Enhancing Patient Care in Low- and Intermediate-Risk Myelodysplastic Syndromes: A Focus on Risk Stratification and Symptom Management

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Great Debates
Hematologic Malignancies
from Lymphoma · Leukemia & Myeloma Congress

Faculty Disclosures

- Honoraria—ACHL, Geron, Great Debates, HemeOnc Pulse, PeerView; Advisory Board—Geron, Kymera Therapeutics, Ryvu Therapeutics; grant/research funding—Kymera Therapeutics, Ryvu Therapeutics; Data Safety Monitoring Board Chair—Servier Pharmaceuticals
- I will not discuss any off-label drug usage

Program Information

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- Supported by an educational grant from Geron Corporation

Learning Objectives

- Evaluate common symptoms and comorbidities in low- and intermediate-risk MDS in order to implement personalized strategies for symptom control and supportive care
- Assess treatment options for low- and intermediate-risk MDS—including growth factors, immunomodulatory drugs, and emerging therapies—to optimally tailor patient care
- Integrate the use of patient-reported outcome measures (PROMs) into clinical practice to enhance treatment decision-making, monitor therapeutic response, and address patient-centered care needs

MDS = myelodysplastic syndrome.

Myelodysplastic Syndromes (MDS) in the United States

10-20K New cases per year, although some estimates are much higher

1 in 3 patients will progress to AML

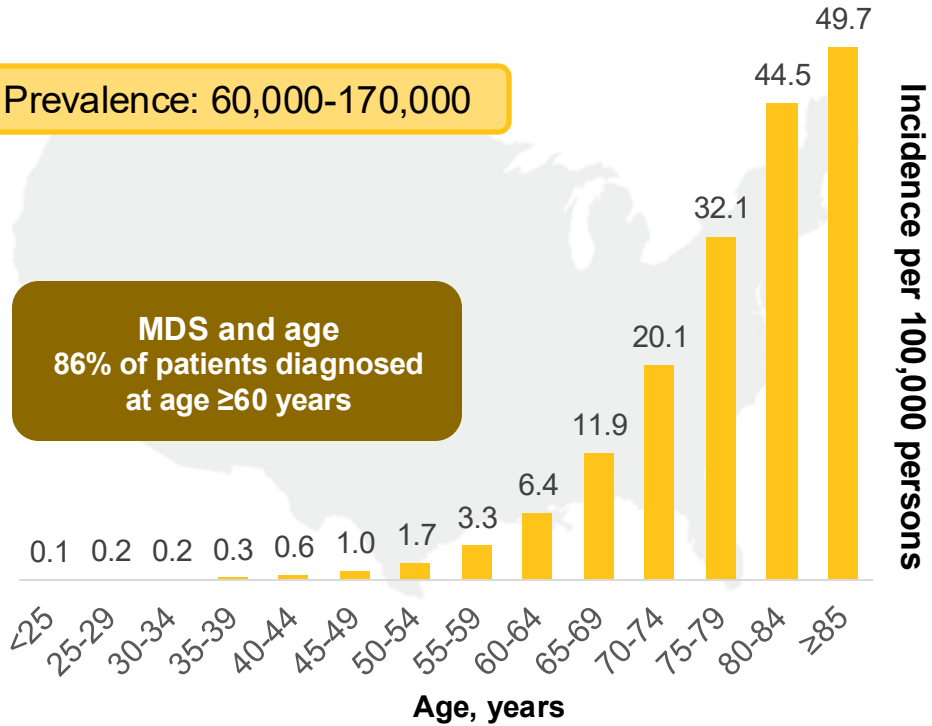
Approximately 5%-10% of cases occur after exposure to previous radiation/chemotherapy

More than 90% of patients harbor somatic mutations

Anemia is the most common clinical feature

Prevalence: 60,000-170,000

MDS and age
86% of patients diagnosed at age ≥60 years



AML = acute myeloid leukemia.

Ma X. *Am J Med*. 2012;125(7):S2-S5. Cogle CR. *Curr Hematol Malig Rep*. 2015;10(3):272-281. American Cancer Society (ACS) [www.cancer.org]. Accessed October 24, 2023. https://www.cancer.org/cancer/types/myelodysplastic-syndrome.html. Leukemia and Lymphoma Society (LLS) [www.lls.org]. Accessed October 24, 2023. https://www.lls.org/myelodysplastic-syndromes/myelodysplastic-syndromes.

IPSS-M: A Novel Prognostic Model That Identified Clear Predictors of Poor and Favorable Outcomes

Unlike IPSS-R model, IPSS-M incorporated gene mutations as well as hematologic and cytogenetic parameters

- With IPSS-M, at least one oncogenic genomic alteration was noted in 94% of patients with MDS (N=2,957)

Top predictors of adverse outcomes	*SF3B1* mutations were associated with favorable outcomes
• *TP53*$^{\text{multihit}}$ • *FLT3* mutations • *MLL*$^{\text{PTD}}$	• Modulated by patterns of comutation

IPPS-R = Revised International Prognostic Scoring System; IPSS-M = Molecular International Prognostic Scoring System.

Bernard E, et al. *NEJM Evid*. 2022;1(7):EVIDoa2200008.

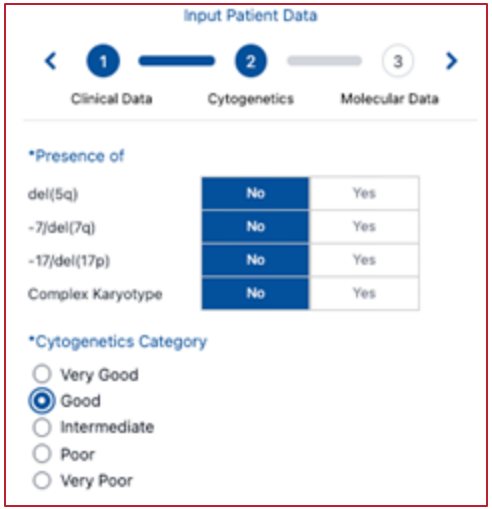
IPSS-M Improved Prognostication Compared with IPPS-R

- IPSS-M resulted in a unique risk score for individual patients (using hematologic parameters, cytogenetics, and somatic mutations)
- 6 IPSS-M risk categories with prognostic differences were derived
- Compared with the IPSS-R, the IPSS-M improved prognostic discrimination across all end points and re-stratified 46% of patients

Bernard E, et al. *NEJM Evid*. 2022;1(7):EVIDoa2200008.

The Online IPSS-M MDS Risk Calculator Is a Simple, Easy-to-Use Tool for Prognostic Assessment

Input relevant patient data…



Calculate Risk

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

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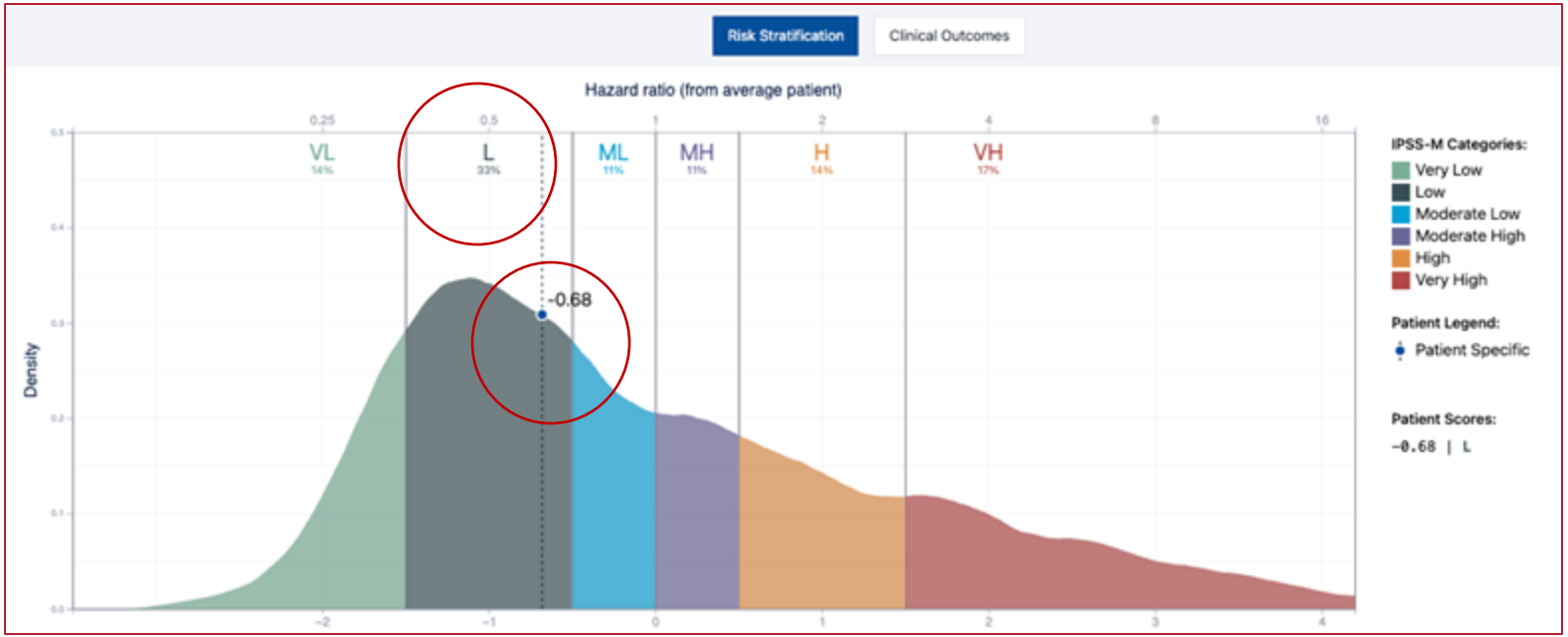
Bernard E, et al. *NEJM Evid*. 2022;1(7):EVIDoa2200008.

The Online IPSS-M MDS Risk Calculator Is a Simple, Easy-to-Use Tool for Prognostic Assessment

…and calculate the risk



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

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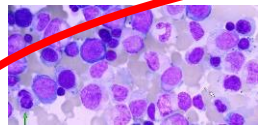
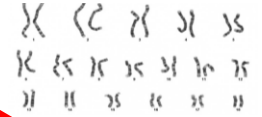
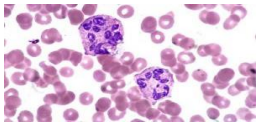
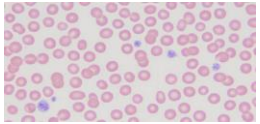
Bernard E, et al. *NEJM Evid*. 2022;1(7):EVIDoa2200008.

Risk Stratification and Clinical Decisions in MDS—IPSS-M 58% of MDS Is Lower Risk

Diagnosis	Classification	Incidence (%)	Median OS (yrs)	Progression risk (% at 4 yrs)*	Treatment goal	Current SoC
	Very low *(Very low/low)*	14	10.6	2.8	Hematologic improvement (lower risk of infection and bleeding)	Transfusion ESAs Watch and wait
	Low *(Very low/low/int)*	33	6.0	5.1		
	Moderate low *(Low/int)*	11	4.6	11.4	?	
	Moderate high *(Low/int/high)*	11	2.8	18.9	Alter disease natural history (higher risk of infection and bleeding)	HMAs/ICT +/- ASCT
	High *(Int/high/very high)*	14	1.7	29.2		
	Very high *(High/very high)*	17	1.0	42.8		

OS = overall survival; SoC = standard of care; ESA = erythropoiesis-stimulating agents; HMA = hypomethylating agent; ICT = induction chemotherapy; ASCT = autologous stem cell transplantation.

Bernard E, et al. *NEJM Evid*. 2022;1(7):EVIDoa2200008. Fenaux P, et al. *Ann Oncol*. 2021;32(2):142-156.

