FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Convegno della Fondazione Italiana Sindromi Mielodisplastiche

30 giugno 2025

La gestione degli effetti collaterali e la durata del trattamento nei pazienti con LR MDS

Valeria Santini

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FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

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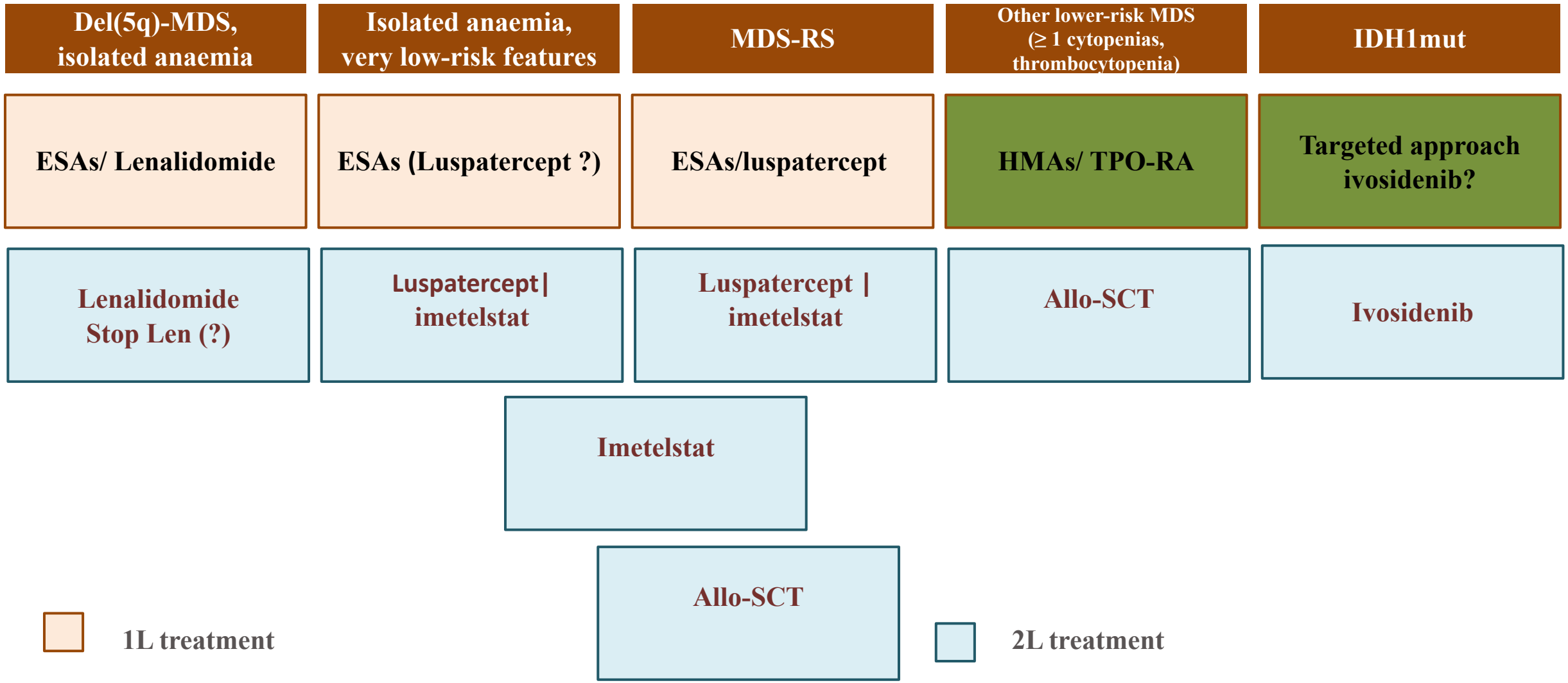
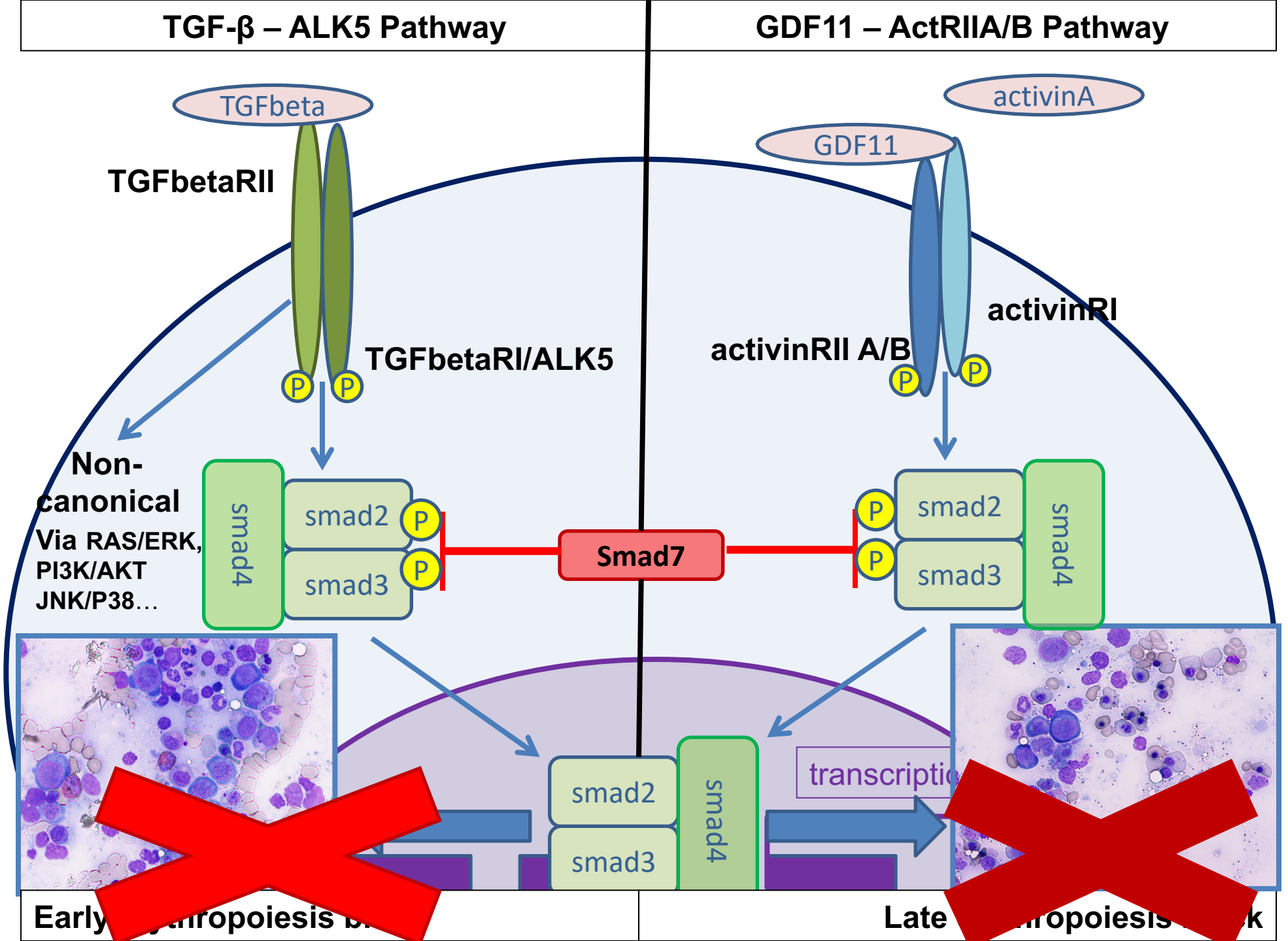
Disclosures of Valeria Santini

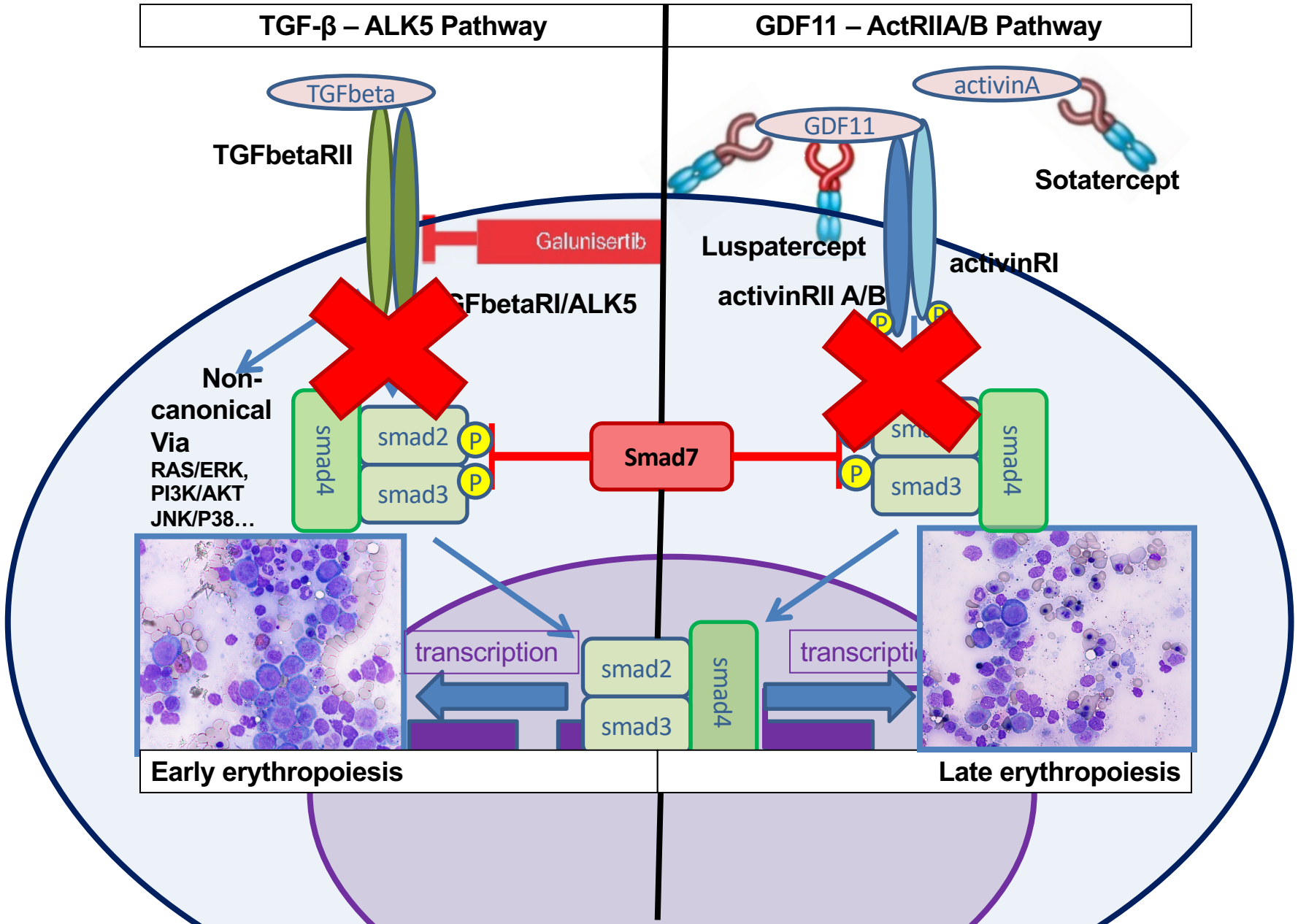
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS CELGENE	x					x	
GERON						x	
GILEAD						x	
OTSUKA						x	
NOVARTIS						x	
TAKEDA						x	
ABBVIE						x	
SYROS						x	
SERVIER						x	
CTI						x	
CURiS						x	

Possible treatment algorithm in 2025 for lower-risk MDS



Background and mechanisms of action


TGF-β – ALK5 Pathway
GDF11 – ActRIIA/B Pathway
TGFbeta
TGFbetaRII
TGFbetaRI/ALK5
activinA
GDF11
activinRII A/B
activinRI
Non-canonical
Via RAS/ERK, PI3K/AKT JNK/P38…
smad4
smad2
smad3
Smad7
P
transcriptio
Early
Late


TGF-β – ALK5 Pathway
GDF11 – ActRIIA/B Pathway
TGFbeta
TGFbetaRII
Galunisertib
GFbetaRI/ALK5
activinA
GDF11
Sotatercept
Luspatercept
activinRII A/B
activinRI
Non-
canonical
Via
RAS/ERK,
PI3K/AKT
JNK/P38…
smad4
smad2
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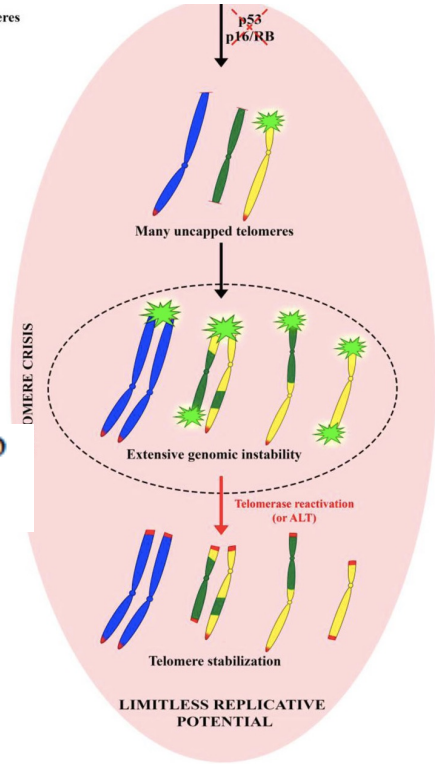
Smad7
transcription
transcripti
Early erythropoiesis
Late erythropoiesis

Telomere dysfunction in MDS

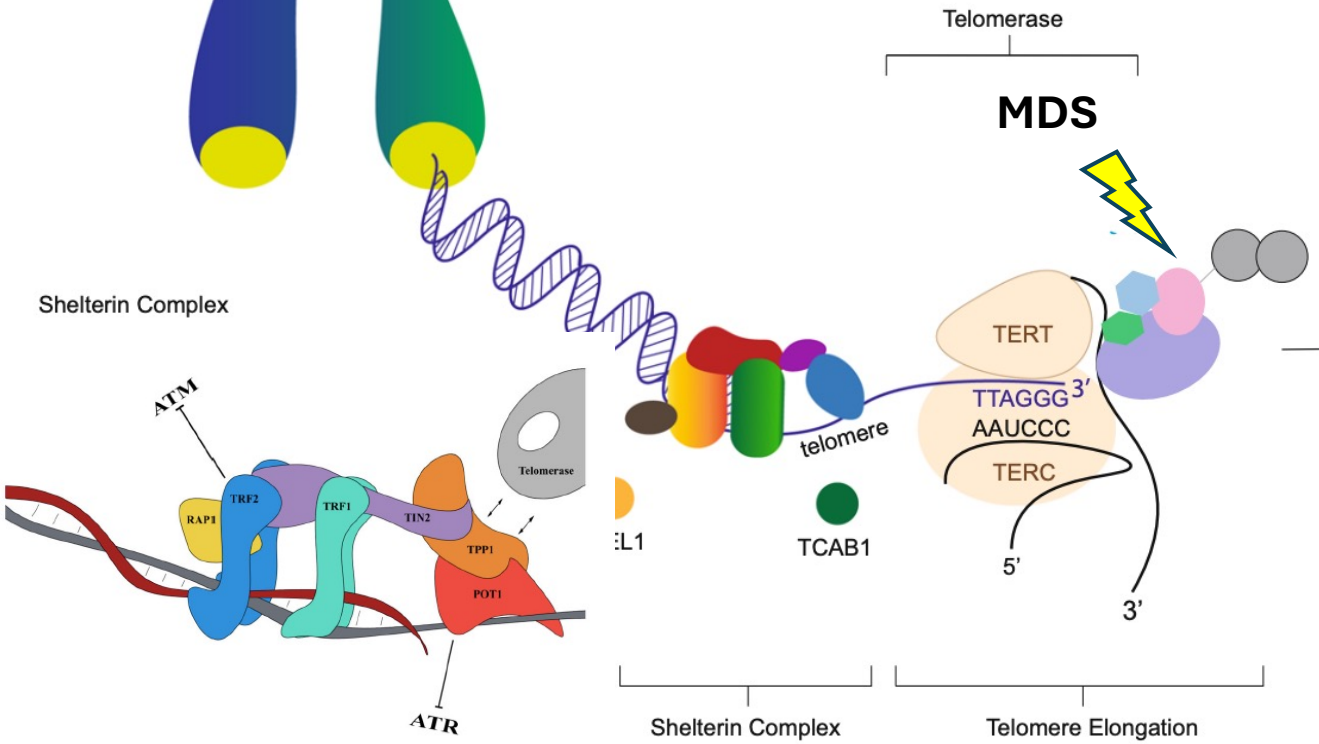
- *TERT* and *TERC* mutations in ≈ 3% of MDS, with a high rate of AML transformation

