Combination of TGR-1202, 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 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.
- Novel, highly active, well tolerated treatments are needed for the majority of patients with relapsed/refractory DLBCL
- 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.

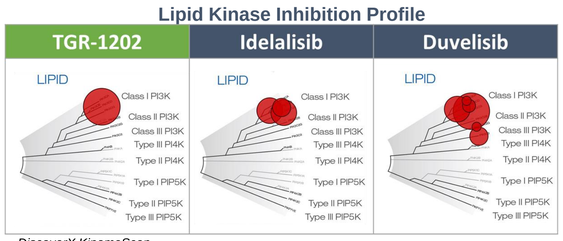
Ublituximab

- 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 ibrutinib or TGR-1202 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

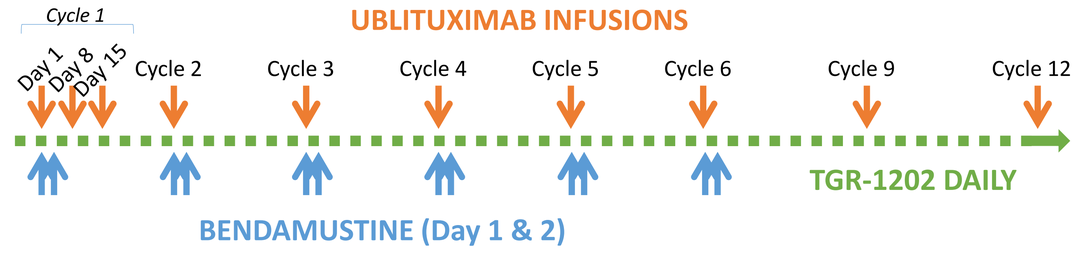
Study UTX-TGR-103 (NCT02006485) is a Phase I/Ib trial evaluating the combination of ublituximab + umbralisib (TGR-1202) in patients with relapsed or refractory NHL and CLL. Following safe evaluation of the UTX + TGR doublet, a triplet cohort was opened evaluating the combination of UTX + TGR + bendamustine restricted to enrollment for DLBCL and Follicular Lymphoma patients, 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	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
- ANC ≥ 1000/μL; platelets ≥ 50 K/μL
- Prior PI3Kδ or BTK inhibitors are eligible.
- Relapse from prior autologous stem cell transplant after 90 days are eligible

Results

Demographics

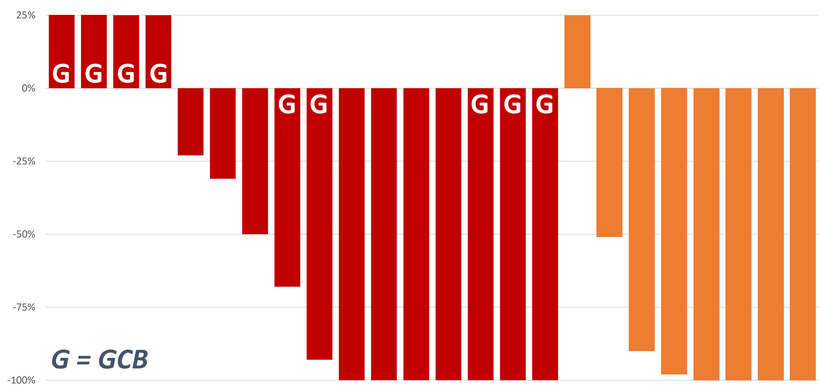
Evaluable for Safety (n)	33	
Evaluable for Efficacy† (n)	24	
Median Age, years (range)	68 (31 – 81)	
Male/Female	20/13	
Histology	DLBCL	23
	FL	10
ECOG, 0/1/2	7/24/2	
Prior Therapy Regimens, median (range)	2 (1 – 6)	
Patients with ≥ 3 Prior Therapies, n (%)	10 (30%)	
Refractory to Prior Therapy, n (%)	21 (64%)	
Refractory to Rituximab, n (%)	20 (61%)	

†9 Patients not evaluable: 7 too early to evaluate, 2 off prior to efficacy assessment (1 non-related AE, 1 investigator decision)

