Patient-Reported Outcomes Among Heavily Pretreated Patients With Lower-Risk Myelodysplastic Syndromes and High Transfusion Burden Treated With Imetelstat in IMerge

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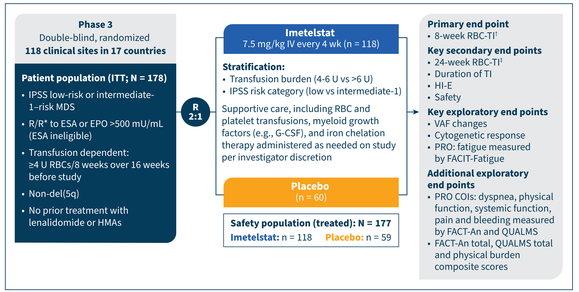
Introduction

- Anemia in patients with LR-MDS can increase the need for RBC transfusions, often leading to transfusion dependency, which is associated with impaired health-related QOL functioning and shortened survival[1-6]
- RBC transfusion dependency is common in patients with MDS, where 50% to 90% need RBC transfusions, and nearly half require ≥1 platelet transfusion[7]
- In the IMerge phase 3 clinical trial (NCT02598661; **Fig. 1**) of patients with RBC-TD non-del(5q) LR-MDS R/R to ESAs or ineligible for ESAs and RBC transfusion burden of ≥4 units, imetelstat, a first-in-class direct and competitive inhibitor of telomerase activity, showed significantly higher RBC-TI for ≥8 weeks, ≥24 weeks, and ≥1 year (40%, 28%, and 18%, respectively) than placebo (15%, 3%, and 2%, respectively)[8]
  - Additionally, the study met the primary PRO hypothesis of no worsening in FACIT-Fatigue and showed a trend to improvement with imetelstat vs placebo
- This poster presents the impact of imetelstat on additional LR-MDS-related PROs in the phase 3 component of IMerge

Figure 1. IMerge 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 HI-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.

Aim

- To assess the impact of imetelstat treatment on additional PRO and COI exploratory analyses identified as relevant for patients with LR-MDS regardless of their transfusion-dependence status

Methods

- A set of PRO concepts relevant to patients with LR-MDS were identified by expert clinicians and from previous research, including a literature review of qualitative research on the experience of 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 endpoints in the study

FACT-An

- A 55-item questionnaire with 47 items scored, 27 constructed from FACT-General at its base, and an additional 13 related specifically to fatigue and 7 to non-fatigue items

QUALMS

- A 38-item questionnaire to assess health-related QOL of patients with MDS

Analyses

- Symptom-specific derived scores for dyspnea, physical function and systemic symptoms, pain, and bleeding (**Table 1**)
- QUALMS total and physical burden (composite) scores (**Table 2**)
- Higher scores indicated improvement

Table 1. PRO Items for FACT-An and QUALMS Symptom-Specific Derived Scores

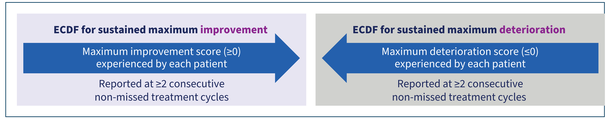
Derived Score	Source Instrument	Scoring Method	Score Range	Items	
Dyspnea	FACT-An & QUALMS	Sum of item scores, with QUALMS item given scale of 0–4, multiplied by 2, divided by items answered (number)	0–8	B1	I have been short of breath
				Q8	Shortness of breath
Physical function	FACT-An	Sum of item scores, multiplied by 3, divided by items answered (number)	0–12	An7	I am able to do my usual activities
				An13	I am motivated to do my usual activities
				An14	I need help to do my usual activities
Systemic symptoms	FACT-An	Sum of item scores, multiplied by 3, divided by items answered (number)	0–12	An10	I get headaches
				GP6	I feel ill
				An9	I feel lightheaded (dizzy)
Pain	FACT-An	Sum of item scores, multiplied by 2, divided by items answered (number)	0–8	GP4	I have pain
				An11	I have pain in my chest
Bleeding	QUALMS	Value of single item	0–4	Q31	Bruising

