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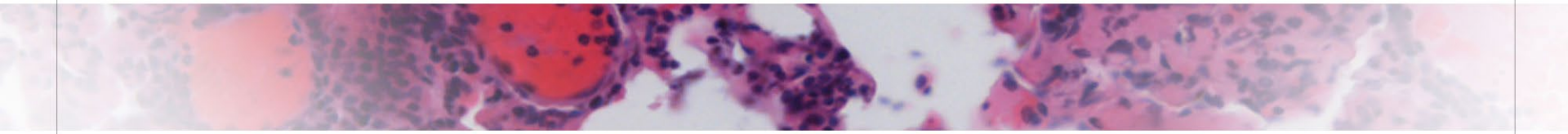

Effect of Prior Treatments on the Clinical Activity of Imetelstat in Transfusion-Dependent Patients with Erythropoiesis-Stimulating Agent, Relapsed or Refractory/Ineligible Lower-Risk Myelodysplastic Syndromes

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Background

- Treatment options for patients with RBC-TD LR-MDS have limited efficacy and durability, and there is a need for evidence to inform optimal treatment sequencing in these patients[1-3]
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity approved for the treatment of adult patients with RBC-TD LR-MDS relapsed or refractory to or ineligible for ESA based on positive efficacy and safety results from the IMerge trial (NCT02598661)[3]
  - A significantly higher proportion of patients who received imetelstat achieved ≥8-week, ≥24-week, and ≥1-year RBC-TI compared with patients who received placebo; patients who received imetelstat also had a greater increase in Hb concentrations and a greater reduction in transfusion burden
- The effect of prior use of other LR-MDS treatments on the clinical activity of imetelstat is currently unknown

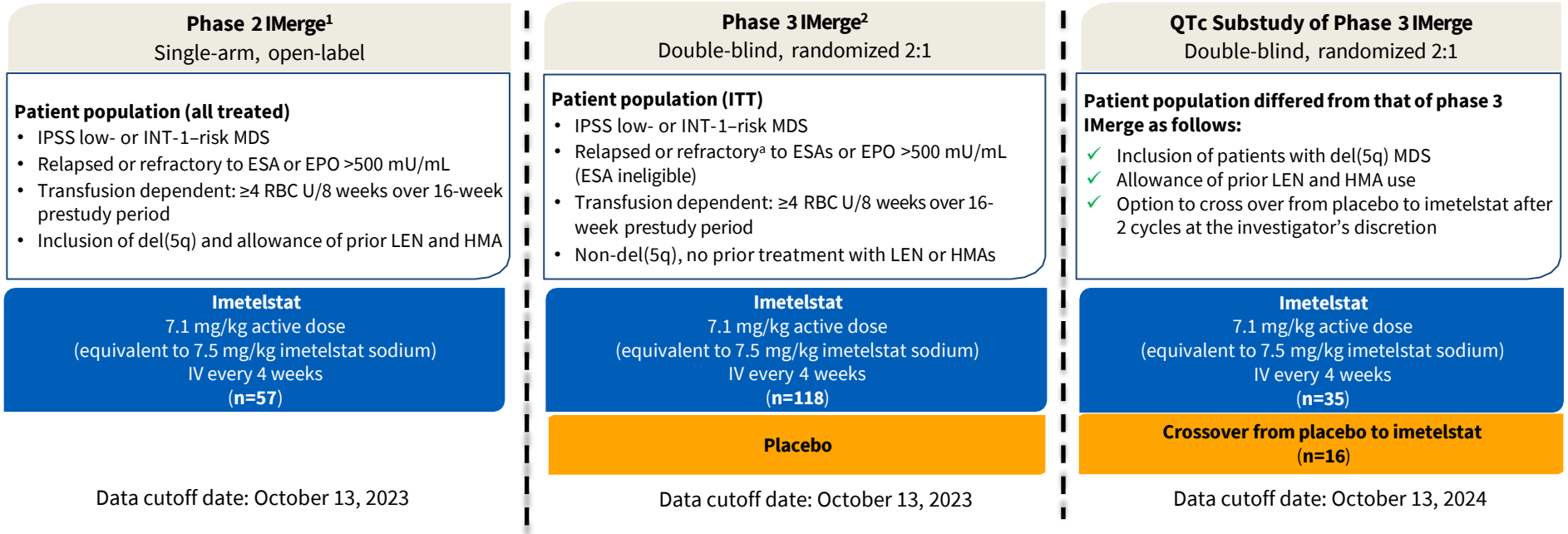
Objective: To investigate the effects of prior therapies on the clinical activity of imetelstat using pooled data from the 3 parts of IMerge (phase 2, phase 3, and QTc substudy)[3,4]

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LR-MDS, lower-risk myelodysplastic syndromes; QTc, QT correction; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independence.

