

HEALTH-RELATED QUALITY OF LIFE OUTCOMES IN PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES TREATED WITH IMETELSTAT IN THE IMERGE TRIAL

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Background

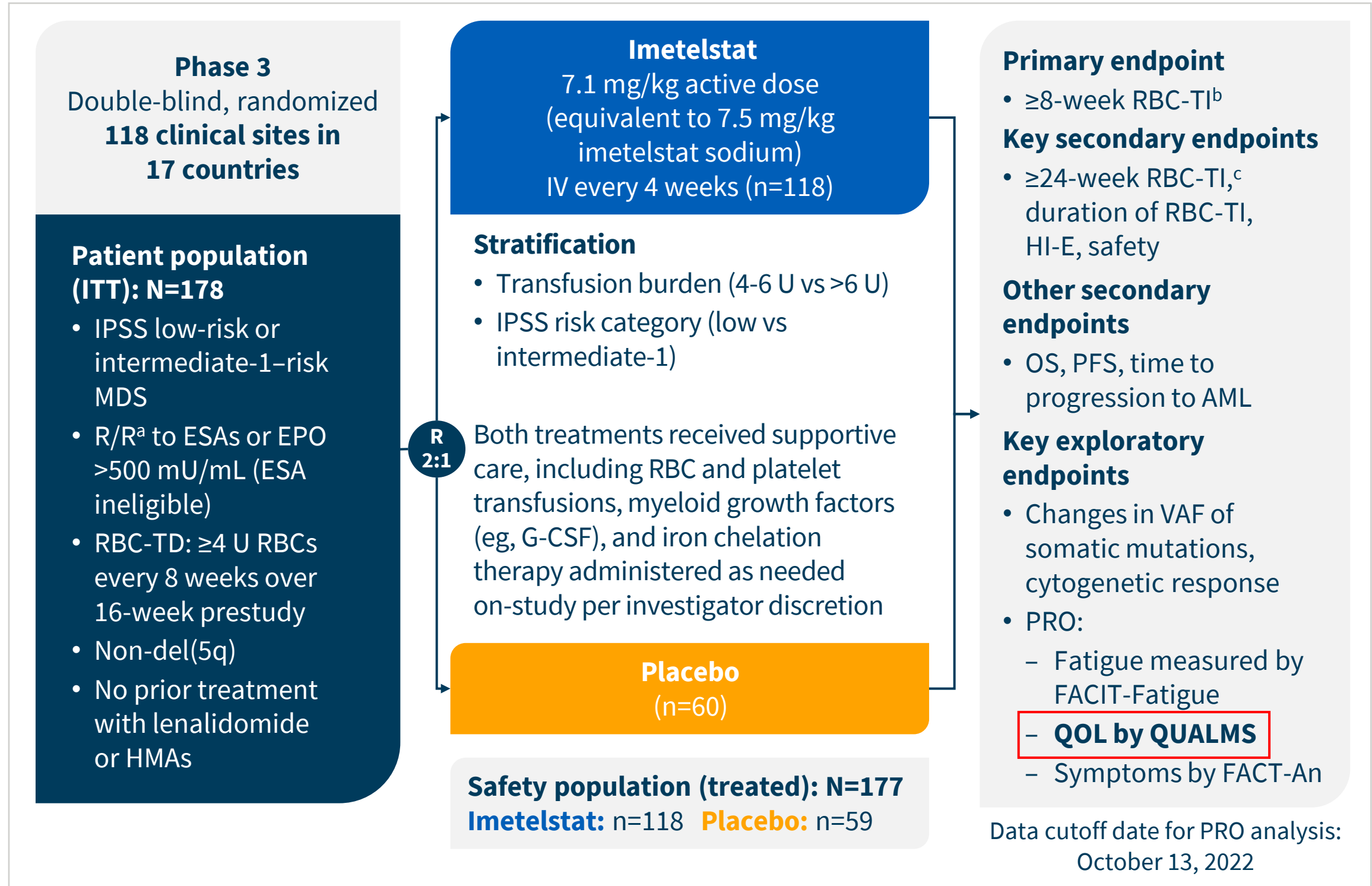
- Quality of life (QOL) in patients with lower-risk myelodysplastic syndromes (LR-MDS) often declines as anemia and associated symptoms worsen, and progressive dependence on red blood cell (RBC) transfusions affects daily life¹
 - Thus, a significant goal of therapy is to reduce symptoms, including anemia-related fatigue, to improve QOL
- Imetelstat, a first-in-class, direct, and competitive inhibitor of telomerase activity, was recently approved in the United States and Europe for certain adult patients with LR-MDS and transfusion-dependent (TD) anemia who have relapsed or refractory/unsatisfactory response to or are ineligible for erythropoiesis-stimulating agents^{2,3}
 - Approval was based on results of the randomized, double-blind, placebo-controlled, Phase 3 IMerge trial (NCT02598661)⁴
- In IMerge, treatment with imetelstat resulted in clinically meaningful and statistically significant benefit, with a higher proportion of patients achieving ≥8-week and ≥24-week RBC transfusion independence (TI) compared with placebo
 - A total of 50% of imetelstat-treated patients and 40% of placebo recipients experienced a sustained, meaningful improvement in patient-reported fatigue as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (exploratory outcome)⁴
- QOL, defined as an individual’s perception of functioning and well-being, encompasses numerous facets, including physical, emotional, and social functioning⁵

