Tolerability and activity of chemo-free triplet combination of TGR-1202, ublituximab, and ibrutinib in patients with advanced CLL and NHL

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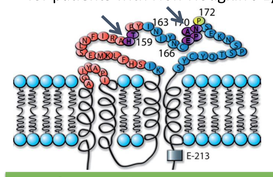
Background

Ublituximab (TG-1101)

- 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).

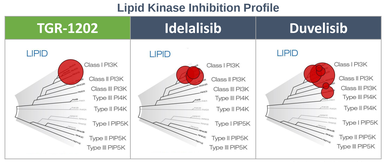


Red: Amino acids contributing to ofatumumab binding
Yellow: Amino acids essential for rituximab, but not ofatumumab binding
Purple: Core amino acids of ublituximab epitope

Umbralisib (TGR-1202)

- 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



DiscoverRx KinomeScan

Study Design

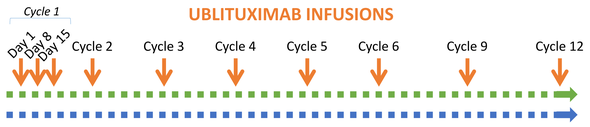
Study UTX-TGR-103 (NCT02006485) is a Ph I/Ib trial evaluating the combination of ublituximab + TGR-1202 in patients with relapsed or refractory NHL and CLL. Following safe evaluation of the UTX + TGR doublet, a triplet cohort was opened evaluating the combination of UTX + TGR + ibrutinib. A 3+3 dose-escalation design was utilized to evaluate escalating doses of TGR-1202 with fixed doses of ublituximab and ibrutinib:

Dose Escalation Schema:

Cohort	Ublituximab Dose	TGR Dose (QD)	Ibrutinib (QD)
1	900 mg	400 mg	420 mg CLL / 560 mg NHL
2	900 mg	600 mg	420 mg CLL / 560 mg NHL
3	900 mg	800 mg	420 mg CLL / 560 mg NHL

Treatment Schedule:

Both ibrutinib and TGR-1202 were administered once-daily starting on Day 1. Efficacy is assessed at Week 8 and every 12 weeks thereafter. After Month 12, all patients remain on TGR-1202 and ibrutinib.



Study Objectives

Primary Objectives

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

Secondary Objectives

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

Key Eligibility Criteria

- Confirmed diagnosis of CLL or NHL
- Relapsed after or refractory to at least 1 prior treatment regimen with no limit on prior therapies (except CLL/SLL – treatment naïve allowed)
- ECOG performance status ≤ 2
- Adequate organ function: ANC ≥ 500/μL; platelets ≥ 30 K/μL
- Patients with Richter's Transformation or patients 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)	38	
Evaluable for Efficacy† (n)	36	
Median Age, years (range)	65 (32 – 85)	
Male/Female	29/9	
Histology	CLL/SLL	20
	DLBCL	6
	FL	6
	MCL	4
	MZL	2
ECOG, 0/1/2	14/21/3	
Prior Therapy Regimens, median (range)	3 (0 – 6)	
Patients with ≥ 3 Prior Therapies, n (%)	21 (55%)	
Refractory to Prior Therapy, n (%)	13 (34%)	
Refractory to Rituximab, n (%)	15 (39%)	

†2 patients discontinued prior to first efficacy assessment (1 Pneumonia, 1 Investigator Discretion)

- 3 CLL patients were treatment naïve, all other patients were relapsed or refractory to prior therapy

