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DISEASE-MODIFYING ACTIVITY OF IMETELSTAT IN PATIENTS WITH HEAVILY TRANSFUSED NON-DEL(5Q) LOWER-RISK MYELODYSPLASTIC SYNDROMES RELAPSED/REFRACTORY TO ERYTHROPOIESIS-STIMULATING AGENTS IN IMERGE PHASE 3

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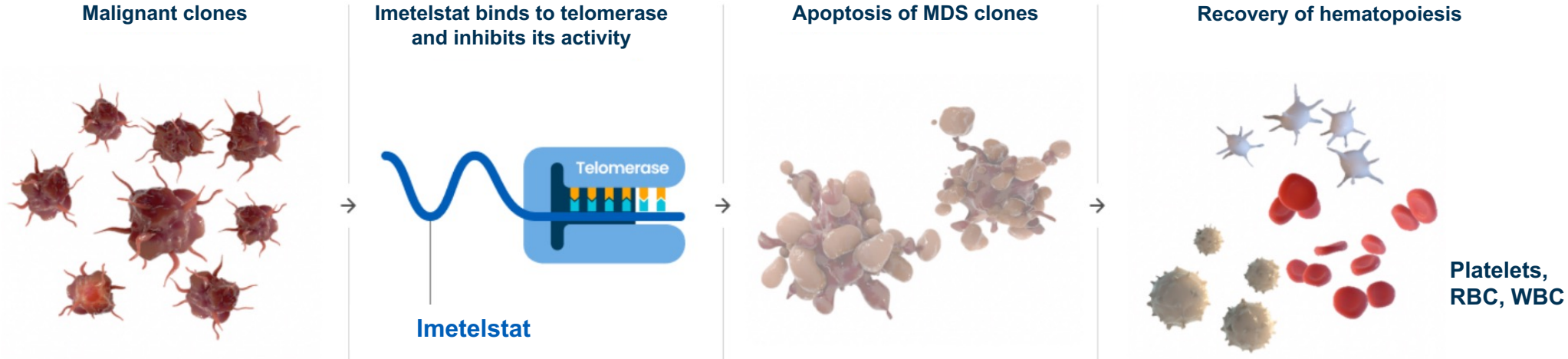
11-06-2023

Session: s448 MDS biology and translational updates

Disclosures (Valeria Santini)

- AbbVie, BMS, CTI, Geron, Gilead, Novartis, Otsuka, Servier, and Syros (Advisory board)
- Janssen (Travel grant)

Imetelstat in Lower Risk MDS



- Imetelstat is a first-in-class direct and competitive inhibitor of telomerase activity that specifically targets MDS clones with abnormally high telomerase activity, enabling the recovery of effective hematopoiesis[1-4]
- In phase 2 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[5]
  - Specifically, 8-week RBC-TI rates were 42% with a median TI duration of 86 weeks
- The phase 3 results from IMerge in the same patient population were highly consistent with the findings from the phase 2 efficacy results[6]
  - Robust RBC-TI rates: 8-week TI=40% with median TI duration approaching 1 year, 24-week TI=28%, 1-year TI=18%
- This analysis reports the results on the reduction of MDS clones, which suggests potential disease-modifying activity of imetelstat

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 B-S, et al. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467; 4. Wang X, et al. *Blood Adv.* 2018;2(18):2378-2388; 5. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56; 6. Platzbecker U, et al. EHA 2023. Oral presentation S165.

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 RBC/8 weeks over 16-week prestudy**
- Non-deletion 5q
- No prior treatment with lenalidomide or HMA

R 2:1

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

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

Placebo
(N=60)

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 points:
- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 units, epoetin beta ≥30,000 units, darbepoetin alfa 150 µg, or equivalent per week) without Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 units/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; R, randomization; RBC, red blood cell; TI, transfusion independence, VAF, variant allele frequency.

Baseline Patient and Disease Characteristics

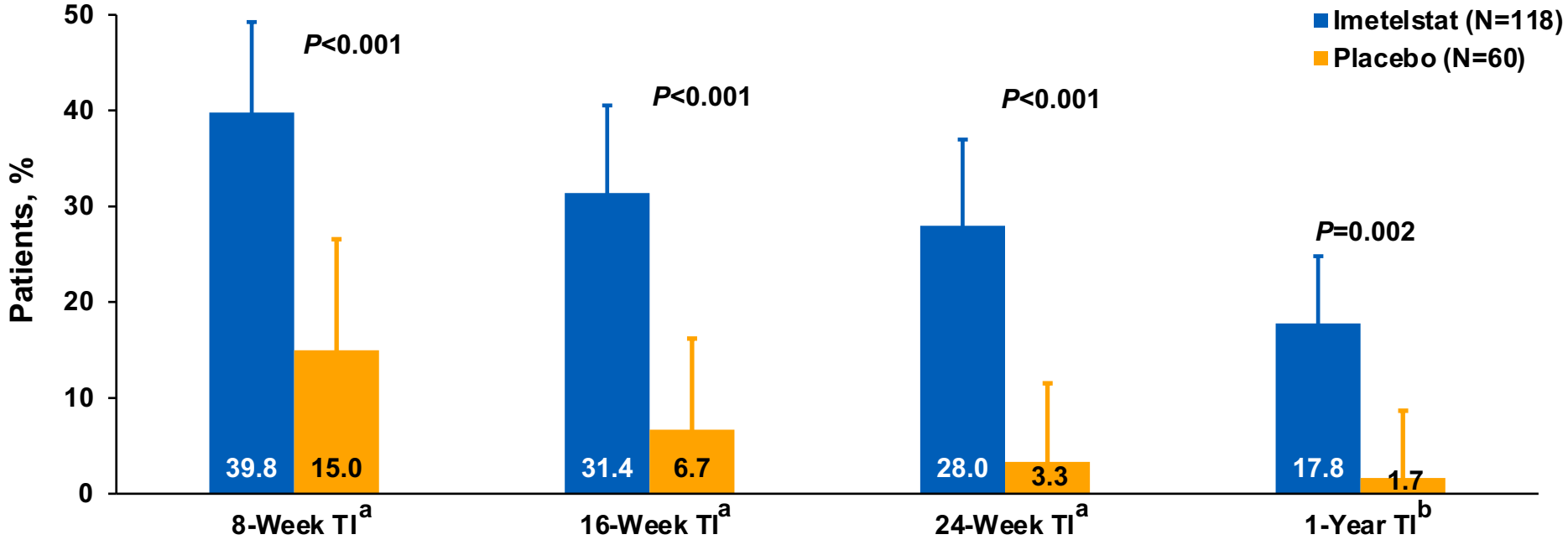
Characteristic	Imetelstat (N=118)	Placebo (N=60)
Median age, years (range)	72 (44–87)	73 (39–85)
Male, n (%)	71 (60)	40 (67)
Median time since diagnosis, years (range)	3.5 (0.1–26.7)	2.8 (0.2–25.7)
WHO classification, n (%)		
RS+	73 (62)	37 (62)
RS−	44 (37)	23 (38)
IPSS risk category, n (%)		
Low	80 (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, n (%)	108 (92)	52 (87)
Prior luspatercept, n (%)[c]	7 (6)	4 (7)

