Targeted Therapy in Heme Malignancies

New Orleans Summer Cancer Meeting

July 21, 2024

Brian Primeaux, PharmD, BCOP

Clinical Pharmacy Specialist, Lymphoma/Myeloma/CART

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Learning Objectives

1. Identify the mechanism of action of the major classes of targeted therapies
2. Recognize unique side effects and dose limiting toxicities of targeted therapies

Contents

1. Monoclonal antibodies (CD20, CD22, CD30, CD33)
2. BCR-ABL Tyrosine kinase inhibitors
3. FMS-like tyrosine kinase 3 (FLT3) inhibitor
4. Isocitrate dehydrogenase 1/2 (IDH1/2) Inhibitor

Monoclonal Antibodies (MAbs)

MAbs- Overview

CD20

- Type I
  - Rituximab
  - Ofatumumab
- Type II
  - Obinutuzumab

CD30

- Brentuximab vedotin

CD33

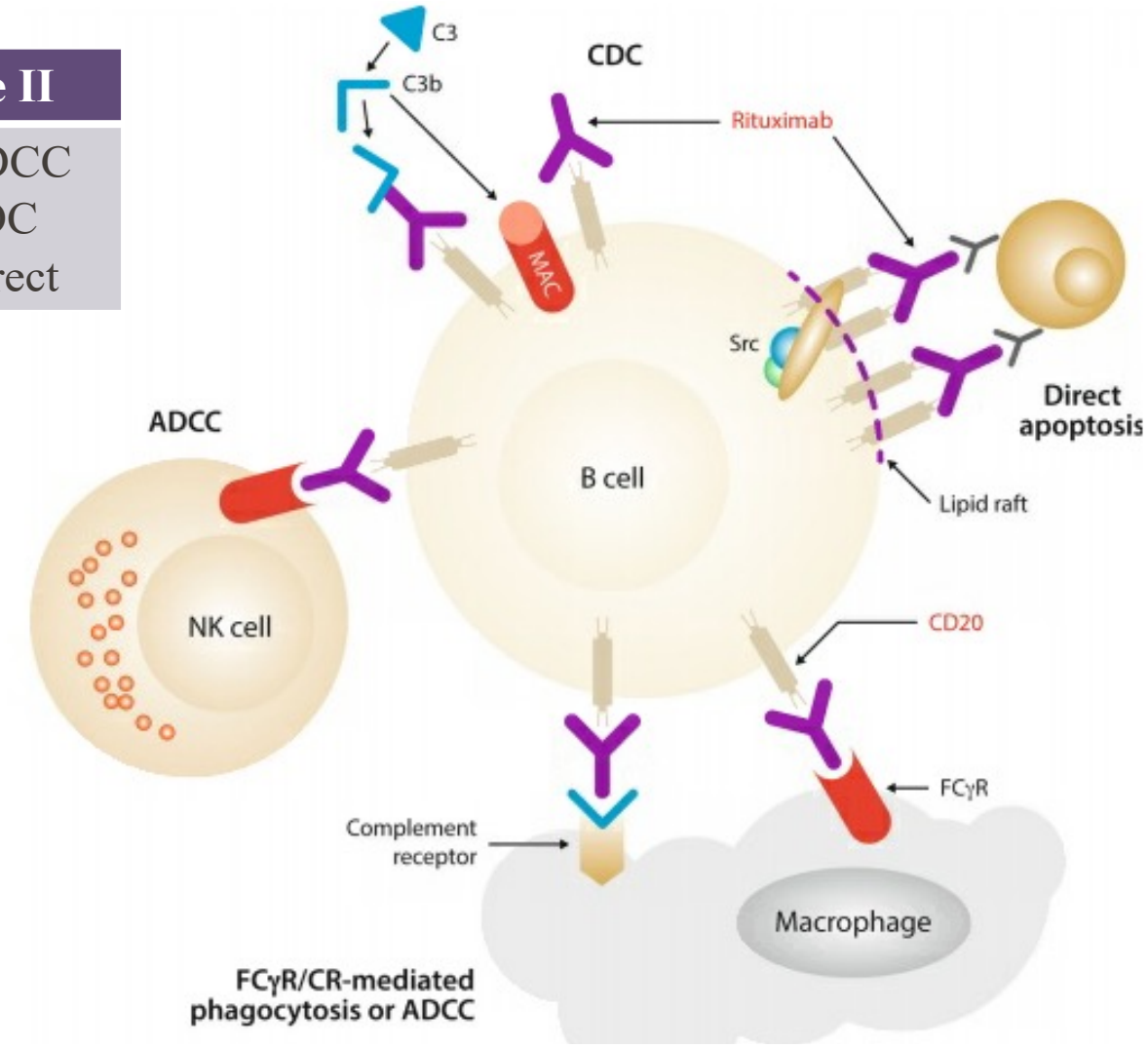
- Gemtuzumab ozogamicin

CD22

- Inotuzumab ozogamicin

CD20 MAbs - Mechanism of Action

Type I	Type II
• ADCC • CDC • Direct	• ↑ADCC • ↓CDC • ↑Direct



Salles G, et al. *Adv Ther*. 2017;34(10):2232-2273.

CD20 MAbs – Indication and Dosing

	Rituximab	Ofatumumab	Obinutuzumab
Type	Type I chimeric	Type I fully human	Type II humanized
Indication	NHL, CLL, ALL, WM	CLL	CLL, FL
Dosing	IV: 375-500 **mg/m²** SubQ: 1400-1600 **mg** with hyaluronidase 23,400-26,800 **units**	IV: 300 **mg** on Day 1, then 1000-2000 **mg** flat dose	IV: 1000 **mg** flat dose CLL: First dose split 100 **mg** Day 1 and 900 **mg** Day 2
Schedule	• Weekly to monthly depending on indication • Varying schedules for maintenance therapy if applicable		
Clinical Pearls	• Require premedication • Infusion rate as tolerated by patient • Rituximab has biosimilars available: Riabni, Ruxience, Truxima • Ofatumumab only available through Arzerra Oncology Access Program		

Arzerra (ofatumumab) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; August 2016.; Gazyva (obinutuzumab) [prescribing information]. South San Francisco, CA: Genentech Inc; July 2022.; Rituxan (rituximab) [prescribing information]. South San Francisco, CA: Genentech Inc; October 2023. ;Rituxan Hycela (rituximab and hyaluronidase human) [prescribing information]. South San Francisco, CA: Genentech Inc; June 2021.

