EHA EUROPEAN HEMATOLOGY ASSOCIATION

# EHA2023

## JUNE 8 - 15 / FRANKFURT & VIRTUAL

**Presentation S165** – 09-06-2023

# CONTINUOUS TRANSFUSION INDEPENDENCE WITH IMETELSTAT IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER-RISK MYELODYSPLASTIC SYNDROMES RELAPSED/REFRACTORY TO ERYTHROPOIESIS STIMULATING AGENTS IN IMERGE PHASE 3

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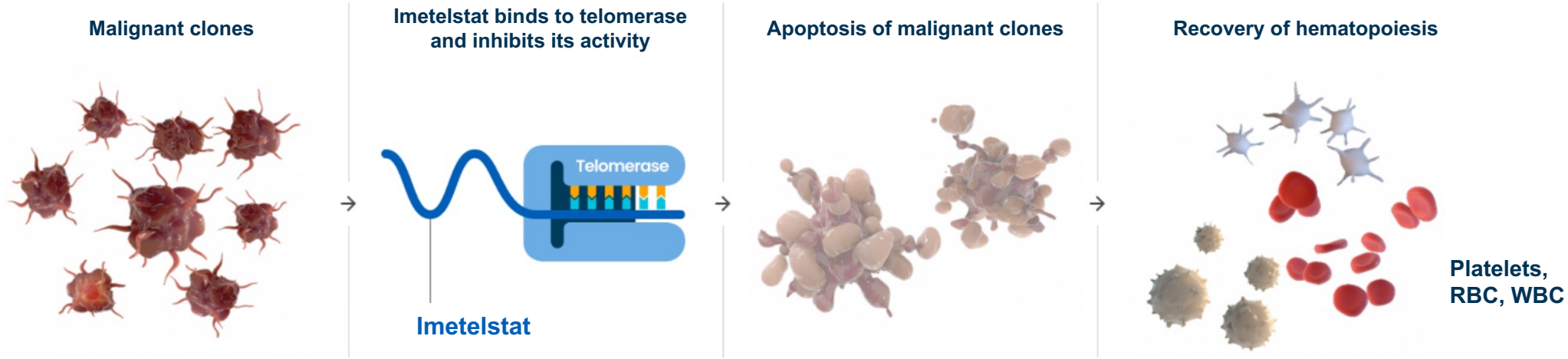
**09-06-2023**

Session: s417 MPN and MDS Targeting red cells and platelets

# Disclosures (Uwe Platzbecker)

Geron, AbbVie, BMS, Janssen, Jazz, Silence Therapeutics, and Takeda (Honoraria)

# Imetelstat in Lower Risk MDS




- Imetelstat is a first-in class direct and competitive inhibitor of telomerase activity that specifically targets malignant clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis[1-4]
- 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[5]
  - Specifically, 8-week RBC-TI rates were 42% with a median TI duration of 86 weeks
- 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 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;

# 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

**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 endpoint:**

- 8-week RBC-TI[b]

**Key secondary endpoints:**

- 24-week RBC-TI[b]
- Duration of TI
- Hematologic improvement-erythroid
- Safety

**Key exploratory endpoints:**

- 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.

# Risk Categorization by IPSS-R or IPSS-M Was Consistent With Baseline IPSS Risk

| | Imetelstat (N=118) | Placebo (N=60) | Total (N=178) |
|---|---|---|---|
| **IPSS-R, n (%)[a]** | | | |
| **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) |

| | Imetelstat (N=103) | Placebo (N=52) | Total (N=155) |
|---|---|---|---|
| **IPSS-M, n (%)[b]** | | | |
| **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) |

**Data cutoff: October 13, 2022.**

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

BCORL1, BCL6 corepressor like 1; GNB1, G protein subunit beta 1; IPSS-M, IPSS, International Prognostic Scoring System-Molecular; IPSS-R, IPSS, International Prognostic Scoring System-Revised; ITT, intention-to-treat; MLL-PTD, mixed lineage leukemia partial tandem duplication; PPM1D, protein phosphatase, Mg2+/Mn2+ dependent 1D; SETBP1, SET binding protein 1.

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

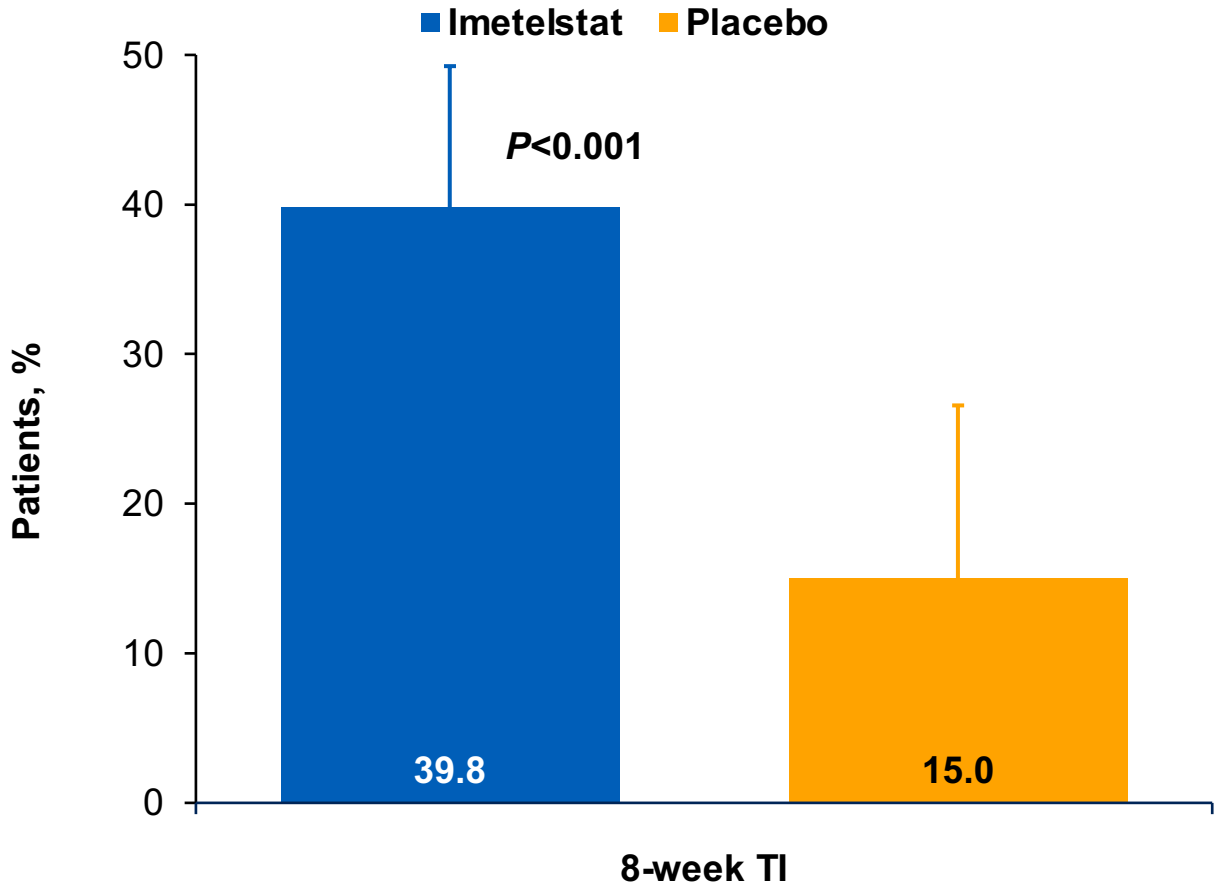
| | Imetelstat (N=118) | Placebo (N=59) |
|---|---|---|
| Treatment duration, median, weeks[a] | 33.9 | 28.3 |
| Treatment ongoing, n (%) | 27 (22.9) | 14 (23.7) |
| Treatment discontinued, n (%) | 91 (77.1) | 45 (76.3) |
| Lack of efficacy | 28 (23.7) | 25 (42.4) |
| Adverse event | 19 (16.1) | 0 |
| Cytopenias | 11 (9.3) | 0 |
| Unrelated | 8 (6.8) | 0 |
| 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) |

