Potential Novel Upfront Treatment Paradigms for Patients with PTCL

Owen A. O'Connor, M.D., Ph.D.

Director, Center for Lymphoid Malignancies
Professor of Medicine and Developmental Therapeutics
The New York Presbyterian Hospital
Columbia University College of Physicians and Surgeons
New York, N.Y.

1st Postgraduate Lymphoma Conference
Rome, Italy
March, 2105

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

Potential Novel Upfront Treatment Paradigms for Patients with PTCL

- Strategies for Up-Front Management
- Targeting Epigenetic Operations in TCL: An HDACi Backbone
- Novel Doublet Based Regimens
  - Hypomethylating agents and HDAC inhibitors
  - Pralatrexate and HDAC inhibitors
  - Aurora Kinase Inhibitor and HDAC inhibitors
- Next Steps

Is Adding Any Drug to a CHOP Backbone the Answer?

Addition Drug	No. of Patients	ORR CR Rate	OS	PFS/DOR	Comments
CAMPATH (Gallamini et al. 2007)	24	75% 71%	53% @ 2 yrs	2 year FFS = 48%	Med F/U = 16 months Infections common CMV (9%)reactivation
CAMPATH (Kim et al. 2007)	20	80% 65%		1 year EFS = 43%	Med F/U = 8 months Febrile neutropenia (55%), CMV (25%)
Bortezomib (Kim et al. 2012)	46	76% 65%	47% @ 3yrs	3 year PFS = 35%	Well tolerated Minimal neuropathy
Denileukin difitox (Foss et al. 2013)	49	65% 55%	65% @ 2 yrs	Me.d PFS = 12 months 2 year PFS 42%	Med F/U = 22 mo
Vorinostat (Oki et al. 2013)	12 evaluable	100% ? 100% ?	Not reached	2 year PFS = 79% Med PFS = 31 months	Phase 1 Med F/U = 27 months
Everolimus (Kim et al. 2013	15	100% 57%	Not reported	13/14 patients relapsed immediately after or shortly after therapy	Phase 1 study Limited duration of benefit data
Bevacizumab (Ganjoo et al. 2014)	44 evaluable	90% 49%	Med OS = 22 months	1 year PFS = 44% Med. PFS = 7.7 months	Med F/U = 3 years
Romidepsin (Cupuis et al. 2014)	35	68% 51%	At 18 months = 76%	18 month PFS = 57%	Med F/U = 17.5 months 18 mo PFS 57% 3 pts had significant cardiac events

International PTCL Project:
At 5 year, OS = 32% and FFS = 22%

Strategies to Advance the Front-Line Treatment of PTCL

CHOP Addition Studies

Pros	Cons
Relatively easy to do	Does adding 1 drug to 4 make real difference?
THE regulatory path	Backbone widely considered poor
Assures 'some' SOC component to care	Toxicity of 4 - drug combo could limit new drug dosing
Lots of experience with the regimen in lymphoma	Its CHOP

Novel : Novel Platforms

Pros	Cons
Exploits drugs with established activity in disease	Starting from scratch
Can target specific pathways/lesions	Takes time……
Prospects for precision therapy (CD30, TET2, IDH2)	Completely unknown efficacy and toxicity
Could produce viable options in front-line and R/R setting	Rare disease mandates larger collaborations

Single Agents for Relapsed or Refractory Peripheral T-cell Lymphoma <100 Patients Accrued in 17 Years!

- Limited data for single-agent treatment of relapsed/refractory NHL
  - Most studies are small, uncontrolled, and single center
  - No central review of histology or response rate
  - Accrued PTCL patients across all studies (1991-2008) = 88 (5/yr)

Where is the data that other drugs are equivalent??

Agent	Author, year*	Total pts accrued	No. PTCL accrued	Response in PTCL	Single or multi-center
Pentostatin	Dearden, *Br J Cancer* 1991	68	6	0/6	single
Gemcitabine	Zinzani, *Ann Oncol* 1998	13	8	5/8	single
Gemcitabine	Sallah, *Br J Haematol* 2001	10*	4		single
Alemtuzumab	Enblad, *Blood* 2004	14	14	5/14	multi-center
Pentostatin	Tsimberidou, *Cancer* 2004	42	8		single
Denileukin	Dang, *Br J Haematol* 2006	27	27	13/27	single
Bortezomib	Zinzani, *JCO* 2007	12	2	1/2	single
Lenalidomide	Reiman, *Blood* 2007	10	10	4/10	multi-center
Nelarabine	Czuczman, *Leuk Lymphoma* 2007	19	8	1/8	multi-center
Pralatrexate	O'Connor, *JCO,* 2009	57	30	14/26	single

Single Agents for Relapsed or Refractory Peripheral T-cell Lymphoma 492 Patients in Last 6 years

