Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agent Who Are Lenalidomide and HMA Naive

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Background: Myelodysplastic Syndromes (MDS) and Imetelstat

- Patients with TD LR-MDS that has relapsed or is refractory to ESA therapy have limited treatment options.

- Higher telomerase activity, expression of hTERT and shorter telomeres predict for shorter overall survival in lower risk MDS.

- Imetelstat is a first-in-class telomerase inhibitor that targets cells with short telomere lengths and active telomerase and has clinical activity in myeloid malignancies:
  - FDA granted Fast-Track designation for LR-MDS (Oct 2017)

- IMerge is an ongoing global phase 2/3 study of imetelstat in RBC TD patients with LR-MDS (IPSS Low or Int-1)

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ESA, erythropoiesis-stimulating agent; hTERT, human telomerase reverse transcriptase; IPSS, International Prognostic Scoring System; Int-1, Intermediate-1; LR, lower risk; RBC, red blood cell; TD, transfusion dependent.

Background: IMerge/NCT02598661 (Part 1) Study Design

Patients with MDS

• IPSS Low or Int-1
• Relapsed / refractory to ESA or ineligible for ESA
• Transfusion dependent (≥ 4u RBC/8 weeks)
• ANC ≥ 1.5 x 10⁹/L
• Platelets ≥ 75 x 10⁹/L

1° Endpoint: 8-Week RBC TI
2° Endpoints: 24-Week RBC TI / Time to TI / TI duration / TR (HI-E: Transfusion Reduction by ≥ 4 RBC units over 8 weeks) / MDS response per IWG / Overall survival / Incidence of AML / Safety

Exploratory: telomerase activity / hTERT / telomere length / genetic mutations

Imetelstat Treatment

7.5 mg/kg IV q4w (2-hr infusion)

Pre-medication: diphenhydramine, hydrocortisone 100-200 mg (or equivalent)

Supportive care: RBC transfusions, myeloid growth factors per local guidelines

AML, acute myeloid leukemia; ANC, absolute neutrophil count; HI-E, hematologic improvement-erythroid; IWG, International Working Group; TI, transfusion independence; TR, transfusion reduction.

Background: Key Efficacy and Safety Outcomes from IMerge (Part 1) 

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Most grade ≥ 3 cytopenias were reversible in < 4 weeks

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All Treated (N=32)</th>
<th>Lenalidomide and HMA naïve and Non-del (5q) (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of 8-week TI, n (%)</td>
<td>11 (34)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Rate of 24-week TI, n (%)</td>
<td>5 (16)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Rate of transfusion reduction (HI-E), n (%)</td>
<td>19 (59)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Most common adverse events, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23 (72)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Grade 3 / 4</td>
<td>8 (25) / 13 (41)</td>
<td>2 (15) / 5 (38)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (56)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Grade 3 / 4</td>
<td>10 (31) / 8 (25)</td>
<td>5 (38) / 3 (23)</td>
</tr>
</tbody>
</table>

HI-E, hematologic improvement-erythroid; HMA, hypomethylating agents; TI, transfusion independence.

An additional 25 lenalidomide and HMA naïve patients without del(5q) were enrolled.

Here we report updated results for 38 patients.

Clinical Cutoff: 26-Oct-2018

Median number of treatment cycles: 8.0 (range: 1–34) cycles
- Mean dose intensity was 6.9 mg/kg/cycle

<table>
<thead>
<tr>
<th>Patients Description</th>
<th>Median Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial 13 lenalidomide and HMA naïve patients without del(5q)</td>
<td>29.1 mo</td>
</tr>
<tr>
<td>25 patients meeting the same criteria</td>
<td>8.7 mo</td>
</tr>
</tbody>
</table>
# IMerge: Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N=38</th>
</tr>
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<tbody>
<tr>
<td>Median age (range), years</td>
<td>71.5 (46-83)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>25 (66)</td>
</tr>
<tr>
<td>ECOG PS 0-1, n (%)</td>
<td>34 (89)</td>
</tr>
<tr>
<td>IPSS risk, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>24 (63)</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>14 (37)</td>
</tr>
<tr>
<td>Baseline median (range) RBC transfusion burden, units/8 weeks</td>
<td>8 (4–14)</td>
</tr>
<tr>
<td>WHO 2001 category, n (%)</td>
<td></td>
</tr>
<tr>
<td>RARS or RCMD-RS</td>
<td>27 (71)</td>
</tr>
<tr>
<td>All others</td>
<td>11 (29)</td>
</tr>
<tr>
<td>Prior ESA use, n (%)</td>
<td>34 (89)</td>
</tr>
<tr>
<td>sEPO &gt; 500 mU/mL, n (%)</td>
<td>12(^a) (32)</td>
</tr>
</tbody>
</table>

\(^a\)Of the 37 patients with sEPO levels reported.
IMerge: Longest Transfusion-Free Interval

Among the patients achieving durable TI, all showed a Hb rise of ≥ 3.0 g/dL compared to baseline during the transfusion-free interval.

