TREATMENT UPDATE: MYELODYSPLASTIC SYNDROMES (MDS)

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1

WELCOMING REMARKS

TREATMENT UPDATE: MYELODYSPLASTIC SYNDROMES (MDS)

Lizette Figueroa-Rivera, MA
Sr. Director, Education & Support
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2

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Updates in

Myelodysplastic Syndromes

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3

DISCLOSURES

TREATMENT UPDATE: MYELODYSPLASTIC SYNDROMES (MDS)

Mikkael A. Sekeres, MD, has affiliations with Bristol Myers Squibb/Celgene, Novartis and Kurome Therapeutics (*Consultant*).

4

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MDS Machinations| Agenda

What kind of MDS do I have?

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5

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 et al. *Blood* 2016;127:2391. 6

6

MDS | Classification

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

Table 1: Local (Data-Entry) vs. Central Pathology Study Assignment

	Central Pathology Study Assignment							
Local Pathology Assignment (Data Entry)	MDS	MDS/MPN overlap	ICUS	AML <30% Blasts	Other AML	Other Malignancy	Other	Total
MDS	193	12	8	3	1	7	40	264
MDS/MPN overlap	3	9	0	0	0	3	0	15
ICUS	9	2	20	0	0	4	27	62
AML <30% Blasts	0	0	0	0	0	0	0	0
Other AML	4	0	0	10	32	0	0	46
Other Malignancy	3	8	0	0	2	26	10	49
Other	54	14	21	2	3	53	335	482
Total	266	45	49	15	38	93	412	918
Agreement Rate	193/266 (72.6%)	9/45 (20.0%)	20/49 (40.8%)	0/15 (0.0%)	32/38 (84.2%)	26/93 (28.0%)	335/412 (81.3%)	

Zhang et al. ASH 2018.

7

7

MDS | IPSS Classification

Calculation of prognostic score

Score	0	0.5	1.0	1.5	2.0
BM Blast %	< 5	5-10		11-20	21-29
Cytogenetics	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Estimation of prognosis

Lower-Risk

Overall Score	IPSS Subgroup	Median Survival (Years)
0	Low	5.7
0.5-1.0	Intermediate-1	3.5
1.5-2.0	Intermediate-2	1.2
≥2.5	High	0.4

Greenberg P, et. al. *Blood* 1997:89:2079-88.

8

8

MDS | IPSS-R Scoring

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 (Yrs)
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 et al. *Blood* 2012;120:2454-65.

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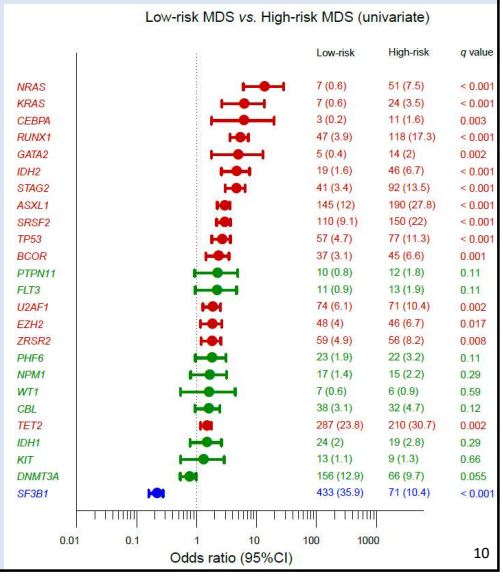
MDS | Mutation Risk

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



Makishima et al. Nat Genetics 2017; 49:204.

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MDS Machinations| Agenda

How should I treat my MDS?

