PS1640

OUTCOMES WITH IMETELSTAT BY SERUM ERYTHROPOIETIN LEVELS IN PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES WHO WERE TREATMENT NAIVE OR WHO HAD PRIOR TREATMENT WITH ERYTHROPOIESIS-STIMULATING AGENTS

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Background

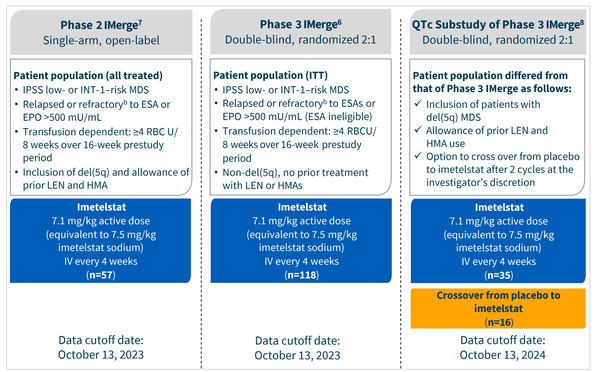
- Erythropoiesis-stimulating agents (ESAs) are the preferred first-line treatment option for patients with non-del(5q) lower-risk myelodysplastic syndromes (LR-MDS) and anemia[1,2]
  - However, ~10% of patients with LR-MDS are ineligible for ESAs due to an elevated baseline serum erythropoietin (sEPO) level >500 mU/mL[3]
  - Current treatment options are limited in number and efficacy for patients who are ineligible for ESAs as well as for those whose disease is relapsed or refractory to ESAs[2]
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase activity approved in the United States and Europe for the treatment of certain adult patients with LR-MDS with red blood cell (RBC) transfusion-dependent anemia who were ineligible for ESAs or had relapsed or refractory/unsatisfactory response to ESAs based on results from the IMerge Phase 3 trial (NCT02598661)[4-6]
  - In IMerge, imetelstat demonstrated clinically significant benefit compared with placebo, including RBC transfusion independence (TI), and a generally manageable safety profile in this patient population

This post hoc analysis examined outcomes with imetelstat by baseline sEPO level in patients with LR-MDS pooled from the 3 parts of IMerge (Phase 2, Phase 3, and QTc substudy)

Methods

- IMerge comprised the following 3 parts: Phase 2, Phase 3, and QTc substudy (**Figure 1**)
  - Patients who had del(5q) or prior therapy with lenalidomide or HMAs were excluded from Phase 3 but were allowed in Phase 2 and the QTc substudy
  - In the QTc substudy, patients assigned to the placebo group could cross over to receive imetelstat after 2 cycles at the investigator's discretion
- In all 3 parts of IMerge, adults received 7.1 mg/kg imetelstat active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo, both administered as a 2-hour intravenous infusion every 4 weeks
- Outcomes for this analysis included ≥8-week, ≥24-week, and ≥1-year RBC-TI rates; hematologic improvement-erythroid (HI-E) per International Working Group (IWG) 2006 (transfusion reduction ≥4 U/8 weeks and hemoglobin rise ≥1.5 g/dL lasting ≥8 weeks) and IWG 2018 (low transfusion burden and high transfusion burden) criteria; and duration of RBC-TI for responders

Figure 1. IMerge Study Design for Pooled Analysis Set[a]



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; INT, intermediate; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; IV, intravenous; LEN, lenalidomide; MDS, myelodysplastic syndromes; QTc, QT correction; RBC, red blood cell.
[a]Seven patients were missing EPO data and are not included in the study population. [b]Received ≥8 weeks of ESA treatment (EPO alfa ≥40,000 U, EPO 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.

Results

Patient Population

- At the data cutoff dates (Phase 2/3, October 13, 2023; QTc substudy, October 13, 2024), 210 imetelstat-treated patients pooled from IMerge were included in this analysis
  - 13 patients were treatment naive (no prior ESA or other prior therapies) and had sEPO >500 mU/mL
  - 112 patients had prior ESA and sEPO <200 mU/mL
  - 43 patients had prior ESA and sEPO 200 to ≤500 mU/mL
  - 42 patients had prior ESA and sEPO >500 mU/mL
- Baseline characteristics for the 13 treatment-naive patients were similar to the other patient groups (**Table 1**)
  - Median age was 71 years (range, 49-81), median transfusion burden was 6 RBC U/8 weeks (range, 4-11), 31% of patients required >6 RBC U/8 weeks, 38% had intermediate-1–risk International Prognostic Scoring System disease, 85% had ring sideroblast–negative status, and the median time since initial diagnosis was 1 year (range, 0.1-8)

