

Imetelstat improves patient-reported outcomes and quality of life in lower-risk myelodysplastic syndromes: results from the phase III IMerge study

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Supplementary Material

Supplemental Methods

Patient population¹

Adult patients with non-del(5q) MDS were eligible if they had low- or intermediate-1–risk disease per IPSS criteria; were RBC-TD, requiring ≥ 4 units over an 8-week period during the 16 weeks before randomization; had disease that was relapsed to, refractory to, or ineligible (endogenous erythropoietin >500 mU/mL) for ESAs; and had not received prior treatment with lenalidomide or hypomethylating agents.

Overview of patient-reported outcome (PRO) scores

The main PRO objective was to explore the hypothesis that, while patients are on treatment, those treated with imetelstat were not more likely to experience a meaningful deterioration in fatigue than those treated with placebo, regardless of their transfusion-dependence status. PROs were measured utilizing the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale and Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-Fatigue), along with the Quality of Life in Myelodysplasia Scale (QUALMS). All PRO assessments were exploratory endpoints. All FACT-An and FACIT-Fatigue analyses were prespecified and improvements in QUALMS scores along with time to improvement were post hoc analyses.

FACIT-Fatigue

The FACIT-Fatigue subscale is a validated tool that encompasses 13 items and is part of the FACT-An questionnaire; it gauges self-reported tiredness, weakness, and difficulty participating in usual activities due to fatigue during the past 7 days. Higher scores indicate better outcomes (lower fatigue). Sustained meaningful improvement or detriment in fatigue was prespecified defined as a ≥ 3 -point increase or decrease in FACIT-Fatigue score for ≥ 2 consecutive nonmissing assessments (equivalent to 2 consecutive treatment cycles or 8 consecutive weeks). The threshold of 3 points as the determinant of *meaningful* was previously established.^{2,3} Sensitivity analyses were conducted to investigate the impact of this definition, which was shown to be valid. The FACIT-Fatigue score can be obtained by applying the same scoring method as the FACT-An to the 13 items comprising the subscale (see **Online Supplementary Table S2** for the list of items in the FACIT-Fatigue). No imputation or assumption was made for missing FACIT-An assessments. For the calculation of FACIT-Fatigue score, missing items or responses were handled according to the FACT-An scoring guidelines.

QUALMS

The QUALMS instrument comprises a Total score and 2 subscale scores: physical burden (QUALMS-P) and emotional burden (QUALMS-E).⁴ Of a total of 38 items, 33 items are included in the Total score, 14 items contribute to the QUALMS-P score, and 11 items contribute to the QUALMS-E score. Per scoring instructions, responses to each question were transformed to a score ranging from 0 to 100, then summed. A higher score indicates better QOL. Sustained meaningful improvements for the QUALMS Total score, QUALMS-P, and QUALMS-E were defined post hoc as a ≥ 9 -, ≥ 8 -, or ≥ 9 -point increase for ≥ 2 consecutive nonmissing assessments (equivalent to 2 consecutive treatment cycles or 8 consecutive weeks), respectively. These thresholds were selected as previously described in relation to improvement in hemoglobin levels ≥ 1.5 g/dL.⁵ Missing QUALMS assessments were not imputed. Missing items or responses were handled according to the QUALMS scoring guidelines.

FACT-An

The FACT-An is a 55-item instrument, of which 47 items are scored for the Total score (exploratory endpoint). It is constructed from the 27-item FACT-General at its base, with an additional 13 items related specifically to fatigue and 7 non-fatigue items. The FACT-An has 5 subscales, including FACIT-Fatigue and Physical Well-Being (exploratory endpoint). The FACT-An Trial Outcome Index is the sum of Physical Well-Being, Functional Well-Being, and Anemia. Patients rated the scale items as they applied to the past 7 days, on a 5-point scale (0=Not at all, 1=A little bit, 2=Somewhat, 3=Quite a bit, 4=Very much). Total scores for the FACT-An range from 0 to 188, with a higher score indicating better outcomes. Missing FACT-An assessments were not imputed. To score the FACT-An, first the negatively stated items were reverse scored. Scores for subscale items were then summed; the sum was multiplied by the number of items in the subscale and then divided by the number of items that were answered (to account for missing responses).