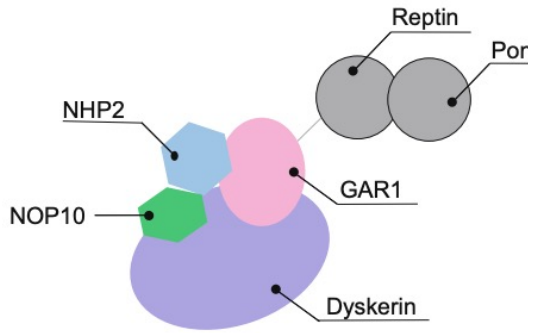
- Shorter telomere lenght in HSC in MDS mouse model and increased hTERT expression in MDS

Extremely complex modulation of HSC



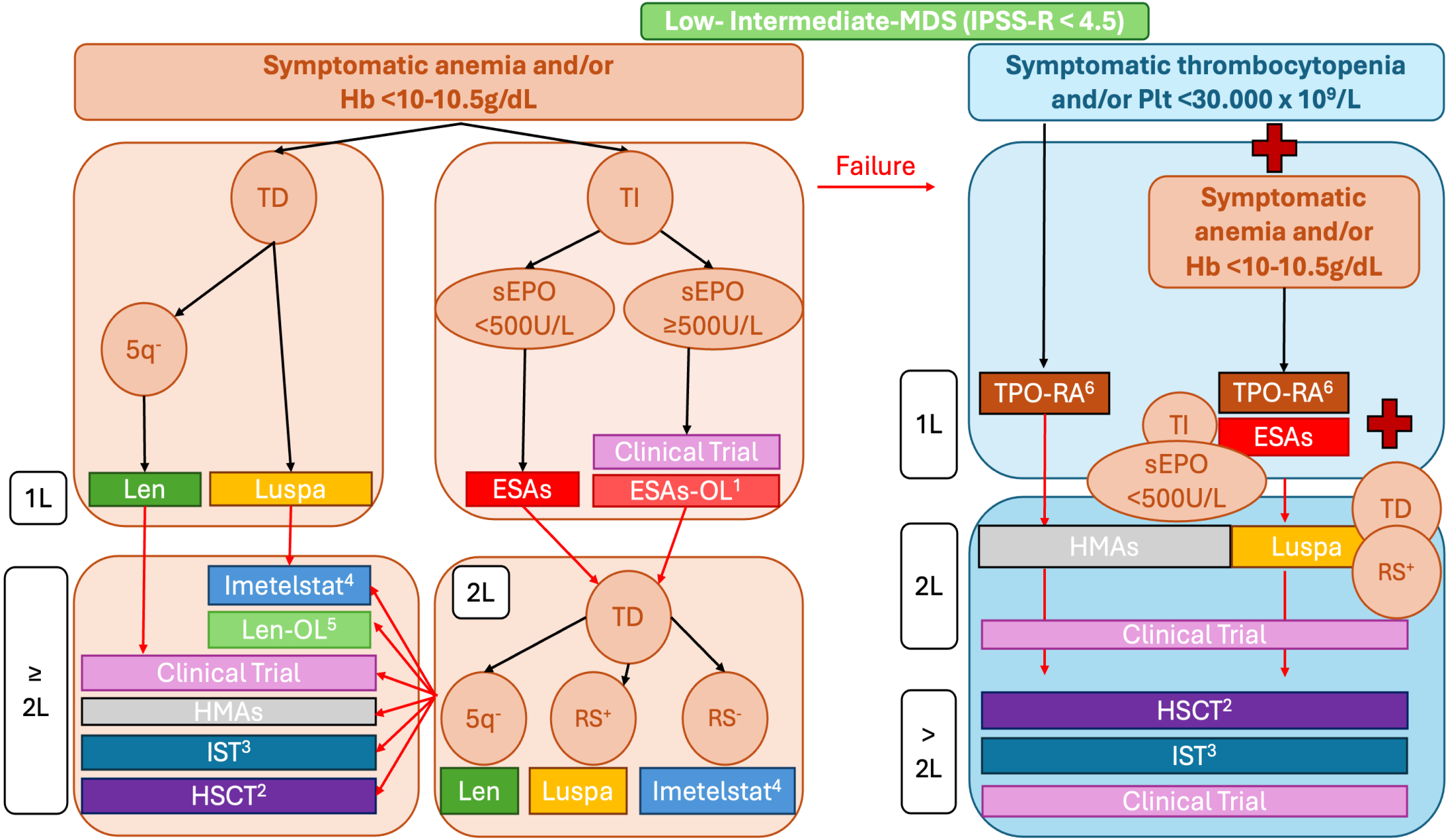
mutant HSCs' residual telomerase activity could be sufficient to maintain the clonal expansion of the cells once they acquire tumorigenic potential.



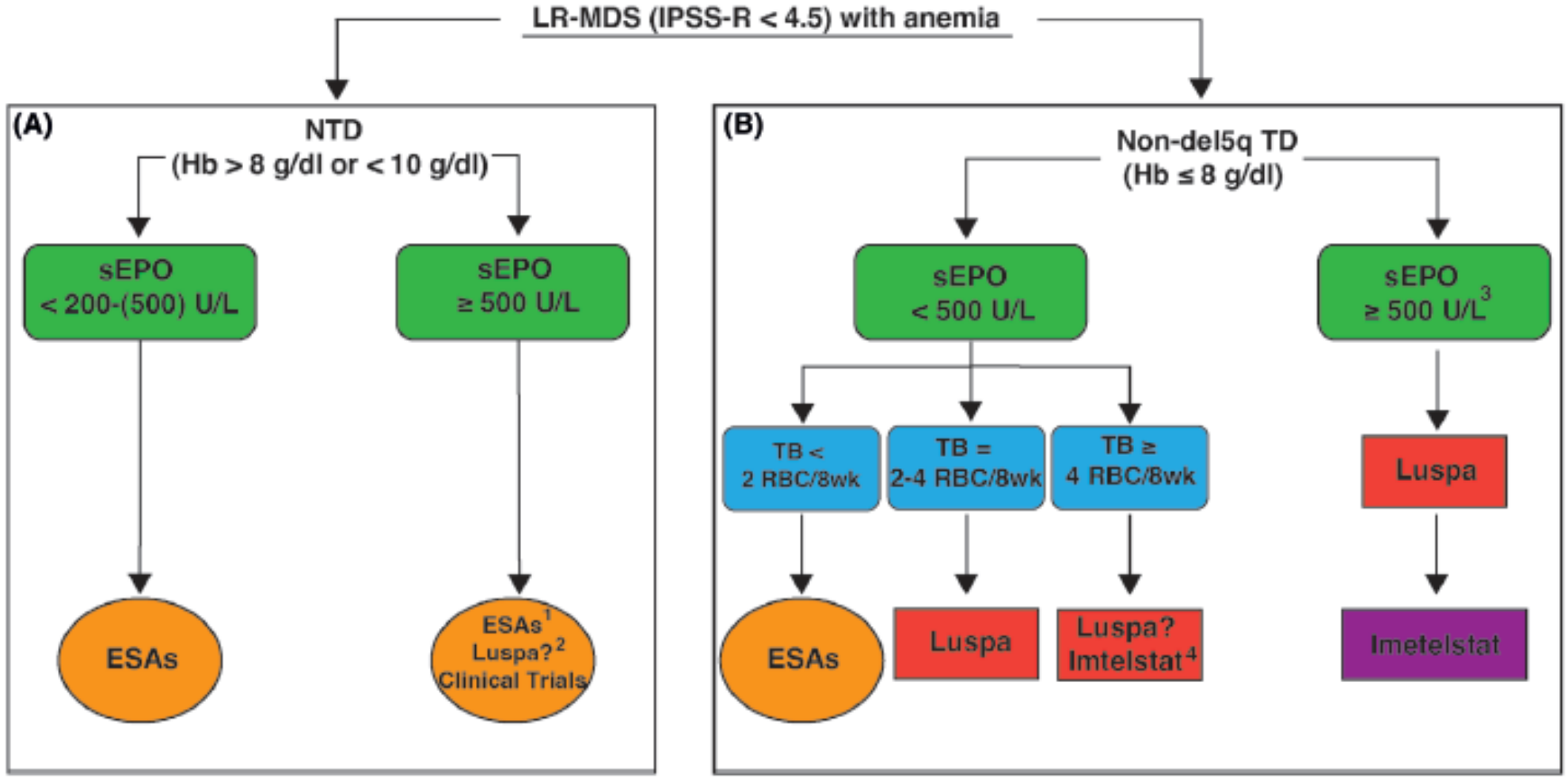


Adapted from Kam et al., NPJ Genom Med 2021

Fiorini E et al *Differentiation* 2018



McMahon, Raddi, Sanjay, and Santini, ASCO 2025 EBook



Santini and Consagra , BJH in press

Dosing and Safety Considerations With Luspatercept

Dosing Considerations[1,2]

Download the Practice Aid!

- Recommended starting dosage is 1 mg/kg SC once every 3 weeks 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. Reblozyl (luspatercept-aamt) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761136orig2lbl.pdf.

Dosing and Safety Considerations With Imetelstat[1]

- **Recommended dose:** 7.1 mg/kg IV over 2 hours every 4 weeks
- Discontinue if no decrease in RBC transfusion burden after 24 weeks of treatment (administration of 6 doses) or if unacceptable toxicity occurs
- **Premedication at least 30 minutes prior to dosing**
  - Diphenhydramine (or equivalent) 25 mg to 50 mg, IV or orally
  - Hydrocortisone (or equivalent) 100 mg to 200 mg, IV or orally

Download the Practice Aid!

Dose Modifications for Grade 3/4 AEs

Dose Reduction	Dose Every 4 Weeks, mg/kg
First dose reduction	5.6
Second dose reduction Consider cycle delay	4.4

SAFETY

SAFETY
SUMMARY

Summary of TEAEs, n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE	134 (87.6)	63 (82.9)
Patients with ≥ 1 TEAE resulting in treatment discontinuation	21 (13.7)	6 (7.9)
Specific TEAEs[a] resulting in discontinuation		
Fatigue	2 (1.3)	0
Diarrhea	0	0
Asthenia	1 (0.7)	0
Dizziness	0	0
Nausea	0	0
Back pain	0	0
Headache	1 (0.7)	0
Dyspnea	0	0

[a] TEAEs occurring more frequently in the luspatercept arm.

- The overall frequency of SAEs was 41.8% in the luspatercept arm and 30.3% in the placebo arm
  - After adjusting for exposure, the incidence of SAEs per 100 patient-years was comparable between the luspatercept (EAIR 42.3/100 patient-years) and placebo (EAIR 55.7/100 patient-years) arms
  - The overall EAIR of SAEs was comparable between the luspatercept arm and placebo arm
- Incidence of grade 3 TEAEs was balanced between treatment arms

EAIR, exposure-adjusted incidence rate; SAE, serious adverse event.

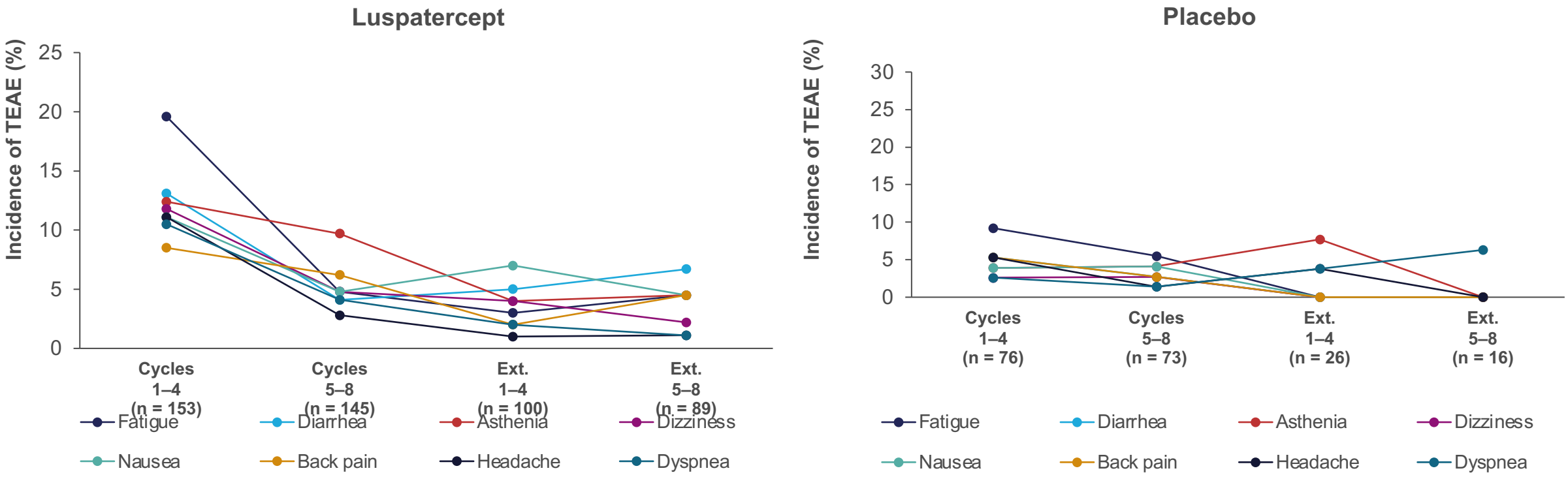
Data cutoff: July 1, 2019.

SAFETY
DISEASE PROGRESSION

Summary of Disease Progression, n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Progression to HR-MDS or AML	8 (5.2)	4 (5.3)
HR-MDS	5 (3.3)	2 (2.6)
AML	3 (2.0)	2 (2.6)

Data cutoff: July 1, 2019.

SAFETY
FREQUENT TEAEs (ANY GRADE) BY TREATMENT CYCLE



- New onset of TEAEs generally decreased over time in both treatment arms during the first 24 weeks of the study

Includes disease assessment at Week 25. TEAEs included AEs that started on or after the day of the first dose and on or before 42 days after the last dose. The onset date of the AE was used to determine the cycle. AEs with a duration overlapping multiple cycles were only counted in the first overlapped cycle. If an AE occurred multiple times in different cycles, it was counted once in each cycle. If an AE occurred multiple times within the same cycle, it was counted only once. If a patient experienced multiple events under the same preferred term, then the patient was counted only once for that preferred term.

Ext., extension cycle.

Data cutoff: July 1, 2019.