**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.

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



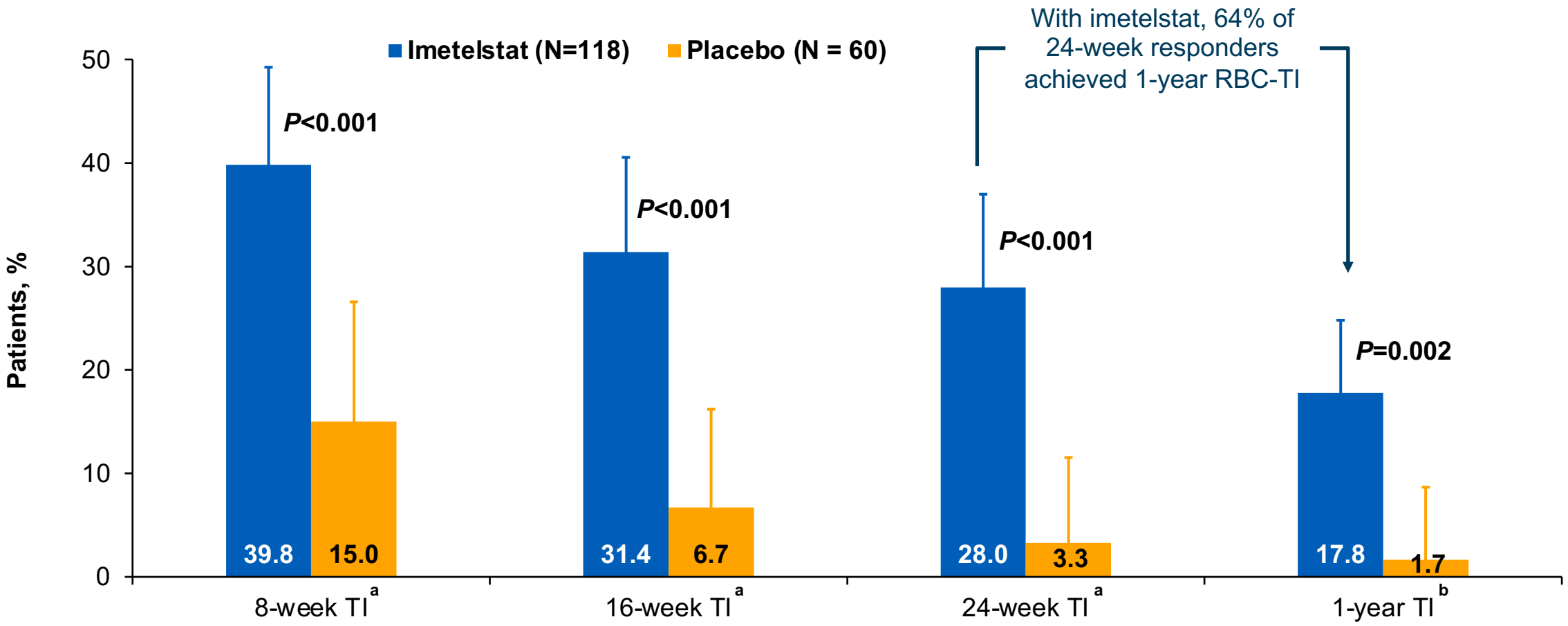

| 8-Week TI Responders | Imetelstat (N=118) | Placebo (N=60) |
|---|---|---|
| n (%) | 47 (39.8) | 9 (15.0) |
| 95% CI[a] | 30.93–49.25 | 7.10–26.57 |
| % Difference (95% CI)[b] | 24.8 (9.9–36.9) | |
| *P*-value[c] | <0.001 | |

