

Telomerase Inhibition With Imetelstat in Patients With Lower-Risk Myelodysplastic Syndromes: Integrating Molecular Findings, Cytopenias, and Clinical Outcomes

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Background

- Telomerase has been shown to be active and upregulated in most cancer cells, including hematologic malignancies, driving uncontrolled proliferation of malignant stem and progenitor cells; it is a key molecular target in oncology¹⁻³
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase activity that specifically targets MDS clones with abnormally high telomerase activity, inducing apoptosis in tumor cells, and enabling the recovery of effective hematopoiesis⁴⁻⁷
- In Europe, imetelstat is approved for the treatment of adult patients with RBC-TD anemia due to very low-, low-, or intermediate-1–risk MDS without an isolated deletion 5q cytogenetic abnormality and who had unsatisfactory response to or are ineligible for ESA-based therapy⁸
 - The approval of imetelstat was based on the pivotal, Phase 3 IMerge trial (NCT02598661)⁹

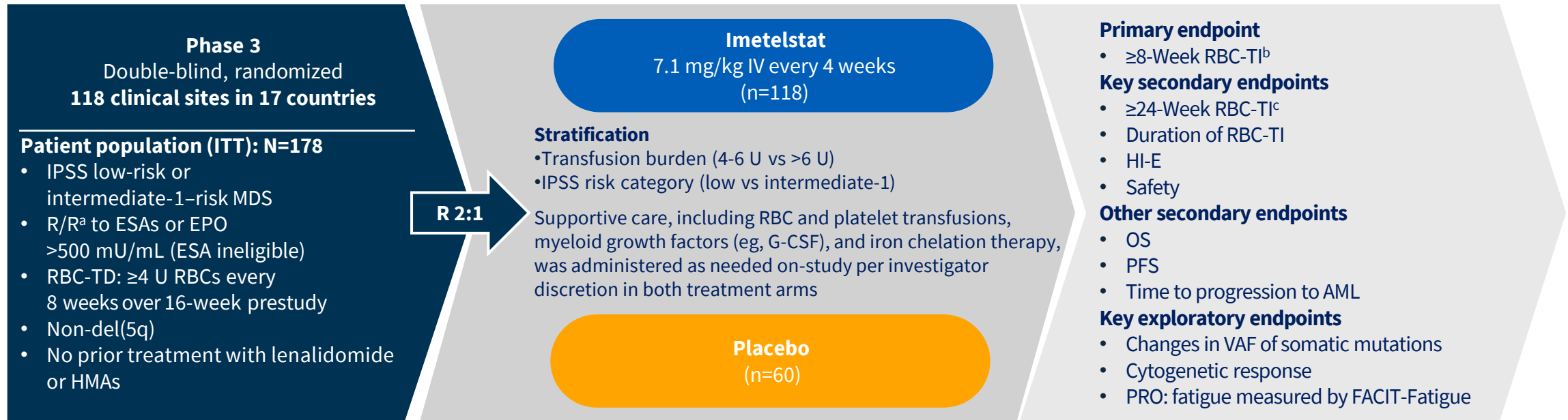
Here, we examine emerging evidence on imetelstat to support clinical practice

ESA, erythropoiesis-stimulating agent; MDS, myelodysplastic syndromes; RBC, red blood cell; TD, transfusion dependent.

1. Waksal JA, et al. *Blood Adv.* 2023;7(16):4302-4314. 2. Shammas MA. *Curr Opin Clin Nutr Metab Care.* 2011;14(1):28-34. 3. Cong Y-S, et al. *Microbiol Mol Biol Rev.* 2002;66(3):407-425. 4. Wang X, et al. *Blood Adv.* 2018;2(18):2378-2388. 5. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939. 6. Herbert B-S, et al. *Oncogene.* 2005;24(33):5262-5268. 7. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467. 8. RYTELO® (imetelstat) summary of product characteristics. Geron Corporation; 2025. 9. Platzbecker U and Santini V, et al. *Lancet.* 2024;403(10423):249-260.

