TREATING MYELODYSPLASTIC SYNDROMES TRANSFORMATION TO ACUTE MYELOID LEUKEMIA

September 19, 2024

Provided by The Leukemia & Lymphoma Society and Medical Learning Institute, Inc.

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WELCOME AND INTRODUCTIONS

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Rye Brook, NY

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TARGET AUDIENCE

This activity is intended for hematologist/oncologists, oncology nurses, and other healthcare professionals involved in the care of patients with hematologic malignancies.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Provide an overview of Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Explain the progression from MDS to AML, including the factors that influence the transformation and the clinical implications
- Discuss the diagnostic criteria for distinguishing MDS from AML
- Describe the treatment options and management strategies for both MDS and AML, including emerging therapies
- Review resources and education to support patients, caregivers, and healthcare professionals

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SPEAKERS

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MDS Clinic Director
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DISCLOSURES

Aref Al-Kali, MD, has a financial interest/relationship or affiliation in the form of:

Consultant/Advisor (support to institution): Novartis

Research Funding (support to institution): ALX Oncology, Aprea, Astex, H3B/Hemavant, Novartis

Jennifer Andres, MSN, RN, FNP-C, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

**All of the relevant financial relationships of individuals for this activity have been mitigated.*

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Polling Question 1

Per WHO, what is a main distinguishing feature between MDS and AML?

1. In MDS the blasts are 19% or less, whereas in AML the blasts are 20% or higher.
2. In MDS the blasts are 15% or less, whereas in AML the blasts are 16% or higher.
3. In MDS the blasts are 10% or less, whereas in AML the blasts are 11% or higher.
4. In MDS the blasts are 5% or less, whereas in AML the blasts are 6% or higher.

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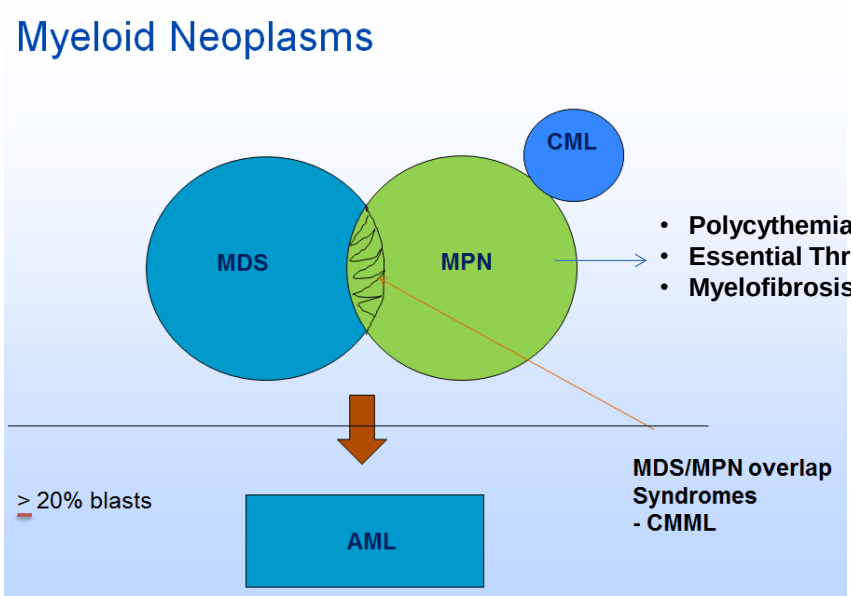
Myeloid Neoplasms



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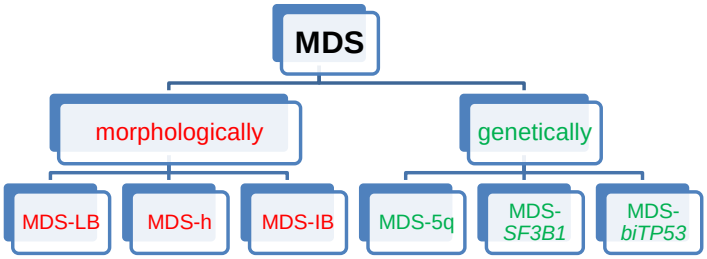
MDS WHO 2022

- **Genetically defined**
  - MDS-5q
  - MDS-*SF3B1m*
  - MDS-*biTP53*
- **Morphologically defined**
  - MDS-LB low blasts
  - MDS-h hypocellular
  - MDS-IB increased blasts
    - IB-1: 2-4% PB blasts, 5-9% BM blasts
    - IB-2: 5-19% PB blasts, 10-19% blasts or Auer rods
    - Fibrosis: 2-19% PB blasts, 5-19% BM blasts



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MDS 2022

WHO	ICC
MDS 5q	MDS Del 5q
MDS *SF3B1*	MDS *SF3B1*
MDS *BiTP53*	MDS or MDS/AML *TP53*
MDS-LB	MDS-NOS (SLD/MLD)
MDS-h	
MDS IB	MDS-EB
	MDS/AML

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Arber D et al, Blood 2022, 1200-28.
Khoury J et al. Leukemia 2022, 1703-1719

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MDS 2022

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WHO	ICC
MDS 5q	MDS Del 5q
MDS *SF3B1*	MDS *SF3B1*
MDS *BiTP53*	MDS or MDS/AML *TP53*
MDS-LB	MDS-NOS (SLD/MLD)
MDS-h	
MDS IB	MDS-EB
	MDS/AML

Arber D et al, Blood 2022, 1200-28.
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Diagnosis and Management of AML in Adults

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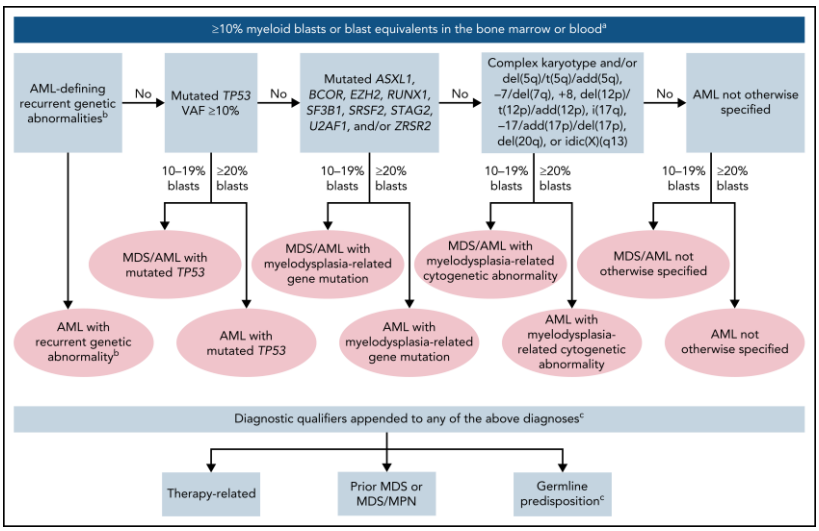

Döhner H et al, Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN, Blood, 2022, Figure 1.

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Diagnosis and Management of AML in Adults

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AML and related neoplams	
AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)* • APL with t(15;17)(q24.1;q21.2)/*PML::RARA*† • 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* • AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*‡ • AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214* • AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*§ • AML with other rare recurring translocations‖ • AML with mutated *NPM1* • AML with in-frame bZIP mutated *CEBPA*¶ • AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1**	**Myeloid sarcoma** **Acute leukemia of ambiguous lineage** • Acute undifferentiated leukemia • MPAL with t(9;22)(q34.1;q11.2)/*BCR::ABL1* • MPAL with t(v;11q23.3)/*KMT2A*-rearranged • MPAL, B/myeloid, not otherwise specified • MPAL, T/myeloid, not otherwise specified
Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB) • AML with mutated *TP53*# • AML with myelodysplasia-related gene mutations Defined by mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* and/or *ZRSR2* • AML with myelodysplasia-related cytogenetic abnormalities** • AML not otherwise specified	**Myeloid proliferations related to Down syndrome** • Transient abnormal myelopoiesis associated with Down syndrome • Myeloid leukemia associated with Down syndrome **Blastic plasmacytoid dendritic cell neoplasm**

Other rare recurring translocations:
- AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*;
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.1)/*RBM15::MRTFA*;
- AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1*;
- AML with t(5;11)(q35.2;p15.4)/*NUP98::NSD1*;
- AML with t(7;12)(q36.3;p13.2)/*ETV6::MNX1*;
- AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*;
- AML with t(10;11)(p12.3;q14.2)/*PICALM::MLLT10*;
- AML with t(11;12)(p15.4;p13.3)/*NUP98::KMD5A*;
- AML with *NUP98* and other partners;
- AML with t(16;21)(p11.2;q22.2)/*FUS::ERG*;
- AML with t(16;21)(q24.3;q22.1)/*RUNX1::CBFA2T3*;
- AML with inv(16)(p13.3q24.3)/*CBFA2T3::GLIS2*.

Döhner H et al, Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN, Blood, 2022, Figure 1.

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Polling Question 2

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Per WHO, to diagnose an AML, which of the following does **NOT** qualify?

