Durable Continuous Transfusion Independence With Imetelstat in IMerge Phase 3 for Patients With Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to or Ineligible for Erythropoiesis-Stimulating Agents

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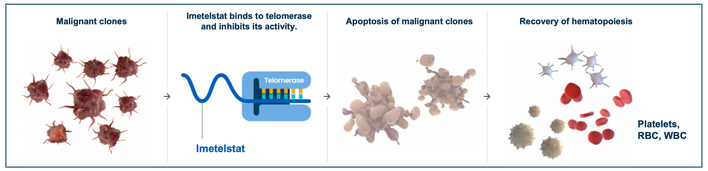
Introduction

- Novel therapies are needed for patients with LR-MDS that is RBC-TD and R/R to or ineligible for ESAs
- Imetelstat is a first-in-class, direct and competitive inhibitor of telomerase activity that specifically targets malignant clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis[1,2] (**Fig. 1**)
- In the IMerge multinational phase 3 clinical trial (NCT02598661) of patients with RBC-TD non-del(5q) LR-MDS R/R to or ineligible for ESAs and naïve to lenalidomide or HMAs, imetelstat showed higher RBC-TI for ≥8 weeks, ≥24 weeks, and ≥1 year (40%, 28%, and 18%) than placebo (15%, 3%, and 2%)[3,4]
- Because RBC-TD is associated with deleterious clinical consequences, identifying the characteristics and clinical benefit of sustained RBC-TI with imetelstat is of interest

Figure 1. Mechanism of Action of Imetelstat



Aim

- To evaluate the characteristics and clinical benefit for patients with sustained RBC-TI for ≥1 year in the IMerge phase 3 trial

Methods

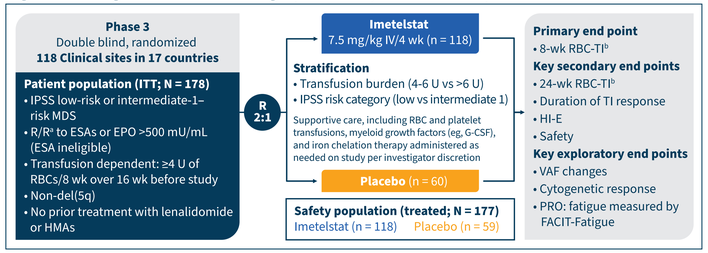
Study design (Fig. 2)

- IMerge phase 3 is a double-blind, randomized (2:1), placebo-controlled, phase 3 trial conducted at 118 sites
- Patients with heavily RBC-TD, non-del(5q) LR-MDS that was R/R to or ineligible for ESAs and naive to lenalidomide/HMA were randomized to receive imetelstat 7.5 mg/kg IV (n = 118) or placebo (n = 60) every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or lack of response
- The primary end point was 8-week TI rate; secondary end points included safety, 24-week TI, duration of response, and HI-E
- Exploratory analyses included assessment of cytogenetic response and mutational status with clinical response

Analysis

- The proportion of patients with >1-year TI and other binary end points, were summarized with percentage and 95% 2-sided exact Clopper-Pearson CI
- The Kaplan-Meier method was used to estimate the distribution of the duration of TI

Figure 2. IMerge Phase 3 Trial Design (MDS3001; NCT02598661)



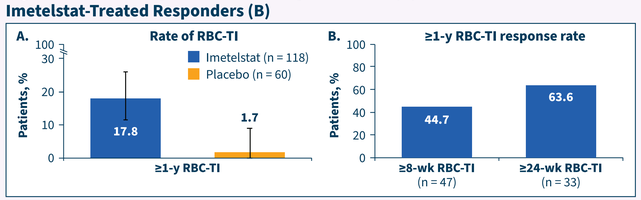
[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, darbepoetin alfa 150 µg, or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 wk or transfusion dependence or reduction in Hb by ≥1.5 g/dL after HI-E from ≥8 weeks of ESA treatment. [b]Percentage of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); percentage of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).

