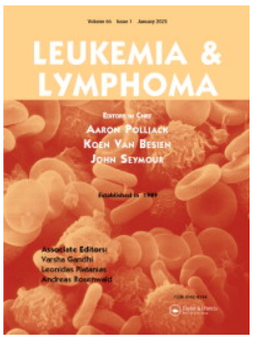

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Sustained benefits of imetelstat on patient-reported fatigue in patients with lower-risk myelodysplastic syndromes ineligible for, or relapsed/refractory to, erythropoiesis-stimulating agents and high transfusion burden in the phase 3 IMerge study

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LETTER TO THE EDITOR

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Sustained benefits of imetelstat on patient-reported fatigue in patients with lower-risk myelodysplastic syndromes ineligible for, or relapsed/refractory to, erythropoiesis-stimulating agents and high transfusion burden in the phase 3 IMerge study

Mikkael A. Sekeres[a], Valeria Santini[b], Maria Díez-Campelo[c], Rami S. Komrokji[d], Pierre Fenaux[e], Michael R. Savona[f], Yazan F. Madanat[g], David Valcárcel-Ferreiras[h], Esther Natalie Oliva[i], Antoine Regnault[j], Kristin Creel[j], Nishan Sengupta[k], Souria Dougherty[k], Sheetal Shah[k], Libo Sun[k], Ying Wan[k], Shyamala Navada[k], Amer M. Zeidan[l] and Uwe Platzbecker[m]

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To the Editor:

One of the most common signs of myelodysplastic syndromes (MDS) is anemia, which is reported in up to 85% of patients at diagnosis [1, 2], with exhaustive fatigue as one of the most significant and debilitating sequelae of anemia [3–6]. Improving quality of life (QOL), including fatigue, in patients with MDS is increasingly being recognized as an important therapeutic and patient-centered goal, particularly for lower-risk (LR)-MDS [7–10]. A fundamental therapeutic intervention for the anemia associated with MDS is red blood cell (RBC) transfusions. Although effective in temporarily improving hemoglobin levels and fatigue, transfusions are associated with risk and significant investment of time for patients [11].

Imetelstat is a recently United States Food and Drug Administration–approved, first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity directed toward malignant clones, allowing for recovery of erythropoiesis [12–15]. IMerge (NCT02598661) is a randomized, double-blind, placebo-controlled, phase 2/3 study of imetelstat versus placebo in adult patients with heavily RBC-transfusion dependent (TD) non-del(5q) LR-MDS who were relapsed or refractory to or ineligible for erythropoiesis-stimulating agents and lenalidomide/hypomethylating agent-naive [16]. Compared with placebo, imetelstat significantly improved ≥8-week and ≥24-week RBC-transfusion independence (TI), with longer RBC-TI duration, higher hematologic improvement-erythroid (HI-E) response rates, and fewer transfusions over time [16]. The safety profile of imetelstat has been well characterized, with the most common treatment-emergent adverse events being neutropenia and thrombocytopenia, and risks of severe bleeding and infection comparable with placebo [16].

Herein, we evaluated the patient-reported outcome (PRO) of fatigue as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score, a reliable and validated instrument for measuring fatigue in patients with MDS [17]. The methodology of the phase 3 IMerge study has been previously described [16]. Fatigue was a prespecified main exploratory PRO endpoint of the study and was part of the statistical analysis plan. Patients rated fatigue using the FACIT-Fatigue scale, with scores calculated as directed by the developer of the scale [17]. Scores ranged from 0 to 52, with higher scores equating to less fatigue. Prior studies conducted in the United States and Germany found mean FACIT-Fatigue scores of 44 for the general population, 24 for patients with cancer and anemia, and 40 for patients with cancer but without anemia [18, 19]. FACIT-Fatigue scores were measured during each 4-week treatment period until the end of treatment (EOT), at EOT (30 ± 3 days after last dose), and every 12–16 weeks during posttreatment follow-up (until death, loss to follow-up, withdrawal of consent, end of study [2 years after randomization of last patients in phase 3], or start of subsequent therapy, whichever occurred first). FACIT-Fatigue was not assessed after study discontinuation. To determine whether the impact of imetelstat on transfusion dependence modified fatigue, the

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proportion of patients who experienced any episode of meaningful change in fatigue (defined as ≥3-point decrease for deterioration and ≥3-point increase for improvement in the FACIT-Fatigue score compared with baseline) for ≥2 consecutive cycles was evaluated. This prespecified threshold has been previously published and was confirmed with methodologic validation using blinded IMerge data [20, 21].