Table 1. Baseline Characteristics Were Similar Across Patient Populations

Characteristics	Treatment naive and sEPO >500 mU/mL (n=13)	Prior ESA and sEPO <200 mU/mL (n=112)	Prior ESA and sEPO 200 to ≤500 mU/mL (n=43)	Prior ESA and sEPO >500 mU/mL (n=42)[a]
Age, median (range), y	71.0 (49-81)	72.5 (46-87)	71.0 (50-85)	70.0 (43-86)
Male, n (%)	6 (46)	71 (63)	26 (60)	29 (69)
Time since diagnosis, median (range), y	0.9 (0.1-7.8)	3.8 (0.3-24.4)	3.5 (0.6-21.9)	3.4 (0.5-12.9)
WHO classification, n (%)				
RS+	2 (15)	83 (74)	31 (72)	22 (52)
RS−	11 (85)	28 (25)	12 (28)	20 (48)
IPSS risk category, n (%)				
Low	8 (62)	79 (71)	28 (65)	24 (57)
Intermediate-1	5 (38)	33 (29)	15 (35)	18 (43)
Pretreatment Hb, median (range), g/dL	75.5 (63-84)	79.4 (51-93)	78.7 (64-101)	75.0 (53-90)
Prior RBC transfusion burden, median (range), RBC U/8 weeks	6 (4-11)	6 (4-17)	7 (4-33)	8 (4-15)
Prior RBC transfusion burden, n (%)				
≤6 RBC U/8 weeks	9 (69)	63 (56)	19 (44)	13 (31)
>6 RBC U/8 weeks	4 (31)	49 (44)	24 (56)	29 (69)
sEPO, median (range), mU/mL	749.9 (535.0-5424.0)	84.4 (6.0-196.0)	307 (200-497.3)	763.5 (509.0-4460.0)
Prior ESA, n (%)	**0**	**112 (100)**	**43 (100)**	**42 (100)**
Prior luspatercept, n (%)	0	11 (10)	10 (23)	10 (24)
Prior lenalidomide, n (%)	0	12 (11)	4 (9)	8 (19)
Prior HMA, n (%)	0	9 (8)	5 (12)	6 (14)

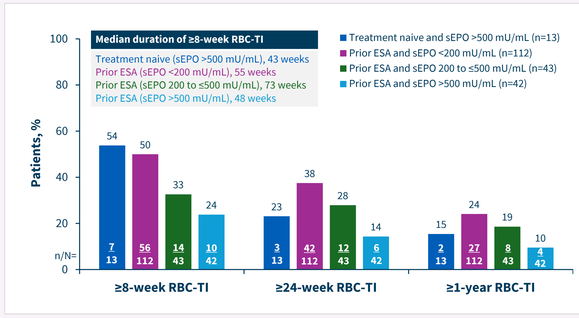
ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; WHO, World Health Organization.
[a]Nine patients with sEPO >500 mU/mL had received prior non-ESA therapies and were excluded from this analysis.
Note percentages are rounded to the nearest whole value.

- Median duration of imetelstat treatment included the following:
  - Treatment naive and sEPO >500 mU/mL: 52 weeks (range, 8-260)
  - Prior ESA and sEPO <200 mU/mL: 50 weeks (range, 0.1-189)
  - Prior ESA and sEPO 200 to ≤500 mU/mL: 30 weeks (range, 0.1-148)
  - Prior ESA and sEPO >500 mU/mL: 20 weeks (range, 0.1-180)

Efficacy

- Among treatment-naive patients, 54% achieved ≥8-week RBC-TI with imetelstat (**Figure 2**)
  - The median duration of ≥8-week RBC-TI was 43 weeks

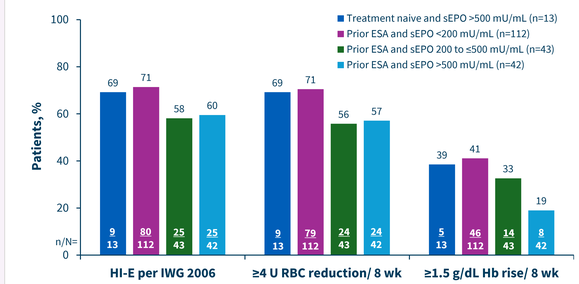
Figure 2. Achievement of RBC-TI by Baseline sEPO Level



ESA, erythropoiesis-stimulating agent; n/N, number with event/number in population; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.

