MDS-157

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

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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 survival (PFS) 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 United States Food and Drug Administration approved, first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity that selectively targets malignant clones and allows for recovery of erythropoiesis[3-5]
- 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 or –refractory (R/R) or ineligible, and non-del(5q) LR-MDS who were naive to treatment with lenalidomide or hypomethylating agents[6]
 - Phase 3 primary analysis demonstrated significantly higher rates of ≥8-week, ≥24-week, and ≥1-year RBC-TI with imetelstat (n=118; 39.8%, 28.0%, and 17.8%, respectively) versus placebo (n=60; 15.0%, 3.3%, and 1.7%, respectively) in the intention-to-treat population
 - Most common adverse events were neutropenia and thrombocytopenia, which were generally resolvable to grade 2 and below and manageable with dose modifications
- This analysis assessed OS and clinical benefit of durable RBC-TI as the secondary end points in IMerge

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; secondary end points included ≥24-week RBC-TI, duration of RBC-TI, hematologic improvement-erythroid (HI-E), OS, and safety
- Primary analysis cutoff was October 2022, with October 2023 cutoff for ≥1-year RBC-TI analyses, and January 2024 for OS

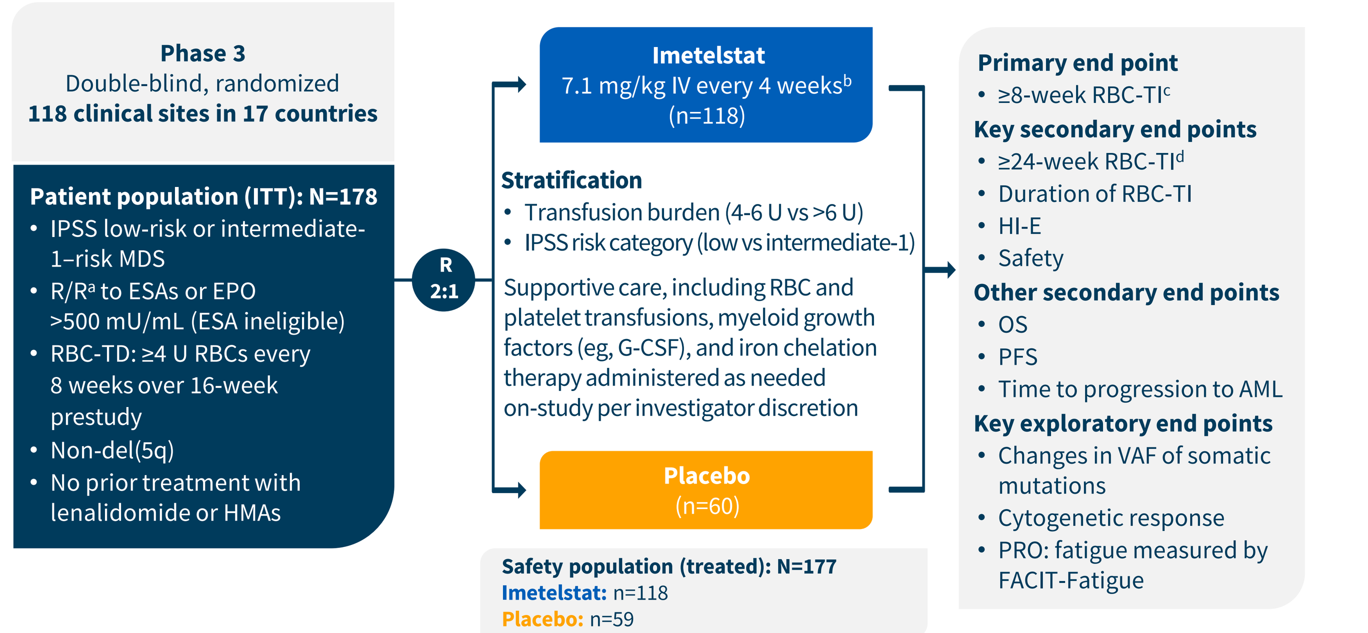
Patients

- Enrollment included patients with RBC-TD (defined as requiring ≥4 RBC U/8 weeks), ESA-R/R or ineligible non-del(5q) LR-MDS naïve to lenalidomide and hypomethylating agents with low-risk or intermediate-1–risk disease per International Prognostic Scoring System (IPSS)

Statistics

- RBC-TI duration and OS were calculated by the Kaplan-Meier method and compared via the stratified log-rank test

