New Drug Updates in Hematologic Malignancies

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THE ANNUAL APSHO MEETING

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- Dr. Held has nothing to disclose.

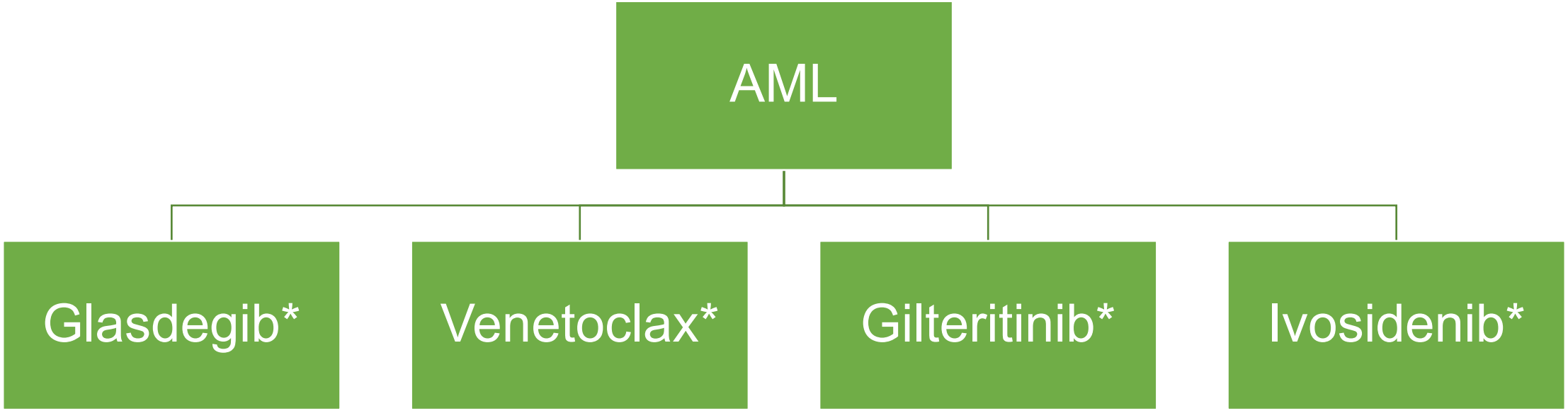
Learning Objectives

1. Evaluate clinical trial data supporting use of oncology drugs approved for initial or expanded indications by the FDA over the past 12 months
2. Apply best practices for medication management, including safe and effective dosing and administration, drug monitoring, and management of adverse events for oncology drugs with recent initial or expanded indications

Outline

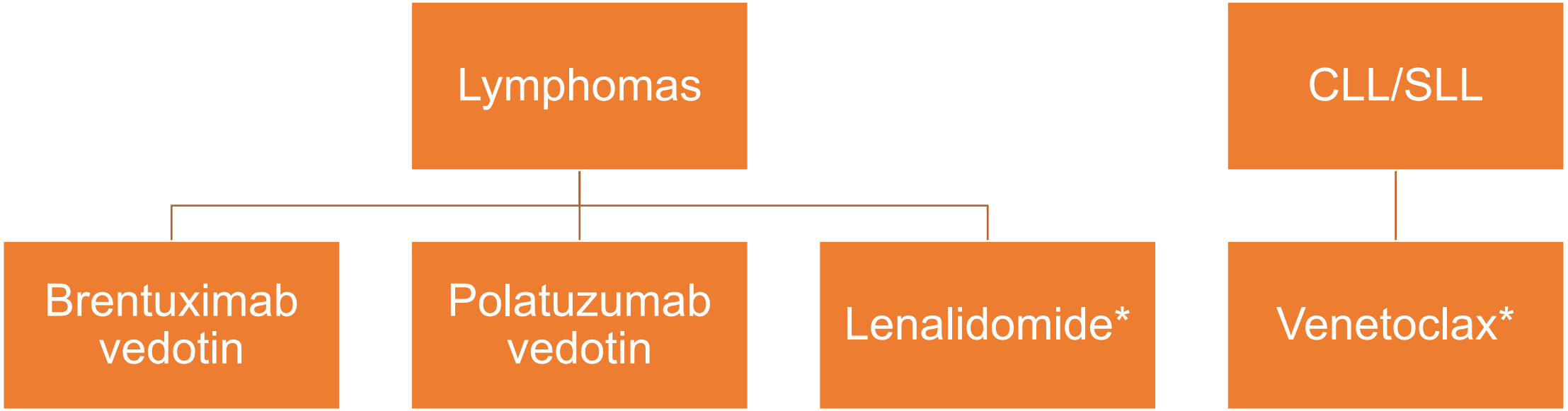
- Discuss the pharmacology and indications of medications approved from late 2018 to October 2019 for the management of patients with hematologic malignancies
- Recall the pivotal clinical trial data considered by the FDA when approving new oncologic agents
- Identify the signs and symptoms of serious or life-threatening adverse effects of newly approved oncology drugs
- Describe the impact of these agents in advanced practice

New Drug Approvals and New Indications in Acute Myeloid Leukemia (AML)



*Oral agent

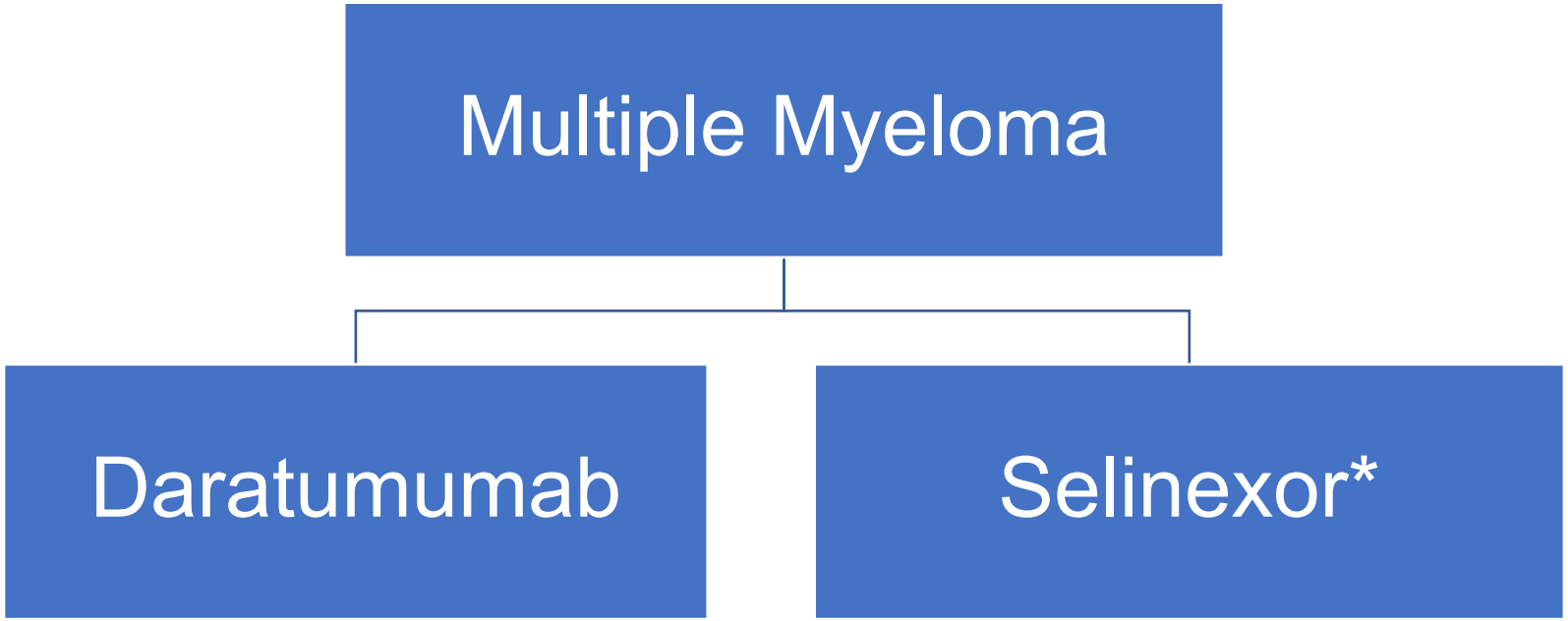
New Drug Approvals and New Indications in Lymphomas and CLL/SLL



