Clinical Benefit Among Lenalidomide (LEN)-Treated Patients With RBC Transfusion-Dependent (RBC-TD) Low/Int-1 Risk Myelodysplastic Syndromes (MDS) Without del(5q)

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INTRODUCTION

• In the phase 3, placebo-controlled MDS-005 study, the efficacy and safety of lenalidomide (LEN) was evaluated in red blood cell transfusion-dependent (RBC-TD) patients with lower-risk non-del(5q) MDS ineligible for or refractory to erythropoiesis-stimulating agents (ESAs)1

• The most common adverse events (AEs) were hematologic, consistent with the known AE profile of LEN in MDS

• Grade 3/4 thrombocytopenia was observed in 19.1% and 12.7% of patients in the LEN and placebo groups, respectively, and grade 3/4 thrombocytopenia in 35.6% and 38.8%, respectively.

• The frequency, timing, and management of treatment-emergent adverse events in the MDS-005 study are described in an e-poster E1171 by Almeida et al.2

• A statistically significant and clinically higher proportion of LEN-treated patients were red blood cell transfusion-independent (RBC-TI) ≥ 8 weeks versus placebo (26.9% versus 2.0%; P < 0.001).

• Other efficacy measures collected included erythroid improvement and cytogenetic response (CyR).

• These measures could be used to assess the overall clinical benefit in addition to RBC transfusion independence so that healthcare providers can inform patients of outcomes associated with LEN.

METHODS

Study Design and Treatment

• Eligible patients had RBC-TD anemia due to International Prognostic Scoring System Low/Intermediate-1 (Int)-1-risk MDS, a non-del(5q) karyotype, and were ineligible for or refractory to ESA or lenalidomide.

• RBC-TD was defined as an average transfusion requirement of ≥ 2 units packed RBCs (pRBCs) per 28 days and no ≥ 8 consecutive weeks without RBC transfusions in the 12 weeks before randomization.

• Patients were randomized 2:1 to oral LEN 10 mg (n = 160) or placebo (n = 79) once daily (Figure 1).

• Patients who were RBC-TI ≥ 8 weeks or had an erythroid response by week 24 continued until disease progression, unacceptable toxicity, or consent withdrawal.

• Treatment continued until erythroid relapse or disease progression.

Study Endpoints

• The primary endpoint of the study was the rate of RBC-TI ≥ 8 weeks.

METHODS (cont.)

• Secondary endpoints included the number of patients who were RBC-TI ≥ 24 weeks, duration of RBC-TI, erythroid response, health-related quality of life, and time to disease progression.

• CyR was assessed in patients with abnormal baseline cytogenetic abnormalities and ≥ 1 follow-up assessment.

• CyR was evaluated by central review using conventional metaphase cytogenetic analysis according to International Working Group (IWG) 2006 criteria.

Assessment of the Composite Endpoint

• Clinical benefit ≥ 8 weeks consisted of any of the following: RBC-TI ≥ 8 consecutive weeks.

• Erythroid response: transfusion reduction ≤ 4 units pRBCs ≤ 8 weeks (IWG 2006 criteria).

• Erythroid response: hemoglobin (Hb) increase > 1.5 g/dL ≤ 8 weeks (IWG 2006 criteria).

• CyR (IWG 2006).

• Timing of assessments is shown in Figure 2.

• To account for in-study differences in transfusion burden, transfusion reduction of ≥ 4 units pRBCs was ≥ 8 weeks was assessed using data collected during a 112-day period.

• CyR was evaluated, independent of the composite endpoint, in patients with baseline cytogenetic abnormalities and ≥ 1 follow-up assessment.

• After treatment discontinuation, patients were followed for ≥ 5 years post-randomization for survival, transformation to acute myeloid leukemia, development of secondary malignancies, and subsequent MDS treatments.

• Transfusion and Hb assessments were performed 28 days post-discontinuation.

Statistical Methods

• Clinical benefit as a composite endpoint.

• Components of the composite endpoint are not mutually exclusive (i.e., a patient may be a responder in one or more component).

• The transfusion endpoint only allows for a patient to be counted once as a binary outcome (i.e., responder or non-responder).

• The cytogenetic endpoint only allows for a patient to be counted once as a binary outcome (i.e., responder or non-responder).

• Statistical significance was determined using a log link function.

• Odds ratio and 95% confidence interval (CI) were obtained by having a log link function.

• Relative risk and 95% CI were obtained by having a log link function.

