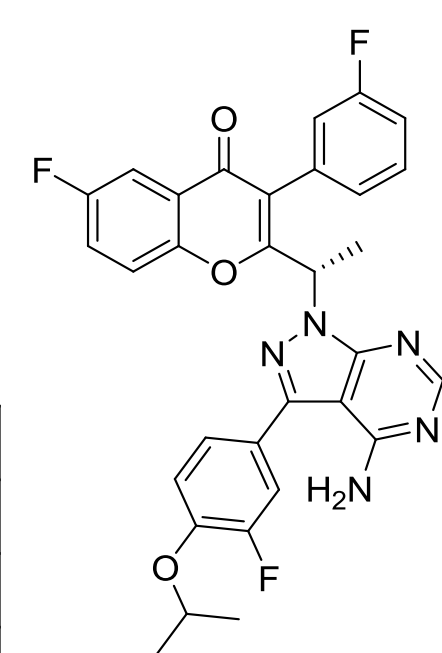


## Background

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- TGR-1202 is a novel, next generation PI3Kδ inhibitor, with a unique structure which contributes to:
  - Extended half-life and accumulation that enables once-daily dosing
  - Differentiated safety profile from other PI3Kδ inhibitors in development, notably absent of hepatotoxicity

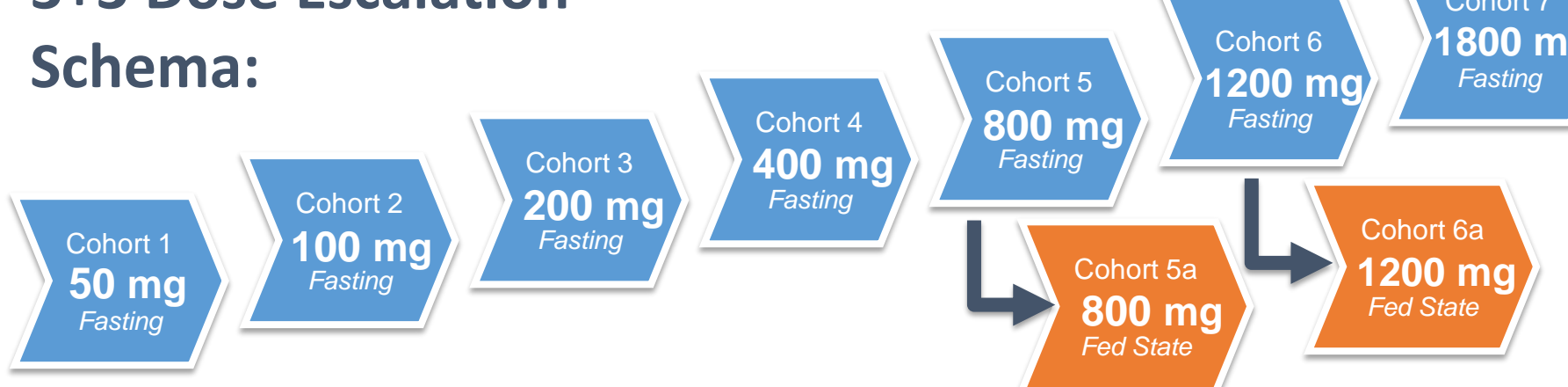


Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>10000	>50	>48	1
<sup>1</sup> Idelalisib	>300	>200	>40	1
<sup>2</sup> PI-145	>640	>34	>11	1

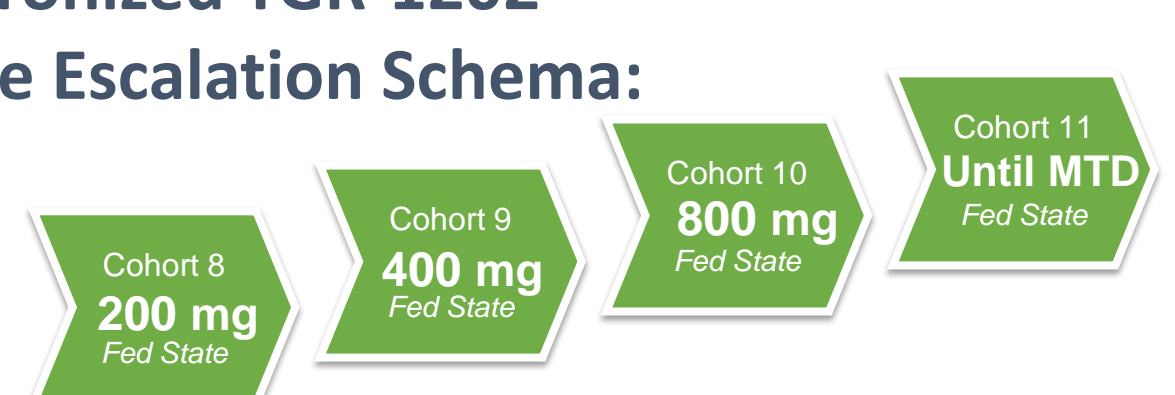
<sup>1</sup>Flinn et al. 2009; <sup>2</sup>Porter et al. 2012

