TG Therapeutics

Introduction

Michael S. Weiss
Executive Chairman & CEO

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY DLBCL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED DLBCL PATIENTS

AGENDA

Topic	Presenter
Welcome / Introductions	Michael Weiss, CEO TG Therapeutics
TGR-1202 Differentiation	Owen O'Connor, MD, PhD
TGR-1202 Safety	Anthony Mato, MD
TGR-1202 Efficacy	Matthew Lunning, DO
Ibrutinib Intolerance	Anthony Mato, MD
CLL & DLBCL Landscape Panel Discussion	Nilanjan Ghosh, MD, PhD Kathryn Kolibaba, MD Matthew Lunning, DO Anthony Mato, MD Owen O'Connor, MD, PhD
Closing Remarks	Michael Weiss

TGR-1202!

TGR-1202 Preclinical Differentiation

Owen O’Connor, MD

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Exploring the Differences Among the PI3 Kinase Inhibitors

Owen A. O'Connor, M.D., Ph.D.
Director, Center for Lymphoid Malignancies
Professor of Medicine and Developmental Therapeutics
The New York Presbyterian Hospital
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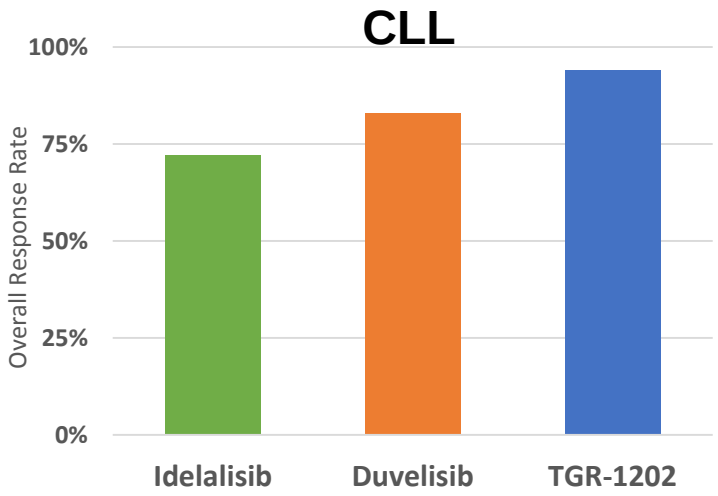
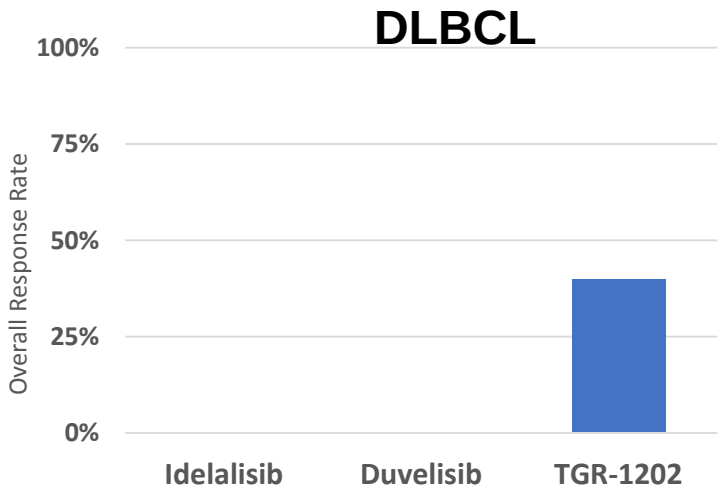
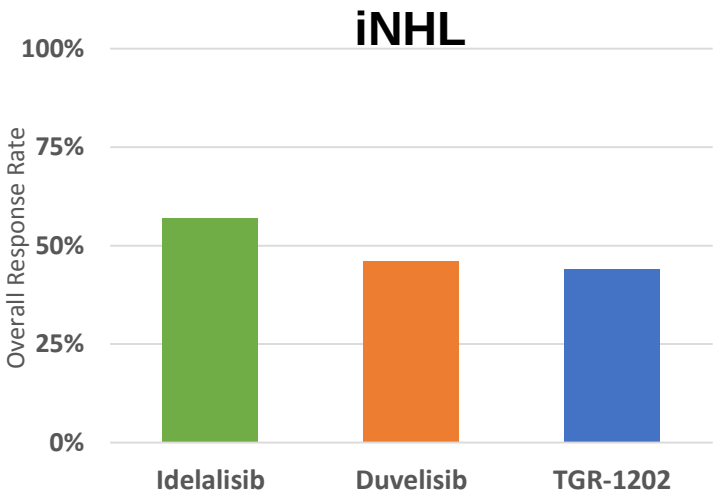
Comparison of Clinical Activity for PI3K Inhibitors
Comparable Activity Across CLL and iNHL





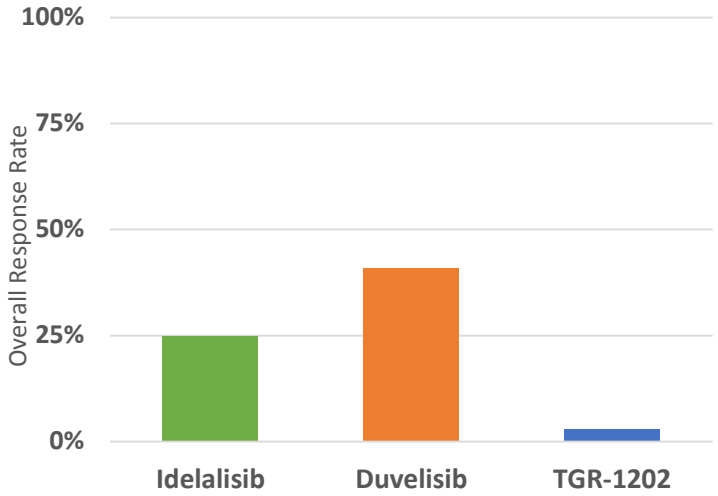


- Comparable activity across CLL and iNHL
- More activity seen in DLBCL
- Small numbers across multiple studies so lots of population variability.

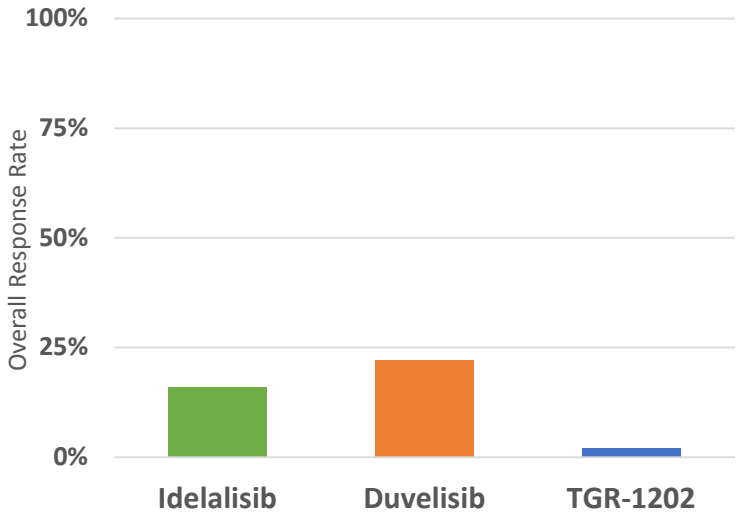
Brown et al, iwCLL 2013
O'Brien et al, ASH 2014
O'Connor et al, ASH 2015
Gopal et al, NEJM 2014
Infinity PR, 2016
O'Connor et al, EHA 2016
Westin et al, 2014
O'Connor et al, EHA 2016

Comparison of Tolerability for PI3K Inhibitors Appears Less for TGR1202 Across the Board

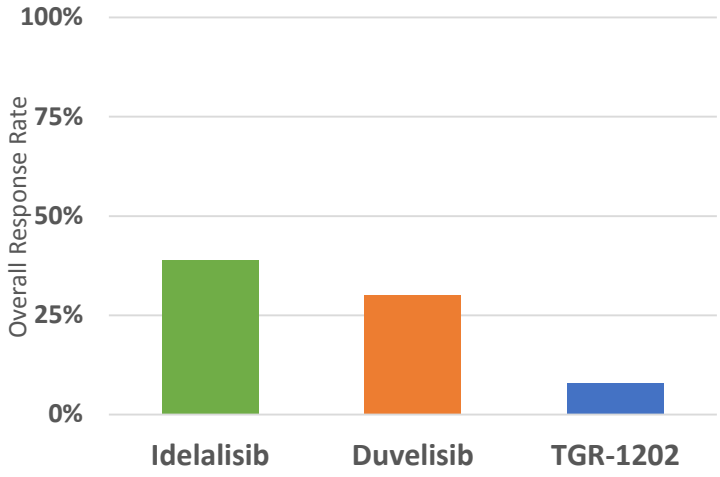
Grade 3 and 4 Hepatotoxicity (LFT elevations)



Grade 3 or 4 Diarrhea & Colitis



Discontinuations Secondary to AE



- Reduced incidence of hepatic toxicity with TGR1202
- Reduced gastrointestinal toxicity with TGR1202
- Fewer discontinuations due to AE with TGR1202

Brown et al, iwCLL 2013; O'Brien et al, ASH 2014; O'Connor et al, ASH 2015; Gopal et al, NEJM 2014; Infinity PR, 2016; O'Connor et al, EHA 2016; Jones et al, ASCO 2016; Coutre et al, 2015; Flinn et al, Blood 2014;

Comparison of Pharmacologic and Pharmacodynamic Features Across the PI3K Inhibitors

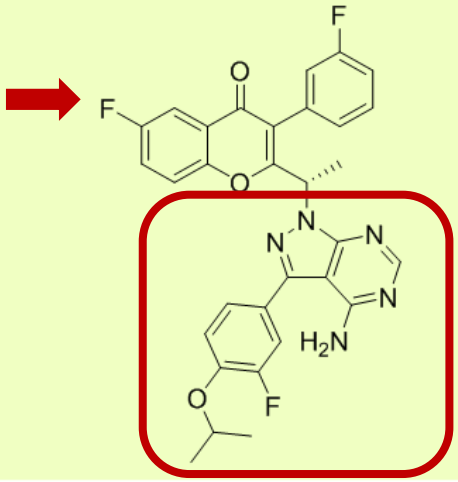
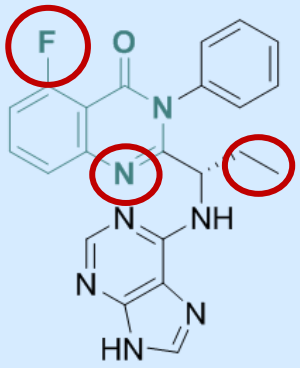
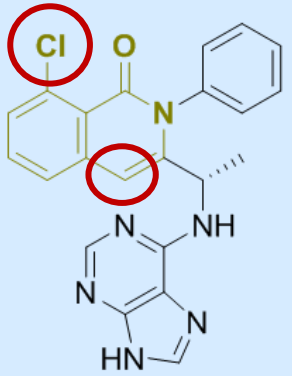
	TGR-1202	Idelalisib	Duvelisib
Enzyme IC_{50} for PI3k-δ (nM)	22.23[1]	8.5	2.5[2]
Whole Blood Assay IC_{50} (nM) FcεR1 induced CD63 expresssion	66.97	65	78
Reported Cmax	~9 μM	~6.5 μM	~3.5 μM
Reported AUC (ng*h/mL)	91,000	13,800	8,129

A 3-log fold difference between the IC50 and plasma concentrations
Massive Excess of Drug Concentration Likely Make Differences in Potency Insignificant

[1]Millipore, 100uM ATP
[2]Assay conducted with 3mM ATP

Lanutti et al 2011, Flinn et al 2009, Lanutti et al, 2009;
Porter et al, ACR 2012; Jin et al, AACR 2013;

The PI3 Kinase Inhibitors
Some Similarities – Some Differences

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

- Similarities in the upper structural motif – differences in the low structural motif
- Subtle pharmacologic and target difference

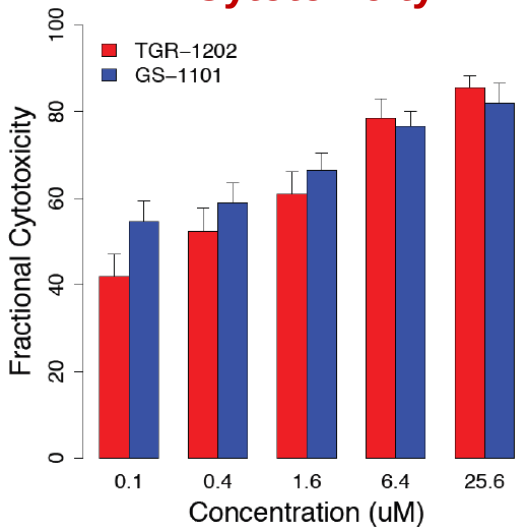
[1]Burris et al, ASCO 2015, Abstract # 7069

Target Selectivity and In Vitro Activity

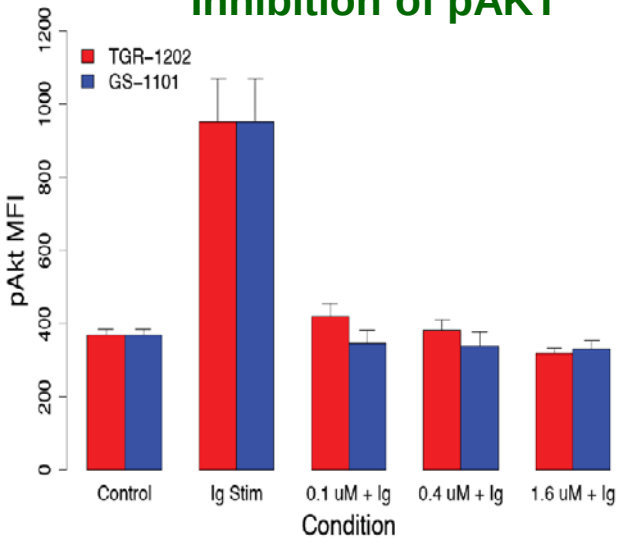
Fold-selectivity				
Isoform	α	β	γ	δ
TGR-1202	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]IPI-145	>640	>34	>11	1

- Blinded *in vitro* study conducted at Duke University comparing TGR-1202 and idelalisib in CLL patient cells (n=7)[3]

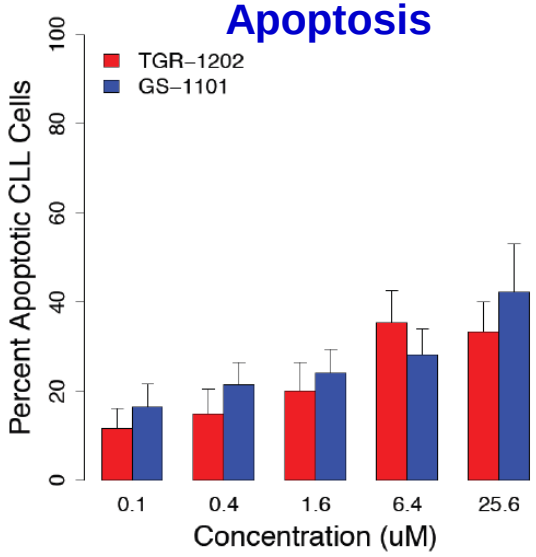
Cytotoxicity



Inhibition of pAKT

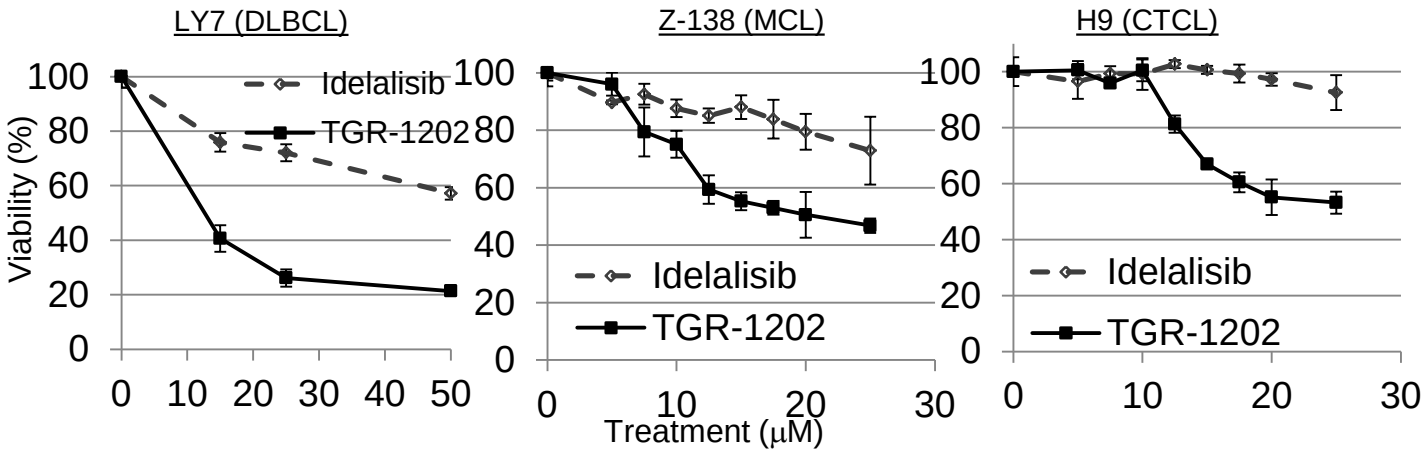


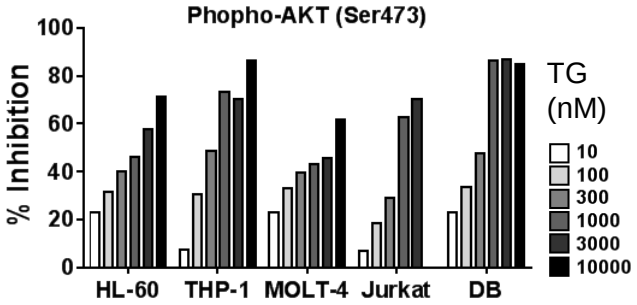
Apoptosis



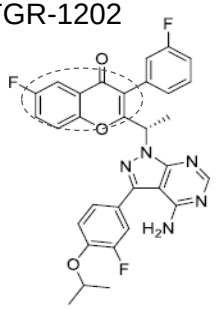
[1]Flinn et al. 2009, [2]Porter et al. 2012, [3]Friedman et al ASH 2012

While Idelalisib, Duvalisib & TGR-1202 Are Comparable Across Many Cell Lines – TGR-1202 Is Superior in a Few ……Why?

