

Effect of Prior Treatment on the Clinical Activity of Imetelstat in Transfusion-Dependent Patients With Erythropoiesis-Stimulating Agent, Relapsed or Refractory/Ineligible Lower-Risk Myelodysplastic Syndromes

6569

Rami S. Komrokji, MD,¹ Valeria Santini, MD,² Amer M. Zeidan, MBBS, MHS,³ Mikkael A. Sekeres, MD,⁴ Pierre Fenaux, MD, PhD,⁵ Azra Raza, MD,⁶ Moshe Mittelman, MD,⁷ Sylvain Thépot, MD,⁸ Rena Buckstein, MD, FRCPC,⁹ Ulrich Germing, MD,¹⁰ Yazan F. Madanat, MD,¹¹ María Díez-Campelo, MD, PhD,¹² David Valcárcel, MD, PhD,¹³ Anna Jonášová, MD, PhD,¹⁴ Sheetal Shah, BA,¹⁵ Qi Xia, PhD,¹⁵ Libo Sun, PhD,¹⁵ Shyamala Navada, MD,¹⁵ Michael R. Savona, MD,¹⁶ Uwe Platzbecker, MD¹⁷

¹Moffitt Cancer Center, Tampa, FL, USA; ²MDS Unit, Hematology, DMSC University of Florence, AOUC, Florence, Italy; ³Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; ⁴Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; ⁵Hôpital Saint-Louis, Université de Paris 7, Paris, France; ⁶Columbia University Medical Center, New York, NY, USA; ⁷Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; ⁸Centre Hospitalier Universitaire d'Angers, Angers, France; ⁹Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ¹⁰Clinic for Haematology, Oncology and Clinical Immunology, Düsseldorf University Hospital, Heinrich Heine University, Düsseldorf, Germany; ¹¹Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; ¹²University Hospital of Salamanca, Salamanca, Spain; ¹³Hospital Universitario Vall d'Hebron, Barcelona, Spain; ¹⁴1st Medical Department – Hematology, General Hospital, Prague, Czech Republic; ¹⁵Geron Corporation, Foster City, CA, USA; ¹⁶Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; ¹⁷National Center for Tumor Disease (NCT), University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany

Introduction

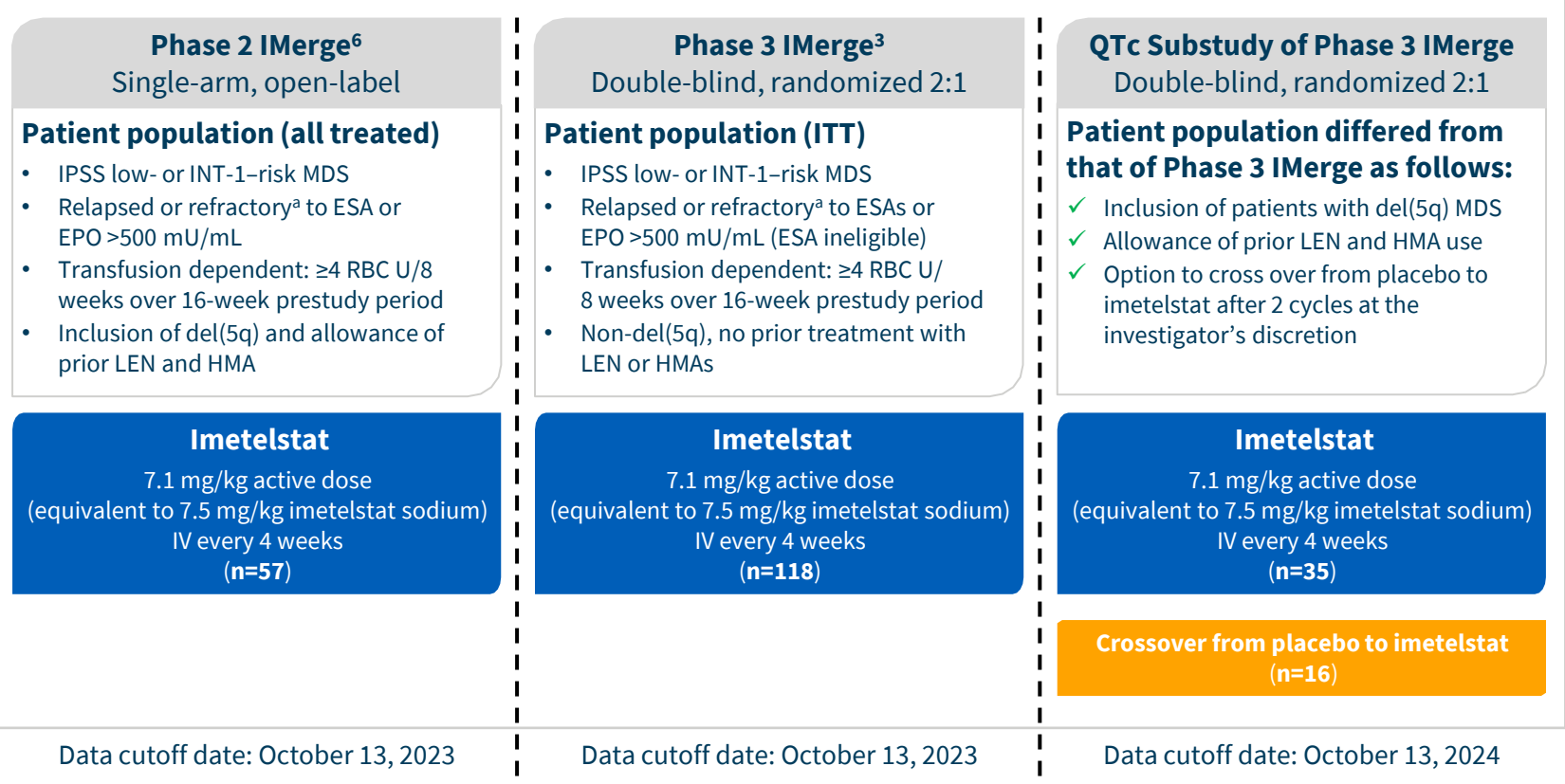
- Treatment options for patients with red blood cell (RBC) transfusion-dependent (TD) lower-risk (LR) myelodysplastic syndromes (MDS) have limited efficacy and durability, and there is a need for evidence to inform optimal treatment sequencing in these patients¹⁻³
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity approved by the United States Food and Drug Administration⁴ and European Commission⁵ for the treatment of certain adult patients with low- to intermediate-1 risk MDS with TD-anemia relapsed or refractory⁴/unsatisfactory response⁵ to or ineligible for erythropoiesis-stimulating agents (ESA) based on positive efficacy and safety results from the IMerge trial (NCT02598661)³
 - A significantly higher proportion of patients who received imetelstat achieved ≥8-week, ≥24-week, and ≥1-year RBC transfusion independence (TI) compared with patients who received placebo
 - These patients also had a greater increase in hemoglobin (Hb) concentrations and a greater reduction in transfusion burden
 - Imetelstat had a generally manageable safety profile
- The effect of prior use of other LR-MDS treatments on the clinical activity of imetelstat is currently unknown

This post hoc analysis investigated the effects of prior therapies on the clinical activity of imetelstat using pooled data from the 3 parts of IMerge (Phase 2, Phase 3, and QTC substudy)^{3,6}

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 (IPSS) low- or intermediate-1-risk, RBC-TD LR-MDS relapsed or refractory to 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 prior treatment as follows: ± ESA, luspatercept, lenalidomide, and hypomethylating agents (HMA)
 - Prior treatment was not exclusive; patients may have received >1 prior therapy
- Efficacy endpoints included ≥8-week and ≥24-week RBC-TI rates, hematologic improvement-erythroid per International Working Group 2006 (transfusion reduction ≥4 U/8 weeks and Hb rise ≥1.5 g/dL lasting ≥8 weeks) and 2018 (low and high transfusion burden) criteria, and safety across prior treatment subgroups
 - Proportion of patients with RBC-TI, and other binary endpoints, were summarized with percentage and 2-sided exact Clopper-Pearson 95% CI