- Single-agent treatment of relapsed/refractory PTCL
  - Studies mostly conducted in PTCL
  - Mostly multicenter
  - About 82 patients per year

Agent	Author, Journal, Year	Total pts accrued	No. PTCL accrued	Response in PTCL	Single or multi-center
Pralatrexate	O'Connor, JCO, 2009 (Phase 1)	57	30	14/26 (54%)	Single
Pralatrexate	O'Connor, JCO, 2011	109	109	32/109 (29%)	Multi-center
Romidepsin	Piekarz Blood, 2011	47	47	17/45 (38%)	Multi-center
Romidepsin	Coiffier, JCO, 2011	130	130	33/130 (25%)	Multi-center
Brentuximab vedotin	Pro, JCO, 2013	58	58	50/58 (86%)	Multi-center
Belinostat	O'Connor, JCO, 2015	120	120	31/120 (26%)	Multi-center

Is PTCL a Disease Characterized by Epigenetic Lesions?

Gene/Protein	Function	Lymphoma	Reference
DNMT3A	DNA methyltransferase	Peripheral T-Cell Lymphoma	Couronne et al., NEJM. 2012
TET	Oxidation of methylated cytosines	Peripheral T-Cell Lymphoma	Lemonnier et al., Blood. 2012
IDH2	Metabolic pathway that controls KDM and TET through 2HG accumulation	Angioimmunoblastic T-Cell Lymphoma	Cairns et al., Blood. 2012
HDAC 2 and 4	Over-expression of HDAC2 and elevated H4 acetylation	Cutaneous T-cell Lymphoma	Marquard et al., Hematopathology. 2008
SWI/SNF complex **hSNF5/INI1/BAF47**	ATP-dependent chromatin remodeler, regulates gene expression; inactivating mutations cause tumorigenesis	T-cell lymphoma	Yuge et al., *Cancer Genet Cytogenetics* 2000

and…..3 histone deacetylase inhibitors carry approvals only in T-cell lymphoma, suggesting a class effect in the disease…..but why?

BUILDING DOUBLETS : WHERE ARE WE?

FDA Approved for PTCL or <u>Some Data</u>

- Pralatrexate
- Romidepsin
- Brentuximab vedotin (CD30)
- Belinostat
- Bendamustine
- Proteasome Inhibitors

Select Doublets in Progress

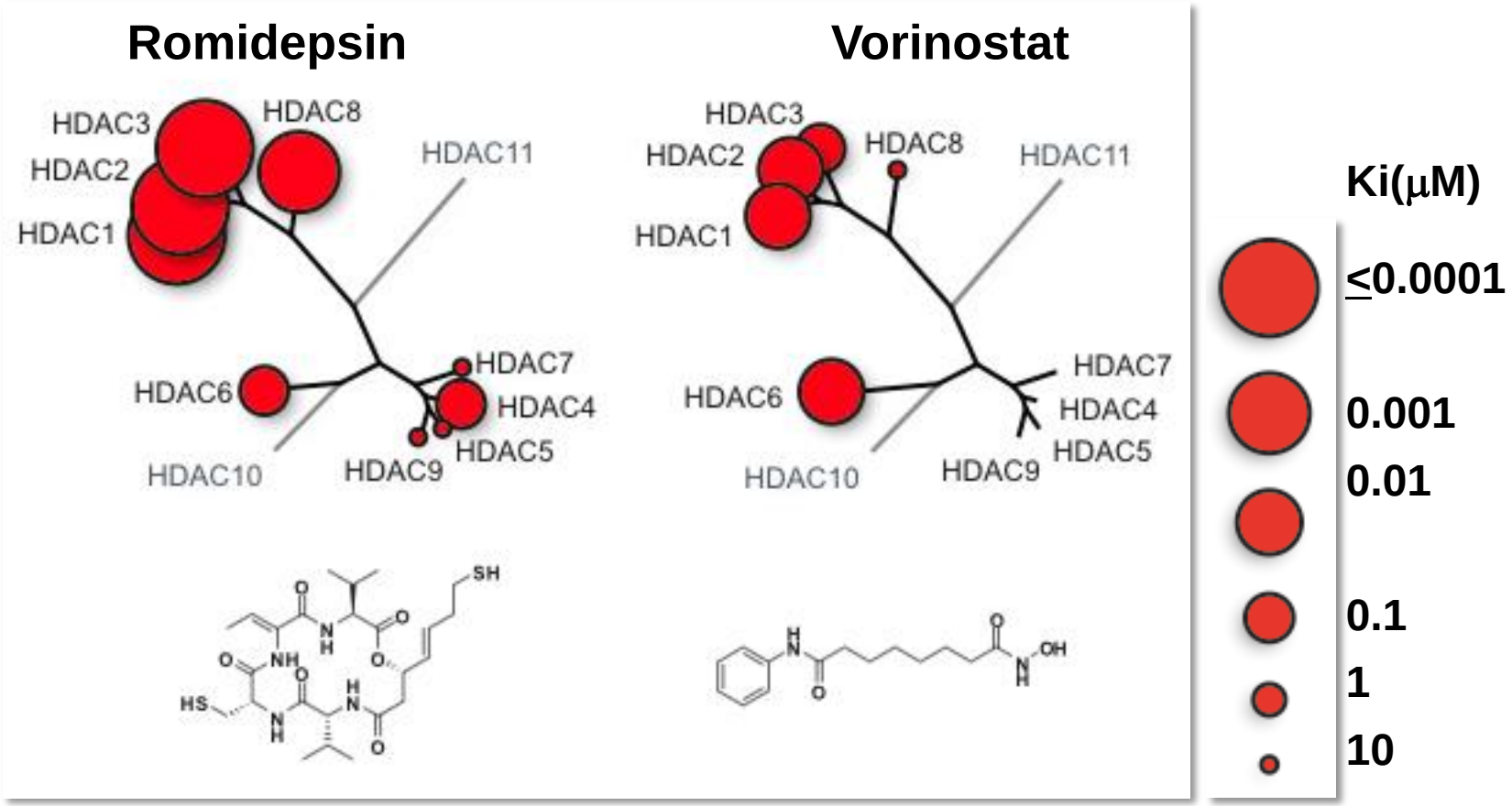
- Pralatrexate + Romidepsin
- Romidepsin + 5-Azacytidine
- Brentuximab vedotin (CD30) + Bendamustine
- Romidepsin + Alisertib

