Treatment of Lower-risk MDS

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Disclosures

- CTI Biopharma, Servier Pharmaceuticals, Geron

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[1-5]

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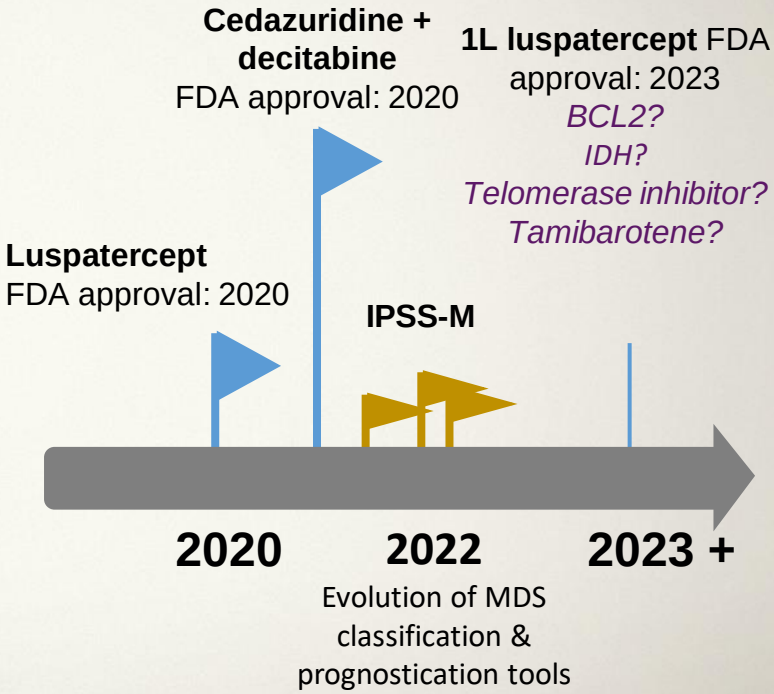
Newer MDS classifications and prognostic tools



1. Platzbecker U et al. N Eng J Med. 2020;382:140-151. 2. Garcia-Manero G et al. Blood. 2020;136:674-683. 3. Garcia-Manero G et al. Blood. 2021;138:66. 4. Bernard E et al. NEJM Evid. 2022;1(7). 5. Platzbecker U et al. Lancet. 2023;402:373-385.

Clinical Consult: Presenting with Anemia

Robert is a 75-year-old man presenting to clinic with fatigue (referred by primary care)

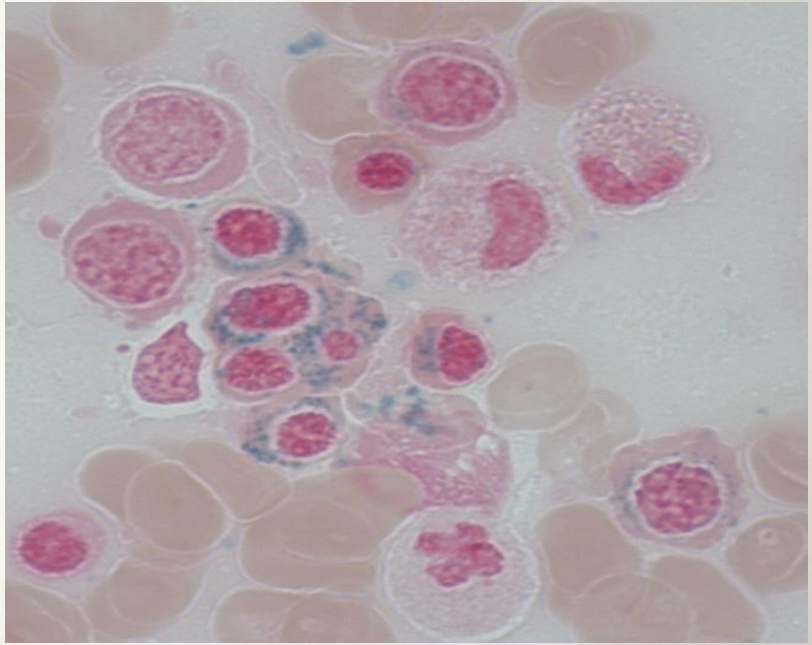
- **Anemia (Hb: 8.5 g/dL over 6 months)**
- Platelets: 250
- ANC: 5,000

What tests should be considered to confirm MDS and rule out other syndromes when assessing anemia?

Clinical Consult: Next Steps for Robert

MDS confirmed based on additional testing

- **Anemia (Hb: drops to 7.5 g/dL over 3 months)**
- Platelets: 250
- ANC: 5,000
- No bleeding or nutritional deficiencies
- **18% RS with erythroid dysplasia**
- 2% BM blasts
- *SF3B1* H662D mutation



Ring sideroblasts

Clinical Consult: Treatment Options for Robert

LR-MDS confirmed by IPSS-M:

Transfusion burden of 6 RBC units over a 2-month period

- **Anemia (Hb: now 6.5 g/dL)**
- Platelets: 150,000
- ANC: 2,000
- No bleeding or nutritional deficiencies
- 18% RS with erythroid dysplasia
- 2% BM blasts
- *SF3B1* H662D mutation

Is this patient considered to be transfusion dependent?
In 2023, what would your next step have been?

Classically, Management of Anemia in MDS Centered on ESA Therapy and Transfusion

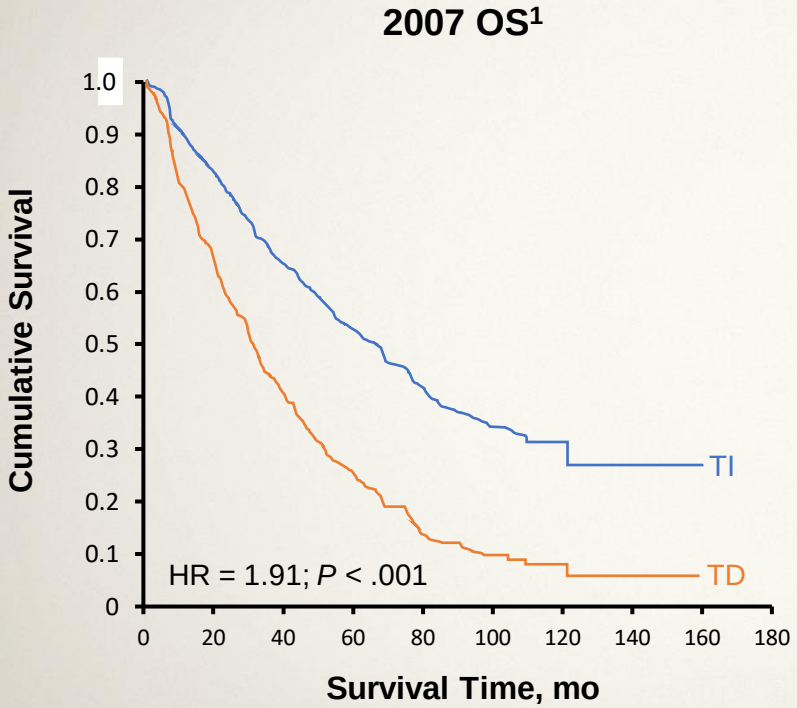
ESA (part of MDS anemia treatment guidelines, although not approved in the United States for MDS)

