FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
24-25 ottobre 2025

Risultati degli studi clinici e traslazionali con imetelstat

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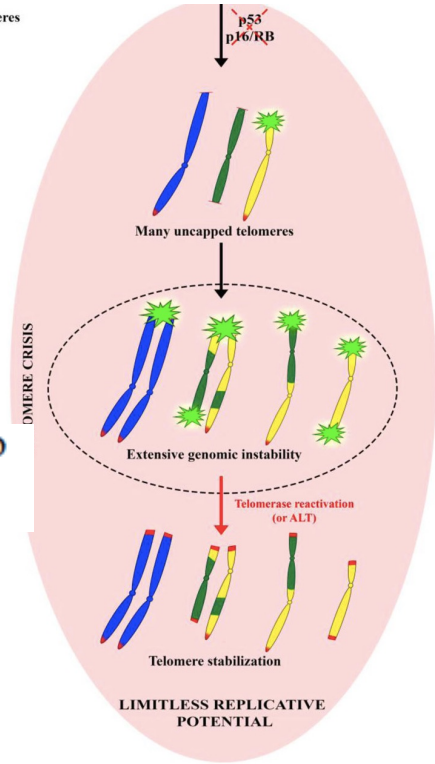
Telomere dysfunction in MDS

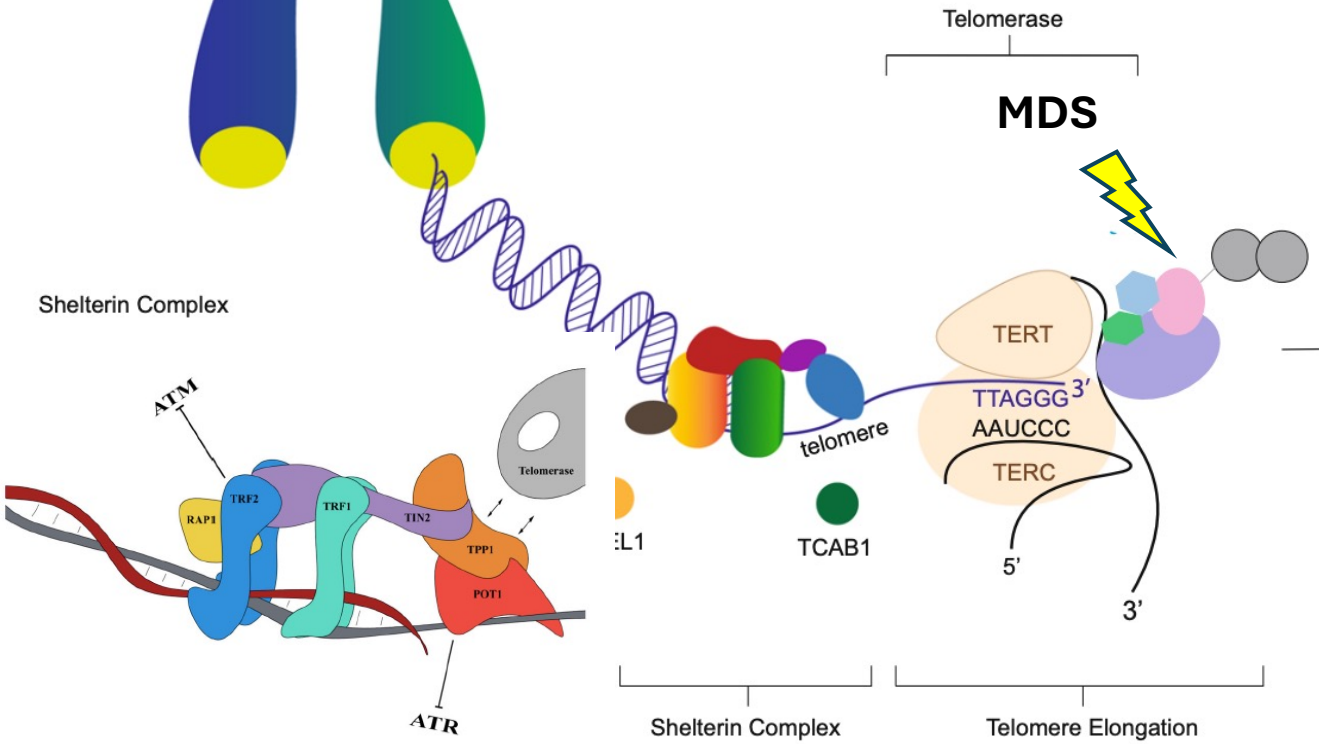
- *TERT* and *TERC* mutations in ≈ 3% of MDS, with a high rate of AML transformation

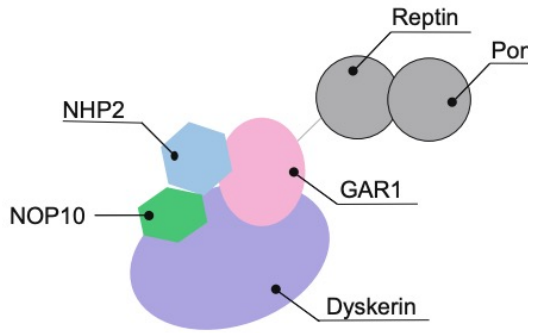
- Shorter telomere lenght in HSC in MDS mouse model and increased hTERT expression in MDS

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.





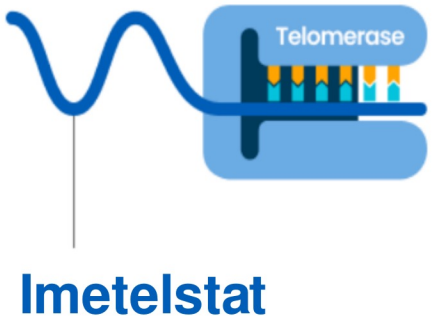
Adapted from Kam et al., NPJ Genom Med 2021

Fiorini E et al *Differentiation* 2018

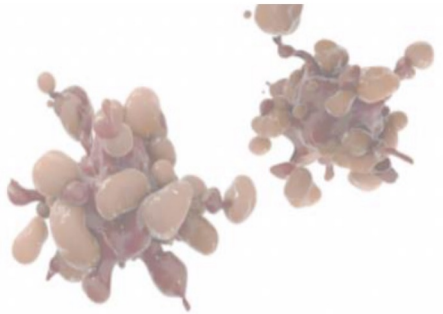
Imetelstat Mechanism of Action for RBC TI

Malignant HSCs/HPCs with elevated telomerase activity

Imetelstat binds to telomerase, inhibits its activity and prevents maintenance of telomeres



Apoptosis of malignant HSCs/HPCs

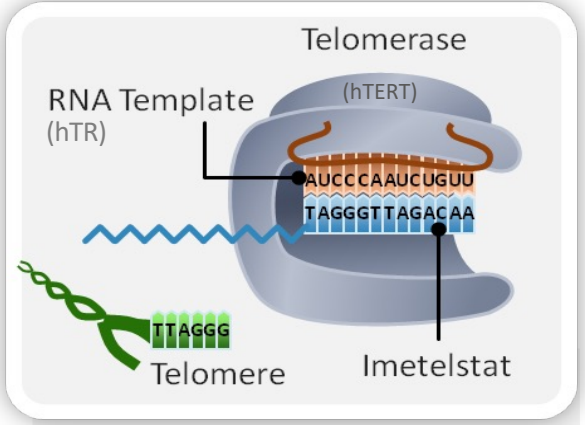


Recovery of erythropoiesis

Increased Hgb leading to RBC TI

HSCs/HPCs = hematopoietic stem/progenitor cells

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.

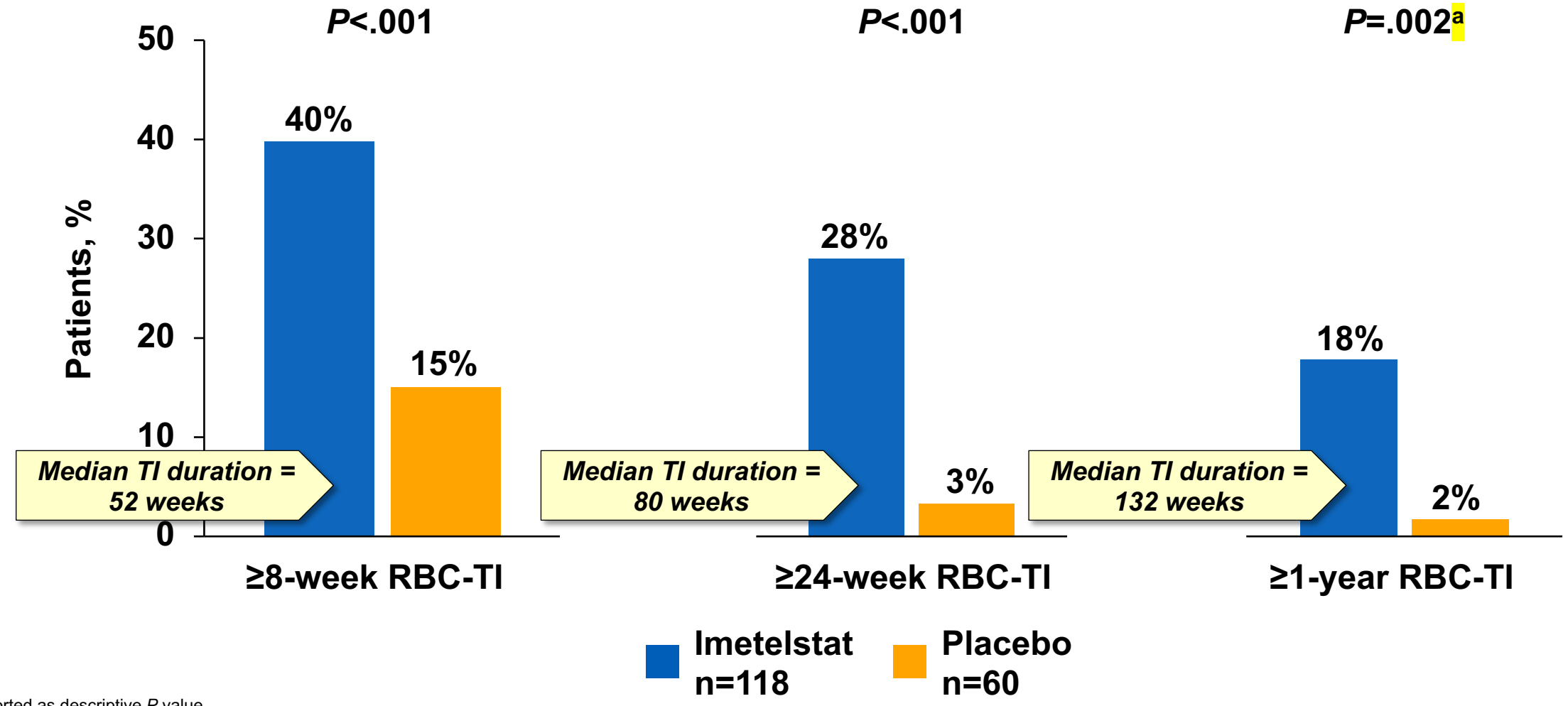
Baseline Characteristics

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.

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

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.

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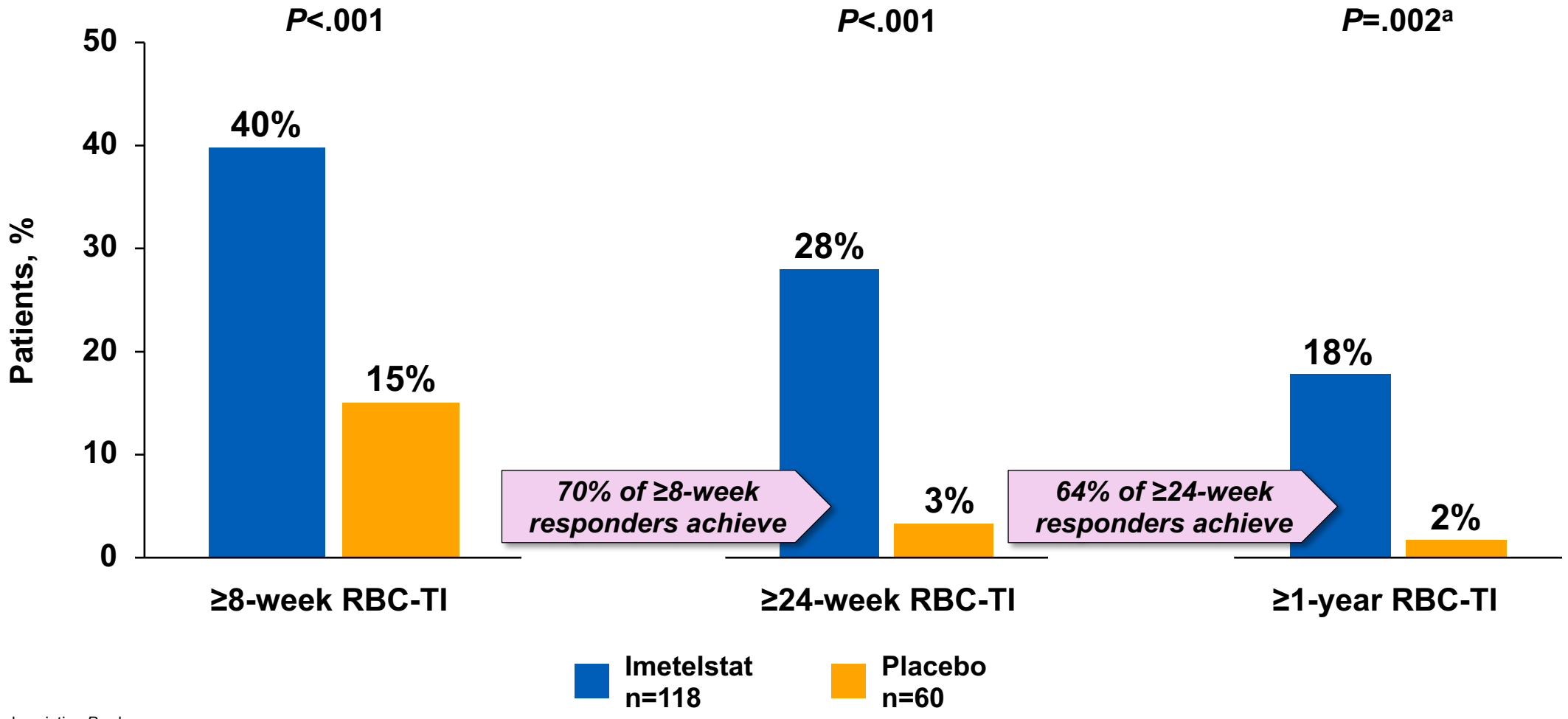

