Long-term follow-up of the next generation PI3Kδ inhibitor TGR-1202 demonstrates a differentiated safety profile and high response rates in CLL: Integrated-analysis of TGR-1202 monotherapy and combined with ublituximab

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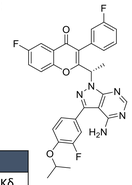
Background

TGR-1202

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- TGR-1202 (TGR) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:
  - A prolonged half-life that enables once-daily dosing
  - A differentiated safety profile from other PI3Kδ inhibitors in development

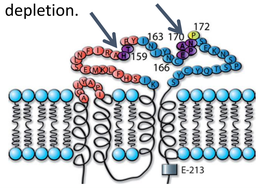


Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]IPI-145	>640	>34	>11	1

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

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.
- Phase I trials of single agent ublituximab in patients with relapsed/refractory CLL and NHL reported impressive response rates with rapid and sustained lymphocyte depletion.



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

Study Design

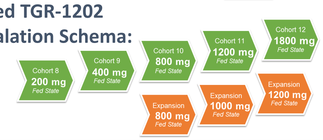
TGR-1202-101: TGR-1202 Monotherapy

Study TGR-1202-101 (NCT01767766) is a first-in-human, Phase I study of TGR-1202 in patients with relapsed or refractory hematologic malignancies

- TGR-1202 dosed orally once-daily (QD) in continuous 28 Day Cycles
- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation
- Intra-patient dose escalation allowed for patients in previous cohorts following establishment of safety at higher doses

3+3 Dose Escalation Schema:

Micronized TGR-1202 Dose Escalation Schema:



UTX-TGR-103: TGR-1202 in Combination with Ublituximab

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. The study is divided into two parts:

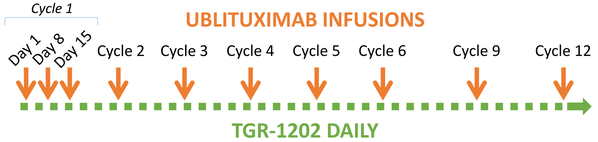
- **Phase I:** 3+3 escalation evaluating Cycle 1 DLTs
- **Phase Ib:** Dose Expansion

Dose Escalation Schema:

Cohort	UTX Dose	TGR Dose (QD)
1	900/600 mg NHL/CLL	800 mg
2	900/600 mg NHL/CLL	1200 mg
3	900 mg	400 mg (micronized)
4	900 mg	600 mg (micronized)
5	900 mg	800 mg (micronized)
6	900 mg	1000 mg (micronized)
7	900 mg	1200 mg (micronized)
Expansion	*TGR-1202 at 800 mg, 1000 mg, and 1200 mg micronized*	

Treatment Schedule:

Efficacy is assessed Week 8, and every 12 weeks thereafter. After Month 12, all patients remain on TGR-1202 single agent. Ublituximab was initially administered on Days 1, 8 and 15 of Cycles 1 & 2 and Day 1 of Cycles 4, 6, 9 & 12. The protocol was amended to use a more convenient schedule as follows:



Results

Demographics

Evaluable for Safety (n)	165 (90 Single Agent, 75 Combo with UTX)	
Median Age, years (range)	65 (22 - 86)	
Male/Female	106/59	
Histology	CLL	43
	FL	42
	DLBCL	40
	MZL	11
	HL	11
	MCL	8
	SLL	3
	WM	3
	T-Cell	2
	HCL	1
	Richter's	1
Median ECOG	1	
Prior Therapies, median (range)	3 (0 - 14)	
Patients with ≥ 3 Prior Therapies (%)	94 (57%)	
Patients Refractory to Prior Therapy (%)	85 (52%)	

Safety

All Causality AE's Occurring in ≥ 10% of Patients (n = 165)

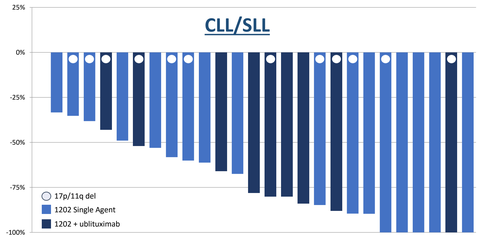
Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	78	47%	5	3%
Nausea	74	45%	2	1%
Fatigue	61	37%	5	3%
Vomiting	44	27%	0	0%
Neutropenia	34	21%	30	18%
Cough	32	19%	0	0%
Dyspnea	30	18%	6	4%
Dizziness	29	18%	0	0%
Headache	28	17%	2	1%
Pyrexia	26	16%	2	1%
Decreased appetite	26	16%	0	0%
Rash	26	16%	6	4%
Sinusitis	25	15%	2	1%
Anemia	24	15%	9	5%
Constipation	24	15%	1	1%
Insomnia	23	14%	0	0%
Hypokalemia	22	13%	5	3%
Back pain	20	12%	1	1%
Abdominal pain	18	11%	4	2%
Upper respiratory infection	18	11%	0	0%

- <8% of patients discontinued due to a TGR-1202 related AE
- 13% of patients had a TGR-1202 dose reduction
- Grade 3/4 AST/ALT increase was 3% (8% all grades), predominantly observed above the Phase 3 dose
- Grade 3/4 pneumonia occurred in 5% of patients (8% all grades)
- Two events of pneumonitis (<1.5%) were reported
- Two cases of colitis (<1.5%) have been reported at doses exceeding the Phase 3 dose and did not appear to be time dependent (1000 mg and 1200 mg, at 4 mos. and 24 mos., respectively, after initiating therapy).