Figure 1. Schematic Overview



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; LR-MDS, lower-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; QTC, QT correction; RBC, red blood cell.
^aReceived ≥8 weeks of ESA treatment (EPO alpha ≥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

- A total of 226 imetelstat-treated patients pooled from IMerge were included in this analysis (**Table 1**)
 - At baseline, most patients were aged ≥65 years, ring sideroblast +, IPSS low risk, and had high transfusion burdens
- Most patients had prior ESA (90%) and no prior lenalidomide (89%), luspatercept (84%), or HMA (90%)
 - Patients with prior ESA (n=204) had a median time since diagnosis to imetelstat treatment of 3.7 years and a median transfusion burden at baseline of 7.0 U/8 weeks
 - ESA-ineligible patients (n=22) had median time since diagnosis to imetelstat treatment of 1.4 years and median transfusion burden at baseline of 6.0 U/8 weeks
 - Prior luspatercept patients (n=36) had median time since diagnosis to imetelstat treatment of 3.8 years and median transfusion burden at baseline of 9.0 U/8 weeks
 - Prior lenalidomide patients (n=26) had median time since diagnosis to imetelstat treatment of 5.4 years and median transfusion burden at baseline of 7.5 U/8 weeks
 - Prior HMA patients (n=22) had median time since diagnosis to imetelstat treatment of 5.8 years and median transfusion burden at baseline of 9.0 U/8 weeks

Table 1. Baseline Characteristics

Baseline patient and disease characteristics	Imetelstat (N=226)
Age, median (range), y	71.0 (43-87)
≥65 y, n (%)	174 (77)
WHO classification, n (%)	
RS+	147 (65)
RS-	78 (35)
IPSS risk category, n (%)	
Low	151 (67)
Intermediate-1	75 (33)
Serum EPO level, n (%)	
≤500 mU/mL	155 (69)
>500 mU/mL	64 (28)
Missing	7 (3)
Prior RBC transfusion burden, n (%)	
≤6 U/8 weeks	112 (50)
>6 U/8 weeks	114 (50)
Transfusion burden per IWG 2018, n (%)	
LTB	38 (17)
HTB	188 (83)

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

- Median treatment duration on imetelstat was 33.6 weeks (**Table 2**)
 - The majority of patients received ≥7 cycles of imetelstat