*Oral agent

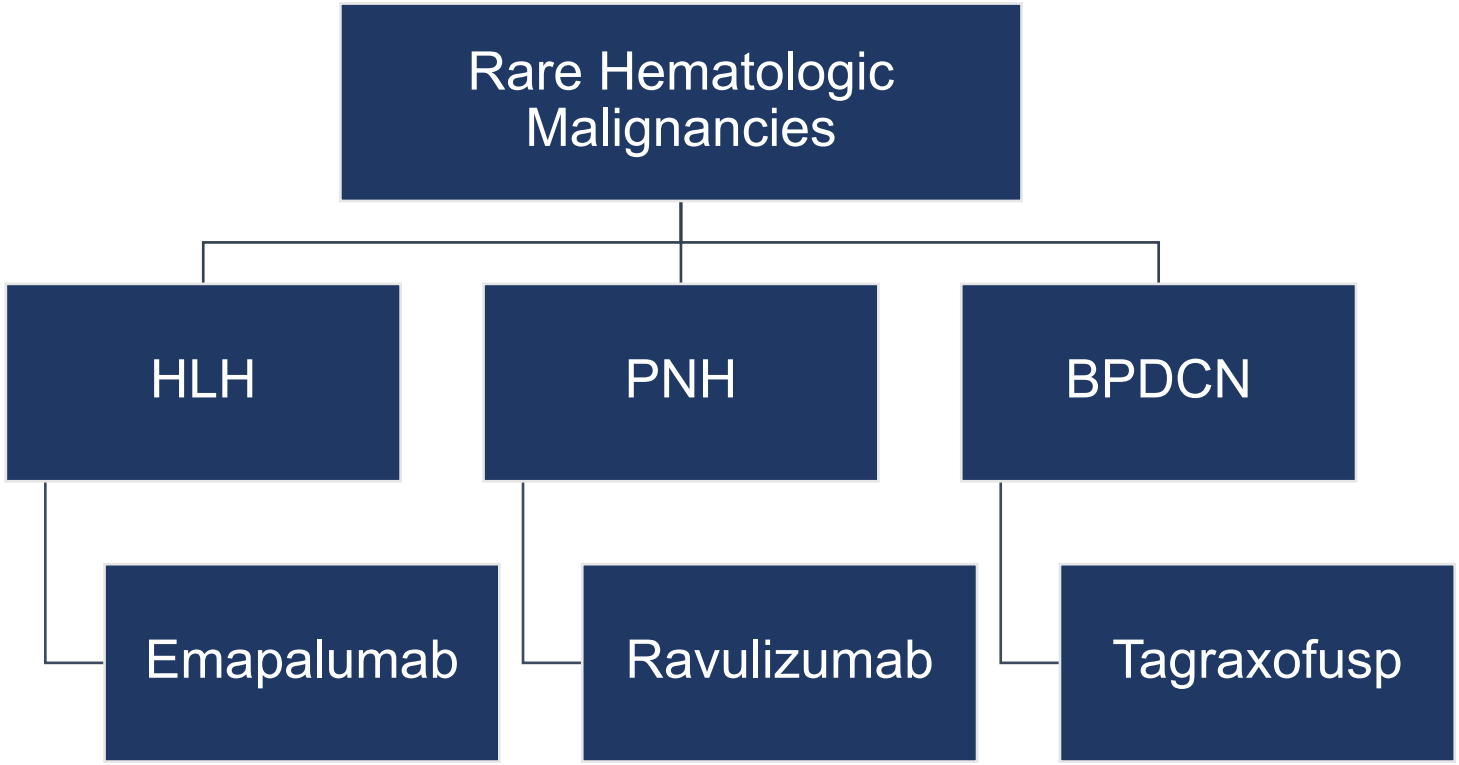
CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma

New Drug Approvals and New Indications in Multiple Myeloma



*Oral agent

New Drug Approvals in Rare Hematologic Malignancies/Disorders



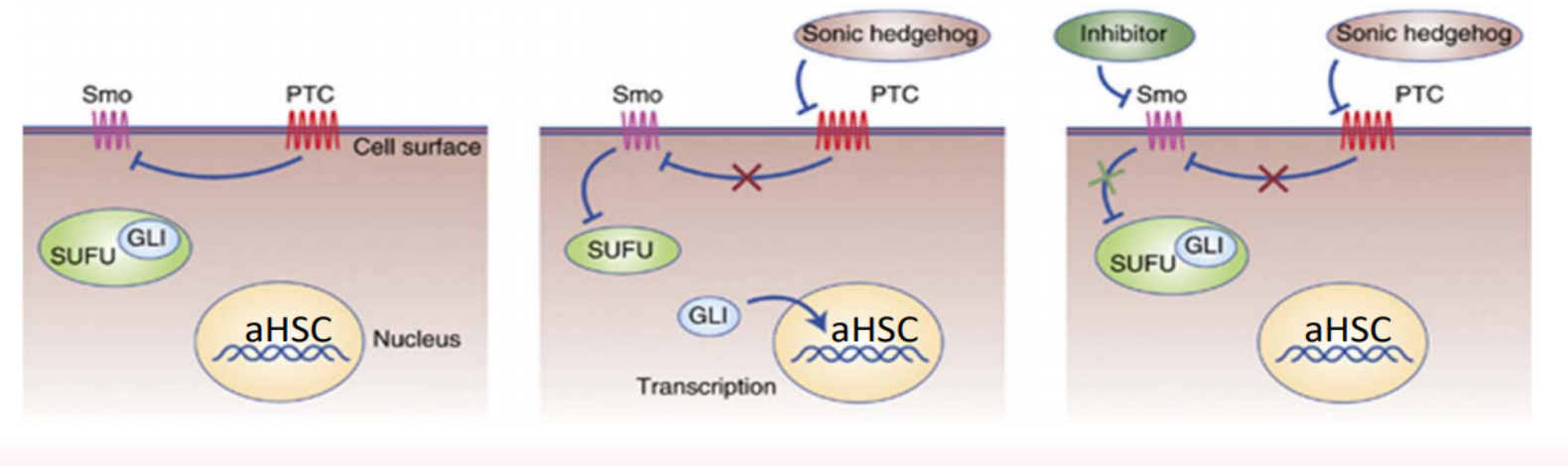
HLH = hemophagocytic lymphohistiocytosis; PNH = paroxysmal nocturnal hemoglobulinuria; BPDCN = blastic plasmacytoid dendritic cell neoplasm

Glasdegib

New Drug Approval in AML: November 2018

Sonic Hedgehog Signaling

- Sonic hedgehog signaling (Shh) pathway is essential for normal embryonic development and plays a role in adult tissue maintenance, renewal, and regeneration



- Glasdegib inhibits smoothened (SMO) involved with downstream signaling effects that lead to cell proliferation and apoptotic suppression

SMO = smoothened; PTC = patched; aHSC = abnormal hematopoietic stem cells

Lear J, et al. *Br J Cancer*. 2014;111(8):1476-81

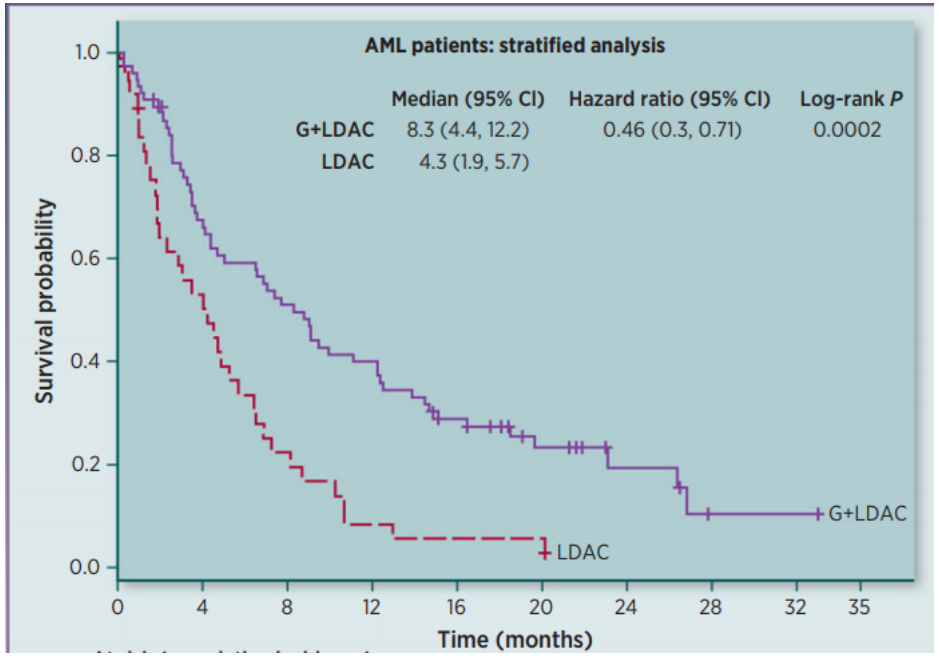
Glasdegib

Indication	Newly diagnosed AML in combination with low-dose cytarabine patients ≥75 years old who have comorbidities that preclude use of intensive induction chemotherapy
Dose	100 mg once daily with or without food (25 mg and 100 mg tablet size)
Drug interactions	Strong CYP3A4 inhibitors and inducers: consider alternatives or monitor Avoid concomitant QTc prolonging drugs or monitor
Warnings & precautions	Embryo-fetal toxicity (Black Box Warning); patients should not donate blood or blood products for at least 30 days after the last dose, QTc interval prolongation
Adverse reactions (≥ 20%)	Anemia, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, and rash

Daurismo™ [package insert]. New York, NY: Pfizer Labs; 2018

Glasdegib Clinical Trial: BRIGHT AML 1003

- Phase II trial including n=115 patients with newly diagnosed AML randomized 2:1 to either:
  - Glasdegib 100 mg daily continuously + low-dose cytarabine (LDAC) 20 mg SQ twice daily x 10 days of each 28-day cycle **OR**
  - Low-dose cytarabine 20 mg SQ twice daily every 28 days
- Overall survival
  - Median OS in glasdegib + LDAC = 8.3 months
  - Median OS in LDAC = 4.3 months
- CR rates were 18.2% vs 2.6% in glasdegib + LDAC vs LDAC, respectively



OS = overall survival; CR = complete response

Norsworthy K, et al. *Clin Cancer Res*. 2019;May 7. doi: 10.1158/1078-0432.CCR-19-0365

