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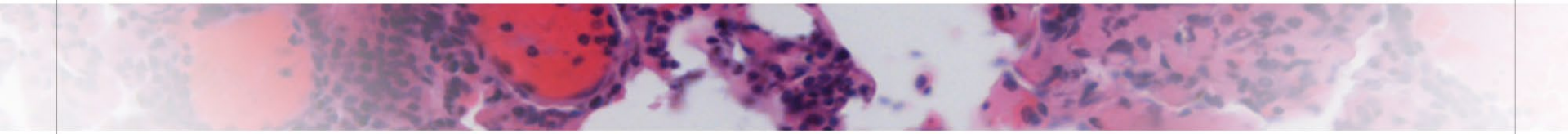

Correlation between Treatment-Emergent Cytopenias and Clinical Response with Imetelstat in Patients with Lower-Risk Myelodysplastic Syndromes: Analysis from the IMerge Trial

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Introduction: Imetelstat

- Imetelstat is a first-in-class, direct, and competitive telomerase inhibitor approved by the FDA and the EC for the treatment of adults with LR-MDS with RBC-TD anemia (defined in the US label as requiring ≥4 RBC units/8 weeks)[1] who are relapsed or refractory to, or ineligible for, ESAs, based on the Phase 3 IMerge trial (NCT02598661)[2,3]
  - A significantly higher proportion of patients treated with imetelstat achieved RBC-TI compared with patients treated with placebo[3]
  - The most common grade 3/4 treatment-emergent adverse events were neutropenia (68%) and thrombocytopenia (62%), mostly occurring within the first 3 cycles of imetelstat treatment[3]
    - These events were generally transient and associated with similar, low rates of grade 3/4 clinical consequences (bleeding, infection, and febrile neutropenia) as placebo[3]

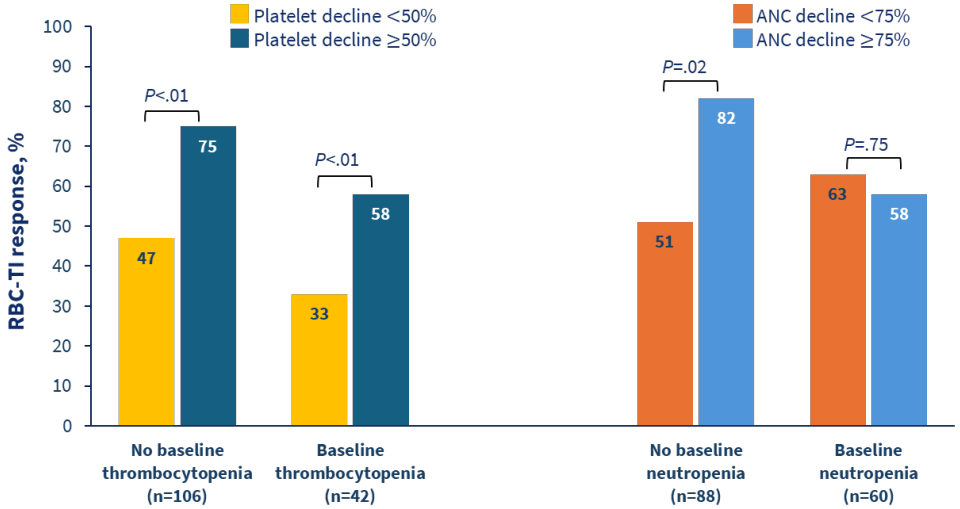
ESA, erythropoiesis-stimulating agent; EC, European Commission; FDA, United States Food and Drug Administration; Hb, hemoglobin; LR, lower risk; MDS, myelodysplastic syndromes; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independence; US, United States.

1. RYTELO® (imetelstat) for injection, for intravenous use. Package insert. Geron Corporation; 2024. 2. RYTELO® (imetelstat) summary of product characteristics. Geron Corporation; 2025.
3. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260.

