Long-Term Outcomes and Overall Survival from the Randomized, Double-Blind, Placebo-Controlled, Phase 3 IMerge Trial of Imetelstat for Lower-Risk Myelodysplastic Syndromes

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Introduction

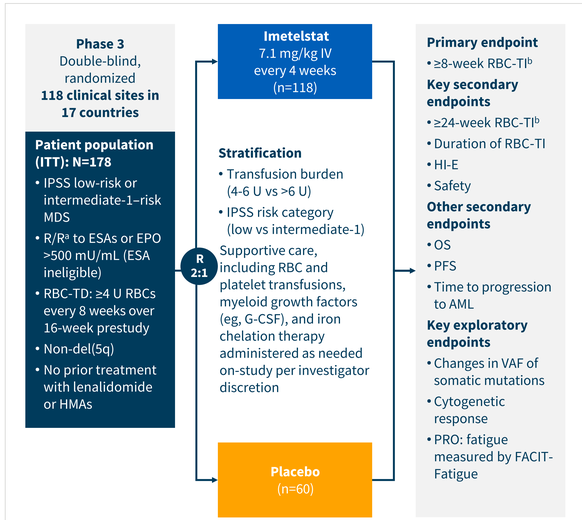
- Patients with lower-risk myelodysplastic syndromes (LR-MDS) who are red blood cell (RBC) transfusion dependent (TD) have shorter overall survival (OS) and progression-free survival (PFS) compared with those who are RBC-transfusion independent (TI), making the achievement of RBC-TI a key goal of therapy[1-4]
- Imetelstat, a first-in-class telomerase inhibitor, was approved in the United States (US) and Europe for the treatment of adult patients with LR-MDS and RBC-TD anemia (defined in the US label as requiring ≥4 RBC units over 8 weeks)[5] who relapsed or are refractory to, or are ineligible for erythropoiesis-stimulating agents based on the results of the Phase 3 IMerge trial (NCT02598661)[6,7]
- In the primary analysis of IMerge (Platzbecker and Santini, 2024; median follow-up, 18.5 months) imetelstat demonstrated statistically significantly higher rates of RBC-TI versus placebo for ≥8-week RBC-TI (primary endpoint; 40% imetelstat vs 15% placebo; *P*<.001), ≥24-week RBC-TI (key secondary endpoint; 28% imetelstat vs 3% placebo; *P*<.001), and ≥1-year RBC-TI (post hoc endpoint; 18% vs 2%; nominal *P*=.0023)[7]
  - At the time of the primary analysis,[7] data were immature to assess OS

Here, we report on secondary endpoints, including OS, PFS, progression to acute myeloid leukemia (AML), safety, and long-term outcomes by subgroups of interest in IMerge, as well as the ad hoc outcome of OS by response

Methods

- The study design for IMerge is presented in **Figure 1**. Patients with RBC-TD LR-MDS were randomized to 7.1 mg/kg imetelstat active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo administered as 2-hour intravenous infusions every 4 weeks
- OS was defined as the interval from randomization date to death from any cause
  - A post hoc landmark OS analysis was performed for patients who survived ≥42 months
- The distributions of OS, PFS, and time to progression to AML were estimated by Kaplan-Meier and compared using stratified log-rank test for the intention-to-treat (ITT) analysis set
- Treatment effect (hazard ratio [HR]) and its 2-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable
- The study was not powered to detect statistical significance in OS, PFS, or time to progression to AML

Figure 1. IMerge Phase 3 Study Design



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; R, randomized; RBC, red blood cell; R/R, relapsed or refractory; TD, transfusion dependent; TI, transfusion independence; VAF, variant allele frequency.
[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 RBC-TD or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment. [b]Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (≥8-week RBC-TI). [c]Proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (≥24-week RBC-TI).

Results

- Of the 178 patients enrolled in IMerge, 118 received imetelstat and 60 received placebo (**Table 1**)
  - Baseline characteristics were similar between treatment groups
  - Median long-term follow-up at data cutoff (May 10, 2025): 45 months

Table 1. Baseline Patient and Disease Characteristics (N=178)

Characteristic	Imetelstat (n=118)	Placebo (n=60)
Age, median (range), y	71.5 (44-87)	73.0 (39-85)
Male, n (%)	71 (60.2)	40 (66.7)
WHO classification, n (%)		
RS+	73 (61.9)	37 (61.7)
RS−	44 (37.3)	23 (38.3)
IPSS risk category, n (%)		
Low	80 (67.8)	39 (65.0)
Intermediate-1	38 (32.2)	21 (35.0)
Pretreatment Hb, median (range),[a] g/dL	7.9 (5.3-10.1)	7.8 (6.1-9.2)
Transfusion burden per IWG 2018, n (%)		
HTB	97 (82.2)	42 (70.0)
LTB	21 (17.8)	18 (30.0)
Prior RBC transfusion burden, n (%)		
≤6 U/8 weeks	62 (52.5)	33 (55.0)
>6 U/8 weeks	56 (47.5)	27 (45.0)
Serum EPO level, n (%)[b]		
≤500 mU/mL	87 (73.7)	36 (60.0)
>500 mU/mL	26 (22.0)	22 (36.7)
Mutation status	(n=107)	(n=54)
>1 mutation, n (%)	76 (71.0)	38 (70.4)
SF3B1 mutation	82 (76.6)	43 (79.6)
TET2 mutation	40 (37.4)	14 (25.9)
ASXL1 mutation	18 (16.8)	6 (11.1)
DNMT3A mutation	19 (17.8)	9 (16.7)

