

Efficacy of imetelstat on red blood cell (RBC)-transfusion independence (TI) in the absence of platelet transfusions or myeloid growth factors in IMerge

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Background

- Imetelstat is a first-in-class direct and competitive inhibitor of telomerase enzymatic activity directed toward malignant clones, allowing for recovery of erythropoeisis^{1,2}
- Unmet need remains for RBC transfusion–dependent patients with lower-risk (per International Prognostic Scoring System [IPSS] low and intermediate-1 risk) myelodysplastic syndromes (LR-MDS) relapsed or refractory (R/R) to, or ineligible for, erythropoiesis-stimulating agents (ESA)^{3,4}
- In the IMerge clinical trial (NCT02598661) of patients who were RBC transfusion–dependent with LR-MDS R/R to or ineligible for ESAs, imetelstat showed significant and durable efficacy versus placebo for ≥8-week, ≥24-week, and ≥1-year RBC-TI, with neutropenia and thrombocytopenia as the most common adverse events.⁵ Supportive care was given to all patients as needed, per investigator discretion
- Here, we report RBC-TI rates in the absence of platelet transfusions or myeloid growth factor use after imetelstat treatment as part of the IMerge clinical trial
- Separately, RBC-TI with a mean central hemoglobin (Hb) rise of ≥1.5 g/dL was assessed in all patients