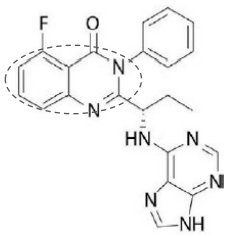




TGR-1202



Idelalisib



Phospho-AKT Inhibition a Relative Constant Across All Cell Lines Studied

Is the Unique Activity in DLBCL a Clue? Strategies to Target c-Myc Translation

eIF4F (eIF4E+ eIF4G + eIF4A) → translation → ***c-Myc***

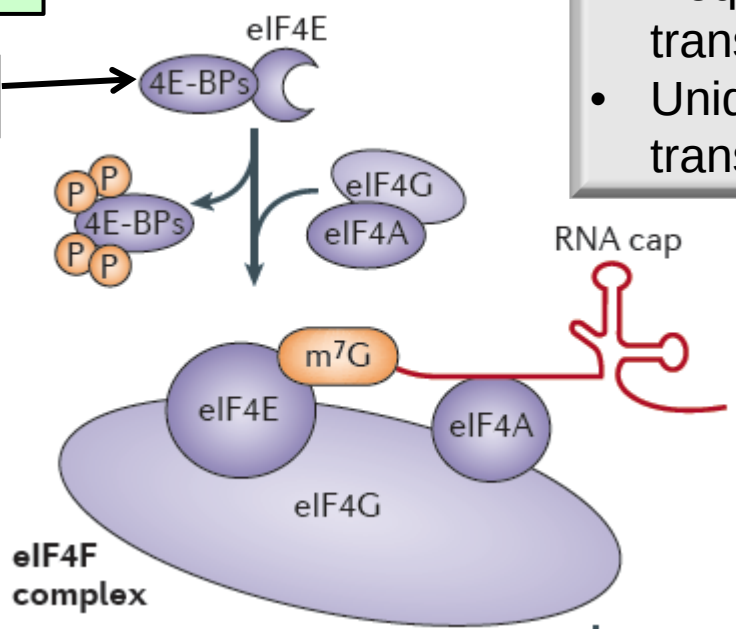
PIK3 → AKT → mTOR

Phos-S6K

Phos-STAT3

The Deng Hypothesis

- C-myc has half-life of 20-30 minutes
- Requires continuous translation
- Unique 5”-UTR controls translation



Free amino acid pools

- PI3K-AKT is the primary upstream activator of mTOR.
- The ubiquitin-proteasome system is required for the activation of mTOR
- mTORC1 induces expression of proteasome subunits via the NRF1
- c-Myc an upstream stimulator of mTOR

Pourdehnad PNAS 2013; Zhang Nature 2014; Hutter Leukemia 2012; Quy JBC 2013; Tang PLOS One 2014; Bhat et al., Nat Rev Drug Disc 2015

Therapeutic Strategies to Target c-Myc
Targeting the Translation of c-Myc via eIF4F

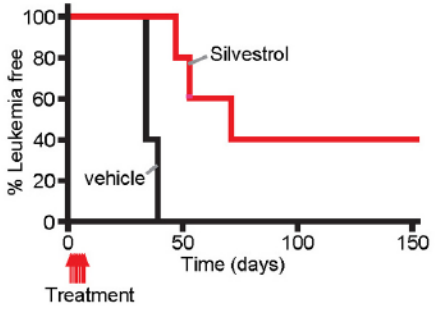
- c-Myc has a very short half life, 20-30 min.(Andresen et al. Nucleic Acids Res 2012)

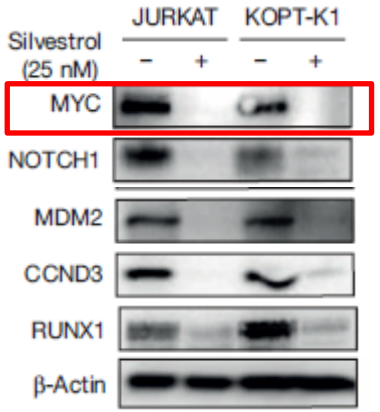
- Myc needs to be translated constantly in Myc-dependent cancer. Translation of Myc is regulated by its own 5' untranslated region (UTR).

- The 5' UTR of Myc is characterized by secondary structures, specifically the (CGG)4 motif which corresponds to G-quadruplexes.

- Translation of c-Myc is highly dependent on the eukaryotic translation initiation factor 4F (eIF4F), comprised of the 4E, 4A, and 4G subunits. Myc expression is exquisitely sensitive to silvelstrol, an inhibitor of eIF4A.

- Myc dependent cancers respond to silvestrol.

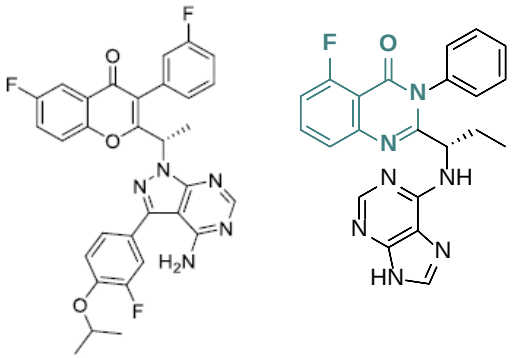


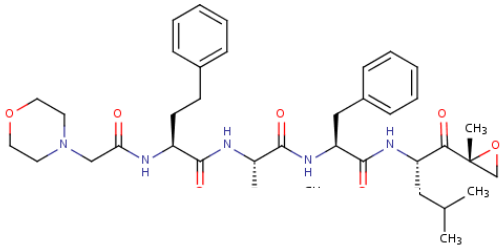


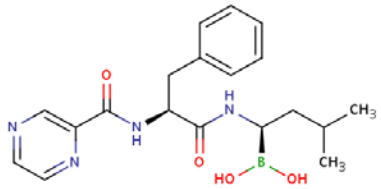
Wendel et al. Nature 2014

Combinations of Proteasome and PI3K Inhibition As A Strategy to Optimize Killing of Myc Dependent Lymphoma

- Study design: Test four combination pairs using HTS
- Method: Cell Titer-Glo

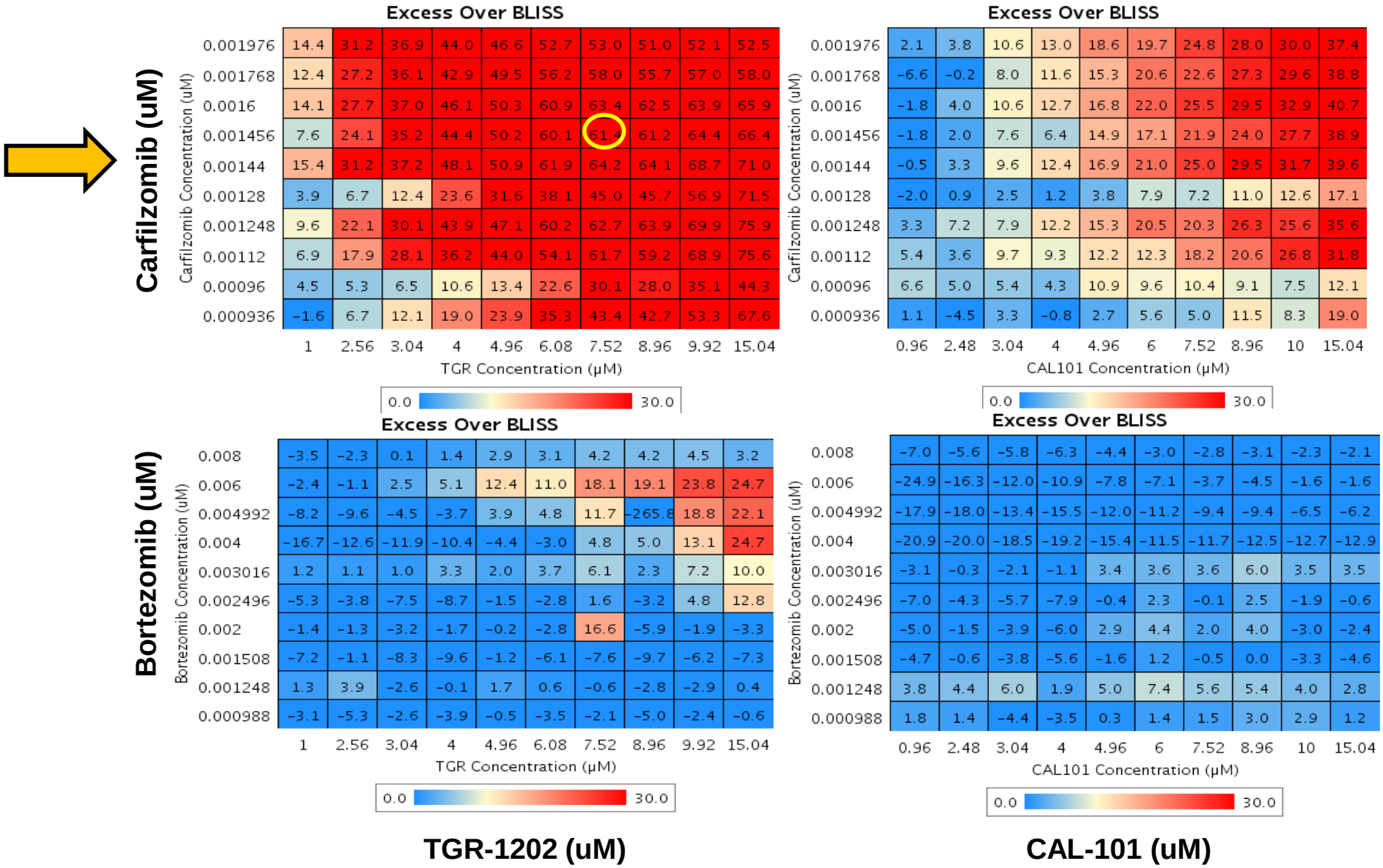






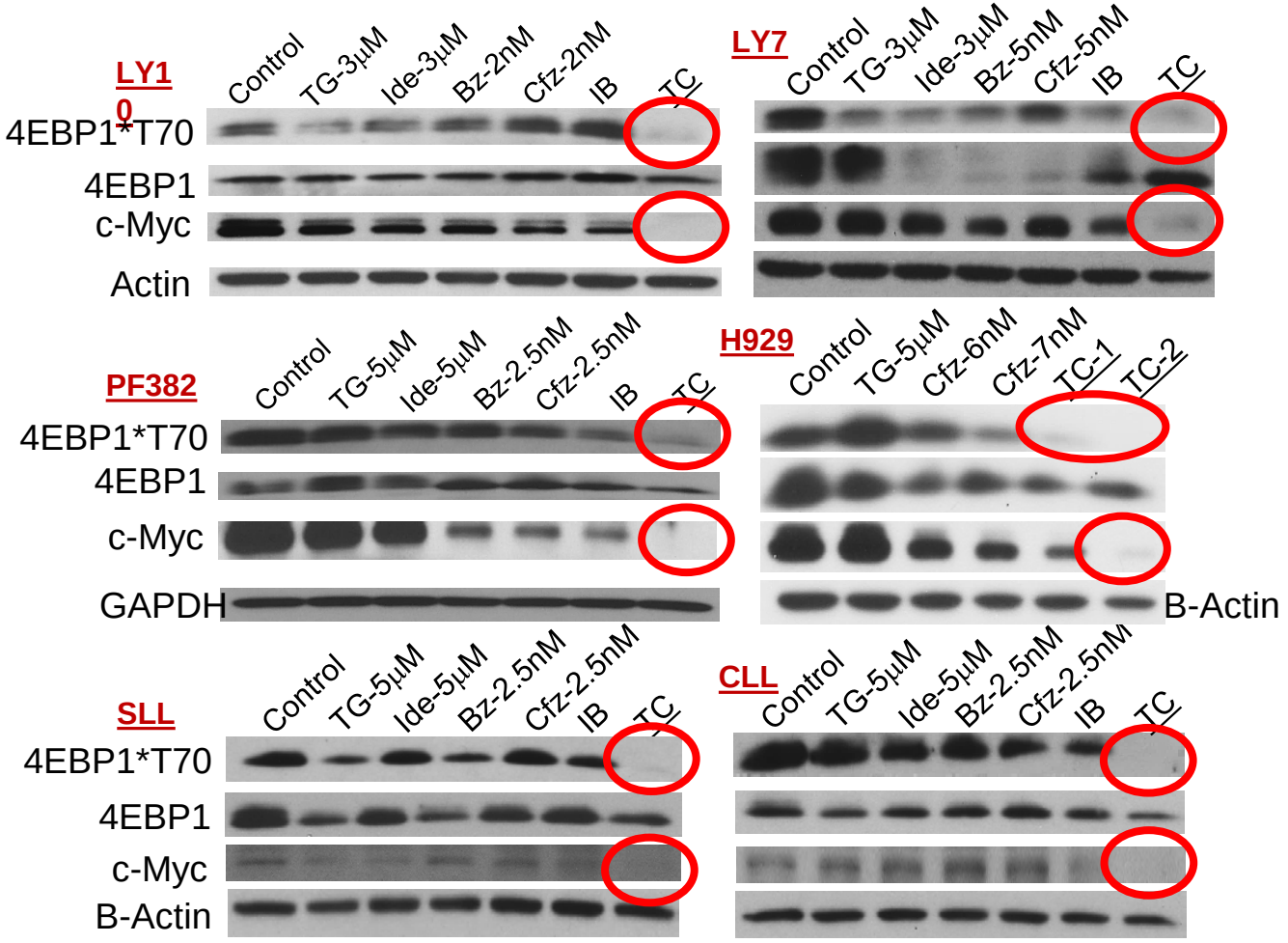
Drugs	TGR-1202 (TG)	Cal-101 (Cal)
Carfilzomib (Cfz)	TG + Cfz	Cal + Cfz
Bortezomib (Bort)	TG + Bort	Cal + Bort

HTS of PI3K Inhibitors PLUS Reveal Highly Synergistic Interactions Unique to the Car - TGR1202 Combination



EOB: > 0 to 100: Synergy

TC Consistently Inhibits Phosphorylation of 4EBP-1 and Turns Off c-Myc Expression



Direct Kinase Screen Across Hundreds of Kinases Shows No Difference Among PI3K Inhibitors

	% Enzyme Activity (relative to DMSO controls)					
	TGR-1202 (TG)		Cal-101 (Cal)		IPI-145 (IPI)	
Kinase:	Data 1	Data 2	Data 1	Data 2	Data 1	Data 2
ABL1	97.80	95.06	101.29	99.51	99.56	97.17
ABL2/ARG	92.26	90.58	92.91	89.12	92.27	91.65
ACK1	94.00	93.57	91.68	90.70	96.19	95.51
AKT1	96.75	93.30	101.09	99.02	99.85	99.59
AKT2	91.97	90.82	91.65	91.60	92.95	91.98
AKT3	101.33	100.11	103.14	102.31	100.54	99.85
ALK	97.30	96.46	101.12	100.18	98.02	96.68
ALK1/ACVRL1	105.13	104.28	100.35	96.57	97.08	96.39
ALK2/ACVR1	95.84	95.54	100.01	93.96	93.92	93.62
ALK3/BMPR1A	92.46	89.45	109.23	104.63	101.25	101.07
ALK4/ACVR1B	107.13	106.22	101.96	101.06	101.96	101.06
ALK5/TGFBR1	109.04	108.90	108.88	108.13	107.67	107.56
ALK6/BMPR1B	114.93	110.07	103.15	103.15	102.84	102.58
ARAF	86.35	84.39	93.23	92.30	86.60	86.37
ARK5/NUAK1	98.91	97.77	104.54	101.66	96.77	94.97
ASK1/MAP3K5	98.92	98.39	101.87	101.86	98.03	97.67
Aurora A	99.66	99.54	105.22	103.96	98.97	96.85
Aurora B	100.65	97.20	98.56	95.57	99.80	95.62
Aurora C	95.49	94.19	90.99	90.80	90.89	89.38
AXL	93.54	91.18	97.88	93.47	96.80	93.89
BLK	101.73	99.74	99.53	97.63	99.51	96.91
BRAF	93.43	92.21	88.56	87.57	88.20	85.90
BRK	99.13	97.89	98.87	97.58	98.62	98.27
BTK	99.65	96.83	98.71	97.34	99.05	98.71
c-Kit	98.33	97.37	103.64	99.36	103.33	103.00
c-MER	104.34	102.11	103.73	103.57	103.69	102.91
c-MET	85.48	84.69	83.86	82.97	90.51	85.28
c-Src	87.70	87.62	86.50	85.15	87.62	86.73

Direct Kinase Screen Across Hundreds of Kinases Shows No Difference Among PI3K Inhibitors

	% Enzyme Activity (relative to DMSO controls)					
	TGR-1202 (TG)		Cal-101 (Cal)		IPI-145 (IPI)	
Kinase:	Data 1	Data 2	Data 1	Data 2	Data 1	Data 2
CAMK1a	99.68	99.58	97.63	96.80	103.60	102.72
CAMK1b	103.71	100.17	102.97	102.53	103.03	102.31
CAMK1d	101.24	99.10	99.64	98.81	97.42	96.02
CAMK1g	100.76	98.91	102.09	101.85	101.04	99.12
CAMK2a	100.90	100.09	101.12	100.70	96.78	95.42
CAMK2b	96.40	92.26	97.21	96.15	96.05	95.77
CAMK2d	105.10	103.33	108.56	107.41	104.93	104.32
CAMK2g	92.85	91.47	91.09	91.05	93.56	92.93
CAMK4	76.22	75.44	82.96	82.51	81.96	80.68
CAMKK1	101.92	101.74	107.62	105.38	98.33	98.12
CAMKK2	100.51	98.46	106.81	105.88	100.26	96.64
CDC7/DBF4	92.08	92.01	92.16	91.62	94.04	93.80
CDK2/cyclin A	107.14	104.50	100.85	100.26	102.50	101.42
CDK2/Cyclin A1	82.03	78.05	86.97	86.71	83.09	79.70
CDK2/cyclin E	100.05	99.03	96.24	96.23	97.37	95.57
CDK2/cyclin O	93.85	92.87	93.48	92.75	90.74	90.74
CDK3/cyclin E	85.81	84.31	87.78	86.83	88.66	88.01
CDK4/cyclin D1	103.76	103.64	109.16	108.42	115.14	110.12
CDK4/cyclin D3	99.72	98.78	101.91	99.26	98.27	97.49
CDK5/p25	92.33	90.35	99.96	99.85	95.40	92.65
CDK5/p35	91.77	91.71	98.34	97.36	97.70	97.09
CDK6/cyclin D1	89.93	89.15	95.62	94.64	91.34	91.29
CDK6/cyclin D3	100.30	97.75	103.74	102.47	96.93	96.48
CDK7/cyclin H	103.06	101.23	100.67	98.06	98.74	95.23
CDK9/cyclin K	89.89	88.84	92.36	91.51	93.22	93.11
CDK9/cyclin T1	98.87	98.47	97.18	89.55	97.62	96.17

Kinase profiling was done on a panel of 365 kinases, each with its own substrates. Activity was detected by transfer of radiolabeked phosphate from ATP to the kinase substrate.