Introduction: Lenalidomide

- Lenalidomide has been shown to reduce RBC transfusion dependence and reverse cytogenetic abnormalities in patients with del(5q) LR-MDS[1,2]
  - Thrombocytopenia and neutropenia are expected TEAEs early in the treatment with lenalidomide, and have been correlated with clinical response in these patients, suggesting an on-target, disease modifying effect on the del(5q) clone[3]

RBC-TI Response to Lenalidomide With and Without Thrombocytopenia or Neutropenia at Baseline[3]

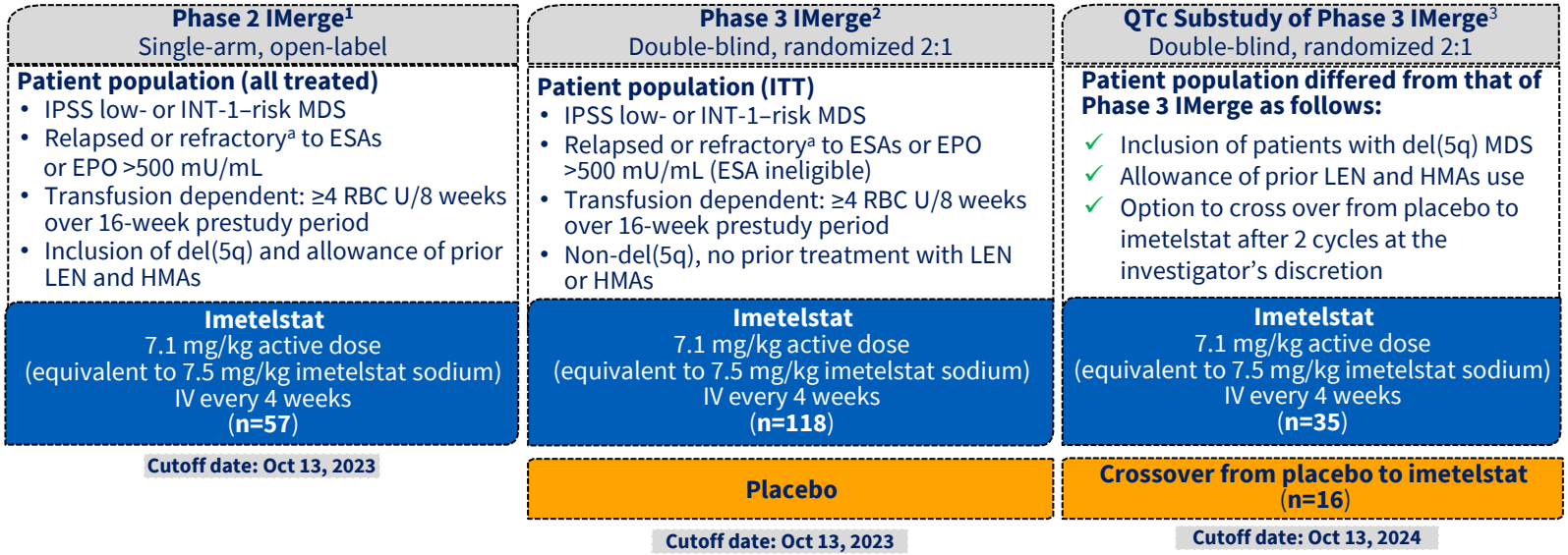


ANC, absolute neutrophil count; LR, lower risk; MDS, myelodysplastic syndromes; RBC, red blood cell; TEAE, treatment-emergent adverse event; TI, transfusion independence.
1. List A, et al. *N Engl J Med*. 2006;355(14):1456-1465. 2. Fenaux P, et al. *Blood*. 2011;118(14):3765-3776. 3. Sekeres MA, et al. *J Clin Oncol*. 2008;26(36):5943-5949.

OBJECTIVE: This post hoc analysis aims to assess the potential association between treatment-emergent cytopenias within the first 2 cycles of imetelstat and clinical response in patients with LR-MDS and RBC-TD anemia, including maximum Hb rise, Hb rise ≥1.5 g/dL lasting ≥8 weeks, and achievement of RBC-TI

Hb, hemoglobin; LR, lower risk; MDS, myelodysplastic syndromes; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independence.

Methods: Study Design



Patients, n				Total, N
Pooled population	57	118	51	226

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.

[a]Received ≥8 weeks of ESA treatment (EPO alfa ≥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.

1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U and Santini V, et al. *Lancet.* 2024;403(10423):249-260. 3. Komrokji RS, et al. *Blood.* 2024;144(suppl 1):4590-4592.

