Results From the Phase 3 Trial of Imetelstat, a First-in-Class Telomerase Inhibitor, in Patients With Red Blood Cell Transfusion-Dependent Non-del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to/Ineligible for Erythropoiesis Stimulating Agents

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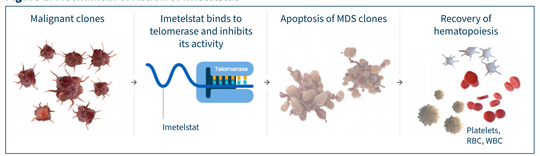
Introduction

- An unmet need exists for patients with LR-MDS who are RBC transfusion dependent and relapsed/refractory to or ineligible for ESAs
- Imetelstat is a first-in-class direct and competitive inhibitor of telomerase activity that specifically targets dysplastic clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis (**Fig. 1**)[1-4]

Figure 1. Mechanism of Action of Imetelstat

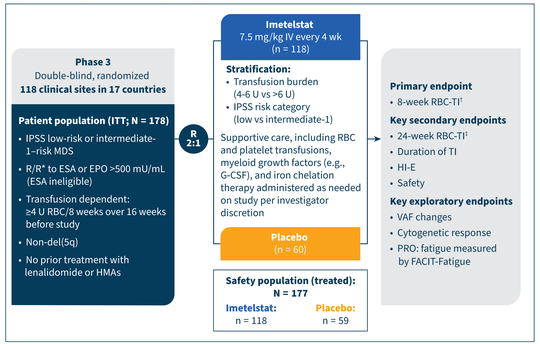


Methods

Study Design

- IMerge phase 3 is a double-blind, randomized (2:1), placebo-controlled, phase 3 trial conducted at 118 sites[5] (**Fig. 2**)
- Patients with heavily RBC-TD, non-del(5q) LR-MDS who were relapsed-refractory to ESAs or ineligible for ESAs and naïve 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 endpoint was 8-week TI rate; secondary endpoints included safety, 24-week TI, duration of response, and HI-E
- Exploratory analyses included assessment of cytogenetic response and mutational status with clinical response

Figure 2. IMerge Phase 3 Study Design



*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 weeks or transfusion dependence or reduction in Hb by ≥1.5 g/dL after Hb E from ≥8 weeks of ESA treatment. †Percentage of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial. ‡Percentage of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial.

Results

Baseline Characteristics

- Baseline characteristics were balanced between study arms[5,6] (**Table 1**)

Table 1. Baseline Characteristics of IMerge Phase 3 Trial

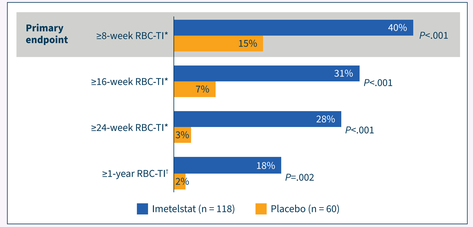
Characteristic	Imetelstat (n = 118)	Placebo (n = 60)
Median age, years (range)	72 (44–87)	73 (39–85)
Male, n (%)	71 (60)	40 (67)
Median time since diagnosis, years (range)	3.5 (0.1–26.7)	2.8 (0.2–25.7)
WHO classification, n (%) RS+ RS−	 73 (62) 44 (37)	 37 (62) 23 (38)
IPSS risk category, n (%) Low Intermediate-1	 80 (68) 38 (32)	 39 (65) 21 (35)
Median pretreatment Hb, g/dL (range)*	7.9 (5.3–10.1)	7.8 (6.1–9.2)
Median prior RBC transfusion burden, RBC U/8 weeks (range)	6 (4–33)	6 (4–13)
Prior RBC transfusion burden, n (%) ≥4 to ≤6 U/8 weeks >6 U/8 weeks	 62 (53) 56 (48)	 33 (55) 27 (45)
Median sEPO, mU/mL (range)	174.9 (6.0–4460.0)	277.0 (16.9–5514.0)
sEPO level, n (%)† ≤500 mU/mL >500 mU/mL	 87 (74) 26 (22)	 36 (60) 22 (37)
Prior ESA, n (%)	108 (92)	52 (87)
Prior luspatercept, n (%)‡	7 (6)	4 (7)

*Average of all Hb values in the 8 weeks prior to the first dose date, excluding values within 14 days after a transfusion, which was considered to be influenced by transfusion. †Data missing for 5 patients in the imetelstat group and 2 in the placebo group. ‡Insufficient number of patients previously treated with luspatercept to draw conclusions about the effect of imetelstat treatment in such patients.

