Combination of Ublituximab, TGR-1202, and Bendamustine Demonstrates Significant Activity in Patients with Advanced DLBCL and Follicular Lymphoma

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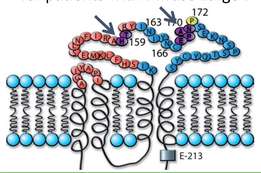
Background

Ublituximab

- Ublituximab (TG-1101, UTX) is a novel, chimeric monoclonal antibody 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.
- Ublituximab is currently in Phase 3 development in combination with ibrutinib or TGR-1202 for patients with chronic lymphocytic leukemia (CLL), and in Phase 2b study for patients with Diffuse Large B-Cell Lymphoma (DLBCL).

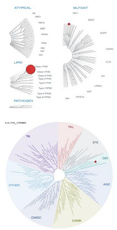


Red: Amino acids contributing to ofatumumab binding
Yellow: Amino acids essential for rituximab, but not ofatumumab binding
Purple: Core amino acids of ublituximab epitope

TGR-1202

- TGR-1202 (TGR) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:
  - High selectivity to the δ isoform of PI3K
  - A prolonged half-life that enables once-daily dosing; and
  - A differentiated safety profile from other PI3Kδ inhibitors in development, notably with respect to hepatic toxicity and colitis observed to date

Kinase Inhibition Profile of TGR-1202



Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Ky	PI3Kδ
TGR-1202	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]IPI-145	>640	>34	>11	1

[1]Flinn et al. 2009, [2]Porter et al. 2012

Study Design

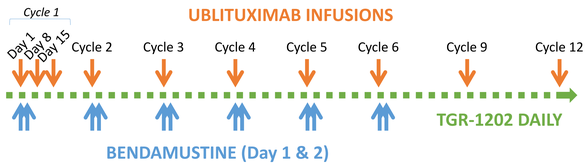
Study UTX-TGR-103 (NCT02006485) is a Ph I/Ib trial evaluating the combination of ublituximab + TGR-1202 in patients with relapsed or refractory NHL and CLL. Following safe evaluation of the UTX + TGR doublet, a triplet cohort was opened evaluating the combination of UTX + TGR + bendamustine restricted to enrollment for DLBCL and Follicular Lymphoma patients:

Dose Escalation Schema:

Ublituximab Dose	TGR Dose (QD)	Bendamustine
900 mg	600 mg	90 mg/m^2
900 mg	800 mg	90 mg/m^2

Treatment Schedule:

Efficacy is assessed at Week 8 and every 12 weeks thereafter. After Month 12, all patients remain on TGR-1202 single agent.



Study Objectives

Primary Objectives

- To determine the Safety and Maximum Tolerated Dose (MTD) of UTX + TGR + Bendamustine

Secondary Objectives

- To assess Efficacy (overall response rate, time to response, duration of response, progression free survival)

Key Eligibility Criteria

- Confirmed diagnosis of Diffuse Large B-Cell (DLBCL) or Follicular Lymphoma (FL)
- Relapsed after, or refractory to, at least 1 prior treatment regimen with no limit on prior therapies
- ECOG performance status ≤ 2
- Adequate organ system function: ANC ≥ 750/μL; platelets ≥ 50 K/μL
- Patients relapsed or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible.
- Patients relapsed from prior autologous stem cell transplant after 90 days are eligible

Results

Demographics

Evaluable for Safety (n)	19	
Evaluable for Efficacy[†] (n)	15	
Median Age, years (range)	68 (31 – 81)	
Male/Female	11/8	
Histology	DLBCL	11
	FL	8
ECOG, 0/1/2	3/15/1	
Prior Therapy Regimens, median (range)	2 (1 – 6)	
Patients with ≥ 3 Prior Therapies, n (%)	7 (37%)	
Refractory to Prior Therapy, n (%)	9 (47%)	
Refractory to Rituximab, n (%)	11 (58%)	

[†]4 Patients not evaluable (3 too early, 1 non-related AE prior to efficacy assessment)

Safety

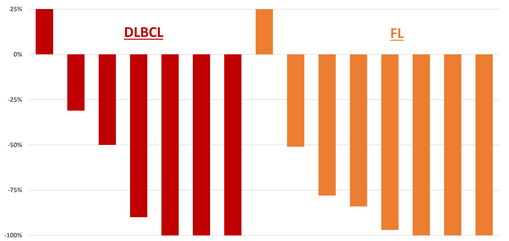
All Causality AE's Occurring in ≥ 15% of Patients (n = 19)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	7	37%	1	5%
Decreased appetite	6	32%	1	5%
Nausea	6	32%	1	5%
Anemia	4	21%	2	11%
Neutropenia	4	21%	4	21%
Vitamin D decreased	4	21%	-	-
Arthralgia	3	16%	-	-
Asthenia	3	16%	-	-
Dysgeusia	3	16%	1	5%
Hypomagnesemia	3	16%	1	5%
Infusion related reaction	3	16%	-	-
Rash	3	16%	1	5%
Thrombocytopenia	3	16%	1	5%

