Improvement of Patient-Reported Fatigue in IMerge Phase 3 Trial of Imetelstat Versus Placebo in Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory/Ineligible to Erythropoiesis Stimulating Agents

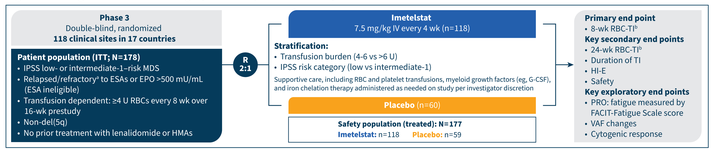
Mikkael A. Sekeres,[1*] Valeria Santini,[2*] Maria Díez-Campelo,[3] Rami S. Komrokji,[4] Pierre Fenaux,[5] Michael R. Savona,[6] Yazan F. Madanat,[7] David Valcárcel-Ferreiras,[8] Thomas Illmer,[9] Anna Jonášová,[10] Petra Bělohlávková,[11] Antoine Regnault,[12] Kristin Creel,[12] Nishan Sengupta,[13] Libo Sun,[13] Shyamala Navada,[13] Amer M. Zeidan,[14**] and Uwe Platzbecker[15**]

[1]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [2]Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; [3]University Hospital of Salamanca, Salamanca, Spain; [4]Moffitt Cancer Center, Tampa, FL, USA; [5]Hôpital Saint-Louis, Université de Paris 7, Paris, France; [6]Vanderbilt University Medical Center, Nashville, TN, USA; [7]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]Hematology Private Practice, Dresden, Germany; [10]General Hospital, Prague, Czech Republic; [11]Charles University Hospital, Hradec Králové, Czech Republic; [12]Modus Outcomes, A Division of THREAD, Lyon, France; [13]Geron Corporation, Parsippany, NJ, USA; [14]Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [15]Cellular Therapy and Hemostaseology, Leipzig University Hospital, Leipzig, Germany. *Contributed equally. **Contributed equally.

Introduction

- 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[1-4]
- A key goal of MDS treatment is to manage anemia with fewer transfusions (thereby improving patient's fatigue and reducing the associated risks) to improve the quality of life of patients, most of whom are elderly and frail
- A recent report showed that patients with MDS had clinically meaningful worse fatigue than the general population, and fatigue worsened with increasing IPSS-R risk even for patients with very low, low, and intermediate risk[5]
- Hence, fatigue was selected as the main PRO concept of interest for the phase 3 part of the IMerge study as measured by the FACIT-Fatigue Scale score, which is a reliable and valid measure of fatigue[6]
- In the phase 3 part of the IMerge study, imetelstat demonstrated clinically meaningful efficacy compared with placebo in patients with heavily transfusion-dependent LR-MDS, including higher rates of 8-, 16-, 24-week and 1-year RBC-TI; longer RBC-TI duration; higher rate of hematologic improvement; and fewer RBC transfusion units over time[7]
- This poster presents the analyses conducted to support the main PRO objective related to deterioration and improvement in fatigue as measured by the FACIT-Fatigue Scale score in the phase 3 part of IMerge (**Fig. 1**)

Figure 1. IMerge Phase 3 Trial Design (MDS3001; NCT02598661)



[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 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. [b]Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).

Aim

Primary PRO objective

- To explore the hypothesis that, while on treatment, patients with LR-MDS who were treated with imetelstat were not more likely to experience meaningful deterioration in fatigue, as measured by the FACIT-Fatigue Scale score, than those treated with placebo, regardless of RBC transfusion status

Methods

Patient-reported outcome

- Previous research, including a literature review of qualitative research on the experience of patients with LR-MDS and input from expert clinicians in LR-MDS, led to the identification of a set of PRO concepts relevant to patients with LR-MDS
- The PRO items collected in IMerge were scrutinized to identify sets of items that would capture these concepts
- Psychometric analyses were conducted using blinded interim IMerge phase 3 data to document the measurement properties of these item sets and define the scores that would be used to specify exploratory PRO end points in the study

FACIT-Fatigue Scale

- A 13-item questionnaire measured during daily activity (**Table 1**)

Analyses

- Proportion of patients in each treatment group reporting any episode of sustained meaningful deterioration or improvement in fatigue (**Fig. 2**)[8,9]
- Sensitivity analyses were performed in alternate populations and with alternate definitions of meaningful deterioration and improvement
- Association of the proportion of patients reporting an episode of sustained meaningful improvement with RBC-TI clinical end points

