009-02. *Blood*. Mar 14 2013;121(11):1968-75. doi:10.1182/blood-2012-09-452375
115. Thalomid® (Thalidomide) [prescribing information]. Summit NCS.
116. Revlimid® (Lenalidomide) [prescribing information]. Summit NCA.
117. Pomalyst® (Pomalidomide) [prescribing information]. Summit NCD.
118. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet*. Nov 14 2020;396(10262):1563-1573. doi:10.1016/S0140-6736(20)32292-3
119. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. *The New England journal of medicine*. Aug 22 2019;381(8):727-738. doi:10.1056/NEJMoa1903455
120. Abecma (idecabtagene vicleucel) [prescribing information]. Summit NCCM.
121. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *New England Journal of Medicine*. 2021;384(8):705-716. doi:10.1056/nejmoa2024850
122. Carvykti (ciltacabtagene autoleucel) [prescribing information]. Horsham PJBIM.
123. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. Jul 24 2021;398(10297):314-324. doi:10.1016/S0140-6736(21)00933-8
124. Tecvayli® (Teclistamab-cqyv) [prescribing information]. Horsham, PA. Janssen; 10/2022.
125. Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *The New England journal of medicine*. Aug 11 2022;387(6):495-505. doi:10.1056/NEJMoa2203478
126. GSK provides an update on Blenrep (belantamab mafodotin-blmf) US marketing authorisation. Available at <https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-blenrep-us-marketing-authorisation/>. Accessed 23 November 2022.



127. Federal Register. Secura Bio, Inc.; Withdrawal of Approval of New Drug Application for FARYDAK (Panobinostat) Capsules, 10 Milligrams, 15 Milligrams, and 20 Milligrams. Available at <https://www.federalregister.gov/documents/2022/03/24/2022-06182/secura-bio-inc-withdrawal-of-approval-of-new-drug-application-for-farydak-panobinostat-capsules-10>. Accessed 23 November 2022.
128. 2022. HRFaDAAAoAahwcgbt-ch-bAS.
129. Longo V, Brunetti O, D'Oronzo S, Dammacco F, Silvestris F. Therapeutic approaches to myeloma bone disease: an evolving story. *Cancer treatment reviews*. Oct 2012;38(6):787-97. doi:10.1016/j.ctrv.2012.03.004
130. Terpos E, Dimopoulos MA. Myeloma bone disease: pathophysiology and management. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Aug 2005;16(8):1223-31. doi:10.1093/annonc/mdi235
131. Anderson K, Ismaila N, Flynn PJ, et al. Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. Mar 10 2018;36(8):812-818. doi:10.1200/JCO.2017.76.6402
132. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol*. Jun 20 2013;31(18):2347-57. doi:10.1200/JCO.2012.47.7901
133. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer*. Oct 15 2003;98(8):1735-44. doi:10.1002/cncr.11701
134. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol*. Feb 1998;16(2):593-602.
135. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. Jan 15 2001;19(2):558-67.
136. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *The lancet oncology*. Mar 2018;19(3):370-381. doi:10.1016/S1470-2045(18)30072-X
137. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol*. Mar 20 2005;23(9):2028-37. doi:10.1200/JCO.2005.00.067
138. Abrahm JL, Banffy MB, Harris MB. Spinal cord compression in patients with advanced metastatic cancer: "all I care about is walking and living my life". *JAMA : the journal of the American Medical Association*. Feb 27 2008;299(8):937-46. doi:10.1001/jama.299.8.937
139. Lawton A, Lee K, Cheville A, et al. Assessment and management of patients with metastatic spinal cord compression: a multidisciplinary review. *Journal of Clinical Oncology*. 2019;37(1):61-71. doi:10.1200/JCO
140. Hung CF, Ma B, Monie A, Tsen SW, Wu TC. Therapeutic human papillomavirus vaccines: current clinical trials and future directions. *Expert opinion on biological therapy*. Apr 2008;8(4):421-39. doi:10.1517/14712598.8.4.421
141. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet*. Aug 20-26 2005;366(9486):643-8. doi:10.1016/S0140-6736(05)66954-1
142. Klimo P, Jr., Thompson CJ, Kestle JR, Schmidt MH. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro-oncology*. Jan 2005;7(1):64-76. doi:10.1215/S1152851704000262
143. Itshayek E, Yamada J, Bilsky M, et al. Timing of surgery and radiotherapy in the management of metastatic spine disease: a systematic review. *International journal of oncology*. Mar 2010;36(3):533-44.
144. Jeremic B, Shibamoto Y, Acimovic L, et al. A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. *International journal of radiation oncology, biology, physics*. Aug 1 1998;42(1):161-7.
145. Maranzano E, Bellavita R, Rossi R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. *J Clin Oncol*. May 20 2005;23(15):3358-65. doi:10.1200/JCO.2005.08.193

146. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *The New England journal of medicine*. Jan 27 2005;352(4):373-9. doi:10.1056/NEJMcp042806
147. Halfdanarson TR, Hogan WJ, Moynihan TJ. Oncologic emergencies: diagnosis and treatment. *Mayo Clin Proc*. Jun 2006;81(6):835-48. doi:10.4065/81.6.835
148. S. AT, S. C. Management of Hypercalcemia of Malignancy. *Journal of Heamatology Oncology Pharmacy*. 2016;6(1):18-21.
149. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. Feb 27 2006;166(4):458-64. doi:10.1001/archinte.166.4.458
150. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *The New England journal of medicine*. Dec 21 2000;343(25):1846-50. doi:10.1056/NEJM200012213432504
151. Petersen LJ. Anticoagulation therapy for prevention and treatment of venous thromboembolic events in cancer patients: a review of current guidelines. *Cancer treatment reviews*. Dec 2009;35(8):754-64. doi:10.1016/j.ctrv.2009.08.009
152. Connolly GC, Khorana AA. Risk stratification for cancer-associated venous thromboembolism. *Best Pract Res Clin Haematol*. Mar 2009;22(1):35-47. doi:10.1016/j.beha.2008.12.006
153. Khorana AA, Carrier M, Garcia DA, Lee AY. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. *J Thromb Thrombolysis*. Jan 2016;41(1):81-91. doi:10.1007/s11239-015-1313-4
154. Khorana AA. Cancer-associated thrombosis: updates and controversies. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. 2012;2012:626-30. doi:10.1182/asheducation-2012.1.626
155. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. *J Clin Oncol*. Sep 1 2011;29(25):3466-73. doi:10.1200/jco.2011.35.5669
156. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood*. Dec 9 2010;116(24):5377-82. doi:10.1182/blood-2010-02-270116
157. Khorana AA, Streiff MB, Farge D, et al. Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. *J Clin Oncol*. Oct 10 2009;27(29):4919-26. doi:10.1200/jco.2009.22.3214
158. Lyman GH, Khorana AA, Kuderer NM, Lee AY. Cancer and thrombosis: back to the future renewed interest in an old problem. *Cancer investigation*. Jun 2009;27(5):472-3. doi:10.1080/07357900902996441
159. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. Jun 10 2013;31(17):2189-204. doi:10.1200/jco.2013.49.1118
160. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. *J Clin Oncol*. Feb 20 2015;33(6):654-6. doi:10.1200/JCO.2014.59.7351
161. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Associated Venous Thromboembolic Disease. V1.2022, 3/11/2022. © National Comprehensive Cancer Network, Inc 2022. All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
162. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. May 15 2008;111(10):4902-7. doi:10.1182/blood-2007-10-116327
163. Key N, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *Journal of Clinical Oncology*. 2019;37:1-25. doi:10.1200/JCO.19

164. Li A, Wu Q, Luo S, et al. Derivation and Validation of a Risk Assessment Model for Immunomodulatory Drug-Associated Thrombosis Among Patients With Multiple Myeloma. *J Natl Compr Canc Netw*. Jul 1 2019;17(7):840-847. doi:10.6004/jnccn.2018.7273
165. Sanfilippo KM, Luo S, Wang TF, et al. Predicting venous thromboembolism in multiple myeloma: development and validation of the IMPEDE VTE score. *American journal of hematology*. Nov 2019;94(11):1176-1184. doi:10.1002/ajh.25603
166. Kakkar AK, Levine MN, Kadziola Z, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). *J Clin Oncol*. May 15 2004;22(10):1944-8. doi:10.1200/jco.2004.10.002
167. Pelzer U, Hilbig A, Stieler JM, et al. Intensified chemotherapy and simultaneous treatment with heparin in outpatients with pancreatic cancer - the CONKO 004 pilot trial. *BMC cancer*. 2014;14:204. doi:10.1186/1471-2407-14-204
168. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *European journal of cancer (Oxford, England : 1990)*. Jun 2012;48(9):1283-92. doi:10.1016/j.ejca.2011.10.017
169. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *The New England journal of medicine*. Feb 21 2019;380(8):711-719. doi:10.1056/NEJMoa1814468
170. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *The New England journal of medicine*. Feb 21 2019;380(8):720-728. doi:10.1056/NEJMoa1814630
171. Farge D, Deboudeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Journal of thrombosis and haemostasis : JTH*. Jan 2013;11(1):56-70. doi:10.1111/jth.12070
172. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. Feb 2012;141(2 Suppl):e195S-226S. doi:10.1378/chest.11-2296
173. Schiffer CA, Mangu PB, Wade JC, et al. Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. Apr 1 2013;31(10):1357-70. doi:10.1200/jco.2012.45.5733
174. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. Feb 2012;141(2 Suppl):e419S-94S. doi:10.1378/chest.11-2301
175. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*. Jul 2 2011;378(9785):41-8. doi:10.1016/s0140-6736(11)60824-6
176. Mantha S, Miao Y, Wills J, Parameswaran R, Soff GA. Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. *J Thromb Thrombolysis*. May 2017;43(4):514-518. doi:10.1007/s11239-017-1478-0
177. Carrier M, Khorana AA, Zwicker J, Noble S, Lee AY. Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH*. Sep 2013;11(9):1760-5. doi:10.1111/jth.12338
178. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *The New England journal of medicine*. Jul 10 2003;349(2):146-53. doi:10.1056/NEJMoa025313
179. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *The New England journal of medicine*. Apr 23 2020;382(17):1599-1607. doi:10.1056/NEJMoa1915103
180. McBane RD, 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. *Journal of thrombosis and haemostasis : JTH*. Feb 2020;18(2):411-421. doi:10.1111/jth.14662
181. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *The New England journal of medicine*. Feb 15 2018;378(7):615-624. doi:10.1056/NEJMoa1711948

182. Young AM MA, Thirlwall J et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2020;36:2017-23. doi:10.1200/JCO.2018.10.1200/JCO.2018
183. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schunemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. Feb 2012;141(2 Suppl):7s-47s. doi:10.1378/chest.1412S3

# PEDIATRIC MALIGNANCIES AND SUPPORTIVE CARE

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## LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for pediatric patients with cancer.
2. Assess the prognostic impact of relevant cancer-related molecular biology testing for a pediatric patient with cancer.
3. Discuss with a pediatric patient who has cancer and his or her caregiver the short- and long-term treatment goals, including post-therapy and survivorship.
4. Assess the regulatory, ethical, and patient rights issues related to conducting research, including informed consent and confidentiality.

**NOTE:** This handout includes a discussion of the following pediatric disease-states: Acute Lymphoblastic Leukemia, Central Nervous System Tumors, Neuroblastoma, Non-Hodgkin Lymphoma (Burkitt), Wilms Tumor, Ewing Sarcoma, and Retinoblastoma. The following pediatric practice & supportive care topics will also be discussed: Febrile Neutropenia, Acute Chemotherapy-Induced Nausea and Vomiting, Pediatric Informed Consent, Compassionate Use and Pediatric Survivorship.

## PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

### **Patient Case #1:**

SW is a 5-year-old female with intermittent fevers, vomiting, fatigue and inability to keep up in play with her brothers for the last week. On the morning of presentation, SW had one episode of blood-tinged emesis and coughed up a large clot which prompted her parents to bring SW to the emergency department.

A CBC is obtained in the emergency department which reveals: Hb 5.4g/dL, PLT 21,000 cell/mm<sup>3</sup>, WBC 102,000 cells/mm<sup>3</sup> with 72% peripheral blasts. After a full evaluation and work-up, SW is diagnosed with precursor B-cell acute lymphoblastic leukemia.

### **What chemotherapy drugs should SW receive as part of her ALL induction therapy?**

- A. Dexamethasone, vincristine, and calaspargase
- B. Prednisone, vincristine, calaspargase, and daunorubicin
- C. Doxorubicin, vincristine, and pegaspargase
- D. Dexamethasone, vincristine, pegaspargase, and daunorubicin

### **I. Risk Estimation<sup>1-5</sup>**

NCI Risk Stratification of B-cell ALL <sup>6</sup>	
Standard Risk	High Risk
Age 1–9.99 years AND Initial WBC < 50,000 cells/mm <sup>3</sup>	Age < 1 year or ≥ 10 years OR Initial WBC ≥ 50,000 cells/mm <sup>3</sup>

- A. While still incorporating the NCI-risk stratification, pediatric research groups have further refined current strategies of risk-stratification to intensify therapy for those at high risk of relapse and avoid treatment-related toxicity in those with lower risk disease.
- B. Biological features refining clinical risk groups:
  - 1. Immunophenotype
    - a. Immunophenotypes: B-cell (85%) or T-cell (15%)
    - b. T-cell ALL is a higher risk disease
  - 2. Involvement of sanctuary sites – regions of the body where leukemia cells may be protected from effects of systemic chemotherapy; require site-specific treatment
    - a. CNS Disease<sup>7,8</sup>
      - 1) CNS 1 = absence of blasts in CSF, regardless of WBC count
      - 2) CNS 2 = WBC in CSF < 5 cells/μl with CSF blasts on cytopspin
      - 3) CNS 3 = WBC in CSF ≥ 5 cells/μl with CSF blasts on cytopspin or clinical symptoms (CNS 3 stratifies patients to high risk)
    - b. Testicular Disease
      - 1) Often stratifies patients to high-risk
  - 3. Genetics<sup>9</sup>

- a. B-cell ALL:
  - 1) Favorable: High hyperdiploidy (51-67 chromosomes), ETV6-RUNX1 fusion
  - 2) Unfavorable: Hypodiploidy (< 44 chromosomes), KMT2A-rearrangement, BCR-ABL1 or BCR-ABL1-like, iAMP21, IKZF1
- C. Steroid Pre-treatment
  1. Definition = administration of more than 24 hours of systemic steroids within the 2 weeks prior to diagnosis
  2. Steroid pre-treatment may cause the initial WBC to be falsely low, which limits the utility of the WBC in risk stratification. Since the presenting WBC is a component of initial risk stratification, steroid pre-treatment is criteria for up-stratification to high risk.
- D. Response to initial therapy
  1. B-cell ALL
    - a. Critical assessment point for B-cell patients is end of induction. Minimal residual disease (MRD) defined as < 0.01%.
  2. T-cell ALL
    - a. Critical assessment point for T-cell patients is end of consolidation rather than end of induction. Residual MRD > 0.1% at end of consolidation is classified as very high risk.

#### General Features of Pediatric ALL Risk Groups<sup>10,11</sup>

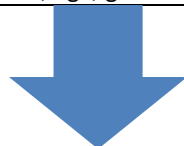
<b>Low Risk</b>	<b><u>Presence of ALL of the following:</u></b> Age 1–9.99 years and initial WBC < 50,000 cells/mm <sup>3</sup> No CNS-3 disease No testicular involvement Presence of either double trisomies 4 and 10, or <i>ETV6-RUNX1</i> Minimal residual disease (MRD) < 0.01% on day 8 and at the end of induction
<b>Standard Risk</b>	Age 1–9.99 years and initial WBC < 50,000 cells/mm <sup>3</sup> with B-cell ALL not otherwise classified as low risk or high risk
<b>High Risk</b>	<b><u>Presence of ANY of the following:</u></b> Age < 1 year or ≥ 10 years Initial WBC > 50,000 cells/mm <sup>3</sup> T-cell lineage ALL Steroid pre-treatment Presence of CNS-3 disease or testicular disease <i>Patients may advance to high risk based on MRD &gt; 0.01% at the end of induction</i>
<b>Very High Risk</b>	<b><u>Presence of ANY of the following:</u></b> Age > 13 years old <i>BCR-ABL</i> <i>KMT2A</i> Hypodiploidy <i>Patients may advance to very high risk if induction failure (&gt;5% blasts at end of induction)</i>

Note: Risk stratification differs by research group/protocol

## II. Treatment <sup>12-16</sup>

- A. Three phases of therapy are required (Induction, Consolidation/Post-Induction Intensive Chemotherapy, and Maintenance)

<b>Induction (4-6 week duration)</b> Goal: Induce a complete morphologic remission 90-95% of patients will achieve first remission at end of induction <sup>17</sup>	
<b>Standard risk (3 drug induction):</b> <ul style="list-style-type: none"> <li>Dexamethasone</li> <li>Vincristine 1.5mg/m<sup>2</sup> (max 2mg) weekly x 4 doses</li> <li>Pegaspargase 2,500 units/m<sup>2</sup> IM or IV x 1 dose</li> </ul>	<b>High risk (4 drug induction):</b> <ul style="list-style-type: none"> <li>Dexamethasone (&lt; 10 years) or prednisone (≥ 10 years)</li> <li>Vincristine 1.5mg/m<sup>2</sup> (max 2mg) weekly x 4 doses</li> <li>Pegaspargase 2,500 units/m<sup>2</sup> IM or IV x 1 dose</li> <li>Daunorubicin 25mg/m<sup>2</sup> IV weekly x 2-4 doses</li> </ul>
Corticosteroid choice based on age for high risk patients <sup>14,18-23</sup> : <ul style="list-style-type: none"> <li>Dexamethasone exhibits increased CNS penetration, more potent cytotoxicity against leukemia cells, prevention of CNS relapse, and improved EFS</li> <li>Dexamethasone also associated with increased bacterial / fungal infections and osteonecrosis in children ≥ 10 years of age</li> <li>Balance of risk vs benefit – patients &lt; 10 years receive dexamethasone while patients ≥ 10 years receive prednisone</li> </ul>	
Intrathecal (IT) therapy: <ul style="list-style-type: none"> <li>IT agents: methotrexate, cytarabine, and/or hydrocortisone               <ul style="list-style-type: none"> <li>Dosing is age-based, to approximate CSF volume</li> </ul> </li> <li>Diagnostic LP with IT cytarabine given on or before day 1 of induction               <ul style="list-style-type: none"> <li>Cytarabine drug of choice for diagnostic LP as it is active in both ALL and AML</li> <li>Platelet threshold of ≥ 100,000/mcl for diagnostic LP to minimize risk of seeding the CSF with leukemic blasts in the event of a traumatic tap</li> </ul> </li> <li>CNS-directed therapy is required for all patients to prevent CNS relapse, even in the absence of CNS disease at diagnosis</li> </ul>	
End of Induction Disease Evaluation: <ul style="list-style-type: none"> <li>Minimal Residual Disease (MRD) testing<sup>10</sup> <ul style="list-style-type: none"> <li>Evaluated at the end of induction (day 29)</li> <li>Remission defined as MRD ≤ 0.01% leukemic cells</li> <li>MRD at end of induction (B-cell patients) is the strongest predictor of EFS and OS (more significant than WBC at diagnosis, age, genetic features, or early response to steroids)<sup>24-26</sup></li> </ul> </li> </ul>	



<b>Consolidation / Interim Maintenance / Delayed Intensification</b> Goal: Eliminate residual disease and eradicate or prevent CNS leukemia Total duration 6-9 months
<b>Consolidation (4-8 weeks):</b> <ul style="list-style-type: none"> <li>Combination chemotherapy incorporating vincristine and mercaptopurine (6-MP)</li> <li>Additional agents added in high risk groups (cyclophosphamide, cytarabine, pegaspargase or calaspargase)</li> <li>Note: T-cell ALL therapy is intensified with the addition of nelarabine during post-induction therapy. Residual MRD &gt; 0.1% at end of consolidation is classified as very high risk for T-cell ALL.</li> </ul>



**Interim Maintenance (8 weeks):**

- Combination chemotherapy, often including IV methotrexate, vincristine, 6-MP and IT methotrexate
- Interim maintenance may be given once, or repeated after delayed intensification depending on the protocol
- Methotrexate is key component of interim maintenance
  - Standard Risk ALL – escalating dose IV methotrexate (Capizzi methotrexate)<sup>27</sup>
  - High / Very High Risk ALL – high dose methotrexate<sup>23</sup>

**Delayed Intensification (8 weeks):**

- Combination chemotherapy with cyclophosphamide, cytarabine, vincristine, pegaspargase or calaspargase, dexamethasone and 6-MP or thioguanine (6-TG)
- Addition of delayed intensification to ALL treatment regimen has significantly improved EFS



**Maintenance**

Goal: Ensure durable remission

Total duration 2 years from the start of interim maintenance

**Standard backbone:**

- Daily 6-mercaptopurine (6-MP) 75mg/m<sup>2</sup>/day PO
- Weekly methotrexate 20mg/m<sup>2</sup> IV or PO
- Intermittent pulses of vincristine
- Intermittent pulses of corticosteroid PO

**Titration of oral chemotherapy:**

- 6-MP and methotrexate doses are adjusted to maintain goal ANC 0.5 x 10<sup>9</sup>/L to 1.5 x 10<sup>9</sup>/L
- If excess myelosuppression (ANC < 0.5 x 10<sup>9</sup>/L):
  - Hold both 6-MP and methotrexate until recovery, then restart at decreased dosing
  - For persistent neutropenia, consider checking thiopurine S-methyltransferase (TPMT) and nudix (nucleoside diphosphate linked moiety X)-type motif 15 (NUDT15) status if not already known
- If inadequate myelosuppression (ANC > 1.5 x 10<sup>9</sup>/L):
  - If sustained for 6-8 weeks, increase 6-MP or methotrexate doses in alternating fashion by 25% with each adjustment
  - If both 6-MP and methotrexate are increased without a response in ANC, non-compliance should be considered
  - May consider sending 6-MP metabolites (6-TGN / 6-MMPN)

**Patient Case #1, Answer:**

**Correct Answer: D. Dexamethasone, vincristine, pegaspargase and daunorubicin**

SW is classified as high risk due to her presenting WBC of > 50,000 cells/mm<sup>3</sup>. High risk patients receive four drug induction with a corticosteroid, vincristine, pegaspargase and daunorubicin. Dexamethasone is the preferred corticosteroid for patients younger than 10 years of age due to increased CNS penetration. Prednisone is the preferred corticosteroids for patients older than 10 years of age due to increased rates of osteonecrosis and fungal infections with dexamethasone.

**B. Additional treatment considerations:**

1. Ph+ ALL patients will receive tyrosine kinase inhibitor therapy (imatinib, dasatinib, nilotinib) with more intensive combination chemotherapy

- a. Addition of TKI has improved EFS<sup>28</sup>
- b. Encourage enrollment in a clinical trial
2. Calaspargase pegol-mknl (Asparlas<sup>®</sup>)
  - a. Calaspargase pegol-mknl contains an asparaginase enzyme derived from *Escherichia coli*, as a conjugate of L-asparaginase and monomethoxypolyethylene glycol with a succinimidyl carbonate linker. Calaspargase pegol-mknl differs from the previously available pegaspargase (Oncaspar<sup>®</sup>) product due to a more hydrolytically stable succinimidyl carbonate linker which results in a longer half-life and more prolonged duration of action
  - b. Indications and dose:
    - 1) For use as a component of multi-agent chemotherapy regimen for treatment of ALL in pediatric and young adult patients aged 1 month to 21 years
    - 2) 2,500 units/m<sup>2</sup> given IV no more frequently than every 21 days
  - c. Toxicities: hypersensitivity reactions, pancreatitis, thrombosis, hemorrhage, hepatotoxicity, hyperglycemia
  - d. Therapeutic drug monitoring: Serum asparaginase activity levels

**Patient Case #1, Continued:**

SW tolerates induction therapy well with minimal residual disease on day 29 of < 0.01%. Her next phase of therapy is consolidation which includes mercaptopurine (6MP). The results of SW's pharmacogenetic testing is below.

TPMT \*3A / \*3A (poor metabolizer)

NUDT15 \*1A / \*1A (normal metabolizer)

**Based on this information, what is the recommended starting dose for mercaptopurine (6MP) for SW?**

- A. 6MP 100% dosing, no adjustment required
- B. 6MP decreased to 50% dosing seven days per week
- C. 6MP decreased to 50% dosing three days per week
- D. 6MP decreased to 10% dosing three days per week

**III. Pharmacogenetic Considerations<sup>29</sup> – TPMT and NUDT15**

TPMT	NUDT15
TPMT catabolizes 6-MP and thioguanine to inactive metabolites <ul style="list-style-type: none"> <li>• Inverse relationship between TPMT activity and active thioguanine nucleotide (TGN) metabolite accumulation in erythrocytes</li> <li>• Variants more common in those of Caucasian and African descent</li> </ul>	NUDT15 catalyzes the conversion of cytotoxic thioguanine triphosphate metabolites to the less toxic thioguanine monophosphate <ul style="list-style-type: none"> <li>• Variants more common in those of Asian and Hispanic descent</li> </ul>
TPMT and NUDT15 results should be used in conjunction when both are available. Patients that are defined poor or intermediate metabolizers for either should be dosed per that enzyme's recommendations. Patients	

that are intermediate metabolizers for both may require further dose reduction as compared to patients that are intermediate metabolizers for only one enzyme.

Consider testing at diagnosis to have results available at time of thiopurine prescribing and administration.

Dosing Recommendations based on TPMT Genotype		
TPMT Genotype	Activity	Recommended Starting Dose
Homozygous wild-type	Normal / High Activity (90% of patients) “Normal metabolizer”	Initiate normal starting dose
Heterozygous	Intermediate Activity (10% of patients) “Intermediate metabolizer”	Initiate at 30-80% of full dose
Homozygous deficient	Low / Absent Activity (0.3% or 1 in 400 patients) “Poor metabolizer”	Initiate at 10% of full dose and administer 3 times per week

Dosing Recommendations based on NUDT15 Genotype		
NUDT15 Genotype	Activity	Recommended Starting Dose
Homozygous wild-type	Normal / High Activity “Normal metabolizer”	Initiate normal starting dose
Heterozygous	Intermediate Activity “Intermediate metabolizer”	Initiate at 30-80% of full dose
Homozygous deficient	Low / Absent Activity “Poor metabolizer”	6-MP: 10 mg/m <sup>2</sup> /day 6-TG: 25% dosing

#### IV. Relapsed ALL<sup>5,30</sup>

- A. Approximately 15-20% of children with ALL will relapse
- B. Isolated BM relapse (50-60% of cases)
- C. Extramedullary relapse
  1. Isolated – If < 5% leukemic cells in BM
  2. Combined – If ≥ 5% leukemic cells in BM
  3. Most common sites of extramedullary relapse are CNS & testicles
  4. Patients with t(1;19), large leukemic burden, T-lineage, and leukemic cells in the CSF at diagnosis are at increased risk of CNS relapse<sup>31</sup>
- D. Prognostic factors<sup>5,30</sup>
  1. Time to relapse
    - a. Early: < 18 months after initial diagnosis (poor prognosis)
    - b. Intermediate: 18 to < 36 months after initial diagnosis OR < 6 months after cessation of frontline treatment (intermediate prognosis)

- c. Late:  $\geq 36$  months after initial diagnosis OR  $> 6$  months after cessation of frontline treatment (favorable prognosis, event-free survival 50%)
  - 2. Site of relapse
    - a. Isolated extramedullary relapse and combined BM/extramedullary relapse both have better prognosis than isolated BM relapse
  - 3. Immunophenotype
    - a. T-cell accounts for  $\sim 15\%$  of relapses
- E. Treatment of relapsed ALL
  - 1. Re-induction therapy – may repeat original therapy if late BM relapse
  - 2. Clinical trial or novel chemotherapy agent/regimen not already utilized
  - 3. Targeted therapy
    - a. Blinatumomab<sup>32</sup>
    - b. Tisagenlecleucel<sup>33</sup> – FDA-indicated for relapsed ( $\geq 2^{\text{nd}}$  relapse) or refractory ALL in patients up to 25 years old
  - 4. Cranial irradiation is utilized in CNS relapse
  - 5. Allogeneic hematopoietic stem cell transplantation (HSCT)<sup>34</sup>
    - a. Allogeneic HSCT has been shown to improve survival in certain high-risk populations. No role for autologous transplant in pediatric ALL.
- F. ASTCT (American Society for Transplantation and Cellular Therapy) 2020 Recommendations for Role of Allogeneic HSCT in Pediatric ALL<sup>35,36</sup>:
  - 1. Patients in first complete remission (CR1)
    - a. Recommended if: primary induction failure with subsequent complete remission
    - b. Consider if: T-ALL, hypodiploid ALL, persistent MRD positivity
    - c. Ph+ ALL t(9;22): landscape is changing with use of intensive chemotherapy + TKIs; no clear advantage of early HSCT
  - 2. Patients in second complete remission (CR2)
    - a. Recommended if: Pre-B ALL with early BM relapse, T-ALL with BM relapse, or ALL with third or greater relapse
    - b. Consider if: late BM relapse, persistent MRD positivity
  - 3. Allogeneic HSCT is NOT recommended for patients who do not reach complete morphologic remission, as disease-free survival is  $<10\%$
  - 4. HSCT for patients with isolated extramedullary relapse remains controversial
- V. **Prognosis of ALL**<sup>37,38</sup>
  - A. Approximately 90% of children with ALL will be long-term survivors

1. Increased survival in recent decades is a result of prophylactic CNS therapy, intensification of treatment regimens, and improved patient risk stratification
- B. MRD at end of induction is the most important prognostic factor

**Patient Case #1, Continued Answer:**

**Correct Answer: D. 6MP decreased to 10% dosing three days per week**

SW's pharmacogenetic testing revealed normal activity of the NUDT15 enzyme with reduced activity of the TPMT enzyme. SW is homozygous deficient for TPMT, with a predicted phenotype of "poor metabolizer," and therefore is expected to have low or absent TPMT enzyme activity. With either significantly reduced or absent TPMT enzyme activity, SW is at risk for severe and potentially fatal myelosuppression if given thiopurines at normal doses. The recommended starting dose of 6MP for poor metabolizers is 10% of the full dose and administered only three times per week versus daily.

## CENTRAL NERVOUS SYSTEM TUMORS

### **Patient Case #2:**

PJ is a 2-year-old boy newly diagnosed with high-risk medulloblastoma. Surgical resection is performed which reveals classical pathology. Post-resection, there is minimal residual tumor ( $< 1.5\text{cm}^2$ ) remaining and he has no evidence of metastatic disease.

You are counseling PJ's parents about his planned course of multi-agent chemotherapy with cyclophosphamide, etoposide, cisplatin, vincristine and high-dose methotrexate. His parents have read that radiation is effective in the treatment of medulloblastoma and ask why this is not a planned component of treatment for PJ.

**What of the following is the most appropriate response to PJ's parents?**

- A. Radiation is reserved for anaplastic histology
- B. Radiation is reserved for relapsed medulloblastoma
- C. There is no benefit of radiation following complete surgical resection
- D. The risk of long-term neurocognitive toxicity

### **I. Medulloblastoma (MB)<sup>39-43</sup>**

- A. Most common malignant brain tumor of childhood
- B. Brain tumor located in the posterior fossa
  - 1. Small round blue cell tumor of the cerebellum
  - 2. Usually arises in the midline cerebellar vermis with variable extension into the 4th ventricle, cerebellar hemisphere, and brain stem
- C. Highly invasive, rapidly growing tumor
  - 1. All medulloblastomas are classified as WHO grade IV
  - 2. High rate of dissemination at diagnosis with subarachnoid seeding in 20–30% of patients
  - 3. Frequently metastasizes via CSF
- D. Genomics
  - 1. Recent clinical advances resulted in identification of 4 distinct MB subtypes which correlate with clinical features and prognosis
  - 2. Subtypes do not currently influence up-front MB treatment algorithm, but this is a very active area of continued research and future therapeutic targets

## E. Risk Estimation

### Medulloblastoma Risk-Stratification<sup>41,43,44</sup>

	<b>Average Risk</b> ( <b>ALL</b> criteria below must be met)	<b>High Risk</b> (Presence of <b>ANY</b> of the below factors)
<b>Age at diagnosis<sup>1</sup></b>	≥ 3 years	< 3 years
<b>Extent surgical resection</b>	< 1.5 cm <sup>2</sup> residual tumor	≥ 1.5 cm <sup>2</sup> residual tumor
<b>Extent of disease<sup>2</sup></b>	M0	M1-M4
<b>Pathology</b>	Not Anaplastic	Anaplastic

<sup>1</sup>Age < 3 years old are automatically treated as high risk due to required omission of up-front CNS radiation therapy (RT). RT may cause devastating neurocognitive outcomes in this age group.

<sup>2</sup>Non-metastatic disease (M0) is defined as no evidence of tumor seeding (subarachnoid or hematogenous metastasis), and CSF cytology must be negative for tumor cells. Metastatic disease (M1-M4) is automatically classified as high risk.

## F. Treatment<sup>39,41,43</sup>

### a. Surgery

- 1) Complete or near complete resection is of critical importance
- 2) Patients may develop cerebellar mutism syndrome (posterior fossa syndrome) post-resection.
  - a) Manifests as: delayed onset of speech, suprabulbar palsies, ataxia, hypotonia, emotional lability

### b. Radiation Therapy (RT)

- 1) Radiosensitive tumor; craniospinal irradiation (CSI) plus local boosts to posterior fossa/tumor bed are utilized to prevent local relapse
- 2) Associated with long-term adverse neurocognitive effects, especially in infants and young children (< 3 years)

### c. Chemotherapy

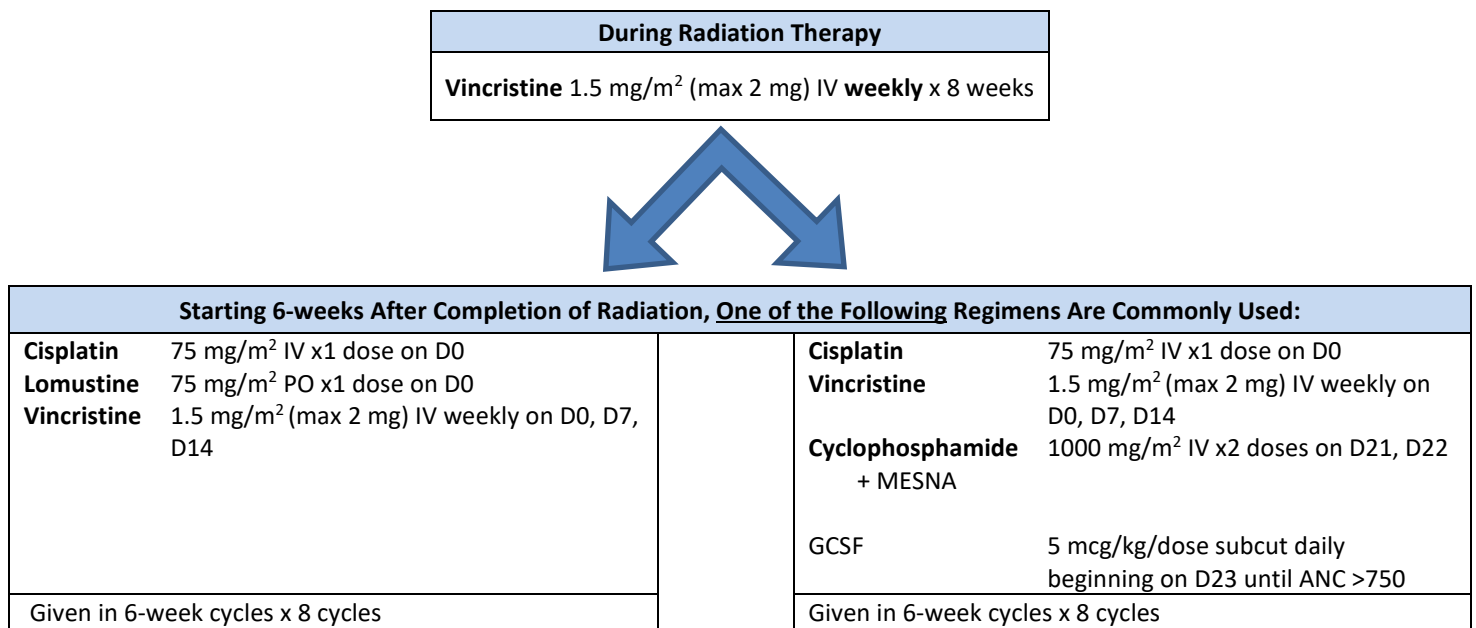
- 1) Standard treatment component for all patients, both for radiosensitization and for post-RT tumor treatment
- 2) Utilized as monotherapy in infants and young children to delay RT
- 3) Unclear if chemotherapy improves survival in average-risk patients, but it has allowed for dose-reduction of CSI in this patient group
- 4) Timing, combinations, and schedules of chemotherapy are not well standardized

## 2. Treatment for Children ≥3 years of age with Average Risk

- a. Overall Strategy: Surgery + “Reduced-dose” RT + Adjuvant Chemotherapy
- b. Surgery – Goal is gross total resection, if possible

- c. Radiation (Reduced Dose) - Initiate soon after surgery; best survival rates if initiated within 4-weeks post-surgery. Delays in RT are associated with worse prognosis<sup>45</sup>
- d. Chemotherapy
  - 1) Vincristine is administered weekly during RT
  - 2) Post-RT, two chemotherapy regimens have been studied, which have demonstrated similar outcomes in event-free survival. Clinically, either of these regimens may be used post-radiation.
    - a) Cisplatin, lomustine, and vincristine<sup>46,47</sup>
    - b) Cisplatin, vincristine, and cyclophosphamide<sup>48,49</sup>

#### Chemotherapy for Treatment of Medulloblastoma – Average Risk Patients<sup>48</sup>



3. Treatment for Children ≥3 years of age with High Risk<sup>50-52</sup>
  - a. Overall Strategy: Surgery + “Standard dose” RT + Chemotherapy -OR- High-dose Chemotherapy Plus Autologous Stem Cell Rescue
    - 1) Treatment strategies vary, and enrollment in a clinical trial is advisable<sup>43</sup>
  - b. Surgery – Goal is gross total resection, if possible
  - c. Radiation (Standard Dose) - Initiate after surgical resection
  - d. Chemotherapy - Agents used to treat average risk disease are the same to treat high risk, but optimal regimen is still unknown



## Treatment Regimen for Medulloblastoma – High Risk Children ≥ 3 Years Old

During Radiation Therapy	
Vincristine	1.5 mg/m <sup>2</sup> (max 2 mg) IV weekly x 6-8 weeks
Starting 6-weeks After Completion of Radiation:	
Vincristine Lomustine Prednisone (VCP) <sup>51</sup>	1.5 mg/m <sup>2</sup> IV weekly (max 2 mg) x 3 weeks 100 mg/m <sup>2</sup> PO on day 1 Prednisone 40 mg/m <sup>2</sup> PO x 14 days  Given as 6-week cycles x 8 cycles

- 1) High-dose chemotherapy plus autologous stem cell rescue<sup>53,54</sup>
  - a) Some studies have utilized high-dose chemotherapy (cisplatin, vincristine, high-dose cyclophosphamide) with autologous stem-cell rescue
  - b) Tandem high-dose chemotherapy with thiotepa and autologous stem cell rescue followed by CSI has also been evaluated, with 5-year EFS = 72%<sup>54</sup>
4. Treatment of Children < 3 years of age
  - a. Overall Strategy: Surgery + aggressive multi-agent adjuvant therapy ± autologous stem cell rescue. Therapeutic approaches attempt to delay or avoid the use of CSI due to adverse neurocognitive outcomes in this age group.
  - b. Surgery - Gross total resection remains paramount, as local control with radiation is omitted.
  - c. Chemotherapy
    - 1) Various regimens: cyclophosphamide, etoposide, cisplatin and vincristine ± HDMTX ± intrathecal or intraventricular chemotherapy
  - i. Relapsed Disease
    - a. Prognosis is poor, with 5-year survival ~25%
    - b. Local recurrence has more favorable outcomes than systemic recurrence
    - c. In children < 3 years who did not receive initial RT, radiation is often used as salvage
  - b. Prognosis<sup>41,53</sup>
    - a. 60%–80% survival is possible with aggressive surgery, radiation, and chemotherapy
      - 1) Average-risk patients ≥ 3 years – EFS ~83%
      - 2) High-risk patients ≥ 3 years – EFS ~70%
      - 3) High-risk patients < 3 years – EFS ~57%

- b. Patients with desmoplastic/nodular histology have superior prognosis
- c. Must consider adverse effects of aggressive treatment
  - 1) Disease and treatment-related morbidity (physical, psychological, etc.) are often significant and often exceed that of other pediatric malignancies

## 2. Astrocytomas<sup>55-58</sup>

- 1. Slow growing, indolent brain tumors (WHO class I & II) that very rarely undergo malignant transformation
  - a. This contrasts with adult low-grade gliomas which are more aggressive in nature
- 2. May be located anywhere in the CNS
  - a. Cerebellum is most common location, followed by cerebrum, deep mid-line structures, optic pathway, and brain stem (discussed in the following section)
  - b. Pilocytic astrocytoma is the most common pediatric low-grade glioma (LGG)
- 3. Treatment<sup>59</sup>
  - a. Surgery
    - 1) Cornerstone of LGG treatment; gross total resection is achieved in 60–80% of surgeries, which is largely influenced by tumor location
      - a) Cerebellar astrocytomas—often cured by surgical excision alone
      - b) Supratentorial midline tumors—resection may not be possible
    - 2) Management of incompletely resected tumors remains controversial
      - a) Can use “watch and wait” approach if there are minimal symptoms, otherwise proceed to adjuvant therapies (below)
  - b. Radiation
    - 1) Indication is controversial due to known radiation toxicities; typically reserved for patients who progress after surgery or who are symptomatic
    - 2) Avoid in children less than 5 years of age if possible due to adverse effects
    - 3) Improves local control and decreases rate of recurrence, but no known impact on survival
  - c. Chemotherapy<sup>60-63</sup>
    - 1) Similar to radiation, chemotherapy is reserved for patients with progressive or symptomatic disease after surgical resection; often chemotherapy is used before resorting to cranial irradiation
    - 2) Carboplatin + vincristine (CV) – most commonly used 1<sup>st</sup> line regimen
      - a) Allergic reactions occur in 10–40% of children receiving frequent carboplatin (typically delayed, median 8<sup>th</sup> dose)
        - i. Reactions vary: facial flushing, urticaria, agitation, abdominal pain, edema, and bronchospasm

- ii. Children with respiratory compromise should not be re-challenged. Some centers will cautiously re-challenge patients with grade 1-2 reactions or use desensitization protocols<sup>64</sup>

CV Regimen	
Induction	
Carboplatin Vincristine (CV)	175 mg/m <sup>2</sup> IV weekly x 4 weeks, then 2 weeks off, then weekly x 4 weeks 1.5 mg/m <sup>2</sup> (0.05 mg/kg if < 12 kg) IV weekly (max 2 mg) x 10 weeks  Administered x 1 cycle
Maintenance	
Carboplatin Vincristine (CV)	175 mg/m <sup>2</sup> IV weekly x 4 weeks 1.5 mg/m <sup>2</sup> (0.05 mg/kg if < 12 kg) IV weekly (max 2 mg) x 3 weeks  Administered x 8 cycles

- 3) Multi-agent regimen TPCV (thioguanine, procarbazine, lomustine, and vincristine)<sup>60</sup>

TPCV Regimen	
Thioguanine Procarbazine Lomustine Vincristine (TPCV)	30 mg/m <sup>2</sup> PO every 6 hours 12 doses Days 0-2 50 mg/m <sup>2</sup> PO every 6 hours x 4 doses Days 2-3 110 mg/m <sup>2</sup> PO x 1 Day 3 1.5 mg/m <sup>2</sup> (0.05 mg/kg if < 12 kg) (max 2 mg) IV Day 14 & Day 28  Administered x 8 cycles

- a. Regimen may be selected by the clinician based on toxicity and patient factors – CV (hypersensitivity, peripheral neuropathy) or TPCV (infertility, secondary malignancy, peripheral neuropathy)
- b. Weekly vinblastine (6 mg/m<sup>2</sup> with a maximum 10 mg/dose weekly for a total duration of 52 weeks) is an alternative for relapsed/refractory patients, or those with hypersensitivity to carboplatin<sup>65</sup>

#### B. Prognosis

1. Excellent long-term overall survival >85%
2. Low grade astrocytomas are often cured with surgical excision; overall 10-year survival rate of 69-100% with complete resection, 67-87% with incomplete resection, and 67-94% with incomplete resection and RT
3. Recurrences of low-grade tumors are often manageable with surgery and/or local RT as recurrence is usually local

### III. Brain Stem Gliomas<sup>66,67</sup>

- A. Heterogeneous group of tumors with differing growth rates and prognoses
- B. WHO classifies these tumors by location (not histology)
- C. Two primary subtypes
  1. Focal brainstem tumors ~20%
    - a. Most are low-grade and slow-growing

- b. Primary histology: low-grade astrocytoma, ganglioglioma
- c. Frequent locations: midbrain and medulla
- d. More favorable prognosis; 4-year OS up to 100%
- e. Genomics: Recent implication of BRAF mutation and subsequent MAPK activation<sup>68</sup>
- f. Treatment:
  - 1) Surgery
    - a) Goal to remove as much tumor as possible while preserving neurologic function.
    - b) Complete surgical resection is usually curative
    - c) Observation post-surgery is a viable treatment method
  - 2) Chemotherapy<sup>69</sup>
    - a) May be considered in patients who have symptomatic, progressive, or recurrent disease
    - b) Carboplatin with vincristine weekly (CV) has activity and stabilizes disease in up to 75% of patients
    - c) Thioguanine, procarbazine, lomustine, vincristine (TPCV) has also been studied
  - 3) Radiation
    - a) Often reserved as last-line option, after failure of chemotherapy due to radiation long-term adverse effects, especially since long-term survival rates are up to 100%

#### E. Prognosis

- 1. Prognostic factors
  - a. Positive: older age, absence of cranial nerve palsies, calcification on histology, neurofibromatosis type 1
  - b. Negative: age < 3 years, short duration of symptoms before diagnosis, early presentation of CNS palsies, mitosis on histology
- 2. Focal – Good prognosis if surgically accessible, +/- chemotherapy or radiation, survival = 90–100%
- 3. DIPG – Dismal outcomes, median survival < 1 year, 2-year survival = 10–20%

**Patient Case #2, Answer:**

**Correct Answer: D: Risk of long-term neurocognitive toxicity**

RJ will not receive radiation therapy due to his age of < 3 years. He is considered high risk because of his age, despite having otherwise favorable risk factors (<1.5cm<sup>2</sup> residual tumor, non-anaplastic histology and no metastatic disease). Patients < 3 years of age are not candidates for radiation therapy due to excess long-term toxicities, and thus are classified as high risk due to the omission of radiation therapy.

## NEUROBLASTOMA

### **Patient Case #3:**

MB is a 2-year-old male who presents to his primary care provider because his mother states that he has been constipated intermittently over the past three months. He is now refusing to eat, refusing to walk, and has lost weight. On physical exam, MB has a distended abdomen, abdominal tenderness, and a palpable mass.

After diagnostic work-up, MB is confirmed to have stage 4 neuroblastoma with metastatic disease, MYCN amplification, unfavorable histology, and diploidy.

### **What induction treatment is the most appropriate for MB?**

- A. Local control with surgical resection and radiation therapy
- B. Carboplatin, etoposide, cyclophosphamide, and doxorubicin plus local control with surgical resection and radiation therapy
- C. Cyclophosphamide, doxorubicin, vincristine (CAV) alternating with cisplatin/etoposide (P-VP) plus local control with surgical resection and radiation therapy
- D. Tandem autologous stem cell transplant

- I. Neuroblastoma (NB) is a solid tumor arising from neural crest cells, which presents as tumors along sympathetic nerve chains, most commonly abdominal tumors involving the adrenal gland. It has a unique and complex clinical pathogenesis, as some tumor subtypes spontaneously regress without intervention, while other subtypes are lethal despite multimodal treatment.
- II. Genomics: Clinically Relevant Genetic Findings<sup>70</sup>
  - A. MYCN amplification
    - 1. Oncogene amplified in approximately 20% of patients
    - 2. Amplification (defined as > 10 copies per diploid genome) is associated with advanced stage disease and a poor prognosis
  - B. Chromosome 11q loss of heterozygosity
    - 1. Present in 30-40% of patients
    - 2. Predicts poor prognosis
  - C. Chromosome 1p loss of heterozygosity or chromosome 17q gain are associated with a poor prognosis
  - D. Tumor DNA content (ploidy)
    - 1. Diploid (DNA index = 1)
    - 2. Hyperdiploid (DNA index >1) = favorable prognostic indicator
    - 3. Most useful as prognostic factor in locoregional disease
  - E. Sporadic ALK oncogene mutations—gene involved in nervous system development

### III. Treatment<sup>70,71</sup>

#### A. Modalities

##### 1. Surgery<sup>72</sup>

- a. Goals of surgery are to establish a diagnosis, excise tumor, determine degree of disease spread, and provide tissue for biologic testing
- b. Lymph node sampling is required
- c. Can be curative for localized disease
- d. Delayed primary (second look) surgery for high-risk patients is used to determine response and remove residual disease

##### 2. Radiation

- a. Radiosensitive tumor, but often not curable with radiation alone due to presence of metastatic disease and limitations of radiation adverse effects
- b. May be used in oncologic emergencies (spinal cord compression or loss of vision) or as palliative treatment
- c. <sup>131</sup>I-MIBG (metaiodobenzylguanidine) – Radio-conjugate therapeutic option for patients with relapsed or refractory NB.

##### 3. Chemotherapy

- a. Major treatment modality for patients with localized, unresectable disease or infants with disseminated disease
- b. Used in all but stage 1 or MS / 4S
- c. Older children with disseminated disease do not respond as well and are less likely to be cured with chemotherapy.
- d. Resistance to chemotherapy is a major barrier to improving survival in high-risk patients, leading to increasing regimen dose-intensity

Neuroblastoma Disease Characteristics and Treatment Strategies by Risk			
Low Risk	Intermediate Risk	High Risk	MS
Localized tumor	Localized tumor with locoregional LN involvement	Metastases to bone or bone marrow	Age < 18 months
Favorable histology		MYCN amplification	Liver, skin or bone marrow metastases
Hyperdiploidy	No MYCN amplification	Multimodal treatment (+immunotherapy)	Observation, likely to spontaneously regress
May be cured with surgery alone	Multimodal treatment		

- B. Treatment of **Low Risk Disease**<sup>73</sup>
1. International Neuroblastoma Staging System (INSS) Stage 1
    - a. Surgery alone is highly effective initial therapy, with OS 99%
    - b. Local recurrences can be managed with second surgery
    - c. Metastatic recurrences salvageable with chemotherapy
  2. INSS Stage 2
    - a. Surgery alone initial treatment of choice; 5-year OS 96%
- C. Treatment of **Intermediate Risk Disease**<sup>74</sup>
1. Heterogeneous group of patients
    - a. Mainly very young patients with metastatic disease or patients of all ages with large, unresectable primary tumors
    - b. Multimodal treatment, no standard chemotherapy regimen
- D. Treatment of **High Risk Disease**<sup>75</sup>
1. Low cure rate, aggressive therapy required
  2. Induction – Induce maximum reduction in tumor bulk at primary and metastatic sites
    - a. Cyclophosphamide / Doxorubicin / Vincristine + Cisplatin / Etoposide is a standard induction regimen example
    - b. Dose-intensity is thought to overcome chemotherapy resistance
    - c. Topotecan, an agent with activity in relapsed neuroblastoma, is now being incorporated in COG induction regimens

**Induction for High Risk Neuroblastoma**<sup>76</sup>

Cycles 1, 2, 4, 6	
Cyclophosphamide	2.1 gm/m <sup>2</sup> /day on days 1, 2 (with MESNA)
Doxorubicin	25 mg/m <sup>2</sup> /day IV as continuous infusion Days 1-3
Vincristine (CAV)	0.67 mg/m <sup>2</sup> /day IV as a bolus or continuous infusion Days 1-3 (max of 2 mg over 72 hrs)
Cycles 3 & 5	
Cisplatin	50 mg/m <sup>2</sup> IV Days 1-4
Etoposide (P-VP)	200 mg/m <sup>2</sup> IV Days 1-3

3. Local Control—Debulking of primary tumor
  - a. Occurs after 4-6 cycles of induction chemotherapy – delayed surgery increases rates of complete resection
  - b. Radiation therapy to eliminate local minimal residual disease after surgery



4. Consolidation—Eliminate resistant tumor clones
  - a. Two consolidation modalities have been studied:
    - 1) Intensive chemotherapy OR
    - 2) Myeloablative chemotherapy with autologous stem cell rescue
  - b. Based on growing body of supportive studies, **tandem autologous stem cell transplant is the preferred strategy for consolidation** in COG studies

**Patient Case #3, Answer:**

**Correct Answer: C. Cyclophosphamide, doxorubicin, vincristine (CAV) alternating with cisplatin/etoposide (P-VP) plus local control with surgical resection and radiation therapy**

For the treatment of high-risk neuroblastoma, MB's treatment should include Induction, Consolidation, and Maintenance phases. Induction will include chemotherapy such as CAV alternating with P-VP, plus local control with surgical resection and radiation therapy after hematopoietic stem cell transplant. Consolidation may include intensive chemotherapy or autologous transplantation. Based on the randomized clinical trial demonstrating improved overall survival, maintenance therapy should include anti-GD2 monoclonal antibody with GM-CSF, and isotretinoin.

**Patient Case #3, Continued:**

**MB has completed induction and consolidation therapy. He presents to clinic today to begin cycle 1 of maintenance immunotherapy with dinutuximab and GM-CSF. Which of the following statements most accurately describes the role of GM-CSF in this regimen?**

- A. Shorten the duration of neutropenia
- B. Potentiate antibody-dependent cell mediated cytotoxicity
- C. Decrease risk of dinutuximab-related infusion reactions
- D. Adjunct for pain management

5. Maintenance therapy—Goal to eradicate any residual tumor, prevent relapse
  - a. Isotretinoin
    - 1) Induces cellular differentiation and decreases proliferation of neuroblastoma cells
    - 2) Standard of care treatment for the last decade
  - b. Immunotherapy<sup>77,78</sup>
    - 1) Target: Glycolipid disialoganglioside (GD2), a surface glycolipid highly expressed by neuroblastomas (100%), gliomas, and some melanomas and sarcomas
      - a) GD2 expression in healthy tissues is limited to melanocytes, neurons, and peripheral sensory nerve fibers – responsible for some of the classic adverse effects of GD2-targeted antibodies

- 2) Anti-GD2 antibody: Dinutuximab<sup>79</sup>
  - a) Indicated in combination with GM-CSF, IL-2 and isotretinoin for treatment of high-risk neuroblastoma patients with at least a partial response to upfront therapy
    - i. Note: IL-2 removed from standard approach due to toxicity contribution without survival benefit<sup>80</sup>
  - b) Dose: 17.5 mg/m<sup>2</sup>/day IV infusion over 10 to 20 hours x 4 consecutive days for maximum of 5 cycles. Infusions should NOT last > 20 hours, even if the total dose has not been delivered.

#### Dinutuximab Supportive Care<sup>79</sup>

<b>Hydration</b>
<ul style="list-style-type: none"> <li>Normal saline 10 mL/kg IV infusion one hour prior to dinutuximab</li> </ul>
<b>Pre-medications as primary prophylaxis for hypersensitivity reactions</b>
<ul style="list-style-type: none"> <li>Diphenhydramine (0.5 to 1 mg/kg; maximum dose 50 mg) or other antihistamine IV over 10 to 15 minutes starting 20 minutes prior to infusion and every 4 to 6 hours as tolerated during the infusion</li> <li>Acetaminophen (10 to 15 mg/kg; maximum dose 650 mg) 20 minutes prior to infusion and every 4 to 6 hours as needed for fever or pain</li> </ul>
<b>Pain</b>
<ul style="list-style-type: none"> <li>Opioid therapy – should be used prophylactically as continuous infusion with bolus PRN</li> <li>Consider adjunctive agents for neuropathic pain</li> </ul>
<b>Miscellaneous</b>
<ul style="list-style-type: none"> <li>Albumin repletion to maintain albumin ≥ 3.0gm/dL to decrease risk of capillary leak</li> </ul>

#### **Patient Case #3, Answer:**

#### **Correct Answer: B – Potentiate antibody-dependent cell mediated cytotoxicity**

GM-CSF stimulates production of monocytes, macrophages and granulocytes. These effector cells help to mediate antibody-dependent cell mediated cytotoxicity. The Fc fragment of the dinutuximab monoclonal antibody binds the Fc receptors on these effector cells, which in turn engulf the bound tumor cell and destroy it.

- E. Treatment of Stage MS (also known as 4S)<sup>81</sup>
  1. Criteria for MS classification: patient < 18 months, metastases limited to skin, liver and / or bone marrow (< 10% malignant cells in BM)
  2. With favorable genetics (no *MYCN* amplification, no 11q aberration), most tumors spontaneously regress – observation is recommended
    - a. If respiratory compromise or other signs of organ dysfunction become evident, moderately intensive chemotherapy is indicated
    - b. RT should be reserved for life-threatening complications that progress despite chemotherapy

3. With unfavorable genetics (*MYCN* amplification or 11q aberration), patients should be treated as HR

VI. Prognosis<sup>72,82</sup>

A. Positive prognostic factors

1. Younger age at diagnosis (< 18 months), locoregional disease, hyperdiploidy, favorable tumor histology, normal *MYCN* copy number, complete resection of primary tumor

B. 5-year survival for infants is ~90% and ~55% for older children. It is important to note that newer treatment paradigms (especially immunotherapy) will likely improve these overall survival rates in the future

C. Survival based on risk group

1. Low risk—95%
2. Intermediate risk—80-90%
3. High risk— < 50%

## NON-HODGKIN LYMPHOMA

### I. Background/Overview<sup>83,84</sup>

- A. Diverse collection of lymphomas
- B. In children, non-Hodgkin lymphoma (NHL) is distinct from that of adults
  - 1. Adult lymphomas are more commonly low- or intermediate-grade
  - 2. Pediatric NHL is typically high-grade
    - a. Systemic disease with hematologic dissemination is similar to what is observed in leukemia (unlike Hodgkin lymphoma)
- C. If disease burden in the bone marrow is high, disease course and treatment is analogous to that of leukemia

Classification of Non-Hodgkin Lymphomas				
	<b>Burkitt Lymphoma</b> 40% childhood NHL	<b>Lymphoblastic Lymphoma</b> 30% childhood NHL	<b>Diffuse Large B-Cell Lymphoma</b> 10% childhood NHL	<b>Anaplastic Large Cell Lymphoma</b> 10% childhood NHL
Lineage	Mature B-cell	Precursor T-cell or B-cell	Mature B-cell	T-cell or null-cell
Treatment strategies	Short course and intensive multi-agent chemotherapy	ALL-type therapy with prolonged maintenance	Treated with intensive therapies similar to Burkitt lymphoma	Low-stage disease treated with short course chemotherapy  Advanced stage treated similar to Burkitt lymphoma / DLBCL
Survival	5 year EFS > 80%	5 year EFS ~90%	5 year EFS > 90%	5 year EFS 60-70%

## BURKITT LYMPHOMA

### **Patient Case #4:**

RG is a 6-year-old male presenting to the emergency department with intermittent vomiting and severe abdominal pain over the past month. A CT scan reveals an intraabdominal mass. RG is referred to a pediatric oncologist. Further work-up includes a biopsy of the mass which reveals small, non-cleaved cells. A PET scan identifies lymph nodes in the cervical region. RG is diagnosed with Burkitt lymphoma. CSF evaluation is positive for disease while bone marrow evaluation is negative for disease.

### **What chemotherapy treatment is most appropriate for RG to receive at this time?**

- A. A single reduction course followed by four cycles of multi-agent chemotherapy
- B. Two cycles of cyclophosphamide, vincristine, prednisone and doxorubicin without an initial reduction course
- C. A single reduction course followed by four cycles of multi-agent chemotherapy and maintenance therapy
- D. High-dose methotrexate and high-dose cytarabine without maintenance therapy.

### I. Genomics<sup>84</sup>

- A. Characteristic translocation of *C-MYC* oncogene with immunoglobulin production genes – most commonly t(8;14)

### II. Treatment Basics<sup>85-89</sup>

- A. Very high risk for tumor lysis syndrome (see Acute Leukemias materials for more information on Tumor Lysis Syndrome)
  - 1. Rapidly growing tumor, cell doubling time 24-48 hours<sup>90</sup>
  - 2. Reduction chemotherapy phase with low-dose cyclophosphamide, vincristine and prednisone is used for tumor de-bulking
    - a. Goal to decrease tumor burden by ~20%; mitigate risk of tumor lysis complications
  - 3. Prophylactic rasburicase may be used prior to starting reduction therapy
- B. Early dose-intensity is critical – short term, multi-agent chemotherapy
- C. Radiation and / or surgery do not play a major role in management
- D. Toxicity remains a significant problem – renal failure, infections, and mucositis are the most common non-hematological toxicities
- E. CNS-directed therapy
  - 1. Essential for all patients, including those without overt CNS involvement
  - 2. Prophylaxis
    - a. Combination of high-dose systemic therapy (methotrexate and cytarabine) and intrathecal therapy with methotrexate, hydrocortisone and cytarabine

- b. No current role for cranial radiation
3. Treatment of patients with CNS disease
  - a. Require additional intensive chemotherapy cycles
  - b. May benefit from higher doses of methotrexate
  - c. CYVE courses add high-dose cytarabine

#### Summary of Treatment Regimens for Burkitt Lymphoma<sup>91,92</sup>

Group	Characteristics	Principles of Treatment	Therapy (NOTE: Rituximab may be added in current protocols)
<b>Group A Low Risk</b>	<ul style="list-style-type: none"> <li>Completely resected stage I and abdominal stage II</li> </ul>	<ul style="list-style-type: none"> <li>With only local control and no systemic chemotherapy <math>\leq 20\%</math> of patients with localized disease will survive free of relapse<sup>93</sup></li> <li>No IT or HDMTX needed</li> </ul>	<b>COPAD x 2 cycles</b> (cyclophosphamide, vincristine, prednisone, doxorubicin)
<b>Group B Intermediate Risk</b>	<ul style="list-style-type: none"> <li>Multiple extra-abdominal sites</li> <li>Non-resected stage I and II, III, IV (marrow &lt; 25% blasts, no CNS disease)</li> </ul>	<ul style="list-style-type: none"> <li>Reduced-dose cyclophosphamide and elimination of maintenance is possible in selected patients based on FAB/LMB 96 study</li> </ul>	<b>COP</b> (cyclophosphamide, vincristine, prednisone) <b>COPADM x 2 cycles</b> (cyclophosphamide, vincristine, prednisone, doxorubicin, HDMTX) <b>CYM x 2 cycles</b> (cytarabine, HDMTX 5 g/m <sup>2</sup> )
<b>Group C High Risk</b>	<ul style="list-style-type: none"> <li>&gt; 25% blasts in marrow and / or CNS disease</li> </ul>	<ul style="list-style-type: none"> <li>Escalated dose of HDMTX and add high-dose cytarabine plus etoposide</li> <li>Includes maintenance</li> </ul>	<b>COP</b> (cyclophosphamide, vincristine, prednisone) <b>COPADM x 2 cycles</b> (cyclophosphamide, vincristine, prednisone, doxorubicin, HDMTX 8 g/m <sup>2</sup> ) *higher dose MTX than Group B <b>CYVE x 2 cycles</b> (high-dose cytarabine, etoposide) <b>Maintenance x 2-4 cycles</b>
<b>Abbreviations:</b> COP (cyclophosphamide, vincristine, prednisone) COPAD (cyclophosphamide, vincristine, prednisone, doxorubicin) COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, high-dose methotrexate) CYM (cytarabine, high-dose methotrexate) CYVE (high-dose cytarabine, etoposide)			

#### F. Treatment Response

1. Response at day 7 and after 2-3 courses of induction/consolidation chemotherapy are used for disease assessment based on LMB and BFM studies
  - a. Response at day 7 after COP of < 20% tumor reduction is a poor prognostic factor
  - b. Poor response or lack of CR after 2-3 cycles may result in intensification of therapy
2. Role of minimal residual disease (MRD) is not yet established and remains an area for further research<sup>94</sup>

- G. Rituximab<sup>95,96,97</sup>
1. Shown to be active in the management of adults with B-cell lymphoma and in some children with refractory or recurrent Burkitt lymphoma/B-ALL
  2. BFM incorporated rituximab in a non-randomized window therapy, prior to the delivery of conventional chemotherapy and confirmed the activity of single agent rituximab in pediatric Burkitt lymphoma
  3. Rituximab added to standard LBM backbone improved EFS (93.9% vs 82.3%) and OS (95.1% vs 87.3%)<sup>97</sup>

#### Burkitt Lymphoma Group B Treatment Example<sup>89</sup>

<b>Reduction (COP)</b> <ul style="list-style-type: none"> <li>• Reduction of tumor bulk</li> <li>• Permits management of metabolic complications</li> </ul>	Cyclophosphamide 300 mg/m <sup>2</sup> IV x 1 Vincristine 1 mg/m <sup>2</sup> IV x 1 (max 2 mg) Prednisone 60 mg/m <sup>2</sup> /day PO divided BID x 7 days
<b>Induction (COPADM)</b> <ul style="list-style-type: none"> <li>• Starts 1 week after COP begins (Day 8 of COP)</li> <li>• 2 courses</li> </ul>	Cyclophosphamide 250 mg/m <sup>2</sup> /dose IV q12h x 6 doses Vincristine 2 mg/m <sup>2</sup> IV x 1 (max 2 mg) Prednisone 60 mg/m <sup>2</sup> /day PO divided BID x 7 days, plus three day taper Doxorubicin 60 mg/m <sup>2</sup> IV after 1 <sup>st</sup> dose of cyclophosphamide Methotrexate 3 gm/m <sup>2</sup> IV over 3 hours with leucovorin rescue
<b>Consolidation (CYM)</b> <ul style="list-style-type: none"> <li>• 2 courses</li> </ul>	Cytarabine 100 mg/m <sup>2</sup> IV as continuous infusion x 5 days Methotrexate 3 gm/m <sup>2</sup> IV over 3 hours with leucovorin rescue

- III. Relapse<sup>83,98,99</sup>
- A. Relapses typically occur within 6 months to 1 year post-treatment
  - B. Prognosis is dismal in light of the fact that aggressive initial therapy was already exhausted
  - C. Multi-agent re-induction
    1. ICE ± R<sup>100</sup> (ifosfamide, carboplatin, etoposide ± rituximab)
    2. DECAL (dexamethasone, etoposide, cisplatin, cytarabine, and L-asparaginase)
    3. DHAP (dexamethasone, high-dose cytarabine, cisplatin)
    4. Novel targeted therapies (obinutuzumab, ibrutinib) +/- chemotherapy
  - D. Autologous HSCT<sup>101-103</sup>
  - E. CAR-T Cell Therapy
- IV. Prognosis<sup>84-86,89</sup>
- A. Advances in treatment strategies and molecular pathogenesis have increased event-free survival to >95% for low-risk (Group A) patients and >90% for higher-risk patients (Groups B & C).

**Patient Case #4, Answer:**

**Correct Answer: C. A single reduction course followed by four cycles of multi-agent chemotherapy and maintenance therapy**

RG would be classified as group C or high risk due to the presence of CNS disease. Group C therapy includes an escalated dose of high-dose methotrexate and high-dose cytarabine plus etoposide when compared to Group B or intermediate risk therapy. Group C patients will also receive a maintenance phase of therapy which Group A and B patients do not.



## WILMS TUMOR

### **Patient Case #6:**

SC is a 3-year-old male who presents to his pediatrician with a mass noted by his parents during his nightly bath. The mass seems to be mobile, as it is not always in the same location in the abdomen. SC does not have pain when the parents palpate the mass. His parents also note mild hematuria the day prior to the office visit. On physical exam, SC is noted to be mildly hypertensive, and an ultrasound reveals an encapsulated mass arising from the left kidney. SC is diagnosed with unilateral Wilms tumor, stage I disease of favorable histology with loss of heterozygosity at chromosomes 1p and 16q. He is stratified as having standard-risk disease.

**Which of the following characteristic classifies SC as standard-risk disease?**

- A. Unilateral disease
- B. Favorable histology
- C. Loss of heterozygosity at chromosomes 1p and 16q
- D. Age of 3 years old

### I. Genomics<sup>104-107</sup>

- A. Appears to result from functional loss of tumor suppressor genes, rather than activation of oncogenes
- B. *WT1* tumor suppressor gene is required for normal renal and gonadal development
  - 1. Deletion of *WT1*, isolated to chromosome 11p13 is present in 15-20% of patients
- C. Also associated with
  - 1. Deletion of *WT2*, a chromosomal aberration at 11p15
  - 2. Familial Wilms tumor loci (17q and 19q)
  - 3. TP53 mutations
- D. NWTs-V study<sup>108</sup> demonstrated that loss of heterozygosity (LOH) at both 16q and 1p in patients with favorable histology WT is an independent poor prognostic factor

### II. Prevention and Screening

- A. No established screening for general population
- B. Approximately 5% of Wilms tumors (WT) are associated with a pre-disposing genetic syndrome (>50 disorders have been implicated)
  - 1. Genitourinary tract abnormalities (cryptorchidism, gonadal dysgenesis)
  - 2. Congenital disorders (aniridia, hemihypertrophy)
  - 3. Predisposing syndromes
    - a. Beckwith-Wiedemann Syndrome (BWS)
    - b. WAGR (Wilms, aniridia, genitourinary abnormalities, mental retardation) - > 50% risk of developing WT

- c. Denys-Drash Syndrome - > 50% risk of developing WT
- d. National Cancer Institute recommends screening at least to the age of 7 in patients with genetic syndromes associated with increased risk

### III. Treatment<sup>109,110</sup>

#### A. Surgery<sup>111,112</sup>

1. May be performed up-front or after a few cycles of chemotherapy
  - a. Rationale for up-front: unaltered histologic and biologic staging, including lymph node involvement (recommended by COG)
  - b. Rationale for delayed: decreased risk of tumor rupture during surgery and lower post-operative staging (recommended by International Society of Pediatric Oncology - SIOP)
    - 1) Tumor spillage results in required whole abdomen RT
2. Inspection of peritoneal surface, liver, and lymph nodes
3. Biopsy of any suspicious lesions + lymph node sample
4. Avoid capsular rupture & tumor spillage if surgery is delayed

#### B. Radiation

1. Reserved for patients with stage III-IV disease, typically 1080 cGy to tumor bed
2. Whole abdomen RT is indicated when peritoneal seeding, spillage during surgery, or pre-operative rupture occurs
3. Patients with pulmonary metastases historically received whole lung irradiation
  - a. Recent data suggest that chemotherapy and surgery may be sufficient, and that only patients with persistent or recurrent nodules need radiation<sup>113</sup>
4. If pulmonary or whole abdominal radiation is required to treat metastases, doses and timing of dactinomycin and doxorubicin should be adjusted per protocol to reduce the risk of radiation dermatitis/radiation recall

#### C. Chemotherapy<sup>114-121</sup>

1. Chemotherapy is used for the majority of patients (excluding very low risk disease)
  - a. Vincristine, dactinomycin, doxorubicin, and cyclophosphamide (added for higher risk patients) are the most active agents
  - b. In relapse, ifosfamide, carboplatin, doxorubicin, and etoposide are utilized

D. Treatment by risk group according to NWTSG<sup>106,110,122</sup>

Very Low Risk	Low Risk	Standard Risk	Higher Risk	High Risk
Patients with all of the following: - Favorable histology - Age < 2 years - Tumor < 550g	Favorable histology PLUS at least one of the following: - Age ≥ 2 years - Tumor weight ≥ 550g - Stage II tumor infiltration	- LOH at chromosomes 1p and 16q in patients ≥ 2 years of age with otherwise favorable risk factors - Patients with stage III tumor infiltration with otherwise favorable risk factors	Favorable histology - LOH at 1p/16q plus stage III/IV tumor infiltration - Stage IV tumor infiltration with a lack of rapid response of lung nodes to initial therapy	Anaplastic histology - Includes all patients with unfavorable-risk histology tumors, regardless of patient age / stage / LOH
Nephrectomy followed by observation	EE-4A regimen (dactinomycin and vincristine)  No RT indicated	DD-4A regimen (dactinomycin, vincristine and doxorubicin) +/- local RT  (Stage I/II tumor infiltration dose not receive RT, stage III tumors receive RT)	DD-4A x 2 cycles with evaluation at week 6 - Patients with rapid resolution of lung nodules or no LOH will receive a total 9 cycles of DD-4A - All other patients escalated to regimen M (vincristine, dactinomycin, doxorubicin with addition of cyclophosphamide and etoposide) for 11 cycles	Treat per COG AREN0321  - Patients receive either DD-4A, Regimen I (cyclophosphamide, doxorubicin, vincristine, etoposide) + RT, UH-1 (cyclophosphamide, doxorubicin, vincristine, carboplatin, etoposide) + RT, surgery alone or window chemotherapy

**Wilms Tumor—EE-4A Regimen<sup>117</sup>**

<b>Dactinomycin</b>
0.045mg/kg/dose IV (max dose 2.3mg) If > 30kg – 1.35mg/m <sup>2</sup> /dose IV (max dose 2.3mg) Given at weeks 0, 3, 6, 9, 12, 15, and 18 <div>Total = 7 doses dactinomycin</div>
<b>Vincristine</b>
Weeks 1-10 (given weekly x 10 doses): 0.05mg/kg/dose IV (max 2mg) - If > 30kg – 1.5mg/m <sup>2</sup> /dose IV (max 2mg) Begin day 7 after nephrectomy (week 1) if peristalsis has been established  Weeks 12-18 (given weeks 12, 15, 18) 0.067mg/kg/dose IV (max 2mg) If > 30kg – 2 mg/m <sup>2</sup> /dose IV (max 2mg) <div>Total = 3 doses vincristine</div>

**Wilms Tumor—DD-4A Regimen<sup>117</sup>**

<b>Dactinomycin</b>
Weeks 1-25: Age < 1 year – Dactinomycin 0.023mg/kg/dose IV (max 2.3mg) Age ≥ 1 year – Dactinomycin 0.045mg/kg/dose IV (max 2.3mg)  Given weeks 1, 7, 13, 19 and 25 <div>Total = 5 doses dactinomycin</div>
<b>Vincristine</b>
Weeks 1-12 (weekly x 10 doses): Age < 1 year – 0.025mg/kg/dose IV (max 2mg) Age 1 – 2.99 years – 0.05mg/kg/dose IV (max 2mg) Age ≥ 3 years – 1.5mg/m <sup>2</sup> /dose IV (max 2mg)  Weeks 13-25 (every 3 weeks x 5 doses): Age < 1 year – 0.034mg/kg/dose IV (max 2mg) Age 1 – 2.99 years – 0.067mg/kg/dose IV (max 2mg) Age ≥ 3 years – 2mg/m <sup>2</sup> /dose IV (max 2mg) <div>Total = 15 doses vincristine</div>
<b>Doxorubicin</b>
Weeks 1-12 (given weeks 4 and 10): Age < 1 year – 1.5mg/kg/dose IV Age ≥ 1 year – 45mg/m <sup>2</sup> /dose IV  Weeks 13-25 (given weeks 16 and 22): Age < 1 year – 1mg/kg/dose IV Age ≥ 1 year – 30mg/m <sup>2</sup> /dose IV <div>Total = 4 doses doxorubicin</div>

1. Bilateral Wilms Tumor
  - a. Includes all patients with bilateral renal involvement (stage V disease), 10% of cases
  - b. Treated according to COG AREN0534, which aims to improve renal-sparing surgery and decrease recurrence rates by administering doxorubicin in addition to vincristine and dactinomycin for 6-12 weeks, followed by nephron-sparing surgery, and lastly risk-stratified adjuvant chemotherapy

IV. Prognosis<sup>106,107,110</sup>

- A. Overall excellent prognosis
  1. Localized disease OS = 90%
  2. Metastatic disease OS = 75%
- B. Positive prognostic Factors
  1. Favorable histology
  2. Localized, unilateral disease
- C. Poor prognostic factors
  1. Diffuse anaplasia histologic subtype
  2. LOH at chromosomes 1p and 16q
  3. Relapsed WT (including those with favorable histology)
- D. Late effects of WT remain problematic
  1. At 25 years after diagnosis, 25% of WT survivors have a grade 3–4 chronic condition
  2. Specific toxicities include doxorubicin-associated cardiac toxicity, pregnancy complications in women who received flank-irradiation, and secondary malignancies

**Patient Case #6, Answer:**

**Correct Answer: C. Loss of heterozygosity at 1p and 16q**

This patient otherwise has favorable risk factors and would be classified as low risk, however the presence of loss of heterozygosity at both 1p and 16q define this patient as standard risk. Loss of heterozygosity at 1p and 16q is an independent poor prognostic factor.

## EWING SARCOMA

### **Patient Case #7:**

SM is a 12-year-old male who presents to his pediatrician with persistent pain of his right leg. His parents originally attributed it to playing sports, but it has continued over the past few months. The physician palpates a mass in the right leg and orders a MRI which confirms the mass. Tumor biopsy confirms small, round, blue cells, identified as Ewing sarcoma. Fortunately, SM's work-up is negative for metastases.

### **Which of the following treatments is the most appropriate for SM?**

- A. Vincristine, doxorubicin, cyclophosphamide (VDC) alternating with ifosfamide/etoposide (IE) every 3 weeks
- B. Vincristine, doxorubicin, cyclophosphamide (VDC) alternating with ifosfamide/etoposide (IE) every 2 weeks
- C. Vincristine, doxorubicin, cyclophosphamide (VDC) every 3 weeks followed by autologous stem cell transplant
- D. Vincristine, topotecan, cyclophosphamide every 2 weeks followed by autologous stem cell transplant

### I. Genomics<sup>123-125</sup>

- A. t(11;22) is characteristic of the disease (85-95% of cases) and results in EWS-FLI1 gene fusion
  - 1. t(11;22) diagnostic for Ewing Sarcoma (ES)
  - 2. Tumors that lack this fusion usually have EWS gene joined to another related gene

### II. Treatment<sup>126-128</sup>

- A. Treatment of Ewing Sarcoma (ES) includes a multidisciplinary team approach with goal to preserve as much function as possible while obtaining complete local control and treating/preventing metastatic disease with systemic therapy.
  - 1. Surgery
    - a. Surgery is a critical component of multi-modal therapy, and the preferred method of local control (if feasible)
    - b. Historically radiation was preferred over surgery, but modern surgical techniques have increased limb-sparing surgeries and modern prosthetics have allowed for the resection of tumors involving essential bones
    - c. Goal of surgery is complete resection with wide margins
    - d. Tumor should be necrotic at the time of resection (due to neoadjuvant chemotherapy)
      - 1) Persistence of > 10% viable tumor cells at resection is associated with poor prognosis
    - e. During standard ES treatment, surgery is performed at week 13
  - 2. Radiation
    - a. ES is extremely radiosensitive, but use is limited by risk of radiation adverse effects such as secondary malignancy and local recurrence rates as high as 35%

- b. Typically reserved for patients with unresectable tumors, incomplete resections, or those opposed to aggressive surgery
  - c. Definitive radiotherapy involves 50-55 Gy to primary tumor with 2-cm margin, and should also include scars from surgery/biopsy
    - 1) Radiation doses greater than 60 Gy have been associated with an excess in secondary sarcomas (20% incidence)
  - d. There are no randomized trials of surgery vs. RT vs. surgery + RT; therefore, it is not known which modality of local control is superior.
3. Chemotherapy
- a. Neoadjuvant / adjuvant chemotherapy is standard of care for all patients, with or without measurable metastases
    - 1) Subclinical metastases are assumed to be present in nearly all patients; adjuvant chemotherapy required

Chemotherapy Evolution for Ewing Sarcoma	
IESS-I	<ul style="list-style-type: none"> <li>Indicated superiority of 4-drug VACD over 3-drug VAC</li> <li>Improved local control (96% vs 86%) and EFS (60% vs 24%)</li> <li>Demonstrated utility of doxorubicin → <b>VACD became standard</b></li> </ul>
IESS-II	<ul style="list-style-type: none"> <li>High-dose intermittent VACD vs low-dose continuous VACD</li> <li>5 year EFS improved with high dose intermittent VACD (77% vs 63%)</li> </ul>
INT-0091	<ul style="list-style-type: none"> <li>Investigated ifosfamide + etoposide alternating with VACD</li> <li>5 year EFS improved and overall survival (72% vs 61%) improved</li> <li>Marked decrease in local relapse led to improvement in outcome</li> </ul>
AEWS0031	<ul style="list-style-type: none"> <li>Interval compression: VDC-IE every 2 weeks vs VDC-IE every 3 weeks</li> <li>Compression provided increased dose intensity with no increased toxicity</li> <li>Improved OS and EFS → <b>VDC-IE every 2 weeks became standard</b></li> </ul>

\*VACD = vincristine, dactinomycin, cyclophosphamide, doxorubicin; VAC = vincristine, dactinomycin, cyclophosphamide; VDC-IE = vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide

#### Treatment of Localized Ewing Sarcoma: VDC-IE regimen<sup>129</sup>

Regimen	Drug	Dose	Week of Administration
VDC	Vincristine	1.5 mg/m <sup>2</sup> IV (max 2 mg) on Day 1	1, 5, 9, 15, 19, 23, 27
	Doxorubicin	37.5 mg/m <sup>2</sup> IV on Days 1 and 2	1, 5, 9, 15, 19
	Cyclophosphamide	1.2 gm/m <sup>2</sup> IV on Day 1	1, 5, 9, 15, 19, 23, 27
Alternating Every 2 Weeks with			
IE	Ifosfamide	1.8 gm/m <sup>2</sup> IV daily x 5 days with MESNA on Days 1-5	3, 7, 11, 17, 21, 25, 29
	Etoposide	100 mg/m <sup>2</sup> IV daily x 5 days on Days 1-5	3, 7, 11, 17, 21, 25, 29

- 2) Metastatic disease
  - a) Currently no standard of care, but may include high-dose chemotherapy with autologous stem cell rescue

**Patient Case #7, Answer:**

**Correct Answer: B. Vincristine, doxorubicin, cyclophosphamide (VDC) alternating with ifosfamide/etoposide (IE) every 2 weeks**

SM should be treated with interval-compressed therapy (every 14 days) based on the AEWS0031 protocol consisting of vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide. SM will also require local control with surgery and/or radiation therapy.

