Examining the Pharmacologic Profiles and Appropriate Integration of Treatment Advances in AML

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Disclosures

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Learning Objectives

- Describe the factors that contribute to poor clinical outcomes and the economic burden of AML
- Identify the challenges with the current standard of AML care and traditional therapeutic options in terms of the initiation, tolerability, and toxicity of treatment; and impact on patient survival, hospitalizations, and quality of life
- Assess the role of novel chemotherapeutic formulations and targeted agents in the treatment of AML in terms of clinical outcomes, pharmacologic profiles, reduced toxicity, and pharmacoeconomic data
- Integrate new chemotherapeutic formulations and targeted agents into AML care and pharmacy medication management plans

AML = acute myeloid leukemia.

AML Epidemiology

- Estimated cases for 2018: 19,250
- Estimated annual deaths: 10,670
  - Almost all are in adults
- Median age at diagnosis: 68 years
- 5-year survival rate (2007-2013): 27%

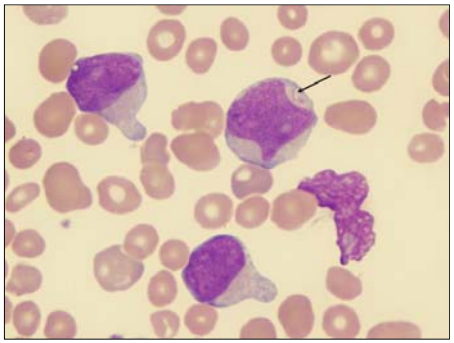
American Cancer Society [website]. Key statistics for AML. https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html/. Accessed January 30, 2018. Howlader N, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/statfacts/html/amyl.html/. Accessed January 30, 2018.

Diagnosis

- At least 20% of cells in peripheral blood or bone marrow are blasts that are myeloid in origin
- Exception includes t(15;17), t(8;21), inv(16), or t(16;16)
  - No blast limit

Vardiman JW, et al. *Blood*. 2009;114(5):937-951.

AML Peripheral Blast Cells



University of Virginia Health System [website]. http://www.healthsystem.virginia.edu/. Accessed January 30, 2018.

AML: Morphologic Classification (FAB Criteria)

Subtype	Description
M0	Undifferentiated; blast cells express myeloid antigens
M1	Acute myeloblastic leukemia with minimal differentiation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M5a	Acute monoblastic leukemia without differentiation
M5b	Acute monoblastic leukemia with differentiation
M6	Acute erythroleukemia
M7	Megakaryocytic leukemia

FAB = French-American-British.
Döhner H, et al. *N Engl J Med*. 2015;373(12):1136-1152.

Risk Factors

- **Age**
  - 50% of people with AML are older than 65 years when diagnosed
- **Smoking**
  - Linked to tobacco smoke exposure
- **Certain chemical exposures**
  - Long-term exposure to products that contain benzene
- **Genetic disorders**
  - Occur more often in people with the following inherited disorders
    - Down syndrome
    - Ataxia telangiectasia
    - Li-Fraumeni syndrome
    - Klinefelter syndrome
    - Fanconi anemia
    - Wiskott-Aldrich syndrome
    - Bloom syndrome
    - Familial platelet disorder

American Cancer Society [website]. What are the risk factors for acute myeloid leukemia? https://www.cancer.org/cancer/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html. Accessed May 30, 2017. Cancer.Net® [website]. American Society of Clinical Oncology (ASCO). 2017. Leukemia – acute myeloid – AML: risk factors. http://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/risk-factors. Approved January 2016. Accessed May 30, 2017.

Risk Factors (cont)

- **High doses of radiation**
  - People who have been exposed to high levels of radiation, such as long-term survivors of nuclear accidents
  - Electromagnetic fields generated by high-voltage electrical wires have not been shown to cause AML
- **Previous cancer chemotherapy**
  - People who have received chemotherapy and/or radiation therapy for other types of cancer, such as breast cancer, ovarian cancer, and lymphoma, have a higher risk of developing AML in the years following treatment
- **Other bone marrow disorders**
  - People who have other bone marrow diseases, including myeloproliferative disorders, can develop AML over time
  - Conditions include
    - Polycythemia vera
    - Myelofibrosis
    - Essential thrombocytosis
    - Myelodysplastic syndrome

American Cancer Society [website]. What are the risk factors for acute myeloid leukemia? https://www.cancer.org/cancer/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html. Accessed May 30, 2017. Cancer.Net® [website]. American Society of Clinical Oncology (ASCO). 2017. Leukemia – acute myeloid – AML: risk factors. http://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/risk-factors. Approved January 2016. Accessed May 30, 2017.