1. T(8;21)
2. NPM1 mutation
3. Inv (16)
4. STAG2 mutation

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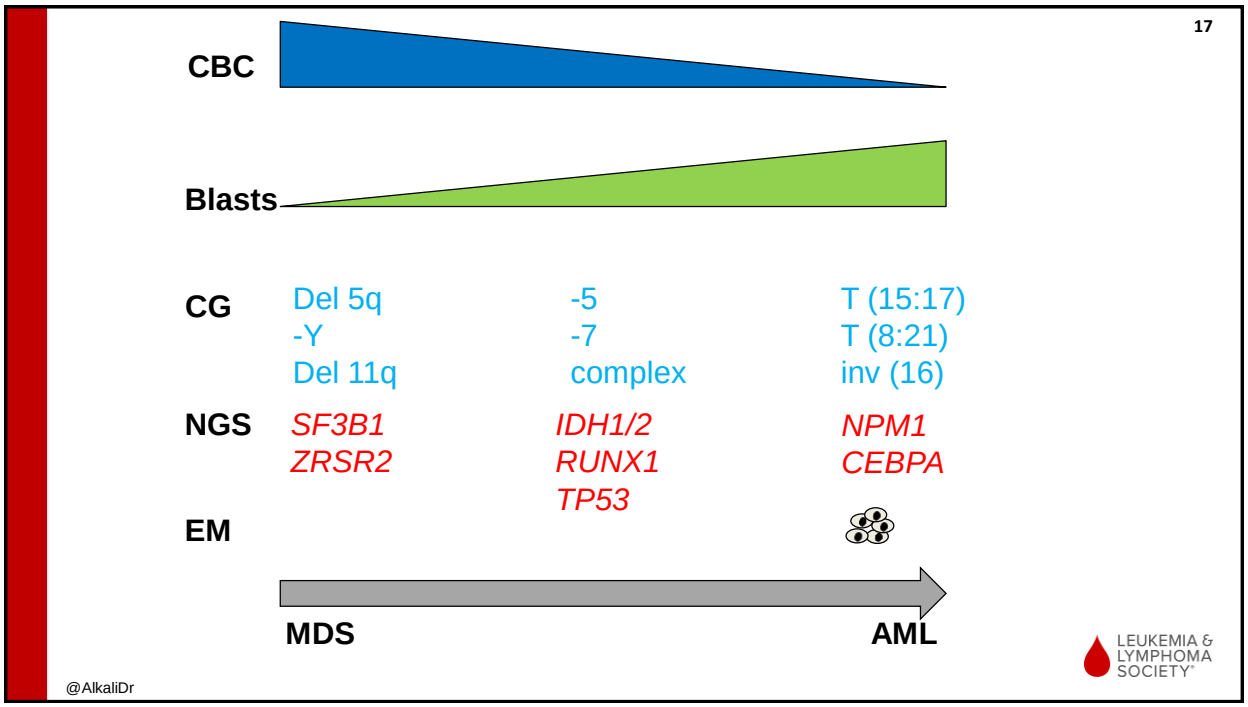
17
CBC
Blasts
CG
Del 5q
-Y
Del 11q
-5
-7
complex
T (15:17)
T (8:21)
inv (16)
NGS
SF3B1
ZRSR2
IDH1/2
RUNX1
TP53
NPM1
CEBPA
EM
MDS
AML
@AlkaliDr
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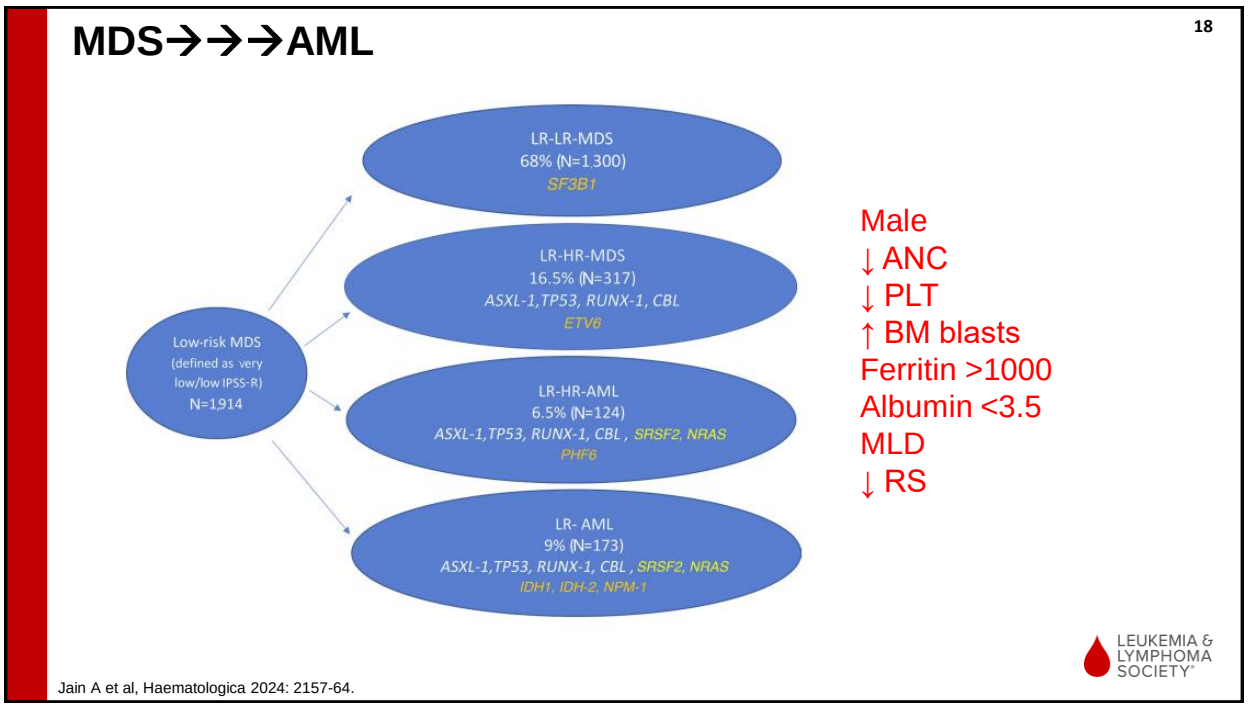
MDS→→→AML
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LR-LR-MDS
68% (N=1,300)
SF3B1
LR-HR-MDS
16.5% (N=317)
ASXL-1,TP53, RUNX-1, CBL
ETV6
Low-risk MDS
(defined as very low/low IPSS-R)
N=1,914
LR-HR-AML
6.5% (N=124)
ASXL-1,TP53, RUNX-1, CBL , SRSF2, NRAS
PHF6
LR- AML
9% (N=173)
ASXL-1,TP53, RUNX-1, CBL , SRSF2, NRAS
IDH1, IDH-2, NPM-1
Male
↓ ANC
↓ PLT
↑ BM blasts
Ferritin >1000
Albumin <3.5
MLD
↓ RS
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Jain A et al, Haematologica 2024: 2157-64.

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ELN2022

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 • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

Döhner H et al, Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN, Blood, 2022, Figure 1.

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ELN2022

Risk category†	Genetic abnormality
Favorable — INTENSIVE	• 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 • bZIP in-frame mutated *CEBPA*‖
Intermediate — INTENSIVE	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse — INTENSIVE / ALLOHCT	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

Döhner H et al, Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN, Blood, 2022, Figure 1.

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Mutations Tips

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Gene	Correlation	Rx
SF3B1	Ring sideroblast	Luspatercept, imetelstat
IDH1	Cbc ~	Ivosidenib/Olutasidenib, HMA+VEN
IDH2	Cbc ~	Enasidenib, HMA+VEN
FLT3	AML transformation	Gilteritinib
NPM1	AML-defining	CTX vs HMA+VEN, Menin-i
RUNX1	AML transformation	HMA+VEN
DDX41	Germline ?, cbc ~	HMA+VEN, LEN
STAT3	LGL	ISA
PIGA1	PNH	Complement inhibitor
UBA1	VEXAS	HMA,, JAKi
TP53	T-MN	? PO DAC

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@AlkaliDr

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The IPSS-M Risk Categories

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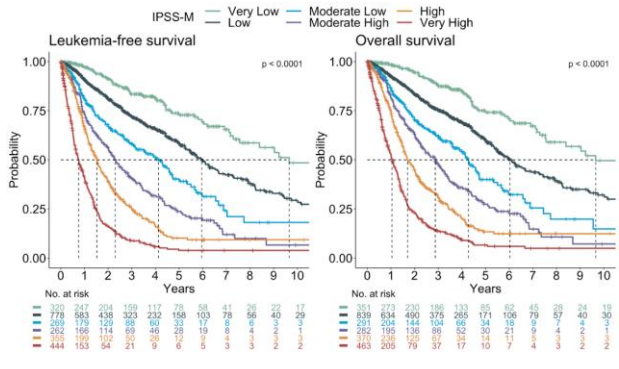
A six-category risk schema

