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 <a>TGR-1202 (TGR) is a ne all variants of FcyRIIIa 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 : Amino acids essential for rituximab, but not ofatumumab binding **Purple**: Core amino acids of ublituximab epitope

TGR-1202

- PI3Kδ is highly express and is often upregulate
- a unique structure and PI3Kδ inhibitors in deve
- ✤A prolonged halfonce-daily dosing
- ΡΙ3Κδ other to hepatic toxicity observed to date

Fold-selectivity					
Isoform	ΡΙ3Κα	ΡΙЗΚβ	ΡΙ3Κγ	ΡΙ3Κδ	
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 ma. 1000 ma. and 1200 ma 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:



Results

sed in cells of hematopoietic origin
ed in lymphoid malignancies
ext generation PI3Kδ inhibitor, with
d activity profile distinct from other
elopment, including:
f-life that enables

✤A differentiated safety profile from development, notably with respect and colitis



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

- non-Hodgkin Confirmed B-cell 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
- **\therefore** ECOG performance status ≤ 2
- Adequate organ system function: ANC \geq 750/µL; platelets \geq 50 K/µL $(ANC > 500/\mu L; platelets > 30 K/\mu L$ permitted with BM infiltration)
- Patients with **Richter's** Transformation, or refractory to prior PI3KS inhibitors or prior BTK inhibitors are eligible.

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

[†]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

All Causality AE's Occurring in \geq 10% of Patients (n = 71) All Grades Grade 3/4 Adverse Event N % N % Nausea 33 46% 1 1% Diarrhea 31 44% 2 3% Patigue 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% - - Pyrexia 13 18% 2 3%	Safety					
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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% 2 3%	Diarrhea	31	44%	2	3%	
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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%	Neutropenia	21	30%	18	25%	
Vomiting 17 24% - - Dyspnea 14 20% 2 3% Back pain 13 18% - - Dizziness 13 18% - - Pyrexia 13 18% 2 3%	Infusion related reaction	18	25%	1	1%	
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Back pain 13 18% - - Dizziness 13 18% - - Pyrexia 13 18% 2 3%	Dyspnea	14	20%	2	3%	
Dizziness 13 18% - - Pyrexia 13 18% 2 3%	Back pain	13	18%	-	-	
Pyrexia 13 18% 2 3%	Dizziness	13	18%	-	-	
	Pyrexia	13	18%	2	3%	
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Insomnia 12 17%	Insomnia	12	17%	-	-	
Sinusitis 11 15% 1 1%	Sinusitis	11	15%	1	1%	
Cough 10 14%	Cough	10	14%	-	-	
Anemia 9 13% 1 1%	Anemia	9	13%	1	1%	
Constipation811%	Constipation	8	11%	-	-	
Headache 8 11% - -	Headache	8	11%	-	-	
Vitamin D decrease 8 11%	Vitamin D decrease	8	11%	-	-	
Hypophosphatemia 7 10% 1 1%	Hypophosphatemia	7	10%	1	1%	
Peripheral edema710%11%	Peripheral edema	7	10%	1	1%	
Rash 7 10%	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 Exposed to TGR-1202 Higher* D					
Туре	Pts	CR	PR	ORR		
	(n)	(n)	(n)	n (%)		
CLL/SLL	10	1	7	8 (80%)		
DLBCL	16	3	2	5 (31%)		
FL/MZL	17	4	8	12 (71%)		
MCL	2	-	-	0		
Richter's	1	-	1	1 (100%)		
	*Higher Dose = 120	00 original	formulatio	n and 600 or > micronized		

Phase 3 UNITY-CLL Study

- Design, Endpoints, and Statistics agreed to via Special Protocol
- Enrolling patients with treatment
- Study Chair: John Gribben, MD, PhD
- Clinical trials.gov #: NCT02612311



~	Ublituximab + TGR-1	202
E (1:1:1:1	Obinutuzumab + Chlorambucil	
ANDOMIZ	Ublituximab	
R	TGR-1202	

study of Ublituximat

+ **TGR-120**2

Available or

progression

COI: Lunning (TG Therapeutics, Spectrum, BMS, Juno, Gilead, Genentech); Vose (Seattle Genetics); Nastoupil (TG erapeutics, Celgene, Janssen, Abbvie, Genentech); Burger (Pharmacyclics); Schreeder (TG Therapeutics); Siddigi (Seattle Genetics, Pharmacyclics/Jannsen, Kite); Flowers (Abbvie, Acerta, Gilead, Infinity, Jannsen, 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