haematologica
Journal of the Ferrata Storti Foundation

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Received: August 21, 2025.
Accepted: January 12, 2026.

Citation: Mikkael A. Sekeres, Amer M. Zeidan, Valeria Santini, Rami S. Komrokji, Pierre Fenaux, Michael R. Savona, Yazan F. Madanat, David Valcárcel, Antoine Regnault, Kristin Creel, Libo Sun, Ying Wan, Shyamala Navada, Tymara Berry, Faye Feller, Uwe Platzbecker, María Díez Campelo and Esther Natalie Oliva. Imetelstat improves patient-reported outcomes and quality of life in lower-risk myelodysplastic syndromes: results from the phase III IMerge study.
Haematologica. 2026 Jan 22. doi: 10.3324/haematol.2025.288956 [Epub ahead of print]

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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Running head: QOL improvements in LR-MDS with imetelstat

ClinicalTrials.gov identifier: NCT02598661

Acknowledgements: 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. The authors also thank Nishan Sengupta, PhD, previously of Geron Corporation, for his critical review of the content.

Disclosures: M.A.S. reports consultancy fees from Bristol Myers Squibb, Schrödinger, Menarini Group, and Kurome, research funding from Bristol Myers Squibb, and travel expenses from Daichi Sankyo; owns stock options in Kurome. **A.M.Z.** reports research funding from, AbbVie, ADC Therapeutics, Aprea, Astex, AstraZeneca, Boehringer-Ingelheim, Cardiff Oncology, Celgene/BMS, Genentech, Geron Corporation, Novartis, Pfizer, Shattuck Labs, Takeda; has served on the Board of Directors, advisory committees, or clinical trial committees for AbbVie, Agios, ALX Oncology, Amgen, Aprea, Astellas, Astex, Beyond Spring, BioCryst, Celgene/BMS, Chiesi, Daiichi Sankyo, Epizyme, Genentech, Gilead, Ionis, Janssen, Jazz, Kura, Mendus, Notable Labs, Novartis, Orum, Otsuka, Pfizer, Regeneron, Seattle Genetics, Syndax, Takeda, and Taiho Oncology. **V.S.** has served on advisory boards for AbbVie, Ascentage, Bristol Myers Squibb, CTI BioPharma, Geron, Gilead, Novartis, Servier, and Syros Pharmaceuticals. **R.S.K.** reports consultancy/speaker bureau fees from AbbVie, Agios Pharmaceutical, Celgene/BMS, Geron, Jazz Pharmaceuticals, and Novartis. **P.F.** reports honoraria from AbbVie and BMS, and research funding from AbbVie, Astex, BMS, Novartis, and Servier. **M.R.S.** reports consultancy fees from AbbVie, BMS, CTI, Forma, Geron, GSK, Rigel, Taiho Oncology, and Treadwell; grants or contracts with Astex and Incyte; patents/royalties from Boehringer and Empath Biosciences; holds equity at Empath Biosciences, Karyopharm, and Ryvu; and has served in the Board of Directors/advisory committees for MDSF Foundation BOD. **Y.F.M.** reports consultancy fees from Blueprint Medicines, BMS, Geron, and Kura Oncology; travel expenses from Blueprint Medicines, MD Education, and MorphoSys; has served in advisory boards for

Blueprint Medicines, Cogent Biosciences, Geron, MorphoSys, Novartis, Rigel Pharmaceuticals, Sierra Oncology, Sobi, Stemline Therapeutics, and Taiho Oncology. **D.V.** reports honoraria/consultancy/speaker bureau fees with AbbVie, Agios, Amgen, Astellas, Brystol Myers Squibb, Gebro, Grifols, Janssen, Jazz Pharmaceuticals, Kite/Gilead, MSD, Novartis, Pfizer, Sanofi, Sobi, and Takeda; travel expenses from AbbVie, Agios, Amgen, Bristol Myers Squibb, Grifols, Jazz Pharmaceuticals, Novartis, Sanofi, and Sobi; research funding from Bristol Myers Squibb; has served in Board of Directors/advisory committees for Amgen, Bristol Myers Squibb, Grifols, Jazz Pharmaceuticals, Novartis, Servier, and Sobi. **A.R.** and **K.C.** report current employment at Modus Outcomes, a Division of Thread, and consultancy for Geron. **L.S.**, **T.B.**, and **F.F.** report current employment at Geron. **Y.W.** and **S.N.** report current employment at/hold stock options from Geron. **U.P.** reports consultancy fees/honoraria from AbbVie, Bristol Myers Squibb, Curis, Geron, Janssen, and Novartis; institutional funding from Amgen, Bristol Myers Squibb, Janssen, Merck, and Novartis. **M.D.-C.** reports consultancy fees/honoraria from Agios, Blueprint Medicines, BMS/Celgene, GSK, and Novartis; travel expenses from Gilead and Otsuka; has served in Board of Directors or advisory committees of Agios, BMS/Celgene, Curis, GSK, Hemavant, Keros Therapeutics, Novartis, Otsuka, and Syros Pharmaceuticals. **E.N.O.** reports consultancy/speaker bureau fees from Alexion, BeiGene, BMS, Daiichi Sankyo, Janssen, Novartis, Pfizer, Ryvu, Sanofi, Sobi, and Syros Pharmaceuticals; patents and royalties from Amgen, BMS, Halia Therapeutics, and Ryvu.

Funding source: This study was funded by Geron Corporation. All authors contributed to and approved the manuscript; writing and editorial support were provided by Meredith Rogers, MS, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation.

Contributions

Mikkael A. Sekeres contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Amer M. Zeidan contributed to data

acquisition, data interpretation, and manuscript writing and revisions. Valeria Santini contributed to data acquisition, data interpretation, and manuscript writing and revisions. Rami S. Komrokji contributed to data acquisition, data interpretation, and manuscript writing and revisions. Pierre Fenaux contributed to data acquisition, data interpretation, and manuscript writing and revisions. Michael R. Savona contributed to data acquisition, data interpretation, and manuscript writing and revisions. Yazan F. Madanat contributed to data acquisition, data interpretation, and manuscript writing and revisions. David Valcárcel contributed to data acquisition, data interpretation, and manuscript writing and revisions. Antoine Regnault contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Kristin Creel contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Libo Sun contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Ying Wan contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Shyamala Navada contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Tymara Berry contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Faye Feller contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. Uwe Platzbecker contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. María Díez-Campelo contributed to data acquisition, data interpretation, and manuscript writing and revisions. Esther Natalie Oliva contributed to data acquisition, data interpretation, and manuscript writing and revisions.

Data sharing statement

De-identified study data will be made available upon request to qualified researchers, to the extent permitted by applicable laws and participant informed consent. Approval of such requests

is at the discretion of Geron Corporation 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.

Abstract

Red blood cell (RBC) transfusions for anemia associated with lower-risk myelodysplastic syndromes/neoplasms (LR-MDS) often contribute to reduced quality of life (QOL). Thus, reduction in RBC transfusion dependency (TD) is a primary therapeutic goal. Imetelstat is a first-in-class, competitive telomerase inhibitor approved to treat certain adult patients with LR-MDS with RBC-TD anemia who have not responded to, have lost response to, or are ineligible for erythropoiesis-stimulating agents. In the phase III IMerge study (NCT02598661), treatment with imetelstat resulted in clinically meaningful, statistically significant increases in the primary endpoint of ≥8-week RBC transfusion independence (TI) *versus* placebo. Because patients with LR-MDS experience detrimental effects on numerous facets of QOL (physical, emotional, social, and functional), these exploratory analyses assessed patient-reported outcomes using the Functional Assessment of Chronic Illness Therapy-Fatigue, Quality of Life in Myelodysplasia Scale, and Functional Assessment of Cancer Therapy-Anemia questionnaires as part of the phase III IMerge study. Nominal *P* values were reported. Fewer imetelstat-treated patients experienced deterioration in fatigue and more imetelstat-treated patients experienced sustained improvement in fatigue and QOL *versus* placebo. In the imetelstat group, 8-week, 24-week, and 1-year RBC-TI responders had sustained improvements in predefined significance thresholds *versus* nonresponders for fatigue (70%, 73%, and 88%, respectively, *vs*. 37%, 41%, and 44%, respectively; $P<0.001$, $P=0.004$, and $P=0.002$) and QOL across different measures of response (43-53% *vs*. 21-30%; $P\leq0.0126$). These results suggest that treatment with imetelstat may be associated with improvement in QOL beyond fatigue while sustaining RBC-TI in patients with LR-MDS with RBC-TD anemia.

