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ELEVENTH ANNUAL MEETING

CONTINUOUS TRANSFUSION INDEPENDENCE WITH IMETELSTAT IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER-RISK MYELODYSPLASTIC NEOPLASMS RELAPSED/REFRACTORY/INELIGIBLE FOR ERYTHROPOIESIS-STIMULATING AGENTS IN IMerge PHASE III

MDS-572

IMerge

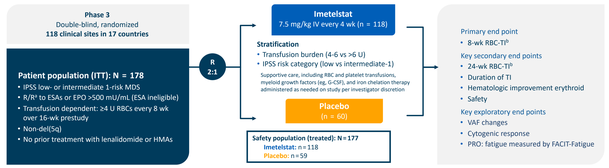
U. PLATZBECKER[1,*], V. SANTINI[2,**], P. FENAUX[3], M.A. SEKERES[4,**], M.R. SAVONA[5], Y.F. MADANAT[6], M. DÍEZ-CAMPELO[7], D. VALCÁRCEL-FERREIRAS[8], T. ILLMER[9], A. JONÁŠOVÁ[10], P. BĚLOHLÁVKOVÁ[11], L. SHERMAN[12], T. BERRY[12], S. DOUGHERTY[12], S. SHAH[12], Q. XIA[12], L. PENG[12], L. SUN[12], Y. WAN[12], F. HUANG[12], A. IKIN[12], S. NAVADA[12], F. FELLER[12], R.S. KOMROKJI[13], A.M. ZEIDAN[14,*]

[1]Leipzig University Hospital, Leipzig, Germany; [2]Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; [3]Hôpital Saint-Louis, Université de Paris 7, Paris, France; [4]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [5]Vanderbilt University Medical Center, Nashville, TN, USA; [6]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [7]University Hospital of Salamanca, Salamanca, Spain; [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]Hematology Private Practice, Dresden, Germany; [10]General Hospital, Prague, Czech Republic; [11]Charles University Hospital, Hradec Kralove, Czech Republic; [12]Geron Corporation, Parsippany, NJ, USA; [13]Moffitt Cancer Center, Tampa, FL, USA; [14]Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA. *Contributed equally. **Contributed equally.

INTRODUCTION

- Imetelstat is a first-in class direct and competitive inhibitor of telomerase that specifically targets malignant clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis[1-4]
- Unmet need remains for RBC transfusion-dependent patients with LR-MDS R/R to or ineligible for ESAs
- In the phase 2 part of the IMerge study, patients with LR-MDS who were heavily RBC transfusion dependent, R/R to or ineligible for ESAs, non-del(5q), and naive to lenalidomide and HMA achieved durable and continuous RBC-TI when treated with imetelstat, with an 8-week RBC-TI rate of 42% and a median TI duration of 86 weeks[5]
- This poster presents the analysis of phase 3 results from IMerge in the same patient population (**Fig. 1**)

Figure 1. IMerge Phase 3 Trial Design (MDS3001; NCT02598661)



[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 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. [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).

AIM

- To assess rates of 8- and 24-week RBC-TI, duration of RBC-TI, and hematologic improvement with imetelstat vs placebo in phase 3 of the IMerge study in patients overall and stratified by prior RBC-TB and IPSS category
- To assess frequency and magnitude of AEs with imetelstat vs placebo

METHODS

Study Design

- IMerge phase 3 is a double-blind, randomized (2:1), placebo-controlled, phase 3 trial conducted at 118 global sites between 2019 and 2022
- Patients with heavily RBC transfusion-dependent, ESA-relapsed/refractory/ineligible non-del(5q) LR-MDS naive to lenalidomide/HMA were randomized to receive imetelstat 7.5 mg/kg (n = 118) or placebo (n = 60) every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or lack of response
- Primary end point was 8-week TI rate; key secondary end points include 24-week RBC-TI, duration of TI, HI-E, and safety

Analysis

- Primary and secondary end points were compared using a Cochran-Mantel-Haenszel test stratified by prior RBC TB and IPSS category, and TI duration was calculated by Kaplan-Meier method and compared via the stratified log-rank test

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- All authors contributed to and approved the presentation
- Writing and editorial assistance was provided by Erin McMullin, PhD, and Mary C. Wiggin of Ashfield MedComms, an Inizio Company