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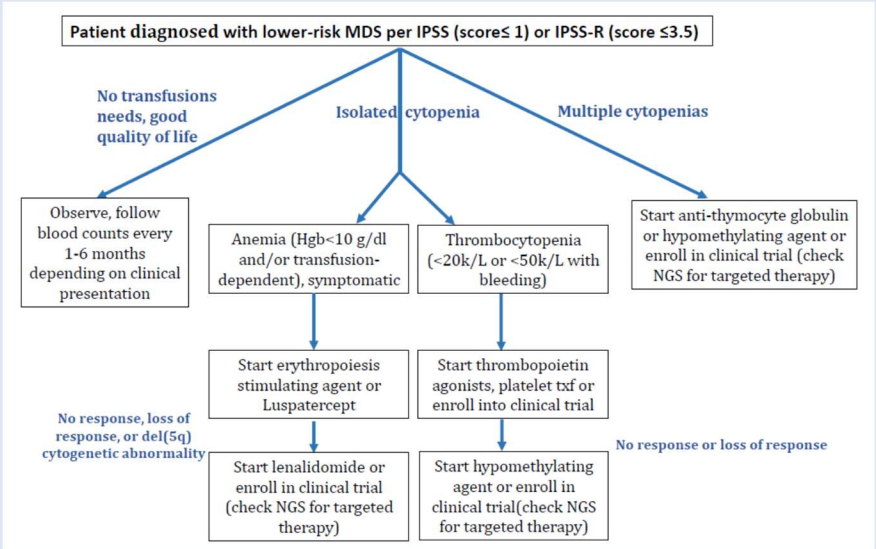
11

MDS | Treatment – Lower-risk



Sekeres and Patel Hematology (ASH Educ Book) 2019.

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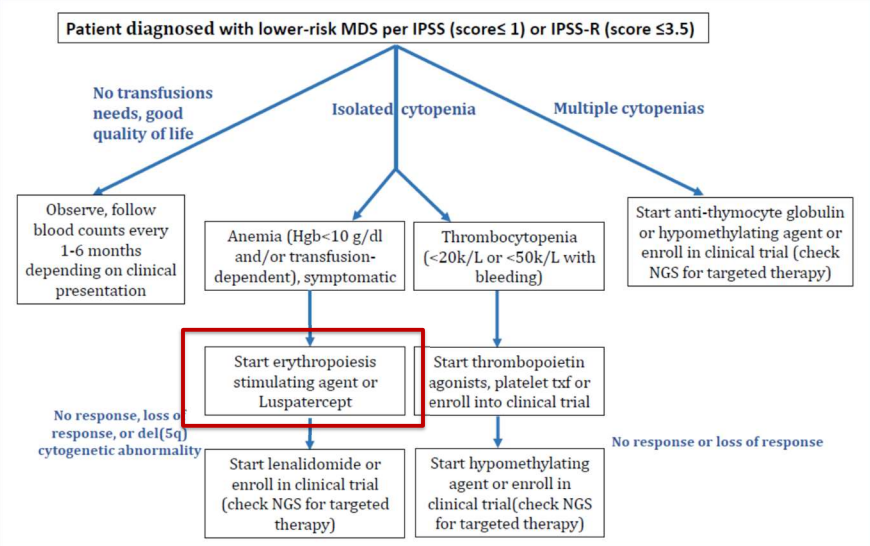
MDS | Ameliorating Anemia



Sekeres and Patel Hematology (ASH Educ Book) 2019.

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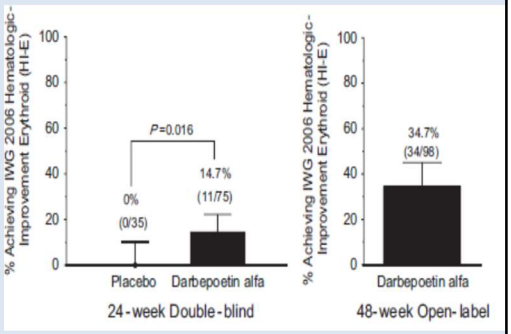
13

