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

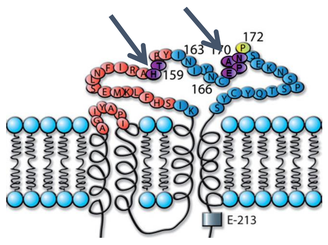
Matthew Lunning, DO[1], Julie Vose, MD[1], Nathan Fowler, MD[2], Loretta Nastoupil, MD[2], Jan A. Burger, MD[2], William G. Wierda, MD[2], Marshall T. Schreeder, MD[3], Tanya Siddiqi, MD[4], Christopher R. Flowers, MD[5], Jonathon B. Cohen, MD[5], Susan Blumel, RN, BSN[1], Myra Miguel, RN[2], Emily K. Pauli, PharmD[3], Kathy Cutter, RN[3], Brianna Phye, BS[4], Peter Sportelli[6], Hari P. Miskin, MS[6], Michael S. Weiss[6], Swaroop Vakkalanka, PhD[7], Srikant Viswanadha, PhD[8] and Susan O'Brien, MD[9]

[1]University of Nebraska Medical Center, Omaha, NE; [2]MD Anderson Cancer Center, Houston, TX; [3]Clearview Cancer Institute, Huntsville, AL; [4]City of Hope National Medical Center, Duarte, CA; [5]Emory University/Winship Cancer Institute, Atlanta, GA; [6]TG Therapeutics, Inc., New York, NY; [7]Rhizen Pharmaceuticals S.A, La Chaux-de-Fonds, Switzerland; [8]Incozen Therapeutics, Hyderabad, India; [9]University of California Irvine, Orange, CA

Background

Ublituximab

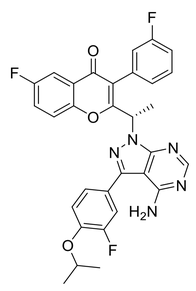
- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab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



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 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 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 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:

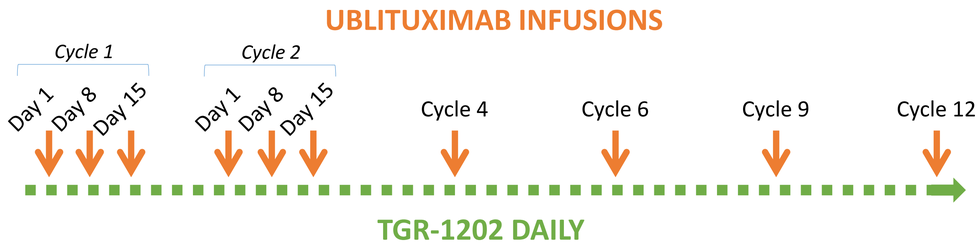
- **Phase I:** 3+3 Dose Escalation evaluating Cycle 1 DLTs (CLL & NHL separately)
- **Phase Ib:** Dose Expansion

Dose Escalation Schema:

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	1200 mg (micronized)
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:



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

- 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 K/μL
- Patients with Richter's Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible

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	17/37/1	
Prior Therapies, median (range)	3 (1 – 9)	
Patients with ≥ 3 Prior Therapies (%)	60%	
Prior RTX Based Tx, median (range)	3 (1 – 7)	
Refractory to Prior Therapy, n (%)	28 (51%)	

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

- Heavily pre-treated patient population with high-risk features, including ~50% refractory to last treatment with multiple previous lines of rituximab (RTX) based therapy

Safety

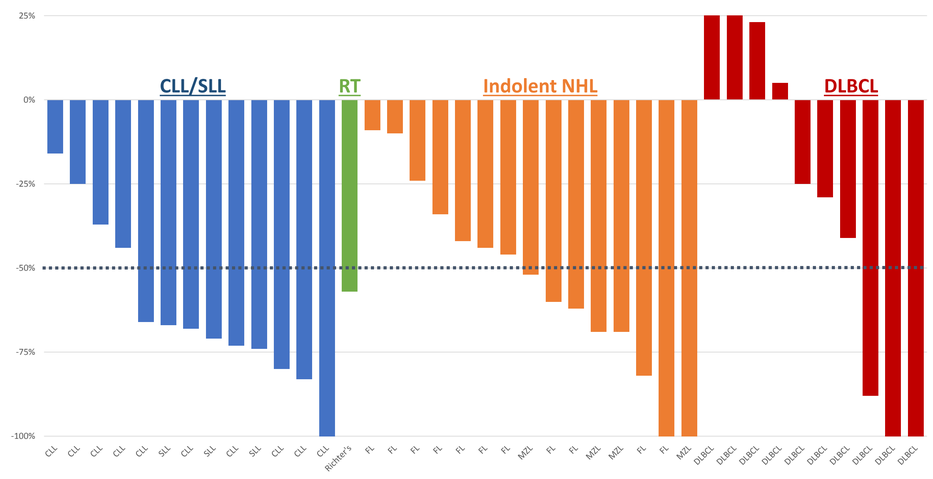
Related AE's Occurring in ≥ 5% of Patients (n = 55)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Infusion Related Reaction	16	29%	1	2%
Neutropenia	15	27%	13	24%
Nausea	15	27%	-	-
Diarrhea	11	20%	1	2%
Fatigue	10	18%	-	-
Vomiting	6	11%	-	-
Abd. Pain/Discomfort	4	7%	-	-
Muscle Cramping	4	7%	-	-
Anemia	3	5%	-	-
Bruising	3	5%	-	-
Hoarseness	3	5%	-	-
Thrombocytopenia	3	5%	-	-

