New Drug Updates in Hematologic Malignancies: CAR T Cells, Targeted Therapeutics, and Other Agents

R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA
Associate Professor, Hematology/Medical Oncology and Pharmacology
Director, Phase I Clinical Trials Section
Emory University and Winship Cancer Institute

2017 JADPRO Live at APSHO

Learning Objectives

1. Discuss the pharmacology and indications of medications approved from late 2016 to 2017 for the management of patients with hematologic cancers
2. Recall the pivotal clinical trial data considered by the FDA when approving new oncologic agents
3. Identify the signs and symptoms of serious or life-threatening adverse effects of newly approved oncology drugs
4. Describe the impact of these agents in advanced practice

Financial Disclosure

Dr. Harvey has received research funding from BMS, and is a consultant to Amgen, BMS, and Takeda.

New Agents/Approvals in Hematologic Cancers

- Midostaurin (April 2017)
- Rituximab SC with hyaluronidase (June 2017)
- Enasidenib (August 2017)
- Ibrutinib (August 2017)
- Liposomal daunorubicin and cytarabine (August 2017)
- Inotuzumab ozogamicin (August 2017)
- Tisagenlecleucel (August 2017)
- Gemtuzumab ozogamicin (September 2017)
- Copanlisib (September 2017)

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Additional Approvals

- Lenalidomide (February 2017)
  - Myeloma: maintenance post-autologous transplant beginning after day +90
  - Dose 10 mg PO daily, may be increased to 15 mg after 3 cycles as tolerated
- Pembrolizumab (March 2017)
  - Classical Hodgkin lymphoma after 3 or more lines, adult (200 mg) and pediatrics (2 mg/kg)
- *JAK2* testing (March 2017)
  - Approved PCR testing for mutations associated with polycythemia vera

PCR = polymerase chain reaction; PO = by mouth.

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Additional Approvals

- Betrixaban (June 2017)
  - VTE prophylaxis in medically ill patients
  - Dosing: 160 mg PO day 1, then 80 mg PO daily for 35-42 days with food
- L-glutamine oral powder (March 2017)
  - Reduction of acute complications in sickle cell disease in adult and pediatric patients
  - 10-30 grams PO (weight based) twice daily mixed with liquid in patients receiving hydroxyurea
- Blinatumomab (July 2017)
  - Expansion to include Philadelphia+ ALL

ALL = acute lymphoblastic leukemia; VTE = venous thromboembolism.

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Additional Approvals

- Ibrutinib (August 2017)
  - First agent approved for chronic graft-versus-host disease following allogeneic stem cell transplant
  - Dose: 420 mg PO daily
  - Trial in 42 patients who failed corticosteroids
    - Overall response rate 67%
    - Median time to response 12.3 weeks (range, 4.1-42.1 weeks)
    - Activity seen in all involved organs

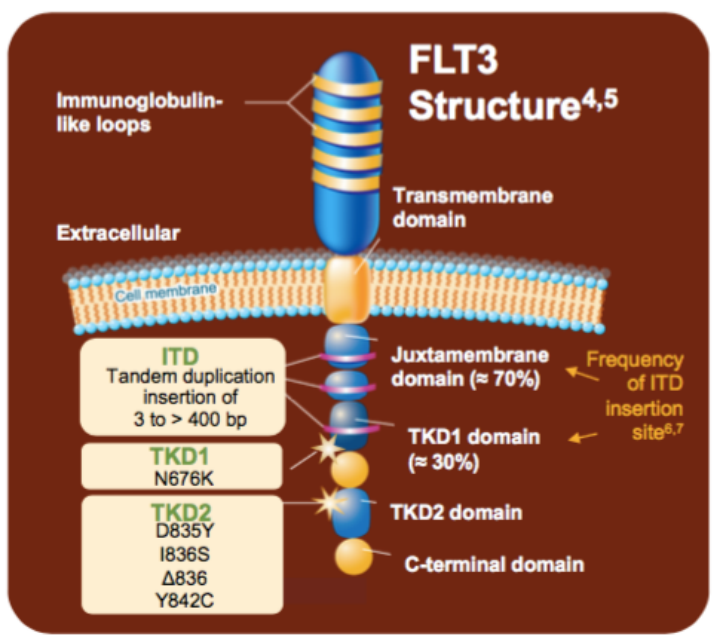
US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Midostaurin: *FLT3*-Positive AML

April 28, 2017

FLT3 and AML

- Type III transmembrane receptor tyrosine kinase
  - Same family as KIT, PDGFR-α/β
- Highly expressed on hematopoietic progenitors and required for myeloid differentiation
- Mutations in the *FLT3* gene cause constitutive activation of the receptor
  - Most common mutation is the ITD



Reprinted with permission from Pemmaraju N, et al. *Cancer*. 2011;117(15):3293-3304. © 2011 John Wiley & Sons, Inc.

AML = acute myeloid leukemia; FLT3 = FMS-like tyrosine kinase 3; ITD = internal tandem duplication; PDGFR = platelet-derived growth factor receptor.

Fathi AT, et al. *Eur J Haematol* 2017;98:330-6.

Midostaurin

- Mechanism: small molecule that inhibits wild-type *FLT3*, *FLT3* mutant kinases (ITD and TKD), KIT (wild-type and D816V-mutant), PDGFRα/β, VEGFR2, as well as members of the serine/threonine kinase PKC family
- Indication: Newly diagnosed AML that is *FLT3* mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation

FDA = US Food and Drug Administration; PKC = protein kinase C; TKD = tyrosine kinase domain; VEGFR2 = vascular endothelial growth factor receptor 2.

Novartis 2017. Rydapt (midostaurin) product information. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/rydapt.pdf.

Midostaurin

- Dose: 50 mg PO BID with food (for nausea prevention) on days 8-21 of induction and consolidation chemotherapy; for maintenance, continuous post-consolidation dosing
  - Prophylactic antiemetics needed (e.g., ondansetron)
  - No change for mild or moderate renal or hepatic function, no data in severe dysfunction
- Hold for
  - Pneumonitis without infectious etiology