This post hoc analysis reports on the effects of imetelstat treatment on patient-reported QOL measures in the Phase 3 IMerge trial

Methods

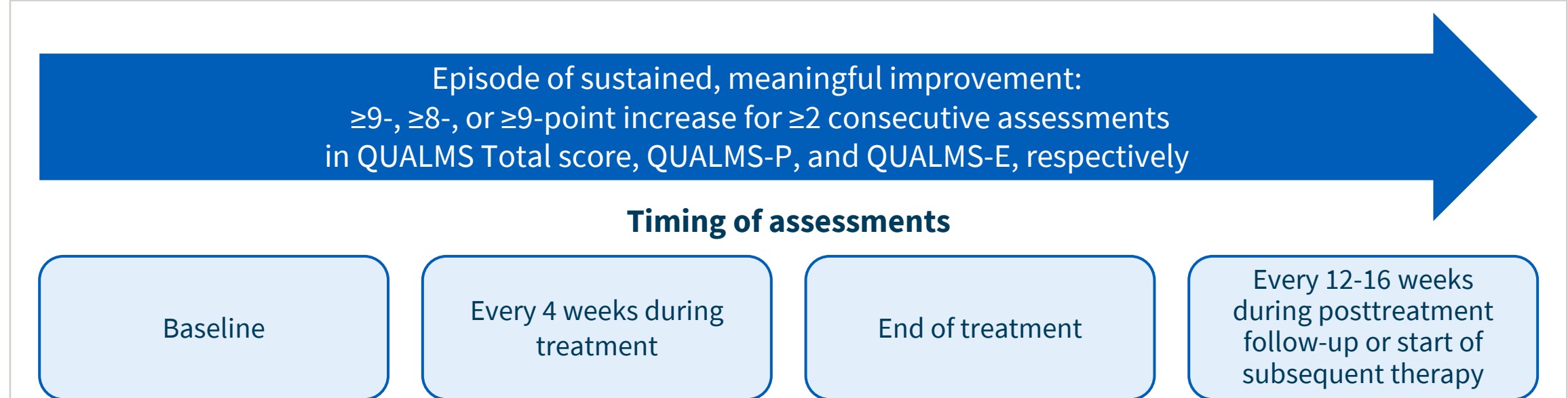
- IMerge is a randomized, double-blind, placebo-controlled Phase 3 trial (**Figure 1**)
- Patient-reported outcomes (PRO) assessed in this post hoc analysis included the Quality of Life in Myelodysplasia Scale (QUALMS) questionnaire: QUALMS Total score and 2 subscale scores, physical burden (QUALMS-P) and emotional burden (QUALMS-E)⁶
 - Definition of response and timing of assessments are presented in **Figure 2**
 - Sustained meaningful improvement was defined based on previously described thresholds in relation to improvement in hemoglobin levels ≥1.5 g/dL⁷

Figure 1. IMerge Phase 3 Study Design



AML, acute myeloid leukemia; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-An, Functional Assessment of Cancer Therapy-Anemia; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; IV, intravenous; MDS, myelodysplastic syndrome; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QOL, quality of life; QUALMS, Quality of Life in Myelodysplasia Scale; R, randomized; RBC, red blood cell; R/R, relapsed or refractory; TD, transfusion dependent; TI, transfusion independence; VAF, variant allele frequency.
^aReceived ≥8 weeks of ESA treatment (epoetin alfa ≤5000 U, or darbepoetin alfa ≥100 U or equivalent per week without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 every 8 weeks or transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment. ^bProportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (≥8-week RBC-TI). ^cProportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (≥24-week RBC-TI).

Figure 2. QUALMS Assessments



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.

Results

Patient Population

- The PRO population comprised 175 patients (imetelstat, n=118; placebo, n=57)
 - Three placebo recipients from the intention-to-treat population were not included in the PRO population because they did not have complete baseline PRO data
- Baseline characteristics were similar across treatment arms (**Table 1**)

Table 1. Baseline Demographic and Disease Characteristics

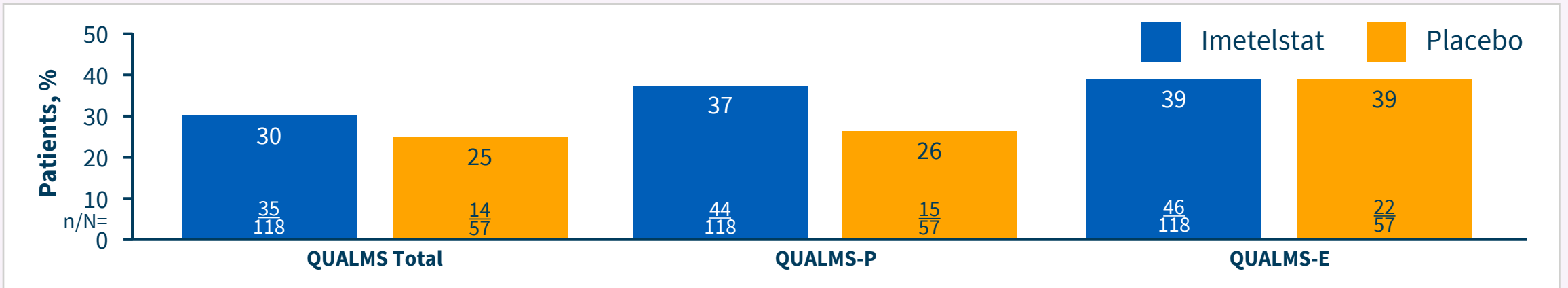
Characteristic	Imetelstat (N=118)	Placebo (N=57)
Age, median (range), y	71.5 (44-87)	73 (39-85)
Male, n (%)	71 (60)	38 (67)
WHO classification, n (%)		
RS+	73 (62)	37 (65)
RS-	44 (37)	20 (35)
IPSS risk category, n (%)		
Low	80 (68)	37 (65)
Intermediate-1	38 (32)	20 (35)
Transfusion burden per IWG 2018, n (%)		
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)
Serum EPO level, n (%) ^b		
≤500 mU/mL	87 (74)	35 (61)
>500 mU/mL	26 (22)	20 (35)
Prior ESA, n (%)	108 (92)	50 (88)

