Ublituximab (TG-1101), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody, in Combination with Ibrutinib Is Highly Active in Patients with Relapsed and/or Refractory CLL and MCL: Results of a Phase II Trial

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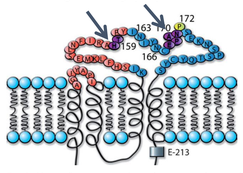
Abstract # 4679

Background

Ublituximab

- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and is 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. Herein we report data from an ongoing Phase 2 study evaluating the combination of ublituximab with ibrutinib in patients with relapsed/refractory CLL and MCL.

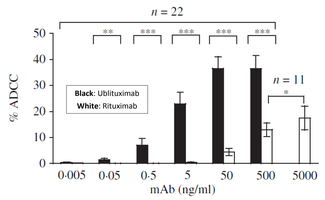
CD20 Antigen Binding Epitope of Ubliutimxab



Red: Key ofatumumab epitope amino acids
Purple: Core amino acids of ublituximab epitope

Figure adapted from Ruuls et al, 2008

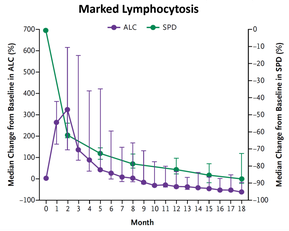
ADCC Comparison of Rituximab and Ublituximab in CLL Patient Cells



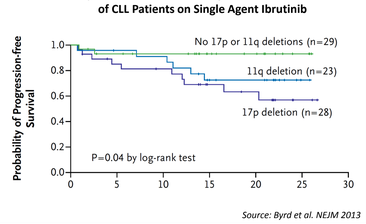
De Romeuf et al, 2008

Single Agent Ibrutinib (Historical Data)

Nodal Reductions in CLL Are Accompanied by Marked Lymphocytosis



Kaplan-Meier Curve for Progression-Free Survival of CLL Patients on Single Agent Ibrutinib



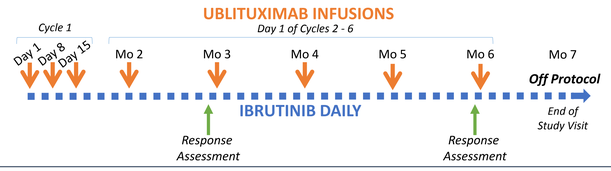
Source: Byrd et al. NEJM 2013

Study Design

Dose Escalation Schema:

Cohort	MCL		CLL/SLL	
	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

A 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 with 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

	CLL	MCL
Evaluable for Safety, (n)	44	8
Evaluable for Efficacy, † (n)	39	8
Median Age, years (range)	71 (39 – 86)	72 (55 – 80)
Male/Female	22/22	7 / 1
ECOG, median	1	1
Prior Regimens, median (range)	2 (1 – 7)	2 (1 – 6)
≥ 3 Prior Regimens	16 (36%)	3 (38%)
Prior Anti-CD20	41 (93%)	8 (100%)
Prior Alkylating Agent	28 (64%)	8 (100%)
Prior Purine Analog	22 (50%)	-

†5 patients came off study prior to first disease assessment: 1 due to ibrutinib related AE (diarrhea); 2 due to multiple non-drug related AE's; 2 withdrew consent

- 51% of evaluable CLL patients (20/39) were classified as "high-risk" exhibiting a 17p del, 11q del, and/or p53 mutation

Safety

All Causality AE's in > 5% of Patients (n=54†)		
Adverse Event	**All Grades** n (%)	**Grade 3/4** n (%)
Infusion reaction	18 (33%)	3 (6%)
Diarrhea	15 (28%)	2 (4%)
Fatigue	14 (26%)	1 (2%)
Rash	11 (20%)	2 (4%)
Bruising	8 (15%)	-
Nausea	8 (15%)	-
Mucositis	8 (15%)	-
Cough	7 (13%)	-
Edema	7 (13%)	-
Fever	6 (11%)	-
Thrombocytopenia	6 (11%)	2 (4%)
Neutropenia	3 (6%)	3 (6%)

†*Includes 2 patients with SLL*

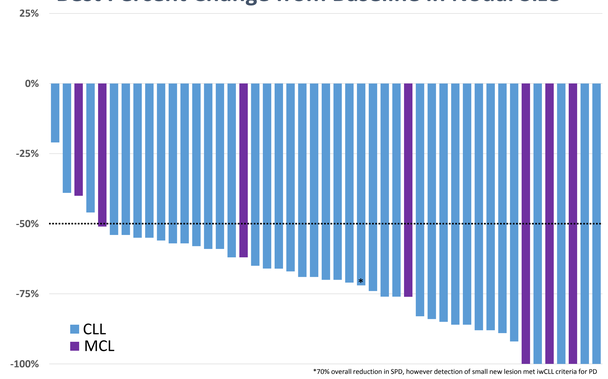
- All rash and Grade 3/4 diarrhea events were deemed related to ibrutinib per investigator assessment. All IRR events related to ublituximab.