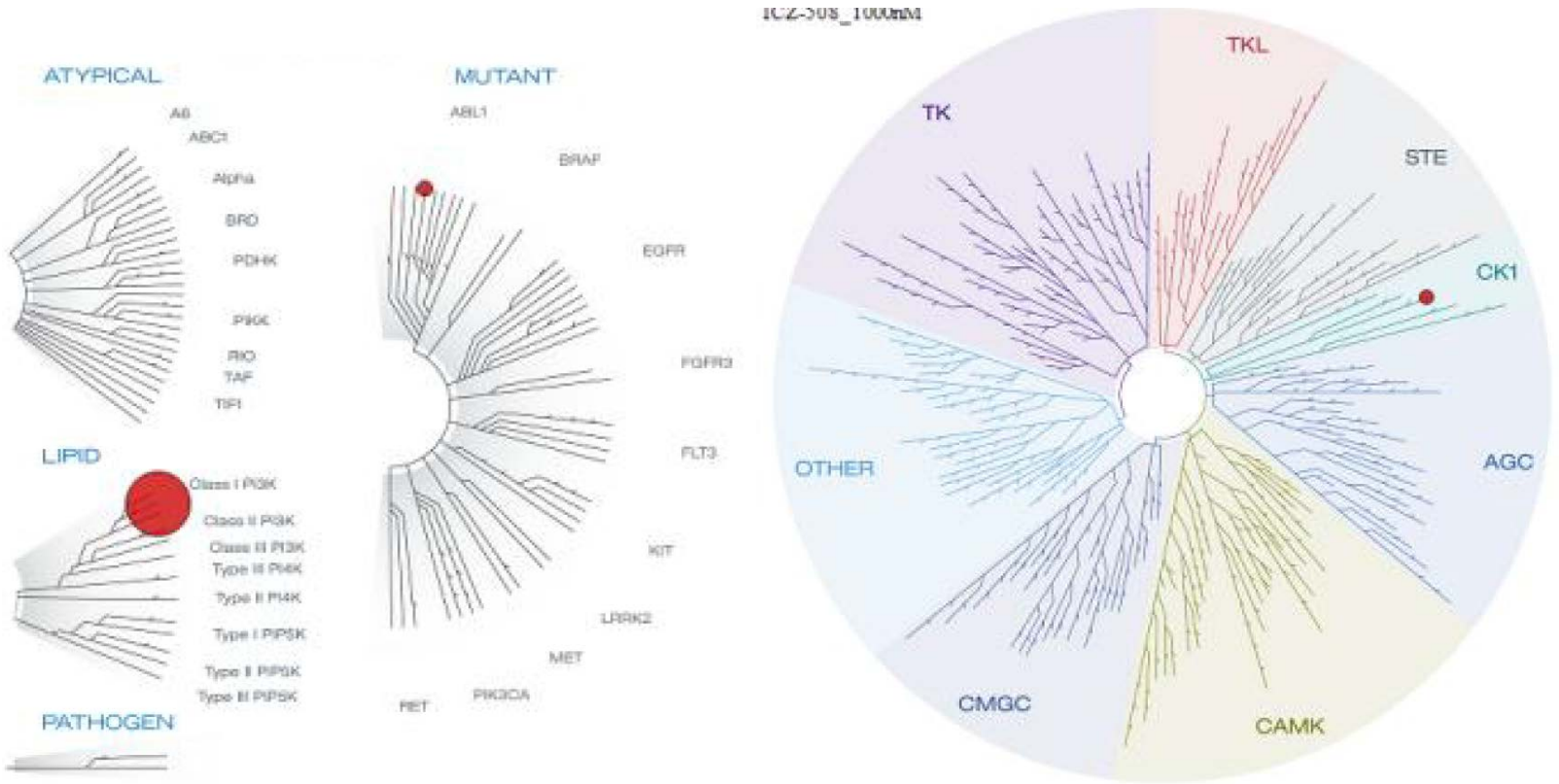
CK-1 EPSILON INHIBITED BY TGR-1202 BUT NOT IDELALISIB NOR DUVELISIB

	% Enzyme Activity (relative to DMSO controls)					
	TGR-1202 (TG)		Cal-101 (Cal)		IPI-145 (IPI)	
Kinase:	Data 1	Data 2	Data 1	Data 2	Data 1	Data 2
CHK1	100.84	95.03	93.37	93.25	96.01	
CHK2	95.20	93.18	96.64	93.69	94.15	
CK1a1	111.14	111.10	110.07	107.15	111.60	
CK1a1L	104.85	102.63	102.48	101.10	103.73	
ARAF	105.36	97.73	96.49	103.52	100.16	
CK1delta	105.36	97.73	96.49	103.52	100.16	
CK1epsilon	**40.37**	**39.93**	**93.06**	**92.90**	**92.84**	
CK1g1	98.99	97.59	104.99	104.59	101.68	
CK1g2	103.96	103.60	102.10	99.65	99.31	
CK1g3	96.02	95.41	93.56	93.10	93.14	
CK2a	83.18	78.16	96.65	95.95	94.65	
CK2a2	86.43	86.37	93.50	91.75	102.34	
CLK1	102.62	102.57	100.36	97.35	105.72	
CLK2	101.65	99.52	97.58	96.88	96.02	
CLK3	94.16	93.68	94.71	89.01	93.74	
CLK4	118.04	116.45	103.22	102.95	108.29	
COT1/MAP3K8	99.80	98.20	101.59	101.10	99.05	
CSK	98.65	94.14	99.47	99.12	98.93	
CTK/MATK	106.04	105.59	107.54	104.89	107.20	
DAPK1	100.68	99.65	98.12	94.96	98.70	
DAPK2	98.40	97.93	107.35	105.85	106.41	
DCAMKL1	90.82	88.33	90.46	89.33	91.30	
DCAMKL2	96.28	94.69	95.53	94.73	94.58	
DDR1	83.64	83.14	83.80	83.80	88.72	
DDR2	106.44	104.13	108.10	106.47	110.90	

CK1 delta and CK1 epsilon are over 95% identical in sequence, but have very different sensitivity to TGR-1202

Kinase profiling was done on a panel of 365 kinases, each with its own substrates. Activity was detected by transfer of radiolabeked phosphate from ATP to the kinase substrate.

TGR-1202 Highly Selective for PI3K Delta



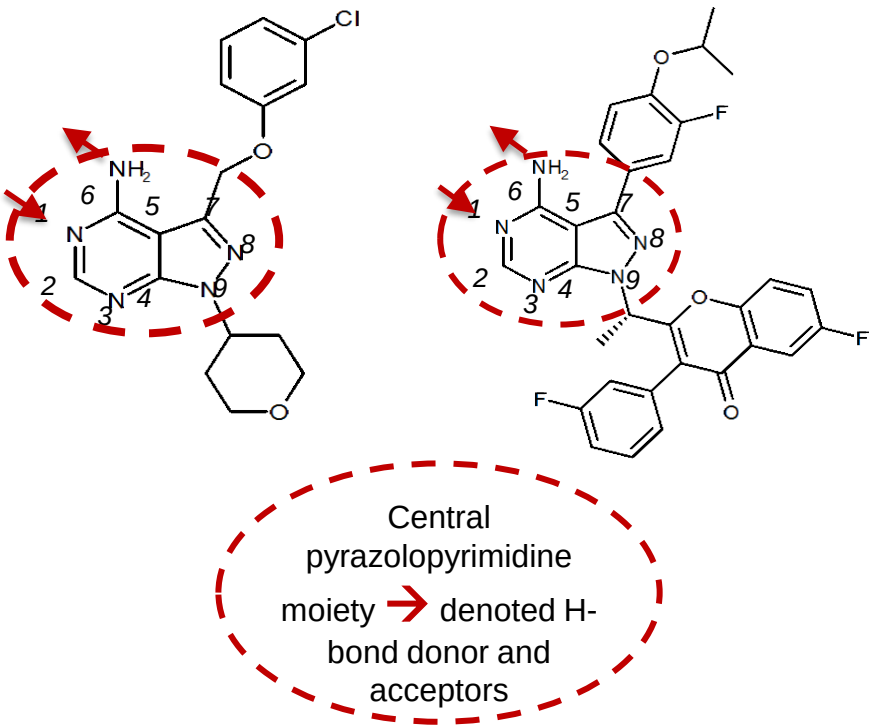
DiscoverRx Kinome Scan against a panel of 442 kinases

TGR-1202 Shares Structural Features with a Known CK-1 epsilon Inhibitor PF4800567

Activity	TG	TG	Ide	Ide	Duv	Duv
CK1a1	111	111	110	107	112	111
CK1a1L	105	103	102	101	104	99
CK1delta	105	98	96	104	100	97
CK1epsilon	***40***	***40***	***93***	***93***	***93***	***91***
CK1g1	99	98	105	105	102	98
CK1g2	104	104	102	100	99	99
CK1g3	96	95	94	93	93	93
CK2a	83	78	97	96	95	84
CK2a2	86	86	94	92	102	100

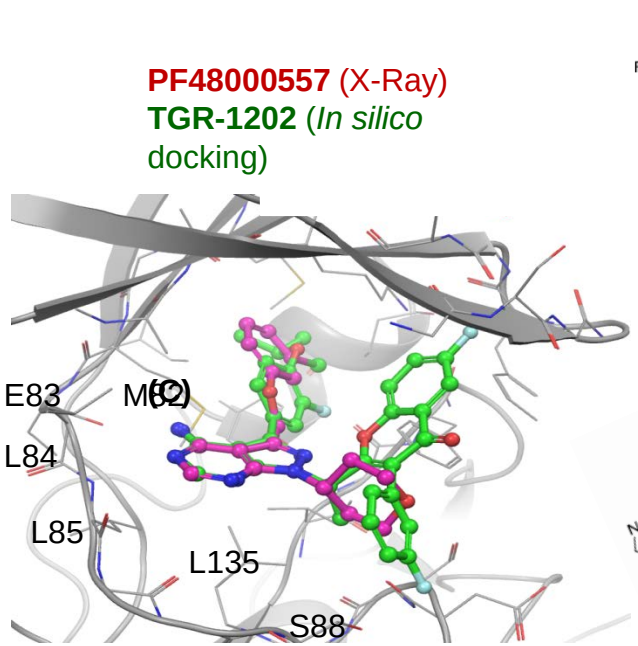
Activity of PI3 kinases against CK-1 demonstrates an isolated CK-1epsilon inhibition for TGR1202 but not the others

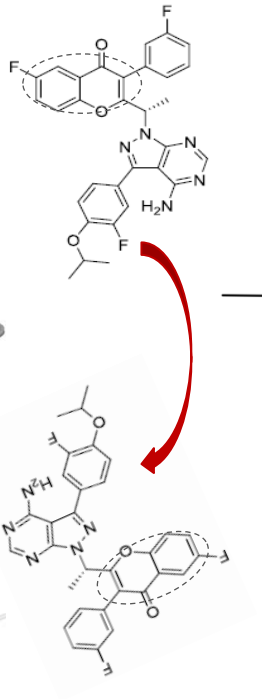
PF4800567 **TGR-1202**

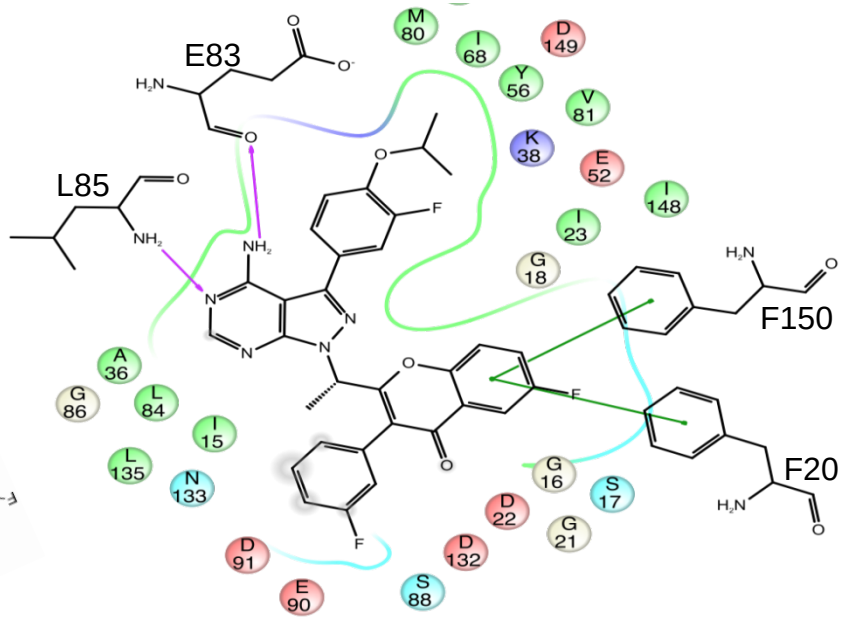


Structural formulae for PF4800567 and TGR1202 with the circled pyrazolopyrimidine moiety shared. PF4800567 is a selective CK-1epsilon inhibitor

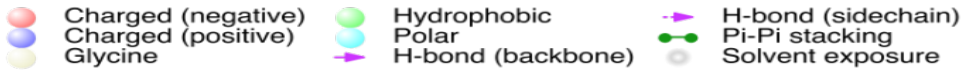
In Silico Docking Demonstrates Similarity Between PF4800557 and TGR-1202 Interaction with CK-1epsilon





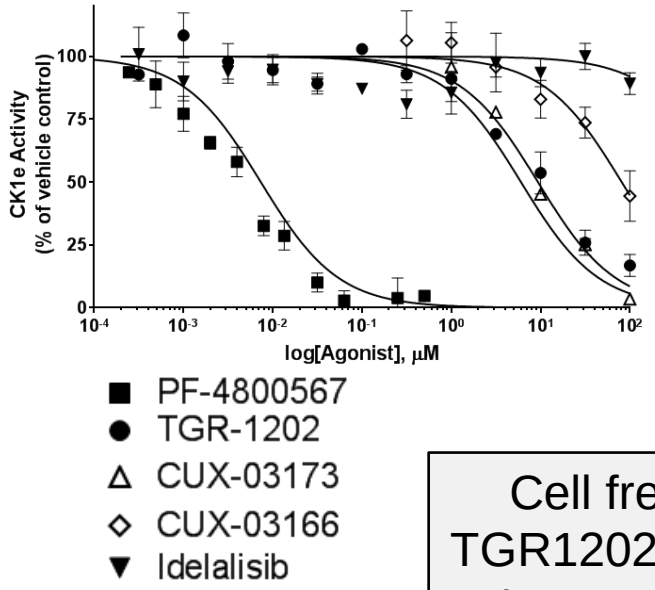


Crystallization of PF48000557 and TGR-1202 in the active binding site of CK-1epsilon



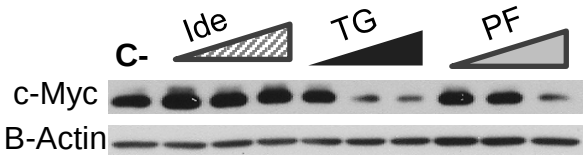
Interaction map of TGR-1202 with the active site amino acids of CK1e

CK-1 EPSILON ACTIVITY INHIBITED BY PF48000567 AND TGR-1202 BUT NOT IDELALISIB



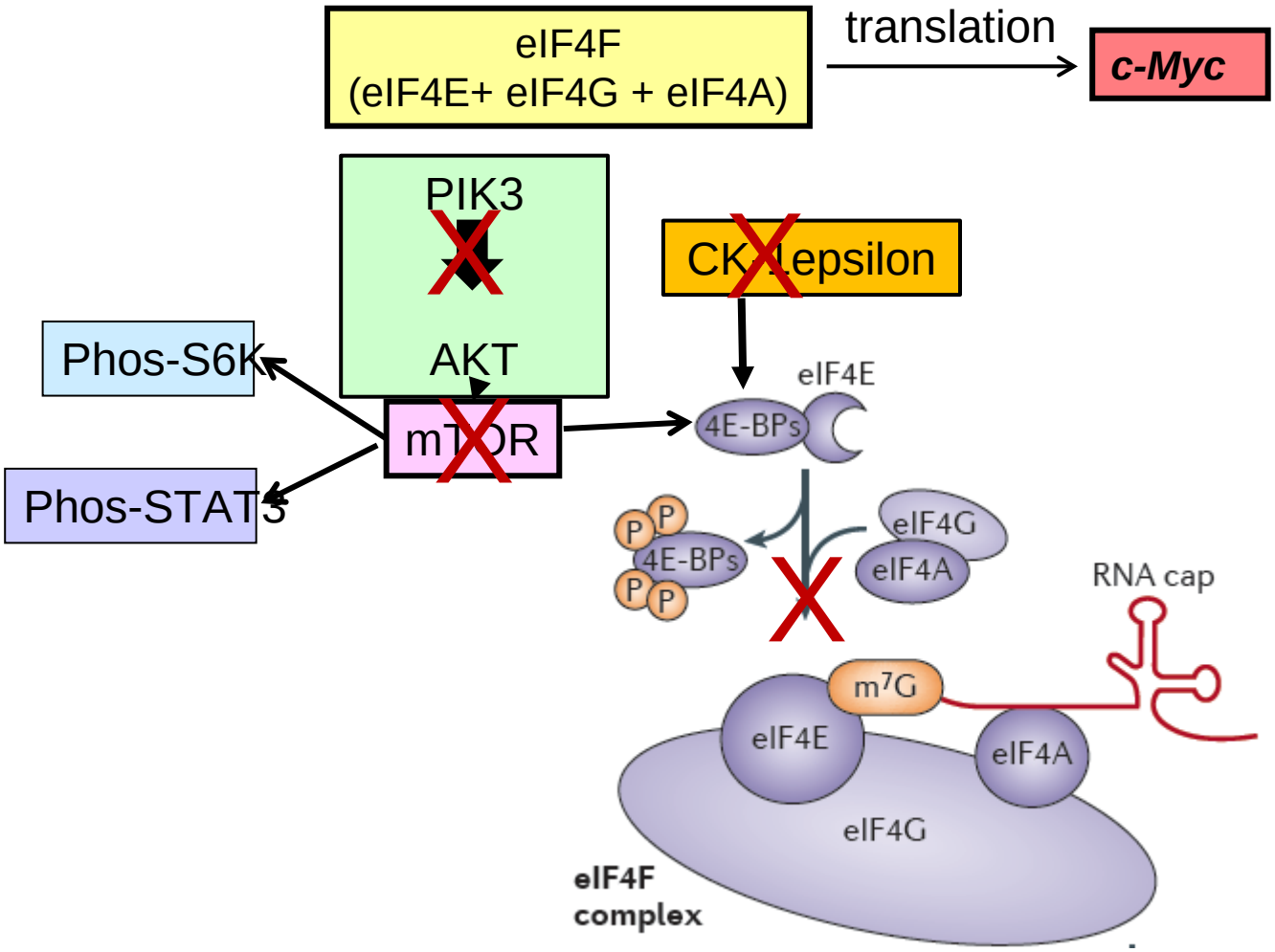
Compound	IC_{50} (μM)	R^2 value
PF-4800567	0.007368	0.9089
TGR-1202	6.038	0.8036
CUX-03173	9.362	0.8313
CUX-03166	81.18	0.4960
Idelalisib	n/a	n/a

