The Oral JAK2/IRAK1 Inhibitor Pacritinib Demonstrates Spleen Volume Reduction in Myelofibrosis Patients Independent of JAK2 V617F Allele Burden

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BACKGROUND

JAK2 Allele Burden in Myelofibrosis

- In patients with primary JAK2-mutated MF, lower JAK2 allele burden is associated with poor prognosis and poor response to treatment.1-3
- Patients with low allele burden (variant allele frequency <50%) have:
  - More anemia and leukopenia
  - Shorter overall survival
  - 5.5-fold lower chance of achieving a spleen volume response (SVR) with ruxolitinib
- Patients with low JAK2 allele burden represent an area of unmet medical need as they are high-risk and underserved by available therapies.

Pacritinib as Therapy for Myelofibrosis

- Pacritinib is an oral JAK2/IRAK1 inhibitor4
- Unlike other JAK2 inhibitors, pacritinib does not inhibit JAK1 in an independent mechanism (e.g., through inhibition of IRAK1).

METHODS

- A retrospective analysis of PERSIST-1 and PERSIST-2 was performed in which outcomes were stratified by JAK2 V617F mutation status and allele burden.
- Baseline JAK2 V617F was quantified by PCR, and variant allele frequencies were binned by quartile.
- The efficacy endpoint was the percentage of patients achieving ≥35% SVR (by MRI or CT scan) at Week 24 based on an intention-to-treat analysis.
- Analysis was based on pooled results across the two studies for patients treated with pacritinib and those treated with BAT.

RESULTS

Table 1: Baseline Characteristics by JAK2 Mutation Status and Allele Burden

<table>
<thead>
<tr>
<th>JAK2 V617F</th>
<th>N=327</th>
<th>Allele burden &lt;50% N=256</th>
<th>Allele burden ≥50% N=200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>66.0 (33-85) years</td>
<td>67.0 (23-87) years</td>
<td>67.0 (27-85) years</td>
</tr>
<tr>
<td>Platelets (median, µL)</td>
<td>97,000 (41-181,000) µL</td>
<td>75,000 (41-180,000) µL</td>
<td>127,000 (55-315,000) µL</td>
</tr>
<tr>
<td>Hemoglobin &lt;10g/dL (%)</td>
<td>61%</td>
<td>53%</td>
<td>35%</td>
</tr>
<tr>
<td>Platelets &lt;50,000/µL (%)</td>
<td>23%</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>Spleen volume (median)</td>
<td>10.0 cm</td>
<td>19.5 cm</td>
<td>15.0 cm</td>
</tr>
<tr>
<td>Primary myelofibrosis (%)</td>
<td>76%</td>
<td>80%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Spleen volume response observed in pacritinib-treated patients regardless of JAK2 allele burden

- Pacritinib was associated with similar SVR response at all levels of allele burden as shown in Figure 1.
- No SVR response was observed for patients treated with BAT (including ruxolitinib) who had low JAK2 allele burden or JAK2 V617F-negative disease.
- Pacritinib was associated with higher rates of SVR response than BAT among patients with low JAK2 allele burden (<50%):
  - Allele burden >0 to 25% response rate for pacritinib vs. BAT = 21% vs. 0% (P<0.001)
  - Allele burden >25 to 50% response rate for pacritinib vs. BAT = 51% vs. 0% (P<0.001)
  - Allele burden >50% response rate for pacritinib vs. BAT = 67% vs. 0% (P<0.001)

Figure 1: Percent Change in Spleen Volume (Week 24) on Pacritinib vs. BAT Stratified by JAK2 Mutation Status and Allele Burden Quartile

CONCLUSIONS

- Pacritinib demonstrated clinical efficacy regardless of JAK2 allele burden or JAK2 mutation status.
- No SVR response was observed for patients treated with best available therapy (including ruxolitinib) who had low JAK2 allele burden or JAK2-negative disease.
- Patients with low JAK2 allele burden and JAK2-negative disease may have non-JAK2 mediated disease. Pacritinib’s efficacy in this population may be mediated by a JAK2-independent mechanism (e.g., through inhibition of IRAK1).

REFERENCES


POSTER INFORMATION

This poster was presented at the 2019 American Society of Hematology Annual Meeting.