AML: Signs and Symptoms

- **Clinical manifestations**
  - Bone marrow failure: Infection, bleeding, anemia
  - Extramedullary tissue invasion: Granulocytic sarcoma
  - Leukostasis secondary to high WBC count
  - Tumor cell breakdown: Dysregulation of electrolytes (eg, elevated potassium, phosphate, and uric acid; depressed calcium)
    - At risk for tumor lysis syndrome

WBC = white blood cell.
Döhner H, et al. *N Engl J Med*. 2015;373:1136-1152.

Impact of Cytogenetics/Genomics

Risk	Cytogenetic Abnormality	Molecular Mutation
Favorable	Inv(16) t(16;16) t(8;21) t(15;17)	Normal cytogenetics with *NPM1* mutation or isolated *CEBPA*
Intermediate	Normal cytogenetics +8 t(9;11)	Inv(16), t(16;16), t(8;21) with c-*KIT* mutation Mutated *NPM1* without *FLT-ITD* Wild-type *NPM1* without *FLT3-ITD*
Adverse	Complex cytogenetics (>3 abnormalities) 11q23 Inversion 3 t(3;3), or t(6;9) or t(9;22)	Normal cytogenetics with *FLT-ITD* mutation Wild-type *NPM1* and *FLT3-ITD* Mutated *RUNX1*, *ASXL1*, or *TP53*

ITD = internal tandem duplication.
Döhner H, et al. *Blood*. 2017;129(4):424-447.

AML Treatment Goals

Treatment Phase	Goal
Induction	Achieve a remission CR criteria Peripheral neutrophil count >1.0 x 10^9 Platelet count >100 x 10^9 Patient independent of transfusions Bone marrow <5% blasts Absence of blasts with Auer rods Absence of extramedullary disease
Post-remission therapy (consolidation)	Maintain remission and ultimately achieve cure

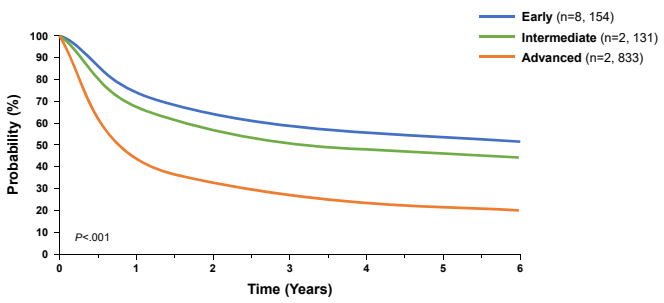
Döhner H, et al. *Blood*. 2010;115(3):453-474.

General Approach to Treatment

Treatment Phase	Drug Therapy
Induction	Cytarabine 100-200 mg/m^2 IV continuous infusion daily x 7 days Daunorubicin 60-90 mg/m^2 IV daily on days 1, 2, and 3 (idarubicin 12 mg/m^2 IV could be substituted for daunorubicin on days 1, 2, and 3) **Bone marrow biopsy conducted at 10-14 days; if residual leukemia, then repeat induction
Consolidation	Cytarabine 3000 mg/m^2 IV Q12H on days 1, 3, and 5 – generally x 4 cycles OR Autologous or allogeneic SCT
Relapse	Reinduction chemotherapy (eg, MEC – mitoxantrone, etoposide cytarabine) Allogeneic SCT Palliative care

IV = intravenous; Q12H = every 12 hours; SCT = stem cell transplantation.
Döhner H, et al. *Blood*. 2017;129(4):424-447.

Allogeneic SCT for AML



Center for International Blood and Marrow Transplant Research [website]. https://www.cibmtr.org/Pages/index.aspx. Accessed February 5, 2018.

Challenges with Traditional Standard of Care with 7+3 Therapy

- 7+3 therapy: 7 days of continuous infusion-dose cytarabine and 3 days of anthracycline, most commonly daunorubicin
  - Typically administered in the inpatient setting
  - Side effects
  - Hospitalizations
  - Complex regimen may increase risk of medication error
- Difficult-to-treat populations
  - Elderly (undertreatment of "healthy" elderly and managing elderly in poor health)
  - Comorbidities
  - Cannot tolerate standard intensive therapy or contraindicated
  - Complex cytogenetics

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Myeloid Leukemia. Version 1.2017. February 24, 2017. www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed December 14, 2017. Nazha A, et al. *Leuk Lymphoma*. 2014;55(5):979-987. Sasine JP, et al. *Blood Rev*. 2015;29:1-9. Meyers J, et al. *Appl Health Econ Health Policy*. 2013;11:275-286.

