

Overall Survival, Clinical Benefit, and Durable Transfusion Independence With Imetelstat in the IMerge Phase 3 Trial of Red Blood Cell Transfusion-Dependent Lower-Risk Myelodysplastic Syndromes

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Disclosures: Valeria Santini

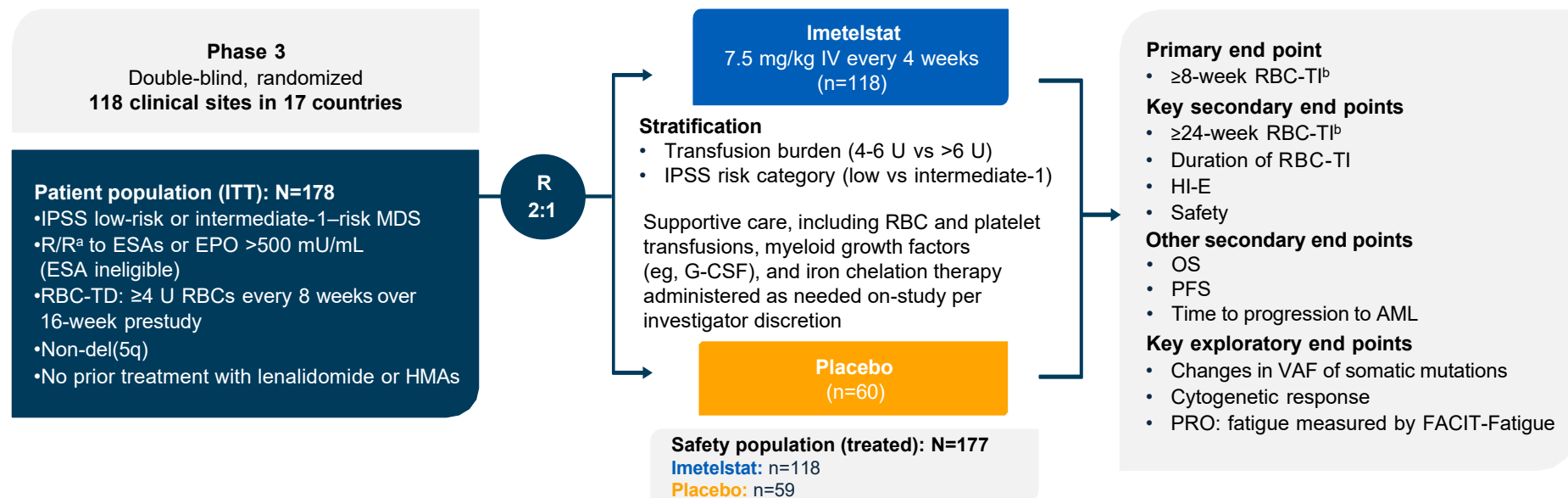
- Advisory boards for AbbVie, Ascentage, Bristol Myers Squibb, CTI BioPharma, Geron, Gilead, Novartis, Servier, and Syros Pharmaceuticals
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Background

- Current treatments for lower-risk myelodysplastic syndromes (LR-MDS) have limitations, and patients often become red blood cell (RBC) transfusion-dependent (TD)^{1,2}
- RBC transfusions negatively affect progression-free and overall survival (OS) in patients with MDS, highlighting the need for therapies that sustain continuous RBC-transfusion independence (TI) and have the potential to improve OS^{1,2}
- Imetelstat is a recently US FDA-approved, first-in-class direct and competitive inhibitor of telomerase enzymatic activity that selectively targets malignant clones and allows for recovery of erythropoiesis³⁻⁵
- IMerge (NCT02598661) is a multinational, randomized, double-blind, phase 2/3 trial of imetelstat versus placebo in patients with heavily RBC-TD, erythropoiesis-stimulating agent (ESA)–relapsed, refractory, or ineligible and non-del(5q) LR-MDS naïve to treatment with lenalidomide or hypomethylating agents⁶
 - Phase 3 primary analysis: significantly higher rates of ≥ 8 -week, ≥ 24 -week, and ≥ 1 -year RBC-TI with imetelstat (n=118; 39.8%, 28.0%, and 17.8%) vs. placebo (n=60; 15.0%, 3.3%, and 1.7%) in the ITT population
 - Most common adverse events were neutropenia and thrombocytopenia, which were generally reversible and manageable with dose modifications
- This analysis assessed OS and clinical benefit of durable RBC-TI as the secondary endpoints in IMerge