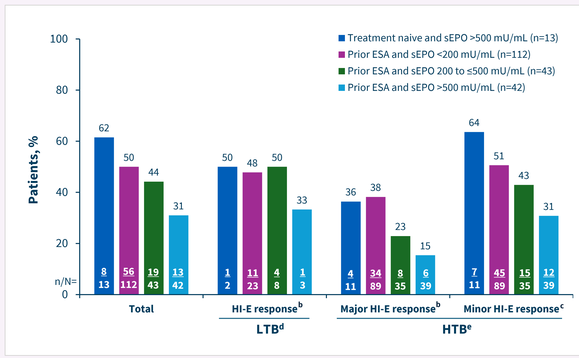
- Among treatment-naive patients, HI-E per IWG 2006 (**Figure 3**) and IWG 2018 (**Figure 4**) was achieved by 69% and 62% with imetelstat, respectively

Figure 3. Achievement of HI-E per IWG 2006 by Baseline sEPO Level[a]



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; IWG, International Working Group; n/N, number with event/number in population; RBC, red blood cell; sEPO, serum erythropoietin.
[a]Hb analyses were based on a central laboratory data in the Phase 3 part of IMerge, but only local laboratory data were collected in the Phase 2 and QTc substudy parts.

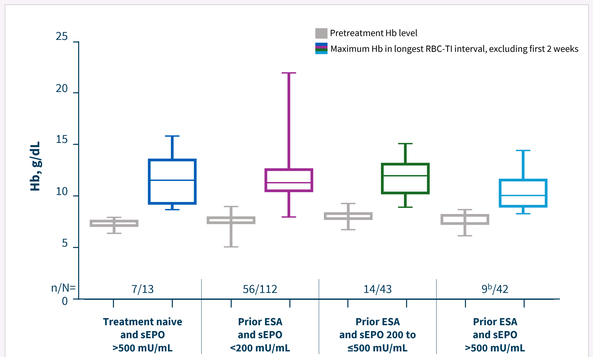
Figure 4. Achievement of HI-E per IWG 2018 by Baseline sEPO Level[a]



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; n/N, number with event/number in population; RBC, red blood cell; sEPO, serum erythropoietin.
[a]Hb analyses were based on a central laboratory data in the Phase 3 part of IMerge, but only local laboratory data were collected in the Phase 2 and QTc substudy parts. [b]16-week RBC-TI. [c]50% RBC U reduction/16 weeks. [d]Defined as 3-7 RBC U/16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. [e]Defined as ≥8 RBC U/16 weeks, or ≥4 RBC U/8 weeks.

- Among imetelstat-treated patients who achieved ≥8-week RBC-TI, median hemoglobin levels increased from baseline, regardless of whether they were treatment naive or had prior ESA across baseline sEPO levels (**Figure 5**)
  - Median hemoglobin rise in the longest RBC-TI interval was 4.2 g/dL for treatment-naive patients with sEPO >500 mU/mL, 3.8 g/dL for patients with prior ESA and sEPO <200 mU/mL, 4.0 g/dL for patients with prior ESA and sEPO 200 to ≤500 mU/mL, and 2.5 g/dL for patients with prior ESA and sEPO >500 mU/mL

Figure 5. Hb Levels in Patients Who Achieved ≥8-Week RBC-TI With Imetelstat[a]



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.
Error bars represent minimum and maximum (range), and box ends represent the interquartile range.
[a]Hb analyses were based on a central laboratory data in the Phase 3 part of IMerge, but only local laboratory data were collected in the Phase 2 and QTc substudy parts.
[b]One patient in the Phase 3 part did not have available central hemoglobin values during the longest TI period and was excluded from the Hb rise analysis.

Conclusions

- In this post hoc pooled analysis, patients with LR-MDS who were treatment naive and had a high sEPO level at baseline experienced clinical benefit with imetelstat
- Additionally, patients who had prior ESA therapy experienced clinical benefit with imetelstat regardless of baseline sEPO levels, including those with sEPO >500 mU/mL
- Together, these findings support the use of imetelstat in the frontline setting in certain patients with LR-MDS with anemia who are ineligible for ESAs, and further support use in patients after ESA therapy regardless of baseline sEPO levels
- Results should be interpreted with caution given the post hoc nature of this analysis and the small sample sizes in some groups

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Acknowledgments

- The authors thank all the patients and caregivers for their participation in this study and acknowledge the collaboration and commitment of all investigators and their research support staff
- This study was funded by Geron Corporation. All authors contributed to and approved the presentation; writing and editorial support were provided by Meredith Rogers, MS, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation