

Correlation of Patient-Reported Outcomes with Red Blood Cell Transfusion Reduction and Rise in Hemoglobin in Patients with Lower-Risk Myelodysplastic Syndromes in the IMerge Trial

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Introduction

- A significant goal of therapy for patients with lower-risk myelodysplastic syndromes (LR-MDS) is to reduce symptoms, including anemia-related fatigue, to lessen the need for red blood cell (RBC) transfusions and improve quality of life (QOL)¹
- Imetelstat, a first-in-class, direct, and competitive inhibitor of telomerase activity, was recently approved by the United States Food and Drug Administration for adult patients with LR-MDS with transfusion-dependent (TD) anemia who have relapsed or are refractory to or ineligible for erythropoiesis-stimulating agents²
 - Approval was based on results of the randomized, double-blind, placebo-controlled, phase 3 IMerge trial (NCT02598661)³
- In IMerge, treatment with imetelstat resulted in statistically significant and clinically meaningful increases in ≥8-week and ≥24-week RBC transfusion independence (TI)
 - A total of 50% of imetelstat-treated patients and 40% of placebo-treated patients experienced a sustained, meaningful improvement in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores³
- Here, we further explore treatment effects and improvement in patient-reported outcomes (PRO) across subgroups in the phase 3 IMerge trial

Methods

Study Design

- IMerge is a randomized, double-blind, placebo-controlled phase 3 trial (**Figure 1**)
 - Data cutoff date for PRO analysis: October 2022

