2023 ASCO® ANNUAL MEETING

IMerge

IMerge: Results From a Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Imetelstat in Patients With Heavily Transfusion Dependent Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis Stimulating Agents

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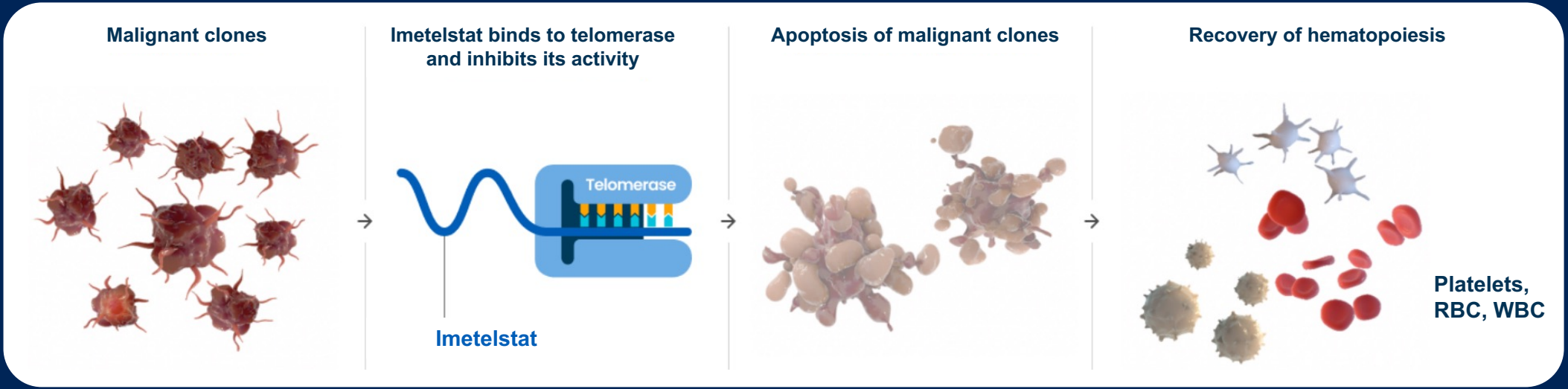
Imetelstat in Lower Risk MDS

- Imetelstat is a first-in-class direct and competitive inhibitor of telomerase activity[1,2]
- Imetelstat specifically targets malignant clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis[3,4]



- In the phase 2 part of the IMerge study (NCT02598661), patients with LR-MDS who were heavily RBC transfusion dependent, ESA relapsed/refractory or ineligible, non-del(5q), and naive to lenalidomide and HMA achieved durable and continuous RBC-TI when treated with imetelstat, specifically 8-week RBC TI rates were 42% with a median TI duration of 86 weeks[5]
- This analysis reports phase 3 results from IMerge in the same patient population

ESA, erythropoiesis stimulating agent; HMA, hypomethylating agent; LR-MDS, lower risk myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence; WBC, white blood cell.

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939. 2. Herbert BS, et al. *Oncogene*. 2005;24(33):5262-5268. 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467. 4. Wang X at al. *Blood Adv.* 2018;25;2(18):2378-2388. 5. Steensma DP, et al. *J Clin Oncol*. 2021;39(1):48-56.

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IMerge Phase 3 Trial Design (MDS3001; NCT02598661)

Phase 3
Double-blind, randomized
118 Clinical sites in 17 countries

Patient Population (ITT N = 178):
- IPSS low- or intermediate 1- risk MDS
- Relapsed/refractory[a] to ESA or EPO >500 mU/mL (ESA ineligible)
- **Transfusion dependent: ≥4 units RBCs/8 weeks over 16-week pre-study**
- Non-deletion 5q
- No prior treatment with lenalidomide or HMAs

RANDOMIZE

2:1

Imetelstat
7.5 mg/kg IV/4 weeks
(N = 118)

Placebo
(N = 60)

Stratification:
- Transfusion burden (4-6 vs >6 units)
- IPSS risk category (low vs intermediate-1)

Supportive care, including RBC and platelet transfusions, myeloid growth factors (e.g., G-CSF), and iron chelation therapy administered as needed on study per investigator discretion

Safety population (treated) N = 177
Imetelstat N = 118
Placebo N = 59

Primary End Point:
- 8-week RBC-TI[b]

Key Secondary End Points:
- 24-week RBC-TI[b]
- Duration of TI
- Hematologic Improvement-Erythroid
- Safety

Key Exploratory End Point:
- VAF changes
- PRO (fatigue measured by FACIT-Fatigue)

[a]Received ≥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 Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 weeks *or* transfusion dependence or reduction in Hgb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment.

[b]Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI)

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hgb, hemoglobin; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; PRO, patient-reported outcome; RBC, red blood cell; TI, transfusion independence, VAF, variant allele frequency.

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Baseline Patient and Disease Characteristics

Characteristic	Imetelstat (N = 118)	Placebo (N = 60)
Median age, years (range)	72 (44–87)	73 (39–85)
Male, n (%)	71 (60)	40 (67)
Median time since diagnosis, years (range)	3.5 (0.1–26.7)	2.8 (0.2–25.7)
WHO classification, n (%)		
RS+	73 (62)	37 (62)
RS−	44 (37)	23 (38)
IPSS risk category, n (%)		
Low	80 (68)	39 (65)
Intermediate-1	38 (32)	21 (35)
Median pretreatment Hgb, g/dL (range)[a]	7.9 (5.3–10.1)	7.8 (6.1–9.2)
Median prior RBC transfusion burden, RBC units / 8 weeks (range)	6 (4–33)	6 (4–13)
Prior RBC transfusion burden, n (%)		
≥4 to ≤6 units/8 weeks	62 (53)	33 (55)
>6 units/8 weeks	56 (48)	27 (45)
Median sEPO, mU/mL (range)	174.9 (6.0–4460.0)	277.0 (16.9–5514.0)
sEPO level, n (%)[b]		
≤500 mU/mL	87 (74)	36 (60)
>500 mU/mL	26 (22)	22 (37)
Prior ESA use, n (%)	108 (92)	52 (87)
Prior luspatercept use, n (%)[c]	7 (6)	4 (7)

[a]Average of all Hgb values in the 8 weeks prior to the first dose date, excluding values within 14 days after a transfusion; thus, considered to be influenced by transfusion. [b]Data missing for 5 patients in the imetelstat group and 2 in the placebo group.
[c]Insufficient number of patients previously treated with luspatercept to draw conclusions about the effect of imetelstat treatment in such patients.
ESA, erythropoiesis stimulating agent; Hgb, hemoglobin; IPSS, International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; WHO, World Health Organization.

