Fred Hutch Cancer Center

Hematology Pharmacology Pearls

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October 9, 2025

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

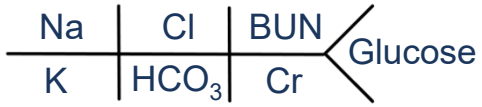
- I am a pharmacist
- I am not a: physician, radiologist, pathologist, geneticist,
- Please focus on the content of the questions and NOT any inaccuracies in the patient cases.

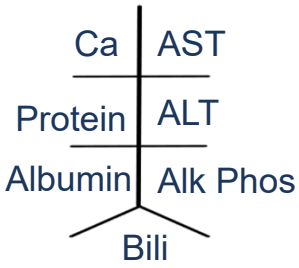
Citations

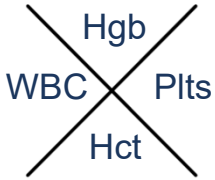
- When specific citation is not indicated, relevant NCCN guidelines were used.

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

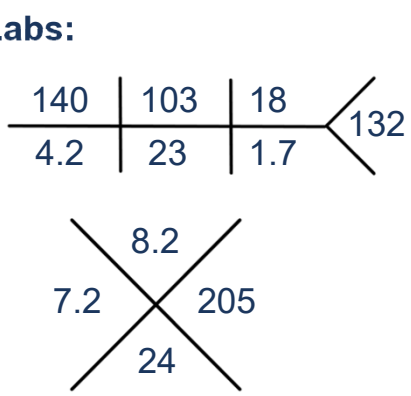
Vitals:

- 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

Correct Answer - ARS Question 1

A. Bortezomib, lenalidomide, dexamethasone (VRd)

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

Wrong Answers - ARS Question 1

B. Carfilzomib, lenalidomide, dexamethasone (KRd)

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].

Wrong Answers - ARS Question 1

C. Daratumumab, lenalidomide, dexamethasone (DRd)

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

Wrong Answers - ARS Question 1

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

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

Correct Answers - ARS Question 2

A. Aspirin 81 mg PO daily

D. Acyclovir 400 mg PO BID

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

Wrong Answers - ARS Question 2

B. Apixaban 5 mg PO BID

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].

Wrong Answers - ARS Question 2

C. Sulfamethoxazole/trimethoprim 800/160 mg PO daily MWF

E. Aprepitant 130 mg IV on days of chemotherapy

F. Posaconazole 300 mg PO daily

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

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

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.

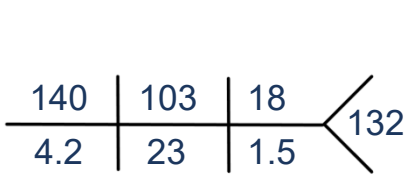
Current medications:

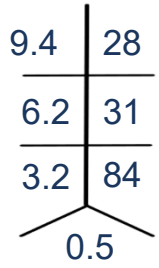
- Acyclovir 400 mg PO BID
- Apixaban 5 mg PO BID
- Metformin 1000 mg PO BID
- Metoprolol 50 mg PO BID
- Lisinopril 40 mg PO daily
- Atorvastatin 20 mg PO daily
- Gabapentin 600 mg PO TID
- Oxycodone 5 mg PO Q6H PRN pain
- Furosemide 20 mg PO daily PRN weight gain

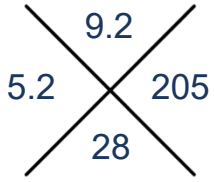
Vitals:

- 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®)

Correct Answer - ARS Question 3

B. Daratumumab, lenalidomide, dexamethasone (DRd)

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.

Wrong Answers - ARS Question 3

A. Carfilzomib, lenalidomide, dexamethasone (KRd)

D. Carfilzomib, pomalidomide, dexamethasone (KPd)

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].

Wrong Answers - ARS Question 3

C. Daratumumab, bortezomib, dexamethasone (DVd)

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.

Wrong Answers - ARS Question 3

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

Correct Answer - ARS Question 4

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

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].

Wrong Answers - ARS Question 4

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)

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

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

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.

