

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

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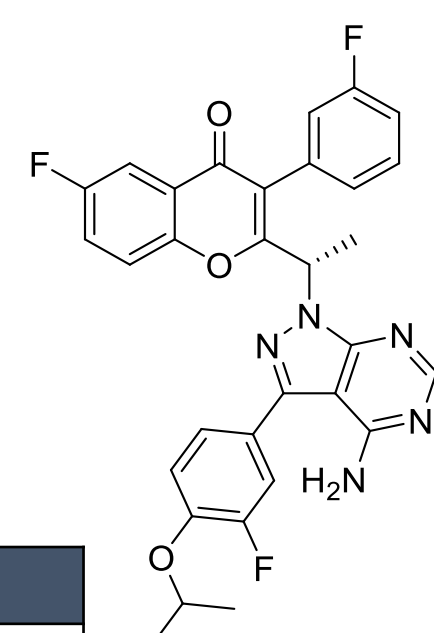
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Background

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

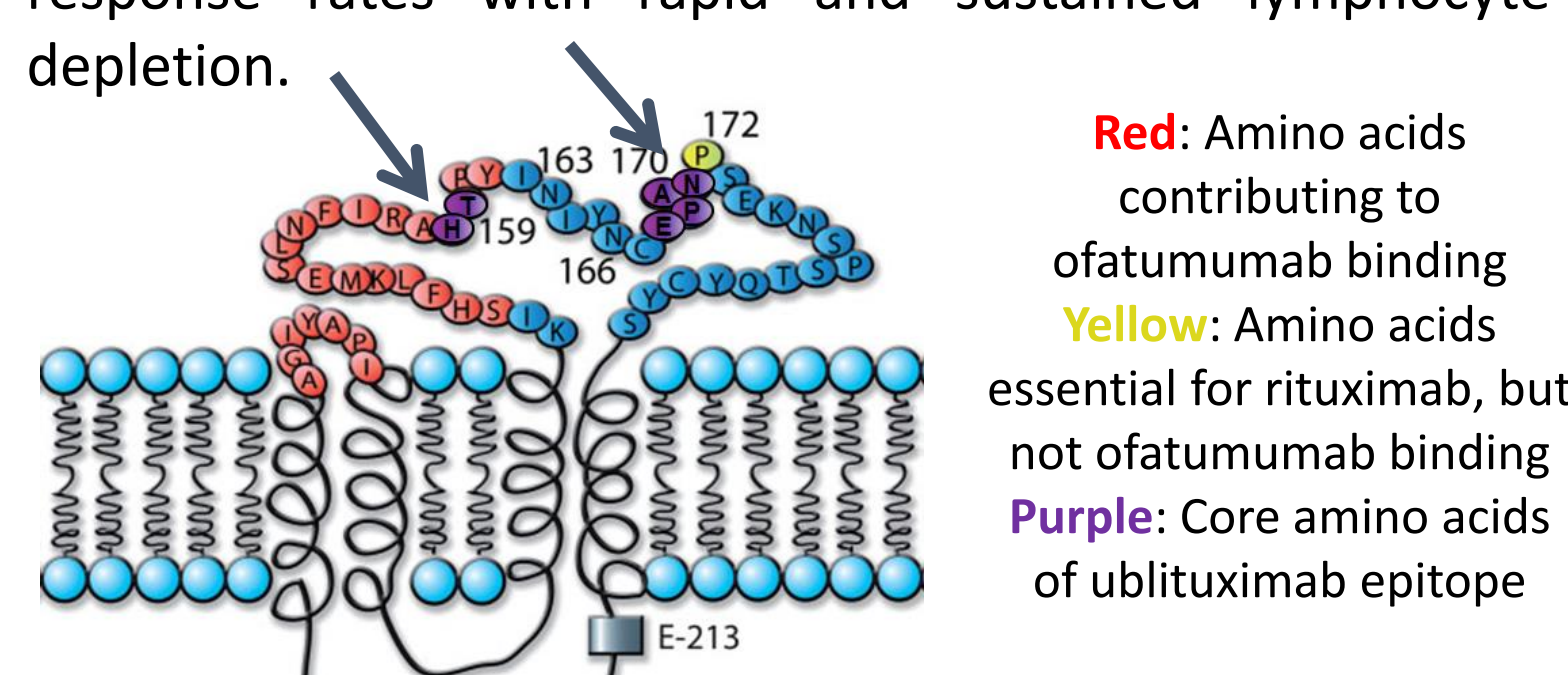


Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>1000	>50	>48	1
¹ Idelalisib	>300	>200	>40	1
² PI-145	>640	>34	>11	1

¹Flinn et al. 2009, ²Porter 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.