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Treatment Exposure and Disposition After 18 Months Median Follow Up (Treated Population)

	Imetelstat (N = 118)	Placebo (N = 59)
Treatment duration, median, weeks[a]	33.9	28.3
Treatment ongoing, n (%)	27 (22.9)	14 (23.7)
Treatment discontinued, n (%)	91 (77.1)	45 (76.3)
Lack of efficacy	28 (23.7)	25 (42.4)
Adverse event	19 (16.1)	0
Cytopenias	11 (9.3)	0
Unrelated	8 (6.8)	0
Disease relapse after a response on study[b]	17 (14.4)	1 (1.7)
Disease progression	7 (5.9)	5 (8.5)
Progression to AML	2 (1.7)	1 (1.7)
Death[c]	1 (0.8)	2 (3.4)
Other[d]	19 (16.1)	12 (20.3)

Data cutoff: October 13, 2022.

[a]Mean (SD) duration of treatment was 46.8 (34.3) weeks and 39.6 (29.2) weeks with imetelstat and placebo, respectively. [b]Per IWG 2006 criteria. [c]Imetelstat group: neutropenic sepsis not related to drug after ~2-year treatment duration (n=1); placebo group: COVID-19 (n=1) and heart value issue (n=1). [d]Included patient decision (n=16 imetelstat, n=10 placebo), investigator decision (n=2 each group), and lost to follow-up (n=1 imetelstat).

AE, adverse event; AML, acute myeloid leukemia; IWG, International Working Group; SD, standard deviation.

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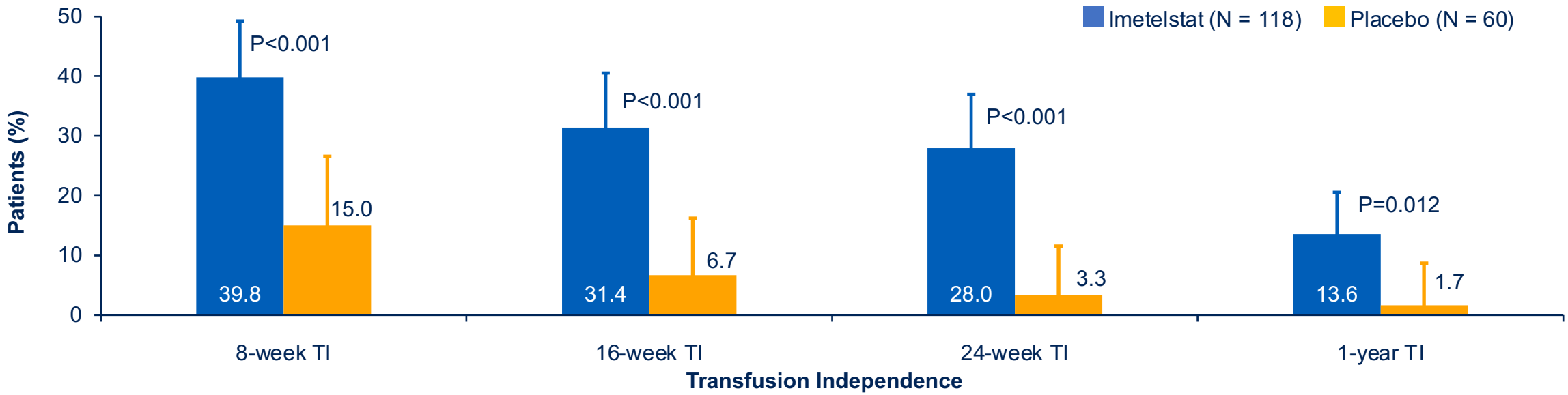
Higher Rates of Longer-Term Duration of RBC TI Observed With Imetelstat vs Placebo[a]



Patients With Response, n (% [95% CI])

	8-week TI	16-week TI	24-week TI	1-year TI
Imetelstat	47 (39.8 [30.9–49.3])	37 (31.4 [23.1–40.5])	33 (28.0 [20.1–37.0])	16 (13.6 [8.0–21.1])
Placebo	9 (15.0 [7.1–26.6])	4 (6.7 [1.9–16.2])	2 (3.3 [0.4–11.5])	1 (1.7 [0.0–8.9])

Data cutoff: October 13, 2022.

[a]Primary end point 8-week and the first secondary end point 24-week TI are statistically significant by study prespecified gatekeeping testing procedure. One-year TI represented a preliminary assessment. P-values determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1) applied to randomization.

IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

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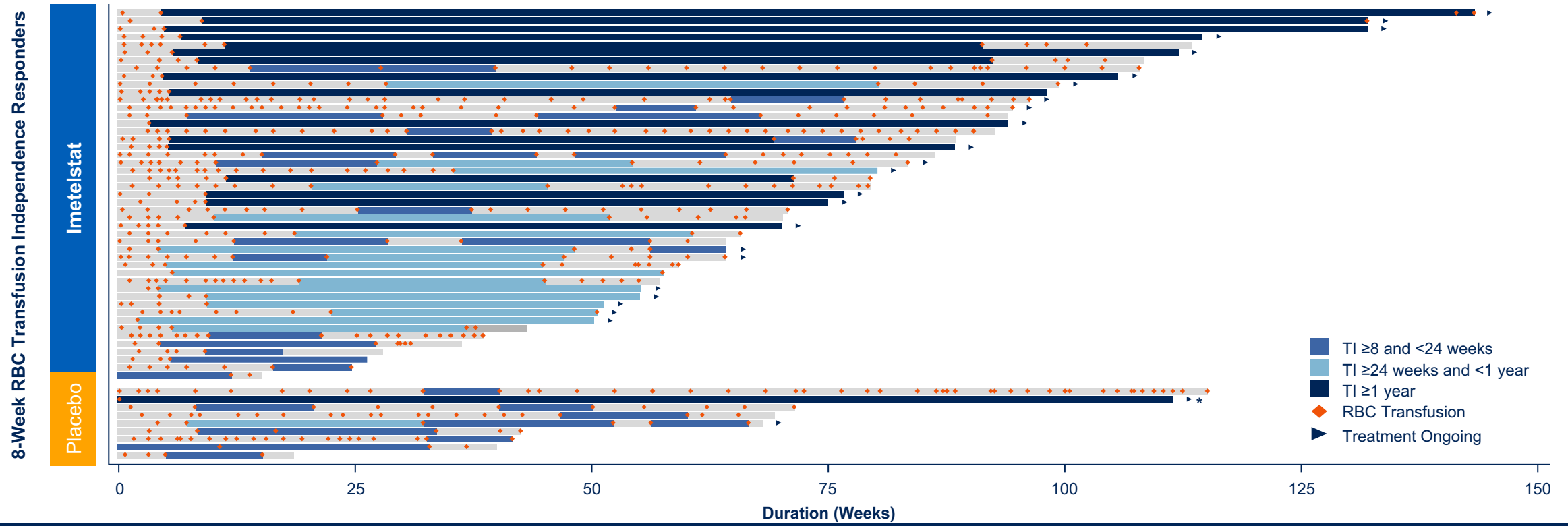
Majority of Imetelstat 8-Week RBC-TI Responders Experienced Durable Continuous RBC-TI Episodes