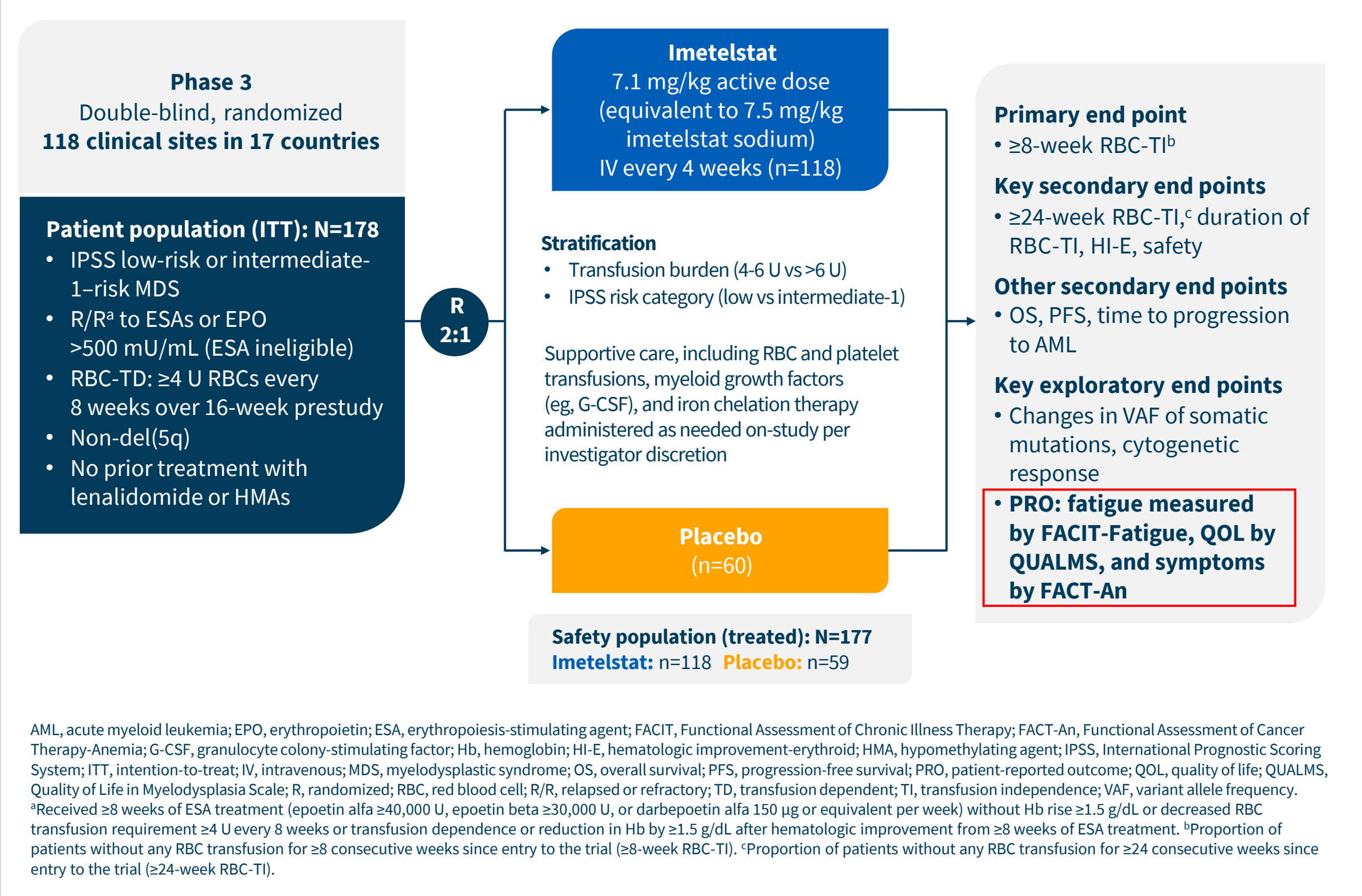
Outcomes

- PROs were assessed with validated FACIT-Fatigue,⁴ Functional Assessment of Cancer Therapy-Anemia (FACT-An),⁴ and the Quality of Life in Myelodysplasia Scale (QUALMS) questionnaires⁵
- Sustained meaningful improvement in fatigue was defined as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments

Analyses

- Subgroup analyses for a proportion of patients in each treatment group for reporting an episode of sustained meaningful improvement in fatigue
- Association of RBC-TI clinical end points with the proportion of patients reporting an episode of sustained meaningful improvement in fatigue
- Least squares mean estimates with nominal *P* values for change from baseline in QUALMS and FACT-An based on a repeated measurement mixed model (RMMM)
 - Change in score was the explained variable; baseline score, time, treatment, time and treatment interaction, and study stratification factors (prior RBC transfusion burden and International Prognostic Scoring System risk group) were covariates (fixed effects) as explanatory variables, and a random effect for individuals to account for the within-individual correlation is included in the longitudinal assessments
- These are exploratory analyses

Figure 1. IMerge Phase 3 Study Design



Results

Population

- PRO population (n=175), which included all patients in the intent-to-treat population who had FACIT-Fatigue data at baseline, consisted of 118 imetelstat-treated patients and 57 who received placebo
- Baseline characteristics were similar across treatment arms (**Table 1**)

