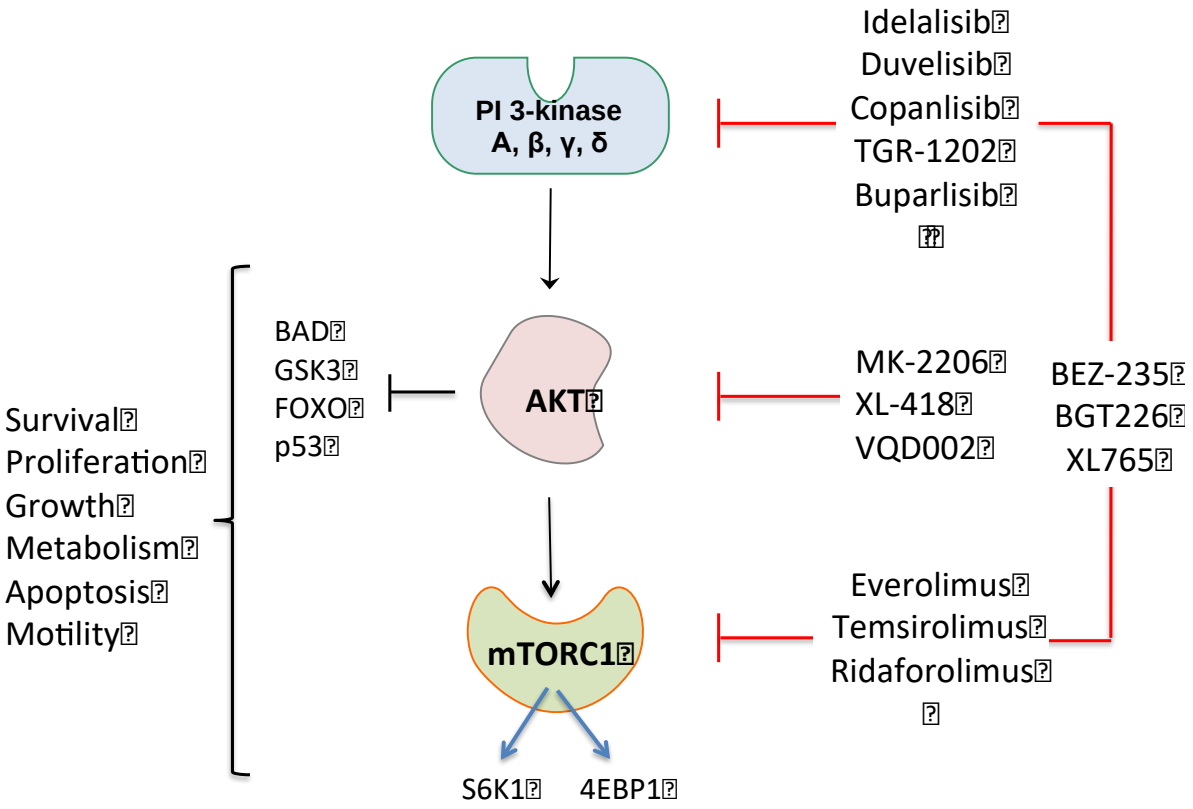
PI3K Inhibitors

Anas Younes, M.D.
chief, Lymphoma Service
Memorial Sloan Kettering Cancer Center

Targeting PI3K/AKT/mTOR Pathway



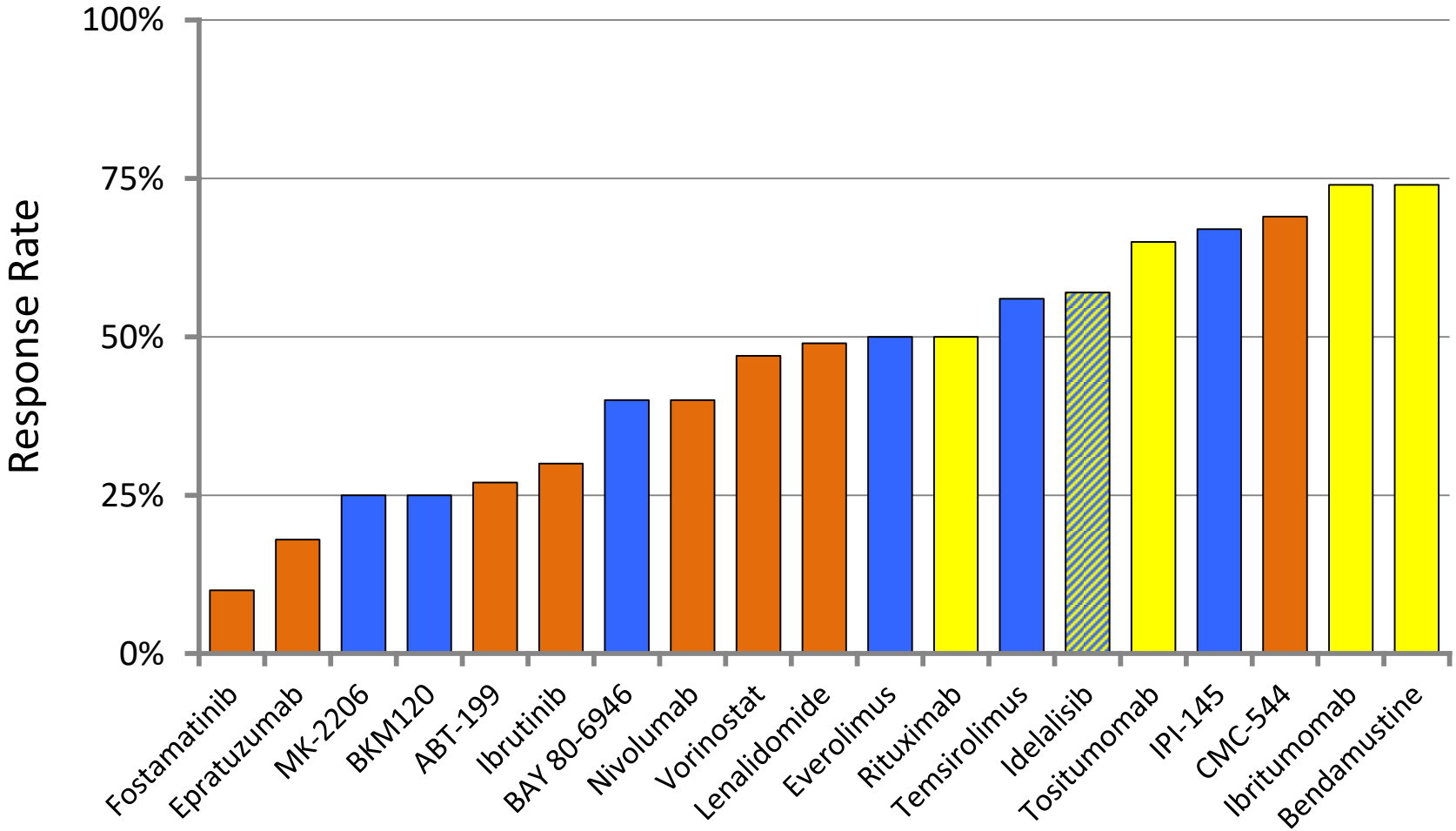
Younesa, A et al, Nature Rev Clinical Oncol 2017

Leading Molecular Targets and Drugs in Lymphoma

Pathway	Target	Drug	Response Rate					
			DLBCL	**FL**	**MCL**	**SLL/CLL**	**T-Cell**	**HL**
PI3K/AKT/mTOR	mTOR	Everolimus	30%	50%	32%	18%	63%	42%
		Temsirolimus	36%	56%	38%	10%	-	-
	AKT	MK2206	0%	25%	9%	(50%)	0%	20%
	PI3K-δ	Idelalisib	-	57%	40%	72%	-	12%
		TGR-1202	11%	42%	33%	63%	-	13%
	PI3K-γδ	Duvelisib	0%	67%	67%	54%	33%	33%
	PI3K-αδ	Copanlisib	25%	46%	71%	67%	50%	-
		BKM120	12%	25%	23%	-	-	-
B Cell Receptor (BCR)	Syk	Fostamatinib	22%	10%	11%	55%	0%	-
	Btk	Ibrutinib	26%	28%	75%	67%	-	-
Apoptosis	Bcl-2	Venetoclax	15%	34%	75%	77%		
Immune checkpoint	PD1	Nivolumab	36%	40%	-	-	-	87%
		Pambrolizumab	-	-	-	-	-	66%

Younes et al, Nature Rev Clin Oncol 2017

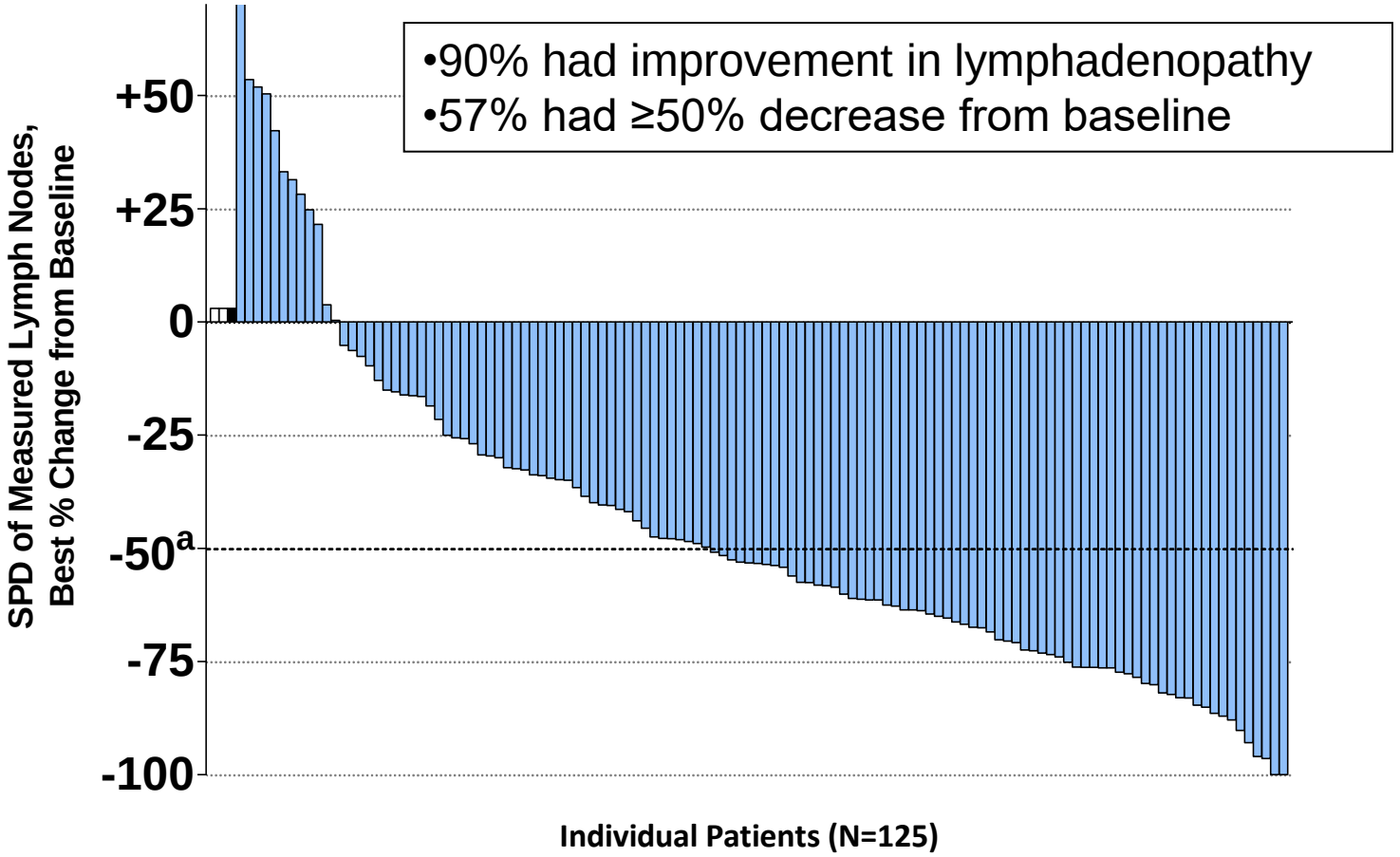
Single-agent Activity in Relapsed Follicular (and indolent) Lymphoma



Updated from Younes A & Berry D. *Nat Rev Clin Oncol* 2012;9:643–653.