- 83% of imetelstat 8-week RBC-TI responders had a single continuous RBC-TI period



Data cutoff: October 13, 2022.

Pre-treatment Hgb was 6.2 g/dL with transfusion burden of 5 units/8 weeks before study start; on-study Hgb was <6.5 g/dL during majority of TI period, yet no transfusions given.

Hgb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

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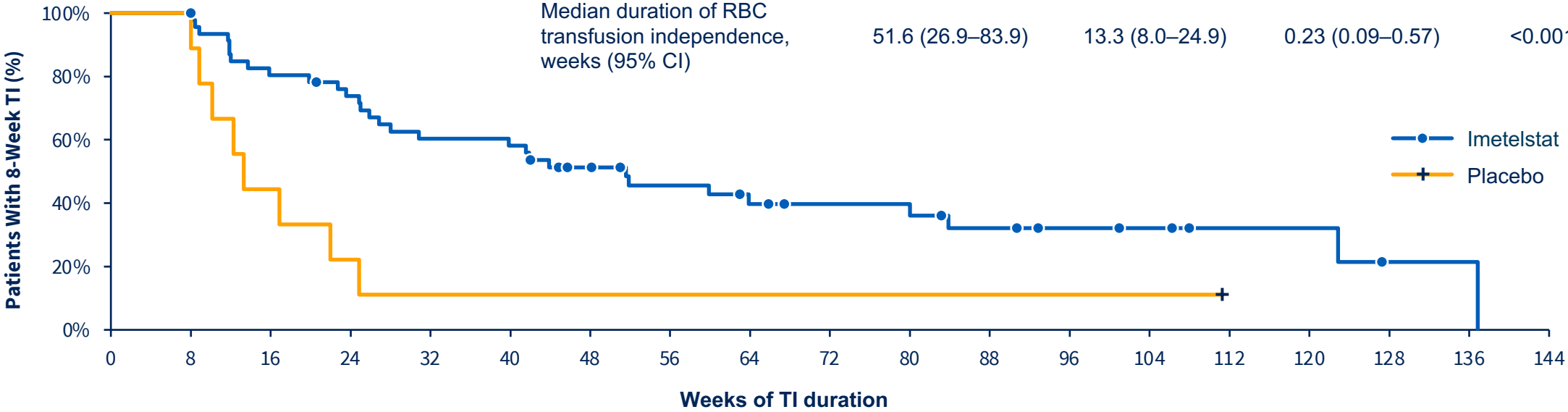
Imetelstat 8-Week RBC-TI Responders Have Significantly Longer Duration of Transfusion Independence vs Placebo

8-Week TI Responders	Imetelstat (N = 47)	Placebo (N = 9)	HR (95%CI)	P-Value
Median duration of RBC transfusion independence, weeks (95% CI)	51.6 (26.9–83.9)	13.3 (8.0–24.9)	0.23 (0.09–0.57)	<0.001



Patients, N																			
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0				

Data cutoff: October 13, 2022.

[a]HR (95% CI) from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate. [b]P value (2-sided) for superiority of imetelstat vs placebo in HR based on stratified log-rank test.

HR, hazard ratio; IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

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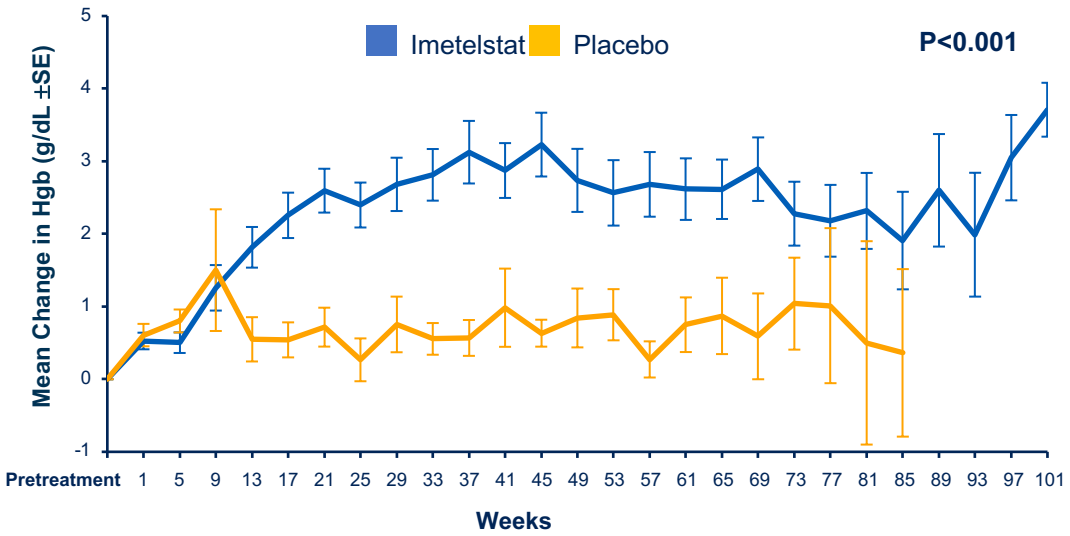
Significant and Sustained Increase in Hemoglobin Among Patients Treated With Imetelstat

8-Week TI Responders[a]	Imetelstat (N = 47)	Placebo (N = 9)
Median Hgb rise, g/dL (range)	3.6 (−0.1 to 13.8)	0.8 (−0.2 to 1.7)
Median Hgb peak, g/dL (range)	11.3 (8.0–21.9)	8.9 (7.9–9.7)

Mean Change in Hemoglobin Over Time[b]



Patients, N

Imetelstat	118	59	53	54	47	42	48	48	43	43	31	37	31	35	32	25	26	24	23	21	19	18	11	11	9	9	5
Placebo	60	37	29	17	16	18	15	8	10	10	11	7	3	9	8	9	7	7	5	5	4	2	4				

[a]Among patients achieving 8-week TI, analysis performed during TI. Hgb rise defined as the maximum Hgb value in the longest TI interval excluding the first 2 weeks minus the pretreatment Hgb level.
[b]Mean changes from the minimum Hgb of the values that were after 14 days of transfusions in the 8 weeks prior to the first dose date are shown. Data points that have <4 patients are not shown. P-value based on a mixed model for repeated measures with Hgb change as the dependent variable, week, stratification factors, minimum Hgb in the 8 weeks prior to the first dose date, treatment group, and treatment and week interaction term as the independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.
Hgb, hemoglobin; RBC, red blood cell; SE, standard error; TI, transfusion independence.

