TGR-1202, a Novel Once Daily PI3Kδ Inhibitor, Demonstrates Clinical Activity with a Favorable & Differentiated Safety Profile as a Single Agent and in Combination with a Novel Glycoengineered anti-CD20 mAb, Ublituximab, in Patients with Rel/Ref CLL

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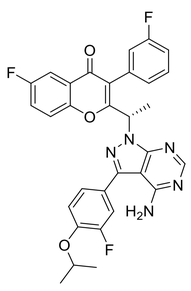
Background

TGR-1202

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- TGR-1202 is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:



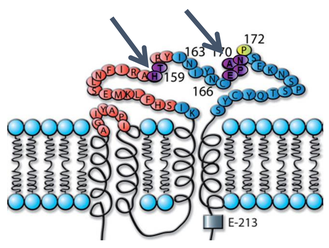
  - A prolonged half-life that enables once-daily dosing
  - A differentiated safety profile from other PI3Kδ inhibitors in development, notably with respect to hepatic toxicity and colitis to date
- Marked single agent activity for TGR-1202 has been demonstrated in CLL and indolent and aggressive NHL (ASCO/EHA/ICML 2015)

Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>10000	>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) is a novel, chimeric monoclonal antibody (mAb) 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
- Two Phase I trials of single agent ublituximab in patients with relapsed/refractory CLL reported response rates of 67% (ASCO 2014) and 45% (EHA 2013), 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 Designs

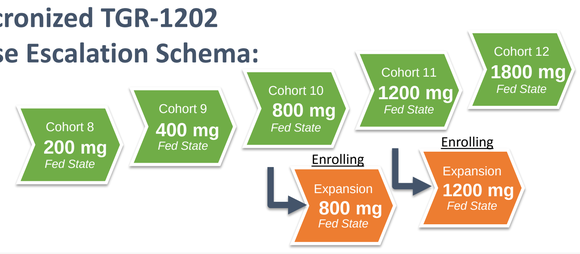
TGR-1202 Single Agent

Study TGR-1202-101 (NCT01767766) is an ongoing 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:



TGR-1202 in Combination with Ublituximab

Study UTX-TGR-103 (NCT02006485) is an ongoing Phase 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:

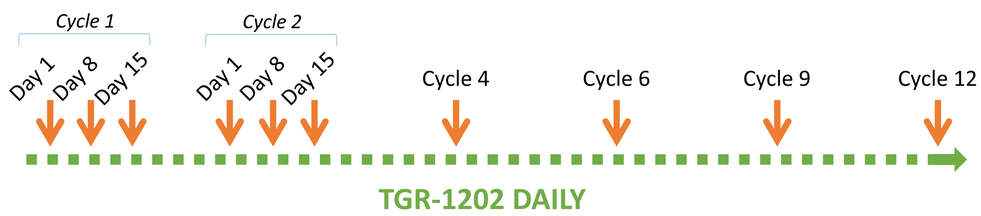
- **Phase I:** 3+3 Dose Escalation evaluating Cycle 1 DLTs
- **Phase Ib:** Dose Expansion

Dose Escalation Schema:

Cohort	Ublituximab Dose	TGR Dose (QD)
1	600 mg	800 mg
2	600 mg	1200 mg
3	900 mg	400 mg (micronized)
4	900 mg	600 mg (micronized)
5	900 mg	800 mg (micronized)
6	900 mg	1200 mg (micronized)
Expansion	*Enrolling at 800, 1000, and 1200 mg TGR-1202*	

Treatment Schedule:

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



Results

TGR-1202 Single Agent

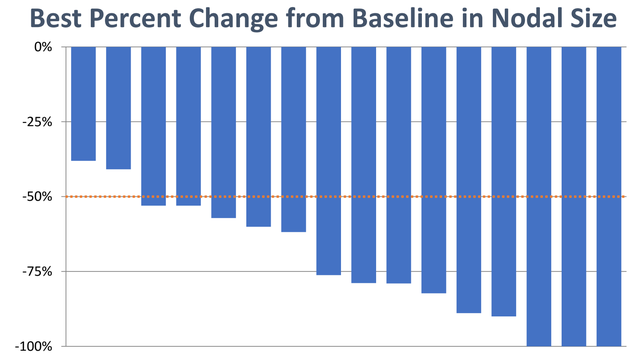
Demographics

Evaluable for Safety (n)	66
CLL Patients Enrolled to Date (n)	21
CLL Patients Evaluable for Efficacy (n)†	16
Median Age, years (range)	64 (46 – 78)
Male/Female	15/6
ECOG, 0/1/2	6/15/0
Prior Therapies, median (range)	2 (1 – 8)
Pts with ≥ 3 Prior Therapies (%)	29%
Refractory to prior Therapy (%)	33%

