# Phase I/II Study of Pembrolizumab in Combination with Ublituximab (TG-1101) and Umbralisib (TGR-1202) in Patients with Relapsed/Refractory CLL and Richter's Transformation (RT)

Anthony R. Mato, MD[1], Colleen Dorsey, BSN, RN[1], Elizabeth T. Chatburn, BS[1], Jessica Geoghegan[2], Stephen J. Schuster, MD[1], Jakub Svoboda, MD[1], Pamela S. Becker, MD, PhD[2], Elise A. Chong, MD[1], Sunita Dwivedy Nasta, MD[1], Daniel J. Landsburg, MD[1], Kaitlin Kennard, RN, BSN[1], Eline T. Luning Prak, MD, PhD[1], Patricia Tsao, MD, PhD[1], Mitchell E. Hughes, PharmD, BCPS, BCOP[1], Michelle Purdom, PhD, RN[3], Dana Paskalis[3], Peter Sportelli, BS[3], Hari P. Miskin, MS[3], Michael S. Weiss[3] and Mazyar Shadman, MD[2]

*[1]Center for CLL, University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; [2]Fred Hutchinson Cancer Research Center, Seattle, WA; [3]TG Therapeutics, Inc., New York, NY*

Abstract # 3010

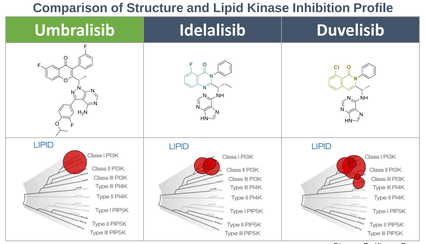
## Background / Rationale

- Data suggests that PD-1 and its ligands PD-L1/PD-L2 mediate immune evasion in CLL. However, recent work (Ding et al, *Blood* 2017) demonstrates that pembrolizumab (pembro) alone is ineffective in patients (pts) with CLL (ORR 0%, median PFS 2.4 months). In 5 pts with relapsed/refractory (r/r) CLL, 3 responded to the combination of ibrutinib / nivolumab (Jain ASH, 2016). A key interaction exists between PI3K signaling and immune checkpoint surveillance by which inhibition of PI3K decreases PD-L1 tumor expression.
- We therefore hypothesized synergistic activity with PD-1 + PI3K blockade. We tested the safety and activity of umbralisib, a next generation highly-specific PI3Kδ inhibitor, in combination with pembro and the glycoengineered anti-CD20 mAb ublituximab in r/r CLL and RT, representing the first reported combination of a PD-1 inhibitor with a PI3Kδ inhibitor.

### Umbralisib

- Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:
  - A differentiated safety profile from other PI3Kδ inhibitors, notably with respect to hepatic toxicity and colitis;
  - A prolonged half-life that enables once-daily dosing;
  - High selectivity to the δ isoform of PI3K; and
  - Also targets casein kinase-1 epsilon (CK-1ε), a protein which may inhibit regulatory T-cell function (Deng et al, 2016)

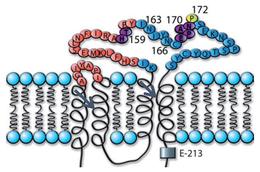
Comparison of Structure and Lipid Kinase Inhibition Profile




DiscoverRx KinomeScan

### 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.
- Ublituximab is currently in Phase 3 development in combination with ibrutinib or umbralisib for patients with chronic lymphocytic leukemia (CLL), and in Phase 2b study for patients with NHL (DLBCL, FL, SLL, MZL).




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

## Study Design

- Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety and efficacy of pembro in combination with umbralisib and ublituximab (UTX) in pts with relapsed or refractory CLL and RT (NCT02535286).
- DLT evaluation period: CLL Cohort - Cycles 3 and 4; RT Cohort- Cycle 1
- Key DLT criteria are events below considered at least possibly related to either pembro, umbralisib or UTX:
  - GR4 anemia, neutropenia, or thrombocytopenia lasting >7 days; GR≥3 febrile neutropenia;
  - GR≥3 non-hematologic tox unresponsive to supportive care except GR≥3 ALT/AST that resolves to ≤GR2 within 7 days;
  - Treatment delay of ≥ 14 days due to unresolved toxicity unresponsive to standard supportive care measure; or
  - Any non-hematologic toxicity of Grade 2 that is dose-limiting in the judgment of the Study Chair.