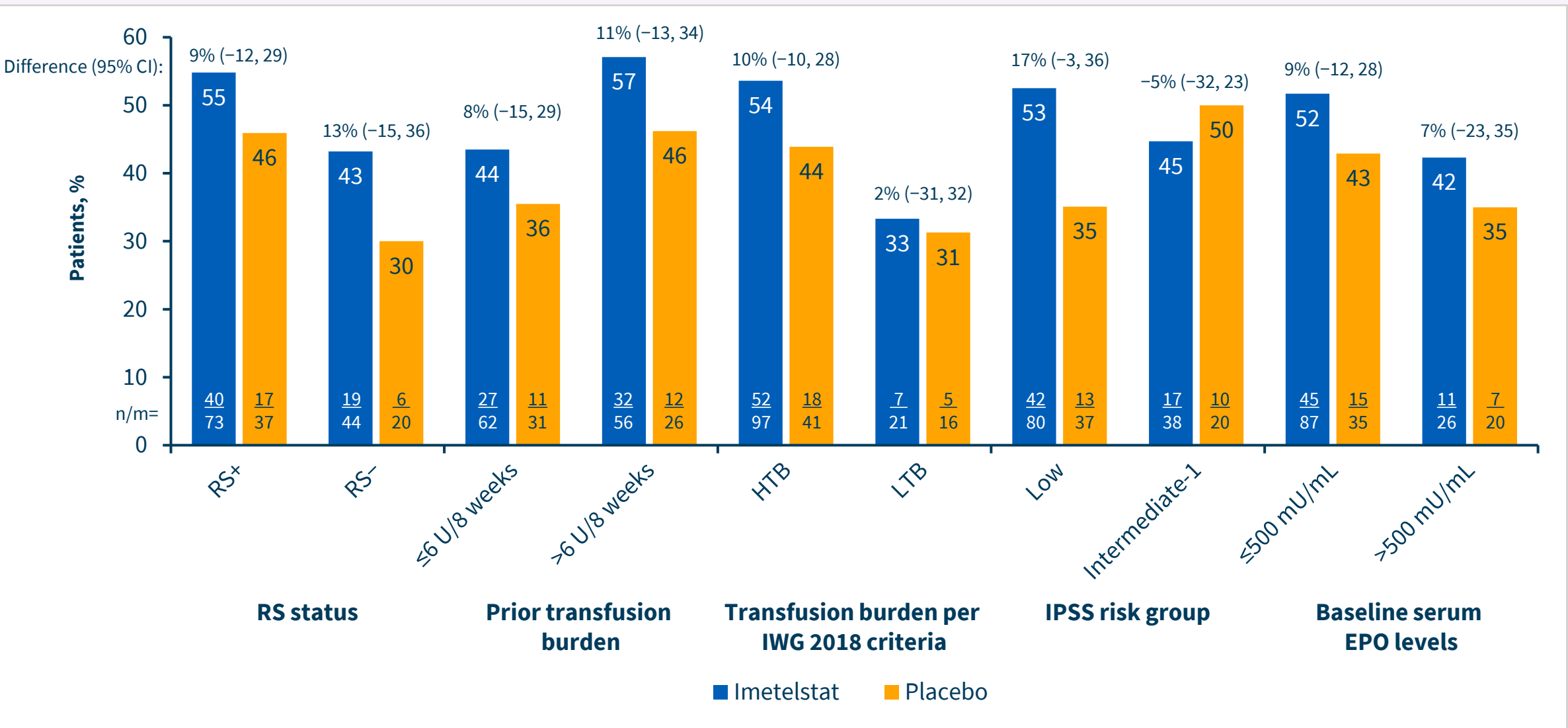
Table 1. Baseline Demographic and Disease Characteristics

	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)
Prior RBC transfusion burden, n (%)		
≤6 U/8 weeks	62 (53)	31 (54)
>6 U/8 weeks	56 (47)	26 (46)
Transfusion burden per IWG 2018, n (%)		
HTB	97 (82)	41 (72)
LTB	21 (18)	16 (28)
IPSS risk category, n (%)		
Low	80 (68)	37 (65)
Intermediate-1	38 (32)	20 (35)
sEPO level, n (%)		
≤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.

- For all subgroups except 1, more patients treated with imetelstat than placebo reported sustained improvement in fatigue (**Figure 2**)