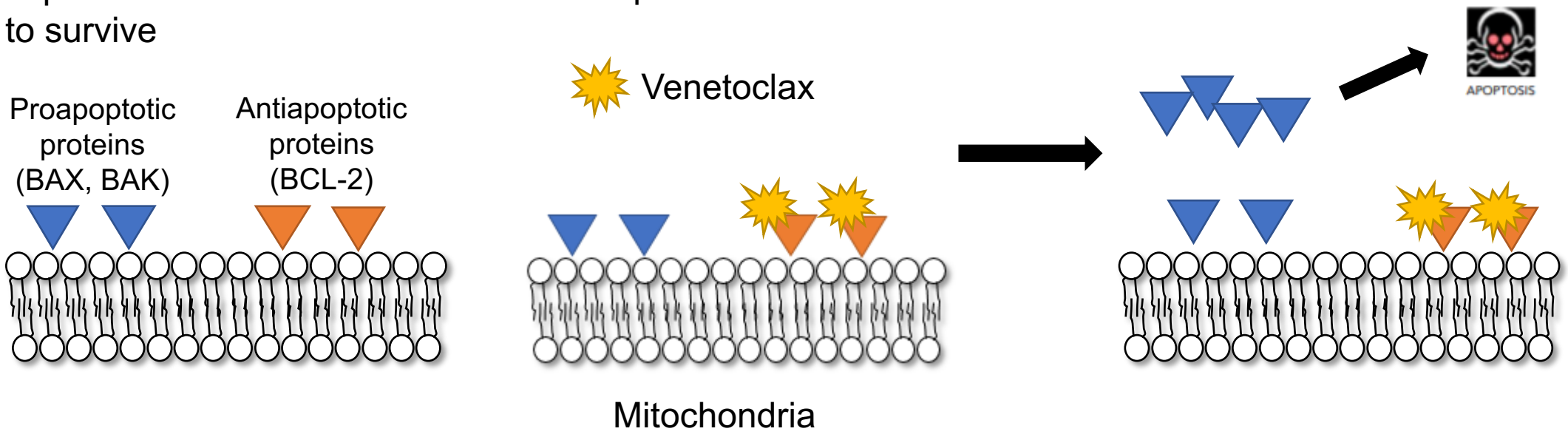
Venetoclax

New Indication in AML: November 2018

BCL-2 and Venetoclax

Venetoclax inhibits B-cell lymphoma-2 (BCL-2)

1. An increase in BCL-2 expression allows the cell to survive
2. Venetoclax binds to and inhibits overexpressed BCL-2
3. Apoptosis is initiated



Adapted from Kumar S. et al. ASCO 2015. Abstract 8576

Venetoclax in AML

- Indication: In combination with azacitidine or decitabine **OR** low-dose cytarabine in patients ≥75 years old with newly diagnosed AML or who have comorbidities that preclude the use of intensive chemotherapy
- Dosing: Take with food; ensure white blood cell count < 25 x 10^9/L prior to initiation

Day	Venetoclax Daily Dose	
Day 1	100 mg	
Day 2	200 mg	
Day 3	400 mg	
Days 4 and beyond	400 mg when in combination with azacitidine or decitabine	600 mg when in combination with low-dose cytarabine

- Adverse reactions (≥30%)
  - Nausea, diarrhea, cytopenias, constipation, febrile neutropenia, fatigue, vomiting, peripheral edema, pyrexia, pneumonia, dyspnea, hemorrhage, rash, abdominal pain, sepsis, back pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension

Venclexta [package insert]. North Chicago, Il: AbbVie Inc. 2019

Venetoclax in AML

Drug interactions and management

Coadministered Drug	Initiation and Ramp-Up Phase	Steady Daily Dose (After Ramp-Up)
Posaconazole	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	Reduce venetoclax dose to 70 mg
Other strong CYP3A4 inhibitor	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	Reduce venetoclax dose to 100 mg
Moderate CYP3A4 inhibitor or P-gp inhibitor	Reduce venetoclax dose by at least 50%	

Venclexta [package insert]. North Chicago, Il: AbbVie Inc. 2019

Venetoclax Packaging

Packaging Presentation	Number of Tablets
CLL/SLL Starting Pack	Each pack contains four weekly wallet blister packs: • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg tablets)
Wallet containing 10 mg tablets	14 x 10 mg tablets
Wallet containing 50 mg tablets	7 x 50 mg tablets
Unit dose blister containing 10 mg tablets	2 x 10 mg tablets
Unit dose blister containing 50 mg tablet	1 x 50 mg tablet
Unit dose blister containing 100 mg tablet	1 x 100 mg tablet
Bottle containing 100 mg tablets	120 x 100 mg tablets
Bottle containing 100 mg tablets	180 x 100 mg tablets

Venclexta [package insert]. North Chicago, Il: AbbVie Inc. 2019

Venetoclax: Clinical Trials in AML

Non-randomized, open-label phase Ib trial in combination with azacitidine (n=67) or decitabine (n=13) in newly diagnosed AML

- In combination with azacitidine, 25 patients achieved a CR (37%) with a median observed time in remission of 5.5 months
- In combination with decitabine, 7 patients achieved a CR (54%) with a median observed time in remission of 4.7 months

Non-randomized, open-label phase Ib/II trial in combination with LDAC (n=61) in newly diagnosed AML including patients previously exposed to a hypomethylating agent

- 13 patients achieved a CR (21%) with a median observed time in remission of 6 months

DiNardo C., et al. *Blood* 2019;133(1):7-17

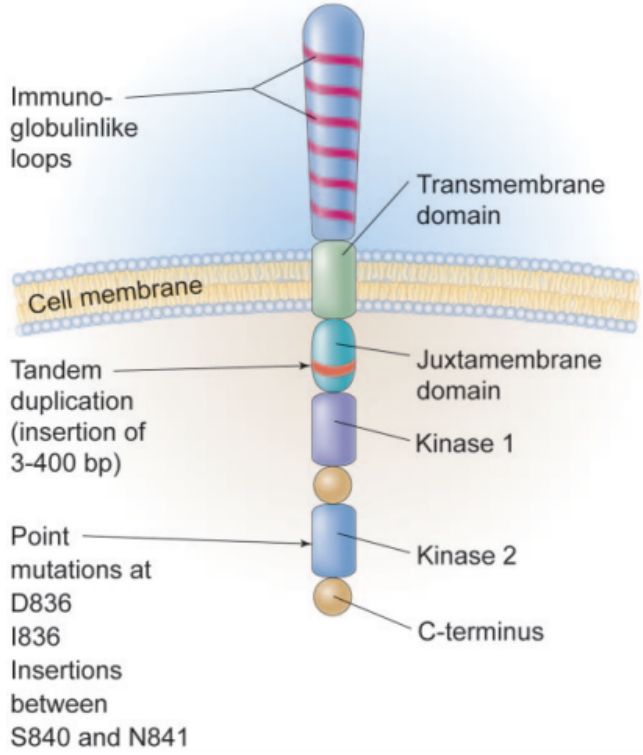
Wei AH., et al. *J Clin Oncol* 2019;37(15):1277-84

Gilteritinib

New Drug Approval in AML: November 2018

FLT3 and AML

- FMS-like tyrosine kinase 3 (FLT3) is expressed on the cell surface of hematopoietic progenitors
- Mutations in FLT3 occur in approximately 30% of all AML cases
  - Internal tandem duplication (FLT3-ITD) occurs in 25% of cases and confers a poor prognosis
  - Tyrosine kinase domain (FLT3-TKD) occurs in 7-10% of cases with an unknown prognostic value
- Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases, including cells expressing FLT3-ITD and tyrosine kinase mutations (TKD)



Litzow MR et al. *Blood*. 2005;106:3331-2

Gilteritinib

Indication	Adult patients with relapsed/refractory AML with a FLT3-mutation as detected by an FDA-approved test
Dose	120 mg once daily with or without food (40-mg tablet size)
Drug interactions	Strong CYP3A4 inhibitors: consider alternatives or monitor Combined P-gp and strong CYP3A4 inducers: avoid use
Warnings & precautions	Differentiation syndrome (Black Box Warning), posterior reversible encephalopathy syndrome (PRES), prolonged QTc interval, pancreatitis, embryo-fetal toxicity
Adverse reactions (≥20%)	Myalgia/arthralgia, transaminase increase, fatigue/malaise, fever, noninfectious diarrhea, dyspnea, edema, rash, pneumonia, nausea, stomatitis, cough, headache, hypotension, dizziness, and vomiting
Grade 3-4 toxicities	Febrile neutropenia (39%), anemia (24%), thrombocytopenia (13%), sepsis (11%), and pneumonia (11%)

Xospata [package insert]. Northbrook, Il: Astellas Parma Inc.

Gilteritinib: ADMIRAL Trial

- Phase III open-label trial included n=371 patients with relapsed or refractory AML having a FLT3-mutation* randomized 2:1 to receive gilteritinb or salvage chemotherapy

Gilteritinib 120 mg daily over continuous 28-day cycles	OR	Salvage chemotherapy (LDAC, azacitidine, MEC, or FLAG-IDA)

- CR + CRh rate
  - 21% with a median duration of response of 4.6 months
- Overall survival
  - 9.3 vs. 5.6 months in gilteritinib and chemotherapy arms, respectively

MEC=etoposide, cytarabine, mitoxantrone; FLAG-IDA=fludarabine, cytarabine, idarubicin, filgrastim

