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Myelodysplastic Syndromes: Patient Forum

Michael Keng, MD
December 15, 2018



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Disclosures

- Agios – Advisory Board

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MDS: Overview

- Epidemiology and “Staging”
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease
- Clinical Trials and Future Directions
- Conclusions

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MDS: Overview

- **Epidemiology and “Staging”**
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MDS: Epidemiology and Staging

- 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: Epidemiology and Staging

- Shared features:
 - Ineffective differentiation and low blood counts
 - Clonal expansion of abnormal cells
 - Risk of transformation to acute leukemia
- Afflicts 15,000 – 45,000 people annually
- Incidence rises with age (mean age 71)

MDS Staging: Epidemiology



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Cross-sectional analysis of 4514 MDS patients in the U.S. in 2005-7

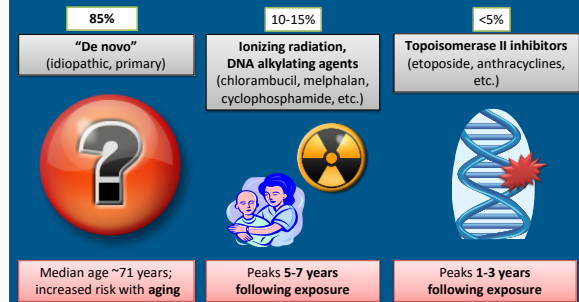
Age (Median)	Newly diagnosed	71 years
	Established	72-75 years
Sex (Mean)	Male (Newly diagnosed) (Established)	55% 51-57%
Duration of MDS (Median)		13-16 months
MDS Status	Primary	88 – 93%
	Secondary	7 – 12%
Secondary Cause	Chemotherapy	55 – 80%
	Radiation	6 – 21%
	Chemical exposure	2 – 9%

Sekeres et al. J National Cancer Inst 2008;100:1542

MDS Staging: Epidemiology



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Slide by Dr. David Steensma

MDS Staging: Epidemiology



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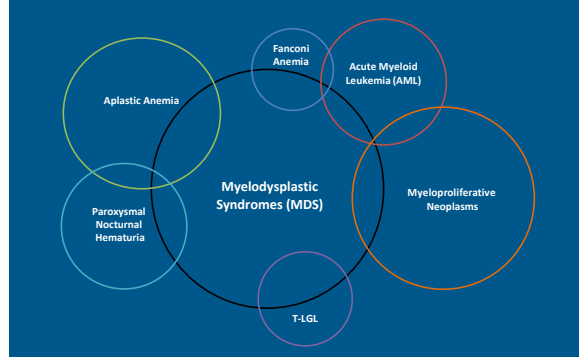
Environmental	Inborn
AGING	Fanconi anemia
Exposure to DNA alkylating agents (chlorambucil, melphalan, cyclophosphamide)	Familial Platelet Disorder with AML Predisposition ("FPD-AML") (RUNX1 , GATA2 mutant)
Exposure to topoisomerase II inhibitors (etoposide, anthracyclines)	(MonoMAC syndrome: monocytopenia, B/NK lymphopenia, atypical mycobacteria and viral and other infections, pulmonary proteinosis, neoplasms)
Exposure to ionizing radiation	Other congenital marrow failure syndromes or DNA repair defects (Bloom syndrome, ataxia-telangiectasia, etc.)
Environmental / occupational exposures (hydrocarbons, etc.)	Familial syndromes of unknown origin
Antecedent acquired hematological disorders	
Aplastic anemia (15-20%)	
PNH (5-25%)	

Slide by Dr. David Steensma

MDS Staging: Diagnosis



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MDS Staging: Diagnosis



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NCCN Guidelines Version 2.2019 Myelodysplastic Syndromes

INITIAL EVALUATION

- H&P
- Complete blood count (CBC), platelets, differential, reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping^{1,2}
- Serum erythropoietin (prior to red blood cell [RBC] transfusion)
- RBC folate, serum B₁₂
- Serum ferritin, iron, total iron-binding capacity (TIBC)
- Documentation of transfusion history
- Thyroid-stimulating hormone (TSH)
- Lactate dehydrogenase (LDH)

Cytopenia(s) suspect myelodysplasia³

- Consider genetic testing for somatic mutations (ie, acquired mutations) in genes associated with MDS⁴
- Consider additional molecular and genetic testing for hereditary hematologic malignancy predisposition in a subset of patients, particularly in younger patients⁵
- HIV testing if clinically indicated
- Consider evaluation of copper deficiency in patients with GI malabsorption, severe malnutrition, gastric bypass surgery, or patients on zinc supplementation
- Consider distinction from congenital sideroblastic anemia (CSA)^{6,7}

Diagnosis of MDS established based on morphologic, cytogenetic, and clinical criteria^{1,2}

Diagnostic criteria for MDS not met but cytopenias present

See Additional Testing and Classification (MDS-3)

See Spectrum of Indolent Myeloid Hematopoietic Disorders (MDS-3)

MDS Staging: Diagnosis



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For MDS diagnosis, you will need:

Bone Marrow Aspirate/Biopsy
Complete Blood Count with white cell differential
Karyotype (chromosome analysis)

Additionally:

MDS FISH panel and Flow cytometry
Genetic Testing

MDS Staging: IPSS-R Prognostic Score

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					

IPSS-R 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

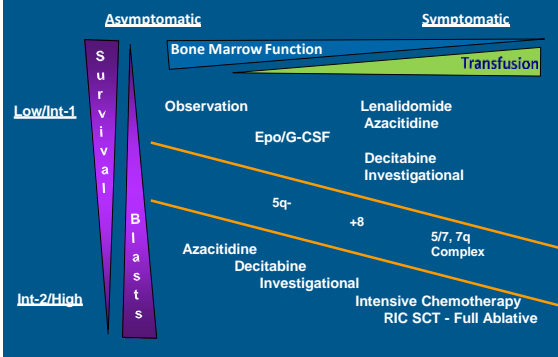
Greenberg et al. Blood 2012;120:2454-65.

MDS Staging: Prognosis

MDS Prognosis Made Easy!!!

- **Lower Risk**
 - RA, RARS
 - RCMD, RCUD
 - MDS-U, MDS del (5q)
 - IPSS Low, Int-1 (0-1.0); **IPSS-R V. Low, Low**
- **Higher Risk**
 - RAEB (-1, -2)
 - IPSS Int-2, High (≥ 1.5); **IPSS-R High, V. High**

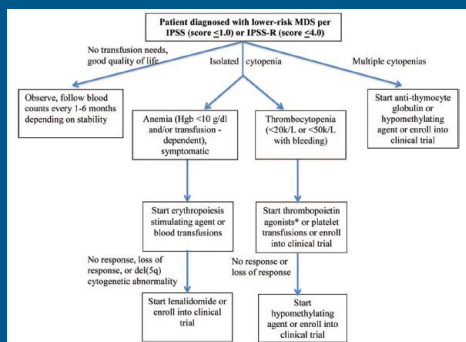
MDS Staging: Prognosis



MDS: Overview

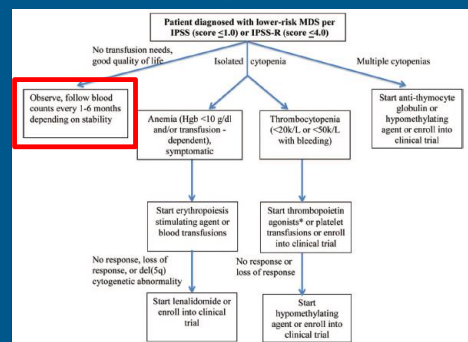
- Epidemiology and "Staging"
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MDS: Lower-Risk Treatment Algorithm



Sekeres and Gerds Hematology 2014.