Data cutoff: October 13, 2022.

[a]Average of all Hgb values in the 8 weeks prior to the first dose date, excluding values within 14 days after a transfusion, which was 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.

Primary End Point of 8-Week RBC-TI Rate Was Significantly Higher With Imetelstat vs Placebo



Patients with response, n (%) 95% CI	8-Week TI[a]	16-Week TI[a]	24-Week TI[a]	1-Year TI[b]
Imetelstat	47 (39.8) 30.9–49.3	37 (31.4) 23.1–40.5	33 (28.0) 20.1–37.0	21 (17.8) 11.4–25.9
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

[a]**Data cutoff: October 13, 2022.** [b]**Data cutoff: January 13, 2023.**

Note: Primary end point 8-week TI and the first secondary end point 24-week TI were statistically significant by the study prespecified gate-keeping testing procedure. *P* value 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

Most Common AEs With Imetelstat Were Hematologic

- Median duration of grade 3–4 thrombocytopenia and neutropenia was <2 weeks and >80% of events were reversible to grade ≤2 within 4 weeks
- Clinical consequences of grade 3–4 infection and bleeding were low and similar for imetelstat and placebo

Hematologic AEs (≥10% of patients), n (%)	Imetelstat (N=118)		Placebo (N=59)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
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

Grade 3–4 cytopenias (per lab value)	Imetelstat (N=118)	Placebo (N=59)
Thrombocytopenia events		
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 events		
Median duration, weeks (range)	1.9 (0–15.9)	2.2 (1.0–4.6)
Resolved within 4 weeks, %	81.0	50.0

Data cutoff: October 13, 2022.
AE, adverse event.

Higher Percentage of Patients Achieved a Cytogenetic Response With Imetelstat vs Placebo

- Among patients with cytogenetic abnormalities at baseline, the cytogenetic response rate was 35% (9/26) in the imetelstat group and 15% (2/13) in the placebo group
- Among cytogenetic responders, 89% (8/9) of patients in the imetelstat group and 50% (1/2) in the placebo group also achieved 8-week RBC-TI

Cytogenetic response[a]	Imetelstat (N=118)	Placebo (N=60)
Patients with baseline cytogenetic abnormality based on central laboratory review, n (%)[b]	26 (22)	13 (22)
Cytogenetic best response, n (%)[c,d]		
Cytogenetic CR	5 (19)	1 (8)
Cytogenetic PR	4 (15)	1 (8)
Cytogenetic CR or PR criteria not met	5 (19)	5 (39)
Not evaluable	12 (46)	6 (46)
Cytogenetic CR or PR, n (%)[d]	9 (35)	2 (15)
95% CI[e]	17–56	2–45
% Difference (95% CI)[f]	19 (−16 to 44)	
P value[g]	0.216	

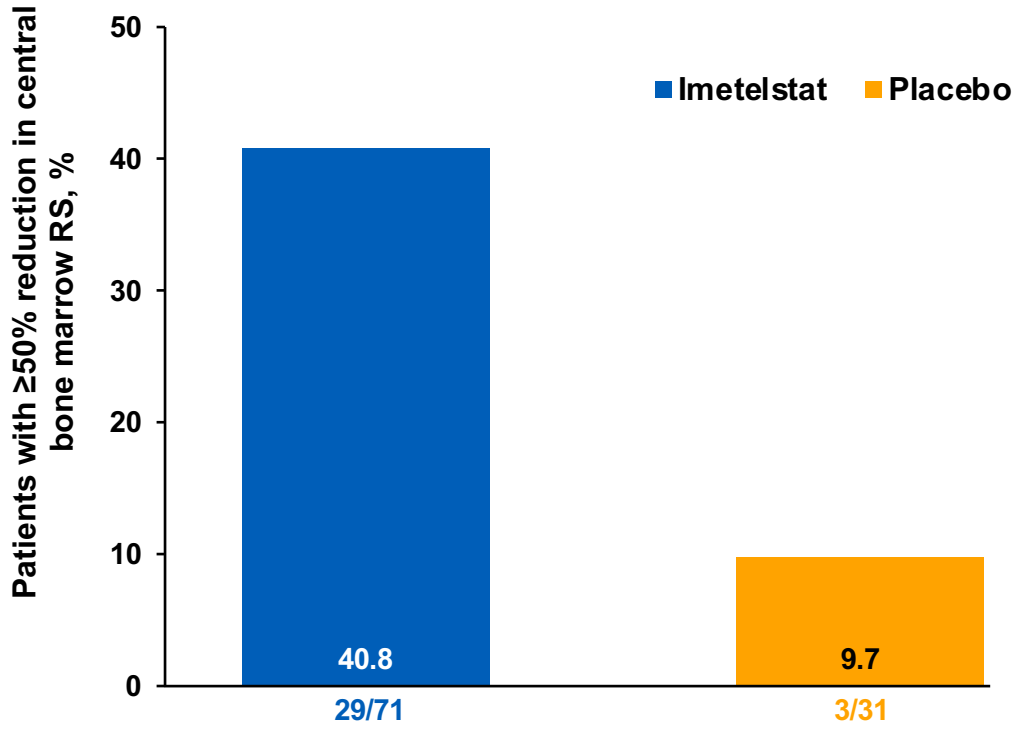
Data cutoff: October 13, 2022.