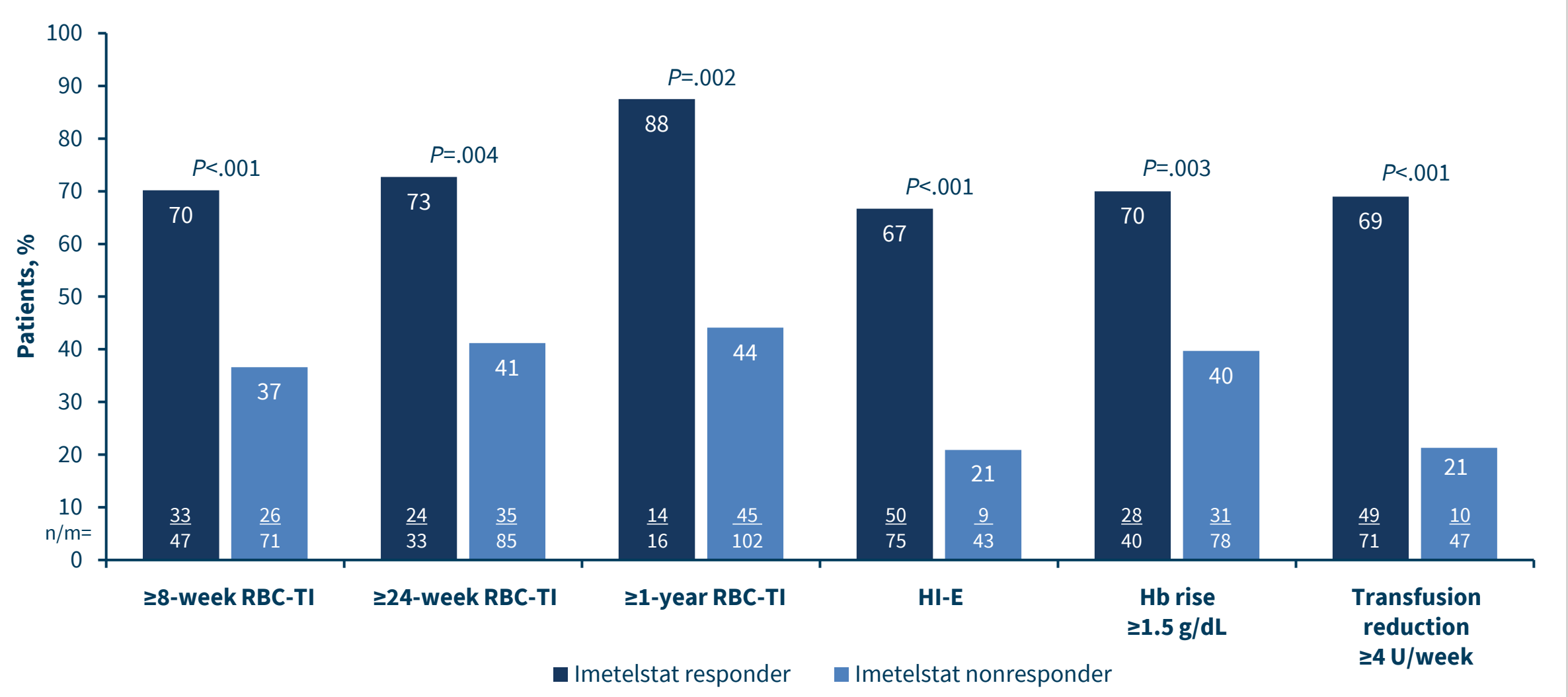
Figure 2. Proportion of Patients Who Reported Sustained Improvement in Fatigue as Measured by FACIT-Fatigue by Subgroup



EPO, erythropoietin; FACIT, Functional Assessment of Chronic Illness Therapy; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; n/m, number with event/number in population; RS, ring sideroblast.

- Improvement in fatigue was seen in more patients who responded to imetelstat versus those who did not across measures of response (**Figure 3**)

Figure 3. Proportion of Patients Who Reported Sustained Improvement in Fatigue as Measured by FACIT-Fatigue by Response Status



Hb, hemoglobin; HI-E, hematologic improvement-erythroid; FACIT, Functional Assessment of Chronic Illness Therapy; n/m, number with event/number in population; RBC-TI, red blood cell transfusion independence. Nominal *P* values by Fisher exact test are shown.

QUALMS and FACT-An

- The QUALMS and FACT-An analyses suggested that imetelstat maintained QOL and anemia symptoms, while placebo recipients experienced worsening QOL and anemia symptoms (**Figure 4**)
- For imetelstat versus placebo, respectively, least squares mean changes from baseline to cycle 30 scores are shown in **Table 2**