Safety

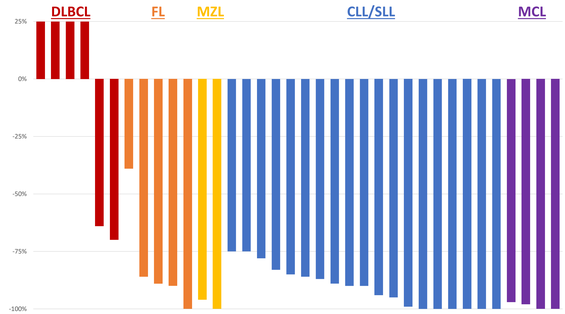
All Causality AE's Occurring in > 20% of Patients (n = 38)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	18	47%	1	3%
Fatigue	18	47%	-	-
Dizziness	14	37%	1	3%
Insomnia	13	34%	-	-
Nausea	13	34%	-	-
Neutropenia	12	32%	7	18%
Cough	12	32%	-	-
Infusion related reaction	12	32%	-	-
Thrombocytopenia	11	29%	3	8%
Pyrexia	11	29%	1	3%
Rash	11	29%	1	3%
Anemia	10	26%	1	3%
Sinusitis	9	24%	-	-
Dyspnea	8	21%	1	3%
Stomatitis	8	21%	1	3%

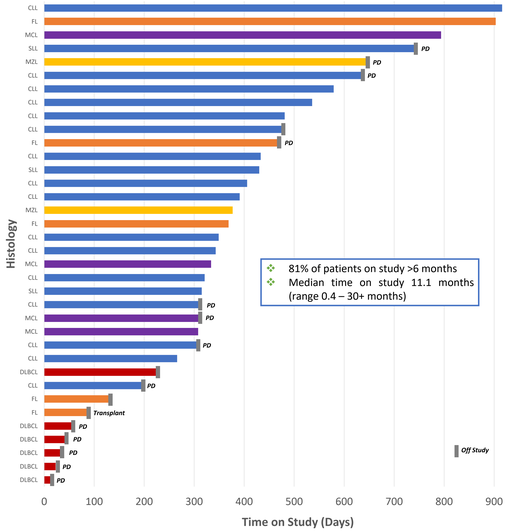
- 1 DLT (*reactivated varicella zoster*) was observed in the CLL cohort at level 1. No other DLT's were observed.
- Diarrhea was majority Gr. 1 (32%) and Gr. 2 (13%), with no Gr. 4 event reported. Pneumonia (18% all grades, 11% Gr. 3/4) and neutropenia were the only Gr. 3/4 AE's in >10% of patients
- Two patients discontinued due to an AE (sepsis and pneumonia)
- Median time on study 11.1 months (range 0.4 – 30+ months)

Efficacy

Best Percent Change from Baseline in Disease Burden



Duration on Study



Best Overall Response

Type	Pts (n)	CR† (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	19	6	13	**19 (100%)**	-	-
MZL	2	1	1	**2 (100%)**	-	-
MCL	4	2	2	**4 (100%)**	-	-
FL	5	1	3	**4 (80%)**	1	-
DLBCL	6	-	1	**1 (17%)**	-	5
Total	**36**	**10**	**20**	**30 (83%)**	**1**	**5**

†CLL: 4/6 CR's pending bone marrow confirmation

- 8 CLL patients (50%) had a 17p and/or 11q deletion
- All 3 treatment naïve CLL patients achieved a PR
- 3 CLL patients had prior BTK and/or PI3Kδ inhibitor therapy, including one patient refractory to both idelalisib and ibrutinib who attained a complete response (ongoing for 1.5+ years)
- FL patients were heavily pretreated including 2 with prior ASCT, 1 refractory to prior ibrutinib, and 1 with 5 prior lines of rituximab based therapy
- DLBCL patients had a median of 4 prior therapies, and 4/6 were of non-GCB subtype

Conclusions

- With a median follow up of 11.1 months, the combination of ublituximab, umbralisib (TGR-1202), and ibrutinib appears to be well tolerated and demonstrates favorable efficacy in advanced CLL and NHL.
- The safety profile of this novel combination was favorable suggesting that TGR-1202 may be safely combined with targeted agents to overcome mechanisms of resistance.
- The efficacy profile of this novel combination was observed across several NHL subtypes.
- Many patients continue on therapy, with approximately half beyond 1 year and are experiencing a manageable safety profile.
- Correlative studies are planned to understand the potential synergism and identify the most optimal subtype to pursue additional study

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