1. Germing U, et al. *Hemasphere.* 2019;3(6):e314. 2. Komrokji RS, et al. *Blood*. 2023;142(suppl 1):2440. 3. Platzbecker U and Santini V, et al. *Lancet.* 2024;403(10423):249-260. 4. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56.

Methods

- A total of 226 patients with LR-MDS who were treated with imetelstat 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; LR-MDS, lower risk myelodysplastic syndromes; 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.

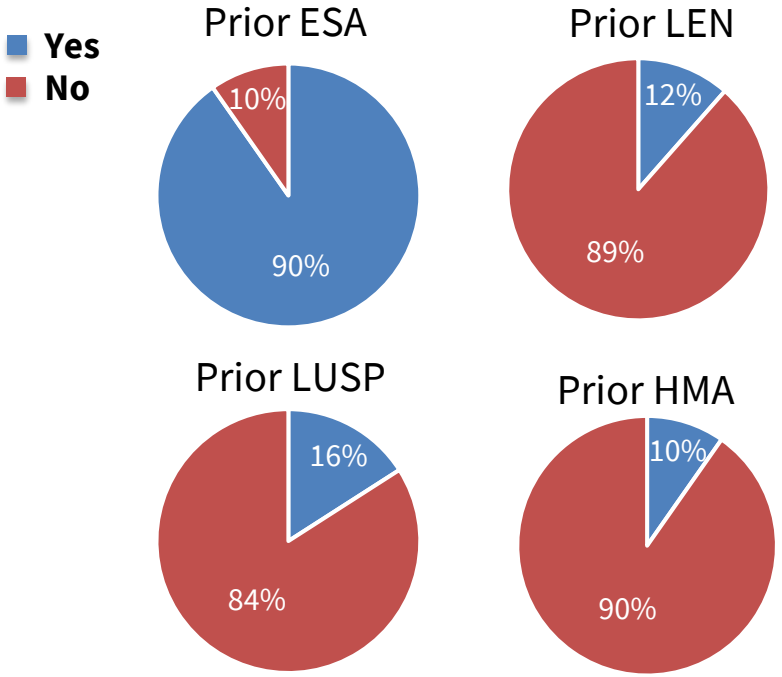
Baseline Characteristics and Imetelstat Exposure in the Pooled Patient Population

Baseline patient and disease characteristics	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)
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)

Imetelstat treatment exposure	Imetelstat (N=226)
Imetelstat treatment duration, median (range), weeks	33.6 (0.1-260.1)
Number of imetelstat treatment cycles, n (%)	
1-3 cycles	34 (15)
4-6 cycles	56 (25)
7-12 cycles	46 (20)
≥13 cycles	90 (40)

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.

