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

TG Therapeutics

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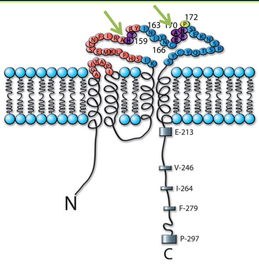
BACKGROUND

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% (ASH 2011, EHA 2013). Two Phase I/II studies are currently ongoing with ublituximab in patients with rituximab relapsed and refractory B-cell lymphoma. 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 Phase I, dose-escalation portion of both of these ongoing 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 Lymphoma

STUDY DESIGN

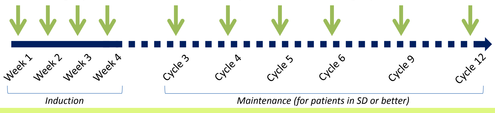
Study TG-1101-101 (Clinical Identifier NCT01647971) is a Phase I/II trial currently ongoing with the following endpoints:

- **Primary**: Safety and Maximum Tolerated Dose (MTD)
- **Secondary**: Efficacy as defined by overall response rate (CR + PR), Pharmacokinetic (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

- ***Induction***: ublituximab administered weekly x 4 in Cycle 1 (cycle = 28 days)
- ***Maintenance***: monthly infusions for patients with SD or better response starting Cycle 3, and infusions every 3 months starting Cycle 6



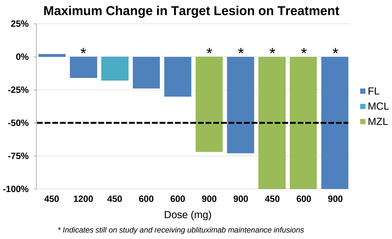
Key Inclusion Criteria

- 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 Non-Hodgkin's Lymphoma 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

Efficacy

- 10 of 12 patients are evaluable for efficacy (2 patients are too early for response assessment), of which 5 patients have achieved an objective response, including 3 CRs and 2 PRs (**ORR = 50%**) per Cheson criteria.
- Response assessment was first evaluated at 8 weeks and then every 12 weeks thereafter. 90% of evaluable patients had a reduction in target lesion (Figure on right)



** Indicates still on study and receiving ublituximab maintenance infusions*

Responses have been observed in both rituximab relapsed and rituximab refractory patients, including patients who have seen several lines of rituximab therapy. **2/5 evaluable rituximab refractory patients (40%) achieved a CR after 8 weeks on ublituximab**. Preliminary response rate data indicates similar activity in rituximab relapsed and rituximab refractory patients.

Dose	Diagnosis	# Prior RTX Therapies	RTX Status	RTX Response	UTX Response	Months on Study
450	Nodal MZL	3	Refractory	PD	CR	10+
600	Extra-Nodal MZL	2	Relapsed	PR	CR	7+
900	Extra-Nodal MZL	1	Relapsed	SD	PR	5+
900	FL	1	Relapsed	PR	PR	6+
900	FL	3	Refractory	PD	CR	4+

DEMOGRAPHICS

Evaluable for Safety (n)	12
Evaluable for Efficacy (n)	10
Too Early to Evaluate (n)	2
Male / Female (n)	6 / 6
Median Age, years (range)	63 (50 – 82)
Type of Lymphoma (n)	Follicular (7)
	Marginal Zone (3)
	Mantle Cell (2)
ECOG 0/1 (n)	7/5
Median Prior Therapies (range)	4 (2 – 6)
Patients ≥ 4 Prior Therapies (%)	7 (58%)
≥ 2 Prior Rituximab Regimens (%)	9 (75%)
Rel / Ref to Prior Treatment (n)	7 / 5
Rel / Ref to Prior Rituximab (n)	6 / 6

Safety

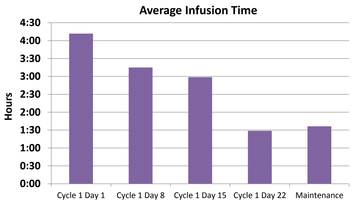
Among the 12 patients treated in the dose-escalation Phase I component of this study, no DLTs have been observed, and thus no MTD has been achieved. All adverse events (CTCAE v 4.0) are summarized as follows:

Definite, Probable, or Possibly Related Grade 1 or 2 AE's (N=12)

Adverse Event	Grade 1	Grade 2
Arthralgia	1	
Chills / Jittery Feeling	1	1
Dysgeusia	1	
Flushing	1	
Hyperhidrosis	1	
Lung Infiltration		1
Lymph Node Pain	1	
Muscle Spasm	1	
Pain		1
Pruritus	1	
Throat Irritation	1	1

Only 1 Grade 3 event observed: Gr. 3 anemia in a Cohort 1 patient deemed *possibly related* to study drug.

