JADPRO CE
Regional Lectures

Clinical Management of Novel Therapies for Hematologic Malignancies: Targeted Therapies, CAR-T, and Beyond

Risk-Adapted Treatment of Acute Myelogenous Leukemia

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Faculty Financial Disclosures

- Ms. Kurtin has served as a consultant for AbbVie, Celgene, Genentech, and Pharmacyclics.
- Ms. Goodrich has served on the speakers bureau for Gilead.
- Dr. Kiel has served on speakers bureaus for Celgene, Genentech, Gilead, and Takeda.
- Ms. Ridgeway has served on the speakers bureau for Abbvie and Phamacyclics
- Ms. Rogers has served on advisory boards for Gilead, Merck, and Takeda, and has served on speakers bureaus for Bristol-Myers Squibb, Genentech, Seattle Genetics, and Teva Pharmaceuticals.

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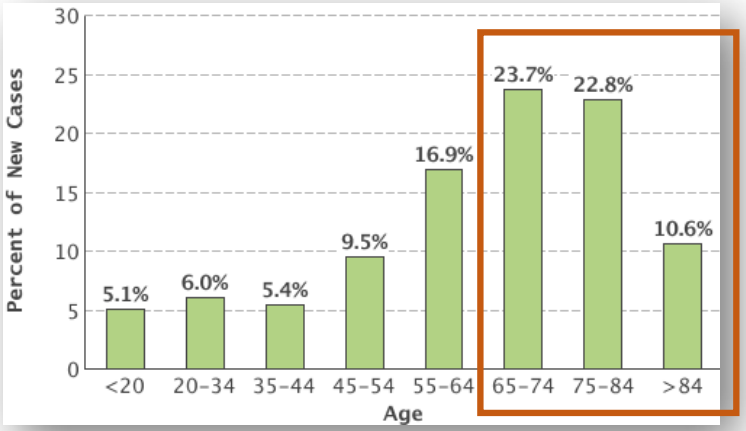
Learning Objectives

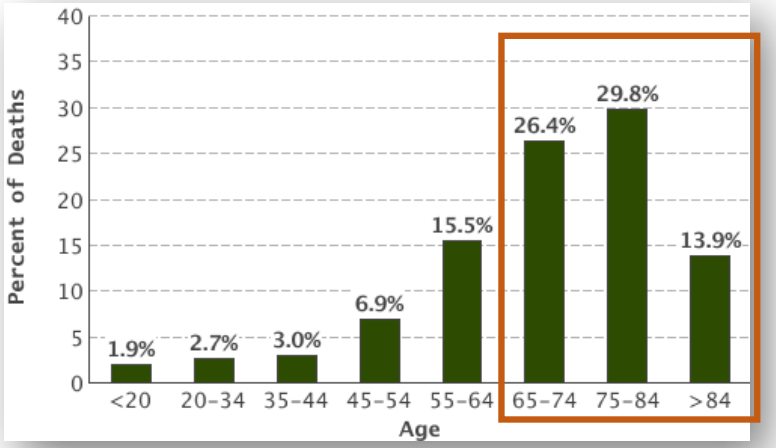
- Discuss newly approved and investigational therapies and clinical trials for AML
- Describe mitigation strategies to manage side effects of emerging therapies in AML
- Discuss advancements in diagnostic tests used in risk stratification for AML including next-generation sequencing (NGS) for the discovery of novel molecular abnormalities as defined by the World Health Organization (WHO) and European Leukemia Network
- Discuss management of minimal residual disease

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

OS = overall survival

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 hematologic 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. (2018) Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D., Gobel B.H., Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 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 germline predisposition
Review of medication profile	Identification of any drug-induced cytopenias and 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. (2018) Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D., Gobel B.H., Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* 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. (2018) Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D., Gobel B.H., Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* Jones & Bartlett, Burlington, MA; Dohner 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 morphologic 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 [22.5 cm])	Evaluate cellularity, topography, exclusion of other bone marrow disorders Two cores may be obtained in patients who are dry taps Peripheral blood may assist in cases in patients with elevated WBC and circulating blasts

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

Kurtin, S. (2018) Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D., Gobel B.H., Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* Jones & Bartlett, Burlington, MA; Dohner 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*
- Screening for gene rearrangements
  - PML-RARA, CBFB-MYH11, RUNX1-RUNX1T1, BCR-ABL1, other fusion genes

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

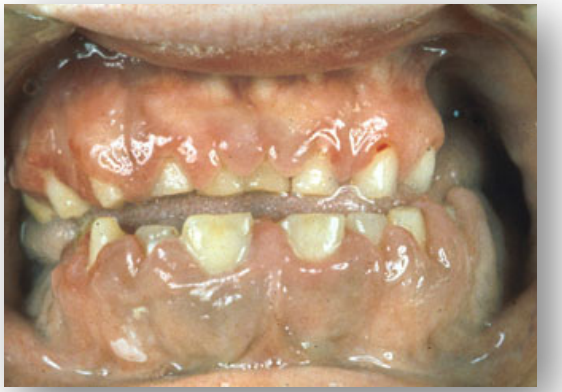
Diagnostic Evaluation: Radiology

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

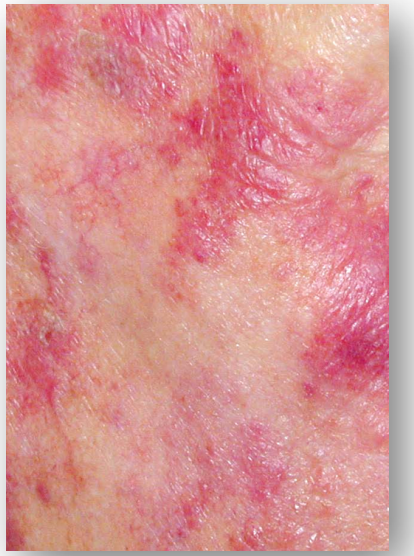
CT = computed tomography; EKG = electrocardiogram; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PET = positron emission tomography.

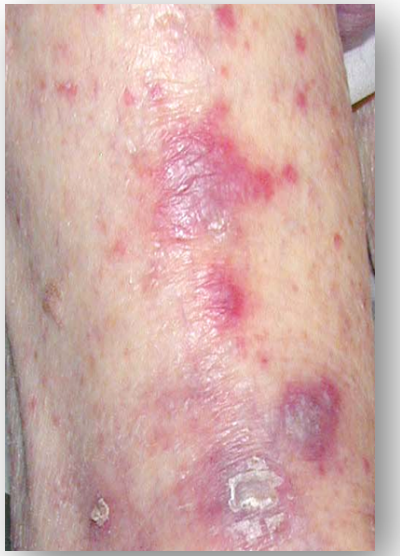
Kurtin, S. (2018) Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D., Gobel B.H., Eds. *Cancer Nursing, Principles and Practice, 8th Edition.* Jones & Bartlett, Burlington, MA; O'Donnell MR, et al. *J Natl Compr Canc Netw* 2017;15(7):926-57.

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 germline predisposition without a preexisting disorder or organ dysfunction**
  - AML with germline *CEBPA* mutation
  - Myeloid neoplasms with germline *DDX41* mutation
- **Myeloid neoplasms with germline predisposition and preexisting platelet disorders**
  - Myeloid neoplasms with germline *RUNX1* mutation
  - Myeloid neoplasms with germline *ANKRD26* mutation
  - Myeloid neoplasms with germline *ETV6* mutation
- **Myeloid neoplasms with germline predisposition and other organ dysfunction**
  - Myeloid neoplasms with germline *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.

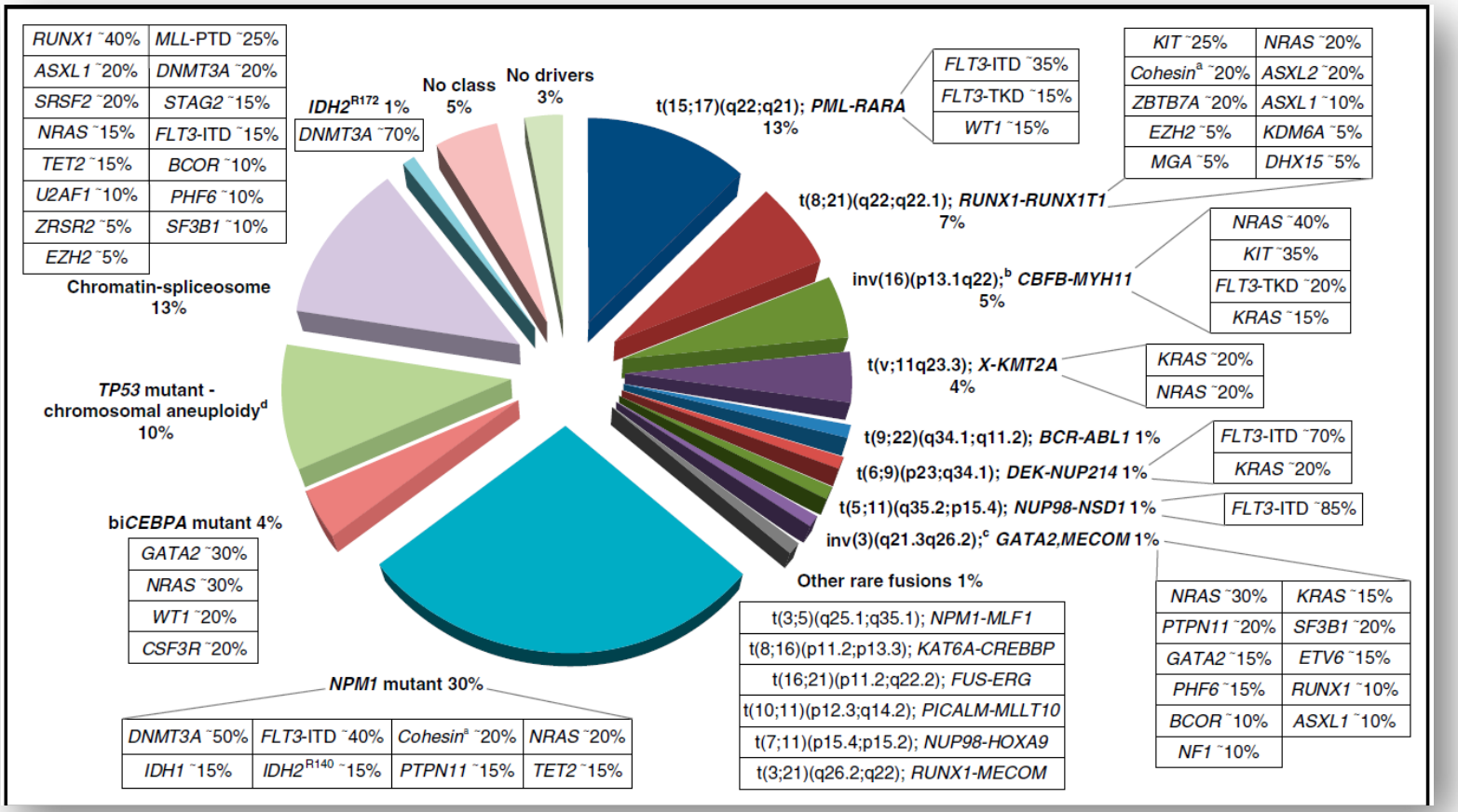
2016 Revision of the WHO Classification: AML and Related Neoplasms