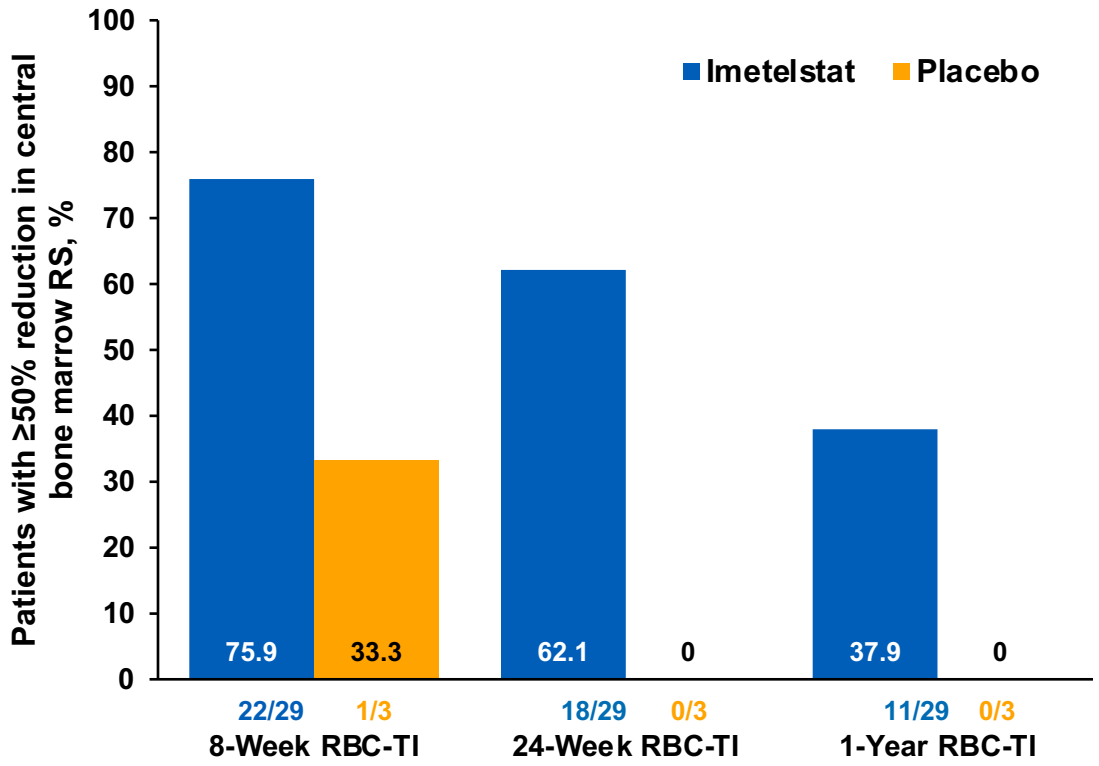
[a]Cytogenetic testing was done centrally, and the cytogenetic response was assessed by IRC. [b]Percentages calculated using the number of patients in each treatment group as the denominator. [c]Only patients considered for IRC adjudication are those assessed as having baseline cytogenetic abnormality by the IRC based on central laboratory data. [d]Percentages calculated using the number of patients with a baseline cytogenetic abnormality per central laboratory review within each treatment group as the denominator. [e]Exact Clopper-Pearson CI. [f]Wilson score CI. [g]*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.

CR, complete response; IPSS, International Prognostic Scoring System; IRC, independent review committee; PR, partial response; RBC, red blood cell; TI, transfusion independence.

More Patients Treated With Imetelstat vs Placebo Had ≥50% Reduction in Central Bone Marrow RS, Which Associated With TI Responses

- A higher percentage of patients treated with imetelstat vs placebo had a ≥50% reduction in central bone marrow RS
- RBC-TI responders enriched in patients achieving a ≥50% reduction in central bone marrow RS