Cell free kinase activity assay of CK1e for PF48000567, TGR1202, CU analogs and Idelalisib demonstrates TGR1202 but NOT idelalisib inhibits CK1e albeit is less potent than PF48000567 with statistically significant R^2 values



Only TGR1202 and PF48000567 effect c-myc levels

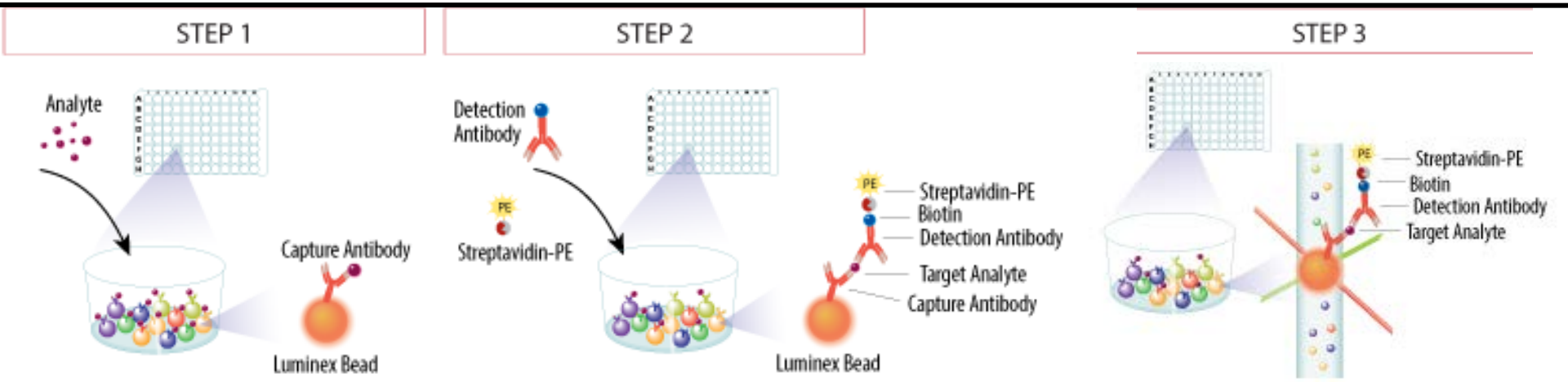
The Model for CK-1 epsilon Inhibition and it Effects on Translation



Pourdehnad PNAS 2013; Zhang Nature 2014; Hutter Leukemia 2012; Quy JBC 2013; Tang PLOS One 2014; Bhat et al., Nat Rev Drug Disc 2015

Probing Differences in Immunologic Effects of PI3K Inhibitors

LUMINEX ASSAY: COMPARISON OF PI3K



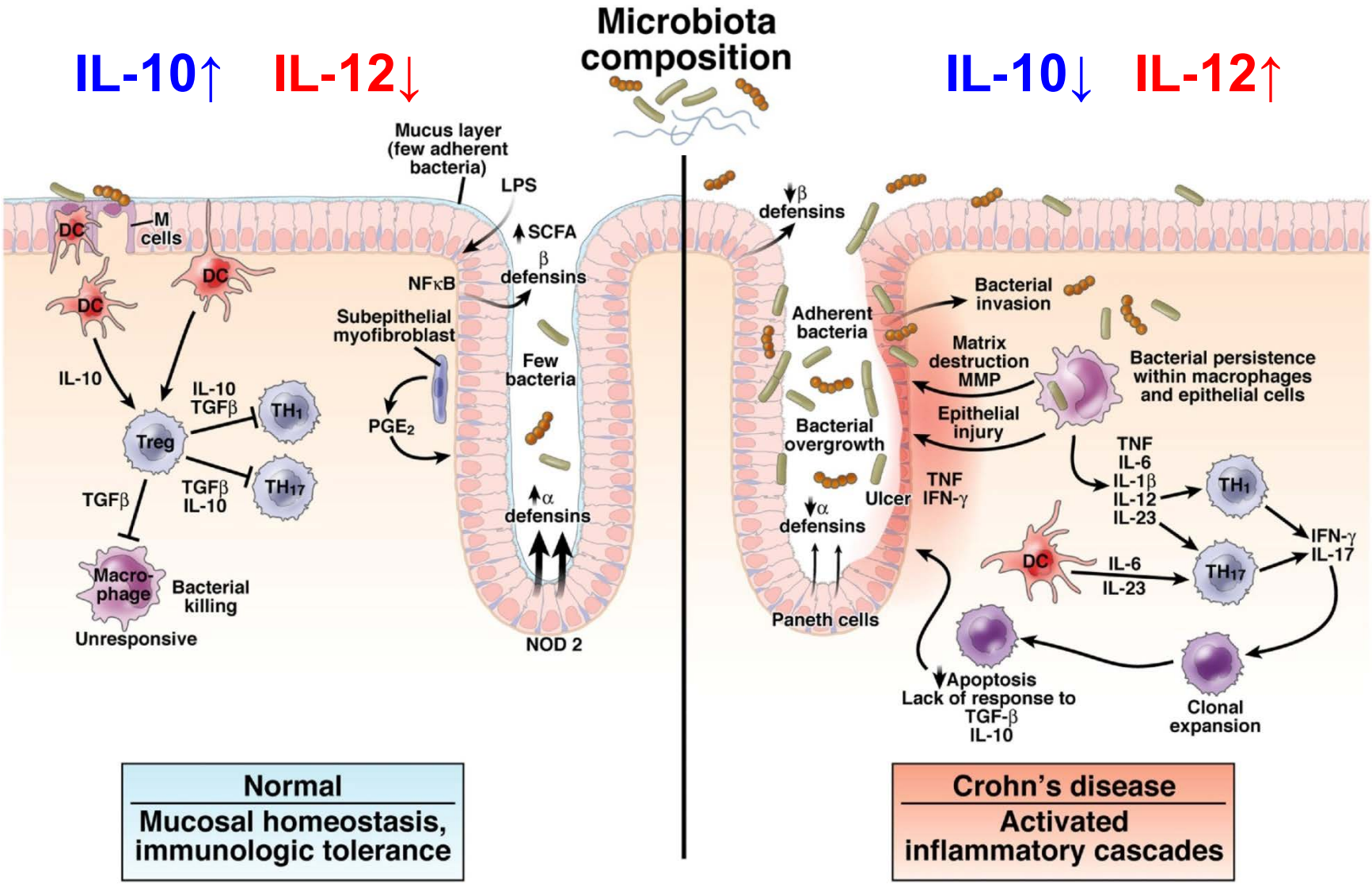
#	Analyte	Pathway
1	IFNg	Inflammation
2	IL-1a	Inflammation
3	IL-1b	Inflammation
4	IL-1Ra	Suppression
5	IL-4	Th2
6	IL-6	Inflammation
7	IL-8/CXCL8	Inflammation
8	IL-10	Suppression
9	IL-12p40	Inflammation
10	IL-12p70	Inflammation
11	IL-13	Th2
12	IL-15	Inflammation
13	IL-17A/CTLA8	IL-17
14	IP-10/CXCL10	Inflammation
15	MCP-1/CCL2	Inflammation
16	MDC/CCL22	Inflammation
17	TNFa	Inflammation

#	Analyte	Pathway
1	IL-10	Suppression
2	IL-12p70	Inflammation
3	IL-17A/CTLA8	IL-17
4	IL-17E/IL-25	IL-17
5	IL-17F	IL-17
6	IL-22	Suppression
7	IL-23	Inflammation
8	IL-27	Inflammation

The two tables include all of the cyokines from the two luminex plates used

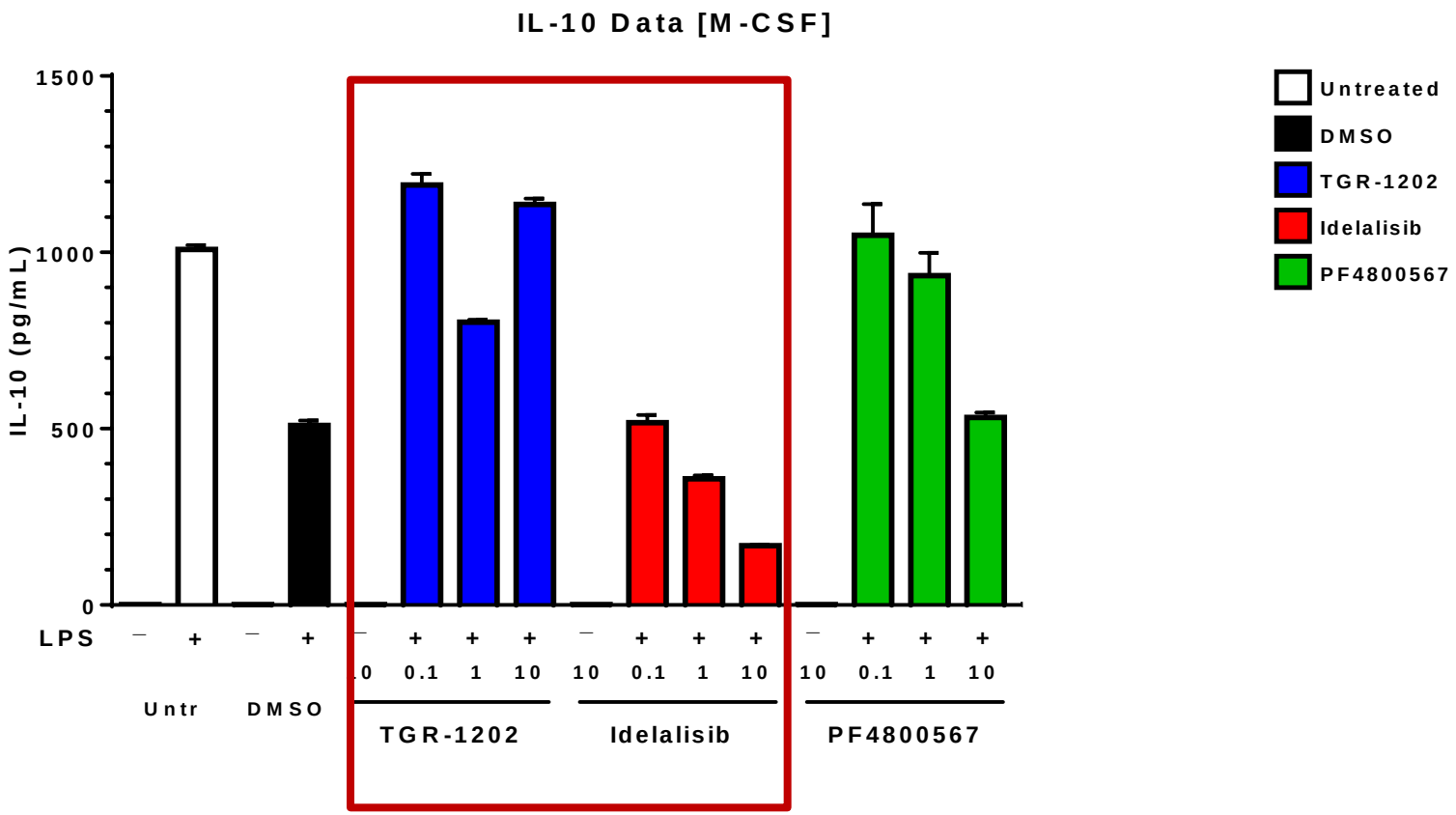
Courtesy Michael Mangone, Columbia University

IL-10 and IL-12: The Yin and Yang of Gut Homeostasis



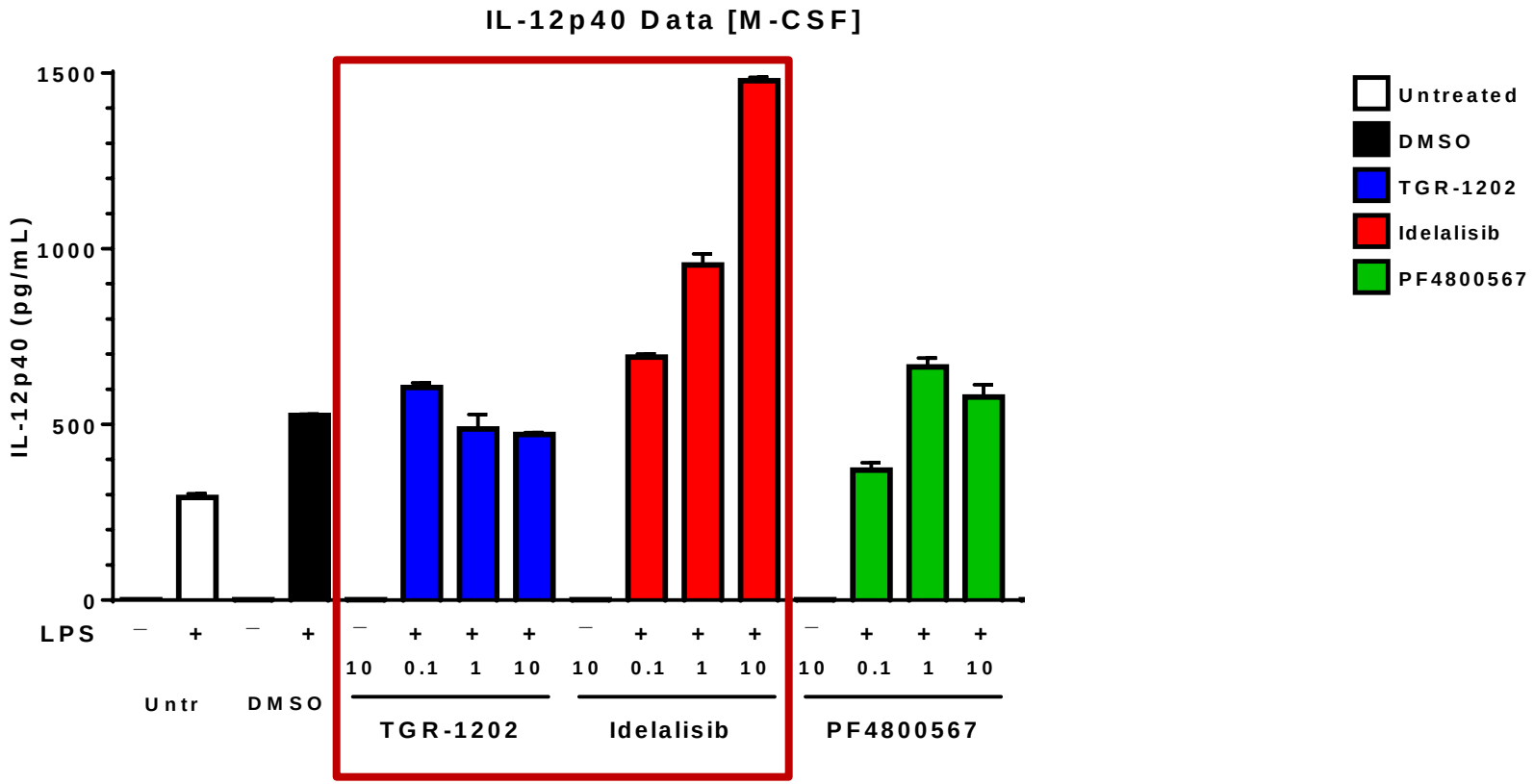
Gastroenterology 2010 139, 1816-1819DOI: (10.1053/j.gastro.2010.10.036)

IDELALISIB EXHIBITS A CONCENTRATION DEPENDENT SUPPRESSION OF ANTI-INFLAMMATORY IL10 WHILE TGR-1202 EXHIBITS NULL EFFECT



Courtesy Michael Mangone, Columbia University

Idelalisib exhibits a Concentration Dependent Induction of Pro-Inflammatory IL12 while TGR-1202 Exhibits Null Effect



Courtesy Michael Mangone, Columbia University

Modulation of T cell Compartment in a Preclinical CLL Murine Model by a Selective PI3K delta Inhibitor, TGR-1202