MDS: Lower-Risk Treatment Algorithm



Sekeres and Gerds Hematology 2014.

MDS: Lower-Risk Treatment Algorithm

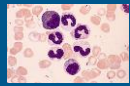
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Anemia

Packed red blood cells

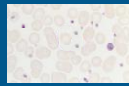
Adverse effects due to immune mechanisms
Iron overload
Volume overload



Neutropenia

Granulocyte transfusion

Laborious, short-lived effect, not widely available, Clinical utility unproven



Thrombocytopenia

Platelet transfusion

Transfusion reactions, HLA sensitization

MDS: Lower-Risk Treatment Algorithm

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Red cell growth factors

Medicare only pays for these if Hb <10 g/dL. Safety concerns in solid tumors, not (yet) in MDS

Epoetin alfa (Procrit™)

Darbepoetin alfa (Aranesp™)

White cell growth factors

No survival benefit but may help decrease infx. Sometimes combined with red cell factors

Filgrastim, G-CSF (Neupogen™)

Pegfilgrastim (Neulasta™)

Platelet growth factors

New; risks still being defined in MDS. Reports of increased blasts in a few patients.

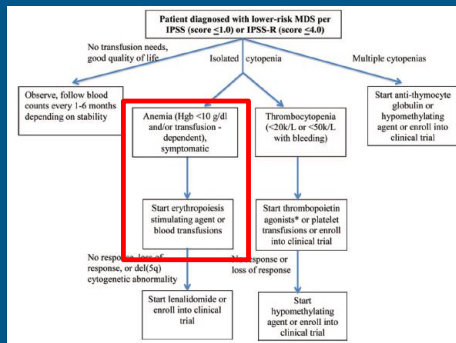
Only FDA-approved for immune thrombocytopenia and AA

Romiplostim (NPLate™)

Eltrombopag (Promacta™)

MDS: Lower-Risk Treatment Algorithm

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Sekeres and Gerds Hematology 2014.

MDS: Lower-Risk ESA Response Rate

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N = 1587 (1985-2005)

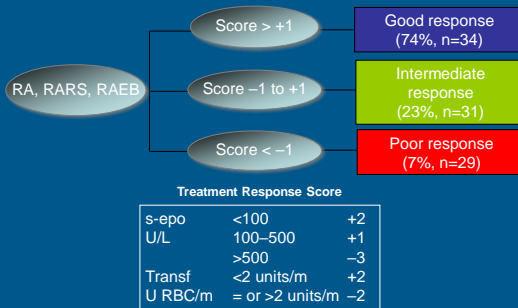
	Patients (%)	Response rate	IWG response			Duration of response (median months, range)
			CR/PR	HI-E	HI-N/P	
Growth factors	100	39.5	9.1	66.8	24.1	18 (1-116)
EPO	57.3	39.4	6.1	93.9	—	17 (1-93)
EPO + G-CSF	23.4	47.8	23.2	60.6	7.1	19 (2-62)
GM-CSF	6.2	37.8	—	—	100	6 (1-18)
EPO + GM-CSF	5.8	33.7	—	81.3	18.7	24 (1-116)
G-CSF	3.0	47.9	—	4.5	95.5	3 (1-6)

ESAs RR ~40%

Golshayan et al. Br J Haem 2007;137:125.

MDS: Lower-Risk ESA Patient Selection

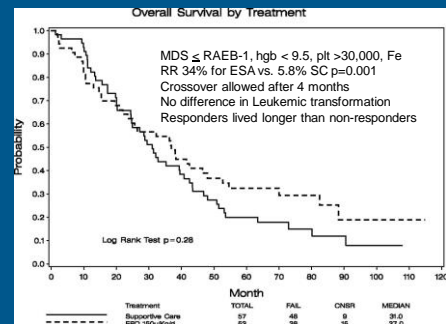
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Hellström-Lindberg E et al. Br J Haematol. 2003;120:1037

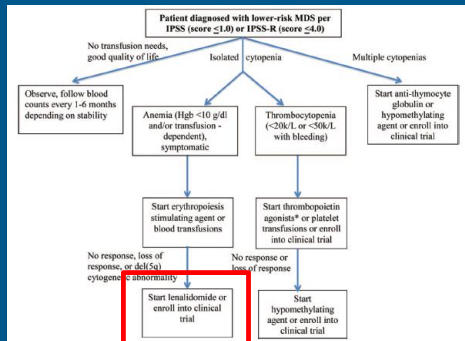
MDS: Lower-Risk ESA Patient Selection

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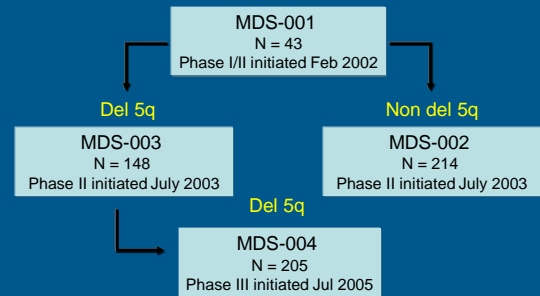
Greenberg P., et al. Blood. 2009;114:2393.

MDS: Lower-Risk Treatment Algorithm



Sekeres and Gerds Hematology 2014.

MDS: Lower-Risk Lenalidomide



MDS: Lower-Risk Lenalidomide in del(5q)

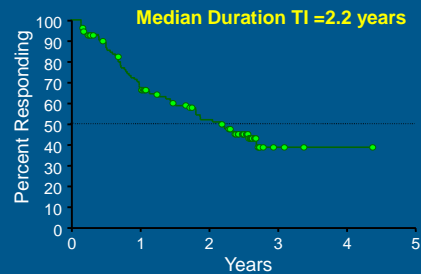


	RBC-TI, n (%) [95% CI]		
	Placebo n = 51	Lenalidomide 5 mg n = 47	Lenalidomide 10 mg n = 41
mITT population			
Protocol defined (≥ 26 weeks)	3 (5.9) [1.2-16.2]	20 (42.6) [28.3-57.8]*	23 (56.1) [39.7-71.5]*
IWG 2000 ¹² (≥ 8 weeks)	4 (7.8) [2.2-18.9]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*
IWG 2006 ¹⁴ (≥ 8 weeks)	3 (5.9) [1.2-16.2]	24 (51.1) [36.1-65.9]	25 (61.0) [44.5-75.8]*

RBC TI in 61%

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

MDS: Lower-Risk Lenalidomide in del(5q)



List et al. Leukemia 2014;28:1033.