Dose Reductions & Treatment Discontinuations

- Ibrutinib was dose reduced in 4 patients (diarrhea, rash, cough, fatigue)
- No patient had their ublituximab dose reduced
- 2 patients discontinued due to ibrutinib related AEs (rash, diarrhea)
- 2 patients discontinued due to non-related AEs (pre-existing AE's)

Overall Efficacy

Best Percent Change from Baseline in Nodal Size

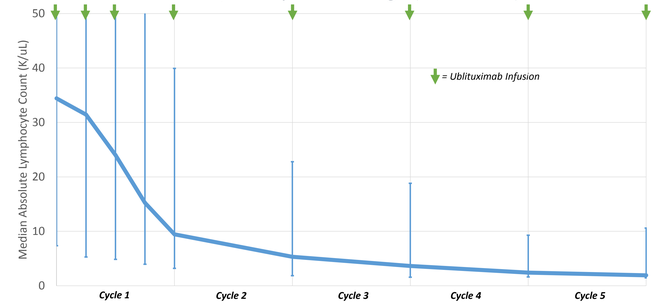


**70% overall reduction in SPD, however detection of small new lesion met iwCLL criteria for PD*

- 30% of patients were considered anti-CD20-refractory, progressing on or within 6 months of an anti-CD20 based regimen
- Prior anti-CD20 therapy included rituximab, ofatumumab, and obinutuzumab

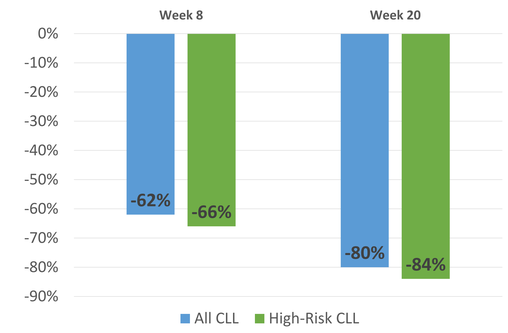
Absolute Lymphocytes in CLL Patients by Month on Treatment

Median, Interquartile Range (25% - 75%)

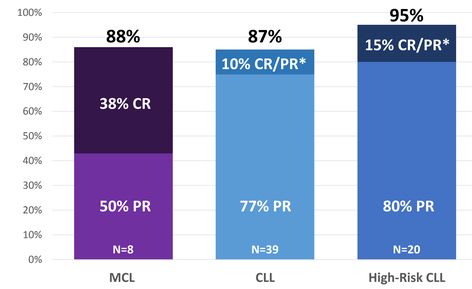


- Addition of ublituximab appears to control ibrutinib-related lymphocytosis in patients with CLL, with a median 75% decrease in ALC from baseline by the end of Cycle 3
- More than 50% of CLL patients had lymphocyte counts in normal range (<4000/uL) within 6 cycles of therapy

Median Nodal Reduction at First and Second Scan



Best Overall Response Rate



Per study design, all patients were evaluated for efficacy at Month 2 and 5 only

Type	Pts (n)	CR (n)	PR* (n)	PR (n)	nPR (n)	SD (n)	PD (n)	ORR (%)
CLL	**39**	1	3	30	1	3	1	87%
High-Risk Subset	*20*	*1*	*2*	*16*	-	-	*1*	*95%*
MCL	**8**	3		4		1	-	88%

CLL assessed by iwCLL (Hallek 2008) Criteria; MCL/SLL assessed by Cheson, 2007 Criteria
PR = Complete Response per iwCLL criteria, pending bone marrow confirmation*

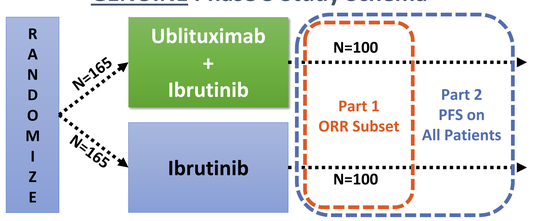
Future Steps

The GENUINE Trial: A Phase 3 Study of Ibrutinib vs. Ublituximab + Ibrutinib

- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Enrolling 330 patients with High-Risk CLL (17p del, 11q del, and/or p53 mutation)
- Study Chair: Jeff Sharman, MD
- Clinical trials.gov #: NCT02301156

GENUINE
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB PLUS IBRUTINIB

GENUINE Phase 3 Study Schema



Conclusions

- Data from this ongoing study 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 CLL and MCL
- Contrary to non-clinical data describing antagonism between BTK inhibition and ADCC, the addition of ublituximab appears to improve ORR in patients with CLL and MCL over that published historically with single agent ibrutinib in these patient populations
- A 95% ORR in patients with high-risk CLL (17p del, 11q del, and/or p53 mutation) suggests the combination may be an effective treatment regimen in this patient population; supporting a planned randomized Phase 3 clinical trial (the GENUINE trial)
- Additional studies are ongoing evaluating ublituximab in combination with other novel, targeted agents, with Phase III studies in development

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