No imputation or assumption was made for missing PRO assessments. A sensitivity analysis was performed with an alternate rule for managing missing FACIT-Fatigue assessments in which missing assessments were imputed immediately before or after the 2 consecutive nonmissing assessments to count as meaningful improvement. This sensitivity analysis showed no substantial differences from the main analysis. Data on the proportion of patients achieving the exploratory endpoint of meaningful changes from baseline in FACIT-Fatigue are reported with exact Clopper-Pearson confidence intervals. Differences between treatment groups are reported with confidence intervals based on the Wilson Score method. *p* values were based on Cochran-Mantel-Haenszel controlling for prior RBC transfusion burden (≤6 vs. >6 units RBC) and International Prognostic Scoring System (IPSS) risk group (low vs. intermediate-1) applied to randomization. The overall effect of imetelstat on the FACIT-Fatigue score was evaluated from the model comparing the least squares (LS) means of change in FACIT-Fatigue score estimated in the two treatment groups using all available data up to cycle 30 (i.e. up to the cycle at which data for both treatment arms was available). A mixed model for repeated measures (MMRM) was used to derive the *p* value between treatment arms for FACIT-Fatigue score change from baseline over time, with change in FACIT-Fatigue score as the explained variable, and baseline score, time, treatment, time and treatment interaction, and study stratification factors (prior RBC transfusion burden and IPSS risk group) as covariate (fixed effects) explanatory variables. PROs were not controlled for type I error and are considered exploratory with nominal *p* values.

Complete baseline demographic criteria for the intent-to-treat (ITT) population of IMerge ($n = 118$ imetelstat; $n = 60$ placebo) have been reported [16]. The median (interquartile range [IQR]) age was 72 years (66–77) and most patients were male (62%) and White (80%). Median (IQR) hemoglobin before treatment was 7.9 g/dL (7.3–8.3) for the imetelstat group and 7.8 g/dL (7.4–8.4) for the placebo group [16]. This population had a high transfusion burden at baseline, with a median of 6 units RBC received over an 8-week period during the 16 weeks before randomization. The PRO population (all patients in the ITT population who had FACIT-Fatigue data at baseline) comprised 118 patients in the imetelstat group and 57 patients in the placebo group. FACIT-Fatigue scores were similar between treatment groups at baseline (mean [standard deviation]: imetelstat, 32.0 [11.1]; placebo, 31.3 [12.3]) and were indicative of a high level of fatigue [18, 19]. PRO completion rates for each cycle were generally between 85% and 95%; comparable completion rates were observed between treatment arms at each cycle, with 76.7% and 78.6% completion rates in the imetelstat and placebo arms at EOT. Assessment of fatigue ended at EOT.

Numerically more patients treated with imetelstat versus placebo experienced a sustained episode of meaningful improvement (≥3-point increase) in fatigue for ≥2 consecutive cycles (50.0% vs. 40.4%, respectively; $p = .228$) [16] and also for ≥1 cycle (67.8% vs. 59.6%; $p = .279$). Similar rates of sustained meaningful improvement in fatigue with imetelstat were observed among patients who experienced grade 3 or 4 neutropenia (52.5%) or thrombocytopenia (53.4%) as the total imetelstat group. Imetelstat-treated patients also demonstrated a numerically shorter median time to first sustained improvement in fatigue versus placebo (28.3 vs. 65.0 weeks; hazard ratio: 1.34 [95% CI: 0.82–2.20]) (Figure 1A) [16]. In the PRO population for imetelstat versus placebo, respectively, achievement of ≥8-week RBC-TI was 39.8% versus 15.8%, ≥24-week RBC-TI was 28.0% versus 3.5%, and HI-E per International Working Group 2006 criteria was 63.6% versus 54.4%. In the imetelstat group, a significantly higher proportion of ≥8- and ≥24-week RBC-TI responders and patients who achieved HI-E per International Working Group 2006 criteria [22] experienced sustained meaningful improvement in fatigue as compared with nonresponders (70.2% vs. 36.6%, $p < .001$; 72.7% vs. 41.2%, $p = .004$; and 66.7% vs. 20.9%, $p < .001$, respectively; Figure 1B) [16]. This association was not observed in the placebo group (33.3% vs. 41.7%, $p = .726$; 50.0% vs. 40.0%, $p > .999$; and 41.9% vs. 38.5%, $p > .999$, respectively) [16]. In the PRO population for imetelstat versus placebo, respectively, a hemoglobin increase of ≥1.5 g/dL lasting ≥8 weeks was 33.9% versus 10.5%. Of these 40 imetelstat-treated patients and 6 placebo recipients who exhibited *a* ≥1.5-g/dL hemoglobin increase lasting ≥8 weeks, 28 (70.0%) and 4 (66.7%), respectively, had sustained meaningful improvements in fatigue. These results support the robustness of the fatigue endpoint and its connection with the clinical endpoint of a hemoglobin increase of ≥1.5 g/dL that is associated with restoration of hematopoiesis and improvement of anemia. It should be noted that the number of patients in some groups was small, and the significance of the differences between responders and nonresponders, and between imetelstat and placebo, may have been different given larger populations.

