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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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 (clinicaltrials.gov identifier: 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 levels and more imetelstat-treated patients experienced sustained improvement in fatigue levels 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* non-responders 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.

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 (ESA).[16,17] Approval was based on results of the randomized, double-blind, placebo-controlled, phase III IMerge study (clinicaltrials.gov identifier: 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* non-responders 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 (PRO) 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 PRO 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 *Online Supplementary Methods*.[18] Patients were randomized 2:1 to 7.1 mg/kg imetelstat active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo administered intravenously every four 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

Patient-reported outcomes 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 was 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 *Online Supplementary 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, USA). 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

Patient-reported outcome 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.

Patient-reported outcomes for imetelstat-treated *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, have been explored in detail in previous publications.[18,20] A higher percentage of patients treated with imetelstat (50%) experienced any episode of

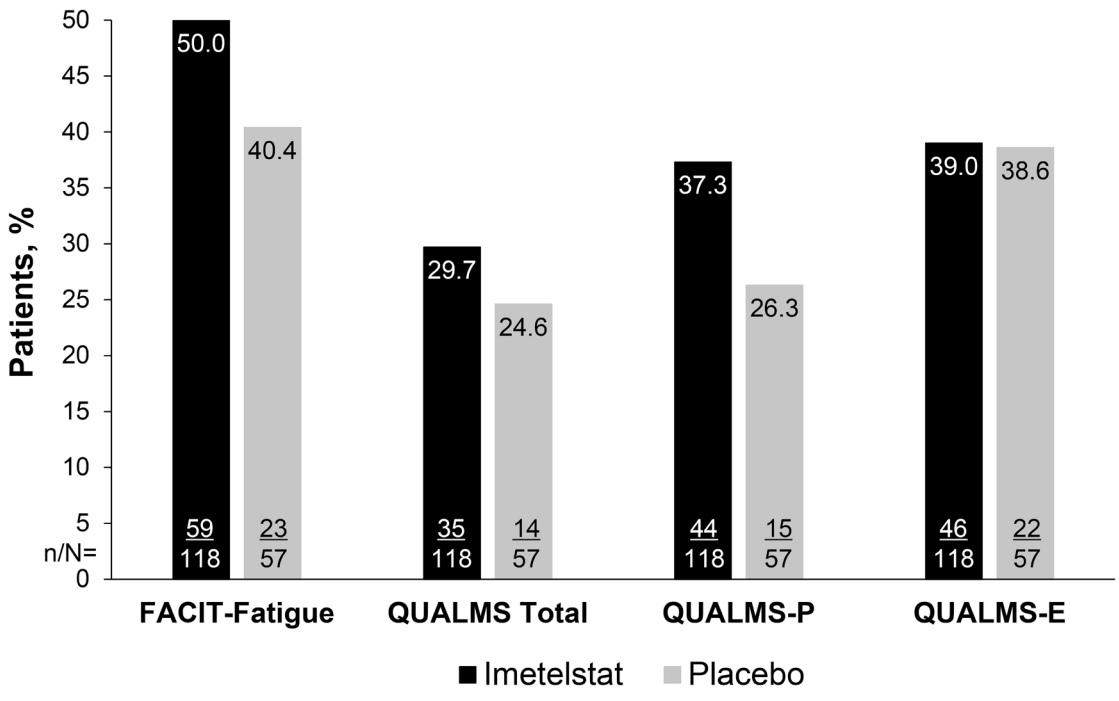

Figure 1. Sustained meaningful improvement[a] in FACIT-Fatigue, QUALMS Total, QUALMS-P, and QUALMS-E scores (patient-reported outcomes population). [a]Defined for fatigue as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments, for QUALMS as ≥9-, ≥8-, or ≥9-point increase for ≥2 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.