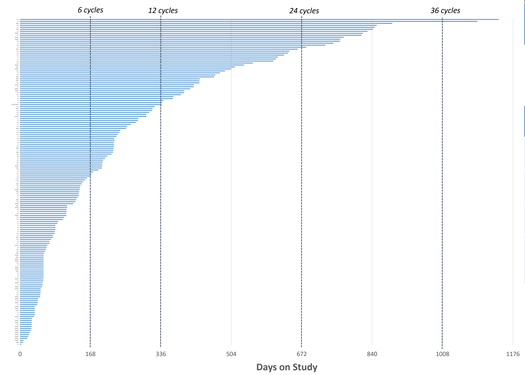
Efficacy

Patients Treated at "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden

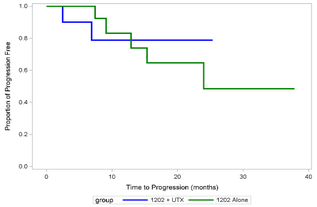


Duration on Study (n=165)



- Extended durations of exposure:
  - 80 patients for 6+ cycles
  - 43 patients for 12+ cycles
  - 14 patients for 24+ cycles
  - Longest patients on daily TGR-1202 for 3+ years

Progression-Free Survival at Higher Doses



- Median PFS for TGR-1202 Monotherapy: 24 Months
- Median PFS and DOR not reached for TGR-1202 + UTX

Overall Response Rate At Phase 3 Dose

Patients Exposed to TGR-1202 at 800 Micro						
Type	Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	16	2	12	**14 (88%)**	2	0

- PR includes 1 patient with persistent lymphocytosis (PR-L)

Ibrutinib Refractory Patients treated with TGR + UTX

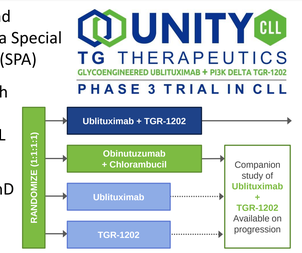
Cyto-genetics	# of Prior Lines	Prior Therapies	% SPD reduction	ORR	Status
11q	4	1. R-Benda 2. Ofatumumab 3. Ibrutinib 4. Ibrutinib	-100%	PR	On Study
17p	2	1. R-Fludarabine 2. Ibrutinib	-37%	SD	Off (PD)
17p, p53	2	1. Ibrutinib 2. Bendamustine & CAR T-cell	-55%	PD	Off (PD)
No del	5	1. FCR 2. R-Benda 3. FCR 4. Campath+R 5. Ibrutinib	+25%	PD	Off (PD)

- All patients were treated with 800 mg of TGR-1202 in combination with ublituximab
- Higher Doses: 1200 mg of the initial formulation, or ≥600 mg of the micronized formulation
- An exploratory subset of patients with ibrutinib refractory CLL were treated with TGR + UTX and analyzed separately due to the aggressive nature of their disease
- A strong dose response was observed, with patients exposed to 800 mg of the micronized formulation achieving higher rates of response

UNITY Registration Program

Phase 3 UNITY-CLL Study

- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Enrolling patients with treatment naïve and previously treated CLL
- Study Chair: John Gribben, MD, PhD
- Clinical trials.gov #: NCT02612311



Conclusions

- TGR-1202 is well tolerated and highly active in a broad population of heavily pretreated & high-risk patients with CLL as well as NHL (see EHA 2016 Poster P315), with the addition of ublituximab to TGR-1202 exhibiting greater frequency and depth of response over TGR-1202 monotherapy
- Discontinuations due to adverse events have been limited (~8%); GR3/4 events most associated with PI3K delta inhibitors have been rare, including pneumonia (~5%) and pneumonitis (<1.5%), ALT/AST elevations (~3%) and colitis (<1.5%), the latter occurring with no apparent association to time on therapy
- Safety profile supports additional multi-drug regimens: triple therapy combinations adding novel agents to ublituximab and TGR-1202 are ongoing (including ibrutinib, bendamustine, and pembrolizumab) with additional triple therapy studies planned
- Marked activity observed in CLL is being explored further in registration directed UNITY-CLL Phase 3 Study, with additional registration directed programs underway in DLBCL (UNITY-DLBCL Phase 2b study) and planned in iNHL by YE2016

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