

Outcomes of Imetelstat Therapy in Patients With Ring Sideroblast–Negative Lower-Risk Myelodysplastic Syndromes From the Pooled IMerge Study Populations

MDS-330

Valeria Santini, MD,¹ Uwe Platzbecker, MD,² Amer M. Zeidan, MBBS, MHS,³ Mikkael A. Sekeres, MD,⁴ Azra Raza, MD,⁵ Moshe Mittelman, MD,⁶ Sylvain Thépot, MD,⁷ Rena Buckstein, MD, FRCP,⁸ Ulrich Germing, MD,⁹ Yazan F. Madanat, MD,¹⁰ María Díez-Campelo, MD, PhD,¹¹ David Valcárcel, MD, PhD,¹² Anna Jonášová, MD, PhD,¹³ Souria Dougherty, MBA,¹⁴ Qi Xia, PhD,¹⁴ Libo Sun, PhD,¹⁴ Shyamala Navada, MD,¹⁴ Faye Feller, MD,¹⁴ Michael R. Savona, MD,¹⁵ Rami S. Komrokji, MD,¹⁶ Pierre Fenaux, MD, PhD¹⁷

¹MDS Unit, Hematology, DMSC University of Florence, AOUC, Florence, Italy; ²National Center for Tumor Diseases (NCT), University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; ³Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; ⁴Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; ⁵Columbia University Medical Center, New York, NY, USA; ⁶Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; ⁷Centre Hospitalier Universitaire d'Angers, Angers, France; ⁸Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ⁹Clinic for Haematology, Oncology and Clinical Immunology, Düsseldorf University Hospital, Heinrich Heine University, Düsseldorf, Germany; ¹⁰Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; ¹¹University Hospital of Salamanca, IBSAL, Universidad de Salamanca, Salamanca, Spain; ¹²Hospital Universitario Vall d'Hebron, Barcelona, Spain; ¹³1st Medical Department – Hematology, General Hospital, Prague, Czech Republic; ¹⁴Geron Corporation, Foster City, CA, USA; ¹⁵Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; ¹⁶Moffitt Cancer Center, Tampa, FL, USA; ¹⁷Hôpital Saint-Louis, Université de Paris 7, Paris, France

Background

- The majority of lower-risk myelodysplastic syndromes (LR-MDS) are in the heterogenous group of ring sideroblast (RS)–negative disease¹
- Current treatment options are limited in number and efficacy, particularly for patients who are either ineligible for erythropoiesis-stimulating agents (ESAs) or whose disease is relapsed or refractory to ESAs^{1,2}
- First-line luspatercept treatment demonstrated differential efficacy in RS-positive compared with RS-negative disease; a benefit in RS-positive disease was also observed with luspatercept in the second-line setting compared with placebo^{3,4}
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase activity approved in the United States and Europe for the treatment of certain adult patients with LR-MDS with red blood cell (RBC) transfusion-dependent (TD) anemia who were relapsed or refractory⁵/had unsatisfactory⁶ response to or ineligible for ESAs based on the results of the pivotal IMerge trial (NCT02598661)⁷
 - Overall, results showed a clinically significant benefit with imetelstat versus placebo and a generally manageable safety profile in this patient population
 - Of the RS-negative LR-MDS subpopulation in Phase 3 IMerge (imetelstat, n=44; placebo, n=23), higher proportions treated with imetelstat versus placebo (32% vs 9% [nominal *P*=.038] and 20% vs 0% [nominal *P*=.019]) achieved ≥8-week and ≥24-week RBC-transfusion independence (TI), respectively

This post hoc analysis reports outcomes of patients with RS-negative disease from the pooled IMerge populations