## Study Design

### 3+3 Dose Escalation Schema:



### Micronized TGR-1202 Dose Escalation Schema:



- 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

## Study Objectives

### Primary Objectives

- To determine the Safety, Pharmacokinetics (PK), and Maximum Tolerated Dose (MTD) of TGR-1202

### Secondary Objectives

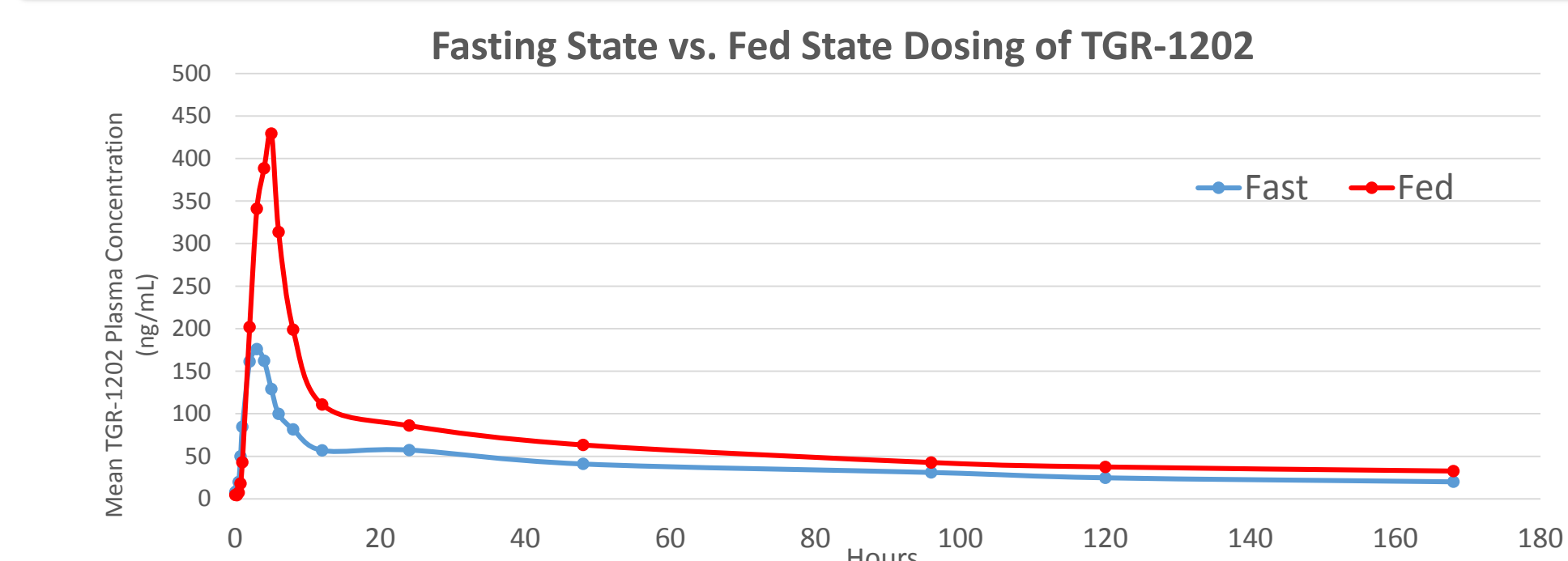
- To determine the Pharmacodynamics of TGR-1202 and assess Efficacy (overall response rate and duration of response)

## Key Eligibility Criteria

- Histologically confirmed B-cell non-Hodgkin lymphoma (NHL), CLL/small lymphocytic lymphoma (SLL), Hodgkin's Lymphoma (HL), and select other B-cell lymphoproliferative disorders
- Relapsed after, or refractory to, at least 1 prior treatment regimen with no limit on prior therapies
- ECOG performance status ≤ 2
- Adequate organ system function: ANC ≥ 750/μL; platelets ≥ 50 K/μL
- Patients with prior therapy with any drug that specifically inhibits PI3K and/or mTOR are excluded

