Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

Vijaya Raj Bhatt, MD
Associate Professor
Medical Director, Leukemia Program
Division of Oncology and Hematology
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Mikkael A. Sekeres, MD
Professor of Medicine
Director, Leukemia Program
Vice Chair for Clinical Research
Cleveland Clinic
Taussig Cancer Institute
Cleveland, Ohio

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Faculty Disclosures

- **Dr. Vijaya Bhatt** has received honoraria as a consultant from AbbVie Inc., Agios, Incyte Corporation, Omeros Corporation, Partnership for Health Analytic Research (funded by Jazz), Rigel Pharmaceuticals, Inc., and Takeda Oncology. He has received grant support related to research activities from AbbVie, Incyte, Jazz Pharmaceuticals plc, National Marrow Donor Program, Pfizer Inc., and Tolero Pharmaceuticals. He has also disclosed a financial relationship with Oncoceutics, Inc.
- **Dr. Mikkael Sekeres** has received honoraria related to formal advisory activities from Bristol-Myers Squibb Company and Celgene Corporation – A Bristol-Myers Squibb Company.

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Planning Committee Disclosures

- The individuals listed below from MediCom Worldwide, Inc. reported the following for this activity: Joan Meyer, RN, MHA, Executive Director, Isabelle Vacher, Vice President of Educational Strategy, Wilma Guerra, Program Director, and Andrea Mathis, Project Manager, have no relevant financial relationships
- The individuals listed below from the University of Nebraska Medical Center, Center for Continuing Education and College of Nursing Continuing Education (UNMC) reported the following for this activity: Brenda Ram, CMP, CHCP, Director, Educational Programs, Heidi Keeler, PhD, RN, Director, UNMC College of Nursing Continuing Nursing Education have no relevant financial relationships

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Learning Objectives

- Apply updated recommendations for diagnostic and prognostic evaluation of AML and MDS in clinical practice, including optimal use of cytogenetic and molecular testing
- Incorporate new and emerging therapies into the treatment paradigm to provide optimal care for patients with newly diagnosed or relapsed/refractory AML
- Develop individualized treatment plans for patients with AML based on age, risk assessment, and other patient- or disease-related factors
- Manage anemia and other disease-related conditions in elderly patients with MDS

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Diagnostic, Prognostic and Therapeutic Importance of Cytogenetic and Molecular Abnormalities in MDS and AML

Vijaya Raj Bhatt, MD
Associate Professor
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AML Work-up: ASH-CAP 2017 and NCCN 2020

- Bone marrow core biopsy and aspirate analyses including immunophenotyping and cytochemistry
  - CD33: GO
- Cytogenetic analyses (karyotype + FISH)
- Molecular analyses

Arber DA, et al. *Arch Pathol Lab Med.* 2017;141:1342-1393.; National Comprehensive Cancer Network. NCCN Guidelines®. Acute myeloid leukemia. Version 3.2020 – December 23, 2019. Available at: www.nccn.irg. Accessed August 14, 2020.

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AML Work-up: NCCN 2020

- Molecular analyses (*ASXL1, c-KIT, FLT3* [*ITD* and *TKD*], *NPM1, CEBPA* (biallelic), *IDH1, IDH2, RUNX-1, TP53,* and other mutations)
- Multiplex gene panels and comprehensive NGS

National Comprehensive Cancer Network. NCCN Guidelines®. Acute myeloid leukemia. Version 3.2020 – December 23, 2019. Available at: www.nccn.irg. Accessed August 14, 2020.

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AML Work-up: 2017 ELN and NCCN 2020

NCCN[1]

- To appropriately stratify available intensive therapy options, expedite test results of molecular and cytogenetic analyses

ELN[2]

- Results from cytogenetics: preferably within 5 to 7 days
- Results from *NPM1* and *FLT3* mutational screening within 48 to 72 hours, and results from additional molecular genetics within the first treatment cycle

1. National Comprehensive Cancer Network. NCCN Guidelines®. Acute myeloid leukemia. Version 3.2020 – December 23, 2019. Available at: www.nccn.irg. Accessed August 14, 2020. 2. Döhner H, et al. *Blood.* 2017;129(4):424-447.

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Implications of Genomic Testing

- 2016 WHO classification based on several recurrent cytogenetic abnormalities and mutations[1]
  - AML with mutated *NPM1* or *RUNX1*
  - AML MRC diagnosis based on cytogenetic changes
- 2017 ELN risk categorization[2]
  - *RUNX1, ASXL1,* or *TP53* mutation identify adverse risk
- Therapeutic implications
  - *IDH1, IDH2, FLT3* inhibitors
  - CPX 351 indication for AML MRC

1. Arber DA, et al. *Blood.* 2016;127(20):2391-2405. 2. Döhner H, et al. *Blood.* 2017;129(4):424-447.

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MDS: Definition

- A heterogeneous clonal hematopoietic disorder derived from an abnormal multipotent progenitor cell
- Characterized by a hyperproliferative bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis

MDS is a Cancer!!!

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MDS: WHO Classification

2008 Name	Abbrev.	2016 Name	Abbrev.
Refractory cytopenia with unilineage dysplasia	RCUD (includes RA, RN and RT)	**MDS with single lineage dysplasia**	MDS-SLD
Refractory anemia with ring sideroblasts	RARS	**MDS with ring sideroblasts**	MDS-RS
MDS w/ isolated del(5q)	Del(5q)	*unchanged*	*unchanged*
Refractory cytopenia with multilineage dysplasia	RCMD	**MDS with multilineage dysplasia**	MDS-MLD
		(with ring sideroblasts)	MDS-RS-MLD
Refractory anemia with excess blasts, type 1	RAEB-1	**MDS with excess blasts, type 1**	MDS-EB-1
Refractory anemia with excess blasts, type 2	RAEB-2	**MDS with excess blasts, type 2**	MDS-EB-2
MDS, Unclassifiable	MDS-U	*unchanged*	*unchanged*
Refractory cytopenia(s) of childhood	RCC	*unchanged*	*unchanged*

Adapted from Arber DA, et al. *Blood.* 2016;127(20):2391-2405.

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MDS: IPSS-R Cytogenetics

Prognostic Subgroup	Abnormality			Overall Survival		
	Single	Double	Complex	n (%)	Median (months; 95% CI *P* < .01)	HR (95% CI)
Very good	del(11q) −Y	—	—	81 (2.9)	60.8 (50.3 to NR)	0.5 (0.3 to 0.7)+
Good (reference)	Normal del(5q) del(12p) del(20q)	Including del(5q)	—	1809 (65.7)	48.6 (44.6 to 54.3)	1.0 (0.8 to 1.3)
Intermediate	del(7q) +8 i(17q) +19 Any other Independent clones	Any other	—	529 (19.2)	26.0 (22.1 to 31.0)	1.6 (1.4 to 1.8)+
Poor	inv(3)/t(3q)/del(3q) −7	Including −7/del(7q)	3 abn.	148 (5.4)	15.8 (12.0-18.0)	2.6 (2.0 to 3.3)+
Very poor	—	—	> 3 abn.	187 (6.8)	5.9 (4.9 t0 6.9)	4.2 (3.4 to 5.3)+

Schanz J, et al. *J Clin Oncol.* 2012;30(8):820-829.

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MDS: IPSS-R Classification

VARIABLE	0	0.5	1	1.5	2	3	4
Cytogenetics	V. Good		Good		Intermediate	Poor	V. Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Prognostic Risk Categories/Scores

RISK GROUP	Risk Score	Median Survival (Years)
Very Low	≤1.5	8.8
Low	>1.5-3	5.3
Intermediate	>3-4.5	3.0
High	>4.5-6	1.6
Very High	>6	0.8

Greenberg PL, et al. *Blood.* 2012;120(12):2454-2465.