Wrong Answers - ARS Question 4

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

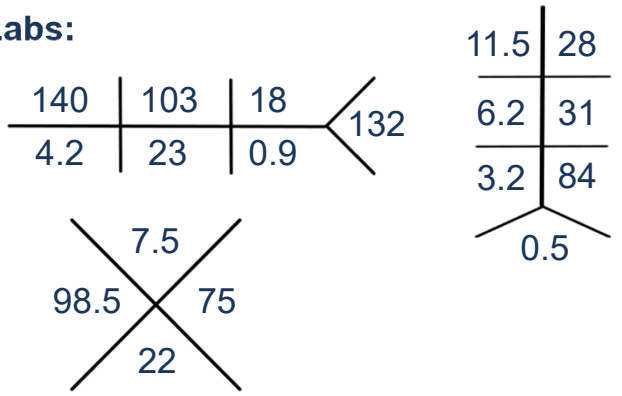
Vitals:

- 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®)

Correct Answer - ARS Question 5

C. Poor risk AML / Cytarabine + doxorubicin/daunorubicin (7+3)

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)

Wrong Answers - ARS Question 5

A. Poor risk AML / Liposomal cytarabine + daunorubicin (CPX351; Vyxeos®)

B. Favorable risk AML by molecular mutation / Fludarabine + cytarabine + filgrastim + idarubicin (FLAG-Ida)

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

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.

Wrong Answers - ARS Question 5

D. Intermediate risk AML / Azacitidine + Venetoclax

E. Favorable risk AML by cytogenetics / Cytarabine + doxorubicin/daunorubicin (7+3) + gemtuzumab ozogamicin (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.

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.

Correct Answer - ARS Question 6

D. GI toxicities are more commonly seen with conventional dosing of cytarabine.

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].

Wrong Answers - ARS Question 6

A. Conjunctivitis is a universal side effect of cytarabine and is seen in both dosing schemes.

E. Severe myelosuppression is more commonly associated with conventional dosing of cytarabine.

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].

Wrong Answers - ARS Question 6

B. Ara-C syndrome, characterized by fever, myalgia, and rash, is typically seen immediately after therapy begins.

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].

Wrong Answers - ARS Question 6

C. Cerebellar toxicity seen with high-dose cytarabine is typically mild and does not require dose reductions.

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).

Correct Answer - ARS Question 7

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

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].

Wrong Answers - ARS Question 7

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

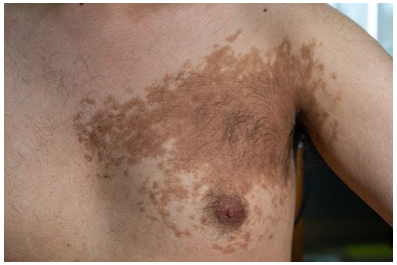
C. Busulfan is commonly associate with skin discoloration or hyperpigmentation, which typically occurs 2-3 week after therapy and can last for 2-3 months.

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.

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



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

Wrong Answers - ARS Question 7

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).

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 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.

Cyclophosphamide [package insert].
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.

Correct Answer - ARS Question 8

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

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].

Wrong Answers - ARS Question 8

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.

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].

Wrong Answers - ARS Question 8

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

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].

Wrong Answers - ARS Question 8

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.

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.

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.

Gilterinib [package insert].
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.

Correct Answer - ARS Question 9

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

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

Wrong Answers - ARS Question 9

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

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

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.

Wrong Answers - ARS Question 9

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

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

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.

Correct Answers - ARS Question 10

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.

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.

Wrong Answers - ARS Question 10

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

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.

Wrong Answers - ARS Question 10

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

Correct Answers - ARS Question 11

C. Glofitamab (Columvi®)

D. Axicabtagene ciloleucel (Yescarta®)

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].

Wrong Answers - ARS Question 11

A. Epcoritamab (Epkinly®)

B. Mosunetuzumab (Lunsumio®)

D. 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.

Mosunetuzumab is only indicated in follicular lymphoma.

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].
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

Correct Answers - ARS Question 12

A. Hepatotoxicity **E. Nephrotoxicity**

C. Mucositis **F. Neurotoxicity**

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.

Wrong Answers - ARS Question 12

B. Infection **G. Pneumonitis**

D. Myelosuppression

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.

Correct Answer - ARS Question 13

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

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].

Wrong Answers - ARS Question 13

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

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

D. Leucovorin reduces the risk of hematologic toxicity.

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

Wrong Answers - ARS Question 13

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.

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

Correct Answers - ARS Question 14

A. Continue imatinib treatment and recheck at 6 months

D. Evaluate patient for adherence

E. Switch to dasatinib

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.

Wrong Answers - ARS Question 14

B. Switch to ponatinib

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

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.

Correct Answer - ARS Question 15

C. The most common mechanism for resistance mutations to BCR-ABL TKIs is translocation.

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

Wrong Answers - ARS Question 15

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.

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.

Wrong Answers - ARS Question 15

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.

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.

Correct Answer - ARS Question 16

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

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].

Wrong Answers - ARS Question 16

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.

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

- This smaller size confers higher tumor penetration.