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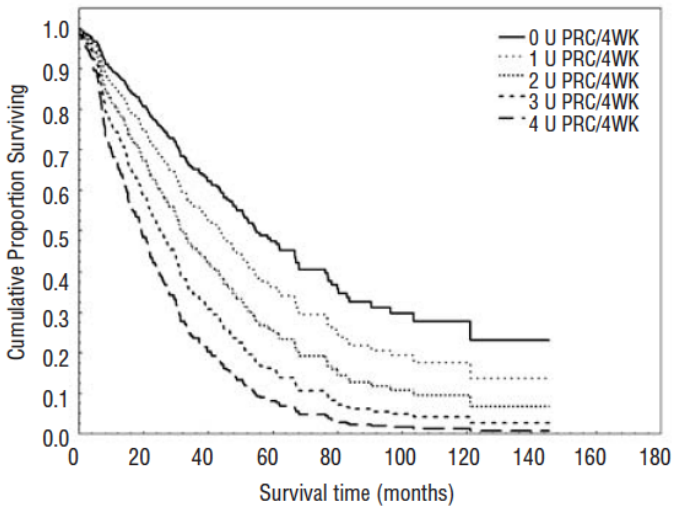
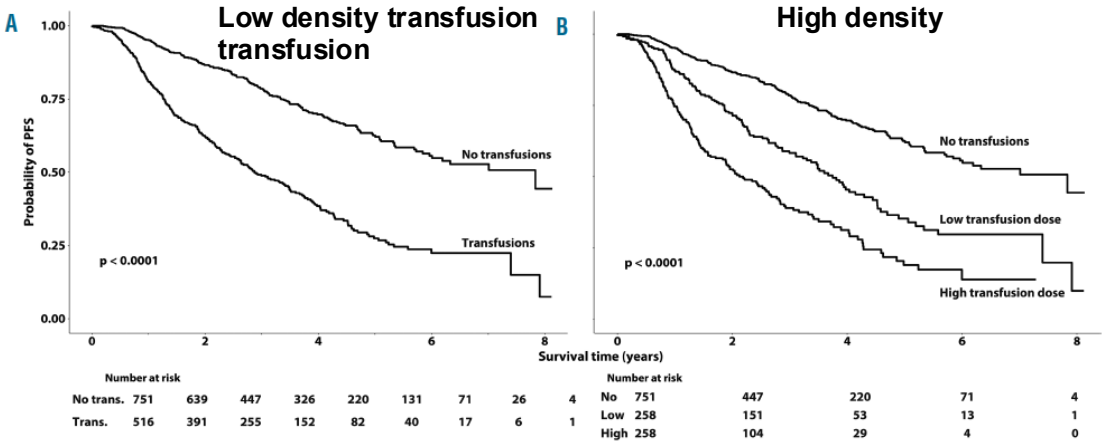
Transfusion Dependency Negatively Affects Survival

Cumulative probability of survival among patients with MDS



PFS and risk of progression according to transfusion status



Negative effect of transfusion burden and density on PFS already visible at low transfusion burden of 3 units/16 weeks

PFS = progression-free survival.

Malcovati L, et al. *Haematologica*. 2006;91(12):1588-1590. de Swart L, et al. *Haematologica*. 2020;105(3):632-639.

Hematological Response to Frontline Treatment in Lower Risk Myelodysplastic Syndromes (LRMDS) Is Associated with Better Overall Survival

331 pts (55%) received SL therapy which included HMA 43% (n=142), lenalidomide 39% (n=130), luspatercept 7% (n=24), ATG 2% (n=8), investigational agent 4% (n=14), and other 4% (n=13) .

The HI rate was 27% (91/331).

No difference in HI based on RS nor RBC-TD was observed. The median duration on SL treatment was 6 mo (.1-93).

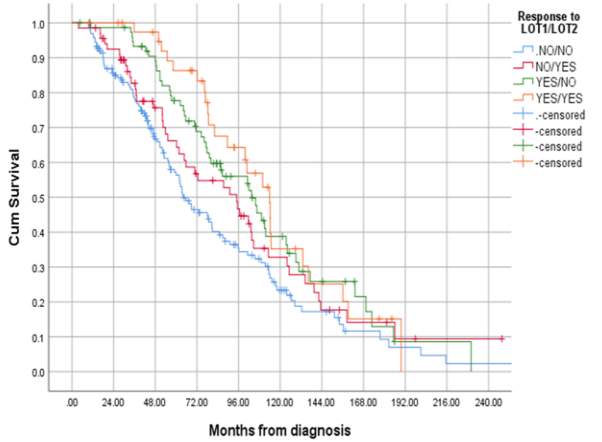
170 pts (28%) received 3rd line of therapy with 7% HI

88 pts (15%) received 4th line of therapy with 3% HI

39 pts (7%) had 5th line of therapy with 2% HI.

- Among the 331 pts who received at least FL and SL, pts were divided into 4 groups based on response to both lines of therapy
- The mOS was 114 mo among yes/yes response group, 103 mo among yes/no group, 97 mo among no/yes and 64 mo among no/no (*P*=.007)
- **Response to FL was significantly associated with better OS after adjusting for RS (HR .74 ,95% CI .55-.99, *P*=.043).**

Table-2	Baseline characteristics of the groups based on response to FL and SL				
	NO/NO (n=163)	NO/YES (n=60)	YES/NO (n=77)	YES/YES (n=31)	*P*-value
Age (median)	72	73	69.6	68.2	.15
Sex (male)	111 (68%)	36 (60%)	50 (65%)	22 (71%)	.65
Race (white)	151 (93%)	58 (97%)	72 (95%)	31 (100%)	.27
SF3B1 MT	41/86	16/26	23/40	16/18	.051
IPSS-R Very low low	 39 (24%) 127 (76%)	 6 (10%) 54 (90%)	 19 (25%) 58 (75%)	 11 (36%) 20 (64%)	.03
RBC-TD	101 (62%)	38 (63%)	36 (47%)	16 (52%)	.1



SL = second-line; ATG = anti-thymocyte globulin; HI = hematological improvement; RS = ring sideroblast; RBC-TD = red blood cell transfusion dependency; FL = first-line; mOS = median OS; MT = mutated.

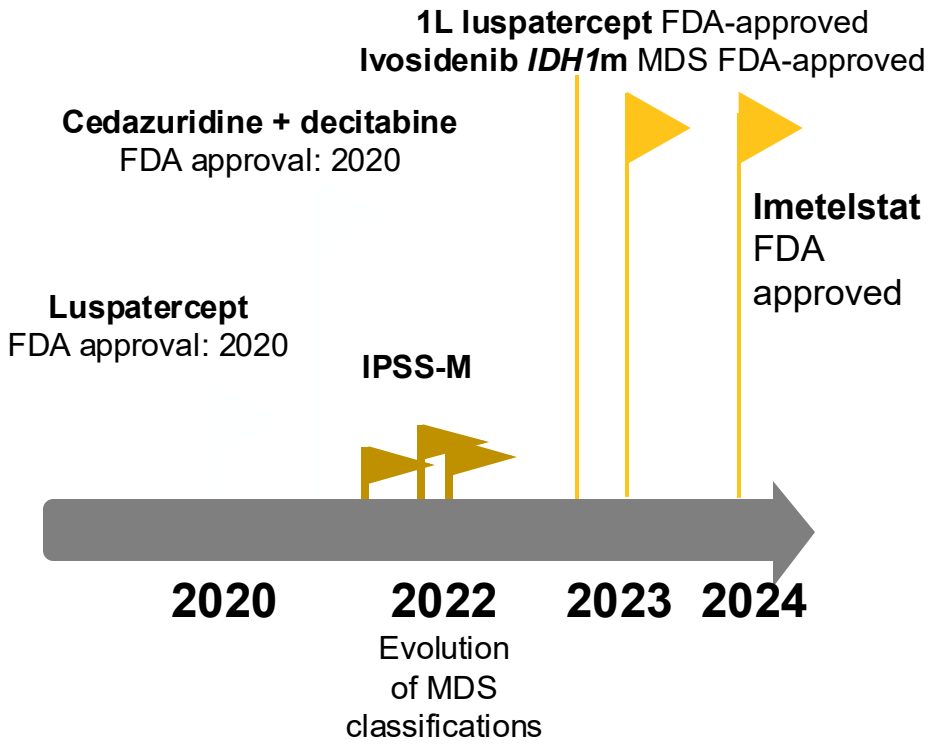
Komrokji RS, et al. Presented at: 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, California. Abstract 1867.

How Recent Developments Are Changing MDS Care

Since 2020, there has been an increase in the pace of innovation, with several new MOAs established or emerging in LR- or HR-MDS

+

newer classifications and prognostic tools



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MOA = mechanism of action; LR = lower-risk; HR = higher-risk; FDA = US Food and Drug Administration.

Case 1

- 58-year-old female, past medical history of hypothyroidism with C/O fatigue noted to have macrocytic anemia by her PCP; CBC WBC 4.0/ANC 3/HGB 10.2 g/dl/plat 470
- The patient was referred to hematology, nutritional deficiencies ruled out; a bone marrow aspirate and biopsy performed revealing erythroid hypoplasia, no increased myeloblasts, micromega
- Karyotype revealed del5q 15/20 metaphases; FISH for + del5q (80/200 cells); NGS revealed *TP53* MT VAF 13%
- Follow up CBC—Hgb dropped to 8.5 g/dl

c/o = complaints of; PCP = primary care provider; CBC = complete blood count; WBC = white blood cell count; ANC = absolute neutrophil count; HGB = hemoglobin; FISH = fluorescence in situ hybridization; NGS = next-generation sequencing; VAF = variant allele frequency.

Case 1

- What is the classification and risk stratification of this patient?
  A. MDS-TP53- low risk IPSS-M
  B. MDS-TP53- VH risk IPSS-M
  C. MDS- del5q- VL risk IPSS-M
  D. MDS- del5q- MH risk IPSS-M

VH = very high; VL = very low; MH = moderate-high.

Case 1

- How should this patient be treated for her anemia?
  A. Supportive blood transfusions
  B. Observation
  C. Lenalidomide
  D. Start azacitidine and referral to AHSCT given *TP53* mutation

AHSCT = autologous hematopoietic stem cell transplantation

Abstract #1001: TP53 Gene Allelic State in Myelodysplastic Syndromes (MDS) with Isolated 5q Deletion

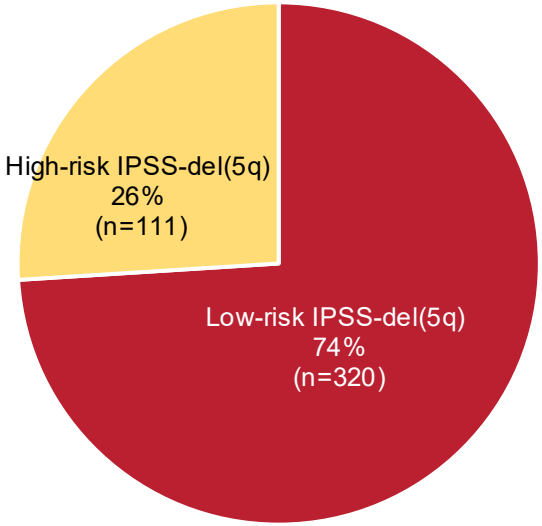
- **18.7% of MDS-del5q presented *TP53* mutations**
- **72.7%** were classified as *TP53*-monoallelic
- The most recurrent mutations were ***SF3B1* (21%),** *DNMT3A* (18%), *TP53* (18%), *TET2* (14%), *ASXL1* (10%), *CSNK1A1* (6%) and *JAK2* (6%)
- MDS-del5q with *TP53*-multihit mutations presented worse OS and higher risk to AML evolution compared to *TP53*-wt and *TP53*-monoallelic MDS-del5q
- ***TP53*-monoallelic MDS with a *TP53* VAF >20% showed similar prognosis to *TP53*-multihit patients** (median OS of 43.7 and 55.2 months, and AML evolution at 60 months of 36.7% and 40.4%, respectively)

Montoro MJ, et al. Presented at: 65th ASH Annual Meeting; December 9-12, 2023; San Diego, California. Abstract 1001.

IPSS-del(5q) Scoring System for Leukemia-Free Survival

LASSO-Cox analysis

Variable	Points
Sex, male	1
Hemoglobin ≤ 10 g/dL	2
Platelet ≤ 100 x10^9/L	2
≥ 2 additional mutations	2
SF3B1 mutations	1
HR-*TP53 status*	1



0-3 points	Standard-risk
>3 points	High-risk

Montoro MJ, et al. Presented at: 66th ASH Meeting; December 7-10, 2024; San Diego, California. Abstract 666.

Lenalidomide in MDS-del(5q)

Phase II MDS 003 Trial

FDA Approval: 12/17/2005

Patient Population

- ✓ *Low-risk, or intermediate-risk MDS (IPSS)*
- ✓ *5q31 deletion ± additional cytogenetic abnormalities*
- ✓ *Transfusion-dependent anemia*

Most Common Grade 3-4 AEs with Lenalidomide

- *Neutropenia (55%)*
- *Thrombocytopenia (44%)*
- *Anemia (7%)*
- *Leukopenia (6%)*
- *Rash (6%)*
- *Fatigue (3%)*
- *Febrile neutropenia (1%)*

Lenalidomide

N = 148

67%

Transfusion independence by week 24

76%

Total transfusion response by week 24

4.6 wk

Median time to response

Long-Term Outcomes

Median Follow-Up 3.2 yrs

2.2 years

Median duration of transfusion independence

AE = adverse event.