III. Prognosis<sup>128</sup>

- A. The most important prognostic factor is extent of disease at diagnosis (presence or absence of metastases)
  - 1. Localized disease at diagnosis – OS = 65-75%
  - 2. Metastatic disease at diagnosis – 5-year OS < 30%
    - a. Isolated pulmonary metastases have more favorable prognosis, 3-year OS up to 52%
  - 3. Poor prognostic factors:
    - a. Tumors of axial skeleton (reduced resectability)
    - b. Large tumor size – primary tumor volume > 200mL or maximal diameter > 8cm
    - c. Bone marrow involvement
    - d. Poor histologic response to neoadjuvant chemotherapy
    - e. Older age at diagnosis
    - f. Fever at presentation
    - g. Elevated LDH at presentation



## RETINOBLASTOMA

### **Patient Case #8:**

CH is a 2-year-old female who presents to the pediatrician with her mother, who states she is concerned about her daughter's left eye. The mother says that when she takes flash photographs of the child, her left eye appears white, while her right eye appears red. CH is otherwise asymptomatic. The pediatrician notes no extra-ocular findings on exam and makes CH an appointment with an ophthalmologist for an eye exam under anesthesia.

The pediatric oncologist completes CH's diagnostic work-up and she is found to have unilateral retinoblastoma measuring 4 mm with vitreous seeding within 2 mm of the tumor (intraocular International Classification of Intraocular Retinoblastoma (ICIR) group C disease).

**Which of the following is the most appropriate treatment for CH?**

- A. Focal therapy only
- B. External beam radiation
- C. Vincristine, etoposide, and carboplatin x 2 cycles
- D. Focal therapy and vincristine, etoposide, and carboplatin x 6 cycles

### I. Genomics<sup>130,131</sup>

- A. Familial tendency—Patients with germinal mutations have 45% chance of having a child with the disease; genetic counseling/testing is recommended
- B. Hereditary cases are associated with *RB1* gene mutation at chromosome 13q14
  - 1. First discovered tumor-suppressor gene
  - 2. Autosomal dominant inheritance
- C. Two-Hit Hypothesis<sup>130</sup>
  - 1. Two mutational events or “hits” produce malignancy
    - a. Hereditary RB (40% of cases):
      - a. Germ cell (*RB1* gene mutation) + somatic cell mutation
      - b. 85% develop bilateral disease; 15% develop unilateral disease
    - b. Non-Hereditary / Sporadic RB (60% of cases):
      - a. Somatic cell mutation + somatic cell mutation
      - b. More than 99% develop unilateral disease; rarely bilateral

### II. Prevention and Screening<sup>132,133</sup>

- A. At-risk children with a positive family history should undergo routine dilated funduscopy exams starting shortly after birth
- B. Frequency of exams is dependent on degree of risk and different algorithms have been proposed, but generally exams should occur monthly then gradually decrease in frequency, with screening lasting until at least 2-4 years of age

### III. Treatment<sup>131,134-136</sup>

- A. Treatment is individualized to preserve vision and maximize cure rates. Initial treatment strategies are defined by unilateral vs. bilateral involvement, disease extension (intraocular vs. extraocular), possibility of maintaining vision.
- B. Surgery
  - 1. Enucleation (surgical removal of affected eye) is necessary in patients when preservation of vision is not possible, such as those with tumor invasion into the anterior chamber, those with secondary glaucoma, or tumors occupying >75% of the vitreous space.
    - a. Now performed less frequently due to advancement of eye-sparing local and systemic treatments
- C. Focal therapy
  - 1. Utilized for small tumors (< 3 - 6 mm)
  - 2. Methods include: laser photocoagulation, cryotherapy
  - 3. Thought to be synergistic with chemotherapy
- D. Radiation
  - 1. Highly radiosensitive malignancy
  - 2. Plaque RT/brachytherapy (focal radiation)
    - a. Used for smaller tumors and for salvage
    - b. Radioactive implant is placed on sclera at center of tumor
    - c. Average treatment lasts 2-4 days
  - 3. External beam radiation therapy (EBRT)
    - a. Reserved for intraocular RB when conservative therapy has failed, for orbital disease, or for CNS/metastatic disease
    - b. Associated with an increased risk of second cancers
- E. Periocular & Intraocular Chemotherapy
  - 1. Provides high local drug concentration
    - a. Chemotherapy distribution into the vitreous cavity is highly variable when given intravenously
  - 2. Intravitreal or subtenon chemotherapy
    - a. Carboplatin and melphalan are most commonly used agents
    - b. Complications
      - i. Carboplatin diffusion into orbit tissue results in severe myositis; treat with systemic corticosteroids
      - ii. Optic neuropathy and fibroblastic proliferation further complicate subsequent enucleation, if needed

3. Intra-arterial (IA) chemotherapy
  - a. Local chemotherapy administration into ophthalmic artery via catheter placement in femoral or other artery
  - b. Maximizes penetration to retina and vitreous space and increases rate of globe salvage, while mitigating systemic toxicities
  - c. Most commonly used agents: melphalan, topotecan, carboplatin
  - d. Reported adverse effects include neutropenia, periocular edema, vasculopathy
  - e. Overall, IA chemotherapy results in prevention of enucleation in 70-80% of eyes
- F. Systemic Chemotherapy
  1. Indications
    - a. Intraocular disease with high-risk features (optic nerve involvement, significant choroidal infiltration > 3 mm, or a combination of features such as involvement of uvea, anterior chambers, or optic nerve<sup>137</sup>) requires systemic chemotherapy. This may include ICIR (International Classification for Intraocular Retinoblastoma) Group B-C eyes and Group D-E eyes as a means to prevent enucleation.
      - i. Patients who undergo enucleation and subsequent pathology reveals high-risk features also require systemic chemotherapy
      - ii. Bilateral disease patients often receive systemic chemotherapy in an effort to preserve vision
      - iii. ICIR Group A eyes do not require up-front systemic chemotherapy
    - b. Extraocular disease requires systemic chemotherapy
  2. Effective agents include: platinum compounds, etoposide, cyclophosphamide, doxorubicin, vincristine, and ifosfamide<sup>138-140</sup>
- G. Treatment of Extraocular Disease
  1. Orbital/locoregional disease<sup>141-143</sup>
    - a. Neoadjuvant chemotherapy, delayed enucleation, adjuvant chemotherapy and EBRT
    - b. Regimens include vincristine, cisplatin, cyclophosphamide, doxorubicin, or etoposide split with 2-3 cycles before surgery and 4-6 cycles post-operatively
    - c. Local control with EBRT (40-45 Gy) is a standard component of treatment
    - d. Screening for metastatic disease is paramount, as 30-40% of patients with locoregional disease will present with distant metastases
    - e. Cure can be achieved in up to 85% of patients
  2. Metastatic, No CNS Involvement
    - a. Very rare in developed countries

- b. Metastases may develop in the bone, bone marrow, and less commonly visceral organs
  - c. Previously poor outcomes with standard-dose systemic chemotherapy, which has improved with the use of myeloablative regimens
  - d. Induction chemotherapy such as vincristine, cisplatin, cyclophosphamide, etoposide
  - e. Consolidation with high-dose chemotherapy with autologous stem cell rescue
    - i. Chemotherapy agents vary, inclusion of thiotepa is hypothesized as improving outcomes due to CNS penetration, but data are lacking
  - f. Radiation therapy is sometimes used, not standardized
- 3. Metastatic, CNS Involvement
  - a. Very rare in developed countries
  - b. Platinum-based chemotherapy
  - c. Prognosis is dismal

#### IV. Prognosis<sup>17</sup>

- A. Local control can be achieved in 70-80% of patients
- B. More than 90% of children survive retinoblastoma itself, but the incidence of a secondary malignancy is 3-6%
  - 1. Frequently osteosarcoma within previous RT field
- C. Survival with useful vision decreases with higher intraocular staging
  - 1. Visual acuity is dependent on tumor location, with greatest reduction in tumors involving the macula
- D. Metastatic disease is still associated with a poor prognosis

# General Treatment Strategies for Retinoblastoma<sup>131,136,143,144</sup>

ICIR Group →	Treatment of Intraocular Disease				Treatment of Extraocular Disease		
	A	B	C-D	E	Orbital/ Locoregional	Metastatic	
Focal Therapy	yes	yes	Yes	enucleation may be unavoidable	enucleation after start of chemotherapy	Non-CNS based on intraocular staging	CNS based on intra-ocular staging
Intra-arterial Chemotherapy	only if progression	consider	consider	consider as salvage <sup>137</sup>	-	-	-
Systemic Chemotherapy	only if progression	yes, VC used commonly	yes, VEC used commonly	consider as salvage <sup>137</sup>	yes (neoadjuvant & adjuvant)	yes, as induction	yes
External-beam Radiation Therapy	only if progression	only if progression	if progression or high-risk features	not used post-enucleation for intraocular disease	yes	consider	consider
High-Dose Chemotherapy + Autologous Rescue	-	-	-	-	-	yes, as consolidation	consider
Approximate Rate of Globe Salvage	100%	100%	75-100%	30-36%	enucleation recommended	-	-
VC = vincristine, carboplatin x 8 cycles VEC = vincristine, carboplatin, etoposide x 6 cycles							

## Patient Case #8, Answer:

### Correct Answer: D. Focal therapy and vincristine, etoposide, and carboplatin

The patient has intraocular ICIR group C disease, and therefore should receive focal therapy (laser therapy, cryotherapy, etc.), and systemic chemotherapy. Systemic regimen of vincristine, etoposide, and carboplatin for at least 6 cycles has been successfully used, and is associated with significantly higher rates of globe salvage than only 2 cycles. Intra-arterial chemotherapy can also be considered. External beam radiation may be reserved as rescue therapy for non-responders.

## PEDIATRIC FEBRILE NEUTROPENIA

### **Patient Case #9:**

KM is a 7-year-old male with relapsed high-risk B-cell ALL receiving re-induction therapy with dexamethasone, vincristine, pegaspargase and daunorubicin. On day 6 of induction, KM becomes neutropenic with an ANC of 50 cells/mm<sup>3</sup>. The oncology team anticipates that KM may stay neutropenic through his 28 day induction cycle given his planned weekly doses of daunorubicin and high leukemic burden within his bone marrow at relapse.

### **Is KM a candidate for antibacterial prophylaxis with levofloxacin?**

- A. No, KM should not receive levofloxacin prophylaxis since it is not recommended in children younger than 10 years.
- B. Yes, KM should receive levofloxacin prophylaxis until his ANC recovers to greater than 500 cells/mm<sup>3</sup>.
- C. No, KM is not anticipated to experience prolonged neutropenia so is not a candidate for prophylaxis.
- D. Yes, KM should receive levofloxacin prophylaxis until his ANC recovers to greater than 1,000 cells/mm<sup>3</sup>.

- I. Febrile neutropenia (FN) is a medical emergency
  - A. Definition of FN in children is the same as utilized in adults
    - 1. Temperature  $\geq 38.3^{\circ}\text{C}$  once or  $\geq 38^{\circ}\text{C}$  sustained over 1 hour
    - 2. Neutropenia with ANC  $< 500$  cells/mm<sup>3</sup> or  $< 1000$  cells/mm<sup>3</sup> and a predicted decline
  - B. Differences in adult versus pediatric cancer patients<sup>145</sup>
    - 1. Higher percentage of acute leukemias and brain tumors in pediatric patients
    - 2. More intensive chemotherapy in pediatric protocols
    - 3. Physiologic differences
    - 4. Inability to communicate with young patients
- II. Treatment
  - A. Empiric IV antibiotics in High-Risk FN<sup>146,147</sup>
    - 1. Monotherapy with anti-pseudomonal  $\beta$ -lactam or carbapenem
    - 2. Reserve addition of second gram-negative antimicrobial or glycopeptide (i.e. vancomycin) for patients who are hemodynamically unstable, in whom there is a high clinical suspicion for a resistant organism, or for hospitals with a high rate of resistant pathogens
  - B. Outpatient management of low-risk FN<sup>147</sup>
    - 1. Low risk patient population not defined in pediatrics, left to institutions
    - 2. Consider unique challenges to oral antibiotic compliance in pediatric patients (palatability, cooperation, drug availability as an oral liquid, presence of mucositis or impaired gastrointestinal absorption)
    - 3. Management of pediatric febrile neutropenia in the outpatient setting is not common
  - C. Modification to empiric antibiotic therapy<sup>147</sup>

1. Discontinue duplicate gram-negative and/or empiric vancomycin therapy after 24-72 hours if there is no positive microbiologic culture requiring continuation of that agent
  2. Do not modify initial empiric therapy based on persistent fever alone if the patient is hemodynamically stable and well-appearing
  3. Escalate antimicrobial therapy if a child with persistent fever becomes clinically unstable
    - 1) Cover for resistant gram-negatives, resistant gram-positives, and anaerobic bacteria
- D. Discontinuation of empiric antibiotic therapy<sup>147</sup>
1. Discontinue antibiotics when ALL of the following criteria have been met:
    - 1) Evidence of bone marrow recovery (no specific ANC threshold recommended)
    - 2) Blood cultures are negative  $\geq 48$  hours
    - 3) Afebrile  $\geq 24$  hours
  2. Low-risk patients only (not defined in pediatrics): *Consider* discontinuation of empiric antibiotics at 72 hours if blood cultures are negative and patient is afebrile for  $\geq 24$  hours, even without marrow recovery
- E. Evaluating a patient's risk of developing invasive fungal disease (IFD)<sup>147</sup>
1. Patients at high-risk for invasive fungal disease
    - 1) Disease states: AML, high-risk ALL, relapsed acute leukemia, HSCT patients
    - 2) Other factors: Patients with prolonged neutropenia or receiving high-dose corticosteroids
- F. Empiric antifungal therapy in patients with prolonged fever  $\geq 96$  hours while on broad-spectrum antibiotics<sup>147</sup>
1. Unique recommendations for children at high-risk of fungal infection
    - 1) Do not use  $\beta$ -D-glucan testing in children for clinical decisions until further pediatric evidence has accumulated (not well validated in pediatrics)
    - 2) *Consider* CT of sinuses in children over 2 years of age (less clinical utility in young children)
  2. High-Risk Patients (for IFD): Initiate caspofungin or liposomal amphotericin-B at 96 hours of persistent fever while neutropenic

### III. Antibacterial Prophylaxis<sup>148</sup>

- A. Goal: Reduce the rate of bacteremia, bacterial infections and mortality
- B. Risk: Increased *Clostridioides difficile* infections, invasive fungal disease and antibiotic resistance
- C. Summary recommendations:
  1. Antibacterial prophylaxis should be considered in patients with AML and relapsed ALL receiving chemotherapy with anticipated ANC nadir to  $< 500$  cells/mm<sup>3</sup> for 7 days or longer
  2. Levofloxacin is preferred agent for antibacterial prophylaxis

3. Antibacterial prophylaxis should be stopped when ANC recovers to  $\geq 500$  cells/mm<sup>3</sup>

**Patient Case #9, Answer:**

**Correct Answer: B. Yes, KM should receive levofloxacin prophylaxis until his ANC recovers to greater than 500 cells/mm<sup>3</sup>.**

Levofloxacin prophylaxis is recommended in pediatric patients with AML or relapsed ALL receiving chemotherapy with an anticipated nadir of ANC  $< 500$  cells/mm<sup>3</sup> for at least 7 days. KM has relapsed ALL with a current ANC of  $< 500$  cells/mm<sup>3</sup> which is anticipated to persist through his induction block of therapy. Levofloxacin is the preferred agent for antibacterial prophylaxis in pediatrics.



## PEDIATRIC ACUTE CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

### **Patient Case #10:**

AM is a 3-year-old male with medulloblastoma being admitted for chemotherapy with cisplatin, lomustine and weekly vincristine.

**Which of the following prophylactic antiemetic regimens would be most appropriate for AM?**

- A. Aprepitant, dexamethasone and 5-HT<sub>3</sub> antagonist
- B. Fosaprepitant, dexamethasone and 5-HT<sub>3</sub> antagonist
- C. Aprepitant and 5-HT<sub>3</sub> antagonist
- D. Dexamethasone and 5-HT<sub>3</sub> antagonist

### **I. Acute Chemotherapy-Induced Nausea and Vomiting (CINV) in Children<sup>149-151</sup>**

- A. Younger age is a known risk factor for increased CINV in adult patients as well as female gender, history of motion sickness, anxiety, and lack of history of alcohol consumption
- B. Unfortunately, no patient-specific factors in children that increase risk of nausea and vomiting have been established
- C. Additionally, there are inadequate data to recommend any specific antiemetic regimen for delayed CINV, therefore it is important to note that the following information is for acute CINV only. Regimens for delayed CINV are generally extrapolated from adult data/regimens.

### **II. Emetic Risk According to Chemotherapy Drug**

- A. Defined by propensity of an individual or combination of chemotherapies to cause nausea/vomiting/retching in the absence of effective prophylaxis<sup>149,152</sup>
- B. Guideline for classifying acute emetic potential of chemotherapy agents in pediatric patients<sup>153</sup>
  - 1. Provides emetic risk allocation for single-agent and combination chemotherapy regimens, with notations for the clinician indicating which recommendations are supported by studies in children
  - 2. In cases where pediatric data are unavailable, adult data are used to inform recommendations

### **III. Multinational Association of Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO) Guideline for the Prevention of Acute CINV in Children<sup>154</sup>**

## Emetic Potential of Chemotherapies in Children<sup>153</sup>

Emetogenicity	Percentage of Patients Experiencing Emesis without Appropriate Nausea Prophylaxis	Associated Single-Agent Chemotherapies	
<b>High (HEC)</b>	>90%	Dactinomycin Carboplatin Carmustine >250 mg/m <sup>2</sup> Cisplatin Cyclophosphamide ≥1 gm/m <sup>2</sup> Cytarabine 3 gm/m <sup>2</sup> /dose	Dacarbazine Methotrexate 12 gm/m <sup>2</sup> Mechlorethamine Procarbazine (oral) Streptozocin Thiotepa 300 mg/m <sup>2</sup>
<b>Moderate (MEC)</b>	30–90%	Aldesleukin >12 to 15 million U/m <sup>2</sup> Amifostine >300 mg/m <sup>2</sup> Arsenic trioxide Azacitidine Bendamustine Busulfan Carmustine ≤250 mg/m <sup>2</sup> Clofarabine Cyclophosphamide <1 gm/m <sup>2</sup> Cyclophosphamide (oral) Cytarabine >200 mg to <3 gm/m <sup>2</sup> Daunorubicin Doxorubicin Epirubicin	Etoposide (oral) Idarubicin Ifosfamide Imatinib Intrathecal therapy (methotrexate, hydrocortisone, and cytarabine) Irinotecan Lomustine Melphalan >50 mg/m <sup>2</sup> Methotrexate ≥250 mg to <12 gm/m <sup>2</sup> Oxaliplatin >75 mg/m <sup>2</sup> Temozolomide (oral) Vinorelbine (oral)
<b>Low (LEC)</b>	10–30%	Amifostine ≤300 mg/m <sup>2</sup> Busulfan (oral) Capecitabine Cytarabine ≤200 mg/m <sup>2</sup> Docetaxel Doxorubicin (liposomal) Etoposide Fludarabine (oral) 5-Fluorouracil Gemcitabine Ixabepilone	Methotrexate >50 to <250 mg/m <sup>2</sup> Mitomycin Mitoxantrone Nilotinib Paclitaxel Paclitaxel-albumin Pemetrexed Teniposide Thiotepa <300 mg/m <sup>2</sup> Topotecan Vorinostat
<b>Minimal</b>	<10%	Many, please refer to guidelines for comprehensive list	

### IV. Acute Chemotherapy-Induced Nausea and Vomiting Pediatric Guideline [Supported by Pediatric Oncology Group of Ontario (POGO)]<sup>149,152,155</sup>

#### A. Updated in 2017

1. Expands the use of aprepitant to patients down to 6 months of age

2. Provides recommendations regarding the preferential use of palonosetron (over alternate 5-HT3-antagonists) in certain patient populations not able to receive dexamethasone as an antiemetic
- B. Developed by multi-disciplinary expert panel
- V. **Aprepitant**<sup>154,155</sup>
- A. Should be administered with all HEC nausea/vomiting regimens and MEC regimens not eligible for dexamethasone, according to the MASCC/ESMO and POGO guidelines
  - B. Of note, consider clinical significance of drug-drug interactions between aprepitant and chemotherapy
    1. If a concerning chemotherapy drug-drug interaction with aprepitant exists, guidelines recommend to omit aprepitant (there are no formal recommendations on which CYP3A4 metabolized chemotherapies this includes, it is left up to clinician discretion)
  - C. **FDA-labeled pediatric aprepitant dosing for the prevention of nausea/vomiting associated with highly or moderately emetogenic chemotherapy**<sup>156</sup>
    1. Children/Adolescents aged ≥12 years able to swallow aprepitant capsules:
      - a. Day 1 = 125 mg capsule PO x 1, 30 mins prior to chemotherapy
      - b. Day 2-3 = 80 mg capsule PO daily x 2 doses
      - c. If dexamethasone is co-administered, reduce corticosteroid dose by 50%
    2. Children aged 6 months to < 12 years (or patients unable to swallow aprepitant capsules):
      - a. Aprepitant oral suspension now commercially available for this population as 125 mg powder packets for suspension
      - b. Day 1 = 3 mg/kg PO x 1 (max: 125 mg/dose), 30 mins prior to chemotherapy
      - c. Day 2-3 = 2 mg/kg PO (max 80 mg/dose) daily x 2 doses
      - d. If dexamethasone is co-administered, reduce corticosteroid dose by 50%
  - D. Phase III randomized pediatric trial<sup>157</sup>
    1. Study in children 6 months–7 years (n=307) randomized to ondansetron ± aprepitant, and addition of dexamethasone was allowed
      - a. Aprepitant dosing (6 months to < 12 years) Day 1: Take 3 mg/kg PO x1, Days 2 & 3: Take 2 mg/kg PO daily
      - b. Complete response in the delayed phase was 51% in the aprepitant arm versus 26% in the control arm (P<0.001)
      - c. Author's conclusion: addition of aprepitant to ondansetron with or without dexamethasone is effective for the prevention of chemotherapy-induced nausea and vomiting in pediatric patients being treated with moderately or highly emetogenic chemotherapy
  - E. **Fosaprepitant IV**<sup>158</sup> – FDA approved in 2018 for prevention of nausea / vomiting associated with HEC and MEC in pediatric patients. Patients receiving single day HEC/MEC regimens may receive

fosaprepitant following dosing below on day 1. Patients receiving multi-day HEC/MEC regimens should also receive oral aprepitant on days 2-3 as outlined below.

1. Single day regimens, day 1:
  - a. Children 6 months (min 6 kg) – < 2 years: 5mg/kg (max 150mg) IV over 60min
  - b. Children 2 years - < 12 years: 4mg/kg (max 150mg) IV over 60min
  - c. Children 12 – 17 years: 150mg IV over 30min
2. Multi-day regimens:
  - a. Children 6 months (minimum 6 kg) – 12 years  
Day 1 – Fosaprepitant 3mg/kg (max 115mg) IV over 60min  
Day 2-3 –Aprepitant 2mg/kg (max 80mg) PO QD x 2
  - b. Children 12 -17 years  
Day 1 – Fosaprepitant 115mg IV over 30min  
Day 2-3 – Aprepitant 80mg PO QD x 2

F. IV aprepitant (Cinvanti™) is not FDA-approved for use in the pediatric population

#### **VI. Special Considerations Regarding the Use of Dexamethasone for CINV in Children<sup>149,152,154</sup>**

- A. Dexamethasone is routinely omitted from CINV prophylaxis in pediatric leukemia and brain tumor patients due to concern for:
  1. Interference with apoptosis in steroid-sensitive tumors
  2. Risk of fungal infections in leukemia populations
  3. Potential decrease of chemotherapy penetration across the blood-brain-barrier due to anti-inflammatory effects
  4. Risk of decreased efficacy of immunotherapeutic modalities due to impaired lymphocyte function and lympholytic effects

**Pediatric Acute Chemotherapy-Induced Nausea & Vomiting Guideline Recommendations:**

MASCC/ESMO 2016 Guidelines <sup>154</sup>	Pediatric Oncology Group of Ontario (POGO) 2017 Guideline Update <sup>155</sup>
<b>High Emetic Risk</b>	
Aprepitant (if > 6 months)  Dexamethasone (if permitted)  5-HT <sub>3</sub> antagonist	Aprepitant (if ≥6 months and no clinically significant drug-drug interaction with chemotherapy)  Dexamethasone (if no contraindications)  5-HT <sub>3</sub> antagonist <ul style="list-style-type: none"> <li>• If patient is receiving dexamethasone: administer granisetron, ondansetron, or palonosetron</li> <li>• If patient is NOT receiving dexamethasone: palonosetron preferred</li> </ul>
<b>Moderate Emetic Risk</b>	
5-HT <sub>3</sub> antagonist + Dexamethasone (if permitted)  <i>For patients who cannot receive dexamethasone:                      5-HT<sub>3</sub> antagonist + aprepitant</i>	Dexamethasone (if no contraindications)  5-HT <sub>3</sub> antagonist +/-aprepitant (if no dexamethasone) <ul style="list-style-type: none"> <li>• If patient is receiving dexamethasone: administer granisetron, ondansetron, or palonosetron + dexamethasone WITHOUT aprepitant</li> <li>• If patient is NOT receiving dexamethasone and is old enough to receive aprepitant (≥6 months): granisetron, ondansetron, or palonosetron WITH aprepitant</li> <li>• If patient is NOT receiving dexamethasone and is too young for aprepitant (&lt; 6 months): palonosetron (preferred 5-HT<sub>3</sub> antagonist) as monotherapy</li> </ul>
<b>Low Emetic Risk</b>	
5-HT <sub>3</sub> antagonist	5-HT <sub>3</sub> antagonist
<b>Minimal Emetic Risk</b>	
No routine prophylaxis	No routine prophylaxis

**Patient Case #10, Continued:**

**Correct Answer: C. Aprepitant and 5-HT<sub>3</sub> antagonist**

Since cisplatin is highly emetogenic, AM should receive antiemetics appropriate for highly emetogenic chemotherapy regimens. As AM is being treated for a CNS malignancy, medulloblastoma, he should not receive dexamethasone as an antiemetic due to dexamethasone's potential to decrease chemotherapy penetration of the blood brain barrier. For patients receiving highly emetogenic chemotherapy unable to receive dexamethasone, guidelines recommend utilization of aprepitant and a 5-HT<sub>3</sub> antagonist (palonosetron preferred by the POGO guidelines in this setting).

## PEDIATRIC INFORMED CONSENT

### **Patient Case #11:**

AJ is a 12-year-old female with newly relapsed rhabdomyosarcoma. The oncology team is reviewing the diagnosis and treatment options with AJ and her parents. Unfortunately, AJ's prognosis is poor and there is no standard of care. The team informs the family of an open clinical trial of a new targeted investigational agent for which AJ would qualify. The clinical trial is an excellent match for AJ based on the genetic profile of her tumor and her team is optimistic she may have a good response.

**What consent from the family would be required to enroll AJ on study?**

- A. Assent from the child and permission from both parents
- B. Assent from the child and permission from one parent
- C. Permission from both parents
- D. Permission from one parent

### **I. Principles of Informed Consent<sup>159,160</sup>**

- A. Informed consent is a course of dialogue between a clinician and a patient/patient's surrogate about a proposed course of action. After this discussion, if the patient/patient's surrogate voluntarily agrees to participate in the therapeutic plan as outlined, he/she provides informed consent.
- B. Informed consent is based around the principle of patient autonomy, the right of an individual to make decisions based on his or her own reason and agency
- C. It was originally developed following the Nuremberg trials in the 1940's after World War II, surrounding distrust in doctors and violation of research ethics
- D. Founding ethical principles of informed consent:
  - 1. Beneficence
  - 2. Justice
  - 3. Respect for autonomy
- E. Serves 3 Purposes:
  - 1. Discloses information to patients or their representative
    - a. Protects and communicates health-related interests
    - b. Involves and engages the patient/family in the medical decision-making process
  - 2. Allows the practitioner to assess the patient or their representative's capacity for medical decision-making and their comprehension of the disclosed information
  - 3. Provides an opportunity to obtain consent/voluntary agreement before treatment
- F. Content to be Discussed During Informed Consent
  - 1. Variable, but coinciding, recommendations/definitions exist<sup>160</sup>
    - a. What an experienced physician would tell his or her patients

- b. The information which a “reasonable person in the patient’s condition would need and want to know”
    - c. “What a particular patient would need to know to make a decision to evaluate the extent of disclosure”
  - 2. In general, this includes discussion of the following: nature of the medical diagnosis, aspects of the suggested treatment, disclosure of the risks, probability of success, anticipated benefits, risks of potential alternative treatments (including no treatment)
    - a. There is some variation in the specific requirements between states
  - 3. Professionalism, transparency, and honesty are key
  - 4. Patient/patient’s surrogate should be assured that they have liberty to make their own decision in this matter, and that his/her choice should be made without coercion, pressuring, or manipulation
- G. Individuals who can participate in informed consent discussions:
  - 1. Physician or health care provider of record
  - 2. Patient/patient’s surrogate
    - a. In order for an individual to give their informed consent he/she must have both of the following:
      - 1) Legal authority to do so
      - 2) Confirmed capacity to understand medical information and process medical decisions, as assessed by the provider

## II. Informed Consent in the Pediatric Setting<sup>159,160</sup>

- A. Minors in the health care system are most commonly defined as patients < 18 years of age
- B. Minors often lack the ability to act autonomously and/or the capability to make informed decisions regarding medical care
- C. Definitions: Assent vs. Consent
  - 1. Consent – voluntary agreement
  - 2. Assent – affirmative agreement (of the child), which is usually coupled with informed permission of the parent/patient’s surrogate
  - 3. Dissent – refusal
- D. Obtaining assent for medical care from children
  - 1. Generally defined as the parents/patient’s surrogate obtaining the minor’s “informed permission” for medical care, through the following talking points:
    - a. Aiding the child in understanding the nature of his/her diagnosis
    - b. Stating what the child can expect with the tests and treatments
    - c. Assessing his/her understanding
    - d. Soliciting an expression of the child’s willingness to accept the treatment plan

2. Children should not be asked for assent for required treatments, such as those that must occur with or without the child's assent. Minors should not be deceived that they have a choice in matters where there is no option to choose.
  3. The parent/patient's surrogate is the final decision-maker, not the child.
    - a. If the benefits of a treatment outweigh the risks/burdens, the parent can opt for a treatment plan even if the child expresses dissent.
  4. Dissent is more meaningful when it concerns a procedure or therapy which can be changed or deferred without incurring substantial harm/risk
- E. Strategies for providing conformed consent in pediatrics
1. Guided by the same moral and ethical principles as informed consent in adult patients (beneficence, justice, respect for autonomy)
  2. Autonomy must be respected in non-traditional ways, such as the respect for parental authority in health care decision-making, respect for the family as a unit, and respect for the child's emerging autonomy
  3. Language used by the pediatrician must be appropriate for the developmental status of the child or adolescent, and bear in mind educational maturity, language barriers, and severity of illness sensitivities, as are also necessary in dialog with adult patients
  4. If the patient and the surrogate make a medical decision that places the patient at substantial risk of significant harm, it is the physician's moral and legal responsibility to contest this choice
- F. Children/Adolescents as Health Care Decision-Makers
1. There is no concrete age definition or otherwise for when a child or adolescent becomes mature enough to make their own medical decisions including informed consent or dissent
  2. There is significant value in involving minors in their own medical decision-making, such as fostering empowerment and supporting adherence with the selected therapy
  3. Factors to consider in evaluating a minor's readiness to be involved in medical decision-making: cognitive facilities, maturity of judgement, and moral functioning
  4. Adolescents
    - a. Circumstances under which a minor can legally make his/her own medical decisions
      - 1) "Mature Minor" Exception
        - a) Mature minor doctrine establishes that minors with sufficient maturity and mental capacity as confirmed by judicial determination may make their own medical decisions
      - 2) Legal Emancipation
        - a) Addresses legal status (not decision-making ability), but also results in allowing adolescents to consent for their own medical care



- b) Adolescents who are married or self-supporting and live independently from their parents or are active duty in the military are usually considered legally emancipated
  - 3) For adolescents who are parents, these young parents are automatically given authority to give informed consent for his/her child's health care, even if they are not legally able to make medical decisions regarding their own health
- G. Emergency Situations
  - 1. Informed consent is not required when urgent/emergent treatment of a minor is required to prevent imminent and significant harm
- H. Legal facilitation should be reserved for situations that cannot be solved by other means

**Patient Case #11, Answer:**

**Correct Answer: D. Permission from one parent**

AJ has potential to receive significant benefit herself by receiving this agent which is not available outside of the clinical study. Since AJ does have the prospect of direct patient benefit, permission would be required from one parent without assent from the child. If there was no prospect of direct benefit to AJ, then it would require assent from her as well.

**III. Surrogate Decision-Making<sup>159,160</sup>**

- A. Adults
  - 1. Surrogate decision making is implemented when the patient has lost his/her capacity to make his/her own medical decisions
  - 2. Implements **substituted judgement**— in which a family member or other patient's surrogate acts on his/her knowledge of the patient's own wishes, in a sense, "substituting" in his/her discernment of the patient's wants
- B. Pediatrics
  - 1. Substituted judgement is **not** often utilized in pediatrics because children and adolescents have seldom verbalized their own wishes regarding end-of-life care, and may not have developed a level of maturity or understanding in which they can express core values and goals of care in the capacity of that of an adult
  - 2. Instead, there are several standards which provide framework for parents to act as surrogate decision makers for their children

## Pediatric Standards/Methods of Surrogate Decision Making<sup>159,160</sup>

<b>Best-Interest Standard</b>
<ul style="list-style-type: none"> <li>• Parent/surrogate maximizes benefits and minimizes harms to the child</li> <li>• Parent maintains a holistic perspective on the patient's care while maximizing the benefit-to-burden ratio</li> </ul>
<b>Constrained Parental Autonomy</b>
<ul style="list-style-type: none"> <li>• Parent/surrogate balances the child's best interests with the family's best interests, as long as the child's basic needs are still being fulfilled</li> <li>• Recognizes the child's basic needs, with medical care being one facet of that</li> </ul>
<b>Shared, Family-Centered Decision-Making</b>
<ul style="list-style-type: none"> <li>• Open, shared communication between the family and the medical team</li> <li>• Family discusses the goals of care with the medical team so that a treatment strategy is established to meet those goals</li> </ul>
<b>Harm Principle</b>
<ul style="list-style-type: none"> <li>• Establish a threshold below which parental decision-making will not be tolerated and outside intervention is necessary to protect the minor</li> <li>• More useful when there is a concern for the minor's safety</li> </ul>

## IV. Consent for Research Purposes<sup>161,162</sup>

- A. Established on the idea of respect for persons, as in Belmont report from 1978 published by National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- B. Differs from the clinical setting - Informed consent from the parent AND assent from the child is required by federal guidelines
  1. Federal guidelines are not specific regarding at what ages assent must be attained or how, therefore local IRB's have different standards
- C. Child has the right to refuse participation in research; Dissent from the child means that the patient should not be enrolled in the protocol
  1. **Exception:** If the research is thought to provide significant benefit to the patient and is not available outside of the research setting
- D. Federal Guidelines from the U.S. Department of Health & Human Services: Protection of Human Subjects – Title 45 Code of Federal Regulations Part 46, Subpart D<sup>163</sup>
  1. Requires the assent of children prior to participation in research protocols, and allows the IRB to consider age, maturity level, and psychological state of the children in determining which are capable of assent
  2. Establishes standards on how many parents must provide permission before enrolling the child on a research protocol
- E. NIH Guidelines for Assent in Children in Research Studies<sup>164</sup>
  1. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research & The American Academy of Pediatrics recommend obtaining assent for all children ≥7 years old

**Federal Assent/Consent Requirements for Children Participating in Research from The Department of Health & Human Services<sup>163,164</sup>**

Study Risk/Benefit Level	Additional Protocol Requirements	Assent from the Child Required?	Permission from the Parent(s) Required?
<b>No Greater than Minimal Risk</b>	<ul style="list-style-type: none"> <li>None</li> </ul>	<b>YES</b> <i>Exception: If the research is thought to provide significant benefit to the patient and is not available outside the research setting, assent not required</i>	YES – ONE PARENT
<b>Greater than Minimal Risk with Prospect of Direct Patient Benefit</b>	<ul style="list-style-type: none"> <li>Risk must be justified by the anticipated benefits</li> <li>Anticipated benefit must be at least as promising to the patient as treatment alternatives</li> </ul>	<b>YES</b> <i>Exception: If the research is thought to provide significant benefit to the patient and is not available outside the research setting, assent not required</i>	YES – ONE PARENT
<b>Greater Than Minimal Risk with <u>NO</u> Prospect of Direct Patient Benefit</b>	<ul style="list-style-type: none"> <li>Must be likely to generate universal knowledge regarding the diagnosis</li> <li>The risk must be only a minor increase over minimal risk</li> <li>Intervention experience must be reasonably comparable to the patient's expected medical, dental, psychological, social, or educational situations</li> </ul>	<b>YES</b>	YES – <b>BOTH PARENTS</b>
<b>All Other Research</b>	<ul style="list-style-type: none"> <li>Must provide opportunity to prevent, understand, or treat a serious problem affecting children's health</li> <li>Must be conducted in accordance with sound ethical principles</li> </ul>	<b>YES</b>	YES – <b>BOTH PARENTS</b>

**VI. Ethical Issues**<sup>159,160</sup>

- A. For adolescents with chronic illnesses who refuse further life-sustaining treatment, shared communication and collaboration between the patient, family, and health care team is paramount
- B. Involvement of supportive consulting teams such as palliative care, ethics, psychology, or chaplain services should be sought
- C. Legal facilitation should be reserved for situations that cannot be solved by other means

## PEDIATRIC COMPASSIONATE USE

### I. Overview and Definitions<sup>165</sup>

- A. Compassionate use is defined as access to investigational therapies outside of a clinical trial
- B. Similar terms: Expanded access, single patient investigational new drug (IND), temporary authorization for use
- C. FDA defines Expanded Access as “a potential pathway for a patient with an immediate life-threatening or serious disease to gain access to an investigational medicinal product for treatment outside of a clinical trial when no comparable or satisfactory alternative therapy options are available.

### II. Three types of expanded use programs<sup>165</sup>:

- A. Individual patient (single patient IND) – request for an individual patient, may be emergency use
  - 1. Most common
- B. Intermediate-size population – drug sponsor opens an intermediate-size IND when anticipating more than 10 patients will receive the drug via compassionate use
- C. Widespread treatment use (treatment IND) – used for late-stage products

### III. Pediatric Focus

- A. Compassionate use is especially important for pediatric patients
  - 1. Relatively few cancer drugs are approved specifically for pediatrics
  - 2. Adult studies typically completed before pediatric studies initiated
  - 3. Even with no prior data in pediatrics, drugs may be considered for compassionate use in a pediatric patient if the patient has a potential to experience benefit from the medication based on a unique mechanism of action
- B. Practical pediatric considerations
  - 1. Formulations – younger patients may not be able to swallow intact tablets / capsules, potential lack of data on crushed / suspended drug or tube administration
  - 2. Dosing – consider pharmacokinetic differences in patients younger than 2 years old, data often lacking
  - 3. Pediatric-specific toxicity – consider effects on growth and development

### IV. Single Patient IND Process<sup>165</sup>

- A. Physician contacts drug sponsor. If the company agrees, they submit a Letter of Authorization to the FDA. Participation by the sponsor is voluntary, sponsors have no obligation to provide drugs for compassionate use.
- B. Physician contacts the FDA and fills out Form 3926, which includes patient-specific information. The FDA reviews the application and provides authorization.
- C. Physician obtains IRB approval and informed consent from the patient / family.

## PEDIATRIC SURVIVORSHIP

### **Patient Case #13:**

JM is a 34-year-old female long-term survivor of Hodgkin lymphoma (treated when she was 17 years of age) who received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) therapy, along with radiation to the chest. Her total cumulative doxorubicin dose = 300 mg/m<sup>2</sup>.

**According to the Children's Oncology Group (COG) Long-Term Follow-Up Guidelines, how often should JM have an echocardiogram?**

- A. Every year
- B. Every 2 years
- C. Every 3 years
- D. Every 5 years

### **V. Overview and Scope of the Issue<sup>166-168</sup>**

- A. Advances in the treatment and supportive management of pediatric malignancies have resulted in increased OS of these children to approximately 80-85%<sup>169</sup>
  - 1. Subsequently, >360,000 childhood cancer survivors (or approximately 1 in every 530 young adults) are currently living in the US today<sup>169,170</sup>
- B. Unfortunately, after achieving cure, many (two-thirds) of adult survivors of pediatric cancer will suffer from long-term health conditions and toxicities of cancer treatment
  - 1. Examples include ocular, auditory, cardiovascular, renal, endocrine, reproductive, neurocognitive, nervous system, or mental health complications, among others
  - 2. May have resultant effects on quality of life<sup>171</sup> as well as late morbidity and mortality<sup>170</sup>
- C. Incidence of late-onset complications increases with higher treatment intensity
  - 1. Consider treatment modality, dose of medication or radiation, age at the time of treatment, concomitant therapies, etc.
  - 2. Modern risk-adaptive treatment regimens reserve intensive therapy for high-risk groups, and de-escalate therapy if possible, in low-risk groups while maintaining cure rates
- D. Increase in population of pediatric cancer survivors has created need for appropriate follow-up care and monitoring

### **VI. Childhood Cancer Survivor Study (CCSS)<sup>172-174</sup>**

- A. One of the first multicenter, comprehensive data pools for collecting and reporting long-term health outcomes of pediatric cancer survivors
- B. Retrospective cohort study based on patient-completed 289-item questionnaires<sup>173</sup>
- C. Two groups of study participants:
  - 1. Survivors diagnosed before 21 years of age, between 1970–1986, who have survived for at least 5 years after cancer treatment

2. Siblings of the survivors
  - D. CCSS reported high rate of chronic health conditions in adult survivors of pediatric cancers<sup>173</sup>
    1. 10,397 survivors and 3034 siblings were included in the initial publication
    2. Survivors demonstrated a high risk of chronic conditions, especially cardiovascular disorders, renal impairment, secondary malignancies, endocrinopathies, and musculoskeletal disorders
    3. Overall, 62% of survivors suffered from a chronic health condition and 28% had a grade 3-4 chronic condition, compared to their siblings which had 37% and 5%, respectively
    4. Female survivors had higher incidence of chronic conditions, and were 1.5 times more likely to have a condition  $\geq$  grade 3
    5. Malignancies associated with highest risk of chronic condition included bone tumors, CNS tumors, and Hodgkins lymphoma
- II. The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG-LTFU Guidelines) Version 5.0<sup>175-177</sup>**
- B. Risk-based, exposure-related clinical practice guidelines for screening and management of late effects resulting from therapeutic exposures used during treatment for pediatric malignancies
  - C. Consensus recommendations from a panel of experts on multidisciplinary task forces
  - D. Initially released in 2003; Current guideline - version 5.0 updated October 2018
  - E. Goal is to increase quality of life and decrease complication-related healthcare costs for pediatric cancer survivors by providing standardized and enhanced follow-up care throughout the lifespan that:
    1. Promotes healthy lifestyles
    2. Provides for ongoing monitoring of health status
    3. Facilitates early identification of late effects
    4. Provides timely intervention for late effects
  - F. Screening of patients using COG-LTFU guidelines should begin two or more years after completion of cancer therapy
- VII. Significant Late Complications of Cancer and Cancer Treatment**
- A. **Neurologic Late Effects**
    1. Report from the CCSS<sup>178</sup> regarding late-occurring neurological sequelae
      - a. Studied 4,151 adult survivors of pediatric ALL
      - b. Median time to follow-up since ALL diagnosis was 14.1 years
      - c. 65% of the survivors received cranial radiation and 94% received IT chemotherapy
      - d. Survivors, when compared to sibling controls, were at increased risk for late-onset auditory-vestibular-visual sensory deficits (rate ratio (RR), 1.8; 95% CI, 1.5 to 2.2), coordination problems (RR, 4.1; 95% CI 3.1 to 5.3), headaches (RR, 1.6;

95% CI, 1.4 to 1.7), motor problems (RR, 5; 95% CI 3.8 to 6.7), and seizures (RR, 4.6, 95% CI; 3.4 to 6.2)

#### Late Effects in Pediatric Survivors - Neurocognitive Defects

Neurocognitive Defects Associated with Chemotherapy <sup>175</sup>	
Associated with: High-dose cytarabine, methotrexate	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• Age &lt; 3 years at time of treatment</li> <li>• Females</li> <li>• Personal or family history of learning or attention problems</li> <li>• Increased radiation exposure</li> </ul>	<b>Monitoring:</b> Yearly educational and/or vocational progress  <b>Screening:</b> Neuropsychological evaluation
<b>Notes</b> <ul style="list-style-type: none"> <li>• Survivors of leukemia/lymphoma have deficits in intelligence &amp; information processing<sup>179</sup></li> <li>• Survivors of brain tumors have more global deficits</li> </ul>	
Neurocognitive Defects Associated with Radiation <sup>175</sup>	
Associated with: Cranial, Ear/Infratemporal, TBI	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• Age &lt; 3 years at time of treatment</li> <li>• Female sex</li> <li>• Personal or family history of learning/attention problems</li> <li>• Primary malignancy (ex. primary CNS tumor)</li> <li>• Radiation combined with certain chemotherapies</li> <li>• Increased radiation dosage</li> <li>• Patients further out from treatment</li> </ul>	<b>Monitoring:</b> Yearly: educational milestones and/or vocational progress  <b>Screening:</b> Neuropsychological evaluation

1. Neurocognitive function after Cranial Radiation Therapy<sup>180</sup>
  - a. Study following 34 children treated for malignant posterior fossa tumors receiving cranial radiation
  - b. Results showed 2 – 4 point decline/year in intelligence scores
    - 1) Function declined quickly in first few years, then more gradually
    - 2) Declines in visual-motor integration, visual memory, verbal fluency, and executive functioning were also documented



## B. Ototoxicity

### Late Effects in Pediatric Survivors - Ototoxicity

Ototoxicity Associated with Chemotherapy <sup>175</sup>	
Associated with: Cisplatin, carboplatin at myeloablative doses	
<b>Risk Factors</b> <ul style="list-style-type: none"><li>• Age &lt; 4 years at treatment</li><li>• Chemotherapy combined with cranial/ear radiation or ototoxic medications</li><li>• CNS malignancy</li><li>• High cumulative cisplatin dose <math>\geq 360</math> mg/m<sup>2</sup> or high cisplatin dose per cycle</li><li>• Carboplatin for HSCT conditioning</li></ul>	<b>Monitoring:</b> Complete audiological evaluation yearly  <b>Screening:</b> Complete audiological evaluation, completed yearly for patients $\leq 5$ years old

## C. Peripheral Sensory Neuropathy

### Late Effects in Pediatric Survivors - Peripheral Sensory Neuropathy or Motor Neuropathy

Peripheral Sensory Neuropathy or Motor Neuropathy Associated with Chemotherapy <sup>175</sup>	
Associated with: Carboplatin, cisplatin, vincristine, vinblastine	
<b>Risk Factors</b> <ul style="list-style-type: none"><li>• Cisplatin cumulative dose <math>\geq 300</math> mg/m<sup>2</sup></li><li>• Combined treatment with vincristine, taxanes, gemcitabine, platinum compounds</li><li>• Certain medical conditions: anorexia, severe weight loss, Charcot-Marie-Tooth disease</li></ul>	<b>Monitoring:</b> Symptom history, yearly until 2-3 years post-therapy or yearly if symptoms persist  <b>Screening:</b> Neurologic exams

## D. Gonadal Dysfunction

1. Green and colleagues<sup>181</sup> analyzed ovarian function and reproductive outcomes in participants in the Childhood Cancer Survivor Study (CCSS) which contains data from 14,000, 5-year survivors of childhood/adolescent cancer who were diagnosed between 1970 and 1986
  - a. 1,227 male survivors fathered 2,323 pregnancies
  - b. 1,915 female survivors mothered 4,029 pregnancies
  - c. Acute ovarian failure occurred in 6.3% of survivors and associated risk factors included drug therapy with procarbazine or alkylating agents, or RT in which ovaries were in the treatment field
  - d. Premature non-surgical menopause occurred in 8% of patients which was significantly higher than patient siblings (0.8%) ( $P < 0.001$ )
    - 1) This was also associated with increased alkylating agent use, as well as diagnosis of Hodgkin's lymphoma and radiation of the ovaries
  - e. Children of the survivors had no increase in simple malformations, cytogenetic syndromes, or single-gene defects

## Late Effects in Pediatric Survivors - Gonadal Dysfunction

Testicular Hormonal Dysfunction <sup>175</sup>	
Associated with: Alkylating agents, heavy metals (cisplatin, carboplatin), dacarbazine, temozolomide	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• Aging (<math>\geq 30</math> years)</li> <li>• Higher cumulative doses of alkylating agents or combinations of alkylating agents</li> <li>• Chemotherapy combined with radiation to abdomen/pelvis, testes, brain/cranium or TBI</li> <li>• Unilateral orchiectomy</li> </ul>	<b>Monitoring:</b> pubertal status, sexual function, testicular volume yearly  <b>Screening:</b> hormone evaluation at baseline, age 14, and as clinically indicated
<b>Notes:</b> <ul style="list-style-type: none"> <li>• Pre-pubertal status at the time of treatment does not prevent males from having gonadal toxicity</li> <li>• Males typically lose gonadal function at lower cumulative doses than females</li> </ul>	
Ovarian Hormone Deficiencies <sup>175</sup>	
Associated with: Alkylating agents, heavy metals (cisplatin, carboplatin), dacarbazine, temozolomide	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• Older age at treatment</li> <li>• Higher cumulative doses of alkylating agents or combinations of alkylating agents</li> <li>• Chemotherapy combined with radiation to abdomen/pelvis, lumbar or sacral spine, or brain/cranium</li> <li>• Any alkylating agent combined with pelvic radiation or TBI</li> </ul>	<b>Monitoring:</b> pubertal status, sexual function yearly  <b>Screening:</b> Hormone evaluation in patients with possibly associated symptoms

### E. Cardiovascular Complications<sup>182</sup>

1. Radiation of the neck/mediastinum & anthracycline use are the most frequent causes of late cardiovascular dysfunction
  - a. Chronic and late-onset cardiac dysfunction secondary to anthracycline use is likely caused by free radical myocyte damage, is dose-related, and usually develops years to decades after treatment
2. Clinical presentation is commonly ventricular dysfunction or arrhythmia
3. Onset of cardiomyopathy may occur during times of cardiac stress such as pregnancy, extreme exertion, general anesthesia, or growth hormone treatment, but may also be sporadic

## Late Effects in Pediatric Survivors - Cardiac Toxicity

Cardiac Toxicity Associated with Chemotherapy <sup>175</sup>	
Associated with: Anthracyclines	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• &lt; 5 years of age at treatment</li> <li>• Anthracyclines combined with radiation involving the heart</li> <li>• Higher cumulative anthracycline dose (doxorubicin equivalents) <ul style="list-style-type: none"> <li>○ <math>\geq 550 \text{ mg/m}^2</math> in patients <math>\geq 18</math> years at treatment</li> <li>○ <math>\geq 250 \text{ mg/m}^2</math> in patients &lt; 18 years at treatment</li> </ul> </li> <li>• Chest radiation <math>\geq 15 \text{ Gy}</math> combined with <math>\geq 100 \text{ mg/m}^2</math> anthracycline</li> <li>• Longer elapsed time since treatment</li> <li>• Co-morbid conditions which increase CV risk</li> <li>• Smoking, drug use</li> </ul>	<b>Monitoring:</b> Cardiovascular symptoms or nausea/vomiting in young adults  <b>Screening:</b> EKG at baseline then as clinically indicated; echocardiogram periodically based on risk factors (see below)
<b>Recommended echocardiogram (ECHO) Frequency:</b> <ul style="list-style-type: none"> <li>• No screening <ul style="list-style-type: none"> <li>○ No anthracycline exposure + &lt; 15Gy radiation dose</li> </ul> </li> <li>• Every 2 years <ul style="list-style-type: none"> <li>○ No anthracycline exposure + <math>\geq 35 \text{ Gy}</math> radiation dose</li> <li>○ &lt; 250mg/m<sup>2</sup> doxorubicin equivalents + <math>\geq 15 \text{ Gy}</math> radiation dose</li> <li>○ <math>\geq 250 \text{ mg/m}^2</math> doxorubicin equivalents + any (or no) radiation</li> </ul> </li> <li>• Every 5 years <ul style="list-style-type: none"> <li>○ No anthracycline exposure + 15 to &lt; 35 Gy radiation dose</li> <li>○ &lt; 250mg/m<sup>2</sup> doxorubicin equivalents + &lt; 15Gy radiation (or none)</li> </ul> </li> </ul> <p>*Based on radiation to chest, abdomen, spine (thoracic, whole), TBI</p>	
<b>Notes</b> <ul style="list-style-type: none"> <li>• Dose levels associated with cardiotoxicity are derived from adult studies</li> <li>• Pediatric oncology patients display clinical and subclinical cardiac toxicity at lower doses than adults</li> </ul>	

## F. Renal Toxicity

### Late Effects in Pediatric Survivors – Renal Toxicity

Renal Toxicity <sup>175</sup>	
Associated with: Ifosfamide, carboplatin, cisplatin	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• Age &lt; 4 years at time of treatment</li> <li>• Higher cumulative dose or chemotherapy combined with other nephrotoxic agents or renal radiation</li> <li>• Tumor infiltration of kidney(s)</li> <li>• Pre-existing renal impairment, DM, HTN, nephrectomy / mononephric</li> </ul>	<b>Monitoring:</b> blood pressure yearly  <b>Screening:</b> BUN, creatinine, electrolytes at baseline and repeat when indicated

## G. Growth Hormone Deficiency

### Late Effects in Pediatric Survivors - Growth Hormone Deficiency

Growth Hormone Deficiency Associated with Radiation <sup>175</sup>	
Associated with: Head/Brain/TBI	
<b>Risk Factors</b> <ul style="list-style-type: none"><li>• Younger age at treatment</li><li>• Increased radiation dose, including TBI dose/fractionation</li><li>• Pre-transplant radiation/cranial radiation</li><li>• Certain CNS surgeries</li></ul>	<b>Monitoring:</b> nutritional status, growth charts (height, weight, BMI) every 6 months until growth completed, then yearly  <b>Screening:</b> Tanner staging (a scale of physical development in children and adolescents based on external primary and secondary sex characteristics)

## H. Metabolic Syndrome/Obesity

### Late Effects in Pediatric Survivors - Obesity

Obesity Associated with Radiation	
Associated with: Head / brain RT	
<b>Risk Factors</b> <ul style="list-style-type: none"><li>• &lt; 4 years of age at treatment</li><li>• Females</li><li>• Higher cranial and hypothalamic radiation dose</li><li>• Inability to exercise</li><li>• Treatment with steroids</li><li>• Familial dyslipidemia</li><li>• Growth hormone deficiency</li><li>• Hypothyroidism</li></ul>	<b>Monitoring:</b> height, weight, BMI, blood pressure yearly  <b>Screening:</b> fasting blood glucose, fasting lipid profile (every 2 years)

## I. Subsequent Malignant Neoplasms

1. Successive, histologically distinct cancer diagnosed in patients previously treated for primary neoplasm
2. Most frequent subsequent neoplasms diagnosed in survivors of pediatric cancer include MDS/AML and solid tumors such as non-melanoma skin cancers, and tumors located in the CNS, thyroid, breast, genitourinary tract, bone, digestive tract, and respiratory tract<sup>166</sup>
  - a. Subsequent MDS/AML patients most frequently present within 3 years of primary malignancy diagnosis
  - b. Subsequent solid tumors associated with radiation usually present >10 years after original diagnosis
3. Bassal and colleagues<sup>183</sup> reported the outcomes from CCSS regarding risk of secondary malignancies

- a. A total of 13,136 participants diagnosed between 1970 and 1986 (age < 21 years) who had survived  $\geq 5$  years post-malignancy were reviewed
  - b. Used participants of the CCSS to calculate standardized incidence ratios (SIRs)
  - c. A total of 71 cancers diagnosed in 71 patients indicating a four-fold increase of carcinomas
    - 1) Median age of onset was 27 years
    - 2) Malignancies have increasing incidence from ages 41 - 50 years with peak of 50 - 70 years
  - d. Median elapsed time of 15 years was found
  - e. Incidence of secondary malignancies per site:
    - 1) Genitourinary system – 35%
    - 2) Head and Neck area – 32%
    - 3) Gastrointestinal tract – 23%
    - 4) Other site – 10%
  - f. Radiotherapy had been administered in 59 out of 71 patients (83%) with 42/59 (59%) developing a second malignancy in the previous radiation field
  - g. Risk of developing a secondary malignancy was significantly elevated following all pediatric diagnoses except CNS neoplasms
4. Guerin and colleagues<sup>184</sup> published case control study of 4,581 patients who were treated for a childhood solid tumor
- a. 147 patients developed secondary malignancies; were compared to 417 matched controls
  - b. A significant increased risk for developing a secondary malignancy was observed after treatment for Hodgkin lymphoma, retinoblastoma, malignant bone tumors, soft tissue sarcoma, and germ cell tumor
  - c. Risk of developing a sarcoma was highest in patients who had retinoblastoma ( $OR_a=7.5$ ; 95% CI, 1.2 to 4.6), malignant bone cancer ( $OR_a=13.3$ , 95% CI, 1.5 to 117), soft tissue sarcoma ( $OR_a=4.8$ , 95% CI, 1.3 to 18) or a carcinoma ( $OR_a=9.4$ , 95% CI, 1.1 to 82) as a first malignancy

## Late Effects in Pediatric Survivors – Secondary Neoplasms

<b>Secondary AML, Myelodysplasia Associated with Chemotherapy<sup>175</sup></b>	
<b>Associated with:</b> alkylating agents, heavy metals (cisplatin, carboplatin), dacarbazine, temozolomide, anthracyclines, etoposide, teniposide	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• Autologous HSCT</li> <li>• Higher cumulative dose or combination therapy</li> <li>• &lt; 10 years since alkylating agent exposure</li> <li>• &lt; 5 years since anthracycline, etoposide, or teniposide exposure</li> </ul>	<b>Monitoring:</b> fatigue, bleeding/bruising  <b>Screening:</b> dermatologic exam (examining for pallor, purpura, petechiae) yearly for up to 10 years post-exposure
<b>Secondary Benign or Malignant Neoplasm Associated with Radiation<sup>175</sup></b>	
<b>Associated with:</b> All radiation fields, including TBI	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• Cancer predisposing mutation</li> <li>• Increasing doses of radiation exposure</li> </ul>	<b>Monitoring:</b> inspect of skin of irradiated field(s)  <b>Screening:</b> Varies based on specific field of radiation
<b>Secondary Breast Cancer Associated with Radiation<sup>175</sup></b>	
<b>Associated with:</b> ≥10 Gy to areas including the axilla and chest, or TBI of any dose	
<b>Risk Factors</b> <ul style="list-style-type: none"> <li>• BRCA1, BRCA2, ATM or p53 mutations</li> <li>• Family history of breast cancer</li> <li>• Higher radiation dose</li> <li>• Longer elapsed time since radiation</li> </ul>	<b>Monitoring:</b> Breast exam yearly, beginning at puberty until 25 years of age, then every 6 months thereafter  <b>Screening<sup>185</sup>:</b> <ul style="list-style-type: none"> <li>• Mammogram yearly, beginning 8 years after radiation or age 25, whichever occurs last</li> <li>• Breast MRI yearly as adjunct to mammography</li> </ul>

## VIII. Additional Documented Late Effects of Treatment According to COG-LTFU Guidelines Include:

- A. Associated with Any Therapy: fatigue, mental health disorders, limitations in access to healthcare, decreased quality of life
- B. Associated with Chemotherapy: dental abnormalities, pulmonary toxicity, cataracts, urinary tract toxicity, hepatic dysfunction, decreased bone mineral density, avascular necrosis, Raynaud's phenomenon
- C. Associated with Radiation Therapy: skin, bone, brain, colorectal, bladder, or thyroid cancers, cerebrovascular complications, craniofacial abnormalities, chronic sinusitis, precocious puberty, endocrine disorders, ocular toxicity, ototoxicity, xerostomia, dental abnormalities, carotid artery disease, pulmonary toxicity, cardiac toxicity, functional asplenia, esophageal stricture, DM/impaired glucose tolerance, dyslipidemia, hepatic fibrosis/cirrhosis, bowel complications, renal toxicity, urinary tract toxicities, uterine vascular insufficiency, gonadal dysfunction, vaginal fibrosis, musculoskeletal problems, scoliosis/kyphosis, fractures

**Patient Case #13, Answer:**

**Correct Answer: B. Every two years**

This recommendation is due to JM's total cumulative doxorubicin isotoxic equivalent dose  $\geq 250 \text{ mg/m}^2$ . She also had radiation with potential impact to the heart. As an integral part of her long-term follow-up, the COG survivorship guidelines recommend that she receive an echocardiogram or MUGA every 2 years.

## RECOMMENDED READINGS - PEDIATRICS

1. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. *N Eng J Med*. 2015; 373:1541-1552. <https://pubmed.ncbi.nlm.nih.gov/26465987/>
2. Lehrnbecher T, Robinson P, Fisher B et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol*. 2017; 35(18): 2082-94. <https://www.ncbi.nlm.nih.gov/pubmed/28459614>.
3. Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation. *Clin Infect Dis*. 2020; 71(1): 226-236. <https://pubmed.ncbi.nlm.nih.gov/31676904/>
4. Patel P, Robinson PD, Thackray J et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: A focused update. *Pediatr Blood Cancer*. 2017; 64(10). <https://www.ncbi.nlm.nih.gov/pubmed/28453189>.
5. AAP Committee on Bioethics. Informed consent in decision-making in pediatric practice. *Pediatrics*. 2016; 138(2):e20161484. <https://www.ncbi.nlm.nih.gov/pubmed/27456514>.
6. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, version 5.0. Children's Oncology Group. October 2018; Available at: [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)

## REFERENCES

1. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1996;14(1):18-24.
2. Trueworthy R, Shuster J, Look T, et al. Ploidy of lymphoblasts is the strongest predictor of treatment outcome in B-progenitor cell acute lymphoblastic leukemia of childhood: a Pediatric Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1992;10(4):606-613.
3. Shurtleff SA, Buijs A, Behm FG, et al. TEL/AML1 fusion resulting from a cryptic t(12;21) is the most common genetic lesion in pediatric ALL and defines a subgroup of patients with an excellent prognosis. *Leukemia*. 1995;9(12):1985-1989.
4. Braoudaki M, Tzortzatou-Stathopoulou F. Clinical cytogenetics in pediatric acute leukemia: an update. *Clin Lymphoma Myeloma Leuk*. 2012;12(4):230-237.
5. Cooper SL, Brown PA. Treatment of Pediatric Acute Lymphoblastic Leukemia. *Pediatr Clin North Am*. 2015;62(1):61-73.
6. Mastrangelo R, Poplack D, Bleyer A, Riccardi R, Sather H, D'Angio G. Report and recommendations of the Rome workshop concerning poor-prognosis acute lymphoblastic leukemia in children: biologic bases for staging, stratification, and treatment. *Med Pediatr Oncol*. 1986;14(3):191-194.
7. Borowitz MJ, Pullen DJ, Shuster JJ, et al. Minimal residual disease detection in childhood precursor-B-cell acute lymphoblastic leukemia: relation to other risk factors. A Children's Oncology Group study. *Leukemia*. 2003;17(8):1566-1572.
8. Johnston DL, Alonzo TA, Gerbing RB, Lange BJ, Woods WG. The presence of central nervous system disease at diagnosis in pediatric acute myeloid leukemia does not affect survival: a Children's Oncology Group study. *Pediatr Blood Cancer*. 2010;55(3):414-420.



9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia. V.1.2022, 10/1/2021, © 2020 National Comprehensive Cancer Network, Inc., All Rights Reserved. *NATIONAL COMPREHENSIVE CANCER NETWORK®*, *NCCN®*, *NCCN GUIDELINES®*, *NCCN IMAGING AUC™*, *NCCN COMPENDIUM®*, *NCCN BIOMARKERS COMPENDIUM®*, *NCCN RADIATION THERAPY COMPENDIUM™*, *NCCN IMAGING AUC COMPENDIUM™*, *NCCN TEMPLATES®*, *NCCN EVIDENCE BLOCKS™*, *NCCN FRAMEWORK™*, *NCCN HARMONIZED GUIDELINES™*, *NCCN FLASH UPDATES™*, *NCCN TRENDS™* Surveys & Data, Powered by NCCN™, *NCCN ONCOLOGY INSIGHTS REPORTS™*, and *NCCN GUIDELINES FOR PATIENTS®* are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
10. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111(12):5477-5485.
11. Schultz KR, Pullen DJ, Sather HN, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). *Blood*. 2007;109(3):926-935.
12. Ortega JA, Nesbit ME, Jr., Donaldson MH, et al. L-Asparaginase, vincristine, and prednisone for induction of first remission in acute lymphocytic leukemia. *Cancer Res*. 1977;37(2):535-540.
13. Kaspers GJ, Veerman AJ, Popp-Snijders C, et al. Comparison of the antileukemic activity in vitro of dexamethasone and prednisolone in childhood acute lymphoblastic leukemia. *Med Pediatr Oncol*. 1996;27(2):114-121.
14. Hurwitz CA, Silverman LB, Schorin MA, et al. Substituting dexamethasone for prednisone complicates remission induction in children with acute lymphoblastic leukemia. *Cancer*. 2000;88(8):1964-1969.
15. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *British journal of haematology*. 2005;129(6):734-745.
16. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. *Pediatr Clin North Am*. 2008;55(1):1-20, ix.
17. Imbach P, Kühne T, Arceci RJ. Pediatric Oncology A Comprehensive Guide. 2014;Springer, New York. 3rd ed.
18. Balis FM, Lester CM, Chrousos GP, Heideman RL, Poplack DG. Differences in cerebrospinal fluid penetration of corticosteroids: possible relationship to the prevention of meningeal leukemia. *J Clin Oncol*. 1987;5(2):202-207.
19. Ito C, Evans WE, McNinch L, et al. Comparative cytotoxicity of dexamethasone and prednisolone in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 1996;14(8):2370-2376.
20. Mattano LA, Jr., Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. *Lancet Oncol*. 2012;13(9):906-915.
21. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2003;101(10):3809-3817.
22. Winick NL, Salzer WL, Devidas M, et al. Dexamethasone (DEX) versus prednisone (PRED) during induction for children with high risk acute lymphoblastic leukemia (HR-ALL): a report from the Children's oncology group study AALL0232. *Journal of Clinical Oncology*. 2011;29 (suppl 15 Abstract 9504).

23. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016;34(20):2380-2388.
24. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood*. 2010;115(16):3206-3214.
25. Hunger SP. Integrated Risk Stratification Using Minimal Residual Disease and Sentinel Genetic Alterations in Pediatric Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2018;36(1):4-6.
26. Stow P, Key L, Chen X, et al. Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia. *Blood*. 2010;115(23):4657-4663.
27. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2011;118(2):243-251.
28. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(31):5175-5181.
29. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. *Clinical pharmacology and therapeutics*. 2019;105(5):1095-1105.
30. Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia*. 2008;22(12):2142-2150.
31. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. 2009;360(26):2730-2741.
32. Blincyto (blinatumomab) for injection, for intravenous use [package insert]. Thousand Oaks, CA: Amgen Inc; December 2014.
33. Kymriah (tisagenlecleucel) suspension for intravenous infusion [package insert]. East Hanover, NJ: Novartis; Sept 2017.
34. Oliansky DM, Camitta B, Gaynon P, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: update of the 2005 evidence-based review. ASBMT Position Statement. *Biol Blood Marrow Transplant*. 2012;18(7):979-981.
35. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2015;21(11):1863-1869.
36. Kanate AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2020;26(7):1247-1256.

37. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(14):1663-1669.
38. Maloney KW, Devidas M, Wang C, et al. Outcome in Children With Standard-Risk B-Cell Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0331. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020;38(6):602-612.
39. Gajjar A, Bowers DC, Karajannis MA, Leary S, Witt H, Gottardo NG. Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(27):2986-2998.
40. Packer RJ, Macdonald T, Vezina G. Central nervous system tumors. *Hematol Oncol Clin North Am*. 2010;24(1):87-108.
41. Millard NE, De Braganca KC. Medulloblastoma. *J Child Neurol*. 2015.
42. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114(2):97-109.
43. Massimino M, Biassoni V, Gandola L, et al. Childhood medulloblastoma. *Crit Rev Oncol Hematol*. 2016;105:35-51.
44. Partap S, Fisher P. Embryonal Tumors. In: Gupta N, Banerjee A, Haas-Kogan D, eds. *Pediatric CNS Tumors*. Berlin; Heidelberg: Springer; 2010:89-114.
45. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(26):3187-3193.
46. Goldwein JW, Radcliffe J, Packer RJ, et al. Results of a pilot study of low-dose craniospinal radiation therapy plus chemotherapy for children younger than 5 years with primitive neuroectodermal tumors. *Cancer*. 1993;71(8):2647-2652.
47. Packer RJ, Siegel KR, Sutton LN, et al. Efficacy of adjuvant chemotherapy for patients with poor-risk medulloblastoma: a preliminary report. *Ann Neurol*. 1988;24(4):503-508.
48. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(25):4202-4208.
49. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. *Neuro Oncol*. 2013;15(1):97-103.
50. Verlooy J, Mosseri V, Bracard S, et al. Treatment of high risk medulloblastomas in children above the age of 3 years: a SFOP study. *Eur J Cancer*. 2006;42(17):3004-3014.
51. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1999;17(3):832-845.

52. Packer RJ, Sutton LN, Elterman R, et al. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. *J Neurosurg*. 1994;81(5):690-698.
53. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol*. 2006;7(10):813-820.
54. Dufour C, Kieffer V, Varlet P, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive neuro-ectodermic tumors. *Pediatr Blood Cancer*. 2014;61(8):1398-1402.
55. Freeman CR, Farmer JP, Montes J. Low-grade astrocytomas in children: evolving management strategies. *Int J Radiat Oncol Biol Phys*. 1998;41(5):979-987.
56. Bonfield CM, Steinbok P. Pediatric cerebellar astrocytoma: a review. *Childs Nerv Syst*. 2015;31(10):1677-1685.
57. Sievert AJ, Fisher MJ. Pediatric low-grade gliomas. *J Child Neurol*. 2009;24(11):1397-1408.
58. Nageswara Rao AA, Packer RJ. Advances in the management of low-grade gliomas. *Curr Oncol Rep*. 2014;16(8):398.
59. Gan G, Haas-Kogan D. Low-Grade Gliomas. In: Gupta N, Banerjee A, Haas-Kogan D, eds. *Pediatric CNS Tumors*. Berlin; Heidelberg: Springer; 2010:1-35.
60. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(21):2641-2647.
61. Bouffet E, Jakacki R, Goldman S, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(12):1358-1363.
62. Lafay-Cousin L, Holm S, Qaddoumi I, et al. Weekly vinblastine in pediatric low-grade glioma patients with carboplatin allergic reaction. *Cancer*. 2005;103(12):2636-2642.
63. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. *J Neurosurg*. 1997;86(5):747-754.
64. Shah AC, Minturn JE, Li Y, et al. Carboplatin Rechallenge After Hypersensitivity Reactions in Pediatric Patients With Low-Grade Glioma. *Pediatr Blood Cancer*. 2016;63(1):21-26.
65. Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II Weekly Vinblastine for Chemotherapy-Naive Children With Progressive Low-Grade Glioma: A Canadian Pediatric Brain Tumor Consortium Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016.
66. Green AL, Kieran MW. Pediatric brainstem gliomas: new understanding leads to potential new treatments for two very different tumors. *Curr Oncol Rep*. 2015;17(3):436.
67. Sanai N, Prados M. Brainstem Gliomas. In: Gupta N, Banerjee A, Haas-Kogan D, eds. *Pediatric CNS Tumors*. Berlin; Heidelberg: Springer; 2010:49-65.

68. Plant-Fox AS, O'Halloran K, Goldman S. Pediatric brain tumors: the era of molecular diagnostics, targeted and immune-based therapeutics, and a focus on long term neurologic sequelae. *Current problems in cancer*. 2021;45(4):100777.
69. Jenkin RD, Boesel C, Ertel I, et al. Brain-stem tumors in childhood: a prospective randomized trial of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Childrens Cancer Study Group. *J Neurosurg*. 1987;66(2):227-233.
70. Pinto NR, Applebaum MA, Volchenboun SL, et al. Advances in Risk Classification and Treatment Strategies for Neuroblastoma. *J Clin Oncol*. 2015;33(27):3008-3017.
71. Modak S, Cheung NK. Neuroblastoma: Therapeutic strategies for a clinical enigma. *Cancer Treat Rev*. 2010;36(4):307-317.
72. Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1993;11(8):1466-1477.
73. Perez CA, Matthay KK, Atkinson JB, et al. Biologic variables in the outcome of stages I and II neuroblastoma treated with surgery as primary therapy: a children's cancer group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2000;18(1):18-26.
74. Matthay KK, Perez C, Seeger RC, et al. Successful treatment of stage III neuroblastoma based on prospective biologic staging: a Children's Cancer Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1998;16(4):1256-1264.
75. Barker E, Mueller BM, Handgretinger R, Herter M, Yu AL, Reisfeld RA. Effect of a chimeric anti-ganglioside GD2 antibody on cell-mediated lysis of human neuroblastoma cells. *Cancer Res*. 1991;51(1):144-149.
76. Kreissman SG, Seeger RC, Matthay KK, et al. Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A3973): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(10):999-1008.
77. Matthay KK, George RE, Yu AL. Promising therapeutic targets in neuroblastoma. *Clin Cancer Res*. 2012;18(10):2740-2753.
78. Gilman AL, Ozkaynak MF, Matthay KK, et al. Phase I study of ch14.18 with granulocyte-macrophage colony-stimulating factor and interleukin-2 in children with neuroblastoma after autologous bone marrow transplantation or stem-cell rescue: a report from the Children's Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(1):85-91.
79. Unituxin (dinutuximab) injection, for intravenous use [package insert]. Silver Spring, MD: United Therapeutics Corp.; 2015.
80. Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. *The Lancet Oncology*. 2018;19(12):1617-1629.
81. Nickerson HJ, Matthay KK, Seeger RC, et al. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy: a Children's Cancer Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2000;18(3):477-486.

82. Brodeur GM, Seeger RC, Barrett A, et al. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1988;6(12):1874-1881.
83. Minard-Colin V, Brugieres L, Reiter A, et al. Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(27):2963-2974.
84. Allen CE, Kelly KM, Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. *Pediatr Clin North Am*. 2015;62(1):139-165.
85. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood*. 2007;109(7):2736-2743.
86. Reiter A, Schrappe M, Tiemann M, et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. *Blood*. 1999;94(10):3294-3306.
87. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. *Blood*. 2005;105(3):948-958.
88. Patte C, Auperin A, Michon J, et al. The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. *Blood*. 2001;97(11):3370-3379.
89. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood*. 2007;109(7):2773-2780.
90. Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. *Lancet (London, England)*. 2012;379(9822):1234-1244.
91. Cairo MS, Sposto R, Gerrard M, et al. Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age ( $\geq 15$  years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: results of the FAB LMB 96 study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(4):387-393.
92. Children's Oncology Group. Combination Chemotherapy With or Without Rituximab in Treating Younger Patients With Stage III-IV Non-Hodgkin Lymphoma or B-Cell Acute Leukemia. *ClinicalTrials.gov [Internet] Bethesda (MD): National Library of Medicine (US)*. 2000- [cited 2015 Oct 25]. Available from: <http://clinicaltrials.gov/show/NCT01595048>.
93. Jenkin RD, Anderson JR, Chilcote RR, et al. The treatment of localized non-Hodgkin's lymphoma in children: a report from the Children's Cancer Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1984;2(2):88-97.
94. Shiramizu B, Goldman S, Kusao I, et al. Minimal disease assessment in the treatment of children and adolescents with intermediate-risk (Stage III/IV) B-cell non-Hodgkin lymphoma: a children's oncology group report. *British journal of haematology*. 2011;153(6):758-763.
95. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4):235-242.

96. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7(5):379-391.
97. Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children. *The New England journal of medicine*. 2020;382(23):2207-2219.
98. Cairo MS, Sposto R, Perkins SL, et al. Burkitt's and Burkitt-like lymphoma in children and adolescents: a review of the Children's Cancer Group experience. *British journal of haematology*. 2003;120(4):660-670.
99. Dozzo M, Carobolante F, Donisi PM, et al. Burkitt lymphoma in adolescents and young adults: management challenges. *Adolescent health, medicine and therapeutics*. 2017;8:11-29.
100. Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2009;52(2):177-181.
101. Giulino-Roth L, Ricafort R, Kernan NA, et al. Ten-year follow-up of pediatric patients with non-Hodgkin lymphoma treated with allogeneic or autologous stem cell transplantation. *Pediatr Blood Cancer*. 2013;60(12):2018-2024.
102. Harris RE, Termuhlen AM, Smith LM, et al. Autologous peripheral blood stem cell transplantation in children with refractory or relapsed lymphoma: results of Children's Oncology Group study A5962. *Biol Blood Marrow Transplant*. 2011;17(2):249-258.
103. Sandlund JT, Bowman L, Heslop HE, et al. Intensive chemotherapy with hematopoietic stem-cell support for children with recurrent or refractory NHL. *Cytotherapy*. 2002;4(3):253-258.
104. Call KM, Glaser T, Ito CY, et al. Isolation and characterization of a zinc finger polypeptide gene at the human chromosome 11 Wilms' tumor locus. *Cell*. 1990;60(3):509-520.
105. Koufos A, Grundy P, Morgan K, et al. Familial Wiedemann-Beckwith syndrome and a second Wilms tumor locus both map to 11p15.5. *Am J Hum Genet*. 1989;44(5):711-719.
106. Szychot E, Apps J, Pritchard-Jones K. Wilms' tumor: biology, diagnosis and treatment. *Translational pediatrics*. 2014;3(1):12-24.
107. Dome JS, Fernandez CV, Mullen EA, et al. Children's Oncology Group's 2013 blueprint for research: renal tumors. *Pediatr Blood Cancer*. 2013;60(6):994-1000.
108. Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005;23(29):7312-7321.
109. Metzger ML, Dome JS. Current therapy for Wilms' tumor. *Oncologist*. 2005;10(10):815-826.
110. Dome JS, Graf N, Geller JI, et al. Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(27):2999-3007.
111. Shamberger RC, Guthrie KA, Ritchey ML, et al. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. *Ann Surg*. 1999;229(2):292-297.

112. Kalapurakal JA, Li SM, Breslow NE, et al. Intraoperative spillage of favorable histology wilms tumor cells: influence of irradiation and chemotherapy regimens on abdominal recurrence. A report from the National Wilms Tumor Study Group. *Int J Radiat Oncol Biol Phys*. 2010;76(1):201-206.
113. Grundy PE, Green DM, Dirks AC, et al. Clinical significance of pulmonary nodules detected by CT and Not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and -5: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59(4):631-635.
114. Farber S. Chemotherapy in the treatment of leukemia and Wilms' tumor. *JAMA*. 1966;198(8):826-836.
115. D'Angio GJ, Evans AE, Breslow N, et al. The treatment of Wilms' tumor: Results of the national Wilms' tumor study. *Cancer*. 1976;38(2):633-646.
116. D'Angio GJ, Evans A, Breslow N, et al. The treatment of Wilms' tumor: results of the Second National Wilms' Tumor Study. *Cancer*. 1981;47(9):2302-2311.
117. Green DM, Breslow NE, Beckwith JB, et al. Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the National Wilms' Tumor Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1998;16(1):237-245.
118. Green DM, Breslow NE, Beckwith JB, et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1998;16(12):3744-3751.
119. D'Angio GJ, Breslow N, Beckwith JB, et al. Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. *Cancer*. 1989;64(2):349-360.
120. Dome JS, Cotton CA, Perlman EJ, et al. Treatment of anaplastic histology Wilms' tumor: results from the fifth National Wilms' Tumor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(15):2352-2358.
121. Reinhard H, Semler O, Burger D, et al. Results of the SIOP 93-01/GPOH trial and study for the treatment of patients with unilateral nonmetastatic Wilms Tumor. *Klin Padiatr*. 2004;216(3):132-140.
122. Davidoff AM. Wilms' tumor. *Curr Opin Pediatr*. 2009;21(3):357-364.
123. Delattre O, Zucman J, Melot T, et al. The Ewing family of tumors--a subgroup of small-round-cell tumors defined by specific chimeric transcripts. *N Engl J Med*. 1994;331(5):294-299.
124. Zucman J, Delattre O, Desmaze C, et al. Cloning and characterization of the Ewing's sarcoma and peripheral neuroepithelioma t(11;22) translocation breakpoints. *Genes Chromosomes Cancer*. 1992;5(4):271-277.
125. Aurias A, Rimbaut C, Buffe D, Dubousset J, Mazabraud A. [Translocation of chromosome 22 in Ewing's sarcoma]. *C R Seances Acad Sci III*. 1983;296(23):1105-1107.
126. Bernstein M, Kovar H, Paulussen M, et al. Ewing's sarcoma family of tumors: current management. *Oncologist*. 2006;11(5):503-519.
127. Balamuth NJ, Womer RB. Ewing's sarcoma. *Lancet Oncol*. 2010;11(2):184-192.