Baseline Patients and Disease Characteristics

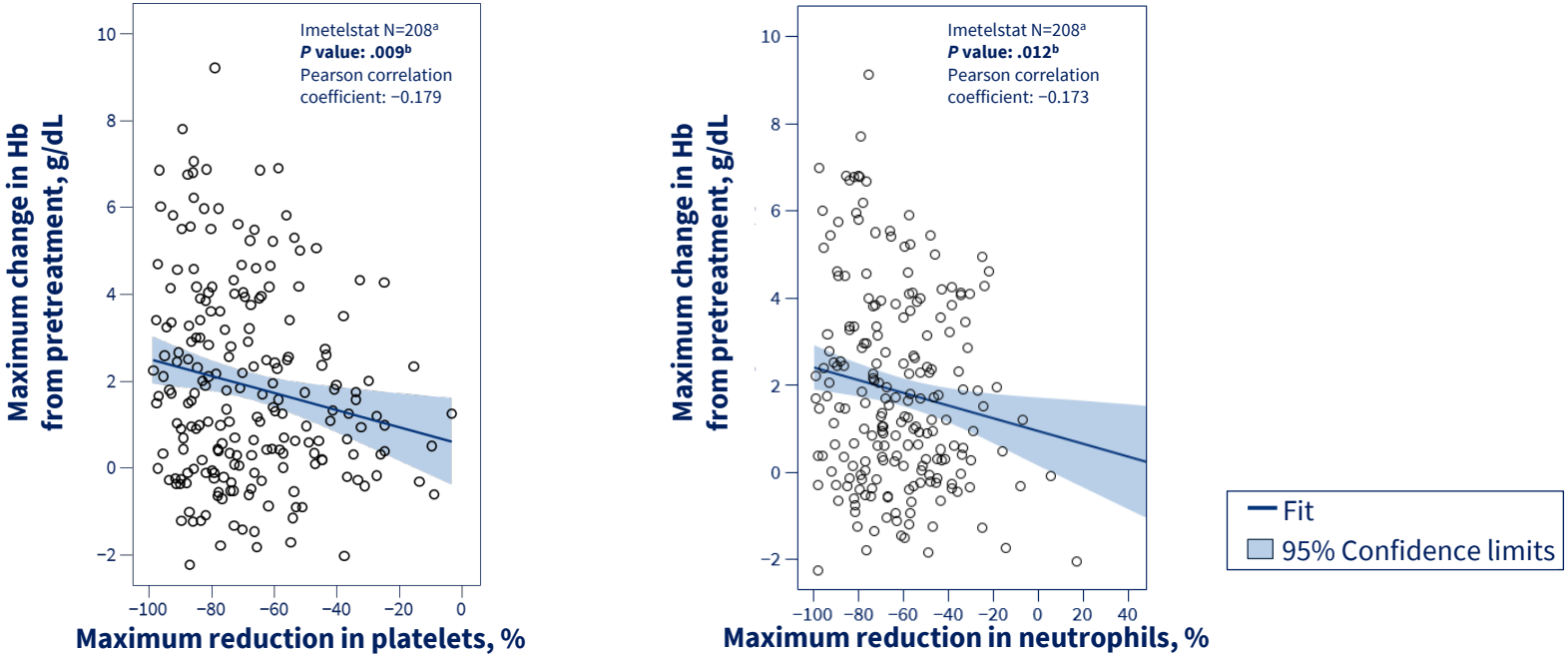
Characteristic	IMerge pooled population (N=226)
Age, median (range), y	71 (43-87)
Male, n (%)	144 (64)
Median pretreatment Hb level[a] (range), g/dL	7.8 (5.1-10.1)
Median prior RBC transfusion burden (range), U/16 weeks	7 (4-33)
>6 units, n (%)	114 (50)
Median sEPO level (range), mU/mL	187 (6-5424)
≤500, n (%)	155 (69)
>500, n (%)	64 (28)
Missing, n (%)	7 (3)
Median platelet level (range), ×10⁹ L	236 (41-807)
≤150, n (%)	38 (17)
>150, n (%)	188 (83)
Median neutrophil level (range), ×10⁹ L	2.6 (0.5-31.3)
<1.5, n (%)	17 (8)
≥1.5, n (%)	209 (92)
WHO classification, n (%)	
RS+	147 (65)
RS−	78 (35)
Missing	1 (<1)
IPSS category, n (%)	
Low	151 (67)
Intermediate-1	75 (33)
Number of cytopenias at pretreatment, n (%)	
0-1	180 (80)
2-3	46 (20)