## Pharmacokinetics

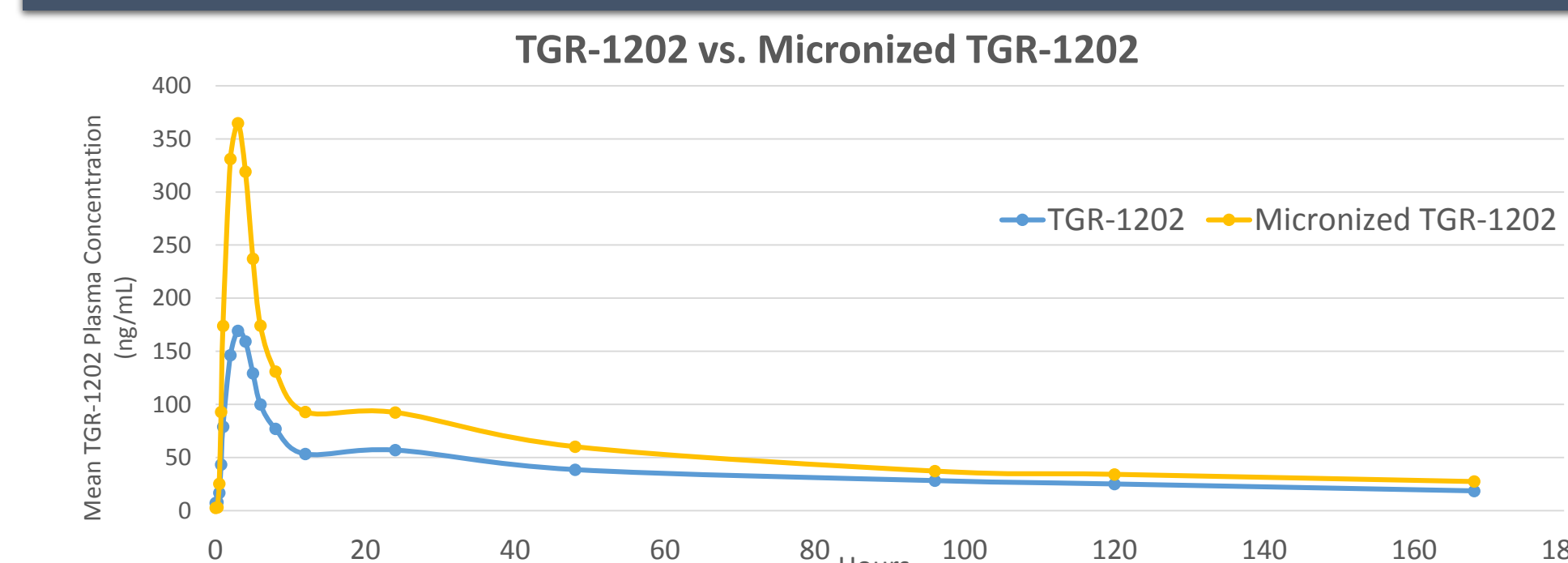
### Pharmacokinetic Food Effect on TGR-1202



Parameters	Geometric LS Means		Ratio	90% C.I.
	Fasting State	Fed State		
AUC <sub>0-t</sub> (ng·hr/mL)	6029.87	9692.02	1.61	1.40 – 1.84
AUC <sub>0-inf</sub> (ng·h r/mL)	8391.35	14047.17	1.67	1.42 – 1.98
C <sub>max</sub> (ng/mL)	176.78	483.15	2.73	2.34 – 3.19

- 24 subject healthy volunteer crossover study
- TGR-1202 dosed in a fasting state or within 30 min. of a high fat meal
- Mean t<sub>1/2</sub> under fed conditions: 96.0 hours