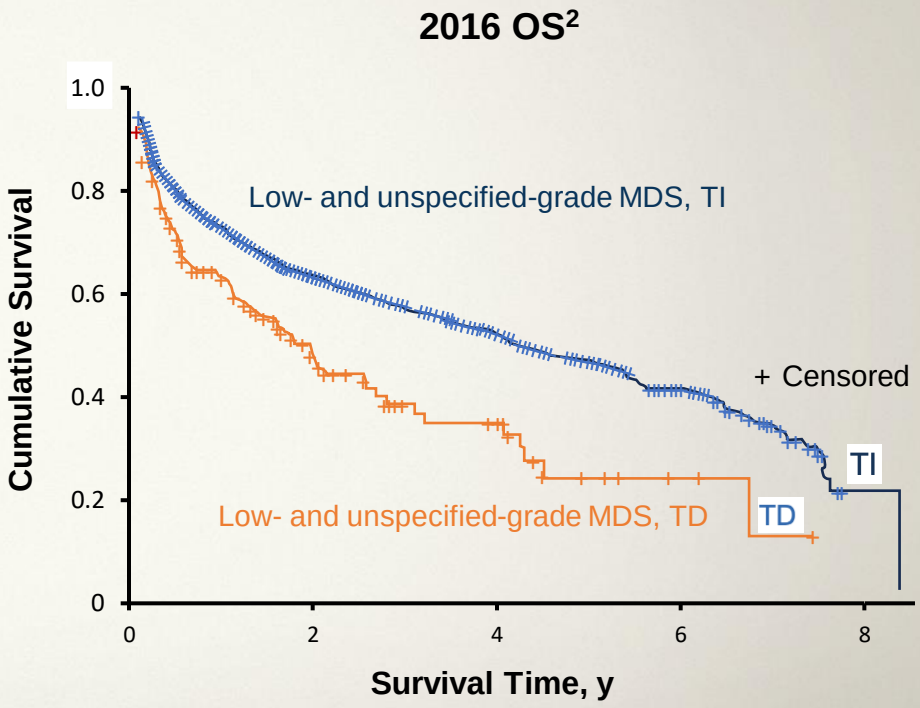
- Larger doses may be necessary
- Loss of effect over time

RBC transfusion

- Iron overload risk
- Burden on patients and rare infection risk
- Transfusion dependency and increased risk of AML transformation

In LR-MDS, the Impact of Transfusion Dependence (TD) On Survival Has Been a Long-Standing Challenge





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1. Malcovati L. *Leuk Res*. 2007;31(suppl 3):S2-S6. 2. Mehra M et al. *Blood*. 2016;128:5974.

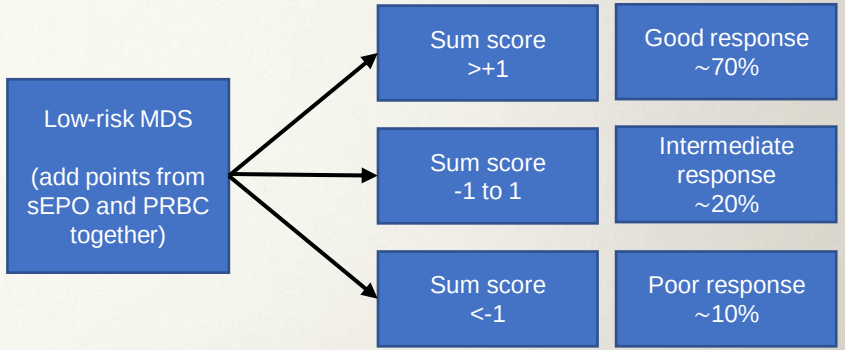
Characterizing ESA Resistance and Refractory Status

Primary resistance to ESA is frequent[1]

- Relapse in 70% of cases, likely due to loss of sensitivity of erythroid progenitors to ESAs
- Median DOR for ESA treatment is 18 to 24 months

Scoring System for Prediction of Response to ESA-Based Therapy in MDS Patients[2]

Feature	Range	Points Assigned
sEPO, units/L	<100	+2
	100-500	+1
	>500	-3
Transfusion pRBC, units/mo	<2	+2
	≥2	-2



✓ Higher sEPO and transfusion burden are hallmarks of ESA failure/poor response

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1. Kubasch AS, Platzbecker U. *Int J Mol Sci*. 2019;20:3853. 2. Hellström-Lindberg E et al. *Br J Haematol*. 2003;120:1037-1046.

Clinical Consult: What if Robert Had Presented with ESA-Refractory Disease?

Assume Robert received ESA therapy for anemia after diagnosis

Initial diagnosis of LR-MDS (RS) with anemia

Treatment:

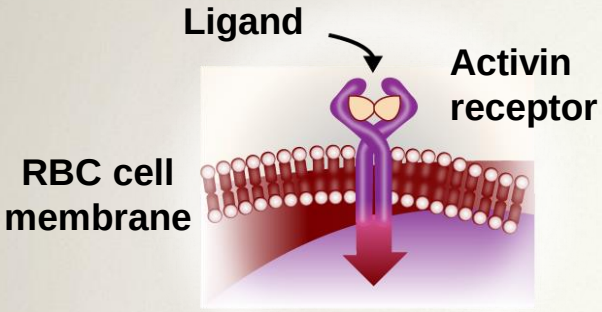
- ESA and RBC transfusion
- After 14 months, **transfusion requirement increased to 6 units/month** (+ ↑ sEPO)

Is this considered ESA failure? Or is more time on therapy needed?

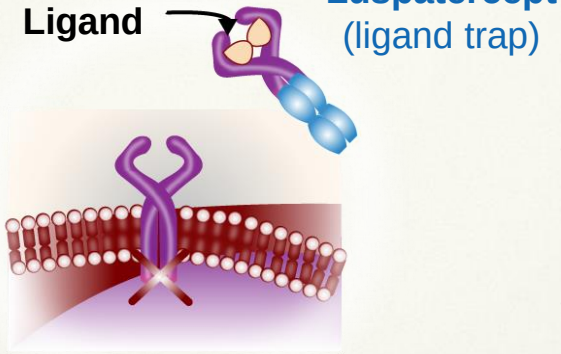
What are the available options in the ESA-refractory setting?

- Luspatercept?
- Imetelstat?
- Lenalidomide?
- Oral cedazuridine/decitabine?

Enhancing Late-Stage Erythropoiesis to Alleviate Anemia[1-3]



Smad2 phosphorylation
Inhibits RBC maturation



Smad2 signaling inhibited
Promotes RBC maturation

- Luspatercept is a fusion protein that consists of a modified activin receptor (ActRIIB)—a member of the TGFβ superfamily—and the Fc of human IgG1
- Inhibits Smad2/3 signaling and traps GDF8, GDF11, and ActB
- Stimulates RBC production

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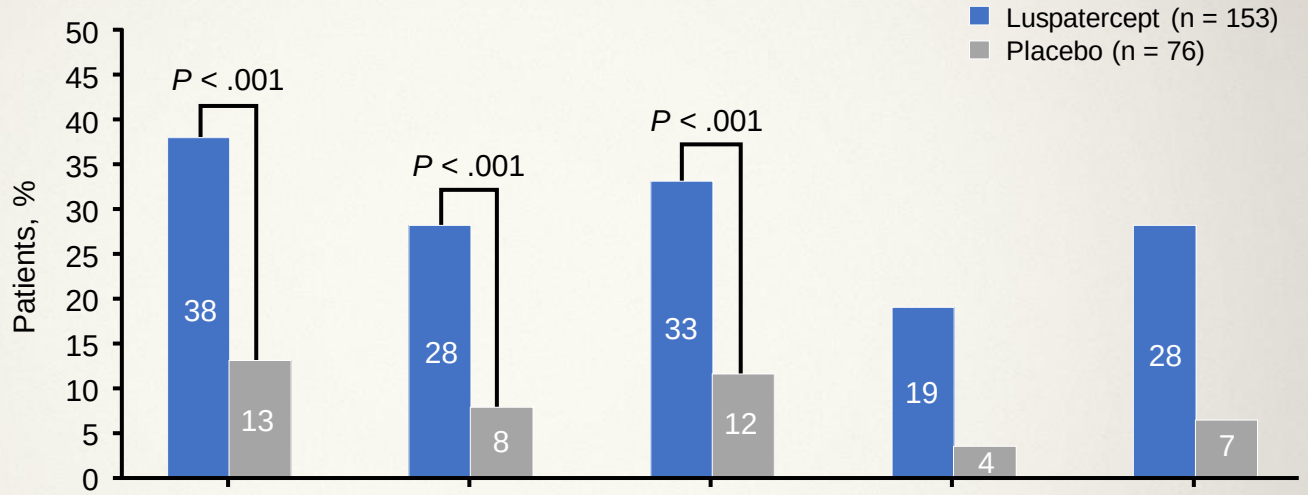
1. Piga A et al. EHA 2018. Abstract S844. 2. Attie K et al. *Am J Hematol.* 2014;89:766-770. 3. Suragani R et al. *Nat Med.* 2014;20:408-414.