IPSS-M	Very Low VL	Low L	Moderate Low ML	Moderate High MH	High H	Very High VH
Patients, % (n=2,701)	14% (381)	33% (889)	11% (302)	11% (291)	14% (379)	17% (469)
Risk score	≤ -1.5	> -1.5 to -0.5	> -0.5 to 0	> 0 to 0.5	> 0.5 to 1.5	>1.5
Hazard ratio* (95% CI)	0.51 (0.39 - 0.67)	1.0 reference	1.5 (1.2 - 1.8)	2.5 (2.1 - 3.1)	3.7 (3.1 - 4.4)	7.1 (6.0 - 8.3)
Median LFS, yrs 25-75% LFS range, yrs	9.7 5.0 - 17.4	5.9 2.6 - 12.0	4.5 1.6 - 6.9	2.3 0.91 - 4.7	1.5 0.80 - 2.8	0.76 0.33 - 1.5
Median OS, yrs 25-75% OS range, yrs	10.6 5.1 - 17.4	6.0 3.0 - 12.8	4.6 2.0 - 7.4	2.8 1.2 - 5.5	1.7 1.0 - 3.4	1.0 0.5 - 1.8
AML-t by 1 yr, % 2 yrs 4 yrs	0.0 1.2 2.8	1.7 3.4 5.1	4.9 8.8 11.4	9.5 14.0 18.9	14.3 21.2 29.2	28.2 38.6 42.8
Death w/o AML by 1 yr, % 2 yrs 4 yrs	2.2 7.0 15.9	8.5 16.2 29.5	12.0 19.8 33.6	18.0 31.1 51.1	19.3 39.8 54.2	30.6 45.6 51.3



Very Low | Low | Moderate Low | Moderate High | High | Very High
Prognostic separation of the IPSS-M risk categories

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Bernard E et al, NEJM 2022, DOI: 10.1056

The NEW ENGLAND JOURNAL of MEDICINE

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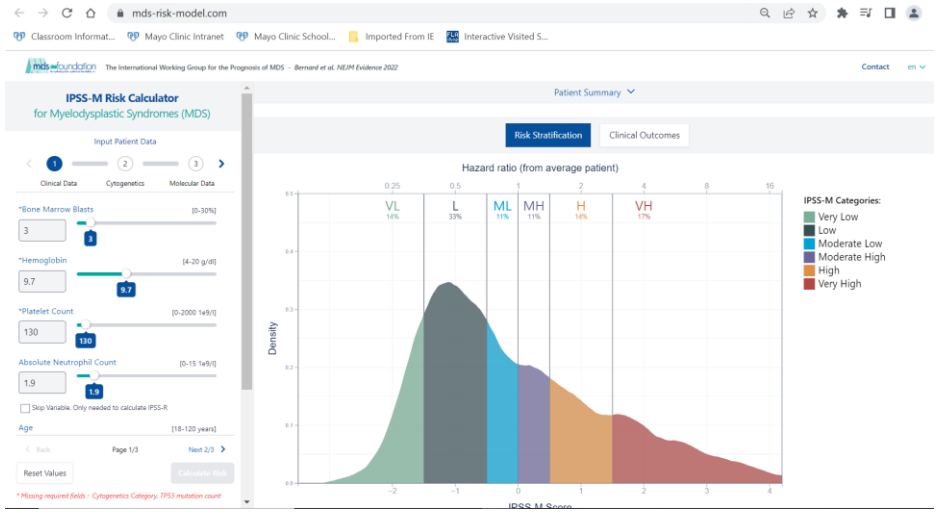
IPSS-M Calculator

https://mds-risk-model.com/



Bernard E et al, NEJM 2022, DOI: 10.1056

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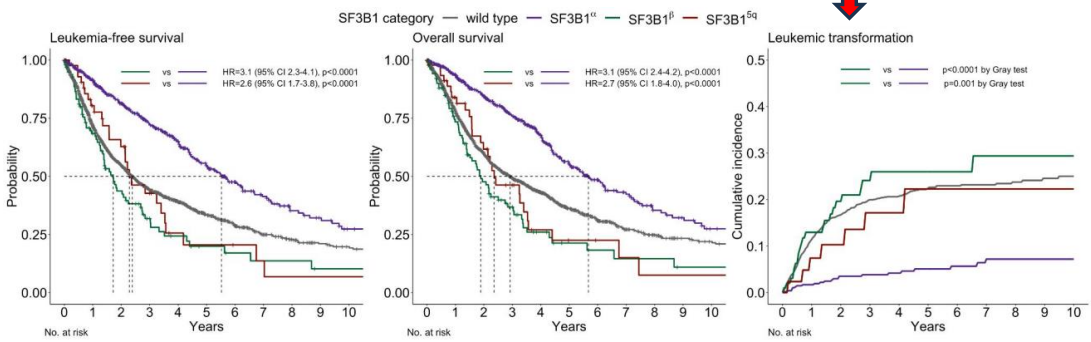
SF3B1

***SF3B1a* (78%)**

***SF3B1* 5q (7%)**

***SF3B1b* (15%)**
BCOR BCORL1 NRAS RUNX1
SRSF2 STAG2



Bernard E et al, NEJM 2022, DOI: 10.1056

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Goals of Treatment

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- **For lower-risk MDS**
  - Reduce transfusions
  - Restore effective blood cell production
  - Maximize quality of life
- **For higher-risk MDS (similar to goals of patients with AML)**
  - Attain a partial or complete remission
  - Prolong survival
  - Maximize quality of life

Patients should also be evaluated and treated for symptomatic anemia and receive supportive care.

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Polling Question 3

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What are treatment options for high-risk MDS?

1. Observation and transfusion support only
2. Hypomethylating agents (HMAs), such as decitabine and azacitidine
3. Hypomethylating agents and allogeneic stem cell transplant
4. Hypomethylating agents, HMA + venetoclax, lenalidomide, or allogeneic stem cell transplant

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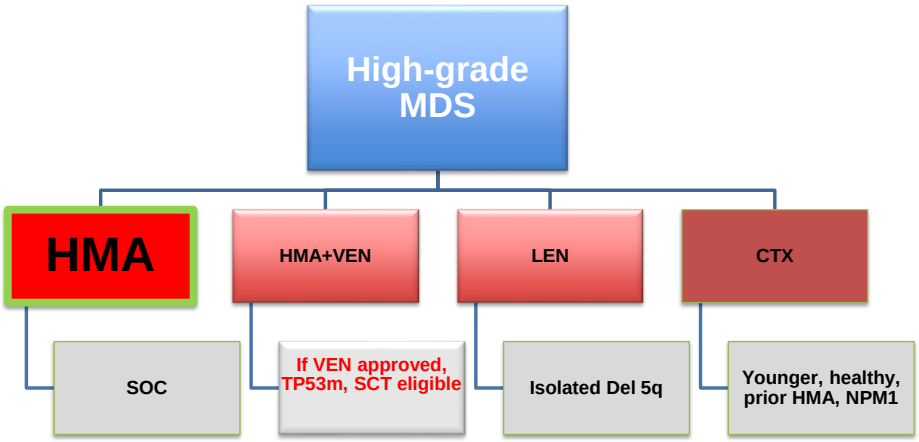

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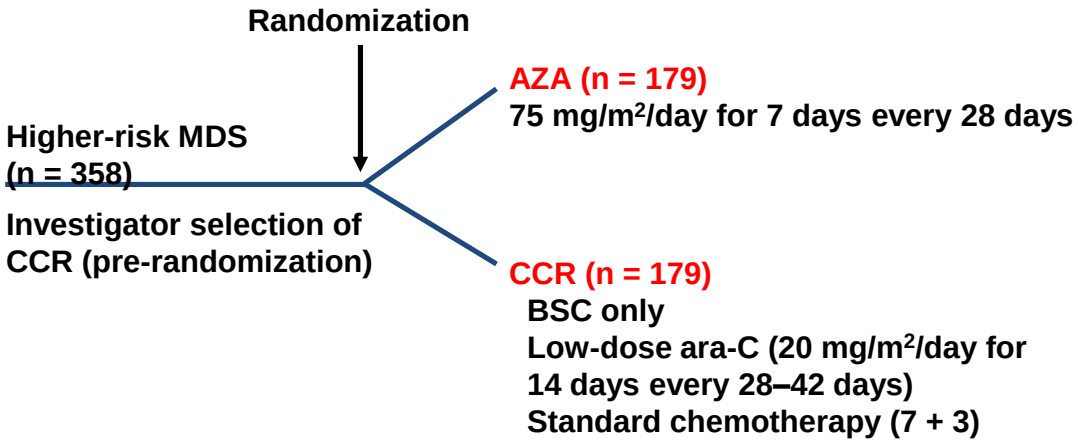
AZA-001: Phase III Study



BSC was included in each arm. Treatment continued until unacceptable adverse events or transformation to AML or disease progression.

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Fenaux P, et al. Lancet Oncol. 2009;10:223-32.

