Clinical activity and safety profile of TGR-1202, a novel once daily PI3Kδ inhibitor, in patients with CLL and B-Cell lymphoma.

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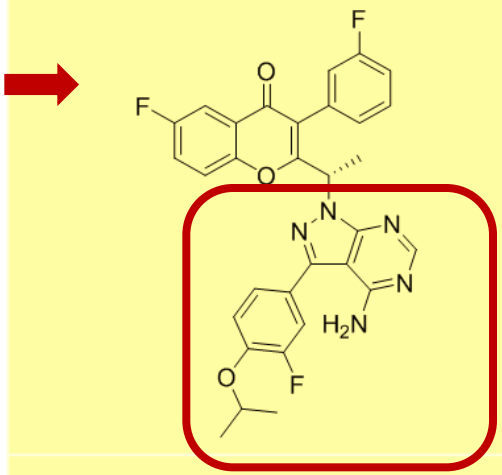
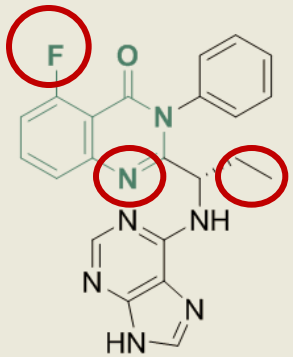
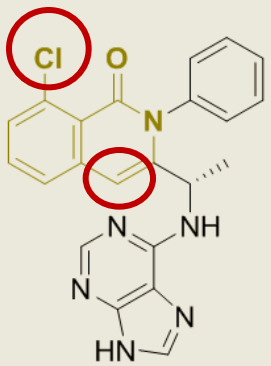
TGR-1202: Next Generation PI3Kδ Inhibitor

TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

- Significant structural differences compared to other PI3Kδ
- Favorable PK profile that allows once-daily oral dosing
- Initial clinical experiences observed; significant nodal response in R/R CLL (88%)[1]