MEDALIST: Red Cell Transfusion Independence With Luspatercept in MDS-RS[1]



No. of patients with response (% [95% CI])	≥8 wk (Wk 1-24)	≥12 wk (Wk 1-24)	≥12 wk (Wk 1-48)	≥16 wk (Wk 1-24)	≥16 wk (Wk 1-48)
Luspatercept	58 (38 [30-46])	43 (28 [21-36])	51 (33 [26-41])	29 (19 [13-26])	43 (28 [21-36])
Placebo	10 (13 [6-23])	6 (13 [3-16])	6 (12 [6-21])	3 (4 [1-11])	5 (7 [2-15])

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1. Fenaux P et al. *N Engl J Med.* 2020;382:140-151.

MEDALIST: RBC-TI ≥8 Weeks[1,2]

RBC-TI ≥8 Weeks Over the Entire Treatment Period	Luspatercept (n = 153)	Placebo (n = 76)	Luspatercept Minus Placebo	
			OR (95% CI)[a]	*P*[a]
Average baseline RBC transfusion requirement, n/N (%)				
≥6 U/8 weeks	14/66 (21.2)	2/33 (6.1)	4.17 (.98-19.6)	.0547
≥4 to <6 U/8 weeks	20/41 (48.8)	2/23 (8.7)	10 (2.07-48.28)	.0013
<4 U/8 weeks	39/46 (84.8)	8/20 (40)	8.36 (2.51-27.83)	.0002

More luspatercept-treated patients achieved RBC-TI ≥8 weeks over the entire treatment period compared with those receiving placebo, regardless of baseline transfusion burden

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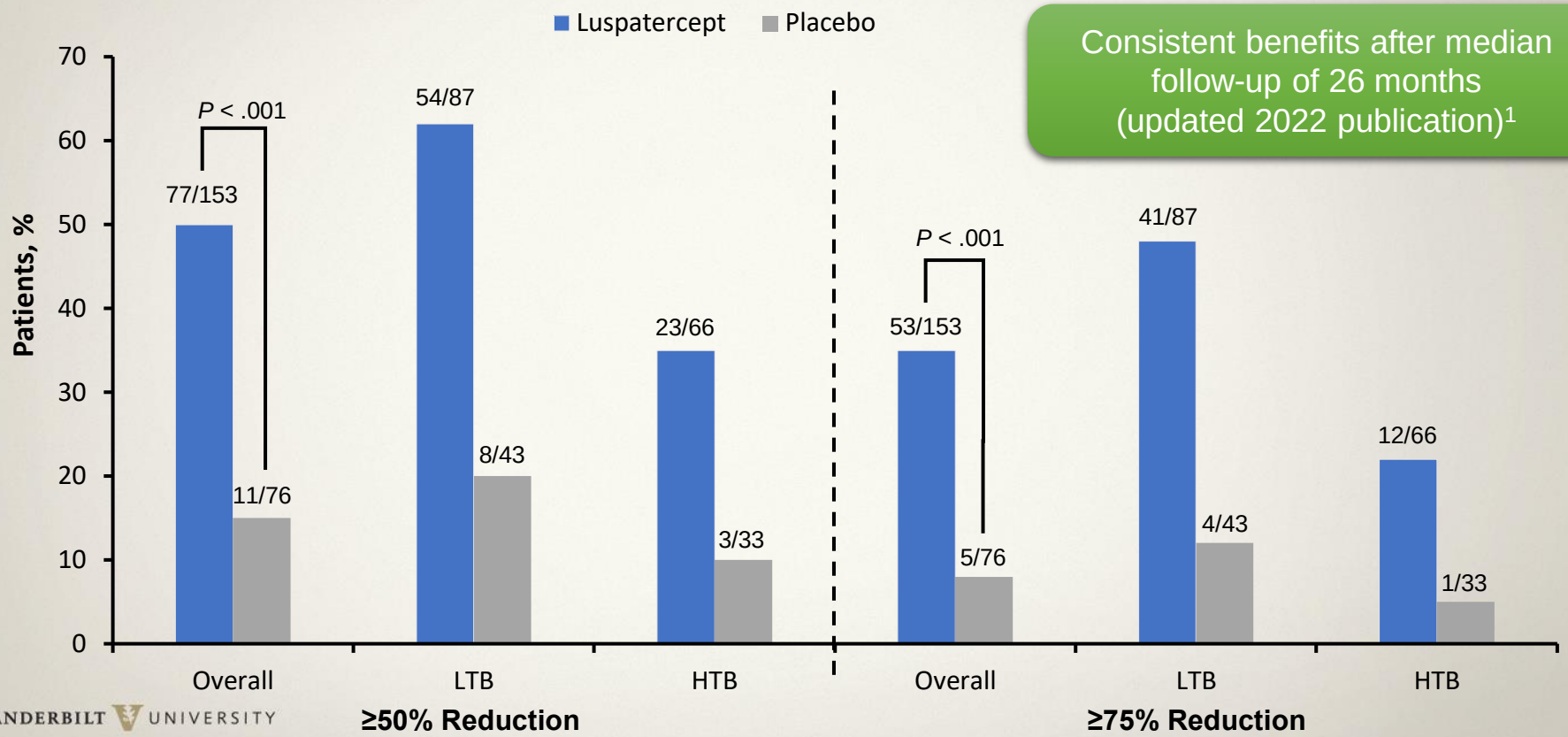
[a] Determined using a Cochran-Mantel-Haenszel test.

1. Fenaux P et al. *N Engl J Med.* 2020;382:140-151. 2. Fenaux P et al. ASH 2019. Abstract 841.

MEDALIST: Longer-Term Evidence Confirms Substantial Reduction in Transfusion Burden With Luspatercept



Consistent benefits after median follow-up of 26 months (updated 2022 publication)[1]

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1. Zeidan AM et al. *Blood.* 2022;140:285-289.

Phase 3 COMMANDS Trial Tested Luspatercept vs Epoetin Alfa as *Upfront* Management of MDS[1]

- Aged ≥18 y
- IPSS-R very low-, low-, or intermediate-risk MDS (with or without RS) by WHO 2016, with <5% blasts in BM[a]
- Required RBC transfusions (2-6 pRBC units/ 8 wk for a minimum of 8 wk immediately prior to randomization)
- Endogenous sEPO <500 units/L
- ESA-naïve

R 1:1

Luspatercept (n = 178)
1.0 mg/kg SC every 3 wk
titration up to 1.75 mg/kg

Epoetin alfa (n = 178)[b]
450 units/kg SC every wk
titration up to 1,050 units/kg

Response assessment at d 169 and every 24 wk thereafter

EOT
Due to lack of clinical benefit[c] or disease progression per IWG criteria

- **Patients stratified by:** baseline sEPO level, baseline RBC transfusion burden, and RS status
- **Post-treatment safety follow-up**
  - Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, and survival
  - For 5 y from first dose or 3 y from last dose, whichever is later