**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.

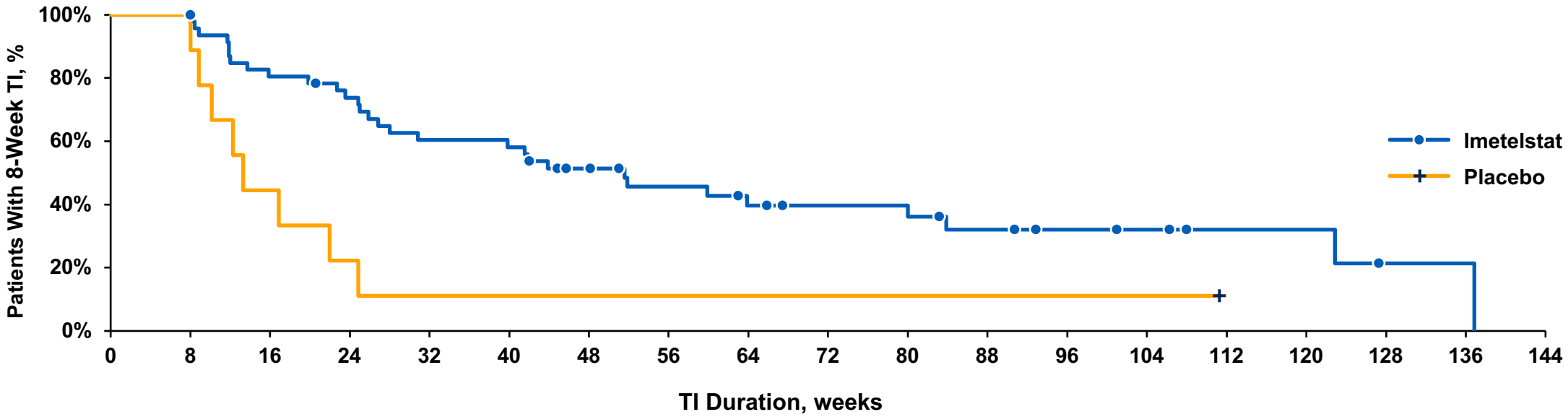
# Higher Rates of Longer-Term Duration of RBC-TI Observed With Imetelstat vs Placebo, Including 1-Year RBC-TI With Additional 3 Month Follow-up




[a]Data cutoff: October 13, 2022. [b]Data cutoff: January 13, 2023.
*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 International Prognostic Scoring System risk category (low vs intermediate-1) applied to randomization.
RBC, red blood cell; TI, transfusion independence.

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

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



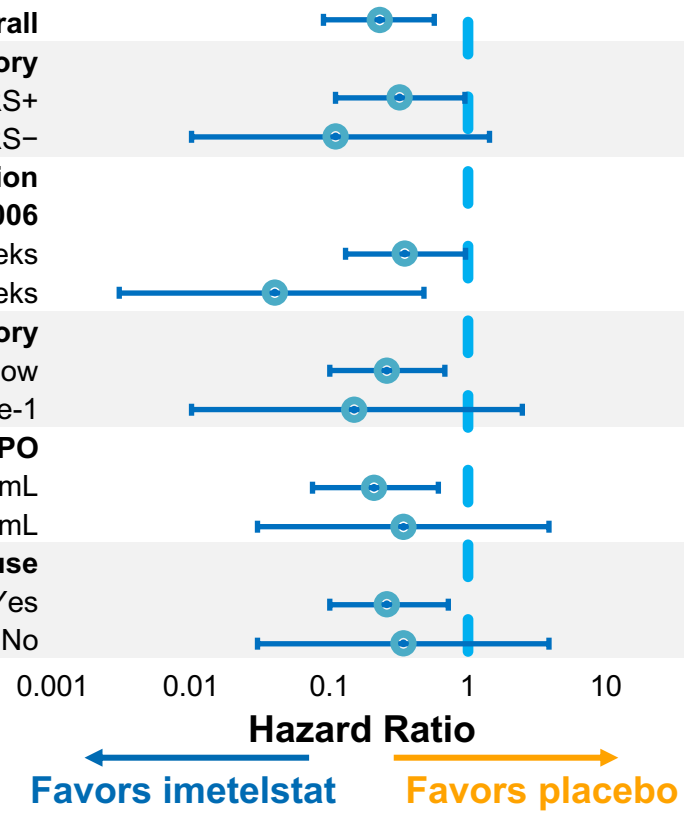

| Patients, N | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imetelstat | 47 | 47 | 37 | 33 | 27 | 26 | 20 | 16 | 13 | 11 | 11 | 8 | 6 | 5 | 3 | 3 | 1 | 1 | 0 |
| Placebo | 9 | 9 | 4 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |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

# Durability of RBC-TI for 8-Week TI Responders Across Key LR-MDS Subgroups




| | Imetelstat median, weeks (95% CI) | Placebo median, weeks (95% CI) | 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) | **<0.001** |
| **WHO category** | | | | |
| RS+ | 46.9 (25.9–83.9) | 16.9 (8.0–24.9) | 0.32 (0.11–0.95) | **0.035** |
| RS− | 51.6 (11.9–NE) | 11.2 (10.1–NE) | 0.11 (0.01–1.43) | **0.062** |
| **Prior RBC transfusion burden per IWG 2006** | | | | |
| 4–6 units/8 weeks | 51.9 (24.9–122.9) | 16.9 (10.1–24.9) | 0.35 (0.13–0.96) | **0.035** |
| >6 units/8 weeks | 39.9 (15.9–NE) | 8.4 (8.0–NE) | 0.04 (0.003–0.48) | **<0.001** |
| **IPSS risk category** | | | | |
| Low | 43.9 (25.0–NE) | 15.1 (8.0–24.9) | 0.26 (0.10–0.68) | **0.004** |
| Intermediate-1 | 51.6 (11.9–NE) | 10.1 (NE–NE) | 0.15 (0.01–2.47) | 0.128 |
| **Baseline sEPO** | | | | |
| ≤500 mU/mL | 51.6 (26.9–83.9) | 13.3 (8.0–24.9) | 0.21 (0.075–0.61) | **0.002** |
| >500 mU/mL | 122.9 (8.14–NE) | 14.6 (12.3–NE) | 0.34 (0.03–3.85) | 0.364 |
| **Prior ESA use** | | | | |
| Yes | 43.9 (26.9–80.0) | 13.3 (8.0–24.9) | 0.26 (0.10–0.72) | **0.006** |
| No | 122.9 (8.14–NE) | 14.6 (12.3–NE) | 0.34 (0.03–3.85) | 0.364 |