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

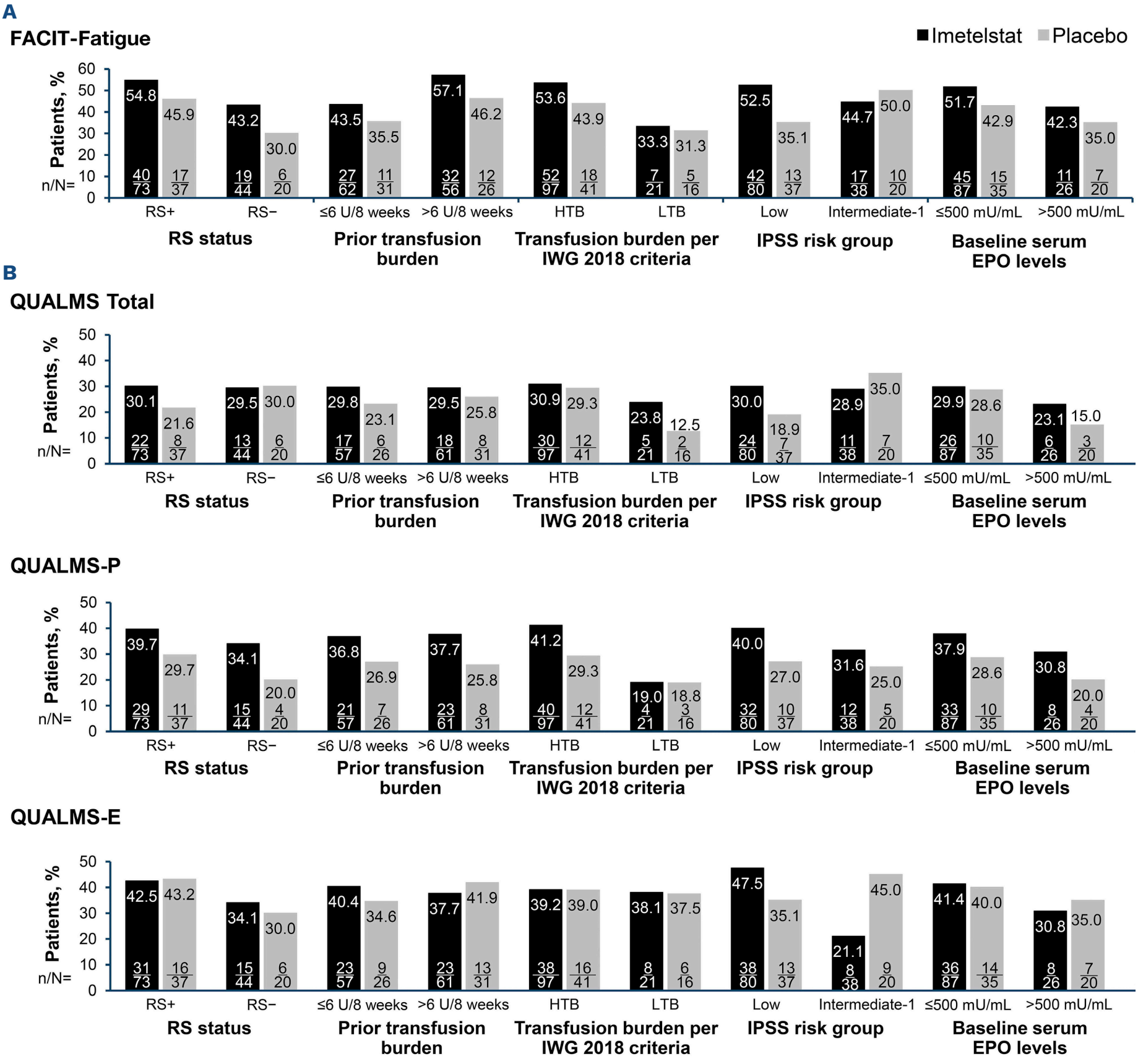

Figure 2. Sustained meaningful improvement[a] in different quality of life measures by subgroup (patient-reported outcomes population). FACIT-Fatigue (A) and QUALMS Total, QUALMS-P, and QUALMS-E (B) scores. [a]Defined for fatigue as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments, 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; 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.

(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).

Repeated measurement mixed models 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, C).

Patient-reported outcomes for imetelstat responders *versus* non-responders

Significant improvement in fatigue was seen in more imetelstat responders *versus* non-responders 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* non-responders. 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 non-responders 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* non-responders (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 or QUALMS-E ≥1-year RBC-TI responders.