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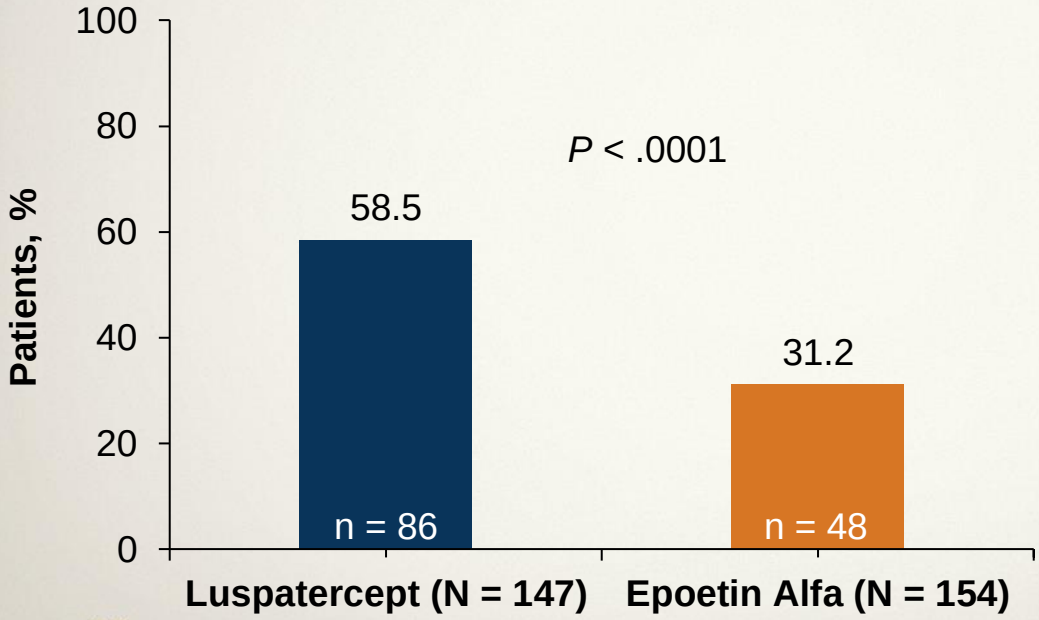
[a] MDS with del(5q) were excluded. [b] Two patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose. [c] Clinical benefit defined as transfusion reduction of ≥2 pRBC units/8 wk versus baseline.

1. https://clinicaltrials.gov/ct2/show/NCT03682536.

COMMANDS Primary Endpoint: Luspatercept Superior to Epoetin Alfa[1,2]

- Of 301 patients included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) receiving epoetin alfa achieved the primary endpoint



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

August 2023: FDA approval of luspatercept to treat anemia in ESA-naïve adults with very low- to intermediate-risk MDS who may require regular RBC transfusions

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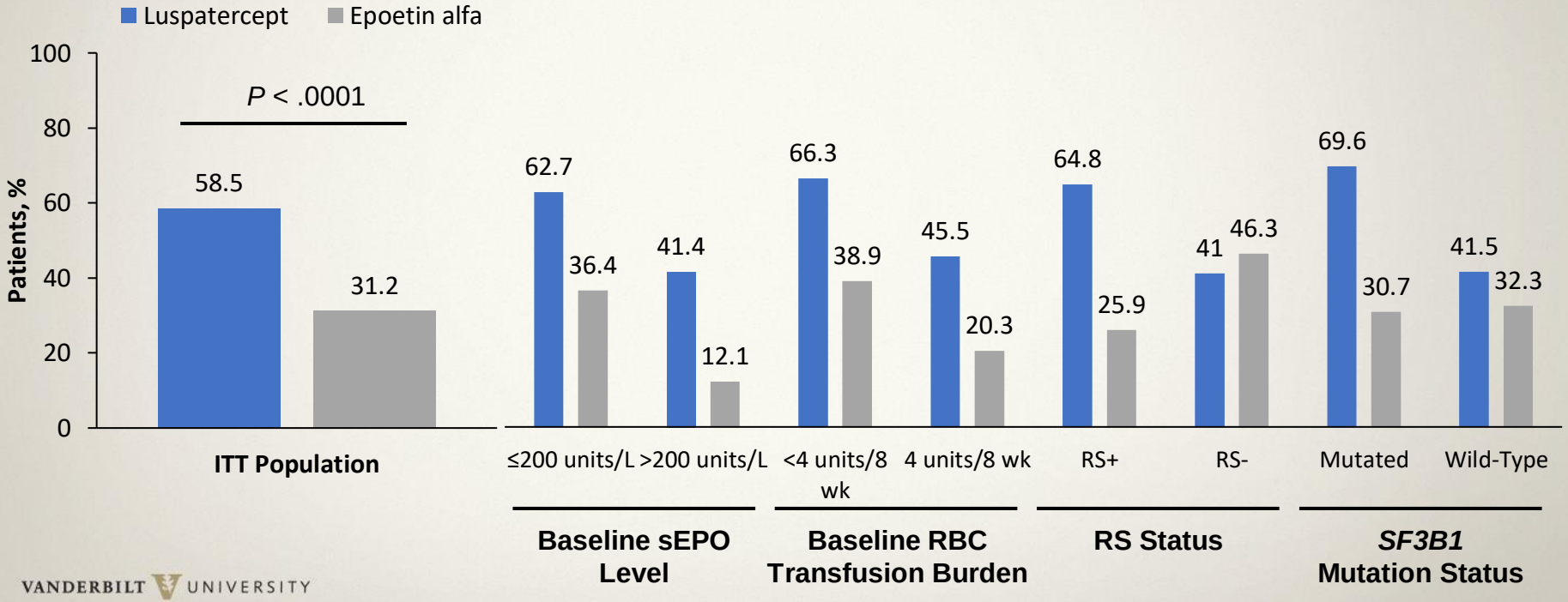
1. Garcia-Manero G et al. ASCO 2023. Abstract 7003. 2. Platzbecker U et al. *Lancet.* 2023;402:373-385.

Luspatercept and RBC-TI Across Subgroups[1,2]

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



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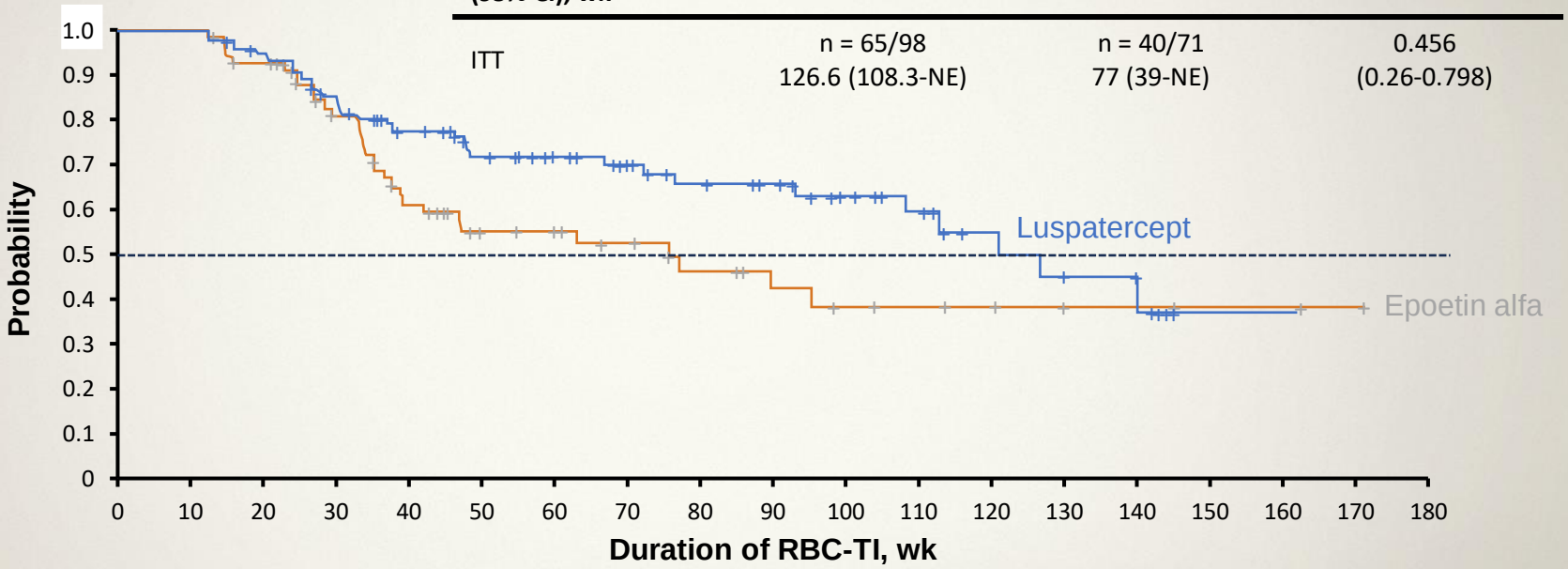
1. Garcia-Manero G et al. ASCO 2023. Abstract 7003. 2. Platzbecker U et al. *Lancet.* 2023;402:373-385.

