Proteasome Inhibitors in Mantle Cell Lymphoma

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Columbia University Medical Center

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

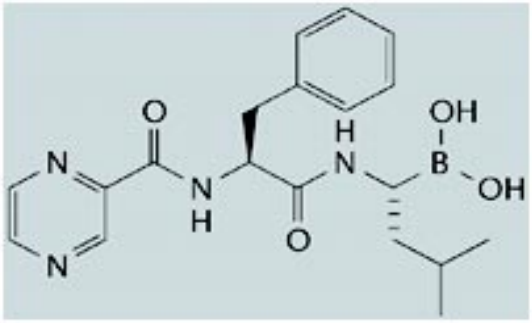
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Proteasome Inhibitors in Mantle Cell Lymphoma

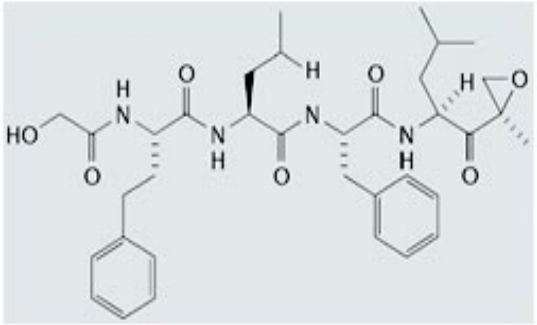
- Proteasome Inhibitors and the Proteasome : A Gentle Reminder
- Mantle Cell Lymphoma
- Indolent Lymphomas
- Diffuse Large B-Cell Lymphoma
- Peripheral T-Cell Lymphoma
- Summary : Novel - Novel Prospects

Proteasome Inhibitors in Lymphoma

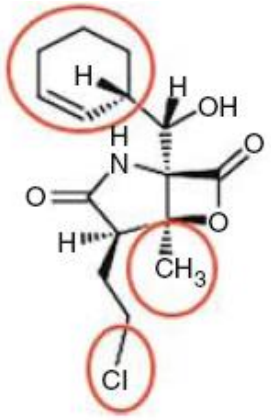
- Rationale
  - Disrupts pathways involved in pathogenesis of lymphoma
  - Preclinical models show sensitivity of lymphoma cell lines to proteasome inhibitors



Bortezomib
Reversible inhibitor
Approved for MCL



Carfilzomib (PR-171)
Irreversible inhibitor
Phase I testing

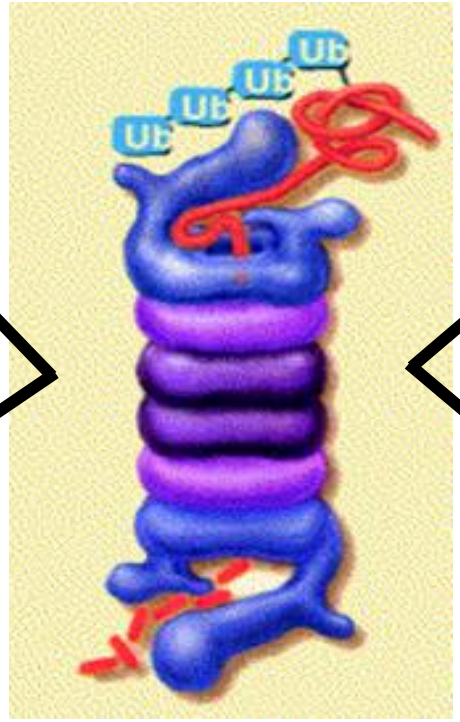


NPI-0052
Irreversible inhibitor
Early phase I testing

Effects of Bortezomib on Tumor and Stromal Targets : Pleiotropic Drugs

Microenvironment
↓ NF-κB, ↓ cytokines,
↓ cell adhesion molecules,
↓ VEGF, ↓ TNF-α

Apoptosis
↑ p53, ↑ p21, ↑ Bax,
↑ tBID, ↑ Bcl-2,
↓ MAPK, ↓ survivin,
↓ XIAP, ↓ cIAP
↑ Caspases



Stress Response
↓ DNA repair, ↓ Pgp,
↑ TopII, ↑ TopI,
↓ NF-κB, ↓ MAPK,
chemo- and
radiosensitization

Cell-Cycle Arrest
↑ p53, ↑ p21, ↑ p27,
↓ NF-κB, ↓ MAPK,
↑ cyclins A/B/D/E,
↑ c-fos/c-jun, ↑ Myc,
↑ beta catenin

MAPK=mitogen-activated protein kinase; NF-κB=nuclear factor kappa B.

Kyle. *N Engl J Med*. 2004;351:1860; Adams. *Drug Disc Today*. 2003;8:307; Adams. *Invest New Drugs*. 2000;18:109; Voorhees. *Clin Cancer Res*. 2003;6:6316; Leonard. *Int J Cancer*. 2006;119:971; Richardson. *Cancer Control*. 2003;10:361; Ling. *Mol Cancer Ther*. 2002;1:841.

Novel Targets/Therapies: Proteasome Inhibitors

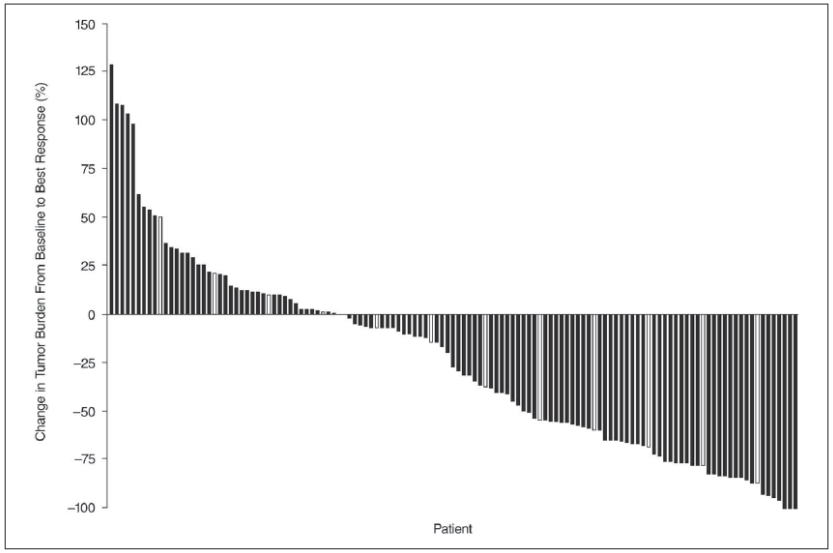
- Proteasome Inhibitors and the Proteasome : A Gentle Reminder
- Mantle Cell Lymphoma
- Indolent Lymphomas
- Diffuse Large B-Cell Lymphoma
- Peripheral T-Cell Lymphoma
- Summary: Novel - Novel Prospects

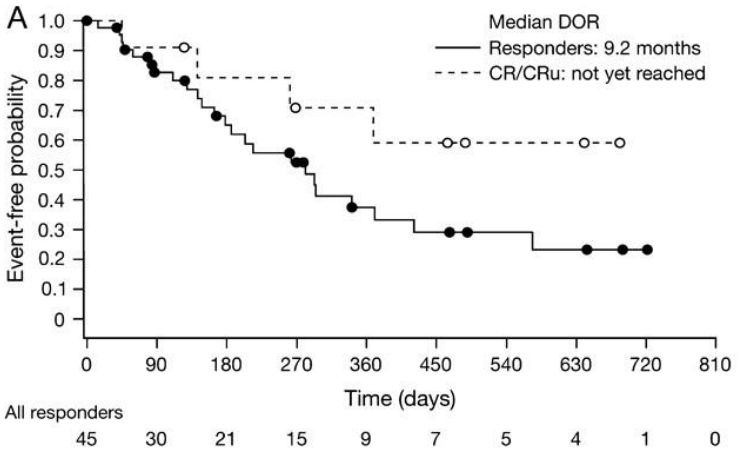
Single-agent Activity of Bortezomib in Mantle Cell Lymphoma

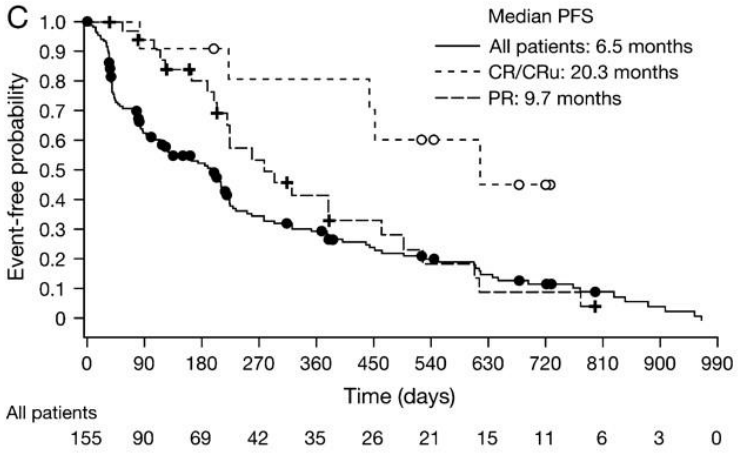
Study	Bortezomib Regimen	Evaluable Patients (n)	CR/CRu	PR	OR
O'Connor (ICML 2005)	1.5 mg/m^2 days 1, 4, 8, 11 21-day cycle	37	13%	27%	40%
Goy (JCO 2005)	1.5 mg/m^2 days 1, 4, 8, 11 21-day cycle	29	21%	21%	41%
Strauss/Lister (IMCL 2005)	1.3 mg/m^2 days 1, 4, 8, 11 21-day cycle	24	4%	25%	29%
Belch (ASH 2004)	1.3 mg/m^2 days 1, 4, 8, 11 21-day cycle	13 untreated 15 treated	0% 7%	46% 40%	46% 47%
PINNACLE (ASCO 2005)	1.3 mg/m^2 days 1, 4, 8, 11 21-day cycle	141	8%	26%	33%

Bortezomib in Relapsed / Refractory MCL

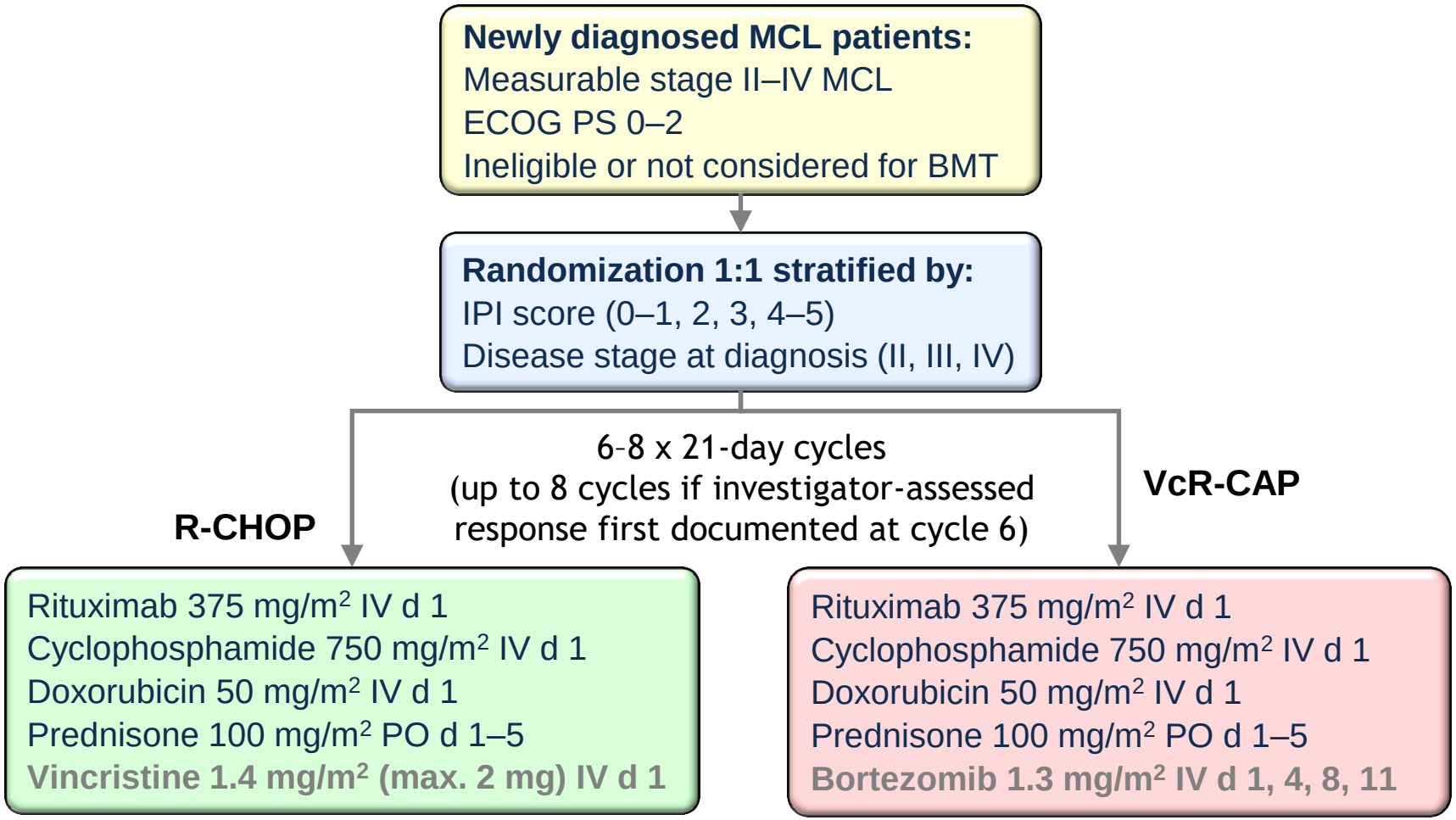
	Dose	n	ORR	CRR
Fisher JCO 2006 Goy Ann Onc 2009	1.3 BIW	141	31%	8%







LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT



Cavalli F et al. ASCO 2014, abstract #8500

LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

Secondary outcomes: Response and DOR by IRC, TTP, TTNT, TFI, OS

Response-evaluable population	R-CHOP (n=244)	VcR-CAP (n=243)	HR	P
CR+CRu*, %	42	53	OR 1.69	0.007
ORR (CR+CRu+PR), %	90	92	OR 1.43	0.275
Median time to initial response, mos	1.6	1.4	HR 1.54	<0.001
Median DOR (CR+CRu+PR), mos	15.1	36.5	NA	NA
In patients with CR+CRu*	18.5	42.1	NA	NA
Median duration of CR/CRu, mos	18.0	42.1	NA	NA
Median TTP by IRC, mos	16.1	30.5	HR 0.58	<0.001
By investigator, mos	16.8	35.0	HR 0.47	<0.001
Median time to next therapy (TTNT), mos	24.8	44.5	HR 0.50	<0.001
Median treatment-free interval (TFI), mos	20.5	40.6	HR 0.50	<0.001
Median OS, mos	56.3	NR	HR 0.80	0.173
4-year OS rate, %	53.9	64.4	–	–

