Ublituximab (TG-1101), A Novel Glycoengineered Anti-CD20 mAb, in Combination with Ibrutinib in Patients with CLL and MCL; Results of an Ongoing Phase II Trial

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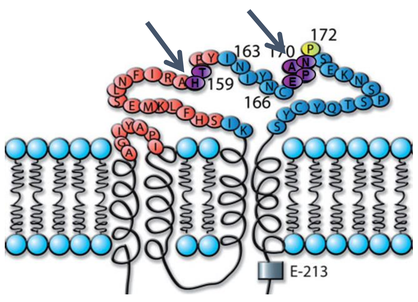
Background

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, particularly against tumor cells that express low CD20 levels. Glycoengineered anti-CD20 mAbs have recently demonstrated greater efficacy (ORR, PFS) than rituximab in CLL (NEJM, 2014). 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. Ibrutinib, a novel oral BTK inhibitor is approved for previously treated CLL and MCL patients. Ibrutinib has been combined with both rituximab and ofatumumab, but has not been combined with a glycoengineered mAb. Herein we report the first data of ublituximab, a glycoengineered mAb, in combination with ibrutinib from an ongoing Phase 2 trial in patients with relapsed/refractory CLL and MCL.



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

Study Design

Study UTX-IB-104 (NCT02013128) is a two part Phase II trial with a safety run-in portion (Part 1) evaluating the combination of ublituximab + ibrutinib in CLL and MCL patients. The trial is currently active with enrollment ongoing. As of June 6, 2014, 18 trial sites are open for enrollment in 13 states in the United States

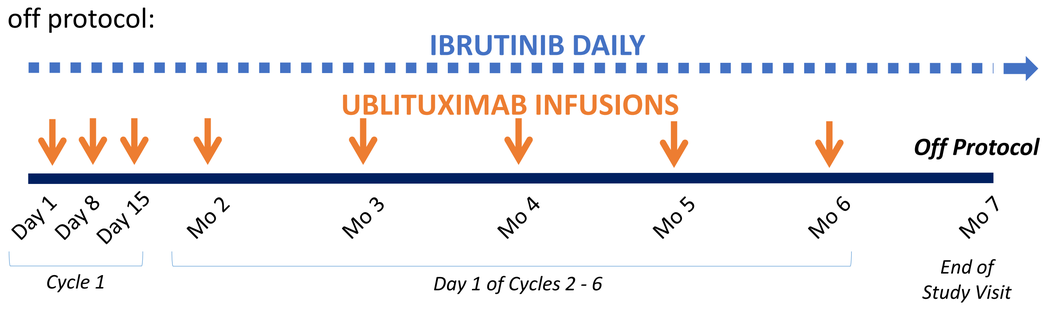
The study endpoints are as follows:

- **Part 1**: Safety of the combination for CLL and MCL patients (6 pts per cohort)
- **Part 2**: ORR (CR + PR), CR rate and Minimal Residual Disease rate (MRD)

Dose Escalation Schema:

	MCL		CLL/SLL	
Cohort	UTX Dose (Days 1, 8, 15)	Ibrutinib (Daily)	UTX Dose (Days 1, 8, 15)	Ibrutinib (Daily)
1	900 mg	560 mg	600 mg	420 mg
2	-	-	900 mg	420 mg

Safety run-in (Part 1) of the study is designed to enroll 6 patients per cohort. Efficacy is assessed at 3 and 6 months. After month 6, all patients can stay on ibrutinib single agent, off protocol:



Key Eligibility Criteria

- Patients with previously treated CLL or MCL with measurable disease requiring treatment according to standard criteria for CLL (IWCLL, Hallek, 2008) and for MCL (Cheson, 2007)
- ECOG ≤ 2; No Hepatitis B/C or HIV; Prior Allogeneic Stem Cell transplant excluded
- Adequate organ / marrow function with baseline
  - ANC ≥ 1,000/μL and platelets ≥ 50k/μL for Part 1; and
  - ANC ≥ 750/μL and platelets ≥ 50k/μL for Part 2
- Prior treatment with a BTK inhibitor and/or a PI3K inhibitor is permitted
- Patients with Richter's transformation are excluded