### Pharmacokinetics of Micronized TGR-1202

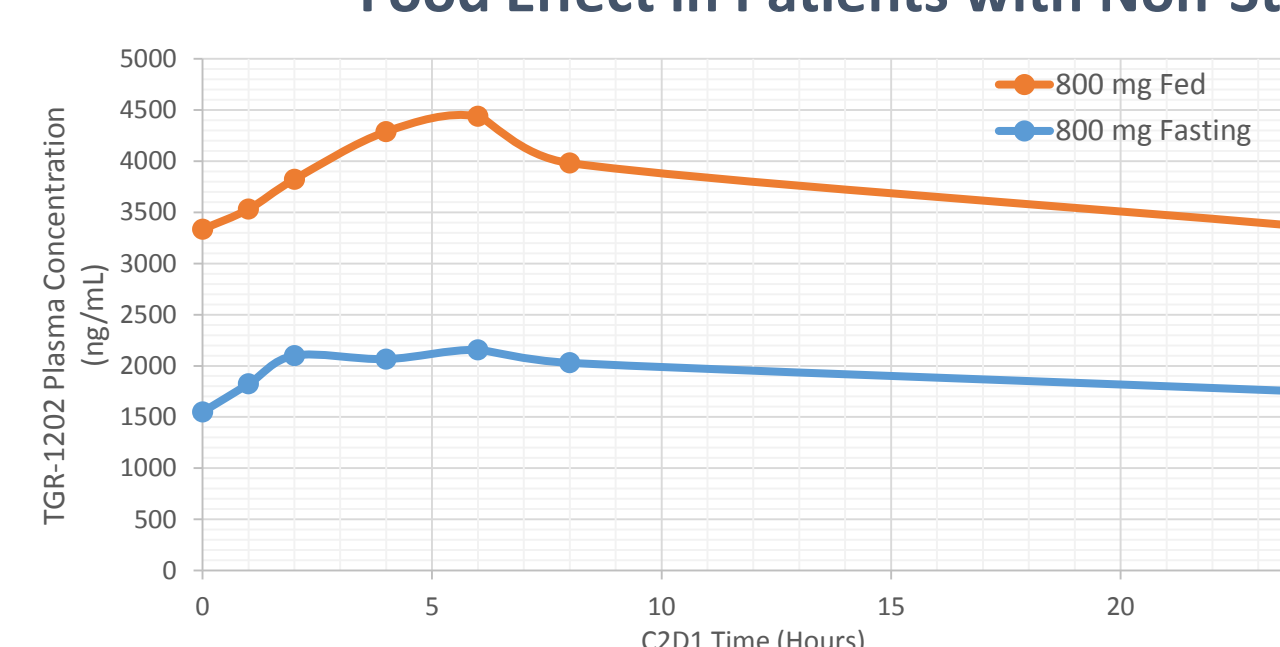


Parameters	Geometric LS Means		Ratio	90% C.I.
	Current TGR-1202	Micronized TGR-1202		
AUC <sub>0-t</sub> (ng·hr/mL)	5906.11	9439.82	1.60	1.49 – 1.71
AUC <sub>0-inf</sub> (ng·h r/mL)	7715.67	12378.19	1.60	1.46 – 1.76
C <sub>max</sub> (ng/mL)	166.20	371.70	2.24	2.02 – 2.47

- 24 subject healthy volunteer crossover study
- Subjects dosed either TGR-1202 or improved micronized formulation
- Mean t<sub>1/2</sub> of micronized TGR-1202: 73.1 hours

## Pharmacokinetics in Patients

### Food Effect in Patients with Non-Standardized Meals



	800 mg		1200 mg	
	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ugXhr/mL)	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ugXhr/mL)
Fasting	N=7 641 (63)	7.88 (56)	N=3 709 (46)	8.68 (78)
Fed	N=10 1097 (51)	11.28 (62)	N=4 2047 (54)	21.04 (62)
Fed/Fast Ratio	1.7	1.4	2.9	2.4

- Patients in expansion Cohorts 5a and 6a were instructed to take TGR-1202 with food
- Results are comparative to a randomized, two-way crossover trial in healthy subjects receiving a standard FDA breakfast
- Figure shows steady-state pharmacokinetics for CLL & FL patients at 800 mg fast (n=3) and 800 mg fed (n=5) patients

## Results

### Demographics

Evaluable for Safety (n)	40	
Evaluable for Efficacy* (n)	33	
Median Age, years (range)	60.5 (22 – 82)	
Male/Female	30/10	
Histology	13 CLL	2 MCL
	10 FL	2 MZL
	6 HL	1 HCL
	5 DLBCL	1 LPL
ECOG 0/1/2	13/27/0	
Prior Therapies, median (range)	3 (1 – 14)	
Patients with ≥ 3 Prior Therapies (%)	22 (55%)	
Patients with prior Rituximab-Chemo	34 (85%)	

\*Not evaluable: 3 Too Early To Evaluate (all at 1200 mg Fed), 2 Non-Compliant (both at 1800 mg), 1 Failed Inclusion/Exclusion (Richter's Transformation prior to entry), 1 Rapid PD within 6 days of enrollment at lowest dose level