[1]Burris et al, ASCO 2015

STUDY DESIGN: PHASE 1 FIRST-IN-HUMAN STUDY

- 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

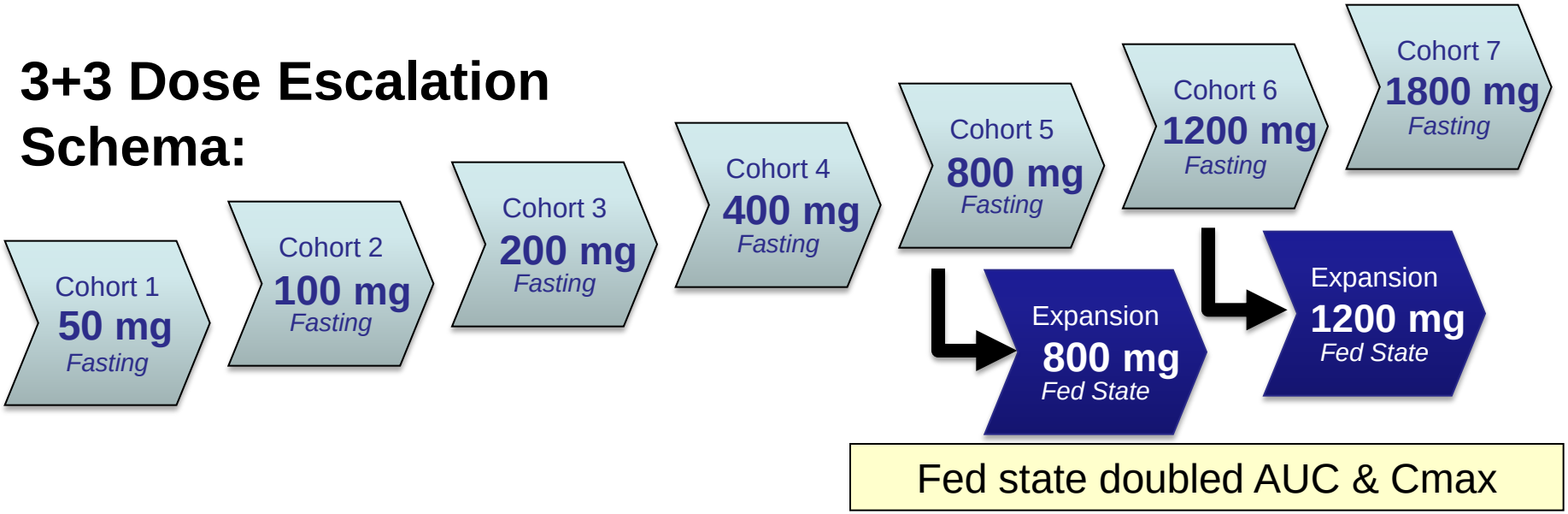
[1]Burris et al, ASCO 2015

Study Design: Eligibility & Objectives

- Histologically confirmed B- and T-cell NHL, CLL/SLL, Hodgkin's lymphoma (HL)
  - Relapsed after, or refractory to, at least 1 prior treatment regimen with no limit on prior therapies
- ECOG performance status ≤ 2 with 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 in dose-escalation cohorts only (allowed in expansions)
- Primary Objectives: Evaluate safety, PK, MTD, DLT
- Secondary Objectives: PD, ORR, DOR

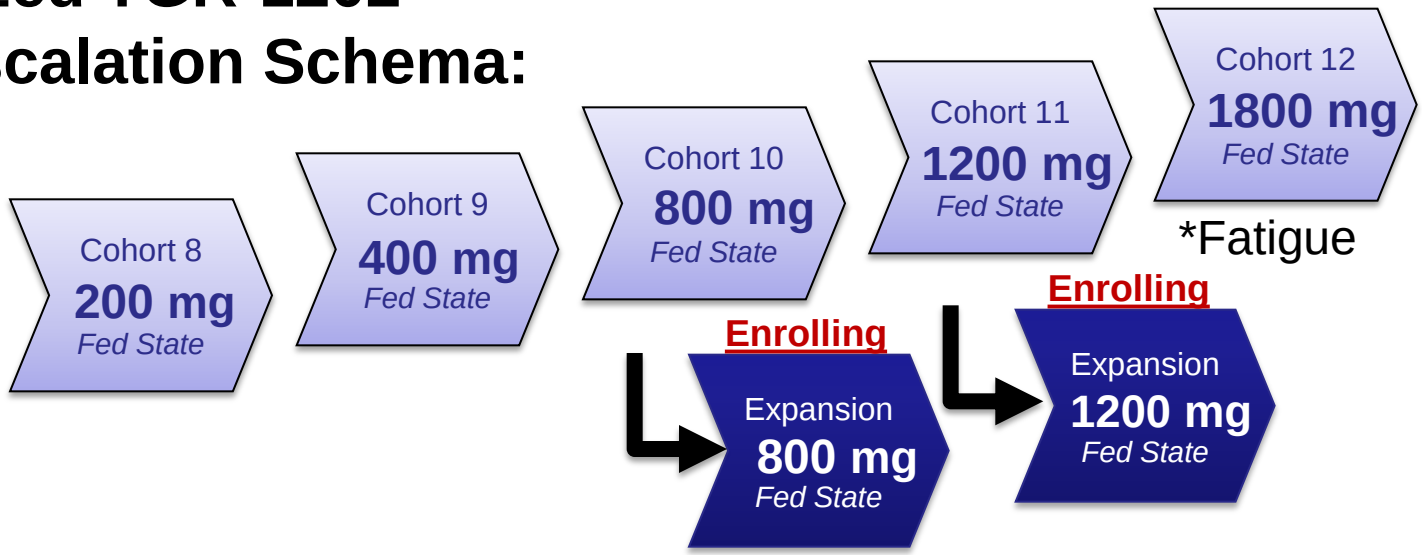
TGR-1202-101: Dose Escalation Schema

3+3 Dose Escalation Schema:



Fed state doubled AUC & Cmax

Micronized TGR-1202 Dose Escalation Schema:



TGR-1202-101: DEMOGRAPHICS

Evaluable for Safety (n)	**66**	
Evaluable for Efficacy (n)	**51**	
Median Age, years (range)	**66 (22 – 85)**	
Male/Female	**46/20**	
Histology	**20 CLL**	**5 MCL**
	17 FL	**3 MZL**
	10 DLBCL	**1 HCL**
	9 HL	**1 WM**
ECOG 0 / 1 / 2	**22 / 43 / 1**	
Prior Therapies, median (range)	**3 (1 – 14)**	
Patients with ≥ 3 Prior Therapies (%)	**36 (55%)**	
Patients Refractory to Prior Therapy	**34 (52%)**	