128. Gaspar N, Hawkins DS, Dirksen U, et al. Ewing Sarcoma: Current Management and Future Approaches Through Collaboration. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(27):3036-3046.
129. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(33):4148-4154.
130. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971;68(4):820-823.
131. Rodriguez-Galindo C, Orbach DB, VanderVeen D. Retinoblastoma. *Pediatr Clin North Am*. 2015;62(1):201-223.
132. Rothschild PR, Levy D, Savignoni A, et al. Familial retinoblastoma: fundus screening schedule impact and guideline proposal. A retrospective study. *Eye (Lond)*. 2011;25(12):1555-1561.
133. Wallach M, Balmer A, Munier F, et al. Shorter time to diagnosis and improved stage at presentation in Swiss patients with retinoblastoma treated from 1963 to 2004. *Pediatrics*. 2006;118(5):e1493-1498.
134. Shields JA, Shields CL. Current management of retinoblastoma. *Mayo Clin Proc*. 1994;69(1):50-56.
135. Pandey AN. Retinoblastoma: An overview. *Saudi J Ophthalmol*. 2014;28(4):310-315.
136. Wilson MW. Treatment of Intraocular Retinoblastoma. In: Gupta N, Banerjee A, Haas-Kogan D, eds. *Pediatric CNS Tumors*. Berlin; Heidelberg: Springer; 2010:91-101.
137. Shields CL, Kaliki S, Al-Dahmash S, et al. Management of advanced retinoblastoma with intravenous chemotherapy then intra-arterial chemotherapy as alternative to enucleation. *Retina*. 2013;33(10):2103-2109.
138. Wilson MW, Haik BG, Liu T, Merchant TE, Rodriguez-Galindo C. Effect on ocular survival of adding early intensive focal treatments to a two-drug chemotherapy regimen in patients with retinoblastoma. *Am J Ophthalmol*. 2005;140(3):397-406.
139. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of intraocular retinoblastoma with vincristine and carboplatin. *J Clin Oncol*. 2003;21(10):2019-2025.
140. Gunduz K, Shields CL, Shields JA, et al. The outcome of chemoreduction treatment in patients with Reese-Ellsworth group V retinoblastoma. *Arch Ophthalmol*. 1998;116(12):1613-1617.
141. Doz F, Khelifaoui F, Mosseri V, et al. The role of chemotherapy in orbital involvement of retinoblastoma. The experience of a single institution with 33 patients. *Cancer*. 1994;74(2):722-732.
142. Chantada G, Fandino A, Casak S, Manzitti J, Raslawski E, Schwartzman E. Treatment of overt extraocular retinoblastoma. *Med Pediatr Oncol*. 2003;40(3):158-161.
143. Chantada GL, Dunkel IJ. Treatment of Extraocular and Metastatic Retinoblastoma. In: Gupta N, Banerjee A, Haas-Kogan D, eds. *Pediatric CNS Tumors*. Berlin; Heidelberg: Springer; 2010:103-114.
144. Kaliki S, Shields CL. Retinoblastoma: achieving new standards with methods of chemotherapy. *Indian J Ophthalmol*. 2015;63(2):103-109.
145. Pulsipher MA. Pediatric-specific guidelines for fever and neutropenia: a catalyst for improving care and focusing research. *J Clin Oncol*. 2012;30(35):4292-4293.

146. Meckler G, Lindemulder S. Fever and neutropenia in pediatric patients with cancer. *Emerg Med Clin North Am.* 2009;27(3):525-544.
147. Lehnbecher T, Robinson P, Fisher B, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017;35(18):2082-2094.
148. Lehnbecher T, Fisher BT, Phillips B, et al. Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2020;71(1):226-236.
149. Dupuis L, Boodhan S, Holdsworth M, et al. Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients. Toronto: Pediatric Oncology Group of Ontario; 2012:1-199.
150. Vol H, Flank J, Lavoratore SR, et al. Poor chemotherapy-induced nausea and vomiting control in children receiving intermediate or high dose methotrexate. *Support Care Cancer.* 2016;24(3):1365-1371.
151. Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol.* 2010;21 Suppl 5:v232-243.
152. Dupuis LL, Boodhan S, Holdsworth M, et al. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer.* 2013;60(7):1073-1082.
153. Dupuis LL, Boodhan S, Sung L, et al. Guideline for the classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer.* 2011;57(2):191-198.
154. Patel P, Robinson PD, Thackray J, et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: A focused update. *Pediatric blood & cancer.* 2017;64(10).
155. Dupuis LL, Sung L, Molassiotis A, Orsey AD, Tissing W, van de Wetering M. 2016 updated MASCC/ESMO consensus recommendations: Prevention of acute chemotherapy-induced nausea and vomiting in children. *Support Care Cancer.* 2017;25(1):323-331.
156. Emend (aprepitant) capsules, for oral use [package insert]. Whitehouse Station, NJ: Merk Sharp & Dohme Corp.; Dec 2015.
157. Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16(4):385-394.
158. Emend (fosaprepitant) injection, for intravenous use [package insert]. Whitehouse Station, NJ: Merck, Sharpe & Dohme Corp; 2018.
159. AAP Committee on Bioethics. Informed Consent in Decision-Making in Pediatric Practice. *Pediatrics.* 2016;138(2).
160. Katz AL, Webb SA. Informed Consent in Decision-Making in Pediatric Practice. *Pediatrics.* 2016;138(2).
161. Whittle A, Shah S, Wilfond B, Gensler G, Wendler D. Institutional review board practices regarding assent in pediatric research. *Pediatrics.* 2004;113(6):1747-1752.

162. Roth-Cline M, Nelson RM. Ethical Considerations in Conducting Pediatric and Neonatal Research in Clinical Pharmacology. *Curr Pharm Des*. 2015;21(39):5619-5635.
163. Code of Federal Regulations Title 45 Part 46 Protection of Human Subjects. *Subpart D Additional Protections for Children Involved as Subjects in Research*. Office for Human Research Protections;U.S. Department of Health & Human Services, 2009. <http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.408>.
164. NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.National Institutes of Health. <http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.408>.
165. Gerasimov E, Donoghue M, Bilenker J, Watt T, Goodman N, Laetsch TW. Before It's Too Late: Multistakeholder Perspectives on Compassionate Access to Investigational Drugs for Pediatric Patients With Cancer. *American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting*. 2020;40:1-10.
166. Bhatia S, Armenian SH, Armstrong GT, et al. Collaborative Research in Childhood Cancer Survivorship: The Current Landscape. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(27):3055-3064.
167. Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, Version 4.0. Monrovia, CA: Children's Oncology Group. October 2013; [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org).
168. Long-term follow-up care for pediatric cancer survivors. *Pediatrics*. 2009;123(3):906-915.
169. American Cancer Society. Cancer Facts & Figures 2014. Special Section: Cancer in Children & Adolescents. 2014:25-42.
170. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(12):1218-1227.
171. Benadiba J, Michel G, Auquier P, et al. Health status and quality of life of long-term survivors of childhood acute leukemia: the impact of central nervous system irradiation. *Journal of pediatric hematology/oncology*. 2015;37(2):109-116.
172. Leisenring WM, Mertens AC, Armstrong GT, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(14):2319-2327.
173. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *The New England journal of medicine*. 2006;355(15):1572-1582.
174. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Medical and pediatric oncology*. 2002;38(4):229-239.
175. Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers. Version 5.0. 2018.
176. Eshelman D, Landier W, Sweeney T, et al. Facilitating care for childhood cancer survivors: integrating children's oncology group long-term follow-up guidelines and health links in clinical practice. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses*. 2004;21(5):271-280.

177. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(24):4979-4990.
178. Goldsby RE, Liu Q, Nathan PC, et al. Late-occurring neurologic sequelae in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(2):324-331.
179. Iyer NS, Balsamo LM, Bracken MB, Kadan-Lottick NS. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and meta-analysis. *Blood*. 2015;126(3):346-353.
180. Spiegler BJ, Bouffet E, Greenberg ML, Rutka JT, Mabbott DJ. Change in neurocognitive functioning after treatment with cranial radiation in childhood. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(4):706-713.
181. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *American journal of obstetrics and gynecology*. 2002;187(4):1070-1080.
182. Shankar SM, Marina N, Hudson MM, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. *Pediatrics*. 2008;121(2):e387-396.
183. Bassal M, Mertens AC, Taylor L, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(3):476-483.
184. Guerin S, Hawkins M, Shamsaldin A, et al. Treatment-adjusted predisposition to second malignant neoplasms after a solid cancer in childhood: a case-control study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007;25(19):2833-2839.
185. Mulder RL, Kremer LC, Hudson MM, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *The Lancet Oncology*. 2013;14(13):e621-629.

## **PHARMACOGENOMICS in ONCOLOGY**

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### **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Identify appropriate considerations for genetic interpretation in both the germline and somatic settings utilizing a variety of next generation sequencing techniques.
2. Apply the results from somatic and germline genetic testing into therapy recommendations based on prognostic, predictive and patient characteristics.
3. Recognize the place in therapeutic decision making for companion diagnostic testing.

## PHARMACOGENOMICS IN ONCOLOGY

### I. Background

- A. Both somatic (tumor) genomic testing and germline (hereditary) testing of variants for cancer risk and genes related to pharmacogenetics and pharmacodynamics have led to the translation of genetic testing into standard clinical practice
- B. Value of interrogating the tumor genome<sup>1</sup>
  - 1. Genetic alterations in molecular pathways are involved in tumor development, survival and progression/metastases
  - 2. Cost of genomic testing has decreased over time along with turn-around time, making testing amenable for incorporation into standard clinical practice.
  - 3. Targeted anticancer drugs are available commercially and in clinical trials
- C. The value of genetic tumor testing is underscored by the role of driver genes in tumor progression<sup>2</sup>

#### **Patient Case #1**

BT is a 62-year-old man with metastatic, castration resistant prostate cancer. A recent tumor biopsy is sent for next-generation sequencing and is notable for a splice variant in the androgen receptor known as **AR-V7**.

Men with prostate cancer who were treated with enzalutamide had lower prostate-specific antigen response rates and overall survival if their tumors were found to harbor the AR-V7 alteration. Currently, it is not known whether patients with AR-V7 alterations have poorer overall outcomes than patients without the alteration, regardless of therapy. **Based on this information, AR-V7 would be classified as what type of biomarker?**

- A. Prognostic only
- B. Predictive only
- C. Both prognostic and predictive
- D. Neither prognostic nor predictive

### II. Types of genomic variants

- A. **Germline:** inherited genetic variation from the sperm and egg of the parents.
  - 1. Hereditary diseases including cancer
    - a. Examples:
      - 1) BRCA1 and BRCA2: association with risk of developing primarily breast, ovarian, pancreatic and prostate cancers
      - 2) VHL: association with renal cell carcinoma

- b. The American College of Medical Genetics (ACMG) has numerous guidelines devoted to specific cancer testing, classification of hereditary variants, and many other hereditary syndromes. All of these can be found at: <https://www.acmg.net/>.
  - c. Additionally, the National Comprehensive Cancer Network® (NCCN) has Guidelines for the Genetic/Familial High-Risk Assessment of patients with breast, ovarian, pancreatic and colorectal cancers.<sup>3,4</sup>
2. Predictors of drug exposure and toxicity
- a. Differences in genes involved in drug pharmacokinetic properties or drug targets can influence response and toxicity, especially in drugs with narrow therapeutic indices
  - b. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has dosing recommendations for several agents commonly used in patients with cancer (<https://cpicpgx.org/guidelines/>)
    - 1) The purpose of CPIC is not to recommend when pharmacogenomic testing should be done but rather focuses on developing peer-reviewed, evidence based gene/drug practice guidelines aimed at providing specific recommendations based on reported genetic test results<sup>5</sup>
    - 2) The guideline list is not all inclusive for gene/drug pairs known to be clinically relevant. Prioritization of guideline development is based on several factors including prescribing actionability of the genetic alteration, severity of clinical consequences if genetics are not used, how commonly the affected drug is used, how common the high-risk alleles are found in the population and others.<sup>5</sup>

**Select Drug/Gene pairs with CPIC Guidelines commonly used in oncology patients<sup>5</sup>**

Drug	Gene
Allopurinol	HLA-B
Azathioprine, mercaptopurine, thioguanine	TPMT, NUDT15
Capecitabine, fluorouracil	DPYD
Irinotecan ( <i>provisional guidelines in process</i> )	UGT1A1
Ondansetron	CYP2D6
Dabrafenib, doxorubicin, rasburicase, trametinib	G6PD
Tacrolimus	CYP3A5
Tamoxifen	CYP2D6
Voriconazole	CYP2C19
Warfarin	CYP2C9, CYP4F2 and VKORC1

- B. **Somatic:** acquired genetic variation (in oncology, typically is from the tumor, which may include blood or bone marrow in hematologic malignancies)
- 1. Clinical considerations
    - a. Prognostic biomarkers<sup>6</sup>

- 1) Provide information about cancer outcomes, such as progression free and overall survival, independent of treatment received and demonstrates the underlying biology and natural history of the cancer
  - 2) Clinically, prognostic biomarkers are frequently used in hematologic malignancies like chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS).
  - 3) Examples of prognostic biomarkers:
    - a) PIK3CA mutations in patients with Her2 positive breast cancer are associated with worse progression free survival<sup>7</sup> (see Breast Cancer handout for more information)
    - b) NOTCH1 mutations in CLL patients are associated with shorter progression free survival and the development of Richter's transformation<sup>8</sup> (see Chronic Leukemias handout for more information)
- b. Predictive biomarkers
- 1) Provide information regarding response to a specific treatment. This is determined from comparing at least two groups and assessing whether the treatment outcome is different for biomarker-positive patients compared with patients lacking the biomarker<sup>6</sup>
  - 2) Clinically, tumor genetic testing can be used to help direct therapy for a variety of cancers
    - a) Patients with standard of care, targeted therapy options such as:
      - i. Activating EGFR alterations are assessed at diagnosis in patients with non-small cell lung cancer
      - ii. BRAF V600E alterations are assessed at diagnosis in patients with locally advanced and advanced melanoma
    - b) Patients in whom there may not be many beneficial standard therapy options such as sarcoma, Merkel Cell or cancer of unknown primary
    - c) Patients with advanced disease who may have limited treatment options
    - d) Patients undergoing consideration for biomarker-driven clinical trial enrollment
      - i. Numerous examples of biomarker driven clinical trials that are both histology specific and histology agnostic exist
      - ii. Basket trials<sup>9</sup>
        - (a) Clinical trials that match specific genetic alterations to targeted therapy independent of disease histology
      - iii. Umbrella trials<sup>9</sup>
        - (a) Clinical trial that matches specific genetic alterations to targeted therapy within the same tumor type
  - 3) Examples of predictive biomarkers: include numerous "drug/gene" pairs
    - a) Activating EGFR mutations in lung cancer are associated with increased response to EGFR-inhibitors like erlotinib, gefitinib, afatinib and osimertinib<sup>10</sup>

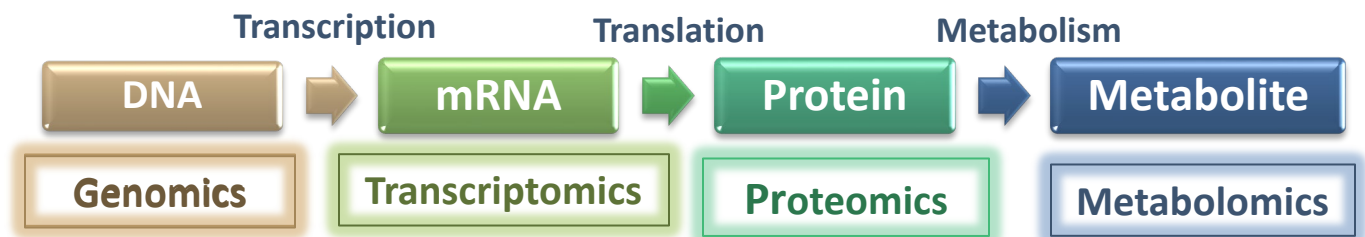


- b) KRAS mutations in colorectal cancer associated with resistance to monoclonal antibodies directed against EGFR such as cetuximab and panitumumab<sup>11</sup>
    - c) BRAF V600E/K mutations in melanoma are associated with response to the combination of BRAF and MEK inhibitors like dabrafenib/trametinib, vemurafenib/cobimetinib and encorafenib/binimetinib<sup>12</sup>
  - c. Some biomarkers can be both predictive and prognostic
    - 1) TP53 mutations in CLL are associated with poor survival outcomes and lack of response to chemoimmunotherapy<sup>8</sup> (see Chronic Leukemias handout)
    - 2) FLT3 internal tandem duplication in AML is associated with increased relapse rate and reduced overall survival as well as response to inhibitors of FLT3 such as gilteritinib and midostaurin<sup>13</sup> (see Acute Leukemias handout)
- 2. Clinical interpretation<sup>2,14</sup>
  - a. Driver mutations
    - 1) Mutations that confer a selective advantage to cancer cell growth, development and/or survival
    - 2) Metastatic or advanced solid tumors generally have about 2 to 8 driver mutations
    - 3) Can be classified into 12 signaling pathways that regulate cell fate, cell survival and genome maintenance
    - 4) Examples of common driver mutations:
      - a) Tumor suppressor genes like TP53, RB1, ATM, and PTEN
      - b) Oncogenes like BRAF, EGFR, KRAS, MET, and PIK3CA
    - 5) These mutations are the most clinically relevant in assessing tumor genetics and determining prognostic or predictive value
  - b. Passenger mutations
    - 1) A mutation that does not have an effect on a cancer cell's growth, development or survival
    - 2) These mutations may have developed during the normal growth cycles of dividing cells
    - 3) These genes are less clinically relevant and generally do not determine prognostic or predictive value
    - 4) Whether a gene alteration is a driver or a passenger can differ between cancer type (i.e. A BRCA2 pathogenic alteration can be a driver mutation in a prostate cancer however BRCA2 pathogenic alterations may also be seen in colorectal cancer with MMR deficiency/microsatellite instability. In this latter case, the BRCA2 alteration may not be driving the cancer and may have occurred secondary to a very unstable genome. It can be difficult to determine driver vs. passenger alterations and functional/phenotype-based assays, such as those looking at loss of heterozygosity or homologous recombination (HR) deficiency (in the case of BRCA1/2 and other HR genes) may eventually help discern the pathways driving cancer growth).

**Patient Case #1 Discussion: Correct answer is B.**

AR-V7 is associated with a lower response to enzalutamide, which classifies it as a **predictive biomarker** because it provides information about response to a specific therapy. Insufficient information is available to determine whether AR-V7 is prognostic in nature; this requires treatment-independent cancer outcome analysis.

### III. Sequencing technologies



#### A. Testing platforms<sup>15,16</sup>

A full review of genomic principles is beyond the scope of this module but the “Cancer Genome Landscapes” paper under the recommended reading section provides a more complete discussion of basic genomic terminology and technology (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749880/>)

1. Deoxyribonucleic acid (DNA) sequencing
  - a. Assessment of the order of nucleotides in a DNA molecule
2. Transcriptomic ribonucleic acid (RNA) sequencing
  - a. The transcriptome is the total amount of mRNA and consists of the genes that are actively expressed at the time of analysis
  - b. Very helpful for assessing chromosome rearrangements/fusions but also detects splicing variants, expression profiles, and mutations in coding regions.
3. Proteomics
  - a. The proteome is comprised of all the expressed proteins in a cell
  - b. Helps with understanding functionality of proteins and pathways
  - c. Reflects both the impact of genes and the environment
4. Metabolomics
  - a. Assesses the profiles of metabolites within a system like a cancer cell
  - b. Metabolites are the final product of gene transcription and amplify changes in the transcriptome and proteome
  - c. Comprised of diverse biological molecules making it a more complex process of analysis

5. Epigenomics
  - a. Assess DNA methylation and histone modification profiles
  - b. Comprise and regulate the cancer transcriptome
  
- B. Next generation sequencing (NGS)<sup>17</sup>
  1. Also known as massively parallel sequencing (MPS) or high-throughput sequencing that is able to sequence millions of DNA fragments per run
  2. NGS is typically compared to “first generation sequencing” with Sanger sequencing being the primary technology used
  3. Sanger sequencing involved a targeted/candidate gene approach of amplifying exonic (coding) regions of genes of interest by polymerase chain reaction (PCR) and then sequencing these amplified DNA products. Sanger sequencing is only able to sequence a single DNA fragment at a time.
  4. Benefits of NGS compared with Sanger sequencing:
    - a. Significantly decreased cost
    - b. Improved sensitivity and scalability to analyze large genomes
    - c. Ability to detect multiple types of genetic alterations (single nucleotide variants, deletions, insertions, copy number alterations and rearrangements)
  5. The majority of the commercially available genetic tests now use NGS technology
  
- C. Breadth of genetic testing: typically, the broader the test, the lower the depth of testing
  1. Hotspot sequencing
    - a. Sequence only a targeted area of genes of interest
    - b. Allows for deeper coverage (more sequencing reads) and cheaper
    - c. May miss alterations outside of the targeted region
    - d. Clinical example:
      - 1) EGFR mutations are common in both lung cancer and glioblastoma. The EGFR mutations in lung cancer are most commonly found in the intracellular domain of EGFR while the EGFR alterations in glioblastoma are commonly located in the extracellular region. If only the intracellular region is sequenced on a test, this assay would not be very helpful for a glioblastoma patient where the mutations of interest are in a different location of the gene.<sup>18</sup>
  2. Whole exome sequencing (WES)<sup>19</sup>
    - a. Sequences all of the protein-coding genes in the genome
    - b. Contains about 85% of the known disease-related variants (though consists of < 2% of the total genome)
    - c. More cost-effective and more manageable amount of data than whole genome sequencing

- d. May not identify structural variants such as deletions, insertions, rearrangements and copy number alterations like amplifications
  - e. Unclear role in standard clinical practice currently
3. Whole genome sequencing (WGS)
- a. Sequences all the variants in the whole genome
  - b. Lower coverage of areas due to cost and time required
  - c. Produces a large amount of data, requiring large storage capacity and bioinformatics expertise for useful interpretation
  - d. Unclear role in standard clinical practice currently

**Patient Case #2:**

TL is a 67-year-old female with metastatic lung adenocarcinoma found to have an EGFR L858R activating mutation. She has metastatic disease involving the spine. She was initially treated with osimertinib and responded well to therapy for 16 months. Recent imaging shows progression in the lung and a new lesion in the brain. The medical team is planning to change therapy, but would like to assess for the presence of specific resistance mutations to guide this decision. Is TL an appropriate candidate for a cfDNA plasma based assay?

- A. No, because she has advanced disease that has progressed on first line therapy
- B. No, because cfDNA assays are not yet recommended in standard clinical practice
- C. Yes, because she is progressing on current therapy and has several sites of metastatic disease
- D. Yes, because she has a new lesion in the brain

**IV. Considerations for genetic testing**

- A. The American Society of Clinical Oncology (ASCO) published a Provisional Clinical Opinion focused on Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer on 2/17/2022.<sup>14</sup>
  - 1. Provides guidance on when NGS should be performed, what type of assay should be performed and how these results should guide treatment selection as well as lists definitions of commonly used Precision Oncology terminology including definitions of different type of alterations
  - 2. Patients with metastatic or advanced cancer should undergo NGS in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease
  - 3. Multi-gene panel-based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease
  - 4. The tumor agnostic approvals for high tumor mutational burden (TMB), deficient mismatch repair (dMMR)/microsatellite instability high (MSI-High) and neurotrophic tyrosine receptor kinase (NTRK)

fusions (discussed later in this module) provide rationale for genomic testing of all advanced solid tumors

5. The functional impact of the targeted alteration in addition to the expected efficacy of the genomic guided biomarker-driven therapy options should be considered relative to other approved or investigational treatments

## B. Selection of the type of genetic test

### 1. Tumor genetic testing<sup>20</sup>

- a. “Gold standard” for genetic analysis
- b. May be significantly invasive depending on the location of the tumor or metastases and other patient characteristics including performance status and comorbidities making sequential monitoring challenging
- c. Preparation of certain types of tissue biopsies (like bone) can make genetic analysis challenging
- d. Only part of the tumor is sent for analysis so genetic analysis may not account for tumor heterogeneity<sup>2,21</sup>
  - 1) Within a single tumor, different tumor cells may express different genetic mutations
  - 2) Tumor metastases can also have different genetic mutations compared with the original tumor
  - 3) The extent of tumor heterogeneity can provide insights into the evolution of the tumor
- e. Numerous commercial assays are available as well as many cancer centers also have their own internal NGS testing platforms

### 2. “Liquid” biopsies<sup>20,22</sup>

- a. Circulating tumor cells (CTC)
  - 1) Tumor cells that have passed from the tumor into the bloodstream
  - 2) Quantity of CTC in blood has been associated with survival outcomes in some studies of solid tumors
  - 3) CTCs can be used in both *in vivo* and *in vitro* functional assays to interrogate a cancer’s unique biology and test response to different treatments
  - 4) Current application into standard clinical practice remains controversial, primary place is in research at present
- b. Cell free DNA (cfDNA) assays<sup>20,23</sup>
  - 1) Cell free DNA is comprised of small circulating DNA fragments that are generated as a result of tumor apoptosis or necrosis and ultimately shed into the plasma
  - 2) May better reflect tumor heterogeneity though cannot tell the origin of each alteration
  - 3) Detection assays must have high specificity to detect the low numbers of tumor cfDNA in the presence of the more abundant normal cfDNA

- 4) Less invasive nature may be more amenable to sequential sampling to assess progression and resistance mutations after therapies
- 5) Patients who are currently responding to therapy may have a false negative test result due to low volume of active disease
- 6) Concordance between tumor and cfDNA<sup>23</sup>
  - a) 283 patients with advanced or metastatic solid tumors enrolled in the MOSCATO trial and had paired tumor and cfDNA samples that both underwent NGS analysis for 50 cancer genes
  - b) Sensitivity was 55% (121 patients had mutations in both samples, 99 in tumor only and 5 in cfDNA only)
  - c) Increased sensitivity associated with:
    - i. Higher number of metastatic sites
    - ii. Lower albumin level (below normal limit)
    - iii. Gastrointestinal and breast tumors compared with head/neck and lung
    - iv. Increased number of prior therapies
  - d) Patients with the above characteristics had an improved sensitivity (around 83%)
- 7) Examples of commercial cfDNA assays:
  - a) **cobas® EGFR Mutation test v.2** is a lung cancer companion diagnostic for erlotinib and osimertinib and detects 42 EGFR mutations, including exon 19 deletions and EGFR S768I, L861Q, L858R and mutations in plasma
  - b) **Guardant360, Foundation One Liquid and TEMPUS xF** are cfDNA assays for solid tumors that assess multiple clinically relevant genes (listed below)

**Patient Case #2 Discussion: Correct answer is C**

This patient would be a good candidate for cfDNA plasma based testing because she has a high volume of disease that is currently progressing on osimertinib. Though she does have a brain lesion that may not shed enough cfDNA across the blood-brain barrier, she has other sites of progressive disease outside the brain. Several commercial cfDNA assays are available for use in clinical practice and in patients with advanced disease.

- C. Both tumor-based and cfDNA-based assays can differ based on a variety of different characteristics.
- Clinical consideration for test selection:
1. What variants are detected on the test?
  2. What hotspot areas of genes of interest are included?

3. What types of alterations are detected (single nucleotide variants, amplifications, deletions, truncations, fusions, etc.)?
  4. What is the lower limit of detection of the assay?
  5. What is the depth of variant coverage?
  6. Is matched-normal tissue also assessed?
  7. Is RNA assessed in addition to DNA?
  8. Is tumor mutation burden or microsatellite instability reported as part of the assay?
  9. What is the cost and turn-around time?
- D. Clinical interpretation of variants<sup>24,25</sup>
1. Definition of **clinical actionability**
    - a. Predicts response to a treatment
    - b. Is a specific eligibility criteria for a clinical trial
    - c. Helps to establish a diagnosis or prognosis
    - d. Is a germline alteration that predicts for a hereditary condition or alters drug pharmacokinetics or dynamics
  2. Levels of clinical actionability
    - a. FDA approved therapy in **patient's** tumor type
    - b. FDA approved therapy in **different** tumor type
    - c. Clinical trial based on specific mutation being part of the inclusion criteria
    - d. Clinical trial based on application of pathway biology
    - e. Prognostic information
    - f. Not clinically actionable at this time
  3. Quality of supporting data (strongest to weakest)
    - a. FDA approved for the same tumor type and included in guideline recommendations
    - b. Adequately powered, prospective trial with biomarker stratification or a large meta-analysis
    - c. Single arm or retrospective cohort or case-control trial
    - d. Case studies or case reports
    - e. Preclinical data from *in vitro* or *in vivo* models
  4. Variants of **known** significance
    - a. Clinical impact of the genetic alteration has been described in the literature
    - b. Determined by evaluation of available knowledge bases and other bioinformatics tools (table 4)
    - c. Typically used to direct treatment recommendations
    - d. Example: BRAF V600E in melanoma and lung cancer to predict benefit from BRAF and MEK inhibitors
  5. Variants of **unknown** significance (VUS)

- a. Clinical impact of the genetic alteration is unknown
  - b. Generally not used to direct treatment decisions at this time
6. Germline variants
- a. Can be subtracted out and/or reported separately if matched normal tissue is analyzed with tumor tissue. Not all clinical tests include normal sample analysis
  - b. Cross referencing with databases like ExAC and ClinVar can indicate if the variant has been seen in normal samples previously. This data can be race/ethnicity specific so this needs to be considered in context with the patient's characteristics
  - c. Allele frequency of near 50% or 100% may also be indicative of a germline alteration (though this is based on the percent tumor in the sample being analyzed and other testing characteristics)
  - d. ACMG has recommendations for reporting of suspected germline mutations related to hereditary syndromes that are found as incidental findings.<sup>26</sup> Patients with these alterations should be referred for germline genetic testing
  - e. **Tissue-based and cfDNA based assays are typically not optimized for detecting germline alterations. If a clinically relevant germline alteration is suspected based on a somatic focused assay, then referral to a Clinical Geneticist and/or Genetic Counselor is recommended for discussion of germline testing.**
- E. Patient-Oncologist discussion and decision
- 1. Consideration of patient specific factors to put the genetic test results into clinical context
    - a. Does the patient qualify for a clinical trial?
    - b. Is the patient interested and willing to travel for a clinical trial?
    - c. What type of insurance does the patient have and will it cover off label therapy?
    - d. Consideration of future options/clinical trials when sequencing therapy
    - e. Strength of available data to support benefit compared with non-targeted treatment options



Selected bioinformatics resources for determining clinical actionability of genetic mutations<sup>25</sup>

Category	Resource	Utility
Variants of Unknown Significance	<b>1000 Genomes Project</b> ( <a href="http://www.1000genomes.org/">http://www.1000genomes.org/</a> )	Provide a probability of the variant being germline
	<b>Exome Variant Server</b> ( <a href="http://evs.gs.washington.edu/EVS/">http://evs.gs.washington.edu/EVS/</a> )	Provide a probability of the variant being germline
	<b>Genome Aggregation Database (GnomAD)</b> ( <a href="http://gnomad.broadinstitute.org/">http://gnomad.broadinstitute.org/</a> )	Summary of data from a variety of large-scale sequencing projects
Inherited Cancer Risk	<b>International Agency for Research on Cancer (IARC)</b> ( <a href="http://p53.iarc.fr/">http://p53.iarc.fr/</a> )	Frequency of a TP53 mutation in germline and tumor samples
	<b>HCI Breast Cancer Gene Prior Probabilities (BRCA)</b> ( <a href="http://priors.hci.utah.edu/PRIORS">http://priors.hci.utah.edu/PRIORS</a> )	Provides data on all possible single nucleotide substitutions in BRCA1/2 including likelihood of being deleterious. <b>AlignGVGD scores</b> are reported on a scale of <b>C0 to C65</b> with C0 being likely benign and C65 being likely pathogenic
	<b>ClinVar</b> ( <a href="http://www.ncbi.nlm.nih.gov/clinvar/">http://www.ncbi.nlm.nih.gov/clinvar/</a> )	Association of a variant with an inherited disease and somatic actionability
	<b>American College for Clinical Genetics (ACMG)</b> <a href="https://www.acmg.net/">https://www.acmg.net/</a>	Association of a variant with an inherited disease
Variants from across Cancer Types	<b>cBioPortal</b> ( <a href="http://www.cbioportal.org/">http://www.cbioportal.org/</a> )	Frequency of a variant across cancer types and the location of the variant in the functional domains of the gene
	<b>Catalogue of Somatic Mutations in Cancer (COSMIC)</b> ( <a href="http://cancer.sanger.ac.uk/cosmic">http://cancer.sanger.ac.uk/cosmic</a> )	The frequency of a variant across cancer types
Therapeutic Association	<b>MyCancerGenome</b> ( <a href="http://www.mycancergenome.org/">http://www.mycancergenome.org/</a> )	Association of mutation with tumorigenesis, related therapeutic implications and available clinical trials
	<b>PharmGKB</b> ( <a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a> )	Interactive tool for researchers investigating how genetic variation affects drug response
	<b>Precision Oncology Knowledge Base (OncoKB)</b> ( <a href="http://oncokb.org/#/">http://oncokb.org/#/</a> )	Effects and treatments for specific cancer gene alterations including available clinical trials
	<b>ClinicalTrials.gov</b> ( <a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a> )	Provides information about current ongoing clinical research studies

**Patient Case #3:**

MS is a 38-year-old woman with metastatic cervical cancer who has received 2 prior lines of chemotherapy. Her original tissue is found to have a PD-L1 Combined Positive Score (CPS) of 80 on the PD-L1 22C3 PharmDx assay. Based on this, her oncology team is considering immune checkpoint inhibitor therapy. Which of the following is the best choice for MS at this time?

- A. Nivolumab
- B. Atezolizumab
- C. Pembrolizumab
- D. Avelumab

**V. Companion and Complementary Diagnostics<sup>27,28</sup>**

A. Companion diagnostic test

1. A test that is an *in vitro* diagnostic device that provides information **essential** for the safe and effective use of the associated drug
2. These tests resulted from the identification of predictive biomarkers and subsequent analytical and clinical validation of these biomarkers
3. Examples:
  - a. COBAS 4800 BRAF V600 Mutation Test: The presence of BRAF V600 alterations in melanoma are associated with therapeutic benefits, however giving BRAF inhibitors to patients without an activating BRAF mutation can result in harm due to compensatory signaling.
  - b. PD-L1 IHC 22C3 PharmDx: Indicated in NSCLC to determine a Tumor Proportion Score (TPS) (percentage of viable tumor cells showing partial or complete membrane staining at any intensity). Pembrolizumab is indicated in the first line metastatic setting for NSCLC tumors with TPS  $\geq$  50% and for treatment of NSCLC following progression on a platinum-based regimen in tumors with  $\geq$  1%. (A more complete list of pembrolizumab FDA approvals is discussed below)

FoundationOne CDx is a companion diagnostic for the following therapies and indications:

Indications	Biomarker	FDA-Approved Therapies
<b>Non-Small Cell Lung Cancer</b>	EGFR exon 19 deletions and EGFR exon 21 L858R alterations	EGFR tyrosine kinase inhibitors (TKI) approved by the FDA
	EGFR exon 20 T790M alterations	Osimertinib
	ALK rearrangements	Alectinib, brigatinib, crizotinib or ceritinib
	BRAF V600E	Dabrafenib in combination with trametinib
	MET exon 14 skipping alterations	Capmatinib
<b>Melanoma</b>	BRAF V600E	BRAF inhibitors (TKI) approved by the FDA
	BRAF V600E or V600K	Trametinib or BRAF/MEK inhibitor combinations approved by the FDA
	BRAF V600 mutation-positive	Atezolizumab in combination with cobimetinib and vemurafenib
<b>Breast Cancer</b>	ERBB2 (Her2) amplification	Trastuzumab, ado-trastuzumab emtansine or pertuzumab
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Alpelisib
<b>Colorectal Cancer</b>	KRAS wild-type (absence of mutations in codons 12 and 13)	Cetuximab
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3 and 4)	Panitumumab
<b>Ovarian Cancer</b>	BRCA 1/2 alterations	Rucaparib, olaparib
<b>Cholangiocarcinoma</b>	FGFR2 fusions and select rearrangements	Pemigatinib or infigratinib
<b>Prostate Cancer</b>	Homologous Recombination Repair (HRR) gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L) alterations	Olaparib
<b>Solid Tumors</b>	Tumor mutation burden $\geq 10$ mutations per megabase	Pembrolizumab
	MSI-high	Pembrolizumab
	NTRK 1/2/3 fusions	Larotrectinib

**Selected oncology companion diagnostic tests (not including Foundation One CDx discussed above)**

Gene	Drug(s)	Cancer	Test
<b>KRAS</b>	Cetuximab, panitumumab	Colorectal	cobas KRAS Mutation test (IHC) <i>therascreen</i> KRAS RGO PCR Kit
<b>KRAS G12C</b>	Sotorasib	NSCLC	Guardant360 CDx
<b>EGFR exon 19 deletions, L858R and T790M</b>	Osimertinib	NSCLC	Guardant360 CDx
<b>EGFR exon 20 insertions</b>	Amivantamb-vmjw	NSCLC	Guardant360 CDx
<b>EGFR</b>	Osimertinib, erlotinib	NSCLC	cobas EGFR Mutation test v2 (PCR)
<b>KIT</b>	Imatinib	Gastrointestinal stromal tumor (GIST)	DAKO C-KIT PharmDx (IHC)
<b>Her2-Neu</b>	Trastuzumab	Breast	Numerous FISH, IHC, CISH and ISH tests
<b>Her2-Neu</b>	Trastuzumab, pertuzumab, ado-trastuzumab	Breast	HERCEPTEST (IHC) Her2 FISH PharmDx Kit
<b>PD-L1</b>	Pembrolizumab	NSCLC	PD-L1 IHC 22C3 PharmDx
<b>BRCA1, BRCA2</b>	Olaparib	Ovarian	BRACAnalysis CDx (PCR)
<b>Homologous Recombination Deficiency (HRD) score</b>	Olaparib and bevacizumab Niraparib	Ovarian	Myriad myChoice CDx
<b>BRAF</b>	Dabrafenib, trametinib	Melanoma	THxID BRAF Kit (PCR)
<b>BRAF</b>	Vemurafenib	Melanoma	Cobas 4800 BRAF V600 Mutation test (PCR)
<b>FLT3</b>	Midostaurin, gilteritinib	AML	LeukoStrat CDx FLT3 Mutation Assay (PCR)
<b>TP53, ATM, D13S319</b>	Venetoclax	CLL	Vysis CLL FISH Probe Kit
<b>ALK fusions</b>	Crizotinib Crizotinib, ceritinib and alectinib	NSCLC	VYSIS ALK Break Apart FISH Probe Kit VENTANA ALK (D5F3) CDx Assay (IHC)
<b>PIK3CA activating mutations</b>	Alpelisib	ER + Breast	<i>therascreen</i> PIK3CA RGQ PCR Kit
<b>MMR</b>	Dostarlimab-gxly	Solid tumors	VENTANA MMR RxDx Panel

IHC: Immunohistochemistry; PCR: real-time polymerase chain reaction; FISH: fluorescence *in situ* hybridization; ISH: *in situ* hybridization; CISH: chromogenic *in situ* hybridization

c. PD-L1 companion diagnostic tests

1) **Pembrolizumab, atezolizumab** and more recently **nivolumab** currently have companion diagnostic tests which specify cut off values associated with each cancer histology.

2) Pembrolizumab<sup>29</sup>

a) The PD-L1 22C3 PharmDx assay can report both Tumor Proportion Score and Combined Positive Score

b) PD-L1 Tumor Proportion Score (**TPS**)

i. Measures the percentage of viable tumor cells showing partial or complete membrane staining of any intensity

$$TPS = \left( \frac{\text{\# of viable tumor cells with any intensity of PD-L1 staining}}{\text{Total number of viable tumor cells}} \right) \times 100$$

c) Combined Positive Score (**CPS**):

i. Measures both tumor and tumor associated immune cells

ii. The score may be > 100 but the reported maximum score is 100

$$CPS = \left( \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total number of viable tumor cells}} \right) \times 100$$

3) Nivolumab<sup>30</sup>

a) PD-L1 IHC 28-8 PharmDx assay measures the percentage of viable tumor cells showing partial or complete membrane staining of any intensity similar to the TPS described above for pembrolizumab

4) Atezolizumab<sup>31</sup>

a) VENTANA PD-L1 (SP 142) Assay reports both:

i. The proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity

ii. Percentage of PD-L1 expressing cells (% TC) of any intensity

### Indications with PD-L1 threshold companion diagnostic requirements\*<sup>29-31</sup>

Drug	Cancer Type	PD-L1 status	Indication
<b>Pembrolizumab</b>	NSCLC	TPS $\geq$ 1%	<ul style="list-style-type: none"> <li>Single agent therapy for <b>first-line</b> treatment of metastatic or unresectable stage III NSCLC without EGFR or ALK alterations</li> <li>Single agent for metastatic NSCLC after platinum-based chemotherapy (or targeted therapy if ALK or EGFR positive)</li> </ul>
	Cervical	CPS $\geq$ 1	<ul style="list-style-type: none"> <li>Single agent therapy for recurrent or metastatic cervical cancer after progression on or after prior chemotherapy</li> <li>In combination with chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer</li> </ul>
	Head and Neck squamous cell carcinoma (HNSCC)	CPS $\geq$ 1	<ul style="list-style-type: none"> <li>Single agent therapy for <b>first-line</b> treatment of metastatic or unresectable, recurrent HNSCC</li> </ul>
	Esophageal Squamous cell carcinoma	CPS $\geq$ 10	<ul style="list-style-type: none"> <li>Single agent after at least one prior line of systemic therapy for patients with squamous cell carcinoma histology</li> </ul>
<b>Nivolumab</b>	NSCLC	PD-L1 $\geq$ 1%	<ul style="list-style-type: none"> <li>Combination therapy with ipilimumab for <b>first-line</b> treatment of metastatic NSCLC without EGFR or ALK alterations</li> </ul>
<b>Atezolizumab</b>	Bladder	IC $\geq$ 5%	<ul style="list-style-type: none"> <li>Single agent therapy for <b>first-line</b> treatment of locally advanced or metastatic urothelial carcinoma in patients who are <b>not eligible for cisplatin-based</b> therapy</li> <li>Patients not eligible for <b>ANY</b> platinum-based therapy may receive regardless of IC score</li> </ul>
	NSCLC	TC $\geq$ 50% IC $\geq$ 10%	<ul style="list-style-type: none"> <li>Single agent therapy for <b>first-line</b> treatment of metastatic NSCLC with no EGFR or ALK genomic tumor alterations</li> </ul>

\* This is not an inclusive list of all approvals for the agents listed. Some tumor types listed above have additional approvals with these drugs that do not include PD-L1 expression thresholds. Please refer to the package insert of associated disease modules for a more complete discussion of places in therapy.

#### B. Complementary diagnostic test

1. A test that improves the risk/benefit ratio of a specific drug but **does not restrict access** to the drug based on presence of the biomarker
2. These are associated with drugs for which therapeutic benefit has been described for all patients, regardless of presence of the biomarker, but can help identify patients who may have enhanced benefits
3. Examples:
  - a. PD-L1 IHC 28-8 test for nivolumab in patients with melanoma

**Patient Case #3 Discussion: Correct answer is C**

The PD-L1 22C3 assay is the companion diagnostic for pembrolizumab. Nivolumab uses the IHC 28-8 assay and atezolizumab uses the PD-L1 SP142 assay. Pembrolizumab is FDA approved as single agent in patients with metastatic cervical cancer following disease progression on or after chemotherapy for tumors that express PD-L1 CPS  $\geq 1$ . This patient's CPS score was 80.

**Patient Case #4**

RM is a 55 year-old female with metastatic endometrioid adenocarcinoma of the endometrium who was initially treated with carboplatin and paclitaxel followed by a phase I clinical trial with a novel PI3K inhibitor. She developed a new lower quadrant mass that was biopsied and confirmed to be recurrent disease. The sample was sent for NGS testing and found to be MSI-High. Which of the following treatment options is the most appropriate for RM at this time?

- A. Nivolumab
- B. Nivolumab and ipilimumab
- C. Pembrolizumab
- D. Atezolizumab

**VI. DNA Mismatch Repair Deficiency (dMMR) and Microsatellite Instability (MSI)<sup>32</sup>**

- A. DNA mismatch repair (MMR) enzymes correct errors that occur during normal DNA replication. Inactivation of these MMR enzymes result in more errors occurring and the development of microsatellite fragments
- B. Presence of dMMR or microsatellite instability (MSI) is most common in colorectal cancer (around 15-19%) and endometrial cancer (22-33%). Presence of dMMR or MSI has been associated with response to immunotherapy<sup>33</sup>
- C. dMMR and MSI testing
  - 1. Tumor is tested for microsatellite instability (MSI) or testing for loss of expression of genes involved in DNA mismatch repair (*MLH1*, *MSH2*, *MSH6*, and *PMS2*)
    - a. MMR status is determined by using immunohistochemistry (IHC) to assess the expression of *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes that are involved in DNA mismatch repair
      - 1) pMMR = proficient mismatch repair (all 4 genes are expressed)
      - 2) dMMR = defective mismatch repair (loss of expression of  $\geq 1$  of the genes)
    - b. MSI is indicative of a hypermutated phenotype in the tumor and consists of insertion or deletion alterations in stretches of short tandem DNA repeats called microsatellites, in addition to a higher number of gene mutations throughout the tumor DNA
    - c. The number of repeated nucleotide sequences should be the same within a cell, but when the number of nucleotides has gained or lost repeat units, MSI is present
    - d. MSI testing is typically performed via genetic analysis

- 1) MSS = microsatellite-stable tumor
  - 2) MSI-L = low level microsatellite instability
  - 3) MSI-H = high level microsatellite instability
- e. Patients with dMMR status are biologically the same as those with MSI-H status
- D. Immune checkpoint inhibitor approvals
1. Pembrolizumab<sup>29,33</sup>
    - a. Approved for the treatment of adult and pediatric patients with unresectable or metastatic MSI-high or dMMR **solid tumors** (following prior therapy with no satisfactory alternatives)
    - b. Approved for the treatment of adult and pediatric patients with unresectable or metastatic MSI-high or MMR deficient **colorectal cancer** as first-line therapy (see Lower GI module for more discussion)
    - c. Currently not yet established for pediatric patients with MSI-high central nervous system tumors
  2. Nivolumab with or without ipilimumab<sup>30</sup>
    - a. Approved for the treatment of adult and pediatric patients with MSI-H or dMMR metastatic **colorectal cancer** following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan
  3. Dostarlimab-gxly<sup>34</sup>
    - a. Granted accelerated approval for adult patients with dMMR recurrent or advanced solid tumors who have progressed on or following prior treatment with no satisfactory alternatives.
    - b. Granted accelerated approval for adult patients with dMMR recurrent or advanced endometrial cancer who have progressed following a prior platinum-based regimen (see Gynecologic Oncology module for more discussion)

## VII. Tumor Mutation Burden (TMB)<sup>35</sup>

- A. TMB is defined as the number of non-synonymous mutations (i.e. mutations that ultimately result in a change of amino acid) in tumor
1. Mutations found in a tumor can create novel antigens, called “neoantigens” that can be recognized as foreign by T-cells. A higher number of mutations may increase the chance of a neoantigen developing and thus can increase the chance of benefit from immunotherapy like immune checkpoint inhibitors
  2. High TMB is most commonly seen in tumors that are associated with environmental exposures like tobacco exposure and UV light as well as certain DNA damage deficiencies like dMMR as discussed above
- B. Correlation between TMB and response to immune checkpoint inhibitor therapy
1. Initially described in melanoma patients treated with CTLA4-inhibitors and NSCLC patients treated with ipilimumab and nivolumab, independent of PD-L1 status<sup>36,37</sup>
  2. A review of 1662 solid tumor patients treated on the MSK-IMPACT trial showed that across most histologies, higher somatic tumor mutation burden (defined as the highest 20% of each histology) was associated with better overall survival from immune checkpoint inhibitors.



- a. Notable exceptions to this included gliomas, ER-negative breast cancer and, to a lesser extent, renal cell carcinoma. Some of these histologies had a smaller sample size that may have limited the assessment however<sup>38</sup>
- 3. KEYNOTE-158 trial<sup>39</sup>
  - a. A total of 805 patients across different tumor histologies were treated with pembrolizumab and evaluable for TMB. A high TMB (defined as  $\geq 10$  mutations/Mb by the Foundation CDx<sup>®</sup> panel) was found in 105 patients.
    - 1) In the high TMB group, 33% of patients had SCLC, 16% had cervical cancer, 15% had endometrial cancer, 14% had anal cancer, 12% had vulvar cancer, 5% had neuroendocrine cancer and the remaining patients (1-3%) had salivary, thyroid or mesothelioma.
  - b. The primary endpoint was overall response rate (ORR) by RECIST v1.1 by independent central review
    - 1) The ORR was 29% for all high TMB patients and 28% when the patients with MSI-H were excluded compared with an ORR of 6% in those with non-high TMB tumors.
    - 2) In those with high TMB, excluding the 21 patients with MSI-high tumors, the complete response rate was 3%, partial response rate 25% and stable disease in 14%
    - 3) The median duration of response had not yet been reached in either high TMB or non-high TMB groups yet.
  - c. Based on the results of the KEYNOTE-158 trial, pembrolizumab was granted accelerated approval by the FDA for adult and pediatric patients with unresectable or metastatic TMB  $\geq 10$  mutations/Mb that have progressed following prior treatment and who have no satisfactory alternative treatment options. Notably, this excludes pediatric patients with high TMB central nervous system cancers

**Patient Case #4 Discussion: Correct answer is C**

Currently, pembrolizumab and dostarlimab-gxly are indicated for MSI-high non-colorectal solid tumors. Nivolumab with or without ipilimumab is an option for patients with MSI-high colorectal cancers following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan. Atezolizumab is currently not approved for any MSI-high tumors.

### **Patient Case #5**

OB is a 38-year-old male with metastatic soft tissue sarcoma that has progressed on 3 prior lines of therapy. A cfDNA test is performed and revealed a **TPM3-NTRK1 fusion** predicted to result in intron 7 of TPM3 fused to intron 9 of NTRK1. The medical team is considering starting therapy with larotrectinib.

Is larotrectinib appropriate for this patient at this time?

- A. Yes, larotrectinib is appropriate for activating NTRK1 fusions
- B. No, larotrectinib is only approved for pediatric sarcomas
- C. No, larotrectinib is only approved for activating NTRK1 missense mutations
- D. No, because this was a cell free DNA rather than tumor based NGS test

### **VIII. Solid tumors with neurotrophic receptor tyrosine kinase (NTRK) fusions<sup>40</sup>**

- A. NTRK fusions<sup>41</sup>
  - 1. NTRK family of kinases includes NTRK1, NTRK2 and NTRK3 which encode the transmembrane receptors TRKA, TRKB and TRKC, respectively and are involved in neural development
  - 2. The NTRK family can fuse with numerous reported gene partners and can result in constitutively active, ligand independent signaling
  - 3. Up to 1% of all solid tumors may have an NTRK fusion, however they are most prevalent in salivary-gland tumors, soft tissue sarcomas, infantile fibrosarcoma and thyroid tumors
- B. Larotrectinib<sup>40,41</sup>
  - 1. First tyrosine kinase inhibitor approved for a tissue agnostic indication in both pediatric and adult patients (FDA approved 11/26/2018)
  - 2. Clinical data<sup>40,42</sup>
    - a. A total of 55 patients (age range 4 months to 76 years old) with NTRK-fusion positive solid tumors were enrolled on one of 3 protocols trials including a phase I trial in adults, a phase I trial in children and a phase 1-2 trial in adults and adolescents
      - 1) 17 different solid tumor types were represented
      - 2) The overall response rate was 75% (95% CI 61-85) by independent review
      - 3) After 1 year, 71% of the responses were ongoing and 55% of the patients were free of progression
      - 4) No patient discontinued the drug due to adverse effects<sup>40</sup>
    - b. Expanded data includes 159 patients from one of 3 protocols including a phase I trial in adults, a phase I/II trial in children and a phase II trial in adolescents
      - 1) Included the original 55 patients from the above analysis
      - 2) Median age (range): 43 (< 1 month to 84 years)
      - 3) Objective response rate was 79% with 24 complete responses
      - 4) Median duration of response was 35.2 months (95% CI 22.8 to not estimable)

- 5) 8% of patients required a dose reduction due to toxicity with 2% ultimately discontinuing treatment<sup>42</sup>

3. Dosing

- a. Available as 25 mg and 100 mg capsules and 20 mg/mL oral solution
- b. For body surface area (BSA)  $\geq 1 \text{ m}^2$ : 100 mg PO BID
- c. For BSA  $< 1 \text{ m}^2$ : 100 mg/m<sup>2</sup> PO BID

- C. Entrectinib<sup>43</sup>

1. FDA approved 8/15/2019

2. Pan-TRK oral kinase inhibitor FDA approved for adult and pediatric patients 12 years of age and older with solid tumors that:

- a. Have an NTRK gene fusion without known acquired resistance mutation AND
- b. Have metastatic disease or where surgical resection is likely to result in severe morbidity AND
- c. Have no satisfactory alternative treatments or have progressed following treatment

3. Also inhibits ROS1 and ALK and is FDA approved for adult patients with metastatic ROS1 fusion positive NSCLC (see Lung Cancer handout for more discussion)

4. Dosing

- a. Available as 100 and 200 mg capsules
- b. Adults: 600 mg PO once daily
- c. Pediatric dosing is based on body surface area (BSA).
  - 1) BSA  $> 1.50 \text{ m}^2$ : 600 mg PO once daily (adult dose)
  - 2) BSA  $1.11 - 1.50 \text{ m}^2$ : 500 mg PO once daily
  - 3) BSA  $0.91 - 1.10 \text{ m}^2$ : 400 mg PO once daily

5. Metabolism is predominantly CYP3A4 so avoid moderate and strong inhibitors or inducers or use package insert dose reductions

6. Common adverse effects

- a. Fatigue, taste alterations, visual changes, edema, increased weight, cognitive impairment, nausea, dizziness, constipation and diarrhea

7. Clinical data<sup>43,44</sup>

- a. Four clinical trials evaluated 54 patients with NTRK-fusion positive solid tumors
- b. The most common cancers enrolled were lung, salivary gland, breast, thyroid and colorectal
  - 1) ETV6-NTRK3 was the most commonly reported NTRK fusion (46% of patients)
  - 2) Median age (range): 58 (48-67) years
- c. Overall response rate was 57%
  - 1) Complete response rate: 7%

- 2) Partial response rate: 50%
- d. Median duration of response was 10 months
- e. 4% of patients discontinued due to adverse effects

**Patient Case #5 Discussion: Correct answer is A**

Larotrectinib would be appropriate at this time. This patient has an activating NTRK1 fusion in a metastatic tumor that has progressed on three prior lines of therapy. Larotrectinib is approved for use in both pediatric and adult patients with NTRK1-3 gene fusions, consistent with this TPM3-NTRK1 fusion. Clinically relevant missense NTRK1-3 mutations are typically described in the acquired resistance setting. Both cell free DNA and tumor-based NGS assays are acceptable for identifying NTRK1-3 fusions.

**IX. Solid tumors with BRAF V600E mutations**

- A. The combination of dabrafenib and trametinib has been FDA approved for certain melanomas with BRAF V600E/K mutations, metastatic NSCLC with BRAF V600E mutations and locally advanced or metastatic anaplastic thyroid cancers with BRAF V600E mutations.
- B. The combination is now also **approved for adults and pediatric patients  $\geq 6$  years of age with unresectable or metastatic solid tumors with the BRAF V600E mutation who have no satisfactory alternative treatment options.**
  - 1. **Patients with BRAF V600E mutated colorectal cancer are excluded from this approval**
  - 2. Dosing for pediatric patients  $\leq 50$  kg is weight based
- C. Approval is based on data from three clinical trials: NCI-MATCH subprotocol H, phase 2 Rare Oncology Agnostic Research (ROAR) trial and Study X2102
  - 1. NCI-MATCH subprotocol H<sup>45</sup>
    - a. Open-label, single arm subprotocol of the larger NCI-MATCH basket trial
    - b. Patients with advanced solid tumor (excluding melanoma, thyroid, colorectal and later NSCLC) were treated with dabrafenib 150 mg BID and trametinib 2 mg daily.
    - c. The primary efficacy analysis included 29 patients and demonstrated a confirmed objective response rate of 38% (90% CI, 22.9 to 54.9%) with  $p < 0.0001$  vs. the null rate of 5% per the MATCH statistical rules.
    - d. The median progression free survival (PFS) was 11.4 months (90% CI 8.4 to 16.3 months) with 4 patients having a duration of response  $> 24$  months.
    - e. Responses were seen in patients with 7 different tumor types including those with primary CNS, cholangiocarcinoma and gynecologic malignancies.
  - 2. ROAR

- a. Ongoing, phase 2, open-label single arm basket trial for patients with BRAF V600E-mutated rare cancers. All patients were treated with the standard dabrafenib 150 mg BID and trametinib 2 mg daily.
  - b. Primary glioma cohort of 45 patients with high-grade glioma and 13 patients with low-grade glioma<sup>46</sup>
    - 1) In the high-grade glioma cohort (including 31 patients with glioblastoma), the objective response rate was 33% (95% CI, 20-49%). This included 3 complete responses and 12 partial responses.
    - 2) In the low-grade glioma cohort, the objective response rate was 69% (95% CI, 39-91%). This included one complete response, 6 partial responses and 2 minor responses.
  - c. Biliary tract cohort of 43 patients<sup>47</sup>
    - 1) The independent review-assessed overall response rate was 47% (95% CI, 31-62%). This included 20 partial responses.
3. Study X2102
- a. Limited information available for this trial that focused on pediatric patients with BRAF V600E mutated cancers and demonstrated acceptable safety with clinical benefit.

#### **X. Solid tumors positive for RET-fusions<sup>48</sup>**

- A. Selpercatinib has been FDA approved for adult patients with locally advanced or metastatic NSCLC with a RET gene fusion, adult and pediatric patients  $\geq 12$  with advanced or metastatic medullary thyroid cancer with a RET mutation and thyroid cancer with a RET gene fusion who required systemic therapy (and are radioactive iodine (RAI)-refractory (if RAI is appropriate).
- B. Selpercatinib is now also **FDA approved for adult patients with locally advanced or metastatic tumors with a RET fusion who have progressed on or following prior systemic therapies and who have no satisfactory alternative treatment options**
  - 1. The tumor agnostic approval is based on data from the LIBRETTO-001 trial
    - a. The LIBRETTO-001 trial is a phase 1/2, open-label, multi-cohort study that included arms for NSCLC and thyroid cancer, which were previously published and are discussed in the associated disease modules (See the Lung Cancer and Head, Neck, Thyroid and CNS Handouts).
    - b. The tumor-agnostic cohort included 45 patients with RET-fusion positive solid tumors representing 14 different histologies (excluding NSCLC and thyroid cancer).
    - c. Forty-one patients were evaluable and the ORR by independent review was 43.9% (95% CI 28.5-60.3%) with a complete response seen in 2 patients (one with breast cancer and the second with cancer of the small intestine).
    - d. The mPFS was 13.2 months (95% CI 7.4-26.2 months) by independent review

## Appendix 1: Gene Names

(Not all of the gene names are abbreviations but the common genes that are discussed in this module associated with abbreviations are listed below based on [www.genecards.com](http://www.genecards.com))

1. **APC**: Adenomatous Polyposis Coli
2. **ATM**: Ataxia Telangiectasia Mutated
3. **CYP2D6, CYP2C19, CYP2D6, CYP4F2**: Cytochrome P-450 2D6, 2C19, 2D6 AND 4F2
4. **DPYD**: Dihydropyrimidine Dehydrogenase
5. **EGFR**: Epidermal Growth Factor Receptor
6. **FBXW7**: F-Box and WD Repeat Domain
7. **FLT3**: Fms Related Tyrosine Kinase
8. **G6PD**: Glucose-6-Phosphate Dehydrogenase
9. **KRAS**: Kirsten Rat Sarcoma (2 Viral Oncogene Homolog)
10. **PIK3CA**: Phosphatidylinositol-4,5-Bisphosphonate 3-Kinase Catalytic Subunit
11. **PTEN**: Phosphatase and Tensin Homolog
12. **RB1**: Retinoblastoma 1
13. **TP53**: Tumor Protein P53
14. **TPMT**: Thiopurine S-Methyltransferase
15. **VHL**: Von Hippel-Lindau
16. **VKORC1**: Vitamin K Epoxide Reductase Complex Subunit 1

## SUGGESTED READINGS

1. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. *J Clin Oncol*. 2022;40(11):1231-58. <https://ascopubs.org/doi/full/10.1200/JCO.21.02767>
2. Ballman KV. Biomarker: predictive or prognostic. *J Clin Oncol*. 2015;33:3968-71. <http://ascopubs.org/doi/full/10.1200/jco.2015.63.3651>
3. Vogelstein B, et al. Cancer genome landscapes. *Science*. 2013;339:1546-58. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749880/> : This is an excellent reference for basic definitions pertaining to oncology related genomic principles and tests.
4. Doroshow DB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol*. 2021;18:345-62.

## REFERENCES

1. Garraway LA: Genomics-driven oncology: framework for an emerging paradigm. *J Clin Oncol* 31:1806-14, 2013
2. Vogelstein B, Papadopoulos N, Velculescu VE, et al: Cancer genome landscapes. *Science* 339:1546-58, 2013
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, v.2.2022, 3/9/2022 © 2022 National Comprehensive Cancer Network, Inc 2022. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, v.2.2022, 3/9/2022 © 2022 National Comprehensive Cancer Network, Inc 2022. All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal, v.1.2022, 6/8/2022 © 2022 National Comprehensive Cancer Network, Inc 2022. All rights reserved. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal, v.1.2022, 6/8/2022 © 2022 National Comprehensive Cancer Network, Inc 2022. All rights reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
5. Relling MV, Klein TE: CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther* 89:464-7, 2011
6. Ballman KV: Biomarker: Predictive or Prognostic? *Journal of Clinical Oncology* 33:3968-3971, 2015
7. Baselga J, Cortes J, Im SA, et al: Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in human epidermal growth factor receptor 2-positive, first-line metastatic breast cancer. *J Clin Oncol* 32:3753-61, 2014
8. Nabhan C, Raca G, Wang YL: Predicting Prognosis in Chronic Lymphocytic Leukemia in the Contemporary Era. *JAMA Oncol* 1:965-74, 2015
9. Sleijfer S, Bogaerts J, Siu LL: Designing transformative clinical trials in the cancer genome era. *J Clin Oncol* 31:1834-41, 2013
10. Thomas A, Liu SV, Subramaniam DS, et al: Refining the treatment of NSCLC according to histological and molecular subtypes. *Nat Rev Clin Oncol* 12:511-26, 2015
11. Allegra CJ, Jessup JM, Somerfield MR, et al: American Society of Clinical Oncology Provisional Clinical Opinion: Testing for KRAS Gene Mutations in Patients With Metastatic Colorectal Carcinoma to Predict

Response to Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Therapy. *Journal of Clinical Oncology* 27:2091-2096, 2009

12. Ribas A, Flaherty KT: BRAF targeted therapy changes the treatment paradigm in melanoma. *Nat Rev Clin Oncol* 8:426-33, 2011
13. Pratz KW, Levis M: How I treat FLT3-mutated AML. *Blood* 129:565-571, 2017
14. Chakravarty D, Johnson A, Sklar J, et al: Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. *Journal of Clinical Oncology* 40:1231-1258, 2022
15. Dienstmann R, Rodon J, Barretina J, et al: Genomic medicine frontier in human solid tumors: prospects and challenges. *J Clin Oncol* 31:1874-84, 2013
16. Horgan RP, Kenny LC: 'Omic' technologies: genomics, transcriptomics, proteomics and metabolomics. *The Obstetrician & Gynaecologist* 13:189-195, 2011
17. MacConaill LE: Existing and emerging technologies for tumor genomic profiling. *J Clin Oncol* 31:1815-24, 2013
18. Huang PH, Xu AM, White FM: Oncogenic EGFR signaling networks in glioma. *Sci Signal* 2:re6, 2009
19. van Dijk EL, Auger H, Jaszczyszyn Y, et al: Ten years of next-generation sequencing technology. *Trends Genet* 30:418-26, 2014
20. Siravegna G, Marsoni S, Siena S, et al: Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol* 14:531-548, 2017
21. McGranahan N, Swanton C: Biological and therapeutic impact of intratumor heterogeneity in cancer evolution. *Cancer Cell* 27:15-26, 2015
22. Krebs MG, Metcalf RL, Carter L, et al: Molecular analysis of circulating tumour cells-biology and biomarkers. *Nat Rev Clin Oncol* 11:129-44, 2014
23. Jovelet C, Ileana E, Le Deley MC, et al: Circulating Cell-Free Tumor DNA Analysis of 50 Genes by Next-Generation Sequencing in the Prospective MOSCATO Trial. *Clin Cancer Res* 22:2960-8, 2016
24. Meric-Bernstam F, Johnson A, Holla V, et al: A decision support framework for genomically informed investigational cancer therapy. *J Natl Cancer Inst* 107, 2015
25. Knepper TC, Bell GC, Hicks JK, et al: Key Lessons Learned from Moffitt's Molecular Tumor Board: The Clinical Genomics Action Committee Experience. *Oncologist* 22:144-151, 2017
26. Kalia SS, Adelman K, Bale SJ, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med* 19:249-255, 2017
27. Van Heertum RL, Scarimbolo R, Ford R, et al: Companion diagnostics and molecular imaging-enhanced approaches for oncology clinical trials. *Drug Des Devel Ther* 9:5215-23, 2015
28. Scheerens H, Malong A, Bassett K, et al: Current Status of Companion and Complementary Diagnostics: Strategic Considerations for Development and Launch. *Clin Transl Sci* 10:84-92, 2017
29. Pembrolizumab (Keytruda(R)) Prescribing Information, Merck & Co., Inc, Whitehouse Station, NJ, [https://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf) (Accessed 7/12/2022)
30. Nivolumab (Opdivo) Prescribing Information, Bristol-Myers Squibb Company, Princeton, NJ. [http://packageinserts.bms.com/pi/pi\\_opdivo.pdf](http://packageinserts.bms.com/pi/pi_opdivo.pdf) (Accessed 9/10/2022).
31. Atezolizumab (Tecentriq(R)) Prescribing Information, Genentech, Inc, South San Francisco, CA, <https://www.tecentriq-hcp.com/> (Accessed 7/12/2022)
32. Gatalica Z, Vranic S, Xiu J, et al: High microsatellite instability (MSI-H) colorectal carcinoma: a brief review of predictive biomarkers in the era of personalized medicine. *Fam Cancer* 15:405-12, 2016
33. Le DT, Uram JN, Wang H, et al: PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *New England Journal of Medicine* 372:2509-2520, 2015
34. Dostarlimab-gxly (Jemperli(R)) Prescribing Information, GlaxoSmithKlein, Research Triangle Park, NC, [https://gskpro.com/content/dam/global/hcpportal/en\\_US/Prescribing\\_Information/Jemperli/pdf/JEMPERLI-PI-MG.PDF](https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Jemperli/pdf/JEMPERLI-PI-MG.PDF) (Accessed 9/13/2021).
35. Havel JJ, Chowell D, Chan TA: The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer* 19:133-150, 2019
36. Snyder A, Makarov V, Merghoub T, et al: Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 371:2189-2199, 2014



37. Hellmann MD, Ciuleanu T-E, Pluzanski A, et al: Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *New England Journal of Medicine* 378:2093-2104, 2018
38. Samstein RM, Lee CH, Shoushtari AN, et al: Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet* 51:202-206, 2019
39. Marabelle A, Fakih M, Lopez J, et al: Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 21:1353-1365, 2020
40. Drilon A, Laetsch TW, Kummar S, et al: Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. *New England Journal of Medicine* 378:731-739, 2018
41. Schram AM, Chang MT, Jonsson P, et al: Fusions in solid tumours: diagnostic strategies, targeted therapy, and acquired resistance. *Nat Rev Clin Oncol* 14:735-748, 2017
42. Hong DS, DuBois SG, Kummar S, et al: Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* 21:531-540, 2020
43. Entrectinib (Rozlytrek) Prescribing Information G, South San Francisco, CA. [www.gene.com/download/pdf/rozlytrek\\_prescribing.pdf](http://www.gene.com/download/pdf/rozlytrek_prescribing.pdf) (accessed 9/19/2019):
44. Doebele RC, Drilon A, Paz-Ares L, et al: Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 21:271-282, 2020
45. Salama AKS, Li S, Macrae ER, et al: Dabrafenib and Trametinib in Patients With Tumors With BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. *Journal of Clinical Oncology* 38:3895-3904, 2020
46. Wen PY, Stein A, van den Bent M, et al: Dabrafenib plus trametinib in patients with BRAF(V600E)-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol* 23:53-64, 2022
47. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600–Mutant Anaplastic Thyroid Cancer. *Journal of Clinical Oncology* 36:7-13, 2018
48. Subbiah V, Wolf J, Konda B et al: Tumor-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol* 23:1261-73, 2022

# PROSTATE CANCER

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## Learning Objectives:

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with prostate cancer.
2. Discuss short- and long-term treatment goals, including post-therapy and survivorship, with a patient with prostate cancer and his caregiver.
3. Select relevant information and guidance for the public regarding prostate cancer-related issues (e.g., risk factors, prevention, screening).

## PROSTATE CANCER

**Patient Case #1:** DR is a 40-year-old Caucasian male with a past medical history of seasonal allergies. His primary care physician checked a PSA which resulted at 9 ng/ml and he had an abnormal digital rectal exam (DRE). Further imaging and biopsy reveal a very low risk prostate adenocarcinoma. He prefers a treatment strategy that minimizes adverse effects. **What is the most appropriate treatment option for DR at this time?**

- A. Active surveillance
- B. Radical prostatectomy + short term androgen deprivation therapy
- C. Radiation therapy + short term androgen deprivation therapy
- D. Observation

### I. Genomics, Etiology and Pathogenesis

- A. Dysregulation of signaling pathways are involved in initiation and progression of prostate cancer; however, the exact genes and pathways are not fully understood. Altered expression of NKX3.1, Forkhead box A1 (FOXA1), the androgen receptor (AR) and Myc are involved in early stage prostate cancer.<sup>1</sup>
  - 1. AR: Most well studied receptor involved in prostate cancer. Understood to be reactivated in disease that progresses despite castrate levels of testosterone. The term androgen-independent is no longer used. Castration resistant prostate cancer (CRPC) is the appropriate nomenclature. Several mechanisms for reactivation of AR are noted below and thought to be the mechanisms of resistance to hormonal manipulations.<sup>1</sup>
  - 2. Intratumoral androgen synthesis (autocrine androgen production): CYP17A1 and HSD17B2 are key enzymes in conversion of cholesterol to androgen precursors. These enzymes have been found to be 10-fold higher in metastatic prostate cancer cells. SRD5A1/2 codes for 5-alpha-reductase and is responsible for conversion of testosterone to dihydrotestosterone, which is also elevated in metastatic prostate cancer cells.<sup>1</sup>
- B. Family history plays a large role in prostate cancer risk. Prostate cancer is associated with Hereditary Breast and Ovarian Cancer (HBOC) syndrome, due to germline mutations in homologous recombination repair mutations (HRRm), as well as Lynch syndrome, due to germline mutations in DNA mismatch repair genes.<sup>1</sup>
- C. Tumor cells may have mutations in MLH1, MSH2, MSH6 or PMS2 resulting in microsatellite instability (MSI) or deficient mismatch repair (dMMR). The incidence of MSI-high tumors has been reported to be around 3% in studies of prostate cancer patients.<sup>2</sup> This may be due to germline mutations (as described above) or more often, due to somatic mutations. NCCN Clinical Practice Guidelines (NCCN®) state that somatic MSI/dMMR testing could be considered for regional or castrate sensitive metastatic disease and is recommended in metastatic castrate resistant disease (if not conducted previously).<sup>3</sup>
- D. Prostate cancer is also associated with somatic HRRm (mutations found in tumor DNA rather than germline). Mutations in HRR genes may be somatic or germline and the prevalence in the metastatic castrate-resistant setting has been reported up to 33%.<sup>4</sup> Knowledge of germline mutations can impact family genetic screening, prognosis (BRCA1/2 germline mutations known to have increased risk of progression on local therapy and decreased overall survival), and potential implications for treatment in advanced disease.<sup>5</sup>

1. NCCN Guidelines® recommend germline testing for all high-risk, very high-risk, regional, or metastatic prostate cancer (regardless of family history) as well as those with prostate cancer and a positive family history, or Ashkenazi Jewish ancestry. Germline testing may also be considered in patients with intermediate-risk prostate cancer and intraductal histology or those with personal history of prostate cancer and a second cancer (exocrine pancreas, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary, or small intestine). NCCN strongly recommends somatic tumor testing for all patients with metastatic prostate cancer, and notes that it can be considered for regional prostate cancer.
2. Mutations known to directly or indirectly impact HRR include: BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L.<sup>6</sup>

## I. Screening & Prevention<sup>3,5</sup>

### A. Screening

1. Screening for prostate cancer continues to be controversial with several organizations making different recommendations based on current data.
2. Must balance the benefits of screening to prevent mortality in an often-indolent malignancy versus the harms of over-diagnosis and over-treatment.
3. Screening generally refers to periodic PSA ± digital rectal examination (DRE) evaluations in asymptomatic men. Most organizations endorse a detailed discussion of the risks and benefits between provider and patient prior to the start of screening.
4. Prostate Specific Antigen<sup>3,5</sup>
  - a. PSA is a glycoprotein produced by epithelial cells of the prostate. It is a kallikrein-like serine protease which liquefies seminal secretions.
  - b. PSA is specific to the prostate, but not specific for cancer. In conjunction with DRE, PSA is the most common test used to screen for prostate cancer, but can be affected by other factors.
    - 1) Increased by: prostatic manipulation, prostate biopsy, transurethral resection of the prostate (TURP), benign prostatic hyperplasia (BPH), and prostatitis
    - 2) Decreased by: finasteride<sup>5</sup>

### Factors Affecting the PSA<sup>7</sup>

Factor	Effect on PSA	Interpretation
Finasteride, dutasteride	50% decrease in PSA (although may vary from 40-60%) within 6-12 months	Note use and duration; Consider doubling PSA (due to variability and over estimating PSA and unreliable cancer)
Saw palmetto	Unpredictable	Record in history
Androgen receptor blockers	Variable, but usually increase	Record in history
Ejaculation	Increase	Abstain for 48 hours prior to getting PSA drawn
Prostatic manipulation, biopsy or DRE	Increase, however, not clinically significant – not specified to when to perform	Measure PSA prior or immediately post DRE <sup>8</sup>

- c. Total PSA measurements are used widely for prostate cancer screening in the United States.
    - 1) The normal range for total PSA is  $\leq 4$  ng/mL and this cut-off is primarily based on a prospective study by Gann and colleagues, which demonstrated that a single PSA level  $> 4.0$  ng/mL had a sensitivity of 73%, with a specificity of 91% in detecting prostate cancer within 4 years.<sup>7</sup>
    - 2) It is estimated that there is a greater than 67% chance of prostate cancer for PSA levels  $> 10$  ng/mL. PSA elevations between 4 and 10 ng/mL cannot distinguish between BPH and prostate cancer and it is estimated that 15% of men with PSA  $< 4$  ng/mL and a normal DRE will have biopsy-confirmed prostate cancer.<sup>9</sup>
  - d. PSA velocity may be another predictor of prostate cancer risk.
    - 1) Carter and colleagues found men with an initial PSA of  $< 4$  ng/mL but with a PSA velocity  $> 0.35$  ng/mL per year had a higher relative risk of prostate cancer death as compared to men with a PSA velocity of  $\leq 0.35$  ng/mL per year (RR = 4.7, 95% CI = 1.3 to 16.5; p = 0.02).<sup>10</sup>
    - 2) Based on these results, some experts recommend further work-up for individuals with a PSA  $< 4$  ng/mL, if their PSA velocity is  $> 0.35$  ng/mL per year. This decision should be made in conjunction with other factors such as age, comorbidity, ethnicity and family history. Of note, PSA velocity is not useful in patients with high PSA ( $> 10$  ng/mL) and prostatitis may cause a dramatic increase in PSA confounding PSA velocity as well.
5. US Preventive Services Task Force (USPSTF) does not recommend screening. As of May 2018, the USPSTF recommends against utilizing PSA for screening based on lack of evidence that PSA test saves lives. PSA screening may result in over-diagnosed prostate cancer, which may not otherwise cause clinical problems in men's lifetime. It may lead to unnecessary testing and treatment.<sup>11</sup>
- a. In May of 2018, USPSTF provided a supplement to their earlier statements to individualize decision-making about prostate cancer screening for men ages 55 to 69, including informing each man about the potential benefits and harms of screening.
  - b. The USPSTF continues to recommend against screening men 70 years and older. They concluded that evidence was insufficient to make specific recommendations regarding earlier screening discussions for higher-risk groups: African-American men and those with a family history of prostate cancer.
  - c. American Society of Clinical Oncology (ASCO) published a provisional clinical opinion paper on PSA screening in 2012. They recommend against general screening in men with a life expectancy  $< 10$  years. For men with a  $> 10$ - year life expectancy, ASCO recommends patient-physician discussion about the benefits vs. harms of PSA screening. They also recommend literature written in lay language be provided to the patient prior to ordering PSA tests.<sup>12</sup>
  - d. For patients choosing screening, when to initiate further workup for abnormal PSA is debated. General agreement is that a PSA  $> 4$  ng/mL should require further workup. However, some would argue a cutoff PSA  $> 2.5$  ng/mL based on the Goteborg study which illustrated reduction in prostate cancer related death of Swedish men through screening and included PSA  $> 2.5$  ng/mL.<sup>13</sup>
6. Harms vs benefits

- a. Harms: Complications from biopsy (hematuria, hematochezia, hematospermia, dysuria, urinary retention, infection, pain). Estimated that 1/3 of patients will have some type of complication from biopsy and 4% may be hospitalized. Over-diagnosis and over-treatment: American Urological Association (AUA) estimates 1 in 4 are over-diagnosed. Over-treatment leads to complications of surgery and/or radiation including urinary complications, erectile dysfunction, infections, bleeding, and death.<sup>14</sup>
  - b. Benefits: Lower stage and grade of cancer at diagnosis; possible reduction in prostate cancer mortality; limit morbidity from advanced disease such as bladder outlet obstruction, hematuria, bone pain.<sup>14</sup>
7. Prostate-cancer screening guidelines summary
- a. Screening guidelines as well as treatment are often determined by a patient's life expectancy. Life expectancy may be estimated by using the Minnesota Metropolitan Life Insurance calculator or the Social Security Administration Life Insurance calculator. It may then be adjusted for individual patients by adding or subtracting 50% if the patient is in the healthiest quartile or the unhealthiest quartile, respectively.

