Combination of Umbralisib, Ublituximab, and Bendamustine is Safe and Highly Active in Patients with Advanced DLBCL and Follicular Lymphoma

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Background

Study Rationale

- Relapsed/refractory DLBCL and iNHL represents a significant unmet need, especially those unable to tolerate HD chemotherapy or transplant (HDC/SCT)
- In a meta-analysis of refractory DLBCL, ORR to standard therapy was 26% (CR of 8%, PR of 18%) and Median OS was 6.6 months (Crump et al, ASCO 2016)
- CD19 CAR-T therapy has demonstrated activity in this population, however similar limitations of HDC/SCT may apply due to aggressive conditioning regimens, significant associated Gr ≥3 AEs, and the need to wait several weeks without treatment.
- The combination of ublituximab and umbralisib (TGR-1202), the "U2 regimen", has shown significant activity across multiple B-cell malignancies, including rel/ref DLBCL and iNHL (Lunning et al, ASH 2015)
- Due to its tolerability and activity, the ublituximab + umbralisib combination ("U2") has served as a backbone regimen in combination with kinase inhibitors, targeted immunotherapy, and chemotherapy
- Given the aggressiveness of rel/ref DLBCL and FL and the established activity of bendamustine in the treatment of NHL, we hypothesized that we can safely enhance the benefit of the ublituximab + umbralisib regimen through combination treatment with bendamustine.

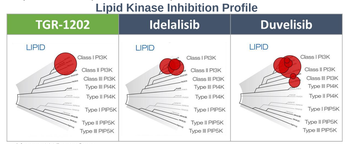
Ublituximab

- 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 umbralisib for patients with chronic lymphocytic leukemia (CLL), and in Phase 2b study for patients with Non-Hodgkin's Lymphoma (NHL).

Umbralisib (TGR-1202)

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- Umbralisib (TGR-1202, TGR) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:
  - Greater selectivity to the δ isoform of PI3K
  - A prolonged half-life that enables once-daily dosing
  - A differentiated safety profile from other PI3Kδ inhibitors, notably with respect to hepatic toxicity and colitis observed to date

Lipid Kinase Inhibition Profile



DiscoverX KinomeScan

Study Design

Study Schema

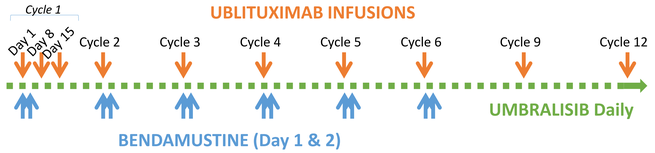
Study UTX-TGR-103 (NCT02006485) is a Phase I/Ib trial evaluating the combination of ublituximab + umbralisib ("U2") in patients with relapsed or refractory NHL and CLL. Following safe evaluation of the U2 doublet, a triplet cohort was opened evaluating the combination of U2 + bendamustine restricted to enrollment for DLBCL and Follicular Lymphoma patients, which included patients refractory to any prior agent, and those not able to tolerate aggressive chemotherapy, stem-cell transplant, or CD19 CART directed therapy.

Dose Escalation Schema:

Ublituximab Dose	Umbralisib Dose	Bendamustine
900 mg	600 mg QD	90 mg/m^2
900 mg	800 mg QD	90 mg/m^2

Treatment Schedule:

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



Study Objectives

Primary Objectives

- To determine the Safety and Maximum Tolerated Dose (MTD) of U2 + 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
- ANC ≥ 1000/μL; platelets ≥ 50 K/μL
- Prior PI3Kδ or BTK inhibitors were eligible
- Relapse from prior autologous stem cell transplant after 90 days were eligible

Results

Demographics

Evaluable for Safety (n)	39	
Evaluable for Efficacy[†] (n)	38	
Median Age, years (range)	68 (31 – 81)	
Male/Female	23/16	
Histology	DLBCL	26
	FL	13
ECOG, 0/1/2	12/25/2	
Prior Therapy Regimens, median (range)	2 (1 – 6)	
Patients with ≥ 3 Prior Therapies, n (%)	13 (33%)	
Refractory to Prior Therapy, n (%)	22 (56%)	
Refractory to Rituximab, n (%)	21 (54%)	

[†]1 Patient not evaluable: 1 DLBCL subject discontinued due to related AE, prior to first efficacy assessment

