Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence Across Different Risk Subgroups in Patients With Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis-Stimulating Agents in IMerge Phase 3 Study

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Background

• Patients with RBC-TD LR-MDS R/R to or ineligible for ESAs remain in need of safe and effective treatments
• Imetelstat is a first-in-class, potent, and competitive inhibitor of telomerase activity that selectively induces apoptosis of malignant hematopoietic progenitor cells while sparing the normal counterparts, thus enabling recovery of bone marrow function and erythropoiesis\(^1,2\)
• IMerge (NCT02598661) is a multinational phase 2/3 study comparing imetelstat with placebo in patients with LR-MDS that were heavily RBC-TD, ESA relapsed/refractory or ineligible, non-del(5q), and naive to lenalidomide and HMA
• In phase 3 of IMerge, rates of RBC-TI for ≥8 weeks, ≥24 weeks, and ≥1 year were significantly higher with imetelstat than placebo\(^3\)
• The most common treatment-emergent AEs were neutropenia and thrombocytopenia. AEs were generally of short duration and were reversible. Rates of grade ≥3 bleeding and infection with imetelstat were similar to placebo\(^3\)
• Here, we report the clinical efficacy of imetelstat across different IPSS, IPSS-R, IPSS-M, and IPSS-R cytogenetic risk categories

AE, adverse event; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IPSS-M, IPSS-molecular; IPSS-R, revised IPSS; LR-MDS, lower-risk MDS; MDS, myelodysplastic syndrome; RBC, red blood cell; R/R, relapsed/refractory; TD, transfusion-dependent; TI, transfusion independence.

**IMerge Phase 3 Trial Design**

**Patient population (ITT; N = 178)**
- IPSS low-risk or intermediate-1-risk MDS
- R/R to ESA or EPO >500 mU/mL (ESA ineligible)
- Transfusion-dependent: ≥4 U RBCs/8 wk over 16 wk before study
- Non-del(5q)
- No prior treatment with lenalidomide or HMA

**Phases 3**
- Double-blind, randomized
- 118 clinical sites in 17 countries

**Imetelstat**
- 7.5 mg/kg IV every 4 wk (n = 118)

**Placebo**
- (n = 60)

**Primary end point**
- 8-wk RBC-TI

**Key secondary end points**
- 24-wk RBC-TI
- Duration of TI
- HI-E
- Safety

**Key exploratory end points**
- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

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

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

**Safety population (treated; N = 177)**
- Imetelstat (n = 118)
- Placebo (n = 59)

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*Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, darbepoetin alfa 150 µg, or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 wk or transfusion dependence or reduction in Hb by ≥1.5 g/dL after HI-E from ≥8 weeks of ESA treatment. 1Percentage of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); percentage of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement–erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; PRO, patient-reported outcome; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; TI, transfusion independence; VAF, variant allele frequency.

Overall Population: Higher Rates of Longer-Term Duration of RBC-TI With Imetelstat vs Placebo\textsuperscript{1,2}

The \( P \) value was determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (\( \geq 4 \) to \( \leq 6 \) vs \( > 6 \) RBC U/8 wk during a 16-week period before randomization) and baseline IPSS (low-risk vs intermediate-1-risk) applied to randomization.

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

\textsuperscript{1} Zeidan A, et al. ASCO 2023. Abstr 7004.


American Society of Hematology
## Risk Classification at Baseline

<table>
<thead>
<tr>
<th>Risk group, n (%)</th>
<th>Imetelstat</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPSS</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>80 (67.8)</td>
<td>39 (65.0)</td>
<td>119 (66.9)</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>38 (32.2)</td>
<td>21 (35.0)</td>
<td>59 (33.1)</td>
</tr>
<tr>
<td><strong>IPSS-R</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>3 (2.5)</td>
<td>2 (3.3)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Low</td>
<td>87 (73.7)</td>
<td>46 (76.7)</td>
<td>133 (74.7)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>20 (16.9)</td>
<td>8 (13.3)</td>
<td>28 (15.7)</td>
</tr>
<tr>
<td>High</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>IPSS-M</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>4 (3.9)</td>
<td>0</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Low</td>
<td>65 (63.1)</td>
<td>33 (63.5)</td>
<td>98 (63.2)</td>
</tr>
<tr>
<td>Moderate low</td>
<td>22 (21.4)</td>
<td>10 (19.2)</td>
<td>32 (20.6)</td>
</tr>
<tr>
<td>Moderate high</td>
<td>7 (6.8)</td>
<td>6 (11.5)</td>
<td>13 (8.4)</td>
</tr>
<tr>
<td>High</td>
<td>4 (3.9)</td>
<td>3 (5.8)</td>
<td>7 (4.5)</td>
</tr>
<tr>
<td>Very high</td>
<td>1 (1.0)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Data cutoff date: October 13, 2022. <sup>a</sup>Based on the ITT population: 118 imetelstat; 60 placebo. <sup>b</sup>Data were missing for a total of 11 patients (7 imetelstat; 4 placebo). <sup>c</sup>For IPSS-M, the 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: 103 imetelstat; 52 placebo. Molecular data for MLL-PTD, BCOXL1, GNB1, PPM1D, and SETBP1 were not assessed in the study.  
BCOXL1, BCL6 corepressor-like 1; GNB1, G protein subunit beta 1; IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS; ITT, intent-to-treat; MLL-PTD, mixed lineage leukemia partial tandem duplication; PPM1D, protein phosphatase, Mg2+/Mn2+ dependent 1D; SETBP1, SET-binding protein 1.
Patient Reclassification Between Risk Groups