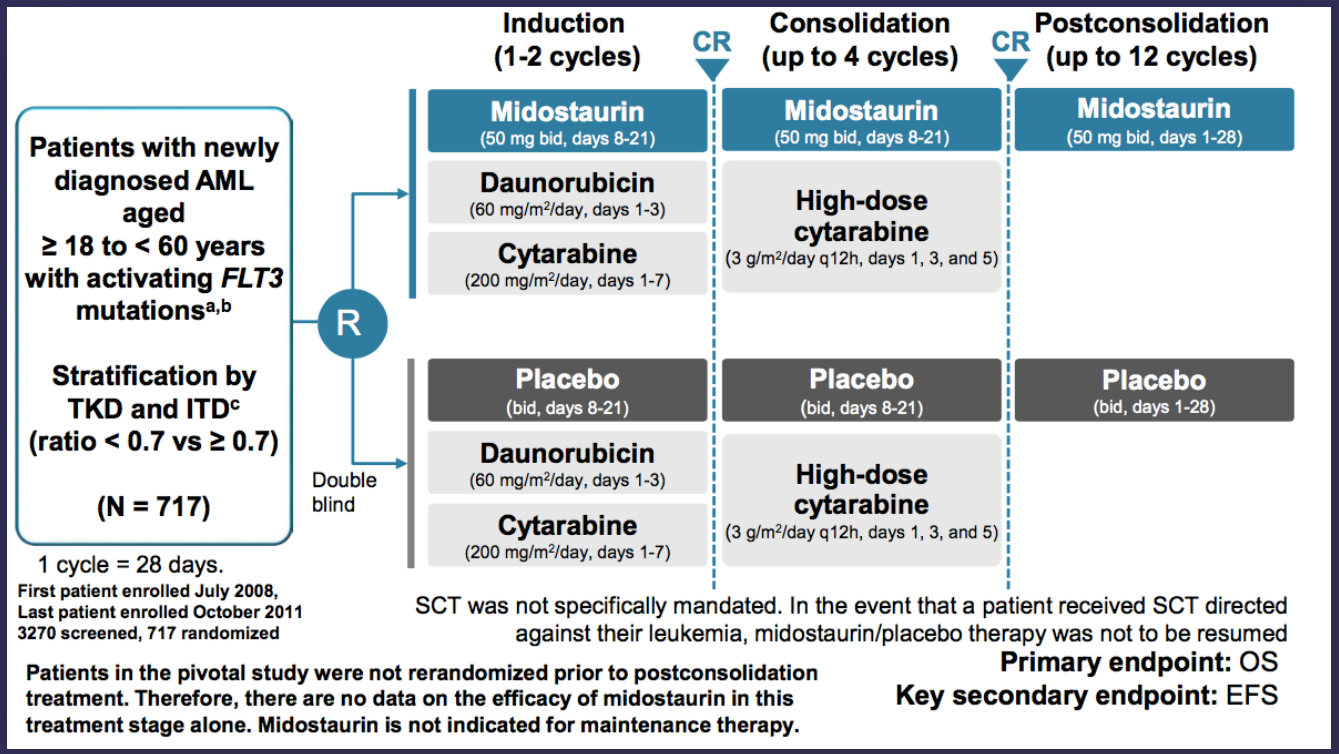
Midostaurin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

Midostaurin

- **Warnings and precautions**
  - Embryo-fetal toxicity: may cause fetal harm when administered to a pregnant woman; advise of the potential risk to a fetus
  - Pulmonary toxicity: monitor for symptoms of interstitial lung disease or pneumonitis; discontinue in patients with signs or symptoms of pulmonary toxicity
- **Try to avoid strong CYP3A inhibitors (e.g., posaconazole, voriconazole) and inducers**
  - Most pronounced effects early in therapy
- **Common adverse events (> 20%):** febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, and upper respiratory tract infections
- **Grade 3/4 adverse reactions (≥ 10%)**: febrile neutropenia, device-related infection, and mucositis

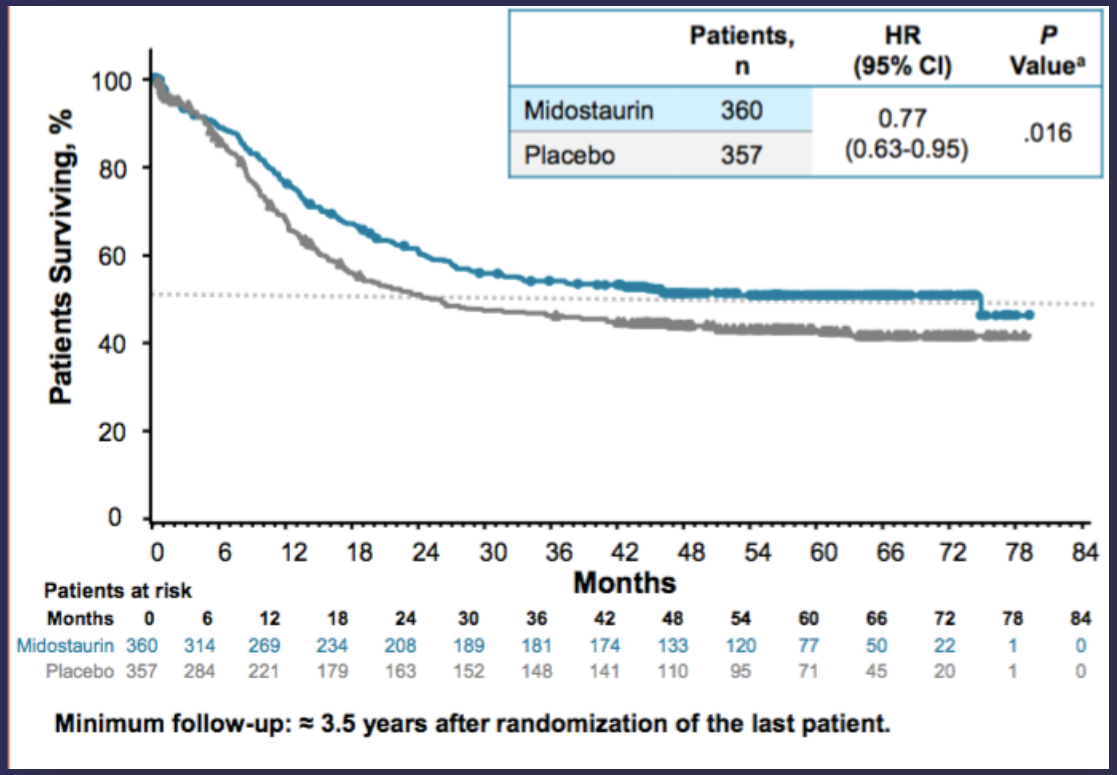
Midostaurin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

Midostaurin Phase III Clinical Trial



Midostaurin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

Midostaurin Phase III Clinical Trial



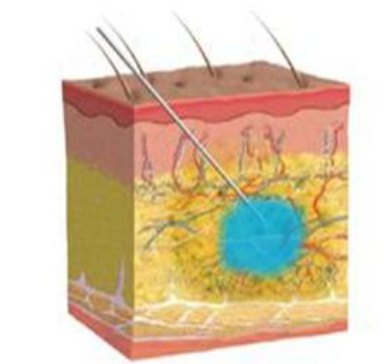
Midostaurin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

Rituximab SC With Hyaluronidase

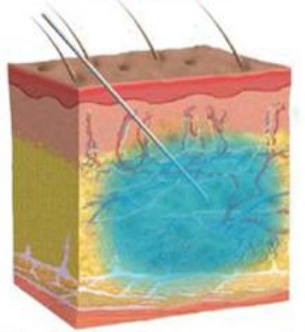
June 22, 2017

Hyaluronidase and Subcutaneous Tissue

- Hyaluronan (hyaluronic acid)
  - Carbohydrate polymer that forms an extracellular matrix in subcutaneous tissue
  - Forms tight junctions and barriers to interstitial fluid flow
- Hyaluronidase
  - Cleaves hyaluronan through depolymerization
  - Allows for large volume injections and systemic absorption



SC administered drug depot



rHuPH20 disperses SC administered drugs

SC = subcutaneously.