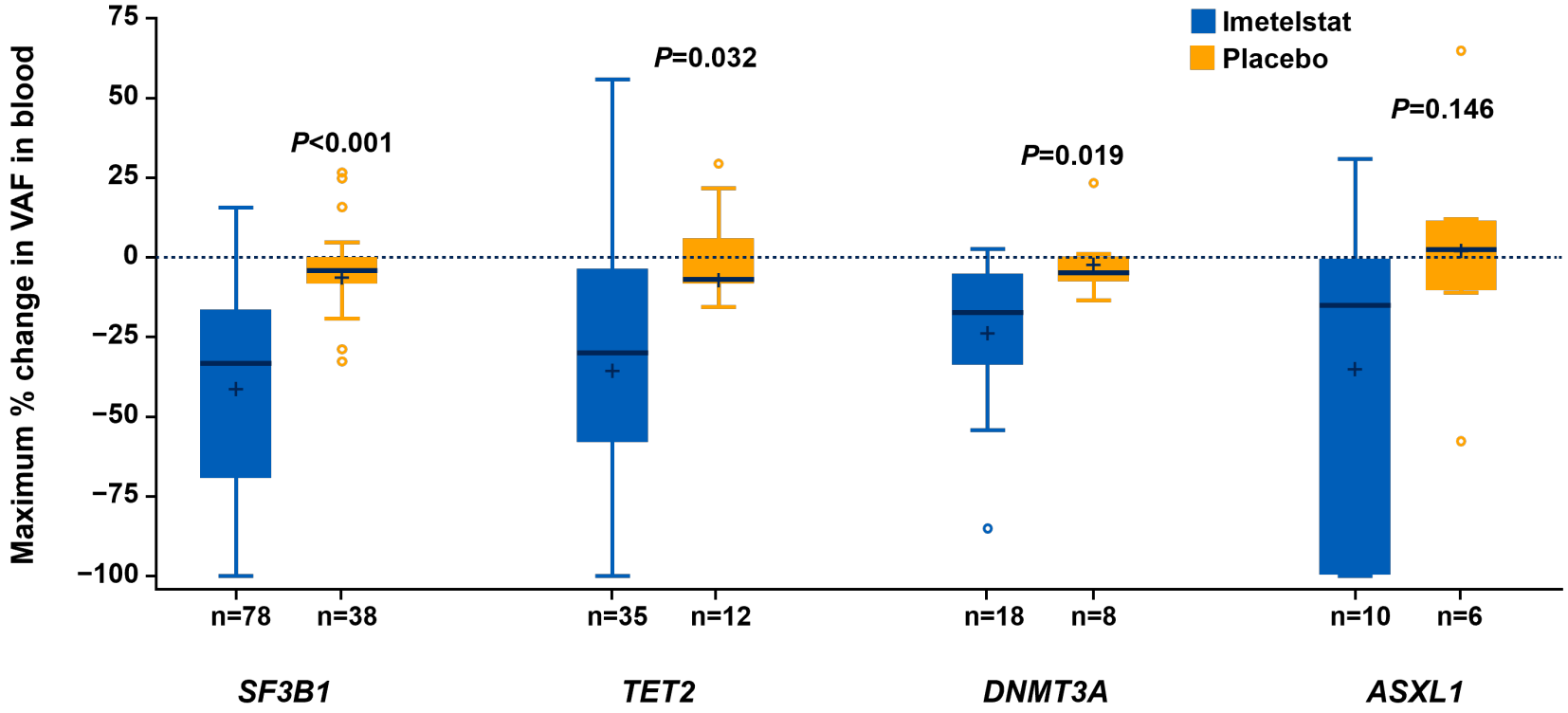




Data cutoff: October 13, 2022.
Note: Assessment was evaluated by central pathology review. Patients with baseline RS ≥15% and ≥1 postbaseline assessment were considered.
RBC, red blood cell; RS, ring sideroblasts; TI, transfusion independence.

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

- Mutations on 36 genes associated with MDS were tested by NGS on samples taken from baseline and post-treatment
- Among patients with evaluable mutation data, the maximum reductions in VAF of the *SF3B1*, *TET2*, *DNMT3A, and ASXL1* genes were greater with imetelstat than placebo

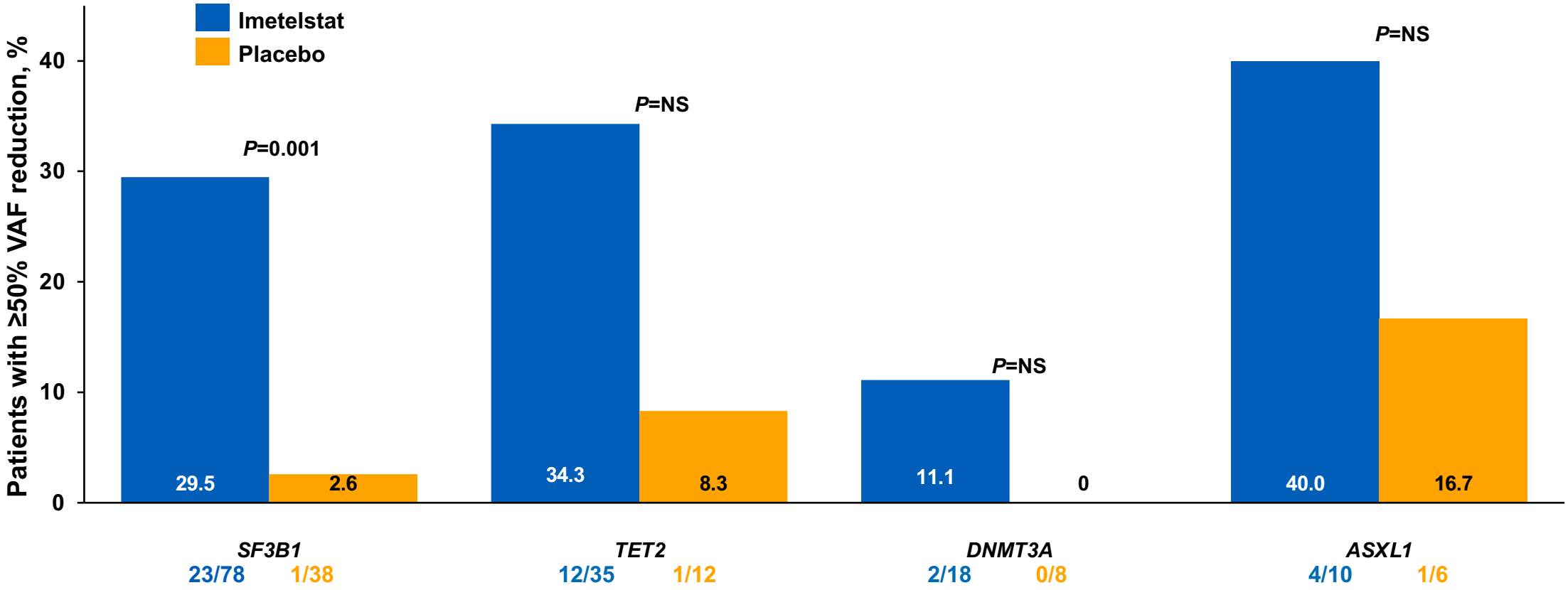


Data cutoff: October 13, 2022.

Note: Figure shows the comparison between each treatment group in the maximum percentage change from baseline in mutant VAF of the indicated gene. *P* value 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; MDS, myelodysplastic syndromes; NGS, next-generation sequencing; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.

