Hematology Pharmacology Pearls

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UW Medicine and Fred Hutchinson Cancer Center
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Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

Objectives

1. Select the best treatment option for a patient based on the mechanism of action, pharmacology, and side effect profile of the therapy.
2. Identify the need for dose adjustments of cancer therapies based on various patient factors.
3. Recognize common and unique adverse drug reactions of cancer therapies and associated prevention and management strategies.

Disclosure

Financial

- I have no financial disclosures to make.

Content

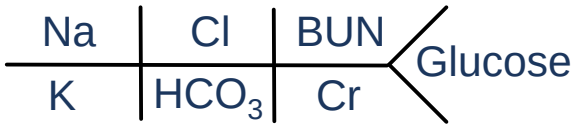
- I am a pharmacist
- I am not a: physician, radiologist, pathologist, geneticist,
- Please focus on the content of the questions and NOT any inaccuracies in the patient cases.

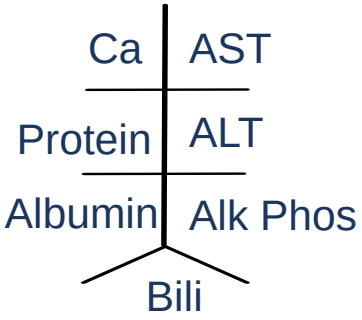
Citations

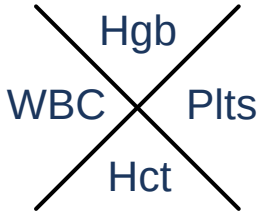
- When specific citation is not indicated, relevant NCCN guidelines were used.

Explanation of lab value presentation

- For space I will utilize standardized skeletons to display pertinent lab values.
- Please refer here for what each value indicates.







Patient Case 1: Part 1

AB, a 58-year-old man, presents with increasing feelings of fatigue and back pain.

PMH:

- Heart failure with reduced ejection fraction
- Diabetes
- Hyperlipidemia

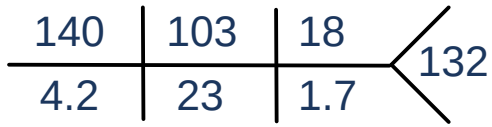
Vitals:

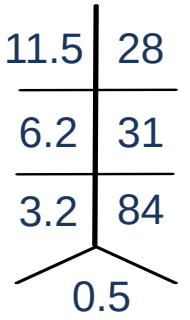
- Weight: 96 kg
- Blood pressure: 124/76

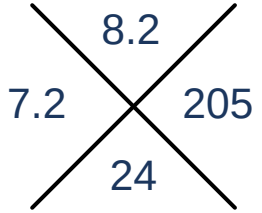
Current medications:

- Metformin 1000 mg PO BID
- Metoprolol 50 mg PO daily
- Lisinopril 20 mg PO daily
- Atorvastatin 20 mg PO daily
- Gabapentin 300 mg PO BID
- Furosemide 20 mg PO daily PRN weight gain

Labs:







- MSpike 9.7 g/dL
- Kappa free light chains (KFLC): 746.9 mg/dL
- Lambda free light chains (LFLC): 0.6 mg/dL
- Free light chain ratio (FLCR): 1244
- Beta 2 Micro (B2M): 7.1 µg/mL
- IgG: 10,385 mg/dL IgA: 14 mg/dL IgM: 23 mg/dL

Patient Case 1: Part 1

Imaging:

- MRI
  - Spine: Diffuse lumbar spine marrow replacing process compatible with infiltrative disorder such as multiple myeloma. At the L1 vertebral body level, there is enhancing epidural tumor, greater to the left of midline results in mild to moderate AP spinal canal stenosis without compression of the conus medullaris
  - Pelvis: diffuse malignant process. No evidence of fracture

Procedures:

- Bone marrow biopsy:
  - Abnormal plasma cell population 24% by flow cytometry.
  - >60% plasma cells by CD138 immunohistochemistry.
  - FISH with t(11;14)
  - Cytogenetics abnormal with loss of Y chromosome in 7 of 20 cells.

ARS Question 1

AB is diagnosed with standard risk IgG Kappa multiple myeloma. What would you recommend as first line therapy for AB?

A. Bortezomib, lenalidomide, dexamethasone (VRd)

B. Carfilzomib, lenalidomide, dexamethasone (KRd)

C. Daratumumab, lenalidomide, dexamethasone (DRd)

D. Bortezomib, lenalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide (VRD-PACE)

E. Daratumumab, bortezomib, melphalan, prednisone

ARS Question 1

AB is diagnosed with standard risk IgG Kappa mul
recommend as first line therapy for AB?

A. Bortezomib, lenalidomide, dexamethasone (VRd)

B. Carfilzomib, lenalidomide, dexamethasone (KRd)

C. Daratumumab, lenalidomide, dexamethasone (DRd)

D. Bortezomib, lenalidomide, dexamethasone, cisplatin, d

E. Daratumumab, bortezomib, melphalan, prednisone

Correct Answer

This regimen is a category 1 recommendation by NCCN for first-line therapy in transplant and non-transplant candidates.

ARS Question 1

AB is diagnosed with standard risk IgG Kappa mul recommend as first line therapy for AB?

A. Bortezomib, lenalidomide, dexamethasone (VRd)

B. Carfilzomib, lenalidomide, dexamethasone (KRd)

C. Daratumumab, lenalidomide, dexamethasone (DR

D. Bortezomib, lenalidomide, dexamethasone, cisplati

E. Daratumumab, bortezomib, melphalan, prednisone

While this is an NCCN category 2A recommendation for first line treatment:

- Carfilzomib is not a preferred drug in patients with known cardiac comorbidities.
  - Peripheral edema (20% to 21%)
  - Hypertension (15% to 42%; including hypertensive crisis)
  - Cardiac arrhythmia (13%)
  - Chest pain (3% to 21%)
  - Heart failure (7%)
  - Ischemic heart disease (3%)
  - Cardiomyopathy (2%)
  - Venous thromboembolism (2%)

Carfilzomib [package insert].

ARS Question 1

AB is diagnosed with standard risk IgG Kappa mult recommend as first line therapy for AB?

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B. Carfilzomib, lenalidomide, dexamethasone (KRd)

C. Daratumumab, lenalidomide, dexamethasone (DRd)

D. Bortezomib, lenalidomide, dexamethasone, cisplatin

E. Daratumumab, bortezomib, melphalan, prednisone

DRd is an NCCN category 1 recommendation for first line treatment in NON-TRANSPLANT candidates

- At this time, there is nothing to suggest that AB would not be an eventual transplant candidate.
- Daratumumab, lenalidomide, BORTEZOMIB, and dexamethasone is a potential first line option for transplant candidates.
  - Data around daratumumab and stem cell collection is still not fully elucidated.

Dara/Bor/Mel/Pred is an NCCN category 1 recommendation for first line treatment in NON-TRANSPLANT candidates

- Alkylating agents, like melphalan, are generally avoided in patients to avoid hindering future autologous stem cell collection

ARS Question 1

AB is diagnosed with standard risk IgG Kappa mult recommend as first line therapy for AB?

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B. Carfilzomib, lenalidomide, dexamethasone (KRd)

C. Daratumumab, lenalidomide, dexamethasone (DRd)

D. Bortezomib, lenalidomide, dexamethasone, cisplatin,

E. Daratumumab, bortezomib, melphalan, prednisone

PACE regimens are generally reserved for aggressive multiple myeloma or plasma cell leukemia

- Aggressive myeloma usually defined by:
  - Extramedullary disease
  - Rapidly progressive disease
  - High risk disease as determined by molecular and cytogenetic findings

ARS Question 2

Based on the initial treatment you selected, what ancillary medications would AB require in addition to the chemotherapy? **(Choose all that apply)**

A. Aspirin 81 mg PO daily
B. Apixaban 5 mg PO BID
C. Sulfamethoxazole/trimethoprim 800/160 mg PO daily MWF
D. Acyclovir 400 mg PO BID
E. Aprepitant 130 mg IV on days of chemotherapy
F. Posaconazole 300 mg PO daily

ARS Question 2

Based on the initial treatment you selected, wh
addition to the chemotherapy? **(Choose a**

A. Aspirin 81 mg PO daily

B. Apixaban 5 mg PO BID

C. Sulfamethoxazole/trimethoprim 800/

D. Acyclovir 400 mg PO BID

E. Aprepitant 130 mg IV on days of ch

F. Posaconazole 300 mg PO daily

Correct Answer

Because we chose VRd, which contains an immunomodulator (IMiD; lenalidomide) and a proteasome inhibitor (PI; bortezomib) we need to ensure the patient has:

- VTE prophylaxis due to the combination of IMiD and high dose dexamethasone.
  - Depending on the patient's VTE risk, anything from aspirin 81 mg daily to full anticoagulation is appropriate.
  - Nothing about this patient suggest he is at higher-than-average risk for VTE currently, so low dose aspirin therapy is appropriate.
- HSV/VZV prophylaxis due to PI.
  - Alternatives: valacyclovir 500 mg PO BID, famciclovir 250 mg PO BID
  - **Note**: these drugs will likely need dose reduction for renal impairment, which is common in myeloma

ARS Question 2

Based on the initial treatment you selected, wh
addition to the chemotherapy? **(Choose a**

A. Aspirin 81 mg PO daily
B. Apixaban 5 mg PO BID
C. Sulfamethoxazole/trimethopr
D. Acyclovir 400 mg PO BID
E. Aprepitant 130 mg IV on days of ch
F. Posaconazole 300 mg PO daily

There is nothing to suggest a need for higher level anticoagulation in this patient. Patients with history of blood clots, atrial fibrillation, etc. would be at higher risk and therefore require higher levels of anticoagulation. Full dose anticoagulation can include:

- Warfarin with INR monitoring
- Any available direct oral anticoagulant (DOAC; rivaroxaban, edoxaban, etc.)
- Low molecular weight heparin (enoxaparin, fondaparinux, etc.)

Apixaban [package insert].

ARS Question 2

Based on the initial treatment you selected, what addition to the chemotherapy? **(Choose all th**

A. Aspirin 81 mg PO daily
B. Apixaban 5 mg PO BID
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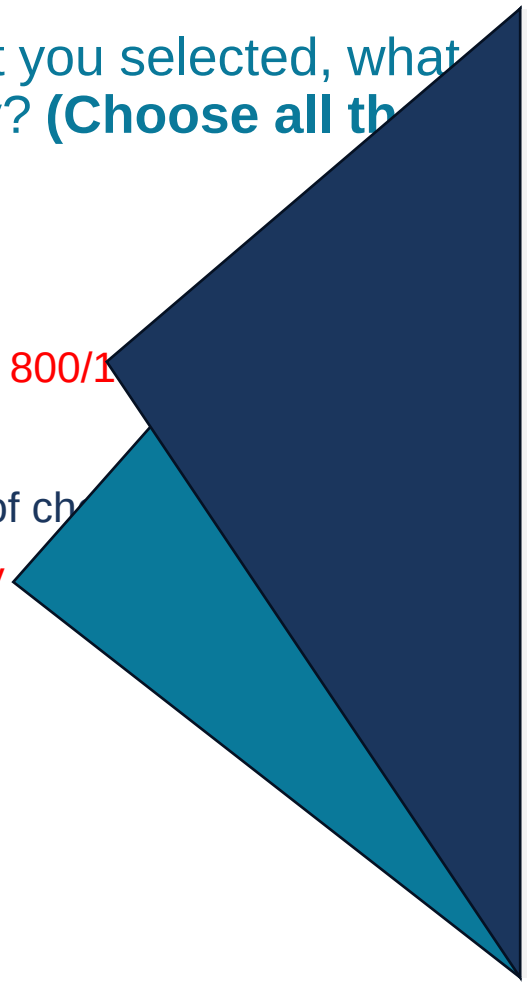

Myeloma therapies are not traditionally lymphotoxic or known to cause prolonged cytopenias.

- Pneumocystis prophylaxis is not traditionally required.
- Antifungal prophylaxis is not traditionally required.

ARS Question 2

Based on the initial treatment you selected, what a
addition to the chemotherapy? **(Choose all that a**

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C. Sulfamethoxazole/trimethoprim 800/160 mg PO dai
D. Acyclovir 400 mg PO BID
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F. Posaconazole 300 mg PO daily

VRd is not a highly emetogenic regimen, and therefore a neurokinin-1 (NK1) inhibitor is not a recommended premedication.

- Commonly ondansetron will be used on days of bortezomib injection

Patient Case 1: Part 2

AB has undergone 6 cycles of VRd with his oncologist. He has had worsening neuropathy leading to delays in treatment. He has also developed atrial fibrillation (AFib). His myeloma markers have all plateaued.

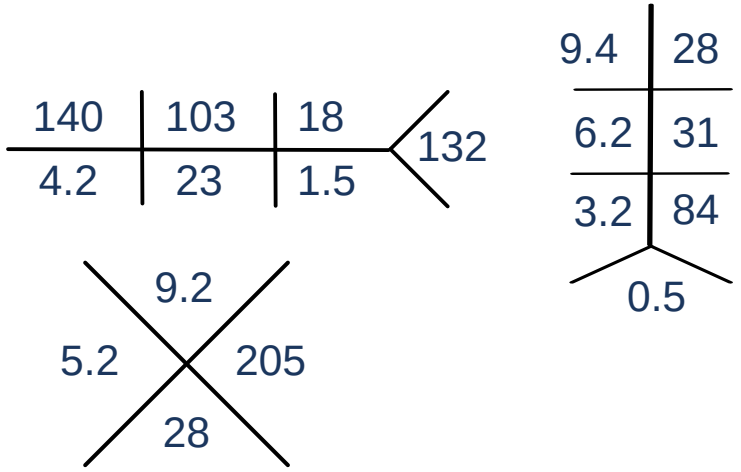
Current medications:

- Acyclovir 400 mg PO BID
- Apixaban 5 mg PO BID
- Metformin 1000 mg PO BID
- Metoprolol 50 mg PO BID
- Lisinopril 40 mg PO daily
- Atorvastatin 20 mg PO daily
- Gabapentin 600 mg PO TID
- Oxycodone 5 mg PO Q6H PRN pain
- Furosemide 20 mg PO daily PRN weight gain

Vitals:

- Weight: 89 kg
- Blood pressure: 142/96

Labs:



- MSpike 2.1 g/dL
- Kappa free light chains (KFLC): 22.7 mg/dL
- Lambda free light chains (LFLC): 1.1 mg/dL
- Free light chain ratio (FLCR): 20.6
- Beta 2 Micro (B2M): 2.2

ARS Question 3

What regimen do you recommend for AB as second line therapy?

A. Carfilzomib, lenalidomide, dexamethasone (KRd)
B. Daratumumab, lenalidomide, dexamethasone (DRd)
C. Daratumumab, bortezomib, dexamethasone (DVd)
D. Carfilzomib, pomalidomide, dexamethasone (KPd)
E. Idecabtagene vicleucel (Abecma®)

ARS Question 3

What regimen do you recommend for AB as secon

A. Carfilzomib, lenalidomide, dexamethasone (KRd)

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Correct Answer

Anti-CD38 monoclonal antibody therapy is recommended for relapsed/refractory myeloma patients.