Rituximab SC with Hyaluronidase

- Mechanism: hyaluronidase (an endoglycosidase) cleaves hyaluronan; anti-CD20 monoclonal antibody
- Indications: newly diagnosed diffuse large B-cell lymphoma with CHOP, chronic lymphocytic leukemia with FC, follicular lymphoma single agent or with chemotherapy
- Key points
  - **Patients must have had at least one prior rituximab IV infusion**
  - Not indicated for non-malignant disorders

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; FC = fludarabine, cyclophosphamide.

Rituximab and hyaluronidase product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf.

Rituximab SC with Hyaluronidase

- Dosing: premedicate with acetaminophen and antihistamine (and corticosteroid)
- Inject into abdomen
  - FL/DLBCL: 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase) – 11.7 mL over approx. 5 minutes
  - CLL: 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase) – 13.4 mL over approx. 7 minutes
- Observe 15 minutes following administration

CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FC = follicular lymphoma.

Rituximab and hyaluronidase product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf.

Rituximab SC with Hyaluronidase

- **Warnings and precautions**
  - Hypersensitivity and local administration reactions
  - Tumor lysis syndrome
  - Infections
  - Hepatitis B reactivation
- **Common adverse events (> 20%):** infections, neutropenia, nausea, injection site erythema
- **Grade 3/4 adverse reactions (≥ 10%)**: neutropenia

Rituximab and hyaluronidase product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf.

Rituximab SC with Hyaluronidase: DLBCL

	RITUXAN HYCELA + CHOP (n=381)	RITUXAN (rituximab) + CHOP (n=195)
Complete Response Rate		
Number of responders (CR/CRu achieved)[a]	179	82
Response rate (% [95% CI])	47% [42; 52]	42% [35; 49]
Difference in response rates [95% CI][b]	4.9% [−3.6; 13.5]	

The median observation time was approximately 28 months.
[a] Four patients in the RITUXAN HYCELA group and one patient in the RITUXAN group had their response downgraded due to their bone marrow data.
[b] Difference in response rates (RITUXAN HYCELA minus RITUXAN).

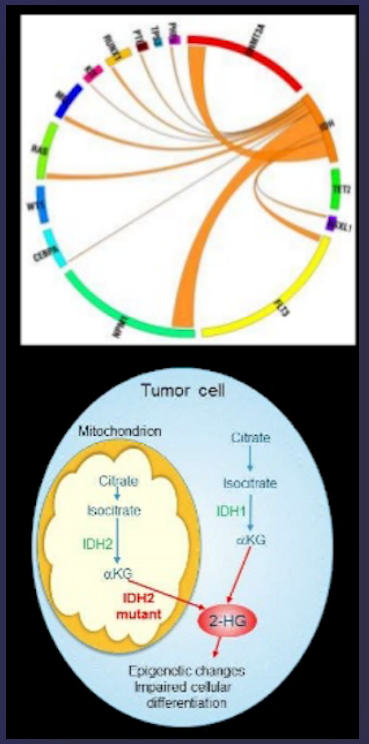
Rituximab and hyaluronidase product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf.

Enasidenib

August 1, 2017

IDH Mutations in AML

- Occur in 20% of cases
- *IDH2* – 8-18% of all patients
- Increased prevalence as age increases
- Present at diagnosis, not progression
- Impacts cellular metabolism
- Also important in gliomas and cholangiocarcinomas



IDH = isocitrate dehydrogenase.

Chou WC, et al. *Leukemia* 2011;25:246-53; Patel JP, et al. *N Engl J Med* 2012;366:1079-89.

Enasidenib

- Mechanism: IDH2 inhibitor
- Indications: adult patients with relapsed or refractory AML with an *IDH2* mutation as detected by an FDA-approved test
  - Abbott Real*Time*™ IDH2 PCR assay
- Dosing: 100 mg PO once daily continuously
- No significant interactions (food, antacids, other agents)

Enasidenib product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209606s000lbl.pdf.

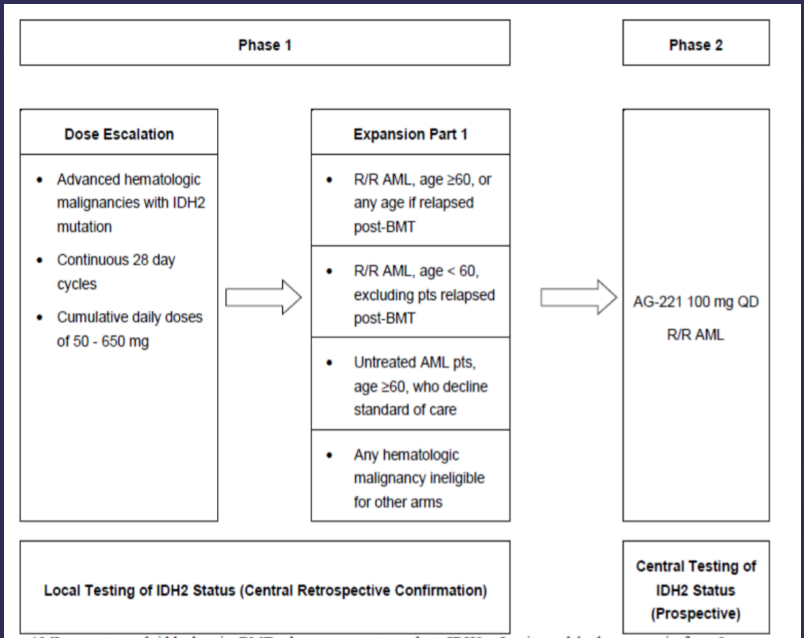
Enasidenib

- **Warnings and precautions**
  - Tumor lysis syndrome
  - Differentiation syndrome
    - Similar to that seen with arsenic trioxide, all-trans-retinoic acid in promyelocytic leukemia
    - Treat with hemodynamic monitoring and support, corticosteroids
  - Leukocytosis
    - May initiate hydroxyurea until WBC < 30,000/mm^3
  - Bilirubin elevation > 3 x ULN
    - Reduce dose to 50 mg; may resume 100 mg if resolution to 2 x ULN or lower
- **Common adverse events (> 20%):** nausea, vomiting, diarrhea, elevated bilirubin, decreased appetite
- **Grade 3/4 adverse reactions (≥ 5 %)**: nausea, diarrhea, tumor lysis syndrome, differentiation syndrome, leukocytosis

ULN = upper limit of normal; WBC = white blood cell.

Enasidenib product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209606s000lbl.pdf.

Enasidenib



AML = acute myeloid leukemia; BMT = bone marrow transplant; IDH2 = Isocitrate dehydrogenase, isoform 2; pts = patients; QD = once daily; R/R = relapsed/refractory.

	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Complete Response	17 (16.5)	13 (12.5)	30 (14.5)
95% CI	(9.9, 25.1)	(6.8, 20.4)	(10.0, 20.0)
Median Duration of Response (months)	11.5	6.5	9.7
95% CI	(5.5, NA)	(3.7, NA)	(5.5, NA)
(Range)	(1.4-16.7)	(1.0-8.4)	(1.0-16.7)
Overall Response Rate	32 (31.1)	31 (29.8)	63 (30.4)
95% CI	(22.3, 40.9)	(21.2, 39.6)	(24.3, 37.2)
Median Duration of Response (months)	5.6	5.6	5.6
95% CI	(2.6, 11.5)	(3.7, NA)	(3.7, 9.7)

Enasidenib product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209606s000lbl.pdf.