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AZA-001: Phase III Study

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	Total ITT (n=358)			BSC only (n=222)			Low-dose cytarabine (n=94)			Intensive chemotherapy (n=42)		
	Azacitidine (n=179)	CCR (n=179)	p value*	Azacitidine (n=117)	BSC (n=105)	p value*	Azacitidine (n=45)	Low-dose cytarabine (n=49)	p value*	Azacitidine (n=17)	Intensive chemotherapy (n=25)	p value*
Haematological response												
Any remission	51 (29%)	21 (12%)	0·0001	32 (27%)	5 (5%)	<0·0001	14 (31%)	6 (12%)	0·042	5 (29%)	10 (40%)	0·53
Complete remission	30 (17%)	14 (8%)	0·015	14 (12%)	1 (1%)	0·0008	11 (24%)	4 (8%)	0·047	5 (29%)	9 (36%)	0·75
Partial remission	21 (12%)	7 (4%)	0·0094	18 (15%)	4 (4%)	0·0058	3 (7%)	2 (4%)	0·67	0	1 (4%)	1·00
Stable disease	75 (42%)	65 (36%)	0·33	52 (44%)	41 (39%)	0·50	15 (33%)	18 (37%)	0·83	8 (47%)	6 (24%)	0·18
Haematological improvement†												
Any improvement	87/177 (49%)	51/178 (29%)	<0·0001	57/115 (50%)	32/105 (31%)	0·0058	24/45 (53%)	12/48 (25%)	0·0061	6/17 (35%)	7/25 (28%)	0·74
Major erythroid improvement	62/157 (40%)	17/160 (11%)	<0·0001	39/100 (39%)	8/96 (8%)	<0·0001	19/43 (44%)	4/41 (10%)	0·0005	4/14 (29%)	5/23 (22%)	0·70
Major platelet improvement	46/141 (33%)	18/129 (14%)	0·0003	27/89 (30%)	8/78 (10%)	0·0020	14/37 (38%)	6/31 (19%)	0·12	5/15 (33%)	4/20 (20%)	0·45
Major neutrophil improvement	25/131 (19%)	20/111 (18%)	0·87	13/85 (15%)	13/66 (20%)	0·52	9/33 (27%)	3/28 (11%)	0·12	3/13 (23%)	4/17 (24%)	1·00

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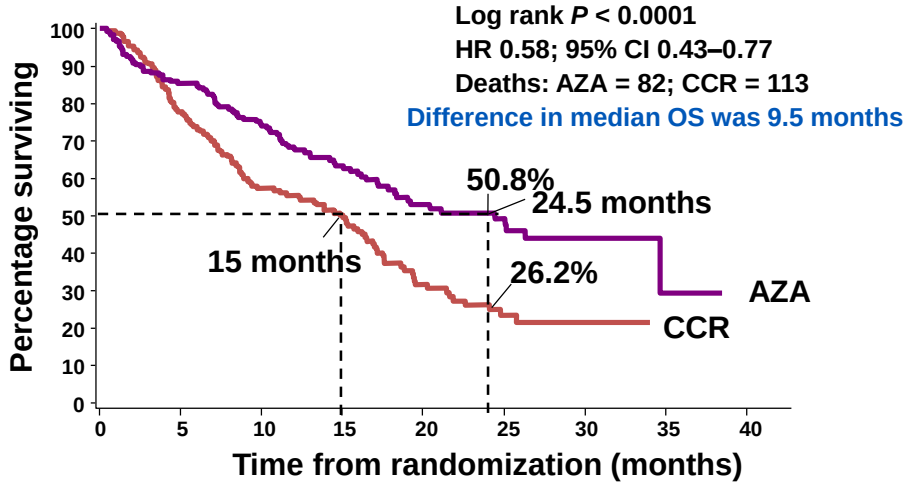
Fenaux P, et al. Lancet Oncol. 2009;10:223-32.

29

AZA-001: Primary Study Results OS

30



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Fenaux P, et al. Lancet Oncol. 2009;10:223-32.

30

Hypomethylating Agents

31

- **They change the signaling in the bone marrow and help to:**
  - Improve survival
  - Improve blood counts
  - Slow down progression to leukemia
- **Decitabine: must be given IV**
- **Azacitidine: IV or subcutaneous**
- **No head-to-head comparison**
- **Given 5-7 days once a month**

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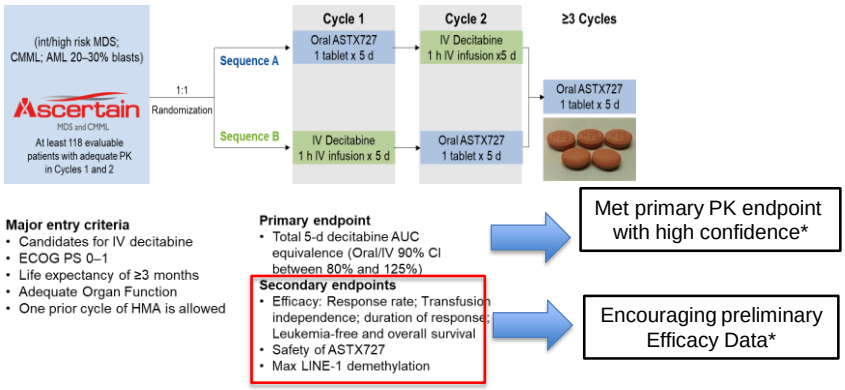
Oral Decitabine

32



With median follow up > 24 months, efficacy data are more mature

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*Garcia-Manero, et al, [ASH Abstract 846] Blood. 2019;134 (suppl 1).

32

Results: Efficacy Response

33

Response category	Treated Patients (N=133), n (%)	95% CI
Complete response (CR)	29 (22)	(15.1,29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3%)	(24.5,41.0)
mCR with hematologic improvement	22 (16.5%)	(10.7,24.0)
Hematologic improvement (HI)	10 (7.5%)	(3.7,13.4)
HI-erythroid	2 (1.5%)	(0.2,5.3)
HI-neutrophils	1 (0.8%)	(0.0,4.1)
HI-platelet	7 (5.3%)	(2.1,10.5)
Overall response (CR + PR + mCR + HI)	82 (61.7)	(52.8,69.9)
Progressive Disease	6 (4.5%)	(1.7,9.6)
No Response	28 (21.1%)	(14.5, 29.0)
Non-evaluable	17 (12.8%)	(7.6, 19.7)

- **Median CR duration was 14.0 months**
- **Median duration of best response was 12.7 months**
- **34 (26%) of subjects proceeded to HCT**

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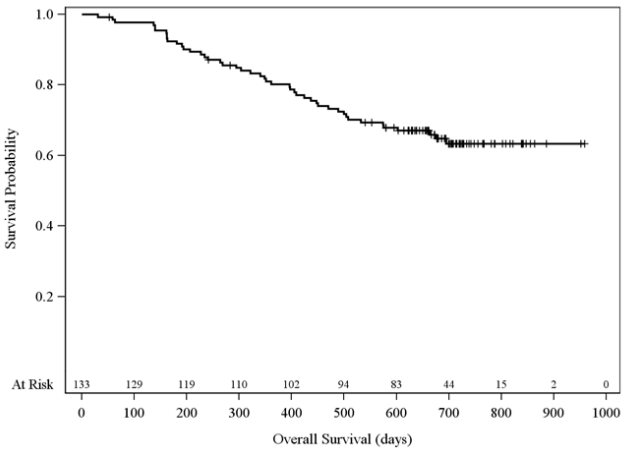
Results: Overall Survival

34



- **Median follow up is 24.7 months**
- **mOS has not yet been reached**
- **Patients will continue to be followed**

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Prolonged Survival in Bi-Allelic TP53-Mutated (TP53mut) MDS Subjects Treated with Oral Decitabine/Cedazuridine in the Ascertain Trial (ASTX727-02)

125 pts; 35% *TP53m*

Figure 1.

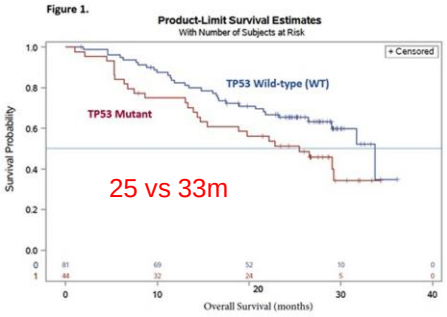
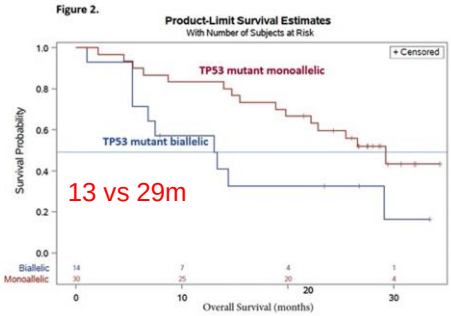


Figure 2.