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<td>Rate of 8-week TI, n (%)</td>
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<td>Rate of 24-week TI, n (%)</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Median time to onset of TI (range), weeks</td>
<td>8.1 (0.1-33.1)</td>
</tr>
<tr>
<td>Median duration of TI (range), weeks</td>
<td>NE (17.0-NE)</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; HI-E, hematologic improvement-erythroid; TI, transfusion independence; TR, transfusion reduction.
IMerge: Hemoglobin and Imetelstat Dosing Among Patients with Durable TI

Hemoglobin Levels (g/L)

Prior RBC Transfusion Burden (units/8 weeks)

- 6
- 11
- 4

Hgb (g/L)

- 6

- 11

- 4

Dose

- 4.7 mg/kg
- 6.0 mg/kg
- 7.5 mg/kg

Transfusions

Start Date of Latest Cycle
Parameters | N=38
---|---
Rate of transfusion reduction (HI-E), n (%) | 27 (71)
Mean relative reduction of RBC transfusion burden from baseline, % | -68

HI-E, hematologic improvement-erythroid; RBC, red blood cell; TI, transfusion independence; TR, transfusion reduction.
# IMerge: Key Efficacy Outcomes

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<tr>
<td>Rate of transfusion reduction (HI-E), n (%)</td>
<td>27 (71)</td>
</tr>
<tr>
<td>Mean relative reduction of RBC transfusion burden from baseline, %</td>
<td>-68</td>
</tr>
<tr>
<td>CR + marrow CR + PR (per IWG), n (%)</td>
<td>8 (21)</td>
</tr>
</tbody>
</table>

CR, complete remission; HI-E, hematologic improvement-erythroid; IWG, International Working Group; NE, not estimable; PR, partial remission; RBC, red blood cell; TI, transfusion independence.
IMerge: Efficacy Results in EPO and RS Subgroups

Similar efficacy was observed across these subgroups

EPO, erythropoietin; RARS, refractory anemia with ringed sideroblasts; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RS, ring sideroblast; TI, transfusion independence.

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19 patients (50%) had dose reductions and 26 patients (68%) had cycle delays.

Reversible grade 3 LFT elevations were observed in 3 (8%) patients on study. Independent Hepatic Review Committee considered these not drug-related.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; TEAE, treatment-emergent adverse event.
# IMerge: Occurrence/Reversibility of Grade 3/4 Cytopenias

<table>
<thead>
<tr>
<th></th>
<th>All events, n (%) of patients (N=38)</th>
<th>Recovered in &lt; 4 weeks, n (%) of patients with an event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutrophils, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>10 (26)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>12 (32)</td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Platelets, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>14 (37)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>10 (26)</td>
<td>9 (90)</td>
</tr>
</tbody>
</table>

- 2 patients had febrile neutropenia
- 12 patients received G-CSF for neutropenia
- 7 patients received platelet transfusions
- 3 patients with Grade 1 bleeding events
6 patients had SF3B1 mutations at baseline, with reduction of variant frequency observed in patients 200088 and 200095, both of whom had durable TI

Patient 200088 also had reduction in DNMT3A mutation, and substantial reduction in bone marrow ringed sideroblasts (75% to 3%)
Conclusions: Overall Efficacy and Safety

- In this cohort of 38 non-del(5q) LR-MDS patients with a high RBC transfusion burden who were ESA relapsed/refractory and naïve to lenalidomide/HMA, single-agent imetelstat yielded:
  - 8-week TI rate of 37%
  - 24-week TI rate of 26%
  - 24-week TI responses were accompanied by Hb rise of ≥ 3.0 g/dL
  - Median duration of TI was not reached
  - HI-E rate of 71%

- Side effects were limited, mainly cytopenias that were predictable, manageable and reversible
Conclusions: Overall Efficacy and Safety (con’t)

- Similar efficacy was seen in EPO high/low and RS+/RS- subgroups, supporting broad clinical activity

- Reductions in mutation burden and RS noted among responding patients, suggesting potential disease modification

- These results support the planned Phase 3 study, expected to start mid-2019
The authors thank all the patients for their participation in this study and acknowledge the collaboration and commitment of all investigators and their staff.

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