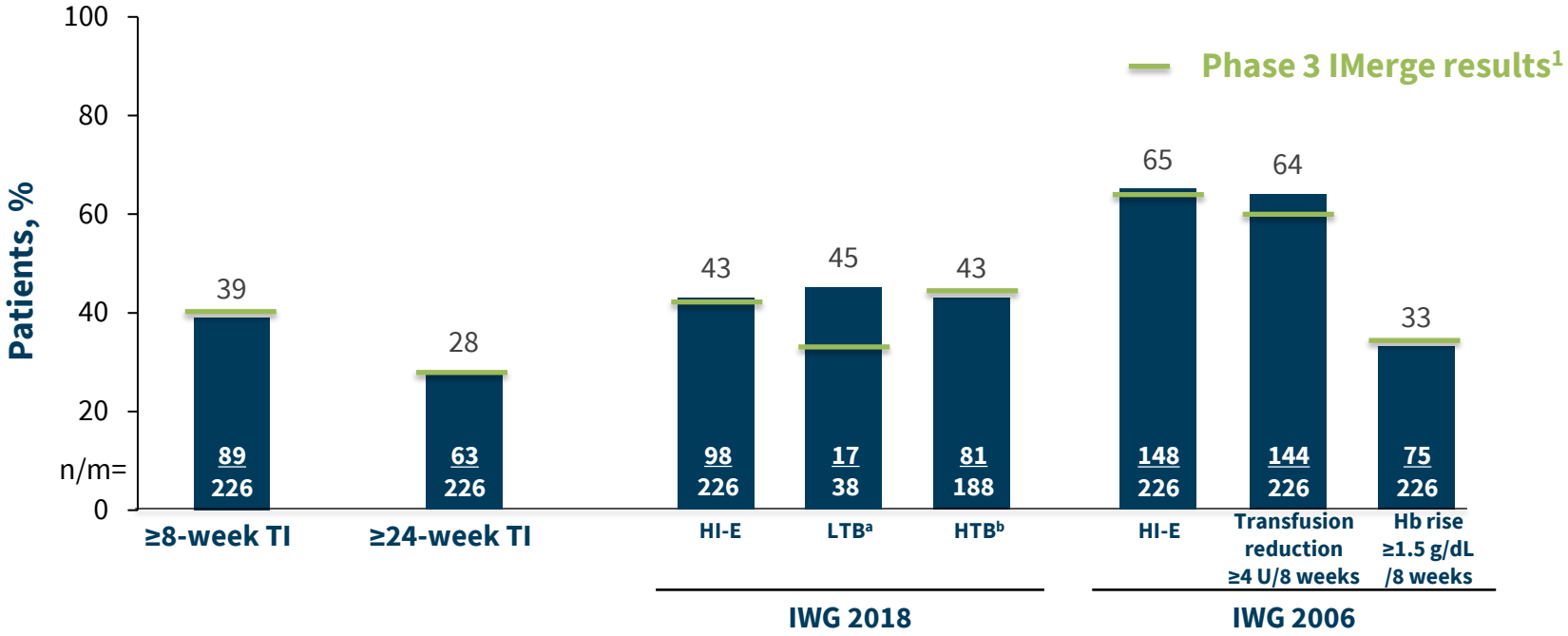
Most Patients Had Prior ESA and No Prior LEN/LUSP/HMA[a]



	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*; Results Were Consistent With Phase 3 IMerge