## Safety

Adverse Events	Possibly/Probably/Related to TGR-1202 (n=40)	
	All Grades (>5% of Patients) Patients, n (%)	Grade 3 Patients, n (%)
Diarrhea	7 (18)	1 (3)
Nausea	6 (16)	-
Vomiting	5 (13)	-
Fatigue	4 (10)	-
Headache	4 (10)	-
Neutropenia	3 (8)	2 (5)
Hypokalemia	3 (8)	1 (3)
Weakness	3 (8)	-

- No Grade 4 or greater related events reported

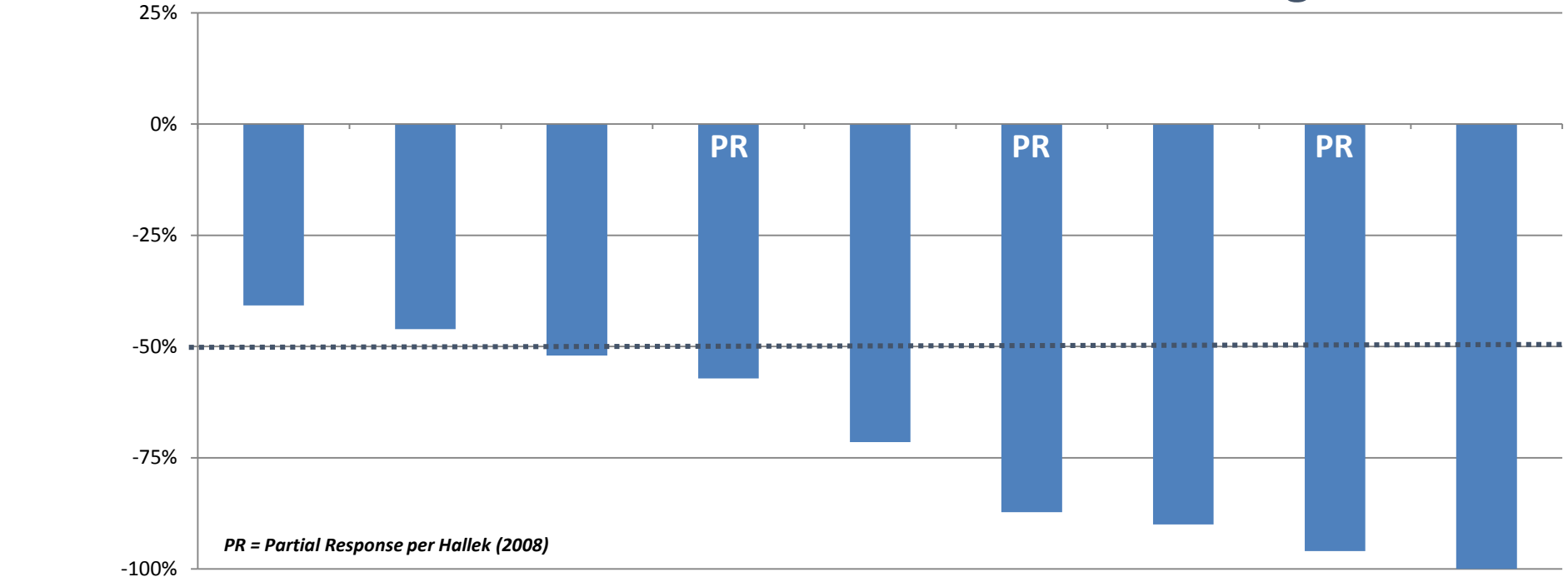
### Select Adverse Events At Doses ≥ 800 mg Possibly/Probably/Related Fed State (n=14) vs. Fasting State (n=13)

	Grades 1/2 Patients, n (%)		Grade 3 Patients, n (%)	
	Fasting	Fed	Fasting	Fed
Nausea	5 (38)	1 (7)	-	-
Vomiting	4 (31)	1 (7)	-	-
Diarrhea	2 (15)	1 (7)	1 (8)	-
Fatigue	1 (8)	1 (7)	-	-
Increase ALT/AST	-	-	-	-
Colitis	-	-	-	-

- No patient has been discontinued due to a drug related adverse event
- MTD has not been reached and dose escalation is ongoing with micronized TGR-1202 starting at 200 mg QD

