

Durable Clinical Outcomes With Imetelstat in Korean Patients With Lower-Risk Myelodysplastic Syndromes

Ho-Jin Shin,¹ Valeria Santini,² Amer M. Zeidan,³ Rami S. Komrokji,⁴ Michael R. Savona,⁵ Uwe Platzbecker,⁶ Ashley L. Lennox,⁷ Qi Xia,⁷ Libo Sun,⁷ Michelle Mudge-Riley,⁷ Joseph Eid⁷

¹Division of Hematology-Oncology, Department of Internal Medicine, Biochemical Research Institution, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea; ²MDS Unit, Hematology, DMSC University of Florence, AOUC, Florence, Italy; ³Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; ⁴Moffitt Cancer Center, Tampa, FL, USA; ⁵Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; ⁶National Center for Tumor Diseases (NCT), University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; ⁷Geron Corporation, Foster City, CA, USA

Introduction

- Imetelstat is a first-in-class, direct, competitive inhibitor of telomerase activity that restores hematopoiesis by specifically targeting myelodysplastic clones with abnormally high telomerase activity^{1,2}
- Based on findings from the pivotal phase 3 IMerge trial (NCT02598661), imetelstat was approved in the United States and the European Union for the treatment of select adults with lower-risk myelodysplastic syndromes (LR-MDS) and red blood cell (RBC) transfusion-dependent (TD) anemia who are not candidates for erythropoiesis-stimulating agents (ESA) or who have relapsed or are refractory to ESAs³⁻⁵
 - In the primary analysis of IMerge, imetelstat demonstrated statistically significant improvements versus placebo in ≥ 8 -week RBC transfusion independence (TI) (primary endpoint), ≥ 24 -week RBC-TI (secondary endpoint), and ≥ 1 -year RBC-TI (exploratory endpoint)³

OBJECTIVE:
To report on 2 Korean patients with LR-MDS who achieved >1-year RBC-TI with imetelstat and to explore associations between cytopenias and treatment outcomes with imetelstat in 13 Korean patients from the Phase 2/3 study and the QTc substudy of IMerge

Methods

Figure 1. IMerge Study Design

	Phase 2 IMerge ⁶ Single-arm, open-label	Phase 3 IMerge ³ Double-blind, randomized 2:1	QTc Substudy of Phase 3 IMerge ⁷ Double-blind, randomized 2:1	
Patient population (all treated)	- 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 - Inclusion of del(5q) MDS - Allowance of prior LEN and HMA use	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) MDS only - No prior treatment with LEN or HMAs	Patient population differed from that of Phase 3 IMerge as follows: - Inclusion of 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)	7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium) IV every 4 weeks (n=118)	7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium) IV every 4 weeks (n=35)	
		Placebo	Crossover from placebo to imetelstat (n=16)	
Patients, n				Total, N
Pooled population	57	118	51	226
Korean subgroup	2	8	3	13

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating agent; INT, intermediate; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; LEN, lenalidomide; MDS, myelodysplastic syndromes; QTc, corrected QT interval; RBC, red blood cell.
^aReceived ≥ 5 weeks of ESA treatment (EPO $\alpha\alpha \geq 40,000$ U, EPO $\beta\alpha \geq 30,000$ U, or darbepoetin α 150 U/g or equivalent per week) without Hb rise ≥ 1.5 g/dL or decreased RBC transfusion requirement ≥ 4 U every 8 weeks or had transfusion dependence or reduction in Hb by ≥ 1.5 g/dL after hematologic improvement from ≥ 8 weeks of ESA treatment.