Platelets ≥75×10^9/L independent of platelet transfusion, and ANC ≥1.5×10^9/L independent of growth factor support were IMerge eligibility requirements

- Median (range) duration of imetelstat treatment was 34 weeks (0.1-260)

ANC, absolute neutrophil count; Hb, hemoglobin; IPSS, International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; WHO, World Health Organization.
[a]Pretreatment Hb level was defined as the average of all Hb values in the 8 weeks prior to the first dose date, including the value on the first dose date and excluding values within 14 days after transfusion (considered to be influenced by transfusion), for all treated patients.

Maximum Reductions in Platelets and Neutrophils Within the First 2 Cycles of Imetelstat Are Significantly Correlated With Maximum Hb Rise

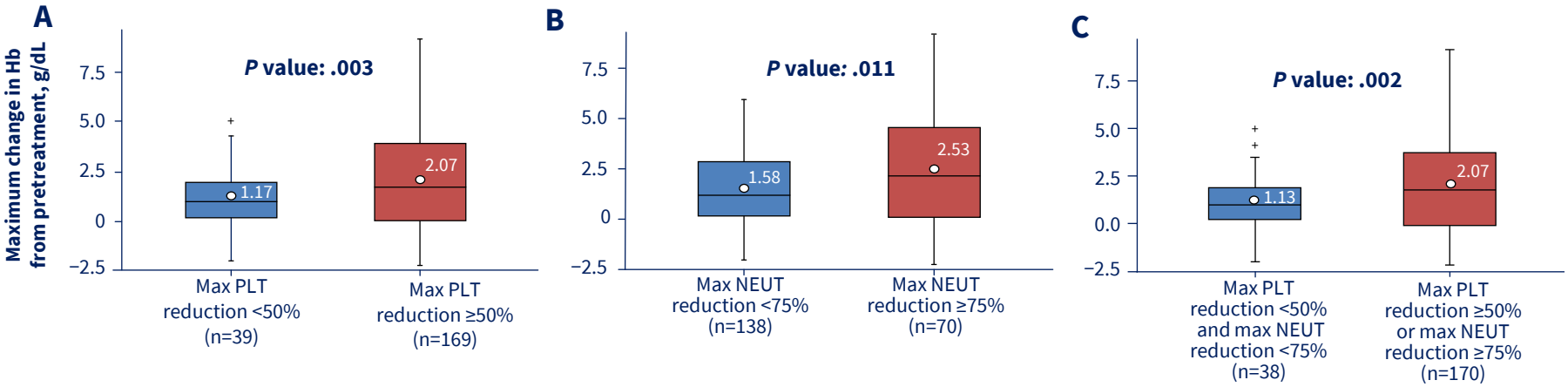


- A significant correlation between maximum reductions from baseline in neutrophils and platelets was observed (N=226; PCC=0.494, *P*<.001)[b]

Hb, hemoglobin; PCC, Pearson correlation coefficient; RBC, red blood cell.
[a]Hb 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. [b]Unadjusted nominal *P* values are presented.