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



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

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 response; MRD = minimal residual disease

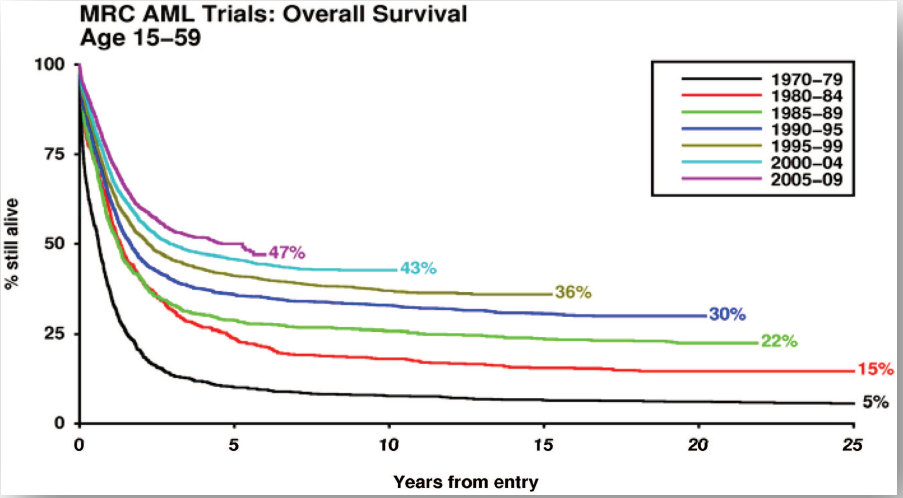
Kurtin, S. (2018) Leukemia and Myelodysplastic Syndromes., In Yarbro C, Wujick D., Gobel B.H., Eds. *Cancer Nursing, Principles and Practice, 8th Edition*. Jones & Bartlett, Burlington, MA; O'Donnell MR, et al. *J Natl Compr Canc Netw* 2017;15(7):926-57.

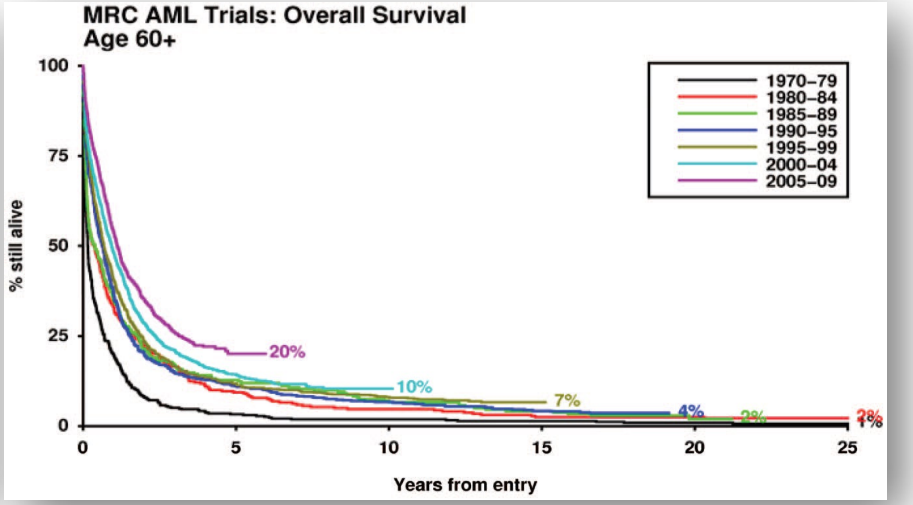
Risk Stratification: Factors Associated With Poor Risk

- 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.

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 ≤ 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 x ULN, or AST/ALT > ULN to 2.5 x 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 (cont.)

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 x ULN, or AST/ALT > 2.5 x 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.

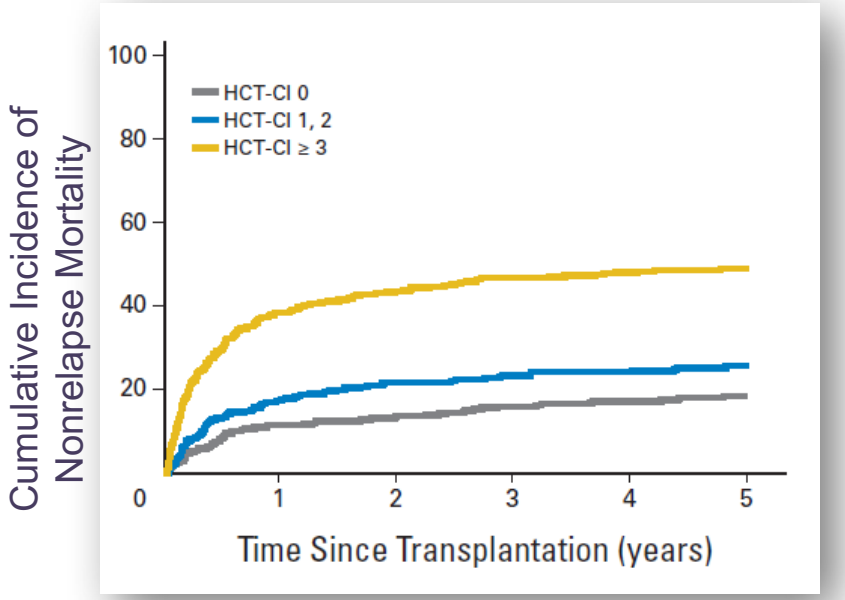
Sorror ML et al. *Blood* 2005;106:2912–9; Sorror ML, et al. *J Clin Oncol* 2014;32:3249-56; Sorror ML, et al. *JAMA Oncol* 2017 [Epub ahead of print]; Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), http://www.hctci.org.

Eligibility for Intensive Therapy: HCT-CI AML Composite Score

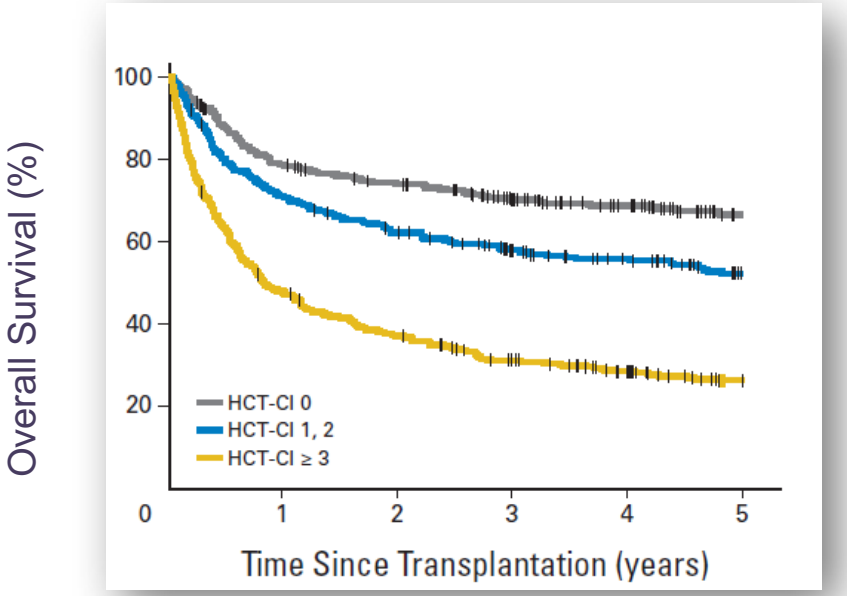
Additional factors	Definition in HCT-CI	Score
Age	0–49	0
	50–59	1
	60–69	2
	≥ 70	2
Cytogenetic/molecular risks	Favorable	0
	Intermediate	1
	Adverse	2

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



Eligibility for Intensive Therapy: HCT-CI AML Composite Score

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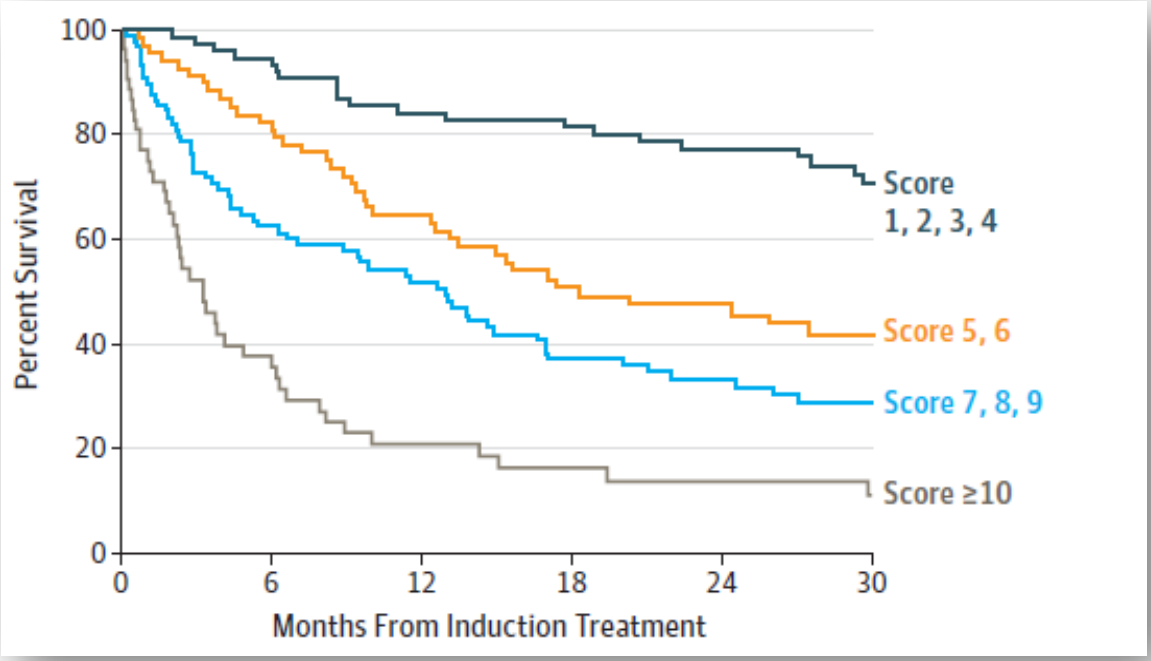
	50–59	1
	60–69	2
	≥ 70	2
Cytogenetic/ molecular risks	Favorable	0
	Intermediate	1
	Adverse	2

Additional factors	Definition in HCT-CI	Score
Albumin	< 4.0–3.5	0
	< 3.5–3.0	1
Platelet count x 10^3 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].