Results

- Baseline patient and disease characteristics were generally comparable between the Korean patient subgroup (n=13) and the total pooled IMerge population (Table 1)

Table 1. Baseline Patient and Disease Characteristics in the Total Pooled IMerge Population and the Korean Patient Subgroup

Characteristic	Total pooled population (N=226)	Korean patients (N=13)
Age, median (range), years	71 (43-87)	67 (44-77)
Sex, n (%)		
Male	144 (64)	10 (77)
Prior ESAs, n (%)	204 (90)	9 (69)
Prior RBC transfusion burden, n (%)		
≤ 6 U/8 weeks	112 (50)	11 (85)
> 6 U/8 weeks	114 (50)	2 (15)
Serum EPO level, n (%)		
≤ 500 mU/mL	155 (69)	7 (54)
> 500 mU/mL	64 (28)	6 (46)
Missing	7 (3)	0
WHO classification, n (%)		
RS+	147 (65)	8 (62)
RS-	78 (35)	5 (38)
IPSS risk category, n (%)		
Low	151 (67)	8 (62)
Intermediate-1	75 (33)	5 (39)
Transfusion burden per IWG 2018, n (%)		
LTB	38 (17)	3 (23)
HTB	188 (83)	10 (77)

EPO, erythropoietin; 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; WHO, World Health Organization.

Analysis in Korean Patients With >1-Year RBC-TI

- Two of 13 Korean patients achieved >1-year RBC-TI
 - Both patients had Intermediate-1 disease; 1 was RS-, Baseline EPO and platelet counts differed, whereas neutrophil counts were similar (Table 2)

Table 2. Baseline Patient and Disease Characteristics for the 2 Korean Patients With >1-Year RBC-TI

Characteristic	Patient 1	Patient 2
Age, years	66	72
Sex	Female	Male
IPSS category	Intermediate-1	Intermediate-1
RS status	RS+	RS-
Transfusion burden per IWG 2018	LTB	HTB
EPO, mU/mL	62.5	1287
Pretreatment Hb, g/dL	7.82	6.95
Prior treatments		
ESA	Yes	Yes
Lenalidomide	No	No
HMA	No	No
Luspatercept	No	No
Platelet count ($\times 10^9$/L)	480	117
Neutrophil count ($\times 10^9$/L)	2.26	2.5

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HMA, hypomethylating 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; TI, transfusion independence.
Differences between patients are shown in red.

Imetelstat Treatment Exposure

- Imetelstat treatment duration was 92.6 and 90.1 weeks, and the mean dose was 5.7 mg/kg/cycle and 4.9 mg/kg/cycle for Patient 1 and Patient 2, respectively (Table 3)

Table 3. Imetelstat Treatment Exposure for the 2 Korean Patients With >1-Year RBC-TI^a

Imetelstat treatment exposure	Patient 1	Patient 2
Imetelstat, mg/kg per cycle	5.7	4.9
Treatment duration, weeks	92.6	90.1
Treatment cycles, n	22	17
Treatment status	Discontinued (disease relapse)	Ongoing
Dose reduction	Yes	Yes
Reasons	Neutropenia	Thrombocytopenia, neutropenia
Cycle delay	Yes	Yes
Reasons	Neutropenia, influenza-like illness, GI disorder	Thrombocytopenia, neutropenia, joint abscesses

GI, gastrointestinal; RBC, red blood cell; TI, transfusion independence.
^aData cutoff: October 13, 2023, for Patient 1 and May 10, 2025, for Patient 2.

Efficacy Outcomes and Biomarkers

- RBC-TI with imetelstat was 80.4 and 54.7 weeks, and the maximum Hb rise during the RBC-TI period was 3.2 g/dL and 2.6 g/dL for Patient 1 and Patient 2, respectively (Table 4)
- Patient 1 had 3 genes with variant allele frequency reductions of approximately 50%: *ASXL1*, *DNMT3A*, and *SF3B1*
 - Data were unavailable for Patient 2