KEY WORDS: imetelstat, myelodysplastic syndromes, fatigue, quality of life, transfusions

Introduction

Myelodysplastic syndromes/neoplasms (MDS) are a collection of clonal myeloid malignancies with a heterogenous spectrum of clinical presentation and differential risk of progressing to acute myeloid leukemia (AML). As per the Revised and Molecular International Prognostic Scoring Systems (IPSS-R and IPSS-M, respectively), overall survival (OS) and risk for progression to AML are based on morphologic characteristics, laboratory variables, and cytogenetic and molecular markers, which are combined to determine a risk score.[1,2]

Patients with lower-risk MDS (LR-MDS) have a low probability of transforming to AML and have better prognosis with longer OS compared with patients with higher-risk MDS.[2] These characteristics have helped define risk-specific treatment priorities. In patients with anemia associated with LR-MDS, reducing red blood cell (RBC) transfusion dependence (TD) and improving quality of life (QOL) are often primary goals of therapy.

Compared with the general population, patients with MDS report significantly worse QOL, including physical and emotional aspects, with an impact on social and role functioning.[3,4] Fatigue is one of the most common and debilitating symptoms associated with MDS and is associated with impaired QOL.[5,6] Patients also experience detrimental effects on physical and emotional functioning, such as mobility issues, pain/discomfort, anxiety/depression, and distress related to dyspnea or bleeding risk, that negatively impact QOL.[3,4]

Anemia is a primary driver of fatigue in MDS.[6-8] To ameliorate anemia, most patients with MDS will require RBC transfusions over the course of their illness, and about 40-50% of patients with LR-MDS will become RBC-TD.[9-11] The need for frequent RBC transfusions and related complications (e.g., iron overload), which increase over time, have been associated with worse outcomes in patients with MDS, including impaired OS and QOL.[3,10,12-15]

Imetelstat, a first-in-class, direct, and competitive inhibitor of telomerase activity, was recently approved for certain adult patients with LR-MDS with RBC-TD anemia who have not responded to, have lost response to, or are ineligible for erythropoiesis-stimulating agents (ESAs).[16,17] Approval was based on results of the randomized, double-blind, placebo-controlled, phase III IMerge study (NCT02598661).[18] In IMerge, treatment with imetelstat resulted in clinically meaningful and statistically significant increases in the primary endpoint of ≥8-week RBC transfusion independence (TI), which was achieved by 40% of imetelstat-treated patients *versus* 15% in placebo recipients (95% confidence interval [CI] of difference: 9.9, 36.9; *P*=0.0008). The key secondary endpoint of ≥24-week RBC-TI was achieved by 28% and 3% in the imetelstat and placebo groups, respectively (95% CI of difference: 12.6, 34.2; *P*=0.0001).

Treatment with imetelstat was associated with improvement in fatigue as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale;[19] 50% of imetelstat-treated patients (*vs*. 40% placebo) experienced a sustained, meaningful improvement in FACIT-Fatigue scores. Greater proportions of imetelstat responders *versus* nonresponders experienced sustained improvements in FACIT-Fatigue across measures of response (≥8-week RBC-TI, ≥24-week RBC-TI, and hematologic improvement-erythroid as per International Working Group 2006 criteria [exploratory endpoints]).[20] Using patient-reported outcomes (PROs) as indicators of change in QOL provides relevant information regarding the effects of a given intervention from the patient's own perspective that other QOL instruments cannot measure. Thus, the present analyses were conducted to extend previous reports focusing on FACIT-Fatigue measures by ascertaining the effects of imetelstat on PROs in patients with LR-MDS across subgroups and using different PRO assessment tools to capture the impact and symptoms of disease and treatment as part of the phase III IMerge study.

Methods

Study overview

IMerge is a randomized, double-blind, placebo-controlled, multicenter, phase III study. A full description of the methods has been published, and details regarding the patient population are provided in the **Supplemental Methods**.[18] Patients were randomized 2:1 to imetelstat 7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo administered intravenously every 4 weeks. The study was conducted in accordance with institutional guidelines and the laws of the applicable authorities; an Institutional Review Board or ethics committee at each site approved the protocol. All patients or their legal representative provided written informed consent. The data cutoff date for both the primary analysis and PRO analysis was October 13, 2022.

Outcomes

PROs were assessed using the validated Quality of Life in Myelodysplasia Scale (QUALMS)[21] and Functional Assessment of Cancer Therapy-Anemia (FACT-An) with FACIT-Fatigue[19] subscale questionnaires at baseline, at each cycle while on treatment, and during post-treatment follow-up. FACIT-Fatigue was prespecified and the main exploratory PRO endpoint for all intention-to-treat (ITT) patients and across subgroups. Improvements in QUALMS scores were post hoc analyses. An overview of these scales are presented in the **Supplemental Methods**.

Subgroup analyses by baseline disease-related characteristics were performed for a proportion of patients in each treatment group for FACIT‑Fatigue and QUALMS assessments. Associations of RBC-TI clinical endpoints with the proportion of patients reporting an episode of sustained meaningful improvement in FACIT‑Fatigue or QUALMS score were also evaluated. In addition, time to first meaningful improvement in FACIT-Fatigue and QUALMS was assessed; this analysis was previously published for FACIT-Fatigue and will not be presented here.[20]

Statistical analyses

Continuous variables were described by the number of available data points, mean, standard deviation, standard error of the mean, median, first and third quartiles, extreme values (minimum and maximum values), and number of missing values. Categorical variables were described by the frequency and percentage of each response choice, with missing data being included in the calculation of the percentage. Missing items within an available PRO instrument were handled according to the guidelines defined by the authors of the instruments, and missing PRO assessments were not imputed. Time to first meaningful improvement was examined using Kaplan-Meier estimate. Data analyses were performed using SAS® software, version 9.4 (SAS Institute, Cary, NC). All PRO analyses were not controlled for type I error and are considered exploratory, with nominal *P* values reported.

A prespecified repeated measurement mixed model (RMMM) was conducted to summarize the change in FACIT-Fatigue, QUALMS, and FACT-An scores from baseline over time, using all available longitudinal data and adjusting for stratification factors. The RMMM included the change in scores 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 and is based on all data up to cycle 30 (i.e., up to the cycle at which data for both treatment arms are available). The overall effects of treatment with imetelstat on the FACIT-Fatigue, QUALMS, and FACT-An scores were evaluated from the model comparing the least squares (LS) mean of change in scores estimated in the 2 treatment groups using all available data up to cycle 30.

Results

PRO analyses were performed on data from 175 patients (imetelstat, n=118; placebo, n=57). Three placebo recipients from the ITT population were not included in the PRO analyses

because they did not have PRO data at baseline. With the exception of the 3 patients from the ITT population who were not included in the PRO analyses, follow-up and patient disposition for the PRO analyses corresponded with the ITT population published previously.[18]

Baseline characteristics were similar across treatment arms and similar to the overall ITT population (***Online Supplementary Table S1***).[18] Most patients were ≥65 years of age (77% in the imetelstat arm and 86% in the placebo arm), had MDS with ring sideroblasts (RS; 62% in the imetelstat arm and 65% in the placebo arm), and had high transfusion burden per International Working Group 2018 criteria (82% in the imetelstat arm and 72% in the placebo arm). PRO completion rates (percent of patients with valid PRO data for whom PRO data were expected) for the ITT population were generally comparable between treatment arms through cycle 12 and were based on the number of patients who completed all PRO instruments (FACIT-Fatigue, QUALMS, FACT-An, EuroQol-EQ-5D-5L, and Patient Global Impression of Change) through that time point (***Online Supplementary Figure S1***). The number of patients continuing past cycle 8 was limited.

PROs for imetelstat- versus placebo-treated patients

In this exploratory analysis, meaningful deterioration in fatigue (defined as a decrease in the FACIT-Fatigue score of ≥3 points for ≥2 consecutive cycles or 8 consecutive weeks) was experienced by 43.2% of patients in the imetelstat group, compared with 45.6% in the placebo group (*P*=0.770). Additional analyses of fatigue, as measured by the FACIT-Fatigue instrument, were explored in detail in previous publications.[18,20] A higher percentage of patients treated with imetelstat (50%) experienced any episode of sustained, meaningful improvement in fatigue (defined as an increase in the FACIT-Fatigue score of ≥3 points for ≥2 consecutive cycles or 8 consecutive weeks) compared with placebo (40%, *P*=0.228) (**Figure 1**).[18,20] Among imetelstat-treated patients, 30%, 37%, and 39% experienced meaningful improvements in QUALMS Total, QUALMS-P, and QUALMS-E scores at ≥2 consecutive visits (2 consecutive cycles or 8

consecutive weeks), respectively, compared with 25%, 26%, and 39%, of placebo recipients (*P*=0.4814, 0.1824, and 0.9608, respectively) (**Figure 1**).

