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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

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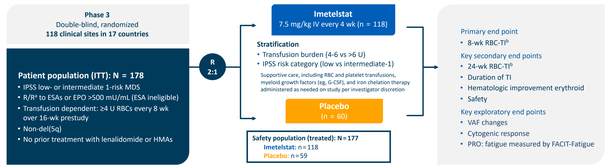
INTRODUCTION

- 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
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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)

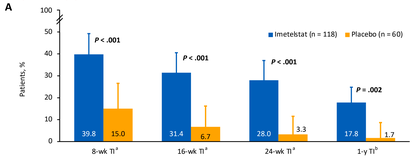
[a]*Mean (SD) duration of treatment was 46.8 (34.3) and 39.6 (29.2) weeks with imetelstat and placebo, respectively.* [b]*Per IWG 2006 criteria.* [c]*Imetelstat group: neutropenic sepsis not related to drug after >2-year treatment duration (n = 1); placebo group: COVID-19 (n = 1) and heart valve issue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

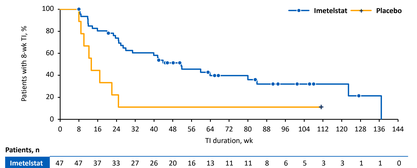


Patients with response, n (%) 95% CI				
Imetelstat	47 (39.8)	37 (31.4)	33 (28.0)	21 (17.8)
	30.9-49.3	23.1-40.5	20.1-37.0	11.4-25.9
Placebo	9 (15.0)	4 (6.7)	2 (3.3)	1 (1.7)
	7.1-26.6	1.9-16.2	0.4-11.5	0.0-8.9

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)[a]	*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				

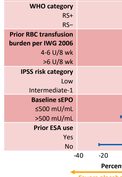
[a]*HR (95% CI) from the Cox proportional hazard model, stratified by prior RBC TB (≥4 to ≤6 vs >6 RBC U per 8 weeks during a 16-week period prerandomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate.* [b]*P Value (2-sided) for superiority of imetelstat 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

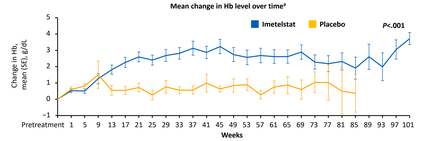


	Imetelstat n/N (%)	Placebo, n/N (%)	% Difference (95% CI)	*P* Value
Overall	33/118 (28.0)	2/60 (3.3)	24.6 (12.64-34.18)	<.001
WHO category				
RS+	24/73 (32.9)	2/37 (5.4)	27.5 (10.00-40.37)	.003
RS−	9/44 (20.5)	0/23 (0.0)	20.5 (−0.03 to 35.75)	.019
Prior RBC transfusion burden per IWG 2006				
4-6 U/8 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).

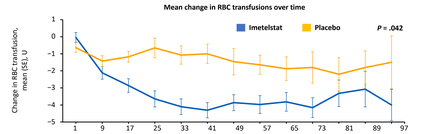
Figure 3. Improvement in Hb Levels (A), Transfusion Burden (B), and HI-E Response (C) With Imetelstat vs Placebo

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