- Given that disease responded to initial VRd, the patient should not be considered refractory to any drugs in that regimen.
- Current side effects/concomitant diseases would be least impacted by this drug combination.
- Dose of dexamethasone can be reduced in diabetic patients based on blood sugar control.

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What regimen do you recommend for AB as seco

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C. Daratumumab, bortezomib, dexamethasone (DVd)
D. Carfilzomib, pomalidomide, dexamethasone (KPd)
E. Idecabtagene vicleucel (Abecma®)

Given the new diagnosis of atrial fibrillation and the history of heart failure and current uncontrolled blood pressure, carfilzomib should be avoided.

- Carfilzomib is associated with new-onset or worsening heart failure
- Cardiac arrhythmia: 13%
- Chest pain: 3% to 21%
- Hypertension: 15% to 42%
- Peripheral edema: 20% to 21%

Carfilzomib [package insert].

ARS Question 3

What regimen do you recommend for AB as secon

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E. Idecabtagene vicleucel (Abecma®)

While this is considered a category 1 recommendation for relapsed/refractory myeloma, given AB's neuropathy leading to delays in therapy, bortezomib should be avoided if possible.

- COULD consider treating through neuropathy and increasing gabapentin, but because there are alternatives, it can be avoided.
- PI Rates of Neuropathy:
  - Bortezomib: 28-54%
  - Carfilzomib: <20%
  - Ixazomib: 32%
  - Bortezomib induced peripheral neuropathy (BIPN) as been shown to be decreased with use of the subcutaneous formulation over IV (RR: 0.63).

Mu SD et al. Curr Med Sci. 2018;38(1):43-50.

ARS Question 3

What regimen do you recommend for AB as seco

A. Carfilzomib, lenalidomide, dexamethasone (KRd)
B. Daratumumab, lenalidomide, dexamethasone (
C. Daratumumab, bortezomib, dexamethasone
D. Carfilzomib, pomalidomide, dexamethaso
E. Idecabtagene vicleucel (Abecma®)

Ide-cel is FDA approved after <u>TWO OR MORE</u> lines of prior therapy, including an IMiD, PI, and anti-CD38 monoclonal antibody

- AB has only received one line thus far, and has not received anti-CD38 therapy yet.
- Carvykti® (ciltacabtagene autoleucel) is approved in the second line setting after IMiD and PI therapy but requires the patient to be refractory to lenalidomide.

Idecabtagene vicleucel [package insert].

ARS Question 4

Which of the following statements is **INCORRECT** about high dose melphalan conditioning?

A. High-dose melphalan is associated with high rates of emetogenicity and therefore should be given with a combination anti-emetic regimen (i.e. NK1 antagonist + 5HT3 antagonist + corticosteroid)

B. Patients with renal dysfunction (CrCl <30 mL/min, SCr >2.0 mg/dL, etc.) are recommended to receive full dose (200 mg/m^2) because melphalan is primarily metabolized by the liver

C. Most sources recommend a dose reduction to 140 mg/m^2 for patients with poor performance status, older age, and/or decreased LVEF

D. Nitrogen mustards, including melphalan, are associated with high rates of male infertility after treatment due to azoospermia in males

E. Treatment related MDS/AML is one type of secondary malignancy associated with alkylating agents. It is commonly seen 5-7 years after treatment and is associated with del5q or del7q

F. The dose limiting toxicity, mucositis, associated with high dose melphalan can be significantly reduced with the use of cryotherapy

ARS Question 4

Which of the following statements is **INCORRECT**

A. High-dose melphalan is associated with high rates of em
combination anti-emetic regimen (i.e. NK1 antagonist +

**B. Patients with renal dysfunction (CrCl <30 mL/min,
full dose (200 mg/m^2) because melphalan is primar**

C. Most sources recommend a dose reduction to 140 mg/
age, and/or decreased LVEF

D. Nitrogen mustards, including melphalan, are associated
azoospermia in males

E. Treatment related MDS/AML is one type of secondary ma
commonly seen 5-7 years after treatment and is associate

F. The dose limiting toxicity, mucositis, associated with high d
the use of cryotherapy

Correct Answer

While melphalan is hepatically metabolized, MOST metabolism is done via spontaneous hydrolysis.

- This gives melphalan it's short stability once prepared (1 hour).
- Excretion of the drug is primarily renal (mostly as metabolites).
- One study showed that a decrease in CrCl from 100 mL/min to 30 mL/min reduced clearance of melphalan by 28.2%.

Melphalan [package insert].

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the use of cryotherapy

Melphalan is categorized as a "high" or "moderate" emetic risk drug depending on the dose.

- NCCN categorizes doses ≥140 mg/m^2 as highly emetogenic (>90% of people will experience nausea)
- Doses <140 mg/m^2 are moderately emetogenic (30-90% of people will experience nausea)
- Most groups recommend a three-drug regimen for highly emetogenic chemotherapy

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the use of cryotherapy

This is as opposed to secondary MDS/AML that is associated with topoisomerase II inhibitors (etoposide, doxorubicin, etc.).

- These are most associated with mutations like 11q23.
- Typically seen 2-3 years after therapy.

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the use of cryotherapy

Cryotherapy: Placing ice chips in mouth 30 minutes before melphalan infusion until 6 hours after the infusion.

- Patients allow ice to melt and replenish continuously.
- Patients in the cryotherapy arm showed a significant reduction in the incidence of grade 3-4 mucositis (14% vs. 74%).
- There are studies showing that shorter cryotherapy treatment (2 hours) is non-inferior to this original length.

Lilleby K et al. Bone Marrow Transplant. 2006;37(11):1031-5.

Patient Case 2

CD, a 52-year-old woman, presents with progressive history of worsening fatigue and bruising.

PMH:

- History of breast cancer treated with lumpectomy and 4 cycles of doxorubicin/cytarabine followed by weekly paclitaxel x 12 doses. Completed about 2 years ago.

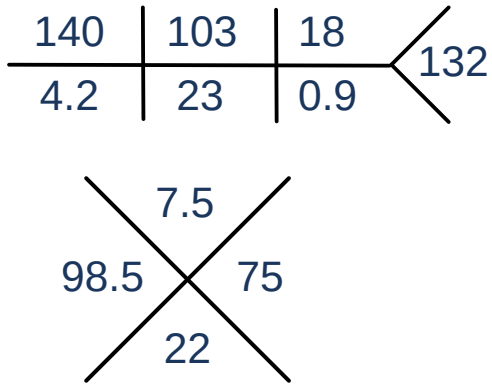
Vitals:

- Weight: 89 kg
- Blood pressure: 118/72

Current medications:

- None

Labs:



Procedures:

- Bone marrow biopsy:
  - 47,XX,+8
  - Flow Cytometry: 60% abnormal blasts
  - Pathology: 54% blasts
  - Immunohistochemistry: 40-50% blasts
  - Cytogenetics/FISH: t(11;19)(q23;p13.1), trisomy 8

ARS Question 5

Which of the following diagnosis/induction treatment options best fits CD?

A. Poor risk AML / Liposomal cytarabine + daunorubicin (CPX351; Vyxeos®)
B. Favorable risk AML by molecular mutation / Fludarabine + cytarabine + filgrastim + idarubicin (FLAG-Ida)
C. Poor risk AML / Cytarabine + doxorubicin/daunorubicin (7+3)
D. Intermediate risk AML / Azacitidine + Venetoclax
E. Favorable risk AML by cytogenetics / Cytarabine + doxorubicin/daunorubicin (7+3) + gemtuzumab ozogamicin (Mylotarg®)

ARS Question 5

Which of the following diagnosis/induction treatme

A. Poor risk AML / Liposomal cytarabine + daunorubicin (
B. Favorable risk AML by molecular mutation / Fludarab
C. Poor risk AML / Cytarabine + doxorubicin/daunc
D. Intermediate risk AML / Azacitidine + Venetoclax
E. Favorable risk AML by cytogenetics / Cytarabine + dc (Mylotarg®)

Correct Answer

CD is considered Poor Risk because she has therapy related AML (history of anthracycline/topoisomerase II inhibitor with mutations showing 11q23/KMT2A rearrangement)

- KMT2A – Lysine [K]-specific Methyltransferase 2A (previously called Mixed Lineage Leukemia gene or MLL)

ARS Question 5

Which of the following diagnosis/induction treatm

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B. Favorable risk AML by molecular mutation / Fludara
C. Poor risk AML / Cytarabine + doxorubicin/daunorubic
D. Intermediate risk AML / Azacitidine + Venetoclax
E. Favorable risk AML by cytogenetics / Cytarabine + dox (Mylotarg®)

This combo of diagnosis and treatment regimen is correct. However, it is the recommended treatment option for patients over 60 years old.

ARS Question 5

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B. Favorable risk AML by molecular mutation / Fludara
C. Poor risk AML / Cytarabine + doxorubicin/daunorubi
D. Intermediate risk AML / Azacitidine + Venetoclax
E. Favorable risk AML by cytogenetics / Cytarabine + do (Mylotarg®)

This combo is technically accurate (though not a "preferred" regimen). However, this patient does not have favorable risk AML given that it is most likely therapy related.

- Some institutions will utilize higher intensity regiments such as FLAG-Ida or CLAG-M in fit patients regardless of risk category.

ARS Question 5

Which of the following diagnosis/induction treatme

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B. Favorable risk AML by molecular mutation / Fludarab
C. Poor risk AML / Cytarabine + doxorubicin/daunorub
D. Intermediate risk AML / Azacitidine + Venetoclax
E. Favorable risk AML by cytogenetics / Cytarabine + (Mylotarg®)

This diagnosis does not match our patient because she is considered high risk.

This combination could be considered correct, however azacitidine + venetoclax isn't traditionally "intensive induction" and would likely be reserved for someone with poor performance status and/or otherwise expected to be intolerant of intensive induction.

ARS Question 5

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B. Favorable risk AML by molecular mutation / Fludarabin
C. Poor risk AML / Cytarabine + doxorubicin/daunorubici
D. Intermediate risk AML / Azacitidine + Venetoclax
E. Favorable risk AML by cytogenetics / Cytarabine + (Mylotarg®)

This combo is technically accurate. However, this patient does not have favorable risk AML given that it is most likely therapy related.

- 7+3+gemtuzumab ozogamicin is a recommended combination for favorable risk AML with CD33+
- Mylotarg and SOS:
  - The original dosing of Mylotarg lead to higher-than-expected rates of sinusoidal obstructive syndrome (SOS; previously hepatic venoocclusive disease or VOD) when patients were brought to transplant.
  - New dosing (3 mg/m^2 on days 1, 4, and 7) significantly reduces the risk of SOS (but does not eliminate it).

ARS Question 6

Which statement below is **MOST ACCURATE** about toxicities associated with cytarabine?

A. Conjunctivitis is a universal side effect of cytarabine and is seen in both dosing schemes.
B. Ara-C syndrome, characterized by fever, myalgia, and rash, is typically seen immediately after therapy begins.
C. Cerebellar toxicity seen with high-dose cytarabine is typically mild and does not require dose reductions.
D. GI toxicities are more commonly seen with conventional dosing of cytarabine.
E. Severe myelosuppression is more commonly associated with conventional dosing of cytarabine.

ARS Question 6

Which statement below is **MOST ACCURATE** abou

A. Conjunctivitis is a universal side effect of cytarabine and i
B. Ara-C syndrome, characterized by fever, myalgia, and ra
C. Cerebellar toxicity seen with high-dose cytarabine is typi
D. GI toxicities are more commonly seen with conventi
E. Severe myelosuppression is more commonly associated

Correct Answer

Conventional cytarabine (low dose, continuous infusion; like that seen in 7+3) is more commonly associated with GI toxicities (nausea, vomiting, diarrhea, etc.).

- GI toxicities can be seen at any dosing, but likely more common with prolonged exposure in conventional dosing.

Cytarabine [package insert].

ARS Question 6

Which statement below is **MOST ACCURATE** abo

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D. GI toxicities are more commonly seen with conventiona
E. Severe myelosuppression is more commonly associate

Conjunctivitis and severe myelosuppression are major side effects associated with high-dose cytarabine (high, intermittent dosing like that seen in HiDAC).

- Conjunctivitis
  - Common symptoms: eye pain, foreign body sensation, blurred vision, photophobia.
  - Prophylaxis with steroid eye drops starting prior to therapy and up to 72 hours after completion.
- Myelosuppression
  - Can be seen at any dosing schema, however SEVERE neutropenia is associated with high-dose regimens.

Cytarabine [package insert].

ARS Question 6

Which statement below is **MOST ACCURATE** abo

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E. Severe myelosuppression is more commonly associated

Cytarabine (or Ara-C) syndrome is most commonly seen at conventional doses.

- Common symptoms:
  - Fever
  - Myalgia
  - Bone pain
  - Maculopapular rash
  - Malaise
- This syndrome generally occurs 6 to 12 hours following administration.

Cytarabine [package insert].

ARS Question 6

Which statement below is **MOST ACCURATE** abo

A. Conjunctivitis is a universal side effect of cytarabine and
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D. GI toxicities are more commonly seen with conventiona
E. Severe myelosuppression is more commonly associated

Cerebellar syndrome is considered a dose limiting toxicity for high-dose cytarabine therapy.

- Risk factors: Age, kidney dysfunction, cumulative dose.
- Common symptoms:
  - Ataxia
  - Confusion
  - Drowsiness
  - Dysarthria
  - Impaired consciousness
  - Nystagmus disorder
- Serious reactions:
  - Seizure
  - Coma
- Common cerebellar assessments:
  - Finger to nose
  - Writing a sentence

Cytarabine [package insert].

ARS Question 7

Which statement is **INACCURATE** regarding busulfan and cyclophosphamide conditioning for allogeneic stem cell transplant?

A. The dose of cyclophosphamide commonly used in this regimen has a high incidence of hemorrhagic cystitis and therefore requires uroprotection with mesna.

B. Busulfan is associated with seizures and requires seizure prophylaxis, except in instances when the busulfan is pharmacokinetically monitored and dose adjusted.

C. Busulfan is commonly associate with skin discoloration or hyperpigmentation, which typically occurs 2-3 week after therapy and can last for 2-3 months.

D. High-dose cyclophosphamide has been linked to cardiovascular toxicities such as atrial fibrillation, acute myocardial infarction, hypertension, palpitations, and cardiogenic shock.

E. Pharmacokinetic dosing of busulfan has resulted in lower rates of hepatic sinusoidal obstructive syndrome (SOS).

ARS Question 7

Which statement is **INACCURATE** regarding busul for allogeneic stem cell transplant?

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C. Busulfan is commonly associate with skin discoloration after therapy and can last for 2-3 months.