## Efficacy in Chronic Lymphocytic Leukemia

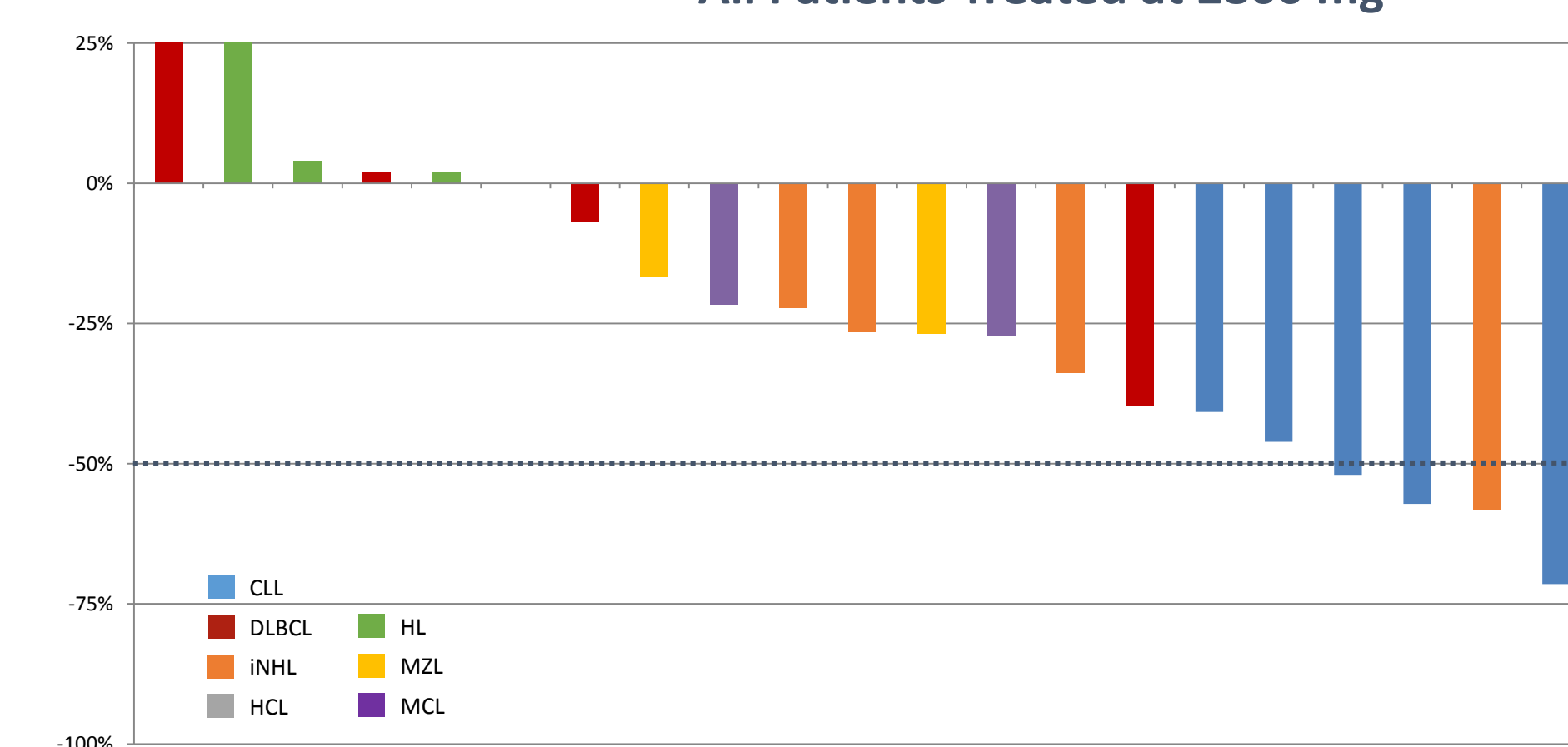
### Best Percent Change from Baseline in Nodal Size Evaluable CLL Patients Treated at ≥800 mg



- 78% (7/9) of CLL patients treated at 800 mg or higher achieved a nodal PR (median nodal reduction of 71%)
- Remaining two patients achieved >40% nodal reduction at first response assessment and remain on study awaiting next scan
- Nodal reductions shown to improve with time on TGR-1202