Discussion

Because patients with LR-MDS and RBC-TD anemia have

Table 1. Least squares mean estimates in change in FACIT-Fatigue, QUALMS Total, QUALMS-P, QUALMS-E, FACT-An Total, FACT-An Physical Well-Being, and FACT-An Trial Outcome Index scores from baseline by repeated measurement mixed model (intention-to-treat 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; LS: least squares; N: number; 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.

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 RBC 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

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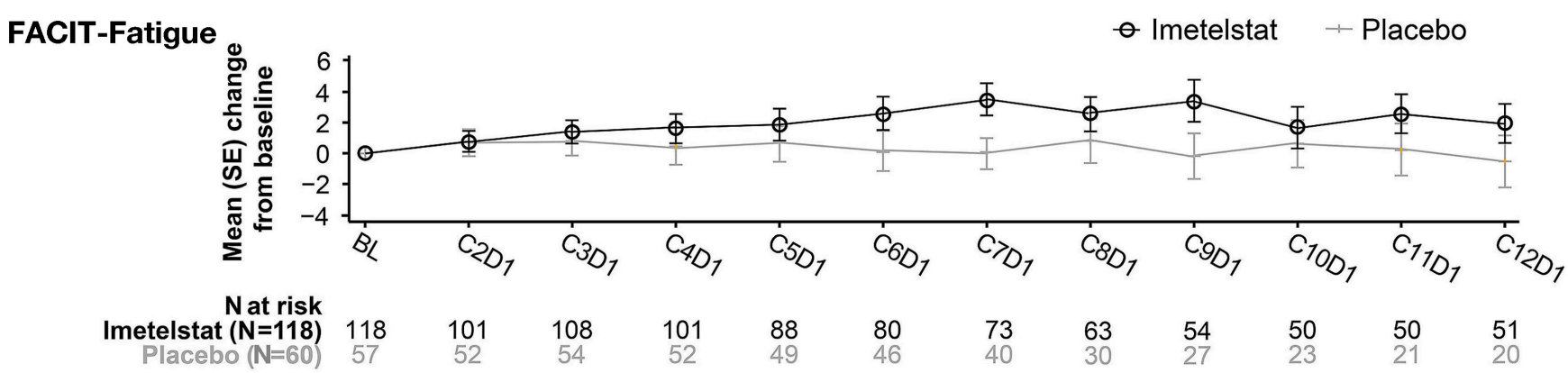

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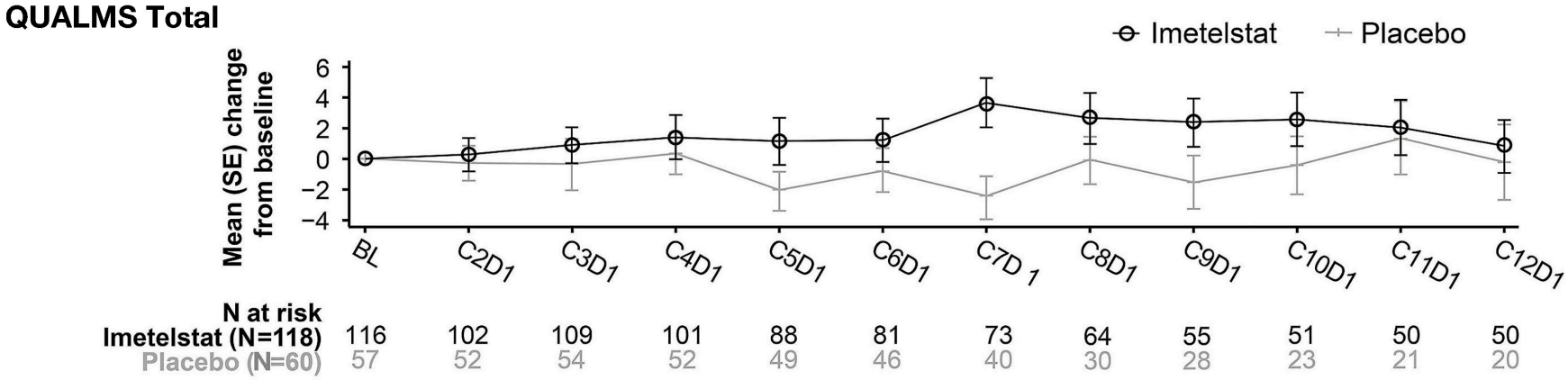