D. High-dose cyclophosphamide has been linked to cardiov myocardial infarction, hypertension, palpitations, and car

E. Pharmacokinetic dosing of busulfan has resulted in lower (SOS).

Correct Answer

Pharmacokinetic monitoring and dose adjustment does not lower incidence of seizures associated with busulfan. Seizure prophylaxis is required for all transplant dosing.

- Original studies used phenytoin
- Now levetiracetam is more commonly used.

Busulfan [package insert].

ARS Question 7

Which statement is **INACCURATE** regarding busul
for allogeneic stem cell transplant?

A. The dose of cyclophosphamide commonly used in this r
and therefore requires uroprotection with mesna.

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after therapy and can last for 2-3 months.

D. High-dose cyclophosphamide has been linked to cardiova
myocardial infarction, hypertension, palpitations, and card

E. Pharmacokinetic dosing of busulfan has resulted in lower
(SOS).

Doses of cyclophosphamide >1500-2000 mg/m2 require uroprotection with mesna. Dosing commonly used in BuCy regimen is 60 mg/kg/day x 2 days

- It's common to give a mesna dose in a 1:1 ratio to the cyclophosphamide dose.
- Usually split the dosing into 4 given at 15 minutes prior to and 3, 6, and 8 hours post cyclophosphamide infusion.

Cyclophosphamide [package insert].

ARS Question 7

Which statement is **INACCURATE** regarding busul for allogeneic stem cell transplant?

A. The dose of cyclophosphamide commonly used in this re and therefore requires uroprotection with mesna.

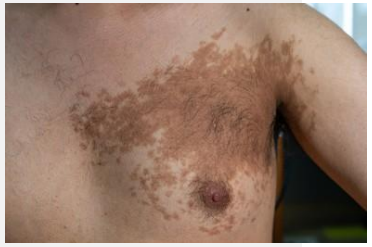
B. Busulfan is associated with seizures and requires seizu is pharmacokinetically monitored and dose adjusted.

C. Busulfan is commonly associate with skin discoloratio after therapy and can last for 2-3 months.

D. High-dose cyclophosphamide has been linked to cardi myocardial infarction, hypertension, palpitations, and ca

E. Pharmacokinetic dosing of busulfan has resulted in lowe (SOS).

This is the correct timeline for skin discoloration associated with busulfan. Commonly associated sites:



- Around joints
- Under nails
- Mouth
- Under areas compressed by tape/dressings

High-dose cyclophosphamide has been associated with numerous cardiac effects.

- Arrhythmias, heart failure, myocarditis, pericarditis, etc.
- Mechanism: metabolites, like acrolein, cause oxidative stress to the myocardium and direct endothelial capillary damage.
- Risk Factors: Age, high doses, preexisting cardiac conditions, chest irradiation, heavy pretreatment.

Busulfan [package insert].
Cyclophosphamide [package insert].

ARS Question 7

Which statement is **INACCURATE** regarding busul for allogeneic stem cell transplant?

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D. High-dose cyclophosphamide has been linked to cardiov myocardial infarction, hypertension, palpitations, and ca

E. Pharmacokinetic dosing of busulfan has resulted in low (SOS).

Busulfan absorption and exposure is extremely variable and unpredictable between patients. Increased exposure (higher concentration vs. time AUC) can lead to hepatotoxicity, primarily in the form of SOS.

- Pharmacokinetic monitoring takes patient blood samples to more accurately adjust busulfan doses to optimize the AUC while preventing over-exposure.

Cho YH et al. Clin Transplant. 2007;21(3):417-22.

ARS Question 8

A patient with newly diagnosed, AML is seen for consult regarding options for induction therapy. Which of the following statements regarding targeted therapies is **CORRECT**?

A. Patients with FLT3 ITD mutations are recommended to receive midostaurin as part of their therapy but requires QTc monitoring due to risk of prolonged QT and TDP.

B. Young, fit patients with IDH1 mutation are recommended to receive ivosidenib as part of their induction, consolidation, and maintenance treatment.

C. Patients with FLT3 ITD mutations are recommended to receive quizartinib as part of their induction, consolidation, and maintenance treatment.

D. Patients with FLT3 TKD mutations are recommended to receive gilteritinib as part of their induction, consolidation, and maintenance treatment.

E. Elderly and/or unfit patients with IDH1 mutation are recommended to receive olutasidenib as part of their therapy.

ARS Question 8

A patient with newly diagnosed, AML is seen for co
therapy. Which of the following statements regardi

A. Patients with FLT3 ITD mutations are recommended to re
requires QTc monitoring due to risk of prolonged QT and

B. Young, fit patients with IDH1 mutation are recommended
consolidation, and maintenance treatment.

**C. Patients with FLT3 ITD mutations are recommended
consolidation, and maintenance treatment.**

D. Patients with FLT3 TKD mutations are recommended to
consolidation, and maintenance treatment.

E. Elderly and/or unfit patients with IDH1 mutation are recon
therapy.

Correct Answer

Quizartinib and midostaurin are both options for addition to intensive induction, consolidation, and maintenance for patients with FLT3 ITD mutations.

- Quizartinib is NOT recommended or FLT3 TKD mutations (midostaurin remains the only option).

Quizartinib [package insert].
Midostaurin [package insert].

ARS Question 8

A patient with newly diagnosed, AML is seen for co
therapy. Which of the following statements regardi

A. Patients with FLT3 ITD mutations are recommended to r
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B. Young, fit patients with IDH1 mutation are recommended
consolidation, and maintenance treatment.
C. Patients with FLT3 ITD mutations are recommended to re
consolidation, and maintenance treatment.
D. Patients with FLT3 TKD mutations are recommended to r
consolidation, and maintenance treatment.
E. Elderly and/or unfit patients with IDH1 mutation are recom
therapy.

Midostaurin can cause prolonged QT, but there is not any specific recommendations regarding QT monitoring.

- Quizartinib has a black box warning (BBW) and REMS program surrounding its risk of QT prolongation.
- Quizartinib requires an ECG prior to therapy initiation, weekly during induction and consolidation, weekly for the first month of maintenance, and then periodically thereafter.
- Electrolytes (especially potassium and magnesium) should be monitored periodically as well.

Quizartinib [package insert].
Midostaurin [package insert].

ARS Question 8

A patient with newly diagnosed, AML is seen for co
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C. Patients with FLT3 ITD mutations are recommended to
consolidation, and maintenance treatment.

D. Patients with FLT3 TKD mutations are recommended to
consolidation, and maintenance treatment.

E. Elderly and/or unfit patients with IDH1 mutation are recom
therapy.

IDH inhibitors are not recommended in combination with intensive induction therapy. Guidelines currently only recommend first-line treatment with IDH inhibitor for unfit or elderly patients otherwise unable to tolerate intensive induction therapy.

- Azacitidine + ivosidenib (for IDH1 mutation) or dnasidenib (for IDH2 mutation) are options for lower intensity therapy.
- Ivosidenib is the only IDH inhibitor FDA approved in frontline therapy.

Ivosidenib [package insert].

ARS Question 8

A patient with newly diagnosed, AML is seen for co
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B. Young, fit patients with IDH1 mutation are recommended
consolidation, and maintenance treatment.
C. Patients with FLT3 ITD mutations are recommended to
consolidation, and maintenance treatment.
D. Patients with FLT3 TKD mutations are recommended t
consolidation, and maintenance treatment.
E. Elderly and/or unfit patients with IDH1 mutation are reco
therapy.

Gilteritinib is only approved for use in relapsed/refractory AML. For fit patients, there are no guideline recommendations of up-front use of gilteritinib

- Azacitidine + gilteritinib is an option for lower intensity therapy.
- Gilteritinib has more data for use in R/R AML and as maintenance therapy post allogeneic transplant.

Gilterinib [package insert].

ARS Question 8

A patient with newly diagnosed, AML is seen for co
therapy. Which of the following statements regardi

A. Patients with FLT3 ITD mutations are recommended to re
requires QTc monitoring due to risk of prolonged QT and
B. Young, fit patients with IDH1 mutation are recommended
consolidation, and maintenance treatment.
C. Patients with FLT3 ITD mutations are recommended to
consolidation, and maintenance treatment.
D. Patients with FLT3 TKD mutations are recommended to
consolidation, and maintenance treatment.
E. Elderly and/or unfit patients with IDH1 mutation are re
therapy.

Olutasidenib is not approved or recommended for first-line therapy regardless of patient's fitness or age.

- Currently, olutasidenib is only recommended in R/R AML with IDH1 mutation.

Olutasidenib [package insert].

ARS Question 9

A 43-year-old man presents to the ED with worsening fatigue and frequent bouts of epistaxis. CBC reveals a WBC of 20.3 and Hgb of 7.4. A bone marrow biopsy is performed with results suggesting an acute leukemia with t(15;17) by FISH. Which of the following statements regarding treatment for this patient is **INCORRECT**?

A. Arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) are the backbone of therapy for this leukemia diagnosis.

B. Prior to initiating therapy with ATO, patients should have an ECG to check for underlying QT prolongation.

C. Patients with high-risk APL, defined as a WBC at diagnosis >10, benefit from addition of anthracycline to their induction regimen.

D. Fever, shortness of breath, and increasing white blood count are signs that the disease is not responding to induction therapy.

E. Gemtuzumab ozogamicin can be used as an alternative to ATO in a patient with prolonged QTc.

ARS Question 9

A 43-year-old man presents to the ED with worseni
epistaxis. CBC reveals a WBC of 20.3 and Hgb of
with results suggesting an acute leukemia with t(15
statements regarding treatment for this patient is I

A. Arsenic trioxide (ATO) and all-trans retinoic acid (ATRA)
diagnosis.

B. Prior to initiating therapy with ATO, patients should have

C. Patients with high-risk APL, defined as a WBC at diagn
induction regimen.

**D. Fever, shortness of breath, and increasing white bl
responding to induction therapy.**

E. Gemtuzumab ozogamicin can be used as an alternative

Correct Answer

These are all signs and symptoms of APL differentiation syndrome (fever, shortness of breath, hypoxemia, pleural or pericardial effusions).

- Close monitoring of volume overload and pulmonary status.
- Initiate dexamethasone at first signs of respiratory compromise
  - 10 mg BID for 3–5 days with a taper over 2 weeks
- Consider interrupting ATRA therapy until hypoxia resolves.
- For patients diagnosed with high-risk APL, initiate prophylaxis with corticosteroids
  - Prednisone 0.5 mg/kg/day
  - Dexamethasone 10 mg BID
  - Taper the steroid dose over several days

ARS Question 9

A 43-year-old man presents to the ED with worsen
epistaxis. CBC reveals a WBC of 20.3 and Hgb of
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A. Arsenic trioxide (ATO) and all-trans retinoic acid (ATR
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B. Prior to initiating therapy with ATO, patients should hav

C. Patients with high-risk APL, defined as a WBC at diag
induction regimen.

D. Fever, shortness of breath, and increasing white blood
induction therapy.

E. Gemtuzumab ozogamicin can be used as an alternative

Given the finding of t(15;17) this patient would be diagnosed with acute promyelocytic leukemia (APL). ATO and ATRA are both agents widely studied for use in APL.

- High-risk versus low-risk APL is defined based on WBC value.
- High-risk patients have been shown to benefit from anthracycline addition (idarubicin, daunorubicin, mitoxantrone).
  - Anthracyclines can aid in cytoreduction and prevention of differentiation syndrome.
- ATO + ATRA alone is sufficient for induction in low-risk patients.

ARS Question 9

A 43-year-old man presents to the ED with worseni
epistaxis. CBC reveals a WBC of 20.3 and Hgb of
with results suggesting an acute leukemia with t(1
statements regarding treatment for this patient is

A. Arsenic trioxide (ATO) and all-trans retinoic acid (ATRA)
diagnosis.

B. Prior to initiating therapy with ATO, patients should hav

C. Patients with high-risk APL, defined as a WBC at diagn
induction regimen.

D. Fever, shortness of breath, and increasing white blood
induction therapy.

E. Gemtuzumab ozogamicin can be used as an alternati

Arsenic itself can significantly prolong QT interval. There are monitoring recommendations for ECGs when thinking of starting ATO.

- ECG once before initiation of ATO.
- Weekly ECG during induction
- ECG prior to each cycle of post-remission therapy.
- Minimize use of other QT prolonging drugs (azole antifungals, certain antiemetics, etc.).
- Monitor electrolytes regularly (potassium and magnesium especially).

In patients with baseline QTc >500 msec, it's recommended to avoid ATO. Gemtuzumab can be added in these instances

- Higher doses (6-9 mg/m2) are still utilized because HSCT is not routinely used for APL.

Arsenic trioxide [package insert].
Gemtuzumab ozogamicin [package insert].

ARS Question 10

Which statements below are **MOST ACCURATE** regarding polatuzumab vedotin (Polivy®)? **(Choose all that apply)**

A. Despite the increase in survival, pola-R-CHP has not been shown to be cost effective compared to RCHOP in newly diagnosed DLBCL.

B. Grade 3-4 hematologic side effects were significantly increased when adding polatuzumab to bendamustine + rituximab for R/R DLBCL.

C. Polatuzumab for R/R DLBCL significantly increased incidence of peripheral neuropathy, unlike its use for newly diagnosed DLBCL.

D. In trials, Pola-R-CHP utilized higher rates of primary prophylaxis of neutropenia, leading to lower rates of neutropenia/neutropenic fevers.

ARS Question 10

Which statements below are **MOST ACCURATE** regardi
all that apply)

A. Despite the increase in survival, pola-R-CHP has not be
newly diagnosed DLBCL.

**B. Grade 3-4 hematologic side effects were significan
bendamustine + rituximab for R/R DLBCL.**

**C. Polatuzumab for R/R DLBCL significantly increase
for newly diagnosed DLBCL.**

D. In trials, Pola-R-CHP utilized higher rates of primary pr
neutropenia/neutropenic fevers.

Correct Answers

Polatuzumab increased rates of all hematologic side effects when added to BR.

- Anemia:
  - Pola-BR: 28.2% vs. BR: 17.9%
- Neutropenia rates:
  - Pola-BR: 46.2% vs. BR: 33.3%
- Thrombocytopenia rates:
  - Pola-BR: 41.0% vs. BR: 23.1%

Peripheral neuropathy was increased in Pola-BR (compared to BR) but was not increased in Pola-R-CHP (compared to RCHOP).

- Pola-BR: 43.6% vs. BR: 7.7%
- Pola-R-CHP: 52.9% vs. RCHOP: 53.9%
- Likely related to the fact that in newly diagnosed patients, vincristine was replaced, which is known to cause neuropathy.

Sehn LH et al. J Clin Oncol. 2020 Jan 10;38(2):155-65.
Tilly H et al. N Engl J Med. 2022;386(4):351-63.

ARS Question 10

Which statements below are **MOST ACCURATE** regard
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A. Despite the increase in survival, pola-R-CHP has not b
newly diagnosed DLBCL.