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.

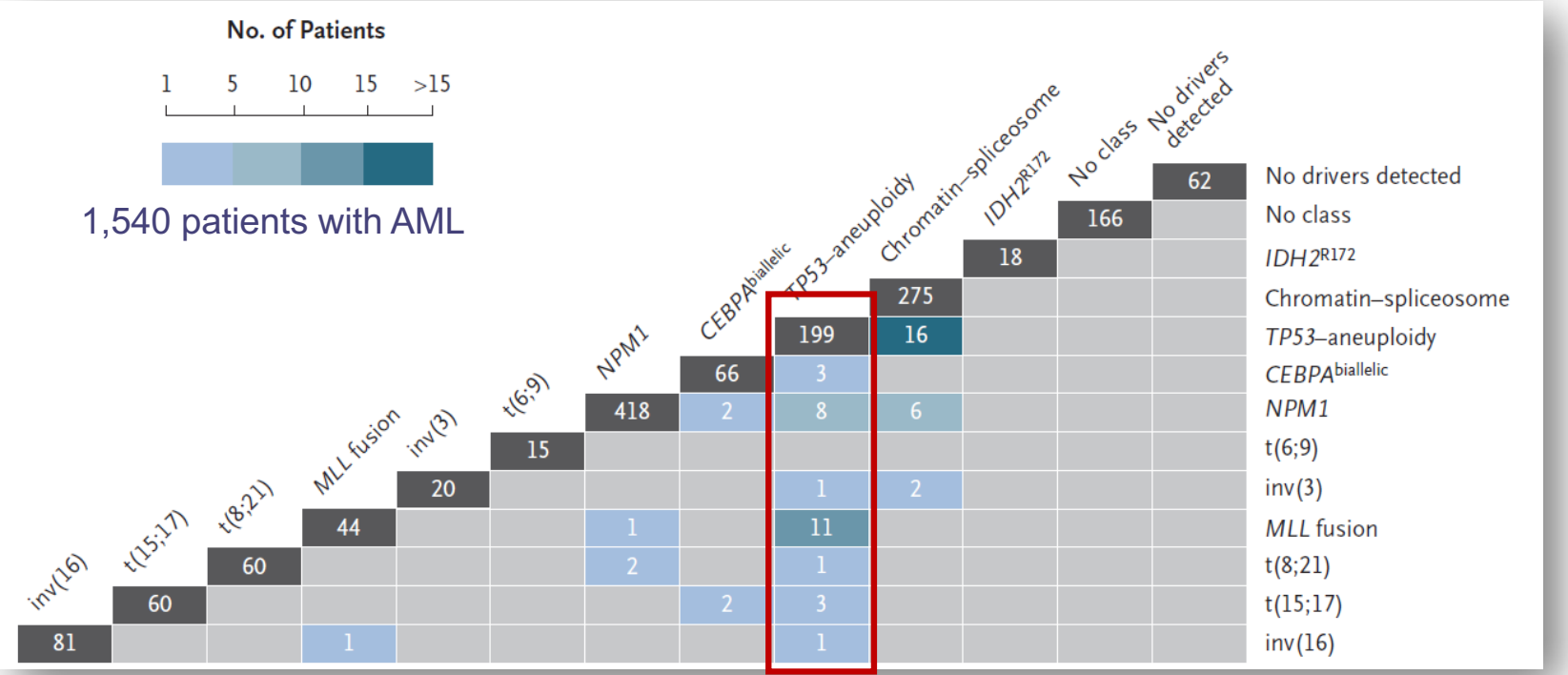
Dohner H, et al. *Blood* 2017;129(4):424-47.

2017 ELN Risk Stratification by Genetics: AML (cont.)

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

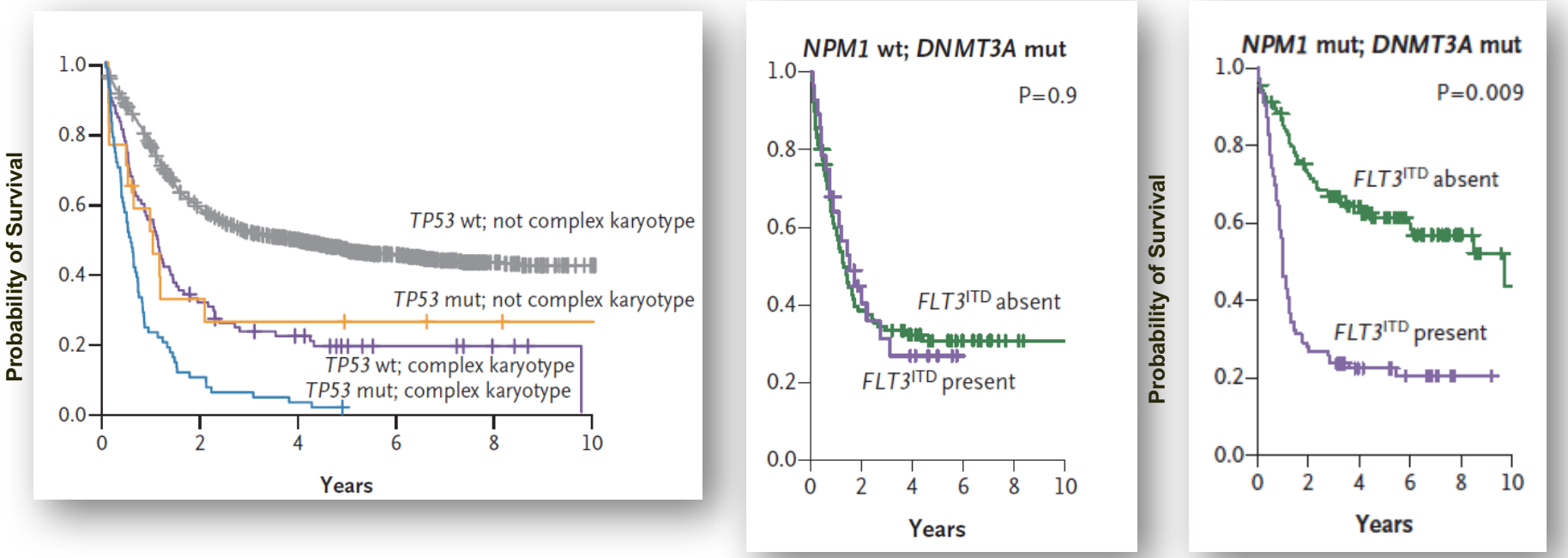
Dohner H, et al. *Blood* 2017;129(4):424-47.

Predominant Driver Mutations in AML



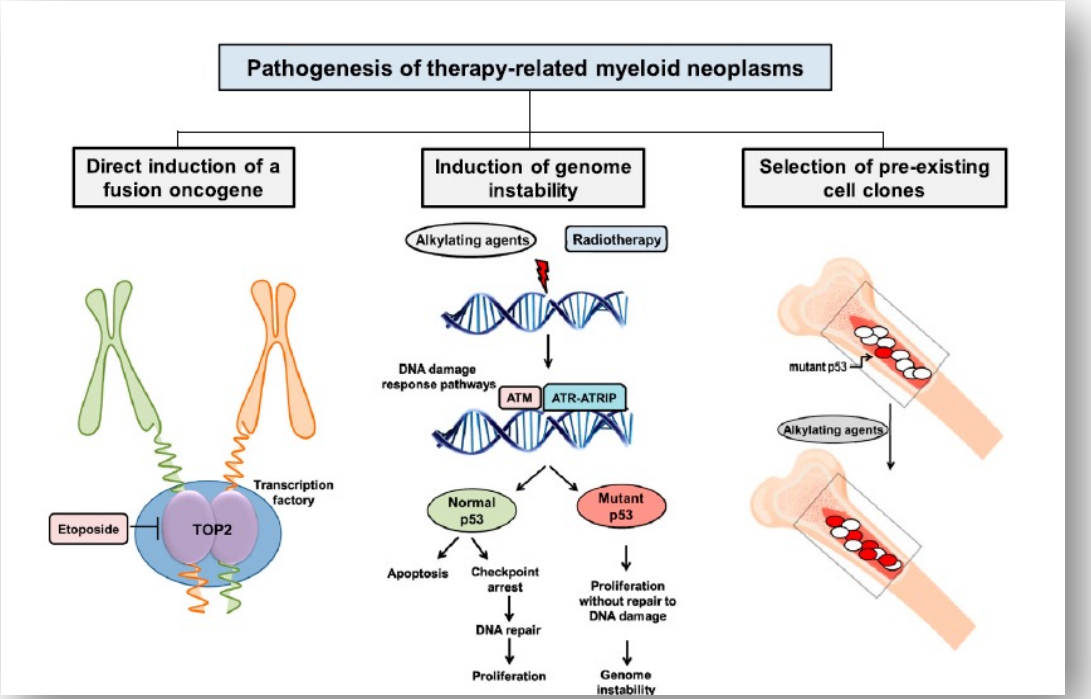
Papaemmanuil E, et al. *N Engl J Med* 2016;374(23):2209-21.