Long-term evaluation of luspatercept in erythropoiesis-stimulating agent-intolerant/refractory patients with lower-risk myelodysplastic syndromes in the phase 3 MEDALIST study

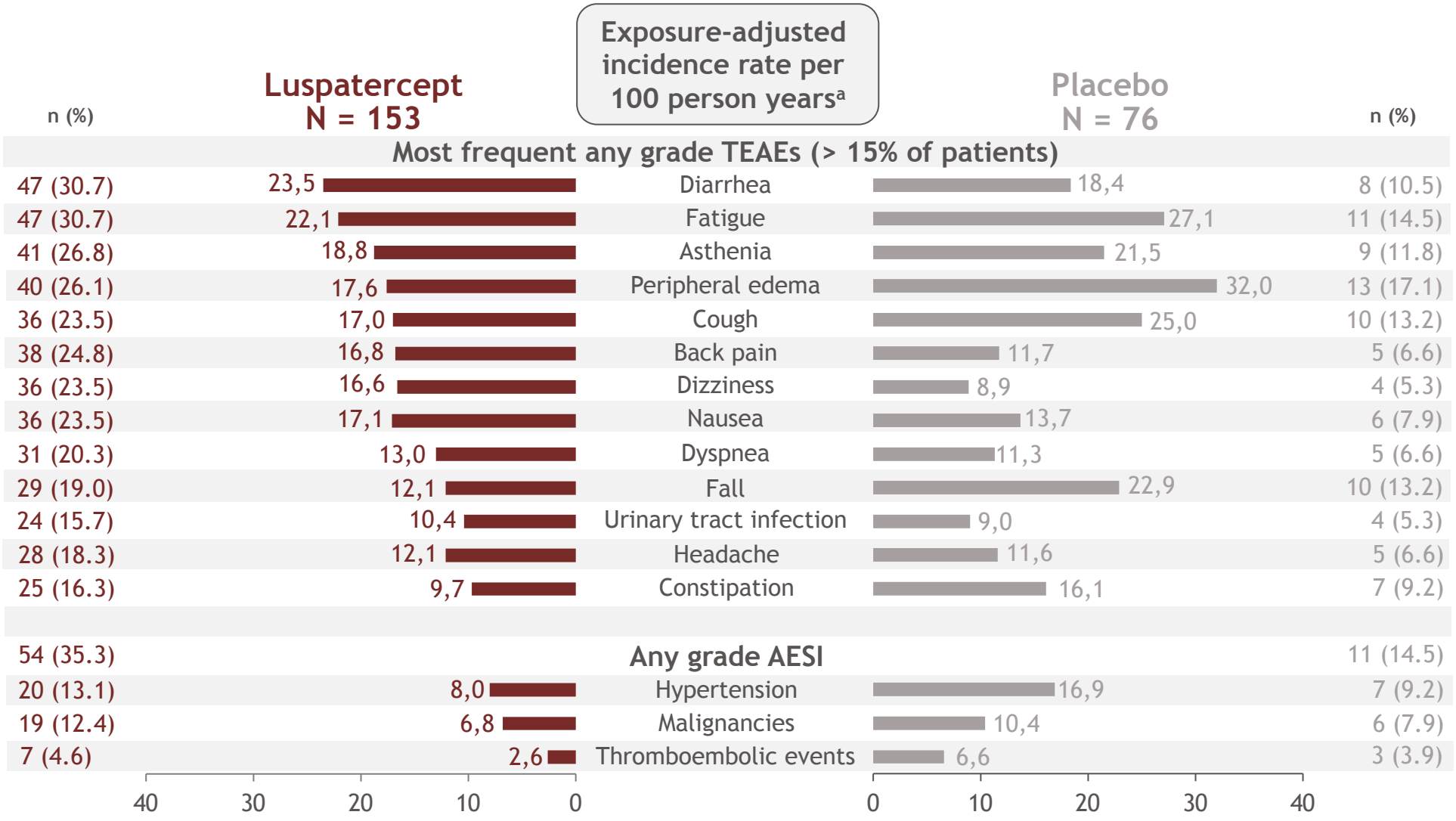
Valeria Santini,[1] Rami S. Komrokji,[2] Guillermo Garcia-Manero,[3] Rena Buckstein,[4] Esther N. Oliva,[5] Karen L. Keeperman,[6] Shelonitda Rose,[6] Ana Carolina Giuseppi,[6] Valérie Vilmont,[7] Yinzhi Lai,[6] Dimana Miteva,[7] Barkha Aggarwal,[6] Uwe Platzbecker,[8] Pierre Fenaux,[9] Amer M. Zeidan[10]

[1]MDS Unit, Hematology, University of Florence, AOUC, Florence, Italy; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]U.O.C. Ematologia, Grande Ospedale Metropolitano Bianchi Melacrino Morelli, Reggio di Calabria, Italy ;

[8]Department of Hematology, Cell Hematology and Hemostaseology, Leipzig University Hospital, Leipzig, Germany; [9]Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France; [10]Department of Internal Medicine, Yale Cancer Center and Smilow Cancer Hospital, New Haven, CT, USA

ASH 2023, Presentation 915

Safety: AEs and rates of progression to HR-MDS and AML



Rates of progression to HR-MDS and AML were low at an earlier data cutoff[1]

Patients who progressed to HR-MDS
9 (5.9%)
3 (3.9%)

Patients who progressed to AML
4 (2.6%)
3 (3.9%)

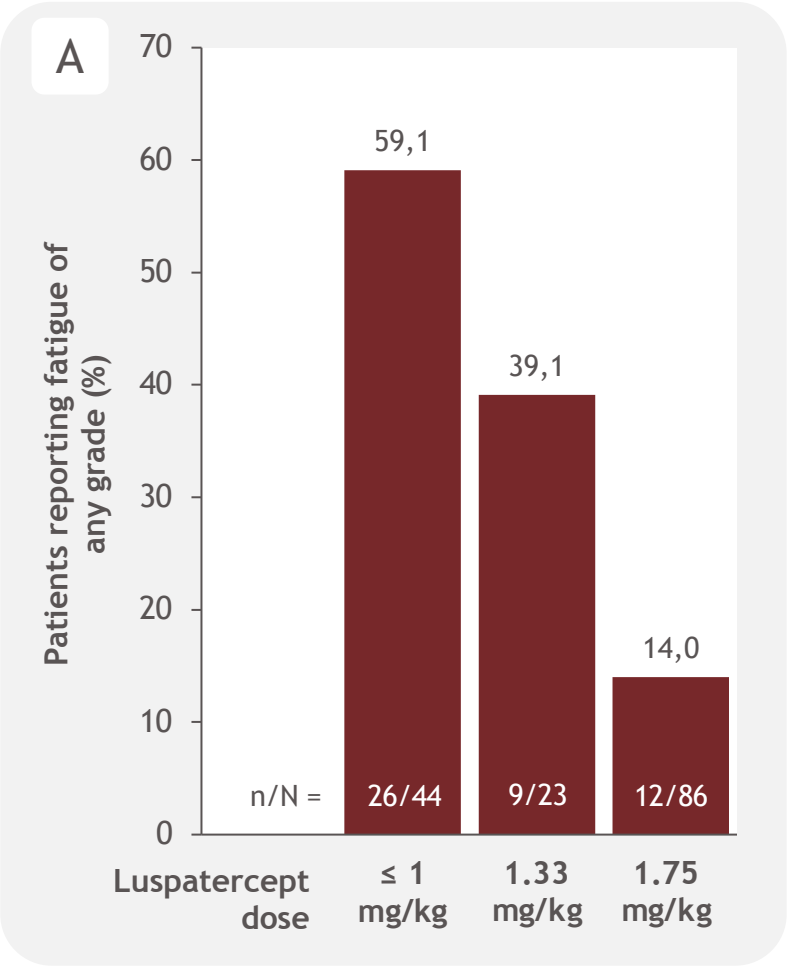
No new progression to HR-MDS or AML events have been reported since the last data cutoff[1]

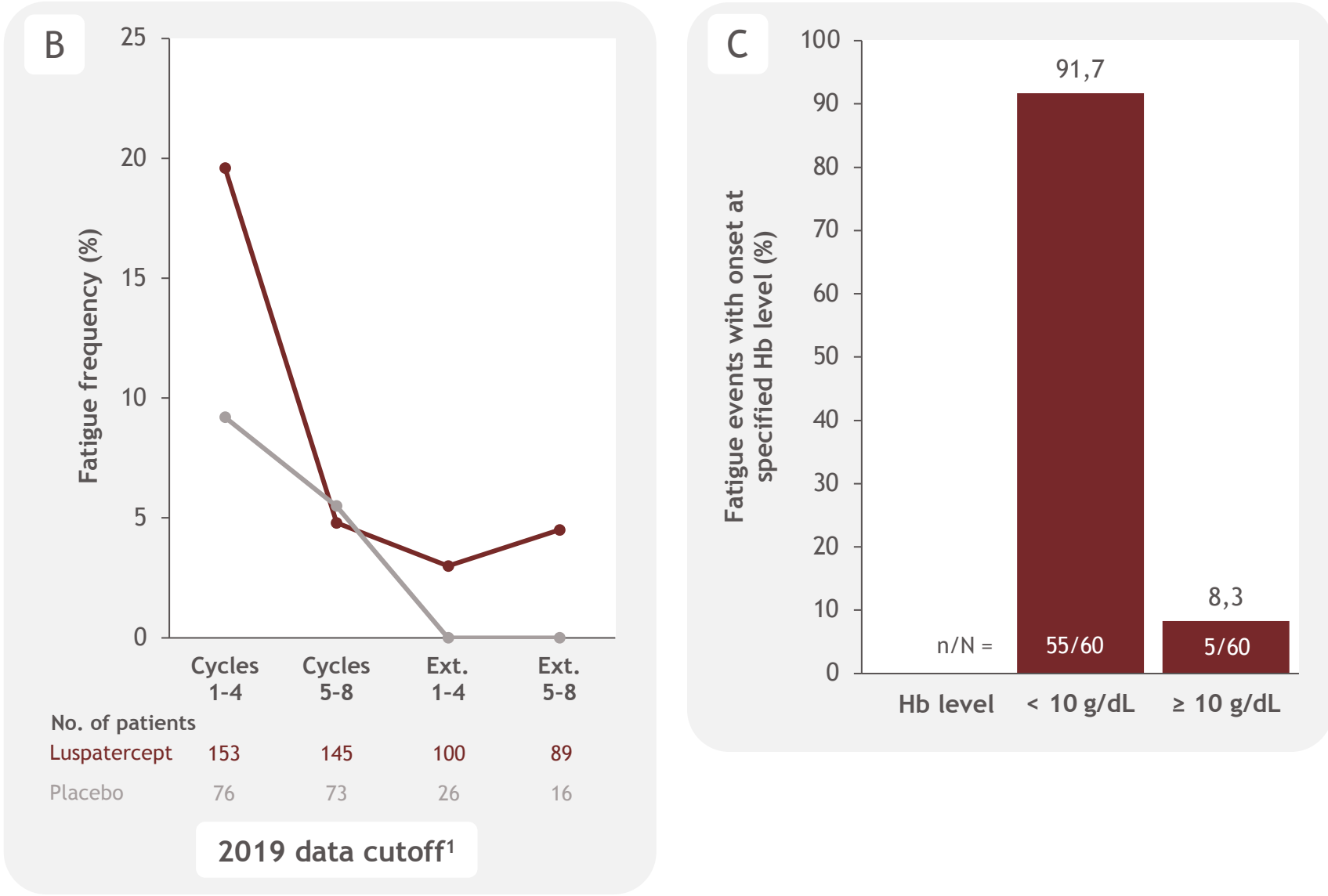
No treatment-related deaths were reported in either group

[a]Exposure-adjusted incidence rates per 100 person years are defined as 100 times the number of patients with a specific event divided by the total exposure time (in years) to the event; exposure time is the overall treatment exposure for patients without the event and the time up to the first event start date for patients with the event

1. Platzbecker U, et al. *Leukemia* 2023 Nov;37(11):2314-2318.

Relationship of fatigue with (A) luspatercept dose, (B) treatment cycle, and (C) Hb level





1. Fenaux P, et al. *Blood* 2019;134(suppl 1). Abstract 841.
Ext., extension phase.

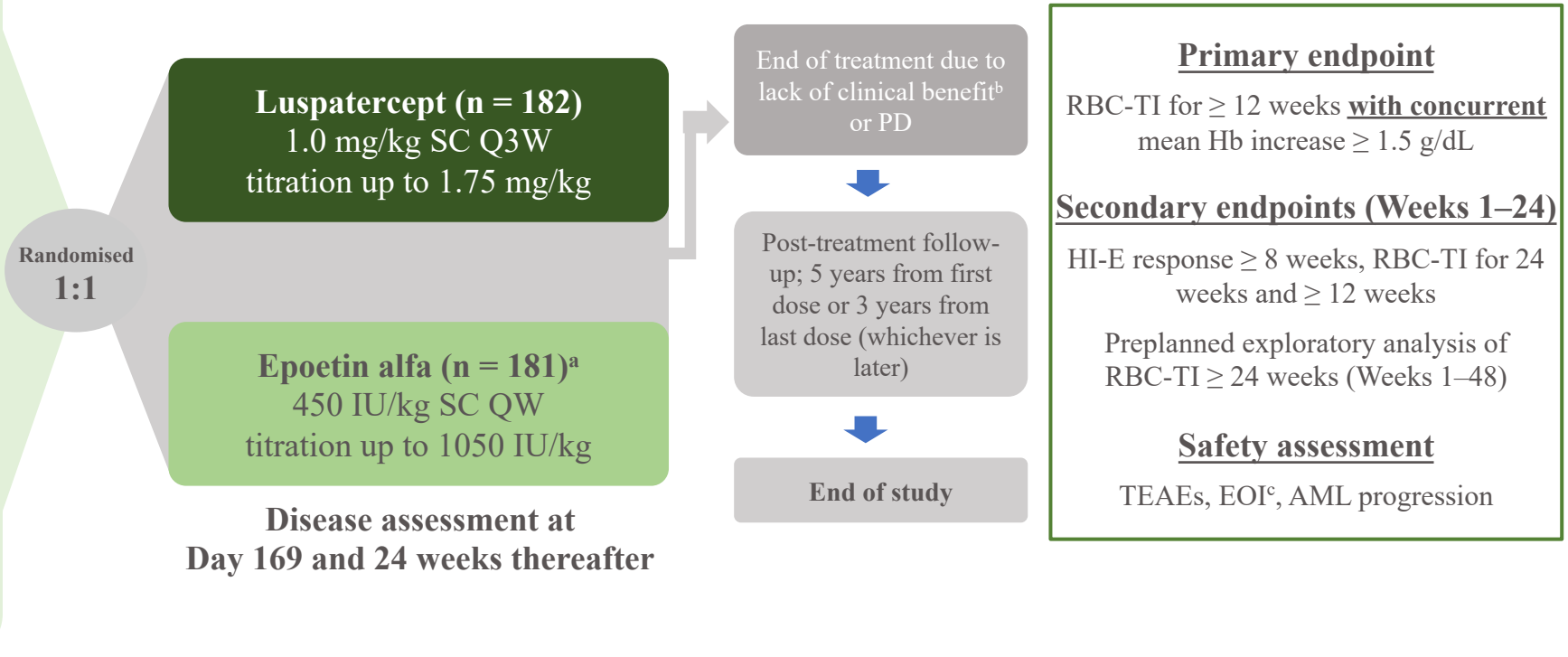
Luspatercept vs. epoetin alfa in ESA-naïve, lower-risk MDS COMMANDS Phase 3 global trial[1,2]

Key patient eligibility criteria

- IPSS-R very low-, low- or intermediate-risk MDS (with or without RS), with < 5% blasts in bone marrow
- Required RBC transfusions (2–6 units/8 weeks for a minimum of 8 weeks immediately prior to randomisation)
- Endogenous sEPO < 500 U/L
- ESA-naïve
- Patients with del(5q) were excluded

Patients stratified by:

- Baseline RBC transfusion burden
- Baseline sEPO level
- RS status



[a] Two patients randomised to the epoetin alfa arm withdrew consent prior to receiving their first dose; [b] Clinical benefit defined as transfusion reduction of ≥ 2 units/8 weeks vs. baseline; [c] EOI are safety events selected based on findings from nonclinical or clinical phase 2 and 3 luspatercept trials.
AML: acute myeloid leukaemia; del(5q): deletion 5q; ESA: erythropoiesis-stimulating agent; EOI: events of interest; Hb: haemoglobin; HI-E: haematological improvement – erythroid response; IPSS-R: Revised International Prognostic Scoring System; MDS: myelodysplastic syndromes; PD: progressive disease; QW: every week; Q3W: every 3 weeks; RBC: red blood cell transfusion independence; RS: ring sideroblasts; SC: subcutaneous; sEPO: serum erythropoietin; TEAE: treatment-emergent adverse event.
1. Platzbecker U, et al. *Lancet* 2023;402:373–385. 2. Garcia-Manero G, et al. ASH 2023; (Abstract 193; oral).