MDS: Lower-Risk Lenalidomide in Non-del(5q)

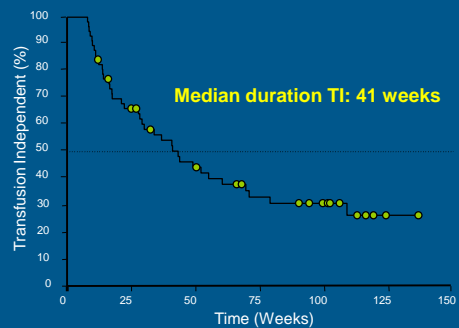


Variable	Daily Dose N = 100	21-Day Dose N = 114	All Patients N = 214
Erythroid response, n (%)	41 (41)	51 (45)	92 (43)
Transfusion Independence	26 (26)	30 (26)	56 (26)
Median Hgb change (g/dl)	3.3	3.2	3.2
Range	(1.5-9.2)	(1.0-9.8)	(1.0-9.8)
Time to initial response, weeks			
Median	6.4	3.6	4.5
Range	4.1-9.0	2.3-6.4	2.7-6.7

RBC TI in 26%

Raza et al. Blood 2008;111:86.

MDS: Lower-Risk Lenalidomide in Non-del(5q)



Raza et al. Blood 2008;111:86.

MDS: Lower-Risk Lenalidomide in Non-del(5q)



MDS-002/003: Treatment-Related Adverse Events

Grade ≥ 3 Adverse Events, %	Non-del(5q)	del(5q)
Thrombocytopenia	20	44
Neutropenia	25	55
Pruritus	1	3
Rash	4	6
Diarrhea	1	3
Fatigue	4	3

List AF, et al. *N Engl J Med*. 2006;355:1456-1465.
Raza A, et al. *Blood*. 2008;111:86-93.

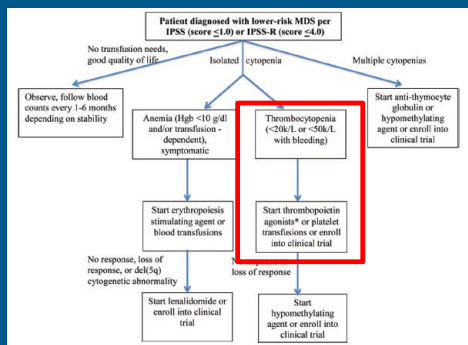
MDS: Lower-Risk Lenalidomide Summary



- MDS-004/005 confirmed results of MDS-003/002^[1,2]
 - Efficacy of 10 mg comparable between studies
 - Transfusion independence by IWG (61% vs 67%)
 - MDS-004 supports 10 mg as appropriate starting dose
 - Higher TI for 10 mg
 - Mean duration of TI: 106 wks
 - Greater proportion of cytogenetic responses vs 5 mg (41% vs 17%)
 - No significant differences in hematological toxicity
 - The rate of transformation to AML is comparable to the literature
- MDS-002/005 provided evidence that lenalidomide could be a choice for anemia treatment in lower-risk non-del(5q) pts with adequate platelets and neutrophil count^[3,4]
- Lenalidomide mechanism of action is karyotype dependent, suppressing the clone in del(5q) and promoting erythropoiesis in non-del(5q)^[5]

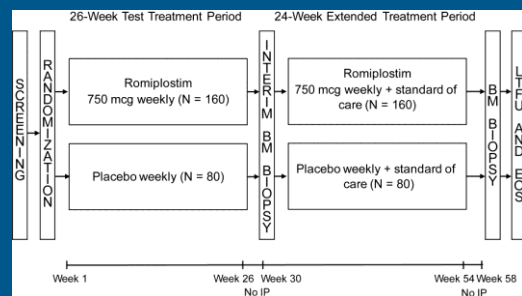
1. Fenaux P et al. *Blood*. 2011;118:3765-3776. 2. List AF, et al. *N Engl J Med*. 2006;355:1456-1465. 3. List AF, et al. *N Engl J Med*. 2005;352:549-557. 4. Raza A, et al. *Blood*. 2008;111:86-93. 5. Sekeres MA, et al. *J Clin Oncol*. 2008;26:5943-5949.

MDS: Lower-Risk Treatment Algorithm



Sekeres and Gerds Hematology 2014.

MDS: Lower-Risk TPO Agonists



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

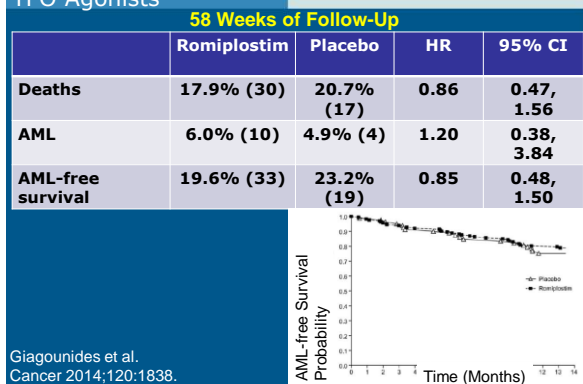
MDS: Lower-Risk TPO Agonists



	Baseline platelets < 20x10 ⁹ /L		Baseline platelets ≥ 20x10 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 = 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	

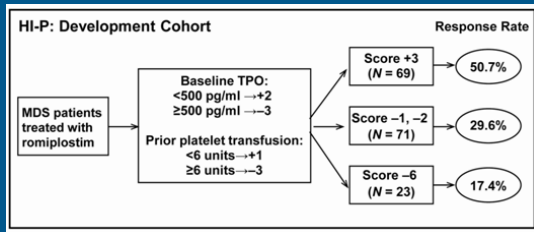
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MDS: Lower-Risk TPO Agonists



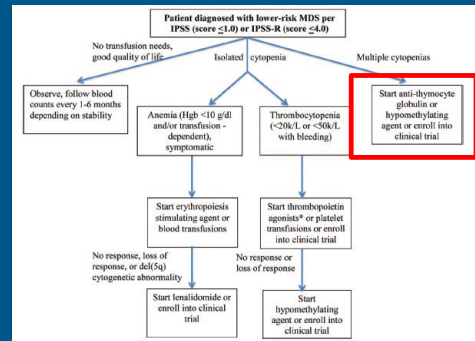
Giagounides et al.
Cancer 2014;120:1838.

MDS: Lower-Risk TPO Agonists



Sekeres et al. Br J Haematol 2014;167:337.

MDS: Lower-Risk Treatment Algorithm



Sekeres and Gerds Hematology 2014.

