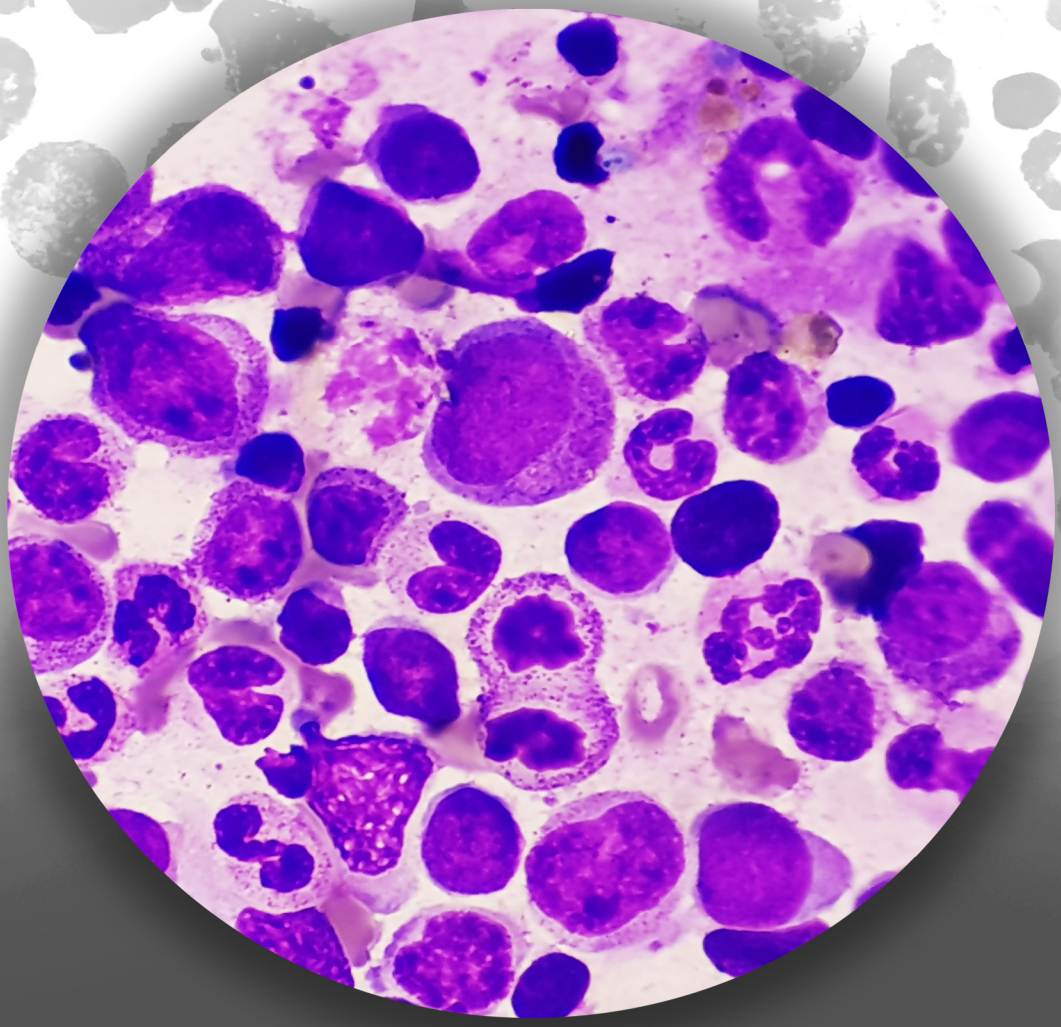

How Can You Use Newer Therapies
to Improve Clinical Decision-Making and
Long-term Health Outcomes for Patients with

ACUTE MYELOID LEUKEMIA?

This activity is provided by Med Learning Group.
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This activity is supported by educational grants from AbbVie Inc. and Bristol Myers Squibb.

How Can You Use Newer Therapies to Improve Clinical Decision-Making and Long-term Health Outcomes for Patients with Acute Myeloid Leukemia?

PROGRAM CHAIR

David Rizzieri, MD
Senior Vice President and Director
Novant Health Cancer Institute
Charlotte, NC

SPEAKER FACULTY

Anjali Advani, MD Director, Inpatient Leukemia Unit Cleveland Clinic Taussig Cancer Institute Professor of Medicine, Cleveland Clinic Lerner College of Medicine Chair, Data Safety and Monitoring Committee Case Comprehensive Cancer Center Cleveland, OH	**Hetty Carraway, MD, MBA** Director, Leukemia Program Vice Chair, Strategy and Enterprise Development Professor, Oncology Taussig Cancer Institute, Cleveland Clinic Cleveland, OH	**Tapan M. Kadia, MD** Associate Professor Department of Leukemia The University of Texas MD Anderson Cancer Center Houston, TX
Jeffrey E. Lancet, MD Senior Member, Chair Department of Malignant Hematology Moffitt Cancer Center Professor of Oncologic Sciences University of South Florida Tampa, FL	**Alice S. Mims, MD, MSCR** Acute Leukemia Clinical Research Director Associate Professor of Internal Medicine The James Comprehensive Cancer Center The Ohio State University Columbus, OH	**Joshua Zeidner, MD** Assistant Professor of Medicine Chief, Leukemia Research Associate Chief of Research, Hematology Division of Hematology University of North Carolina, Lineberger Comprehensive Cancer Center Chapel Hill, NC

PROGRAM OVERVIEW

This activity will cover the assessment, monitoring, and treatment of Acute Myeloid Leukemia (AML).

TARGET AUDIENCE

This educational activity is intended for community oncologists and advanced practice oncology clinicians involved in the assessment, monitoring, and treatment of AML.

LEARNING OBJECTIVES

On completing the program, attendees should be able to:

- Evaluate how genetic and molecular markers aid in determining treatment strategies for patients with AML
- Assess clinical efficacy and safety data for newer formulations and novel targeted therapies used to manage patients with AML
- Personalize therapy for the treatment of newly diagnosed, relapsed/refractory (R/R), and secondary AML based on disease- and patient-specific factors to communicate these treatment plans using shared decision-making strategies in the inpatient and outpatient settings
- Identify adverse events associated with AML treatment to appropriately prevent and/or manage these potential effects

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved and/or interested in the assessment, monitoring, and treatment of AML.

CNE Credits: 1.0 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT

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David Rizzieri, MD	Dr. Rizzieri reports that he serves on the speakers bureaus for Celgene, Gilead, Seattle Genetics and Stemline, Novartis, Pfizer, Sanofi, Incyte, Morphosys, BMS, Jazz, Astellas. He is also on the advisory board for AbbVie, Agios, AROG, Bayer, Celgene, Gilead, Jazz, Novartis, Pfizer, Sanofi, Seattle Genetics, Stemline, Teva, Kite, Incyte, Amgen, Acrobiotech, Cellectis, and Chimerix, Inc. Dr. Rizzieri is a consultant for AbbVie, Agios, AROG, Bayer, Celgene, Celltrion, Mustang, Pfizer, Seattle Genetics, Stemline, Kite, Incyte, Amgen, Acrobiotech, Cellectis, and Chimerix, Inc and Gilead. He has also done Data Safety Monitoring for Chimerix, Inc. and Cellectis, in addition to the UCARRT Study.
Anjali Advani, MD	Dr. Advani reports that she serves as a consultant for Pfizer, Amgen, BEAM, Kite, Glycomimetics, and Seattle Genetics. She also provides contracted research for Macrogenics, Glycomimetics, Immunogen, Seattle Genetics, Incyte, OBI, Pfizer, Amgen, and AbbVie.
Hetty Carraway, MD, MBA	Dr. Carraway reports that she serves as a consultant for Agios, BMS, Celgene, Novartis, Jazz, and Stemline. She is also on the speakers bureaus for Agios, BMS, Celgene, Novartis, Jazz, and Stemline. Dr. Carraway provides contracted research for Celgene and is on the Independent Review Committee for Takeda, ASTEX727, and AbbVie.
Tapan M. Kadia, MD	Dr. Kadia reports that he is on the speakers bureau for Cure, and also serves as a consultant for AbbVie, Agios, Daiichi Sankyo, Genentech, Jazz, Liberum, Novartis, Pfizer, and Sanofi-Aventis.
Jeffrey E. Lancet, MD	Dr. Lancet reports that he serves as a consultant for Jazz, Astellas, AbbVie, Agios, BerGenBio, Daiichi Sankyo, ElevateBio, Bristol Myers Squibb/Celgene, Millenium, and Novartis. He also provides contracted research paid to his institution for Pfizer. An immediate family member also owns stock in Arvinas.
Alice S. Mims, MD, MSCR	Dr. Mims reports that she serves as a consultant for AbbVie, Genentech, Jazz Pharmaceuticals, Daiichi Saynko, BMS, and Syndax Pharmaceuticals.
Joshua Zeidner, MD	Dr. Zeidner reports that he serves on the Advisory Board and consults for Bristol Myers Squibb, Genentech, Gilead, Servier, and Shattuck Labs. He also provides contracted research for Arog, Astex, Gilead, Merck, Sumitomo Dainippon Pharma, and Takeda.

