# Erythropoiesis-Stimulating Agents

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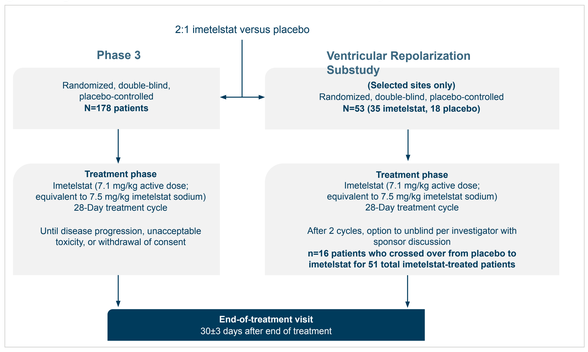
## Introduction

- Imetelstat is a first-in-class, direct and competitive inhibitor of telomerase enzymatic activity
  - Approved by the United States Food and Drug Administration (FDA) in June 2024 for adult patients with lower-risk myelodysplastic syndromes (LR-MDS) and red blood cell (RBC) transfusion-dependent (TD) anemia who have relapsed or are refractory to, or ineligible for erythropoiesis-stimulating agents (ESA) based on the results of the pivotal phase 3 IMerge trial (NCT02598661)[1,2]
- In the IMerge phase 3 trial, imetelstat demonstrated a clinically meaningful and statistically significant RBC transfusion independence (TI) rate versus placebo for the primary end point[1]
  - ≥8-Week RBC-TI: 40% imetelstat versus 15% placebo (*P*<.001)
  - Imetelstat had a generally manageable safety profile
- A ventricular repolarization substudy of IMerge was conducted per FDA guidance[3-5]
- Here, we report the first efficacy and safety results from this substudy

## Methods

- As part of the phase 3 IMerge trial of imetelstat in TD patients with International Prognostic Scoring System low- or intermediate-1–risk MDS who were relapsed or refractory/ineligible to ESA treatment, a separate ventricular repolarization substudy was included as a double-blind, randomized, placebo-controlled assessment (**Figure 1**)
- Adult patients were randomized to imetelstat 7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo, both administered as 2-hour intravenous infusions every 4 weeks
- The primary objective of the substudy was to evaluate the relationship between imetelstat plasma concentration and QTc interval changes (using change from baseline Fridericia QT correction [△QTcF]) with a linear mixed-effect modeling approach
  - Triplicate electrocardiograms and time-matched postdose pharmacokinetic samples were collected on cycle 1, day 1 (−1, −0.5, and 0 hours predose, and at 0.5, 1, 2, 4, 6, and 8 hours after the start of infusions)
- Efficacy end points included ≥8-week and ≥24-week RBC-TI rates, RBC transfusion dependence, hematologic improvement-erythroid, Hb rise ≥1.5 g/dL lasting ≥8 weeks, and progression to acute myeloid leukemia (AML)
  - Proportion of patients with RBC-TI, and other binary end points, were summarized with percentage and 2-sided exact Clopper-Pearson 95% CI. Kaplan-Meier methodology estimated the distribution of duration of TI
- This substudy differed from the IMerge phase 3 trial in its crossover design, the inclusion of patients with del(5q) MDS, and by allowing prior lenalidomide and hypomethylating agent (HMA) therapy besides ESAs
  - Patients could cross over from placebo to imetelstat after 2 cycles at the investigator's discretion

**Figure 1. Schematic Overview of the Substudy**




## Results

- QTc substudy population comprised 53 treated patients (n=35 imetelstat, n=18 placebo)
  - Baseline characteristics were comparable between imetelstat and placebo arms
- As of the data cutoff (May 10, 2024), 16/18 placebo recipients crossed over to receive imetelstat
  - 57% of imetelstat, including crossover (n=51) were receiving >6 U RBC/8 weeks and median Hb was 7.5 g/dL at baseline (**Table 1**)
  - Median treatment duration on imetelstat, including crossover (n=51) was 29.3 weeks
  - Median duration in the imetelstat group (n=35) was 37.0 weeks