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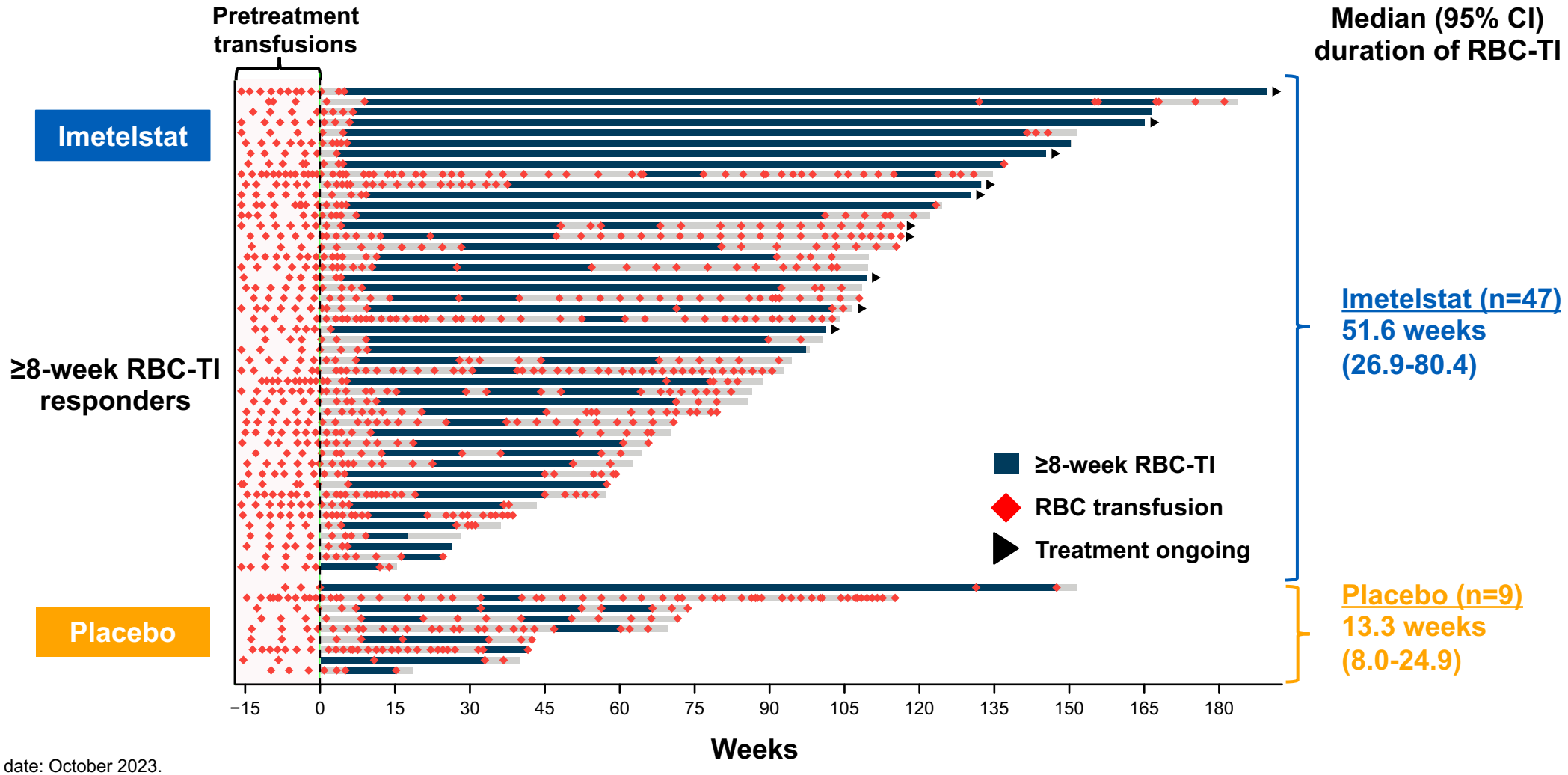
Data cutoff date: October 2023.
RBC, red blood cell; TI, transfusion independence.

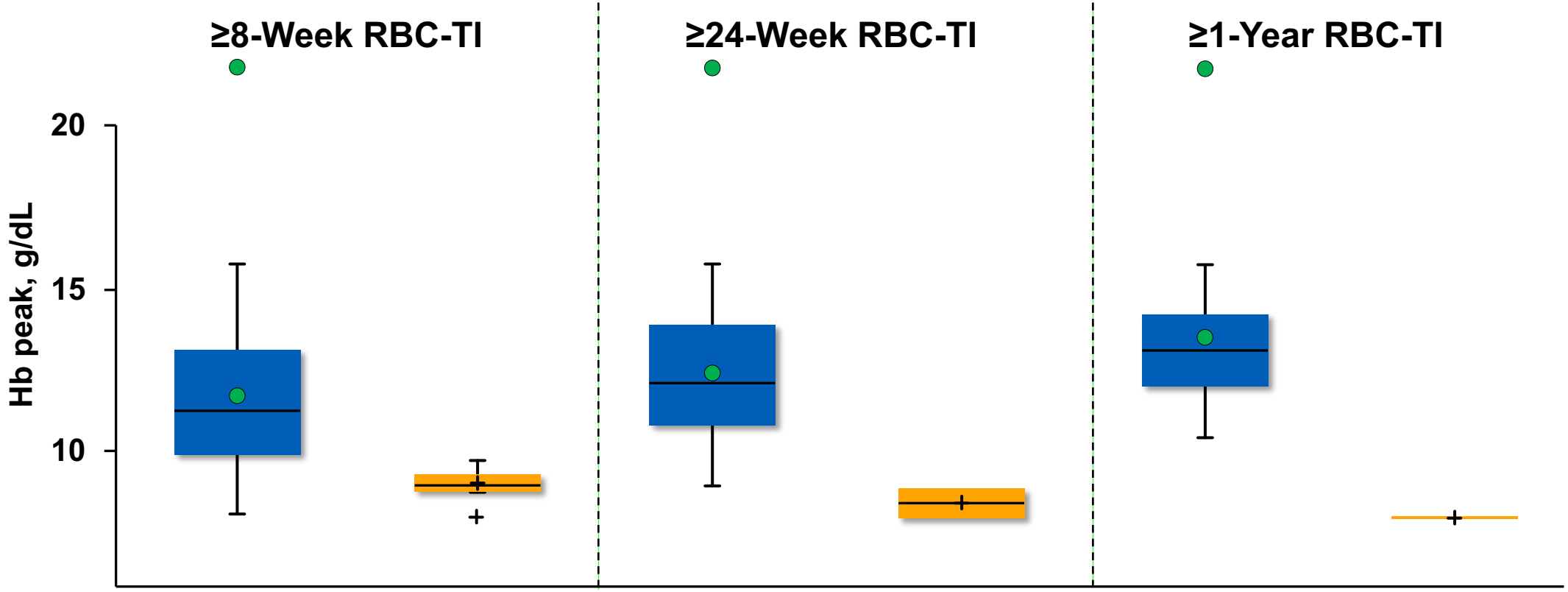
Platzbecker , Santini et al, Lancet. 2024 Jan 20;403(10423):249-260.

83% of Imetelstat Responders Had a Single Continuous RBC-TI Period



Data cutoff date: October 2023.
RBC, red blood cell; TI, transfusion independence.

Imetelstat Responders Had Higher Central Hb Peaks Versus Placebo Responders



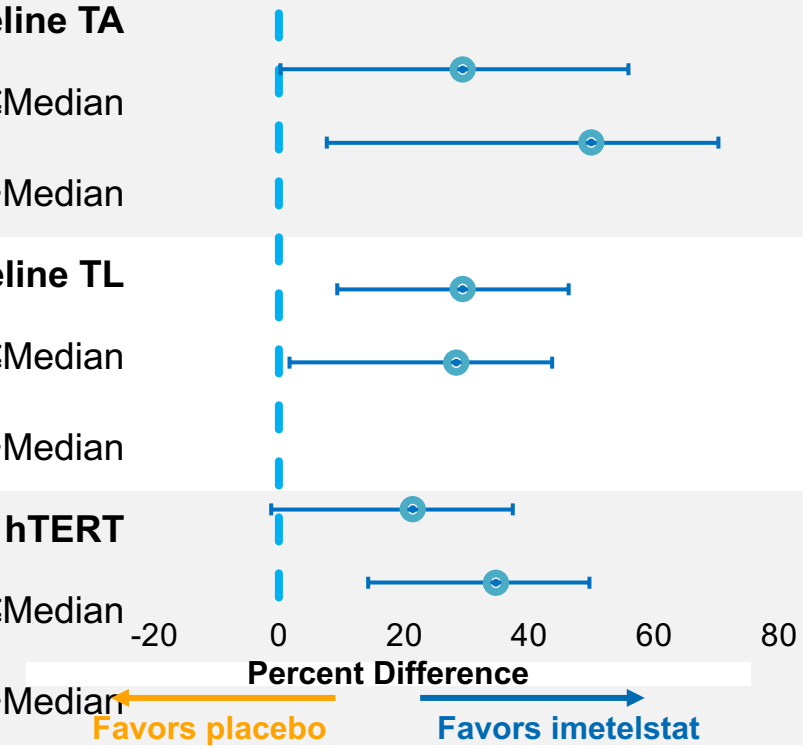
	Imetelstat	Placebo	Imetelstat	Placebo	Imetelstat	Placebo
Median Hb peak	**11.3**	**8.9**	**12.1**	**8.4**	**13.1**	**7.9**
N (responders)	47	9	33	2	21	1

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.

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

Comparable 24-Week RBC TI Rate Regardless of Baseline TA, TL or hTERT Level

	Imetelstat, Event/Total (%)	Placebo, Event/Total (%)	% Difference (95% CI)	P-value
Baseline TA				
≤Median	5/17 (29.4)	0/17	29.4 (0.25–55.95)	**0.074**
>Median	12/24 (50.0)	0/9	50.0 (7.67–70.35)	**0.018**
Baseline TL				
≤Median	13/40 (32.5)	1/32 (3.1)	29.4 (9.34–46.38)	**0.001**
>Median	18/53 (34.0)	1/18 (5.6)	28.4 (1.70–43.74)	**0.025**
Baseline hTERT				
≤Median	15/51 (29.4)	2/25 (8.0)	21.4 (-1.23–37.44)	**0.042**
>Median	17/49 (34.7)	0/26	34.7 (14.29–49.71)	**<0.001**



Data cutoff: October 13, 2022.
P-values were determined by the Cochran-Mantel-Haenszel test. Mutation Biomarker Analysis Set included all the patients who received ≥1 dose of study drug and had baseline mutation data available.
TA, telomerase activity; TL, telomerase length; hTERT, human telomerase reverse transcriptase.

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

Higher Percentage of Patients Achieved a Cytogenetic Response With Imetelstat vs Placebo

- Among patients with cytogenetic abnormalities at baseline, the cytogenetic response rate was 35% (9/26) in the imetelstat group and 15% (2/13) in the placebo group
- Among cytogenetic responders, 89% (8/9) of patients in the imetelstat group and 50% (1/2) in the placebo group also achieved 8-week RBC-TI

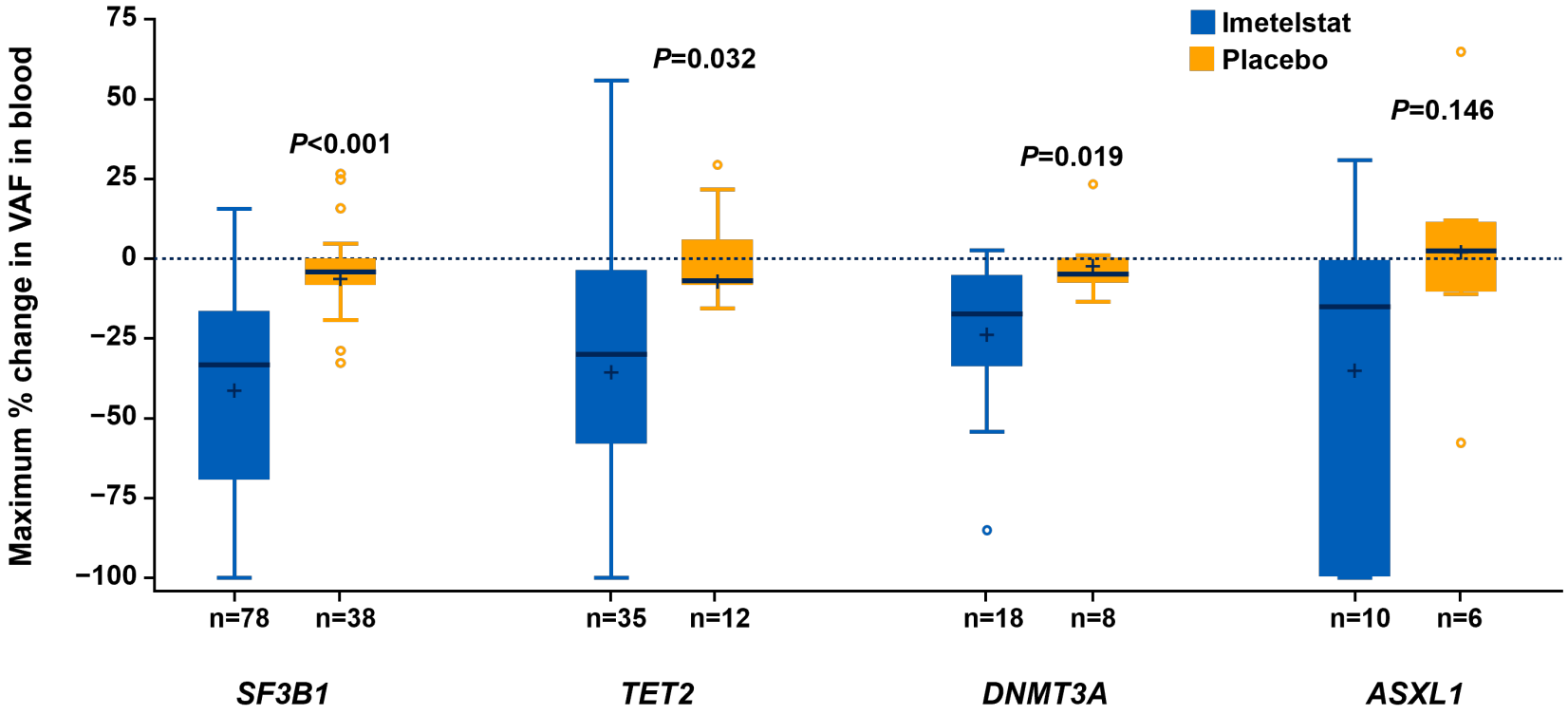
Cytogenetic response[a]	Imetelstat (N=118)	Placebo (N=60)
Patients with baseline cytogenetic abnormality based on central laboratory review, n (%)[b]	26 (22)	13 (22)
Cytogenetic best response, n (%)[c,d]		
Cytogenetic CR	5 (19)	1 (8)
Cytogenetic PR	4 (15)	1 (8)
Cytogenetic CR or PR criteria not met	5 (19)	5 (39)
Not evaluable	12 (46)	6 (46)
Cytogenetic CR or PR, n (%)[d]	9 (35)	2 (15)
95% CI[e]	17–56	2–45
% Difference (95% CI)[f]	19 (−16 to 44)	
P value[g]	0.216	

Data cutoff: October 13, 2022.