Methods

IMerge Phase 3 Study Design¹



- A qualitative evaluation of primary, exploratory, and post hoc analyses from the IMerge trial of interest for hematologists and oncologists published between January 1, 2024, and March 1, 2026, was conducted
- Available clinical and mechanistic evidence on imetelstat was summarized to inform clinical decision-making

AML, acute myeloid leukemia; BL, baseline; 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 syndromes; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; R, randomized; RBC, red blood cell; R/R, relapsed or refractory; TD, transfusion dependent; TI, transfusion independence.

^aReceived ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin 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. ^bProportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial. ^cProportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial.

1. Platzbecker U and Santini V, et al. Lancet. 2024;403(10423):249-260.

IMerge Phase 3: Demographics and Disease Characteristics

- The ITT study population comprised 118 and 60 patients in the imetelstat and placebo arms, respectively

Treatment	Age, median (range), y	Male, n (%)	Time since diagnosis, median (range), y	WHO classification, n (%)	IPSS risk category, n (%)	Pretreatment Hb, ^a median (range), g/dL
Imetelstat (N=118)	72 (44-87)	71 (60)	3.5 (0.1-26.7)	RS+: 73 (62) RS-: 44 (37)	Low: 80 (68) INT-1: 38 (32)	7.9 (5.3-10.1)
Placebo (N=60)	73 (39-85)	40 (67)	2.8 (0.2-25.7)	RS+: 37 (62) RS-: 23 (38)	Low: 39 (65) INT-1: 21 (35)	7.8 (6.1-9.2)

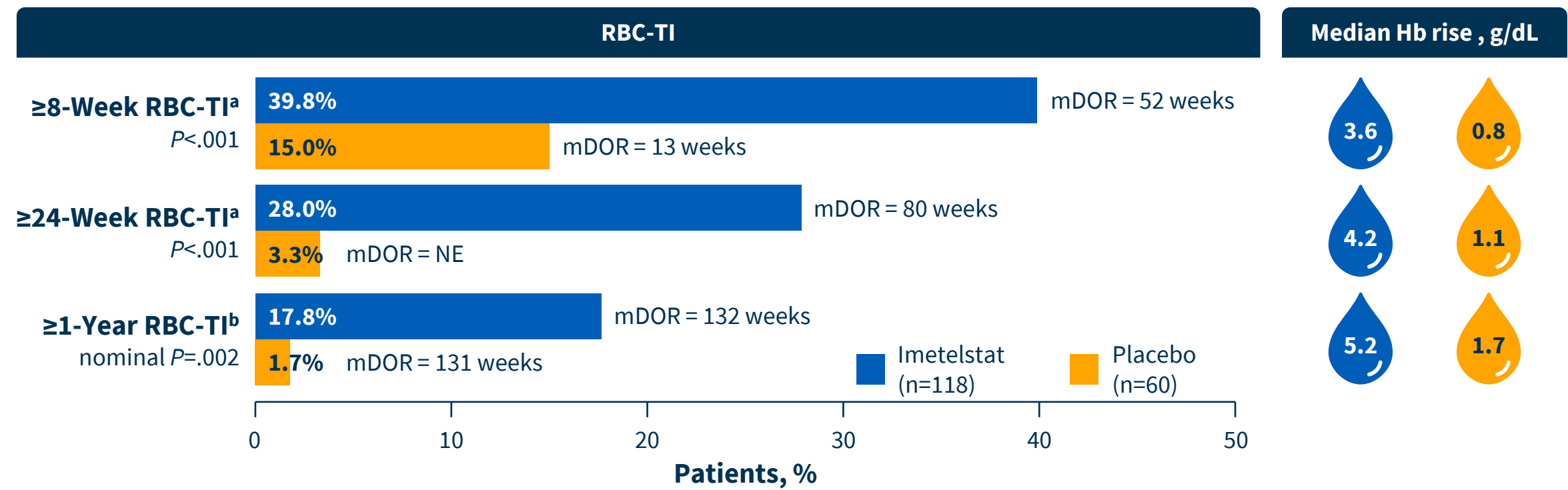
Treatment	Prior RBC transfusion burden, median (range), RBC U/8 weeks	Prior RBC transfusion burden, n (%)	sEPO, median (range), mU/mL	sEPO level, n (%) ^b	Prior ESA, n (%)	Prior luspatercept, n (%)
Imetelstat (N=118)	6 (4-33)	≥4 to ≤6 U/8 weeks: 62 (53) >6 U/8 weeks: 56 (48)	174.9 (6.0-4460.0)	≤500 mU/mL: 87 (74) >500 mU/mL: 26 (22)	108 (92)	7 (6)
Placebo (N=60)	6 (4-13)	≥4 to ≤6 U/8 weeks: 33 (55) >6 U/8 weeks: 27 (45)	277.0 (16.9-5514.0)	≤500 mU/mL: 36 (60) >500 mU/mL: 22 (37)	52 (87)	4 (7)