Savona MR et al, Prolonged Survival in Bi-Allelic TP53-Mutated (TP53mut) MDS Subjects Treated with Oral Decitabine/Cedazuridine in the Ascertain Trial (ASTX727-02), Blood, 2022, Figure 1. Abs 854

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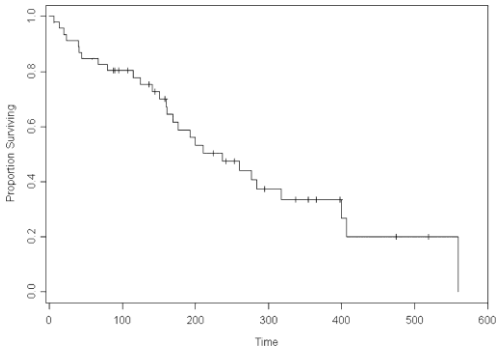
Efficacy and Safety of Lenalidomide in Intermediate-2 or High-Risk Myelodysplastic Syndromes with 5q Deletion: Results of a Phase 2 Study

36

47 pts

Factor Category	n	No. of CRs	CR, %	*P*
Cytogenetic				
Isolated del 5q	9	6	**67**	< .001
Single additional abnormality	11	1	9	
> 1 additional abnormalities	27	0	0	
Bone marrow blasts, %				
< 20%	29	6	21	.16
> 20%	18	1	5	
Baseline platelet count, G/L				
> 100	20	7	35	< .001
< 100	27	0	0	



Ades L et al. Efficacy and safety of lenalidomide in intermediate-2 or high-risk myelodysplastic syndromes with 5q deletion: results of a phase 2 study. Blood, 2009, 113:3947-52,

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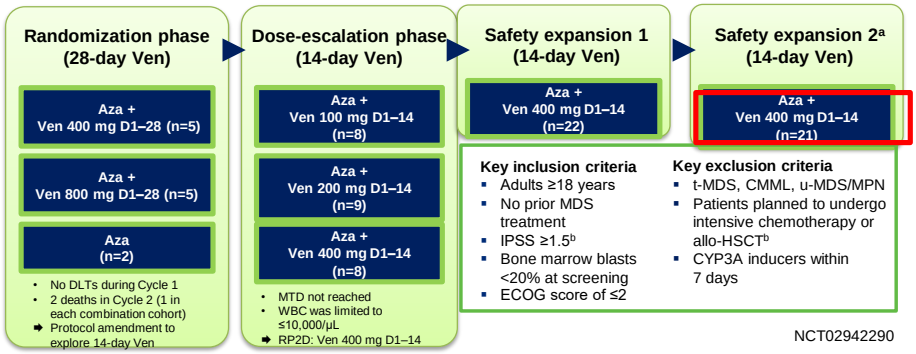
37

AZA+VEN

Treatment cohorts (28-day cycles); Aza 75 mg/m^2 D1–7



NCT02942290

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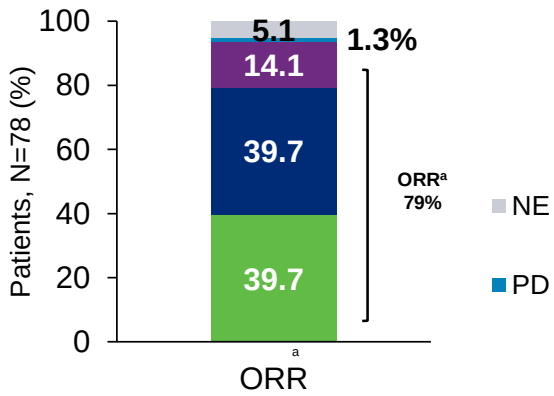
Garcia J et al, ASH 2020

37

38

Response Rates and Transfusion Independence



- Median DoR: 12.9 months (min–max, 12.1–16.8)
- Median DoR after CR: 13.8 months (min–max, 6.5–20.9)
- Median time to CR: 2.6 months (min–max, 1.2–19.6)
- For patients receiving Ven 400 mg (RP2D; n=51)[b]
  - 84% of patients achieved ORR[a]
    - 47% achieved ORR by Cycle 2; 78% achieved ORR by Cycle 3
  - 35% of patients achieved CR

Transfusion independence rate	n (% of N=78)
RBC and platelet	51 (65)
RBC	52 (67)
Platelet	60 (77)

- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant

Data cutoff: June 30, 2020

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Garcia J et al, ASH 2020

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Summary of AE

39

Any AEs, n (%)	78 (100)
Neutropenia[a]	65 (83)
Febrile neutropenia	38 (49)
Nausea	43 (55)
Constipation	42 (54)
Diarrhea	38 (49)
Thrombocytopenia[b]	38 (49)
Vomiting	32 (41)
Leukopenia[c]	30 (38)
Anemia[d]	23 (29)
Fatigue	20 (26)
Hypokalemia	16 (21)

Grade 3/4 AEs, n (%)	75 (96)
Neutropenia[a]	64 (82)
Febrile neutropenia	38 (49)
Thrombocytopenia[b]	33 (42)
Leukopenia[c]	30 (38)
Anemia[d]	18 (23)

Any SAEs, n (%)	57 (73)
Neutropenia[a]	38 (49)
Febrile neutropenia	35 (45)
Pneumonia	5 (6)
Diverticulitis	4 (5)

- **Overall, 74 patients (95%) required a cycle delay; median time to delay 15.0 days (range 3–99)**
- **43 patients (55%) had ≥2 Ven dose interruptions**
  - AEs 59 (80%); hematologic toxicity 27 (37%); logistics/scheduling 19 (26%), other 41 (55%)
- **A total of 35% of patients required ≥1 Ven dose reduction[e]**
  - AEs 6 (21%); starting CYP3A inhibitor 20 (71%);
    other 7 (25%)
- **A total of 33% of patients required ≥1 Aza dose reduction[e]**
- **30-day mortality after first dose was 1%**

Data cutoff: June 30, 2020

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Garcia J et al, ASH 2020

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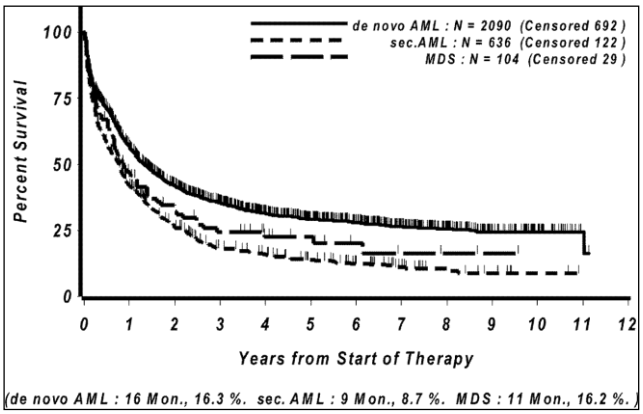
MDS with Intensive CTX AMLCG99

40



	HR-MDS	AML	sAML
N	104	2051	636
CR%	48%	67%	47%
mOS, d	320	484	282

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ASH 2011, Abstract 2773, Krug U

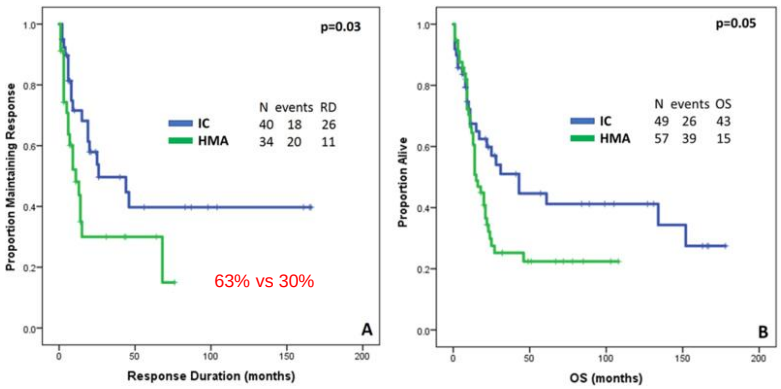
40

Intensive Chemotherapy (IC) vs HMA in Young MDS-EB Patients

41

NPM1, <50, FL **-CG**

106 pts



Strati P et al. Am J Hematol. 2019 Jul; 94(7): E188–E190.

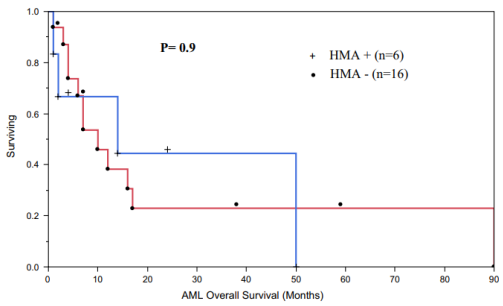
41

Prior Hypomethylating Agent use Lacks Impact on Clinical Outcome in Patients with Secondary Acute Myeloid Leukemia Arising from Myelodysplastic Syndromes Treated with Standard Induction Chemotherapy

42

96 pts

Rx	HMA+	HMA-
Age, yr	58	65
Time to AML, m	24.5	4.5
CR	50%	63%
mOS, m	14	10

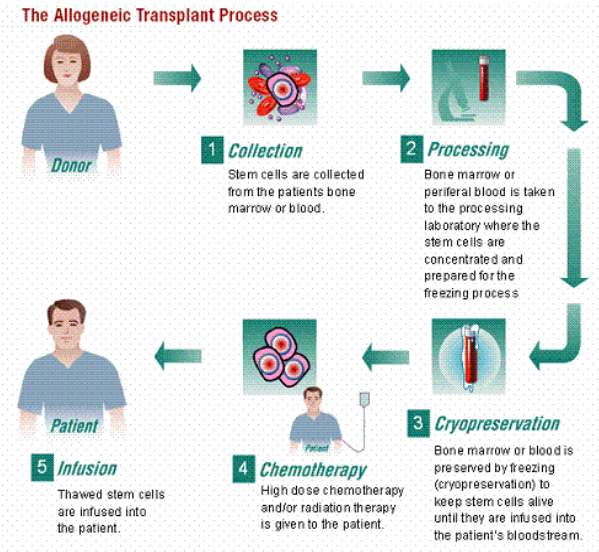


Subari et al. I J Hematol. 2016 Apr; 103(4): 409–15.