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

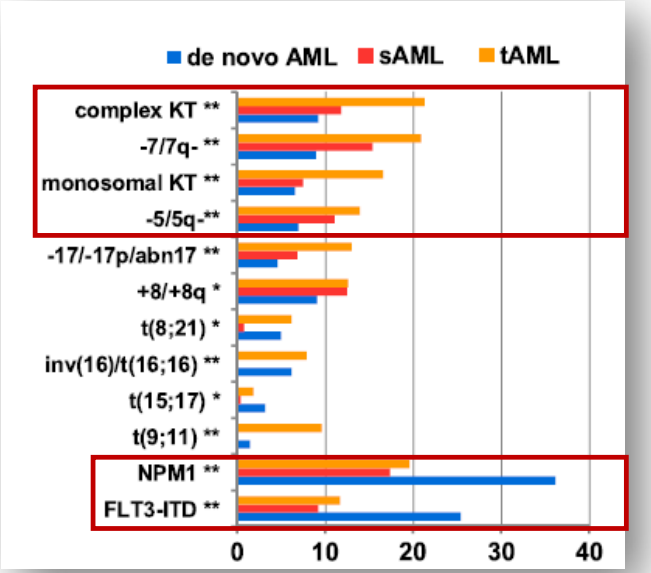


Therapy-Related Myeloid Neoplasms

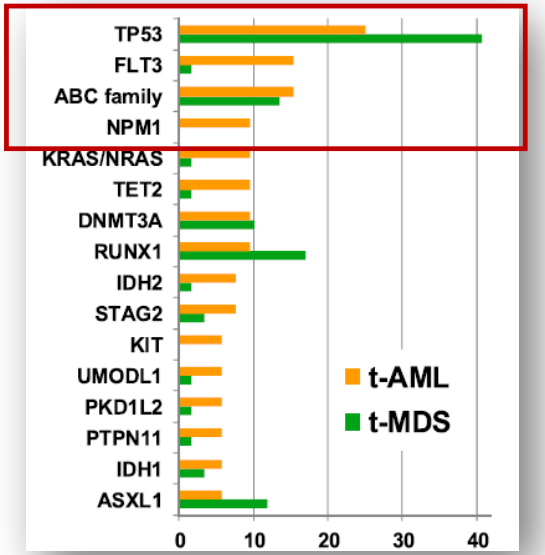
- Time to onset varies by treatment
- Alkylating agents/radiotherapy: latency period of 5–10 years
- Topoisomerase II inhibitors: latency period 2–3 years



Cytogenetic and Molecular Attributers in tAML, tMDS, and sAML



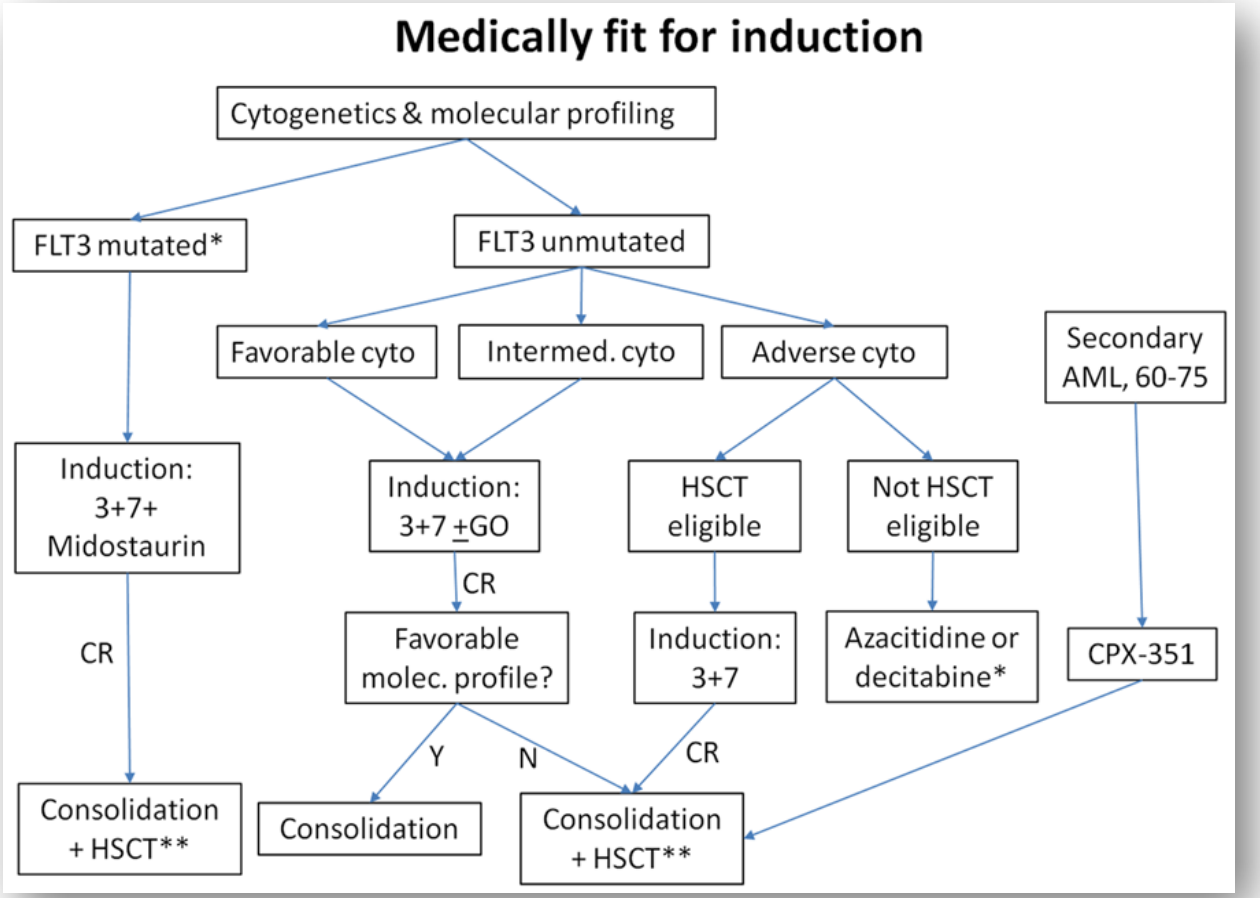
Frequency % of cytogenetic aberrations (n = 3,654)



Frequency % of molecular aberrations (n = 102)

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

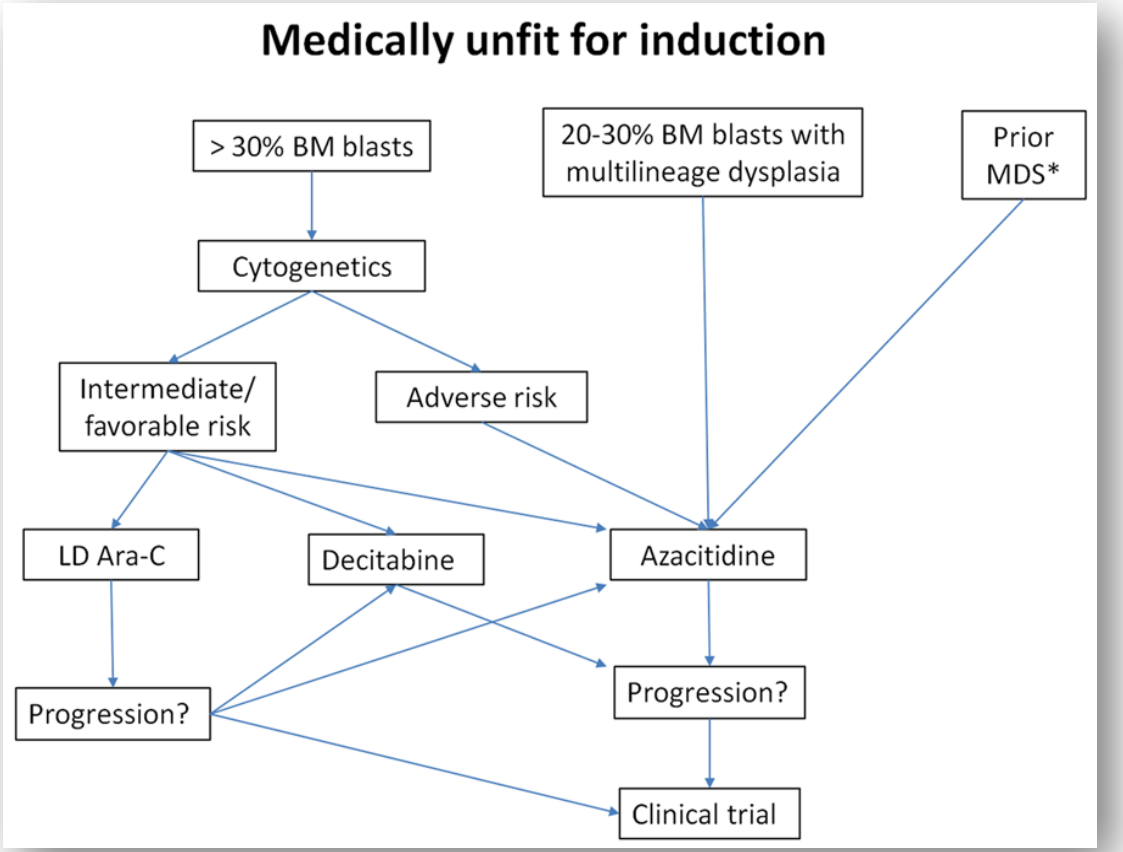
Treatment Approach for Newly Diagnosed AML



*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.

Treatment Approach for Newly Diagnosed AML (cont.)