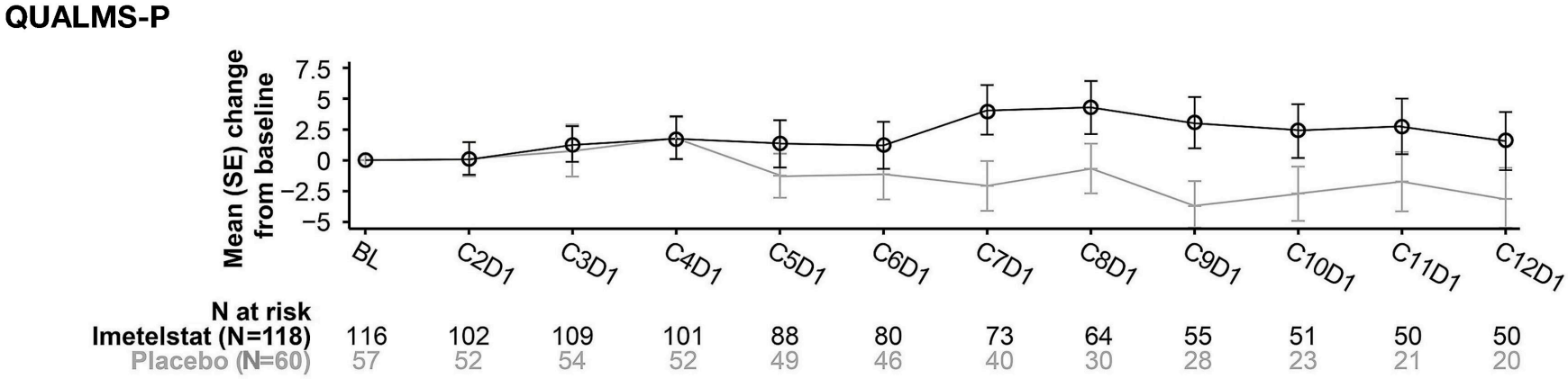

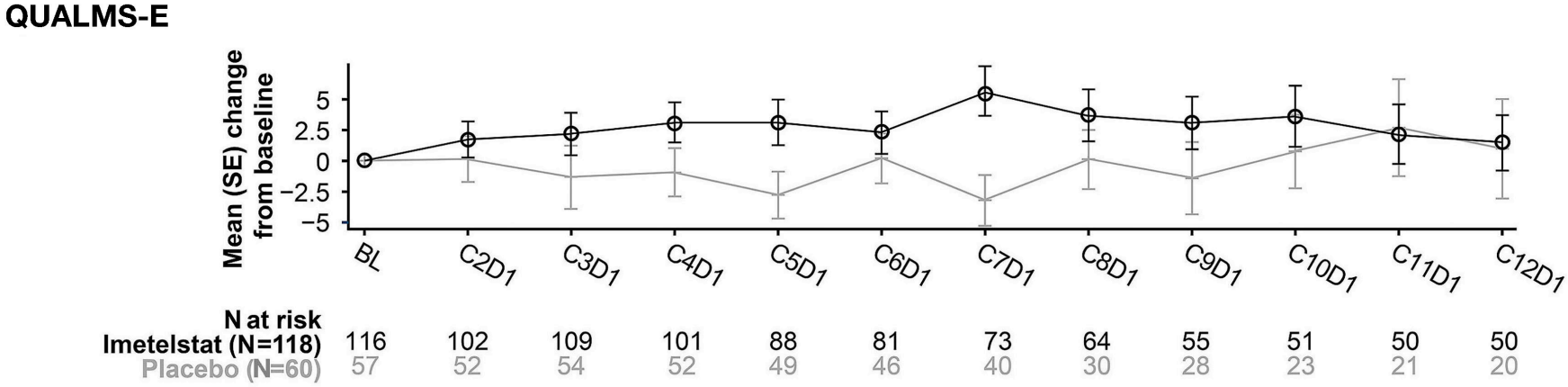

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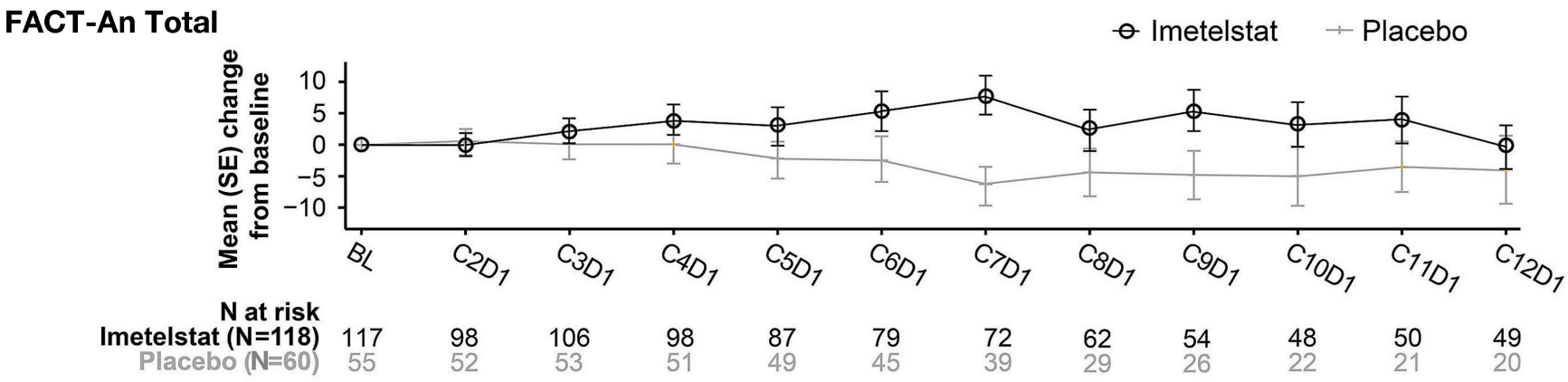

Figure 3. Change from baseline in different measures of quality of life by cycle (ITT population). FACIT-Fatigue (A), QUALMS Total, QUALMS-P, and QUALMS-E (B), and FACT-An (C) scores. C: cycle; D: day; FACIT: Functional Assessment of Chronic Illness Therapy; FACT-An: Functional Assessment of Cancer Therapy-Anemia; ITT: intention-to-treat; N: number; 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; SE: standard error.

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 ten 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

