TG Therapeutics

2014 ASH Analyst & Investor Event

December 8, 2014

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Event Agenda & Speakers

AGENDA	SPEAKER
Overview & Introductions	Michael S. Weiss, CEO of TGTX
TG-1101 + ibrutinib	Dr. Jeff P. Sharman
Q&A Session	Dr. Sharman
TG-1101 (ublituximab) Overview	Dr. Owen A. O'Connor
TGR-1202 Data Review	Dr. Manish R. Patel
TG-1101 + TGR-1202 Data Review	Dr. Nathan Fowler & Dr. Matthew Lunning
Patient Experience Anecdote	
Q&A Session	Dr.'s O'Connor, Patel, Fowler & Lunning
Closing Remarks	

Ublituximab (TG-1101), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody, in Combination with Ibrutinib Is Highly Active in Patients with Relapsed and/or Refractory CLL and MCL: Results of a Phase II Trial

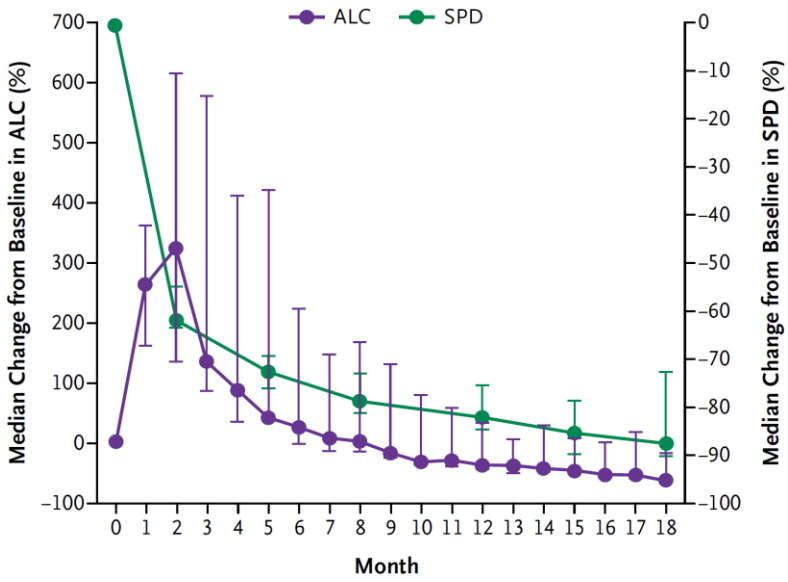
Jeff P. Sharman, MD

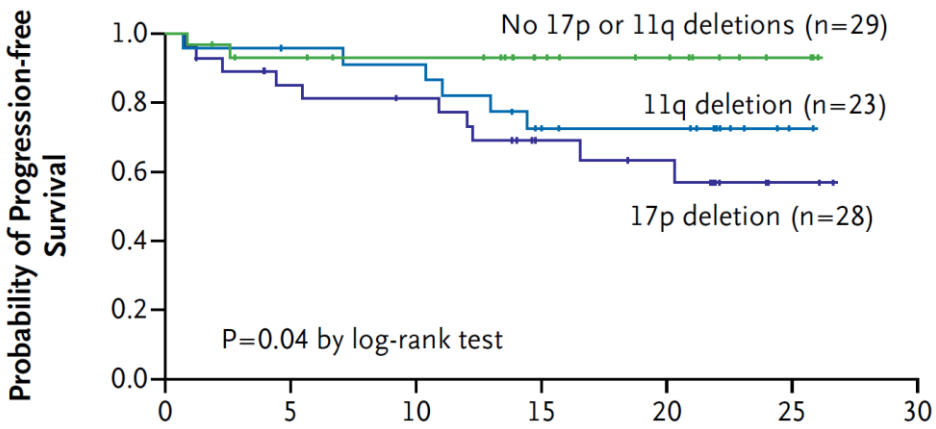
Jeff P. Sharman, MD[1,2], Charles M. Farber, MD, PhD[3], Daruka Mahadevan, MD, PhD[4], Marshall T. Schreeder, MD[5], Heather D. Brooks, MD[1,6], Kathryn S. Kolibaba, MD[1,7], Suzanne R. Fanning, DO[1,8], Leonard M. Klein, MD[1,9], Peter Sportelli[10], Hari P. Miskin, MS[10], Michael S. Weiss[10] and Daniel R. Greenwald, MD[1,11]

[1]US Oncology Research, The Woodlands, TX; [2]Willamette Valley Cancer Institute, Springfield, OR; [3]Carol G. Simon Cancer Center, Morristown, NJ; [4]West Cancer Center/UTHSC, Memphis, TN; [5]Clearview Cancer Institute, Huntsville, AL [6]Blue Ridge Cancer Care, Blacksburg, VA; [7]Compass Oncology, Vancouver, WA; [8]Greenville Heath System Cancer Institute, Greenville, SC; [9]Illinois Cancer Specialists, Niles, IL; [10]TG Therapeutics, Inc., New York, NY; [11]Cancer Center of Santa Barbara, Santa Barbara, CA

Single Agent Ibrutinib (Historical Data)

- Ibrutinib was approved for the treatment of patients with CLL with 17p deletion, and patients with CLL who have received at least one prior therapy based on the following data:





- Nodal reductions on ibrutinib monotherapy are accompanied by marked lymphocytosis
- Patients with “high-risk” cytogenetic abnormalities have been shown to have poorer prognoses on ibrutinib monotherapy

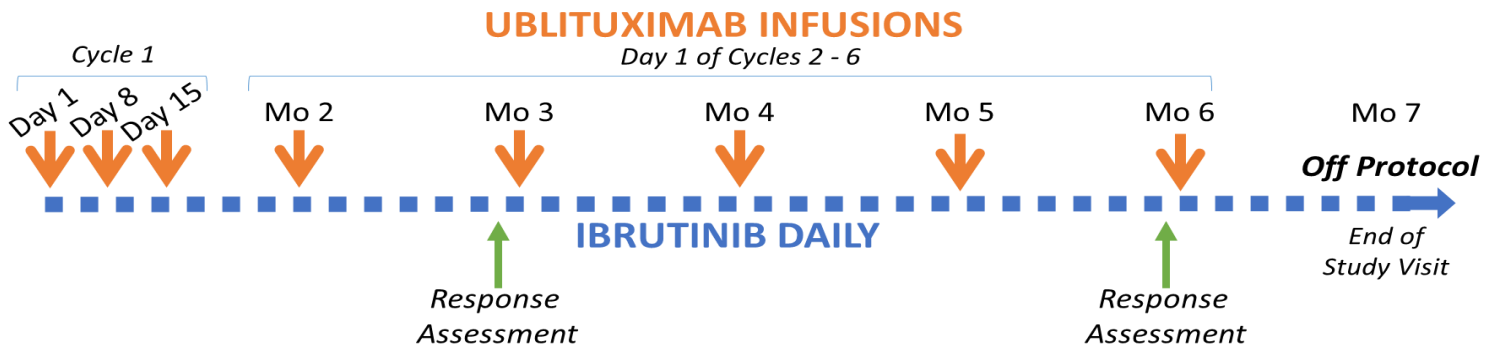
Source: Ibrutinib FDA Label; Byrd et al. NEJM 2013

Study Design

A safety run-in (Part 1) of the study is designed to enroll 6 patients per cohort. Efficacy is assessed at 3 and 6 months. After month 6, all patients can stay on ibrutinib single agent, off protocol.

Dose Escalation Schema:

	MCL		CLL/SLL	
Cohort	UTX Dose (Days 1, 8, 15)	Ibrutinib (Daily)	UTX Dose (Days 1, 8, 15)	Ibrutinib (Daily)
1	900 mg	560 mg	600 mg	420 mg
2	-	-	900 mg	420 mg



Patient Demographics

	CLL	MCL
Evaluable for Safety, (n)	44	8
Evaluable for Efficacy, † (n)	39	8
Median Age, years (range)	71 (39 – 86)	72 (55 – 80)
Male/Female	22/22	7 / 1
ECOG, median	1	1
Prior Regimens, median (range)	2 (1 – 7)	2 (1 – 6)
≥ 3 Prior Regimens	16 (36%)	3 (38%)
Prior Anti-CD20	41 (93%)	8 (100%)
Prior Alkylating Agent	28 (64%)	8 (100%)
Prior Purine Analog	22 (50%)	-

†5 patients came off study prior to first disease assessment: 1 due to ibrutinib related AE (diarrhea); 2 due to multiple non-drug related AE's; 2 withdrew consent

- 51% of evaluable CLL patients (20/39) were classified as "high-risk" exhibiting a 17p del, 11q del, and/or p53 mutation

