A Pilot Trial of Lirilumab with or without Azacitidine (AZA) for Patients with Myelodysplastic Syndrome

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Abstract

Objectives
- Primary Objective:
  - To determine the safety of lirilumab, as a single agent or in combination with AZA, in patients with MDS
- Secondary Objectives:
  - Overall survival
  - Event-free survival
  - Response by IWG criteria

Methods/Study Design
- Single Institution Phase I Study Design
- Eligibility:
  - Patients were assigned to 2 cohorts based on their IPSS* risk evaluation
  - Lower Risk MDS cohort (Lower and Intermediate-1)
    - Lirilumab single agent 3mg/kg IV; Q4 weeks
  - Higher Risk MDS cohort (Intermediate-2 and High)
    - AZA 75mg/day for 1-7 days with lirilumab 3mg IV on D7; Q4 weeks

Eligibility
- Previously untreated MDS of any risk or CMML
- ECOG Performance Status 0-2
- Adequate hepatic and renal function
- New York Heart Association heart failure class I-II
- Patients with uncontrolled infection or autoimmune diseases excluded

Response Criteria
- MDS
- Response by IWG criteria

Overall Survival
- From start of treatment to last follow-up or death at any time
- Analysis performed using Kaplan-Meier method according to intention-to-treat principle

Event-Free Survival
- From start of treatment to the date of lack of response, loss of response to transformation to AML, or death

Background
- Natural killer (NK) cells are essential components of the innate immune system and play a critical role in host immunity against various malignancies
- NK cell function is governed by a balance between receptors received from inhibitory receptors, notably the killer immunoglobulin-like receptors (KIRs), and activating receptors

Blockage of KIR receptors with a fully human monoclonal antibody is known to enhance NK-mediated killing of tumor cells
- Lirilumab (PFH1102MSB-00815) is a fully human IgG4 monoclonal antibody that is designed to block the interaction between KIR2DL1/2/3 and HLA-C inhibitory receptors and their ligands
- Blockade of KIRs by lirilumab may improve outcomes in patients with myelodysplastic syndrome

Table 1: Patient Characteristics (n=10)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=10)</th>
<th>Azacitidine (n=8)</th>
<th>Lirilumab (n=2)</th>
<th>Lirilumab (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years, median (range)</td>
<td>70 (50-84)</td>
<td>70 (50-84)</td>
<td>70 (50-84)</td>
<td>70 (50-84)</td>
</tr>
<tr>
<td>N, n (%)</td>
<td>7 (70)</td>
<td>6 (75)</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (50)</td>
<td>4 (50)</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>1</td>
<td>4 (40)</td>
<td>3 (38)</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>2</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PF3 risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1 (100)</td>
<td>1 (12)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory values, median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>9.1 (7.9-10)</td>
<td>9.2 (8-10)</td>
<td>7.9 (7.5-8.6)</td>
<td>7.5 (7.2-8.3)</td>
</tr>
<tr>
<td>ANC</td>
<td>2.6 (1.6-4.3)</td>
<td>2.6 (1.6-4.3)</td>
<td>2 (1.7-5)</td>
<td>2 (1.7-5)</td>
</tr>
<tr>
<td>BOC</td>
<td>4.6 (2.7-7.7)</td>
<td>4.4 (2.7-7.7)</td>
<td>4.3 (2.1-7.8)</td>
<td>4.2 (1.7-6.1)</td>
</tr>
<tr>
<td>Platelehs, 10^3/µL</td>
<td>28 (8-13)</td>
<td>28 (8-13)</td>
<td>14 (9-20)</td>
<td>15 (7-20)</td>
</tr>
<tr>
<td>CR/10%</td>
<td>11 (1 0-18)</td>
<td>11 (1 0-18)</td>
<td>4 (2-8)</td>
<td>4 (2-8)</td>
</tr>
</tbody>
</table>

Table 2: Overall Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (n=10)</th>
<th>Azacitidine (n=8)</th>
<th>Lirilumab (n=2)</th>
<th>Lirilumab (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of treatment cycles, median (range)</td>
<td>4 (2-14)</td>
<td>4 (2-14)</td>
<td>3 (1-14)</td>
<td>3 (1-14)</td>
</tr>
<tr>
<td>Best Overall Response, n (%)</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
<tr>
<td>CR</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
<tr>
<td>mCR</td>
<td>5/5 (100)</td>
<td>5/5 (100)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
<tr>
<td>SD</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
<tr>
<td>NR</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
<tr>
<td>Grade transformation to AML</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
</tbody>
</table>

Table 3: Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0-1 (%)</th>
<th>Grade 2-3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4 (50)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (50)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infections</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Asteroid nodules</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Results
- A total of 10 patients included (Table 1). Higher-risk MDS patients received a median of 4 cycles (range, 2-13 cycles) of treatment with AZA in combination with AZA, and lower-risk patients received a median of 9 cycles (range, 5-14 cycles) of single agent AZA.
- A total of 2 patients (20%) achieved CR (both in combination arm). 5 patients (50%) had marrow CR (n=4, 50% and n=1, 10%) in combination and single arm, respectively and 3 patients had stable disease (n=2, 20% and n=1, 10%) in combination and single arm, respectively (Table 2).
- Drug related AEs were reported in all patients in the higher-risk and in 1 patient in the lower-risk cohort. Five patients (n=4, 50% and n=1, 10%) in combination and single arm, respectively experienced a total of 8 episodes of grade 3 AEs attributable to study drug with the most frequent being infection or neutropenic fever (n=6 out of 6, 75%) (Table 3).
- The median EFS for the entire cohort was 8 months (95% CI, 4 months to not reached), and the median OS has not yet been reached (Figure).

Figure: Overall and Event-Free Survival Curves

Conclusions
- This is the first report of efficacy and safety with the anti-KIR antibody in patients with MDS.
- Lirilumab is effective and well tolerated either as a single agent or in combination with AZA, in patients with MDS.

References