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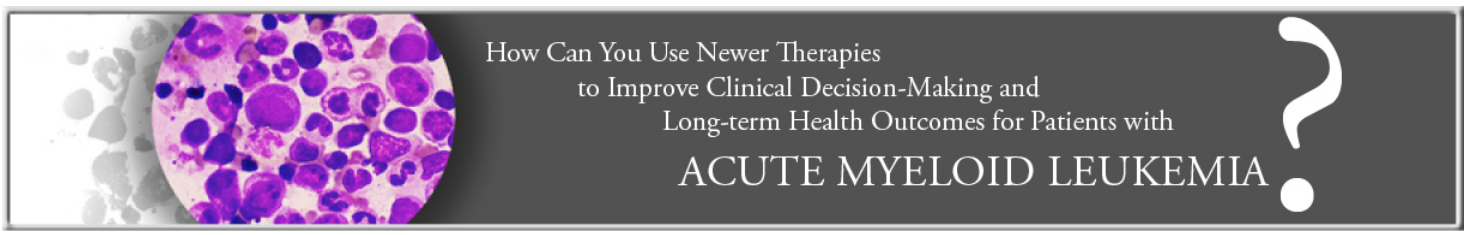

Agenda

I. AML: An Overview
- a. Review of epidemiology, disease pathophysiology, and course
- b. Treatment options and standard of care
  - i. *De novo*, secondary, and relapsed/refractory (R/R) AML

II. The Genomics of AML and the Role of Biomarkers in AML
- a. Common genetic aberrations
  - i. Diagnostic and prognostic value
  - ii. Role in treatment decision-making
  - iii. Guidelines and recommendations for testing

  Animation Theme: AML translocations and mutations (primary and secondary) and the patient experience (symptoms, etc)

III. Personalizing treatment
- a. Analysis of patient-specific factors that affect outcomes including genetic characteristics
  - i. How to discuss findings with patients and families
- b. Strategies to improve physician-patient interactions
  - i. Avenues of engagement for patients with AML and their families
  - ii. Incorporate shared decision-making practices into a value-based approach to high-quality care

IV. Currently Approved Novel Agents for the Management of Patients with AML
- a. Indications and efficacy and safety studies
  - i. Liposomal 7+3/CPX-351 (newer formulation)
  - ii. BCL-2 inhibitor
  - iii. Hedgehog pathway inhibitor
  - iv. FLT3 inhibitor
  - v. IDH1 inhibitor
  - vi. IDH2 inhibitor
  - vii. CD33 drug-antibody conjugate
  - viii. CC-486 (oral azacitidine; newer formulation)

  Animation Theme: Mechanisms of action (MOAs) of novel and targeted therapies
- b. Role of HSCT
- c. Investigational agents

V. Conclusions

VI. Questions and answers

VII. Adjournment

How Can You Use Newer Therapies to Improve Clinical Decision-Making and Long-Term Health Outcomes for Patients with Acute Myeloid Leukemia?

PROGRAM CHAIR:

David Rizzieri, MD

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Charlotte, NC

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Disclosures

- Please see Program Overview for specific speaker disclosure information
- During the course of this lecture, the presenter will discuss the use of medications for both FDA-approved and non-approved indications.

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2

Learning Objectives

- Evaluate how genetic and molecular markers aid in determining treatment strategies for patients with acute myeloid leukemia (AML)
- Assess clinical efficacy and safety data for newer formulations and novel targeted therapies used to manage patients with AML
- Personalize therapy for the treatment of newly diagnosed, relapsed/refractory (R/R), and secondary AML based on disease- and patient-specific factors to communicate these treatment plans using shared decision-making strategies in the inpatient and outpatient settings
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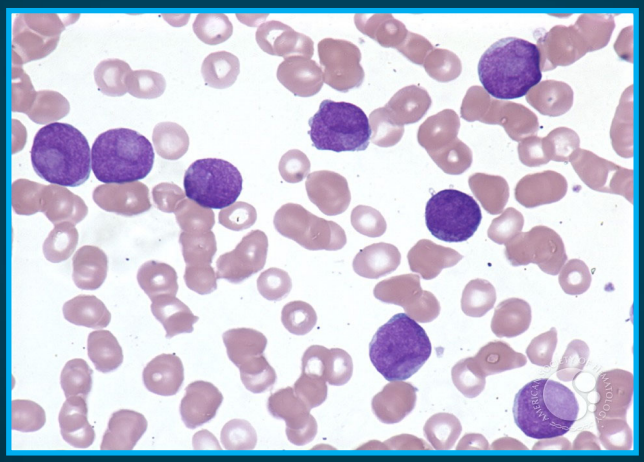
4

Acute Myeloid Leukemia (AML)

≥20% myeloid blasts in blood or marrow

- if t(8;21), inv(16)- AML regardless of blast %

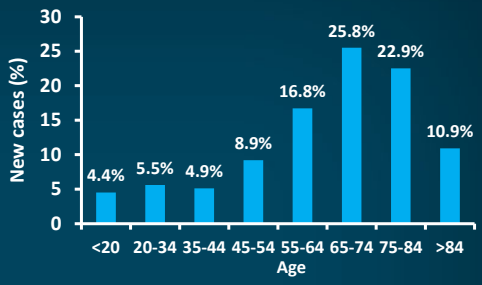


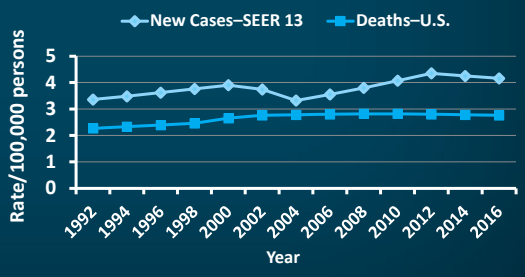
Arber DA, et al *Blood.* 2016;127:2391-2405.

5

Key Statistics on AML

- 20,240 estimated new cases in 2021
  - 1.1% of all new cancer cases
  - 1.9% of all cancer deaths
- 4.3 cases per 100,000 population
- 11,400 deaths per year
- Median age at diagnosis is 68 years
- 29.5% of patients survive ≥5 years

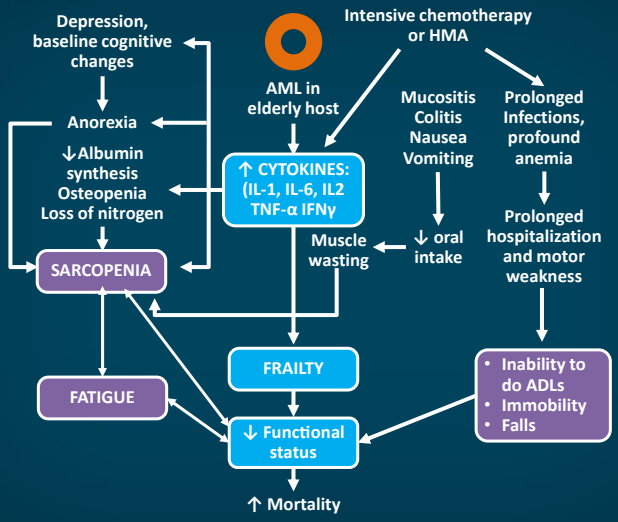




Siegel RL, et al. *CA Cancer J Clin*. 2021;71:7-33. Surveillance, Epidemiology, and End Results (SEER), 2021 (https://seer.cancer.gov/statfacts/html/amyl.html). Accessed 6/24/2021.

6

Comorbidities and Quality of Life

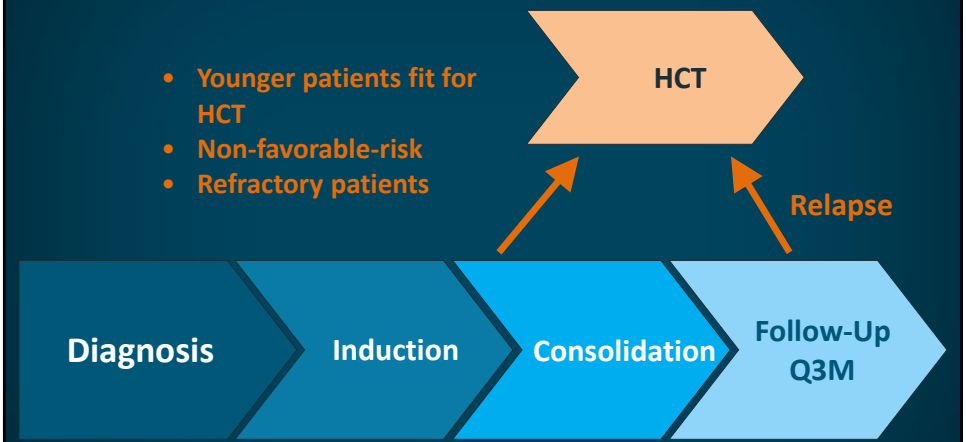


HMA = hypomethylating agent; IL = interleukin; TNF = tumor necrosis factor; IFN = interferon; ADL = activities of daily living.

Rao AV. *Hematology Am soc Hematol Educ Program.* 2016;2016:339-347.

7

AML: Course of the Disease



HCT = hematopoietic cell transplantation; Q3M = every 3 months.

8

Personalizing Treatment

Emerging understanding of disease biology, coupled with newer therapies, provide numerous treatment options, which require patient involvement regarding the preferred approach

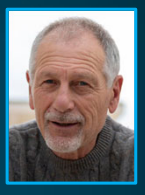
9

Shared Decision-Making (SDM) When Choosing Treatment Approach

Patient JR

- 57-yo active female with fatigue and bruising
- Evaluation reveals WBC: 25,000, platelets: 40,000, Hgb: 8.2; abn circ cells
- BM reveals 37% AML blasts, CD33, CD34, CD123+
- Cytogenetics: normal
- Molecular studies: FLT3+, NPM1+

Patient MS



- 60-yo male w/weight loss, bruising, and fatigue presents to ED with fever
- WBC: 1.0, ANC: 200, Hgb: 7.5, platelets: 80,000
- Treated with antibiotics; further evaluation with BM reveals: 80% blasts, CD34+, CD123
- Cytogenetics: complex cytogenetics w/at least 3 alterations, including monosomy 7
- Molecular studies non-contributory

yo = year old; WBC = white blood (cell) count; Hgb = hemoglobin; abn circ = abnormal circulating; FLT3 = Fms-like tyrosine kinase 3; BM = bone marrow; w/ = with; ED = emergency department; ANC = absolute neutrophil count.

10

Impact of Cytogenetics and Age on Median Overall Survival

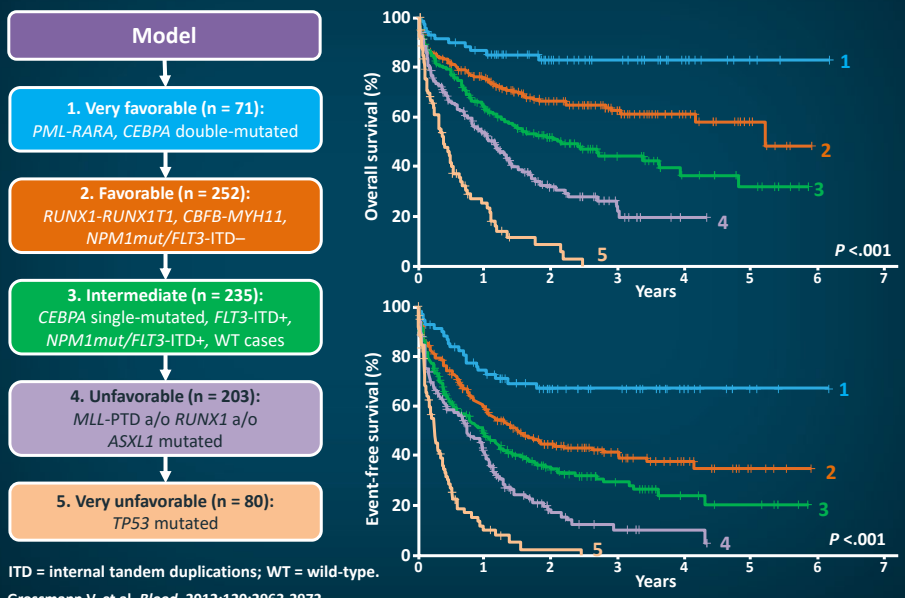
Median overall survival in patients with AML			
Age group	Risk Cytogenetics by Age		
	Unfavorable	Intermediate	Favorable
<56 years	11 mos	26 mos	Median OS not yet reached
56–56 years	5 mos	12 mos	
66–75 years	4 mos	8 mos	12 mos (>65 years)
>75 years	4 mos	7 mos	

mo(s) = month(s); OS = overall survival; yr(s) = year(s).