Study Results - Safety

All Causality AE's in > 5% of Patients (n=54)		
Adverse Event	**All Grades** n (%)	**Grade 3/4** n (%)
Infusion reaction	18 (33%)	3 (6%)
Diarrhea	15 (28%)	2 (4%)
Fatigue	14 (26%)	1 (2%)
Rash	11 (20%)	2 (4%)
Bruising	8 (15%)	-
Nausea	8 (15%)	-
Mucositis	8 (15%)	-
Cough	7 (13%)	-
Edema	7 (13%)	-
Fever	6 (11%)	-
Thrombocytopenia	6 (11%)	2 (4%)
Neutropenia	3 (6%)	3 (6%)

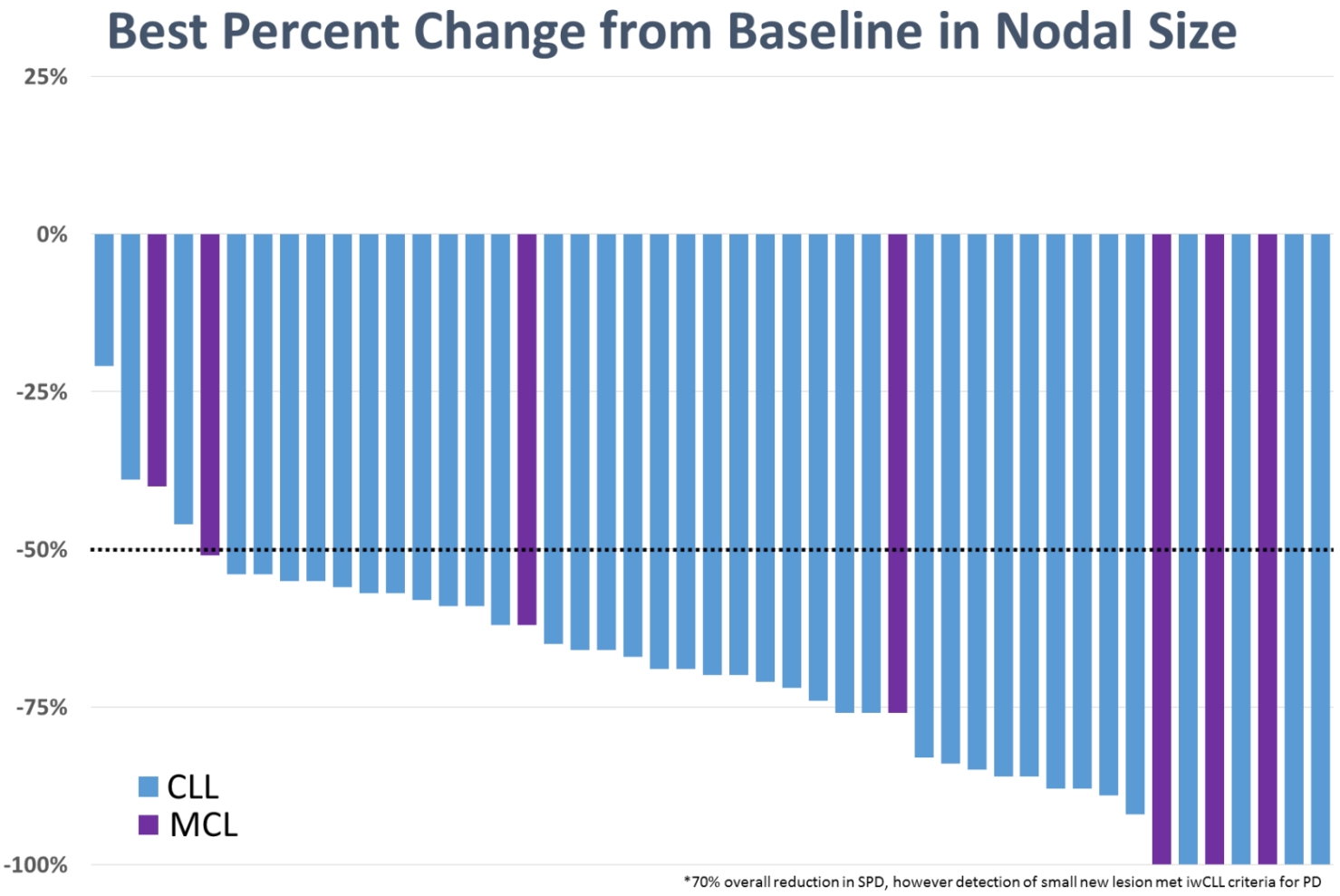
- All rash and Grade 3/4 diarrhea events deemed related to ibrutinib per investigator assessment.

Dose Reductions & Treatment Discontinuations

- Ibrutinib dose reduced in 4 patients (diarrhea, rash, cough, fatigue)
- No patients had their ublituximab dose reduced
- 2 patients discontinued due to ibrutinib related AEs (rash, diarrhea)
- 2 patients discontinued due to non-related AEs (pre-existing AE's)

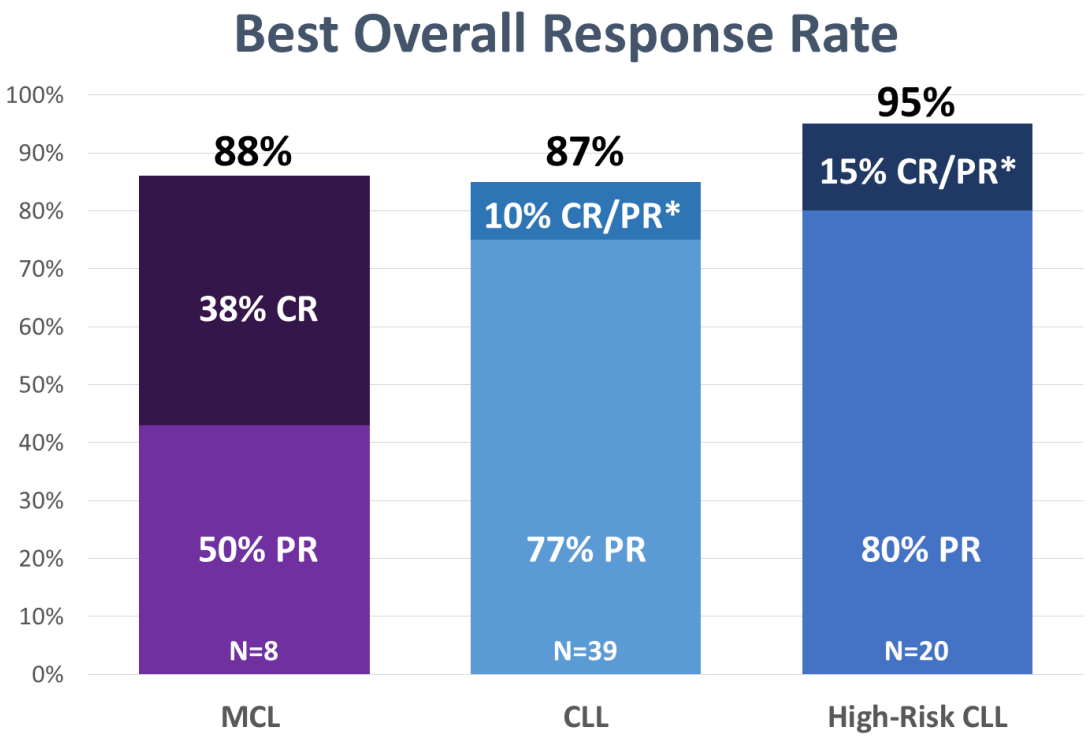
Sharman et al, ASH 2014

Study Results - Efficacy



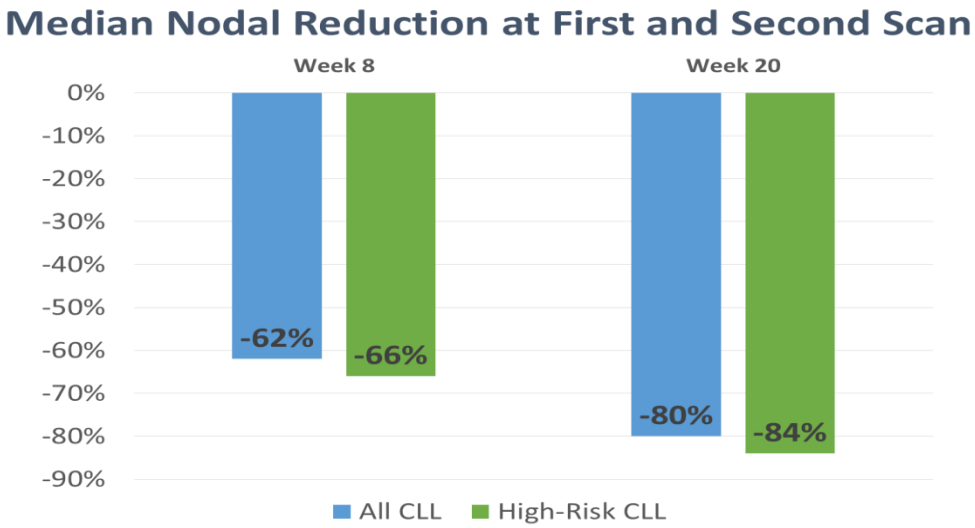
- 30% of patients were considered anti-CD20-refractory, progressing on or within 6 months of an anti-CD20 based regimen
- Prior anti-CD20 therapy included rituximab, ofatumumab, and obinutuzumab