B. Grade 3-4 hematologic side effects were significantly in
rituximab for R/R DLBCL.

C. Polatuzumab for R/R DLBCL significantly increased inci
newly diagnosed DLBCL.

D. In trials, Pola-R-CHP utilized higher rates of primary prop
neutropenia/neutropenic fevers.

A cost effectiveness study of POLARIX showed that pola-R-CHP was cost effective at a willingness-to-pay of $150,000/QALY.

- This is highly reliant on the 5-year PFS found in POLARIX (62.7%) and a reduction in patients moving to CAR-T cell therapy.
- Actual wholesale prices:
  - Polatuzumab $154.88/mg
  - Vincristine $18-22/mg

Kambhampati S et al. Blood. 2022;140(25):2697-708.

ARS Question 10

Which statements below are **MOST ACCURATE** regardi
all that apply)

A. Despite the increase in survival, pola-R-CHP has not bee
newly diagnosed DLBCL.

B. Grade 3-4 hematologic side effects were significantly inc
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C. Polatuzumab for R/R DLBCL significantly increased inci
newly diagnosed DLBCL.

D. In trials, Pola-R-CHP utilized higher rates of primary pr
neutropenia/neutropenic fevers.

Rates of primary prophylaxis with GCSF and neutropenia/neutropenic fevers were not different between the RCHOP and Pola-R-CHP groups.

- Primary Prophylaxis rates:
  - Pola-R-CHP: 90.1% vs. RCHOP: 93.2%
- Neutropenia rates:
  - Pola-R-CHP: 30.8% vs. RCHOP: 32.6%
- Neutropenic fever rates:
  - Pola-R-CHP: 14.3% vs. RCHOP: 8.0%

Tilly H et al. N Engl J Med. 2022;386(4):351-63.

Patient Case 3: Part 1

EF if a 56-year-old man with a history of stage III diffuse large B-cell lymphoma (DLBCL). He was initially treated with 6 cycles of RCHOP with good response, however 6 months later he presented with fevers, chills, and fatigue and was found to be in relapse on PET scan. He was treated with 2 cycles of RICE followed by autologous stem cell transplant (ASCT). He now presents 5 years post ASCT with increased lymphadenopathy and fatigue with concerns of relapse.

SH:

- Works full time to support family.
- Lives with wife and 2 teenage children about 90 minutes from clinic.

ARS Question 11

Which treatment option would be the best fit for EF? **(Choose all that apply)**

A. Epcoritamab (Epkinly®)
B. Mosunetuzumab (Lunsumio®)
C. Glofitamab (Columvi®)
D. Axicabtagene ciloleucel (Yescarta®)
E. Haplo-identical stem cell transplant

ARS Question 11

Which treatment option would be the best fit for EF

A. Epcoritamab (Epkinly®)
B. Mosunetuzumab (Lunsumio®)
C. Glofitamab (Columvi®)
D. Axicabtagene ciloleucel (Yescarta®)
E. Haplo-identical stem cell transplant

Correct Answers

Glofitamab is approved for R/R DLBCL after 2 lines of therapy.

- It's given weekly for 3 doses, then Q21days, which could be feasible for patients who live further from clinic.
- Finite number of cycles (12).

Axicabtagene ciloleucel is also approved for R/R LBCL after 2 lines of therapy.

- Large up-front time commitment for work-up, treatment, and monitoring.
- No maintenance or long-term therapy necessary (until relapse).
- Can 'quickly' return to normal routines.

Glofitamab [package insert].
Axicabtagene ciloleucel [package insert].

ARS Question 11

Which treatment option would be the best fit fo

A. Epcoritamab (Epkinly®)
B. Mosunetuzumab (Lunsumi
C. Glofitamab (Columvi®)
D. Axicabtagene ciloleucel (Yescarta
E. Haplo-identical stem cell transplant

While epcoritamab is approved for R/R DLBCL after 2 lines of therapy, the dosing scheme isn't ideal for someone who has to travel a far distance for treatment.

- Weekly dosing for C1-3 (12 weeks)
- Q2week dosing for C4-9
- Q28day dosing for C10+ (no definite end point)
- Subcutaneous formulation may be ideal to reduce chair time, other factors seem to outweigh use for this patient.

Given the other options, EF's life would be greatly impacted by any form of allogeneic transplant.

- There is no clear guidance on order of therapies (CAR T-cell vs. BsAbs vs. Transplant).

Epcoritamab [package insert].

ARS Question 11

Which treatment option would be the best fit for EFS

A. Epcoritamab (Epkinly®)
B. Mosunetuzumab (Lunsumio®)
C. Glofitamab (Columvi®)
D. Axicabtagene ciloleucel (Yescarta®)
E. Haplo-identical stem cell transplant

Mosunetuzumab is only indicated in follicular lymphoma.

Mosunetuzumab [package insert].

ARS Question 12

Which toxicities are seen more commonly in high-dose methotrexate regimens? **(Choose all that apply)**

A. Hepatotoxicity
B. Infection
C. Mucositis
D. Myelosuppression
E. Nephrotoxicity
F. Neurotoxicity
G. Pneumonitis

ARS Question 12

Which toxicities are seen more commonly in high [illegible] **apply)**

A. Hepatotoxicity

B. Infection

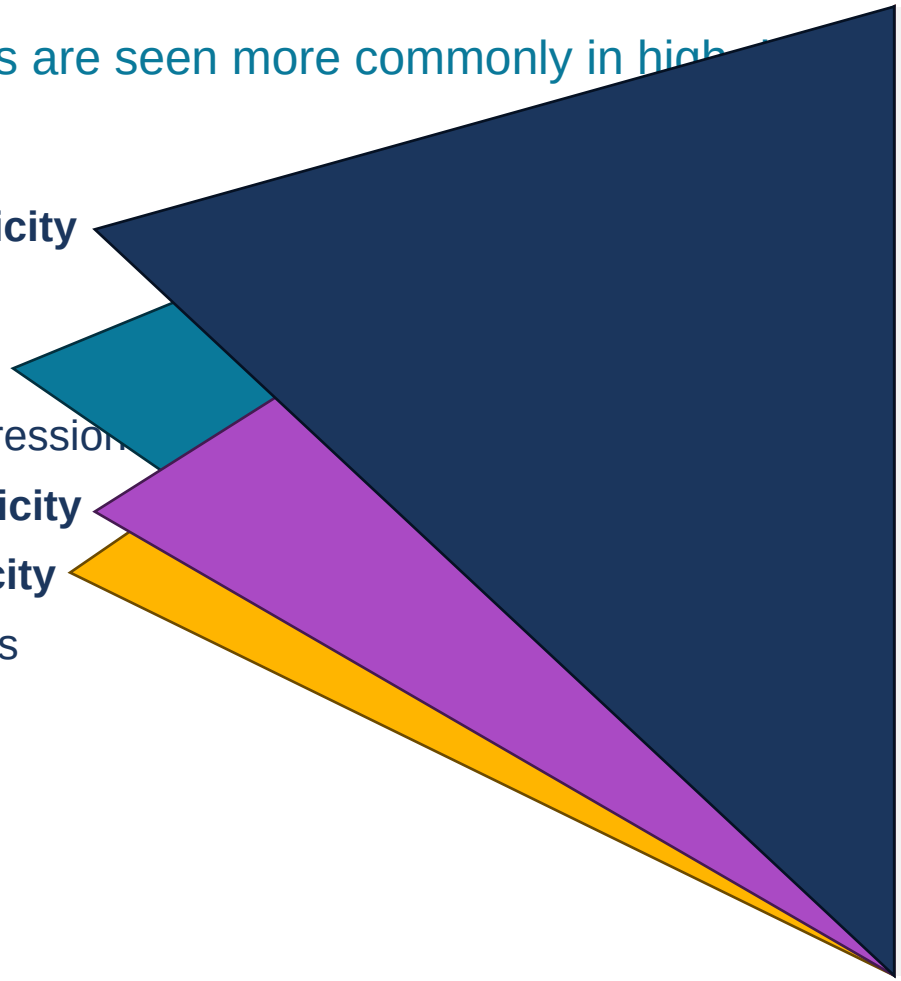
C. Mucositis

D. Myelosuppression

E. Nephrotoxicity

F. Neurotoxicity

G. Pneumonitis



Impaired function of folate cell transporters leads to excessive methotrexate accumulation in liver cells.

- **Risk Factors**: Alcohol consumption; female; metabolic syndrome; kidney disease; older age.

Caused by cellular damage along entire GI tract.

- Can be seen in lower doses if patient has poor clearance and extended exposure.
- **Risk Factors**: Concurrent use of NSAIDs

Crystal nephropathy and direct tubular toxicity from methotrexate crystalizing.

- **Risk Factors**: Age >49; concurrent use of salicylates, sulfonamides, NSAIDs, etc.; male, volume depletion; acidic urine.

Can manifest as encephalopathy, headache, seizure.

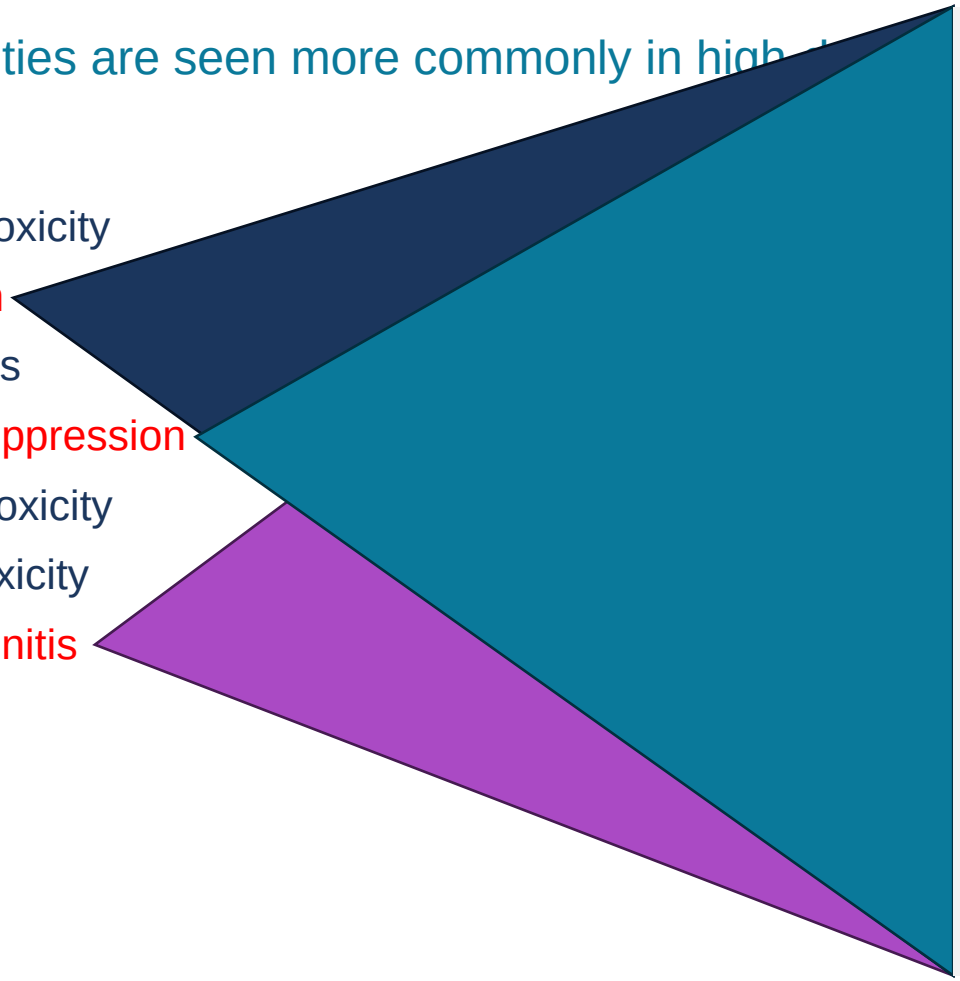
- May be related to accumulations of adenosine and homocysteine in the CNS.
- **Risk Factors**: concurrent CNS XRT; hypertension; female; higher cumulative dose.

Chabner BA and Young RC. J Clin Invest. 1973;52:1804-11.

ARS Question 12

Which toxicities are seen more commonly in high-dose MTX? (Select all that apply)

A. Hepatotoxicity
B. Infection
C. Mucositis
D. Myelosuppression
E. Nephrotoxicity
F. Neurotoxicity
G. Pneumonitis



Likely related to T-cell apoptosis and clonal deletion.

- **Risk Factors**: Extended treatment duration; concurrent use of salicylates, sulfonamides, NSAIDs, etc.

Studies have shown that levels as low as 0.01 µmol/L for over 24 hours can lead to significant bone marrow suppression.

- **Risk Factors**: Age >65; hypoalbuminemia; fluid accumulations/third spacing; kidney impairment; concurrent use of salicylates, sulfonamides, NSAIDs, etc.

Possibly an immune or hypersensitivity reaction to toxic accumulations of methotrexate in lung tissues.

- **Risk Factors**: low-dose methotrexate therapy; age >60; CKD; diabetes; male; preexisting lung disease.

Chabner BA and Young RC. J Clin Invest. 1973;52:1804-11.

ARS Question 13

Which of the following is **MOST ACCURATE** regarding the role of leucovorin in high-dose methotrexate?

A. Leucovorin binds to and inactivates acrolein, a metabolite of methotrexate, preventing kidney damage.

B. Leucovorin provides a ‘rescue’ to healthy cells by providing a reduced form of folic acid necessary for DNA/RNA synthesis.

C. Leucovorin stabilizes the binding of methotrexate and thymidylate synthetase, enhancing the activity of methotrexate.

D. Leucovorin reduces the risk of hematologic toxicity.

E. Leucovorin provides a source of tetrahydrofolate that aids the body in eliminating methotrexate.

F. Leucovorin rapidly hydrolyzes the carboxyl-terminal glutamate residue from extracellular methotrexate into inactive metabolites.

ARS Question 13

Which of the following is **MOST ACCURATE** regarding t
methotrexate?

A. Leucovorin binds to and inactivates acrolein, a metaboli
**B. Leucovorin provides a 'rescue' to healthy cells by
DNA/RNA synthesis.**
C. Leucovorin stabilizes the binding of methotrexate and t
methotrexate.
D. Leucovorin reduces the risk of hematologic toxicity.
E. Leucovorin provides a source of tetrahydrofolate that aid
F. Leucovorin rapidly hydrolyzes the carboxyl-terminal gluta
inactive metabolites.

Correct Answer

Methotrexate inhibits dihydrofolate reductase (DHFR) and thymidylate synthetase (TS), which are essential for DNA synthesis and repair.

- Leucovorin, a reduced folate, can be used by healthy cells.
- Malignant cells have a reduced capacity for the uptake of leucovorin, and thus do not gain this benefit.

Methotrexate [package insert].

ARS Question 13

Which of the following is **MOST ACCURATE** regarding t
methotrexate?