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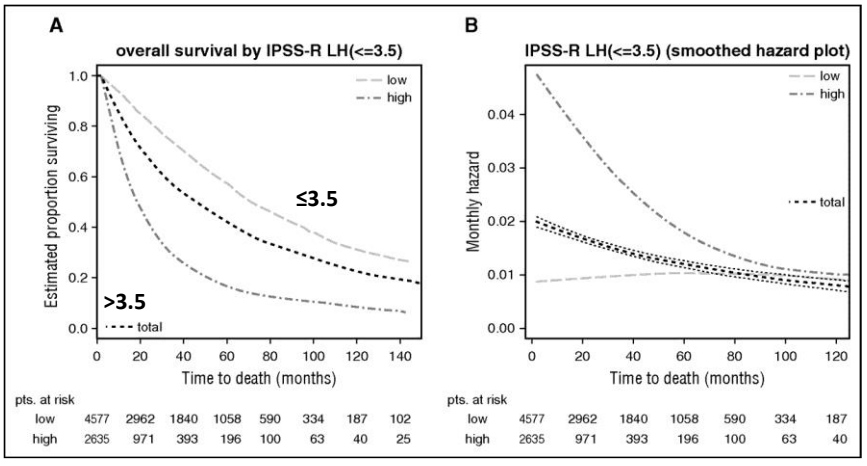
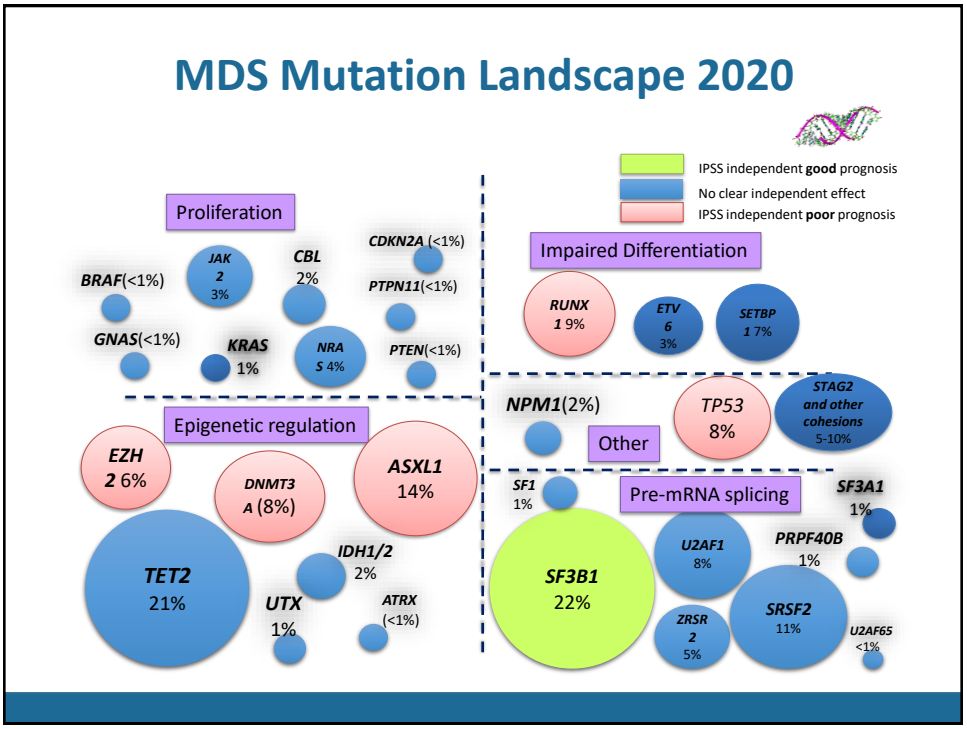
MDS: IPSS-R Classification



Pfeilstocker M, et al. *Blood.* 2016;128(7):902-910.

14



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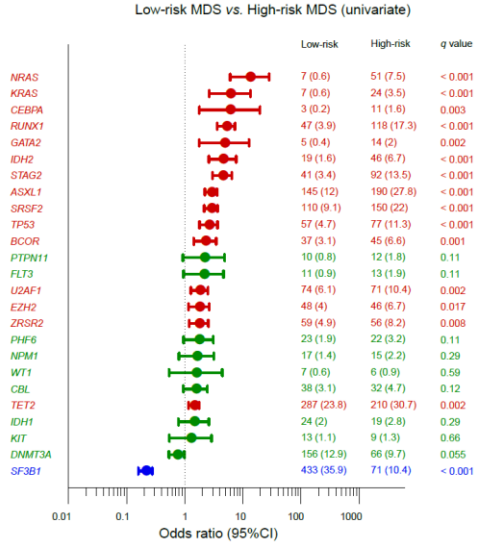
MDS: Mutation Risk

- Driver genes can be classified into molecular subtypes differentially associated with disease severity



Makishima H, et al. *Nat Genetics.* 2017;49(2):204-212.

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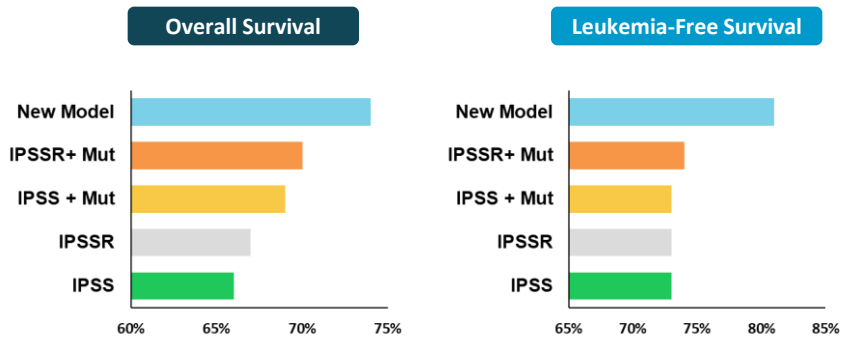
MDS: Machine Learning

Parameter	Training No. (%)/[range]	Validation No. (%)/[range]	*P Value*
Total	1471	831	
Median age, years	71 [19-99]	69 [4-93]	NS
Clinical Variables			
Median WBC, 10^9/L	4.2 [0.6-82.6]	4 [0.1-25.6]	NS
Median ANC, 10^9/L	2.1 [0-65.1]	2 [0-8.5]	NS
Median Hb, g/dL	9.9 [3.9-15.6]	10 [3.4-17.1]	NS
Median Plts, 10^9/L	120 [4-975]	117 [7-1280]	NS
Median BM blasts %	4 [0-19]	3 [0-19]	NS
2008 WHO Category			
RCMD/RCUD	578 (38)	350 (42)	NS
RARS	209 (11)	128 (15)	
RAEB-1/RAEB-2	573 (37)	302 (36)	
MDS-U	49 (9)	18 (2)	
MDS with del (5q)	62 (5)	33 (4)	

Nazha A, et al. *Blood.* 2018;132(supplement 1):793.

17

MDS: Machine Learning



Nazha A, et al. *Blood.* 2018;132(supplement 1):793.

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The Treatment Landscape for AML: Current and Emerging Therapies

Vijaya Raj Bhatt, MD
Associate Professor
Medical Director, Leukemia Program
Division of Oncology and Hematology
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

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Recent FDA-Approved Drugs

Intensive Chemotherapy

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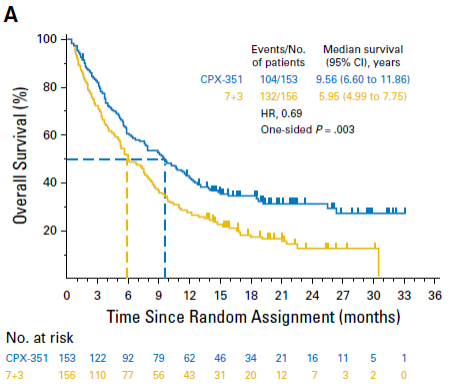
CPX 351

- Liposomal preparation of daunorubicin and cytarabine
- Indication: tAML and AML MRC
- NCCN Category 1 for >60 years, 2A for <60 years

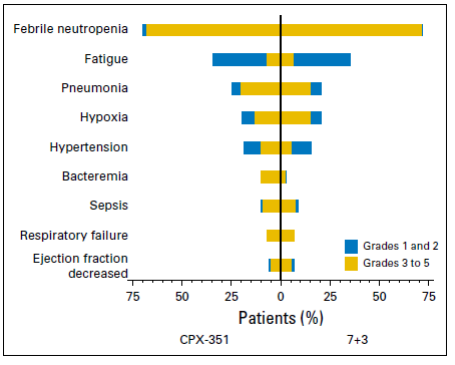


Lancet JE, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

21

CPX 351

- Toxicities similar to 7+3
- Prolonged cytopenias: consolidation 5 to 8 weeks
- Post-hoc analysis: lower post-transplant mortality due to deeper remission

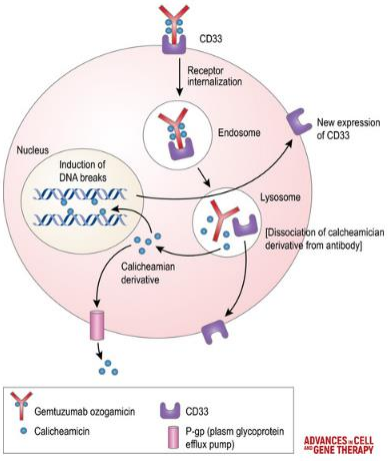


Lancet JE, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

22

Gemtuzumab Ozogamicin

- In combination with 7+3
- Single-agent for initial treatment in older unfit patients
- RR AML

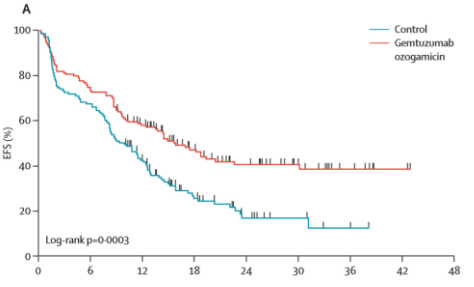


Boddu P, Ravandi F. *Adv Cell Gene Ther.* 2018;1(3):e21.