Phase 2 Idelalisib Monotherapy in Refractory iNHL

Lymph Node Response



[a]Criterion for lymphadenopathy response [Cheson 2007]

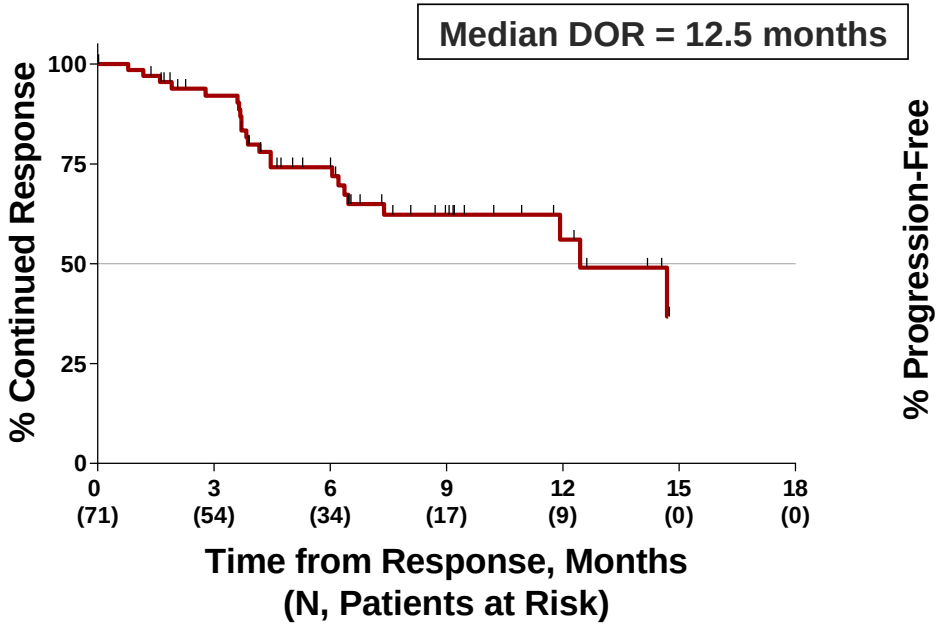
[b] 3 subjects no post baseline eva

□ 2 subjects NE ■ 1 subject PD luation:by Lymph Node biopsy

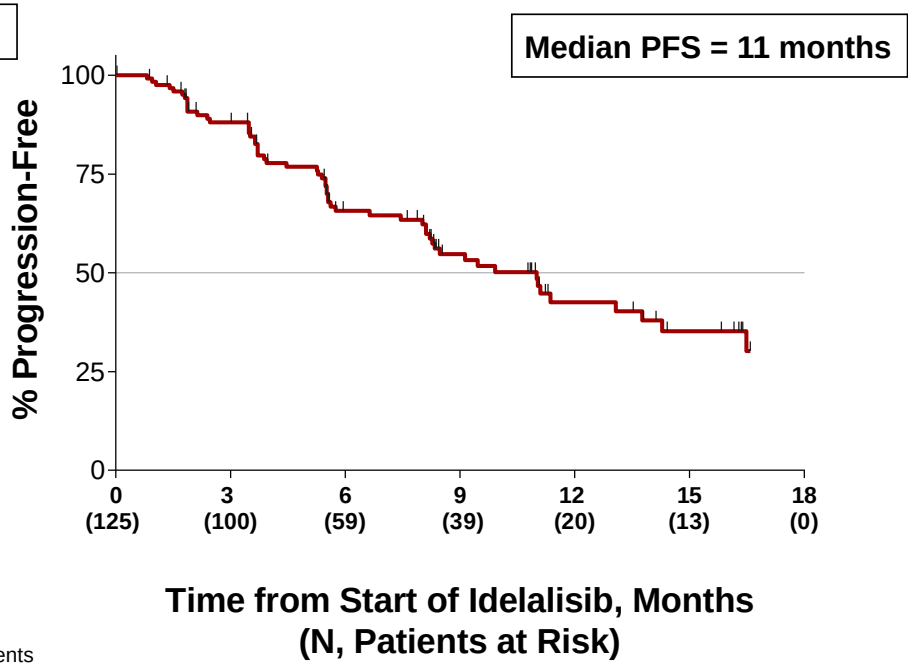
Gopal et al. NEJM 2014

Phase 2 Idelalisib Monotherapy in Refractory iNHL

Duration Of Response and PFS



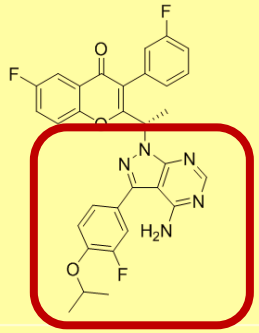
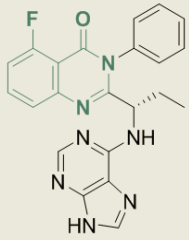
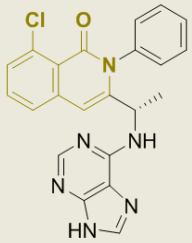
Analysis includes subjects who achieved a CR or PR (or MR for WM subjects) according to IRC assessments



Gopal et al. NEJM 2014

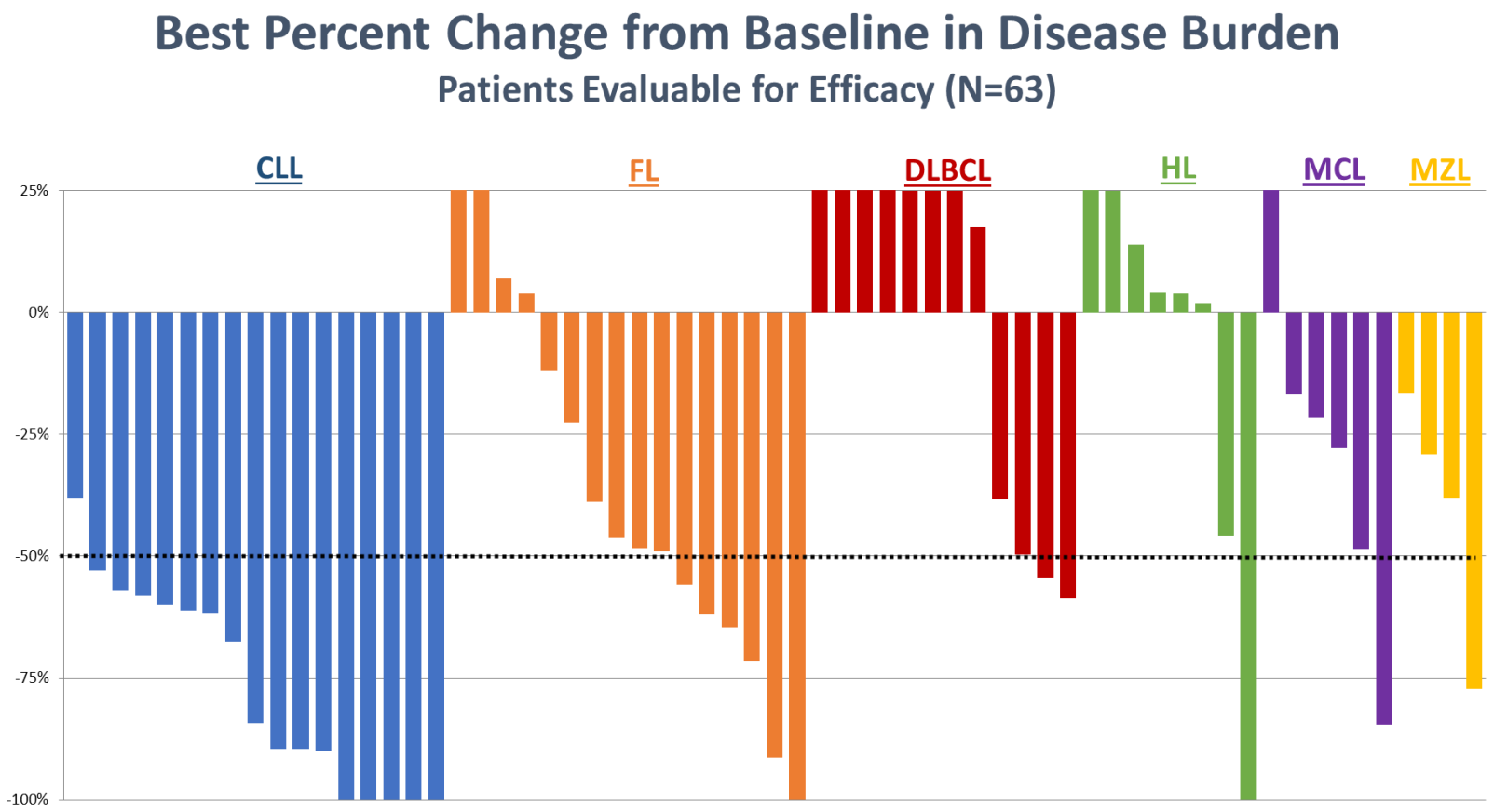
TGR-1202 Profile

- Next generation PI3Kδ Inhibitor
- Significant structural differences compared to other PI3Kδ inhibitors
- Favorable PK profile that allows once-daily oral dosing
- Differentiated safety profile from other PI3Kδ inhibitors