Methods

- IMerge was a Phase 2/3 trial with a separate ventricular repolarization substudy that was included as a double-blind, randomized 2:1, placebo-controlled assessment
 - IMerge included patients with International Prognostic Scoring System low- or intermediate-1–risk, RBC-TD LR-MDS relapsed or refractory to/ineligible for ESAs
 - Differences between the patient populations in the QTc substudy and the Phase 3 trial are presented in **Figure 1**
 - Notably, patients in the QTc substudy could cross over from placebo to imetelstat after 2 cycles at the investigator's discretion
- In each part of IMerge, adult patients were randomized to 7.1 mg/kg imetelstat active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo, both administered as a 2-hour intravenous infusion every 4 weeks
- In this post hoc analysis, imetelstat-treated patients were pooled from Phase 2, Phase 3, and the QTc substudy of IMerge and analyzed on the basis of World Health Organization (WHO) 2008⁸ classification for RS status
- Efficacy endpoints included ≥8-week and ≥24-week RBC-TI rates, and hematologic improvement-erythroid per International Working Group 2006 (transfusion reduction ≥4 U/8 weeks and hemoglobin rise ≥1.5 g/dL lasting ≥8 weeks) and 2018 (low and high transfusion burden) criteria across prior treatment subgroups
 - Proportion of patients with RBC-TI, and other binary endpoints, were summarized with percentage and a 2-sided 95% CI using the exact Clopper-Pearson method
- Patient-reported outcomes were assessed with validated Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue⁹
 - Sustained meaningful improvement in fatigue was defined as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments

Figure 1. Pooled Patient Population From the 3 Parts of the IMerge Trial

Phase 2 IMerge ¹⁰ Single-arm, open-label	Phase 3 IMerge ⁷ Double-blind, randomized 2:1	QTc Substudy of Phase 3 IMerge ¹¹ Double-blind, randomized 2:1
Patient population (all treated) - IPSS low- or INT-1–risk MDS - Relapsed or refractory^a to ESA or EPO >500 mU/mL - Transfusion dependent: ≥4 RBC U/8 weeks over 16-week prestudy period - Inclusion of del(5q) and allowance of prior LEN and HMA	Patient population (ITT) - IPSS low- or INT-1–risk MDS - Relapsed or refractory^a to ESAs or EPO >500 mU/mL (ESA ineligible) - Transfusion dependent: ≥4 RBC U/8 weeks over 16-week prestudy period - Non-del(5q), no prior treatment with LEN or HMAs	Patient population differed from that of Phase 3 IMerge as follows: - Inclusion of patients with del(5q) MDS - Allowance of prior LEN and HMA use - Option to cross over from placebo to imetelstat after 2 cycles at the investigator's discretion
Imetelstat 7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium) IV every 4 weeks (n=57)	Imetelstat 7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium) IV every 4 weeks (n=118)	Imetelstat 7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium) IV every 4 weeks (n=35)
		Crossover from placebo to imetelstat (n=16)
Data cutoff date: October 13, 2023	Data cutoff date: October 13, 2023	Data cutoff date: October 13, 2024

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; INT, intermediate; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; IV, intravenous; LEN, lenalidomide; MDS, myelodysplastic syndromes; QTc, QT correction; RBC, red blood cell.
^aReceived ≥8 weeks of ESA treatment (EPO αfa ≥40,000 U, EPO beta ≥30,000 U, or darbepoetin alfa 150 µg or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U every 8 weeks or transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment.

Results

Patient Population

- Baseline characteristics for the 78 patients with RS-negative MDS included in this analysis are presented in **Table 1**; mutations for patients with available mutation data at baseline are presented in **Table 2**
 - The median RBC transfusion burden was 6.5 U/8 weeks, and most patients had prior ESA exposure
- Patients with RS-negative LR-MDS in this pooled population had a median follow-up of 26 months (range, 1-87)
 - Median imetelstat treatment duration was 25 weeks (range, 0.1-260), and median number of cycles of imetelstat was 6.5 (range, 1-66)

Table 1. Baseline Disease Characteristics

Characteristic	RS negative ^a (n=78)
Age, median (range), y	71.0 (44-86)
Sex, n (%)	
Female	29 (37)
Male	49 (63)
Time since diagnosis, median (range), y	2.8 (0.1-12.9)
IPSS risk category, n (%)	
Low	47 (60)
Intermediate-1	31 (40)
Pretreatment Hb, median (range), g/dL	77 (51-101)
Prior RBC transfusion burden, median (range), RBC U/8 weeks	6.5 (4-33)
Prior RBC transfusion burden, n (%)	
≤6 U/8 weeks	39 (50)
>6 U/8 weeks	39 (50)
Serum EPO, median (range), mU/mL	422 (16-5424)
Serum EPO level, n (%)	
≤500 mU/mL	40 (51)
>500 mU/mL	36 (46)
Missing	2 (3)
Prior therapies, n (%)	
ESA	62 (79)
Luspatercept	5 (6)
Lenalidomide	8 (10)
HMA	7 (9)

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast.
^aRS negative determination as reported by investigator based on 2008 WHO classification.