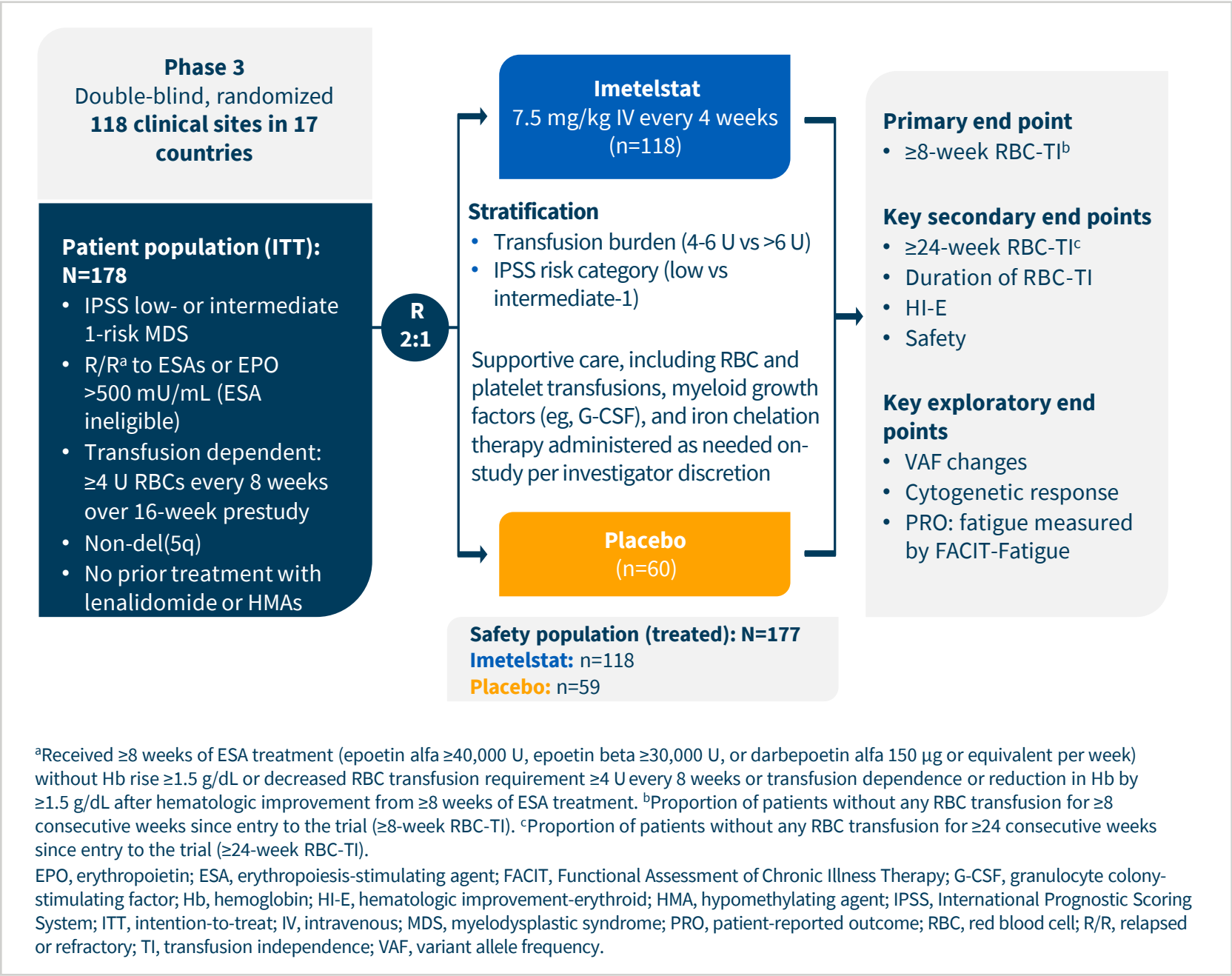
Methods

- Study design**
- IMerge was a double-blind, randomized (2:1), placebo-controlled, phase 3 clinical trial conducted at 118 global sites that enrolled patients between 2019 and 2022 (**Figure 1**)
 - The primary end point was ≥8-week RBC-TI rate; key secondary end points included ≥24-week RBC-TI, duration of RBC-TI, hematologic improvement-erythroid (HI-E), and safety
 - Primary analysis cutoff was October 2022, with October 2023 cutoff for ≥ 1-year RBC-TI analyses

- Patients**
- Enrollment included patients with RBC transfusion–dependent (defined as requiring ≥4 units of RBC/ 8 weeks), ESA-R/R/ineligible non-del(5q) LR-MDS naive to lenalidomide and hypomethylating agents with low or intermediate risk-1 disease per IPSS

- Statistics**
- Primary and key secondary end points were compared using a Cochran-Mantel-Haenszel test stratified by prior RBC transfusion burden and IPSS category, and RBC-TI duration was calculated by the Kaplan-Meier method and compared via the stratified log-rank test

Figure 1. IMerge phase 3 study design



Results

- Patients**
- Patient and disease characteristics were balanced across treatment arms (**Table 1**)
 - Imetelstat (n=118) and placebo (n=60) arms had similar baseline transfusion burden and Hb levels

