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]

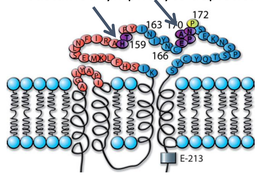
[1]University of Nebraska Medical Center, Omaha, NE; [2]MD Anderson Cancer Center, Houston, TX; [3]Clearview Cancer Institute, Huntsville, AL; [4]City of Hope National Medical Center, Duarte, CA; [5]Emory University/Winship Cancer Institute, Atlanta, GA; [6]TG Therapeutics, Inc., New York, NY; [7]Rhizen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

TG Therapeutics

Background

Ublituximab

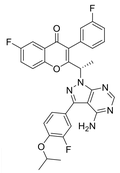
- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab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

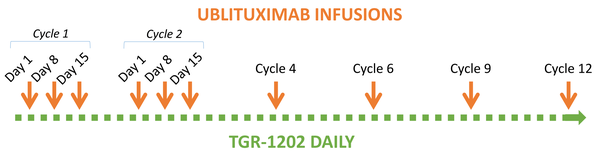
- **Phase I:** 3+3 Dose Escalation evaluating Cycle 1 DLTs (CLL & NHL separately)
- **Phase Ib:** Dose Expansion

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 Therapies, 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

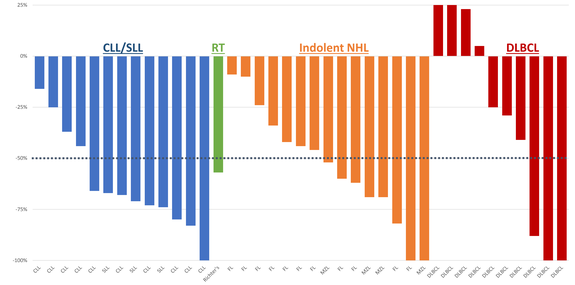
Related AE's Occurring in ≥ 5% of Patients (n = 55)

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%	-	-

- Adverse event profile has been similar across all cohorts to date
- 3 patients (~5%) have come off study due to an adverse event, including, 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

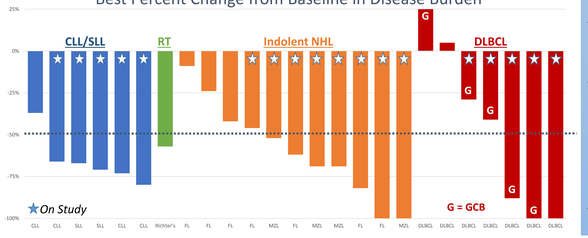


Type	TGR-1202 Higher* Doses						Type	TGR-1202 Lower** Doses					
	Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)		Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	6	-	5	**5 (83%)**	1	-	CLL/SLL	7	1	3	**4 (57%)**	3	-
DLBCL	7	2	1	**3 (43%)**	3	1	DLBCL	3	-	-	**-**	1	2
FL/MZL	11	2	5	**7 (64%)**	4	-	FL/MZL	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

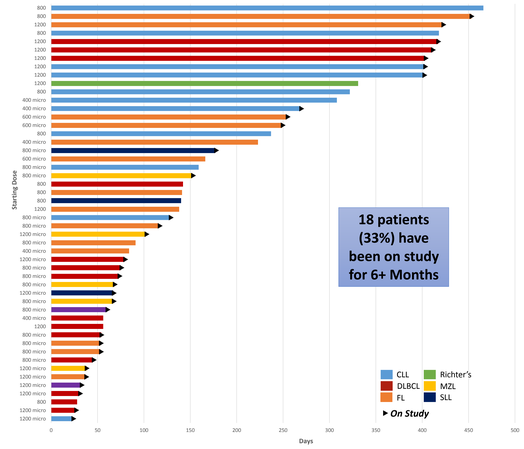
*Higher Dose = 1200 original formulation and 600 or > micronized **Lower Dose = 800 original formulation and 400 micronized

- 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



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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