Figure 1. IMerge phase 3 study design


Phase 3
Double-blind, randomized
118 clinical sites in 17 countries
Patient population (ITT): N=178
IPSS low-risk or intermediate-1–risk MDS
R/Rᵃ to ESAs or EPO >500 mU/mL (ESA ineligible)
RBC-TD: ≥4 U RBCs every 8 weeks over 16-week prestudy
Non-del(5q)
No prior treatment with lenalidomide or HMAs
R 2:1
Imetelstat
7.1 mg/kg IV every 4 weeksᵇ
(n=118)
Stratification
Transfusion burden (4-6 U vs >6 U)
IPSS risk category (low vs intermediate-1)
Supportive care, including RBC and platelet transfusions, myeloid growth factors (eg, 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 end point
≥8-week RBC-TIᶜ
Key secondary end points
≥24-week RBC-TIᵈ
Duration of RBC-TI
HI-E
Safety
Other secondary end points
OS
PFS
Time to progression to AML
Key exploratory end points
Changes in VAF of somatic mutations
Cytogenetic response
PRO: fatigue measured by FACIT-Fatigue

[a]Received ≥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. [b]Equivalent to 7.5 mg/kg imetelstat sodium. [c]Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (≥8-week RBC-TI). [d]Proportion 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 syndromes; 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.

Results

- Baseline demographic and disease characteristics were similar across treatment arms (**Table 1**)

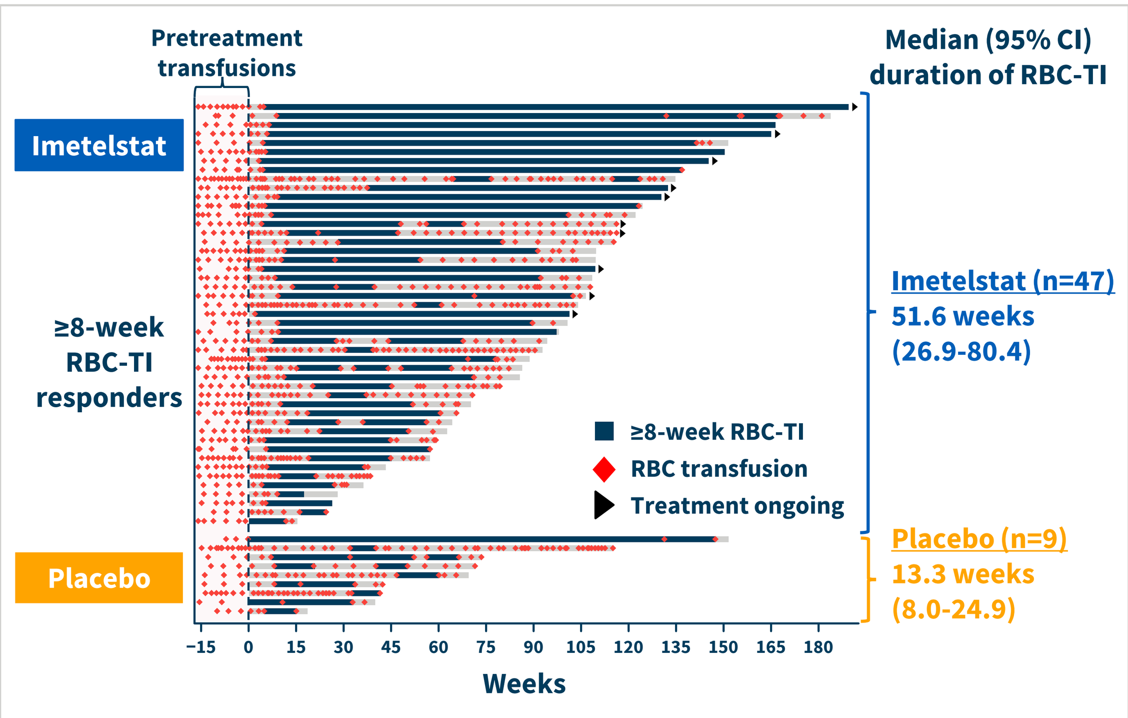
Table 1. Baseline Characteristics

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.