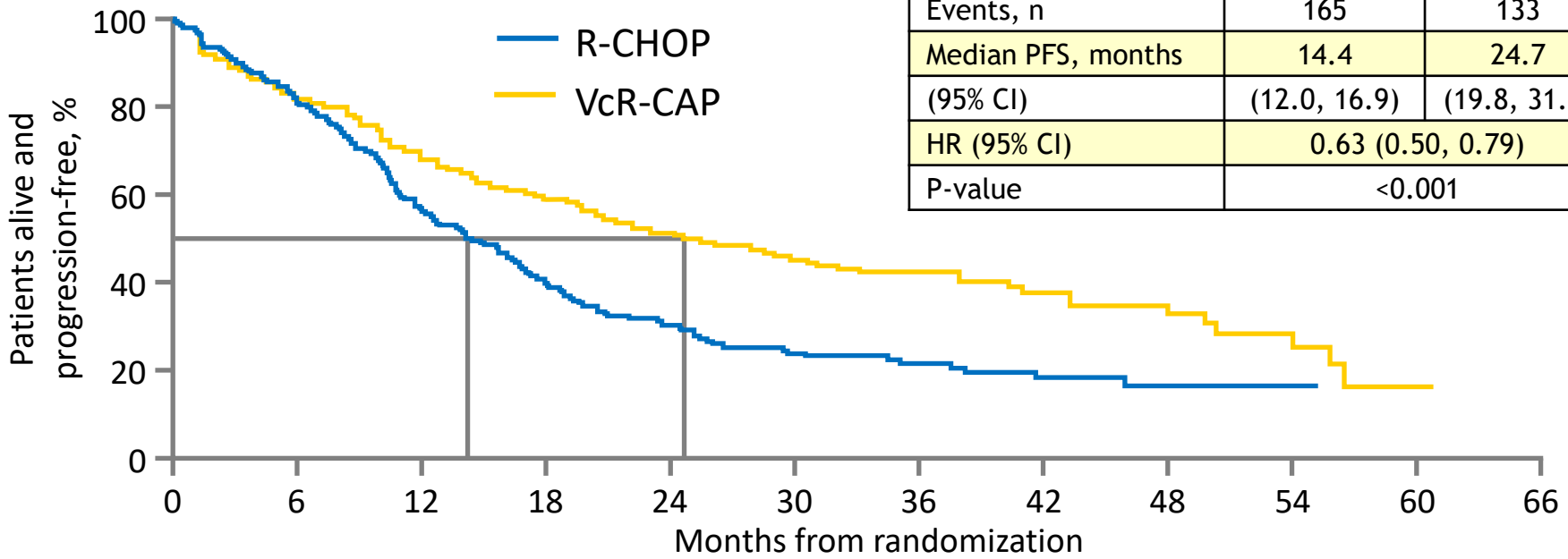
*CR/CRu verified by bone marrow and LDH; † data shown are odds ratio (OR), except for hazard ratio (HR) for time to response; NA, not applicable; NR: not reached

Cavalli F et al. ASCO 2014, abstract #8500

LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

59% improvement in PFS by IRC with VcR-CAP vs R-CHOP (median follow-up 40 mos)

	R-CHOP	VcR-CAP
Events, n	165	133
Median PFS, months	14.4	24.7
(95% CI)	(12.0, 16.9)	(19.8, 31.8)
HR (95% CI)	0.63 (0.50, 0.79)	
P-value	<0.001	



Number of patients at risk:

R-CHOP	244	181	116	79	55	36	22	16	9	3	0	0
VcR-CAP	243	187	146	122	94	66	42	28	17	8	1	0

Median PFS by investigator was 16.1 vs 30.7 mos with R-CHOP vs VcR-CAP; 307 (63%) events; HR 0.51, p<0.001; 96% improvement with VcR-CAP

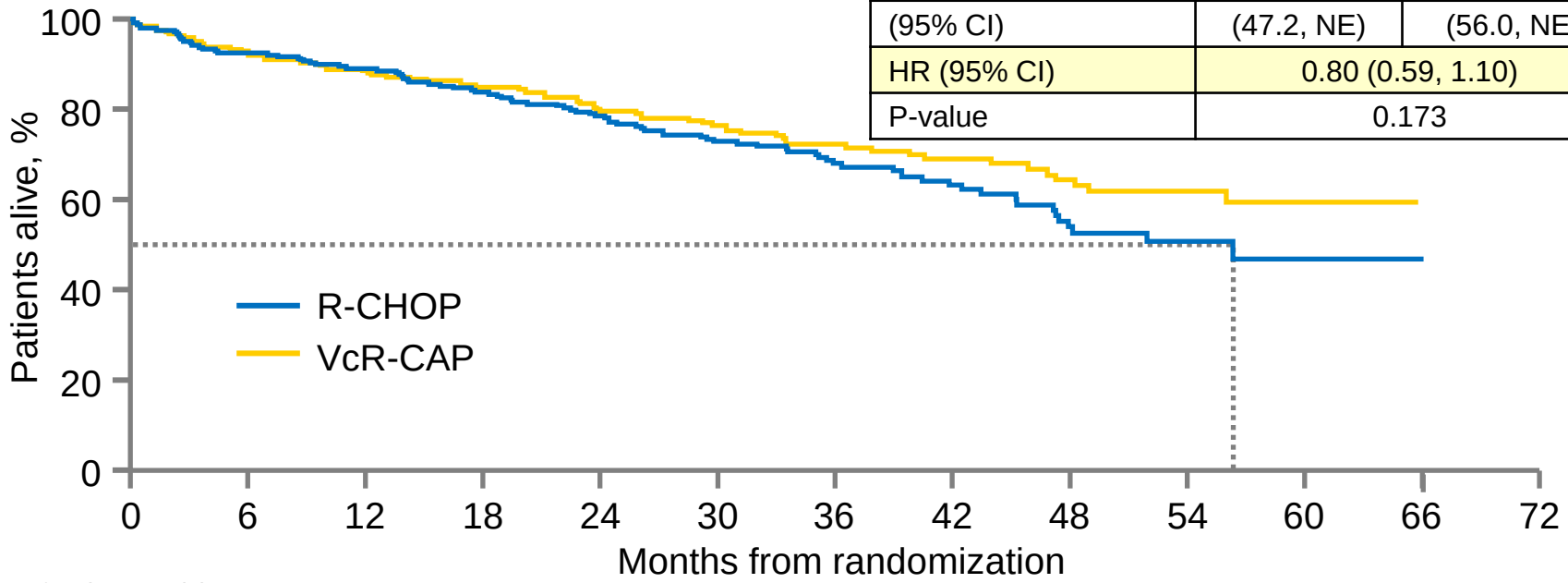
At Cost of More Toxicity : Neuropathy

Cavalli F et al. ASCO 2014, abstract #8500

LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

Secondary outcomes: OS (Median follow-up 40 mos)

	R-CHOP	VcR-CAP
Events, n	87	71
Median OS, months	56.3	Not reached
(95% CI)	(47.2, NE)	(56.0, NE)
HR (95% CI)	0.80 (0.59, 1.10)	
P-value	0.173	



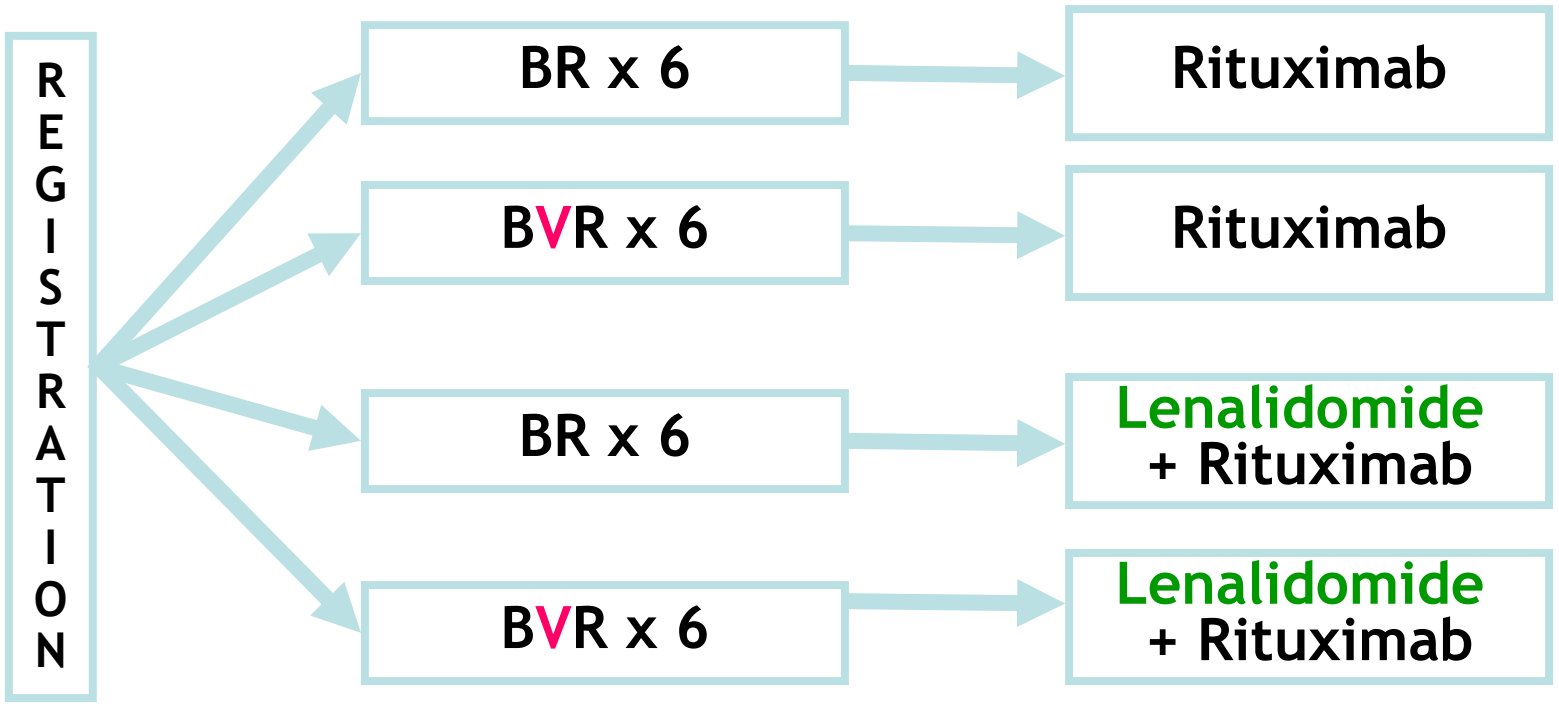
Number of patients at risk:

R-CHOP	244	214	204	192	177	141	100	70	43	21	7	1	0
VcR-CAP	243	212	200	191	171	140	100	75	52	28	8	1	0

There was a trend to prolonged survival with VcR-CAP (not statistically significant)

Cavalli F et al. ASCO 2014, abstract #8500

E1411 - Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma in patients ≥ age 60



BR = Bendamustine, Rituximab

V= Bortezomib

BBR (VERTICAL) ; ORR 88%, complete response rate 53%, median PFS 15 mos (Fowler, et al, JCO 2011)

Proteasome Inhibitors in Mantle Cell Lymphoma: Summary of Clinical Status

- In lymphoma, MCL remains the only US FDA approval for the drug
- Most use now has matured to combination use in R-CHOP and R-Bendamustine, though ECOG results are pending
- Activity appreciated in MZL, PTCL, perhaps sub-types of DLBCL
- Novel : novel combinations are proving interesting……

How Do We Improve the Merits of Proteasome Inhibitors?

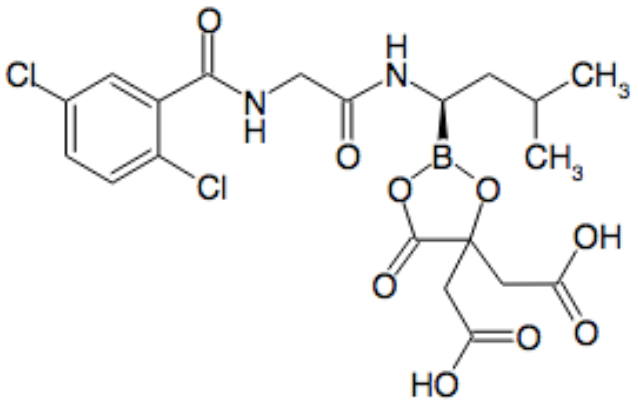
Make Better Ones

Or

Identify Synergistic Combinations (not predicated on genotoxic chemtherapy)

IXAZOMIB (MLN2238)

- First orally bioavailable proteasome inhibitor in clinical trials
- Binds to the chymotrypsin-like site of the 20S proteasome
- Similar selectivity and potency to bortezomib, but shorter 20S proteasome dissociation half-life

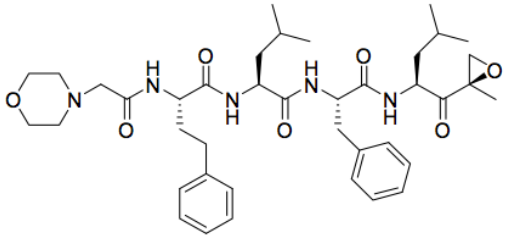


Phase 1 Study of IV Ixazomib in Lymphoma

- IV administration on days 1, 8, 15 of 28 days
- 30 subjects with relapsed/refractory NHL
  - FL 11, DLBCL 5, PTCL 4, HL 3, MF 2, MCL 2, Other 2
- MTD determined to be 2.34 mg/m2
- DLTs: Neutropenia, diarrhea, renal failure
- Most common AEs: fatigue (43%), diarrhea (33%), nausea, thrombocytopenia, rash (each 27%)
- 26 evaluable for response, 5 responders (19%)
  - 1 CR (FL), 4 PRs (3 FL, 1 PTCL)

Assouline et al. Blood Can J 2014

Carfilzomib



- Tetrapeptide ketoepoxide-based irreversible inhibitor of the 20S proteasome.
- Higher affinity for proteasome than bortezomib, and demonstrated activity in bortezomib resistant NHL cell lines
- Phase 1 trial reached 20/27 mg/m2 on days 1,2, 8, 9, 15, 16 of a 28 day cycle. No MTD reached.
- Anemia, thrombocytopenia, nausea, fatigue, constipation, pyrexia, cough, anorexia
- Among 15 NHL, 5 SD (4 FL, 1 CLL/SLL)

Proteasome Inhibitors Synergize with BTK Targeted Drugs

bjh research paper

The Bruton tyrosine kinase (BTK) inhibitor PCI-32765 synergistically increases proteasome inhibitor activity in diffuse large-B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) cells sensitive or resistant to bortezomib