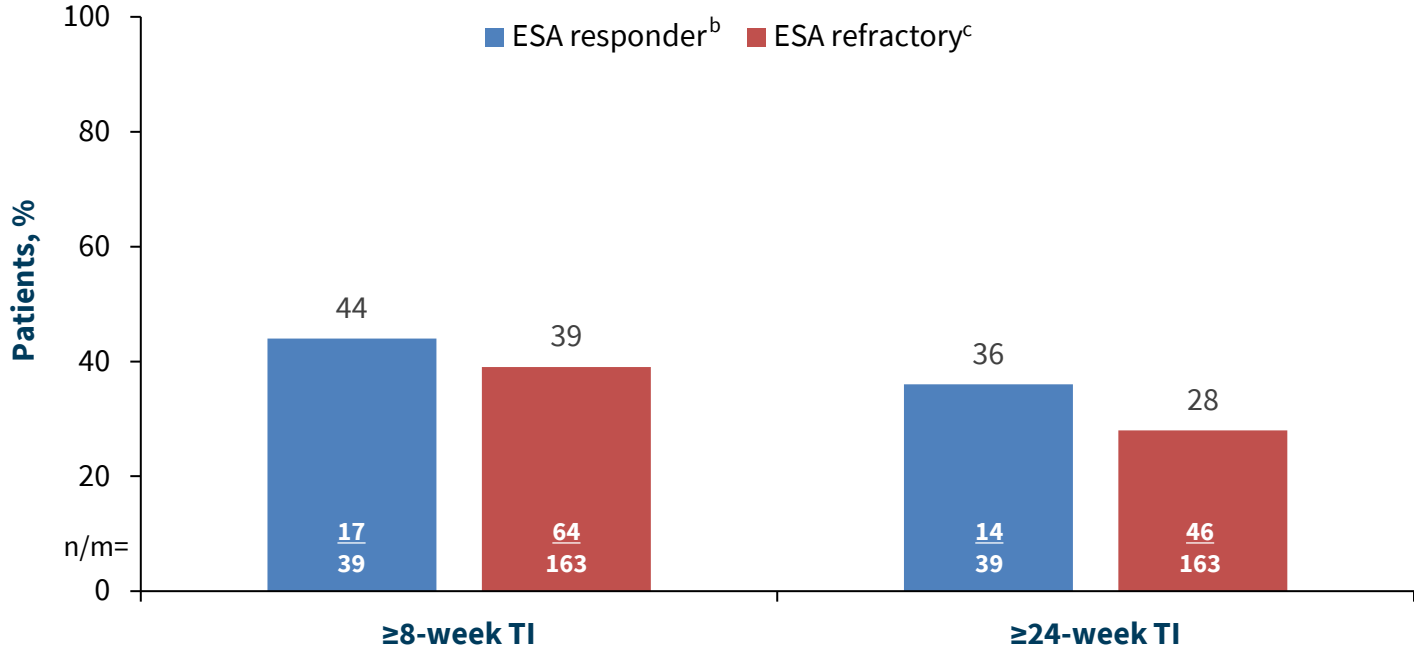


Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; n/m, number with event/number in population; RBC, red blood cell; TI, transfusion independence.

[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.

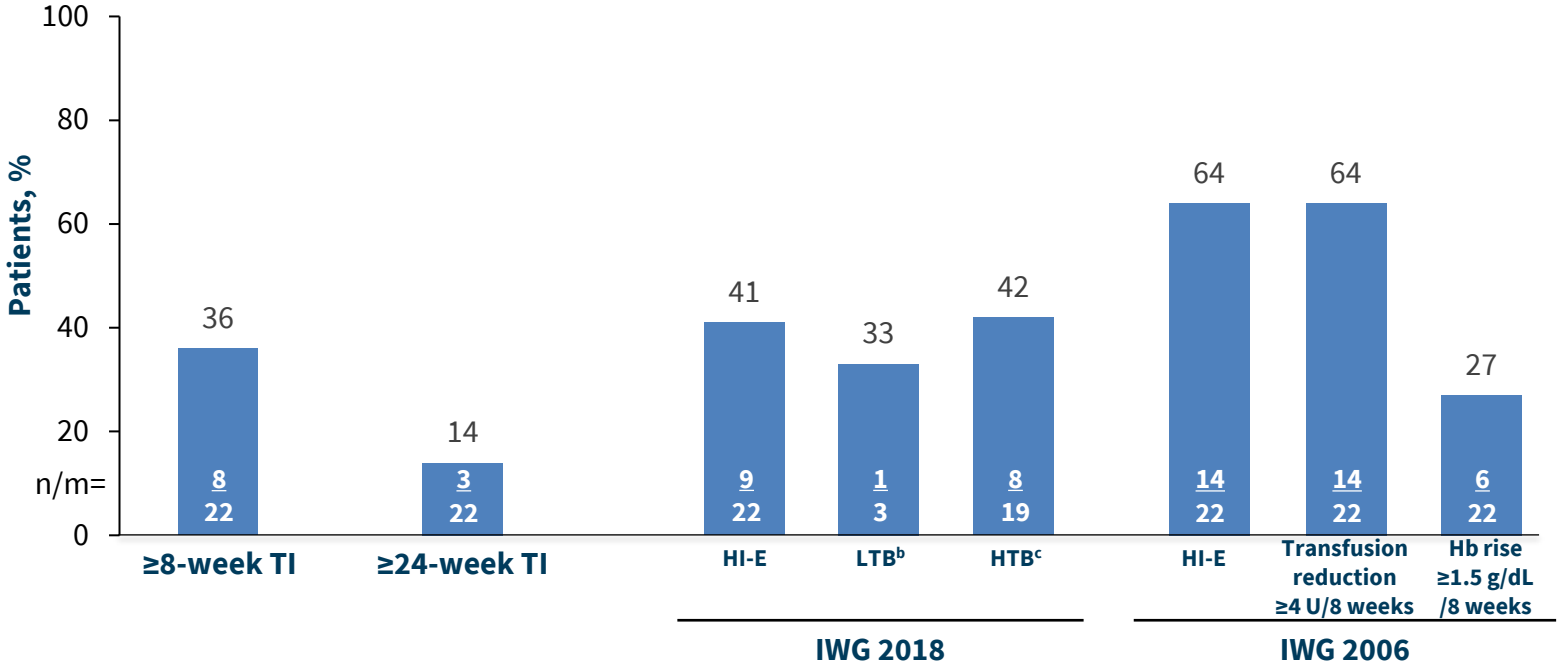
1. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.