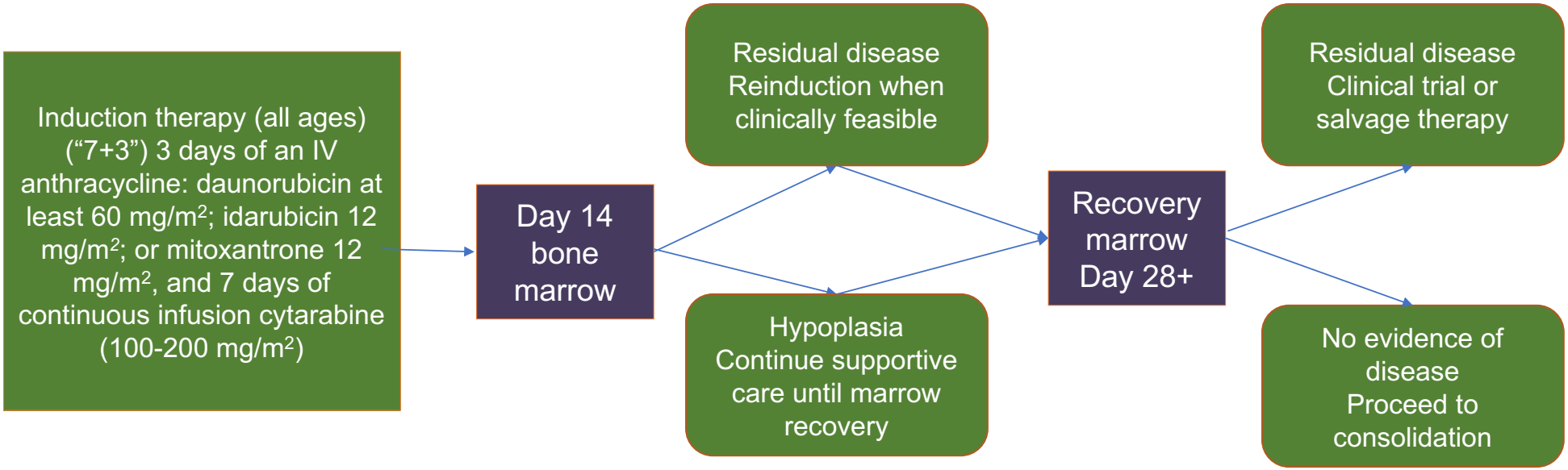


*If no prior exposure to hypomethylating agents.

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 and Consolidation in AML



IV = intravenous.

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%–75%
  - CR rate in patients older than age 60 years: 35%–50%
- Relapse is 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

Audience Response Question #15

Mr. M is a 62-year-old male with newly diagnosed AML with antecedent myelodysplastic syndrome with bone marrow blasts of 80%. He had been feeling well and exercising regularly, until 3 weeks ago when he became progressively more fatigued, had low-grade fevers, and noticed bruises in the absence of any trauma. He was started on liposomal daunorubicin and cytarabine (CPX-351) with the intent to proceed to allogeneic stem cell transplant. He is at day 28 after induction with persistent cytopenias.

Given the mechanism of action of the drug, you plan to:

A. Repeat the bone marrow biopsy, as you are concerned he has residual disease
B. Plan to re-induce with a second cycle of CPX-351
C. Plan to wait 2–3 more weeks to allow for marrow recovery prior to a bone marrow biopsy
D. Inform Mr. M that he has failed induction and will need to shift to palliative care or consider a hypomethylating agent
E. Unsure

Audience Response Question #16

Ms. T is a 38-year-old female with relapsed AML 4 months after induction and consolidation. She is awaiting an allogeneic stem cell transplant, but does not have a donor available. Repeat bone marrow biopsy shows a complex karyotype with IDH2+ disease. You are seeing Ms. T on day 21 of treatment with enasidenib. Her WBCs have increased to 38 x 10^9/L, she reports feeling more short of breath, has gained 10 pounds in 1 week, and has been having low-grade fevers. She is not hypoxic. You obtain a CXR that is non-diagnostic. CT of the chest shows mild interstitial edema.

What will you do next?

A. Proceed with a workup for infection/sepsis. Plan to repeat the bone marrow biopsy, as you are concerned she has progressed. Discontinue enasidenib. Consult Infectious Disease.

B. Proceed with a workup for infection/sepsis. Consult Infectious Disease and Pulmonary. Stop the enasidenib and start dexamethasone 10 mg bid, as you suspect differentiation syndrome.

C. Proceed with a workup for infection/sepsis. Consult Infectious Disease and Pulmonary. Stop the enasidenib and start levofloxacin. You suspect pneumonia.

D. Proceed with a workup for infection/sepsis. Consult Infectious Disease and Pulmonary. Continue the enasidenib and start dexamethasone 10 mg bid and furosemide as you suspect differentiation syndrome.

E. Unsure

CXR = chest x-ray.

Selected Novel Agents Used to Treat AML

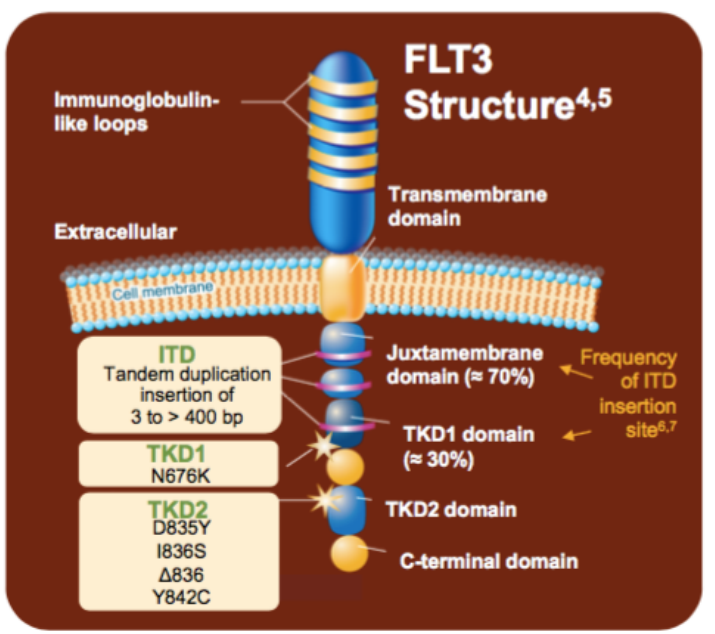
Agent	Mechanism of action	Suggested population	Notes
CPX-351	Liposomal 7+3 in 5:1 molar ratio	sAML fit for induction chemotherapy	Phase II: OS benefit in sAML; phase III: OS, EFS benefit; FDA approval August 2017
Midostaurin PKC-412	Inhibitor of FLT3, c-KIT, PDGFRB, VEGFR-2, and protein kinase C	Newly 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; CRi = CR with incomplete marrow recovery; FDA = US Food and Drug Administration; EFS = event-free survival; HMA = hepatic membrane antibody; MOA = mechanism of action; ORR = objective response rate; RR = relapsed/refractory.

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

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.

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

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

Midostaurin (cont.)

- **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

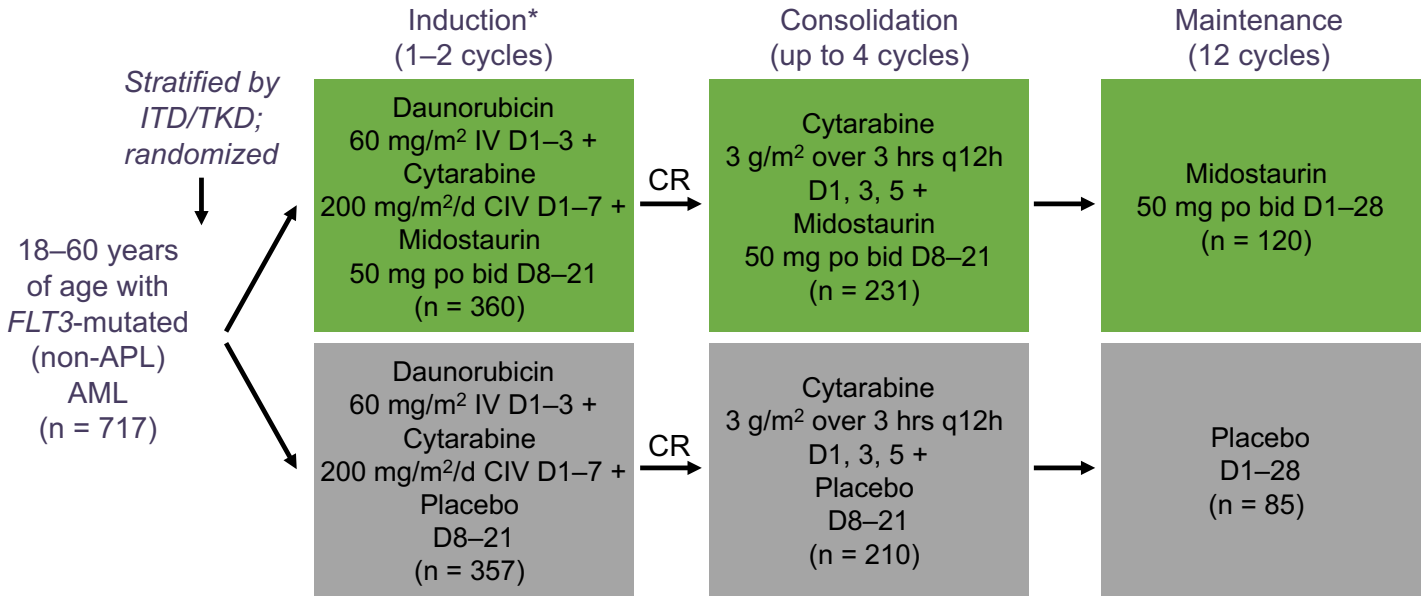
Midostaurin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

Midostaurin (cont.)

- **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

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.