Della Porta MG , Garcia Manero G et al, Lancet Hematol 2024

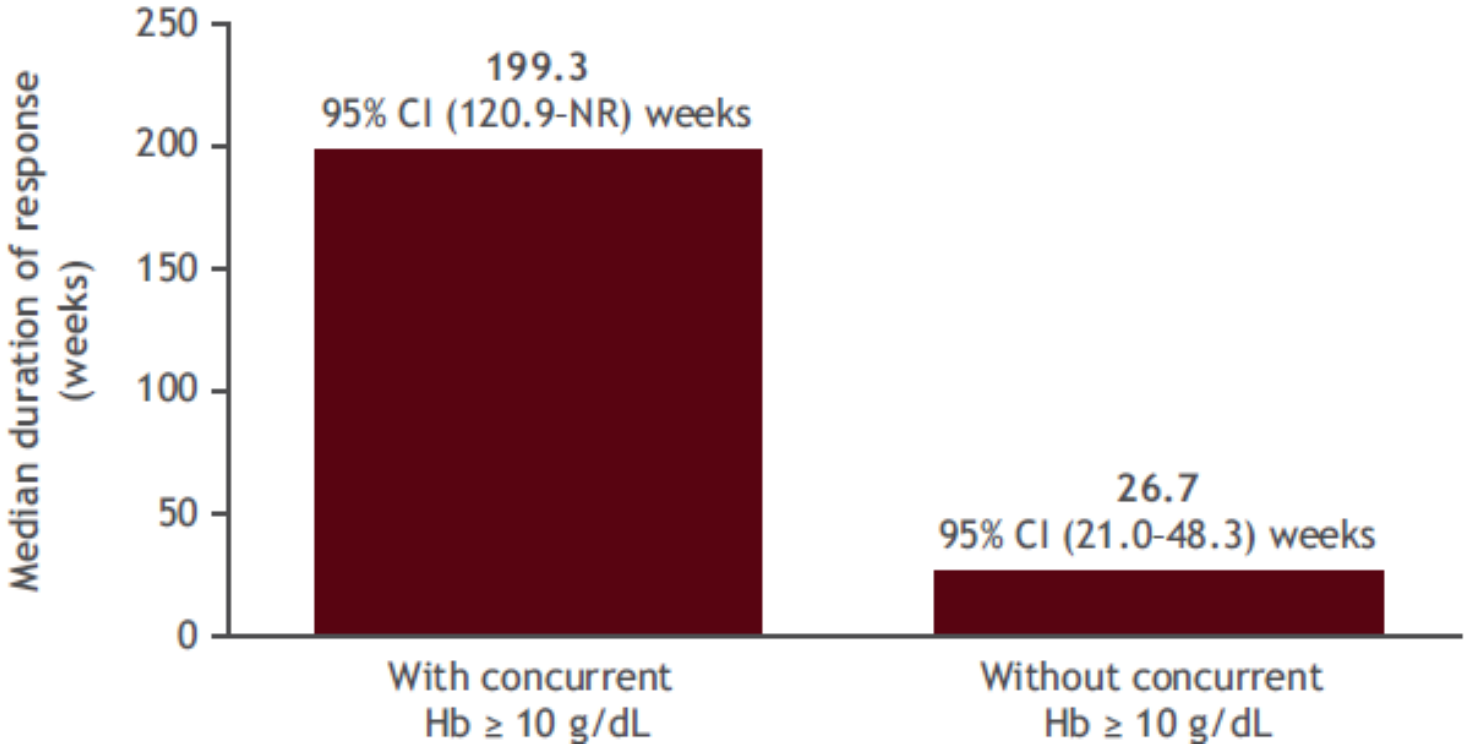
Clinical benefits of achieving hemoglobin levels ≥ 10 g/dL in transfusion-dependent erythropoiesis-stimulating agent-naive patients with lower-risk myelodysplastic syndromes treated with luspatercept in the COMMANDS trial

Valeria Santini,[1] Amer M. Zeidan,[2] Uwe Platzbecker,[3] Rami S. Komrokji,[4] Guillermo Garcia-Manero,[5] Dimana Miteva,[6] Aylin Yucel,[7] Veronika Pozharskaya,[7] Shelonitda Rose,[7] Yinzhi Lai,[7] Ana Carolina Giuseppi,[7] David Valcárcel,[8] Pierre Fenaux,[9] Jake Shortt,[10] Matteo Giovanni Della Porta[11]

[1]University of Florence, Florence, Italy; [2]Yale University, New Haven, CT, USA; [3]University Hospital in Leipzig, Leipzig, Germany; [4]Moffitt Cancer Center, Tampa, FL, USA; [5]University of Texas MD Anderson Cancer, Houston, TX, USA ; [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]Hôpital Saint-Louis, Université Paris 7, Paris, France; [10]Monash University and Monash Health, Clayton, Australia; [11]Humanitas University, Milan, Italy

ASH 2024, Presentation 1818

Achievement and duration of RBC-TI ≥ 12 weeks with or without concurrent Hb ≥ 10 g/dL (week 1-EOT)



- Among RBC-TI ≥ 12-week responders with concurrent Hb ≥ 10 g/dL, 72/108 (66.7%) patients maintained their response at the cutoff date; median duration of longest response was 199.3 weeks (95% CI, 120.9-NR)
  - Median duration of cumulative response was similar to the longest response, 199.3 weeks (95% CI, 135.9-NR)
- Among RBC-TI ≥ 12-week responders without concurrent Hb ≥ 10 g/dL, 6/31 (19.4%) patients maintained their longest response at the cutoff date; median duration of longest response was 26.7 weeks (95% CI, 21.0-48.3)
  - Median duration of cumulative response was similar to the longest response, 27.0 weeks (95% CI, 22.6-48.3)

Data cutoff: September 22, 2023.
Median is from un-stratified Kaplan–Meier method.
NR, not-reached.

Santini V, et al. ASH 2024 [Abstract #1818]

Safety

	Max luspatercept dose 1.0 mg/kg (n = 40)		Max luspatercept dose 1.33 mg/kg (n = 24)		Max luspatercept dose 1.75 mg/kg (n = 118)		Total (N = 182)	
	≥ 1 event, n (%)	EAIR/100 PY	≥ 1 event, n (%)	EAIR/100 PY	≥ 1 event, n (%)	EAIR/100 PY	≥ 1 event, n (%)	EAIR/100 PY
TEAE[a]								
Any-grade	38 (95.0)	708.9	24 (100.0)	905.6	116 (98.3)	535.1	178 (97.8)	599.5
Grade 3/4	28 (70.0)	92.8	16 (66.7)	80.3	73 (61.9)	67.3	117 (64.3)	73.8
Serious	20 (50.0)	44.7	14 (58.3)	60.4	56 (47.5)	41.2	90 (49.5)	44.2
Suspected related TEAE[a]								
Any-grade	12 (30.0)	29.1	10 (41.7)	52.5	42 (35.6)	32.7	64 (35.2)	33.9
Grade 3/4	3 (7.5)	6.0	3 (12.5)	10.2	10 (8.5)	5.9	16 (8.8)	6.4
Serious	1 (2.5)	1.9	0	0	0	0	1 (0.5)	0.4

- TEAEs were reported in 178/182 (97.8%) patients treated with luspatercept
  - Grade 3/4 TEAEs were reported in 117/182 (64.3%) patients
  - TEAEs were similar across different luspatercept dose levels
- Suspected treatment-related AEs were reported in 64/182 (35.2%) patients
  - No clinically significant differences in frequencies or EAIR per 100 PY of treatment-related any-grade TEAEs were observed across dose levels
  - The frequencies of grade 3/4 treatment related TEAEs and EAIR/100 PY were similar across luspatercept maximum dose levels

Data cutoff: September 22, 2023.
[a]TEAEs include adverse events (AEs) that started on or after the first dose of investigational product (IP) until 42 days after the last dose of IP, along with any serious AEs reported to the investigator afterward that are suspected to be related to IP. EAIR/PY is defined as 100 times the number of patients with the specific TEAE divided by the total exposure time (in years) to the event.
EAIR, exposure-adjusted incidence rate; PY, patient year; TEAE, treatment-emergent adverse events.

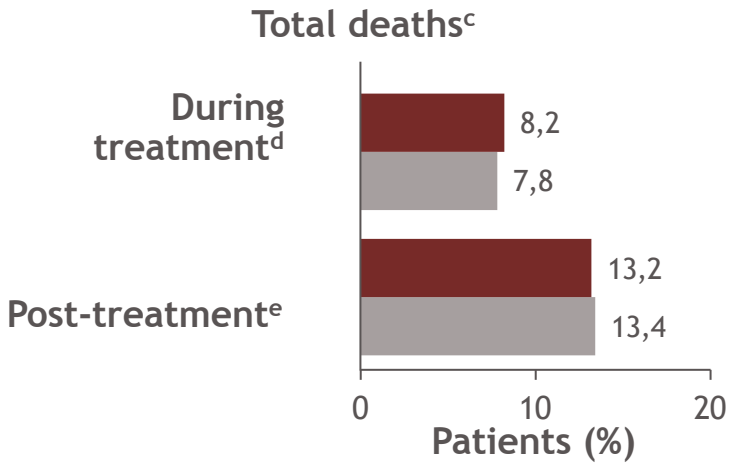
Santini V, et al. ASH 2024 [Abstract #1818]

COMMANDS: summary of safety[a]

- The median (range) duration of treatment was longer in the luspatercept arm compared with the epoetin alfa arm: 51.3 (3-196) weeks versus 37.0 (1-202) weeks
  - 143 (78.6%) of luspatercept patients and 146 (81.6%) of epoetin alfa patients had ≥ 1 dose escalation[a]
- Similar proportions of patients in the luspatercept and epoetin alfa arms died at any time during the study
- Rates of progression to AML[b] were low (2.7% vs 3.3% of patients for luspatercept versus epoetin alfa)

Most common TEAEs in ≥ 10% of patients	Luspatercept (N = 182)	Epoetin alfa (N = 179)
Diarrhea	32 (17.6)	25 (14.0)
Fatigue	32 (17.6)	13 (7.3)
COVID-19	27 (14.8)	28 (15.6)
Hypertension	27 (14.8)	16 (8.9)
Dyspnea	26 (14.3)	14 (7.8)
Nausea	26 (14.3)	15 (8.4)
Peripheral edema	26 (14.3)	14 (7.8)
Asthenia	25 (13.7)	29 (16.2)
Dizziness	23 (12.6)	16 (8.9)
Anemia	22 (12.1)	19 (10.6)
Back pain	22 (12.1)	16 (8.9)
Headache	20 (11.0)	15 (8.4)

Follow-up duration,[b] median (range)
17.2 (1-46) months for luspatercept arm
16.9 (0-46) months for epoetin alfa arm



Data cutoff date: March 31, 2023.
[a]Assessed in the safety population; [b]Median follow-up for overall survival assessed in the ITT population; [c]Total number of deaths includes number of deaths during treatment period and post-treatment period; [d]Any death that occurred on or after first dose of treatment until 42 days after the last dose of treatment; [e]Any death that occurred after 42 days of the last dose date of treatment.

COMMANDS: events of interest

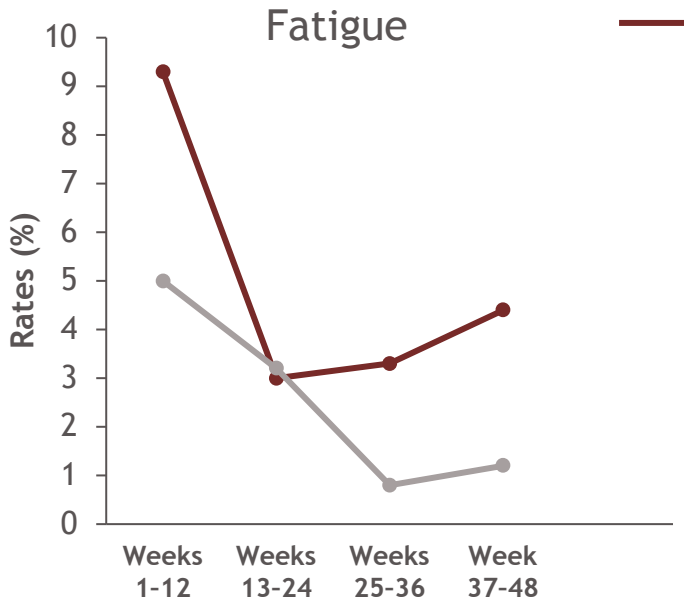
- EOI were reported in 105 (57.7%) and 81 (45.3%) patients receiving luspatercept and epoetin alfa, respectively

	Luspatercept (N = 182)		Epoetin alfa (N = 179)	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
EOI	105 (57.7)	77.1	81 (45.3)	68.2
Asthenia (incl. fatigue, malaise, and lethargy)	56 (30.8)	30.9	44 (24.6)	31.2
Hypertension	29 (15.9)	14.5	17 (9.5)	10.4
Malignancies	17 (9.3)	7.6	12 (6.7)	7
Premalignant disorders	9 (4.9)	3.9	11 (6.1)	6.3
Kidney toxicity	16 (8.8)	7.4	12 (6.7)	7.1
Thromboembolic events	9 (4.9)	4	5 (2.8)	2.9
Immunogenicity hypersensitivity type reactions	7 (3.8)	3.1	3 (1.7)	1.7
Immunogenicity injection local type reactions	5 (2.7)	2.2	1 (0.6)	0.6
Liver toxicity	3 (1.6)	1.3	5 (2.8)	2.9

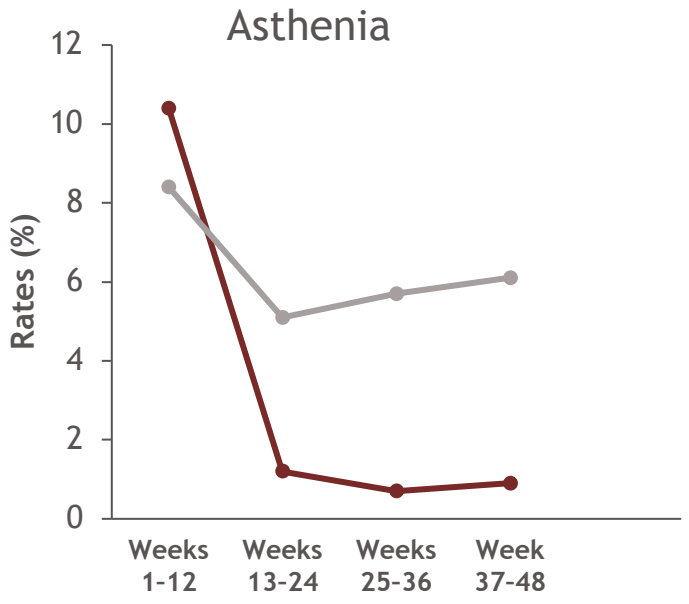
Data cutoff date: March 31, 2023.
EAIR, exposure-adjusted incidence rates; PY, person-year.

COMMANDS: fatigue and asthenia

- Reported rates of fatigue and asthenia during weeks 1–24 decreased over time
- Most fatigue and asthenia events in the luspatercept arm were grade 1/2 and were not considered clinically significant
  - One grade 3 fatigue event was reported, which did not lead to dose reduction nor result in discontinuation of study drug



No. of patients				
Luspatercept	182	169	151	113
Epoetin alfa	179	156	122	82



No. of patients				
Luspatercept	182	169	151	113
Epoetin alfa	179	156	122	82

Data cutoff date: March 31, 2023.

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)

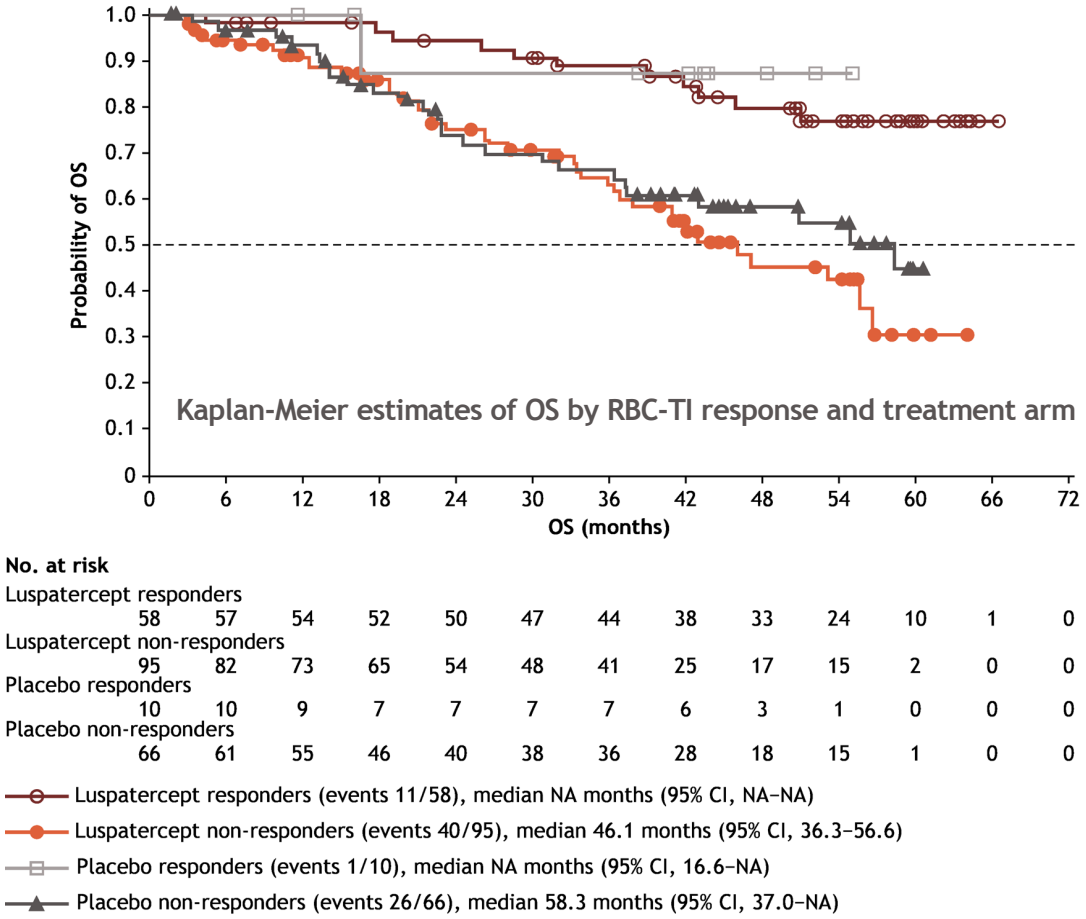
Data cutoff: February 7, 2025. Median follow-up (range) was 30.6 (1-65) months for luspatercept and 28.8 (0-69) months for epoetin alfa.
[a]Higher-risk category comprises high and very high-risk categories per IPSS-R. [b]PY is calculated from the treatment start date to HR-MDS onset date or from the 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.