More Patients Treated With Imetelstat vs Placebo Had ≥50% VAF Reduction in *SF3B1*, *TET2*, *DNMT3A*, and *ASXL1* Mutations

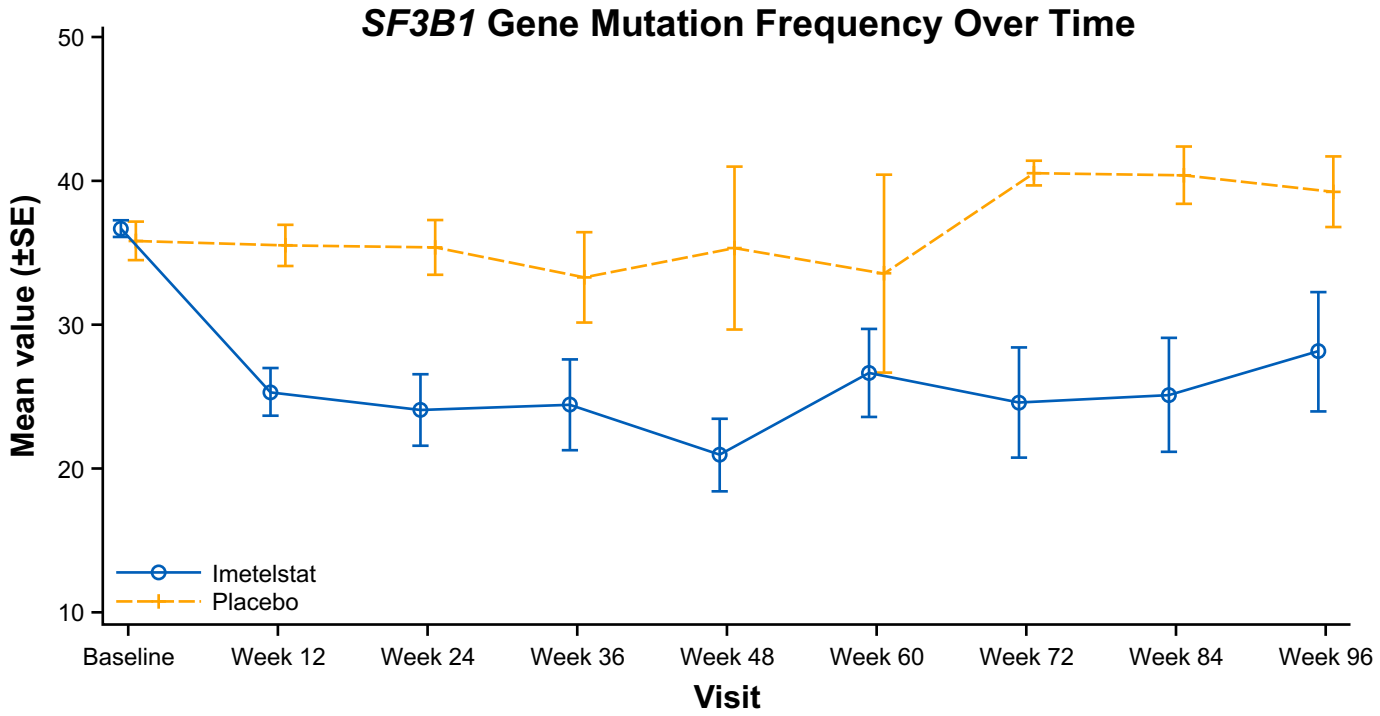


Data cutoff: October 13, 2022.

Note: 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**.** Ratios underneath the bars represent the number of patients with ≥50% VAF reduction as numerator and the total number of patients with detectable assessment (≥5% VAF) in specified mutation at baseline and any postbaseline mutation assessment as denominator. *P* value based on Cochran-Mantel-Haenszel test stratified for prior RBC transfusion burden (≤6 units or >6 units of RBC/8 weeks) and baseline IPSS risk score (low or intermediate-1).

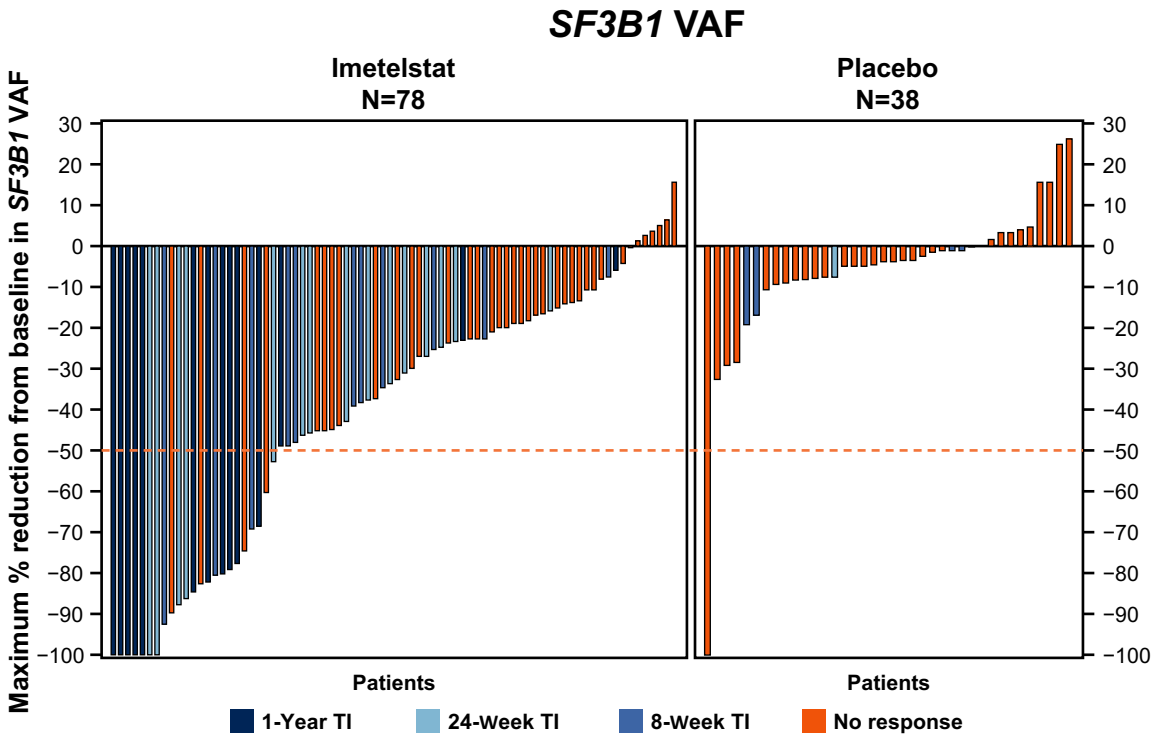
ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; IPSS, International Prognostic Scoring System; NS, not significant; RBC, red blood cell; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.