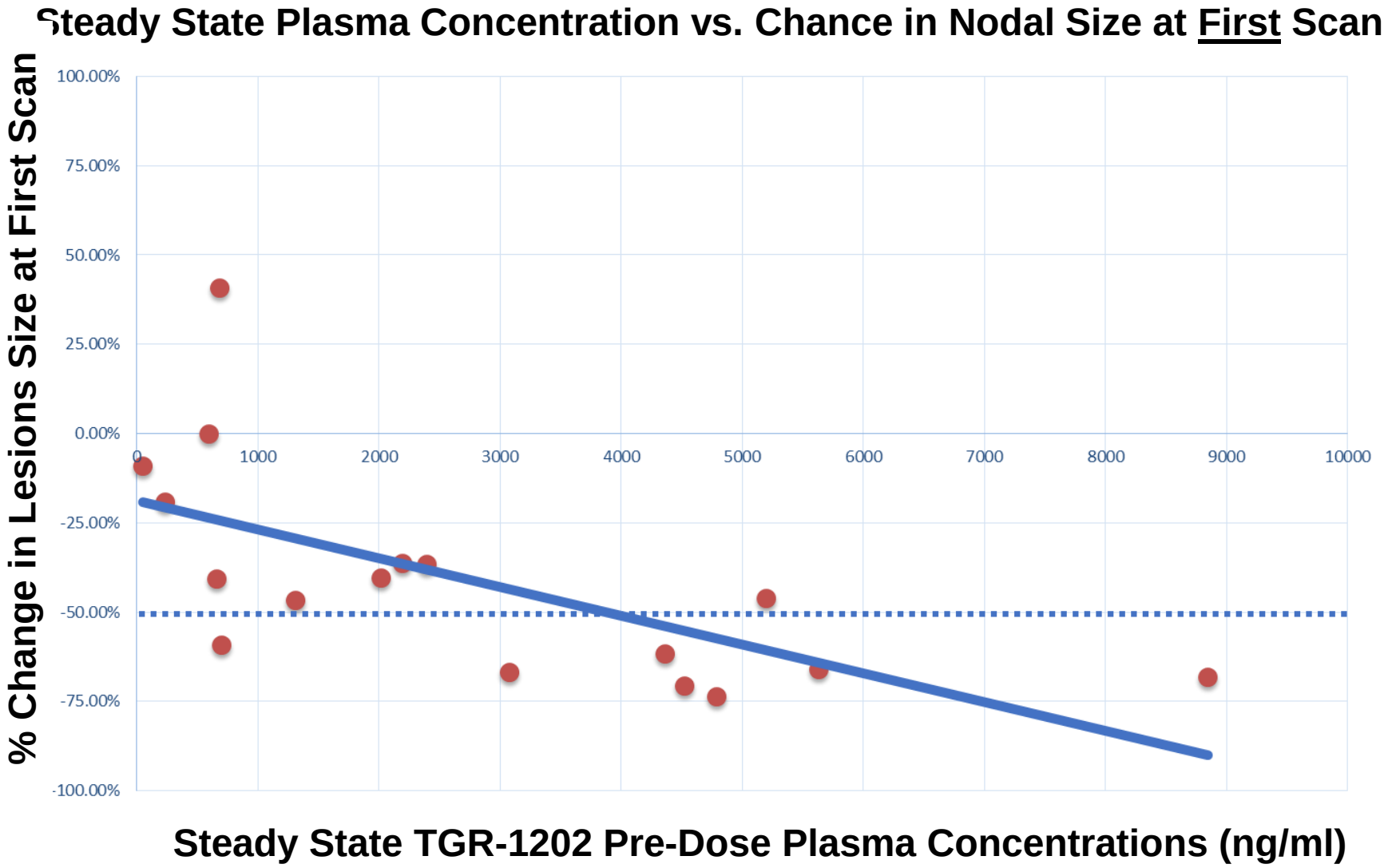
TGR-1202-101: SAFETY

All Events in >10% of Pts (N=66)				
AE	All Grades		Gr. ¾	
	N	%	N	%
Nausea	27	41%	0	0%
Diarrhea	21	32%	1	2%
Fatigue	21	32%	2	3%
Headache	15	23%	0	0%
Vomiting	15	23%	0	0%
Cough	14	21%	0	0%
Decreased Appetite	11	17%	0	0%
Rash	11	17%	3	5%
Constipation	9	14%	1	2%
Hypokalemia	9	14%	3	5%
Anemia	8	12%	5	8%
Dizziness	8	12%	0	0%
Dyspnea	8	12%	3	5%
Neutropenia	8	12%	7	11%
Pyrexia	8	12%	0	0%
Abdominal Pain	7	11%	0	0%