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Significant Improvement in HI-E With Imetelstat vs Placebo

Hematologic Improvement	Imetelstat (N = 118)	Placebo (N = 60)	% Difference, P-Value
HI-E (IWG 2018[1]), n (%) (95% CI)[a]	50 (42.4) (33.3–51.8)	8 (13.3) (5.9–24.6)	29.0 <0.001
Patients with LTB, n[b]	21	18	
HI-E response (16-week RBC-TI), n (%) (95% CI)[a]	7 (33.3) (14.6–57.0)	4 (22.2) (6.4–47.6)	11.1 0.562
Patients with HTB, n[b]	97	42	
Major HI-E response (16-week RBC-TI)	30 (21.9–41.1)	0 (0.0–8.4)	30.9 <0.001
Minor HI-E response (50% RBC units reduction in 16 weeks)	43 (34.2–54.8)	4 (2.7–22.6)	34.8 <0.001

[a]Exact Clopper-Pearson confidence interval. [b]Per revised IWG 2018, patient with LTB is a patient who received 3 to 7 RBC units in the 16 weeks prior to study entry in ≥2 transfusion episodes and a patient with HTB is a patient who received ≥8 RBC units in the 16 weeks prior to study entry in ≥2 transfusion episodes.

HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; TI, transfusion independence.

1. Platzbecker U, et al. *Blood*. 2019;133(10):1020–1030.

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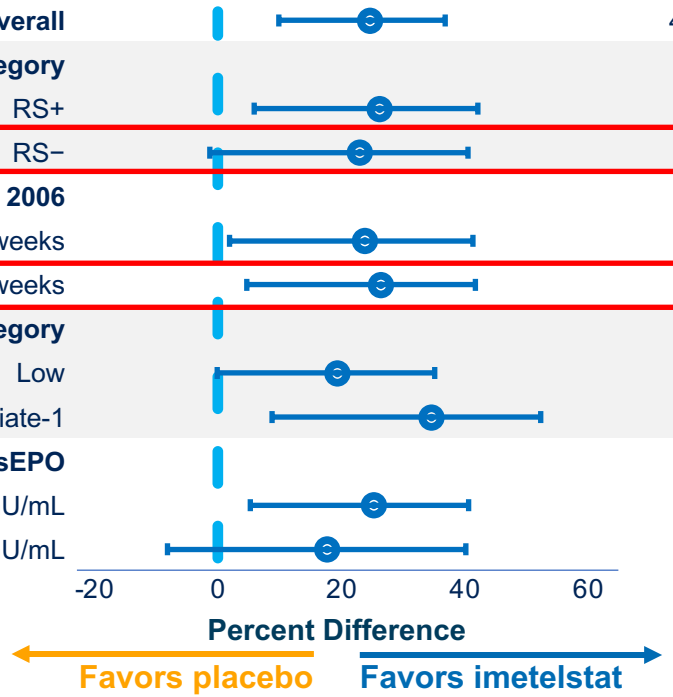
Primary End Point: 8-Week RBC-TI Rate Significantly Higher With Imetelstat vs Placebo Across Key LR-MDS Subgroups

	Imetelstat, n/N (%)	Placebo, n/N (%)	% Difference (95% CI)	P-Value
Overall	47/118 (39.8)	9/60 (15.0)	24.8 (9.9–36.9)	**<0.001**
WHO category				
RS+	33/73 (45.2)	7/37 (18.9)	26.3 (5.9–42.2)	**0.016**
RS−	14/44 (31.8)	2/23 (8.7)	23.1 (−1.3 to 40.6)	**0.038**
Prior RBC transfusion burden per IWG 2006				
4–6 units/8 weeks	28/62 (45.2)	7/33 (21.2)	23.9 (1.9–41.4)	**0.027**
>6 units/8 weeks	19/56 (33.9)	2/27 (7.4)	26.5 (4.7–41.8)	**0.023**
IPSS risk category				
Low	32/80 (40.0)	8/39 (20.5)	19.5 (−0.1 to 35.2)	**0.034**
Intermediate-1	15/38 (39.5)	1/21 (4.8)	34.7 (8.8–52.4)	**0.004**
Baseline sEPO				
≤500 mU/mL	39/87 (44.8)	7/36 (19.4)	25.4 (5.3–40.7)	**0.011**
>500 mU/mL	7/26 (26.9)	2/22 (9.1)	17.8 (−8.2 to 40.3)	**0.107**



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P-values determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1) applied to randomization.

IPSS, International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TI, transfusion independence.

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Consistent With Prior Clinical Experience, the Most Common AEs Were Hematologic

- Grade 3–4 thrombocytopenia and neutropenia were the most frequently reported AEs, most often reported during Cycles 1–3
  - There were no fatal hematologic AEs
- Nonhematologic AEs were generally low grade
- Although ≈75% of patients treated with imetelstat had dose modifications due to AEs, <15% of patients discontinued treatment due to TEAEs
- No cases of Hy's Law or drug-induced liver injury observed
  - The incidence of grade 3 liver function test laboratory abnormalities was similar in both treatment groups

AE (≥10% 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)
Leukopenia	12 (10)	9 (8)	1 (2)	0
Other				
Asthenia	22 (19)	0	8 (14)	0
COVID-19	22 (19)[a]	2 (2)[b]	8 (14)[a]	3 (5)[b]
Headache	15 (13)	1 (1)	3 (5)	0
Diarrhea	14 (12)	1 (1)	7 (12)	1 (2)
ALT increased	14 (12)	3 (3)	4 (7)	2 (3)
Edema peripheral	13 (11)	0	8 (14)	0
Hyperbilirubinemia	11 (9)	1 (1)	6 (10)	1 (2)
Pyrexia	9 (8)	2 (2)	7 (12)	0
Constipation	9 (8)	0	7 (12)	0

Data cutoff: October 13, 2022.