23

7+3 +/- Gemtuzumab Ozogamicin

- CD33+
- Core binding factor AML, ie, inv (16) or t(8;21)



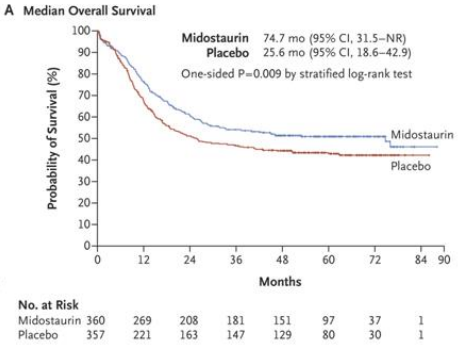
EFS at 2 years: 40.8% vs 17.1%

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

24

7+3 +/-Midostaurin

- Phase 3 trial: <60 years
- Phase 2 trial: all ages
- FLT3 ITD and TKD
- Approved: all ages



Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464.

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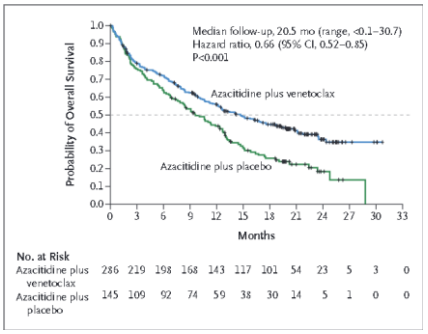
Recent FDA-Approved Drugs

Less Intensive Chemotherapy

26

Venetoclax in Combination with HMA or LDAC

- Promotes apoptosis
- Indication: older, unfit patients



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

27

Venetoclax in Combination with HMA or LDAC

- Myelosuppression and infection duration/ dose adjustment
- Interaction with azoles
- IDH1/IDH2: better responses
- FLT3/RAS pathway, monocytic-resistance

Pei S. *Cancer Discov.* 2020;10(4):536-551.; DiNardo CD, et al. *Blood.* 2020;135(11):791-803.; DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

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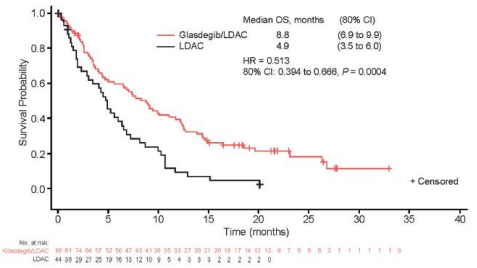
Glasdegib in Combination with LDAC

- Hedgehog pathway inhibitor
- Indication: older unfit AML
- QT prolongation

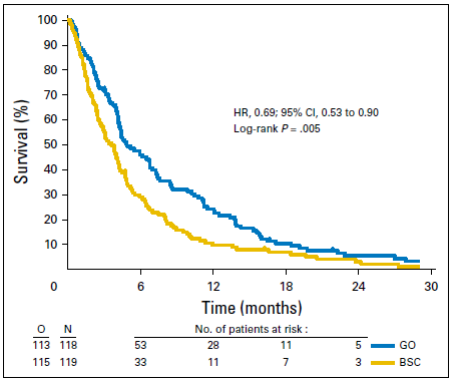


Cortes JE, et al. *Leukemia*. 2019;33(2):379-389.

29

Gemtuzumab Ozogamicin Single-agent vs BSC

- High CD33 expression status
- Favorable/intermediate cytogenetic risk profile
- Women



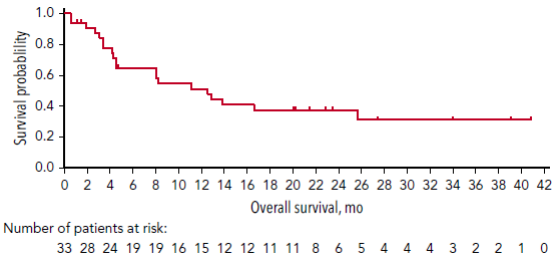
OS at 1 year: 24.3% vs 9.7%

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

30

Ivosidenib Upfront

- IDH1 inhibitor
- CR/CRh 42%
- 61% in remission at 1 year
- 43% transfusion independent
- Median overall survival 12.6 months



Roboz GJ, et al. *Blood.* 2020;135(7):463-471.

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Upfront Management: Novel Drugs

Fit

- **7+3 + GO if core binding factor AML**
- **7+3 + midostaurin: *FLT3* mutated**
- **CPX 351: tAML and AML MRC**
- **7+3**

Unfit

- **Venetoclax + azacitidine (or LDAC)**
- **Alternative: Glasdegib + LDAC, or GO**
- **Ivosidenib: *IDH1* mutated**

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Recent FDA-Approved Drugs

RR AML

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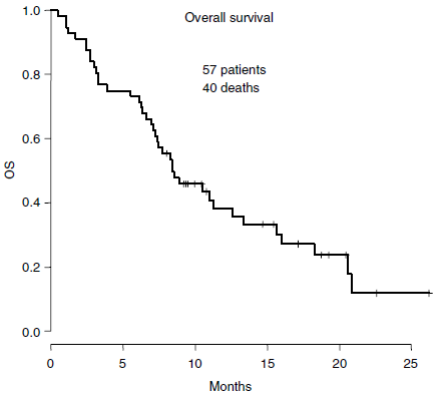
Gemtuzumab Ozogamicin Single-agent for RR AML

- 26% CR, 7% CRp
- Median OS 8.4 months

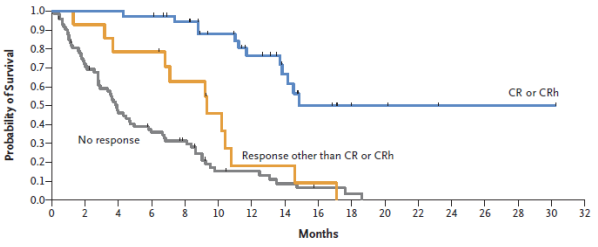


Taskin A-L, et al. *Leukemia.* 20017;21(1):66-71.

34

Ivosidenib: RR AML

- ORR 42%
- DOR 6.5 months
- 35% transfusion independence
- Median OS 8.8

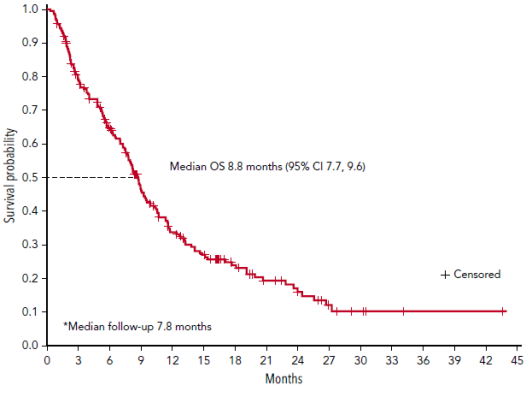


DiNardo CD, et al. *N Engl J Med.* 2018;378(25):2386-2398.

35

Enasidenib

- IDH2 inhibitor
- Indication: RR AML
- ORR 39%
- DOR 5.6 months
- >40% transfusion independence
- Median OS 8.8



Stein EM, et al. *Blood.* 2019;133(7):676-687.