Table 4. Efficacy Outcomes for the 2 Korean Patients With >1-Year RBC-TI^a

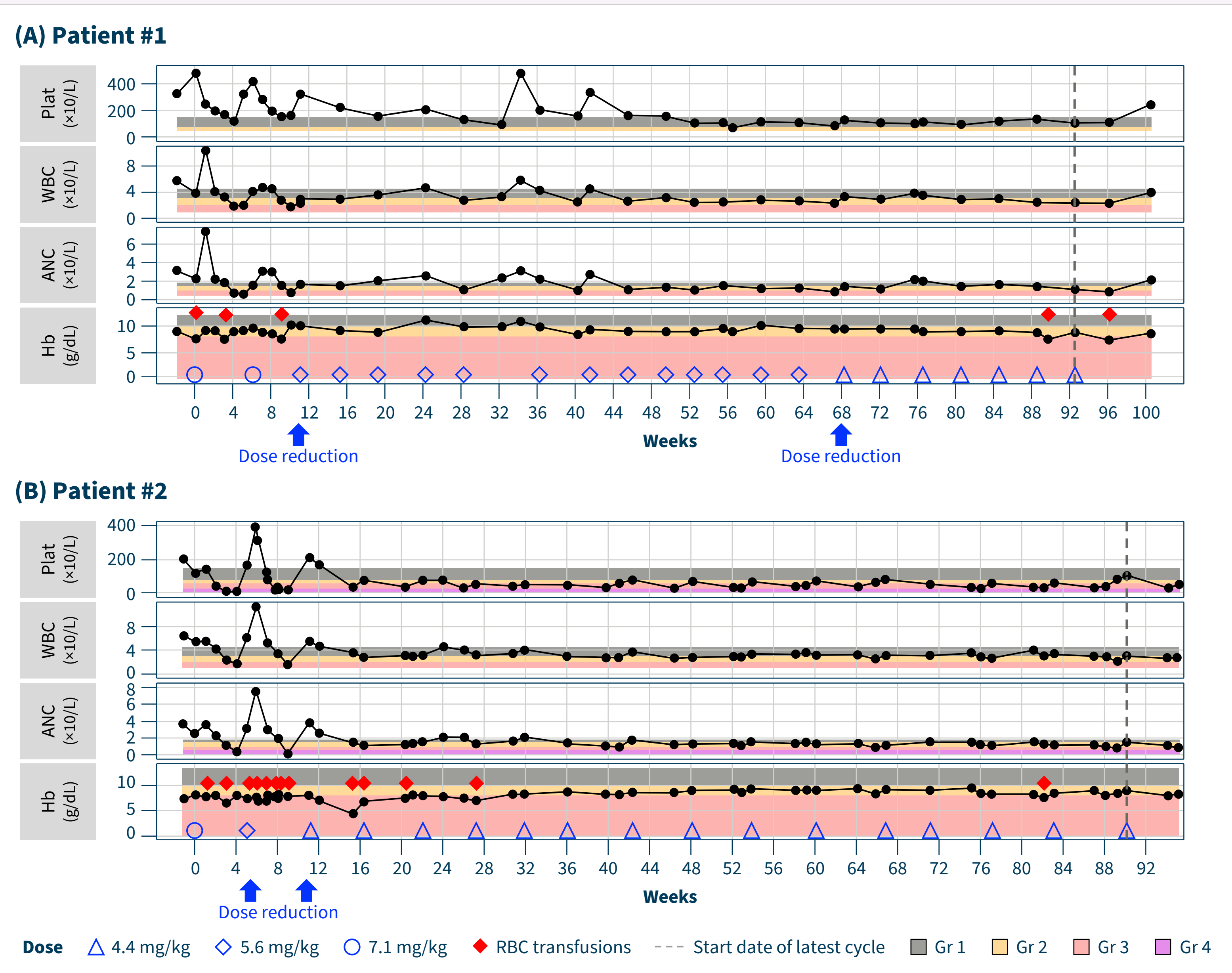
Efficacy parameter	Patient 1	Patient 2
Longest RBC-TI duration, weeks	80.4	54.7
Time to longest RBC-TI, weeks	9.3	27.4
Maximum Hb, g/dL	11.0	9.6
Maximum Hb rise from baseline, g/dL	3.2	2.6
Maximum improvement in fatigue score^b	15	NA

Hb, hemoglobin; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Scale; NA, not available; RBC, red blood cell; TI, transfusion independence.
^aData cutoff: October 13, 2023, for Patient 1 and May 10, 2025, for Patient 2.
^bDefined as any occurrence of ≥ 2 consecutive nonmissing FACIT-F assessments with an increase in score of ≥ 3 points compared with baseline.