### Screening Recommendations

Recommendation	AUA, ASCO <sup>14</sup>	NCCN® v.1.2022 <sup>3</sup>	USPSTF <sup>11</sup>	ACS <sup>15</sup>
Shared decision between patient and clinician	Yes	Yes	Yes	Yes
Age to begin screening		For those who choose to be screened	For those who choose to be screened	For those who choose to be screened
Average-risk patient (years old)	55	45	55	50 (begin discussion)
High-risk patient* (years old)	Consider at 40-54	Consider at age 40	No firm stance	40-45 (begin discussion)
Screening test	PSA only - don't recommend DRE or %PSA, etc (not as primary screening)	PSA +/-DRE	PSA only for age 55-69 for those who choose to be screened	PSA +/- DRE
Frequency of screening	Every 2 years or more	Every 1-4 years depending on baseline PSA	Every 2-4 years	PSA < 2.5 ng/ml, every 2 years PSA ≥ 2.5 ng/ml, annually
Discontinue screening / Do not offer	Age < 40 or ≥70 years or life expectancy <10-15 yr	Life expectancy < 10 yr OR up to 75 y/o (unless little to no comorbidities)	Age ≥ 70 years	Life expectancy < 10 yr

\*High Risk: African American, men with first-degree relative diagnosed with prostate cancer at age <65 years.  
AUA: American Urological Association; NCCN®: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology; USPSTF: United States Preventative Services Task Force; ACS: American Cancer Society

### B. Prevention

## 1. Chemoprevention

- a. Interest in preventing prostate cancer exists and several large chemoprevention trials are sponsored and ongoing by the National Cancer Institute.
- b. Currently, there is a lack of data supporting the use of vitamins or dietary supplements for the prevention of prostate cancer.
- c. 5-alpha reductase inhibitors

### 1) Prostate Cancer Prevention Trial (PCPT)

- a. The first large chemoprevention trial in prostate cancer. It began in 1994 and randomized 18,882 men older than 55 years with a low risk of prostate cancer (PSA  $\leq$  3.0 ng/mL and normal DRE) to receive 5 mg finasteride daily or placebo for 7 years to determine if inhibition of dihydrotestosterone synthesis in the prostate for a prolonged period would lead to a decreased incidence of prostate cancer.<sup>16</sup>
- b. Finasteride demonstrated a 24.8% reduction in prostate cancer prevalence during the 7-year period.
- c. For all men in whom prostate cancer developed during the study period, the treated group had a higher Gleason score, suggesting more aggressive disease compared to the placebo group for all men in whom prostate cancer developed during the study period.
- d. The 18- year follow up data confirmed a reduction in the risk of prostate cancer (10.5% of men receiving finasteride vs 14.9% of men receiving placebo were diagnosed.  $P < 0.001$ ). High-grade cancer was diagnosed in 3.5% of finasteride group versus 3.0% in placebo (RR 1.17; 95% CI 1.0-1.37,  $p = 0.05$ ). The 15 year overall survival rate was 78% and 78.2% for finasteride and placebo, respectively.<sup>17</sup>
- e. A number of biases in cancer detection caused by finasteride have been proposed, including improved detection of overall and high-grade prostate cancer, increased sensitivity of DRE, and increased sensitivity of biopsy for high-grade cancer detection.

### 2) The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) Trial<sup>18</sup>

- a. Phase III trial of dutasteride versus placebo in over 8000 men with PSA between 2.5-10 ng/mL and a negative biopsy.
- b. There was a 22.8% risk reduction of prostate cancer in the dutasteride arm ( $p < 0.001$ ). A non-significant increase in high-grade tumors was seen in the dutasteride group ( $p = 0.81$ ).
- c. There was a significant increase in high-grade tumors detected during years 3 and 4 in the dutasteride group ( $p = 0.003$ ).

### 3) The American Society of Clinical Oncology and the American Urological Association published a joint practice guideline for prostate cancer chemoprevention.<sup>19</sup>

- a. In men who are taking dutasteride or finasteride for benign conditions such as BPH, the potential benefits and risks of dutasteride or finasteride should be discussed.
  - b. The guideline does not recommend the use of finasteride or dutasteride for prostate cancer chemoprevention.
  - c. The higher incidence of high-grade cancer in the finasteride group seen in the PCPT is most likely related to bias. Cancer induction or promotion by finasteride cannot be excluded with certainty.
- 4) Neither finasteride nor dutasteride is FDA approved for preventing or reducing risk of prostate cancer.

## I. Treatment

- A. Treatment determined by risk stratification rather than solely based on stage.

### Management of Prostate Cancer with Low and Intermediate Recurrence Risk<sup>3</sup>

Recurrence Risk		Expected Survival	Initial Therapy
<b>Very Low</b> cT1c, Grade Group 1, PSA < 10, < 3 Bx cores (+) and ≤ 50% cancer in each core, PSA density < 0.15 ng/ml/g		< 10 y	Observation
		10-20y	Active Surveillance (AS)
		≥ 20 y	AS (preferred), EBRT or brachytherapy, or RP (± EBRT ± ADT if adverse features <sup>a</sup> )
<b>Low</b> cT1-2a, Grade Group 1, PSA < 10		< 10 y	Observation
		≥ 10 y	AS (preferred), EBRT or brachytherapy, or RP (± EBRT ± ADT if adverse features) <sup>a</sup>
<b>Intermediate</b> ≥1 intermediate risk factors (IRF): cT2b-cT2c Grade group 2-3 PSA 10-20 ng/ml	<b>Favorable</b> Meets all of: 1 IRF, Grade Group 1-2, < 50% Bx cores (+)	< 5 y	Observation <sup>c</sup>
		5- 10 y	Observation (preferred), or EBRT or brachytherapy
		> 10 y	AS, EBRT or brachytherapy, or RP ± PLND (± EBRT ± ADT if adverse features or positive lymph nodes) <sup>a,b</sup>
	<b>Unfavorable</b> Has one or more of: 2-3 IRF, Grade group 3, ≥ 50% Bx cores (+)	< 5 y	Observation <sup>c</sup>
		5- 10 y	Observation, or EBRT + ADT, or EBRT + brachytherapy ± ADT
		> 10 y	RP + PLND (± EBRT ± ADT if adverse features or positive lymph nodes) <sup>a,b</sup> , or EBRT + ADT, or EBRT + brachytherapy ± ADT

*a adverse features: positive margin(s); seminal vesicle invasion; extracapsular extension; detectable PSA; b If lymph node metastasis ADT (category 1) ± EBRT (category 2B) or observation. If adverse features only EBRT± ADT (6 months) or observation ADT=Androgen deprivation therapy, c for asymptomatic patients with life expectancy <5 years, no imaging or treatment indicated until patient becomes symptomatic (then ADT should be given); AS=Active surveillance; Bx=Biopsy; RP=Radical prostatectomy; EBRT= External beam radiation therapy; PLND = pelvic lymph node dissection*

- B. Localized Disease (T1a-c, T2a-c, N0M0): Treatment will depend primarily on the stage and grade, but also takes into consideration the patient's age, general health and preferences.

#### 1. Observation<sup>3</sup>

- a. Preferred for those with low-risk prostate cancer with life expectancy less than 10 years
  - 1) Expectation to deliver palliative therapy if necessary (symptomatic or symptoms are imminent; PSA > 100 ng/mL or change in exam)
  - 2) Monitor with PSA no more than every 6 months.
  - 3) Repeat prostate biopsy not recommended
  - 1) Advantage: avoid immediate morbidity associated with treatment



- 2) Disadvantage: Risk of disease complications such as urinary retention or pathologic fracture without symptoms
2. Active surveillance (AS): Based on the premise that prostate cancer is a benign and indolent disease<sup>3</sup>
    - 1) Preferred in those with very-low risk disease and life expectancy at least 20 years and for low risk and life expectancy of at least 10 years
    - 2) Expectation to deliver potentially curative therapy upon progression of disease
    - 3) Involves actively monitoring the disease.
      - i. PSA no more often than every 6 months unless clinically indicated
      - ii. DRE no more often than every 12 months unless clinically indicated
      - iii. Repeat prostate biopsies no more than every 12 months unless clinically indicated, and
      - iv. MRI no more than every 12 months unless clinically indicated
  3. Radiation Therapy (RT): External Beam (EBRT) or Brachytherapy<sup>3</sup>
    - a. Appears equivalent to surgery in outcome, although the only head- to- head comparison has been greatly criticized for bias
      - 1) Option for patients who are not surgical candidates
      - 2) Benefits versus surgery: less bleeding, avoids risks of anesthesia, low risk of urinary incontinence and stricture, short term preservation of erectile function
      - 3) Disadvantages versus surgery: treatment course of 8-9 weeks; 50% have temporary bowel or bladder symptoms during therapy, erectile dysfunction increases over time, radiation proctitis
    - b. External Beam (EBRT)<sup>3</sup>
      - 1) 3D conformational or IMRT (intensity modulated radiation therapy) should be employed in preference to standard techniques
      - 2) High risk cancers: may also have pelvic lymph nodes irradiated and the addition of adjuvant ADT for 1-3 years (4-6 months of ADT if only 1 high-risk factor).
      - 3) Intermediate risk cancers: may have pelvic lymph node irradiation and 4-6 months of ADT
      - 4) Low risk cancer: no pelvic lymph node irradiation or ADT
    - c. Brachytherapy<sup>3</sup>
      - 1) Traditionally an option for -low-risk prostate cancers. However, new advancements may increase use in intermediate to high-risk cancers.
      - 2) Low dose rate (LDR) brachytherapy
        - i. Permanent seed implantation
        - ii. Allows delivery of radiation to prostate and limits exposure of bladder and rectum

- iii. Monotherapy in -low-risk patients; combined with EBRT  $\pm$  ADT for intermediate risk; used as a “boost” of radiation
  - iv. Advantages: 1 day therapy, control rates comparable to surgery for -low-risk tumors, minimal risk for incontinence, erectile function preserved in short term
  - v. Disadvantages: requires general anesthesia, acute urinary retention
  - vi. Avoid in patients post-transurethral resection of the prostate (TURP)
- 3) High dose rate (HDR) brachytherapy
  - i. Temporary insertion of radiation source to provide “boost” radiation
  - ii. Used in addition to EBRT in patients at high risk for recurrence
- 4. Radical Prostatectomy (RP)  $\pm$  Pelvic lymph node dissection (PLND)<sup>3</sup>
  - a. RP appropriate if tumor confined to prostate and is definitive curative therapy
  - b. Significant perioperative morbidity, therefore, reserved for those with life expectancy  $\geq 10$  years. The PIVOT trial compared radical prostatectomy to observation in 731 men with localized prostate cancer. No significant difference was found in overall mortality or prostate cancer specific mortality through 20 years of follow up. However, 21% of patients undergoing surgery had an adverse event within 30 days of surgery.<sup>20, 21</sup>
  - c. 85% of men with disease confined to the prostate are cured at 10 years
  - d. PLND
    - 1) Indicated if probability of lymph node involvement is  $>2\%$
    - 2) Extensive PLND is preferred and includes removal of all lymph node bearing tissue from the area.
  - e. Complications
    - 1) Early mortality (0.3%)
    - 2) Bladder contracture (1-22%)
    - 3) Incontinence (0-17%)
    - 4) Impotence (63% retain potency with bilateral nerve sparing procedure)
- 5. Androgen Deprivation Therapy (ADT)<sup>3</sup>
  - a. Goal of therapy is to induce castrate levels of testosterone
    - 1) Surgical castration: orchiectomy
    - 2) Medical/chemical castration: Luteinizing hormone-releasing hormone (LHRH) agonist or antagonist
    - 3) Goal serum testosterone  $<50$  ng/dl after 1 month of therapy
  - b. Combination with RT in low and intermediate risk disease
    - 1) D’Amico et al. evaluated 206 patients with T1b to T2b disease, a PSA  $\geq 10$  ng/ml, Gleason of at least 7, or evidence of extraprostatic disease. Patients were randomized to RT in

combination with 6 months of ADT vs. RT alone. Five-year survival was 88% in the RT + ADT group vs. 78% in the RT alone group ( $p=0.04$ ).<sup>22</sup>

- 2) RTOG 94-08 Trial: Eligible patients had T1b, T1c, T2a, or T2b prostate cancer, and PSA of 20 ng/mL or less and were randomized to RT alone or RT + 4 months of ADT. The androgen suppression was started 2 months before radiation therapy. In the study of 1979 evaluable patients combined radiation therapy with androgen suppression had significantly better 10-year overall survival compared with radiation alone (62% vs. 57%;  $P=0.03$ ). The re-analysis according to recurrence risk suggested overall and disease-specific mortality rate benefit primarily in intermediate-risk patients.<sup>23</sup>

- c. No role for adjuvant ADT after prostatectomy in -low-risk patients. Use after prostatectomy in patients with positive lymph nodes has shown mixed results.

**Patient Case #1, Answer:**

**Correct answer = A (active surveillance).** BF is classified as very low risk and has life expectancy >20 years. Active surveillance is the preferred option for this risk category/life expectancy. Active surveillance minimizes toxicity of treatment. Observation is not appropriate for a young healthy patient. Adjuvant radiation is not indicated in very low risk disease.

**Management of Prostate Cancer with High and Very High Recurrence Risk**

Recurrence Risk	Expected Survival	Initial Therapy
<b>High Risk</b> One high risk feature (HRF) : T3a or Grade 4 or 5 or PSA > 20	≤ 5 years and asymptomatic	Observation or ADT or EBRT
	>5 years or symptomatic	EBRT + 1.5-3y ADT (Category 1) ± Abiraterone (very high risk only)
<b>Very High Risk</b> One or more of: cT3b-cT4, Primary Gleason pattern 5, or >4 cores with Grade Group 4 or 5, 2-3 HRF	>5 years or symptomatic	EBRT + brachytherapy + 1-3y ADT (ADT Category 1)
		RP + PLND (± EBRT ± ADT if adverse features or positive lymph nodes) <sup>a,b</sup>
<b>Regional</b> Any T, N1, M0	≤ 5 years and asymptomatic	Observation or ADT
		ADT + EBRT + abiraterone (preferred)
		ADT + EBRT
	>5 years or symptomatic	ADT ± abiraterone
		RP + PLND (± EBRT ± ADT if adverse features or positive lymph nodes) <sup>a,b</sup>

*a adverse features: positive margin(s); seminal vesicle invasion; extracapsular extension; detectable PSA*

*b If lymph node metastasis ADT (category 1) ± EBRT (category 2B) or monitoring/observation. If adverse features only EBRT± ADT (6 months) or monitoring/observation*

*ADT=Androgen deprivation therapy; AS=Active surveillance; Bx=Biopsy; RP=Radical prostatectomy; EBRT=External beam radiation therapy; PLND = pelvic lymph node dissection*

**C. Treatment of High- Risk, Locally Advanced Disease, or Very High Risk (T3 and T4)<sup>3</sup>**

**1. External Beam Radiation Therapy + Neoadjuvant/Adjuvant/Concurrent Hormonal Therapy**

- a. Multiple studies have evaluated the combination of ADT with EBRT in patients with -high-risk disease compared with either therapy alone. Studies have also compared short term ADT to long term ADT in -high-risk patients. Results are summarized in the table below.

- b. A recent meta-analysis evaluated hormonal therapy after primary therapy of radiation or prostatectomy for men with locally advanced prostate cancer. ADT with EBRT improved 5-year overall survival, clinical disease-specific survival, and biochemical disease-free survival. No significant difference in overall survival in the prostatectomy groups was observed.<sup>24</sup>
- c. ADT usually starts prior to radiation, continues during radiation and for 2-3 years after radiation. Optimal duration of neoadjuvant therapy for those with high recurrence risk is 2-3 years.

#### Summary of studies including EBRT and ADT in high-risk patients

	Inclusion	Randomized Arms	Findings
RTOG 85-31 <sup>25</sup> n=977	T3 or N1	Arm 1: RT + ADT indefinitely  Arm 2: RT -> ADT at progression	-10-year survival rate was improved with Arm 1 (49% vs 39%, p=0.002) -10-year local failure rate was better for Arm 1 (23% vs 38%, p<0.0001) -Secondary analysis found ADT > 5 years was associated with improved survival and disease-free survival <sup>26</sup>
RTOG 92-02 <sup>27, 28</sup> n=1521	T2c-T4	4 months of ADT with RT then randomized to:  Arm 1: no further ADT  Arm 2: ADT x 2 years	At 10 years, -DFS improved with Arm 2 (13.2% vs 22.5%, p<0.0001) -distant metastases improved with Arm 2 (22.8% vs 14.86%, p<0.0001) -biochemical failure improved with Arm 2 (68.1% vs 51.9%, p≤ 0.0001) -Overall survival was no different (51.6% vs 53.9%, p=0.36) -Subgroup of patients with Gleason 8-10 found improvement in overall survival with Arm 2 (31.9% vs 45.1%, p=0.0061) At median 19.6 years, DFS, OS, and biochemical failure all favored the longer duration ADT arm across the entire cohort. Relative reduction for OS was 12% (p=0.03).
EORTC 22961 <sup>29</sup> n=970	pT1c to pT2a-b + pN1 to pN2 + M0 or cT2c to cT4 + cN0 to cN2 + M0	6 months of ADT with RT then randomized to:  Arm 1: no further ADT  Arm 2: ADT x 2.5 years	-Noninferiority study -5-year overall mortality was 15.2% for Arm 2 and 19% for Arm 1 (p=0.65 for noninferiority)
EORTC 22863 <sup>30</sup> n=415	T1-2 and grade 3 Or T3-4	Arm 1: RT alone  Arm 2: RT + ADT x 3 years	-10-year overall survival was improved for Arm 2 (39.8% vs 58.1%, p=0.0004) -10-year prostate cancer mortality was improved in Arm 2 (30.4% vs 10.3%, p<0.0001)
NCIC CTG PR.3/MRC UK PR07 Trial <sup>31</sup> n=1205	T2 and PSA >40 or PSA>20 and Gleason ≥8; T3-4	Arm 1: ADT indefinitely  Arm 2: ADT + RT	-7-year overall survival was improved for Arm 2 (66% vs 74%, p=0.033)

EBRT: External Beam Radiation therapy; ADT: androgen deprivation therapy; DFS: disease free survival

2. Radical Prostatectomy with pelvic lymph node dissection +/- Neoadjuvant/Adjuvant/Concurrent Hormonal Therapy<sup>3</sup>
  - a. Currently, neoadjuvant and adjuvant hormonal therapy are not recommended in combination with prostatectomy. Use is restricted to where positive lymph nodes are found, although there are mixed results with this approach. Clinical trials are ongoing.

**Patient Case #2:** LB is a 60-year-old male with history of myocardial infarction 3 months ago and low risk prostate cancer treated with external beam radiation 6 months ago. He follows up with his oncologist regularly and his PSA has doubled in the last four months. He presents today to discuss recent imaging which shows no sites of metastatic disease. He is not a candidate for further local treatment and is hesitant to pursue androgen deprivation therapy due to fear of adverse cardiac effects. **Which of the following options is most appropriate for LB?**

- A. Continuous ADT with leuprolide
- B. Intermittent ADT with relugolix
- C. Intermittent ADT with leuprolide
- D. Treatment is not indicated at this time

#### D. Androgen Deprivation Therapy

1. Androgen Deprivation Therapy (Bilateral orchiectomy or LHRH Agonist or Antagonist)
  - a. Bilateral Orchiectomy (removal of the testes)
    - 1) Immediate drop in testosterone levels
    - 2) Previous gold standard
    - 3) Benefits of adding antiandrogen to surgical castration is unclear
    - 4) Side effects: Impotence, hot flashes
    - 5) Recent evidence suggests bilateral orchiectomy may have fewer long term adverse effects than LHRH agonists<sup>32</sup>
      - i. Population based cohort of 3295 men with metastatic prostate cancer treated with orchiectomy vs. LHRH agonist (from 1995 to 2009)
      - ii. Decreased risk of fracture [(HR), 0.77; p = 0.01], peripheral arterial disease (HR, 0.65; p = 0.004), and cardiac-related complications (HR, 0.74; p = 0.01)
      - iii. No difference in incidence of diabetes, or cognitive disorders
  - b. Luteinizing hormone-releasing hormone (LHRH) agonists

**Luteinizing hormone-releasing hormone agonists<sup>33</sup>**

<b>Agents</b>	<b>Dosing</b>	<b>Adverse Events</b>
Goserelin (Zoladex®)	3.6 mg SQ every 4 weeks 10.8 mg SQ every 12 weeks	Acute events: Tumor flare, gynecomastia, hot flashes, edema, injection site reaction, erectile dysfunction, shrinkage of testes and penis, fatigue, depression, etc.
Leuprolide (Lupron®, Eligard®)	7.5 mg IM/SQ every month 22.5 mg IM/SQ every 3 months 30 mg IM/SQ every 4 months 45 mg IM/SQ every 6 months	
Triptorelin (Trelstar®)	3.75 mg IM every 4 weeks 11.25 mg IM every 12 weeks 22.5 mg IM every 24 weeks	Long-term: Osteoporosis, clinical fracture, obesity, decreased muscle mass, insulin resistance, alteration in lipids, increased risk of diabetes and CV events  See Supportive Care section for more information

- 1) LHRH agonists are a reversible method of androgen ablation and are as effective as orchiectomy in treating prostate cancer. Also referred to as gonadotropin-releasing hormone (GnRH) agonists.
  - 2) Several randomized trials have demonstrated that leuprolide and goserelin are effective agents when used alone in patients with advanced prostate cancer. Response rates around 80% have been reported, with a lower incidence of adverse effects compared with estrogens.
  - 3) No direct comparative trials but a recent meta-analysis reported that there is no difference in efficacy or toxicity between triptorelin, histrelin (recently discontinued by manufacturer), leuprolide, and goserelin. Therefore, the choice between the four agents is usually made based on institution formulary, cost and patient and physician preference for a dosing schedule.<sup>34</sup>
  - 4) Disease flare with LHRH agonist is thought to be caused by initial induction of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the LHRH agonist and manifests clinically as either increased bone pain or increased urinary symptoms. This flare reaction usually resolves after 2 weeks and has a similar onset and duration pattern for the depot LHRH agonists.
  - 5) Antiandrogen therapy (with first generation anti-androgen such as bicalutamide, flutamide, nilutamide) should precede LHRH agonist and be continued in combination for at least 7 days for patients with overt metastasis to attenuate the tumor flare.
  - 6) In practice, antiandrogen therapy is often started seven days prior to GnRH agonist initiation for men at high risk of flare symptoms, or concurrently for asymptomatic patients. Antiandrogen therapy is then continued for two to four weeks.
- c. LHRH antagonist: Degarelix (Firmagon®)
- 1) Loading dose: 240 mg SubQ as two 120 mg injections
  - 2) Maintenance dose: 80 mg SubQ every 28 days

- 3) The major advantage of degarelix over LHRH agonists is the speed at which it can achieve the drop in testosterone levels with no surge of LH or FSH levels; castrate levels are achieved in 7 days or less with degarelix, compared to 28 days with leuprolide, eliminating the tumor flare seen and need for antiandrogens.
  - 4) In a trial of 610 men with advanced prostate cancer, degarelix was shown to be equivalent to leuprolide in lowering testosterone levels for up to one year and is approved by the FDA for the treatment of advanced prostate cancer.<sup>35</sup>
  - 5) Degarelix has not been studied in combination with antiandrogens and routine use of the combination cannot be recommended. Currently, degarelix can be considered in first-line setting where tumor flare up from LHRH agonist is a major concern (i.e. spinal cord injury compression concern).
  - 6) Recent studies have evaluated the cardiovascular effects of LHRH agonists vs. antagonists.
    - i. Initially, a pooled post-hoc analysis of 6 phase III trials comparing LHRH agonists (leuprolide, goserelin) to LHRH antagonist (degarelix) evaluated differences in death from any cause or cardiac events. The authors found no difference in patients with no pre-existing cardiac history. However, in those with history of cardiac event, the incidence of death or cardiac event was significantly lower (HR: 0.44, p = 0.002) for those treated with the LHRH antagonist.<sup>36</sup>
    - ii. This prompted a prospective phase II study in patients with history of cardiac events, comparing LHRH agonists vs. LHRH antagonist (n = 80). While the primary outcome of endothelial function at 12 months was not statistically different, the secondary outcome of a new cardiovascular event was higher in those randomized to receive the LHRH agonist (33.3% vs. 4.8%; p = 0.001).<sup>37</sup>
    - iii. A large phase III study comparing degarelix to LHRH agonists in men with concomitant atherosclerotic cardiovascular disease was terminated prematurely due to slow enrollment and a smaller than expected number of primary outcome events.<sup>38</sup>
      1. No major difference in cardiovascular events at 1 year was observed.
  - 7) Disadvantage: Must be given monthly and more local site reactions.
- d. Oral LHRH Antagonist: Relugolix (Orgovyx®)<sup>40</sup>
- 1) Drug information:
    - i. Mechanism of Action: Oral GnRH antagonist (competitive pituitary GnRH receptor such antagonist → ↓ LSH + FSH → ↓ testosterone)
    - ii. Dosing: 360mg orally (3 tablets) x 1 day, then 120mg orally (1 tablet) daily (reload if interrupted ≥ 7 days)
    - iii. Adverse Effects: Similar to other ADT, diarrhea
      1. Lower risk of major cardiovascular events compared to LHRH agonists
    - iv. Drug-drug Interactions: CYP2C8 (minor/major substrate), CYP3A4 (minor substrate), PGP/ABCB1 (major substrate)

- v. Pearls: Has not been adequately studied with other prostate cancer therapies (should not be used in combination; studies are still ongoing); adherence >99% in trial (consider patient compliance, testosterone monitoring)
- 2) HERO Phase III Trial:<sup>41</sup>
- i. Enrolled men with advanced adenocarcinoma of the prostate who were candidates for at least one year of ADT (biochemical or clinical relapse after primary intervention, newly diagnosed m1CSPC, advanced localized disease unlikely to be cured with primary intervention), n = 622
    - 1. Randomized 2:1 to relugolix 360mg x1 then 120mg PO daily OR leuprolide 22.5mg IM every 3 months
  - ii. Primary outcome: sustained testosterone suppression through 48 weeks: 96.7 vs. 88.8% (p<0.001)
  - iii. Safety:
    - 1. Adverse effects similar between arms
    - 2. Diarrhea: 12.2% vs. 6.8%
    - 3. Can cause QTc prolongation
    - 4. Major cardiovascular adverse events (MACE): 2.9% vs. 6.2% across all patients (HR 0.46)
      - a. With history of MACE: 3.6% vs. 17.8%
- 3) Limitations:
- i. Most outcomes related to fast on and off-set of testosterone suppression. No published data related to overall or progression free survival endpoints available.
  - ii. Study reported >99% compliance for both arms – difficult to replicate in real world setting and important considering fast off-set of action (consider monitoring testosterone, carefully consider compliance when choosing appropriate patients).
  - iii. No drug-drug interaction studies with other prostate cancer therapies (abiraterone, docetaxel, enzalutamide, apalutamide, etc.). At progression, patients could add docetaxel or enzalutamide per protocol – data on these patients not yet available. Not recommended to use in combination at this time. Concerns
- 4) Benefits: offers an oral agent with fewer cardiac risks and fast on/off-set of action for patients who need treatment with ADT alone. Ideal properties for intermittent ADT.
- e. Antiandrogens: Flutamide (Eulexin®), Bicalutamide (Casodex®), Nilutamide (Nilandron®)
- 1) Antiandrogens have been used as monotherapy in previously untreated patients, but a recent meta-analysis determined that monotherapy with antiandrogens is less effective than LHRH agonist therapy and is not currently recommended to be used alone (unless patient had orchiectomy).
  - 2) Bicalutamide is generally preferred due to better toxicity profile.
  - 3) For advanced prostate cancer, all currently available antiandrogens are indicated only in combination with androgen-ablation therapy; flutamide and bicalutamide are indicated



in combination with an LHRH agonist, and nilutamide is indicated in combination with orchiectomy.

- 4) The most common antiandrogen-related adverse effects are listed in the table below. In the only randomized comparison of bicalutamide plus an LHRH agonist versus flutamide plus an LHRH agonist, diarrhea was more common in flutamide-treated patients.

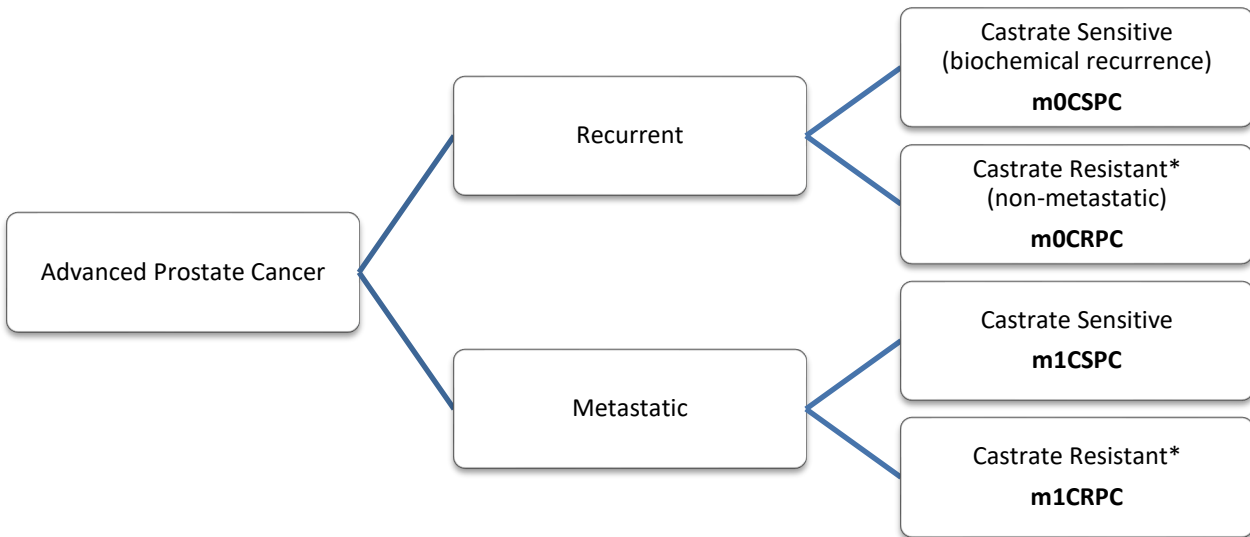
**Comparison of the Antiandrogens<sup>33</sup>**

Drug	Half-life	Dose	Adverse Effects
Flutamide	9.6 hours	250 mg PO TID	Diarrhea 12-26% (all grades) Hematuria
Bicalutamide	1 week	50 mg PO daily	Diarrhea 2-12% (all grades) Hematuria 12% (all grades)
Nilutamide	41-49 hours	300 mg PO daily x 1 month, then 150 mg PO daily	Diarrhea 2% Disulfiram-like reaction Decreased visual accommodation 13% Interstitial pneumonia 2%

f. Combined androgen blockade (CAB) LHRH + anti-androgen (AA)

- 1) Although up to 80% of patients with advanced prostate cancer will respond to initial hormonal manipulation, almost all patients will relapse within 2 to 4 years after initiating therapy.
- 2) Two mechanisms have been proposed to explain this tumor resistance. The tumor could be heterogeneously composed of cells that are hormone-dependent and hormone-independent, or the tumor could be stimulated by extratesticular androgens that are converted intracellularly to DHT.
- 3) A meta-analysis of 21 trials compared monotherapy (orchiectomy or LHRH agonist) to combination therapy (orchiectomy or LHRH agonist plus an antiandrogen). It found a statistically significant difference in -5-year survival with CAB (HR 0.871; 95% CI 0.805-0.942). The good prognosis subgroup had no difference in survival. Adverse events causing withdrawal from therapy occurred more in the CAB group.<sup>42</sup>
- 4) Other trials and meta-analyses have reported no advantage to CAB.
- 5) CAB is associated with more adverse events leading to withdrawal from therapy.
- 6) Although some investigators now consider CAB to be the initial hormonal therapy of choice for newly diagnosed patients, the clinician is left to weigh the costs of combined therapy against potential benefits in light of conflicting results in the randomized trials and the modest benefit seen in the meta-analysis.
- 7) CAB may be most beneficial for improving survival in patients with minimal disease and for preventing tumor flare, particularly in those with advanced metastatic disease. All other patients may be started on LHRH monotherapy, and an antiandrogen may be added after several months if androgen ablation is incomplete.<sup>3</sup>

## E. Treatment of Recurrent or Metastatic Disease<sup>3</sup>



*\*Castrate Resistant (progression despite testosterone <50ng/dL)*

### 1. Biochemical Recurrence (m0CSPC)

- a. Need to distinguish between a PSA recurrence and overt metastatic disease. Those with a PSA recurrence alone may not need to immediately start ADT. PSA velocity, toxicity of ADT and patient wishes are taken into consideration with treatment decisions. Consider intermittent ADT in this clinical setting. In patients with long PSA doubling time (PSADT; >10 months) or older age, observation may be appropriate. Those with the following criteria may be considered for initiation of ADT:

- 1) Rapid PSA velocity and short PSADT (<10 months)
- 2) Long life expectancy

### b. Intermittent androgen deprivation (IAD)

- 1) With IAD, patients are started on either an LHRH analog alone or on combined androgen blockade. They are monitored and when PSA has returned to a pre-specified baseline (typically  $\leq 4$  ng/mL) androgen suppression is discontinued. PSA is monitored while the patient is off androgen ablation therapy and therapy is re-started at a pre-defined PSA (typically 10-20 ng/mLdL) as described below.
  - i. Advantages of IAD include decreased cost and potentially decreased adverse effects.
  - ii. Crook et al. evaluated intermittent ADT compared to continuous ADT in men with a rising PSA after primary or salvage RT (no distant metastases). Intermittent ADT consisted of 8-month treatment cycles. ADT was held if no evidence of disease progression and PSA was <4ng/ml. PSA was then monitored every 2 months until it was >10ng/ml at which time ADT was reinitiated. The study randomized 1386 men and found that intermittent ADT was noninferior to continuous ADT with regards to overall survival with median overall survival of 8.8 years in the intermittent group versus 9.1 years in the continuous group (HR 1.02;95% CI 0.86-1.21). Intermittent

ADT was associated with better quality of life scores for hot flashes, desire for sexual activity, and urinary symptoms.<sup>43</sup>

- iii. Hussain et al. conducted a noninferiority trial (SWOG 9346) that compared IAD to continuous androgen deprivation (CAD) in 1535 newly diagnosed metastatic prostate cancer patients. Patients received 7 months of an LHRH agonist and an antiandrogen. Those with a PSA of  $\leq 4$  ng/ml at 7 months were randomized to CAD or IAD. ADT was resumed for an additional 7 months in the IAD group once the PSA was  $\geq 20$  ng/ml (or over baseline for those with PSA  $< 20$  ng/ml at enrollment). Median survival was 5.8 years in the CAD group versus 5.1 years in the IAD group. However, the findings were statistically inconclusive as the CI exceeded the upper boundary for noninferiority. IAD was associated with better erectile function and mental health.<sup>44</sup>
- iv. Niraula et al. conducted a systematic review of 9 trials including 5508 men comparing IAD to CAD in men with relapsing, locally advanced or metastatic disease. The pooled HR for overall survival of IAD compared with CAD was 1.02 (95% CI 0.94-1.11) and PFS was 0.96 (95% CI 0.76-1.20). There tended to be more prostate cancer specific deaths in the IAD group but more deaths not related to prostate cancer in the CAD group. IAD had less treatment related adverse effects such as hot flashes, sexual dysfunction, and impaired physical function.<sup>45</sup>
- v. An additional critical review of IAD versus CAD was published evaluating 7 phase 3 trials. The evaluation found that most patients spent more time on ADT rather than off. It also confirmed that in metastatic cases, IAD and CAD have similar results with HR for overall survival ranging from 0.98-1.08. Treatment related adverse effects tended to be improved for IAD, however the overall quality of life benefit for IAD was minimal.<sup>46</sup>
- vi. Summary: For men with biochemical relapse only, consider IAD since no difference in overall survival was observed and the largest trial was inconclusive. Close monitoring and follow up are required, especially during off treatment periods.

**Patient Case #2, Answer:**

**Correct answer = B (Intermittent ADT with relugolix).** LB has a biochemical recurrence (castrate sensitive). Appropriate treatments include ADT and active surveillance. Due to his short doubling time, ADT is a good choice for him. Intermittent ADT is an option for biochemical recurrence. With regard to cardiac events, relugolix showed a benefit over leuprolide in the HERO trial, making it preferable for this patient. It is also a good option for intermittent ADT because of its short half-life.

**Patient Case #3:** RC is a 62-year-old that presents to your clinic with a history of high risk prostate cancer status post EBRT, currently on adjuvant leuprolide. Six months prior PSA level was 2.4 ng/mL and testosterone levels less than 20ng/dL. Three months prior PSA of 4.7ng/ml. Today's lab values are within normal limits except PSA level of 25 ng/ml and testosterone less than 20ng/dL. CT scan shows no metastatic disease. **Which is the most appropriate change in RC's treatment at this time?**

- A. Stop leuprolide, start docetaxel + prednisone
- B. Stop leuprolide, start relugolix
- C. Continue leuprolide, add darolutamide
- D. Continue leuprolide, add abiraterone + prednisone

2. Non-metastatic Castrate Resistant Prostate Cancer (m0CRPC)
  - a. Treatment based upon PSA doubling time
    - 1) If doubling time greater than 10 months, observation or secondary hormonal therapy recommended
  - b. Apalutamide<sup>47</sup>
    - 1) NCCN® Category 1 for M0 castration-resistant prostate cancer and PSADT ≤10 mo
    - 2) SPARTAN trial
      - i. Phase III International, double-blind, randomized, placebo controlled
      - ii. N = 1207 patients with m0CRPC at high risk to develop metastatic disease, PSADT ≤10 months
      - iii. Randomly assigned in a 2:1 ratio to apalutamide 240 mg per day or placebo. All patients continued ADT.
      - iv. Median metastasis-free survival was 40.5 months in the apalutamide group versus 16.2 months in the placebo group (HR 0.28; 95% CI 0.23 to 0.35; P<0.001).
      - v. Time to symptomatic progression was significantly longer with apalutamide than with placebo (HR 0.45; 95% CI 0.32 to 0.63; P<0.001)
      - vi. Final overall survival, published in 2021, favored apalutamide at 73.9 vs. 59.9 months (HR 0.784, p value 0.016).<sup>48, 49</sup>
  - c. Enzalutamide
    - 1) NCCN® Category 1 for M0 castration-resistant prostate cancer and PSADT ≤10 mo
    - 2) PROSPER trial<sup>50</sup>
      - i. Phase III, international, double-blind, randomized, placebo controlled.
      - ii. 1401 patients with m0CRPC on ADT and no evidence of metastatic disease, PSADT ≤10 months
      - iii. Randomized in a 2:1 ratio to receive enzalutamide 160 mg daily or placebo.
      - iv. Median metastasis-free survival was 36.6 months vs 14.7 months (HR 0.29; 95% CI, 0.24-0.35; P<0.001).
      - v. The time to first antineoplastic agent was longer 39.6 vs. 17.7 months.
      - vi. 2020 Final mOS update: 67 vs. 56.3 months (HR 0.73; p = 0.001)<sup>51</sup>
  - d. Darolutamide
    - 1) NCCN® Category 1 for M0 castration-resistant prostate cancer and PSADT ≤10 mo
      - i. Approved in July 2019 for the treatment of non-metastatic, castration resistant prostate cancer
      - ii. AR antagonist. Darolutamide also inhibits nuclear translocation and transcription.
      - iii. Novel structure versus enzalutamide and apalutamide; may have fewer CNS adverse effects and drug-drug interactions

2) ARAMIS trial<sup>52, 53</sup>

- i. Phase III, international, randomized, double blind, placebo controlled
  - ii. N = 1509 with mCRPC, PSADT ≤10 months
  - iii. Randomized 2:1 to receive ADT + darolutamide 600mg PO BID or ADT + placebo
  - iv. Median metastasis-free survival was 40.4 months (95% CI: 34.3, not reached) for patients treated with darolutamide compared with 18.4 months (95% CI: 15.5, 22.3) for those receiving placebo (hazard ratio 0.41; 95% CI: 0.34, 0.50; p<0.001). OS data were not mature.
  - v. Final 2020 OS update: median OS not reached in either arm but HR for death 0.69, p = 0.003
- e. The three second-generation antiandrogens have not been compared head- to- head, but there are differences in side effect profile, CYP drug interactions, and administration (i.e. with food) between enzalutamide/apalutamide vs. darolutamide that are summarized below.

**Comparison of 2<sup>nd</sup> Generation Antiandrogens**

	<b>Enzalutamide</b>	<b>Apalutamide</b>	<b>Darolutamide</b>
Indications	m1CSPC, m1CRPC, m0CRPC	m1CSPC, m0CRPC	m0CRPC, m1CSPC (in combination with docetaxel)
Dosing	160mg daily	240mg daily	600 mg <u>BID with food</u>
Adverse Effects* (vs. placebo, %)	Fatigue (33 vs. 14), falls + fracture (17 vs 8), hypertension (12 vs 5), seizure (0.3)	<u>Rash</u> (23.8 vs 5.5), fracture (11.7 vs 6.5), fatigue (30.4 vs 21.1) <u>hypothyroidism</u> (8 vs 2), hypertension (24.8 vs. 19.8), seizures (0.2)	Fatigue (12.1 vs. 8.7), hypertension (6.6 vs. 5.2) rash (2.9 vs. 0.9), seizures (0.2 vs. 0.2)
Pearls			Renal dose adjustment (300mg BID if CrCl 15-29, has not been studied with CrCl <15), hepatic dose adjustment (300mg BID for moderate impairment), poor blood-brain barrier penetration

\*adverse effects taken from the m0CRPC trials (SPARTAN, PROSPER, and ARAMIS) to better compare among similar patient populations

\*\* SPARTAN and PROSPER trials excluded patients with seizure history or predisposition to seizures, whereas ARAMIS trial did not

### Common Drug-Drug Interactions with 2<sup>nd</sup> Generation Antiandrogens

	Enzalutamide	Apalutamide	Darolutamide
Substrate	CYP3A4/5, CYP2C8	CYP3A4, CYP2C8	CYP3A4, P-gp
Inhibits	CYP2C8 (weak) P-gp	CYP2B6, CYP2C8, (moderate) CYP3A4 (weak) CYP2C9, CYP2C19	BCRP
Induces	CYP3A4 (strong), CYP2C9, CYP2C19, CYP2D6 (moderate), CYP1A2 (weak)	CYP3A4, CYP2C19 (strong), OATP1B1, CYP2C9 (weak), UGT, P-gp, BCRP	CYP3A4 (weak)
Common drug-drug interactions	Statins, direct-acting oral anticoagulants (DOACs), warfarin, calcium channel blockers, opioids, PPIs, losartan, citalopram	Statins, DOACs, clopidogrel, warfarin, calcium channel blockers, opioids, PPIs, citalopram	Rosuvastatin

- f. Second Line Hormonal Therapy (not a *preferred* option in NCCN guidelines)
  - 1) Antiandrogen withdrawal (for those treated with ADT + antiandrogen)
    - i. 20-30% respond from androgen withdrawal alone. Generally short duration of response.
    - ii. Mechanism unknown, but potentially new mutations and androgen receptor changes over time that make the tumor cells resistant to antiandrogen therapy.
    - iii. Half-life of the antiandrogen will determine the time to response.
  - 2) Corticosteroids<sup>3</sup>
    - i. Dexamethasone or prednisone
    - ii. Mechanism of action: Suppression of ACTH and subsequently adrenal androgens
    - iii. Dose: Prednisone 5-10mg, Dexamethasone PO 0.5-1.5 mg daily
  - 3) Ketoconazole<sup>3</sup>
    - i. Inhibits androgen synthesis in the testes and the adrenal gland and it has rapid onset of action
    - ii. Dose: 400 mg PO q 8h
    - iii. Adverse effects: Nausea and vomiting (33%), impotence, gynecomastia, dry skin, increased LFTs, and rarely, hepatitis
    - iv. Drug interaction with cytochrome p450s
    - v. Corticosteroid replacement with hydrocortisone is recommended due to potential adrenal insufficiency induced by ketoconazole. The typical hydrocortisone dose is 20 mg PO every morning and 10 mg PO every evening.

**Patient Case #3, Answer:**

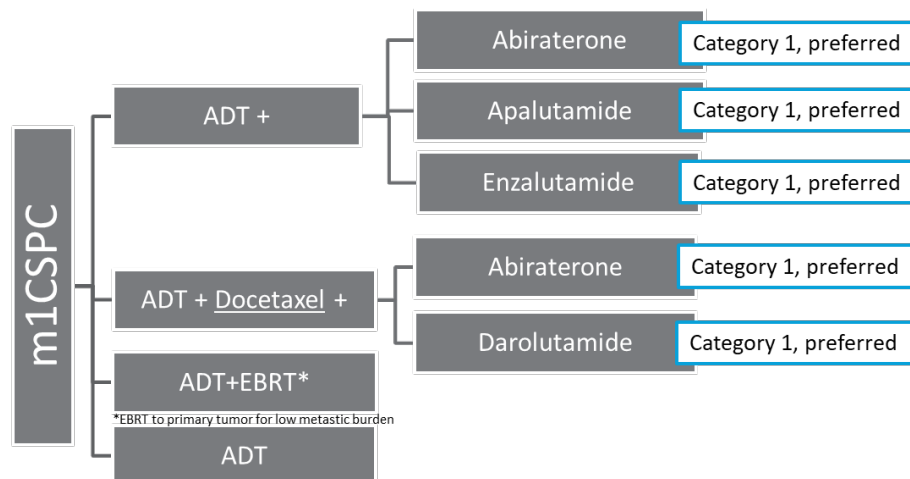
**Correct answer = C (Continue leuprolide, add darolutamide).** Based on laboratory and imaging data, RC has non-metastatic castration resistant prostate cancer. Darolutamide is indicated in this setting, supported by data from the ARAMIS trial. Docetaxel and abiraterone are indicated in the metastatic setting but not in the M0 setting. ADT should be continued despite progression to castration-resistant disease. Relugolix is an alternative to leuprolide for ADT but is not indicated after progression on leuprolide as a single agent.

**Patient Case #4:**

- A. AC is a 65-year-old male with history of hypertension (controlled with amlodipine). After initially presenting with back pain, imaging and biopsy revealed prostate cancer metastatic to the liver and spine. Current ECOG performance status is zero. All lab values are within normal limits except for a PSA of 87ng/dl. In addition to starting ADT, **which of the following is the most appropriate treatment option for AC at this time?** Abiraterone + prednisone
- B. Lutetium-177 PSMA
- C. Docetaxel + darolutamide
- D. Docetaxel + enzalutamide
- E.

3. Metastatic Castrate Sensitive Prostate Cancer (m1CSPC)

- a. ASCO guidelines published in 2021<sup>54</sup> establish four options (in combination with ADT) for m1CSPC, consistent with the preferred, Category 1 options from NCCN guidelines<sup>3</sup>:
  - 1) Docetaxel
  - 2) Abiraterone + prednisone
  - 3) Enzalutamide
  - 4) Apalutamide
- b. However, based on recently published trials, NCCN released new guidelines in 2022 removing ADT+ docetaxel as a treatment option. Instead, ADT + Docetaxel + Abiraterone + prednisone or ADT + Docetaxel + Darolutamide are options for men with high-volume disease m1CSPC.
- c. Treatment overview: m1CSPC



- d. Docetaxel + ADT

- 1) NCCN® Category 1 for M1 castration-naïve prostate cancer (recommended in combination with abiraterone or darolutamide for high-volume disease); ASCO guidelines recommend only for patients with high volume disease
  - i. High volume disease: defined as visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column
- 2) Prednisone is not a required part of the docetaxel regimen when used for metastatic hormone sensitive disease (referred to as castrate sensitive disease in NCCN Guidelines® as patients are not on ADT at time of progression).
- 3) Sweeney et al conducted a phase 3 trial (ECOG 3805; CHAARTED trial) comparing ADT alone to ADT + docetaxel for 6 cycles in 790 men with metastatic hormone sensitive prostate cancer (ADT-naïve). There was a significant improvement in OS with the addition of docetaxel. Median time to development of castration resistant prostate cancer was significantly improved as well.
  - i. Docetaxel was associated with additional toxicities including fatigue, diarrhea, stomatitis and neuropathy. Approximately 6% of patients developed neutropenic fever.<sup>55</sup>
  - ii. Subgroup analysis showed survival benefit was greater in patients with high volume disease. Survival benefit was uncertain in patients with low volume disease.

#### Outcomes of ECOG 3805 – CHAARTED Trial<sup>55, 56</sup>

	ADT + Docetaxel 75mg/m <sup>2</sup> IV every 3 weeks x 6 cycles	ADT	HR; 95% CI
Median overall survival	57.6 mo	44 mo	0.61; 0.47-0.80 (p<0.001)
Median OS in high-volume disease	49.2 mo	32.2 mo	0.60; 0.45-0.81 (p<0.001)
Median time to development of castration-resistant prostate cancer	20.2 mo	11.7 mo	0.61; 0.51-0.72 (p<0.001)

\*ADT: androgen deprivation therapy; HR: hazard ratio; CI: confidence interval; mo: month

- 4) Kyriakopoulos et al published the phase III matured data from the CHAARTED trial confirming OS benefit in high-volume disease with a median OS of 51.2 months ADT + docetaxel versus months vs 34.4 months in ADT alone. For those with low volume disease no OS benefit was observed (HR 1.04; p =0.86).<sup>57</sup>
- 5) James et al conducted Phase 2/3 trial known as the STAMPEDE trial that confirmed the survival advantage seen in the CHAARTED trial. Overall survival of 5.4 years in ADT + docetaxel versus 3.6 years in ADT only arm. However, the extent of disease (high vs low volume) was not evaluated.<sup>58</sup>
- 6) A meta-analysis of CHAARTED + GETUG-AFU15 compared overall survival for ADT + docetaxel vs. ADT alone and found a benefit for high volume disease (HR=0.68; p<0.001) but no benefit for low volume disease (HR=1.03)<sup>59</sup>
- 7) ARASENS Trial: ADT+ Docetaxel + Darolutamide<sup>60</sup>



- i. FDA approved in July 2022
  - ii. Based on the Phase III ARASENS Trial
    - 1. Enrolled 1,306 men with m1CSPC, ECOG 0-1 with no prior chemotherapy, immunotherapy, or ADT
      - a. 86% had de-novo metastatic disease, ~17% had visceral metastases
    - 2. Background therapy:
      - a. ADT (investigator's choice) – started within 12 weeks prior to start of study drug
      - b. Docetaxel 75mg/m<sup>2</sup> IV every 3 weeks x 6 cycles (started within 6 weeks of start of study drug)
    - 3. Study drug:
      - a. Randomized 1:1 to:
        - i. Darolutamide 600mg twice daily with food
        - ii. Matching placebo twice daily with food
    - 4. Efficacy:
      - a. Median OS: NR vs. 48.9 months (HR 0.68; p<0.001)
      - b. Time to CRPC: NR vs. 19.1 months (HR 0.36; p<0.0001)
    - 5. Safety:
      - a. Serious adverse events: 44.8% vs. 42.3%
      - b. No significant difference in fatigue, falls, fractures, mental impairment, rash, hypertension, and cardiovascular events
- 8) PEACE-1 Trial: ADT+ Docetaxel + Abiraterone + Prednisone<sup>61</sup>
- i. Phase III trial published in 2022; enrolled 1173 men with de novo m1CSPC
    - 1. More than half of patients had high burden of metastatic disease (as defined by Sweeney, et al.)<sup>55</sup> and around 10-12% of patients had visceral metastases.
    - 2. Patients were randomized 1:1:1:1 to the following arms:
      - a. ADT ± docetaxel
      - b. ADT ± docetaxel + radiotherapy
      - c. ADT ± docetaxel + abiraterone
      - d. ADT ± docetaxel + radiotherapy + abiraterone
    - 3. Treatment notes:
      - a. Patients receiving abiraterone started within 6 weeks of ADT and received prednisone 5mg by mouth twice daily (accrual started prior to publication of LATTITUDE and STAMPEDE which used prednisone 5mg daily in the castrate sensitive setting)

- b. Patients receiving docetaxel started at least 6 weeks after initiation of ADT. Primary growth factor prophylaxis was recommended until a protocol amendment made it mandatory for all patients mid-way through the trial
    - c. Patients receiving radiotherapy did initiated that 3 to 8 weeks after completion of docetaxel
  - 4. When comparing all patients who received abiraterone (n = 583) to those who did not, radiographic PFS (HR 0.54; p <0.0001) and OS (HR 0.82; p=0.003) both favored abiraterone. When comparing all patients who received docetaxel (n=355) to those who did not, radiographic PFS (HR 0.5; p<0.001) and OS (HR 0.75; p=0.017) both favored docetaxel.
    - a. Median overall survival with vs. without docetaxel separated by volume of disease:
      - i. High-volume disease: 5.1 vs. 3.5 years (HR 0.72; 0.55 to 0.95)
      - ii. Low-volume disease: NR vs. NR (HR 0.83; 0.5-1.39)
  - 5. When looking specifically at patients who received docetaxel as standard of care, the addition of abiraterone improved overall survival (NR vs. 4.43 years (HR 0.75; 0.59-0.95; p=0.017)) in the total population.
    - i. High-volume disease: 5.14 vs. 3.47 years (HR 0.72; p=0.019)
    - ii. Low-volume disease: data not mature
  - 6. Adverse events
    - a. No significant increase in docetaxel-related adverse events was seen with the addition of abiraterone.
      - i. Grade 3 neutropenia: 10 vs. 9%
      - ii. Grade 3 peripheral neuropathy: 1 vs. 2%
    - b. The incidence of adverse events with the addition of abiraterone was consistent with known side effect profile (increased hypertension, hepatotoxicity).
- e. Abiraterone Acetate + ADT
  - 1) NCCN® Category 1 for M1 castration-naïve prostate cancer<sup>3</sup>; ASCO 2021 Guidelines recommend only for use in patients with de novo metastatic disease<sup>54</sup>
  - 2) Approval based on the results of two trials
    - i. LATITUDE: men that were high risk, metastatic, castration naïve randomized ADT with abiraterone 1000mg + prednisone 5mg once daily or ADT + placebo. 95% of patients had de-novo metastatic disease.
      - 1. 3-year OS 66% versus 49%. HR, 0.62; 95% CI, 0.51-0.76; P<0.001
      - 2. 2020 update:
        - a. Median OS 53.3 vs 36.5 months; HR 0.66, p<0.0001

3. Time until pain progression, next subsequent prostate cancer therapy, initiation of chemotherapy, and prostate-specific antigen progression also improved
4. Adverse events included hypertension, hypokalemia, edema, LFT elevation, cardiovascular disorder, fatigue, hot flushes.<sup>62</sup>
- ii. STAMPEDE: 1,917 patients that were de-novo metastatic, high risk with multiple risk factors. The study also permitted those with non-metastatic, nodal and metastatic disease. Patients were randomized to ADT alone or ADT plus abiraterone 1000mg + prednisolone 5mg daily
  1. 3-year OS 83% versus 76% HR, 0.63; 95% CI, 0.52-0.76; P<0.0001
  2. 2021 update:
    - a. Median OS: 6.6 vs. 3.8 years; HR 0.6, p<0.0001
    - i. Low risk: HR 0.66 (p=0.041)
    - b. High risk: HR 0.54 (p<0.001)
  3. Adverse events included hypertension, endocrine, fatigue and cardiovascular disorders.<sup>63</sup>
- 3) Note on corticosteroid with abiraterone:<sup>64</sup>
  - i. Abiraterone (the active metabolite of abiraterone acetate) is CYP17A1 inhibitor, responsible for blocking androgen biosynthesis. Other downstream effects of blocking this enzyme include a reduction in serum cortisol and compensatory increase in adrenocorticotrophic hormone (ACTH). This ultimately results in mineralocorticoid-related adverse events such as hypokalemia, edema, and hypertension. Administration of glucocorticoid replacement compensates for the reduction in cortisol and compensatory increase in ACTH, therefore decreasing the incidence of these adverse effects.
  - ii. In the castrate-resistant setting, abiraterone is approved with prednisone 5mg PO BID, while the studies in the castrate-sensitive setting used a dose of 5mg once daily. Additionally, the fine-particle abiraterone formulation was approved with methylprednisolone 4mg twice daily. Various glucocorticoid replacement strategies have been utilized and may be effective, but should be prescribed as they were studied and FDA approved.
  - iii. Available data suggests that the low doses of glucocorticoids used with abiraterone do not result in immunosuppression seen at higher doses, however long-term use of glucocorticoids does come with inherent risks. It is important to consider patient-specific factors when choosing an initial regimen for management of prostate cancer.
- f. Enzalutamide + ADT
  - 1) NCCN® Category 1 for M1 castration-sensitive prostate cancer; ASCO 2021 guidelines recommend for all m1CSPC patients (although survival benefit after docetaxel treatment in castrate sensitive setting is unclear)
  - 1) ENZAMET trial, open-label, randomized phase III trial<sup>65</sup>

- i. N = 1125, castrate sensitive prostate cancer (up to 12 weeks of prior ADT allowed and after protocol amendment, prior docetaxel allowed)
    - 1. 45% were planned to received prior docetaxel
  - ii. ADT + Enzalutamide 160 mg PO daily vs ADT + first generation antiandrogen
  - iii. Primary end point was OS met at first analysis HR for death, 0.67; 95% CI, 0.52-0.86;  $P = 0.002$
  - iv. Secondary end points
    - 1. PSA PFS (defined as 25% increase in PSA from nadir value), 174 and 333 events, respectively; HR, 0.39;  $P < 0.001$
    - 2. Clinical PFS, 167 and 320 events, respectively; HR, 0.40;  $P < 0.001$
  - v. Subgroup analysis
    - 1. With prior docetaxel, PFS was improved (HR 0.48; 95% CI 0.37-0.62) but OS was not at this time (HR 0.9; 95% CI 0.62-1.31)<sup>66</sup>
- 2) ARCHES trial, double-blind, randomized phase III trial<sup>67</sup>
- i. N = 1,150, metastatic castrate sensitive prostate cancer (prior ADT and up to 6 cycles of docetaxel were allowed)
  - ii. Enzalutamide 160mg PO daily + ADT vs. placebo PO daily + ADT
  - iii. Primary endpoint was radiographic PFS; median rPFS: NR vs. 19 months (HR 0.39,  $p < 0.001$ )
  - iv. Secondary endpoints all favored enzalutamide – time to PSA progression, time to initiation of new antineoplastic therapy, objective response rate, PSA undetectable rate
  - v. Subgroup analysis
    - 1. In those with prior docetaxel, radiographic PFS was improved (HR 0.52; 95% CI 0.3-0.89), OS not reported
- g. Apalutamide + ADT<sup>68</sup>
- 1) NCCN® Category 1 for M1 castration-naïve prostate cancer; recommend for all m1CSPC patients (although survival benefit after docetaxel treatment in castrate sensitive is unclear)<sup>3, 54</sup>
  - 2) TITAN trial double-blind, phase 3 trial
    - i. ADT + Apalutamide 240 mg PO daily vs ADT + placebo
    - ii. OS end point met at first analysis, with 24-month OS: 82.4% vs 73.5%; HR, 0.67 ( $p = 0.005$ )
    - iii. 2021 OS Update: 48--month OS: 65% vs. 52%; HR 0.65 ( $p < 0.001$ )
    - iv. rPFS end point met at first analysis, with rPFS 68.2% vs 47.5% at 24 months; HR 0.48;  $p < 0.001$

- v. In a subgroup analysis, patients who received prior docetaxel had median rPFS of NR vs. 22.1 months; HR 0.47 (95% CI 0.22 to 1.01)
- h. Note: see section on m0CRPC for comparison of second generation androgen antagonist agents

**Patient Case #4; Answer:**

**Correct answer = C (Docetaxel + darolutamide).** This patient has m1CSPC – treatment options include docetaxel + abiraterone, docetaxel + darolutamide, abiraterone + prednisone, apalutamide or enzalutamide. Lutetium-177 PSMA is not approved for m1CSPC. Docetaxel + enzalutamide has not been approved as a combination regimen in any setting. This patient has high volume disease, making a docetaxel-containing regimen preferred. Additionally, he is having pain from his cancer, making docetaxel an attractive option to provide quick relief of his pain. He is otherwise healthy with minimal comorbidities making him a good candidate for docetaxel.

**Patient Case #5:**

AB is a 60-year-old male with castration resistant prostate cancer that was initially treated with ADT + docetaxel x 6 cycles and at progression started on ADT + abiraterone + prednisone. He did well for 2 years with this regimen and then presented with a rising PSA (14ng/ml, then 20ng/ml, over 3 months) and increased back pain. Today, his PSA is 35ng/ml and imaging shows progression of skeletal metastases and several new small liver metastases. His ECOG PS is 0. In addition to continuing ADT, **what is the most appropriate next line of treatment for AB?**

- A. Enzalutamide
- B. Radium-223
- C. Mitoxantrone + prednisone
- D. Cabazitaxel + prednisone

4. Metastatic Castrate Resistant Prostate Cancer (m1CRPC)

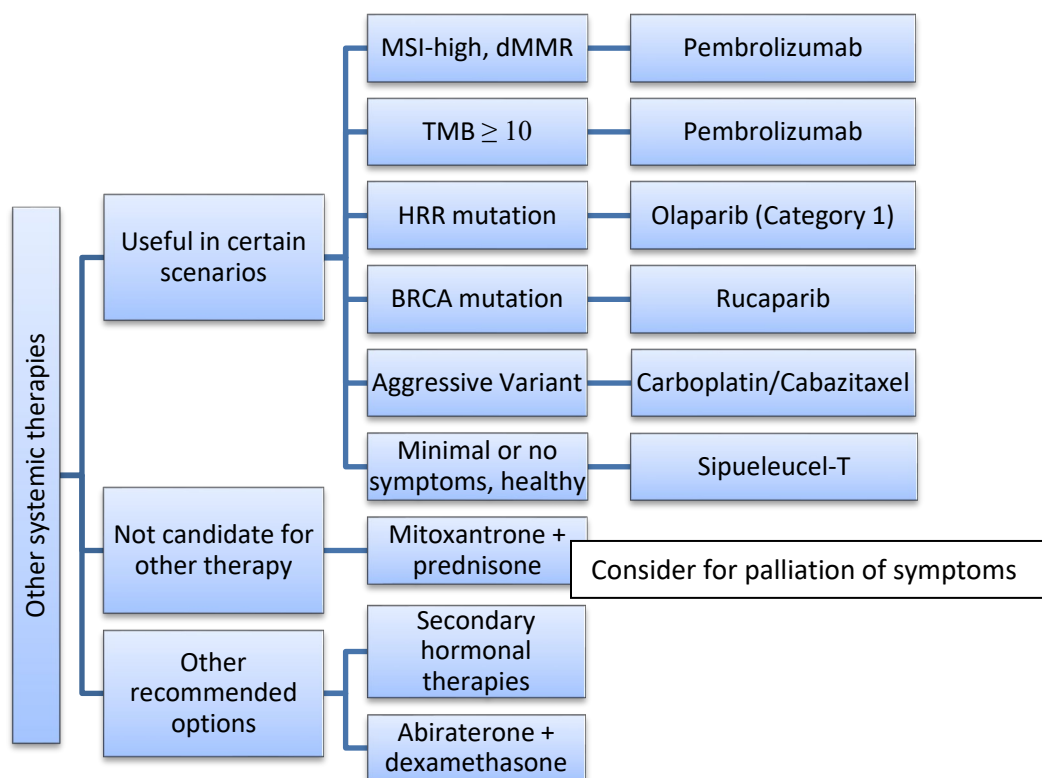
a. NCCN® Recommendations<sup>3</sup>

- 1) Continue ADT and maintain castrate testosterone suppression

**Summary of NCCN preferred recommendations for treatment of metastatic castrate-resistant prostate cancer based on prior therapies<sup>3</sup>**

<b>Prior ADT only</b> <ul style="list-style-type: none"> <li>•Docetaxel (Category 1)</li> <li>•Abiraterone (Category 1)</li> <li>•Enzalutamide (Category 1)</li> </ul>	<b>Prior hormonal therapy only</b> <ul style="list-style-type: none"> <li>•Docetaxel (Category 1)</li> </ul>
<b>If bone-only metastases:</b> Radium-223 (Category 1)	
<b>Prior docetaxel (T) only</b> <ul style="list-style-type: none"> <li>•Abiraterone (Category 1)</li> <li>•Enzalutamide (Category 1)</li> <li>•Cabazitaxel</li> </ul>	<b>Prior docetaxel and hormonal therapies</b> <ul style="list-style-type: none"> <li>•Cabazitaxel (Category 1)</li> <li>•Lu-177-PSMA-617 (If PSMA+, Category 1)</li> <li>•Docetaxel rechallenge (<i>if no prior progression</i>)</li> </ul>

### NCCN guidelines recommendations for subsequent therapeutic options for CRPC following progression<sup>3</sup>



#### b. Docetaxel + Prednisone

- 1) TAX 327: Over 1,000 patients with metastatic CRPC were randomized to 1 of 2 regimens of docetaxel/prednisone or mitoxantrone/prednisone. The initial and updated follow up showed a significant improvement in median survival for patients receiving docetaxel q3 weeks/prednisone compared to mitoxantrone/prednisone.<sup>69, 70</sup>
- 2) The benefit of docetaxel/prednisone is seen in patients with and without symptoms. Per NCCN®, this regimen may be considered for rapid progression or visceral metastases despite lack of symptoms

## Results of TAX 327 Study<sup>70</sup>

	Initial median survival <sup>70</sup> (months)	Follow up median survival <sup>69</sup> (months)	Toxicity (%)
Docetaxel 75 mg/m <sup>2</sup> every 3 weeks + prednisone 5 mg (n=332)	18.9	19.2	Neutropenia: 32% Febrile Neutropenia: 3% Septic Death: 0 Neuropathy: 30% Diarrhea: 32%
Docetaxel 30 mg/m <sup>2</sup> every week + prednisone 5 mg (n=330)	17.4	17.8	Neutropenia: 1.5% Febrile Neutropenia: 0% Septic Death: 0.3% Neuropathy: 24% Diarrhea: 34%
Mitoxantrone 12 mg/m <sup>2</sup> every 3 weeks + prednisone 5 mg (n= 335)	16.5	16.3	Neutropenia: 22% Febrile Neutropenia: 2% Septic Death: 0.3% Neuropathy: 7% Diarrhea: 10%

### c. Abiraterone

- 1) Should be given with corticosteroid (see note on corticosteroids with abiraterone in castrate-sensitive section above)
  - i. In this setting, approved with prednisone 5mg BID
- 2) COU-AA-302 Trial: Randomized, phase III, double-blind trial of 1,088 patients with castration-resistant prostate cancer who **had not** received any previous chemotherapy. Patients were eligible if they were asymptomatic or mildly symptomatic. Patients were randomized to receive abiraterone plus prednisone or placebo plus prednisone. The median radiographic progression free survival was 16.5 months with abiraterone compared with 8.3 months with placebo (HR 0.53, 95% CI 0.45-0.62; p<0.001).
  - i. At interim analysis of 22 months follow-up period, median overall survival was not reached for abiraterone, but it was 27.2 months for the placebo (HR 0.75), however the boundary for statistically significance was not met.
  - ii. In the final analysis, after a median of 49 months of follow-up, overall survival was significantly improved with abiraterone plus prednisone despite 44% of the placebo group receiving abiraterone as crossover per protocol or as subsequent therapy (34.7 months v 30.3 months; hazard ratio 0.81 [95% CI 0.7-0.93]; p=0.0033).<sup>71</sup>
    1. Overall, patients receiving abiraterone had longer time to initiation of chemotherapy, initiation of opiates for cancer-related pain, greater time to PSA progression and greater time to decline in performance status.<sup>71, 72</sup>
- 3) COU-AA-301 Trial: A phase III, randomized, double-blind, placebo-controlled trial abiraterone plus prednisone was evaluated in 1,195 patients with prostate cancer who

**had** received previous docetaxel therapy. Abiraterone significantly improved median overall survival (14.8 vs. 10.9 months,  $p < 0.001$ ) compared with placebo. At the preplanned interim analysis, there was a 35.4% reduction in risk of death (HR 0.65; 95% CI, 0.54-0.77;  $p < 0.001$ ).

- i. In addition, abiraterone showed significant improvements in time to PSA response rate, PSA progression time and progression free survival.
  - ii. Abiraterone had significant higher incidence mineralocorticoid-related adverse events of fluid retention, hypertension and hypokalemia compared with placebo. Patients also had muscle discomfort, hot flashes, diarrhea, and urinary tract infection.<sup>73</sup>
- 4) STAAR trial: Phase 2 trial of 53 men with metastatic CRPC not treated with abiraterone, enzalutamide, radium-223 or chemotherapy except docetaxel for metastatic CRPC at least 1 year prior to enrollment. Patients were randomized to 500mg PO daily of fine-particle abiraterone with 4mg of methylprednisolone PO twice daily or the originator formulation plus 5mg of prednisone PO twice daily regardless of food
- i. Bioequivalence was confirmed based on PSA response, testosterone levels and abiraterone pharmacokinetics
  - ii. Rates of adverse grade 3/4 adverse effects were similar only musculoskeletal and connective tissue disorders occurring more frequently.<sup>74</sup>
- 5) Abiraterone + Dexamethasone
- i. In patients with asymptomatic PSA progression on abiraterone + prednisone, a switch from prednisone 10mg/day to dexamethasone 0.5mg/day has shown to induce PSA stabilization or decrease in some studies. While corticosteroids are used to prevent the mineralocorticoid excess induced by abiraterone, they also have an antitumor effect through inhibition of ACTH production (and therefore adrenal androgen synthesis). The exact mechanism explaining why switching steroids would induce a response is unclear, however possible mechanisms include differences in effect on glucocorticoid receptor (and development of resistant mutations), differences in pharmacokinetic properties of the two drugs, and differences in effect on cellular growth factors.<sup>75</sup>
  - ii. The Phase II, single arm, SWITCH study evaluated 26 patients with mCRPC who had been on abiraterone + prednisone for at least 12 weeks with limited radiographic, asymptomatic progression were eligible for enrollment.<sup>76</sup>
    1. The primary endpoint was PSA decline of at least 30% at 6 weeks: 46.2%
    2. Time to PSA progression: 5.3 months; Time to radiographic progression: 11.8 months
  - iii. A single center, retrospective analysis evaluated 48 patients on abiraterone + prednisone with asymptomatic PSA progression who were switched to abiraterone + dexamethasone 0.5mg/day.<sup>77</sup>
    1. 56.25% of patients experienced a stabilization or decline in PSA after the switch.
    2. Median time to PSA progression: 8.94 months



3. Factors associated with response to switch: long hormone-sensitivity duration (>5 years), low PSA at time of switch (<50ng/mL), and short time to PSA progression on abiraterone + prednisone (<6 months).
- iv. Switching steroids may be a cost-effective option with limited toxicity in patients experiencing an asymptomatic progression on abiraterone + prednisone, however large, randomized trials need to be done to confirm a survival benefit.

d. Enzalutamide

- 1) PREVAIL trial: Phase 3 trial of 1,717 patients with asymptomatic or minimally symptomatic metastatic CRPC who had not received cytotoxic chemotherapy or abiraterone. Patients could have visceral metastases but were excluded if they had history of seizures. Patients were randomized to enzalutamide 160mg po daily or placebo. Co-primary end points were radiographic PFS and overall survival.
  - i. Radiographic PFS at 12 months was 65% in enzalutamide versus 14% in placebo. There was an 81% risk reduction of radiographic progression or death (HR 0.19; 95% CI, 0.15-0.23) and a 29% reduction in risk of death (HR 0.71; 95% CI, 0.60-0.84).
  - ii. Median OS was estimated at 32.4 months in enzalutamide versus 30.2 months in placebo. At 18 months, 82% of enzalutamide patients were alive versus 73% of placebo patients.
  - iii. Median time to PSA progression (11.2 months v 2.8 months), PSA decline at least 50% (78% v 3%), and soft tissue response (59% v 5%) were all significantly improved in the enzalutamide group.<sup>78</sup>
- 2) AFFIRM Trial: Randomized, phase III, double-blind, placebo-controlled trial comparing enzalutamide to placebo in 1,199 men with castration-resistant prostate cancer who were previously treated with docetaxel. Patients with history of seizure activity or risk of seizure were excluded. Overall survival was the primary end point. The median number of previous docetaxel cycles given was 8 in each group.
  - i. Study showed significantly longer median overall survival of 18.4 months with enzalutamide compared with 13.6 months with placebo (HR 0.63, 95% CI 0.53-0.75, p<0.001).
  - ii. PSA response (54% vs 2%) and time to PSA progression (8.3 vs 3.0 months) was significantly improved with enzalutamide. Radiographic progression free survival was 8.3 vs. 2.9 months and time to first skeletal related events was 16.7 vs. 13.3 months.
  - iii. Fatigue, diarrhea, hot flashes musculoskeletal pain and headache were more common in the enzalutamide receiving patients. Seizure was reported in 0.6% of patients receiving enzalutamide.<sup>79</sup>
- 3) TERRAIN Trial: Randomized, phase II, double blind trial comparing enzalutamide to bicalutamide in 375 asymptomatic or minimally symptomatic men with CRPC with disease progression on ADT. Primary endpoint of PFS.
  - i. The enzalutamide group had improved median PFS of 15.7 months vs 5.8 months (HR 0.44, 95% CI 0.34–0.57, p<0.0001) in the bicalutamide group. Median time to PSA progression 19.4 months (95% CI 16.6–not reached) for patients assigned to

enzalutamide and 5.8 months (5.6–8.3) for patients assigned to bicalutamide (HR 0.28, 95% CI 0.20–0.39;  $p < 0.0001$ ).

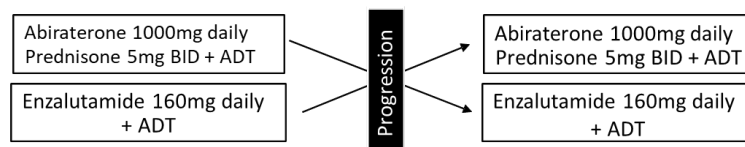
- ii. The adverse events occurring in a higher proportion of patients who received enzalutamide were fatigue, back pain, hot flashes, hypertension, diarrhea, weight loss, and pain in the extremities. Seizure was reported in 1% ( $n=2$ ) of enzalutamide arm.<sup>80</sup>

- 4) STRIVE Trial: Randomized, phase II, double-blind trial comparing enzalutamide to bicalutamide in 396 men with CRPC with disease progression on ADT. Exclusion criteria included previous chemotherapy, brain metastasis, or a history of seizure. Primary end point was PFS.
  - i. The enzalutamide group had a reduction in risk of progression or death by 76% compared with bicalutamide (HR, 0.24, 95% CI, 0.18 to 0.32,  $P < 0.001$ ). Median PFS was 19.4 months with enzalutamide and 5.7 months with bicalutamide.
  - ii. Median time to PSA progression (HR, 0.19, 95% CI, 0.14 to 0.26,  $P < 0.001$ ); proportion of patients with  $\geq 50\%$  PSA response (81% v 31%  $P < 0.001$ ), and radiographic PFS in metastatic patients (HR, 0.32; 95% CI, 0.21 to 0.50,  $P < 0.001$ ).<sup>81</sup>

e. Sequencing of hormonal therapies

- 1) Phase II trial of 202 newly diagnosed m1CRPC<sup>82</sup>

- i. Randomized patients to either:



- ii. Patients crossed to second line treatment at progression (defined as PSA increase, radiation to symptomatic bone metastases, or unacceptable toxicity)
- iii. Efficacy endpoints:

	Time to PSA Progression 2	PSA response (>30%) 2	Time to PSA Progression 1	PSA response (>30%) 1	Median OS
Group A	19.3 months	36%	11.2 months	68%	28.8 months
Group B	15.2 months	4%	10.2 months	82%	24.4 months
	HR 0.66; $p=0.036$	$p < 0.0001$	HR 0.95; $p=0.78$	$p=0.023$	HR 0.79; $p=0.23$

- iv. Time to first PSA progression was similar between the two groups (11.2 vs. 10.2 months HR 0.95;  $p=0.78$ ), indicating similar efficacy in the first line setting. This led the authors to conclude that the overall benefit from sequencing therapies was derived from the improved response to enzalutamide in the second-line setting. The authors theorize this may be due to difference in mechanism of action between the two drugs and mechanisms of resistance.
- 2) Further studies are needed to confirm a survival benefit from sequencing therapies as this study was not powered to detect a difference in mOS and the 4 month benefit was not statistically significant.

f. Cabazitaxel (Jevtana®)

- 1) Not indicated in the first line setting
- 2) TROPIC Trial: Phase III, randomized, open-label, multi-center trial in 755 patients with metastatic CRPC who had received prior docetaxel therapy. Patients were randomized to receive cabazitaxel 25 mg/m<sup>2</sup> or mitoxantrone with daily prednisone every 3 weeks up to total of 10 cycles.
  - i. Study showed median PFS of 2.8 months with cabazitaxel vs. 1.4 months with mitoxantrone (p<0.0001). The median OS was significantly better with cabazitaxel at 15.1 vs. 12.7 months (p<0.0001).
    1. There were significantly higher incidences of severe neutropenia, diarrhea and febrile neutropenia (8%) in the cabazitaxel arm. Another side effect of concern is the 30-day mortality after last dose of drug of 4.9% in cabazitaxel group compared with 2% in mitoxantrone. It is more likely due to higher incidences of neutropenia and diarrhea.<sup>83</sup>
- 3) PROSELICA Trial: Phase III, noninferiority trial assessed 20mg/m<sup>2</sup> vs 25mg/m<sup>2</sup> in post docetaxel patients with metastatic CRPC<sup>84</sup>
  - i. Confirmed efficacy and noninferiority of 20mg/m<sup>2</sup> in post-docetaxel patients
  - ii. PFS, prostate-specific antigen (PSA) response favored 25mg/m<sup>2</sup>
  - iii. Health-related quality of life, and safety favored 20mg/m<sup>2</sup>
  - iv. Dosing 20 mg/m<sup>2</sup> every 3 weeks in combination with prednisone recommended
  - v. . It is important to pre-medicate patient with an antihistamine, a corticosteroid, and an H2 antagonist<sup>84</sup> to prevent hypersensitivity reaction
- 4) FIRSTANA Trial:<sup>85</sup> Phase III superiority trial comparing cabazitaxel to docetaxel for mCRPC. Randomized 1,168 patients 1:1:1 to cabazitaxel 20mg/m<sup>2</sup> (C20) to cabazitaxel 25mg/m<sup>2</sup> (C25) to docetaxel 75mg/m<sup>2</sup> (D75) IV every 3 weeks plus prednisone.
  - i. Primary endpoint: median OS (C20 vs. C25 vs. D75)
    1. 24.5 vs. 25.2 vs. 24.3 months (no difference between either cabazitaxel regimen and D75)
  - ii. Median PFS was not different between the groups. Tumor response rate was numerically higher with C25 vs. D75 (41.6 vs. 30.9%, p =0.37)
  - iii. Adverse effects:
    1. Rate of grade 3 or 4 AE: 41.2%, 60.1%, and 46.0% (C20 vs. C25 vs. D75)
    2. D75 had higher rates of peripheral neuropathy, edema, and nail disorders. C25 had higher rates of febrile neutropenia, diarrhea and hematuria.
  - iv. In first line setting, cabazitaxel is not superior to docetaxel. Only FDA approved after treatment with docetaxel-containing regimen.
- 5) CARD Trial<sup>86</sup>:

- i. Phase III, open label, randomized 225 men with mCRPC previously treated with docetaxel and one novel hormonal therapy (abiraterone or enzalutamide) randomized to:
  1. Cabazitaxel 25mg/m<sup>2</sup> IV every 3 weeks + prednisone + WBC growth factor
  2. The alternate novel hormonal therapy (abiraterone or enzalutamide)
- ii. Primary outcome: median radiographic PFS: 8 vs. 3.7 months (HR 0.54; p < 0.001)
- iii. Median OS: 13.6 vs. 11 months (HR 0.64; p = 0.008)
- iv. PSA response: 35.7 vs. 13.5% (p<0.001)
- v. Limitations: Study done in Europe where 25mg/m<sup>2</sup> is still standard of care, in US – 20mg/m<sup>2</sup> dose is used based on PROESLICA trial above. If giving higher dose, must use growth factor. Previous studies showed rates of febrile neutropenia 8-9.3%, with growth factor in the CARD trial incidence was 3%. Consider patient selection and performance status.
- vi. Based on this trial, if a patient is a candidate for chemotherapy, it may be preferred over a second novel hormonal therapy in the castrate resistant setting.

**Patient Case #5: Answer = D (Cabazitaxel).**

Mitoxantrone has no overall survival benefit and should be reserved for patients with no other appropriate treatment options. Radium-223 is only indicated for pts with bone-only mets. Cabazitaxel and alternate novel hormonal therapy were compared in this setting in the CARD trial and cabazitaxel had superior survival benefit. Therefore, cabazitaxel is preferred over enzalutamide for this patient.