Dasmahapatra et al, Br J Haematol 2013

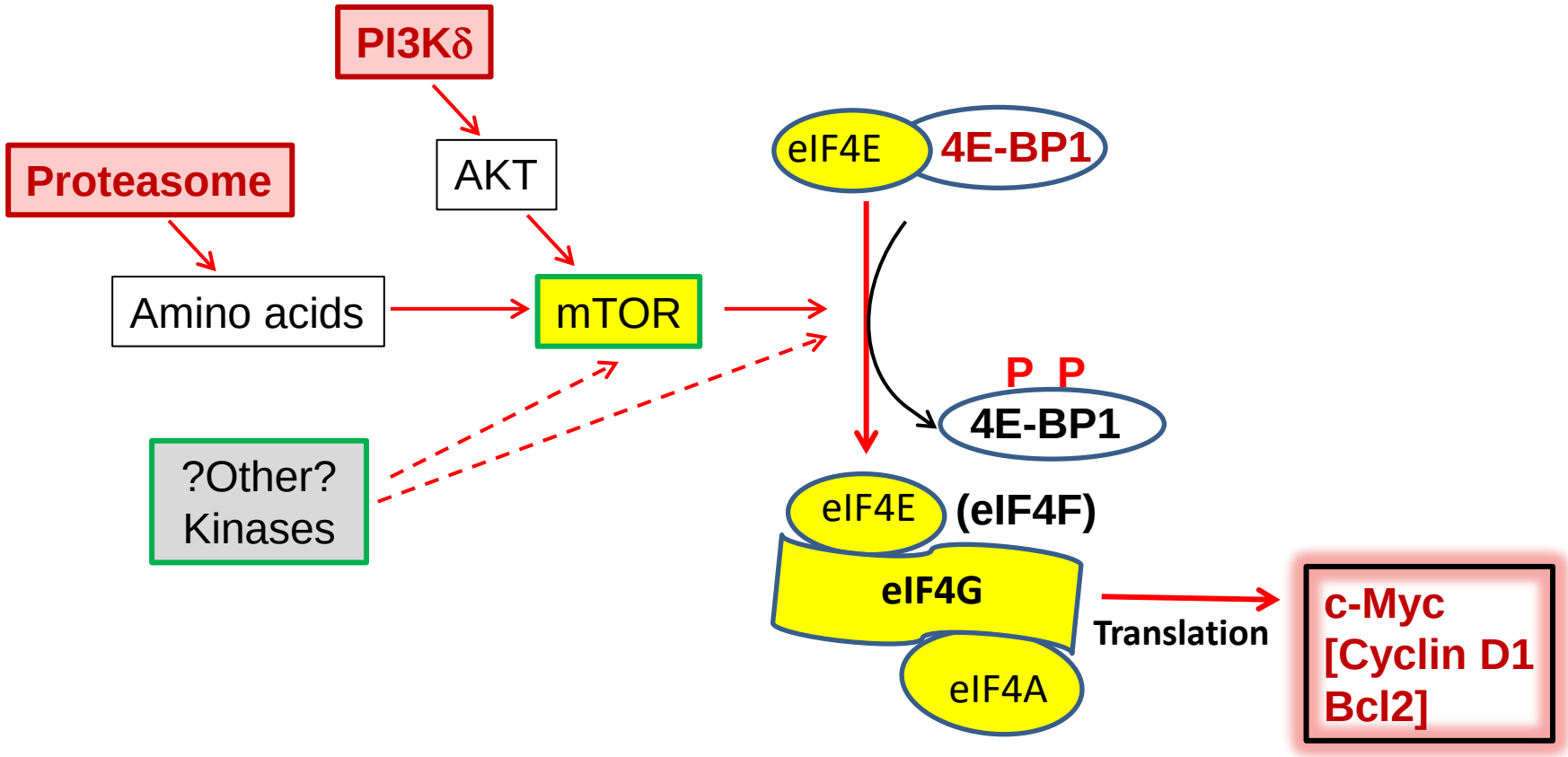
The bruton's tyrosine kinase inhibitor ibrutinib synergized with the proteasome inhibitor carfilzomib and overcame immunoproteasome-mediated carfilzomib resistance in mantle cell lymphoma

Ou, et al, AACR abstract #2432, 2013

Combinatorial drug screening identifies synergistic co-targeting of Bruton's Tyrosine Kinase and the proteasome in Mantle Cell Lymphoma

Axelrod, Ou, Brett et al, Leukemia 2013

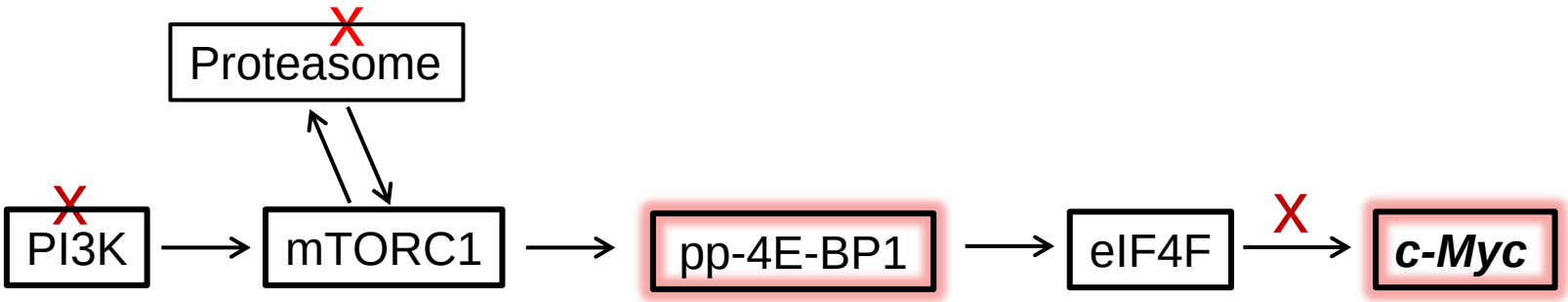
Targeting Translation with Proteasome and PI3K Inhibitors by Inhibiting Phosphorylation of 4E-BP1



Suraweera, A., et al., Mol Cell, 2012
Quy, P.N., et al., J Biol Chem, 2013
Hutter, G., et al., Leukemia, 2012
Zhang, Y., et al., Nature, 2014

Dibble CC and Cantley LC.
Trends Cell Biol, 2015
Andresen et al., Nucleic Acids Res 2012
Wolfe et al., Nature 2014

Combining PI3K and Proteasome Inhibitors Synergistically Inhibits Translation of c-Myc with Potent Cytotoxicity: Experimental Design



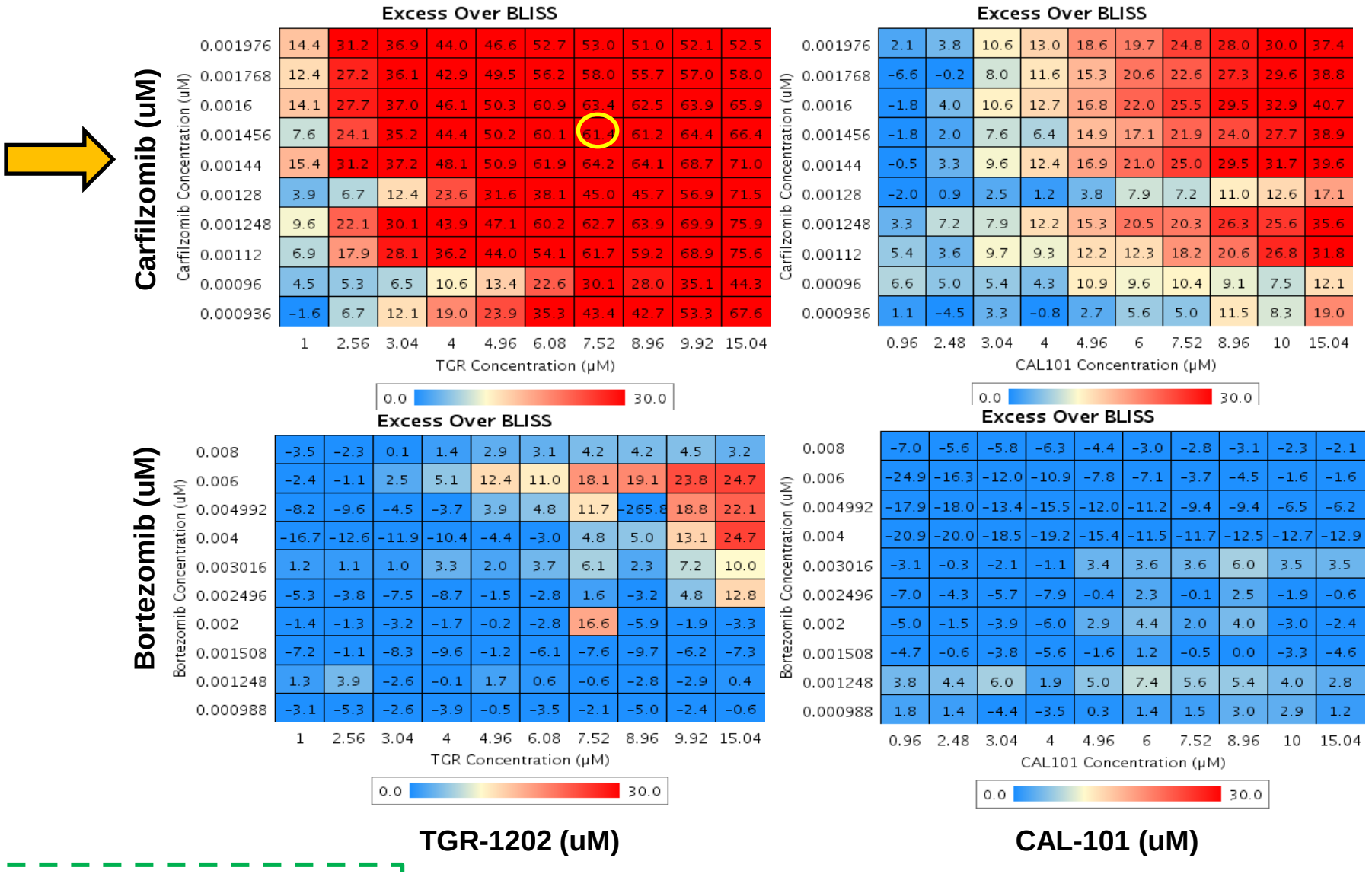
PI3Kδ Inhibitors

Proteasome Inhibitors

Drugs	TGR-1202 (TG)	Idelalisib (Ide)
Carfilzomib (Cfz)	TC	IC
Bortezomib (Bz)	TB	IB

Deng et al., 2017. Blood

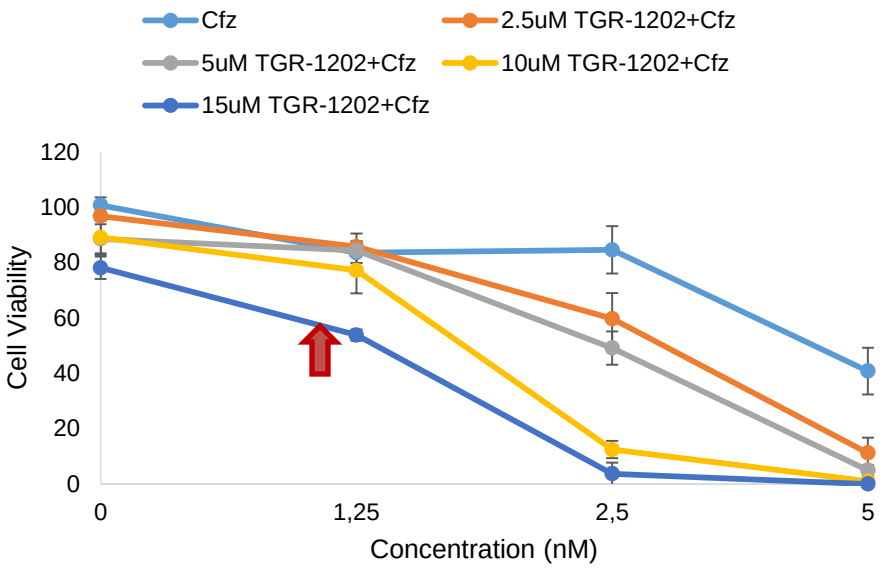
Highly Synergistic Interactions Unique to the Car - TGR1202 Combination