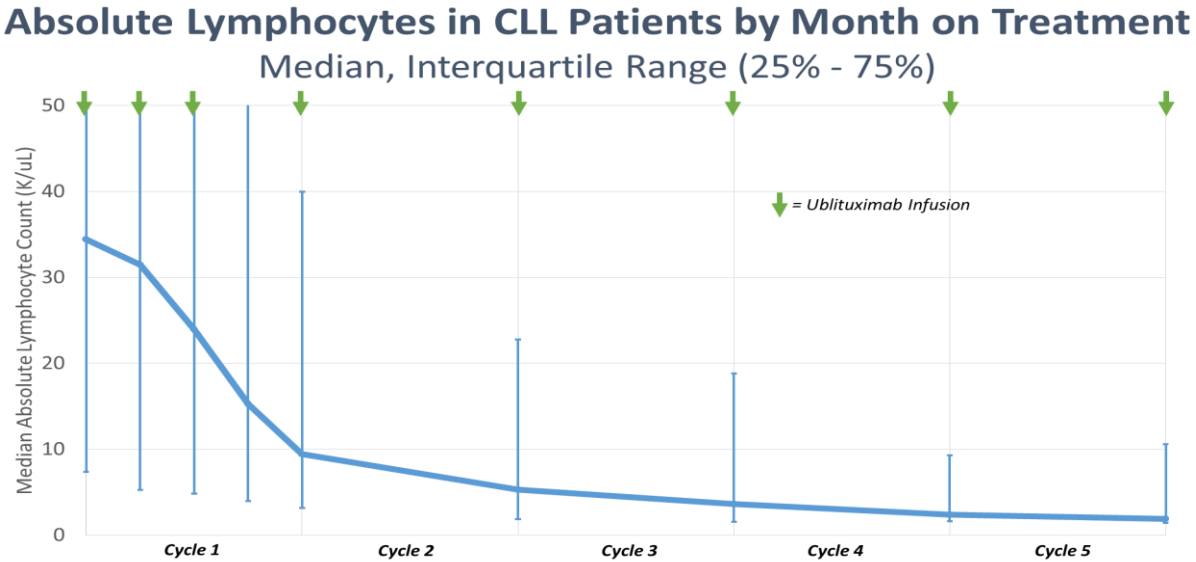
Study Results - Efficacy



Type	Pts (n)	CR (n)	PR* (n)	PR (n)	nPR (n)	SD (n)	PD (n)	ORR (%)
CLL	**39**	1	3	30	1	3	1	87%
High-Risk Subset	*20*	*1*	*2*	*16*	-	-	*1*	*95%*
MCL	**8**	3		4		1	-	88%

Study Results - Efficacy





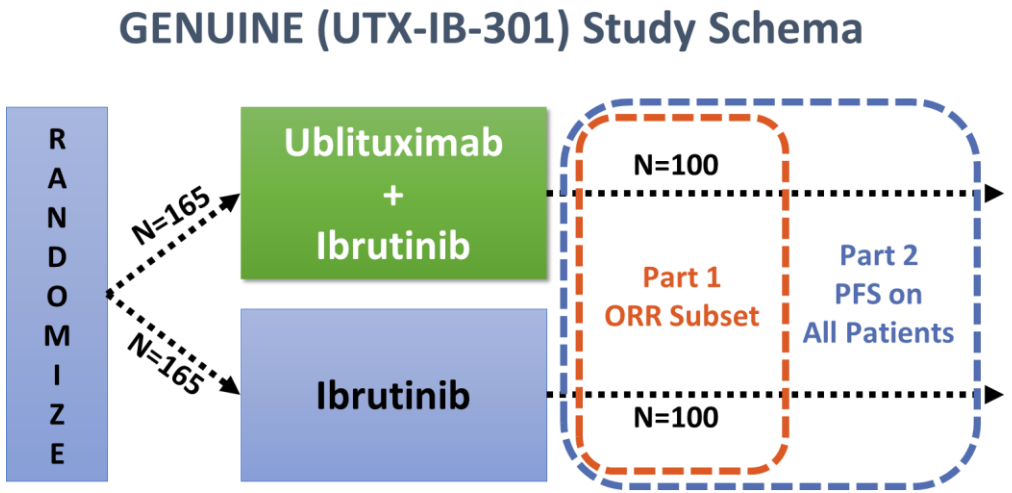
- Addition of ublituximab appears to control ibrutinib-related lymphocytosis in patients with CLL, with a median 75% decrease in ALC from baseline by the end of Cycle 3
- More than 50% of CLL patients had lymphocyte counts in normal range (<4000/uL) within 6 cycles of therapy

Study Conclusions

- Data from this ongoing study suggests ublituximab, a glycoengineered anti-CD20 mAb, in combination with ibrutinib is both a well tolerated and highly active regimen for patients with relapsed or refractory CLL and MCL
- Contrary to non-clinical data describing antagonism between BTK inhibition and ADCC, the addition of ublituximab appears to improve ORR in patients with CLL and MCL over that published historically with single agent ibrutinib in these patient populations
- A 95% ORR in patients with high-risk CLL (17p del, 11q del, and/or p53 mutation) suggests the combination may be an effective treatment regimen in this patient population; supporting a planned randomized Phase 3 clinical trial (the GENUINE trial)
- Additional studies are ongoing evaluating ublituximab in combination with other novel, targeted agents, with Phase III studies in development

Phase III Clinical Trial

GENUINE
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB PLUS IBRUTINIB
Phase 3 Clinical Trial



- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Enrolling ~330 patients with high-risk CLL
- ORR amongst first 200 patients for accelerated approval
- PFS amongst all enrolled patients for full approval
- Study Chair: Dr. Jeff Sharman

Q&A

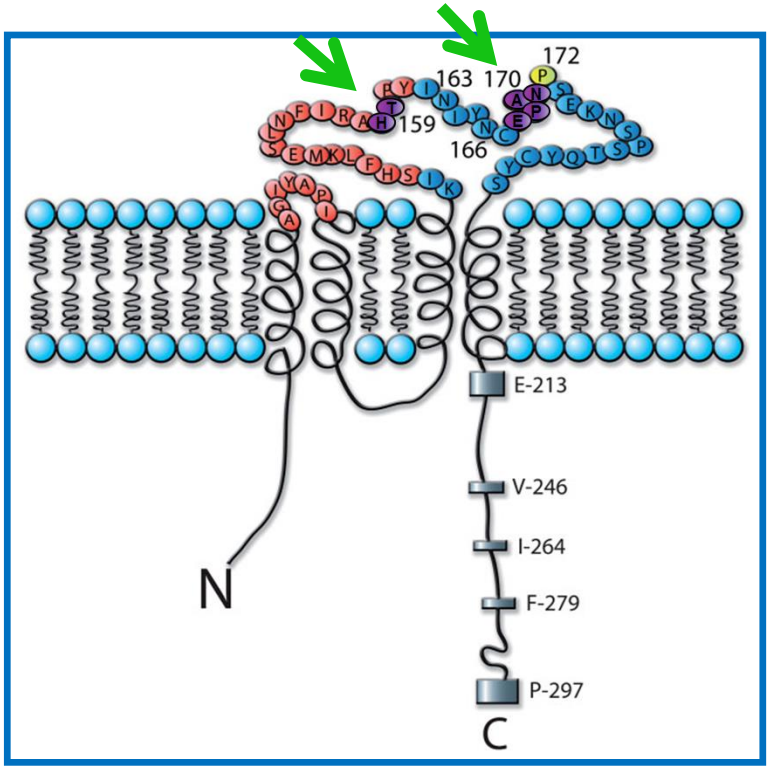
Questions?