**Patient Case #6:** GC has metastatic castration resistant prostate cancer with no other comorbidities. He was initially treated with leuprolide and apalutamide and when he progressed, he was started on docetaxel. His most recent PSMA PET scan shows numerous sites of progressing disease in the lung and bones. In addition to continuing his leuprolide, **which of the following is the most appropriate next line of treatment for AB?**

- A. Enzalutamide
- B. Radium-223
- C. Mitoxantrone + prednisone
- D. Lutetium-177 PSMA

**g. Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)**

- 1) Novel radiopharmaceutical FDA approved in 2022 for treatment of PSMA-positive m1CRPC
  - i. Approved for patients with at least one PSMA-positive lesion and/or metastatic disease that is primarily PSMA-positive (with no dominant PSMA-negative lesions) and have been treated with at least two prior therapies (one novel hormonal therapy and one taxane-based therapy)
- 2) Prostate-Specific Membrane Antigen (PSMA) is a transmembrane protein that is present on the cell surface. It is expressed in normal prostate tissue but is known to have increased expression in prostate cancer tissue. Over 90% of prostate cancers are thought to over-express PSMA. Androgen deprivation leads to upregulation of PSMA.<sup>87</sup>

- i. Levels of PSMA expression are thought to correlate with cancer aggressiveness and inversely with prognosis.
  - ii. PSMA-targeted PET imaging was initially approved by the FDA and used as a more sensitive imaging test for metastatic disease compared to the standard fluciclovine-based PET scans. Currently there are three FDA approved products for PSMA PET imaging.<sup>88, 89</sup>
- 3) VISION trial<sup>90</sup>
  - i. Open-label, international phase III trial
    - 1. Enrolled 831 patients with PSMA-positive castrate-resistant metastatic prostate cancer who had received at least one prior novel hormonal therapy and one prior taxane
      - a. Around 40% had two prior novel hormonal therapies
    - 2. Randomized 2:1 to Lu-PSMA-617 + Standard Care vs. Standard Care Alone
      - a. Standard Care allowed androgen deprivation, bisphosphonates/denosumab, novel hormonal therapies
        - i. Excluded chemotherapy, immunotherapy, radium-223, and other investigational drugs
      - b. Lu-PSMA was given every 6 weeks x 4-6 cycles (cycles 5 and 6 at discretion of investigator based on response)
        - i. Median 5 cycles given; 17.6% require dose delay and 5.7% required dose reduction
    - 3. Primary endpoints:
      - a. Imaging-based PFS: 8.7 vs. 3.4 months (HR 0.4, p<0.001)
      - b. Median OS: 15.3 vs. 11.3 months (0.62, p<0.001)
    - 4. Safety endpoints:
      - a. Grade 3/4 in 52.7% vs. 38%
        - i. 23.4% bone marrow suppression, 3.4% renal effects
      - b. Adverse effects of all grades that occurred in >30% of patients: fatigue, dry mouth, nausea, anemia
- 4) Phase II TheraP Trial:<sup>91</sup>
  - i. N = 200 m1CRPC, PSMA positive, previously treated with docetaxel (could also be treated with prior novel hormonal therapy, which 90% had)
  - ii. Randomized patients 1:1 (open label)
    - 1. Lutetium-177 PSMA 6-8.5GBq IV every 6 weeks up to 6 cycles
    - 2. Cabazitaxel 20mg/m<sup>2</sup> IV every 3 weeks up to 10 cycles
  - iii. Efficacy:
    - 1. Primary endpoint was PSA response (defined as a 50% reduction in PSA)

- a. 66 vs. 37%;  $p = 0.0016$
- 2. Progression free survival:
  - a. Kaplan Meier curves cross around 6 months for the two groups. Median PFS was 5.1 months in each arm but hazard ratio favored Lutetium-177 PSMA (0.63). 12 month PFS was 19% vs. 3%
- 5) Lutetium-177 PSMA (Pluvicto®)<sup>92</sup>
  - i. Mechanism of action:
    - 1. Radiopharmaceutical: Lutetium-177 bound to PSMA-617
    - 2. Selectively delivers beta-particle radiation to PSMA-positive cells and surrounding microenvironment
  - ii. Indication: m1CRPC (PSMA-positive) previously treated with one taxane-based therapy and one androgen-receptor pathway inhibitor
  - iii. Dosing: 7.4 GBq (200 mCi) IV every 6 weeks (up to 6 doses)
  - iv. Toxicities: fatigue, dry mouth, nausea/vomiting, decreased appetite, and constipation/diarrhea, renal toxicity, myelosuppression, infertility
  - v. Drug-drug interactions: Not evaluated
  - vi. Pearls: Patient precautions (avoid close contact for 3-7 days); antiemetic pre-medications recommended; dose reduce for dry mouth, GI toxicity, renal toxicity, myelosuppression

**Patient Case #6: Answer = D (Lutetium-177 PSMA).** The patient meets criteria to receive this agent, as he has PSMA-positive disease that has progressed through a taxane and a novel hormonal therapy. Enzalutamide is not appropriate after progression on apalutamide. Radium-223 is not recommended with visceral disease. Mitoxantrone does not provide a survival benefit in this setting.

- h. Radium-223 – for patients with symptomatic bone only disease
    - 1) Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) Trial: A phase III, double-blind, randomized trial comparing radium-223 to placebo in 921 patients with CRPC and symptomatic bone metastases and no visceral metastases. Approximately 60% had received previous docetaxel therapy and 13% were ECOG  $\geq 2$ . Approximately 30% of the patients had  $>20$  bone metastases, 45% had 6-20 bone metastases and 15% had  $< 6$  bone metastases. Patients were randomized to receive 6 injections of radium-223 given 1 injection every 4 weeks or placebo. Patients also received other standard of care prostate cancer therapy.<sup>93</sup>
      - i. At the interim analysis, radium-223 not only delayed time to first skeletal related events, but showed survival advantage (only seen when all 6 injections were given).
      - ii. The median overall survival was 14 months compared with 11.2 months in placebo group ( $P = 0.002$ ). The updated analysis confirmed the survival benefit (14.9 months vs 11.3 months,  $p < 0.001$ ).
      - iii. Median time to first skeletal related events was 15.6 months vs. 9.8 months ( $p < 0.001$ ). Median time to PSA progression was 3.6 mo v 3.4 mo ( $p < 0.001$ ).

- iv. There was also a significant improvement in quality of life by FACT-P score associated with radium 223.
  - v. Grade 3 or 4 toxicities of radium-223 are anemia 10%, neutropenia 2%, and thrombocytopenia 4%.
- 2) NCCN® Category 1 for patients with symptomatic bone metastases and **no known visceral metastases** prior to and after docetaxel therapy.<sup>3</sup>
  - 3) Not approved to be used in combination with docetaxel or any other chemotherapy due to potential of additive myelosuppression. Prior to initial dose, ANC should be  $\geq 1,500/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$ , and hemoglobin  $\geq 10 \text{ g/dL}$ ; prior to subsequent doses, ANC should be  $\geq 1,000/\text{mm}^3$  and platelets  $\geq 50,000/\text{mm}^3$ . Neutrophils and platelet nadirs typically occurred 2 to 3 weeks after administration; recovery generally occurred ~6 to 8 weeks after administration. If recovery does not occur within 6 to 8 weeks from the last dose (despite supportive care), treatment should be discontinued.
  - 4) Should not be used with any therapy other than ADT and bone-directed therapies (denosumab, zoledronic acid). Studies in combination with abiraterone showed no benefit with respect to skeletal event-free survival and an increase in risk of fracture.<sup>94</sup>
- i. Sipuleucel-T– For asymptomatic or minimally symptomatic patients
    - 1) IMPACT Trial: Phase III, randomized, double-blind, placebo-controlled trial in patients with metastatic CRPC who were asymptomatic or minimally symptomatic. Patients had a  $\geq 6$  month life expectancy and PSA  $\geq 5 \text{ ng/ml}$  without visceral metastases. 341 patients received sipuleucel-T and 171 placebo.<sup>95</sup>
      - i. There was a 22% relative reduction in risk of death (HR 0.78; 95% CI, 0.61-0.98). Median overall survival was 25.8 months in patients receiving sipuleucel-T compared with 21.7 months in patients receiving placebo (P=0.03).
      - ii. Median time to disease progression was not significantly different between the 2 groups (14.6 weeks v 14.4 weeks, p=0.63).
    - 2) Sipuleucel-T is not recommended for patients with small cell/neuroendocrine prostate cancer.
    - 3) Sipuleucel-T should be considered for patients with metastatic CRPC and have the following:<sup>3</sup>
      - i. No or minimal symptoms or requiring opioids
      - ii. Good performance status
      - iii.  $\geq 6$  months life expectancy
      - iv. No visceral disease
  - j. Mitoxantrone/Prednisone – generally for symptomatic patients who are not candidates for docetaxel therapy as there is no difference in overall survival<sup>3</sup>
  - k. Cabazitaxel + Carboplatin<sup>96</sup>
    - 1) This regimen was added to the NCCN guidelines based on a phase 1-2 study (below) and could be considered for select patients with features of aggressive-variant prostate cancer (AVPC) and a good performance status.<sup>3</sup>

- 2) Phase 1-2 study, open-label, randomized patients with m1CRPC previously treated with docetaxel and one prior novel hormonal therapy
- 3) Initial phase 1 study enrolled 9 patients with no dose-limiting toxicities.
- 4) Phase 2 study enrolled 160 patients and randomized 1:1 to:
  - i. Cabazitaxel 25mg/m<sup>2</sup> + carboplatin AUC 4 IV every 3 weeks + prednisone 10mg daily + WBC growth factor
  - ii. Cabazitaxel 25mg/m<sup>2</sup> + prednisone 10mg daily + WBC growth factor
- 5) Patients were stratified based on presence of AVPC clinicopathologic features (AVPC-C) or molecular findings suggestive of AVPC (AVPC-MS) in an attempt to identify an androgen-indifferent subtype:
  - i. AVPC-C:
    1. Small cell histology, exclusively visceral metastases, predominantly lytic bone metastases, bulky lymphadenopathy or Gleason ≥ 8 at diagnosis, PSA ≤ 10 + high volume (≥ 20) bone metastases, elevated LDH or CEA, ≤ 6 month response to ADT
  - ii. AVPC-MS:
    1. Defect in 2 of 3 tumor suppressor genes (TP53, RB1, and PTEN) on ctDNA or immunohistochemistry
    2. Only available in 56 patients

6) Median PFS:

All patients	AVPC-C	AVPC-MS (post-hoc)
7.3 vs. 4.5 months	NR	6 vs 2.2 months
HR 0.69; p = 0.018	HR 0.58; p = 0.013	HR 0.35; p = 0.00033

7) Median OS:

All patients	AVPC-C	AVPC-MS (post-hoc)
18.5 vs. 17.3 months	NR	17.4 vs. 9.9 months
HR 0.89; p = 0.5	NR	HR 0.39; p = 0.0024

Note: NCCN guidelines recommend lower cabazitaxel dosing of 20mg/m<sup>2</sup> (in combination with carboplatin AUC 4 and WBC growth factor)



**Patient Case #7:** RC is a 65-year-old male with metastatic prostate cancer and tumor mutation testing revealed BRCA1 mutation. His previous lines of therapy include leuprolide + abiraterone + prednisone, leuprolide + Radium-223, and leuprolide + docetaxel + prednisone. He has received 3 cycles of docetaxel and his PSA has been increasing over the 2 months. Repeat staging scans show worsening bone and liver metastases. He now requires scheduled morphine for bone pain. His ECOG performance status is 1. **In addition to continuing ADT, which of the following is the most appropriate treatment option for RC at this time?**

- A. Olaparib
- B. Sipuleucel T
- C. Mitoxantrone
- D. Pembrolizumab

I. Olaparib

- 1) PROFOUND Trial: Phase III open label trial. Enrolled 387 men with mCRPC who had progressed on either abiraterone or enzalutamide and had one of 15 prespecified HRR mutations. Patients were randomized 2:1 to olaparib 300mg PO BID or physician's choice of abiraterone or enzalutamide (all patients continued ADT).<sup>6</sup>
  - i. Of note, 2,792 had tumor tissue screened for HRRm and 28% had a mutation in 1 of the 15 prespecified genes. Of these, 387 met criteria for enrollment. The most common mutations were BRCA2, ATM, and CDK12.
  - ii. Patients were separated into 2 cohorts. Cohort A included patients with BRCA1, BRCA2, or ATM mutations. Cohort B included the 12 remaining pre-specified HRRm.
    1. Approximately 18% of patients in control arm had received both abiraterone and enzalutamide in the past. Around over 60% of patients had received a prior taxane.
  - iii. Primary endpoint was imaging-based PFS
    1. Cohort A: 7.4 vs. 3.6 months (HR 0.34, p <0.001)
    2. Cohort A + B: 5.8 vs. 3.5 months (HR 0.49, p <0.001)
    3. Not reported for cohort B alone. Unclear how much the benefit across all groups is driven by Cohort A (specifically BRCA2 mutation).
    4. In subgroup analysis, patients with PPP2R2A mutation, HR for progression or death significantly favored the control arm (6.61; 95% CI 1.41 to 46.41). NCCN recommends against use in these patients.
  - iv. Overall Survival Update:<sup>97</sup>
    1. mOS in Cohort A: 19.1 vs. 14.7 months (HR 0.69, p = 0.02)
    2. mOS in Cohort B:
      - a. 14.1 vs. 11.5 months (HR 0.96; 95% CI 0.63 – 1.495.98) before adjusting for crossover
      - b. Post-hoc analysis excluding PPP2R2A from cohort B:
        - i. mOS 14.2 vs. 10.8 months (HR 0.79; 95% CI 0.5-1.25)
    3. mOS in total population:

- a. 17.3 vs. 14 months (HR 0.79; 95% CI 0.61-1.03)
  - v. FDA approved for mCRPC with any germline or somatic HRRm after progression on either abiraterone or enzalutamide.
- m. Rucaparib
  - 1) FDA approved for m1CRPC with germline or somatic BRCA1/2 mutation and prior treatment with taxane and androgen-receptor directed therapy.
  - 2) TRITON 2, an ongoing single-arm phase II trial of rucaparib 600mg PO BID in mCRPC with any HRRm after progression on 1 prior taxane and 1-2 prior androgen-receptor directed therapies.<sup>98</sup>
  - 3) BCRCA1/2 Cohort n = 115
    - i. Response rate of 43.5% in 66 BRCA2 mutated patients
  - 4) Non-BRCA HRRm cohort (n =78) not reported at this time but authors state limited radiographic or PSA responses.
  - 5) Awaiting confirmatory efficacy and safety results from TRITON3. A randomized trial of rucaparib versus physician's choice of treatment.

**Patient Case #7, Answer:**

**Correct answer = A (Olaparib).** Sipuleucel-T is not indicated in this setting. Mitoxantrone has no overall survival benefit and is generally reserved for patients who cannot tolerate any other treatment option. This patient has a homologous recombinant repair mutation making him a candidate for a PARP inhibitor. Olaparib is FDA indicated for any HRRm (and NCCN guidelines recommend for any HRRm except PPP2R2A). Pembrolizumab is only indicated for dMMR or MSI-high cancers. Olaparib is the most appropriate option for the patient based on available evidence.

**Patient Case #8:**

LL has prostate cancer that progressed during adjuvant ADT with increasing PSA, testosterone <50ng/dL, and bone scans showing new skeletal metastases. His oncologist is planning to add enzalutamide to his ADT at this time. The oncologist asks if there are any other supportive care medications that you would recommend.

**What of the following is most appropriate to initiate in LL at this time?**

- A. Denosumab 120 mg every 4 weeks
- B. Calcium plus vitamin D 500mg-400 IU twice daily
- C. Alendronate 70 mg every 4 weeks and calcium plus vitamin D 500mg-400 IU twice daily
- D. Denosumab 120 mg every 4 weeks and calcium plus vitamin D 500mg-400 IU twice daily

**I. Supportive Care and Survivorship**

**A) Osteoporosis in Prostate Cancer**

- 1. ADT increases the risk for osteoporosis and is associated with a 21%-54% increase in fracture risk.<sup>3</sup>
- 2. Screening and treatment based on normal population. Calcium 1200mg daily and vitamin D3 800-1000 IU daily are recommended for all men over the age of 50 years.
- 3. Additional treatment indicated if 10-year probability of hip fracture is  $\geq 3\%$  or 10-year probability of major osteoporosis related fracture  $\geq 20\%$ .

4. Fracture risk assessment using FRAX
  - a. -10-year risk of fracture based on clinical factors and baseline bone mineral density
5. Baseline DEXA scan prior to initiating therapy for those at risk
6. Bisphosphonates
  - a. Zoledronic acid: Randomized, placebo-controlled trial evaluated zoledronic acid 4mg IV x 1 versus placebo in 40 men with non-metastatic prostate cancer on ADT therapy with at T score > -2.5. The mean bone mineral density (BMD) of the lumbar spine decreased by 3.1% in placebo arm and increased by 4% in zoledronic acid arm after 1 year. A significant difference in BMD was also seen in the total hip and trochanter. The study did not assess the impact on fracture rate.<sup>99</sup>
  - b. Alendronate: A randomized, double-blind trial evaluated 112 men with non-metastatic prostate cancer on ADT and randomized them to alendronate 70mg PO weekly or placebo. After 1 year, men receiving alendronate had BMD increased by 3.7% at the spine and 1.6% at the femoral neck vs a 1.4% and 0.7% loss in the placebo group, respectively. The study did not assess the impact on fracture rates.<sup>100</sup>
7. Denosumab
  - a. A randomized, double-blind trial evaluated denosumab 60mg SQ every 6 months versus placebo in over 1400 men with non-metastatic prostate cancer receiving ADT. Patients had T-score less than -1.0 or history of osteoporotic fracture. At 24 months, bone mineral density was increased by 5.6% in with denosumab compared with loss of 1% in with placebo. Out of 1468 men, 1.5% on denosumab and 3.9% on placebo (P=0.006) had incidence of new vertebral fractures.<sup>101</sup>
8. Current NCCN® recommendations for patients with a fracture risk that warrants drug therapy include zoledronic acid 5mg IV annually, alendronate 70mg PO weekly, or denosumab 60mg SQ every 6 months.<sup>3</sup>

#### B) Bone Metastasis and Bone Pain in Prostate Cancer

1. Skeletal-related events (SRE) include pathologic fractures (vertebral or non-vertebral), spinal cord compression, surgery to bone, radiation therapy to bone, or change in antineoplastic therapy to treat bone pain.
2. Bisphosphonates: Zoledronic acid is recommended to prevent skeletal related events in men with castration resistant recurrent prostate cancer with bone metastases. It can be given every 3-4 weeks. Overall ideal duration of treatment is unknown. Pamidronate has not been shown to be efficacious compared with placebo in patients with metastatic CRPC.
  - a. Over 600 patients with CRPC and bone metastases were randomized to zoledronic acid 4mg, zoledronic acid 8 mg (subsequently reduced to 4mg due to toxicity), or placebo every 3 weeks for 15 months. Zoledronic acid significantly reduced the incidence of SRE and extended the time to first SRE.<sup>102</sup>
    - 1) A follow up of this study extended treatment out to a total of 24 months. In the 122 patients who completed 24 months, zoledronic acid patients had fewer SRE than those in placebo and no additional toxicity.<sup>103</sup>

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- a. Patients should also receive calcium and vitamin D due to the risk of hypocalcemia and periodic monitoring of serum calcium levels
- b. In patients with normal renal function, hypocalcemia occurs twice as often with denosumab than zoledronic acid.

**Patient Case #8 Answer:**

**Correct answer = D (Denosumab 120 mg every 4 weeks and calcium plus vitamin D 500mg-400 IU twice daily).**

LL now has castrate resistant prostate cancer with bony disease, so it is reasonable to initiate therapy for prevention of a skeletal-related event. Denosumab is a preferred agent for this indication. Alendronate is reasonable to prevent osteoporosis but is not indicated for prevention of skeletal-related events. Denosumab has been shown to delay time to first skeletal related events in patients with bone metastases from prostate cancer. Calcium plus vitamin D should be added to therapy to prevent hypocalcemia.

5. Radiation Therapy<sup>108</sup>

- a. Strontium 89 (Metastron<sup>®</sup>) and samarium-153 (Quadramet<sup>®</sup>)
  - 1) 60-80% analgesic response rates, median duration 3-6 months
  - 2) Major dose limiting toxicity is myelosuppression due to marrow suppression by the beta particle penetration. Palliative radiation can increase the risk of bone marrow suppression and prevent patients from receiving future systemic chemotherapy.
  - 3) No advantage in overall survival as seen with Radium 223
- b. External beam radiation
  - 1) Used to control pain and prevent impending fractures from individual lesions.
  - 2) Pain relief seen in greater than 90% of patients
  - 3) Local control rates range from 75-90%

C) Diabetes and Heart Disease in prostate cancer

1. ADT therapy causes physiologic effects such as increased fat mass, decreased lean muscle mass, increased cholesterol and triglycerides, and decreased insulin sensitivity. These events have been linked to diabetes and cardiovascular disease.<sup>3</sup>
2. A population based study of 73,196 patients with locoregional prostate cancer found that use of ADT was associated in an increased risk of diabetes (HR 1.44; p<0.001), coronary artery heart disease (HR 1.16; p<0.001), myocardial infarction (HR 1.11; p=0.03) and sudden cardiac death (HR 1.16; p=0.004).<sup>109</sup>
3. Usual population screening and interventions for diabetes and heart disease are recommended at this time.<sup>3</sup>

D) Sexual and Urinary Dysfunction<sup>110, 111</sup>

1. 90% of prostate cancer survivors report erectile dysfunction (ED)
2. NCCN<sup>®</sup> recommends asking about sexual function at regular intervals and provides a questionnaire for clinic use<sup>9</sup>
3. The American Cancer Society has published guidelines for prostate cancer survivors<sup>110</sup> that includes sexual and urinary dysfunction

- a. Surgery
  - 1) Long-term sexual dysfunction manifested as ED, lack of ejaculation, orgasm changes, and penile shortening
  - 2) Long-term urinary dysfunction manifested as stress incontinence, symptoms of urgency, frequency, nocturia, dribbling and urethral stricture
- b. Radiation
  - 1) Long-term sexual dysfunction manifested by progressive ED and decreased semen volume
  - 2) Long-term urinary dysfunction manifested by incontinence, dysuria, urgency, frequency, nocturia, dribbling, hematuria, and urethral stricture
  - 3) Late urinary and sexual dysfunction manifested by urethral stricture, hematuria, and delayed ED 6 to 36 months after therapy
- c. ADT
  - 1) Sexual dysfunction manifested by loss of libido and ED
  - 2) Discusses assessment and management of physical and psychosocial long-term and late toxicities
  - 3) Recommends patients with persistent symptoms be referred to a urologist
- 4. Treatments for ED
  - a. Modification of risk factors, such as decreasing alcohol consumption, increasing physical activity, smoking cessation, and weight loss
  - b. PDE-5 (phosphodiesterase type 5) inhibitors early following surgery to improve sexual outcomes post-surgery
    - i. Contraindicated in patients on nitrates
    - ii. Start conservatively and titrate to maximum dose if needed
    - iii. Adequate trial for an agent is defined as 5 separate occasions at maximum dose.
    - iv. If second-line agent fails, urology referral
- 5. Treatment of urinary symptoms
  - a. Anticholinergic medications may be an option in men with urge incontinence, frequency, nocturia, or urgency.

## RECOMMENDED READING AND REFERENCES

### Recommended Readings

1. Virgo KS, Rumble RB, Wit RD, et al. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: ASCO guideline update. *Journal of Clinical Oncology*. 2021; 39(11): 1274-305.  
<https://pubmed.ncbi.nlm.nih.gov/33497248/>
2. Sartor O and de Bono J. Metastatic prostate cancer. *N Engl J Med*. 2018; 378(7): 645-57.  
<https://www.ncbi.nlm.nih.gov/pubmed/29412780>
3. Sartor O and de Bono J. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. 2021; 385:1091-1103. <https://pubmed.ncbi.nlm.nih.gov/33581798/>
4. Ratta R, Guida A, Scotté F, et al. PARP inhibitors as a new therapeutic option in metastatic prostate cancer: a systematic review. *Prostate Cancer Prostatic Dis*. 2020; 23(4): 549-560.  
<https://pubmed.ncbi.nlm.nih.gov/32367009/>

### References

- 1 Schreengost R and Knudsen KE. Molecular pathogenesis and progression of prostate cancer. *Seminars in oncology*. 2013; 40(3): 244-58.
- 2 Abida W, Cheng ML, Armenia J et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. *JAMA Oncol*. 2019; 5(4): 471-78.
- 3 Nccn clinical practice guidelines in oncology (nccn guidelines®) for prostate cancer. V.1.2023, 09/16/2022. © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.
- 4 Mateo J, Carreira S, Sandhu S et al. DNA-repair defects and olaparib in metastatic prostate cancer. *New England Journal of Medicine*. 2015; 373(18): 1697-708.
- 5 Nccn clinical practice guidelines in oncology (nccn guidelines®) in prostate cancer early detection. V.1.2022, 02/16/2022. © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK.
- 6 de Bono J, Mateo J, Fizazi K et al. Olaparib for metastatic castration-resistant prostate cancer. *The New England journal of medicine*. 2020; 382(22): 2091-102.
- 7 Gann PH, Hennekens CH and Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *Jama*. 1995; 273(4): 289-94.
- 8 Chybowski FM, Bergstralh EJ and Oesterling JE. The effect of digital rectal examination on the serum prostate specific antigen concentration: Results of a randomized study. *The Journal of urology*. 1992; 148(1): 83-86.
- 9 Nccn clinical practice guidelines in oncology (nccn guidelines®) in survivorship. V.1.2022, 03/30/2022. © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK.
- 10 Carter HB, Ferrucci L, Kettermann A et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *Journal of the National Cancer Institute*. 2006; 98(21): 1521-7.
- 11 Force USPST. Screening for prostate cancer: Us preventive services task force recommendation statement. *Jama*. 2018; 319(18): 1901-13.

- 12 Basch E, Oliver TK, Vickers A et al. Screening for prostate cancer with prostate-specific antigen testing: American society of clinical oncology provisional clinical opinion. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012; 30(24): 3020-5.
- 13 Hugosson J, Carlsson S, Aus G et al. Mortality results from the göteborg randomised population-based prostate-cancer screening trial. *The Lancet Oncology*. 2010; 11(8): 725-32.
- 14 Carter HB, Albertsen PC, Barry MJ et al. Early detection of prostate cancer: Aua guideline. *The Journal of urology*. 2013; 190(2): 419-26.
- 15 Wolf AM, Wender RC, Etzioni RB et al. American cancer society guideline for the early detection of prostate cancer: Update 2010. *CA Cancer J Clin*. 2010; 60(2): 70-98.
- 16 Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003; 349(3): 215-24.
- 17 Thompson IM, Jr., Goodman PJ, Tangen CM et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med*. 2013; 369(7): 603-10.
- 18 Andriole GL, Bostwick DG, Brawley OW et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010; 362(13): 1192-202.
- 19 Kramer BS, Hagerty KL, Justman S et al. Use of 5alpha-reductase inhibitors for prostate cancer chemoprevention: American society of clinical oncology/american urological association 2008 clinical practice guideline. *The Journal of urology*. 2009; 181(4): 1642-57.
- 20 Wilt TJ, Brawer MK, Jones KM et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012; 367(3): 203-13.
- 21 Wilt TJ, Jones KM, Barry MJ et al. Follow-up of prostatectomy versus observation for early prostate cancer. *New England Journal of Medicine*. 2017; 377(2): 132-42.
- 22 D'Amico AV, Manola J, Loffredo M et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *Jama*. 2004; 292(7): 821-7.
- 23 Jones CU, Hunt D, McGowan DG et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med*. 2011; 365(2): 107-18.
- 24 Shelley MD, Kumar S, Coles B et al. Adjuvant hormone therapy for localised and locally advanced prostate carcinoma: A systematic review and meta-analysis of randomised trials. *Cancer treatment reviews*. 2009; 35(7): 540-6.
- 25 Pilepich MV, Winter K, Lawton CA et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase iii rtog 85-31. *International journal of radiation oncology, biology, physics*. 2005; 61(5): 1285-90.
- 26 Souhami L, Bae K, Pilepich M et al. Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: A secondary analysis of rtog 85-31. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27(13): 2137-43.
- 27 Horwitz EM, Bae K, Hanks GE et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: A phase iii trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26(15): 2497-504.
- 28 Lawton CAF, Lin X, Hanks GE et al. Duration of androgen deprivation in locally advanced prostate cancer: Long-term update of nrg oncology rtog 9202. *Int J Radiat Oncol Biol Phys*. 2017; 98(2): 296-303.
- 29 Bolla M, de Reijke TM, Van Tienhoven G et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009; 360(24): 2516-27.
- 30 Bolla M, Van Tienhoven G, Warde P et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an eortc randomised study. *The Lancet. Oncology*. 2010; 11(11): 1066-73.
- 31 Warde P, Mason M, Ding K et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial. *Lancet*. 2011; 378(9809): 2104-11.
- 32 Sun M, Choueiri TK, Hamnvik OP et al. Comparison of gonadotropin-releasing hormone agonists and orchiectomy: Effects of androgen-deprivation therapy. *JAMA Oncol*. 2016; 2(4): 500-7.
- 33 Lexi-Comp Online. 2019.



- 34 Seidenfeld J, Samson DJ, Hasselblad V et al. Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. *Annals of internal medicine*. 2000; 132(7): 566-77.
- 35 Klotz L, Boccon-Gibod L, Shore ND et al. The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group phase iii study in patients with prostate cancer. *BJU international*. 2008; 102(11): 1531-8.
- 36 Albertsen PC, Klotz L, Tombal B et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *European Urology*. 2014; 65(3): 565-73.
- 37 Margel D, Peer A, Ber Y et al. Cardiovascular morbidity in a randomized trial comparing gnrh agonist and gnrh antagonist among patients with advanced prostate cancer and preexisting cardiovascular disease. *J Urol*. 2019; 202(6): 1199-208.
- 38 Lopes RD, Higano CS, Slovin SF et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: The primary results of the pronounce randomized trial. *Circulation*. 2021; 144(16): 1295-307.
- 39 Melloni C, Slovin SF, Blemings A et al. Cardiovascular safety of degarelix versus leuprolide for advanced prostate cancer. *The PRONOUNCE Trial Study Design*. 2020; 2(1): 70-81.
- 40 Relugolix [package insert]. Brisbane ca; myovant sciences. 2020.
- 41 Shore ND, Saad F, Cookson MS et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020; 382(23): 2187-96.
- 42 Samson DJ, Seidenfeld J, Schmitt B et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer*. 2002; 95(2): 361-76.
- 43 Crook JM, O'Callaghan CJ, Duncan G et al. Intermittent androgen suppression for rising psa level after radiotherapy. *N Engl J Med*. 2012; 367(10): 895-903.
- 44 Hussain M, Tangen CM, Berry DL et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*. 2013; 368(14): 1314-25.
- 45 Niraula S, Le LW and Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: A systematic review of randomized trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31(16): 2029-36.
- 46 Sciarra A, Abrahamsson PA, Brausi M et al. Intermittent androgen-deprivation therapy in prostate cancer: A critical review focused on phase 3 trials. *European urology*. 2013; 64(5): 722-30.
- 47 Smith MR, Saad F, Chowdhury S et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *New England Journal of Medicine*. 2018; 378(15): 1408-18.
- 48 Small EJ, Saad F, Chowdhury S et al. Final survival results from spartan, a phase iii study of apalutamide (apa) versus placebo (pbo) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmcrpc). *Journal of Clinical Oncology*. 2020; 38(15\_suppl): 5516-16.
- 49 Smith MR, Saad F, Chowdhury S et al. Apalutamide and overall survival in prostate cancer. *Eur Urol*. 2021; 79(1): 150-58.
- 50 Hussain M, Fizazi K, Saad F et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine*. 2018; 378(26): 2465-74.
- 51 Sternberg CN, Fizazi K, Saad F et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine*. 2020; 382(23): 2197-206.
- 52 Fizazi K, Shore N, Tammela TL et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine*. 2019; 380(13): 1235-46.
- 53 Fizazi K. Overall survival (os) results of phase iii aramis study of darolutamide (daro) added to androgen deprivation therapy (adt) for nonmetastatic castration-resistant prostate cancer (nmcrpc). *J Clin Oncol*. 2020; 38.
- 54 Virgo KS, Rumble RB, Wit Rd et al. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: Asco guideline update. *Journal of Clinical Oncology*. 2021; 39(11): 1274-305.
- 55 Sweeney CJ, Chen YH, Carducci M et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015; 373(8): 737-46.
- 56 Kyriakopoulos CE, Chen YH, Carducci MA et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase iii e3805 chaarted trial. *J Clin Oncol*. 2018; 36(11): 1080-87.

- 57 Kyriakopoulos CE, Chen Y-H, Carducci MA et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase iii e3805 chaarted trial. *Journal of Clinical Oncology*. 2018; 36(11): 1080-87.
- 58 James ND SM, Clarke NW, Mason MD, Dearnaley DP, Spears MR et al. *Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial*. 2016; 387: 1163-77.
- 59 Gravis G, Boher JM, Chen YH et al. Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: Further analyses of chaarted and getug-afu15 studies. *Eur Urol*. 2018; 73(6): 847-55.
- 60 Smith MR, Hussain M, Saad F et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022; 386(12): 1132-42.
- 61 Fizazi K, Foulon S, Carles J et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (peace-1): A multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet*. 2022; 399(10336): 1695-707.
- 62 Fizazi K, Tran N, Fein L et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine*. 2017; 377(4): 352-60.
- 63 James ND, de Bono JS, Spears MR et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *New England Journal of Medicine*. 2017; 377(4): 338-51.
- 64 Auchus RJ, Yu MK, Nguyen S et al. Use of prednisone with abiraterone acetate in metastatic castration-resistant prostate cancer. *Oncologist*. 2014; 19(12): 1231-40.
- 65 Davis ID, Martin AJ, Stockler MR et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *New England Journal of Medicine*. 2019; 381(2): 121-31.
- 66 Davis I, et al. ANZUP Trial Update - The ENZAMET Trial. In proceedings from Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) Mini Annual Scientific Meeting (ASM). November 2020.
- 67 Armstrong AJ, Szmulewitz RZ, Petrylak DP et al. Arches: A randomized, phase iii study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019; 37(32): 2974-86.
- 68 Chi KN, Agarwal N, Bjartell A et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine*. 2019; 381(1): 13-24.
- 69 Berthold DR, Pond GR, Soban F et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the tax 327 study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26(2): 242-5.
- 70 Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004; 351(15): 1502-12.
- 71 Ryan CJ, Smith MR, Fizazi K et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (cou-aa-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *The Lancet. Oncology*. 2015; 16(2): 152-60.
- 72 Ryan CJ, Smith MR, de Bono JS et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013; 368(2): 138-48.
- 73 de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011; 364(21): 1995-2005.
- 74 Stein CA, Levin R, Given R et al. Randomized phase 2 therapeutic equivalence study of abiraterone acetate fine particle formulation vs. Originator abiraterone acetate in patients with metastatic castration-resistant prostate cancer: The staar study. *Urologic Oncology: Seminars and Original Investigations*. 2018; 36(2): 81.e9-81.e16.
- 75 Roviello G, Sobhani N, Corona SP et al. Corticosteroid switch after progression on abiraterone acetate plus prednisone. *Int J Clin Oncol*. 2020; 25(2): 240-46.
- 76 Romero-Laorden N, Lozano R, Jayaram A et al. Phase ii pilot study of the prednisone to dexamethasone switch in metastatic castration-resistant prostate cancer (mcrpc) patients with limited progression on abiraterone plus prednisone (switch study). *British Journal of Cancer*. 2018; 119(9): 1052-59.

- 77 Fenioux C, Louvet C, Charton E et al. Switch from abiraterone plus prednisone to abiraterone plus dexamethasone at asymptomatic psa progression in patients with metastatic castration-resistant prostate cancer. *BJU Int*. 2019; 123(2): 300-06.
- 78 Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014; 371(5): 424-33.
- 79 Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012; 367(13): 1187-97.
- 80 Shore ND, Chowdhury S, Villers A et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (terrain): A randomised, double-blind, phase 2 study. *The Lancet Oncology*. 17(2): 153-63.
- 81 Penson DF, Armstrong AJ, Concepcion R et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The strive trial. *Journal of Clinical Oncology*. 2016; 34(18): 2098-106.
- 82 Khalaf DJ, Annala M, Taavitsainen S et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: A multicentre, randomised, open-label, phase 2, crossover trial. *The Lancet Oncology*. 2019; 20(12): 1730-39.
- 83 de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet*. 2010; 376(9747): 1147-54.
- 84 Eisenberger M, Hardy-Bessard A-C, Kim CS et al. Phase iii study comparing a reduced dose of cabazitaxel (20 mg/m<sup>2</sup>) and the currently approved dose (25 mg/m<sup>2</sup>) in postdocetaxel patients with metastatic castration-resistant prostate cancer—proselica. *Journal of Clinical Oncology*. 2017; 35(28): 3198-206.
- 85 Oudard S, Fizazi K, Sengeløv L et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: A randomized phase iii trial—firstana. *Journal of Clinical Oncology*. 2017; 35(28): 3189-97.
- 86 de Wit R, de Bono J, Sternberg CN et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *New England Journal of Medicine*. 2019; 381(26): 2506-18.
- 87 Chang SS. Overview of prostate-specific membrane antigen. *Rev Urol*. 2004; 6 Suppl 10(Suppl 10): S13-S18.
- 88 Bouchelouche K, Choyke PL and Capala J. Prostate specific membrane antigen- a target for imaging and therapy with radionuclides. *Discov Med*. 2010; 9(44): 55-61.
- 89 Lenzo NP, Meyrick D and Turner JH. Review of gallium-68 psma pet/ct imaging in the management of prostate cancer. *Diagnostics (Basel)*. 2018; 8(1).
- 90 Sartor O, de Bono J, Chi KN et al. Lutetium-177-psma-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021; 385(12): 1091-103.
- 91 Hofman MS, Emmett L, Sandhu S et al. [(177)lu]lu-psma-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (therap): A randomised, open-label, phase 2 trial. *Lancet*. 2021; 397(10276): 797-804.
- 92 Pluvicto [package insert]. millburn, nj: advanced accelerator applications USA, inc.; 2022.
- 93 Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013; 369(3): 213-23.
- 94 Smith M, Parker C, Saad F et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (era 223): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2019; 20(3): 408-19.
- 95 Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-t immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010; 363(5): 411-22.
- 96 Corn PG, Heath EI, Zurita A et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: A randomised, open-label, phase 1-2 trial. *Lancet Oncol*. 2019; 20(10): 1432-43.
- 97 Hussain M, Mateo J, Fizazi K et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *New England Journal of Medicine*. 2020; 383(24): 2345-57.
- 98 Abida W, Patnaik A, Campbell D et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a brca1 or brca2 gene alteration. *J Clin Oncol*. 2020; 38(32): 3763-72.

- 99 Michaelson MD, Kaufman DS, Lee H et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(9): 1038-42.
- 100 Greenspan SL, Nelson JB, Trump DL et al. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: A randomized trial. *Annals of internal medicine*. 2007; 146(6): 416-24.
- 101 Smith MR, Egerdie B, Hernandez Toriz N et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2009; 361(8): 745-55.
- 102 Saad F, Gleason DM, Murray R et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *Journal of the National Cancer Institute*. 2002; 94(19): 1458-68.
- 103 Saad F, Gleason DM, Murray R et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *Journal of the National Cancer Institute*. 2004; 96(11): 879-82.
- 104 Smith MR, Halabi S, Ryan CJ et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: Results of calgb 90202 (alliance). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014; 32(11): 1143-50.
- 105 Himmelstein AL QR, Novotny PJ, et al. Calgb 70604 (alliance): A randomized phase iii study of standard dosing vs. Longer interval dosing of zoledronic acid in metastatic cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015; 33(suppl): abstract 9501.
- 106 Fizazi K, Carducci M, Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. *Lancet*. 2011; 377(9768): 813-22.
- 107 Smith MR, Saad F, Coleman R et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: Results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012; 379(9810): 39-46.
- 108 Saylor PJ, Armstrong AJ, Fizazi K et al. New and emerging therapies for bone metastases in genitourinary cancers. *European urology*. 2013; 63(2): 309-20.
- 109 Keating NL, O'Malley AJ and Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006; 24(27): 4448-56.
- 110 Skolarus TA WA, Erb NL et al. . American cancer society prostate cancer survivorship care guidelines. *CA: A Cancer Journal for Clinicians*. 2014; 64(4): 225-49.
- 111 Denlinger CS CR, Are M et al. Survivorship: Sexual dysfunction (male). *Journal of the National Comprehensive Cancer Network*. 2014; 12(3): 356-63.

# RESEARCH DESIGN, STATISTICS, AND EVALUATING ONCOLOGY LITERATURE

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## LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to successfully:

1. Evaluate the oncology literature, including study design, identification of sources of bias, methodology, statistical analysis, and applicability of results to clinical practice for the oncology patient population.
2. Interpret the validity and results of various types of oncology studies (e.g., meta-analyses, noninferiority trials).
3. Interpret findings from the use of study endpoints (e.g., objective response, time to progression, adverse events, quality of life, overall survival) in oncology research.
4. Interpret sensitivity, specificity, positive and negative predictive values, measures of effect, correlation, and regression for an oncology study.

## I. Evaluating Primary Literature

### A. Introduction

1. What is the rationale for conducting the study?
2. What are the study objectives?
3. What is the null hypothesis and is it clear?
4. Is the introduction free of bias and written clearly?

### B. Methods – think about specific study designs (observational and experimental), internal validity, and external validity

1. Type of study – is it appropriate for the investigation?
2. Are the eligibility criteria clearly defined? Are they appropriate?
  - a. Selection bias – what measures were taken to prevent this bias? How were the subjects selected?
  - b. How do they affect external validity?
  - c. Misclassification bias – what measures were taken to prevent this bias? Are there specific definitions for the study parameters? How were subjects classified in order to be in the study?
3. Allocation – how are subjects allocated to the different treatment groups? Randomization vs non-randomization
4. Study treatment interventions
  - a. Are they practical?
  - b. Compliance bias - how was compliance defined? What measures were taken to control for compliance bias?
  - c. What measures were taken to blind the interventions? Were they adequate?
  - d. What other medications or interventions were the subjects allowed to take during the study
    - 1) Are they practical?
    - 2) Compliance bias?
5. Study outcomes - are they appropriate to answer the study objective?
  - a. Which is the primary versus secondary/exploratory objective(s)?
  - b. Is the primary outcome a surrogate measure and has it been previously shown to be an adequate predictor of a more conservative outcome?
6. Measurements – what measures were set in place to prevent measurement bias?
  - a. Are the measurements standardized and validated?
  - b. Were the measurements evaluated by same person or laboratory?
  - c. Were the measurements specific or sensitive?
7. Data Analysis – does the type of analysis (intention-to-treat, modified intention-to-treat, as-treated, per protocol) make sense for the study design?

8. Statistical analysis
  - a. Was the statistical analysis clearly defined?
  - b. Are the tests appropriate for the type of data?
  - c. Was power or sample size defined?
- C. Results
  1. Study population
    - a. Can you follow the subjects through the study (eg, CONSORT diagram<sup>1</sup>)?
    - b. Attrition bias – are the number of and reasons for withdrawals given and explained? Are the numbers and reasons fairly similar for each treatment intervention?
    - c. What are the baseline demographics? Are the groups similar? What kinds of confounding variables are present?
  2. Data presentation
    - a. Are the results complete? Are data presented for all measurements described in the methods section?
    - b. Are the data for each outcome understandable and clear?
    - c. Are charts, graphs, and figures accurate?
- D. Discussion
  1. Are the limitations of the study described objectively?
  2. Are the conclusions valid based on results and study purpose?
  3. Is there a discussion regarding future research on or related to the topic?
  4. How will the study impact clinical practice?
- E. Other aspects to consider
  1. Title – is it descriptive and accurate? Does it reflect the study?
  2. Investigators/authors – are they qualified to conduct the trial?
  3. Abstract – does it summarize the study appropriately? Does it describe the results accurately? Does it give the reader an idea of what the study is describing?
  4. Funding – what is the funding source? Is there potential conflict of interest and how was it managed?
  5. Journal – what is the reputation of the journal (impact factor)? Is it peer-reviewed?
  6. References – do the authors cite themselves repeatedly? Are the references current? Do they represent the literature on the topic?

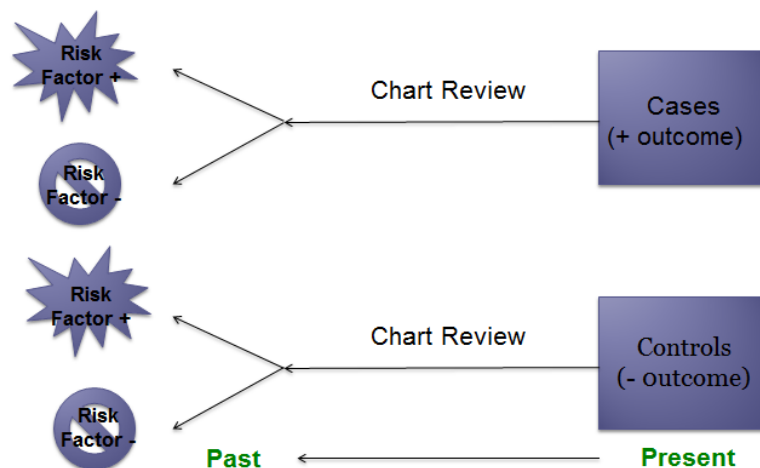
## II. Study Design<sup>1</sup>

- A. Internal and external validity
  1. Internal validity – within the study itself. How the study was conducted, study design, and statistical analysis. The results are accurate and credible, and the interpretation by the investigators is supported and agrees with the results.

2. External validity – how can I apply the study to my practice or patients? What is the generalizability of the study?

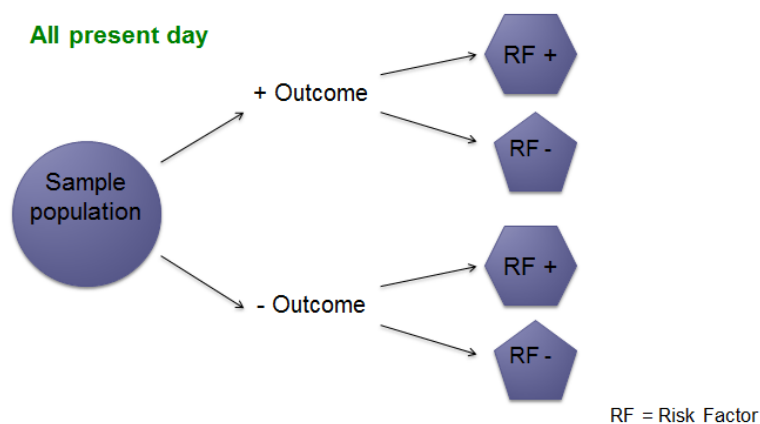
B. Three main types of study designs

1. **Descriptive** - have no comparisons or interventions. They describe a set of collected data and trends or lack of trends. They are typically hypothesis generating. They lack external validity and contain anecdotal evidence.
2. **Observational** – determine associations only. Cannot determine cause/effect given nature of the study design. All observational designs are comparative, but they do not have any treatment interventions.
  - a. Case-control (retrospective) – look in the past to assess risk factors for patients who have the outcome of interest (cases) and those who do not have the outcome of interest (controls). Often used for new diseases or outbreaks, when there are multiple risk factors (RF). They are inexpensive and easy to conduct. This type of study is prone to bias – selection, misclassification, information, and confounding.

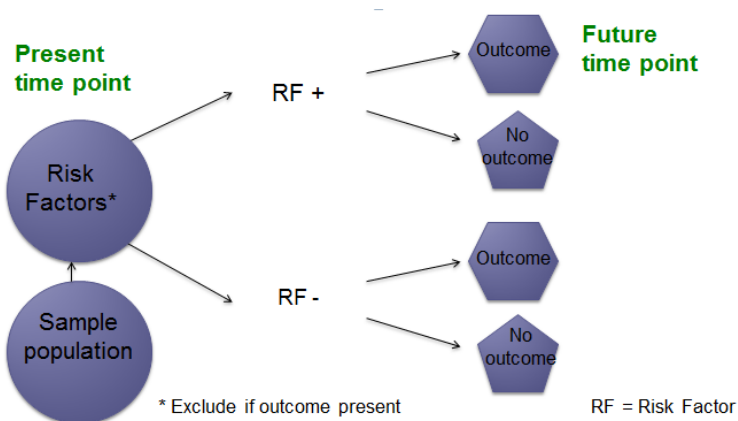


- b. Cross-sectional (prevalence) – compare presence or absence of risk factors in patients with outcome and those without the outcome. These studies occur in present day only. Start with a sample population and classify into groups based on outcome or not. Use this study design to help determine the commonality of an event. They are inexpensive and easy to conduct. This study design also is prone to bias (e.g., misclassification, confounding, selection).



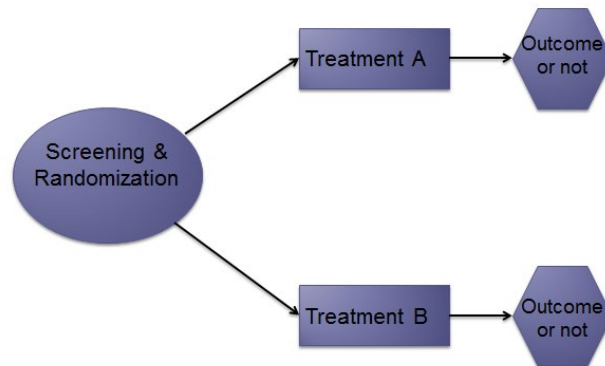


- c. Cohort (follow-up) – follow patients over time to see if the outcome of interest occurs. Classify based on risk factors present or absent. Only include those individuals from the study population who are free of the outcome of interest. This design is the strongest of the observational study designs because there is more control over the quality of the data. Data are collected prospectively; however, depending on study setup, data may be collected retrospectively, too. These studies are more expensive and harder to conduct. This design predicts incidence. There is bias associated with this type of design (eg, selection, misclassification, attrition, surveillance)

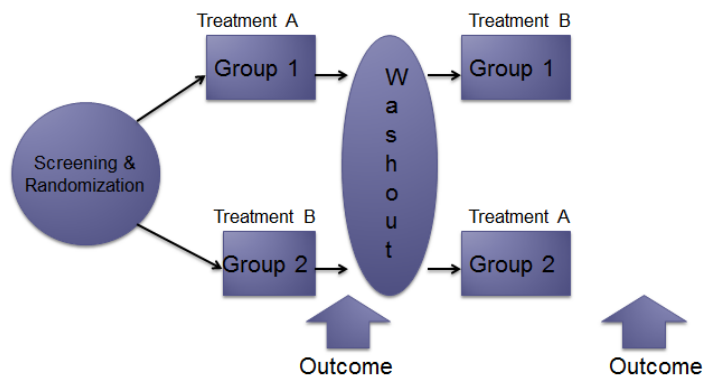


3. **Experimental** – determine cause and effect. Includes treatment interventions and makes a comparison. This design allows you to control for more variables. Bias still exists in this study design. Concerns for generalizability depending on the study methods. **Strongest study design** because of these attributes.

a. Parallel – patients receive one intervention only. There is interpatient variability.



- b. Crossover – subjects receive both interventions. Concern for appropriate length of washout period. Each patient is his/her own control, but the results may be impacted by the intervention (eg, which order) and disease progression. See Section VI. E., Oncology Trial Issues – Endpoints.



**Case - Study Bias Example:**

Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. Andre F, Ciruelos E, Rubovszky G, et al. *N Engl J Med*. 2019;380:1929-40.

This *study design* is experimental. It is a randomized, double-blind, placebo-controlled, multicenter trial evaluating alpelisib for the treatment of PIK3CA-mutated, hormone receptor-positive advanced breast cancer.

**Treatment Interventions**

Subjects randomized to the following:

- Alpelisib 300 mg by mouth with food plus fulvestrant 500 mg IM on days 1 and 15 cycle 1 then day 1 other cycles
- Placebo by mouth with food plus fulvestrant 500 mg IM on days 1 and 15 cycle 1 then day 1 other cycles

**Q1: If the study team did not use a structured definition for measurable disease, what type of bias may be occurring?**

- A. Allocation
- B. Compliance
- C. Misclassification
- D. Selection

**Q2: A study is evaluating a new therapy for prostate cancer. The study excluded patients with a Gleason score of 7 or higher. What type of bias is the study team trying to prevent?**

- A. Allocation
- B. Confounding
- C. Measurement
- D. Selection

**III. Types of Bias<sup>1</sup>**

- A. There are many types of study bias. These are some of the more common types of bias.
  1. Selection – assess eligibility criteria. Is the study population adequately defined? Helpful to review the baseline demographics of the study population (typically Table 1 in articles).
  2. Misclassification – do the investigators use structured definitions for outcomes and pertinent eligibility criteria? Sources of information need to be reliable and complete. If not, may lead to inappropriate inclusion or exclusion of subjects.
  3. Allocation – were subjects assigned appropriately into treatment interventions? Was the process truly random? Randomization helps control for this bias by ensuring equal distribution of subjects in treatment groups. Stratifying into groups before randomization ensures equal placement within the prespecified stratification categories. This information is often described in the methods section.
  4. Compliance – evaluate medication adherence and effects of nonadherence on study results. How was compliance assessed (eg, medication diaries, pill counts, electronic devices)? Not always defined in the article; sometimes discussed in supplementary material, if available.
  5. Attrition – evaluation of dropouts/study withdrawals within each treatment group. Problems arise when there are more subjects from 1 treatment group who withdrew or when there are more side effects in one treatment group compared with another. May be issues if reasons for withdrawal between different treatment groups vary.

6. Investigator/interviewer – subjects may be influenced to respond one way or another depending on interaction and relationship with the observer (eg, “sympathetic face”). Data may be collected and endpoints may be measured differently. Need standardization among all observers to obtain appropriate and clinically meaningful observation.
7. Measurement – way of measuring outcomes. Are the tools appropriate for the outcomes? Are the tools standardized and validated? Were the measurements conducted at the same time centrally vs locally?
8. Confounding – attribute outcome to a risk not related to the outcome. Difference in exposure or treatment group affects the outcome variable. Very difficult to prevent. Look at eligibility criteria and baseline demographics to help determine if there are any confounders. Were subjects ‘sicker’ in one group compared with another?

#### **Case - Study Bias Example:**

Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. Andre F, Ciruelos E, Rubovszky G, et al. *N Engl J Med*. 2019;380:1929-40.

Selection bias – evaluating inclusion and exclusion criteria, do the criteria make sense?

Inclusion criteria

- Men and postmenopausal women with confirmed HR-positive, HER2-negative advanced breast cancer
- Eligible for additional endocrine therapy after progression or relapse
- Measurable disease or  $\geq 1$  lytic bone lesion
- ECOG 0 or 1
- Adequate bone marrow and organ function

Exclusion criteria

- Previous denosumab or bisphosphonate therapy
- Inflammatory breast cancer
- Uncontrolled CNS metastases
- Type 1 diabetes or uncontrolled type 2 diabetes
- Pneumonitis

Misclassification bias

Used a clear definition of primary resistance and secondary resistance for endocrine therapy to help prevent this bias

Allocation bias

Randomization 1:1 (total randomized = 572)

- Alpelisib (n = 284)
- Placebo (n = 288)

Stratification

- *PIK3CA* mutation
- Liver or lung metastases

Baseline Characteristics – reported as equal for both treatment groups

- Age
- Performance status (ECOG  $\leq$  1)
- Site of metastases and number of metastatic sites
- Previous treatment and line of treatment in advanced disease
- Endocrine status

#### Compliance bias

Authors did not describe compliance or measures to assess compliance. With oral medications, it would be nice to know how compliance was assessed.

#### Attrition bias

Assess subjects no longer taking medication

Assess reasons for discontinuation

-Authors describe reasons for discontinuation (page 1932)

Measurement bias – how were these tests performed? Who “read” the results? Can any differences confound the study?

\*\*In this study, the presence or absence of *PIK3CA* mutation was centrally determined.

#### Confounding bias

Stratification

- Lung or liver metastases: yes/no
- Previous CDK4/6 inhibitor therapy
- *PIK3CA* mutation: yes/no

**Q1: If the study team did not use a structured definition for measurable disease, what type of bias may be occurring?**

The correct answer is C. Misclassification bias occurs if structured definitions are not used. This leads to possible issues with including or excluding incorrect patients into the study.

**Q2: A study is evaluating a new therapy for prostate cancer. The study excluded patients with a Gleason score of 7 or higher. What type of bias is the study team trying to prevent?**

The correct answer is B. To try to prevent confounding bias, patients who are sicker may be excluded from a study. This exclusion helps remove bias from any other conditions or the role disease severity plays in contributing to how well the study treatment works.

## **IV. Statistical Analysis**

### **A. Descriptive**

1. Measures of central tendency
2. Measures of variability

### **B. Inferential**

1. Evaluating the null hypothesis
  - a. Evaluates how well results from a sample can be inferred to the general population (confidence interval concepts)
  - b. Examines the likelihood that the results were due to chance (power concepts)

### **C. Types of analysis<sup>2</sup>**

1. Intention-to-treat (ITT)
  - a. Analysis includes **all** randomized subjects. Helps determine treatment effect under normal conditions. Prevents bias introduced by differences in study patients in each group
  - b. This is the most conservative type of analysis

2. Modified intention-to-treat
  - a. Analysis includes all randomized subjects who **received at least 1 dose** of study medication
  - b. Subject data grouped according to what treatment subject was randomized
3. As treated
  - a. Analysis includes all randomized subjects
  - b. Subject data grouped according to what treatment subject actually received
4. Per protocol
  - a. Analysis includes only those subjects who followed the protocol exactly as written
  - b. Does not help distinguish between bias and treatment-related effects due to baseline differences
  - c. More generous estimate of the difference between treatment groups
  - d. May use in a noninferiority trial after analyzing data from ITT
- D. Types of trials
  1. Superiority – is the new intervention better or worse than control?
  2. Equivalence – is the range for new product similar to the established equivalence range?
  3. Noninferiority – is the new intervention no worse than control?
- E. Types of Data<sup>1</sup>
  1. Nominal
    - a. Discrete data with no implied rank or order
    - b. Each measurement must go into 1 category; yes/no
    - c. Examples
      - 1) Dead or alive
      - 2) Race
      - 3) Adverse event or not
    - d. No mathematical relationship between classifications
    - e. Multiple groups or categories
      - 1) No ranking
      - 2) Assess if yes/no as far as belonging to each group
    - f. Expressed as percentages
      - 1) May appear as if continuous, but the reader really needs to determine if the patient had a response (or outcome) or not
  2. Ordinal
    - a. Discrete data with an implied rank or order
    - b. Limited categories

- c. Distance between each category is not mathematically equal
  - d. Examples
    - 1) Pain scales (not Visual Analog Scale)
    - 2) Cancer staging
    - 3) Quality of life scale
    - 4) Performance status
  - e. Data presented numerically – may look like continuous, but it is not
  - f. Use median as measure of central tendency to describe ordinal data
    - 1) Means (averages) are not used to represent ordinal data
3. Continuous
- a. Ratio (absolute zero) and interval (zero point arbitrarily set) data
  - b. Defined units of measure that remain constant
  - c. Equal distance between each increment
  - d. Examples
    - 1) Time to disease progression
    - 2) Platelet count
    - 3) White blood cell count
  - e. Data presented as percent (%) likely not continuous
  - f. Watch for continuous data that are changed to another type
    - 1) At least 30% reduction in pain = nominal
    - 2) Mild, moderate, or severe disease = ordinal
4. Data distribution<sup>1</sup>
- a. Normal
    - 1) Bell-shaped curve or Gaussian distribution
    - 2) Data are symmetric around the mean
  - b. Binomial
    - 1) Independent trials with only 2 outcomes
    - 2) Example – flipping of a coin
  - c. Poisson
    - 1) Use when evaluating random events in a given time frame
    - 2) Example – serious adverse event of a new chemotherapy agent over 1 year

**ARS Q1: A study evaluated changes in hemoglobin as a safety outcome. What type of data is being evaluated for this safety outcome?**

- A. Continuous
- B. Descriptive
- C. Nominal
- D. Ordinal

**ARS Q2: Subjects were enrolled in a trial evaluating changes in serum sodium concentrations. Participants received a new chemotherapy agent and 4 weeks later the participants received placebo. The washout period between doses was long enough to fully clear the chemotherapy agent. Results followed a bell-shaped curve. What type of statistical test is most appropriate when analyzing these results?**

- A. Paired t-test
- B. Student t-test
- C. Wilcoxon rank sum
- D. Wilcoxon signed rank

**ARS Q3: Subjects were enrolled in a trial (n = 250) evaluating overall survival of a new drug compared with a placebo (2:1 randomization). Baseline demographics included disease site. What type of statistical test is most appropriate when analyzing differences in disease site?**

- A. ANOVA
- B. Chi-square
- C. Mann-Whitney U
- D. Wilcoxon rank sum

D. Tests for Nominal Data<sup>1</sup> (see Table under section H)

- 1. 2 treatment groups with different subjects
  - a. Chi-square: expected frequency (total of row x total of column/total n) needs to be at least 5 and  $n > 20$ .
  - b. Fisher's exact test
- 2. Paired subjects or 2-related samples: McNemar's test
- 3. 3 treatment groups with same samples: Cochran Q
- 4. 3 treatment groups with different subjects
  - a. Chi-square: expected frequency (total of row x total of column/total n) needs to be at least 5 and  $n > 20$ .

E. Tests for Ordinal Data<sup>1</sup>

- 1. 2 treatment groups with different subjects
  - a. Mann-Whitney U



- b. Wilcoxon rank sum
- 2. Paired subjects or 2-related samples: Wilcoxon signed rank
- 3. 3 treatment groups with different subjects: Kruskal-Wallis
- 4. Multiple treatments in same sample/subjects: Friedman two-way ANOVA
- F. Tests for Continuous Data – Normal distribution (parametric)<sup>1</sup>
  - 1. Parametric tests are generally more powerful. They make assumptions on defining properties.
  - 2. 2 treatment groups with different subjects: student t-test
  - 3. Paired subjects or 2-related samples: paired t-test
  - 4. 3 treatment groups with different subjects: ANOVA (analysis of variance)
  - 5. Multiple treatments in same sample/subjects: Repeated measures analysis of variance
  - 6. Associations between 2 variables: Pearson correlation
- G. Tests for Continuous Data - Not normal distribution (nonparametric)<sup>1</sup>
  - 1. Nonparametric tests are generally less powerful than parametric tests. There are generally no assumptions with these tests.
  - 2. 2 treatment groups with different subjects: Mann-Whitney U or Wilcoxon rank sum
  - 3. Paired subjects or 2-related samples: Wilcoxon signed rank sum
  - 4. 3 treatment groups with different subjects: Kruskal-Wallis
  - 5. Multiple treatments in same sample/subjects: Friedman statistic
  - 6. Associations between 2 variables: Spearman rank correlation

#### H. Table describing statistical tests<sup>3</sup>

Data Type	2 Groups Same Samples	2 Groups Different Samples	3 or more Groups Same Samples	3 or more Groups Different Samples
<b>Nominal data</b>	McNemar	Fisher's exact: N<20 OR N = 20 to 40 and expected frequency* is <5  Chi-square: N>40 OR expected frequency ≥ 5	Cochrane Q	Chi-square
<b>Ordinal data</b>	Wilcoxon signed rank	Wilcoxon rank sum Mann-Whitney U	Friedman two-way ANOVA	Kruskal-Wallis
<b>Continuous data (normal distribution; parametric)</b>	Paired t-test	Student t-test	Two-way repeated ANOVA	One-way ANOVA
<b>Continuous data (not normal distribution; nonparametric)</b>	Wilcoxon signed rank	Wilcoxon rank sum Mann-Whitney U	Friedman two-way ANOVA	Kruskal-Wallis

Reprinted from Annals of Emergency Medicine, 12, Robert M. Elenbass, et al., Evaluating the medical literature. Part ii:

Statistical analysis, 610-620, Copyright 1983, with permission from Elsevier

\*expected frequency = [(total of row) x (total of column)]/total N

#### I. Components of Statistical Power and Various Pearls<sup>1</sup>

1. Power = the ability to detect a difference if one does exist
2. Alpha (aka Type I error, usually set at 0.05)
  - a. False-positive rate investigators are willing to accept
  - b. Probability of concluding there is a difference, when in truth, there is no difference
  - c. Probability of rejecting the null hypothesis when it is true
  - d. To decrease the probability of this type of error (ie, Type I), increase the number of subjects in the study
3. Beta error (aka Type II error)
  - a. False-negative rate investigators are willing to accept
  - b. Probability of concluding there is no difference when in fact there is a difference
  - c. Probability of failing to reject the null hypothesis when it isn't true
  - d. Power = 1 – beta. Customarily, beta = 0.2, power = 80%
  - e. To decrease the probability of making this type of error (ie, Type II), increase the power (eg, increase the power to 90% by increasing the number of subjects in the study). One can also increase the size of difference thought to be important for the outcome.

4. Delta – effect size
  - a. The effect size is the expected or observed change in outcome as a result of the intervention
  - b. One uses effect size when determining the number of subjects needed to meet statistical power
  - c. Alpha and sample size/power are directly proportional
    - 1) Increase sample size, increase power
    - 2) More variability within the data increases the need for a larger sample size
5. *P* values
  - a. Determine level of significance *a priori* (alpha)
  - b. Probability results are due to chance alone
  - c. If *P* value < alpha = statistical significance; reject null hypothesis
  - d. Generally, *P* < 0.05 is considered statistically significant
  - e. *P* value does not infer magnitude or direction of effect
  - f. Pearls
    - 1) Small *P* value may suggest there is some difference between treatment groups
    - 2) Stating that there is insufficient evidence demonstrating 2 treatments are different does not mean they are the same
    - 3) If alpha is 0.05, *P* > 0.05 means there is a lack of evidence to reject the null hypothesis

**ARS Q1: A study evaluated changes in hemoglobin as a safety outcome. What type of data is being evaluated for this safety outcome?**

The correct answer is A - continuous. You need to decide the type of data described for this specific question. Hemoglobin concentration is a type of continuous data because the units of measure between values remains constant across the spectrum, and there is equal distance between each increment / value.

**ARS Q2: Subjects were enrolled in a trial evaluating changes in serum sodium concentrations. Participants received a new chemotherapy agent and 4 weeks later the participants received placebo. The washout period between doses was long enough to fully clear the chemotherapy agent. Results followed a bell-shaped curve. What type of statistical test is most appropriate when analyzing these results?**

The correct answer is A – paired t-test. First, you need to decide what type of data you have. In this example, serum sodium concentrations is a type of continuous data as the values are numerical with no implied rank or order. You were told subjects received the new chemotherapy agent followed by placebo 4 weeks later; therefore, the study design is experimental, crossover design with 2 groups with same samples. You are also told the data are normally distributed (bell-shaped curve). You need to use all of these parameters to determine the appropriate test. Paired t-test is the most appropriate test based on the provided information and use of the table describing statistical tests.

**ARS Q3: Subjects were enrolled in a trial (n = 250) evaluating overall survival of a new drug compared with a placebo (2:1 randomization). Baseline demographics included disease site. What type of statistical test is most appropriate when analyzing differences in disease site?**

The correct answer is B – Chi-square. First, you need to decide what type of data you have. In this example, you are interested in disease sites, which are a type of nominal data. You have 2 groups with different samples given 2:1 randomization to new drug or placebo. With this information, you can determine the appropriate test. Chi-square is the correct answer using the table of tests and when to use them.

I. Confidence Intervals (CI)<sup>4</sup>

1. Calculated based on standard error of the mean (SEM):  $95\% \text{ CI} = \text{mean} \pm 1.96 \text{ SEM}$ 
  - a. If samples of the same size are drawn repeatedly 100 times from a population and a CI is calculated for each sample, then the intervals will contain the value of the larger population 95 times out of 100.
  - b. The intervals will not contain the value of the larger population 5 times out of 100.
2. Used with any type of data, but most commonly used to estimate the true, but unmeasured mean of the population for continuous data normally distributed
3. Interpretation
  - a. For ratio data (OR, RR, HR) – see visual in section M
    - 1) If CI contains 1, then no difference between groups
  - b. All other data (ie, “non-ratio” world)
    - 1) If CI contains 0, then no difference between groups
4. Confidence intervals do not control for errors in study design
5. Wider CI reflect more uncertainty in the data

6. To decrease CI width
  - a. Increase sample size
  - b. Decrease confidence level (eg, 95% CI to 90% CI)
  - c. Decrease variability of data
7. The closer the point estimate lies in the middle of the interval, the more confident the point represents the population

#### **Case Study 1**

Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade nonmuscle-invasive bladder cancer on tumor recurrence. SWOG S0337.

Messing EM, Tangen CM, Lerner SP et al. *JAMA*. 2018; 319(18):1880-8.

Randomized, double-blind, multicenter (n = 406)

-Gemcitabine instillation (n = 201)

-Saline instillation (n = 205)

Primary outcome = reoccurrence of nonmuscle invasive bladder cancer

Nonmuscle invasive bladder cancer recurrences

Gemcitabine: 67/201

Saline: 91/205

Hazard Ratio 0.66 (95% CI, 0.48 to 0.9),  $P < 0.001$

**ARS Q4: The relative risk of nonmuscle invasive bladder cancer recurrence was 0.75 with gemcitabine compared with saline in subjects with low-grade disease at randomization. The HR was 0.66 (95% CI, 0.48 to 0.9). Calculate the relative risk reduction of nonmuscle invasive bladder cancer recurrence.**

- A. 25%
- B. 42%
- C. 66%
- D. 75%

**ARS Q5: Calculate the absolute risk reduction of nonmuscle invasive bladder cancer in patients treated with gemcitabine compared with saline among all randomized patients. Nonmuscle invasive bladder cancer reoccurred in 67 subjects (out of 201) where gemcitabine was instilled and 91 subjects (out of 205) where saline was instilled. The HR was 0.66 (95% CI, 0.48 to 0.9).**

- A. 11%
- B. 19%
- C. 24%
- D. 44%

**ARS Q6: Gemcitabine decreased the absolute risk of nonmuscle invasive bladder cancer recurrence by 11% and the relative risk reduction by 25%. How many subjects will be needed in order to prevent one reoccurrence?**

- A. 36
- B. 14
- C. 10
- D. 4

J. Measures of Effect (Odds Ratio, Relative Risk, Hazard Ratio)<sup>5,6</sup>

2x2 table to use for measures of effect calculations (except hazard ratio)

Risk Factor (treatment)	Outcome of Interest (Disease)		Totals
	Yes	No	
Experimental intervention	A	B	A+B
Control intervention	C	D	C+D

1. Odds Ratio (OR) =  $(A/B) / (C/D)$ 
  - a. Based on prevalence (# of cases at a certain point in time/# persons in group at a time)
  - b. Used for case-control and cross-sectional study designs
  - c. The control is a representative of the general population as far as risk factors
  - d. Interpretation
    - 1)  $OR < 1$ : odds of outcome lower with treated than control
    - 2)  $OR = 1$ : no difference in odds of outcome
    - 3)  $OR > 1$ : odds of outcome greater in treated than control
2. Relative Risk (RR) =  $(A/A+B) / (C/C+D)$  = Experimental event rate (EER) / control event rate (CER)
  - a. Based on incidence (# of NEW cases occurring at a certain point in time/# persons in group at the same time interval)
  - b. Provides a proportion between the 2 groups
  - c. Provides an association between exposure and disease
  - d. Used in cohort and experimental study designs
  - e. Interpretation
    - 1)  $RR < 1$ : risk of outcome lower in treated than control
    - 2)  $RR = 1$ : no difference
    - 3)  $RR > 1$ : risk of outcome greater in treated than control
3. Hazard Ratio (HR)
  - a. Similar to relative risk, but it is the weighted RR **over time** (*dependent variable is time dependent*)
    - 1) Adjusts for change over time and censoring due to incomplete follow up
    - 2) Data not derived from 2 x 2 table – data are derived from time-to-event or number of person-years at risk (Cox proportional hazards regression modeling)
  - b. Interpretation
    - 1)  $HR < 1$ : fewer events observed with comparator vs control
    - 2)  $HR = 1$ : no effect produced by treatment

- 3)  $HR > 1$ : more events observed with comparator vs control
4. Relative Risk Reduction (RRR) =  $1 - RR$ 
    - a. Reported as a percentage
    - b. Optimistic way to report data
    - c. Estimates percentage of baseline risk that is removed due to new therapy
    - d. Difference in proportions
  5. Absolute Risk Reduction (ARR) =  $(C/C+D) - (A/A+B)$ 
    - a. Also called risk difference or attributable risk
    - b. Represents the difference between the incidences between treatment groups– ie, CER-EER
    - c. Accounts for actual values; not proportions (remember RRR accounts for proportions)
    - d. Used for cohort and experimental studies because they capture incidence. None of the others do!
  6. Number Needed to Treat (NNT) =  $1/ARR$ 
    - a. Number of subjects to treat in order to see a benefit for 1 subject
    - b. Only pertains to confines of the study itself; cannot generalize/extrapolate
    - c. Remember to use ARR as a decimal and not percentage
  7. Number Needed to Harm (NNH) =  $1/ARR$ 
    - a. Calculated like NNT
    - b. Number of subjects treated to see the adverse event in 1 subject
    - c. Use adverse event data for calculations
    - d. Remember to use ARR as a decimal and not percentage
  8. Use clinical judgment when interpreting NNT and NNH. In general, a smaller number is ideal for NNT and a larger number is ideal for NNH.

	<b>Benefit</b>	<b>Risk</b>
<b>RRR = 1 - RR</b>	Relative benefit increase	Relative risk reduction
<b>CER - EER</b>	Absolute benefit increase (could be decrease)	Absolute risk reduction (could be increase)
<b>1/ARR</b>	Number needed to treat	Number needed to treat or harm

**Case Study 1**

Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade nonmuscle-invasive bladder cancer on tumor recurrence. SWOG S0337.

Messing EM, Tangen CM, Lerner SP et al. *JAMA*. 2018; 319(18):1880-8.

	Outcome Yes	Outcome No	Total
Gemcitabine	67	134	201
Saline	91	114	205

**ARS Q4: The relative risk of nonmuscle invasive bladder cancer recurrence was 0.75 with gemcitabine compared with saline in subjects with low-grade disease at randomization. The HR was 0.66 (95% CI, 0.48 to 0.9). Calculate the relative risk reduction of nonmuscle invasive bladder cancer recurrence.**

The correct answer is A – 25%. The relative risk reduction is  $1 - RR$ . Therefore,  $1 - 0.75 = 0.25 = 25\%$ .

**ARS Q5: Calculate the absolute risk reduction of nonmuscle invasive bladder cancer in patients treated with gemcitabine compared with saline among all randomized patients. Nonmuscle invasive bladder cancer reoccurred in 67 subjects (out of 201) where gemcitabine was instilled and 91 subjects (out of 205) where saline was instilled. The HR was 0.66 (95% CI, 0.48 to 0.9).**

The correct answer is B – 11%. Calculate the ARR by subtracting the control event rate from the experimental event rate. If you get a negative number, take the absolute of the number to make it a positive.

$$ARR = (C/C+D) - (A/A+B) = (91/205) - (67/201) = 0.44 - 0.33 = 0.11 \times 100 = 11\%.$$

**ARS Q6: Gemcitabine decreased the absolute risk of nonmuscle invasive bladder cancer recurrence by 11% and the relative risk reduction by 25%. How many subjects will be needed in order to prevent one reoccurrence?**

The correct answer is C - 10. Calculate the number needed to treat by  $1/ARR$ . Make sure to use the decimal value. If you get a decimal for the NNT, always round the number up to get the accurate NNT value.

$$NNT = 1/0.11 = 9.09 = 10.$$



## Case Study 2

Trametinib versus standard of care in patients with recurrent low-grade serous, ovarian cancer (GOG 281 / LOGS). Gershenson et al. Lancet 2022;399: 541-53.

Randomized, open-label, placebo-controlled, multicenter trial

Recurrent low-grade serous carcinoma following initial diagnosis of ovarian or peritoneal low-grade serous carcinoma or serous borderline tumor (n = 260)

### *Treatment Interventions*

Subjects randomized (1:1) to the following:

- Trametinib 2 mg by mouth once daily
- Standard of care (selected prior to randomization), permitted to crossover over to trametinib following disease progression

Primary outcomes = progression-free survival (PFS)

Secondary outcomes (main) = overall survival, adverse events, objective response rate

### *Statistical analysis*

Kaplan-Meier analysis and stratified log-rank tests

Power = 80% assuming 50% or greater improvement in PFS with trametinib, 213 PFS events

Interim futility analysis performed after 106 PFS events

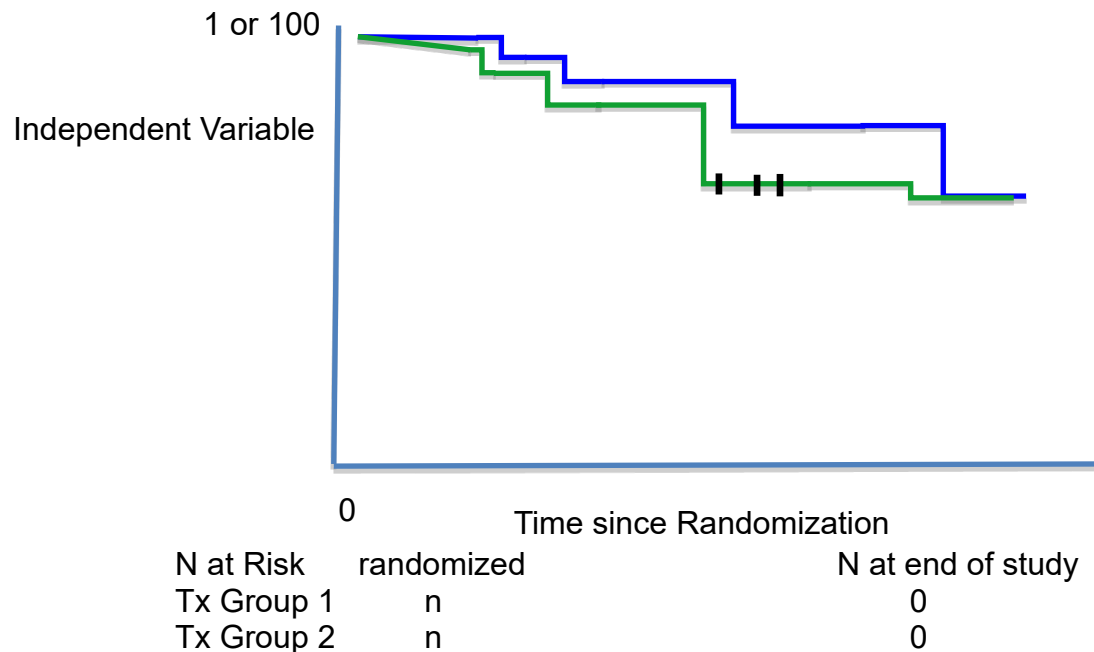
**ARS Q7: A study evaluated progression-free survival (PFS) (primary outcome) associated with trametinib vs standard of care (SOC) in participants with low-grade serous ovarian or peritoneal cancer. The result for the primary outcome was as follows: HR 0.48 (95% CI 0.36 to 0.64). What is the best interpretation of the study result?**

- A. PFS is the same for trametinib and SOC
- B. PFS is longer with SOC
- C. PFS is longer with trametinib
- D. The results are inconclusive

## K. Survival Analysis<sup>7-10</sup>

1. Time-to-event analysis (eg, death, relapse, adverse event)
2. Helps adjust for varying lengths of follow-up
3. Weighted relative risk over a study – expressed as a hazard ratio; weighted for number of subjects available for survival
4. Data representation
  - a. Kaplan-Meier curve (see example below) – each drop in the curve represents an event
  - b. Hazard ratio when comparing event rates between groups
5. Cox proportional hazards regression for multivariate analyses
6. Log-rank test to compare relative event rates between survival curves and targets hazard function
7. Censoring – represented as vertical tick marks on Kaplan Meier curve. Accounts for incomplete or missing data (eg, lost to follow-up, death).<sup>11</sup> Note: There are usually more tick marks indicating censorship on a curve in a trial.

### Example of Kaplan Meier Curve



### Case Study 2

Trametinib versus standard of care in patients with recurrent low-grade serous, ovarian cancer (GOG 281 / LOGS). Gershenson et al. Lancet 2022;399: 541-53.

Progression-free survival, HR 0.48 (95% CI, 0.36 to 0.64),  $P < 0.0001$

- Trametinib: 13 months

- Placebo: 7.2 months

**ARS Q7: A study evaluated progression-free survival (PFS) (primary outcome) associated with trametinib vs standard of care (SOC) in participants with low-grade serous ovarian or peritoneal cancer. The result for the primary outcome was as follows: HR 0.48 (95% CI, 0.36 to 0.64). What is the best interpretation of the study result?** The correct answer is C – PFS is longer with trametinib. The confidence interval does not cross 1, and the HR is less than 1 indicating a difference in progression-free survival between treatment groups.