DISCLOSURES

Uwe Platzbecker received honoraria from Geron, AbbVie, BMS, Janssen, Jazz, Silence Therapeutics, and Takeda

CONTACT INFORMATION

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

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ABBREVIATIONS

AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AARM(1,1), autoregressive moving average; *BCORL1*, *BCL6* corepressor like 1; COVID-19, coronavirus disease of 2019; DCO, data cutoff; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte-colony stimulating factor; *GNB1*, G protein subunit beta 1; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; HR, hazard ratio; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System-Revised; IPSS-M, International Prognostic Scoring System-Molecular; ITT, intent-to-treat; IV, intravenous; IWG, International Working Group; LR, lower risk; LTB, low transfusion burden; MDS, myelodysplastic neoplasms; NE, not estimable; *MLL-PTD*, mixed lineage leukemia partial tandem duplication *PPM1D*, protein phosphatase; PRO, patient-reported outcome; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; RS, ring sideroblast; sEPO, serum erythropoietin; *SETBP1*, SET binding protein 1; TEAE, treatment-emergent adverse event; TB, transfusion burden; TI, transfusion independence; WHO, World Health Organization.

RESULTS

Demographics and Disease Characteristics

- The study comprised 118 and 60 patients in the imetelstat and placebo arms, respectively (**Table 1A**)
- Imetelstat and placebo arms had similar distributions of patients by demographics, disease characteristics, and IPSS-R and IPSS-M risk categories (**Table 1A and B**)
- Similar percentages of patients discontinued treatment in the imetelstat and placebo arms (**Table 1C**)
- Discontinuations due to AEs were reported by 19 of 118 patients (16.1%) treated with imetelstat and 0 of 59 patients (0%) treated with placebo; 11 of 118 patients (9.3%) treated with imetelstat discontinued due to cytopenias
- Discontinuation due to disease progression occurred in 7 of 118 patients (5.9%) treated with imetelstat and 5 of 59 patients (8.5%) treated with placebo

Table 1. Demographics and Disease Characteristics (A), Risk Categorization (B), and Treatment Exposure and Disposition With 18 Month Median Follow-up (C)

A

Characteristic	Imetelstat (n = 118)	Placebo (n = 60)
Age, median (range), y	72 (44-87)	73 (39-85)
Male, n (%)	71 (60)	40 (67)
Time since diagnosis, median (range), y	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)
Pretreatment Hb, median (range),[a] g/dL	7.9 (5.3-10.1)	7.8 (6.1-9.2)
Prior RBC transfusion burden, median (range), RBC U/8 wk	6 (4-33)	6 (4-13)
Prior RBC transfusion burden, n (%)		
≥4 to ≤6 U/8 wk	62 (53)	33 (55)
>6 U/8 wk	56 (48)	27 (45)
sEPO, median (range), mU/mL	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)

DCO date, October 13, 2022. [a]Average 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. [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.

B

IPSS-R, n (%)[a]	Imetelstat (n = 118)	Placebo (n = 60)	Total (N = 178)
Very low	3 (2.5)	2 (3.3)	5 (2.8)
Low	87 (73.7)	46 (76.7)	133 (74.7)
Intermediate	20 (16.9)	8 (13.3)	28 (15.7)
High	1 (0.8)	0	1 (0.6)
Very high	0	0	0
Missing	7 (5.9)	4 (6.7)	11 (6.2)

IPSS-M, n (%)[a]	Imetelstat (n = 103)	Placebo (n = 52)	Total (N = 155)
Very low	4 (3.9)	0	4 (2.6)
Low	65 (63.1)	33 (63.5)	98 (63.2)
Moderate low	22 (21.4)	10 (19.2)	32 (20.6)
Moderate high	7 (6.8)	6 (11.5)	13 (8.4)
High	4 (3.9)	3 (5.8)	7 (4.5)
Very high	1 (1.0)	0	1 (0.6)

[a]For IPSS-R, the number included the ITT population. [a]For IPSS-M, mutation biomarker analysis set included all the patients who received ≥1 dose of study drug and had baseline mutation data and central cytogenetic data available. Molecular data MLL-PTD, BCORL1, GNB1, PPM1D, and SETBP1 were not assessed in the study.