† Efficacy subset includes only patients treated with 800 mg of initial formulation or higher and any micronized dose level, of which 1 pt is too early to evaluate, and 1 patient not evaluable due to failed I/E criteria

Efficacy (CLL n=16)

Best Percent Change from Baseline in Nodal Size



- 88% of CLL patients (14/16) achieved a nodal PR, remaining 2 patients still on study pending further evaluation
- 63% of CLL patients (10/16) achieved a response per iwCLL (Hallek 2008) criteria

Safety

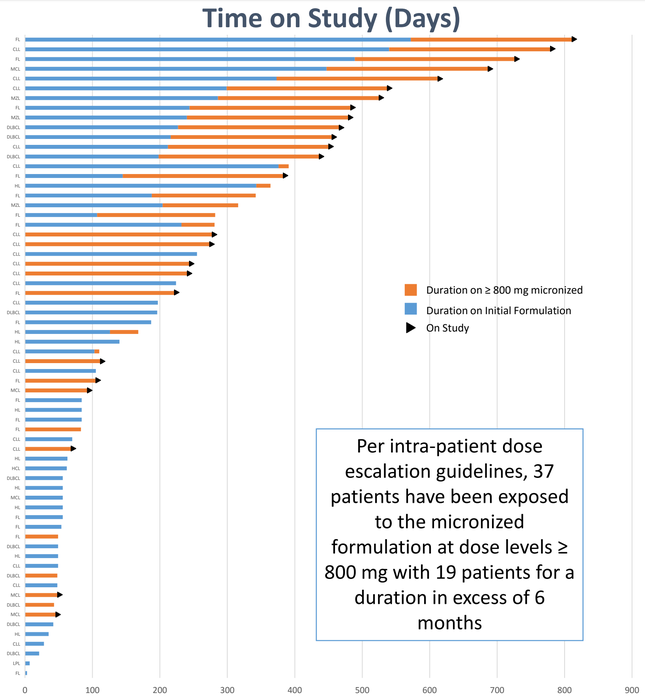
Related AE's in ≥ 5% of Patients (n = 66)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	20	30%	1	2%
Nausea	15	23%	-	-
Fatigue	13	20%	2	3%
Vomiting	13	20%	-	-
Decreased Appetite	7	11%	-	-
Neutropenia	6	9%	5	8%
Dizziness	5	8%	-	-
Dysguesia	4	6%	-	-
Headache	4	6%	-	-
Rash	4	6%	1	2%

- AE profile on all enrolled pts (including NHL)
- TGR-1202 has been well-tolerated, with limited Gr. 3/4 events and no significant dose or time dependent trends in AEs observed with 31 patients on study 6+ months
- 3 patients (< 5%) have come off study due to an adverse event: pulmonary infection, Legionnaire's disease, and fatigue
- GI related adverse events have been primarily mild and transient

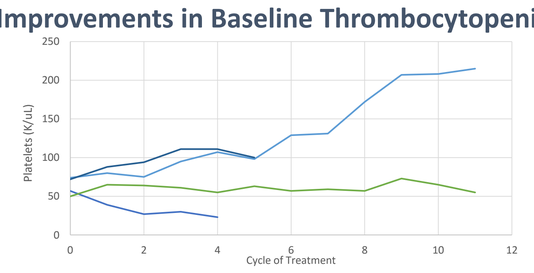
Duration of Exposure

Time on Study (Days)

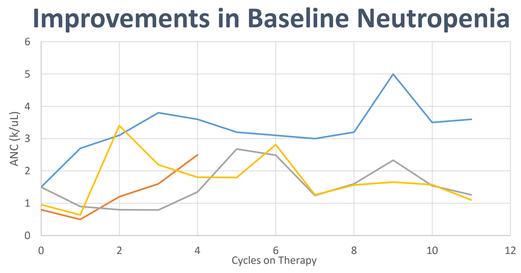


Per intra-patient dose escalation guidelines, 37 patients have been exposed to the micronized formulation at dose levels ≥ 800 mg with 19 patients for a duration in excess of 6 months