Figure 4A. Model-Based Mean Changes in QUALMS Total Score by RMMM

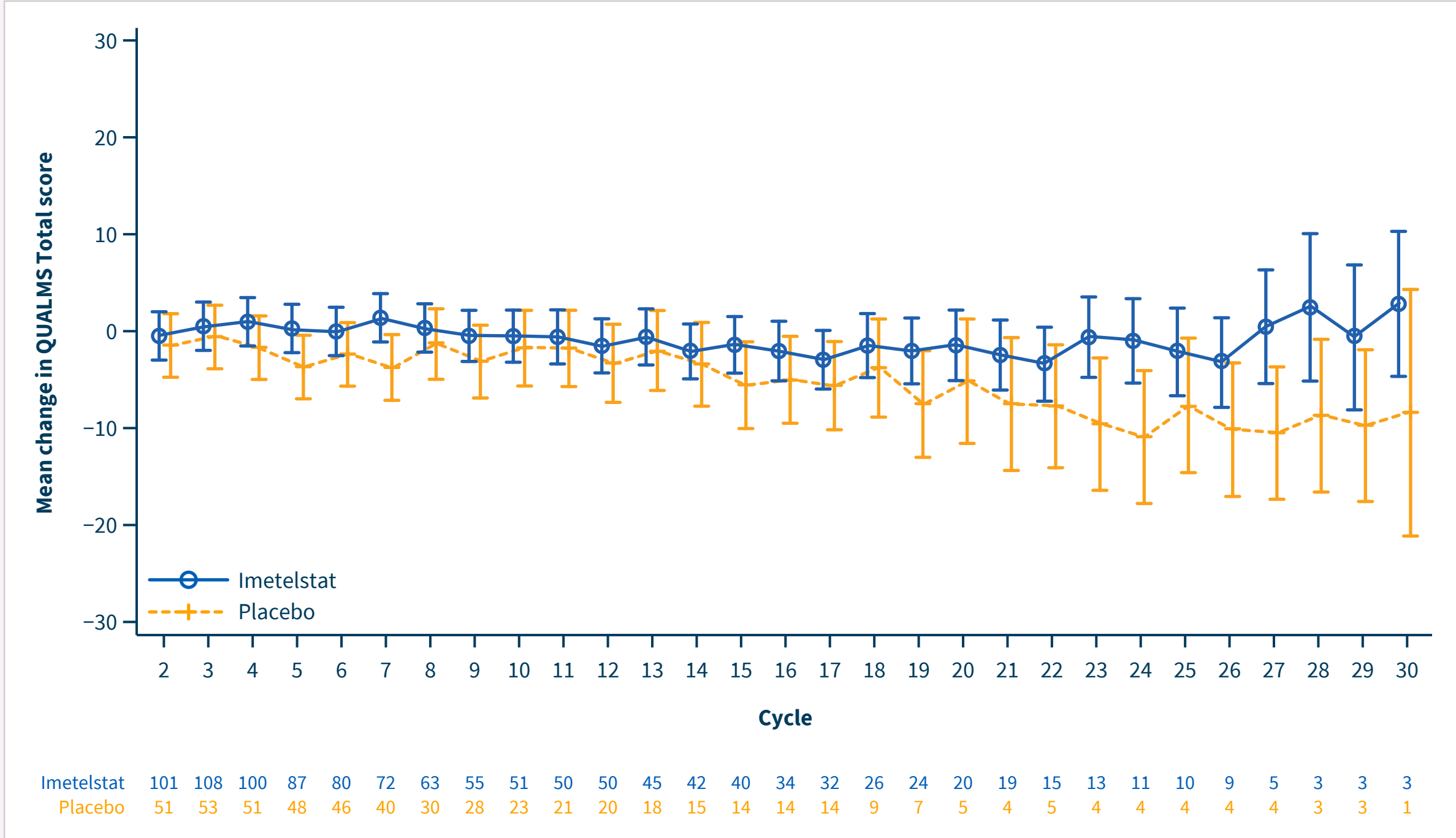