Imetelstat Treatment Resulted in Sustained Reduction of *SF3B1* VAF Over Time



Data cutoff: October 13, 2022.
Note: Mutation biomarker analysis set included all patients who received ≥1 dose of study drug and had baseline mutation on *SF3B1* gene and ≥1 postbaseline assessment. Data points exclude 1 ongoing patient.
SE, standard error; SF3B1, splicing factor 3b subunit 1; VAF, variant allele frequency.

RBC-TI Responders Enriched in Patients Achieving ≥50% Reduction in *SF3B1* VAF in the Imetelstat Group

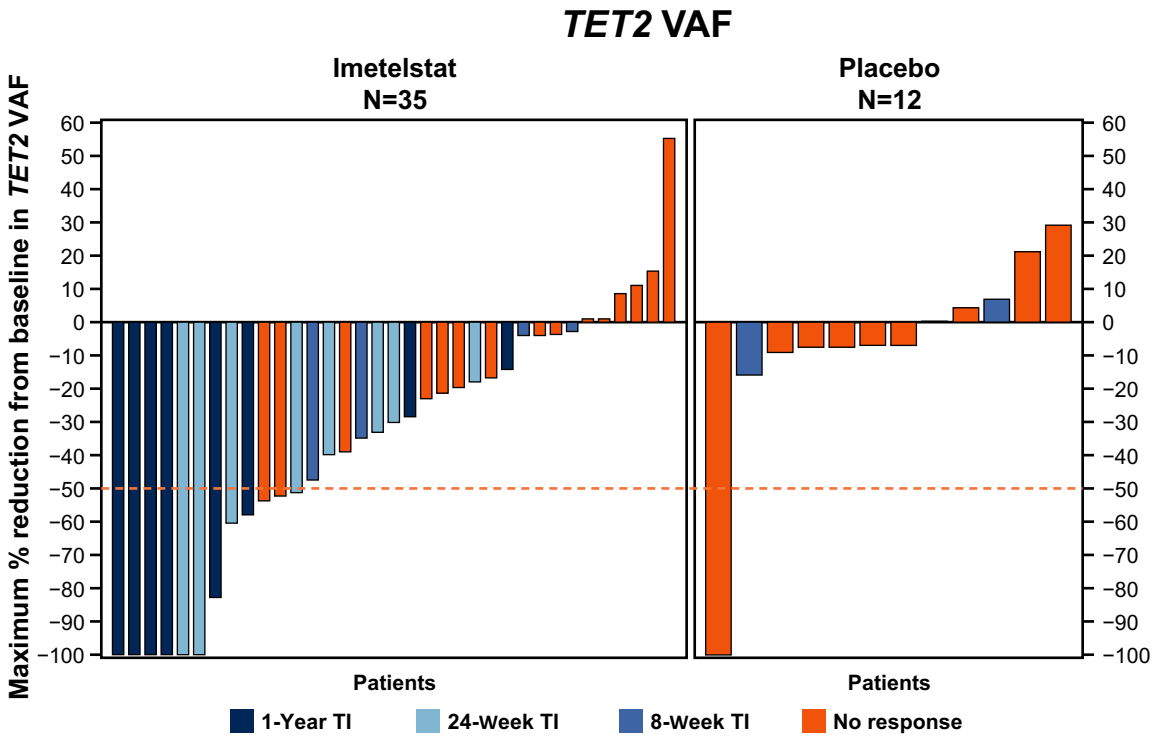


Patients, n (%)	Imetelstat *SF3B1* VAF ≥50% Reduction			
	Yes (N=23)	No (N=55)	Total (N=78)	*P* Value (Fisher exact test)
8-Week RBC-TI				
Yes	19 (82.6)	21 (38.2)	40 (51.3)	<0.001
No	4 (17.4)	34 (61.8)	38 (48.7)	
24-Week RBC-TI				
Yes	16 (69.6)	13 (23.6)	29 (37.2)	<0.001
No	7 (30.4)	42 (76.4)	49 (62.8)	
1-Year RBC-TI				
Yes	11 (47.8)	3 (5.5)	14 (17.9)	<0.001
No	12 (52.2)	52 (94.5)	64 (82.1)	

- Among patients treated with imetelstat who achieved ≥50% *SF3B1* VAF reduction, 83% were 8-week RBC-TI responders
- ≥24-week and ≥1-year RBC-TI responders were also enriched in patients achieving ≥50% reduction in *SF3B1* VAF

Data cutoff: October 13, 2022.
Note: Analyses included patients in the intent-to-treat population with a detectable *SF3B1* mutant allele (≥5%) prior to treatment and ≥1 postbaseline mutation assessment.
RBC, red blood cell; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

RBC-TI Responders Enriched in Patients Achieving ≥50% Reduction in *TET2* VAF in the Imetelstat Group



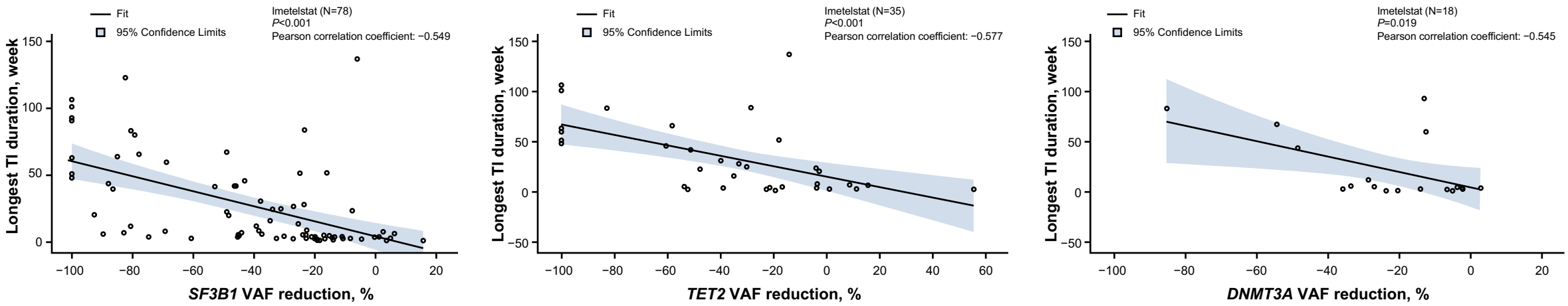
Patients, n (%)	Imetelstat *TET2* VAF ≥50% Reduction			
	Yes (N=12)	No (N=23)	Total (N=35)	*P* Value (Fisher exact test)
8-Week RBC-TI				
Yes	10 (83.3)	10 (43.5)	20 (57.1)	0.034
No	2 (16.7)	13 (56.5)	15 (42.9)	
24-Week RBC-TI				
Yes	10 (83.3)	6 (26.1)	16 (45.7)	0.003
No	2 (16.7)	17 (73.9)	19 (54.3)	
1-Year RBC-TI				
Yes	6 (50.0)	2 (8.7)	8 (22.9)	0.011
No	6 (50.0)	21 (91.3)	27 (77.1)	