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; RBC, red blood cell; sEPO, serum erythropoietin; WHO, World Health Organization.

^aAverage of all Hb values in the 8 weeks before the first dose date, excluding values within 14 days after a transfusion, which was considered to be influenced by transfusion. ^bData missing for 5 patients in the imetelstat group and 2 in the placebo group.

Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.

IMerge Phase 3: Higher RBC-TI Rates, Greater Hb Rise, and Longer RBC-TI Duration in Patients Treated With Imetelstat Versus Placebo¹⁻³



- Increase in Hb level was noted in some imetelstat RBC-TI responders within ≤4 weeks of treatment

Hb, hemoglobin; mDOR, median duration of response; NE, not evaluable; RBC, red blood cell; TI, transfusion independence.
^aData cutoff date, October 13, 2022. ^bData cutoff date, January 13, 2023.
1. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260. 2. Madanat YF, et al. Presentation presented at: NCCN Annual Conference; April 5-7, 2024; Orlando, FL. 3. Geron Corporation. Data on file. 2025.

IMerge Phase 3: Well-Characterized Safety Profile With Generally Manageable and Short-Lived Thrombocytopenia and Neutropenia^{1,a}

- Hematologic AEs were the most common imetelstat AEs¹
 - Cytopenias suggest an on-target, disease-modifying effect of imetelstat on clonal progenitor cells
- Most grade 3/4 thrombocytopenia and neutropenia occurred during cycles 1-3, and were resolved to grade ≤2 in under 4 weeks in >80% of patients
- Severe clinical consequences of neutropenia and thrombocytopenia were similar in imetelstat and placebo arms

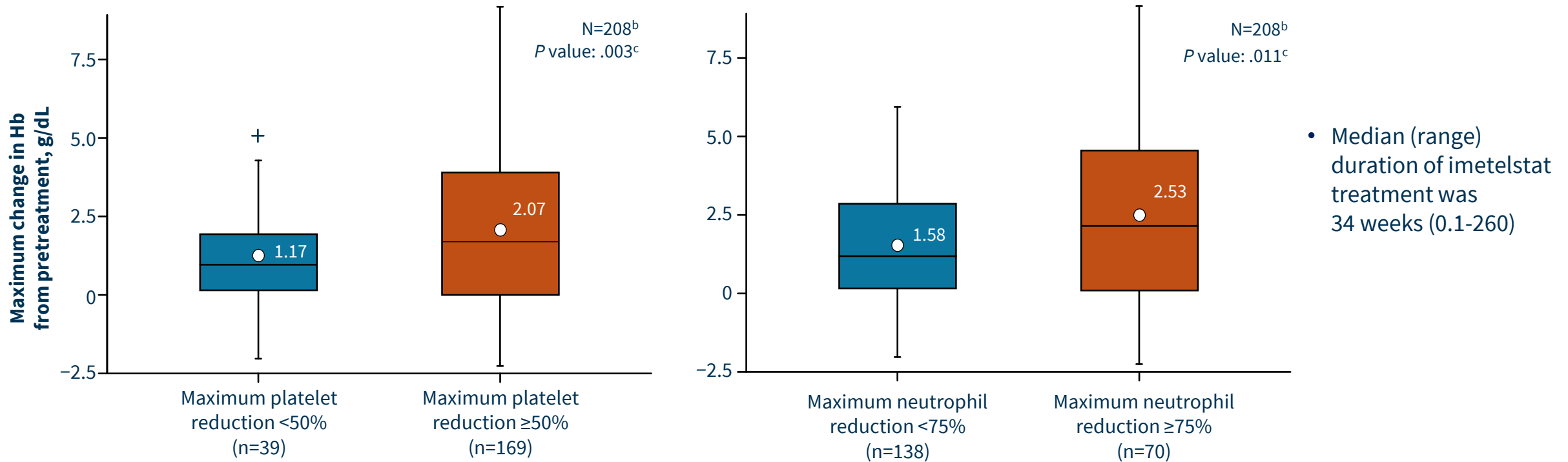
AEs (≥15% of patients), n (%)	Imetelstat (N=118)		Placebo (N=59)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Thrombocytopenia	89 (75)	73 (62)	6 (10)	5 (8)
Neutropenia	87 (74)	80 (68)	4 (7)	2 (3)
Anemia	24 (20)	23 (19)	6 (10)	4 (7)