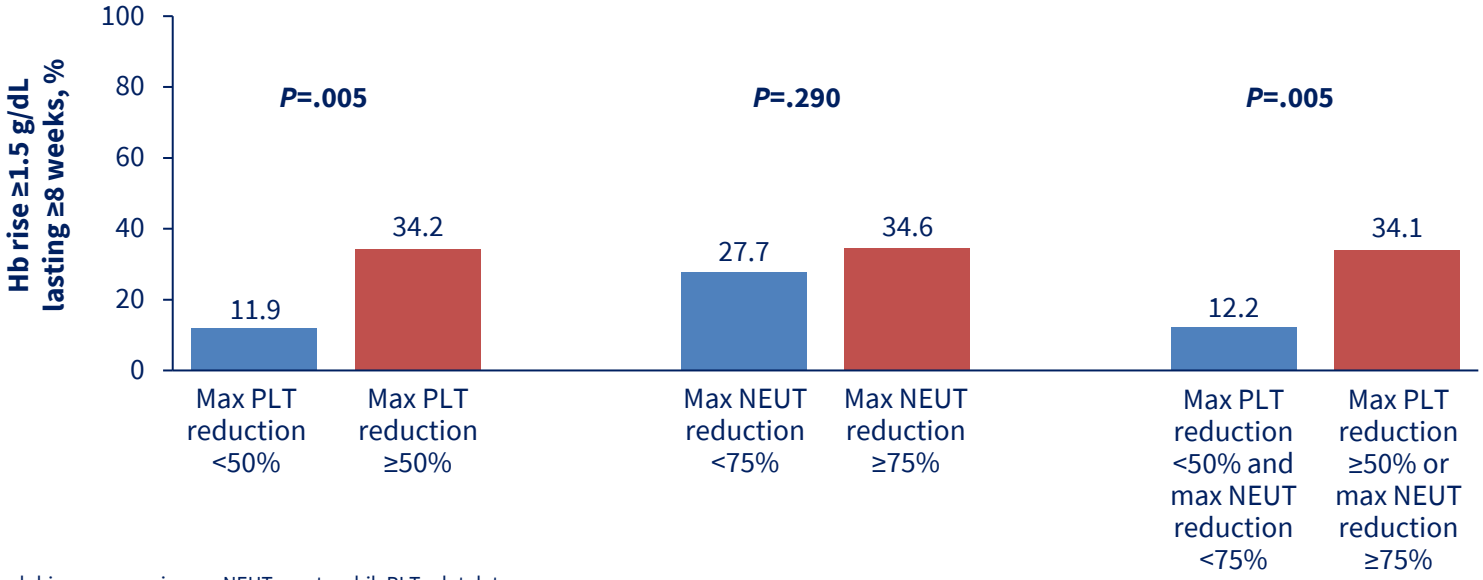
Maximum Reduction ≥50% in Platelets or ≥75% in Neutrophils Within the First 2 Cycles of Imetelstat Is Associated With Greater Maximum Hb Rise[a,b]

- Patients with ≥50% maximum platelet reduction (A), ≥75% maximum neutrophil reduction (B), or ≥50% maximum platelet reduction *or* ≥75% maximum neutrophil reduction (C) had a significantly greater mean maximum Hb rise from pretreatment



Hb, hemoglobin; max, maximum; NEUT, neutrophils; PLT, platelets; RBC, red blood cell.
[a]Hb 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. [b]Unadjusted nominal *P* values are presented.
Note: the white dots inside the blue and red boxes represent the mean value. + symbols represent outliers.

Maximum Reduction ≥50% in Platelets or ≥75% in Neutrophils Within the First 2 Cycles of Imetelstat Is Associated With Greater Rates of Hb Rise ≥1.5 g/dL Lasting ≥8 Weeks[a]



Hb, hemoglobin; max, maximum; NEUT, neutrophil; PLT, platelet.
[a]Unadjusted nominal *P* values are presented.