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

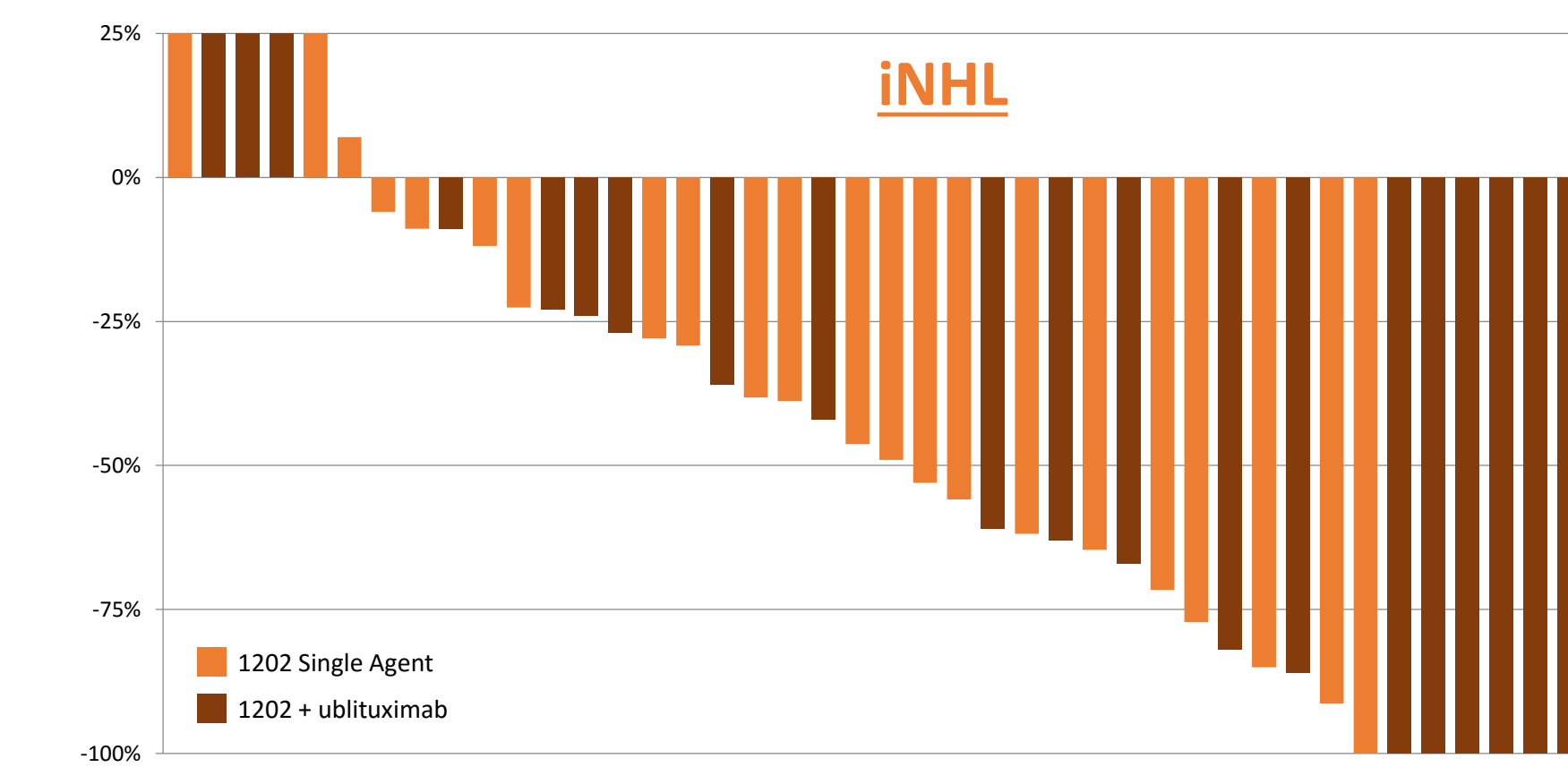