Garcia-Manero G, et al. ASH 2023 [Abstract #193]

Overall survival

OS and PFS by RBC-TI ≥ 8 weeks in MEDALIST study

Responders were patients who achieved RBC-TI ≥ 8 weeks during the first 24 weeks of double-blind treatment



OS

Luspatercept responders had significantly ($P < 0.0001$) longer OS than luspatercept non-responders

PFS

Median PFS (95% CI) was not reached for luspatercept responders (NA months) or luspatercept non-responders (NA; 223.57–NA months) at week 25 (HR, < 0.01; $P = 0.1205$)

Luspatercept responders vs placebo responders: HR, 1.47 (95% CI, 0.19-11.46); $P = 0.7088$; Luspatercept non-responders vs placebo non-responders: HR, 1.28 (95% CI, 0.78-2.10); $P = 0.3355$; Luspatercept responders vs luspatercept non-responders: HR, 0.26 (95% CI, 0.13-0.52); $P < 0.0001$. Data cut: January 15, 2022. OS was defined as time from randomization to death from any cause. PFS was time from MDS diagnosis to AML progression. CI, confidence interval; NA, not applicable; OR, odds ratio.

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Results: achievement of response

Patients, n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Responders[a] by baseline RBC transfusion burden	**n = 58**	**n = 10**
≥ 6 units/8 weeks	6 (10.3)	1 (10.0)
4 to < 6 units/8 weeks	15 (25.9)	1 (10.0)
< 4 units/8 weeks	37 (63.8)	8 (80.0)
Non-responders[a] by baseline RBC transfusion burden	**n = 95**	**n = 66**
≥ 6 units/8 weeks	60 (63.2)	32 (48.5)
4 to < 6 units/8 weeks	26 (27.4)	22 (33.3)
< 4 units/8 weeks	9 (9.5)	12 (18.2)
RBC-TI ≥ 8 weeks during		
Entire study period	75 (49.0)	12 (15.8)
Weeks 1–24[b,c]	58 (37.9)	10 (13.2)
Weeks 1–48[b]	69 (45.1)	12 (15.8)
RBC-TI ≥ 24 weeks during		
Entire study period	46 (30.1)	4 (5.3)
Weeks 1–24[d]	20 (13.1)	1 (1.3)
Weeks 1–48	38 (24.8)	2 (2.6)

Data cut: January 15, 2022.
[a]Response defined as RBC-TI ≥ 8 weeks during weeks 1-24; [b]Data presented previously in Fenaux P, et al. *N Engl J Med* 2020;382:140–151 with a data cut of May 8, 2018; [c]OR, 5.07 (95% CI, 2.28-11.26); [d]*P* = 0.003. *P* < 0.0001 for RBC-TI.

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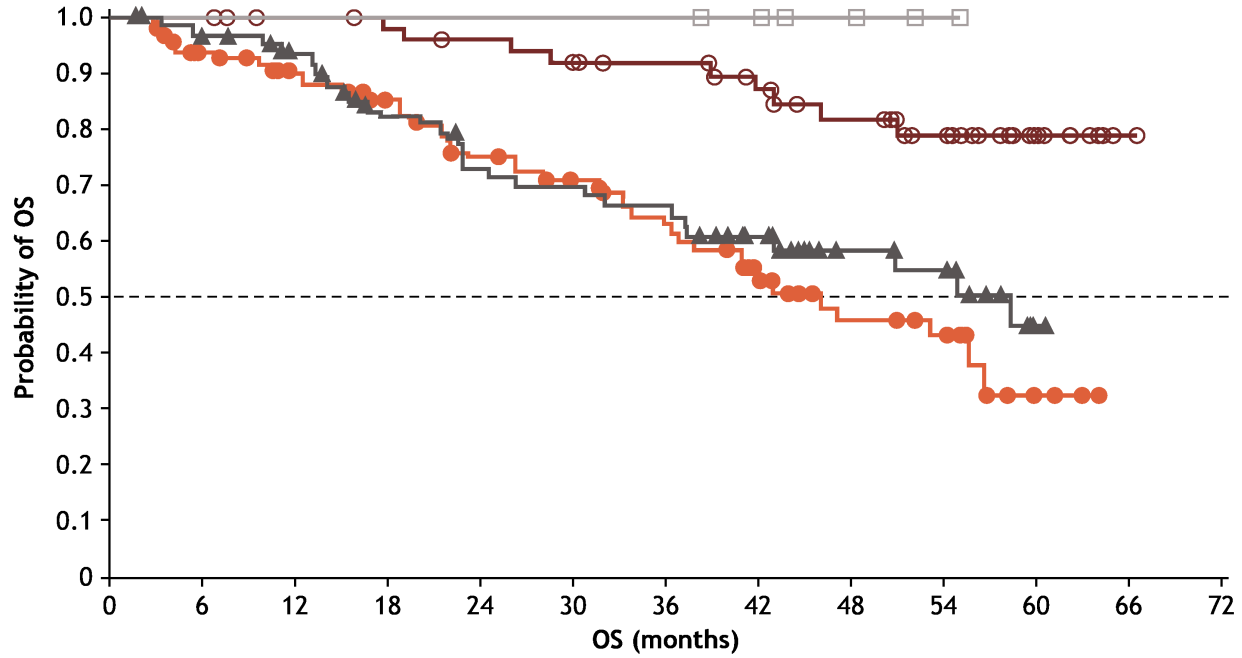
Results: OS by Hb response

Kaplan-Meier estimates of OS by mean increase in Hb ≥ 1 g/dL response during weeks 1-24

Responders were defined as patients who achieved a mean Hb increase ≥ 1 g/dL during weeks 1–24 of double-blind treatment

Response	Events	Median OS (95% CI), months
Luspatercept responders	9/54	NA (NA-NA)
Luspatercept non-responders	42/99	46.1 (36.3-56.6)
Placebo responders	0/6	NA (NA-NA)
Placebo non-responders	27/70	58.3 (37.0-NA)



No. at risk

Luspatercept responders	54	54	51	49	47	44	42	36	31	23	9	1	0
Luspatercept non-responders	99	85	76	68	57	51	43	27	19	16	3	0	0
Placebo responders	6	6	6	6	6	6	6	5	3	1	0	0	0
Placebo non-responders	70	65	58	47	41	39	37	29	18	15	1	0	0

Luspatercept non-responders vs placebo non-responders: HR, 1.25 (95% CI, 0.77-2.04); $P = 0.3617$.
Luspatercept responders vs luspatercept non-responders: HR, 0.23 (95% CI, 0.11-0.48); $P < 0.0001$.
Data cut: January 15, 2022. OS was defined as time from randomization to death from any cause.
Hb, hemoglobin.

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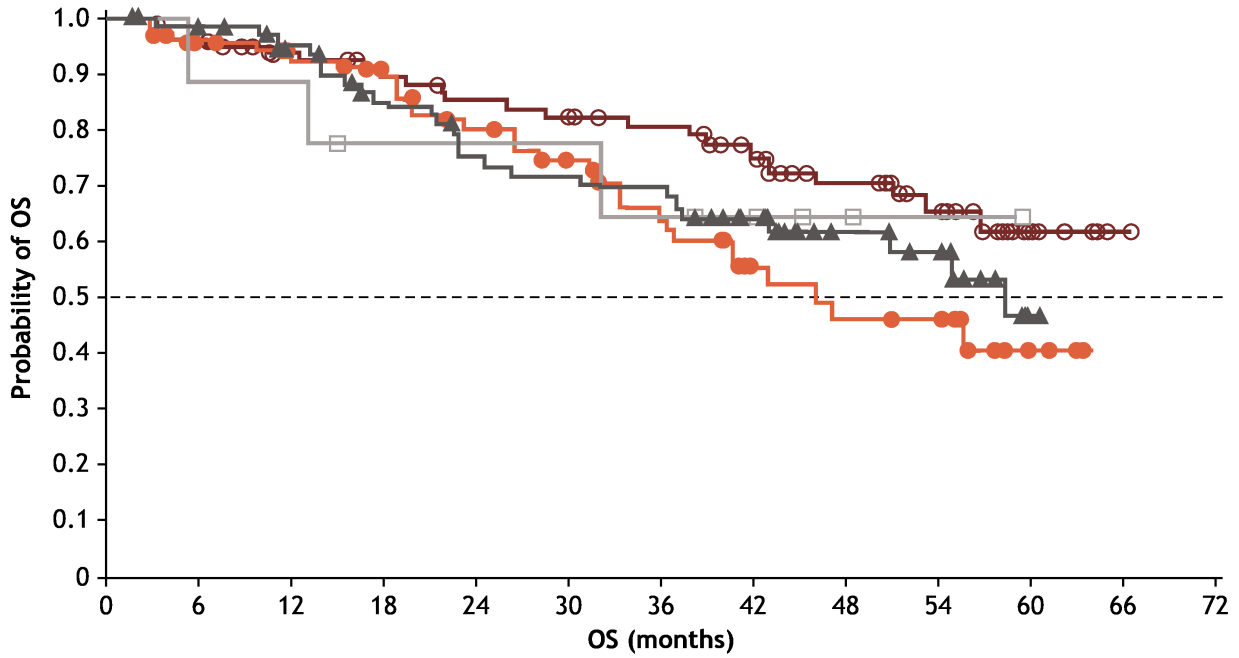
Results: OS by mHI-E response

Kaplan-Meier estimates of OS by mHI-E response during weeks 1-24

Responders were defined as patients who achieved mHI-E during weeks 1-24 of double-blind treatment

Response	Events	Median OS (95% CI), months
Luspatercept responders	23/81	NA (56.6-NA)
Luspatercept non-responders	28/72	46.1 (36.3-NA)
Placebo responders	3/9	NA (5.4-NA)
Placebo non-responders	24/67	58.3 (43.1-NA)



No. at risk

Luspatercept responders	81	77	69	64	60	57	54	45	35	25	9	1	0
Luspatercept non-responders	72	62	58	53	44	38	31	18	15	14	3	0	0
Placebo responders	9	8	8	6	6	6	5	4	2	1	0	0	0
Placebo non-responders	67	63	56	47	41	39	38	30	19	15	1	0	0

Luspatercept responders vs placebo responders: HR, 0.7 (95% CI, 0.21-2.33); *P* = 0.5552.
Luspatercept non-responders vs placebo non-responders: HR, 1.23 (95% CI, 0.71-2.12); *P* = 0.4634.
Luspatercept responders vs luspatercept non-responders: HR, 0.53 (95% CI, 0.31-0.93); *P* = 0.0243.
Data cut: January 15, 2022. OS was defined as time from randomization to death from any cause.
mHI-E, modified hematologic improvement-erythroid.

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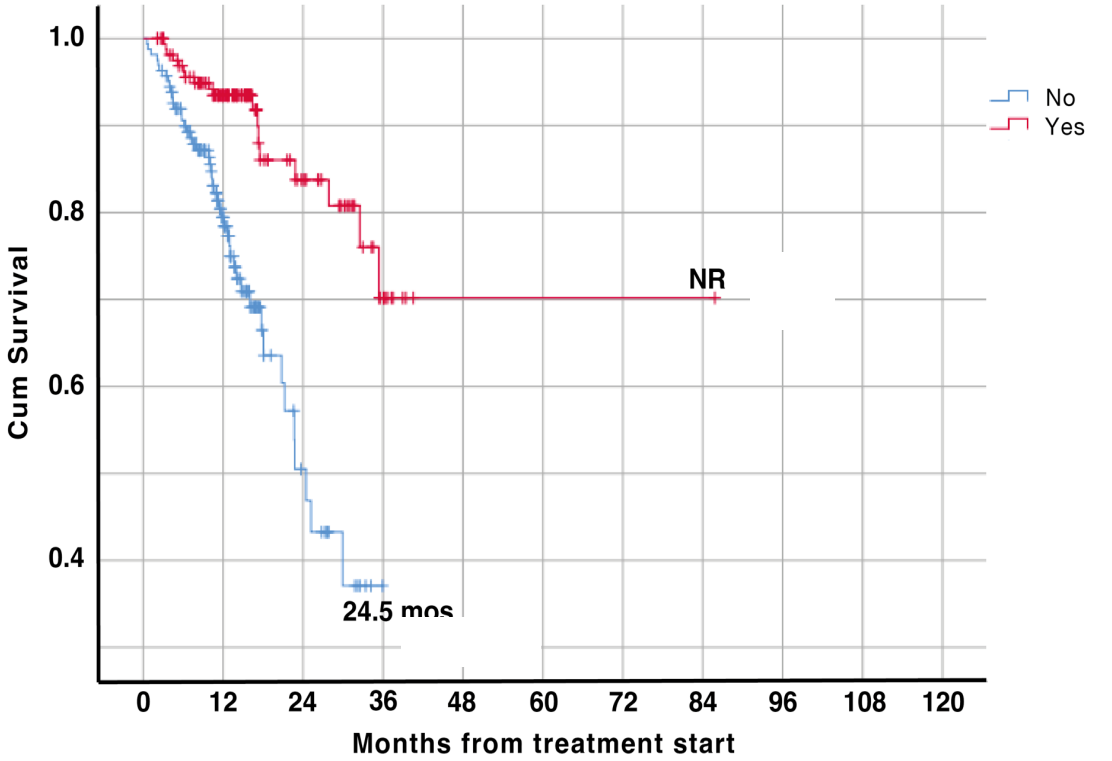
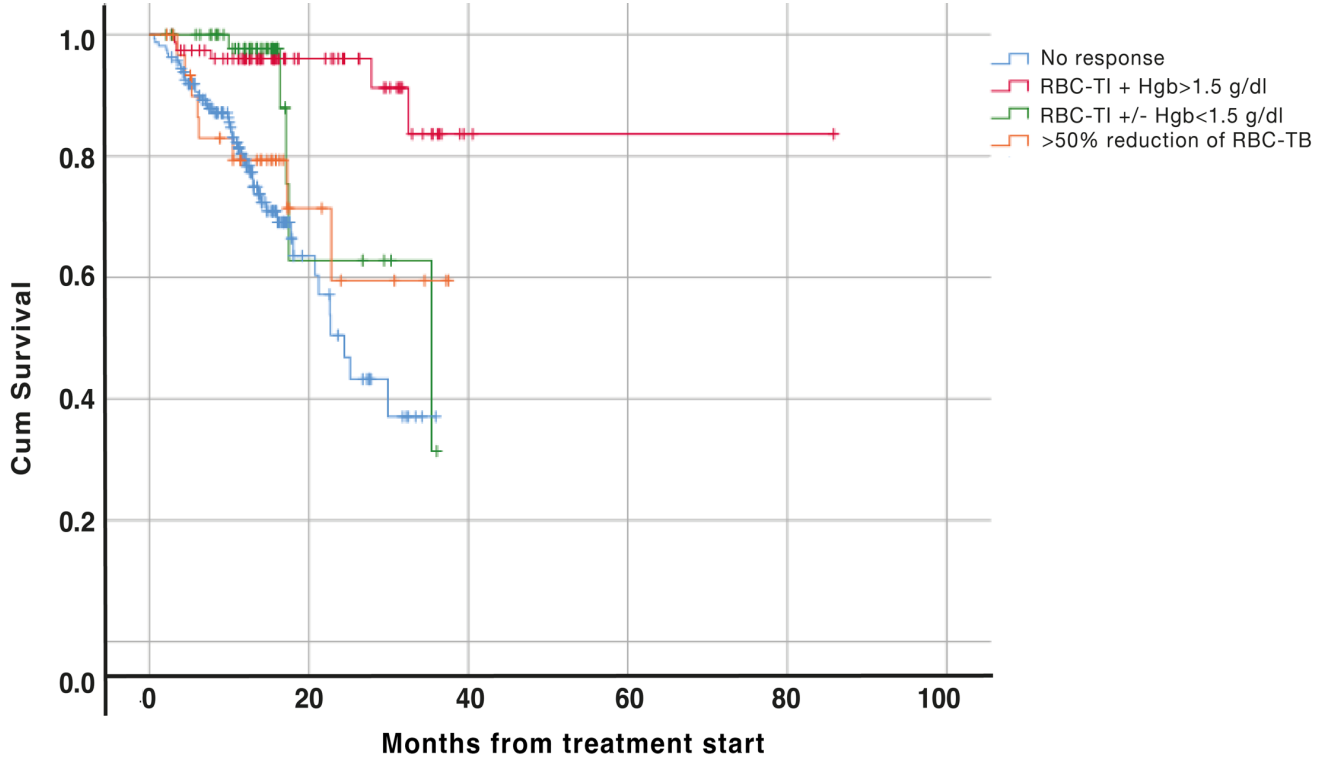
Luspatercept Responders: Improved Overall Survival and Predictors of Response in real world

With a median follow up of 14.6 months from start of luspatercept treatment, median OS was not reached (NR) among responders compared to 24.5 months for non-responders (p <.001) (Figure-1).