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

Imetelstat Versus Placebo

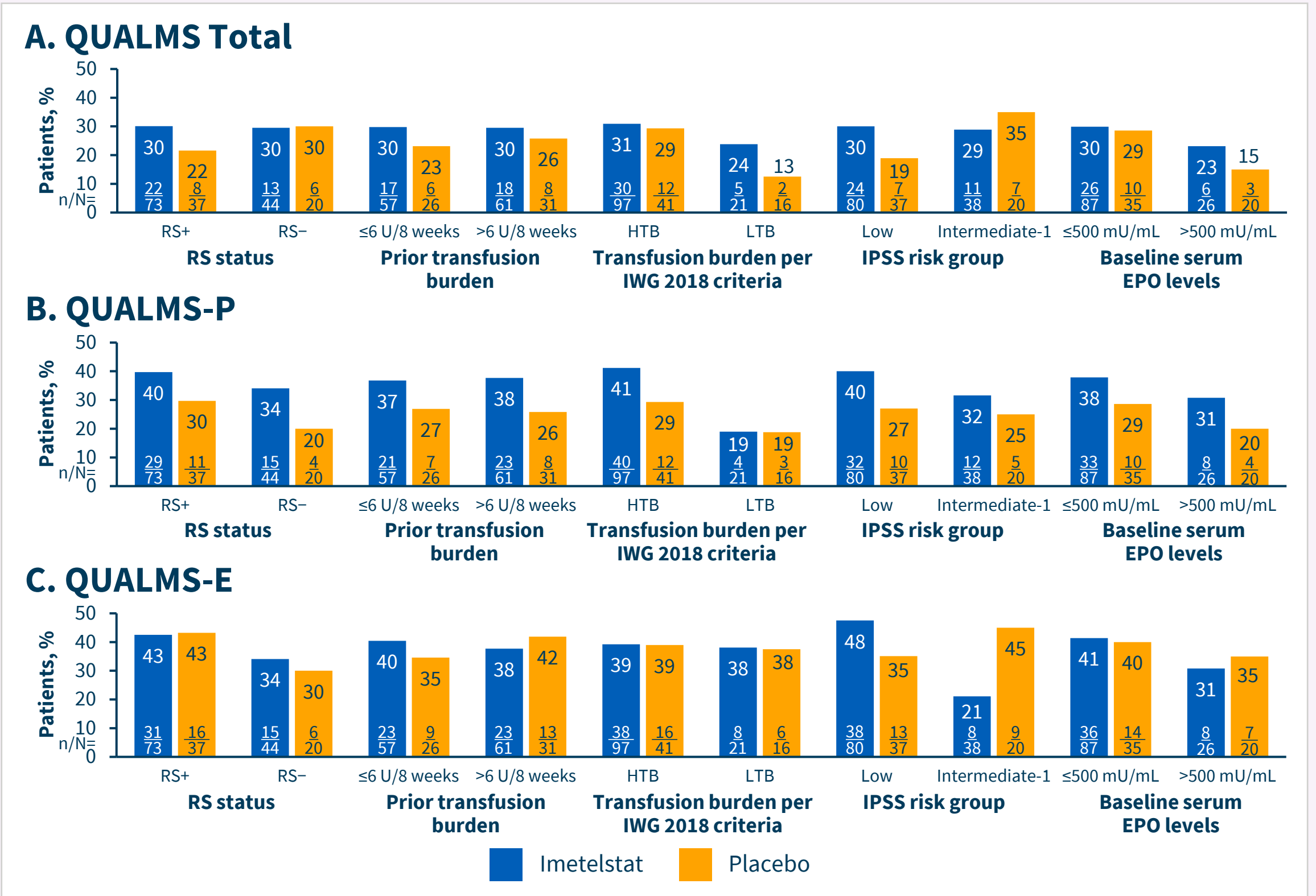
- Improvements in QUALMS Total and QUALMS-P scores were observed in more patients treated with imetelstat versus placebo (**Figure 3**), and in patients with certain baseline characteristics (**Figure 4**)

Figure 3. Sustained Meaningful Improvement in QUALMS Total, QUALMS-P, and QUALMS-E Scores



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.