## Overall Efficacy

### Best Percent Change from Baseline in Nodal Size All Patients Treated at ≥800 mg



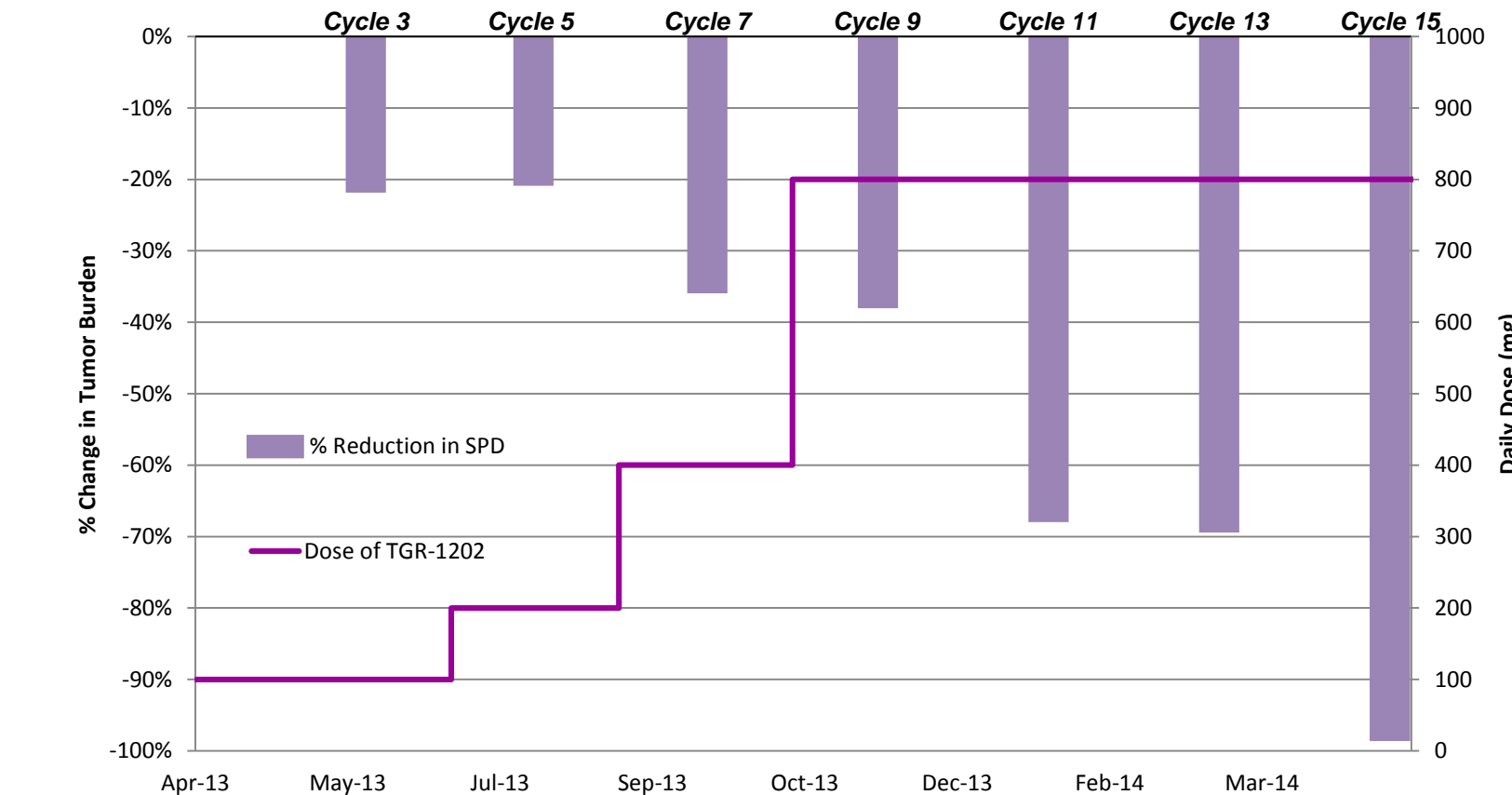
- Responses reported at dose levels ≥800 mg QD in:
  - FL (1 PR of 2 evaluable patients started at ≥800 mg)
  - Hodgkin's Lymphoma (1 PR of 4 evaluable)
  - CLL (7 nPR of 9 evaluable, 3 of which are in PR per Hallek 2008 criteria)

## Conclusions

- TGR-1202 is a once-daily PI3Kδ inhibitor with single agent activity observed in patients with a variety of relapsed/refractory hematologic malignancies
- Marked activity has been observed in patients with relapsed refractory CLL, with a 78% nodal response rate at doses ≥ 800 mg (median time on study of 6+ months)
- TGR-1202 has been well tolerated, with no drug related transaminase elevations and no events of colitis reported, with 38% (10/26) of evaluable patients treated at ≥ 800 mg on study over 6 months and some on daily TGR-1202 for over a year, demonstrating an adverse event profile which supports combination therapy
- No MTD has been achieved and dose escalation continues with micronized formulation and fed state dosing which is projected to provide a 3-4X increase in exposure over dosing to date, with better GI tolerability demonstrated
- Additional studies are ongoing evaluating TGR-1202 in combination with approved and novel agents, with Phase III studies in development