Figure 4B. Model-Based Mean Changes in QUALMS Physical Burden Score by RMMM

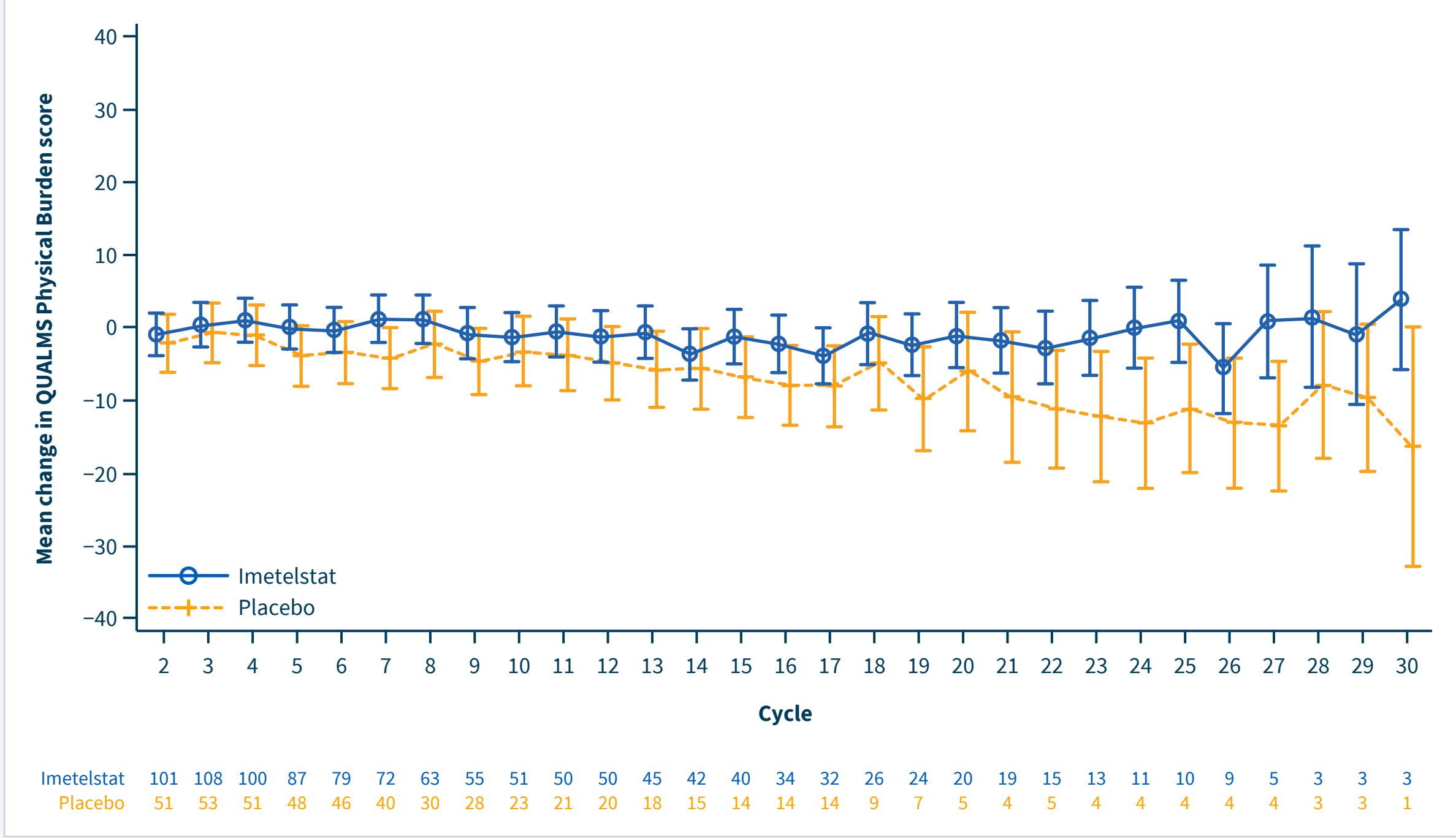


Figure 4C. Model-Based