Results

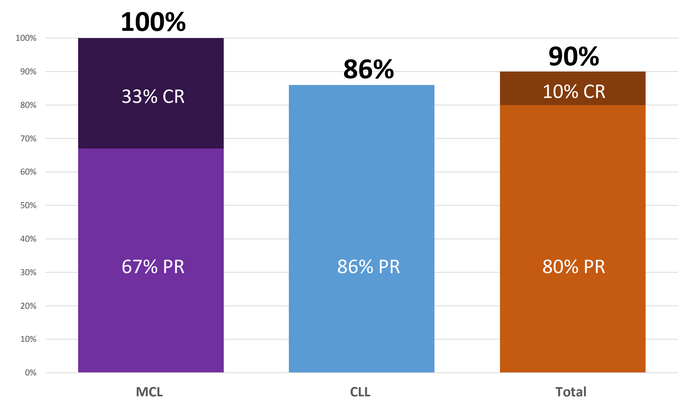
Demographics

Evaluable for Safety, (n)	28	
Evaluable for Efficacy,† (n)	10	
Median Age, years (range)	72 (52 – 86)	
Male/Female	17/11	
Histology, (n)	CLL	21
	MCL	7
% High Risk CLL Patients (17p, 11q)	7 (33%)	
ECOG, median (range)	1 (0 – 2)	
Prior Therapies, median (range)	2 (1 – 6)	
Patients with ≥ 3 Prior Therapies	12 (43%)	
Prior anti-CD20	27 (96%)	
Prior Purine Analog	13 (46%)	
Prior Alkylating Agent	22 (79%)	
Prior Purine + Alkylator	17 (61%)	

† *1 patient not evaluable due to study withdrawal because of ibrutinib related AE (diarrhea); All other patients are too early for response assessment*

Efficacy

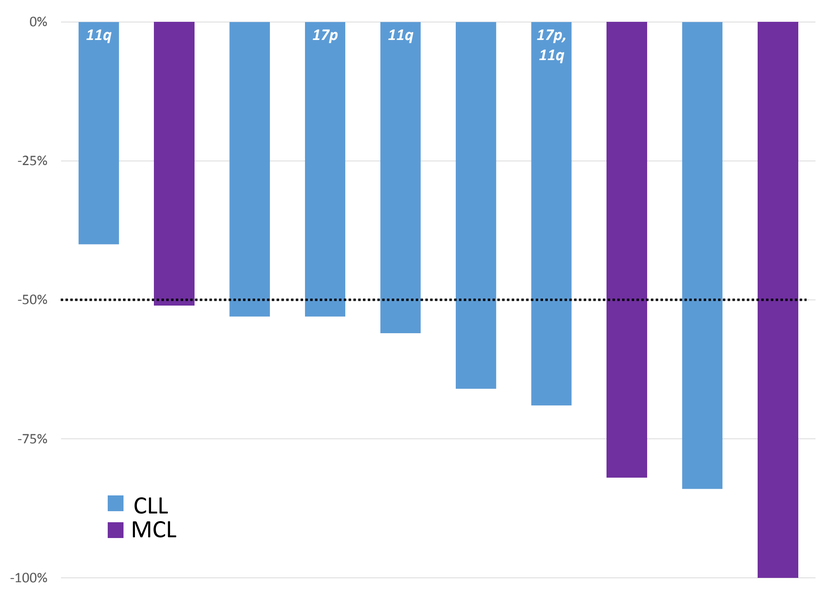
Overall Response at First Efficacy Assessment