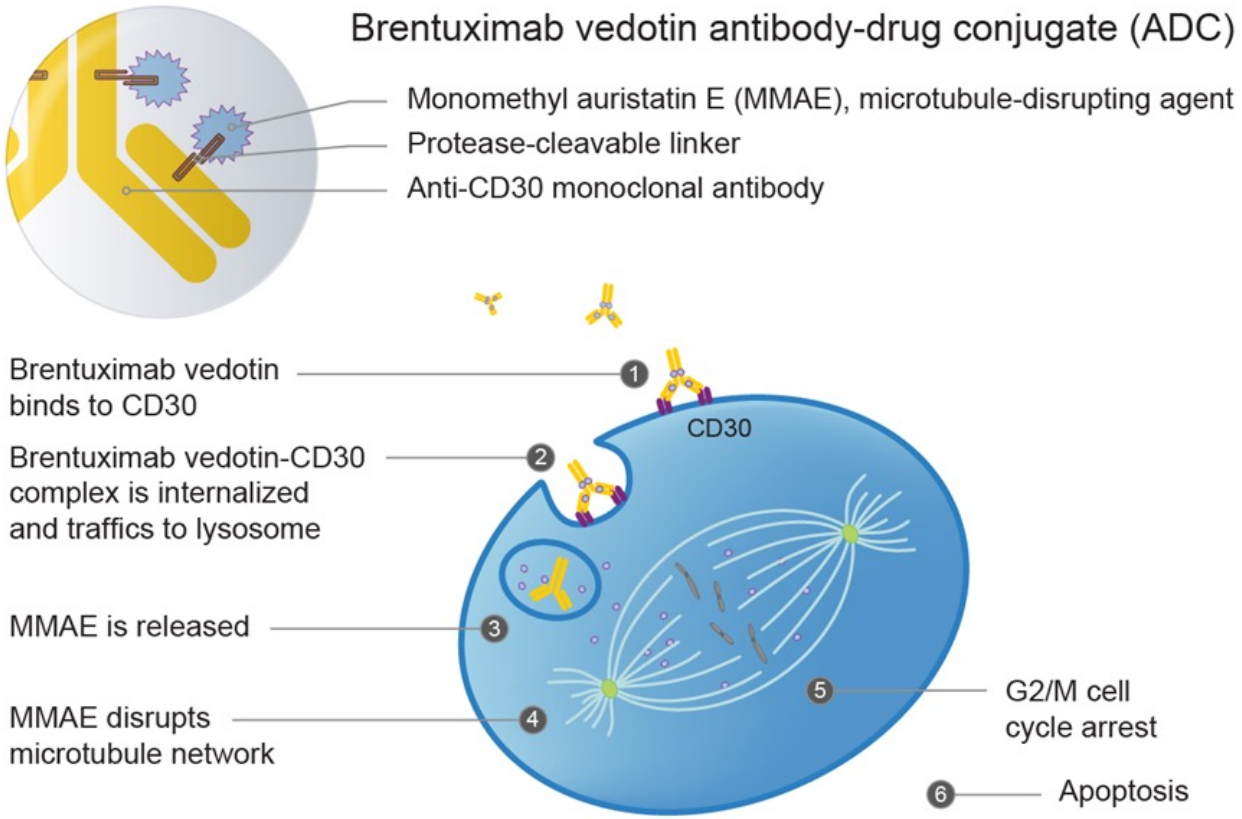
CD20 MAbs - Adverse Effects

- **Hepatitis B reactivation – BBW**
  - Hep B surface antigen and core antibody should be checked prior to therapy initiation
  - If positive, prophylaxis with entecavir should be started and Hep B DNA levels checked every month during therapy
  - Patients should remain on prophylaxis throughout therapy and for up to a year post chemotherapy completion.
- **Progressive multifocal leukoencephalopathy (PML) - BBW**
- **Infusion reactions – BBW for Rituximab**
  - Occurs in 80% of patients receiving first dose rituximab
- **Severe mucocutaneous reactions – BBW for Rituximab**
- **Tumor lysis syndrome**
  - Prophylaxis with fluids and allopurinol should initiated in patients at risk
- **Cytopenias (neutropenia)**

Arzerra (ofatumumab) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; August 2016.; Gazyva (obinutuzumab) [prescribing information]. South San Francisco, CA: Genentech Inc; July 2022.; Rituxan (rituximab) [prescribing information]. South San Francisco, CA: Genentech Inc; October 2023. ;Rituxan Hycela (rituximab and hyaluronidase human) [prescribing information]. South San Francisco, CA: Genentech Inc; June 2021.

Brentuximab vedotin- Mechanism of Action

- **Chimeric CD30 antibody-drug conjugate designed to deliver MMAE to malignant cells**



Adcetris (brentuximab vedotin) [prescribing information]. Bothell, WA: Seattle Genetics; June 2023.
Younes, A et al, *N Engl J Med,* 2010; Fanale, M et al, *Clin Cancer Res,* 2012

Brentuximab vedotin – Indication and Dosing

- **Advanced previously untreated HL**
  - 1.2 **mg/kg** IV over 30 minutes every 2 weeks (in combination with AVD)
  - Administer ~1 hour after completion of AVD
  - Maximum dose 120 mg
- **Other indications (PTCL, MF, ALCL, R/R HL)**
  - 1.8 **mg/kg** IV over 30 minutes every 2 weeks
  - Maximum dose 180 mg
- **Dose reductions**
  - Reduce to 0.9 **mg/kg** or 1.2 **mg/kg** for moderate hepatic impairment
  - Avoid use in CrCl < 30 ml/min and severe hepatic impairment

Adcetris (brentuximab vedotin) [prescribing information]. Bothell, WA: Seattle Genetics; June 2023.