MDS: Lower-Risk ATG

Measure	Treatment Arm	
	ATG + CSA (n = 45)	BSC (n = 43)
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†		
No. of patients	13	4
%	29	9
Hematologic response (CR+PR+HI) by 6 months (IWG criteria)††		
No. of patients	31	4
%	69	9
Median response duration, months	16.4 (3 relapses)	NA

IWG RR = 31%
Median Duration = 16.4 Months

Passweg et al. JCO 2011;29:303.

Komrokji et al. Haematologica 2014;99:1176.

MDS: Lower-Risk ATG

- Age is the strongest variable for IST response^{1,2}
 - Pathogenetic difference in MDS of younger adults
- Responses are durable and may modify adverse effect of RBC-TI on OS²
- Karyotype may influence IST response and disease biology
 - Low frequency of IST response in del(5q)²
 - High response rate in trisomy 8³
 - NIH 8/17 (47%)
 - WT1 amplification with specific cellular response
 - Autoimmune hematopoietic suppression may select for +8 expansion

1. Saunthararajah Y, et al. Blood. 2002;100:1570-1574.

2. Sloand EM, et al. J Clin Oncol. 2008;26:2505-2511.

3. Sloand E, et al. ASH 2004. Abstract 1431.

MDS: Lower-Risk DAC

Randomized Phase 2 Study in Low/Int-risk MDS (n=65)

Schedule A: DAC 20mg/m² D 1, 3, 5

Schedule B: DAC 20mg/m² D 1, 8, 15

Variable	Schedule A (n = 43)		Schedule B (n = 22)	
	No.	%	No.	%
Response				
Overall improvement rate	10	23	5	23
Complete response	7	16	0	0
Marrow complete response	0	0	1	5
Partial response	0	0	1	5
Hematologic improvement	3	7	3	14

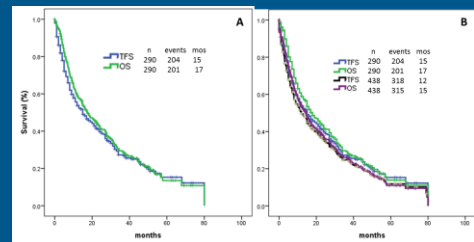
Garcia-Manero et al. JCO 2013;31:2548

MDS: Lower-Risk HMA

Lower-risk MDS Patients Treated with HMA (N=290/438)

Median TFS = 15 months

Median OS = 17 months



Jabbour et al. for MDS CRC Cancer 2014.

MDS: **Lower-Risk**
HMA

Study Design

Adult pts with de novo or secondary IPSS low- or intermediate-1-risk MDS, including CMML, ECOG PS ≤ 3, adequate organ function, no prior HMA treatment (N = 113)

Decitabine
20 mg/m² IV Days 1-3 Q4W
(n = 73)

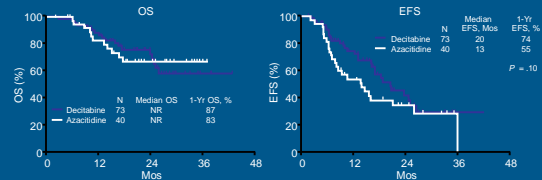
Azacitidine
75 mg/m² IV/SC Days 1-3 Q4W
(n = 40)

- Open-label phase II study
 - Randomized by Bayesian adaptive design; pts more likely to be assigned to better-performing treatment arm
 - Median follow-up: 20 mos
- Primary endpoint: OIR defined as CR, PR, marrow CR, or hematologic improvement
 - Response assessed by modified IWG 2006 criteria
- Secondary endpoints: safety, cytogenetic response, transfusion independence, EFS, OS

Jabbour EJ, et al. ASH 2016. Abstract 226.
ClinicalTrials.gov. NCT01720225.

MDS: **Lower-Risk**
HMA

OS and EFS



- Strongest predictors of EFS included BM blasts ≥ 5%, MDS/MPN or CMML diagnosis, high MDA LR MDS score, and adverse mutation risk
- Among pts in both arms (N = 113): 1-yr EFS 65%, 1-yr OS 85%

Jabbour EJ, et al. ASH 2016. Abstract 226.
ClinicalTrials.gov. NCT01720225.

MDS: **Lower-Risk**
HMA

Safety

Nonhematologic AEs,* n (%)	Decitabine (n = 73)	Azacitidine (n = 40)
Nausea	11 (15)	6 (15)
Fatigue	6 (8)	4 (10)
Constipation	3 (4)	6 (15)
Infection/neutropenic fever	5 [†] (7)	2 (5)
Diarrhea	2 (3)	3 (8)

*All grade 1/2 except where indicated. [†]Grade 3 in 4 of 5 pts.

- Both HMAs well tolerated; no grade 4 AEs
- Cycle delays: 38% in decitabine arm, 20% in azacitidine arm
- Dose reductions: 12% in decitabine arm, 5% in azacitidine arm

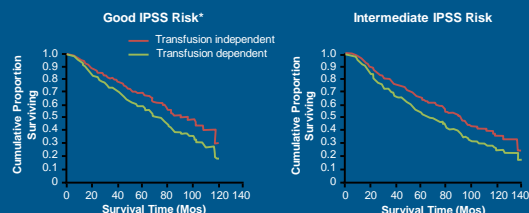
Jabbour EJ, et al. ASH 2016. Abstract 226.
ClinicalTrials.gov. NCT01720225.

MDS: **Lower-Risk**
HMA

Conclusions

- Both low-dose HMAs showed activity, were well tolerated in adult pts with LR MDS and no prior HMA use
 - ORR: 60%
 - 1-yr EFS: 65%
 - 1-yr OS: 85%
- Significantly higher ORR (70% vs 49%; $P = .03$) reported with decitabine vs azacitidine; particularly among pts with ≥ 5% blasts (100% vs 36%; $P < .001$)
- Open-label, randomized phase II trial now ongoing to compare low-dose decitabine, low-dose azacitidine, azacitidine x 5 days, and best supportive care in a LR MDS pt population

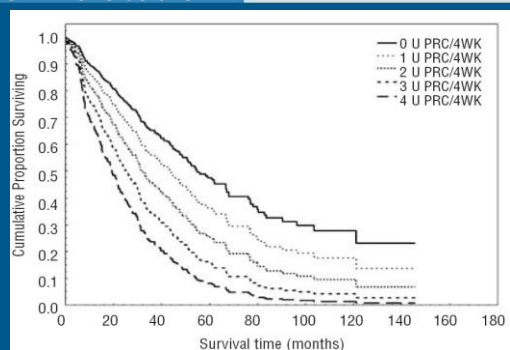
Jabbour EJ, et al. ASH 2016. Abstract 226.
ClinicalTrials.gov. NCT01720225.