Safety Outcomes

- As expected, both patients experienced cytopenias early during treatment with imetelstat (Figure 2), which were manageable (Table 5)
 - Both patients had grade 3/4 neutropenia and grade 3/4 thrombocytopenia events; most resolved to grade ≤ 2 in < 4 weeks

Figure 2. Laboratory Parameters for the 2 Korean Patients With >1-Year RBC-TI^a



ANC, absolute neutrophil count; Gr, grade; Hb, hemoglobin; INT, intermediate; Plat, platelets; RBC, red blood cell; TI, transfusion independence; WBC, white blood cell.
^aData cutoff: October 13, 2023, for Patient 1 and May 10, 2025, for Patient 2.

Table 5. Safety Outcomes for the 2 Korean Patients With >1-Year RBC-TI^a

Safety parameters	Patient 1	Patient 2
Grade 3/4 TEAEs (other than cytopenias)	Grade 3 influenza-like illness, GI disorder ^b	Grade 3 infection or infestation (joint abscesses) ^c
Grade 3/4 cytopenia	Grade 3 neutropenia	Grade 3/4 neutropenia, thrombocytopenia, leukopenia
Clinical consequences of grade 3/4 cytopenia (bleeding or infection within ≤ 7 days of grade 3/4 cytopenia event)	None	None
Number of grade 3/4 neutropenia events, N	5	6
Resolved to grade ≤ 2 within < 4 weeks, n (%)	4 (80.0)	5 (83.3)
Number of grade 3/4 thrombocytopenia events, N	0	15
Resolved to grade ≤ 2 within < 4 weeks, n (%)	0	15 (100)

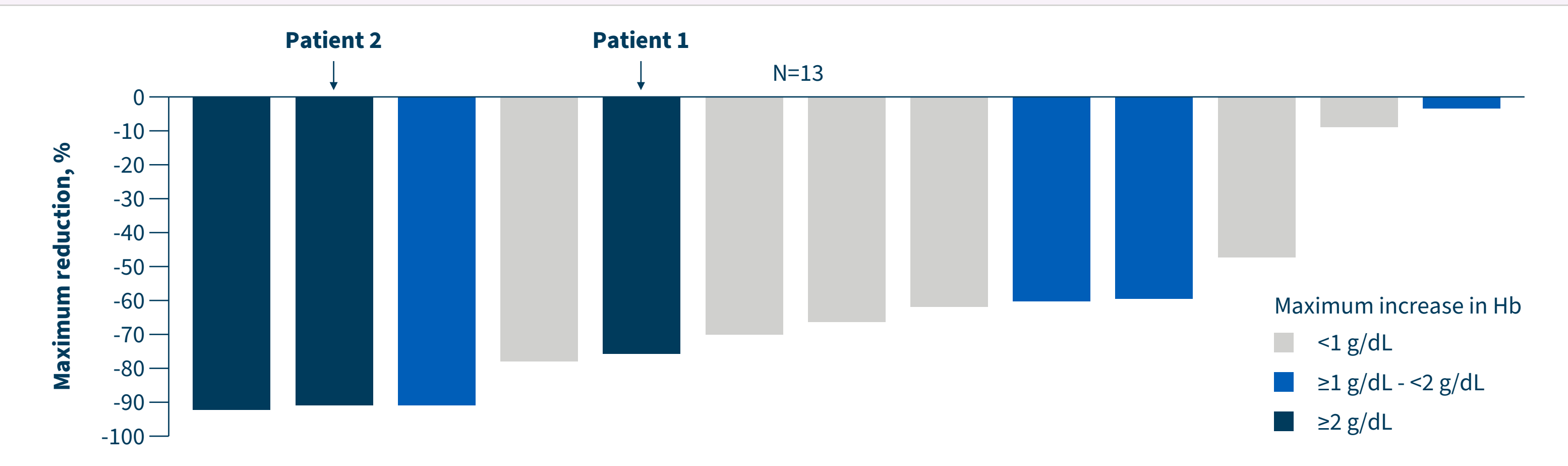
GI, gastrointestinal; RBC, red blood cell; TEAE, treatment-emergent adverse event; TI, transfusion independence.
^aData cutoff: October 13, 2023, for Patient 1 and May 10, 2025, for Patient 2.
^bConsidered not related to treatment; recovered/resolved.
^cConsidered not related to treatment; resolving.