C

	Imetelstat (n = 118)	Placebo (n = 59)
Treatment duration, median, wk[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
Loss of response[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)

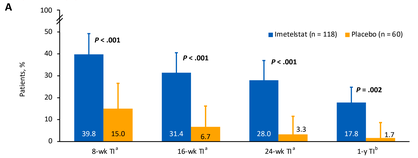
[a]Mean (SD) duration of treatment was 46.8 (34.3) and 39.6 (29.2) weeks with imetelstat and placebo, respectively. [b]Per IWG 2006 criteria. [c]Imetelstat group: neutropenic sepsis not related to drug after >2-year treatment duration (n = 1); placebo group: COVID-19 (n = 1) and heart valve issue (n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

Efficacy

- Primary end point of 8-week RBC-TI rate was significantly higher with imetelstat vs placebo (**Fig. 2A**)
- Imetelstat 8-week RBC-TI responders had significantly longer duration of TI vs placebo (**Fig. 2B**)
- Among patients treated with imetelstat, there was a significant and sustained increase in Hb levels (**Fig. 3A**)
- Greater reduction in mean RBC transfusion units over time with imetelstat vs placebo (**Fig. 3B**)
- HI-E rates with imetelstat vs placebo are shown in **Fig. 3C**
- Durability of RBC-TI for 8-week TI responders across key LR-MDS subgroups is shown in **Table 2A**
- 24-Week RBC-TI rates were comparable across key LR-MDS subgroups (**Table 2B**)

Figure 2. RBC-TI Rates at 8 Weeks to 1 Year (A) and Duration of RBC-TI in 8-Week Responders (B) With Imetelstat vs Placebo

A

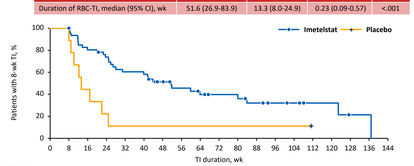


Patients with response, n (%) 95% CI				
Imetelstat	47 (39.8)	37 (31.4)	33 (28.0)	21 (17.8)
	30.9-49.3	23.1-40.5	20.1-37.0	11.4-25.9
Placebo	9 (15.0)	4 (6.7)	2 (3.3)	1 (1.7)
	7.1-26.6	1.9-16.2	0.4-11.5	0.0-8.9

Primary end point 8-week TI and the first secondary end point 24-week TI were statistically significant by the study's prespecified gate-keeping testing procedure. P Value determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC-TB (≥4 to ≤6 vs >6 RBC U every 8 weeks during a 16-week period prerandomization) and baseline IPSS risk category (low vs intermediate-1) applied to randomization. [a]DCO date, October 13, 2022. [b]DCO date, January 13, 2023.

B

8-wk TI responders	Imetelstat (n = 47)	Placebo (n = 9)	HR (95% CI)*	P Value[b]
Duration of RBC-TI, median (95% CI), wk	51.6 (26.9-83.9)	13.3 (8.0-24.9)	0.23 (0.09-0.57)	<.001

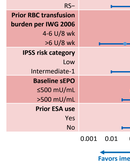


Patients, n															
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0				

[a]HR (95% CI) from the Cox proportional hazard model, stratified by prior RBC TB (≥4 to ≤6 vs >6 RBC U per 8 weeks during a 16-week period prerandomization) 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.

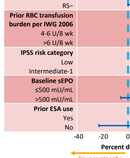
Table 2. Durability of RBC-TI for 8-Week TI Responders (A) and 24-Week RBC-TI Rate (B) Across Key LR-MDS Subgroups

A



	Imetelstat median (95% CI), wk	Placebo median (95% CI), wk	Hazard ratio (95% CI)	P Value
Overall	51.6 (26.9-83.9)	13.3 (8.0-24.9)	0.23 (0.09-0.57)	<.001
WHO category				
RS+	46.9 (25.9-83.9)	16.9 (8.0-24.9)	0.32 (0.11-0.95)	.035
RS−	51.6 (11.9-NE)	11.2 (10.1-NE)	0.11 (0.01-1.43)	.062
Prior RBC transfusion burden per IWG 2006				
4-6 U/8 wk	51.9 (24.9-122.9)	16.9 (10.1-24.9)	0.35 (0.13-0.96)	.035
>6 U/8 wk	39.9 (15.9-NE)	8.4 (8.0-NE)	0.04 (0.003-0.48)	<.001
IPSS risk category				
Low	43.9 (25.0-NE)	15.1 (8.0-24.9)	0.26 (0.10-0.68)	.004
Intermediate-1	51.6 (11.9-NE)	10.1 (NE-NE)	0.15 (0.01-2.47)	.128
Baseline sEPO				
≤500 mU/mL	51.6 (26.9-83.9)	13.3 (8.0-24.9)	0.21 (0.075-0.61)	.002
>500 mU/mL	122.9 (8.14-NE)	14.6 (12.3-NE)	0.34 (0.03-3.85)	.364
Prior ESA use				
Yes	43.9 (26.9-80.0)	13.3 (8.0-24.9)	0.26 (0.10-0.72)	.006
No	122.9 (8.14-NE)	14.6 (12.3-NE)	0.34 (0.03-3.85)	.364