[a]Included COVID-19, asymptomatic COVID-19, and COVID-19 pneumonia. [b]Only COVID-19 pneumonia events were grade 3–4 COVID-19.

AE, adverse event; ALT, alanine aminotransferase.

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Grade 3–4 Cytopenias Were of Short Duration and Manageable

- Median duration of grade 3–4 thrombocytopenia and neutropenia was <2 weeks and >80% of events were reversible to grade ≤2 within 4 weeks
- 41 patients (34.7%) in the imetelstat group and 2 patients (3.4%) in the placebo group had ≥1 dose of a myeloid growth factor mostly within Cycles 2–4
- There were no fatal cytopenia events
- **Clinical consequences of infection and bleeding were low and similar for imetelstat and placebo**

Grade 3–4 Cytopenias (per lab value)	Imetelstat (N = 118)	Placebo (N = 59)
Thrombocytopenia		
Median duration, weeks (range)	1.4 (0.1–12.6)	2.0 (0.3–11.6)
Resolved within 4 weeks, %	86.3	44.4
Neutropenia		
Median duration, weeks (range)	1.9 (0–15.9)	2.2 (1.0–4.6)
Resolved within 4 weeks, %	81.0	50.0

Event, n (%)	Imetelstat (N = 118)	Placebo (N = 59)
Grade ≥3 bleeding events	3 (2.5)	1 (1.7)
Grade ≥3 infections	13 (11.0)	8 (13.6)
Grade 3 febrile neutropenia	1 (0.8)	0

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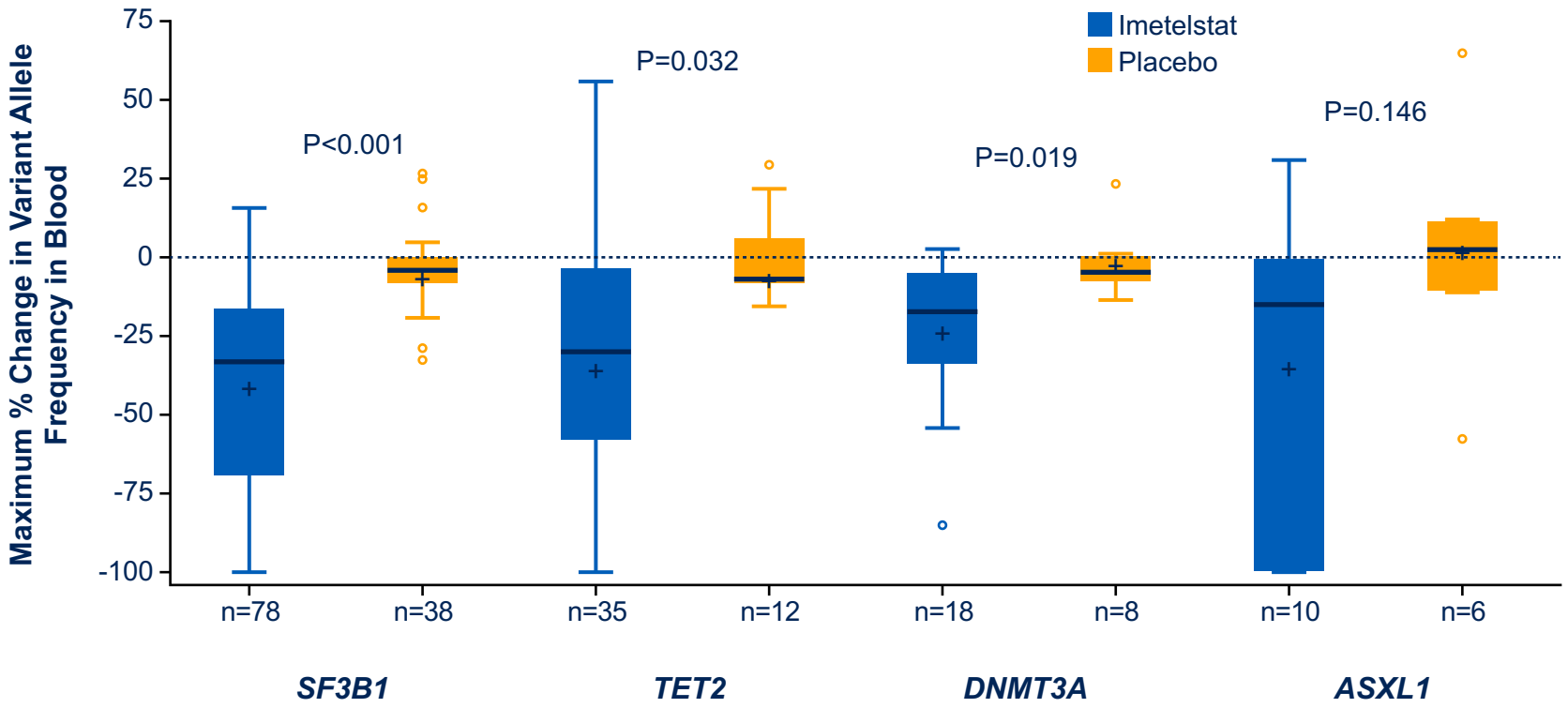
Reductions in VAF of Genes Frequently Mutated in MDS Were Greater With Imetelstat vs Placebo



Note: Figure shows the comparison between each treatment group in the maximum percentage change from baseline in mutant VAF of the indicated gene. P-values based on the two-sample t-test. Analyses included patients in the intent-to-treat population with a detectable mutant allele for the indicated gene (≥5%) prior to treatment and ≥1 postbaseline mutation assessment.
ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.