Supplementary Table S1. Baseline demographic and disease characteristics.

	Imetelstat (n=118)	Placebo (n=57)
Median (range) age, y	71.5 (44-87)	73 (39-85)
Male, n (%)	71 (60)	38 (67)
WHO classification, n (%)		
RS+	73 (62)	37 (65)
RS-	44 (37)	20 (35)
IPSS risk category, n (%)		
Low	80 (68)	37 (65)
Intermediate-1	38 (32)	20 (35)
Transfusion burden per IWG 2018		
HTB	97 (82)	41 (72)
LTB	21 (18)	16 (28.)
Prior RBC transfusion burden, n (%)		
≤6 U/8 weeks	62 (53)	31 (54)
>6 U/8 weeks	56 (48)	26 (46)
sEPO level, n (%)^b		
≤500 mU/mL	87 (74)	35 (61)
>500 mU/mL	26 (22)	20 (35)
Prior ESA, n (%)	108 (92)	50 (88)

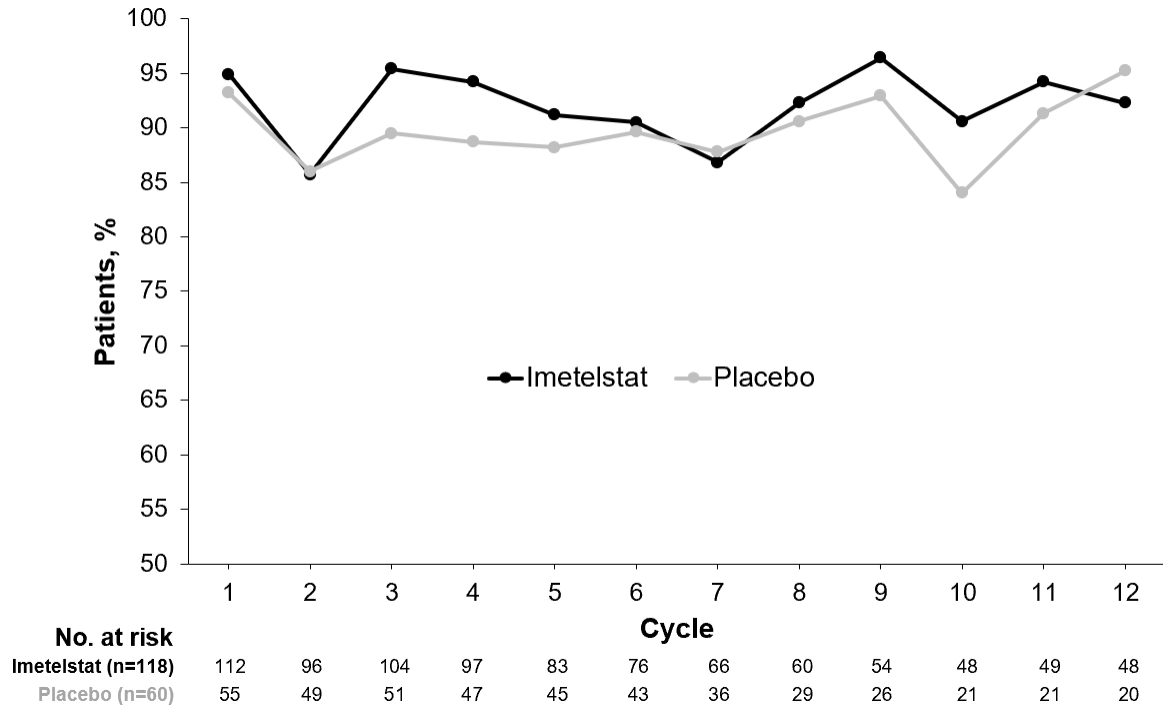
ESA: erythropoiesis-stimulating agent; HTB: high transfusion burden; IPSS: International Prognostic Scoring System; IWG: International Working Group; LTB: low transfusion burden; RBC: red blood cell; RS: ring sideroblast; sEPO: serum erythropoietin; WHO: World Health Organization.