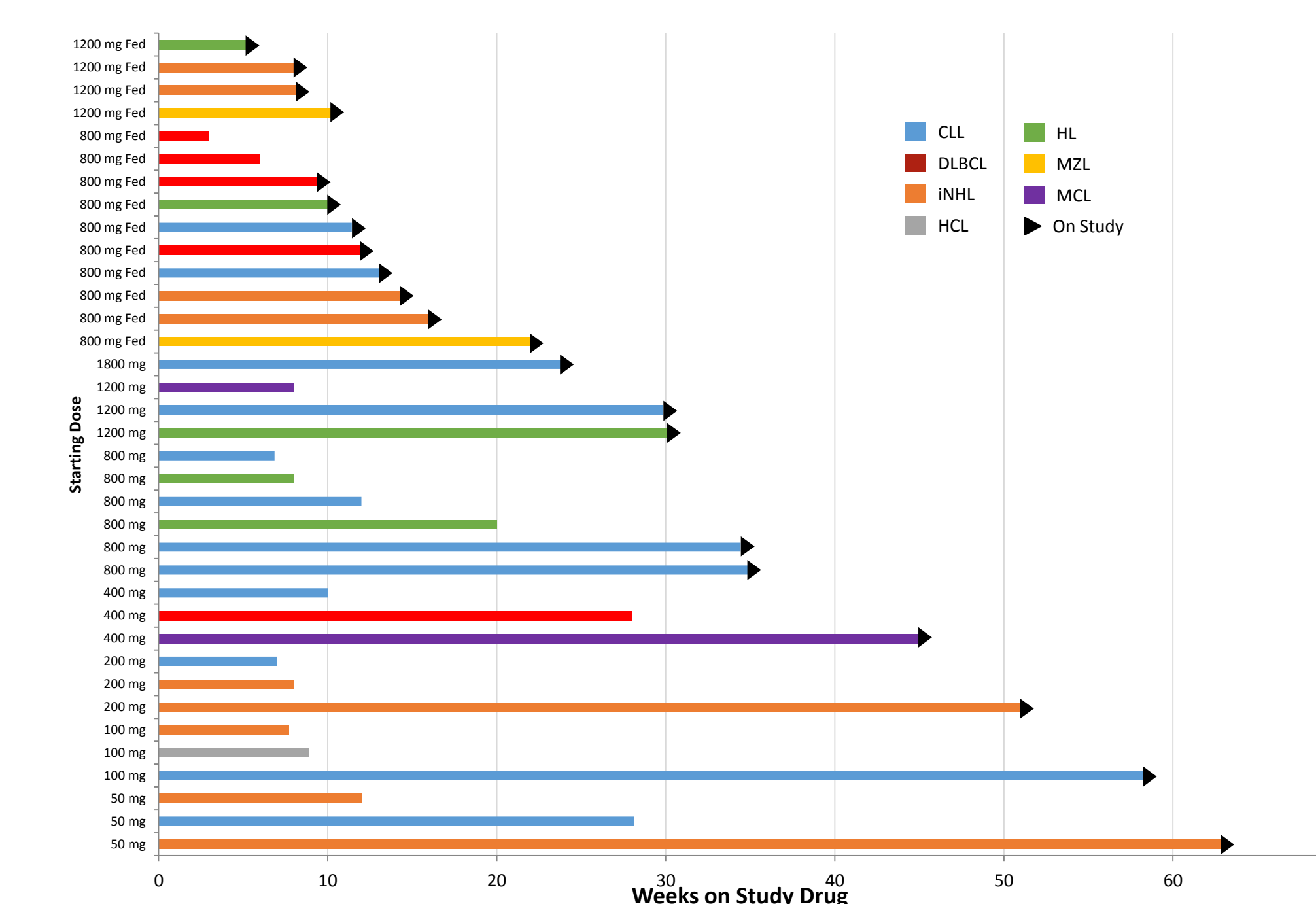
## Evolving Responses with TGR-1202 in CLL

### CLL Patient Enrolled at 100 mg QD, Currently in PR at 800 mg QD



- Patients in previous cohorts are allowed to dose-escalate once a new dose level has cleared safety evaluation
- All patients on study are currently being treated at 800 mg QD or higher
- Strong threshold effect seen at 800 mg QD
- Decreasing lymph node SPD correlates with higher TGR-1202 dose levels and extended duration of dosing

## Current Status of Evaluable Patients



- 2 patients at 1800 mg QD were removed due to non-compliance