MDS: **Lower-Risk**
Other - Transfusions

*Excludes isolated 5q-

Transfusion-dependent patients had a significantly shorter OS than transfusion-independent patients (HR: 2.16; $P < .001$ overall)

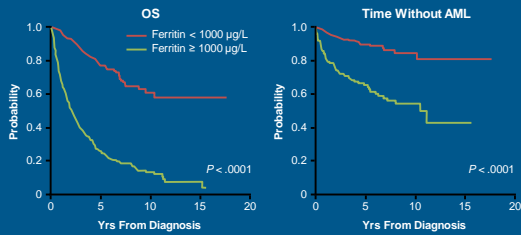
Malcovati L, et al. J Clin Oncol. 2005;23:7594-7603.

MDS: **Lower-Risk**
Other - Transfusions

Malcovati L, et al. Haematologica 2006;91(12):1588-90

MDS: Lower-Risk Other - Ferritin

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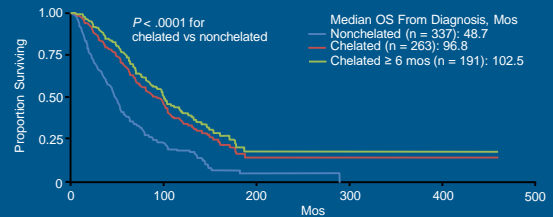


Development of transfusional iron overload is a significant independent prognostic factor for overall survival and evolution to AML

Sanz G, et al. 2008 ASH. Abstract 640.

MDS: Lower-Risk Other - Ferritin

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- 5-yr noninterventonal registry study of 600 patients with lower-risk MDS and transfusional iron overload treated with or without chelation
- At 48 mos, chelated patients had significantly longer OS vs nonchelated

Lyons RM, et al. Leukemia Research 2014;38:149-154

MDS: Lower-Risk Other - Chelation

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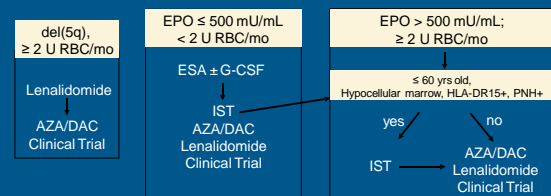
Characteristic	NCCN	MDS Foundation
Transfusion status	<ul style="list-style-type: none"> Received > 20 RBC transfusions Continuing transfusions 	<ul style="list-style-type: none"> Transfusion dependent, requiring 2 units/mo for > 1 yr
Serum ferritin level	<ul style="list-style-type: none"> > 2500 µg/L 	<ul style="list-style-type: none"> 1000 µg/L
MDS risk	<ul style="list-style-type: none"> IPSS: low or intermediate-1 risk 	<ul style="list-style-type: none"> IPSS: Low- or Int-1 WHO: RA, RARS and 5q-
Patient profile	<ul style="list-style-type: none"> Candidates for allografts 	<ul style="list-style-type: none"> Life expectancy > 1 yr and no comorbidities that limit progress A need to preserve organ function Candidates for allografts

NCCN. Clinical practice guidelines in oncology. MDS. v2.2017.
Bennett JM. J Hematol. 2008;83:858-861.

MDS: Lower-Risk Summary Anemia

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- Assess potential causes of anemia
- Supplement with iron, folate, vitamin B as needed
- RBC transfusion support for symptomatic patients



Adapted from NCCN. Clinical practice guidelines in oncology. MDS. v2.2017.

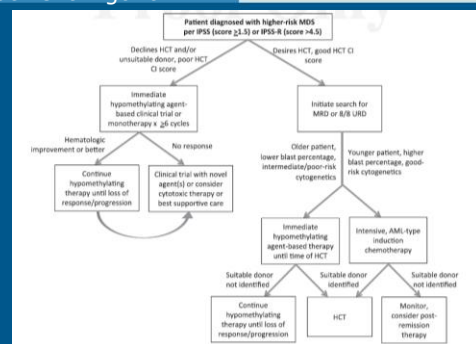
MDS: Overview

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- Epidemiology and "Staging"
- Treatment of Lower-risk Disease
- **Treatment of Higher-risk Disease**
- Clinical Trials and Future Directions
- Conclusions

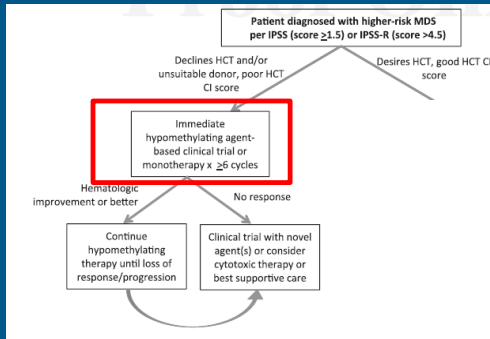
MDS: Higher-Risk Treatment Algorithm

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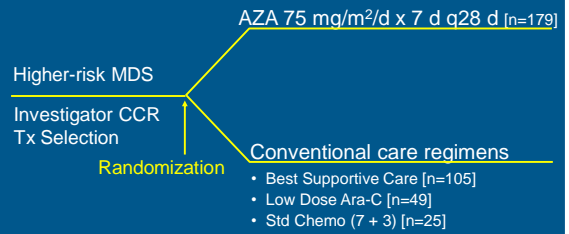
Sekeres and Cutler Blood 2014;123:829.

MDS: Higher-Risk Treatment Algorithm



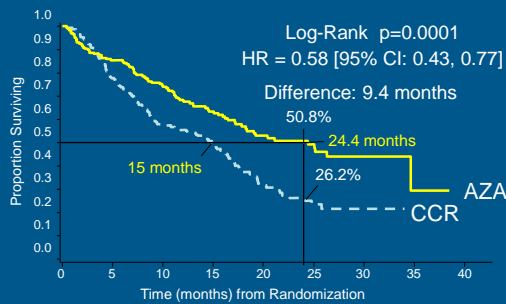
Sekeres and Cutler Blood 2014;123:829.

MDS: Higher-Risk AZA



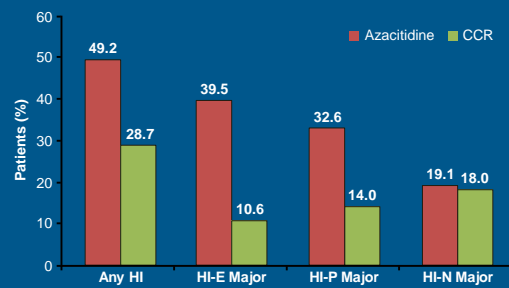
Fenaux P, et al. Lancet Oncology 2009;10:223-232.