Lower-risk 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

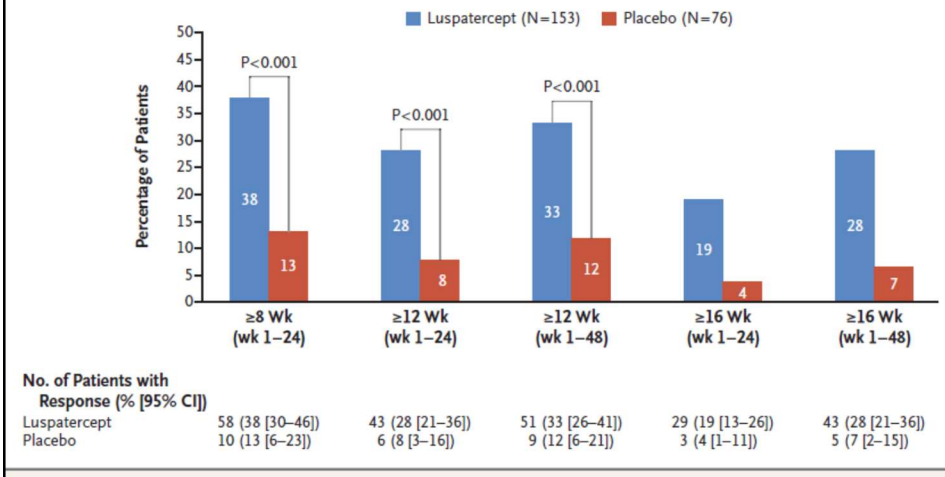
N = 147 (2:1)

Golshayan et al. Br J Haem 2007;137:125.
Platzbecker et al. Leukemia 2017;31:1944.

14

14

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])

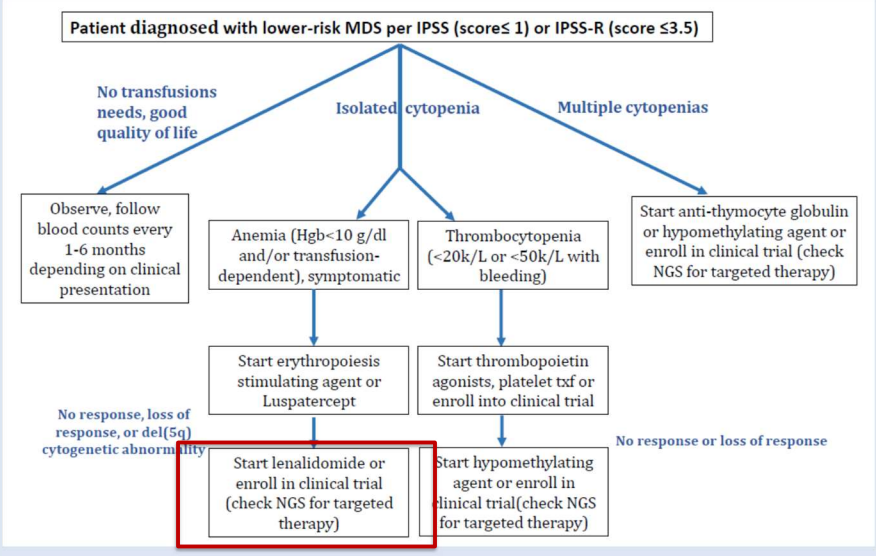
Figure 1. Independence from Red-Cell Transfusion.

Fenaux et al. NEJM 2020;382:140-151.

15

15

MDS | Treatment – Lower-risk



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16

16

Lower-risk MDS | Ameliorating Anemia: LEN

Del (5q)

	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[13] (≥ 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[14] (≥ 8 weeks)	3 (5.9) [1.2-16.2]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*

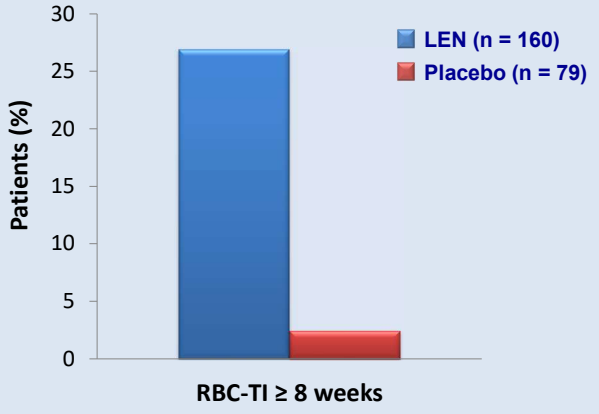
Fenaux et al. *Blood* 2011;118:3765-76.