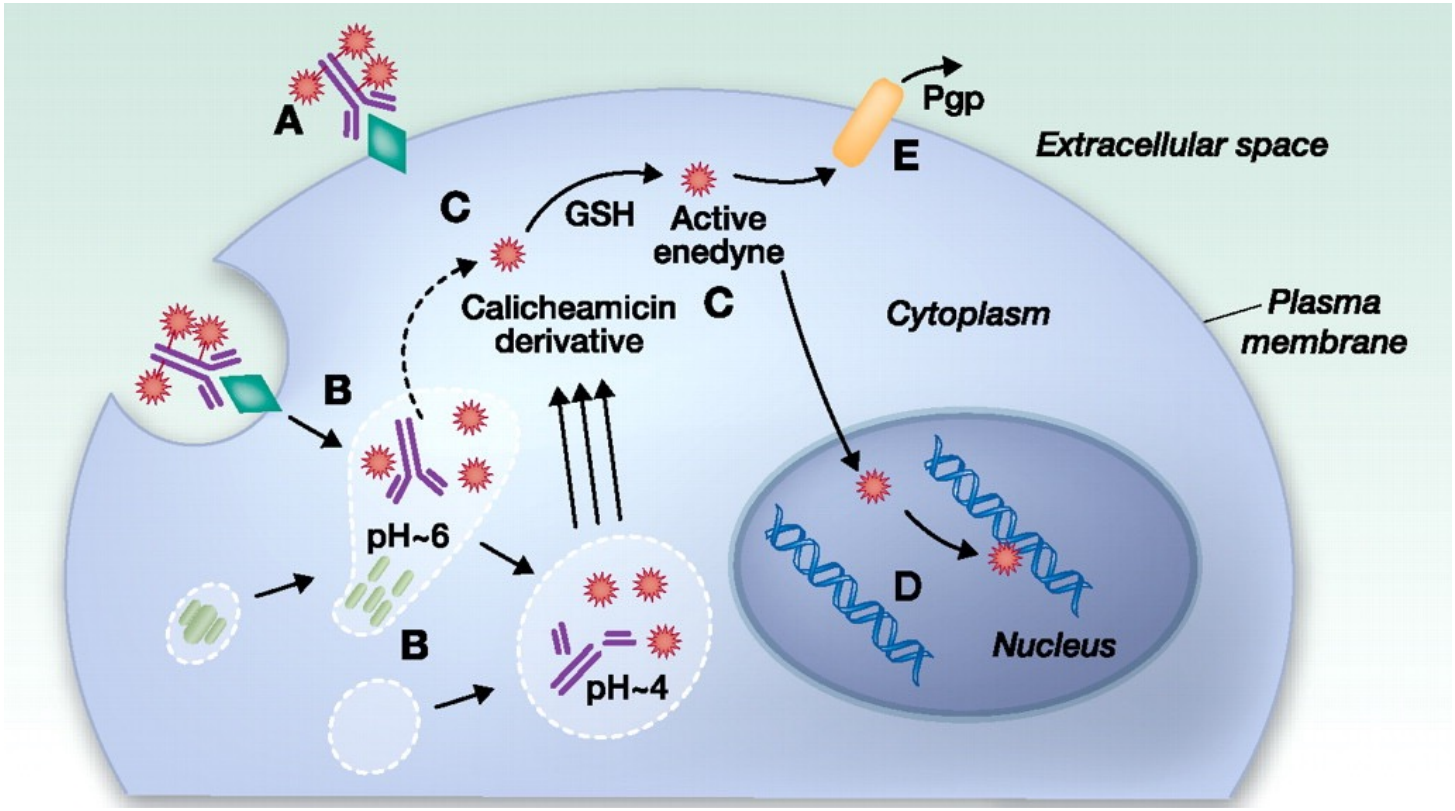
Brentuximab vedotin - Adverse Effects

- **Progressive multifocal leukoencephalopathy (PML) - BBW**
- Peripheral neuropathy
- Pyrexia
- Neutropenia
- Nausea/vomiting/diarrhea/constipation
- Pulmonary toxicity
- Pruritus

Adcetris (brentuximab vedotin) [prescribing information]. Bothell, WA: Seattle Genetics; June 2023.