Prolonged Duration of RBC-TI with Luspatercept vs Epoetin Alfa[1,2]

Duration, Median (95% CI), wk	Luspatercept	Epoetin Alfa	HR (95% CI)
ITT	n = 65/98 126.6 (108.3-NE)	n = 40/71 77 (39-NE)	0.456 (0.26-0.798)



No. at Risk																			
Luspatercept	98	98	91	74	61	49	42	37	31	28	21	17	11	8	6	1	1	0	0
Epoetin alfa	71	71	63	47	33	24	23	19	15	11	9	8	7	5	5	2	2	1	0

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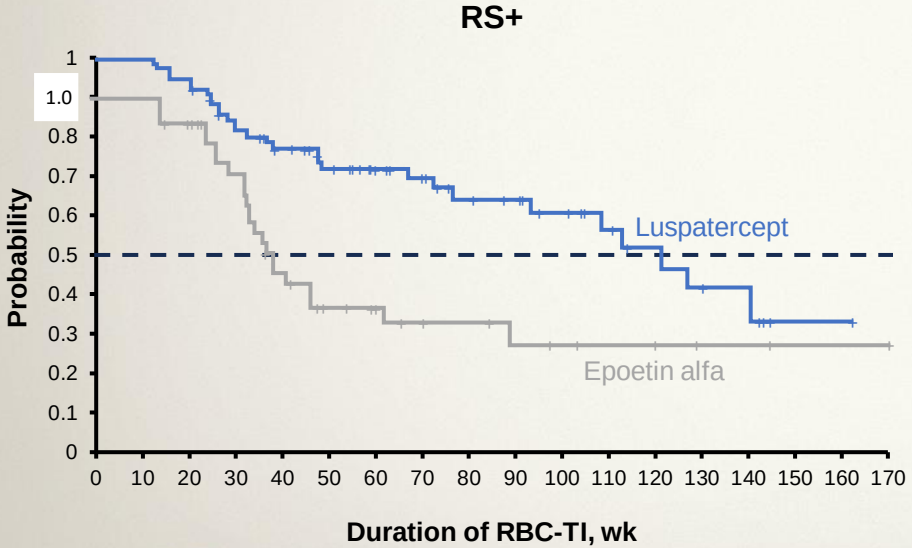
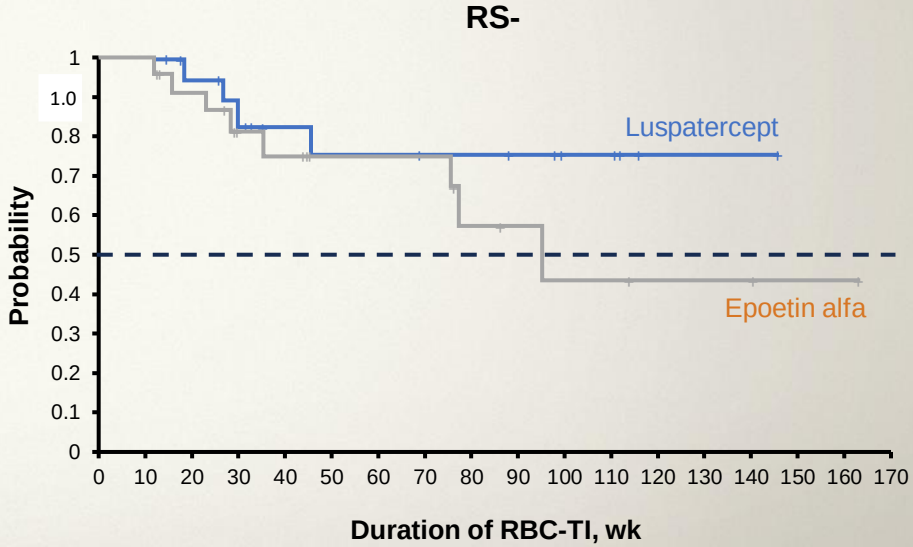
1. Garcia-Manero G et al. ASCO 2023. Abstract 7003. 2. Platzbecker U et al. *Lancet.* 2023;402:373-385.

COMMANDS: DOR in RS+ and RS- Settings[1,2]

Duration, Median (95% CI), wk	Luspatercept	Epoetin Alfa	HR (95% CI)
RS+	n = 48/77 120.9 (76.4-NE)	n = 25/48 47.0 (36.6-NE)	0.626 (0.361-1.085)
RS-	n = 17/21 NE (46-NE)	n = 15/23 95.1 (35.3-NE)	0.492 (0.148-1.638)





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1. Garcia-Manero G et al. ASCO 2023. Abstract 7003. 2. Platzbecker U et al. *Lancet.* 2023;402:373-385.

Clinical Consult: Treatment Options for Robert

LR-MDS confirmed by IPSS-M:

Transfusion burden of 6 RBC units over a 2-month period

- **Anemia (Hb: now 6.5 g/dL)**
- Platelets: 150,000
- ANC: 2,000
- No bleeding or nutritional deficiencies
- 18% RS with erythroid dysplasia
- 2% BM blasts
- *SF3B1* H662D mutation

Does evidence from COMMANDS support 1L luspatercept?

Clinical Consult: Practical Aspects Of Anemia Management in LR-MDS

Assume Robert is preparing to initiate luspatercept therapy

- **Anemia (Hb: now 6.5 g/dL)**
- Platelets: 150,000
- ANC: 2,000
- No bleeding or nutritional deficiencies
- 18% RS with erythroid dysplasia
- 2% BM blasts
- *SF3B1* H662D mutation

What are the practical considerations with luspatercept for the management team?

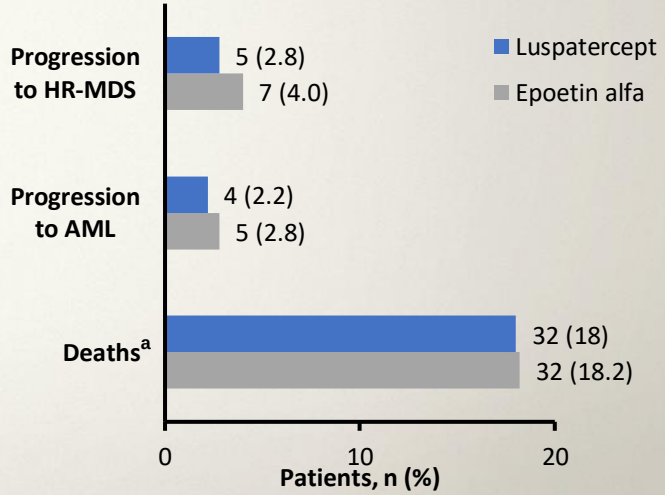
- Safety?
- Dosing?
- Formulary?

COMMANDS: Safety Summary[1,a]

Patients, n (%)	Luspatercept (n = 178)		Epoetin Alfa (n = 176)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Heme-related TEAEs				
Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
Peripheral edema	23 (12.9)	0	12 (6.8)	0
Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
Nausea	21 (11.8)	0	13 (7.4)	0
Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
TEE	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)

TEAEs of any grade
- 164 (92.1%) luspatercept
- 150 (85.2%) epoetin alfa

Median treatment duration
- 41.6 (range, 0-165) weeks of luspatercept
- 27.0 (range, 0-171) weeks of epoetin alfa



[a] Safety data are not exposure-adjusted.

1. Garcia-Manero G et al. ASCO 2023. Abstract 7003.

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Key Practical Considerations with Luspatercept

Dosing Considerations[1,2]

- Recommended starting dose is 1 mg/kg once every 3 weeks SC in LR-MDS
- Prior to each dose, review the patient's Hb and transfusion record
- Dose titration based on response is recommended; in COMMANDS titration was up to 1.75 mg/kg[1]

- **Recommendation for HTN management:** monitor BP prior to each administration
- Manage new-onset HTN or exacerbations of pre-existing HTN using antihypertensives

1. Garcia-Manero G et al. ASCO 2023. Abstract 7003. 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761136orig2lbl.pdf.