1. Platzbecker U, et al. *Leukemia*. 2021;35:2182-2198. 2. Harnan S, et al. *Acta Haematol*. 2016;136:23-42. 3. Asai A, et al. *Cancer Res*. 2003;63(14):3931-3939. 4. Herbert B-S, et al. *Oncogene*. 2005;24(33):5262-5268. 5. RYTELO (imetelstat) for injection, for intravenous use [package insert]. Foster City, CA; Geron Corporation; 2024. 6. Platzbecker U, Santini V, et al. *Lancet*. 2024;403(10423):249-260.

IMerge Phase 3 Study Design



- Duration of RBC-TI and OS were calculated by Kaplan-Meier method and compared by stratified log-rank test
- Data cutoff dates were October 2023 and January 2024 (for OS)

^aReceived ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin 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. ^bProportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (≥8-week RBC-TI). ^cProportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (≥24-week RBC-TI).

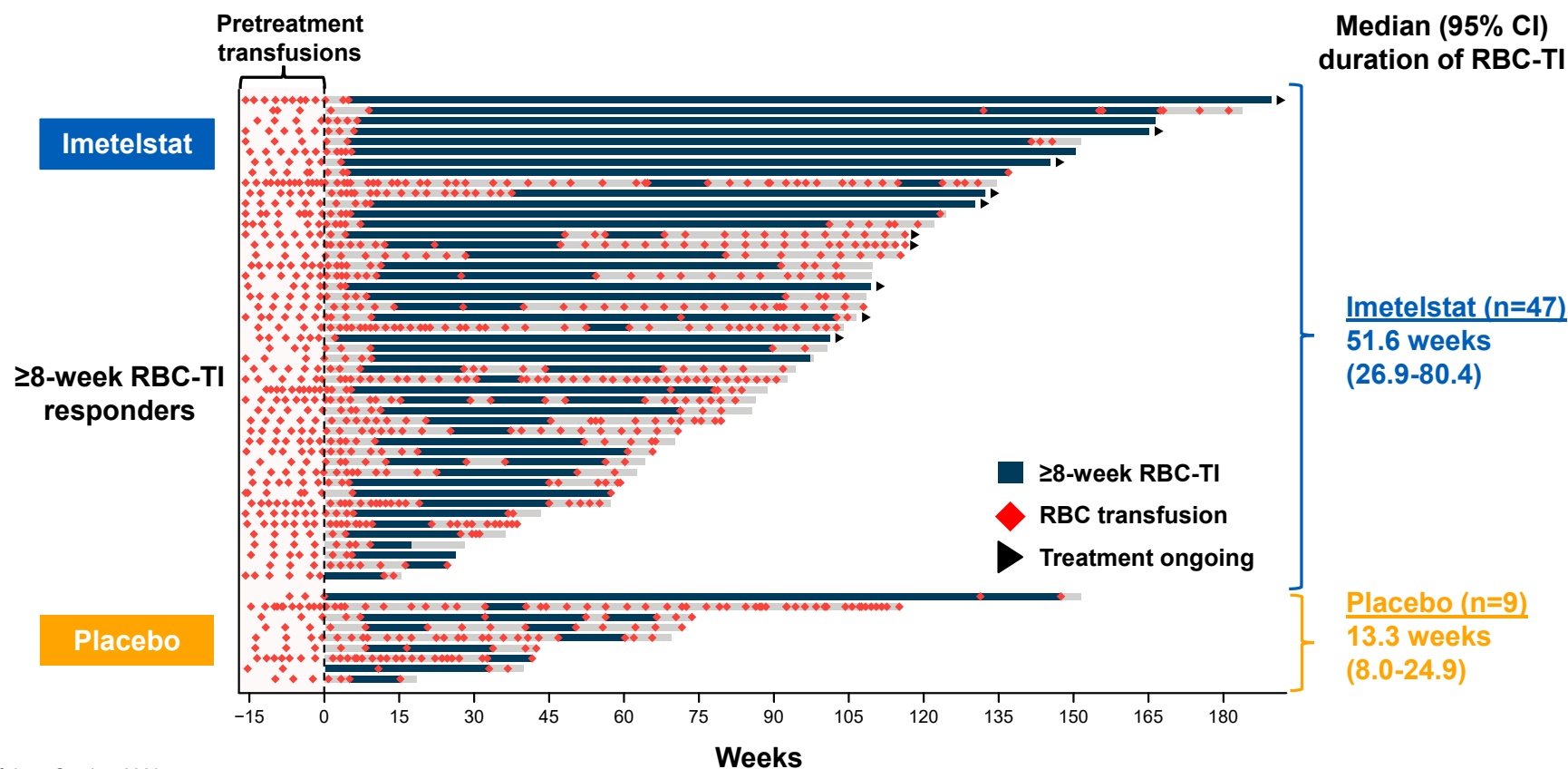
AML, acute myeloid leukemia; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; IV, intravenous; MDS, myelodysplastic syndrome; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RBC, red blood cell; R/R, relapsed or refractory; TD, transfusion dependent; TI, transfusion independence; VAF, variant allele frequency.