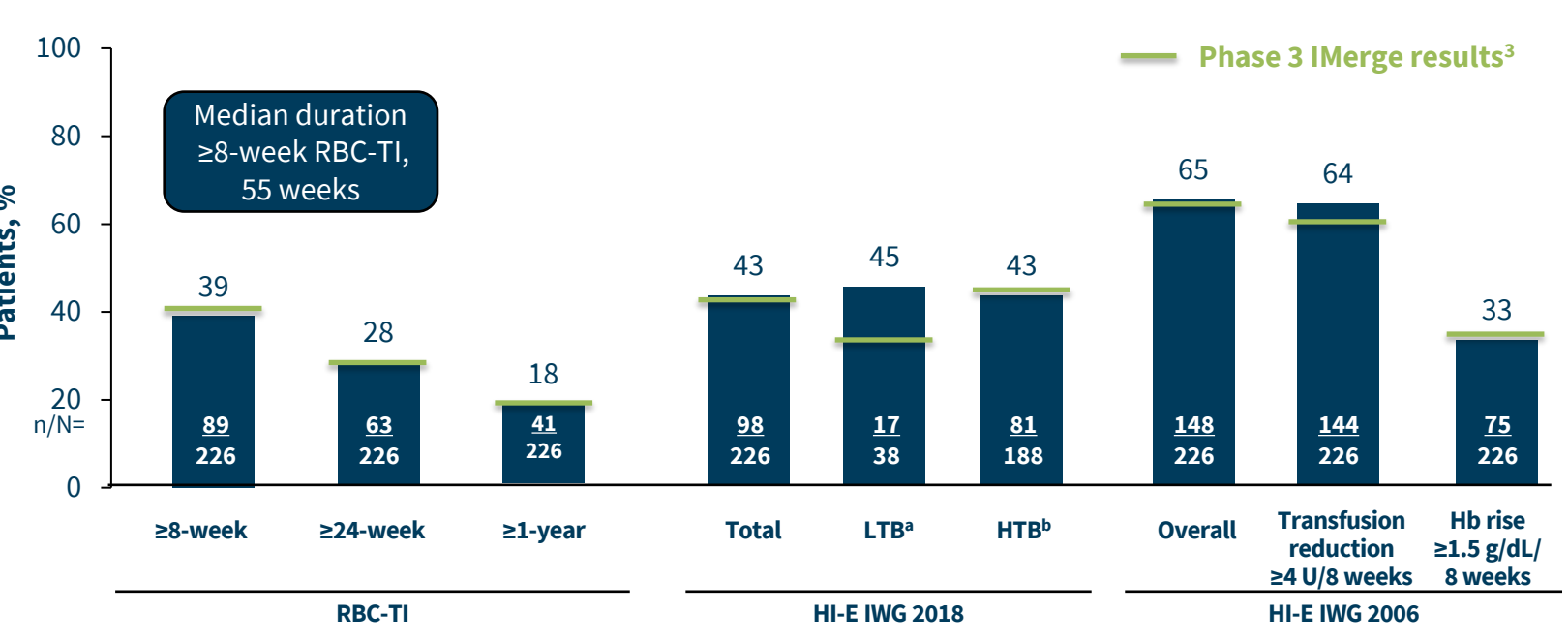
Table 2. Imetelstat Treatment Exposure

Imetelstat treatment exposure	Imetelstat (N=226)
Imetelstat treatment duration, median (range), weeks	33.6 (0.1-260.1)
Number of imetelstat treatment cycles, n (%)	
1-3 cycles	34 (15)
4-6 cycles	56 (25)
7-12 cycles	46 (20)
≥13 cycles	90 (40)

Efficacy

- Among pooled patients, 39% achieved ≥8-week RBC-TI and 28% achieved ≥24-week RBC-TI (**Figure 2**)

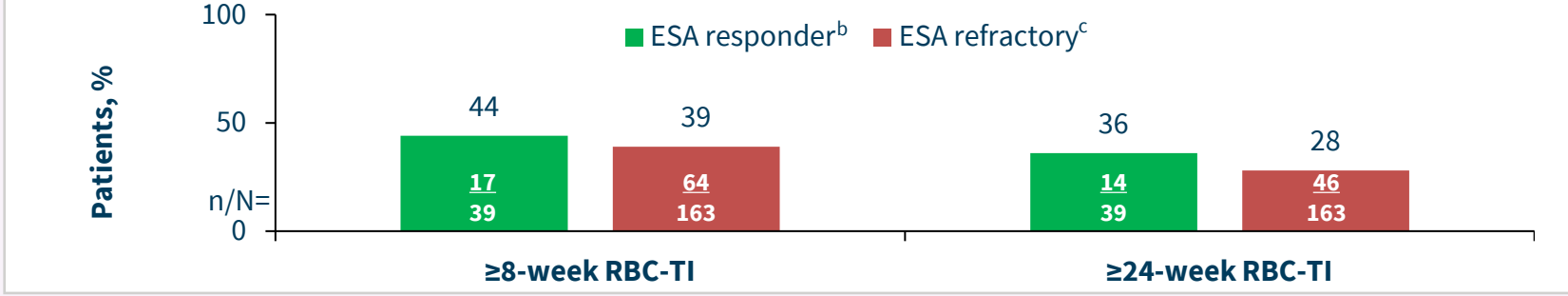
Figure 2. Efficacy in the Total Imetelstat Population (N=226)



Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; n/N, number with event/number in population; RBC, red blood cell; 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.