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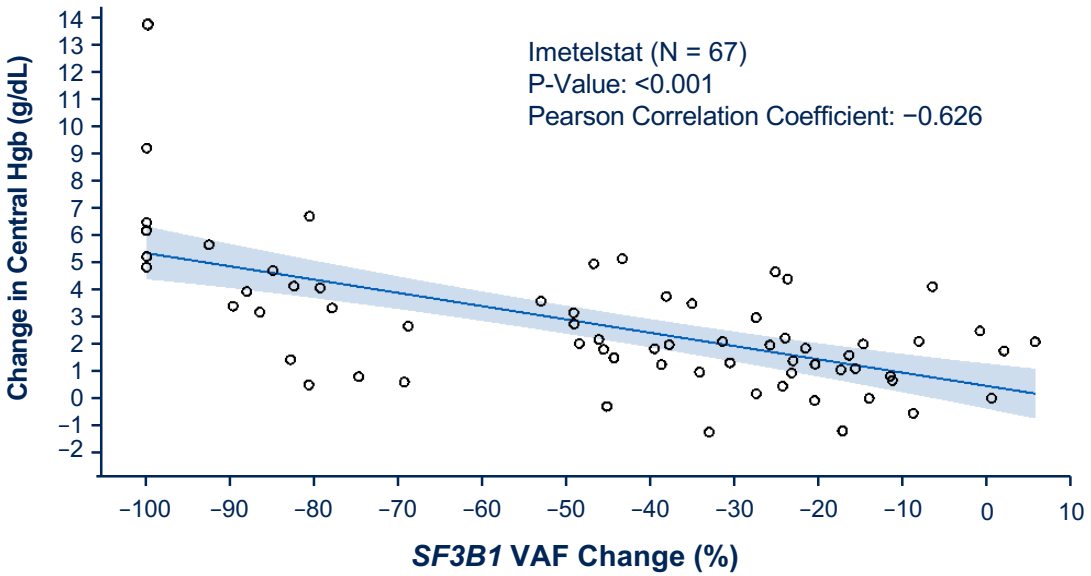
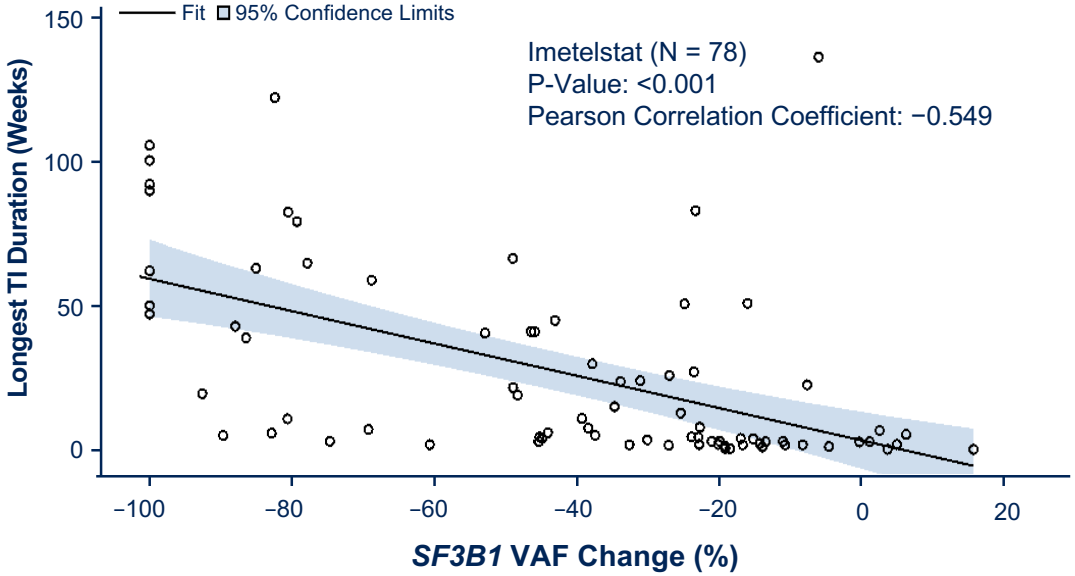
SF3B1 VAF Reduction in Patients Treated With Imetelstat Correlated With Clinical Outcomes[a]

Maximum Increase in Hgb vs Maximum Reduction in *SF3B1* VAF[b,c]



Longest RBC-TI Duration vs Maximum Reduction in *SF3B1* VAF[c]



- With imetelstat, a greater reduction in *SF3B1* VAF correlated with a greater increase in Hgb and longer RBC-TI duration
- A greater VAF reduction in *TET2, DNMT3A* or *ASXL1* also correlated with longer RBC-TI duration

[a]Analyses included patients in imetelstat treatment group with detectable SF3B1 mutant allele (≥5%) pretreatment and any post-baseline mutation assessment. [b]Analysis included patients with post-baseline Hgb assessment, excluding assessments within 14 days post-RBC transfusion. [c]Fitted lines and P values based on linear regression with maximum increase in Hgb from pretreatment (left) and RBC-TI duration (right) as the dependent variable and the maximum percentage reduction from baseline in *SF3B1* VAF as independent variable.

ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; Hgb, hemoglobin; RBC, red blood cell; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; TI, transfusion independence; VAF, variant allele frequency.

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Conclusions

- Imetelstat demonstrated highly statistically significant and clinically meaningful benefit compared with placebo in this heavily transfusion dependent LR-MDS population in need of novel therapy
  - Robust RBC-TI rates: 8-week TI = 40% and 24-week TI = 28%
  - Median RBC-TI duration approaching 1 year for 8-week RBC-TI responders
  - Sustained increase in Hgb and HI-E per IWG 2018 (P<0.001 each)
- The rate of 8-week RBC-TI was significantly higher with imetelstat vs placebo across subgroups: RS status, RBC transfusion burden status, IPSS risk category, or sEPO status
- Safety results are consistent with prior imetelstat clinical experience with no new safety signals
  - Clinical consequences from grade 3-4 neutropenia and thrombocytopenia were similar in patients treated with imetelstat and placebo
- Reduction in VAF of commonly mutated genes *SF3B1, TET2, DNMT3A,* or *ASXL1* and their correlation with clinical end points support the disease-modifying potential of imetelstat

ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; Hgb, hemoglobin; HI-E, hematologic improvement-erythroid; IPSS, International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower risk myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; SF3B1, splicing factor 3b subunit 1; sEPO, serum erythropoietin; TET2, Tet methylcytosine dioxygenase 2; TI, transfusion independence; VAF, variant allele frequency.