Baseline Characteristics Were Similar Across Arms

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)

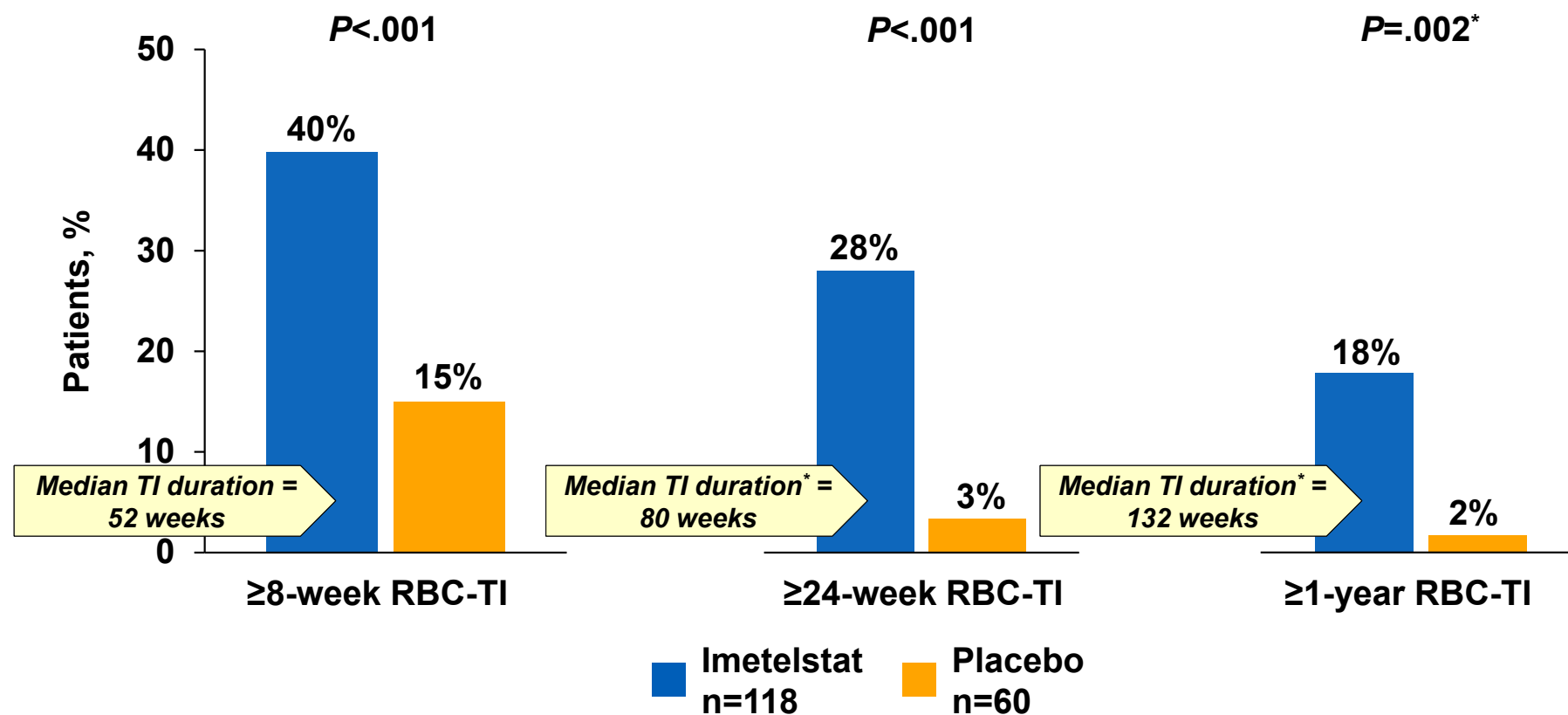
Data cutoff date: October 2022. ^aAverage of all Hb values in the 8 weeks before the first dose date, excluding values within 14 days after a transfusion, which was considered to be influenced by transfusion. ^bData missing for 5 patients in the imetelstat group and 2 in the placebo group. ^cInsufficient 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.