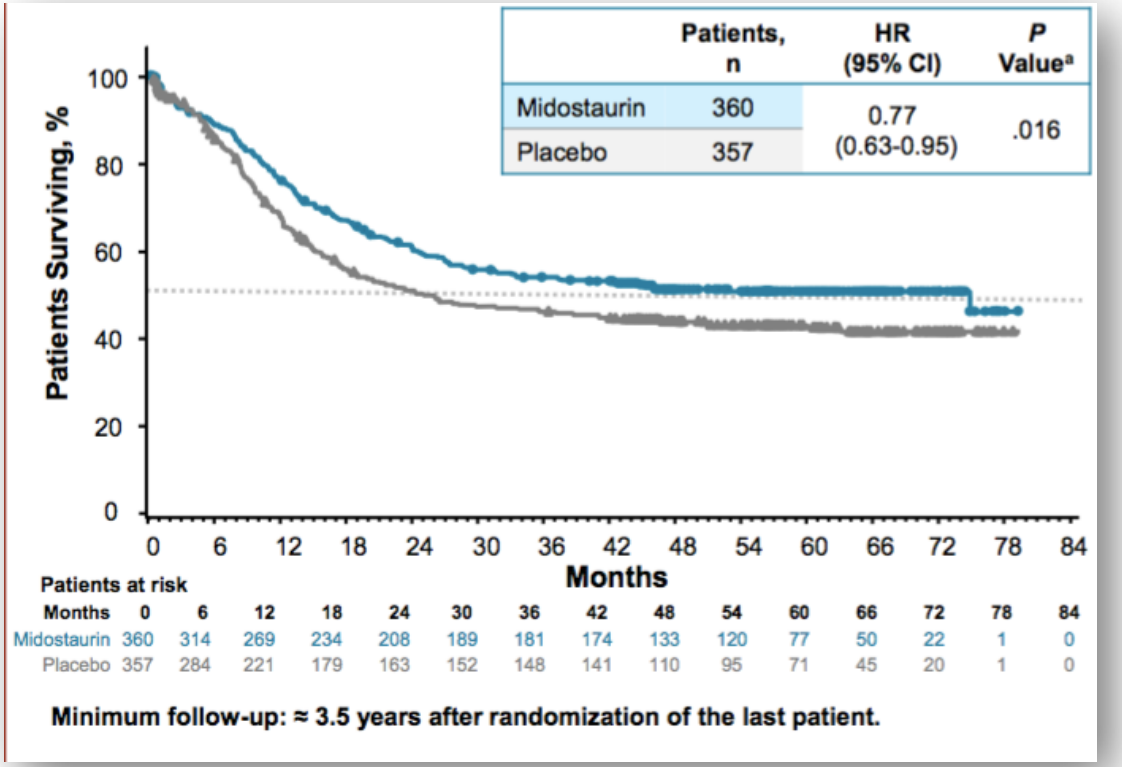
Midostaurin: Efficacy (Based on RATIFY Trial)

Outcome	Midostaurin + 7+3	Placebo + 7+3	*p* value
4-year OS, %			
• Uncensored[a]	51.4 (46.0–57.0)	44.2 (39.0–50.0)	.0074
• Censored for SCT[b]	63.8 (56.0–71.0)	55.7 (47.0–63.0)	.04
Complete response, n (%)			
• Any time	212 (59)	191 (53)	.15
• CR1 only	239 (66)	211 (59)	.045
Median EFS[c], months			
• Overall	8.0 (5.1–10.6)	3.0 (1.9–5.9)	.0025
• CR in induction/consolidation	11.3 (8.4–15.1)	6.1 (4.7–7.5)	.0002

23% reduced risk of death in midostaurin arm

[a]HR: 0.77.
[b]HR: 0.75.
[c]Event: no CR within 60 days, relapse, or death.

Midostaurin Phase III Clinical Trial



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

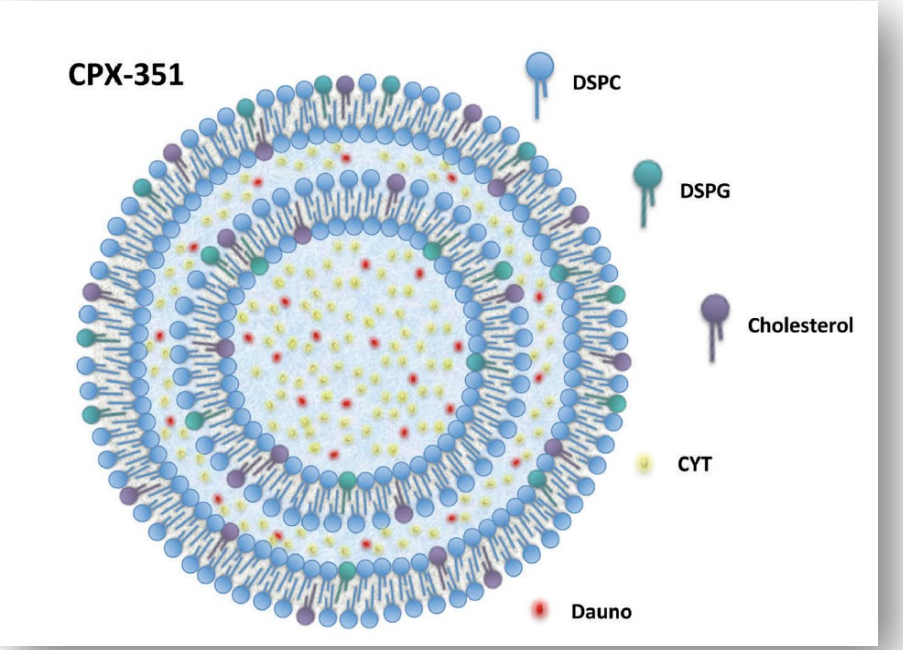
Midostaurin Safety: Grade ≥ 3 Adverse Events With Statistically Significant Differences

Adverse event	Midostaurin (n = 355), n (%)	Placebo (n = 354), n (%)	*p* value
Anemia	329 (93)	311 (88)	.03
Rash or desquamation	50 (14)	27 (8)	.0008
Nausea	20 (6)	34 (10)	.05

Remainder of adverse events were similar across the two arms.

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 liposome composed of phosphatidylcholine (DSPC)
- This gives the drug the deep purple color DSPG: cholesterol

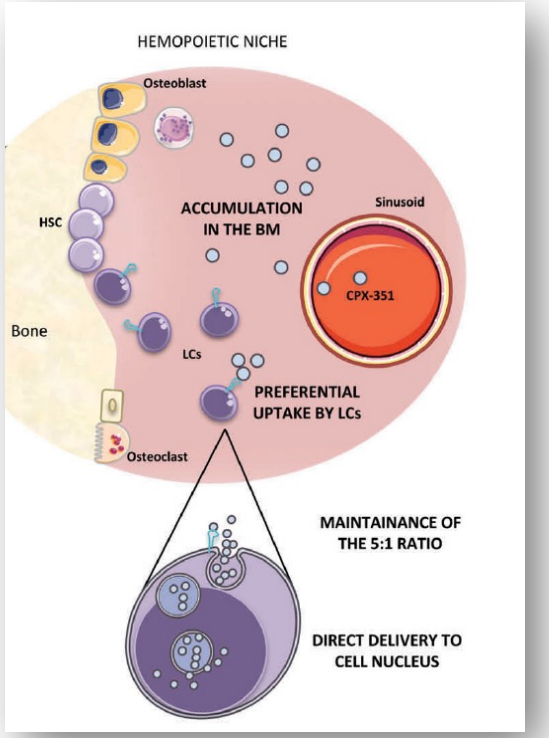


DSPC = distearoylphosphatidylcholine; DSPG = distearylphosphatidylglycerol.

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 environment



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

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.

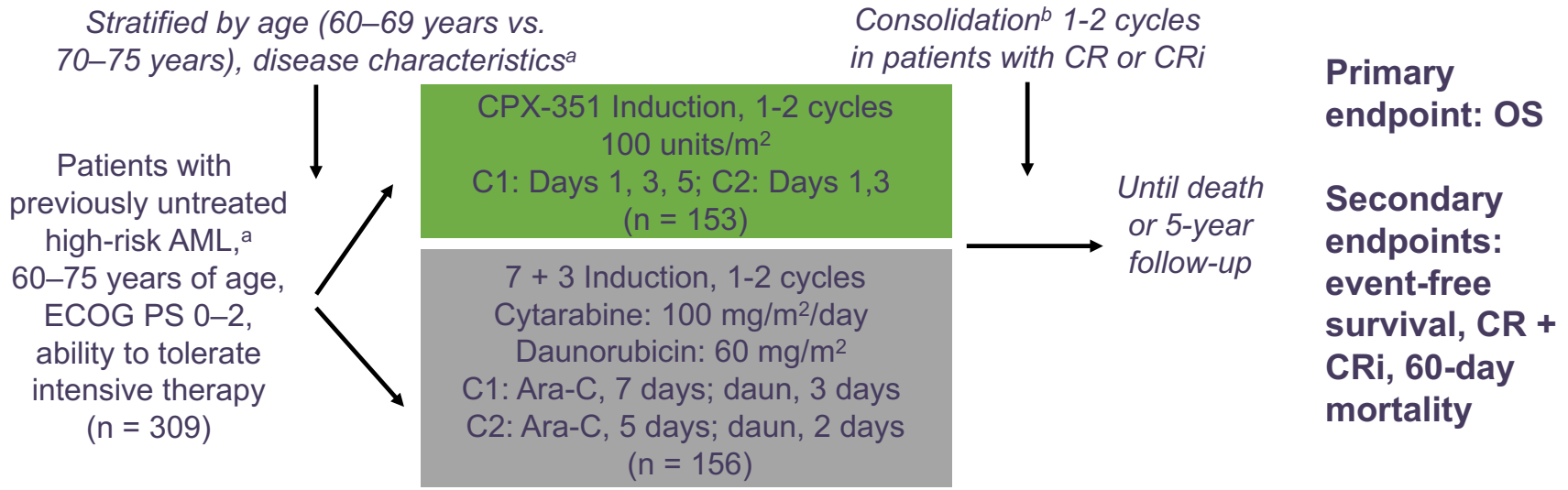
Daunorubicin and cytarabine liposomal product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209401s000lbl.pdf.

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.

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



[a]Therapy-related AML; AML with history of MDS ± prior HMA therapy or CMML; de novo AML with MDS karyotype.
[b]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).