TG-1101 Overview

Owen A. O'Connor, MD, PhD
Professor of Medicine and Experimental Therapeutics
Director of the Center for Lymphoid Malignancies
Columbia University Medical Center

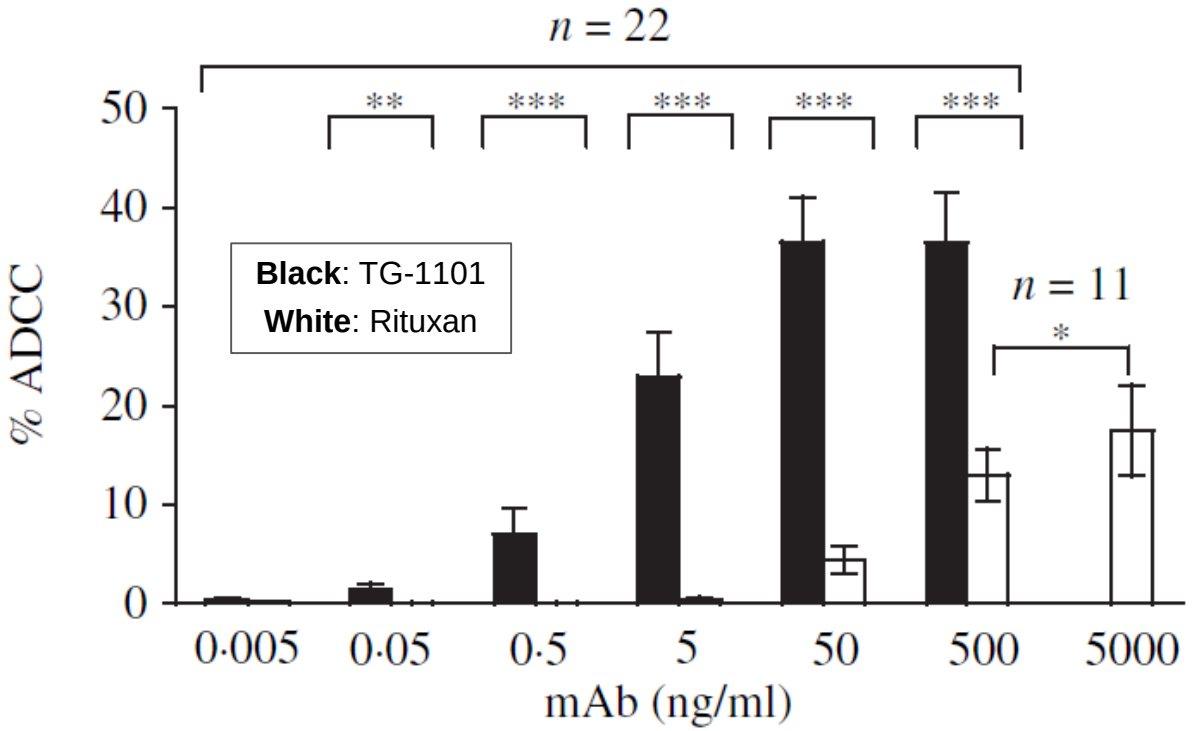
Ublituximab: A Novel Glycoengineered Anti-CD20 mAb

- Unique protein sequence
- Type 1 Chimeric IgG1 mAb
- Potential advantages over current standard of care:
  - Glycoengineered for significantly enhanced ADCC
  - Activity in “low” CD20 expressing cell lines, a characteristic of rituximab resistance
  - Binds to a novel epitope on CD20



Glycoengineering for Enhanced ADCC

TG-1101 vs. Rituxan
ADCC Induction in CLL Patient Donor Cell Lines



Source: de Romeuf et al, 2008

TG 1101-101: Phase I/II of Ublituximab in Patients with B-Cell Lymphoma - Relapsed/Refractory to Rituximab

Study Chair:
Owen O'Connor, MD, PhD
Columbia Presbyterian Medical Center, NY, NY

Phase I Dose Escalation

- Cohort 1: 450 mg, N=3
- Cohort 2: 600 mg, N=3
- Cohort 3: 900 mg, N=3
- Cohort 4: 1200 mg, N=3

Cohort Expansion / Phase II

NHL/CLL 900 mg	*N=11*
CLL/SLL *600 mg*	*N=5*
NHL 1200 mg	*N=3*

Safety of Ublituximab

- Day 1 Infusion Related Reaction most common adverse event
  - manageable with infusion interruptions only and recovered without sequelae
- Infusion times decreased to an average of 90 minutes for the 4th and all subsequent infusions

At Least Possibly Related AE's

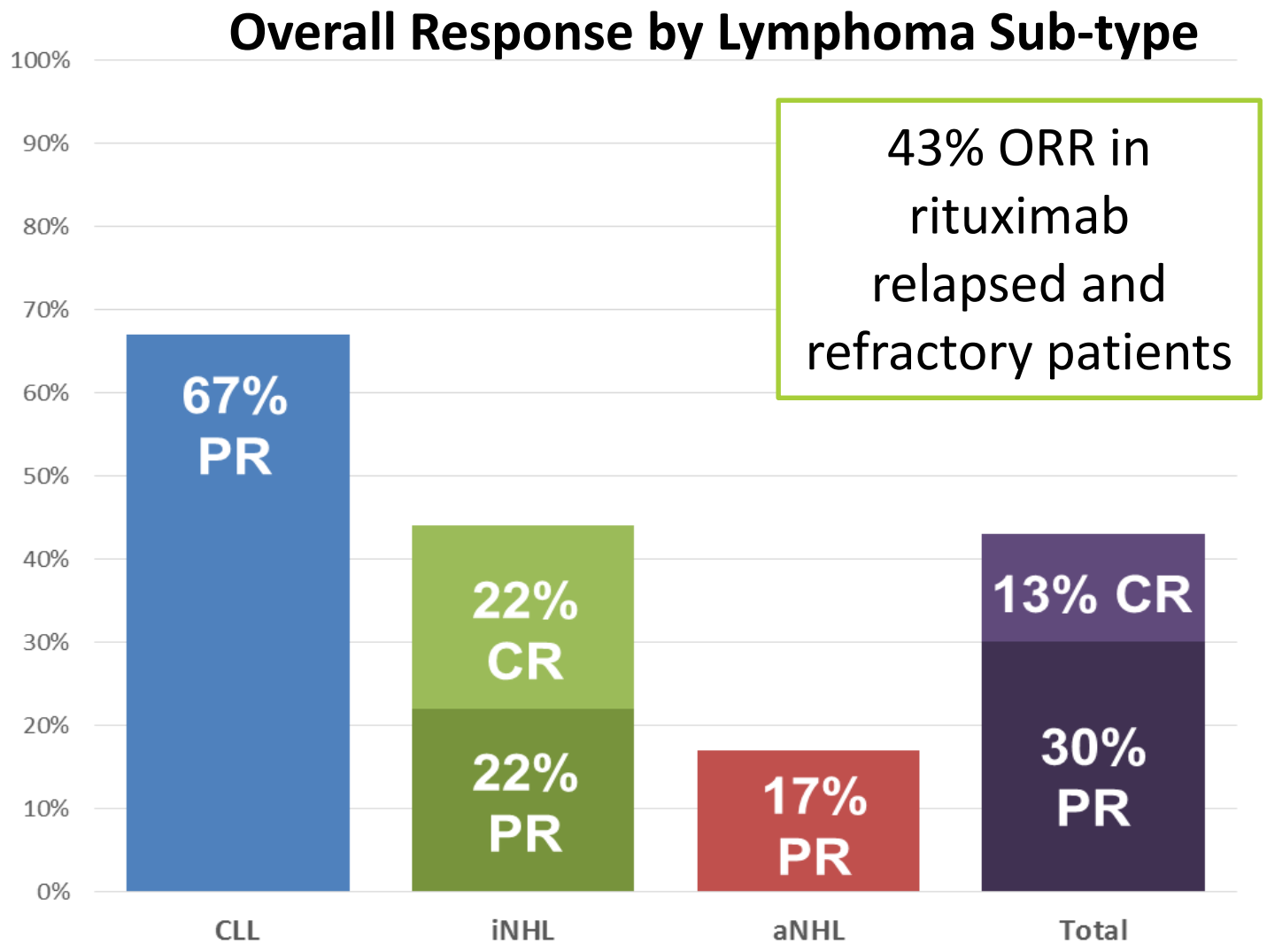
All Patients (n = 35)		
AE	All Grades n (%)	Grade 3/4 n (%)
Infusion Related Reaction*	10 (29%)	0
Fatigue	5 (14%)	1 (3%)
Diarrhea	4 (11%)	0
Pain (General)	4 (11%)	0
Dysgeusia	3 (9%)	0
Bilirubin Increase	2 (6%)	0
Pruritus	2 (6%)	0

At Least Possibly Related Lab Abnormalities

AE	CLL (n=8)		NHL (n=27)	
	Grade 1/2 n	Grade 3/4 n	Grade 1/2 n	Grade 3/4 n
Neutropenia	1	3	0	0
Thrombocytopenia	1	1	0	0
Anemia	0	0	0	1

Demonstrated single agent activity:

TG-1101 Phase 1 Efficacy Results ASCO/EHA 2014



Ublituximab – Take Home Messages

- Well tolerated with minimal IRR complications
- Promising activity in both rituximab relapsed and rituximab refractory patients across all histologies
- Interesting activity in MZL—one rituximab refractory patient transition from hospice to durable (2+ year) Complete Response
- 11 of 30 evaluable patients remained on study >1 year with no complications (2 patients on study >2 years)