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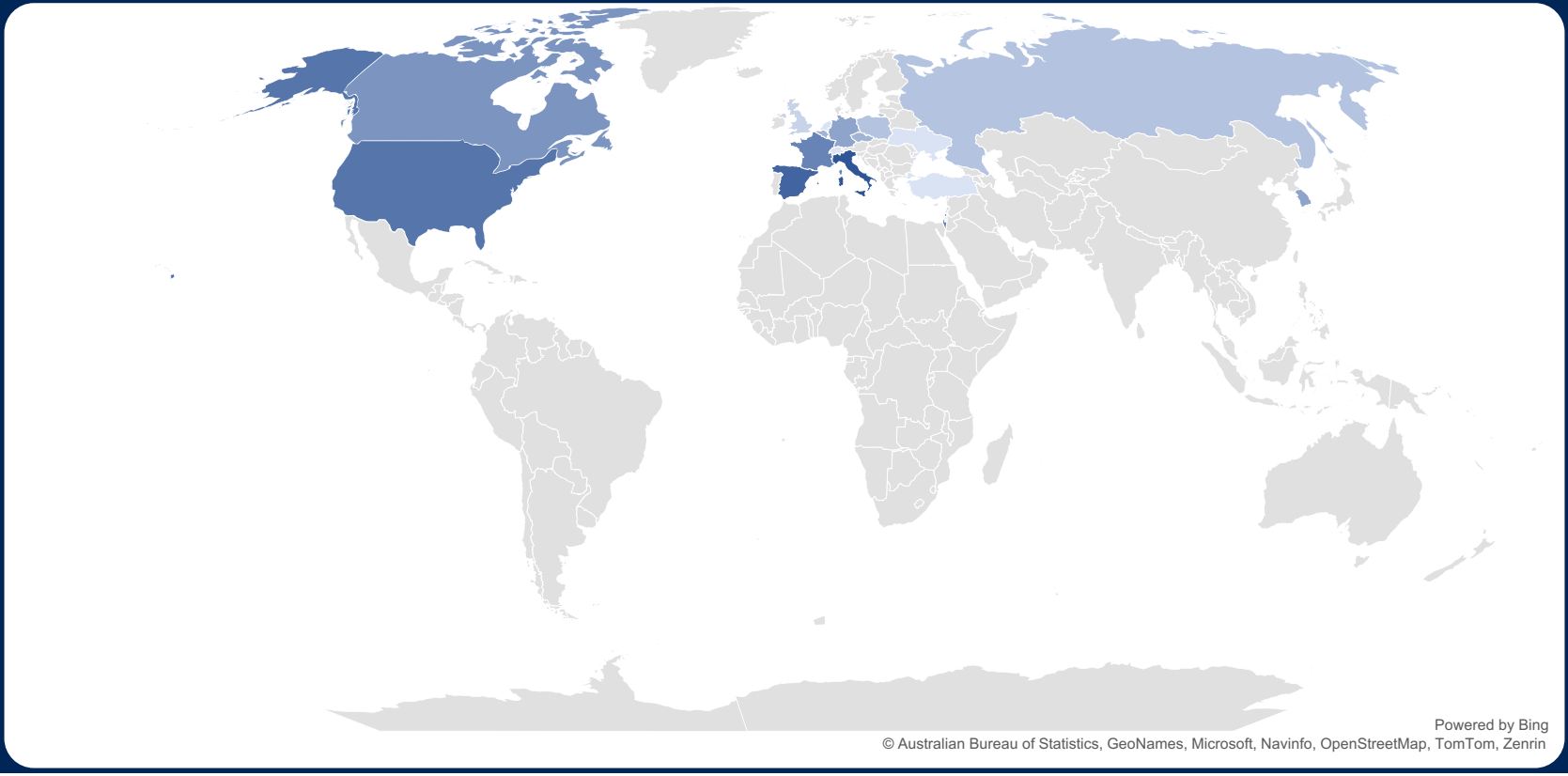

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CONTACT INFORMATION

- IMerge (MDS3001): https://www.geron.com/patients/imerge-study
- ClinicalTrials.gov: NCT02598661; email mds3001-info@geron.com

Thank you!

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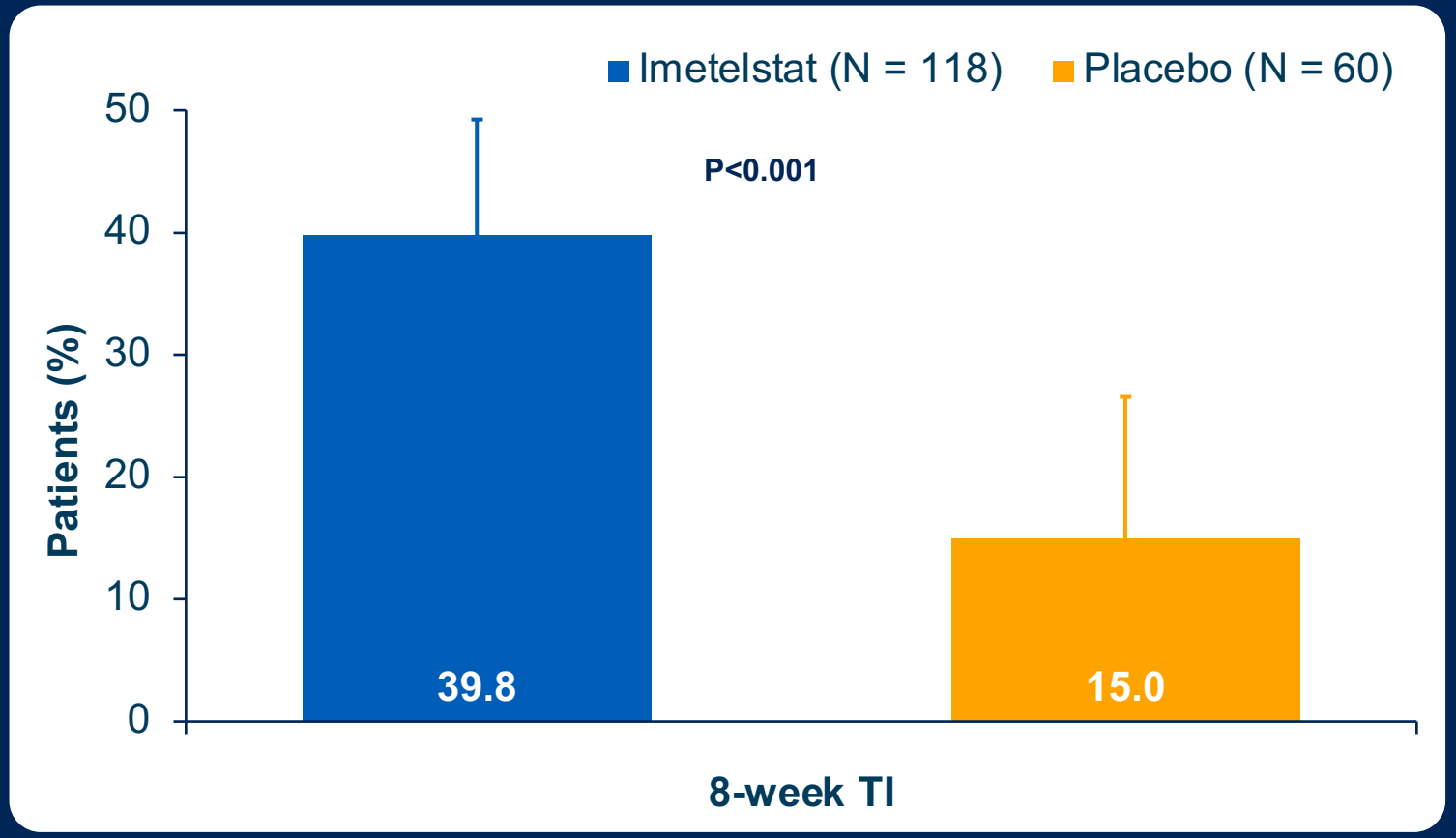
Primary End Point: 8-Week RBC TI Rate Significantly Higher With Imetelstat vs Placebo Overall