- Approximately 11% of patients classified as low risk by IPSS were reclassified as intermediate risk by IPSS-R.
- Approximately 28% of patients classified as intermediate-1 risk by IPSS were reclassified as intermediate risk by IPSS-R.

**IPSS**
- Low (n = 110): 98 (89.1%)
- Intermediate-1 (n = 57): 40 (70.2%)

**IPSS-R**
- Very low/low (n = 138): 12 (10.9%)
- Intermediate (n = 28): 16 (28.1%)
- High (n = 1)

IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS.
Patient Reclassification Between Risk Groups (cont.)

- Approximately 14% of patients classified as low or intermediate-1 risk by IPSS and 13% of those classified as very low/low or intermediate risk by IPSS-R were reclassified as higher-risk disease (moderate high/high/very high risk) by IPSS-M.

IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS.
RBC-TI by IPSS Subgroup

- Imetelstat treatment resulted in significantly higher 8- and 24-week RBC-TI response rates than did placebo, regardless of IPSS risk group

Data cutoff date: October 13, 2022. *For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period

Hb, hemoglobin; IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.
RBC-TI by IPSS-R Subgroup

- Imetelstat treatment had higher RBC-TI response rates than did placebo, regardless of IPSS-R risk group.
- Among imetelstat-treated patients reclassified as intermediate risk by IPSS-R, response rates were similar to those reclassified as low risk; no response was noted in placebo-treated patients reclassified as intermediate risk.
- For the very low and high IPSS-R categories, the number of patients was too low (≤3 patients) in both groups to assess differences in RBC-TI response.

Data cutoff date: October 13, 2022. *For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period.

Hb, hemoglobin; IPSS-R, revised International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.
Imetelstat treatment resulted in significantly higher 8- and 24-week RBC-TI rates than did placebo, regardless of IPSS-R cytogenetic risk group.

Data cutoff date: October 13, 2022. *For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period.

Hb, hemoglobin; IPSS-R, revised International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.
RBC-TI by IPSS-M Subgroup

- Imetelstat treatment had higher RBC-TI response rates than did placebo, regardless of IPSS-M risk group.
- 4 out of 12 patients (33%) reclassified as having higher risk MDS by IPSS-M had ≥8-week RBC-TI with imetelstat.

Data cutoff date: October 13, 2022.
Hb, hemoglobin; IPSS-M, molecular International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.
Risk Classifications and TI Responses: 8-week RBC-TI Responders

- RBC-TI response with imetelstat treatment was achieved in patients across all risk subgroups defined per IPSS, IPSS-R, IPSS-M, and IPSS-R cytogenetic.
- Among the 47 patients who achieved the primary end point of 8-week RBC-TI with imetelstat, 15 responders (32%) who had intermediate/higher risk, across all the classification systems used, also achieved long-term TI responses of ≥24 weeks and ≥1 year.
- None of the two ≥8-week TI responders with intermediate/higher risk in the placebo group achieved durable TI responses of ≥24 weeks and ≥1 year.

IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; RBC, red blood cell; TI, transfusion independence.
Conclusions

- In the IMerge clinical trial, 16% of patients were intermediate risk by IPSS-R.
- IPSS to IPSS-M reclassification upstaged a total of 21 patients (10 with low and 11 with intermediate-1) to moderate high, high, or very high risk.
- The results of this subgroup analysis of IMerge showed that imetelstat consistently had higher RBC-TI response rates than did placebo across different risk subgroups defined per IPSS, IPSS-R, IPSS-M, and IPSS-R cytogenetic.
- Overall, durable RBC-TI responses of ≥24-week and ≥1-year were observed with imetelstat in all lower- and higher-risk subgroups.
- Reclassifying patients by IPSS-M revealed that one-third of the patients identified as higher-risk IPSS-M derived RBC-TI benefit from imetelstat for ≥8 weeks.
- In contrast, higher-risk subgroups receiving placebo failed to achieve long-term RBC-TI, regardless of the risk classification scheme used.
- In summary, in heavily transfused patients with LR-MDS R/R to ESAs or ineligible for ESAs, the clinical efficacy of imetelstat was maintained irrespective of risk category.
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