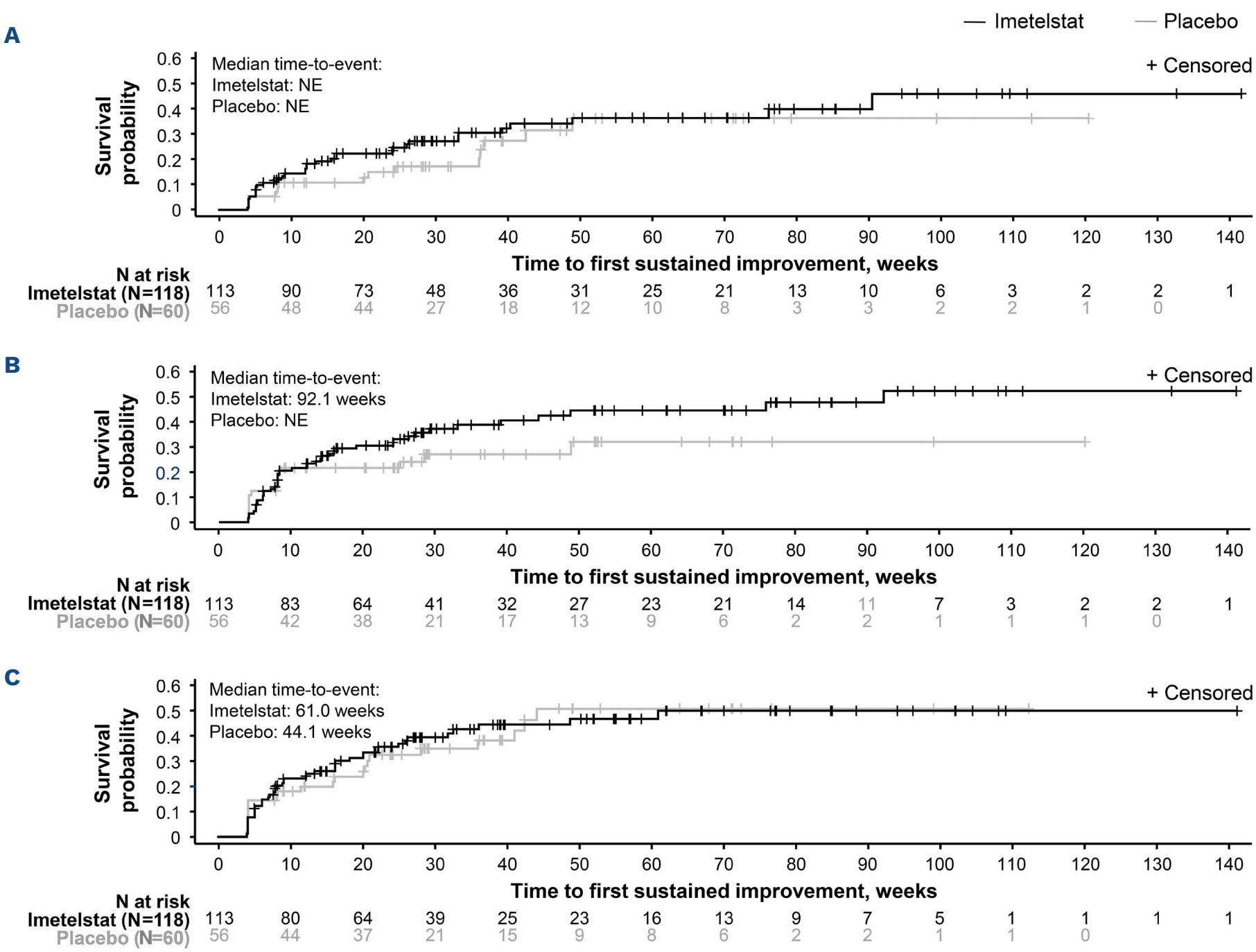

Figure 4. Time to first sustained improvement[a] in QUALMS scores (patient-reported outcomes population). QUALMS Total (A), QUALMS-P (B), and QUALMS-E (C). [a]Sustained meaningful improvement was defined for QUALMS as ≥9-, ≥8-, or ≥9-point increase for ≥2 consecutive assessments in QUALMS Total, QUALMS-P, and QUALMS-E scores, respectively.[35] NE: not estimable; 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.