CRh=complete remission with partial hematologic recovery

Perl AE., et al. *Lancet Oncol* 2017;8:1061-75

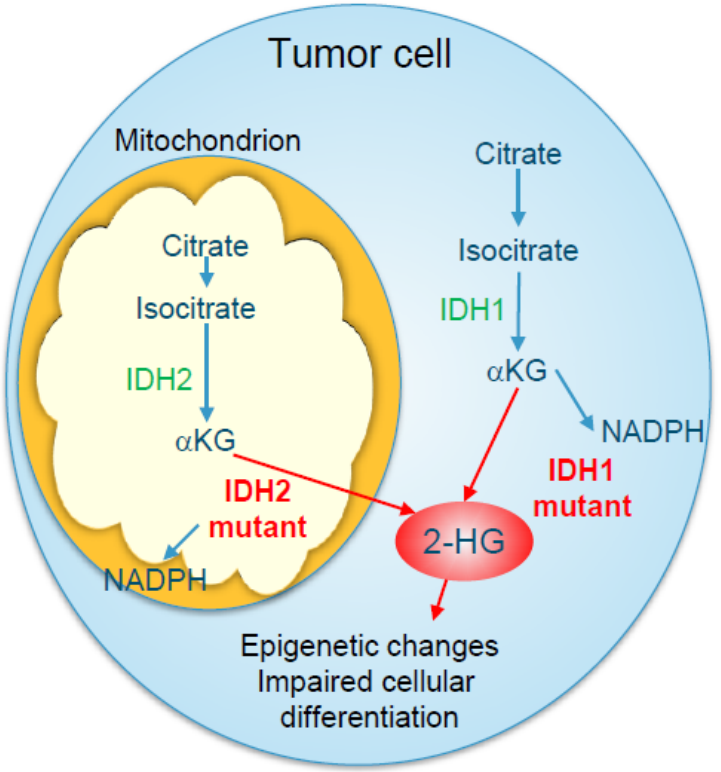
*As detected by an FDA-approved test

Ivosidenib

Expanded Indication in AML: May 2019

Isocitrate Dehydrogenase (IDH) Mutations

- IDH mutations occur in approximately 20% of patients with AML
  - Results in gain-of-function gene (2-HG)
    - IDH1 mutations occur in ~6-9% of AML cases
    - IDH2 mutations occur in ~8-12% of AML cases
- IDH1 inhibitor = ivosidenib
- IDH2 inhibitor = enasidenib



Dang L, et al. *Nature.*2009;462:739-744

Ivosidenib

Indication	Relapsed/refractory and newly-diagnosed AML with IDH1 mutation* in patients ≥75 years old or who have comorbidities that preclude intensive chemotherapy
Dose	500 mg once daily with or without food (250 mg tablets) Avoid a high-fat meal (~1000 calories and 58 grams of fat)
Drug Interactions	Strong CYP3A4 inhibitors: reduce ivosidenib to 250 mg once daily Strong CYP3A4 inducers: avoid use QTc prolonging drugs: monitor
Warnings & Precautions	Differentiation syndrome (Black Box Warning), QTc internal prolongation, Guillain-Barré syndrome
Adverse Reactions (≥20%)	Fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, QT prolongation, rash, pyrexia, cough, and constipation

Tibsovo [package insert]. Cambridge, MA: Agios Pharmaceuticals; 2018

*As detected by an FDA-approved test

Ivosidenib

- Black Box Warning: Differentiation syndrome
  - Can develop as early as 1 day after start of therapy and during the first 3 months of treatment
    - IDH differentiation syndrome was seen in 25% of patients with newly diagnosed AML and 19% of patients with relapsed/refractory AML
  - Symptoms: fever, cough or difficultly breathing, rash, decreased urinary output, hypotension, rapid weight gain, or swelling of arms or legs
    - Initiate dexamethasone 10 mg IV every 12 hours (or equivalent dose) until improvement and for a minimum of 3 days

Tibsovo [package insert]. Cambridge, MA: Agios Pharmaceuticals; 2018

Ivosidenib: Study AG120-C-001

- Ivosidenib demonstrated durable remissions in IDH1 relapsed/refractory AML (approved July 2018)
  - 32.8% of patients (n=57 of 174) achieved CR/CRh
- An extension of the study enrolled untreated AML patients ≥ 75 years or with comorbidities (n=28)
  - CR/CRh rate was 12/28 (42.9%) (2.8 months, range 1.9 – 12.9 mo)
  - 7/17 (41.2%) became independent of red blood cell and/or platelet transfusions who were previously transfusion dependent

CRh = complete remission with partial hematologic recovery

DiNardo C., et al. *N Eng J Med* 2018;378:2386-98

AML Oral Agents Recap

Mutation	Newly Diagnosed	Relapsed/Refractory
FLT3-ITD/TKD	Midostaurin with 7+3	Gilteritinib
IDH1	Ivosidenib (≥75 years old or comorbidities)	Ivosidenib
IDH2	--	Enasidenib

- Newly diagnosed AML in patients ≥75 years or with comorbidities
  - Venetoclax + HMA/LDAC
  - Glasdegib + LDAC

7+3 = daunorubicin and cytarabine; HMA = hypomethylating agent

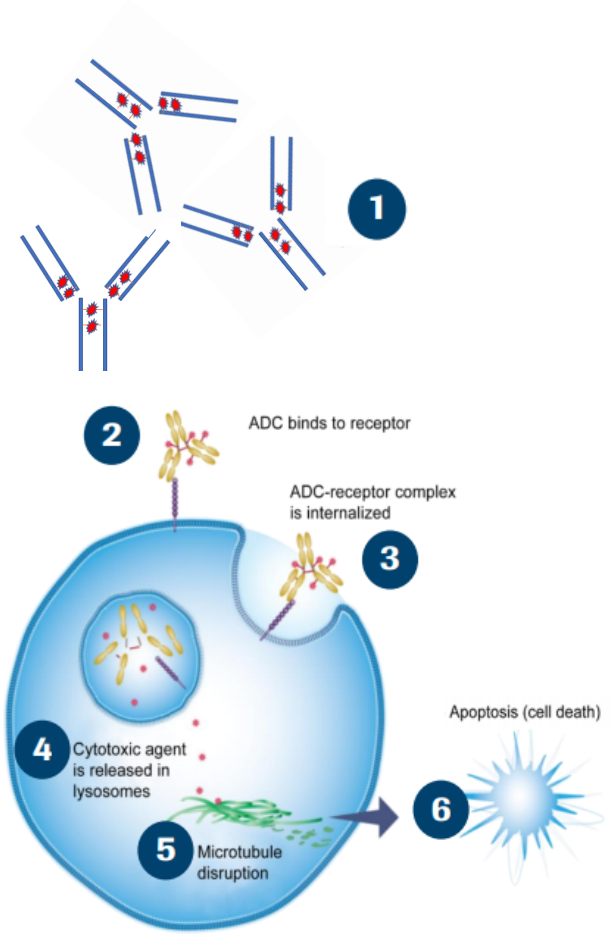
Brentuximab Vedotin

Expanded Indication in sALCL and PTCL: November 2018

sALCL = systemic anaplastic large cell lymphoma; PTCL = peripheral T-cell lymphomas

Brentuximab Vedotin

- Antibody drug conjugate (ADC)
  - Recombinant monoclonal antibody (mAB)
  - Cytotoxic agent
  - Synthetic linker
- CD30-directed monoclonal antibody conjugated to monomethylauristatin E (MMAE)
  - MMAE is a microtubule destabilizer arresting cell cycle at G2/M phase



Adapted from Adcetris™ Package Insert

Brentuximab Vedotin

Indication (expanded)	Previously untreated CD30-expressing peripheral T-cell lymphoma or systemic anaplastic large cell lymphoma in combination with cyclophosphamide, doxorubicin, and prednisone (A+CHP)
Doses of A+CHP	• Brentuximab vedotin 1.8 mg/kg IV (max dose: 180 mg) on day 1 • Cyclophosphamide 750 mg/m^2 IV on day 1 • Doxorubicin 50 mg/m^2 IV on day 1 • Prednisone 100 mg daily x 5 days • Administer granulocyte colony stimulating factor (G-CSF) prophylaxis
DDI	CYP3A4 inhibitors: monitor for increased adverse reactions
Warnings & Precautions	Progressive multifocal leukoencephalopathy (Black Box Warning), anaphylaxis and infusion reactions, hematologic toxicities, infections, TLS, hepatotoxicity, pulmonary toxicity, dermatologic reactions, GI complications, hyperglycemia, embryo-fetal toxicity

Adcetris [package insert]. Bothell, WA: Seattle Genetics; 2018

Brentuximab Vedotin: ECHELON-2

- Phase III double-blind trial in n=452 patients with previously untreated CD30-positive T-cell lymphomas randomized 1:1
  - Brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone (A+CHP)
  - Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)

	A+CHP (n=226)	CHOP (n=226)
Primary Endpoint: PFS	48.2 months	20.8 months

- Adverse reactions (≥ 20%) observed ≥ 2% more in patients receiving A+CHP include nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia
- Peripheral neuropathy occurred in 52% and 55% of patients treated with A+CHP and CHOP, respectively

Horwitz S, et al. *Lancet*. 2019;393:229-40

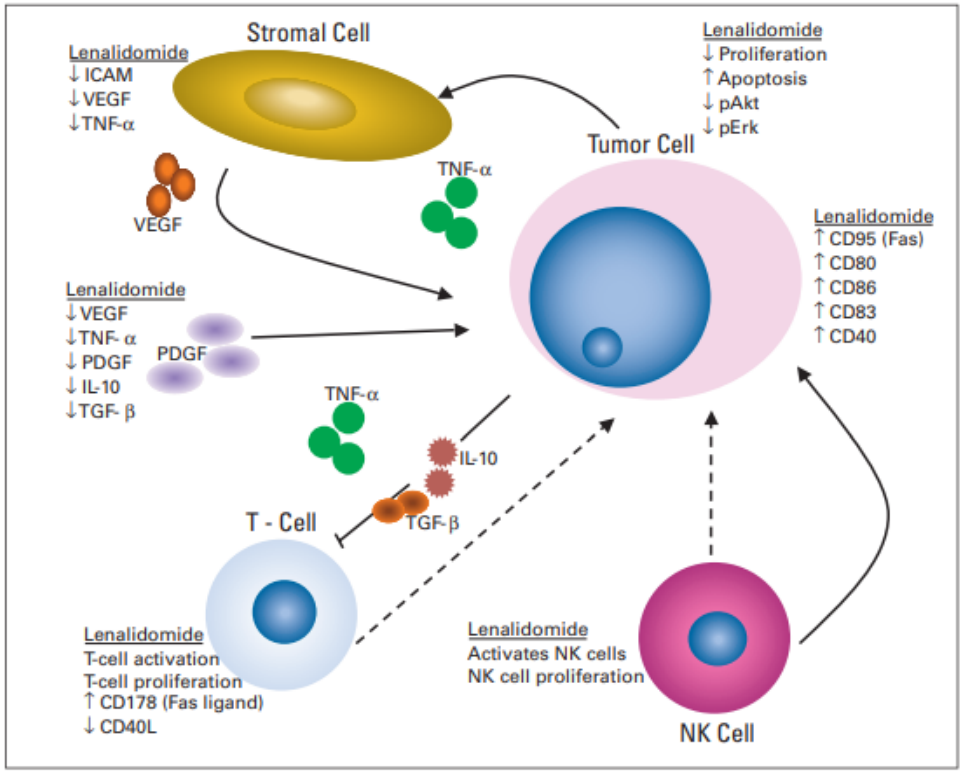
Lenalidomide

Expanded Indication in FL and MZL: May 2019

FL = follicular lymphoma; MZL = marginal zone lymphoma

Lenalidomide

- Immunomodulatory agent (IMiD) with multiple affects on the tumor cell and microenvironment →
  - Downregulation of prosurvival cytokines
  - Increased activation of immune effector cells and costimulatory molecules
- Collectively shift the balance from an antiapoptotic to a proapoptotic environment