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

Reductions in VAF of Genes Frequently Mutated in MDS Were Greater With Imetelstat vs Placebo

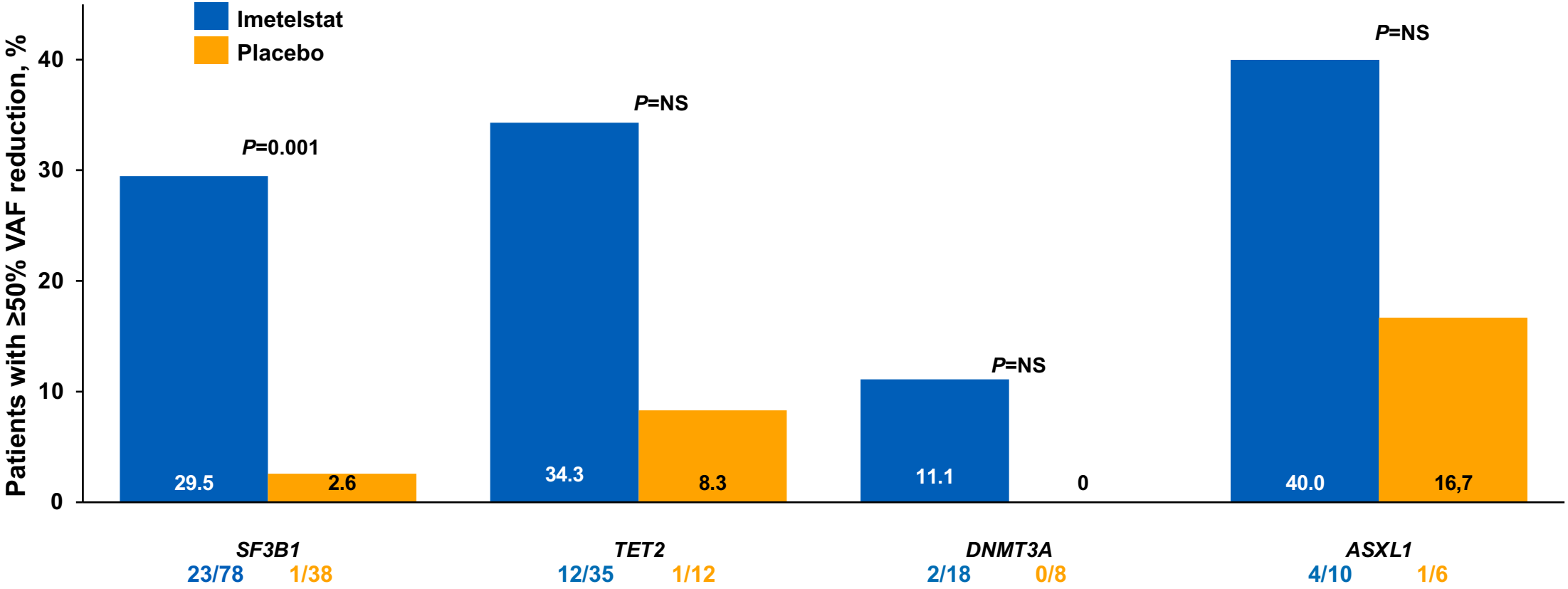
- Mutations on 36 genes associated with MDS were tested by NGS on samples taken from baseline and post-treatment
- Among patients with evaluable mutation data, the maximum reductions in VAF of the *SF3B1*, *TET2*, *DNMT3A, and ASXL1* genes were greater with imetelstat than placebo



Data cutoff: October 13, 2022.
Note: Figure shows the comparison between each treatment group in the maximum percentage change from baseline in mutant VAF of the indicated gene. *P* value based on the .

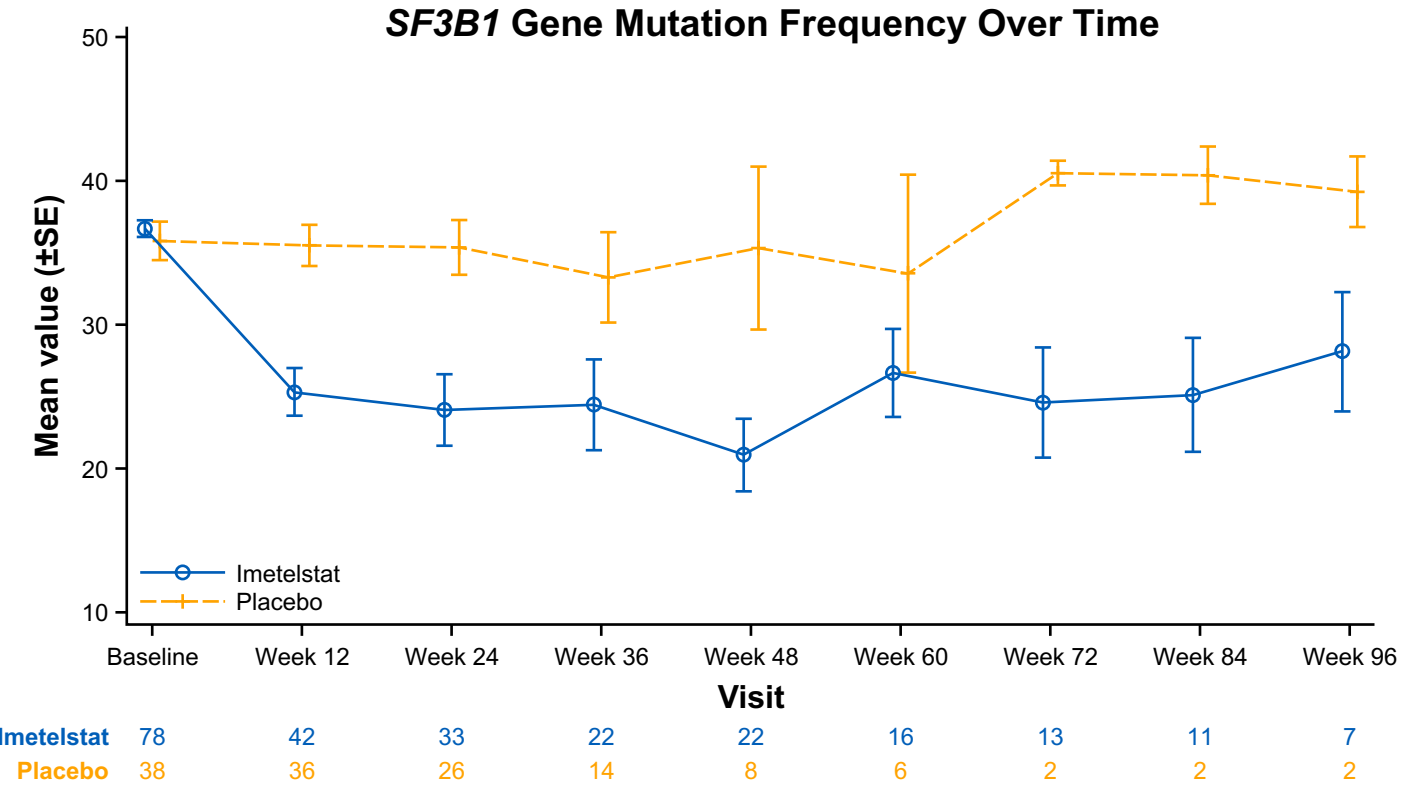
Platzbecker , Santini et al, Lancet. 2024 Jan 20;403(10423):249-260.

In PB More Patients Treated With Imetelstat vs Placebo Had ≥50% VAF Reduction in *SF3B1*, *TET2*, *DNMT3A*, and *ASXL1* Mutations



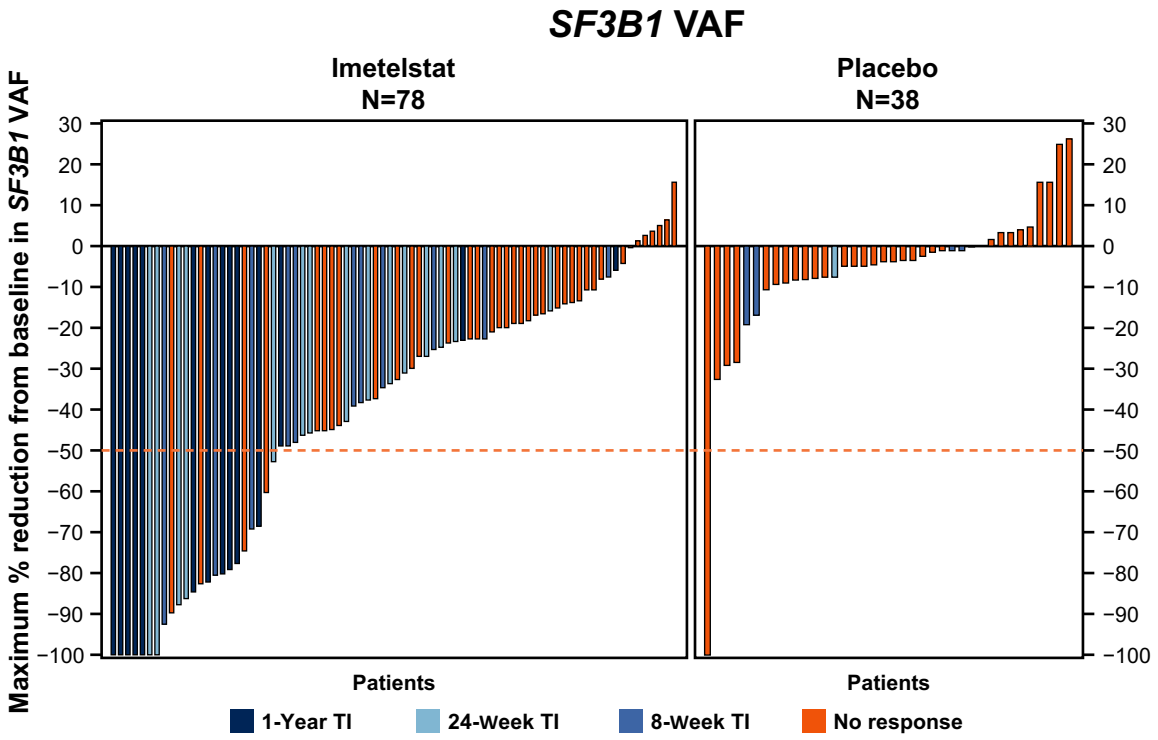
Platzbecker , Santini et al, Lancet. 2024 Jan 20;403(10423):249-260.

Imetelstat Treatment Resulted in Sustained Reduction of *SF3B1* VAF Over Time in PB



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

RBC-TI Responders Enriched in Patients Achieving ≥50% Reduction in *SF3B1* VAF in the Imetelstat Group

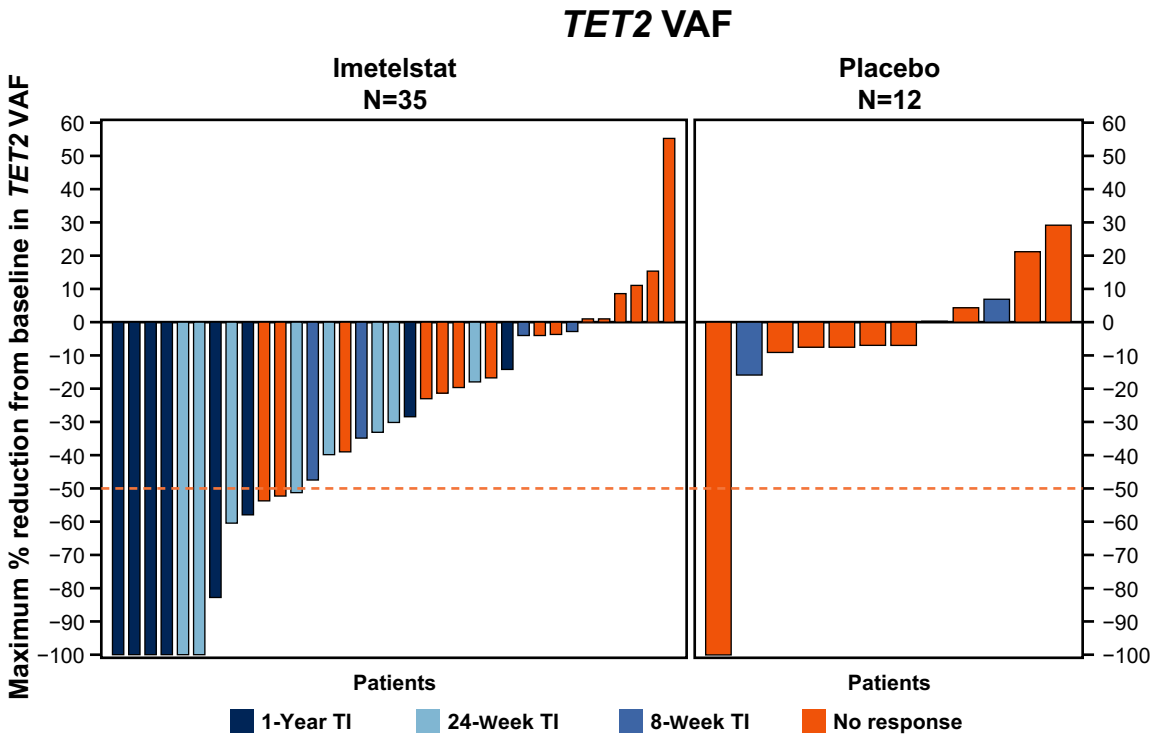


Patients, n (%)	Imetelstat *SF3B1* VAF ≥50% Reduction			
	Yes (N=23)	No (N=55)	Total (N=78)	*P* Value (Fisher exact test)
8-Week RBC-TI				
Yes	19 (82.6)	21 (38.2)	40 (51.3)	<0.001
No	4 (17.4)	34 (61.8)	38 (48.7)	
24-Week RBC-TI				
Yes	16 (69.6)	13 (23.6)	29 (37.2)	<0.001
No	7 (30.4)	42 (76.4)	49 (62.8)	
1-Year RBC-TI				
Yes	11 (47.8)	3 (5.5)	14 (17.9)	<0.001
No	12 (52.2)	52 (94.5)	64 (82.1)	

- Among patients treated with imetelstat who achieved ≥50% *SF3B1* VAF reduction, 83% were 8-week RBC-TI responders
- ≥24-week and ≥1-year RBC-TI responders were also enriched in patients achieving ≥50% reduction in *SF3B1* VAF

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

RBC-TI Responders Enriched in Patients Achieving ≥50% Reduction in *TET2* VAF in the Imetelstat Group



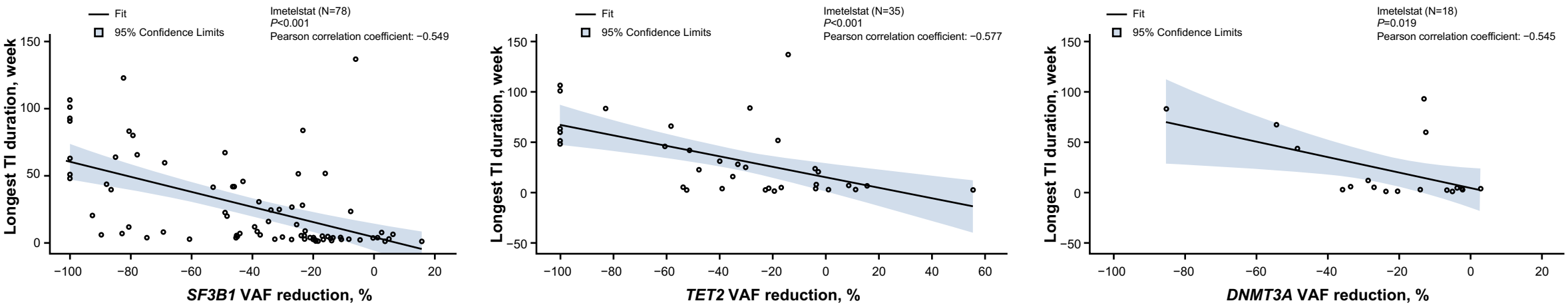
Patients, n (%)	Imetelstat *TET2* VAF ≥50% Reduction			
	Yes (N=12)	No (N=23)	Total (N=35)	*P* Value (Fisher exact test)
8-Week RBC-TI				
Yes	10 (83.3)	10 (43.5)	20 (57.1)	0.034
No	2 (16.7)	13 (56.5)	15 (42.9)	
24-Week RBC-TI				
Yes	10 (83.3)	6 (26.1)	16 (45.7)	0.003
No	2 (16.7)	17 (73.9)	19 (54.3)	
1-Year RBC-TI				
Yes	6 (50.0)	2 (8.7)	8 (22.9)	0.011
No	6 (50.0)	21 (91.3)	27 (77.1)	