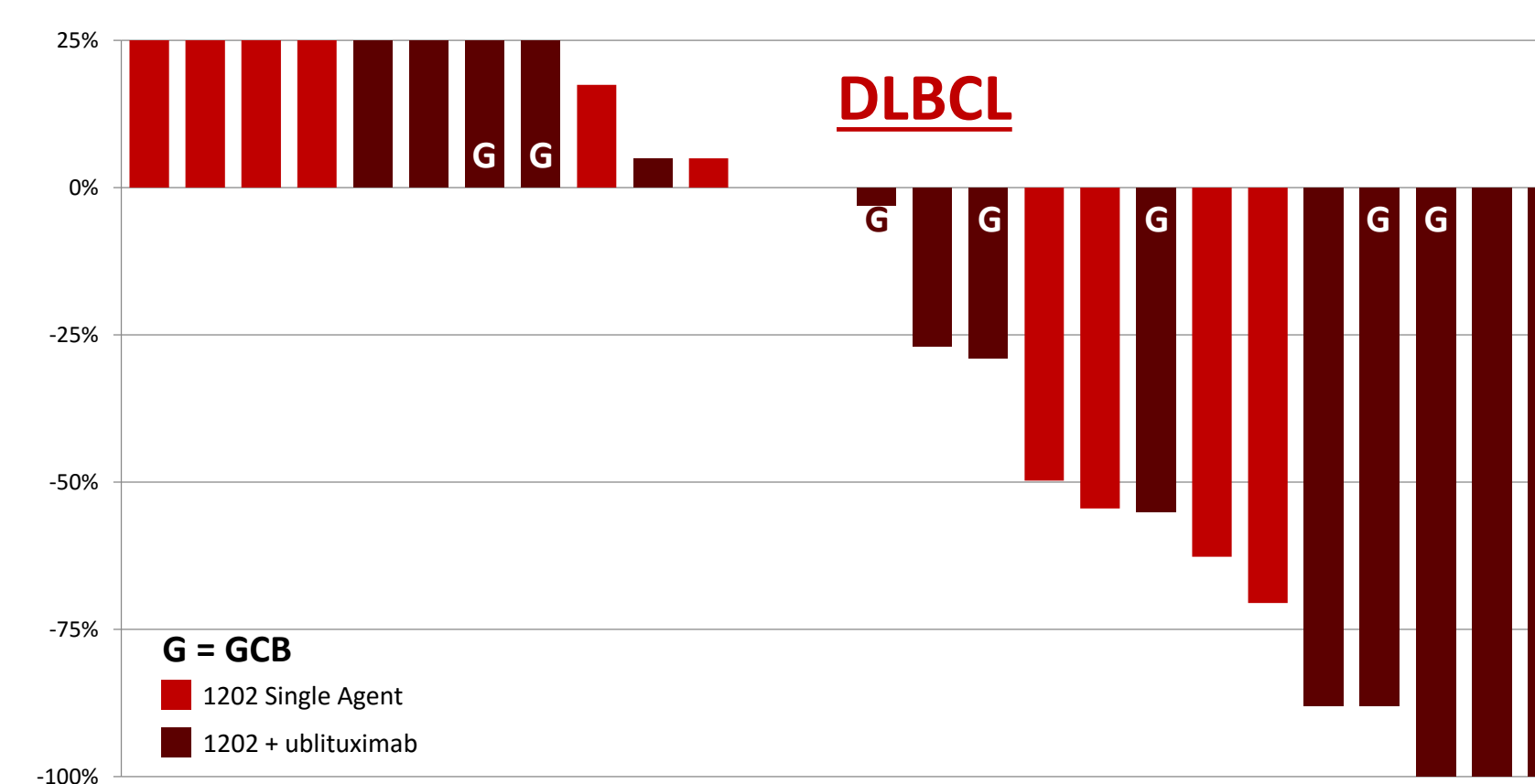
All Causality AE's Occurring in ≥ 10% of Patients (n = 165)