Results

IMerge phase 3 LR-MDS patients achieving ≥1-year RBC-TI

- Of patients enrolled in IMerge phase 3 receiving imetelstat, 21 of 118 (17.8%) achieved ≥1-year sustained TI (95% CI, 11.4-25.9), and 1 of 60 patients (1.7%; 95% CI, 0-8.9) receiving placebo plus supportive care achieved ≥1-year TI (**Fig. 3A**); ≥1-year TI was achieved by 44.7% and 63.6% of ≥8- and ≥24-week imetelstat-treated responders, respectively (**Fig. 3B**) (Data cutoff date, May 10, 2023)
- Baseline characteristics are shown in **Table 1**
- ≥1-year TI responders received imetelstat for a median of 101.1 weeks (range, 75.1-163.9 weeks) and a median of 24 cycles (range, 18-41 cycles)
- Imetelstat ≥1-year TI responders had a median duration of TI of 123 weeks (95% CI, 80.4-NE) and a median maximum central Hb increase of 5.18 g/dL (range, 2.67-13.76 g/dL) during the longest TI interval; no patients with ≥1-year TI in either group progressed to AML (**Table 2**)
- At the time of data cutoff (May 10, 2023), 13 ≥1-year TI responders receiving imetelstat and the patient receiving placebo were ongoing (**Fig. 4**)
- Of the 8 ≥1-year TI responders who discontinued treatment, 7 had loss of response, and 1 had an AE
- Duration of TI ≥1 year and Hb increases during the longest TI interval are shown in **Fig. 5**

Figure 3. Rate of ≥1-y RBC-TI Overall by Treatment (A) and in ≥8-wk and ≥24-wk Imetelstat-Treated Responders (B)



Data cutoff date: May 10, 2023.

Table 1. Baseline Characteristics of IMerge Phase 3 LR-MDS Patients Achieving ≥1-y RBC-TI

Baseline characteristic	Imetelstat (n = 21)	Placebo (n = 1)
IPSS category		
Low	14 (67)	1 (100)
Intermediate-1 risk	7 (33)	0
MDS-RS+	15 (71)	1 (100)
IPSS-R category		
Low	15 (71)	1 (100)
Intermediate	4 (19)	0
Missing	2 (10)	0
Prestudy RBC-TB, median (range),[a] U	6.0 (4-9)	5.0
Prior ESAs	19 (90)	1 (100)
≥2 y since initial diagnosis	15 (71)	1 (100)
Pretreatment Hb level, median (range), g/dL	7.8 (6.5-8.8)	6.2
Normal karyotype[b]	12 (57)	1 (100)

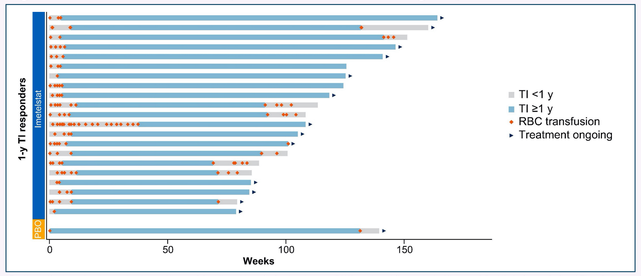
Values shown are n(%) unless otherwise indicated.
[a]Number of transfusions in 8 weeks during the 16 weeks before study. [b]Missing karyotype data for 2 patients.

Table 2. Treatment Exposure and Clinical Response

	Imetelstat (n = 21)	Placebo (n = 1)
Treatment exposure		
Median (range), wk	101.1 (75.1-163.9)	139.4
No. of cycles, median (range)	24 (18-41)	36 (100)
Follow-up, median, months	28.8	32.1
Clinical response		
Duration of TI in ≥1-y TI responders, median (95% CI), wk	123 (80.4-NE)	131 (NE)
Central Hb increase during the longest TI interval, median (range), g/dL	5.18 (2.7-13.8)	1.7
Progression to AML	0	0
Median PFS	NE	NE

Data cutoff date: May 10, 2023.

Figure 4. Treatment Summary of 22 Patients Achieving ≥1-y TI*†



*For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period.
†Data cutoff date, May 10, 2023.

Figure 5. Mean Change in Central Hb* Over Time in ≥1-y TI Responders†

*The mean changes from the minimum Hb values in the 8 weeks prior to the first dose date are shown and values within 14 days of RBC transfusions were excluded.
†Data cutoff date, May 10, 2023. Data points that have <4 patients in the imetelstat group are not shown.
BL, baseline.