**Data cutoff: October 13, 2022.**

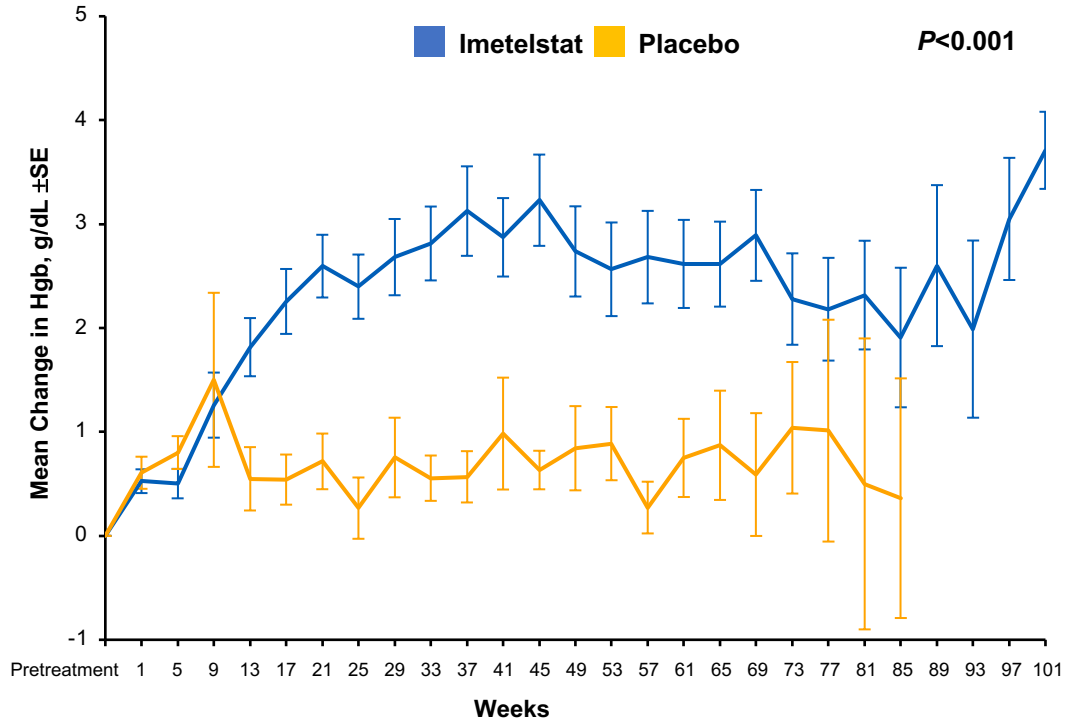
Hazard ratio (95% CI) from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8 weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate. *P*-value (2-sided)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

ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; NE, not estimable; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TI, transfusion independence.

# 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 Hgb Over Time[b]**




**Patients, N**

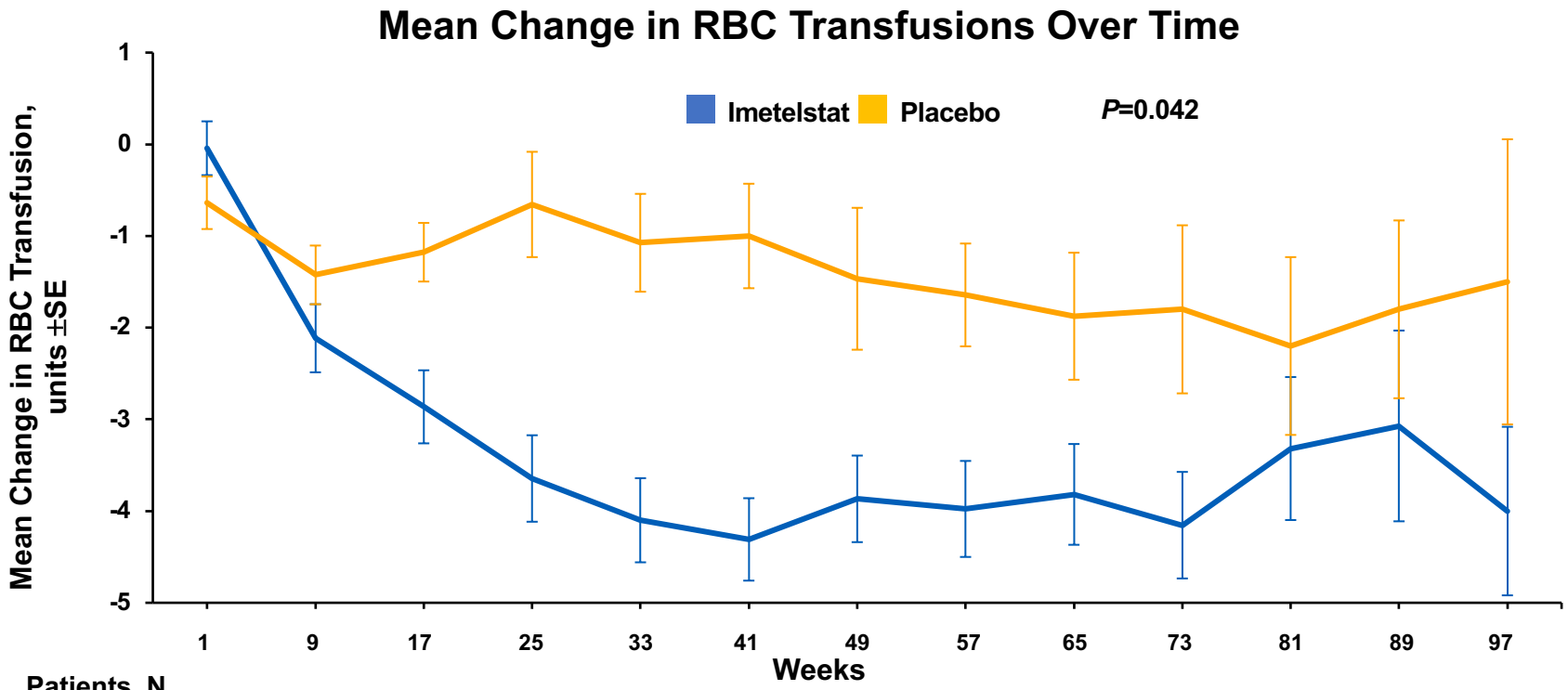
| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imetelstat | 118 | 59 | 53 | 54 | 47 | 42 | 48 | 48 | 43 | 43 | 31 | 37 | 31 | 35 | 32 | 25 | 26 | 24 | 23 | 21 | 19 | 18 | 11 | 11 | 9 | 9 | 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 | | | | |

**Data cutoff: October 13, 2022.**

[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. *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.