Event, n (%)	Imetelstat (N=118)	Placebo (N=59)
	Grade 3/4	Grade 3/4
Bleeding events ^b	3 (3)	1 (2)
Infections ^c	13 (11)	8 (14)
Febrile neutropenia ^d	1 (1)	0

- AEs were generally manageable with supportive care and dose modifications; <15% of patients discontinued treatment due to TEAEs generally late in treatment (median, 21.1 weeks)
 - ~74% of patients required infusion or dose modification (cycle delay, dose reduction, or treatment interruption)
 - ~49% of patients required dose reduction
- Nonhematologic AEs were generally low grade; no cases of Hy’s Law or drug-induced liver injury observed¹
- IRR occurred in 8% of patients (grade 3/4: 1.7%, including hypertensive crisis of 0.8%); headache was the most common (4.2%)²

AE, adverse event; IRR, infusion-related reaction; SmPC, Summary of Product Characteristics; TEAE, treatment-emergent adverse event.
^aThese data from IMerge Phase 3 differ from data reported in the SmPC, which are from a pooled IMerge Phase 2 and Phase 3 safety population (N=175).³ ^bNo grade ≥3 bleeding events in the setting of grade 3/4 thrombocytopenia; on imetelstat: 2 patients with grade 4 gastrointestinal bleeding, unrelated and resolved, and 1 grade 3 hematuria, unrelated and resolved. ^cOn imetelstat: 3 patients with grade 3/4 infections in the setting of grade 3/4 neutropenia; all 3 were sepsis and resolved with only 1 considered related. ^dOccurred at day 33 and lasted 8 days; assessed by investigator as possibly related to imetelstat; patient subsequently achieved transfusion independence >40 weeks and remains on treatment at data cutoff.
1. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260. 2. RYTELO® (imetelstat) for injection, for intravenous use. Package insert. Geron Corporation; 2024. 3. RYTELO® (imetelstat) summary of product characteristics. Geron Corporation; 2025.