Table 1. Baseline demographic and disease characteristics

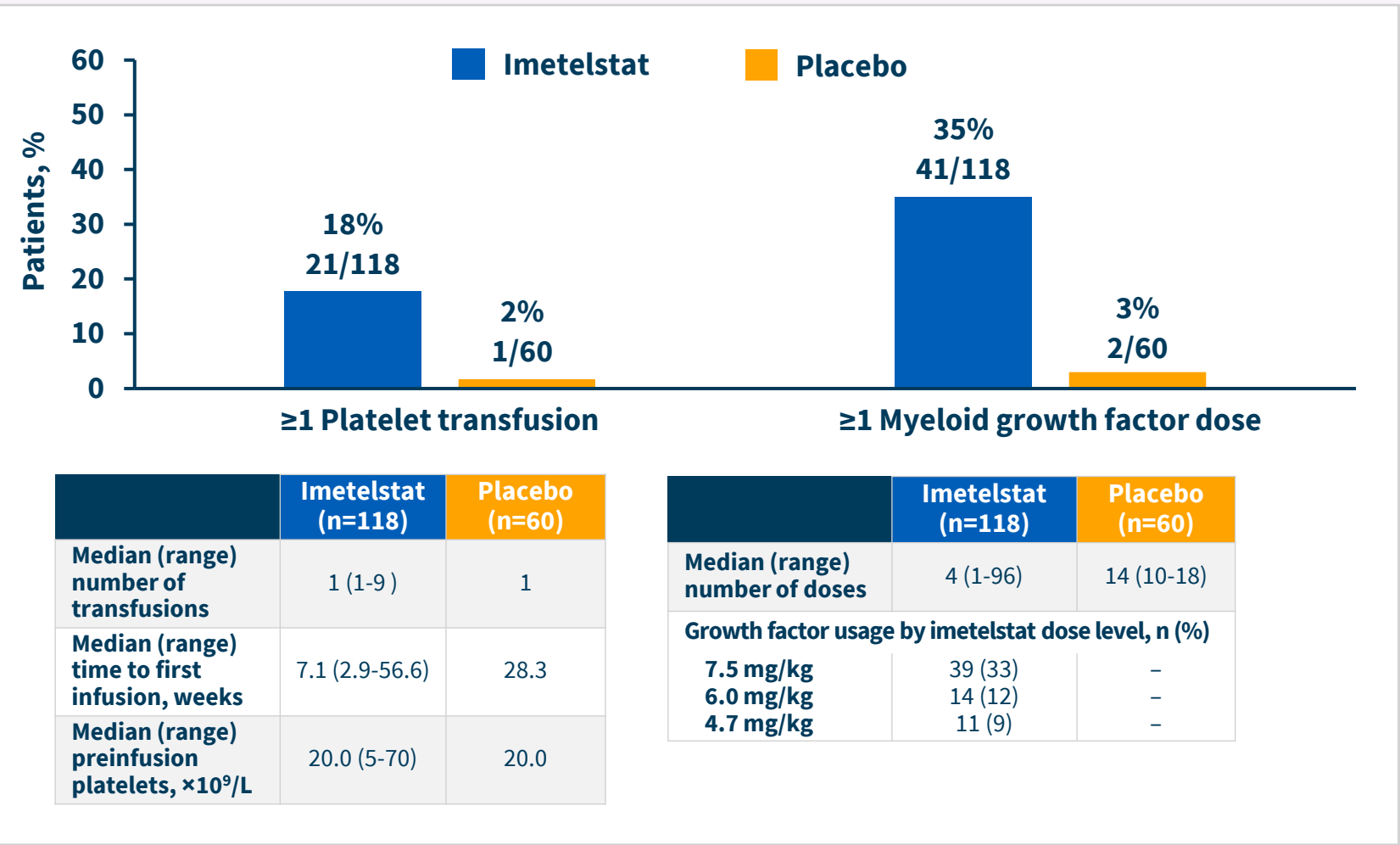
Characteristic	Imetelstat (n=118)	Placebo (n=60)
Median (range) age, y	72 (44-87)	73 (39-85)
Male, n (%)	71 (60)	40 (67)
Median (range) time since diagnosis, y	3.5 (0.1-26.7)	2.8 (0.2-25.7)
WHO classification, n (%)		
RS+	73 (62)	37 (62)
RS-	44 (37)	23 (38)
IPSS risk category, n (%)		
Low	80 (68)	39 (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 13, 2022. ^aAverage 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. ^bData missing for 5 patients in the imetelstat group and 2 in the placebo group. ^cInsufficient 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.

Platelet transfusion and myeloid growth factor support

- A total of 21 (18%) and 1 (2%) patients in the imetelstat and placebo arms, respectively, received platelet transfusions (**Figure 2**)
 - The median number of platelet transfusions in both arms was 1 transfusion per patient
- A total of 41 (35%) and 2 (3%) patients from the respective arms received myeloid growth factors (**Figure 2**)
 - Myeloid growth factor use was intermittent, not chronic or long-term, and predominantly in patients receiving the highest imetelstat dose level

