Abstract # 8524

A PHASE I TRIAL OF UBLITUXIMAB (TG-1101), A NOVEL ANTI-CD20 MONOCLONAL ANTIBODY (MAB) IN B-CELL LYMPHOMA PATIENTS WITH PRIOR EXPOSURE TO RITUXIMAB

TG Therapeutics

Owen A. O'Connor[1], Changchun Deng[1], Jennifer E. Amengual[1], Mazen Y. Khalil[2], Marshall T. Schreeder[3], Daruka Mahadevan[4], Petros Nikolinakos[5], Ahmed Sawas[1], Jasmine M. Zain[1], Molly Patterson[1], Amber Moon[2], Kathy Cutter[3], Emily K. Pauli[3], Marnie Brotherton[4], Jamie Hodgson[5], Christen N. Cooper[5], Michelle A. Mackenzie[6], Peter Sportelli[7], Hari P. Miskin[7] and Charles M. Farber[6]

[1]Columbia University Medical Center /New York Presbyterian Hospital, New York, NY; [2]Clopton Clinic, Jonesboro, AR; [3]Clearview Cancer Institute, Huntsville, AL; [4]The West Clinic, Memphis, TN; [5]University Cancer and Blood Center, Athens, GA; [6]Hematology-Oncology Associates of Northern NJ, Morristown, NJ; [7]TG Therapeutics, Inc., New York, NY

INTRODUCTION

Ublituximab is a novel chimeric mAb targeting a unique epitope (Figure 1) on the CD20 antigen. Ublituximab has been glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, and thus demonstrates greater ADCC activity than rituximab (RTX) *in-vitro* (Le Garff-Tavernier, 2011), specifically in low-CD20 tumors (ASH 2011). In non-Hodgkin's lymphoma *in vivo* models, ublituximab also displayed greater antitumor activity than rituximab (ASH 2011). A completed Phase I trial with ublituximab used as a single agent in patients with relapsed/refractory CLL reported a response rate of 45% (EHA 2013). Herein we report on the Phase I dose-escalation of ublituximab in patients with rituximab (RTX) relapsed/refractory B-cell lymphoma.

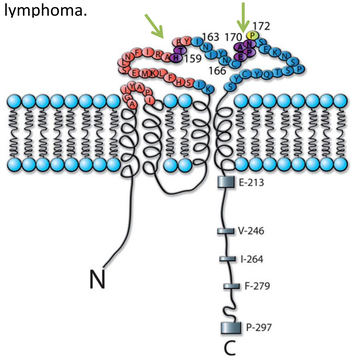


Figure 1:
Ublituximab epitope recognition differs from both rituximab and ofatumumab

RED: Amino acids contributing to ofatumumab binding

YELLOW: Amino acids essential for rituximab, but not ofatumumab binding

PURPLE: Core amino acids of ublituximab epitope

Source: Adapted from Ruuls et al 2008

STUDY DESIGN

Study TG-1101-101 (NCT01647971) is a Phase I/II trial currently closed to enrollment with patients ongoing. The study endpoints are as follows:

- **Primary**: Safety and Maximum Tolerated Dose (MTD)
- **Secondary**: Overall response rate (CR + PR), Pharmacokinetics (PK) and PFS

Phase I Cohort Design: 3 + 3 dose-escalation design of 4 cohorts

Cohort 1	Cohort 2	Cohort 3	Cohort 4
450 mg	600 mg	900 mg	1200 mg

Cohort Expansion: NHL (900 & 1200 mg) / CLL (600 & 900 mg)
Induction NHL: ublituximab administered weekly x 4 in Cycle 1 (cycle = 28 days)
Induction CLL: ublituximab administered Days 1, 8, 15 of Cycles 1 & 2
Maintenance: monthly infusions for patients with SD or better response starting Cycle 3, and infusions every 3 months starting Cycle 6