Need for New Regimens and Targeted Agents

NCCN® AML Guideline Updates

- February 8, 2018: National Comprehensive Cancer Network (NCCN®) adds daunorubicin/cytarabine liposome for injection to the Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for AML
- NCCN Guidelines now include a Category 1 recommendation* for use of daunorubicin/cytarabine liposome for adult patients aged 60 years and older with newly diagnosed t-AML or AML-MRC
- Multiple regimens were added to the preferred section of the treatment induction for high-risk disease recommendations
- Relapsed or refractory disease, a sub-section for clinical trials, was added
- Categories for therapy for AML with IDH2 mutation and therapy for CD33-positive AML were added
- Enasidenib was added as a regimen to AML with IDH2 mutation
- Gemtuzumab ozogamicin was added as a regimen to CD33-positive AML

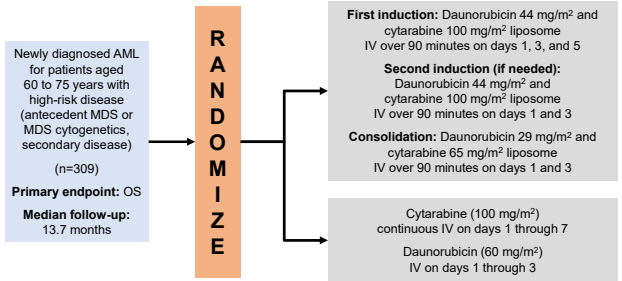
***Category 1 recommendation indicates there is uniform NCCN consensus that daunorubicin/cytarabine liposome is appropriate for these patients based on high-level evidence.**
NCCN = National Comprehensive Cancer Network; t-AML = therapy-related AML; MRC = myelodysplasia-related changes; IDH2 = isocitrate dehydrogenase-2.
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Myeloid Leukemia. Version 1.2017. February 24, 2017. www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed February 15, 2018. Journal of Clinical Pathways [website]. NCCN issues extensive updates to acute myeloid leukemia guideline. February 9, 2018. https://www.journalofclinicalpathways.com/news/nccn-issues-extensive-updates-acute-myeloid-leukemia-guideline. Accessed February 21, 2018.

Daunorubicin/Cytarabine Liposome (CPX-351)

FDA Approval	August 3, 2017
FDA-labeled indication	Treatment of adult patients with newly diagnosed t-AML or AML with MRC
Pharmacology	Combination of anthracycline–DNA intercalation and polymerase inhibition/topoisomerase II inhibitor, and cytarabine (antimetabolite) in 5:1 molar ratio encapsulated in liposomes
Dosing	**First induction:** Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome IV over 90 minutes on days 1, 3, and 5 **Second induction (if needed):** Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome IV over 90 minutes on days 1 and 3 **Consolidation:** Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome IV over 90 minutes on days 1 and 3

FDA = US Food and Drug Administration.
FDA [website]. Approved drugs. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm569950.htm. Accessed February 5, 2018.

Daunorubicin/Cytarabine Liposome (CPX-351)



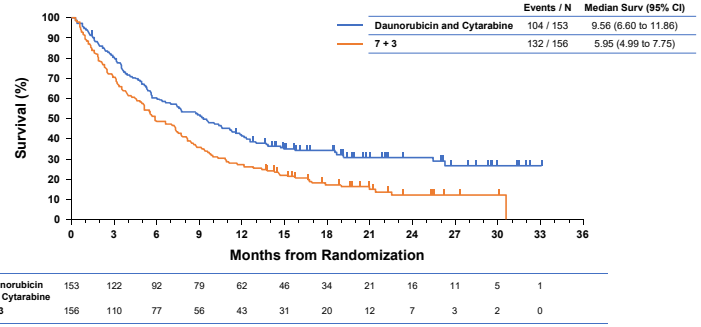
MDS = myelodysplastic syndrome; OS = overall survival.
Lancet JE, et al. *Proc Am Soc Clin Oncol.* 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.

