Impact of Imetelstat Treatment on PROs and Health Care Resource Utilization in Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis Stimulating Agents: IMerge Phase 3 Trial

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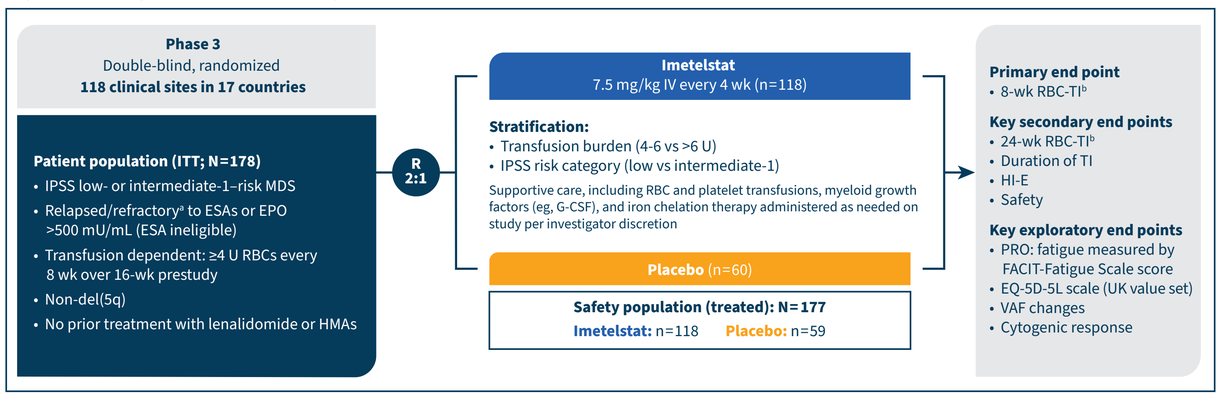
Introduction

- 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 impact of imetelstat on PRO and HCRU 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, epoetin 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. [b]Percent of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); percent of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).

Aim

- To explore the hypothesis that, while receiving treatment for LR-MDS, imetelstat-treated patients were not more likely than placebo-treated patients to experience meaningful deterioration in fatigue or general health, as measured by FACIT-Fatigue Scale and EQ 5D-5L VAS, regardless of RBC transfusion status

Methods

- 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
- HCRU data were collected throughout the study by the investigator and study-site personnel for all patients including the posttreatment long-term follow-up period

FACIT-Fatigue Scale

- A 13-item questionnaire measured during daily activity (**Table 1**)
- Meaningful deterioration/improvement was defined as ≥3 points decrease/increase reported at ≥2 consecutive nonmissed treatment cycles

Table 1. PRO Items for FACIT-Fatigue Scale

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

EQ-5D-5L

- A 5-item questionnaire assessed 5 health status domains (**Table 2**)

Table 2. PRO Items for EQ-5D-5L Index Score

Derived score	Source instrument	Scoring method	Problem level	
Health status	EQ-5D-5L	**5 Dimensions with 1-5 problem levels each** 1. Mobility 2. Self-care 3. Usual activities 4. Pain or discomfort 5. Anxiety or depression	**Level 1** **Level 2** **Level 3** **Level 4** **Level 5**	None Slight Moderate Severe Extreme
		Health state Problem levels are scored to produce a 5-digit number describing patient's health state	**12345**	• No problems with mobility • Slight problems with self-care • Moderate problems with usual activities • Severe pain or discomfort • Extreme anxiety or depression
		VAS score Quantitative measure of respondent's self-rated health	**0** **100**	Worst imaginable health state Best imaginable health state
		Index score 5 Categorical dimension score of health state converted into a single UK set index value (range, 0-1; higher = better)		

Analyses

- Percent of patients in each treatment group reporting any episode of sustained meaningful deterioration or improvement in fatigue[8,9]
- Sensitivity analyses were performed in alternate populations and with alternate definitions of meaningful deterioration and improvement
- Association of the percent of patients reporting an episode of sustained meaningful improvement with RBC-TI clinical end points
- Frequency and duration of hospitalization, outpatient medical encounters, and treatments
- EQ-5D-5L and HCRU analyses were descriptive, with no comparisons between groups

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 3**)
- Most patients were men and had an ECOG PS of 1 (restricted in strenuous activity but ambulatory)

Table 3 . 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

- The imetelstat-treated group had a similar percentage of patients who experienced any episode of sustained meaningful deterioration than the placebo-treated group (43.2% vs 45.6%)
- There was a trend with the imetelstat-treated group showing slower time to sustained meaningful deterioration in fatigue than the placebo-treated group: 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 percent of imetelstat-treated than placebo-treated patients (36.4% vs 42.1%, 30.5% vs 38.6%, and 28.0% vs 29.8%, respectively), albeit differences were not statistically significant

Sustained meaningful improvement in FACIT-Fatigue Scale score

- 50% of patients in the imetelstat-treated group reported sustained meaningful improvement in fatigue versus 40% of those in the placebo-treated group
- Median time to first sustained meaningful improvement in fatigue was shorter with imetelstat than placebo (**Fig. 2**)
- After 12 weeks, more imetelstat-treated than placebo-treated patients reported improvement in fatigue (**Fig. 2**)