Table 2. Baseline Mutations

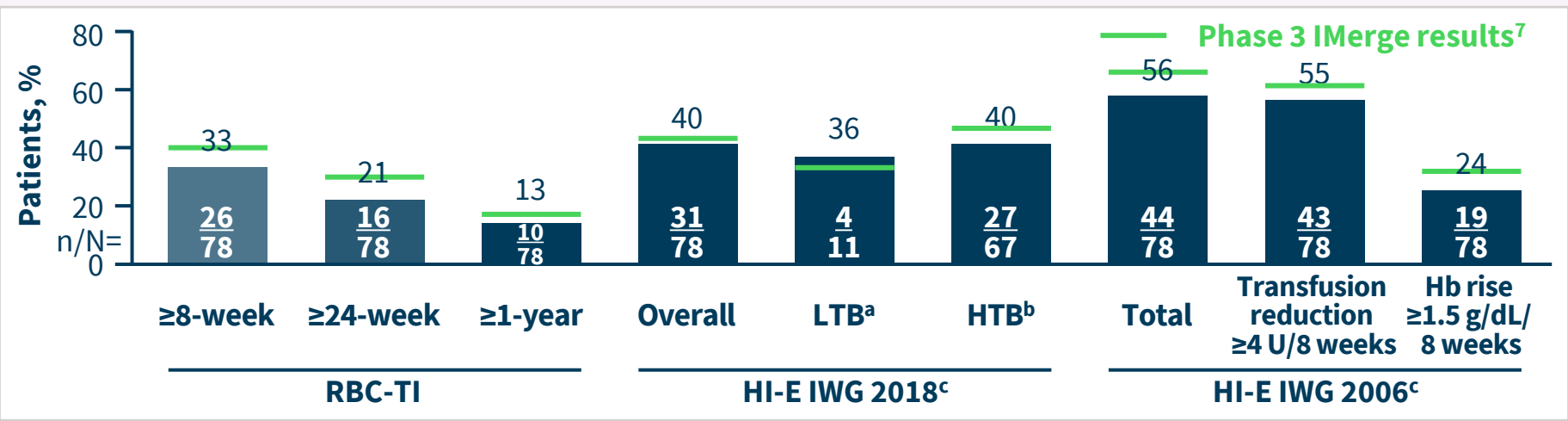
Characteristic	With baseline mutations ^a (n=54)
Characteristic	
Mutations at baseline, n (%)	
>1	33 (61)
>2	15 (28)
Missing ^b	7 (13)
Mutated genes, n (%)	
SF3B1 ^c	20 (37)
TET2	16 (30)
ASXL1	10 (19)
DNMT3A	8 (15)
SRSF2	9 (17)

^aPatients with available baseline mutation data and investigator reported 2008 WHO classification of RS- and additional Sponsor assessment of RS- per 2022 WHO classification (excluding patients with bone marrow RS cells ≥5% by local assessment and SF3B1 mutation at baseline). ^bSeven patients with mutation sample available for whom mutation status at baseline was not defined. ^cIn 20 patients with SF3B1 mutation, local bone marrow RS cells were confirmed ≤5% or missing and the SF3B2 mutation was confirmed. 10 out of the 20 patients had a K700E mutation and the remainder were a mixture of different hotspots (K666R, H662D, H662Q, H662Y, E622D, R625C, T663P).

Efficacy

- Efficacy results are presented in **Figure 2**, showing clinical activity in patients with RS-negative LR-MDS
 - Results from the IMerge Phase 3 registration trial are shown in green overlaid lines