- No significant dose or time dependent trends in AE's
- 31 patients on study 6+ months
- 3 patients (<5%) have discontinued due to an AE

TGR-1202: Dose & Exposure Related Response

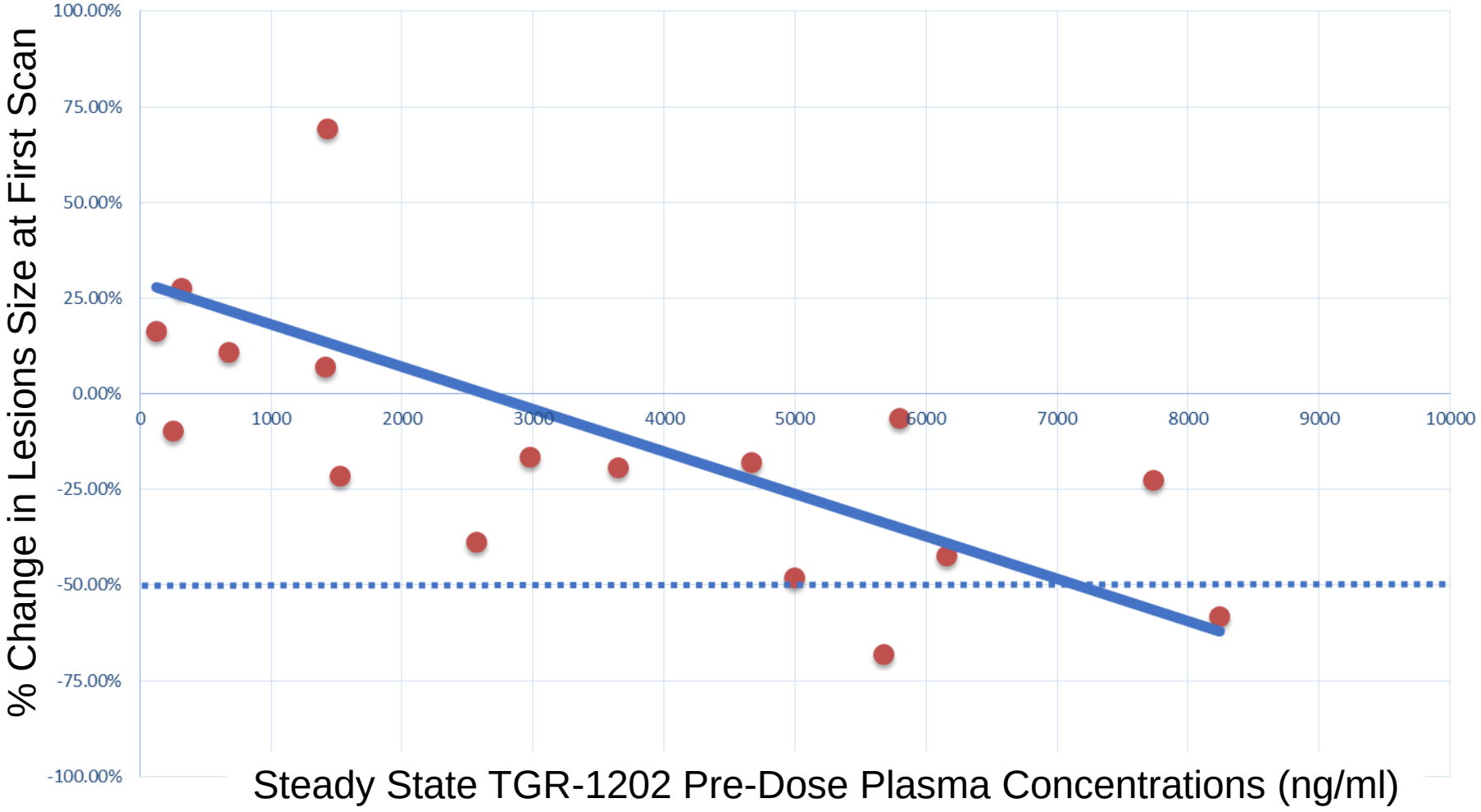
Exposure Response Relationship in CLL



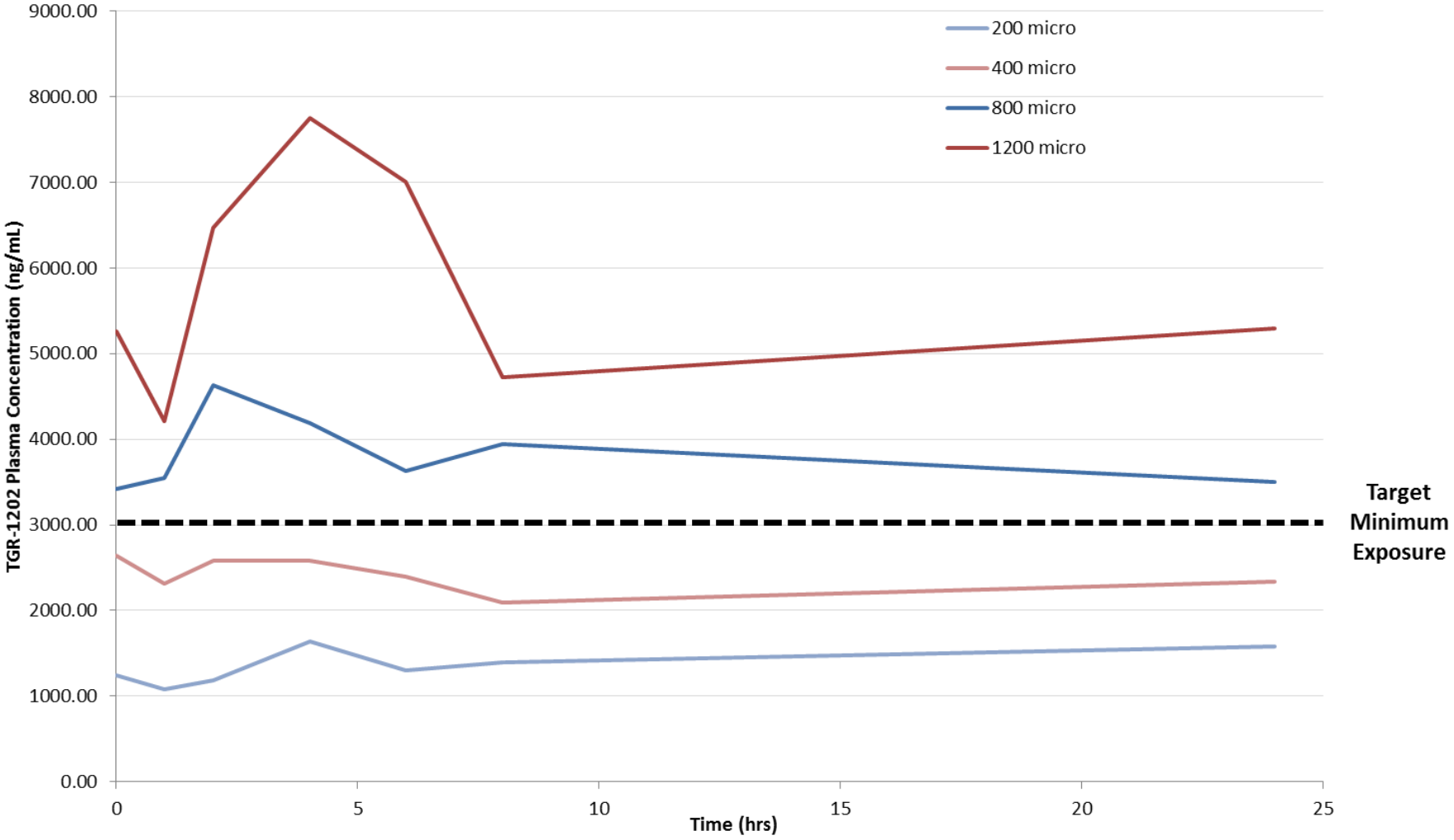
TGR-1202: Dose & Exposure Related Response

Exposure Response Relationship in iNHL (FL & MZL)