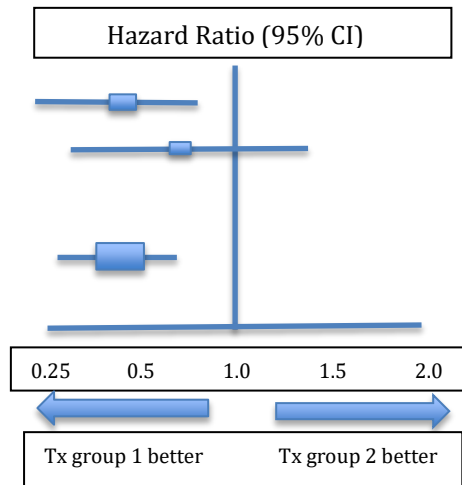
#### L. Subgroup Analysis<sup>7</sup>

1. Allocation no longer applies
2. Power typically not calculated for subgroups
3. Data dredging – keep analyzing data for different subgroups until a significant result is found
4. May be misleading and overstate data

#### M. Forest Plots<sup>7</sup>

1. Used to represent subgroup analysis and meta-analysis data
2. Bar on the plot represents the confidence interval

3. Box location represents the location of HR or RR
4. Box size represents the number of people in the analysis
5. Shorter bars = larger boxes = smaller CI range = more confident in result
  - a. If bar crosses 1, then the result is not statistically significant if the analysis is using HR or RR
  - b. If bar crosses 0, then the result is not statistically significant if the analysis is using anything other than HR or RR
6. Pictorial representation



#### N. Waterfall Plots<sup>12,13</sup>

1. Descriptive representation of tumor response/individual patient response during clinical trials
2. Display the magnitude of the response to treatment from baseline for each patient
3. Response represents a continuous variable and no longer a categorical variable
4. Typical representation is a histogram-type graph
  - a. X axis = baseline measure
  - b. Y axis = percent change from baseline
  - c. Vertical bar = one patient and response to treatment over time. Additionally, each vertical bar may represent some key characteristic depicted using different colors for the bars.
    - 1) Bars above baseline or X axis = progressive disease or nonresponders
    - 2) Bars below baseline or X axis = reduction in tumor size or some type of positive response to treatment
    - 3) Generally, the vertical bars on the left-hand side of the graph represent greatest progression of disease or worst value. Vertical bars on right-hand side of graph represent greatest tumor reduction or best value. The length of each vertical bar increases from left to right. This depiction gives the appearance of a waterfall.
  - d. Advantages of waterfall plots

- 1) Novel efficacy measure by representing tumor response or growth due to treatment in each patient
- e. Interpretation of stable disease according to RECIST – Response Evaluation Criteria in Solid Tumors
  - 1) Some waterfall plots include dotted lines representing RECIST progression vs response. Bars that fall in between are technically considered stable disease
- f. Disadvantages of waterfall plots
  - 1) Better to use for small clinical trials because less patients to plot. Larger populations in a clinical trial may lead to confusion and hard to read plots.
  - 2) Better to use for trials employing a 1:1 randomization. Displaying other randomization schemes may lead to hard to read plots.
  - 3) Errors in measurement of tumor response may influence the waterfall plot.
  - 4) Measurement bias if treatment is unblinded
  - 5) Variability in generation of the waterfall plot

### **Case Study 3**

Clinical outcomes of immune checkpoint inhibitor therapy in patients with advanced non-small cell lung cancer and pre-existing interstitial lung diseases. Zhang M et al. Chest 2022;161(6): 1675-86.

Databases used are as follows:

- PubMed (239 trials), EMBASE (100 trials), Cochrane library (56 trials)
- 2 independent reviewers to determine trial inclusion with a third reviewer who reconciled discrepancies
- Newcastle Ottawa Scale
- Predetermined inclusion criteria – retrospective and prospective trials, efficacy and safety of immune checkpoint inhibitors, and patients with cancer with pre-existing interstitial lung disease (ILD)

Clinical efficacy outcomes with ILD vs no ILD – evaluated overall response rate and disease control rate

Safety outcomes – checkpoint inhibitor pneumonitis, any grade or grade 3 or higher

$I^2$  statistic for degree of heterogeneity defined: low (<25%), intermediate (25% to 50%), and high (>50%)

Publication bias assessed using a funnel plot and Egger test

6 trials initially met inclusion criteria for the meta-analysis

**ARS Q8: A meta-analysis (n = 6 trials) evaluated clinical outcomes with immune checkpoint inhibitors in patients with pre-existing interstitial lung disease (ILD) and non-small cell lung cancer. Two individuals reviewed trials for incorporation into the analysis. A third individual was the tie breaker for discrepancies. Grade 3 or higher checkpoint inhibitor pneumonitis occurred more in patients with ILD (OR 2.91; 95%CI, 1.47 to 5.74;  $I^2 = 0\%$ ).**

**What statement is the most appropriate?**

- A. Publication bias is present so you can't trust the results
- B. More individuals were needed to assess trial eligibility
- C. No heterogeneity exists between the trials
- D. Additional trials should have been included in the analysis

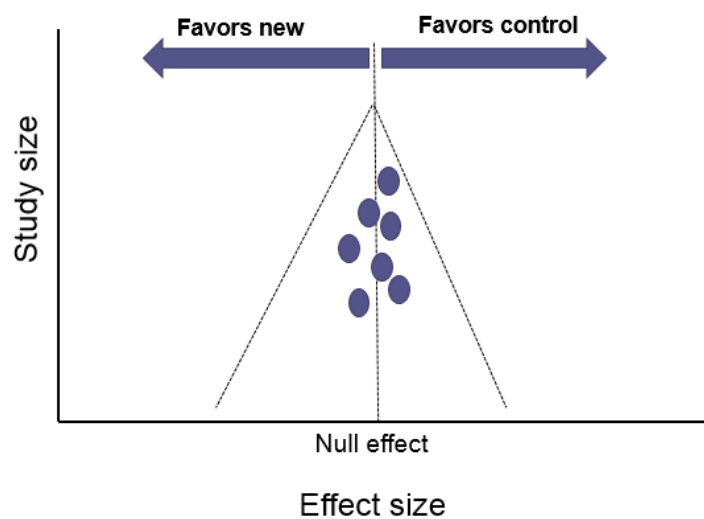
O. Meta-analysis <sup>7,14,15</sup>

1. Combine results from multiple studies to give best estimate of true outcome

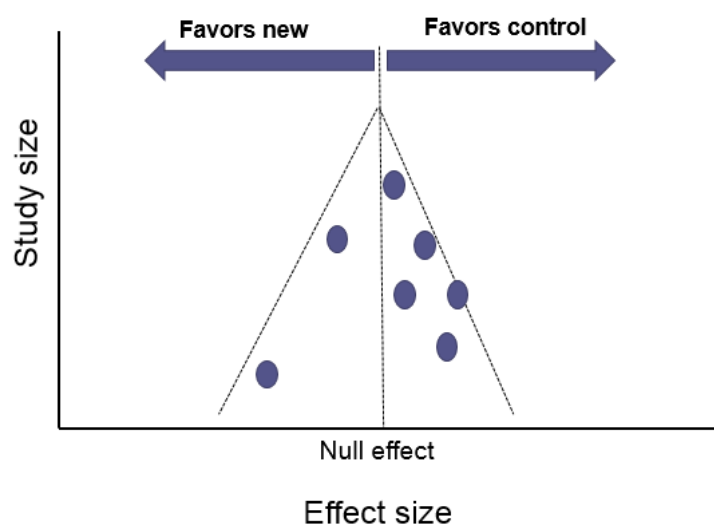
- a. Does combining the data make sense?
  - 1) For example - comparing response rate by CT scan vs combining studies reporting by CT and PET scans
- b. There are issues with manipulating data to be consistent across studies
  - 1) Could result in loss of granular data
  - 2) Data changed from continuous to nominal
  - 3) Example: Change glucose concentration from actual value à reached glucose concentration goal or not
2. Should adequately describe literature search
3. Better to use at least 2 databases (e.g., PubMed, CINAHL, EMBASE)
4. Selection bias of trials used in the meta-analysis may come into play. Evaluate the literature search criteria to see if it makes sense for what the authors of the meta-analysis want to accomplish.
5. Poor trials included in the meta-analysis typically gives poor results from the meta-analysis (ie, garbage in = garbage out)
6. Attributes of meta-analysis
  - a. Focused clinical question
  - b. Comprehensive search strategy
  - c. Criteria used to select studies determined prior to search and analysis
  - d. Rigorous critical appraisal of studies – evaluate the validity of the studies; any bias; interstudy differences
  - e. Quantitative synthesis of results – heterogeneity, subgroup analyses
  - f. Construction of evidence-based inferences – may not be able to construct inferences
7. Heterogeneity – This is an important concept because it would be hard to interpret the results from pooled data if the trials are very different from each other (ie, heterogeneous).
  - a. Cochran Q
    - 1) Traditional test for heterogeneity between included studies
    - 2) Interpretation
      - a)  $P < 0.05$  = high heterogeneity
      - b)  $P < 0.01$  = even more heterogeneity
    - 3) Limitations
      - a) Underpowered studies could underestimate heterogeneity
      - b) Overpowered studies could overestimate heterogeneity (saying there is heterogeneity when there really is not)
  - b.  $I^2$  statistic
    - 1) Percent variability across studies because of true treatment effect

- 2) Based on Q-test, but adjusted for power
- 3) Interpretation
  - a)  $I^2 = 0\%-25\%$ : low heterogeneity
  - b)  $I^2 = 26\%-50\%$ : moderate heterogeneity
  - c)  $I^2 = >50\%$ : high heterogeneity
  - d) Helps determine the similarity of the included studies. If heterogeneity is high, changing practice should be carefully considered.
8. Fixed effect vs Random effects model – Use of these concepts depends on the studies included in the meta-analysis. It is important to use the correct model depending on the effect size in the trials.
  - a. Fixed Effect
    - 1) Assumes there is 1 true result
    - 2) Variation within studies due to sampling
    - 3) All studies weighted the same. Total sample size does not matter.
    - 4) Use if NO significant heterogeneity
    - 5) More powerful if effect is similar between studies
  - b. Random Effects
    - 1) Assumes there is a range of effects
    - 2) Variation with the study itself and between all studies
    - 3) Studies weighted depending on sample size and total number of studies
    - 4) Use if heterogeneity exists
    - 5) Less powerful – P values are larger and CI wider
9. Funnel Plots
  - a. Effect size against sample size
  - b. Addresses publication and selection bias of the studies included in the meta-analysis
  - c. Interpretation
    - 1) Small studies spread over both sides of the average (null effect)
    - 2) Large studies usually represented near the average (null effect)
  - d. Limitations
    - 1) Watch out for y-axis scale discrepancy
    - 2) May give wrong impression of publication bias due to effect size of different studies

Funnel plot with no bias depicted<sup>14,15</sup>



Funnel plot with bias depicted<sup>14,15</sup>



### Case Study 3

Clinical outcomes of immune checkpoint inhibitor therapy in patients with advanced non-small cell lung cancer and pre-existing interstitial lung diseases. Zhang M et al. Chest 2022;161(6): 1675-86.

Risk of checkpoint inhibitor pneumonitis (CIP)

Grade 3 or higher CIP (5 trials included in this analysis)

OR 2.91 (95% CI, 1.47 to 5.74)

- Grade 3 or higher CIP occurred more in patients with non-small cell lung cancer and ILD

Figure 5 in article displays the Forest plot for this outcome

**ARS Q8: A meta-analysis (n = 6 trials) evaluated clinical outcomes with immune checkpoint inhibitors in patients with pre-existing interstitial lung disease (ILD) and non-small cell lung cancer. Two individuals reviewed trials for incorporation into the analysis. A third individual was the tie breaker for discrepancies. Grade 3 or higher checkpoint inhibitor pneumonitis occurred more in patients with ILD (OR 2.91; 95%CI, 1.47 to 5.74;  $I^2 = 0\%$ ).**

**What statement is the most appropriate?**

The correct answer is C – no heterogeneity exists between trials. The  $I^2$  statistic = 0% indicating there is no degree of heterogeneity among trials. More trials and more individuals will not necessarily be needed for analyses. A funnel should be provided to assess publication bias.

### Case Study 4

Randomized, double-blind, phase III study of fosnetupitant versus fosaprepitant for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting: CONSOLE.

Hata A et al. J Clin Oncol 2022;40: 180-88.

**ARS Q9: A noninferiority trial evaluated the safety and efficacy of fosnetupitant vs fosaprepitant to prevent highly emetogenic chemotherapy-induced nausea and vomiting (total n = 795). The prespecified noninferiority margin was -10%. The authors stated fosnetupitant was noninferior to fosaprepitant to prevent nausea and vomiting from highly emetogenic chemotherapy. Which result most accurately reflects the authors' conclusion?**

A. 4.1% (95% CI, -2.1% to 10.3%)

B. -3.6% (95% CI -10.3% to 2.1%)

C. 1.3% (95% CI -10.3% to 10.3%)

D. -5.7% (95% CI, -12% to -0.87%)

10. Noninferiority – is new therapy no worse than control?<sup>16-19</sup>

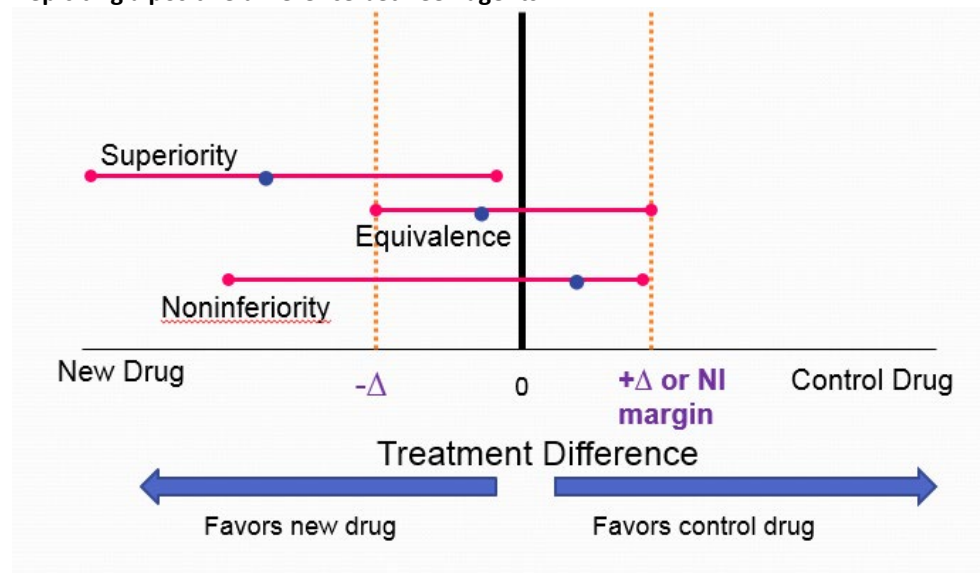
- a. Why conduct a noninferiority study
  - 1) Treatment is expected to be similar to the control/standard or is not unacceptably worse than control/standard; new treatment may have some advantage over standard (eg, fewer side effects, better compliance)
  - 2) Treatment is already expected to be better than placebo
  - 3) Unethical to conduct placebo-controlled trial
- b. Null hypothesis – the treatment groups are not noninferior to each other
- c. Most trials test the primary outcomes for noninferiority while secondary outcomes are tested for superiority; can also test primary outcomes for superiority if noninferiority criteria are met.
- d. Set noninferiority margin (delta or largest clinically acceptable difference) and confidence interval threshold



- 1) Determine a priori
  - 2) Must have clinical relevance
  - 3) Make a reasonable assumption of control effect
    - a) Estimate from historical data
    - b) Take into account uncertainty in the estimated difference over placebo
  - 4) Choose the portion of control effect that can be lost;  $\frac{1}{2}$  is usually acceptable
  - 5) Biocreep = phenomenon where efficacy of investigational drug could degrade over time if repeatedly compared with less efficacious treatments. May lead to inferior treatments getting to market.
- e. Usual values for alpha (0.05) and beta (0.1-0.2)
- f. May see a one-sided test because only concerned about one direction in noninferiority trials. The confidence interval may be 97.5% with a  $P$  value less than 0.025.
- g. Interpretation of noninferiority results – see graphs below comparing 3 types of trials
- 1)  $P < 0.05$  = new treatment is noninferior to standard
  - 2)  $P > 0.05$  = new treatment is not noninferior
  - 3) Does not determine superiority; however, may conduct a superiority analysis after noninferiority analysis is completed.
- h. Common traps in noninferiority trials
- 1) Is the noninferiority margin reasonable and acceptable based on previous studies? Sometimes a larger margin is chosen than should be, which makes it easier to demonstrate the treatments are noninferior.
  - 2) What dosing is used in the trial; is it equipotent? If a lower dose or subclinical dose is used for the standard agent, then it is easier to demonstrate the treatments are noninferior.
  - 3) Per protocol data should be used for data analysis. If using intention-to-treat data, it is easier to demonstrate the treatments are noninferior. In an ideal world, per protocol and intention-to-treat data should be reported.

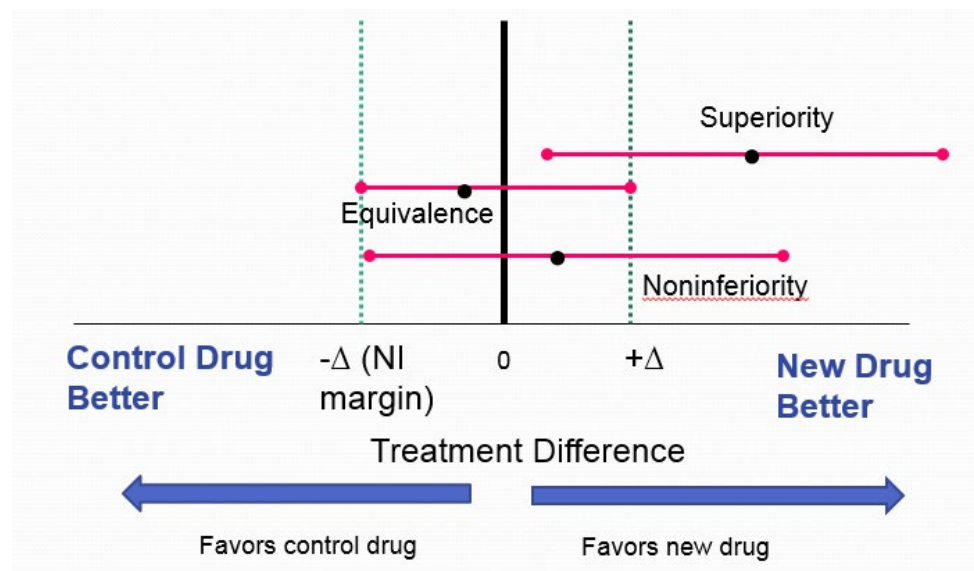
Graphical representation of types of trials when efficacy is measured by success rates

Depicting a positive difference between agents<sup>2</sup>

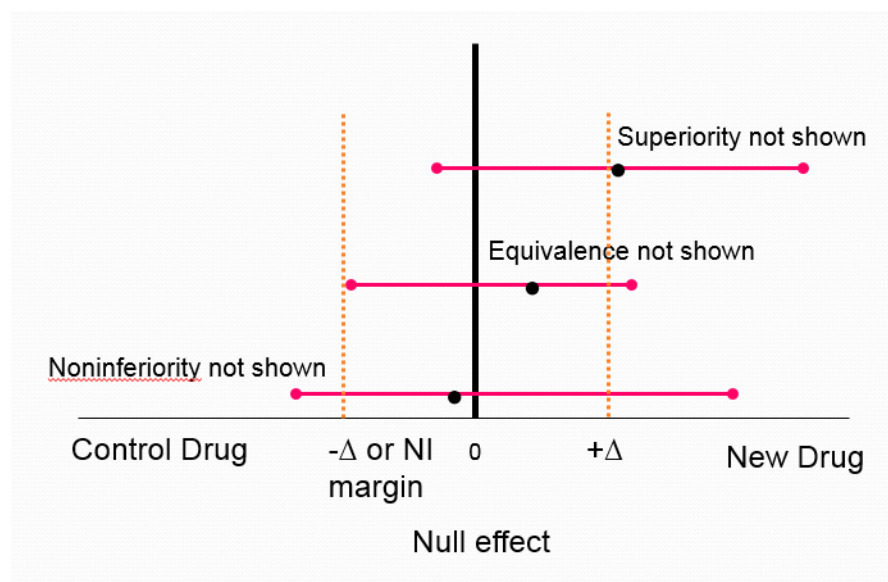


Graphical representation of types of trials when efficacy is measured by success rates

Depicting a negative difference between agents<sup>2</sup>



## Graphical representation of types of trials and failed tests for each type of trial<sup>2</sup>



### Case Study 4

Randomized, double-blind, phase III study of fosnetupitant versus fosaprepitant for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting: CONSOLE.

Hata A et al. J Clin Oncol 2022;40: 180-88

Study design: randomized (1:1), double-blind, noninferiority

Adult participants with cancer who were to receive cisplatin  $\geq 70 \text{ mg/m}^2$

Fosnetupitant 235 mg infused for 30 minutes (n = 397) in same bag with the following:

Palonosetron 0.75 mg

Dexamethasone 9.9 mg

\*\*Followed by normal saline infusion to maintain blind

Fosaprepitant 150 mg infused for 30 minutes (n = 398) in separate bag followed by the following:

Palonosetron 0.75 mg

Dexamethasone 9.9 mg

Primary outcomes – complete response following single chemotherapy cycle (S cycle)

Noninferiority margin = lower bound of CI cannot include -10%

**ARS Q9: A noninferiority trial evaluated the safety and efficacy of fosnetupitant vs fosaprepitant to prevent highly emetogenic chemotherapy-induced nausea and vomiting (total n = 795). The prespecified noninferiority margin was -10%. The authors stated fosnetupitant was noninferior to fosaprepitant to prevent nausea and vomiting from highly emetogenic chemotherapy. Which result most accurately reflects the authors' conclusion?**

The correct answer is A – 4.1% (95% CI, -2.1% to 10.3%). The predetermined noninferiority margin was -10%. For noninferiority, the 95% CI cannot contain this number.

## V. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value

### Case Study 5

Multitarget Stool DNA Testing for Colorectal-Cancer Screening. Imperiale TF, Ransohoff DF, Itzkowitz SH. *New Engl J Med*. 2014;370(14):1287-97.

This trial evaluated a noninvasive, multitarget stool DNA test for screening colorectal cancer. Enrolled subjects were asymptomatic and at average risk for colorectal cancer. Excluded subjects had a history of inflammatory bowel disorders, colonoscopy in previous 9 years, and family history of colorectal cancer.

Of the 9,989 subjects who were evaluated, there were 823 positive diagnoses by colonoscopy for colorectal cancer. The multitarget DNA test diagnosed 379 positive results. The prevalence was 23.6%.

**ARS Q10: A study (n = 9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The new test identified colorectal cancer in 379 patients. Colonoscopy identified colorectal cancer in 823 patients. The positive predictive value is 23.6%. What is the negative predictive value of the test diagnostic test?**

- A. 3.8%
- B. 8.2%
- C. 76.4%
- D. 94.7%

#### A. The "Other" 2x2 Table<sup>20</sup>

		Truth or Gold Standard		
		Positive	Negative	
Test Evaluated	Positive	A True Positive	B False Positive	A+B
	Negative	C False Negative	D True Negative	C+D
		A+C	B+D	A+B+C+D

#### B. Sensitivity<sup>20</sup>

1. The ability of the test to correctly identify patients with the condition
2. The probability a patient with the condition will have a positive test
3. Tests with high sensitivity will be less likely to "miss" patients who have the condition
4. Higher sensitivity = fewer false negatives
5. Calculating sensitivity =  $A/A+C$  = true positive/(true positive + false negatives)
  - a. See "other 2x2 table" (above)

#### C. Specificity<sup>20</sup>

1. The ability of the test to correctly identify patients without the condition
2. The probability a patient without the condition will have a negative test

3. Tests with high specificity will be less likely to identify patients as having the condition when they do not
  4. High specificity = fewer false positives
  5. Calculating specificity =  $D/B+D = \text{true negatives}/(\text{false positives} + \text{true negatives})$ 
    - a. See “other 2x2 table” (above)
- D. Interpreting sensitivity and specificity
1. Sensitivity - How well does the test identify those with the condition?
    - a. True positives vs false negatives
  2. Specificity – How well does the test identify those without the condition?
    - a. True negatives vs false positives
- E. Clinical consequences
1. Patients with the condition (Sensitivity)
    - a. Number of people who will pursue additional tests and receive treatment, if appropriate
    - b. Number of people who will be told they do not have a condition when they might really have the condition
  2. Patients without the condition (Specificity)
    - a. Number of people who will be told they do not have a certain condition, and they really do not
    - b. Number of people who will pursue additional tests and receive treatment even though they don't really need to pursue the tests
- F. Positive Predictive Value (PPV)<sup>20</sup>
1. The probability that a person with a positive test truly has the condition
  2. Positively affected by increasing prevalence (ie, as prevalence ↑, the PPV ↑)
  3. Reflects the predictive value of a positive test result in a specific population
  4.  $PPV = A/A+B = \text{true positives}/(\text{true positives} + \text{false positives})$
- G. Negative Predictive Value (NPV)<sup>20</sup>
1. The probability that a person with a negative test truly does not have the condition
  2. Negatively affected by increasing prevalence (ie, as prevalence ↑, the NPV ↓)
  3. Reflects the predictive value of a negative test result in a specific population
  4.  $NPV = D/C+D = \text{true negatives}/(\text{false negatives} + \text{true negatives})$
- H. Interpretation of PPV and NPV
1. PPV – if a person is ‘positive’ for a condition
    - a. Probability that a person truly has a condition (true positive)
    - b. Probability that a person truly does not have a condition (false positive)

2. NPV = if a person is 'negative' for a condition
  - a. Probability that a person truly does not have a condition (true negative)
  - b. Probability that a person truly does have a condition (false negative)

#### Case Study #5

Multitarget Stool DNA Testing for Colorectal-Cancer Screening. Imperiale TF, Ransohoff DF, Itzkowitz SH. *New Engl J Med*. 2014;370(14):1287-97.

This trial evaluated a noninvasive, multitarget stool DNA test for screening colorectal cancer. Enrolled subjects were asymptomatic and at average risk for colorectal cancer. Excluded subjects had a history of inflammatory bowel disorders, colonoscopy in previous 9 years, and family history of colorectal cancer.

Of the 9,989 subjects who were evaluated, there were 823 positive diagnoses by colonoscopy for colorectal cancer. The multitarget DNA test diagnosed 379 positive results. The prevalence was 23.6%.

Steps to determine sensitivity, specificity, PPV, and NPV for the new test compared with colonoscopy. Colonoscopy is considered the gold standard.

Step 1: set up 2x2 table

Step 2: calculate sensitivity

Step 3: calculate specificity

Step 4: complete rest of table

		Colonoscopy		Totals
		Positive	Negative	
Multitarget DNA test	Positive	379*	1227 <sup>§</sup>	1606 <sup>#</sup>
	Negative	444 <sup>§</sup>	7939 <sup>§</sup>	8383 <sup>§</sup>
		823*	9166 <sup>§</sup>	9989*

\*Green shaded cells = information directly taken from article

#Purple shaded cells = calculated from PPV

$$PPV = 0.236 = 379/x$$

$$x = 1606$$

§Pink shaded cells = calculated from other values in table

**Q10: A study (n = 9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The new test identified colorectal cancer in 379 patients. Colonoscopy identified colorectal cancer in 823 patients. The positive predictive value is 23.6%. What is the negative predictive value of the test diagnostic test?**

The correct answer is D= 94.7%. The NPV is calculated after populating the 2x2 table with the correct values based on pulling the correct numbers from the article and performing subtraction. NPV is calculated by  $D/C+D = 7939/8383 = 0.947 = 94.7\%$ .

**ARS Q11: The coefficient of determination is 0.98 for a study evaluating if continued smoking affects complete response (CR) of small cell lung cancer when taking a new oral chemotherapy. The alpha level is set at < 0.05. The P value was determined to be 0.052. What is the best way to interpret these findings?**

- A. Smoking positively impacts CR
- B. Smoking negatively impacts CR
- C. Smoking has no effect on CR
- D. The results are inconclusive

## V. Correlation and Regression

### A. Correlation<sup>21</sup>

1. Correlation analysis
  - a. Relationship between 2 random variables
  - b. Strength of association between the variables
  - c. Cannot imply causality
  - d. Need to determine clinical significance
2. Correlation coefficient ( $r$ )
  - a. Suggests linear relationship between 2 variables
  - b. Defines strength and direction of the relationship
  - c.  $r = -1$  to  $1$
  - d. Sign (+ or -) = direction of relationship
  - e. Number = strength of relationship
  - f. Interpretation
    - 1)  $r = -1$ : The 2 variables are perfectly negatively (inversely) correlated
    - 2)  $r = 0$ : No correlation (linear relationship) between the 2 variables; weaker relationship
    - 3)  $r = +1$ : The 2 variables are perfectly positively correlated
3. Calculating correlation coefficient
  - a. Pearson
    - 1) Strength between 2 continuous variables
    - 2) Parametric correlation
    - 3) Normal distribution of data
  - b. Spearman rank order
    - 1) Based on rank order of individual data
    - 2) Nonparametric correlation
    - 3) Not normal distribution of data

### B. Regression<sup>21</sup>

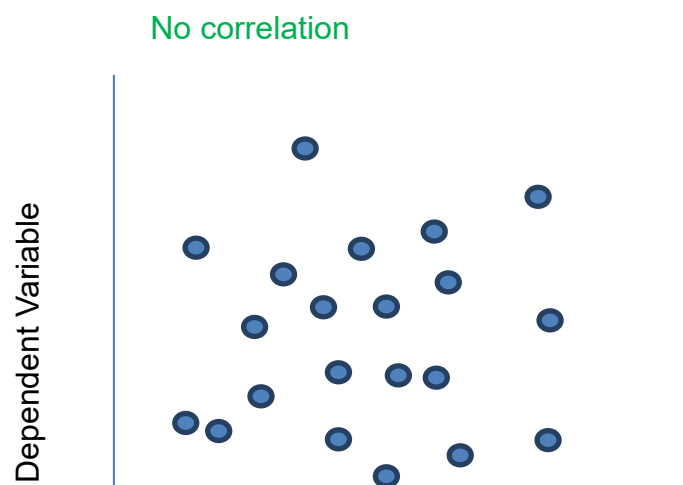
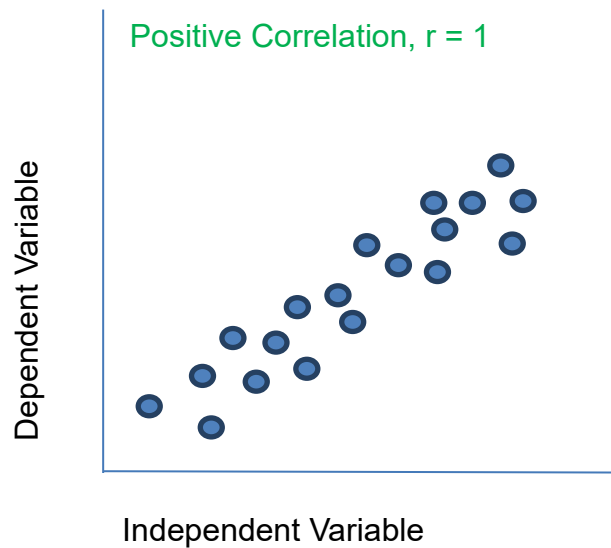
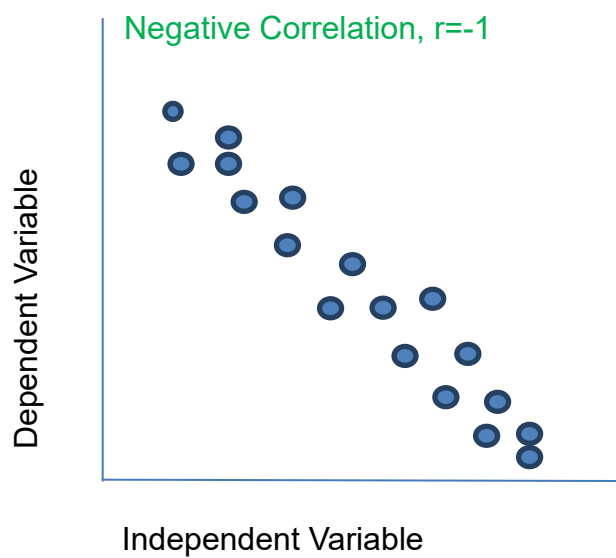
1. Regression analysis
  - a. Estimate value of one variable if given value of the second variable
  - b. Cause and effect relationship between variables
2. Coefficient of determination ( $r^2$ )
  - a. Defines strength of the relationship but NOT direction
  - b. Variation in one variable attributed to variation in the second variable

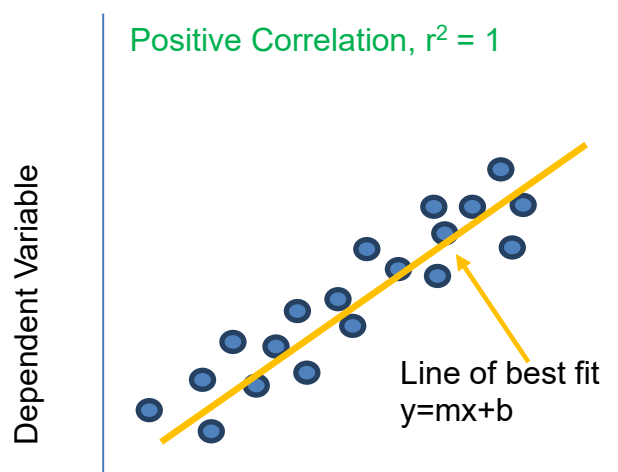
- 1) X variable (independent): selected by study team
- 2) Y variable (dependent): influenced by X
- c. Line of best fit:  $y=mx+b$
- d.  $r^2 = 0$ : no variation in Y attributed to X
- e.  $r^2 = 1$ : all variation in Y attributed to X
- f. Only predicts values within X for the sample
- g. Cannot determine relationship outside the range of sample
3. The method of least squares finds the best fit line for a data set in regression analysis
4. Multiple linear regression (or multiple regression)
  - a. Use with multiple independent variables to predict the outcome on the dependent variable
5. Logistic regression
  - a. Not continuous scale
  - b. Preferred for use for ordinal scale
  - c. Provides OR

**ARS Q11: The coefficient of determination is 0.98 for a study evaluating if continued smoking affects complete response (CR) of small cell lung cancer when taking a new oral chemotherapy. The alpha level was set at < 0.05. The P value was determined to be 0.052. What is the best way to interpret these findings?**

The correct answer is C = smoking has no effect on CR. You use regression concepts to determine this answer. Regression cannot show direction of a relationship; it only shows strength of a relationship. The P value is greater than the alpha level, so smoking has no effect on CR.







**ARS Q12: A study team asks for your advice on determining a primary outcome for a randomized, phase 3 trial evaluating overall survival in participants with renal cell carcinoma following treatment with a new agent. The team wishes to randomize 525 participants. Which statement is the most correct regarding this new trial?**

- A. Longer follow-up timeframe is needed
- B. Complete response is a more appropriate primary outcome
- C. Smaller sample population is required
- D. The primary outcome is more susceptible to bias

## **VI. Oncology Trial Issues**

- A. Are the dosage and regimen appropriate for disease state or patient population?
- B. Are the combination regimens adequate and appropriate? Is anything missing?
- C. How are the results represented?
- D. Are there cost considerations? How does cost affect clinical outcomes?
- E. Endpoints<sup>22-24</sup>
  - 1. Overall Survival (OS)
    - a. Definition – time from randomization until death (from any cause) or lost to follow up
    - b. Most objective and widely accepted endpoint
    - c. Less vulnerable to bias
    - d. Feasibility may be difficult because of disadvantages listed below
    - e. Used in randomized trials; blinding is not required
    - f. A common measure of clinical benefit for standard drug approvals
    - g. Advantages
      - 1) Direct measure of clinical benefit
      - 2) Clear endpoint that is easily and precisely measured
    - h. Disadvantages
      - 1) Larger and longer studies are required
      - 2) OS includes all deaths, not just cancer-related death
      - 3) Additional therapy or crossover therapy (post-progression therapy) may impact endpoint
  - 2. Progression-free survival (PFS)
    - a. Definition – time from randomization until objective tumor progression, death (from any cause) or lost to follow up
    - b. Used in randomized, blinded trials; blinding is preferred
    - c. Used in studies when there is evidence of disease when starting the study
    - d. Surrogate for accelerated or standard drug approvals

- e. RECIST and iRECIST are standards for measuring response and progression to standard chemotherapy and immunotherapy, respectively
  - f. Advantages
    - 1) PFS requires shorter follow-up and smaller overall sample size compared with survival studies
    - 2) Additional therapy or crossover therapy (post-progression therapy) does not impact endpoint
    - 3) Preferred over time-to-progression because it includes deaths
  - g. Disadvantages
    - 1) Numerous definitions used
    - 2) Not precisely measured so subject to measurement bias
      - a) Subjective due to different tools used
      - b) Are the tools validated?
      - c) Blinding may help or a centralized audit process
    - 3) Not statistically validated as a surrogate endpoint for survival in all areas
    - 4) Assessment-time bias: requires balanced assessment among treatment groups; hard to determine exact progression date/time
3. Disease-free survival (DFS)
- a. Definition – time from randomization until recurrence of tumor or death (from any cause)
  - b. Used in randomized, blinded trials; blinding is preferred
  - c. Used in studies where patients are cancer free at the time of the study (eg, adjuvant therapy trials)
  - d. Surrogate for accelerated or standard drug approvals
  - e. Advantages
    - 1) DFS requires shorter follow-up and smaller sample size compared with overall survival studies
  - f. Disadvantages
    - 1) Numerous definitions used
    - 2) Not precisely measured so subject to bias
    - 3) Not statistically validated as a surrogate endpoint for survival in all areas
4. Objective (also, Overall) response rate (ORR)
- a. Definition – proportion of patients with tumor-size reduction of a predefined amount for a predefined time
  - b. Different responses that can be recorded are progressive disease, stable disease, partial response, and complete response
  - c. Used in randomized, comparative trials or single-arm trials; blinding is preferred

- d. Surrogate for accelerated or standard drug approvals
  - e. Advantages
    - 1) Effect is attributed to the intervention
    - 2) Single-arm studies
    - 3) May assess ORR earlier and in smaller studies
  - f. Disadvantages
    - 1) Not a direct measure of benefit (ie, survival)
    - 2) Not a comprehensive measure
    - 3) Only a subset of patients who benefit
5. Complete response (CR)
- a. Definition – no target lesions remain and pathological lymph nodes are < 10 mm
  - b. Used in randomized, comparative trials or single-arm trials; blinding is preferred
  - c. Surrogate for accelerated or standard drug approvals
  - d. May combine with partial response to get ORR
  - e. Advantages
    - 1) Effect is attributed to the intervention
    - 2) Single-arm studies
    - 3) May assess ORR earlier and in smaller studies
  - f. Disadvantages
    - 1) Not a direct measure of benefit
    - 2) Not a comprehensive measure
    - 3) Only subset of patients who benefit
6. Time-to-progression (TTP)
- a. Definition – time from study entry until objective tumor growth
  - b. Surrogate for accelerated or standard drug approvals
  - c. Advantages
    - 1) TTP requires shorter follow-up and sample size compared with survival studies
    - 2) Additional therapy or crossover therapy (post-progression therapy) does not impact endpoint
  - d. Disadvantages
    - 1) Less preferred than PFS
7. Patient-reported outcome
- a. Definition – may vary based on endpoint, but is typically a symptom-based endpoint (eg, disease burden, satisfaction with treatment)

- b. Used in randomized, blinded trials
  - c. Clinical benefit for accelerated or standard drug approvals
  - d. Advantages
    - 1) Patient perspective of the direct clinical benefit
  - e. Disadvantages
    - 1) Blinding may be a challenge
    - 2) Data are missing or incomplete
    - 3) Lack of validated instruments
- F. Clinically Meaningful Outcomes<sup>25</sup>
1. Significant improvement in survival, quality of life, or both
  2. Working group established for following areas:
    - a. Breast cancer
    - b. Colon cancer
    - c. Lung cancer
    - d. Pancreatic cancer
  3. Determined targets for primary outcomes and secondary outcomes
  4. Influenced by the following:
    - a. Clinical context
    - b. Side effect profiles
    - c. Effectiveness
    - d. Patient goals
  5. Balancing toxicity and efficacy
    - a. Less toxic, less improvement in efficacy may be okay if focusing on quality of life or palliation
    - b. More toxic, much greater improvement in efficacy may be okay if focusing on aggressive treatment goals (eg, cure)
  6. Overall survival = primary outcome to measure clinically meaningful results
    - a. Longer follow up
    - b. Confounders – additional therapies after study
  7. Other outcomes still important
  8. Improvement over baseline for clinically meaningful outcome
    - a. Pancreatic cancer, FOLFIRINOX-eligible
      - 1) Baseline OS – 10 to 11 months
      - 2) Improvement – 4 to 5 months

- b. Lung cancer, non-squamous cell carcinoma
  - 1) Baseline OS – 13 months
  - 2) Improvement – 3.25 to 4 months
- c. Breast cancer, metastatic, triple negative
  - 1) Baseline OS – 18 months
  - 2) Improvement – 4.5 to 6 months
- d. Colon cancer, disease progression with all other therapies
  - 1) Baseline OS – 4 to 6 months
  - 2) Improvement – 3 to 5 months

**ARS Q12: A study team asks for your advice on determining a primary outcome for a randomized, phase 3 trial evaluating overall survival in participants with renal cell carcinoma following treatment with a new agent. The team wishes to randomize 525 participants. Which statement is the most correct regarding this new trial?**

The answer is A – longer follow-up timeframe is needed. Overall survival is less susceptible to bias than PFS. It may take a longer time to reach this time point. Overall survival is the most objective and widely accepted primary outcome for oncology trials.

## VII. Phase 1 Oncology<sup>26-34</sup>

### A. Objectives

- 1. Determine the drug's clinical pharmacology, pharmacokinetics, and pharmacodynamics
- 2. Determine the **maximum-tolerated dose (MTD)** and recommended phase 2 dose (RP2D)
- 3. Describe drug-related toxicities in terms of severity, duration, acute and cumulative **dose limiting toxicity (DLT)**
  - a. Single ascending dose (SAD) studies – small number of patients given one dose of drug and observed over a certain time frame
  - b. Multiple ascending dose (MAD) studies – small number of patients given low doses of drug and observed. The dose is increased up to a certain limit and given to additional patients.

### B. Determination of therapeutic activity is limited

### C. Limitations include the following:

- 1. Many patients are treated at subtherapeutic doses of a new drug
- 2. Inpatient dose escalation may not be permitted
- 3. Can take an extended period to complete
- 4. Limited information regarding patient variability and cumulative toxicity

### D. Starting dose

- 1. LD<sub>10</sub> = Mouse lethal dose 10; dose that kills one-tenth of the mice tested
- 2. 1/10 LD<sub>10</sub> = starting dose level (may be fixed or flat, mg/kg, or mg/m<sup>2</sup>)
- 3. Dog toxic low dose (TLD) is the minimum dose at which any toxicity is observed

4. NOAEL – no observable adverse effect level
- E. Hansen and colleagues published<sup>29</sup> an article in 2014 evaluating the different Phase 1 trial designs currently being utilized in clinical trials. The reader is referred to this document for additional information. Figure 1 illustrates the differences between the standard 3 + 3, accelerated titration, pharmacokinetically guided dose-escalation and an adaptive model-based design. The article also illustrates the challenges of working with target agents, which do not exhibit classic DLT to assist with dose escalation decisions.
- F. Standard cohort escalation design (“3+3”)
  1. Typically, 4 to 8 dose escalations planned
  2. 3 patients per cohort, unless toxicity, then expand that cohort to 6. See Section M for information on dose-limiting toxicity.
  3. Approximately 95% of phase 1 trials have been based on this method; however, the design may be inferior in the identification of the actual MTD. Numerous other cohort designs have been reported in the literature<sup>35</sup>
- G. Multistage design “up and down” dose increases and decreases based on toxicity at each level; poor design by itself; high percentage of patients can be treated at 50% toxicity rates.
- H. Continual Reassessment Method (CRM) - pretrial selection of a sample size and target toxicity rate (eg, 33%).<sup>36-38</sup>
  1. Utilizes a form of Bayesian statistics and modeling
    - a. Estimate of probability of DLT at each dose
    - b. Initial guess of the MTD
    - c. Parametric dose toxicity model that fits the assumptions
    - d. A priori distribution for each parameter in the model (eg, logistic regression)
    - e. Update the model based on new toxicity data and number of patients
    - f. Obtain a new MTD estimate and continue escalations
  2. Advantages: improved MTD estimates, fewer patients per study, few patients per subtherapeutic, low doses. Does not result in more rapid completion, but escalation occurs with fewer patients. May limit PK data, as fewer numbers of subjects required at lower dose levels.
- I. Modified CRM: 3 patients in the first cohort at the conventional dose assignment, then escalate single patients at each level, until toxicities noted, then expand level if toxicities, then begin following 33% rule. Uses a model based MTD estimate for escalations beyond the current dose.
- J. A pharmacokinetically guided scheme accounts for individual variability and calculates a maximum tolerated systemic exposure. The advantage is increased efficacy with decreased toxicity; major disadvantages are expense and logistics.
- K. Pharmacodynamically guided, or assessment of clinical activity via biomarkers is evolving
- L. Dose escalations
  1. *Fixed-conditional scheme* - 100% increases until minimal toxicity, then 50% increase until unacceptable toxicity, then only 25% increases



2. *Modified Fibonacci method* - 100%, 67%, 50%, 45%, 33%, (2x, 3.3x, 5x, 9x, 12x, 16x)
- M. Dose-limiting toxicity rate = proportion of patients that develop a DLT; a minimal number that would limit future drug development (33%, 50%)
1. *Dose-Limiting Toxicity (DLT)* = the dose in which 2/3 or 2/6 patients experience a serious, life-threatening toxicity (eg, grade 4 hematologic, grade 3 or 4 nonhematologic, except for nausea, vomiting, alopecia)
    - a. NOTE: most studies enroll 3 patients per cohort – if a serious adverse event is seen in 1 of these 3 patients then another 3 patients are enrolled into the same cohort. If a 2<sup>nd</sup> patient has a serious adverse event, then that dose level is defined as a DLT. If 2 out of 3 patients in a cohort have a serious adverse event, then an additional 3 patients DO NOT need to be added and this is the DLT.
  2. *Maximum-Tolerated Dose* = 1 dose level below the DLT (recommended phase 2 dose)
- N. Dose-Expansion Cohorts<sup>39,40</sup>
1. Once MTD established, expand patient population to specified tumor types to better characterize PK, PD, safety & efficacy profile in specific disease states.
  2. Define method to include toxicities in these patients in the MTD determination which may result in a change in the MTD that was previously established.
- O. Phase 1 Endpoints
1. Minimal toxicity, dose escalation may not be important
  2. Plasma Concentration, IC50
  3. Target effect in tumor biopsy (Requires 2 research only tumor biopsies)
  4. Target effect in surrogate tissue (eg, hair follicles, skin biopsy)
  5. Plasma growth factors
  6. CT and PET scans
- P. Many publications discussing risk versus benefit of phase 1 trial participation have been published. Recent review by Mahipal and Nguyen<sup>41</sup> provides a good overview of the topic.

**Phase 1 Clinical Trial Design:** A phase 1 clinical trial is being conducted at your institution. The protocol is using a standard 3 + 3 titration design.

Dose level 1: 0.5 mg/kg – 0 / 3 patients experience DLT

Dose level 2: 1 mg/kg – 0 / 3 patients experience DLT

Dose level 3: 1.5 mg/kg – 1 / 3 patients experience DLT, then 3 more patients are enrolled and 0 / 3 experiences DLT

Dose level 4: 2 mg/kg – 1 / 3 patients experience DLT, then 3 more patients are enrolled and 1 / 3 experiences DLT

**Which of the dose levels above would be considered the MTD?** Dose level 3 (1 out of 6 patients experienced DLT) would be considered the maximum tolerated dose.

## **VIII. Guideline development: evidence-based and consensus-based**

### **A. Evaluating Guidelines**

1. Appraisal of Guidelines for Research and Evaluation (AGREE II) – 6 quality domains for evaluating guidelines (score for each domain)
  - a. <http://www.agreetrust.org/>
  - b. Scope and purpose
    - 1) Overall objective is specifically described
    - 2) Health question specifically described
    - 3) Population to whom the guideline applies is specifically described
  - c. Stakeholder involvement
    - 1) Relevant professional groups included
    - 2) Target population views and preferences
    - 3) Target users clearly defined
  - d. Rigor of development
    - 1) Systematic methods used to find evidence
    - 2) Criteria for selecting evidence clearly defined
    - 3) Limitations and strengths of evidence described
    - 4) How recommendations are made is clearly described
    - 5) Benefits and risks evaluated
    - 6) Clear link between evidence and recommendations
    - 7) External review by experts prior to release
    - 8) Updating method provided
  - e. Clarity and presentation
    - 1) Specific and unambiguous
    - 2) Different options clearly presented
    - 3) Key recommendations easily identifiable
  - f. Applicability
    - 1) Has tools for application
    - 2) Organizational barriers discussed
    - 3) Resource implications considered
    - 4) Key review criteria for monitoring or auditing purposes
  - g. Editorial independence

- 1) Independent from the funding body
- 2) Conflicts of interested recorded
- h. Overall Assessment of Guidelines
  - 1) Determine quality of guideline
  - 2) Would you recommend these guidelines for use in practice?
- B. National Guidelines Clearinghouse - public resource for evidence-based clinical practice guidelines
  1. <http://www.guidelines.gov/>
  2. Agency for Healthcare Research and Quality (AHRQ)
  3. Guideline comparison: Search select guidelines to compare - Add to my collection - Compare guidelines
  4. Funding for this website ended in July 2018.
  5. Study is being conducted to identify other models to access evidence-based guidelines.

## Additional Practice

### Q13. Statistical Tests

Subjects were their own control in a trial evaluating changes in platelet concentrations from baseline following the administration of 2 different oncology medications. Results were normally distributed. What type of statistical test is most appropriate when analyzing these results?

- A. McNemar
- B. Wilcoxon signed rank
- C. Paired t-test
- D. Mann Whitney U

**Answer:** C. Paired t-test - Subjects as their own control indicates a crossover study design, which means same samples. Platelet concentrations is a type of continuous data. The question tells you there are 2 groups (2 new oncology medications). Using the table will help you determine the correct answer based on the provided parameters.

### Measures of Effect – Additional Case Study 1

Goss PE, Ingle JN, Ales-Martinez JE et al. Exemestane for Breast-Cancer Prevention in Postmenopausal Women. *New Engl J Med*. 2011; 364(25):2381-91.

Outcome = invasive ER positive breast cancer

	Outcome Yes	Outcome No	Total
Exemestane	7 (0.12%)	2,278	2,285
Placebo	27 (0.46%)	2,248	2,275
Hazard Ratio 0.27 (95% CI 0.12 to 0.6), p<0.001			

**Q14. Calculate the relative risk reduction of invasive ER positive breast cancer in patients treated with exemestane compared with placebo.**

- A. 12%
- B. 25%
- C. 75%
- D. 95%

**Q15. Calculate the absolute risk reduction of invasive breast cancer in patients treated with exemestane compared with placebo (n = 4,560). The annual incidence of invasive breast was 0.09% with exemestane and 0.34% with placebo.**

- A. 0.02%
- B. 0.25%
- C. 0.74%
- D. 0.81%

**Q16. Exemestane decreased the absolute risk of invasive breast cancer by 0.25%. How many subjects will be needed in order to prevent one breast cancer occurrence?**

- A. 5
- B. 11
- C. 123
- D. 400

**Q17. There was a significant difference in musculoskeletal arthritis during this trial. Exemestane increased the absolute risk of arthritis by 2%. How many subjects will be needed in order to have one report of arthritis?**

- A. 2
- B. 5
- C. 50
- D. 75

**Measures of Effect – How to Calculate the Correct Answers**

Goss PE, Ingle JN, Ales-Martinez JE et al. Exemestane for Breast-Cancer Prevention in Postmenopausal Women. *New Engl J Med*. 2011; 364(25):2381-91.

Outcome = invasive ER positive breast cancer

	Outcome Yes	Outcome No	Total
Exemestane	7 (0.12%)	2,278	2,285
Placebo	27 (0.46%)	2,248	2,275
Hazard Ratio 0.27 (95% CI, 0.12 to 0.6), $P < 0.001$			

**Q14. Calculate the relative risk reduction of invasive ER positive breast cancer in patients treated with exemestane compared with placebo?**

Answer = C. You calculate a relative risk reduction using the relative risk. You need to calculate the RR first.

$$RR = (A/A+B) / (C/C+D)$$

$$RR = (7/2285)/(27/2275) = 0.003/0.012$$

$$RR = 0.25 = \text{RR of invasive ER positive breast cancer in patients who took exemestane compared with placebo}$$

$$\text{Relative risk reduction} = 1 - \text{relative risk} = 1 - 0.25 = 0.75 = 75\%.$$

**Q15. Calculate the absolute risk reduction of invasive breast cancer in patients treated with exemestane compared with placebo (n = 4,560). The annual incidence of invasive breast was 0.09% with exemestane and 0.34% with placebo?**

Answer = B.

$$ARR = CER - EER = 0.34\% - 0.09\% = 0.25\%$$

**Q16. How many subjects will be needed in order to prevent one breast occurrence in the scenario in question 2?**

Answer = D.

$$NNT = 1/ARR = 1/0.0025 = 400$$

**Q17. There was a significant difference in musculoskeletal arthritis during this trial. Exemestane increased the absolute risk of arthritis by 2%. How many subjects will be needed in order to have one report of arthritis.**

Answer = C

$$ARR = 9\% - 11\% = -2\% = 2\%$$

$$NNH = 1/0.02 = 50$$

### **Sensitivity, Specificity, PPV, NPV – Additional Case Study 2**

Multitarget Stool DNA Testing for Colorectal-Cancer Screening. *New Engl J Med.* 2014;370(14):1287-97

This trial evaluated a noninvasive, multitarget stool DNA test for screening colorectal cancer. Enrolled subjects were asymptomatic and at average risk for colorectal cancer. Excluded subjects had a history of inflammatory bowel disorders, colonoscopy in previous 9 years, and family history of colorectal cancer.

A study (n = 9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The new test identified colorectal cancer in 379 patients. Colonoscopy identified colorectal cancer in 823 patients. The positive predictive value is 23.6%.

Do not forget to setup your 2x2 to help with the calculations.

**Q18. A new study (n = 9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The specificity of the new test was 84%, and the sensitivity is 92%. Which statement is most accurate regarding this new test?**

- A. High likelihood to miss a diagnosis
- B. Expect fewer false negatives
- C. Expect many false positives
- D. Low likelihood to make a positive diagnosis

**Q19. A study (n=9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The new test identified colorectal cancer in 60 patients. Colonoscopy identified colorectal cancer in 65 patients. What is the specificity of the new diagnostic test if the positive predictive value is 3.7%?**

- A. 83.7%
- B. 84.3%
- C. 92.3%
- D. 99.9%

### **Sensitivity, Specificity, PPV, NPV – How to Calculate the Correct Answers**

Multitarget Stool DNA Testing for Colorectal-Cancer Screening. *New Engl J Med.* 2014;370(14):1287-97

This trial evaluated a noninvasive, multitarget stool DNA test for screening colorectal cancer. Enrolled subjects were asymptomatic and at average risk for colorectal cancer. Excluded subjects had a history of inflammatory bowel disorders, colonoscopy in previous 9 years, family history of colorectal cancer.

A study (n=9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The new test identified colorectal cancer in 60 patients. Colonoscopy identified colorectal cancer in 65 patients. The PPV is 3.7%.

Set up the “other” 2x2 table.

		Colonoscopy		
		Positive	Negative	
Multitarget DNA test	Positive	60	1561	1621
	Negative	5	8363	8368
		65	9924	9989

**Q18. A study (n = 9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The specificity of the new test was 84%, and the sensitivity is 92%. Which statement is most accurate regarding this new test?**

The correct answer is B – expect fewer false negatives. The sensitivity of the test is high (92%); therefore, one would expect fewer false negatives and less likely to miss a diagnosis. The specificity (84%) is higher for this test. One would expect fewer false positive diagnoses and less likely to identify patients as having the condition when they really do not have it.

**Q19. A study (n=9,989) was conducted to evaluate a new test developed to improve screening for colorectal cancer. The new test identified colorectal cancer in 60 patients. Colonoscopy identified colorectal cancer in 65 patients. What is the specificity of the new diagnostic test if the positive predictive value is 3.7%?**

Sensitivity =  $60/65 = 92.3\%$

Specificity =  $8,363/9,924 = 84.3\%$

PPV =  $60/1,621 = 3.7\%$

NPV =  $8,363/8,368 = 99.9\%$

**Q20: Correlation and Regression**

**The correlation coefficient is 0.98, and the coefficient of determination is 0.96 for a study evaluating a new chemotherapy agent to treat advanced pancreatic cancer. What percentage best estimates the variation in the outcome due to the independent variable?**

- A. 2%**
- B. 19%**
- C. 96%**
- D. 98%**

Answer: C = 96%. By definition the coefficient of determination estimates the variation in the outcome due to the independent variable.

## RECOMMENDED READINGS

1. DiCenzo R ed. Clinical pharmacist's guide to biostatistics and literature evaluation. 2nd ed. Lenexa, KS: American College of Clinical Pharmacy; 2015.
2. Redfern JS and Thompson D. The risks and hazards of interpreting and reporting health study measures: A simple, practical overview. *AMWA Journal*. 2011; 26(3): 111-26. Link to free version of article: [http://www.amwa.org/files/Journal/2011v26n3\\_online.pdf](http://www.amwa.org/files/Journal/2011v26n3_online.pdf)
3. De Muth JE. Overview of biostatistics used in clinical research. *American Journal of Health-System Pharmacy*. 2009;66:70-81. Abstract link: <http://www.ajhp.org/content/66/1/70.abstract>
4. Mounsey A, Viera AJ and Dominik R. 7 questions to ask when evaluating a noninferiority trial. *The Journal of Family Practice*. 2014; 63(3): E4-8. Link to free version of article: <http://www.jfponline.com/the-publication/past-issue-single-view/7-questions-to-ask-when-evaluating-a-noninferiority-trial/015e59dcc11919c3b62d10aa3b67ac99.html>
5. Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: user's guide to the medical literature. *J Am Med Assoc* 2014;312:171-9. Abstract link: <http://jama.jamanetwork.com/article.aspx?articleid=1886196>

## REFERENCES

1. DiCenzo R, ed. *Clinical Pharmacist's Guide to Biostatistics and Literature Evaluation*. 2nd ed. Lenexa, KS: American College of Clinical Pharmacy; 2015.
2. Guyatt G, Rennie D, Meade MO, Cook DJ, eds. *Users' Guides to the Medical Literature: A Manual for Evidence-based Clinical Practice*. 2nd ed. New York, NY: McGraw Hill Medical Publishing; 2008.
3. Elenbaas RM, Elenbaas JK, Cuddy PG. Evaluating the medical literature. Part II: Statistical analysis. *Ann Emerg Med*. 1983;12(10):610-620.
4. Montoria VM, Kleinbart J, Newman TB, et al. Tips for learners of evidence-based medicine: 2. Measures of precision (confidence intervals). *CMAJ*. 2004;171(6):611-615.
5. Barratt A, Wyer PC, Hatala R, et al. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. *CMAJ*. 2004;171(4):353-358.
6. Redfern JS, Thompson D. The risks and hazards of interpreting and reporting health study measures: A simple, practical overview. *AMWA Journal*. 2011;26(3):111-126.
7. Hatala R, Keitz S, Wyer PC, et al. Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results. *CMAJ*. 2005;172(6):661-665.
8. Sedgwick P. Survival (time to event) data I. *BMJ*. 2010;341:c3537.
9. Sedgwick P. Survival (time to event) data II. *BMJ*. 2010;341:c3665.
10. Sedgwick P. Survival (time to event): Median survival times. *BMJ*. 2011;343:d4890.
11. Sedgwick P. Survival (time to event): Censored observations. *BMJ*. 2011;343:d4816.
12. Gillespie TW. Understanding waterfall plots. *J Adv Pract Oncol*. 2012;3(2):106-111.
13. Shao T, Wang L, Templeton AJ, et al. Use and misuse of waterfall plots. *J Natl Cancer Inst*. 2014;106(12).
14. Crowther M, Lim W, Crowther MA. Systematic review and meta-analysis methodology. *Blood*. 2010;116(17):3140-3146.
15. Sterne JA, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;342:d4002.
16. Mounsey A, Viera AJ, Dominik R. 7 questions to ask when evaluating a noninferiority trial. *J Fam Pract*. 2014;63(3):E4-8.
17. Mulla SM, Scott IA, Jackevicius CA, You JJ, Guyatt GH. How to use a noninferiority trial: users' guides to the medical literature. *JAMA*. 2012;308(24):2605-2611.
18. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, Group C. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594-2604.
19. Sedgwick P. Non-inferiority trials. *BMJ*. 2011;342:d3253.
20. Gaddis GM, Gaddis ML. Introduction to biostatistics: Part 3, Sensitivity, specificity, predictive value, and hypothesis testing. *Ann Emerg Med*. 1990;19(5):591-597.
21. Gaddis ML, Gaddis GM. Introduction to biostatistics: Part 6, Correlation and regression. *Ann Emerg Med*. 1990;19(12):1462-1468.



22. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28(3):509-518.
23. Herzog TJ, Armstrong DK, Brady MF, et al. Ovarian cancer clinical trial endpoints: Society of Gynecologic Oncology white paper. *Gynecol Oncol*. 2014;132(1):8-17.
24. McKee AE, Farrell AT, Pazdur R, Woodcock J. The role of the U.S. Food and Drug Administration review process: clinical trial endpoints in oncology. *Oncologist*. 2010;15 Suppl 1:13-18.
25. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014;32(12):1277-1280.
26. Critical role of phase I clinical trials in cancer treatment. American Society of Clinical Oncology. *J Clin Oncol*. 1997;15(2):853-859.
27. Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. *J Clin Oncol*. 2000;18(3):684-692.
28. Frei E, 3rd. Clinical trials of antitumor agents: experimental design and timeline considerations. *Cancer J Sci Am*. 1997;3(3):127-136.
29. Hansen AR, Graham DM, Pond GR. Phase 1 trial design: Is 3 + 3 the best? *Cancer Control*. 2014;21(3):200-208.
30. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. *N Engl J Med*. 2005;352(9):895-904.
31. Koyfman SA, Agrawal M, Garrett-Mayer E, et al. Risks and benefits associated with novel phase 1 oncology trial designs. *Cancer*. 2007;110(5):1115-1124.
32. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst*. 2009;101(10):708-720.
33. Roberts TG, Jr., Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. *JAMA*. 2004;292(17):2130-2140.
34. Simon R.M. Autologous stem cell transplantation. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and practice of oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:704-722.
35. Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. *J Clin Oncol*. 2013;31(14):1785-1791.
36. Cheung YK, Chappell R. A simple technique to evaluate model sensitivity in the continual reassessment method. *Biometrics*. 2002;58(3):671-674.
37. Normolle D, Lawrence T. Designing dose-escalation trials with late-onset toxicities using the time-to-event continual reassessment method. *J Clin Oncol*. 2006;24(27):4426-4433.
38. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics*. 1990;46(1):33-48.
39. Iasonos A, O'Quigley J. Design considerations for dose-expansion cohorts in phase I trials. *J Clin Oncol*. 2013;31(31):4014-4021.
40. Manji A, Brana I, Amir E, et al. Evolution of clinical trial design in early drug development: systematic review of expansion cohort use in single-agent phase I cancer trials. *J Clin Oncol*. 2013;31(33):4260-4267.
41. Mahipal A, Nguyen D. Risks and benefits of phase 1 clinical trial participation. *Cancer Control*. 2014;21(3):193-199.

## **ONCOLOGY PRACTICE MANAGEMENT**

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### **LEARNING OBJECTIVES**

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Evaluate oncology pharmacy services for compliance with established regulations, professional practice standards, and procedures for handling, administration, and disposal of hazardous drugs.
2. Select quality-improvement activities that enhance the safety and effectiveness of the medication-use process in oncology patient care.
3. Explain national accreditation and federal regulatory requirements for the care of cancer patients receiving chemotherapy or other hazardous drugs.
4. Explain medication reimbursement and patient assistance programs to optimize drug availability for oncology patients.
5. Evaluate policies and procedures related to conducting research involving investigational drugs, including drug management in patients with cancer.

## CLINICAL PRACTICE AND REGULATORY STANDARDS

### Question #1:

Which of the following is most correct about the standards set forth in USP<800>?

- a. The term “must” indicates a requirement and “should” indicates a recommendation
- b. Only applies in hospital settings
- c. Outlines requirements for medical surveillance for health care workers handling hazardous drugs for the first time
- d. Recommendations mirror those in USP<797>

- A. **Annotated summary of Hazardous Drugs – Handling in Healthcare Settings USP Chapter <800>.<sup>2</sup> Compliance is required effective December 1, 2019.** Recommendations – “must” is used to denote a requirement; “should” indicates a generally acceptable recommendation

I.

- B. Introduction and Scope:

1. Describes practice and quality standards for handling HDs, promoting patient safety, worker safety and environmental protection. Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and non-sterile hazardous products and preparations.
2. Applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs including pharmacies, hospitals, other healthcare institutions, patient treatment clinics, physicians’ practice facilities, veterinary offices. Personnel impacted include but are NOT limited to pharmacists, pharmacy technicians, nurses, physicians, physician assistants, home healthcare workers, veterinarian, and veterinary technicians.
3. Occupational safety plan must include:
  - a. A list of HDs
  - b. Facility and engineering controls
  - c. Competent personnel
  - d. Safe work practices
  - e. Proper use of appropriate PPE
  - f. Policies for HD waste segregation and disposal

- C. List of HDs

1. The National Institute for Occupational Safety (NIOSH) maintains a list of antineoplastic and other HDs used in healthcare. Facilities must maintain a list of HDs which are present and on-site, which must include any items on the current NIOSH list that the entity handles. This list must be reviewed at least every 12 months. Newly approved

agents or investigational drugs must be considered for addition to the list if potentially hazardous based on NIOSH criteria.

#### Answers to Question #1

Choice A is correct because the nomenclature consistently utilized by USP <800> for requirements is “must” and for recommendations is “should”.

Choice B is incorrect because while USP<800> is enforceable in hospitals, it also enforceable in other non-hospital treatment settings such as physician-owned ambulatory infusion centers.

Choice C is incorrect because USP <800> outlines recommendations for surveillance for healthcare professionals handling hazardous drugs but the recommendations are not requirements.

Choice D is incorrect because the standards set forth in USP<800> have been removed from the updated USP<797> chapter.

#### Question #2:

Which of the following best summarizes the requirements for maintaining a hazardous drug list per USP<800>??

- a. The institution can opt out of maintaining a HD list if they have a low volume of chemotherapy patients
- b. The institution is required to prepare a HD list and update it annually
- c. The HD list must mirror the NIOSH list exactly
- d. Investigational agents are exempt from the institutional HD list

#### Comparison of 2014 2016 NIOSH and 1990 ASHP Definitions of Hazardous Drugs<sup>1</sup>

\*\*\*Drugs are defined as hazardous if they meet one of the criteria in the table below.

<u>NIOSH</u>	<u>ASHP</u>
Carcinogenicity	Carcinogenicity in animal models, in the patient population, or both as reported by the International Agency for Research on Cancer.
Teratogenicity or other developmental toxicity*	Teratogenicity in animal studies or in treated patients.
Reproductive toxicity*	Fertility impairment in animal studies or in treated patients.
Organ toxicity at low doses*	Evidence of serious organ or other toxicity at low doses in animal models or treated patients.
Genotoxicity**	Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems).
Structure and toxicity profile of new drugs that mimic existing drugs determined hazardous by the above criteria	

## Containment Requirements

- Drugs on the NIOSH list that must follow the requirements in the chapter include:
  - Any HD API (active pharmaceutical ingredient)
  - Any antineoplastic requiring HD manipulation
- Drugs on the NIOSH list that do not have to follow all the containment requirements of this chapter if an assessment of risk is performed and implemented include:
  - Final dosage forms of compounded HD preparations and conventionally manufactured HD products, including antineoplastic dosage forms that do not require any further manipulation other than counting or repackaging (unless required by the manufacturer)
- For dosage forms of other HDs on the NIOSH list, the entity may perform an assessment of risk to determine alternative containment strategies and work practices.

2. Some dosage forms of HDs may not constitute a significant risk of direct occupational exposure (e.g., tablets or capsules – solid, intact medications that are administered to patients without modifying the formulation). However, dust from tablets and capsules may present a risk of exposure by skin contact and/or inhalation. If an assessment of risk is not performed, all HDs must be handled with all containment strategies defined in this chapter.
  3. Assessment of risk for above intact dosage forms (must be reviewed annually):
    - a. Type of HD (e.g., antineoplastic, non-antineoplastic, reproductive risk only)
    - b. Dosage form
    - c. Risk of exposure
    - d. Packaging
    - e. Manipulation
- D. Types of Exposure
1. HD exposure routes: dermal and mucosal absorption, inhalation, injection, and ingestion (e.g., contaminated foodstuffs, spills, or mouth contact with contaminated hands). Containers of HDs have been shown to be contaminated upon receipt. Both clinical and nonclinical personnel at risk.

### Examples of Potential Opportunities of Exposure Based on Activity

Activity	Potential Opportunity of Exposure
Receipt	Contacting HD residue present on drug containers, individual dosage units, outer containers, work surfaces, or floors
Dispensing	Counting or repackaging tablets and capsules
Compounding and other manipulations	Crushing or splitting tablets or opening capsules Pouring oral or topical liquids from one container to another Weighing or mixing components Constituting or reconstituting powdered or lyophilized HDs Withdrawing or diluting injectable HDs from parenteral containers Expelling air or HDs from syringes Contacting HD residue present on PPE or other garments Deactivating, decontaminating, cleaning, and disinfecting areas contaminated with or suspected to be contaminated with HDs Maintenance activities for potentially contaminated equipment and devices
Administration	Generating aerosols during administration of HDs by various routes (e.g., injection, irrigation, oral, inhalation, or topical application) Performing certain specialized procedures (e.g., intraoperative intraperitoneal injection or bladder instillation) Priming an IV administration set
Patient-care activities	Handling body fluids (e.g., urine, feces, sweat, or vomit) or body-fluid contaminated clothing, dressings, linens, and other materials
Spills	Spill generation, management, and disposal
Transport	Moving HDs within a healthcare setting
Waste	Collection and disposal of hazardous waste and trace contaminated waste

### Answers to Question #2:

**Choice B is correct because USP<800> specifies the requirement for creating an institutional HD list and ensuring that it is updated at least annually.**

**Choice A is incorrect because institutions are required to maintain a HD list regardless of their volume of chemotherapy dispensed.**

**Choice C is incorrect because institutions are provided flexibility to deviate from the NIOSH list of hazardous drugs based on their own internal risk assessment of individual drugs as potential HDs.**

**Choice D is incorrect because investigational agents should undergo a risk assessment to determine if they should be classified as an HD.**

**Question #3:**

**Which is the most appropriate setting for admixing HD compounded sterile products (CSPs)?**

- a. BSC (biologic safety cabinet) in a positive pressure room
- b. BSC in a negative pressure room
- c. LAFW (laminar air flow workbench) in a positive pressure room
- d. LAFW in a negative pressure room

E. Responsibilities of Personnel Handling HDs

- 1. A responsible person who is qualified and trained must be designated for USP 800 compliance and ongoing monitoring.
- 2. All personnel who handle HDs are responsible for understanding risks associated with handling HDs and compliance with institutional standards for safety and compliance.

F. Facilities and Engineering Controls

- 1. Signage must be present for areas where HDs are handled, and access limited to authorized personnel. HD handling areas must not be proximal to breakrooms and refreshment areas for personnel, patients, or visitors.
- 2. Designated areas must be available for:
  - a. Receipt, unpacking and storage of HDs
  - b. Sterile and nonsterile HD compounding
- 3. Negative pressure engineering controls are required for compounding /manipulating areas for sterile and nonsterile HDs
- 4. Receipt: Unpacking must take place in an area that is neutral/normal or negative pressure relative to the surrounding areas and not in sterile areas.
- 5. Storage: HDs must be stored in a manner that prevents spillage or breakage if the container fails. No storage of HDs on the ~~floor~~-floor. HDs must be stored in an externally ventilated, negative pressure room with at least 12 air exchanges per hour (ACPH). Non-antineoplastic, reproductive risk only and final dosage forms of antineoplastic HDs may be stored with other inventory. Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH.
- 6. Containment:

- A containment primary engineering control (C-PEC) is a ventilated device designed to minimize worker and environmental HD exposure when directly handling HDs. The containment secondary engineering control (C-SEC) is the room in which the C-PEC is placed. Supplemental engineering controls (e.g., CSTD) are adjunct controls to offer additional levels of protection.
- When compounding HD preparations in a C-PEC, a plastic-backed preparation mat should be placed on the work surface of the C-PEC. The mat should be changed immediately if a spill occurs and regularly during use and should be discarded at the end of the daily compounding activity.
- For entities that compound both nonsterile and sterile HDs, the respective C-PECs must be placed in separate rooms, unless ISO 7 classification for the room is maintained. If the C-PECs used for sterile and nonsterile compounding are placed in the same room, they must be kept 1 meter apart.
- Engineering control specifications for non-sterile and sterile compounding can be found in table below.

#### Engineering Controls for Nonsterile HD Compounding

C-PEC	C-SEC Requirements
Externally vented (preferred) or redundant-HEPA filtered in series  Examples: CVE (Containment Ventilated Enclosure, Class I or II BSC, CACI	Externally vented  12 ACPH  Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas  Surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets must be smooth, impervious, and non-shedding

#### Engineering Controls for Sterile HD Compounding

Configuration	C-PEC	C-SEC	Maximum BUD
<b>ISO Class 7 buffer room with an ISO 7 anteroom</b>	Externally vented  Examples: Class II BSC or CACI	Externally vented  30 ACPH  Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in <797>
<b>Unclassified C-SCA (containment segregated compounding area)</b>	Externally vented  Examples: Class II BSC or CACI	Externally vented  12 ACPH  Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in <797> for CSPs prepared in a segregated compounding area



**Answers to Question #3:**

**Choice B is correct because USP<800> defines the requirement for HD CSPs to be prepared in a BSC externally vented in a negative pressure environment.**

**Choice A is incorrect because HD CSP must never be conducted in a positive pressure environment.**

**Choice C is incorrect because a LAFW is never appropriate for compounding HD CSPs nor is a positive pressure environment.**

**Choice D is incorrect because a LAFW is never appropriate for compounding HD CSPs.**

7. Sink: A hand-washing sink must be placed in the anteroom at least 1 meter from the entrance to the HD buffer room to avoid contamination migration into the negative pressure HD buffer room.
  8. Containment segregated compounding area (C-SCA): The C-PEC is placed in an unclassified C-SCA that has fixed walls, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas, and a minimum of 12 ACPH that is externally ventilated. A hand-washing sink must be placed at least 1 meter from the C-PEC.
  9. Containment Supplemental Engineering Controls: Containment supplemental engineering controls, such as CSTDs, provide adjunct controls to offer an additional level of protection during compounding or administration.
    - a. Until a published universal performance standard for evaluation of CSTD containment is available, users should carefully evaluate the performance claims associated with available CSTDs based on independent, peer-reviewed studies and demonstrated containment reduction.
    - b. A CSTD **must** not be used as a substitute for a C-PEC when compounding. CSTDs **should** be used when compounding HDs when the dosage form allows. CSTDs **must** be used when administering antineoplastic HDs when the dosage form allows. CSTDs known to be physically or chemically incompatible with a specific HD must not be used for that HD.
- G. Environmental Quality and Control
1. Environment wipe sampling for HD surface residue **should** be performed routinely (e.g., initially as a benchmark and at least every 6 months). Surface wipe sampling should include:
    - a. Interior of the C-PEC and equipment contained in it
    - b. Pass-through chambers
    - c. Surfaces in staging or work areas near the C-PEC
    - d. Areas adjacent to C-PECs (e.g., floors directly under C-PEC, staging, and dispensing area)
    - e. Areas immediately outside the HD buffer room or the C-CSA
    - f. Patient administration areas
  2. There is currently no standard for acceptable limits for HD surface contamination. Common marker HDs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, fluorouracil, and platinum-containing drugs. An example of measurable contamination would be cyclophosphamide levels  $>1.00 \text{ ng/cm}^2$ , which were shown in

some studies to result in uptake of the drug in exposed workers. Any measurable contamination must be contained. Repeat the wipe sampling to validate that mitigation steps have been effective.

**Question #4:**

**According to USP<800>, which of the following is most correct regarding PPE requirements?**

- a. ~~Double-gloving~~Double gloving is required only for compounding of HDs
- b. Laminate coated gowns are only required for administration of HDs
- c. Eye and face protection is required when working outside of a C-PEC or at eye level with HDs
- d. PPE that has not been subject of a spill event is not required to be disposed of as hazardous waste

**H. Personal Protective Equipment**

1. Additional PPE may be required for treating a patient or cleaning a spill. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE use.
2. Gowns, head, hair, and shoe covers, and two pair of chemotherapy gloves are required for compounding sterile and nonsterile HDs. Two pairs of chemotherapy gloves are required when administering antineoplastic HDs. Gowns shown to resist permeability by HDs are required when administering injectable antineoplastic HDs. For all other activities, the entity's SOP must describe the appropriate PPE to be worn based on its occupational safety plan and assessment of risk (if used).
3. Appropriate PPE must be worn during all phases of handling HDs from receipt to administration. Deactivation, cleaning, disinfecting, spill control and waste disposal are included in the phases of handling for HDs.
4. Gloves: When chemotherapy gloves are required, they must meet American Society for Testing and Materials (ASTM) standard D6978 (or its successor). Chemotherapy gloves should be worn for handling all HDs including non-antineoplastics and for reproductive risk only HDs. Chemotherapy gloves must be powder-free and be inspected for physical defects before use. When used for sterile compounding, the outer chemotherapy gloves must be sterile. Chemotherapy gloves should be changed every 30 minutes unless otherwise recommended by the manufacturer's documentation and must be changed when torn, punctured, or contaminated. Hands must be washed with soap and water after removing gloves.
5. Gowns: When gowns are required, they must be disposable and shown to resist permeability by HDs. Disposable gowns made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials. Gowns must close in the back (i.e., no open front), be long sleeved, and have closed cuffs that are elastic or knit. Gowns must not have seams or closures that could allow HDs to pass through. Cloth laboratory coats, surgical scrubs, isolation gowns, clothing or other absorbent material are not appropriate outer wear when handling HDs because they permit the permeation of HDs and can hold spilled drugs against the skin. Washing of non-disposal clothing contaminated with HD residue should only be done according to facility policy as drug residue may be transferred to other clothing. Potentially contaminated clothing must not be taken home under any circumstances. Gowns must be changed per the manufacturer's information for permeation of the gown. If no permeation information is available for the gowns used, change them every 2 to 3 hours or immediately after a spill or splash. Gowns worn in HD handling areas must not be worn to other areas outside of the HD handling areas. Head, hair, shoe, and

sleeve covers: Head and hair covers (including beard and moustache, if applicable), shoe covers, and sleeve covers provide protection from contact with HD residue. When compounding HDs, a second pair of shoe covers must be donned before entering the C-SEC and doffed when exiting the C-SEC. Shoe covers worn in HD handling areas must not be worn to other areas. Disposable sleeve covers may be used to protect areas of the arm that may come in contact with HDs. Disposable sleeve covers made of polyethylene-coated polypropylene or other laminate materials offer optimal protection.

6. Eye and face protection: Appropriate eye and face protection must be worn when there is a risk for spills and splashes of HDs when working outside of a C-PEC (e.g., administration in the surgical suite, working at or above eye level, or cleaning a spill). A full-facepiece respirator provides eye and face protection. Face shields in combination with goggles provide a full range of protection against splashes to the face and eyes.
7. Respiratory protection: Personnel who are unpacking HDs that are not contained in plastic should wear an elastomeric half-mask with a multi-gas cartridge and P100-filter until assessment of the packaging integrity can be made to ensure no breakage or spillage occurred during transport. Surgical masks do not provide respiratory protection from drug exposure and must not be used when respiratory protection from HD exposure is required. A surgical N95 respirator provides the respiratory protection of an N95 respirator, and like a surgical mask provides a barrier to splashes, droplets, and sprays around the nose and mouth. For most activities requiring respiratory protection, a fit-tested NIOSH-certified N95 or more protective respirator is sufficient to protect against airborne particles. However, N95 respirators offer no protection against gases and vapors and little protection against direct liquid splashes (see the Centers for Disease Control and Prevention's (CDC's) Respirator Trusted-Source Information). An appropriate full-facepiece, chemical cartridge-type respirator or powered air-purifying respirator (PAPR) should be worn when there is a risk of respiratory exposure to HDs, including when:
  - a. Attending to HD spills larger than what can be contained by a spill kit
  - b. Deactivating, decontaminating, and cleaning underneath the work surface of a C-PEC
  - c. There is known or suspected airborne exposure to powders or vapors
8. Disposal of Used Personal Protective Equipment: Consider all PPE worn when handling HDs to be contaminated with, at minimum, trace quantities of HDs. PPE must be placed in an appropriate waste container and further disposed of per local, state, and federal regulations. PPE worn during compounding should be disposed of in the proper waste container before leaving the C-SEC or contained in a sealable bag for discarding outside of the C-PEC. Chemotherapy gloves and sleeve covers (if used) worn during compounding must be carefully removed and discarded immediately into a waste container approved for trace contaminated waste inside the C-PEC or contained in a sealable bag for discarding outside the C-PEC.

- I. Hazard Communication Program
  - 1. SOP s for training regarding proper labeling, transport, storage, and disposal of the HDs and use of Safety Data Sheets (SDS).
  - 2. Hazard communication program:
    - a. Written standards
    - b. Containers of HDs must be labeled
    - c. SDS for all HDs
    - d. SDS are readily available
    - e. Staff potentially exposed to HDs must receive training prior to handling them
    - f. Written consent from personnel of reproductive capability to handle HDs
- J. Personnel Training
  - 1. HDs used on site and associated risks
  - 2. SOP's related to handling of HDs
  - 3. PPE use
  - 4. Proper use of equipment and devices (e.g., C-PEC)
  - 5. SOP for HD exposure for staff members
  - 6. Spill management
  - 7. Management of hazardous waste
- K. Receiving
  - 1. The entity must establish SOPs for receiving HDs. HDs should be received from the supplier impervious plastic to segregate them from other drugs and to allow for safety in the receiving and internal transfer process. HDs must be delivered to the HD storage area immediately after unpacking. PPE, including chemotherapy gloves, must be worn when unpacking HDs (see Personal Protective Equipment). A spill kit must be accessible in the receiving area.
  - 2. The entity must enforce policies that include a tiered approach, starting with visual examination of the shipping container for signs of damage or breakage (e.g., visible stains from leakage, sounds of broken glass). Table below summarizes the steps for receiving and handling of damaged shipping containers.

