UBLITUXIMAB (TG-1101), A NOVEL ANTI-CD20 MONOCLONAL ANTIBODY FOR RITUXIMAB RELAPSED/REFRACTORY B-CELL MALIGNANCIES

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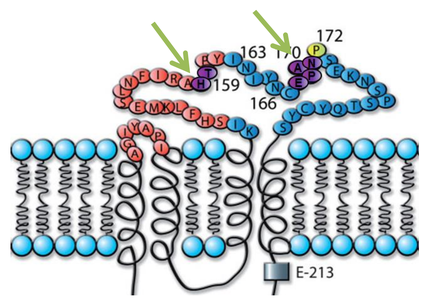
BACKGROUND

Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen. Ublituximab has been glycoengineered to enhance affinity for all variants of FcγRIIIa receptors and therefore demonstrates greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab, particularly against tumor cells that express low CD20 levels. A completed Phase I trial of single agent ublituximab in patients with relapsed/refractory CLL reported a response rate of 45% (EHA 2013). Two clinical studies (Phase I/II and Phase I) were completed with ublituximab in patients with rituximab relapsed and refractory B-cell lymphoma (NHL and CLL). TG-1101-101 is a study of single agent ublituximab in this patient population, while TG-1101-102 is a study of ublituximab administered in combination with lenalidomide, an immunomodulating agent that has displayed activity in lymphoma and has been shown to enhance the ADCC activity of anti-CD20 antibodies. Herein we report on the clinical results of both studies.

UBLITUXIMAB



Ublituximab, a next generation anti-CD20 antibody currently in clinical development, is characterized by a specific glycosylation pattern containing a high percentage of non-fucosylated antibody molecules at the Fc site. This specific pattern of glycosylation increases the affinity of antibodies for human FcγRIIIa (CD16), resulting in an increased antibody dependent cell-mediated cytotoxicity (ADCC) by human FcγRIIIa-expressing effector cells.

Red: Amino acids contributing to ofatumumab binding
Yellow: Amino acids essential for rituximab, but not ofatumumab binding
Purple: Core amino acids of ublituximab epitope

TG-1101-101: Single Agent Ublituximab in Rituximab Relapsed and Refractory NHL and CLL

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**: ORR (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 wkly 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 = PD on or within 6 months of RTX: relapsed = PD > 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.

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

RESULTS

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:

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

All Patients (n = 35)		
AE	All Grades n (%)	Grade 3/4 n (%)
Infusion 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*

4 CLL / 6 NHL pts had IRR's
- 6 pts had IRR's on the Day 1 infusion only
- IRR's were manageable with infusion interruptions and recovered w/o sequelae
- Patients received all scheduled infusions

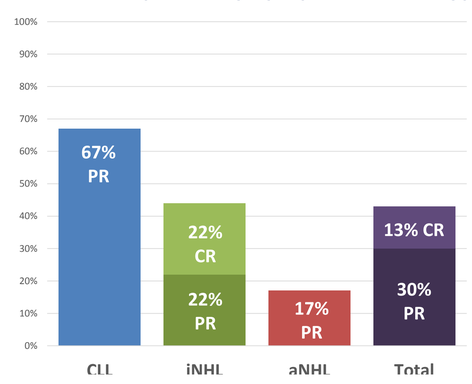
Infusion times decreased to an average of 90 minutes for the 4th and all subsequent infusions