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%

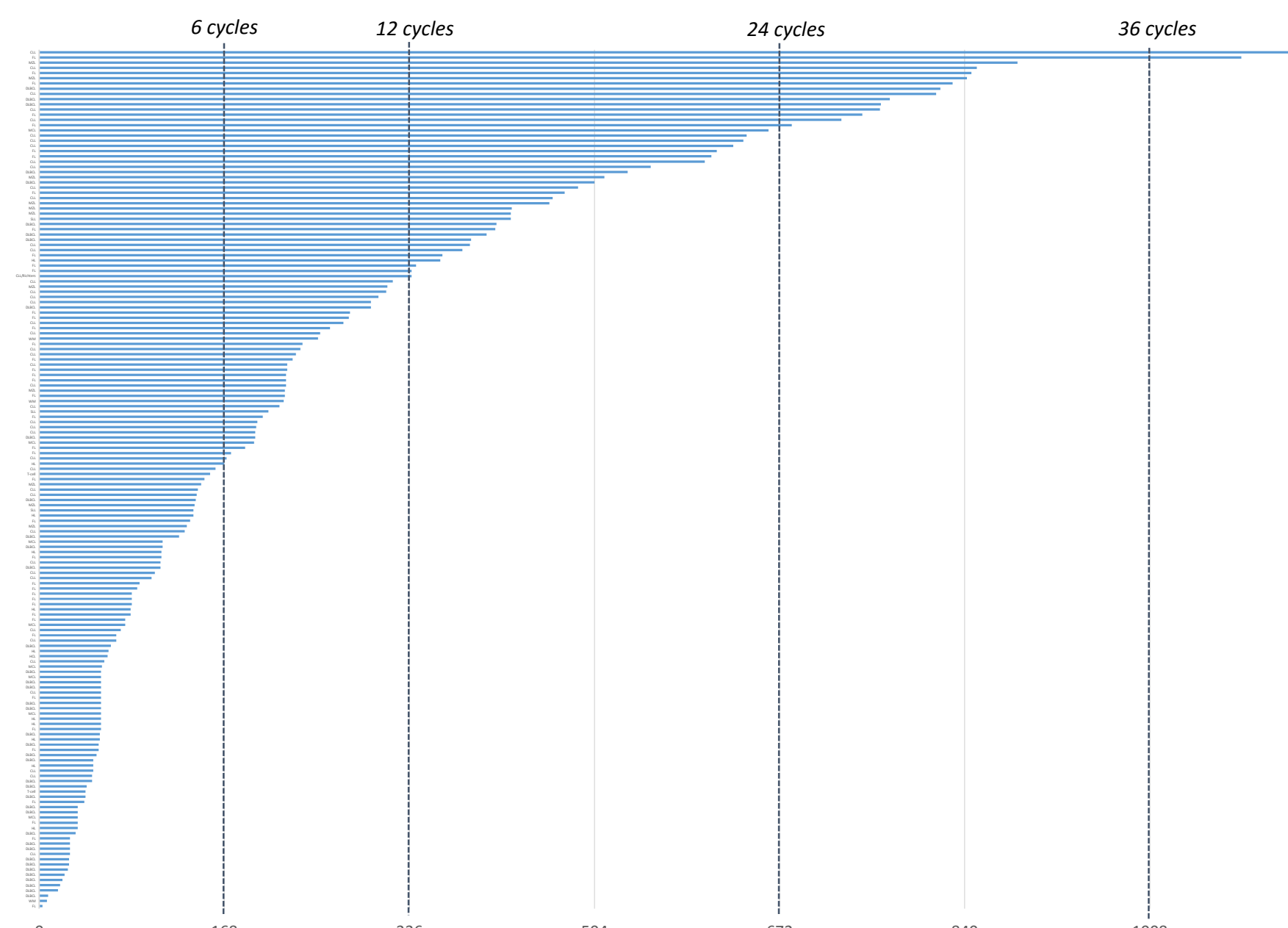
- <8% of patients discontinued due to a TGR-1202 related AE
- 13% of patients had a TGR-1202 dose reduction
- Grade 3/4 AST/ALT increase was 3% (8% all grades), predominantly observed above the Phase 3 dose
- Grade 3/4 pneumonia occurred in 5% of patients (8% all grades)
- Two events of pneumonitis (<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