B

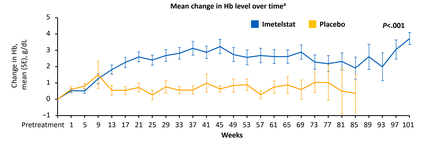


	Imetelstat n/N (%)	Placebo, n/N (%)	% Difference (95% CI)	P Value
Overall	33/118 (28.0)	2/60 (3.3)	24.6 (12.64-34.18)	<.001
WHO category				
RS+	24/73 (32.9)	2/37 (5.4)	27.5 (10.00-40.37)	.003
RS−	9/44 (20.5)	0/23 (0.0)	20.5 (−0.03 to 35.75)	.019
Prior RBC transfusion burden per IWG 2006				
4-6 U/8 wk	19/62 (30.6)	2/33 (6.1)	24.6 (5.68-38.66)	.006
>6 U/8 wk	14/56 (25.0)	0/27 (0)	25.0 (6.44-38.65)	.012
IPSS risk category				
Low	23/80 (28.8)	2/39 (5.1)	23.6 (7.23-35.75)	.003
Intermediate-1	10/38 (26.3)	0/21 (0)	26.3 (3.46-43.39)	.009
Baseline sEPO				
≤500 mU/mL	29/87 (33.3)	2/36 (5.6)	27.8 (10.46-39.71)	.002
>500 mU/mL	4/26 (15.4)	0/22 (0)	15.4 (−5.81 to 35.73)	.050
Prior ESA use				
Yes	31/108 (28.7)	2/52 (3.8)	24.9 (11.61-35.00)	<.001
No	2/10 (20)	0/8	20.0 (−23.47-55.78)	.225

(A) HR (95% CI) from the Cox proportional hazard model and (B) 95% CI based on Wilson Score method. P Value determined by the Cochran-Mantel-Haenszel test, stratified by prior RBC TB (≥4 to ≤6 vs >6 RBC U per 8 weeks during a 16-week period before randomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate. P Value (2-sided) for superiority of imetelstat vs placebo in HR based on stratified log-rank test (A).

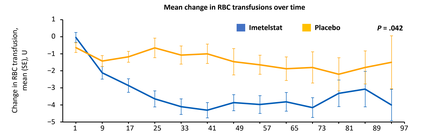
Figure 3. Improvement in Hb Levels (A), Transfusion Burden (B), and HI-E Response (C) With Imetelstat vs Placebo

A



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				

B



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												

[a]Mean changes from the minimum Hb levels of the values that were after 14 days of transfusions in the 8 weeks before the first dose date are shown (A). Data points that have <4 patients are not shown (B). P Value based on a mixed model for repeated measures with Hb change (A) or change in RBC transfusions (B) as the dependent variable, week, stratification factors, minimum Hb level in the 8 weeks before the first dose date (A) or prior TB (B), treatment group, and treatment and week interaction term as the independent variables with ARMA(1,1) covariance structure.