Table 2. PRO Items for FACT-An and QUALMS Composite Scores

Derived Score	Source Instrument	Scoring Method	Score Range	Items
Total score	FACT-An	Sum:		
		• Physical Well-Being	0–28	GP1-7
		• Functional Well-Being	0–28	GF1-7
		• Anemia	0–80	HI7, HI12, An1-10, B1, An11, An12, BL4, An13-16
		• Social or Family Well-Being	0–28	GS1-7
		• Emotional Well-Being	0–24	GE1-6
Total score	QUALMS	Recode items on a scale 0–100, then average items • Never = 0 • Always = 100	0–100	1–33 (items 13, 17, 29, and 30 reverse scored)
Physical burden	QUALMS-P	Recode items on a scale 0–100 • Never = 0 • Always = 100	0–100	6–11, 13 (reverse scored), 18, 20, 23–26, 33

- RMMM-model analyses were conducted to investigate the impact of imetelstat PRO (dyspnea, physical function and systemic symptoms, pain, bleeding) in the ITT population using symptom-derived scores from questionnaires and composite scores; LSM of change in score estimated in the 2 treatment groups using all available data while on treatment up to cycle 30 was compared
- As no thresholds for meaningful within-patient change were predefined for the symptom-specific derived scores, ECDFs for the maximum change in PRO scores by each patient at 2 consecutive cycles was applied to provide comparable information for various levels of change in these PRO scores (**Fig. 2**)

Figure 2. Maximum Change in PRO Scores by ECDF

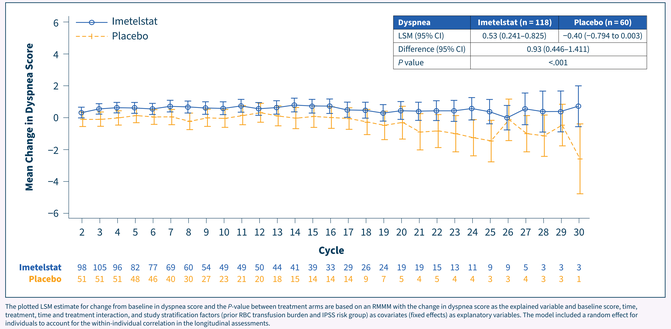


Results

RMMM for the Change From Baseline in Dyspnea Score

- RMMM analysis showed an overall mean change in dyspnea score from baseline with imetelstat vs placebo, with a significant LSM difference between groups (**Fig. 3**)

Figure 3. RMMM for the Change From Baseline in Dyspnea Score

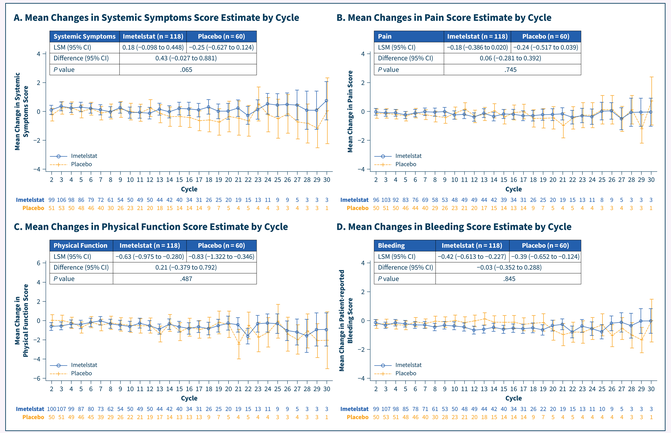


The plotted LSM estimate for change from baseline in dyspnea score and the *P*-value between treatment arms are based on an RMMM with the change in dyspnea score as the explained variable and baseline score, time, treatment, time and treatment interaction, and study stratification factors (prior RBC transfusion burden and IPSS risk group) as 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.

