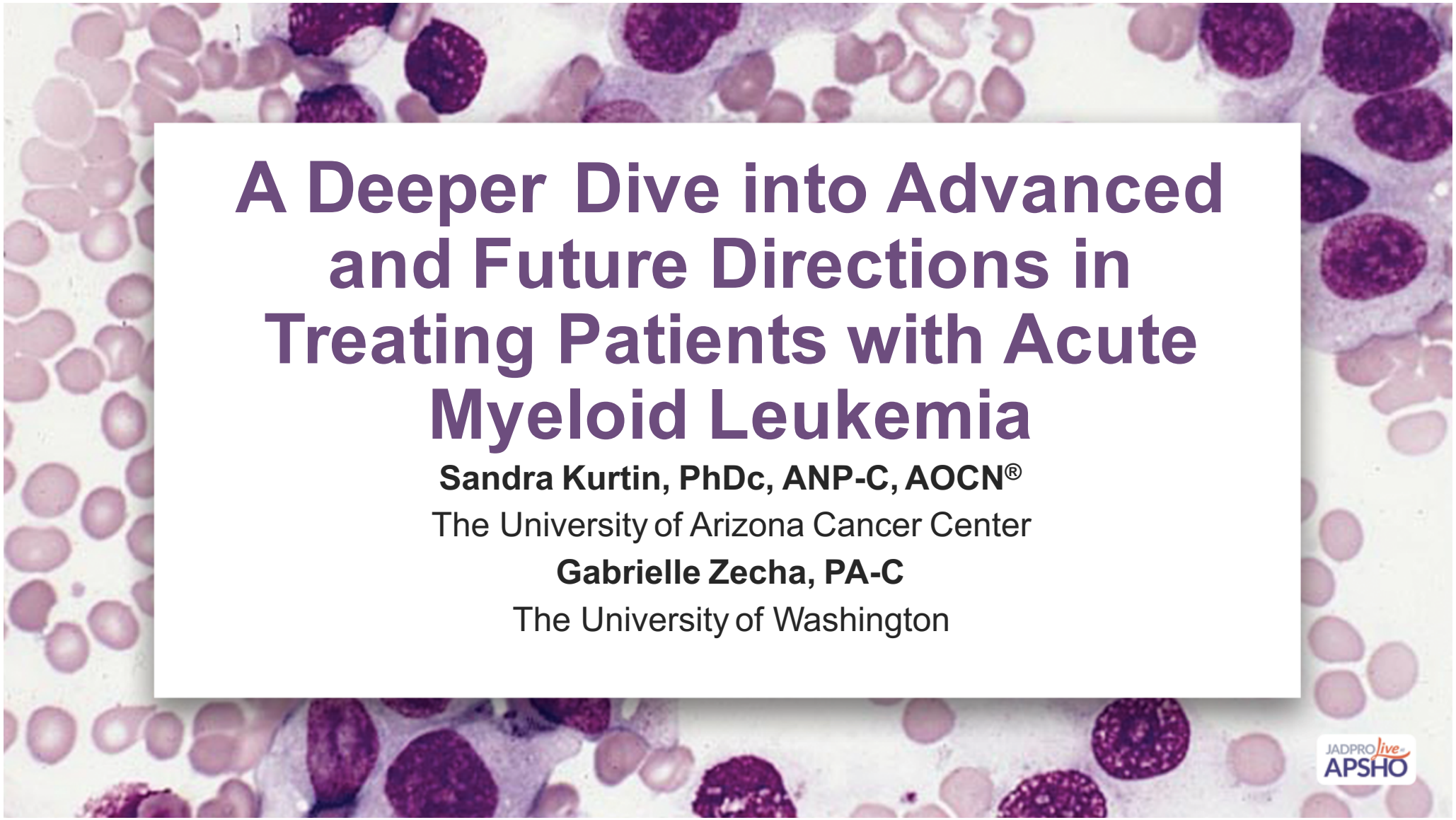


A Deeper Dive into Advanced and Future Directions in Treating Patients with Acute Myeloid Leukemia

Sandra Kurtin, PhDc, ANP-C, AOCN®
The University of Arizona Cancer Center
Gabrielle Zecha, PA-C
The University of Washington

JADPRO Live APSHO

Learning Objectives

- Describe the latest WHO disease definitions for AML
- Recall the mechanism of action for novel therapies for treatment of AML
- Summarize the clinical relevance of molecular mutations in AML, including *FLT3* and *IDH2*
- Identify germline mutations in patients with a predisposition for AML

Financial Disclosure

- Ms. Kurtin served as a consultant for Jazz, Celgene, Novartis, Genentech, and Incyte.
- Ms. Zecha has no disclosures to report.

This activity is supported by unrestricted educational grants from Astellas Pharma Global Development, Inc. and Jazz Pharmaceuticals.

Audience Response Questions

Please indicate the clinical role that best represents you:

1. Physician
2. PA
3. Nurse practitioner
4. Clinical nurse specialist
5. Nurse
6. Pharmacist
7. Other

Please indicate the practice setting that best represents your practice:

1. Academic medical center, teaching hospital, or comprehensive cancer center
2. Community hospital or community cancer center
3. Private/group practice
4. Government or VA
5. Managed care, insurance, employer, or other payer
6. Pharmaceutical/biotech/device industry
7. Other

Please indicate your clinical specialty:

1. Medical oncology
2. Hematology/oncology
3. Radiation oncology
4. Internal medicine
5. Gynecologic oncology
6. Genetics/genetic counseling
7. Other

Please indicate your years in practice:

1. < 1 year
2. 1–5 years
3. 6–10 years
4. 11–15 years
5. 16–20 years
6. > 20 years

Question #1

Your 74-year-old patient was just started on enasidenib, an oral mIDH2 inhibitor that promotes myeloid differentiation of leukemic blasts. He complains of shortness of breath and fever; on auscultation, you hear crackles and note he has pitting ankle edema and a temperature of 101.7 degrees. You suspect:

1. He has neutropenia and has contracted pneumonia
2. He has IDH inhibitor–associated differentiation syndrome
3. He has a cardiac history and needs a cardiac consult
4. He has retinoic acid syndrome
5. I'm unsure

Question #2

Your patient has been diagnosed with relapsed AML after initial treatment. Testing with next-generation sequencing has revealed an *IDH2* mutation. What is your choice of treatment?

1. Enasidenib
2. Gemtuzumab
3. Midostaurin
4. Quizartinib
5. I'm unsure

Question #3

Which recently approved anti-CD33 monoclonal antibody has a history that underscores the importance of examining alternative dosing, scheduling, and administration of therapies for patients with acute myeloid leukemia (AML), especially in those who may be most vulnerable to the side effects of treatment?

1. Ofatumumab
2. Rituximab
3. Gemtuzumab ozogamicin
4. Ipilimumab
5. I'm unsure

Question #4

You have a 67-year-old male patient with *FLT3*-positive AML who received a standard dose of cytarabine and daunorubicin 1 year ago and is now presenting with a relapse. The phase I/II CHRYSALIS study results were the first demonstration of molecular response to a FLT3 inhibitor in AML. Your patient may be a good candidate for the ongoing registrational ADMIRAL trial for patients with relapsed/refractory *FLT3*+ AML. Which therapy is being studied in this trial?

1. Enasidenib
2. Quizartinib
3. Midostaurin
4. Gilteritinib
5. I'm unsure

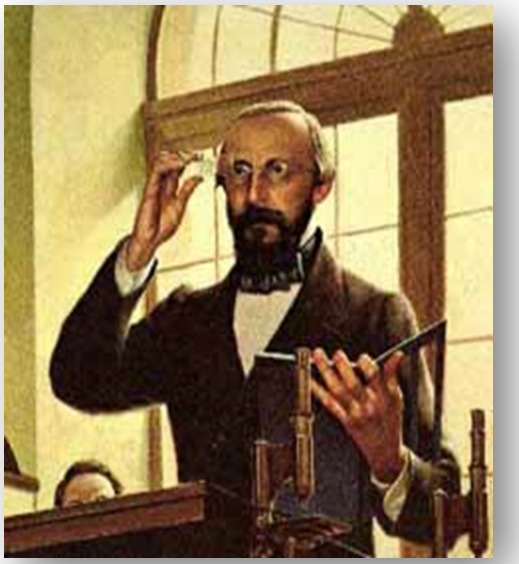
Question #5

Patients receiving high-dose chemotherapy for the treatment of AML are at an increased risk of neutropenic fever and sepsis. So timely initiation of antibiotic treatment is critical. A 2006 study of 2,154 patients showed a survival rate of 80%, if antibiotics are administered within how long after documented hypotension?

1. 24 hours
2. 3 days
3. 1 hour
4. 12 hours
5. I'm unsure

The History of AML

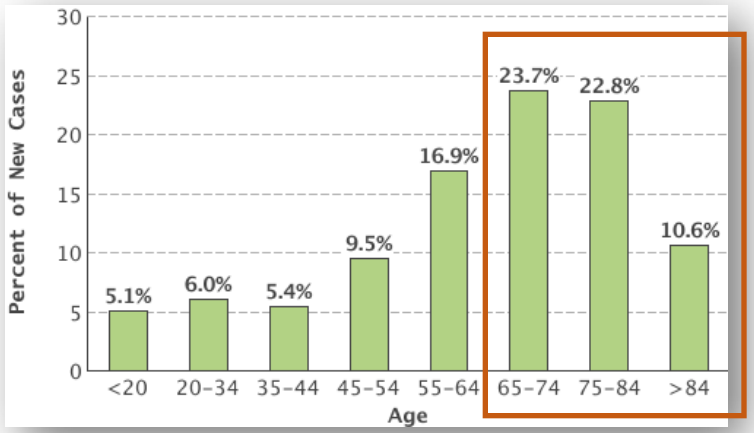
- Acute leukemias represent a group of clonal neoplastic disorders of hematopoietic progenitor cells
- They were first described in 1845 by Dr. Rudolph Virchow



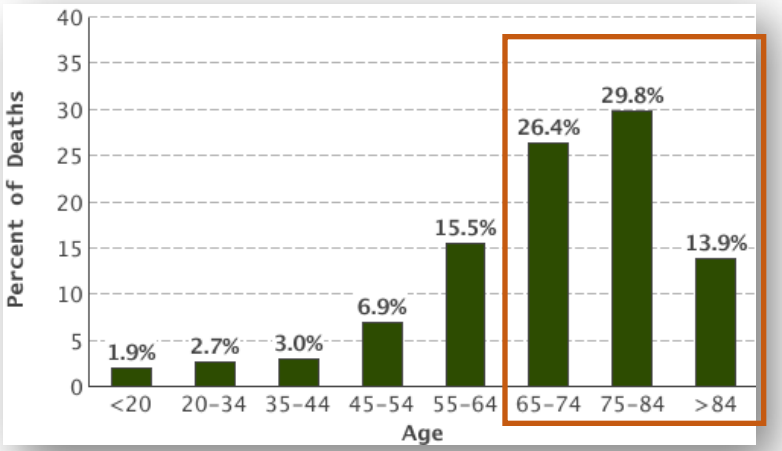
Gilliand, G., & Reffel, G. Molecular Biology of Acute Leukemias. In *Cancer: Principles and Practice of Oncology*, Vincent T. DeVita, Jr., MD; Samuel Hellman, MD; and Steven A. Rosenberg, MD, PhD, eds. Lippincott Williams & Wilkins, 2005 Edition; 2077-2088

AML: New Cases and Deaths

New Cases (US, 2017)	Deaths (US, 2017)	Mean Age at Diagnosis, Years	5-Year OS (US, 2017)
21,380	10,590	68	26.9%



Median Age at Diagnosis = 68



Median Age at Death = 78

National Cancer Institute, Cancer Stat Facts: Acute Myeloid Leukemia (AML), https://seer.cancer.gov/statfacts/html/amyl.html.

Risk Factors

- Unknown in > 80% of patients
- Age, male gender
- Mutagenic/genotoxic stress
- Antineoplastic therapies
  - Therapeutic alkylators (e.g., cyclophosphamide)
  - Topoisomerase II inhibitors (e.g., mitoxantrone, etoposide)
  - HSCT (autologous or allogeneic)
  - Prior treatment for ALL, especially as a child
- Environmental/occupational
  - Ionizing radiation
  - Chemical exposures
    - Benzenes, insecticides
    - Hydrocarbons
- Tobacco, especially after age 60
- Antecedent hematological malignancies - MDS
- Rare, inherited congenital abnormalities
  - Fanconi anemia, familial MDS, Down syndrome

ALL = acute lymphoblastic leukemia; HSCT = hematopoietic stem cell transplantation; MDS = myelodysplastic syndrome.

Presenting Signs and Symptoms

- Generally abrupt onset
- Fever
- Shortness of breath
- Easy bruising, bleeding, petechiae
- Progressive fatigue, malaise
- Weight loss or loss of appetite
- Skin nodules or gingival hyperplasia in selected subtypes

Kurtin S. Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D, Gobel BH, Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 2018. Jones & Bartlett, Burlington, MA.

Diagnostic Evaluation: History and Physical

Evaluation	Clinical Significance
Document onset of suspicious symptoms, acute episodes of illness transfusion history, historical labs	Assist in establishing time for onset of disease Thorough family history needed to identify potential myeloid neoplasms with germ-line predisposition
Review of medication profile	Identification of any drug induced cytopenias potential drug interactions
Comorbid conditions	Effective management of comorbid conditions may play a critical role in selecting potential therapies History of CHF, history of herpes simplex, transfusion history, previous malignancies and treatment of particular interest in AML
Physical Exam	Establish a baseline and identification of any abnormal findings, which may require immediate intervention

AML = acute myelogenous leukemia; CHF = congestive heart failure.

Kurtin S. Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D, Gobel BH, Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 2018. Jones & Bartlett, Burlington, MA.

Diagnostic Evaluation: Peripheral Blood

Diagnostic Study	Clinical Significance
LDH, uric acid, PO4,Ca++, K+	Tumor lysis screen, elevated LDH is a poor prognostic indicator
LDH, haptoglobin, reticulocyte count, coombs	Evaluate for possible underlying hemolysis
Coagulation profile Fibrinogen, PT, PTT, D-dimer	Presence of DIC—particularly important in APL
HLA typing	For possible BMT
Lumbar puncture	CNS involvement
Hepatitis A, B, C; HIV-1 testing	Increased risk of treatment-related morbidity
Serum pregnancy testing	Women of childbearing age

APL = acute promyelocytic leukemia; BMT = bone marrow transplant; CNS = central nervous system; DIC = disseminated intravascular coagulation; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time.

Kurtin S. Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D, Gobel BH, Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 2018. Jones & Bartlett, Burlington, MA; Döhner H, et al. *Blood* 2017;129(4):424-47.

Diagnostic Evaluation: Bone Marrow

Diagnostic Study	Clinical Significance
Aspirate (should include spicules and be cellular enough to assess at least 500 cells)	• Evaluation of morphological abnormalities of hematopoietic precursors to allow WHO classification • Used for flow cytometry (immunophenotyping), FISH, cytogenetics, and molecular testing • A marrow or blood blast count of ≥ 20% is required, except for AML with t(15;17), t(8;21), inv(16), or t(16;16); myeloblasts, monoblasts, and megakaryoblasts are included in the blast count • In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents
Biopsy (should be adequate size for evaluation [2 cm-2.5 cm])	• Evaluate cellularity, topography, exclusion of other bone marrow disorders • Two cores may be obtained in patients that are dry taps • Peripheral blood may assist in the these cases in patients with elevated WBC and circulating blasts

FISH = fluorescent in situ hybridization; WBC = white blood cell; WHO = World Health Organization.

Kurtin S. Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D, Gobel BH, Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 2018. Jones & Bartlett, Burlington, MA.
Döhner H, et al. *Blood* 2017;129(4):424-47.