Steady State Plasma Concentration vs. Chance in Nodal Size at First Scan



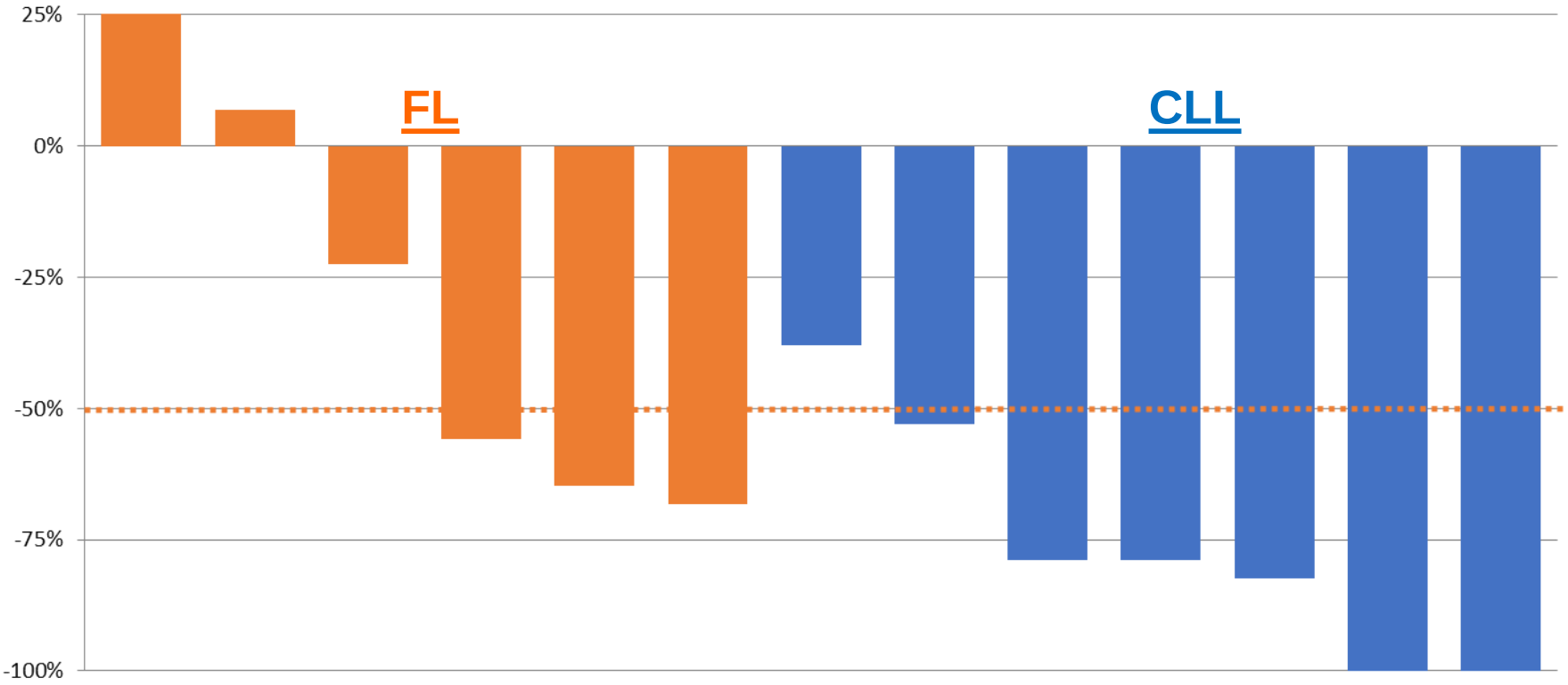
TGR-1202: Steady State Pharmacokinetics



EFFICACY WITH "HIGHER DOSE" TGR-1202

Best Percent Change from Baseline in Nodal Size

Evaluable CLL & FL Patients Treated at "Higher Doses"