MDS: Higher-Risk AZA



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

MDS: Higher-Risk AZA



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

MDS: Higher-Risk AZA

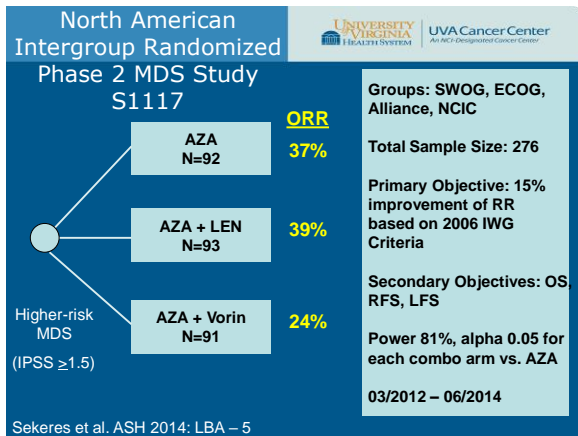
Adverse Events – Grades 3 and 4, n (%)	Azacitidine (n = 175)	BSC Only (n = 102)
Neutropenia	159 (91)	70 (69)
Thrombocytopenia	149 (85)	72 (71)
Leukopenia	26 (15)	1 (1)
Anemia	100 (57)	67 (66)
Febrile neutropenia	22 (13)	7 (7)
Pyrexia	8 (5)	1 (1)
Abdominal pain	7 (4)	0
Dyspnea	6 (3)	2 (2)
Fatigue	6 (3)	2 (2)
Hematuria	4 (2)	1 (1)
Hypertension	2 (1)	2 (2)

*When any grade of the reactions occurs in ≥ 5% of azacitidine-treated patients.

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

MDS: Higher-Risk

Drug Combinations ?



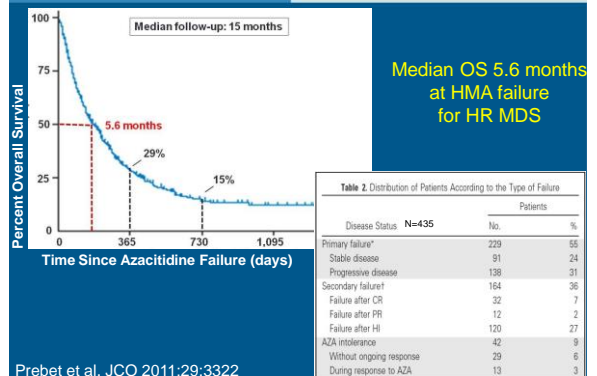
MDS: Overview

- Epidemiology and “Staging”
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease
- **Clinical Trials and Future Directions**
- Conclusions

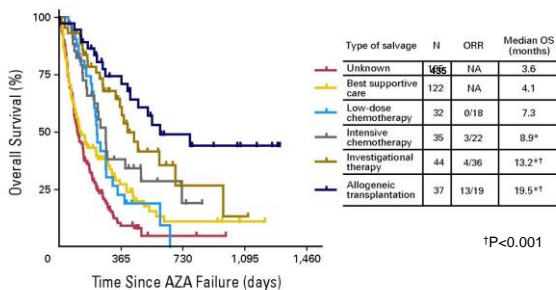
MDS: Clinical Trials and Future Direction

We have to do **BETTER**.

MDS: Clinical Trials and Future Direction HRMDS



MDS: Clinical Trials and Future Direction HRMDS



MDS: Clinical Trials and Future Direction

Immunotherapy

- Early results with short follow-up (median 3 cycles) suggest nivolumab and ipilimumab well tolerated as single agent or with azacitidine
- Nearly 30% ORR with ipilimumab in pts who failed HMA therapy shows promising single-agent activity as salvage therapy
- Nivolumab did not show single-agent activity as salvage therapy
 - Encouraging early 65% ORR when combined with azacitidine in previously untreated pts
- Additional treatment cohorts ongoing
- Investigators suggest that future randomized trials are warranted

Garcia-Manero G, et al. ASH 2016. Abstract 344.

MDS: Clinical Trials and Future Direction



ETCTN Trial 10026 - Ipilimumab and Decitabine
- Relapsed MDS patients with 5% blasts or greater
After allogeneic stem cell transplant
OR
After 4 cycles of hypomethylating agent

MDS: Clinical Trials and Future Direction

**SGI-110**

Second-generation hypomethylating agent

- SC dinucleotide of decitabine and deoxyguanosine
- longer half-life; more extended decitabine exposure

15 pts with higher-risk MDS

- Median age 74; **all had previous aza/decitabine**
- **5 responders (33%)**, duration 28-224 days

O'Connell C et al, EHA 2013, abstract P189

MDS: Clinical Trials and Future Direction



SG-110 in MDS/CMML/AML after AZA failure

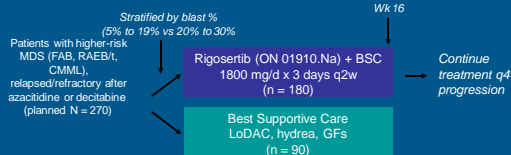
- GDAC 60 mg/m²/day Day 1-5 q 28 days
– Median 3 cycles
- N=56; 15 refractory and 41 relapsed
- 9 responded (16%)
– 1 CR, 2CRp, 5 marrow CR, 1 HI
- Median duration of response 9 months
- Median OS 6.7 mos
– 33 died: 14 progression, 13 infection, 1 bleeding, 5 other

Sebert et al. ASH 2016 Abstract 347. *Blood* 2016;128:347

MDS: Clinical Trials and Future Direction



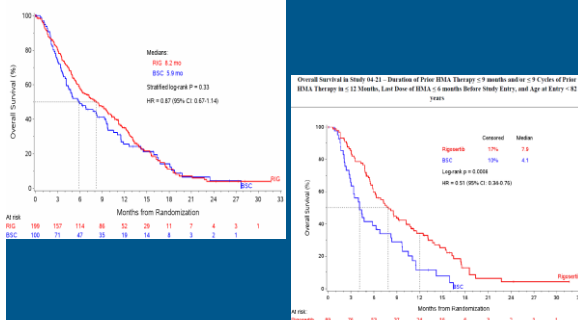
Phase III ONTIME: Rigosertib: PLK and PI3K inhibitor; a novel synthetic benzyl styryl sulfone that is cytotoxic against a variety of human tumor cell lines



- Primary endpoint: OS (HR: 0.62)
- Secondary endpoints: IWG response, transformation to AML, infection, bleeding, QoL

Garcia-Manero et al. *Lancet Oncology*; 2016;17:496-508

MDS: Clinical Trials and Future Direction

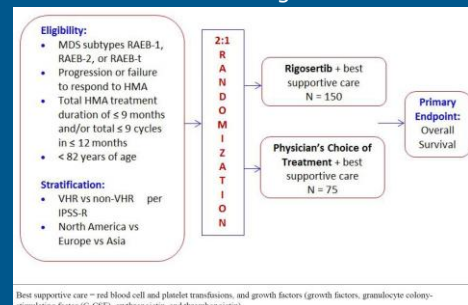


Garcia-Manero et al. *Lancet Oncology*; 2016;17:496-508

MDS: Clinical Trials and Future Direction



ONTIME 2 - Rigosertib



Garcia-Manero et al. *Lancet Oncology*; 2016;17:496-508

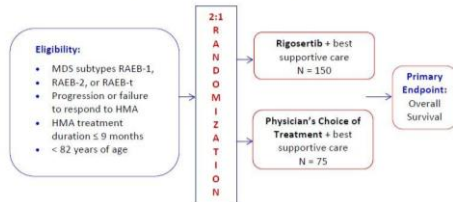
MDS: Clinical Trials and Future Direction