Chanan-Khan A, et al. *J Clin Oncol*. 2008;26:1544-52

Lenalidomide

Indication (expanded)	Previously treated FL and MZL in combination with rituximab
Dose	Lenalidomide 20 mg orally once daily on days 1-21 for up to 12 cycles Rituximab 375 mg/m^2 every week in cycle 1 and on day 1 of cycles 2-5 (R^2) Cycle length = 28 days
Contraindications	Pregnancy Severe hypersensitivity to lenalidomide
Warnings & precautions	Hepatotoxicity, cutaneous reactions, tumor lysis syndrome, tumor flare reaction, impaired stem cell mobilization, early mortality, second primary malignancies
Adverse reactions in NHL (≥15%)	Neutropenia, thrombocytopenia, anemia, leukopenia, diarrhea, constipation, nausea, fatigue, pyrexia, cough, upper respiratory tract infection, and rash

Revlimid [package insert]. Summit, NJ: Celgene Corporation; 2019

AUGMENT Trial	MAGNIFY Trial
Phase III, multicenter, randomized trial in n=358 patients with previously treated FL or MZL	Phase IIIb, multicenter, open-label study in patients with relapsed/refractory FL, MZL, and mantle cell lymphoma (MCL)
Treatment with R^2 or R + placebo (control): • R^2 = Lenalidomide + rituximab 375 mg/m^2 on days 1, 8, 15, and 21 of cycle 1 and day 1 of cycles 2 to 5 every 28 days	Treatment with R^2 induction: • R^2 = Lenalidomide + rituximab 375 mg/m^2 on days 1, 8, 15, and 22 of cycle 1 and on day 1 of subsequent odd cycles • Ongoing in maintenance phase

• Primary endpoint: PFS
  • 39.5 vs. 14.1 months in treatment and control arms, respectively
  • PFS improvements were seen in all subgroups except MZL
• FL: ORR 80% in R^2 arm vs 55% in control
• MZL: ORR 65% in R^2 arm vs 44% in control
	• FL → ORR was 59%
	• MZL → ORR was 55%

ORR = overall response rate; PFS = progression-free survival

Leonard et al. *J Clin Oncol* 2019;37(14):1188-99
Coleman M, et al. *Hematol Oncol* 2017;Abstract 139

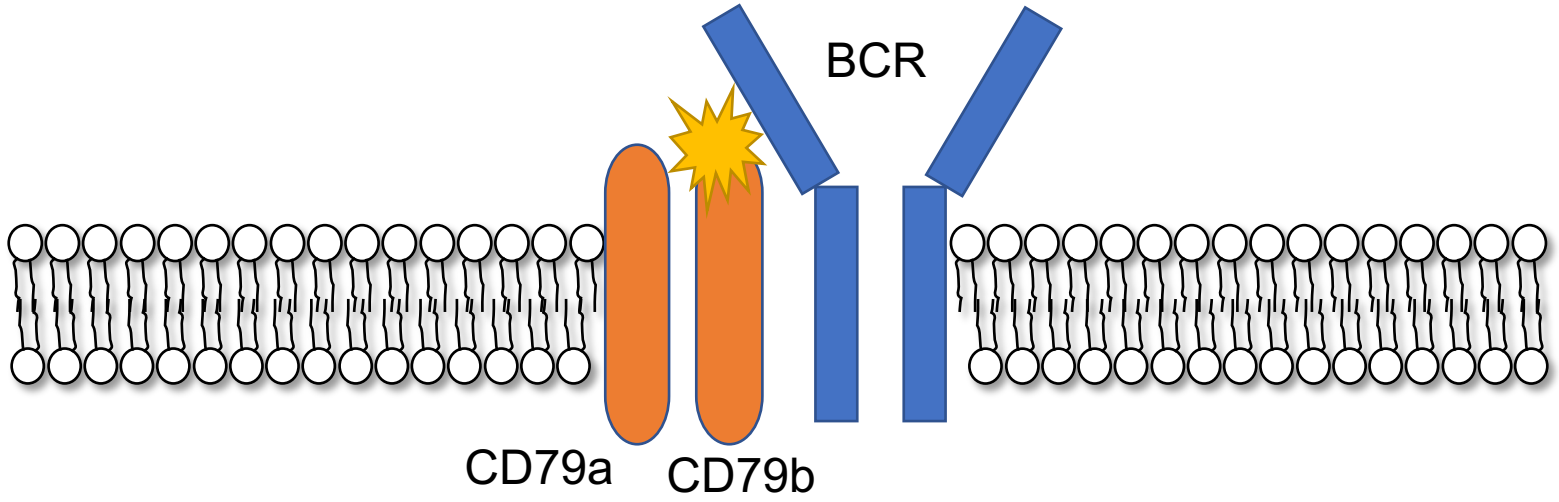
Polatuzumab Vedotin

New Drug Approved in DLBCL: June 2019

DLBCL = diffuse large B-cell lymphoma

CD79b-Monoclonal Antibody

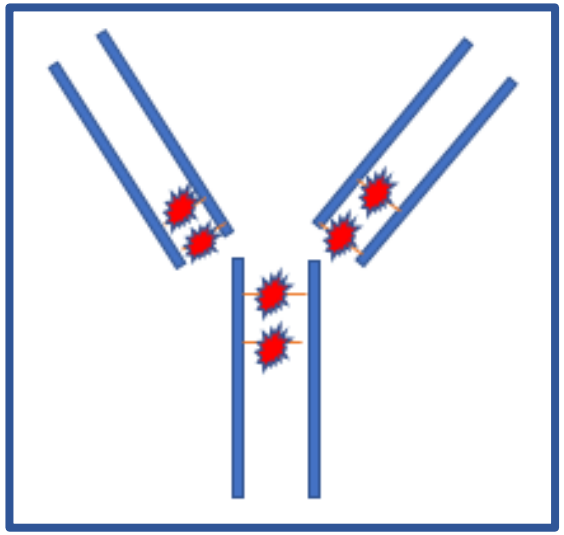
- CD79 is a transmembrane protein that forms a complex with the B-cell receptor (BCR)
  - Consists of two proteins: CD79a and CD79b
  - Expressed in mature B cells and B-cell lymphomas



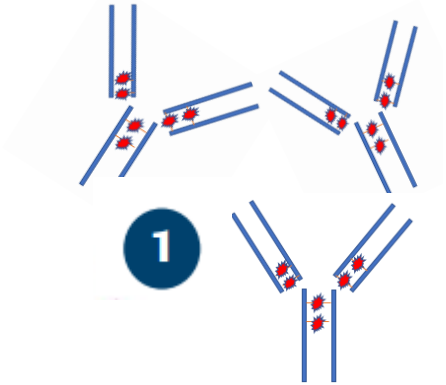
Adapted from Shroeder, H, Torres RM. *Clinical Immunology* (Fifth Edition), 2019

Polatuzumab Vedotin Mechanism of Action (MOA)

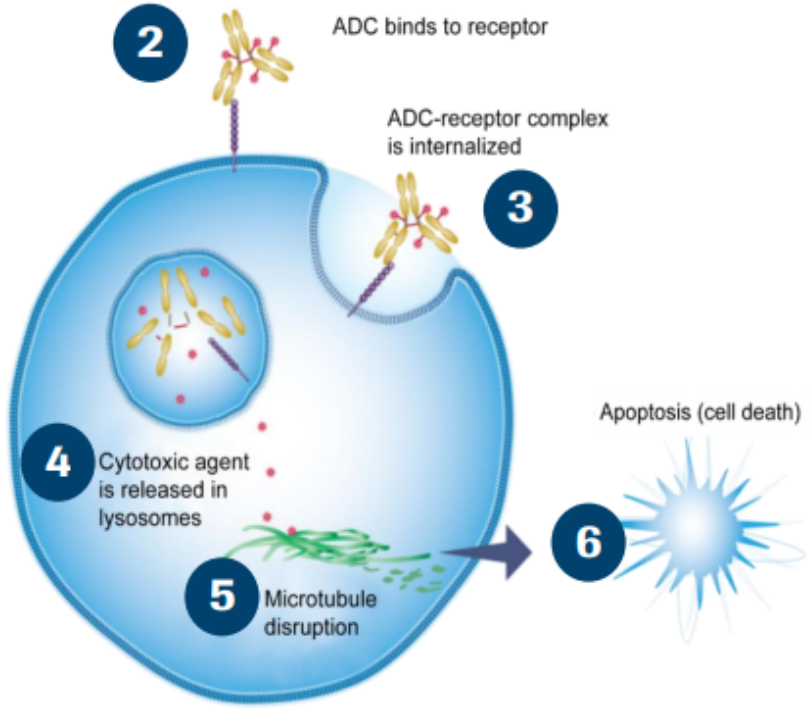
- CD79b-directed antibody-drug conjugate (ADC)