- 18/26 (69%) DLBCL patients refractory to immediate prior therapy

Safety

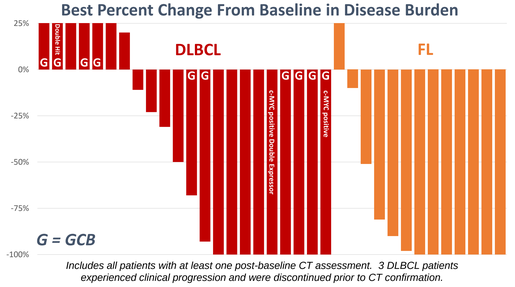
All Causality AE's Occurring in ≥ 15% of Patients (n = 39)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	21	54%	6	15%
Nausea	19	49%	2	5%
Vomiting	15	38%		
Neutropenia	13	33%	13	33%
Pyrexia	12	31%		
Decreased appetite	11	28%	1	3%
Fatigue	11	28%		
Hypomagnesemia	11	28%	1	3%
Asthenia	10	26%	2	5%
Infusion related reaction	9	23%		
Thrombocytopenia	8	21%	5	13%
Back pain	7	18%		
Hypokalemia	6	15%	4	10%
Hypophosphatemia	6	15%	1	3%
Rash	6	15%		
Vitamin D decreased	6	15%		

- Median duration of treatment: 6 months (range 0.6 – 36+ months)
- Growth factor support was initially restricted during Cycle 1 for DLT evaluation purposes; now allowed prophylactically
- Grade 3/4 LFT elevation occurred in 1 patient (3%)
- One patient discontinued due to a drug-related AE (neutropenia) as related to both umbralisib and bendamustine

Efficacy

Best Percent Change From Baseline in Disease Burden

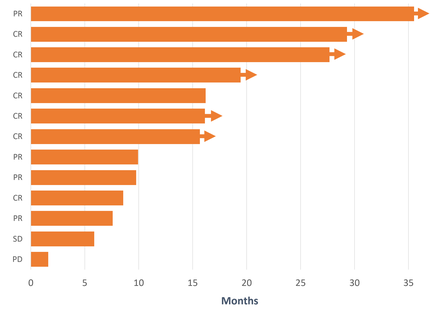


Includes all patients with at least one post-baseline CT assessment. 3 DLBCL patients experienced clinical progression and were discontinued prior to CT confirmation.

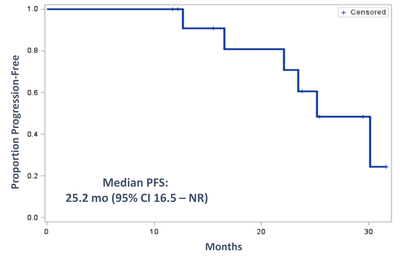
Best Overall Response Rate

Type	Pts N	CR n (%)	PR n (%)	ORR n (%)	SD n	PD N
DLBCL	25	9 (36%)	3 (12%)	**12 (48%)**	3	10
Relapsed	*8*	*4 (50%)*	*2 (25%)*	***6 (75%)***	*-*	*2*
Refractory	*17*	*5 (29%)*	*1 (6%)*	***6 (36%)***	*3*	*8*
FL	13	7 (54%)	4 (31%)	**11 (85%)**	1	1
Relapsed	*9*	*6 (67%)*	*2 (22%)*	***8 (89%)***	*-*	*1*
Refractory	*4*	*1 (25%)*	*2 (50%)*	***3 (75%)***	*1*	*-*

Disposition and Duration on Study for FL



Kaplan-Meier Plot of Progression-Free Survival for FL



FL Case Studies

- 77 y/o Male with 3 prior lines: R-Benda (refractory), R-idelalisib (refractory), and an investigational EZH2 inhibitor (refractory)
  - *Attained a PR (72% reduction) at first assessment, CR by Week 44, now ongoing for ~29+ months*
- 57 y/o Male with 3 prior lines of therapy: CHOP, R-ICE, and ASCT
  - *Attained a PR (88% reduction) at first response, and PET-negative CR at second assessment*
- 48 y/o Male with 3 prior lines of therapy: R-Benda, R-CHOP, and R-ICE
  - *Attained a PR (88% reduction) within 6 months, and PET-negative CR by Week 32, ongoing for 19+ months*
- 60 y/o Male primary refractory to first-line R-CHOP
  - *Attained a PR at first response (now at 98% reduction), ongoing for 36+ months*

Phase 2b UNITY-NHL Study

- Global, multi-center, registration directed study exploring Umbralisib +/- Ublituximab +/- Bendamustine
- Enrolling previously treated DLBCL, FL, SLL, MCL, & MZL

Conclusions

- The non-chemotherapy doublet of ublituximab + umbralisib is a safe and efficacious backbone regimen on which to build novel multi-drug combinations
- The combination of ublituximab + umbralisib + bendamustine is well tolerated and highly active in patients with advanced indolent and aggressive NHL, including those not eligible for HD/SCT or CD19 CART therapy, with:
  - An 85% ORR with 54% CR rate in relapsed or refractory FL, including a 75% ORR in refractory FL;
  - A 48% ORR with 36% CR rate in relapsed or refractory DLBCL
- The activity demonstrated with the triple combination of ublituximab + umbralisib + bendamustine is being explored further in registration directed studies (UNITY-NHL)

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