Molecular/Genetic Testing

- Cytogenetics
  - Metaphase: 20 metaphases, ≥ 2 metaphases considered non-random
  - FISH
- Screening for gene mutations
  - *NPM1, CEBPA, RUNX1, FLT3, TP53, ASXL1, IDH2*
- Screening for gene rearrangements
  - PML-RARA, CBFB-MYH11, RUNX1-RUNX1T1, BCR-ABL1, other fusion genes

Döhner H, et al. *Blood* 2017;129(4):424-47.

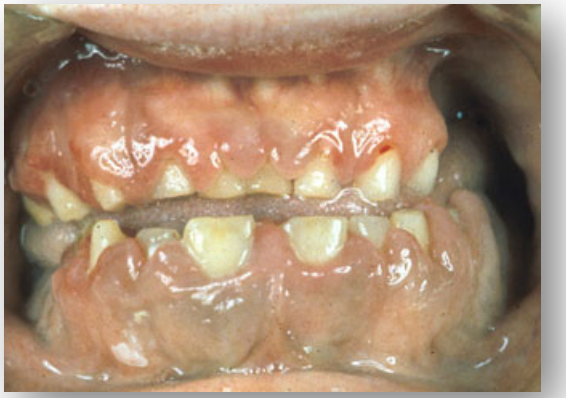
Diagnostic Evaluation: Radiology

Diagnostic Study	Clinical Significance
Chest x-ray	Baseline evaluation, presence of infection
12 lead EKG	Baseline cardiac function
MUGA scan, echocardiogram	Baseline cardiac function
CT of the brain without contrast	If CNS disease or hemorrhage is suspected
MRI of the brain	If leukemic meningitis is suspected
PET/CT	if clinical suspicion for extramedullary disease
Central line placement	Required for treatment and supportive care

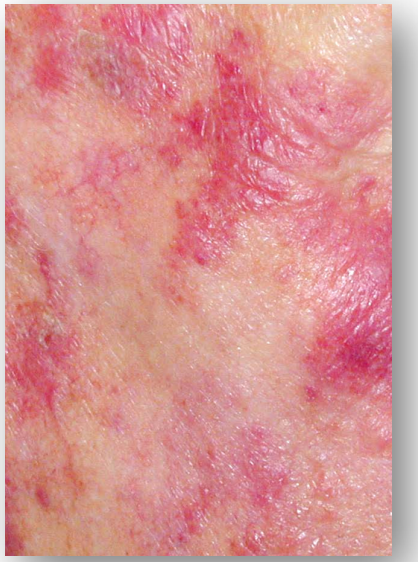
CT = computed tomography; EKG = electrocardiogram; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PET = positron emission tomography.

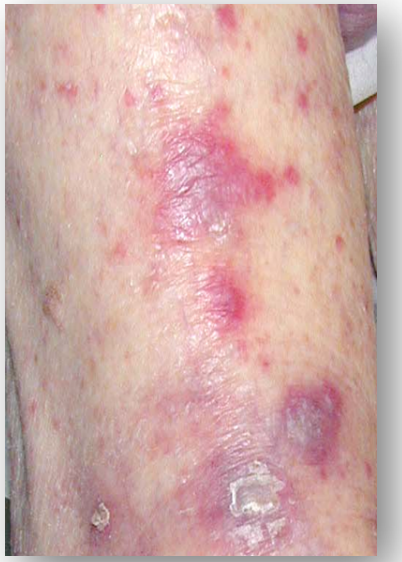
Kurtin S. Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D, Gobel BH, Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 2018. Jones & Bartlett, Burlington, MA; O'Donnell MR, et al. *J Natl Compr Canc Netw* 2017;15(7):926-57.

Cutaneous Manifestations



Gingival Hyperplasia





Leukemia Cutis

Images courtesy of Sandra Kurtin, University of Arizona Cancer Center.

2016 Revision of the WHO Classification of Myeloid Neoplasms

New classification system is focused on underlying mutations/molecular profile

- **Myeloid neoplasms with germ-line predisposition without a preexisting disorder or organ dysfunction**
  - AML with germ-line *CEBPA* mutation
  - Myeloid neoplasms with germ-line *DDX41* mutation
- **Myeloid neoplasms with germ-line predisposition and preexisting platelet disorders**
  - Myeloid neoplasms with germ-line *RUNX1* mutation
  - Myeloid neoplasms with germ-line *ANKRD26* mutation
  - Myeloid neoplasms with germ-line *ETV6* mutation
- **Myeloid neoplasms with germ-line predisposition and other organ dysfunction**
  - Myeloid neoplasms with germ-line *GATA2* mutation
  - Myeloid neoplasms associated with bone marrow failure syndromes
  - Juvenile myelomonocytic leukemia associated with neurofibromatosis, Noonan syndrome, or Noonan syndrome-like disorders
  - Myeloid neoplasms associated with Noonan syndrome
  - Myeloid neoplasms associated with Down syndrome

Arber DA, et al. *Blood* 2016;127(20):2391-405.

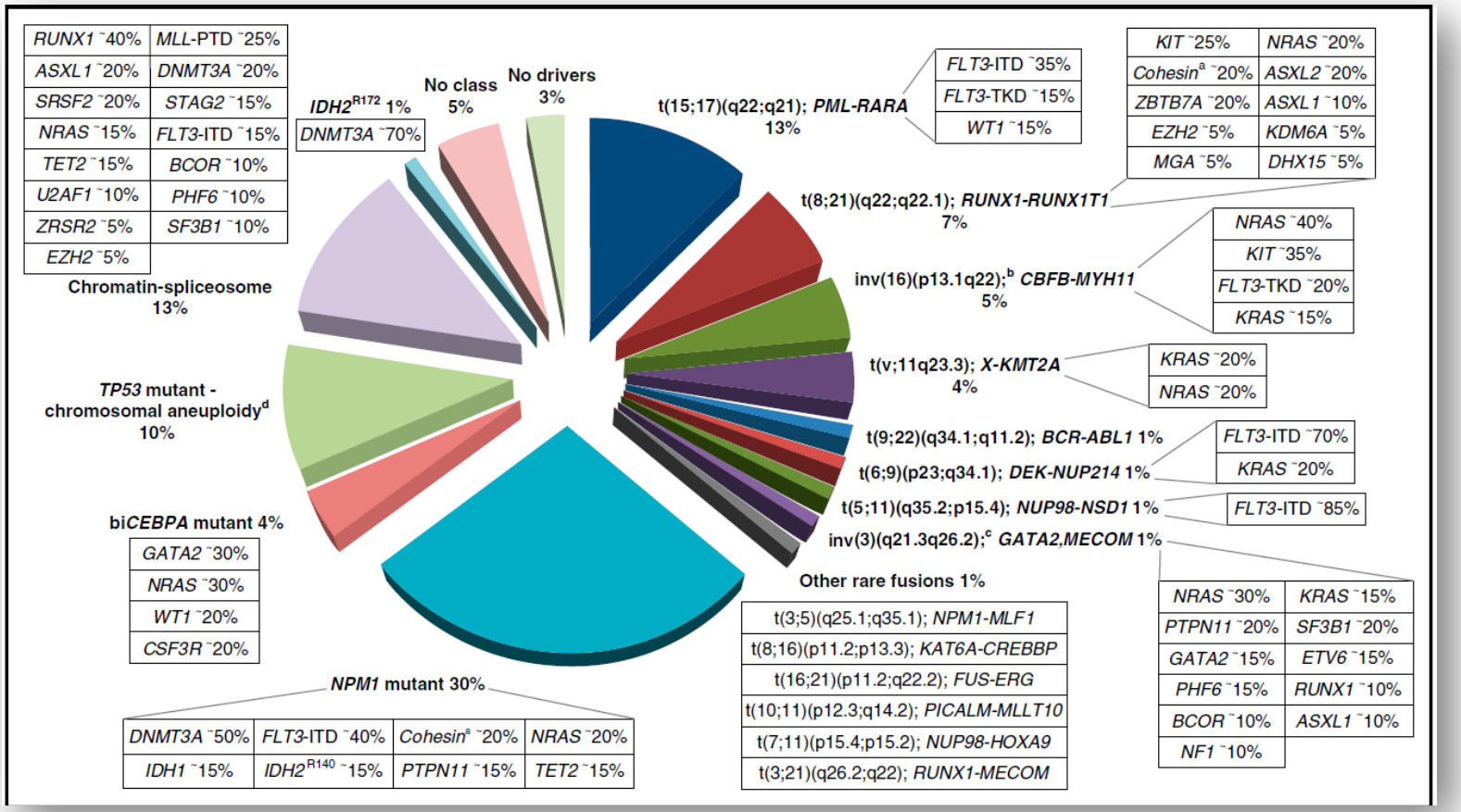
2016 Revision of the WHO Classification: AML and Related Neoplasms

AML is a complex, dynamic disease, characterized by multiple somatically acquired driver mutations, coexisting competing clones, and disease evolution over time.

- **AML with recurrent genetic abnormalities**
  - AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
  - APL with PML-RARA
  - AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
  - AML with t(6;9)(p23;q34.1);DEK-NUP214
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
  - Provisional entity: AML with *BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - Provisional entity: AML with mutated *RUNX1*
- **AML with myelodysplasia-related changes**
- **Therapy-related myeloid neoplasms**
- **AML, not otherwise specified**
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Pure erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis

Arber DA, et al. *Blood* 2016;127(20):2391-405.

Molecular Classes of AML and Concurrent Gene Mutations in Adult Patients up to age ~65 Years



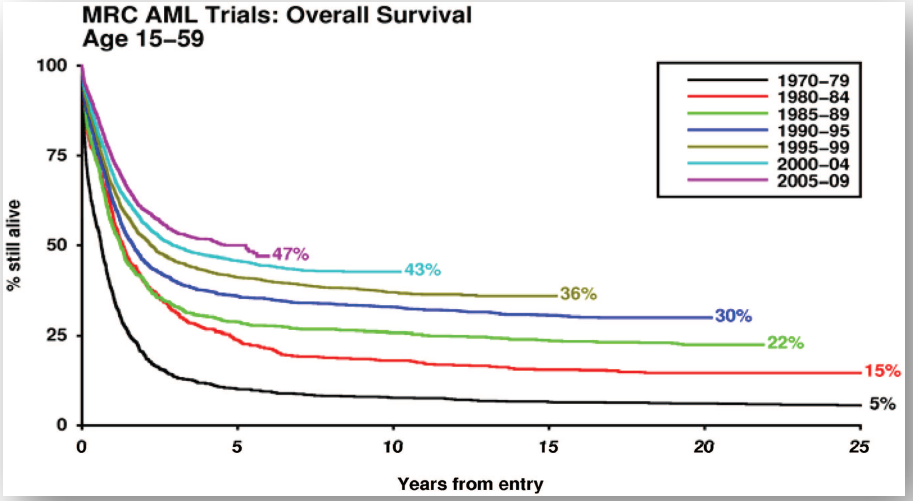
Döhner H, et al. *Blood* 2017;129(4):424-47.

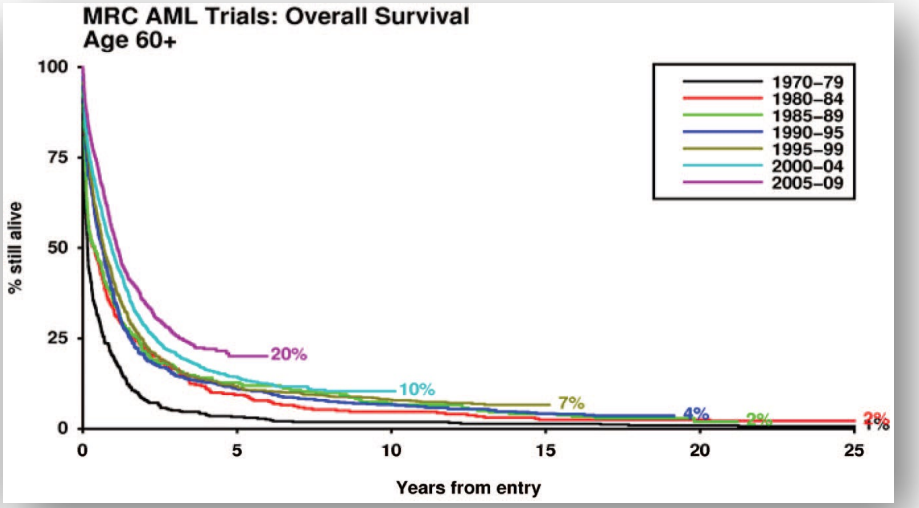
Risk Stratification: Factors Associated with Poor Risk

- Not considered candidates for intensive therapy
  - Physiologic age
  - Poor performance status
  - Complex or poorly controlled comorbidities
- AML-related genetic factors

Arber DA, et al. *Blood* 2016;127(20):2391-405.

Risk Stratification: Age





Burnett AK. *Hematology Am Soc Hematol Educ Program* 2012;2012:1-6.

2017 ELN Risk Stratification by Genetics: AML

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{Low}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{High}
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{Low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse

ELN = European Leukemia Network; ITD = internal tandem duplication.

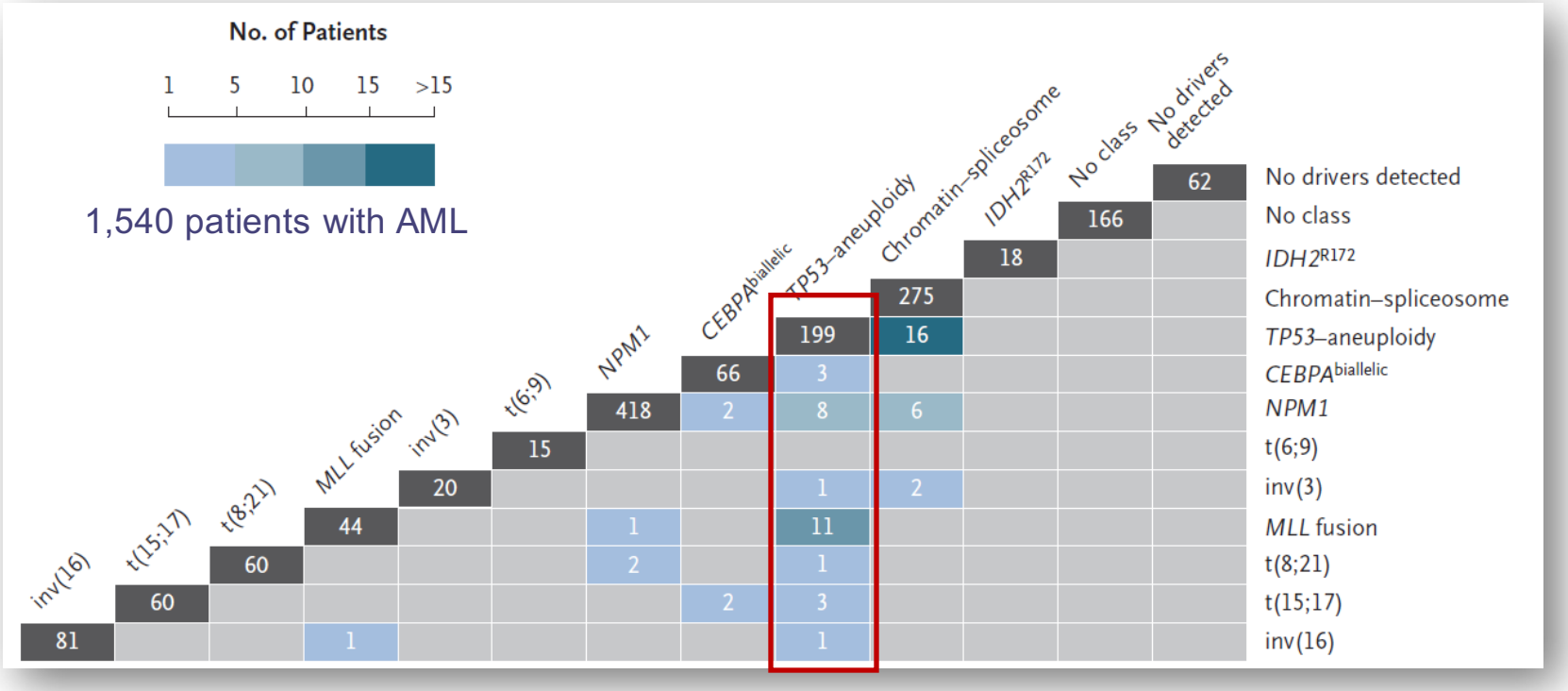
Döhner H, et al. *Blood* 2017;129(4):424-47.