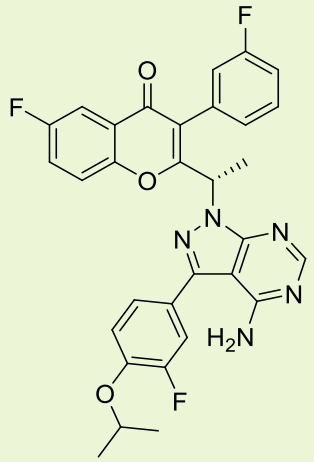
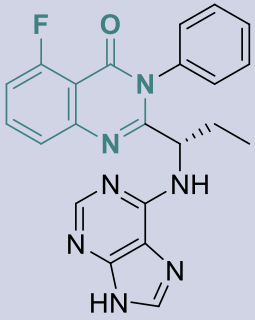
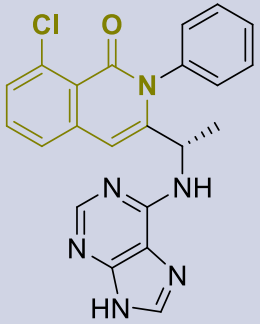
TGR-1202, a Novel Once Daily PI3Kδ Inhibitor, Demonstrates Clinical Activity with a Favorable Safety Profile, Lacking Hepatotoxicity, in Patients with Chronic Lymphocytic Leukemia and B-Cell Lymphoma

Manish R. Patel, MD

Howard A. Burris III, MD[1,2], Manish R. Patel, MD[1,3], Danielle M. Brander, MD[4], Owen A. O'Connor, MD, PhD[5], Changchun Deng, MD, PhD[5], Timothy S. Fenske, MD[6], Martin Gutierrez, MD[7], Suzanne Jones, PharmD[1], John Kuhn, PharmD[8], Hari P. Miskin, MS[9], Peter Sportelli[9], Swaroop Vakkalanka, PhD[10] and Ian Flinn[1,11]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Tennessee Oncology, PPLC, Nashville, TN; [3]Florida Cancer Specialists, Ft. Myers, FL; [4]Duke University Medical Center, Durham, NC; [5]Columbia University Medical Center, New York, NY; [6]Medical College of Wisconsin, Milwaukee, WI; [7]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; [8]University of Texas Health Science Center at San Antonio, San Antonio, TX; [9]TG Therapeutics, Inc., New York, NY; [10]Rhizen Pharmaceuticals SA, La Chaux-de-Fonds, Switzerland; [11]Tennessee Oncology, PLLC, Nashville, TN

TGR-1202: A Next Generation, Once Daily PI3Kδ Inhibitor

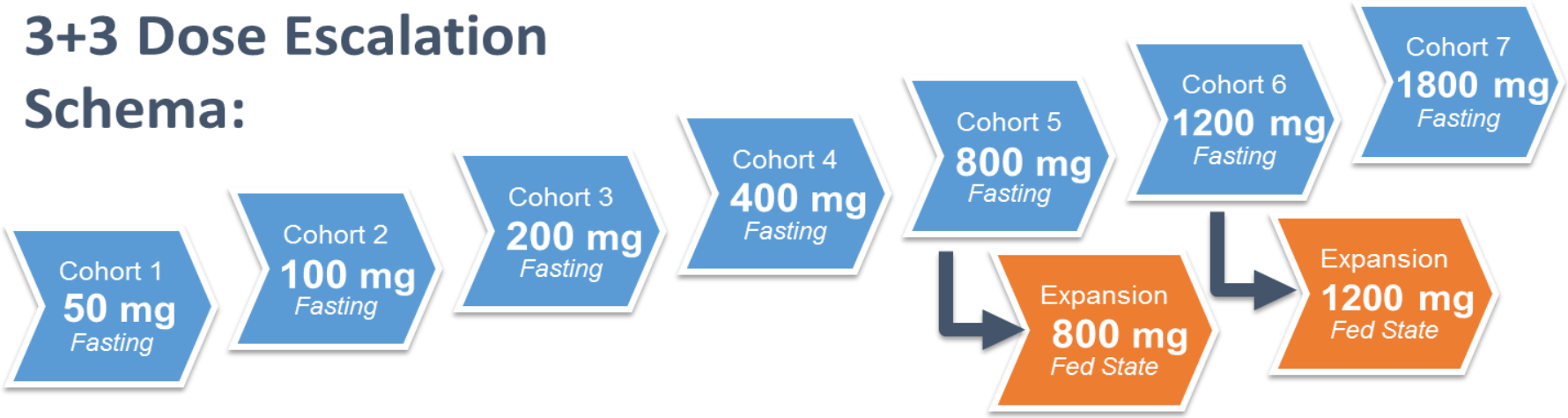
TGR-1202	Idelalisib	IPI-145
		

- Unique structure of TGR-1202 contributes to:
  - An extended half-life and accumulation that enables once-daily dosing
  - Differentiated safety profile from other PI3Kδ inhibitors in development, notably absent of hepatic toxicity to date[1]

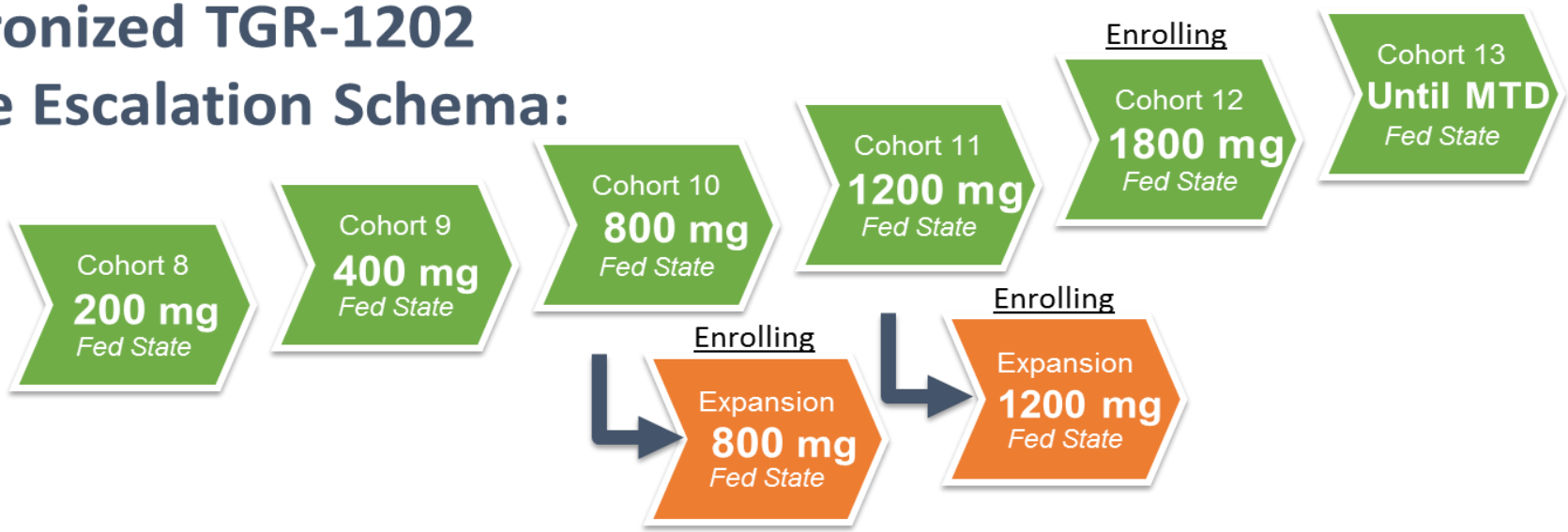
[1]Burris et al, ASH 2014, Abstract # 1984