Appelbaum FR, et al. *Blood*. 2006;107:3481-3485.

11

Impact of Molecular Mutations on Outcome



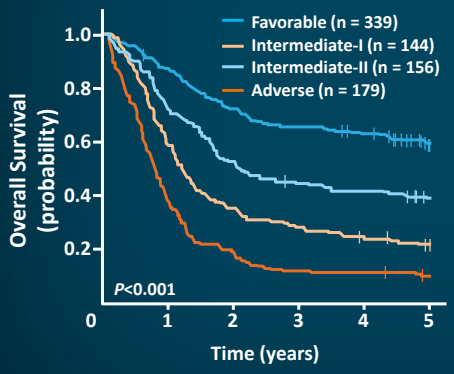
ITD = internal tandem duplications; WT = wild-type.

Grossmann V, et al. *Blood*. 2012;120:2963-2972.

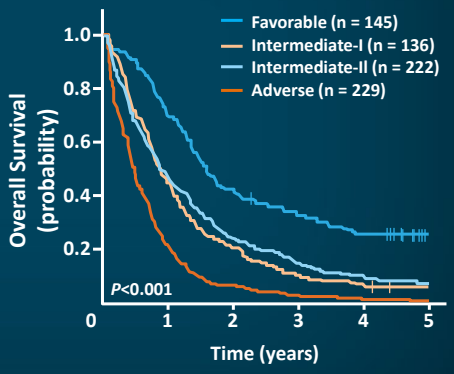
12

Impact of Molecular Mutations on Outcome by Age

Overall Survival of Patients Younger Than Age 60 Years



Overall Survival of Patients Age 60 Years or Older

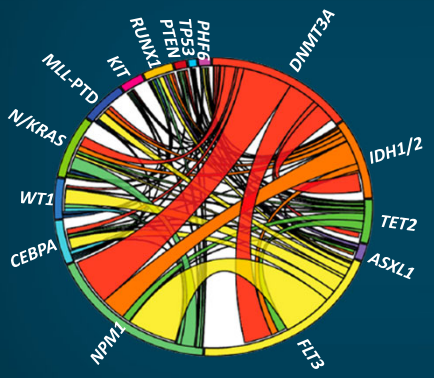


Mrózek K, et al. *J Clin Oncol*. 2012;30(36):4515-4523.

13

AML Genetic Profile Is Complex, Heterogenous, Meaningful—and Necessary

Mutational complexity in ECOG E1900 trial



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30,7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

>95% of patients have ≥1 mutation; most have ≥2.

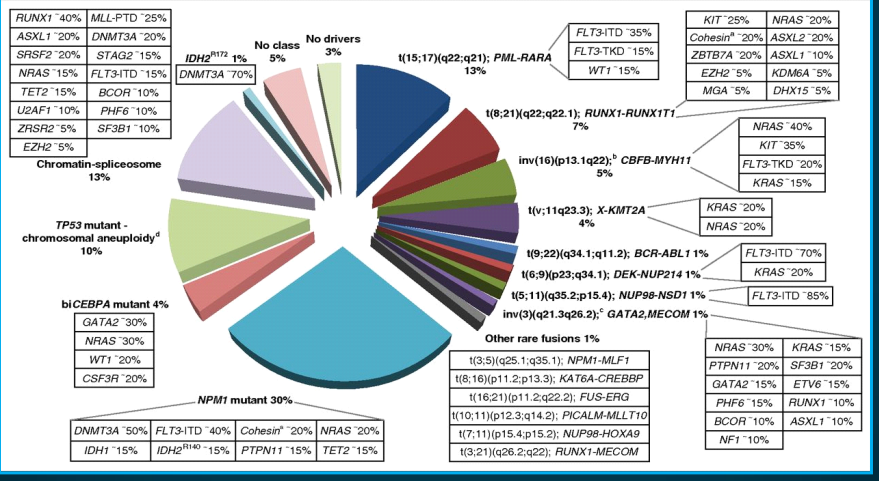
ECOG = Eastern Cooperative Oncology Group; ITD = internal tandem duplication; TKD = tyrosine kinase domain; PTD = partial tandem duplication.

Patel JP, et al. *N Engl J Med*.2012;366:1079-1089 and supplement.

14

Overlap of Cytogenetic and Molecular Abnormalities in AML

Molecular classes of AML and concurrent gene mutations in adult patients up to the age of ~65 years

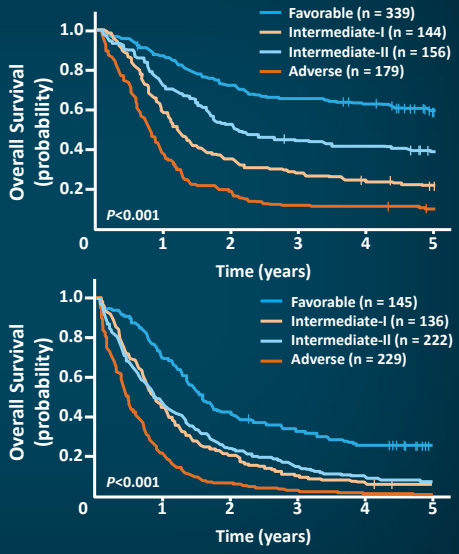


Döhner H, et al. *Blood.* 2017;129:424-447.

15

2017 ELN Risk Stratification

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* • Biallelic mutated *CEBPA* • Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
Intermediate	• Mutated *NPM1* and *FLT3*-ITD^{high} • WT *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
JR →	• **WT *NPM1* and *FLT3*-ITD^{high}**
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/abn(17p)
Patients MS →	• **Complex karyotype, monosomal karyotype** • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*



Modified from Döhner H, et al. *Blood.* 2017;129:424-447.

ELN = European LeukemiaNet; *FLT3* = Fms-like tyrosine kinase 3.
Mrozek et al , *J Clin Oncol* 2012

16

Genetic Testing of AML

https://youtu.be/NyV8tqStzqs

17

What Therapy Will JR and MS Choose?

- Avenues of engagement for patients with AML and their families:
  - Increasing opportunities with more available therapies
  - Patients with similar disease risk may evaluate risks and potential benefits of therapies differently, thereby choosing different approaches for the “same disease”
- Incorporating shared decision-making (SDM) practices
  - Value-based approach to high-quality care
  - Allows patient and caregivers direct input in choosing options for treating the illness based on their values

LeBlanc TW, et al. *Psychooncology*. 2017;26:2063-2068.

18

Shared Decision-Making

SDM: communication between clinicians and patients to make optimal healthcare decisions that align with patient preferences

Stage of cancer
Available treatments
Treatment type (chemotherapy vs immunotherapy)
Sociodemographic characteristics
Preference for involvement (high- vs low-input patients)
Goals of treatment(s)
Complex data delivered in a patient-centered manner
Maintain and update knowledge

SDM goals

- Ensure that each patient understands risks and benefits of his/her options
- Incorporate patient preference(s) and goals to reach clinical decisions

National Quality Forum (NQF). *National Quality Partners Playbook™: Shared Decision Making in Healthcare.* Washington, DC: NQF;2018. SDM Action Brief.

19

5 Essential Steps of SDM
SHARE Approach

1. **S**eek your patient's participation
2. **H**elp your patient explore and compare treatment options
3. **A**ssess your patient's values and preferences
4. **R**each a decision with your patient
5. **E**valuate your patient's decision

It's all about communication!

Agency for Healthcare Research and Quality (AHRQ) Share Approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Accessed 6/20/2021.

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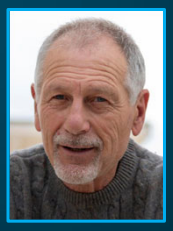
Applying SDM to JR and MS

- Applying SDM to a particular patient requires:
  - Understanding the therapeutic options
  - Understanding his/her risks and benefits
  - Understanding the long-term implications, costs, and requirements of caregivers as well as for the patient
- This information is then partnered with the patient's preferences to develop a personalized care plan that respects the patient's choices and overall goals



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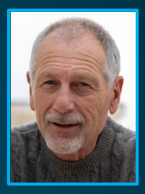
JR and MS: Issues to Consider in SDM

JR

- 57-yo active female
- Cytogenetics: normal
- Molecular studies: FLT3+, NPM1+
- Intermediate- to high-risk
- No comorbidities, BMI: 24, strong family support; employer-provided insurance; lives 35 min from treatment center; jogs 2 miles/d; wants to do "all she can for a cure"



MS

- 60-yo male with complex cytogenetics
- High-risk
- Smokes 1ppd, HTN, BMI 35
- Does not exercise or do much physical labor; lives alone 1 hour from treatment facility; no family in the area
- Concerned about being in hospital too long and missing work

BMI = body mass index; d = day; ppd = packs per day; HTN = hypertension.