Median OS was significantly longer among patients with RBC-TI and Hgb> 1.5 g/dl increase compared with other HI-E and non-responders (p<.000)





ASH 2023, Abstract 1871

Consagra et al , HemaSphere, 2025

Note to authors: this is an oral presentation for ~10 minutes followed by a 5-minute Q&A session.

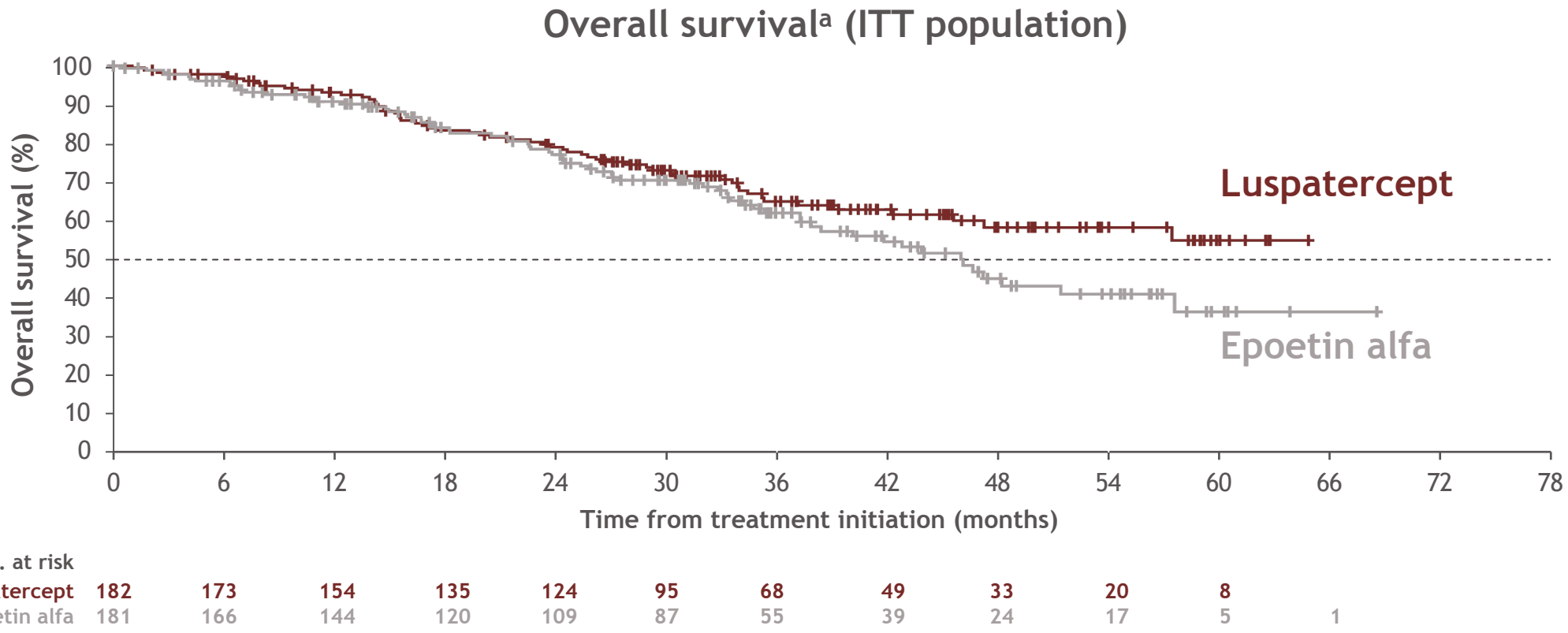
Overall survival and duration of transfusion independence for first-line ESA-naive patients with lower-risk myelodysplastic syndromes treated with luspatercept versus epoetin alfa in the COMMANDS trial

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;

[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

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.
NR, not reached.
[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.

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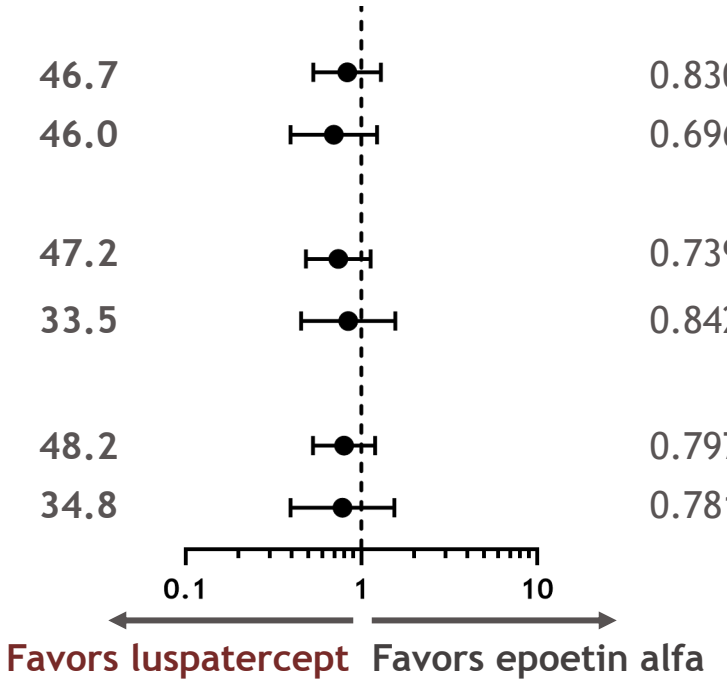
COMMANDS: subgroup analysis of overall survival (> 2.5 years of follow-up)

	Luspatercept		Epoetin alfa		HR (95% CI)[b]
	Deaths, n/N (%)	Median OS[a] (months)	Deaths, n/N (%)	Median OS[a] (months)	
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.

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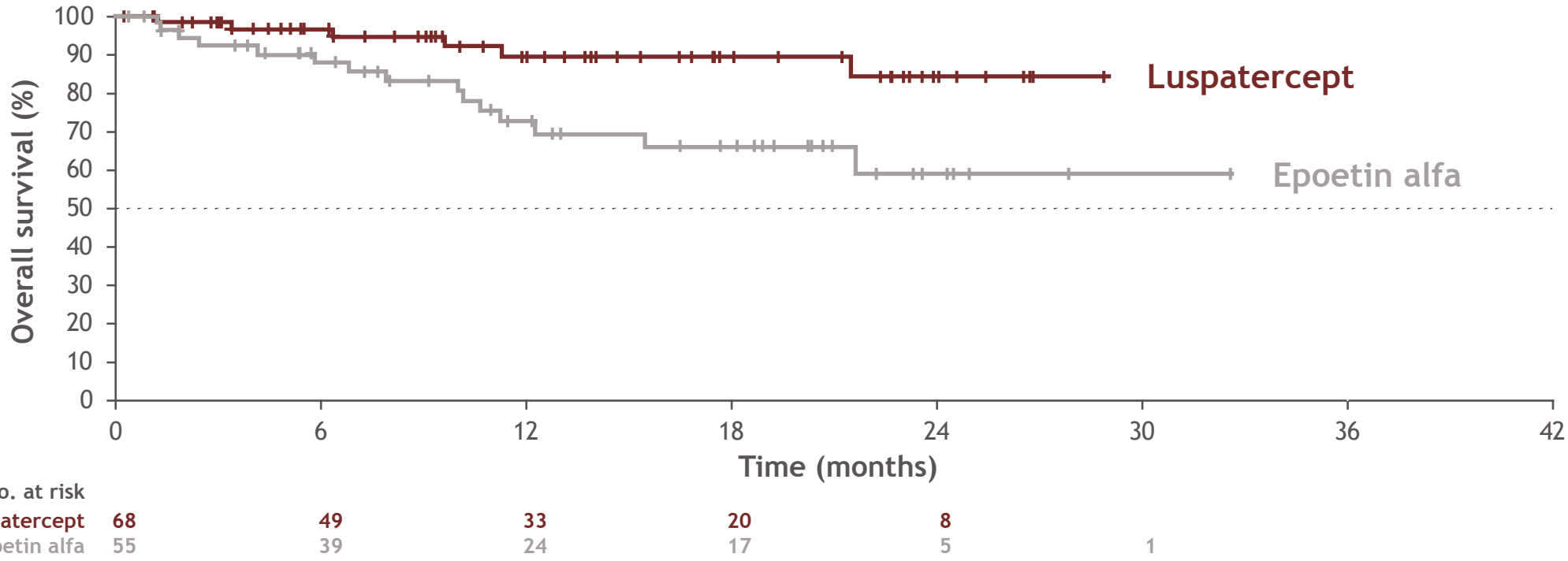
COMMANDS: landmark analysis of overall survival (≥ 36 months)

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 (i.e., 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.

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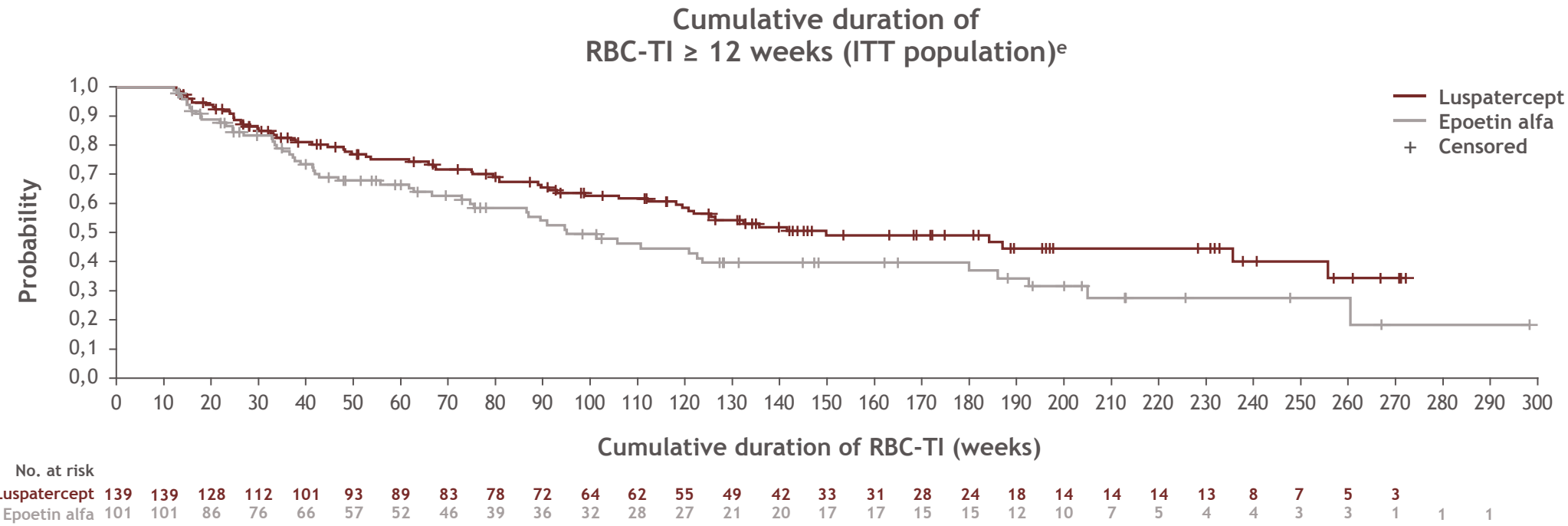
COMMANDS: RBC-TI ≥ 12 weeks (Week 1-EOT) (> 2.5 years of follow-up)

	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



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; OR, odds ratio.
[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.

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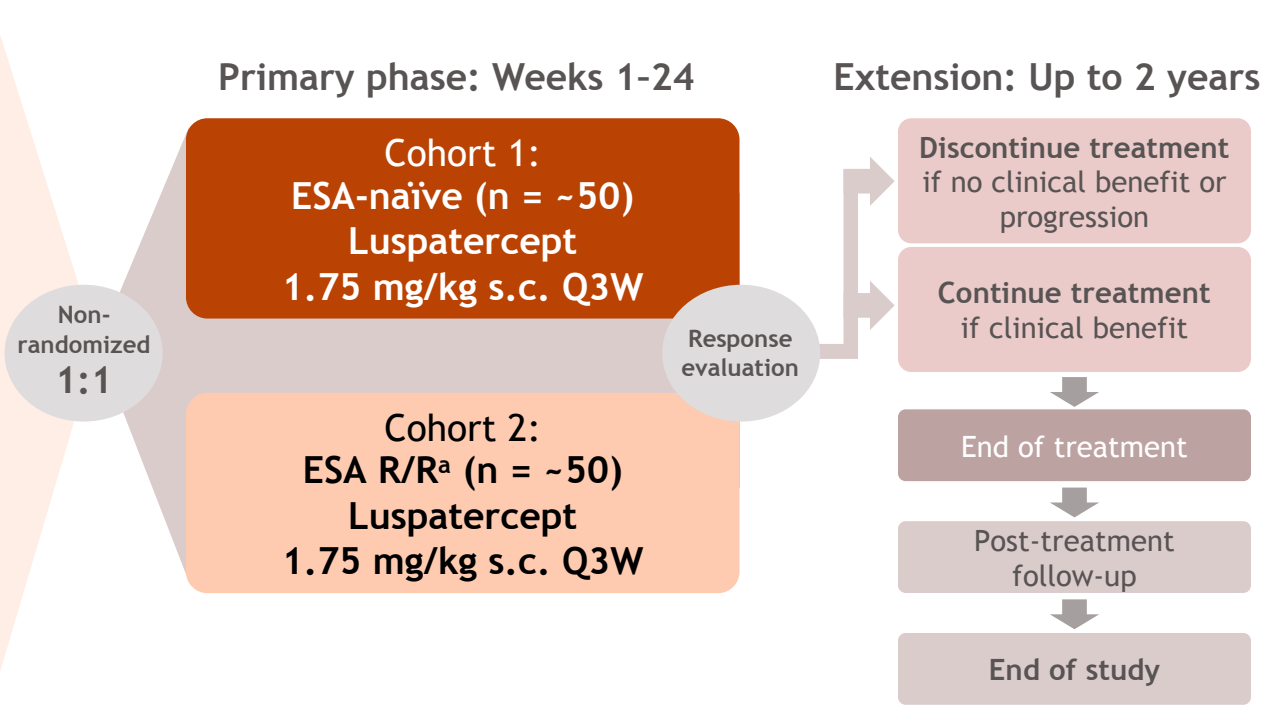
Luspatercept: Start with maximum approved dose?