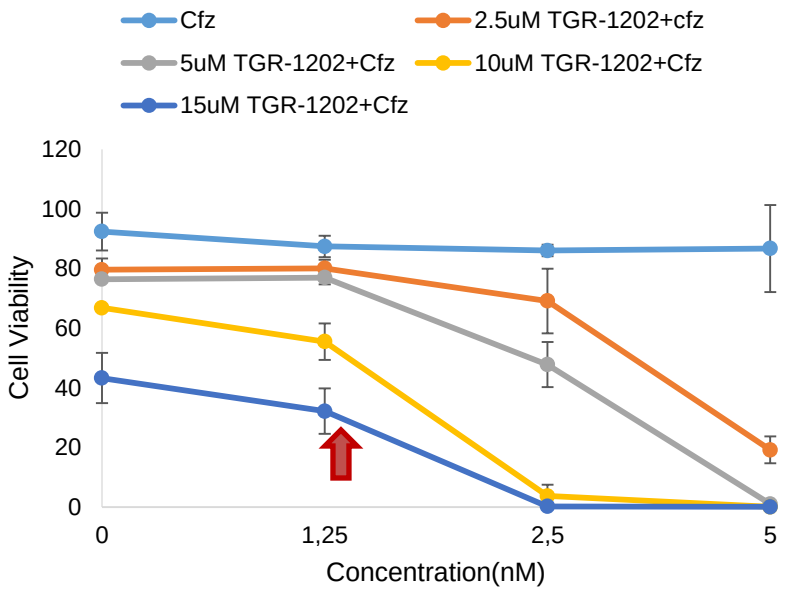
EOB: > 0 to 100: Synergy

Deng et al., 2017. Blood

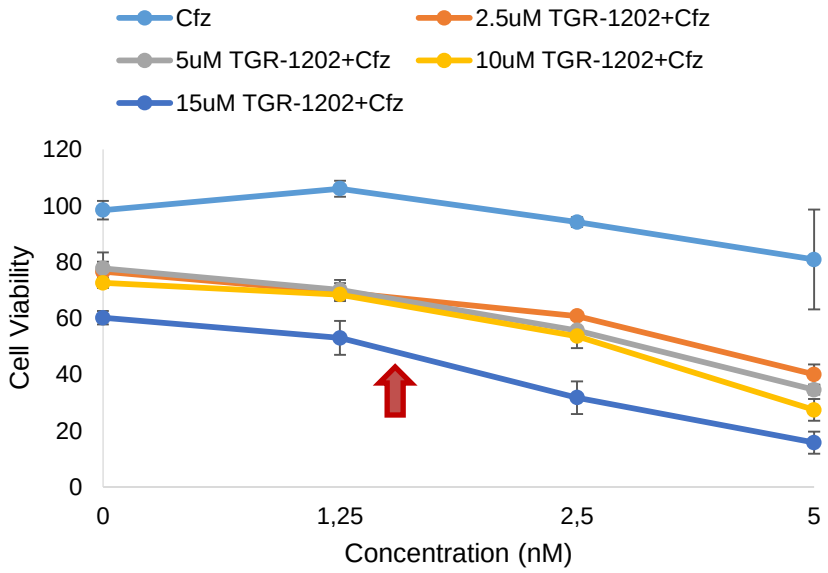
Jeko-1-48 hrs



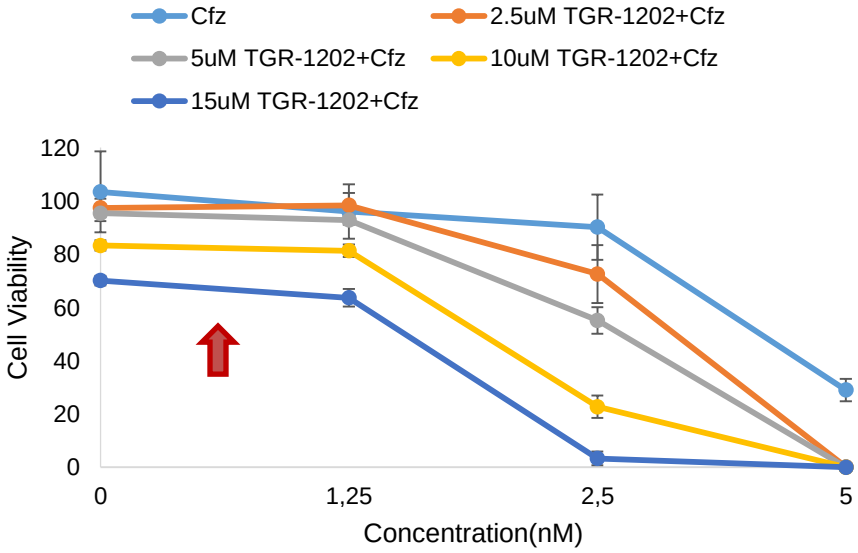
Rec-1_48 hrs



JVM-2_48 hrs



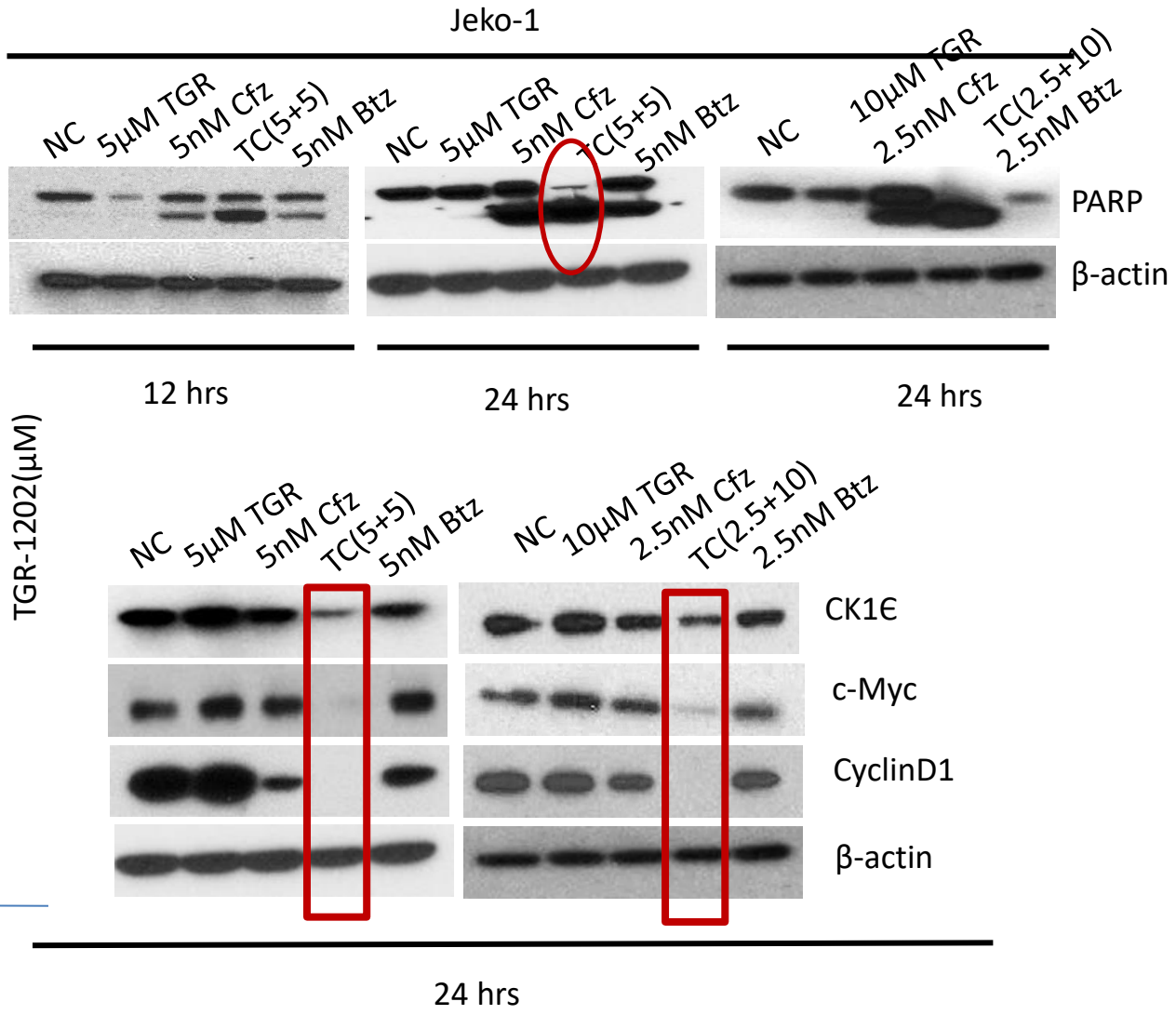
Z-138_48 hrs



TC is Synergistic and Superior to Comparators in Cleaving PARP and Eliminating c-Myc and Cyclin D1 in Mantle Cell Lymphoma

		1.25	2.5	5
Jeko-1	2.5	7.18	20.06	27.44
	5	9.75	25.52	39.46
	10	-0.61	9.23	26.02
Rec-1	2.5	-12.4	4.44	40.56
	5	-9.56	22.99	67.6
	10	-13.1	-6.92	40.31
Z-138	2.5	-2.86	-0.6	17.9
	5	-2.12	10.66	30.62
	10	-6.93	24.96	35.98
JVM-2	2.5	7.41	12.1	-0.74
	5	4.93	14.7	2.21
	10	5.12	13.09	9.95

Carfilzomib(nM)



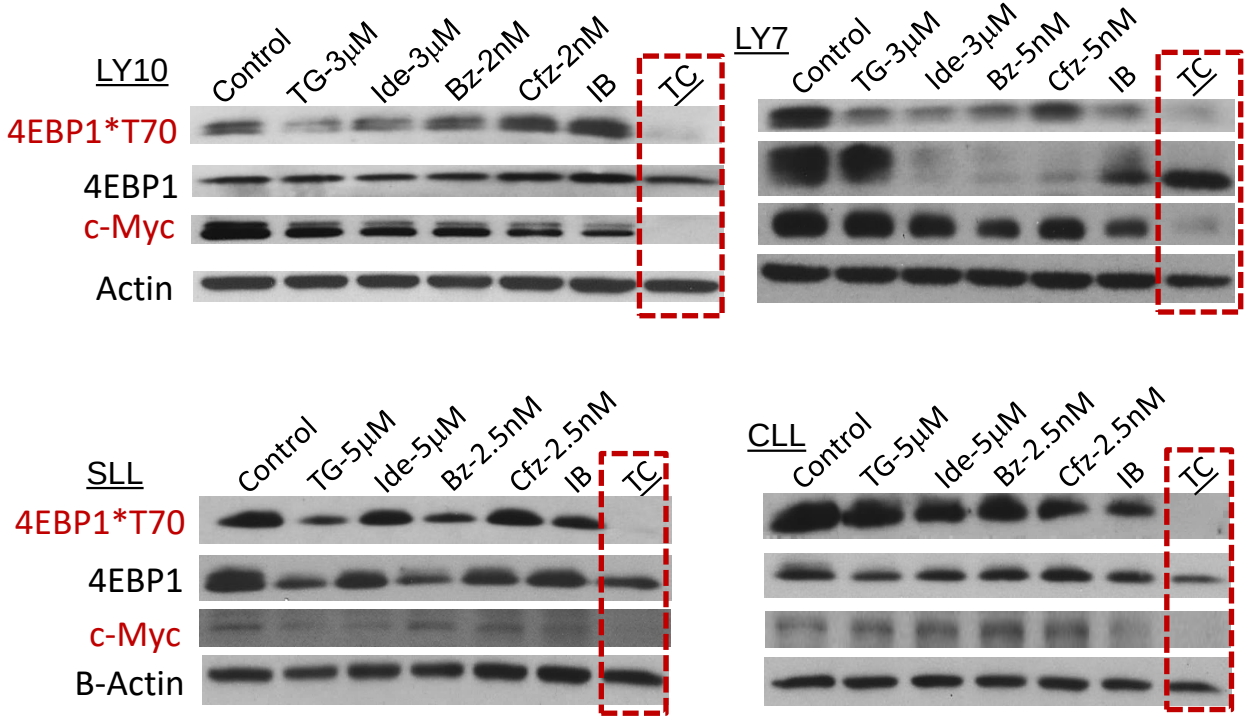
TC Is Highly Synergistic and Superior to Other Combinations

Summary of Findings

- TC is highly synergistic in 12 cell line models of DLBCL, MM, T-ALL, CTCL and Mantle Cell Lymphoma
- In MCL the combination eliminates c-myc and Cyclin D1
- TC is highly synergistic in primary CLL, MCL, and MZL cells.
- TC synergistically induces apoptosis.

Deng et al., Blood 2017

TC Uniquely and Synergistically Inhibits Translation of c-Myc and Phosphorylation of 4E-BP1

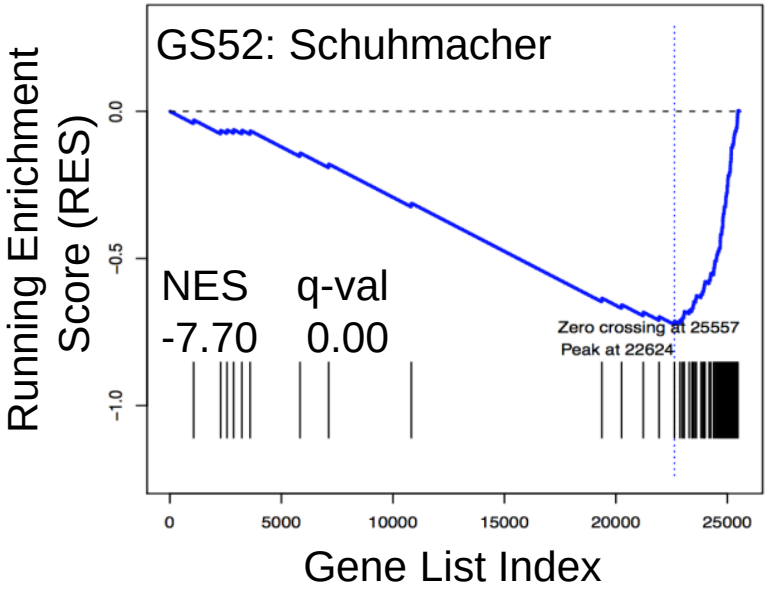


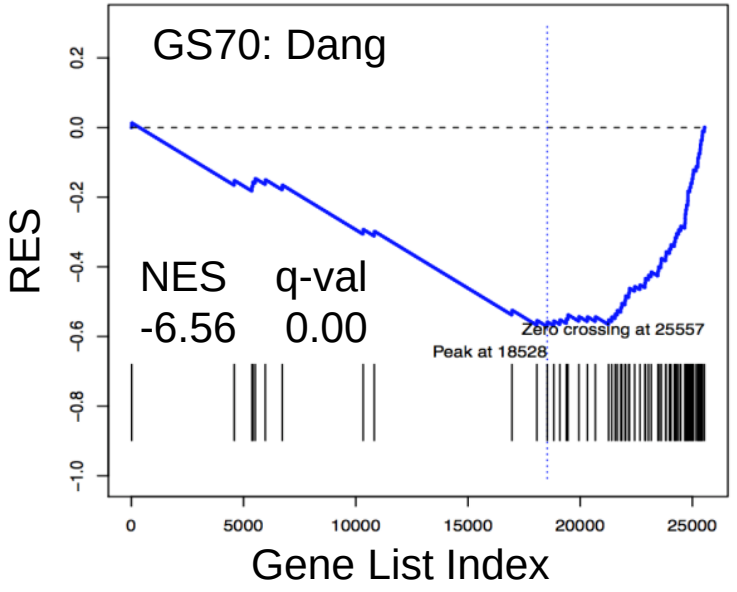
Additionally…..

- TC does not inhibit the mRNA level of c-Myc.
- A reporter of *MYC 5'UTR* confirms TC inhibits translation of c-Myc.

Deng et al., Blood 2017

TC Inhibits the Transcription of c-Myc Target Genes : GSEA Confirms c-Myc as Target





Additionally…

- Cytotoxicity of TC is rescued by forced overexpression of c-Myc.
- Cytotoxicity of TC is rescued by forced overexpression of eIF4E.

Deng et al., Blood 2017

TGR-1202 and carfilzomib, but not combinations of other drugs in the same class, synergistically inhibit c-Myc translation and c-Myc dependent gene transcription, by potently inhibiting phosphorylation of 4E-BP1.

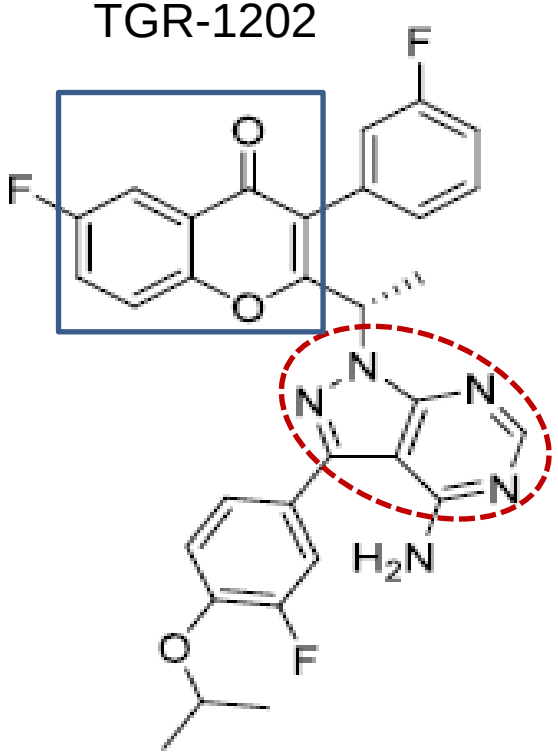
TGR-1202 and carfilzomib synergistically induce apoptosis In lymphoma cells through targeting c-Myc.

But, what accounts for the differences between the PI3 kinase inhibitors?

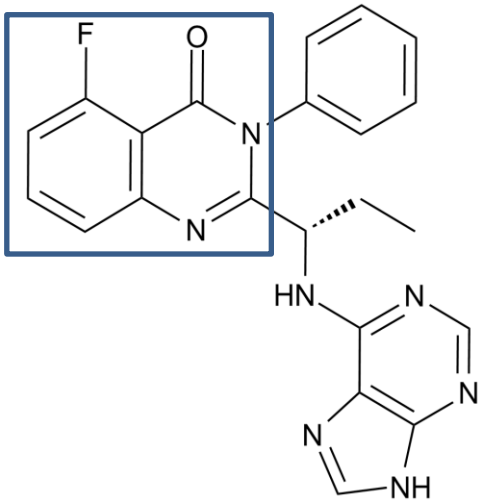
Deng et al., Blood 2017

TGR-1202 Is Structurally Distinct from Idelalisib and Duvelisib

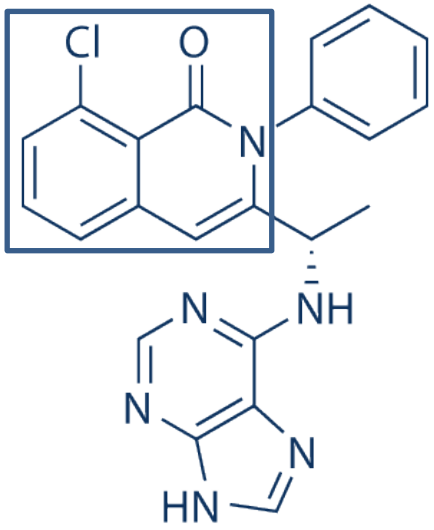
TGR-1202



Idelalisib



Duvelisib



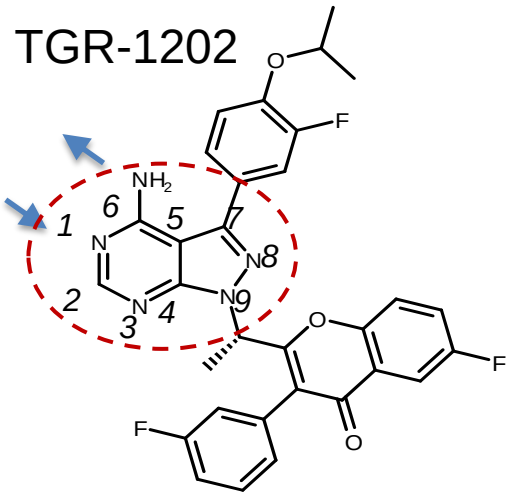
TGR-1202, but not Idelalisib or Duvelisib, Inhibits Casein Kinase 1 Epsilon (CK1e)

Kinase activity (% of control) using the Reaction Biology Kinome Profiling (i.e. functional) platform