Mean Changes in FACT-An Total Score by RMMM

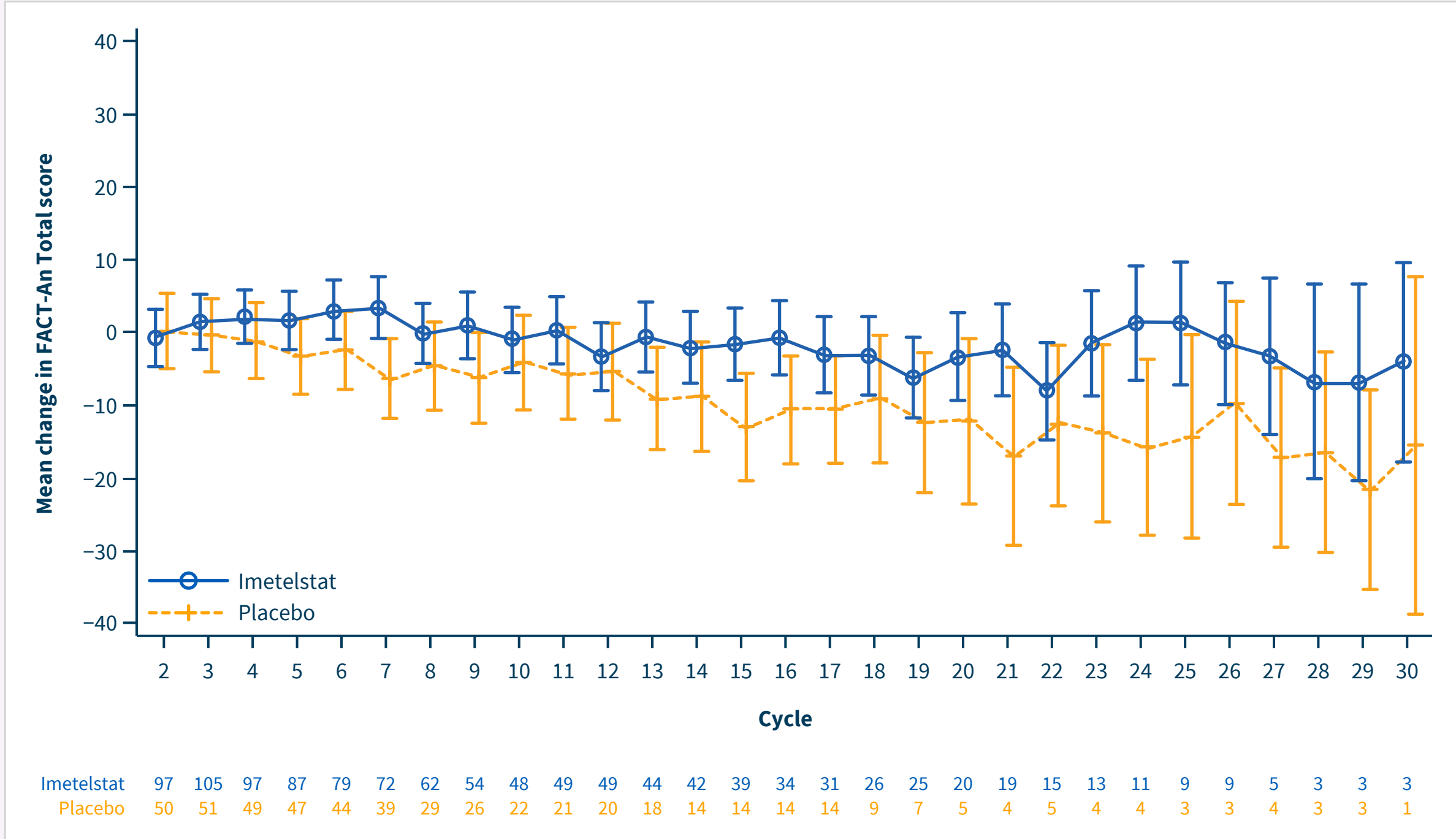
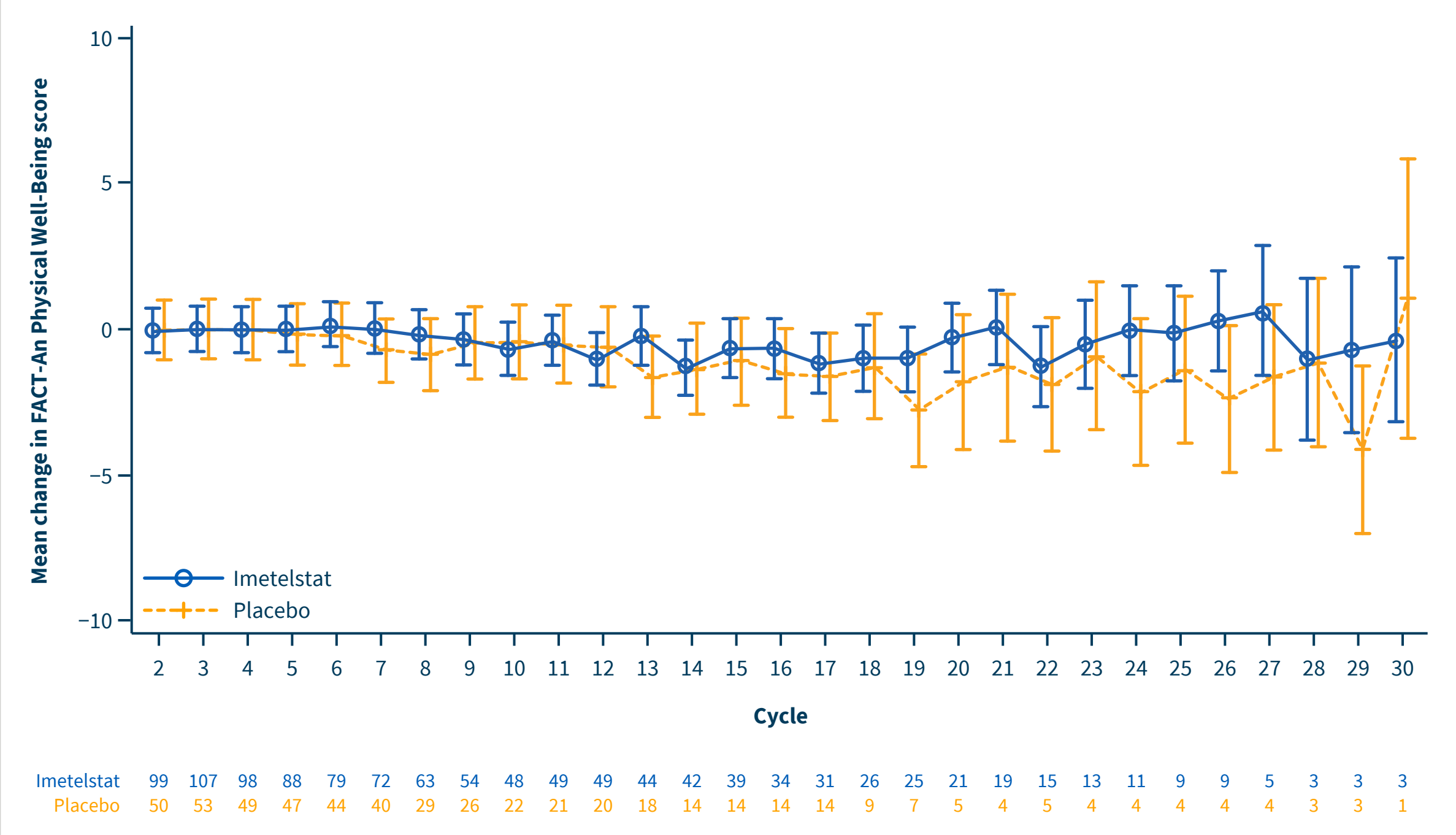