- Figure 3** shows prior ESA response status had no clinically meaningful effect on imetelstat activity

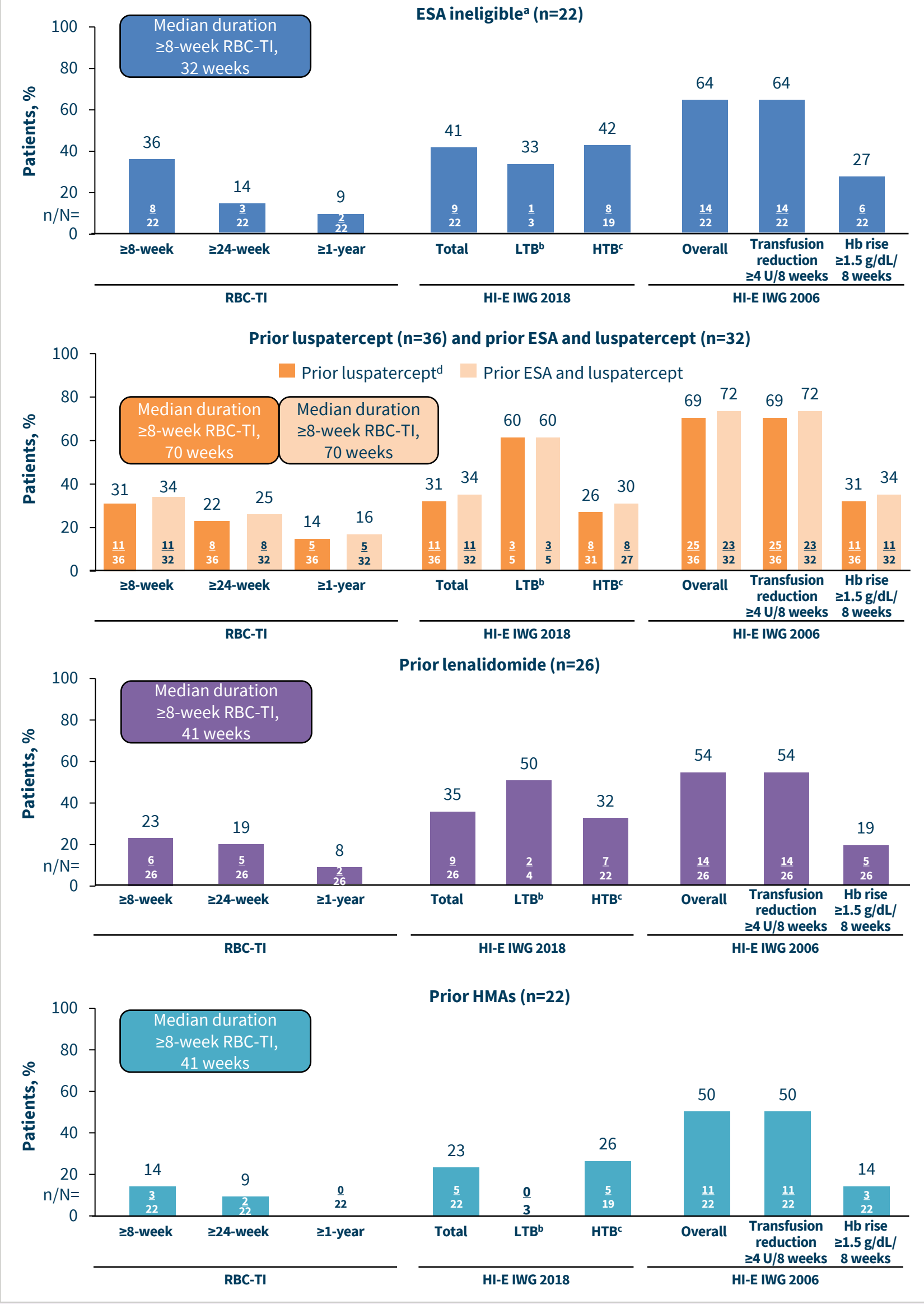
Figure 3. Clinical Activity of Imetelstat by Response to Prior ESA Therapy Subgroup (n=202)^a