Ongoing: MAXILUS Phase 3 trial[1,2]

Key eligibility criteria

- IPSS-R very low-, low- or intermediate-risk MDS (with or without RS)
- **Requiring RBC transfusions** (≥ 1 RBC unit within 8 weeks prior to treatment)
- **Hb ≤ 10 g/dL**
- Endogenous sEPO < 500 U/L for ESA-naïve cohort



Primary endpoint

RBC-TI for ≥ 8 weeks and concurrent Hb increase of ≥ 1 g/dL (weeks 1-24)

Secondary endpoints

RBC-TI over any consecutive 8-/12-/16-/24-week period

Time to onset and maximum duration of RBC-TI periods

Mean Hb increases (≥ 1 g/dL and ≥ 1.5 g/dL from baseline)

Change in total RBC units transfused over 16 weeks

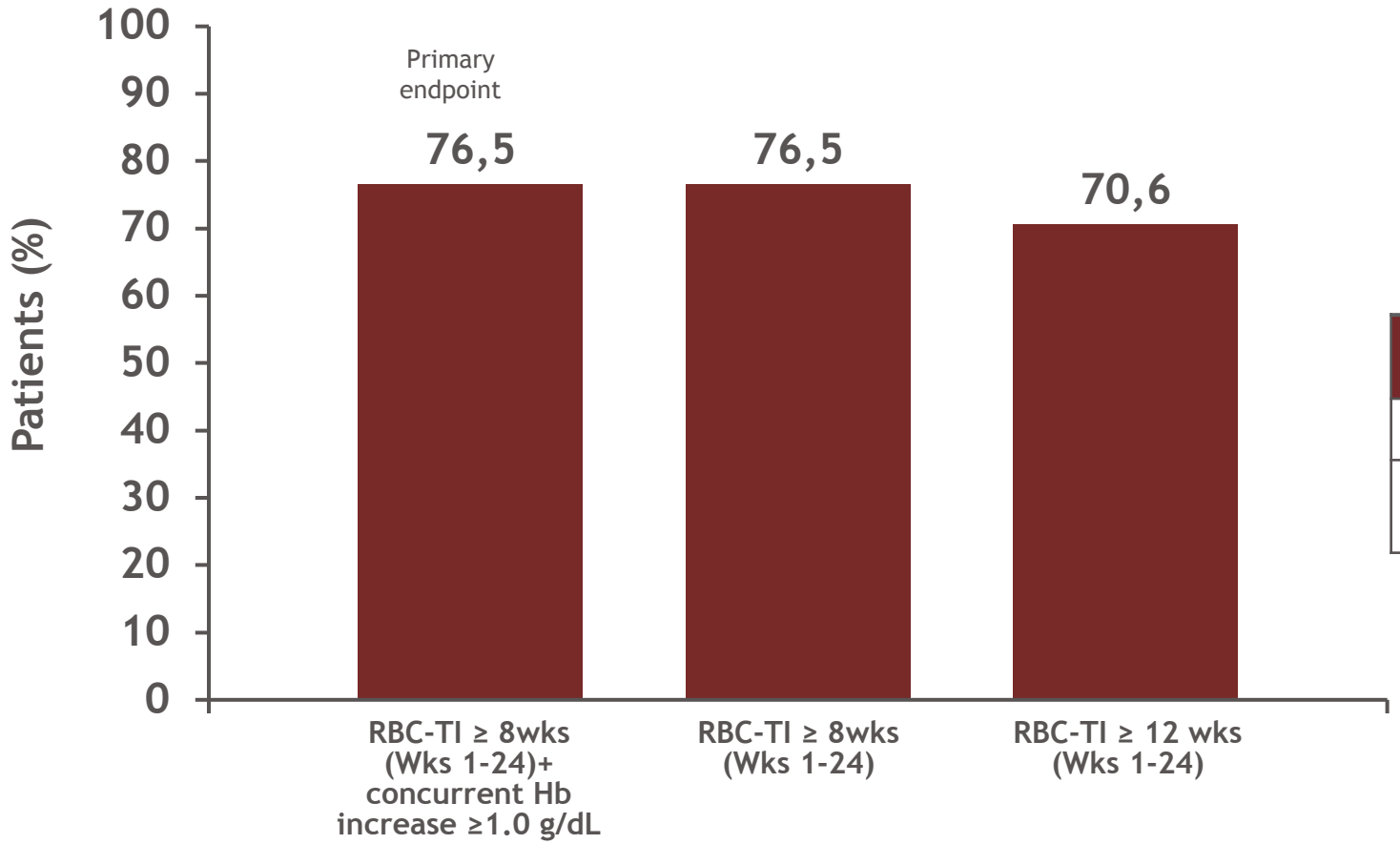
OS, progression to AML, QoL, safety

[a] R/R or intolerant to prior ESA.

AML: Acute myeloid leukaemia; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; IPSS-R: International Prognostic Scoring System-Revised; MDS: myelodysplastic syndromes; OS: overall survival; Q3W: once every 3 weeks; QoL: quality of life; RBC: red blood cell; R/R: relapsed/refractory; RBC-TI: red blood cell transfusion independence; RS: ring sideroblast; s.c.: subcutaneous; sEPO: serum erythropoietin.

1. https://clinicaltrials.gov/study/NCT06045689 (Accessed Jun 2024); 2. Della Porta MG, et al. EHA 2024. Abstract PB2622.

ESA-naive cohort preliminary efficacy: RBC-TI (n = 17[a]) and Hb change (n = 15[b])



	Median (IQR) g/dL
Baseline Hb	**8.1 (7.3-8.6)**
Hb change from Baseline(Weeks1-24)	2.8 (2.3-3.8)

Data cutoff: January 15, 2025.
[a]Data are among the efficacy-evaluable population, which includes patients who received their first treatment ≥ 24 weeks prior to data cutoff (ESA-naive, n = 17). [b]Data are among patients in the efficacy-evaluable population who have both baseline and post-baseline values (ESA-naive, n = 15). [c]Data are among the all-treated population, defined as all patients who received ≥ 1 dose of study intervention (ESA-naive, n = 40).
ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; RBC-TI, red blood cell-transfusion independence.

Della Porta et al, EHA 2025

Summary of safety, including TEAEs[a]

Patients with ≥ 1 event, n (%)	ESA-naive (n = 40)		ESA-R/R/I (n = 50)	
Any-grade TEAE	29 (72.5)		42 (84.0)	
Any-grade treatment-related TEAE	5 (12.5)		17 (34.0)	
Grade 3/4 TEAE	15 (37.5)		21 (42.0)	
Grade 3/4 treatment-related TEAE	1 (2.5)		3 (6.0)	
Serious TEAEs[b]	9 (22.5)		15 (30.0)	
TEAEs leading to drug interruption	2 (5.0)		8 (16.0)	
TEAEs leading to dose reduction	1 (2.5)		1 (2.0)	
TEAEs leading to permanent discontinuation of study intervention	0		1 (2.0)	
Progression to AML	0		0	
	n (%)	EAIR	n (%)	EAIR
Patients with ≥ 1 treatment-emergent EOI[c]	9 (22.5)	68.8	22 (44.0)	119.7
Asthenia (incl. fatigue)	3 (7.5)	20.9	13 (26.0)	65.4
Hypertension	3 (7.5)	21.4	3 (6.0)	13.3
Fractures	2 (5.0)	13.6	5 (10.0)	22.9
Kidney toxicity	2 (5.0)	13.8	3 (6.0)	13.5
Malignancies	0	0	2 (4.0)	8.8

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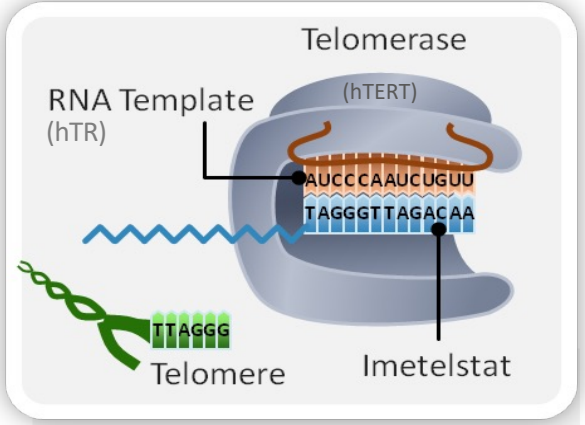
Imetelstat in TD LR MDS
IMerge Phase 3 Trial Design
(MDS3001; NCT02598661)



Phase 3
Double blind, randomized
118 Clinical sites in 17 countries

Patient Population (ITT N = 178)

- IPSS low- or intermediate 1- risk MDS
- **relapsed/refractory[a] to ESA or EPO >500 mU/mL (ESA ineligible)**
- **Transfusion dependent: ≥4 units RBCs/8 weeks over 16-week pre-study**
- Non-deletion 5q
- No prior treatment with lenalidomide or HMAs

R 2:1

Imetelstat
7.5 mg/kg IV/4 weeks
(N = 118)

Stratification:
- Transfusion burden (4-6 vs >6 units)
- IPSS risk category (low vs Intermediate 1)

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

Placebo
(N = 60)

Safety population (treated) N = 177
Imetelstat N = 118
Placebo N = 59

Primary endpoint:
- 8-week RBC-TI

Key secondary endpoints:
- 24-week RBC-TI
- Duration of TI
- Hematologic improvement-erythroid
- Safety

Key exploratory endpoints:
- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

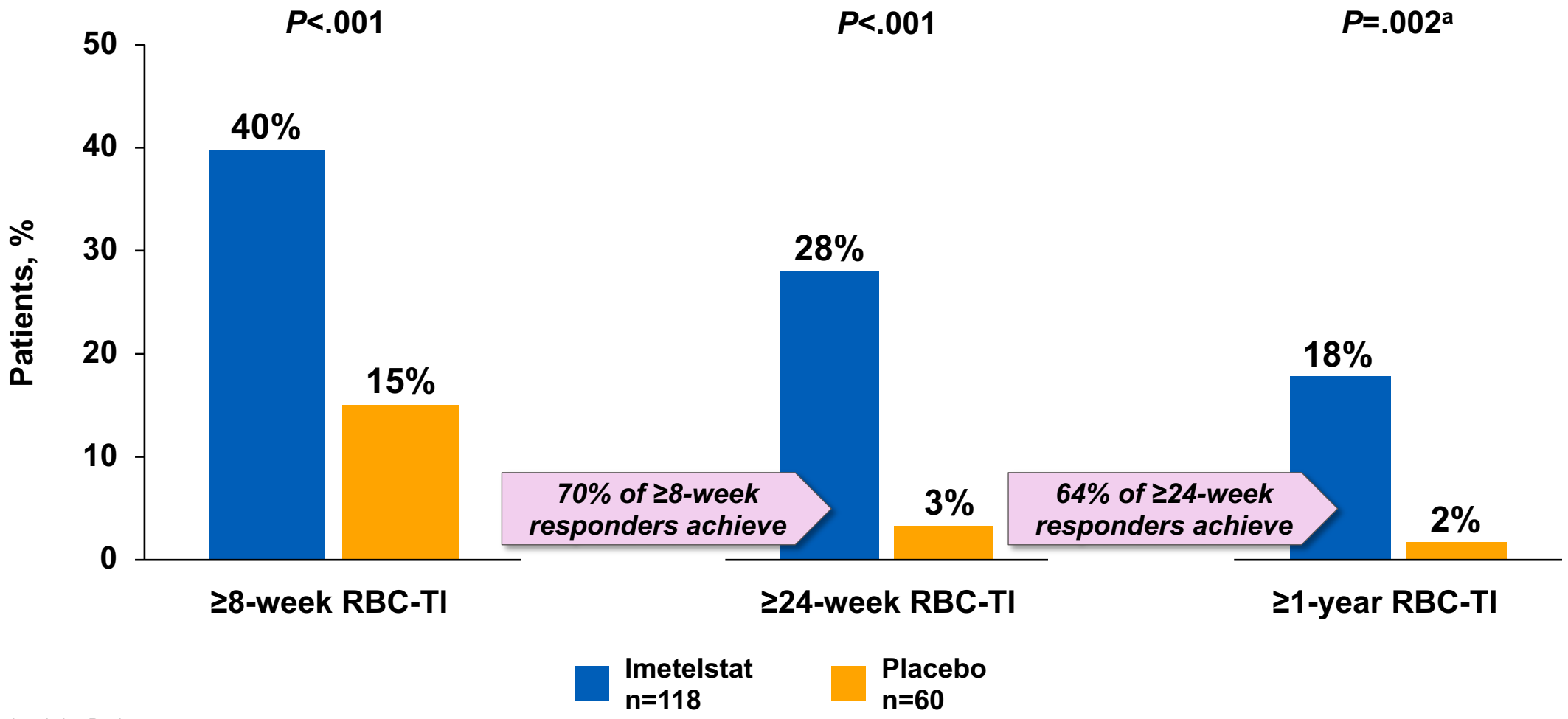
Platzbecker , Santini et al, Lancet. 2024 Jan 20;403(10423):249-260.

Baseline Characteristics

Baseline demographic and disease characteristics	Imetelstat (n=118)	Placebo (n=60)
Median (range) age, y	72 (44-87)	73 (39-85)
Male, n (%)	71 (60)	40 (67)
Median (range) time since diagnosis, y	3.5 (0.1-26.7)	2.8 (0.2-25.7)
WHO classification, n (%)		
RS+	73 (62)	37 (62)
RS−	44 (37)	23 (38)
IPSS risk category, n (%)		
Low	80 (68)	39 (65)
Intermediate-1	38 (32)	21 (35)
Median (range) pretreatment Hb,[a] g/dL	7.9 (5.3-10.1)	7.8 (6.1-9.2)
Median (range) prior RBC transfusion burden, RBC U/8 weeks	6 (4-33)	6 (4-13)
Prior RBC transfusion burden, n (%)		
≥4 to ≤6 U/8 weeks	62 (53)	33 (55)
>6 U/8 weeks	56 (48)	27 (45)
Median (range) sEPO, mU/mL	174.9 (6.0-4460.0)	277.0 (16.9-5514.0)
sEPO level, n (%)[b]		
≤500 mU/mL	87 (74)	36 (60)
>500 mU/mL	26 (22)	22 (37)
Prior ESA, n (%)	108 (92)	52 (87)
Prior luspatercept, n (%)[c]	7 (6)	4 (7)

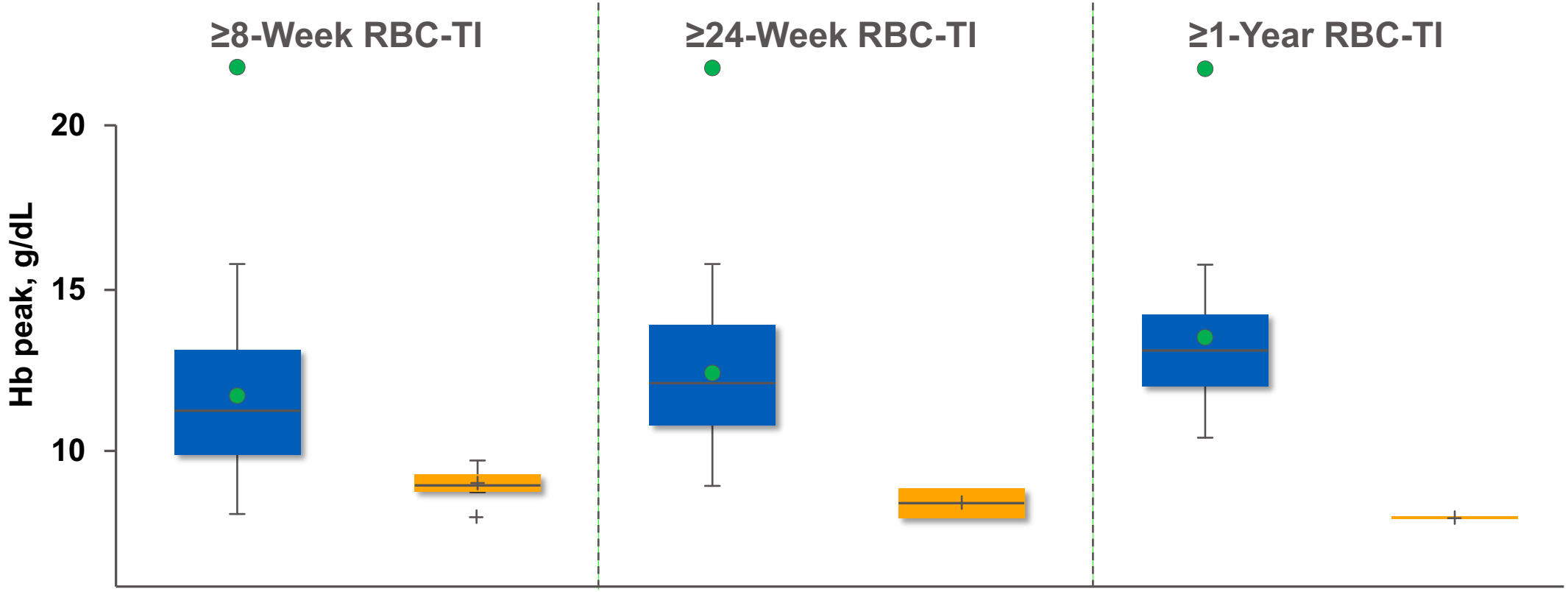
Data cutoff date: October 2022. [a]Average of all Hb values in the 8 weeks before the first dose date, excluding values within 14 days after a transfusion, which was considered to be influenced by transfusion. [b]Data missing for 5 patients in the imetelstat group and 2 in the placebo group. [c]Insufficient number of patients previously treated with luspatercept to draw conclusions about the effect of imetelstat treatment in such patients.
Hb, hemoglobin; ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast, sEPO, serum erythropoietin; WHO, World Health Organization.