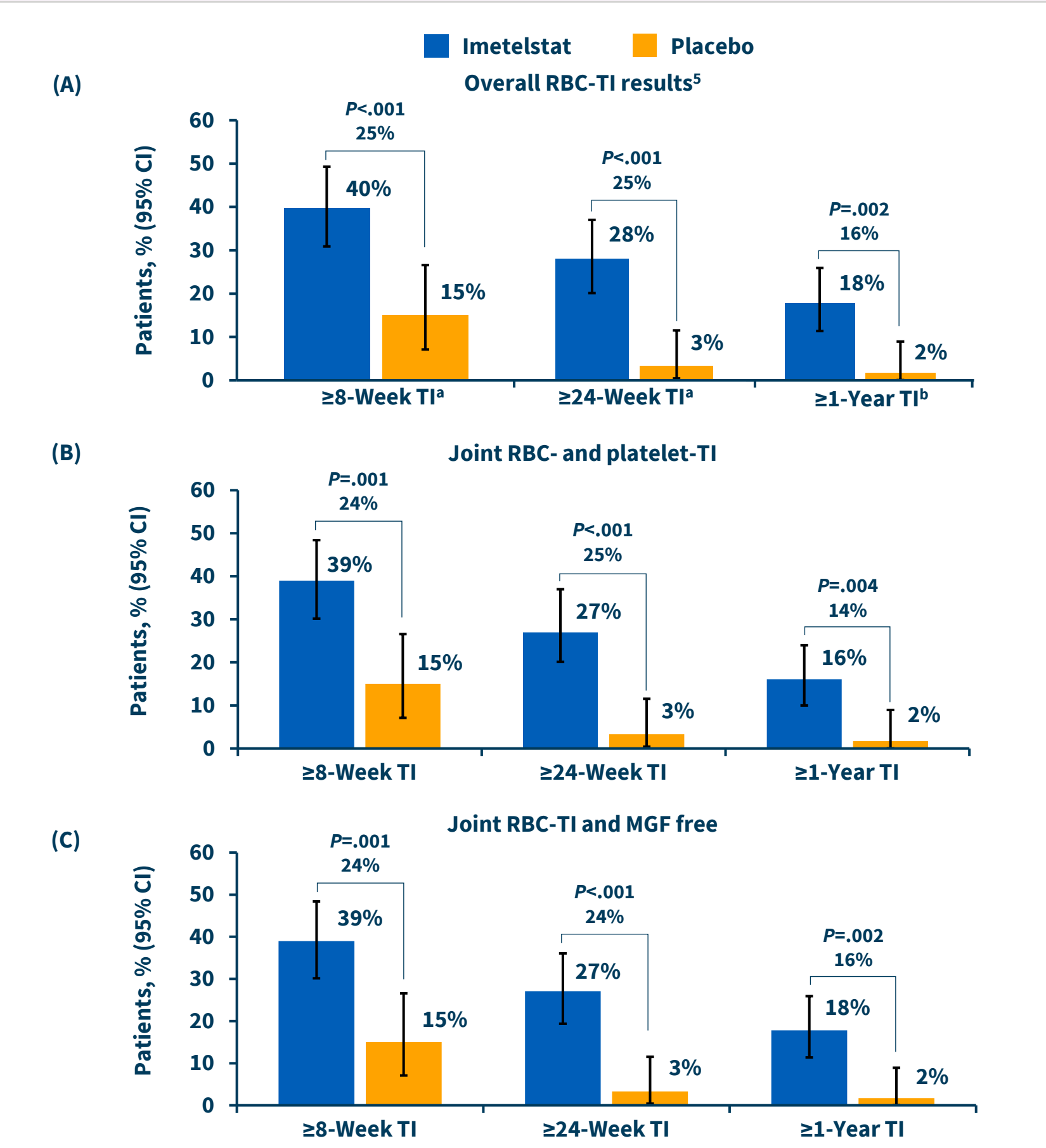
Figure 2. Platelet transfusions and myeloid growth factor usage



RBC-TI by independence from platelet transfusion and myeloid growth factor support

- Significantly higher percentages of patients achieved ≥8-week, ≥24-week, and ≥1-year RBC-TI with imetelstat compared with placebo in the absence of either platelet transfusions or myeloid growth factor support (**Figure 3**)