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INSPIRE - Rigosertib

International Study of Phase III Intravenous Rigosertib

A Phase III, International, Randomized, Controlled Study of Rigosertib versus Physician's Choice of Treatment in Patients with Myelodysplastic Syndrome after Failure of a Hypomethylating Agent



MDS: Clinical Trials and Future Direction

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BCL-2 Inhibitor - Venetoclax

- Current studies in both treatment naïve and HMA failure settings

New Hypomethylating Agents

- guadecitabine (SGI-110, oral)
- CC486 (oral form of azacitidine)
- cedazurine (ASTX727, orally fixed-dose combination of decitabine and a cytidine deaminase inhibitor)

Imetelstat (telomerase inhibitor)

- studied in myeloproliferative neoplasms and transfusion independence rates were ~30%

MDS: Clinical Trials and Future Direction

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Other Targets

- IDH 1 and 2 – Ivosidenib and Enasidenib
- HIF – Roxadustat
- Need targets for TP53
 - Decitabine – 10 day regimen
 - APR-246, a TP53 modulator

MDS: Clinical Trials and Future Direction

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The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia With Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

Pierre Fenaux, Uwe Platzbecker, Giuliana J. Muftic, Guillermo Garcia-Manero, Rene Buckstein, Valeria Santini, Maria Diaz-Campelo, Carlo Finelli, Mario Cazzola, Osman Iltan, Mikael A. Sekeres, José F. Palentes, Beatriz Arribas-Ala, Flavia Salvi, Valentina Gial, Parvash Vyas, David Bowen, Dominik Seltschag, Amy B. Dicker, Joseph G. Juris, Ulrich Gernig, Katharina S. Götze, Bruno Quisenberry, Odile Beyne-Rausy, Thomas Cluzeau, Maria Teresa Voso, Dominik Mazurek, Edo Vellenga, Peter L. Greenberg, Eva Hellström-Lindberg, Amer M. Zeidan, Abderrahmane Ladem, Aziz Benzohra, Jennie Zhang, Anita Rampersad, Peter G. Linde, Matthew L. Sherman, Rami S. Komrokji, Alan T. List

List A, et al. ASH 2018. Abstract 001.

MDS: Clinical Trials and Future Direction

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MEDALIST Trial
Background and Rationale

- Patients with lower-risk (LR)^a transfusion-dependent MDS have a poorer prognosis, with greater risk of progression to AML and inferior overall survival compared with patients with transfusion-independent MDS
- RBC transfusion-dependent LR, non-del(5q) MDS patients have a transient response to ESAs, with an attendant risk of iron overload and secondary organ complications
- Few treatment options exist for the large number of patients with LR MDS who are either refractory to or become unresponsive to ESAs¹

^aIPSS-R-defined criteria.
AML, acute myeloid leukemia; ESAs, erythropoiesis-stimulating agents; IPSS-R, revised International Prognostic Scoring System.

1. Fenaux P, and others. Blood. 2015;125:4239-4246.

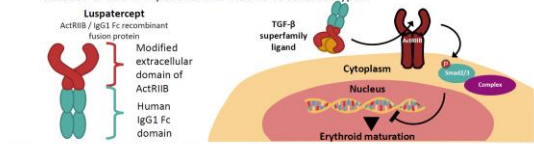
List A, et al. ASH 2018. Abstract 001.

MDS: Clinical Trials and Future Direction

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MEDALIST Trial
Luspatercept

- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF- β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models¹
- In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes²



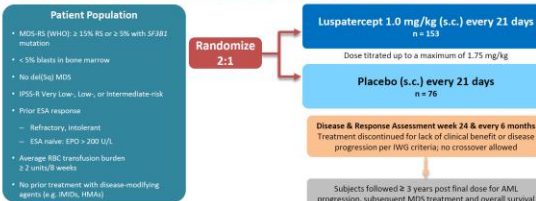
ActRIIB, human activin receptor type IIb; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence.

1. Sungam P, et al. Blood. 2014;123:459-464.

2. Platzbecker U, et al. Lancet Oncol. 2017;18:1558.

List A, et al. ASH 2018. Abstract 001.

MDS: Clinical Trials and Future Direction

MEDALIST Trial
Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Data cutoff: May 8, 2018 includes last subject randomized + 48 weeks.
 WHO, World Health Organization; MDS, myelodysplastic syndrome; EPO, erythropoietin; IMiD, imatinib mesylate; HMAs, hypomethylating agents; IPSS-R, International Prognostic Scoring System; ESA, erythropoiesis-stimulating agent; AML, acute myeloid leukemia.

List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction

MEDALIST Trial
Study Endpoints

Primary endpoint:

- Red blood cell transfusion independence ≥ 8 weeks (weeks 1–24)

Key secondary endpoints:

- Red blood cell transfusion independence ≥ 12 weeks (weeks 1–24)
- Red blood cell transfusion independence ≥ 12 weeks (weeks 1–48)

Additional secondary endpoints:

- HI-E (IWG 2006 criteria)^a for any consecutive 56-day period
 - Reduction in red blood cell transfusion burden ≥ 4 RBC units/8 weeks^a or
 - Mean Hb increase of ≥ 1.5 g/dL/8 weeks^b
- Duration of response
- Hb change from baseline

^a In patients with baseline RBC transfusion burden ≥ 4 units/8 weeks, ^b In patients with baseline RBC transfusion burden < 4 units/8 weeks.

HI, hemoglobin; Hb, hemoglobin measurement without.

1. Cheson BS, et al. Blood. 2006;108:429-435.

List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction

MEDALIST Trial
Demographics and Baseline Disease Characteristics

Characteristic	Luspatercept (n = 153)	Placebo (n = 76)
Age, median (range), years	71 (40–95)	72 (26–91)
Male, n (%)	94 (61.4)	50 (65.8)
Time since original MDS diagnosis, median (range), months	44.0 (3–421)	36.1 (4–193)
WHO classification		
< 5% blasts, n (%)	145 (94.8)	74 (97.4)
5–15% blasts, n (%)	5 (3.3)	5 (6.6)
> 15% blasts, n (%)	3 (2.0)	3 (4.0)
5–15% blasts, n (%)	66 (43.1)	33 (43.4)
> 15% blasts, n (%)	87 (56.9)	43 (56.6)
Pre-transfusion Hb, median (range), g/dL	7.6 (6–10)	7.6 (5–9)
IPSS-R risk category ^a		
Very Low, Low, n (%)	127 (83.0)	63 (82.9)
Intermediate, n (%)	25 (16.3)	13 (17.1)
SF382 mutation, n (%)	141 (92.2)	65 (85.5) ^b
Severe EPO		
< 200 U/L, n (%)	88 (57.5) ^c	50 (65.8)
≥ 200 U/L, n (%)	64 (41.8) ^c	26 (34.2)

^a In the 26 patients prior to randomization, 11 (42%) patients in the luspatercept arm were classified as IPSS-R high-risk. ^b Data were missing for 1 patient. ^c EPO, erythropoiesis-stimulating agent; WHO, World Health Organization; IPSS-R, International Prognostic Scoring System.