Overall RBC-TI Rates

- Imetelstat showed significant efficacy vs placebo for 8-week, 24-week, and 1-year RBC-TI[5,6] (**Fig. 3**)
- Among imetelstat responders, median duration of TI was 52 weeks, 80 weeks, and 132 weeks for 8-week, 24-week, and 1-year RBC-TI, respectively

Figure 3. RBC-TI Rates in the ITT Population

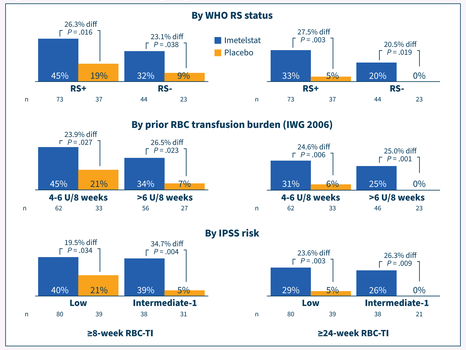


*Data cutoff date: October 13, 2022. †Data cutoff date: October 13, 2023.

RBC-TI Rates in Subgroups

- 8-week and 24-week RBC-TI favored imetelstat in various subgroups[5] (**Fig. 4**)

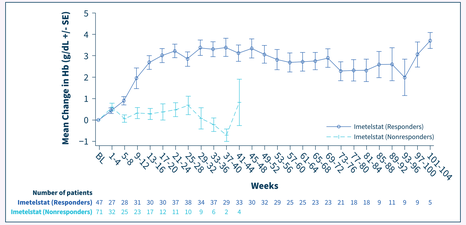
Figure 4. RBC-TI Rates in Subgroups



Hb Increase in Imetelstat RBC-TI Responders

- In the imetelstat group, median Hb increase from baseline was 3.6 g/dL, 4.2 g/dL, and 5.2 g/dL, for ≥8-week, ≥24-week, and ≥1-year RBC-TI responders, respectively
- Increase in Hb level was noted in imetelstat TI responders within ≤4 weeks of treatment (**Fig. 5**)

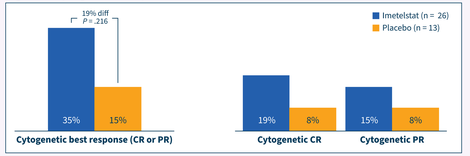
Figure 5. Hb Increase in Imetelstat RBC-TI Responders vs Nonresponders (n = 118)



Cytogenetic Response

- At baseline, 22% of patients had cytogenetic abnormalities, as measured by karyotyping[8] (**Fig. 6**)
- Complete or partial cytogenetic responses were observed in 35% (9/26) of patients in the imetelstat group and 15% (2/13) of patients in the placebo group, as assessed by an independent review committee[5]
- Among cytogenetic responders, 89% (8/9) of patients in the imetelstat group and 50% (1/2) in the placebo group also achieved ≥8-week RBC-TI[6]

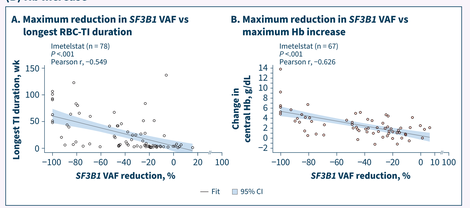
Figure 6. Cytogenetic Response



SF3B1 VAF Changes

- Mean percentage of *SF3B1* VAF reduction was −6% with placebo and −42% with imetelstat
- *SF3B1* VAF reduction significantly correlated with continuous TI response and Hb increase[5,6] (**Fig. 7**)
- Among 18 patients who achieved ≥1-year RBC-TI and had available mutational data, 13 (72%) had ≥50% *SF3B1* VAF reduction, including 7 patients with complete elimination of VAF[7]

