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

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Background

Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab.

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

TGR-1202

PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies

TGR-1202 is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:

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

Study Design

Study UTX-TGR-103 (NCT02004845) is an ongoing Phase I/ib trial evaluating the combination of ublituximab + TGR-1202 in patients with relapsed or 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 Ib: Dose Expansion

Dose Escalation Schema:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Ublituximab NHL Dose</th>
<th>Ublituximab CLL Dose</th>
<th>TGR Dose (QD)</th>
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</table>

Expansion

Currently Enrolling Expansion Cohorts with TGR-1202 at 800 mg and 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:

**UBLITUXIMAB INFUSIONS**

**TGR-1202 DAILY**

Results

Demographics

- Evaluable for Safety (n) = 55
- Evaluable for Efficacy (n) = 39
- Median Age, years (range) = 64 (29 – 86)
- Male/Female = 36/19

Histology

- CLL/SLL = 15
- DLBCL = 16
- FL = 16
- MZL = 5
- MCL = 2
- Richter’s = 1

ECOG, 0/1/2

- Prior Therapies, median (range) = 3 (1 – 9)
- Patients with ≥ 3 Prior Therapies (%) = 60%
- Prior RTX based therapy, median (range) = 3 (1 – 7)
- Refractory to Prior Therapy, n (%) = 28 (51%)

Study Objectives

- To determine the Safety, and Maximum Tolerated Dose (MTD) of UTX+TGR

Secondary Objectives

- To assess efficacy (overall response rate, time to response, duration of response, progression free survival)

Key Eligibility Criteria

- Histologically confirmed B-cell non-Hodgkin lymphoma (NHL) or CLL/small lymphocytic lymphoma (SLL), and select other B-cell malignancies
- Relapsed after, or refractory to, at least 1 prior treatment regimen with no limit on prior therapies
- ECOG performance status ≤ 2
- Adequate organ system function: ANC ≥ 750/μL; platelets ≥ 50/μL
- Patients with Richter’s Transformation, or refractory to prior PI3Kδ inhibitors or prior RTX inhibitors are eligible

Efficacy

Best Percent Change from Baseline in Disease Burden

- 70% of CLL patients had high-risk cytogenetics (17p del and/or 11q del)
- FL patients were heavily pretreated with 80% of patients having been exposed to ≥ 3 prior therapies (range 1-9)
- 71/100 DLBCL patients with GCB subtype, including one patient with triple hit lymphoma (BCL2, BCL6, and MYC rearrangements)

Safety

Related AE’s Occurring in ≥ 5% of Patients (n = 55)

- AE profile has been similar across all cohorts to date
- 3 patients (∼5%) have come off study due to an adverse event: itching (Gr. 1), pneumonitis, and hypoxia
- No patients at 800 mg micronized TGR-1202 have discontinued due to AE
- Neutropenia well managed through dose delays
- 1 DLT occurred—CLL Cohort 1 (Gr. 4 neutropenia in a patient with baseline Gr. 3 neutropenia), no other DLT’s were observed permitting continued dose escalation

Conclusions

- Ublituximab in combination with TGR-1202 is well tolerated and highly active in a broad population of heavily pretreated 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 pretreated indolent NHL, and Germinal Center (GCB) Diffuse 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 multidrug combination regimens; triple therapy combinations adding novel agents to ublituximab and TGR-1202 are ongoing (including ibritumomab: ASCO 2015 Abstract #8501 & Lugano ICM 2015 Abstract #106) with additional triple therapy studies planned
- International Phase III studies for the combination are planned