Idelalisib given front-line for the treatment of CLL results in frequent and severe immune-mediated toxicities

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Background

• Idelalisib inhibits the p110δ isoform of PI3K
  • P110δ expression is primarily limited to leukocytes¹

• P110δ integrates and transduces signals that are important for lymphocyte growth, survival, and migration

• The combination of idelalisib with rituximab improved ORR, PFS, and OS compared to rituximab monotherapy in patients with R/R CLL²


CLL = chronic lymphocytic leukemia; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI3K = phosphatidylinositol 3-kinase; R/R = relapsed/refractory
This was a phase II study of idelalisib plus ofatumumab in previously untreated CLL/SLL

As of September 11, 2015, the trial was ongoing with 24 subjects enrolled

Median time on therapy was 7.7 months (range: 0.7–16.1)

*bid = twice a day*
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib + Ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients enrolled, n</td>
<td>24</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>75</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>67.4 (57.6–84.9)</td>
</tr>
<tr>
<td>Prior number of therapies</td>
<td>0</td>
</tr>
<tr>
<td><strong>CLL genetics, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Unmutated IGHV</td>
<td>13 (54%)</td>
</tr>
<tr>
<td>Del(17p)/TP53 mutations</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Del(13q)</td>
<td>13 (54%)</td>
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</tbody>
</table>

CLL = chronic lymphocytic leukemia; del(11q) = deletion 11q; del(13q) = deletion 13q; del(17) = deletion 17p; IGHV = immunoglobulin heavy chain variant; TP53 = tumour protein 53
Frequent and Severe Hepatotoxicity with Idelalisib

The majority of patients had grade ≥3 hepatotoxicity (52%).

$ALT = \text{alanine aminotransferase}; \text{CTCAE} = \text{Common Terminology Criteria for Adverse Events}$
## Incidence of Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Overall relapsed</th>
<th>Upfront patients aged ≥65</th>
<th>Upfront idelalisib + ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>54</td>
<td>760</td>
<td>64</td>
<td>24</td>
</tr>
<tr>
<td>Median prior therapies (range)</td>
<td>5 (2–14)</td>
<td>≥1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>63 (37–82)</td>
<td>66 (21–91)</td>
<td>71 (65–90)</td>
<td>67.4 (58–85)</td>
</tr>
<tr>
<td>Median time on therapy, months (range)</td>
<td>15 (0.2–48.7)</td>
<td>—</td>
<td>22.4 (0.8–45.8)</td>
<td>7.7 (0.7–16.1)</td>
</tr>
<tr>
<td>Grade ≥3 transaminitis, %</td>
<td>1.9</td>
<td>14</td>
<td>23</td>
<td>52</td>
</tr>
<tr>
<td>Grade ≥3 colitis/diarrhea, %</td>
<td>5.6</td>
<td>14</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>Any grade pneumonitis, %</td>
<td>5.6</td>
<td>3</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

Reference


• An analysis of previous studies suggested that toxicities were more common in less heavily pretreated patients.
Age Was a Risk Factor for Early Hepatotoxicity

- All patients with age ≤65 years (n = 7) required systemic steroids for toxicities
Idelalisib Toxicities are Likely Due to On-Target Immune-Mediated Effects

• Activated immune infiltrate was found on liver biopsy

• Intestinal biopsies from patients with idelalisib-related colitis showed intraepithelial CD8+ lymphocytosis and crypt cell apoptosis

CD = cluster of differentiation
Responsiveness to Steroids:
Kaplan-Meier Time to Initiation of Steroids

![Graph showing Kaplan-Meier Time to Initiation of Steroids](image)
Twelve subjects with grade ≥2 transaminitis were rechallenged with the drug after holding for toxicity

- Five patients were rechallenged while off steroids; four developed recurrent transaminitis within 1–4 days (grade 2: n = 1; grade 3: n = 2; grade 4: n = 1)

- Seven patients were rechallenged while on steroids; two developed recurrent transaminitis within 3–4 days (grade 2: n = 1; grade 3: n = 1)
The Connection between p110δ and Regulatory T-Cells

- Mice with genetic inactivation of p110δ developed autoimmune colitis\(^1\)

- Mutations that disrupted the function of regulatory T-cells in mice and humans led to autoimmune syndromes with hepatitis, enteritis, and pneumonitis\(^2,3\)

- Mice with genetic inactivation of p110δ had decreased numbers and function of regulatory T-cells\(^4\)

Decrease in Regulatory T-Cells While on Therapy

- Eleven out of 15 patients with matched samples (73%) had a decrease in the percentage of regulatory T-cells over time.
Change in Ratio of Regulatory T-Cells to Conventional T-Cells
Change in CD95 Level on Regulatory T-Cells

- CD95 is a pro-apoptotic marker

CD = cluster of differentiation
Summary and Conclusion

• An early fulminant hepatotoxicity developed in a subset of primarily younger patients treated with idelalisib monotherapy in the front-line setting

• Multiple lines of evidence suggest that this early hepatotoxicity is immune-mediated

• The proportion of regulatory T-cells in the peripheral blood decreased on idelalisib therapy, providing a possible explanation for the development of early hepatotoxicity