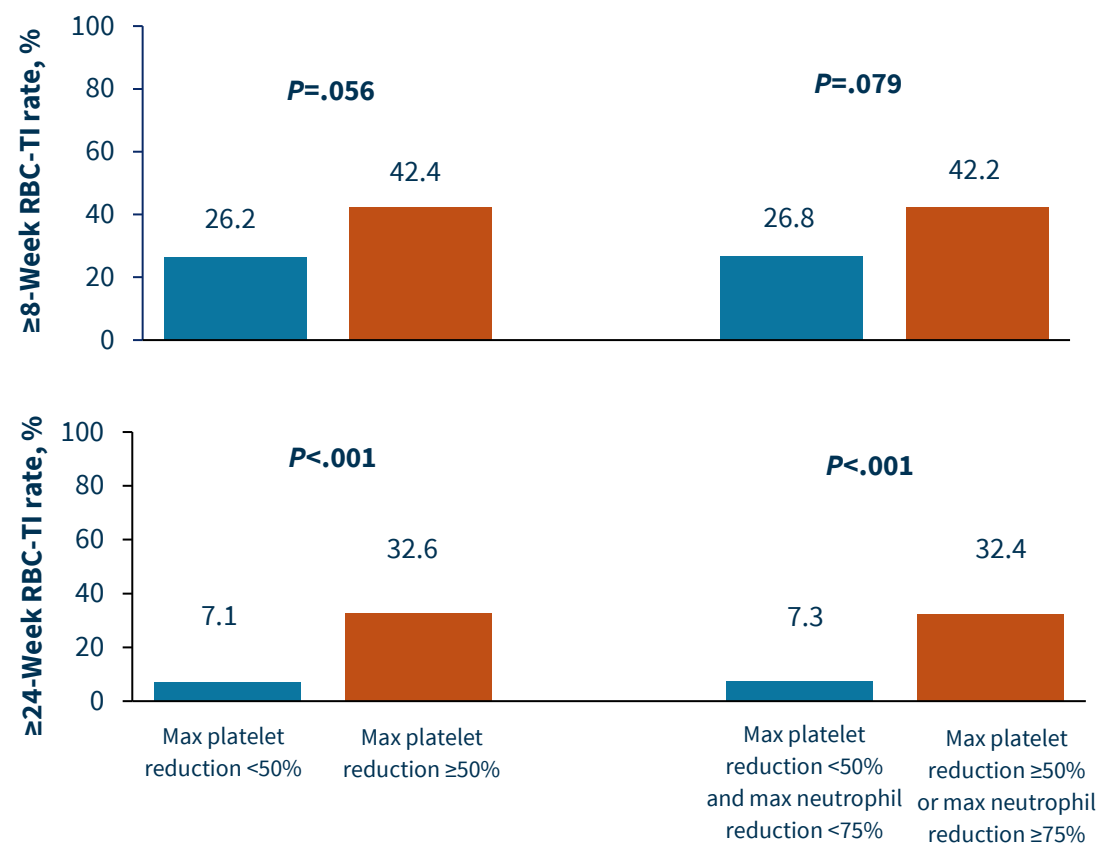
Pooled Population^a: Maximum Percent Reduction in Platelets or Neutrophils, $\geq 75\%$ Neutrophil Reduction Within the First 2 Imetelstat Cycles, or $\geq 50\%$ Platelet Reduction Within the First 2 Imetelstat Cycles Were Significantly Associated With Greater Hb Rise



Hb, hemoglobin.

^aPatients pooled from IMerge Phase 2, Phase 3, and QTc substudy who received 7.1 mg/kg imetelstat active dose (7.5 mg/kg imetelstat sodium equivalent). ^bHb values within 14 days of red blood cell transfusion are excluded due to impact of transfusions. Eighteen patients did not have Hb values outside 14 days of transfusion; thus, their Hb change from pretreatment is not available. ^cUnadjusted nominal P values are presented. Zeidan AM, et al. *Blood Cancer J.* 2026;16(1):55.

Pooled Population^a: The Greater Hb Rise From Pretreatment Emerged as a Main Driver for Achieving ≥8-Week and ≥24-Week RBC-TI



Multivariate Analysis on RBC-TI in 208 Pooled Patients With Hb Values Not Within 14 Days of RBC Transfusion^b

	≥8-Week RBC-TI	≥24-Week RBC-TI
Factors	P value	P value
Max increase in Hb	<.001	<.001
Pretreatment Hb	<.001	NS
IPSS risk	.004	NS

- Potential baseline prognostic factors included in stepwise variable selection: platelet and absolute neutrophil count, pretreatment Hb, serum erythropoietin levels, IPSS risk, revised IPSS risk, RBC transfusion burden, RS status, karyotype, age, sex, ECOG PS, and time from diagnosis

ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; IPSS, International Prognostic Scoring System; NS, not significant; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence.
^aPatients pooled from IMerge Phase 2, Phase 3, and QTc substudy who received 7.1 mg/kg imetelstat active dose (7.5 mg/kg imetelstat sodium equivalent). ^bHb values within 14 days of RBC transfusion are excluded due to impact of transfusions. Eighteen patients did not have Hb values outside 14 days of transfusion; thus, their Hb change from pretreatment is not available.
Zeidan AM, et al. *Blood Cancer J.* 2026;16(1):55.