# 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 cutoff: October 13, 2022.**

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.

# Improvement in HI-E Rates With Imetelstat vs Placebo

| Hematologic Improvement | Imetelstat (N=118) | Placebo (N=60) | % Difference *P*-value[a] |
|---|---|---|---|
| HI-E (IWG 2018[1]), n (%)<br>95% CI[b] | 50 (42.4)<br>33.3–51.8 | 8 (13.3)<br>5.9–24.6 | 29.0<br><0.001 |
| Patients with LTB, n[c] | 21 | 18 | |
| HI-E response (16-week RBC-TI), n (%)<br>95% CI[b] | 7 (33.3)<br>14.6–57.0 | 4 (22.2)<br>6.4–47.6 | 11.1<br>0.562 |
| Patients with HTB, n[c] | 97 | 42 | |
| Major HI-E response (16-week RBC-TI), n (%)<br>95% CI[b] | 30 (30.9)<br>21.9–41.1 | 0<br>(0.0–8.4) | 30.9<br><0.001 |
| Minor HI-E response (50% RBC units reduction in 16 weeks), n (%)<br>95% CI[b] | 43 (44.3)<br>34.2–54.8 | 4 (9.5)<br>2.7–22.6 | 34.8<br><0.001 |

**Data cutoff: October 13, 2022.**

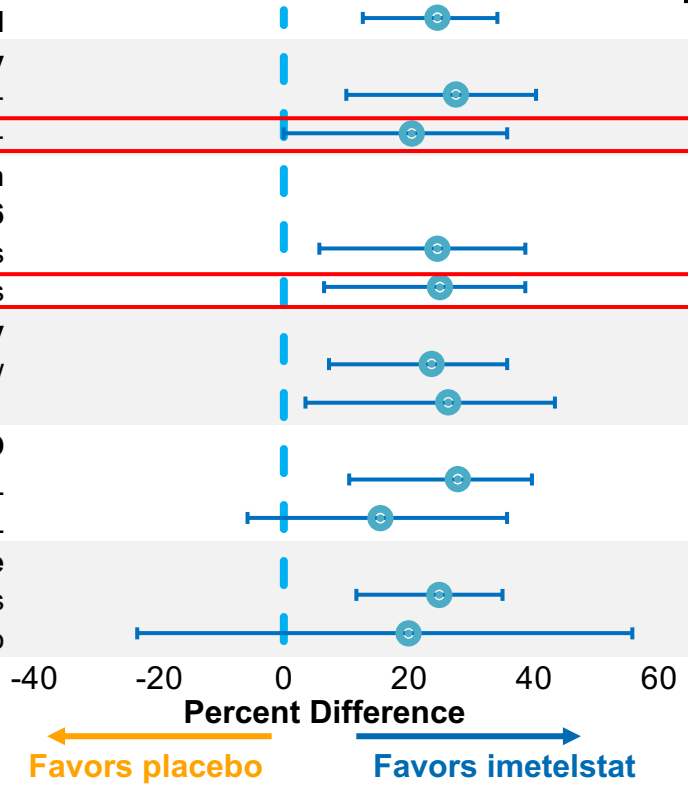
[a]*P*-value based on Cochran-Mantel-Haenszel controlling for prior RBC transfusion burden (≤ 6 vs > 6 units RBC) and IPSS risk group (low vs intermediate-1) applied to randomization. [b]Exact Clopper-Pearson confidence interval. [c]Per revised IWG 2018, patient with LTB is a patient who received 3 to 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.

# Comparable 24-Week RBC-TI Rate Across Key LR-MDS Subgroups

| | 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) | **<0.001** |
| **WHO category** | | | | |
| RS+ | 24/73 (32.9) | 2/37 (5.4) | 27.5 (10.00–40.37) | **0.003** |
| RS− | 9/44 (20.5) | 0/23 (0.0) | 20.5 (−0.03–35.75) | **0.019** |
| **Prior RBC transfusion burden per IWG 2006** | | | | |
| 4–6 units/8 weeks | 19/62 (30.6) | 2/33 (6.1) | 24.6 (5.68–38.66) | **0.006** |
| >6 units/8 weeks | 14/56 (25.0) | 0/27 (0) | 25.0 (6.44–38.65) | **0.012** |
| **IPSS risk category** | | | | |
| Low | 23/80 (28.8) | 2/39 (5.1) | 23.6 (7.23–35.75) | **0.003** |
| Intermediate-1 | 10/38 (26.3) | 0/21 (0) | 26.3 (3.46–43.39) | **0.009** |
| **Baseline sEPO** | | | | |
| ≤500 mU/mL | 29/87 (33.3) | 2/36 (5.6) | 27.8 (10.46–39.71) | **0.002** |
| >500 mU/mL | 4/26 (15.4) | 0/22 (0) | 15.4 (−5.81–35.73) | **0.050** |
| **Prior ESA use** | | | | |
| Yes | 31/108 (28.7) | 2/52 (3.8) | 24.9 (11.61–35.00) | **<0.001** |
| No | 2/10 (20) | 0/8 | 20.0 (-23.47–55.78) | 0.225 |



