PI3K Inhibitors in Follicular Lymphoma

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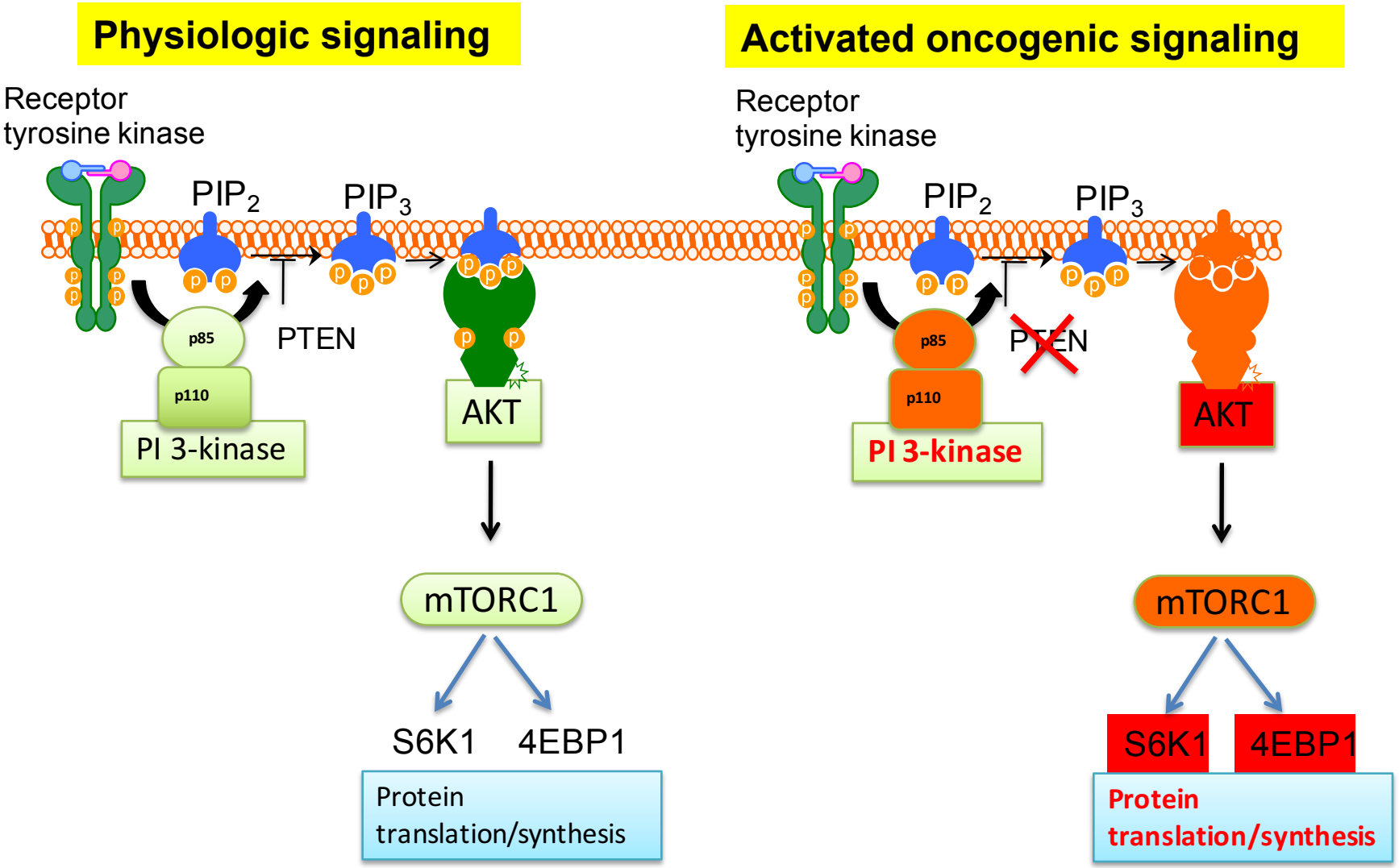
PI3K Pathway mutations do correlate with pathway activation in lymphoma

How to measure pathway activation?



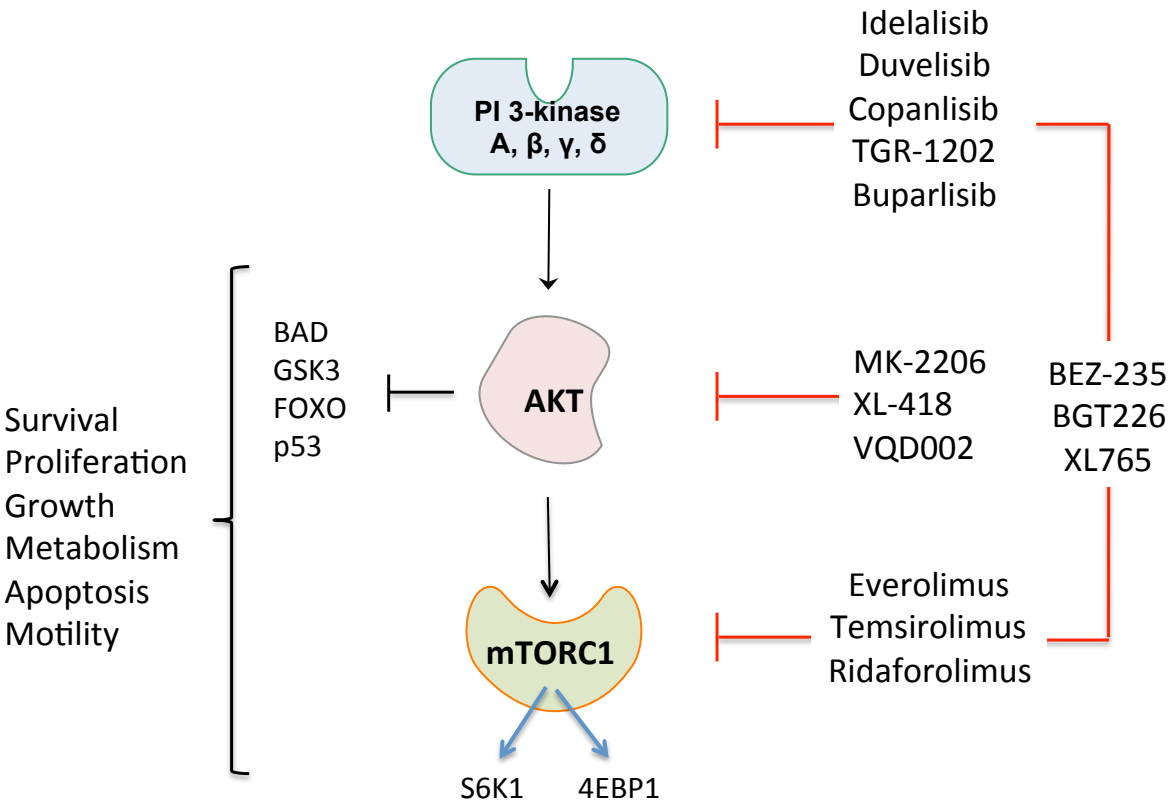
Recurrent mTORC1-activating *RRAGC* mutations in follicular lymphoma

Jessica Okosun, Rachel L Wolfson, Jun Wang, Shamzah Araf, Lucy Wilkins, Brian M Castellano, Leire Escudero-Ibarz, Ahad Fahad Al Seraihi, Julia Richter, Stephan H Bernhart, Alejo Efeyan, Sameena Iqbal, Janet Matthews, Andrew Clear, José Afonso Guerra-Assunção, Csaba Bödör, Hilmar Quentmeier, Christopher Mansbridge, Peter Johnson, Andrew Davies, Jonathan C Strefford, Graham Packham, Sharon Barrans, Andrew Jack, Ming-Qing Du, Maria Calaminici, T Andrew Lister, Rebecca Auer, Silvia Montoto, John G Gribben, Reiner Siebert, Claude Chelala, Roberto Zoncu, David M Sabatini & Jude Fitzgibbon