Gemtuzumab ozogamicin - Mechanism of Action

- **Humanized IgG4κ monoclonal antibody targeted against CD33 designed to deliver calicheamicin to malignant cells**



Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; August 2021.
Ricart AD. *Clin Cancer Res.* 2011;17(20):6417-27.

Gemtuzumab ozogamicin – Indication and Dosing

- **Indication: AML, CD33+**
- **Combination therapy with daunorubicin and cytarabine**
  - Induction: 3 **mg/m²** IV Days 1, 4, 7 for 1 cycle
  - Consolidation: 3 **mg/m²** IV Day 1 for 2 cycles
- **Single-agent therapy**
  - Induction: 6 **mg/m²** IV Day 1 and 3 **mg/m²** IV Day 8 for 1 cycle
  - Consolidation: 2 **mg/m²** IV Day 1 every 4 weeks for up to 8 cycles
  - Relapsed/refractory: 3 **mg/m²** IV Days 1, 4, 7 for 1 cycle
- **Requires premedication**

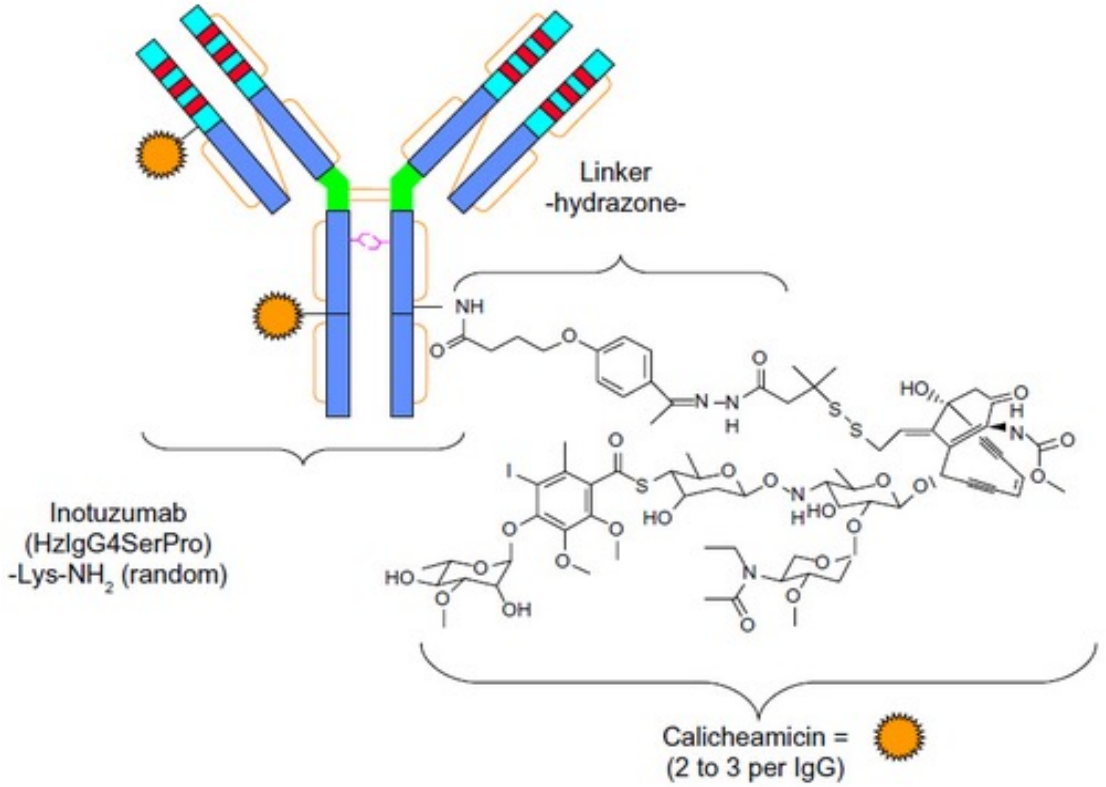
Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; August 2021.