The mean change in FACIT-Fatigue score from baseline was consistently higher (indicating less fatigue) from cycle 3 onwards in the imetelstat group versus placebo (Figure 2). A statistically significant difference in overall change in FACIT-Fatigue score from baseline through cycle 30 was observed for patients treated with imetelstat versus placebo, in whom fatigue worsened over time (1.08 [95% CI: −0.36, 2.53] vs. −2.48 [−4.48, −0.49]; LS mean difference: 3.57 [1.16–5.97], $p = .004$). This was associated with a significant ($p = .042$) trend of decreasing RBC transfusion burden in the imetelstat group versus the placebo group as reported in the primary analysis [16].

Taken together, these analyses from IMerge demonstrate that in patients with LR-MDS and a high transfusion burden at baseline, treatment with imetelstat led to durable improvement in fatigue, and this was associated with clinical response, providing additional validity to the findings [20, 21]. No additional fatigue burden due to any

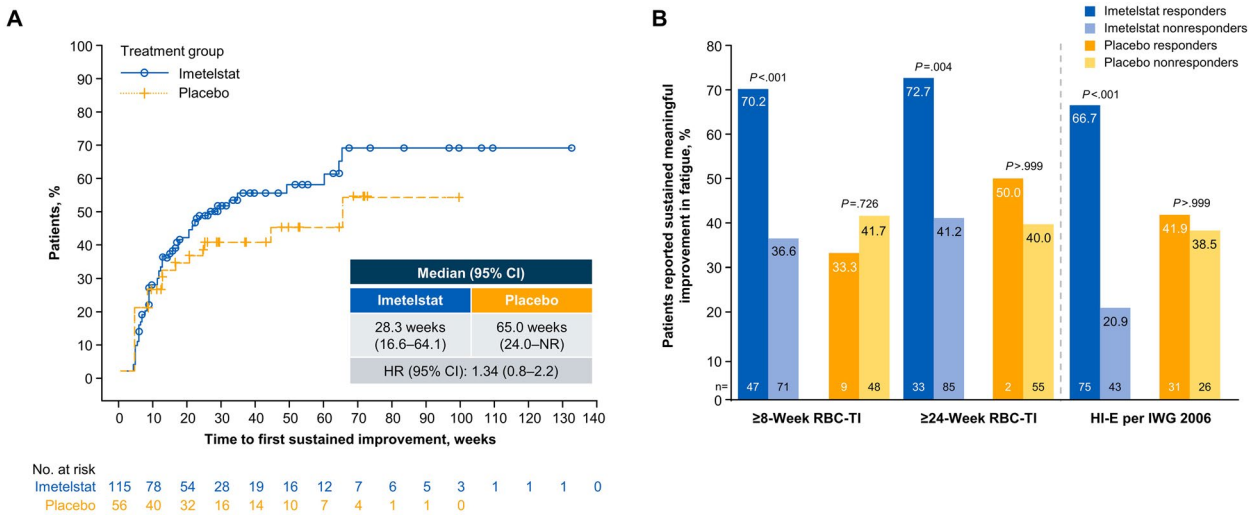

Figure 1. (A) Time to first sustained improvement in fatigue in the PRO population. (B) Proportion of patients achieving sustained, meaningful improvement in fatigue by clinical responder status, defined as ≥8-week RBC-TI, ≥24-week RBC-TI, or achievement of HI-E per IWG 2006 [16].
CI, confidence interval; HI-E, hematologic improvement-erythroid; HR, hazard ratio; IWG, International Working Group; PRO, patient-reported outcome; RBC, red blood cell; TI, transfusion independence.
p values are based on Fisher's exact test within each treatment group.