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.

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

Bispecific Antibodies (BsAbs)

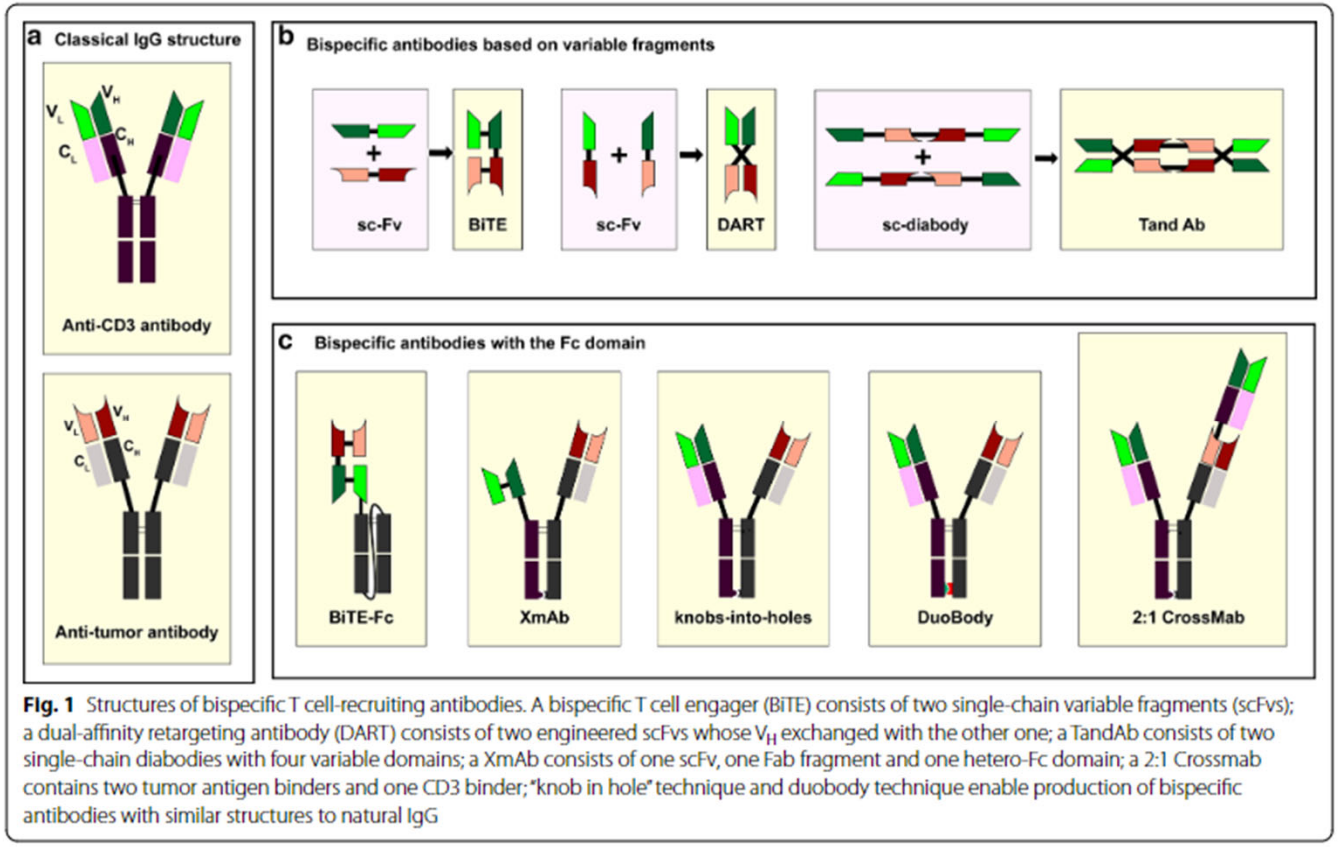


Fig. 1 Structures of bispecific T cell-recruiting antibodies. A bispecific T cell engager (BiTE) consists of two single-chain variable fragments (scFvs); a dual-affinity retargeting antibody (DART) consists of two engineered scFvs whose V_H exchanged with the other one; a TandAb consists of two single-chain 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.

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.

Correct Answer - ARS Question 17

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

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].

Wrong Answers - ARS Question 17

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

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.

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.

Wrong Answers - ARS Question 17

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

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

Correct Answer - ARS Question 18

A. TPMT deficiency / 6-mercaptopurine

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].

Wrong Answers - ARS Question 18

B. NUDT15 deficiency / cytarabine

C. UGT1A1*28 / pegaspargase

D. DPYD*2A / vincristine

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.

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Thank you