Clinical Activity Was Observed With Imetelstat in Pooled Patients *Regardless of Prior ESA Response Status* (n=202[a])



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] Two patients with prior ESA but missing best response to ESA were excluded. [b]Response included RBC-TI and HI-E response. [c]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.

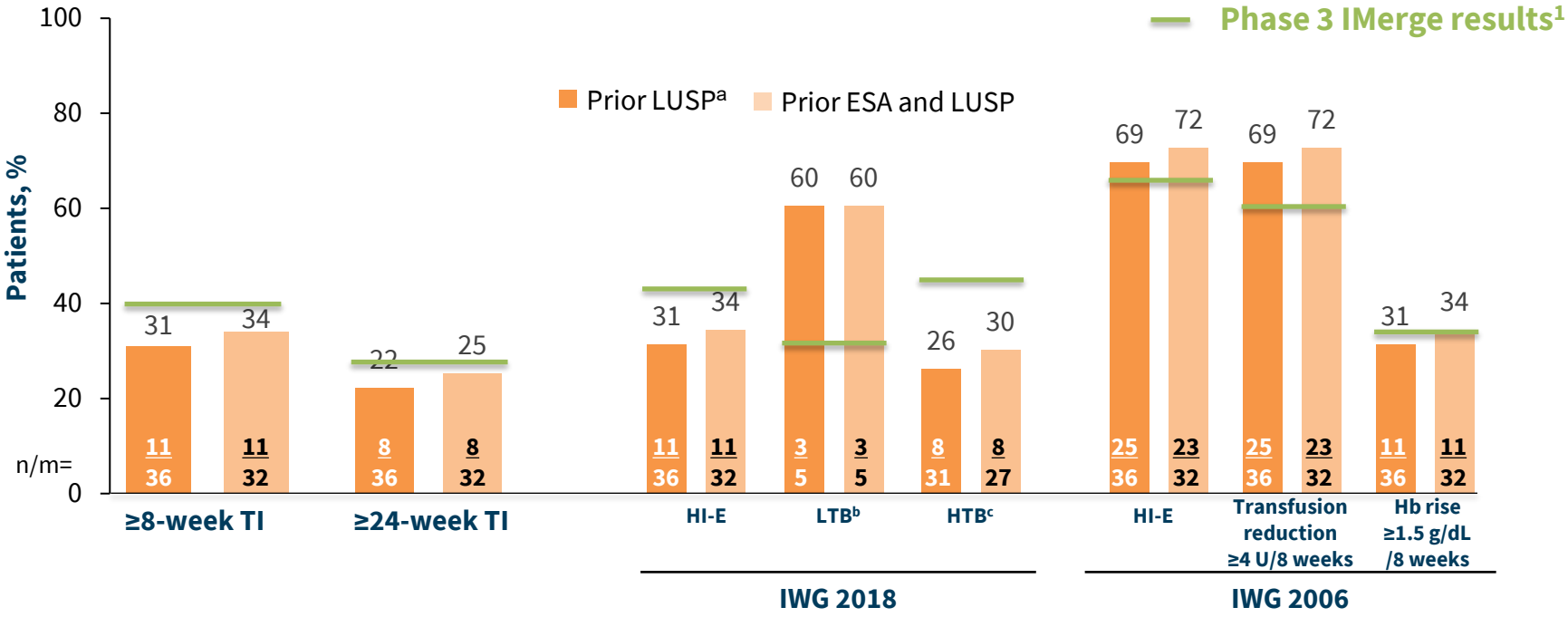
Imetelstat Showed Clinical Activity *in ESA-Ineligible[a] Patients* (n=22)



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; 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]ESA ineligibility per inclusion criteria was defined as EPO >500 mU/mL. [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.