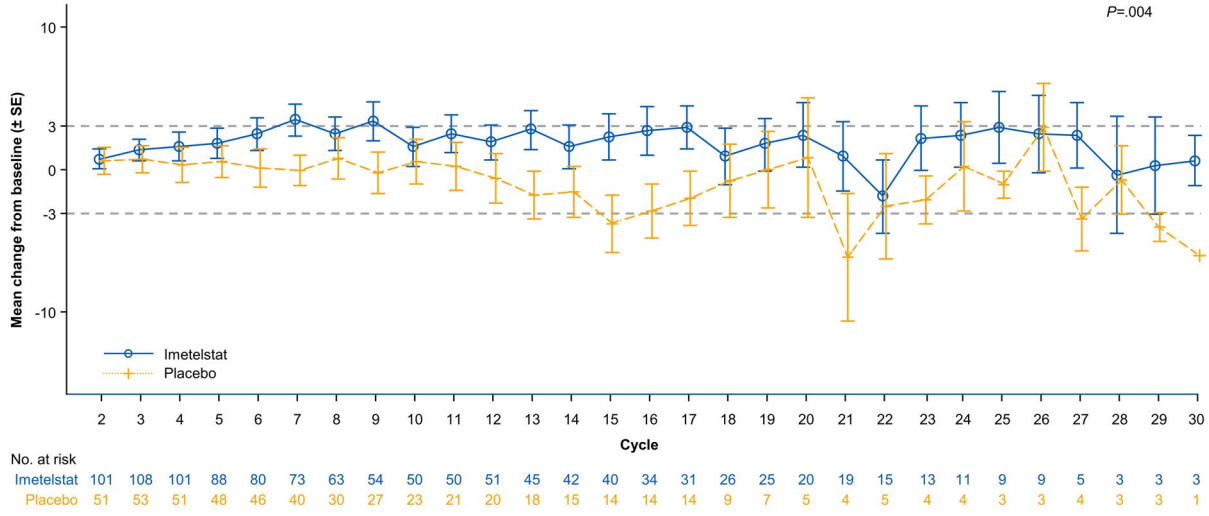

Figure 2. Mean change from baseline in FACIT-fatigue score at each cycle (ITT population).
p values between treatment arms based on a repeated measurement mixed model.
FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; SE, standard error.

cytopenia-related side effects of imetelstat was observed. Although the sample size in some groups was small, imetelstat-treated patients consistently reported numerically lower levels of fatigue than those in the placebo group, despite patients in the placebo group continuing to receive RBC transfusions. This point is poignant when comparing imetelstat RBC-TI responders who need fewer transfusions with RBC-TD patients treated with placebo who continue to need transfusions, as RBC transfusions are known to improve anemia and fatigue [23]. Therefore, improvement in fatigue in the imetelstat group may reflect the biologic activity of the drug with restoration of hematopoietic activity in addition to exogenous amelioration of anemia.

Patients with LR-MDS experience worsening QOL with disease progression, commonly resulting in increasing transfusion burden and dependency [24]. Therefore, maintaining stability in PRO measures of QOL over time is considered clinically beneficial by patients with MDS and providers alike [5]. However, studies of other treatments for LR-MDS have generally failed to demonstrate benefit with regard to PRO measures such as fatigue. In the phase 3, randomized MEDALIST study of luspatercept versus placebo, no clinically meaningful difference in fatigue was observed within or between groups [25]. Likewise, in the phase 3, randomized clinical trial of lenalidomide versus placebo in patients with non-del(5q) LR-MDS, no clinically meaningful change in fatigue was

observed between groups [26]. IMerge is the first randomized, global, phase 3 study of patients with LR-MDS with a high transfusion burden and level of fatigue at baseline to demonstrate a beneficial and sustained impact of treatment on patient-reported fatigue over time while reducing overall transfusion burden. Although these analyses were limited by small sample sizes, these results support the efficacy and safety results presented in the primary analysis [16], and extend and correlate improvements in clinical and biologic endpoints to how patients feel.

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Data availability statement

De-identified study data will be made available upon request to qualified researchers after approval of imetelstat in myelodysplastic syndromes, to the extent permitted by applicable laws and participant informed consent. Approval of such requests is at Geron Corporation's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to medinfo@geron.com

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