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



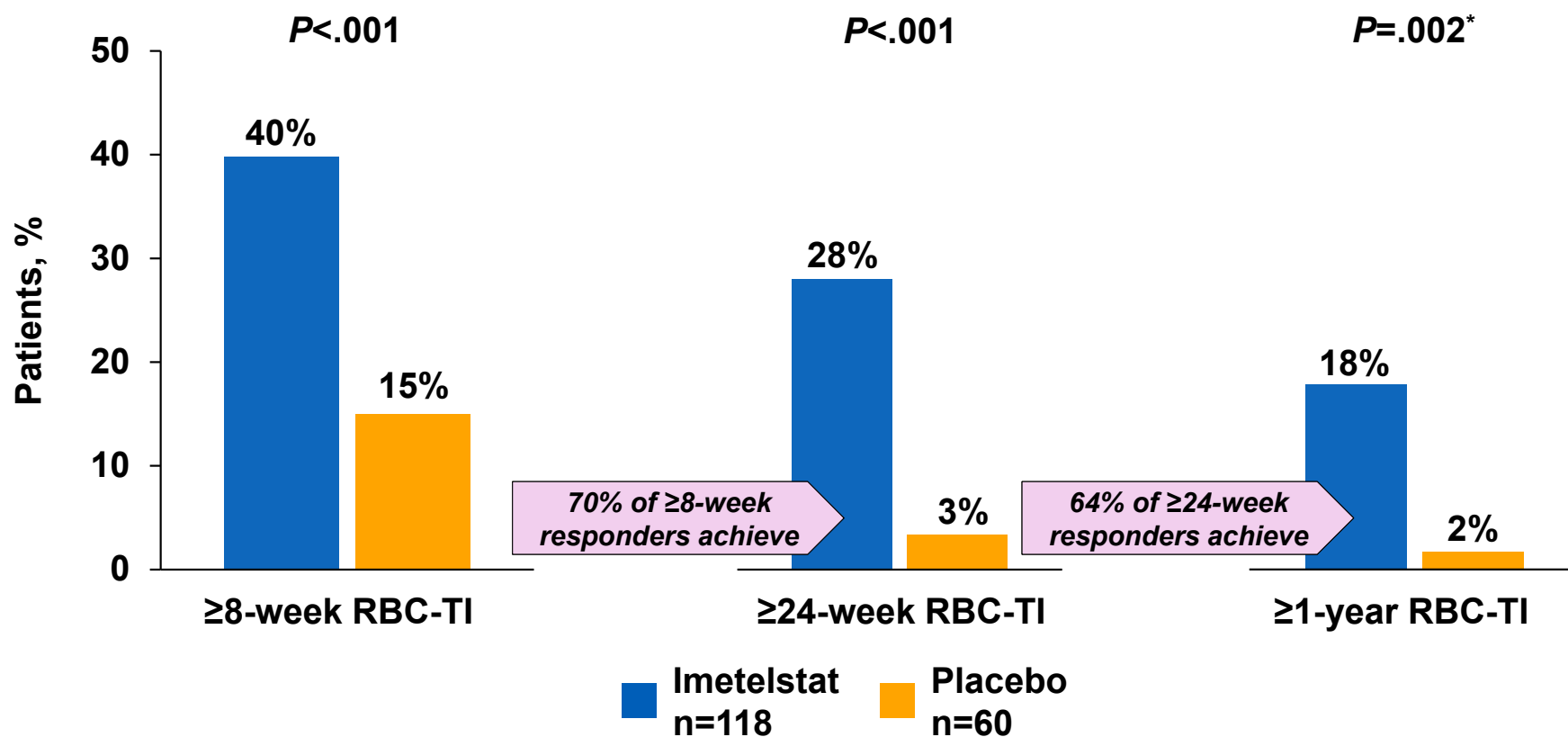
Data cutoff date: October 2023.
RBC, red blood cell; TI, transfusion independence.