Lab Abnormalities at Least Possibly Related

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

Efficacy

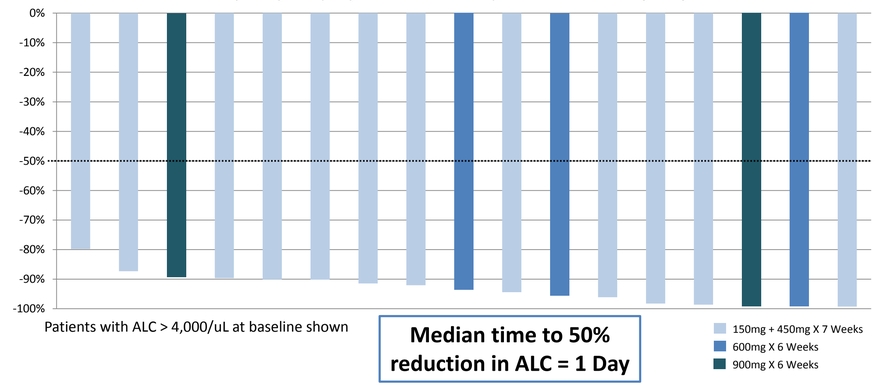
Overall Response by Lymphoma Sub-type



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)**

% Change in ALC at First Efficacy Assessment

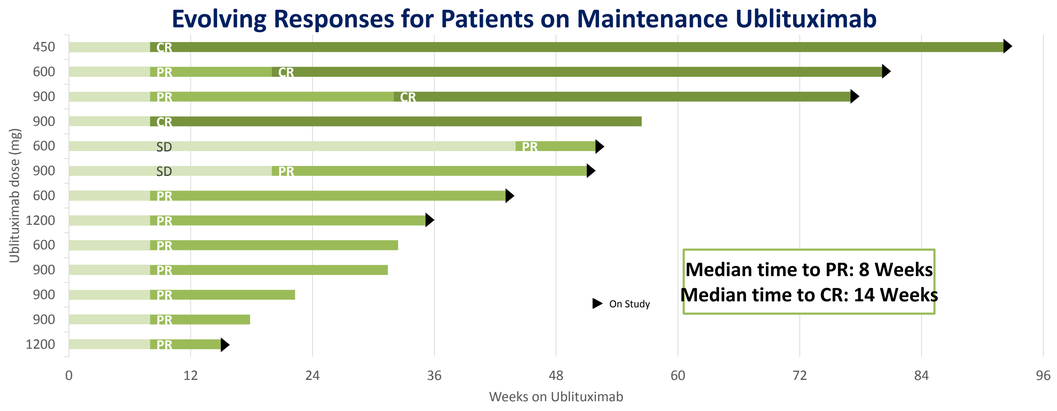
Meta-analysis of CLL pts from current and past studies on single agent UTX



Patients with ALC > 4,000/uL at baseline shown

Median time to 50% reduction in ALC = 1 Day

Evolving Responses for Patients on Maintenance Ublituximab



Median time to PR: 8 Weeks
Median time to CR: 14 Weeks

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).

CONCLUSIONS TG-1101-101

- **Ublituximab is well tolerated even at the highest dose levels tested, with no DLT's observed and no MTD reached. Safety profile supports combination therapy.**
- **Day 1 IRR's are the most frequent AE (G 1/2 only). G 3/4 events have been limited. Infusion times declined 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 iNHL**
- **Rapid and profound lymphocyte depletion observed in CLL patients (median time to >50% reduction of 1 day)**
- **Responses have been durable (patients in response >1 year on single agent ublituximab) with some improving in response over time with continued ublituximab maintenance**
- **Studies of ublituximab in combination with PI3K delta and BTK inhibitors are ongoing. Phase III studies in B-cell malignancies are currently in development**

TG-1101-102: Ublituximab + Lenalidomide in Rituximab Relapsed and Refractory NHL and CLL

STUDY DESIGN

Key Inclusion Criteria

- Relapsed or Refractory B-cell NHL or CLL/SLL following at least one prior line of anti-CD20 therapy
- Measurable / evaluable disease; ECOG ≤ 2
- Adequate organ / marrow function with baseline ANC ≥ 1,000 cells/μL and platelets ≥ 50k/μL.

Dose Escalation Schema

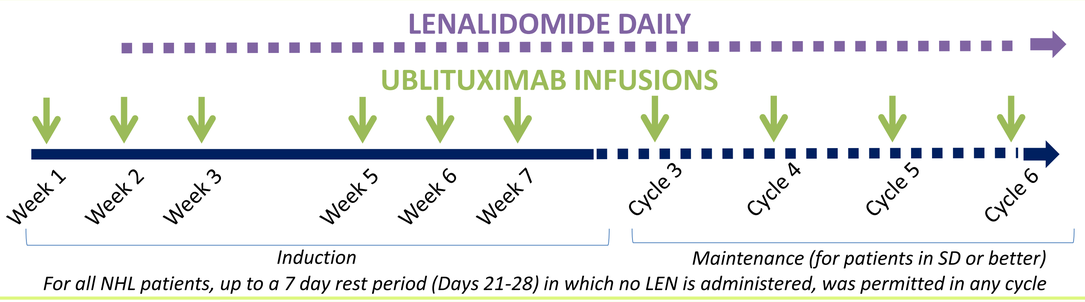
Cohort	Patients	Ublituximab	Lenalidomide
1	3 – 6	450 mg	10 mg
2	3 – 6	450 mg	15 mg
3	3 – 6	600 mg	10 mg*
4	3 – 6	900 mg	10 mg*