Figure 4D. Model-Based Mean Changes in FACT-An Physical Well-Being Score by RMMM



FACT-An, Functional Assessment of Cancer Therapy-Anemia; QUALMS, Quality of Life in Myelodysplasia Scale; RMMM, repeated measurement mixed model.

Table 2. Imetelstat Maintained QOL and Anemia Symptoms at Cycle 30

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 <i>P</i> 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
FACT-An Total	-1.6 (-5.00, 1.80)	-9.72 (-14.43, -5.01)	8.12 (2.44, 13.81)	.005
FACT-An Physical Well-Being	-0.43 (-1.10, 0.24)	-1.16 (-2.08, -0.24)	0.73 (-0.38, 1.84)	.197

FACT-An, Functional Assessment of Cancer Therapy-Anemia; LS, least squares; QOL, quality of life; QUALMS, Quality of Life in Myelodysplasia Scale.

Conclusions

- Data from the pivotal IMerge phase 3 trial demonstrate that improvement in fatigue with imetelstat was associated with reduced transfusion burden and a rise in hemoglobin
- A higher percentage of imetelstat- versus placebo-treated patients had sustained improvement in fatigue, regardless of ring sideroblast status or baseline transfusion burden
- Patients treated with imetelstat largely experienced maintenance of QOL and anemia symptoms compared with a worsening of QOL with placebo, as measured using validated PRO questionnaires
- Imetelstat appears to offer the advantage of sustained RBC-TI benefit while maintaining QOL in patients with LR-MDS with TD anemia

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