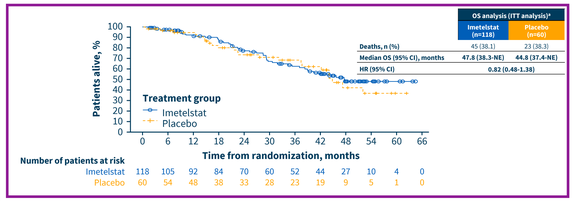
EPO, erythropoietin; Hb, hemoglobin; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblast; WHO, World Health Organization.
[a]Average of all Hb values in the 8 weeks before 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.

Imetelstat Versus Placebo

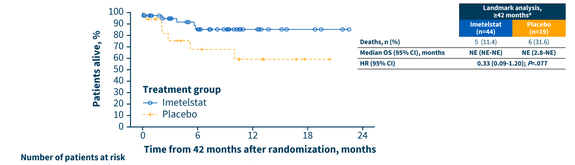
- Patients treated with imetelstat had an 18% lower risk of death than placebo recipients (**Figure 2**)
  - In the ITT population, the median (95% CI) OS was 47.8 months (38.3-not estimable [NE]) for the imetelstat group and 44.8 months (37.4-NE) for placebo (HR, 0.82 [95% CI, 0.48-1.38], favoring imetelstat)
  - For the landmark OS analysis for patients who were alive at ≥42 months (n=63), the HR was 0.33 (95% CI, 0.09-1.20; *P*=.077), favoring imetelstat
- Median (95% CI) PFS in the ITT population was 47.6 months (29.2-NE) for imetelstat and 42.2 months (16.7-NE) for placebo (HR, 0.82 [95% CI, 0.43-1.54], favoring imetelstat) (**Table 2**)
- Progression to AML remained low in both treatment arms at 1.7% (2/118) for imetelstat versus 3.3% (2/60) for placebo (HR, 0.45 [95% CI, 0.06-3.23]) (**Table 2**)

Figure 2. Long-Term Follow-Up OS[a] Analysis (ITT Population; N=178) and Landmark Analysis (≥42 months, n=63)

ITT Analysis (N=178)



Landmark Analysis (≥42 months, n=63)



HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival.
[a]Data cutoff (May 10, 2025); median follow-up of 45 months.

Table 2. Progression-Free Survival and Time to Progression to AML in the ITT Population (N=178)[a]

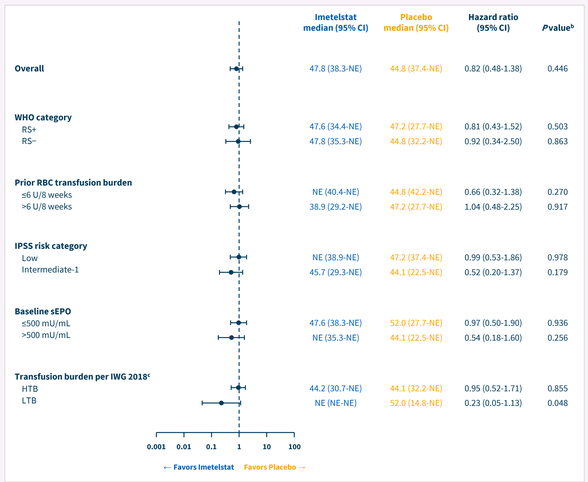
	Imetelstat (n=118)	Placebo (n=60)
PFS		
Number of events (%)	31 (26.3)	15 (25.0)
Median PFS (95% CI), months	47.6 (29.2-NE)	42.2 (16.7-NE)
HR (95% CI)	0.82 (0.43-1.5)	
Progression to AML		
Number of events (%)	2 (1.7)	2 (3.3)
Median progression to AML (95% CI), months	NE (NE-NE)	NE (NE-NE)
HR (95% CI)	0.45 (0.06-3.23)	

AML, acute myeloid leukemia; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable.
[a]Data cutoff (May 10, 2025); median follow-up of 45 months.