HDAC Inhibitors Are Not Created Equally Variable

Romidepsin Consistently Synergistic

Compound	t(h)	Cell line			
		P12	PF382	H9	HH
Panobinostat (nM)	24	16.8	20.6	8.7	82.9
	48	6.4	6.1	4.9	18.7
	72	7.9	2.4	7.4	9.9
Vorinostat (nM)	24	2136	3052.1	1147.8	4725
	48	1109	886.7	501	635
	72	921.5	1066.4	874.9	425
Romidepsin (nM)	24	6.2	6.1	5	14
	48	2.4	1.7	2.1	2.6
	72	2.1	1.5	2.2	2.6
Belinostat (nM)	24	386.9	267	108.1	240
	48	99.9	135.7	35.7	67.6
	72	97.8	118.3	29.4	39
Decitabine (μM)	24	*>20*	*>20*	*>20*	*>20*
	48	*>20*	*>20*	*>20*	*>20*
	72	1.8	0.4	7.4	*>20*
5-Azacytidine (μM)	24	*>20*	*>20*	*>20*	*>20*
	48	*>20*	*>20*	*>20*	*>20*
	72	*>20*	*>20*	*>20*	*>20*

Phylogenetic Relationships Between Vorinostant and Romidepsin



Chemical Phylogenetics Of Histone Deacetylase Inhibitors

Bradner et al. Nature Chem Biol 6:238 – 243, 2010

Evidence for Select Emerging Doublets in PTCL

Pralatrexate

+

Romidepsin

PROPEL

SUMMARY OF RESPONSE

70% of Responders did so in Cycle 1		Central Review (N=109)		Investigator Assessment (N=109)	
		n	Percent	n	Percent
Best Response	CR+CRu+PR	32	29%	43	39%
	CR	11	10%	17	16%
	CRu	1	1%	3	3%
	PR	20	18%	23	21%
	SD	21	19%	22	19%
	PD	40	37%	40	37%
	UE	2	2%	0	0%
	ND: off-treatment in Cycle 1	14	13%	5	5%

O. A. O'Connor et al., JCO, 2011; 29(9): 1182-1189

Single-Agent Romidepsin in Relapsed Peripheral T-Cell Lymphoma: Efficacy

Response	Independent Review Committee Analysis (n = 130)
Overall Response Rate	34 (26%)
Complete response	10 (8%)
Unconfirmed complete response	7 (5%)
Duration of Response	**Median (Range)**
Overall	12 (< 1.0-26.0+) months
Complete response/unconfirmed complete response	Not reached (< 1.0-26.3+) months)

- **Responses reported in PTCL (not otherwise specified) (29%), angioimmunoblastic TCL (33%), and ALK1$^-$ ALCL (24%)**
- **Similar response rates in patient subgroups according to number of prior therapies (< 3 vs. ≥ 3), prior SCT (yes vs. no), and refractory to most recent therapy (yes vs. no)**

Coiffier et al. JCO, 2012; Jan. 23

BELIEF

Response Assessed by Central Review

	Efficacy Analysis Set (N=120)	
Response	**n (%)**	**(95% CI)**
ORR	**31 (26)**	**(18-35)**
CR	13 (11)	(6-18)
PR	18 (15)	
SD	18 (15)	
PD	48 (40)	
NE	23 (19)	