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Ivosidenib and Enasidenib

- Differentiation syndrome
- QT prolongation
- Higher co-mutational burden and RAS pathway mutations – lower response

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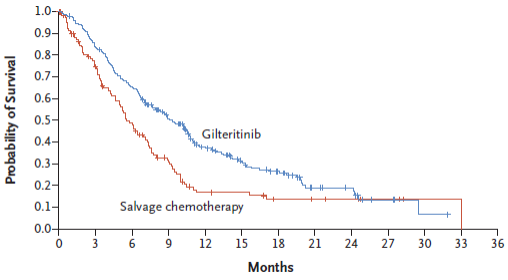
Gilteritinib vs Chemotherapy

- FLT3 inhibitor
- Indication: RR AML
- Interaction with posa/vori
- QT prolongation



CR/CRp 34% vs 15%
1-year OS 37% vs ~17%

Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

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Novel Drugs for R/R AML

Ivosidenib	• *IDH1* mutated AML
Enasidenib	• *IDH2* mutated AML
Gilteritinib	• *FLT3* mutated AML
GO	• Mutation non-specific

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Treatment for RR AML: NCCN 2020

- Clinical trial
- Targeted therapy: ivosidenib, enasidenib, gilteritinib, GO
- Cytotoxic therapy, eg, CLAG or FLAG +/-Ida, HiDAC, EC+/-mitoxantrone
- Ven-based, HMA (less aggressive)

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The Treatment Landscape for MDS: Current and Emerging Therapies

Mikkael A. Sekeres, MD
Professor of Medicine
Director, Leukemia Program
Vice Chair for Clinical Research
Cleveland Clinic
Taussig Cancer Institute
Cleveland, Ohio

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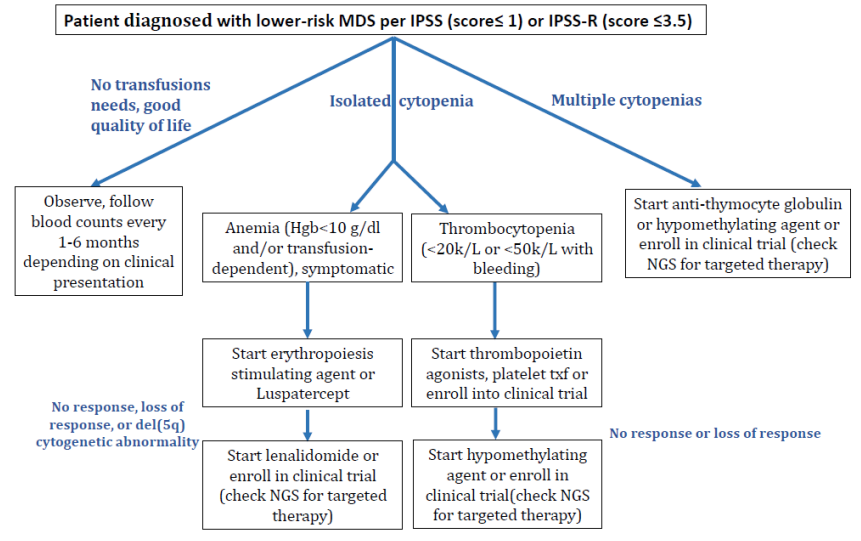
MDS: Treatment – Lower-risk



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):267-372.

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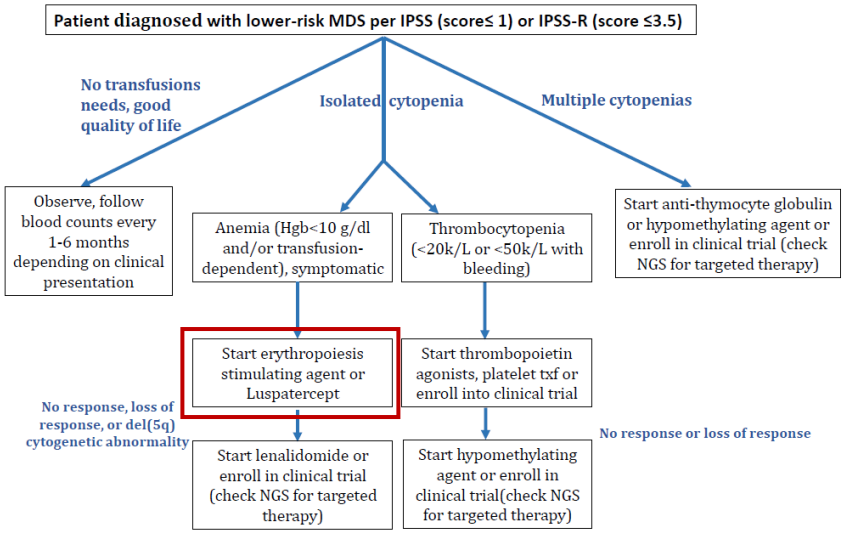
MDS: Ameliorating Anemia



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):267-372.

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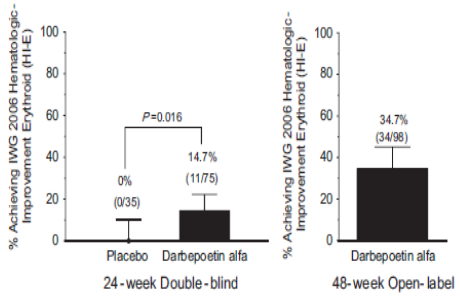
MDS: Ameliorating Anemia – ESAs

ESAs RR 15 - 40%

Table II. Response results.

	Patients (%)	Response rate
Growth factors	100	39·5
EPO	57·3	39·4
EPO + GCSF	23·4	47·8
GMCSF	6·2	37·8
EPO + GMCSF	5·8	33·7
GCSF	3·0	47·9
IL3	3·0	17·0
IL6	1·3	38·1



N = 1587

N = 147 (2:1)

Golshayan A-R, et al. *Br J Haematol.* 2007;137(2):125-132.; Platzbecker U, et al. *Leukemia.* 2017;31(9):1944-1950.

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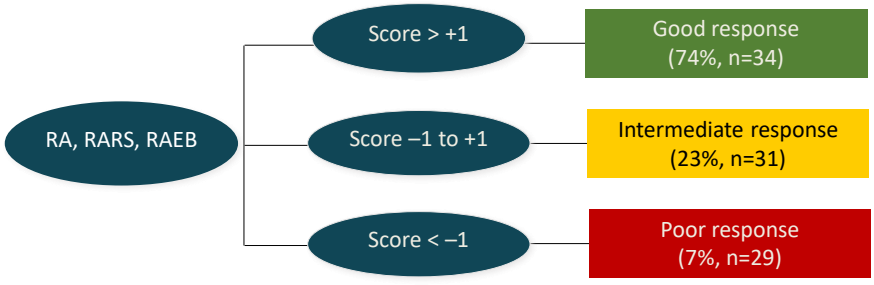
MDS: Ameliorating Anemia – ESAs



Treatment response score

s-epo	<100	+2
U/L	100–500	+1
	>500	–3
Transf	<2 units/m	+2
U RBC/m	= or >2 units/m	–2

Hellström-Lindberg E, et al. *Br J Haematol*. 2003;120(6):1037-1046.

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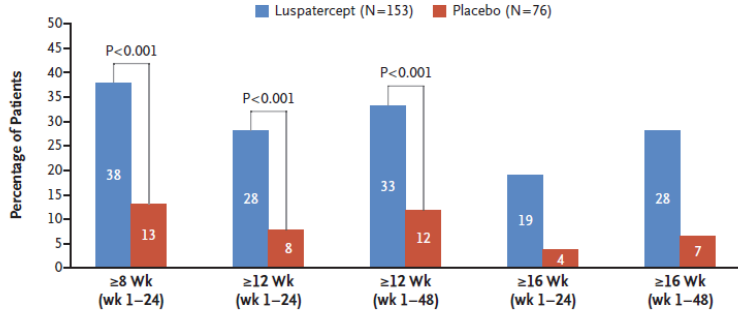
MDS: Ameliorating Anemia – LUSPAT



No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

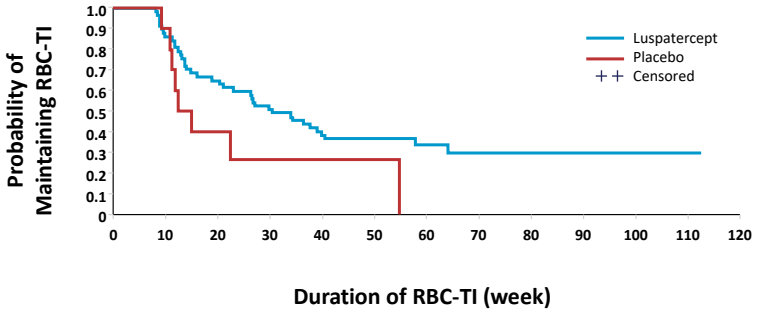
Figure 1. Independence from Red-Cell Transfusion.

Fenaux P, et al. *N Engl J Med*. 2020;382(2):140-151.