Efficacy Results

Parameter	CPX-351 (n=153)	Standard Cytarabine + Daunorubicin (n=156)
Median OS	9.6 months	5.9 months
EFS	HR=0.74 (*P*=.021)	
CR	38%	26%
All-cause 30-day mortality	6%	11%
60-day mortality	14%	21%

*Similar numbers of patients received SCT in each arm.
EFS = event-free survival; CR = complete remission; HR = hazard ratio.
Lancet JE, et al. *Proc Am Soc Clin Oncol.* 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.

Kaplan-Meier OS Curve



CI = confidence interval.
Lancet JE, et al. *Proc Am Soc Clin Oncol.* 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.

Toxicity (≥ Grade III)

Parameter	CPX-351 (n=153)	Standard Daunorubicin and Cytarabine (n=151)
Hemorrhage	10%	6%
Febrile neutropenia	66%	68%
Bacteremia (excluding sepsis)	23%	21%
Pneumonia (excluding fungal)	20%	17%
Hypoxia	12%	15%
Dyspnea	11%	10%
Non-conduction cardiotoxicity	9%	10%
Fungal infection	7%	6%
Diarrhea/colitis	3%	7%
Delirium	3%	6%
Renal insufficiency	5%	5%

Lancet JE, et al. *Proc Am Soc Clin Oncol.* 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.

CPX-351 Outcomes Summary

- CPX-351 improved outcomes in newly diagnosed, high-risk AML and t-AML
- 53% fewer deaths within 100 days of patients receiving transplantation following a response from induction therapy vs those who received 7+3 regimen
- Long-term analysis: More patients lived longer after transplantation vs those treated with standard 7+3 regimen

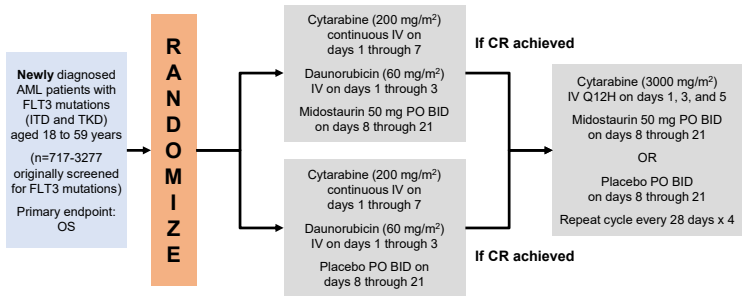
Castellino AM. CPX-351: Better Outcomes in Older High-Risk AML Patients. December 14, 2016. www.medscape.com/viewarticle/873267. Accessed December 14, 2017. Lancet JE, et al. *J Clin Oncol.* 2017;35(15 suppl):7035-7035. Medeiros BC, et al. *J Clin Oncol.* 2017;35:5.

Midostaurin

FDA Approval	April 28, 2017
FDA-labeled indication	Treatment of adult patients with newly diagnosed AML that is FLT3 mutation positive detected by an FDA-approved test in combination with standard cytarabine and daunorubicin and cytarabine consolidation
Pharmacology	• Tyrosine kinase inhibitor of multiple kinases, including FLT3 – including mutant kinases ITD and KIT • Inhibits FLT3 mediated receptor signaling and cell proliferation in leukemic cells
Dosing	**First Induction:** 50 mg PO BID with food on days 8 through 21 **Consolidation:** 50 mg PO BID with food on days 8 through 21 ***Maintenance:** Midostaurin 50 mg PO BID or placebo every 28 days x 12

*Not part of the FDA-labeled dosing.
PO = to take orally; BID = twice daily.
FDA [website]. Approved drugs. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm555756.htm. Accessed February 5, 2018.

Midostaurin in *FLT3* AML



*Maintenance: Midostaurin 50 mg PO BID or placebo every 28 days x 12.

Stone RM, et al. *New Engl J Med*. 2017;377:454-464.

Efficacy Results

Parameter	Midostaurin (n=355)	Placebo (n=354)
Median OS	74.7 months	25.6 months
4-year OS	51.4%	44.3%
Median EFS	8.2 months	3 months
4-year EFS	28.2%	20.6%
Median disease-free survival	26.7 months	15.5 months
SCT performed in first remission (57% of all patients received SCT at some point)	28.1%	22.7%
Protocol-specified CR	59%	54%
Median time to CR	35 days	35 days

Stone RM, et al. *New Engl J Med*. 2017;377:454-464.