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; n/N, number with event/number in population; RBC, red blood cell; TI, transfusion independence.
^aTwo patients with prior ESA but missing best response to ESA were excluded. ^bResponse included RBC-TI and HI-E response. ^cReceived ≥8 weeks of ESA treatment (EPO alpha ≥40,000 U, EPO beta ≥30,000 U, or darbepoetin alfa 150 µg or equivalent per week) without having achieved an Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement by ≥4 U every 8 weeks or having transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of treatment with therapies.

- Imetelstat showed clinical activity in ESA-ineligible patients and across prior luspatercept, lenalidomide, and HMA (alone) therapy subgroups (**Figure 4**)

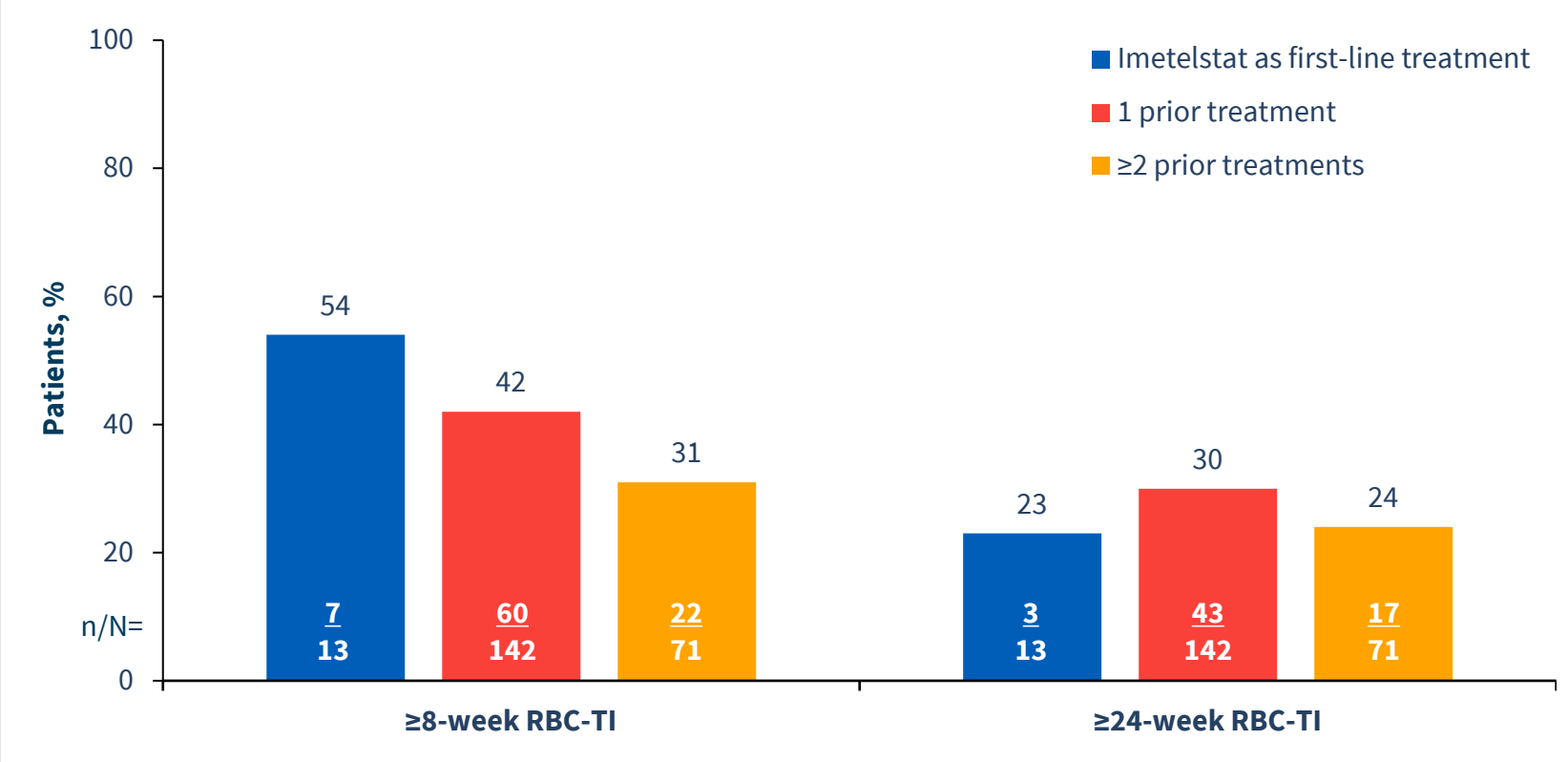
Figure 4. Clinical Activity of Imetelstat by Prior Therapy Subgroup