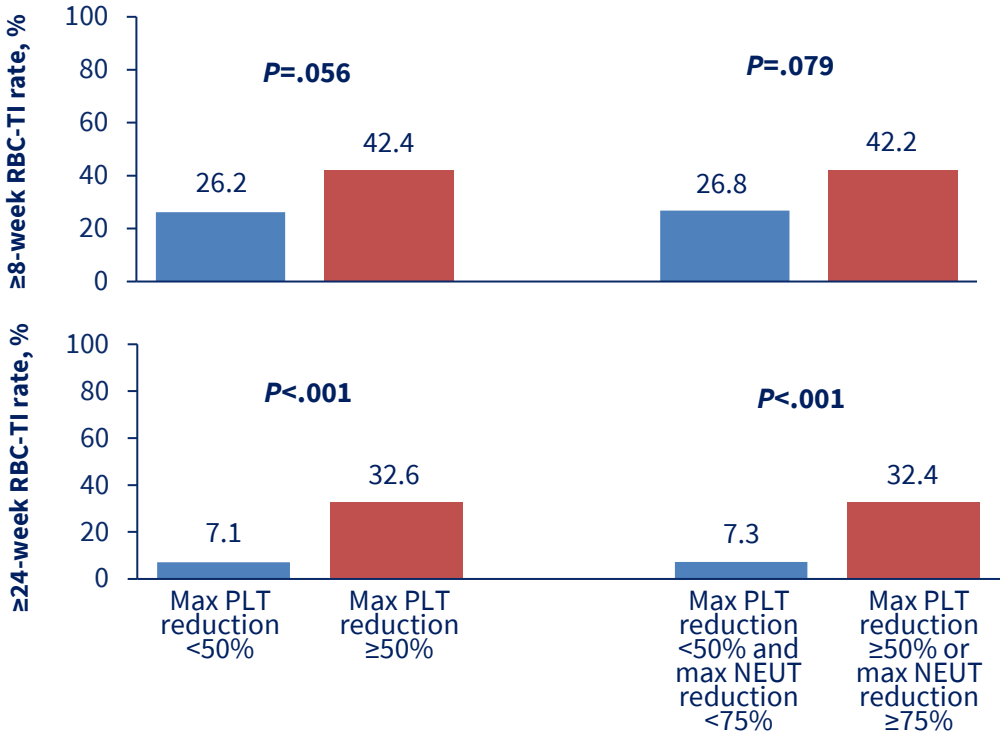
Likelihood of Achieving Hb Rise ≥1.5 g/dL Lasting ≥8 Weeks or Maximum Hb Rise Are Significantly Associated With ≥50% Reduction in Platelets or ≥75% in Neutrophils Within the First 2 Cycles of Imetelstat, Respectively

Multivariate analysis	Clinical response	
	Hb rise ≥1.5 g/dL lasting ≥8 weeks (N=226)	
Selected variables	**OR (95% CI)**	***P* value[a]**
Maximum reduction in platelets ≥50% within the first 2 cycles of imetelstat treatment (yes vs no)	4.16 (1.54-11.23)	.005
Time from diagnosis, years	0.99 (0.98-1.00)	.018
	Maximum Hb rise from pretreatment (N=226)	
Selected variables	**Coefficient estimate (95% CI)**	***P* value[a]**
Maximum reduction in neutrophils ≥75% within the first 2 cycles of imetelstat treatment (yes vs no)	0.943 (0.32-1.57)	.003
Pretreatment Hb level, g/dL	−0.698 (−1.08, −0.31)	<.001
RBC transfusion burden, units	−0.150 (−0.25, −0.05)	.003

- 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, ring sideroblast status, karyotype, age, sex, ECOG performance status, and time from diagnosis

ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; IPSS, International Prognostic Scoring System; OR, odds ratio; RBC, red blood cell.
[a]Unadjusted nominal *P* values are presented.

Patients With Maximum Reduction ≥50% in Platelets or ≥75% in Neutrophils Within the First 2 Cycles of Imetelstat Have Greater ≥8-Week and ≥ 24-Week RBC-TI Rates[a]



Max, maximum; NEUT, neutrophil; PLT, platelet; RBC, red blood cell; TI, transfusion independence.
[a]Unadjusted nominal *P* values are presented.