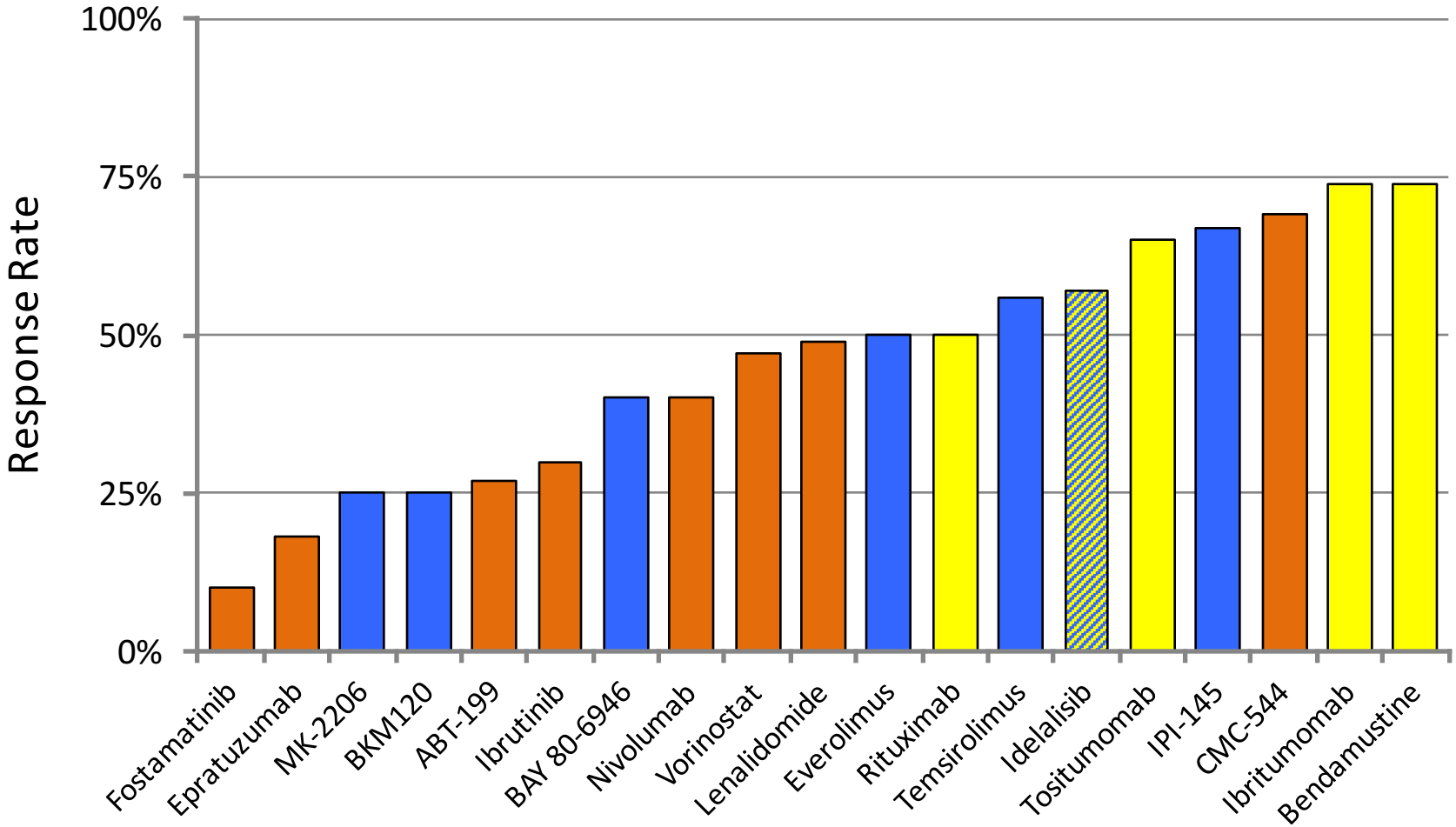
Nature Genetics **48**, 183–188 (2016)

Frequency 17%

Targeting PI3K/AKT/mTOR Pathway



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



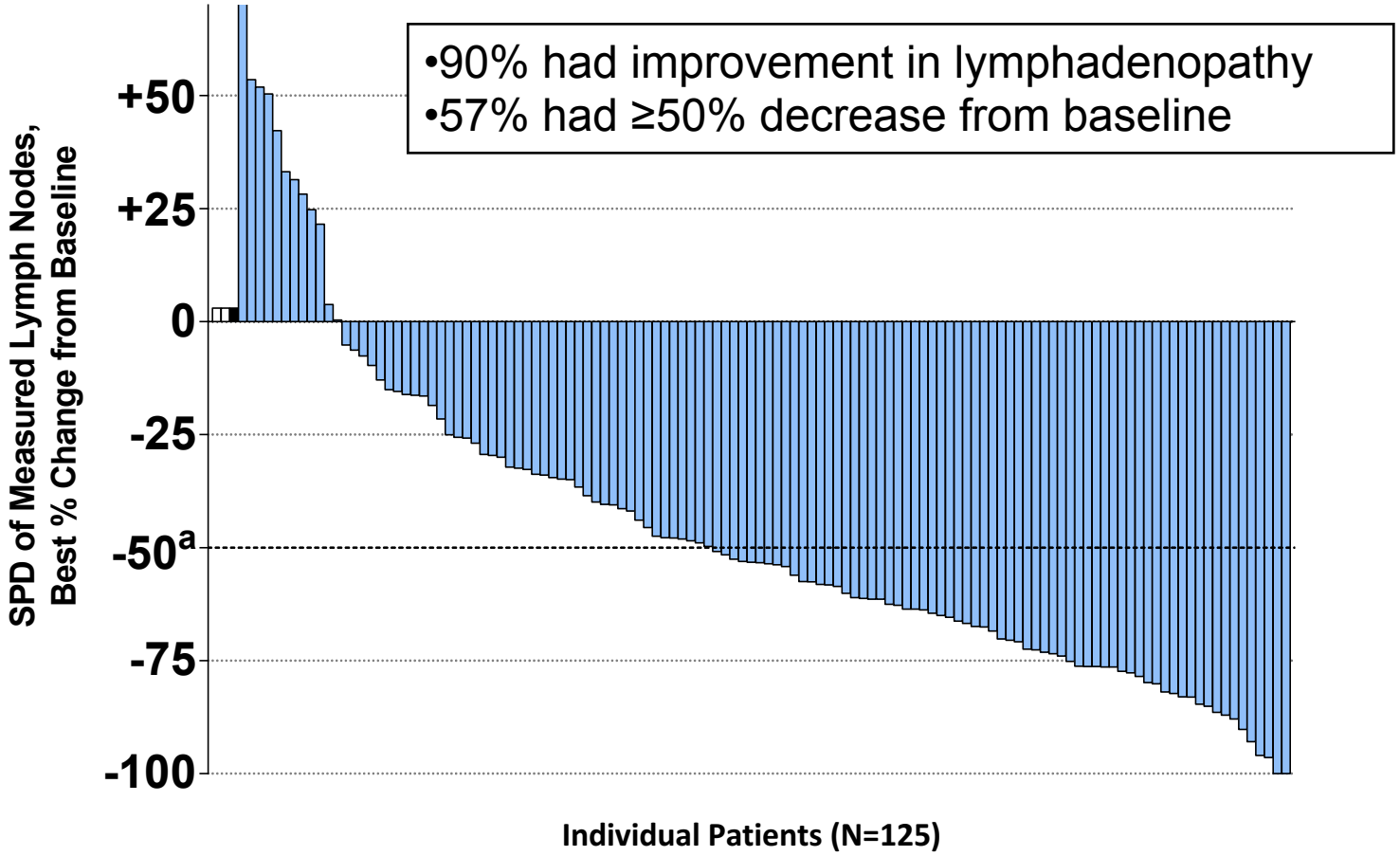
Updated from Younes A & Berry D. *Nat Rev Clin Oncol* 2012;9:643–653.

