Ublituximab, a Novel Glycoengineered Anti-CD20 mAb, In Combination with TGR-1202, a Next Generation Once Daily PI3Kδ Inhibitor, Demonstrates Activity in Heavily Pre-Treated and High-Risk Chronic Lymphocytic Leukemia and B-Cell Lymphoma

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Disclosures

- Consultant: Onyx, Alexion, Gilead, Genentech, and Spectrum Pharmaceuticals
Ublituximab: Glycoengineered Anti-CD20 mAb

- Type 1 chimeric IgG1 mAb
- Unique binding sequence on CD20 (Green arrows in figure)
- Potential advantages over current standards of care:
  - Glycoengineered for enhanced ADCC
  - Demonstrated activity in “low” CD20 expressing cell lines:
    - CLL/SLL
    - Refractory B-NHL
  - Single agent responses observed in rituximab refractory patients\(^1\)

Source: Adapted from Ruuls et al 2008

(1) O’Connor et al, ASCO 2014
## TGR-1202: Novel PI3Kδ (delta) Inhibitor

<table>
<thead>
<tr>
<th>TGR-1202</th>
<th>Idelalisib (GS-1101)</th>
<th>Duvelisib (IPI-145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Delta</td>
<td>Delta</td>
<td>Delta/Gamma</td>
</tr>
<tr>
<td>QD</td>
<td>BID</td>
<td>BID</td>
</tr>
</tbody>
</table>

- PK profile that allows **once-daily oral** dosing
- **Absence of hepatic toxicity** in rel/ref hematologic malignances\(^1\)
- 93% nodal PR rate in patients with rel/ref CLL\(^1\)
- Dose escalation ongoing—dose-response relationship observed\(^1\)

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\(^1\)Burris et al, ASH 2014, Abstract # 1984
Trial Design: TGR-1202 + Ublituximab

- Enrolling B-cell NHL and CLL/SLL
- No limit on prior therapies
- Allows for prior BTK and/or PI3K inhibitors use
- 3+3 Dose escalation

**Ublituximab**

- CLL: 600mg
- NHL: 900mg
- 900mg
- 900mg
- 900mg

**TGR-1202**

- Completed
- Completed
- Completed
- Completed
- Enrolling

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**Dose Escalation Until MTD**

**TGR-1202 Once Daily Continuously (Days 1-28 = 1 Cycle)**
Demographics: TGR-1202 + Ublituximab

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for Safety (n)</td>
<td>27</td>
</tr>
<tr>
<td>Evaluable for Efficacy † (n)</td>
<td>26</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>65 (35 – 82)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>17/10</td>
</tr>
<tr>
<td>ECOG, 0/1/2</td>
<td>12/15/0</td>
</tr>
<tr>
<td>Prior Therapies, median (range)</td>
<td>3 (1 – 9)</td>
</tr>
<tr>
<td>Histologies</td>
<td></td>
</tr>
<tr>
<td>CLL/SLL, n</td>
<td>9/1</td>
</tr>
<tr>
<td>Follicular, n</td>
<td>9</td>
</tr>
<tr>
<td>DLBCL, n</td>
<td>7</td>
</tr>
<tr>
<td>Richter’s, n</td>
<td>1</td>
</tr>
<tr>
<td>≥ 2 Prior R–Chemo Regimens, n</td>
<td>18 (67%)</td>
</tr>
<tr>
<td>Refractory to Prior Therapy, n</td>
<td>11 (41%)</td>
</tr>
</tbody>
</table>

- 67% of CLL had 17p and/or 11q del
- Median Prior Tx in FL: 5 (range 1 – 9)
- 5/7 DLBCL with Germinal Center (GCB) Subtype
Safety: TGR-1202 + Ublituximab

Adverse Events in ≥10% (All Causality) n=27

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades n (%)</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>14 (52)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (41)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (37)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (33)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (30)</td>
<td>-</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (30)</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (22)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (19)</td>
<td>-</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3 (11)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (11)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Upper Resp Inf</td>
<td>3 (11)</td>
<td>-</td>
</tr>
</tbody>
</table>

- IRR mostly on Day 1
- 3 patients enrolled with Gr 3 neutropenia
  - 2 improved & 1 worsened (DLT)
  - GCSF restricted in Cycle 1
- TGR-1202 dose reduced in 1 patient in Cycle 5
  - Grade 1 diarrhea
- Notably, no hepatic toxicity observed
Activity in CLL/SLL: TGR-1202 + Ublituximab
Interim Data From Early Dose Escalation Cohorts

- 67% PR rate iwCLL (Hallek 2008)
- 6/9 patients with 17p and/or 11q
- All CLL patients remain on study (3+ to 9+ months)
**TGR-1202 + Ublituximab: Activity in CLL**

- **End of Cycle 3:**
  - All patients achieved >50% reduction of ALC
  - 88% achieved ALC <5000/uL
Activity in NHL: TGR-1202 + Ublituximab
Interim Data From Early Dose Escalation Cohorts

% Change in Nodal Size

- FL: 1 PET(-) CR and 1 PR
  - 78% of FL (N=9) patients have not progressed on study
- DLBCL: ORR 43% (3/7);
  - 2 CR’s confirmed by independent radiologic review
  - 3 patients remain on study > 7 months
"Triplet": TGR-1202 + Ublituximab + Ibrutinib

- Initial cohorts for both NHL and CLL (n=5)
  - Ongoing enrollment with 600 mg dose of TGR-1202 in NHL cohort

- Safety: All Grade 1/2 AEs (no Grade 3/4 events to date)
  - AEs included IRR, nausea, fatigue, and diarrhea
  - No dose reductions or delays with patients treated up to 4+ months

Clinical Response at First Assessment (8 Weeks)

<table>
<thead>
<tr>
<th>Histology</th>
<th>Description</th>
<th>Prior # Rx</th>
<th>Prior Ibrutinib</th>
<th>Rel/Ref</th>
<th>Rituximab Refractory</th>
<th>Response</th>
<th>% ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>Stage IV</td>
<td>4</td>
<td>Refractory</td>
<td>Refractory</td>
<td>Yes</td>
<td>PR</td>
<td>74%</td>
</tr>
<tr>
<td>MCL</td>
<td>Advanced</td>
<td>2</td>
<td>No</td>
<td>rAuto txp</td>
<td>No</td>
<td>CR</td>
<td>PET-</td>
</tr>
<tr>
<td>Richter’s</td>
<td>17p</td>
<td>3</td>
<td>No</td>
<td>Refractory</td>
<td>Yes</td>
<td>PD</td>
<td>N/A</td>
</tr>
<tr>
<td>CLL</td>
<td>17p</td>
<td>2</td>
<td>No</td>
<td>Refractory</td>
<td>Yes</td>
<td>Too Early</td>
<td>N/A</td>
</tr>
<tr>
<td>Follicular</td>
<td>Stage IV</td>
<td>1</td>
<td>No</td>
<td>Refractory</td>
<td>Refractory</td>
<td>Too Early</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Conclusions

- Ublituximab and TGR-1202 has significant activity:
  - CLL: ORR 67% iwCLL (Hallek 2008)
  - FL: 78% have not progressed on study
  - DLBCL: ORR 43%, with 2 confirmed CRs (activity in GCB)

- Favorable toxicity profile
  - No hepatic toxicity to date in 87 pts
    - 32 pts in current study + 55 pts in single agent TGR-1202 Ph 1

- Both the “Doublet” and “Triplet” continue to accrue
  - Clinicaltrials.gov: NCT02006485
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- Families
- Patients