C

Hematologic improvement	Imetelstat (n = 118)	Placebo (n = 60)	% Difference P value[a]
HI-E (IWG 2018[b]), n (%)	50 (42.4)	8 (13.3)	29.0
95% CI[b]	33.3-51.8	5.9-24.6	<.001
Patients with LTB, n[c]	21	18	
HI-E response (16-wk RBC-TI), n (%)	7 (33.3)	4 (22.2)	11.1
95% CI[b]	14.6-57.0	6.4-47.6	.562
Patients with HTB, n[c]	97	42	
Major HI-E response (16-wk RBC-TI), n (%)	30 (30.9)	0	30.9
95% CI[b]	21.9-41.1	(0.0-8.4)	<.001
Minor HI-E response (50% RBC U reduction in 16 wk), n (%)	43 (44.3)	4 (9.5)	34.8
95% CI[b]	34.2-54.8	2.7-22.6	<.001

[a]P Value based on Cochran-Mantel-Haenszel controlling for prior RBC TB (≥6 vs >6 RBC U) and IPSS risk group (low vs intermediate-1) applied to randomization. [b]Exact Clopper-Pearson CI. [c]Per revised IWG 2018, patient with LTB was a patient who received 3 to 7 RBC U in the 16 weeks before study entry in ≥2 transfusion episodes and a patient with HTB was a patient who received ≥8 RBC U in the 16 weeks before study entry in ≥2 transfusion episodes.

Safety

- Consistent with prior clinical experience, the most common AEs were hematologic, consisting of grade 3-4 thrombocytopenia and neutropenia most often reported during cycles 1-3 (**Table 3**)
  - No fatal hematologic AEs occurred
  - Nonhematologic AEs were generally low grade
  - Incidence of grade 3 liver function test laboratory abnormalities was similar in imetelstat vs placebo
  - No cases of Hy's Law or drug-induced liver injury observed

Table 3. AEs With Imetelstat vs Placebo

AEs (≥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

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

- Cytopenias were of short duration and were manageable (**Table 4A**)
  - Median duration of grade 3-4 thrombocytopenia and neutropenia was <2 weeks
  - Greater than 80% of events resolved 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
  - Clinical consequences of grade 3-4 infection and bleeding were low and similar for imetelstat and placebo (**Table 4B**)

Table 4. Duration (A) and Clinical Consequences (B) of Grade 3-4 Cytopenias

A

Grade 3-4 cytopenias per lab value	Imetelstat (n = 118)	Placebo (n = 59)
Thrombocytopenia		
Duration, median (range), wk	1.4 (0.1-12.6)	2.0 (0.3-11.6)
Resolved within 4 wk, %	86.3	44.4
Neutropenia		
Duration, median (range), wk	1.9 (0-15.9)	2.2 (1.0-4.6)
Resolved within 4 wk, %	81.0	50.0

B

Grade ≥3 AEs, n (%)	Imetelstat (n = 118)	Placebo (n = 59)
Bleeding events	3 (2.5)	1 (1.7)
Infections	13 (11.0)	8 (13.6)
Febrile neutropenia	1 (0.8)	0

- Imetelstat TEAEs were managed with dose modification (**Table 5**)
  - Most AEs leading to dose modifications were grade 3–4 neutropenia and thrombocytopenia
  - 74% of patients treated with imetelstat had dose modifications due to AEs but <15% discontinued treatment due to TEAEs
  - Median time to discontinuation of imetelstat due to a TEAE was 21.1 weeks (range, 2.3 to 44.0 weeks)

Table 5. Frequency of Dose Modification and Treatment Discontinuation for TEAEs

Patients with dose modifications, n (%)	Imetelstat (n = 118)	Placebo (n = 59)
Any dose delay due to TEAEs	81 (68.6)	14 (23.7)
Dose reduction due to TEAE	58 (49.2)	4 (6.8)
Treatment discontinuation due to TEAE	17 (14.4)	0

CONCLUSIONS

- In this heavily transfusion dependent LR-MDS population in need of novel therapy, imetelstat demonstrated statistically significant and clinically meaningful efficacy compared with placebo
  - Robust RBC-TI rates: 40% with 8-week RBC-TI and 28% with 24-week RBC-TI (DCO date, October 13, 2022) and 18% with 1-year RBC-TI (DCO date, January 13, 2023)
  - Median RBC-TI duration approached 1 year for 8-week RBC-TI responders
  - Increased Hb levels and HI-E per IWG 2018
  - Rate of 24-week RBC-TI was higher with imetelstat vs placebo across subgroups grouped by RS status, RBC TB, IPSS risk category, or sEPO status
- Safety results were consistent with prior imetelstat clinical experience, with no new safety signals
  - Severe clinical consequences from grade 3-4 cytopenias were similar in patients treated with imetelstat and placebo
  - Encouraging durability was observed with imetelstat treatment in LR-MDS patients who were heavily RBC transfusion dependent and R/R to or inelegible for ESAs