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	IPI-145	0%	67%	67%	54%	33%	33%
	PI3K-αδ	BAY80-6946	13%	40%	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%

Phase 2 Idelalisib Monotherapy in Refractory iNHL

Lymph Node Response



[a]Criterion for lymphadenopathy response [Cheson 2007]

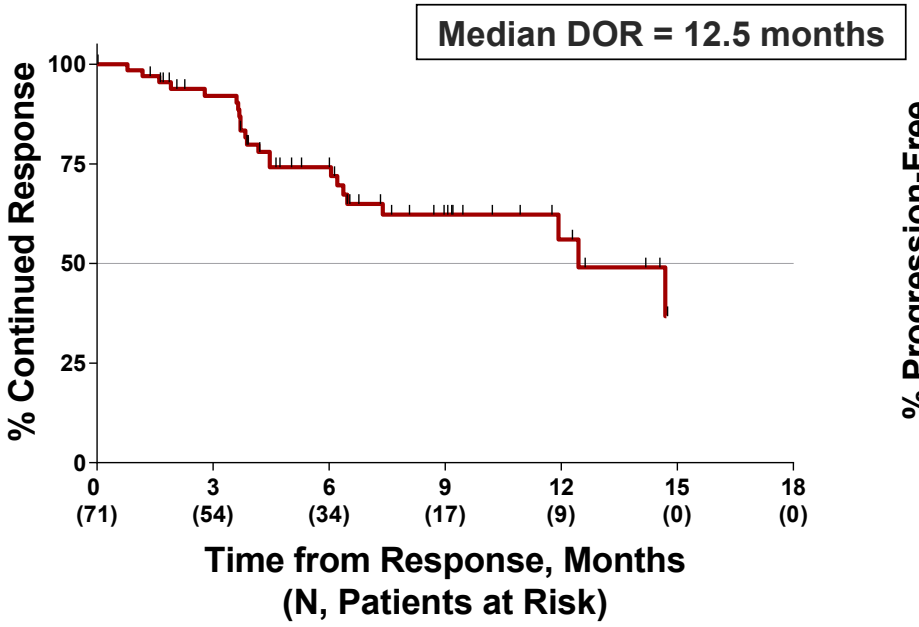
[b] 3 subjects no post baseline eva

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

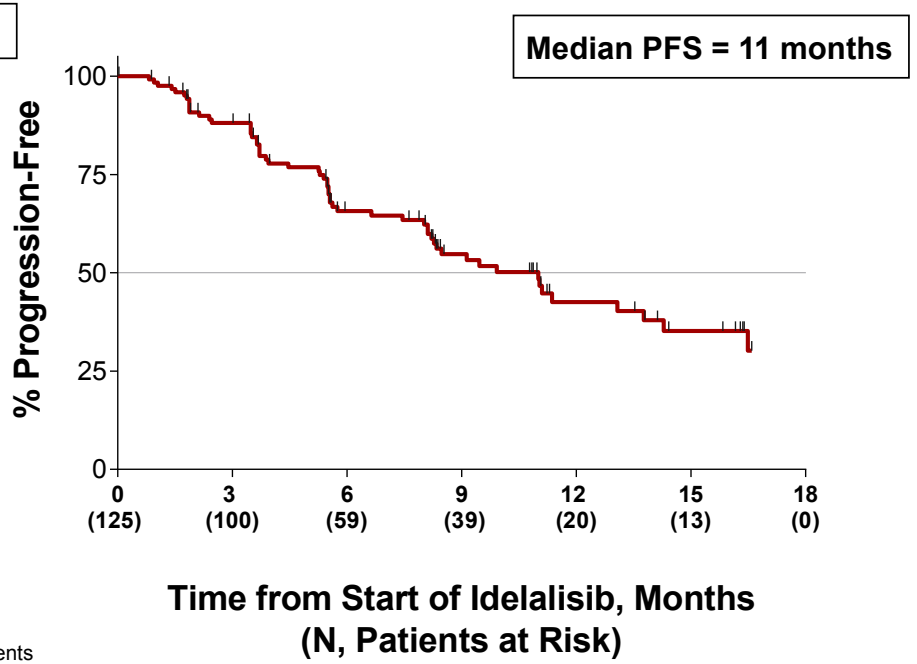
Gopal et al. NEJM 2014

Phase 2 Idelalisib Monotherapy in Refractory iNHL

Duration Of Response and PFS

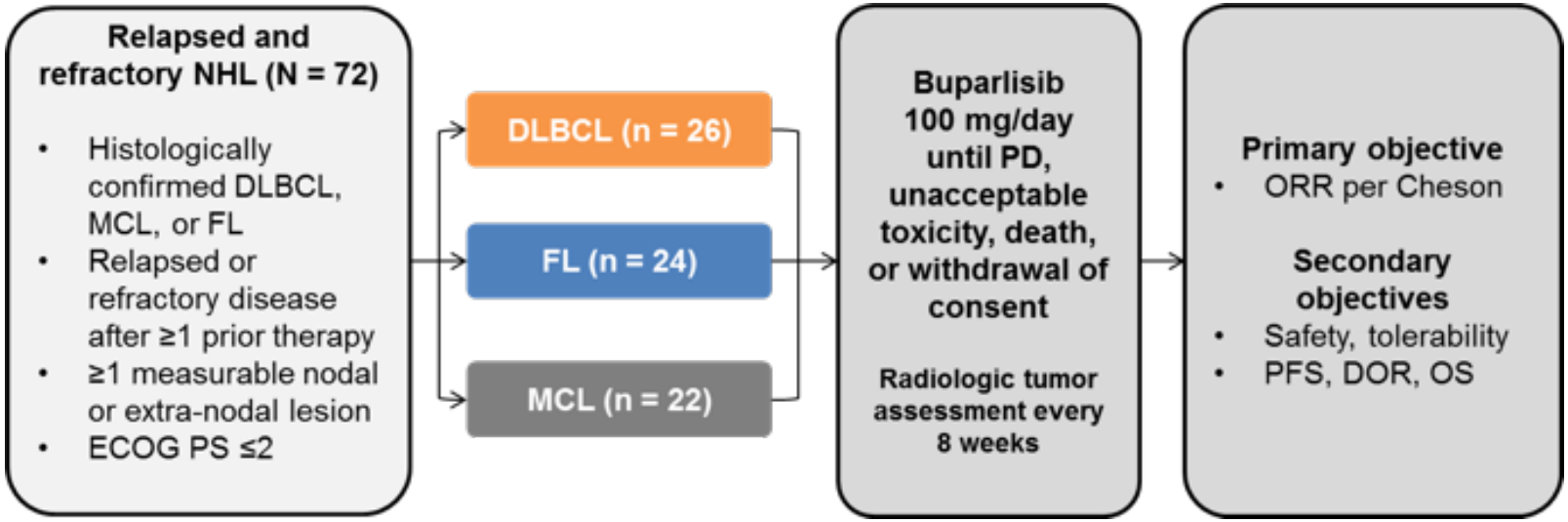


Analysis includes subjects who achieved a CR or PR (or MR for WM subjects) according to IRC assessments