42

Allogeneic Stem Cell Transplant

43



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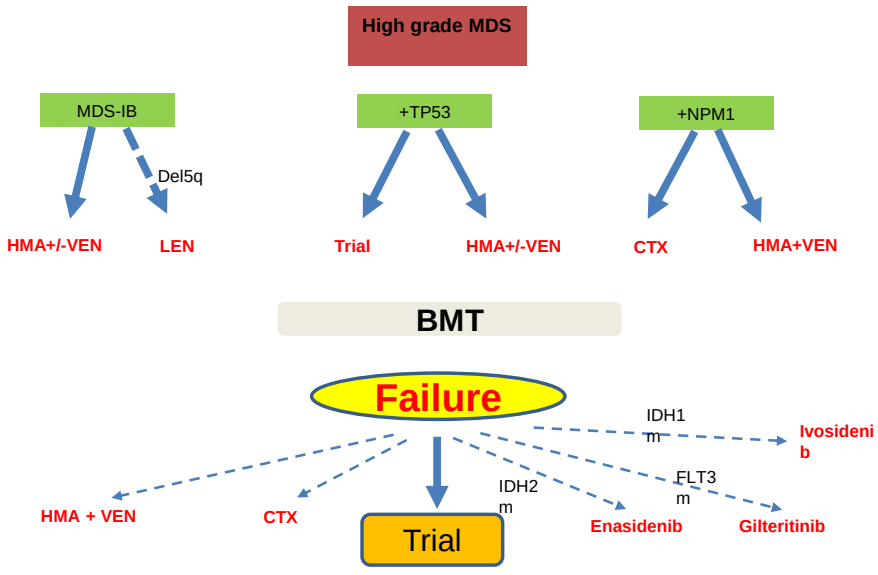

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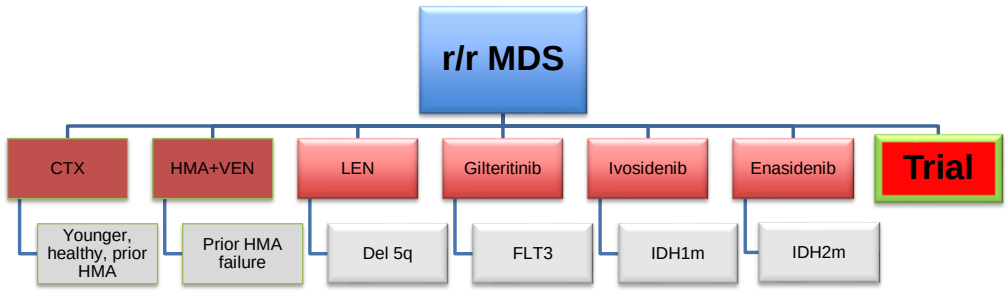

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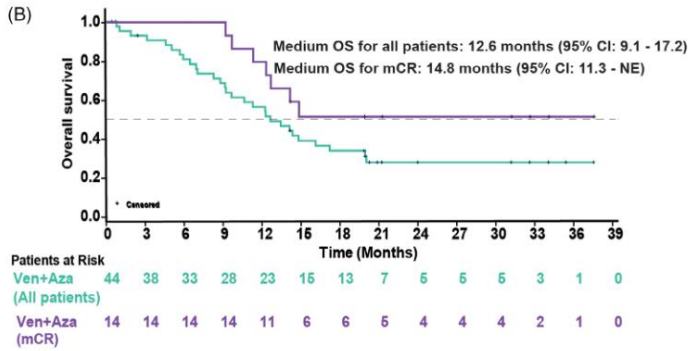
46

AZA + VEN -R/R MDS

75MG/M2 X7 400MG X14 DAYS

	Venetoclax + azacitidine (*N* = 44)
Duration of study follow-up, months, median (range)	21·2 (0·4–37·5)
Response rates, *n* (%)	
mORR	17 (38·6)
CR	3 (6·8)
mCR	14 (31·8)
Not evaluable	7 (15·9)
Time to response, months, median (range)	
Time to mORR	1·2 (0·7–6·3)
Time to mCR	1·4 (0·7–6·3)
Duration of response (DoR), months, median (95% CI)	
DoR for mORR	8·6 (6·0–13·3)
DoR for CR	9·1 (6·3–NE)
DoR for mCR	8·6 (6·0–23·8)
Composite response rate[a] (CR + PR + mCR + HI[b]), *n*/*N* (%)	19/44 (43·2)



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Zeidan A et al. AJH 2023 Feb;98(2):272-281

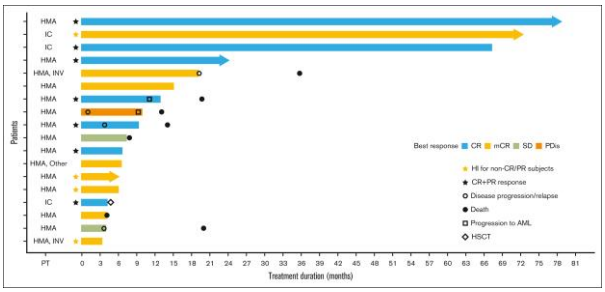
46

Final Phase 1 Results of Ivosidenib for Patients with Mutant IDH1 Relapsed/Refractory Myelodysplastic Syndrome

47

26% MDS-EB

Efficacy outcomes	MDS substudy efficacy analysis set (N = 18)
CR + PR	7 (38.9%)
Time to CR + PR, median mo (min, max)	1.87 (1.0, 5.6)
mCR	8 (44.4%)
ORR	15 (83.3%)
Any HI lineage (CR/PR-)	4 (36.4%)
7-y OS	46.3 %



DiNardo CD. Final phase 1 substudy results of ivosidenib for patients with mutant IDH1 relapsed/refractory myelodysplastic syndrome, Blood Adv, 2024,

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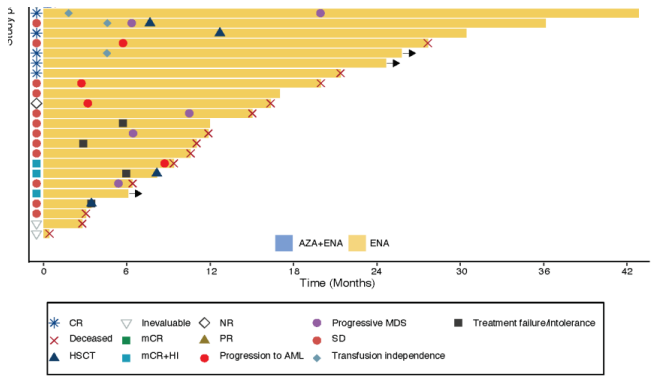
ENASIDENIB 100MG

48

- **23 r/r MDS**
- **Response**
  - CR 22%
  - ORR 35%
  - TTR 4.6m
- **Safety**
  - Neutropenia 40%, nausea 36%, constipation 32%, fatigue 26%, High bilirubin 14%, DS 16%



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DiNardo C et al Blood Advances 2022

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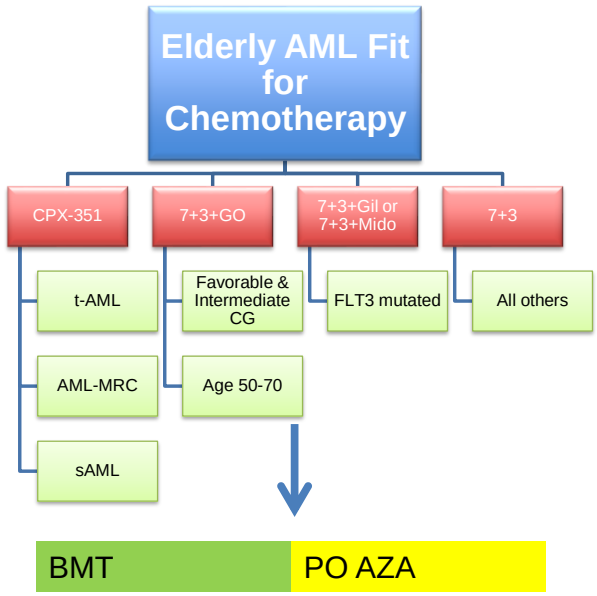

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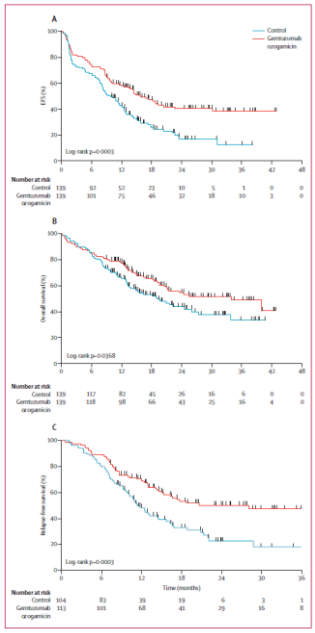
50

ALFA-0701
7+3 +/- GEMTUZUMAB

3MG/M2 DAYS 1,4,7

- **280 patients**
- **Age 50-70**
- **CD33+ or-**
- **Benefit is lost in unfavorable cytogenetic group**



Castaigne S et al. Lancet 2012; 1508-16.