Liposomal Daunorubicin and Cytarabine

August 3, 2017

Liposomal Daunorubicin and Cytarabine

- Indications: adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
- This is not your grandmother's 7 + 3
- Liposomal cholesterol membrane of cytarabine and daunorubicin in a 5:1 molar ratio
- Dosing: induction: daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2; liposome over 90 minutes on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed
- Consolidation: daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome over 90 minutes on days 1 and 3

AML-MRC = AML with myelodysplasia-related changes; t-AML = therapy-related AML.

Daunorubicin and cytarabine liposomal product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209401s000lbl.pdf.

Liposomal Daunorubicin and Cytarabine

- **Warnings and precautions**
  - Same as those with 7 + 3
    - Cardiotoxicity, cytopenias, extravasation (daunorubicin)
- **Common adverse events (> 25%):** hemorrhage, febrile neutropenia, rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, decreased appetite, arrhythmia, pneumonia, bacteremia, chills, sleep disorders, and vomiting
- **Grade 3/4 adverse reactions (≥ 10 %)**: febrile neutropenia, dyspnea, pneumonia, bacteremia, hypoxia

Daunorubicin and cytarabine liposomal product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209401s000lbl.pdf.

Liposomal Daunorubicin and Cytarabine

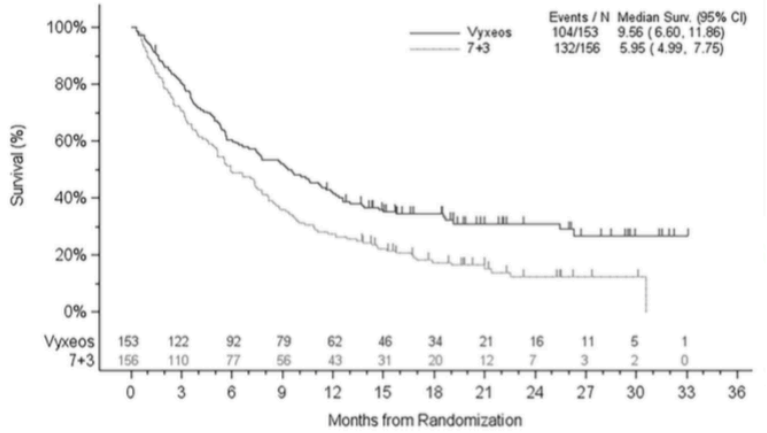


Table 6: Efficacy Results for Study 1

	VYXEOS N=153	7+3 N=156
Overall Survival		
Median survival, months (95% CI)	9.6 (6.6, 11.9)	5.9 (5.0, 7.8)
Hazard ratio (95% CI)	0.69 (0.52, 0.90)	
p–value (2–sided) [a]	0.005	
Complete Response Rate		
CR, n (%)	58 (38)	41 (26)
p value (2–sided) [b]	0.036	

Abbreviations: CI = Confidence interval; CR = Complete Remission
[a] p-value from stratified log rank test stratifying by age and AML sub-type
[b] p-value from Mantel-Haenszel test stratifying by age and AML sub-type

Adverse Reaction [a]	All Grades [b]		Grades 3 to 5 [b]	
	VYXEOS N=153 n (%)	7+3 N=151 n (%)	VYXEOS N=153 n (%)	7+3 N=151 n (%)
Hemorrhage [a]	107 (70)	74 (49)	15 (10)	9 (6)
Febrile Neutropenia	104 (68)	103 (68)	101 (66)	102 (68)
Rash [a]	82 (54)	55 (36)	8 (5)	2 (1)
Edema [a]	78 (51)	90 (60)	2 (2)	5 (3)
Nausea	72 (47)	79 (52)	1 (1)	1 (1)
Diarrhea/Colitis [a]	69 (45)	100 (66)	4 (3)	10 (7)
Mucositis [a]	67 (44)	69 (46)	2 (1)	7 (5)
Constipation	61 (40)	57 (38)	0	0
Musculoskeletal pain [a]	58 (38)	52 (34)	5 (3)	4 (3)
Abdominal pain [a]	51 (33)	45 (30)	3 (2)	3 (2)
Cough [a]	51 (33)	34 (23)	0	1 (1)
Headache [a]	51 (33)	36 (24)	2 (1)	1 (1)
Dyspnea [a]	49 (32)	51 (34)	17 (11)	15 (10)
Fatigue [a]	49 (32)	58 (38)	8 (5)	8 (5)
Arrhythmia [a]	46 (30)	41 (27)	10 (7)	7 (5)
Decreased appetite	44 (29)	57 (38)	2 (1)	5 (3)
Pneumonia (excluding fungal) [a]	39 (26)	35 (23)	30 (20)	26 (17)
Sleep disorders [a]	38 (25)	42 (28)	2 (1)	1 (1)
Bacteremia (excluding sepsis) [a]	37 (24)	37 (25)	35 (23)	31 (21)

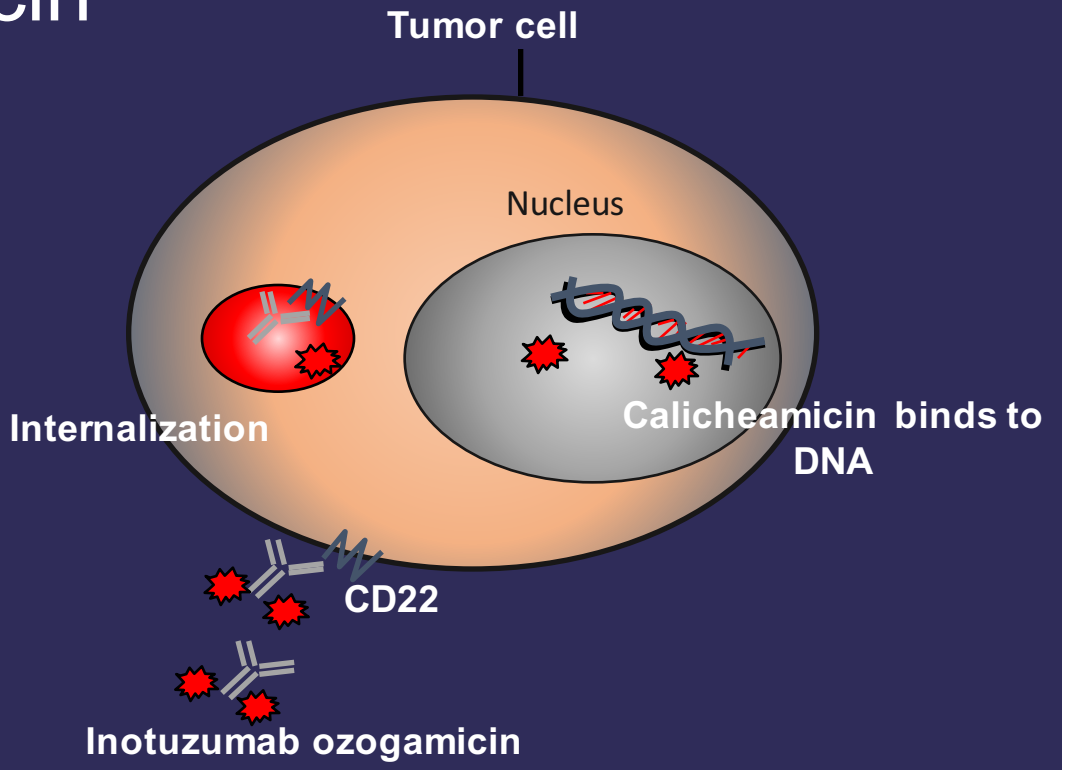
Daunorubicin and cytarabine liposomal product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209401s000lbl.pdf.