O. A. O'Connor et al., JCO, 2015; Submitted

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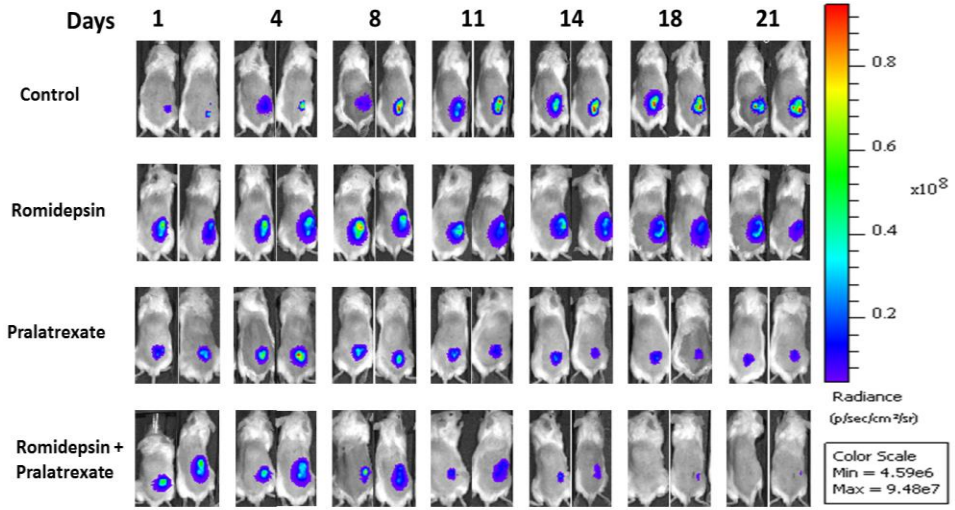

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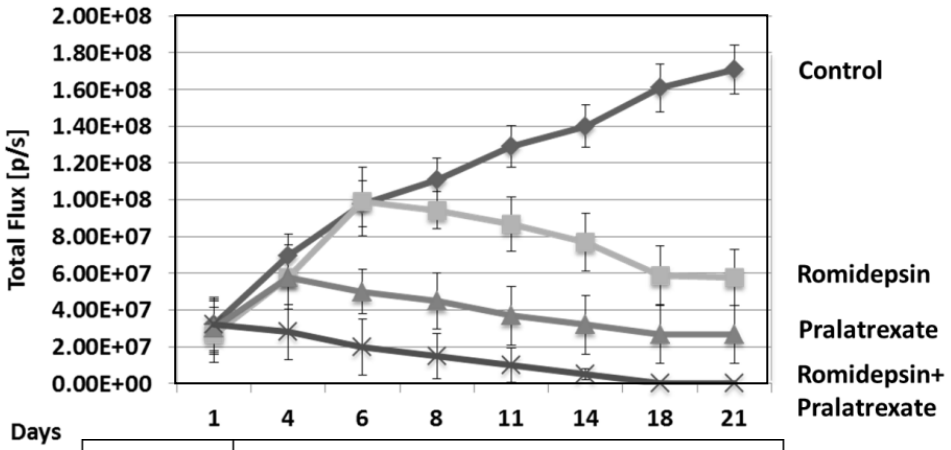

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Treatment group	Estimated log-intensity (p-value)			
	4th day	6th day	11th day	18th day
Control	7.82	7.88	8.04	8.27
Romidepsin	7.76 (0.002)	7.77 (0.002)	7.81 (0.002)	7.85 (0.002)
Pralatrexate	7.65 (0.003)	7.62 (0.003)	7.55 (0.003)	7.46 (0.003)
Romidepsin + Pralatrexate	7.41 (0.002)	7.30 (0.002)	7.04 (0.002)	6.67 (0.002)

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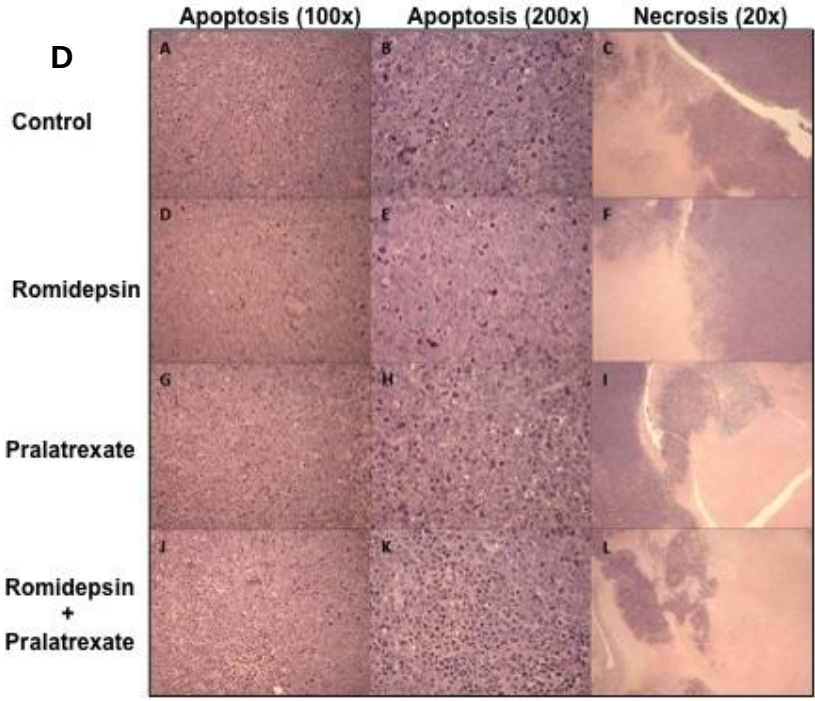