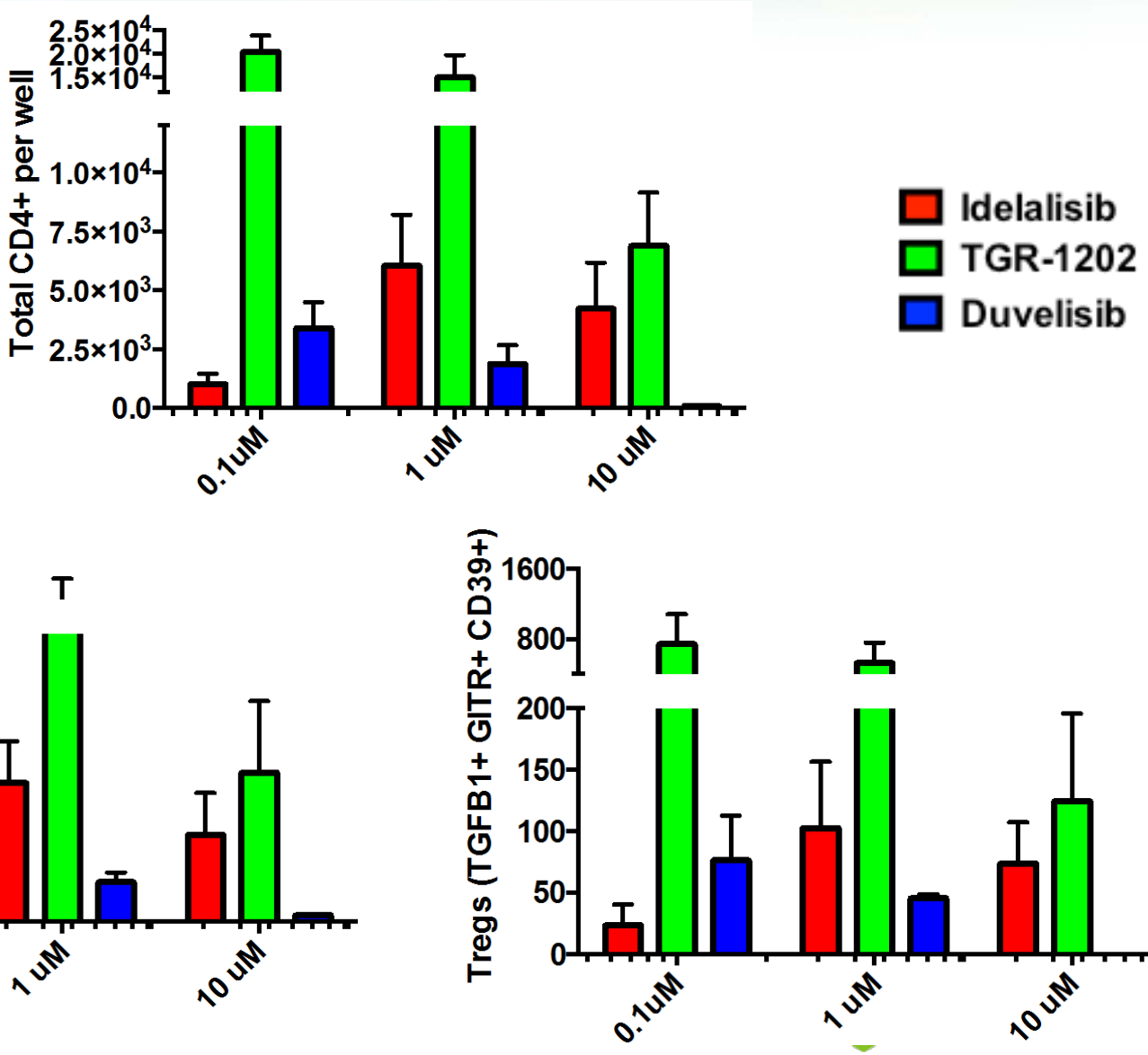
***Kamira K. Maharaj*[1,3], John Powers[1,2], Mibel Pabon-Saldana[1], Susan Deng[1], Alex Achille[1], Renee M. Fonseca [1], Hari P. Miskin[4], Dave Maryanski[4], Eva Sahakian[1,2] and Javier Pinilla-Ibarz[1,3]**

ASH 2016 Poster Session 642, CLL therapies Sunday Dec 4th

MOFFITT CANCER CENTER

TG Therapeutics

Ex-vivo T regs induction: TGR-1202 maintains Treg number & expression of suppressive Treg markers



Maharaj Panilla et al, ASH 2016

CONCLUSIONS

- The marked differences among the PI3K inhibitors in the clinic are unlikely explained by differences in potency – **all are highly selective potent low nanomolar inhibitors of PI3K δ (+/– γ)**

- **The class of drugs targeting PI3K are not dead, we just need to understand differences among the available agents, including mechanisms of toxicity**

- **Fortuitous inhibition of a complementary kinase – casein kinase 1 epsilon [CK-1) - in the PI3k-mTOR-eIF4F pathway likely accounts for effects on 4E-BP1 mediated translation ad c-myc**

- ***It is possible that the lack of 'autoimmune effects' by one PI3 K inhibitor could relate not merely to the potency of δ inhibition, but is counter-balanced by the effects of CK-1 mediated function (i.e. antiinflammatory effects) which mitigate the pro-inflammatory response.***

TG Therapeutics

TGR-1202 Clinical Safety

Anthony Mato, MD
University of Pennsylvania

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY DLBCL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED DLBCL PATIENTS

TGR-1202 Safety Summary – Common Toxicities GR 3/4 Events

	ASH 2016 TGR-1202 DATA				ASCO 2016	TOTAL
	1101+1202 +Benda	1202+ Ibrutinib	1202+ Ruxolitinib	1202+ Brentuximab	Integrated Analysis	TOTAL
n=	19	31	12	14	165	241
Diarrhea	5%	-	17%	7%	3%	4%
Colitis	5%	-	-	7%	1%	2%
AST/ALT	-	-	-	14%	3%	3%
Pneumonia	-	-	8%	-	1%	1%
Neutropenia	21%	13%	8%	43%	18%	19%
URI	-	-	-	-	-	0%
Thrombocytopenia	5%	3%	-	-	5%	4%

TGR-1202 + Ibrutinib: Safety

Toxicities of Special Interest (n=31)

- Diarrhea: 11/31 (35%) pts (29% Gr 1, 6% Gr 2, with no inflammatory colitis)
- Transaminitis: 7/31 (23%) pts, all Gr 1 and self-limited without the need for treatment interruption
- Pneumonitis: 1/31 (3%) pts, Gr 1
- Bleeding events: Gr 1 epistaxis, hematuria, vitreous hemorrhage in 1 CLL pt each
- Atrial fibrillation: 2/31 (6%) pts
- Infection: 7/31 (23%) pts

Davids et al, ASH 2016

TG-1101 + TGR-1202 + Benda: Safety

All Causality AE's Occurring in ≥ 15% of Patients (n = 19)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	7	37%	1	5%
Decreased appetite	6	32%	1	5%
Nausea	6	32%	1	5%
Anemia	4	21%	2	11%
Neutropenia	4	21%	4	21%
Vitamin D decreased	4	21%	-	-
Arthralgia	3	16%	-	-
Asthenia	3	16%	-	-
Dysgeusia	3	16%	1	5%
Hypomagnesemia	3	16%	1	5%
Infusion related reaction	3	16%	-	-
Rash	3	16%	1	5%
Thrombocytopenia	3	16%	1	5%

- Mean time on study 6 cycles
- No patient has discontinued due to a treatment-related AE
- Growth factor support was restricted during Cycle 1 for DLT evaluation purposes
- No Grade 3/4 transaminase elevations have been reported
- 1 transient event of Grade 3 diarrhea (duration of 1 day) was reported
- No events of pneumonia or pneumonitis have been reported to date

Lunning et al, ASH 2016

PI3K-Delta AE Profile

- TGR-1202 has a differentiated safety profile from other PI3K delta inhibitors, including with long term follow-up

Grade 3/4 AEs All Causality	**Idela + Ofa (ASCO '16)[1] (n=173)**	**TGR-1202 (ASCO '16)[2] (n=165)**
Diarrhea/ Colitis	**23%**	**4%**
Pneumonia	**20%**	**5%**
ALT/AST Elevations	**13%** (35% All Grades)	**3%** (8% All Grades)
Discontinuations due to AE	**39%**	**<8%**

[1] Jones et al, ASCO 2016
[2] Burris et al, ASCO 2016

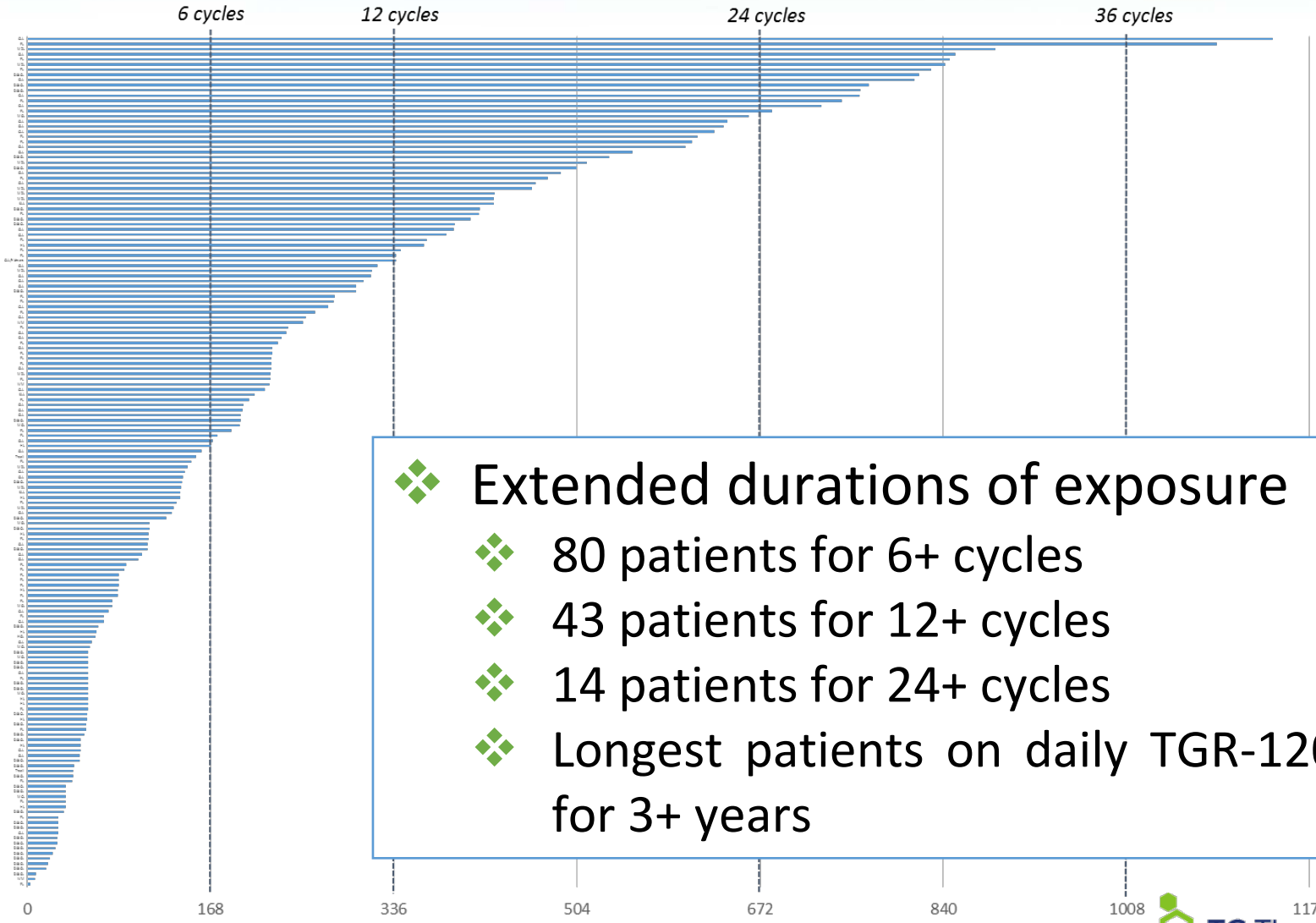
Integrated Analysis: Common “Delta” Toxicities

Toxicities (Gr. 3/4)	800mg Dose n=40	All Patients n=165
AST/ALT	5% (2)*	3% (5)*
Pneumonitis	0% (0)	1.5% (2)
Colitis	0% (0)	1.5% (2)

* Fisher's exact test: The two-tailed P value equals 0.6243

Burris et al, ASCO 2016

Integrated Analysis: Duration of Treatment



- 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

Burris et al, ASCO 2016

Idelalisib Caused Rapid and Serious Liver Toxicity in Front-Line Patients

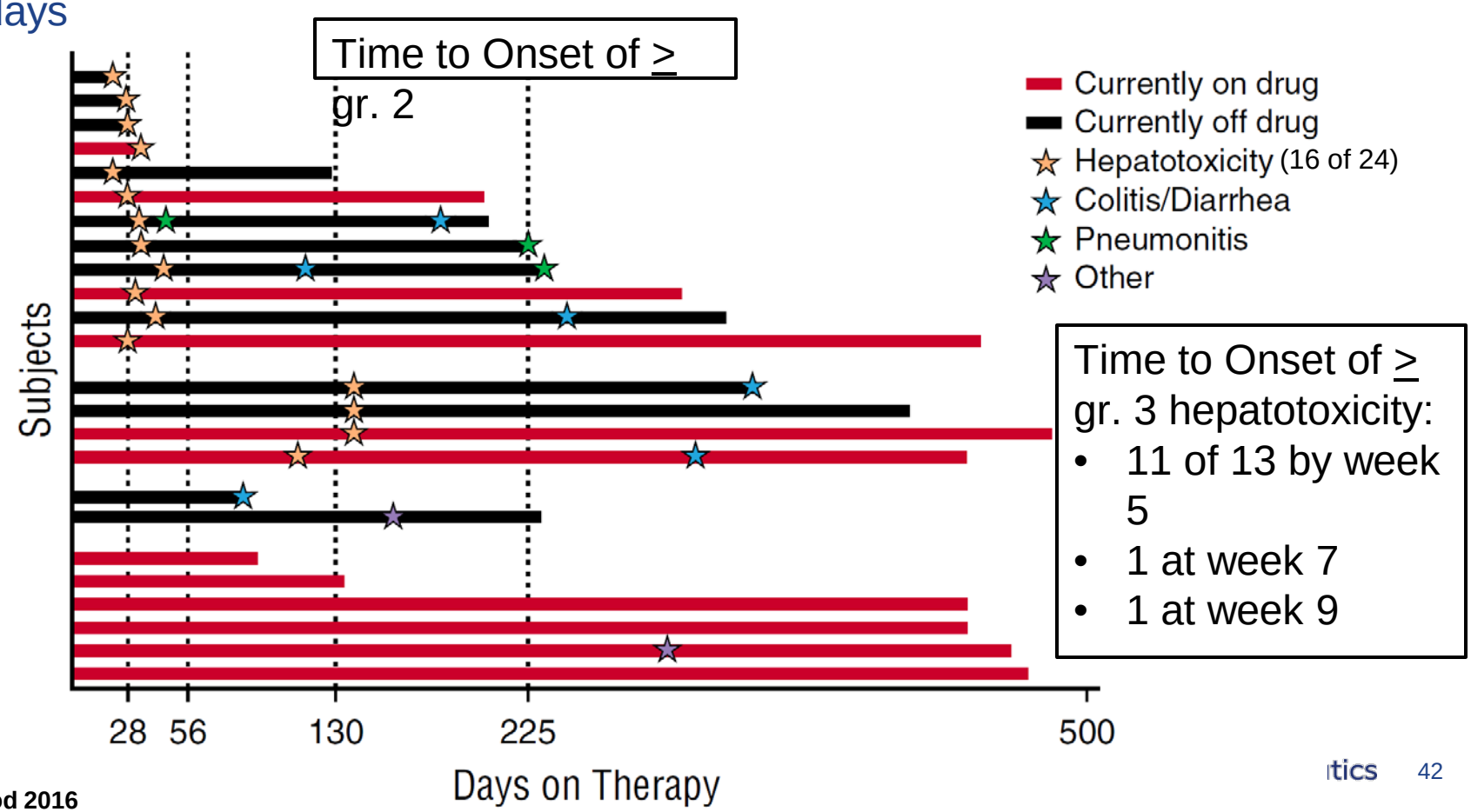
CLINICAL TRIALS AND OBSERVATIONS

Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity

Benjamin L. Lampson, Jennifer R. Brown, et.al.
BLOOD, 14 JULY 2016 x VOLUME 128, NUMBER 2

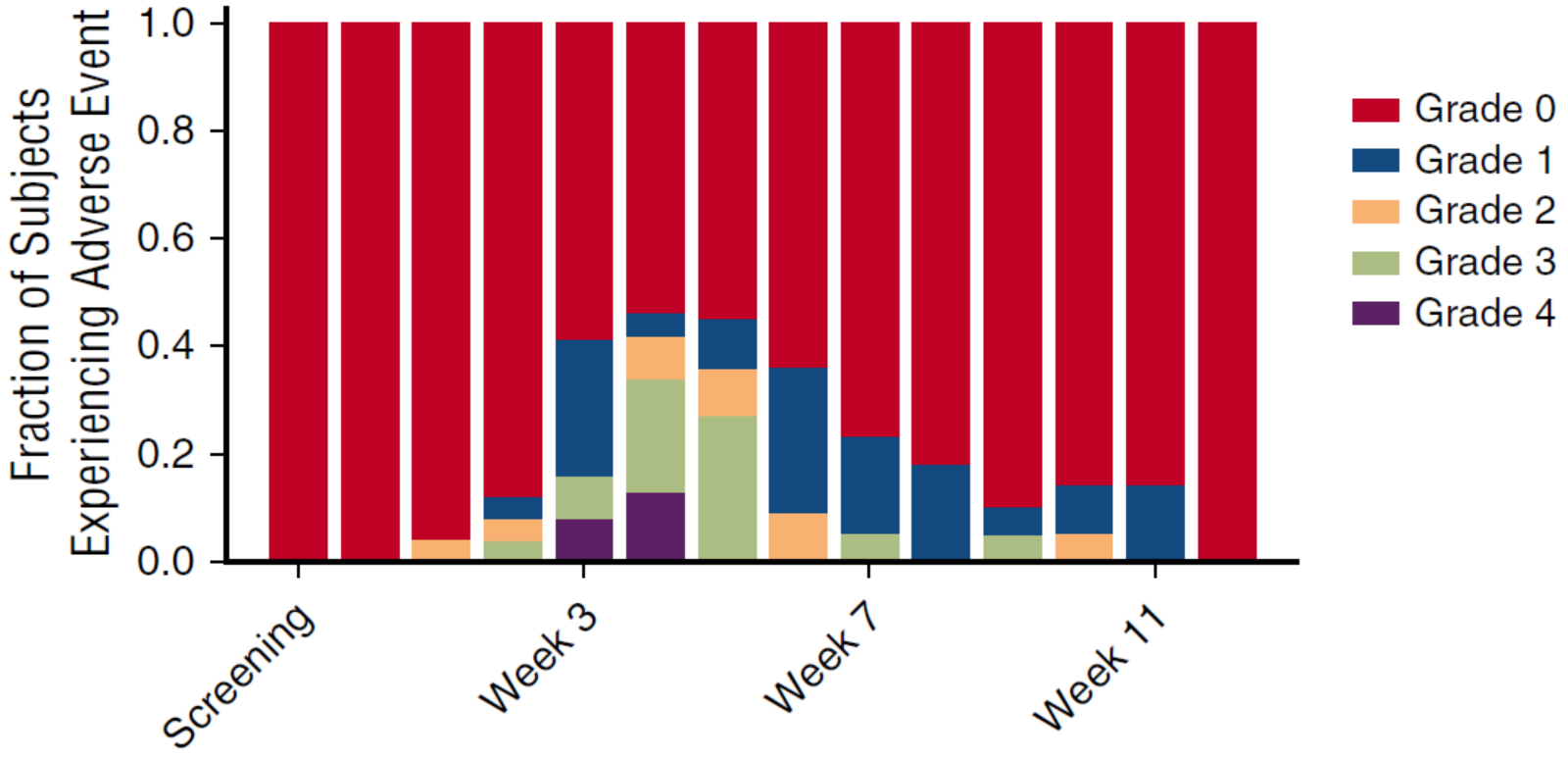
Idelalisib Related Hepatotoxicity

- Brown et al reported high rates of immune-mediated hepatotoxicity in patients with front-line CLL treated with idelalisib
- Decreases in Treg population implicated
- Transaminitis rates of 79% all grades (gr.3/4 of 54% (13 of 24)), with median onset at 28 days