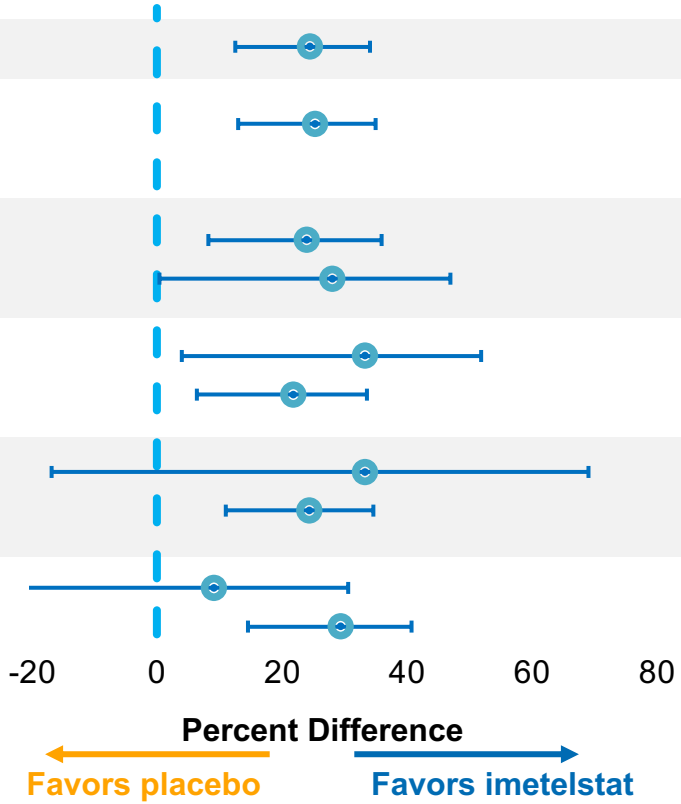

- Similar trends were observed across subgroups for 8-week RBC-TI rates

**Data cutoff: October 13, 2022.**

95% CI based on Wilson Score method. *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.

ESA, erythropoiesis-stimulating agent; 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.

# Comparable 24-Week RBC-TI Rate Regardless of Baseline Mutation Status



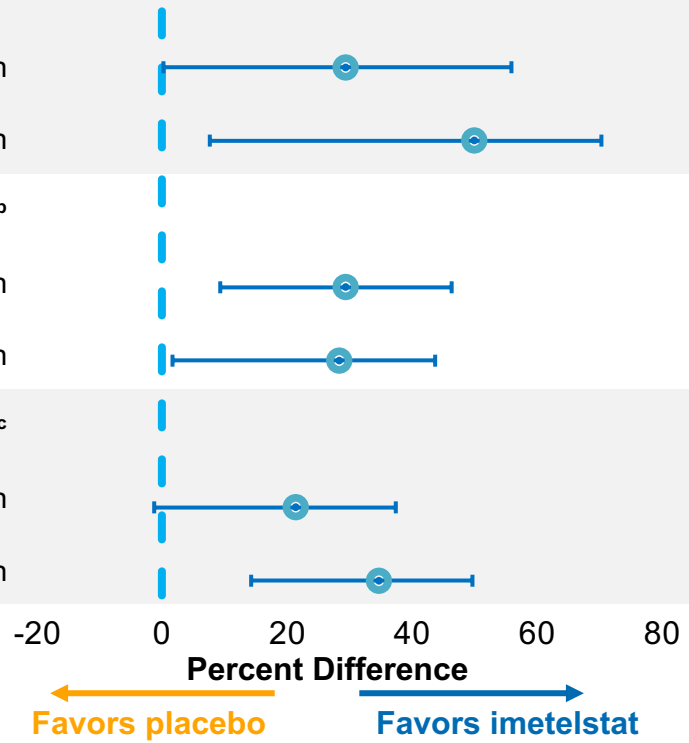

| | | Imetelstat n/N (%) | Placebo n/N (%) | % Difference (95% CI) | *P*-value |
|---|---|---|---|---|---|
| **Overall** | | 29/110 (26.4) | 1/55 (1.8) | 24.5 (12.55–34.11) | **<0.001** |
| **Mutation status** | Yes | 29/107 (27.1) | 1/54 (1.9) | 25.3 (13.01–35.01) | **<0.001** |
| | No | 0/3 | 0/1 | NE (NE–NE) | **NE** |
| **>1 mutation** | Yes | 20/75 (26.7) | 1/38 (2.6) | 24.0 (8.24–35.97) | **0.003** |
| | No | 9/32 (28.1) | 0/16 | 28.1 (0.41–46.98) | **0.019** |
| **>2 mutations** | Yes | 11/33 (33.3) | 0/15 | 33.3 (3.99–51.90) | **0.014** |
| | No | 18/74 (24.3) | 1/39 (2.6) | 21.8 (6.40–33.62) | **0.005** |
| **>3 mutations** | Yes | 3/9 (33.3) | 0/7 | 33.3 (-16.85–69.08) | **0.117** |
| | No | 26/98 (26.5) | 1/47 (2.1) | 24.4 (11.03–34.65) | **<0.001** |
| **Poor prognosis** | Yes | 2/22 (9.1) | 0/11 | 9.1 (-23.92–30.62) | **0.199** |
| | No | 27/85 (31.8) | 1/43 (2.3) | 29.4 (14.58–40.76) | **<0.001** |

- Similar trends were observed for 8-week RBC-TI rates

**Data cutoff: October 13, 2022.**
95% CI based on Wilson Score method. *P*-value determined by the Cochran-Mantel-Haenszel test. Mutation Biomarker Analysis Set included all the patients who received ≥1 dose of study drug and had baseline mutation data available.
NE, not estimable; RBC, red blood cell; TI, transfusion independence.

# Comparable 24-Week RBC-TI Rate Regardless of Baseline TA, TL or hTERT Level

| | Imetelstat n/N (%) | Placebo n/N (%) | % Difference (95% CI) | *P*-value |
|---|---|---|---|---|
| **Baseline TA[a]** | | | | |
| ≤Median | 5/17 (29.4) | 0/17 | 29.4 (0.25–55.95) | **0.074** |
| >Median | 12/24 (50.0) | 0/9 | 50.0 (7.67–70.35) | **0.018** |
| **Baseline TL[b]** | | | | |
| ≤Median | 13/40 (32.5) | 1/32 (3.1) | 29.4 (9.34–46.38) | **0.001** |
| >Median | 18/53 (34.0) | 1/18 (5.6) | 28.4 (1.70–43.74) | **0.025** |
| **Baseline hTERT[c]** | | | | |
| ≤Median | 15/51 (29.4) | 2/25 (8.0) | 21.4 (-1.23–37.44) | **0.042** |
| >Median | 17/49 (34.7) | 0/26 | 34.7 (14.29–49.71) | **<0.001** |




**Data cutoff: October 13, 2022.**

**Note:** 95% CI based on Wilson Score method. *P*-value determined by the Cochran-Mantel-Haenszel test. Mutation Biomarker Analysis Set included all the patients who received ≥1 dose of study drug and had baseline mutation data available. [a]Assessed by by Q-TRAP. [b]Assessed by HT Q FISH. [c]Assessed by RT-PCR.