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

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

TGR-1202-101: Single Agent Efficacy



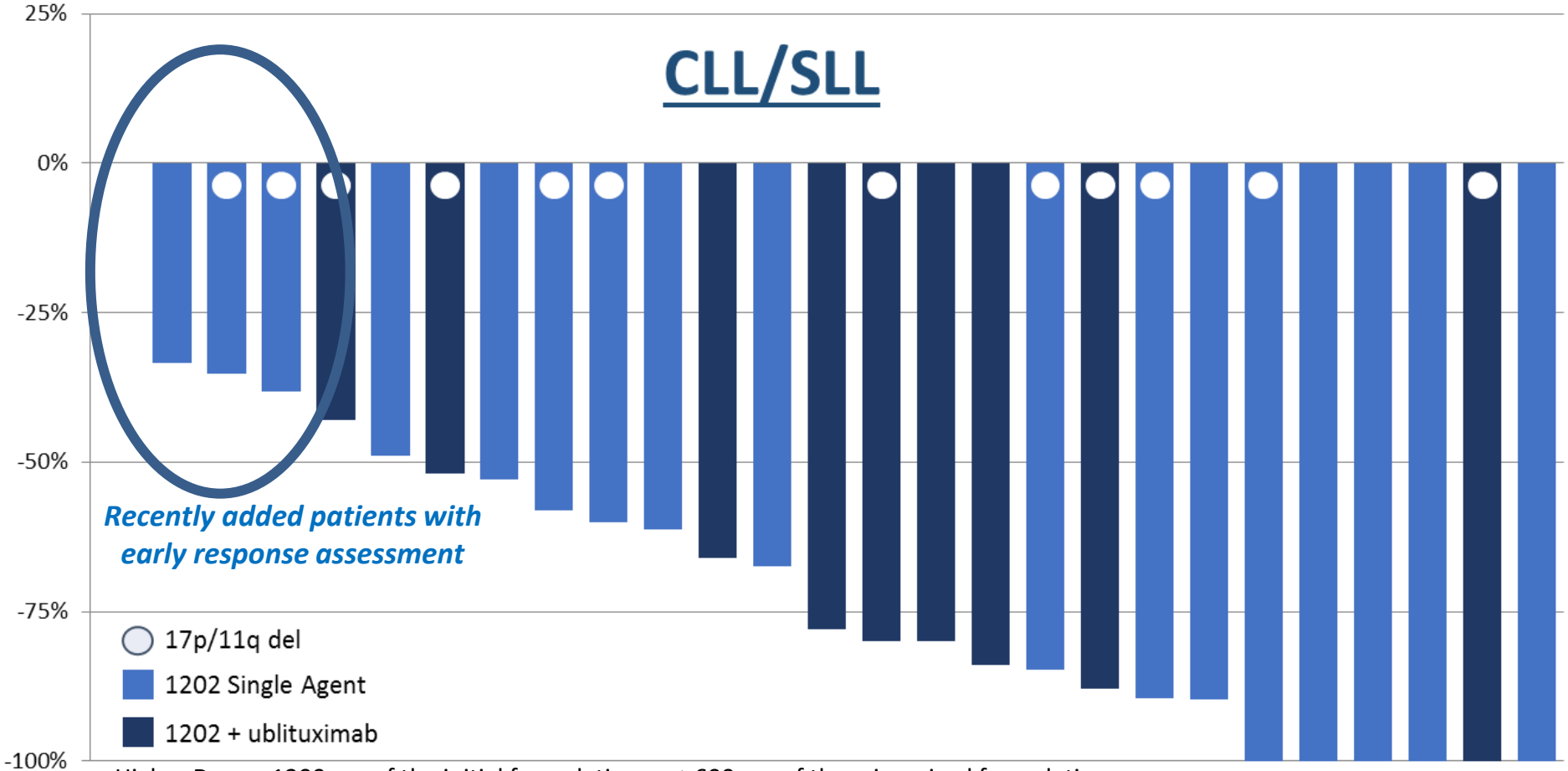
- **94% of CLL patients (16/17) achieved a nodal PR, remaining patients still on study pending further evaluation**
- **59% (10/17) achieved a response per iwCLL (Hallek 2008) criteria**

O'Connor et al, ASH 2015

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

Patients Treated at "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden



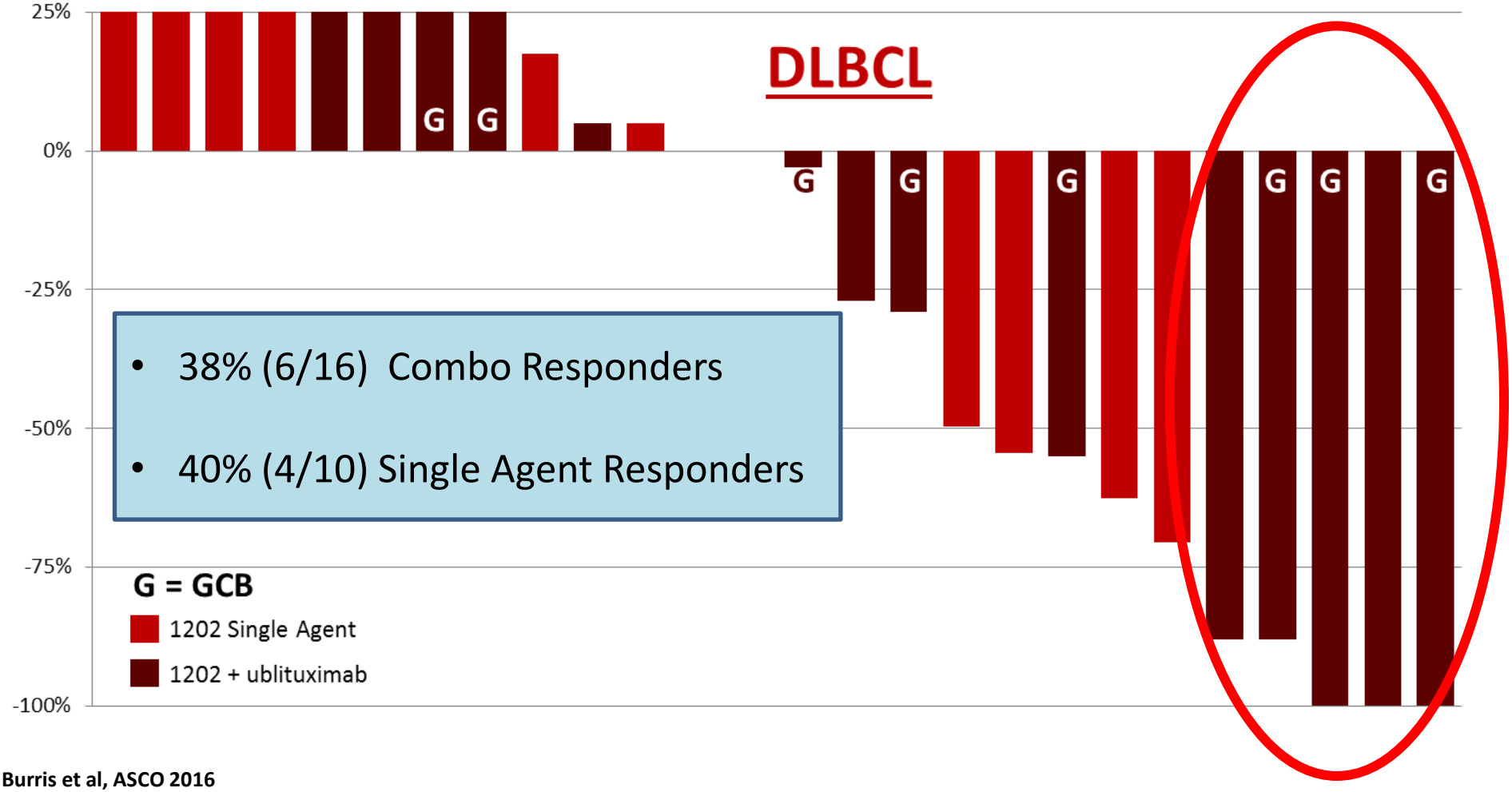
Higher Doses: 1200 mg of the initial formulation, or ≥600 mg of the micronized formulation

Burris et al, ASCO 2016, Mato et al EHA 2016

Integrated Analysis: TGR-1202 Monotherapy and TGR-1202 + Ublituximab: DLBCL Efficacy

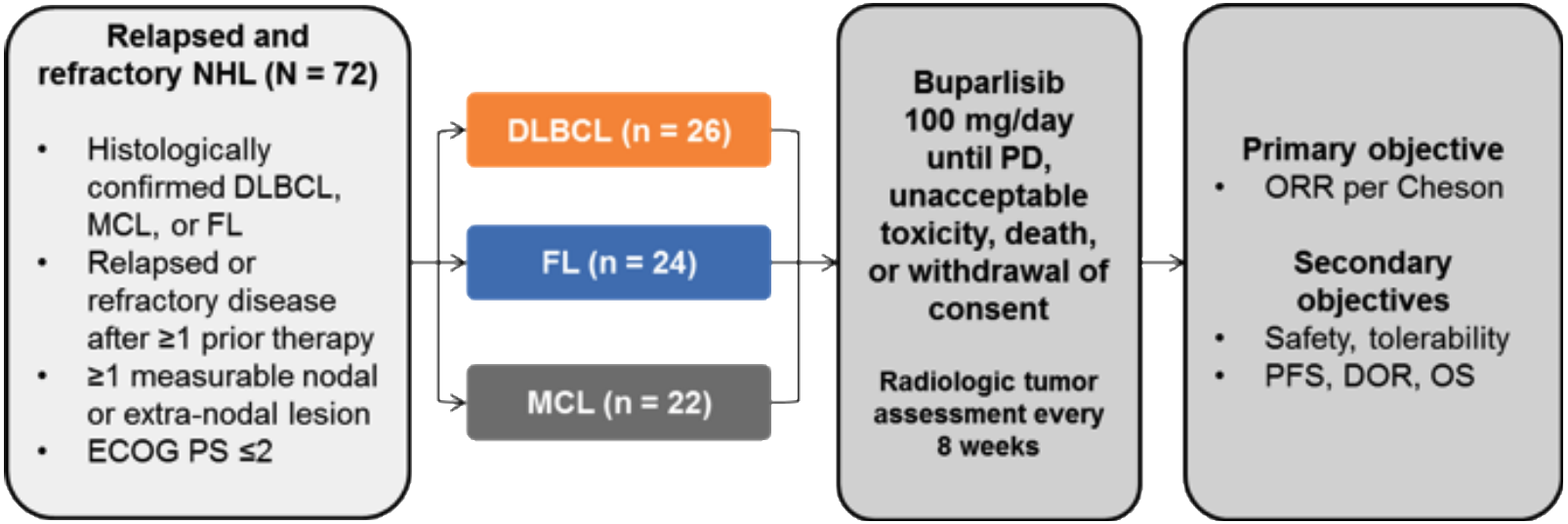
Patients Treated at "Higher Doses" of TGR-1202