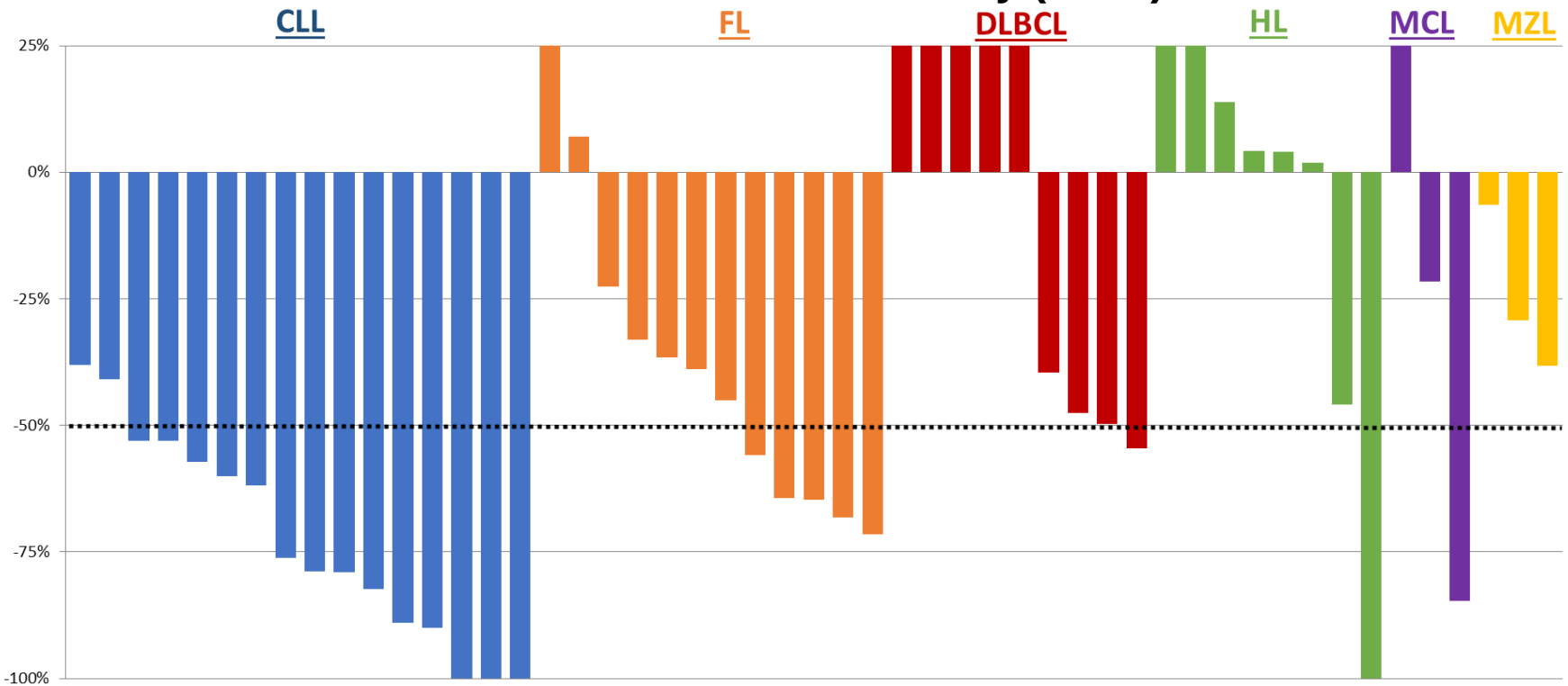


- "Higher Doses" of TGR-1202 (1200 mg initial formulation, or ≥ 600 mg micronized) demonstrated rapid and profound responses