- 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 an 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

Efficacy

Best Percent Change from Baseline in Disease Burden



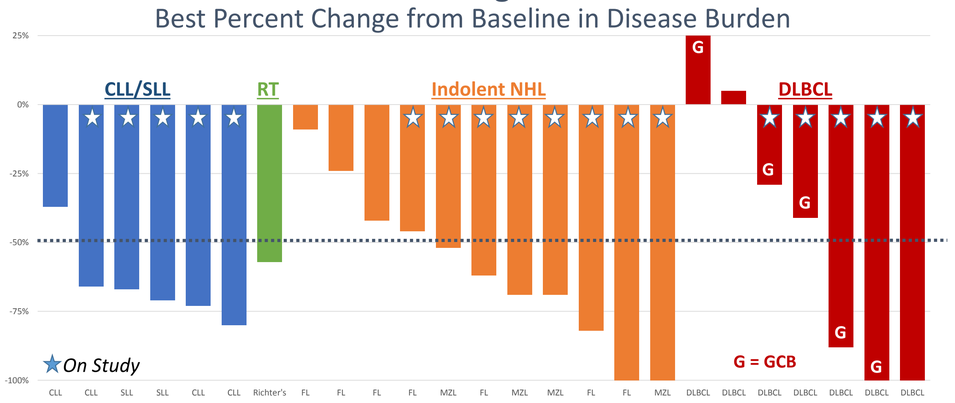
Type	TGR-1202 Higher* Doses						Type	TGR-1202 Lower** Doses					
	Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)		Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	6	-	5	5 (83%)	1	-	CLL/SLL	7	1	3	4 (57%)	3	-
DLBCL	7	2	1	3 (43%)	3	1	DLBCL	3	-	-	-	1	2
FL/MZL	11	2	5	7 (64%)	4	-	FL/MZL	4	-	1	1 (25%)	3	-
Richter's	1	-	1	1 (100%)	-	-	Richter's	-	-	-	-	-	-
Overall	25	4	12	16 (64%)	8	1	Overall	14	1	4	5 (36%)	7	2

*Higher Dose = 1200 original formulation and 600 or > micronized **Lower Dose = 800 original formulation and 400 micronized

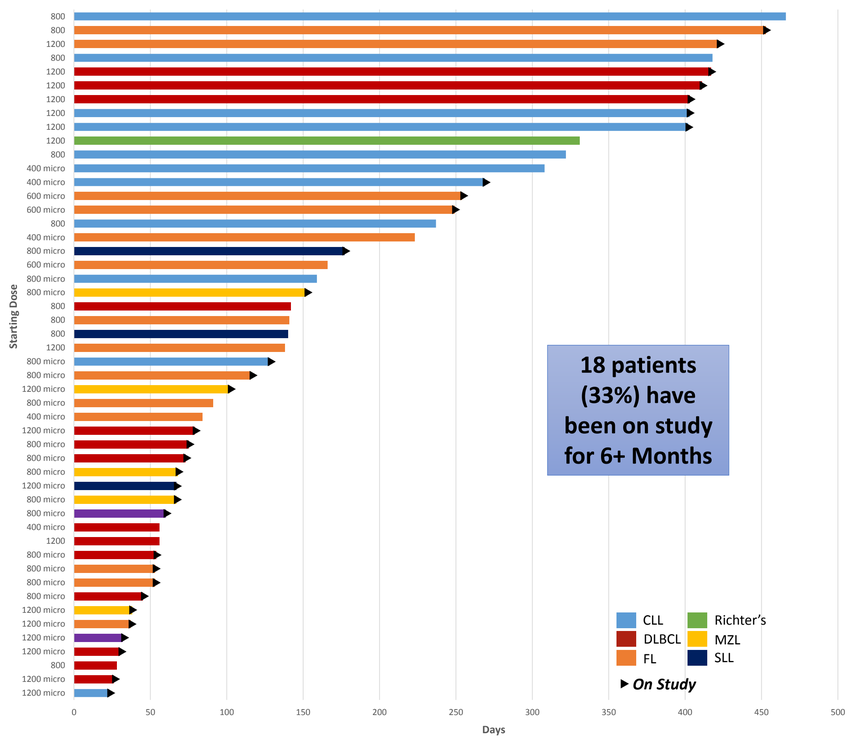
- 70% of CLL patients had high-risk cytogenetics (17p del and/or 11q del)
- FL patients were heavily pretreated with 80% of patients having been exposed to ≥ 3 prior therapies (range 1-9)
- 7/10 DLBCL patients with GCB subtype, including one patient with triple hit lymphoma (BCL2, BCL6, and MYC rearrangements)

Patients Treated at the "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden



Time on Study



18 patients (33%) have been on study for 6+ Months

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 multi-drug combination regimens; triple therapy combinations adding novel agents to ublituximab and TGR-1202 are ongoing (including ibrutinib: ASCO 2015 Abstract #8501 & Lugano ICML 2015 Abstract #106) with additional triple therapy studies planned
- International Phase III studies for the combination are planned

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