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



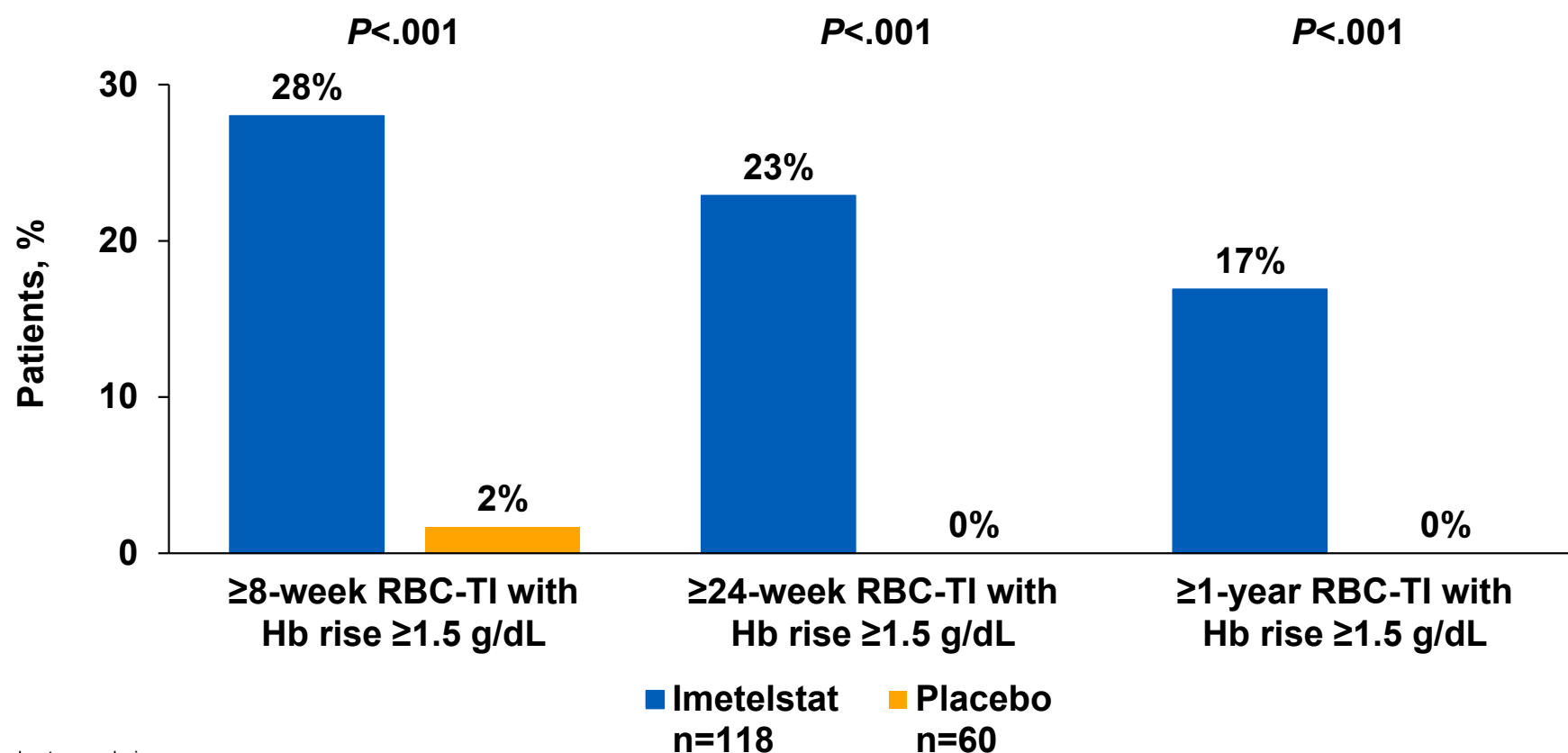
*Reported as descriptive *P* value.
Data cutoff date: October 2023.