46

MDS: Ameliorating Anemia – LUSPAT

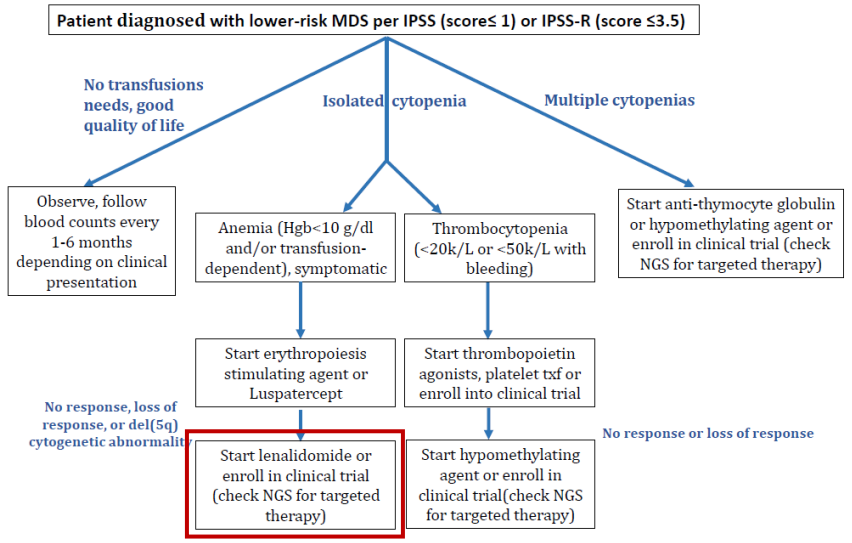
Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)



Fenaux P, et al. *N Engl J Med*. 2020;382(2):140-151.

47

MDS: Ameliorating Anemia



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):267-372.

48

MDS: Ameliorating Anemia – LEN

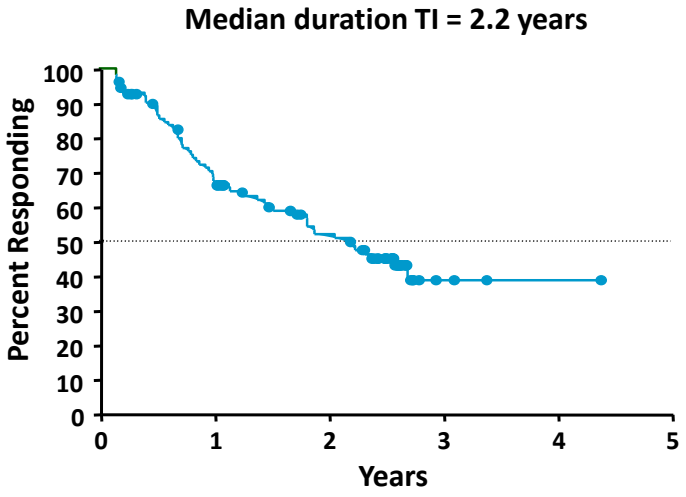
	RBC-TI, n (%) [95% CI]		
	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
mITT population	**n = 51**	**n = 47**	**n = 41**
Protocol defined (≥26 weeks)	3 (5.9) [1.2-16.2]	20 (42.6) [28.3-57.8]*	23 (56.1) [39.7-71.5]*
IWG 2000 (≥8 weeks)	4 (7.8) [2.2-18.9]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*
IWG 2006 (≥8 weeks)	3 (5.9) [1.2-16.2]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*

*$P < .001$ versus placebo

Fenaux P, et al. *Blood.* 2011;118(14):3765-3776.; Cheson BD, et al. *Blood*. 2000;96(12):3671-3674.; Cheson BD, et al. *Blood*. 2006;108(2):419-425.;

49

MDS: Ameliorating Anemia – LEN

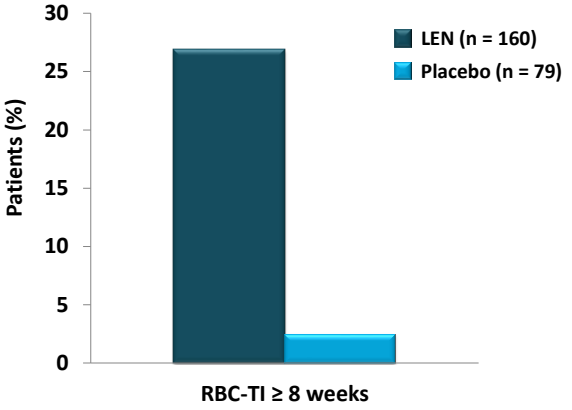


List AF, et al. *Leukemia.* 2014;28(5):1033-1040.

50

MDS: Ameliorating Anemia – LEN

Significantly more LEN patients achieved RBC-TI ≥8 weeks versus placebo (*P* < .001)

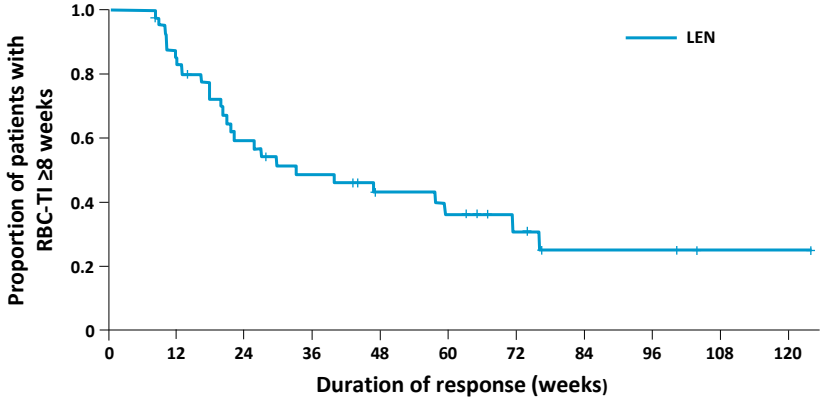


Santini V, et al. *J Clin Oncol.* 2016;34(25):2988-2996.

51

MDS: Ameliorating Anemia – LEN

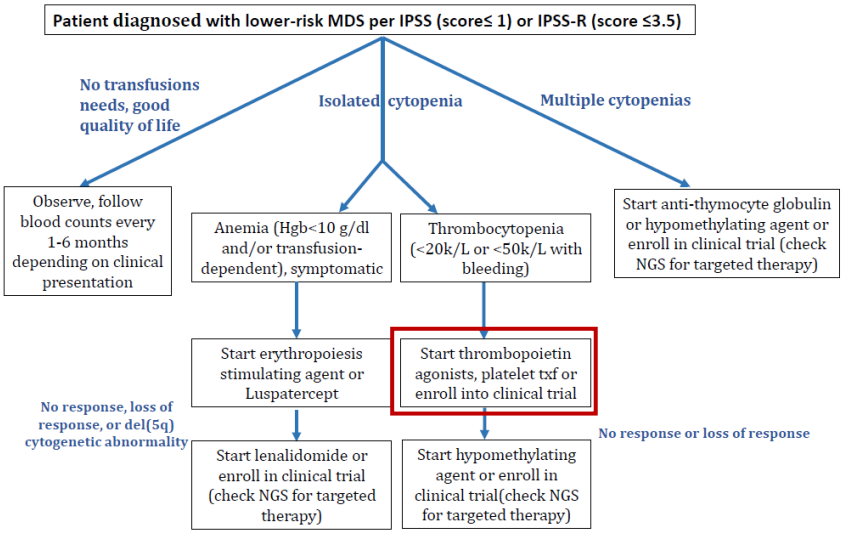
The median duration of response was 32.9 weeks (95% CI 20.7–71.1) among RBC-TI ≥8 weeks responders with LEN



Santini V, et al. *J Clin Oncol.* 2016;34(25):2988-2996.

52

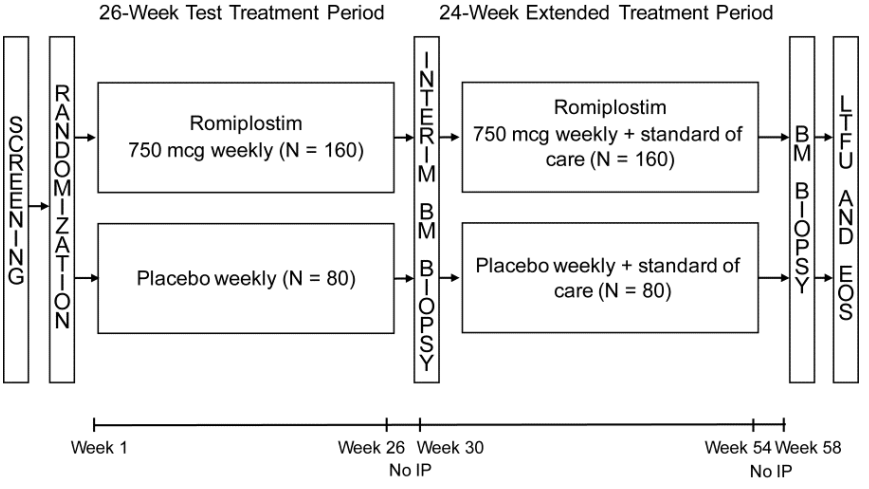
MDS: Tackling Thrombocytopenia



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):267-372.