List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction

MEDALIST Trial
Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks

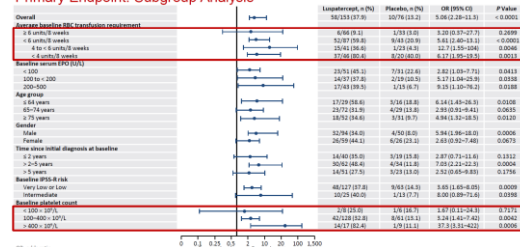
RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	58 (37.9)	10 (13.2)
95% CI	30.2–46.1	6.5–22.9
P value ^a	< 0.0001	

^a Chi-square test; median (range) not adjusted for average baseline RBC transfusion requirement (≥ 4 units or < 4 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).

CI, confidence interval.

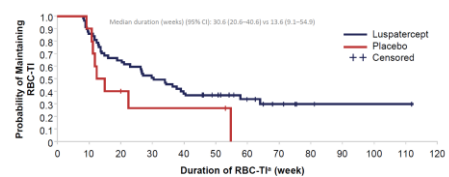
List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction

MEDALIST Trial
Primary Endpoint: Subgroup Analysis

List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction

MEDALIST Trial
Duration of RBC-TI Response in Primary Endpoint Responders

^a During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction



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MEDALIST Trial Secondary Endpoint: Erythroid Response (HI-E)

	Luspatercept (n = 153)	Placebo (n = 76)
Achieved HI-E* (weeks 1-24), n (%)	81 (52.9)	9 (11.8)
Reduction of ≥ 4 RBC units/8 weeks (baseline transfusion burden ≥ 4 units/8 weeks)	52/107 (48.6)	8/56 (14.3)
Hb increase of ≥ 1.5 g/dL (baseline transfusion burden < 4 units/8 weeks)	29/46 (63.0)	1/20 (5.0)
95% CI	44.72-61.05	5.56-21.29
P value [†]	< 0.0001	
Achieved HI-E* (weeks 1-48), n (%)	90 (58.8)	13 (17.1)
Reduction of ≥ 4 RBC units/8 weeks (baseline RBC transfusion burden ≥ 4 units/8 weeks)	58/107 (54.2)	12/56 (21.4)
Hb increase of ≥ 1.5 g/dL (baseline RBC transfusion burden < 4 units/8 weeks)	32/46 (69.6)	1/20 (5.0)
95% CI	50.59-66.71	9.43-27.47
P value [†]	< 0.0001	

*Defined as the proportion of patients meeting the HI-E criteria per 2012 criteria (Cheson et al. 2006) sustained over a consecutive 30-day period during the indicated treatment period.

[†]Luspatercept compared with placebo, Cochran-Mantel-Haenszel test.

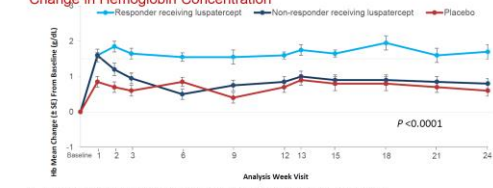
List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction



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MEDALIST Trial Change in Hemoglobin Concentration



Number of patients	Responder	Non-responder	Placebo
Baseline	253	24	36
Week 1	253	24	36
Week 2	253	24	36
Week 3	253	24	36
Week 6	253	24	36
Week 9	253	24	36
Week 12	253	24	36
Week 15	253	24	36
Week 18	253	24	36
Week 21	253	24	36
Week 24	253	24	36

List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction



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MEDALIST Trial Safety Summary

	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE, n (%)	150 (98.0)	70 (92.1)
Patients with ≥ 1 serious TEAE	48 (31.4)	23 (30.3)
Patients with ≥ 1 Grade 3 or 4 TEAE	65 (42.5)	34 (44.7)
Patients with TEAEs leading to death ^a	5 (3.3)	4 (5.3)
Patients with ≥ 1 TEAE causing discontinuation, n (%)	13 (8.5)	6 (7.9)

^a Progression to AML occurred in 4 patients (3/153 [2.0%] in the luspatercept arm; 1/76 [1.3%] in the placebo arm)

^a Luspatercept arm: sepsis (n=2), multiple organ dysfunction syndrome, renal failure, and hemorrhagic shock; in placebo arm: sepsis, varicella, general physical health deterioration, and respiratory failure.

TEAE, treatment-emergent adverse event.

List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction



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MEDALIST Trial Conclusions

- In lower-risk, RS-positive MDS, treatment with luspatercept resulted in a significantly higher percentage of patients who achieved RBC-TI, major RBC transfusion reduction, or hemoglobin increase, compared with placebo
- Erythroid responses are durable, with approximately 40% of patients achieving RBC-TI sustained at 12 months of treatment
- Luspatercept was well tolerated in this patient population
- Luspatercept is a potential new therapy for the treatment of patients with lower-risk, RS-positive MDS with RBC transfusion-dependent anemia

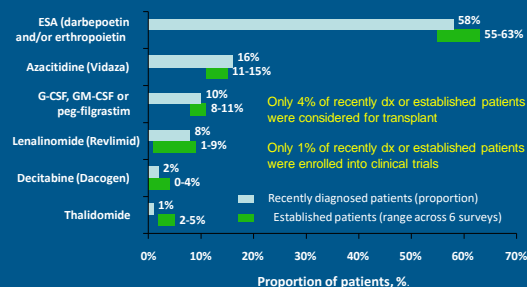
List A, et al. ASH 2018, Abstract 001.

MDS: Clinical Trials and Future Direction



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Overall proportion of recently diagnosed patients (n = 670) and range of established patients across six surveys (n = 3844) taking specific types of therapies at the time of the survey



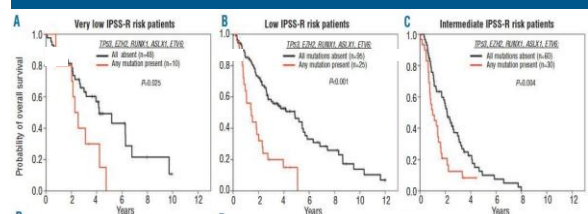
Sekeres, et al. J National Cancer Inst. 2008;100:1542

MDS: Clinical Trials and Future Direction



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Somatic Gene Mutations Improve Precision of the IPSS-R



Gene Mutations with Prognostic Relevance

Favorable: SF3B1

Unfavorable: RUNX1, ASXL1, EZH2, TP53, ETV6, DNMT3A, U2AF1, NRAS

Bejar R. Haematologica 2014; 99: 956.