22

Standard and FDA-Approved Therapies for AML

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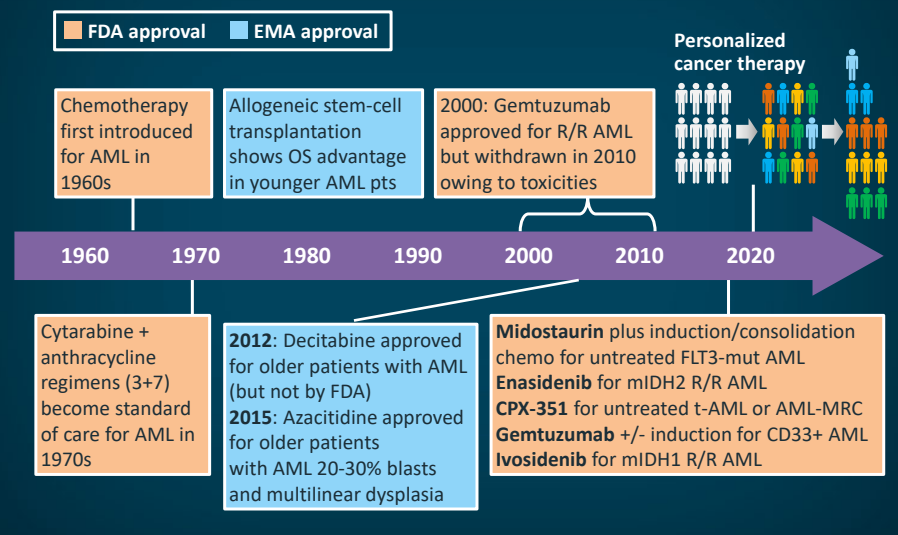
Developments in the Treatment of AML



DiNardo CD, Perl AE. *Nat Rev Clin Oncol*. 2019;16(2):73-74.

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Summary of Therapies
Newly Diagnosed AML

Fit patients		Specific populations
• 7+3		
• 7+3 + midostaurin	→	FLT3-mutated AML
• 7+3 + gemtuzumab ozogamicin	→	Consider in favorable-risk +/- intermediate-risk CD33-positive AML
• Liposomal 7+3 (CPX-351)	→	Consider in AML arising from MDS and therapy-related AML

Less-fit patients		
• Venetoclax + HMA (or LDAC)		
• Glasdegib + LDAC		
• Ivosidenib	→	Can consider in IDH1-mutated AML
• Gemtuzumab ozogamicin	→	Can consider in CD33-positive AML

MDS = myelodysplastic syndrome; LDAC = low-dose cytarabine.

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MOA of Targeted Therapies

https://youtu.be/iOOGBdXTRpc

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JR Chooses Aggressive Therapy

- What options does this include?
- What do we relate as the expected benefits?
- What are the common risks?
- How do we relay the above information in the context of SDM?

1. **S**eek participation
2. **H**elp explore and compare options
3. **A**ssess preferences
4. **R**each a decision
5. **E**valuate the decision

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AML in the Elderly: Outcomes

	Age, in years			
	<55 n = 368	55–65 n = 246	65–75 n = 274	>75 n = 80
CR	64%	46%	39%	33%
Median OS	18.8 mos	9.0 mos	6.9 mos	3.5 mos
Mortality within 30 days of induction	n = 364	n = 242	n = 270	n = 79
	2.7%	11.2%	20.0%	31.6%

Significant room for improvement

CR = complete response.

Appelbaum FR, et al. *Blood.* 2006;107:3481-3485.

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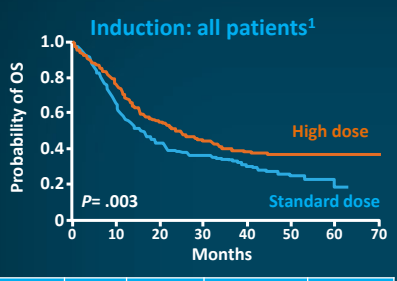
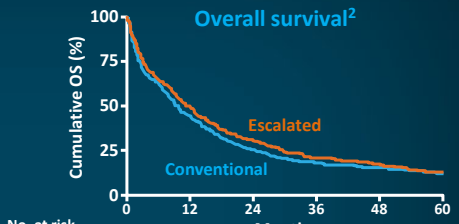
AML Induction: Does Dose Matter?

Low-Dose vs High-Dose Daunorubicin



Dose*	Total	Deaths	Censored	mOS
Standard	330	199	131	15.7 mos
High	327	168	159	23.7 mos

Conclusion: high-dose daunorubicin **did** improve OS in patients up to age 60 with untreated AML



No. at risk

Conventional	411	179	99	55	36	13
Escalated	402	193	115	63	40	16

Dose*	Total	Deaths
Conventional	411	340
Escalated	402	325

Conclusion: High-dose daunorubicin **did not** improve OS in patients older than age 60 newly diagnosed with AML

So how do we address this issue of "does dose matter"?

*Standard/conventional dose = 45 mg/m^2/day; high/escalated dose = 90 mg/m^2/day

1. Fernandez HF, et al. *N Engl J Med.* 2009;361:1249-1259. 2. Löwenberg B, et al. *N Engl J Med.* 2009;361:1235-1248.

29

Statistically Significant Toxicities With 7+3

	Conventional Dose	Escalated Dose	*P*-value
Maximal grade infections[1]			.005
• Grade 0–1	19%	13%	
• Grade 2	1%	1%	
• Grade 3	71%	76%	
• Grade 4	8%	11%	
Days from start of chemotherapy to last platelet transfusion[1]	Median: 19 Mean: 21.6±10.8	Median 20 Mean: 22.1±9.4	.004
Interval between beginning of first cycle and beginning of second cycle—days[1]	Median: 36 Mean: 38±15	Median: 39 Mean: 43±17	.001
Dyspnea, grade 3/4/5[2]	5.7%	4.4%	
Cardiac event, grade 3/4/5[2]	7.2%	7.9%	

1. Löwenberg B, et al. *N Engl J Med.* 2009;361:1235-1248. 2. Fernandez HF, et al. *N Engl J Med.* 2009;361:1249-1259.

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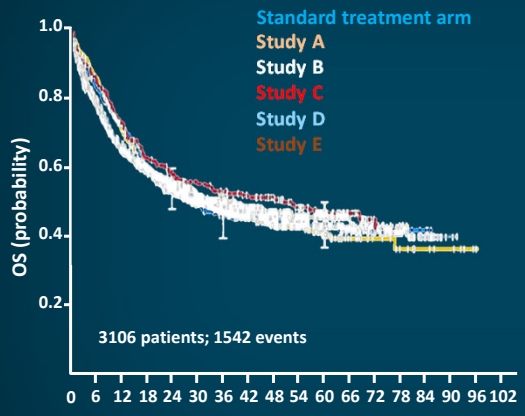
Rearranging Chemotherapy
A Decade of Futility



A) VP16 added to induction
B) HiDAC induction, auto or allo BMT
C) 7+3x2 then HiDAC (1 gm) + daunorubicin; then HiDAC or auto or allo BMT
D) TAD-HAM or HAM-HAM+ auto BMT or maintenance TAD
E) HiDAC vs auto or allo BMT

VP16 = idarubicin, cytarabine, and etoposide; HiDAC = high-dose cytarabine; auto = autologous; allo = allogeneic; BMT = bone-marrow transplant; TAD = thioguanine, cytarabine, and daunorubicin; HAM = high-dose cytarabine and mitoxantrone.

Büchner T, et al. *J Clin Oncol.* 2012;30:3604-3610.

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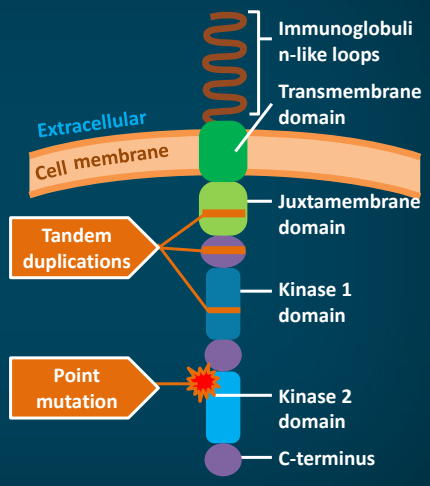
Aggressive Induction for FLT3+-Positive Patients

- *FLT3* mutations result in survival and proliferation of leukemic blasts and confer a poor prognosis
- *FLT3* mutations can be *FLT3*/ITD and/or *FLT3*/TKD
- Midostaurin is an oral multikinase inhibitor that has activity with regard to *FLT3* receptor- type I FLT3 inhibitor



Pemmaraju N, et al. *Cancer.* 2011;117:3293-3304.

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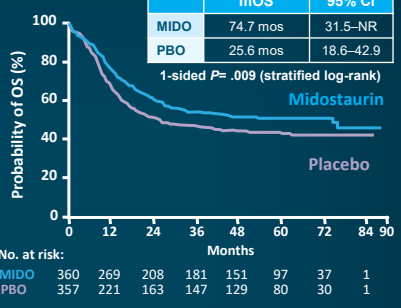
Midostaurin

- 717 FLT3-mutated pts randomized
  - 360 to midostaurin (MIDO) group
  - 357 to PBO group
- Patients received induction with 7+3 and consolidation with high-dose cytarabine + MIDO or PBO
- In primary analysis and analysis with data for transplanted pts censored, benefit of MIDO was consistent across all FLT3 subtypes
- Common AEs included nausea, mucositis, vomiting, headache, musculoskeletal pain, hyperglycemia

Median OS

	mOS	95% CI
MIDO	74.7 mos	31.5–NR
PBO	25.6 mos	18.6–42.9

1-sided *P*= .009 (stratified log-rank)



No. at risk:

MIDO	360	269	208	181	151	97	37	1
PBO	357	221	163	147	129	80	30	1

Subgroup analysis of OS

	No. of Patients	HR (95% CI)	*P*-value
Overall	717	0.78 (0.63–0.96)	.009 (1-sided)
ITD (high)	214	0.80 (0.57–1.12)	.19 (2-sided)
ITD (low)	341	0.81 (0.60–1.11)	.19 (2-sided)
TKD	162	0.65 (0.39–1.08)	.10 (2-sided)

PBO = placebo; pts = patients; 7+3 = cytarabine + daunorubicin; AE = adverse event; mOS = median OS; CI = confidence interval; NR = not reached; HR = hazard ratio.

Stone RM, et al. *N Engl J Med*. 2017;377:454-464. Midostaurin (Rydapt®) prescribing information (PI), 2021 (www.novartis.us/sites/www.novartis.us/files/rydapt.pdf). Accessed 6/20/2021.