List AF, et al. *N Engl J Med*. 2006;355(14):1456-1465. List AF, et al. *Leukemia*. 2014;28(5):1033-1040.

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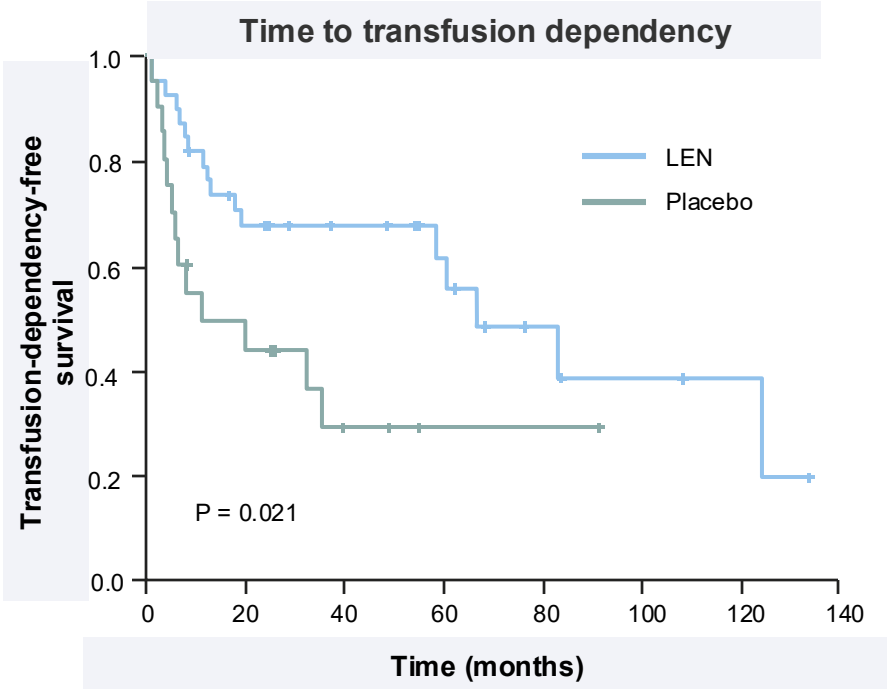
Sintra-REV: Phase 3, Multicenter Trial Investigating LEN versus Placebo in Non-Transfusion-Dependent LR-MDS del(5q) Patients

- Patients were randomized 2:1 to receive LEN 5 mg/day (n=40) or placebo (n=21) on days 1 to 28 of every 28-day cycle
- Treatment phase: 108 weeks
- Follow-up phase: 108 weeks
- Median follow-up: 60.6 months (IQR: 32.3-73.9)
- **Primary endpoint** (time to transfusion dependency)
  - LEN—66.3 months (95% CI: 37.0, 95.5)
  - Placebo—11.6 months (HR 0.414; 95% CI: 0.196, 0.875; *P*=0.021)



LEN = lenalidomide.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated February 15, 2023. Accessed June 2023. https://clinicaltrials.gov/study/NCT01243476. Cadenas FL, et al. Blood. 2022;140(Suppl. 1):1109-1111.

Lenalidomide Discontinuation: HARMONY Alliance Study (n=118)

- 42% of patients lost RBC-TI
- 48 patients were re-treated with LEN because of loss of response; 42 patients were evaluable for response and 28 of them (67%) achieved RBC-TI again

Prognostic factors for event-free survival on multivariate analysis

Variables	HR	95,0% CI		
		Lower	Upper	*P* value
Age at diagnosis*	1.04	1.01	1.07	0.005
RBC unit/8 weeks >4 at lenalidomide start	1.28	1.05	1.56	0,013
IPSS-R very low vs low/intermediate	0.33	0,16	0.70	0.004
Lenalidomide cycles ≥12	0.55	0.32	0.95	0.031
Hemoglobin level at lenalidomide stop*	0.82	0.69	0.98	0.028

RBC-TI = red blood cell-transfusion independence.
Crisà E, et al. *Leukemia*. 2024;38(10):2259-2265.

Case 2

- 68-year-old female, past medical history of HTN, presented to ER with shortness of breath; CBC WBC 4.0/ANC 2.0/HGB 7.0 g/dl/plat 270
- The patient received 2 units PRBC, and hematology consulted
- A bone marrow aspirate and biopsy performed revealing hypercellular bone marrow, erythroid dysplasia, no increased myeloblasts, and 30% ring sideroblasts
- Karyotype was normal; NGS revealed *SF3B1* K700E VAF 30%, *TET-2* VAF 30%
- IPSS-M: -0.87 (low), IPSS-R 2.5 (low)
- Endogenous erythropoietin level is 225 U/L

HTN = hypertension; ER = emergency room; PRBC = packed red blood cells.

Case 2

- How should this patient be treated?
  A. ESA
  B. Luspatercept
  C. Imetelstat
  D. Lenalidomide

Anemia Management: Luspatercept

Phase III MEDALIST Trial

FDA Approval: 04/06/2020

Patient Population

- ✓ *Very-low-risk, low-risk, or intermediate-risk MDS (IPSS-R) with ring sideroblasts*
- ✓ *Receiving regular RBC transfusions*

Most Common Grade 3-4 AEs with Luspatercept

- *Fatigue (5%)*
- *Asthenia (3%)*
- *Back pain (2%)*
- *Nausea (1%), headache (1%), arthralgia (1%), dyspnea (1%), bronchitis (1%), UTI (1%)*

Luspatercept N=153	Placebo N=76
38% Transfusion Independence ≥ 8 Weeks (Weeks 1-24)	13% Transfusion Independence ≥ 8 Weeks (Weeks 1-24)
28% Transfusion Independence ≥ 12 Weeks (Weeks 1-24)	8% Transfusion Independence ≥ 12 Weeks (Weeks 1-24)
33% Transfusion Independence ≥ 12 Weeks (Weeks 1-48)	12% Transfusion Independence ≥ 12 Weeks (Weeks 1-48)

***P*<.001 for all comparisons**

UTI = urinary tract infection.

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

Luspatercept for Frontline Treatment

Phase III COMMANDS Trial

Patient Population

- ✓ *Very-low-risk, low-risk, or intermediate-risk MDS (IPSS-R) with ring sideroblasts*
- ✓ *Require RBC transfusions*
- ✓ *ESA-naïve*

Most Common TRAEs with Luspatercept

- *Diarrhea (17.6%)*
- *COVID-19 (14.8%)*
- *Hypertension (15.9%)*
- *Asthenia (13.7%)*
- *Anemia (12.1%)*

FDA Approval: 08/28/2023

Luspatercept

N = 147

59%

RBC TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (wk 1-24)

Epoetin alfa

N = 154

31%

RBC TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (wk 1-24)

Response Rates from ASH 2023—Data cutoff 3/31/23

	Luspatercept	Epoetin alfa
Overall, n/N (%)	110/182 (60.4%)	63/181 (34.8%)
SF3B1 mutated, n/N (%)	80/114 (70.2%)	33/101 (32.2%)
SF3B1 non-mutated, n/N (%)	29/65 (44.6%)	26/72 (36.1%)
sEPO ≤ 200 U/L, n/N (%)	96/145 (66.2%)	59/144 (41.0%)
sEPO > 200 U/L, n/N (%)	14/37 (37.8%)	4/37 (10.8%)
RS positive, n/N (%)	87/133 (65.4%)	38/130 (29.2%)
RS negative, n/N (%)	23/49 (46.9%)	25/50 (50.0%)

Luspatercept

128.1 weeks

Median Duration of TI ≥ 12 wks

Epoetin alfa

89.7 weeks

Median Duration of TI ≥ 12 wks

HR 0.534 (95% CI, 0.330-0.864)

TRAE = treatment-related adverse event; sEPO = serum erythropoietin.

Garcia-Manero G, et al. Presented at: 65th ASH Annual Meeting; December 9-12, 2023; San Diego, California. Abstract 7003. Platzbecker U, et al. *Lancet.* 2023;402(10399):373-385. Della Porta MG, et al. Presented at: European Hematology Association (EHA) 2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S102. Garcia-Manero G, et al. *Blood.* 2023;142(Suppl 1):193.

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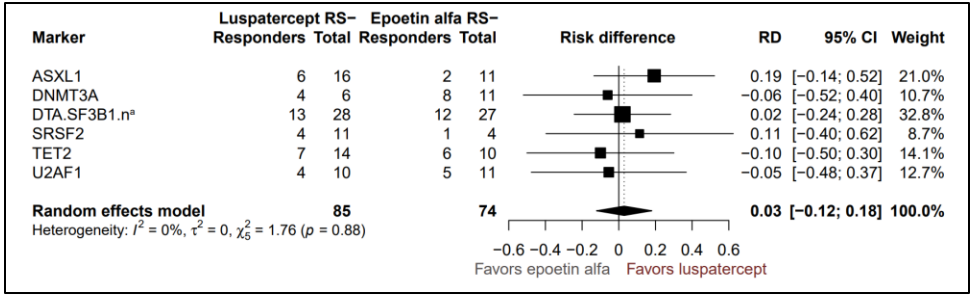
Results: Efficacy in the RS- Subgroup and by MB

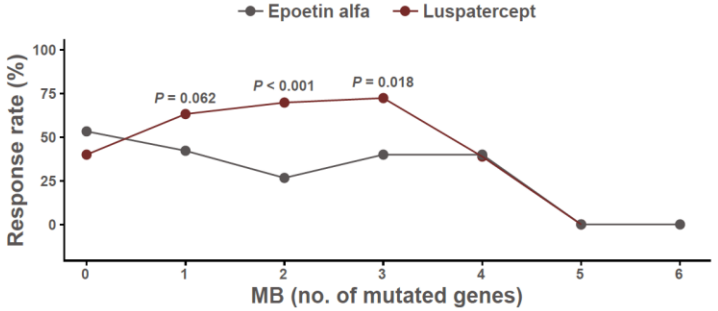
- Overall, both luspatercept and epoetin alfa performed equally well in the RS- subgroup; interestingly, there was no clear evidence of superiority of either agent observed in this subgroup (**Figure 3**)
  - Similar to the overall population, luspatercept showed a trend of better response in patients with an *ASXL1* mutation compared with ESAs in the RS- subgroup
- MB impacted responses to epoetin alfa
- In the overall population (and the RS+ subgroup), compared with epoetin alfa, luspatercept showed robust responses in patients with 1 (63% vs 42%; Fisher's *P*=0.062), 2 (70% vs 27%; Fisher's *P*<0.001), and 3 (72% vs 40%; Fisher's *P*=0.018) gene mutations (**Figure 4**)

Figure 3. Luspatercept showed similar benefit in patients who were RS- across multiple MDS-associated mutations



Solid vertical line represents absence of treatment effect (no favorability or benefit with treatment); dotted line represents overall favorability based on the random effects model. [a]*DTA.SF3B1.n* = *SF3B1* wt + *DNMT3A* mut or *TET2* mut or *ASXL1* mut.

Figure 4. Luspatercept showed broad activity across various baseline MBs



No. of patients (responders/total)							
Epoetin alfa	8/15	19/45	16/60	12/30	4/10	0/8	0/3
Luspatercept	6/15	31/49	44/63	21/29	7/18	0/5	0/0

MB = mutational burden.

Komrokji RS, et al. Presented at: 65th ASH Annual Meeting; December 9-12, 2023; San Diego, California. Abstract 4591.