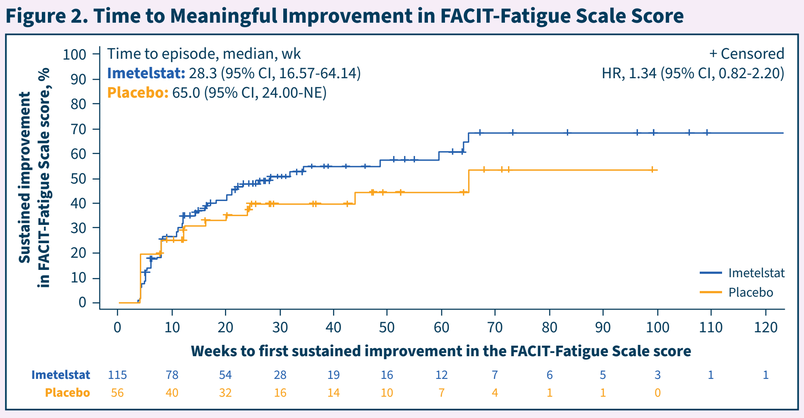
Association of improvement in fatigue and clinical responses

- Most 8-week RBC-TI responders in the imetelstat-treated group consistently had sustained meaningful improvement in FACIT-Fatigue Scale scores through the durable TI intervals (**Fig. 3A**)
- In the imetelstat-treated group, a higher percent of responders had sustained meaningful improvement in fatigue scores consistently vs nonresponders across 8- and 24-week TI (primary and secondary end points); this association was not observed among placebo-treated patients (**Fig. 3B**)

Supplementary analyses

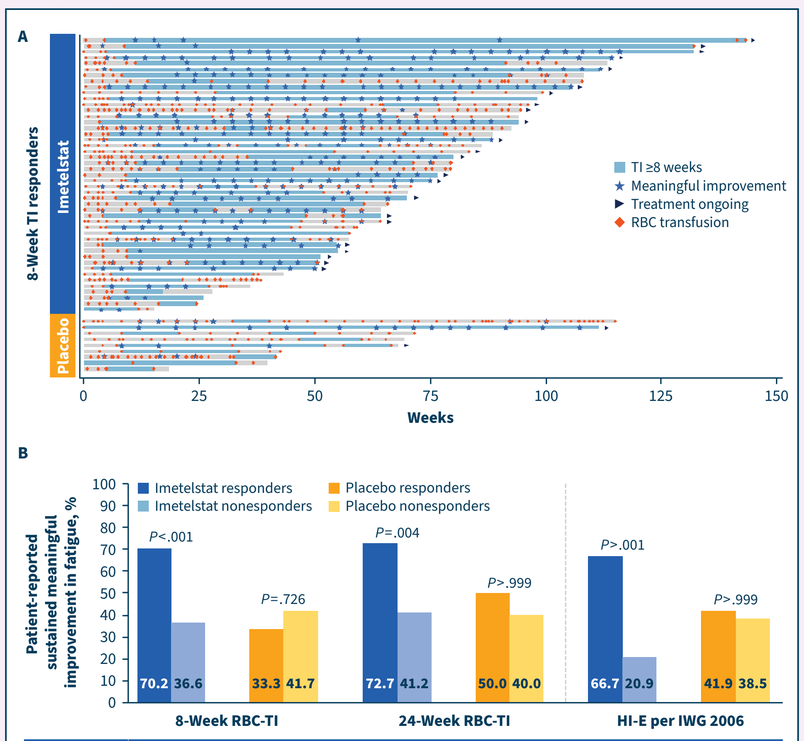
- An RMMM analysis showed an overall change in FACIT-Fatigue Scale score from baseline of 1.08 (by LSM with 95% CI, −0.36 to 2.53) with imetelstat vs −2.48 (by LSM with 95% CI, −4.48 to −0.5) with placebo, with a significant difference between the treatment groups (LSM difference, 3.57 [95% CI, 1.16-5.97]; *P*=.004; **Fig. 4**)
- 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 2. Time to 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.

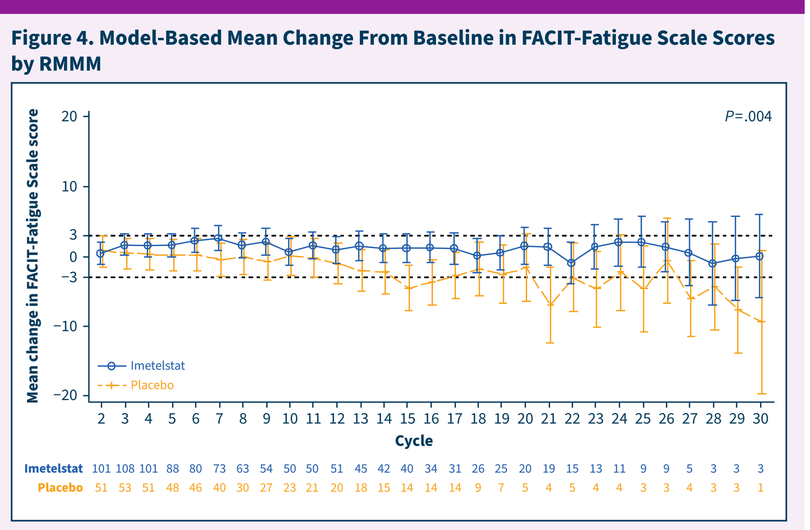
Figure 3. RBC-TI and HI-E Response by Meaningful Improvement in FACIT-Fatigue Scale Score



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.