- Of imetelstat responders (n=47), 83% had a single, continuous RBC-TI period (**Figure 2**)
- Median duration of RBC-TI in imetelstat responders was longer (51.6 weeks) than with placebo (n=9; 13.3 weeks)

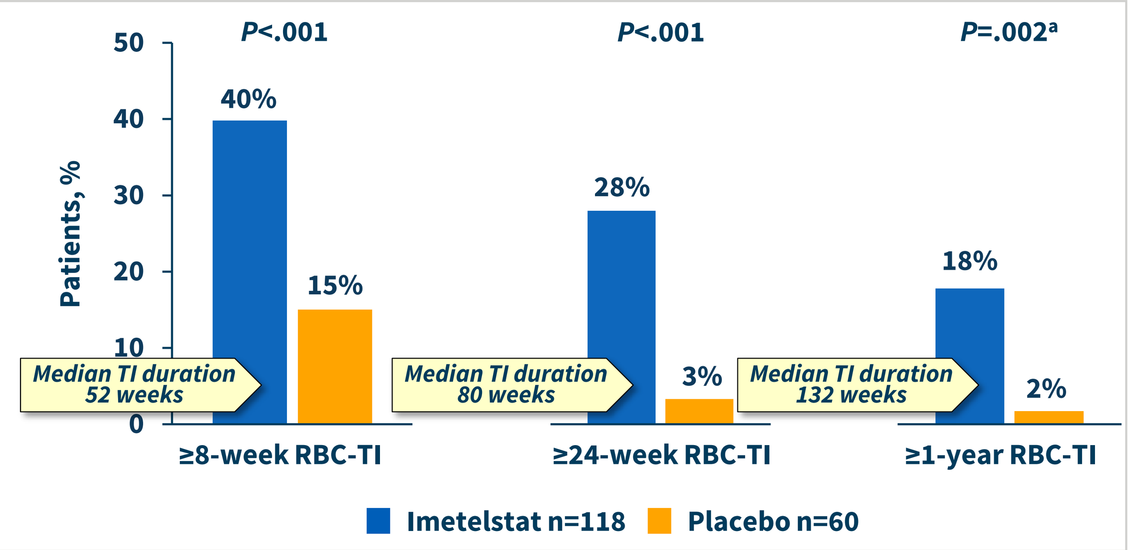
Figure 2. Continuous RBC-TI Periods in ≥8-Week RBC-TI Responders


Pretreatment transfusions
Median (95% CI) duration of RBC-TI
Imetelstat
≥8-week RBC-TI responders
Placebo
≥8-week RBC-TI
RBC transfusion
Treatment ongoing
Imetelstat (n=47)
51.6 weeks
(26.9-80.4)
Placebo (n=9)
13.3 weeks
(8.0-24.9)
−15 0 15 30 45 60 75 90 105 120 135 150 165 180
Weeks

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

- Among imetelstat responders, RBC-TI was durable and sustained over time (**Figure 3**)
 - Median RBC-TI duration for the imetelstat ≥8-week, ≥24-week, and ≥1-year RBC-TI responders was 52, 80, and 132 weeks, respectively
 - 70% of ≥8-week RBC-TI responders achieved ≥24-week RBC-TI response
 - 64% of ≥24-week RBC-TI responders achieved ≥1-year RBC-TI response

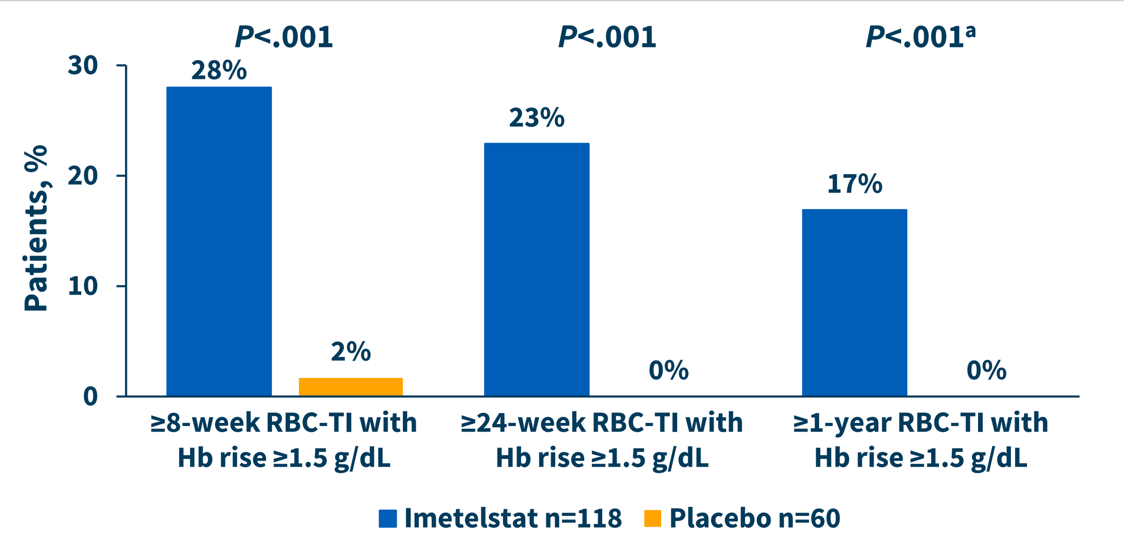
Figure 3. Achievement and Durability of RBC-TI