Supplementary Table S2. List of items included in the FACIT-Fatigue subscale.

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
An4	I have trouble finishing things because I am tired
An5	I have energy
An7	I am able to do my usual activities
An12	I am too tired to eat
An8	I need to sleep during the day
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	I have to limit my social activity because I am tired

FACIT: Functional Assessment of Chronic Illness Therapy.

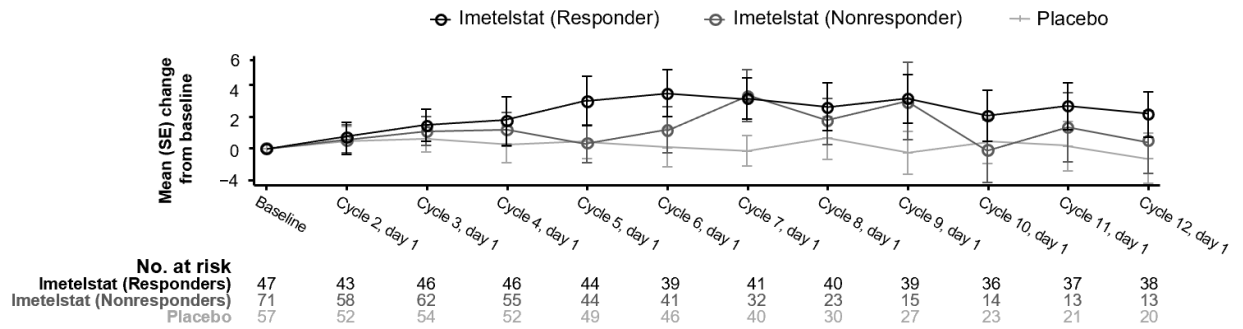
Supplementary Figure S1. PRO completion rates at each cycle (ITT population).



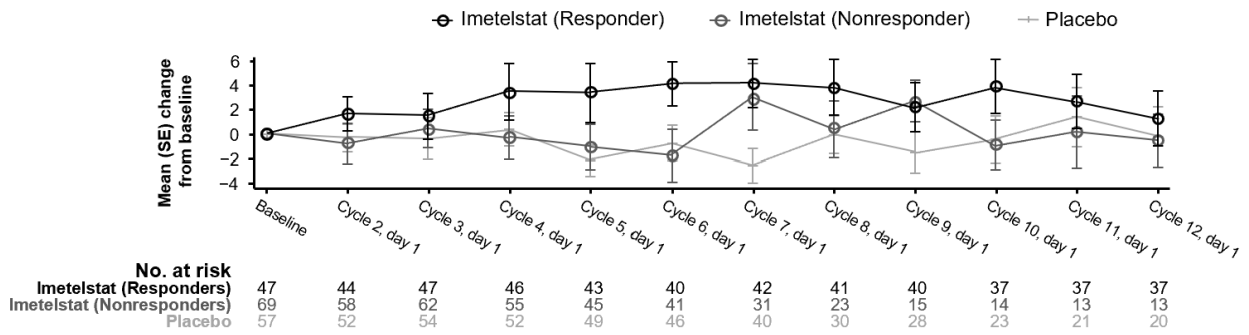
ITT: intention-to-treat; PRO: patient-reported outcome.

Supplementary Figure S2. Change from baseline for FACIT-Fatigue (A) and QUALMS Total score (B) at each cycle (ITT population).

A



B



FACIT: Functional Assessment of Chronic Illness Therapy; ITT: intention-to-treat; QUALMS: Quality of Life in Myelodysplasia Scale; SE: standard error.

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