Figure 4. Model-Based Mean Change From Baseline in FACIT-Fatigue Scale Scores by RMMM

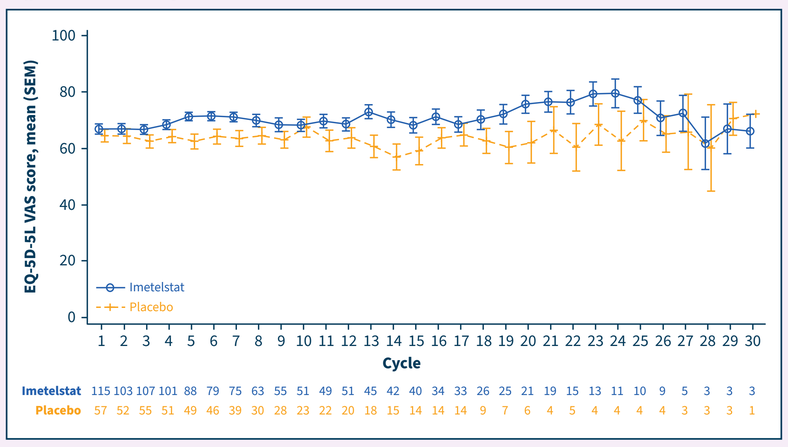


Changes of −3 and +3 in FACIT-Fatigue Scale score from baseline represent meaningful deterioration and improvement, respectively. The plotted LSM estimates for change from baseline in FACIT-Fatigue Scale score and the *P* value between treatment arms are based on an RMMM with the change in FACIT-Fatigue 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.

EQ-5D-5L

- The EQ-5D-5L index score based on UK value set was consistent over time in both groups through cycle 30 (0.75 for imetelstat and 0.69 for placebo)
- The EQ-5D-5L VAS score was stable for each group over time; however, the mean score for the imetelstat-treated group was consistently higher than that of the placebo-treated group up to cycle 30 (70.6 vs 63.8, respectively) (**Fig. 5**)

Figure 5. Mean EQ-5D-5L VAS Scores



HCRU Outcomes

- Overall outpatient health care encounters occurred in both the imetelstat-treated (36.4%) and placebo-treated (40.0%) groups
- There was a trend with the imetelstat-treated group showing shorter length of hospital stay than the placebo-treated group (median, 6 vs 25.5 days, respectively); however, this study was not powered to test for statistical difference in length of hospital stay

Conclusions

- **The IMerge phase 3 trial is the first randomized multinational 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**
- **A numerically higher percentage of the imetelstat-treated patients reported a sustained meaningful improvement in fatigue and experienced a shorter median time to first sustained clinically meaningful improvement in fatigue than placebo-treated patients**
- **After 12 weeks, greater sustained and meaningful improvement in FACIT-Fatigue Scale score was reported with imetelstat compared with placebo**
- **In the imetelstat-treated 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-treated group**
- **EQ-5D-5L VAS mean scores were consistently higher with imetelstat than with placebo, indicating an overall improvement in patients' quality of life**
- **HCRU data collection in a multinational trial setting has limitations. Despite that, this exploratory analysis indicates that patients with LR-MDS and high transfusion burden were not likely to use incrementally more health care resources (outpatient visits or hospital stay) when treated with imetelstat vs placebo. Moreover, imetelstat-treated patients showed a durable TI vs placebo-treated patients (28% vs 3% [*P*<.001] at 24 weeks and 18% vs 2% [*P*=0.002] at 1 year, respectively)[7]**
- **Further studies in real-world clinical practice may demonstrate additional benefit of reducing transfusion burden in heavily pretreated patients with LR-MDS who have a high unmet need**

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DISCLOSURES

The presenter, David Valcárcel, reports consultancy/advisory board for and speaker for/honoraria from Amgen, BMS, GSK, Jazz, Novartis, and Pfizer; speaker for/honoraria from Astellas, Gebro Pharma, and Kyte; consultancy/advisory board for Sanofi, SOBI, and Takeda.

ABBREVIATIONS

ECOG PS, Eastern Cooperative Oncology Group performance status; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; EQ-5D-5L, EuroQol 5-Dimensions 5-Level Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte-colony stimulating factor; Hb, hemoglobin; HCRU, health care resource utilization; 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; NE, not evaluable; R, randomization; RBC, red blood cell; RMMM; repeated measurement mixed model; TI, transfusion independence; VAF, variant allele frequency; VAS, visual analog scale.

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