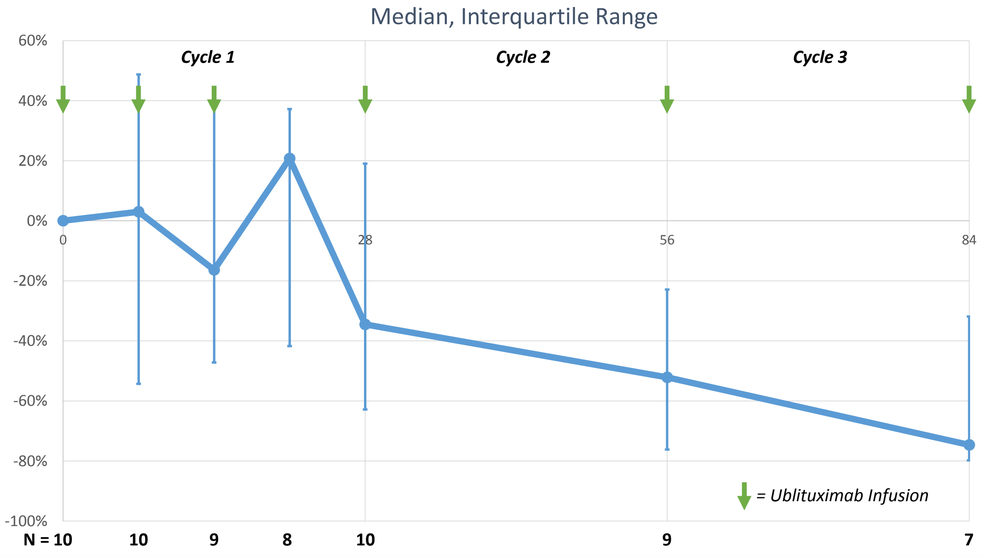
Type	Pts (n)	CR n (%)	PR n (%)	nPR n (%)	SD n (%)	PD n (%)	ORR n (%)
CLL	**7**	-	6 (86)	-	1 (14)	-	6 (86)
MCL	**3**	1 (33)	2 (67)	-	-	-	3 (100)
Total	**10**	1 (10)	8 (80)	-	-	-	9 (90)

CLL assessed by Hallek, 2008 Criteria; MCL assessed by Cheson, 2007 Criteria

Percent Change from Baseline in Nodal Size at First Assessment



Percent Change in ALC from Baseline
Median, Interquartile Range



- Addition of ublituximab appears to control ibrutinib related lymphocytosis in patients with CLL, with a median 79% decrease in ALC from baseline by Cycle 4
- 60% of CLL patients for whom data was available had lymphocyte counts in normal range (<4000/uL) by Cycle 4, with ALC continuing to decline

Safety

Related AE's Occurring in ≥ 2 patients (n = 28)			
Adverse Event	All Grades n (%)	G 1/2 n	G 3/4 n
Infusion Reaction	8 (29%)	7	1
Diarrhea	6 (21%)	4	2
Rash	6 (21%)	4	2
Fatigue	5 (18%)	5	0
Elevated Creatinine	3 (11%)	3	0
Thrombocytopenia	3 (11%)	2	1
Neutropenia	2 (7%)	0	2
Leukocytosis	2 (7%)	1	1
Mucositis	2 (7%)	2	0
Nausea	2 (7%)	2	0

- All rash, elevated creatinine, and Grade 3/4 diarrhea events deemed related to ibrutinib per investigator assessment. All IRR events related to ublituximab.

Dose Reductions & Treatment Discontinuations

- Ibrutinib was dose reduced in 2 patients (1 diarrhea, 1 rash)
- 1 patient stopped treatment due to ibrutinib related diarrhea
- No patients had their ublituximab dose reduced (infusion interruptions only due to IRR's)

Serious Adverse Events (SAEs)

- 2 drug related SAE's occurred in the same patient
  - 1 G3 diarrhea (deemed ibrutinib related)
  - 1 G4 thrombocytopenia (deemed ibrutinib related)

Conclusions

- Preliminary data suggests ublituximab, a glycoengineered anti-CD20 mAb, in combination with ibrutinib is both a well tolerated and highly active regimen for patients with relapsed or refractory MCL and CLL
- The addition of ublituximab appears to mitigate ibrutinib related lymphocytosis producing earlier clinical responses than historically seen with ibrutinib monotherapy
- Preliminary signs of increased depth of response seen with the combination of ublituximab and ibrutinib, with one MCL patient achieving a complete response at first efficacy assessment
- Additional studies are ongoing evaluating ublituximab in combination with other novel, targeted agents, with Phase III studies in development

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