Subgroup OS Analyses

- Subgroup analyses of median OS favored imetelstat over placebo for most patient subgroups (**Figure 3**)
- Patients treated with imetelstat who had *SF3B1* mutations had superior median OS versus those without this mutation (HR, 0.32 [95% CI, 0.16-0.64]; nominal *P*<.001; data not shown)

Figure 3. Median OS[a] by Baseline Subgroups in the ITT Population (N=178)



HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; ITT, intention-to-treat; LTB, low transfusion burden; NE, not estimable; OS, overall survival; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; WHO, World Health Organization.
[a]Data cutoff (May 10, 2025), median follow-up 45 months. [b]P value (2-sided) for superiority of imetelstat versus placebo in hazard ratio, using log-rank test. [c]Per revised IWG 2018, LTB is defined as a patient who requires ≥ 7 RBC units in the 16 weeks before study entry in ≥2 transfusion episodes; HTB is defined as a patient who requires ≥8 RBC units in the 16 weeks before study entry in ≥2 transfusion episodes.

OS Analysis in Imetelstat Responders Versus Nonresponders

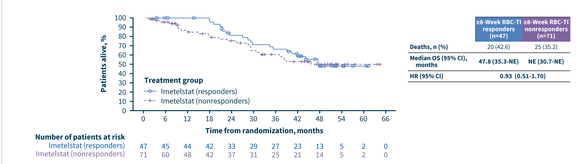
- Although not statistically significant, median OS was generally greater for patients who responded to imetelstat compared with nonresponders among different measures of clinical response
  - ≥8-week RBC-TI: HR, 0.93 (95% CI, 0.51-1.70; **Figure 4A**)
  - ≥24-week RBC-TI: HR, 0.72 (95% CI, 0.37-1.38; **Figure 4B**)
  - ≥1-year RBC-TI: HR, 0.73 (95% CI, 0.35-1.53; **Figure 4C**)
  - ≥1.5 g/dL central hemoglobin rise from pretreatment lasting ≥8 weeks (IWG 2006 hematologic improvement-erythroid criteria: HR, 0.74 (95% CI, 0.40-1.37; **Figure 4D**)

Safety

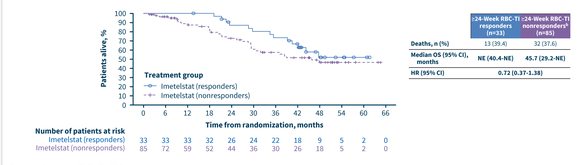
- No new safety signals emerged from the primary analysis[7]
- Of the 45 patients treated with imetelstat who died, 11 (24.4%) died between 6 months and 1 year after the last dose of imetelstat and 20 (44.4%) died >1 year after the last dose of imetelstat
- In the placebo group, 23 patients died: 5 (21.7%) between 6 months and 1 year after their last dose and 14 (60.9%) >1 year after their last dose
  - Two patients died in the imetelstat group and 1 patient in the placebo group died from adverse events within 30 days of their last dose

Figure 4. OS in Imetelstat Responders Versus Nonresponders (n=118)[a]

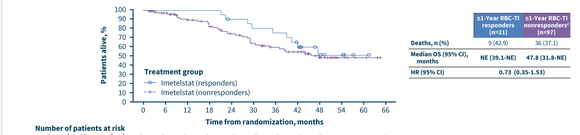
A ≥8-Week RBC-TI



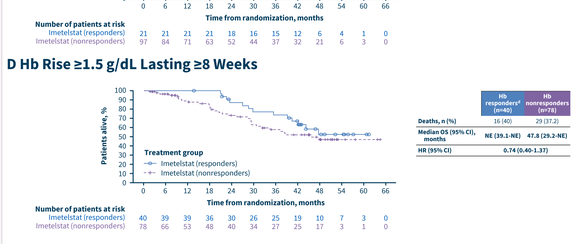
B ≥24-Week RBC-TI



C ≥1-Year RBC-TI



D Hb Rise ≥1.5 g/dL Lasting ≥8 Weeks



Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HR, hazard ratio; IWG, International Working Group; NE, not estimable; OS, overall survival; RBC, red blood cell; TI, transfusion independence.
[a]Data cutoff (May 10, 2025), median follow-up 45 months. [b]Includes patients who achieved ≥8-week but <24 months RBC-TI responders and ≥8-week RBC-TI nonresponders. [c]Includes patients who achieved ≥8-week but <1-year RBC-TI responders and ≥8-week RBC-TI nonresponders. [a]Hb responders = Hb rise ≥1.5 g/dL lasting ≥8 weeks per IWG 2006 HI-E criteria.

Conclusions

- Imetelstat resulted in a favorable trend in OS, PFS, and time to progression to AML versus placebo in the overall population
- OS favored imetelstat versus placebo in most subgroups (HR <1.0)
- Numerical improvement in OS was observed in imetelstat-treated patients who had RBC-TI or hemoglobin rise
  - Hemoglobin rise may be the primary driver of OS with imetelstat
- No new safety signals than those observed in the primary analysis[7]
- Although not statistically powered to detect significance, these long-term follow-up data support the sustained clinical benefit of imetelstat in patients with RBC-TD LR-MDS

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