Patients, %
50 40 30 20 10 0
P<.001
P<.001
P=.002ᵃ
40%
15%
28%
3%
18%
2%
Median TI duration 52 weeks
Median TI duration 80 weeks
Median TI duration 132 weeks
≥8-week RBC-TI
≥24-week RBC-TI
≥1-year RBC-TI
Imetelstat n=118
Placebo n=60

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

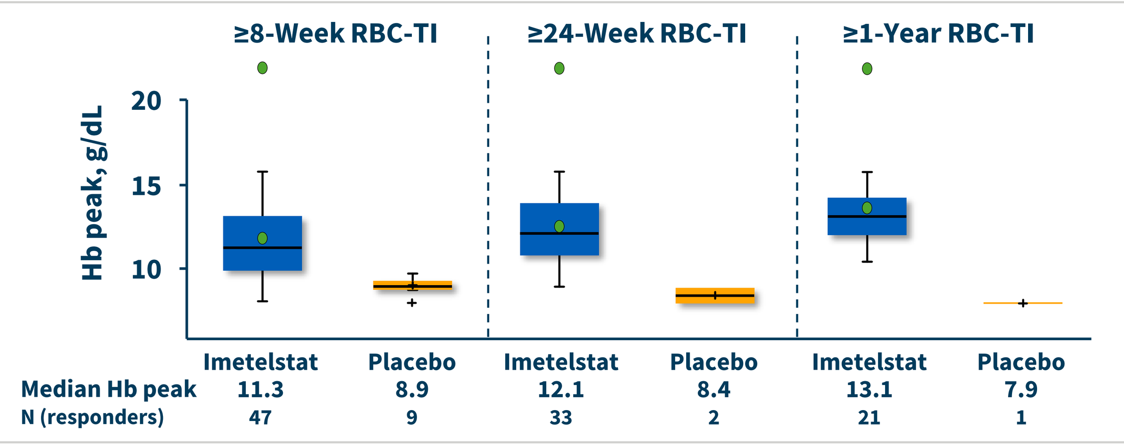
- In an exploratory analysis of the total imetelstat-treated population, significantly more patients achieved RBC-TI with concurrent Hb increase ≥1.5 g/dL (**Figure 4**)
- Imetelstat responders had higher central Hb peaks versus placebo responders (**Figure 5**)
- There was no apparent detriment with imetelstat treatment on OS (**Figure 6**)
 - 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
 - Two-year OS rates were 78% in the imetelstat group (81% in ≥8-week RBC-TI responders and 75% in nonresponders) versus 74% in the placebo group

Figure 4. Achievement of RBC-TI With Concurrent Hb Increase ≥1.5 g/dL


Patients, %
30 20 10 0
P<.001
P<.001
P<.001ᵃ
28%
2%
23%
0%
17%
0%
≥8-week RBC-TI with Hb rise ≥1.5 g/dL
≥24-week RBC-TI with Hb rise ≥1.5 g/dL
≥1-year RBC-TI with Hb rise ≥1.5 g/dL
Imetelstat n=118
Placebo n=60