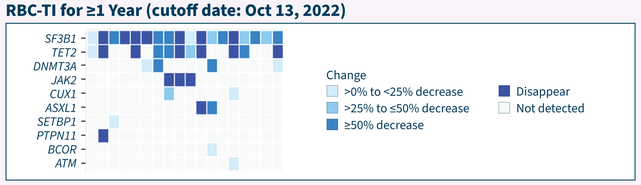
Cytogenetic best response in patients achieving RBC-TI for ≥1 year

- Cytogenetic testing was performed centrally, and response was assessed by IRC
- Of 21 imetelstat-treated ≥1-year TI responders, 7 (33%) had cytogenetic abnormality at baseline and ≥1 posttreatment cytogenetic assessment; of these, 4 (57%) had cCR, 2 (29%) had cPR, and 1 patient (19%) did not meet the response criteria on the October 13, 2022 data cutoff date

Change in mutational burden in patients achieving RBC-TI for ≥1 year

- Mutation data were available for 18 ≥1-year TI responders receiving imetelstat, all with *SF3B1* mutations present at baseline, and many of these patients concurrently had *TET2*, *DNMT3A*, *ASXL1*, or *JAK2* mutations
- Complete elimination of certain mutational clones was observed in 10 of 18 patients (55.5%)
- Of 18 ≥1-year RBC responders with mutational data, 13 (72.2%) achieved ≥50% *SF3B1* VAF reduction, including 7 patients with complete elimination of VAF (**Fig. 6**)

Figure 6. Heatmap of Changes in Mutational Burden in 18 Patients Achieving RBC-TI for ≥1 Year (cutoff date: Oct 13, 2022)



Most common AEs were hematologic

- Grade 3-4 thrombocytopenia and neutropenia occurred in 14 (67%) and 20 (95%) patients with TI ≥1 year
- For grade 3-4 neutropenia and thrombocytopenia events, the mean (SD) duration was 1.78 (1.58) and 2.25 (2.48) weeks, respectively
- 81% of grade 3-4 neutropenia and 89% of grade 3-4 thrombocytopenia were reversible to grade ≤2 within 4 weeks

Conclusions

- **Treatment with imetelstat resulted in ≥1-year of sustained, continuous TI in 17.8% of patients in phase 3 of the IMerge study**
- **During the ≥1-year transfusion-free interval, RBC transfusion burden was reduced from a baseline range of 4-9 U and central Hb improved a median of 5.2 g/dL in ≥1-year imetelstat-treated responders**
- **Safety was consistent with that of prior reports, with the most frequent AEs being grade 3-4 thrombocytopenia and neutropenia**
  - **AEs were generally of short duration and were reversible**
- **In this population with disease R/R to or ineligible for ESAs and with a high prior RBC-TB, a reduction to 0 RBC transfusions for ≥1 year represents an opportunity:**
  - **To achieve relief from iron overload and other transfusion-associated complications**
  - **To decrease demand on an already limited supply of blood product**
- **Durable TI and meaningful reductions in mutational burden suggest imetelstat may have disease-modifying activity**

REFERENCES

1. Bock O, et al. *Leuk Res*. 2004;28(5):457-460. **2.** Briatore F, et al. *Cancer Biol Ther*. 2009;8(10):883-889. **3.** Zeidan AM, et al. ASCO 2023. Abstr 7004. **4.** Platzbecker U, et al. EHA 2023. Abstr S165.

ABBREVIATIONS

AE, adverse event; AML, acute myeloid leukemia; *ASXL1*, additional sex combs like-1; *ATM*, ataxia-telangiectasia mutated; *BCOR*, BCL-6 corepressor; cCR, cytogenetic complete response; cPR, cytogenetic partial response; *CUX1*, cut-like homeobox 1; del(5q), deletion on chromosome 5q; *DNMT3A*, DNA (cytosine-5)-methyltransferase 3A; 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; IRC, independent review committee; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; ITT, intent-to-treat; IV, intravenous; *JAK2*, Janus kinase 2; LR-MDS, lower-risk MDS; MDS, myelodysplastic syndrome; NE, not evaluable; OS, overall survival; PBO, placebo; PFS, progression-free survival; PRO, patient-reported outcomes; *PTPN11*, protein tyrosine phosphatase nonreceptor type 11; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; RS+, ring sideroblast-positive; *SETBP1*, SET-binding protein 1; *SF3B1*, splicing factor 3b subunit 1; TB, transfusion burden; *TET2*, tet methylcytosine dioxygenase 2; TD, transfusion-dependent; TI, transfusion independence; VAF, variant allele frequency; WBC, white blood cell.

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ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT02598661; email: info@geron.com

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