Average Infusion Time



Infusion times decreased to an average of ~90 minutes by the 4th infusion of ublituximab during induction, and for maintenance doses.

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

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

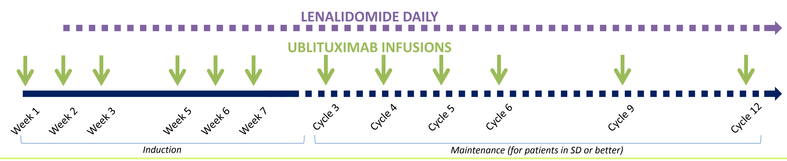
Cohort	Patients	Ublituximab	Lenalidomide
1	3 – 6	450 mg	10 mg
2	3 – 6	450 mg	15 mg
3	3 – 6	600 mg	10 mg*
4	3 – 6	900 mg	10 mg*

**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 all patients would start at 10 mg QD, and titrate dose in 5 mg increments per cycle based on individual tolerability.

Dosing Schedule

Ublituximab is administered on Days 1, 8, and 15 of Cycles 1 and 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.



RESULTS

Safety (CTCAE v 4.0)

AE's Definitely, Probably, or Possibly Related to Ublituximab

Adverse Event	Grade 1	Grade 2	Grade ≥ 3
Decreased Appetite	1		
Elevated alkaline phosphatase	1		
Elevated AST	1		
Dysphonia	1		
Infusion Related Reaction		3	
Leukopenia			1
Neutropenia			1
Urticaria		1	

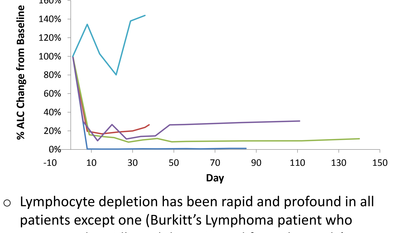
AE's Definitely, Probably, or Possibly Related to Lenalidomide

Adverse Event	Grade 1	Grade 2	Grade ≥ 3
Dysgeusia	1		
Decreased Appetite	1		
Constipation		2	
Diarrhea	2		
Fatigue	1		
Dysphonia	1		
Pruritus	1		
Leukopenia			1
Muscle Spasms	1	1	
Nausea			2
Neutropenia			2
Rash	2		
Tumor Flare		1	

DEMOGRAPHICS

Evaluable for Safety (n)	6
Evaluable for Efficacy (n)	5
Too Early to Evaluate (n)	1
Male / Female (n)	6/0
Median Age, years (range)	65 (60-69)
Type of Lymphoma (n)	CLL/SLL (3)
	Mantle Cell (2)
	Burkitts (1)
ECOG 0/1 (n)	2/4
Median Prior Therapies (range)	3 (3-6)
Prior R-Benda Regimen (%)	100%
≥ 2 Prior Rituximab Regimens (%)	100%
Refractory to Prior Treatment (%)	100%
Refractory to a Rituximab Regimen (%)	67%

Pharmacodynamics



- Lymphocyte depletion has been rapid and profound in all patients except one (Burkitt's Lymphoma patient who progressed rapidly and discontinued from the study)

CONCLUSIONS

TG-1101-101

- **Ublituximab (UTX) monotherapy has been well tolerated at all dose cohort levels with minimal IRR and limited G 3/4 events reported. Infusion times significantly decreased from the 1st to the 4th infusion.**
- **A 50% ORR (3 CR's / 2 PR's) has been achieved with UTX monotherapy in rituximab (RTX) relapsed and refractory patients and 8/12 patients remain on UTX treatment with median PFS not reached.**
- **3/3 MZL patients achieved an objective response (1 CR in RTX refractory, 1 CR & 1 PR in RTX relapsed patients). All MZL patients remain on ublituximab maintenance treatment now at 5, 7, and 10+ months.**
- **Cohort expansions identified based on efficacy/safety: 900 and 1200 mg cohorts opened for NHL patients.**
- **A recent protocol amendment allows for inclusion of CLL patients at 600 mg with future dose escalations planned; enrollment continues in all expansion cohorts.**
- **Future studies in rituximab relapsed/refractory MZL are planned. As ublituximab has been well tolerated, additional combination studies with novel agents for B-cell lymphoma are in development.**

TG-1101-102

- **Rapid lymphocyte depletion has been observed in the majority of patients treated with ublituximab in combination with lenalidomide.**
- **No DLT's to date have been observed.**
- **Lenalidomide administration schedule has been modified to tailor dose per patient tolerance.**
- **Phase II portion of this study is planned, focusing on patients with Mantle Cell Lymphoma.**

Abstract #P325

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