Although differences were not statistically significant for all subgroups except the intermediate-1 IPSS risk group, more patients treated with imetelstat than placebo reported sustained improvement in FACIT-Fatigue regardless of RS status (RS+, 55% *vs*. 46%; RS−, 43% *vs*. 30%), baseline transfusion burden (≤6 U/8 weeks, 44% *vs*. 36%; >6 U/8 weeks, 57% *vs*. 46%), or other baseline characteristics (**Figure 2A**). Similarly, improvements in QUALMS across domains were also observed in more patients treated with imetelstat *versus* placebo recipients for almost all subgroups (*P*>0.05 for all; **Figure 2B**).

RMMMs showed overall mean change from baseline in FACIT-Fatigue significantly improved for imetelstat *versus* placebo (LS mean difference: 3.57 [95% CI: 1.16, 5.97]; *P*=0.004) (**Table 1**). Imetelstat-treated patients demonstrated a consistent mean improvement from baseline in FACIT-Fatigue scores at each cycle, while placebo recipients showed minimal change (**Figure 3A**). For QUALMS Total scores, LS mean differences were significantly improved for the imetelstat group *versus* placebo (4.66 [95% CI: 0.86, 8.46]; *P*=0.016) (**Table 1**). The imetelstat group showed a trend toward improvement in mean change from baseline across QUALMS Total and subscale scores at each cycle, while the placebo group showed minimal change (**Figure 3B**). FACT-An Total (LS mean difference: 8.12 [95% CI: 2.44, 13.81]; *P*=0.005) and Trial Outcome Index (LS mean difference: 6.65 [95% CI: 1.99, 11.32]; *P*=0.005) scores over time were consistently higher, although not significantly different, for the imetelstat group *versus* placebo (**Table 1**); both treatment groups exhibited similar FACT-An Physical Burden scores over time (**Figure 3C**).

Median times to first sustained improvement in QUALMS scores are shown in **Figure 4**. For QUALMS Total, the median time to first sustained improvement was not estimable for either

the imetelstat or placebo group (**Figure 4A**). For QUALMS-P and QUALMS-E, shorter times to first sustained improvement were observed for imetelstat (92 weeks and 61 weeks, respectively) compared with placebo (not estimable and 44 weeks, respectively) (**Figure 4B and 4C**).

PROs for imetelstat responders versus nonresponders

Significant improvement in fatigue was seen in more imetelstat responders *versus* nonresponders across measures of response (**Figure 5A**). The proportion of patients with improvements in FACIT-Fatigue at ≥2 consecutive visits was significantly higher among those who achieved ≥8-week (70% *vs*. 37%; *P*<0.001), ≥24-week (73% *vs*. 41%; *P*=0.004), or ≥1-year (88% *vs*. 44%; *P*=0.002) RBC-TI with imetelstat *versus* nonresponders. Similar results were seen for imetelstat-treated patients who achieved hematologic improvement-erythroid, hemoglobin rise ≥1.5 g/dL, and transfusion reduction ≥4 U/week. Analyses of changes in FACIT-Fatigue and QUALMS Total scores over time show that fatigue and QOL consistently improved over time in imetelstat responders, while scores fluctuated in imetelstat nonresponders and placebo recipients, suggesting that effects were drug related and not placebo artifacts (***Online Supplementary Figure S2***).

The proportion of patients with improvements in QUALMS Total, QUALMS-P, and QUALMS-E at ≥2 consecutive visits was significantly higher among those who achieved the primary endpoint of ≥8-week RBC-TI with imetelstat *versus* nonresponders (43% *vs*. 21% [*P*=0.0126]; 53% *vs*. 27% [*P*=0.004]; and 53% *vs*. 30% [*P*=0.0100], respectively) (**Figure 5B**). Similar trends were observed for the other measures of response, although statistical significance was not reached for QUALMS Total ≥24-week RBC-TI responders and QUALMS-E ≥1-year RBC-TI responders.

Discussion

Because patients with LR-MDS and RBC-TD anemia have worse OS and impaired QOL compared with patients who are not RBC-TD,[3,4] one goal of therapy is to ameliorate transfusion needs and improve how patients feel. It is a challenge to demonstrate improved QOL in randomized trials because anemia and its attendant QOL sequelae are addressed by effective therapies in both treatment arms and by continued R BC transfusions in control arms in which patients receive placebo.

These data from the pivotal IMerge study suggest that treatment with imetelstat may improve patient-reported fatigue and QOL, regardless of RS status or baseline transfusion burden, in patients with LR-MDS and RBC-TD anemia. Numerically fewer imetelstat-treated patients experienced deterioration in fatigue, and more imetelstat-treated patients experienced sustained improvement in fatigue and QOL as measured by FACIT-Fatigue, QUALMS Total, QUALMS-P, and FACT-An scores compared with placebo across baseline disease characteristics. Effects of treatment with imetelstat on fatigue and QOL were durable across 12 cycles of treatment. It is reassuring that multiple instruments corroborated QOL improvement across disease subtypes with the same therapeutic intervention, suggesting that the conclusion that QOL was improved by treatment with imetelstat is reliable. Further, improvements in QOL, including fatigue, for the imetelstat arm compared with the control arm are more notable given that imetelstat had to overcome the effect of an intervention in the control arm (continued RBC transfusions) that can ameliorate symptoms such as fatigue [22], raising the plausibility that QOL improvements would have been even more substantial for imetelstat-treated patients.

Further analyses demonstrated an association between clinical endpoints and improvement in QOL. In the imetelstat group, statistically significant improvements in sustained meaningful fatigue were seen in more patients who responded to imetelstat *versus* those who did not across different measures of response, including achievement of ≥8-week and ≥1-year RBC-TI. This further validates the use of these instruments to assess improvements in how patients felt

during treatment with imetelstat in the IMerge study. The association between fatigue and achievement of ≥8-week, ≥1-year RBC-TI, or hematologic improvement-erythroid in placebo recipients was previously presented.[18,20] The numbers of placebo recipients who achieved a response and who exhibited improvement in fatigue or QUALMS (data not shown) were too small to draw any conclusions. It should also be noted that thrombocytopenia was reported as an adverse event in the primary analysis of IMerge, but there was no increased risk of bleeding,[18] and an analysis of the QUALMS Bleeding subscore demonstrated no differences *versus* placebo (data not shown).

Maximizing QOL is a key consideration in the development of any pharmacotherapeutic intervention when the pursuit of a cure is not the primary goal of treatment, such as with LR-MDS. Furthermore, numerous studies in patients with cancer have found that many would choose not to undergo treatment if it would compromise their QOL.[23] In the case of LR-MDS, patients may require therapy for 10 years or longer; therefore, it is imperative that the treatment of choice does not impact QOL more than the associated symptoms of the disease.[24,25]

The original hypothesis for this PRO analysis was that, while on treatment, patients treated with imetelstat were not more likely to experience meaningful deterioration in fatigue than those treated with placebo, regardless of RBC transfusion status (mainstay of treatment for anemia and thereby fatigue).[6-8] The analyses of the FACIT-Fatigue support this hypothesis. Although the correlation between higher hemoglobin levels and better QOL has been previously reported,[3] fatigue frequently persists despite increases in hemoglobin, and receiving RBC transfusions is in and of itself a significant burden because of the disruption to a patient's routine and the potential for adverse effects, such as fatigue, dizziness, and pain.[26,27] Furthermore, in both observational studies and clinical trials, patients who were RBC-TD reported lower QOL across domains compared with those who were RBC-TI.[3] Thus, treatments that can reduce a patient's reliance on transfusions are advantageous. In the IMerge study, treatment with

imetelstat resulted in significantly more patients achieving RBC-TI than placebo, and more imetelstat-treated patients had sustained RBC-TI than placebo recipients.[18] Importantly, the significant clinical responses to imetelstat did not compromise how patients felt while receiving treatment. While the proportion of PRO improvements were consistently higher in imetelstat-treated patients, especially in clinical responders, *versus* placebo recipients, due to the supportive care received in clinical trials (e.g., RBC transfusions), the limitation of the PRO thresholds, the design of the PRO questionnaires, and the placebo effect or randomness, it is natural to have some level of PRO improvements also observed in placebo or in imetelstat nonresponders. It should also be noted that patients with MDS are generally older with frailties and/or comorbidities that may affect QOL and could complicate assessment by instruments, such as QUALMS, that include aspects of general functioning.[28] In a study of patients being assessed for suspected MDS, 33% were considered vulnerable, defined as older and at risk for health deterioration; these patients reported worse health-related QOL compared with patients not classified as vulnerable.