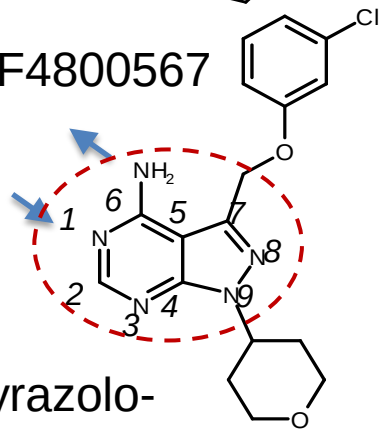
	TGR-1202		Idelalisib		Duvelisib	
Kinase	#1	#2	#1	#2	#1	#2
CK1a1	111	111	110	107	112	111
CK1a1L	105	103	102	101	104	99
CK1delta	105	98	96	104	100	97
CK1epsilon	*40*	*40*	*93*	*93*	*93*	*91*
CK1g1	99	98	105	105	102	98
CK1g2	104	104	102	100	99	99
CK1g3	96	95	94	93	93	93
CK2a	83	78	97	96	95	84
CK2a2	86	86	94	92	102	100

TGR-1202 and the CK1ε Inhibitor PF4800567 Share an Identical Structural Moiety

TGR-1202

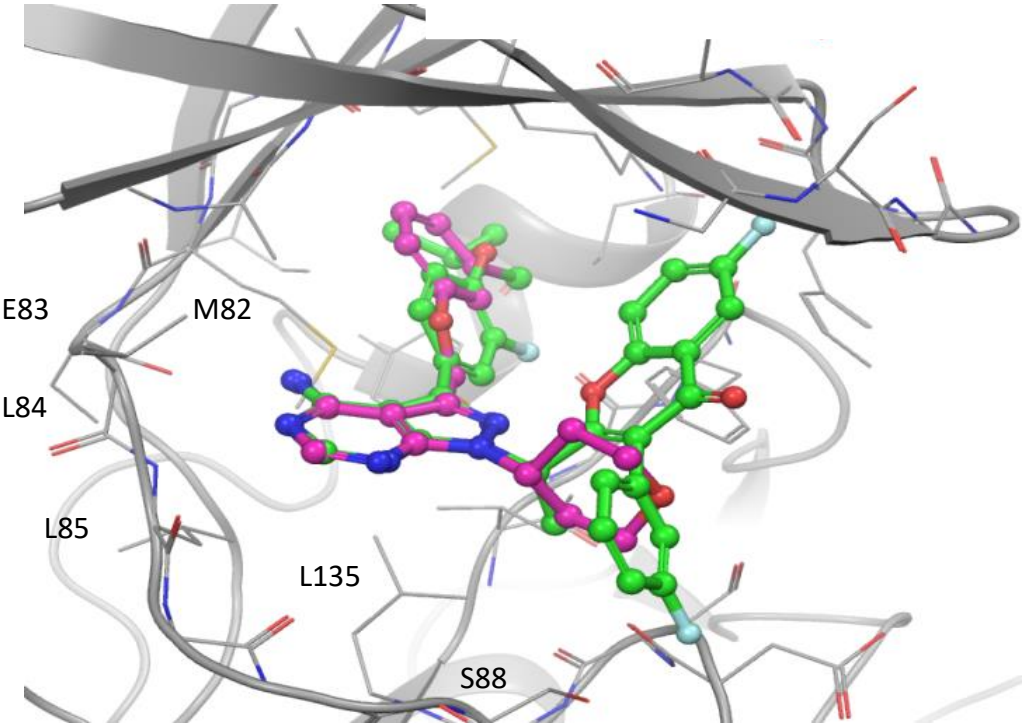


PF4800567

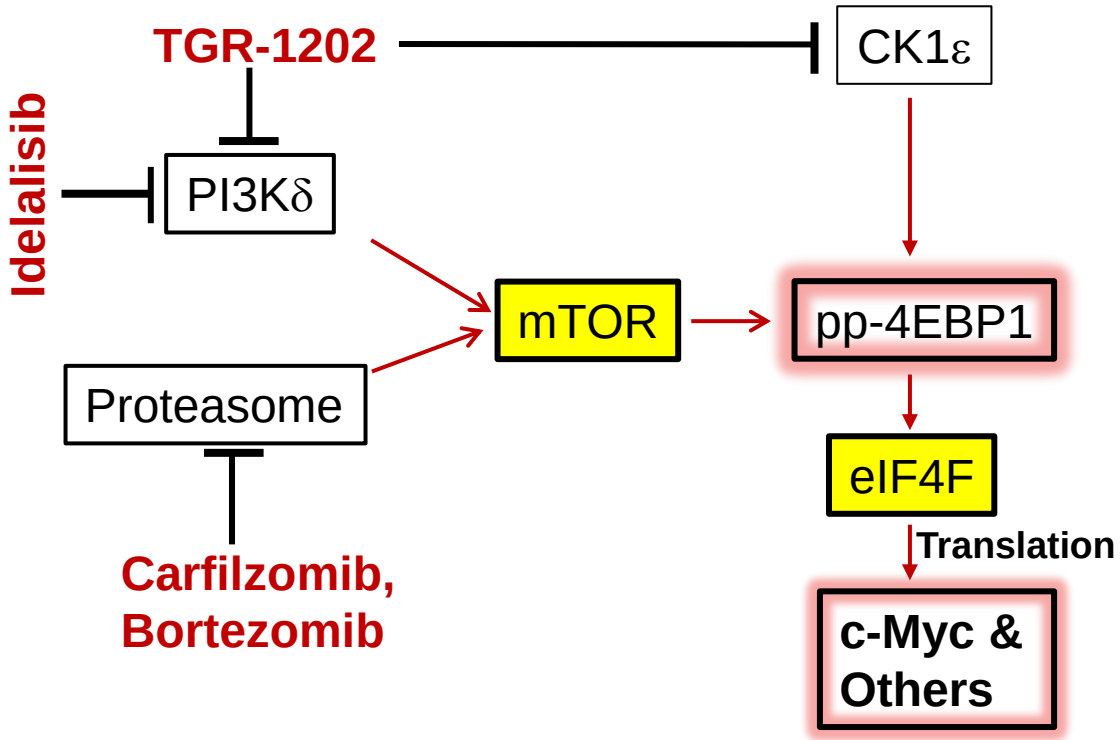


Central pyrazolo-pyrimidine moiety

PF4800567 (X-Ray)
TGR-1202 (*In silico* docking)



TGR-1202 as the First CK1ε Inhibitor Available for Patients May Have a Unique Therapeutic Role in c-Myc /Cyclin D1 Driven Lymphoma with Proteasome Inhibitors



NCT02867618: actively enrolling patients

Phase I/II Study of TGR-1202 and Carfilzomib in the Treatment of Patients with Relapsed or Refractory Lymphoma

Novel Targets/Therapies: Proteasome Inhibitors

- 20 years later, we have much to learn about how these drugs work
- These drugs are pleiotropic drugs, MOA may be very cell context specific (i.e, MCL-1, NOXA, etc.) but others exist too
- Proteasome inhibitors are the prototypical companion drug; they synergize with almost everything…..
- Espicially ….targeting the proteasome with unique PI3K inhibitors could emerge as a novel c-myc targeted strategy

Center for Lymphoid Malignancies at Columbia University Medical Center

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Thank You!

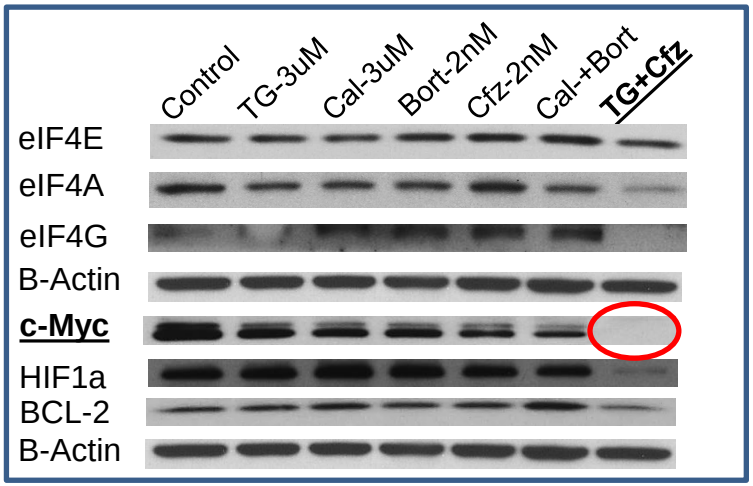
Columbia University Medical Center

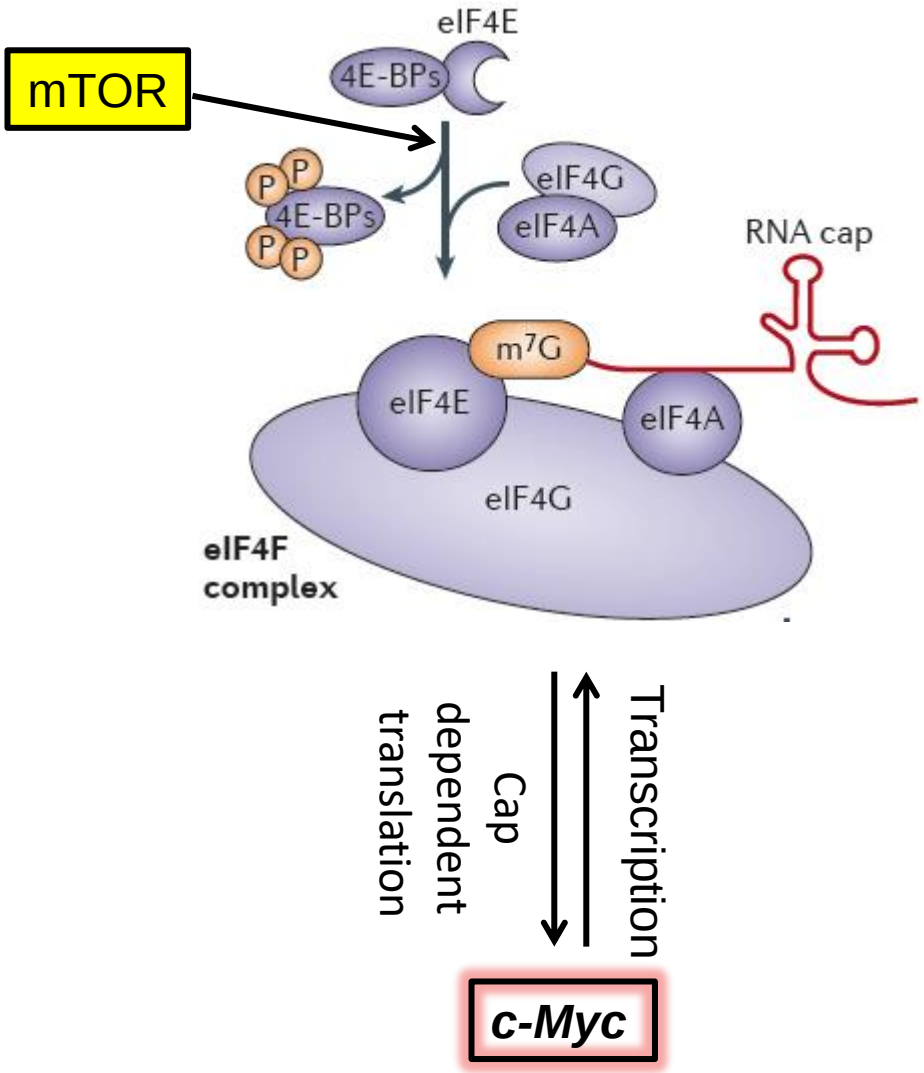
NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

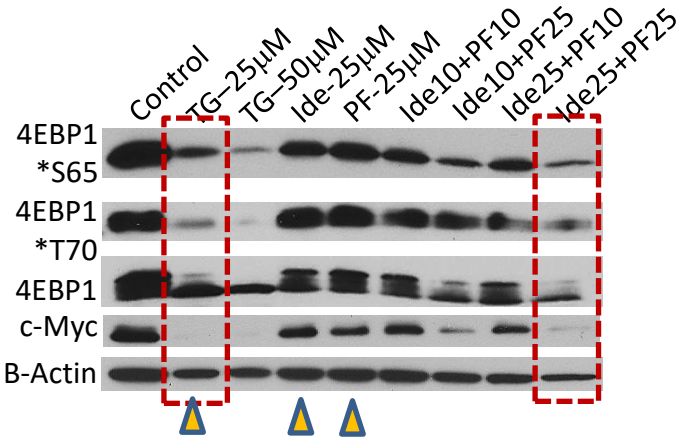
TARGETING THE EIF4E COMPLEX AS A MEANS TO 'TURN-OFF' C-MYC

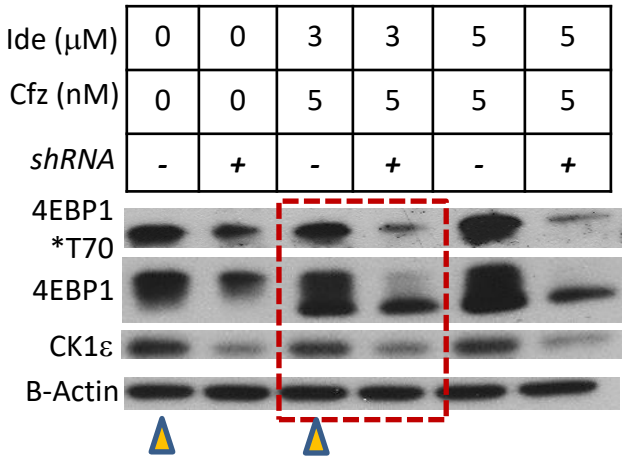
(LY10 DLBCL)





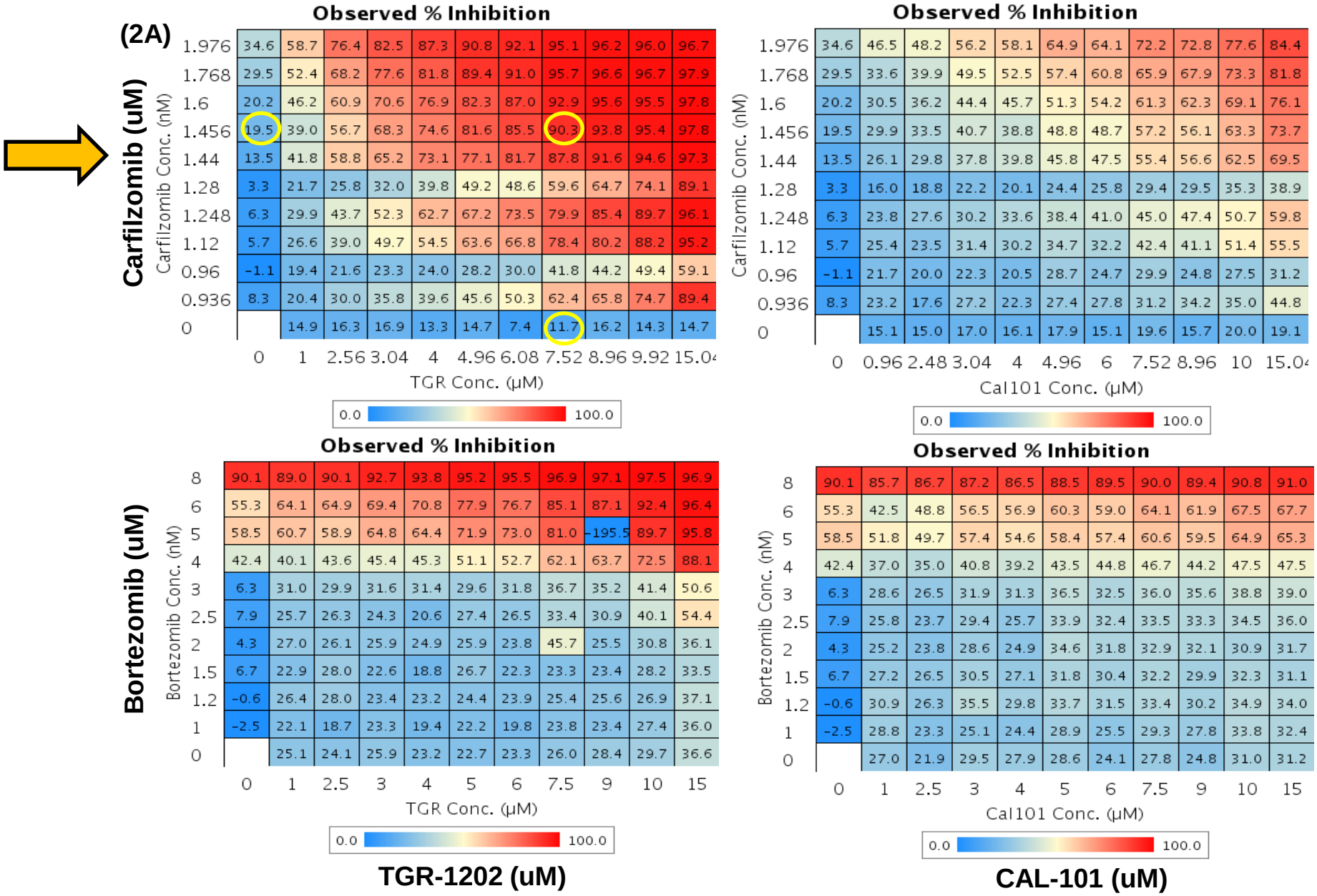
Dual Targeting of PI3Kδ and CK1ε Underscores the Unique Activity of TGR-1202 in DLBCL