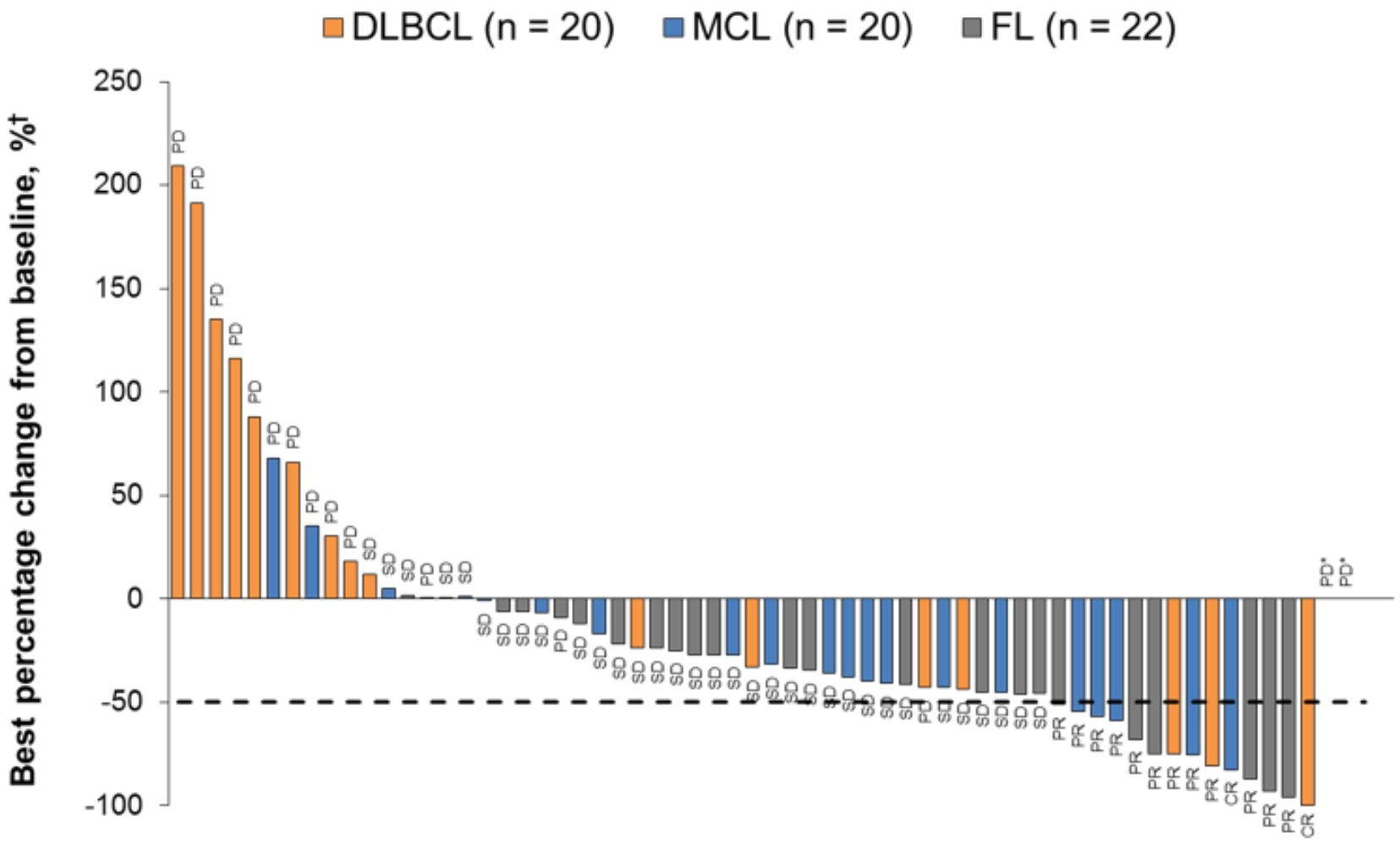
Gopal et al. NEJM 2014

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



Younes. A, et al, ASH 2015

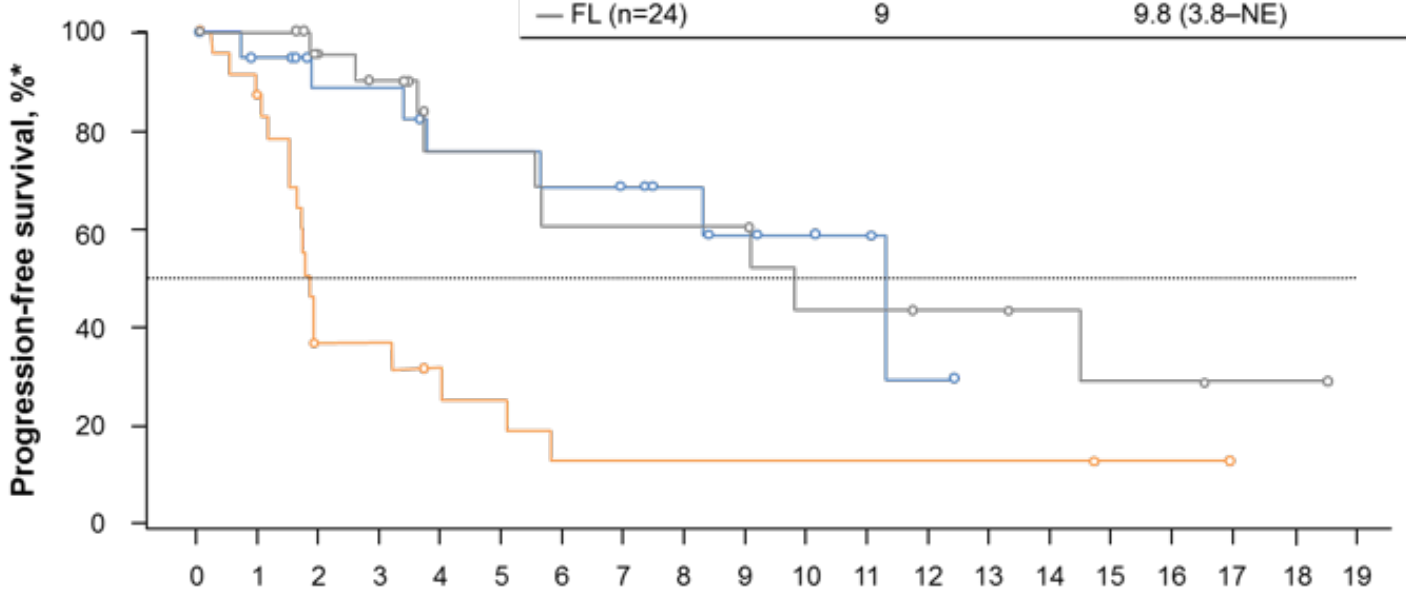
Phase II Study of Buparlisib (BKM120) in Patients with Relapsed/Refractory Lymphoma



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

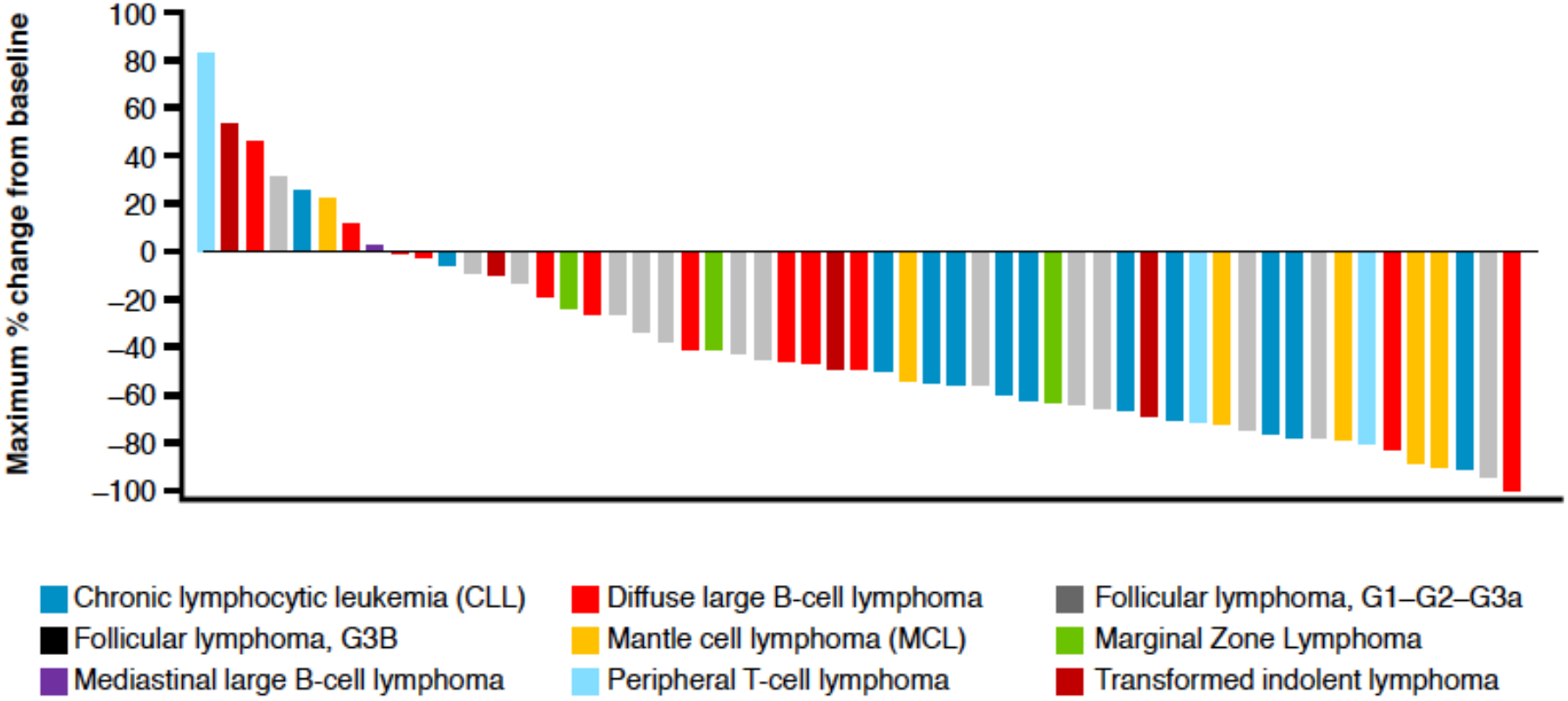
Median follow-up time: DLBCL, 1.7 months; MCL, 4.7 months; FL, 3.7 months.