Phase I Single Agent Study of TGR-1202

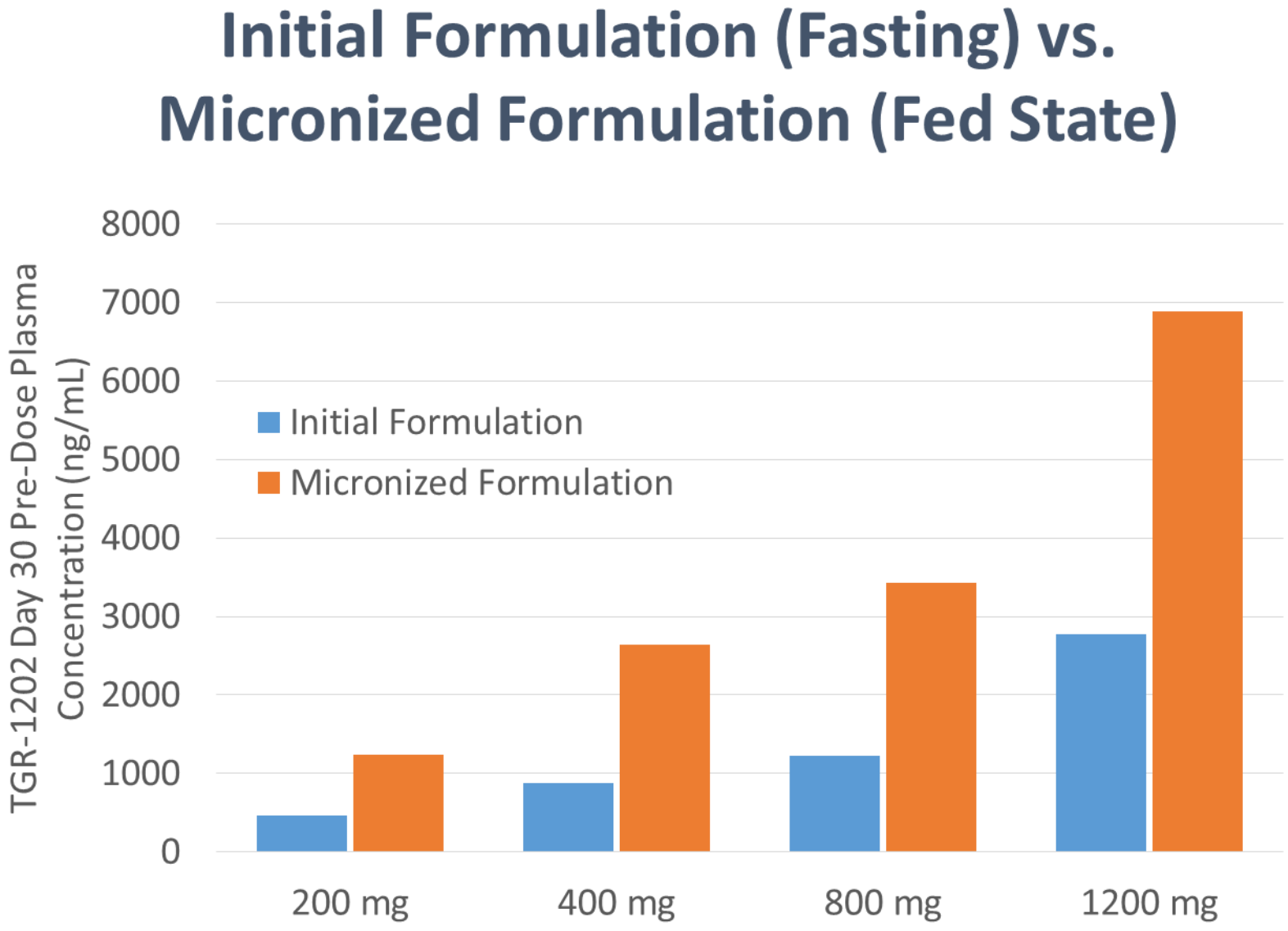
3+3 Dose Escalation Schema:



Micronized TGR-1202 Dose Escalation Schema:



Single Agent TGR-1202 Pharmacokinetics



Burris et al, ASH 2014

TGR-1202-101: Demographics

Evaluable for Safety (n)	55	
Evaluable for Efficacy (n)	43	
Median Age, years (range)	62 (22 – 82)	
Male/Female	40/15	
Histology	18 CLL	2 MCL
	15 FL	2 MZL
	9 HL	1 HCL
	7 DLBCL	1 WM
ECOG 0/1/2	19/35/1	
Prior Therapies, median (range)	3 (1 – 14)	
Patients with ≥ 3 Prior Therapies (%)	28 (51%)	
Patients with prior Rituximab-Chemo	44 (80%)	

Efficacy subset includes all patients treated with 800 mg of initial formulation or higher, and any micronized dose level. Not evaluable: 8 patients treated at less than 800 mg initial formulation, 1 Too Early To Evaluate (1200 mg micronized Fed), 2 Non-Compliant (both at 1800 mg Fasted), 1 Failed Inclusion/Exclusion (Richter's Transformation prior to entry)

Burris et al, ASH 2014

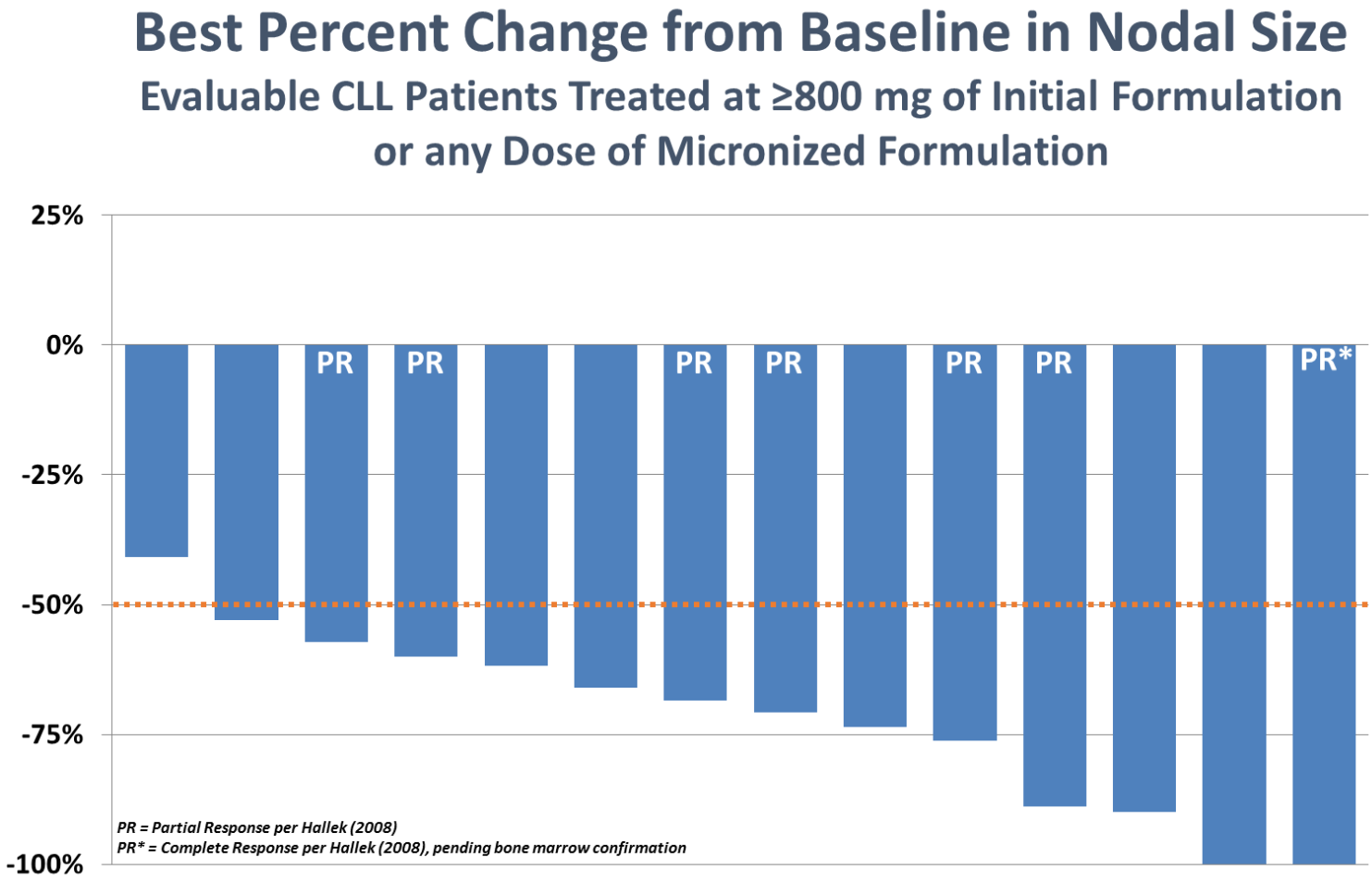
Safety of TGR-1202

All Events (All Causality) in >10% (n=55)				
	All Grades		Grade 3/4	
	Events	%	Events	%
Diarrhea	17	31%	1	2%
Nausea	16	29%	-	-
Fatigue	14	25%	-	-
Cough	13	24%	-	-
Anorexia	11	20%	-	-
Headache	10	18%	-	-
Vomiting	10	18%	-	-
Rash	9	16%	2	4%
Neutropenia	8	15%	7	13%
Constipation	6	11%	-	-
Dyspnea	6	11%	2	4%
Thrombocytopenia	6	11%	4	7%

- No drug related hepatotoxicity, colitis, or pneumonitis observed to date
- Only 2 patients (< 4%) have come off study due to an adverse event (one unrelated, one possibly related)