Toxicity (≥ Grade III)

Event	Midostaurin (n=355)	Placebo (n=354)
Neutropenia	95%	96%
Leukopenia	26%	30%
Thrombocytopenia	97%	97%
Anemia	93%	88%
Lymphopenia	19%	22%
Infections	52%	50%
Febrile neutropenia	82%	82%
Diarrhea	16%	15%
Hypokalemia	14%	17%
Rash	14%	8%
Fatigue	9%	10%
Pneumonitis/infiltrates	8%	8%

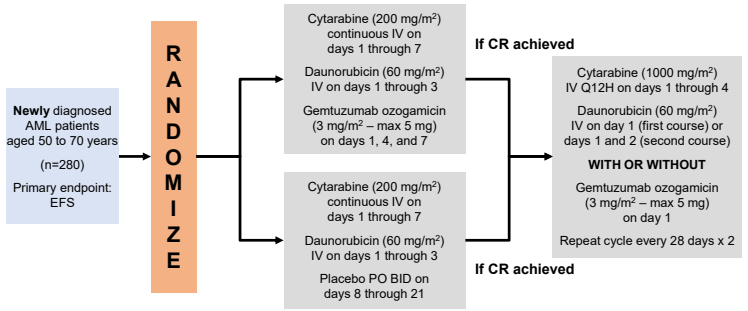
Stone RM, et al. *New Engl J Med*. 2017;377:454-464.

Gemtuzumab Ozogamicin

FDA Approval	September 1, 2017
FDA-labeled indication	Treatment of adult patients with newly diagnosed CD33+ AML or relapsed/refractory CD33+ AML in adults and pediatric patients 2 years and older
Pharmacology	Antibody-drug conjugate with the antibody portion (gemtuzumab) binding to CD33 on AML blast cells and calicheamicin inducing double-strand DNA breaks when released from the linkage to the antibody intracellularly
Dosing	**Induction:** 3 mg/m^2 IV on days 1, 4, and 7 in combination with daunorubicin and cytarabine or 6 mg/m^2 IV on day 1 and 3 mg/m^2 IV on day 8 when given as a single agent **Consolidation:** 3 mg/m^2 (max 4.5 mg) IV on day 1 with daunorubicin and cytarabine or 2 mg/m^2 IV on day 1 every 4 weeks following single-agent induction **Relapsed disease:** 3 mg/m^2 IV on days 1, 4, and 7

FDA [website]. Approved drugs. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574518.htm. Accessed February 5, 2018.

Gemtuzumab Ozogamicin: Front Line



Castaigne S, et al. *Lancet*. 2012;379(9825):1508-1516.

Efficacy Results

Parameter	Gemtuzumab Ozogamicin (n=139)	Standard Chemotherapy (n=139)
EFS	15.6 months	9.7 months
EFS at 24 months	41%	17%
Median OS	34 months	19 months
OS at 24 months	53%	42%
CR	81%	75%
Relapse	35%	44%
Relapse-free survival	28 months	11 months
Resistant disease	12%	21%

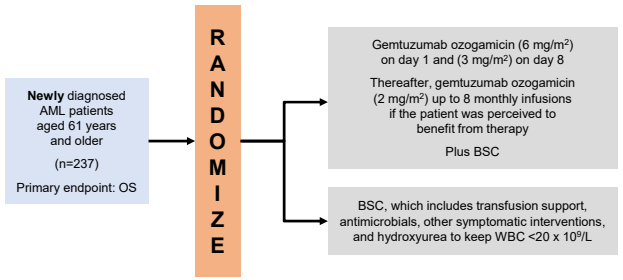
Castaigne S, et al. *Lancet*. 2012;379(9825):1508-1516.

Toxicity (≥ Grade III)

Event	Gemtuzumab Ozogamicin (n=139)	Standard Chemotherapy (n=139)
Neutropenia (<500 mm^3)		
• Post induction	22 days	22 days
• Post 1st consolidation	13 days	10 days
• Post 2nd consolidation	15 days	13 days
Thrombocytopenia		
• Post induction	25 days	21 days
• Post 1st consolidation	17 days	9 days
• Post 2nd consolidation	24 days	13 days
Induction deaths	6%	4%
Transfer to intensive care unit	14%	12%
Infection	47%	41%
Hemorrhage	9%	3%
Cardiac	3%	4%
Hepatic	13%	6%

Castaigne S, et al. *Lancet*. 2012;379(9825):1508-1516.

Gemtuzumab Ozogamicin: Single Agent



BSC = best-supportive care.
Amadori S, et al. *J Clin Oncol.* 2016;34(9):972-979.