Younes. A, et al, ASH 2015

Copanlisib (BAY 80-6946)

Tumor shrinkage

Tumor shrinkage (best response) by most recent tumor histology at screening (best response measured by maximum % change from baseline)

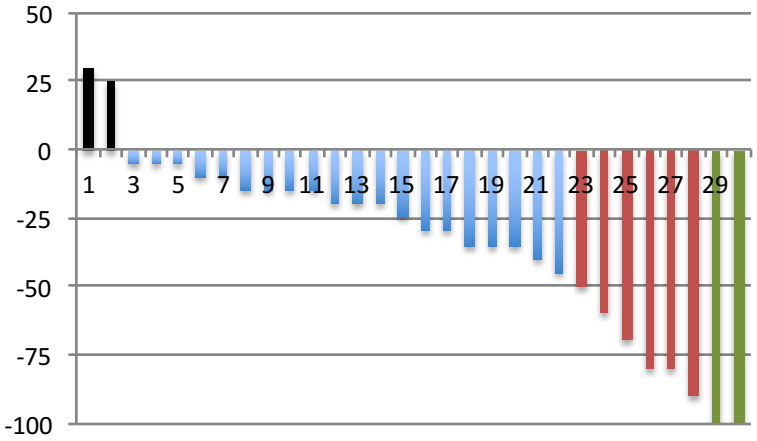


Copanlisib (BAY 80-6946)

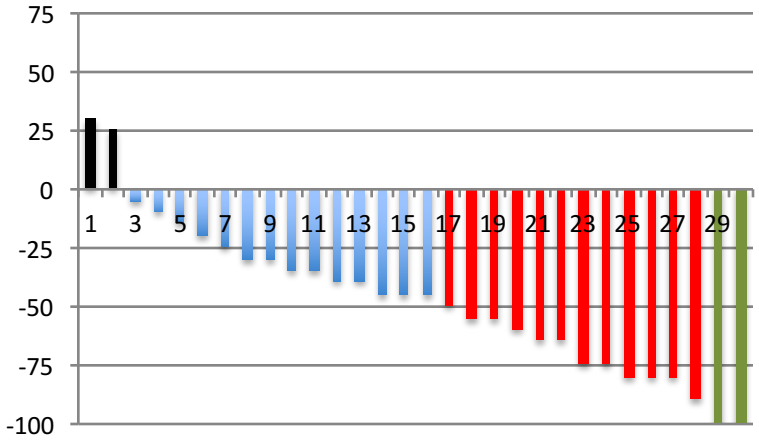
Histology	*n*	Response
Diffuse large B-cell lymphoma	15	2 CR / CRu; 3 SD; 10 PD (ORR 13%)
Mediastinal large B-cell lymphoma	1	1 PD
Transformed indolent lymphoma	6	1 PR; 5 PD (ORR 17%)
T-cell lymphoma	4	1 CRu; 1 PR; 2 PD (ORR 50%)
Mantle cell lymphoma	7	1 CRu; 4 PR; 2 PD (ORR 71%)
Follicular lymphoma G3b	1	1 N/A
Follicular lymphoma	16	1 CR; 5 PR; 9 SD; 1 N/A (ORR 40%)
Chronic lymphocytic leukemia / SLL	14	6 PR; 6 SD; 1 PD; 1 N/A (ORR 43%)
Marginal zone lymphoma	3	2 PR; 1 SD (ORR 66%)