**Table 1. Baseline Characteristics**

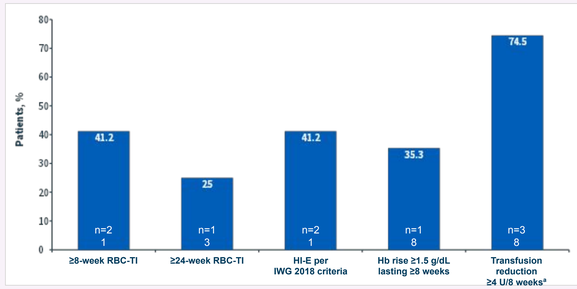
| Characteristic | Imetelstat (n=35) | Crossover (n=16) | Imetelstat total (n=51) |
|---|---|---|---|
| **Age, median (range), y** | 71 (43-84) | 71 (54-81) | 71 (43-84) |
| ≥65 y, n (%) | 29 (83) | 11 (69) | 40 (78) |
| **Male, n (%)** | 27 (77) | 14 (88) | 41 (80) |
| **Median (SD) time since diagnosis, y** | 2.8 (5.3) | 2.9 (5.4) | 2.8 (5.3) |
| **Median (range) Hb, g/dL** | 7.7 (5.1-9.0) | 7.4 (6.3-8.9) | 7.5 (5.1-9.0) |
| **WHO classification, n (%)** | | | |
| RS+ | 25 (71) | 14 (88) | 39 (76) |
| RS− | 10 (29) | 2 (13) | 12 (24) |
| **IPSS risk category, n (%)** | | | |
| Low | 24 (69) | 11 (69) | 35 (69) |
| Intermediate-1 | 11 (31) | 5 (31) | 16 (31) |
| **Transfusion burden per IWG 2018, n (%)** | | | |
| HTB | 28 (80) | 12 (75) | 40 (78) |
| LTB | 7 (20) | 4 (25) | 11 (22) |
| **Prior RBC transfusion burden, n (%)** | | | |
| ≤6 U/8 weeks | 16 (46) | 6 (38) | 22 (43) |
| >6 U/8 weeks | 19 (54) | 10 (62) | 29 (57) |
| **Serum EPO level** | | | |
| Median (range) | 228 (33-4453) | 191 (38-5424) | 213 (33-5424) |
| ≤500 mU/mL, n (%) | 24 (69) | 11 (69) | 35 (69) |
| >500 mU/mL, n (%) | 11 (31) | 5 (31) | 16 (31) |
| **Prior ESA use, n (%)** | 32 (91) | 13 (81) | 45 (88) |
| **Prior HMA, n (%)** | 11 (31) | 3 (19) | 14 (27) |
| **Prior luspatercept use, n (%)** | 15 (43) | 8 (50) | 23 (45) |
| **Prior lenalidomide, n (%)** | 9 (26) | 4 (25) | 13 (25) |

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblast; SD, standard deviation; TI, transfusion independence; WHO, World Health Organization.

## Efficacy

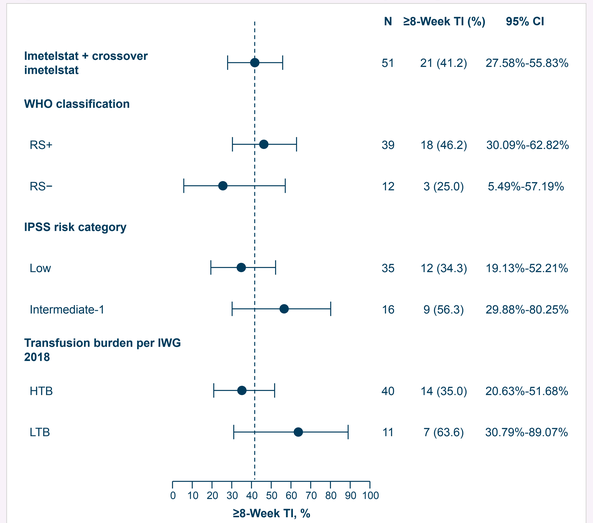
- In the total imetelstat population, including crossover (n=51), 41% achieved ≥8-week RBC-TI (**Figure 2**)
  - By subgroup is shown in **Figure 3**
  - Median duration of RBC-TI among responders (n=21) was 52.6 weeks (95% CI, 40.9-not estimable; **Figure 4**)
- Proportion of patients who achieved ≥8-week and ≥24-week RBC-TI by prior therapy subgroup is shown in **Figure 5**
- Progression to AML was 0 imetelstat versus 1 placebo (before crossover)