Great Debates Hematologic Malignancies
from Lymphoma · Leukemia & Myeloma Congress

Activity of Luspatercept and ESAs Combination for Treatment of Anemia in Lower-Risk Myelodysplastic Syndromes

Baseline characteristics (n=28)	% (n)
Age (median)	72 (51-94)
Gender (male)	68(19)
Race (white)	96 (27)
MDS classification WHO 2016	
MDS-SLD	10.7 (3)
MDS-MLD	10.7 (3)
MDS-SLD-RS	32.1 (9)
MDS-MLD-RS	21.4 (6)
MDS del 5q	3.6 (1)
MDS/MPN-RS-T	21.4 (6)
R-IPSS	
Very low	21.4 (6)
Low	67.9 (19)
Intermediate	7.1 (2)
High	3.6 (1)
Hgb (mean) g/dl	8 (6.6-9.4)
Platelets (mean) $x10^9$/L	259 (16-814)
ANC (mean) $x10^9$/L	2.53 (.45-9.1)
Myeloblasts % (mean)	2 (0-4)
Serum erythropoietin level (median) U/L	119.5 (n=18)
RBC transfusion burden	
NTD	11 (3)
LTB	46 (13)
HTB	43 (12)
Prior ESA treatment	89 (24)
Prior HMA treatment	42 (12)
Prior Lenalidomide treatment	39 (11)
Somatic mutations	
SF3B1	85.7 (24)
TET-2	44 (12/27)
DNMT3A	22 (6/27)
ASXL-1	4 (1/27)
TP53	4 (1/27)
JAK-2	12 (3/27)

	% (n)
Overall response (n=28)	36 (10)
Hgb increase more than 1.5 g/dl in NTD or Hgb increase more than 1.5 g/dl with RBC-TI in RBC-TD	18 (5/28)
RBC-TI without Hgb 1.5 g/dl increase	14 (4/28)
>50% reduction in RBC-TB	4 (1/28)
Response in NTD (n=3)	
Hgb increase more than 1.5 g/dl	33 (1/3)
Response in LTB (n=13)	38 (5/13)
Hgb increase more than 1.5 g/dl and RBC-TI	15 (2/13)
RBC-TI without Hgb 1.5 g/dl increase	23 (3/13)
>50% reduction in RBC-TB	0
Response in HTB (n=12)	33 (4/12)
Hgb increase more than 1.5 g/dl and RBC-TI	17 (2/12)
RBC-TI without Hgb 1.5 g/dl increase	8 (1/12)
>50% reduction in RBC-TB	8 (1/12)

Predictors of response included

- Prior response to luspatercept monotherapy/or frontline combination compared to primary luspatercept failure
- Endogenous serum epo levels <500
- *SF3B1* mutation
- HMA/len treatment naïve

SLD = single lineage dysplasia; MLD = multilineage dysplasia; MPN-RS-T = myeloproliferative neoplasms with ring sideroblasts and thrombocytosis; NTD = not transfusion dependent; LTB = low transfusion burden; HTB = high transfusion burden.

Komrokji RS, et al. *Blood Adv*. 2023;7(14):3677-3679.

Great Debates Hematologic Malignancies
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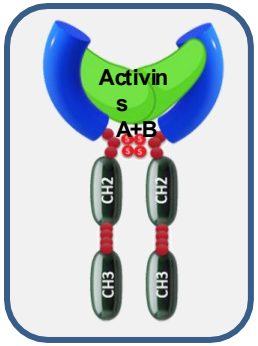
KER-050 (Elritercept) Is Designed to Target Bone Marrow Disorders of Ineffective Hematopoiesis Including MDS



KER-050 (elritercept)

Designed to inhibit select TGF-beta ligands, including **Activin A**, which has been associated with **ineffective hematopoiesis, disease** pathogenesis, and progression

Domain	Effect
Erythropoiesis	ALL stages of differentiation and maturation
Thrombopoiesis	ALL stages of differentiation and maturation
Bone	Increased bone formation
Iron metabolism	Improved iron utilization

- Preclinical data showed that **KER-050 (elritercept) acts on early and late stages of hematopoiesis**, supporting a differentiated MOA
- KER-050 has the potential to
  - Treat a broad range of patients with lower-risk (LR) MDS
  - Provide clinical benefit beyond improving hematopoiesis (Chee, et al. ASH 2023. Poster #1089)

Preliminary results from an ongoing open-label phase 2 trial evaluating KER-050 (elritercept) in participants with LR-MDS Presented ASH 2023 Diez-Campelo, et al.

TGF = transforming growth factor.

Verma A, et al. *J Clin Invest*. 2020;130(2):582-589. Portale F, et al. *Haematologica*. 2019;104(3):533-545. Feigenson M, et al. Presented at: EHA 2021 Congress; June 9-17, 2021; virtual. Abstract EP758.

Hematological Responses Observed in Broad Array of Participants

Responders/N (%)	$mITT_{24}$[a]		$mITT_{24}$ + EPO n < 500 U/L[b]	
	All (N=87)	HTB (N=51)	All (N=71)	HTB (N=39)
Overall Response[c]	48/87 (55.2)	25/51 (49)	43/71 (60.6)	22/39 (56.4)
Modified IWG 2006 HI-E[d]	42/87 (48.3)	24/51 (47.1)	37/71 (52.1)	21/39 (53.8)
RS+	33/59 (55.9)	19/35 (54.3)	29/52 (55.8)	16/30 (53.3)
non-RS	9/28 (32.1)	5/16 (31.3)	8/19 (42.1)	5/9 (55.6)
TI ≥8 weeks[e]	27/69 (39.1)	16/51 (31.4)	26/55 (47.3)	15/39 (38.5)
RS+	22/47 (46.8)	13/35 (37.1)	21/41 (51.2)	12/30 (40.0)
non-RS	5/22 (22.7)	3/16 (18.8)	5/14 (35.7)	3/9 (33.3)

- Overall response rates in participants with HTB were similar to those observed in the overall ($mITT_{24}$) population.
- Higher response rate was observed in the EPO < 500 U/L population, particularly in non-RS participants.

[a]Includes data for Weeks 0–24 in $mITT_{24}$ participants; [b]Includes data for Weeks 0–24 in $mITT_{24}$ participants with baseline EPO < 500 U/L, excluding one participant with del5q MDS. 9 $mITT_{24}$ participants (2 LTB RS+, 1 LTB non-RS, 4 HTB RS+, 2 HTB non-RS) had missing Baseline EPO measures and were conservatively classified as having EPO < 500 U/L. Two (both HTB, 1 RS+, 1 non-RS) of these 9 participants had EPO values ≥ 500 U/L post-baseline; both achieved a HI-E response, but not TI; [c]Defined as achieving modified IWG 2006 HI-E and/or TI; [d]Modified IWG 2006 HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC U/8 Wks (HTB) on treatment compared to 8-week pre-treatment period; [e]TI-evaluable participants received at least 2 RBC units in the 8-wk pre-treatment period.

Giagounidis A, et al. Presented at: 66th ASH Annual Meeting; December 7-10, 2024; San Diego, California. Abstract 1825.

Hot off the press—EHA update!

Overall Survival and Duration of Transfusion Independence for First-Line ESA-Naive Patients with Lower-Risk Myelodysplastic Syndromes Treated with Luspatercept versus Epoetin Alfa in the COMMANDS Trial

Valeria Santini,[1] Matteo Giovanni Della Porta,[2] Amer M. Zeidan,[3] Rami S. Komrokji,[4] Veronika Pozharskaya,[5] Shelonitda Rose,[5] Karen L. Keeperman,[5] Yinzhi Lai,[5] Sameer Kalsekar,[6] Barkha Aggarwal,[5] Dimana Miteva,[7] David Valcárcel,[8] Pierre Fenaux,[9] Jake Shortt,[10] Uwe Platzbecker,[11] Guillermo Garcia-Manero[12]

[1]University of Florence, Florence, Italy; [2]Cancer Center IRCCS Humanitas Research Hospital, Milan, Italy; Humanitas University, Milan, Italy;[3]Yale University School of Medicine, New Haven, CT, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5]Bristol Myers Squibb, Princeton, NJ, USA; [6]Bristol Myers Squibb, Hyderabad, Telangana, India; [7]Bristol Myers Squibb, Boudry, Switzerland; [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]Hôpital Saint-Louis, Université Paris 7, Paris, France; [10]Monash University and Monash Health, Melbourne, VIC, Australia; [11]University Hospital Leipzig, Leipzig, Germany; [12]University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

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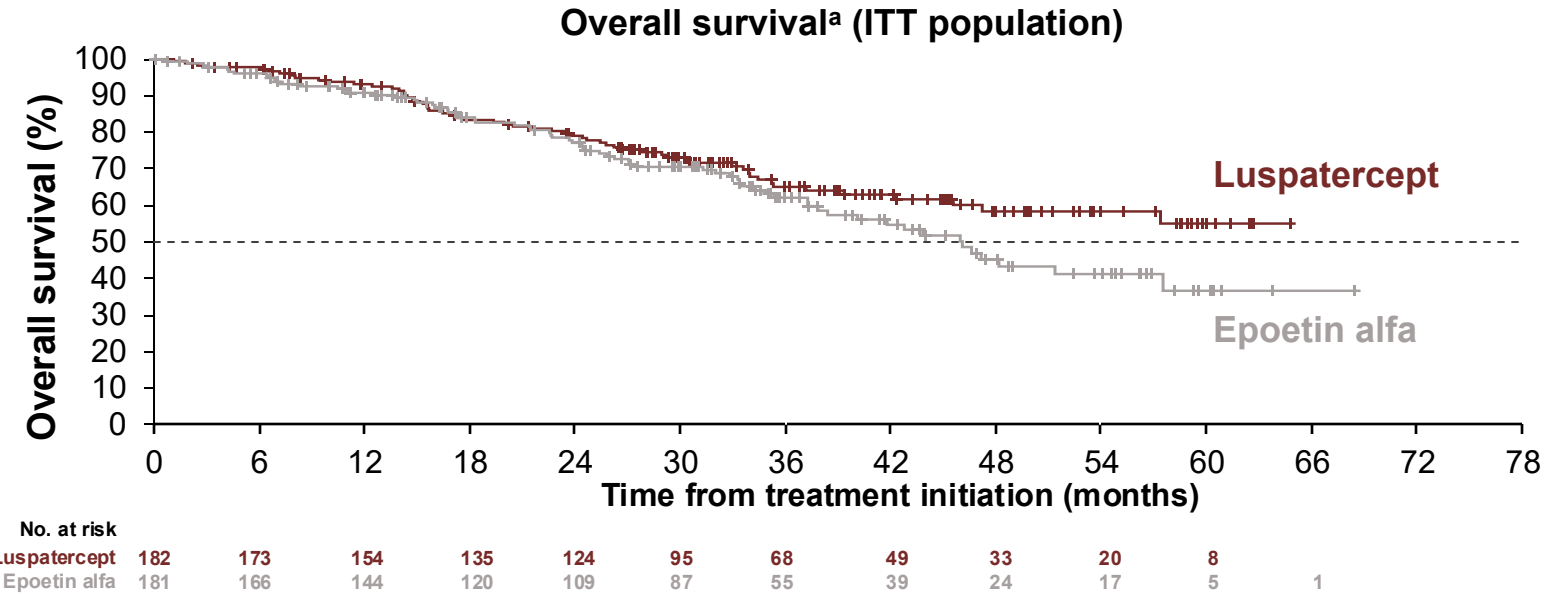
Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

COMMANDS: Overall Survival (>2.5 Years of Follow-Up)

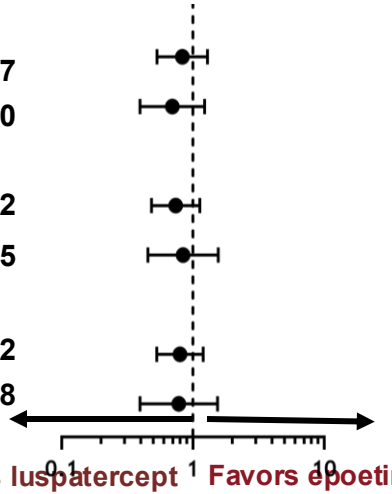


	Luspatercept	Epoetin alfa	HR (95% CI)[b]
Median OS,[c] months	NR	46.0	0.805 (0.565–1.146)

Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
[a]Overall survival is defined as the time between randomization and death of any cause. [b]HR (95% CI) is calculated by stratified Cox proportional hazard model. *P* value is from stratified log-rank test. [c]Median is from unstratified Kaplan-Meier method.
ITT = intention-to-treat.
Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

COMMANDS: Subgroup Analysis of Overall Survival (>2.5 Years of Follow-Up)

	Luspatercept		Epoetin alfa		
	Deaths, n/N (%)	Median OS[a] (months)	Deaths, n/N (%)	Median OS[a] (months)	HR (95% CI)[b]
Baseline TB (pRBC U/8 weeks)					
< 4	39/118 (33.1)	**NR**	39/111 (35.1)	**46.7**	0.830 (0.532-1.294)
≥ 4	20/64 (31.3)	**NR**	30/70 (42.9)	**46.0**	0.696 (0.395-1.227)
RS status					
RS+	41/133 (30.8)	**NR**	45/130 (34.6)	**47.2**	0.739 (0.484-1.130)
RS-	18/49 (36.7)	**NR**	23/50 (46.0)	**33.5**	0.842 (0.454-1.561)
Baseline sEPO (U/L)					
≤200	45/145 (31.0)	**NR**	48/144 (33.3)	**48.2**	0.797 (0.530-1.197)
>200	14/37 (37.8)	**39.4**	21/37 (56.8)	**34.8**	0.781 (0.396-1.540)