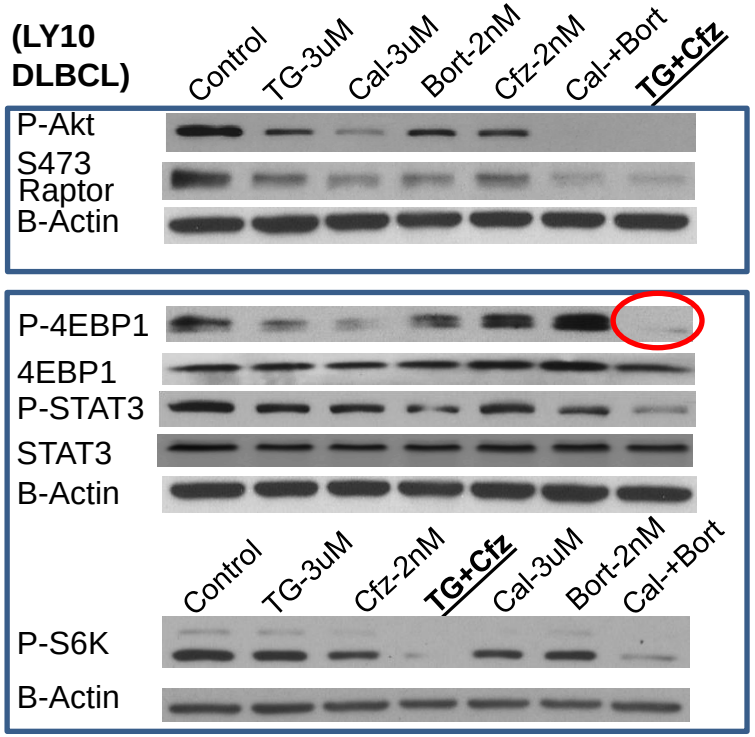


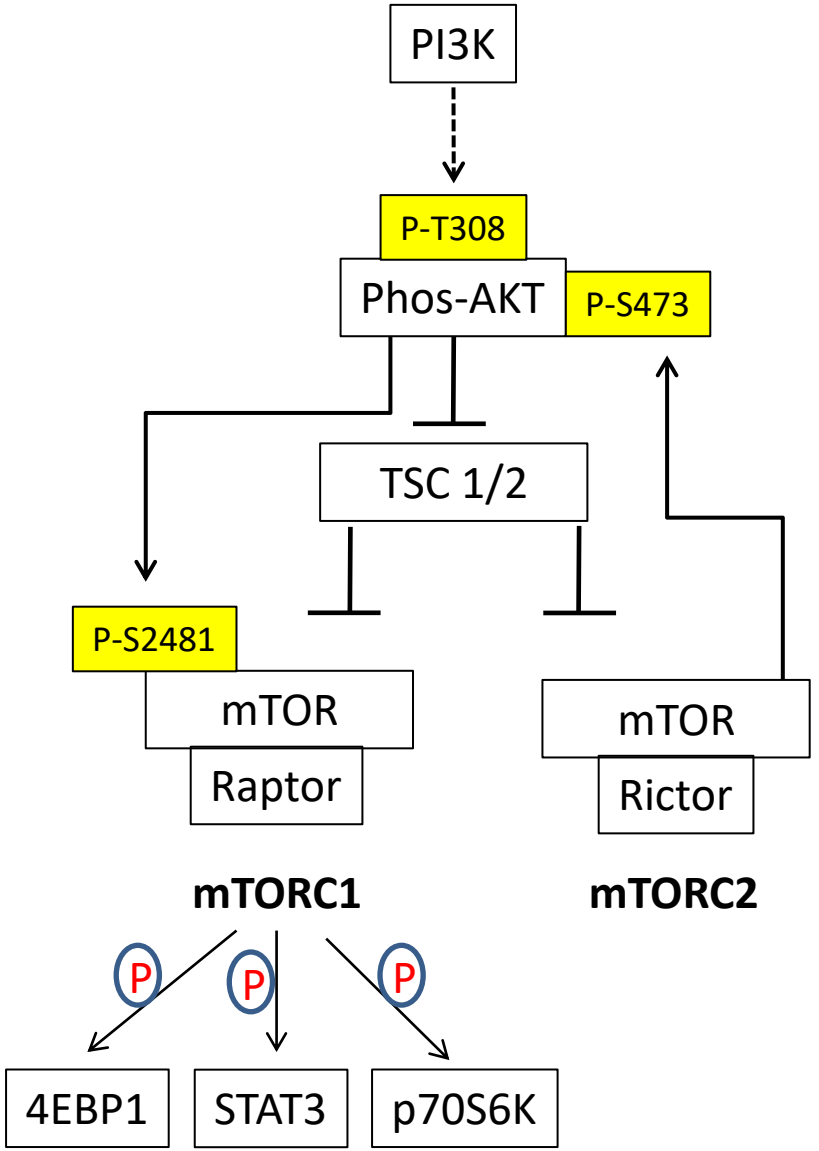
CARFILZOMIB AND TGR-1202 DEMONSTRATES HIGHEST SYNERGY

(2A)



THE COMBINATION OF CAR – TGR-21202 UNIQUE TURNS OFF P4EBP1

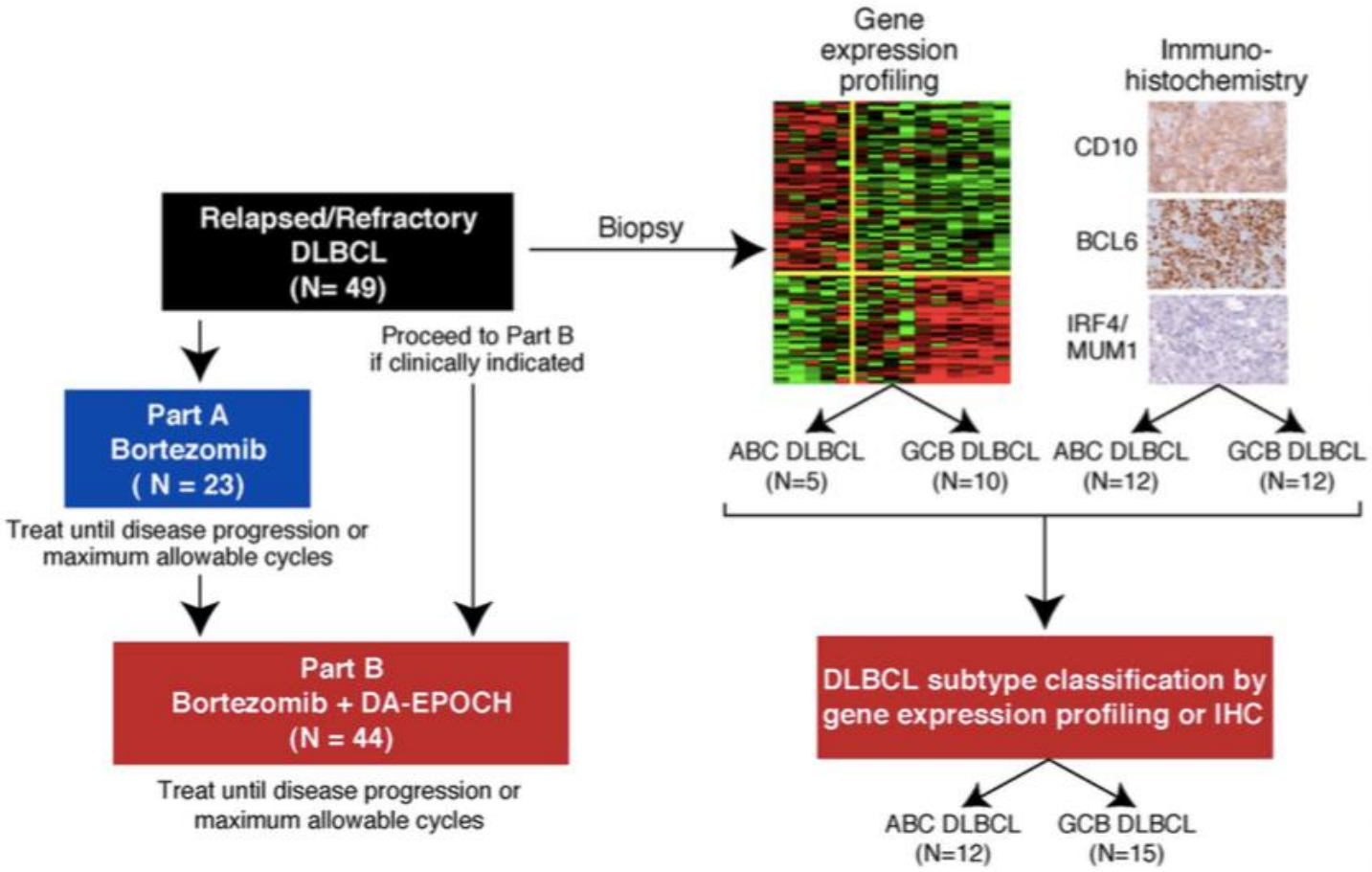




Novel Targets/Therapies: Proteasome Inhibitors

- Proteasome Inhibitors and the Proteasome : A Gentle Reminder
- Mantle Cell Lymphoma
- Indolent Lymphomas
- Diffuse Large B-Cell Lymphoma
- Peripheral T-Cell Lymphoma
- Summary: Novel - Novel Prospects

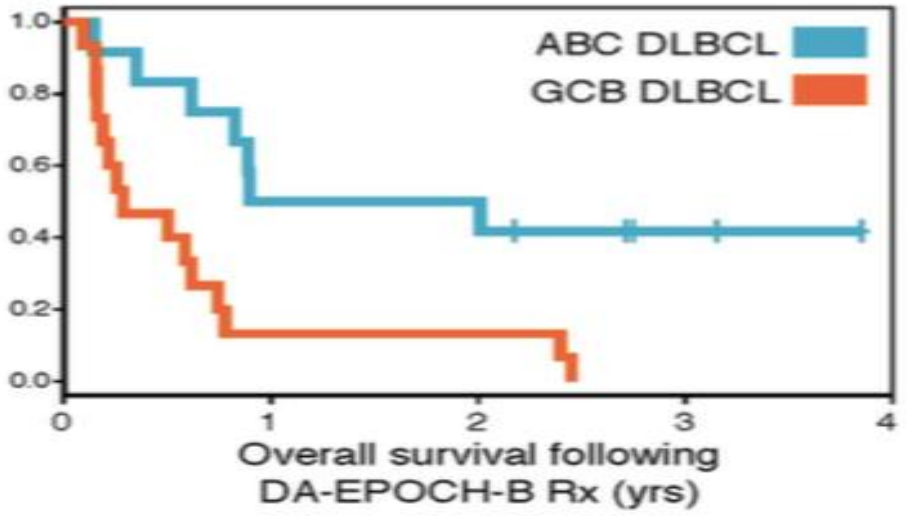
Bortezomib in Relapsed/Refractory DLBCL

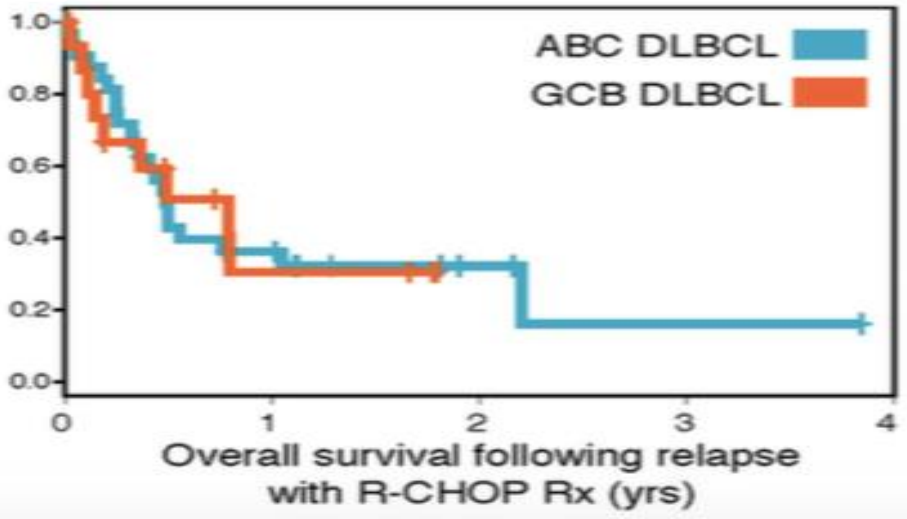


Dunleavy et al. Blood 2009.

Bortezomib plus DA-EPOCH-R in Relapsed DLBCL

	ORR	CRR	OS
All	42%	23%	8 mo
ABC	83%	42%	11 mo
GCB	13%	7%	3 mo

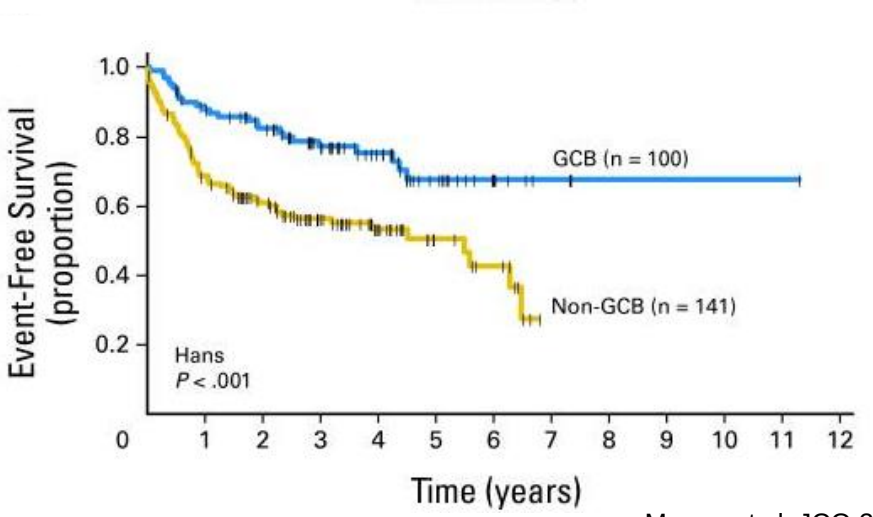




Dunleavy et al. Blood 2009.