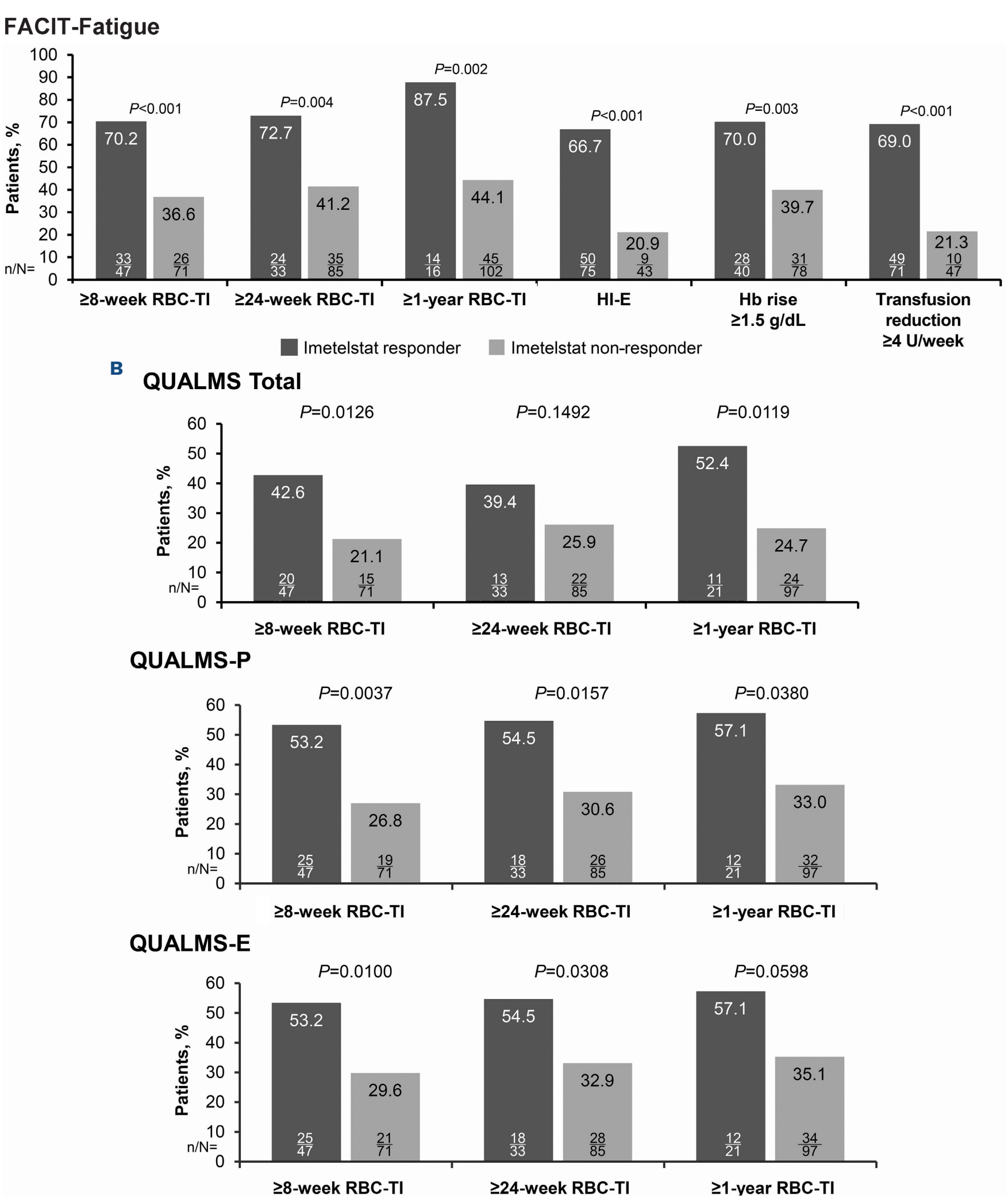

Figure 5. Improvements[a] in quality of life measures by response to imetelstat (patient-reported outcomes population). FACIT-Fatigue[b] (A) and QUALMS Total,[c] QUALMS-P,[c] and QUALMS-E[c] scores (B). [a]Sustained meaningful improvement was defined for fatigue as a ≥3-point increase in FACIT-Fatigue 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 χ^2 test. FACIT: Functional Assessment of Chronic Illness Therapy; Hb: hemoglobin; HI-E: hematologic improvement-erythroid; n/N: number with event/number in population; 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.

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 non-responders. 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 ESA, 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 were 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 the 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 (e.g,, 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 a 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 offer not only 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.

Disclosures

MAS reports consultancy fees from Bristol Myers Squibb, Schrödinger, Menarini Group, and Kurome, research funding from Bristol Myers Squibb, travel expenses from Daiichi Sankyo, and owns stock options in Kurome; AMZ reports research funding from AbbVie, ADC Therapeutics, Aprea, Astex, AstraZeneca, Boehringer Ingelheim, Cardiff Oncology, Celgene/BMS, Genentech, Geron Corporation, Novartis, Pfizer, Shattuck Labs, and Takeda, and 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; VS has served on advisory boards for AbbVie, Ascentage, Bristol Myers Squibb, CTI BioPharma, Geron, Gilead, Novartis, Servier, and Syros Pharmaceuticals; RSK

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Contributions

MAS, AR, KC, LS, YW, SN, TB, FF and UP contributed to study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions; AMZ, VS, RSK, PF, MRS, YFM, DV, MD-C and ENO contributed to data acquisition, data interpretation, and manuscript writing and revisions.

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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.

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