Figure 4. Improvement in QUALMS Total, QUALMS-P, and QUALMS-E Scores by Subgroup (PRO Population)

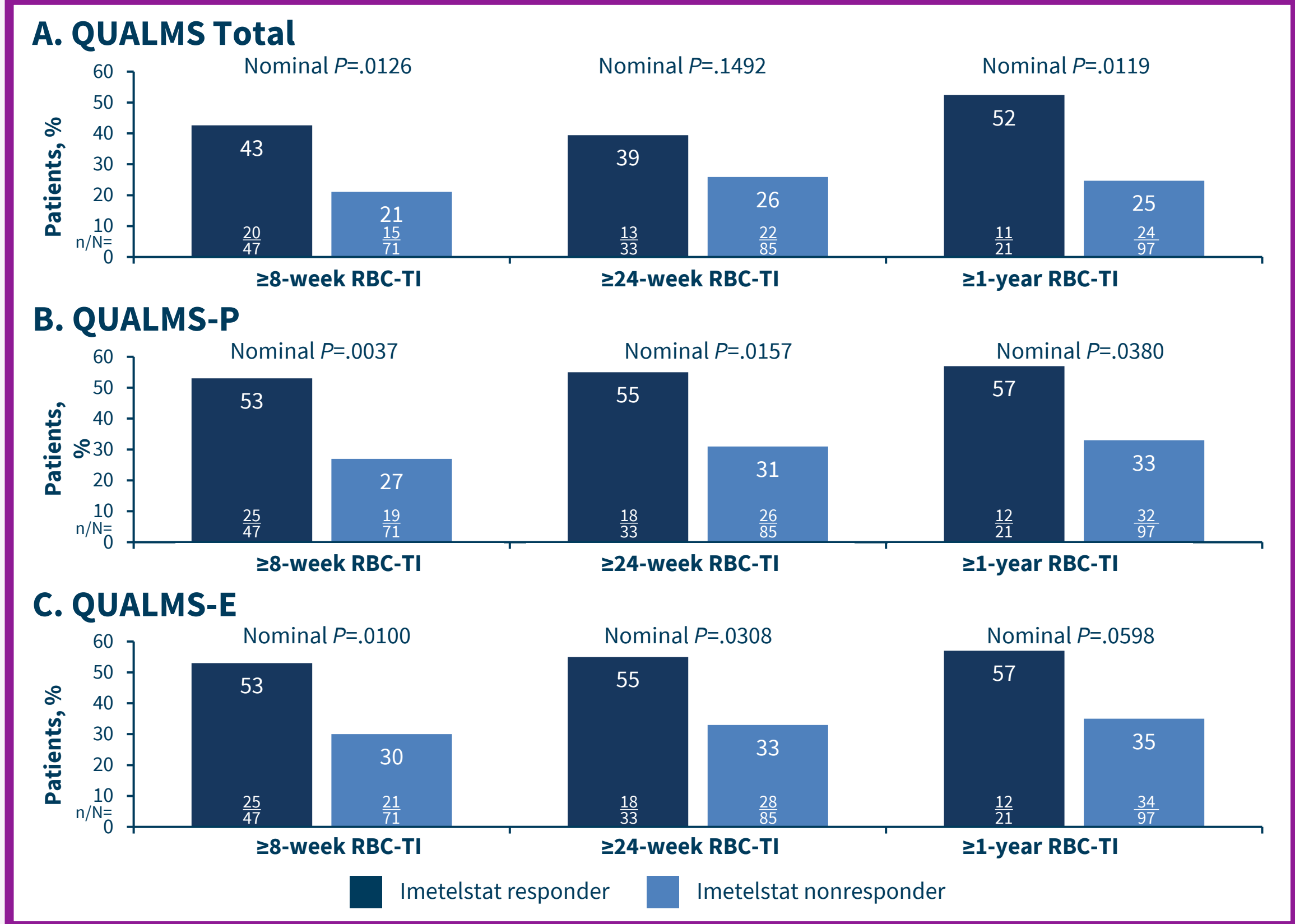


EPO, erythropoietin; IPSS, International Prognostic Scoring System; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; n/N, number with event/number in population; PRO, patient-reported outcome; QUALMS, Quality of Life in Myelodysplasia Scale; QUALMS-E, Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P, Quality of Life in Myelodysplasia Scale – physical burden; RS, ring sideroblast.