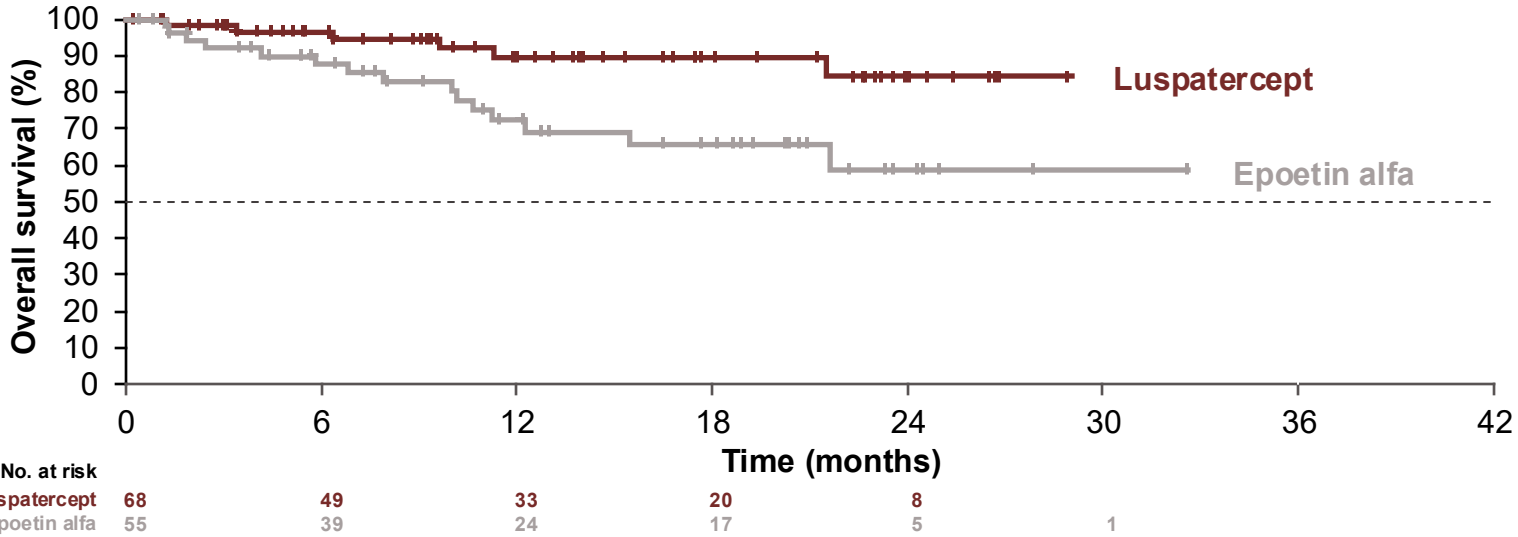
Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

[a]Median is from unstratified Kaplan-Meier method. [b]HR is calculated by unstratified Cox proportional hazard model.

Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

COMMANDS: Landmark Analysis of Overall Survival (≥36 Months)

Landmark analysis of overall survival[a] from 36 months after randomization



	Luspatercept	Epoetin alfa	HR (95% CI)[b]
Median OS,[c] months	NR	NR	0.330 (0.128–0.852); *P* = 0.0161

Data cutoff: February 7, 2025. Median follow-up (range) 30.6 (1-65) months for luspatercept arm and 28.8 (0-69) months for epoetin alfa.
[a]Overall survival is defined as the time between the landmark (ie, 36 months after randomization) and death of any cause. [b]HR (95% CI) is calculated by stratified Cox proportional hazard model.
P value is from stratified log-rank test. [c]Median is from unstratified Kaplan-Meier method.
Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

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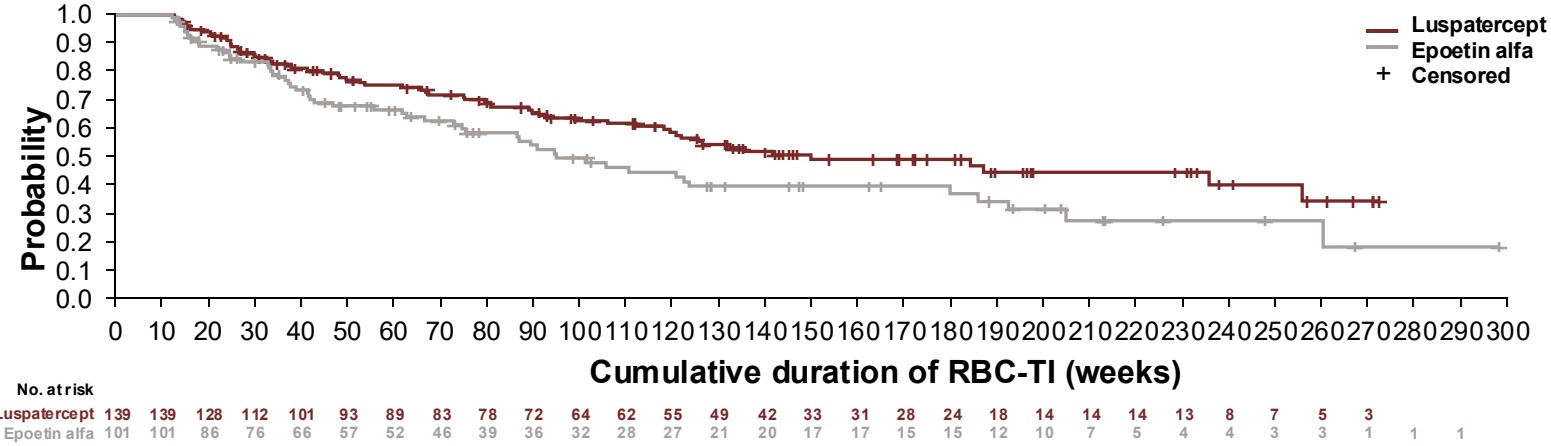
COMMANDS: RBC-TI ≥ 12 Weeks (Week 1-EOT) (> 2.5 Years of Follow-Up)

	Luspatercept	Epoetin alfa	OR[a]/HR[b] (95% CI)
RBC-TI ≥ 12 weeks response rate, % (n/N)	76.4 (139/182)	55.8 (101/181)	OR,[a] 2.8 (1.7-4.5); *P*<0.0001
Median (95% CI) duration,[c] weeks			
Duration of the longest RBC-TI ≥ 12-week period[d]	126.6 (81.0-154.1)	86.7 (55.9-105.9)	HR,[b] 0.632 (0.434-0.919); *P*=0.0156
Cumulative duration of RBC-TI ≥ 12 weeks[e]	150.0 (119.6-256.0)	95.1 (74.9-180.1)	HR,[b] 0.523 (0.353-0.777); *P*=0.0011

Cumulative duration of RBC-TI ≥ 12 weeks (ITT population)[e]



Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
EOT = end of treatment; RBC-TB = red blood cell transfusion burden.
[a]Based on Cochran-Mantel-Haenszel test stratified by baseline RBC TB, RS status, and sEPO levels. One-sided *P* value is presented.
[b]HR is calculated by stratified Cox proportional hazard model. *P* value is from stratified log-rank test. [c]Median is from unstratified Kaplan-Meier method. [d]Duration of RBC-TI ≥12 weeks is defined as the longest RBC-TI period from week 1 to EOT. [e]Cumulative duration is defined as the sum of all durations of RBC-TI ≥12-week episodes from week 1 through EOT.
Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

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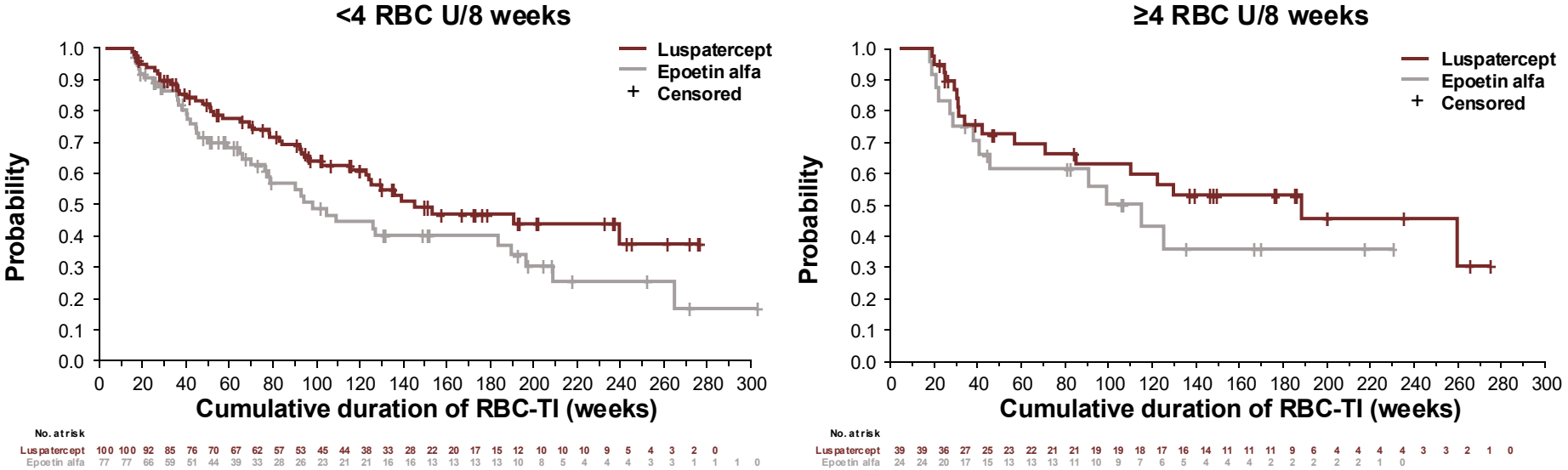
COMMANDS: Cumulative Duration of RBC-TI ≥12 Weeks (Week 1-EOT) by Baseline TB (>2.5 Years of Follow-Up)

Cumulative duration of RBC-TI ≥ 12 weeks (ITT population)[a]



Median (95% CI) duration,[b] weeks	Luspatercept	Epoetin alfa	HR (95% CI)[c]
< 4 RBC U/8 weeks	141.9 (119.6-NE)	95.1 (66.7-186.1)	0.671 (0.438-1.028)
≥ 4 RBC U/8 weeks	184.4 (66.9-NE)	110.9 (33.9-NE)	0.687 (0.332-1.421)

Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
[a]Cumulative duration is defined as the sum of all durations of RBC-TI ≥12 weeks episodes from week 1 through EOT.
[b]Median is from unstratified Kaplan-Meier method. [c]HR is calculated by unstratified Cox proportional hazard model.
Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

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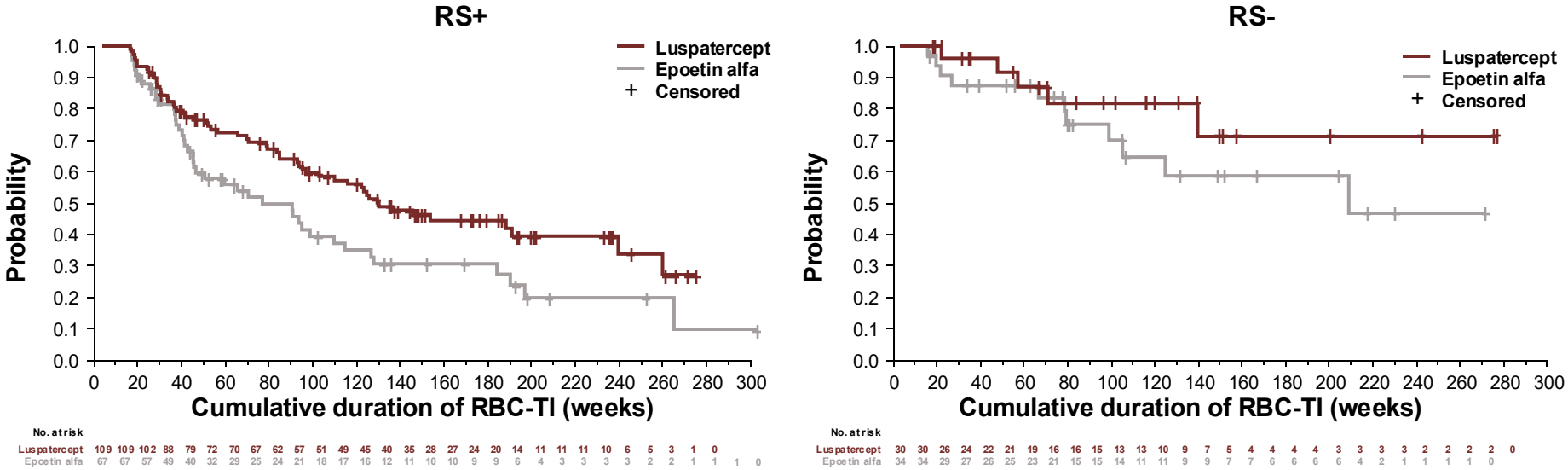
COMMANDS: Cumulative Duration of RBC-TI ≥12 Weeks (Week 1-EOT) by RS Status (>2.5 Years of Follow-Up)

Cumulative duration of RBC-TI ≥ 12 weeks (ITT population)[a]



Median (95% CI) duration,[b] weeks	Luspatercept	Epoetin alfa	HR (95% CI)[c]
RS+	126.6 (93.0-235.9)	73.1 (41.6-110.9)	0.614 (0.413-0.914)
RS-	NE (135.9-NE)	205.1 (95.1-NE)	0.531 (0.184-1.530)

Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.