CPX-351: Efficacy

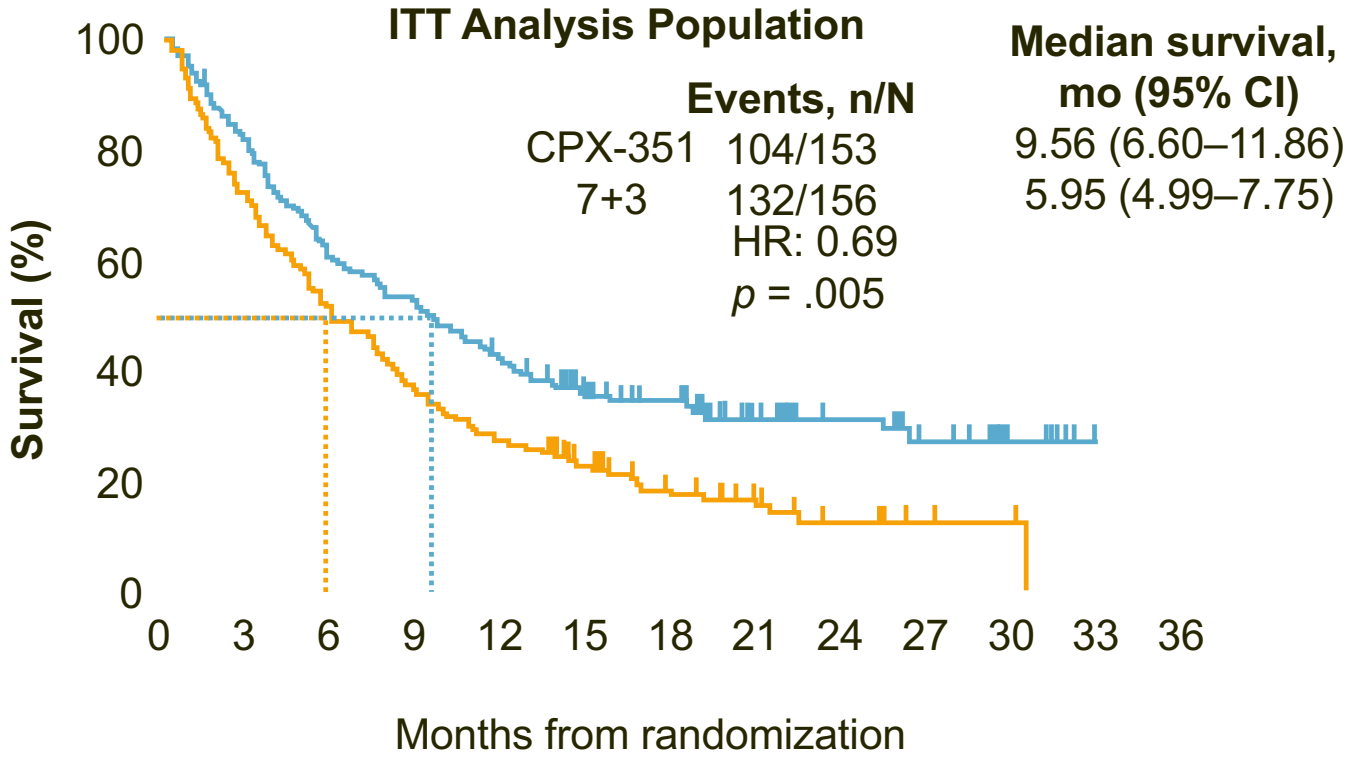
- CPX-351 demonstrated superior efficacy vs. standard 7+3 induction.
- In patients undergoing transplantation, OS higher with CPX-351 (n = 52) vs. 7+3 (n = 39): NR vs. 10.25 mo (HR: 0.46; 95% CI = 6.21–16.69; *p* = .0046)
- 30- and 60-day mortality rates lower with CPX-351 vs. 7+3

Outcome	CPX-351 (n = 153)	7+3 (n = 156)	HR	Odds Ratio (95% CI)	*p* value
Median OS, mo (95% CI)	9.56 (6.60–11.86)	5.95 (4.99–7.75)	0.69	NA	.005
Median EFS, mo (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.

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

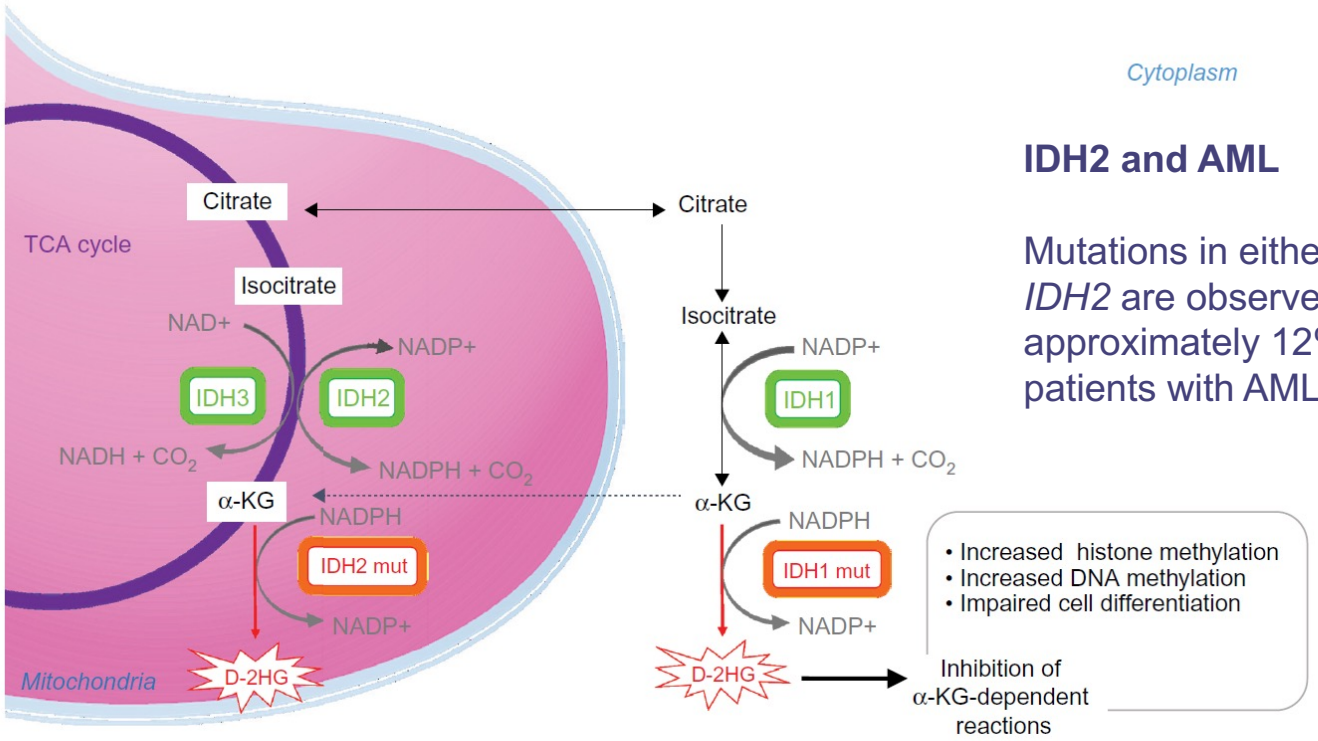
CPX-351: Prolonged Time to Recovery of Cytopenias Associated with CPX-351

	Induction		Consolidation (at least 1 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).

Enzymatic Activities of Wild Type and Mutated IDH Enzymes



IDH2 and AML

Mutations in either *IDH1* or *IDH2* are observed in approximately 12% of patients with AML

Enasidenib

- **Mechanism:** IDH2 inhibitor
  - Acts by inducing bone marrow differentiation and maturation rather than ablation
- **Indications:** Adult patients with relapsed or refractory AML with an IDH2 mutation as detected by an FDA-approved test
  - Abbott RealTime™ IDH2 PCR assay
- **Dosing:** 100 mg po once daily continuously
  - 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
  - No significant interactions (food, antacids, other agents)

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

Enasidenib (cont.)

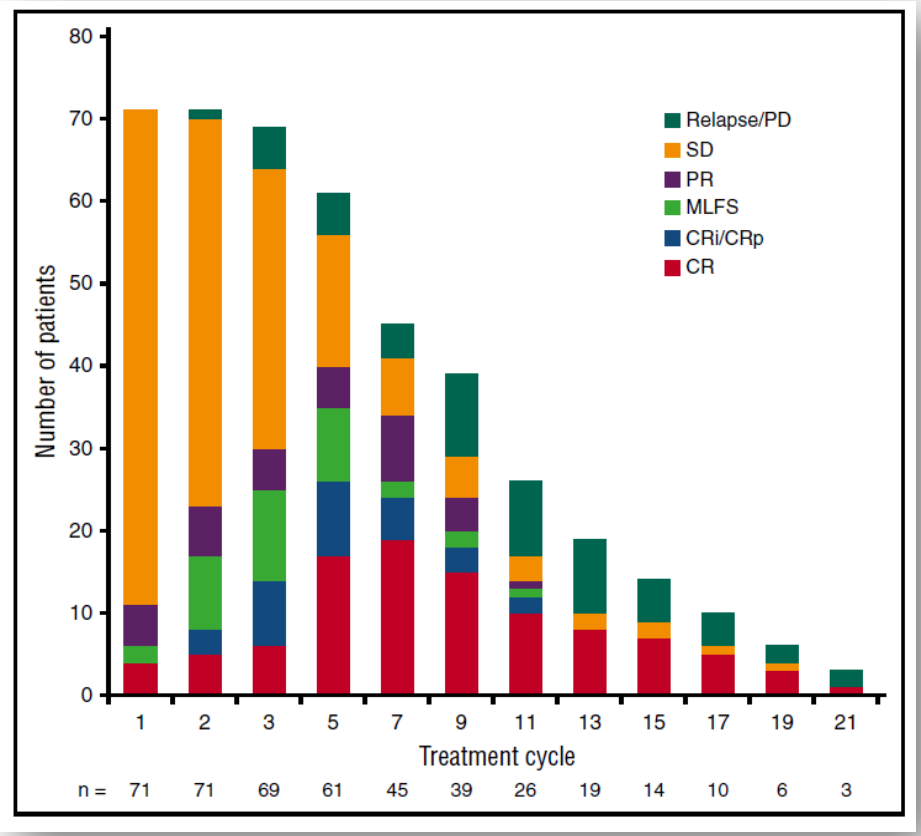
- **Warnings and precautions**
  - Tumor lysis syndrome
  - Differentiation syndrome
    - Similar to that seen with arsenic trioxide, all-*trans* retinoic acid in promyelocytic leukemia
    - Treat with hemodynamic monitoring and support, corticosteroids
  - Leukocytosis
    - May initiate hydroxyurea 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 (cont.)