Among Imetelstat Responders, RBC-TI Was Durable and Sustained Over Time



[a]Reported as descriptive *P* value.
Data cutoff date: October 2023.
RBC, red blood cell; TI, transfusion independence.

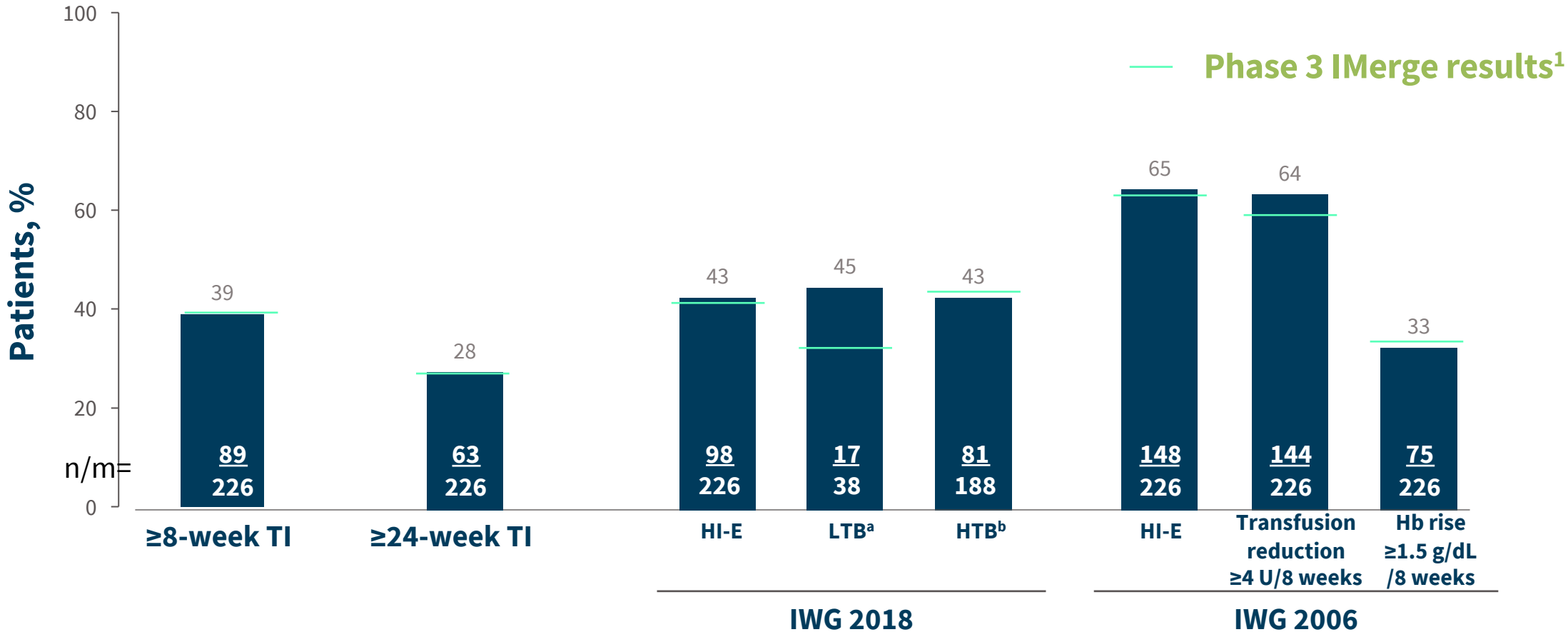
Imetelstat Responders Had Higher Central Hb Peaks Versus Placebo Responders



	Imetelstat	Placebo	Imetelstat	Placebo	Imetelstat	Placebo
Median Hb peak	**11.3**	**8.9**	**12.1**	**8.4**	**13.1**	**7.9**
N (responders)	47	9	33	2	21	1

Exploratory analysis. Hb peak is the maximum Hb value in the longest transfusion free interval excluding the first 2 weeks.
Data cutoff date: October 2023.
Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Clinical Activity Was Observed With Imetelstat *in Pooled Patients Regardless of Prior Treatment*



Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; n/m, number with event/number in population; RBC, red blood cell; TI, transfusion independence.

[a]LTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. [b]HTB defined as ≥8 RBC U in 16 weeks, or ≥4 RBC U in 8 weeks.

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

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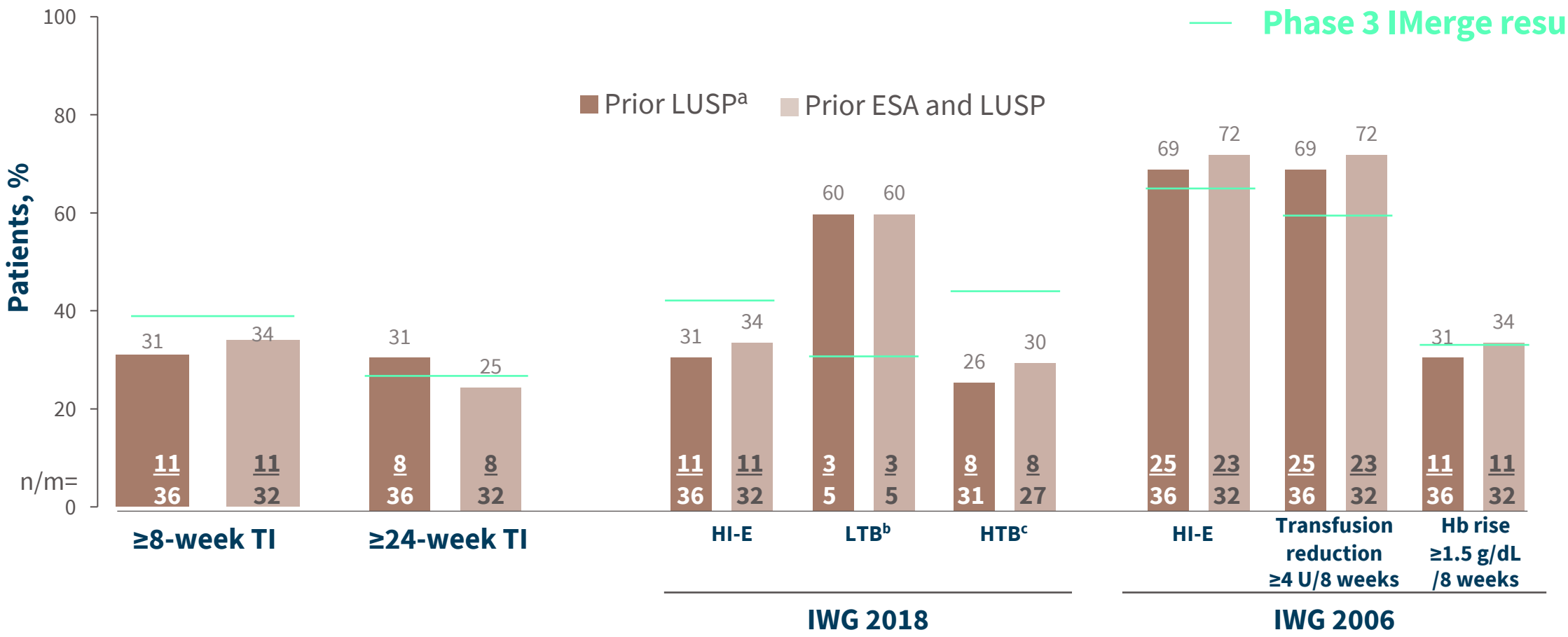
Imetelstat Showed Clinical Activity in Patients *With Prior Luspatercept* (n=36)



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; LUSP, luspatercept; n/m, number with event/number in population; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence.

[a]Of these patients, 31 had RS+ status. [b]LTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. [c]HTB defined as ≥8 RBC U in 16 weeks, or ≥4 RBC U in 8 weeks.

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

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SAFETY

Most Common AEs of imetelstat Were Hematologic

- Grade 3–4 thrombocytopenia and neutropenia were the most frequently reported AEs, most often reported during Cycles 1–3
  - There were no fatal hematologic AEs
- Nonhematologic AEs were generally low grade
- No cases of Hy's Law or drug-induced liver injury observed
  - The incidence of grade 3 liver function test laboratory abnormalities was similar in both treatment groups

AEs (≥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)[a]	2 (2)[b]	8 (14)[a]	3 (5)[b]
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

Data cutoff: October 13, 2022.

[a]Included COVID-19, asymptomatic COVID-19, and COVID-19 pneumonia. [b]Only COVID-19 pneumonia events were grade 3–4 COVID-19.

AE, adverse event; ALT, alanine aminotransferase.

Low Rates of Disease Progression and Progression to AML

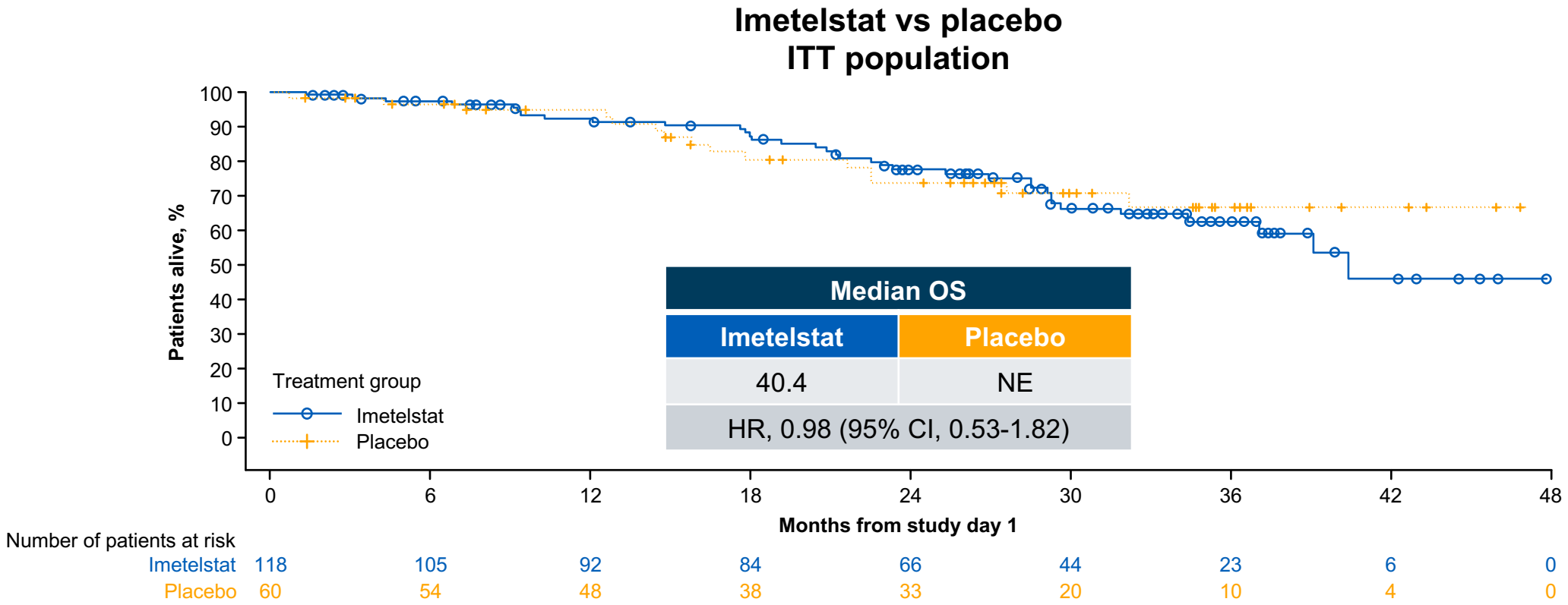
	Imetelstat (n=118)	Placebo (n=60)
Progression-free survival		
Number of PFS events, n (%)	29 (24.6)	14 (23.3)
Median (95% CI), months	NE (29.2-NE)	NE (16.7-NE)
HR (95% CI)[a] [*P* value*]	0.85 (0.44-1.64) [0.631]	
Disease progression, n (%)	13 (11.0)	8 (13.3)
Progression to AML		
n (%)	2 (1.7)	2 (3.3)
Median (95% CI), months	NE (NE-NE)	NE (NE-NE)
HR (95% CI)[a] [*P* value*]	0.45 (0.06-3.23) [0.418]	

- Median estimated PFS has not been reached in either arm
- The rate of progression to AML was low in both treatment arms

Data cutoff date: January 2024.
[a]Cox proportional hazard model, stratified by prior RBC transfusion burden (≤6 U vs >6 U RBC) and International Prognostic Scoring System risk category (low vs intermediate-1), with treatment as the only covariate;
*Reported as descriptive *P* value.
AML, acute myeloid leukemia; HR, hazard ratio; MDS, myelodysplastic syndrome; NE, not estimable; PFS, progression-free survival.

Overall survival

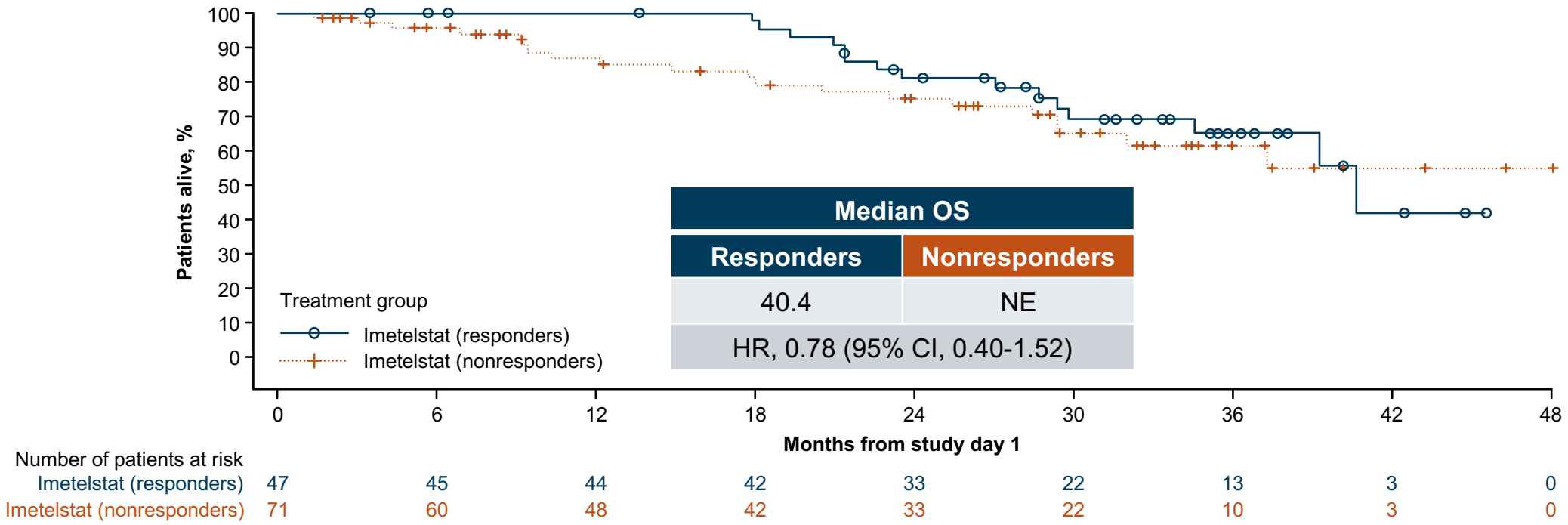
No Detriment With Imetelstat Treatment on OS*



- As of January 2024, 55 (47%) and 26 (43%) patients were in follow-up in the imetelstat and placebo groups, respectively
- Median duration of follow-up was 32 months for imetelstat and 28 months for placebo

*Exploratory analysis. Data cutoff date: January 2024.
HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival.

OS in Imetelstat ≥8-Week RBC-TI Responders vs Nonresponders*



- Two-year OS rates: 78% in the imetelstat group (81% in ≥8-week RBC-TI responders, and 75% in nonresponders) versus 74% in the placebo group

*Exploratory analysis. Data cutoff date: January 2024.
HR, hazard ratio; NE, not estimable; OS, overall survival; RBC, red blood cell; TI, transfusion independence.

Thanks!

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INTERCEPT-MDS

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 953407