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

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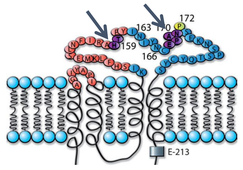
Background

Ublituximab

- Ublituximab (TG-1101 or UTX) 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) than rituximab and ofatumumab, particularly against tumor cells that express low CD20 levels.
- In patients with rel/ref CLL, the combination of UTX plus ibrutinib was well-tolerated and highly active demonstrating an 88% ORR (95% ORR in high-risk CLL) with responses attained rapidly (median time to iwCLL response of 8 weeks).
- Ibrutinib has demonstrated single agent activity in Mantle Cell Lymphoma (MCL), achieving a 66% ORR (17% CR) as per investigator assessment in a single arm trial in rel/ref MCL pts (*ibrutinib Prescribing Information, 2015*).
- Herein we report the final Phase 2 data on the first combination of ibrutinib with a glycoengineered anti-CD20 mAb, UTX, in patients with MCL.

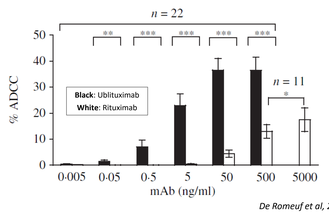
Figure 1: CD20 Antigen Binding Epitope of Ubliutimxab



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

Figure adapted from Ruuls et al, 2008

Figure 2: ADCC Comparison of Rituximab and Ublituximab in CLL Patient Cells

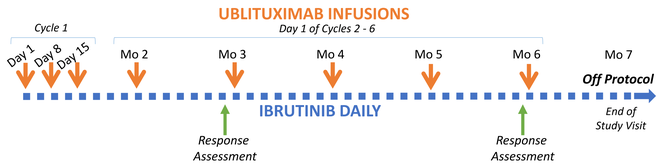


De Romeuf et al, 2008

Study Design

- **Ublituximab IV: 900 mg on Days 1, 8 and 15 in Cycle 1 followed by Day 1 of Cycles 2 – 6.**
- **Ibrutinib: 560 mg on Day 1 and continued daily through Cycle 6.**

A safety run-in (Part 1) of the study was designed to enroll 6 patients. If no unacceptable safety concerns were observed, enrollment opened to the expansion phase (Part 2). Efficacy was assessed at 3 and 6 months. After month 6, all patients were permitted to stay on ibrutinib single agent, off protocol:



Study Endpoints

- **Primary endpoints: Safety and ORR**
- **Secondary: Time to Response and CR rate**

Key Eligibility Criteria

- Patients with previously treated MCL with measurable disease requiring treatment according to standard criteria for MCL (Cheson et al, 2007)
- No limit on prior type or # of therapies or regimens
- 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 ≥ 30k/μL for Part 2
- Prior treatment with a BTK inhibitor and/or a PI3K inhibitor was permitted
- 21 day washout from prior therapy; Prior allogeneic SCT was excluded

Results

Demographics

	MCL
Evaluable for Safety, (n)	15
Evaluable for Efficacy, (n)	15
Median Age, years (range)	71 (55 – 80)
Male/Female	13 / 2
ECOG, 0 / 1	9 / 6
Stage 4 Disease, n (%)	10 (67%)
Prior Regimens, median (range)	3 (1 – 8)
≥ 3 Prior Regimens	9 (60%)
≥ 2 Prior Anti-CD20	8 (53%)
Prior R-CHOP and/or R-Benda	15 (100%)
Prior Bortezomib	6 (40%)

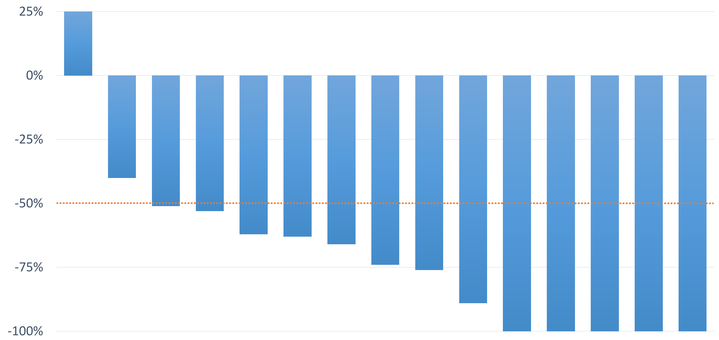
Safety

All Causality AE's in > 2 Patients (n=15)		
Adverse Event	All Grades n (%)	Grade 3/4 n (%)
Fatigue	8 (53%)	1 (7%)
Diarrhea	6 (40%)	-
Rash	6 (40%)	1 (7%)
Muscle spasms	5 (33%)	-
Nausea	5 (33%)	-
Stomatitis	5 (33%)	-
Constipation	4 (27%)	-
Hypomagnesemia	4 (27%)	-
Neutropenia	4 (27%)	3 (20%)
Thrombocytopenia	4 (27%)	-
Contusion	3 (20%)	-
Cough	3 (20%)	-
Decreased appetite	3 (20%)	-
Night sweats	3 (20%)	-