Association of Improvement in QUALMS and Clinical Response

- Improvement in sustained meaningful QUALMS was seen in more patients who responded to imetelstat versus those who did not respond across measures of response (**Figure 5**)
- The proportion of patients with improvements in QUALMS-P was significantly higher among those who achieved ≥8-week, ≥24-week, or ≥1-year RBC-TI with imetelstat versus nonresponders
 - A similar trend was observed for QUALMS Total and QUALMS-E scores

Figure 5. Improvement in QUALMS Total, QUALMS-P, and QUALMS-E Scores by Response to Imetelstat (PRO Population)

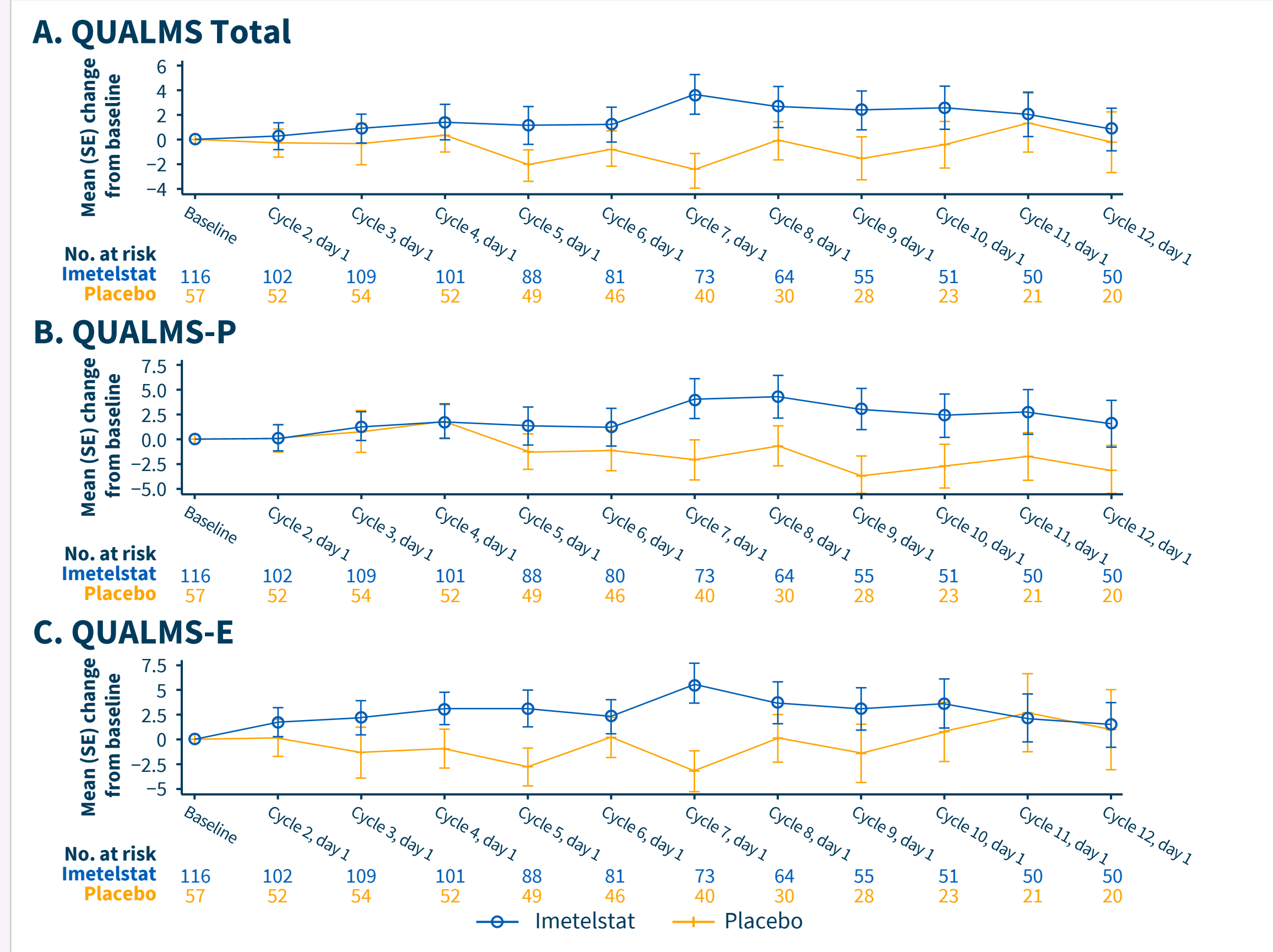


n/N, number with event/number in population; PRO, patient-reported outcome; QUALMS, Quality of Life in Myelodysplasia Scale; QUALMS-E, Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P, Quality of Life in Myelodysplasia Scale – physical burden; RBC, red blood cell; TI, transfusion independence. P values were calculated by chi-square test.