Monoclonal antibody conjugated to monomethyl auristatin E (MMAE), which is a microtubule inhibitor



ADC in circulation



Polivy [package insert]. San Francisco, CA; Genentech, Inc; 2019

Polatuzumab Vedotin

Indication	Relapsed or refractory DLBCL after at least 2 prior therapies in combination with bendamustine and rituximab (P+BR)

Dose	P+BR
	• Polatuzumab vedotin 1.8 mg/kg IV on day 1
	  • Initial infusion: over 90 minutes
	  • Subsequent infusions (if previously tolerated): over 30 minutes
	• Bendamustine 90 mg/m^2/day IV on days 1 and 2
	• Rituximab 375 mg/m^2 IV on day 1
	• Cycle length = 21 days
	• Pre-medication: antihistamine and antipyretic at least 30 minutes prior

Warnings & precautions	Peripheral neuropathy, infusion-related reactions, myelosuppression, opportunistic infections, progressive multifocal leukoencephalopathy, tumor lysis syndrome, hepatotoxicity, embryo-fetal toxicity
Adverse reactions	Neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, pneumonia Grade 3-4 adverse reactions (10-20%): neutropenia, leukopenia, thrombocytopenia

Polivy [package insert]. San Francisco, CA; Genentech, Inc; 2019

Polatuzumab Vedotin: Study G029365

- Phase 1b/II study included a cohort of n=80 relapsed/refractory DLBCL transplant ineligible patients randomized 1:1 to receive:
- Treatment

Polatuzumab vedotin 1.8 mg/kg
+
BR

OR

BR

- BR = bendamustine 90 mg/m^2 x 2 days and rituximab 375 mg/m^2 **every 21 days** x 6 cycles
- Primary endpoint
  - Complete response (CR) rate at end of treatment

Sehn LH, et al. *Blood* 2018;132: Abstract 1683

Polatuzumab Vedotin: Study G029365

Response Rates	P+BR (n=40)	BR (n=40)
Complete response	16 (40%)	7 (18%)
Best overall response rate (CR and PR)	25 (63%)	10 (25%)
Median overall survival	11.8 months	4.7 months
Median PFS	6.7 months	2 months

Sehn LH, et al. *Blood* 2018;132: Abstract 1683

Venetoclax

Expanded Indication in CLL/SLL: May 2019

Venetoclax in CLL/SLL

April 2016

- Venetoclax first approved for patients with CLL/SLL with 17p deletion who have received ≥1 prior therapy

June 2018

- Approval expanded to include patients with CLL/SLL with or without 17p deletion who have received ≥1 prior therapy

May 2019

- Approval expanded to include patients with previously untreated CLL/SLL with coexisting medical conditions

Venclexta [package insert]. North Chicago, Il: AbbVie Inc. 2019

Venetoclax Dosing in CLL/SLL

- **Combination with obinutuzumab**
  - Cycle 1 Day 1 and 2: Obinutuzumab 100 mg followed by 900 mg
  - Cycle 1 Day 8 and 15: Obinutuzumab 1000 mg
  - Cycle 1 Day 22: Venetoclax according to 5-week ramp-up to continue 400 mg once daily until the last day of cycle 12
  - Cycles 2–6: Obinutuzumab 1000 mg on day 1 of each 28-day cycle for a total of 6 cycles
- **Combination with rituximab**
  - Start rituximab after the patient has completed the 5-week ramp-up schedule with venetoclax and has received 400 mg daily x 7 days
  - Cycle 1: Rituximab 375 mg/m^2
  - Cycles 2–6: Rituximab 500 mg/m^2 on day 1 of each 28-day cycle for a total of 6 cycles
  - Venetoclax 400 mg once daily continues for 24 months from cycle 1 day 1 of rituximab
- **Monotherapy**
  - Venetoclax 400 mg once daily following the 5-week ramp-up

Venclexta [package insert]. North Chicago, Il: AbbVie Inc. 2019

Venetoclax in CLL/SLL

- Dose according to weekly ramp-up schedule over 5 weeks

	Venetoclax Daily Dose
Week 1	20 mg
Week 2	50 mg
Week 3	100 mg
Week 4	200 mg
Week 5 and beyond	400 mg

- Starting pack provides the first 4 weeks of venetoclax according to ramp-up schedule
- The 400-mg dose is achieved using 100-mg tablets supplied in bottles

Venclexta [package insert]. North Chicago, Il: AbbVie Inc. 2019

Venetoclax in CLL/SLL

- Warnings and Precautions
  - Tumor lysis syndrome, neutropenia, infections, immunizations, embryo-fetal toxicity
  - *Always assess tumor lysis syndrome risk prior to starting and administer appropriate hydration, anti-hyperuricemics, and ensure adequate lab monitoring!*
- Adverse reactions (≥20%)
  - Cytopenias, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema
- Drug interactions
  - Concomitant use with strong CYP3A4 inhibitors at initiation and during ramp-up phase is contraindicated
  - Substrate of CYP3A4 and P-glycoprotein → dose modifications are recommended with strong or moderate CYP3A4 inhibitors and P-glycoprotein substrates

Venclexta [package insert]. North Chicago, Il: AbbVie Inc. 2019

Venetoclax: CLL14 Clinical Trial

- Open-label, phase III trial included n=432 patients with previously untreated CLL and coexisting conditions * randomized 1:1 to:
- Treatment

VEN + G (study arm)		GClb (Control arm)
• Obinutuzumab (G) IV q28 days x 6 cycles • Venetoclax (VEN) PO as a 5-week ramp-up to a final dose of 400 mg daily q28 days x 12 cycles • Initiated on day 22 of cycle 1	OR	• Obinutuzumab (G) IV q28 days x 6 cycles • Chlorambucil (Clb) PO on days 1 and 15 q28 days x 12 cycles

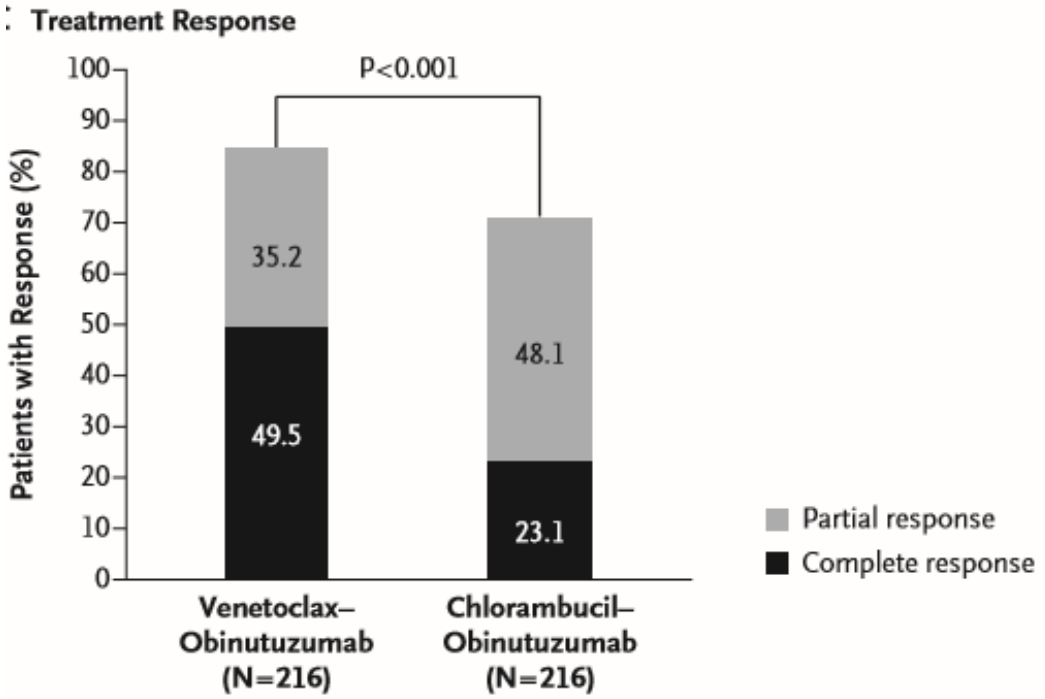
- Primary endpoint: PFS

*Score >6 on the Cumulative Illness Rating Scale or a calculated CrCl <70 ml/min

Fisher, et al. *N Engl J Med.* 2019;380:2225-36

Venetoclax: CLL14 Clinical Trial Results

- Improvement in PFS for patients who received VEN+G compared to GClb
  - PFS benefit was observed in subgroups with *TP53* deletion, mutation, or both, and in patients with unmutated IGHV
- ORR was 85% in VEN+G arm compared to 71% in GClb arm (*p*=.0007)