**Lenalidomide dose titrated per patient tolerability*

- As CLL and NHL patients tolerability vary, the protocol was amended during Cohort 2 to allow a revised administration schedule for lenalidomide in which patients would start at 10 mg QD, and titrate dose in 5 mg increments per cycle based on individual tolerability.

Dosing Schedule

Ublituximab administered on Days 1, 8, and 15 of Cycles 1 & 2 (Cycle = 28 days) during the induction period, followed by maintenance infusions for patients achieving stable disease or better on Day 1 of Cycles 3-6, and every 3 months thereafter. Lenalidomide started Week 2 and administered daily. Response assessments occurred at Week 8, and every 12 weeks thereafter.



For all NHL patients, up to a 7 day rest period (Days 21-28) in which no LEN is administered, was permitted in any cycle

Demographics

Evaluable for Safety:	10	**7 Male / 3 Female**	
Evaluable for Efficacy†:	9	**Median Age:**	66 (range 47 – 76)
ECOG 0/1:	2/8	**Median Prior Therapies:**	3 (range 3-6)
Refractory to Prior Tx: 90%		**Rituximab Refractory: 70%**	
Prior R-Benda: 90%	**Prior BTK/PI3K: 30%**	**≥ 2 Prior Rituxan: 100%**	
Lymphoma Subtype			
CLL/SLL: 5	**Follicular:** 1	**Mantle Cell:** 3	**Burkitt's:** 1

†1 patient not evaluable due to non-related SAE

Safety

Related AE's Occurring in ≥ 2 patients (n = 10)

Adverse Event	Total AE's All Grades	UTX Related G 1/2 n	UTX Related G 3/4 n	LEN Related G 1/2 n	LEN Related G 3/4 n
Infusion Reaction	**6**	*5*	*1*	*0*	*0*
Neutropenia	**5**	*0*	*2†*	*1*	*4†*
Diarrhea	**4**	*0*	*0*	*4*	*0*
Constipation	**3**	*0*	*0*	*3*	*0*
Fatigue	**3**	*2†*	*0*	*3†*	*0*
Nausea	**4**	*1*	*0*	*3*	*0*
Anemia	**2**	*0*	*1†*	*1*	*1†*
Hoarseness	**2**	*1*	*0*	*1*	*0*
Rash	**2**	*0*	*0*	*2*	*0*
Tumor Flare	**2**	*0*	*0*	*2*	*0*

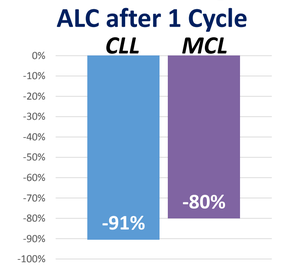
†Causality of some events were attributed to both UTX and LEN

- 3 patients had their LEN dose reduced or withdrawn (2 neutropenia, 1 nausea); 1 had their UTX dose reduced due to neutropenia.
- Although no DLT's were reported, dose interruptions or reductions occurred in 6/10 patients while on study.

Efficacy

- 2/9 patients achieved a PR while 2 additional patients (CLL) achieved SD > 6 months.
  - 1 PR in a MCL patient refractory to idelalisib and rituximab
  - 1 PR in a patient with rituximab refractory FL.
- Lymphocyte depletion was rapid and profound with > 90% reduction in CLL and 80% reduction in MCL after 1 cycle (3 infusions of UTX)

Median % Change in ALC after 1 Cycle



CONCLUSIONS TG-1101-102

- **The combination of UTX+LEN was explored in a heavily pre-treated pt. population (70% RTX refractory, 30% BTK/PI3Kδ refractory)**
- **The majority of AE's observed were G 1/2 in severity and managed by dose reductions and delays, and a titrating regimen for LEN**
- **A >90% median reduction in ALC was observed in heavily refractory patients with CLL following 1 Cycle of therapy**
- **Responses were observed in patients refractory to rituximab and the PI3Kδ inhibitor, idelalisib**

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