Robust improvements in QOL have not been observed for other treatments commonly used in LR-MDS. In the phase III MEDALIST study in patients who had MDS with RS, no difference in QOL measures (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items [EORTC QLQ-C30; secondary endpoint] and the Quality of Life Assessment in MDS questionnaire [QOL-E; exploratory endpoint]) between groups or from baseline was observed for luspatercept *versus* best supportive care.[29] In the phase III MDS-005 study of lenalidomide *versus* placebo in RBC-TD patients with non-del(5q) LR-MDS ineligible for or refractory to ESAs, no differences between treatment arms were observed at week 12 in change from baseline in EORTC QLQ-C30 scores (secondary endpoint), but at week 24, lenalidomide was associated with less fatigue and better emotional functioning *versus* placebo.[30] An online survey of patients with MDS in the United States who had filled a prescription for oral decitabine/cedazuridine asked about the effect of treatment on their QOL

using a free-text question, and about 30% mentioned side effects when describing the negative impact of therapy on their QOL and 85% indicated they experienced an improvement in QOL after switching from intravenous/subcutaneous hypomethylating agents to oral decitabine/cedazuridine.[31]

This study is limited by the exploratory nature of these analyses and the small sample sizes in some subgroups. In addition, the number of patients with data over time should be viewed within the context of an oncology study, as noted in the statistical design[32,33]; reductions in number of patients with available PRO data over time could be the result of many factors, including study discontinuation due to disease progression. While no firm rules exist regarding the amount of missing data that is acceptable in a clinical trial, as missing data increases to 30% to 50%, the ability to draw conclusions from the data becomes restricted.[34] Thus, following these guidelines, in the present study, any data after cycle 8 should be interpreted with caution since at cycle 9, <50% of patients from each treatment group contributed data. Regarding the QUALMS results, as no strong anchor for meaningful within-patient change analyses is available in the pivotal IMerge study, the definitions of meaningful change thresholds from previously published literature were used.[35] These thresholds were in relation to improvement in hemoglobin levels ≥1.5 g/dL as previously described.[35] Strong correlations of improvements in QUALMS scores per these thresholds with clinical RBC-TI responses were also observed in this study. Nevertheless, we feel that the thresholds chosen were conservative, as other studies have defined clinical significance using lower values.[21,36,37] Although other validated PRO measurement tools were available (eg, EuroQol-EQ-l5D-5L), it was decided to present the results for the FACIT-Fatigue, QUALMS, and FACT-An instruments because they are specific to the clinical signs and symptoms of LR-MDS.

It is becoming increasingly recognized that QOL should be an endpoint in clinical trials since patients' perception of their well-being often supersedes more quantitative clinical measures,

such as hemoglobin levels.[38] Herein, we show that treatment with imetelstat may be associated with improved QOL across multiple domains in patients with LR-MDS and RBC-TD anemia. Although fatigue is the primary symptom reported by patients with MDS,[6] many other symptoms, such as pain/discomfort, mobility issues, and anxiety/depression, contribute to poor QOL in patients with MDS, for which additional instruments beyond FACIT-Fatigue, such as QUALMS and FACT-An, provide more comprehensive insight into the true impact of a given treatment.[4] Along with the clinical efficacy data presented for the pivotal phase III IMerge study,[18] these data suggest that treatment with imetelstat may not only offer the advantage of sustained RBC-TI benefit, but may also be associated with improved QOL beyond fatigue in patients with LR-MDS and RBC-TD anemia.

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Table 1. LS mean estimates in change in FACIT-Fatigue, QUALMS Total, QUALMS-P, and QUALMS-E scores from baseline by RMMM (ITT population).

Score	Imetelstat LS mean change from baseline (95% CI) (n=118)	Placebo LS mean change from baseline (95% CI) (n=60)	LS mean (95% CI) difference	Nominal *P* value
FACIT-Fatigue	1.08 (−0.36, 2.53)	−2.48 (−4.48, −0.49)	3.57 (1.16, 5.97)	0.004
QUALMS Total	−0.55 (−2.85, 1.76)	−5.21 (−8.35, −2.07)	4.66 (0.86, 8.46)	0.016
QUALMS-P	−0.41 (−3.18, 2.36)	−6.75 (−10.53, −2.98)	6.34 (1.77, 10.91)	0.007
QUALMS-E	−0.16 (−3.12, 2.80)	−4.52 (−8.56, −0.48)	4.36 (−0.53, 9.25)	0.080
FACT-An Total	−1.6 (−5.00, 1.80)	−9.72 (−14.43, −5.01)	8.12 (2.44, 13.81)	0.005
FACT-An Physical Well-Being	−0.43 (−1.10, 0.24)	−1.16 (−2.08, −0.24)	0.73 (−0.38, 1.84)	0.197
FACT-An Trial Outcome Index	−0.18 (−2.97, 2.61)	−6.83 (−10.70, −2.97)	6.65 (1.99, 11.32)	0.005

CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; FACT-An: Functional Assessment of Cancer Therapy-Anemia; ITT: intention-to-treat; LS: least squares; QUALMS: Quality of Life in Myelodysplasia Scale; QUALMS-E: Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P: Quality of Life in Myelodysplasia Scale – physical burden; RMMM: repeated measurement mixed model.

Figure legends

Figure 1. Sustained meaningful improvement[a] in FACIT-Fatigue, QUALMS Total, QUALMS-P, and QUALMS-E scores (PRO population).

[a]Defined for fatigue as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments, for QUALMS as ≥9-, ≥8-, or ≥9-point increase for ≥2 consecutive assessments in QUALMS Total, QUALMS-P, and QUALMS-E scores, respectively.[35] FACIT: Functional Assessment of Chronic Illness Therapy; n/N: number with event/number in population; PRO: patient-reported outcome; QUALMS: Quality of Life in Myelodysplasia Scale; QUALMS-E: Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P: Quality of Life in Myelodysplasia Scale – physical burden.

Figure 2. Sustained meaningful improvement[a] in different QOL measures by subgroup: FACIT-Fatigue (A) and QUALMS Total, QUALMS-P, and QUALMS-E (B) scores (PRO population).

[a]Defined for fatigue as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments, for QUALMS as ≥9-, ≥8-, or ≥9-point increase for ≥2 consecutive assessments in QUALMS Total, QUALMS-P, and QUALMS-E scores, respectively.[35] EPO: erythropoietin; FACIT: Functional Assessment of Chronic Illness Therapy; IPSS: International Prognostic Scoring System; HTB: high transfusion burden; IWG: International Working Group; LTB: low transfusion burden; n/N: number with event/number in population; PRO: patient-reported outcome; QOL: quality of life; QUALMS: Quality of Life in Myelodysplasia Scale; QUALMS-E: Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P: Quality of Life in Myelodysplasia Scale – physical burden; RS: ring sideroblast.

Figure 3. Change from baseline in different measures of QOL by cycle: FACIT-Fatigue (A) QUALMS Total, QUALMS-P, and QUALMS-E (B) and FACT-An (C) scores (ITT population).

C: cycle; D: day; FACIT: Functional Assessment of Chronic Illness Therapy; FACT-An: Functional Assessment of Cancer Therapy-Anemia; ITT: intention-to-treat; PRO: patient-reported outcome; QOL: quality of life; QUALMS: Quality of Life in Myelodysplasia Scale; QUALMS-E: Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P: Quality of Life in Myelodysplasia Scale – physical burden; SE: standard error.

Figure 4. Time to first sustained improvement[a] QUALMS scores: QUALMS Total (A), QUALMS-P (B), and QUALMS-E (C; PRO population).

[a]Sustained meaningful improvement was defined for QUALMS as ≥9-, ≥8-, or ≥9-point increase for ≥2 consecutive assessments in QUALMS Total, QUALMS-P, and QUALMS-E scores, respectively.[35] NE: not estimable; PRO: patient-reported outcome; QUALMS: Quality of Life in Myelodysplasia Scale; QUALMS-E: Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P: Quality of Life in Myelodysplasia Scale – physical burden.

Figure 5. Improvements[a] in QOL measures by response to imetelstat: FACIT-Fatigue[b] (A) and QUALMS Total,[c] QUALMS-P,[c] and QUALMS-E[c] scores (B) (PRO population).

[a]Sustained meaningful improvement was defined for fatigue as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments, for QUALMS as ≥9-, ≥8-, or ≥9-point increase for ≥2 consecutive assessments in QUALMS Total, QUALMS-P, and QUALMS-E scores, respectively,.[35] [b]*P* values by Fisher exact test. [c]*P* values by chi-square test. FACIT: Functional Assessment of Chronic Illness Therapy; HI-E: hematologic improvement-erythroid; n/N: number with event/number in population; PRO: patient-reported outcome; QOL: quality of life; QUALMS: Quality of Life in Myelodysplasia Scale; QUALMS-E: Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P: Quality of Life in Myelodysplasia Scale – physical burden; RBC: red blood cell; TI: transfusion independence.