TA, telomerase activity; TL, telomerase length; hTERT, human telomerase reverse transcriptase; HT Q FISH, high throughput quantitative fluorescence in situ hybridization; Q-TRAP, quantitative telomeric repeat amplification protocol; RT-PCR, reverse transcription-polymerase chain reaction.

# 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
- 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

| 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 |

**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.

# 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
- **Clinical consequences of grade 3–4 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 |

Data cutoff: October 13, 2022.

# Imetelstat AEs Were Manageable With Dose Modifications

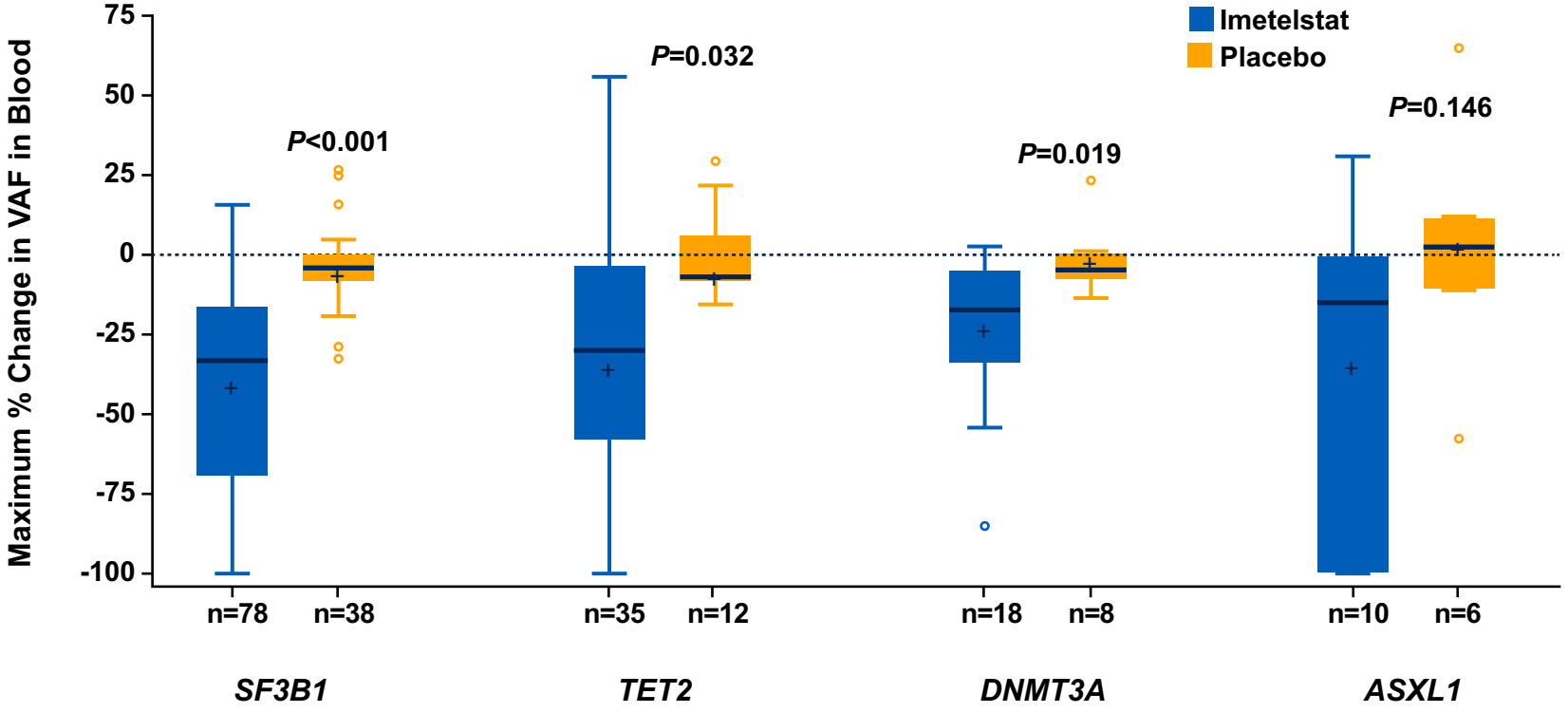
- Most AEs leading to dose modifications were grade 3–4 neutropenia and thrombocytopenia
- Although 74% of patients treated with imetelstat had dose modifications due to AEs, <15% of patients discontinued treatment due to TEAEs
- Discontinuation of imetelstat due to a TEAE generally occurred late in 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.

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

- Mutations on 36 genes associated with MDS was 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



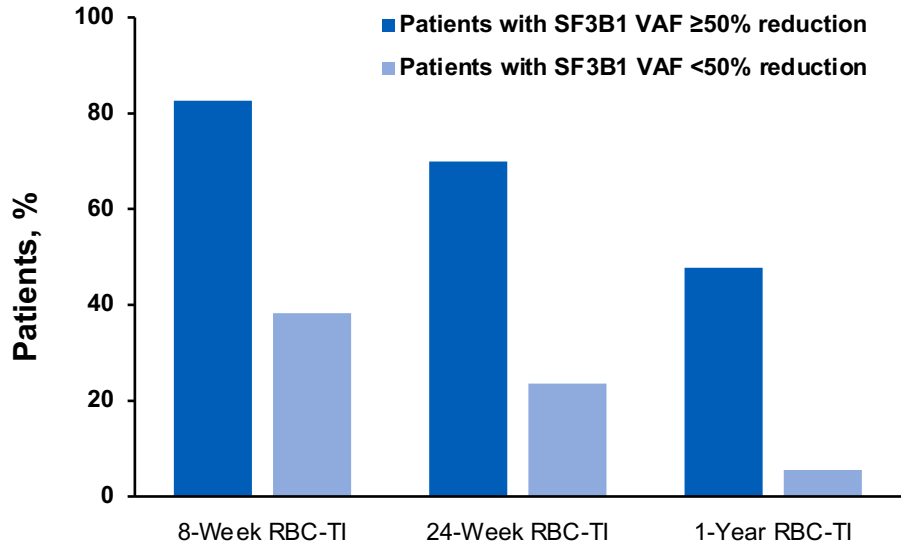

**Data cutoff: October 13, 2022.**

**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 2-sample *t*-test. Analyses included patients in the ITT 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; ITT, intent-to-treat; MDS, myelodysplastic syndromes; NGS, next-generation sequencing; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.