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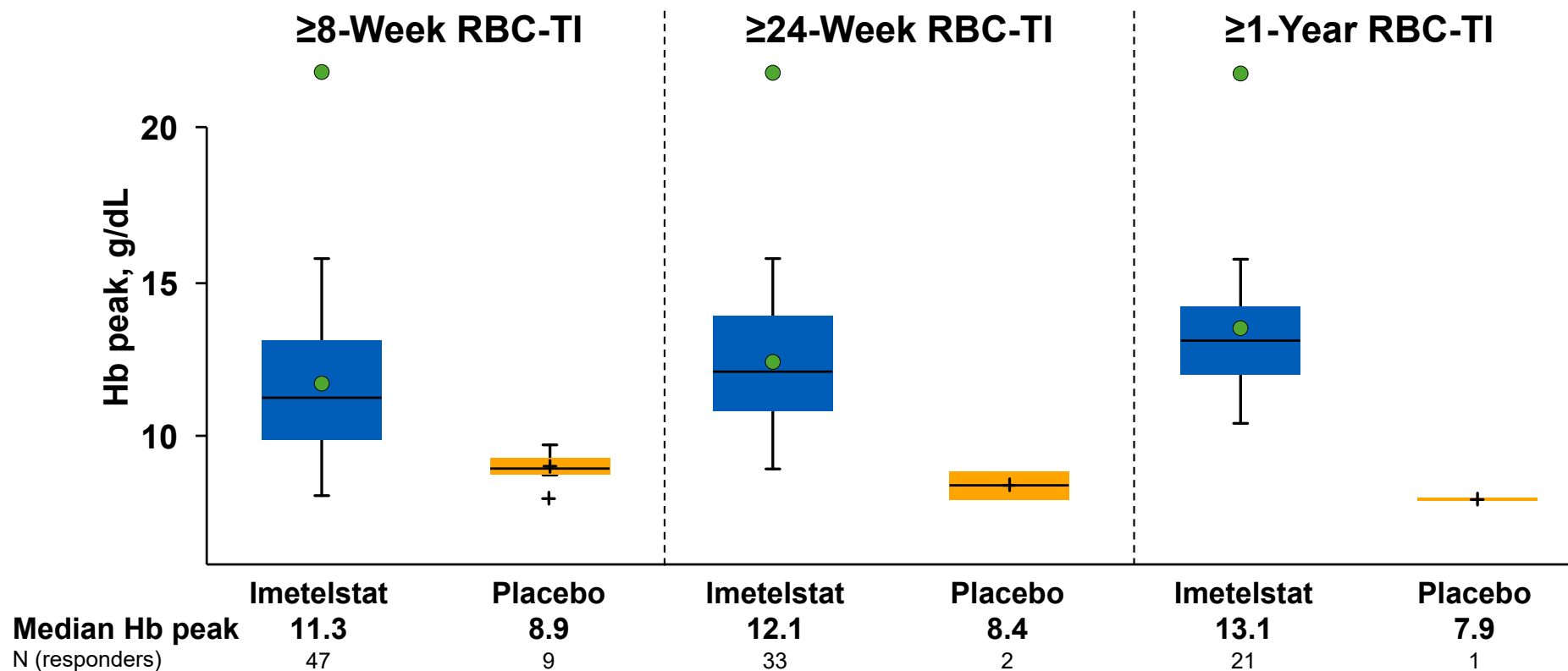
*Reported as descriptive *P* value.
Data cutoff date: October 2023.
RBC, red blood cell; TI, transfusion independence.