Improvements in Baseline Thrombocytopenia



Improvements in Baseline Neutropenia



TGR-1202 in Combination with Ublituximab

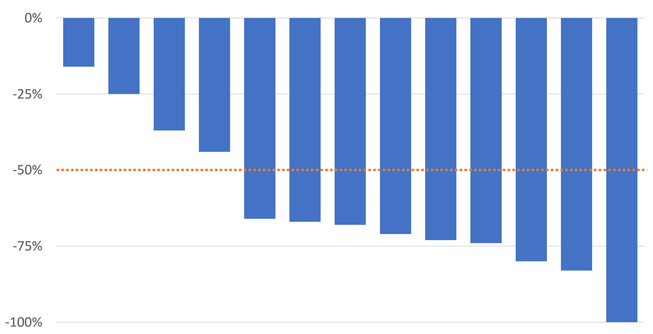
Demographics

Evaluable for Safety (n)	55
CLL/SLL Patients Enrolled to Date (n)	14
CLL/SLL Patients Evaluable for Efficacy (n)†	13
Median Age, years (range)	65 (35 – 80)
Male/Female	10/4
ECOG, 0/1/2	2/12/0
Prior Therapies, median (range)	2 (1 – 8)
Pts with ≥ 3 Prior Therapies (%)	43%
Prior RTX Based Tx, median (range)	2 (1 – 5)

† 1 CLL Pt too early to evaluate

Efficacy (CLL/SLL n=13)

Best Percent Change from Baseline in Nodal Size



- 73% of CLL patients (8/11) had high-risk cytogenetics (17p del and/or 11q del)
- Ublituximab abrogates TGR-1202 induced lymphocytosis, with all patients exhibiting >50% nodal reduction achieving a response by iwCLL 2008 criteria

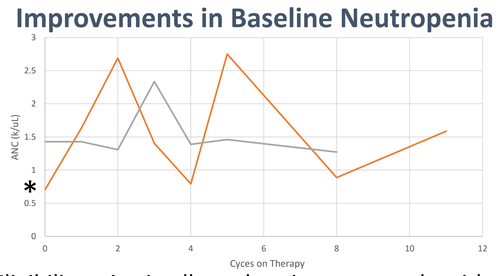
Safety

Related AE's in ≥ 5% of Patients (n = 55)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Infusion Reaction	16	29%	1	2%
Neutropenia	15	27%	13	24%
Nausea	15	27%	-	-
Diarrhea	11	20%	1	2%
Fatigue	10	18%	-	-
Vomiting	6	11%	-	-
Abd. Pain/Discomfort	4	7%	-	-
Muscle Cramping	4	7%	-	-
Anemia	3	5%	-	-
Bruising	3	5%	-	-
Hoarseness	3	5%	-	-
Thrombocytopenia	3	5%	-	-

- AE profile on all enrolled pts (including NHL)
- 3 patients (~5%) have come off study due to an AE: itching (Gr. 1), pneumonitis, and hypoxia
- No patients at ≥800 mg micronized TGR-1202 have discontinued due to an AE

Improvements in Baseline Neutropenia



- Eligibility criteria allowed patients on study with an ANC > 500/uL
- *Pt. enrolled with Gr. 3 neutropenia, ECOG 1, with co-morbidities. Achieved PR at Wk 8, continuing on daily TGR-1202 maintenance 18+ months

Conclusions

- TGR-1202 is a once-daily PI3Kδ inhibitor with a single agent activity observed in patients with a variety of relapsed/refractory hematologic malignancies, including CLL, and a differentiated safety profile from other PI3K-delta inhibitors, especially with respect to hepatic-toxicity and colitis to date
- Safety and activity profile supports combination therapy with other novel targeted agents
- TGR-1202 in combination with ublituximab is well tolerated and highly active
- Amongst both studies, Grade 3/4 adverse events and discontinuations due to adverse events have been limited (~5%)
- Safety profile of the combination supports additional multi-drug combination regimens; triple therapy combinations adding novel agents to ublituximab and TGR-1202 are ongoing (including ibrutinib: ASCO 2015 Abstract #8501) with additional triple therapy studies planned
- International Phase III studies for TGR-1202 both as a single agent and in combination with ublituximab are planned

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