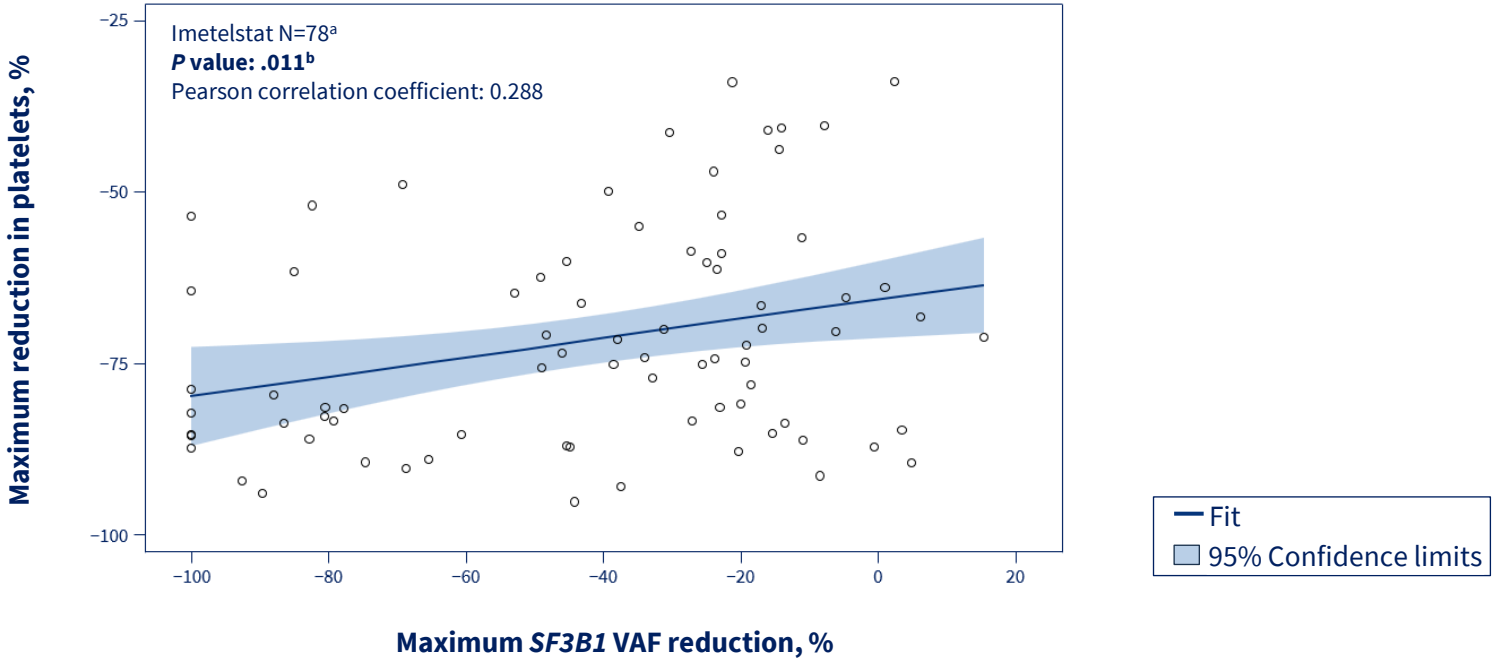
The Greater Hb Rise From Pretreatment Emerged as a Main Driver for Achieving ≥8-Week and ≥24-Week RBC-TI

Multivariate analysis	Clinical response	
	≥8-week RBC-TI (N=208)[a]	
Selected variables	**OR (95% CI)**	***P* value[b]**
Maximum change in Hb from pretreatment, g/dL	1.21 (1.14-1.27)	<.001
Pretreatment Hb level, g/dL	1.15 (1.07-1.25)	<.001
IPSS risk status: intermediate-1	4.62 (1.64-13.05)	.004
	≥24-week RBC-TI (N=208)[a]	
Selected variables	**OR (95% CI)**	***P* value[b]**
Maximum change in Hb from pretreatment, g/dL	3.87 (2.66-5.64)	<.001

- 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, ring sideroblast status, karyotype, age, sex, ECOG performance status, and time from diagnosis

ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; IPSS, International Prognostic Scoring System; OR, odds ratio; RBC, red blood cell; TI, transfusion independence.
[a]Eighteen patients did not have Hb values outside 14 days of transfusion; thus, their Hb change from pretreatment is not available. [b]Unadjusted nominal *P* values are presented.

Maximum Reduction in Platelets Within the First 2 Cycles of Imetelstat Are Significantly Correlated With Maximum Reduction in *SF3B1* VAF in IMerge Phase 3



VAF, variant allele frequency.
[a]N represents imetelstat arm patients in mutation biomarker analysis set (Phase 3 study) only who had assessment ≥10 in *SF3B1* at pretreatment and had any postbaseline mutation assessment.
[b]Unadjusted nominal *P* value is presented.

