A Phase I Trial Of Ublituximab, A Novel Glycoengineered Anti-CD20 mAb, In Combination With TGR-1202, A Next Generation PI3Kδ Inhibitor, In Patients With Chronic Lymphocytic Leukemia And Non-Hodgkin's Lymphoma

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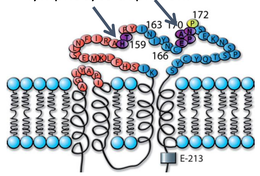
Background

Ublituximab

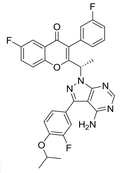
- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab 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 novel, next generation PI3Kδ inhibitor, with a unique structure which contributes to:
  - Extended half-life and accumulation that enables once-daily dosing
  - Differentiated safety profile from other PI3Kδ inhibitors in development, notably absent of hepatotoxicity 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:

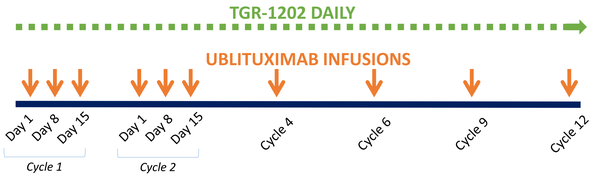
- **Phase I:** 3+3 Dose Escalation evaluating Cycle 1 DLTs for CLL & NHL separately
- **Phase Ib:** Dose confirmation

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)

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 lymphoproliferative disorders
- 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)	21	
Evaluable for Efficacy† (n)	15	
Median Age, years (range)	64 (35 – 82)	
Male/Female	12/9	
Histology	CLL/SLL	8
	Richter's	1
	FL	5
	DLBCL	7
ECOG, 0/1/2	8/13/0	
Prior Therapies, median (range)	3 (1 – 9)	
Patients with ≥ 3 Prior Therapies (%)	57%	
Prior RTX Based Therapies, median (range)	2 (1 – 7)	
Refractory to Prior Therapy, n (%)	8 (38%)	

†6 Patients Too Early To Evaluate

- Enrollment is ongoing, currently in dose-escalation Cohort 3

Safety

Related AE's Occurring in ≥ 2 Patients (n = 21)

Adverse Event	Total AE's All Grades n (%)	UTX Related G 1/2 n	UTX Related G 3/4 n	TGR-1202 Related G 1/2 n	TGR-1202 Related G 3/4 n
Infusion Related Reaction (IRR)	10 (48%)	9	1	0	0
Neutropenia†	8 (38%)	3	4	3	5
Diarrhea	6 (29%)	0	0	6	0
Nausea†	6 (29%)	2	0	6	2
Hoarseness†	2 (10%)	1	0	2	0
Muscle Aches	2 (10%)	0	0	2	0
Fatigue†	2 (10%)	1	0	2	0

†Causality of some events was attributed to both UTX and TGR-1202

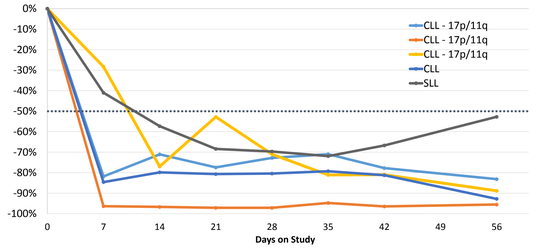
- Adverse event profile has been similar across all cohorts to date
- No patients had their UTX or TGR dose reduced
- No drug related increases in ALT/AST observed to date
- IRR and Neutropenia were managed through dose delays
  - 1 neutropenia related dose delay met the criteria for a DLT in a CLL patient at UTX 600 mg + TGR 800 mg, necessitating enrollment of additional patients into this cohort
- 1 patient came off study (without progressive disease) due to Gr. 1 itching, assessed as possibly related to TGR-1202, no other patients discontinued due to an adverse event