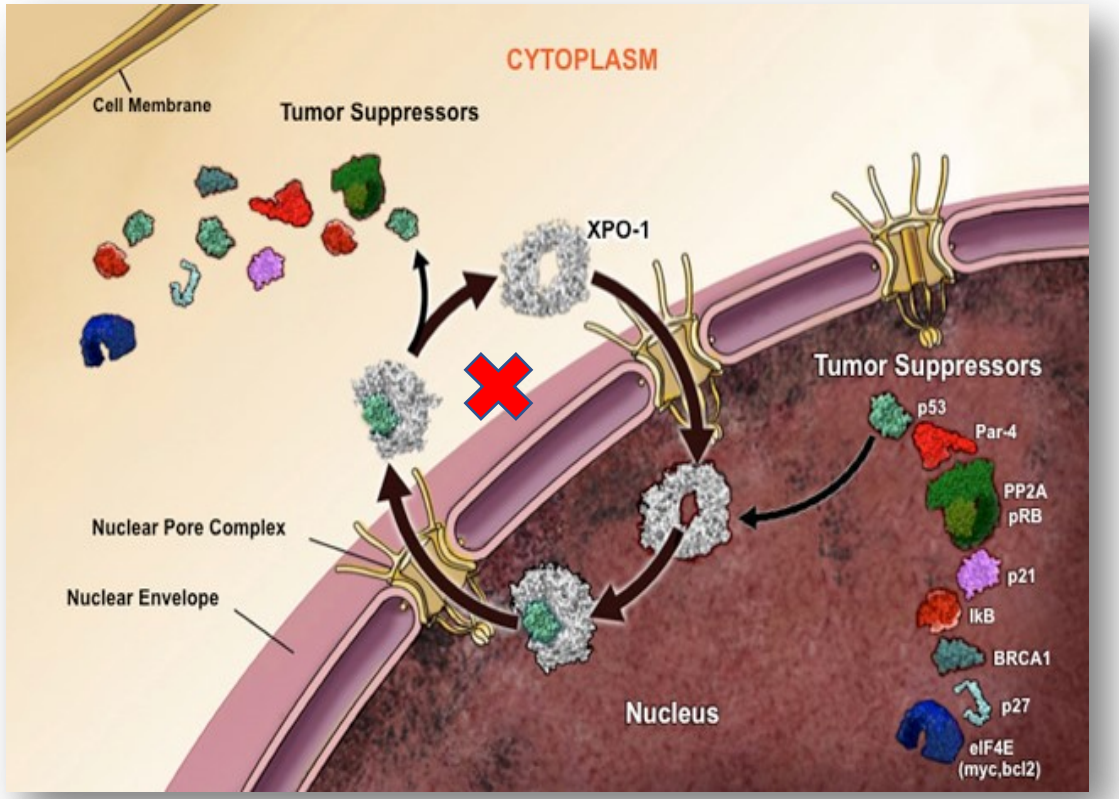
Fisher, et al. *N Engl J Med.* 2019;380:2225-36

Selinexor

New Drug Approval in Multiple Myeloma: July 2019

Selinexor

- Oral selective inhibitor of nuclear export (SINE)
- Selinexor blocks exportin 1 (XPO1) and reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and of oncogenic proteins
  - Accumulation of TSPs in the nucleus → cell cycle arrest → apoptosis



https://www.myelomacrowd.org/the-storm-study-selinexor-the-active-clinical-trials-using-this-drug/#post/0

Xpovio [package insert]. Newton, MA: Karyopharm Therapeutics Inc. 2019

Selinexor

Indication	RRMM in combination with dexamethasone who have received at least four prior therapies and refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody
Dose	80 mg (four 20 mg tablets) once daily with or without food in combination with dexamethasone on days 1 and 3 of each week
Drug interactions	Substrate of CYP3A4, UDP-glucuronosyltransferase, and glutathione S-transferases No drug interaction studies have been preformed
Adverse reactions (≥20%)	Thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection
Grade 3-4 adverse events	Thrombocytopenia (61%), anemia (44%), neutropenia (21%), hyponatremia (22%)

RRMM = relapsed/refractory multiple myeloma

Xpovio [package insert]. Newton, MA: Karyopharm Therapeutics Inc. 2019

Selinexor: STORM Clinical Trial

- Multicenter, single-arm, open-label study of patients with RRMM
  - Previously received ≥ 3 anti-myeloma treatment regimens → alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody
- Approval based on efficacy and safety in a subgroup analysis of n=83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
  - Overall response rate = 25.3%
  - Median time to first response = 4 weeks (range: 1 to 10 weeks)
  - Median response duration = 3.8 months

Chari A., et al. *N Engl J Med* 2019;381:727-38

Daratumumab

Expanded Indication in Multiple Myeloma: September 2019

Daratumumab: MAIA Trial

Newly diagnosed transplant ineligible

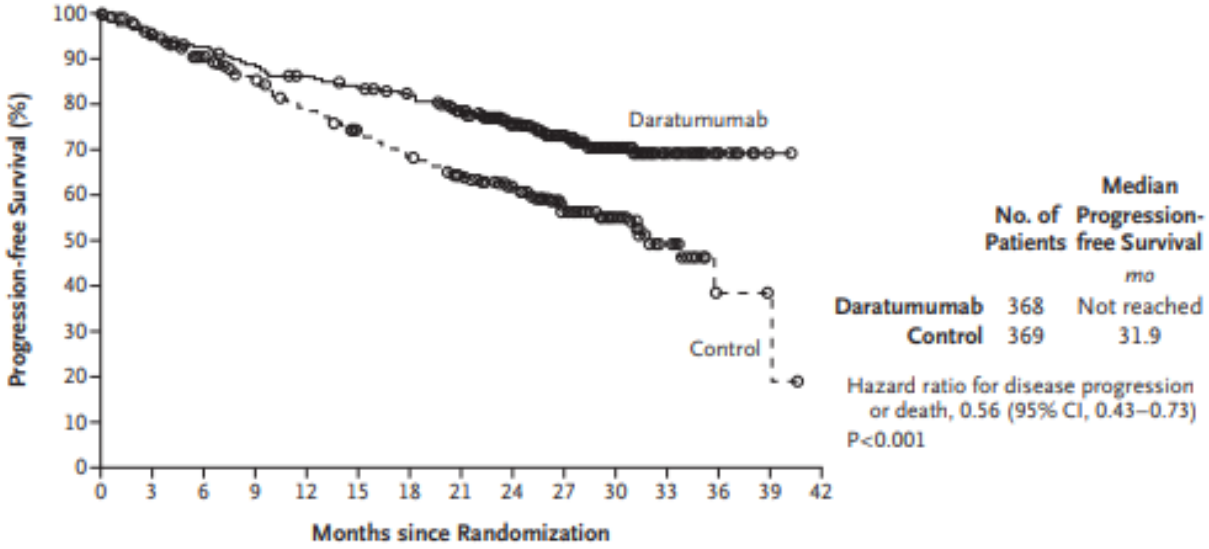
- Indication: Daratumumab in combination with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant
- Phase III study in n=737 newly diagnosed patients with multiple myeloma who were transplant ineligible randomized 1:1
- Treatment: Rd vs. DRd
  - Rd → Lenlidomide 25 mg days 1-21 every 28 days + Dexamethasone 40 mg weekly
  - DRd → Rd + daratumumab 16 mg/kg weekly x 8 doses, then every 2 weeks for 8 doses, followed by every 4 weeks
- Primary Endpoint: PFS

Facon T, et al. *N Engl J Med*. 2019;380:2104-15

Daratumumab: MAIA Clinical Trial

Newly diagnosed transplant ineligible

- At a median follow-up of 28 months
  - Median PFS for DRd was not reached vs 31.9 months for Rd alone
- Complete response rates or better:
  - DRd=48% vs Rd=25%



- Adverse reactions (≥20%):
  - Infusion reactions, diarrhea, constipation, nausea, peripheral edema, fatigue back pain, asthenia, pyrexia, upper respiratory tract infection, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea and cough

Facon T, et al. *N Engl J Med*. 2019;380:2104-15

Daratumumab: CASSIOPEIA Trial

Newly diagnosed transplant eligible

Phase III study in n=1085 newly diagnosed multiple myeloma who are transplant eligible randomized 1:1

	D-VTd	VTd

Induction phase (4 cycles)	• Daratumumab 16 mg/kg IV
	  • Weekly (cycles 1-2)
	  • Every 2 weeks (cycles 3-4)
	• VTd
		• VTd
		  • Bortezomib 1.3 mg/m^2 SQ on days 1, 4, 8, and 11
		  • Thalidomide 100 mg daily
		  • Dexamethasone

Stem cell mobilization, conditioning, and transplant		
Consolidation phase (2 cycles)	• Daratumumab 16 mg/kg every 2 weeks • VTd	• VTd
Maintenance phase (Part 2 - ongoing)		

Moreau P, et al. *Lancet*. 2019;394:29-38

Daratumumab: CASSIOPEIA Trial

Newly diagnosed transplant eligible

- Primary endpoint = stringent complete response after consolidation

Response	D-VTd (n=543)	VTd (n=542)	P value
Stringent complete response	157 (29%)	110 (20%)	0.0010
Complete response or better	211 (39%)	141 (26%)	<0.0001

- Adverse events (≥20% in either group):
  - Peripheral sensory neuropathy, constipation, asthenia, peripheral edema, nausea, neutropenia, pyrexia, paresthesia, and thrombocytopenia

Moreau P., et al. *Lancet* 2019; 394:29-38

Tagraxofusp

New Drug Approved in BPDCN: December 2018

BPDCN and Tagraxofusp

- BPDCN is an uncommon hematopoietic malignancy arising from the precursors of myeloid-derived plasmacytoid dendritic cells (pDC)
  - Overexpression of interleukin-3 receptor subunit alfa (IL3RA or CD123) occurs in virtually all cases of BPDCN
- Tagraxofusp is a CD123-directed cytotoxin composed of recombinant human interleukin-3 (IL-3) and truncated diphtheria toxin (DT) that inhibits protein synthesis and causes cell death in CD123-expressing cells

Sullivan JM. Hematology Am Soc Educ Program. 2016;1:16-23; Pemmaraju N, et al. *N Engl J Med*. 2019;380:1628-37