Efficacy Results

Parameter	Gemtuzumab Ozogamicin (n=118)	BSC (n=119)
Median OS	4.9 months	3.6 months
6-month OS	46%	29%
12-month OS	24%	10%
All-cause 30-day mortality	11%	14%
CR + CRi (induction)	24%	N/A
CR + Cri (best response)	27%	N/A
Progressive disease	14%	N/A
Induction death	7%	N/A

Amadori S, et al. *J Clin Oncol.* 2016;34(9):972-979.

Toxicity (≥ Grade III)

Parameter	Gemtuzumab Ozogamicin (n=119)	BSC (n=118)
Infection	35%	34%
Febrile neutropenia	18%	24%
Bleeding	13%	12%
Fatigue	12%	21%
Liver	7%	6%
Cardiac	6%	16%
Metabolic	4%	6%
Renal	4%	4%
Death due to any adverse effect	17%	20%

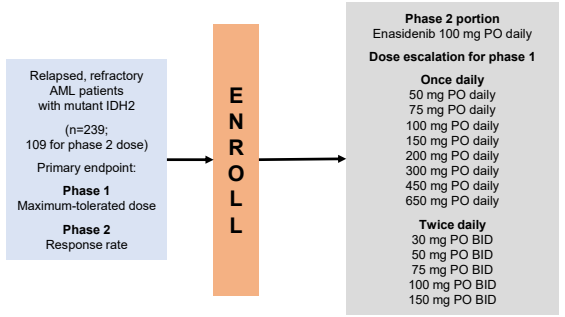
Amadori S, et al. *J Clin Oncol.* 2016;34(9):972-979.

Enasidenib

FDA Approval	August 1, 2017
FDA-labeled indication	IDH2 inhibitor indicated for the treatment of adult patients with relapsed or refractory AML with an IDH2 mutation as detected by an FDA-approved test
Pharmacology	Small-molecule inhibitor of the IDH2 enzyme. Targets the mutant IDH2 variants R140Q, R172S, and R172K leading to decreased 2-HG levels, thereby inducing myeloid differentiation with a net result of reduced blast counts and increased percentages of mature myeloid cells
Dosing	100 mg PO daily until disease progression or unacceptable toxicity – with or without food

2-HG = 2-hydroxyglutarate.
FDA [website]. Approved drugs. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm569482.htm. Accessed February 5, 2018.

Enasidenib



Stein EM, et al. *Blood*. 2017;130(6):722-731. FDA [website]. Approved drugs. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209606orig1s000toc.cfm. Accessed February 5, 2018.

Efficacy Results

Parameter	Enasidenib 100 mg Daily (n=109)	Enasidenib (All Doses) (n=176)
Overall response rate	38%	40%
CR	20%	19%
CRi	6%	7%
PR	3%	6%
Morphologic leukemia-free state	9%	8%
Stable disease	53%	48%
Progressive disease	5%	5%
Median time to first response	1.9 months	1.9 months
Median duration of response	5.6 months	5.8 months

Stein EM, et al. *Blood*. 2017;130(6):722-731. FDA [website]. Approved drugs. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209606orig1s000toc.cfm. Accessed February 5, 2018.

Toxicity (≥ Grade III)

Parameter	Enasidenib 100 mg Daily (n=153)	Enasidenib (All Doses) (n=239)
Hyperbilirubinemia	8%	12%
IDH differentiation syndrome	7%	6%
Anemia	7%	5%
Thrombocytopenia	5%	6%
Tumor lysis syndrome	3%	3%
Decreased appetite	2%	3%
Leukocytosis	1%	3%
Fatigue	1%	3%
Nausea	1%	2%
Lipase increased	1%	2%

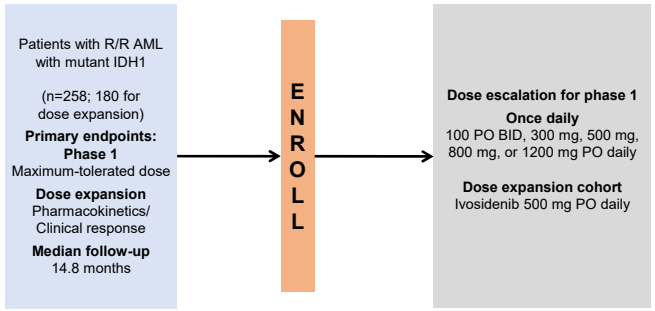
Stein EM, et al. *Blood*. 2017;130(6):722-731. FDA [website]. Approved drugs. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209606orig1s000toc.cfm. Accessed February 5, 2018.