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

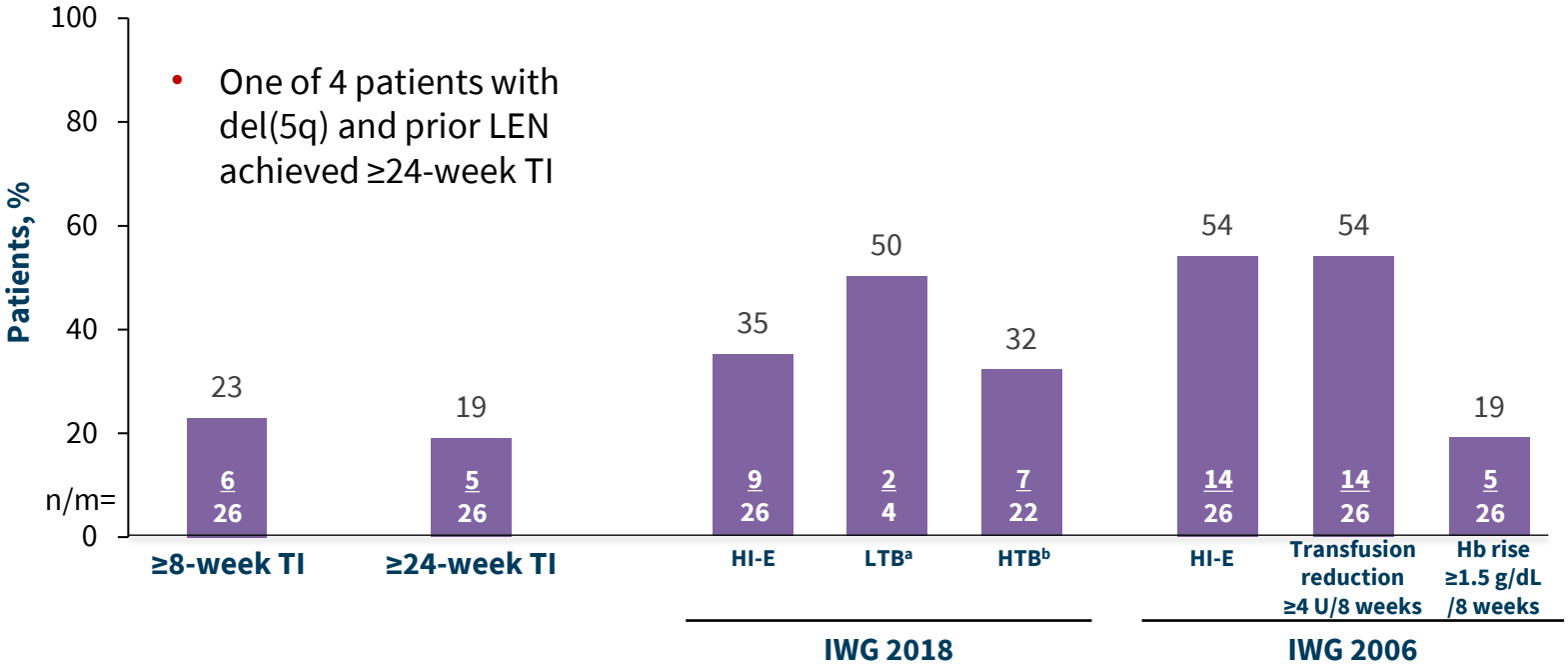


ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; LUSP, luspatercept; n/m, number with event/number in population; RBC, red blood cell; RS, ring sideroblast; TI,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