Gemtuzumab ozogamicin - Adverse Effects

- **Hepatotoxicity/Veno-Occlusive Disease – BBW**
- Infusion reactions
- Hemorrhage
- QT prolongation
- Infection
- Fever
- Nausea
- Rash

Inotuzumab ozogamicin - Mechanism of Action

- **Humanized IgG4κ monoclonal antibody targeted against CD22 designed to deliver calicheamicin to malignant cells**



Besponsa (inotuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; March 2024.
[Picture] https://www.drugbank.ca/drugs/DB05889

Inotuzumab ozogamicin – Indication and Dosing

- **Indication – R/R B-cell ALL**
- **Dosing**
  - Cycle 1
    - 0.8 **mg/m^2** IV on Day 1 and 0.5 **mg/m^2** on Day 8 and 15 of a 21 day cycle
  - Subsequent Cycles
    - CR/CRi achieved: 0.5 **mg/m^2** on Days 1, 8, and 15 of a 28 day cycle
    - CR/CRi not achieved: 0.8 **mg/m^2** IV on Day 1 and 0.5 **mg/m^2** on Day 8 and 15 of a 28 day cycle
    - If CR/CRi not achieved within 3 cycles, discontinue treatment
- **Requires premedication**
- **Recommended duration of 2 cycles for those planned for HCT**
- **Observe for symptoms of infusion reactions during and for at least 1 hour after the end of infusion**

Besponsa (inotuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; March 2024.

Inotuzumab ozogamicin - Adverse Effects

- **Hepatotoxicity/Veno-Occlusive Disease – BBW**
- **Higher Day 100 post-HSCT mortality rate - BBW**
- Infusion reactions
- Myelosuppression
- QT prolongation
- Fatigue
- Fever
- Nausea
- Headache

Besponsa (inotuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; March 2024.

BCR-ABL Tyrosine Kinase Inhibitors

BCR-ABL TKIs - Mechanism of Action and Indication

- **Inhibits BCR-ABL tyrosine kinase which is the constitutive abnormal gene product of the Philadelphia chromosome in CML**
- **Blocks proliferation and induces apoptosis in BCR-ABL positive cell lines**

TKI	Target
Imatinib	BCR-ABL, PDGF, SCF, c-KIT
Dasatinib	BCR-ABL, SRC, c-KIT, EPHA2, PDGFRβ
Nilotinib	BCR-ABL, PDGF, c-KIT
Bosutinib	BCR-ABL, SRC family
Ponatinib	BCR-ABL, VEGFR, FGFR, PDGFR, EPH, SRC kinases, KIT, RET, TIE2, FLT3 *active against BCR-ABL T315I mutation
Asciminib	BCR-ABL (first in class STAMP inhibitor) *active against BCR-ABL T315I mutation

BCR-ABL TKIs - Dosing

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
Dose	400-800 **mg** by mouth daily	100-140 **mg** by mouth daily	300-400 **mg** by mouth **twice daily**	500 **mg** by mouth daily	45 **mg** by mouth daily	80 **mg once daily** or 40 **mg twice daily** 200 **mg twice daily**
Dose Adjustments	Dose depends on indication CrCl 20-39 ml/min: ↓dose 50% Severe hepatic impairment: ↓dose 25%	None	Dose depends on indication Hepatic impairment: 200-300 mg twice daily	Dose depends on indication Renal impairment: 200-400 mg Hepatic impairment: 200 mg	Hepatic impairment: 30 mg	Dose depends on indication No dose adjustments