IMerge Phase 3: Higher Rates of $\geq 50\%$ Reductions in Genes Frequently Mutated in MDS With Imetelstat Versus Placebo, Which Correlated With Improved Outcomes^{1,2}

- VAF reduction by $\geq 50\%$ in *SF3B1*, *TET2*, *DNMT3A*, and *ASXL1* mutations in patients with evaluable mutation data

	Imetelstat	Placebo	Nominal <i>P</i> value ^a
VAF reduction, n/N (%)			
$\geq 50\%$ <i>SF3B1</i>	23/78 (30)	1/38 (3)	.001
$\geq 50\%$ <i>TET2</i>	12/35 (34)	1/12 (8)	NS
$\geq 50\%$ <i>DNMT3A</i>	2/18 (11)	0/8 (0)	NS
$\geq 50\%$ <i>ASXL1</i>	4/10 (40)	1/6 (17)	NS

- VAF reductions with imetelstat correlated with longer RBC-TI duration and increased Hb levels compared with placebo (not shown)
- Both ≥ 8 weeks and ≥ 24 weeks of RBC-TI correlated with reduction in RS+ cells, cytogenetic responses, and VAF reduction in patients treated with imetelstat

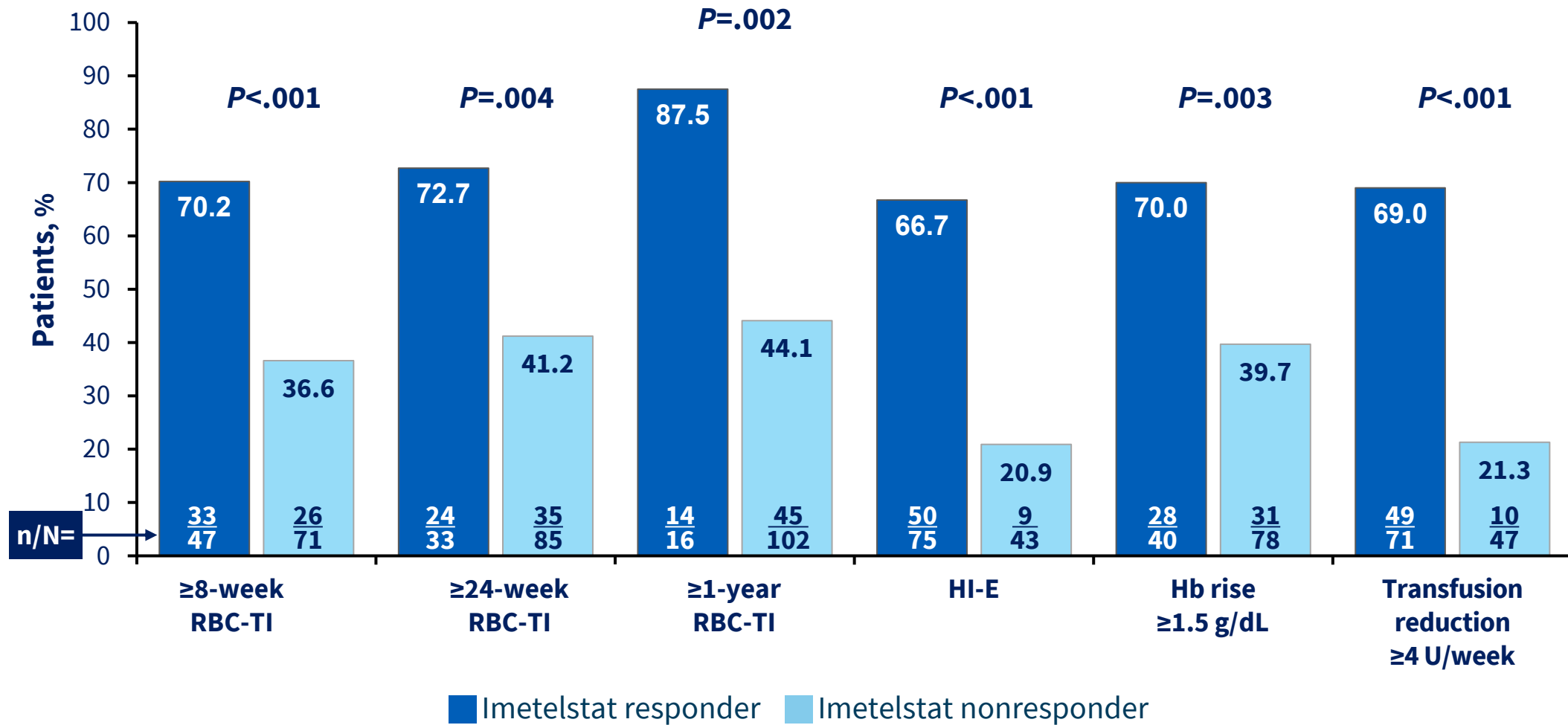
	Imetelstat responders	Imetelstat nonresponders	Nominal <i>P</i> value
≥ 8-Week RBC-TI correlations, n/N (%)			
$\geq 50\%$ BM RS reduction	22/29 (75.9)	16/42 (38.1)	.003
Cytogenetic CR/PR per IRC	8/9 (88.9)	6/17 (35.3)	.014
VAF reduction			
$\geq 50\%$ <i>SF3B1</i>	19/23 (82.6)	21/55 (38.2)	<.001
$\geq 50\%$ <i>TET2</i>	10/12 (83.3)	10/23 (43.5)	.034
$\geq 50\%$ <i>DNMT3A</i>	2/2 (100)	4/16 (25.0)	.098
$\geq 50\%$ <i>ASXL1</i>	3/4 (75.0)	1/6 (16.7)	.190
≥ 24-Week RBC-TI correlations, n/N (%)			
$\geq 50\%$ BM RS reduction	18/29 (62.1)	11/42 (26.2)	.003
Cytogenetic CR/PR per IRC	6/9 (66.7)	3/17 (17.6)	.028
VAF reduction			
$\geq 50\%$ <i>SF3B1</i>	16/23 (69.6)	13/55 (23.6)	<.001
$\geq 50\%$ <i>TET2</i>	10/12 (83.3)	6/23 (26.1)	.003
$\geq 50\%$ <i>DNMT3A</i>	2/2 (100)	3/16 (18.8)	.065
$\geq 50\%$ <i>ASXL1</i>	2/4 (50.0)	0/6 (0)	.133