Inotuzumab Ozogamicin

August 17, 2017

Inotuzumab Ozogamicin

- Antibody-chemotherapy complex internalized into tumor cells upon binding to CD22 on cell surface
- Cytotoxin calicheamicin is released from the complex inside the tumor cell
  - More potent than other cytotoxic chemotherapeutic agents
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- DNA break development followed by apoptosis of the tumor cell



Jabbour E, et al. ASH 2014. Abstract 794.

Inotuzumab Ozogamicin

- Mechanism: anti-CD22 monoclonal antibody-drug conjugate with calicheamicin
- Indications: adults with relapsed or refractory B-cell precursor ALL
- Dosing
  - Premedicate with corticosteroid, acetaminophen, diphenhydramine

	Day 1	Day 8	Day 15
Dosing regimen for Cycle 1			
All patients:			
Dose	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	21 days[a]		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR or CRi:			
Dose	0.5 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days		
Patients who have not achieved a CR or CRi:			
Dose	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days		

[a] For patients who achieve a CR or a CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e., 7-day treatment-free interval starting on Day 21).

Inotuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf.

Inotuzumab Ozogamicin

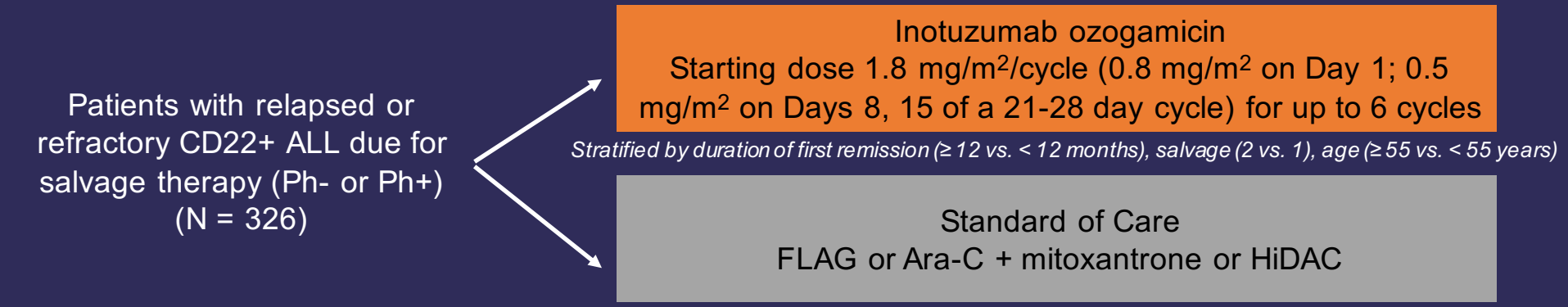
- **Warnings and precautions**
  - Hepatotoxicity/VOD or sinusoidal obstruction syndrome and increased risk of post-stem cell transplant non-relapse mortality
  - Myelosuppression
  - Infusion reactions
  - QT prolongation
- **Common adverse events (> 20%):** thrombocytopenia, neutropenia, infection, anemia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, increased ALT, GGT, bilirubin, abdominal pain
- **Grade 3/4 adverse reactions (≥ 20 %)**: thrombocytopenia, neutropenia, infection, anemia, febrile neutropenia

ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; VOD = veno-occlusive disease.

Inotuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf.

Phase III Trial of Inotuzumab Ozogamicin in Relapsed/Refractory CD22+ ALL

- Multicenter, randomized, open-label phase III study
- Primary endpoints: CR and OS



Inotuzumab dose reduced to 1.5 mg/m^2/cycle once patient achieves CR/Cri.
CR = complete remission; CRi = complete remission with incomplete blood count recovery; OS = overall survival.

ClinicalTrials.gov. NCT01564784.

Inotuzumab Ozogamicin

	CR[a]		CRi[b]		CR/CRi[a,b]	
	BESPONSA (N=109)	HIDAC, FLAG, or MXN/Ara-C (N=109)	BESPONSA (N=109)	HIDAC, FLAG or MXN/Ara-C (N=109)	BESPONSA (N=109)	HIDAC, FLAG, or MXN/Ara-C (N=109)
Responding (CR/CRi) patients						
n (%) [95% CI]	39 (35.8) [26.8-45.5]	19 (17.4) [10.8-25.9]	49 (45.0) [35.4-54.8]	13 (11.9) [6.5-19.5]	88 (80.7) [72.1-87.7]	32 (29.4) [21.0-38.8]
p-value[c]					<0.0001	
DoR[d]						
n	39	18	45	14	84	32
Median, months [95% CI]	8.0 [4.9-10.4]	4.9 [2.9-7.2]	4.6 [3.7-5.7]	2.9 [0.6-5.7]	5.4 [4.2-8.0]	3.5 [2.9-6.6]
MRD-negativity[e]						
n	35	6	34	3	69	9
Rate[f] (%) [95% CI]	35/39 (89.7) [75.8-97.1]	6/19 (31.6) [12.6-56.6]	34/49 (69.4) [54.6-81.7]	3/13 (23.1) [5.0-53.8]	69/88 (78.4) [68.4-86.5]	9/32 (28.1) [13.7-46.7]

Inotuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf.