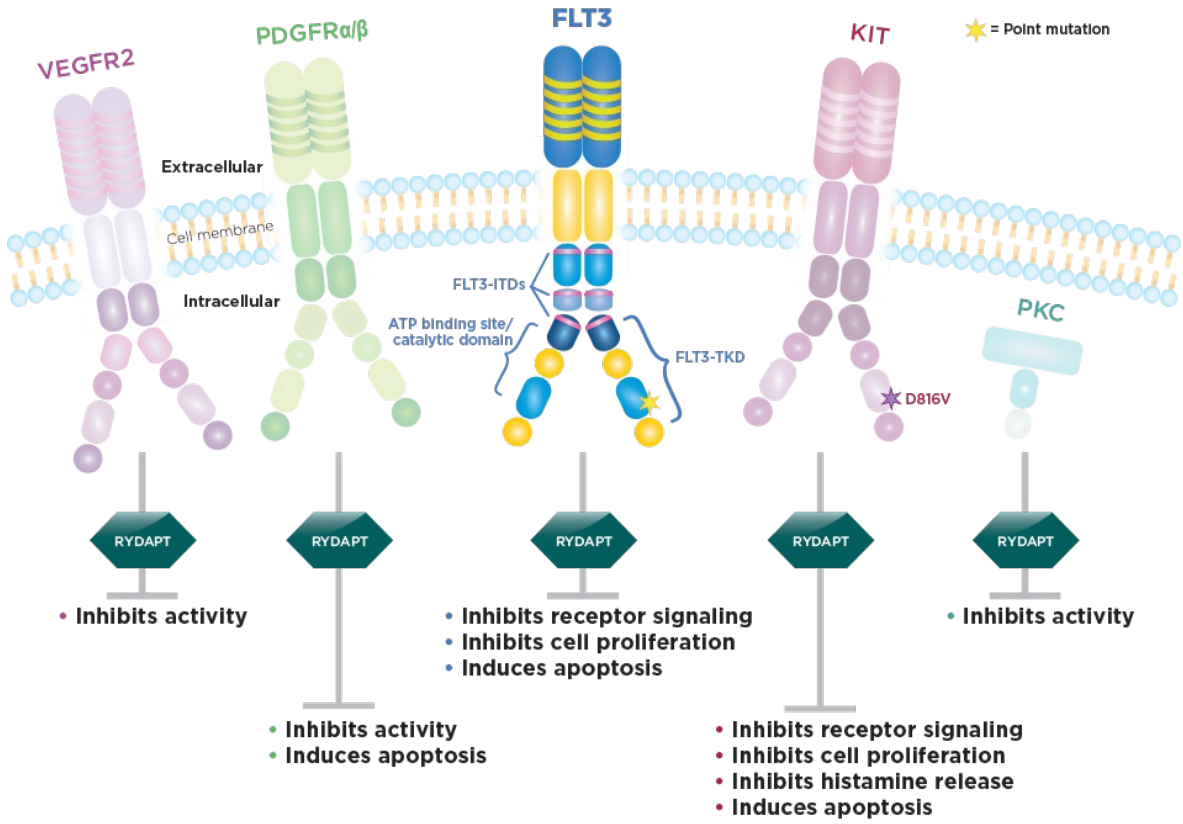
BCR-ABL TKIs – Adverse Effects

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
Myelosuppression						
Neutropenia	+	++	+	+	+	++
Thrombocytopenia	+	++	+	+	+	++
Edema	+++	++	+	+	+	+
Pleural Effusions	+	++	+	+	+	--
Hepatotoxicity	++	--	++	+	++	++
Diarrhea	+	+	+	+++	+	+
Rash	+	+	+	+	+	+

FMS-like tyrosine kinase 3 (FLT3) Inhibitor

FLT3 Inhibitor - Mechanism of Action

- **Inhibits FLT3 by autophosphorylation of its cytoplasmic tail which antagonizes downstream signaling pathways**