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)
DLBCL	7	1	3	4 (57%)	2	1
iNHL	17	3	6	9 (53%)	6	2

- iNHL = FL & MZL
- Higher Doses: 1200 mg of the initial formulation, or ≥600 mg of the micronized formulation
- ORR in iNHL for patients treated at Higher Doses was not only greater with the combo (55%) as opposed to monotherapy (41%), but the depth of response was significantly greater with the addition of UTX (CR rate of 5% for monotherapy vs. 30% for the combo)
- Similarly, 3 complete responses observed in patients with DLBCL treated at Higher Doses occurred in patients receiving TGR + UTX
- A strong dose response was observed, with patients exposed to 800 mg of the micronized formulation achieving higher rates of response

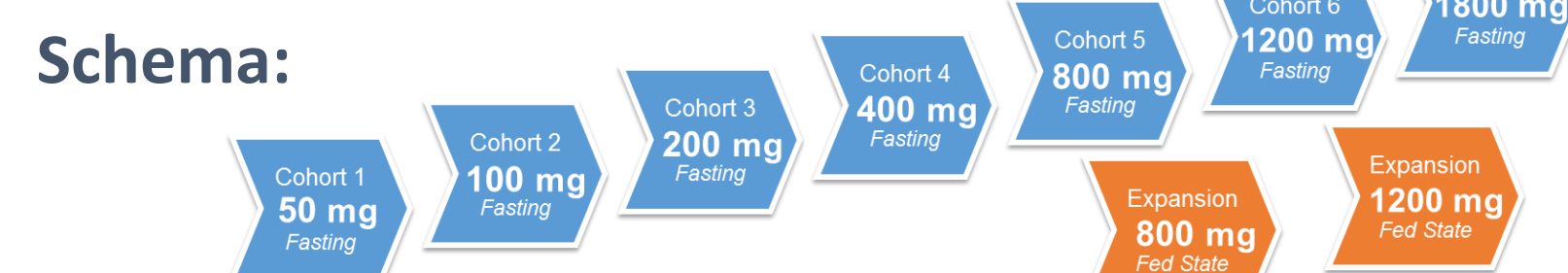
Study Design

TGR-1202-101: TGR-1202 Monotherapy

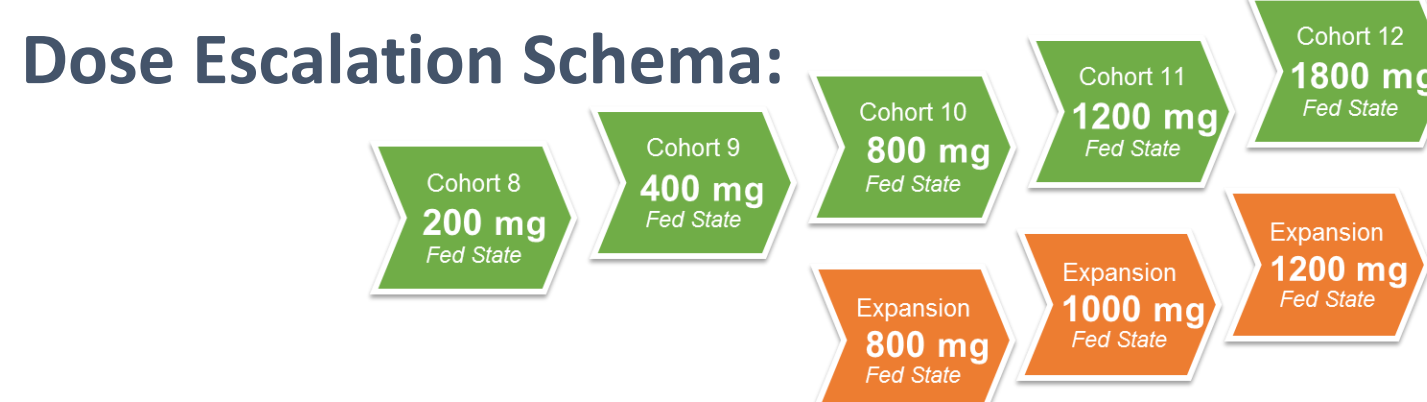
Study TGR-1202-101 (NCT01767766) is a first-in-human, Phase I study of TGR-1202 in patients with relapsed or refractory hematologic malignancies