In the Total Imetelstat-Treated Population, Significantly More Patients Achieved RBC-TI With Concurrent Hb Increase ≥ 1.5 g/dL*



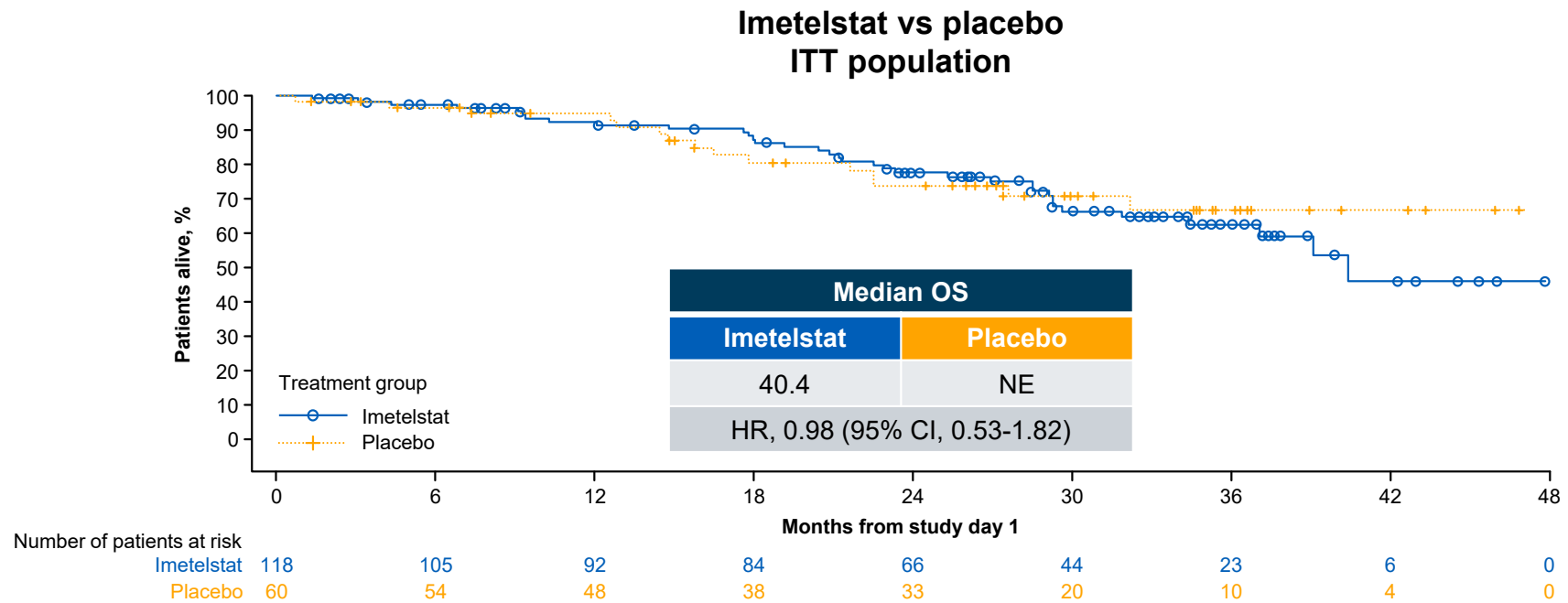
*Exploratory analysis.
Data cutoff date: October 2023.
Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Imetelstat Responders Had Higher Central Hb Peaks Versus Placebo Responders



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.