Lampson, Blood 2016

Idelalisib Liver Toxicity in Front-line Patients



- Almost all Gr. 3/4 liver tox for idela was observed by week 5
  - Gr. 3/4 Liver Tox at 6 weeks 46% (11/24 patients)
  - All Grades Liver Tox at 6 weeks 79% (19/24 patients)

Lampson et al, Blood 2016

First Unity-CLL DSMB on November 21

"The DSMB did not find any safety concerns and recommended the study continue without modification"

TG Therapeutics

TGR-1202 Clinical Activity

Matthew Lunning, DO
University of Nebraska Medical Center

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY DLBCL
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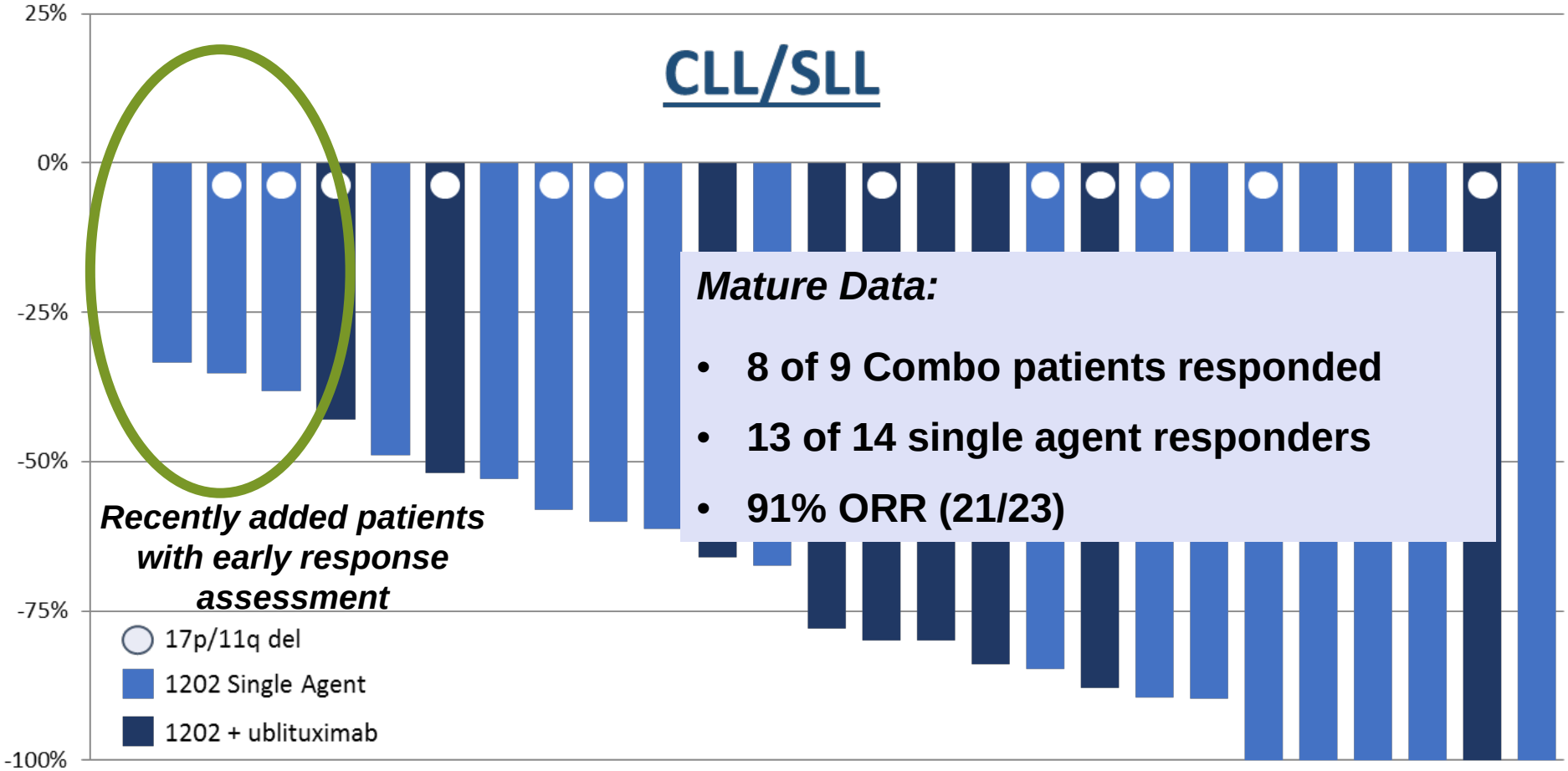
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED DLBCL PATIENTS

Integrated Analysis: TGR-1202 Monotherapy and TGR-1202 + Ublituximab - CLL/SLL Efficacy

Patients Treated at "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden

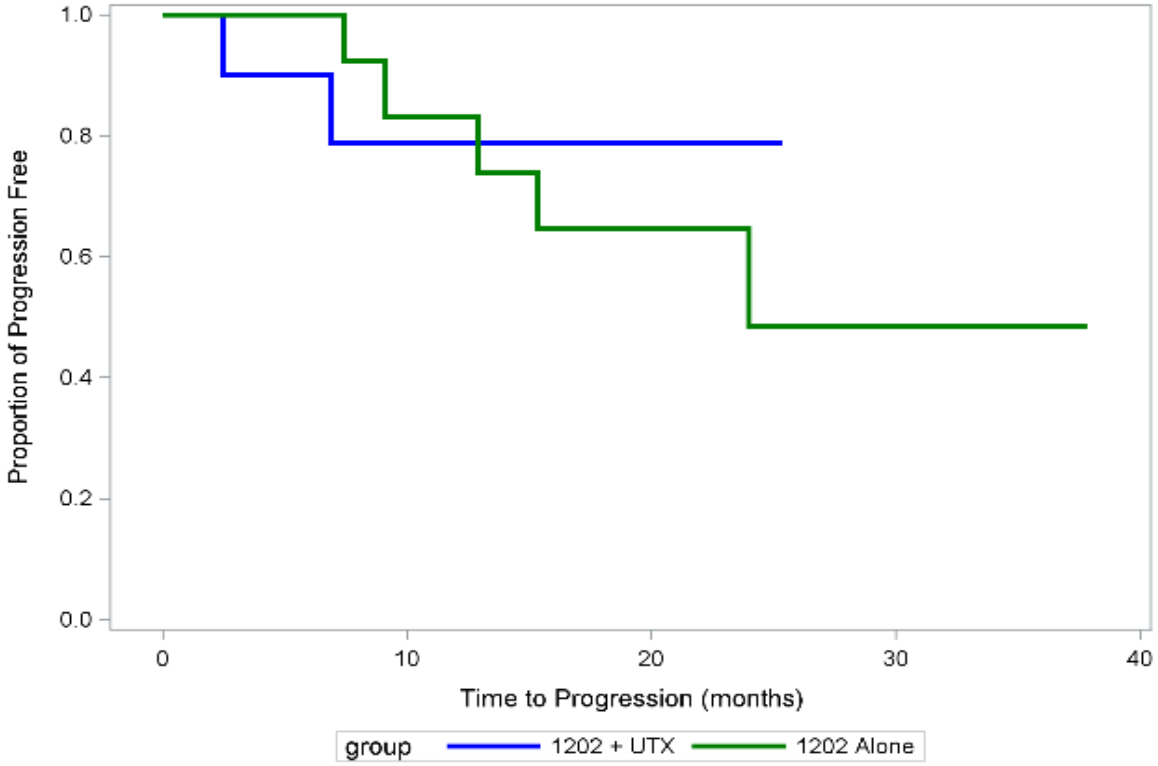


Higher Doses: 1200 mg of the initial formulation, or ≥600 mg of the micronized formulation

Burris et al, ASCO 2016

TGR-1202 Integrated Analysis: PFS

CLL Progression-Free Survival at Higher Doses



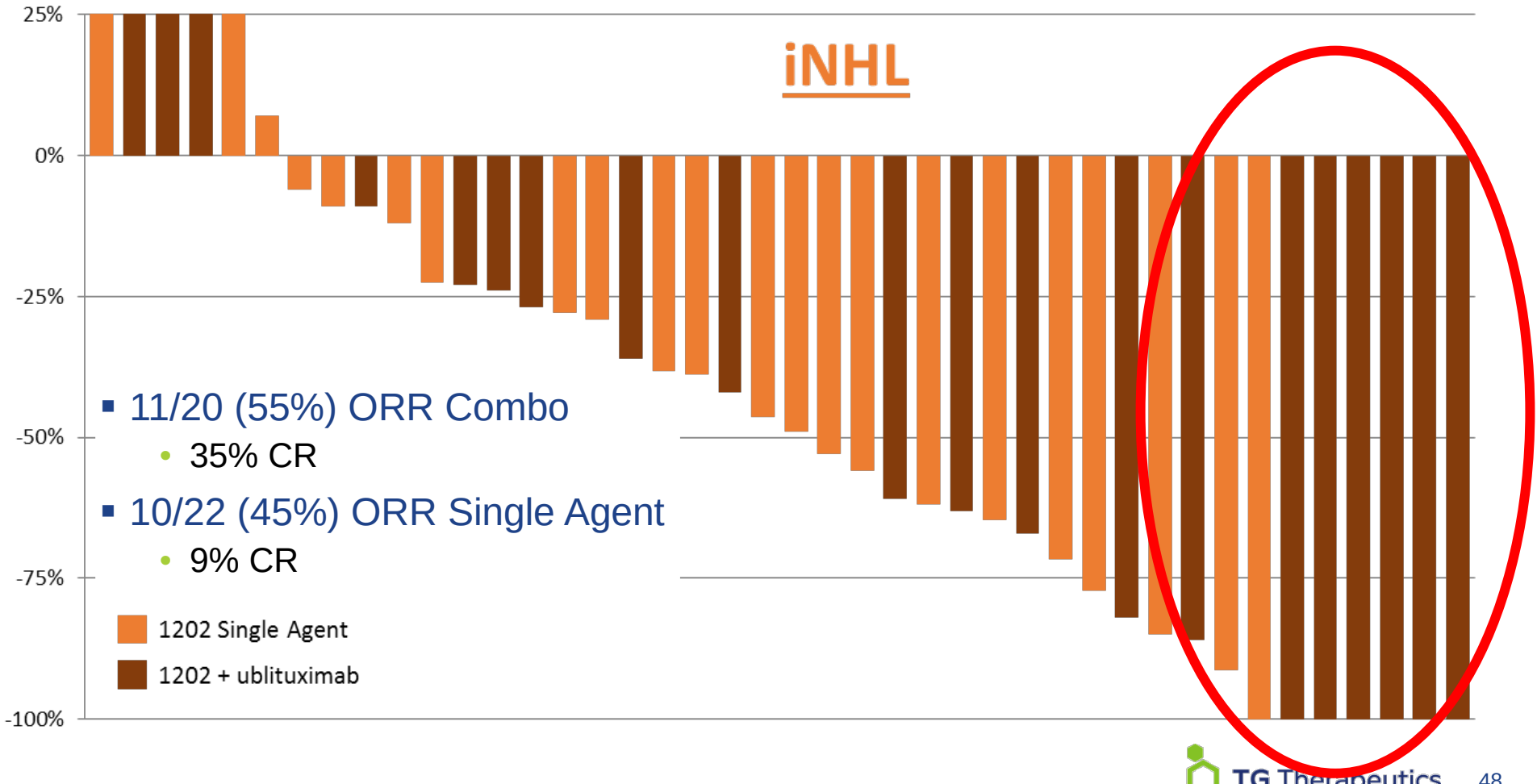
- Median PFS for TGR-1202 Monotherapy: 24 Months
- Median PFS and DOR not reached for TGR-1202 + UTX

Mato, Burris et al, EHA 2016

Integrated Analysis TGR-1202 Monotherapy and TGR-1202 + TG-1101: iNHL Efficacy

Patients Treated at "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden

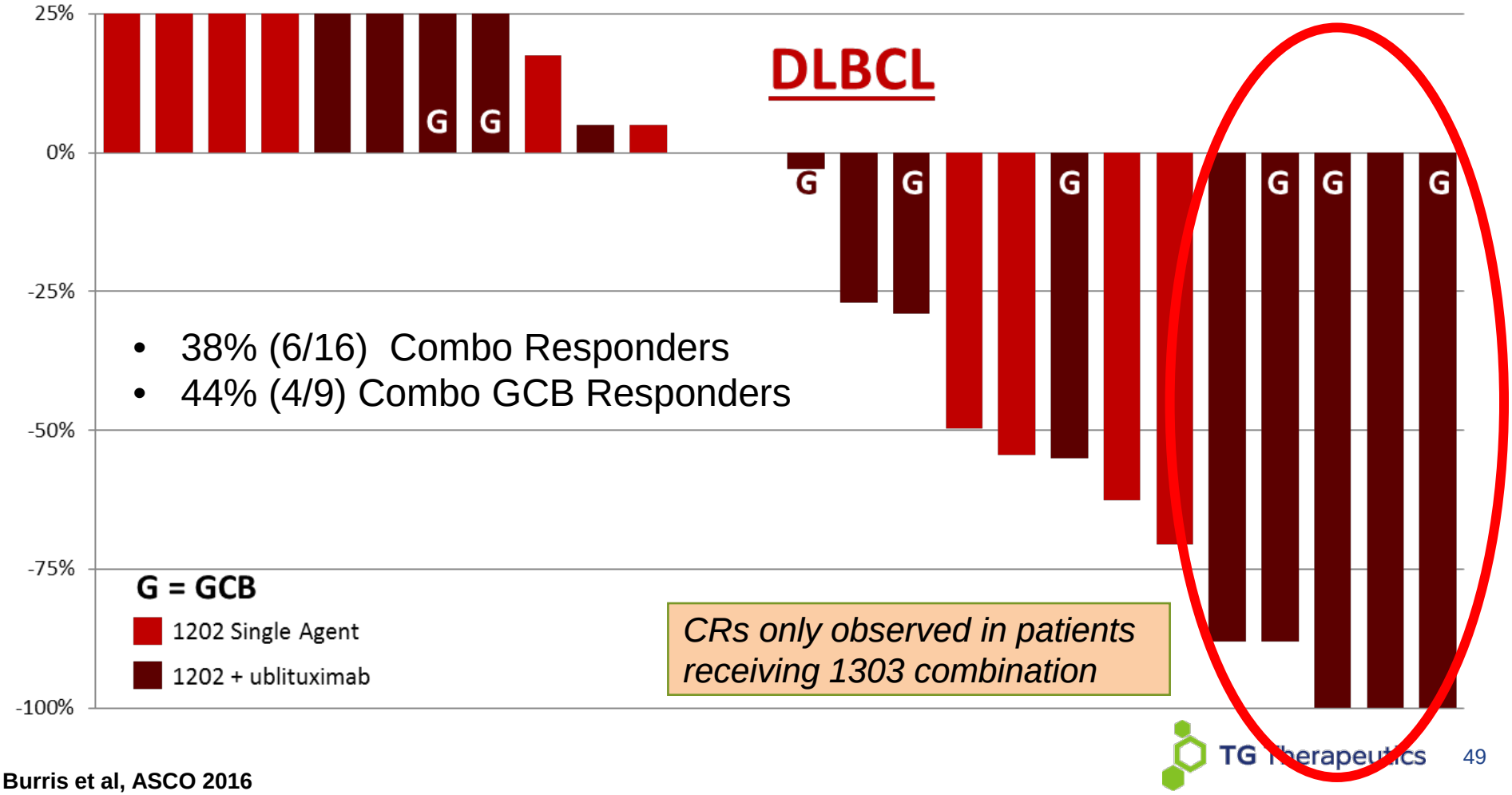


Burris et al, ASCO 2016

Integrated Analysis TGR-1202 Monotherapy and TGR-1202 + TG-1101: DLBCL Efficacy

Patients Treated at "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden



Burris et al, ASCO 2016

DLBCL Case Study: Univ. of Nebraska Patient on TG-1101 (Ublituximab) + TGR-1202

Background

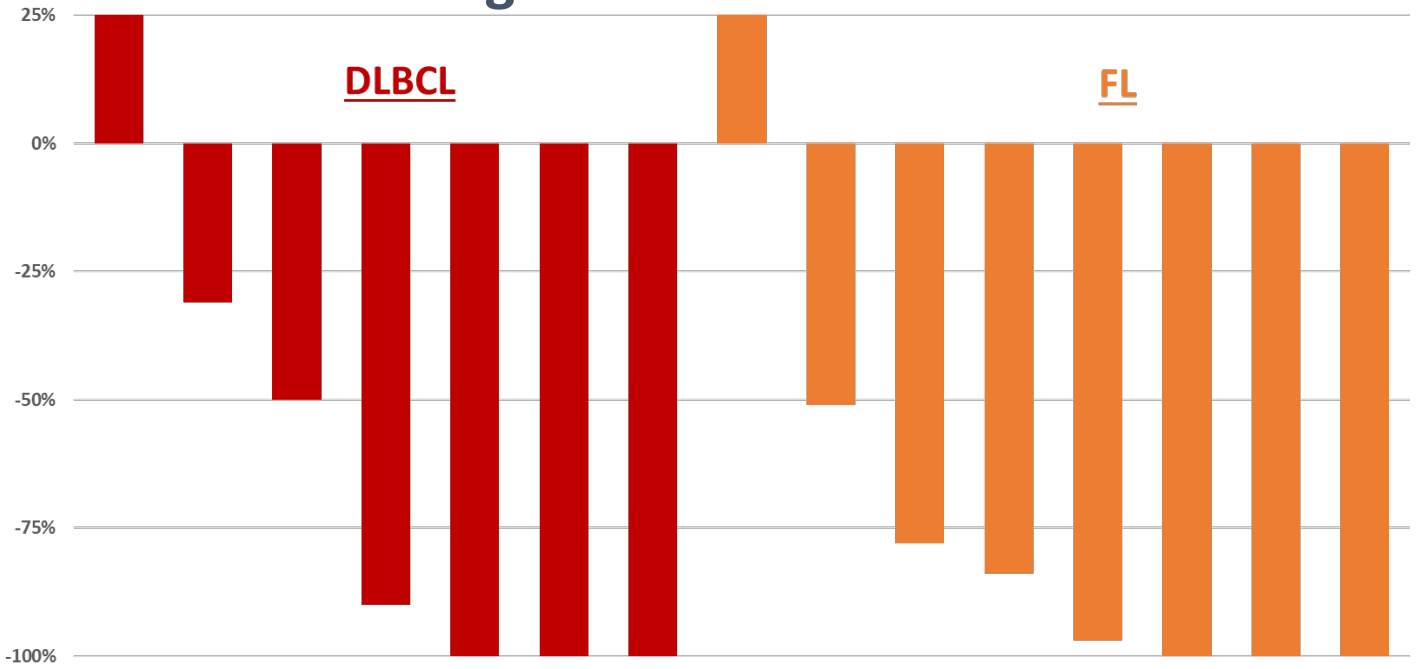
- 74 yo Female
- GCB Subtype
- Received R-CHOP frontline therapy
  - Relapsed within 1 year
- Received R-Gem/Ox
  - Relapsed within 6 months