Elzonris [package insert]. New York, NY: Stemline Therapeutics: 2018

Tagraxofusp

Indication	BPDCN in adult and pediatric patients 2 years or older
Dose	• Tagraxofusp 12 µg/kg IV over 15 minutes once daily on days 1 to 5 of a 21-day cycle • Premedications: H1-histamine antagonist + APAP + corticosteroid + H2-histamine antagonist • Administer the first cycle in the inpatient setting • Subsequent cycles may be administered in the inpatient or appropriate outpatient setting
Warnings & precautions	Capillary leak syndrome (Black Box Warning), hypersensitivity, hepatotoxicity
Adverse reactions & laboratory abnormalities	Incidence ≥30%: Capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia, and weight increase Incidence ≥50%: Decreases in albumin, platelets, hemoglobin, calcium, sodium, and increases in glucose, ALT, and AST

Elzonris [package insert]. New York, NY: Stemline Therapeutics: 2018

Tagraxofusp: STML-401-0114 Trial

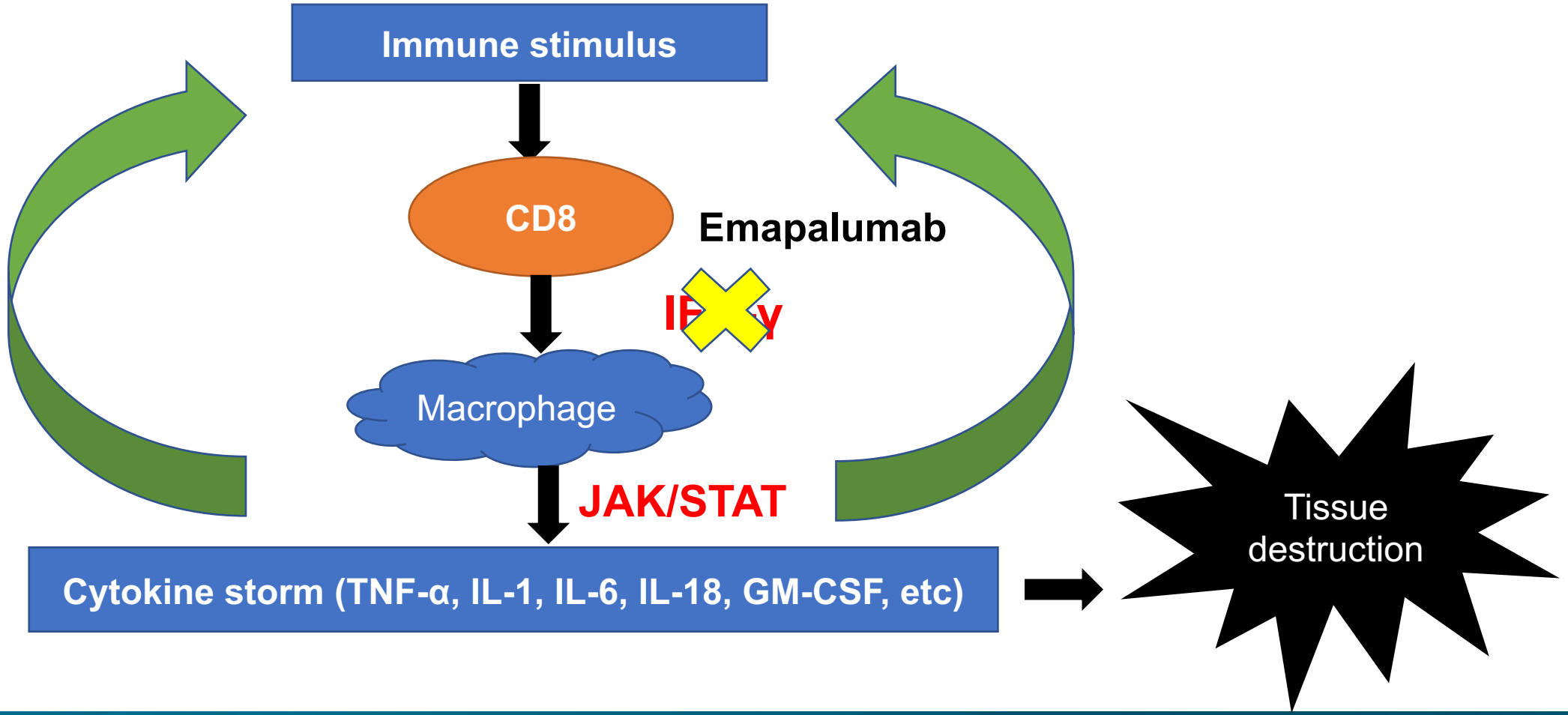
- Multicenter, multicohort, open-label, single-arm study in patients with untreated or relapsed/refractory BPDCN
- Treatment
  - Tagraxofusp 12 µg/kg IV over 15 minutes on days 1 to 5 of a 21-day cycle
- Untreated BPDCN (n=13)
  - 7/13 (53.8%) achieved complete response
- Relapsed/refractory BPDCN (n=15)
  - 1 patient achieved complete response (duration 111 days) and 1 patient achieved a clinical complete response (duration 424 days)

Pemmaraju N., et al. *N Engl J Med* 2019; 380:1628-37

Emapalumab

New Drug Approved in HLH: November 2018

HLH and Emapalumab



Adapted from Albeituni S, et al. *Blood*. 2019;134(2):147-159

Emapalumab

Indication	Adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy
Dose	Emapalumab 1 mg/kg IV over 1 hour twice per week • Emapalumab dose may be titrated up if disease response is unsatisfactory and decreased to previous level once condition is stabilized Administer dexamethasone concomitantly with emapalumab
Warnings & precautions	Infections (test for latent tuberculosis, administer prophylactic treatment against HSV, PJP, and fungal infections), infusion-related reactions, avoid live vaccines
Adverse reactions (≥20%)	Infections, hypertension, infusion-related reactions, and pyrexia

Gamifant [package insert]. Geneva, Switzerland: Novimmune SA; 2018

Emapalumab: Study NI-0501-04

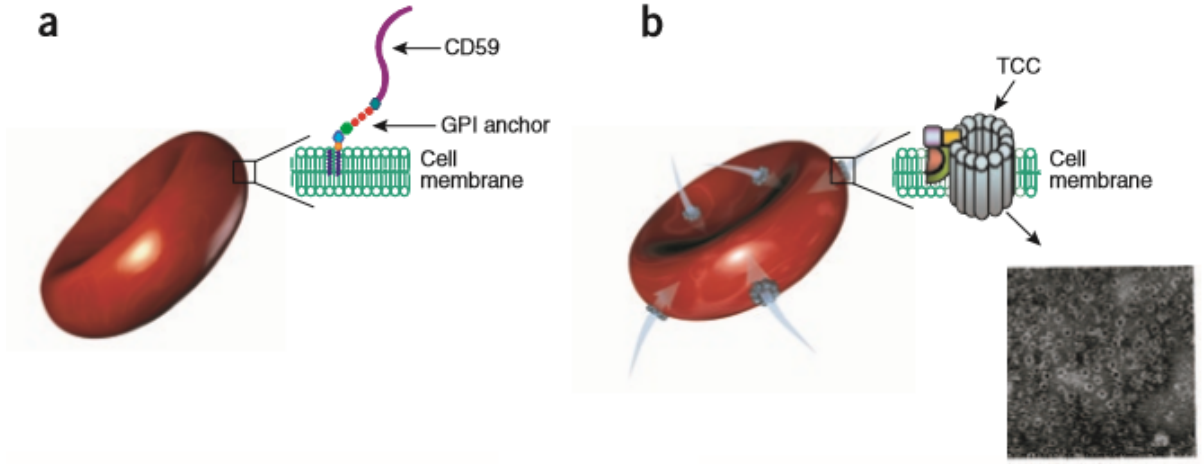
- Multicenter, open-label, single-arm trial in n=27 pediatric patients with suspected or confirmed primary HLH with either refractory, recurrent, or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy
- Treatment
  - Emapalumab 1 mg/kg every 3 days and dexamethasone 5-10 mg/m^2/day
  - Prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections prior to administration
- ORR was 63% (p=.013)
  - 7 complete responses, 8 partial responses, and 2 patients had improvement (≥3 HLH abnormalities improved by at least 50% from baseline)

Ravulizumab

New Drug Approval in PNH: December 2018

Paroxysmal Nocturnal Hemoglobulinuria (PNH)

- PNH is a rare hematologic disorder manifested by a genetic deficiency in linking compliment inhibitors to the blood cell surface
  - PNH clones are deficient in complement inhibitor proteins due to mutations in *PIGA*, which is critical in the GPI-anchoring pathway on RBCs
- Reduced GPI-anchored proteins leads to complement-mediated hemolysis
  - All pathways of complement activation converge at protein C5



PIGA = phosphatidylinositol glycan anchor biosynthesis, class A; GPI = glycosylphosphatidylinositol

Rother PR, et al. *Nat Biotechnol*. 2007;11:1256-64

Ravulizumab vs Eculizumab

- C5 compliment inhibitor indicated for the treatment of adult patients with PNH
  - Substitution of 4 amino acids on the eculizumab backbone → results in augmented C5 inhibition and recycling of ravulizumab to the vascular compartment → half-life is ~4 times longer than eculizumab
- Weight-based loading and maintenance dosing
- Switching from eculizumab → Administer loading dose 2 weeks after eculizumab infusion followed by maintenance dose 2 weeks later and then once every 8 weeks
- Black Box Warning for serious meningococcal infections (REMS program)
  - Immunize patients with meningococcal vaccines at least 2 weeks prior to the first dose
  - If unvaccinated patients should receive 2 weeks of antibiotics with vaccinations

Ultomirus [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc. 2018

More Questions?

Come see me at Booth **#829** (next to the APSHO Booth)
in the Exhibit Hall from **10:15 to 11:15** tomorrow morning.

SMARTIE

This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019