Measuring Drug Efficacy
Response Rate vs PFS

Drug A: HDACi

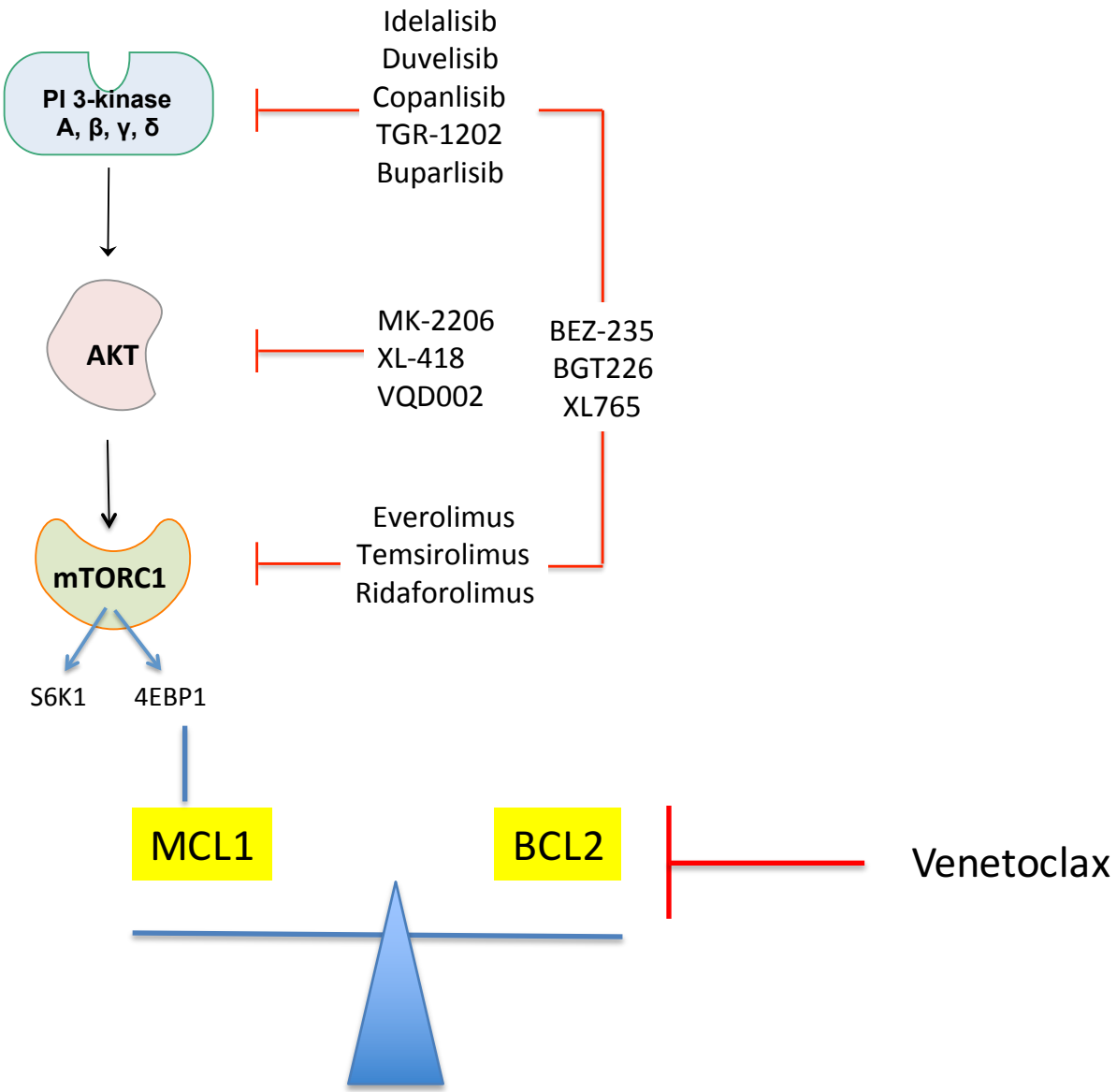


Drug B: r BV

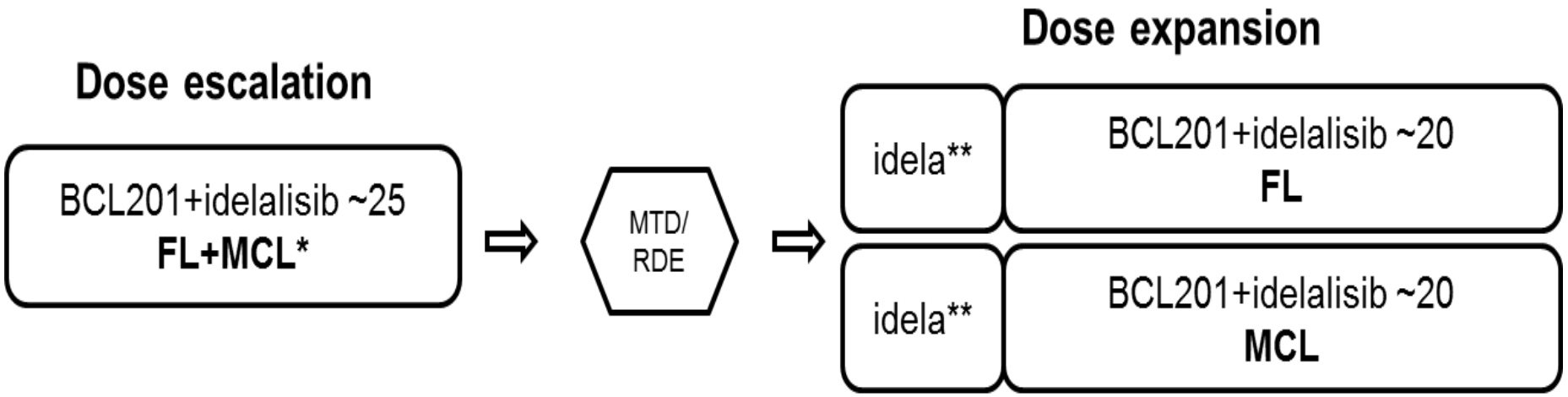


Blocking Resistance Mechanisms

Rationale for combining PI3Ki and BCL2i



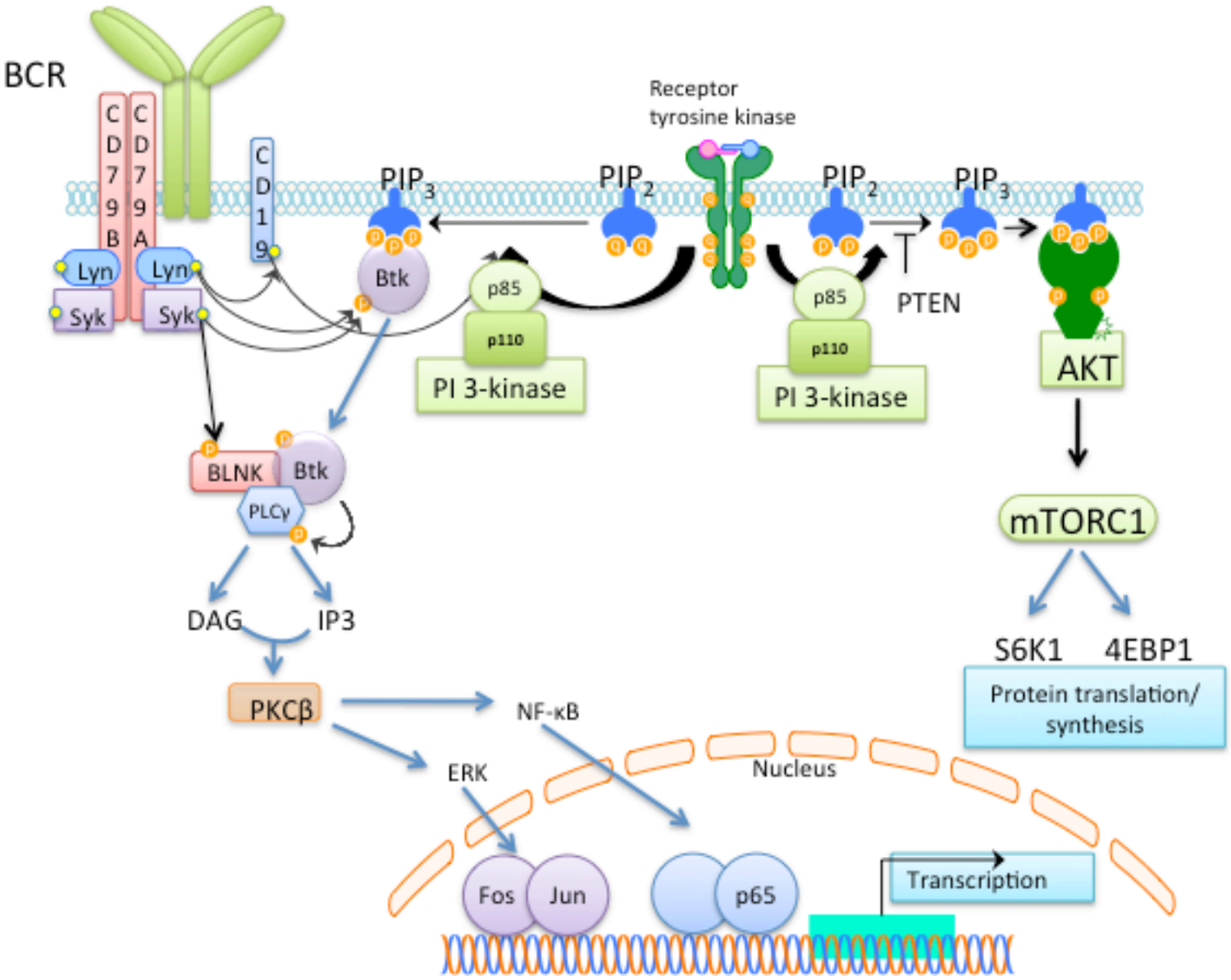
BCL201/idelalisib combo in FL and MCL



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

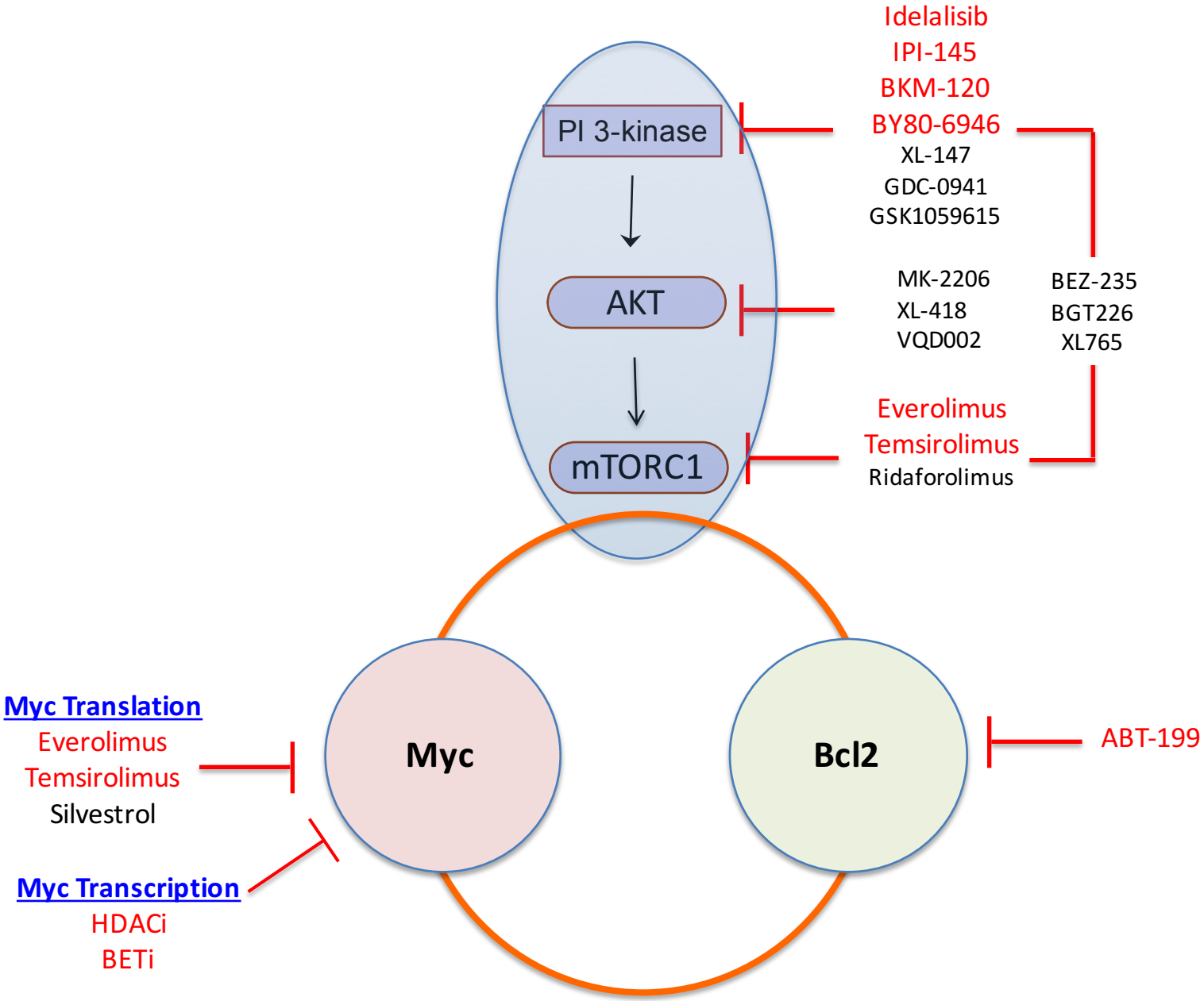
*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Dose levels may be added below the MTD in order to better understand safety, PK or PD.

