Abstract # 8575

A PHASE I DOSE-ESCALATION TRIAL OF UBLITUXIMAB (TG-1101), A NOVEL ANTI-CD20 MONOCLONAL ANTIBODY (MAB) FOR RITUXIMAB RELAPSED AND/OR REFRACTORY B-CELL LYMPHOMA PATIENTS

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INTRODUCTION

Ublituximab (UTX) 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% (ASH 2011). Herein we report on the Phase I dose-escalation of ublituximab in patients with rituximab (RTX) relapsed/refractory B-cell lymphoma.

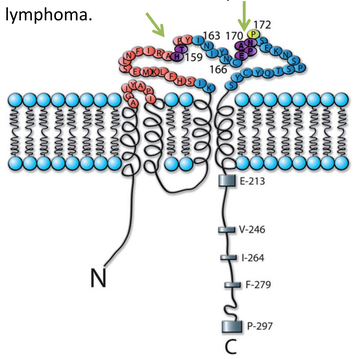


Figure 1:
Ublituximab epitope recognition differs from both rituximab and ofatumumab

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 (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
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

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

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

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:

Ublituximab has been well tolerated to date, with only 1 Grade 3 event observed: Gr. 3 anemia in a Cohort 1 patient deemed *possibly related* to study drug. The dose of ublituximab was not changed nor held for this patient, and the adverse event resolved without sequelae.

All 12 patients received all planned infusions. 4/12 had an infusion interruption. However, all patients finished their dose on the planned day:

- 3 patients had their dose interrupted in Cycle 1/Day 1 (Infusion Related Reaction-IRR)
- 1 patient had their dose interrupted in Cycle 1/Day 8 (IRR)

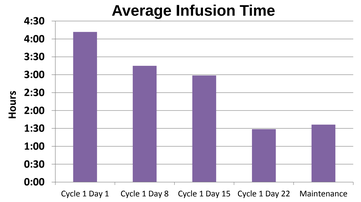
> 1 reported AE – Any Causality (N=12)

Adverse Event	Grade 1	Grade 2
Chills / Jittery Feeling	1	1
Cough	2	
Fatigue	2	
Pain	1	1
Pyrexia	2	
Rhinorrhea	2	
Throat Irritation	1	1

Definite, Probable, or Possibly Related G 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

Average Infusion Time



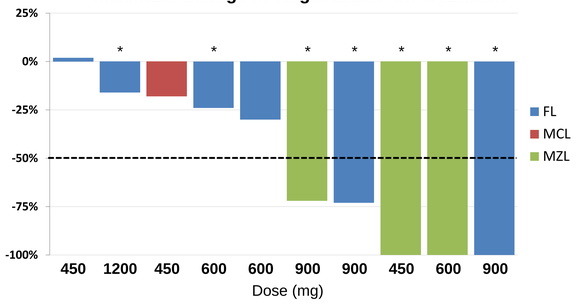
Consistent with the reduction in observed IRR's, infusion times decreased to an average of ~90 minutes by the 4th infusion of ublituximab during induction, and for maintenance doses.

Efficacy

To date, 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:

Maximum Change in Target Lesion on Treatment



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

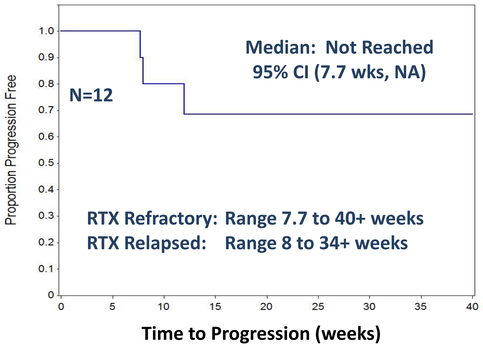
Responses observed in both rituximab relapsed and rituximab refractory patients, including patients who have seen several lines of rituximab therapy. **2/5 evaluable rituximab refractory patients (40%) achieved a CR after 8 weeks on ublituximab**. Preliminary response rate data indicates similar activity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

Ublituximab (UTX) Response Compared to Response to Prior Rituximab (RTX) Therapy

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+

Progression Free Survival Analysis

Median Progression Free Survival (PFS) for all patients has not been reached. 9/12 patients (4 rituximab refractory / 5 rituximab relapsed) remain on study treatment ranging from 1+ month to 10+ months in duration.



CONCLUSION

- **Ublituximab 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 in rituximab relapsed and refractory patients and 9/12 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.**

P. Sportelli, H. Miskin: Employment & Stock Ownership in TG Therapeutics. No relevant relationships to disclose for all other authors.