- 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:

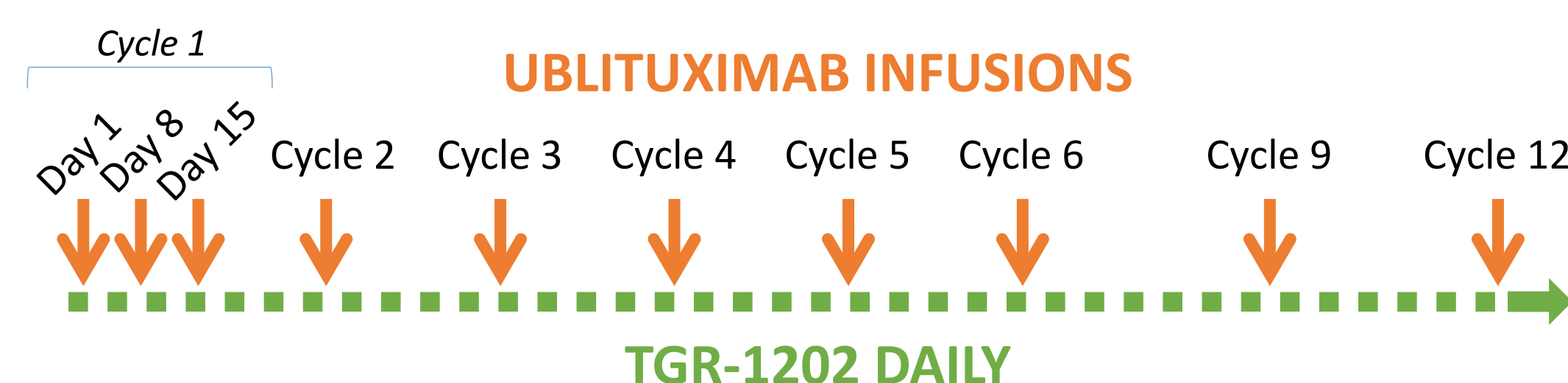
- Phase I:** 3+3 escalation evaluating Cycle 1 DLTs
- Phase Ib:** Dose Expansion

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:

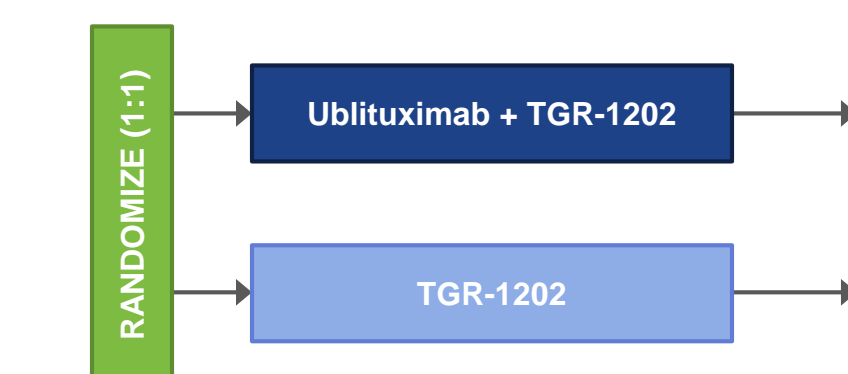
Efficacy is assessed Week 8, and every 12 weeks thereafter. After Month 12, all patients remain on TGR-1202 single agent. Ublituximab was initially administered on Days 1, 8 and 15 of Cycles 1 & 2 and Day 1 of Cycles 4, 6, 9 & 12. The protocol was amended to use a more convenient schedule as follows:



UNITY Registration Program

Phase 2b UNITY-DLBCL Study

- Enrolling patients with previously treated DLBCL of all subtypes
- US Study Chair: Owen A. O'Connor, MD, PhD
- Ex-US Study Chair: Pier-Luigi Zinzani, MD, PhD



Conclusions

- TGR-1202 is well tolerated and highly active in a broad population of heavily pretreated & high-risk patients with NHL as well as CLL (see EHA 2016 Poster P207), 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 DLBCL being explored further in registration directed UNITY-DLBCL Phase 2b Study, with a UNITY-iNHL study to commence by YE 2016. A Phase 3 study in patients with CLL, the UNITY-CLL study, is currently underway