UBLITUXIMAB (TG-1101), A NOVEL GLYCOENGINEERED ANTI-CD20 MAB, IN COMBINATION WITH IBRUTINIB ACHIEVES 95% ORR IN PATIENTS WITH HIGH-RISK RELAPSED/REFRACTORY CLL

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Ublituximab: Glycoengineered Anti-CD20 mAb

- Type 1 chimeric IgG1 mAb

- Unique binding sequence on CD20 (Green arrows in figure)

- Glycoengineered to contain low fucose content

- Activity in “low” CD20 expressing cell lines

O’Connor et al, ASCO 2014

Figure Adapted from Ruuls et al 2008
Properties of ublituximab in preclinical and phase I studies

- Leads to higher NK cell-mediated ADCC than rituximab (black vs. white bars)
- Has significant single-agent activity in CLL and other B-cell malignancies, including rituximab-refractory

Study Design: Ublituximab + Ibrutinib

• Two part study to determine the safety and efficacy of ublituximab in combination with ibrutinib
  – Part 1: 6 patient per cohort safety run-in
  – Part 2: Open enrollment at fixed dose
• After cycle 6, all patients off study and may remain on single agent ibrutinib per investigator discretion
Endpoints

• Part 1 (safety run-in)
  – Primary: safety

• Part 2 (expansion)
  – Primary: ORR
  – Secondary: safety, CR rate, MRD negativity in CLL

• Responses in CLL determined by IWCLL 2008
Eligibility Criteria

- Relapsed CLL, small lymphocytic lymphoma, mantle cell lymphoma
- Preliminary overall results presented as poster at ASH 2014

CLL eligibility criteria
- Age at least 18 years
- At least 1 prior regimen
- Indication for therapy
- Cytogenetic and/or FISH available (determined locally)
- ECOG ≤ 2
- Bilirubin ≤ 1.5 x ULN, AST ≤ 2.5-5 x ULN
- Creatinine ≤ 2 mg/dL or clearance ≤ 50 mL/min
- ANC > 1,000/µL and platelets > 50k/µL for Part 1; and
- ANC > 750/µL and platelets > 30k/µL for Part 2
- Prior treatment with a BTK inhibitor and/or a PI3K inhibitor permitted
- Patients with Richter’s transformation excluded

### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for Safety, (n)</td>
<td>44</td>
</tr>
<tr>
<td>Evaluable for Efficacy, † (n)</td>
<td>40</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>71 (39 – 86)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>22/22</td>
</tr>
<tr>
<td>ECOG, median</td>
<td>1</td>
</tr>
<tr>
<td>Prior Regimens, median (range)</td>
<td>2 (1 – 7)</td>
</tr>
<tr>
<td>≥ 3 Prior Regimens</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>Prior Anti-CD20 (rituximab, ofatumumab, obintuzumab)</td>
<td>41 (93%)</td>
</tr>
<tr>
<td>Refractory to anti-CD20</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>Prior Alkylating Agent</td>
<td>28 (64%)</td>
</tr>
<tr>
<td>Prior Purine Analog</td>
<td>22 (50%)</td>
</tr>
<tr>
<td>High-risk (17p del, 11q del, p53 mutated)</td>
<td>21 (48%)</td>
</tr>
</tbody>
</table>

†4 patients not evaluable: 2 patients withdrew consent and 2 patients came off study prior to first disease assessment: 1 due to ibrutinib related AE (diarrhea); 1 due to multiple non-drug related AE’s
## Safety

### All Causality AE’s in > 10% of Patients (n=44)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Infusion reaction</strong></td>
<td>20 (45%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>16 (36%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>13 (30%)</td>
<td>1 (2%)</td>
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<tr>
<td><strong>Nausea</strong></td>
<td>11 (25%)</td>
<td>-</td>
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<tr>
<td><strong>Rash</strong></td>
<td>10 (23%)</td>
<td>-</td>
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<tr>
<td><strong>Pyrexia</strong></td>
<td>8 (18%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>7 (16%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>7 (16%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>7 (16%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Muscle Spasms</strong></td>
<td>7 (16%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Peripheral Edema</strong></td>
<td>7 (16%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Upper Respiratory Tract Infection</strong></td>
<td>7 (16%)</td>
<td>-</td>
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<tr>
<td><strong>Dizziness</strong></td>
<td>6 (14%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>5 (11%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td><strong>Contusion</strong></td>
<td>5 (11%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>5 (11%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Myalgia</strong></td>
<td>5 (11%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>5 (11%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>5 (11%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>
Efficacy: Nodal Reductions

Best Percent Change from Baseline in Nodal Size

Efficacy Assessed at Week 8 and Week 20 Only

- 37/40 (93%) achieved > 50% reduction in nodal size
Efficacy: First vs. Second Scan

- “High-Risk” = 17p del, 11q del, or p53 mutation

Week 8:
- All CLL: -62%
- High-Risk CLL: -64%

Week 20:
- All CLL: -76%
- High-Risk CLL: -85%
Efficacy: Best Overall Response Rate

Per study design, all patients were evaluated for efficacy at Month 2 and 5 only.

88% ORR
- 10% CR/PR*
- 78% PR
N=40

95% ORR
- 15% CR/PR*
- 80% PR
N=20

15% of High Risk patients were MRD negative within 6 months of therapy.

*2 patients had CR per iwCLL criteria without bone marrow confirmation.
Efficacy: Lymphocytosis

- Median 75% decrease in ALC from baseline by the end of Cycle 3
- 70% of CLL patients had ALC in normal range (<4000/uL) within 6 cycles of therapy
Conclusions

• Addition of ublituximab to ibrutinib in relapsed CLL is safe and effective.
  – Adverse events were as expected and not usually serious
  – Overall response rate 88%, 95% in high-risk
  – Complete response rate 10%, and 3 patients achieved MRD-negative status
  – Mitigates the transient lymphocytosis seen with ibrutinib alone
  – Whether the combination leads to improved clinical outcomes compared with ibrutinib alone is unknown

• Future directions
  – Phase 3 trial of ibrutinib +/- ublituximab in relapsed, high-risk CLL is underway
  – Additional combinations being studied – e.g. ublituximab + ibrutinib + PI3 kinase inhibitor (TGR-1202)
The “GENUINE” Phase 3 Trial: High-Risk CLL

- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA) with U.S. FDA
- Enrolling 330 patients with High-Risk CLL
  - Presence of 17p del, 11q del, and/or p53 mutation
- Study Chair: Jeff Sharman, MD