FLT3 Inhibitors – Indication and Dosing

	Midostaurin	Gilteritinib	Quizartinib
Targets	FLT3, VEGFR2, PDGFR, KIT, PKC	FLT3, AXL, ALK	FLT3
Indication	AML	AML	AML
Dosing	50 **mg** by mouth twice daily on days 8-21 of each induction/consolidation cycle in combination (AML) 100 **mg** by mouth twice daily (Mast Cell Leukemia)	120 **mg** by mouth once daily	35.4 **mg** once daily days 8 to 21 of induction cycle and days 6-19 of each consolidation cycle 26.5 **mg** days 1-14 of maintenance, may increase to 35.4 mg if QTc remains ≤ 450 msec
Dose Adjustments	None	None	Reduce to 35.4 mg, 26.5 mg or 17.7 mg for toxicities
Comments	• Confirm FLT3 positivity • Take with food 12 hours apart • Administer prophylactic antiemetics prior to doses	• Confirm FLT3 positivity • Administer with or without food at approximately the same time each day	• Confirm FLT3 positivity • Administer with or without food at approximately the same time each day

FLT3 Inhibitors – Adverse Effects

	Midostaurin	Gilteritinib	Quizartinib
Adverse Effects	• **Increased serum creatinine** • **Mucositis** • **Diarrhea** • **Prolonged QT interval** • **Musculoskeletal pain** • **Arthralgia** • Bone marrow suppression • Interstitial lung disease and pneumonitis • Nausea/vomiting • Increased amylase/lipase • Edema	• **Differentiation syndrome** • **Prolonged QT interval** • GI toxicity • Pancreatitis • Skin rash • Hyperglycemia • Electrolyte abnormalities • Increased serum creatinine	• **Prolonged QT interval** • Electrolyte abnormalities • GI toxicity • Increased LFTs • Fungal infections • Infection • Increased creatine phosphokinase

Isocitrate dehydrogenase 1/2 (IDH1/2) Inhibitors

IDH1/2 Inhibitor - Mechanism of Action

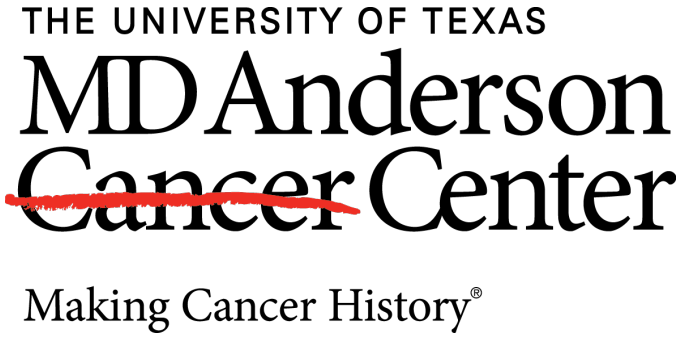
- **Targets the mutant IDH1/2 variants resulting in decreased 2-hydroxyglutarate levels, reduced abnormal histone hypermethylation, and restored myeloid differentiation**

IDH1/2 Inhibitors- Dosing and Clinical Pearls

	Ivosidenib	Olutasidenib	Enasidenib
IDH	IDH 1 inhibitor	IDH 1 inhibitor	IDH 2 inhibitor
Indication	AML	AML	AML
Dosing	500 **mg** by mouth once daily	150 **mg** by mouth **twice** daily	100 **mg** by mouth once daily
Dose Adjustments	None	None	None
Clinical Pearls	• Confirm IDH1 mutation status in blood or bone marrow prior to treatment • Administer at the same time each day, with or without food	• Confirm IDH1 mutation status in blood or bone marrow prior to treatment • Administer at the same time each day, with or without food. Do not administer two doses within 8 hours	• Confirm IDH2 mutation status in blood or bone marrow prior to treatment • Administer antiemetics prior to treatment

IDH1/2 Inhibitors- Adverse Effects

Ivosidenib	Olutasidenib	Enasidenib
• **Differentiation syndrome** • GI toxicity • QT prolongation • Tumor Lysis Syndrome • Guillain-Barre syndrome	• **Differentiation syndrome** • **Hepatotoxicity** • Electrolyte imbalance • GI toxicity • Skin rash	• **Differentiation syndrome** • Leukocytosis • Electrolyte imbalance • Hepatotoxicity • GI toxicity • Tumor Lysis Syndrome • Nausea/Vomiting


THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center
Making Cancer History®