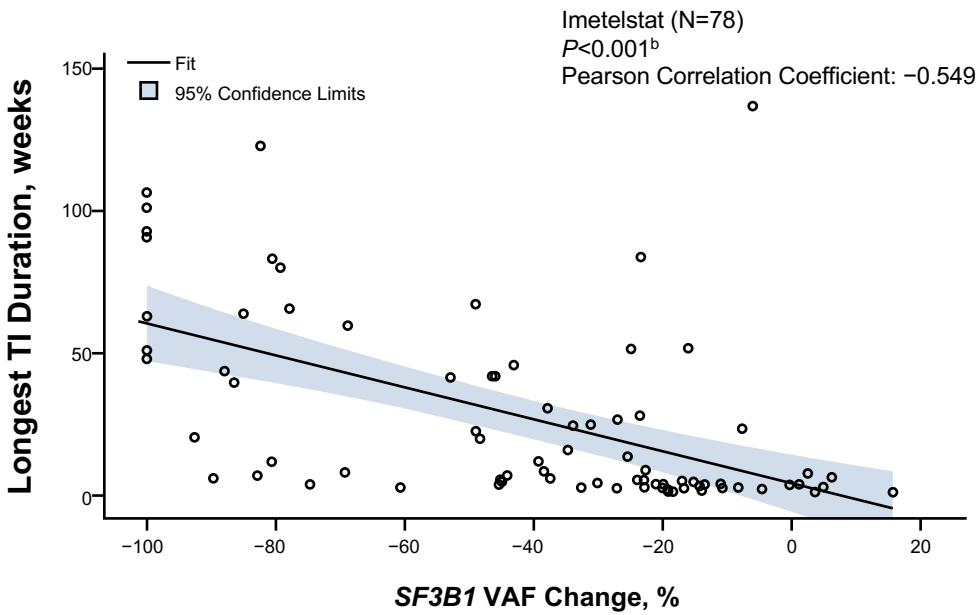
# In the Imetelstat Group *SF3B1* VAF ≥50% Reductions Associated With Durable RBC-TI Rates and Longer RBC-TI Duration

### RBC-TI Rate by *SF3B1* VAF Reduction




| Patients With RBC-TI, n/N (%) | | | |
|---|---|---|---|
| In patients with ≥50% VAF reduction | 19/23 (82.6) | 16/23 (69.6) | 11/23 (47.8) |
| In patients with <50% VAF reduction | 21/55 (38.2) | 13/55 (23.6) | 3/55 (5.5) |
| ***P*-value[a]** | <0.001 | <0.001 | <0.001 |

### Longest RBC-TI Duration vs Maximum Reduction in *SF3B1* VAF




- With imetelstat, a greater reduction in *SF3B1* VAF correlated with longer RBC-TI duration, validating the result from the phase 2 study

**Data cutoff: October 13, 2022.**

[a]*P*-value based on Fisher's exact test. Analyses included patients in the imetelstat ITT population with detectable mutant allele for the indicated gene (≥5%) pretreatment and any postbaseline mutation assessment. [b]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 *SF3B1* VAF as independent variable.

ITT, intent-to-treat; RBC, red blood cell; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

# Higher Cytogenetic Response Rate Per IWG 2006 Criteria With Imetelstat vs Placebo

| 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]**<br>**95% CI[e]** | 9 (35)<br>17-56 | 2 (15)<br>2-45 |
| % Difference (95% CI)[f]<br>*P*-value[g] | 19 (-16 to 44)<br>0.216 | |

- Complete or partial cytogenetic responses were observed in 9 patients (35%) in the imetelstat group and 2 patients (15%) in the placebo group
- Among cytogenetic responders, 6/9 patients (67%) in the imetelstat group also achieved 24-week RBC-TI, none in the placebo group

**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 were 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 confidence interval. [f]Wilson score confidence interval. [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.

# Conclusions

Imetelstat demonstrated highly statistically significant and clinically meaningful efficacy compared with placebo in this heavily transfusion dependent LR-MDS population in need of novel therapy

- Robust RBC-TI rates: 40% with 8-week RBC-TI[a], 28% with 24-week RBC-TI[a], and 18% with 1-year RBC-TI[b]
- Median RBC-TI duration approached 1 year for 8-week RBC-TI responders
- Increased Hgb and HI-E per IWG 2018
- Rate of 24-week RBC-TI was higher with imetelstat vs placebo across subgroups: RS status, RBC transfusion burden, IPSS risk category, or sEPO status
  - The higher rate of 24-week responses was observed regardless of number of mutations, telomerase activity, telomere length, and hTERT expression at baseline
- Safety results were consistent with prior imetelstat clinical experience, with no new safety signals
- Clinical consequences from grade 3–4 cytopenias were similar in patients treated with imetelstat and placebo
- Reduction in VAF of commonly-mutated genes, association of reduced VAF and durable RBC-TI, and correlation of *SF3B1* VAF reduction and RBC-TI duration support the disease-modifying potential of imetelstat
- Cytogenetic response was associated with durable RBC-TI
- Durability of response reported with imetelstat treatment was not previously observed with other treatments in LR-MDS

**[a]Data cutoff: October 13, 2022. [b]Data cutoff: January 13, 2023.**
Hgb, hemoglobin; HI-E, hematologic improvement-erythroid; hTERT, human telomerase reverse transcriptase; IPSS, International Prognostic Scoring System; IRC, independent review committee; LR-MDS, lower risk myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblasts; sEPO, serum erythropoietin; TI, transfusion independence; VAF, variant allele frequency.

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