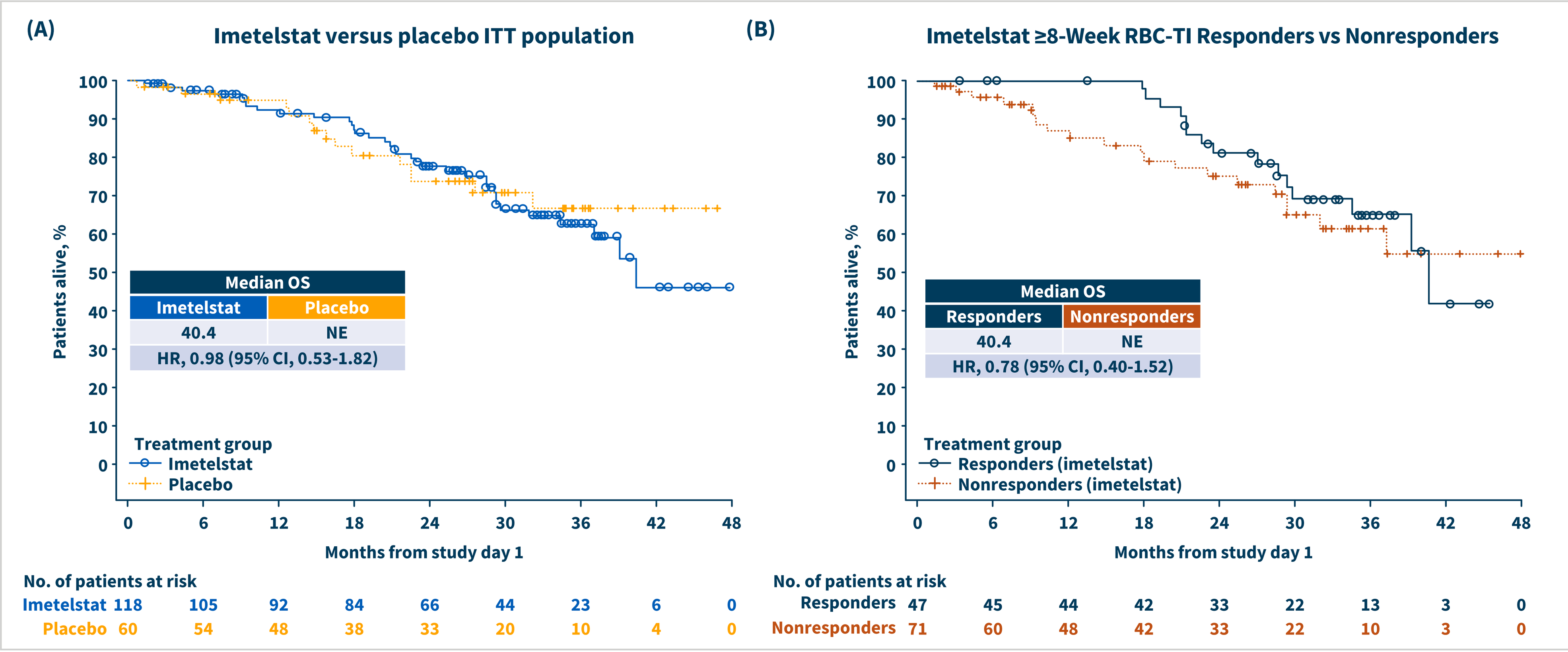
Exploratory analysis.
[a]Reported as descriptive *P* value.
Data cutoff date: October 2023.
Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Figure 5. Median Hb Peak in RBC-TI Responders


≥8-Week RBC-TI
≥24-Week RBC-TI
≥1-Year RBC-TI
Hb peak, g/dL
20 15 10
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.

Figure 6. OS in IMerge for (A) Imetelstat Versus Placebo and (B) Imetelstat Responders Versus Nonresponders


(A)
Imetelstat versus placebo ITT population
Patients alive, %
Median OS
Imetelstat Placebo
40.4 NE
HR, 0.98 (95% CI, 0.53-1.82)
Treatment group
Imetelstat
Placebo
0 6 12 18 24 30 36 42 48
Months from study day 1
No. of patients at risk
Imetelstat 118 105 92 84 66 44 23 6 0
Placebo 60 54 48 38 33 20 10 4 0
(B)
Imetelstat ≥8-Week RBC-TI Responders vs Nonresponders
Patients alive, %
Median OS
Responders Nonresponders
40.4 NE
HR, 0.78 (95% CI, 0.40-1.52)
Treatment group
Responders (imetelstat)
Nonresponders (imetelstat)
0 6 12 18 24 30 36 42 48
Months from study day 1
No. of patients at risk
Responders 47 45 44 42 33 22 13 3 0
Nonresponders 71 60 48 42 33 22 10 3 0

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

- Median estimated PFS has not been reached in either treatment arm (**Table 2**)
- The rate of progression to acute myeloid leukemia was low in both treatment arms (imetelstat [1.7%] and placebo [3.3%]) (**Table 2**)

Table 2. Disease Progression and Progression to AML

	Imetelstat (n=118)	Placebo (n=60)
PFS		
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[b]]	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[b]]	0.45 (0.06-3.23) [0.418]	

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.
[b]Reported as descriptive *P* value.
AML, acute myeloid leukemia; HR, hazard ratio; 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 appeared to normalize
- 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[a] higher with imetelstat versus placebo
- OS analysis, with follow-up of 32 months, suggested no detriment for imetelstat-treated patients[a]
- These data further support the efficacy and clinical benefit of imetelstat in RBC-TD patients with LR-MDS R/R to or who were ineligible for ESAs

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

References

1. Platzbecker U, et al. *Leukemia*. 2021;35(8):2182-2198.
2. Harnan S, et al. *Acta Haematol*. 2016;136(1):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). Package insert. Geron Corporation; 2024.
6. Platzbecker U, Santini V, et al. *Lancet*. 2024;403(10423):249-260.

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