TGR-1202: Overall Efficacy

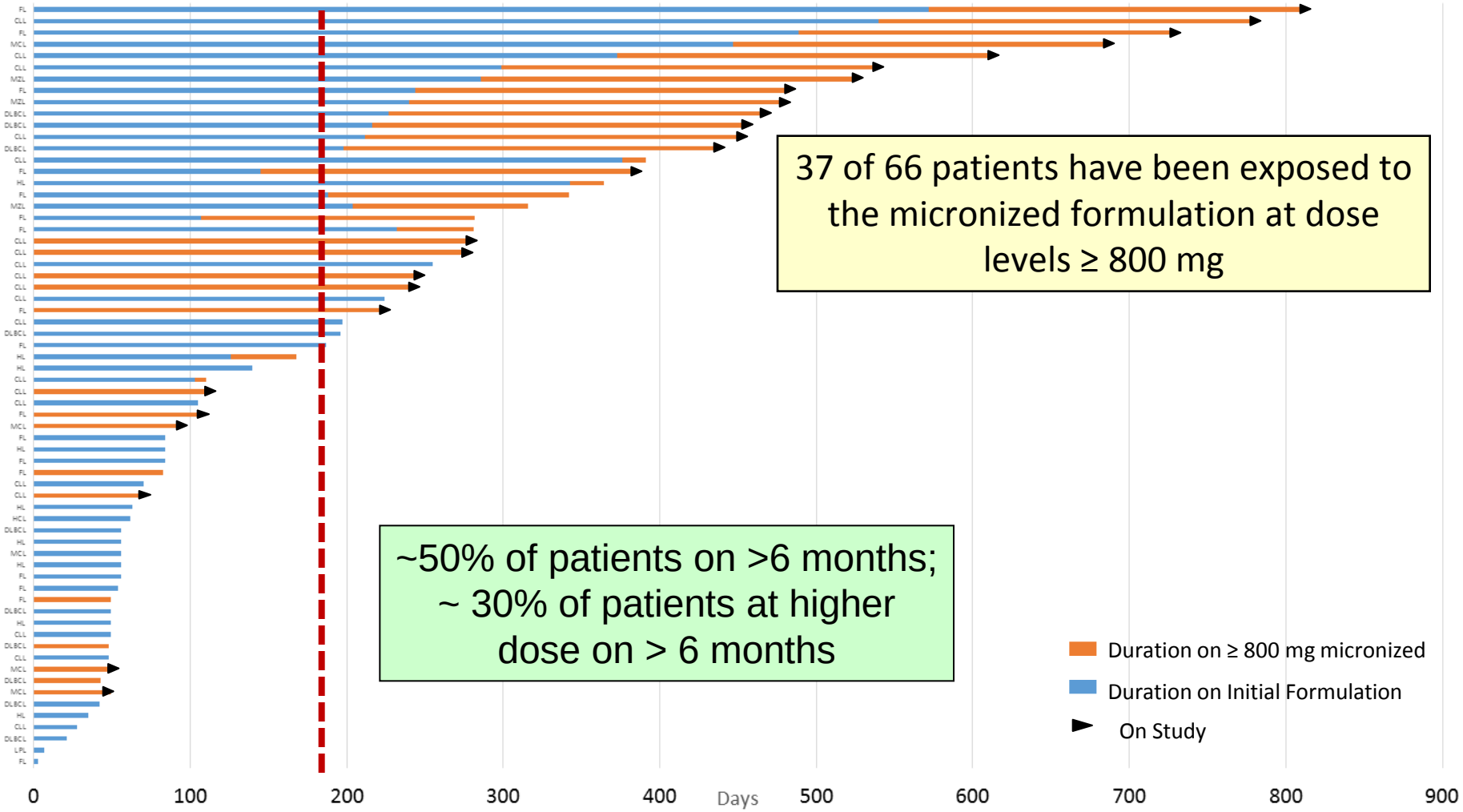
Best Percent Change from Baseline in Nodal Size

Patients Evaluable for Efficacy (N=51)



- 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

TGR-1202-101: Time on Study



- 25 of 37 patients exposed to ≥ 800 mg micronized currently remain on study
  - **Median PFS of 9.5+ months amongst these patients**

Comparison of Safety Profiles of Other PI3K Inhibitors

	Idela + Ofa (ASCO '15)[2] (n=173)	Duvelisib (ASCO '15)[3] (n=18)	Idelalisib Label (CLL & NHL)[1] (n=256)	TGR-1202 All Studies (ASCO 2015)[4] (n=137)
	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Diarrhea/ Colitis	20%	22%	10%	1%**
Pneumonia	13%	N/A	16%	4%
ALT Elevations	N/A	N/A	11%	2%
AST Elevations	N/A	N/A	7%	2%
ALT/AST Elevations	13%	17%	N/A	2%
Discontinuations due to AE	31%	33%	12%	4%

****No Cases of Colitis Reported with TGR-1202**

[1]Aggregated from Idelalisib Prescribing Information; [2]Jones et al, ASCO 2015; [3]Patel et al, ASCO 2015; [4]Aggregated from Burris et al, Lunning et al, Fowler et al, ASCO 2015

CONCLUSIONS

- TGR-1202 is a once-daily PI3Kδ inhibitor with single agent activity in a variety of relapsed and refractory hematologic malignancies.
- Well tolerated with patients on daily TGR-1202 for upwards of 2+ years
  - Differentiated AE profile: hepatic-toxicity and colitis
  - Discontinuations due to AE's minimal
- Safety and activity profile supports combination therapy with other novel targeted agents
- Expansion cohorts open and enrolling at the 800 mg and 1200 mg dose levels of the micronized formulation with Phase III studies in development

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- **Thank you to the patients and families for their participation**

- **Participating Centers:**

SARAH CANNON
Fighting Cancer Together.

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Thank You!

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