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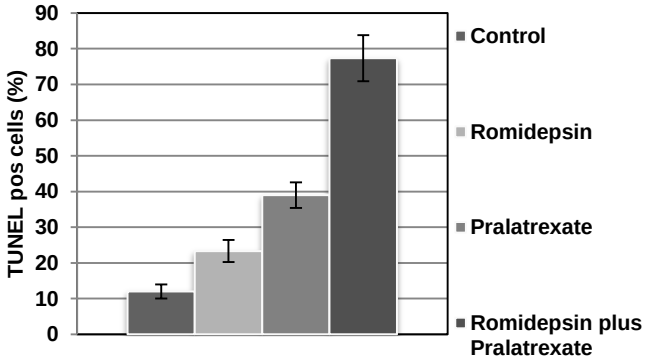

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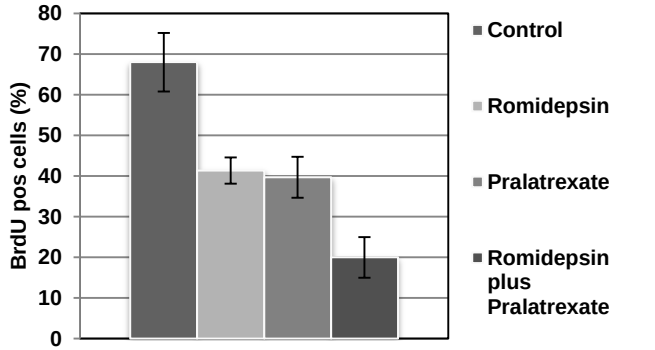
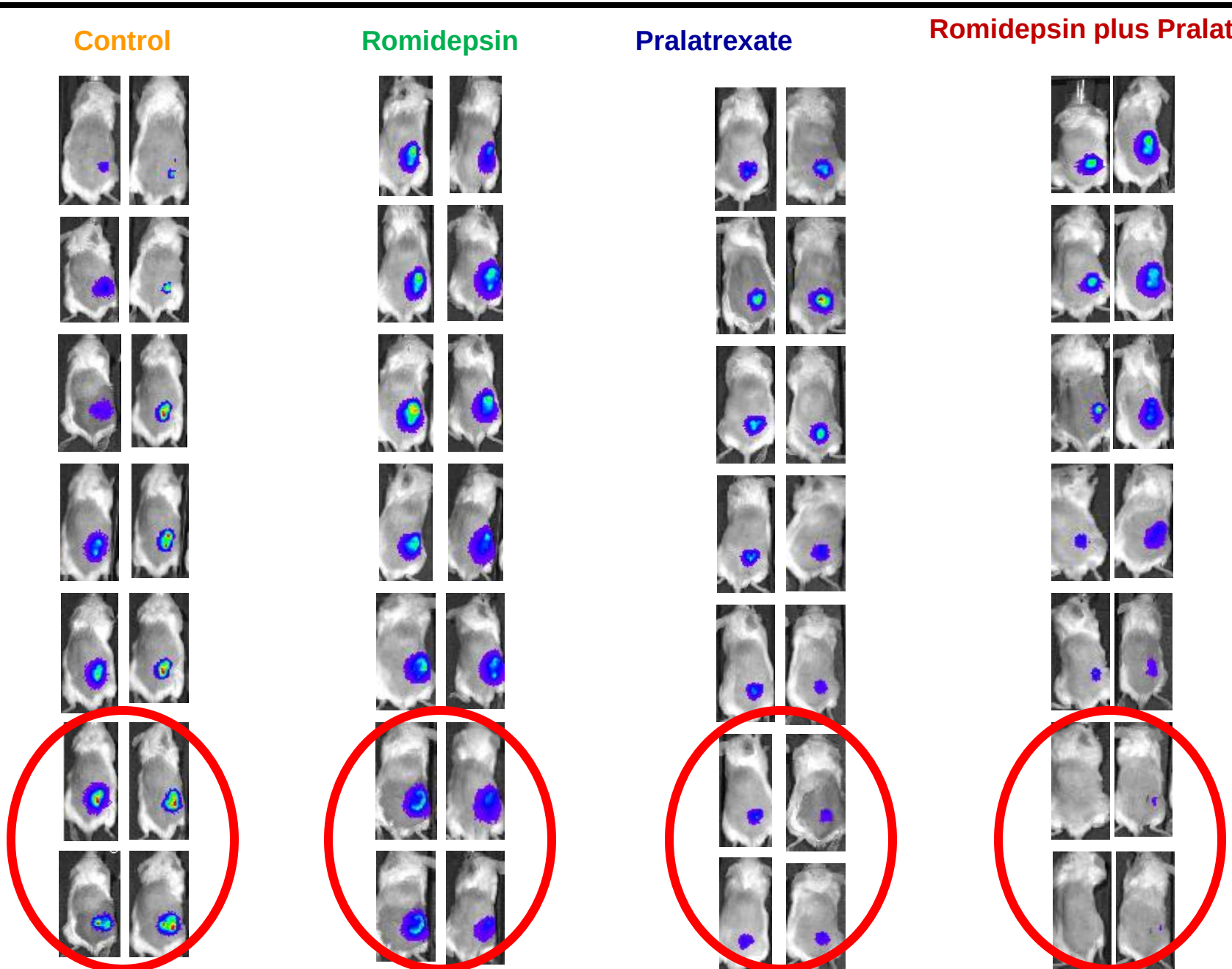