Tisagenlecleucel: CAR T-Cell Therapeutics

August 30, 2017

CAR T-Cell Derivation

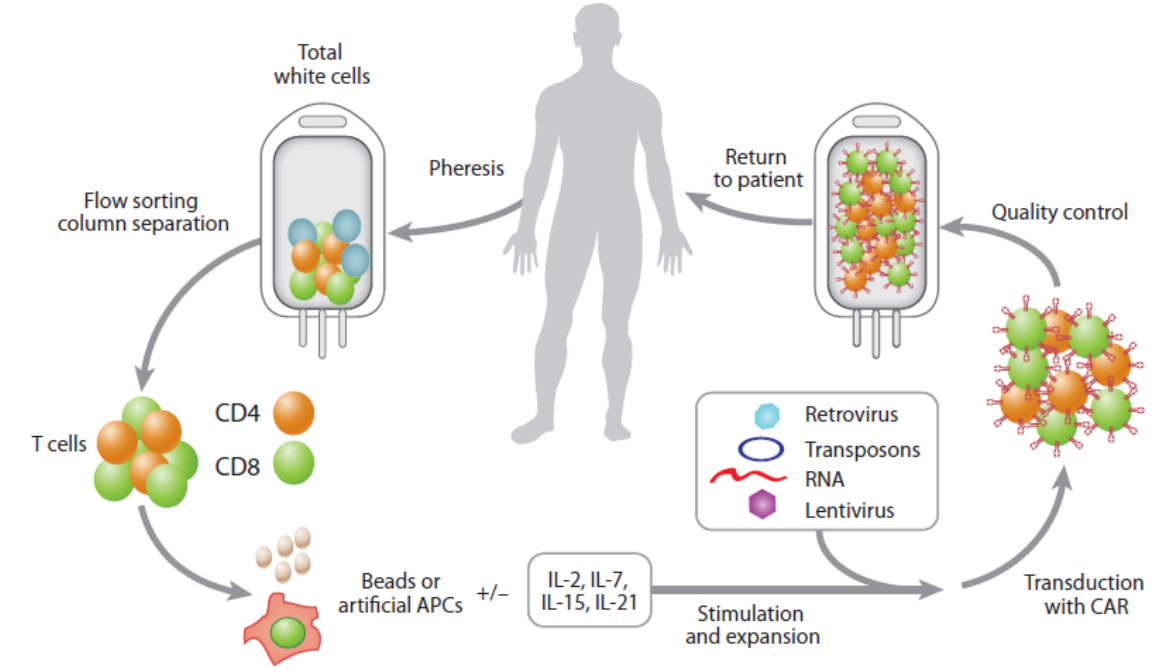


Figure 2

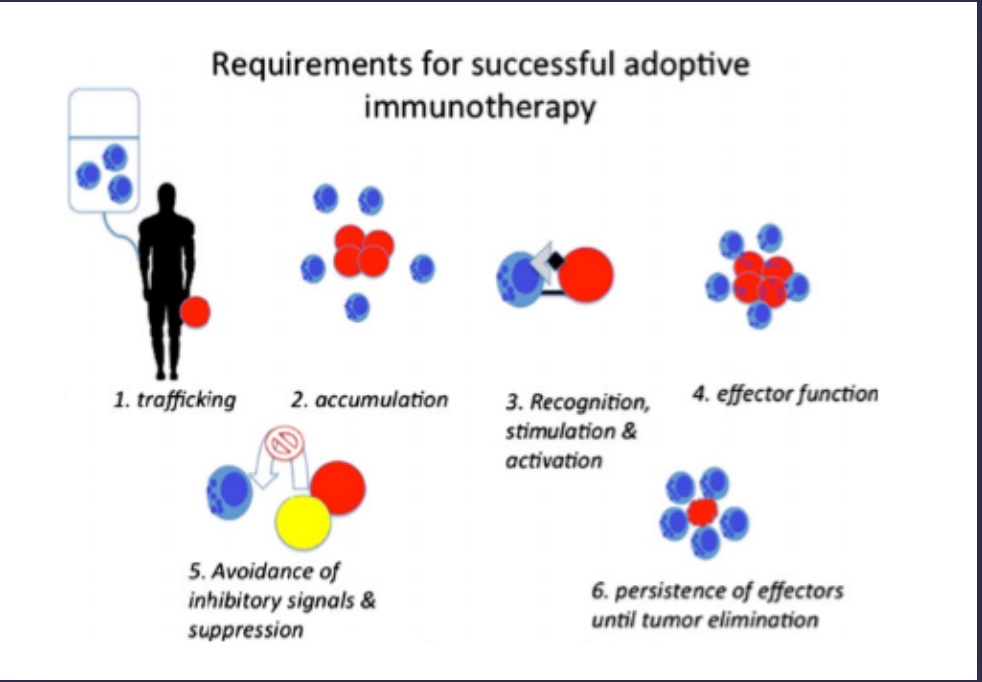
Chimeric antigen receptor (CAR) therapy is similar to an autologous bone marrow transplantation procedure. T cells are collected from the patient by apheresis, and the T cells are expanded and genetically modified using several approaches before they are returned to the patient. Abbreviation: APCs, antigen-presenting cells.

CAR = chimeric antigen receptor.

Barrett DM, et al. *Annu Rev Med* 2014;65:333-47.

CAR T Cells After Infusion

1. T cells traffic to site of disease
2. T cells accumulate at the site of disease by a combination of trafficking and proliferation
3. T cells recognize their cognate target and are activated
4. Leads to induction of effector functions
5. T cells must avoid inhibitor and suppressive signals from the target cells, regulatory immune cells, and the tumor microenvironment
6. T cells must persist until elimination of the tumor



Gill S, et al. *Transl Res* 2013;161:365-79.

CAR T Cells for B-Cell Malignancies

- First investigated at City of Hope and Fred Hutchinson in 2008
- July 1, 2014, FDA granted breakthrough therapy to CTL019
  - Anti-CD19 CAR T developed at U Penn for patients with high-risk B-cell malignancies
- On August 30, 2017, FDA granted regular approval to tisagenlecleucel for the treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse
  - Approval based on single-arm trial of 63 patients with relapsed or refractory pediatric precursor B-cell ALL, including 35 patients who had a prior hematopoietic stem cell transplantation
  - Overall remission rate was 82.5%, consisting of 63% of patients with CR and 19% with CRi

US Food and Drug Administration, FDA approval brings first gene therapy to the United States, August 30, 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm.

Tisagenlecleucel

- Mechanism: CD19-directed genetically modified autologous T-cell immunotherapy
- Indications: patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse
- Dosing
  - One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy followed by infusion of CAR-positive T cells in the product
  - Lymphodepleting chemotherapy: fludarabine (30 mg/m^2 daily for 4 days) and cyclophosphamide (500 mg/m^2 daily for 2 days starting with the first dose of fludarabine)
  - Infuse tisagenlecleucel 2 to 14 days after completion of the lymphodepleting chemotherapy
    - Verify the patient's identity prior to infusion
    - Premedicate with acetaminophen and diphenhydramine
    - Confirm availability of tocilizumab prior to infusion
    - Dosing is based on the number of CAR-positive viable T cells
    - For patients 50 kg or less, administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells
    - For patients above 50 kg, administer 0.1 to 2.5 x 10^8 total CAR-positive viable T cells (non-weight based)

Tisagenlecleucel product information. 2017. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

