# Ublituximab + TGR-1202 Demonstrates Activity and a Favorable Safety Profile in Relapsed/Refractory B-Cell NHL and High-Risk CLL: Phase I Results


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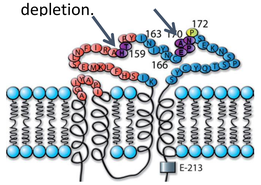
## Background

### Ublituximab

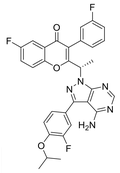
- Ublituximab (TG-1101, UTX) is a novel, chimeric monoclonal antibody targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab.
- Phase I trials of single agent ublituximab in patients with relapsed/refractory CLL and NHL reported impressive response rates with rapid and sustained lymphocyte depletion.




**Red**: Amino acids contributing to ofatumumab binding
**Yellow**: Amino acids essential for rituximab, but not ofatumumab binding
**Purple**: Core amino acids of ublituximab epitope

### TGR-1202

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- TGR-1202 (TGR) 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 toxicity and colitis observed to date



| Fold-selectivity | | | | |
|---|---|---|---|---|
| Isoform | PI3Kα | PI3Kβ | PI3Kγ | PI3Kδ |
| TGR-1202 | >10000 | >50 | >48 | 1 |
| [1]Idelalisib | >300 | >200 | >40 | 1 |
| [2]IPI-145 | >640 | >34 | >11 | 1 |

[1]Flinn et al. 2009, [2]Porter et al. 2012

## Study Design

Study UTX-TGR-103 (NCT02006485) is a Ph 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:

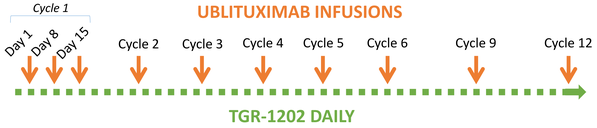
- **Phase I:** 3+3 Dose Escalation evaluating Cycle 1 DLTs (CLL & NHL separately)
- **Phase Ib:** Dose Expansion

**Dose Escalation Schema:**

| Cohort | Ublituximab NHL Dose | Ublituximab CLL Dose | TGR Dose (QD) |
|---|---|---|---|
| 1 | 900 mg | 600 mg | 800 mg |
| 2 | 900 mg | 600 mg | 1200 mg |
| 3 | 900 mg | 900 mg | 400 mg (micronized) |
| 4 | 900 mg | 900 mg | 600 mg (micronized) |
| 5 | 900 mg | 900 mg | 800 mg (micronized) |
| 6 | 900 mg | 900 mg | 1000 mg (micronized) |
| 7 | 900 mg | 900 mg | 1200 mg (micronized) |
| Expansion | *TGR-1202 at 800 mg, 1000 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 was initially administered on Days 1, 8 and 15 of Cycles 1 & 2 and Day 1 of Cycles 4, 6, 9 & 12. The protocol was amended to use a more convenient schedule as follows:




### Study Objectives

**Primary 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

- 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 K/μL *(ANC > 500/μL; platelets > 30 K/μL permitted with BM infiltration)*
- Patients with Richter's Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible.

## Results

### Demographics

| | | |
|---|---|---|
| Evaluable for Safety (n) | 71 | |
| Evaluable for Efficacy† (n) | 58 | |
| Median Age, years (range) | 65 (26 – 86) | |
| Male/Female | 47/24 | |
| Histology | DLBCL | 24 |
| | CLL/SLL | 19 |
| | FL | 19 |
| | MZL | 6 |
| | MCL | 2 |
| | Richter's | 1 |
| ECOG, 0/1/2 | 20/47/4 | |
| Prior Therapy Regimens, median (range) | 3 (1 – 10) | |
| Patients with ≥ 3 Prior Therapies (%) | 61% | |
| Prior RTX Based Therapies, median (range) | 3 (1 – 7) | |
| Refractory to Prior Therapy, n (%) | 41 (58%) | |

†13 Patients not evaluable (9 too early, 2 non-related AE, 1 removed per investigator discretion, 1 for SAE, 1 ineligible)

- Heavily pre-treated population with high-risk features, including 58% refractory to last treatment with multiple previous lines of rituximab (RTX) based therapy

### Safety

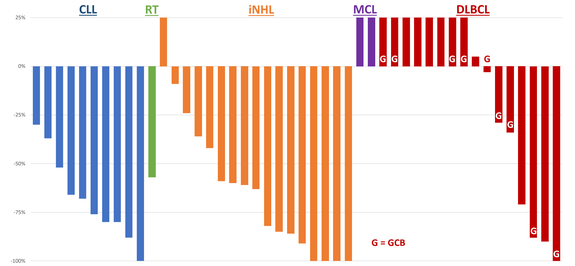
**All Causality AE's Occurring in ≥ 10% of Patients (n = 71)**