Figure 1.

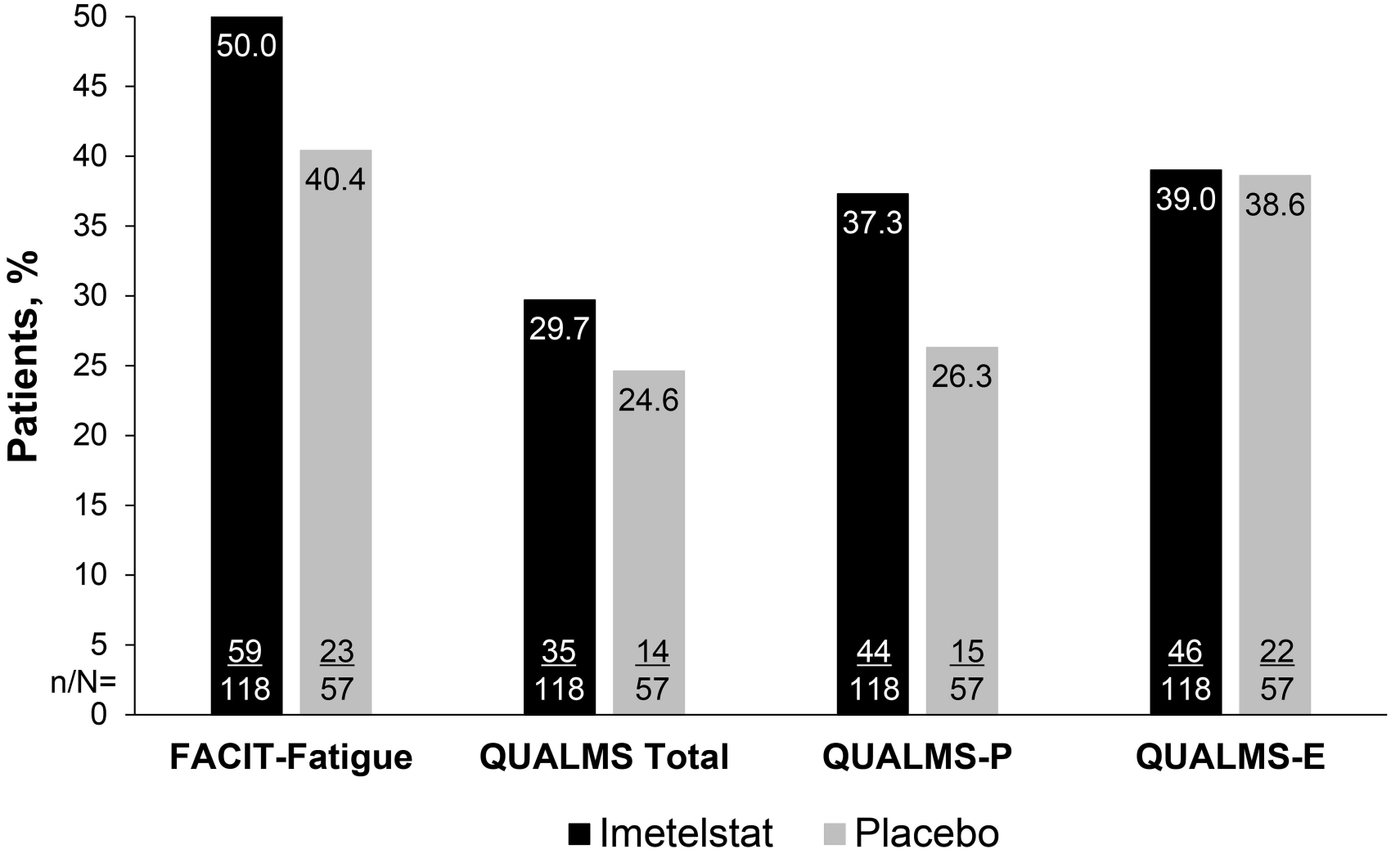

Patients, %
50
45
40
35
30
25
20
15
10
5
0
n/N=
50.0
40.4
29.7
24.6
37.3
26.3
39.0
38.6
59/118
23/57
35/118
14/57
44/118
15/57
46/118
22/57
FACIT-Fatigue
QUALMS Total
QUALMS-P
QUALMS-E
Imetelstat
Placebo

Figure 2

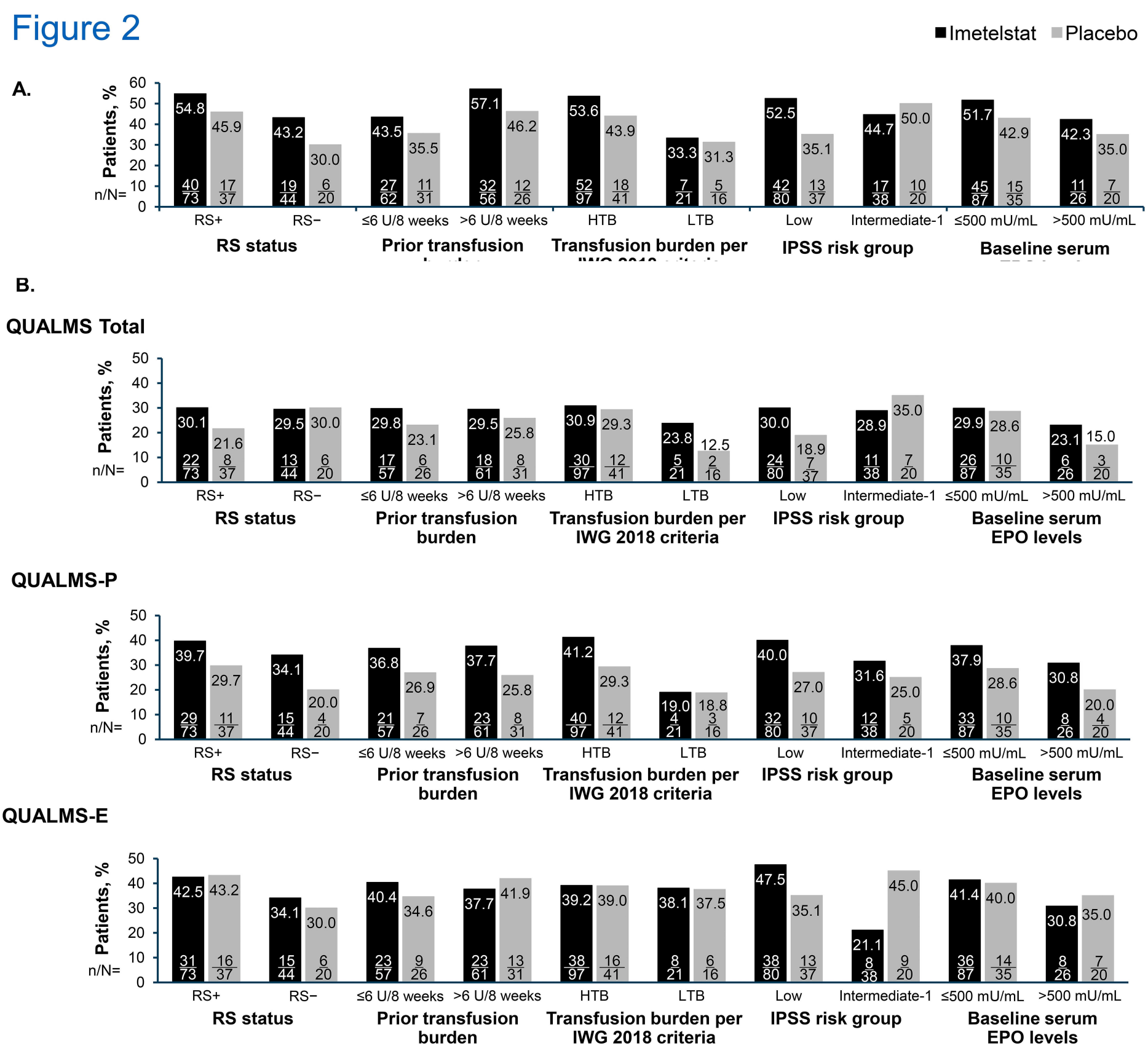

Imetelstat
Placebo
A.
Patients, %
n/N=
RS+
RS−
≤6 U/8 weeks
>6 U/8 weeks
HTB
LTB
Low
Intermediate-1
≤500 mU/mL
>500 mU/mL
RS status
Prior transfusion
Transfusion burden per
IPSS risk group
Baseline serum
B.
QUALMS Total
Prior transfusion burden
Transfusion burden per IWG 2018 criteria
Baseline serum EPO levels
QUALMS-P
QUALMS-E

Figure 3.