Cooperation Between PI3K and BCR Signaling Pathway



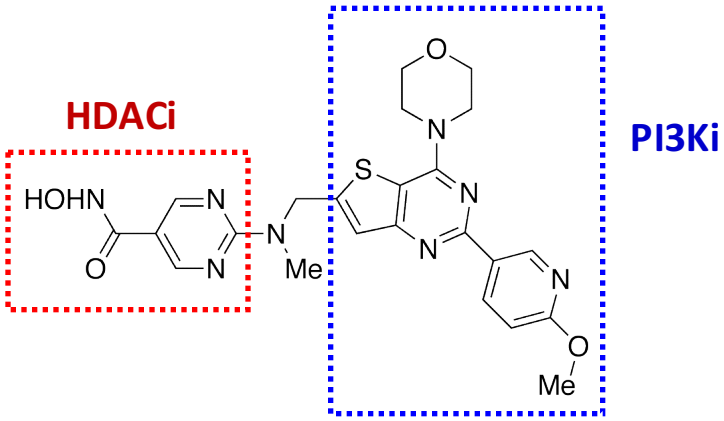
Phase I/II Of Ibrutinib + BKM120 in relapsed lymphoma

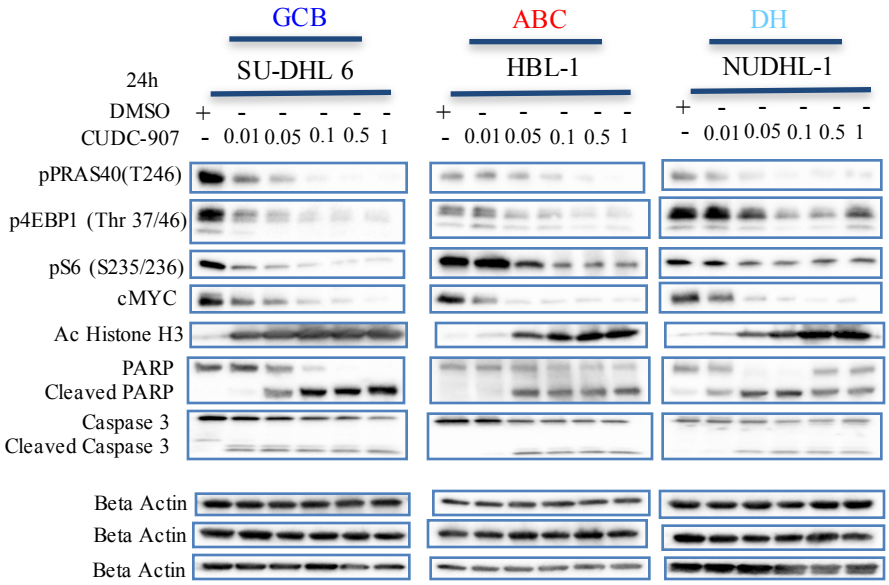
Dose Level	Buparlisib Mg/day taken daily for 4 wks	Ibrutinib Mg/day taken daily for 4 wks
Cohort 1	60	420
	80	420
	100	420
Cohort 2	60	560
	80	560
	100	560


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

CUDC-907

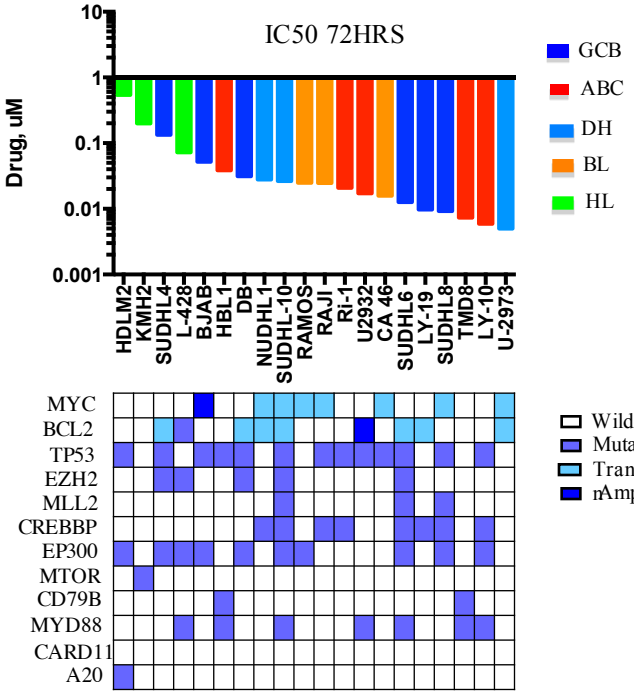
Oral, dual inhibitor of HDAC and PI3K

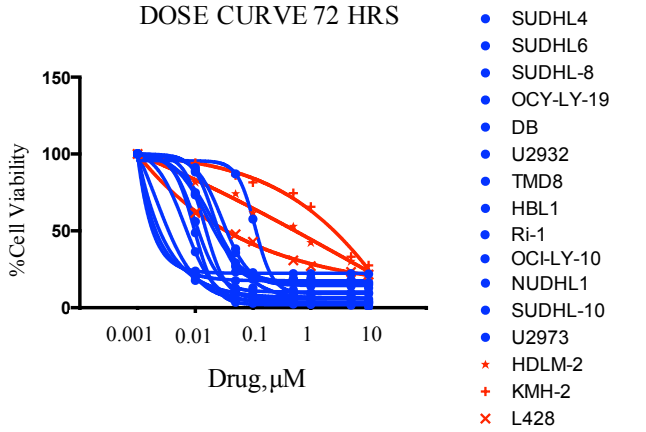


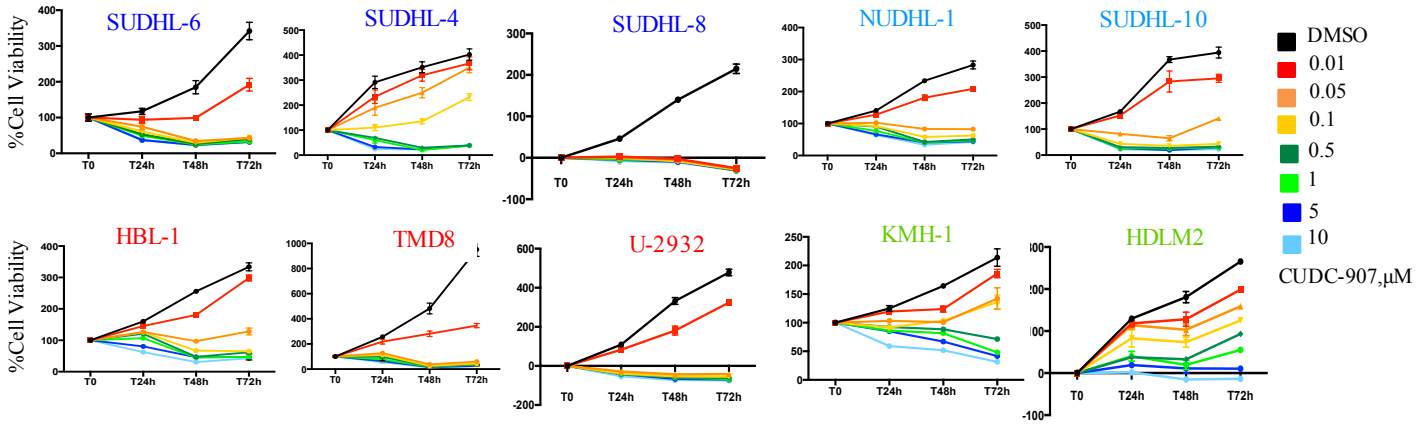


Enzyme	HDAC					PI3K			
Isotype	1	2	3	6	10	α	δ	β	γ
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