2017 ELN Risk Stratification by Genetics: AML

Risk Category	Genetic Abnormality
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM (EVI1)*
	-5 or del(5q); -7; -17/ abnormal (17p)
	Complex karyotype; monosomal karyotype
	Wild-type *NPM1* and *FLT3*-ITD^{High}
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*

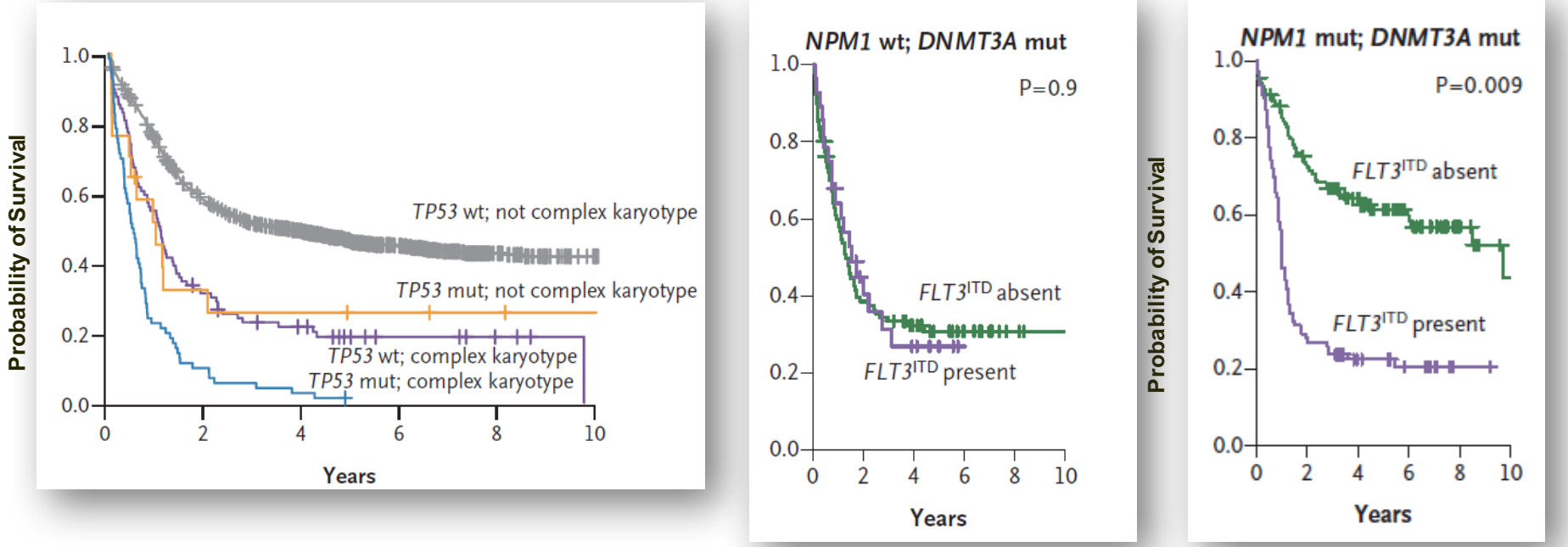
Döhner H, et al. *Blood* 2017;129(4):424-47.

Predominant Driver Mutations in AML



Papaemmanuil E, et al. *N Engl J Med* 2016;374(23):2209-21.

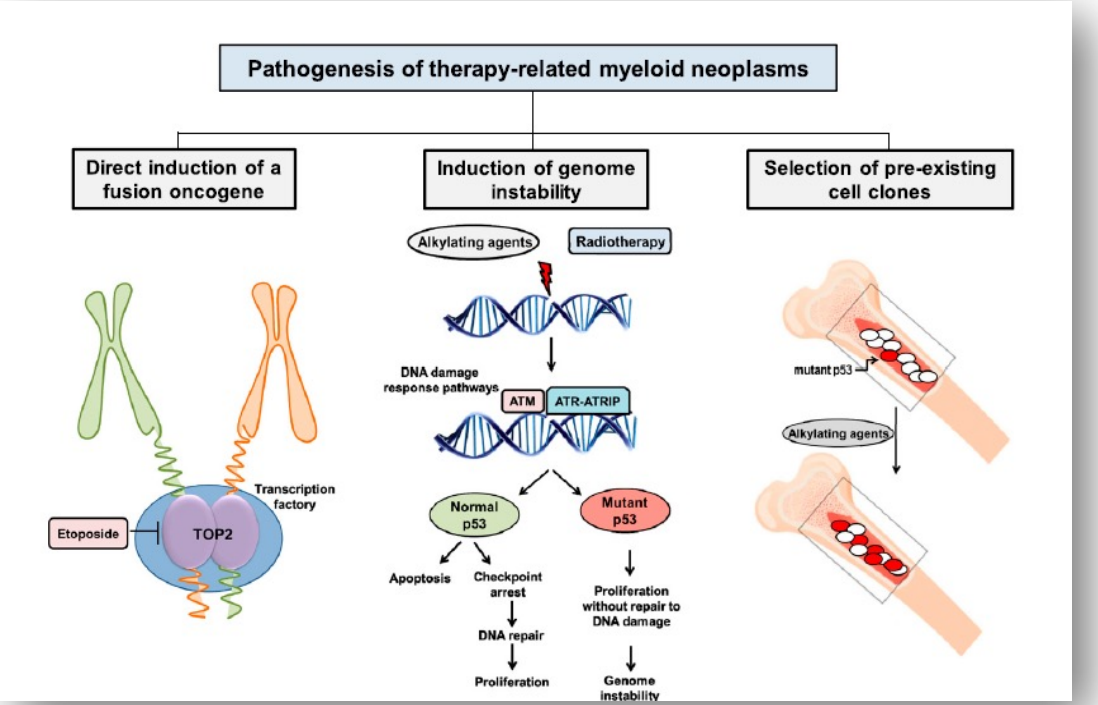
Probability of Survival Estimates: *TP53, NPM1, FLT3*



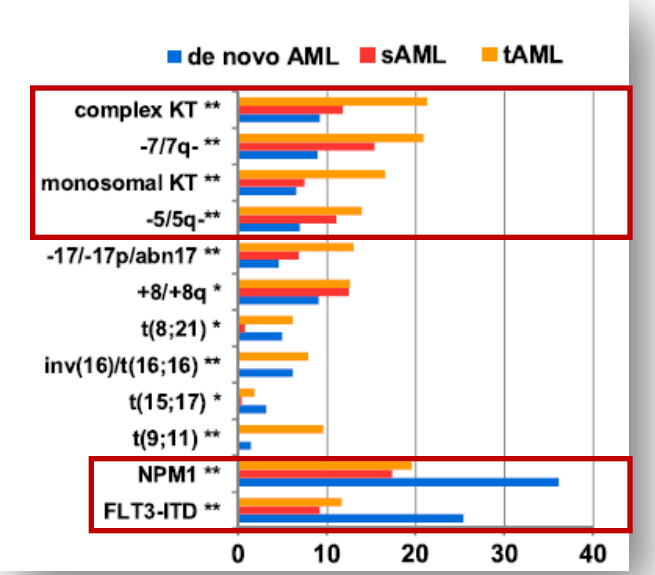
Papaemmanuil E, et al. *N Engl J Med* 2016;374:2209-21.

Therapy-Related Myeloid Neoplasms

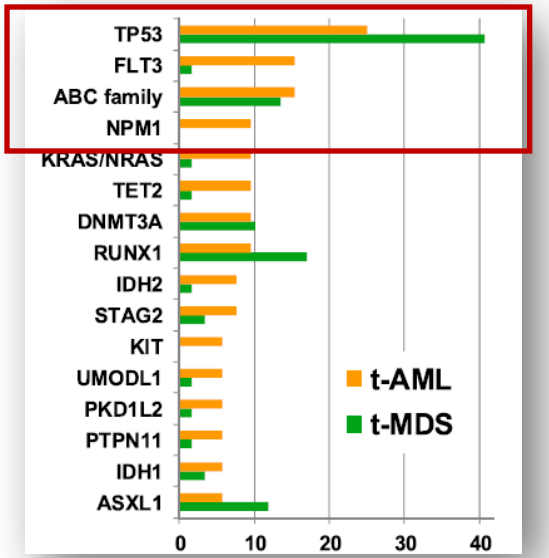
- Time to onset varies by treatment
- Alkylating agents/radiotherapy: latency period of 5-10 years
- Topoisomerase II inhibitors: latency period 2-3 years



Cytogenetic and Molecular Attributers in tAML, tMDS, and sAML



Frequency % of cytogenetic aberrations (n = 3,654)



Frequency % of molecular aberrations (n = 102)

sAML = secondary AML; tAML = therapy-related AML; tMDS = therapy-related MDS.

Indications to Treat and Goals of Therapy

- Treatment is initiated at the time of diagnosis
  - Delay in induction therapy for 7 days does not effect outcomes in older patients—allows for complete characterization of disease
  - The majority of adults with AML who achieve a CR eventually relapse and few are cured
  - Determining suitability for transplant is a critical part of treatment decision making
  - Aggressive therapy as bridge to transplant vs. palliative approach
- Induction therapy
  - Suppression of the malignant clone with induced hypoplasia, resolution of extramedullary sites of disease
- Consolidation and maintenance therapy
  - Achieving a durable molecular remission with eradication of minimal residual disease
  - Sustain MRD-negative status
- Allogeneic bone marrow transplantation remains the only potentially curative therapy for AML
- Aggressive supportive care required regardless of therapeutic intent (transfusions, antibiotics)

CR = complete remission.

Kurtin S. Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D, Gobel BH, Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 2018. Jones & Bartlett, Burlington, MA; O'Donnell MR, et al. *J Natl Compr Canc Netw* 2017;15(7):926-57.

Eligibility for Intensive Therapy: HCT-CI

Comorbidity	Definition in HCT-CI	Score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or EF $\leq$ 50%	1
Gastrointestinal	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring insulin or oral hypoglycemic	1
Cerebrovascular disease	TIA or CVA	1
Psychiatric	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 ULN, or AST/ALT > ULN to 2.5 ULN	1
Obesity	Patients with a BMI > 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CVA = cerebrovascular accident; EF = ejection fraction; HCT-CI = Hematopoietic Cell Transplantation-Comorbidity Index; TIA = transient ischemic attack; ULN = upper limit of normal.

Sorror ML et al. *Blood* 2005;106:2912–9; Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56; Sorror ML, et al. *JAMA Oncol* 2017 [Epub ahead of print].

Eligibility for Intensive Therapy: HCT-CI

Comorbidity	Definition in HCT-CI	Score
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or PMR	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLco and/or FEV1 66–88% of dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer	3
Heart valve disease	Except mitral valve disease	3
Severe pulmonary	DLco and/or FEV1 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 ULN, or AST/ALT > 2.5 ULN	3

CTD = connective tissue disorder; DLco = diffusing capacity of lungs for carbon monoxide; FEV1 = forced expiratory volume 1 sec; PMR = polymyalgia rheumatica; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

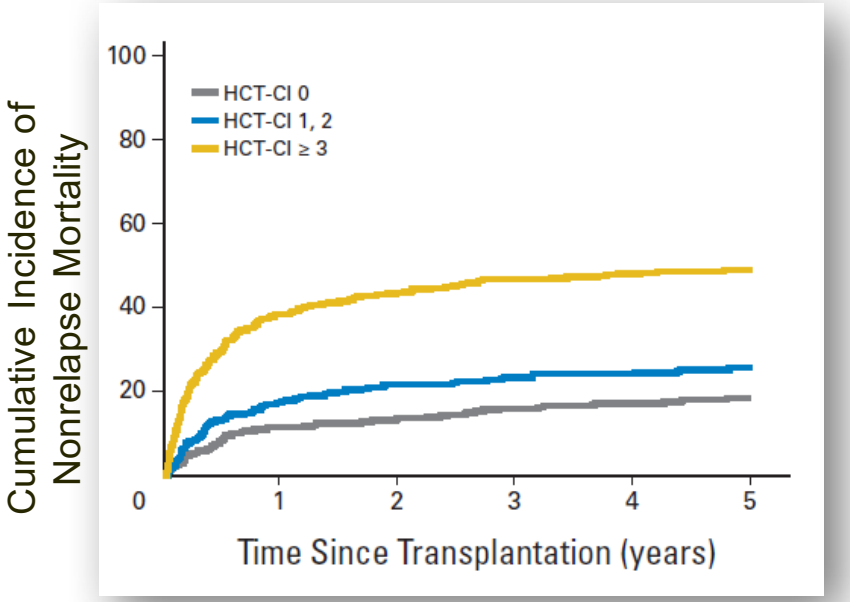
Sorror ML et al. *Blood* 2005;106:2912–9; Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56; Sorror ML, et al. *JAMA Oncol* 2017 [Epub ahead of print]; Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), http://www.hctci.org.

Eligibility for Intensive Therapy: HCT-CI AML Composite Score

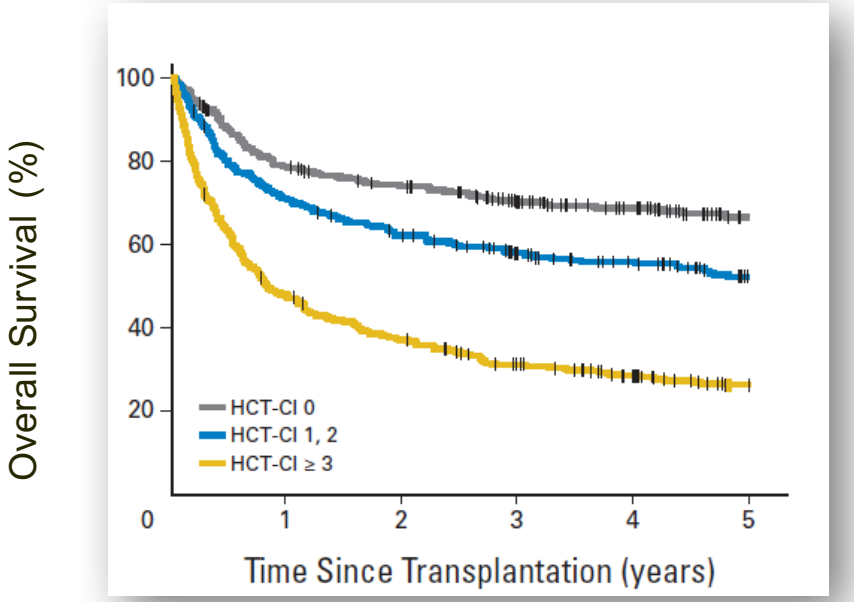
Additional Factors	Definition in HCT-CI	Score
Age	0-49	0
	50-59	1
	60-69	2
	≥ 70	2
Cytogenetic/molecular risks	Favorable	0
	Intermediate	1
	Adverse	2

Sorror ML et al. *Blood* 2005;106:2912–9; Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56; Sorror ML, et al. *JAMA Oncol* 2017 [Epub ahead of print]; Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), http://www.hctci.org.