Key Inclusion Criteria

- Relapsed or refractory to prior RTX-based regimen (refractory = progressing on or within 6 months of RTX: relapsed = progressing > 6 months after RTX)
- B-cell Lymphoma (NHL & CLL) with measurable / evaluable disease
- ECOG ≤ 2, No Hepatitis B/C or HIV
- Adequate organ/marrow function with baseline ANC > 1,000 cells/μL and platelets > 50k/μL

RESULTS

Patient Demographics

Evaluable for Safety:	35	18 Female / 17 Male
Evaluable for Efficacy†:	30	**Median Age:** 66 (range 45 – 88)

Type of B-cell Lymphoma (n)		
Indolent NHL (20)	**CLL/SLL (8)**	**Aggressive NHL (7)**
Follicular (12)	CLL (8)	Mantle Cell (5)
Marginal Zone (8)		DLBCL (2)

Demographic	All Pts	iNHL	CLL	aNHL
ECOG 0/1/2 (n)	13 / 20 / 2	9 / 11 / 0	2 / 5 / 1	2 / 4 / 1
Median Prior Therapies: n (range)	3 (1 – 9)	3 (1 – 6)	3 (1 – 6)	2 (1 – 9)
≥ 4 Prior Therapies: n (%)	12 (34)	7 (35)	3 (38)	2 (29)
≥ 2 Prior Rituximab Regimens: n (%)	25 (71)	15 (75)	5 (63)	5 (71)
Refractory to Prior Treatment: n (%)	15 (43)	11 (55)	2 (25)	2 (29)
Refractory to Prior Rituximab: n (%)	15 (43)	12 (60)	1 (13)	2 (29)

†5 pts not evaluable: 4 patients off study prior to first efficacy assessment (2 for non-related AE, 1 for SAE, 1 withdrew consent), 1 too early to evaluate

Safety

Among the 12 patients treated in the dose-escalation Phase I and the 23 patients in the expansion cohorts to date, no DLTs were observed, and no MTD was reached. Adverse events (CTCAE v 4.0) are summarized as follows:

All Patients (n = 35)		
AE	**All Grades n (%)**	**Grade 3/4 n (%)**
Infusion Related Reaction*	10 (29%)	0
Fatigue	5 (14%)	1 (3%)
Diarrhea	4 (11%)	0
Pain (General)	4 (11%)	0
Dysgeusia	3 (9%)	0
Bilirubin Increase	2 (6%)	0
Pruritus	2 (6%)	0

**IRR also includes chills, itching, dyspnea, throat irritation*

At Least Possibly Related AE's Occurring in > 5% of Pts (n=35)

4 CLL and 6 NHL pts had IRR's
- 6 pts had IRR's on the Day 1 infusion only
- IRR's were manageable with infusion interruptions only and recovered without sequelae
- Patients received all scheduled infusions

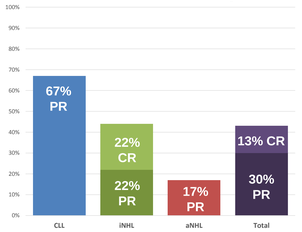
Infusion times decreased to an average of 90 minutes for the 4th and all subsequent infusions

Lab Abnormalities at Least Possibly Related

AE	CLL (n=8)		NHL (n=27)	
	Grade 1/2 n	Grade 3/4 n	Grade 1/2 n	Grade 3/4 n
Neutropenia	1	3	0	0
Thrombocytopenia	1	1	0	0
Anemia	0	0	0	1