BM, bone marrow; CR, complete response; Hb, hemoglobin; IPSS, International Prognostic Scoring System; IRC, independent review committee; MDS, myelodysplastic syndromes; NS, not significant; PR, partial response; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence; VAF, variant allele frequency.

^a*P* values based on Cochran-Mantel-Haenszel test stratified for prior RBC transfusion burden (≤ 6 U or >6 U of RBC every 8 weeks) and baseline IPSS risk score (low or intermediate-1).

1. Santini V, et al. Presentation presented at: SOHO 2023 Annual Meeting; September 6-9, 2023; Houston, TX. 2. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.

IMerge Phase 3: Improvement in FACIT-Fatigue in Imetelstat Responders^a



FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; n/N, number with event/number in population; RBC, red blood cell; TI, transfusion independence.

^aDefined for fatigue as a ≥3-point increase in FACIT-Fatigue score for ≥2 consecutive assessments.

This analysis was performed in the PRO population, defined as the intention-to-treat population who had PRO data at baseline.

Sekeres MA, et al. *Haematologica*. Published online January 2022, 2026. doi: 10.3324/haematol.2025.288956.

Conclusions

- Imetelstat, a first-in-class telomerase inhibitor, may potentially alter the underlying biology of LR-MDS by reducing or eliminating malignant ineffective hematopoietic clones and improving effective erythropoiesis
- As a result, patients experience an increase in hemoglobin and improvement of anemia, leading to durable transfusion independence
- Transient cytopenias observed early in treatment are likely the result of an on-target effect of imetelstat and may be predictive of a better therapeutic response¹
- Certain patients with LR-MDS and TD anemia who experience sustained RBC-TI (≥ 8 -week, ≥ 24 -week, or ≥ 1 -year) with imetelstat may experience improved health-related outcomes, including fatigue, QUALMS Total, QUALMS-P, and QUALMS-E scores²
- Collectively, these data support imetelstat as a biologically and clinically meaningful treatment option for patients with LR-MDS

LR-MDS, lower-risk myelodysplastic syndromes; 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; TD, transfusion dependent.

1. Zeidan AM, et al. *Blood Cancer J.* 2026;16(1):55. 2. Sekeres MA, et al. *Haematologica.* Published online January 2022, 2026. doi: 10.3324/haematol.2025.288956.

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