HCT-CI Score >3 Associated with Inferior Outcomes

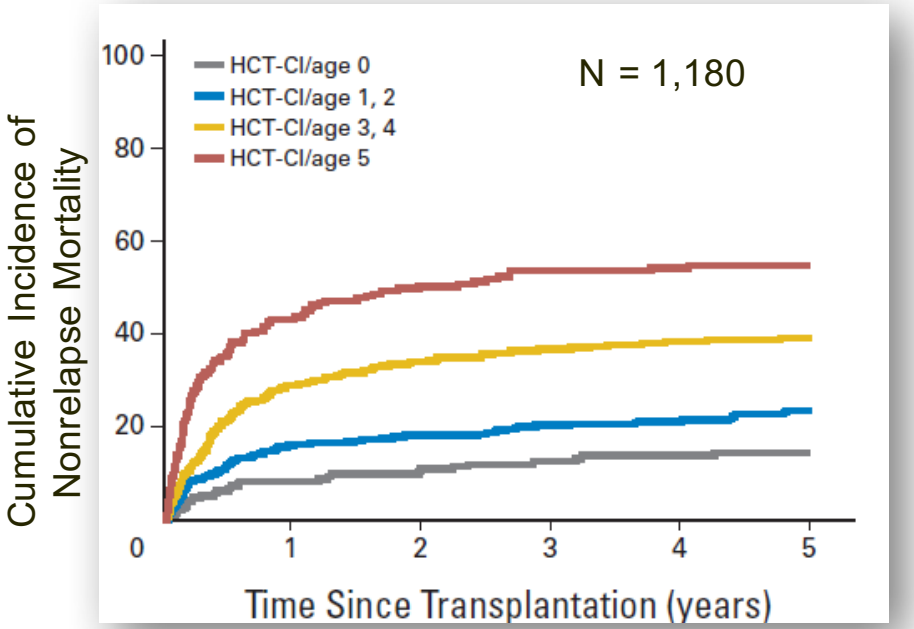


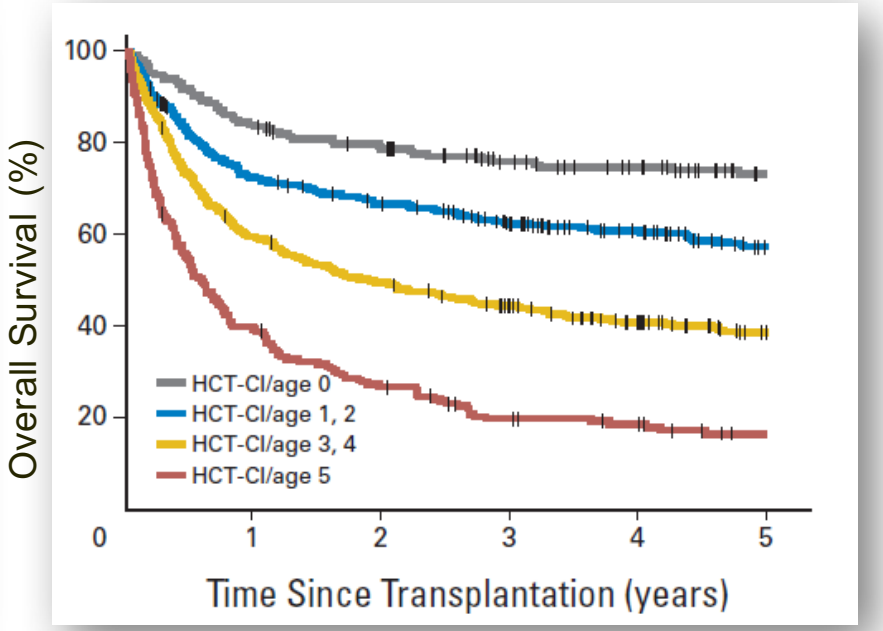
n = 1,180



Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56.

HCT-CI + Chronological Age: Composite Score





Age ≥ 40 years was assigned a score of 1 to be added to the HCT-CI scores

Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56.

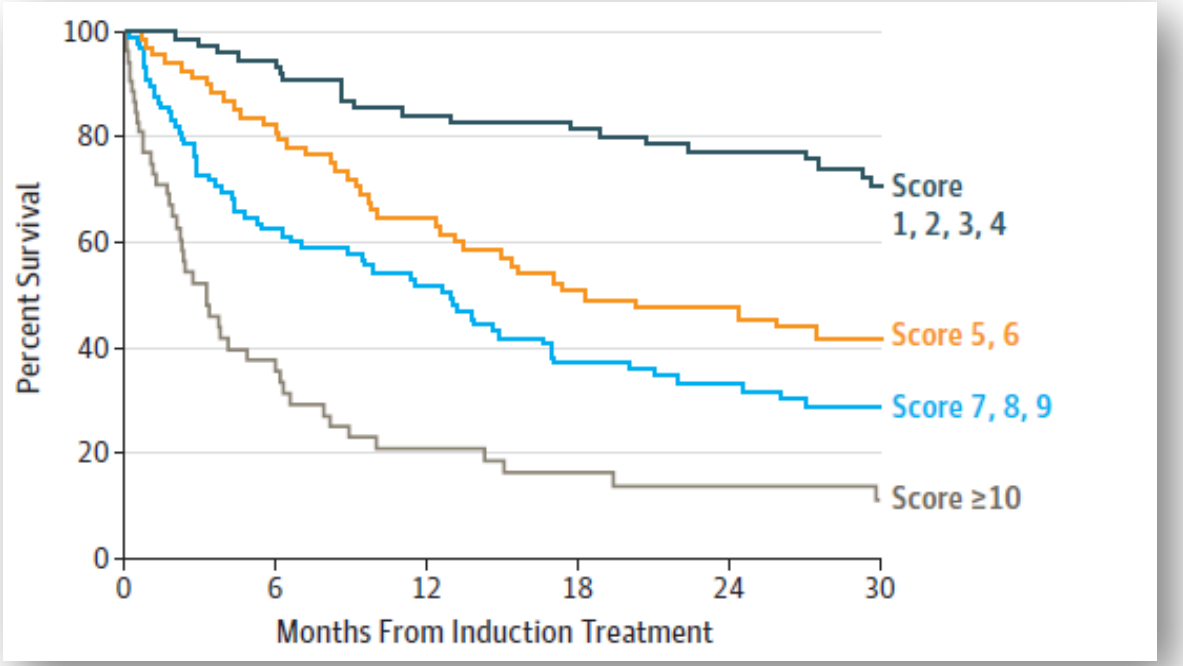
Eligibility for Intensive Therapy: HCT-CI AML Composite Score

Additional Factors	Definition in HCT-CI	Score
Age	0-49	0
	50-59	1
	60-69	2
	≥ 70	2
Cytogenetic/ molecular risks	Favorable	0
	Intermediate	1
	Adverse	2

Additional Factors	Definition in HCT-CI	Score
Albumin	< 4.0-3.5	0
	< 3.5-3.0	1
Platelet count $x10^3$ µL	< 100-50	0
	< 50-20	0
	< 20	1
LDH level, U/L	> 200-500	1
	> 500-1000	1
	> 1000	2

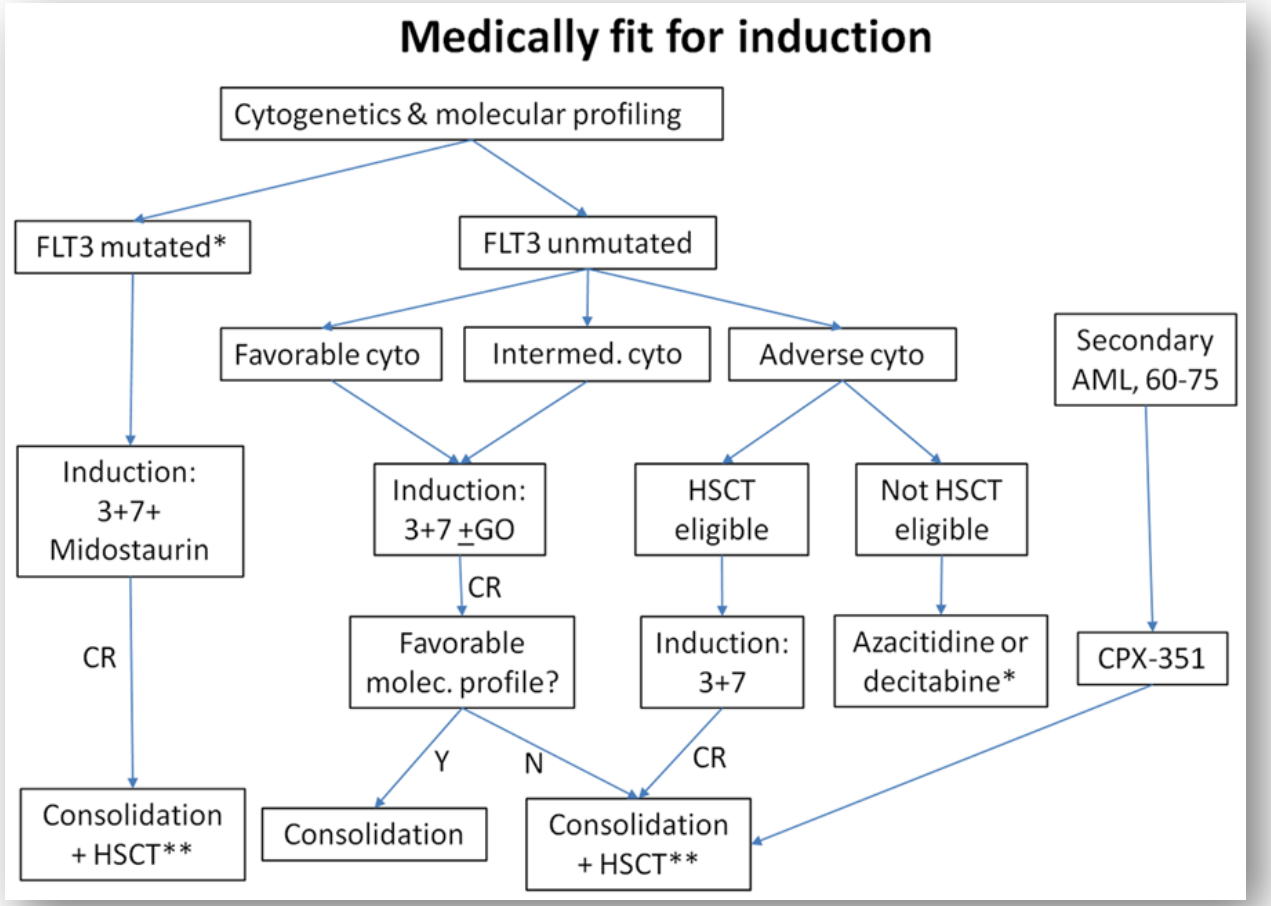
Sorror ML et al. *Blood* 2005;106:2912–9; Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56; Sorror ML, et al. *JAMA Oncol* 2017 [Epub ahead of print]; Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), http://www.hctci.org.

The AML Composite Model



Sorror ML, et al. *Blood* 2005;106:2912–9; Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56; Sorror ML, et al. *JAMA Oncol* 2017 [Epub ahead of print].

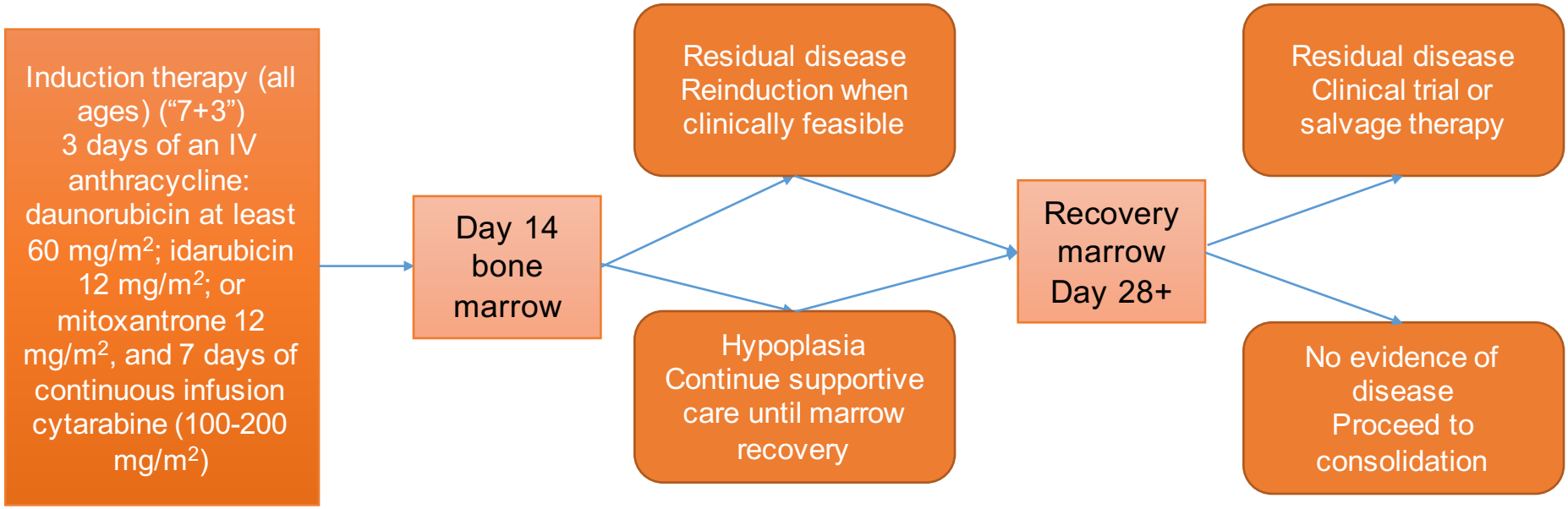
Treatment Approach for Newly Diagnosed AML



*If not yet received hypomethylating agent.
**If HSCT eligible
Cyto = cytogenetics.

Brandwein JM, et al. *Am J Blood Res* 2017;7(4):30-40; O'Donnell MR, et al. *J Natl Compr Canc Netw* 2017;15(7):926-57.

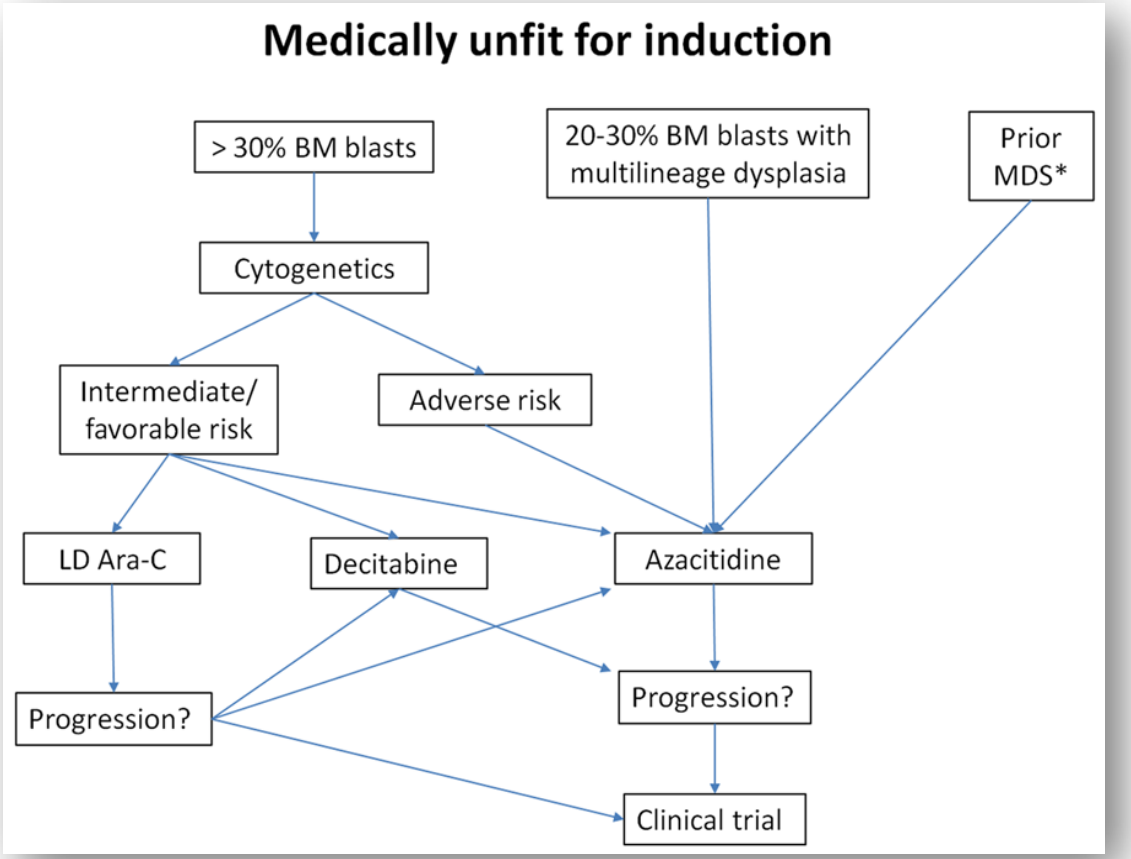
Induction and Consolidation in AML



IV = intravenously.