Bioluminescent Model of a Peripheral T-Cell Lymphoma



PDX + Romi Effective Based on 3-D Ultrasound Under 'Bulky' Conditions

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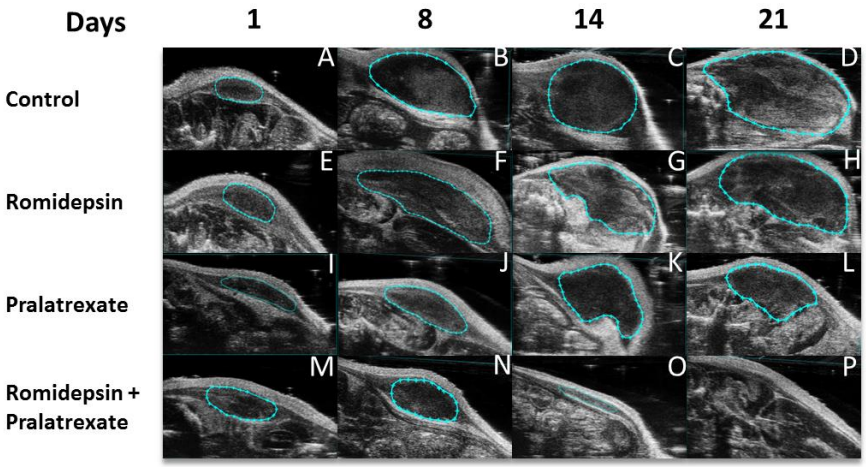

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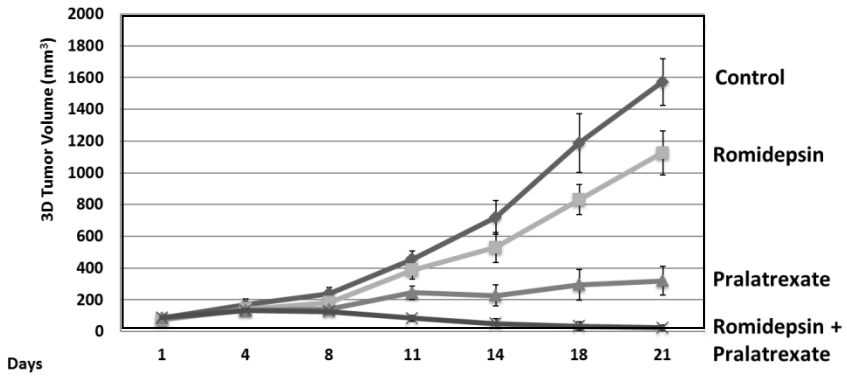
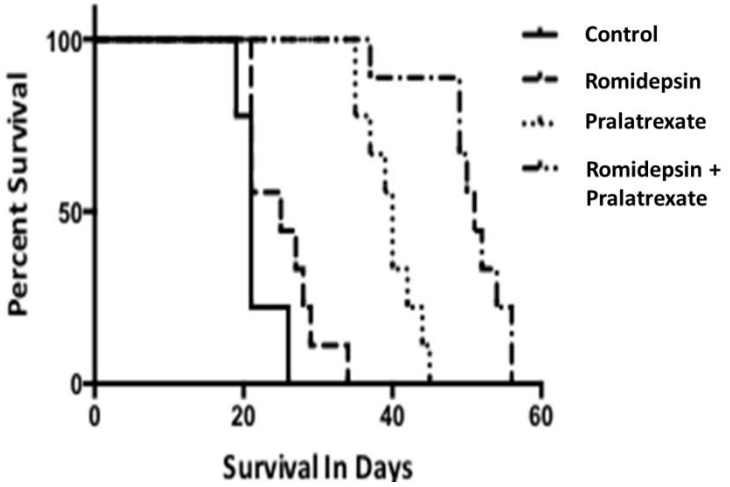