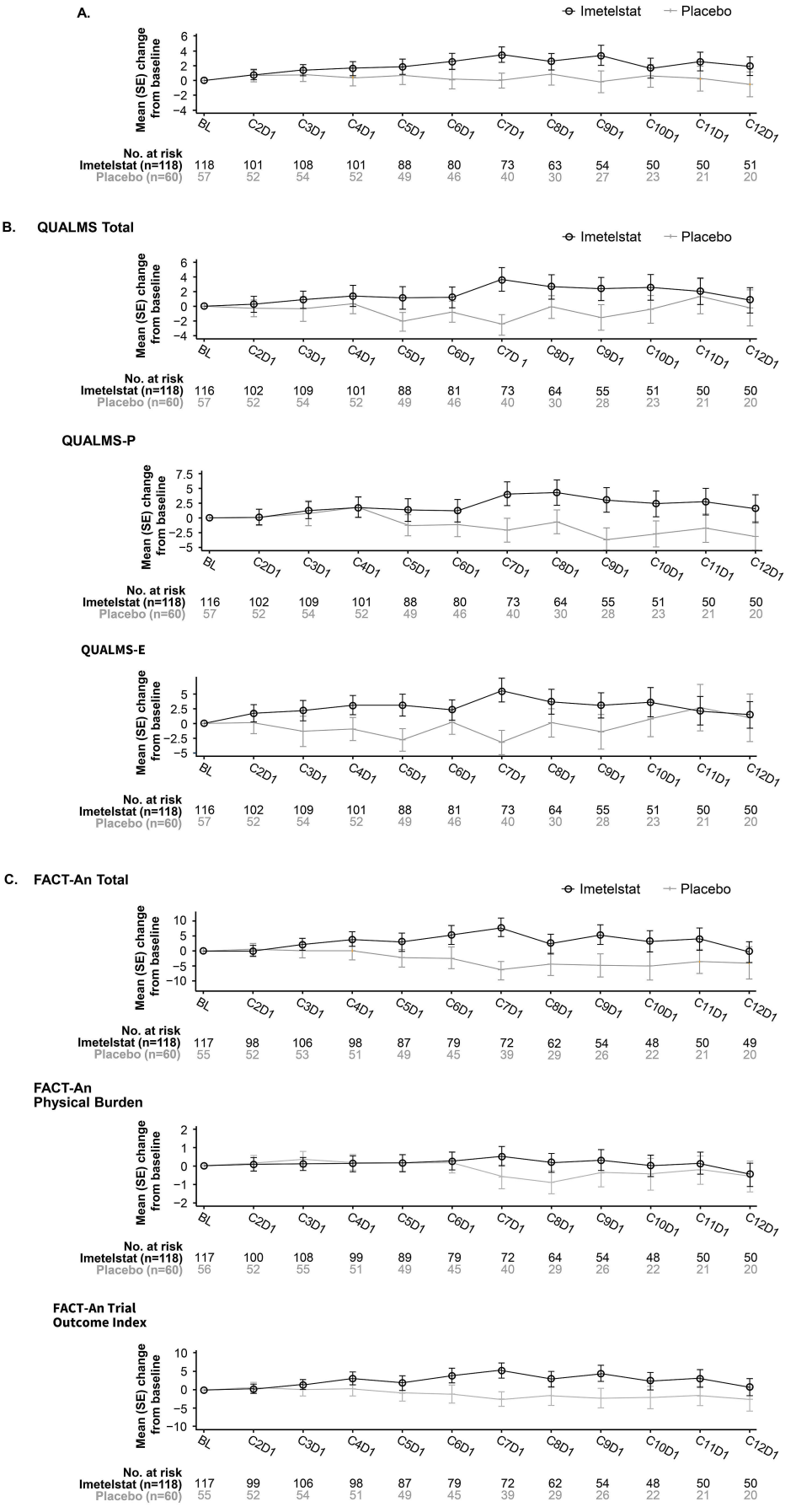

A.
Imetelstat
Placebo
Mean (SE) change from baseline
BL C2D1 C3D1 C4D1 C5D1 C6D1 C7D1 C8D1 C9D1 C10D1 C11D1 C12D1
No. at risk
Imetelstat (n=118) 118 101 108 101 88 80 73 63 54 50 50 51
Placebo (n=60) 57 52 54 52 49 46 40 30 27 23 21 20
B. QUALMS Total
Imetelstat
Placebo
Mean (SE) change from baseline
BL C2D1 C3D1 C4D1 C5D1 C6D1 C7D 1 C8D1 C9D1 C10D1 C11D1 C12D1
No. at risk
Imetelstat (n=118) 116 102 109 101 88 81 73 64 55 51 50 50
Placebo (n=60) 57 52 54 52 49 46 40 30 28 23 21 20
QUALMS-P
Mean (SE) change from baseline
BL C2D1 C3D1 C4D1 C5D1 C6D1 C7D1 C8D1 C9D1 C10D1 C11D1 C12D1
No. at risk
Imetelstat (n=118) 116 102 109 101 88 80 73 64 55 51 50 50
Placebo (n=60) 57 52 54 52 49 46 40 30 28 23 21 20
QUALMS-E
Mean (SE) change from baseline
BL C2D1 C3D1 C4D1 C5D1 C6D1 C7D1 C8D1 C9D1 C10D1 C11D1 C12D1
No. at risk
Imetelstat (n=118) 116 102 109 101 88 81 73 64 55 51 50 50
Placebo (n=60) 57 52 54 52 49 46 40 30 28 23 21 20
C. FACT-An Total
Imetelstat
Placebo
Mean (SE) change from baseline
BL C2D1 C3D1 C4D1 C5D1 C6D1 C7D1 C8D1 C9D1 C10D1 C11D1 C12D1
No. at risk
Imetelstat (n=118) 117 98 106 98 87 79 72 62 54 48 50 49
Placebo (n=60) 55 52 53 51 49 45 39 29 26 22 21 20
FACT-An Physical Burden
Mean (SE) change from baseline
BL C2D1 C3D1 C4D1 C5D1 C6D1 C7D1 C8D1 C9D1 C10D1 C11D1 C12D1
No. at risk
Imetelstat (n=118) 117 100 108 99 89 79 72 64 54 48 50 50
Placebo (n=60) 56 52 55 51 49 45 40 29 26 22 21 20
FACT-An Trial Outcome Index
Mean (SE) change from baseline
BL C2D1 C3D1 C4D1 C5D1 C6D1 C7D1 C8D1 C9D1 C10D1 C11D1 C12D1
No. at risk
Imetelstat (n=118) 117 99 106 98 87 79 72 62 54 48 50 50
Placebo (n=60) 55 52 54 51 49 45 39 29 26 22 21 20

Figure 4.