### Summary of Requirements for Receiving and Handling Damaged HD Shipping Containers

If the shipping container appears damaged	<p>Seal the container without opening and contact the supplier</p> <p>If the unopened package is to be returned to the supplier, enclose the package in an impervious container and label the outer container “Hazardous”</p> <p>If the supplier declines return, dispose of hazardous waste</p>
If a damaged shipping container must be opened	<p>Seal the container in plastic or an impervious container</p> <p>Transport it to a C-PEC and place on a plastic-backed preparation mat</p> <p>Open the package and remove undamaged items</p> <p>Wipe the outside of the undamaged items with a disposable wipe</p> <p>Enclose the damaged item(s) in an impervious container and label the outer container “Hazardous”</p> <p>If the supplier declines return, dispose of as hazardous waste</p> <p>Deactivate, decontaminate, and clean the C-PEC (See Deactivating, Decontaminating, Cleaning and Disinfecting below) and discard the mat and cleaning disposables as hazardous waste</p>

3. Damaged packages or shipping cartons must be considered spills that must be reported to the designated person and managed according to the entity’s SOP.
- L. Beyond Use Dating, Labeling, Packaging, Transport and Disposal
1. The entity must establish SOPs for the labeling, packaging, transport, and disposal of HDs. The SOPs must address prevention of accidental exposures or spills, personnel training on response to exposures, and use of a spill kit.
  2. Beyond Use Dating (more detailed discussion in the USP<797> section that follows): HD CSPs prepared in an ISO Class 7 buffer room with an ISO Class 7 anteroom may use the BUDs described in <797>, based on the categories of CSP, sterility testing, and storage temperature.
  3. Labeling: HDs must always be clearly labeled during their transport.
  4. Packaging: Personnel must select and use packaging containers and materials that will maintain physical integrity, stability, and sterility (if needed) of the HDs during transport.
  5. Transport: HDs that need to be transported must be labeled, stored, and handled in accordance with applicable federal, state, and local regulations. HDs must be transported in containers that minimize the risk of breakage or leakage. Pneumatic tubes must not be used to transport any liquid HDs or any antineoplastic HDs because of the potential for breakage and contamination.

6. Disposal: Disposal of all HD waste, including, but not limited to, unused HDs and trace-contaminated PPE and other materials, must comply with all applicable federal, state, and local regulations.
- M. Dispensing Final Dosage Forms
1. HDs that do not require any further manipulation, other than counting or repackaging of the final dosage forms, may be prepared for dispensing without any further requirements for containment unless required by the manufacturer or if visual indicators of HD exposure hazards are present (e.g., HD dust or leakage).
  2. Counting or repackaging of HDs must be done carefully. Clean equipment should be dedicated for use with HDs and should be decontaminated after every use. Tablet and capsule forms of antineoplastic HDs must not be placed in automated counting or packaging machines, which subject them to stress and may create powdered contaminants.
- N. Compounding
1. Standards for USP<795> and <797> must be followed.
  2. When compounding in a C-PEC, a plastic-backed preparation mat should be placed on the work surface of the C-PEC.
  3. Change the mat with each spill and regularly during use, discard at the end of each day.
  4. Disposable or clean equipment for compounding (e.g., mortar, pestles, and spatulas) must be dedicated for use with HDs.
  5. Bulk containers of liquid and API HD must be handled carefully to avoid spills. APIs and powdered HDs must be handled in a C-PEC to protect against occupational exposure, especially during particle generating activities (e.g., crushing tablets, opening capsules, or weighing powder).
- O. Administering
1. HDs must be administered safely using protective medical devices and techniques. Examples of protective medical devices include needleless and closed systems. Examples of protective techniques include spiking and priming of IV tubing with a non-HD solution in a C-PEC and crushing tablets in a plastic pouch.
  2. Appropriate PPE must be worn when administering HDs.
  3. CSTDs must be used for administration of antineoplastic HDs when the dosage form allows.
  4. Healthcare personnel should avoid manipulating HDs such as crushing tablets or opening tablets if possible.

**Answers to Question #4:**

Choice A is incorrect because USP<800> requires use of ~~double-gloving~~ **double gloving** for handling activities of HDs beyond compounding such as administration.

Choice B is incorrect because laminate gowns are required for activities beyond administration such as dispensing.

Choice C is correct because USP<800> requires eye and face protection only for specialized procedures that may induced splashing or risk of HDs infiltrating the eyes.

Choice D is incorrect because all PPE must be discarded as hazardous waste following HD handling activities.

- P. Deactivating, Decontaminating, Cleaning and Disinfecting
1. All areas where HDs are handled and all reusable equipment and devices must be deactivated, decontaminated, and cleaned. Additionally, sterile compounding areas and devices must be subsequently disinfected.
  2. The entity must establish written procedures for decontamination, deactivation, and cleaning, and for sterile compounding areas disinfection. Written procedures for cleaning must include procedures, agents used, dilutions (if used), frequency, and documentation requirements.
  3. All personnel who perform deactivation, decontamination, cleaning, and disinfection activities in HD handling areas must be trained in appropriate procedures to protect themselves and the environment from contamination. All personnel performing these activities must wear appropriate PPE.
  4. The deactivating, decontaminating, cleaning, and disinfecting agents selected must be appropriate for the type of HD contaminant(s), location, and surface materials. The products used must be compatible with the surface material.

**Cleaning Steps:**

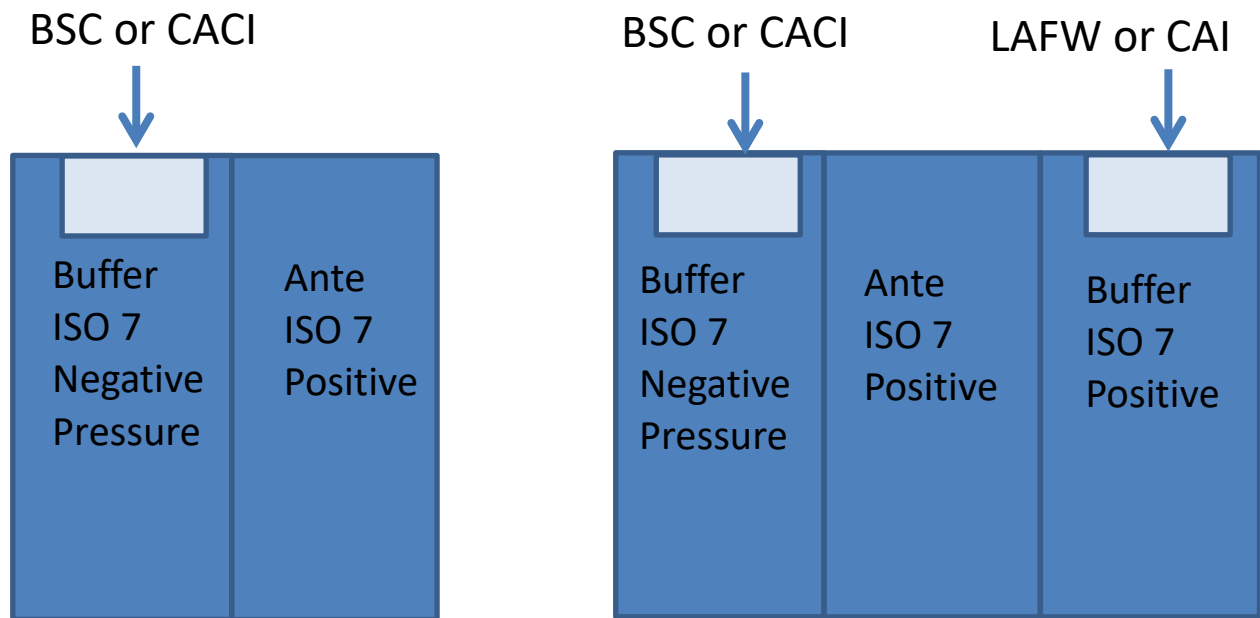
Cleaning Step	Purpose	Example Agents
Deactivation	Render compound inert or inactive	As listed in the HD labeling or other agents which may incorporate Environmental Protection Agency (EPA)-registered oxidizers (e.g., peroxide formulations, sodium hypochlorite, etc.)
Decontamination	Remove HD residue	Materials that have been validated to be effective for HD decontamination, or through other materials proven to be effective through testing, which may include alcohol, water, peroxide, or sodium hypochlorite
Cleaning	Remove organic and inorganic material	Germicidal detergent
Disinfection	Destroy microorganisms	EPA-registered disinfectant and/or sterile alcohol as appropriate for use

5. Deactivation: Renders a compound inert or inactive. Residue from deactivation must be removed by decontaminating the surface. There is not one proven method for deactivating all compounds. The goal should be complete surface decontamination. Damage to surfaces is exhibited by corrosion to stainless steel surfaces caused by sodium hypochlorite if left untreated.
6. Decontamination: Occurs by inactivating, neutralizing, or physically removing HD residue from non-disposable surfaces and transferring it to absorbent, disposable materials (e.g., wipes, pads, or towels) appropriate to the area being cleaned. It is imperative to adhere to manufacturer's use instructions. The work surface of the C-PEC must be decontaminated between compounding of different HDs. The C-PEC must be decontaminated at least daily (when used), any time a spill occurs, before and after certification, any time voluntary interruption occurs, and if the ventilation tool is moved. C-PECs may have areas under the work tray where contamination can build up. These areas must be deactivated, decontaminated, and cleaned at least monthly to reduce the decontamination level in the C-PEC.
7. Cleaning: Cleaning agents used on compounding equipment should not introduce microbial contamination. No cleaning step may be performed when compounding activities are occurring.
8. Disinfection: Disinfection must be done for areas intended to be sterile, including the sterile compounding areas after adequate cleaning.

Q. Spill Control



1. All personnel who may be required to clean up a spill of HDs must receive proper training in spill management and the use of PPE and NIOSH-certified respirators (see Personal Protective Equipment). Spills must be:
  - a. Contained and cleaned immediately only by qualified personnel with appropriate PPE who are available at all times
  - b. Appropriate signage for restricting access to the spill area.
  - c. Spill kits containing all the materials needed to clean HD spills must be readily available in all areas where HDs are routinely handled.
- b. All spill materials must be disposed of as hazardous.
  - a. The circumstances and management of spills must be documented. Develop SOPs for exposed staff members or patients/visitors for medical evaluation.
  - b. SOPs must be developed to prevent spills and to direct the clean-up of HD spills.
- R. Documentation and Standard Operating Procedures
  1. The entity must maintain SOPs for the safe handling of HDs for all situations in which these HDs are used with review of these SOPs every 12 months.
  2. The SOPs for handling of HDs should include:
    - a. Hazard communication program
    - b. Occupational safety program
    - c. Receipt
    - d. Storage
    - e. Compounding
    - f. Maintenance and use of proper engineering controls (e.g., C-PECs, C-SECs, and CSTDs)
    - g. Hand hygiene and use of PPE based on activity (e.g., receipt, transport, compounding, administration, spill, and disposal)
    - h. Deactivation, decontamination, cleaning, and disinfection
    - i. Dispensing
    - j. Transport
    - k. Administration
    - l. Environmental monitoring (e.g., wipe sampling)
    - m. Disposal
    - n. Spill control
    - o. Medical surveillance
  3. Document their training according to OSHA standards (see OSHA standard 1910.120 Hazardous Waste Operations and Emergency Response)
- S. Medical Surveillance (Recommendations only)
  1. Documentation of any exposure of potentially health-related changes due to HD exposure
  2. Population health analysis of workers who handle HDs
  3. Baseline evaluation of workers health and potential risk to health secondary to HD exposure
  4. Plan for HD surveillance embedded in HR policies
  5. Follow-up plan
- T. Examples of Designs for Hazardous Drug Compounding Areas



## II. ASHP Guidelines for Hazardous Drug Handling – updated in 2018

### U. Purpose

1. Provide updates regarding new and continuing concerns for health care workers handling hazardous drugs (HDs)
2. Provide information on recommendations and requirements, including those regarding controls and equipment, for handling and compounding HDs.
3. Newer studies demonstrate that contamination is widespread in healthcare settings and that more workers than previously thought are exposed. These recommendations extend to any areas where HDs are received, stored, prepared, administered, or disposed.

### V. Background

1. Routes of exposure:
  - a. Entry of hazardous drugs through inhalation, accidental injection, ingestion of contaminated food or mouth contact with contaminated hands.
  - b. Dermal contact with contaminated surfaces is the primary route of exposure to HDs
2. Hazard Assessment – two components:
  - a. Identification – qualitative evaluation of the toxicity of a given drug
  - b. Exposure assessment – the amount of worker contact with the drug
  - c. NIOSH and USP<800> assessment of risk ~~are~~is supported by ASHP

### W. HDs as Sterile Preparations

1. USP<797> outlines sterile product preparation guidelines
  2. USP<800> describes containment strategies and engineering controls
- X. Recommendations – “must” is used to denote a requirement; “should” indicates a generally acceptable recommendation
1. Safety Program (Specific details for USP<800> standards are outlined in the discussion section for USP<800>)
    - a. Comprehensive program for managing hazardous drugs must apply to all aspects of use throughout the facility and be a product of collaboration between pharmacy, nursing, medical staff, environmental services, transportation, facilities, employee health, risk management, clinical laboratories, and safety/security.
    - b. ASHP endorses facilities selecting a designated person to overseeing compliance with USP<800> standards
    - c. Ready access to Safety Data Sheets (SDS) (formerly Material Safety Data Sheets) for all staff is imperative. SDS sheets define appropriate handling precautions, necessary protective equipment, and spill management for individual drugs.
    - d. ASHP endorses maintenance of a list of all hazardous chemicals (drugs) in the workplace as part of the written hazard communication program per USP<800>
    - e. ASHP endorses annual training for employees handling HDs per USP<800> standards
    - f. Labels for HDs should clearly indicate that safe handling precautions are required during transport, storage, and use.
    - g. Outside of vials for HDs should be expected to be contaminated – this includes the package inserts and inside of the packing cartons. This impacts any staff member receiving shipping containers and repackaging drug product.
    - h. Manufacturer packing should be labeled with a distinctive identifier that notifies personnel receiving them to wear appropriate personal protective equipment (PPE) while handling. PPE provides workers protection to reduce exposure to HD aerosols and residues.
    - i. ASHP endorses the standard operating procedures (SOP) for handling and the return of damaged cartons or containers of HDs and policies and procedures for labeling, packaging, and transport of HDs per USP<800> standards.
  2. Labeling, Packaging, Storing and Transport of HDs from Point of Receipt
    - a. ASHP endorses the USP<800> standards for drug packages, bins, shelves, and storage areas for HDs must bear distinctive labels for identifying special handling precautions.
    - b. ASHP endorses USP<800> procedures for unpacking HDs listed as antineoplastic HDs on the NIOSH HD list and all HD active pharmaceutical ingredients (APIs) and processing damaged shipping containers.
    - c. ASHP endorses USP<800> procedures for ensuring availability of spill kits and use of respirators when appropriate.

- d. ASHP endorses USP<800> standards for segregation of HD stock from other drug inventory and overall drug storage recommendations. Consider “look-alike, sound-alike” drugs when organizing stock and label accordingly.
- e. ASHP endorses uses of PPE as outlined in USP<800> and by NIOSH.
- f. Carts and transport devices should be designed with guards to protect against falling and breakage of a HD package.
- g. Individuals transporting HDs must have safety training that includes spill control and have spill kits readily available.

### 3. Environment

- a. HDs should be compounded in a controlled area where access is limited to authorized personnel trained in handling requirements.
- b. Sterile and non-sterile HDs must be compounded in environments that have a negative pressure relative to all adjacent areas. Nurses who administer HDs and care for patients receiving chemotherapy should meet the requirements of the Oncology Nursing Society (ONS) position statement on administration
- c. During administration, access to the administration areas should be limited to patient receiving therapy and essential personnel. Eating, drinking, applying makeup and the presence of food should be avoided while HDs are being administered.
- d. For inpatient units, administering HDs should be coordinated to avoid exposure of family members visiting a patient, and arrival of dietary trays.
- e. For outpatient infusion clinics, care should be taken to minimize environmental contamination and maximize effectiveness of decontamination procedures.
- f. Design of areas where HDs are administered must include surfaces that are readily cleaned and decontaminated – avoid carpeted and upholstered surfaces.
- g. Administration of hazardous medications in unique treatment settings such as the operating rooms requires specialized procedures to prevent contamination and provide training to staff. Spill kits, containment bags, and hazardous drug disposal containers must be available in all areas where HDs are handled.
- h. Techniques and ancillary devices which minimize the risk of open systems should be used when administering HDs through unusual routes or in nontraditional locations. All staff handling HDs should receive safety training that includes recognition of HDs and appropriate spill response.

### 4. Ventilation Controls

- a. ASHP endorses **ALL** the engineering/ventilation controls for compounding sterile and non-sterile HDs outlined in USP<800>
- b. Class II BSCs have limitations wherein contamination with HDs has been shown in HD work areas and in urine of healthcare workers that handle HDs. Studies unequivocally show that HD contamination is present on the outside of vials from the manufacturers of HD drugs, work practices to maximize the effectiveness of the Class II BSC are not rigorously followed, and the potential vaporization of HD can all

place healthcare workers at risk. Class II BSCs do not eliminate contamination within the workspace of the BSC and effectiveness of the cabinet depends on the operator's use of proper technique and strict adherence to policies and procedures.

- c. Class II BSC types A2, B1 or B2 are acceptable under USP <800> for compounding sterile HDs. Most Class II BSCs recirculate contaminated air within the cabinet through HEPA filters which may NOT trap all HDs. Specifics on the use of Class II BSCs are listed in Appendix B of the Guidelines.
- d. Class III BSC is a totally enclosed, ventilated cabinet of leak-tight construction. The cabinet is maintained under negative pressure with the supply air drawn into the cabinet through HEPA filtration and exhaust air treated with double HEPA filtration. These cabinets are not exhausted through the general exhaust system. This equipment is typically reserved for highly infectious or toxic material and seldom used for extemporaneous compounding of sterile products because of the high cost.
- e. CACI is a form of compounding isolator specifically designed for compounding pharmaceutical ingredients or preparations that provides worker protection from exposure to undesirable levels of airborne drug the compounding and material transfer processes and to provide an aseptic environment with unidirectional airflow for compounding sterile preparations. For compounding sterile preparations, the filtered air and airflow must achieve an ISO class 5 environment within the CACI. CACI must be continuously monitored for leaks in the gloves and in the fixed glove assembly. CACIs do not prevent the generation of contamination within the cabinet workspace and their effectiveness in containing contamination depends on proper technique.
- f. The totally enclosed design of isolators may reduce the escape of contaminants during the compounding process and be less responsive to environmental drafts. However, isolators do not prevent generation of contamination within the cabinet workspace and there still exists the risk of drug contamination from the main cabinet to the pass-through.
- g. Isolators that discharge air into the workroom, even though high-efficiency filters present exposure concerns like those of unvented Class II BSCs with vaporized HDs during compounding. USP<800> requires outside exhausting of CACIs.

5. Containment Supplemental Engineering Controls

- a. Closed system drug-transfer device (CSTD) is a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system (NIOSH definition). NIOSH has NOT yet assigned a specific performance standard for CSTDs.
- b. CSTDs are designated by the FDA as Class II medical devices, not requiring premarket approval. The FDA 510(k) process does not establish independent performance for devices submitted as "substantially equivalent" nor does it test or approve these devices. FDA created the product code (ONB) for closed antineoplastic and HD reconstitution and transfer system, although applications under this code are not independently tested by the FDA. Products that are

marketed as CSTDs but have not been cleared by FDA under the product code ONB should not be considered CSTDs.

- c. Some CSTDs have been shown to limit the potential of generating aerosols and reduce HD contamination in the workplace, not all marketed CSTDs have been studied and no surrogate marker HD has been shown to be superior in measuring CSTD effectiveness.
- d. NIOSH is attempting to develop protocols to test containment performance of both the physical and barrier type of CSTD and those designed to operate using air-cleaning technologies.
- e. During administration of sterile HD product, no additional safeguards (e.g., ventilated engineering controls) exist for worker protection so USP<800> requires use of CSTDs for administration of HDs when the dosage forms allows whereas for compounding HDs the use of CSTDs is a recommendation.

6. Personnel Protective Equipment (PPE)

- a. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE for use in the healthcare setting. USP<800> requires institutions to develop their own SOPs for use of PPE when handling HDs. ASHP endorses USP<800> and NIOSH standards for PPE.

7. Work Practices

- a. Compounding Sterile HDs
  - i. Work practices differ from Class II and III BSCs and isolators
  - ii. All activities not requiring a critical environment (e.g., checking labels, dose calculations) should be done outside the BSC/isolator.
  - iii. Two pair of ASTM D6978 gloves must be worn to gather HDs and supplies.
  - iv. Fresh ASTM D6878 gloves should be donned and appropriately sanitized before aseptic manipulation. The outer pair of gloves must be sterile for sterile HD compounding.
  - v. Only supplies and drugs essential to compounding the dose or batch should be placed in the work area of the BSC or main chamber of the isolator.
  - vi. Spiking an IV set containing HDs or priming an IV set with HDs in an uncontrolled environment must be avoided. Priming the IV set with the diluent prior to adding the HD inside the C-PEC is an acceptable practice.
  - vii. CSTDs should be used if the dosage form allows when compounding sterile HDs. CSTD should achieve a dry connection between the administration set and the HD's final container. This connection allows for the container to be spiked with a secondary IV set and the set to be primed with backflow from a primary non-hazardous solution. This may be done outside of a BSC or isolator to reduce the potential for surface contamination. A new IV set must be used with each dose of HD.
  - viii. Avoid placing the IV set on the surface of the C-PEC during compounding to reduce the transfer of HD residue to the surface of the IV set.

- ix. Transport bags must never be placed in the BSC or isolator work chamber to avoid inadvertent contamination on the outer surface of the bag.
  - x. Final preparations must be surface decontaminated after compounding is complete.
  - xi. In either a BSC or isolator, clean inner gloves must be worn when labeling and placing the final preparation into the transport bag.
  - xii. Handling final preparations with contaminated gloves transfers contamination to other workers or potentially patients. Don fresh gloves whenever there is doubt as to the cleanliness of the inner or outer gloves.
8. Working in any C-PEC
- a. None of the ventilated engineering controls can provide 100% protection for the worker. The effectiveness of C-PECs in containing HD contamination depends on worker technique.
  - b. HD residue may be introduced into the workroom area via pass-throughs and airlocks.
  - c. Surface decontamination of the preparation before removal from the main chamber of an isolator is recommended with isopropyl alcohol, sterile water, peroxide, or sodium hypochlorite solutions provided that the packaging is not permeable to the solution and the labels remain intact.
  - d. In depth recommendations for working in C-PECs are listed in Appendix F of the original publication.
9. BSCs
- a. Before working in the BSC, wash hands and don PPE per USP<797> recommendations
  - b. Non-sterile D6978 gloves are appropriate for cleaning activities
  - c. BSCs use vertical flow, HEPA-filtered air (ISO class 5) as their controlled aseptic environment.
  - d. The front shield of the cabinet should be lowered to the proper level to protect the face and eyes.
  - e. All drugs and supplies should be sanitized with 70% sterile alcohol.
  - f. All items should be placed away from the front of the unfiltered air at the front of the cabinet and perform manipulations at least 6 inches away from the sidewalls of the cabinet.
  - g. Do not obstruct airflow through the front and back grilles of the BSC.
  - h. A small waste-sharps container may be placed along the sidewall towards the back of the BSC.
  - i. A plastic-backed absorbent preparation pad should be placed on the work surface of the BSC. Avoid larger pads that could obstruct airflow from the front and back grilles of the BSC. Change the mat after any spills.

- j. Equipment for HD compounding must be dedicated.
10. Class III BSCs and CACIs
- a. ASTM D6978 gloves should be worn to prepare for working in a Class III BSC or CACI. For sterile compounding, the gloves closest to the sterile preparation must be sterile.
  - b. All drugs and supplies should be sanitized with 70% sterile alcohol.
  - c. An enclosed tray with drug and supplies may be introduced into the main chamber for compounding use.
  - d. Contaminated materials are removed using the closed trash system of the unit.
  - e. A second sealable bag should be used for transport of the compounded product.
  - f. Additional work practices for cleaning off the gloves or gauntlets and final preparation are recommended.
11. Aseptic Technique
- a. When reconstituting HDs in vials, it is critical to avoid pressurizing contents of the vial which increases risk of drug aerosolization. Too much negative pressure can cause leakage from the needle when it is withdrawn from the vial.
  - b. Safe handling of HD solutions and vials or ampules requires the use of a syringe that is no more than 3/4 full when filled with the solution, to minimize the risk of plunger separating from the syringe barrel.
  - c. HDs removed from an ampule should use an appropriate filter needle or filter straw attached to a syringe large enough that it will not be more than 3/4 full.
  - d. Small volumes of diluent should be transferred slowly into the HD vial as equal volumes of air are removed.
  - e. The final preparation should be labeled, including an auxiliary warning and the injection port covered with a protective shield.
  - f. The final container should be placed, using clean gloves, into a sealable bag to contain any leakage.
12. Training and demonstration of competence
- a. OSHA and USP<800> require that all staff that will handle HDs require training.
  - b. Compounding personnel of reproductive capability must confirm in writing that they understand the risks of handling HDs.
  - c. Personnel must be trained PRIOR to handling HDs as part of their job responsibilities.
  - d. Competency must be demonstrated by an objective method and assessed every 12 months.
13. Preparation and handling of non-sterile HD dosage forms
- a. Non-sterile compounding of HD dosage forms must adhere to USP<795> and <800>



- b. USP<800> requires that compounding of non-sterile HDs take place in a C-PEC. A Class I BSC, CVE, Class II BSC or CACI may be used for this task. For occasional compounding of non-sterile ~~HDs~~HDs, a C-PEC used for sterile compounding can be utilized but must be decontaminated, cleaned and disinfected before resuming sterile compounding. A plastic-backed preparation mat should be placed on the work surface of the C-PEC. or CVE is acceptable for that task
- c. A C-PEC is not required if manipulations are limited to handling of final dosage forms. (~~counting~~Counting or repackaging of tablets or capsules).
- d. Dedicated clean ~~equipment should~~equipment should be used for compounding non-sterile HDs.
- e. Manual counting of solid medications may be problematic if, for example, repeated handling of a large container of tablets has created a loose powder or residue of tablet dust. Exposure to the dust or residue may present a risk of powder inhalation or skin contact. USP <800> notes that an assessment of risk should be conducted to determine the appropriate containment strategies for the HD tasks required of the worker.
- f. Procedures for the preparation and use of equipment (e.g., BSCs, bench-top hoods with HEPA filters) must be developed to avoid release of aerosolized powder or liquid into the environment during manipulation of hazardous drugs. Recommendations for preparation and handling of non-sterile HD dosage forms are listed in Appendix G of the document.

#### 14. Decontamination, deactivation, and cleaning

- a. ASHP endorses the USP<800> standards for decontamination, deactivation, cleaning, and disinfection. Decontamination occurs by inactivating, neutralizing, or physically removing HD residue from non-disposable surfaces (e.g., stainless steel C-PECs) and transferring it to absorbent, disposable materials (e.g., wipes, pads, towels) appropriate to the area being cleaned. The decontaminating, deactivating, cleaning, and disinfecting agents selected must be appropriate for the type of HD contaminant(s), location, and surfaces to be cleaned. Consult manufacturer or supplier information for compatibility with cleaning agents used. Agents used for decontamination, deactivation, and cleaning should be applied using wipes wetted with appropriate solution and not delivered as a spray to avoid aerosolizing and/or spreading HD residue.
- b. The area under the work tray of the BSC should be cleaned at least monthly to reduce contamination levels.
- c. The selection and use of disinfectants in healthcare facilities is guided by several properties, such as microbicidal activity, inactivation by organic matter, residue, and shelf life.

#### 15. Administration of HDs

- a. Contamination of infusion areas where HDs are administered document significant surface contamination with HDs.

- b. Extensive guidelines for HD administration have been published by OSHA and the Oncology Nursing Society (ONS).
- 16. Spill management
  - a. ASHP endorses the USP<800> standards for spill management.
- 17. Worker contamination
  - a. Procedures must be in place to address worker contamination, and protocols for medical attention must be developed before the occurrence of any such incident. OSHA requires suitable facilities for quick drenching or flushing of the eyes and body where workers may be exposed to injurious corrosive materials.
  - b. Isotonic eyewash supplies and soap ~~should~~must be readily available in areas where HDs are handled.
  - d. Workers who have skin or eye contamination with HDs require immediate medical attention. Covered below in section on disposing of HD waste/RCRA standards
- 18. Medical Screening and Surveillance; Alternative Duty
  - a. Medical screening and surveillance should be part of the comprehensive safety program for controlling workplace exposure to HDs, which must include engineering controls, training, work practices, and PPE.
  - b. Because reproductive risks have been associated with exposure to HDs, alternative duty (work assignments that do not involve handling HDs) should be offered to individuals who are pregnant, breast-feeding, or attempting to conceive or father a child.
  - c. Medical surveillance involves the collection and interpretation of data for the purpose of detecting changes in the health status of working populations. Medical surveillance programs involve assessment and documentation of symptom complaints, physical findings, and laboratory values (such as a blood count) to determine whether there is a deviation from the expected norms.
- 19. Robotics
  - a. There are currently several robots and automated devices that are marketed for sterile HDs and manufacturers should provide evidence-based data to support the use of any of these devices in compounding sterile HD doses to provide patient safety and worker safety. There may also be legal requirements when using these devices in a pharmacy licensed through a state board of pharmacy, and these devices must also meet provisions of USP Chapter 797 when used for sterile compounding.
  - b. Limited studies have been published examining the ability for robotics to reduce HD surface contamination during sterile compounding or to impact the safety of healthcare workers interacting with the robot during HD compounding.
- 20. Environmental Sampling for HDs
  - a. Surface wipe sampling should be done routinely, first to determine a benchmark of contamination and then at least every 6 months to monitor the effectiveness of safe handling programs. As no acceptable levels of HD surface contamination have been determined by any regulatory agency, surface wipe sampling should

determine an operational baseline of at least several marker HDs from which a facility action level may be determined.

- b. Surface wipe sampling provides a way to determine the efficacy of HD handling equipment, ancillary devices, work practices, cleaning methods, and disposal, and is currently the method of choice to determine surface contamination of the workplace with these drugs.
- c. No regulations or standards exist for allowable or acceptable HD surface concentrations in healthcare settings and many questions remain about the potential health risks associated with exposure to existing levels of environmental surface contamination. However, prudent practice dictates that levels of HD surface contamination should be reduced to as low as reasonably achievable.

### III. USP<797> Revised Chapter published on November 1, 2022.<sup>3</sup>

- A. Scope: Minimum standards for preparing compounded sterile products (CSPs) for humans and animals. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging or otherwise altering a drug or bulk drug substance to create a sterile medication. Requirements in the chapter aim to minimize harm/death from microbial contamination (non-sterility), excessive bacterial endotoxins, variability from the intended strength of correct ingredients, physical and chemical incompatibilities, chemical and physical contaminants and/or use of ingredients of inappropriate quality. Aseptic technique must be used when preparing CSPs and procedures must be in place to minimize contact with nonsterile surfaces, minimize introduction of particulate matter or biologic fluids and/or mix-ups with other products or CSPs.
- B. Updated Beyond Using Dating Criteria:

Risk Category	Revised USP<797> Criteria for Beyond Use Dating (BUD)
Category 1	<p>≤12 hours at room temperature</p> <p>≤24 hours refrigerated</p>
Category 2	<p>Aseptically processed, no sterility testing, only sterile starting components:</p> <ul style="list-style-type: none"> <li>• 4 days at room temperature</li> <li>• 10 days refrigerated</li> <li>• 45 days in the freezer</li> </ul> <p>Aseptically processed, no sterility testing, one or more nonsterile starting components:</p> <ul style="list-style-type: none"> <li>• 1 day at room temperature</li> <li>• 4 days refrigerated</li> <li>• 45 days in the freezer</li> </ul> <p>Aseptically processed, passed sterility testing:</p> <ul style="list-style-type: none"> <li>• 30 days at room temperature</li> <li>• 45 days refrigerated</li> </ul>

	<ul style="list-style-type: none"> <li>• 60 days in the freezer</li> </ul> <p>Terminally sterilized, no sterility testing:</p> <ul style="list-style-type: none"> <li>• 14 days at room temperature</li> <li>• 28 days refrigerated</li> <li>• 45 days in the freezer</li> </ul> <p>Terminally sterilized, passed sterility testing</p> <ul style="list-style-type: none"> <li>• 45 days at room temperature</li> <li>• 60 days refrigerated</li> <li>• 90 days in the freezer</li> </ul>
Category 3	<p>Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs:</p> <ul style="list-style-type: none"> <li>• 60 days at room temperature</li> <li>• 90 days refrigerated</li> <li>• 120 days in the freezer</li> </ul> <p>Terminally sterilized, passed sterility tested, and passing all applicable tests for Category 3 CSPs:</p> <ul style="list-style-type: none"> <li>• 90 days at room temperature</li> <li>• 120 days refrigerated</li> <li>• 180 days in the freezer</li> </ul>

**Question #5:**

The ASCO standards for safe handling of hazardous drugs call for more research to inform a recommended practice standard in which of the following areas?

- a. The need for negative pressure rooms when compounding hazardous drugs
- b. Use of ~~double-gloving~~ **double gloving** with outer sterile gloves when compounding sterile hazardous drug products
- c. Generation of an institutional hazardous drug list
- d. Use of closed-system transfer devices

**IV. Safe Handling of Hazardous Drugs: ASCO standards<sup>6</sup>** - Goal was to determine was constituted best evidence for safe handling of hazardous drugs and extensive review of the literature was conducted yielding five standards

- Standard #1: Endorsement of existing standards – endorsement of existing standards for safe handling of hazardous drugs issued by OSHA, UPS<800>, NIOSH 2004 Alert and ONS
- Standard #2: Medical Surveillance – workplace occupational health programs should include policies and procedures demonstrated to effectively monitor HD contamination in the health care setting and to monitor individuals who have been involved in an acute exposure (e.g., spill).

The role of routine monitoring programs for surveillance including medical screening, laboratory screening or other biologic monitoring is unclear.

- There are currently no data from well-designed programs to inform whether screening and monitoring within medical surveillance programs increases or decreases benefits or harms related to health outcomes for workers who handle HDs. In addition, there is a lack of valid tests or techniques for detecting early signs of disease, no established levels of exposure that have been linked to adverse health effects, and other limitations that are outlined in the main text of this document.
  - As an alternative to routine ongoing medical surveillance programs, this ASCO standard endorses larger-scale data collection in the context of a registry of health care workers. This standard also endorses the collection of data to test research hypotheses, provided that the necessary sample size to detect significant differences can reasonably be achieved, that peer-reviewed publication plans are determined a priori, and that approval has been given by a research ethics board. Gathering data with the purpose of examining it periodically for a small alteration is not recommended.
  - Workers should be encouraged to report occupational health issues to employee health services at the time that they are experienced.
  - The Expert Panel will continue to monitor the literature for robust studies of the link between biologic markers and health outcomes and for studies that assess the outcomes of medical screening and biologic monitoring programs that may already be in place within specific institutions.
- 
- Standard #3: CSTD – to inform a standard on this topic, a standardized testing protocol is needed for CSTDs. In addition, there is a need for a process to identify and certify effective CSTDs.
    - Within a recent systematic review, the quality of the published literature on CSTDs was rated as low quality and at high risk of bias using the GRADE methodology. After implementation of CSTDs, some studies have noted a decrease in the percentage of surface sampling wipes that have detectable levels of antineoplastic drugs and/or a decrease in the percentage of workers who have detectable levels of antineoplastic drugs in their urine. There are no short- or long-term data to inform whether specific CSTDs have an impact on health outcomes.
    - NIOSH recommends using CSTDs when transferring HDs from primary packaging to infusion bags, bottles, or pumps. USP <800> requires use of CSTDs for nursing administration of hazardous drugs and recommends use for sterile product compounding of hazardous drugs.
    - Currently, there is no standardized testing protocol to assess the performance of available CSTDs. NIOSH is in the process of developing an independent vapor containment performance protocol for CSTDs in healthcare settings. These ASCO standards will be revised to incorporate the NIOSH CSTD testing protocol when it becomes available.
    - ASCO encourages NIOSH to develop a certification process so that practices can identify effective CSTDs.

- Standard #4: External ventilation of C-SECs and C-SCAs may be viewed as suite of protective measures that are designed to reduce the likelihood of exposure. Institutions should assess current engineering controls and may choose to incorporate external ventilation where it has not already been implemented
  - Although there is no long-term clinical evidence to inform a standard, engineering controls such as barriers, enclosures, negative pressure, contaminant capture, and elimination (e.g., use of external venting) are protective measures that may be used to potentially reduce health care workers' risk of exposure to HDs. None of these controls are expected to eliminate the risk of exposure to workers as standalone measures.
  - External ventilation of C-SECs or C-SCAs is required by USP 800.
  - Preparing HDs off site and consolidating preparation activities in an externally ventilated location are alternative options that may be considered where external ventilation is not possible within existing facilities because of structural or other constraints.
  - More research is needed on the optimal environment for workers who handle HDs.
- Standard #5: Alternative duty: The health care setting has a policy that identifies potential alternative work options, where possible, for workers who are actively trying to conceive, are pregnant, or are breastfeeding. Health care workers are given information at the time of hire regarding the capacity of the organization to reassign to alternative duty. Reviewing the options for alternative work, where available, should be the shared responsibility of the employee and employer.

**V. Joint Position Statement from the ONS and the Hematology/Oncology Pharmacy Association (HOPA) Ensuring Healthcare Worker Safety When Handling Hazardous Drugs<sup>7</sup>**

- Settings in which HDs are present will establish evidence-based policies and procedures for safe handling that comply with regulatory requirements and standards.
- Settings in which HDs are present will ensure that PPE indicated for handling HDs is available to all staff to minimize exposure.
- Settings in which antineoplastic HDs are prepared and administered will provide and maintain primary engineering controls, such as biologic safety cabinets and compounding aseptic containment isolators, in conjunction with secondary engineering controls, such as buffer rooms or segregated compounding areas, consistent with USP chapters.
- Settings in which antineoplastic HDs are administered will ensure the use of supplemental engineering controls at the point of compounding and administration when the dosage form allows
- Settings in which HDs are present will provide education and training specific to each staff member whose work puts them at risk for exposure to HDs. Education, training, and competency evaluation will include the risks of exposure, including the reproductive and developmental effects, the recommended precautions for specific handling activities, safe handling of contaminated patient excreta, proper disposal of contaminated waste, and how to handle acute exposure.
- Settings in which HDs are present will protect the rights of staff who are trying to conceive, who are pregnant, or who are breast feeding to engage in alternative duty that does not require HD handling.
- Settings in which HDs are present will ensure that patients who receive these drugs and their caregivers receive education about safe handling to minimize unintended exposure in both the institutional and home setting.
- Settings in which HDs are present will ensure that HD waste is disposed of according to regulatory guidelines and in a manner that protects staff and the environment.
- Settings in which HDs are present should engage in medical surveillance of staff.
- Settings in which HDs are present should conduct surface wipe testing as a measure of exposure control to aid in the continuous process improvement for handling HDs.
- Our professional societies support and encourage continued research and the generation of new knowledge about the risks of HD exposure and the efficacy of risk-reduction strategies.
- Our professional societies will continue to explore evidence-based strategies for mitigation of risk associated with handling HDs and share recommendations with our respective members.
- Our professional societies support and encourage compliance with all NIOSH recommendations, USP compounding standards, and regulatory requirements.
- Our professional societies support and encourage advocacy efforts to make recommendations and standards into enforceable laws that best protect staff and the environment.

### Comparison of the Major Safe Handling Statements

Parameter	USP<800>	ASHP	ASCO	HOPA/ONS
Definition of HD	✓	✓		
HD List Generation	✓	✓		
Chain of Custody for HDs	✓	✓		✓
Exposure Risks for HDs	✓	✓		
Staff Responsibilities for Handling HDs	✓	✓		✓
Engineering Controls	✓	✓	+/-	
PPE	✓	✓		
Training for Staff	✓	✓		✓
Compounding	✓	✓		✓
Administration	✓	✓		✓
CSTDs	✓	✓	+/-	✓
Wipe Studies	✓	✓		✓
Cleaning Procedures	✓	✓		
Spills	✓	✓		
Documentation Procedures	✓	✓		✓
Medical Surveillance	✓	✓	+/-	
Pharmacy Work Practices		✓		✓
Pregnant/Attempting to Conceive Staff			+/-	✓
Future Research			✓	✓
Codify Existing Regulations into Law				

#### Answers to Question #5:

Choice D is correct because ASCO states in the guidelines that a certified standard is needed to gauge the effectiveness of the commercially available CSTDs.

Choice A is incorrect because negative pressurization is required by USP<800> and ASCO states that in their guidelines that unless otherwise stated that they endorse the USP<800> standards.

Choice B is incorrect because double-gloving when handling HDs is required by USP<800> and ASCO states that in their guidelines that unless otherwise stated that they endorse the USP<800> standards.

Choice C is incorrect because creation of an institutional HDs list is required by USP<800> and ASCO states that in their guidelines that unless otherwise stated that they endorse the USP<800> standards.



**Question #6:**

**Which of the following FDA-approved agents can now be discarded as non-hazardous waste because of the Hazardous Waste Pharmaceuticals amendment to RCRA?**

- a. Warfarin
- b. Cyclophosphamide
- c. Nicotine patches
- d. Melphalan

**VI. Hazardous Waste**

**A. Hazardous Waste Containment and Disposal<sup>3,4</sup>**

**1. Resource Conservation and Recovery Act (1976):**

- a. EPA had established guidance for management of hazardous waste (HW) under the Resource Conservation and Recovery Act (RCRA). However, until 2019 there were no regulations under RCRA Subtitle C regulations that govern HW from hospitals, pharmacies, reverse distributors, and other healthcare-related facilities.
- b. A new proposal which creates Subpart P under 40 CFR part 266 will provide tailored, sector-specific regulatory framework for managing HW – these new regulations will replace the current regulations in RCRA Subtitle C which were not drafted specifically with managing HDs generated at healthcare facilities. Health care facilities are left to interpret compliance standards that were written for other industries that generate HW. The “generator” requirements in Subtitle C for transporting, storing, treating, and disposing of HW are typically what health care facilities adhere to. RCRA divides HW into three categories – Small Quantity Generators (SQG), Large Quantity Generators (LQG), and Conditionally Exempt Small Quantity Generators (CESQGs) depending on the total amount of monthly HW production.

**RCRA Definitions:**

Characteristic Waste: Waste that is **ignitable, corrosive, reactive, or toxic**. Some pharmaceuticals are prepared in alcohol bases which may result in their classification as hazardous.

LQG: Facilities that generate 1,000 kg or more of HW or more than 1 kg of acute HW (e.g., P-listed waste), or more than 100 kg of any residue or contaminated soil, waste or other debris resulting from the clean-up of a spill, into or on any land or water of any acute HW.

SQG: Facilities that generate more than 100 kg but less than 1000 kg of HW.

CESQG Facilities that generate less than or equal to 100 kg of HW and less than or equal to 1 kg of acutely HW (i.e., P-listed) and less than or equal to 100 kg of any residue or contaminated soil, waste or other debris resulting from the clean-up of a spill, into or on any land or water of any acute HW.

**P-listed waste:** Commercial chemical products that are categorized as acutely hazardous under RCRA. One of the primary criteria for including a drug on the P-list as acutely hazardous is an oral lethal dose of 50 mg/kg (LD50) or less. LD50 is the amount of a material, given all at once which causes the death of 50% of a group of test animals.

**U-listed waste:** Agents are listed primarily for their toxicity. Similar to P-listed waste, when a drug waste containing one of these chemicals is discarded, it must be managed as HW if two conditions are satisfied:

1. The discarded drug waste contains a sole active ingredient that appears on the U list.
2. It has not been used for its intended purpose.

As with P-listed waste, there is no concentration limit or dilution exclusion for U-listed waste.

Empty Containers of U-Listed Wastes: Considered "RCRA empty" if:

1. All the contents have been removed that can be removed using normal means, such as drawing liquid out with a syringe
2. No more than 3% by weight remains

\*If both criteria are not met, the container must be managed as HW. Any residues removed from the empty container must be managed as HW

#### General Categories of Hazardous Waste:

Examples of P-listed Waste	Examples of U-listed Waste
Arsenic trioxide	Azaserine
Epinephrine	Chloral Hydrate
Nicotine	Chlorambucil
Nitroglycerin	Chloroform
Phentermine	Cyclophosphamide
Physostigmine salicylate	Daunomycin
Physostigmine	Dichlorodifluoromethane
Warfarin (greater than 0.3%)	Diethylstilbestrol
	Formaldehyde
	Hexachlorophene
	Lindane
	Melphalan
	Mercury
	Mitomycin C
	Paraldehyde
	Phenacetin
	Phenol
	Reserpine
	Resorcinol
	Selenium sulfide
	Streptozocin
	Trichloromonofluoromethane
	Uracil mustard
	Warfarin ( $\leq 0.3\%$ )

- c. Trace-contaminated HD waste may include “RCRA-empty” containers, needles, syringes, trace-contaminated gowns, gloves, pads and empty IV sets which may be incinerated at regulated medical waste incinerator.
- 2. Bulk HW
  - a. Differentiates containers that held either (1) RCRA-listed or characteristic HW or (2) any HDs that are not RCRA empty or any materials from HD spill cleanups.
  - b. These wastes should be managed as hazardous.
- 3. HDs not listed as HW
  - a. RCRA regulations have not kept up with drug development and consequently there are over 100 HDs that are not listed as HW.
  - b. Regulations may vary by state – for example, Minnesota listed hormonal agents as HW.
- 4. HW and mixed infectious-hazardous waste
  - a. Most HW vendors cannot manage regulated medical waste or infectious waste; therefore, they cannot accept used needles or other items contaminated with blood. Hazardous waste must not be combined with needles or blood. For example, yellow bucket (trace chemo), red bucket (Blood), and black bucket (HD waste >3%)
  - b. Properly labeled, leak proof, and spill-proof containers of non-reactive plastic are required for areas where HW is generated.
  - c. HDs may be in thick, sealable, plastic bags before being placed in approved satellite accumulation containers.
  - d. Waste contaminated with blood or other body fluids should not be mixed with HW.
  - e. Transport of HW containers from satellite accumulation to storage sites must be done by individuals who have completed OSHA mandated HW awareness training.
  - f. More information on hazardous waste disposal may be found at [www.hercenter.org](http://www.hercenter.org)

**B. Amendment to RCRA:** Hazardous Waste Pharmaceuticals and Amendment to Nicotine Listing (P075) Final Rule – April 2019 – published in Federal Register February 22, 2019

- 1. Goals:
  - a. Creates regulation to better fit healthcare sector for management of HW
  - b. Eliminate intentional sewerage of HW pharmaceuticals
  - c. Provide regulatory clarity and national consistency on how RCRA applies to reverse distribution and reverse logistics
  - d. Reevaluate whether nicotine replacement therapies should be regulated as acute HW
- 2. Nicotine replacement therapies that are FDA-approved for over-the-counter use will no longer be included in the P075 listing for HDs

- a. Nicotine patches, gums, and lozenges can be discarded as non-HW
  - b. Nicotine continues to be listed as acute HW – this includes e-liquids in e-cigarettes/cartridges, prescription nicotine, nicotine in pesticides, nicotine used in research facilities
3. Reverse logistics/distribution – logistics centers that evaluate unsold retail items including nonprescription pharmaceuticals, analyze secondary markets and assess the suitability of the unsold retail items for reuse in those secondary markets
- a. Final rule reaffirms EPA’s long-standing policy that **nonprescription** pharmaceuticals (e.g., OTCs) that are sent through reverse logistics are not wastes at the healthcare or retail facility if they have a reasonable expectation of being lawfully reused for their intended purpose.

**Reverse distribution for prescription pharmaceuticals moving through reverse distributors are considered wastes at the healthcare facility**

Reverse Distribution	Reverse Logistics
Rx Pharmaceuticals	Non-Rx pharmaceuticals <ul style="list-style-type: none"> <li>E.g., OTCs, dietary supplements</li> </ul> All other unsold retail items
No redistribution occurs	Redistribution sometimes occurs via: <ul style="list-style-type: none"> <li>Donation</li> <li>Liquidation (secondary market)</li> </ul>
Rx pharmaceuticals sent to reverse distributors are solid wastes at the healthcare facility	Non-Rx pharmaceuticals and other unsold retail items sent to reverse logistics <u>are not solid wastes</u> IF there is a reasonable expectation of legitimate use/reuse or reclamation
In Part 266 Subpart P, which is <ul style="list-style-type: none"> <li>Effective in non-authorized states August 21, 2019</li> <li>Effective in authorized states when states adopt Subpart P</li> </ul>	Newly codified in Part 266 Subpart P. Affirms existing policy <ul style="list-style-type: none"> <li>Effective immediately federally</li> <li>Check with your state</li> </ul>

4. Revised definitions:

s – Includes, but not limited to:

- Dietary supplements
- Prescription drugs
- OTC drugs
- Homeopathic drugs
- Compounded drugs
- Investigational new drugs
- Pharmaceuticals remaining in non-empty containers
- PPE contaminated with pharmaceuticals
- Electronic nicotine delivery systems (e.g., e-cigarettes, vaping pens)
- Does NOT include dental amalgam, sharps, medical waste

**Types of Hazardous Waste Pharmaceuticals**

- Non-creditable HW pharmaceutical – broken, leaking, repackaged, dispensed, expired (>1 year), investigational new drug, contaminated PPE, floor sweepings, clean-up material
- Potentially creditable HW pharmaceutical – original manufacturer packaging (except recalls), undispensed, unexpired or less than 1-year past expiration

- Evaluated HW pharmaceutical – no further evaluation or verification of manufacturer credit is necessary

#### **Healthcare facility**

- Wholesale distributors
  - Third-party logistics providers
  - Military medical logistics facilities
  - Hospitals/psychiatric hospitals
  - Ambulatory surgical centers, health clinics, physician offices
  - Optical and dental providers
  - Chiropractors
  - Long-term care facilities
  - Ambulance services
  - Pharmacies, long-term care pharmacies, mail-order pharmacies, retailers of pharmaceuticals (includes vape shops), veterinary clinics and hospitals
5. Scope/Application
    - a. No generator categories under Part 266 Subpart P
    - b. All healthcare facilities are regulated the same for their HW pharmaceuticals
    - c. All reverse distributors are regulated the same for their HW pharmaceuticals
    - d. Healthcare facilities and reverse distributors do not have to keep track of how much HW pharmaceuticals they generate per month or segregate the acute and non-acute HW pharmaceuticals
  6. Not subject to RCRA regulation:
    - a. Pharmaceuticals that are not solid wastes because they are legitimately reused or reclaimed
    - b. OTC pharmaceuticals, dietary supplements or homeopathic drugs that are not solid waste because they have a reasonable expectation of being legitimately used/reused or reclaimed
    - c. Recalled pharmaceuticals
    - d. Pharmaceuticals under preservation order, or during an investigation or judicial proceeding
    - e. Investigational new drugs
    - f. Household waste pharmaceuticals
  7. Healthcare facility management standards
    - a. Accumulation containers must be labeled with the words “Hazardous Waste Pharmaceutical”
    - b. No HW codes or other labeling requirements
    - c. Containers must be structurally sound, nor react with contents and remain closed and secured in a manner that prevents unauthorized access to contents – accumulation time limit – 1 year
    - d. No labeling, container standards or accumulation time for potentially creditable HW pharmaceuticals
  8. Sewer prohibition
    - HW pharmaceuticals may not be sewered (e.g., no disposal down the drain and no flushing)
    - Sewer prohibition applies to:

- All healthcare facilities, including VSQG
  - All reverse distributors
  - Hazardous wastes that are DEA controlled substances are also subject to the sewer prohibition
  - EPA discourages sewerage of ANY pharmaceuticals by any entity
9. Take back of controlled substances
- a. Applies to RCRA hazardous wastes that are also DEA controlled substances
  - b. Retail pharmacies and hospitals can amend DEA registration to become “collectors” of household pharmaceuticals – kiosks for collection may be installed at the facilities
  - c. Pharmaceuticals must be destroyed after being collected
  - d. Agents include chloral hydrate, fentanyl sublingual spray, phenobarbital, testosterone, diazepam

**Answers to Question #6:**

**Choice C is correct because the Hazardous Waste Pharmaceutical amendment to RCRA allows for FDA-approved nicotine replacement therapies such as patches and gum to be discarded as non-hazardous waste.**

**Choice A is incorrect because warfarin is still listed as a U-listed hazardous waste drug per RCRA.**

**Choice B is incorrect because cyclophosphamide is still listed as a U-listed hazardous waste drug per RCRA.**

**Choice D is incorrect because melphalan is still listed as a U-listed hazardous waste drug per RCRA.**

**VII. NIOSH: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in the Health Care Settings<sup>8</sup>**

- A. NIOSH Warning: Working with or near HDs in health care settings may cause skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancers.
- B. Adherence to guidelines for handling HDs is sporadic and measurable concentrations of some HDs have been found in the urine of health care workers.
- C. Potential for Worker Exposure
  - 1. Exposure may occur from manufacture to transport/distribution to use in health care
  - 2. The number of workers exposed to HDs in the US is approximately 5.5 million. These include shipping and receiving personnel, pharmacists, pharmacy technicians, nursing personnel, physicians, operating room personnel, environmental services personnel, and workers in veterinary practices.
- D. Conditions for Exposure – recommendations have been incorporated into USP<800>
- E. Exposure Routes
  - 1. Exposure to HDs may occur through inhalation, skin contact, skin absorption, ingestion, or injection.
  - 2. Detectable concentrations of HDs have been found on BSCs, floors, counter tops, storage areas, tables and chairs in patient treatment areas, and locations adjacent to drug-handling areas.
- F. Evidence for Worker Exposure
  - 1. Evidence indicates that workers are being exposed to HDs and are experiencing serious health consequences despite current work practice guidelines.
  - 2. Factors that affect worker exposure include:
    - Drug handling circumstances (preparation, administration, or disposal)
    - Amount of drug prepared

- Frequency and duration of drug handling
- Potential for absorption
- Use of ventilated cabinets
- PPE
- Work practices

3. CSTD usage for 6 months reduced both the concentration of cyclophosphamide and ifosfamide in the urine of exposed health care workers and the percentage of samples containing these drugs.

G. Evidence for Health Effects in Workers

1. Mutagenicity - Multiple ~~studies documents~~ ~~studies documents~~ that antineoplastic drugs may cause increased genotoxic effects in pharmacists and nurses exposed in the workplace.
2. Developmental and Reproductive Effects - Antineoplastic drugs have reproductive effects such as increased fetal loss, congenital malformations, low birth weight, congenital abnormalities, and infertility.
3. Cancers - An increased risk of leukemia has been reported in oncology nurses from a Danish cancer registry from 1943-87.

**VIII. NIOSH List of Antineoplastic and Other HDs in Healthcare Settings, 2016<sup>9</sup>**

- G. History – First NIOSH Alert (Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings) originally published in September 2004 (<http://cdc.gov/niosh/docs/2004-165/>). Appendix A listed a sample list of major HDs, which was updated in 2010, 2012, 2014 and ~~2016-2016~~. See below regarding the proposed updated from NIOSH in 2020, which has not yet been finalized.
- H. Current Format for Listing of HDs per NIOSH as of 2016.
1. Group 1: Antineoplastic drugs (AHFS classification 10:00) – Many of these drugs pose a reproductive risk for susceptible populations.
  2. Group 2: Non-antineoplastic drugs that meet one or more of the NIOSH criteria for a HD. Some of these drugs may pose reproductive risks for susceptible populations.
  3. Group 3: Drugs that primarily pose a reproductive risk to men and women who are actively trying to conceive and women who are pregnant or breast feeding, because some of the drugs may be present in breast milk.
- I. Listing of the individual drugs is found within the publication with Tables for Groups 1, 2, and 3 noted above
- J. NIOSH has published a draft of the NIOSH List of Hazardous Drugs in Healthcare Settings, 2020. (<https://www.cdc.gov/niosh/topics/hazdrug/default.html>) – Comments were accepted through June 30, 2020. The finalized document will be published on the NIOSH website.

**Drugs in the proposed/revised Table 1 meet the following classification criteria:**

- Drugs which contain manufacturer special handling information (MSHI), and/or
- Drugs which meet NIOSH definition of a hazardous drug and are classified by National Toxicology Program (NTP) as “known to be human carcinogen” and/or/ classified by International Agency for Research in Cancer (IARC) as “carcinogenic” or “probably carcinogenic”
- Many of these drugs are cytotoxic and the majority are hazardous to males or females who are actively trying to conceive, women who are pregnant or may become pregnant and women who are breast feeding because the drugs are excreted in breast milk.
- Not all drugs in Table 1 are antineoplastic
- Drugs reviewed for this update were new drug approvals or received safety related new warnings from FDA in the period between Jan 2014 and Dec 2015.
- New drugs were added in 2020 were specified in red in the table published on the NIOSH website



<ul style="list-style-type: none"> <li>• This table provides information for each drug on AHFS classification, whether MSHI guidance is available and supplemental information specific to each drug</li> </ul>
<p><b><u>Drugs in the proposed/revised Table 2 meet the following classification criteria:</u></b></p> <ul style="list-style-type: none"> <li>• The drugs in Table 2 meet the NIOSH definition of a hazardous drug but are not drugs which have MSHI and are not classified by the NTP as “known to be a human carcinogen” and/or classified by the IARC as “carcinogenic” or “probably carcinogenic”</li> <li>• These drugs exhibit one or more of the types of toxicity described in the NIOSH definition of a hazardous drug</li> <li>• Some of these drugs may present an occupational hazard to males or females who are actively trying to conceive, women who are pregnant or may become pregnant and women who are breast feeding because they may present in breast milk</li> <li>• Drugs reviewed for this update were new drug approvals or received safety related new warnings from FDA in the period between Jan 2014 and Dec 2015.</li> <li>• New drugs were added in 2020 were specified in red in the table published on the NIOSH website</li> <li>• This table provides information for each drug on AHFS classification and supplemental information specific to each drug generally focusing on what specific NIOSH criteria was used to classify the agent as hazardous</li> </ul>

\*Changes from the 2016 list are annotated in a third table

## Other Regulatory Agencies of Interest to Oncology Practitioners

### Regulatory Agencies:

Agency	Role
<b>Food and Drug Administration (FDA)</b> <sup>10</sup>	<ul style="list-style-type: none"> <li>• The FDA is an agency within the U.S. Department of Health and Human Services. It consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations.</li> <li>• Website houses information on drug approvals links to product labeling, deliberations of advisory committee meetings, and drug shortages.</li> <li>• Drug Quality and Security Act of 2013 expands FDA's authority to regulate compounding such that a compounding outsourcing facility must comply with current good manufacturing practices, be subject to inspection by the FDA, and report information about compounded products including adverse events.<sup>12</sup></li> <li>• Other regulated items include medical devices, radiation-emitting products, vaccines, veterinary medications, cosmetics, and tobacco products.</li> </ul>
<b>State Boards of Pharmacy</b>	<ul style="list-style-type: none"> <li>• Oversee licensure for individual states for pharmacists and pharmacy technicians</li> <li>• Set regulations for controlled substance prescribing within a state</li> <li>• Outline standards for physical pharmacy space – retail and institutional</li> </ul>
<b>Drug Enforcement Agency (DEA)</b> <sup>11</sup>	<ul style="list-style-type: none"> <li>• Section of the United States Department of Justice</li> <li>• Enforcement agency for controlled substance act</li> <li>• Provides registration for providers to prescribe, procure and dispense controlled substances</li> </ul>
<b>Joint Commission</b> <sup>12</sup>	<ul style="list-style-type: none"> <li>• Mission is to improve health care for the public by evaluating health care organizations and inspiring them to excel in providing safe and effective care of highest quality and value</li> <li>• Accredits and certifies more than 20,000 health care organizations and programs in the US.</li> <li>• Establishes standards for hospitals and other health care organizations to adhere to for regulatory compliance</li> <li>• Publishes annual report on Quality and Safety</li> <li>• Sets National Patient Safety Goals</li> </ul>

## 2022 Joint Commission Hospital National Patient Safety Goals<sup>12</sup>

NPSG.01.01: Identify patients correctly: Two patient identifiers (name and date of birth) when providing care, treatment, and services

NPSG.02.03.01: Improve effectiveness of communication among caregivers: Report critical test results and diagnostic procedures on a timely basis.

NPSG.03.04.01: Improve the safety of using medications: Label all medications, medication containers and other solutions on and off the sterile field in perioperative and other procedural settings. Note – medication containers include syringes, medicine cups and basins. Medications or other solutions in unlabeled containers are unidentifiable. This unsafe practice neglects basic principles of safe medication management.

NPSG.03.05.01: Reduce the likelihood of harm associated with the use of anticoagulant therapy – this does NOT apply to routine situations in which short-term prophylaxis anticoagulation is used for preventing venous thromboembolism (for example, related to procedures or hospitalization)

NPSG.03.06.01: Maintain and communicate accurate patient medication information.

NPSG.06.01.01: Improve the safety of clinical alarm systems.

NPSG. 07.01.01: Reduce the risk of health care-associated infections. Comply with either the current Center for Disease Control and Prevention (CDC) hand hygiene guidelines or the current World Health Organization (WHO) hand hygiene guidelines.

NPSG.15.01.01: The hospital identifies safety risks inherent in its patient population. Identify patients at risk for suicide. This requirement applies only to psychiatric hospitals and patients being treated for emotional or behavioral disorders in general hospitals.

UP.01.01: Conduct a pre-procedure verification process

UP.01.01.01: Mark the procedure site.

UP.01.03.01: A time-out performed before the procedure.

### Question #7:

Which of the following is not addressed in the ASCO/ONS safety standards with relevance to oncology pharmacy practice?

- a. Guidelines for preparation and handling of hazardous drugs
- b. Adjudication of verbal orders for chemotherapy regimens
- c. Policy requirements for preparation of intrathecal chemotherapy
- d. Tracking of cumulative doses of chemotherapy drugs with significant end-organ toxicity

## QUALITY

### I. Quality Oncology Practice Initiative (QOPI)

- A. QOPI® is a quality measurement tool developed by the ASCO to benchmark oncology outpatient practices against accepted standards of practice. Certified practices are evaluated against a comprehensive set of quality measures and standards.
- B. For details on the requirements to achieve QOPI Certification please review the materials below. QOPI Certification Program measures performance thresholds and site standards against publicly available standards. Standards and measures are continually re-assessed to maintain certification.
- C. **ASCO/ONS Chemotherapy Administration Safety Standards<sup>13</sup>**
1. American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) initiated a collaborative project in 2008 (most recently updated in 2016) to develop standards for safe chemotherapy administration to adult cancer patients in the outpatient setting. The most recent update includes standards for pediatric oncology.
  2. The scope of the project was limited to patient safety and included both parenteral and oral chemotherapy regimens. Summary of the standards are listed in the table below i

#### QOPI Safety Standards are based on the ASCO/ONS Chemotherapy Safety Standards<sup>13</sup>

Domain 1: Creating a safe environment – Staffing and general policy
<ul style="list-style-type: none"><li>• Detailed institutional policy for health care providers that order, prepare, and administer chemotherapy</li><li>• Baseline training and ongoing educational requirements for all staff</li><li>• At least one clinical staff member is BLS certified during chemotherapy administration</li><li>• Before administration of a new chemotherapy regimen, the following is documented in the medical record: Pathologic confirmation of diagnosis; staging; medical history/physical exam/pregnancy status; allergy history; patient/caregiver comprehension of diagnosis and treatment; psychosocial assessment; chemotherapy treatment plan; patient follow-up schedule, and monitoring plan</li><li>• For each clinical encounter or day of treatment, the following patient assessments are documented: Functional/performance status; vital signs; weight; height; age; allergies and/or previous treatment toxicities; new treatment toxicities; pain assessment</li><li>• Staff assesses and documents psychosocial concerns with each treatment cycle</li><li>• Referrals for financial, psychosocial, or other cancer support services</li><li>• Medication lists are updated when a change occurs</li><li>• 24/7 triage and access to an oncology savvy provider for treatment-related toxicities and emergencies</li><li>• Standard documentation and communication for toxicities, modifications in dose/schedule of treatment or discontinuation of treatment</li><li>• Policy for safe handoff between treatment settings</li><li>• Policy for reporting adverse events and near misses with a formal process for collecting and reviewing such data</li></ul>
Domain 2: Treatment Planning, Patient Consent and Education
<ul style="list-style-type: none"><li>• Policy that documents a standardized process for obtaining and documenting chemotherapy consent or assent which is obtained prior to starting treatment</li></ul>

- Patients are providing verbal and written or electronic information as part of a formal education program, the content of which is documented
- Education will include: diagnosis; goals of treatment (e.g. cure vs. palliation); planned duration of treatment; treatment schedule; drug names including supportive medications; information on drug-drug and/or drug-food interactions; plan for missed doses; long-term and short-term toxicities; symptoms/adverse events that require the patient to contact the health care setting or seek immediate attention; symptoms/events that require immediate discontinuation of oral or self-administered medications; procedures for handling medications at home – including storage, safe-handling; and management of unused medications; procedures for handling body secretions and waste in the home; follow-up plans – e.g. labs, provider visits; contact information for providers including after hours; follow-up for missed appointments; education of family/caregivers for the patient

### Domain 3: **Ordering, Preparing, Dispensing and Administering Chemotherapy**

- Institution defines standard treatment regimens – including references
- Institution verifies IRB review of research protocols
- Chemotherapy orders are signed manually or by electronic signature code by licensed independent practitioners who are determined to be qualified by the institution
- Policy exists to handle chemotherapy regimens that vary from standard practice – supporting reference or authorization from a second license independent practitioner are required
- Rationale for exception orders as above are documented in the medical record
- No verbal orders for chemotherapy are allowed except to hold or stop chemotherapy; new orders and/or change orders are documented in the medical record
- Institution uses standardized, regimen-level, pre-printed or electronic forms for IV chemotherapy regimens
- **Chemotherapy orders** include the following elements: Patient name; second patient identifier; date; regimen/protocol name; cycle number and day; use of generic drug names; drug dose is written following standards for abbreviations, trailing and leading zeros; dose calculation and methodology for the dose calculation; variables used to calculate the dose including frequency by which they are re-calculated; date of administration; route of administration; allergies; supportive care including premedications, hydration, growth factors and hypersensitivity medications; parameters for holding a dose of a particular medication; sequence of drug administration when applicable; rate of drug administration; number of cycles for which the order is valid
- **Prescriptions for oral chemotherapy** include the following elements: patient name with a second identifier; full generic drug name; date; calculation methodology; drug dose including standards for abbreviations and preceding/trailing zeros; route of administration including special instructions; drug quantity to be dispensed; schedule of administration; duration of therapy; number of refills
- Chemotherapy is prepared by a licensed pharmacist, pharmacy technician, physician or registered nurse with documented chemotherapy preparation training and annual competence validation
- Licensed pharmacist verifies all orders before administration or dispensing of chemotherapy in health care settings that treat pediatric patients under age 18
- A second person – a practitioner or other personnel approved by the health care setting to prepare or administer chemotherapy- performs **three independent verifications**: two patient identifiers; drug name and dose; route and rate of administration; calculations for dosing including variable utilized; treatment cycle and day of cycle
- Upon **preparation** – a second person approved by the health care setting to prepare parenteral chemotherapy verifies – the drug vials; concentration; diluent type and volume; administration fluid type and tubing

- Prior to each chemotherapy **administration**, at least two practitioners approved by the health care setting to administer or prepare chemotherapy verify and document the accuracy of the following elements: drug name and dose; infusion volume or drug volume in a syringe; rate and route of administration; expiration dates and times; appearance and physical integrity of the drugs; rate set on IV infusion pump
- Elements required on **chemotherapy labels**: patient name; second patient identifier; full generic name; drug dose; drug administration route; total volume required to administer the drug; date of administration; expiration dates/times; sequencing of drug administration and total number of products to be given when medication is provided in divided doses; warning or precautionary sticker for storage or handling.
- **Labels** for medications dispensed by the health care setting to be **taken at home** include: patient name; second patient identifier; full generic name; drug dosage form and strength; quantity dispensed; within each container; number of pills per dose when the container holds more than one dose; administration schedule for number of doses per day, food ingestion and other medications; warning or precaution statement with respect to handling/storage; warning or precautionary sticker; storage conditions; prescriber name. Medication label requirements must also meet state board of pharmacy regulations.
- **Intrathecal chemotherapy**: policy outlining preparation guidelines; storage in an isolated container or location following preparation; labeled with uniquely identifiable intrathecal administration medication label; delivered to patient only with other medication intended for CNS administration; administered immediately following a time out, double-check procedure that involves two licensed practitioners
- **Health care settings that administer intrathecal chemotherapy have a policy that specifies that intravenous vinca alkaloids are only to be administered by infusion** – e.g., minibags.
- Chemotherapy mixed off-site: the health care setting maintains a policy that accounts for quality control of that chemotherapy including that the off-site pharmacy complies with applicable regulations
- Health care setting that maintains its own pharmacy – policy regarding the safe storage of chemotherapy including the separation of look-alike, sound-alike products and investigational drugs
- Chemotherapy is administered by a qualified physician, physician assistant, registered nurse, or advanced practice nurse
- Before initiation of each chemotherapy administration cycle, the practitioner who is administering the chemotherapy confirms the treatment with the patient, including at a minimum name of drug, route of administration, any infusion-related symptoms to report
- Two individuals in the presence of the patient confirm that patient's identity using two patient identifiers; when treatment is in the home setting a single practitioner may use another identifier such as a driver's license
- Documentation of chemotherapy administration confirms the verification of the eight elements of chemotherapy administration identified previously
- Extravasation management procedures are defined and align with current literature and guidelines; antidote order sets and antidote medications are available within an appropriate timeframe

#### Domain 4: **Monitoring after chemotherapy is administered, including adherence, toxicity, and complications**

- Health care setting uses standard, disease-specific processes, to monitor treatment response and has a policy that determines the appropriate time interval for regimen-specific laboratory and organ-function tests that are based on evidence and national guidelines when available

- Health care setting has a policy for emergent treatment of patients that aligns with current literature guidelines and addresses: availability of appropriate treatment agents; procedures to follow and to plan for escalation of care when required for life-threatening emergencies
- Availability of appropriate treatment agents
- Procedures to monitor an initial assessment of adherence to chemotherapy that is administered outside the health care setting
- Policy that requires ongoing assessment of each patient's chemotherapy adherence and toxicity at each clinical encounter to address any issues identified
- Cumulative doses of chemotherapy are tracked for agents associated with cumulative toxicity

**Answers to Question #7:**

**Choice A is correct because the 2016 update of the ASCO/ONS safety standards does not address safe handling of hazardous drugs or engineering controls required to compound cytotoxic agents safely.**

**Choice B is incorrect because Domain 3 states that no verbal orders for chemotherapy should be accepted except to hold or discontinue the orders.**

**Choice C is incorrect because Domain 3 speaks to the requirement for a policy for preparation of intrathecal chemotherapy and assurance that vinca alkaloids will be prepared in an IV piggyback to avoid inadvertent intrathecal instillation.**

**Choice D is incorrect because Domain 4 requires that cumulative dose of chemotherapy be tracked such that agents such as anthracyclines can be monitored for the risk of cardiac toxicity.**

**Question #8:**

**Which of the following is most correct regarding core measures assessed by QOPI?**

- On-site reviewers from ASCO will abstract chart data for compliance**
- Reported core measures are the sole criteria for QOPI certification**
- Core measures are required for each malignancy that has treatment guidelines written by National Comprehensive Cancer Network (NCCN)**
- Institutions are required to self-report compliance with core measures to ASCO ahead of an on-site visit**

## QOPI Core Certification Measures (2022):<sup>14</sup>

Core Measures
1. Pathology report confirming malignancy
2. Staging documented within one month of first office visit
3 - 6. Pain addressed appropriately and intensity documented (by at least second office visit)
9. Documented plan for chemotherapy, including doses, route, and time intervals
10. Chemotherapy intent (curative vs. palliative) documented
11. Chemotherapy intent discussion with patient documented
13. Chemotherapy planning completed appropriately (document performance status, plan for oral chemotherapy monitoring)
14-16. Signed consent for chemotherapy with documentation in the clinician note
21-23. Smoking status/tobacco use documented in past year/Cessation efforts
24. Patient emotional well-being assessed by second office visit
25. Action taken to address emotional well-being by second office visit
25b. Height, weight and BSA documented prior to chemotherapy
Symptom/Toxicity Management Module measures
30. Appropriate antiemetic therapy with moderate/high emetic risk chemotherapy
31. Antiemetic therapy for low/minimal emetic risk chemotherapy - avoidance of overuse
33. Infertility risks discussed prior to chemotherapy with patients of reproductive age
Breast Cancer Module measures
52. Combination chemotherapy <b>recommended</b> within 4 months of diagnosis by women under 70 with AJCC stage I (T1c) to III ER/PR negative breast cancer*
52a. Complete staging for women with invasive breast cancer including HER-2, and ER/PR status
53. Combination chemotherapy <b>received</b> within 4 months of diagnosis by women under 70 with AJCC stage I (T1c) to III ER/PR negative breast cancer
54. Test for Her-2/neu gene overexpression
55 Trastuzumab prescribed for Her-2/neu positive disease in Stage I – III patients
57a. Appropriate treatment for patients with stage I (T1c) – III HER-2 (+) breast cancer
58-59. Tamoxifen or AI received within 1 year of diagnosis by patients with AJCC stage I (T1c) to III ER or PR positive breast cancer*
61. Bone modifying agents (IV bisphosphonate or denosumab) administered for breast cancer bone metastasis; renal function assessed for bisphosphonate use
62. PET, CT or radionuclide bone scan ordered by practice with 60 days after diagnosis to Stage I, IIA or IIB breast cancer or between day 61 and 365 for those treated with curative intent
62c. Serum tumor marker ordered by practice within 30 and 365 days after diagnosis of breast cancer with curative intent treatment
62d. GCSF administered to patients who received chemotherapy for metastatic breast cancer <b>(lower is better)</b>
Colorectal Cancer Module measures
68. Adjuvant chemotherapy received within 4 months of diagnosis by patients with AJCC stage III colon cancer*
74. KRAS/NRAS testing for patients with metastatic colorectal cancer who receive MoAb therapy.
Non-Small Cell Lung Cancer Module measures
81. Adjuvant cisplatin-based chemotherapy received within 60 days after curative resection – stage II or IIIA NSCLC.
82. Adjuvant cisplatin-based chemotherapy received within 60 days after curative resection – stage IA NSCLC. <b>(Lower is better)</b>



83. Adjuvant radiation therapy recommended for patients with AJCC stage IB or II NSCLC. <b>(Lower is better)</b>
84. Performance status documented for patients with initial stage IV or distant metastatic NSCLC.
88. Patients with Stage IV NSCLC with adenocarcinoma histology with an activating EGFR mutation or ALK gene rearrangement who received first-line EGFR tyrosine kinase inhibitor or other targeted therapy
89. Patients with Stage IV NSCLC with adenocarcinoma histology with unknown EGFR mutation or ALK gene rearrangement who received first-line EGFR tyrosine kinase inhibitor or other targeted therapy <b>(lower is better)</b>
89a. GCSF administered to patients who received chemotherapy for metastatic NSCLC <b>(lower is better)</b>
90. PET or PET-CT ordered by the practice between 0 and 12 months after treatment with curative intent for patients with Stage I or II NSCLC <b>(lower is better)</b>
91-92. Molecular testing/turnaround time for patients with Stage IV NSCLC with adenocarcinoma histology
93. Concurrent chemoradiation for patients with a diagnosis of Stage IIIB NSCLC
Small Cell Lung Cancer Module measures
118. Prophylactic Cranial Irradiation for Patients with Limited Stage (LS) Small Cell Lung Cancer (SCLC)
119. Overtreatment of SCLC Patients with Platinum-Based Chemotherapy <b>(lower is better)</b>
120. Early Thoracic Radiotherapy (TRT) for Patients with a Diagnosis of Limited Stage SCLC

#### Answers to Question #8:

**Choice D is correct because institutions are required to collate data from select patient chart on compliance with QOPI core measures and submit to ASCO for review prior to an on-site certification visit.**

**Choice A is incorrect because institutional staff are required to do the data abstraction for core measures from patient charts, not ASCO staff.**

**Choice B is incorrect because performance with core measures is only part of the criteria for QOPI certification. An on-site visit by an ASCO surveyor assessing practice compliance with ASCO/ONS safety standards also is an important determinant of certification.**

**Choice C is incorrect because the number of diseases represented in the core measure reporting is limited to lung, prostate, breast, colon, and gynecologic oncology.**

#### Question #9:

**Which of the following are quality metrics that oncology practices, participating in the Center for Medicare and Medicaid Services (CMS) Oncology Care Model, are required to submit to CMS?**

- a. Appropriateness of prescribing erythroid colony stimulating factors
- b. Percentage of patients that utilize the emergency room during cancer treatment
- c. Number of patients that a practice enrolls in NCI-sponsored phase III clinical trials
- d. Patient compliance with oral oncolytic therapy

## II. CMS Oncology Care Model (OCM)<sup>15</sup>

- A. The innovation Center at CMS published the first major payment modification for oncology services in February 2015. The OCM focuses on an episode of cancer care, specifically a chemotherapy episode of care.

- B. The goals of OCM are to utilize appropriate aligned financial incentives to improve:
1. Care Coordination
  2. Appropriateness of care
  3. Access for Medicare beneficiaries undergoing chemotherapy
- C. Financial incentives encourage participating oncology practices to work collaboratively to comprehensively address the complex care needs of beneficiaries receiving chemotherapy treatment and encourage the use of services that improve health outcomes.
- D. How does OCM work?
1. Episode based: Payment model targets chemotherapy and related care during a 6-month period following the initiation of chemotherapy treatment.
  2. Emphasizes practice transformation: Physician practices are required to engage in practice transformation to improve the quality of care they deliver.
  3. Multi-payer model: Includes Medicare fee-for-service (FFS) and other payers working in tandem to leverage the opportunity to transform care for oncology patients across the population.
- E. Physician practices that are Medicare providers and furnish chemotherapy may apply to participate in OCM – there are six requirements for participation:
1. Provide 24/7 patient access to an appropriate clinician who has real-time access to the patient's medical records.
  2. Use an ~~oncology-certified~~ oncology certified EMR and attest to Stage 2 of meaningful use (MU) by the end of the third model performance year and MU Stage 1 by the end of the first model performance year.
  3. Utilize data for continuous quality improvement – The CMS Innovation Center will provide participating practices with rapid cycle data feedback reports to aid in quality improvement. Practices are expected to use this data to continuously improve OCM patient care management.
  4. Provide core functions of patient navigation: Practices are required to provide patient navigation to all OCM patients. The National Cancer Institute provides a sample list of patient navigation activities.
  5. Document a care plan for every OCM patient that contains the 13 components in the Institute of Medicine's Care Management Plan. Plan components include treatment goals, care team, psychosocial support and estimated out-of-pocket costs.
  6. Treat patient with therapies consistent with nationally recognized clinical guidelines. Practices must report which clinical guidelines (NCCN® or ASCO) they follow for OCM patients or provide a rationale for not following the clinical guidelines.
- F. Payers
1. OCM covers Medicare fee-for service (OCM-FFS) and other payers (OCM-OP). Other payers may include commercial payers, state Medicaid agencies, or other governmental payers (including Tricare, FEHBP and state employee health plans).

2. Payer participation will drive the geographic scope of the model. The CMS Innovation Center will publish lists of payers and practices who submit letters of intent to participate in OCM and expects other payers to plan for OCM participation with their associated practices.
- G. Operations of OCM:
1. Commit to participation in OCM for its 5-year duration and begin performance period within 90 days.
  2. Sign a memorandum of understanding with the Innovation Center.
  3. Enter into agreements with OCM practices that include requirements to provide high quality care.
  4. Share model methodologies with the Innovation Center.
  5. Provide payments to practices for enhanced services and performance as described in the RFA (request for applications).
- H. Quality Improvement Measures – Align practice quality and performance measures with OCM.
- I. Data Sharing – Provide participating practices with aggregate and patient-level data about payment and utilization for their patients receiving care in OCM, at regular intervals.
- J. Medicare beneficiaries who meet each of the following criteria will be included in OCM-FFS:
1. Eligible for Medicare Part A and enrolled in Medicare Part B.
  2. Have Medicare FFS as their primary payer.
  3. Do not have end-stage renal disease.
  4. Are not covered by United Mine Workers.
  5. Receiving treatment with chemotherapy for cancer under management of an OCM participating practice.
- K. Episode Definition:
1. OCM-FFS includes nearly all types of cancer.
  2. Episodes initiate when a beneficiary starts chemotherapy
  3. The Innovation Center has devised a list of chemotherapy drugs that trigger OCM-FFS episodes, including endocrine therapies but excluding topical formulations of drugs.
  4. All Medicare A and B services that Medicare FFS beneficiaries receive during episodes will be considered included services. Certain Part D expenditures will also be included.
  5. OCM-FFS episodes extend 6 months after a beneficiary's chemotherapy initiation.
  6. Beneficiaries may initiate multiple episodes during the 5-year model performance period.
- L. Payment
1. Per-beneficiary-per-month (PBPM) payment – Monthly Enhanced Oncology Service (MEOS)

- a. \$160 payment is given to the practice each month for enhanced services required by OCM that is paid during the chemotherapy for 6 month “episodes” – while the patient is receiving active treatment for cancer
- b. If the beneficiary enters hospice, the payments cease.