Best Percent Change from Baseline in Disease Burden



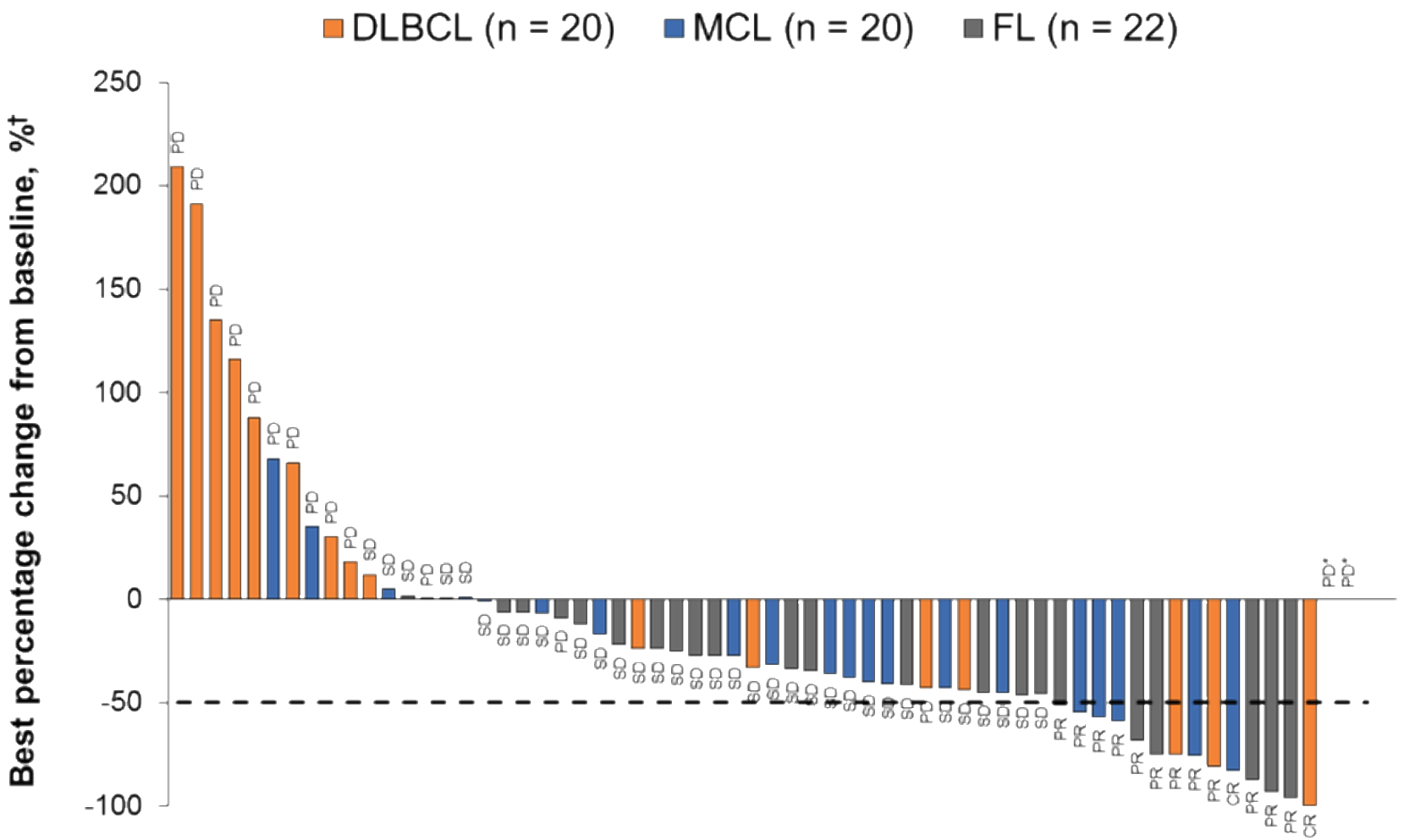
Burris et al, ASCO 2016

Phase II Study of Buparlisib (BKM120) in Patients with Relapsed/Refractory Lymphoma



Younes. A, et al, ASH 2015

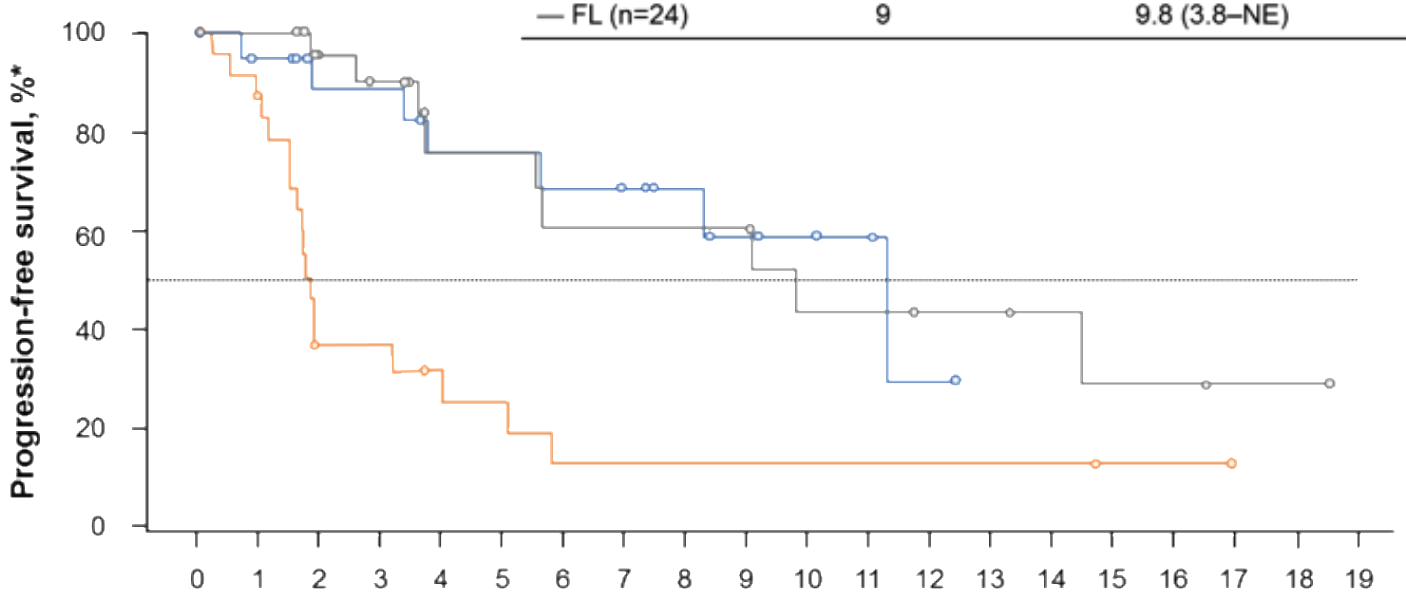
Phase II Study of Buparlisib (BKM120) in Patients with Relapsed/Refractory Lymphoma



Younes. A, et al, ASH 2015

Phase II Study of Buparlisib (BKM120) in Patients with Relapsed/Refractory Lymphoma

	No. of Events	Median PFS (95% CI), months
DLBCL (n=26)	18	1.8 (1.5–4.0)
MCL (n=22)	7	11.3 (3.8–NE)
FL (n=24)	9	9.8 (3.8–NE)



No. of Patients Still at Risk

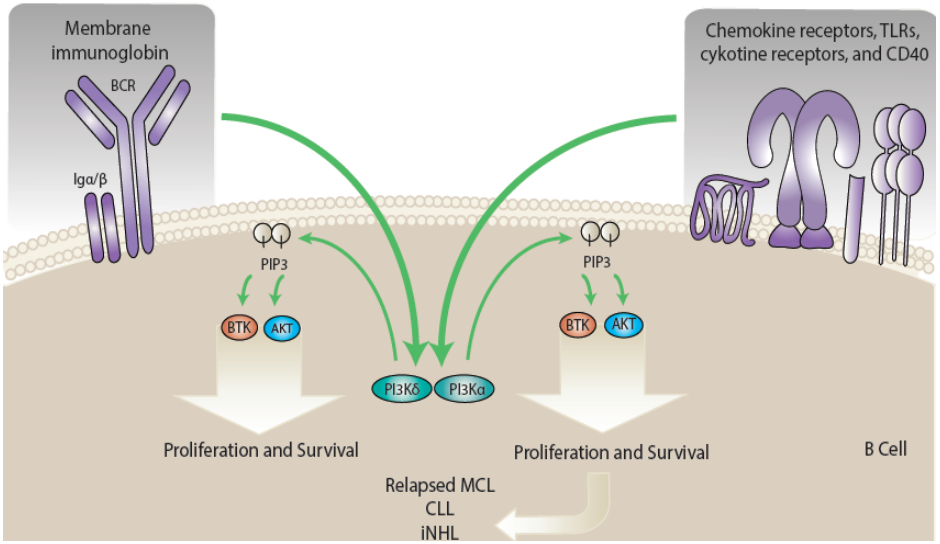
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
DLBCL	26	20	7	7	5	4	2	2	2	2	2	2	2	2	2	1	1		
MCL	22	18	14	14	11	11	10	9	7	5	4	3	1						
FL	24	22	18	16	10	10	8	8	8	8	5	5	4	4	3	2	2	1	1

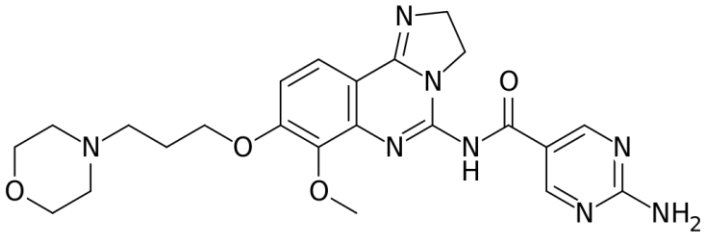
Median follow-up time: DLBCL, 1.7 months; MCL, 4.7 months; FL, 3.7 months.

Younes. A, et al, ASH 2015

Copanlisib, a selective inhibitor of PI3K-δ and PI3K-α

- Copanlisib demonstrates inhibitory activity against PI3K-α and PI3K-δ at sub-nanomolar concentrations[1]
- PI3K-δ is an established oncogenic driver in indolent NHL, and is the predominant PI3K isoform expressed in both FL and DLBCL[2,3]
- Recent emerging data indicate that PI3K-α is upregulated in relapsed/refractory mantle cell lymphoma (MCL) and is postulated to be a tumor escape mechanism[4]





Copanlisib

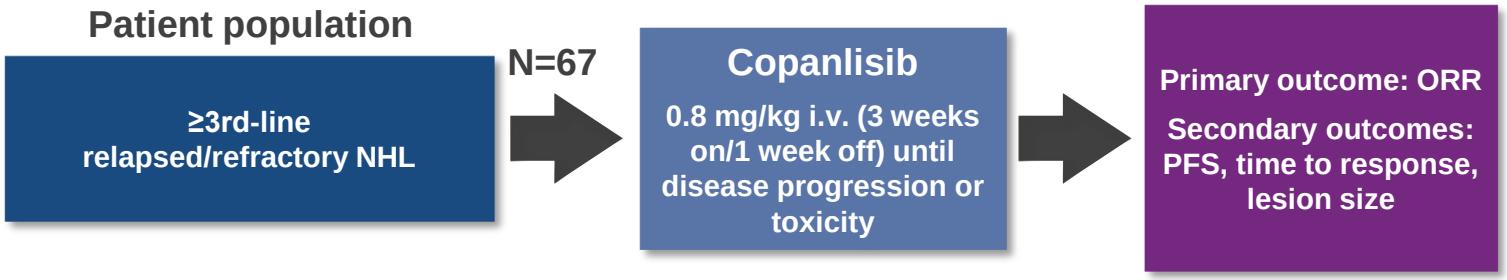
Biochemical activity	Copanlisib [1]	Idelalisib [5]
PI3K-α IC_{50}	0.5 nM	820 nM
PI3K-β IC_{50}	3.7 nM	565 nM
PI3K-γ IC_{50}	6.4 nM	89 nM
PI3K-δ IC_{50}	0.7 nM	2.5 nM

IC_{50}, half-maximal inhibitory concentration

1. Liu N et al. Mol Cancer Ther 2013;12:2319–2330. 2. Tzenaki N et al. Front Oncol 2013;3:40. 3. Thye LS et al. Hematol Oncol 2015;33:181–243 (abstr 267).4. Iyengar S et al. Blood 2012;121:2274–2284. 5. Lannutti BJ et al. Blood 2011;117:591–594.