Tisagenlecleucel

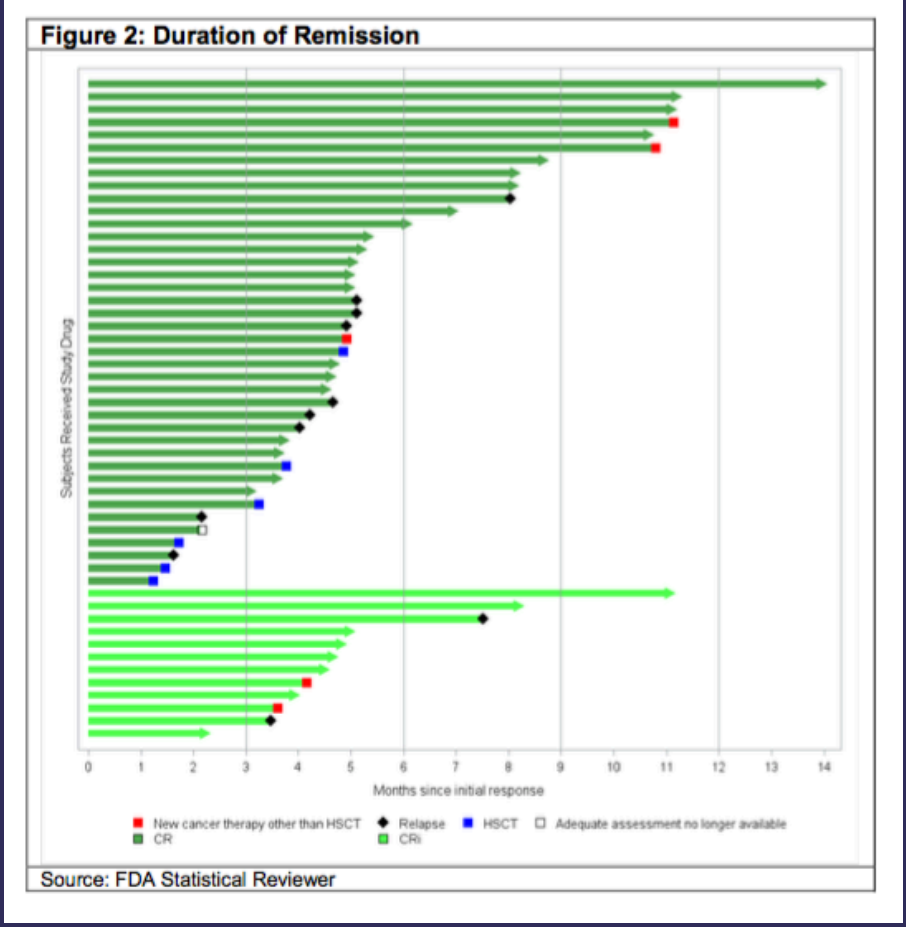
- **Warnings and precautions**
  - Hypersensitivity reactions
  - Serious infections
  - Prolonged cytopenias: patients may exhibit cytopenias for several weeks
  - Hypogammaglobulinemia: monitor and provide replacement therapy until resolution
  - Secondary malignancies
  - Effects on ability to drive and use machines
- **Common adverse events (> 20%): cytokine release syndrome**, hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, and delirium
- **Grade 3/4 adverse reactions (≥ 10 %)**: pyrexia, **cytokine release syndrome**, infections (viral, bacterial), anorexia, encephalopathy, acute kidney injury, hypoxia, pulmonary edema, hypotension, increased AST/ALT/bilirubin, hypokalemia, hypophosphatemia

AST = aspartate transaminase.

Tisagenlecleucel product information. 2017. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

Tisagenlecleucel

- N = 107 patients screened, 88 enrolled, 68 treated, 63 evaluable for efficacy
- Of n = 63
  - 35 males
  - Median age 12 years (3-23)
  - 53 received bridging chemotherapy
  - 30 had one prior allogeneic BMT, 2 had two



BMT = bone marrow transplantation.

Tisagenlecleucel product information. 2017. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf; US Food and Drug Administration, https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm573706.htm.

Gemtuzumab Ozogamicin

September 1, 2017

Gemtuzumab Ozogamicin

- Mechanism: anti-CD33 monoclonal antibody-drug conjugate with calicheamicin
- Indications: treatment of newly diagnosed CD33-positive AML in adults and treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older
- Dosing
  - Premedicate with corticosteroid, acetaminophen, diphenhydramine
  - Newly diagnosed, de novo AML (combination regimen)
    - Induction: 3 mg/m^2 (up to one 4.5-mg vial) on days 1, 4, and 7 in combination with daunorubicin and cytarabine
    - Consolidation: 3 mg/m^2 on day 1 (up to one 4.5-mg vial) in combination with daunorubicin and cytarabine
  - Newly diagnosed AML (single-agent regimen)
    - Induction: 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8
    - Continuation: For patients without evidence of disease progression following induction, up to 8 continuation courses of 2 mg/m^2 day 1 every 4 weeks
  - Relapsed or refractory AML (single-agent regimen)
    - 3 mg/m^2 on days 1, 4, 7

Gemtuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf.

Gemtuzumab Ozogamicin

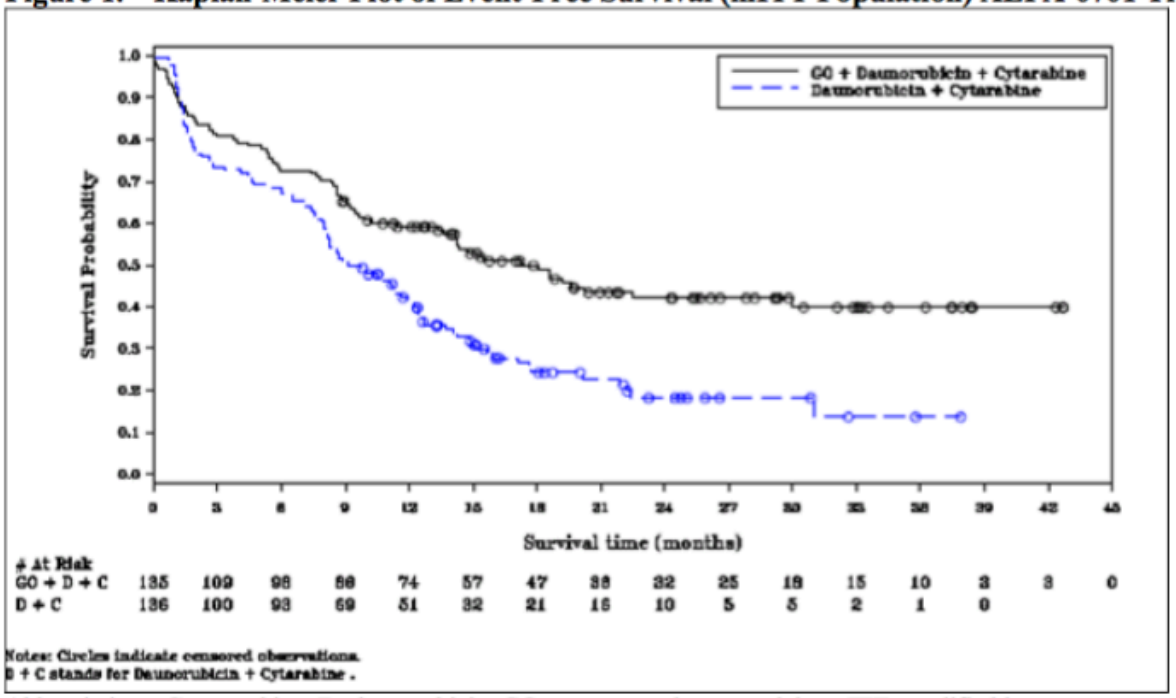
- **Warnings and precautions**
  - Hepatotoxicity, including severe or fatal hepatic VOD, aka SOS
  - Infusion-related reactions (including anaphylaxis); monitor patients during and for at least 1 hour after the end of the infusion; interrupt the infusion, administer steroids or antihistamines, or permanently discontinue treatment as necessary
  - Hemorrhage: severe, including fatal, hemorrhage may occur at recommended doses; monitor platelet counts frequently
- **Common adverse events (> 15%):** hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis
- **Grade 3/4 adverse reactions (≥ 20%)**: fatigue, thrombocytopenia, neutropenia, infection, anemia, febrile neutropenia

SOS = sinusoidal obstruction syndrome.

Gemtuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf.

Gemtuzumab Ozogamicin

Figure 1. Kaplan-Meier Plot of Event-Free Survival (mITT Population) ALFA-0701 Trial



Abbreviations: C=cytarabine; D=daunorubicin; GO=gemtuzumab ozogamicin; mITT=modified intent-to-treat.

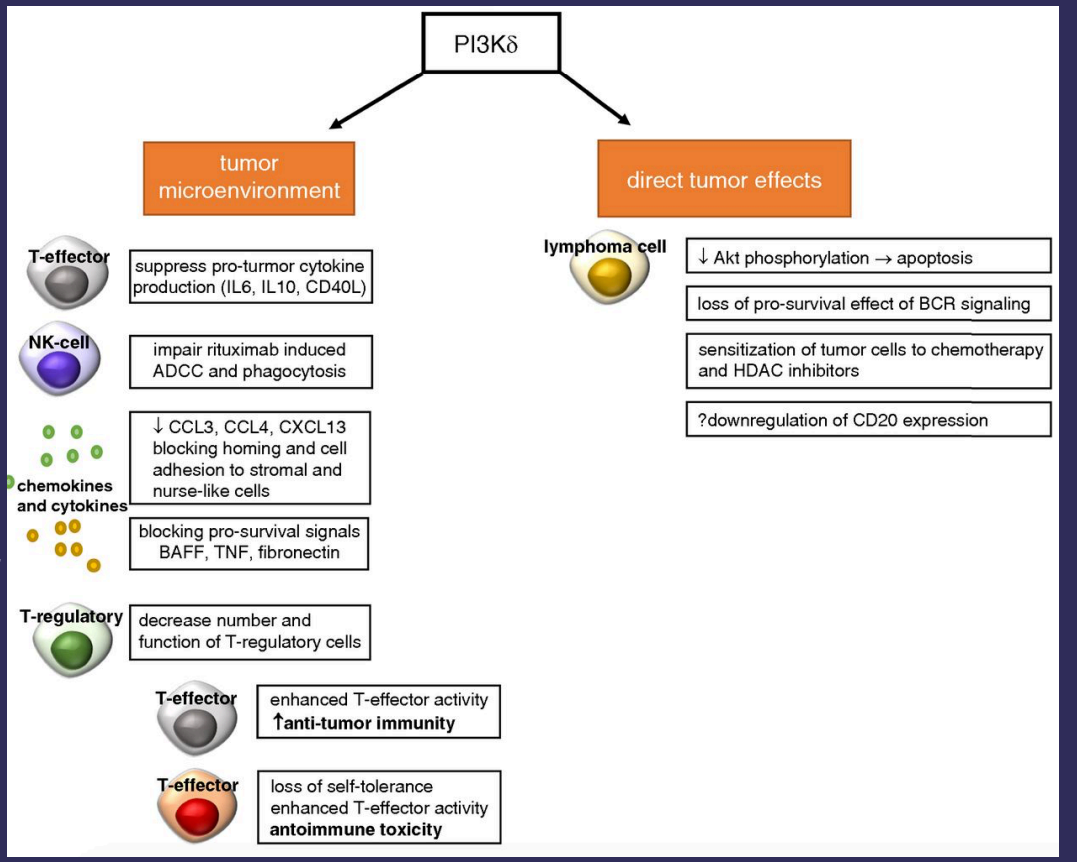
Gemtuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf.

Copanlisib

September 14, 2017

PI3K in Lymphoma

- PI3K regulates
  - Proliferation
  - Differentiation
  - Trafficking
- Four isoforms: α, β, γ, δ
- Copanlisib
  - Inhibits PI3K-α and PI3K-δ isoforms
  - Induces apoptosis and inhibits proliferation of primary malignant B cells
  - Inhibits several key cell-signaling pathways, including BCR signaling, CXCR12 mediated chemotaxis of malignant B cells, and NFκB signaling in lymphoma cell lines



BCR = B-cell receptor; PI3K = phosphotidylinositol-3-kinase.

Cheah CY, et al. *Blood* 2016;128:331-6.

Copanlisib

- Mechanism: PI3Kα and δ inhibitor
- Indications: adult patients with relapsed FL who have received at least two prior systemic therapies (accelerated approval)
- Dosing: 60 mg administered as a 1-hour IV infusion on days 1, 8, and 15 of a 28-day treatment cycle (3 weeks on, 1 week off)
- Drug Interactions
  - Avoid concomitant use with strong CYP3A inducers
  - Strong CYP3A inhibitors: reduce dose to 45 mg

Copanlisib product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf.

Copanlisib

- **Warnings and precautions**
  - Infections: withhold treatment for grade 3 and higher infections until resolution
  - Hyperglycemia: start each infusion once optimal blood glucose control is achieved; withhold treatment, reduce dose, or discontinue treatment depending on the severity and persistence of hyperglycemia
  - Hypertension: withhold treatment in patients until both the systolic less than 150 mmHg and the diastolic less than 90 mmHg; consider reducing dose if anti-hypertensive treatment is required; discontinue in patients with BP that is uncontrolled or with life-threatening consequences
  - NIP: treat NIP and reduce dose; discontinue treatment if grade 2 NIP recurs or in patients experiencing grade 3 or higher NIP
  - Neutropenia: monitor blood counts at least weekly while under treatment; withhold treatment until ANC ≥ 500
  - Severe cutaneous reactions: withhold treatment, reduce dose, or discontinue treatment depending on the severity and persistence of severe cutaneous reactions
- **Common adverse events (> 20%):** hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, thrombocytopenia

ANC = absolute neutrophil count; BP = blood pressure; NIP = non-infectious pneumonitis.

Copanlisib product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf.

Copanlisib

Characteristics	ALIQOPA N=104
Age, years; median (range)	62 (25 to 81)
Caucasian	83%
Male	52%
ECOG performance status (0 or 1)	96%
Number of prior therapies; median (range)	3 (2 to 8)
Time since diagnosis, years; median (range)	5.8 (0.75 to 33.9)
Percent of patients refractory* to:	
last regimen	62%
last anti-CD20 immunotherapy	57%
last alkylating agent	38%
last combination anti-CD20 immunotherapy and alkylating agent	41%

*Refractory: No response or progression of disease within six months of last treatment.

	ALIQOPA N=104
ORR, n (%)	61 (59%)
(95% CI)	(49, 68)
CR, n (%)	15 (14%)
PR, n (%)	46 (44%)
Median* DOR, months (range)	12.2 (0+, 22.6)

ORR = overall response rate; CI = confidence interval; CR = complete response; PR = partial response; DOR = duration of response
*Kaplan-Meier estimate

The median time to response was 1.7 months (range 1.3 to 9.7 months).

Copanlisib product information.2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf.

Conclusions

- A number of novel, first-in-class agents have been approved for the treatment and supportive care of patients with hematologic malignancies
- Each agent has unique profiles and use criteria that should be reviewed prior to prescribing
- Evolving safety and efficacy data, alone and in combinations, are expected over the coming months

2017 JADPRO live AT APSHO