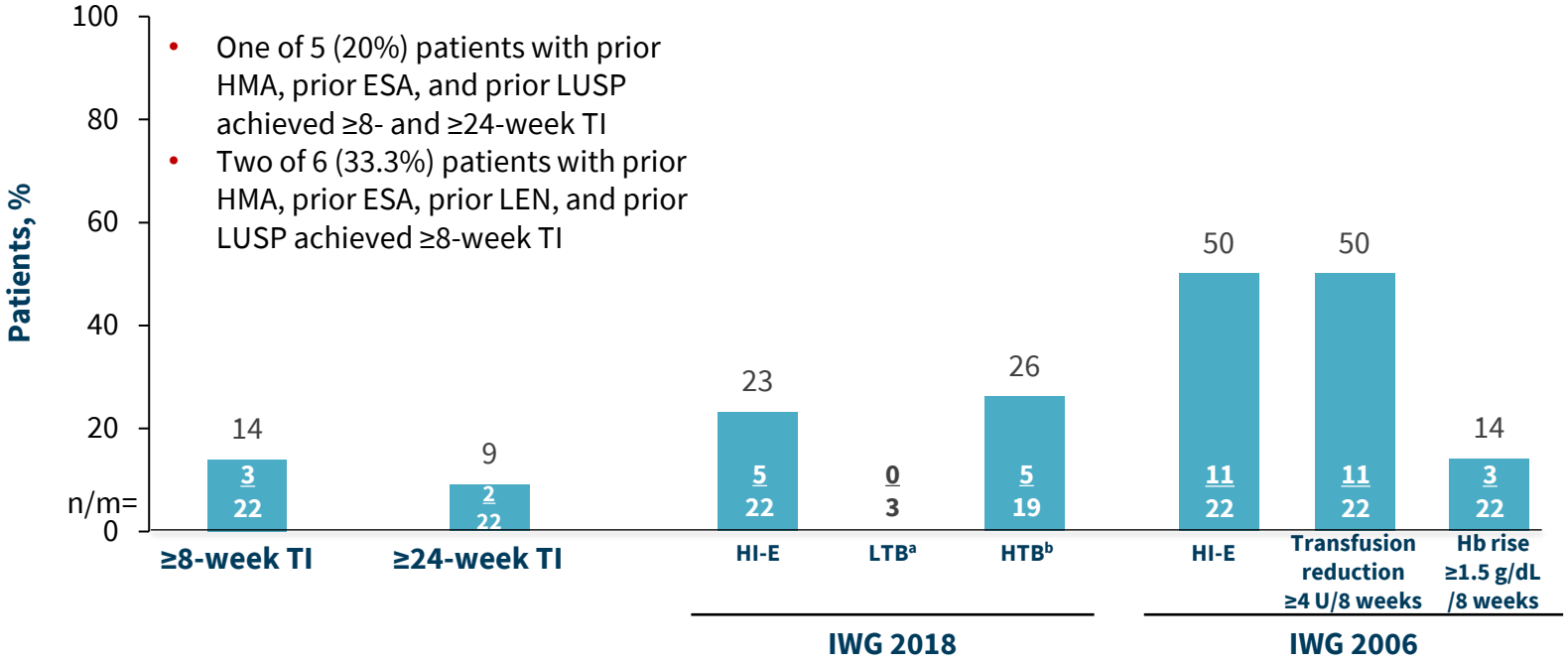
Imetelstat Showed Clinical Activity in Patients *With Prior Lenalidomide* (n=26)