- Among patients treated with imetelstat who achieved ≥50% *TET2* VAF reduction, 83% were 8-week RBC-TI responders
- ≥24-week and ≥1-year RBC-TI responders were also enriched in patients achieving ≥50% reduction in *TET2* VAF

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

VAF Reduction in *SF3B1*, *TET2*, and *DNMT3A* Correlated With Longer RBC-TI Duration in Patients Treated With Imetelstat

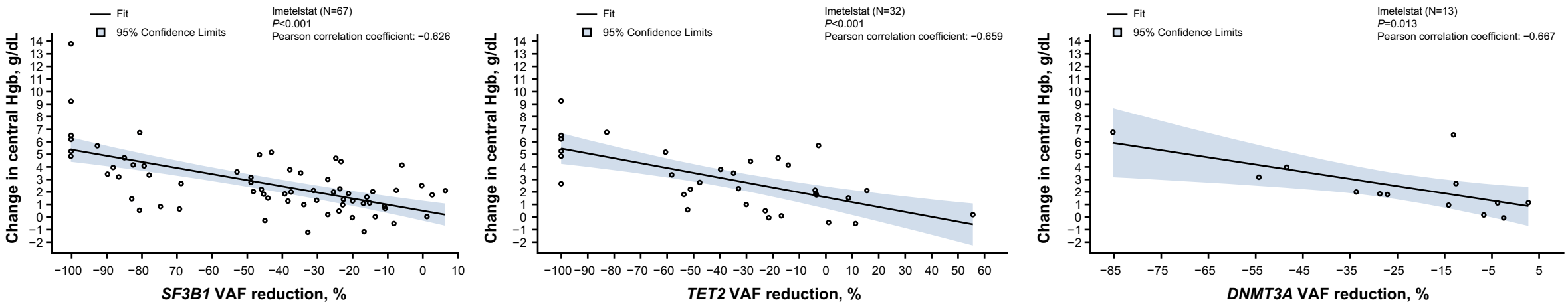
Longest RBC-TI Duration vs Maximum Reduction in *SF3B1* (left), *TET2* (middle), and *DNMT3A* (right) VAF



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

VAF Reduction in *SF3B1*, *TET2*, and *DNMT3A* Correlated With Increases in Hgb Levels in Patients Treated With Imetelstat

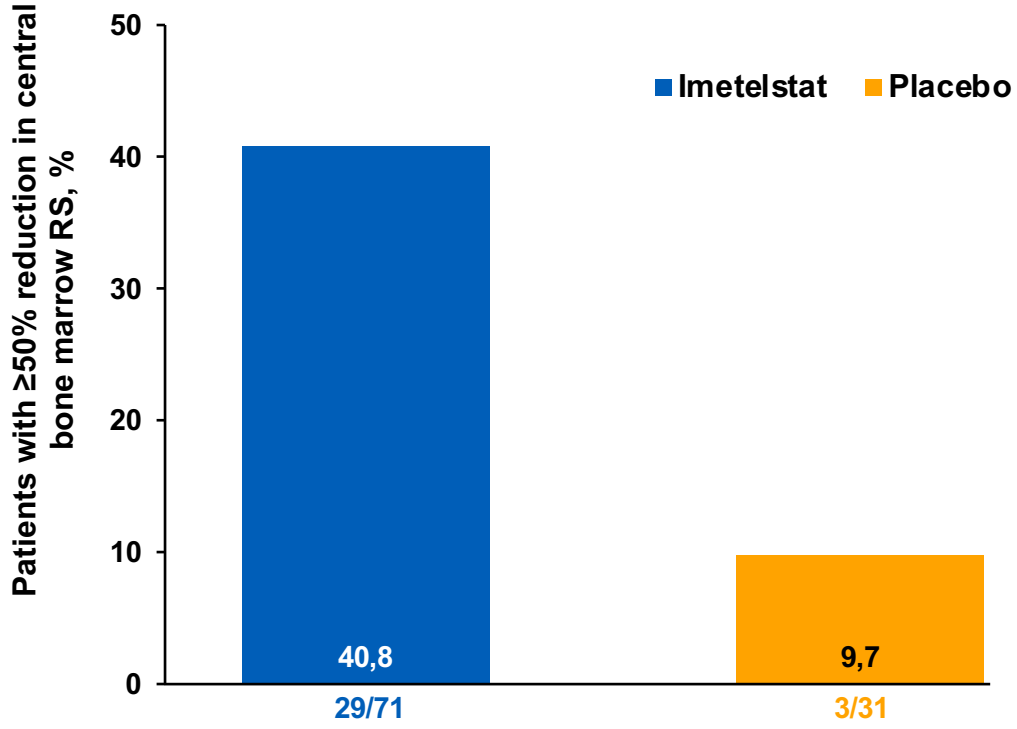
Maximum Increase in Hgb vs Maximum Reduction in *SF3B1* (left), *TET2* (middle), and *DNMT3A* (right) VAF

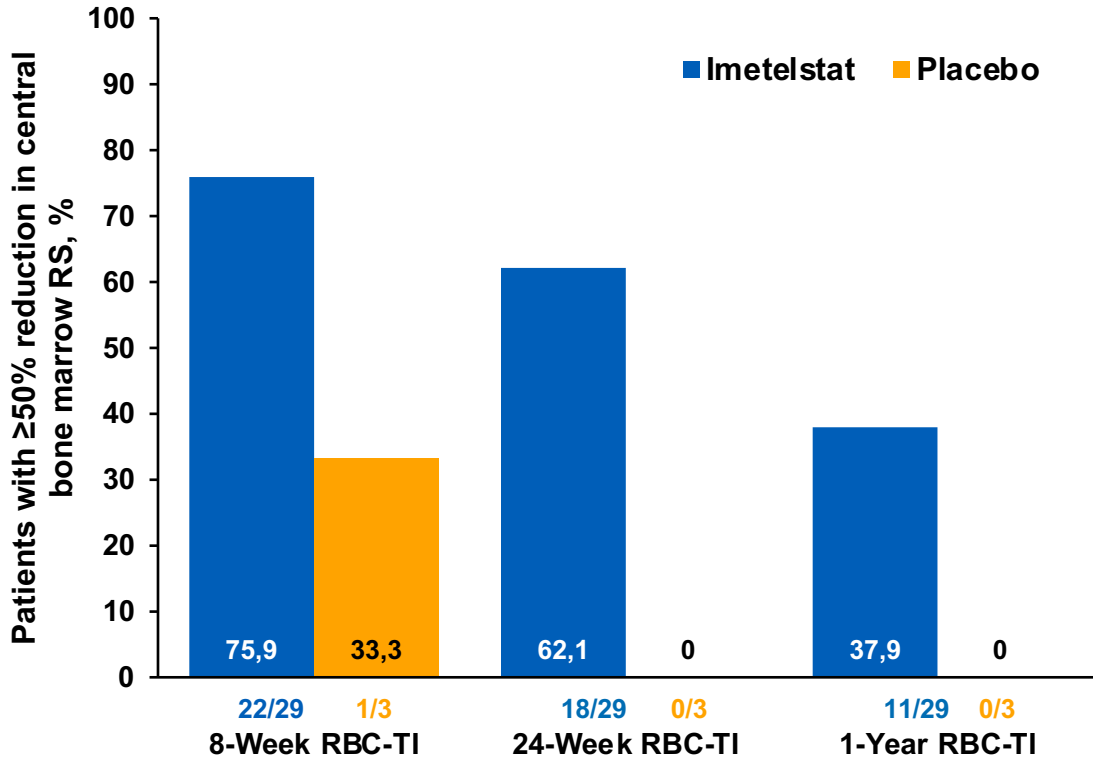


Platzbecker , Santini et al, Lancet. 2024 Jan 20;403(10423):249-260.

More Patients Treated With Imetelstat vs Placebo Had ≥50% Reduction in Central Bone Marrow RS, Which Associated With TI Responses

- A higher percentage of patients treated with imetelstat vs placebo had a ≥50% reduction in central bone marrow RS
- RBC-TI responders enriched in patients achieving a ≥50% reduction in central bone marrow RS





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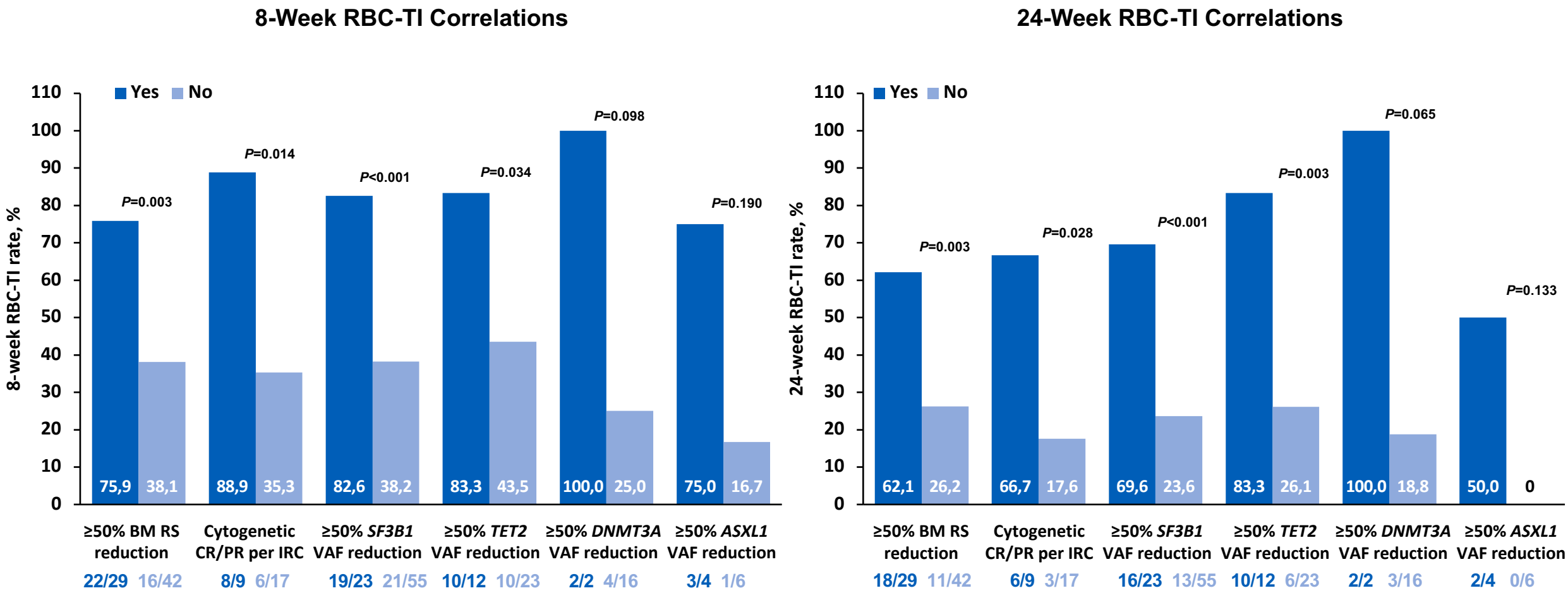
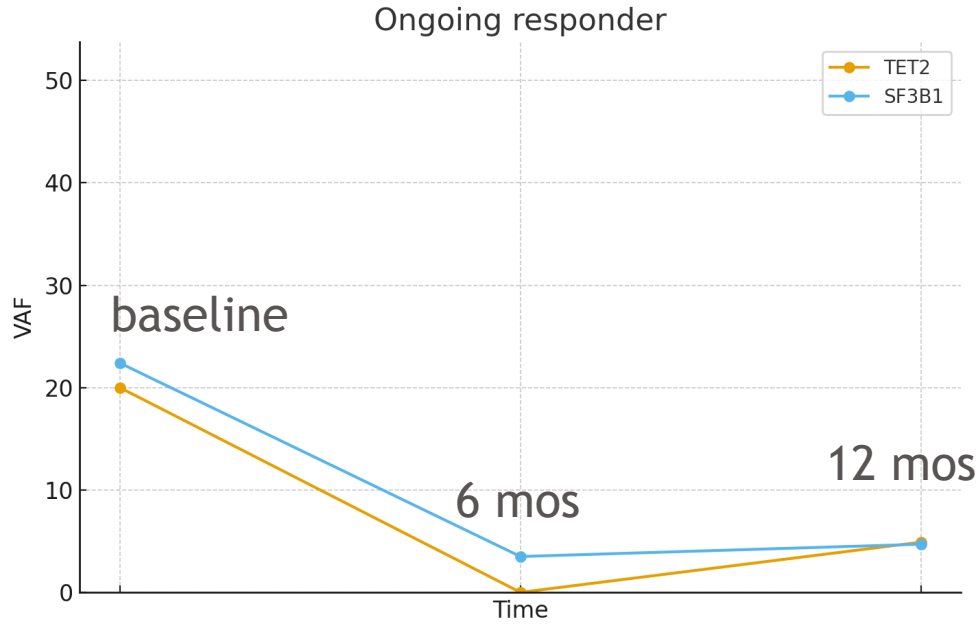
Imetelstat has disease modifying activity

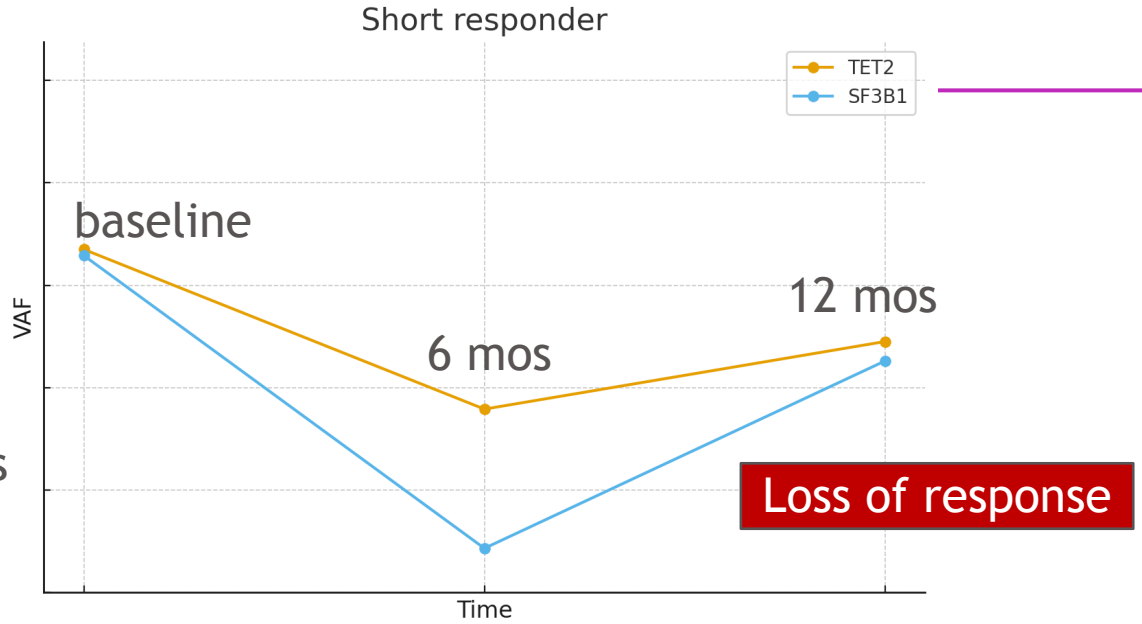


Data cutoff: October 13, 2022.
Note: *P* value calculated using Fisher exact test between yes vs no in each outcome.
ASXL1, additional sex combs like-1; BM, bone marrow; CR, complete response; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; IRC, independent review committee; PR, partial response; RBC, red blood cell; RS, ring sideroblasts; TET2, Tet methylcytosine dioxygenase 2; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