53

MDS: Tackling Thrombocytopenia



Giagounides A, et al. *Cancer.* 2014;120(21):1838-1846.

54

MDS: Tackling Thrombocytopenia

	Baseline platelets <20 x 10^9/L		Baseline platelets ≥20 x 10^9/L	
	Placebo (N = 43)	Romiplostim (N = 87)	Placebo (N = 40)	Romiplostim (N = 80)
CSBE (rate/100 pt-yr)	501.2	514.9	**226.4**	**79.5**
	RR = 1.03, *P* = .827		**RR = 0.35, *P* < .0001**	
PTE (rate/100 pt-yr)	**1778.6**	**1250.5**	179.8	251.8
	RR = 0.71, *P* < .0001		RR = 1.38, *P* = .1479	

Giagounides A, et al. *Cancer.* 2014;120(21):1838-1846.

55

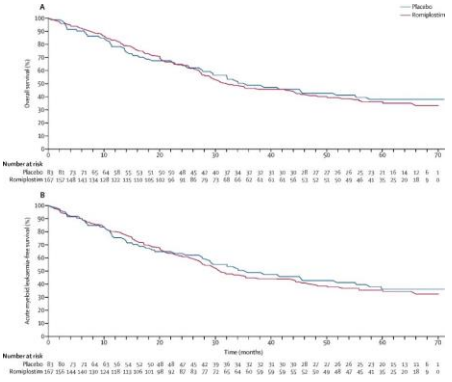
MDS: Tackling Thrombocytopenia

	Romiplostim	Placebo	HR	95% CI
Deaths	17.9% (30)	20.7% (17)	0.86	0.47, 1.56
AML	6.0% (10)	4.9% (4)	1.20	0.38, 3.84
AML-free survival	19.6% (33)	23.2% (19)	0.85	0.48, 1.50

5 years of follow-up

OS

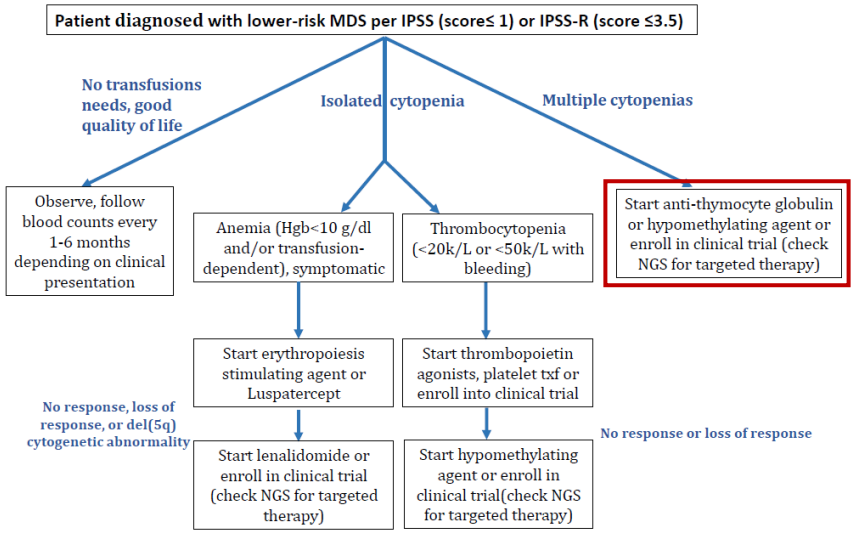
LFS



Giagounides A, et al. *Cancer.* 2014;120(21):1838-1846.; Fenaux P, et al. *Br J Haematol.* 2017;178(6):906.

56

MDS: Modifying MLD



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):267-372.

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MDS: Modifying MLD – HMA

- Regimens:
  - **DAC 20 mg/m^2 IV D1-3** every 4 weeks
  - **AZA 75 mg/m^2 IV/SC D1-3** every 4 weeks
- 113 patients with LR-MDS treated and evaluable for response
- Median duration of follow-up = 14 months (range: 2-30 months)
- Randomized follow-up study **NCT02269280**

Jabbour E, et al. *Blood.* 2017;130(13):1514-1522.

58

MDS: Modifying MLD – HMA

Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	54 (59)
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Jabbour E, et al. *Blood.* 2017;130(13):1514-1522.

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MDS: Modifying MLD – ATG

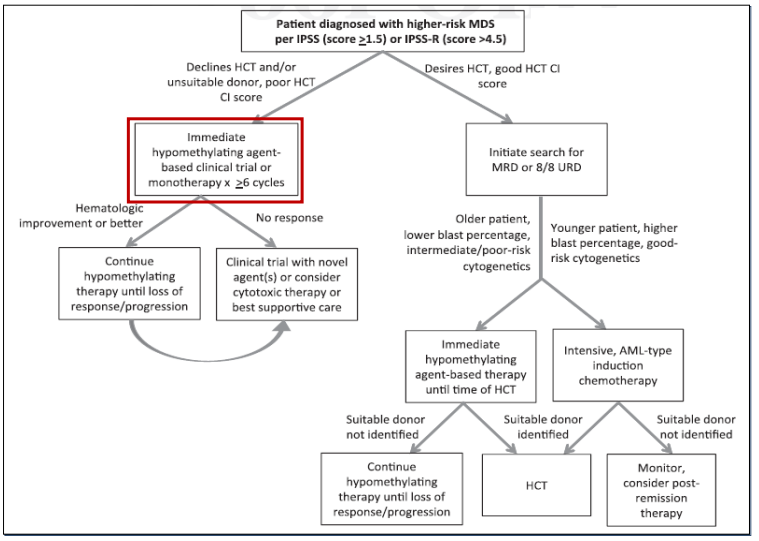
	N. (total)	% (95%CI)
All responses - intent to treat	9 (27)	33.3 (17-54)
HI-E[#]	7 (18)	38.9
HI-E, major	6	
HI-E, minor	1	
HI-N, major%	3 (10)	30.0
HI-P, major[§]	3 (13)	23.0
No response - intent to treat	18 (27)	66.7 (46-83)

Measure	Treatment Arm ATG+CSA (n = 45)	BSC (n = 43)	P
No treatment, No. of patients*	5	—	
Crossed over to ATG+CSA, No. of patients	—	14	
Hematologic response (CR+PR) by 3 months			
No. of patients	9	4	
%	20	9	
Hematologic response (CR+PR) by 6 months†			.016
No. of patients	13	4	
%	29	9	
Hematologic response (CR+PR+HI) by 6 months (IWG criteria)†‡			.009
No. of patients	14	4	
%	31	9	

Komrokji RS, et al. *Haematologica.* 2014;99(7):1176-1183.; Passweg JR, et al. *J Clin Oncol.* 2011;29(3):303-309.

60

Higher-risk MDS: HMA



Sekeres MA, Cutler C. *Blood.* 2014;123(6):829-836.

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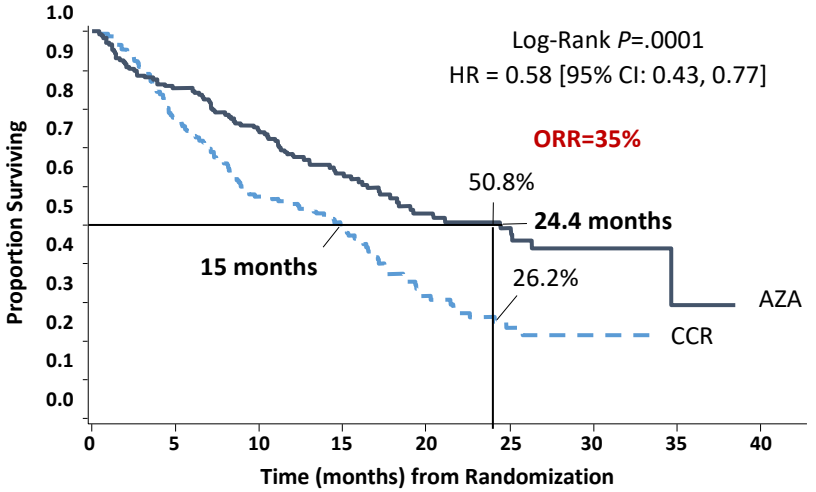
Higher-risk MDS: HMAs – AZA



Fenaux P, et al. *Lancet Oncol.* 2009;10(3):223-232.