Table 1. PRO Items for FACIT-Fatigue Scale

Derived score	Source instrument	Scoring method		Items
Fatigue	FACIT-Fatigue	Sum of item scores, multiplied by 13, divided by the number of items answered	HI7	I feel fatigued
			HI12	I feel weak all over
			An1	I feel listless ("washed out")
			An2	I feel tired
			An3	I have trouble starting things because I am tired
		Score range 0-52	An4	I have trouble finishing things because I am tired
			An5	I have energy
		Higher score = better	An7	I am able to do my usual activities
			An8	I need to sleep during the day
			An12	I am too tired to eat
			An14	I need help to do my usual activities
			An15	I am frustrated by being too tired to do the things I want to do
			An16	Have to limit my social activity because I am tired

Figure 2. End Point: PRO Fatigue

Results

Demographics and disease characteristics

- The PRO population, which included all patients in the ITT population who had FACIT-Fatigue Scale data at baseline, comprised 118 patients receiving imetelstat and 57 patients receiving placebo, for a total of 175 patients (**Table 2**)
- Most patients were men and had an ECOG PS of 1 (restricted in strenuous activity but ambulatory)

Table 2. PRO Population Demographics

	Imetelstat (n=118)	Placebo (n=57)
Age, median (range), y	72 (44-87)	73 (39-85)
Sex, n (%)		
Men	71 (60)	38 (67)
Women	47 (40)	19 (33)
Region, n (%)		
Europe	80 (68)	38 (67)
North America	13 (11)	9 (16)
Other	25 (21)	10 (18)
ECOG PS, n (%)		
0-Fully active	42 (36)	21 (37)
1-Restricted in strenuous activity, but ambulatory	70 (59)	36 (63)
2-Ambulatory, but unable to work	6 (5)	0

PRO completion rate (ITT population)[10]

- Percent of patients with PRO data for whom data were expected
- Completion rates were good throughout the study, >85% at most cycles

Sustained meaningful deterioration in FACIT-Fatigue Scale score

- Imetelstat group had a numerically lower percentage of patients who experienced any episode of sustained meaningful deterioration than the placebo group (43.2% vs 45.6%)
- Patients receiving imetelstat were slower than those receiving placebo to report sustained meaningful deterioration in fatigue; median 66.3 vs 43.1 weeks (HR, 0.91 [95% CI, 0.56-1.47])

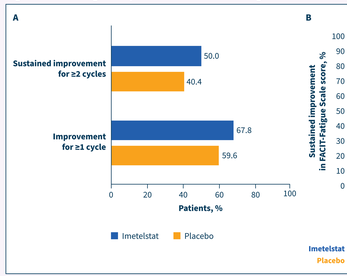
Sensitivity analyses

- In the ITT population, the sensitivity analysis showed that 43% of patients in either group experienced any episode of meaningful deterioration in fatigue for ≥2 consecutive cycles
- In the PRO population, 67% of patients in either group reported any episode of meaningful deterioration in fatigue for ≥1 cycle
- Meaningful deterioration in fatigue using a threshold of 4-, 5-, and 6-point decreases in score occurred in a smaller proportion of patients receiving imetelstat vs placebo (36.4% vs 42.1%, 30.5% vs 38.6%, and 28.0% vs 29.8%, respectively)

Sustained meaningful improvement in FACIT-Fatigue Scale score

- In the imetelstat group, there was a numerically higher percentage of patients reporting any episode of sustained meaningful improvement in fatigue than in the placebo group (**Fig. 3A**)
- Patients treated with imetelstat were quicker to report sustained meaningful improvement in fatigue than those receiving placebo (**Fig. 3B**)
- Compared with placebo, imetelstat treatment resulted in more frequent reports of improvement in fatigue after week 12 (**Fig. 3B**)

Figure 3. Meaningful Improvement in FACIT-Fatigue Scale Score

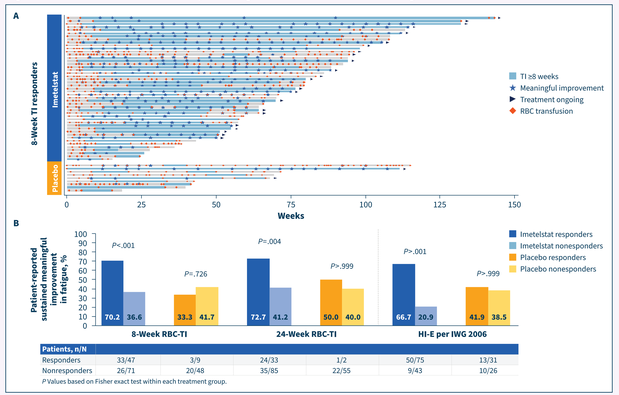


Kaplan-Meier estimate of time to first sustained meaningful improvement in the FACIT-Fatigue Scale score. HR is from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≤4 to ≤6 vs >6 RBC U every 8 weeks during a 16-week period prerandomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate.