Patients With Response	Imetelstat (N = 118)	Placebo (N = 60)
n (%)	47 (39.8)	9 (15.0)
95% CI[a]	30.93–49.25	7.10–26.57
% Difference (95% CI)[b] P-value[c]	24.8 (9.9–36.9) <0.001	

Data cutoff: October 13, 2022.

[a]Exact Clopper-Pearson confidence interval. [b]Wilson score confidence interval. [c]P-value derived from the Cochran-Mantel-Haenszel test controlling for prior RBC transfusion burden (≤6 vs >6 units RBC) and IPSS risk group (low vs intermediate-1) applied to randomization.

IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

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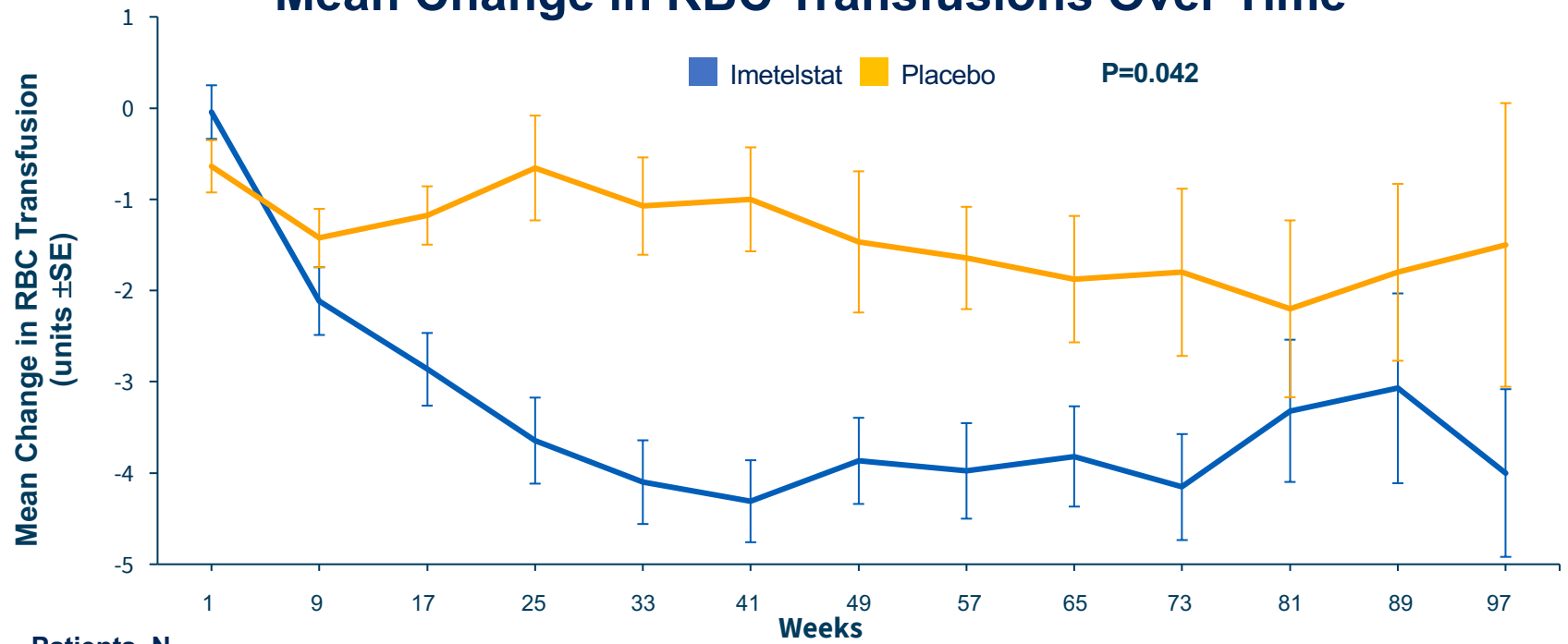
Greater Reduction in Mean RBC Transfusion Units Over Time With Imetelstat vs Placebo



Patients, N													
Imetelstat	115	104	95	76	60	55	45	43	33	26	22	14	10
Placebo	58	53	48	32	27	22	15	14	8	5	5	5	4

Data points that have <4 patients are not shown. P-value based on a mixed model for repeated measures with change in RBC transfusions as the dependent variable, week, stratification factors, prior transfusion burden, treatment group, and treatment and week interaction term as the independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.
RBC, red blood cell; SE, standard error.

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Imetelstat AEs Were Manageable With Dose Modifications

- Most AEs leading to dose modifications were grade 3–4 neutropenia and thrombocytopenia
- Although ≈75% of patients treated with imetelstat had dose modifications due to AEs, <15% of patients discontinued treatment due to TEAEs
- Discontinuation of imetelstat due to a TEAE generally occurred late in treatment, with a median time to treatment discontinuation of 21.1 weeks (range, 2.3 to 44.0 weeks)

Dose Modifications, n (%)	Imetelstat (N = 118)	Placebo (N = 59)
Patients with any dose delay due to TEAE	81 (68.6)	14 (23.7)
Patients with dose reduction due to TEAE	58 (49.2)	4 (6.8)
Patients with treatment discontinuation due to TEAE	17 (14.4)	0

Data cutoff: October 13, 2022.
AE, adverse event; TEAE, treatment-emergent adverse event.

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