### Study Objectives

**Primary Objective**

- To determine the safety of umbralisib + UTX + pembro in CLL and RT pts

**Secondary Objectives**

- To evaluate efficacy (ORR, PFS)
- To describe the immunophenotypic and cytokine profiles of B and T cells in subjects

### Key Eligibility Criteria

- CLL or RT pts who have progressed on at least one prior therapy.
  - Amendment in Aug 2017 requires CLL pts to be BTK refractory (progression on or within 6 mos of prior BTK) and RT pts must be chemo-immunotherapy refractory (ie. R-CHOP) or not eligible for high-dose chemotherapy
- No limit on # of prior therapy treatment regimens
- ANC > 750/μL, platelet count > 40,000/μL

## Results

### Demographics

| | |
|---|---|
| Evaluable for Safety, n | 11 |
| Evaluable for Efficacy†, n | 10 |
| Median Age, years (range) | 70 (60 - 81) |
| Male/Female | 7 / 4 |
| ECOG, 0/1 | 6 / 5 |
| Prior Therapy Regimens, median (range) | 2 (1 – 7) |
| 17p del and P53 mutated, n (%) | 2 (18%) |
| Complex Karyotype, n (%) | 5 (45%) |
| Notch 1, ATM mut, SF3B1 mut, n (%) | 4 (36%) |
| Bulky Disease, n (%) | 7 (64%) |
| Prior BTK, n (%) | 7 (64%) |
| Refractory to Prior BTK, n (%) | 6 (55%) |
| Median Follow-up, mos (range) | 7 (1 – 24) |

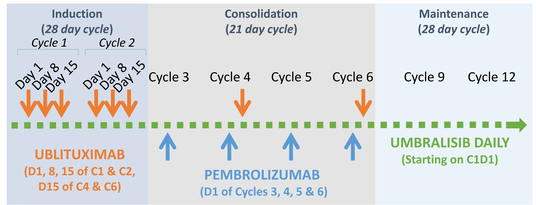
†1 patient too early for response assessment

### Treatment Schedule

**Dose Escalation Schema:**

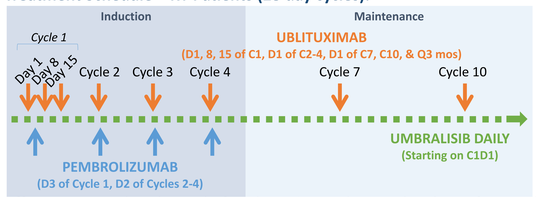
| Cohort | UTX Dose | Umbralisib | Pembro |
|---|---|---|---|
| 1 | 900 mg | 800 mg | 100 mg |
| 2 | 900 mg | 800 mg | 200 mg |

**Treatment Schedule – CLL Patients:**




Efficacy assessed at the end of Cycles 2, 6 & 12. After Month 12, efficacy is assessed per investigator discretion.

**Treatment Schedule – RT Patients (28 day cycles):**




Efficacy assessed at the end of Cycles 2 & 4 and Q3 cycles thereafter until Month 12. After Month 12, efficacy assessed per investigator discretion.

### Safety

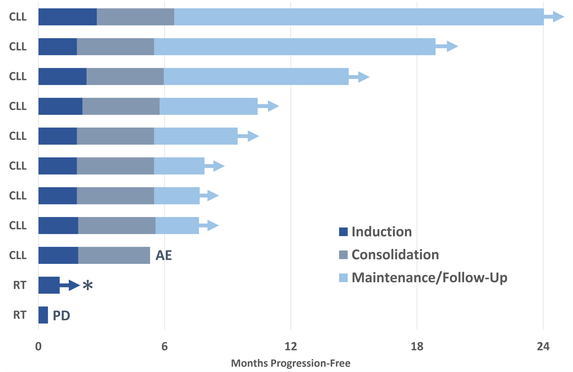
All Causality / All Grade AE's >10% or Grade 3/4 > 5% (N = 11)