17

17

Lower-risk MDS | Ameliorating Anemia: LEN

Significantly more LEN patients achieved RBC-TI ≥ 8 weeks versus placebo ($P < 0.001$)

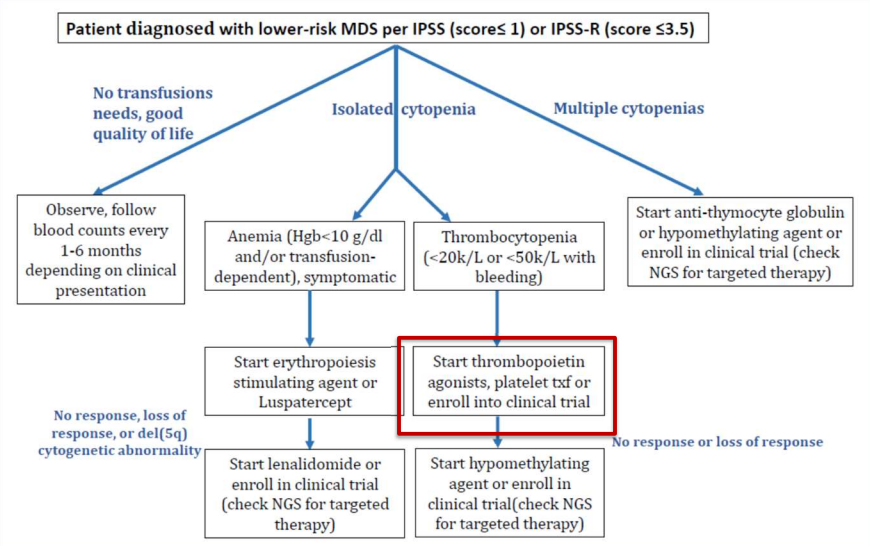


Santini et al. JCO 2016;34:2988

18

18

MDS | Tackling Thrombocytopenia



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19

19

Lower-risk MDS | Tackling Thrombocytopenia

	Baseline platelets < 20x10⁹/L		Baseline platelets ≥ 20x10⁹/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 = 0.827		**RR = 0.35, p<0.0001**	
PTE (rate/100 pt-yr)	**1778.6**	**1250.5**	179.8	251.8
	RR = 0.71, p<0.0001		RR = 1.38, p = 0.1479	

Giagounides et al. *Cancer* 2014;120:1838.

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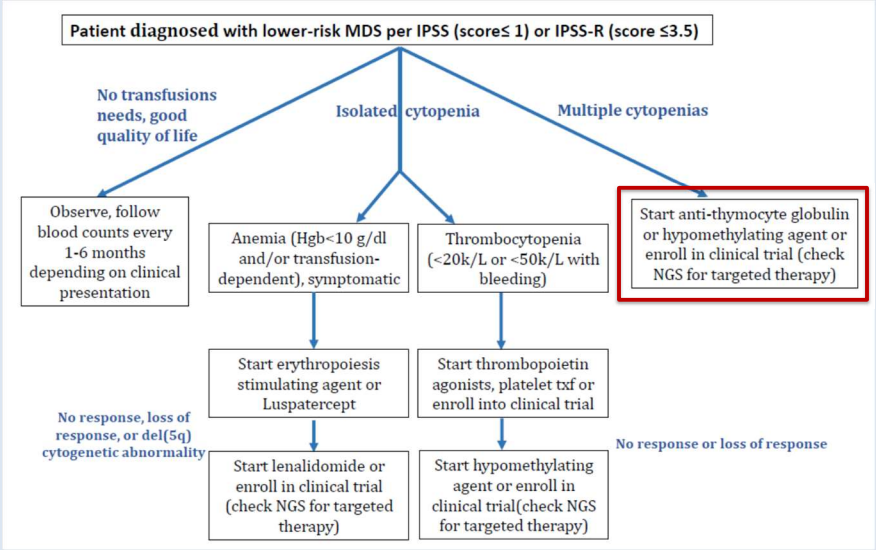
20

MDS | Modifying MLD



Sekeres and Patel Hematology (ASH Educ Book) 2019.