A. Leucovorin binds to and inactivates acrolein, a metabo
B. Leucovorin provides a ‘rescue’ to healthy cells by pro
DNA/RNA synthesis.
C. Leucovorin stabilizes the binding of methotrexate a
methotrexate.
D. Leucovorin reduces the risk of hematologic toxici
E. Leucovorin provides a source of tetrahydrofolate t
F. Leucovorin rapidly hydrolyzes the carboxyl-termin
inactive metabolites.

Mechanism for mesna with cyclophosphamide

- Mesna supplies a free thiol group which binds to and inactivates acrolein, the toxic metabolite of cyclophosphamide that can lead to hemorrhagic cystitis

Mechanism for leucovorin with 5FU

- Stabilizes the binding of 5-dUMP to thymidylate synthetase, enhancing the activity of 5FU.

Mechanism for leucovorin use with pyrimethamine for opportunistic infections

Mechanism for leucovorin in methanol toxicity management

- Administering a source of tetrahydrofolate may aid the body in eliminating formic acid, the toxic metabolite of methanol.

Mechanism for glucarpidase rescue in methotrexate toxicity

ARS Question 14

GH is a 68-year-old female. She was diagnosed 3 months ago with chronic-phase CML and started treatment with imatinib. Her qPCR for BCR::ABL1 came back as 11%. What is your next step?
(Choose all that apply)

A. Continue imatinib treatment and recheck at 6 months

B. Switch to ponatinib

C. Send for BCR::ABL1 kinase domain mutational analysis

D. Evaluate patient for adherence

E. Switch to dasatinib

ARS Question 14

GH is a 68-year-old female. She was diagnosed 3 mont
treatment with imatinib. Her qPCR for BCR::ABL1 ca
(Choose all that apply)

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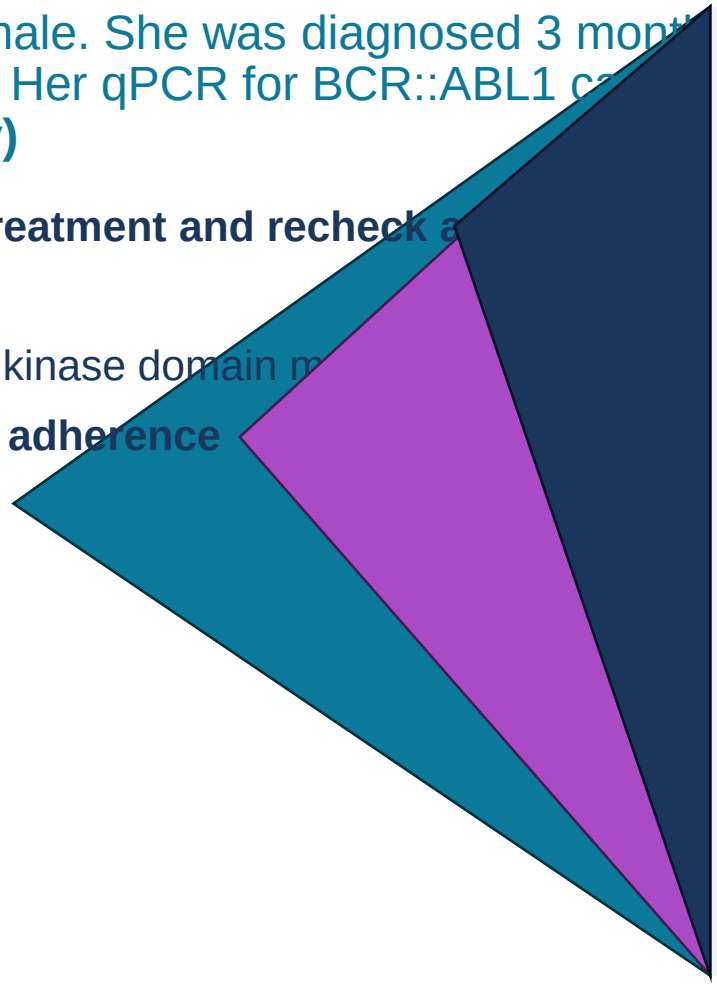
E. Switch to dasatinib



Correct Answers

More information is technically needed to make the decision between continuing imatinib and switching to dasatinib.

- Studies have shown that a steep decline to just over 10% at 3 months generally yields favorable outcomes by 6 months.
- qPCR results from diagnosis and more clinical context would be necessary.

Adherence should ALWAYS be assessed if optimal response is not obtained with oral therapies.

ARS Question 14

GH is a 68-year-old female. She was diagnosed 3 mon
treatment with imatinib. Her qPCR for BCR::ABL1
(Choose all that apply)

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B. Switch to ponatinib
C. Send for BCR::ABL1 kinase doma
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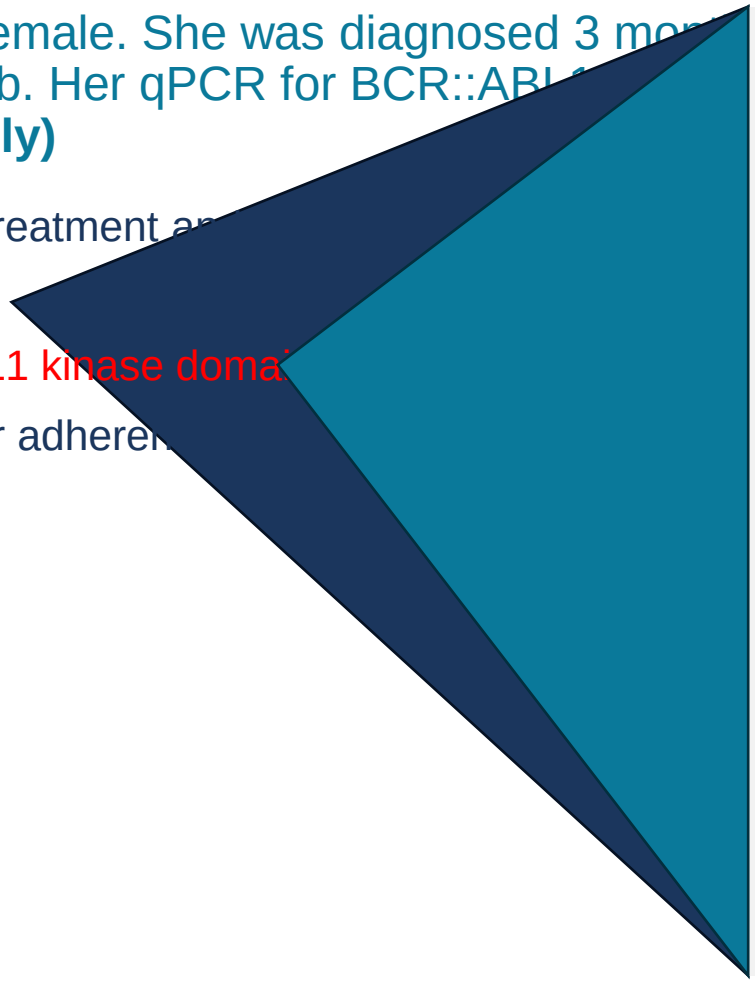

There isn't a clinical need to switch to ponatinib at this time.

- Without mutation testing, ponatinib isn't recommend until 2 or more TKIs have been trialed.

The response to therapy at this point seems to be sufficient that point mutation resistance is unlikely.

- While there isn't a specific threshold to consider genetic testing, clinical context should always be taken into consideration.

ARS Question 15

Which statement regarding BCR-ABL TKIs is **INACCURATE**?

A. T315I mutation is a contraindication for treatment with imatinib, bosutinib, dasatinib, and nilotinib.
B. Ponatinib is the preferred TKI for CML with T315I mutation in any phase.
C. The most common mechanism for resistance mutations to BCR-ABL TKIs is translocation.
D. Imatinib and ponatinib are the only BCR-ABL TKIs that can be taken without regard to gastric acid suppressant use.
E. Many of the toxicities associated with BCR-ABL TKIs are related to off-target effects.

ARS Question 15

Which statement regarding BCR-ABL TKIs is **INACCUR**

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D. Imatinib and ponatinib are the only BCR-ABL TKIs that suppressant use.
E. Many of the toxicities associated with BCR-ABL TKIs ar

Correct Answer

The most common mechanism for resistance is point mutations.

- See below for common mutations and the drugs they confer resistance to:

Drug	Contraindicated Mutations
Asciminib	A337T, P465S, M244V, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib	None

ARS Question 15

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E. Many of the toxicities associated with BCR-ABL TKIs ar

See previous slide for mutation table

- Only ponatnib and asciminib are active in T315I mutations.

If T315I mutation is found, ponatinib is considered the preferred agent for any phase.

- Asciminib is considered an option for CP-CML with T315I mutation.

ARS Question 15

Which statement regarding BCR-ABL TKIs is **INACCUR**

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B. Ponatinib is the preferred TKI for CML with T315I mutati
C. The most common mechanism for resistance mutation
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E. Many of the toxicities associated with BCR-ABL TKIs a

All other BCR-ABL TKIs require separation of acid suppression therapy from TKI.

- The TKIs require the stomach acid to support absorption of drug into the system.
- Given mechanism of PPIs, H2RAs or antacids are preferred, but should still be separated by >2 hours.

All of the BCR-ABL TKIs have affects on numerous other targets. These off-target effects cause most of the toxicities associated with therapy.

- PDGFR, c-KIT, VEGFR, FGFR, SRC family, SCF, STAMP, etc.

ARS Question 16

Which of the following statements about bispecific monoclonal antibodies (BsAbs) is **INACCURATE**?

A. Currently approved bispecific T-cell recruiting antibodies are only indicated in hematologic malignancies.

B. Variable fragment based BsAbs have higher tumor penetration and shorter half-life when compared to IgG based BsAbs.

C. CD3 is the immune cell bridge used most commonly for t-cell engaging due to low variance.

D. Blinatumomab (Blincyto®) is the only currently available BiTE® indicated for hematologic malignancies.

ARS Question 16

Which of the following statements about bispecific mono

A. Currently approved bispecific T-cell recruiting anti

B. Variable fragment based BsAbs have higher tumor pen based BsAbs.

C. CD3 is the immune cell bridge used most commonly for

D. Blinatumomab (Blincyto®) is the only currently available

Correct Answer

This statement was true up until May 2024 when tarlatamab-dlle (Imdelltra®) was approved for small cell lung cancer.

- Other BsAbs approved in solid tumors did not engage T-cells or other immune cells directly.
  - Amivantamab (EGFR + MET)
- Drugs like tebentafusp are used in solid tumors, but are not *technically* antibodies (they are proteins)

Tarlatamab [package insert].
Amivantamab [package insert].
Tabentafusp [package insert].

ARS Question 16

Which of the following statements about bispecific monc

A. Currently approved bispecific T-cell recruiting antibodies
B. Variable fragment based BsAbs have higher tumor per based BsAbs.
C. CD3 is the immune cell bridge used most commonly fo
D. Blinatumomab (Blincyto®) is the only currently availabl

Variable fragment based BsAbs are much smaller molecules compared to IgG based antibodies.

- This smaller size confers higher tumor penetration.

BiTE® is a trademark of Amgen.

- All BiTEs are bispecific antibodies, but not all BsAbs are BiTEs.
- Legally only Amgen products can be considered BiTEs.
- Tarlatamab (Imdelltra®) is a solid tumor BiTE recently approved.

Tian Z et al. J Hematol Oncol. 2021;14(1):75.

Bispecific Antibodies (BsAbs)

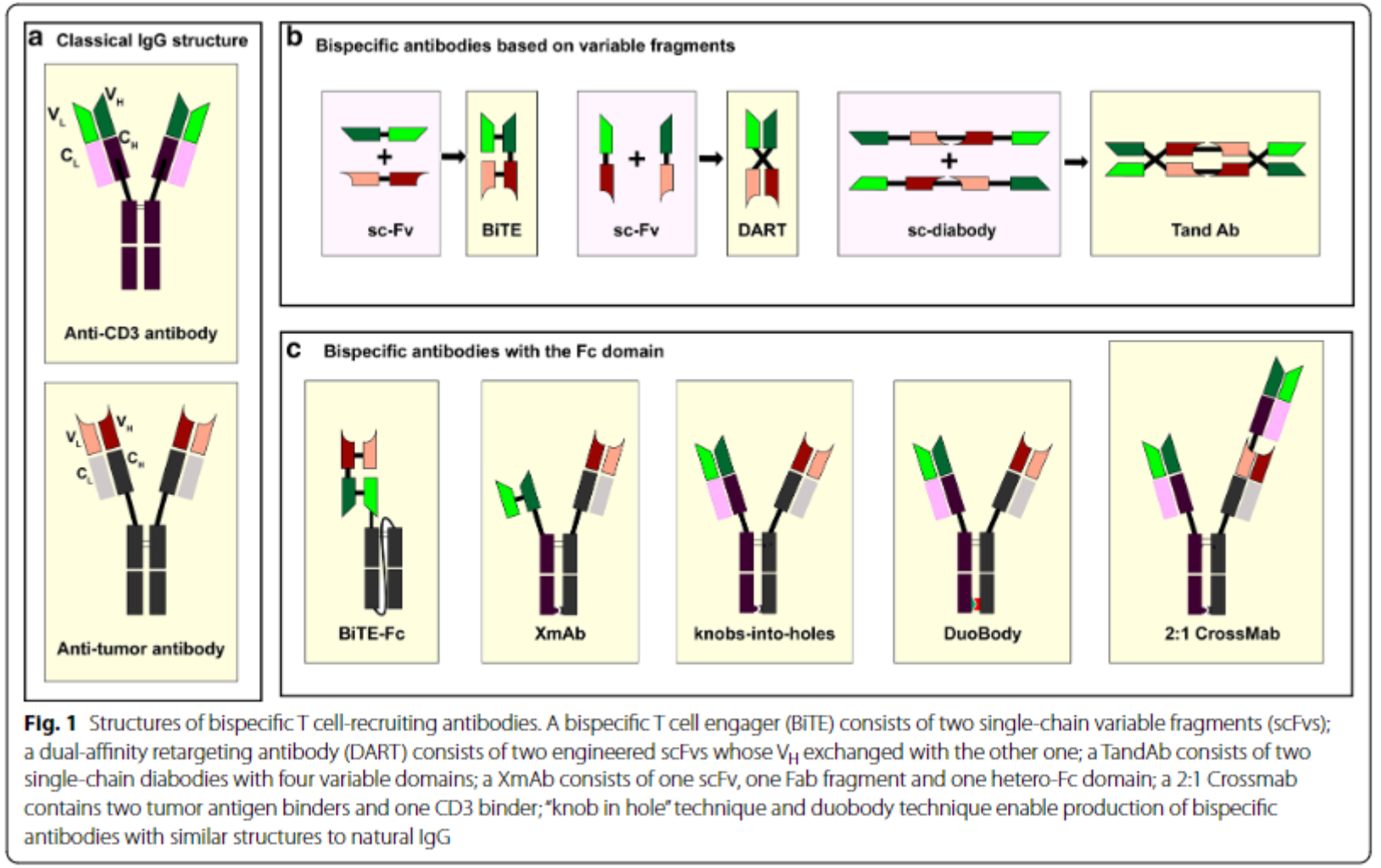

FIg. 1 Structures of bispecific T cell-recruiting antibodies. A bispecific T cell engager (BiTE) consists of two single-chain variable fragments (scFvs); a dual-affinity retargeting antibody (DART) consists of two engineered scFvs whose V_H exchanged with the other one; a TandAb consists of two single-chain diabodies with four variable domains; a XmAb consists of one scFv, one Fab fragment and one hetero-Fc domain; a 2:1 Crossmab contains two tumor antigen binders and one CD3 binder; "knob in hole" technique and duobody technique enable production of bispecific antibodies with similar structures to natural IgG

Tian Z et al. J Hematol Oncol. 2021;14(1):75.