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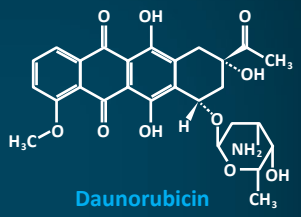
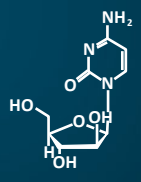
Aggressive Induction for MRC-related AML
Liposomal "7+3" (CPX-351)

- CPX-351 is liposomal combination of daunorubicin (anthracycline topoisomerase inhibitor) and cytarabine (nucleoside metabolic inhibitor) in fixed 1:5 molar ratio
- Induction
  - Cytarabine 100 mg/m^2 and daunorubicin 44 mg/m^2 on days 1, 3, and 5
  - C2 induction, if needed, on days 1 and 3 only
- Post-remission therapy
  - Cytarabine 65 mg/m^2 and daunorubicin 29 mg/m^2 on days 1 and 3



Daunorubicin



Cytarabine

MRC = myelodysplasia-related changes.

Daunorubicin + cytarabine (Vyxeos®) PI, 2021 (http://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf). Accessed 6/20/3021. Lancet JE, et al. *Blood*. 2014;123:3239-3246. Mayer LD, et al. *Mol Cancer Ther*. 2006;5:1854-1863.

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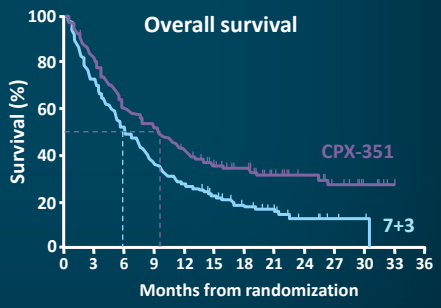
Liposomal "7+3" (CPX-351): Results

- Phase 3 trial: patients 60–75 years old with untreated AML
  - Hx of prior cytotoxic treatment
  - Antecedent MDS or CMML
  - With WHO-defined MDS-related cytogenetic abnormalities
- 309 patients randomized 1:1 to CPX-351 or conventional 7+3
- CPX-351 resulted in superior OS
  - **Median OS = 9.33 vs 5.95 months** (*P*= .003)
  - CR+CRi response = 47.7% vs 33.3% (*P*= .016)
  - Grade 3–5 AEs similar (92% vs 91%)

OS: ITT Analysis Population		
	Events/n	mOS, mos (95% CI)
CPX-351	104/153	9.56 (6.60–11.86)
7+3	132/156	5.95 (4.99–7.75)

HR = 0.69 (95% CI, 0.52–0.90)
1-sided *P*= .003



Hx = history; CMML = chronic myelomonocytic leukemia; WHO = World Health Organization; CRi = CR with incomplete neutrophil or platelet recovery; ITT = intention-to-treat.
Lancet JE, et al. *J Clin Oncol.* 2018;36:2684-2692. Lancet JE, et al. *J Clin Oncol.* 2016;34(suppl): abstract 7000. Lancet JE, et al. *Lancet.* 2021;8(7):e481-e491

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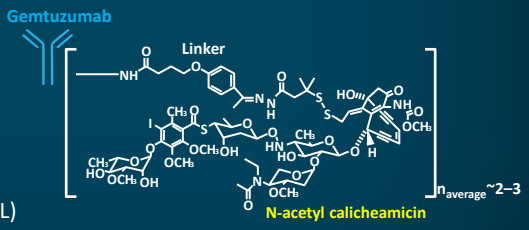
Do You Add Gemtuzumab Ozogamicin (GO) in Aggressive Therapies?

- Gemtuzumab ozogamicin is CD33-directed antibody-drug conjugate
- Initially granted accelerated approval by FDA in 2000 for adults with relapsed AML
- Withdrawn from US market in 2010 and reapproved in 2017
  - Increased risk of death from treatment toxicity; sinusoidal obstructive syndrome (SOS)
- Continued investigation
  - ALFA-0701 (newly diagnosed AML, age 50–70 years)
  - AML-19 (elderly/unfit newly diagnosed AML)
  - MyloFrance-1 (R/R CD33+ AML)



FDA = US Food and Drug Administration; SOS = sinusoidal obstructive syndrome; R/R = relapsed/refractory.

Gemtuzumab ozogamicin (Mylotarg™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=9548). GO overview (www.ncbi.nlm.nih.gov/books/ NBK548438/pdf/Bookshelf_NBK548438.pdf). FDA PR (www.fda.gov/newsevents/newsroom/pressannouncements/ucm574507.htm). Ingram I. Cancer Network, 2017. (www.cancernetwork.com/acute-myeloid-leukemia/fda-approves-gemtuzumab-ozogamicin-acute-myeloid-leukemia). All URLs accessed 6/20/2021.

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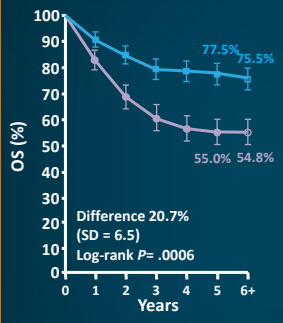
Gemtuzumab Ozogamicin: Meta-analysis

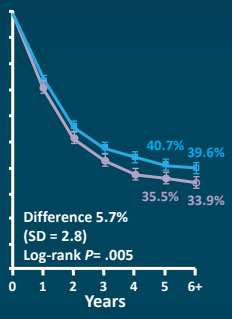
Favorable



Annual event rate	Years 1–5 % (SD)	Years 6+ % (SD)
GO	5.8 (1.1)	2.3 (1.3)
No GO	14.1 (1.9)	0.0 (0.0)

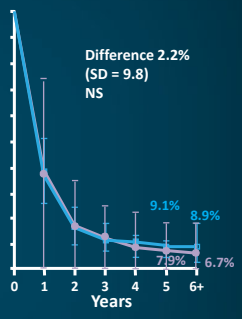
Intermediate

Allocated to GO Allocated to no GO



Annual event rate	Years 1–5 % (SD)	Years 6+ % (SD)
GO	22.4 (1.0)	2.7 (0.9)
No GO	26.2 (1.1)	4.9 (1.3)

Adverse



Annual event rate	Years 1–5 % (SD)	Years 6+ % (SD)
GO	73.8 (4.6)	2.4 (2.4)
No GO	76.7 (4.8)	21.1 (10.5)

SD = standard deviation; NS = not significant.

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

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When to Use GO

- FDA approved in September 2017
  - Treatment of newly diagnosed CD33-positive AML in ≥1 month
  - Treatment of R/R CD33-positive AML in adults and in pediatric patients ≥2 years
- SOS in 6/131 (5%) of patients
- Also investigated as single agent for elderly/unfit AML and for R/R AML (AML-19 and MyloFrance-1)
- Added NCCN recommendation
  - Option for APL induction and consolidation in high-risk and/or cardiac patients and in relapsed APL

----------DOSAGE AND ADMINISTRATION----------

- 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 (2.2).
  - *Consolidation:* 3 mg/m^2 on Day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine. (2.2).
- Newly-diagnosed AML (single-agent regimen):
  - *Induction:* 6 mg/m^2 on Day 1 and 3 mg/m^2 on Day 8 (2.2).
  - *Continuation:* For patients without evidence of disease progression following induction, up to 8 continuation courses 2 mg/m^2 on Day 1 every 4 weeks (2.2).
- Relapsed or refractory AML(single-agent regimen):
  - 3 mg/m^2 on Days 1, 4, and 7 (2.2).
- Premedicate with a corticosteroid, antihistamine, and acetaminophen 1 hour prior (2.1).

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use (5.1, 6.1)

APL = acute promyelocytic leukemia.

Gemtuzumab ozogamicin (Mylotarg™) PI, 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=9548&format=PDF). Ingram I. Cancer Network. 2017. (www.cancernetwork.com/acute-myeloid-leukemia/fda-approves-gemtuzumab-ozogamicin-acute-myeloid-leukemia). National Comprehensive Cancer Network (NCCN) AML. V3.2021. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). All URLs accessed 6/2021.

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Post-Remission Therapy
Consolidation and Maintenance

- High-dose cytarabine (HiDAC)[1]
  - 3 g/m^2 IV BID days 1, 3, and 5 for 3–4 cycles[1,2]
  - Several alternates (eg, 1.5 g IV BID Days 1, 3, and 5) [1]
  - HiDAC 1-2-3 In patients who receive CPX-351 induction-> CPX-351 consolidation[3]
  - In patients who receive 7+3 + GO-> GO+HiDAC+DNR x 2 cycles
- Allogeneic HCT
- Azacitidine maintenance

IV = intravenous; BID = twice daily; HCT = hematopoietic cell transplantation.

1. NCCN. AML, V3.2021 (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed 6/20/2021. 2. Mayer RJ, et al. *N Engl J Med*. 1994;331:896-903. Dumas PY, et al. *Blood Adv* (2020) 4 (16): 3840–3849.

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Allogeneic HCT

- Conditioning regimen—goals
  - Immunosuppression
  - Cytoreduction
- Graft-versus-leukemia (GVL) effect

Regimens

- Busulfan/cyclophosphamide or TBI/cyclophosphamide standard
- Less toxic preparations for older and/or more infirm patients

TBI = total body irradiation.

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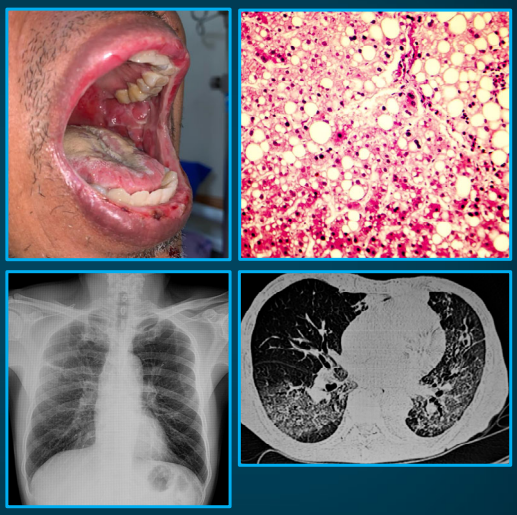
Complications

Regimen-related toxicity

- Mucositis
- Interstitial pneumonitis
- Hepatic VOD (SOS)
- Major organ dysfunction
- Secondary malignancies
- Infections
- GVHD



VOD = veno-occlusive disease; GVHD = graft-versus-host disease.