21

21

Lower-risk 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 et al. for MDS CRC Blood 2017;130:1514

22

22

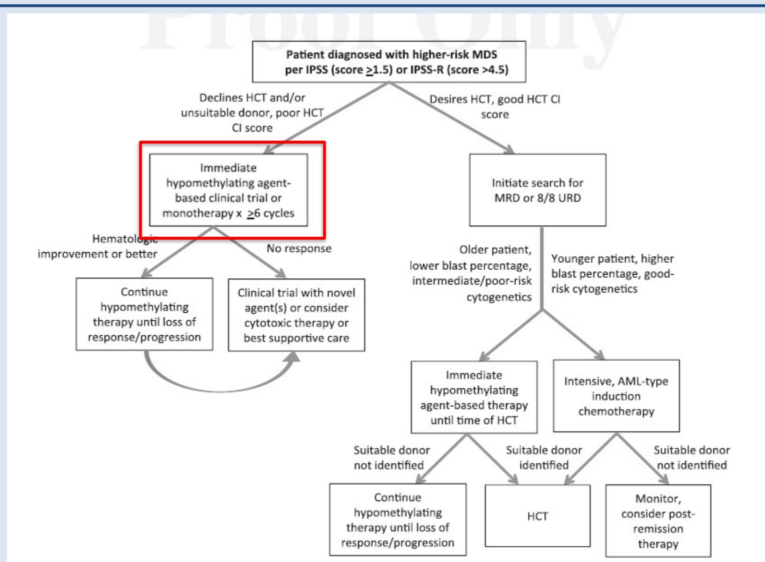
Lower-risk MDS | Modifying MLD: ATG

	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)	Treatment Arm: 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	

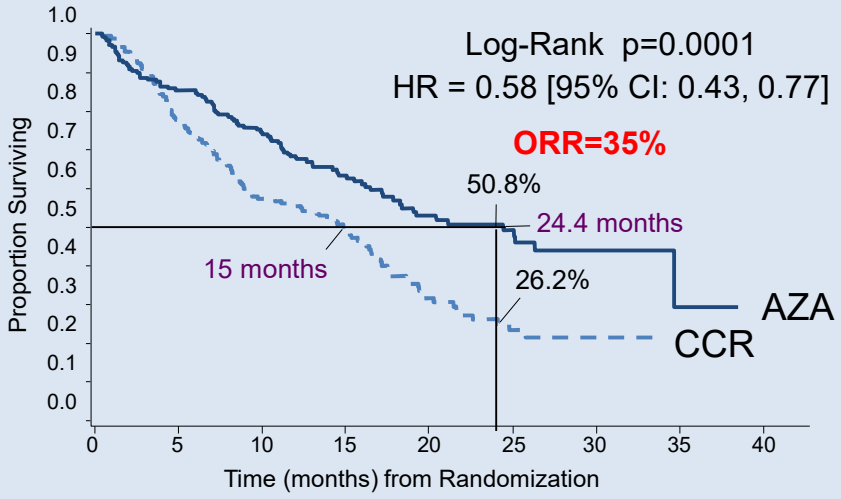
Komrokji et al Haematologica 2014;99:1176.
Passweg et al. JCO 2011;29:303.

Higher-risk MDS | HMA and HCT



Sekeres and Cutler Blood 2014;123:829.

Higher-risk MDS | HMAs: AZA



Fenaux P, et al. Lancet Oncology 2009;10:223-232.

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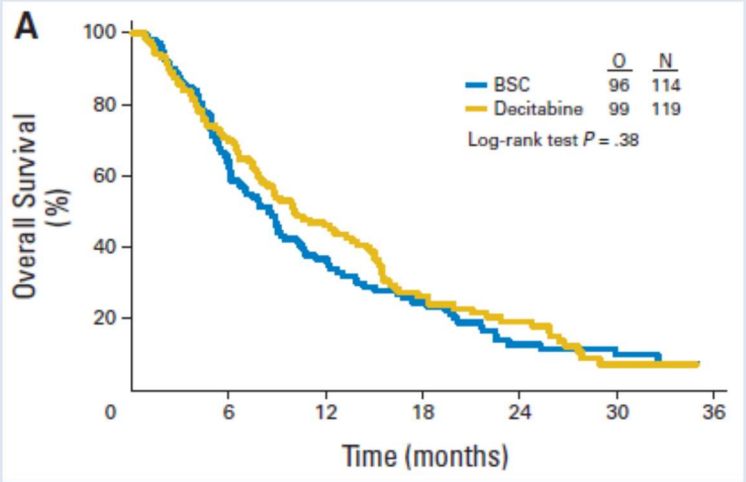
25

Higher-risk MDS | HMAs: DAC



Median OS 10.1 vs. 8.5 months

Lubbert et al. JCO 2011;29:1987.