Ivosidenib

FDA Approval	July 20, 2018
FDA-labeled indication	Adult patients with relapsed/refractory AML with a susceptible IDH1 mutation detected by an FDA-approved test
Pharmacology	• Small-molecule inhibitor of the IDH1 enzyme • Targets the mutant IDH1 variant R132 leading to decreased 2-HG levels, thereby inducing myeloid differentiation with a net result of reduced blast counts and increased percentages of mature myeloid cells
Dosing	500 mg PO daily

IDH1 = isocitrate dehydrogenase-1; 2-HG = 2-hydroxyglutarate.
FDA [website]. Approved drugs. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm614128.htm. Accessed September 5, 2018.

Ivosidenib (AG-120) Phase 1 and Dose Expansion



DiNardo CD, et al. *N Engl J Med.* 2018;378;2386-2398.

Toxicity (≥ Grade III)

Event	R/R AML with 500 mg/d (n=179)	Overall Population (n=258)
≥1 treatment-related event ≥ grade III	21%	26%
Prolongation of QT interval on ECG	8%	7%
IDH differentiation syndrome	4%	5%
Anemia	2%	2%
Thrombocytopenia	2%	2%
Leukocytosis	2%	1%
Febrile neutropenia	1%	1%
Diarrhea	1%	1%
Platelet count decreased	3%	1%
Hypoxia	1%	1%

DiNardo CD, et al. *N Engl J Med.* 2018;378;2386-2398.

Efficacy Results

Parameter	Primary Efficacy Population (n=125)	Relapsed or Refractory AML (n=179)
CR or CRh	30%	30%
Overall RR	42%	39%
Median duration of response	6.5 months	NR
Median time to response	1.9 months	NR
Median overall survival	8.8 months	NR
18-month survival	50%	NR
Transfusion independence*	35% for 56 days or more	NR

*Based on 84 patients who required transfusions.
NR = not reported.
DiNardo CD, et al. *N Engl J Med.* 2018;378;2386-2398.

Economic Burden of AML

- **Cost drivers**
  - Hospital reimbursement
  - Physician payments
  - Outpatient hospital payments
  - Home healthcare payments
- **Indirect costs**
  - Caregiver burden
  - Transportation costs
  - Time spent in hospital
  - Home care

Menzin J, et al. *Arch Intern Med.* 2002;162(14):1597-1603. Leunis A, et al. *Leuk Res.* 2013;37(3):245-250. Vaughn JE, et al. *JAMA Oncol.* 2015;1(8):1120-1127. Meyers J, et al. *Value Health.* 2012;15(4)A214. Walter RB, et al. *Clin Adv Hematol Oncol.* 2013;11(9):571-577.

Economic Burden of AML (cont)

- Average direct costs/patient vary widely: $14,000 (BSC) to $353,700 (allogeneic SCT)
- Average direct costs (2012)
  - Induction of remission (1 cycle): $56,802
  - Consolidation (2 cycles): $113,176
- Healthcare costs among patients with AML are primarily driven by inpatient care

Bahmoud D, et al. *Blood*. 2012;120:3614. Zeidan AM, et al. *Exp Rev Hematol*. 2016;9(1):79-89. Leunis A, et al. *Leuk Res*. 2013;37(3):245-250. Vaughn JE, et al. *JAMA Oncol*. 2015;1(8):1120-1127. Meyers J, et al. *Value Health*. 2012;15(4)A214. Walter RB, et al. *Clin Adv Hematol Oncol*. 2013;11(9):571-577.

Drug Acquisition Costs

Drug	Cost
Cytarabine 100 mg	$19.81
Daunorubicin 20 mg	$125.40
Daunorubicin/cytarabine liposome (CPX-351) 44 mg/100 mg	$7750.00
Midostaurin 25 mg (#112)	$15,889.00
Gemtuzumab ozogamicin 4.5 mg	$8200.00
Enasidenib 100 mg (#30)	$24,872.00

Grosse SD, et al. *Thromb Res*. 2016;137:3-10. The University of Utah [website]. Research profiles. Indiana University Health Department of Pharmacy, January 30, 2018.