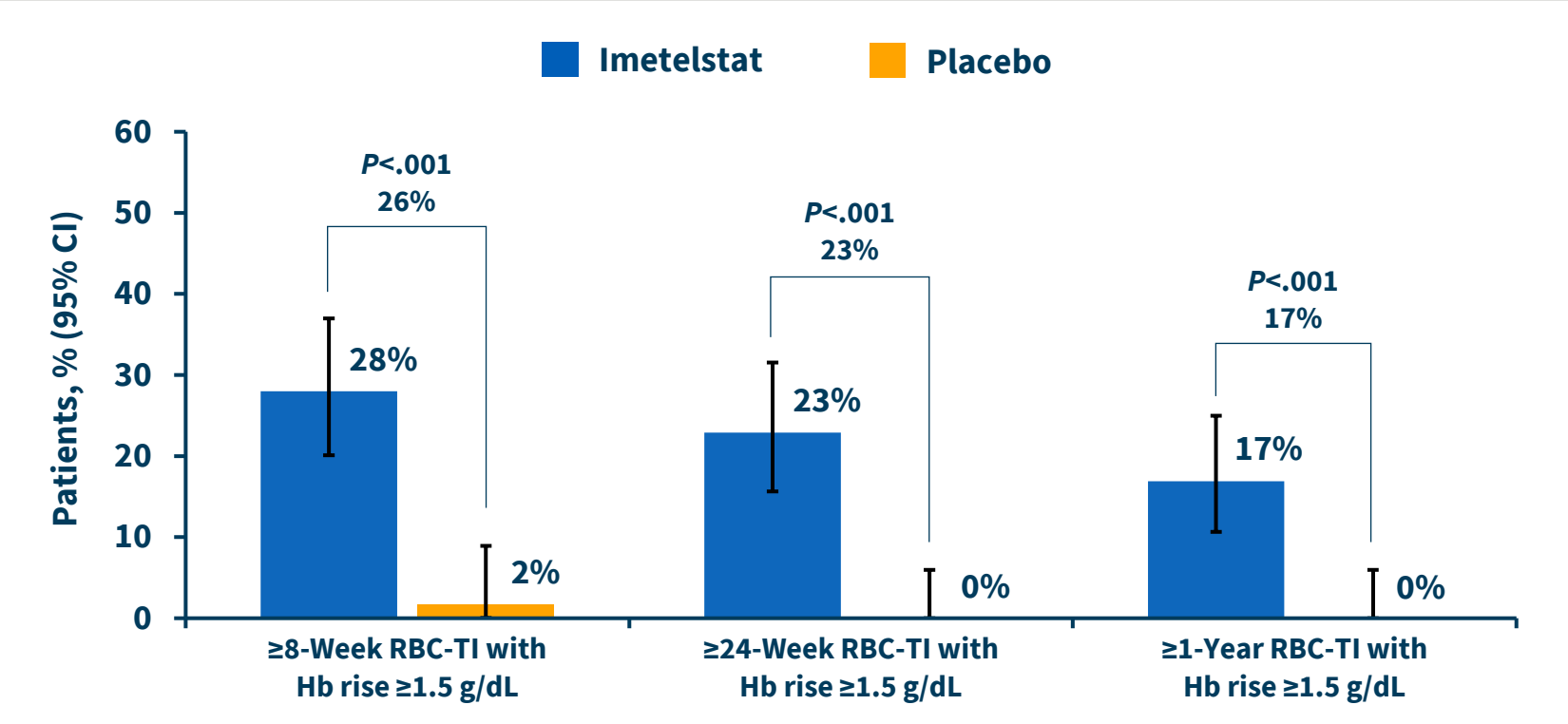
Figure 3. Rates of (A) overall RBC-TI; (B) joint RBC- and platelet-TI; and (C) joint RBC-TI and MGF free (ITT population)



^aData cutoff date: October 13, 2022. ^bData cutoff date: October 13, 2023.
ITT, intention-to-treat; MGF, myeloid growth factor; RBC, red blood cell; TI, transfusion independence.

- RBC-TI by Hb rise**
- More patients treated with imetelstat achieved ≥8-week, ≥24-week, and ≥1-year RBC-TI and concurrent Hb rise of ≥1.5 g/dL (**Figure 4**)