[a]Cumulative duration is defined as the sum of all durations of RBC-TI ≥12 weeks episodes from week 1 through EOT. [b]Median is from unstratified Kaplan-Meier method. [c]HR is calculated by unstratified Cox proportional hazard model.

Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

COMMANDS: Summary of Disease Progression (> 2.5 Years of Follow-Up)

	Luspatercept (n = 182)	Epoetin alfa (n = 179)
Progression to HR-MDS,[a] n (%)	**4 (2.2)**	**10 (5.6)**
HR-MDS incidence rate per 100 PY[b] (95% CI)	0.85 (0.32-2.26)	2.41 (1.30-4.48)
HR (95% CI)[c]	0.388 (0.120-1.250); *P*=0.1003	
Median time to HR-MDS progression from treatment start date (95% CI), months	NE (NE–NE)	NE (NE–NE)
Progression to AML,[d] n (%)	**9 (4.9)**	**8 (4.4)**
AML incidence rate per 100 PY[b] (95% CI)	1.91 (1.00-3.68)	1.91 (0.95-3.81)
HR (95% CI)[c]	1.110 (0.420-2.932); *P*=0.8326	
Median time to AML progression from initial MDS diagnosis (95% CI), months	NE (132.1-NE)	NE (NE-NE)

Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
[a]Higher-risk category comprises high- and very high-risk categories per IPSS-R. [b]PY is calculated from the treatment start date to HR-MDS onset date or from the randomization date to AML onset date, or to the last follow-up date for patients without progression to HR-MDS or AML. [c]HR (95% CI) is calculated by stratified Cox proportional hazard model; *P* value is calculated from stratified log-rank test. [d]Based on ITT population.
PY = patient years.
Santini V, et al. Presented at: EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S177.

Case 3

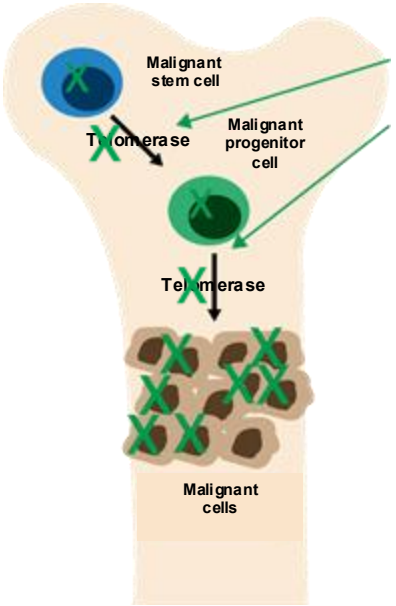
- 74-year-old gentleman, past medical history of CAD diagnosed originally with MDS-MLD, blasts 3%; normal karyotype, *NGS TET-2/DNMT3A;* CBC at diagnosis Hgb 9 g/dl, plat 200, ANC 2000, EPO 64 U/L
- *IPSS-M: -0.99 (low), IPSS-R (AA) 3.14 (INT)*
- The patient was started on erythropoietin 40,000; Hgb improved originally but after one year on escalated-dose treatment Hgb progressively decreased, and patient became RBC-TD requiring 2 units PRBC every 3 weeks
- Repeat bone marrow no disease progression or clonal evolution

CAD = coronary artery disease.

Case 3 Discussion

- How would you treat this patient at this point?
  A. Azacitidine 5 days' regimen
  B. Decitabine 3 days' regimen
  C. Lenalidomide
  D. Imetelstat
  E. Luspatercept

New Mechanisms in LR-MDS: Imetelstat



Imetelstat is an oligonucleotide, competitive enzyme inhibitor that binds and blocks the active site of the enzyme.

- Selectively targets malignant cells with continuously upregulated telomerase, inducing their apoptosis (cell death), and enabling potential recovery of normal hematopoiesis
- Potent activity in myeloid malignancies, including a study that included patients with MDS-RS

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Tefferi A, et al. *Blood Cancer J.* 2016;6(3):e405.

IMerge Phase 3 Trial: Imetelstat in Patients with LR-MDS Relapsed/Refractory to ESA or EPO

Phase 3, double-blind randomized trial

- IPSS low- or intermediate-1 risk MDS
- R/R[a] to ESA or EPO >500 milliunits/mL (ESA-ineligible)
- TD: ≥4 units RBCs/8 wk over 16-wk pre-study
- Non-del(5q)
- No prior treatment with lenalidomide or HMAs

ITT N = 178

R 2:1

Imetelstat 7.5 mg/kg IV/4 wk (n=118)

Placebo (n=60)

Supportive care, including RBC and platelet transfusions, myeloid growth factors (eg, G-CSF), and iron chelation therapy administered as needed in study per investigator discretion

- **Stratified by:** Transfusion burden (4-6 vs >6 units) and IPSS risk category (low vs intermediate-1)
- **Primary endpoint**: 8-week RBC-TI[b]
- **Key secondary endpoints:** 24-wk RBC-TI[b], duration of TI, hematologic improvement (erythroid), and safety
- **Key exploratory endpoints:** VAF changes and PRO (fatigue measured by FACIT-Fatigue)

[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 units, epoetin beta ≥30,000 units, or darbepoetin alfa 150 mcg or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 units/8 weeks or TD or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment. [b]Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).
R/R = relapsed/refractory; G-CSF = granulocyte colony stimulating factor; FACIT = Functional Assessment of Chronic Illness Therapy.
Zeidan AM, et al. *J Clin Oncol*. 2023;41(16 Suppl):7004.

Great Debates Hematologic Malignancies
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Imetelstat

Phase III IMerge Trial

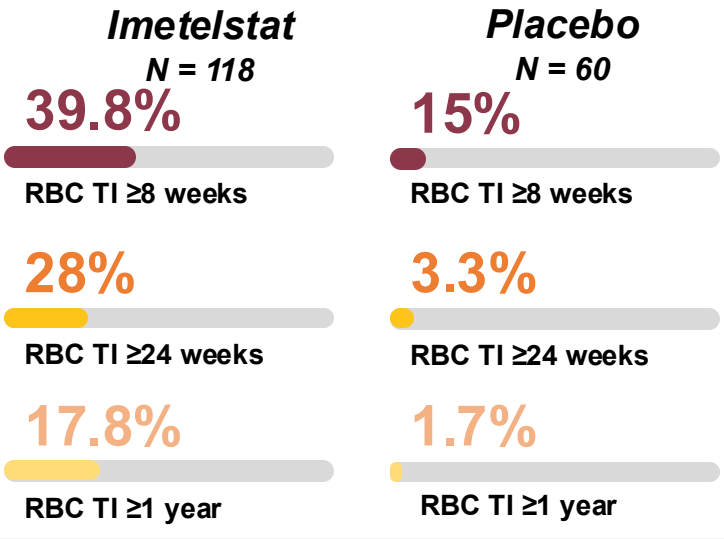
Patient Population

- ✓ *Low-risk or intermediate-risk MDS (IPSS) with ring sideroblasts*
- ✓ *Require RBC transfusions*

Most Common Grade 3/4 AEs with Imetelstat

- *Thrombocytopenia (62%)*
- *Neutropenia (68%)*
- *Anemia (19%)*
- *Leukopenia (8%)*

FDA Approval: 06/06/24



Superior RBC-TI response rates in patients with SF3B1, TET2, ASXL1, DNMT3a, or CUX1 mutations treated with imetelstat

1-year RBC-TI	Imetelstat	Placebo
IPSS		
Low	10/80 (12.5%)	1/39 (2.6%)
Int-1	5/38 (15.8%)	0/21 (0%)
IPSS-R		
Very low	0/3 (0%)	0/2 (0%)
Low	10/87 (11.5%)	1/46 (2.2%)
Int	4/20 (20.0%)	0/8 (0%)
IPSS-M		
Very low/low	10/69 (14.5)	0/33 (0%)

Zeidan AM, et al. *J Clin Oncol*. 2023;41(16 Suppl):7004. Santini V, et al. Presented at: EHA 2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S164. Platzbecker U, et al. Presented at: EHA 2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S165. Komrokji RS, et al. *Blood*. 2023;142(Suppl 1):194. Santini V, et al. Presented at: 65th ASH Annual Meeting; December 9-12, 2023; San Diego, California. Abstract 4603. Platzbecker U, et al. *Blood*. 2023;142(Suppl 1):4605. Platzbecker U, et al. *Lancet*. 2024;403(10423):249-260.

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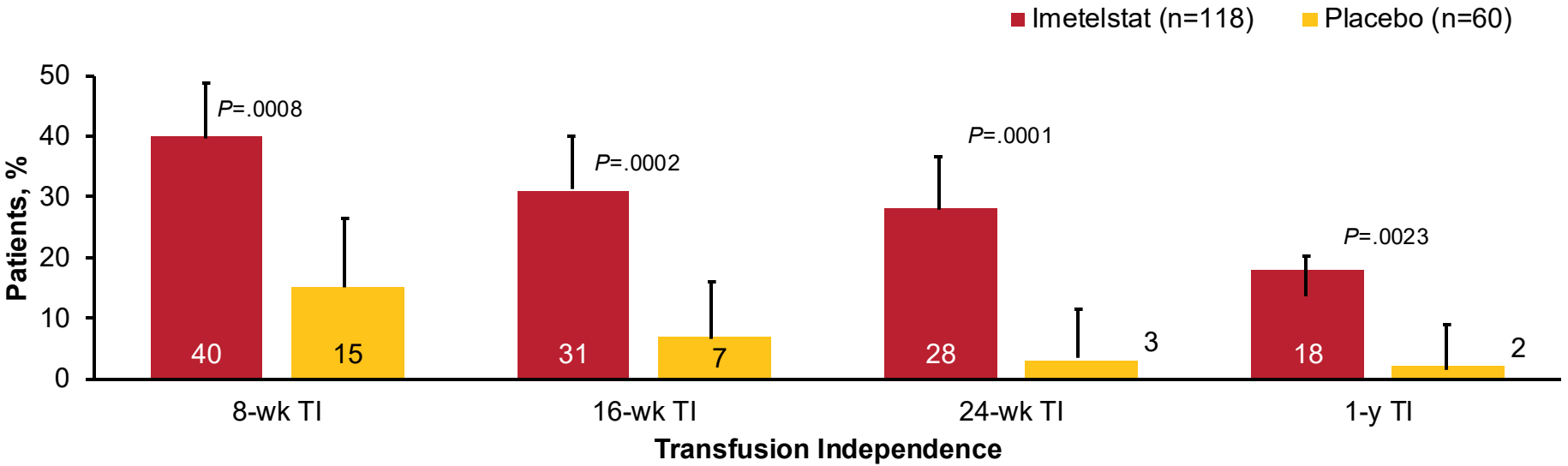
Higher Rates of Longer-Term Duration of RBC-TI Observed with Imetelstat vs Placebo