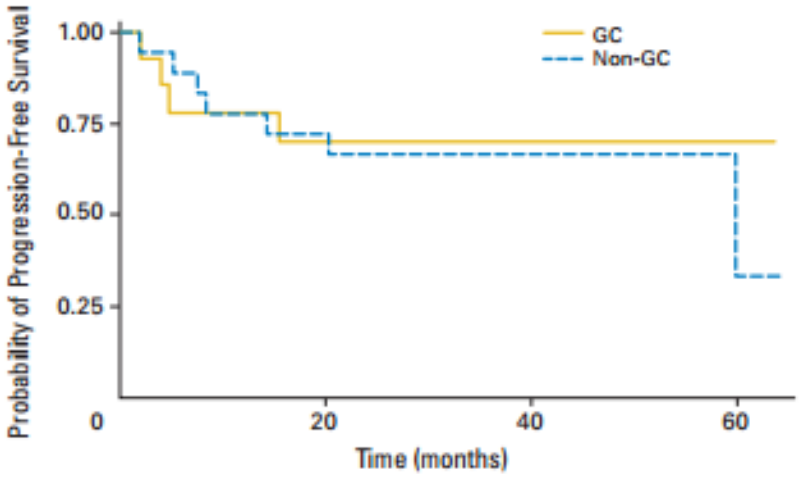
BENEFIT OF BORTEZOMIB IN FRONT-LINE?

R-CHOP



Meyer, et al. JCO 2010

R-CHOP-bortezomib



Ruan et al. JCO 2011

Await results from randomized trials: *PYRAMID, LYM2034, REMoDLB*

Randomized Phase 2 Open Label Study of R-CHOP +/- Bortezomib in Patients with Untreated Non-GCB DLBCL:

Results from the Pyramid Trial

- Non-GCB DLBCL measurable disease confirmed by Hans.
- R-CHOP vs VR-CHOP (Bortezomib 1.3 mg/m2 Day 1 & 4)
- Primary ednpoint : PFS

- 206 patients randomized at 69 sites; 183 had centrally confirmed non-GCB DLBCL)
- 86% and 85% of patients complete study per treatment

Randomized Phase 2 Open Label Study of R-CHOP +/- Bortezomib in Patients with Untreated Non-GCB DLBCL: Results from the Pyramid Trial

Parameter	R-CHOP	VR-CHOP	HR
ORR/CR	98/52	92/54	
2-Y PFS	77%	82%	0.77; p=0.7
HI/H IPI 2-Y PFS	64%	72%	0.66; p = 0.3
Died	15%	11%	0.65
HI/H-2 Y OS	79	92	
2-Y-OS L/LI	98%	98%	

Conclusion: No significant efficacy advantage with theaddition of R-CHOP in patients with previously untreated non-GCB DLBCL

Novel Targets/Therapies: Proteasome Inhibitors

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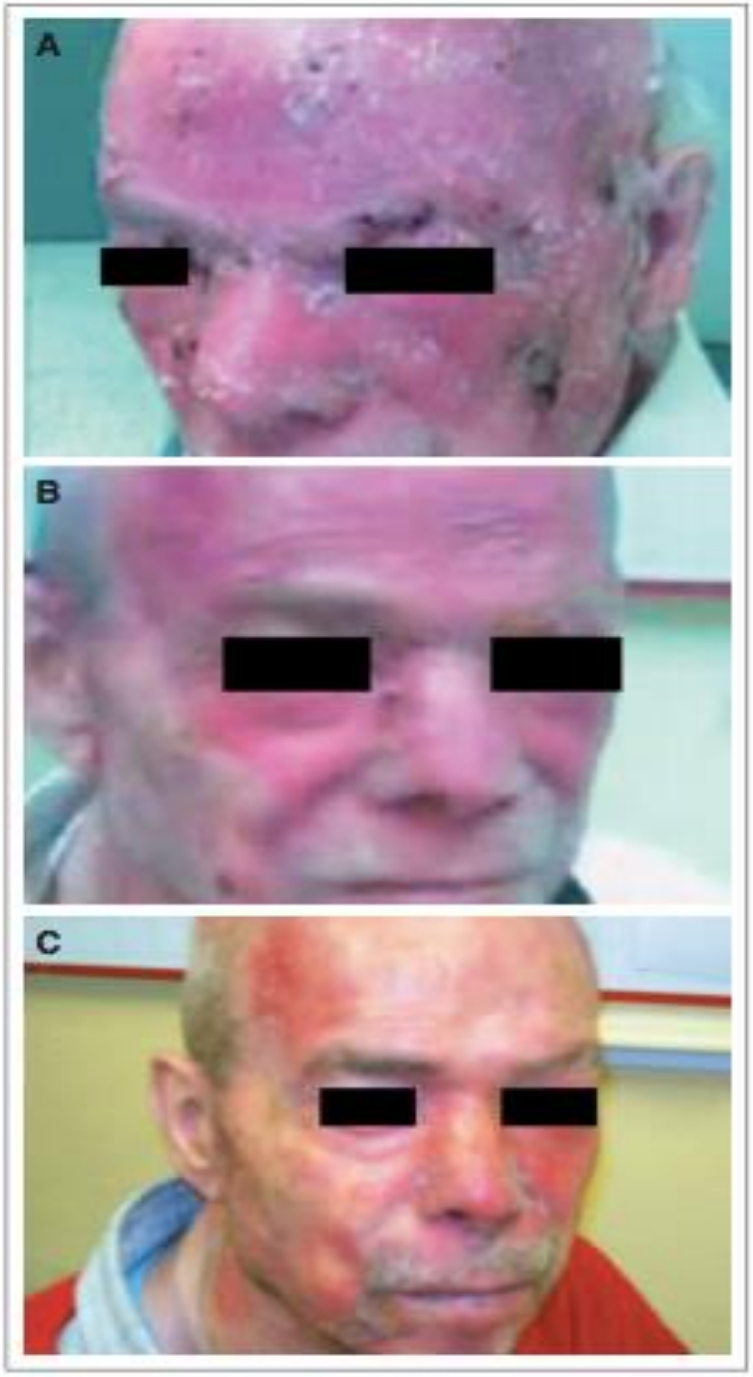
For the T-Cell Enthusiasts

- N=12
  - 10 Mycosis Fungoides,
  - 2 PTCLu
- ORR 67%
- CR Rate 17%



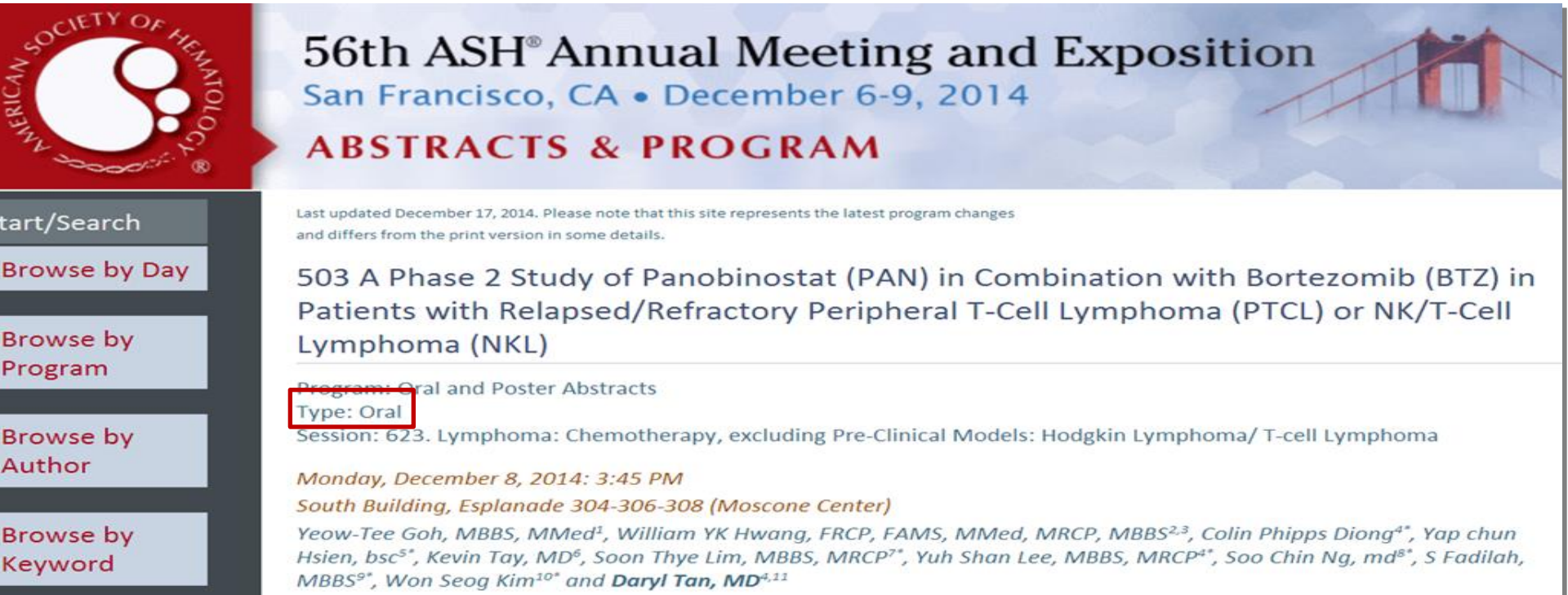
Zinzani et al. JCO 2007

THE LANCET Haematology

Articles

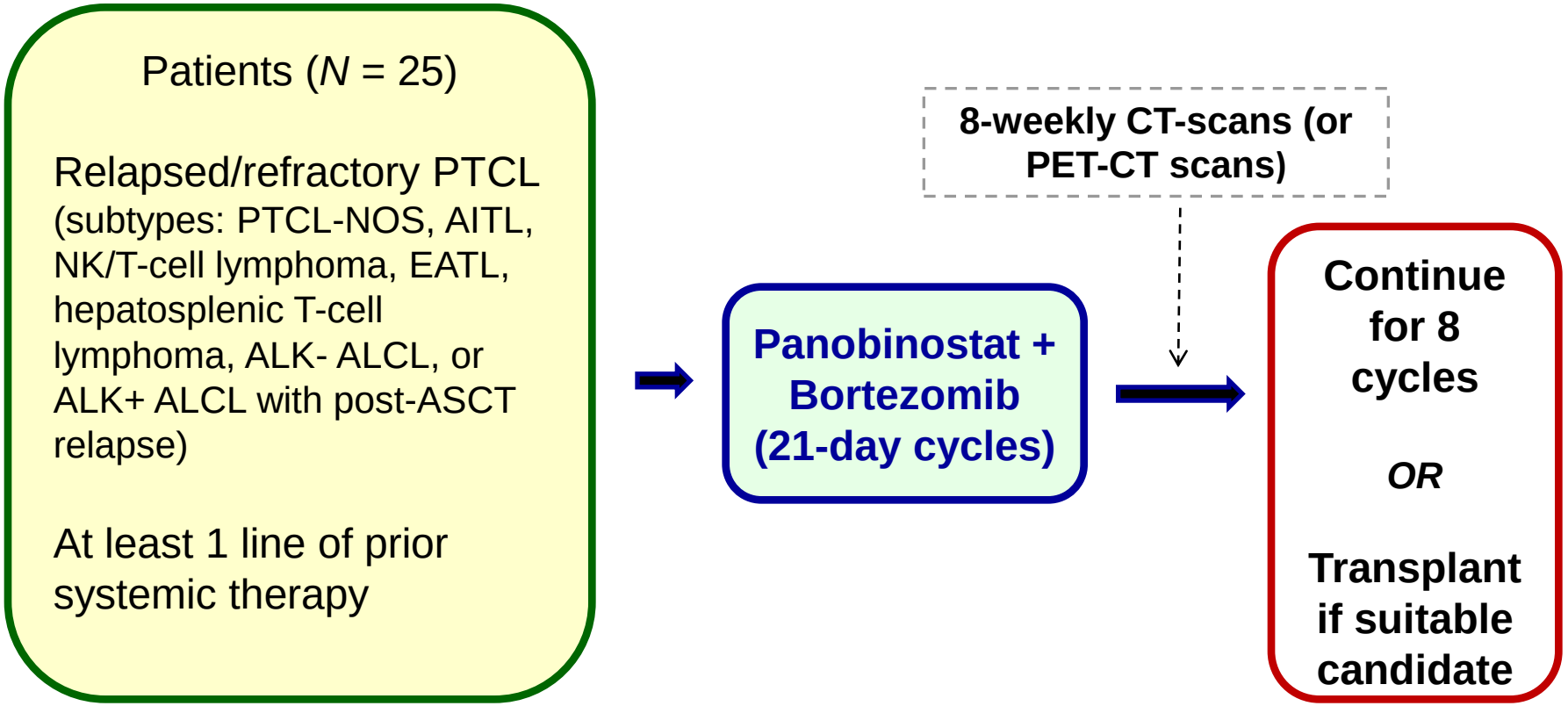
Panobinostat in combination with bortezomib in patients with relapsed or refractory peripheral T-cell lymphoma: an open-label, multicentre phase 2 trial

Daryl Tan, Colin Phipps, William Y K Hwang, Soo Yong Tan, Chun Hsien Yeap, Yiong Huak Chan, Kevin Tay, Soon Thye Lim, Yuh Shan Lee, Sathish Gopalakrishnan Kumar, Soo Chin Ng, S Fadilah, Won Seog Kim, Yeow Tee Goh, for the SGH651 investigators



Study Schema of SGH 651

PHASE II, MULTI-NATIONAL, OPEN LABEL, SINGLE-ARM, INVESTIGATOR-INITIATED STUDY (NCT00901147).