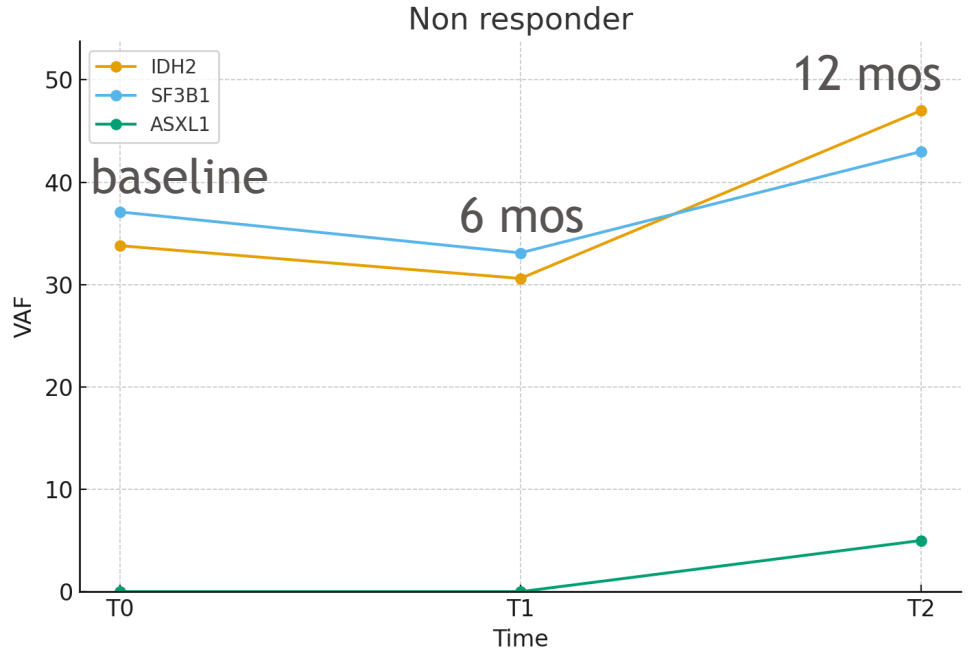
Santini et al , EHA 2023

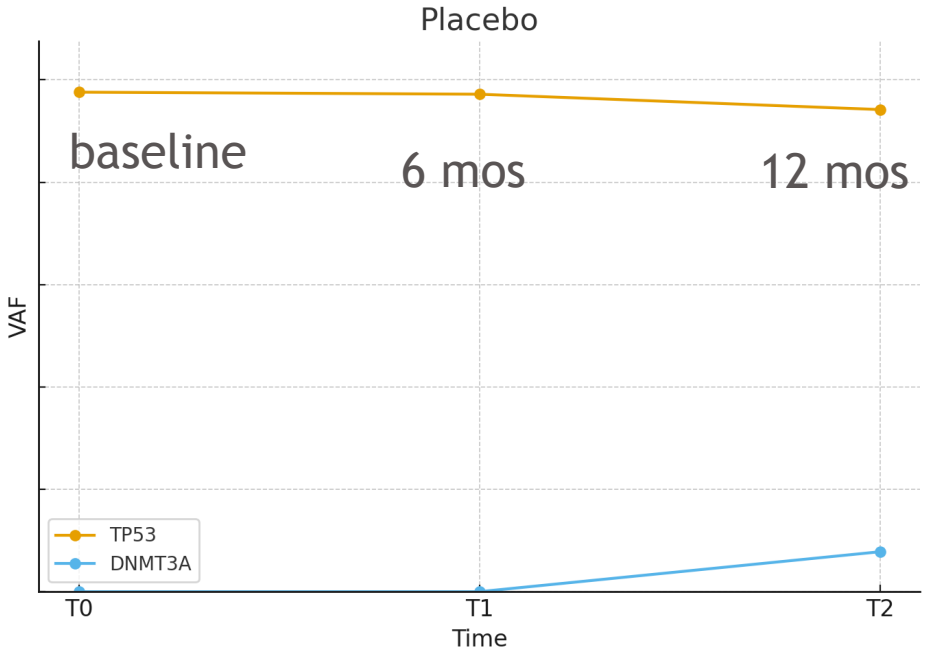
BM progenitor variant allele frequency during Imetelstat treatment



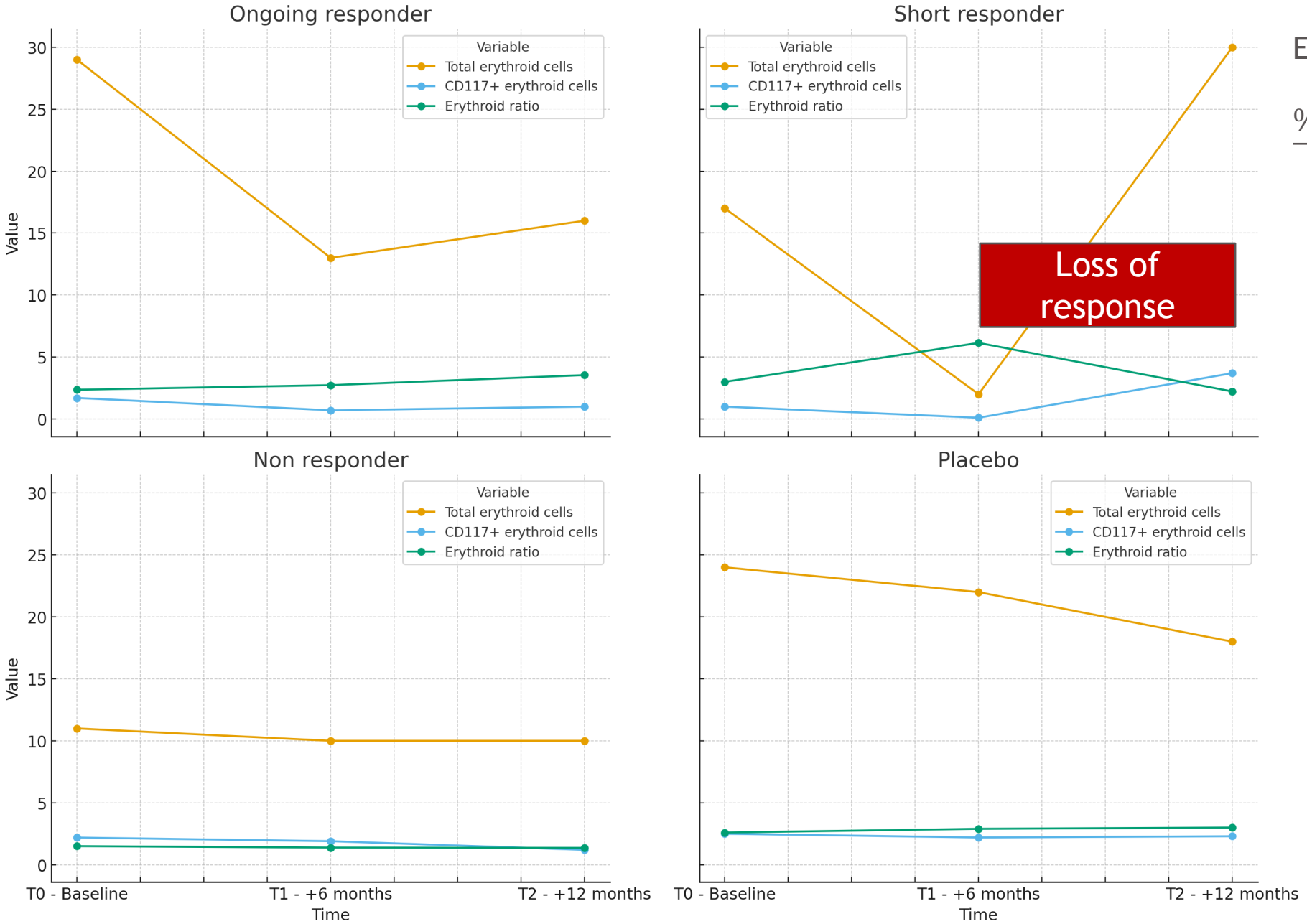


Loss of response





Changes in BM erythroid maturation during Imetelstat treatment

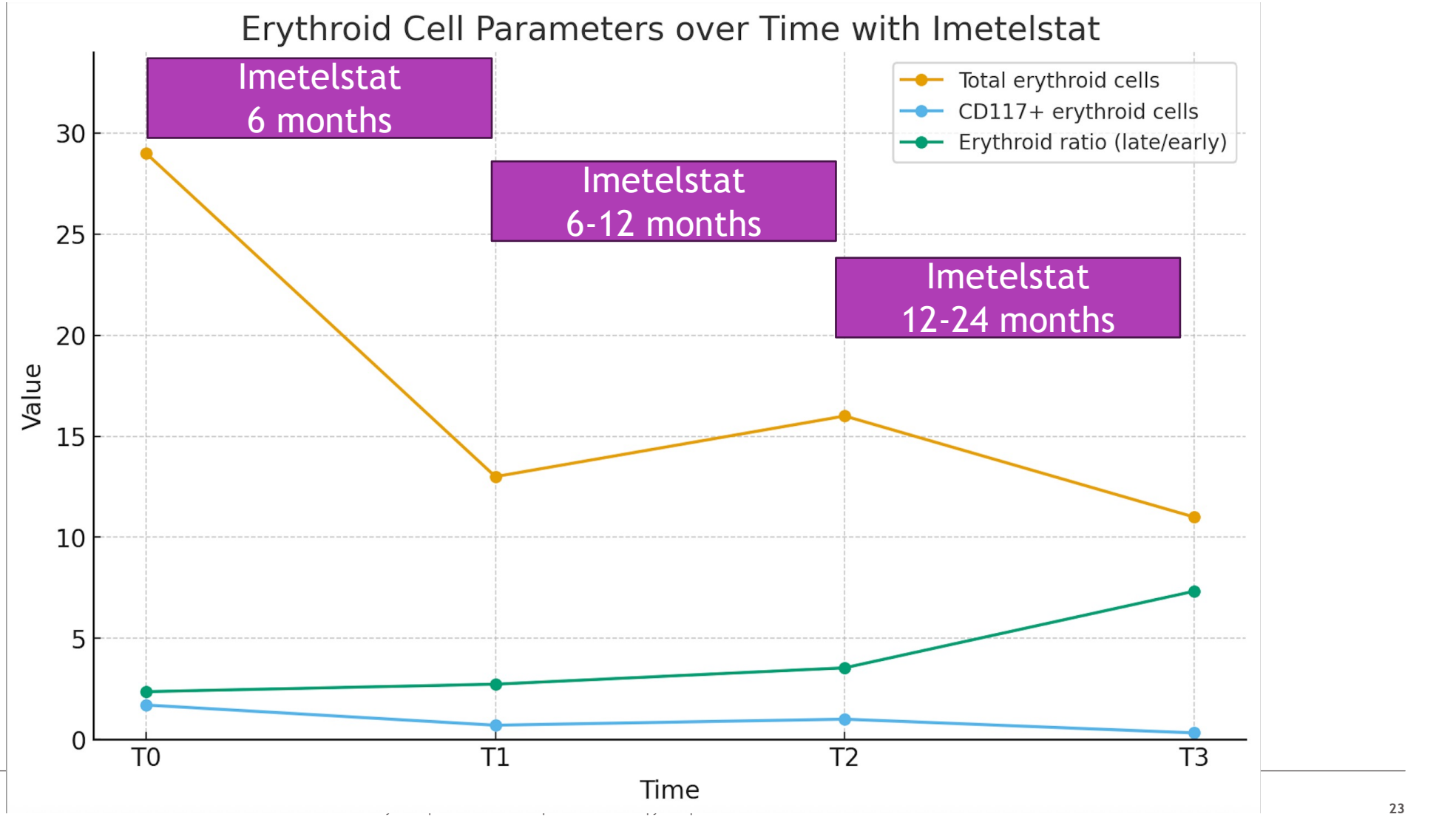


Erythroid ratio =

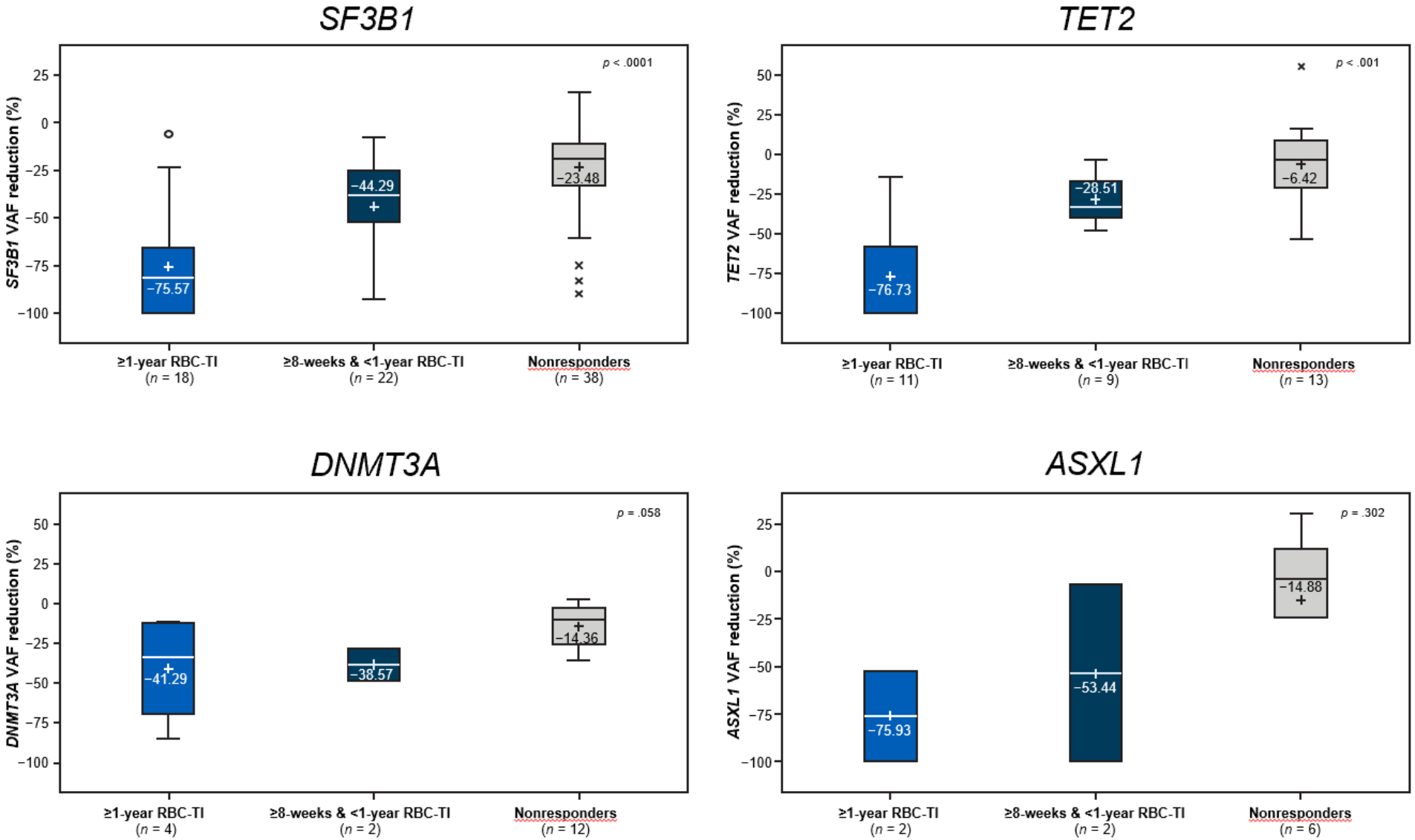
$$\frac{\%\ \text{Late erythroid precursors cells}}{\%\ \text{Early erythroid precursors}}$$