O'Donnell MR, et al. *J Natl Compr Canc Netw* 2017;15(7):926-57.

Treatment Approach for Newly Diagnosed AML



*If no prior exposure to hypomethylating agents.
BM = bone marrow. LD Ara-C = low-dose cytarabine.

Brandwein JM, et al. *Am J Blood Res* 2017;7(4):30-40; O'Donnell MR, et al. *J Natl Compr Canc Netw* 2017;15(7):926-57.

Induction Therapy with 7+3: 44 Years Later

- In 1973, Yates and colleagues reported results from an AML regimen of 7 days of cytarabine and 3 days of daunorubicin, aka “7+3”
- 40 years later, 7+3 induction therapy continues to benefit patients with AML
  - CR rate in younger patients: 60% to 75%
  - CR rate in patients older than age 60 years: 35% to 50%
- Relapse in inevitable for the majority of patients
- Current trials are focused on adding agents to the 7+3 over the course of treatment, changing the pharmacokinetics of daunorubicin + cytarabine, or finding new targets/pathways that are actionable

Yates JW, et al. *Cancer Chemother Rep* 1973;57:485-8; Murphy T, et al. *Expert Opin Pharmacother* 2017:1-16.

Low-Intensity Treatment

- Azacitidine: 75 mg/m^2, SC, d1-7, every 4 weeks, until progression
- Decitabine: 20 mg/m^2, IV, d1-5, every 4 weeks, until progression
- Low-dose cytarabine (20 mg every 12 hours, SC, d1-10, every 4 weeks; until progression); not recommended in patients with adverse-risk genetics
- Best supportive care Including hydroxyurea; for patients who cannot tolerate any antileukemic therapy, or who do not wish any therapy

SC = subcutaneously.

Novel Agents for the Treatment of AML

Selected Novel Agents Used to Treat AML

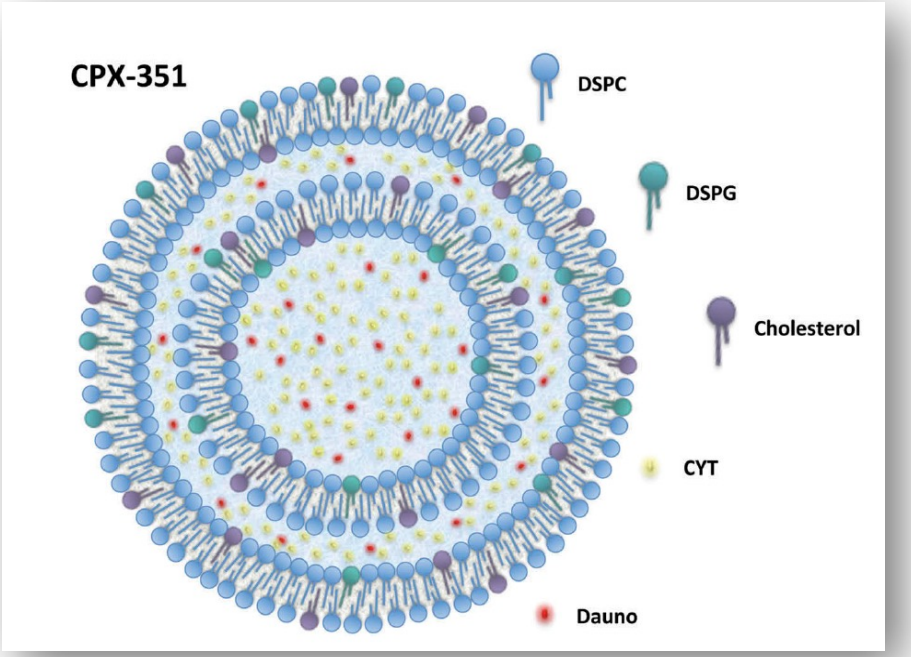
Agent	MOA	Suggested Population	Notes
CPX-351	Liposomal 7+3 in 5:1 molar ratio	sAML fit for induction chemotherapy	Phase II: OS benefit in sAML; phase III: OS, EFS benefit; FDA approval August 2017
Midostaurin PKC-412	Inhibitor of *FLT3, c-KIT, PDGFRB, VEGFR-2*, and protein kinase C	Newly diagnosed, *FLT3*+ in combination with standard 7+3 induction and cytarabine consolidation	Phase III: CR rates and OS benefit; FDA approval April 28, 2017
Vadastuximab talirine	ADC against CD33 with stable linker	HMA+ traditional induction	Significant CR/CRi rate in phase I trials of pts with CD33+ AML; FDA approval
Enasidinib AG-221	IDH2 inhibitor	*IDH2* mutated	Impressive single-agent activity (41% ORR in RR AML); FDA approval
Venetoclax ABT-199	BCL2 inhibitor	Ongoing investigation in newly diagnosed and RR AML	May have increased activity in patients with *IDH* mutations
Vosaroxin	Novel topoisomerase II inhibitor	RR AML	OS benefit in phase III trial when censored for alloSCT; mucositis notable AE
Gilteritinib	FLT3 inhibitor active against mutated TKD	*FLT3*-ITD or *FLT3*-TKD	Single-agent activity (CRc: 43%)

ADC = antibody drug conjugate; AE = adverse event; CRc = composite complete remission; CRi = CR with incomplete marrow recovery; FDA = US Food and Drug Administration; EFS = event-free survival; HMA = hypomethylating agent; MOA = mechanism of action; ORR = objective response rate; RR = relapsed/refractory.

Stein EM, et al. *Blood* 2016;127:71-78.

CPX-351: Liposomal Daunorubicin and Cytarabine

- Cytarabine and daunorubicin are encapsulated in a fixed 5:1 molar ratio to the final dose of 1.0 mg and 0.44 mg, respectively
- The two drugs interact with the copper gluconate/triethanolamine-based buffer and are contained in the aqueous space of a bilamellar liposomecomposed of phosphatidylcholine (DSPC)
- This gives the drug the deep purple color DSPG: cholesterol

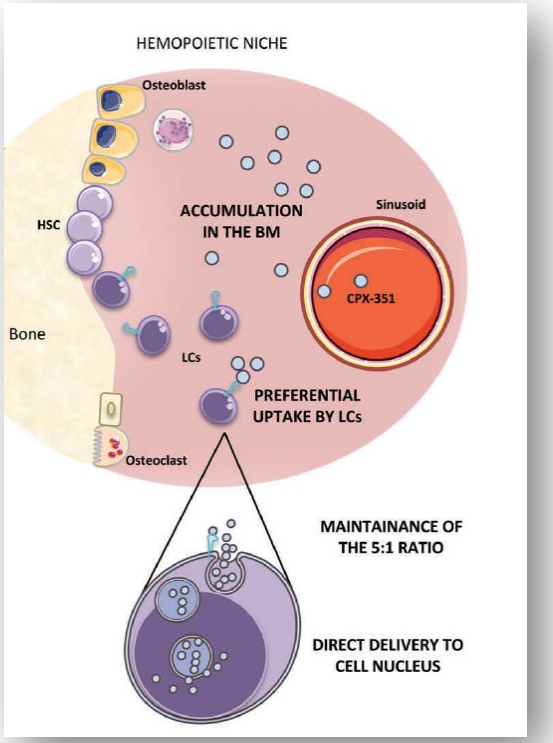


DSPC = distearoylphosphatidylcholine; DSPG = distearylphosphatidylglycerol.

Brunetti C, et al. *Expert Rev Hematol* 2017;10(10):853-62.

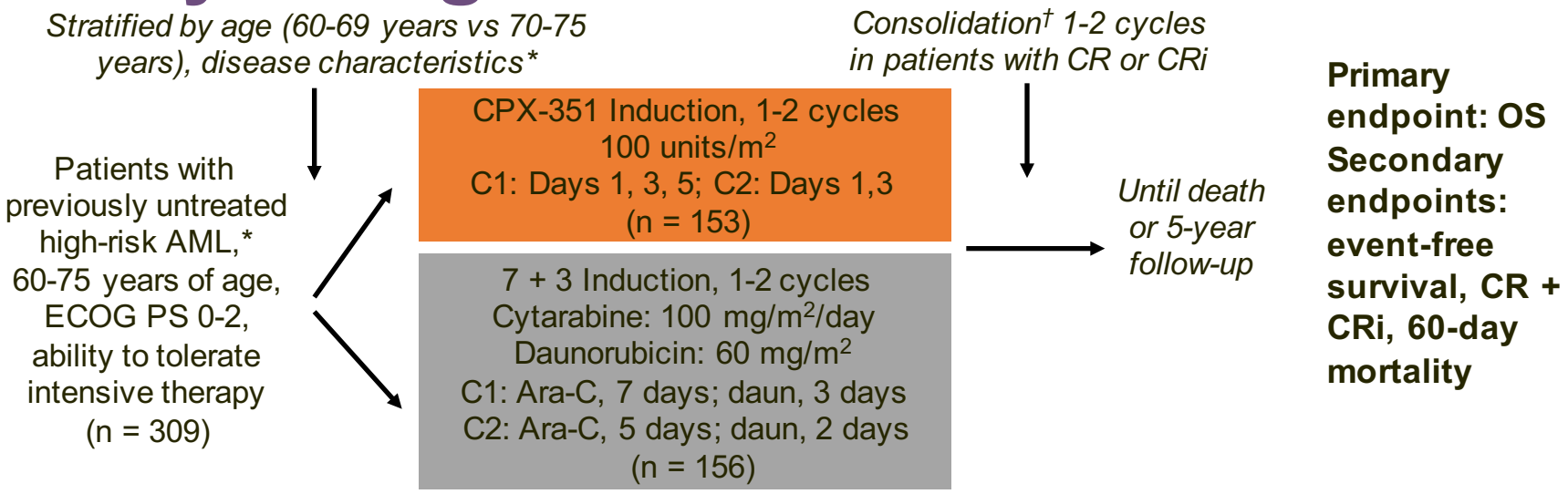
Liposomal Daunorubicin and Cytarabine (CPX-351): Mechanism of Action

- Uptake into the hematopoietic niche (bone marrow)
- Liposomes persist in the bone marrow and are taken up by leukemia cells to a greater extent than by normal bone marrow cells in a murine model
- Liposomes undergo degradation, releasing daunorubicin and cytarabine within the intracellular environment9(7):741-750.



Lim WS, et al. *Exp Hematol* 2011;39:741-50.

CPX-351 in High-Risk AML: Phase III Study Design



*Therapy-related AML; AML with history of MDS ± prior HMA therapy or CMML; de novo AML with MDS karyotype. †CPX-351 arm: 65 units/m^2, Days 1, 3; 7+3 arm: same dosing as reinduction (C2).

CMML = chronic myelomonocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group Performance Status.

Lancet JE, et al. *J Clin Oncol* 2017;34 (suppl; abstr 7000).

JADPRO Live APSHO

CPX-351: Efficacy

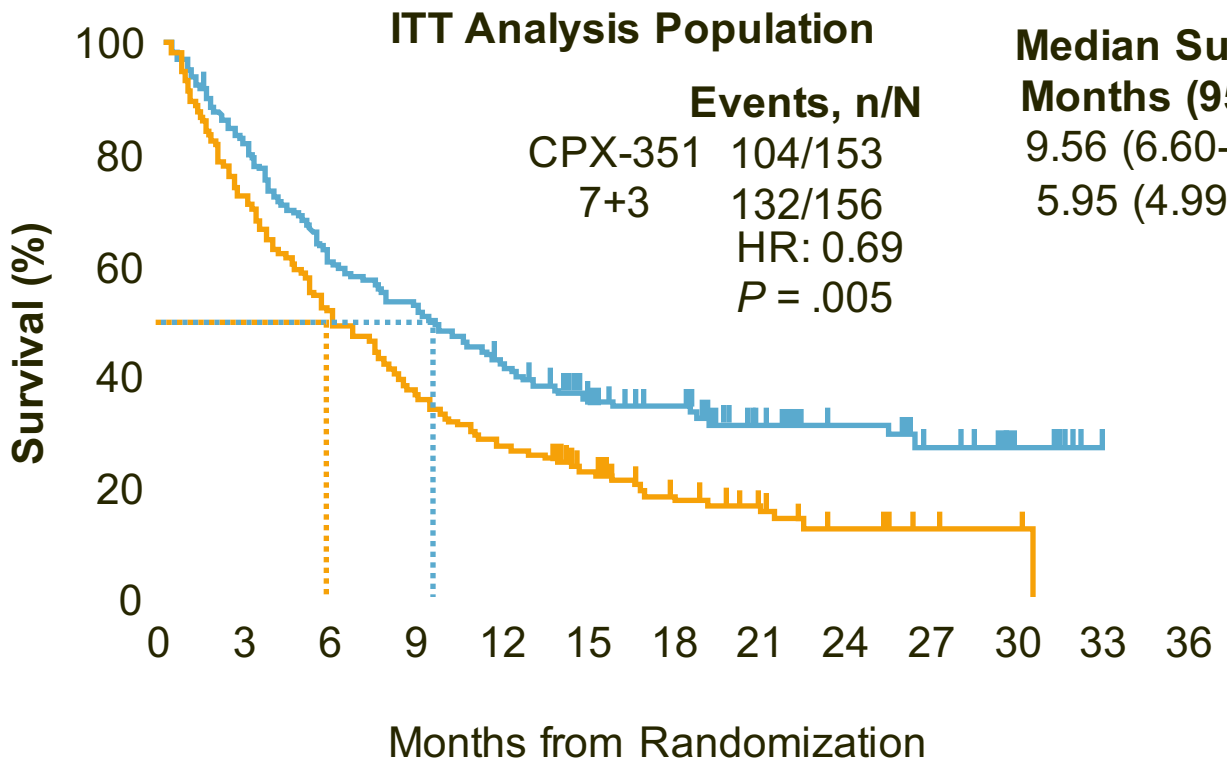
- CPX-351 demonstrated superior efficacy vs standard 7+3 induction.
- In patients undergoing transplantation, OS higher with CPX-351 (n = 52) vs 7+3 (n = 39): NR vs. 10.25 mos (HR: 0.46; 95% CI: 6.21-16.69; *p* = .0046)
- 30- and 60-day mortality rates lower with CPX-351 vs. 7+3

Outcome	CPX-351 (n = 153)	7+3 (n = 156)	HR	Odds Ratio (95% CI)	*p* Value
Median OS, mos (95% CI)	9.56 (6.60-11.86)	5.95 (4.99-7.75)	0.69	NA	.005
Median EFS, mos (95% CI)	2.53 (2.07-4.99)	1.31 (1.08-1.64)	0.74	NA	.021
Response, %					
▪ CR	37.3	25.6	NA	1.69 (1.03-2.78)	.04
▪ CR + CRi	47.7	33.3	NA	1.77 (1.11-2.81)	.016

CI = confidence interval; HR = hazard ratio; NA = not applicable; NR = not recorded.

