Ublituximab + TGR-1202 Demonstrates Activity and Favorable Safety Profile in Relapsed/R refractory B-Cell NHL and High-Risk CLL

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Background

Ublituximab (TG-1301) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the COO antigen, and glyceregenized to enhance affinity for all variants of Fykitra receptors, thereby demonstrating greater physician-dependent cellular cytotoxicity (AC5) activity than rituximab and ofatumumab.

Two Phase I trials of single agent ublituximab in patients with relapsed/refractory CLL reported response rates of 67% (ASC04 2014) and 45% (EHN 2013), with rapid and sustained lymphocyte depletion.

TGR-1202

TGR-1202 is a highly expressed in cells of hematopoietic origin and is overexpressed in advanced malignancies. TGR-1202 is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, leading:

A prolonged half-life that enables once-daily dosing
- A differentiated safety profile from other PI3Kδ inhibitors in development, notably with respect to hepatic toxicity and colitis to date

Study Design

Study UTX-TGR-103 (KCT0004845) is an ongoing Phase I/II trial evaluating the combination of ublituximab + TGR-1202 in patients with relapsed/refractory NHL and CLL. The study is divided into two parts:

- Phase I: 3 + 3 Dose Escalation evaluating Cycle 1 DLTs (CLL & NHL separately)
- Phase II: Dose Expansion

Dose Escalation Schema:

<table>
<thead>
<tr>
<th>TGR-1202 Dose</th>
<th>Ublituximab + TGR-1202 Cycle 1 Dose (Treatment Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500 mg (micronized)</td>
</tr>
<tr>
<td>2</td>
<td>600 mg (micronized)</td>
</tr>
<tr>
<td>3</td>
<td>700 mg (micronized)</td>
</tr>
<tr>
<td>4</td>
<td>800 mg (micronized)</td>
</tr>
<tr>
<td>5</td>
<td>900 mg (micronized)</td>
</tr>
<tr>
<td>6</td>
<td>1000 mg (micronized)</td>
</tr>
<tr>
<td>7</td>
<td>1200 mg (micronized)</td>
</tr>
<tr>
<td>8</td>
<td>1200 mg (micronized)</td>
</tr>
</tbody>
</table>

Current escalating Dose is 1200 mg (micronized).

Treatment Schedule:

- Efficacy is assessed Week 8, and every 12 weeks thereafter. After Month 12, all patients remain on TGR-1202 single agent.
- Patients with 

UBLITUXIMAB INFUSIONS

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
<th>Cycle 7</th>
<th>Cycle 8</th>
<th>Cycle 9</th>
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<tr>
<td>Day</td>
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<td>15</td>
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<td>13</td>
<td>20</td>
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<td>41</td>
<td>48</td>
</tr>
</tbody>
</table>

TGR-1202 Daily

TGR-1202 Infusions

TGR-1202 Infusion

Ublituximab + TGR-1202 in patients with ≥ 3 prior therapies (range 1-59) including, 
- 25% of patients had high-risk cytogenetics (17p del and/or 11q del)
- FL patients were heavily pre-treated with 80% of patients having been exposed to 3 prior therapies (range 1-9)
- 7/10 DLBCL patients with GCB subtype, including one patient with triple hit lymphoma (BCL2, BCL6, and MYC rearrangements)

Patients Treated at the "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden

Conclusions

- Ublituximab in combination with TGR-1202 is well tolerated and highly active in a broad population of heavily pre-treated and high-risk patients with NHL and CLL.
- Grade 3/4 adverse events and discontinuations due to adverse events have been limited (<5%).
- Notably, activity of the combination has been observed in CLL with high-risk cytogenetics, heavily pre-treated indolent NHL, and Germinal Center (GCB) DLBCL LARGE-B-Cell lymphoma.
- As with single agent TGR-1202, a strong dose-response relationship was observed with the combination.
- Safety profile of the combination supports additional multi-drug combination regimens; triple therapy combinations adding novel agents to ublituximab and TGR-1202 are ongoing (including Ibrutinib, ASC061 #85061 with additional triple therapy studies planned).
- Phase III studies for the combination are planned.