ARS Question 16

Which of the following statements about bispecific mono

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C. CD3 is the immune cell bridge used most commonly fo
D. Blinatumomab (Blincyto®) is the only currently available

CD3 is the only immune cell bridge target currently used in FDA approved products.

- Other targets are being studied but have not been approved at this time.

Sun Y et al. Acta Pharm Sin B. 2023;13(9):3583-97.

BsAbs in Development

Table 2 BsAbs bridge two cells in clinical stages.

Bridge immune cell	Bridge tumor cell	Name	Indication	Phase	Clinical trial
CD3	BCMA	BI836909	R/R MM	I	NCT03287908
	CD123	APVO436	AML	I	NCT03647800
	CD19	AMG562	DLBCL	I	NCT03571828
	CD20	GEN3013	DLBCL	I/II	NCT03625037
	CD33	GEM333	AML	I	NCT03516760
	CD38	GBR1342	R/R MM	I	NCT03309111
	CEA	RG7802	Solid tumors	I	NCT02650713
	CLEC12A	MCLA-117	AML	I	NCT03038230
	DLL3	AMG757	AML	I	NCT03541369
	EGFR	AFM24	Advanced solid tumor	I/II	NCT04259450
	EpCAM	MT110	Solid tumors	I	NCT00635596
	FcRH5	RO7187797	MM	I	NCT03275103
	FLT3	AMG427	AML	I	NCT03541369
	GD2	NCT03541369	SCLC	I/II	NCT04750239
	Glypican-3	ERY974	Solid tumors	I	NCT02748837
	gpA33	MGD007	Colorectal carcinoma	I	NCT02248805
	GPRC5D	ERY974	Solid tumors	I	NCT02748837
	HER2	BTRC4017A	Solid tumors	I	NCT03448042
	MAGE-A4 (HLA-A*02:01)	IMC-C103C	Select advanced solid tumors	I/II	NCT03973333
	MUC17	AMG199	MUC17-positive solid tumors	I	NCT04117958
	MUC16	REGN4018	Recurrent ovarian cancer	I/II	NCT03564340
	NY-ESO-1 (HLA-A*02:01)	GSK01	Select advanced solid tumors	I/II	NCT03515551
	P-cadherin	PF-06671008	Neoplasms	I	NCT02659631
	PRAME (HLA-A*02:01)	IMC-F106C	Select advanced solid tumors	I/II	NCT04262466
	PSCA	GEM3PSCA	NSCLC	I	NCT03927573
	PSMA	JNJ-63898081	Neoplasms	I	NCT03926013
	SSTR2	Xmab18087	Neuroendocrine tumor	I	NCT03411915
	STEAP1	AMG509	Prostate cancer	I	NCT04221542
	5T4	GEN1044	Malignant solid tumors	I/II	NCT04424641
γδTCR	CD1d	LAVA-051	CLL	I/II	NCT04887259
	PSMA	LAVA-1207	Metastatic castration resistant prostate cancer	I/II	NCT05369000
CD16A	BCMA	RO7297089	R/R MM	I	NCT04434469
	CD30	AFM13	NHL	I/II	NCT04074746
	EGFR	AFM24	Advanced solid tumor	I/II	NCT04259450

AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung carcinoma; R/R MM, relapsed or refractory multiple myeloma; SCLC, small-cell carcinoma.

Sun Y et al. Acta Pharm Sin B. 2023;13(9):3583-97.

ARS Question 17

Which statement related to small molecules used in CLL management is **MOST ACCURATE**?

A. BCL2 G101V mutation has been implicated in clinical resistance to venetoclax.

B. BTK inhibitors are associated with hepatotoxicity while PI3K inhibitors are associated with bleeding.

C. Resistance to ibrutinib has been linked to mutations in BTK and PLCG2, which can be overcome by using an alternative BTK inhibitor such as acalabrutinib.

D. Both BTK inhibitors and PI3K inhibitors are associated diarrhea, but only PI3K inhibitors are associated with severe colitis.

E. Requirement for anticoagulation and use of gastric acid suppressants are contraindications to treatment with BTK inhibitors.

ARS Question 17

Which statement related to small molecules used in CLL

A. BCL2 G101V mutation has been implicated in clinical res
B. BTK inhibitors are associated with hepatotoxicity while P
C. Resistance to ibrutinib has been linked to mutations in B alternative BTK inhibitor such as acalabrutinib.
D. Both BTK inhibitors and PI3K inhibitors are associ associated with severe colitis.
E. Requirement for anticoagulation and use of gastric acid BTK inhibitors.

Correct Answer

BTK inhibitors have higher rates of diarrhea, however only PI3K inhibitors are associated with colitis.

- Rates of severe colitis (Grade 3-4) is above 10% for idelalisib and duvelisib.
- Idelalisib has a black box warning due to the risk of severe diarrhea and colitis.
  - Also, BBW for hepatotoxicity, pneumonitis, infection, and intenstinal perforation.

Ibrutinib [package insert].
Acalabrutinib [package insert].
Zanubrutinib [package insert].
Pirtobrutinib [package insert].
Idelalisib [package insert].
Duvelisib [package insert].

ARS Question 17

Which statement related to small molecules used in CL

A. BCL2 G101V mutation has been implicated in clinical r
B. BTK inhibitors are associated with hepatotoxicity while
C. Resistance to ibrutinib has been linked to mutations in alternative BTK inhibitor such as acalabrutinib.
D. Both BTK inhibitors and PI3K inhibitors are associated severe colitis.
E. Requirement for anticoagulation and use of gastric acid BTK inhibitors.

The G101V mutation in BCL2 has been seen in patients who develop resistance, however no clinical implications have been determined.

- Mutations have been seen up to 25 months BEFORE clinical progression occurs.

Mutations in BTK and/or PCLG2 have been shown to lead to resistance to ALL covalent BTK inhibitors.

- This includes ibrutinib, acalabrutinib, and zanubritinib.
- Only pirtobrutinib is considered an option with this mutation.

ARS Question 17

Which statement related to small molecules used in CLL

A. BCL2 G101V mutation has been implicated in clinical re

B. BTK inhibitors are associated with hepatotoxicity while

C. Resistance to ibrutinib has been linked to mutations in alternative BTK inhibitor such as acalabrutinib.

D. Both BTK inhibitors and PI3K inhibitors are associated severe colitis.

E. Requirement for anticoagulation and use of gastric aci BTK inhibitors.

These ADRs are swapped. BTKs are more commonly associated with bleeding, while PI3Ks are associated with hepatotoxicity.

- BTK bleeding rates: 8-28% (highest with ibrutinib)
- PI3K hepatotoxicity rates: 28-42%

While anticoagulation is a concern with use of BTK inhibitors because of the risk of bleeding, monitoring can be done to mitigate risk.

- Antacids are only a concern with acalabrutinib
- Must separate administration by 2 hours

Ibrutinib [package insert].
Acalabrutinib [package insert].
Zanubrutinib [package insert].
Pirtobrutinib [package insert].
Idelalisib [package insert].
Duvelisib [package insert].

ARS Question 18

IJ is a 41-year-old man with history of ALL. He has completed induction and one cycle of early intensification course and is getting labs prior to the repeat cycle of early intensification (based on CALGB 8811, Larson et al). His WBC returns as <0.1 and Hgb 6.2. Which genetic mutation/drug combo is the likely culprit for GH's pancytopenia? (More than one answer may be correct)

A. TPMT / 6-mercaptopurine

B. NUDT15 / cytarabine

C. UGT1A1*28 / pegaspargase

D. DPYD*2A / vincristine

ARS Question 18

IJ is a 41-year-old man with history of ALL. He has
early intensification course and is getting labs n
(based on CALGB 8811, Larson et al). His W
mutation/drug combo is the likely culprit f
may be correct)

A. TPMT deficiency / 6-mercaptopurin

B. NUDT15 deficiency / cytarabine

C. UGT1A1*28 / pegaspargase

D. DPYD*2A / vincristine

Correct answer

Deficiency in thiopurine methyltransferase (TPMT) can result in severe bone marrow suppression with 6-mercaptopurine (6MP). This is also a factor if using 6-thioguanine (6TG).

- A heterozygous deficiency can require dose reductions of 30-70%.
- A homozygous deficiency can require dose reductions of 90%.

6-mercaptopurine [package insert].

ARS Question 18

IJ is a 41-year-old man with history of ALL. He has
early intensification course and is getting labs n
(based on CALGB 8811, Larson et al). His W
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A. TPMT deficiency / 6-mercaptopurine
B. NUDT15 deficiency / cytarabine
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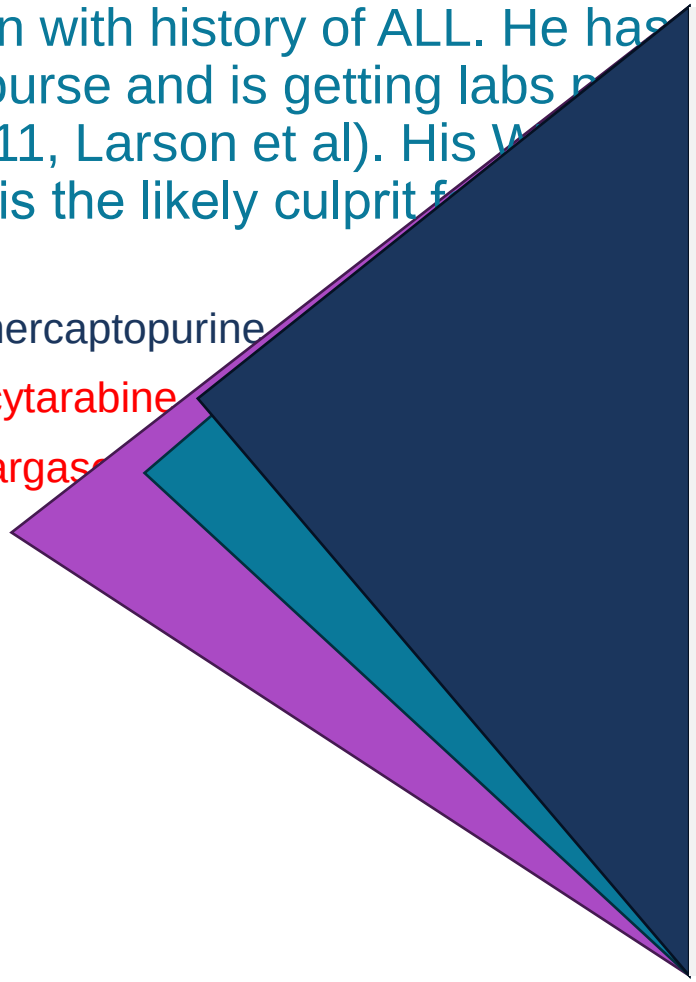


Deficiency in nudix hydrolase 15 (NUDT15) can also result in severe bone marrow suppression related to 6MP and 6TG.

- A heterozygous deficiency can require dose reductions of 30-70%.
- A homozygous deficiency can require dose reductions of 90%.

Variants of UDP-glucuronyltransferase (UGT) (especially *28 and *6) are associated with increase diarrhea with irinotecan.

- Responsible for metabolism of SN-38.

Mutations in dihydropyrimidine dehydrogenase (DPD) is associated with increased adverse effects with 5FU.

- Mucositis, diarrhea, neutropenia, neurotoxicity.

Fred Hutch Cancer Center

Thank you

Hematology Pharmacology Pearls

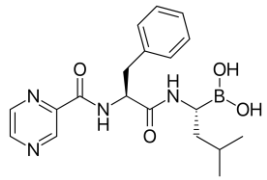
Zak Cerminara, PharmD, BCOP
Lead Clinical Pharmacist, Stem Cell Transplant/Immunotherapy
UW Medicine and Fred Hutchinson Cancer Center
September 26, 2024

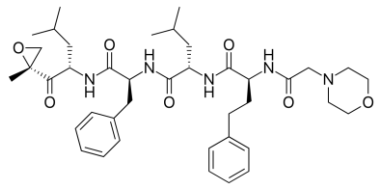
Immunomodulatory Agents (IMiDs)

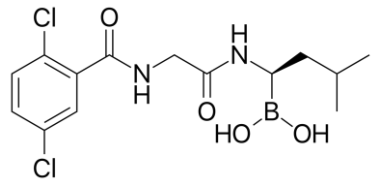
	Thalidomide (Thalomid)	Lenalidomide (Revlimid)	Pomalidomide (Pomalyst)
Uses	Myeloma	Myeloma (including maintenance) MDS (del 5q)	Myeloma
Dose Adjustments	None	Myelosuppression Renal/Dialysis	Myelosuppression
Common Toxicities	Myelosuppression (L/P>>T), neuropathy (T>>L/P), fatigue, weakness, edema, nausea, hypotension, rash		
	Sedation Bradycardia	AFib Bradycardia	AFib Dyspnea Hypercalcemia
Serious Toxicities	Hypersensitivity, SJS/TENs, Angioedema Secondary malignancies		
	Neuropathy (motor/sensory, may be permanent) Seizures	Thrombocytopenia, neutropenia (80% Grade 3-4) TLS	Dizziness, confusion
Notes		PgP substrate	CYP1A2 and 3A4 substrate

Proteasome Inhibitors (PIs)

	Bortezomib (Velcade)	Carfilzomib (Kyprolis)	Ixazomib (Ninlaro)
Uses	Myeloma, mantle cell lymphoma	Myeloma	Myeloma
Admin	**SubQ, IV**	**IV**	**Oral** (empty stomach)
Dosing	1.3 mg/m^2 days 1, 4, 8, 11 Q21 days 1.5 mg/m^2 days 1, 8, 15, 22 Q28 days	C1: 20mg/m^2 days 1, 2; 27 mg/m^2 days 8, 9, 15, 16 Q28 days Can increase up to 56 mg/m^2 ***Cap BSA at 2.2 m^2**	4 mg days 1, 8, 15 Q28 days ***3 mg for CrCl <30 mL/min**
Toxicities	Fatigue, malaise Nausea, vomiting, constipation Neutropenia, thrombocytopenia, peripheral neuropathy Cardiotoxicity: Orthostatic hypotension, edema, HF		
	Most peripheral neuropathy IV>>SubQ	**Most cardiotoxic** Rare: pulmonary toxicity, TLS, liver tox	
Drug Interactions	CYP3A4 and 2C19	PgP	CYP3A4, PgP