26

26

Higher-risk MDS | HMAs: DAC/CED

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

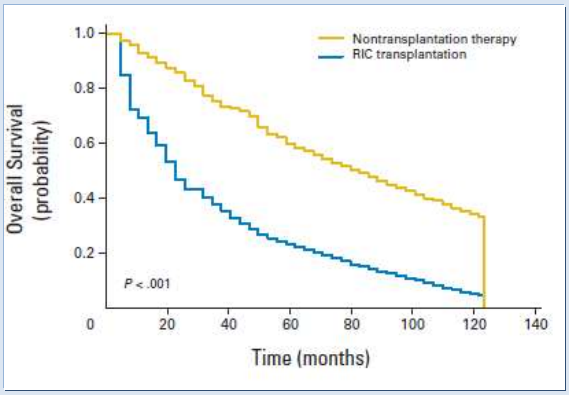
Type of response	Phase 2 overall (N=80)	
	n (%)	95% CI
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
With HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

Garcia-Manero et al. *Blood* 2020

27

27

Lower-risk MDS | HCT



Test of Equality over Strata	
Test	p
Log-Rank	<.0001
Wilcoxon	<.0001
-2Log(LR)	<.0001

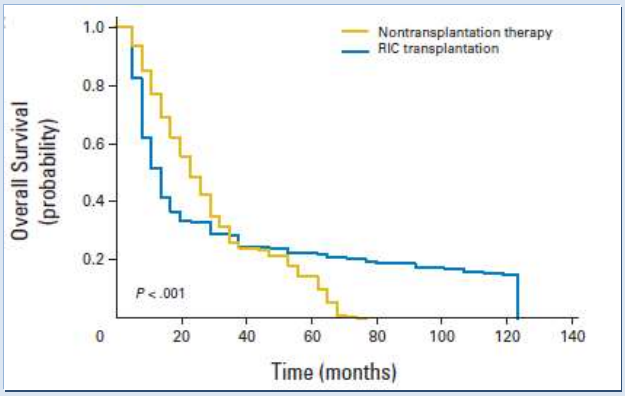
Low/Int-1 MDS

Koreth et al. JCO 2013;31:2662

28

28

Higher-risk MDS | HCT



Test of Equality over Strata	
Test	p
Log-Rank	<.0001
Wilcoxon	<.0001
-2Log(LR)	<.0001

Int-2/High MDS

Koreth et al. JCO 2013;31:2662

29

29

MDS Machinations| Agenda

What can I do to maximize the chance treatment will work?

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30

MDS Machinations | Treatment

- Most side effects are manageable – ask your healthcare team to manage them!
  - e.g., Change AZA from SC to IV
  - Take nausea or constipation meds liberally
- Drugs take a while to work – plan on 4-6 months
- Do not start and stop MDS meds
- This is a marathon, not a race

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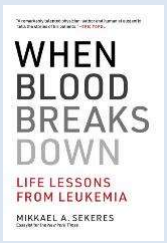
31

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



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32

32

ASK A QUESTION

TREATMENT UPDATE: MYELODYSPLASTIC SYNDROMES (MDS)

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click “Ask a question”

Type your question

Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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35

35

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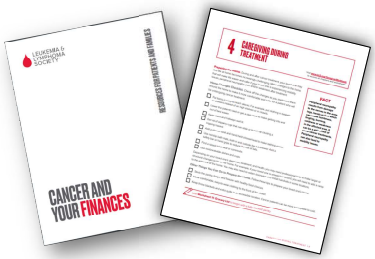
The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**



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36


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