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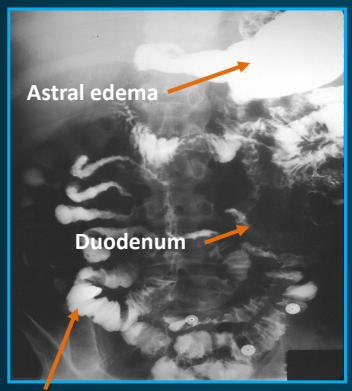
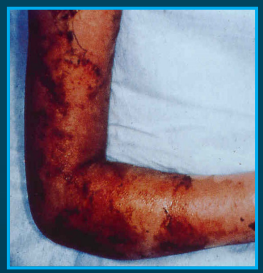
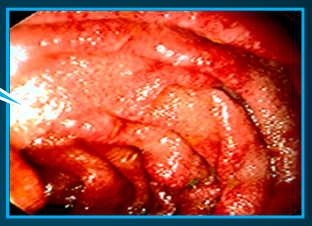
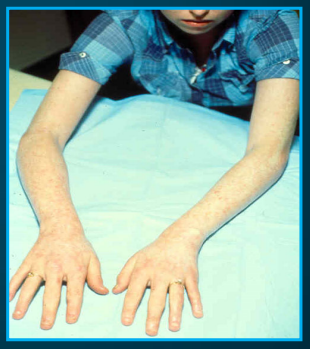
Graft-vs-Host Disease









Courtesy of Dr. Keith Sullivan. Ratanatharathorn V, et al. *Blood*. 1998;92:2303-2314. Nash RA, et al. *Blood*. 2000;96:2062-2068. Martin PJ, et al. *Biol Blood Marrow Transplant*. 2004;10:210-327.

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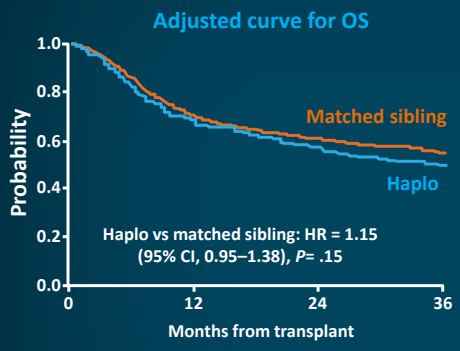
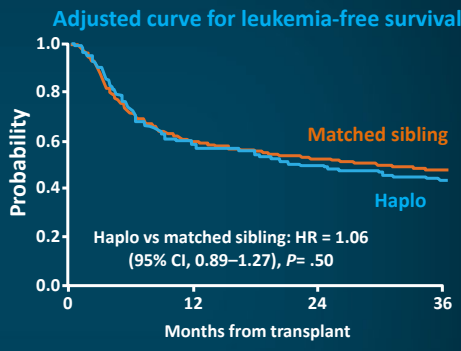
Haploidentical vs Matched Sibling Allogeneic Transplant for AML in CR1





JR attained a CR with 7+3 and proceeded to MUD allo transplant, complicated by grade 2 GVHD of skin and gut. After treatment with steroids, she remains in CR at 2 years.

CR1 = first CR; haplo = haploidentical; MUD = matched unrelated donor.

Rashidi A, et al. *Blood Adv*. 2019;3:1826-1836.

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Additional Aggressive Induction Options

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Patient MS Chooses Less-Intense Therapy

- What options does this include?
- What do we relate as the expected benefits?
- What are the common risks?
- How do we relay the above information in context of SDM?

1. **S**eek participation
2. **H**elp explore and compare options
3. **A**ssess preferences
4. **R**each a decision
5. **E**valuate the decision

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Summary of Therapies
Newly Diagnosed AML

Fit patients

- 7+3
- 7+3 + midostaurin → FLT3-mutated AML
- 7+3 + gemtuzumab ozogamicin → Consider in favorable-risk CD33-positive AML
- Liposomal 7+3 (CPX-351) → Consider in AML arising from MDS and therapy-related AML

Specific populations

Less-fit patients

- Venetoclax + HMA (or LDAC)
- Glasdegib + LDAC
- Ivosidenib → Can consider in IDH1-mutated AML
- Gemtuzumab ozogamicin → Can consider in CD33-positive AML

Patient MS chooses less-intense therapy

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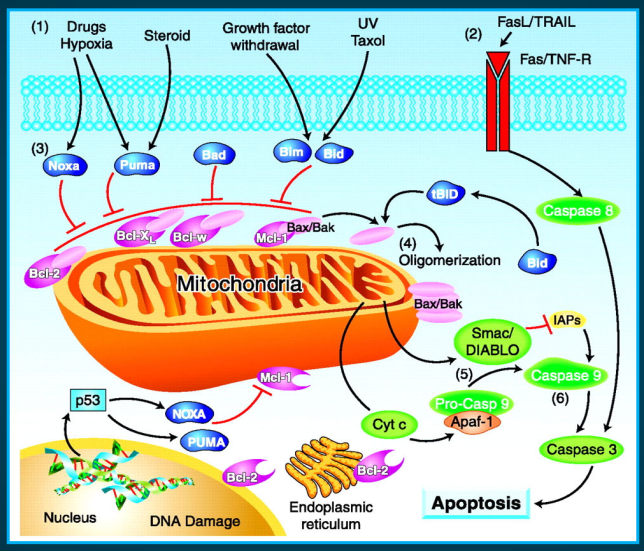
Apoptotic Pathway



DNA = deoxynucleic acid; Bcl = B-cell lymphoma.

Kang MH, Reynolds CP. *Clin Cancer Res.* 2009;15:1126-1132.

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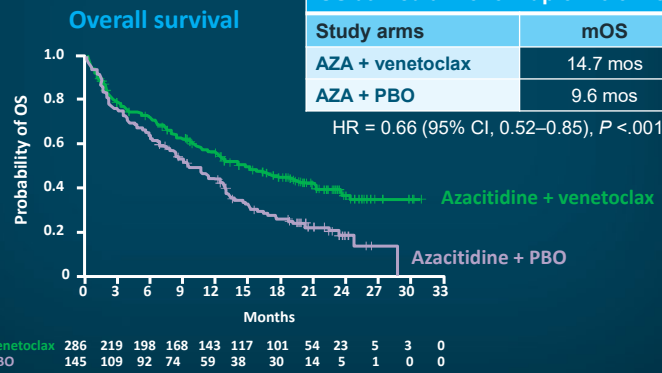
VIALE-A Overall Survival

- Phase 3 study comparing azacitidine (AZA) + venetoclax with AZA + PBO (2:1 randomization)
- 431 previously untreated AML patients ineligible for intensive induction therapy
- Median age 76 years

OS at median follow-up of 20.5 mos	
Study arms	mOS
AZA + venetoclax	14.7 mos
AZA + PBO	9.6 mos

HR = 0.66 (95% CI, 0.52–0.85), *P* <.001



DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629.

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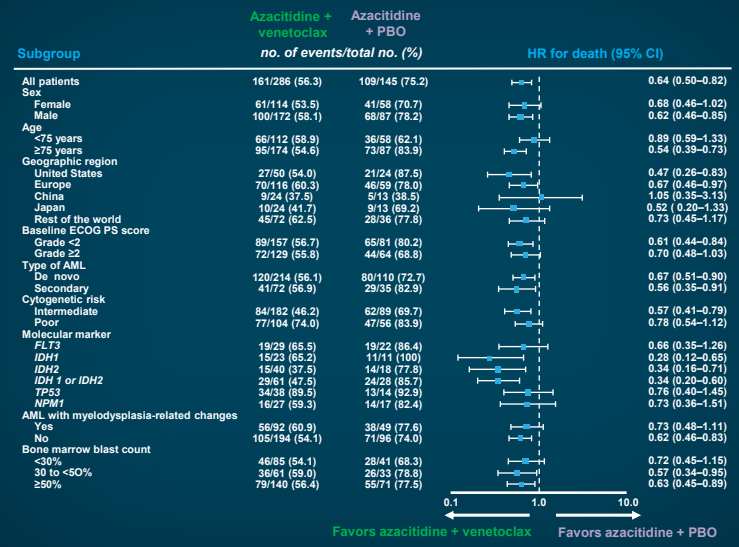
VIALE-A Overall Survival: Subgroup Analysis



PS = performance status.

DiNardo CD, et al. *N Engl J Med* 2020; 383:617-629.

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VIALE-A Adverse Events (AEs)

	Azacitidine-Venetoclax (n = 283)		Azacitidine-PBO (n = 144)	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Event	*number of patients (%)*			
All AEs	283 (100)	279 (99)	144 (100)	139 (97)
Hematologic AEs	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (28)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukemia	58 (21)	58 (21)	20 (14)	17 (12)
Non-hematologic AEs				
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (28)	15 (10)
Peripheral edema	69 (24)	1 (<1)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	12 (4)	25 (17)	1 (1)
Infections	239 (84)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious AEs	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

DiNardo CD et al. *N Engl J Med* 2020;383:617-629.

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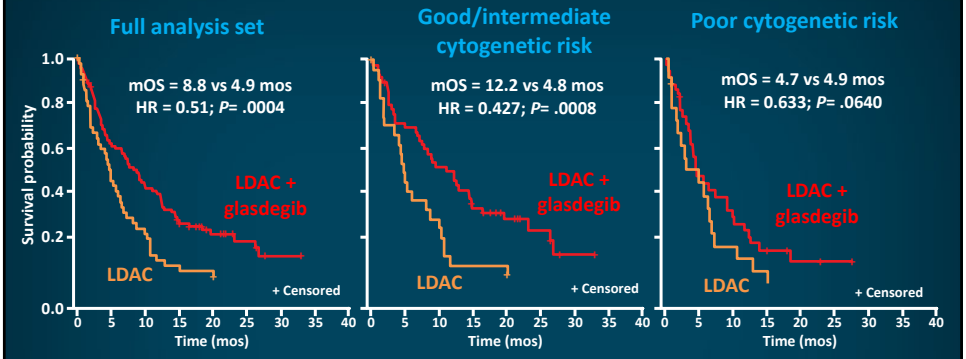
Phase 2 Study of LDAC ± Glasdegib: OS



- Patients with AML or high-risk MDS
- LDAC 20 mg SC BID for 10 days/month + daily glasdegib 100 mg PO vs LDAC
- CR: 15 (17.0%) vs 1 (2.3%) patient(s), *P* <.05
- Nonhematologic grade 3/4 AEs included pneumonia and fatigue; risk of QT prolongation with glasdegib

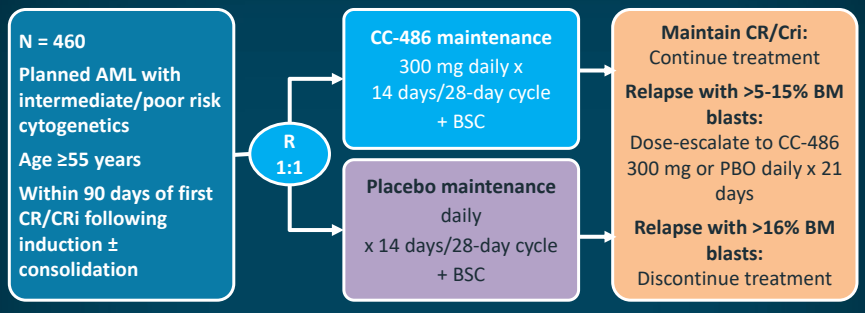
SC = subcutaneous; PO = by mouth (oral).

