Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen. Ublituximab has been glycogenated to enhance affinity for all variants of Fc receptors and therefore demonstrates greater antibody-dependent cellular toxicity (ADCC) activity than rituximab and oblimersen, particularly against tumor cells that express low CD20 levels. A phase I/II trial of single-agent ublituximab achieved 100% response rate at 45% EHA 2015. Two clinical studies (Phase I and Phase II) were completed with patients with rituximab-refractory and oblimersen-refractory B-cell NHL and CLL. TG-1101-101 is a study of a single agent ublituximab in this patient population, while TG-1101-102 is a study of ublituximab administered in combination with lenalidomide, an immunomodulating agent that has displayed activity in lymphoma and has been shown to enhance the ADCC activity of anti-CD20 antibodies. Herein we report on the clinical results of both studies.

### Study Design

**TG-1101-101**

- **Objective:** Single-agent ublituximab in rituximab-refractory and refractory B-cell malignancies
- **Study Type:** I/II
- **Study Design:** Cohort 1: 1101, Cohort 2: 450 mg
- **Inclusion Criteria:**
  - Refractory to prior RTX
  - CD20+ B-cell malignancies
  - ECOG 0-2
  - Prior lenalidomide
  - >3 months off RTX

**TG-1101-102**

- **Objective:** Ublituximab + lenalidomide in rituximab-refractory and refractory B-cell malignancies
- **Study Type:** I/II
- **Study Design:** Days 1, 15, and 28 cycles 1-24
- **Inclusion Criteria:**
  - Refractory to prior RTX
  - CD20+ B-cell malignancies
  - ECOG 0-2
  - Prior lenalidomide

### Key Inclusion Criteria

- Refractory or relapsed B-cell NHL or CLL following at least one prior line of anti-CD20 therapy
- Measurable/monitorable disease (ECOG ≤2)
- Adequate organ / marrow function with baseline ANC ≥ 1,000 cells/µl and platelets ≥150,000

### Dose Escalation Schema

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ublituximab (mg/m²)</th>
<th>Days 1</th>
<th>Days 2</th>
<th>Days 3</th>
<th>Days 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
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<td>3</td>
<td>450</td>
<td>15</td>
<td>10</td>
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<tr>
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<tr>
<td>4</td>
<td>3</td>
<td>900</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

### Dosing Schedule

For all patients, the starting dose for Days 1-21 is 450 mg/m². Ublituximab is administered on Days 1, 15, and 28 cycles for 24 cycles.

### Study Design

**TG-1101-101**

- **Objectives:**
  - Dose escalation and safety
  - Efficacy

**TG-1101-102**

- **Objectives:**
  - Dose escalation and safety
  - Efficacy

### Results

**Safety**

Among the 12 patients treated in the phase-dose escalation phase of the study, no DLTs were observed, and no MTD was reached. Adverse events (CTCAE v.4.0) as summarized as follows:

- **At Least Grade 3 or Grade 4 Adverse Events (n=12):**
  - Occurring in > 5% of Patients (n=9):**
    - Fatigue
    - Constipation
    - Thrombocytopenia
    - LYMPHOCYTE DEPLETION

**Efficacy**

**Overall Response by Lymphoma Sub-type**

- **Adequate** (n=35)
  - **Complete Response (CR)**: 22%
  - **Partial Response (PR)**: 13%
  - ** Stable Disease (SD)**: 6%
  - ** Progression (PD)**: 6%

- **Maintenance (for patients in SD or better)**
  - **Complete Response (CR)**: 8%
  - **Partial Response (PR)**: 31%
  - ** Stable Disease (SD)**: 6%
  - ** Progression (PD)**: 8%

### Conclusions

**TG-1101-101**

- Significant single agent activity observed in patients with rituximab-refractory/acellular CLL and NHL.
- Rapid and profound lymphocyte depletion observed in CLL patients (median time to >95% reduction of 1 day).
- All patients (n=35) received >3 rounds of Ublituximab.
- Overall, >75% of patients achieved durable (patients in response 5+ year on single agent ublituximab) with some improving in response time over continued ublituximab maintenance.
- Studies of ublituximab in combination with P13k delta and BTK inhibitors are ongoing. Phase III studies in B-cell malignancies are currently in development.

**TG-1101-102**

- Ublituximab was well tolerated even at the highest dose levels tested, with no DLT observed and no MTD reached. Safety profile supports combination therapy.
- Of the 12 patients treated in the phase-dose escalation phase, follow up was limited. Infusions were well tolerated. No (Grade 3/4) infusion reactions were reported.
- Significant single agent activity observed in patients with rituximab-refractory/acellular CLL and NHL.
- Rapid and profound lymphocyte depletion observed in CLL patients (median time to >95% reduction of 1 day).
- All patients (n=35) received >3 rounds of Ublituximab.
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