ONGOIN RESPONDER	T0 - Baseline	T1 - +6 months from Imetelstat	T2 - +12 months from Imetelstat	T2 - +24 months from Imetelstat
Erythroid cells/tot. (%)	29	13	16	**11**
CD117+ erythroid cells/tot. (%)	1,7	0,7	1	**0,32**
Late erythroid cells/tot. erythroid (%)	77	82	78	**88**
Erythroid ratio	2,36	2,73	3,54	**7,33**

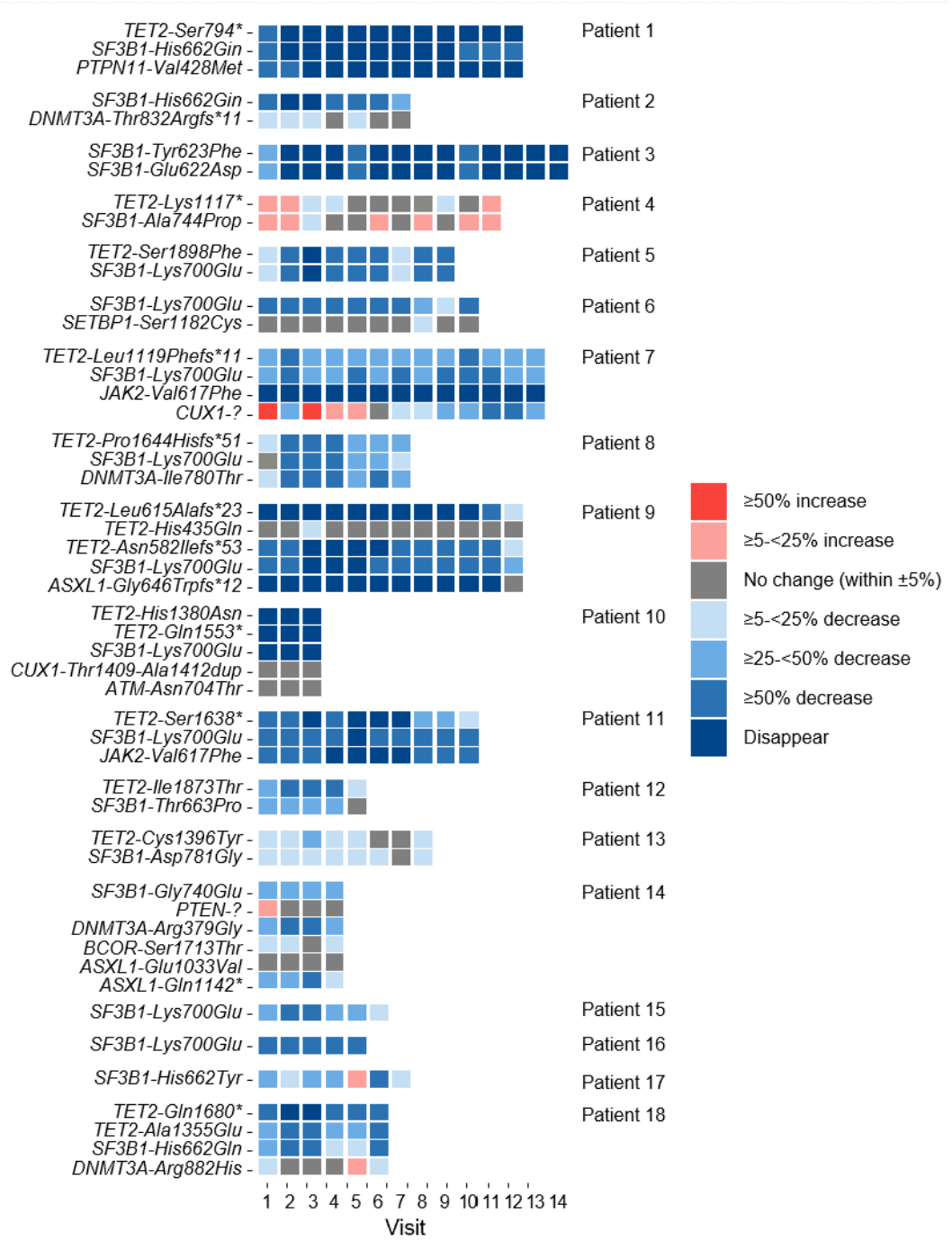
Ongoing Responder



Mutational VAF changes in patients treated with imetelstat according to response



Santini et al, Leukemia 2025, in press

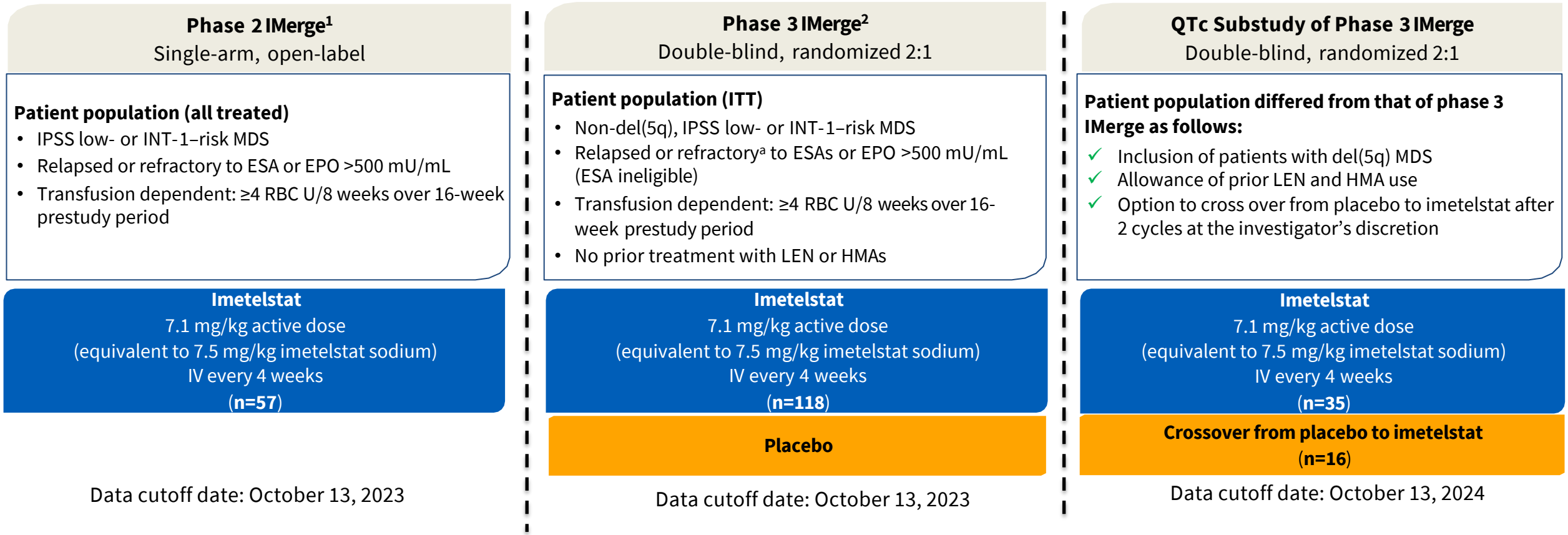


Mutational VAF change over time in patients with ⩾1-year RBC-TI with imetelstat

Santini et al, Leukemia 2025, in press

What about use of imetelstat as second- or third- line therapy??

- A total of 226 imetelstat-treated patients were included in this analysis



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; INT, intermediate; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; IV, intravenous; LEN, lenalidomide; MDS, myelodysplastic syndromes; QTc, QT correction; RBC, red blood cell.

[a]Received ≥8 weeks of ESA treatment (EPO alfa ≥40,000 U, EPO beta ≥30,000 U, or darbepoetin alfa 150 µg or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U every 8 weeks or transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment.

1. Steensma DP, et al. *J Clin Oncol*. 2021;39(1):48-56. 2. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.

Platzbecker et al abs 352 ASH 2024

Baseline Demographic and Disease Characteristics in the Pooled Patient Population

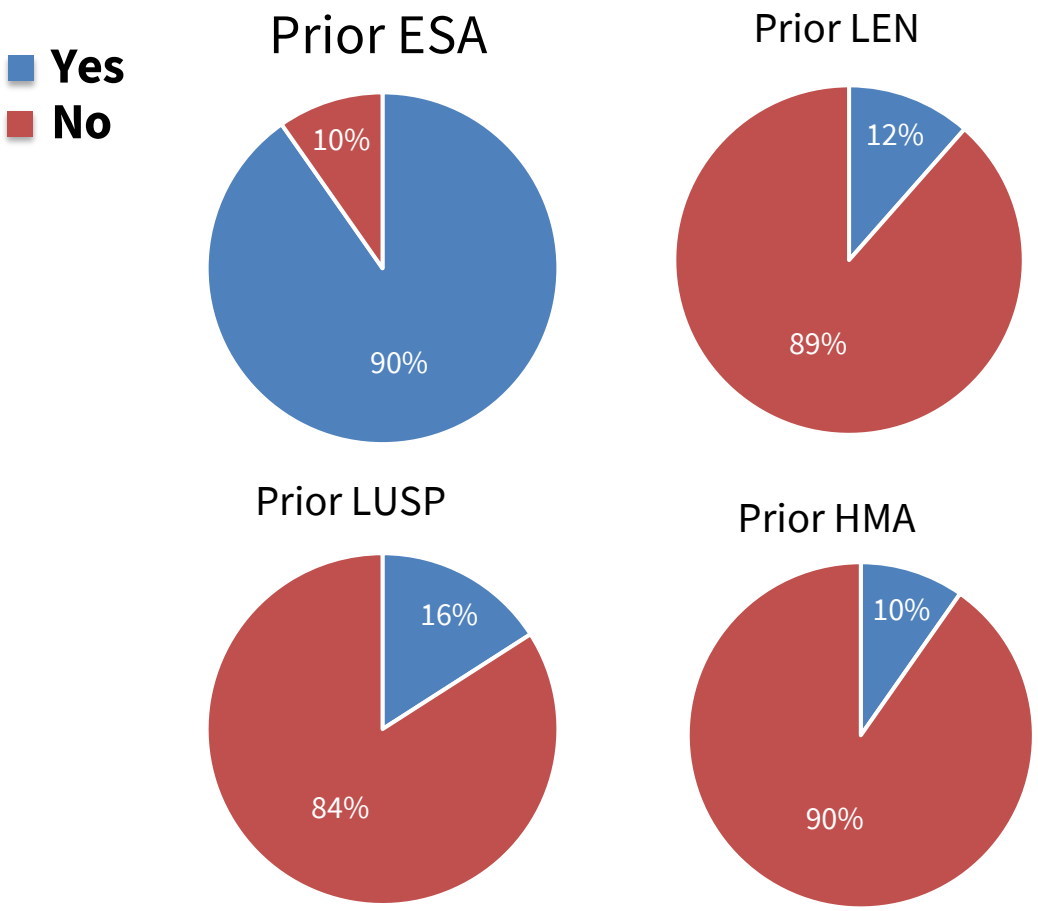
Characteristic	Imetelstat (N=226)
Age, median (range), y	71.0 (43-87)
≥65 y, n (%)	174 (77)
WHO classification, n (%)	
RS+	147 (65)
RS−	78 (35)
IPSS risk category, n (%)	
Low	151 (67)
Intermediate-1	75 (33)
Number of imetelstat treatment cycles, n (%)	
1-2 cycles	35 (15)
4-6 cycles	56 (25)
7-12 cycles	46 (20)
≥13 cycles	90 (40)

Characteristic	Imetelstat (N=226)
Prior RBC transfusion burden, n (%)	
≤6 U/8 weeks	112 (50)
>6 U/8 weeks	114 (50)
Serum EPO level, n(%)	
≤500 mU/mL	155 (69)
>500 mU/mL	64 (28)
Missing	7 (3)
Transfusion burden per IWG 2018, n (%)	
LTB	38 (17)
HTB	188 (83)

- Median imetelstat treatment duration (range) was 33.6 weeks (0.1-260.1)

EPO, erythropoietin; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblast; WHO, World Health Organization.

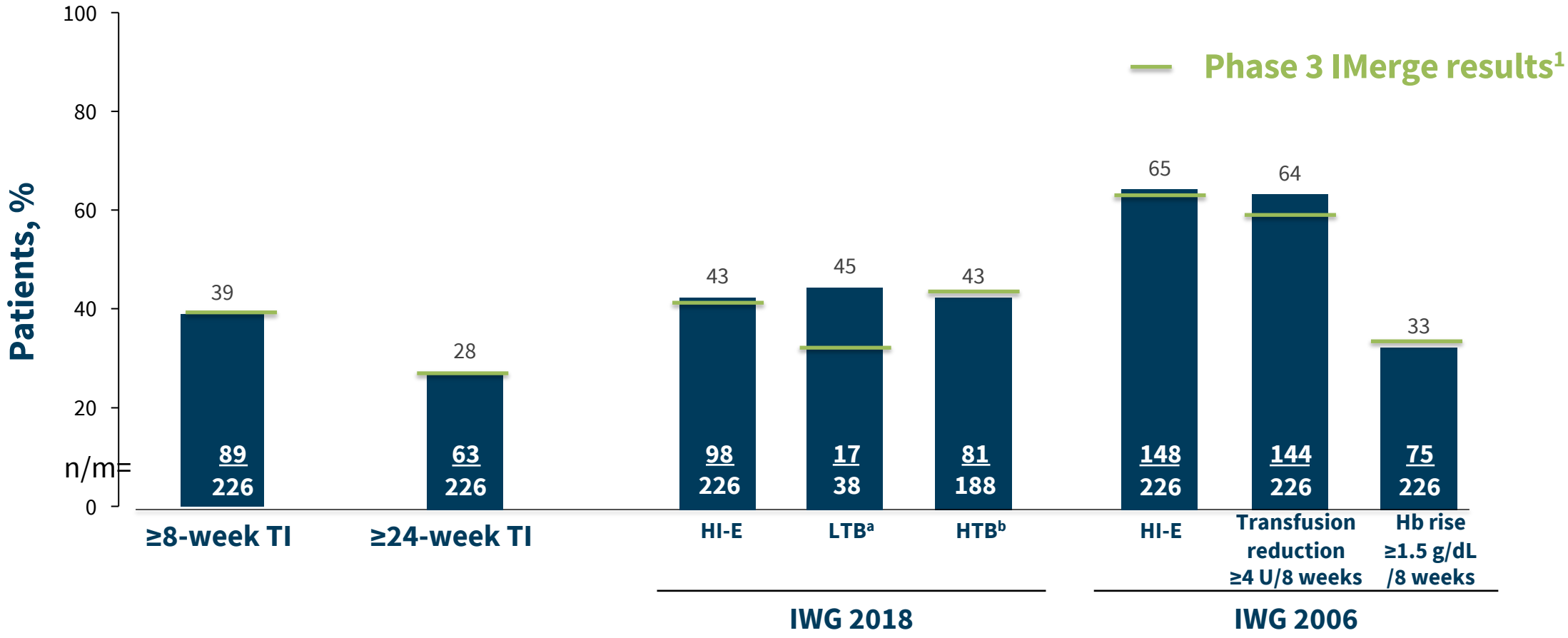
Most Patients Had Prior ESA and No Prior LEN/LUSP/HMA[a]



	Prior ESA (n=204)	ESA ineligible (n=22)	Prior LEN (n=26)	Prior LUSP (n=36)	Prior HMA (n=22)
Median time since initial diagnosis to imetelstat, y	3.7	1.4	5.4	3.8	5.8
Median transfusion burden at baseline, U	7.0	6.0	7.5	9.0	9.0

ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; LEN, lenalidomide; LUSP, luspatercept.
[a]Patients may have received >1 prior therapy.