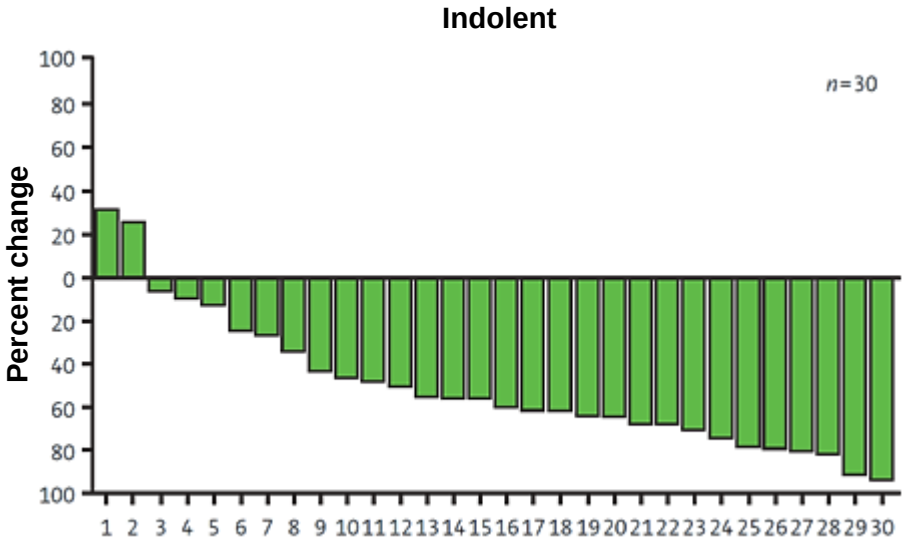
Study 16349 design

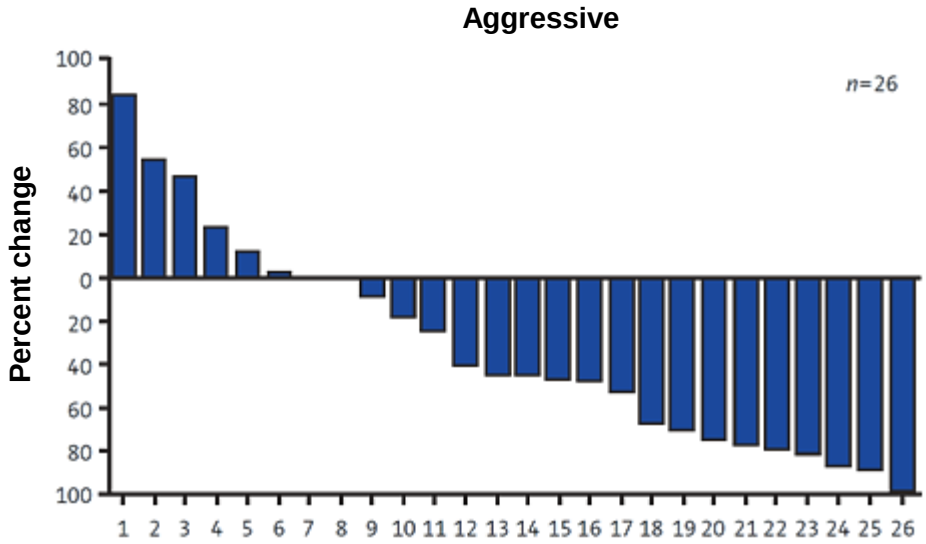
- Phase II open-label study of copanlisib
  - Part A: Open-label, uncontrolled, Phase IIa study to evaluate the efficacy and safety of copanlisib as a single agent in patients with relapsed/refractory NHL



Copanlisib: Tumor shrinkage

Percent best change in target lesion size from baseline in the indolent and aggressive cohorts



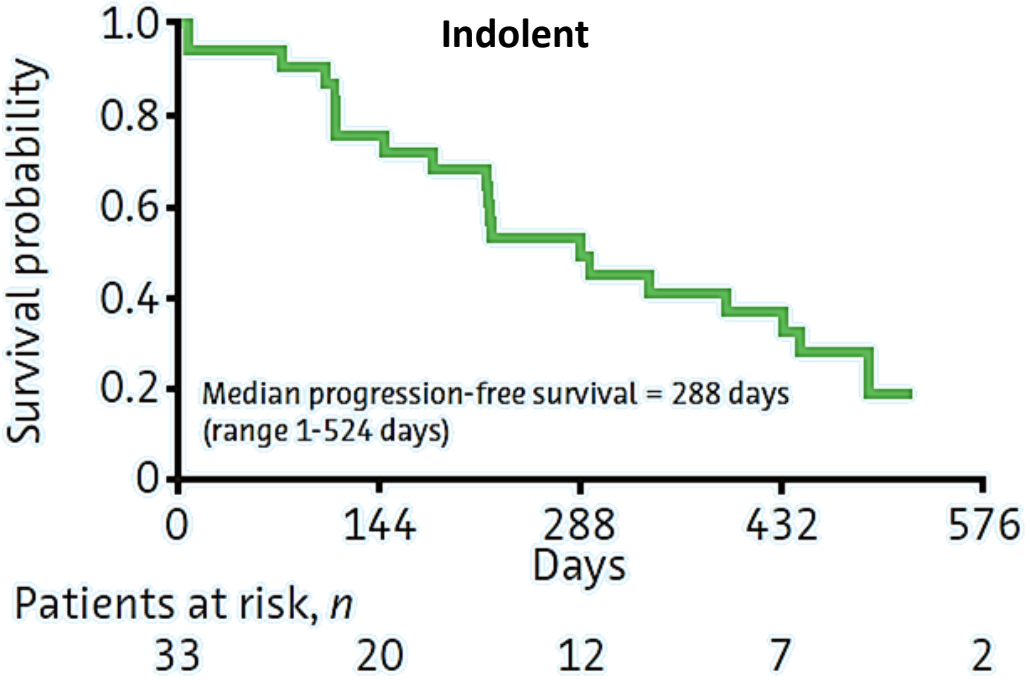


Data cutoff for primary efficacy analysis: November 4, 2013.

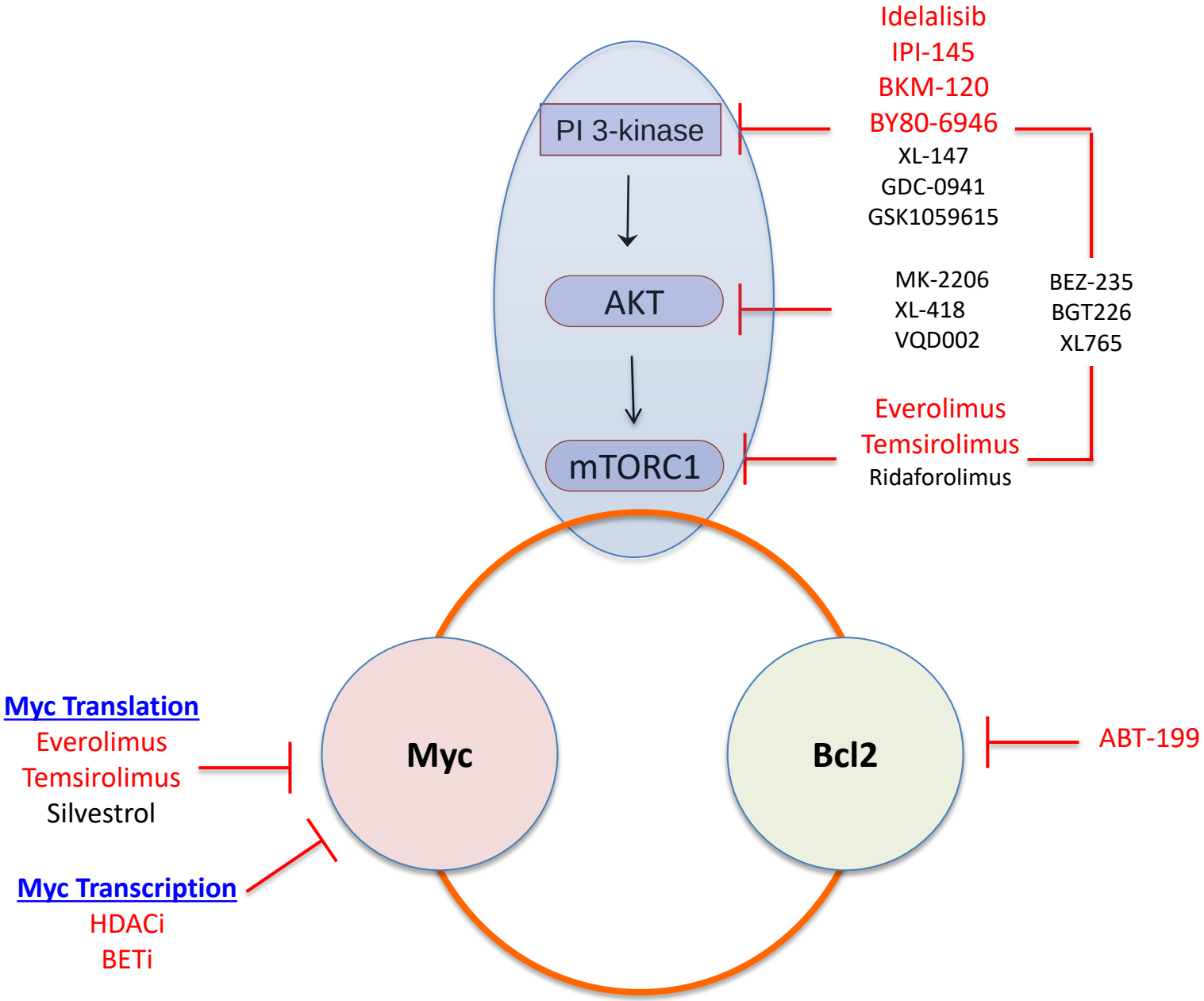
Dreyling A et al. Presented at: the EORTC-NCI-AACR Symposium; November 18–21, 2014; Barcelona, Spain.