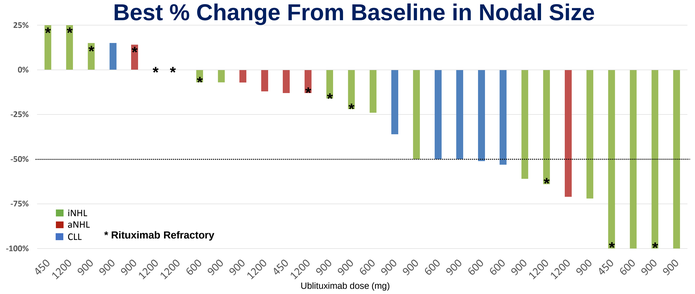
Efficacy

Overall Response by Lymphoma Subtype



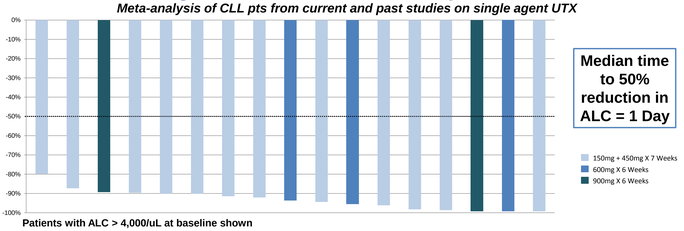
Type	Pts (n)	CR n (%)	PR n (%)	ORR n (%)
CLL	6	-	4 (67)	**4 (67)**
FL	12	2 (17)	2 (17)	**4 (33)**
MZL	6	2 (33)	2 (33)	**4 (67)**
MCL	5	-	-	**-**
DLBCL	1	-	1 (100)	**1 (100)**
Total	**30**	**4 (13)**	**9 (30)**	**13 (43)**

Best % Change From Baseline in Nodal Size

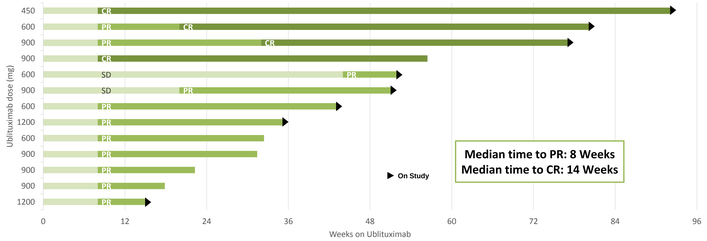


% Change in ALC at First Efficacy Assessment

Meta-analysis of CLL pts from current and past studies on single agent UTX

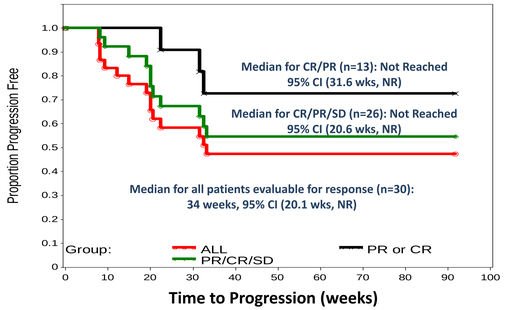


Evolving Responses for Patients on Maintenance Ublituximab



Progression Free Survival Analysis

Median Progression Free Survival (PFS) for patients who achieved ≥ Stable Disease (SD) as best response has not been reached, with median PFS for all study patients at 34 weeks. 14/30 patients have not progressed with 12 patients remaining on study treatment (longest patient on study treatment is 21+ months).



CONCLUSION

- **Ublituximab is well tolerated even at the highest dose cohort levels tested with no DLT's observed. Day 1 IRR's are the most frequent AE (G 1/2 only) and occurred more often in CLL patients. G 3/4 events have been limited. No MTD was reached**
- **Infusion times decreased to an average of 90 minutes for the 4th and subsequent infusions**
- **Significant single agent activity observed in patients with rituximab relapsed/refractory CLL and indolent NHL patients**
- **Rapid and profound circulating lymphocyte depletion in CLL patients with median time to a peripheral response (>50% reduction) of 1 day**
- **Patient responses have been durable (patients in response >1 year on single agent ublituximab) with some having an improvement in response over time with continued ublituximab maintenance**
- **Safety profile of ublituximab supports combination therapy, with studies of ublituximab in combination with PI3K delta and BTK inhibitors ongoing**
- **Phase III studies in B-cell malignancies are currently in development**