2. Performance-based payment

- a. Incentive to lower the total cost of care and improve quality of care for beneficiaries over the 6-month episode period.
- b. Retrospective payment that is calculated based on the practice’s historical Medicare expenditures and achievement on selected quality measures.
- c. CMS will calculate benchmark episode expenditures participating practices based on historical data, geographical variation and trended to applicable performance period.
- d. A discount will be applied to the benchmark to determine a target price for OCM-FFS episodes. (e.g., Benchmark = \$100 with 4% Discount = Target Price of \$96.
- e. If actual OCM-FFS episode Medicare expenditures are below target price, the practice could receive a performance-based payment. (e.g., Actual cost = \$90 from example (d) above the performance-based payout could be up to \$6.)
- f. The amount of the performance-based payment may be reduced based on the participant’s achievement and improvement on a range of quality measures.
- g. Risk Arrangement for Shared Savings may be one-sided or two-sided:
  - i. One-sided: participants are NOT responsible for Medicare expenditures that exceed target price; Medicare discount 4%; must qualify for performance-based payment by the end of year 3.
  - ii. Two-sided: participants are responsible for Medicare expenditures that exceed target price; option to take downside risk beginning in year 3; Medicare discount 2.75%; must qualify for performance-based payment by end of year 3.
  - iii. Clinical trial participants are included.
- h. Risk adjustments will be made for episodic expenditures including beneficiary expenditures, episode characteristics, disease characteristics and type of service furnished.

M. Quality Measures:

- 1. Clinical quality of care
- 2. Communication and care coordination
- 3. Person and caregiver centered experience and outcomes
- 4. Population health
- 5. Efficiency and cost reduction
- 6. Patient safety

7. Quality measures are culled from data sources such as practice-reported data, Medicare claims and patient surveys

**OCM Quality Indicators:**

Quality Domain	Recommended Practice Requirement or Quality Measurement	NQF #	Source
Communication and Care Coordination	# of ED visits per OCM-FFS beneficiary per episode		Claims data
Communication and Care Coordination	# of hospital admissions per OCM-FFS beneficiary per episode		Claims data
Communication and Care Coordination	% of all Medicare FFS beneficiaries managed by the practice admitted to hospice for < 3 days	#0216	Claims data
Communication and Care Coordination	% of all Medicare FFS beneficiaries managed by the practice who experience ≥ 1 ED visit in the last 30 days of life	#0211	Claims data
Person- and Caregiver-Centered Experience and Outcome	% of OCM-FFS beneficiaries face-to-face encounters with the participating practice in which there is a documented plan of care for pain and pain intensity is quantified	#2100	Reported by practice
Person- and Caregiver-Centered Experience and Outcome	Score on patient experience survey (modified CAHPS)		Administered by CMS contractor
Person- and Caregiver-Centered Experience and Outcome	% of OCM-FFS beneficiary face-to-face encounters in which the patient is assessed by an approved patient-reported outcomes tool and that receive psychosocial screening/intervention at least once per episode		Reported by practice

**N. Monitoring and Evaluation**

1. Tracking of claims data
2. Patient surveys
3. Site visits
4. Analysis of quality measurement data
5. Time and motion studies
6. Medical record audits, tracking of patient complaints and appeals
7. OCM will use match-comparison groups to detect changes in utilization, costs and quality that can be attributed to the model
8. The OCM performance period ended on June 30, 2022. The program will be replaced by the Enhancing Oncology Model (EOM) in July 2023.

O. Milestones<sup>16</sup>

Number of Participants	126 practices across the US  5 commercial payers – Aetna, Blue Cross/Blue Shield of South Carolina, Cigna, Priority Health, University of Arizona Health Plan
Impact on Total Episode Payments for Medicare	All episode payments increased (most likely due to increasing drug costs) but the OCM episodes were \$297 less than non-OCM episodes; the impact was exclusively in Part A and B payments, not Part D
Gross savings to Medicare vs. Provider payments for MEOS/PBP	Over 4 performance periods the net loss to Medicare was \$315,665,814
Impact of OCM on Cancer Treatment Patterns	Chemotherapy drugs used to treat common cancers were similar in the OCM and non-OCM practices and evolved similarly over time; no savings was realized by Medicare  Episode payments in the OCM practices increased less for non-chemotherapy drugs (e.g., supportive care) compared to non-OCM practices
Patient Experience	Cancer patients rated their care very highly regardless of OCM participation
ED Visits/Hospitalizations/Chemotherapy-Related Toxicity	Despite efforts to identify and monitor high-risk patients there was no impact on the rates of ED visits, hospitalization, or chemotherapy-related hospitalization
End-of-Life Hospitalization	Hospitalization in the last month of life declined slightly for OCM practices
Hospice Utilization/Timing	Despite utilization of palliative care specialists and efforts for documenting patient EOL wishes there was no observable impact on hospice use, duration, or timing

**Answers to Question #9:**

**Choice B is correct because the OCM has set the number of visits to the emergency room during a specific treatment episode and the usage of the emergency department during the last 30 days of life as reportable quality metrics.**

**Choice A is incorrect because the OCM is not focused on reviewing drug prescribed within a certain class of medications.**

**Choice C is incorrect because OCM is focused more so on continuity of care issues and not whether patients are participating in a clinical trial.**

**Choice D is incorrect because OCM is not focusing on specifics of drug therapy such as adherence.**

**III. Other general quality improvement tools used in oncology pharmacy:**

- A. Root Cause Analysis (RCA) – structured, step-by-step techniques for problem solving. The goal is to determine and correct the ultimate cause(s) of a problem, not just the visible symptoms, to ensure that it does not occur again.<sup>17</sup>
1. RCA consists of determining what happened, why it happened and what can be done to prevent it from happening again
  2. The Joint Commission requires all accredited organizations to conduct an RCA of any sentinel event (an unexpected occurrence involving death or serious physical or psychological injury, or risk thereof).
  3. The five whys technique – consists of asking why an event occurred repeatedly until the root issue is uncovered.
  4. Cause and effect diagram – can use a “fishbone” diagram where the head of the fish is the problem and branches are considered different categories of causes.
- B. Failure Mode Effects Analysis (FMEA) – originally developed by the US military in the 1940’s to assess equipment failure. It has since been adopted in many industries to evaluate service failure. Joint Commission requires use of FMEA or a similar tool to reduce the potential for failure of a process. FMEA classically involves the following steps:<sup>18</sup>
1. Identification of the process to be evaluated.
  2. Team training: use of FMEA in health care will typically involve personnel from multiple department – e.g., pharmacy, nursing, environmental services, laboratory, etc.
  3. Develop a detailed process flowchart, including all steps in the process.
  4. Identify each step in the process
  5. Identify potential failures (e.g., failure modes) at each step in the process
  6. Determine the worst possible outcome of each failure mode.
  7. Identify the contributory factors for each potential failure.
  8. Identify any failure “controls” that are currently present. A control reduces the likelihood of a failure event or reduces the severity of the consequences of a failure.
  9. Rate the severity of each failure (typically a 1 to 10 scale).
  10. Rate the likelihood that each failure cause will occur (typically a 1 to 10 scale).
  11. Rate the effectiveness of each control (again, a 1 to 10 scale).
  12. Multiple the three above ratings by each other to obtain the risk priority number (RPN) for each cause or contributory factor.
  13. Use the RPNs to prioritize problems for corrective actions.
  14. Develop an improvement plan to address the targeted causes.
- C. ASHP outlines MUE objectives, methodology, and pharmacists’ role in MUEs in their published guidelines for MUE.<sup>19</sup>
- D. Institute for Safe Medication Practices (ISMP)- only non-profit organization devoted entirely to medication error prevention and safe medication use.<sup>20</sup> Certified as a Patient Safety Organization by the US Agency for Healthcare Quality and Research.

1. Established targeted medication safety best practices for hospital for 2022-23.
  - a. **Best practice #1 – Dispense vincristine (and other vinca alkaloids) in a mini bag of a compatible solution and not in a syringe.**
  - b. **Best practice #2 – Use a weekly dosage regimen default for oral methotrexate in electronic systems when medication orders are entered. Require a hard stop verification of an appropriate oncologic indication for all daily oral methotrexate orders. Provide specific patient/family education for all oral methotrexate discharge orders.**
  - c. Best practice #3 – Weigh each patient as soon as possible on admission and during each appropriate outpatient or emergency department encounter. Avoid the use of a stated, estimated, or historical weight. Measure and document patient weights in metric units only.
  - d. Best practice #4 – Ensure that all oral liquids that are not commercially available as unit dose products are dispensed by pharmacy in an oral or ENFit syringe that meets the International Organization for Standardization (ISO) 80369 standard. (ARCHIVED)
  - e. Best practice #5 – Purchase oral liquid dosing devices (oral syringes / cups / droppers) that only display the metric scale. (ARCHIVED)
  - f. Best practice #6 - Eliminate glacial acetic acid from all areas of the hospital. (ARCHIVED)
  - g. Best practice #7 – Segregate, sequester, and differentiate all neuromuscular blocking agents (NMBs) from other medications, wherever they are stored in the organization.
  - h. Best practice #8 – Administer medication infusions via a programmable infusion pump utilizing dose error-reduction software.
    - a. Maintain a 95% or greater compliance rate for the use of dose-error reduction systems.
    - b. Monitor compliance with the use of smart pumps monthly.
    - c. If administering a bolus dose (or loading dose) from a continuous infusion, use a smart pump that allows for programming of the bolus and separate limits for both the bolus and continuous IV infusion.
  - i. Best practice #9 – Ensure all appropriate antidotes, reversal agents, and rescue agents are readily available. Have standardized protocols and/or coupled order sets in place that permit the emergency administration of all appropriate antidotes, reversal agents and rescue agents used in the facility. Have directions for use/administration readily available in all clinical areas where the antidotes, reversal agents and rescue agents are used.
  - j. Best practice #10 – Eliminate all 1,000 mL bags of sterile water (labeled for “injection”, “irrigation”, or “inhalation”) from all areas outside the pharmacy. (ARCHIVED)



- k. **Best Practice #11 – When compounding sterile preparations; perform an independent verification to ensure that the proper ingredients (medications and diluents) are added, including confirmation of the proper amount (volume) of each ingredient prior to its addition to the final container.**
- l. **Best Practice #12 – Eliminate the prescribing of fentanyl patches for opioid-naïve patients and/or patients with acute pain.**
- m. **Best Practice #13 – Eliminate injectable promethazine from the formulary.**
- n. Best Practice #14 – Seek out and use information about medication safety risks and errors that have occurred in other organizations outside of your facility and take action to prevent similar errors.
- o. **Best Practice #15 – Verify and document a patient’s opioid status (naïve versus tolerant) and type of pain (chronic vs. acute) before prescribing and dispensing extended-release or long-acting opioids.**
- p. Best Practice #16 - Limit the variety of medications that can be removed from an automated dispensing cabinet (ADC) using the override function. Required a medication order prior to removing any medication from an ADC, including those removed during an override function. Monitor ADC overrides to verify appropriateness, transcription of orders and documentation of administration. Periodically review for appropriateness the list of medications available using the override function.
- q. Best Practice #17 – Safeguard against error with oxytocin use.
- r. **Best Practice #18 - Maximize the use of barcode verification prior to medication and vaccine administration by expanding use beyond inpatient care areas.**
  - a. Target clinical areas with a short/limited patient stay (~~e.g.e.g.,~~ ED, perioperative areas)
  - b. Regularly review compliance and other metric data to assess utilization and effectiveness of this safety technology.
- s. **Best Practice #19 – Layer numerous strategies throughout the medication-use process to improve safety with high-alert medications.**
  - a. Outline a robust set of processes for managing risk
  - b. Address system vulnerabilities in each stage of the medication-use process and apply to prescribers, pharmacists, nurses and other practitioners involved in medication-use.
  - c. Avoid reliance of low-leverage risk-reduction strategies (~~e.g.e.g.,~~ high-alert stickers on medication storage bins)
  - d. Limit the use of independent double-checks to select high-alert medications with the greatest risk for error within the organization (~~e.g.e.g.,~~ chemotherapy, opioids, heparin)

- e. Regularly assess for risk the in the systems and practices used to support the safe use of medications by using information from internal/external sources (~~e.g.e.g.~~, Joint Commission, ISMP)
- f. Establish outcome and process measures to modify safety and routinely collect data to determine the effectiveness of risk-reduction strategies.

## INFORMATICS

### I. Electronic Medical Record (EMRs) – oncology EMRs lagged behind other computerized physician order entry applications<sup>21,22</sup>

- A. Clinical components of an EMR: Results reporting information system (RRIS), computerized physician order entry (CPOE), clinical decision support system (CDSS)
- B. Baseline elements in oncology-specific EMR: Tumor staging; multidisciplinary and data-intensive workflow; chemotherapy dosing and administration; toxicity assessment and management; clinical trial and protocol management; drug inventory management; survivorship care.
- C. Oncology specific EMR functionalities identified by ASCO: Chemotherapy/drug management; oncology-specific billing; calendar/scheduler; clinical trials and research; compliance safeguards.
- D. Error rates with oncology EMRs are significant in oncology patients given the complexity of treatment regimens – 7% in outpatient adults and 18% in pediatrics<sup>23</sup>
- E. Chemotherapy order set development and maintenance<sup>24</sup>
  - 1. Interdisciplinary team identifies clinically relevant chemotherapy treatment plans to create pre-printed orders based on a paper process
  - 2. Orders are transposed to a standard template build for an EMR
  - 3. Build and validation steps are tracked to track barriers and outcomes
  - 4. Newly created oncology regimen content is amenable to CPOE by credentialed physicians and barcode medication administration by nursing
- F. Other relevant technology:
  - 1. Software-based workflow management of IV compounding:
    - a. Volumetric verification - utilizes digital photo and barcoding to verify step-by-step compounding of sterile IV products
    - b. Volumetric and gravimetric - IV software system monitoring of pharmaceutical compounding that uses bar-code scanning and gravimetric analysis<sup>25</sup>
    - c. Gravimetric vs. Robotic<sup>26</sup>

System and Variance Analysis	2016 Robot N=10,684	2016 Gravimetric N=183	2017 Robot N=13,623	2017 Gravimetric N=7,537	2018 Robot N=17,822	2018 Gravimetric N=10,416
Accuracy (%)	3%	8%	3%	2%	2%	1%
Preparations with 4 – 10% variance (%)	2%	5%	2%	1%	2%	<1%
Preparations >10% variance (%)	1%	3%	<1%	1%	<1%	<1%

#### Timing

	Time to Start Preparation (minutes)	Compounding Time (minutes)	Final Validation Time (minutes)
Gravimetric	10:23	2:39	4:50
Robot	13:27	6:07	4:43

#### Error Characterization

	Robot (N=42,129)	Gravimetric (N=18,136)
All Errors	3,677 (8.7%)	3,468 (19.1%)
Operator Error	409 (1%)	89 (0.5%)
Wrong diluent	580 (1.4%)	1,136 (6.3%)
Wrong drug	59 (1.4%)	937 (5.2%)
Preparation	2,629 (6.2%)	1,306 (7.2%)

#### Question #10:

Which of the following characteristics of clinical pathways is being advocated by national professional oncology societies?

- a. Oncology pathways should include issues beyond drug treatment regimens such as survivorship and end-of-life care
- b. Pathway compliance should approximate 100% with well-written pathways
- c. Commercial entities such as drug wholesalers should not draft/support oncology clinical pathways
- d. Diversity and variation in application of commercially pathways supports physician autonomy in therapeutic decision making

#### G. Oncology Clinical Pathways:<sup>28, 29, 30</sup>

1. Goal is to standardize practice for ordering chemotherapy regimens with use of evidenced-based clinical pathways based on disease and stage.
2. Compliance – goal for on-pathway rate approximates 70 to 80% considering patient-specific factors such as end-organ dysfunction, tumor genomics, patient performance status, and access to care.
3. Major commercial vendors: ClinPath (Via) Oncology; US Oncology – McKesson; Cardinal Health.
4. ASCO released a policy statement on clinical pathways

- a. National approach is needed to remove the unsustainable administrative burden of multiple, unmanaged oncology pathways
  - b. Oncology pathways should be developed in a consistent and transparent process
  - c. Oncology pathways should reflect diagnostic, medical, surgical, and radiation treatments which encompass imaging, labs, survivorship, and end-of-life care
  - d. Oncology pathways should reflect best clinical evidence and be updated routinely
  - e. Oncology pathways should recognize physician autonomy, patient variability, and recognize that 100% concordance with pathways is impossible
  - f. Oncology pathways should be implemented in ways that promote administrative efficiencies for oncology providers and payers
  - g. Oncology pathways should promote education, research, and access to clinical trials
  - h. Robust criteria must be developed to support certification of oncology pathways programs
  - i. Pathway developers, users, and private and governmental funding agencies should support research to understand pathway impact on care and outcomes
5. Clinical data:<sup>28</sup>
- a. Data from eight community practices for treatment of NSCLC patients
    - i. Drug costs: on-pathway - \$18,042 vs. off-pathway \$27,737; no difference in overall survival.
  - b. Utilization of clinical pathways among multiple private oncology physician practices demonstrated an 88% compliance rate with physicians and a decrease in regimen usage from 168 to 136

**Answers to Question #10:**

**Choice A is correct because ASCO has advocated that clinical pathways provide guidance to medical oncologists beyond drug prescribing such as recommendations for end-of-life care, survivorship, surgical intervention and radiation therapy.**

**Choice B is incorrect because ASCO and pathway developers both acknowledge that compliance with clinical pathways reaching 70 to 80% is a best-case scenario given patient-specific factors such as end-organ function and performance status.**

**Choice C is incorrect because most of the commercially available pathways are written by corporate entities such as drug wholesalers (e.g., Cardinal, McKesson) and large publication houses (e.g., Elsevier).**

**Choice D is incorrect because ASCO is advocating for a more uniform approach to pathway development and application, not divergent.**

## FINANCE

- I. Reimbursement for outpatient oncology drugs:<sup>31, 32, 33</sup>
  - A. Reimbursement rates under Medicare for IV drugs provided by hospitals/office-based clinics in the outpatient setting —the average sale price (ASP) of the drug plus 6% per CMS guidelines.
  - B. The federal government budget sequester has reduced the payment from ASP plus 6% to ASP plus 4.3%. Payment limits are updated quarterly on the CMS website.
  - C. Medicare Part D for prescription drug coverage:
    - 1. Offers beneficiaries the option of enrolling for prescription drug coverage administered by a private insurer starting in 2006.
    - 2. Costs have been 40% lower than originally forecast by the Congressional Budget Office largely due to competition between plans, use of generic drugs and beneficiary choice of low-premium plans.
    - 3. Most plans have a deductible with a co-insurance of 25%. Once a cumulative expense of approximately \$3,000 is reached the patient is responsible for the full cost of the drugs until total expenditure reaches approximately \$5,000. This coverage gap has been termed the “doughnut hole”. The Affordable Care Act will gradually phase out the doughnut hole.
    - 4. Subsidies are available for economically disadvantaged patients.
    - 5. Medication Therapy Management (MTM) being incorporated into multiple plans and disease states.
- II. Diagnostic related group (DRG) payment (Medicare Part A benefit): CMS payment method for inpatient hospitalization. Chemotherapy drugs are not individually reimbursed as part of a hospitalization stay and therefore the cost would be deducted from a DRG payment to the hospital for a specific hospital admission.<sup>33</sup>
- III. Drug purchasing
  - A. Heterogeneity in Drug Pricing:<sup>34</sup>
    - 1. Average Wholesale Price (AWP) – “sticker price” – that does not directly correspond to any actual market transaction. It is not an average of prices charged by wholesalers to providers, but a price reported to publishing houses (e.g., Redbook). Medicare’s use of AWP for payment on pharmaceuticals ended in January 2005.
    - 2. Wholesale Acquisition Cost (WAC) – this “list” price from wholesalers may not accurately reflect what is being paid by providers due to discounts and price concessions offered by manufacturers. In general terms:  $AWP = 1.2 \times WAC$
    - 3. Average Sales Price (ASP) – Replaced AWP as the basis for most drugs covered under Medicare’s medical benefit (Part B) in January 2005. ASP is calculated by CMS based on market data for manufacturer selling price which includes rebates, volume discounts, etc. Many private payors have gravitated to ASP to base their reimbursement for oncology drugs.

4. 340B – federal program requiring manufacturers to provide significant discounts for outpatient drugs by eligible covered entities. These covered entities include public and not-for-profit hospitals, children’s hospitals, critical access hospitals and federally qualified health centers and specialty clinics that serve a disproportionate percentage of low-income patients (approximately 12% or greater of payor mix). In 2010, the Accountable Care Act expanded the 340B eligibility to free standing cancer centers.<sup>35</sup>
  - a. Physician office practices or inpatient settings are not eligible for 340B drug pricing
  - b. Patients must receive services from providers at the covered entity to be eligible for 340B
  - c. For cancer clinics to be eligible for the 340B program they must be listed on the Medicare cost report for the facility, the clinic must operate under the same license as the hospital, clinical and financial operations must be integrated between the clinic and hospital (including physician and administrative oversight), medical records must be integrated between the clinic and hospital, and the clinic must publicly declare its affiliation with the 340B hospital.
  - d. An oncology clinic may retain eligibility for 340B even if the physicians are not employed by the hospital if the requirements listed in C above are met and the hospital retains ownership of the clinic and purchases the drugs.
  - e. A non-340B hospital may form a contractual agreement with a 340B hospital for joint ownership or equity in a clinic that may be eligible for 340B.
  - f. Typically, eligibility for a new clinic for 340B is determined the summer following the end of the year that the clinic was reported on the 340B hospital’s Medicare cost report. The clinic is not eligible to purchase drugs at the 340B pricing until approved by Health Resources and Services Administration (HRSA) of the federal government, which administers the program.
  - g. Medicaid patients are not eligible for 340B drug pricing since they already qualify for discounted drug pricing.
  - h. CMS has issued a final rule for reimbursement for 340B purchased drugs effective January 1, 2018:<sup>35</sup>
    - i. ASP +6% changes to ASP **minus 22.5%** for 340B purchased drugs
    - ii. Rural sole community hospitals, PPS-exempt cancer hospitals, and children’s hospital will be exempt from this policy in 2018
    - iii. Expected savings is \$1.6 billion
5. The Supreme Court ruled against CMS for the proposed reimbursement cuts going back to 2018 in the summer of 2022. CMS will reimburse hospitals participating in the 340B Drug Pricing Program at the default rate of 22.5%. Hospitals participating in the program will also receive the difference between the default rate and the old rate

(average sales price minus 22.5 percent) for claims paid after the court ruling. It is yet to be determined as to when and how CMS may reimburse hospitals for variance in reimbursement for 340B patients during that time frame. Following the Supreme Court's ruling, HHS announced it would reimburse hospitals for administering 340B-covered drugs the same as non-340B drugs starting Jan. 1, ~~2023~~2023. Average Manufacturer Price (AMP): created by OBRA 1990 for the purpose of calculating rebates paid by manufacturers to states for drugs dispensed to their Medicaid beneficiaries. AMP is defined as the price available to the retail class of trade and reflected any discounting or rebates to the purchasing entity. In 2005, the federal government mandated that AMP be used instead of AWP to calculate the Federal Upper Limit (FUL) for reimbursement to outpatient prescriptions for the facilities classified as retail class of trade (community pharmacies, mail order pharmacies, and physician offices).

6. Group Purchasing Organizations (GPO): Alliances of health care providers or pharmacies that form an alliance to increase negotiating leverage by increasing purchasing volume.

IV. **MACRA (Medicare Access and CHIP Reauthorization Act) – Replaced the SGR (Sustained Growth Rate which detailed physician payments from CMS)** <sup>36</sup>

- A. MIPS (Merit-Based Incentive Payment System)
  1. Consolidates existing programs: Physician Quality Reporting System (PQRS), Value-based Payment Modifier, Electronic Health Record (HER) Incentive program and adds a fourth component: clinical practice improvement activities
  2. Eligible physicians may see +/-4% to payments in 2019 based on 2017 performance
  3. Domain weighting: quality activities (60%), clinical improvement activities (15%), advancing care informatics performance activity (25%), and cost/resource use (0%)
  4. Practices that accrue less than \$30,000 in Medicare Part B allowed charges or see less than or equal to 100 Medicare patients are exempt from participation in MIPS. This represents 32% of Medicare clinicians by 5% of Medicare spending.
- B. APMs (Alternate Payment Models)
  1. Advanced APM – provider that must bear more than nominal risk under the reimbursement model – a potential downside of 8% of all Medicare reimbursements or 3% of the expected expenditures for which the provider is responsible for in the APM
  2. CMS is exploring options for which clinical track may participate in APMs
- C. QPP (Quality Payment Program)
  1. Goal is to reward delivery of high-quality patient care through MIPS and Advanced APMs
- D. PTAC (Physician-Focused Payment Model Technical Advisory Committee)
- E. PFSM (Physician-Focused Payment Models)
- F. Strategic Objectives:
  1. To improve beneficiary outcomes and engage patients through patient centered Advanced APMs and MIPS policies
  2. To enhance clinician experience through flexible and transparent program design and interactions with easy-to-use program tools
  3. To increase the availability and adoption of robust APMs
  4. To promote program understanding and maximize participation through customized communication, education, outreach, and support that meet the needs of the diversity of physician practices and patients, especially the unique needs of small practices



5. To improve data and information sharing to provide accurate, timely and actionable feedback to clinicians and other stakeholders
6. To ensure operational excellence in program implementation and ongoing development

**Question #11:**

Which of the following is most correct regarding the difference between the FDA approval process for generic drugs and biosimilars?

- a. The biosimilar pathway involves drugs with a wide range of molecular weights
- b. The endpoint for approval for generic drugs and biosimilars is +/-20% bioavailability
- c. Biosimilars are generated in the lab from reproducible steps of chemical synthesis
- d. Biosimilars must demonstrate similar safety, purity, and potency

**V. Biosimilars<sup>38,39</sup>**

- A. Definition – A biotechnologic product comparable to an already approved biotechnological product in terms of quality, safety, and efficacy. The FDA requires that biosimilar drug is highly similar to existing reference product (innovator/originator molecule) notwithstanding minor differences in clinically inactive components and that there are **no clinically meaningful differences** between the biosimilar product and the reference product in terms of **safety, purity, and potency**.

- B. Timeline:

Year and Legislation	Impact
1902 – Biologics Control Act	Mandated licensure of manufacturers of “viruses, serums, toxins, and analogous products”
1906 – Pure Food and Drug Act	Instituted rules about labeling of drugs that included mandated disclosures about addictive substances”
1938 – Food, Drug and Cosmetic Act	Required evaluation of drug safety to be submitted to FDA
1944 – Public Health Service Act	Placed biologics under the purview of Public Health Service
1967 – Kefauver-Harris amendments	Mandated assessment of drug efficacy
1972	Biologics oversight transferred to FDA
1984 – Hatch-Waxman Act	Created an abbreviated application for versions of approved drugs (generic drugs) and created the 505(b)(2) pathway which allow for similar but not bioequivalent drugs to be tested

1988 – Creation of CBER and CDER	Post-approval oversight for biologics – Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER)
2009 – Biologics Price and Competition and Innovation Act	Passed as part of the Patient Protection and Affordable Care Act in 2010 created an abbreviated application pathway for biosimilars that was modeled after that for drug in the Hatch Waxman Act

C. Drugs that could be considered for biosimilar product development in oncology<sup>40</sup>

Drug Class	Example
Cytokines/glycoproteins	Granulocyte (and macrophage) colony stimulating factors Interferons/interleukins Epoetin/darbepoetin
Monoclonal antibodies (with and with drug conjugates)	Rituximab Trastuzumab Bevacizumab
Enzymes	Asparaginase Glucarpidase

D. Differences in Biosimilar and Generic Drugs

Property	Biosimilar	Generic Drugs
Molecular composition	High molecular weight, complex biologic agent	Small molecular weight, reproducible structure
Comparison with reference drug	Same amino acid sequence May have different posttranslational modifications, protein folding, excipients	Identical active ingredient Same bioequivalence, purity
Manufacturing	Uses living cellular systems Unique cell lines and production steps	Chemically synthesized Stepwise process of identified chemical reactions
FDA approval process	Biosimilar biologics license application Demonstrates similar safety, purity, potency, and efficacy	Demonstrates bioequivalence

E. Posttranslational modifications (PTMs)

1. Natural consequences of the use of eukaryotic cellular systems in their production. This is observed in both reference (innovator) and biosimilar products. Examples:
  - a. Glycosylation – may impact Fc binding
  - b. Deamidation/oxidation – may cause proteins to aggregate, degrade or denature that may influence the incidence of drug toxicity

F. Requirements of the Biologics Price Competition and Innovation Act

1. Created a new process:
  - a. Allows the FDA to approve a biologic product based on less than a full complement of preclinical and clinical data if the sponsor could provide analytic studies showing the product was highly similar to an approved biologic product
2. Required animal studies data demonstrating:
  - a. “Safety, purity, and potency” and clinical studies for use in which the reference product was originally approved
3. Two specific types of biosimilar specified under the Acct

- a. Standard biosimilar product with “no clinically meaningful differences” in safety, purity and potency compared to the approved biologic
  - b. An interchangeable product – a biosimilar that can be expected to produce the same clinical result as the approved biologic in any given patient. The FDA would determine the level of testing required to meet these standards
4. Naming convention:
- a. FDA adds a random, lower-case four-letter suffix to the generic name of the biologic for each biosimilar product.
  - b. The goal is to optimize pharmacovigilance efforts and to provide consistency in referencing a manufacturer’s specific biosimilar product.
5. Monoclonal Antibody properties evaluated for biosimilars

Quality Attributes	Variable	Relationship with Pharmacokinetics
Physicochemical Properties	Isoelectric Point Metabolic oxidation of CH2 domains High-mannose glycan	Cellular uptake FcRn binding Mannose receptor binding
Biological Properties	Soluble antigen binding Cell-surface antigen binding FcRn binding* FcγR binding	Disposition as an immune complex Disposition via cellular uptake Recycling Disposition via intracellular uptake or phagocytosis

\*FcRn binding – leads to recycling of monoclonal antibodies

\*\* FcγR binding contributes to apoptosis and/or antibody mediated cytotoxicity

#### G. ASCO Policy Statement<sup>41</sup>

Clinical trials to demonstrate sufficiently similar safety, efficacy, and immunogenicity in biosimilars would be necessary in most, if not all, cases.

While FDA should be given substantial discretion in forging the regulatory pathway for approval of individual classes of biosimilars products, transparency in the process is essential so that clinicians and the public can be satisfied that the process contains adequate safeguards. Notice-and-comment procedures would be appropriate in fashioning the contours of the biosimilars pathway on a class-specific basis. Guidance documents—either on a class-specific basis or in some cases on a product-specific basis—should be published to ensure consistency of standards and predictability of regulatory action.

In any instance in which FDA decides that clinical trials are not necessary for follow-on products, the agency should publicly disclose that decision and provide a detailed rationale.

No system should be adopted that would limit physician choice among “biosimilar” products or require substitution of products that have been designated “interchangeable”. In every instance, the physician should decide which among similar products should be prescribed.

Biosimilar products should be subject to initial review and oversight post-approval by the Office to which the original innovator product is assigned, rather than a separate “generics” office.

Every biosimilar product should be subject to meaningful post-marketing safety surveillance.

Interchangeability should be determined only through clinical trials adequate to support substitution of the biosimilar product for the innovator product without sacrificing safety or efficacy.

Non-patent data exclusivity should be adequate to ensure continued innovation both in new products and in new indications for existing products. Additional years of exclusivity should be provided as an incentive to development of new indications.

Legislators should extend “pediatric exclusivity” incentives to biologics in a manner consistent with those for drug products to enhance incentives for research in specific pediatric indications.

Congress should ensure that FDA is provided adequate resources to meet the new demands of assessing bioequivalence in the number of biosimilar products that will be presented to the agency once standards are in place.

#### H. FDA Guidance<sup>42</sup>

Scientific Consideration in Demonstrating Biosimilarity to a Reference Product: Guidance to Industry. Final Guidance April 28, 2015.

Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. Final Guidance. April 28, 2015.

Answers to Question #11:

Choice D is correct because the FDA definition of a biosimilar states that a biosimilar product must show no difference in terms of safety, purity, and potency to the reference product.

Choice A is incorrect because biosimilars are biologically based complex molecules that have a high molecular weight.

Choice B is incorrect because the +/- 20% bioavailability only applies to generic drugs – biosimilars have additional pre-clinical and clinical data requirements to demonstrate being “highly similar”.

Choice C is incorrect because biosimilars are generated from cell lines not from chemical synthesis in the lab.

VI. **Investigational Drug Services**

- A. ASHP Guidelines on Clinical Drug Research<sup>43</sup>

## Health-System Organization and Oversight

Health-system reviews and approves a protocol in the context of federal, state, and local laws. Determine appropriateness of investigational new drug (IND) application for drugs not commercially available and approved drugs for unlabeled uses.

Mechanism for review and approval for financial aspects of drug research including contractual agreements.

All clinical research is reviewed by an IRB per federal regulations. Appropriate pharmacists are members of the IRB and are consulted by the committee whenever drug studies are reviewed.

Investigational drugs are used only under the supervision of the principal investigator or sub investigators – such as pharmacists.

The principal investigator or designee is responsible for obtaining informed consent from each subject eligible for participation in a clinical trial.

The principal investigator is responsible for the proper maintenance of case report forms.

Medication-use system requirements:

- Drugs are properly packaged
- Drugs are properly labeled
- Adequate supply of study drug stock
- SOP for breaking the study drug blind when clinically warranted
- Appropriate information is provided to professional staff called on to dispense or administer investigational drugs
- Proper storage for investigational drugs
- Only authorized providers may prescribe investigational drugs
- Records are maintained for investigational drug receipt, dispensing and return to sponsor for 15 years after study closure
- Suitable arrangements are made for transfer of drug to another facility
- Platform for disseminating pharmacy records for investigational drugs to clinical investigators

**ASHP-recommended Pharmaceutical Services:**

Copy of IRB-approved research protocol and investigator drug brochure is maintained (including all amendments)

Pharmacy should prepare an investigational drug data sheet

When practical, investigational drugs should be stored in a pharmacy

Pharmacy shall maintain a perpetual inventory record for investigational drugs stored in the pharmacy. These records are subject to audit by the sponsor, the sponsor's representatives, or FDA.

Investigational drug services will be integrated into the medication-use system for the institution; however, labels will indicate "investigational drug". Verification that informed consent has been obtained is required.

Patient education and monitoring for investigational drugs should be explicitly spelled out.

When the study concludes, all unused investigational drug should be returned to the sponsor per their instruction.

Annual descriptive summary of investigational drug services including number of studies, list of all investigational drugs and financial records should be included.

Drug costs and other clinical care expense with drug studies should be properly allocated and reimbursed.

Investigational drugs should be stored in appropriate environmental control in a limited-access area separate from routine drug stocks and shall be inventoried on a routine basis.

Develop an SOP for handling investigational drugs provided by an investigator at a nonaffiliated practice setting.

Pharmacists must maintain the integrity of drug studies by managing access to treatment-assignment records in blinded studies.

When necessary, IDS pharmacists can delegate dispensing authority to other pharmacists within the health-system with appropriate control to maintain continuity of quality dispensing services.

Pharmacists' role for promoting adherence in investigational drug studies should be outlined.

**B. ASHP Guidelines for the management of investigation drug products<sup>44</sup>**

1. Clinical research pharmacy models
  - a. Size, scope, and staffing will depend on volume and complexity of research conducted at the institution
  - b. Funding model to sustain services is required – can include direct cost recovery from the sponsor, indirect funding (e.g., overhead costs), foundation underwriting of the research, and/or the institution absorbing the costs



2. Facilities, security, and limited access
  - a. Investigational study drug should be stored in a secure site as specified by the sponsor and in accordance with all applicable regulatory requirements per GCP
  - b. Each institution must evaluate its ability to provide secure storage with limited access to investigational drug products
3. Temperature control and monitoring
  - a. Sponsor communicates appropriate storage temperature, storage conditions (e.g., protect from light), and storage times for PI and/or clinical research pharmacies
  - b. Standards from USP for controlled temperature storage should be followed by clinical research pharmacy and pharmaceutical manufacturers
  - c. Allowable out-of-range temperatures and maximum allowable deviation time should be communicated from sponsor prior to opening the trial
  - d. Study drug that does not meet criteria for storage as outlined by the sponsor should be quarantined and sponsor notified
  - e. Study drug sensitive to humidity may require monitoring as such which would be the responsibility of the clinical research pharmacy
  - f. All locations storing investigational drug (e.g., refrigerators, freezers, ambient room) require temperature monitoring with the temperature monitoring system calibrated to meet standards of National Institute of Standards and Technology
  - g. Daily record of maximum and minimum temperatures must be maintained
  - h. Equipment used to store investigational drug must be supported by a back-up power system
4. Site qualification
  - a. Conducted by sponsor – policies and procedures should be made available to sponsor for study drug storage/dispensing procedures
  - b. Sponsor written reports for site qualification should be shared with clinical research pharmacy
5. Clinical research pharmacy staff responsibilities
  - a. Pre-IRB feasibility assessment for any dispensing/handling, study drug management issues
  - b. Pharmacists should review protocol, investigator drug brochure, pharmacy manual
6. Pharmacist listing on Statement of Investigator
  - a. Listing on Form FDA 1572 depends on the contribution of the pharmacist to the study – e.g., if the pharmacist will make a significant and direct contribution to the data or is involved in the treatment/evaluation of patients then the pharmacist should be listed. Dispensing responsibilities do not constitute criteria for listing on FDA 1572
  - b. Pharmacist should be listed in the investigator study records as an individual to whom specific responsibilities have been delegated (e.g., dispensing)
7. Delegation of authority to technicians and pharmacy support staff
  - a. Pharmacy technicians may be delegated tasks under institutional policy that do not require a pharmacist license
  - b. Clinical research pharmacist is tasked with ensuring compliance for technician work tasks with applicable laws and regulations

8. Clinical research pharmacy staff training
  - a. Pharmacy-specific training from the sponsor should take place to discuss dispensing logistics
  - b. Clinical research pharmacy should provide sponsor standard operation procedures for temperature logs, drug destruction, etc. for review
  - c. Pharmacy responsibilities are documented on the Delegation of Authority form signed by both the PI and pharmacist
  - d. All dispensing staff should receive appropriate training for GCP and study-specific procedures
  - e. Provide pharmacist CV to sponsor if they are listed on the Form FDA 1571 (Investigational New Drug Application) or Form FDA 1572 (Statement of Investigator)
9. Clinical research pharmacy study setup
  - a. Creation of dispensing guidelines, model physician orders, and a template drug label are required
  - b. Initiation of drug study file
  - c. Any repackaging of study drug should include the statement: "Caution: New Drug – Limited by Federal (or United States) law to investigational use."
10. Considerations for blinded studies
  - a. Dispensing guidelines must be designed to maintain the blind to all appropriate personnel
  - b. Minimize communication between blinded and unblinded staff
  - c. Active and placebo drug products must be identical in appearance, labeling, preparation time, expiration date/time, and supplies used
  - d. Unblinding process that allows treatment assignment to be determined
11. Barcoding of investigation drug products
  - a. Lack of a standard system with investigational drugs
12. Investigational drug product accountability and documentation
  - a. Records must identify the investigator to whom study drug is being shipped and date, quantity, and batch of such shipment
  - b. Expiration date may not be provided but can be requested from sponsor
  - c. Routine inventory count should be conducted
  - d. Transfer of stock must be tracked
13. Investigational drug product receipt
  - a. Ensure proper labeling
  - b. Immediate packaging container must include: "Caution: New Drug – Limited by Federal (or United States) law to investigational use."
  - c. Maintain and process packing slip and verify against received stock
  - d. Verify shipment temperature records
14. Investigational drug product dose preparation and dispensing
  - a. Develop study- and site-specific dispensing guidelines
  - b. Partial or empty non-hazardous vials of study drug may be stored in a designated, limited-access site
  - c. Partial or empty hazardous study drug should be destroyed per institutional policies
15. Remote site or clinic dispensing
  - a. Clinical research pharmacy should assess for best dispensing option

- b. Physician-dispensing may be required
  - c. Clinical research pharmacy should perform audits of remote site
- 16. Investigational drug products returned from participants
  - a. PI or clinical research pharmacy (per delegation from PI) may document study drug returns
  - b. Hazardous drug returns should not be stored on-site – they should be destroyed per institutional standards
- 17. Investigational drug product final disposition
  - a. Destruction on-site or returns to sponsor must be documented
  - b. Hazardous drug destruction must follow all applicable regulations
  - c. Controlled substances must follow DEA regulations for shipping if sent back to the study sponsor
- 18. Clinical research study file
  - a. Create to include all necessary documentation associated with each study
  - b. Retain throughout the conduct of the study and must be available for review
  - c. Both sponsor-provided files (e.g., Investigator Drug Brochure) and site-prepared documents (e.g., any IRB-related communications) must be included
- 19. Monitoring visits or audits of the clinical research pharmacy
  - a. Clinical research associate (monitor) will review records and verify accuracy of source documentation
  - b. Accommodation must be made for monitor visits for blinded studies
  - c. Monitor should verify drug accountability, storage conditions and drug returns
- 20. Monitoring visit logs
  - a. Document monitoring visits and reason for visit
  - b. Document any outstanding requests from the monitor
- 21. Study close and archiving of clinical research pharmacy study files
  - a. Retain all records for 2 years following market approval or after investigation is discontinued if the drug is not approved
  - b. Collaborate with PI to determine who will retain pharmacy-related records
- 22. Clinical research pharmacists as IRB members
  - a. Any potential conflicts of interest should be disclosed
  - b. Standard procurement and dispensing activities should not represent a conflict of interest for a study
- C. HOPA Investigational Drug Service (IDS) Best Practice Standards<sup>45</sup>

**Purpose**

Discuss regulatory and guiding principles for medication use in human subject research

Delineate the role of pharmacy department and staff in clinical research

Outline best practices for investigational drug services for pharmacists

Establish uniform IDS practices

**IDS Responsibilities**

Inventory control of investigational drugs

- Study initiation
- Investigational drug acquisition
- Accountability
- Study closeout

Storage and handling of investigational drugs

- Safe handling
- Temperature monitoring

Preparation and dispensing of investigational drugs

- Labeling, blinding, protocol compliance

Disposal, destruction or return of investigational drugs

Investigational drug management

- Transferring investigational drugs between protocols
- Using patient's own investigational drugs
- Using an investigational medication from another institution

Investigational medication shortages

**Inventory Maintenance**

Drug accountability forms should include:

- Investigator name
- Investigator site
- Dispensing location
- Protocol number
- Full protocol title
- Medication name, strength, formulation
- Transaction types (e.g., medication receipt, dispensing, quantity, lot number, medication transfer, undispensed medication disposition)
- Initials and date of recorder
- Unused, patient returns

## **Policy Development**

IDS should develop policies for the following:

- Tracking expiration dates of investigational drugs
- Use of computer software for investigational drugs management
- Audits
- Establishing if an investigational drug warrants hazardous drug handling precaution
- Investigational drug storage, returns and disposal
- Continuous temperature monitoring and reporting
- Establishing IDS study fees to investigators/sponsors
- Coordinating studies across multiple sites
- Mailing investigational drugs
- Use of an investigational drug from another institution
- Study closeout procedures

## **IDS Best Practices for Prescribing Investigational Drugs**

Ensure that protocol information is sufficient for pharmacy staff at the time of prescribing

- Study protocol
- Investigator drug brochure
- Pharmacy manual
- Safety data sheets

IDS to train pharmacy and other personnel on the study team

- Training should be documented

Compile and maintain a list of qualified prescribers

Create a template of protocol-specific (including all study arms) medication order sets

- With CPOE – utilize clinical decision support when feasible
- Participate in investigational order set development
- Review and approve investigational drug order sets as part of a multi-disciplinary team

### Best Practices for Dispensing and Administering Investigational Drugs

IDS facilitates the dissemination of study drug information which should include:

- Medication designation and common synonyms
- Dosage form and strength
- Pharmacology and pharmacokinetics
- Dosing range and schedule
- Preparation information
- Route of administration
- Storage information
- Dispensing information
- Administration instructions
- Monitoring parameters
- Expected therapeutic effect and adverse event profile
- Supportive care for toxicity of the study drug regimen
- Drug-drug and food-drug interactions
- Contraindications
- Special precautions for handling
- Disposal methods

Proper order review and verification by pharmacy staff

Process for verification that informed consent was obtained

Labeling procedures for IV and oral medications

Procedures for dispensing single- or double-blind studies

Administration:

- IDS should identify administration required by sponsors

### **Pharmacist Role in the Protocol Life Cycle for Investigational Drugs**

Pharmacists should develop the medication information section of the protocol

Pharmacist should provide recommendation for supportive care in the protocol that are consistent with institutional standards

Pharmacists should participate in Scientific Review Committees

- Define who will be supplying study and commercial drug stock
- IND requirements
- Appropriateness and completeness of medication information in the protocol
- Assure clarity in the treatment and medication administration section of the protocol
- Assure clarity in the dose modification section of the protocol
- REMS is followed (if applicable)
- Reporting requirements for adverse events
- Protocol-specific order sets
- Multicenter studies – drug distribution model clearly defined

Pharmacists should participate in IRB protocol review

- Review all medication information
- Informed consent review – risks related to drug therapy – investigational or otherwise
- Risks are reasonable in relation to anticipated benefits
- Guidelines for reporting adverse events are clear
- Pharmacists serving on IRBs serve as a liaison to the pharmacy department/IDS following protocol approval

### **Pharmacist Best Practices for Counseling and Monitoring Investigational Drugs**

Pharmacists provide medication counseling to patients receiving investigational drugs

Pharmacist should assess adherence to study drug

Pharmacists should participate in reporting of unanticipated events/adverse events

### **Pharmacy Technician Role**

Institutions should precisely define the role of an IDS pharmacy technician

Minimum qualifications should be established for pharmacy technicians working in IDS

Pharmacy technicians' roles should be established to facilitate IDS operations

- Investigational drug preparation
- Assist with investigational drug accountability
- Monitor storage condition of study drugs
- Ordering of investigational drug supplies and manage the return process
- Assistance with monitoring visits and audit preparation

### Expanded Access Study Drugs

IDS pharmacists should familiarize themselves with gaining access to expanded access study drugs

- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- NCI's Physician Desk Query ([www.cancer.gov](http://www.cancer.gov))
- NCI's Treatment Referral Center ([http://ctep.cancer.gov/branches/pmb/referral\\_center.htm](http://ctep.cancer.gov/branches/pmb/referral_center.htm))
- Company-specific websites

IDS pharmacist should determine whether the manufacturer will make study drug available through a single-patient IND

IDS pharmacist should verify FDA and local IRB approval for use of study drug through non-emergency expanded access

IDS pharmacist should be familiar with the FDA and NCI websites regarding expanded access

- Expanded access and charging for expanded access (~~<https://www.fda.gov/news-events/public-health-focus/expanded-access>~~ (<https://www.fda.gov/news-events/public-health-focus/expanded-access>)
- Treatment use: ([www.fda.gov/RegulatoryInformation/Guidances/ucm126495.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm126495.htm))
- Individual patient IND requests: (<https://www.fda.gov/drugs/investigational-new-drug-ind-application/physicians-how-request-single-patient-expanded-access-compassionate-use>)
- NCI treatment center referral: ([http://ctep.cancer.gov/branches/pmb/referral\\_center.htm](http://ctep.cancer.gov/branches/pmb/referral_center.htm))

### Question #12:

**Which of the following time points is recommended for follow-up by a pharmacist for patients starting a new oral oncolytic therapy?**

- Prior to first refill
- At consistent 6-month intervals
- With first report of patient toxicity
- Within 7 to 14 days following starting the drug

## VII. Specialty Pharmacy

- ASHP Specialty Resource Guide<sup>46</sup>
- Definitions for Specialty Pharmacy and Specialty Pharmaceuticals:
  - Specialty pharmacy practice encompasses the provision of specialty pharmaceuticals requiring unique fulfillment and patient care support services



## Elements for Specialty Pharmacy:

<b>Fulfillment:</b>
<ul style="list-style-type: none"><li>• Coordination of care and facilitating drug access to limited distribution specialty pharmaceuticals</li><li>• Facilitating mail order delivery logistics</li><li>• Negotiating payer contracts</li><li>• Maintaining cold-chain distribution</li><li>• Dispensing and tracking REMS drugs</li><li>• Accounts receivable support/management</li><li>• Program accreditation</li></ul>
<b>Technical and Clinical Patient Care Support:</b>
<ul style="list-style-type: none"><li>• Benefits investigation, prior authorization, and patient assistance program (PAP)</li><li>• Call-center development, staffing, and monitoring</li><li>• Case management, which may include development of protocols and disease state management at a minimum</li><li>• Product device training</li><li>• Data management of technical and clinical patient care services</li></ul>
<b>Characteristics of Specialty Pharmacy:</b>
<ul style="list-style-type: none"><li>• High-cost medications</li><li>• Complex treatment regimens involving intensive patient education and follow-up</li><li>• Special handling, storage, and delivery requirements for medications</li><li>• Need for companion correlative testing for specific medications</li><li>• Limited or exclusive distribution networks</li><li>• Medications that treat rare diseases that may require long-term treatment and have severe symptoms</li><li>• Medications defined by payers as specialty pharmaceuticals</li></ul>

### C. Care Models

1. Traditional Patient Care:
  - a. Specialty medication filled at a retail pharmacy
  - b. Patient education and interaction screening provided on-site by pharmacist
  - c. No use of standardized case management or education protocol
  - d. No programmatic approach to ensuring adherence
2. Coordinated Care
  - a. Pharmacies that focus primarily on specialty pharmaceuticals
  - b. These pharmacies provide reimbursement assistance, patient care coordination, and ongoing monitoring of the patients
  - c. Pharmacy is responsible for obtaining necessary and accurate paperwork from the physician office to start work on financial coverage
  - d. Assistance for prior authorizations is generally offered
  - e. Pharmacy likely does **not** have access to the patient medical record
  - f. Pharmacy may offer help for patient assistance programs sponsored by the drug manufacturer
  - g. Requires coordination between pharmacists and reimbursement specialists

3. Integrated Care
  - a. Requires pharmacists deployed in a comprehensive medication management system and integrated into the primary medical care team
  - b. Pharmacists are often residency trained and board-certified
  - c. Collaborative practice agreement with physician groups is common
  - d. Pharmacist often has a physical presence in the clinic with high-volume specialty pharmacy medications
  - e. Pharmacy team collaborates to manage transitions of care between inpatient and outpatient settings
  - f. Pharmacists have full access to the patient's medical record

**Success Factors for integrated care model:**

- Complete and timely information about the patient and services they are receiving
- Access to EMR
- Adequate resources for patient education and self-management support
- Ability to measure and report on quality of care
- Culture of teamwork between physicians and pharmacy staff

**D. Specialty Pharmacy Business Models:**

1. Build – development from within an organization for the entirety of special pharmacy services
2. Partner – fulfillment and patient care services provided by the entity; other services may be contracted out – e.g., call center, prior authorizations, case management, etc.
3. Outsource – contracting with a vendor to provide all or most of specialty pharmacy services
4. Manage individual patient risk – no formal specialty pharmacy program, utilization of white and or brown bagging

**Specialty Pharmacy Accreditation Agencies (only 1 is required)**

- ACHC ([www.achc.org](http://www.achc.org))
- URAC ([www.urac.org](http://www.urac.org)) –provides accreditation services to multiple health care services including specialty pharmacy

**E. HOPA Best Practices for the Management of Oral Oncolytic Therapy (2018)<sup>47</sup>**

**Prescribing:**

- Patient consent, including intent of therapy should be obtained for oral oncolytic therapy.
- Pharmacists should provide a comprehensive review of new oral oncolytics and determine their place in therapy via an interprofessional formulary committee.
- When feasible, pharmacists should support oral oncolytic prescribing on an individual patient level, taking into consideration both patient- and medication-specific characteristics.
- Pharmacists should be involved in the creation of oral oncolytic templates for electronic prescribing that include all required components and any standard supportive care measures or monitoring

<ul style="list-style-type: none"> <li>• Pharmacists should perform a comprehensive medication review at the time of prescription</li> <li>• Oral oncolytic safety and quality standards should be consistent with intravenous treatment standards</li> <li>• The oncology team should communicate the intent of oral oncolytic therapy, pertinent drug-drug interactions, and potential implications for the patient's comorbidities and management strategies to the patients' primary care provider</li> </ul>
<p><u>Education:</u></p> <ul style="list-style-type: none"> <li>• Pharmacists should be involved in the development or endorsement of standardized education materials and education should be consistent across the oncology care team</li> <li>• A separate education visit- in person or over the phone (virtually) should occur after the oncologist's initial prescribing visit and before the start of oral oncolytic therapy to supplement and reiterate information provided during the oncologist visit</li> <li>• Education should be comprehensive and focus on patient self-care management of oral oncolytic adverse events and the importance of medication adherence</li> <li>• An assessment of patient knowledge, confidence to manage adverse effects and need for follow-up should occur during the education session</li> <li>• Patient and caregiver attendance at the education session is encouraged</li> </ul>
<p><u>Dispensing/Distribution:</u></p> <ul style="list-style-type: none"> <li>• A dedicated medication assistance team (a non-pharmacist) should prospectively screen and provide financial support for oral oncolytic medications</li> <li>• The dispensing pharmacy should have access to necessary information for safely filling the oral oncolytic medication, including laboratory values and progress notes</li> <li>• The dispensing pharmacy should have access to necessary information for safely filling the oral oncolytic medication, including laboratory values and progress notes</li> <li>• The dispensing pharmacy should have a dedicated liaison for the clinic and provide information that includes financial toxicities, refills, medication adherence and any identified medication adverse events</li> <li>• Specialty pharmacists and oncology pharmacy organizations should partner to promote the education of oncology pharmacists and optimize oncology patient care</li> </ul>
<p><u>Monitoring/Follow-up:</u></p> <ul style="list-style-type: none"> <li>• A consistent process with standardized tools should be used in the oncology clinic setting for monitoring and follow-up</li> <li>• An oncology pharmacist should be involved in the creation of monitoring and follow-up materials and ideally in the assessment and monitoring of a patient's symptoms and medication adherence</li> <li>• Initial monitoring of symptoms and adherence, including patient-reported outcomes (PROs), should occur between 7 and 14 days after the start of treatment</li> <li>• Ongoing monitoring of symptoms and adherence including PROs should occur at each clinical encounter or at least before each refill</li> <li>• Medication reconciliation should occur at each assessment point above, ideally by a pharmacist</li> <li>• Adherence assessment should be user friendly, reliable, cost effective and practical</li> </ul>

- Collaborative practice agreements, including laboratory and symptom monitoring, should exist in settings in which clinical oncology pharmacists are part of the interdisciplinary team
- Communication within the oncology team and with the patient's primary care provider should be ongoing

Practice Management:

- Oncology practices should have an oral oncolytic program with pharmacist involvement where possible
- Before oral oncolytic program development, a baseline gap assessment should be performed to assess areas for improvement and baseline performance on oral oncolytic quality measures
- Pre- and post-financial, clinical quality measures including interprofessional and patients experience should be assessed for continuous quality improvement
- Sufficient resources should be provided to meet the above quality measures

F. ASCO NCODA Patient-Centered Standards for Medically Integrated Dispensing (MID) - 2019<sup>48</sup>

Patient Relationships:

- Communications related to the dispensing process, whether directly with the patient or on the patient's behalf should be documented in the patient record
- Direct access for patients to the MID team is required. Patients should have access to direct phone lines and after-hours phone numbers should be available. All calls left on voicemail must be returned by the next business day.

Education:

- Prior to initiation of an oral anticancer drug, a formalized patient education session should occur with an experienced clinical educator such as a nurse, physician, pharmacist, nurse practitioner or physician's assistant. The discussion should include drug name (generic and brand), dose, schedule, potential adverse effects, and how to properly manage them, fertility (where applicable), treatment goal, duration of therapy and financial and affordability considerations.
- An informed consent form (or assent if applicable) that includes the intent of patient therapy should be reviewed by the patient (and caregiver, if applicable) with a patient educator. After signing the informed consent, the patient will receive a copy and the original document will be included in the patient record. The patient should sign the form after all questions are answered with the patient retaining a copy.
- Patient education will include review of the clinical treatment-related parameters for which the patient and/or caregiver should contact the oncology team. Emergency and secondary (non-emergent) points of contact for the patient should be established and documented in the patient record.
- At the time of initiation of any new therapy initiation, written patient education should be provided. This information should be provided in the language of preference, wherever possible and the provider should ensure that the patient understands the information contained in the written materials.
- Prescribing information required by law must be given to patients.

#### Adherence and Persistence:

- Calendars or other scheduling communications are helpful to maximize adherence. If provided, the calendar should include refill dates and medication schedules, clearly outlining specific dates to take medication. Include documentation of calendar information in the patient record.
- A systematic comprehensive follow-up process that is documented in the patient record within 7 days of dispensing the oral oncolytic is required. Communication to patients is an essential element of patient education to assess adherence and toxicities. Communication to patients is an essential element of patient education to assess adherence and toxicities. Communications should be tailored to presentation, specific medications, and patient comorbidities. Subsequent calls to the patient should be based on individual patient requirement and assessment of patient risk factors (education comprehension, performance status, tolerance to previous therapies, etc.). The prescriber must be notified directly when issues related to compliance are identified by the MID team.
- Pill caddies may be appropriate and helpful for patient adherence.
- Continually evaluate electronic and manual tools that may be helpful in advancing patient adherence.
- Establish a plan for assessment of adherence of patient and toxicity at each clinical encounter. Variances should be documented in the patient record.
- Adherence assessment and documentation should include (1) confirmation patient received the prescription (2) start date for the medication (3) verification that the patient understands how to take the medication, including with/without food, taking whole/crushed tablets, safe handling, etc.
- Monitoring of drug toxicity, laboratory testing and any prescription, OTC, or herbal medication changes. Contact prescriber in a timely manner to address potential problems/issues.
- Discussion of any financial issues that may be affecting adherence by the patient and assessment of the need for increased assistance.

#### Safety:

- Patient identity should be verified using two patient identifiers (e.g., name, date of birth, address) at the time of entering the prescription and at the time of dispensing.
- Appropriate diagnosis, allergy, correct drug/dose, and directions must be verified. The most recent provider note should be reviewed to validate treatment plan.
- Prescriptions for an oral oncolytic, either retained internally for processing or referred to an external pharmacy will be reviewed by the MID personnel for potential drug interactions or toxicity risks.
- If a patient does not pick up a prescription or accept delivery for an oncolytic, the pharmacist will notify the prescriber and verify therapy status.
- Patient profile is reviewed for duplicate therapies.
- The prescriptions should only be filled after patient education and consent forms have been completed.
- Drug interactions must be actively reviewed at each patient encounter. This includes a review of the patient record as well as a conversation with the patient about recent medication changes including OTC and/or herbal therapies.
- Do not refill medications unless verified with the prescriber and the patient.

<ul style="list-style-type: none"> <li>• The MID team will verify that a toxicity evaluation and management visit with a provider has been scheduled for approximately 2 weeks after initiation of new oncolytic therapy.</li> <li>• Labeling of prescriptions should follow legal labeling requirements.</li> </ul>
<u>Refilling of Prescriptions:</u> <ul style="list-style-type: none"> <li>• Prior to refilling an oral anticancer drug, the MID team will review patient records for clinically relevant information (laboratory data, prescription changes, latest progress note, and cycle of therapy).</li> <li>• Interventions involving a patient's refill of medication should be documented in the patient record (e.g., coordination with intravenous chemotherapy and new medications prescribed). The MID team may need to clarify this intervention with the patient and be prepared to respond to any questions the patient may ask.</li> </ul>
<u>Documentation:</u> <ul style="list-style-type: none"> <li>• Every clinical encounter with a patient will be documented in the patient record. In most cases this would be an electronic medical record and questions posed by the patient will be documented as well.</li> </ul>
<u>Benefits Investigation:</u> <ul style="list-style-type: none"> <li>• All aspects of benefit investigation and patient assistance will be coordinated by the MID team including prescription coverage and copay determination, copay assistance and foundation/pharmaceutical industry patient assistance programs. All patients will receive evaluation for financial support.</li> <li>• Results of benefit investigation information should be documented in the patient medical record.</li> </ul>
<u>Medication Disposal:</u> <ul style="list-style-type: none"> <li>• The MID will have a standard operating procedure in place to ensure the proper disposal of patients' unused medication and expired drugs.</li> <li>• Patient education will include directions to ensure proper disposal of unwanted or expired medications.</li> <li>• Brochures addressing proper disposal may be helpful in providing locations and addresses of local sites that accept unwanted/unused medications.</li> </ul>
<u>Patient Satisfaction:</u> <ul style="list-style-type: none"> <li>• Practices are encouraged to solicit feedback from patients using surveys such as the National Community Oncology Dispensing Association patient satisfaction survey to identify and address continuous improvement opportunities at MID practices.</li> </ul>

G. Successful Specialty Pharmacy Practice Models

1. Solid Tumor Oncology<sup>49</sup>
2. Hematologic Malignancies<sup>50</sup>

**Answers to Question #12:**

**Choice D is correct because the HOPA best practices for oral oncolytic therapy and the ASCO/NCODA standards for medically integrated dispensing of oral oncolytics recommend 7 to 14 days and within 7 days of therapy initiation, respectively.**

**Choice A, B, and C are incorrect because the HOPA best practices for oral oncolytic therapy and the ASCO/NCODA standards for medically integrated dispensing of oral oncolytics recommend 7 to 14 days and within 7 days of therapy initiation, respectively.**

**VIII. Role of pharmacy technicians in oncology pharmacy – ASHP/HOPA guidelines<sup>51</sup>**

- A. Focus: Define the role and scope of the pharmacy technician in the ambulatory setting including education/training, medication compounding, dispensing/distribution, patient care services, revenue cycle optimization, supply chain management, technology/informatics, and quality improvement.
- B. Education/training:
  - 1. Technicians must have appropriate training and credentials for medication preparation and distribution and for the performance of other functions not necessarily requiring a pharmacist's judgement.
  - 2. Pharmacy Technician Certification Exam (PTCE) established in 1995 but not yet required in a standard fashion
  - 3. Select State Boards of Pharmacy require pharmacy technicians to be licensed.
  - 4. A majority of State Boards of Pharmacy (80%) require pharmacy technicians to complete continuing education credits
- C. Medication compounding/dispensing/distribution:
  - 1. USP <797> and <800> compliance and workflow management
  - 2. Establish best practices per standard references such as ASHP Guidelines for Hazardous Drugs
- D. Patient care services:
  - 1. Technicians may assist in recording medication histories
  - 2. Assist pharmacists with monitoring patients on oral chemotherapy
  - 3. Assist with compliance with REMS programs
  - 4. Record keeping and documentation with investigational drug studies
- E. Revenue cycle optimization:
  - 1. Obtain prior authorizations
  - 2. Validation of drug claims in revenue cycle
  - 3. Management of drug denials from insurance companies
  - 4. Formal program to minimize drug waste
  - 5. Drug inventory management
  - 6. Coordinate drug replacement acquisition
  - 7. Compliance for discarded drug waste billed through JW modifier
  - 8. Tracking off-label drug use for billing purposes
  - 9. Assist with patient assistance programs
- F. Supply chain management:
  - 1. Drug purchasing/procurement
  - 2. Inventory control
  - 3. Drug shortage management

- G. Technology/informatics:
  - 1. Liaison between clinical staff and informatics team
  - 2. Roles of technician involvement may include automation/technology systems management, policy/governance, customer service, charge integrity, reporting interface/database management, automation management new technology assessment, workflow management, and education/training
- H. Quality ~~improvement:Assessment~~~~improvement: Assessment~~ (QA)
  - 1. Environmental monitoring including engineering controls, quality of sterile product preparation and equipment monitoring
  - 2. Policy development and revision
  - 3. Training other pharmacy team members on aseptic technique, PPE and HD spill management

IX. **Dose rounding – Position Statement from HOPA<sup>52</sup>**

- A. Developed by HOPA standards committee to promote uniform practice regarding dose rounding with cytotoxic and biologic antineoplastics
- B. Monoclonal and biologic agents are to be rounded to the nearest vial size within 10% of the prescribed dose
- C. Traditional cytotoxic agents are to be rounded to within 10% of the prescribed dose – NCI Guidelines for Auditing Clinical Trials defines a major deficiency as dose deviations greater or less than 10% which was a rationale for this recommendation. Antibody-drug conjugates are recommended to have dose rounding parameters based on this same convention.
- D. The 10% dose rounding allowance is recommended for both curative-intent and palliative-intent treatment.
- E. For oral chemotherapy, it is advantageous to use a single strength tablet formulation and round the final dose based on that tablet strength to avoid the risk of medication error and multiple copayments for more than one tablet strength for a single prescription.
- F. Institutional standards should develop a policy-driven approach to dose rounding with anticancer agents that is endorsed by a pharmacy and therapeutics committee and/or an oncology practice leadership committee.
- G. Exceptions:
  - 1. Clinical trials where the protocol dictates a rounding procedure that is different from institutional practice.
  - 2. Pharmacokinetically determined doses of anticancer treatment such as high dose busulfan used in conditioning regimens for hematopoietic stem cell transplant.
  - 3. Patients with poor performance status, major organ dysfunction, extensive treatment history, relevant enzyme deficiency/genetic polymorphism (e.g., DYPD and fluorouracil) or history of dose reduction for prior toxicity.

X. **Patient assistance programs<sup>53</sup>**

- A. New oncology drugs (oral and IV) have patient assistance programs available through the manufacturer – contact information is typically available on the drug’s website
  - 1. Drug stock provided by the manufacturer for free to a patient who qualifies for coverage through the manufacturer



2. Coverage of off-label use for specialty oncology drugs (e.g., use of a targeted agent for an indication for which is it not approved based on genomic sequencing results)

B. Co-pays can be a formidable cost for many patients receiving high-cost oncology drugs even with insurance; estimates predict that 1 in 4 prescriptions is not filled if the co-pay exceeds \$200

C. Commonly used resources:

1. Manufacturer co-pay cards:

a. Not eligible for use for patients with government provided insurance (e.g., Medicare, Medicaid, Tricare)

b. Criticized for shunting prescriptions to higher cost drugs

c. Discount prescription programs/cards widely available (~~i.e.~~, Good Rx®)

2. Medicare Part D: Coverage donut hole is 25% for 2022, receding from 50% to 25% by 2020

3. Medicare Part B: 20% out of pocket expense may be picked up by a Medicare supplemental insurance plan or through a charitable foundation

#### Patient assistance funds

Organization	Website:
Assistance Fund	<a href="http://www.theassistancefund.org">www.theassistancefund.org</a>
Cancer Care Co-Pay Foundation	<a href="http://www.cancercarecopay.org">www.cancercarecopay.org</a>
Chronic Disease Fund (CDF)	<a href="http://www.cdfund.org">www.cdfund.org</a>
Genentech Access to Care Foundation	<a href="http://www.genentech-access.com/hcp">www.genentech-access.com/hcp</a>
Healthwell Foundation	<a href="http://www.healthwellfoundation.org">www.healthwellfoundation.org</a>
Johnson and Johnson Patient Assistance Fund	<a href="http://www.jjpaf.org">www.jjpaf.org</a>
The Lois Merrill Foundation	<a href="http://www.thelmf.com">www.thelmf.com</a>
Leukemia and Lymphoma Society	<a href="http://www.lls.org">www.lls.org</a>
Medication Assistance Tool	<a href="http://www.medicineassitancetool.org">www.medicineassitancetool.org</a>
Novartis Oncology Patient Assistance Fund	<a href="http://www.patientassistanzenow.com">www.patientassistanzenow.com</a>
National Organization for Rare Disorders (NORD)	<a href="http://www.rarediseases.org">www.rarediseases.org</a>
Patient Access Network Foundation	<a href="http://www.panfoundation.org">www.panfoundation.org</a>
Patient Advocate Foundation	<a href="http://www.patientadvocate.org/">www.patientadvocate.org/</a>
	/

## **XI. Drug Shortages**

- A. Impact of drug shortages for oncology drugs:<sup>54</sup>
  - 1. Survey data from HOPA membership (n=243 respondents) indicated that delays in chemotherapy treatment were reported by 93% of survey participants
  - 2. 85% of respondents noted a drug budget increase secondary to drug shortages
  - 3. 34% noted at least 1000 hours of additional labor to manage shortages
  - 4. Increase in near-miss events due to drug substitution (16% of respondents)
  - 5. Interference in conduct of clinical trials (44% of respondents)
- B. Causes of drug shortages:<sup>55</sup>
  - 1. Economics for generic drug manufacturing
  - 2. Raw materials shortage
  - 3. Contaminated drug stock
  - 4. Stockpiling of drugs in short supply exacerbates the shortage
- C. Ongoing management:<sup>56</sup>
  - 1. FDA Safety and Innovation Act (FDASIA - 2012) – requires reporting of certain drug shortages by manufacturers to the FDA (drugs that are life-supporting, life-sustaining or intended for prevention of a debilitating illness)
  - 2. FDASIA allows for FDA to expedite review of new or abbreviated drug applications to mitigate the shortage and to maintain an up-to-date list of drugs in short supply; an annual report on drug shortages is provided to Congress
  - 3. FDA has discretion to:
    - a. Release product with quality issues if the issues do not present a risk to public health for drugs in short supply
    - b. Work with other manufacturers to increase production
    - c. Expedite review of production plant changes and upgrades
    - d. Temporary importation
  - 4. Industry perspective on contributing factors:
    - a. Compliance with current good manufacturing practice (cGMP)
    - b. Production measures to ensure performance in manufacturing
    - c. Resourcing for facilities and equipment
    - d. Disruptions in the supply chain
  - 5. Potential solution for consideration
    - a. More favorable reimbursement for generic drugs
    - b. Flexible production capacity from manufacturers
    - c. Improve efficiencies in regulatory review of manufacturing facilities
    - d. Tax incentives for select medications in short supply
    - e. Government support of the market to ensure a baseline demand for select drugs
    - f. Consideration of market exclusivity for older generic drugs
    - g. Contracting – insertion of “failure to supply” clauses that require manufacturers to compensate purchasers for supply interruptions
    - h. Increasing availability of unit-of-use packaging
- D. Review of current shortages:
  - 1. FDA - <https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>

- a. Available as an app for Android or iOS
- 2. ASHP - <https://www.ashp.org/Drug-Shortages/Current-Shortages>

## RECOMMENDED READING AND REFERENCES

### Recommended Reading

1. Golbach AP, McCullough KB, Soefje SA, Mara KC, Shanafelt TD, Merten JA. Evaluation of burnout in a national sample of hematology-oncology pharmacists. *J Oncol Pract* 2021;18:e1278-e1288.
2. McBride A, Hudson-DiSalle S, Pilz J, et al. National Survey on the effect of oncology drug shortages in clinical practice: A Hematology Oncology Pharmacy Association survey. *J Oncol Pract* 2022;18:e1289-e1296

### References

1. American Society of Health-System Pharmacists. ASHP Guidelines on Handling of Hazardous Drugs. *Am J Health-Syst Pharm* 2018;75:1996-2031.
2. Pharmaceutical compounding – hazardous drugs – handling in healthcare settings (general information chapter 800). In: The United States Pharmacopeia 39<sup>th</sup> rev., and the National Formulary 34 ed. Rockville, MD: The United States Pharmacopeial Convention; 2016:285.
3. Pharmaceutical compounding – Sterile preparations (general information chapter 797). In: The United States Pharmacopeia 45<sup>th</sup> rev., and the National Formulary 40th ed. Rockville, MD: The United States Pharmacopeial Convention; 2022:: 1 – 33.
4. <http://www.hercenter.org/hazmat/tenstepblueprint.pdf>. Accessed September 23, 2018.
5. <https://www.epa.gov/hwgenerators/final-rule-management-standards-hazardous-waste-pharmaceuticals-and-amendment-p075>. Accessed July 1, 2019.
6. Celano P, Fausel CA, Kennedy EB, et al. Safe handling of hazardous drug: ASCO standards. *J Clin Oncol* 2019;37:598-609.
7. <https://www.ons.org/sites/default/files/2019-08/Safe%20Handling%20Aug%202019.pdf>. Accessed October 16, 2019.
8. <http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>. Accessed September 24, 2018.
9. NIOSH (2016). NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2014. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O’Callaghan JP. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2016-161 (Supersedes 2014-138).
10. <https://www.cdc.gov/niosh/topics/hazdrug/default.html>. Accessed July 14, 2021.
11. <http://www.fda.gov/Drugs/default.htm> Accessed September 24, 2018.
12. <https://www.dea.gov/drug-information>. Accessed September 24, 2018.
13. [https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2022/npsg\\_chapter\\_hap\\_jan2022.pdf](https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2022/npsg_chapter_hap_jan2022.pdf). Accessed July 18, 2022.
14. Neuss MN, Gilmore TR, Belderson KM, et al. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards, including standards for pediatric oncology. *Oncol Nursing Forum* 2017;44:A1-A13.
15. <https://practice.asco.org/sites/default/files/drupalfiles/2022-02/2022-QOPI-Round-1-Reporting-Track-Public-Posting.pdf>. Accessed July 18, 2022.
16. Oncology Care Model | CMS Innovation Center Accessed July 14, 2021.
17. Evaluation of the Oncology Care Model: Performance Periods 1-5 (cms.gov) Accessed July 14, 2021.
18. Hettinger AZ, Fairbanks RJ, Hegde S et al. An evidence-based toolkit for the development of effective and sustainable root cause analysis system safety solutions. *J Health Risk Manag*. 2013; 33:11-20.
19. Shebl NA, Franklin BE, Barber N. Is failure mode and effects analysis reliable? *J Patient Saf*. 2010; 6:86-94.
20. American Society of Health-System Pharmacists. ASHP guidelines on medication-use evaluation. *Am J Health-Syst Pharm*. 1996;53:1953-5.

21. <https://www.ismp.org/system/files/resources/2022-02/2022-2023%20TMSBP%20final.pdf> Accessed July 16, 2022..
22. Fasola G, Macerelli M, Follador A, Rihawi K, Aprile G, Della Mea V. Health information technology in oncology practice: A literature review. *Cancer Inform* 2014;13:131-9.
23. Walsh KE, Dodd KS, Seetharaman K et al. Medication errors among adults and children with cancer in the outpatient setting. *J Clin Oncol*. 2009; 27:891-6.
24. Gaguski ME, Nguyen HT. An interdisciplinary approach to the development and implementation of electronic treatment orders in a medical oncology department. *Clin J Oncol Nurs* 2016;20:371-3.
25. Reece KM, Lozano MA, Roux R, Spivey SM. Implementation and evaluation of a gravimetric IV workflow software system in an oncology ambulatory care pharmacy. *Am J Health-Syst Pharm* 2016;73:165-73.
26. Pang B, Earl M, Knoer S, Yaniv A, Willner M, Boyd A. Comparison of IV oncology infusion compounded via robotics and gravimetric-assisted workflow processes. *Am J Health-Syst Pharm* 2021;78:122-34.
27. Roberts PA, Willoughby IR, Barnes N, et al. Evaluation of a gravimetric-based technology assisted workflow system on hazardous sterile product preparation. *Am J Health-Syst Pharm* 2018;75:1286-92.
28. Neubauer M, Hoverman JR, Kilodziej M et al. Cost effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *J Oncol Practice*. 2010; 6:12-18.
29. Zon RT, Frame JN, Neuss MN et al. American Society of Clinical Oncology statement on clinical pathways in oncology. *J Oncol Pract* 2016;12:261-6.
30. Feinberg BA, Lang J, Grzegorzcyk J et al. Implementation of cancer clinical care pathways: s successful model of collaboration between payers and providers. *Am J Manag Care*. 2012; 18:e194-9.
31. [2021 ASP Drug Pricing Files | CMS](#) Accessed July 14, 2021.
32. Chan LL, Ko G. Medicare prescription drug plans as perceived by public health providers. *Am J Manag Care*. 2013; 19:e197-204.
33. Centers for Medicare and Medicaid Services (CMS). Medicare program: hospital inpatient prospective payment systems for acute care hospitals and the long-term hospital prospective payment system and Fiscal Year 2014 rates: quality reporting requirements for specific providers: hospital conditions of participation; payment policies related to patient status. Final rules. *Fed Regist* 2013 Aug 19;78(160):50495-1040.
34. Academy of Managed Care Pharmacy. AMCP Guide to Pharmaceutical Payment Methods, 2009 Update (Version 2.0). *J Manag Care Pharm*. 2009; 15(6 Suppl A):S3-S59.
35. Warren A, Shankar A. 2012 Oncology Business Summit – Perspectives. Oncology transactions and the 340B drug pricing program. *J Oncol Pract*. 2013;9:89-91.
36. <https://s3.amazonaws.com/public-inspection.federalregister.gov/2019-24138.pdf>. Accessed November 28, 2019.
37. Centers for Medicare and Medicaid Services, Department of Health and Human Services. Quality Payment Program. October 14, 2016 ([https://qpp.cms.gov/docs/QPP\\_Executive\\_Summary\\_of\\_Final\\_Rule.pdf](https://qpp.cms.gov/docs/QPP_Executive_Summary_of_Final_Rule.pdf)). Accessed October 16, 2016.
38. Sarpatwari A, Barenie R, Curfman G, et al. The US biosimilar market: stunted growth and possible reforms. *Clin Pharmacol Ther* 2019;105:92-100.
39. Ishii-Watabe A, Kuwabara T. Biosimilarity assessment of biosimilar therapeutic monoclonal antibodies. *Drug Metabol Pharmacokinetics* 2019;34:64-70.
40. Harvey RD. Science of biosimilars. *J Oncology Pract* 2017;13 (suppl):17s-23s.
41. Lyman GH, Balaban E, Diaz M, et al. American Society of Clinical Oncology Statement: Biosimilars. *J Clin Oncol* 2018;36:1260-5.
42. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>. Accessed August 30, 2016.
43. American Society of Health-System Pharmacists. ASHP guidelines on clinical drug research. *Am J Health-Syst Pharm* 1998;55:369-76.

44. Kay SC, Luke DG, Tamer HR. ASHP guidelines for the management of investigational drug products. *Am J Health-Syst Pharm* 2018; 75:561-73.
45. Amin SR, Avila JG, Boron MJ, Conley S, Lee JS, Enos R, Galus K, Mays TA, Patil G. HOPA Investigational Drug Service Best Practice Standards. [https://www.hoparx.org/images/hopa/resource-library/guidelines-standards/HOPA16\\_IDS\\_Guidelines.reviewed\\_2018.pdf](https://www.hoparx.org/images/hopa/resource-library/guidelines-standards/HOPA16_IDS_Guidelines.reviewed_2018.pdf) Accessed July 14, 2021.
46. American Society of Health-Systems Pharmacy. ASHP Specialty Pharmacy resource guide. <https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/specialty-pharmacy/specialty-pharmacy-resource-guide.ashx?la=en> Accessed September 18, 2017.
47. Mackler E, Segal EM, Muluneh B, Jeffers K, Carmichael J. 2018 Hematology/Oncology Pharmacist Association best practices for the management of oral oncolytic therapy: Pharmacy practice standard. *J Oncol Pract* 2019;15:e346-e354.
48. Dillmon MS, Kennedy EB, Anderson MK, et al . Patient-centered standards for medically integrated dispensing: ASCO/NCODA standards. *J Clin Oncol* 2019;38:633-44.
49. Stein J, Mann J. Specialty pharmacy services for patients receiving oral medications for solid tumors. *Am J Health-System Pharm* 2016;73:775-96.
50. Fajardo S, Zook F, Dotson E. Specialty pharmacy for hematologic malignancies. *Am J Health-System Pharm* 2016;73:797-809.
51. Bergsbaken J, Roman D, Earl MA, McBride A, Olin JL, Peele A, Reichard JS. ASHP-HOPA guidelines on the roles and responsibilities of the pharmacy technician in ambulatory oncology pharmacy. *Am J Health-Syst Pharm* 2018;75:1304-11.
52. <https://www.hoparx.org/images/hopa/resource-library/professional-tools/Dose-Rounding-Position-Paper-2017-10-23.pdf>. Accessed July 8, 2021.
53. Schwieterman P. Navigating financial assistance options for patients receiving specialty medications. *Am J Health-System Pharm* 2015;72:2190-5.
54. McBride A, Holle LM, Westendorf C, et al. National survey on the effect of oncology drug shortages on cancer care. *Am J Health-Syst Pharm* 2013;70:609-17.
55. Gatesman M, Smith TJ. The shortage of essential chemotherapy drugs in the United States. *N Engl J Med* 2011;365:1653-5.
56. American Society of Health-System Pharmacy. Drug Shortages. <https://www.ashp.org/drug-shortages?loginreturnUrl=SSOCheckOnly> <https://www.ashp.org/-/media/assets/drug-information/docs/drug-resources-2014-drug-shortages-summit.ashx?la=en&hash=6633BADAACA4B34BDE5D2B0CC2E7C5846EA3E118> Accessed December 12, 2022.