• As a binary outcome (i.e. responder or non-responder).

RESULTS

Table 1. Clinical Benefit

<table>
<thead>
<tr>
<th>LEN (n = 160)</th>
<th>Placebo (n = 79)</th>
<th>OR (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyR ≥ 8 weeks</td>
<td>43 (26.9%)</td>
<td>2.40 (1.33–4.38)</td>
<td>10.62 (2.64–42.70)</td>
</tr>
<tr>
<td>Hb increase ≥ 1.5 g/dL ≤ 8 weeks</td>
<td>31 (19.4%)</td>
<td>3.35 (1.60–6.99)</td>
<td>10.14 (2.64–39.70)</td>
</tr>
<tr>
<td>CyR (IWG 2006)</td>
<td>14 (8.8%)</td>
<td>0.40 (0.11–1.38)</td>
<td>0.28 (0.07–1.03)</td>
</tr>
</tbody>
</table>

Figure 2. Timing of Clinical Benefit Response Measurements in Patients in the MDS-005 Study

Table 2. Patients Achieving CyR

<table>
<thead>
<tr>
<th>CyR (n = 27)*</th>
<th>Placebo (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major and minor CyR</td>
<td>57 (23.5%)</td>
</tr>
<tr>
<td>Major CyR</td>
<td>57 (23.5%)</td>
</tr>
<tr>
<td>Major CyR, n (%)</td>
<td>57/100</td>
</tr>
<tr>
<td>Major CyR</td>
<td>57/100</td>
</tr>
<tr>
<td>Major CyR, n (%)</td>
<td>57/100</td>
</tr>
</tbody>
</table>

*Patients eligible for CyR: complete karyotype data for 1st collection absent; assessment of the 2nd collection is instead displayed.

Clinical Benefit ≥ 8 Weeks

• Clinical benefit was observed in a higher proportion of LEN-treated patients than those in the placebo group (Table 1).

• Clinical benefit was defined as the patient achieving ≥ 1 response in the clinical benefit composite endpoint criteria.

• Of 51 (31.9%) LEN patients achieving clinical benefit throughout the study, 23 patients had achieved clinical benefit by the end of cycle 1, 35 by the end of cycle 2, and 41 by the end of cycle 3 (Figure 3).

Cytogenetic Response

• CyR was reported in 9 (33.3%) of 27 LEN-evaluable LEN-treated patients with ≥ 1 follow-up assessment (Table 2).

• 5 patients achieved major CyR and 4 patients achieved minor CyR.

• Among patients with major or minor CyR, 5 (55.6%) also achieved RBC-TI ≥ 8 weeks.

• Of the 5 patients achieving major CyR, all had the -16 abnormality (Table 3).

Table 3. Cytogenetic Abnormalities at Baseline in Patients Achieving CyR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline Karyotype</th>
<th>CyR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN 1</td>
<td>t(11;16)</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 2</td>
<td>46,XX,+17</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 3</td>
<td>46,XX,+8</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 4</td>
<td>46,XX,del(1q)</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 5</td>
<td>46,XX,add(7q)</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 6</td>
<td>46,XX,del(3q)</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 7</td>
<td>46,XX,-5</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 8</td>
<td>46,XX,-20</td>
<td>YES</td>
</tr>
<tr>
<td>LEN 9</td>
<td>46,XX,-14</td>
<td>YES</td>
</tr>
</tbody>
</table>

*Patients eligible for CyR: incomplete karyotype data for 1st collection absent; assessment of the 2nd collection is instead displayed.

DISCUSSIONS

• In RBC-TD patients with lower-risk non-del(5q) MDS who were ineligible for or refractory to ESAs, LEN was associated with significantly greater clinical benefit than placebo.

• This was reinforced using a newly defined composite endpoint, clinical benefit ≥ 8 weeks or had an erythroid response, disease progression, unacceptable toxicity, or consent withdrawal.

• Treatment continued until erythroid relapse or disease progression.

CONCLUSIONS

• In RBC-TD patients with lower-risk non-del(5q) MDS who were ineligible for or refractory to ESAs, LEN was associated with significantly greater clinical benefit than placebo.

• This analysis provides evidence that other measures of response in addition to RBC-TI may be valuable in the management of lower-risk non-del(5q) MDS.

• In addition to RBC-TI, clinically relevant measures of LEN in non-del(5q) patients include CyR, decrease in transfusion rate, and increased Hb level.

REFERENCES

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