| All Causality AE's Cycle 3 through Cycle 6 for CLL and Cycle ≥ 1 for RT | All Grades | | Grade 3/4 | |
|---|---|---|---|---|
| | N | % | N | % |
| Chills | 5 | 45% | - | - |
| Pyrexia | 5 | 45% | - | - |
| Neutropenia | 4 | 36% | 3 | 27% |
| Fatigue | 4 | 36% | 1 | 9% |
| Cough | 4 | 36% | - | - |
| Decreased Appetite | 4 | 36% | - | - |
| Headache | 4 | 36% | - | - |
| Leukopenia | 3 | 27% | 1 | 9% |
| Face Edema | 3 | 27% | - | - |
| Anemia | 2 | 18% | 1 | 9% |
| Nausea | 2 | 18% | 1 | 9% |
| Rash | 2 | 18% | 1 | 9% |
| Arthralgia | 2 | 18% | - | - |
| Blood Alk Phosphate increased | 2 | 18% | - | - |
| Contusion | 2 | 18% | - | - |
| Diarrhea | 2 | 18% | - | - |
| Dry Mouth | 2 | 18% | - | - |
| Hypothyroidism | 2 | 18% | - | - |
| Peripheral Edema | 2 | 18% | - | - |
| Oropharyngeal pain | 2 | 18% | - | - |
| Thrombocytopenia | 2 | 18% | - | - |
| Vomiting | 2 | 18% | - | - |
| AST/ALT increased | 1 | 9% | 1 | 9% |
| Asthenia | 1 | 9% | 1 | 9% |
| Back pain | 1 | 9% | 1 | 9% |
| Blood cholesterol increased | 1 | 9% | 1 | 9% |
| Hypertriglyceridemia | 1 | 9% | 1 | 9% |
| Hypophosphatemia | 1 | 9% | 1 | 9% |

- 5 pts (3 CLL/2 RT) treated at the pembro 100 mg dose and 6 pts (all CLL) at 200 mg dose
- 1 DLT at 200 mg pembro dose (LFT) with no additional DLTs reported; MTD not reached, therefore the primary study endpoint was met
- No events of colitis have been reported. Of the 2 events of diarrhea, 1 each was Grade 1 and Grade 2, with no Grade 3/4 reported
- Pembro was interrupted for 3 pts (Grade 3 Nausea, Grade 2 Pyrexia, Grade 1 Face Edema)
- Umbralisib dose reduced in 2 pts (Arthralgia, Fatigue/Asthenia), discontinued in 2 pts: 1 during Cycles 3 – 6 (Fatigue/Asthenia – same pt above as dose reduced) and 1 patient in cycle 2 (prior to pembro dosing) due to ongoing AST/ALT increase (Grade 3); both patients continued to receive UTX + pembro

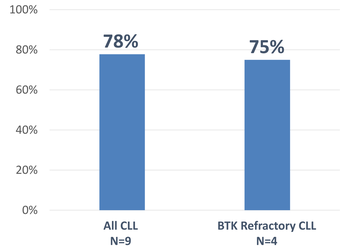
### Efficacy

**Swimmer Plot (N=11)**




*** RT Case**: 62 yo male; 7 prior lines of therapy, including HD chemo, R-CHOP, ASCT, and Ibrutinib (refractory). Initiated study in Oct 2017. As of Dec 2017, no significant AE's or lab abnormalities, with complete resolution of palpable lymphadenopathy. Radiologic assessment pending.

**Overall Response Rate**




- 9 CLL patients evaluable
  - ORR in CLL: 78% (all PR)
  - BTK refractory CLL: 75%
- First RT patient was BTK refractory and initiated on the CLL dosing schedule, and experienced rapid progression. Schedule was later amended specifically for RT to start all 3 agents in C1.
- Responses have been durable, with first patient progression-free now 24+ months

## Conclusions

- Umbralisib + Ublituximab (U2 regimen) + Pembrolizumab is the first study combining a PI3Kδ plus a checkpoint inhibitor in CLL and RT patients
- MTD was not reached therefore primary endpoint was met. One AE of increased LFTs was observed which met criteria for DLT; patient was re-challenged and remains on study treatment with umbralisib maintenance now 15+ months
- Richter's schedule amended to start triple therapy from Day 1 with the first patient through DLT evaluation period with limited AE's and resolution of palpable lymphadenopathy
- Highly active triple combination in BTK refractory patient population warrants further evaluation – enrollment continues specific to this population

Presented at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition, December 9 – 12, 2017, Atlanta, GA