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

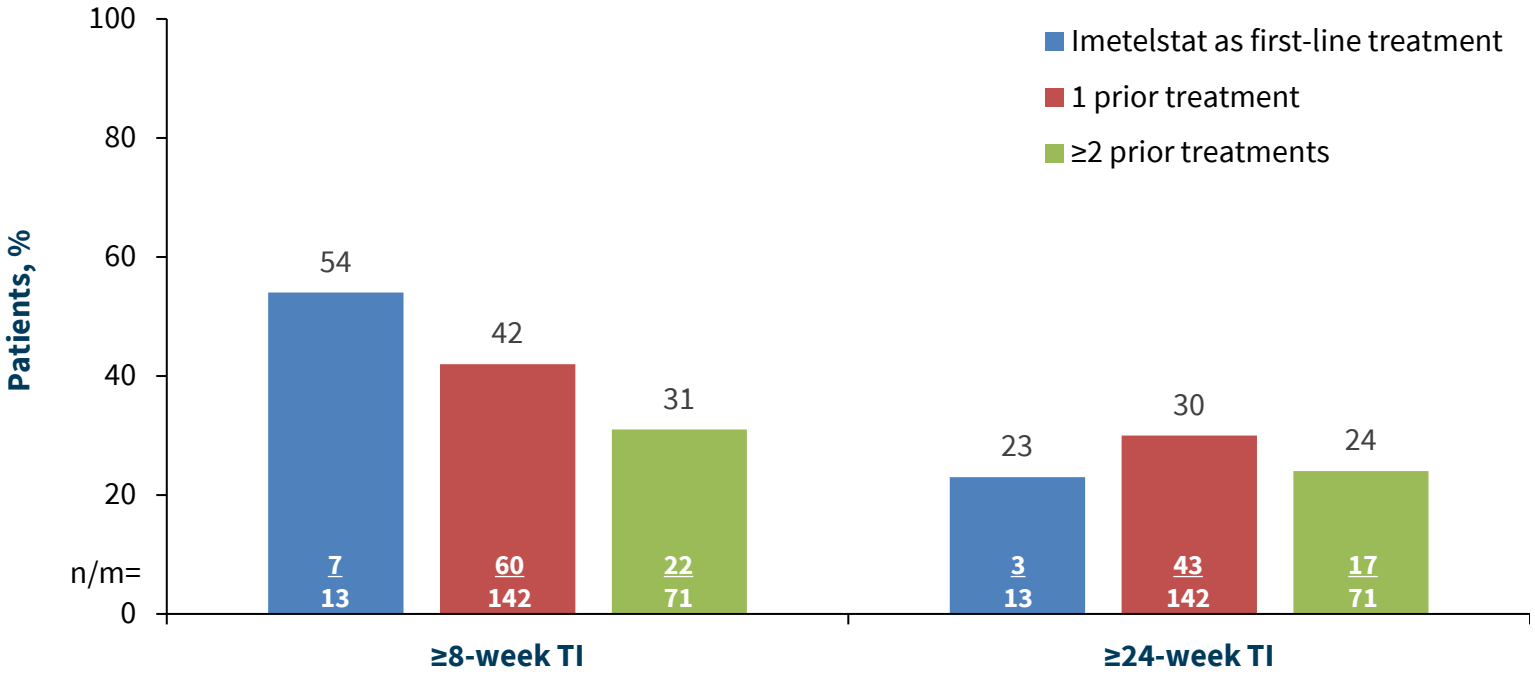
[a]LTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. [b]HTB defined as ≥8 RBC U in 16 weeks, or ≥4 RBC U in 8 weeks.

Imetelstat Showed 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; LEN, lenalidomide; 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.

Imetelstat Showed Clinical Activity *Regardless of Number of Prior Lines of Therapy* (N=226)



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

Safety Results With Imetelstat Were Consistent With Those of Phase 3 IMerge, With No New Signals Identified

	Total (N=226)
TEAEs, n (%)	
Any grade	221 (97.8)
Serious	85 (37.6)
Grade ≥3	200 (88.5)
Most common TEAEs by preferred term in ≥15% of patients, n (%)	
Neutropenia	163 (72.1)
Thrombocytopenia	161 (71.2)
Anemia	48 (21.2)
Diarrhea	36 (15.9)
Alanine aminotransferase increased	35 (15.5)

- Most cytopenia events occurred in earlier treatment cycles/months and were temporary and reversible, with most grade ≥3 neutropenia (82.6%) and thrombocytopenia (86.4%) events resolved to grade ≤2 in <4 weeks

TEAE, treatment-emergent adverse event.

Conclusions

- Patients who were ESA ineligible or who had prior treatment with LUSP or LEN in IMerge experienced clinical benefit from imetelstat treatment, similar to prior results from the IMerge pivotal trial[1]
  - Patients who had prior treatment with HMA showed modest clinical activity with imetelstat
- Clinical activity of imetelstat was evident across lines of therapy and regardless of prior ESA response status
  - The analysis was limited by the small number of patients in each group
- These results have important clinical implications in the evolving therapeutic landscape for LR-MDS, suggesting that imetelstat demonstrates clinical activity regardless of number or type of prior therapies

ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; LEN, lenalidomide; LR-MDS, lower-risk myelodysplastic syndromes; LUSP, luspatercept.

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

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