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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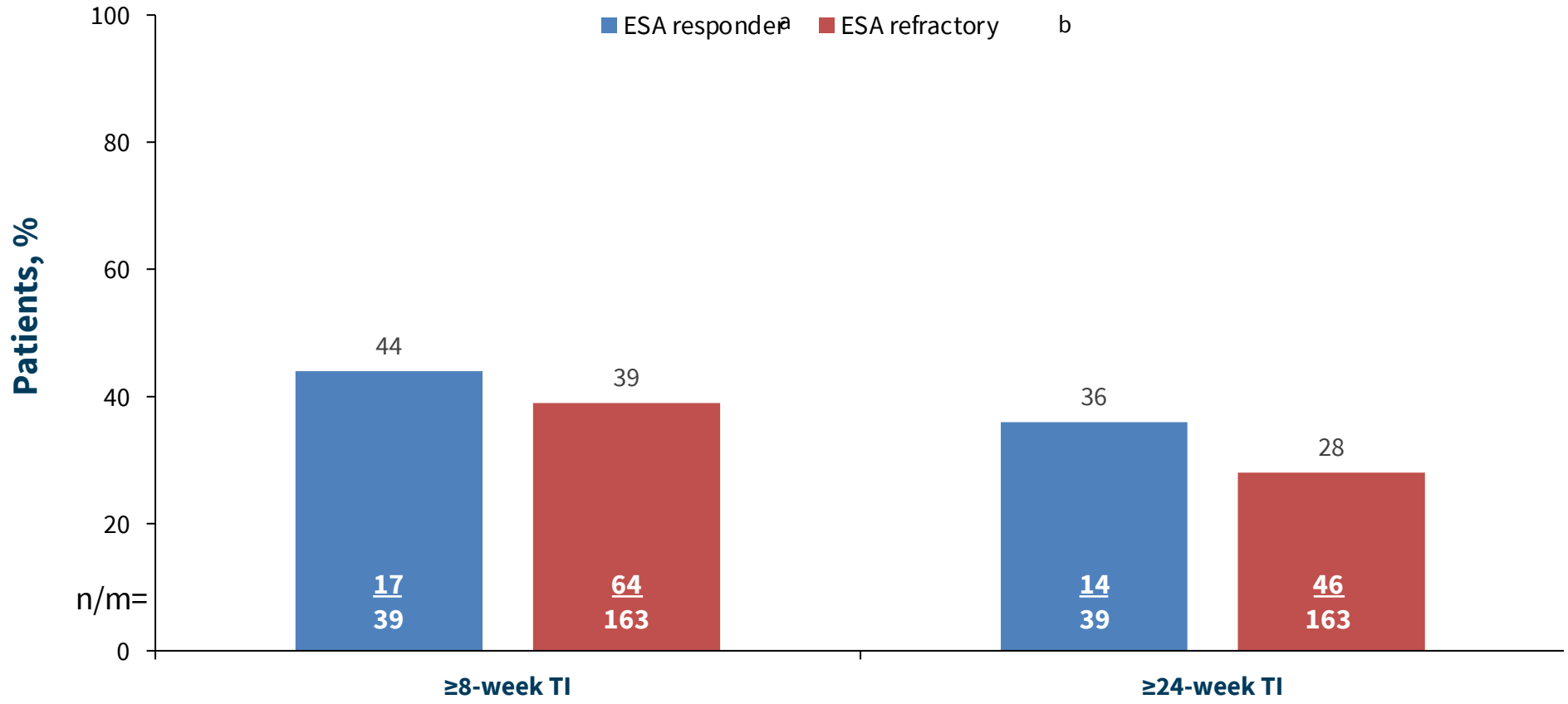
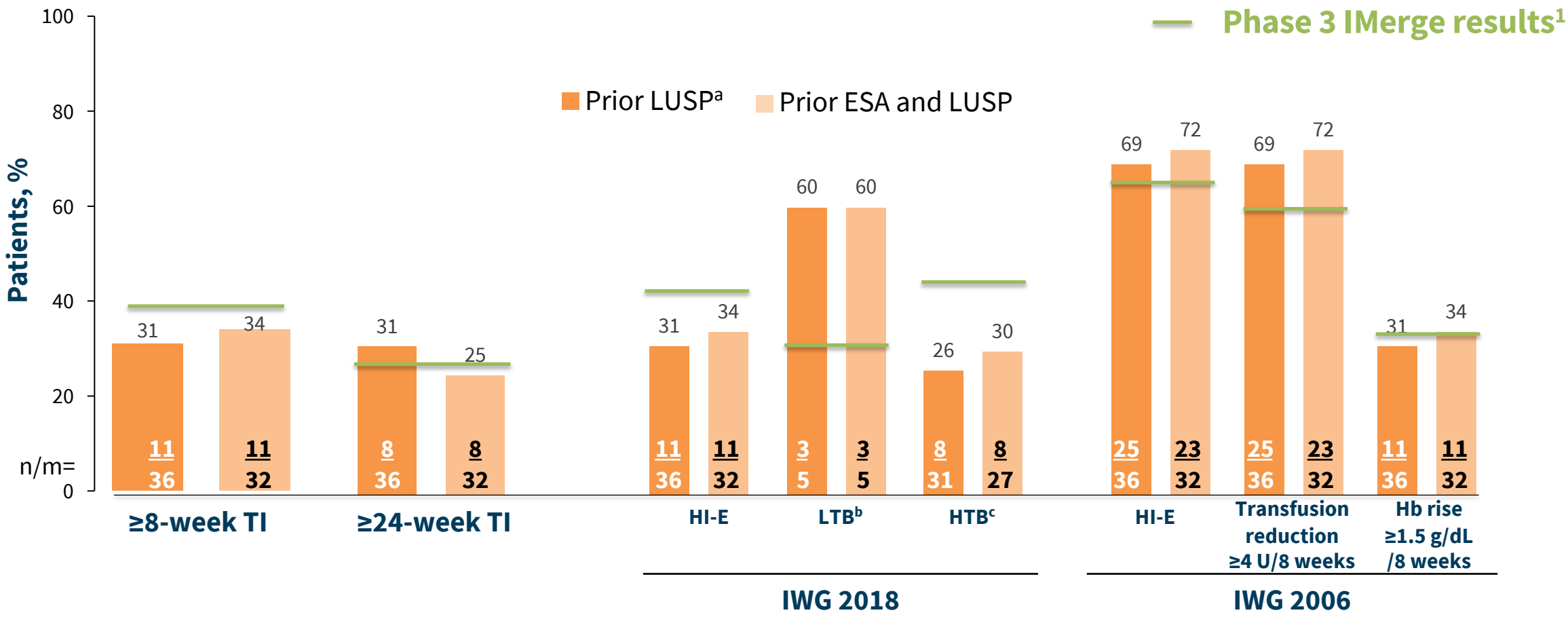
Imetelstat Showed Clinical Activity Regardless of Prior ESA Response Status (N=226)



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; n/m, number with event/number in population; RBC, red blood cell; TI, transfusion independence.
[a]Response included RBC-TI and HI-E response. [b]Received ≥8 weeks of ESA treatment (EPO alfa ≥40,000 U, EPO beta ≥30,000 U, or darbepoetin alfa 150 µg or equivalent per week) without having achieved an Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement by ≥4 U every 8 weeks or having transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of treatment with therapies.

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



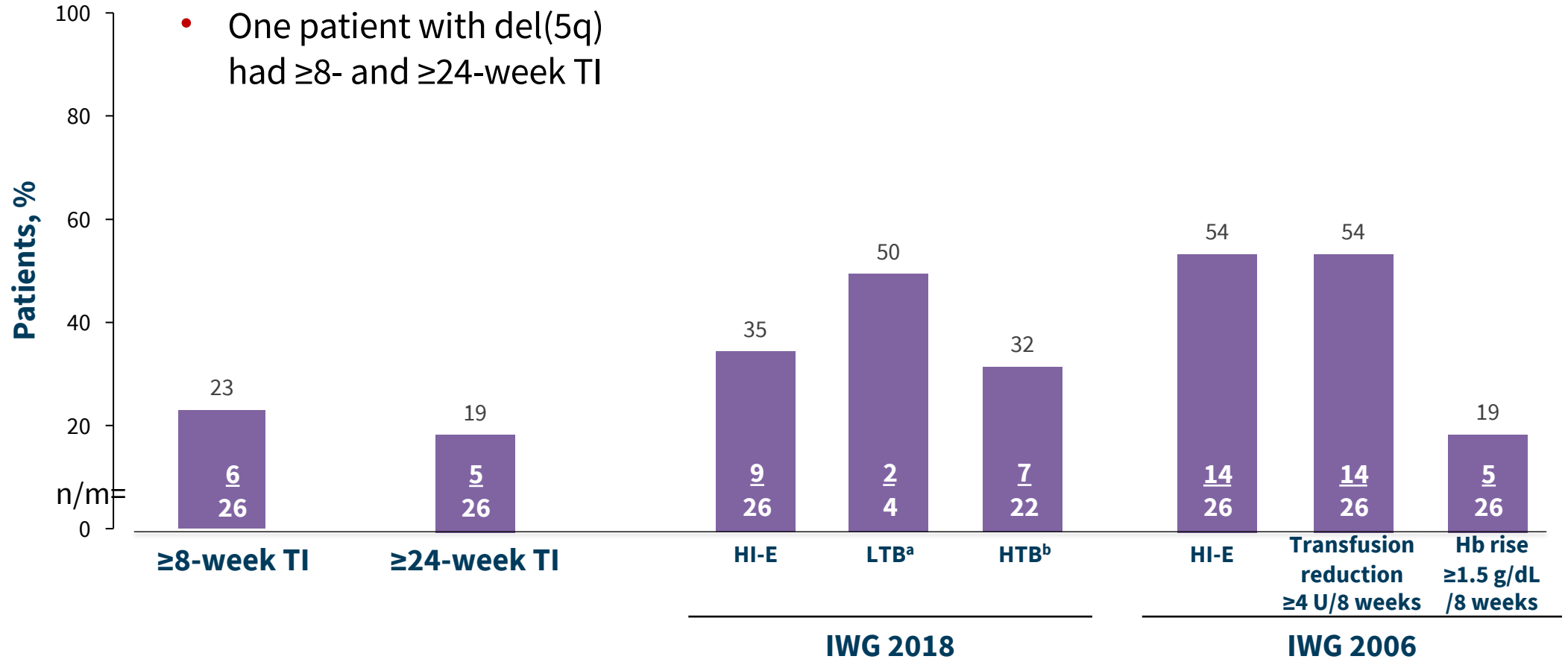
ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; LUSP, luspatercept; n/m, number with event/number in population; RBC, red blood cell; RS, ring sideroblast; TI,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

Platzbecker et al abs 352 ASH 2024

Imetelstat Shows Clinical Activity in Patients With Prior LEN (n=26)

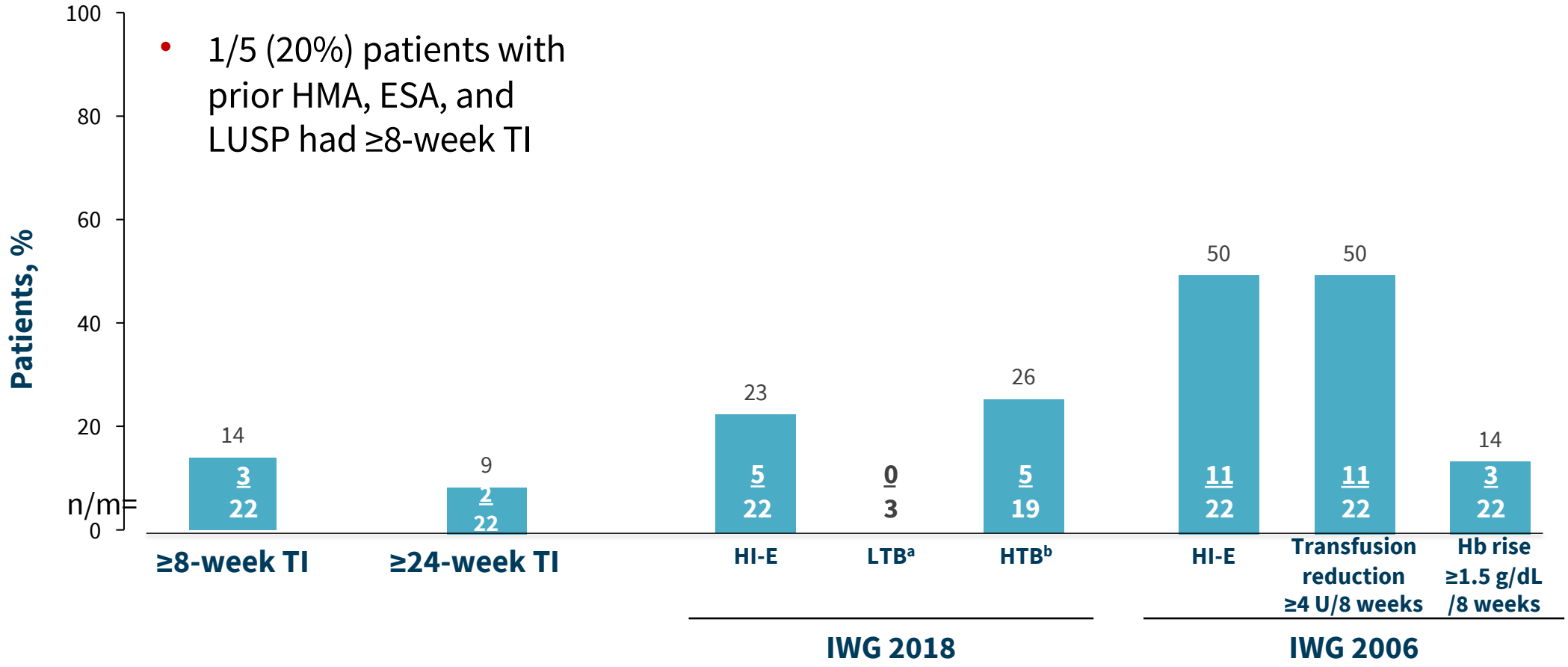


Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; n/m, number with event/number in population; LEN, lenalidomide; LTB, low transfusion burden; RBC, red blood cell; TI, transfusion independence.

[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.

Platzbecker et al abs 352 ASH 2024

Imetelstat Shows Modest Clinical Activity in Patients With Prior HMA (n=22)



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; 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; 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.