Conclusions

- In univariate analyses, maximum percent reduction in platelets or neutrophils, ≥75% neutrophil reduction, or ≥50% platelet reduction within the first 2 cycles of imetelstat treatment were significantly associated with maximum Hb rise
- In multivariate analyses, ≥75% neutrophil reduction was significantly associated with maximum Hb rise, whereas maximum ≥50% platelet reduction was significantly associated with achieving Hb rise ≥1.5 g/dL lasting ≥8 weeks
  - The greater Hb rise from pretreatment emerged as a main driver for achieving ≥8-week and ≥24-week RBC-TI
- In IMerge Phase 3, *SF3B1* VAF reduction was significantly correlated with maximum percent change in platelets from baseline within the first 2 cycles of imetelstat treatment
- Collectively, findings from this post hoc analysis suggest that treatment-emergent cytopenias may be associated with meaningful clinical benefit with imetelstat
- Further research is needed to validate the disease modification potential of imetelstat resulting from its activity on clonal progenitor cells and subsequent recovery of blood cell production

Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence; VAF, variant allele frequency.

Thank You

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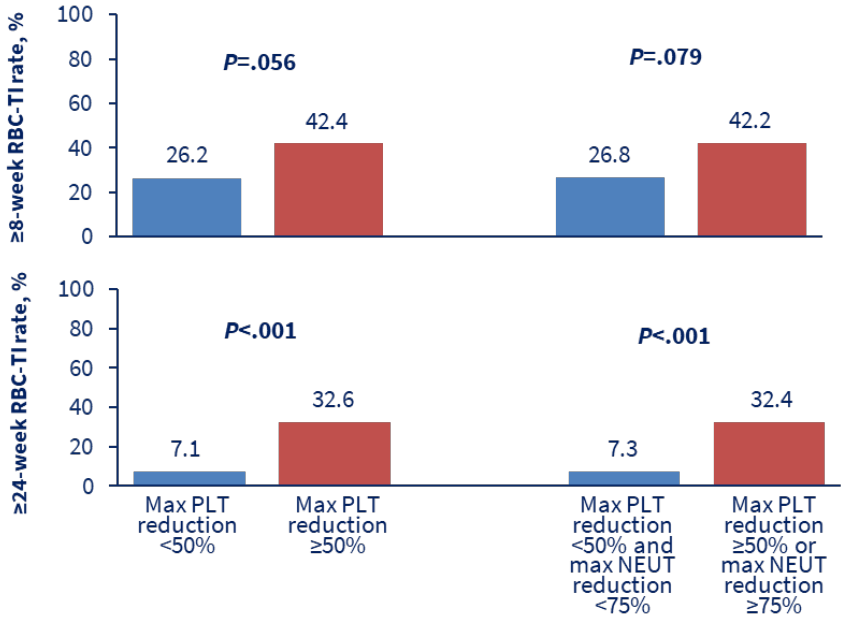
- All authors contributed to and approved the presentation; writing and editorial support were provided by Mohamed Abdelmegeed, MD, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation

Summary

- Imetelstat showed durable RBC-TI, reduction in transfusion burden, and increased Hb in patients with ESA-R/R or ESA-ineligible RBC-TD LR-MDS[1]
- Imetelstat has demonstrated potential for disease modification, as evidenced by cytogenetic responses and reduced mutation burden[1,2]
  - VAF reductions in genes frequently mutated in MDS are associated with platelet reduction, Hb increase, and TI duration[1,2]
- Thrombocytopenia and neutropenia are expected TEAEs early with imetelstat, and are associated with clinical response, including Hb rise and RBC-TI, suggesting an on-target effect on clonal progenitor cells[1,3]

RBC-TI Response to Imetelstat by Maximum Reduction in Platelets or Neutrophils Within the First 2 Cycles of Treatment[3,a]



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LR, lower risk; MDS, myelodysplastic syndromes; NEUT, neutrophil; PLT, platelet; R/R, relapsed or refractory; RBC, red blood cell; TEAE, treatment-emergent adverse events; TI, transfusion independence; VAF, variant allele frequency.

[a]Unadjusted nominal *P* values are presented.

1. Platzbecker U and Santini V, et al. *Lancet*. 2024;403(10423):249-260. 2. Santini V, et al. *Blood*. 2023;142(1): 4603. 3. Zeidan A, et al. Presented at ASH 2025. Abstract 490 (oral).