- Ibrutinib dose reduced in 20%, or 3 pts: hypertension, rash, fatigue
- No patients had their ublituximab dose reduced
- 1 patient discontinued due to ibrutinib related AE (atrial fibrillation) – atrial fibrillation occurred in 2 pts overall
- No Infusion Related Reactions were reported for ublituximab

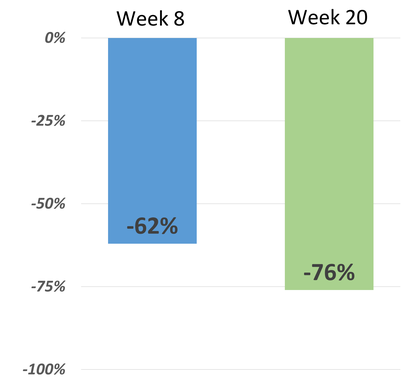
Overall Efficacy

Best % Change in Disease Burden from Baseline

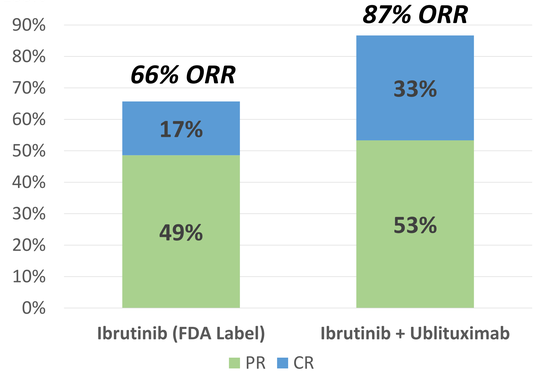


- 93% of patients achieved some reduction in tumor burden on study
- One patient, refractory to prior anti-CD20 therapy, and refractory to prior ibrutinib progressed in Cycle 3

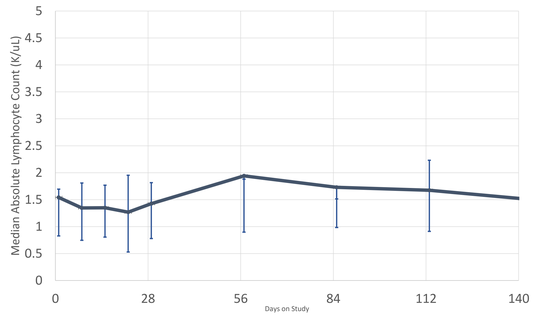
Median % Change in Tumor Burden



Investigator Assessed Overall Response Rate and CR rate
Ublituximab + Ibrutinib vs. Ibrutinib Label



Absolute Lymphocyte Count
Mean, Interquartile Range (25%-75%)



- Approximately 33% of MCL patients treated with single agent ibrutinib experience lymphocytosis (ALC > 5000)

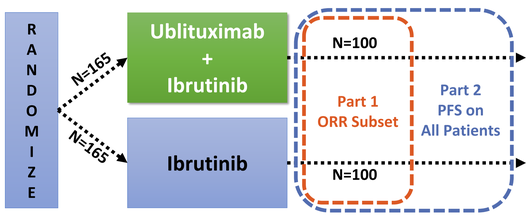
Phase 3 GENUINE Study in High-Risk CLL

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 + IBRUTINIB
PHASE 3 TRIAL IN HIGH-RISK CLL

GENUINE Phase 3 Study Schema



CONCLUSIONS

- Data from this Phase 2 study suggests ublituximab, a glycoengineered anti-CD20 mAb, in combination with ibrutinib is a well-tolerated and highly active regimen for patients with relapsed or refractory MCL
- An 87% ORR with a 33% CR rate in patients with advanced MCL compares favorably to historical single agent ibrutinib (66% ORR and 17% CR rate; *ibrutinib prescribing information, 2015*)
- Increased depth of response as measured by greater CR rate compared to historical ibrutinib single agent data suggests the potential for better long-term outcomes
- Enhanced ORR and depth of response is consistent with results seen for the combination in rel/ref CLL, with a 95% ORR (25% achieved CR and/or MRD negativity) in high-risk CLL (ICML 2015)
- A randomized Phase 3 trial with ibrutinib +/- ublituximab (GENUINE) is currently ongoing in high-risk CLL pts and future studies using this combination in MCL are being evaluated

COI: Kolibaba (Gilead, Acerta, Amgen, Celgene, CTI, Genentech, GSK, Janssen, Novartis, Pharmacyclics, Seattle Genetics, TG Therapeutics); Burke (Seattle Genetics, Gilead, Incyte, Takeda, Janssen, TG Therapeutics); Farber (TG Therapeutics); Fanning (Celgene, Takeda); Schreeder (TG Therapeutics); Boccia (Incyte); Sharman (Celgene, Gilead, Pharmacyclics, Janssen, Roche, TG Therapeutics); Sportelli, Miskin, Weiss (TG Therapeutics/Employment and Equity) . Authors not listed had no relevant conflicts of interest to disclose

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