Copanlisib: Progression-free survival

- Median PFS for patients with indolent NHL was 288 days

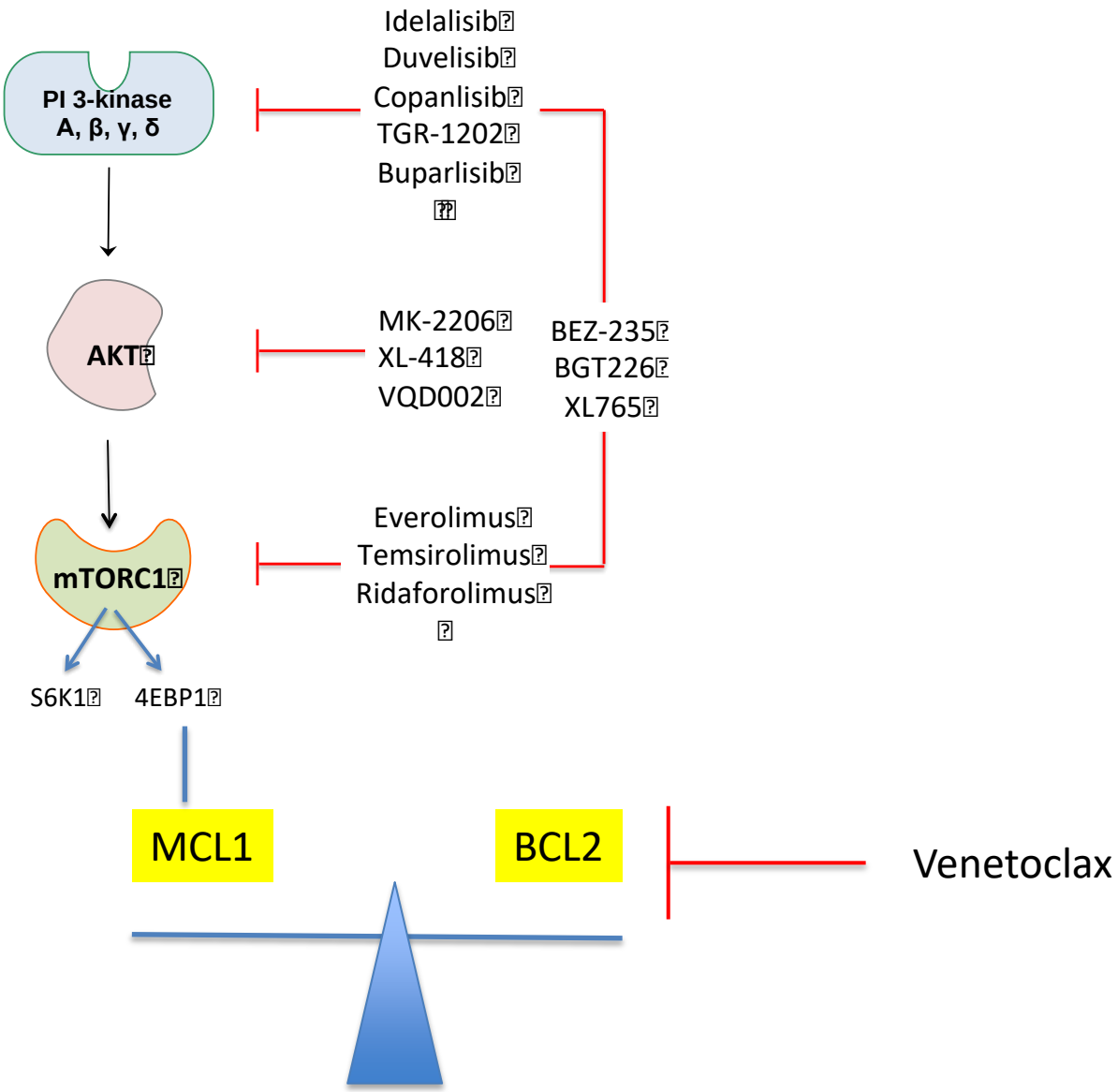


Data cutoff for primary efficacy analysis: November 4, 2013.
Dreyling A et al. Presented at: the EORTC-NCI-AACR Symposium; November 18–21, 2014; Barcelona, Spain.

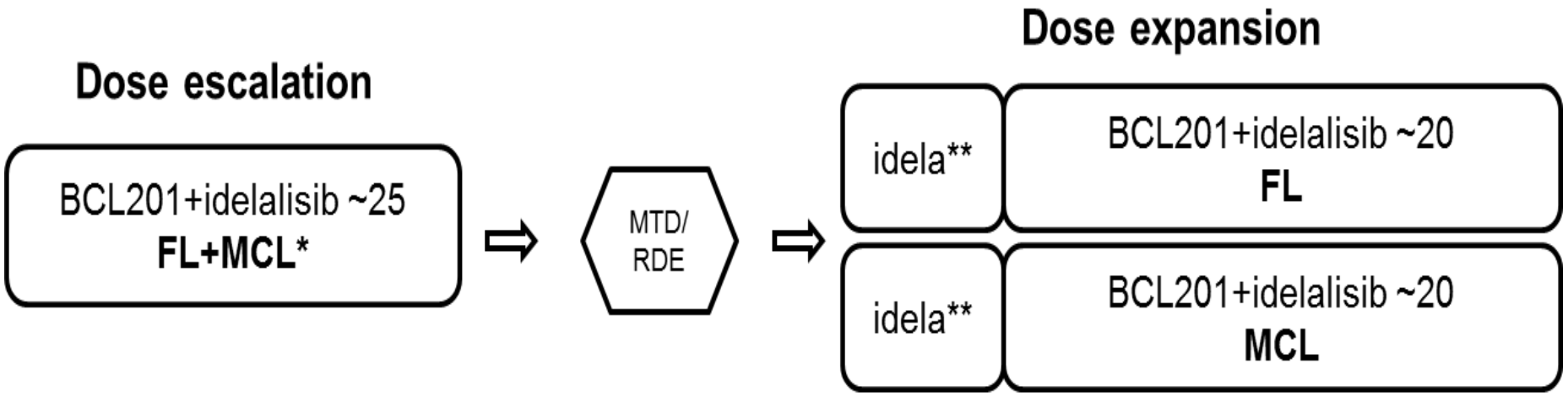

Idelalisib
IPI-145
BKM-120
BY80-6946
XL-147
GDC-0941
GSK1059615
PI 3-kinase
AKT
MK-2206
XL-418
VQD002
BEZ-235
BGT226
XL765
mTORC1
Everolimus
Temsirolimus
Ridaforolimus
Myc Translation
Everolimus
Temsirolimus
Silvestrol
Myc Transcription
HDACi
BETi
Myc
Bcl2
ABT-199

Blocking Resistance Mechanisms

Rationale for combining PI3Ki and BCL2i



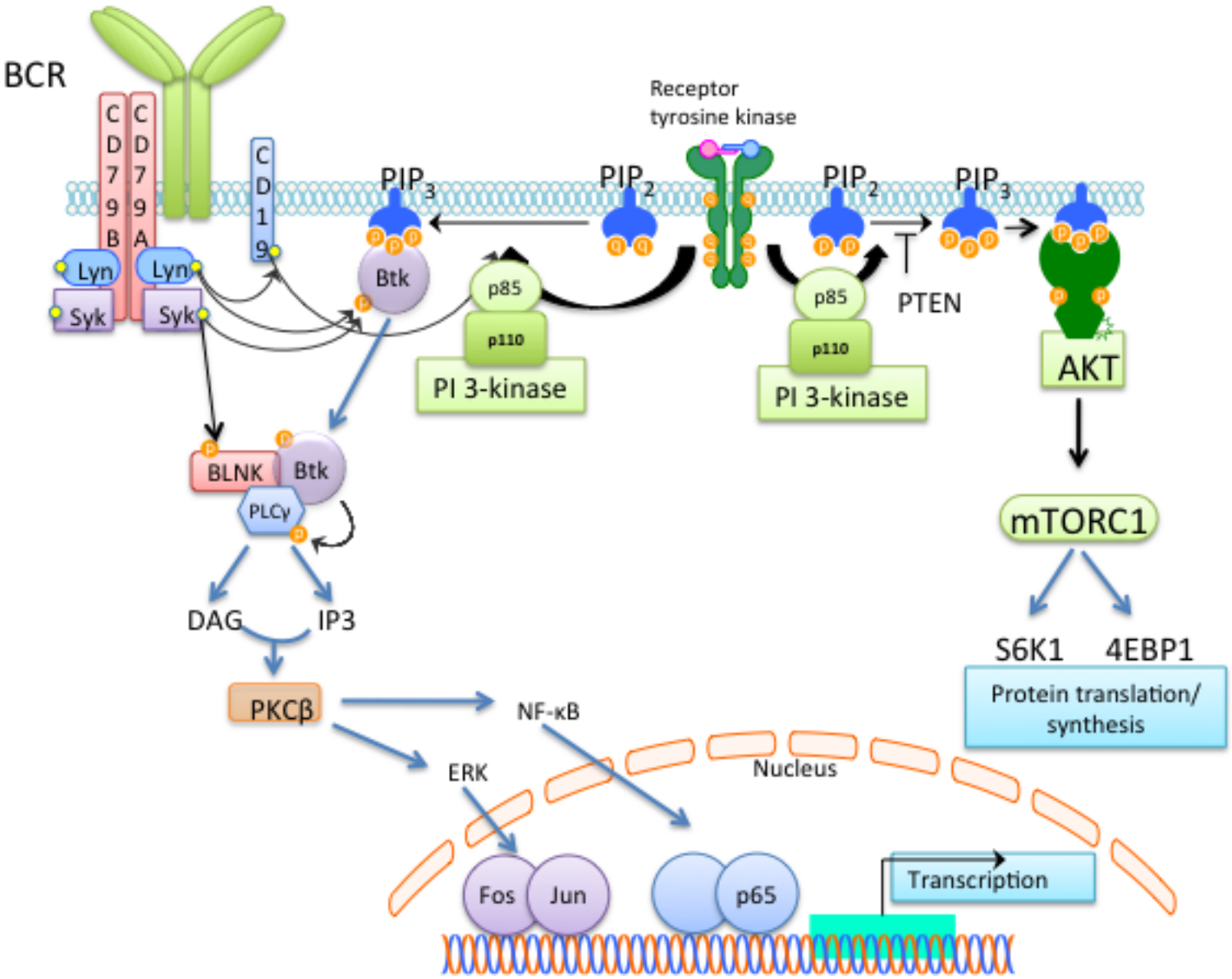
BCL201/idelalisib combo in FL and MCL



Dose level*	BCL201 QD (mg)	Idelalisib (mg)
1 (starting dose)	50	100 mg QD
2	150	100 mg QD
3a	300	100 mg QD
3b	300	100 mg BID
4a	400	100 mg QD
4b	400	100 mg BID
5a	500	100 mg QD
5b	500	100 mg BID

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Dose levels may be added below the MTD in order to better understand safety, PK or PD.

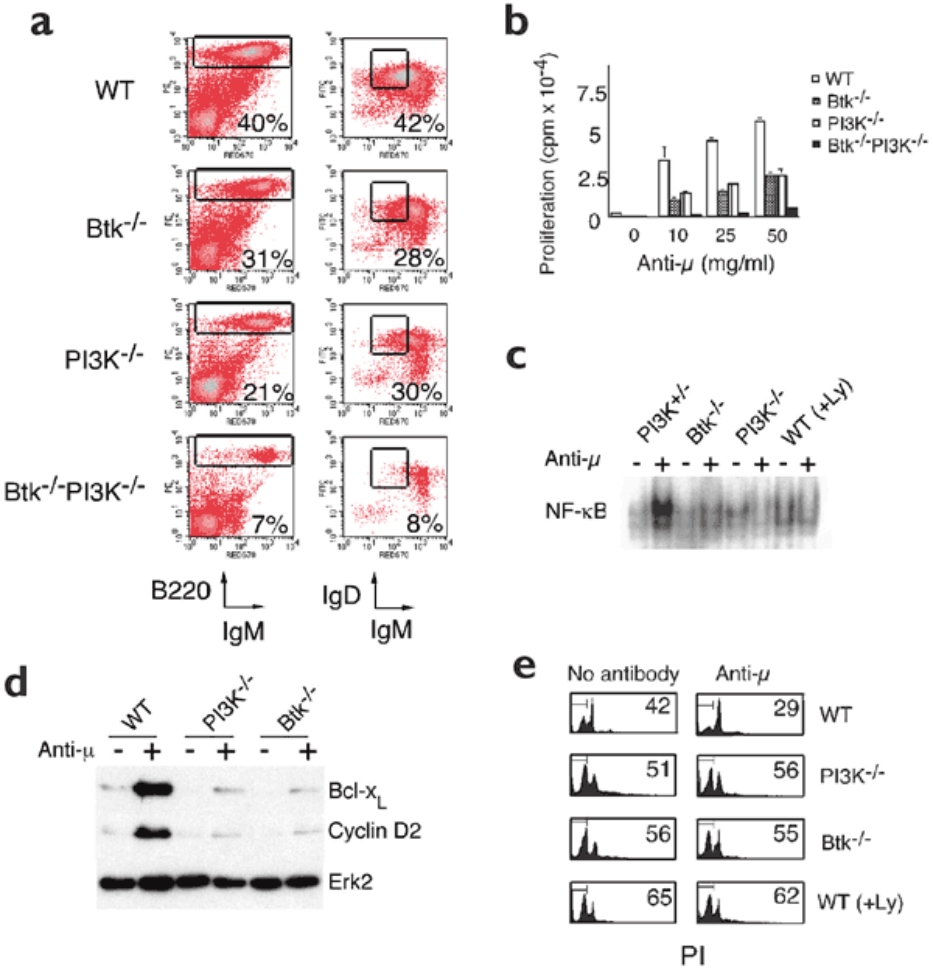
Cooperation Between PI3K and BCR Signaling Pathway