Figure 2. Efficacy Results in RS-Negative LR-MDS After Imetelstat Treatment



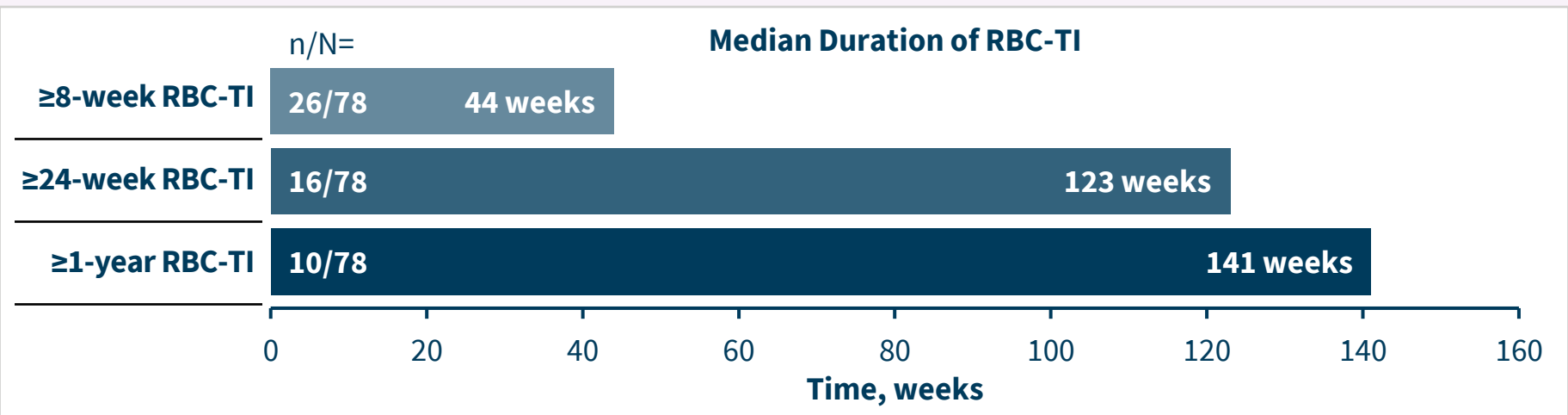
Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; LTB, low transfusion burden; n/N, number with event/number in population; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence.

^aLTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. ^bHTB defined as ≥8 RBC U in 16 weeks, or ≥4 RBC U in 8 weeks. ^cHb analyses were based on a central laboratory data in the Phase 3 part of IMerge, but only local laboratory data were collected in the Phase 2 and QTc substudy parts.

RBC-TI Duration

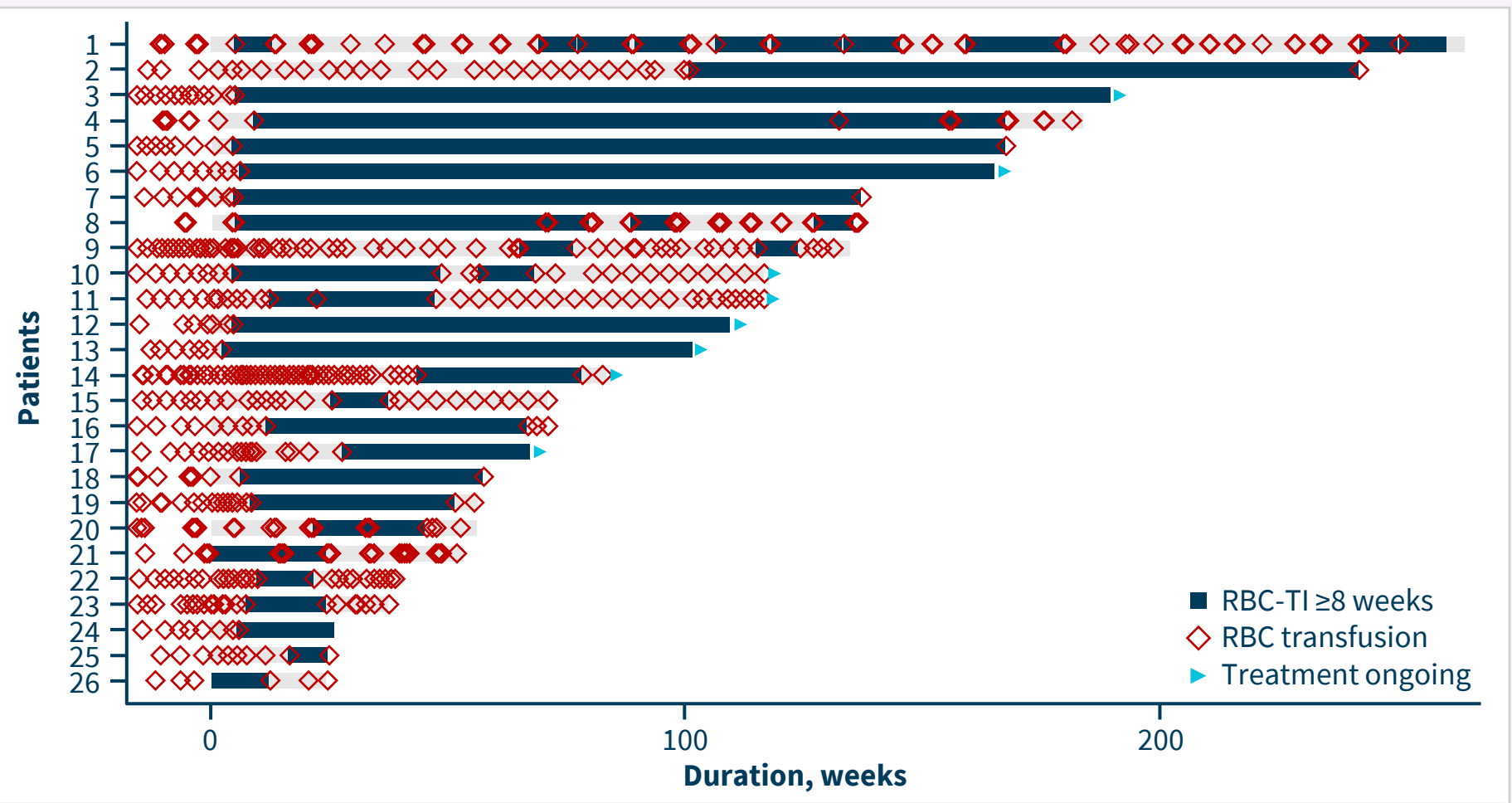
- Median length of the RBC-TI time period for ≥8-week, ≥24-week, and ≥1-year RBC-TI responders indicates durable TI beyond the outcome threshold (**Figure 3**, **Figure 4**)