Take-Homes From the COMMANDS Study[1,2]

- Luspatercept shows superiority versus ESAs, with ~2x patients achieving both TI and Hb increase
- Luspatercept delivers more durable responses, with nearly 2.5 years of median TI, which is ~1 year longer than ESAs
- Luspatercept provides clinical benefit regardless of subgroups
- Luspatercept has a manageable and predictable safety profile that is consistent with previous clinical experience and has convenient (every 3 wk) administration
- Further evaluation of the mature dataset and longer follow-up are planned

Luspatercept is the first and only therapy to demonstrate superiority in a head-to-head study against ESAs and represents a paradigm shift in the treatment of LR-MDS–associated anemia

Clinical Consult: What if Robert Had Presented with ESA-Refractory Disease?

Assume Robert received ESA and Luspatercept therapy for anemia after diagnosis

Initial diagnosis of LR-MDS (RS) with anemia

Treatment:

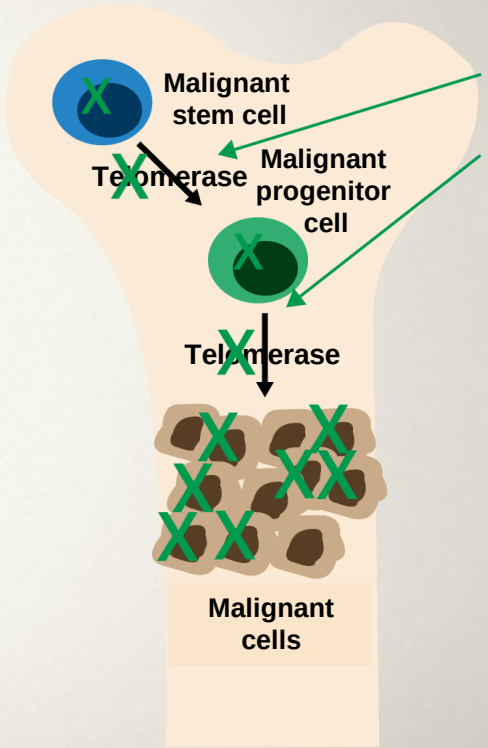
- ESA, Luspatercept and RBC transfusion
- After 14 months, **transfusion requirement increased to 6 units/month** (+ ↑ sEPO)

Does IMerge suggest that imetelstat can be considered as a 2L/3L option?
What are the dosing and safety considerations?

New Mechanisms in LR-MDS: Imetelstat[1]

Imetelstat is a 13-mer oligonucleotide

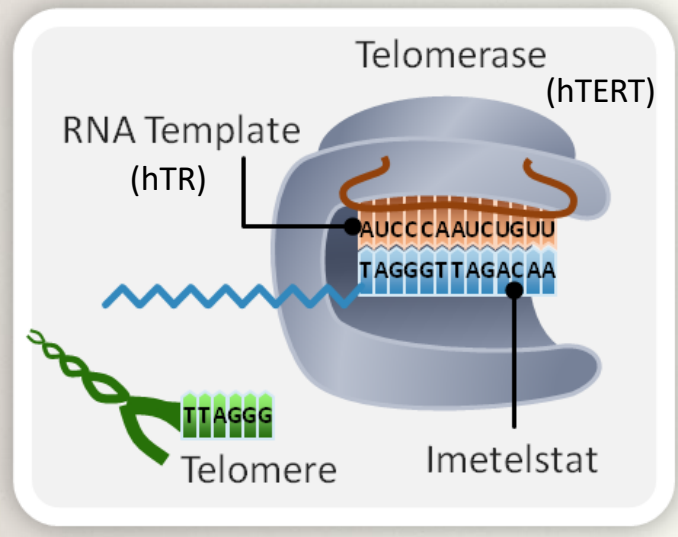
- Selectively targets malignant cells with continuously upregulated telomerase, inducing their apoptosis (cell death) and enabling the potential recovery of normal hematopoiesis
- Has potent activity in myeloid malignancies, as demonstrated in a study that included patients with MDS-RS



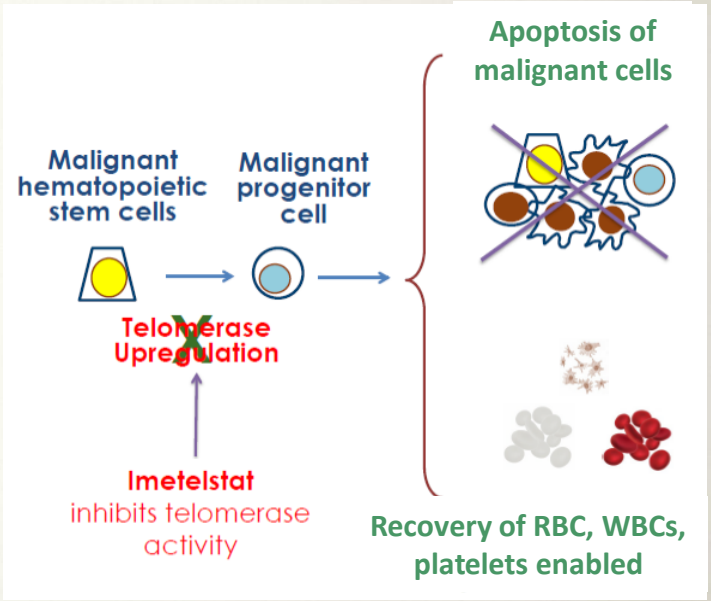
1. Tefferi A et al. *Blood Cancer J*. 2016;11:e405.

Imetelstat: First-in-Class Telomerase Inhibitor

- Imetelstat is a direct and competitive inhibitor of telomerase activity[1,2]



- Imetelstat has disease modifying potential to selectively kill malignant stem and progenitor cells enabling recovery of blood cell production[3,4]



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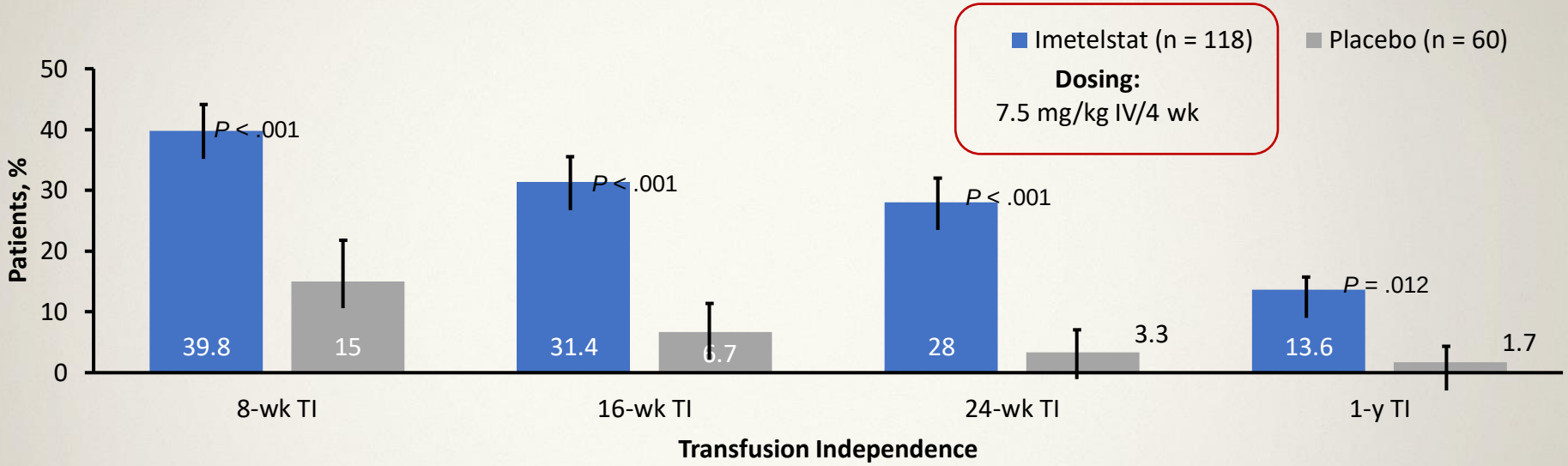
hTERT, human telomerase reverse transcriptase; hTR, catalytic component; RBC, red blood cell; WBC, white blood cell.