- Among patients treated with imetelstat who achieved ≥50% *TET2* VAF reduction, 83% were 8-week RBC-TI responders
- ≥24-week and ≥1-year RBC-TI responders were also enriched in patients achieving ≥50% reduction in *TET2* VAF

Data cutoff: October 13, 2022.
Note: Analyses included patients in the intent-to-treat population with a detectable *TET2* mutant allele (≥5%) prior to treatment and ≥1 postbaseline mutation assessment.
RBC, red blood cell; TET2, Tet methylcytosine dioxygenase 2; TI, transfusion independence; VAF, variant allele frequency.

VAF Reduction in *SF3B1*, *TET2*, and *DNMT3A* Correlated With Longer RBC-TI Duration in Patients Treated With Imetelstat

Longest RBC-TI Duration vs Maximum Reduction in *SF3B1* (left), *TET2* (middle), and *DNMT3A* (right) VAF



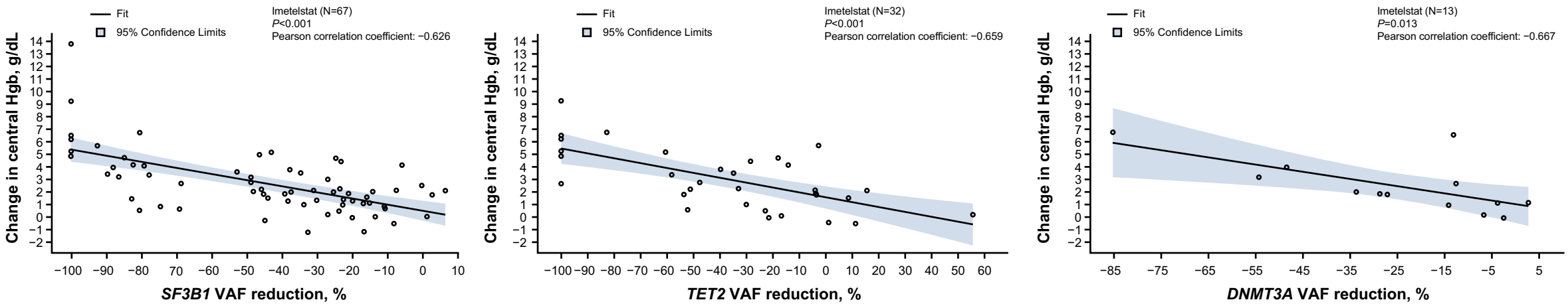
Data cutoff: October 13, 2022.

Note: 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. Fitted lines and *P* value based on linear regression with maximum increase in RBC-TI duration as the dependent variable and the maximum percentage reduction from baseline in each gene VAF as independent variable.

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

VAF Reduction in *SF3B1*, *TET2*, and *DNMT3A* Correlated With Increases in Hgb Levels in Patients Treated With Imetelstat

Maximum Increase in Hgb vs Maximum Reduction in *SF3B1* (left), *TET2* (middle), and *DNMT3A* (right) VAF



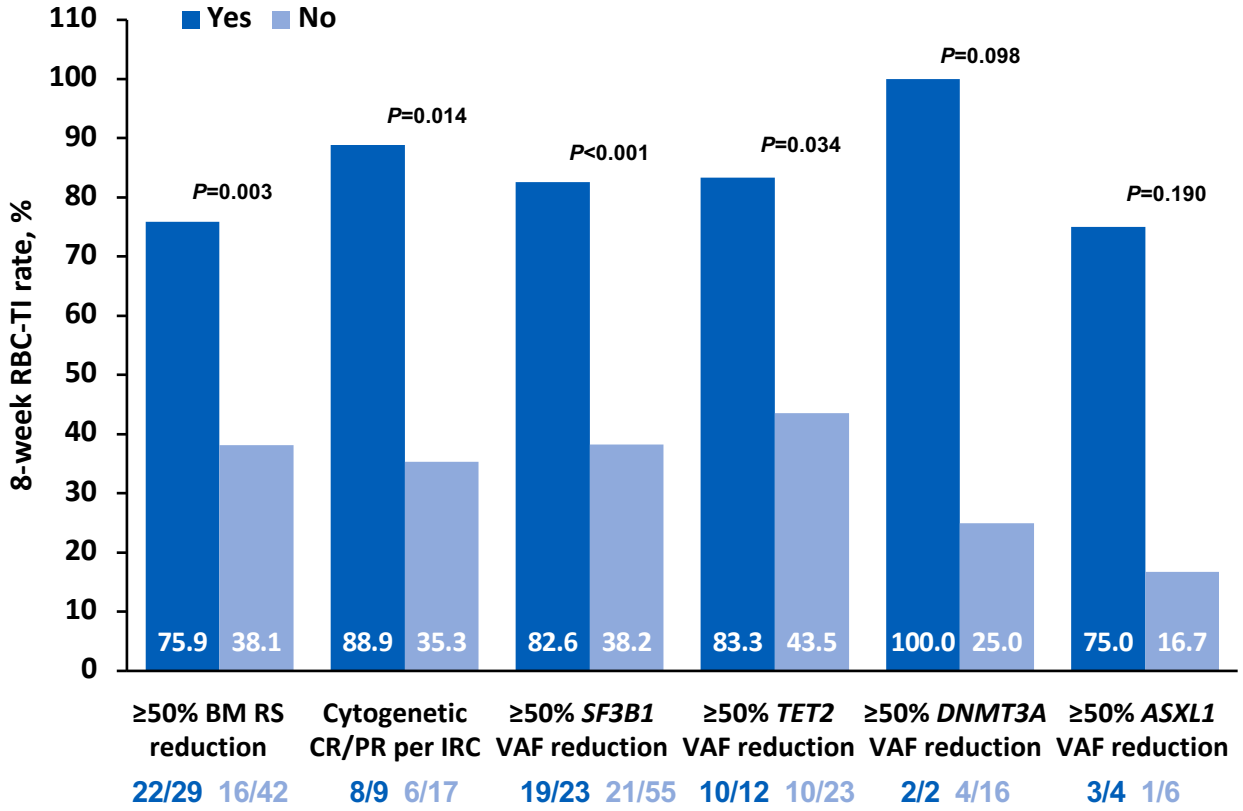
Data cutoff: October 13, 2022.