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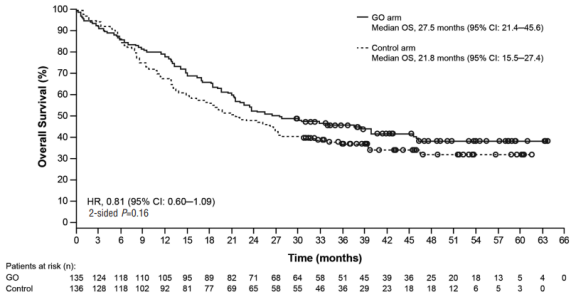
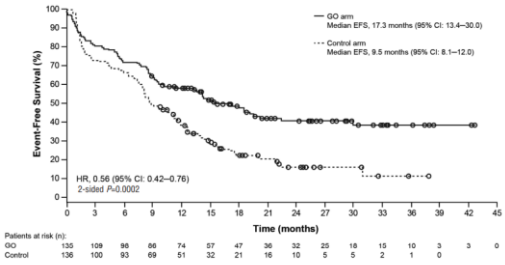
51

ALFA-0701
7+3 +/- GEMTUZUMAB

3MG/M2 DAYS 1,4,7





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Lambert J et al. Hematologica 2019; 113-9.

51

52

Liposomal Daunorubicin/Cytarabine VS 7+3

100 U/M2 DAYS 1, 3, 5 100MG/M2 DAYS 60MG/M2

- **Phase III, elderly AML, age 60-75**
  - Prior CTX, prior MDS/CMML, AML-MRC CG
- **309 pts, randomized 1:1, follow up 13.7 months**
- **OS**
  - 9.56 vs 5.95 m (p =0.005), HR=0.69
- **60 Days mortality**
  - 13.7% vs 21.2%
- **EFS**
  - HR= 0.74 (p= 0.02)
- **CR/CRi**
  - 47.7% vs 33.3% (p=0.016)

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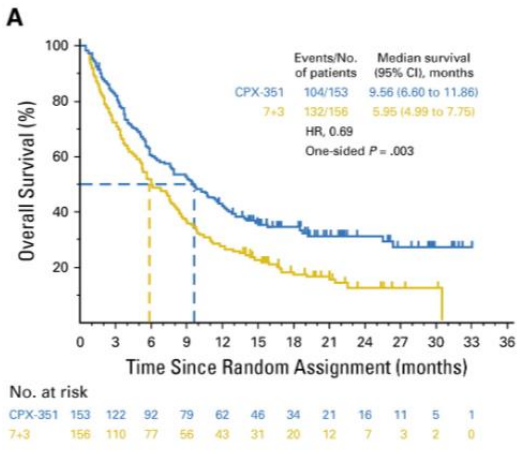
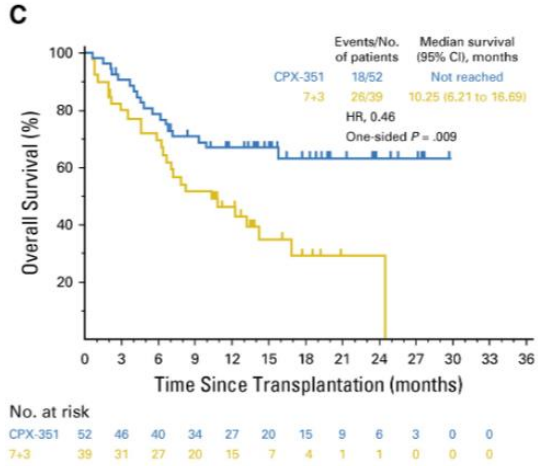
Lancet J et al. ASCO 2016, abs 7000

52

Liposomal Daunorubicin/Cytarabine vs 7+3

53





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Lancet J et al, Journal of Clinical Oncology 2018, 36, 2684-2692

53

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Polling Question 4

For AML secondary to MDS, which is the following is NOT an effective therapy:

1. Intensive chemotherapy “7+3”
2. Intensive liposomal cytarabine plus daunorubicin hypomethylating agent plus venetoclax
3. Hypomethylating agent plus venetoclax
4. JAK inhibitor (ruxolitinib)

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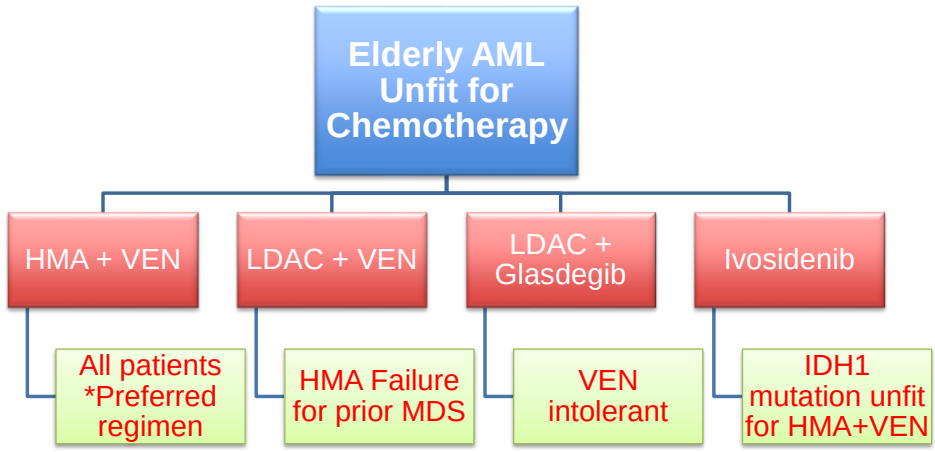

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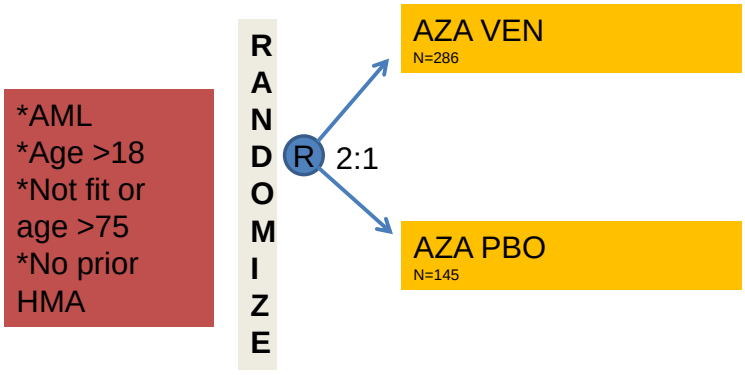
AZA VEN VS AZA PBO (VIALE-A)



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

The NEW ENGLAND JOURNAL of MEDICINE

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AZA VEN VS AZA PBO (VIALE-A)

57

	Aza Ven	Aza PBO	P value
cCR	66.4%	28.3%	<.001
cCR- end of C1	43.4%	7.6%	<.001
CR	36.7%	17.9%	<.001
Median time to response	1.3 m (0.6-9.9)	2.8 (0.8-13.2)	
Median response duration	17.5 m	13.4 m	
mOS	14.7 m	9.6 m	< .001
mEFS	9.8 m	7 m	<.001

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

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AZA VEN VS AZA PBO (VIALE-A)

58

	Aza Ven	Aza PBO	P value
IDH cCR	75.4%	10.7%	<.001
FLT3 cCR	72.4%	36.4%	.02
NPM1 cCR	66.7%	23.5%	.01
P53 cCR	55.3%	0	<.001
MRD-	23.4%	7.6%	

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

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AZA VEN vs AZA PBO (VIALE-A)

59

	Aza Ven	Aza PBO
dn-AML OS	14.1 m	9.6 m
s-AML OS	16.4 m	10.6 m
Int-risk AML OS	20.8 m	12.4 m
Poor risk AML OS	7.6 m	6 m
30-D mortality	7%	6%