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939; 2. Herbert BS, et al. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467;
4. Wang X at al. *Blood Adv.* 2018;25;2(18):2378-2388.

IMerge: Higher Rates of Durable RBC-TI Observed With Imetelstat vs Placebo[1]

Phase 3 trial testing imetelstat vs placebo in 178 patients with LR-MDS relapsed/refractory to ESA or EPO



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 [8.0-21.1])
Placebo	9 (15.0 [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])

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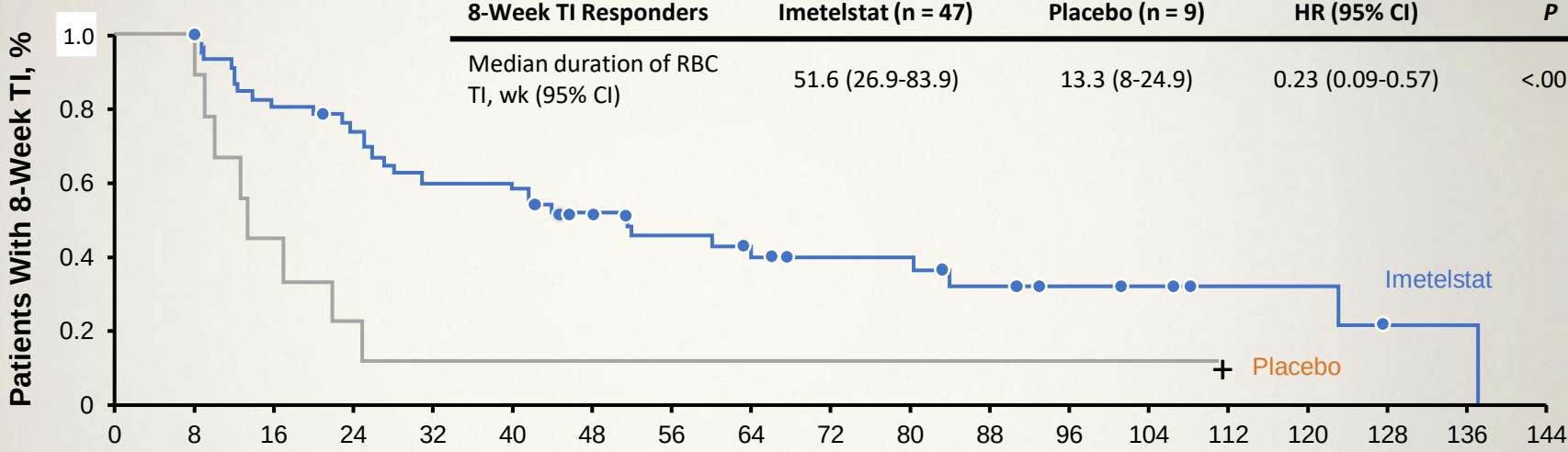
1. Zeidan A et al. ASCO 2023. Abstract 7004.

Imetelstat 8-Week RBC-TI Responders Have Significantly Longer Duration of Transfusion Independence vs Placebo[1]

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)	<.001



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

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1. Zeidan A et al. ASCO 2023. Abstract 7004.

Consistent With Prior Clinical Experience, the Most Common AEs Were Hematologic[1,a]

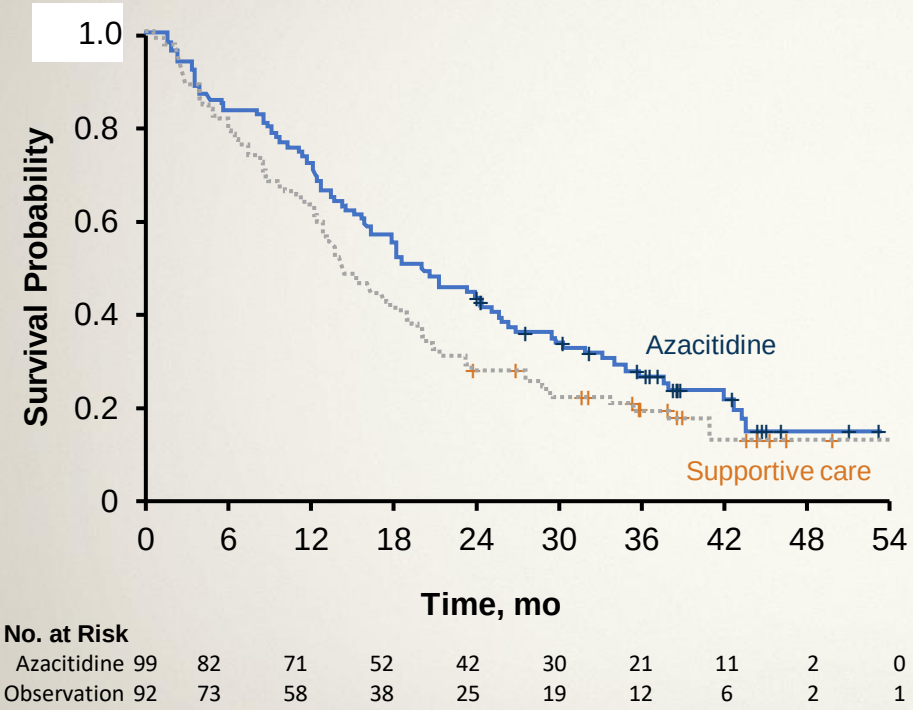
- Grade 3-4 thrombocytopenia and neutropenia were the most frequently reported AEs and were most often reported during cycles 1-3
  - There were no fatal hematologic AEs
- Nonhematologic AEs were generally low grade
- Although ~75% of patients treated with imetelstat had dose modifications due to AEs,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

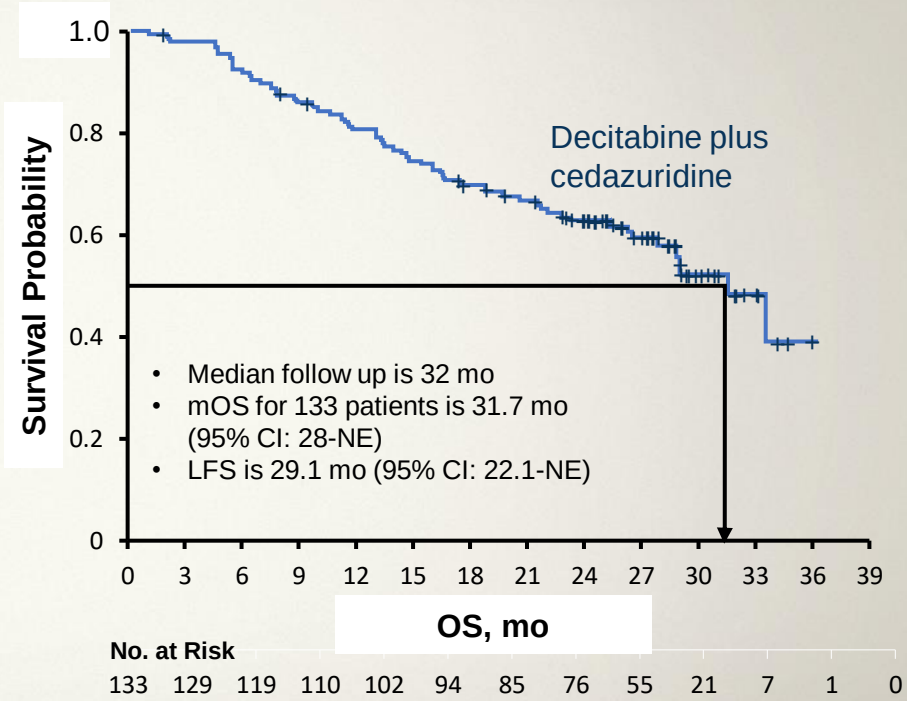
AE (≥10% of patients), n (%)	Imetelstat (n = 118)		Placebo (n = 59)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematologic				
Thrombocytopenia	89 (75)	73 (62)	6 (10)	5 (8)
Neutropenia	87 (74)	80 (68)	4 (7)	2 (3)
Anemia	24 (20)	23 (19)	6 (10)	4 (7)
Leukopenia	12 (10)	9 (8)	1 (2)	0
Other				
Asthenia	22 (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.