Burris et al, ASH 2014

Single Agent TGR-1202 Efficacy in CLL

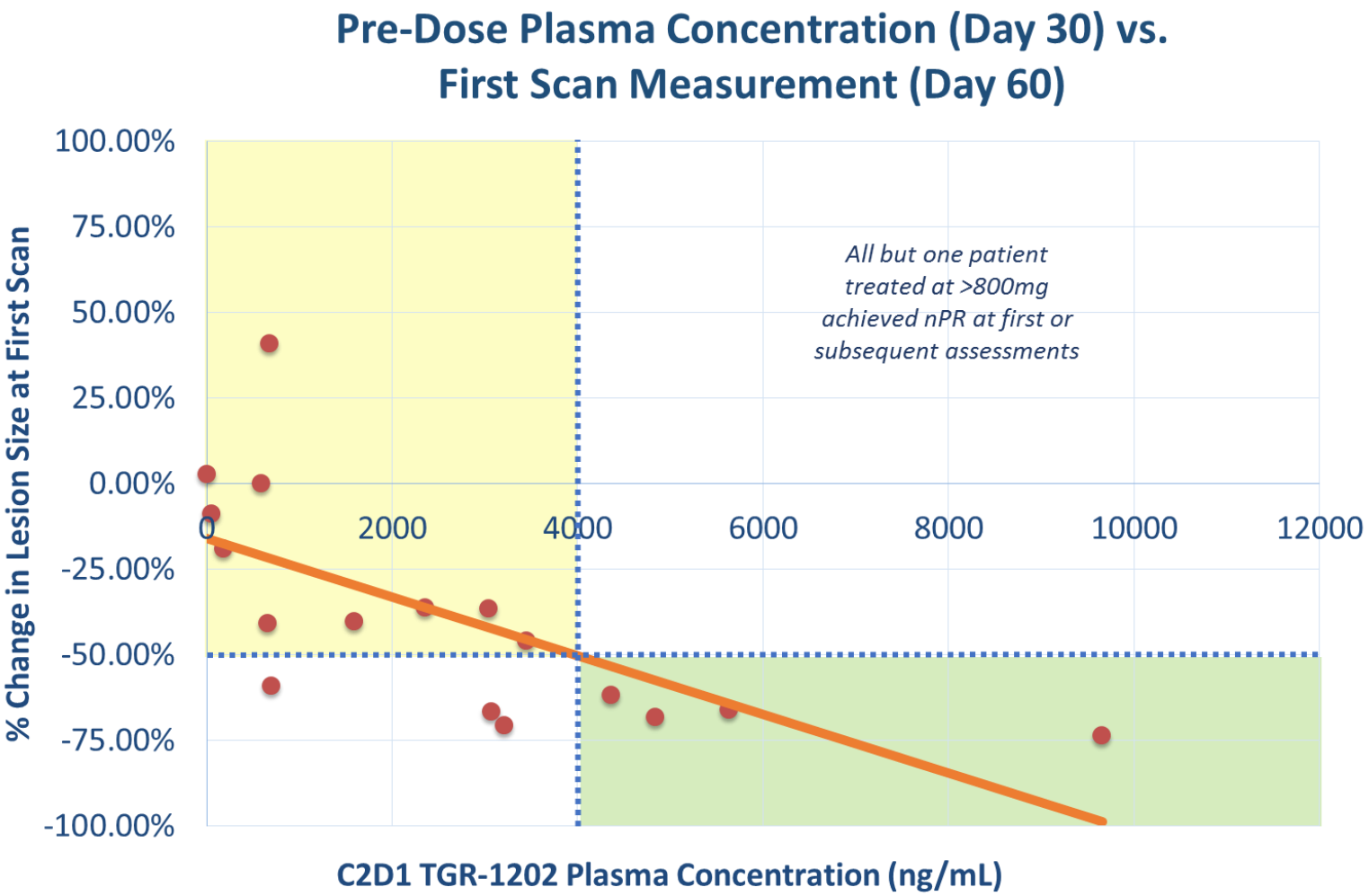


- 93% of CLL patients (13/14) treated at 800 mg or higher achieved a nodal PR (median nodal reduction of 70%)
- Nodal reductions have been shown to improve with time on TGR-1202

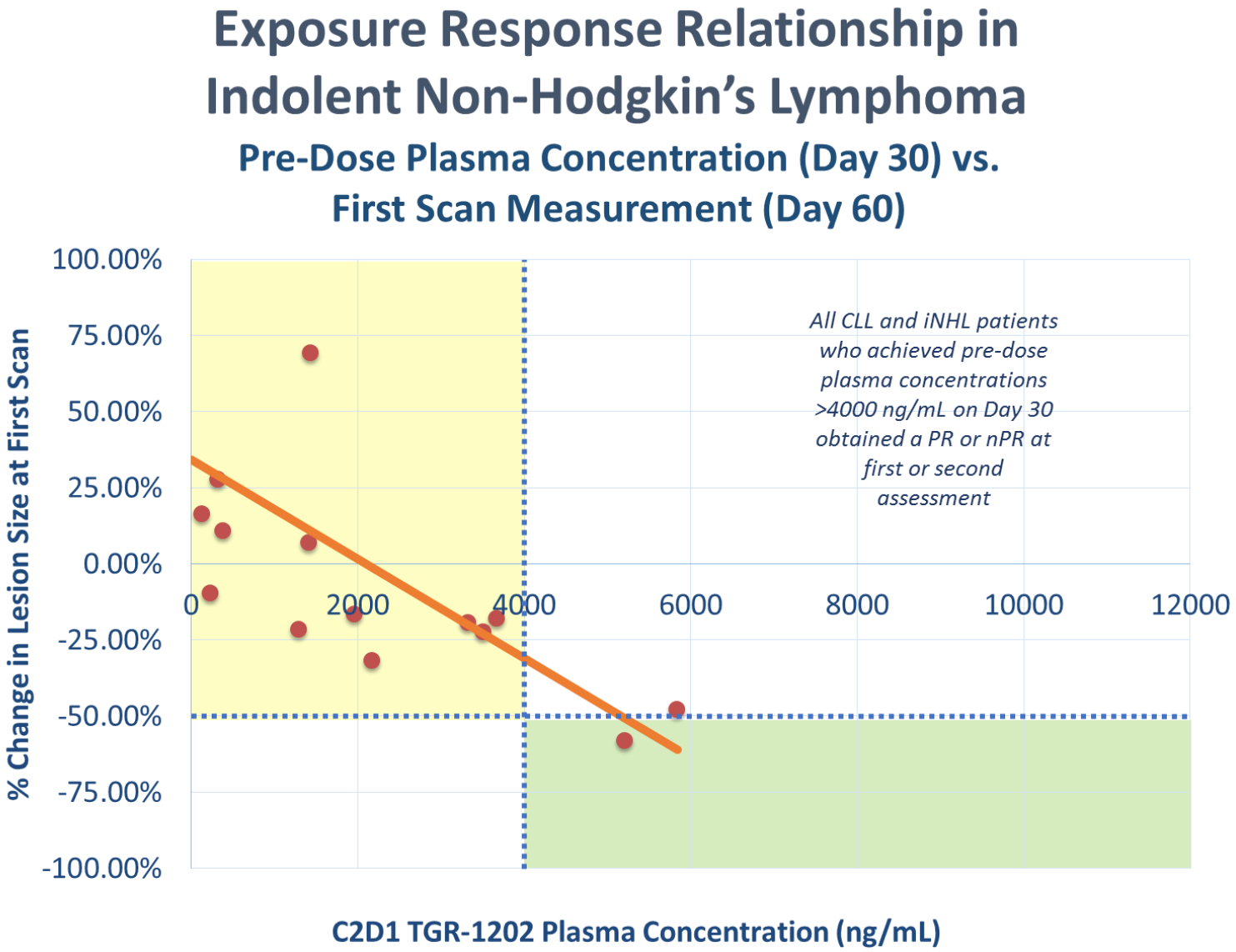
Burris et al, ASH 2014

TGR-1202 – Plasma Concentrations - CLL

Exposure Response Relationship in CLL



TGR-1202 – Plasma Concentrations - NHL



TGR-1202 - Conclusions

- **93% (13/14) nodal response rate** in relapsed/refractory CLL at doses ≥ 800 mg of initial formulation or any dose of micronized formulation.
  - 50% (7/14) of these patients achieved a partial response per iwCLL (Hallek 2008) criteria

- Well tolerated; **no drug related hepatic toxicity or colitis** reported to date; differentiated adverse event profile supportive of combination therapy

- Exposure response trend noted in both CLL and NHL, with higher plasma TGR-1202 exposures correlating with increased nodal responses, with all CLL and iNHL patients who achieved pre-dose plasma concentrations on Day 30 in excess of 4000 ng/ml obtaining a PR or nPR at first or second assessment

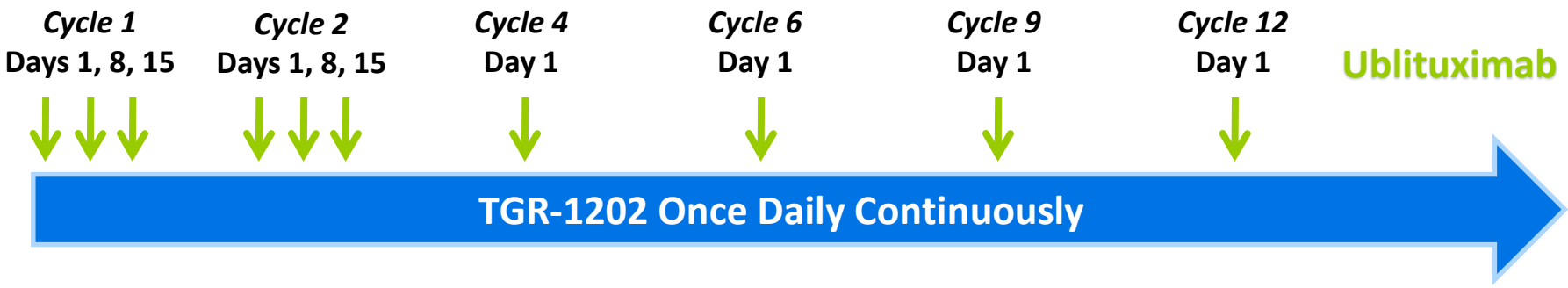
- No MTD has been achieved; dose escalation continues with the micronized formulation