**Figure 2. Efficacy in the Total Imetelstat Population (n=51)**



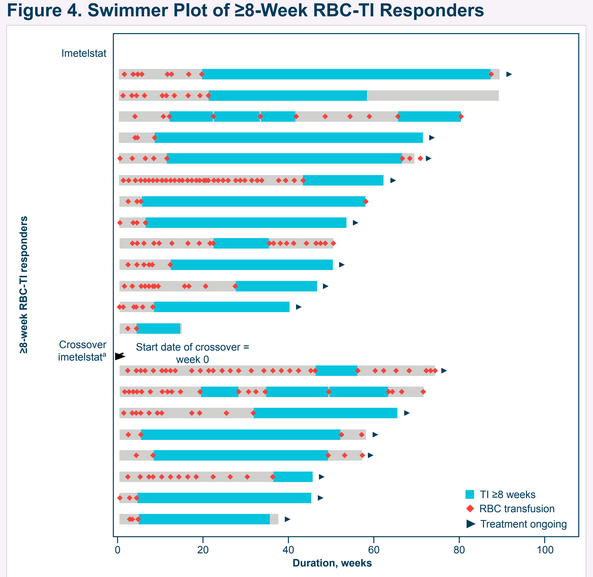

Hb, hemoglobin; HI-E, hematologic improvement-erythroid; RBC-TI, red blood cell transfusion independence.
[a]Per International Working Group 2006 criteria.

**Figure 3. Achievement of ≥8-Week RBC-TI by Subgroup**



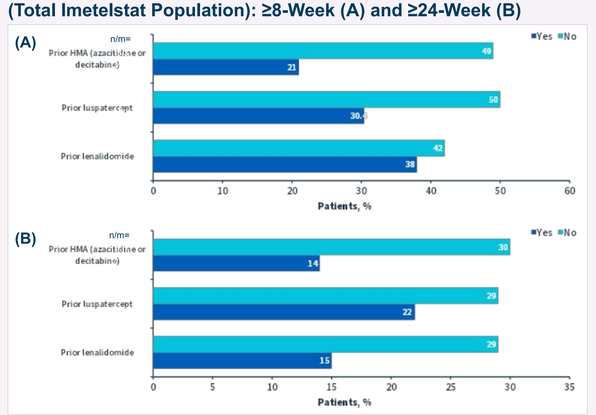

HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence; WHO, World Health Organization.

**Figure 4. Swimmer Plot of ≥8-Week RBC-TI Responders**




RBC, red blood cell; TI, transfusion independence.
[a]Crossover imetelstat arm only includes data after crossover from placebo (patients had the option to cross over from placebo to imetelstat after 2 cycles at the investigator's discretion), and the duration of treatment starts from the start date of crossover imetelstat.

**Figure 5. Achievement of RBC-TI by Prior Therapy[a] Subgroup (Total Imetelstat Population): ≥8-Week (A) and ≥24-Week (B)**




HMA, hypomethylating agent; n/m, number with event/number in population; RBC-TI, red blood cell transfusion independence.
[a]Patients could have received ≥1 prior therapy.

## Safety

- Patients treated with imetelstat showed no treatment-related changes in absolute and △QTcF nor clinically meaningful effects on cardiac repolarization compared with placebo
- No new safety signals emerged in the total imetelstat-treated population
- Grade 3/4 neutropenia and thrombocytopenia by laboratory evaluation occurred in 65% (33/51) and 49% (25/51) of patients, respectively
  - Most cases resolved to grade ≤2 within 4 weeks
  - Incidences were similar to the overall phase 3 imetelstat-treated population[1]

## Conclusions

- In this QTc substudy, imetelstat was associated with an absence of proarrhythmic risk, durable RBC-TI, transfusion reduction, clinically meaningful increases in hemoglobin, and safety profile comparable to the overall population of the pivotal phase 3 IMerge trial[1]
- RBC-TI was attained in imetelstat-treated patients who received prior therapies with HMA, luspatercept, and lenalidomide
- Overall, the results of this IMerge QTc substudy support the use of imetelstat in patients with relapsed or refractory LR-MDS, regardless of prior therapies

## References

1. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.
2. RYTELO (imetelstat) for injection, for intravenous use. Package insert. Geron Corporation; 2024.
3. United States Food and Drug Administration, Health and Human Services. *Fed Regist*. 2005;70(202):61133-4.
4. United States Food and Drug Administration, Health and Human Services. *Fed Regist*. 2005;70(202):61134-5.
5. United States Food and Drug Administration, Health and Human Services. *Fed Regist*. 2022;85(190):61753-5.

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