1. Zeidan A et al. ASCO 2023. Abstract 7004.

DNMTi Are the Backbone of Disease-Modifying Therapy in MDS[1,2]





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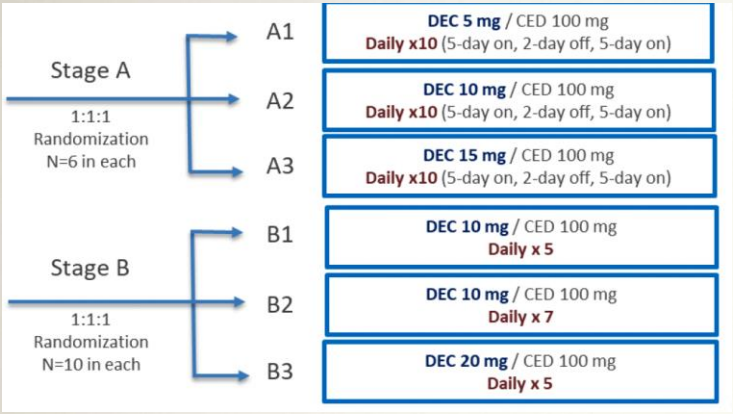
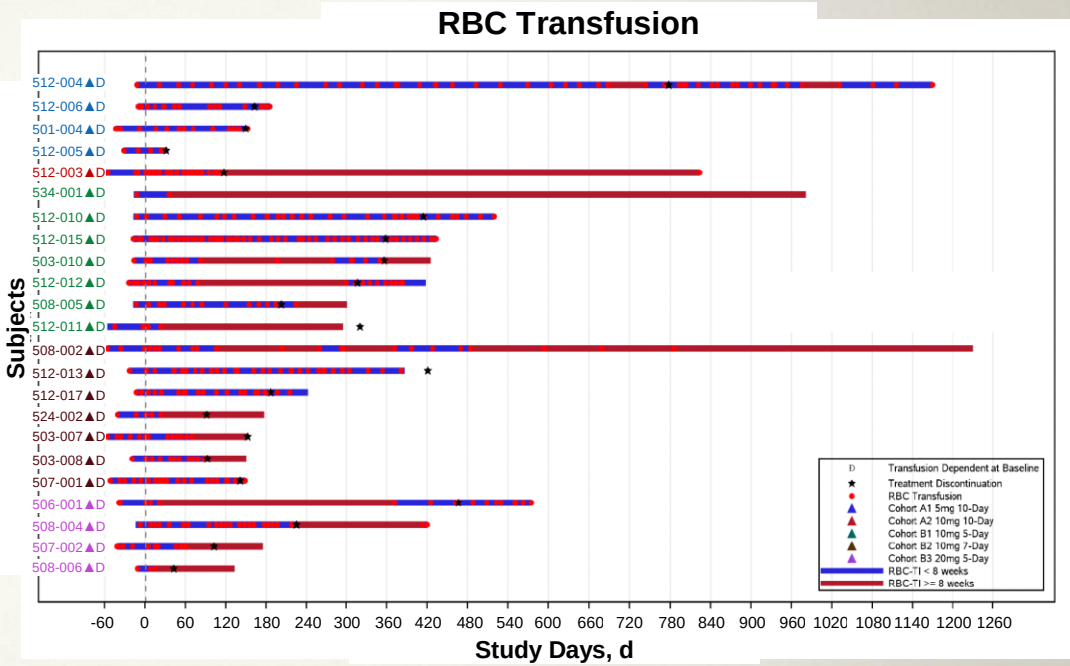
1. Silverman LR et al. *J Clin Oncol*. 2002;20:2429-2440. 2. Savona M et al. MDSF 2021. Abstract 118.

Assessing the Role of Low-Dose Oral Decitabine/Cedazuridine in IPSS Low/Int-1 MDS[1]



- Safety is consistent with the standard dose; AEs mostly consist of myelosuppression with no significant GI effects
- 11 of 23 patients became RBC-TI for 8 weeks; median OS was 31 months



10 mg DEC/100 mg CED daily X 5 days (Cohort B1) selected as the RP2D based on efficacy and safety

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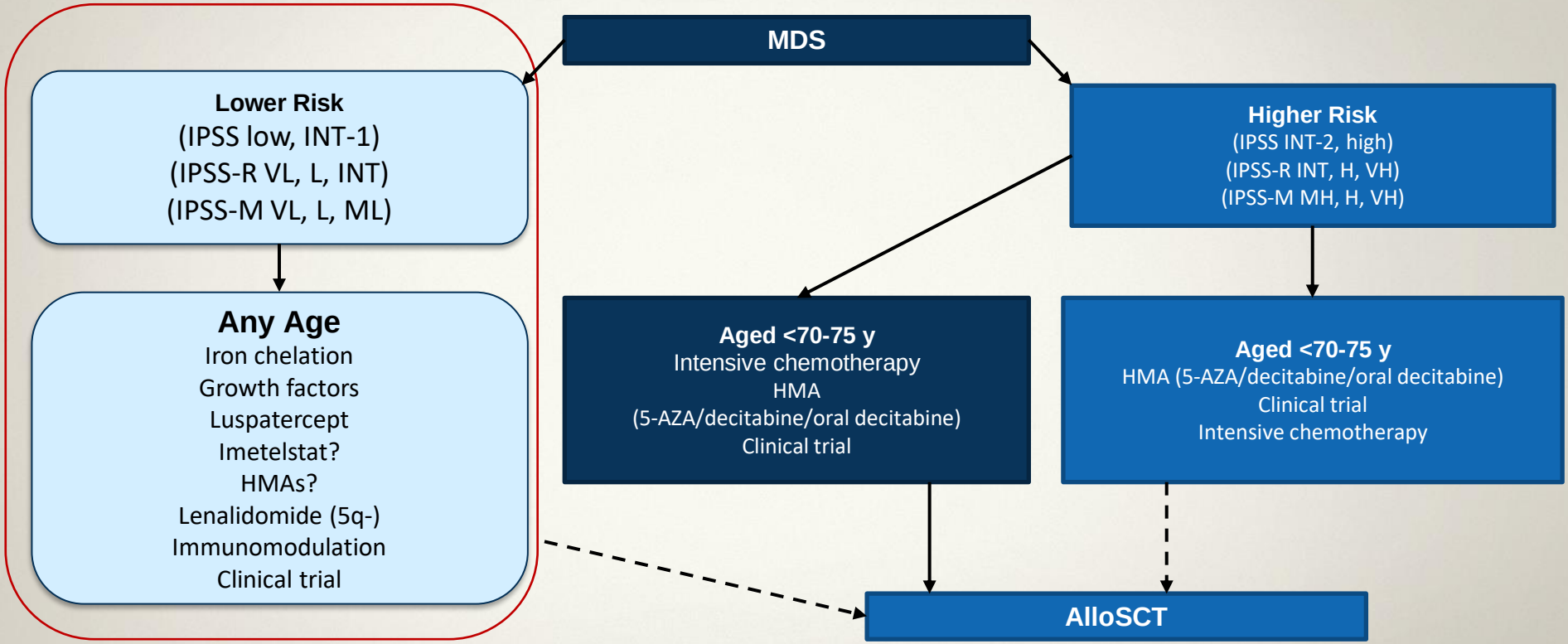
1. Garcia-Manero G et al. The 17th International Congress on Myelodysplastic Syndromes, 2023. Abstract 234.

The Shape of Modern Treatment: LR-MDS[1]



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1. Garcia-Manero G. *Am J Hematol.* 2023;98:1307-1325.

Thank You

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Our Patients!!!!

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Hematology and SCT APPs, RNs and coordinators!