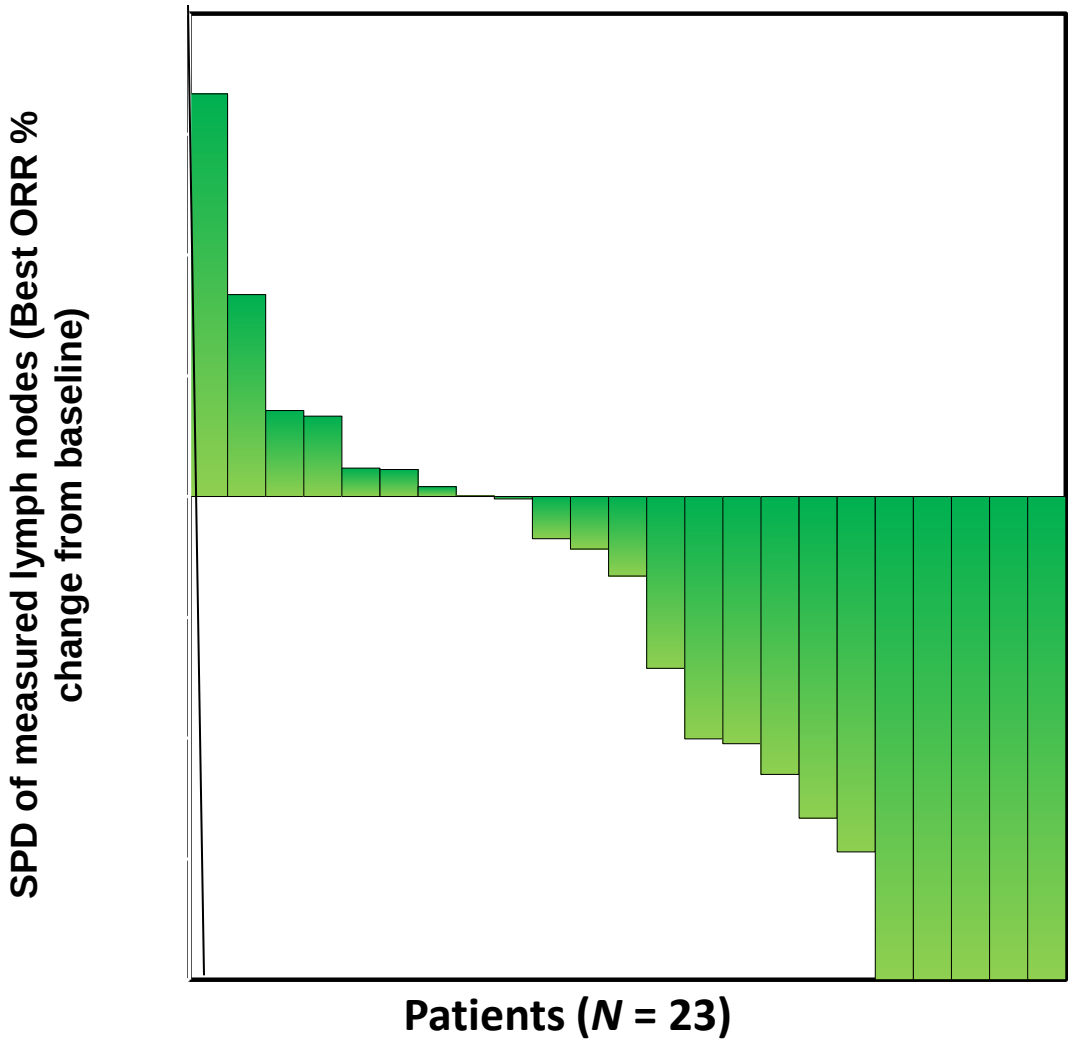
- Primary endpoint: Objective Response Rate (ORR)
- Secondary endpoints: Time-to-response, duration of response, PFS, OS, safety and tolerability

PRIMARY ENDPOINT: OBJECTIVE RESPONSE RATE

Response	N=23 (%)
ORR	**10 (43)**
CR	**5 (22)**
PR	**5 (22)**
SD	**5 (22)**
PD	**8 (35)**
Histological Subtypes	
PTCL-NOS	2/9 (22)
Angioimmunoblastic T-cell lymphoma	4/8 (50)
ALK+ Anaplastic large cell lymphoma	1/1 (100)
ALK- Anaplastic large cell lymphoma	1/4 (25)
NK/T-cell lymphoma, nasal type	1/2 (50)
Subcutaneous panniculitis-like T-cell lymphoma	1/1 (100)

SGH protocol 651

Waterfall Plot
Time-to-Response & Duration of Response



- Median time to response : 6 weeks (range 5 – 18)
- Median duration of response : 5.6 months (range 2 – 33)

SGH protocol 651

Novel Targets/Therapies: Proteasome Inhibitors

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- Peripheral T-Cell Lymphoma
- Summary: Novel - Novel Prospects

Ongoing Studies with Additional Novel Agents

- Bortezomib and Lenalidomide in Treating Patients With Relapsed or Refractory Mantle Cell Lymphoma
- Phase I/II Carfilzomib Plus Lenalidomide and Rituximab in the Treatment of Relapsed/Refractory Mantle Cell Lymphoma
- Bortezomib + obatoclax in MCL
- Ibrutinib in Combination With Carfilzomib in Relapse/Refractory Mantle Cell Lymphoma
- Bortezomib and Azacitidine in Relapsed or Refractory T-Cell Lymphoma
- Everolimus and Bortezomib in Relapsed or Refractory Lymphoma
- Ibrutinib and Bortezomib to Treat Patients With Mantle Cell Lymphoma
- Alisertib, Bortezomib, and Rituximab in Relapsed or Refractory Mantle Cell Lymphoma or B-cell Low Grade Non-Hodgkin Lymphoma

Phase II Combinations in MCL

	Dose	n	ORR	CRR	PFS
Previously treated					
BBR	Friedberg et al Blood 2011	30 (7 MCL)	83%	52%	3y 47%
Initial Therapy					
VcR-CVAD + maint R	Chang et al Blood 2014	75	95%	68%	3y 68%
RiBVD	Gressin et al Proc ASH 2014	74	nr	74%	2y 69%

LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

Overall safety profile

AE, % (safety population)	R-CHOP (n=242)	VcR-CAP (n=240)
All-grade AE	98	99
Drug-related all-grade AE	93	96
Grade ≥3 AE	85	93
Drug-related grade ≥3 AE	80	91
Serious AE	30	38
Drug-related serious AE	21	33
AE leading to discontinuation	7	9
Drug-related AE leading to discontinuation	6	8
On-study deaths (within 30 days of last dose)	6	5
Deaths due to drug-related AE	3	2

- Pts received a median of 6 cycles (1-8) in each arm
- 83% in R-CHOP arm and 84% in VcR-CAP arm received ≥6 cycles

Cavalli F et al. ASCO 2014, abstract #8500

LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

Grade ≥3 AE and SAE (≥5% in either arm)

AE, % (safety population)	R-CHOP (n=242)	VcR-CAP (n=240)
At least one grade ≥3 AE	**85**	**93**
Neutropenia	67	85
Leukopenia	29	44
Thrombocytopenia	6	57
Lymphopenia	9	28
Anemia	14	15
Febrile neutropenia	14	15
Pneumonia	5	7
Fatigue	3	6
Peripheral sensory neuropathy	3	5
Diarrhea	2	5
At least one SAE	**30**	**38**
Febrile neutropenia	8	11
Pneumonia	3	8
Neutropenia	5	5

- Grade ≥3 bleeding events: 1.2% R-CHOP vs 1.7% VcR-CAP
- Grade ≥3 infections: 14% R-CHOP vs 21% VcR-CAP

Cavalli F et al. ASCO 2014, abstract #8500

VR-CAP versus R-CHOP as initial therapy

	n	ORR	CRR
R-CHOP	244	89%	42%
VR-CAP	243	92%	53%

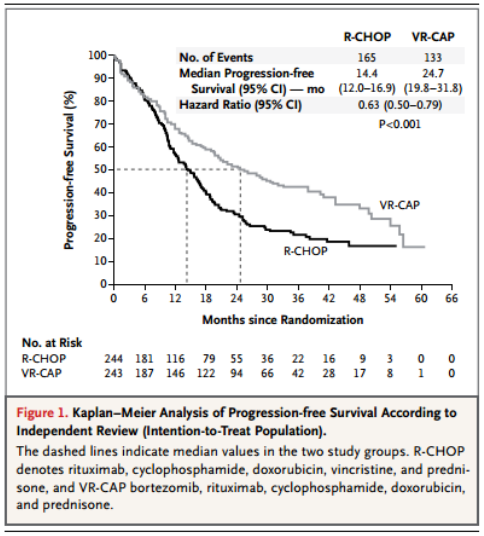


Figure 1. Kaplan–Meier Analysis of Progression-free Survival According to Independent Review (Intention-to-Treat Population).
The dashed lines indicate median values in the two study groups. R-CHOP denotes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, and VR-CAP bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

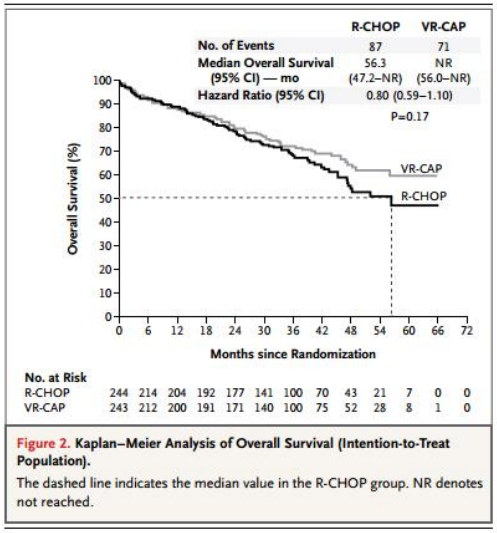


Figure 2. Kaplan–Meier Analysis of Overall Survival (Intention-to-Treat Population).
The dashed line indicates the median value in the R-CHOP group. NR denotes not reached.

Table 3. Most Common Adverse Events (Safety Population).*

Adverse Event	R-CHOP (N=242)		VR-CAP (N=240)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	no. of patients (%)			
Any event	238 (98)	206 (85)	238 (99)	223 (93)
Hematologic event				
Neutropenia	178 (74)	162 (67)	211 (88)	203 (85)
Thrombocytopenia	46 (19)	14 (6)	173 (72)	136 (57)
Anemia	90 (37)	33 (14)	122 (51)	37 (15)
Leukopenia	93 (38)	71 (29)	120 (50)	105 (44)
Lymphocytopenia	32 (13)	21 (9)	74 (31)	67 (28)
Febrile neutropenia	34 (14)	33 (14)	41 (17)	36 (15)
Gastrointestinal event				
Diarrhea	22 (9)	5 (2)	73 (30)	12 (5)
Constipation	38 (16)	2 (1)	60 (25)	1 (<1)
Nausea	33 (14)	0	59 (25)	1 (<1)
Infection or infestation				
Any	112 (46)	33 (14)	143 (60)	51 (21)
Pneumonia	15 (6)	11 (5)	28 (12)	17 (7)
Nervous system disorder				
Peripheral neuropathy not elsewhere classified†	69 (29)	10 (4)	73 (30)	18 (8)
Peripheral sensory neuropathy	48 (20)	6 (2)	54 (22)	12 (5)
Other condition				
Pyrexia	37 (15)	5 (2)	70 (29)	8 (3)
Fatigue	47 (19)	6 (2)	56 (23)	15 (6)
Cough	20 (8)	0	49 (20)	3 (1)
Decreased appetite	23 (10)	2 (1)	46 (19)	2 (1)
Asthenia	26 (11)	2 (1)	38 (16)	7 (3)
Peripheral edema	25 (10)	1 (<1)	37 (15)	1 (<1)

Robak et al NEJM 2015

LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

Peripheral neuropathy NEC*

	R-CHOP (n=242)	VcR-CAP (n=240)
Peripheral neuropathy*, %	29	30
Grade ≥3 peripheral neuropathy, %	4.1	7.5
Treatment discontinuations, %	<1	2
Median time to onset, days (range)	52 (2–158)	83 (8–256)
Events improved/resolved, %	79	90
Events resolved, %	75	81
Median time to improvement/resolution, months (95% CI)	4.8 (2.8, 6.4)	1.5 (0.9, 2.0)
Median time to resolution, months (95% CI)	5.5 (3.9, 8.1)	3.0 (1.6, 4.7)

*Peripheral neuropathy NEC, high-level term including peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Cavalli F et al. ASCO 2014, abstract #8500

LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

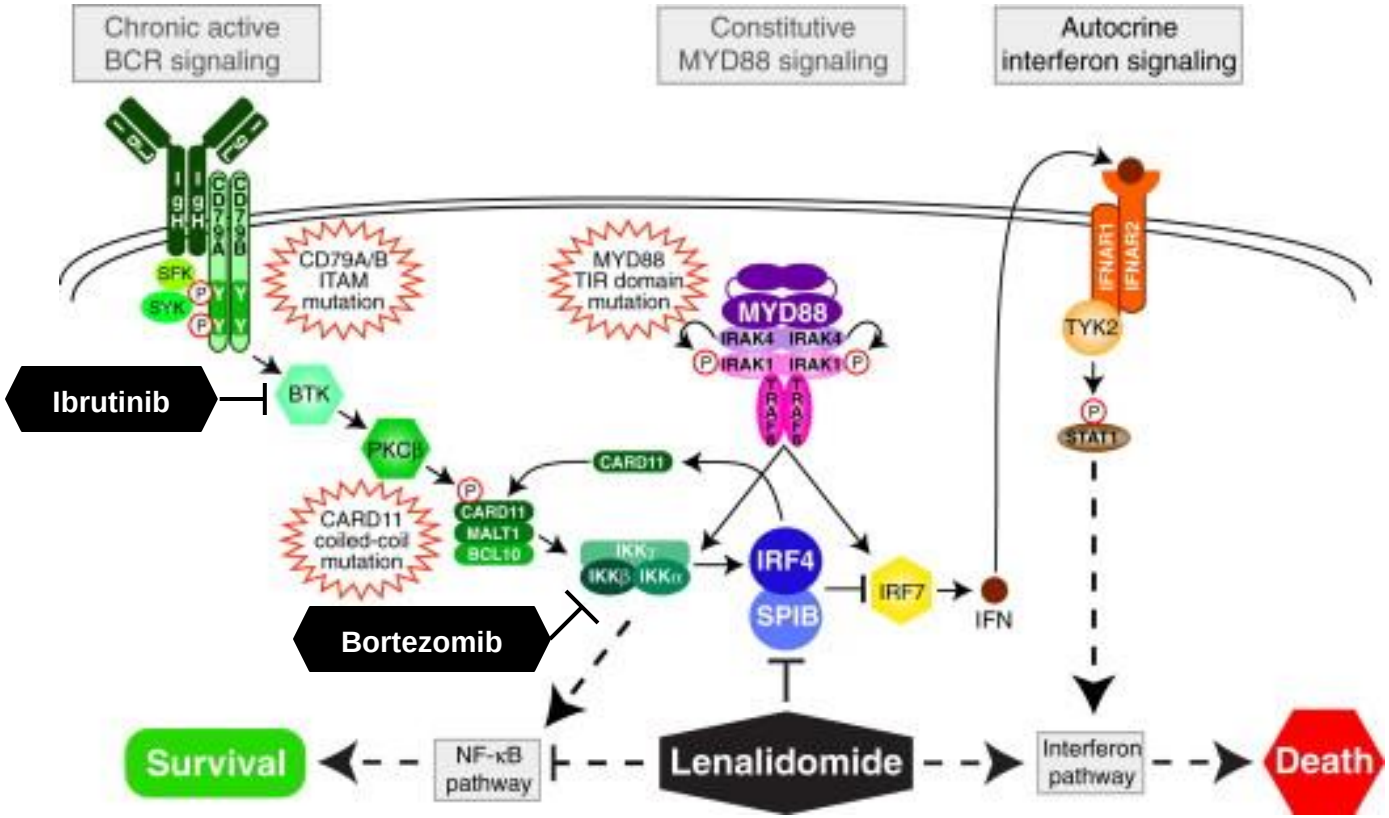
- **Endpoints:** *Primary*: PFS as measured by an independent radiology review committee (IRC). *Secondary*: response by modified IWG criteria[1] [ORR (CR+CRu+PR) and complete response (CR+CRu), TTR, DOR, duration of CR+CRu, TTP, TTNT, TFI, OS, and AE
- **Patients:** 487 pts with previously untreated, measurable stage II-IV MCL, ECOG PS 0-2, ineligible or non considered for SCT

ITT population		R-CHOP (N=244)	VcR-CAP (N=243)
Age	Median, yrs (range) >60 yrs, % (range) >65 yrs, % (range)	66 (34-82) 73 55	65 (26-88) 73 53
ECOG PS, %	0 1 2	35 52 13	46 42 13
IPI score, %	0-1 2 3 4-5	16 29 36 19	16 31 35 19
Disease stage at diagnosis, %	II III IV	7 20 74	6 20 75

1. Cheson et al. JCO 2007

Cavalli F et al. ASCO 2014, abstract #8500

SUBSET-DIRECTED THERAPY IN ABC-DLBCL



Modified from Yang et al. Cancer Cell 2012