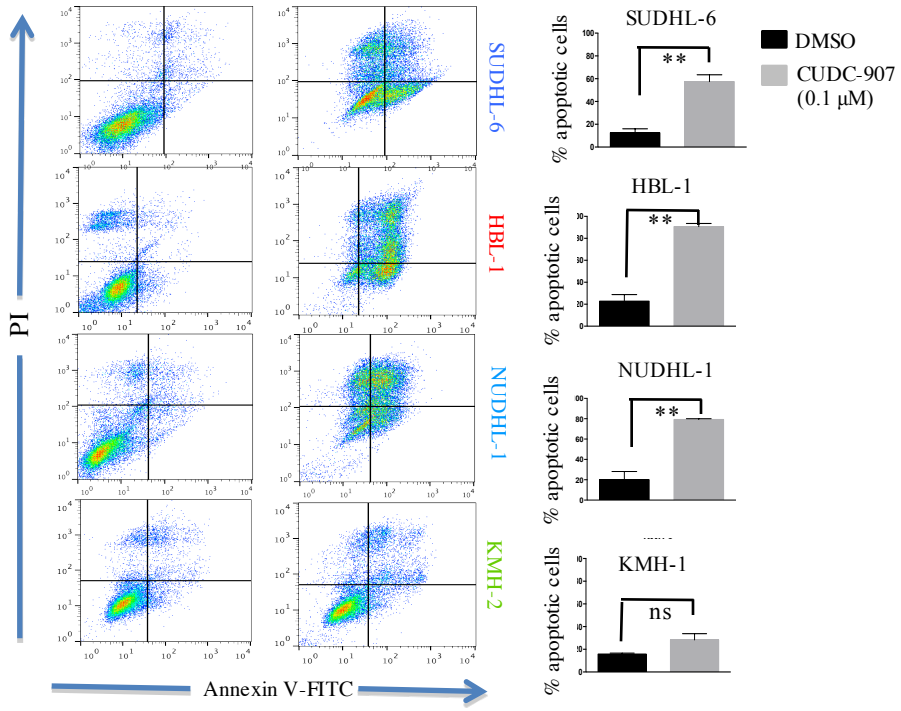
CUDC-907 Activity in Lymphoma

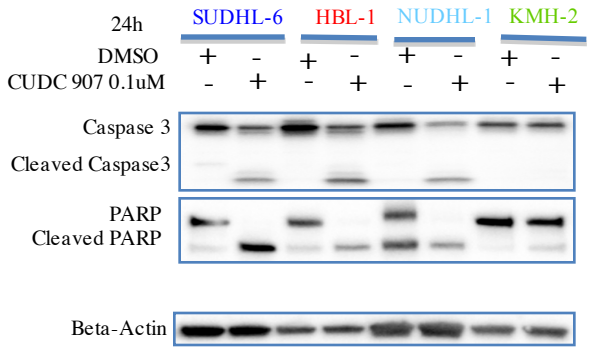


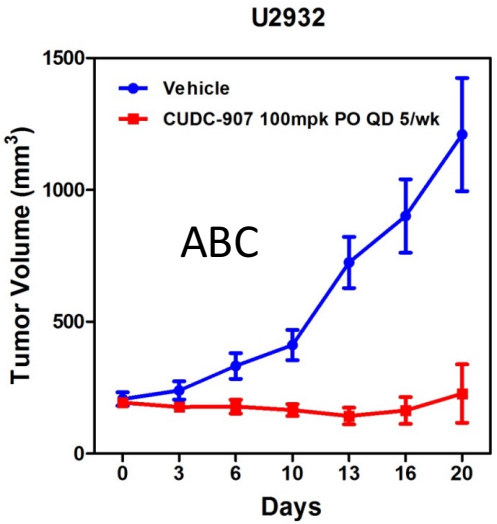


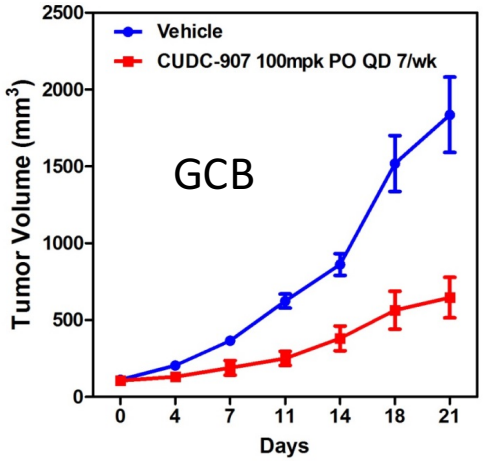


CUDC-907 Induces Apoptosis In Lymphoma Cell Lines



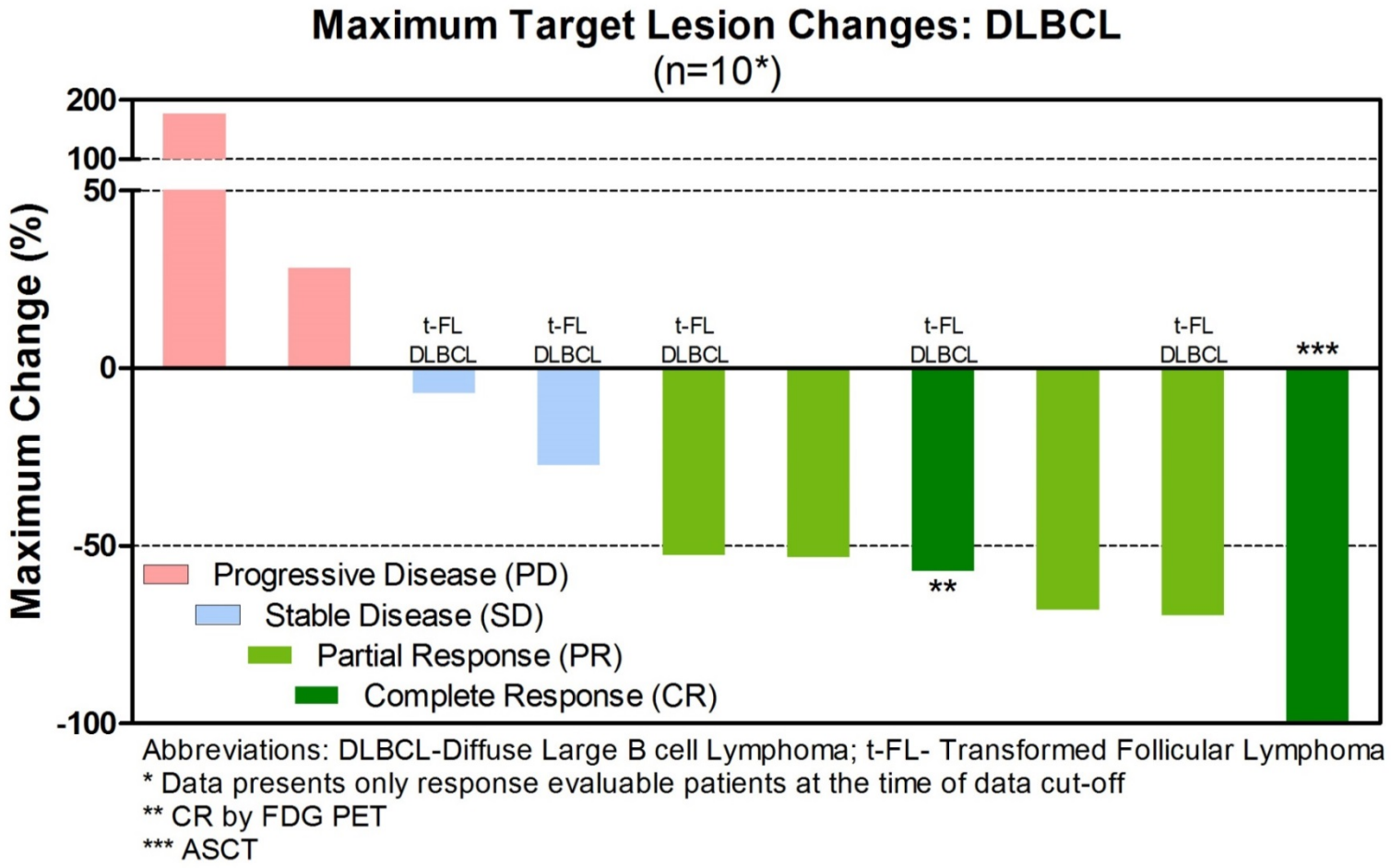






DLBCL: Maximum Target Lesion Change

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 (In Press)

Conclusions

- PI3K Pathway inhibitors have single agent activity in FL, CLL, and MCL
- Idelalisib is approved for reapsed CLL and FL
- Toxicity profile varies based on
  - PI3K isoform selection
  - Duration of administration
  - Combinations

- Mutation in the PI3K/mTOR pathway in FL may explain sensitivity in FL