Cortes JE, et al. *Leukemia*. 2019;33:379-389.

51

QUAZAR AML-001: Maintenance With CC-486*

Study Design



Primary endpoint: OS
Secondary endpoints: RFS, safety, HRQoL, healthcare resource utilization
Stratification: age, history of MDS, cytogenetic risk category, consolidation therapy following induction

*Oral formulation of azacitidine.

BSC = best supportive care; RFS = relapse-free survival; HRQoL = health-related quality of life.

Roboz GJ, et al. *Future Oncol*. 2016;12:293-302.

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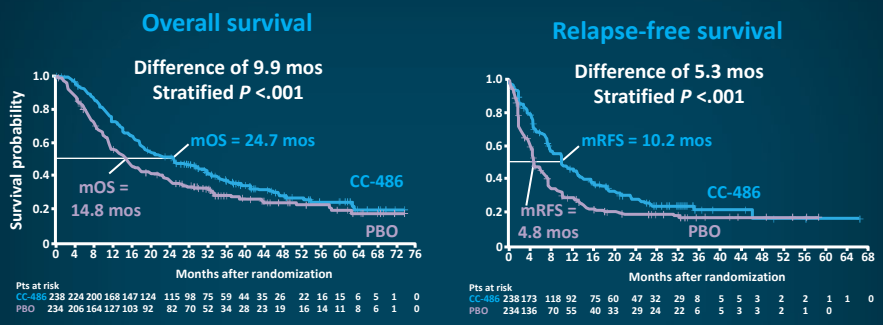
QUAZAR AML-001: Maintenance with CC-486
OS and RFS



- CC-486 had a safety profile consistent with that of parenteral azacitidine
- Received FDA approval September 2020 at 300-mg dose for adults with AML who achieve complete first remission

Wei AH, et al. *N Engl J Med.* 2020;383:2526-2537. Solis-Moreira J. JNCCN 360 (https://jnccn360.org/aml/news/azacitidine-tablets-approved-by-fda-for-patients-with-aml-in-first-remission/?bc_md5=ab23334ef76a2e69802649e75e321b67&utm_medium=email&utm_source=JNCCN-360_AML+%2b+Balance_091520). Accessed 6/20/2021.

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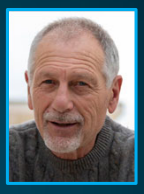
MS Chooses Less-Intensive Therapy

1. **S**eek participation
2. **H**elp explore and compare options
3. **A**ssess preferences
4. **R**each a decision
5. **E**valuate the decision



- HMA-Ven provided CR after 2 cycles, and MS remained on therapy for 6 months; he then chose maintenance even though he did not get intensive induction*
- Maintenance therapy with CC-486 used
- Patient relapsed while on CC-486 2 years following initial induction
- At relapse, cytogenetics and molecular testing repeated
- In addition to complex genetics, patient also has *IDH1* and *p53+* mutations

Ven = venetoclax. *Off-label use

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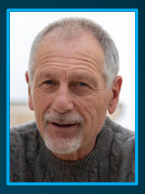
Therapies to Discuss with MS
Relapsed/Refractory AML



Therapies		Specific populations
Gilteritinib	→	FLT3 mutated AML
Ivosidenib	→	IDH1 mutated AML
Enasidenib	→	IDH2 mutated AML
Gemtuzumab ozogamicin	→	CD33 positive AML

- Can still consider previously existing therapies:
  - HMAs
  - Venetoclax
  - Combination chemotherapy (eg, MEC, HiDAC, FLAG, etc)

MEC = mitoxantrone, etoposide, and cytarabine; FLAG = fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor.

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Ivosidenib—IDH1 Inhibitor

- *IDH1* mutations occur in approximately 20% of AML patients
- Phase 1 dose escalation and expansion study
  - 258 pts with R/R AML or other advanced hematologic malignancies with IDH1 mutations
- Efficacy population = 125 R/R AML patients
  - ORR = 41.6%
  - CR+CRh = 30.4% (CR = 21.6% and CRh = 8.8%)
  - Median duration of CR+CRh was 8.2 months
- Differentiation syndrome was reported in 10.6% of patients
- Common AEs (≥20%): diarrhea, leukocytosis, nausea, fatigue, febrile neutropenia, dyspnea, anemia, long QT, peripheral edema, pyrexia, decreased appetite

ORR = overall/objective response ratel CRh = CR with partial hematologic recovery.

DiNardo CD, et al. *N Engl J Med*. 2018;378:2386-2398. Stein E, et al. *J Clin Oncol*. 2018;36(15 suppl): abstract TPS7074. Ivosidenib (Tibsovo®) PI (www.tibsovopro. com/pdf/prescribinginformation.pdf). URLs accessed 6/20/2021. Ward PS, et al. *Cancer Cell*. 2010;17:225-234.

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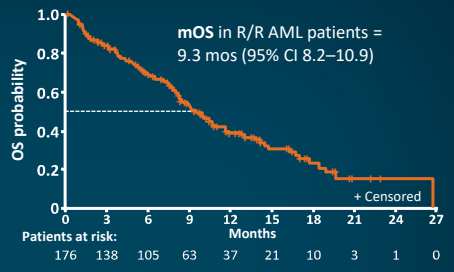
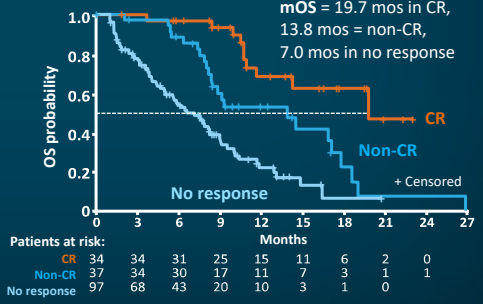
Enasidenib—IDH2 inhibitor

- *IDH2* mutations occur in ~12% of AML patients
- Efficacy of enasidenib in R/R IDH2-mutated AML was studied in 176 patients
- ORR = 40.3%, median response duration = 5.8 mos
- Responses associated with cellular differentiation syndrome = 7%
- Median OS = 9.3 mos
- Among 34 patients (19.3%) achieving CR, OS = 19.7 mos





Stein EM, et al. *Blood*. 2017;130:722-731.

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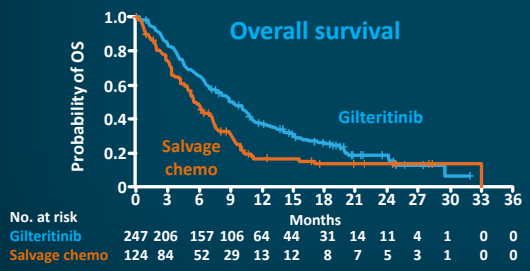
Gilteritinib for FLT3+ R/R AML—ADMIRAL Trial

- 371 adult patients with R/R FLT3-mutated AML randomized 2:1 to gilteritinib or salvage chemotherapy
- CR/CRh rate = 34.0%, CRi = 25.5%, CRp = 7.7%
- AEs = elevated ALT/AST/alkaline phosphatase, neutropenic fever, constipation, fatigue, cough, headache, thrombocytopenia, edema, vomiting, dyspnea
- Gilteritinib can prolong QT interval
- PRES (1%), pancreatitis (5%), differentiation syndrome (3%)



	mOS (95% CI)
Gilteritinib	9.3 mos (7.7–10.7)
Salvage chemo	5.6 mos (4.7–7.3)

HR (death) = 0.64 (95% CI, 0.49–0.83)
P <.001

chemo = chemotherapy; CRp = CR with incomplete platelet recovery; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PRES = posterior reversible encephalopathy syndrome.

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740. Gilteritinib (Xospata®) PI 2019 (https://astellas.us/docs/xospata.pdf). Accessed 6/20/2021.

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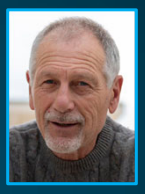
MS Chose Ivosidenib



- Tolerated well, but 3 weeks after starting ivosidenib, he had a rapidly rising white count and fever with pulmonary infiltrates consistent with differentiation syndrome.
- Although workup for infection was unrevealing, broad antibiotics were given.
- Patient also given hydroxyurea and steroids.
- Attained CR by 8 weeks; maintained for 1 year.

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Some Emerging Therapeutic Strategies

- Bispecific therapies
  - CD123/CD3
    - Flotetuzumab
    - XmAb14045
    - JNJ-63709178
  - CD33/CD3
    - AMG 330
- CAR-T cells (auto and allo)
  - CD123
  - FLT3
- Menin, MDM2 inhibition, Aurora kinase inhibition, BET inhibition MCL-1 inhibition

CAR = chimeric antigen receptor; MDM = murine double minute; BET = bromodomain and extra-terminal motif; ADC = antibody-drug conjugate.

- TP53 mutated
  - Eprenetapopt
- ADC
  - CD123
    - IMGN632
  - CD33
    - IMGN779
  - CD25
    - Camidanlumab
- Immune-based therapies:
  - Magrolimab (anti-CD47)
  - Tabituximab (anti-TIM3)
  - Anti-PD-1 agents
  - Pomalidomide (IMiD)
- Microtransplantation
- RAR alpha agonist: Syros-1425

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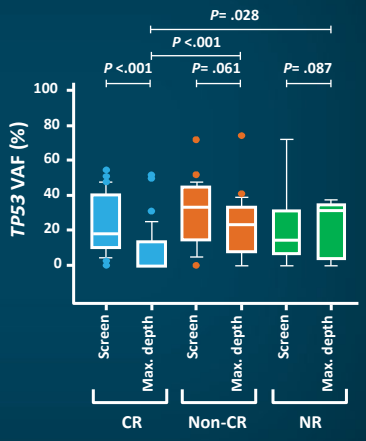
Eprenetapopt + Azacitidine in *TP53*-Mutant MDS

- Eprenetapopt induces apoptosis in *TP53*-mutant cells
- Phase 1b/2 open-label dose-escalation/expansion study
- Patients w/HMA-naïve MDS, MDS/MPN, overlap syndrome, CMML, oligoblastic AML

_TP53_ variant allele frequency by best response



MPN = myeloproliferative neoplasm; VAF = variant allele frequency; NR = not reported; disc = discontinued.