Analysis in the Pooled Korean Patient Subgroup

Correlation Between Cytopenias and Hb Response

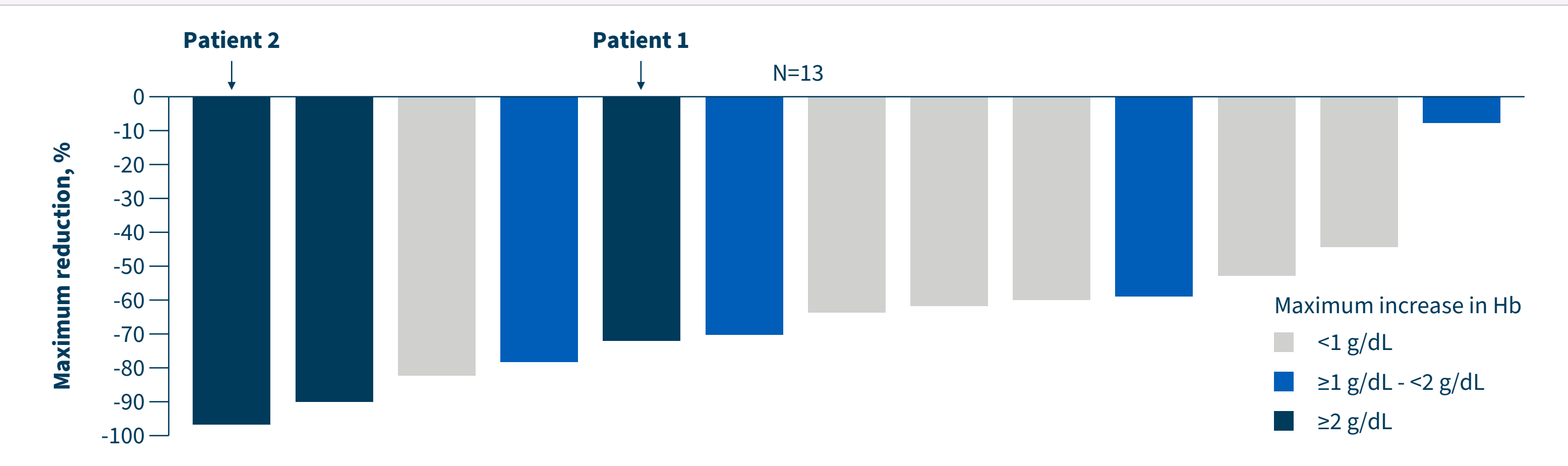
- Of the 13 Korean patients, 10 had a maximum platelet reduction of $\geq 50\%$ in the first 2 cycles, 6 and 3 of whom had an Hb rise of ≥ 1 and ≥ 2 g/dL, respectively (Figure 3)
- Four patients had a maximum neutrophil reduction of $\geq 75\%$ in the first 2 cycles, 3 and 2 of whom had an Hb rise of ≥ 1 and ≥ 2 g/dL, respectively (Figure 4)

Figure 3. Association Between Maximum Platelet Reduction $\geq 50\%$ With Imetelstat Treatment and Hb Rise in the Pooled Korean Subgroup From IMerge^a



Hb, hemoglobin
^aData cutoff: October 13, 2023, for Phase 3 and October 13, 2024, for QTc substudy.

Figure 4. Association Between Maximum Neutrophil Reduction $\geq 75\%$ With Imetelstat Treatment and Hb Rise in the Pooled Korean Subgroup From IMerge^a



Hb, hemoglobin
^aData cutoff: October 13, 2023, for Phase 3 and October 13, 2024, for QTc substudy.

Conclusions

- In this post hoc analysis, 2 Korean patients exhibited durable efficacy with imetelstat regardless of sex, RS status, baseline EPO, or baseline platelet levels
 - The results are consistent with those observed in the overall Korean subgroup and the total IMerge population^{3,8-10}
- Early cytopenias with imetelstat were associated with better clinical outcomes, as previously reported¹¹
- The study included a small number of Korean patients; therefore, the findings should be interpreted accordingly

The Japanese Society of Hematology Authors' COI Disclosure		
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