Molecular Analysis in the Pacritinib Dose-Finding PAC203 Study in Patients with Myelofibrosis Refractory or Intolerant to Ruxolitinib

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BACKGROUND

Myelofibrosis (MF) After Ruxolitinib Discontinuation

- Survival after ruxolitinib discontinuation is poor, particularly for patients with thrombocytopenia (median <1 year) and for patients who acquired new mutations on ruxolitinib (6 months).

Molecular Risk in Myelofibrosis

- Mutation type and number has prognostic significance in patients with MF. Patients with ≥3 total mutations have shorter survival and a decreased spleen volume response (SVR) with ruxolitinib, and shorter time to treatment discontinuation.2
- Prior cohorts suggest that the frequency of ruxolitinib-treated patients harboring ≥3 non-driver mutations is 8.7%.3

Pacritinib in Myelofibrosis

- Pacritinib is an oral JAK2/IRAK1 inhibitor4 that has demonstrated clinical efficacy in two Phase 3 MF trials (PERSIST-1 and PERSIST-2)4,5 and in PAC203, a dose-finding trial in patients who failed to benefit from or were intolerant of ruxolitinib.6
- These studies included patients with severe thrombocytopenia.
- The mutational landscape of the PAC203 "post-ruxolitinib" patient population has not well characterized.

Study Objectives

- To describe the mutational landscape of MF patients after failure of ruxolitinib therapy, including those with severe thrombocytopenia, and to correlate mutational findings with baseline patient characteristics and clinical outcomes (including ≥35% spleen volume reduction and development of grade 3/4 cytopenias).

METHODS

- Baseline mutational analysis was performed on patients enrolled on PAC203.
- Mutational data was obtained in 110 (of 164 recruited; 161 treated) patients using an ISO accredited Illumina TruSeq Custom Amplicon Panel, including 32-gene mutation hotspots and exons (~36,000 bp, 287 ampiclons): ASXL1, ATRX, DNMT3A, EZH2, TET2, CEBPA, ETV6, NPM1, PHF6, RUNX1, SETBP1, SF3B1, SRSF2, TP53, U2AF1, WT1, ZRSR2, CBL, CBLB, CBLC, CSF3R, FLT3, HRAAS, JAK2, KIT, KRAS, MPL, NRPAS, PDGFRA, PTEN, IDH1, IDH2.
- Pathogenic variants were reported at a variant allele frequency (VAF) of ≥1%.
- CALR mutation screening was carried out independently.

RESULTS

- PAC203 patients with available molecular data had a high incidence of anemia and severe thrombocytopenia (platelet counts <50 x 10^9/L).

Table 1. Baseline Patient Characteristics (Subset with DNA Sequencing Available)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N=110)</th>
</tr>
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<tbody>
<tr>
<td>Follow-up time (median, range)</td>
<td>163 (28-476) days</td>
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<tr>
<td>Age (median, range)</td>
<td>67.5 (37-87) years</td>
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<tr>
<td>Primary M (%)</td>
<td>56.4%</td>
</tr>
<tr>
<td>Platelet count (median, range)</td>
<td>63 (13 – 910) x 10^9/L</td>
</tr>
<tr>
<td>Platelet count &lt;50 x 10^9/L (%)</td>
<td>38.3%</td>
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<tr>
<td>Hemoglobin &lt;10 g/dL (%)</td>
<td>65.1%</td>
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Molecular Landscape: MF Post-Ruxolitinib

- The most common driver mutation was JAK2 (77.3%), whereas 1.8% had no driver mutation ("triple negative"), as shown in Figure 1.
- CALR mutation, associated with better prognosis in MF, was relatively rare in this population (12.7%) compared to other previously described MF populations.9
- Non-MF driver mutations (NMD) were present in 76.4% of patients; 43.6% had ≥2 NMD and 18% had ≥3 NMD.
- ASXL1 (25.5%) and TET2 (24.5%) were most prevalent, consistent with prior reports.10
- Splicing factor (SF) mutations, present in 32.3%, were mutually exclusive (SF3B1, n=14; U2AF1, n=14; SRSF2, n=6; ZRSR2, n=2).
- Patients with ≥3 total mutations have shorter survival, decreased spleen volume, and development of grade 3/4 cytopenias.
- Patients with RAS pathway mutations were more likely to have grade 3/4 anemia on study (OR 4.4 [95% CI 1.3-14.8], Figure 3).
- Patients with RAS pathway mutations were more likely to have grade 3/4 thrombocytopenia on study (OR 4.7 [95% CI 1.6-13.9], Figure 3).
- Mutations associated with poor survival in MF (n=5), HMR: IDH1/2, EZH2, ASXL1, SRSF2, U2AF1(Q157).13
- TP53 mutations, associated with poor prognosis and leukemic transformation12 were found in 7.3% of patients.
- RAS mutations (K/NRAS), associated with poor survival in MF, were found at a higher frequency (17.3%) than reported in prior MF cohorts.
- Patients with a RAS mutation (vs. wild type) were more likely to be HMR (68.4% vs. 35.6%, P=.007).
- RAS mutations and TP53 mutations were mutually exclusive.

Longitudinal Outcomes

- Of patients with Week 24 molecular analysis, 13.2% (3/58) acquired at least 1 new mutation. Allele frequency was 5% in all cases.
- ASXL1 (n=3), TET2 (n=1), TP53 (n=1), CBL (n=1), PHF6 (n=1)
- A statistically significant association was not observed between baseline mutation status and efficacy outcomes or treatment discontinuation.

CONCLUSIONS

- The PAC203 cohort is molecularly high risk
- High incidence of HMR, TP53, and RAS mutations
- High mutational burden3
- Low incidence of CALR mutations
- The molecular characteristics of the PAC203 cohort may impact overall response on this study
- Lack of association between mutations and response rate on PAC203 noted but significant inferences cannot be made due to low event rate
- Novel associations between mutation profiles and hematologic parameters and events were identified

REFERENCES


Figure 1. Balloon Plot Showing Relationship Between Driver and Non-Driver Mutations

Figure 2. Mutations Associated with Cytopenias

Figure 3. High Grade Cytopenia Events by Mutation Group