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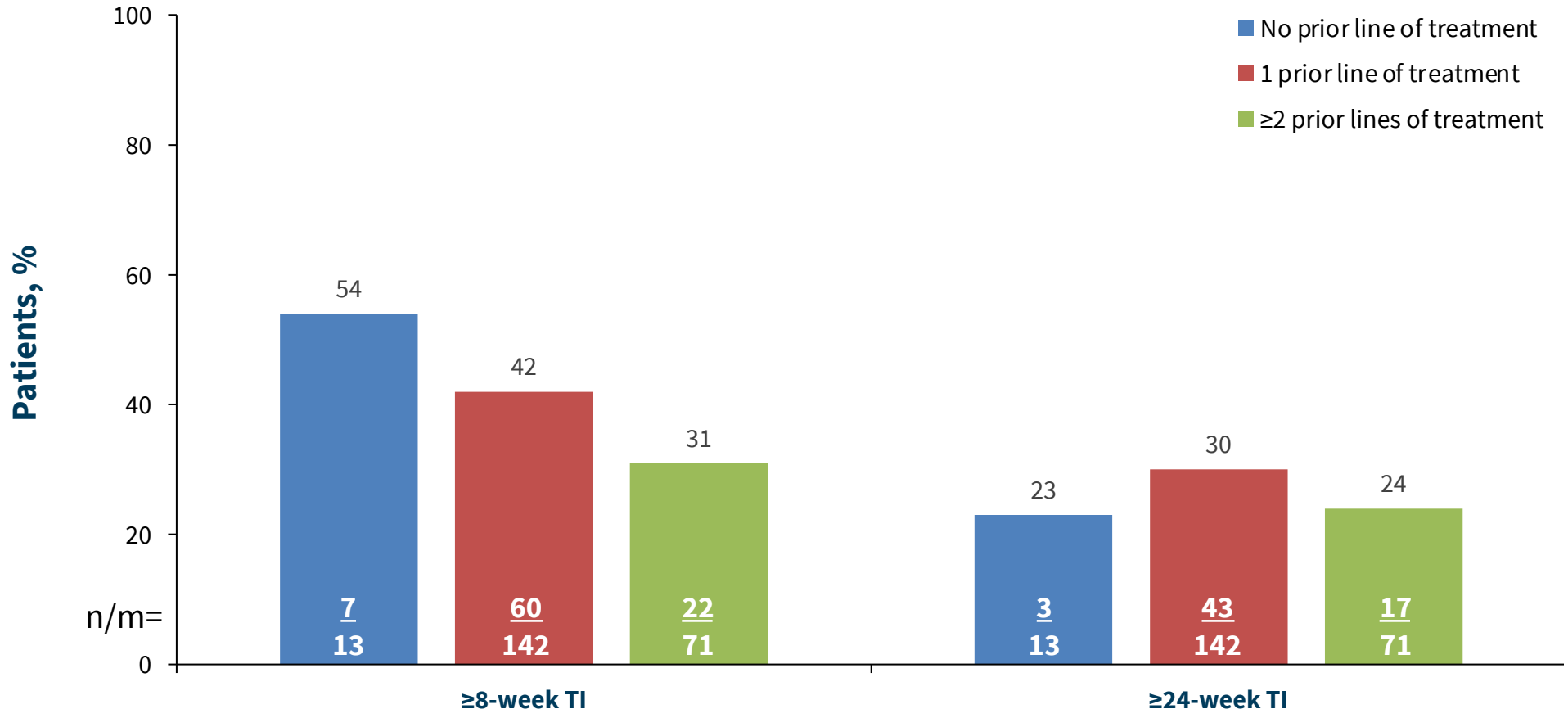
Imetelstat Clinical Activity by Number of Prior Lines of Therapy (N=226)



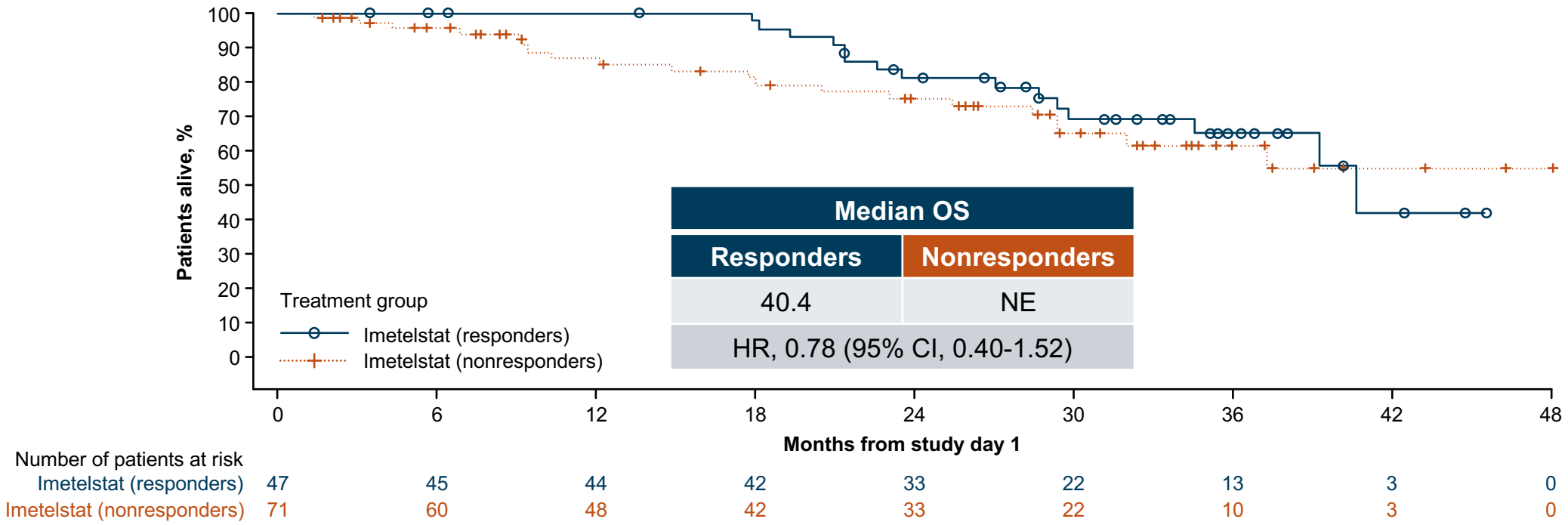
n/m, number with event/number in population; TI, transfusion independence.

No New Safety Signals Were Reported

	Total (N=226)
TEAEs, n (%)	
Any grade	221 (98)
Serious	85 (38)
Grade ≥3	200 (88)
Most common TEAEs by preferred term in ≥15% of patients, n (%)	
Neutropenia	163 (72)
Thrombocytopenia	161 (71)
Anemia	48 (21)
Diarrhea	36 (16)
Alanine aminotransferase increased	35 (15)
Asthenia	33 (15)

TEAE, treatment-emergent adverse event.

Too early!!
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.

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

SAFETY

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.

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

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

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

Dosing and Safety Considerations With Imetelstat

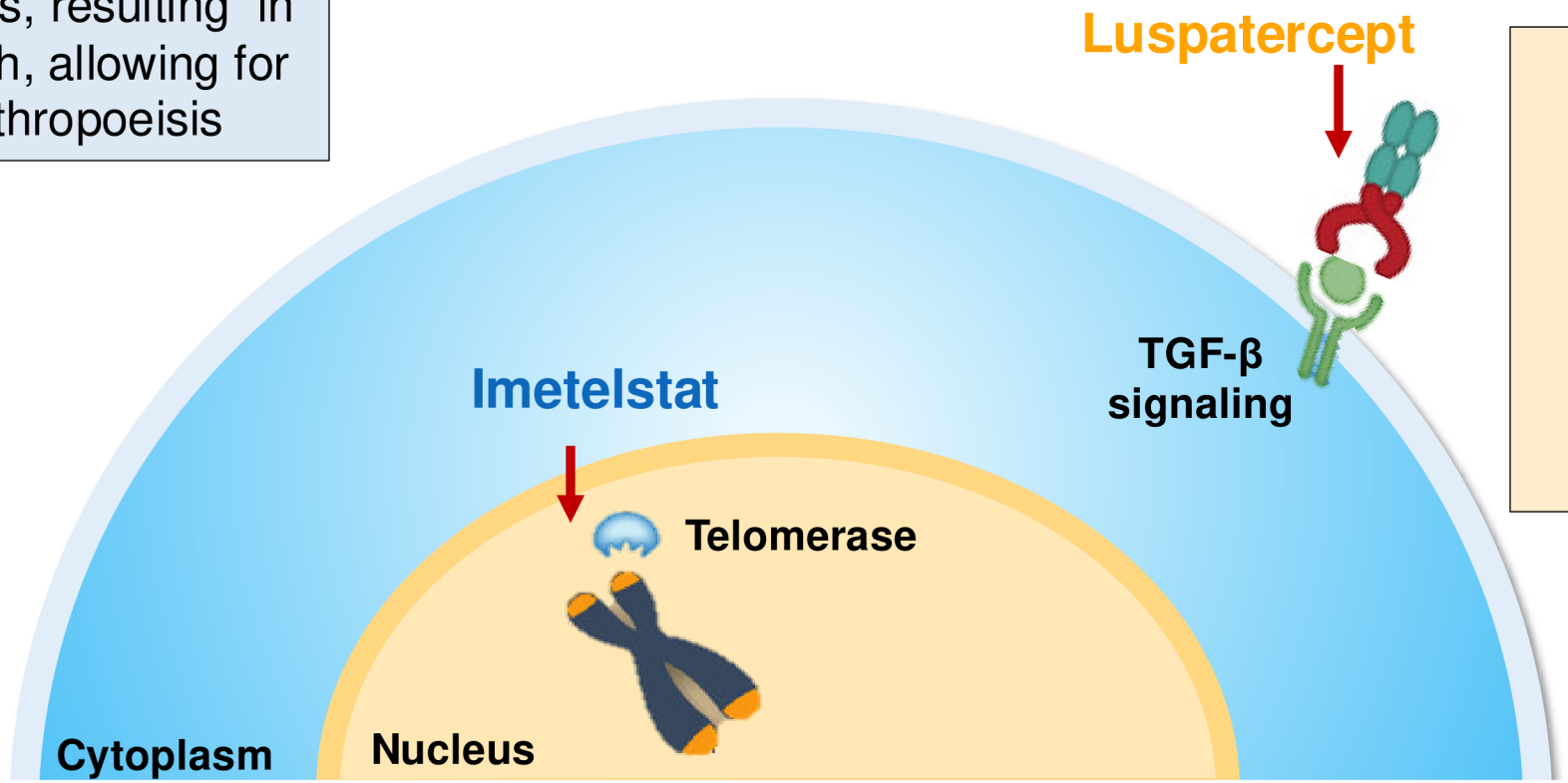
- **Recommended dose:** 7.1 mg/kg IV over 2 hours every 4 weeks
- Discontinue if no decrease in RBC transfusion burden after 24 weeks of treatment (administration of 6 doses) or if unacceptable toxicity occurs
- **Premedication at least 30 minutes prior to dosing**
  - Diphenhydramine (or equivalent)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

Dose Modifications for Grade 3/4 AEs

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

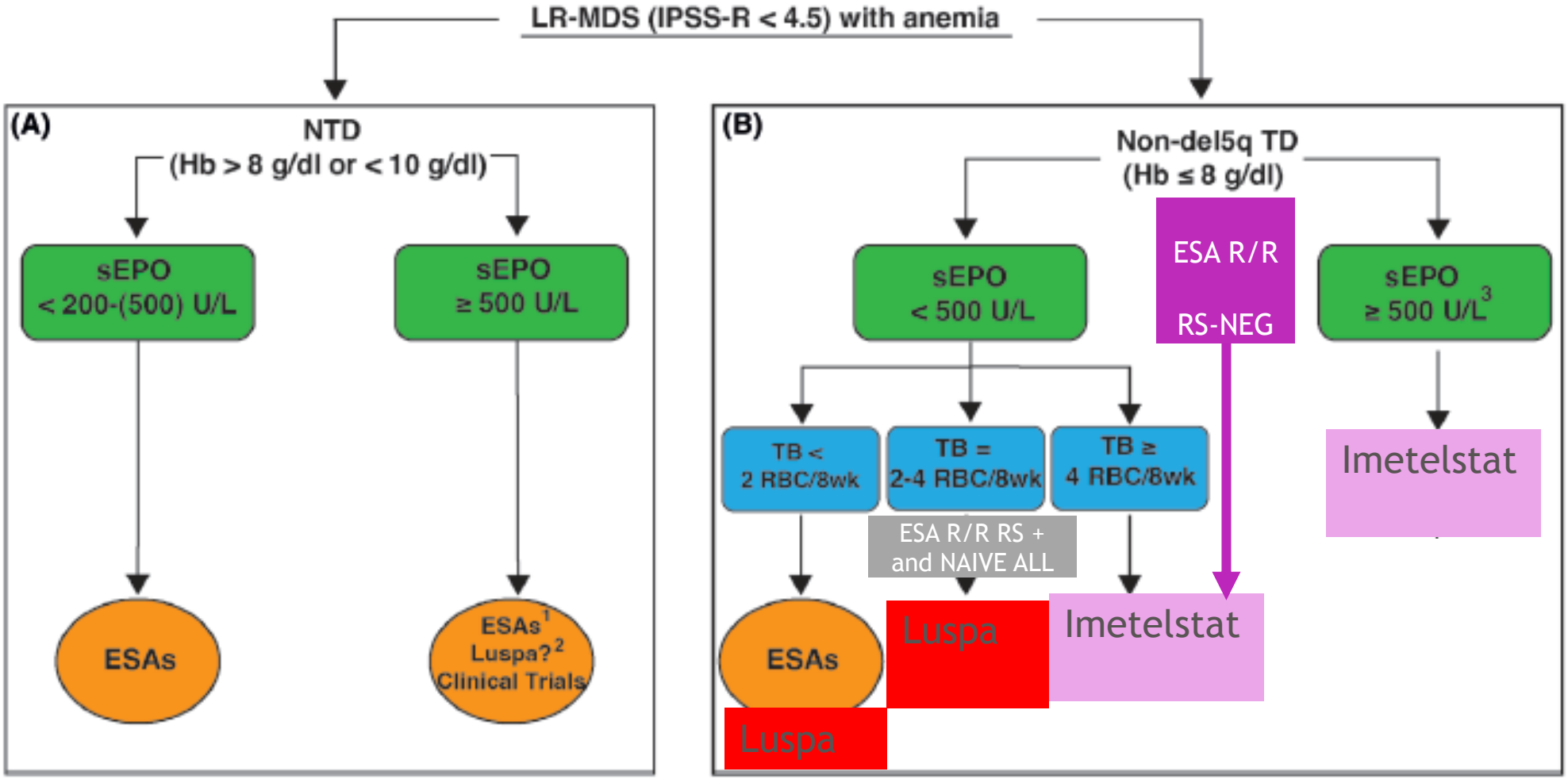
Imetelstat and Luspatercept: Non-overlapping Mechanism of Action

Imetelstat: oligonucleotide inhibitor of telomerase, which is upregulated in malignant stem and progenitor cells, resulting in apoptotic cell death, allowing for recovery of erythropoeisis



Luspatercept: Erythroid maturation agent that results in expansion and differentiation of late-stage erythroid precursors to restore erythropoiesis

Figure based on: Meunier and Park, 2022



MODIFIED from Santini and Consagra , BJH 2025

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DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

Azienda Ospedaliero Universitaria Careggi

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FISiM FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

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