CD38 Antibodies

	Daratumumab (Darzalex, Darzalex Faspro)	Isatuximab (Sarclisa)
Uses	Myeloma	
Admin	**SubQ, IV**	**IV**
Dosing	IV: 16 mg/kg / SubQ: 1800 mg **Weeks 1-8**: once weekly **Weeks 9-24**: Q2 weeks **Weeks 25+**: Q4 weeks	10 mg/kg **C1**: days 1, 8, 15, 22 Q4 weeks **C2+**: days 1 and 15 Q4 weeks
Toxicities	Infusion reactions, URI, neutropenia, thrombocytopenia, anemia, diarrhea	
Premedications	Dexamethasone, acetaminophen, H2 antagonist, H1 antagonist	
Other	May be detected on SPEP and immunofixation assays May result in a positive Coombs test Daratumumab can mask antibody detection to minor antigens	

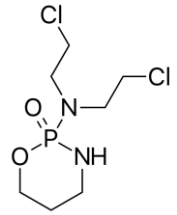
CAR T-Cells: BCMA Targeting

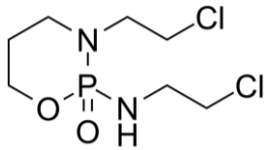
	Idecabtagene vicleucel (Abecma®)	Ciltacabtagene autoleucel (Carvykti®)
Uses	Myeloma After 2 lines: PI, IMiD, and anti-CD38	Myeloma After 1 line: PI and IMiD (and lenalidomide refractory)
Toxicities	**Cytokine release syndrome (CRS) BBW** **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) BBW** **HLH/MAS BBW** **Prolonged Cytopenias BBW** Anemia, neutropenia, lymphopenia, thrombocytopenia	
		Parkonsonism and Guillian-Barre syndrome
Costimulatory Domain (CD)	4-1BB	4-1BB
Lymphodepletion (LD)	Fludarabine 30 mg/m^2 x 3 days Cyclophosphamide 300 mg/m^2 x 3 days	

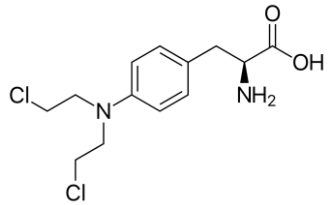
Myeloma Bispecifics

	Teclistamab (Tecvayli®)	Elranatamab (Elrexfio®)	Talquetamab (Talvey®)
Target	BCMA-CD3	BCMA-CD3	GPRC5D-CD3
Indication	4 x R/R Myeloma after IMiD, PI, and anti-CD38		
Dose	**D1**: 0.06 mg/kg **D4**: 0.3 mg/kg **D7**: 1.5 mg/kg **D14+**: 1.5 mg/kg weekly **All doses SubQ*	**D1**: 12 mg **D4**: 32 mg **D8**: 76 mg **Weekly through week 24**: 76 mg **For responders, week 25+**: 76 mg Q2Weeks **All doses SubQ*	**D1**: 0.01 mg/kg **D4**: 0.06 mg/kg **D7**: 0.4 mg/kg **Weekly**: 0.4 mg/kg --- **D1-7**: as above **D10**: 0.8 mg/kg **Q2Weeks**: 0.8 mg/kg **All doses SubQ*
Toxicities	**Cytokine release syndrome (CRS), neurotoxicity (ICANS) BBWs** Neutropenia Hepatotoxicity Injection site reactions		
	Arrhythmias	Dysgeusia, dry mouth, stomatitis	Dysgeusia, dry mouth, stomatitis
Notes	REMS program (same program as talquetamab)	REMS Program	REMS program (same program as teclistamab)

Nitrogen Mustards







	Cyclophosphamide (Cytoxan)	Ifosfamide (Ifex)	Melphalan (Alkeran, Evomela)
Uses	Breast, sarcoma, lymphoma, leukemia, HSCT, immunosuppressive (non-malignant)	Sarcoma, testicular, lymphoma	Ovarian, myeloma, HSCT
Dosing	PO: 300-500 mg/m^2 IV: 250-2000 mg/m^2; 60-100 mg/kg	IV: 1-5 g/m^2	PO: 0.15-0.25 mg/kg; 4-9 mg/m^2 IV: 60-200 mg/m^2
Common Toxicities	Myelosuppression (platelet sparing) Delayed nausea/vomiting (dose related) Alopecia		Myelosuppression Diarrhea, nausea, vomiting Alopecia
Rare/Serious Toxicities	**Hemorrhagic cystitis**		
	Cardiotoxicity (high dose) Interstitial pneumonitis SIADH	Fanconi's syndrome **Encephalopathy** (treat with methylene blue)	
Notes	DDI: warfarin (monitor PT/INR) **Dose reduce for renal dysfunction**		**Dose reduce for renal dysfunction** Only comes orally as 2 mg tablets Cryotherapy for HSCT doses **Stability**: Alkeran 1 hr Evomela 4 hrs
	Uroprotection with mesna (doses >1500-2000 mg/m^2)	Uroprotection with mesna **ALWAYS** (at least 60% dose of ifosfamide given pre/post infusion)	

FLT3 Inhibitors

	Midostaurin (Rydapt®)	Gilteritinib (Xospata®)	Quizartinib (Vanflyta®)
Uses	AML (FLT3 mutated) Mast cell leukemia, systemic mastocytosis	R/R AML (FLT3 mutated)	AML (FLT3 ITD mutated)
Dose	**AML Induction**: 50 mg PO BID days 8-21 **AML Consolidation**: 50 mg PO BID days 8-21 (up to 4 cycles) **AML Maintenance**: 50 mg PO BID (up to 12 cycles) **Other**: 100 mg PO BID	120 mg PO daily	**Induction**: 35.4 mg PO daily days 8-21 **Consolidation**: 35.4 mg PO daily days 8-21 Q28days (up to 4 cycles) **Maintenance C1**: 26.5 mg PO daily days 1-14. Increase to 53 mg PO daily if QTc ≤450 msec **Maintenance C2+**: 26.5 or 53 mg PO daily
Common Toxicities	Nausea, diarrhea, electrolyte abnormalities, increased LFTs, QT prolongation		
	Increased SCr, hyperglycemia, neutropenia, leukopenia, anemia, thrombocytopenia	Increased SCr, hyperglycemia, hypertriglyceridemia, constipation	Neutropenia, leukopenia, anemia, thrombocytopenia
Serious Toxicities		Differentiation Syndrome	**QT Prolongation** (BBW; REMS)
Drug Interactions	CYP3A4 inducers and inhibitors		
Notes			Discontinue 7 days prior to HSCT conditioning

IDH Inhibitors

	Enasidenib (Idhifa®)	Ivosidenib (Tibsovo®)	Olutasidenib (Rezlidhia®)
Uses	R/R AML, IDH2 mutated	Newly diagnosed ***OR*** R/R AML, MDS, cholangiocarcinoma, IDH1 mutated	R/R AML, IDH1 mutated
Dose	100 mg PO daily	500 mg PO daily	150 mg PO BID
Toxicities	Differentiation syndrome (treat with steroids) Electrolyte imbalances (hypocalcemia, hypokalemia)		
	Nausea, vomiting, diarrhea, anorexia Elevated bilirubin	QTc prolongation LFT elevations	Constipation, diarrhea LFT and bili elevations Rash
Notes		ECG monitoring weekly for first month	

CD20 Antibodies

	Rituximab (Rituxan and biosimilars)	Rituximab hyaluronidase (Rituxan Hycela)	Obinutuzumab (Gazyva)
Uses	NHL, CLL, ALL, Waldenstrom's		CLL, FL
Dose	IV: 375-1000 mg/m^2	**CLL C2+**: 1,600 mg SubQ Q28 days **Lymphoma C2+**: 1,400 mg SubQ Q14-21 days	**C1D1**: 100mg IV **C1D2**: 900mg IV **C1D8, 15**: 1000mg IV **C2+**: 1000mg IV Q21-28 days **Maint**: 1000mg IV Q2 months x 2years
Toxicities	PML, HBV reactivation (All BBWs) Infusion reaction (BBW for rituximab)		
			Tumor lysis syndrome
Notes	HBV core antibody and surface antigen testing prior to dose If surface antigen positive, prophylactic entecavir recommended		
		Must have 1 full dose of IV rituximab prior to use Hyaluronidase reversibly opens up interstitial space in SubQ tissue to deliver >2.3ml	

CD20 Bispecifics

	Glofitamab (Columvi)	Epcoritamab (Epkinly)	Mosunetuzumab (Lunsumio)
Uses	Diffuse large B-cell lymphoma	Diffuse large B-cell lymphoma	Follicular lymphoma
Dose	Obinutuzumab given C1D1 **C1D8**: 2.5 mg IV over 4 hours **C1D15**: 10 mg IV over 4 hours **C2D1**: 30 mg IV over 4 hours **C3-12D1**: 30 mg IV over 2 hours	**C1D1**: 0.16 mg SubQ **C1D8**: 0.8 mg SubQ **C1D15, 22**: 48 mg SubQ **C2-3D1, 8, 15, 22**: 48 mg SubQ Q28 days **C4-9D1, 15**: 48 mg SubQ Q28 days **C10+D1**: 48 mg SubQ Q28 days	**C1D1**: 1 mg IV over 4 hours **C1D8**: 2 mg IV over 4 hours **C1D15**: 60 mg IV over 4 hours **C2D1**: 60 mg IV over 2 hours **C3+D1**: 30 mg IV over 2 hours
Toxicities	Cytokine release syndrome (CRS), neurotoxicity (ICANS) Neutropenia Hepatotoxicity Electrolyte abnormalities		
	Tumor flare		Tumor flare
Notes	Obinutuzumab used to saturate CD20 to prevent CRS		

CD19 Antibodies

	Loncastuximab Tesirine (Zynlonta)	Tafasitamab (Monjuvi)
Uses	R/R LBCL	R/R DLBCL
Dose	**C1-2**: 0.15 mg/kg IV Q3 weeks **C3+**: 0.075 mg/kg IV Q3 weeks	12 IV mg/kg **C1**: Days 1, 4, 8, 15, 22 Q28 days **C2-3**: Days 1, 8, 15, 22 Q28 days **C4+**: Days 1, 15 Q28 days
Toxicities	Neutropenia, thrombocytopenia, anemia	
	Increased LFTs Increased serum glucose Edema, cutaneous reactions	Infections Infusion reactions
Notes	Use adjusted body weight for BSA ≥35	Combined with lenalidomide for max of 12 cycles

CD19 BiTEs

	Blinatumomab (Blincyto)
Uses	ALL
Target	CD19
Dose	**MRD+**: 28 mcg daily CIVI Q6 weeks x 4 cycles **R/R**: **C1**: 9 mcg daily CIVI days 1-7; 28 mcg daily CIVI days 8-28 **C2-5**: 28 mcg daily CIVI Q6 weeks **C6-9**: 28 mcg daily CIVI Q12 weeks
Toxicities	Cytokine release syndrome (CRS), neurotoxicity (ICANS) Neutropenia Hepatotoxicity
	Arrhythmias
Notes	

CAR T-Cells: CD19 Targeting

	Tisagenlecleucel (Kymriah)		Axicabtagene ciloleucel (Yescarta)	Brexucabtagene autoleucel (Tecartus)		Lisocabtagene maraleucel (Breyanzi)
Uses	ALL (age <26), DLBCL, **FL**		FL, LBCL	MCL, **ALL**		LBCL
Tox.	**Cytokine release syndrome (CRS) BBW** **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) BBW** Anemia, neutropenia, lymphopenia, thrombocytopenia					
CD	4-1BB		CD28	CD28		4-1BB
LD	**ALL**	Flu 25 mg/m^2 x 4 days Cy 500 mg/m^2 x 2 days	Flu 30 mg/m^2 x 3 days Cy 500 mg/m^2 x 3 days	**MCL**	Flu 30 mg/m^2 x 3 days Cy 500 mg/m^2 x 3 days	Flu 30 mg/m^2 x 3 days Cy 300 mg/m^2 x 3 days
	Lym	Flu 25 mg/m^2 x 3 days Cy 250 mg/m^2 x 3 days		**ALL**	Flu 25 mg/m^2 x 3 days Cy 900 mg/m^2 x 1 days	

Bruton's Tyrosine Kinase Inhibitors

	Ibrutinib (Imbruvica®)	Acalabrutinib (Calquence®)	Zanubrutinib (Brukinsa®)	Pirtobrutinib (Jaypirca®)
Uses	CLL/SLL, MCL, MZL, Waldenstrom's, cGVHD	R/R MCL, CLL/SLL	CLL/SLL, Waldenstrom's, R/R MCL, R/R MZL, R/R FL	R/R CLL/SLL, R/R MCL (after BTK inhibitor)
Dose	**CLL/WM**: 420mg daily **MCL**: 560mg daily	100 mg Q12 hours Avoid PPIs; separate 2h from H2 blockers	160mg BID or 320mg daily with food	200 mg daily
Common ADR	Diarrhea, nausea, fatigue, rash myalgias/arthralgias, myelosuppression		Myelosuppression, hemorrhage, infection	Myelosuppression, hemorrhage, infection
Serious/ Rare ADR	Grade 3/4 bleeding, AFib, infection	Afib/flutter, bleeding, infection, secondary malignancies	Afib/flutter	Afib/flutter, secondary malignancies
Notes	Avoid strong 3A4 inhibitors & inducers - dosing recommendations available Consider holding for 3-7 days around procedures			
	Consider infection prophylaxis for HSV, PJP			

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; cGVHD: chronic graft versus host disease; WM: Waldenstroms macroglobulinemia; PPI: proton pump inhibitor; Afib: atrial fibrillation; ADR: adverse drug reaction

PI3Kδ Targeting TKIs

	Idelalisib (Zydelig®)	Duvelisib (Copiktra®)
Target	Phosphatidylinositol 3-Kinase delta	
		PI3K-gamma
Uses	R/R CLL	R/R CLL/SLL
Dose	150mg BID Dose reduce for strong CYP3A4 inhibitor	25mg BID Dose reduce for 15mg BID if given with strong CYP3A4 inhibitor
ADR	Neutropenia, rash, diarrhea	
	Colitis, GI perf, hepatotoxicity	Colitis, hepatotoxicity
BBW	Hepatotoxicity, diarrhea/colitis, infection (PCP/CMV), pneumonitis, intestinal perforation	Infection (PCP/CMV), diarrhea/colitis, cutaneous reactions, pneumonitis
Notes	PJP prophylaxis during treatment and continue until CD4+>200	

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; FL: follicular lymphoma; MZL: marginal zone lymphoma; GI perf: gastrointestinal perforation; ADR: adverse drug reaction; BBW: black box warning