Cost-Effectiveness of CPX-351 vs 7+3 Regimen based on Health Economic Model

- Phase 3 trial in elderly patients with newly diagnosed t-AML or AML-MRC
- Superior OS (9.56 vs 5.95 months) and improved CR rate (38% vs 26%) with CPX-351 vs 7+3 regimen
- Results
  - Treatment with CPX-351 projected to provide an additional 1.9 years of life vs 7+3 regimen
  - Costs and improved clinical outcomes yield an incremental cost-effectiveness ratio of $111,385/QALY gained over 7+3 regimen
  - Favorable balance between clinical gains and incremental costs of treatment
  - CPX-351 is a cost-effective option in treatment of patients with t-AML or AML-MRC

Kansal A, et al. *Blood*. 2017;130:4674. Lancet J, et al. *J Manag Care Spec Pharm*. 2016;22:4-a:S39.

Summary: Pharmacoeconomics

- Cost of treatment is only one consideration
- Other factors to consider
  - Reduced hospitalizations
  - Improved SE profiles
  - Treatment simplicity to reduce medication errors
  - Genomic testing/targeted agents to reduce inappropriate use of ineffective treatment
  - Newer agents with improved efficacy and tolerability, which may help reduce hospitalizations

Grosse SD, et al. *Thromb Res*. 2016;137:3-10. The University of Utah [website]. Research profiles. Indiana University Health Department of Pharmacy, January 30, 2018.

Emerging Agents

- **Crenolanib:** Phase 2 trials showed positive results; phase 3 trials currently being planned
- **Elacytarabine:** Phase 3 development; received orphan drug designation from FDA and European Medicines Agency; received fast track designation from FDA
- **Gilteritinib:** Phase 3 clinical trials; received orphan drug status and fast track designation from FDA in 2017
- **Quizartinib:** Phase 3 clinical trials (QUANTUM-R studies); granted orphan drug designation from FDA and European Commission in 2015
- **Sapacitabine:** Phase 3 clinical trial (SEAMLESS); alternating schedule with decitabine
- **Sorafenib:** Studied in combination with cytotoxic agents (eg, crenolanib)
- **Vosaroxin:** Phase 3 clinical trials (VALOR)

Fathi AT, et al. *Eur J Haematol*. 2017;98:330-336. Saygin C, et al. *J Hematol Oncol*. 2017;10:93. Kuznar W. OncLive [website]. New AML drugs approved and under investigation in 2017. October 9, 2017. Accessed February 15, 2018. GEN News Highlights. Cyclacel Phase III Sapacitabine AML Study Fails to Meet Primary Endpoint. February 23, 2017. www.genengnews.com/gen-news-highlights/cyclacel-phase-iii-sapacitabine-aml-study-fails-to-meet-primary-endpoint/81253923. Accessed February 15, 2018. Specialist Pharmacy Service [website]. www.sps.nhs.uk. Accessed February 21, 2018.

Role of the Pharmacist

- AML involves a highly specialized patient population
- Supportive care is critical to the survival of these patients, particularly during the induction phase when patients are aplastic for weeks
  - Antibiotics, antifungal, transfusion support
- Risks of bleeding and infection inform all drug-therapy decision making
- Specific training and expertise required
  - Hematology/oncology, infectious diseases, general internal medicine, critical care

Pedersen CA, et al. *Am J Health Sys Pharm*. 2011;68(8):669-688. Gamble KH. Pharmacists' influence growing in hospitals. *Pharmacy Times*. May 31, 2011.

Role of the Pharmacist (cont)

- Reduce medication errors by recommending newer, simplified chemotherapeutic regimens
- Ensure genomic/biomarker testing and recommend therapies that target specific genetic factors to avoid ineffective treatments
- Monitor/mitigate AEs
- Provide patient education on SE potential, treatment regimens, etc
- Educate the clinical team on new and emerging therapies

Pedersen CA, et al. *Am J Health Sys Pharm*. 2011;68(8):669-688. Gamble KH. Pharmacists' influence growing in hospitals. *Pharmacy Times*. May 31, 2011.

Conclusions

- After decades of disappointing clinical research results, the approval of 4 new agents in 2017 has sparked a new wave of interest in the treatment of AML
  - Daunorubicin/cytarabine liposome, gemtuzumab ozogamicin, enasidenib, and midostaurin have generated modest but meaningful improvements in clinical outcomes for patients with AML
  - These new agents require the expertise of pharmacists on the care team to ensure proper education for patients and provision of appropriate supportive care

Questions?