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

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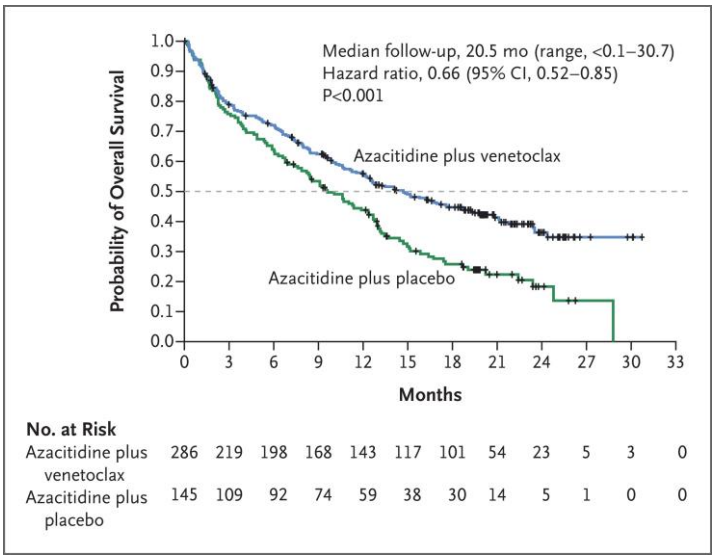

DiNardo CD et al. N Engl J Med 2020;383:617-629

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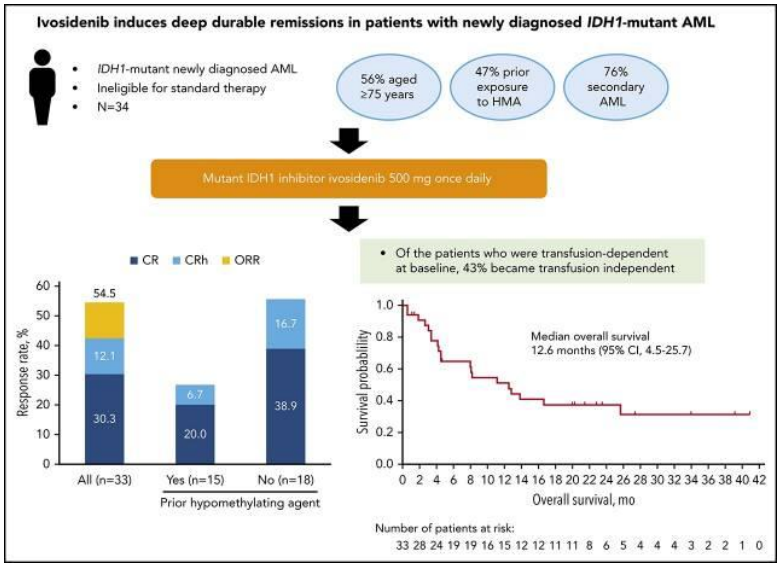

Roboz G et al. Blood 2020:135; 463-71.

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AZA+IVO VS AZA+PBO
AGILE STUDY

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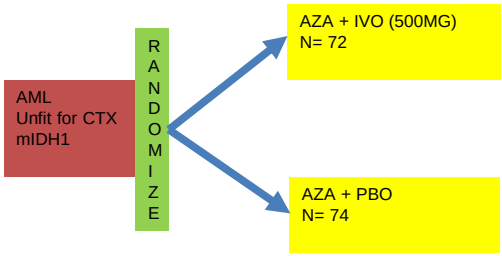

Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Best response — no. (%)		
Complete remission	34 (47)	11 (15)
Complete remission with incomplete hematologic or platelet recovery	5 (7)	1 (1)
Partial remission	4 (6)	2 (3)
Morphologic leukemia-free state	2 (3)	0
Stable disease	7 (10)	27 (36)
Progressive disease	2 (3)	4 (5)
Could not be evaluated	1 (1)	2 (3)
Not assessed	17 (24)	27 (36)

Montesinos P et al. N Engl J Med2022;386:1519-1531

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AZA+IVO VS AZA+PBO
AGILE

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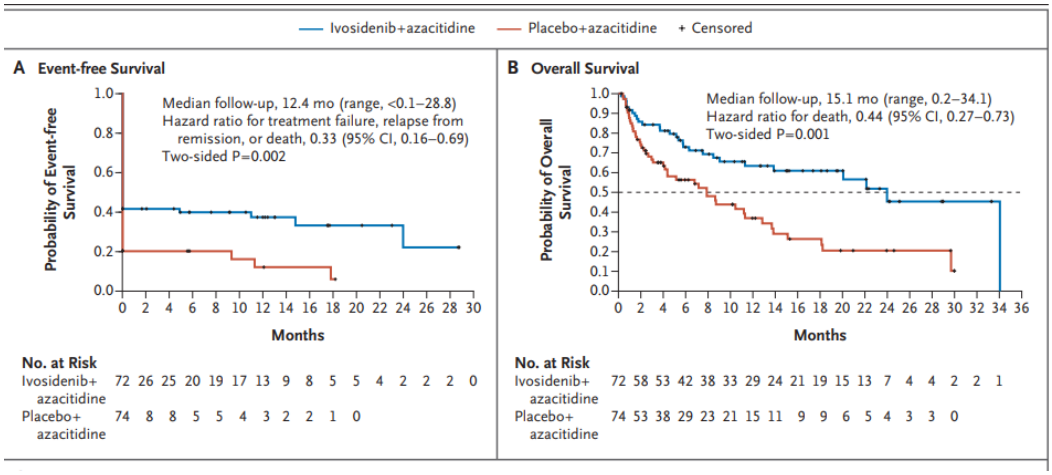

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Montesinos P et al. N Engl J Med2022;386:1519-1531

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THANK YOU

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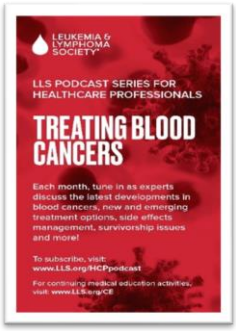
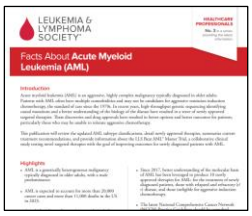
FREE LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

- CME & CE courses: www.LLS.org/CE
- Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- Videos for HCPs: www.LLS.org/HCPvideos
- Podcast series for HCPs: www.LLS.org/HCPpodcast





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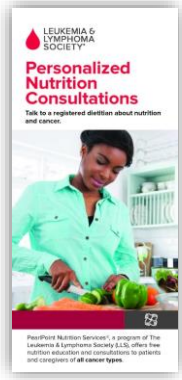
FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - www.LLS.org/IRC
- **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC
- **Nutrition Education Services Center** – one-on-one consultation with a registered dietician for patients/caregivers of all cancer types (NESC).
  - www.LLS.org/Nutrition
- **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: www.LLS.org/ContactUs
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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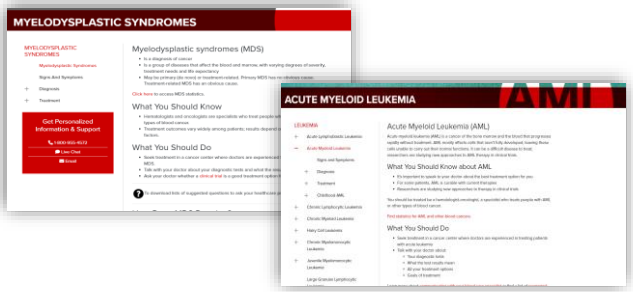
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Webcasts, Videos, Podcasts, booklets**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets



- **www.LLS.org/MDS**
- **www.LLS.org/leukemia/acute-myeloid-leukemia**

- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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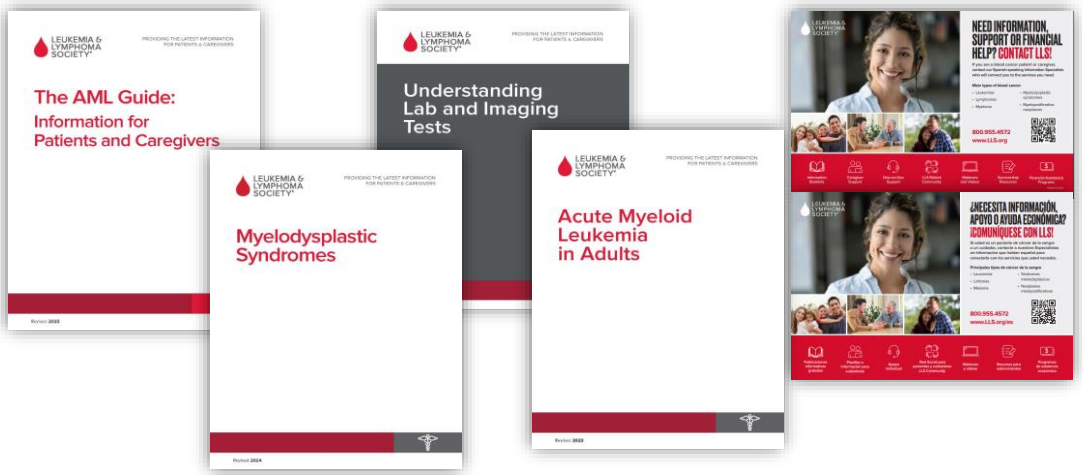
FREE LLS RESOURCES FOR YOUR PATIENTS



BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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Questions?

Ask a question on Zoom:

Please type them in the Q&A box.

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THANK YOU

Instructions For Credit

Participants must complete the evaluation to receive credit.
After completing this process, your certificate will automatically generate.

Link to complete evaluation: **https://lls.link/MDS**

OR scan the QR code:

For questions or concerns, please contact Profeducation@lls.org

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