Association of improvement in fatigue and clinical responses

- Most 8-week RBC-TI responders in the imetelstat group consistently had sustained meaningful improvement in FACIT-Fatigue Scale scores through the durable TI intervals (**Fig. 4A**)
- Among patients treated with imetelstat, a higher proportion of patients with 8-week RBC-TI, 24-week RBC-TI, and HI-E response (per IWG 2006) reported sustained meaningful improvement in fatigue vs nonresponders; such association was not observed in patients receiving placebo (**Fig. 4B**)

Figure 4. RBC-TI and HI-E Response by Meaningful Improvement in FACIT-Fatigue Scale Score



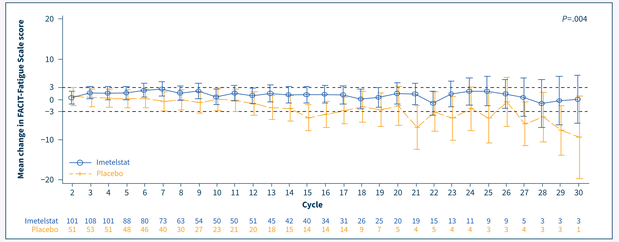
Patients, n/N						
Responders	33/47	3/9	24/33	1/2	50/75	13/31
Nonresponders	26/71	20/48	35/85	22/55	9/43	10/26

P Values based on Fisher exact test within each treatment group.

Supplementary analyses

- An RMMM analysis showed an overall change in FACIT-Fatigue Scale score from baseline of 1.08 (by LSM with 95% CI, −0.36 to 2.53) with imetelstat vs −2.48 (by LSM with 95% CI, −4.48 to −0.5) with placebo, with a significant difference between the treatment groups (LSM difference, 3.57 [95% CI, 1.16-5.97]; *P*=.004; **Fig. 5**)
- Additional analysis showed that patients experiencing grade 3 or 4 neutropenia or thrombocytopenia had the same rates of sustained meaningful improvement in fatigue (52.5% and 53.4%, respectively) as the total imetelstat population (50%)

Figure 5. Model-Based Mean Change From Baseline in FACIT-Fatigue Scale Scores by RMMM



Changes of −3 and +3 in FACIT-Fatigue Scale score from baseline represent meaningful deterioration and improvement, respectively. The plotted LSM estimates for change from baseline in FACIT-Fatigue Scale score and the *P* value between treatment arms are based on an RMMM with the change in FACIT-Fatigue Scale score as the explained variable and baseline score, time, treatment, time and treatment interaction, and study stratification factors (RBC transfusion burden status and IPSS-risk group) as covariates (fixed effects) as explanatory variables. The model included a random effect for individuals to account for the within-individual correlation in the longitudinal assessments. The number of patients at the bottom represents the number of patients with valid FACIT-Fatigue Scale data at each visit.

Conclusions

- **The IMerge phase 3 trial is the first randomized global trial of patients with LR-MDS who had a transfusion burden of ≥4 U every 8 weeks that showed sustained meaningful improvement in patient-reported fatigue when treated with imetelstat (50.0%) vs placebo (40.4%)**
- **Patients treated with imetelstat reported a lower rate than placebo of sustained meaningful deterioration in fatigue (43.2% vs 45.6%), while also receiving fewer RBC transfusion units over time**
- **In the imetelstat group, there was a numerically higher percentage of patients reporting any episode of sustained meaningful improvement in fatigue, and patients receiving imetelstat experienced a shorter median time to first sustained clinically meaningful improvement in fatigue vs placebo (28.3 vs 65.0 weeks)**
- **After 12 weeks, greater sustained and meaningful improvement in FACIT-Fatigue Scale score was reported with imetelstat compared with placebo**
- **In the imetelstat group, there were significant associations between sustained meaningful improvement in fatigue and 8- and 24-week RBC-TI and HI-E response rates; this association was not seen in the placebo group**
- **In patients who achieved TI, imetelstat's improvement of anemia appeared to improve fatigue, one of the core symptoms described by patients with LR-MDS**

ACKNOWLEDGMENTS

Presented as a poster at the European Hematology Association (EHA 2023) and at the Society of Hematologic Oncology (SOHO 2023) congresses. 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. All authors contributed to and approved the presentation. Writing and editorial assistance was provided by Maleeha Fortuin-Seedat, PhD, Mihaela Marina, PhD, and Mary C. Wiggin of Ashfield MedComms, an Inizio Company.

ABBREVIATIONS

ECOG PS, Eastern Cooperative Oncology Group performance status; 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; HR, hazard ratio; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System-Revised; ITT, intent-to-treat; IV, intravenous; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; LSM, least-squares mean; R, randomization; RBC, red blood cell; RMMM, repeated measurement mixed model; TI, transfusion independence; VAF, variant allele frequency.