Lancet JE, et al. *J Clin Oncol* 2017;34 (suppl; abstr 7000).

CPX-351 in Newly Diagnosed High-Risk AML: OS



ITT = intent to treat.

Lancet JE, et al. *J Clin Oncol* 2017;34 (suppl; abstr 7000).

CPX-351: Safety—Similar in the Two Arms

Grade ≥ 3 AEs (≥ 5% Patients), n (%)	CPX-351 (n = 153)	7+3 (n = 151)
Febrile neutropenia	104 (68)	107 (71)
Pneumonia	30 (20)	22 (15)
Hypoxia	20 (13)	23 (15)
Sepsis	14 (9)	11 (7)
Hypertension	16 (10)	8 (5)
Respiratory failure	11 (7)	10 (7)
Fatigue	11 (7)	9 (6)
Bacteremia	15 (10)	3 (2)
Reduced ejection fraction	8 (5)	8 (5)

Lancet JE, et al. *J Clin Oncol* 2017;34 (suppl; abstr 7000).

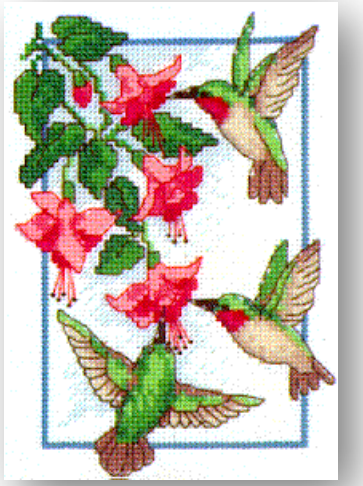
CPX-351: Prolonged Time to Recovery of Cytopenias Associated with CPX-351

	Induction		Consolidation (At Least One Consolidation)	
	CPX-351 (n = 58) n (%)	7+3 (n = 34) n (%)	CPX-351 (n = 48) n (%)	7+3 (n = 32) n (%)
Prolonged thrombocytopenia	16 (28)	4 (12)	12 (25)	5 (16)
Prolonged neutropenia	10 (17)	1 (3)	5 (10)	1 (3)

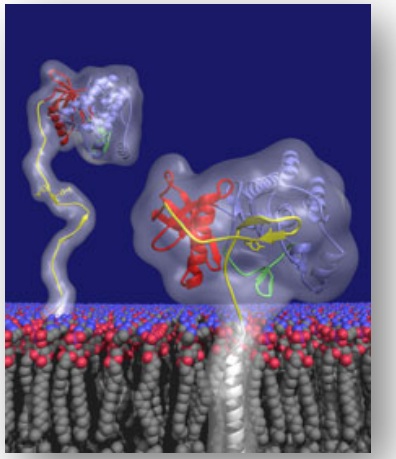
Platelets <50,000 or neutrophils < 500 lasting past Day 42 in the absence of active leukemia

Lancet JE, et al. *J Clin Oncol* 2017;34 (suppl; abstr 7000).

FLT3: What Is It?



Three hummingbirds

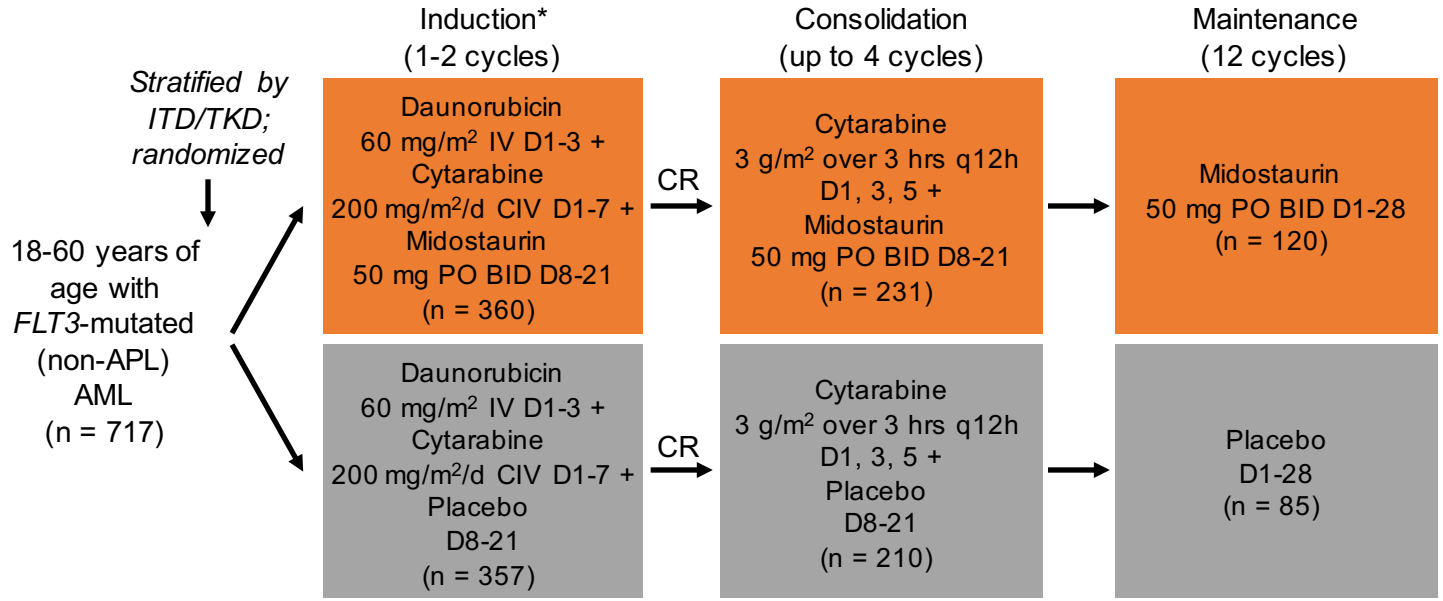


A cell surface tyrosine kinase (protein) commonly mutated in leukemia and associated with leukemogenesis and poor prognostic disease

Three teenagers

Griffith J, et al. *Molecular Cell* 2004;13:169-78.

Phase III RATIFY Trial of Midostaurin + Daunorubicin and Cytarabine in AML



Double-blind, placebo-controlled, randomized phase III study

Primary endpoint: OS (not censored for SCT)

Secondary endpoint: EFS

*Hydroxyurea allowed for ≤ 5 days prior to induction therapy. BID = twice per day; CIV = continuous IV; PO = by mouth.

Stone RM, et al. ASH 2015. Abstract 6.

JADPRO Live APSHO

Midostaurin: Efficacy (Based on RATIFY Trial)

Outcome	Midostuarin + 7+3	Placebo + 7+3	*p* value
4-year OS			
• Uncensored*	51.4 (46.0-57.0)	44.2 (39.0-50.0)	0.0074
• Censored for SCT†	63.8 (56.0-71.0)	55.7 (47.0-63.0)	0.04
Complete Response			
• Any time	212 (59)	191 (53)	0.15
• CR1 only	239 (66)	211 (59)	0.045
Median EFS			
• Overall	8.0 (5.1-10.6)	3.0 (1.9-5.9)	0.0025
• CR in induction/consolidation	11.3 (8.4-15.1)	6.1 (4.7-7.5)	0.0002

23% reduced risk of death in midostaurin arm

*HR: 0.77. †HR: 0.75. ‡Event: no CR within 60 days, relapse, or death.

Stone RM, et al. *N Eng J Med* 2017;377:454-64.

Midostaurin Safety: Grade ≥ 3 Adverse Events with Statistically Significant Differences

Adverse Event	Midostaurin (n = 355)	Placebo (n = 354)	*p* value
Anemia	329 (93)	311 (88)	0.03
Rash or desquamation	50 (14)	27 (8)	0.0008
Nausea	20 (6)	34 (10)	0.05

Remainder of adverse events were similar across the two arms.

Stone RM, et al. *N Eng J Med* 2017;377:454-64.

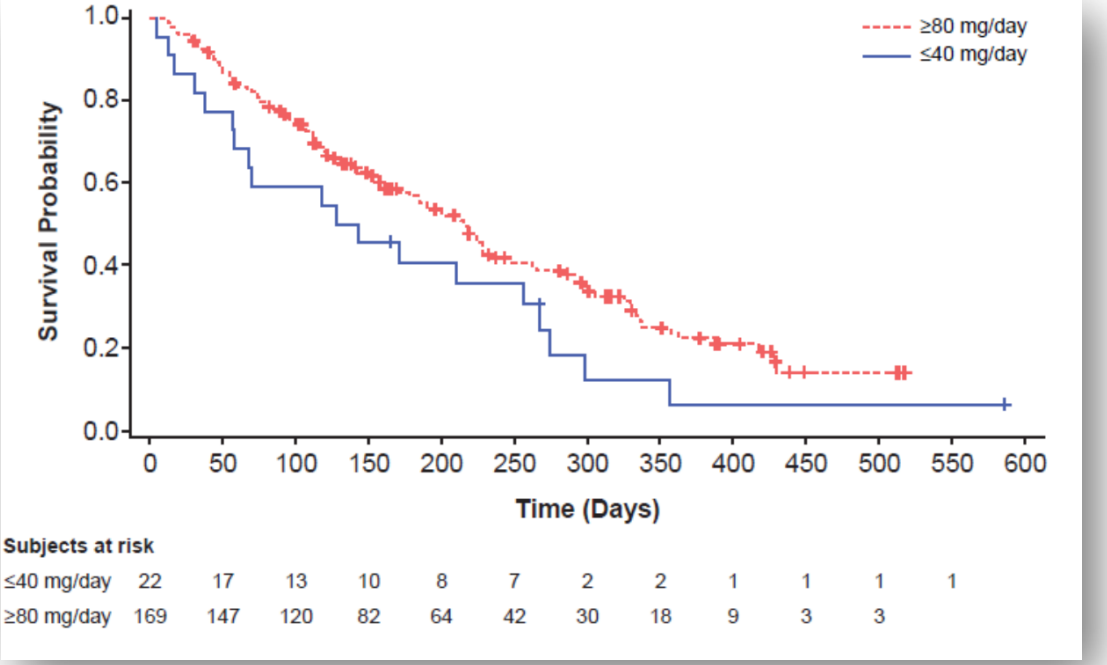
Gilteritinib (ASP2215)

- Highly selective, potent oral FLT3/AXL inhibitor
  - Activity against FLT3-ITD activating and FLT3-D835 resistance mutations
- CHRYSALIS trial: phase I/II study (n = 252)
  - Primary endpoints: safety/tolerability, PK, and PD, antileukemic effects in patients with R/R AML
  - Population: heavily pretreated
  - 194 patients had a locally confirmed *FLT3* mutation (ITD, n = 159; D835, n = 13; ITD-D835, n = 16; other, n = 6)
  - Diarrhea (16%) and fatigue (15%) were the most commonly reported treatment-related adverse events of any grade
  - 7 deaths considered possibly/probably related to treatment (all n = 1)
    - Pulmonary embolism, respiratory failure, hemoptysis, intracranial bleed, ventricular fibrillation, septic shock, and neutropenia

PD = pharmacodynamic; PK = pharmacokinetic; R/R = relapsed/refractory.

Perl A, et al. *Blood* 2016;128:1069.

Overall Survival in *FLT3*+ Patients Treated with Gilteritinib (n = 191)



Gilteritinib ≥ 80 mg/day in *FLT3*+ patients

Median OS: 31 weeks (range: 1.7–61 weeks)

Median Duration of Response: 20 weeks (range: 1.1–55 weeks)

Median Time to Best Response: 7.2 weeks (range: 3.7–52 weeks)

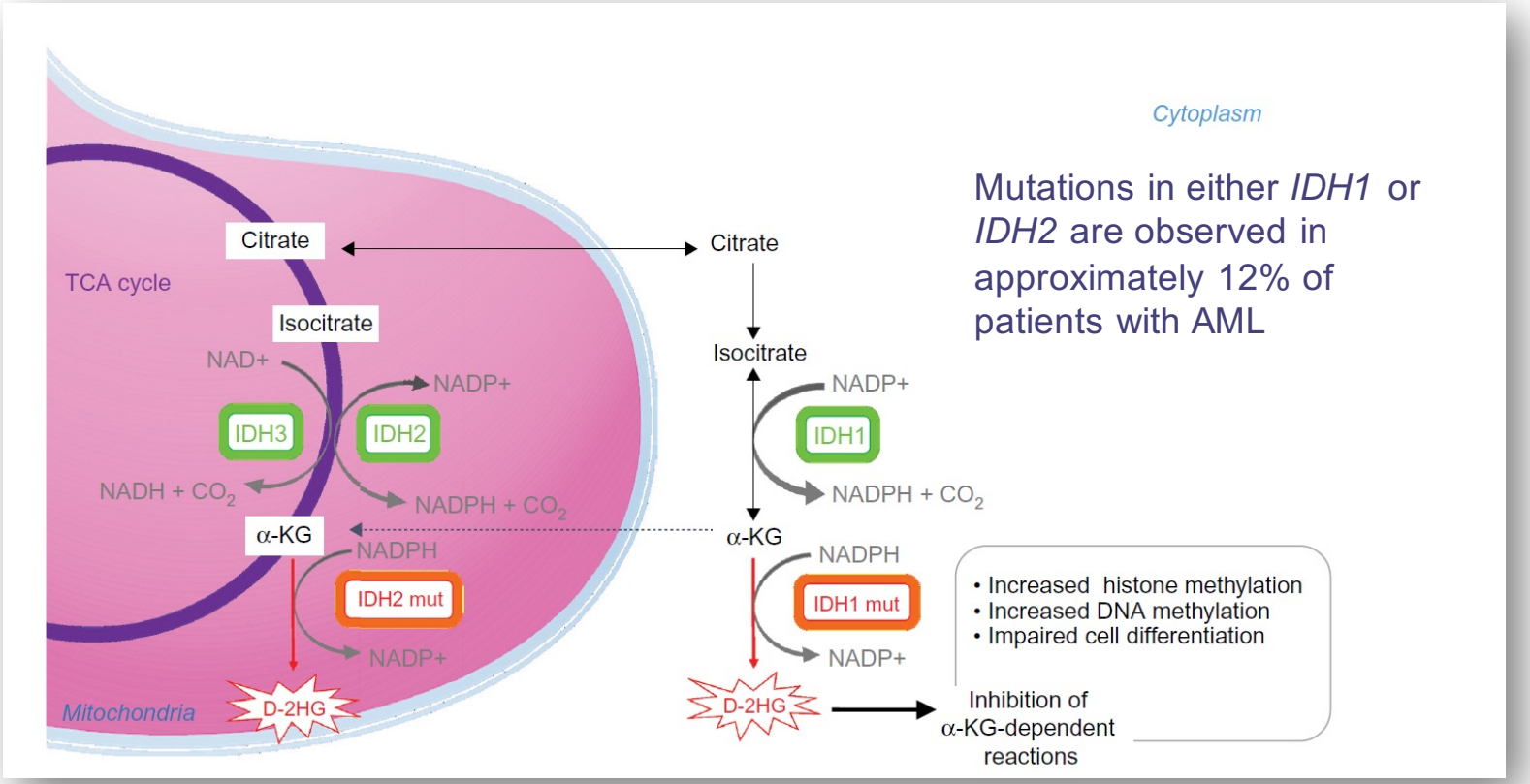
Received FDA Fast Track designation Oct. 10, 2017

Phase III testing of oral gilteritinib 120 mg QD in patients with *FLT3*+ R/R AML after first-line therapy is underway (NCT02421939)

QD = once per day.

Perl A, et al. *Blood* 2016;128:1069.

IDH2 and AML



Mondesir J, et al. *J Blood Med* 2016;7:171-80.

Enasidinib

- Selective oral IDH2 inhibitor, is the first and only drug to specifically target oncogenic IDH2 mutants
  - Mutational analysis is needed to determine whether patients have IDH2 mutations and therefore might benefit from enasidenib
- Enasidenib acts by inducing bone marrow differentiation and maturation rather than ablation
- Several months of treatment may be required before efficacy is observed
- Continuous daily enasidenib treatment was generally well tolerated and induced hematologic responses in patients with prior AML therapy failure

Stein EM, et al. *Blood* 2017;130(6):722-31.

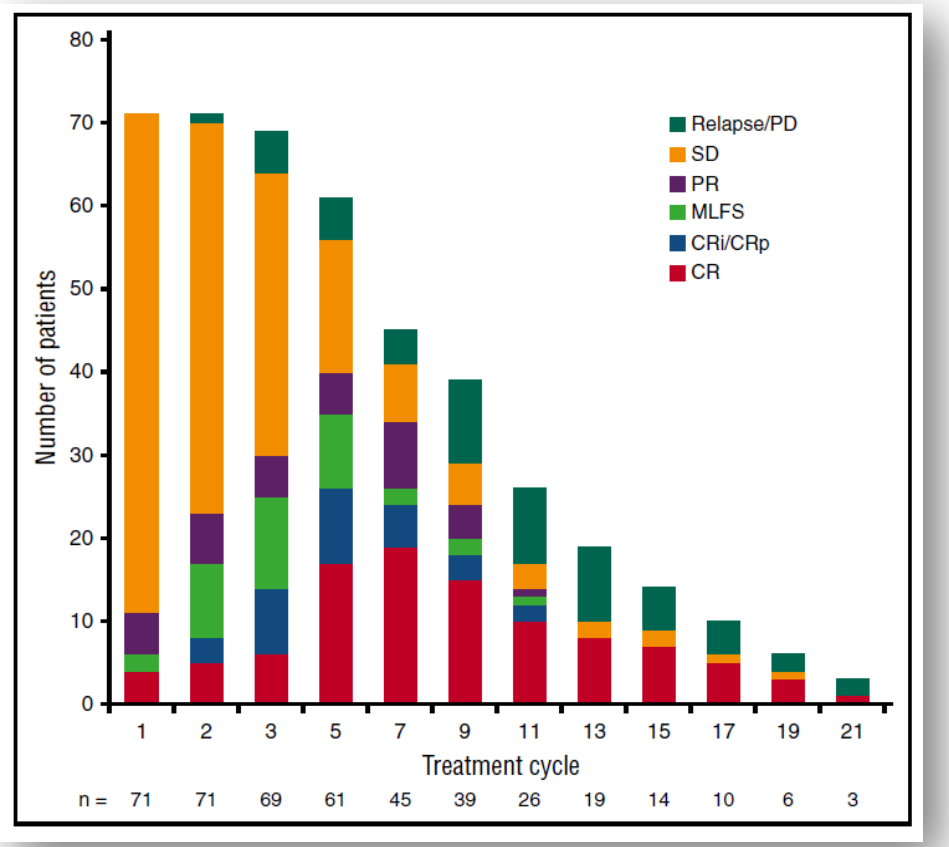
Enasidinib

- In a phase I/II study of enasidenib, the most common treatment-emergent adverse events were nausea (frequency: 48%) diarrhea (41%), and fatigue (41%); most of these events were mild or moderate in severity
- Vomiting was managed with lorazepam, ondansetron, and prochlorperazine; diarrhea was managed with loperamide and diphenoxylate
- Serious treatment-related differentiation syndrome was reported in 7% of patients and was managed with steroids
- Permanent enasidenib withdrawal was not required
- CR, CRi, or CR with incomplete hematologic recovery was 28% in patients who received 100 mg/day; median time to first/best response was 1.9/3.7 months

Stein EM, et al. *Blood* 2017;130(6):722-31.

Enasidenib

- Evolution of response during treatment of responding patients (n=71)



Stein EM, et al. *Blood* 2017;130(6):722-31.

Enasidenib: Safety—Grade ≥ 3 Treatment-Related Adverse Events

Adverse Events	Enasidenib 100 mg per Day (n = 153)		All Patients (n = 235)	
	Number	%	Number	%
Hyperbilirubinemia	13	8	29	12
IDH differentiation syndrome	11	7	15	6
Anemia	10	7	12	5
Thrombocytopenia	8	5	15	6
Tumor lysis syndrome	5	3	8	3
Decreased appetite	3	2	6	3
Leukocytosis	2	1	6	3
Fatigue	2	1	6	3
Nausea	2	1	5	2
Lipase increased	2	1	5	2

Stein EM, et al. *Blood* 2017;130(6):722-31.

Gemtuzumab Ozogamicin

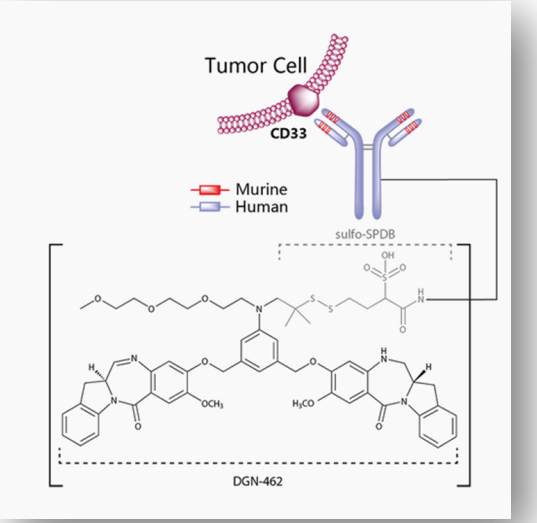
- First antibody-directed therapy (anti-CD33) for AML
  - FDA approved based on a phase II trial in 2000
- Five randomized trials where it was combined with standard induction chemotherapy in adults produced different results
  - Remission rates were not improved
  - Relapse was reduced in 4 of 5 trials with a significant survival benefit in two studies, AML16 and ALFA-0701
- Withdrawn from the US market in June 2010
- Re-analysis of previous trials led to the re-approval of GO on September 1, 2017 with a lower recommended dose

GO = gemtuzumab ozogamicin.

Hills RK, et al. *Lancet Oncol* 2014;15(9):986–96.

Vadastuximab Talirine (Anti-CD33; SGN 33A)

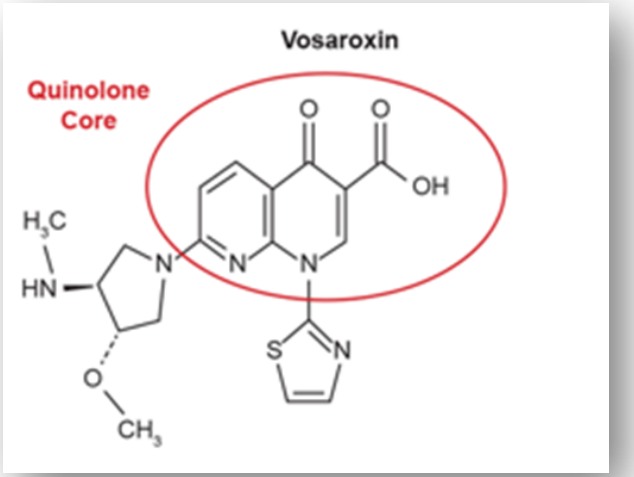
- Novel anti-CD33 ADC
- Coupled to pyrrolobenzodiazepine dimer 9DNA cross-linker
- More stable cross link
- Less affected by P-glycoprotein
- Although clinical trials looked to be favorable, Seattle Genetics has discontinued the phase III CASCADE clinical trial and suspended patient enrollment and treatment in all of its other vadastuximab talirine clinical trials due to patient deaths



Seattle Genetics, Vadastuximab Talirine, http://www.seattlegenetics.com/pipeline/vadastuximab-talirine.

Vosaroxin: A First-in-Class Anticancer Quinolone Derivative

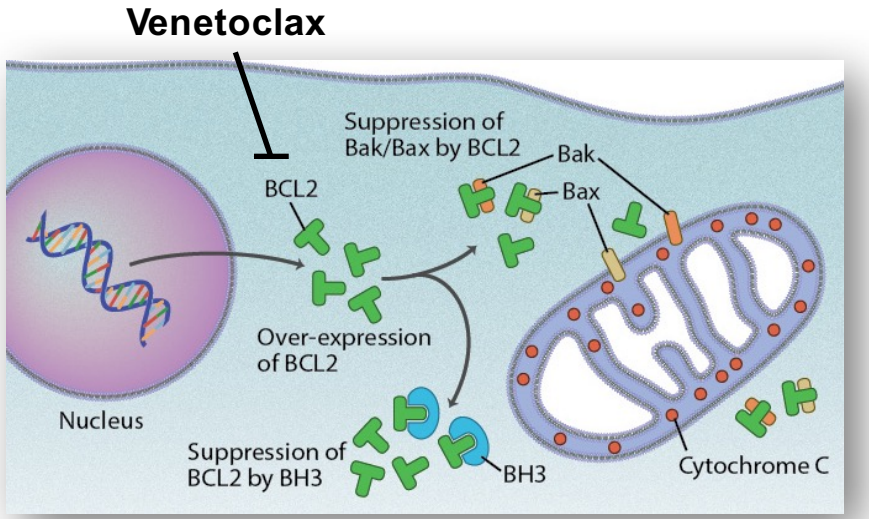
- Intercalates DNA and inhibits topoisomerase II
- Causes replication-dependent, site-selective DNA damage, G2 arrest and apoptosis
- Not a P-gp substrate
- P53-independent activity
- Minimal metabolism and creation of ROS
- Lower potential for off-target organ damage (cardiotoxicity)
- Low risk of drug-drug interaction
- VALOR trial translated to prolonged survival in relapsed/refractory AML, particularly in older patients
- No difference in 30- or 60- day mortality in patients > 60 years of age though higher rates of stomatitis and subsequent infections



Ravandi R, et al. *Lancet Oncol* 2015;16:1025-36; Sayar H, et al. *Onco Targets Ther* 2017;10:3957-63.

BCL2 Inhibition in AML: Venetoclax

- Venetoclax is a highly selective, orally bioavailable BH3 mimetic that specifically targets BCL-2, but lacks affinity for BCL-XL and MCL-1
- BCL-2 proteins play a critical role in mitochondrial mediated apoptosis
- BCL-2 is overexpressed in AML
- AML cells are primed for BCL-2 inhibition



Cassier PA, et al. *Br J Cancer* 2017;117(8):1089-98; original illustration by David Baker, from Kurtin S et al. *JADPRO* 2017 in print.

BCL2 Inhibition in AML: Venetoclax

- Venetoclax is a highly selective, orally bioavailable BH3-mimetic that specifically targets BCL-2, but lacks affinity for BCL-XL and MCL-1
- Phase II study: venetoclax 800 mg/day
  - High-risk relapsed/refractory AML (n = 30) or unfit for chemo (n = 4)
  - ORR: 19%
  - IDH1/2 mutations: 38% of pts
  - BH3 profiling consistent with on-target BCL-2 inhibition
  - Common AEs: nausea, vomiting, febrile neutropenia, hypokalemia

Konopleva M, et al. *Cancer Discov* 2016;6:1106-17.

Phase Ib Study: Venetoclax + HMA in Patients with Newly Diagnosed AML Age 65 or Older

- N = 34; median age: 73 years; adverse risk: 41%
- Treatment: venetoclax 400 or 800 mg/day with either decitabine or azacitidine
- CR + CRi: 71%
- Treatment-emergent AEs:
  - Febrile neutropenia (38%), nausea (53%), diarrhea (41%), peripheral edema (35%)
  - 24/34 had delay/interruption for neutropenia or AE
  - 13 had delay of cycle 2 to allow ANC recovery
  - 23/34 discontinued treatment; 6 for allogeneic SCT
- Combination studies are currently ongoing and preliminary data so far shows significant improvement in response rates especially in the elderly patients, those with adverse cytogenetics and IDH-mutated AML

ANC = absolute neutrophil count.

DiNardo C, et al. ASH 2015. Abstract 327.

Where to Go from Here? Emerging Therapies

Mechanism of Action	Agents
Protein kinase inhibitors	• FLT3 inhibitors (quizartinib, gilteritinib, crenolanib) • KIT inhibitors • PI3K/AKT/mTOR inhibitors • Aurora and polo-like kinase inhibitors, CDK4/6 inhibitors, CHK1, WEE1, and MPS1 inhibitors • SRC and HCK inhibitors
Epigenetic modulators	• New DNA methyltransferase inhibitors (SGI-110) • HDAC inhibitors • IDH1 and IDH2 inhibitors • DOT1L inhibitors • BET-bromodomain inhibitors
Mitochondrial inhibitors	• Bcl-2, Bcl-xL, and Mcl-1 inhibitors • Caseinolytic protease inhibitors

Döhner H, et al. *Blood* 2017;129(4):424-47.

Where to from Here? Emerging Therapies

Mechanism of Action	Agents
Therapies targeting oncogenic proteins	• Fusion transcripts targeting • EVI1 targeting • NPM1 targeting • Hedgehog inhibitors
Antibodies and immunotherapies	• Monoclonal antibodies against CD33, CD44, • CD47, CD123, CLEC12A • Immunoconjugates (e.g., GO, SGN33A) • BiTEs and DARTs • CAR T cells or genetically engineered TCR T cells • Immune checkpoint inhibitors (PD-1/PD-L1,CTLA-4) • Anti-KIR antibody • Vaccines (e.g., WT1)
Therapies targeting AML environment	• CXCR4 and CXCL12 antagonists • Antiangiogenic therapies

BiTEs = bispecific T-cell engagers; CAR = chimeric antigen receptor; DART = dual affinity retargeting; TCR = T-cell receptor

Döhner H, et al. *Blood* 2017;129(4):424-47.

Case Studies in AML

Case #1: Presentation

- 36-year-old male diagnosed with AML in July
- WBC 84.4, Hgb14, platelets131,000 with 30% circulating blasts
  - *NPM1+ FLT3-, IDH2+*
  - Cytogenetics: deletion 16q
- ECHO EF 65%
- Exam was unremarkable

ECHO = echocardiography; Hgb = hemoglobin.

Case #1: Treatment

- July–December 2016
  - Admitted for G-CLAM Induction
    - GCSF + cladribine, cytarabine, mitoxantrone
  - Reinduction with G-CLAM (had MRD)
  - Consolidation with G-CLA
- Toxicities
  - Pancytopenia; transfusion dependent
  - Mucositis
  - Neutropenic fever
  - →Bacteremic with MDR E. coli→SEPSIS!

Neutropenic prophylaxis: ANC < 500: levofloxacin and posaconazole

HSV/VZV prophylaxis with acyclovir starts at induction

ANC < 500, and temp > 38.3 = admission

GCSF = granulocyte colony-stimulating factor; HSV = herpes simplex virus; MDR = multidrug-resistant; MRD = minimal residual disease; VZV = varicella zoster virus.

Initial Management of Suspected Sepsis

Surviving Sepsis Campaign
www.survivingsepsis.org

- qSOFA
  - AMS
  - RR > 22
  - SBP <100
- SIRS criteria (>2)
  - Temperature < 36° C or > 38° C
  - Heart rate > 90 bpm
  - RR > 20 breaths/min
  - WBC > 12,000 or < 4,000 cells/mm^3

"Soft" Indicators:
- Do they look toxic?
  - Change from baseline?
- What does the caregiver/family have to say?

AMS = altered mental status; qSOFA = Quick Sepsis Related Organ Failure Assessment; RR = respiratory rate; SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome.