Nature Immunology **4**, 280 - 286 (2003)

PI3K and Btk differentially regulate B cell antigen receptor-mediated signal transduction

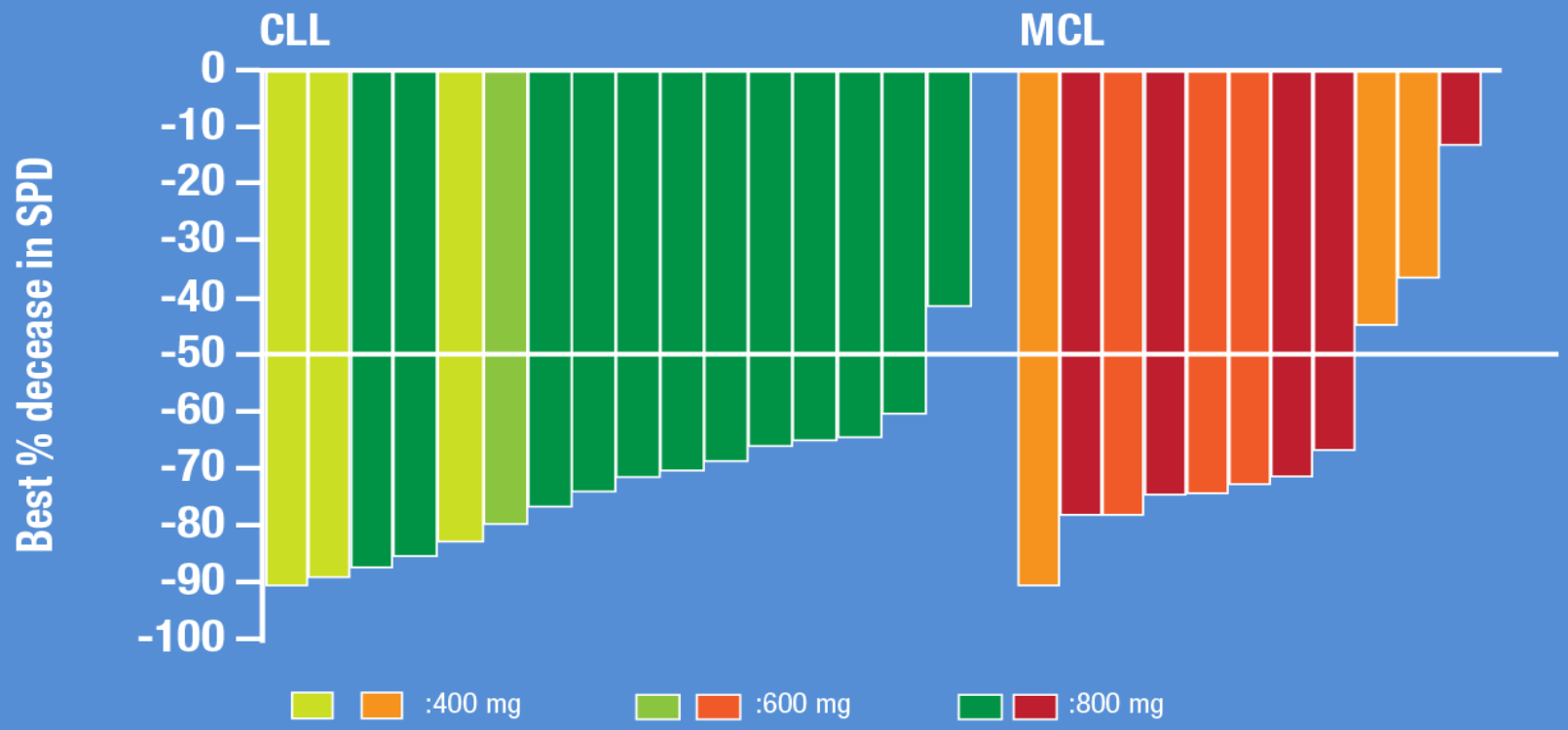
Harumi Suzuki[1, 6, 7], Satoshi Matsuda[1, 2, 6], Yasuo Terauchi[2, 3], Mari Fujiwara[1, 2], Toshiaki Ohteki[1, 8], Tomoichiro Asano[3], Timothy W. Behrens[4], Taku Kouro[5], Kiyoshi Takatsu[5], Takashi Kadowaki[2, 3] & Shigeo Koyasu[1, 2]



Phase I/II Of Ibrutinib + BKM120 in relapsed lymphoma

Dose Level	Buparlisib Mg/day taken daily for 4 wks	Ibrutinib Mg/day taken daily for 4 wks
Cohort 1	60	420
	80	420
	100	420
Cohort 2	60	560
	80	560
	100	560

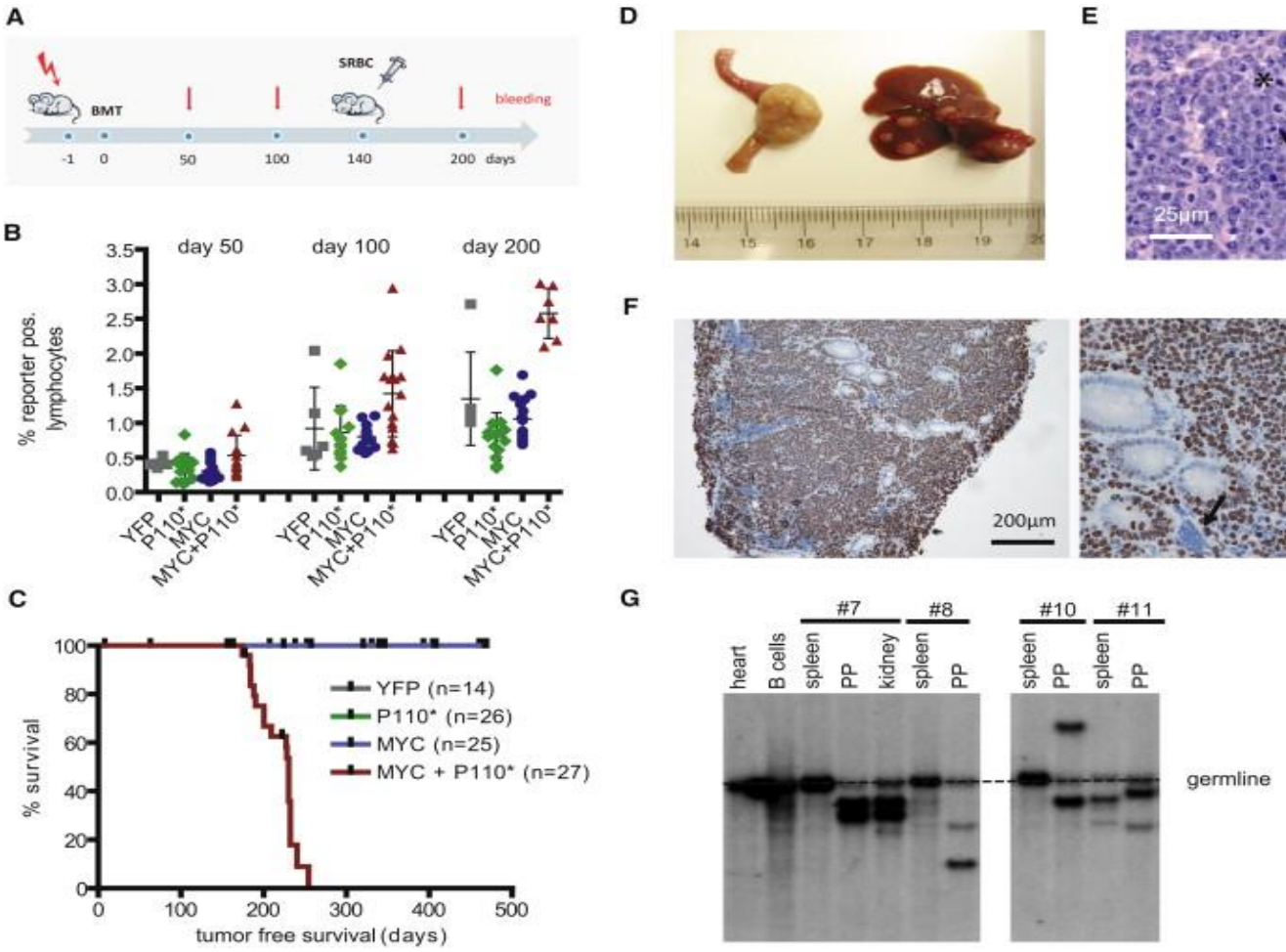
TGR-1202 + Ibrutinib in Relapsed/Refractory CLL or MCL: Efficacy (n=28)



- High response rates in both CLL and MCL
  - **CLL (n=11): ORR 88% (CR 6%; PR 82%)**
    - **5 PRs with >80% SPD decrease, nearing radiographic CR**
    - **Responses in 3 patients with prior PI3Ki and 1 patient with prior ibrutinib**
  - **MCL: ORR 73% (all PR)**
    - **Clinical benefit observed in 2 additional patients**

Davids MS, et al. ASH (Oral Presentation) 2016. Abstract 641.