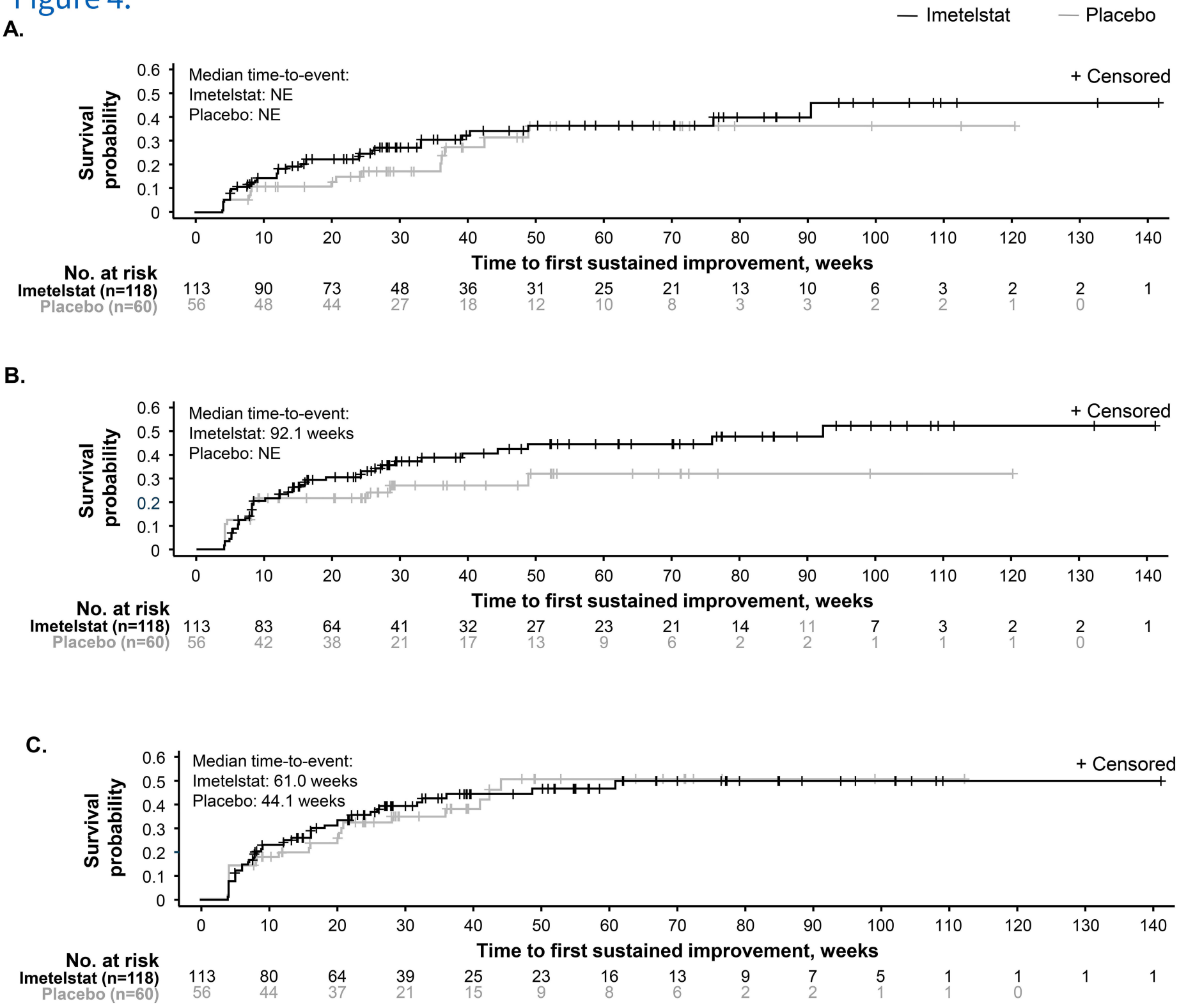
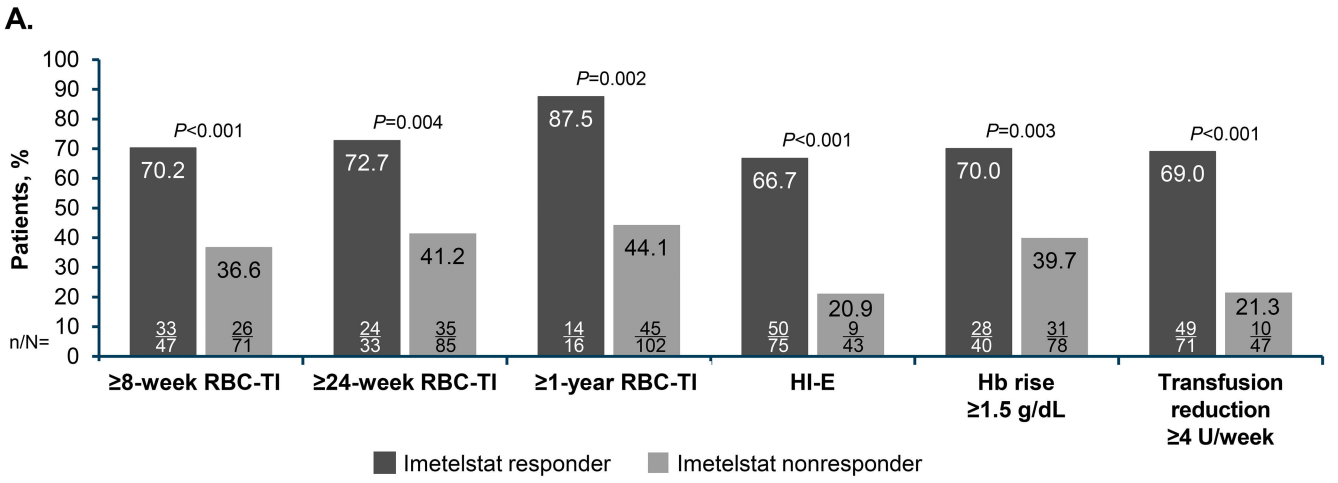
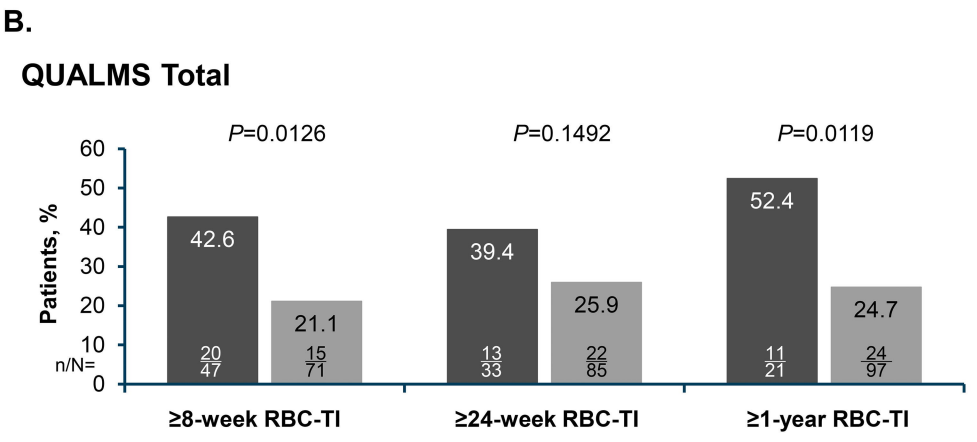
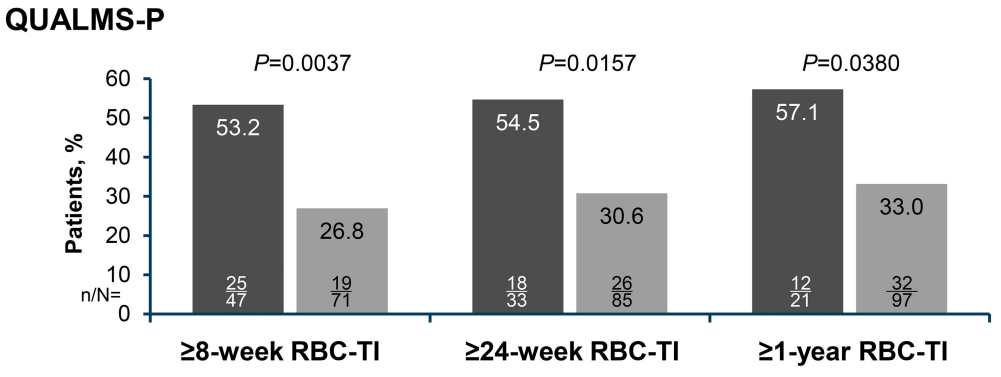
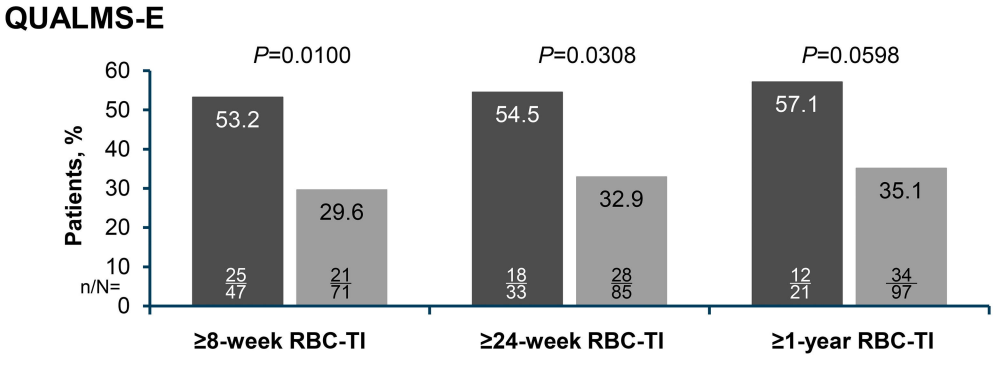

A.
Imetelstat
Placebo
Median time-to-event:
Imetelstat: NE
Placebo: NE
+ Censored
Survival probability
0.6
0.5
0.4
0.3
0.2
0.1
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Time to first sustained improvement, weeks
No. at risk
Imetelstat (n=118) 113 90 73 48 36 31 25 21 13 10 6 3 2 2 1
Placebo (n=60) 56 48 44 27 18 12 10 8 3 3 2 2 1 0
B.
Median time-to-event:
Imetelstat: 92.1 weeks
Placebo: NE
+ Censored
Survival probability
0.6
0.5
0.4
0.3
0.2
0.1
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Time to first sustained improvement, weeks
No. at risk
Imetelstat (n=118) 113 83 64 41 32 27 23 21 14 11 7 3 2 2 1
Placebo (n=60) 56 42 38 21 17 13 9 6 2 2 1 1 1 0
C.
Median time-to-event:
Imetelstat: 61.0 weeks
Placebo: 44.1 weeks
+ Censored
Survival probability
0.6
0.5
0.4
0.3
0.2
0.1
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Time to first sustained improvement, weeks
No. at risk
Imetelstat (n=118) 113 80 64 39 25 23 16 13 9 7 5 1 1 1 1
Placebo (n=60) 56 44 37 21 15 9 8 6 2 2 1 1 0