QUALMS Scores Over Time

- Imetelstat-treated patients maintained QOL measured by QUALMS scores (**Figure 6**), while placebo recipients experienced worsening QOL with a meaningful difference in least squares means in QUALMS Total and QUALMS-P scores (**Table 2**)
 - Median time to first sustained improvement in QUALMS scores (**Figure 7**) showed a trend of shorter time to onset with imetelstat versus placebo

Figure 6. Mean Change From Baseline in QUALMS Total, QUALMS-P, and QUALMS-E Scores by Cycle (ITT Population)



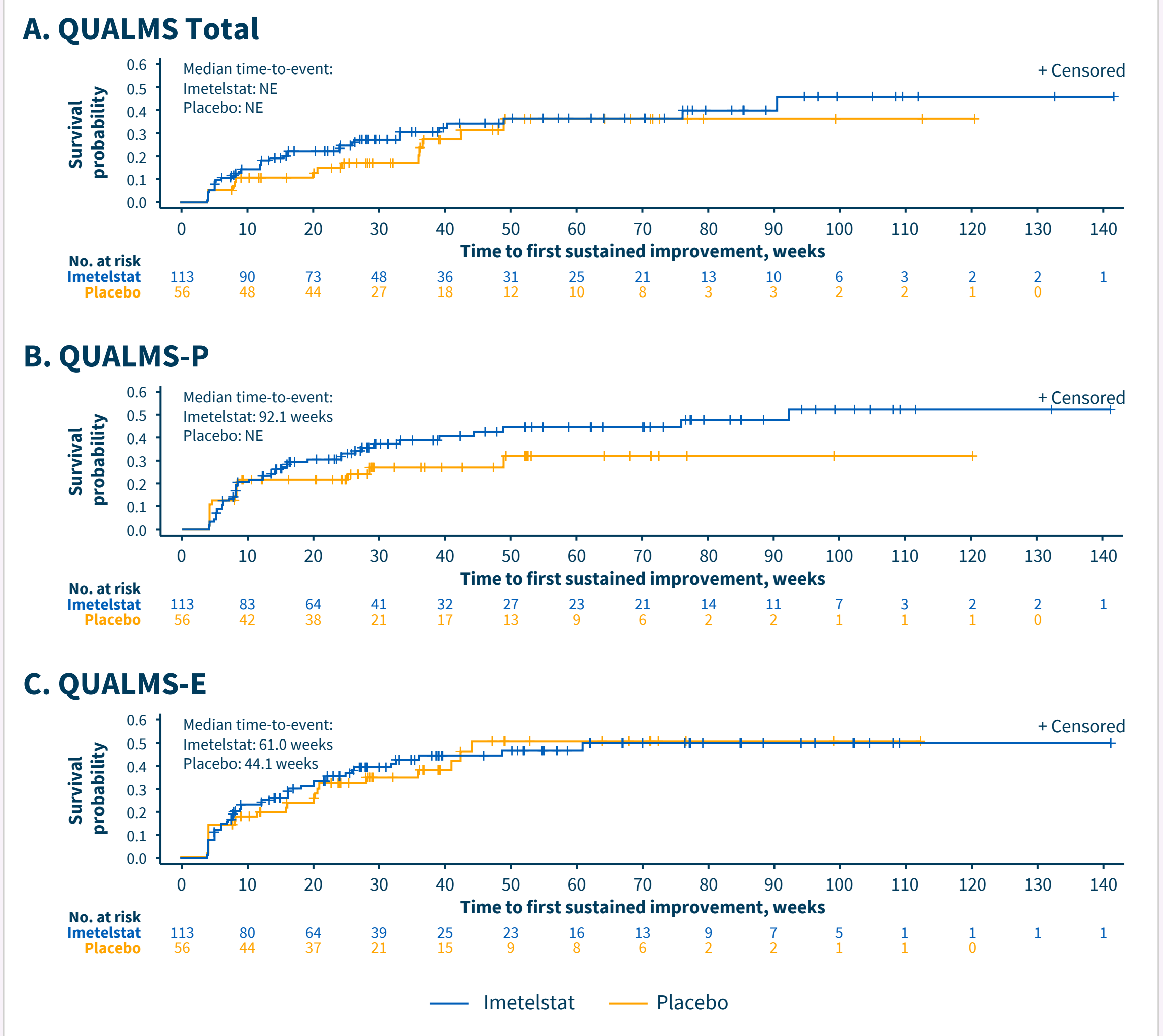
ITT, intention-to-treat; PRO, patient-reported outcome; QUALMS, Quality of Life in Myelodysplasia Scale; QUALMS-E, Quality of Life in Myelodysplasia Scale – emotional burden; QUALMS-P, Quality of Life in Myelodysplasia Scale – physical burden.