REFERENCES

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939. **2.** Herbert B-S, et al. *Oncogene.* 2005;24(33):5262-5268. **3.** Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467. **4.** Wang X, et al. *Blood Adv.* 2018;2(2118):2378-2388. **5.** Efficace F, et al. *Leukemia.* 2020;34(9):2451-2459. **6.** Yellen SB, et al. *J Pain Symptom Manage.* 1997;13(2):63-74. **7.** Zeidan A, et al. Oral Presentation at: Annual Meeting of the American Society of Clinical Oncology; June 2, 2023; Chicago, IL. Abstract 7004. **8.** Nordin Å, et al. *BMC Med Res Methodol.* 2016;16:62. **9.** Cella D, et al. *J Pain Symptom Manage.* 2002;24(6):547-561. **10.** Coens C, et al. *Lancet Oncol.* 2020;21(2):e83-e96.

DISCLOSURES

The presenter, Dylan Supina, is an employee of Geron. **M.A.S.:** consultancy/advisory (ad) board for BMS, Geron, Kurome, and Novartis. **V.S.:** consultancy/ad board for AbbVie, BMS, Geron, Gilead, Menarini, Novartis, Servier, and Syros; speaker for/honoraria from Janssen. **M.D.-C.:** consultancy/ad board for Blueprint Medicines, BMS, GSK, and Novartis; speaker for/honoraria from BMS, Gilead, and Novartis. **R.S.K.:** consultancy/ad board for, ownership/interest in, and speaker for/honoraria from AbbVie and BMS; research funding from BMS; consultancy/ad board for and speaker for/honoraria from CTI, Jazz, and PharmaEssentia; consultancy/ad board for Geron, Gilead, Taiho, and Takeda; consultancy/ad board for and other research support from Servier. **P.F.:** consultancy/ad board for, research funding from, and speaker for/honoraria from BMS. **M.R.S.:** consultancy/ad board for AbbVie, BMS, Forma, Geron, Novartis, Sierra Oncology, and Taiho; research funding from ALX Oncology, Astex, and Incyte; consultancy/ad board for and ownership interest in Karyopharm and Ryvu; consultancy/ad board for and research funding from Takeda and TG Therapeutics. **Y.F.M.:** consultancy/ho/honoraria from Blueprint Medicines, Geron, Kura Oncology, Novartis, OncLive, and Rigel Pharmaceutics; ad board for/honoraria from Blueprint Medicines, Morphosys, Novartis, Sierra Oncology, Stemline Therapeutics, and Taiho; travel reimbursement from Blueprint Medicines and Morphosys. **D.N.-F.:** consultancy/ad board for and speaker for/honoraria from Amgen, BMS, GSK, Jazz, Novartis, and Pfizer; speaker for/honoraria from Astellas, Gebro Pharma, and Kyte; consultancy/ad board for Sanofi, SOBI, and Takeda. **T.A.:** consultancy/ad board for AbbVie, AstraZeneca, and Novartis. **A.J.:** consultancy/ad board for and speaker for/honoraria from AbbVie and BMS; speaker for/honoraria from Novartis. **P.B.:** consultancy/ad board for and speaker for/honoraria from AOP and Novartis. **A.R.** and **K.C.:** employees of Modus Outcomes. **N.S., L.S.,** and **S.N.:** employees of Geron Corporation. **A.M.Z.:** consultancy/ad board for, research funding from, and speaker for/honoraria from AbbVie, Aprea, BMS, Boehringer Ingelheim, Cardiff Oncology, Geron, Incyte, Novartis, Otsuka, Pfizer, Takeda, and Trovagene; consultancy/ad board for and speaker for/honoraria from Acceleron, Agios, ALX Oncology, Astellas, BeyondSpring, BioCryst, Cardinal Health, Chiesi, Daiichi Sankyo, Epizyme, Foran, Genentech, Gilead, Ionis, Janssen, Jazz, Kura Oncology, Mendus, Notable, Orum, Seagen, Servier, Syndax, Syros, Taiho, and Tyme; research funding from ADC Therapeutics, Astex, AstraZeneca, Leukemia and Lymphoma Society, MedImmune, and Shattuck Labs. **U.P.:** speaker for/honoraria from AbbVie, BMS, Geron, Janssen, Jazz, Silence, and Takeda.

CONTACT INFORMATION

IMerge (MDS3001): https://www.geron.com/patients/imerge-study
ClinicalTrials.gov: NCT02598661; email: mds3001-info@geron.com

Presented at the AMCP Nexus Annual Meeting, October 16-19, 2023; Orlando, FL, USA.