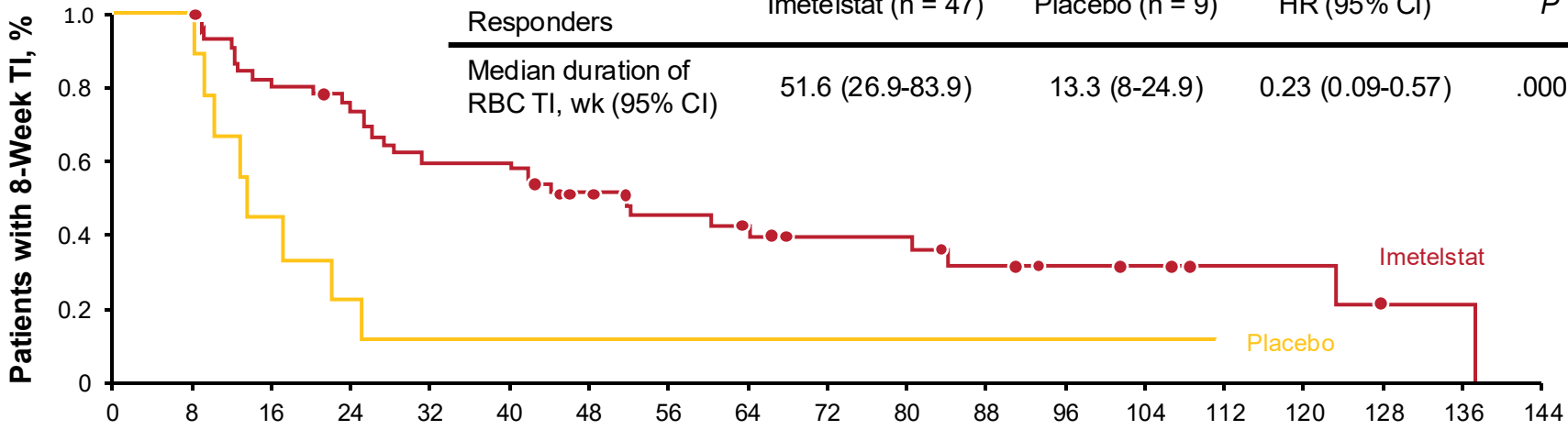
Patients with Response, n (% [95% CI])

Imetelstat	47 (39.8 [30.9-49.3])	37 (31.4 [23.1-40.5])	33 (28.0 [20.1-37.0])	16 (13.6 [8-21.1])
Placebo	9 (15 [7.1-26.6])	4 (6.7 [1.9-16.2])	2 (3.3 [0.4-11.5])	1 (1.7 [0.0-8.9])

Zeidan AM, et al. *J Clin Oncol.* 2023;41(16 Suppl):7004. Platzbecker U, et al. *Lancet.* 2024;403(10423):249-260.

Imetelstat 8-Week RBC-TI Responders Have Significantly Longer Duration of Transfusion Independence vs Placebo

8-Week TI Responders	Imetelstat (n = 47)	Placebo (n = 9)	HR (95% CI)	*P*
Median duration of RBC TI, wk (95% CI)	51.6 (26.9-83.9)	13.3 (8-24.9)	0.23 (0.09-0.57)	.0007



No. at Risk																		
Imetelstat	7	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0

Zeidan AM, et al. *J Clin Oncol.* 2023;41(16 Suppl):7004. Platzbecker U, et al. *Lancet.* 2024;403(10423):249-260.

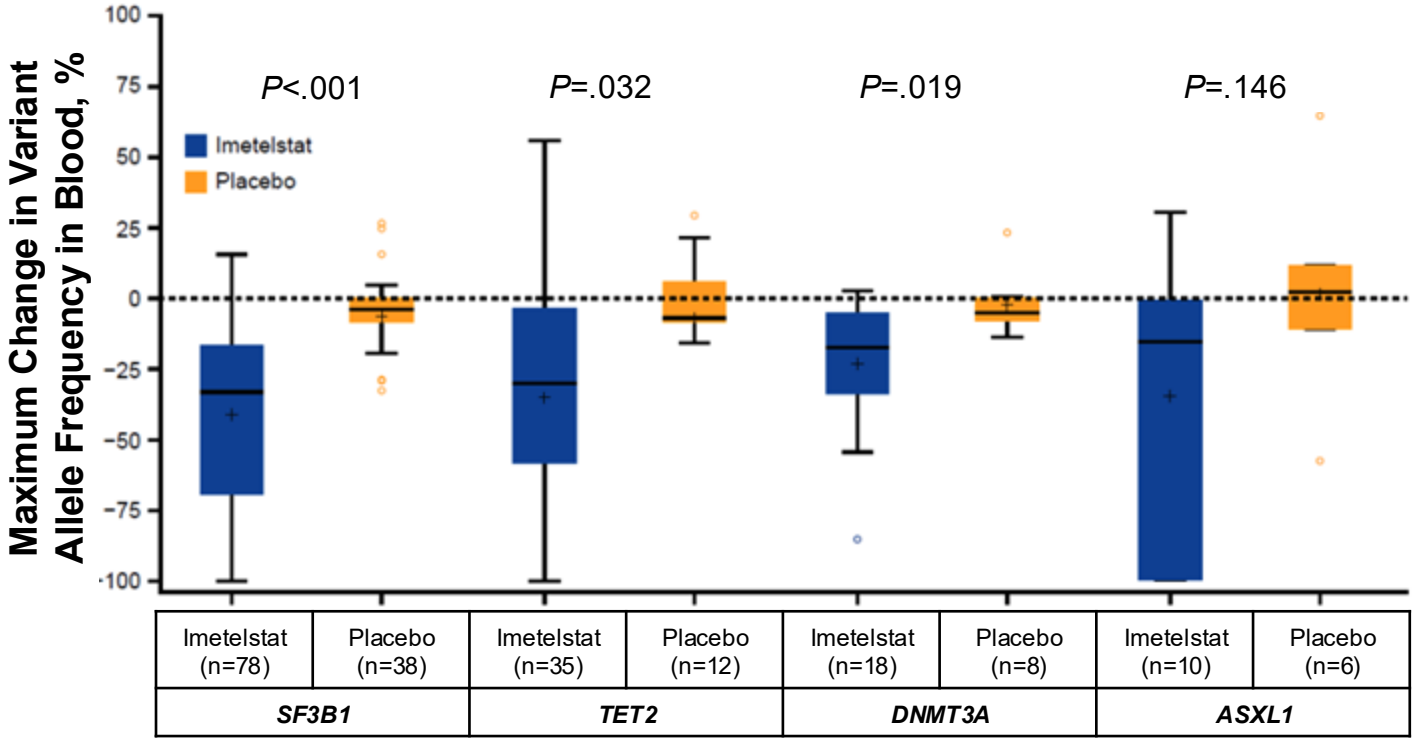
Consistent with Prior Clinical Experience, the Most Common AEs Were Hematologic[a]

- Grade 3-4 thrombocytopenia and neutropenia were the most frequently reported AEs and were most often reported during cycles 1-3
  - There were no fatal hematologic AEs
- Nonhematologic AEs were generally low-grade
- Although ~75% of patients treated with imetelstat had dose modifications due to AEs, <15% of patients discontinued treatment due to TEAEs
- No cases of Hy's law or drug-induced liver injury were observed
  - The incidence of grade 3 liver function test laboratory abnormalities was similar in both treatment groups

AE (≥10% of patients), n (%)	Imetelstat (n = 118)		Placebo (n = 59)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematologic				
Thrombocytopenia	89 (75)	73 (62)	6 (10)	5 (8)
Neutropenia	87 (74)	80 (68)	4 (7)	2 (3)
Anemia	24 (20)	23 (19)	6 (10)	4 (7)
Leukopenia	12 (10)	9 (8)	1 (2)	0
Other				
Asthenia	22 (19)	0	8 (14)	0
COVID-19	22 (19)[b]	2 (2)[c]	8 (14)[b]	3 (5)[c]
Headache	15 (13)	1 (1)	3 (5)	0
Diarrhea	14 (12)	1 (1)	7 (12)	1 (2)
ALT increased	14 (12)	3 (3)	4 (7)	2 (3)
Edema peripheral	13 (11)	0	8 (14)	0
Hyperbilirubinemia	11 (9)	1 (1)	6 (10)	1 (2)
Pyrexia	9 (8)	2 (2)	7 (12)	0
Constipation	9 (8)	0	7 (12)	0

[a]Data cutoff: October 13, 2022. [b]Included COVID-19, asymptomatic COVID-19, and COVID-19 pneumonia. [c]Only COVID-19 pneumonia events were grade 3-4 COVID-19.
ALT = alanine aminotransferase.
Zeidan AM, et al. *J Clin Oncol*. 2023;41(16 Suppl):7004. Platzbecker U, et al. *Lancet*. 2024;403(10423):249-260.

Reduction in VAF with Imetelstat Therapy Correlated with Longer Duration of TI and Increased Hb



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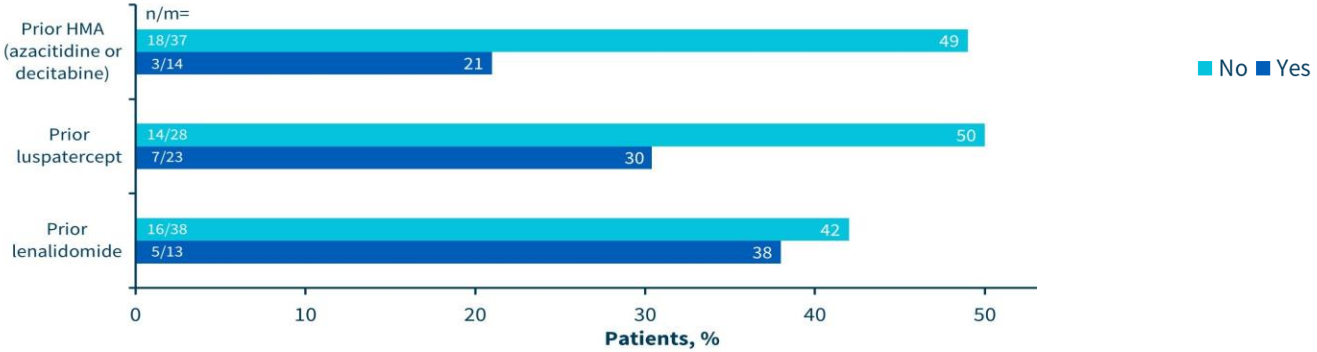
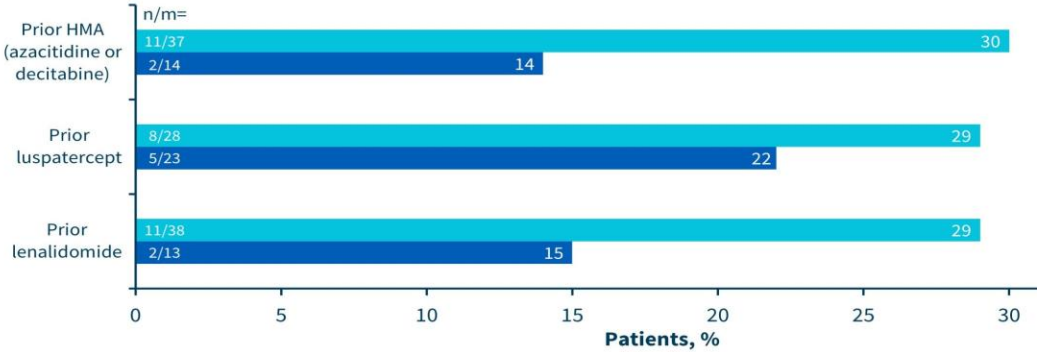
Platzbecker U, et al. *Lancet*. 2024;403(10423):249-260.

Response to Imetelstat Based on Prior Therapies

≥8-week RBC-TI



≥24-week RBC-TI



Komrokji RS, et al. Presented at: 66th ASH Annual Meeting; December 7-10, 2024; San Diego, California. Abstract 4590.

Case 4

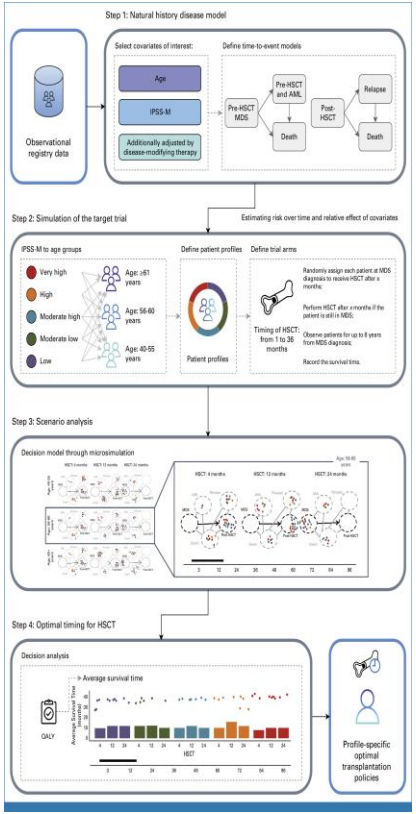
- 63-year-old gentleman, no significant past medical history, presented with fatigue, and SOB to local ER; CBC revealed WBC 3000, ANC 2.0, Hgb 7.2 g/dl, platelets 30
- A bone marrow aspirate and biopsy was obtained, hypercellular bone marrow, 3% myeloblasts, karyotype del 12p (good)
- NGS: *TET-2* mutation VAF 30%; *RUNX1* mutation VAF 20%

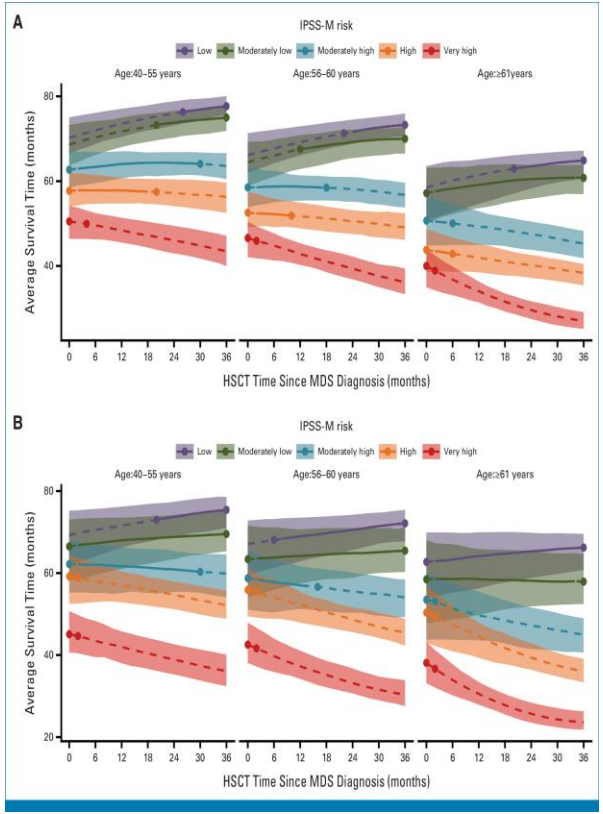
SOB = shortness of breath.

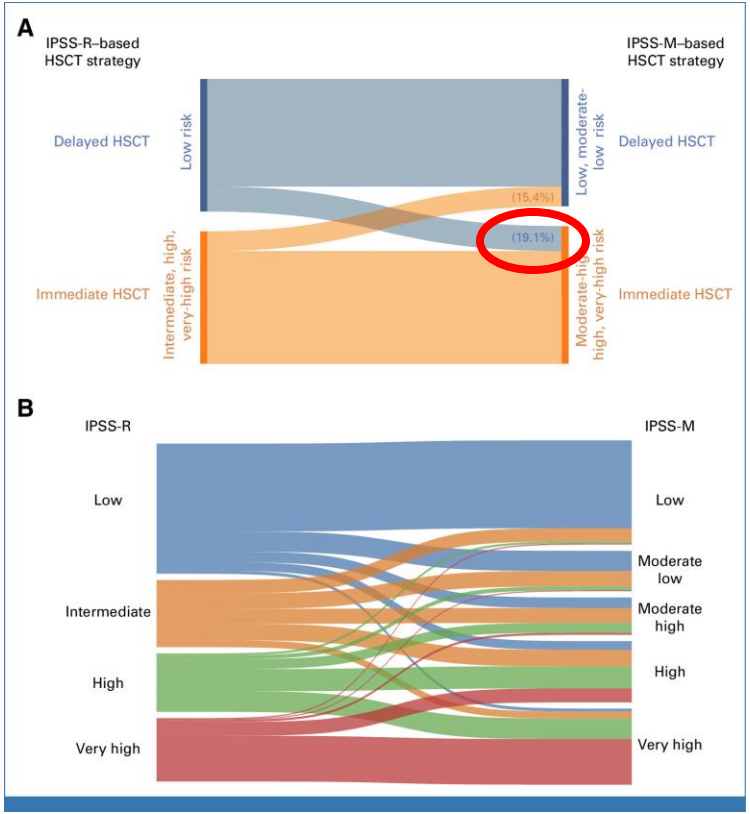
Case 4

- How do you treat this patient?
  A. ESA
  B. Luspatercept
  C. Imetelstat
  D. Hypomethylating agent
  E. Hypomethylating agent and consideration of AHSCT

Comparison of IPSS-R versus IPSS-M for Timing of Allo-SCT







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Tentori CA, et al. *J Clin Oncol.* 2024;42(24):2873-2886.

Targeting R/R *IDH1*/*IDH2*^{mut} MDS with Ivosidenib/Enasidenib

IDIOME: Phase 2 study of Ivo in 3 cohorts (N=26)[1]

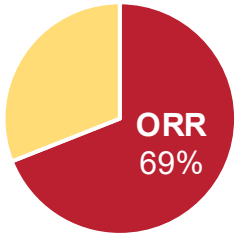
- **A**: HR-MDS, failed AZA (n=13)
- **B**: Untreated HR-MDS (n=11)
- **C**: LR-MDS, failed EPO (n=2)

Median follow-up: 9.1 months

Median DoR: 7.4 months

Median OS: 14 months

Differentiation syndrome, n=4, febrile neutropenia, n=1



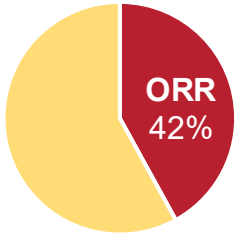
IDEAL: Phase 2 study of Ena in 3 cohorts (N=26)[2]

- **A**: HR-MDS, failed AZA (n=11)
- **B**: Untreated HR-MDS (n=9)
- **C**: LR-MDS, failed ESA (n=6)

Median follow-up: 8.6 months

Median OS: 17.3 months

Differentiation syndrome, n=3; nausea/diarrhea, n=4; thrombocytopenia, n=5



Ivosidenib in R/R *IDH1*/*IDH2*^{mut} MDS[3]

Updated results of a phase 1 dose-escalation study (500 mg QD)

Efficacy outcomes	N=16
ORR	81%
CR	44%
mCR	31%
PR	6%
HI	69%
12-month duration CR+PR	60%

Safety outcomes	N=16
Grade ≥3 AEs	69%
Grade ≥3 TRAEs	13%
SAEs	44%

Both studies reported 50% response in LR-MDS.

AZA = azacitidine; DoR = duration of response; ORR = objective response rate; SAE = serious adverse event; CR = complete response; mCR = metabolic complete response; PR = partial response.

Sebert M, et al. *Blood*. 2021;138(Suppl 1):62. Ades L, et al. *Blood*. 2021;138(Suppl 1):63. Sallman DA, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, Illinois. Abstract 7053/Poster 284.

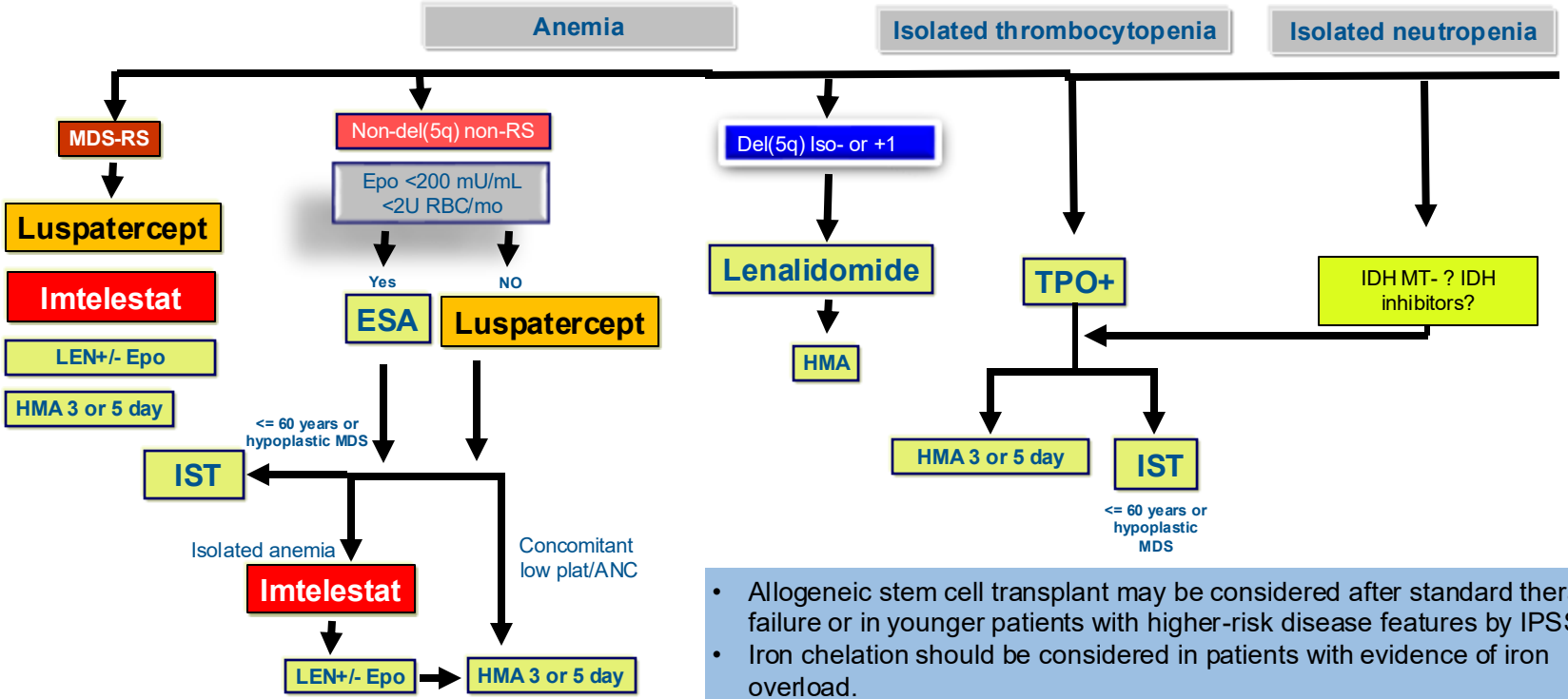
Update on VERONA Trial for Newly Diagnosed Higher-Risk Myelodysplastic Syndromes

"…[T]he global phase 3 VERONA trial evaluating venetoclax in combination with azacitidine in the treatment of newly diagnosed higher-risk myelodysplastic syndrome (HR-MDS) did not meet the primary endpoint of overall survival (OS) with a hazard ratio (HR) of 0.908; stratified log-rank, *P*=0.3772. No new safety signals were observed. Results from the VERONA trial will be available in a future medical congress and/or publication. Any patients who received venetoclax in combination with azacitidine through participation in the MDS clinical trials will be informed by their treating physician."

- 14 days ven too long of a duration, too toxic?
- Lack of efficacy?
- Different biology of MDS vs AML

Yahoo!Finance [finance.yahoo.com]. Last updated June 16, 2025.
https://finance.yahoo.com/news/abbvie-provides-verona-trial-newly-130000574.html.

How I Treat LR-MDS in 2025



- Allogeneic stem cell transplant may be considered after standard therapy failure or in younger patients with higher-risk disease features by IPSS-M
- Iron chelation should be considered in patients with evidence of iron overload.

SGM = somatic gene mutation; IST = immune-suppressive therapy; TPO = thyroid peroxidase; IDH = isocitrate dehydrogenase.

Adapted and modified from Volpe VO, Komrokji RS. *Ther Adv Hematol*. 2021;12:2040620720986641.

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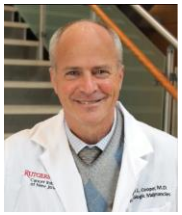
Key Learning Points

- Imetelstat is recommended for patients with low- or intermediate-1 risk MDS relapsed/refractory to ESA or EPO
- Based on IMerge trial criteria, high-risk MDS and del(5q) mutation would exclude a patient from imetelstat therapy for MDS
- Luspatercept therapy is appropriate for ESA-naïve patients with transfusion-dependent, low-risk MDS
- Low-risk, transfusion-independent MDS patients reporting increasing fatigue and reduced ability to perform daily activities may benefit from initiation of ESAs

Cell Therapy, Transplant, and Heme Malignancy Team at Montefiore

Amit Verma, MD
Director, Hematology



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For slide contributions!

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