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



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

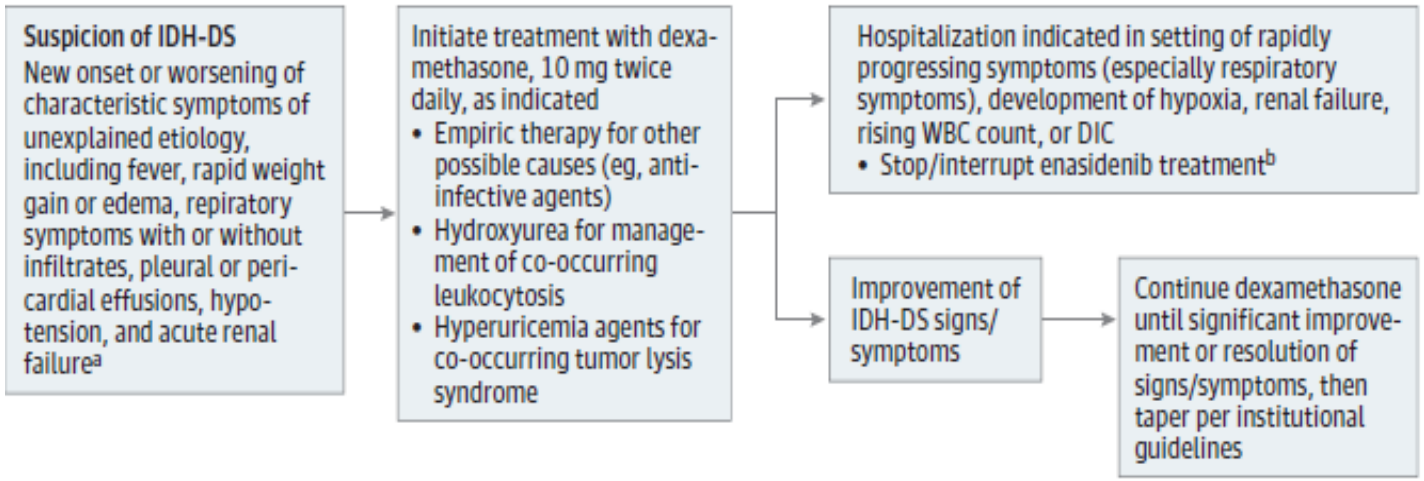
Stein EM, et al. *Blood* 2017;130(6):722-31.

IDH Differentiation Syndrome (IDH-DS)

- 11.7% (33/281) of study participants were identified as having possible or probable IDH-DS
  - Median age = 70 years (range, 38–80 years)
  - 60.6% were male
  - 39.4% (13/33) had concomitant leukocytosis
  - Other risk factors: > 20% blasts, > 1 prior therapy
- Median time to onset = 30 days (range, 7–129 days)
- Most frequent manifestations
  - Dyspnea
  - Fever
  - Pulmonary infiltrates
  - Hypoxia
- Enasidenib dosing was interrupted for 15 patients (45.5%), but permanent discontinuation of treatment was not required

Fathi AT, DiNardo CD, Kline I, et al. JAMA Oncol. 2018: DOI 10.1001/jamaoncol.2017.4695

Differentiation Syndrome Review Committee Amended Protocol for Isocitrate Dehydrogenase Differentiation Syndrome (IDH-DS) Diagnosis and Management



DIC indicates disseminated intravascular coagulation; WBC, white blood cells.

[a] Typical onset is between 7 to 10 days and 5 months from start of enasidenib treatment or reinitiation of enasidenib after prolonged treatment interruption.

[b] Owing to the long half-life of enasidenib, treatment may not immediately reverse symptoms of IDH-DS.

Fathi AT, DiNardo CD, Kline I, et al. JAMA Oncol. 2018: DOI 10.1001/jamaoncol.2017.4695

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

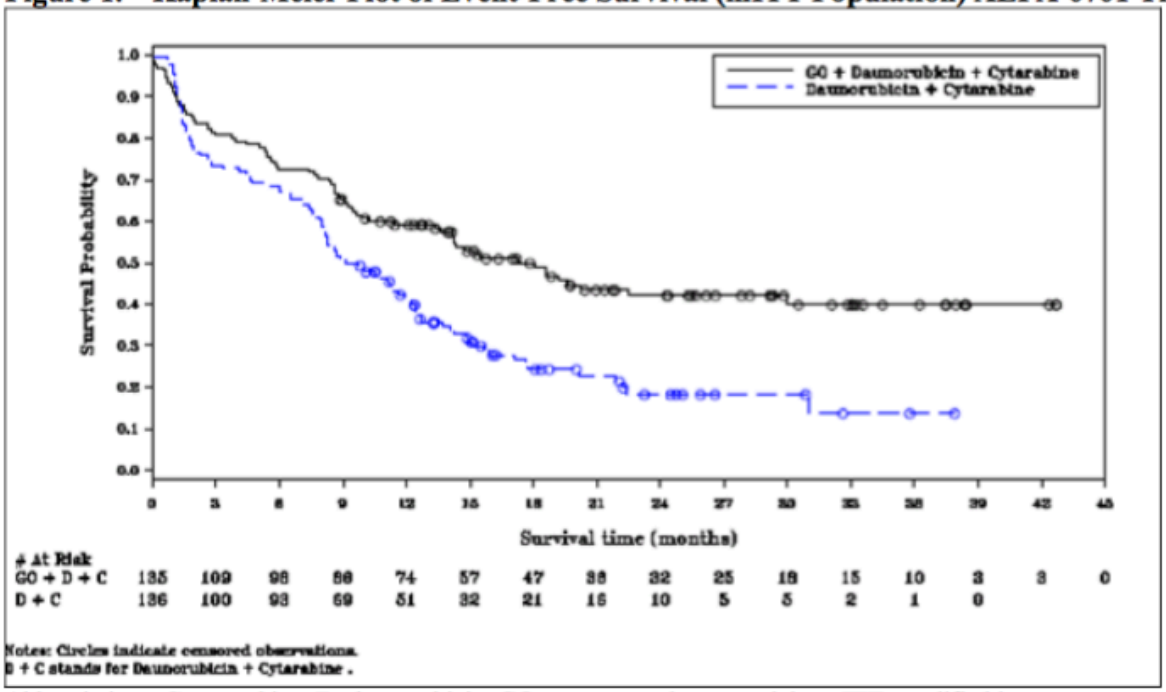
Gemtuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf.

Gemtuzumab Ozogamicin (cont.)

- **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

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

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

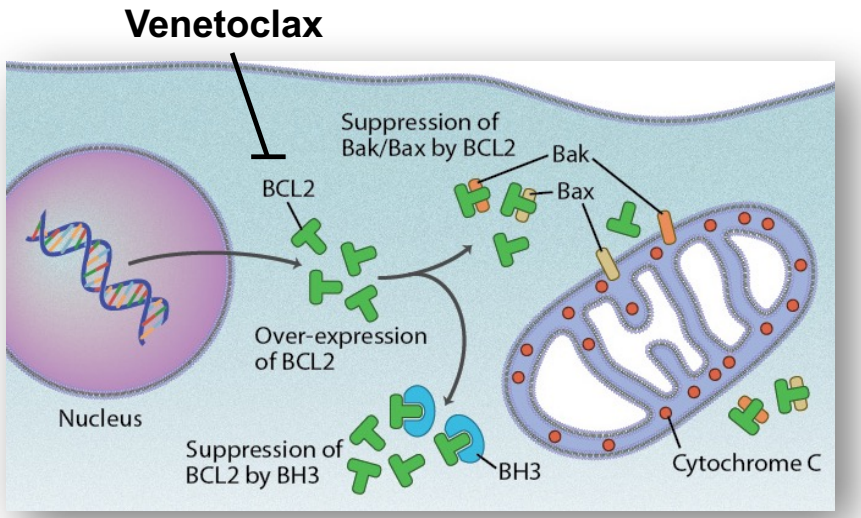


Abbreviations: C=cytarabine; D=daunorubicin; GO=gemtuzumab ozogamicin; mITT=modified intent-to-treat.

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

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



BCL2 Inhibition in AML: Venetoclax

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

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

Where to Go From Here? Emerging Therapies (cont.)

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

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

Audience Response Question #15

Mr. M is a 62-year-old male with newly diagnosed AML with antecedent myelodysplastic syndrome with bone marrow blasts of 80%. He had been feeling well and exercising regularly, until 3 weeks ago when he became progressively more fatigued, had low-grade fevers, and noticed bruises in the absence of any trauma. He was started on liposomal daunorubicin and cytarabine (CPX-351) with the intent to proceed to allogeneic stem cell transplant. He is at day 28 after induction with persistent cytopenias.

Given the mechanism of action of the drug, you plan to:

A. Repeat the bone marrow biopsy, as you are concerned he has residual disease
B. Plan to re-induce with a second cycle of CPX-351
C. Plan to wait 2–3 more weeks to allow for marrow recovery prior to a bone marrow biopsy
D. Inform Mr. M that he has failed induction and will need to shift to palliative care or consider a hypomethylating agent
E. Unsure

Audience Response Question #16

Ms. T is a 38-year-old female with relapsed AML 4 months after induction and consolidation. She is awaiting an allogeneic stem cell transplant, but does not have a donor available. Repeat bone marrow biopsy shows a complex karyotype with IDH2+ disease. You are seeing Ms. T on day 21 of treatment with enasidenib. Her WBCs have increased to 38 x 10^9/L, she reports feeling more short of breath, has gained 10 pounds in 1 week, and has been having low-grade fevers. She is not hypoxic. You obtain a CXR that is non-diagnostic. CT of the chest shows mild interstitial edema.

What will you do next?

A. Proceed with a workup for infection/sepsis. Plan to repeat the bone marrow biopsy, as you are concerned she has progressed. Discontinue enasidenib. Consult Infectious Disease.

B. Proceed with a workup for infection/sepsis. Consult Infectious Disease and Pulmonary. Stop the enasidenib and start dexamethasone 10 mg bid, as you suspect differentiation syndrome.

C. Proceed with a workup for infection/sepsis. Consult Infectious Disease and Pulmonary. Stop the enasidenib and start levofloxacin. You suspect pneumonia.

D. Proceed with a workup for infection/sepsis. Consult Infectious Disease and Pulmonary. Continue the enasidenib and start dexamethasone 10 mg bid and furosemide as you suspect differentiation syndrome.

E. Unsure

CXR = chest x-ray.