- 17/23 (74%) DLBCL patients refractory to immediate prior therapy

Efficacy

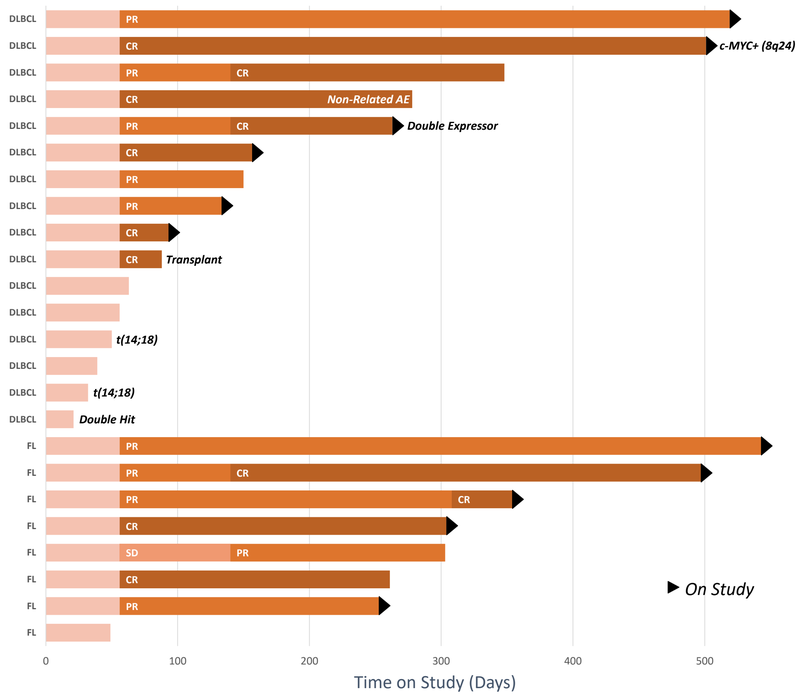
Best Percent Change From Baseline in Disease Burden



Best Overall Response Rate at Month 3

Type	Pts n	CR n (%)	PR n (%)	ORR n (%)	SD n	PD n
DLBCL (Rel)	4	2 (50%)	2 (50%)	**4 (100%)**	-	-
DLBCL (Ref)	12	5 (42%)	1 (8%)	**6 (50%)**	1	5
FL (Rel)	5	3 (60%)	1 (20%)	**4 (80%)**	-	1
FL (Ref)	3	1 (33%)	2 (67%)	**3 (100%)**	-	-
Combined	24	11 (46%)	6 (25%)	17 (71%)	1	6

Disposition and Duration on Study



Safety

All Causality AE's Occurring in ≥ 10% of Patients (n = 33)

Adverse Event	All Grades N	All Grades %	Grade 3/4 N	Grade 3/4 %
Diarrhea	12	36%	3	9%
Decreased appetite	9	27%	1	3%
Nausea	8	24%	1	3%
Neutropenia	8	24%	8	24%
Asthenia	6	18%	1	3%
Hypomagnesaemia	6	18%	1	3%
Thrombocytopenia	5	15%	2	6%
Vitamin D decreased	5	15%	-	-
Hypokalemia	4	12%	3	9%
Anemia	4	12%	2	6%
Arthralgia	4	12%	-	-
Bone pain	4	12%	-	-
Hypophosphatasemia	4	12%	-	-
Infusion related reaction	4	12%	-	-
Pyrexia	4	12%	-	-
Vomiting	4	12%	-	-

- Mean time on study 6 cycles
- Growth factor support was initially restricted during Cycle 1 for DLT evaluation purposes; now allowed prophylactically

DLBCL Case Studies

- 64 y/o Male with 3 prior lines: R-CHOP, R-Adria, and Pembro/acalabrutinib
  - Refractory to rituximab-chemotherapy and refractory to last line of therapy, with baseline SPD of 34.45 cm
  - Attained a PR (77% reduction) at first assessment, now ongoing for 17+ mos
- 70 y/o Female with 5 prior lines: R-CHOP, R-Benda, ASCT, R-Gem/Ox, and Lenalidomide
  - Refractory to prior therapy, with baseline SPD of 13.56 cm, c-MYC+ (8q24)
  - Attained a CR at first assessment now ongoing for 16+ months
- 60 y/o Female with 3 prior lines: R-CVAD, R-ICE, BEAM-ASCT
  - Transplant refractory (within 7 months), with baseline SPD of 27.68 cm
  - Attained a PR (92% reduction) at first assessment, CR by second assessment, duration of 11.4 months

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 ~12+ 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, ongoing for 16+ months

Phase 2b UNITY-NHL Study

- Enrolling patients with previously treated DLBCL, FL, SLL, and MZL
- Exploring Umbralisib (TGR-1202) +/- Ublituximab +/- Bendamustine
- DLBCL Study Chair: Owen A. O'Connor, MD, PhD
- iNHL Study Chair: Nathan Fowler, MD
- Ex-US Study Chair: Pier-Luigi Zinzani, MD, PhD

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA UMBRALISIB (TGR-1202)
PREVIOUSLY TREATED NHL PATIENTS

Conclusions

- The non-chemotherapy doublet of ublituximab + TGR-1202 is a safe and efficacious backbone regimen on which to build novel multi-drug combinations
- The combination of ublituximab + TGR-1202 + 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:
  - A 100% ORR with 50% CR rate in relapsed DLBCL;
  - a 50% ORR with 42% CR rate in refractory DLBCL with durable CR and PR responses observed; and
  - an 88% ORR with 50% CR rate in relapsed or refractory indolent NHL
- The activity demonstrated with the triple combination of ublituximab + ublituximab (TGR-1202) + bendamustine is being explored further in registration directed studies (UNITY-NHL)

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