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; n/N, number with event/number in population; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence.
^aESA ineligibility per inclusion criteria was defined as EPO >500 mU/mL. ^bLTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. ^cHTB defined as ≥8 RBC U in 16 weeks, or ≥4 RBC U in 8 weeks. ^dOf these patients, 31 had RS+ status.

- Clinical activity of imetelstat by number of prior lines of therapy is presented in **Figure 5**

Figure 5. Imetelstat Showed Clinical Activity Regardless of Number of Prior Lines of Therapy (N=226)



n/N, number with event/number in population; TI, transfusion independence.

Safety

- Most cytopenia events occurred in earlier treatment cycles/months and were temporary and reversible, with most grade ≥3 neutropenia (82.6%) and thrombocytopenia (86.4%) events resolved to grade ≤2 in <4 weeks (**Table 3**)

Table 3. Safety Results With Imetelstat Were Consistent With Those of Phase 3 IMerge³

	Total (N=226)
TEAEs, n (%)	
Any grade	221 (97.8)
Serious	85 (37.6)
Grade ≥3	200 (88.5)
Most common TEAEs by preferred term in ≥15% of patients, n (%)	
Neutropenia	163 (72.1)
Thrombocytopenia	161 (71.2)
Anemia	48 (21.2)
Diarrhea	36 (15.9)
Alanine aminotransferase increased	35 (15.5)

TEAE, treatment-emergent adverse event.

Conclusions

- Patients who were ESA ineligible or who had prior treatment with luspatercept or lenalidomide in IMerge experienced clinical benefit from imetelstat treatment in this post hoc analysis, similar to prior results from the IMerge pivotal trial³
 - Patients who had prior treatment with HMA showed modest clinical activity with imetelstat
- Clinical activity of imetelstat was evident across lines of therapy and regardless of prior ESA response status, although the analysis was limited by the small number of patients in each group
- No new safety signals emerged; the most common treatment-emergent adverse events were neutropenia and thrombocytopenia
- Given the limited data available on outcomes in later lines of treatment, these results have important clinical implications in the evolving therapeutic landscape for LR-MDS, suggesting that imetelstat demonstrates clinical activity regardless of number or type of prior therapies

References

- Germing U, et al. *Hemasphere*. 2019;3(6):e314.
- Komrokji RS, et al. *Blood*. 2023;142(suppl 1):2440.
- Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.
- RYTELO[®] (imetelstat) for injection, for intravenous use. Package insert. Geron Corporation; 2024.
- RYTELO[®] (imetelstat) summary of product characteristics. Geron Corporation; 2025.
- Steensma DP, et al. *J Clin Oncol*. 2021;39(1):48-56.

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