C

Treatment group	Estimated log-volume (p-value)			
	4th day	6th day	11th day	18th day
Control	2.16	2.29	2.61	3.06
Romidepsin	2.14 (0.48)	2.25 (0.1)	2.53 (0.004)	2.92 (<0.05)
Pralatrexate	2.08 (0.012)	2.14 (<0.05)	2.27 (<0.05)	2.46 (<0.05)
Romidepsin + Pralatrexate	2.06 (0.002)	1.96 (<0.05)	1.72 (<0.05)	1.39 (<0.05)

D



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1 Cycle at ½ MTD

Treatment group	Median survival time (in days)	95% Confidence Interval		P-value from the Log-rank test
		Lower	Upper	
Control	21	19	26	Reference
Romidepsin	25	21	29	0.0002
Pralatrexate	40	35	44	<0.0001
Romidepsin + Pralatrexate	51	37	56	<0.0001

H9 T-cell lymphoma

Jain, S. et al. Clin. Cancer. Res., 2015

Phase 1/2 Study of Pralatrexate plus Romidepsin in Lymphoma

7 of 7 Patients with R/R PTCL Achieve Response (4 CR)

Cohort	Patient	Disease	Prior Treatment	Toxicities	Response
1 **10mg/m² Pralatrexate** **12mg/m² Romidepsin** **Days 1,8,15(Q28)**	1	ALCL Alk (-), Multiple Myeloma, MF	6 lines of prior treatment	No DLT	CR
	2	Hodgkin's Lymphoma	14 lines of prior treatment	No DLT	SD
	3	Intestinal T-Cell Lymphoma	1 lines of prior treatment	No DLT	PR
2a **15mg/m² Pralatrexate** **12mg/m² Romidepsin** **Days 1 & 8(Q21)**	1	T-Cell Lymphoma	2 lines of prior treatment	No DLT	PR
	2	ATLL	2 lines of prior treatment	No DLT	CR
	3	Follicular Lymphoma	4 lines of prior treatment	No DLT	PR
2b **15mg/m² Pralatrexate** **12mg/m² Romidepsin** **Days 1 & 15(Q28)**	1	CD4+ T-Cell lymphoma	1 line of prior treatment	No DLT	PR
	2	Follicular Lymphoma	9 lines of prior treatment	No DLT	NE
	3	Follicular Lymphoma	3 lines of prior treatment	No DLT	PR
3a **15mg/m² Pralatrexate** **14mg/m² Romidepsin** **Days 1 & 8(Q21)**	1	Follicular	5 lines of prior treatment	DLT – (Thrombocytopenia, Plts=17)	PR
	2	SPTL-AB	2 lines of prior treatment	DLT - (Pancytopenia, Plts=4)	PR (PET neg)
	3	Burkitt's	3 lines of prior treatment	DLT - (Neutropenia, ANC=.244)	POD
3b **15mg/m² Pralatrexate** **14mg/m² Romidepsin** **Days 1 & 15(Q28)**	1	PTCL	2 lines of prior treatment	No DLT	CR
	2	DLBCL, CML	3 lines of prior treatment	DLT - (Thrombocytopenia, Plts=10)	NE
	3	ALCL, ALK (-)	2 lines of prior treatment	DLT - (Thrombocytopenia, Plts=3)	NE

Pralatrexate plus Romidepsin in Lymphoma

7 of 7 Patients with R/R PTCL Achieve Response (4 CR)

Cohort	Patient	Disease	Prior Treatment	Toxicities	Response
4a **20mg/m² Pralatrexate** **12mg/m² Romidepsin** **Days 1 & 8(Q21)**	1	Hodgkin's Lymphoma	16 lines of prior treatment	No DLT	POD
	2	Sezary Syndrome	5 lines of prior therapy	DLT – Grade 3 oral mucositis	TBD
	3	Cohort Expansion			
4b **20mg/m² Pralatrexate** **12mg/m² Romidepsin** **Days 1 & 15(Q28)**	1	Hodgkin's Lymphoma	11 lines of prior treatment	No DLT	POD
	2	ATLL	3 lines of prior treatment	No DLT	TBD
	3				
5a **25mg/m² Pralatrexate** **12mg/m² Romidepsin** **Days 1 & 8(Q21)**	1				
	2				
	3				
4b **25mg/m² Pralatrexate** **12mg/m² Romidepsin** **Days 1 & 15(Q28)**	1				
	2				
	3				