Outcome

- Started on TGR-1202 + TG-1101 clinical trial
  - Cycle 3: PR (54% reduction)
  - Cycle 6: PR (71% reduction)
  - Cycle 9: PR (71% reduction)
  - Cycle 12: PR (88% reduction)
- On study treatment for 13+ months

TG-1101 + TGR-1202 + Benda: Efficacy

Best Percent Change from Baseline in Disease Burden



Type	Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
DLBCL	7	3	2	**5 (71%)**	1	1
FL	8	3	4	**7 (88%)**	-	1
Total	**15**	**6**	**6**	**12 (80%)**	**1**	**2**

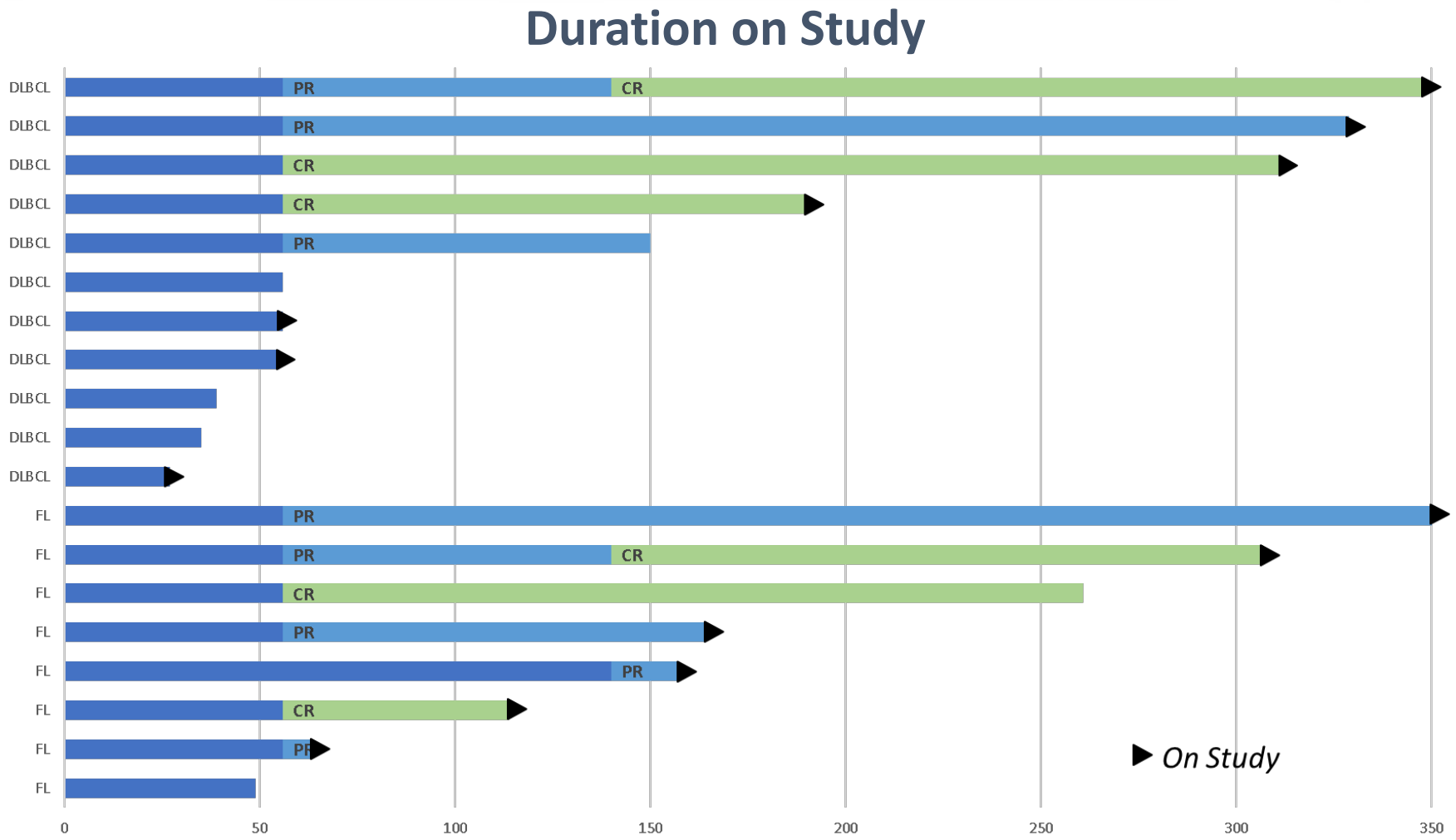
Lunning et al, ASH 2016

TG-1101 + TGR-1202 + Benda: Efficacy

Histology	TGR Dose	Rel/Ref	Prior Therapies	Best ORR
DLBCL	600	Ref	R-CHOP, R-ICE	PD
DLBCL	600	Ref	R-CHOP, R-ICE, BEAM, **ASCT**	SD
DLBCL	600	Rel	R-CHOP	PR
DLBCL	800	Ref	R-CHOP, R-Adria, Pembro + Acalabrutinib	PR
DLBCL	600	Rel	R-CHOP	CR
DLBCL	800	Ref	R-CHOP, R-Benda, **ASCT**, R-GEM/OX, Revlimid	CR
DLBCL	800	Rel	R-CVAD, R-ICE, BEAM, **ASCT**	CR
FL	600	Rel	R-EPOCH, **ASCT**	PD
FL	600	Ref	R-CHOP, Radiation, Rituximab	PR
FL	600	Rel	R-Benda, R + Idelalisib, CPI-1205	PR
FL	600	Rel	R-Benda, Rituximab	PR
FL	800	Ref	R-CHOP	PR
FL	600	Rel	CHOP, R-ICE, **ASCT**	CR
FL	600	Rel	R-CHOP	CR
FL	600	Ref	R-CHOP	CR

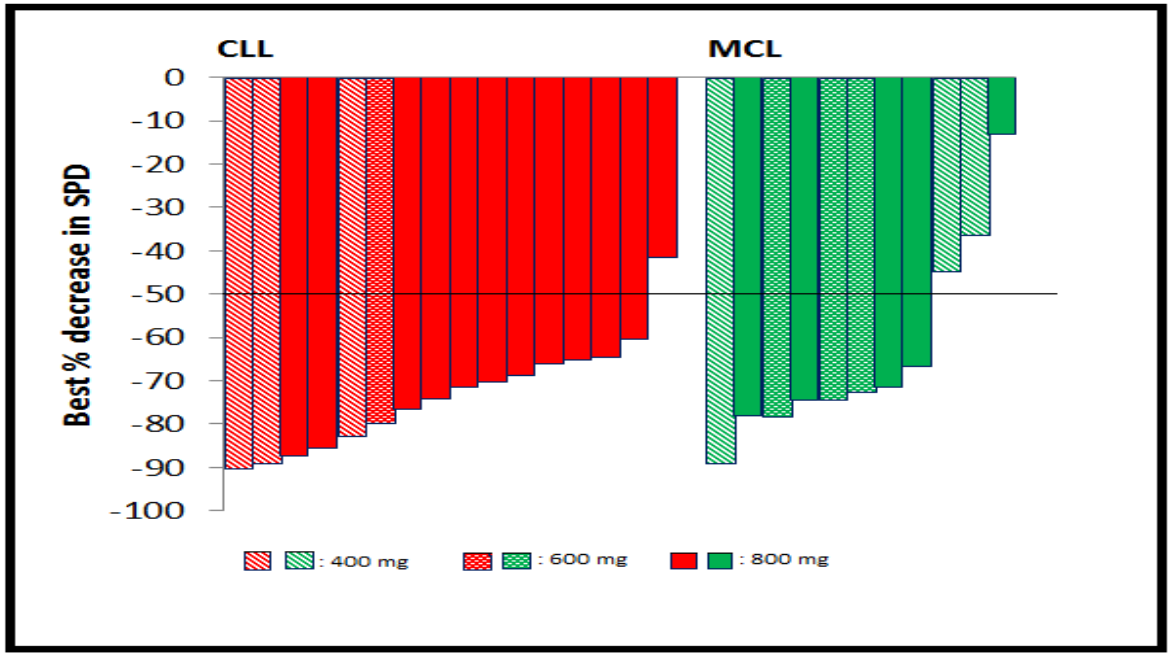
Lunning et al, ASH 2016

TG-1101 + TGR-1202 + Benda: Efficacy



Lunning et al, ASH 2016

TGR-1202 + Ibrutinib: Efficacy (n=28)



CLL (n=17)

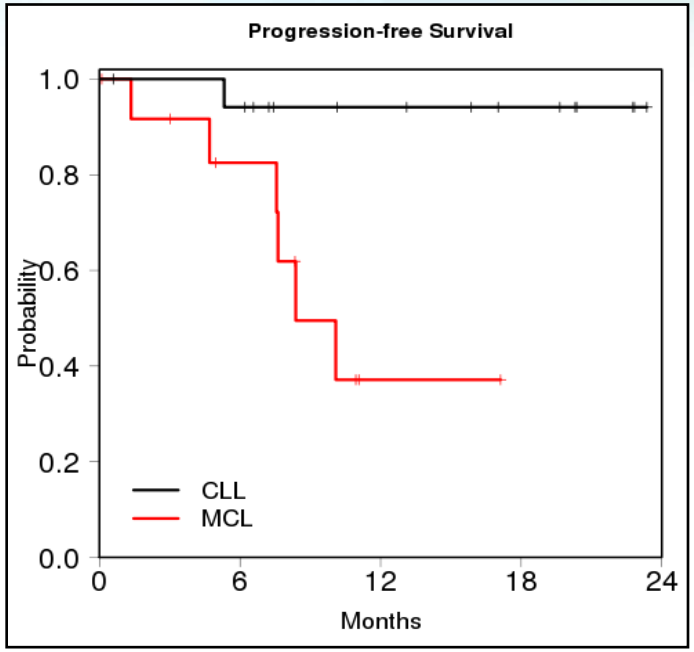
- **ORR: 15/17 (88%)**
  - **-PR or PR-L: 14/17 (82%)**
  - **-CR: 1/17 (6%)**
- **5 PR patients with >80% SPD decrease, nearing radiographic CR**

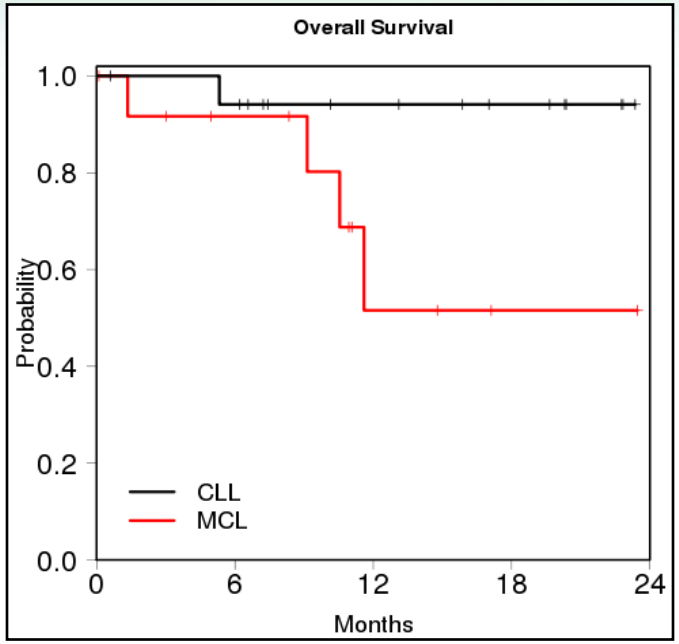
MCL (n=11)

- **ORR: 8/11 (73%), all PRs**
- **Clinical benefit observed in 2 additional patients**

Davids et al, ASH 2016

TGR-1202 + Ibrutinib: Efficacy (n=28)





- **Median follow-up time among survivors: 11 mo. (range 0.1-23.5)**
- **1-year PFS and OS for CLL is 94% (n=17)**
- **1-year PFS and OS for MCL is 37% and 52%, respectively (n=11)**
- **6 MCL patients have died (5 due to PD, 1 due to toxicity from subsequent therapy)**
- **1 CLL patient had sudden death deemed unlikely due to study drugs**

Davids et al, ASH 2016

Toxicities and Outcomes of Ibrutinib-Treated Patients in the United States: Large Retrospective Analysis of 621 Real World Patients

Anthony R. Mato, MD
Center for CLL
University of Pennsylvania

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

TG Therapeutics

Toxicities and Outcomes of Ibrutinib-Treated Patients

Baseline Characteristics		
	Ibrutinib in front line	**Ibrutinib in relapse**
Total Number	80	536
Med age dx (range)	62 (37-88), n=78	60 (22-95), n=532
Med prior tx (range)	0 (0-0), n=80	2 (1-10), n=536
del17p (+)	37%, n=76	26%, n=368
del11q (+)	19%, n=75	35%, n=367
p53 mut (+)	12%, n=42	13%, n =142
Complex karyotype (+) (≥ 3)	40%, n=60	34%, n=214
Med time dx to Ibr (range)	26 months (1-232)	78 months (1-660)
Med Ibr starting dose	420 mg	420 mg
Ibr administered as monotherapy	68%, n=80	89%, n=536
Ibr hold required	30%, n=79	37%, n=310
Ibr dose adjusted	15%, n=79	20%, n=309
Median follow up	17 months	

Mato et al, ASH 2016

Ibrutinib Discontinuation

Reason for ibrutinib Discontinuation	Ibrutinib in front line		Ibrutinib in Relapse	
	Commercial Use (%) n=10	Clinical Trial (%) n=9	Commercial Use (%) n=200	Clinical Trial (%) n=31
Toxicity	**50.0**	**77.7**	**52.5**	**38.7**
CLL progression	10.0	22.2	19.0	35.5
Other/unrelated death	10.0	0.0	12.0	12.9
Physician or patient preference	20.0	0.0	6.0	9.7
RT DLBCL	0.0	0.0	4.5	0.0
Stem cell transplantation/ CAR T-cell	0.0	0.0	3.5	3.2
Financial concerns	0.0	0.0	1.0	0.0
Secondary malignancy	10	0.0	1.0	0.0
RT Hodgkin lymphoma	0.0	0.0	0.5	0.0

Mato et al, ASH 2016

Most Common Ibrutinib Related Toxicity

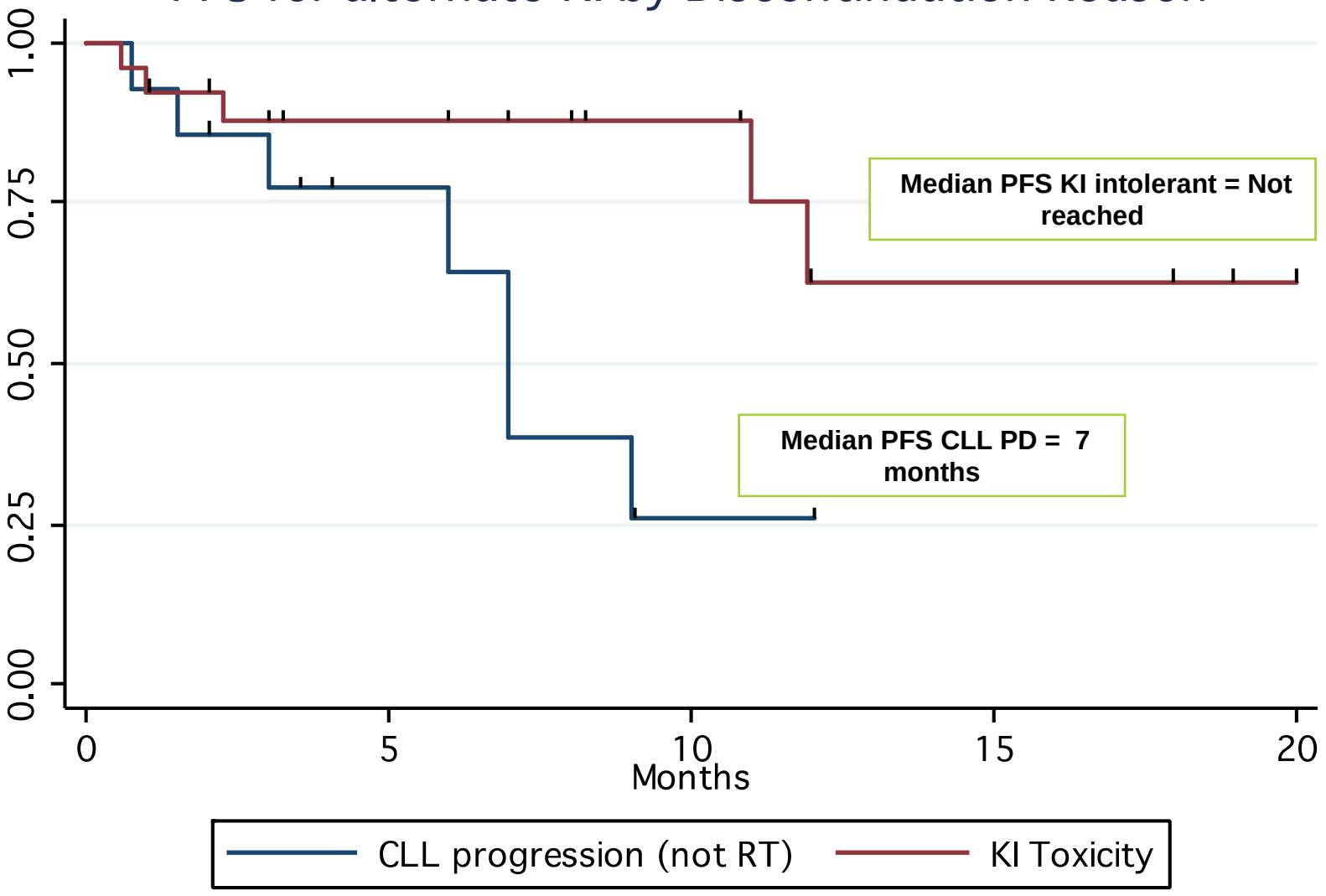
Most common ibrutinib related toxicities as reasons for discontinuation	
Relapsed CLL (%)	**Front-line CLL (%)**
Atrial fibrillation (12.3)	
Infection (10.7)	Arthralgia (41.6)
Pneumonitis (9.9)	Atrial fibrillation (25)
Bleeding (9)	Rash (16)
Diarrhea (6.6)	

Median times to ibrutinib discontinuation stratified by toxicity	
Bleeding	8 months
Diarrhea	7.5 months
Atrial fibrillation	7 months
Infection	6 months
Arthralgia	5 months
Pneumonitis	4.5 months
Rash	3.5 months

- In the largest reported series on ibrutinb treated CLL patients, 40% of patients have discontinued ibrutinib during this observation period.
- Ibrutinib intolerance was the most common reason for discontinuation in all settings.