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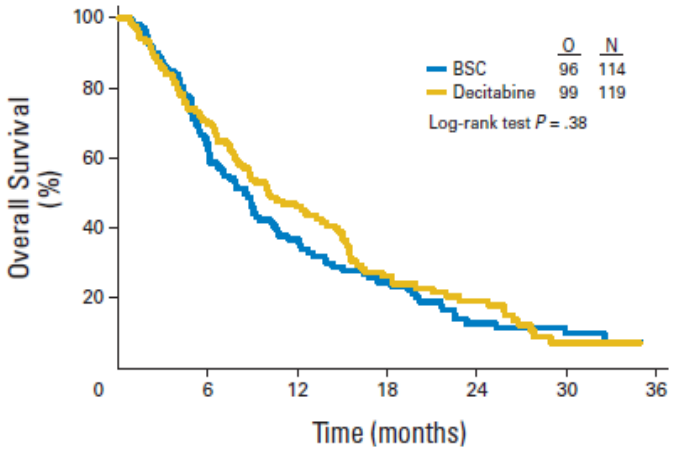
Higher-risk MDS: HMAs – DAC



Median OS 10.1 vs 8.5 months

Lübbert M, et al. *J Clin Oncol*. 2011;29(15):1987-1996.

63

Higher-risk MDS: HMAs – DAC/CED

Oral Cedazuridine/Decitabine Phase 2
In Int-1, Int-2, High, CMML

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
mCR with HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

Garcia-Manero G, et al. *Blood.* 2020;136(6):674-683.

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Higher-risk MDS: Combinations

Study design: AZA +/- pevonedistat

NCT02610777: Phase 2, randomized, open-label, global, multicenter study [proof of concept]

Patients with higher-risk MDS, higher-risk CMML, or low-blast AML:
- No previous HMAs
- Ineligible for allogeneic SCT

Randomization 1:1 N=120

Pevonedistat + azacitidine
Pevonedistat: 20 mg/m^2 (IV) on Days 1, 3, 5
Azacitidine: 75 mg/m^2 (IV or SC) on Days 1–5, 8, 9

Azacitidine
75 mg/m^2 (IV or SC) on Days 1–5, 8, 9

Repeat every 28 days

Stratification:
- IPSS-R risk category for MDS/CMML
  - Intermediate
  - High
  - Very high
- Low-blast AML

Study endpoints
- **EFS** (defined as time to death or transformation to AML in higher-risk MDS/CMML or death in low-blast AML): trial was powered on EFS as the original primary endpoint
- **OS**: original secondary endpoint, changed to primary endpoint based on regulatory feedback after enrollment
- **ORR**: secondary endpoint

EFS=event-free survival; HMAs=hypomethylating agents; IPSS-R=Revised International Prognostic Scoring System; IV=intravenous; ORR=objective response rate; SC=subcutaneous; SCT=stem cell transplant

Adès L, et al. *J Clin Oncol.* 2020;38(suppl):Abstract 7506.

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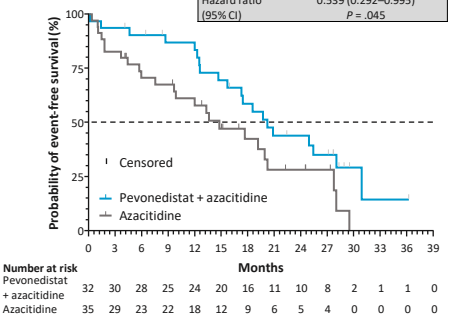
Higher-risk MDS: Combinations

EFS and OS: Higher-risk MDS

EFS*

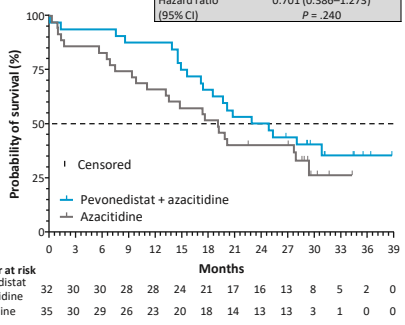
	Pevonedistat + azacitidine	Azacitidine
Median survival (months)	20.2	14.8
Hazard ratio (95% CI)	0.539 (0.292–0.995)	
	P = .045	



Number at risk														
Pevonedistat + azacitidine	32	30	28	25	24	20	16	11	10	8	2	1	1	0
Azacitidine	35	29	23	22	18	12	9	6	5	4	0	0	0	0

OS

	Pevonedistat + azacitidine	Azacitidine
Median survival (months)	23.9	19.1
Hazard ratio (95% CI)	0.701 (0.386–1.273)	
	P = .240	



Number at risk														
Pevonedistat + azacitidine	32	30	30	28	28	24	21	17	16	13	8	5	2	0
Azacitidine	35	30	29	26	23	20	18	14	13	13	3	1	0	0

*EFS defined as time to death or transformation to AML in higher-risk MDS/CMML or death in low-blast AML

Adès L, et al. *J Clin Oncol.* 2020;38(suppl):abstract 7506.

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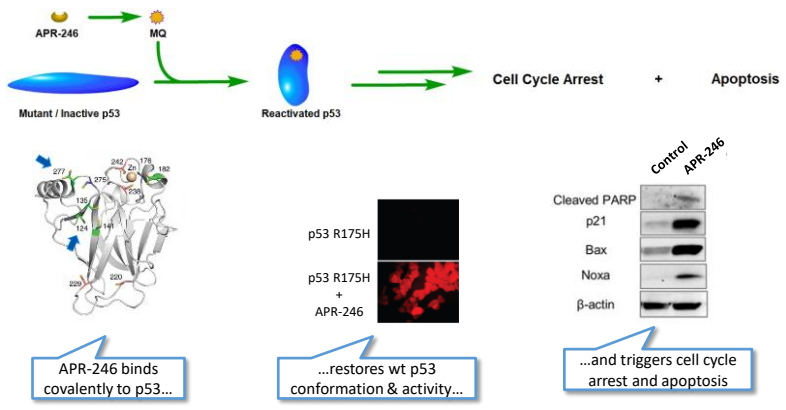
Higher-risk MDS: Targeting *TP53*



Kaar JL, et al. *Prot Sci.* 2010;19(12):2267-2278.; Zhang Q, et al. *Cell Death Dis.* 2018;9(5):439.; Furukawa H, et al. *Cancer Sci Freshet Rep*. 2018;8(1):5495.; Sallman DA, et al. *Blood.* 2019;134(supplement_1):676.; Cluzeau et al. *Blood.* 2019;134(supplement_1):677.

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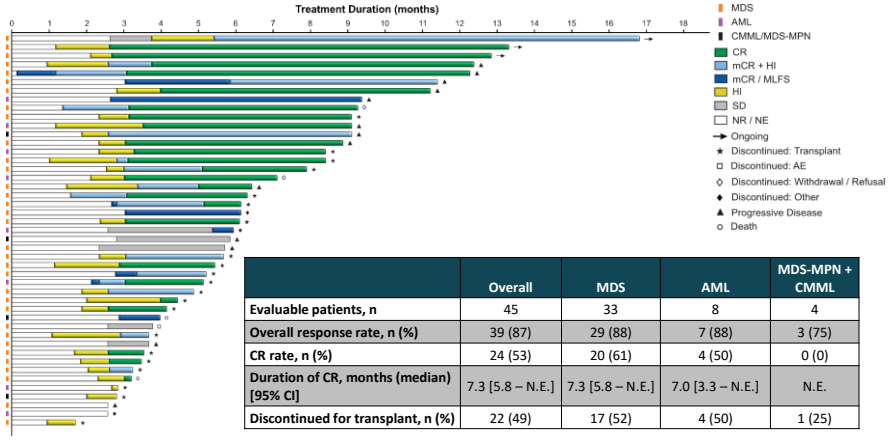
Higher-risk MDS: Targeting *TP53*



	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

Median duration of follow-up = 10.8 months

Sallman DA, et al. *Blood.* 2019;134(supplement_1):676.; Cluzeau T, et al. *Blood.* 2019;134(supplement_1):677.

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AZA Plus Venetoclax for HR-MDS

- Phase 1b study
- Untreated *de novo* MDS, IPSS Int-2 or high risk, not planning intensive chemo or transplant
- Ven days 1-14 (400 mg/day, no ramp up)
  - Prophylactic antimicrobials required
- 57 patients
  - Med age 71 (26-85);
  - IPSS-R very high risk: 60%

Wei AH, et al. *Blood.* 2019;134(supplement_1):568.