BCR-ABL Targeting TKIs

	Imatinib (Gleevec®)	Dasatinib (Sprycel®)	Nilotinib (Tasigna®)
Target	BCR-ABL, PDGF, SCF, c-Kit	BCR-ABL, SRC family, c-Kit, EPHA2, PDGFR	BCR-ABL, c-Kit, PDGFR
Uses	Ph+ CML, Ph+ ALL, GIST, aggressive systemic mastocyctosis, MDS w/PDGF rearrangements	Ph+ CML, newly dx or resistant/intolerant, Ph+ ALL	Ph+ CML, newly dx or resistant/intolerant
Dose	400mg QD with food Range: 100-800mg QD • 3A4 inducer: inc 50% • CrCl<40: dec 50% • Severe hep dz: dec 25% • DDI: warfarin	100-180mg PO daily • 3A4 inh: reduce dose • 3A4 ind: increase dose • Empty stomach • Antacids 2h before/after • Avoid PPI/H2 blockers	300-400mg PO Q12 hours • 3A4 inh: reduce by 100mg • Child-Pugh A/B/C: reduce initial dose, then titrate up • Empty stomach • Antacids 2h before/after
ADR	Bone marrow suppression, cardiovascular dysfunction, edema, hypothyroidism		
	Rash, hepatotoxicity, AKI, TLS, moderate emetogenicity	Rash, PAH, hemorrhage, TLS, QTc prolongation	Electrolyte abnormalities, hepatotoxicity, inc lipase
Notes	Use 400mg tabs to reduce iron exposure	For imatinib resistance except T315I & F317V mut	BBW: QTc prolongation

CML: chronic myelogenous leukemia; ALL: acute lymphocytic leukemia; GIST; gastrointestinal stromal tumor; MDS: myelodysplastic syndrome; dz: disease; AKI: acute kidney injury; TLS: tumor lysis syndrome; PAH: pulmonary arterial hypertension; inc: increased; BBW: black box warning; DDI: drug drug interactions; ADR: adverse drug reaction;

BCR-ABL Targeting TKIs

	Bosutinib (Bosulif®)	Ponatinib (Iclusig®)	Asciminib (Scemblix®)
Target	BCR-ABL, SRC family, c-Kit, PDGFR Activity in imatinib resistance except T315I and V299L	BCR-ABL, VEGFR, FGFR, PDGFR, EPH, and SRC kinases, as well as KIT, RET, TIE2, and FLT3	BCR-ABL, STAMP
Use	Ph+ CML in patients with resistance or intolerance to prior therapy		Ph+CML in CP previously treated with 2 or more TKIs; Ph+CML in CP with the T315I mutation
		Resistant Ph+ ALL or with T315I mut	
Dose	500-600mg PO daily with food • CrCl<50: 400mg daily • CrCl<30: 300mg daily • Child-Pugh A/B/C: 200mg daily	45mg PO daily • 3A4 inh: reduce to 30mg daily • Child-Pugh A/B/C: 30mg daily	80 mg daily or 40 mg BID 200mg BID for T315I mutation
ADR	Bone marrow suppression, edema		URIs, musculoskeletal pain, fatigue, nausea, rash, diarrhea
	Moderate emetogenicity, nausea, diarrhea, pancreatitis, QTc prolongation	Arrhythmias, GI perf, HTN, ocular toxicity, hemorrhage, neuropathy, pancreatitis, TLS, wound healing	Myelosuppression, cardiovascular toxicity, pancreatitis, hypersensitivity (~30%), HTN
BBW		**Arterial occlusion (35%), heart failure, hepatotoxicity, VTE**	
Notes	Antacids/H2 blockers 2h before/after	Optimal dose not identified	On an empty stomach DDIs: Substrate of CYP3A4 also inhibits CYP2C8 and 3A4 and CYP2C9

CML: chronic myelogenous leukemia; TLS: tumor lysis syndrome; HTN: hypertension; GI perf: gastrointestinal perforation; VTE: venous thromboembolism
BBW: black box warning; ADR: adverse drug reaction

JAK Inhibitors

	Ruxolitinib (Jakafi®)	Momelotinib (Ojjaara®)	Fedratinib (Inrebic®)	Pacritinib (Vonjo®)
Uses	Myelofibrosis, polycythemia vera, GVHD JAK1 and JAK2	Myelofibrosis	Myelofibrosis JAK2 + FLT3	Myelofibrosis
Dose	**MF**: 5-25 mg PO BID **PV**: 10-25 mg PO BID **GVHD**: 5-10 mg PO BID	200 mg PO daily	400 mg PO daily	200 mg PO BID
Common Toxicities	Bone marrow suppression, edema		Bone marrow suppression, edema	
	Anemia, infection, lipid abnormalities, non-melanoma skin cancer		Anemia, GI tox (N/V/diarrhea) Less common:hepatotox, amylase/lipase elevations	
Serious Toxicities			Encephalopathy (Wernicke's) **BBW**	
Drug Interactions	Dose reduce for use w/strong CYP3A4 inhibitor		Dose reduce for use w/strong CYP3A4 inhibitor	
Notes	Slow taper required for MF/PV discontinuation		Baseline B1 (thiamine) prior to initiation	

Antibody-Drug Conjugates

	Brentuximab vedotin (Adcetris®)	Inotuzumab ozogamicin (Besponsa®)	Gemtuzumab ozogamicin (Mylotarg®)
Target	CD30	CD22	CD33
Uses	HL, relapsed/refractory HL, after HSCT anaplastic large cell lymphoma	Relapsed/refractory B-cell ALL	Newly diagnosed and relapsed/refractory AML
Dose	1.8mg/kg Q3 weeks (max 180mg) Avoid if CrCl<30ml/min Child-Pugh A: 1.2mg/kg	0.8mg/m2 D1, 0.5mg/m2 D8&15 Q21d • CR/Cri: 0.5mg/m2 Q28d	3mg/m^2 D1, 4, 7 (max 4.5mg) with 7+3 6mg/m^2 D1, 3mg/mg^2 D8
ADR	Infusion reactions, rash, **peripheral neuropathy**, bone marrow suppression, diarrhea, hepatotoxicity	Bone marrow suppression, hepatotoxicity, QTc prolongation, embryo-fetal toxicity	Infusion rxn (anaphylaxis), hemorrhage, LFT elevations, bone marrow suppression, resp distress
BBW	PML	Hepatotoxicity (VOD); Increased risk of post-SCT non-relapse mortality	Hepatotoxicity (VOD)
Premed		APAP, H1 blocker, steroid	
Notes	MMAE – microtubule inh	Calicheamicin – causes dsDNA breaks	

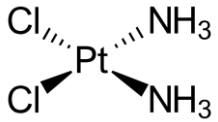
HL: Hodgkin lymphoma; ALL: acute lymphocytic leukemia; AML: acute myelogenous leukemia; HSCT; hematopoietic stem cell transplant; CrCl: creatinine clearance; CR: complete response
Premed: premedication; ADR: adverse drug reaction; PML: progressive multifocal leukencephalopathy; VOD: veno-occlusive disease; ds: double strand

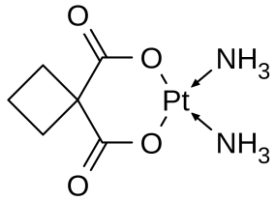
Antibody-Drug Conjugates

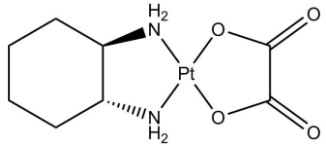
	Polatuzumab vedotin (Polivy®)	Moxetumomab pasudotox (Lumoxiti®)
Target	CD79B	CD22
Uses	DLBCL, relapsed/refractory; DLBCL 1st line IPI ≥ 2 (w/ chemo)	Hairy cell leukemia, relapsed/refractory
Dose	1.8mg/kg Q21d x6 cycles w/BR	0.04mg/kg D1, 3, 5 Q28 days • Requires pre/post hydration • Consider ASA 81 daily for thromboprophylaxis
ADR	Infusion reactions, **peripheral neuropathy**, bone marrow suppression, hepatotoxicity	Hypocalcemia, infusion rxn, AKI, diarrhea
BBW		Capillary leak syndrome, HUS
Premed	H1 blocker, APAP	APAP, H1 blocker, H2 blocker Post-med: dex 4mg; H1 blocker + APAP for 24h after PRN
Notes	Need PJP and HSV prophylaxis	Made in polysorbate 80

DLBCL: diffuse large B-cell lymphoma; BR: bendamustine, rituximab; ASA: aspirin; AKI: acute kidney injury; HUS: hemolytic uremic syndrome
Premed: premedication; ADR: adverse drug reaction; APAP: acetaminophen; BBW: black box warning

Platinum Agents





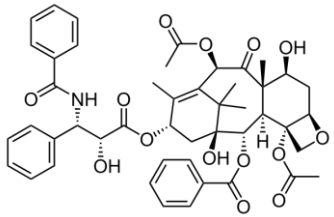


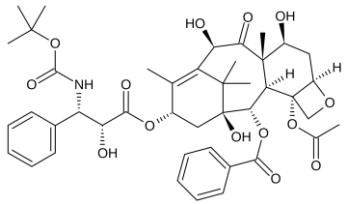
	Cisplatin (Platinol)	Carboplatin (Paraplatin)	Oxaliplatin (Eloxatin)
Uses	Broad spectrum of activity against numerous malignancies		
Dosing	IV: 50-100 mg/m^2	**Calvert Equation**: IV Dose (mg) = AUC x (GFR + 25) NCI recommends dose cap with CrCl 125 mL/min	IV: 85-130 mg/m^2

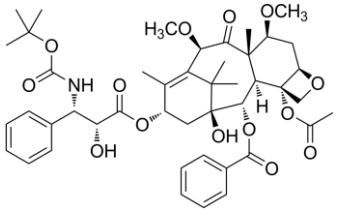
Toxicities	• **Severe N/V**, acute, delayed
	• **Renal dysfunction**
	• Electrolyte wasting
	• Peripheral Neuropathy
	• Reduces clearance of other drugs (give other drug first)
	• **Ototoxicity/tinnitus**, high frequency hearing loss (cumulative, irreversible)
	• SIADH
		• Moderate-severe N/V
		• Peripheral neuropathy
		• **Myelosuppression** (thrombocytopenia)
		• **Hypersensitivity reaction** after dose 7-9 (can desensitize)
			• **Neuropathy**, acute & chronic (sensory/peripheral)
			  • *Acute*: Triggered by cold
			  • Laryngo-pharyngeal dysesthesias with choking sensation
			• Dose-dependent neurotoxicity, typically >850mg/m^2 (reversible)

Notes	Excreted in urine 50% dose reduction for CrCl <60 mL/min (or split dosing)	Can use with dialysis	Rapid and extensive nonenzymatic metabolism

Taxanes

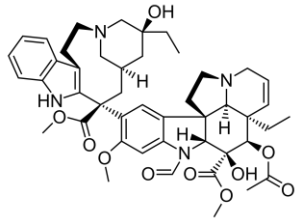


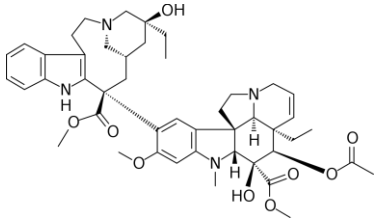


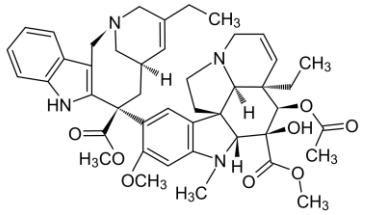


	Paclitaxel (Taxol)	Nab-Paclitaxel (Abraxane)	Docetaxel (Taxotere)	Cabazitaxel (Jevtana)
Uses	Broad spectrum of activity against numerous malignancies			Prostate
Dosing	IV: 80-200 mg/m^2 Variable schedules	IV: 100-260 mg/m^2 Variable schedules	IV: 60-100 mg/m^2 Q21 days	IV: 20-25 mg/m^2 Q21 days
Admin	Variable (1, 3, 24 hours)	30 min		
Toxicities	Myelosuppression (increased with longer infusion) Neuropathy (Abraxane > Paclitaxel; increased with shorter infusion time) Alopecia Arthralgias, myalgias			
	Hypersensitivity to diluent		Rash Edema	Diarrhea (severe) Hypersensitivity
Premedication	Diphenhydramine 25 mg IV Famotidine 20 mg IV Dexamethasone 20 mg IV		Dexamethasone 8 mg PO BID day before, of, and after chemo	Diphenhydramine 25 mg IV Famotidine 20 mg IV Dexamethasone 8 mg IV
Dose Adjustment	Reduce dose for **significant** transaminase elevation or any Tbili elevation		Reduce dose for TBili or transaminase elevations	

Vinca Alkaloids







	Vincristine (Oncovin)	Vinblastine (Velban)	Vinorelbine (Navelbine)
Uses	Leukemias, lymphomas, sarcomas, myeloma	Blader, lymphomas, testicular	Breast, lung
Dosing	IV: 1-1.4 mg/m^2 **2 mg max dose**		
Toxicities	Peripheral neuropathy Autonomic neuropathy (constipation and paralytic ileus)	Myelosuppression	Myelosuppression Neuropathy (less severe than others)
Notes	**FATAL if given intrathecally** Vesicants: treat with heat and hyaluronidase		

Dose Reductions

Adjust for Renal Impairment, Hemodialysis, or Both			
Arsenic trioxide	Bleomycin	Busulfan	Capecitabine
Carboplatin	Carmustine	Cisplatin	Cladribine
Clofarabine	Cyclophosphamide	Cytarabine (high dose ≥1 g/m^2)	Dacarbazine
Daunorubicin	Fludarabine	Idarubicin	Decitabine
Doxorubicin	Eribulin	Etoposide	Ifosfamide
Irinotecan	Ixazomib	Lomustine	Melphalan
Mercaptopurine	Methotrexate	Mitomycin	Oxaliplatin
Pemetrexed	Pentostatin	Pralatrexate	Procarbazine
Streptozocin	Thiotepa	Topotecan	

Mild or Moderate Hepatic Impairment			
Belinostat	Bendamustine	Bortezomib	Cabazitaxel
Carfilzomib	Cladribine	Daunorubicin	Docetaxel
Doxorubicin	Liposomal doxorubicin	Epirubicin	Eribulin
Everolimus	Gemcitabine	Idarubicin	Irinotecan
Ixabepilone	Ixazomib	Mercaptopurine	Nab-paclitaxel
Paclitaxel	Panobinostat	Romidepsin	Temsirolimus
Thiotepa	Trabectedin	Vorinostat	

Only for Severe Hepatic Impairment			
Arsenic trioxide	Azacitidine	Busulfan	Carmustine
Chlorambucil	Clofarabine	Cyclophosphamide	Cytarabine
Dacarbazine	Dactinomycin	Etoposide	Fluorouracil
Ifosfamide	Lomustine	Methotrexate	Midostaurin
Mitomycin	Mitoxantrone	Pemetrexed	Topotecan
Vinblastine	Vincristine	Vinorelbine	

Krens et al. Lancet Oncol. 2019 Apr;20(4):e200-e207. doi: 10.1016/S1470-2045(19)30145-7.