Figure 5


A.
Patients, %
n/N=
P<0.001
70.2
33/47
36.6
26/71
P=0.004
72.7
24/33
41.2
35/85
P=0.002
87.5
14/16
44.1
45/102
P<0.001
66.7
50/75
20.9
9/43
P=0.003
70.0
28/40
39.7
31/78
P<0.001
69.0
49/71
21.3
10/47
≥8-week RBC-TI
≥24-week RBC-TI
≥1-year RBC-TI
HI-E
Hb rise ≥1.5 g/dL
Transfusion reduction ≥4 U/week
Imetelstat responder
Imetelstat nonresponder


B.
QUALMS Total
Patients, %
n/N=
P=0.0126
42.6
20/47
21.1
15/71
P=0.1492
39.4
13/33
25.9
22/85
P=0.0119
52.4
11/21
24.7
24/97
≥8-week RBC-TI
≥24-week RBC-TI
≥1-year RBC-TI


QUALMS-P
Patients, %
n/N=
P=0.0037
53.2
25/47
26.8
19/71
P=0.0157
54.5
18/33
30.6
26/85
P=0.0380
57.1
12/21
33.0
32/97
≥8-week RBC-TI
≥24-week RBC-TI
≥1-year RBC-TI


QUALMS-E
Patients, %
n/N=
P=0.0100
53.2
25/47
29.6
21/71
P=0.0308
54.5
18/33
32.9
28/85
P=0.0598
57.1
12/21
35.1
34/97
≥8-week RBC-TI
≥24-week RBC-TI
≥1-year RBC-TI

Supplementary Material

Supplemental Methods

Patient population[1]

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)

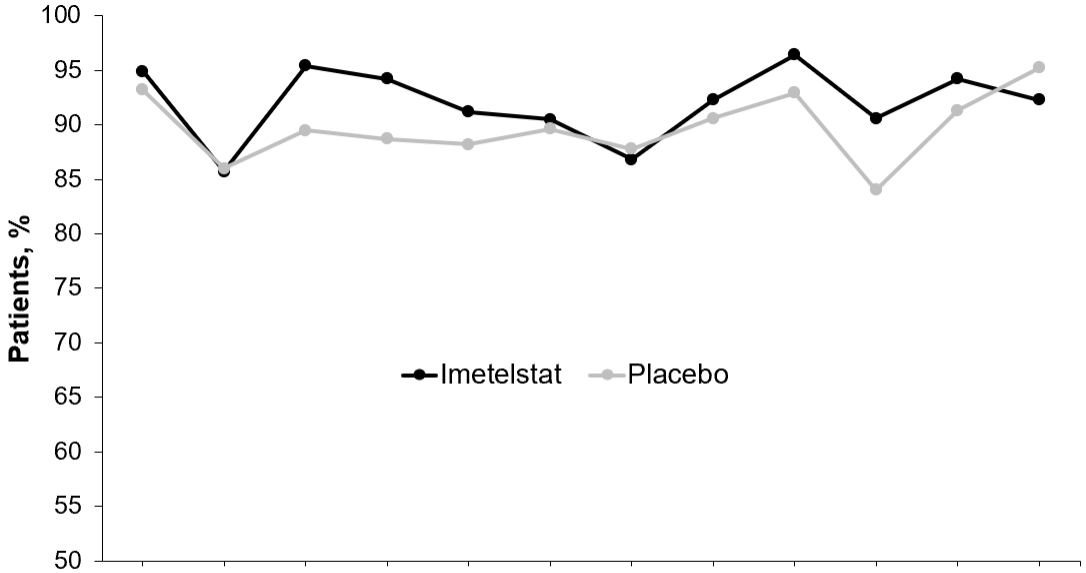
ESA: erythropoiesis-stimulating agent; HTB: high transfusion burden; IPSS: International Prognostic Scoring System; IWG: International Working Group; LTB: low transfusion burden; RBC: red blood cell; RS: ring sideroblast; sEPO: serum erythropoietin; WHO: World Health Organization.

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).

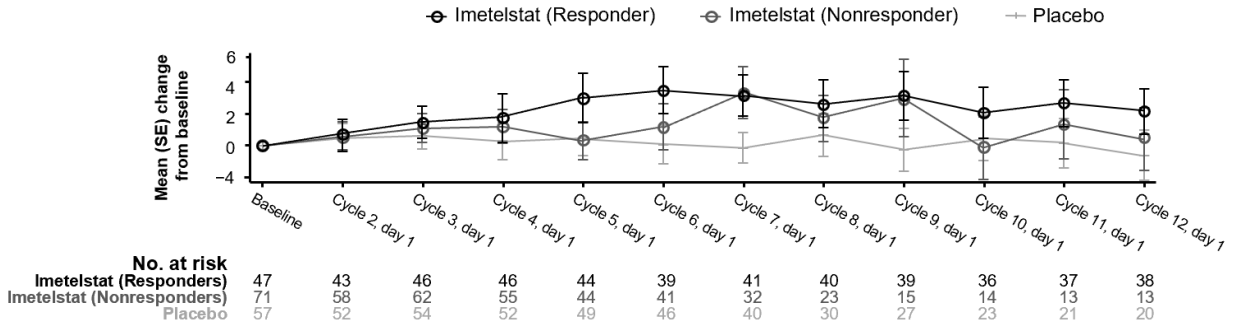


No. at risk												
Imetelstat (n=118)	112	96	104	97	83	76	66	60	54	48	49	48
Placebo (n=60)	55	49	51	47	45	43	36	29	26	21	21	20

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

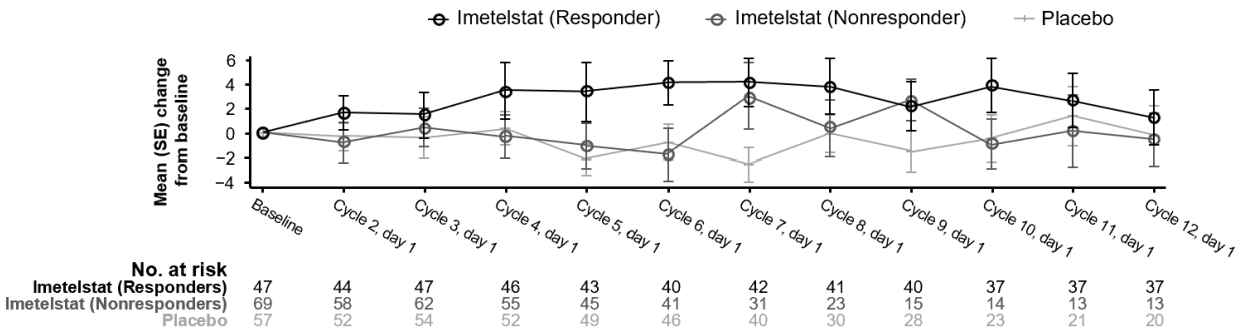
Supplementary Figure S2. Change from baseline for FACIT-Fatigue (A) and QUALMS Total score (B) at each cycle (ITT population).

A



No. at risk												
Imetelstat (Responders)	47	43	46	46	44	39	41	40	39	36	37	38
Imetelstat (Nonresponders)	71	58	62	55	44	41	32	23	15	14	13	13
Placebo	57	52	54	52	49	46	40	30	27	23	21	20

B



No. at risk												
Imetelstat (Responders)	47	44	47	46	43	40	42	41	40	37	37	37
Imetelstat (Nonresponders)	69	58	62	55	45	41	31	23	15	14	13	13
Placebo	57	52	54	52	49	46	40	30	28	23	21	20

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

References

1. Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;403(10423):249-260.
2. Nordin Å, Taft C, Lundgren-Nilsson Å, Dencker A. Minimal important differences for fatigue patient reported outcome measures-a systematic review. BMC Med Res Methodol. 2016;16:62.
3. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage. 2002;24(6):547-561.
4. Abel GA, Efficace F, Buckstein RJ, et al. Prospective international validation of the Quality of Life in Myelodysplasia Scale (QUALMS). Haematologica. 2016;101(6):781-788.
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