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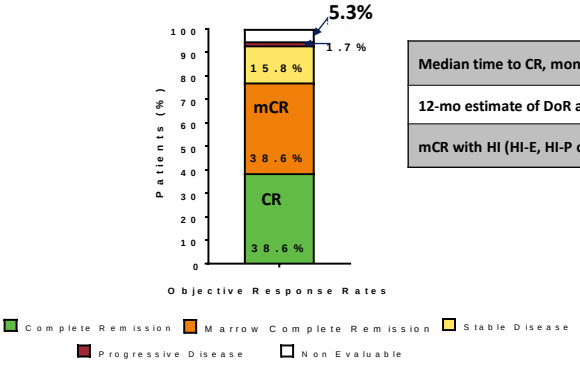
AZA Plus Venetoclax for HR-MDS: Response Rates



Median time to CR, months (range)	2.2 (1.2-11.1)
12-mo estimate of DoR after CR, % (95% CI)	83.3 (2.3, 97.5)
mCR with HI (HI-E, HI-P or HI-N), n/N (%)	10/22 (45.5)

Excludes patients of arm C (Aza only); Objective response rate (ORR) includes [complete remission (CR) + marrow complete remission (mCR) + partial remission (PR)]; # of patients with PR=0; per IWG (Cheson B, et al. *Blood.* 2006;108:419-425.) DoR=duration of response; HI=hematological improvement; HI-E=hematologic improvement in erythroids; HI-N=hematologic improvement in neutrophils; HI-P=hematologic improvement in platelet count; n=patients with favorable outcomes; N=patients eligible for evaluating outcomes

Wei AH, et al. *Blood.* 2019;134(supplement_1):568.

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MDS: Conclusions

- **Biology** >> what we can do about it
- For lower-risk MDS, focus on what bugs patient most:
  - **Anemia**
  - **Thrombocytopenia**
  - **Lots o' penia**
- Same for higher-risk, and focus on response duration, overall survival
- Goals of therapy should reflect goals of patient

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Thanks!!!

MDS The National Myelodysplastic Syndromes Natural History Study
Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

Cleveland Clinic Leukemia/MDS Program

Jaroslaw Maciejewski, MD, PhD
Sudipto Mukherjee, MD, PhD
Hetty Carraway, MD, MBA
Anjali Advani, MD
Matt Kalaycio, MD
Ronald Sobecks, MD
Betty Hamilton, MD
Aaron Gerds, MD, MS
Aziz Nazha, MD
Bhumika Patel, MD
Yogen Saunthararajah, MD
Babal Jha, PhD
Abby Statler, PhD
Tracy Cinalli, RN
Jackie Mau, RN
Christine Cooper, RN
Andrea Smith, RN
Eric Parsons, RN
Samjhana Bogati, RN
Yolanda Curry, RN
Bethany Clayton, RN
Sarah Larson, RN
Rachel Bordwell, RN, NP
Raychel Berardinelli, RN, NP
Kathryn Mohr, RN, NP

Jodi Campo, RN, NP
Barb Tripp, RN, NP
Alicia Bitterice, RN, NP
Meghan Scully, RN, NP
Kaylee Root, BA
Ben Pannell, BA
Eric Wiedenfeld, BA
Nicholas Wright, BA
Allison Unger, BA
George Lucas, BA
Andrew Brezinsky, BA
Melena Sharif, BA
Brielle Barth, BA
Enhxi Myrtaj, BA
Diane Banks, BA
Katarina Paulic, BA
John DeSamito, MD
Renee Gagnon, BA
Rodwin Chua, BA
Olivia Kodramaz
Caitlin Swann, PharmD
Madeline Waldron, PharmD
Kelly Gaffney, PharmD
Jenna Thomas, PharmD

DRESNERFOUNDATION

WHEN BLOOD BREAKS DOWN
LIFE LESSONS FROM LEUKEMIA
MIKKAEL A. SEKERES

April 2020!

And Our Patients!!!

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Case Discussions

Vijaya Raj Bhatt, MD
Associate Professor
Medical Director, Leukemia Program
Division of Oncology and Hematology
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Mikkael A. Sekeres, MD
Professor of Medicine
Director, Leukemia Program
Vice Chair for Clinical Research
Cleveland Clinic
Taussig Cancer Institute
Cleveland, Ohio

73

Case #1: Newly Diagnosed AML

- 72-year-old woman, independent and fully functional
- Presented with fatigue and pancytopenia
- Marrow: 80% cellularity with 25% blast with significant multilineage dysplasia
- Karyotype: 46,XX,del(7)(q22q36)[10]/47,XX,+8[10]
- FISH: Deletion 7q31 , trisomy 8
- **Acute myeloid leukemia with myelodysplasia related changes**
- Underwent a geriatric assessment

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Case #1: Newly Diagnosed AML

- **Geriatric assessment:** KPS 80%, excellent self-report of physical function confirmed on objective assessment (short physical performance battery), normal cognition on MOCA test, comorbidities included osteoporosis

75

Case #1: Newly Diagnosed AML

- Willing to get admitted for intensive chemotherapy
- Treated with **CPX 351 induction**
- Subsequent mutation panel results: IDH2 34% and RUNX1 37%
- Complications: neutropenic fever, bacteremia
- Maintained functional status
- Achieved complete remission including negative flow and FISH
- One cycle of CPX 351 consolidation and then allogeneic stem cell transplant

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Case #2: Relapsed/Refractory AML

- 69-year-old man
- Presented with fatigue, dyspnea on exertion and pancytopenia
- Marrow: 80% cellularity with 40% blast with significant dysplasia
- Karyotype: **complex karyotype**
- **Treatment-related acute myeloid leukemia** (prior radiation)
- Underwent a geriatric assessment

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Case #2: Relapsed/Refractory AML

- **Geriatric assessment:** KPS 70%, good physical function confirmed on objective assessment (short physical performance battery), normal cognition on MOCA test, **multiple comorbidities** including prior testicular and prostate cancer, COPD, diabetes, high BMI

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Case #2: Relapsed/Refractory AML

- Treated with **azacitidine and venetoclax**
- Blast count reduction to 6% but then progressed to 25%
- No FLT3, IDH1, or IDH2 mutations
- Treated with **FLAG** salvage – tolerated well and achieved complete remission
- Underwent **allogeneic stem cell transplant**

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MDS: Patient

- 72-year-old woman with fatigue
- **Laboratory results:**
  - WBC: 4500/uL with ANC 2100, no blasts
  - **Hgb: 7.8 g/dL with MCV of 102**
  - Platelet count: 174,000/uL
  - **Reticulocyte count: 0.4%**
  - **Epo level is: 80 mIU/mL**
- A bone marrow biopsy shows hypercellularity (70%), dyserythropoiesis and 25% ring sideroblasts, diagnosed with **MDS-SLD-RS (2% blasts)**
- Cytogenetics: no growth; **NGS with SF3B1 (26%)**

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MDS: Patient

- Treated with darbepoetin 500 mcg q3w x 10 months with increase in hgb from **7.8** g/dL to **9.4** g/dL
- Hgb then slips to **7.6** g/dL
- Repeat bone marrow essentially unchanged, but cytogenetics (previously NG) show **Del (5q)**
- **NGS with SF3B1, ASXL2**

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81

MDS: Patient

- On LEN, Hgb improves to **11.7** g/dL x 22 months. Then, over the next few months changes in **laboratory results**:
  - **WBC: 1800/uL with ANC 950, no blasts**
  - **Hgb: 7.8 g/dL with MCV of 106**
  - **Platelet count: 24,000/uL**
- A bone marrow biopsy shows hypercellularity (80%), trilineage dyspoiesis, and she is diagnosed with **MDS-MLD-RS (2% blasts)**
- Cytogenetics: Del (5q); **NGS with SF3B1, ASXL2**

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MDS: Patient

- Treated with 3-day AZA, has improvement in Plts to 147k and Hgb to 10.4 g/dL, lasting 15 months. But then has these **laboratory results:**
  - **WBC: 2100/uL with ANC 450, no blasts**
  - **Hgb: 7.9 g/dL with MCV of 106**
  - **Platelet count:21,000/uL**
- A bone marrow biopsy shows hypercellularity (80%), trilineage dyspoiesis, but now with **MDS-EB2 (12% blasts)**. Cytogenetics: Del (5q); **NGS with SF3B1, ASXL2, TP53**

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Key Takeaway Points

- Genetic and molecular analyses have several diagnostic and prognostic for AML and MDS
- The diagnosis of AML MRC is based on the presence of cytogenetic changes
- Targeted agents are available for patients with IDH1, IDH2, or FLT3 mutated AML
- Availability of several novel drugs, discussed today, provide more treatment options for our patients, and can improve patients' survival and quality of life when used appropriately

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