Initial Management of Suspected Sepsis

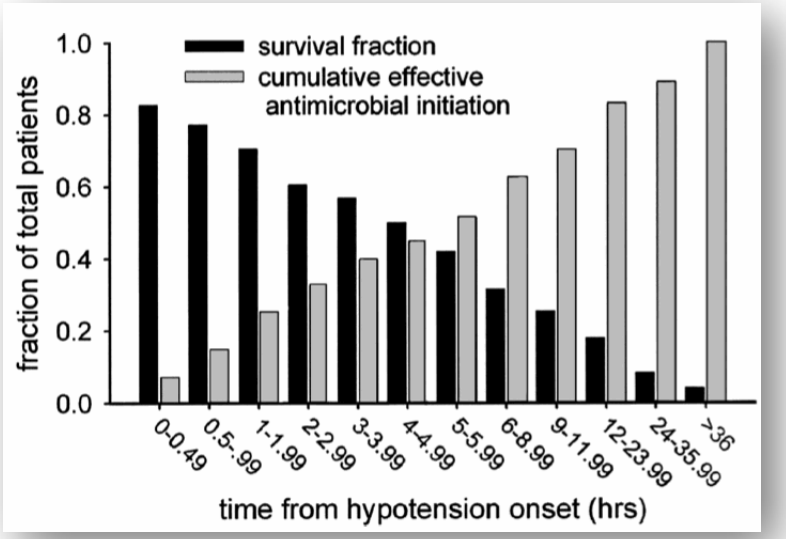
1. Labs
   - Blood cultures (central line and peripheral)
     - Urine cultures if able
   - Venous lactate
2. If hypotensive and/or lactate > 4
   - Fluid bolus (30 mL/kg **per hour**); adjust for heart failure if needed
3. Antibiotics: within 3 hours (ideally within 1 hour)
4. Reassess: vitals and fluid response promptly

Timely Antibiotics Improve Sepsis-Associated Mortality

- *Critical Care Medicine* 2006:
  - Retrospective study of 2,154 patients with septic shock
  - Main outcome measure of survival to hospital discharge looking at the impact on morality of delays in initiation of effective antimicrobial therapy from the initial onset of recurrent/persistent hypotension of septic shock
  - *Time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome*

Survival if antibiotics given in first hour → 80%

Each hour delay → decrease in survival of 7.6%



Kumar A, et al. *CCM* 2006;34:1589-96.

Case #1: Treatment

- July–December 2016
  - Admitted for G-CLAM Induction
    - GCSF + cladribine, cytarabine, mitoxantrone
  - Reinduction with G-CLAM (had MRD) – marrow → NED
  - Consolidation with G-CLA
- February 2017: BM biopsy shows **NED** by morphology/cytogenetics; he also has ***NPM1*-negative** and **normal cytogenetics** (i.e., resolution of 16q deletion)
- Consolidation #2 with HiDAC
  - Circulating blasts present on Day 22

HiDAC = high-dose cytarabine; NED = no evidence of disease.

Case #1: Treatment

- Decitabine + cytarabine
  - No response
  - → Relapsed refractory disease
- September 2017: intermediate dose cytarabine initiated with enasidenib on day 7
- Toxicities
  - Significant nausea, vomiting; anorexia

Enasidenib

Indication/FDA Approval: treatment of adult patients with relapsed or refractory acute myeloid leukemia with an *IDH2* mutation

Toxicities

- Differentiation syndrome
  - *14% of patients may experience this life-threatening toxicity*
- Appetite and taste changes, nausea/vomiting/diarrhea
- Tumor lysis syndrome

Case #2: Presentation

- 72-year-old male who presented to a community hospital with progressive fatigue that had been present for several years but had recently worsened substantially; he had not seen a medical provider for over 16 years and was taking no medications

- At the time of his initial evaluation, he was febrile to 38.5, had flu-like symptoms and profound fatigue; labs were notable for Cr 1.35, LDH 629, albumin 3.1, INR 1.26,
  WBC 161,000, Hgb 6.8, platelets 13,000, 89% circulating blasts

- He was admitted to the hospital for IV antibiotics, administration of hydroxyurea, and fluids while his workup was completed.

- Pertinent past medical history
  - Hodgkin disease age 51 treated with ABVD + radiation
  - Hypertension

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; Cr = creatinine; INR = international normalized ratio.

Tumor Lysis Syndrome: Risks and Management

Risk Factors for Tumor Lysis Syndrome	
Tumor type	• Burkitt lymphoma • Lymphoblastic lymphoma • Diffuse large B-cell lymphoma • ALL • Solid tumors with high proliferative state
Tumor burden/extent of disease	• Bulky disease • Elevated LDH (> 2 x ULN) • Elevated WBC (> 25,000)
Renal function	• Preexisting renal failure • Oliguria
Baseline uric acid	• Baseline uric acid > 7.5mg/dL

Patient Stratification by Risk			
Type of Cancer	Risk		
	High	Intermediate	Low
NHL	Burkitt, lymphoblastic, B cell-ALL	DLBCL	Indolent
ALL	WBC ≥ 100,000	WBC 50,000-100,000	WBC ≤ 50,000
AML	WBC ≥ 50,000 (monoblastic)	WBC 10,000-50,000	WBC ≤ 10,000
CLL		WBC 10,000-100,000 treated with fludarabine	WBC ≤ 10,000
Other heme malignancies and solid tumors		Rapid proliferation with expected rapid response	Remainder of patients

CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; NHL = Non-Hodgkin lymphoma.

Coiffier B, et al. *J Clin Oncol* 2008;26:2767-78.

Tumor Lysis Syndrome: Risks and Management

Cairo-Bishop Definition of Tumor Lysis Syndrome		
Element	**Value**	**Change from Baseline**
Uric acid	> 8 mg/dL	25% increase
Potassium	> 6 mg/L	25% increase
Phosphorus	> 4.5 mg/dL	25% increase
Calcium	< 7 mg/dL	25% decrease
Clinical Criteria: (lab criteria plus >1 of the following): increased creatinine (>1.5x ULN), cardiac arrhythmia, seizure		
Definition: two or more lab changes within 3 days before or 7 days after cytotoxic therapy		

Management
Monitor tumor lysis labs at least every 8 hours: ✓ Uric acid ✓ Potassium ✓ Phosphorus ✓ Calcium ✓ Creatinine
Allopurinol
Aggressive hydration +/- sodium bicarbonate
Rasburicase

Coiffier B, et al. *J Clin Oncol* 2008;26:2767-78.

Case #2: Presentation

- 72-year-old male with a creatinine 1.35, LDH 629, albumin 3.1, INR 1.26, WBC 161,000, Hgb 6.8, platelets 13,000, 89% circulating blasts
- ECHO: LVEF of 52%, Performance Status = 2
- Bone marrow
  - 90% myeloid blasts by flow
  - *NPM1+, FLT3-*
  - Cytogenetics: del(5q) and +8
    - MDS likely preceded presentation of AML

Past Medical History

- Hodgkin disease age 51 treated with ABVD + radiation
- Hypertension
- Hypercholesterolemia

LVEF = left ventricular ejection fraction.

Case #2: Treatment-Related Mortality

Performance status	Age	Platelet count	Albumin	Secondary AML	WBC	% peripheral blasts	Creatinine	TRM
2	72	13	3.1	Yes	161,000	89%	1.35	42

	All Patients				Patients >60 years of age		Patients <=60 years of age	
TRM Score Interval	Patients below/ within/ above TRM Score Interval (%)	TRM Probability if below TRM Score Interval (%)	TRM Probability if within TRM Score Interval (%)	TRM Probability if above TRM Score Interval (%)	Patients below TRM Score Interval (%)	TRM Probability if below TRM Score Interval (%)	Patients above TRM Score Interval (%)	TRM Probability if above TRM Score Interval (%)
0 - 1.9	0/20/80	-	1	12	-	-	67	10
1.91 - 3.9	20/20/60	1	2	16	8	0	39	15
3.91 - 6.9	40/20/40	1	7	20	20	1	21	18
6.91 - 9.2	60/10/30	3	7	24	42	2	14	26
9.21 - 13.1	70/10/20	4	12	31	55	4	9	35
13.11 - 22.8	80/10/10	5	20	41	70	6	5	53
22.81 - 100	90/10/0	6	41	-	85	9	-	

TRM = death within 28 days from initiation of chemotherapy

TRM = treatment-related mortality.

Walter RB, et al. *J Clin Oncol* 2011;29:4417-23.

Case #2: Treatment

- He was enrolled in a phase III clinical trial with CPX-351: liposomal combination of cytarabine and daunorubicin
  - Induction chemotherapy was initiated at a dose of 100 u/m^2 on Day 1, 3, 5 over 90 minutes
  - Infusion was completed in the outpatient setting and was well tolerated
  - Toxicities
    - Pancytopenia/transfusion dependent
    - Nausea, fatigue, taste changes

CPX-351

Indication/FDA Approval: newly diagnosed tAML or AML with MDS-related changes

Toxicities

- Cytopenias
- Febrile neutropenia
- Rash
- Mucositis
- Nausea, vomiting, diarrhea/constipation

Standard transfusion triggers:
Hct $\leq$ 25%, platelets $\leq$ 10k

Case #2

- Day 28 bone marrow revealed persistent disease with 40% blasts
  - Reinduction chemotherapy: CPX-351 100u/m^2 on Day 1, 3, 5 over 90 minutes
  - Infusion was completed in the outpatient setting and was well tolerated
  - Toxicities
    - Admitted with neutropenic fever
    - Pancytopenia/transfusion dependent
    - Fatigue, nausea, anorexia, and taste changes

Case #2

- Count recovery was delayed: Day 36 ANC > 500, platelets > 50,000
- Day 38 marrow was normocellular by morphology; flow cytometry was negative for abnormal blasts population; he remained *NPM1*+
- 2 cycles of consolidation CPX-351 completed in July 2016→ lost to follow-up
- June 2017: called the office for an appointment because he felt poorly; a marrow showed 42% blasts

He got a **full year** from this approach!

Case #3: Presentation

- 62-year-old woman with a 3-year history of thrombocytopenia → progressed to pancytopenia
- WBC 49,000, Hgb 12.2, platelets 45,000, 76% circulating blasts, chemistries were normal with Cr 0.8, LDH 224, uric acid 4.8
- Bone marrow aspirate: 60% blasts
  - Cytogenetics: trisomy 8; *NPM1+, FLT3+*
- Exam was essentially unremarkable but she was very anxious

Case #3: 2017 European LeukemiaNet Risk Stratification by Genetics

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{Low}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{High}
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{Low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM (EVI1)*
	-5 or del(5q); -7; -17/ abnormal (17p)
	Complex karyotype; monosomal karyotype
	Wild type *NPM1* and *FLT3*-ITD^{High}
	Mutated *RUNX1,* Mutated *ASXL1,* Mutated *TP53*

Döhner H, et al. *Blood* 2017;129:424-47.

Case #3: Treatment

- Standard 7+3 induction as an inpatient; no infusion-related or cerebellar toxicities
- Discharged on day 6 after completion of therapy
  - Early discharge criteria: age < 65, within 20 minutes of the medical center, 3x/week labs, caregiver with patient
- Started midostaurin 50 mg PO BID on days 8-21
- Toxicities
  - Pancytopenic; transfusion dependent
  - Nausea, mild mucositis
  - Cellulitis (face) requiring readmission on day 15

Midostaurin

Indication/FDA Approval: adult patients with newly diagnosed *FLT3*+ AML

- Given in combination with standard 7+3 (cytarabine and daunorubicin) induction followed by cytarabine consolidation

Toxicities

- Nausea/vomiting
- Febrile neutropenia
- Mucositis
- Hyperglycemia
- Interstitial lung disease

Case #3: Treatment

- Day 28 marrow: no evidence of residual/recurrent AML
- Consolidation with HiDAC 3 g/m^2 Day 1, 3, 5
  - Early discharge on day 6
- Midostaurin 50 mg PO BID on days 8-21
- Toxicities
  - Nausea, anorexia
  - Neutropenic fever
  - Pancytopenia; transfusion dependent

October update:
Arrived to the BMT service for a planned matched unrelated peripheral blood stem cell transplant in first CR

HCT Comorbidity Index Calculator

HCT-CI is a comorbidity index that comprises 17 different categories of organ dysfunction:

- *Arrhythmia*
- *CV disease*
- *IBD*
- *DM*
- *Cerebrovascular disease*
- *Psychiatric disturbance*
- *Hepatic comorbidity*
- *Obesity*
- *Infection*
- *Rheumatologic comorbidity*
- *Peptic Ulcer*
- *Renal disease*
- *Pulmonary*
- *Prior solid tumor*
- *Heart Valve*
- *Age*

- It provides information with regard to the overall as well as non-relapse mortality risk a patient is likely to experience after hematopoietic cell transplantation
- It can be an important decision-making instrument for choosing appropriate conditioning regimens for patients with acute myeloid leukemia, myelodysplastic syndromes, and those with lymphoma or chronic lymphocytic leukemia
- Does NOT take the place of a formal transplant consult

CV = cardiovascular; DM = diabetes mellitus; IBD = irritable bowel disease.

Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), http://hctci.org.

Summary

- Many tools are now available to identify prognostic and risk factors that will affect treatment decisions—use them!
  - Cytogenetics (low, intermediate, and high risk)
  - Treatment-related mortality indicators (TRM)
  - Transplant comorbidity index (HCT-CI)
  - Genetic risk stratification (ELN)
- Increasing number of targeted treatments are becoming available that are especially useful when using the available tools
  - FLT3 inhibitors
  - *IDH2* mutations
- Keep toxicities in mind
  - Pancytopenia
  - Tumor lysis syndrome
  - Sepsis
  - Differentiation syndrome

Question #1

Your 74-year-old patient was just started on enasidenib, an oral mIDH2 inhibitor that promotes myeloid differentiation of leukemic blasts. He complains of shortness of breath and fever; on auscultation, you hear crackles and note he has pitting ankle edema and a temperature of 101.7 degrees. You suspect:

1. He has neutropenia and has contracted pneumonia
2. He has IDH inhibitor–associated differentiation syndrome
3. He has a cardiac history and needs a cardiac consult
4. He has retinoic acid syndrome
5. I'm unsure

Question #2

Your patient has been diagnosed with relapsed AML after initial treatment. Testing with next-generation sequencing has revealed an *IDH2* mutation. What is your choice of treatment?

1. Enasidenib
2. Gemtuzumab
3. Midostaurin
4. Quizartinib
5. I'm unsure

Question #3

Which recently approved anti-CD33 monoclonal antibody has a history that underscores the importance of examining alternative dosing, scheduling, and administration of therapies for patients with acute myeloid leukemia (AML), especially in those who may be most vulnerable to the side effects of treatment?

1. Ofatumumab
2. Rituximab
3. Gemtuzumab ozogamicin
4. Ipilimumab
5. I'm unsure

Question #4

You have a 67-year-old male patient with *FLT3*-positive AML who received a standard dose of cytarabine and daunorubicin 1 year ago and is now presenting with a relapse. The phase I/II CHRYSALIS study results were the first demonstration of molecular response to a FLT3 inhibitor in AML. Your patient may be a good candidate for the ongoing registrational ADMIRAL trial for patients with relapsed/refractory *FLT3*+ AML. Which therapy is being studied in this trial?

1. Enasidenib
2. Quizartinib
3. Midostaurin
4. Gilteritinib
5. I'm unsure

Question #5

Patients receiving high-dose chemotherapy for the treatment of AML are at an increased risk of neutropenic fever and sepsis. So timely initiation of antibiotic treatment is critical. A 2006 study of 2,154 patients showed a survival rate of 80%, if antibiotics are administered within how long after documented hypotension?

1. 24 hours
2. 3 days
3. 1 hour
4. 12 hours
5. I'm unsure