Figure 3. Duration of Response in Patients Who Achieved RBC-TI With Imetelstat



RBC, red blood cell; TI, transfusion independence.

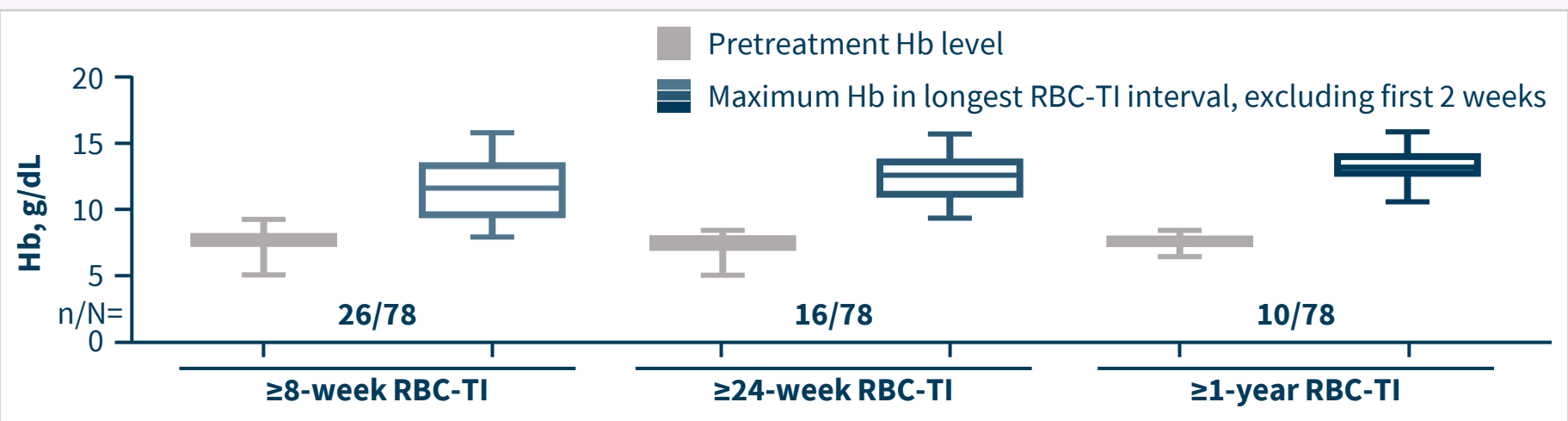
Figure 4. Continuous RBC-TI Period per Patient



