Monitoring of Calr Allele Burden in Patients with Essential Thrombocythemia Treated with Imetelstat, a Telomerase Inhibitor, Reveals Rapid and Substantial Molecular Responses

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In ET, mutations in the calreticulin gene (CALR) are found in the majority of patients that are negative for mutations in the JAK2 and MPL genes.

Patients with mutated CALR have a better prognosis and a lower risk of thrombosis than those with mutated JAK2.

Recently, decreases in the CALR mutant allele burden have been observed with interferon alpha (IFN-α) after long-term treatment of two- and four-years, respectively.

We aimed to assess molecular response to imetelstat therapy in ET patients with CALR mutations by serial measurements of CALR mutant allele burden.
Study Design

Patients with ET resistant/intolerant to prior therapy and requiring cytoreduction → Imetelstat induction (7.5-11.7 mg/kg IV Qwk) → Imetelstat maintenance at platelet count of 250-300 x 10³/µL (7.5-11.7 mg/kg)
Clinical Phase II ET Study with Imetelstat (IT)

Study Design

Patients with ET resistant/intolerant to prior therapy and requiring cytoreduction

Imetelstat induction (7.5-11.7 mg/kg IV Qwk)

Imetelstat maintenance at platelet count of 250-300 x 10^3/µL (7.5-11.7 mg/kg)

Imetelstat

• First telomerase inhibitor in clinical development
• 13-mer modified oligonucleotide with palmitoyl lipid tail
• Competitively binds to RNA template of telomerase
Clinical Phase II ET Study with Imetelstat (IT)

Trial has completed enrollment with a total of 18 ET patients

Patients with ET resistant/intolerant to prior therapy and requiring cytoreduction

Imetelstat induction (7.5-11.7 mg/kg IV Qwk)

Imetelstat maintenance at platelet count of 250-300 x 10³/µL (7.5-11.7 mg/kg)

Endpoints of the Study

<table>
<thead>
<tr>
<th>Endpoint</th>
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</thead>
<tbody>
<tr>
<td>Primary</td>
<td>• Best Overall Hematologic RR (CR + PR) within 1st yr of treatment</td>
</tr>
<tr>
<td>Secondary</td>
<td>• Clinicohematologic response within the 1st yr of therapy</td>
</tr>
<tr>
<td></td>
<td>• Duration of hematologic response</td>
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<tr>
<td></td>
<td><strong>• Molecular response (JAK2 V617F /MPL W515mt/CALRmt patients)</strong></td>
</tr>
<tr>
<td></td>
<td>• Safety and tolerability</td>
</tr>
<tr>
<td>Exploratory</td>
<td>• CFU-Mega spontaneous growth (selected sites)</td>
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## ET Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=18 Median (Range) or N (%)</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>59.5 (21-83)</td>
</tr>
<tr>
<td><strong>Years Since Initial Diagnosis</strong></td>
<td>7.2 (0.3-24.9)</td>
</tr>
<tr>
<td><strong>Platelet Count (x 10³/µL )</strong></td>
<td>788 (521-1359)</td>
</tr>
<tr>
<td><strong>WBC Count (x 10³/µL)</strong></td>
<td>7.8 (3-14.6)</td>
</tr>
<tr>
<td><strong>Splenomegaly</strong></td>
<td>1 (6%)</td>
</tr>
<tr>
<td><strong>More than one prior therapy (anagrelide +/- IFN)</strong></td>
<td>13 (72%)</td>
</tr>
<tr>
<td><strong>Resistant to at least one prior therapy</strong></td>
<td>8 (44%)</td>
</tr>
<tr>
<td><strong>Intolerant of or refused at least one prior therapy</strong></td>
<td>14 (78%)</td>
</tr>
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<table>
<thead>
<tr>
<th><strong>Mutation Status</strong></th>
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</tr>
</thead>
<tbody>
<tr>
<td>JAK2 V617F</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>CALR Mutation</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>MPL W515&lt;sup&gt;mt&lt;/sup&gt;</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>None</td>
<td>3 (17%)</td>
</tr>
</tbody>
</table>

* 17 of 18 patients received prior hydroxyurea
Previously Reported: Secondary Endpoint--JAK2 V617F Allele Burden

PR observed in 7/8 (88%) and maintained for 6/7 (86%) patients

Median JAK2 V617F allelic burden is reduced more than 70% at month 9 and remains more than 60% reduced at month 15 even with less frequent maintenance dosing
Results: Decrease of CALR Mutant Allele Burden

- All 5 patients with CALR mutations demonstrated reduction of allele burden (median 36%), including 3/5 patients who achieved ≥35% decreases, after 3-6 months of treatment.

- Results confirm imetelstat’s inhibition of neoplastic clonogenic cell growth in vivo.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Pt 2</th>
<th>Pt 4</th>
<th>Pt 8</th>
<th>Pt 12</th>
<th>Pt 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>35.7</td>
<td>44.7</td>
<td>40.2</td>
<td>48.6</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>+12</td>
<td>--</td>
<td>-48</td>
<td>-35</td>
<td>-2</td>
</tr>
<tr>
<td>6</td>
<td>-30</td>
<td>-36</td>
<td>--</td>
<td>-31</td>
<td>-6</td>
</tr>
<tr>
<td>9</td>
<td>--</td>
<td>-18</td>
<td>--</td>
<td>-50</td>
<td>-15,-11</td>
</tr>
<tr>
<td>12</td>
<td>-1</td>
<td>-18</td>
<td>--</td>
<td>-55</td>
<td>--</td>
</tr>
</tbody>
</table>

**Best % Reduction**

-30 | -36 | -48 | -55 | -15

**Best Hematologic Response**

CR | CR | CR | CR | PR
RESULTS: Hematologic Response by Baseline Mutation Status

Baseline mutation status is not significantly associated with time to CR (P=0.45)
RESULTS: Durability of Hematologic Response by Mutation Status

- Patients with CALR mutations are trending toward longer time on treatment (P=0.23)
- ≥35% reduction in allele burden (CALR<sub>mt</sub>,JAK2 V617F,MPL<sub>mt</sub>) is associated with longer time on treatment (P=0.03)
Individual Patient Responses

Patient 8

CALR % Mutant Allele Burden

Platelet Count $10^3/\mu l$

Cycle

- % CALR Mutant Allele Burden
- Dosing of imetelstat
- Platelet Count
Individual Patient Responses

Patient 8

CALR % Mutant Allele Burden

-48%

Dosing of imetelstat

Patient 12

CALR % Mutant Allele Burden

-55%

Platelet Count

Dosing of imetelstat

Platelet Count

% CALR Mutant Allele Burden

Platelet Count $10^3/\mu l$
Imetelstat reduces Mutated CALR and JAK2V617F Allele Burden

- In 4 of 5 patients with CALR-mutated ET, imetelstat induced a rapid hematologic CR and in 3 patients this response was associated with a substantial decrease in the allele burden of 35-50% after 3-6 cycles of treatment
- JAK2V617F molecular responses were reached in 7 / 8 patients (as previously reported)
- Overall 9/13 patients with JAK2 or CALR mutations reached a >35% decrease of the mutant clone within 3-6 cycles of treatment
- Mutation status at baseline is not significantly associated with hematologic response

This additional evidence of reduction in the clonal allele burden supports imetelstat’s potential to modify the biology of MPNs long-term
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