Note: 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 and had postbaseline Hgb assessment, excluding assessments within 14 days post-RBC transfusion. Fitted lines and *P* value based on linear regression with maximum increase in Hgb from pretreatment as the dependent variable and the maximum percentage reduction from baseline in each gene VAF as independent variable.

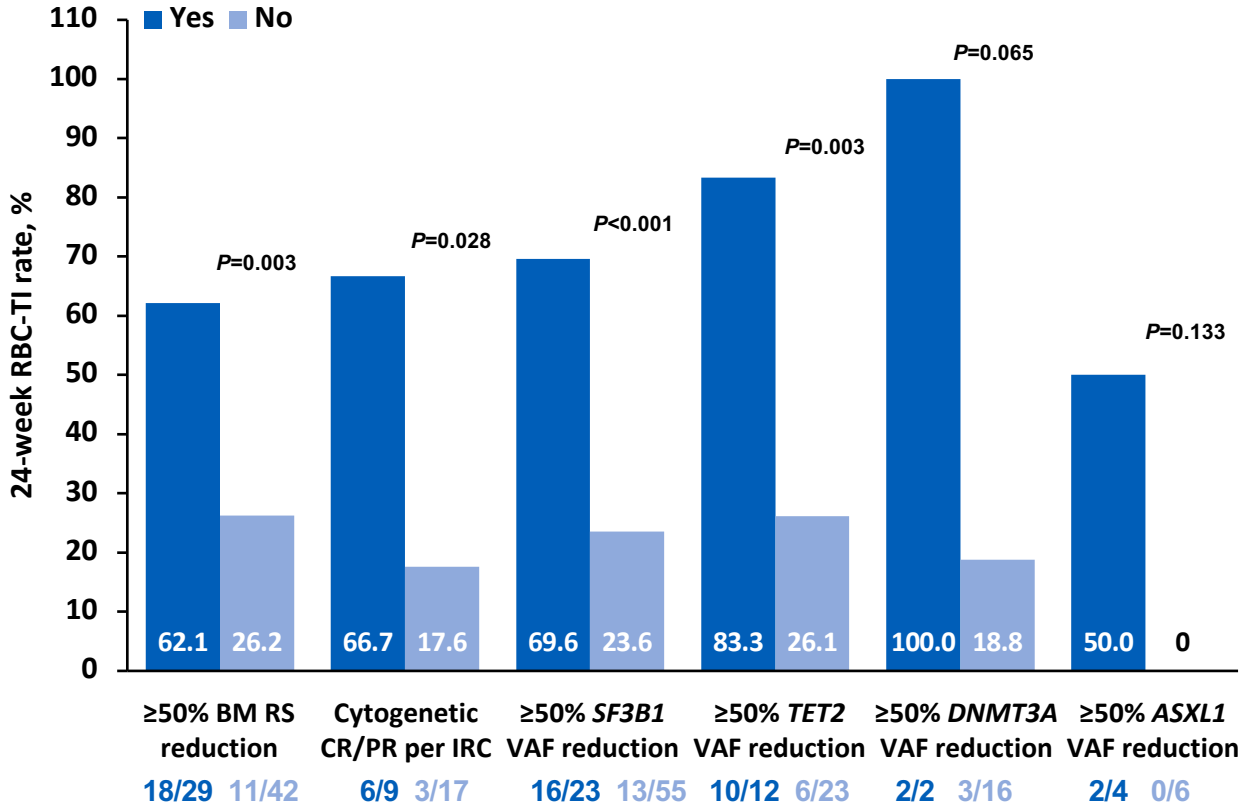
DNMT3A, DNA (cytosine-5)-methyltransferase 3A; Hgb, hemoglobin; RBC, red blood cell; TET2, Tet methylcytosine dioxygenase 2; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

8-Week and 24-Week RBC-TI Correlated With Reduction in RS+ Cells, Cytogenetic Responses, and VAF Reduction in Patients Treated With Imetelstat

8-Week RBC-TI Correlations



24-Week RBC-TI Correlations



Data cutoff: October 13, 2022.

Note: *P* value calculated using Fisher exact test between yes vs no in each outcome.

ASXL1, additional sex combs like-1; BM, bone marrow; CR, complete response; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; IRC, independent review committee; PR, partial response; RBC, red blood cell; RS, ring sideroblasts; TET2, Tet methylcytosine dioxygenase 2; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

Conclusions

In the phase 3 IMerge study of patients who had heavily RBC transfusion-dependent, ESA relapsed/refractory/ineligible, non-del(5q) LR-MDS and were naive to lenalidomide and HMA, treatment with imetelstat vs placebo led to:

- Higher cytogenetic response rate, which was associated with 8-week RBC-TI
- Higher percentage of patients achieving ≥50% reduction in bone marrow RS cells (41% vs 10%)
- Sustained reduction of *SF3B1* VAF over time
- Greater reduction of VAF in multiple genes, which correlated with clinical end points of TI response, longer RBC-TI duration, and increase in Hgb levels

These data, along with the robust and sustained RBC-TI rates, suggest that imetelstat may alter the underlying biology of LR-MDS and can potentially modify the disease by reducing or eliminating malignant clones and improving ineffective erythropoiesis

ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin; HMA, hypomethylating agent; LR-MDS, lower risk myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblasts; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

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Contact Information

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

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