Hemoglobin Rise

- Median (range) changes in hemoglobin from baseline are shown in **Figure 5**
 - Median hemoglobin rises in the longest RBC-TI interval of ≥8-week, ≥24-week, and ≥1-year RBC-TI responders were 4.3 g/dL, 5.2 g/dL, and 5.3 g/dL, respectively

Figure 5. Hb Levels in Patients Who Achieved RBC-TI With Imetelstat^a

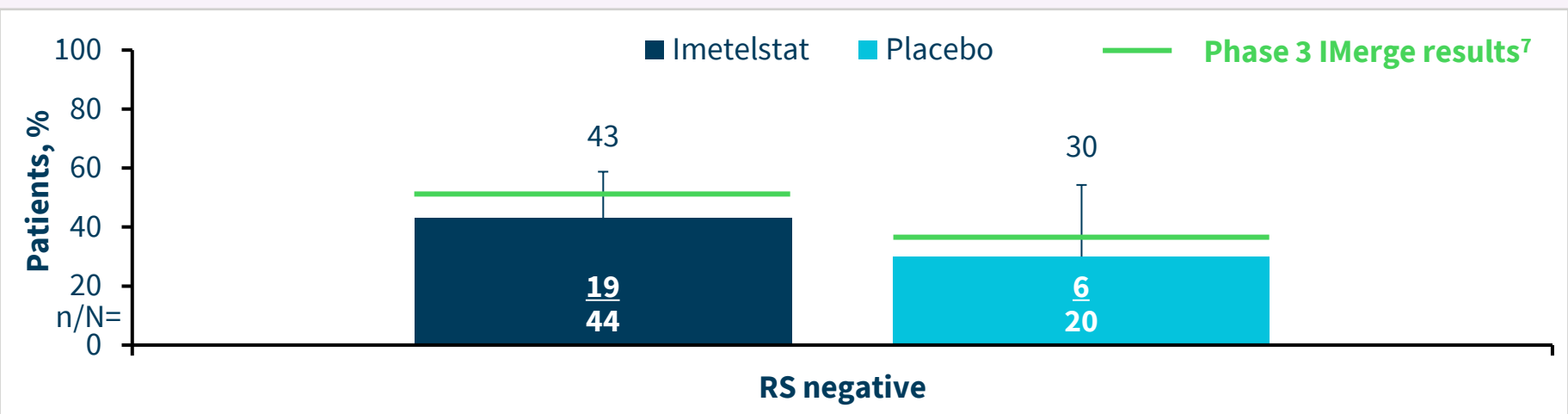


Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence.
Error bars represent minimum and maximum (range), and box ends represent the interquartile range.
^aHb analyses were based on a central laboratory data in the Phase 3 part of IMerge, but only local laboratory data were collected in the Phase 2 and QTc substudy parts.

Patient-Reported Outcome: FACIT-Fatigue

- Patient-reported FACIT-Fatigue was an exploratory outcome analyzed for the Phase 3 part of IMerge only, as data were not available for the Phase 2 and QTc substudy parts
 - Of the 118 imetelstat-treated and 57 placebo-treated patients in the Phase 3 part of IMerge with evaluable data, 44 and 20, respectively, had RS-negative status
 - Nineteen (43%) imetelstat-treated patients and 6 (30%) placebo-treated patients reported fatigue improvement (**Figure 6**)

Figure 6. FACIT-Fatigue Improvement in RS-Negative LR-MDS With Imetelstat Therapy^a



FACIT, Functional Assessment of Chronic Illness Therapy; LR-MDS, lower-risk myelodysplastic syndromes; n/N, number with event/number in population; RS, ring sideroblast.
^aData corresponds to Phase 3 population. The Clopper-Pearson method was used to generate 95% CIs.

Conclusions

- In this post hoc analysis of the 3 parts of IMerge, patients with RS-negative LR-MDS who were relapsed or refractory to or ineligible for ESAs appeared to experience clinical benefit with imetelstat treatment
- A rise in hemoglobin was observed in RS-negative patients who achieved RBC-TI with imetelstat
- More RS-negative patients receiving imetelstat as compared with placebo showed an improvement in fatigue in the Phase 3 portion of IMerge
- These results were consistent with prior findings^{7,10} and support that imetelstat has clinical activity in patients with difficult-to-treat RS-negative disease
- This analysis was limited by differing methodologies of the Phase 2, Phase 3, and QTc substudy parts of IMerge and by the small number of patients in some subgroups

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