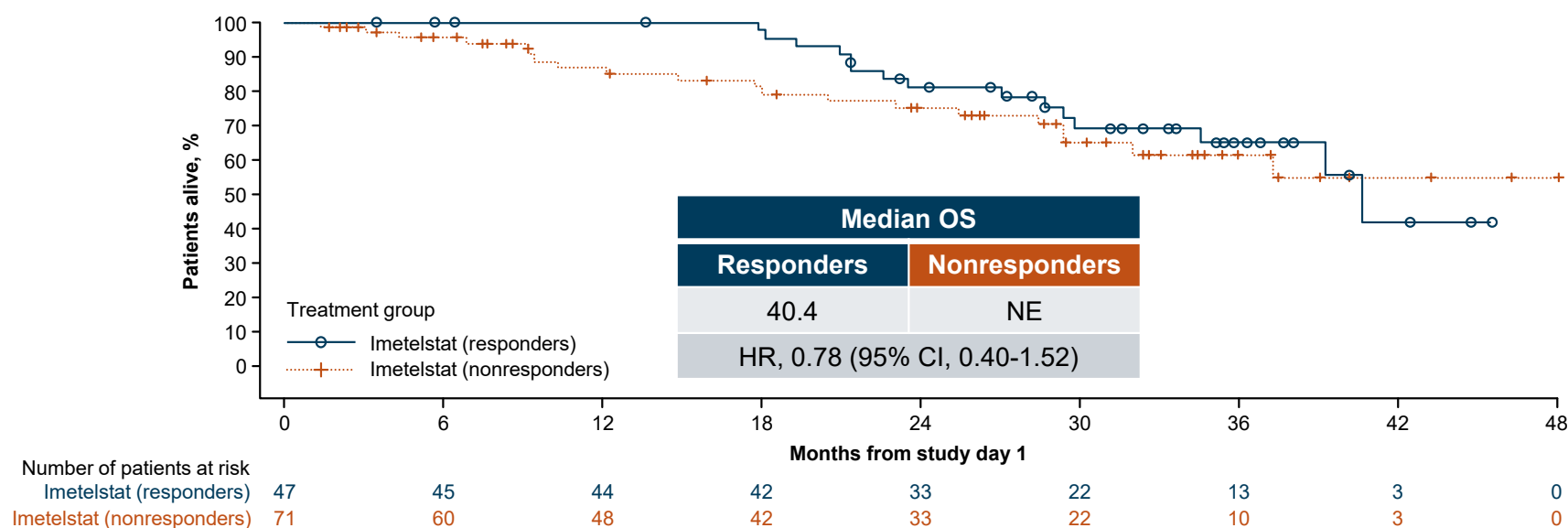
No Detriment With Imetelstat Treatment on OS*



- 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.

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 [<i>P</i> 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 [<i>P</i> 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.

^aCox 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.

Conclusions

- Results from these updated analyses confirm that achievement of RBC-TI with imetelstat was durable and associated with improvement in Hb level
 - Long-term RBC-TI responders achieved Hb levels that approached normal
- In this LR-MDS population with high transfusion burden, rates of ≥ 8 -week, ≥ 24 -week, and ≥ 1 -year RBC-TI concurrent with a rise in Hb of ≥ 1.5 g/dL were significantly* higher with imetelstat versus placebo
- OS analysis, with follow-up of 32 months, suggested no detriment for imetelstat-treated patients*
- These data further support the efficacy and clinical benefit of imetelstat in RBC-TD patients with LR-MDS relapsed or refractory to or who were ineligible for ESAs

* ≥ 1 -year RBC-TI, Hb rise ≥ 1.5 g/dL, and OS are reported with descriptive statistics.

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