RMMM for the Change From Baseline in COI Scores

- Compared with placebo, patients in the imetelstat group did not experience more deterioration in any of the pre-identified COIs (**Fig. 4**)

Figure 4. RMMM for the Change From Baseline in COI Scores



RMMM for the Change From Baseline in Composite Scores

- FACT-An and QUALMS composite scores were better with imetelstat than with placebo (**Table 3**)

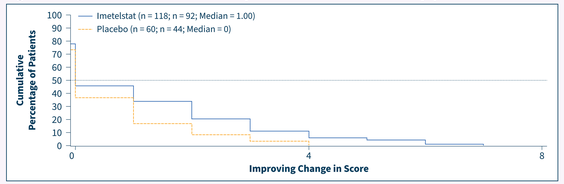
Table 3. RMMM for the Change From Baseline in FACT-An and QUALMS Composite Scores

	Imetelstat (n = 118)	Placebo (n = 60)	*P* value
FACT-An Total			
LSM (95% CI)	−1.60 (−5.001 to 1.803)	−9.72 (−14.428 to −5.012)	
Difference (95% CI)	8.12 (2.436 to 13.805)		.005
QUALMS Total			
LSM (95% CI)	−0.55 (−2.853 to 1.755)	−5.21 (−8.349 to −2.072)	
Difference (95% CI)	4.66 (0.862 to 8.41)		.016
QUALMS Physical Burden			
LSM (95% CI)	−0.41 (−3.181 to 2.355)	−6.75 (−10.528 to −2.981)	
Difference (95% CI)	6.34 (1.771 to 10.913)		.007

ECDF Sustained Maximum Change From Baseline in Dyspnea

- A positive shift in ECDF score towards sustained maximum improvement was observed in the imetelstat group compared with placebo (**Fig. 5**)
  - Regardless of the amount of improvement considered, more patients reached this threshold at 2 consecutive assessments in the imetelstat group than in placebo over the course of the study
  - 33.9% of patients in the imetelstat group had ≥2 points of improvement sustained for ≥2 consecutive cycles compared with 8.3% of patients in the placebo group

Figure 5. ECDF of Sustained Maximum Improvement From Baseline in Dyspnea



Conclusions

- **These IMerge analyses of additional COIs, FACT-An, and QUALMS composite scores are consistent with previous analyses of FACIT-Fatigue, in which patients treated with imetelstat experienced no deterioration in fatigue score, with a trend toward improvement vs those treated with placebo and a shorter median time to first sustained clinically meaningful improvement in fatigue[8]**
- **These data indicate that in addition to reducing transfusion burden, imetelstat shows no worsening vs placebo in dyspnea, physical function, systemic symptoms, pain, or bleeding, five additional core symptoms described in patients with LR-MDS**
- **FACT-An and QUALMS composite score analysis suggests better general health outcomes with imetelstat vs placebo**
- **Further studies in real-world clinical practice may demonstrate additional benefit of reducing RBC transfusion burden in TD patients with LR-MDS who have a high unmet need**

ABBREVIATIONS

CI, confidence interval; COI, concept of interest; ECDF, empirical cumulative distribution function(s); EPO, erythropoietin; ESA, erythropoiesis stimulating agents; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-An, Functional Assessment of Cancer Therapy – Anemia; G-CSF, granulocyte-colony stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; LR-MDS, lower risk myelodysplastic syndromes; LSM, least squares mean; MDS, myelodysplastic syndromes; PRO, patient-reported outcomes; QOL, quality of life; QUALMS, Quality of Life in Myelodysplasia Scale; QUALMS-P, Quality of Life in Myelodysplasia Scale – Physical burden; R, randomization; RBC, red blood cell; RMMM, repeated measurement mixed model; R/R, relapsed/refractory; TD, transfusion dependent; TI, transfusion independence; U, unit; VAF, variant allele frequency.

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DISCLOSURES

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