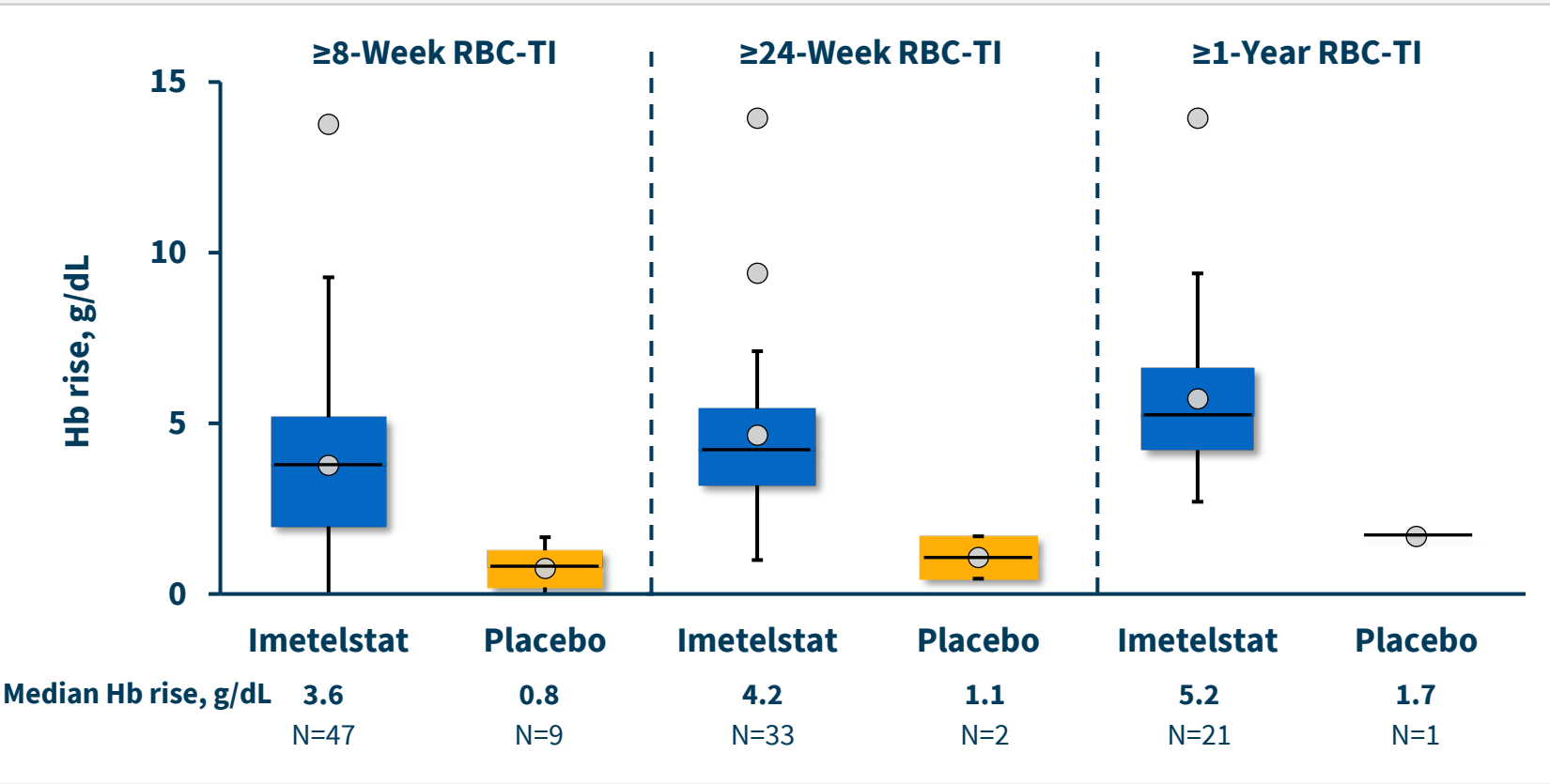
Figure 4. RBC-TI with concurrent mean central Hb rise ≥1.5 g/dL



Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

- RBC-TI by Hb rise**
- Among responders, imetelstat increased median central Hb levels compared with placebo across time points (**Figure 5**)
 - Median Hb rise among responders was 3.6 g/dL versus 0.8 g/dL for ≥8-week, 4.2 g/dL versus 1.1 g/dL for ≥24-week, and 5.2 g/dL versus 1.7 g/dL for ≥1-year RBC-TI

Figure 5. Rise in Hb among responders



Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Conclusions

- In this heavily RBC transfusion-dependent LR-MDS population, the rates of ≥8-week, ≥24-week, and ≥1-year RBC-TI concurrent with platelet-TI or myeloid growth factor support-independence were significantly higher with imetelstat compared with placebo
 - Median number of platelet transfusions was 1 per patient in both imetelstat and placebo arms; median number of myeloid growth factor doses was 4 per patient with imetelstat versus 14 with placebo
- When factoring in Hb rise of ≥1.5 g/dL and concurrent RBC-TI, imetelstat treatment was associated with significantly higher rates of ≥8-week, ≥24-week, and ≥1-year RBC-TI versus placebo, with only 2% of placebo patients achieving ≥8-week RBC-TI and none achieving ≥24-week or ≥1-year RBC-TI
 - Long-term RBC-TI responders achieved Hb levels that approached normal
- These data are consistent with the primary IMerge analysis and further support the totality of clinical benefit of imetelstat in fulfilling an unmet need in RBC transfusion-dependent patients with LR-MDS R/R to or ineligible for ESAs

References

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