Efficacy in Chronic Lymphocytic Leukemia

Cytogenetics	Pts (n)	PR n (%)	SD n (%)	ORR n (%)	PD n (%)
High Risk	3	2 (67%)	1 (33%)	2 (67%)	-
Normal	2	2 (100%)	-	2 (100%)	-
Total	**5**	**4 (80%)**	**1 (20%)**	**4 (80%)**	**-**

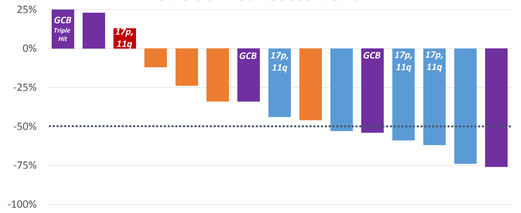
- High Risk = Patients with both 17p del and 11q del
- 80% (4/5) of patients achieved a PR per Hallek/Cheson criteria, with remaining patient with 17p/11q del CLL achieving a 44% nodal reduction at 1st response assessment
- 100% (5/5) of CLL/SLL patients achieved a >50% reduction in ALC by first efficacy assessment

Percent Change in ALC from Baseline



Overall Efficacy

Percent Change from Baseline in Nodal Size at First Assessment



Type	Pts (n)	Median Prior Rx	PR n (%)	ORR n (%)	PD (n)	% pts ≥ SD for 12 wks
CLL/SLL	5	2 (1 – 3)	4 (80%)	**4 (80%)**	-	5 (100%)
Richter's	1	1	-	-	-	1 (100%)
FL	4	6 (3 – 8)	-	-	-	4 (100%)
DLBCL	5	3 (1 – 6)	2 (40%)	**2 (40%)**	1	4 (80%)
Total	**15**	**3 (1 – 8)**	**6 (40%)**	**6 (40%)**	**1**	**14 (93%)**

Heavily Pre-Treated Population

	# of Priors	Prior Therapies	Rel/Ref	Best Response
CLL*	2	FCR, Chlorambucil	REL	PR
CLL*	1	FCR	REL	SD
CLL*	1	FCR	REL	PR
CLL	2	FCR, RTX, CC-292	REL	PR
SLL	3	R-CHOP, R-Benda, RTX	REL	PR
Richter's	1	FCR	REL	SD
FL	8	RTX, RTX+CHL(x 2), Zevalin, R-CHOP, R-Benda (x 2), Prednisone	**REF**	SD
FL	6	CHL, RTX (x 2), R-CVP, Zevalin, R-Benda	REL	SD
FL	5	RTX, R-CHOP, R-ICE, R-EPOCH, SCT	**REF**	SD
FL	3	RTX (x 2), R-ICE	REL	SD
DLBCL	1	R-CHOP	REL	SD
DLBCL†	2	R-CHOP, R-ICE	**REF**	PD
DLBCL†	3	RTX, R-CHOP, R-Gem/Oxaliplatin	**REF**	PR
DLBCL†	6	RTX (x 2), R-CHOP, Benda (x 2), ICE	**REF**	SD
DLBCL	2	R-CHOP, R-Benda	REL	PR

- Patients were heavily refractory, and included high risk subsets:
  - *3/5 CLL patients high risk cytogenetics (both 17p del and 11q del)
  - †3/5 DLBCL patients with GCB subtype, including one patient with triple hit lymphoma (BCL2, BCL6, and MYC rearrangements)

Conclusions

- Preliminary data suggests ublituximab in combination with TGR-1202 is well tolerated and highly active in a heavily pre-treated population of patients with relapsed or refractory NHL and CLL
- No drug related increases in ALT/AST have been observed to date among patients treated with ublituximab + TGR-1202
- Lymphocytosis generally observed in CLL patients treated with TGR-1202 monotherapy appears to be mitigated by the addition of ublituximab, with all CLL patients achieving a > 50% reduction in ALC by first response assessment, leading to 80% of CLL patients (4/5) achieving a PR at first response assessment, despite 3/5 patients having high risk cytogenetics (17p *and* 11q del)
- Additional studies are ongoing with ublituximab and TGR-1202 in combination with novel agents, with Phase III studies in development

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