Figure 7. Correlation Between *SF3B1* VAF Reduction and (A) RBC-TI Duration and (B) Hb Increase



RBC-TI Correlations in Imetelstat Responders vs Nonresponders

- In patients treated with imetelstat, ≥8-week and ≥24-week RBC-TI significantly correlated with achievement of cytogenetic response, reduction in RS+ cells, and *SF3B1* VAF reduction[5,6] (**Table 2**)

Table 2. RBC-TI Correlations in Imetelstat-Treated Patients

	≥8 weeks			≥24 weeks		
Patients, n/n (%)	**Responders**	**Nonresponders**	***P* value**	**Responders**	**Nonresponders**	***P* value**
RBC-TI + cytogenetic CR/PR per IRC	8/9 (89)	6/17 (35)	.014	6/9 (67)	3/17 (18)	.028
RBC-TI + ≥50% bone marrow RS reduction	22/29 (76)	16/42 (38)	.003	18/29 (62)	11/42 (26)	.003
RBC-TI + ≥50% *SF3B1* VAF reduction	19/23 (83)	21/55 (38)	<.001	16/23 (70)	13/55 (24)	<.001

PRO Fatigue Measured by FACIT-Fatigue

- A higher proportion of patients treated with imetelstat vs placebo reported sustained meaningful improvement (increase of ≥3 points for ≥2 consecutive cycles) in fatigue score by FACIT-Fatigue scale and experienced a shorter median time to first sustained clinically meaningful improvement in fatigue[5] (**Fig. 8**)
- Imetelstat TI responders reported significantly sustained meaningful improvement in fatigue in comparison with nonresponders[5] (**Table 3**)

Figure 8. PRO Fatigue Measured by FACIT-Fatigue Scale

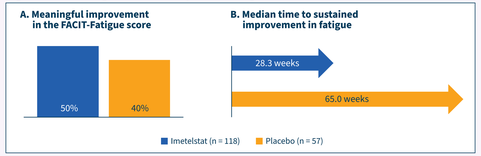


Table 3. Sustained Meaningful Improvement in Fatigue in RBC-TI Imetelstat Responders vs Nonresponders

Patients, n/n (%)	Responders	Nonresponders	*P* value
≥8-week RBC-TI	33/47 (70)	26/71 (37)	<.001
≥24-week RBC-TI	24/33 (73)	35/85 (41)	.004

Safety

- Most common grade 3-4 treatment-emergent AEs with imetelstat vs placebo were neutropenia (68% vs 3%) and thrombocytopenia (62% vs 8%)[5]
- >80% of grade 3-4 cytopenia events were reversible to grade ≤2 within 4 weeks[5]
- 72% and 60% of ≥8-week RBC-TI responders with imetelstat had grade 3-4 neutropenia and thrombocytopenia, respectively[8]
- Clinical consequences of infection and bleeding were low and similar for imetelstat and placebo

Conclusions

- **In IMerge, patients with LR-MDS derived clinical benefit with imetelstat vs placebo**
- **RBC-TI rates were consistently improved with imetelstat vs placebo across subgroups: RS status, prior RBC transfusion burden, or IPSS risk category**
- **Achievement of RBC-TI correlated with reduced mutational burden, Hb rise, and improvement in patient-reported fatigue**
- **Safety results were consistent with prior imetelstat clinical experience, with no new safety signals**
  - **>80% of grade 3-4 cytopenia events were reversible to grade ≤2 within 4 weeks**
  - **Clinical consequences from grade 3-4 neutropenia and thrombocytopenia were similar in patients treated with imetelstat and placebo**

ABBREVIATIONS

AE, adverse event; BL, baseline; CR, complete response; diff, difference; EMA, erythroid maturation agent; 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; IRC, independent review committee; ITT, intent-to-treat; IV, intravenous; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; mut, mutation; PR, partial response; PRO, patient-reported outcome; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; RS, ring sideroblast; SE, standard error; sEPO, serum erythropoietin; SF3B1, splicing factor 3b subunit 1; TD, transfusion dependence; TI, transfusion independence; U, unit; VAF, variant allele frequency; WBC, white blood cell; WHO, World Health Organization.

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DISCLOSURES

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