Sallman DA, et al. *J Clin Oncol*. 2021;39:1584-1594.

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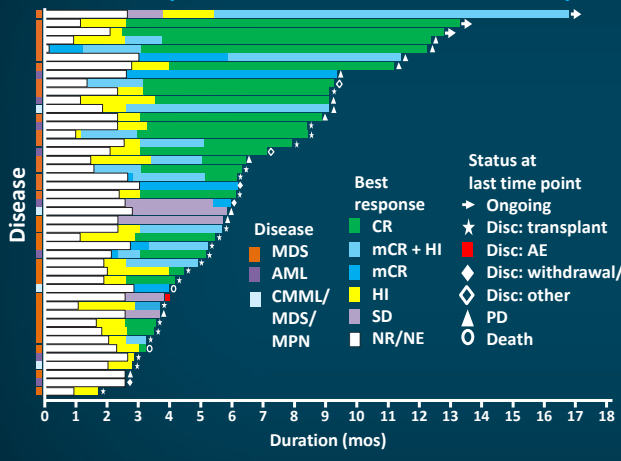
Eprenetapopt + Azacitidine in *TP53*-Mutant MDS (continued)

Treatment response and duration in 45 evaluable patients



A phase 3 study of this combination vs the hypomethylator alone was recently reported to not meet the primary endpoint of a significant difference in remission rates (33.3 vs 22.4% was observed).

HI = hematologic improvement; SD = stable disease; NE = not evaluable; disc = discontinued; PD = progressive disease.

Sallman DA, et al. *J Clin Oncol*. 2021;39:1584-1594; Aprea Therapeutics Announces Results of Primary Endpoint from Phase 3 Trial of Eprenetapopt in TP53 Mutant Myelodysplastic Syndromes (MDS). https://ir.aprea.com/news-releases/news-release-details/aprea-therapeutics-announces-results-primary-endpoint-phase-3

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Magrolimab + Azacitidine: Phase 1b

- Blocks CD47 to induce tumor phagocytosis and eliminate leukemia stem cells
- 52 treatment-naïve patients w/AML (median age 73) unfit for intensive chemo
- 65% w/*TP53*-mutant AML; 64% w/complex cytogenics
- Of 34 evaluable patients:
  - 22 (65%) achieved objective response
  - 15 (44%) achieved CR
  - Median time to response: 2.04 months, faster than expected for AZA alone
- Safety profile similar to that of AZA monotherapy
- Phase 3 study (ENHANCE-2) is ongoing

Sallmon DA, et al. American Society of Hematology (ASH) meeting, 2020: abstract 330 (https://ash.confex.com/ash/2020/ webprogram/Paper134728.html). Accessed 6/20/2021.

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Conclusions

- AML remains a high-risk illness
- Improved understanding of the biology of AML has led to a new evolution with more targeted therapy
- These new therapies have the potential to improve outcomes with better, more durable responses as well as less toxicity
- These advances allow us to involve patients in ongoing discussions of the risks and benefits of multiple therapies so that they can manage this disease as they choose

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How Can You Use Newer Therapies to Improve Clinical Decision-Making and Long-Term Health Outcomes for Patients with Acute Myeloid Leukemia?

Guidelines, Recommendations, and Articles

Resource	Web Address
Agency for Healthcare Research and Quality (AHRQ): SHARE Approach Workshop. Last reviewed February 2021.	www.ahrq.gov/health-literacy/curriculum-tools/shareddecisionmaking/workshop/index.html
Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood.* 2006;107:3481-3485.	https://ashpublications.org/blood/article/107/9/3481/133476/Age-and-acute-myeloid-leukemia
Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127:2391-2405.	https://pubmed.ncbi.nlm.nih.gov/27069254/
Büchner T, Schlenk RF, Schaich M, et al. Acute Myeloid Leukemia (AML): Different treatment strategies versus a common standard arm--combined prospective analysis by the German AML Intergroup. *J Clin Oncol.* 2012;30:3604-3610.	https://pubmed.ncbi.nlm.nih.gov/22965967/
Cortes JE, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. 2019;33:379-389.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6365492/
DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383:617-629.	https://pubmed.ncbi.nlm.nih.gov/32786187/
DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med.* 2018;378:2386-2398.	https://www.ncbi.nlm.nih.gov/pubmed/29860938
Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129:424-447.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5291965/
Fernandez HF, Sun Z, Yao X, et al.	https://www.nejm.org/doi/full/10.1056/NEJ

Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med.* 2009;361:1249-1259.	Moa0904544
Grossmann V, Schnittger S, Kohlmann A, et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. *Blood*. 2012;120:2963-2972.	https://pubmed.ncbi.nlm.nih.gov/22915647/
Hills RK, Castaigne S, Appelbaum FR, et al. The addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: A meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol.* 2014;15:986-996.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4137593/
Ingram I. FDA approves gemtuzumab ozogamicin for acute myeloid leukemia. *Cancer Network.* September 16, 2017.	https://www.cancernetwork.com/acute-myeloid-leukemia/fda-approves-gemtuzumab-ozogamicin-acute-myeloid-leukemia
Kang MH, Reynolds CP. Bcl-2 inhibitors: Targeting mitochondrial apoptotic pathways in cancer therapy. *Clin Cancer Res.* 2009;15(4):1126-1132.	https://pubmed.ncbi.nlm.nih.gov/19228717/
Lancet JE, Cortes JE, Hogge DE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014;123:3239-3246.	https://pubmed.ncbi.nlm.nih.gov/24687088/
Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36:2684-2692.	https://pubmed.ncbi.nlm.nih.gov/30024784/
Lancet JE, Uy GL, Cortes JE, et al. Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. *J Clin Oncol.* 2016;34(15 suppl):7000.	https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.7000
LeBlanc TW, El-Jawahri A, Davis DM, et al. Patient experiences of acute myeloid leukemia: A qualitative study about diagnosis, illness understanding, and	https://pubmed.ncbi.nlm.nih.gov/27862591/

treatment decision-making. Psychooncology. 2017;26:2063-2068.	
Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361:1235-1248.	https://pubmed.ncbi.nlm.nih.gov/19776405/
Martin PJ, McDonald GB, Sanders JE, et al. Increasingly frequent diagnosis of acute gastrointestinal graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2004;10:320-327.	https://pubmed.ncbi.nlm.nih.gov/15111931/
Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med.* 1994;331:896-903.	https://www.nejm.org/doi/full/10.1056/nejm199410063311402
Mylotarg™ (gemtuzumab ozogamicin). Prescribing information. Wyeth Pharmaceuticals LLC; June 2020.	http://labeling.pfizer.com/ShowLabeling.aspx?id=9548
Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Blood.* 2000;96:2062-2068.	https://pubmed.ncbi.nlm.nih.gov/10979948/
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3.2021.	https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
National Quality Forum (NQF). *NQP Playbook™: Shared Decision Making in Healthcare.* Washington, DC: NQF;2018.	https://www.qualityforum.org/National_Quality_Partners_Shared_Decision_Making_Action_Team_.aspx
Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med.* 2012;366:1079-1089.	https://pubmed.ncbi.nlm.nih.gov/22417203/
Pemmaraju N, Kantarjian H, Ravandi F, Cortes J. FLT3 inhibitors in the treatment of acute myeloid leukemia: The start of an era? *Cancer.* 2011;117:3293-3304.	https://pubmed.ncbi.nlm.nih.gov/21319142/
Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or	https://pubmed.ncbi.nlm.nih.gov/31665578/

refractory *FLT3*-mutated AML. *N Engl J Med*. 2019;381:1728-1740.	
Rashidi A, Hamadani M, Zhang MJ, et al. Outcomes of haploidentical vs matched sibling transplantation for acute myeloid leukemia in first complete remission. *Blood Adv*. 2019;3:1826-1836.	https://pubmed.ncbi.nlm.nih.gov/31201170/
Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. *Blood*.1998;92:2303-2314.	https://pubmed.ncbi.nlm.nih.gov/9746768/
Roboz GJ, Montesinos P, Selleslag D, et al. Design of the randomized, phase III, QUAZAR AML maintenance trial of CC-486 (oral azacitidine) maintenance therapy in acute myeloid leukemia. *Future Oncol*. 2016;12:293-302.	https://pubmed.ncbi.nlm.nih.gov/26785287/
Rydapt® (midostaurin). Prescribing information. Novartis Pharmaceuticals Corp; April 2021.	http://www.novartis.us/sites/www.novartis.us/files/rydapt.pdf
Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and azacitidine in *TP53*-mutant myelodysplastic syndromes. *J Clin Oncol*. 2021;39:1584-1594.	https://pubmed.ncbi.nlm.nih.gov/33449813/
Sallmon DA, Asch AS, Kambhampati S, et al. The first-in-class anti-CD47 antibody magrolimab combined with azacitidine Is well-tolerated and effective in AML patients: Phase 1b results. Presented at American Society of Hematology (ASH) meeting, December 6, 2020: abstract 330.	https://ash.confex.com/ash/2020/webprogram/Paper134728.html
SEER Cancer Stat Facts: Leukemia — Acute Myeloid Leukemia (AML). National Cancer Institute. Bethesda, MD. Accessed July 13, 2021.	https://seer.cancer.gov/statfacts/html/amyl.html
Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71:7-33.	https://pubmed.ncbi.nlm.nih.gov/33433946/
Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5572791/

refractory acute myeloid leukemia. *Blood.* 2017;130:722-731.	
Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med.* 2017;377:454-464.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5754190/
US Food and Drug Administration (FDA). FDA approves Onureg (azacitidine tablets) for acute myeloid leukemia. Published September 1, 2020.	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-onureg-azacitidine-tablets-acute-myeloid-leukemia
Vyxeos® (daunorubicin + cytarabine). Prescribing information. Jazz Pharmaceuticals, Inc; March 2021.	http://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf
Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383:2526-2537.	https://pubmed.ncbi.nlm.nih.gov/33369355/
Xospata® (gilteritinib). Prescribing information. Astellas Pharma US, Inc; May 2019.	https://astellas.us/docs/xospata.pdf