TG-1101 + TGR-1202 Overview

Nathan Fowler, MD
Associate Professor
Lead, New Drug Development
MD Anderson Cancer Center

Matthew Lunning, DO
Assistant Professor
University of Nebraska Medical Center

TG-1101 & TGR-1202 – Trial Design



- **Enrolling All Types of B-NHL and CLL**
- **No limit on prior therapies**
- **Allows for prior BTK and/or PI3Kδ inhibitors**
- **3+3 Dose Escalation**

	Ublituximab	TGR-1202	Ibrutinib	
1	CLL: 600mg NHL: 900mg	800mg	*Exploratory Cohorts Opened After Doublet DLT Clearance*	n=9
2	CLL: 600mg NHL: 900mg	1200mg		n=9
3	900mg	400mg micronized	CLL: 420mg NHL: 560mg	
4	900mg	600mg micronized	CLL: 420mg NHL: 560mg	

Phase I/Ib Study of TG-1101 + TGR-1202 Safety Data Presented at Pan Pacific 2014

Heavily Pre-Treated Population

	# of Priors	Prior Therapies	Rel/Ref
CLL*	2	FCR, Chlorambucil	REL
CLL*	1	FCR	REL
CLL*	1	FCR	REL
CLL	2	FCR, RTX, CC-292	REL
SLL	3	R-CHOP, R-Benda, RTX	REL
Richter's	1	FCR	REL
FL	8	RTX, RTX+CHL(x 2), Zevalin, R-CHOP, R-Benda (x 2), Prednisone	**REF**
FL	6	CHL, RTX (x 2), R-CVP, Zevalin, R-Benda	REL
FL	5	RTX, R-CHOP, R-ICE, R-EPOCH, SCT	**REF**
FL	3	RTX (x 2), R-ICE	REL
DLBCL	1	R-CHOP	REL
DLBCL†	2	R-CHOP, R-ICE	**REF**
DLBCL†	3	RTX, R-CHOP, R-Gem/Oxaliplatin	**REF**
DLBCL†	6	RTX (x 2), R-CHOP, Benda (x 2), ICE	**REF**
DLBCL	2	R-CHOP, R-Benda	REL

* 17p del and/or 11q del
† GCB Subtype

- Heavily pre-treated patients:
  - Median 3 prior lines, and median of 2 prior rituximab regimens

Lunning et al, PPLC 2014

Phase I/Ib Study of TG-1101 + TGR-1202 Safety Data Presented at Pan Pacific 2014

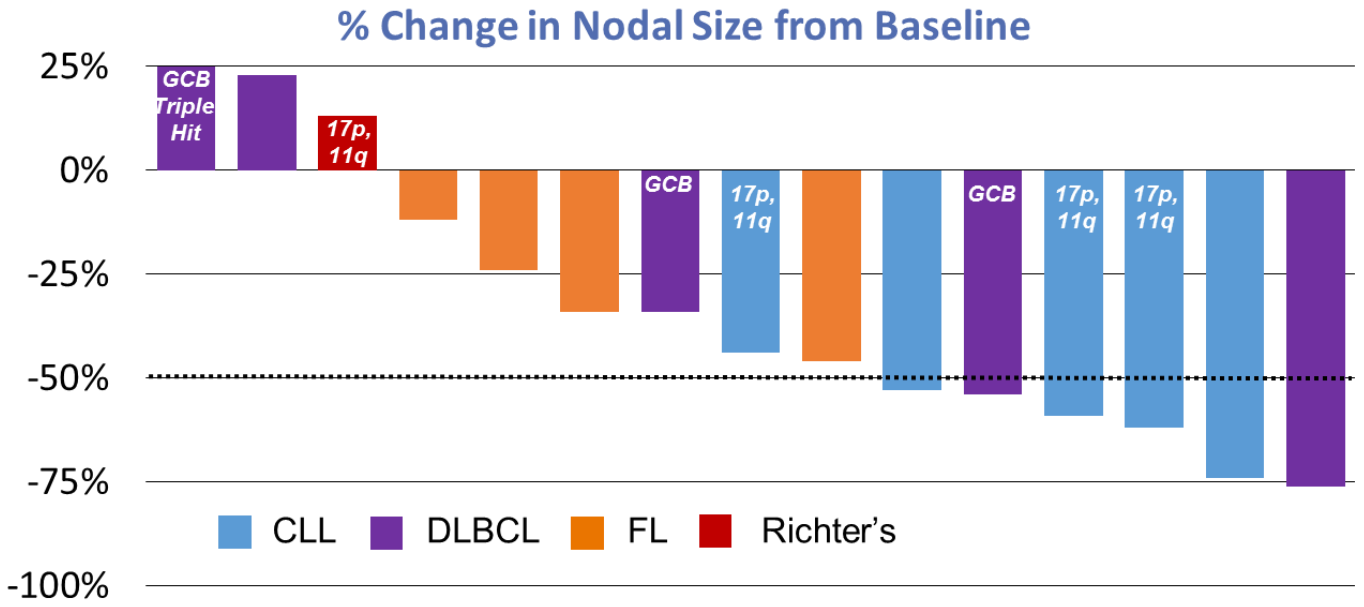
Related AE's Occurring in ≥ 2 Patients (n = 21)

Adverse Event	Total AE's All Grades n (%)	UTX Related		TGR-1202 Related	
		G 1/2 n	G 3/4 n	G 1/2 n	G 3/4 n
Infusion Related Reaction (IRR)	10 (48%)	9	1	0	0
Neutropenia†	8 (38%)	3	4	3	5
Diarrhea	6 (29%)	0	0	6	0
Nausea†	6 (29%)	2	0	6	2
Hoarseness†	2 (10%)	1	0	2	0
Muscle Aches	2 (10%)	0	0	2	0
Fatigue†	2 (10%)	1	0	2	0

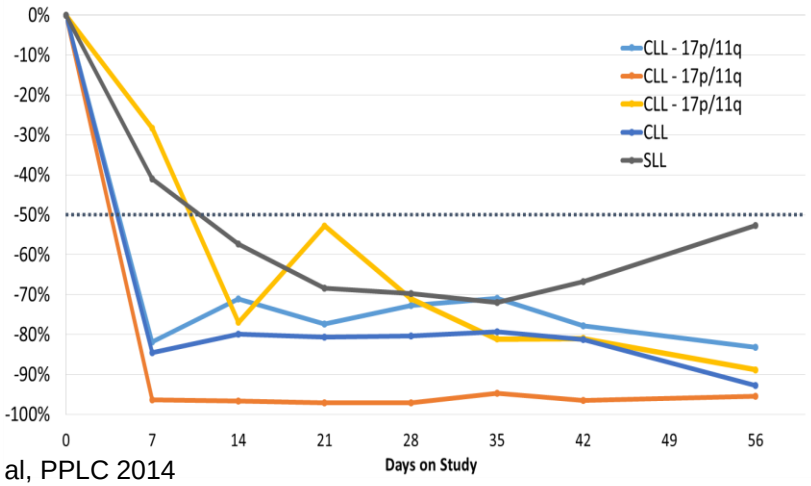
- Combo of TG-1101 + TGR-1202 is well tolerated
- No drug related increases in ALT/AST observed to date

Lunning et al, PPLC 2014

Phase I/Ib Study of TG-1101 + TGR-1202 Efficacy Data Presented at Pan Pacific 2014



Median Change in ALC from Baseline (CLL/SLL)



- Addition of TG-1101 to TGR-1202 appears to control lymphocytosis commonly seen in CLL patients receiving BCR targeted agents.
- All patients achieved a >50% reduction in ALC by first efficacy assessment

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Overall Response by Lymphoma Sub-type

Type	Pts (n)	Median Prior Rx	PR n (%)	ORR n (%)	PD (n)	% pts ≥ SD for 12 wks
CLL/SLL	5	2 (1 – 3)	4 (80%)	**4 (80%)**	-	5 (100%)
Richter's	1	1	-	**-**	-	1 (100%)
FL	4	6 (3 – 8)	-	**-**	-	4 (100%)
DLBCL	5	3 (1 – 6)	2 (40%)	**2 (40%)**	1	4 (80%)
Total	**15**	**3 (1 – 8)**	**6 (40%)**	**6 (40%)**	**1**	**14 (93%)**

- Of the 4 responders in CLL/SLL, 2 were in high risk both 17p del and 11q del
- Remaining CLL patient is a high risk patient with a 44% reduction at first assessment
- Encouraging early signal in DLBCL, with 40% ORR
- Expect responses to improve over time

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Q&A

Questions?

TG Therapeutics