Table 2. Imetelstat Maintained QOL Over the Treatment Period; LS Mean Estimates by RMM^a (ITT Population)

Score	Imetelstat LS mean (95% CI) change from baseline (n=118)	Placebo LS mean (95% CI) change from baseline (n=60)	LS mean (95% CI) difference	Nominal P value
QUALMS Total	-0.55 (-2.85, 1.76)	-5.21 (-8.35, -2.07)	4.66 (0.86, 8.46)	.016
QUALMS – physical burden	-0.41 (-3.18, 2.36)	-6.75 (-10.53, -2.98)	6.34 (1.77, 10.91)	.007
QUALMS – emotional burden	-0.16 (-3.12, 2.80)	-4.52 (-8.56, -0.48)	4.36 (-0.53, 9.25)	.080

ITT, intention-to-treat; IPSS, International Prognostic Scoring System; LS, least squares; QOL, quality of life; QUALMS, Quality of Life in Myelodysplasia Scale; RMM^a, repeated measurement mixed model. ^aThe RMM was conducted to summarize the change in QUALMS scores from baseline over time, using all available longitudinal data and adjusting for stratification factors. The RMM included the change in scores as the explained variable and baseline scores, 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 (ie, up to the cycle at which data for both treatment arms is available). The overall effects of imetelstat on QUALMS scores were evaluated from the model comparing the LS means of change in scores estimated in the 2 treatment groups using all available data up to cycle 30.

Figure 7. Time to First Sustained Improvement in QUALMS Total, QUALMS-P, and QUALMS-E Scores (PRO Population)



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.

Conclusions

- In this post hoc analysis, numerically more imetelstat-treated patients experienced sustained improvement in QOL as measured by QUALMS Total and QUALMS-P scores compared with placebo across baseline disease characteristics
 - The sustained improvement in QUALMS Total and QUALMS-E were experienced earlier in patients who received imetelstat versus placebo
- A higher proportion of imetelstat responders who achieved ≥8-week, ≥24-week, or ≥1-year RBC-TI experienced sustained meaningful improvement in QUALMS Total, QUALMS-P, and QUALMS-E scores compared with nonresponders
- Together, these data suggest that certain patients with LR-MDS and TD anemia who experience sustained RBC-TI with imetelstat may experience improved health-related QOL beyond fatigue
- Results should be interpreted with caution given the post hoc nature of this analysis, the small sample sizes in some groups, and the limitations in the definition of meaningful change thresholds for QUALMS

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