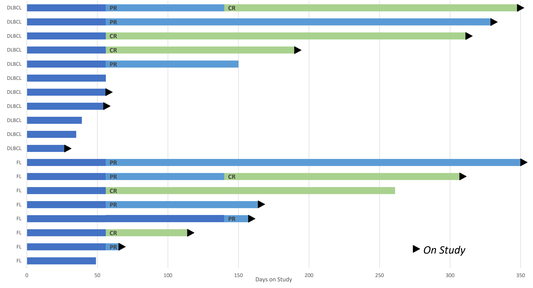
- Mean time on study 6 cycles
- No patient has discontinued due to a treatment-related AE
- Growth factor support was restricted during Cycle 1 for DLT evaluation purposes
- No Grade 3/4 transaminase elevations have been reported
- 1 transient event of Grade 3 diarrhea (duration of 1 day) was reported
- No events of pneumonia or pneumonitis have been reported to date

Efficacy

Best Percent Change from Baseline in Disease Burden



Duration on Study



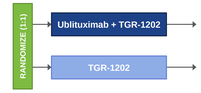
Type	Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
DLBCL	7	3	2	**5 (71%)**	1	1
FL	8	3	4	**7 (88%)**	-	1
Total	**15**	**6**	**6**	**12 (80%)**	**1**	**2**

Histology	TGR Dose	Rel/Ref	Prior Therapies	Best ORR
DLBCL	600	Ref	R-CHOP, R-ICE	PD
DLBCL	600	Ref	R-CHOP, R-ICE, BEAM-ASCT	SD
DLBCL	600	Rel	R-CHOP	PR
DLBCL	800	Ref	R-CHOP, R-Adria, Pembro + Acalabrutinib	PR
DLBCL	600	Rel	R-CHOP	CR
DLBCL	800	Ref	R-CHOP, R-Benda, ASCT, R-GEM/OX, Revlimid	CR
DLBCL	800	Rel	R-CVAD, R-ICE, BEAM-ASCT	CR
FL	600	Rel	R-EPOCH, ASCT	PD
FL	600	Ref	R-CHOP, Radiation, Rituximab	PR
FL	600	Rel	R-Benda, R + Idelalisib, CPI-1205	PR
FL	600	Rel	R-Benda, Rituximab	PR
FL	800	Ref	R-CHOP	PR
FL	600	Rel	CHOP, R-ICE, ASCT	CR
FL	600	Rel	R-CHOP	CR
FL	600	Ref	R-CHOP	CR

Phase 2b UNITY-DLBCL Study

- Enrolling patients with previously treated DLBCL of all subtypes
- US Study Chair: Owen A. O'Connor, MD, PhD
- Ex-US Study Chair: Pier-Luigi Zinzani, MD, PhD
- Amendment forthcoming to further evaluate UTX + TGR + Benda

UNITY DLBCL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED DLBCL PATIENTS



Conclusions

- The combination of ublituximab + TGR-1202 + bendamustine is well tolerated and highly active in patients with advanced indolent and aggressive NHL, with an encouraging CR rate observed (40%)
- The non-chemotherapy doublet of ublituximab + TGR-1202 is a safe and efficacious backbone regimen on which to build novel multi-drug combinations with several triple therapy combinations ongoing (including with ibrutinib, pembrolizumab, and bendamustine)
- The ublituximab + TGR-1202 doublet regimen is in registration directed UNITY-CLL Phase 3 Study and UNITY-DLBCL Study, with additional registration studies planned in the UNITY program
- The activity demonstrated with the triple combination of ublituximab + TGR-1202 + bendamustine is intended to be explored further in registration directed studies

COI: **Lunning**: Bristol-Myer-Squibb, AbbVie, Pharmacyclics, Juno, TG Therapeutics, Inc. (Consultancy), Gilead, Genentech, Spectrum, Celgene. **Siddiqi**: Seattle Genetics, Pharmacyclics/Janssen, Kite. **Blumel**: TG Therapeutics, Inc. (Consultancy). **Sportelli**: TG Therapeutics, Inc. (Employment, Equity Ownership). **Miskin**: TG Therapeutics, Inc. (Employment, Equity Ownership). **Weiss**: TG Therapeutics, Inc. (Employment, Equity Ownership)

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