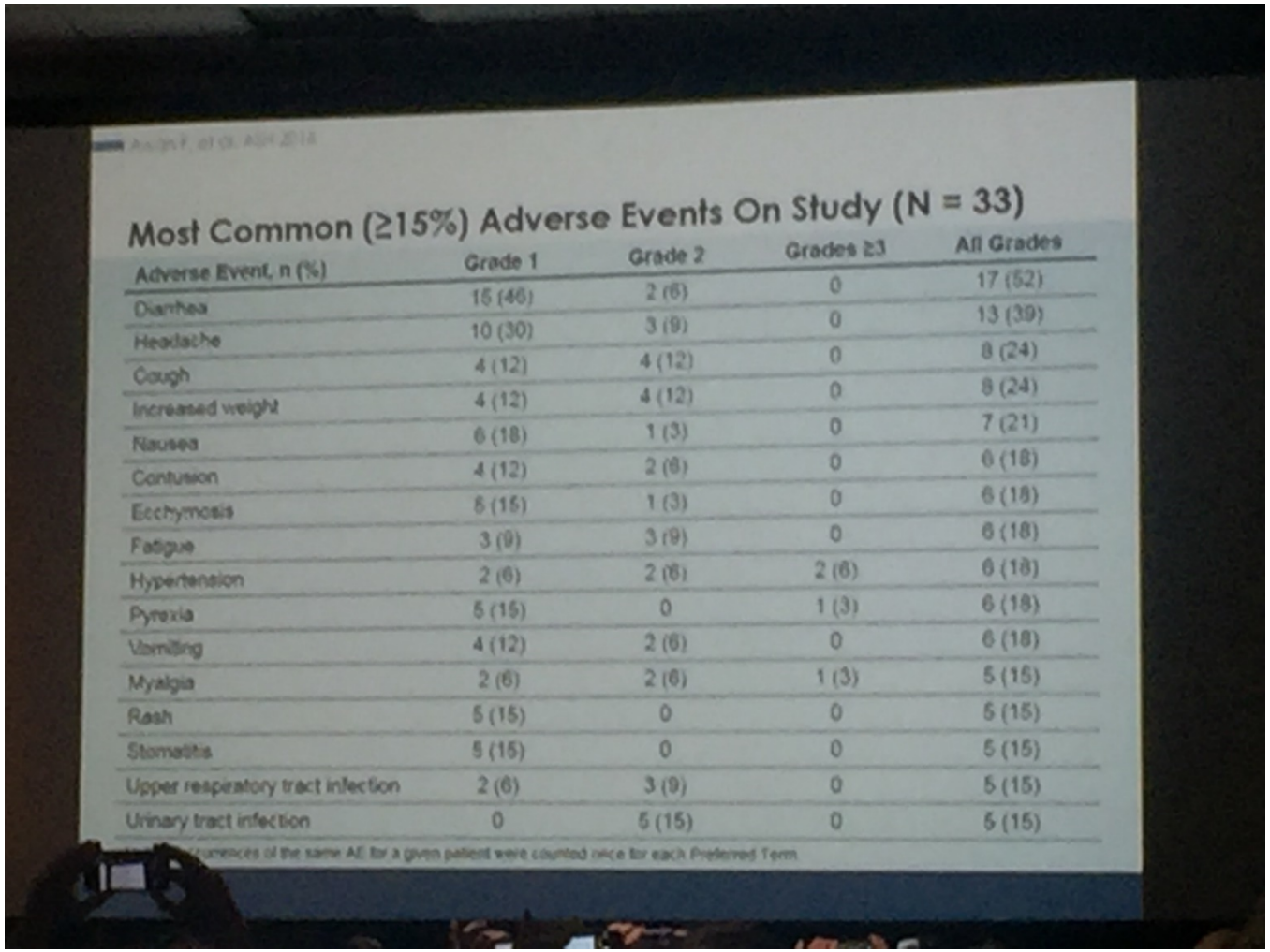
Mato et al, ASH 2016

PFS for alternate KI by Discontinuation Reason



RT excluded from analysis

Acalabrutinib Monotherapy in Patients with Ibrutinib Intolerance. Results from the Phase I/2 ACE-CL-001 Clinical study



Most Common (≥15%) Adverse Events On Study (N = 33)

Adverse Event, n (%)	Grade 1	Grade 2	Grades ≥3	All Grades
Diarrhea	15 (46)	2 (6)	0	17 (52)
Headache	10 (30)	3 (9)	0	13 (39)
Cough	4 (12)	4 (12)	0	8 (24)
Increased weight	4 (12)	4 (12)	0	8 (24)
Nausea	6 (18)	1 (3)	0	7 (21)
Contusion	4 (12)	2 (6)	0	6 (18)
Ecchymosis	5 (15)	1 (3)	0	6 (18)
Fatigue	3 (9)	3 (9)	0	6 (18)
Hypertension	2 (6)	2 (6)	2 (6)	6 (18)
Pyrexia	5 (15)	0	1 (3)	6 (18)
Vomiting	4 (12)	2 (6)	0	6 (18)
Myalgia	2 (6)	2 (6)	1 (3)	5 (15)
Rash	5 (15)	0	0	5 (15)
Stomatitis	5 (15)	0	0	5 (15)
Upper respiratory tract infection	2 (6)	3 (9)	0	5 (15)
Urinary tract infection	0	5 (15)	0	5 (15)

- 36% (12 of 33) patients experienced AE recurrence most of which decreased or the same severity

TG Therapeutics

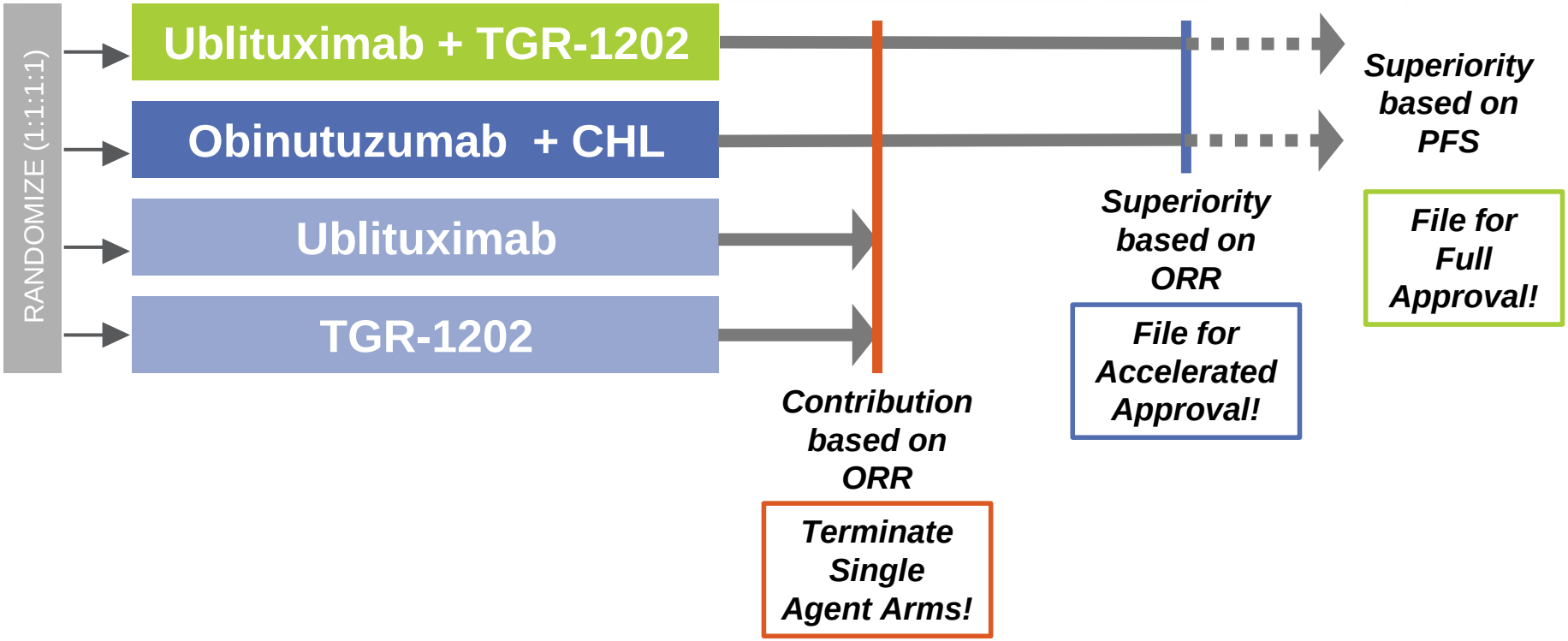
Michael S. Weiss

UNITY Phase 3 Overview & Panel Discussion

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY DLBCL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED DLBCL PATIENTS

UNITY-CLL – Phase 3 Trial



- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Enrolling ~450 patients with previously treated and previously untreated CLL
- Primary Endpoint: PFS

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY-CLL Study Update

- ~90 sites for UNITY-CLL open to date, with an estimated 20 more planned in US
- Ex-US sites to open bringing site total to 150+
- Early enrollment trends robust
  - On track for completing enrollment by 1H 2018 (~2 year enrollment period)

Panel Participants

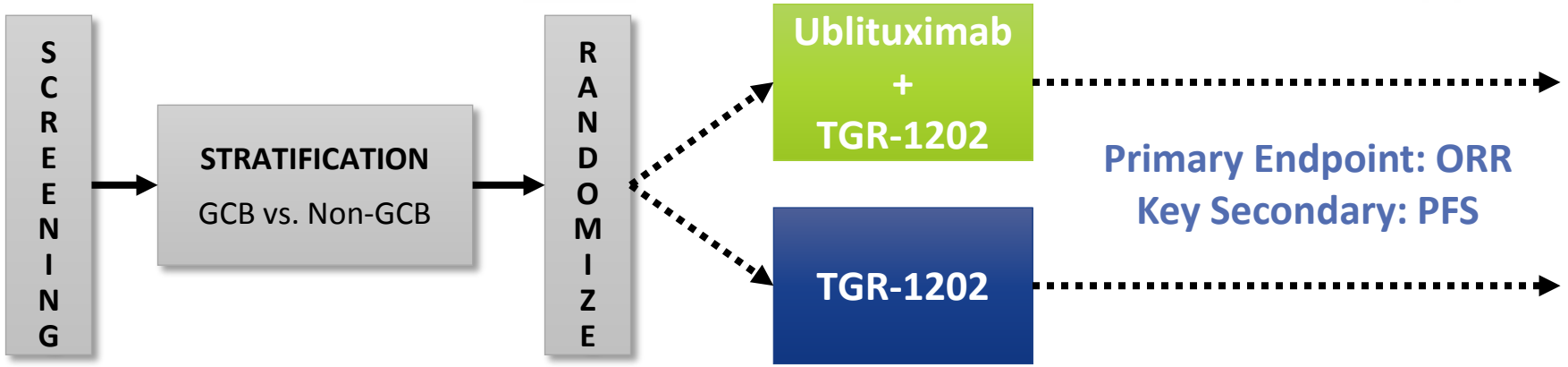
Panelist	Affiliation
Nilanjan Ghosh, MD, PhD	Carolinas Healthcare/Levine Cancer Center
Kathryn Kolibaba, MD	Compass Oncology, Vancouver, WA; US Oncology Research, The Woodlands, TX
Matthew Lunning, DO	University of Nebraska
Anthony Mato, MD	University of Pennsylvania
Owen O'Connor, MD, PhD	Columbia University Medical Center

CLL Panel Discussion

	CLL PROJECTED TREATMENT LANDSCAPE					
Front-Line	FCR/ BR	TG-1101 + TGR-1202 *(UNITY-CLL)*	Ibrutinib or Ibrutinib +Gazyva	Novel BTK + Gazyva	Venetoclax + Gazyva	Gazyva + CHL
Relapsed/ Refractory	BR	TG-1101 + TGR-1202 *(UNITY-CLL)*	Ibrutinib or Ibrutinib +Gazyva	Ibrutinib + TG-1101 *(GENUINE)*	Venetoclax or Venetoclax + Benda Rituxan	Idela + BR Idela + R

FCR: Fludarabine Cyclophosphamide Rituxan; BR: Bendamustine Rituxan; Idela: Idelalisib; R:Rituxan; Chloram: Chlorambucil

UNITY-DLBCL – Phase 2b Trial



- **Up to 100 US and Ex-US sites**
- **Site contracting underway…**
- **Study Chair US:** Owen A. O'Connor, MD PhD
- **Study Chair Ex-US:** Pier-Luigi Zinzani, MD

UNITY DLBCL
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GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED DLBCL PATIENTS

DLBCL Landscape Panel Discussion

	DLBCL PROJECTED TREATMENT LANDSCAPE		
Front-Line	R-CHOP		
Relapsed/Refractory (not eligible for transplant)	• BR • GEMOX • Rev • ICE • R-ICE • R-DHAP	TG-1101 + TGR-1202 *(UNITY-DLBCL)*	CAR-T

BR: Bendamustine Rituxan; GEMOX: Gemcitabine Oxaliplatin; Rev: Revlimid; ICE: Lfosfamide Carboplatin Etoposide; RICE: Rituxan Lfosfamide Carboplatin Etoposide; R-DHAP: Rituxan Dexamethasone Cisplatin Cytarabine

TG Therapeutics

Concluding Remarks

Michael S. Weiss
Executive Chairman & Interim CEO

UNITY CLL
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PREVIOUSLY TREATED DLBCL PATIENTS

Highlights of ASH 2016

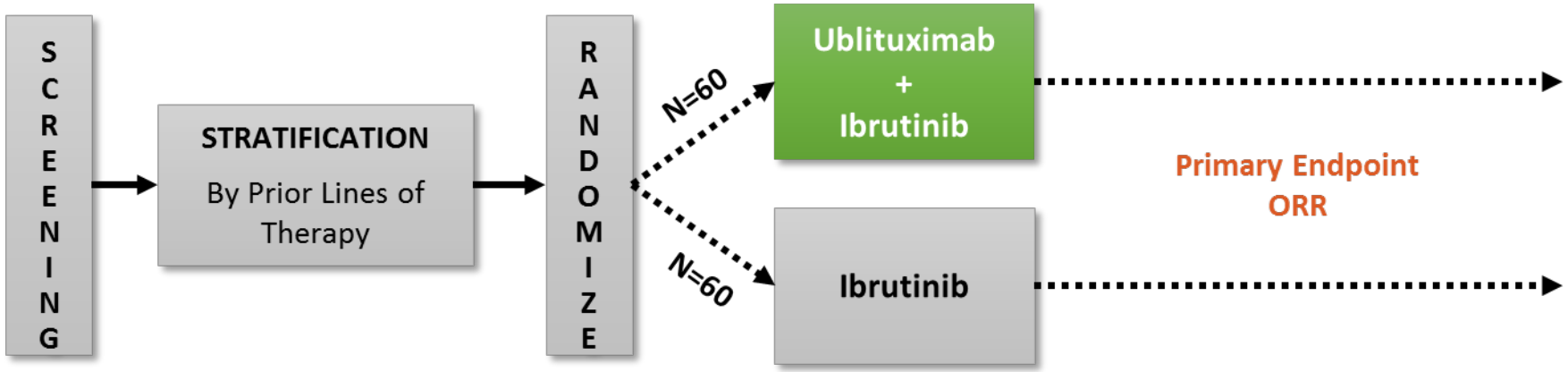
- Safety Profile Preserved:
  - ASH Data 2016 plus ASCO 2016 integrated analysis
  - >240 patients treated
  - Across 6 clinical trials
  - Incidence of transaminitis 3%; colitis 2%; pneumonia/pnuemonitis 1%

- Significant activity seen in:
  - 1303 + Benda in DLBCL (71% ORR) and FL (88% ORR)
  - 1202 + Ibrutinib (88% CR, PR and PR+L)
  - 1202 plus Brentuximab (50% ORR in BV refractory patients)

Announcing…

Target Enrollment Complete!!!

GENUINE
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB PLUS IBRUTINIB



- **Topline Data Expected mid-2017**