| Adverse Event | All Grades | | Grade 3/4 | |
|---|---|---|---|---|
| | N | % | N | % |
| Nausea | 33 | 46% | 1 | 1% |
| Diarrhea | 31 | 44% | 2 | 3% |
| Fatigue | 29 | 41% | 2 | 3% |
| Neutropenia | 21 | 30% | 18 | 25% |
| Infusion related reaction | 18 | 25% | 1 | 1% |
| Vomiting | 17 | 24% | - | - |
| Dyspnea | 14 | 20% | 2 | 3% |
| Back pain | 13 | 18% | - | - |
| Dizziness | 13 | 18% | - | - |
| Pyrexia | 13 | 18% | 2 | 3% |
| Decrease appetite | 12 | 17% | - | - |
| Insomnia | 12 | 17% | - | - |
| Sinusitis | 11 | 15% | 1 | 1% |
| Cough | 10 | 14% | - | - |
| Anemia | 9 | 13% | 1 | 1% |
| Constipation | 8 | 11% | - | - |
| Headache | 8 | 11% | - | - |
| Vitamin D decrease | 8 | 11% | - | - |
| Hypophosphatemia | 7 | 10% | 1 | 1% |
| Peripheral edema | 7 | 10% | 1 | 1% |
| Rash | 7 | 10% | - | - |

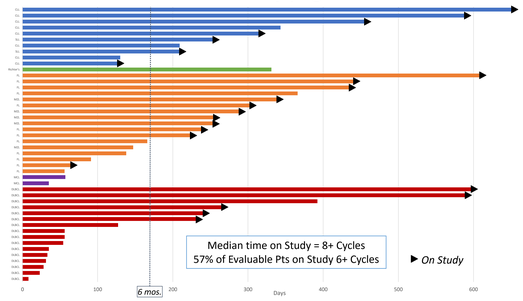
- 6 patients (8%) discontinued due to a TGR-1202 related AE
- Grade 3/4 AST/ALT increase was 3% (8% all grades)
- 7 patients (10%) had their TGR-1202 dose reduced: 2 diarrhea, 2 neutropenia, 1 nausea, 1 fatigue, 1 dizziness
- Colitis has not been reported to date

### Efficacy

**Patients Treated at the "Higher Doses" of TGR-1202**
Best Percent Change from Baseline in Disease Burden




**Duration on Study (Higher Doses)**



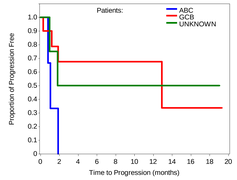

| Type | Patients Exposed to TGR-1202 Higher* Doses | | | | | |
|---|---|---|---|---|---|---|
| | Pts (n) | CR (n) | PR (n) | ORR n (%) | SD (n) | PD (n) |
| CLL/SLL | 10 | 1 | 7 | **8 (80%)** | 2 | - |
| DLBCL | 16 | 3 | 2 | **5 (31%)** | 2 | 9 |
| FL/MZL | 17 | 4 | 8 | **12 (71%)** | 4 | 1 |
| MCL | 2 | - | - | **0** | - | 2 |
| Richter's | 1 | - | 1 | **1 (100%)** | - | - |

*Higher Dose = 1200 original formulation and 600 or > micronized

- Dose-response trend was observed, with "Higher Doses" corresponding to greater clinical activity (N=46 at Higher Doses)
- 75% of CLL patients had high-risk cytogenetics (17p and/or 11q del)
- FL patients were heavily pretreated with 75% of patients having been exposed to ≥ 3 prior therapies (range 1-9)
- 94% of DLBCL patients were refractory to prior regimen with 69% rituximab refractory, including one patient with triple hit lymphoma (BCL2, BCL6, and MYC rearrangements)

### Patients with DLBCL

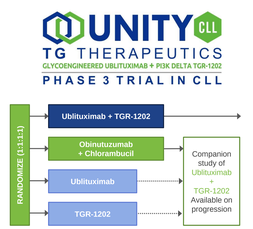
- 16 DLBCL patients evaluable:
- ORR: 33% (3/9) GCB, 0% (0/3) ABC, 50% (2/4) subtype unknown
- Notable activity has been observed particularly in patients with GCB DLBCL
- UNITY-DLBCL randomized study opening soon




### Phase 3 UNITY-CLL Study

**A Phase 3 Study of Ublituximab + TGR-1202**

- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Enrolling patients with treatment naïve and previously treated CLL
- Study Chair: John Gribben, MD, PhD
- Clinical trials.gov #: NCT02612311




## 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
- Discontinuations due to adverse events have been limited (8%) and the only Grade 3/4 AE reported in > 5% of patients was neutropenia
- Safety profile supports multi-drug regimens: triple therapy combinations adding novel agents to ublituximab and TGR-1202 are ongoing (including with ibrutinib, bendamustine, and pembrolizumab) with additional triple therapy studies planned
- Marked activity observed in CLL, iNHL, and DLBCL being explored further in registration directed UNITY-CLL Phase 3 Study and UNITY-DLBCL Study, with additional registration studies planned in the UNITY program


COI: Lunning (TG Therapeutics, Spectrum, BMS, Juno, Gilead, Genentech); Vose (Seattle Genetics); Nastoupil (TG Therapeutics, Celgene, Janssen, Abbvie, Genentech); Burger (Pharmacyclics); Schreeder (TG Therapeutics); Siddiqi (Seattle Genetics, Pharmacyclics/Janssen, Kite); Flowers (Abbvie, Acerta, Gilead, Infinity, Janssen, Takeda, Onyx, Celgene, Pharmacyclics, Spectrum, Genentech, OptumRx, Seattle Genetics); Pauli (TG Therapeutics); Sportelli, Miskin, Weiss (TG Therapeutics, Employment & Equity). Authors not listed had no relevant conflicts of interest to disclose



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