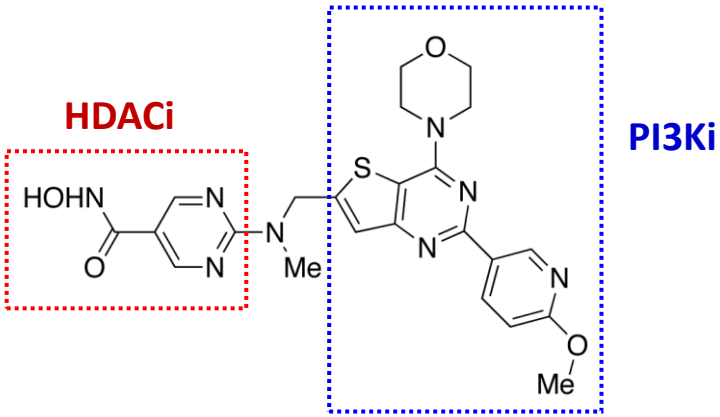
MYC and PI3K Cooperate in Lymphomagenesis

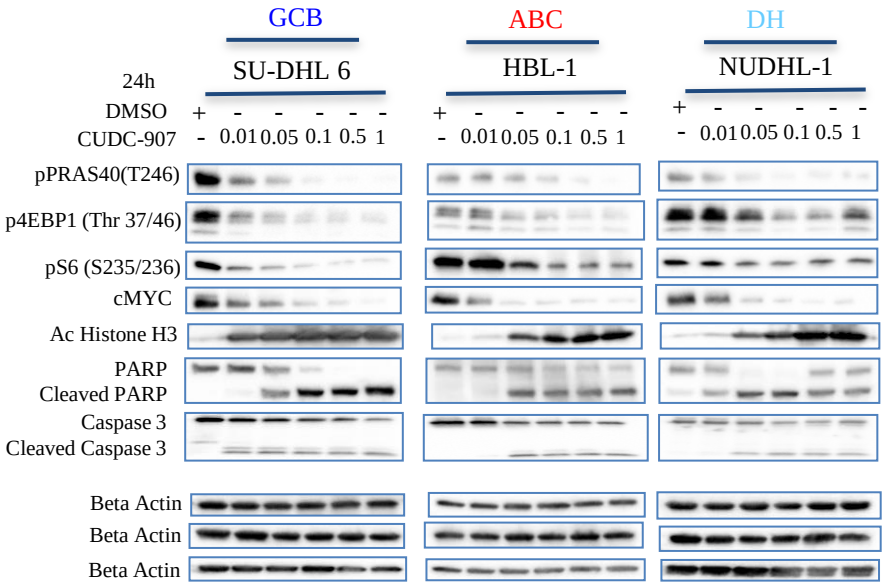


Sander, S…and Rajewsky, K: Cancer Cell (2012) 167 - 179

CUDC-907

Oral, dual inhibitor of HDAC and PI3K

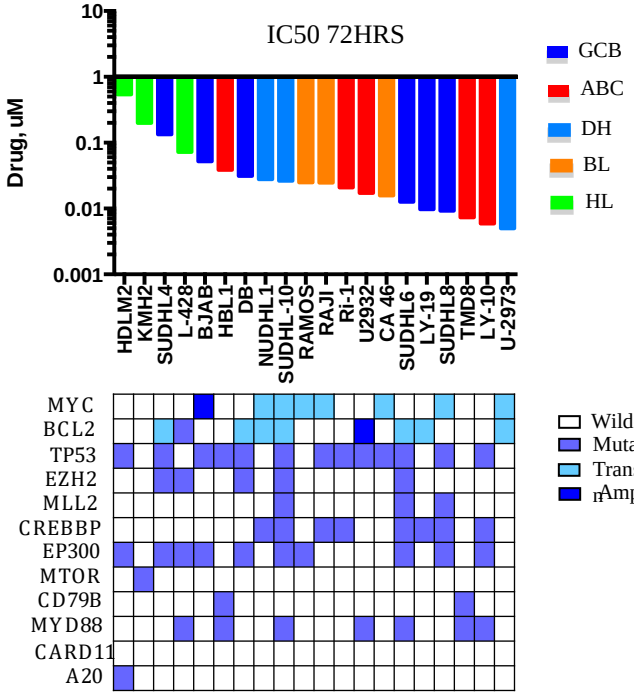


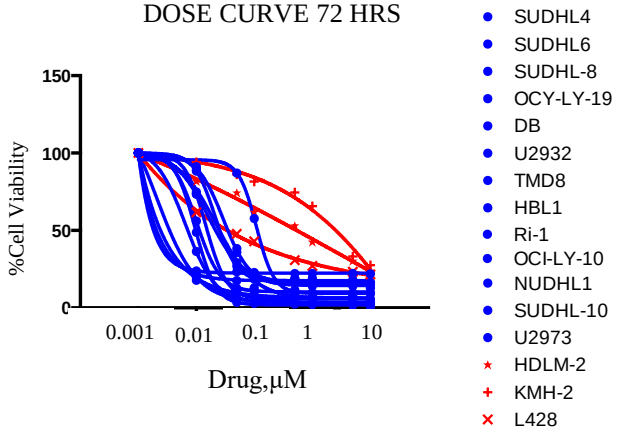


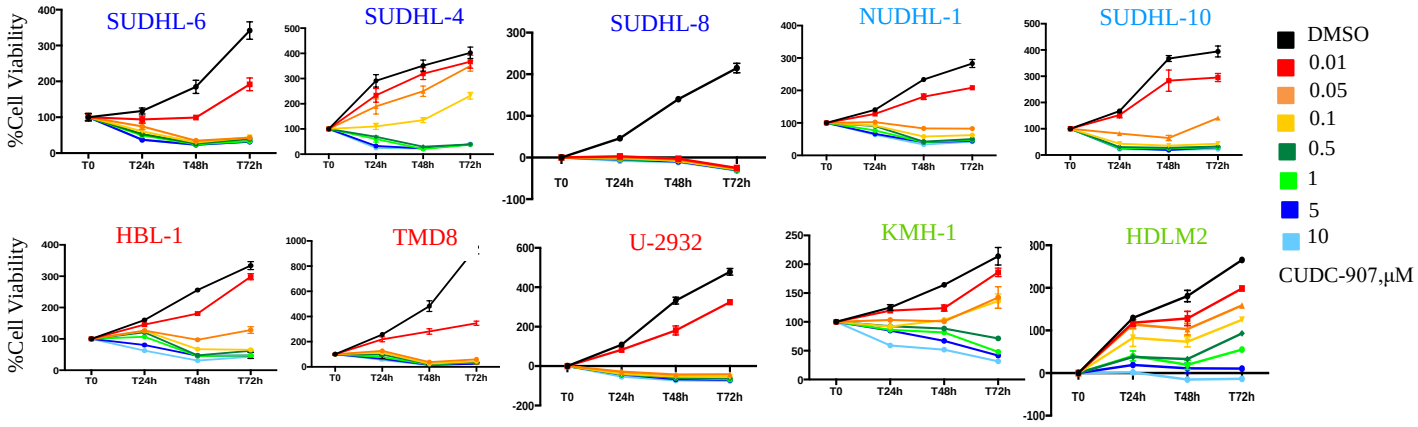
Enzyme	HDAC					PI3K			
Isotype	1	2	3	6	10	α	δ	β	γ
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

Mondello P, et al: Oncotarget 2017

CUDC-907 Activity in Lymphoma



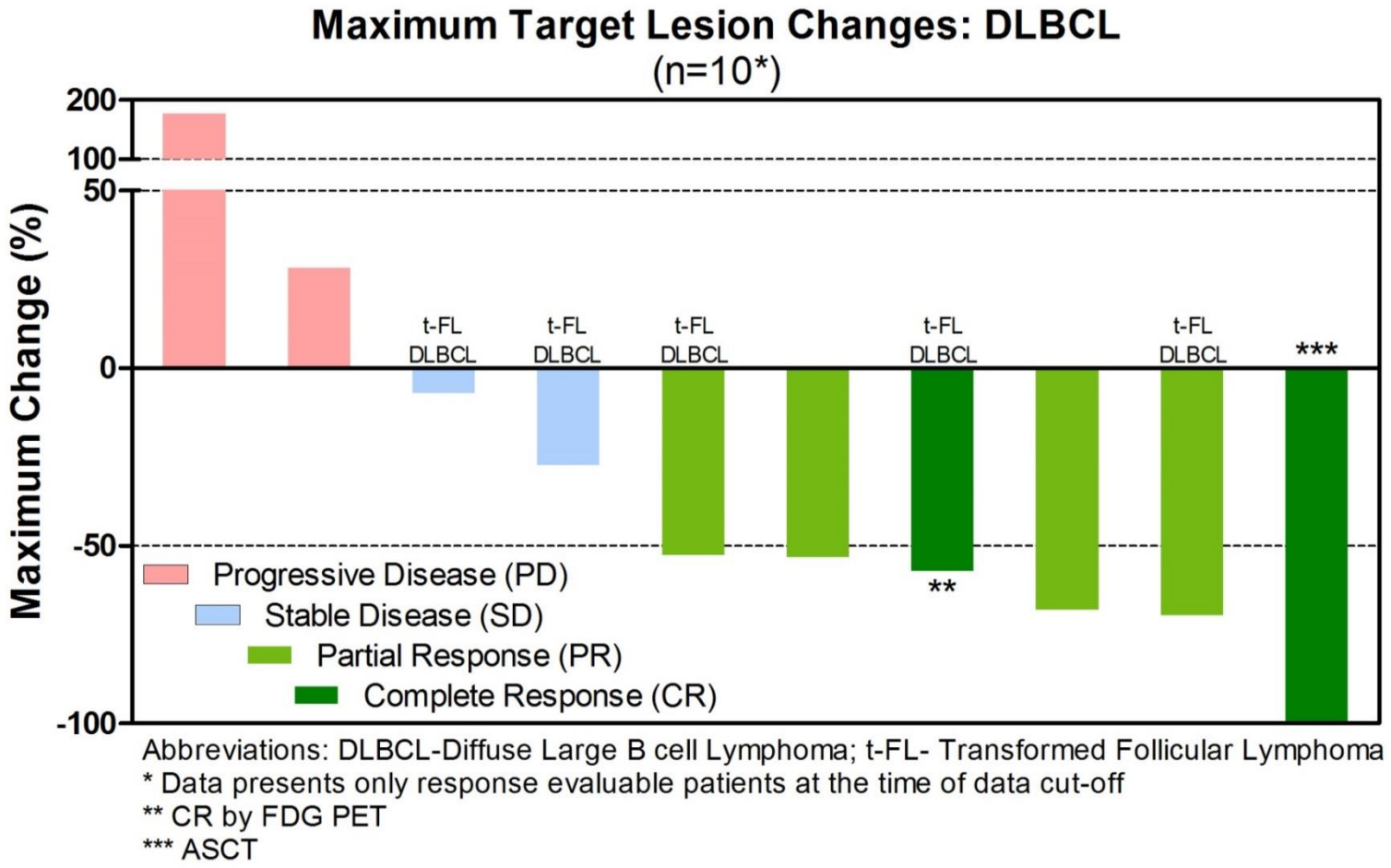




Mondello P, et al: Oncotarget 2017

DLBCL: Maximum Target Lesion Change

per Investigator Assessment



Abbreviations: DLBCL-Diffuse Large B cell Lymphoma; t-FL- Transformed Follicular Lymphoma

* Data presents only response evaluable patients at the time of data cut-off

** CR by FDG PET

*** ASCT

Younes, A et al, Lancet Oncology 2016

Conclusions

- Activated PI3K Pathway is frequently observed in a variety of lymphomas
- PI3K inhibitors have high single agent activity in FL, CLL, and MCL
- Idelalisib is the only PI3K inhibitor approved by the FDA and EMA (relapsed CLL and FL/SLL)
- Toxicity profile of PI3Ki vary based on
  - PI3K isoform selection
  - Duration of administration
  - Combinations
- Mechanism-based combination strategies will be required to improve treatment outcome, but should be balanced by safety

SAVE THE DATE

MSK SYMPOSIUM ON LYMPHOMA

STATE-OF-THE-ART IN BIOLOGY, THERAPY AND PATIENT CARE

May 5-6, 2017

Memorial Sloan Kettering Cancer Center
Zuckerman Research Center
417 East 68th Street
New York, NY 10065

Course Director
Anas Younes, MD, Chief, Lymphoma Service

Memorial Sloan Kettering Cancer Center