Evidence for Select Emerging Doublets in PTCL:
Pure Targeting of Epigenetic Operations

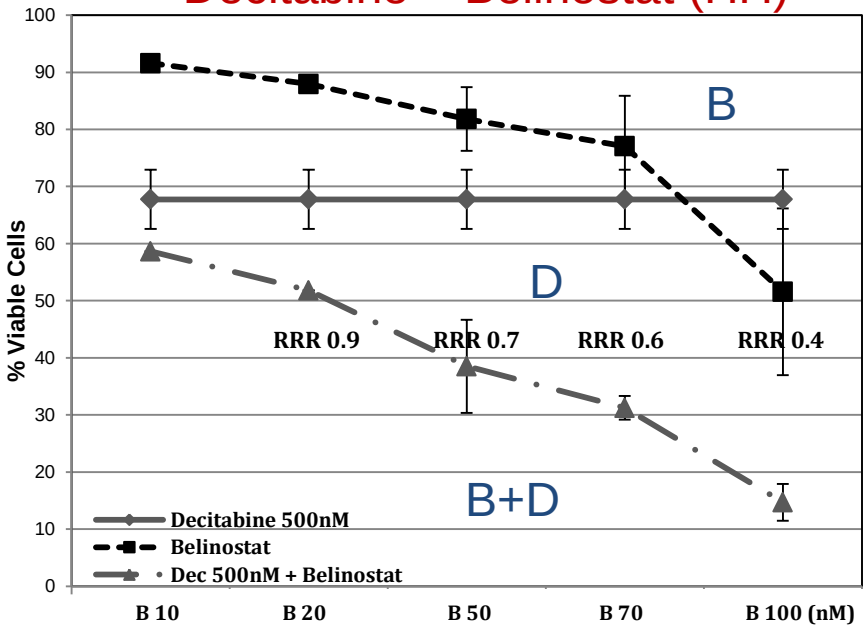
Romidepsin

+

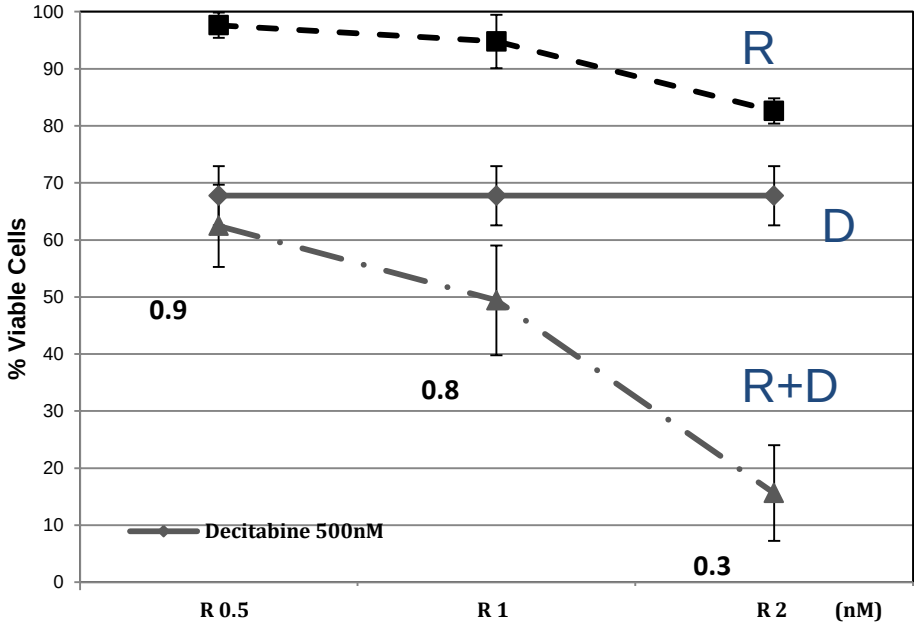
5-Azacytidine

Decitabine plus HDAC Inhibitor Produced Marked Synergy in Panel of T-Cell NHL

Decitabine + Belinostat (HH)



Decitabine + Romidepsin (HH)



H9	(uM)	
(nM)	D 0.5	D 1
B 50	0.6	0.6
B 70	0.6	0.5
B 100	0.4	0.5
R 0.5	0.9	0.9
R 1	0.7	0.7
R 2	0.3	0.2
L 4	0.6	0.5
L 5	0.6	0.4
L 7	0.3	0.3
S 600	0.6	0.6
S 800	0.4	0.4
S 1000	0.3	0.5

HH	(uM)	
(nM)	D 1	D 10
B 20	0.5	0.9
B 50	0.5	0.7
B 100	0.5	0.8
R 0.5	0.4	0.9
R 1	0.6	0.6
R 2	0.5	0.1
L 6	0.8	0.6
L 8	0.7	0.7
L 10	0.5	0.7
S 600	0.8	0.8
S 800	0.8	0.7
S 1000	0.7	0.7

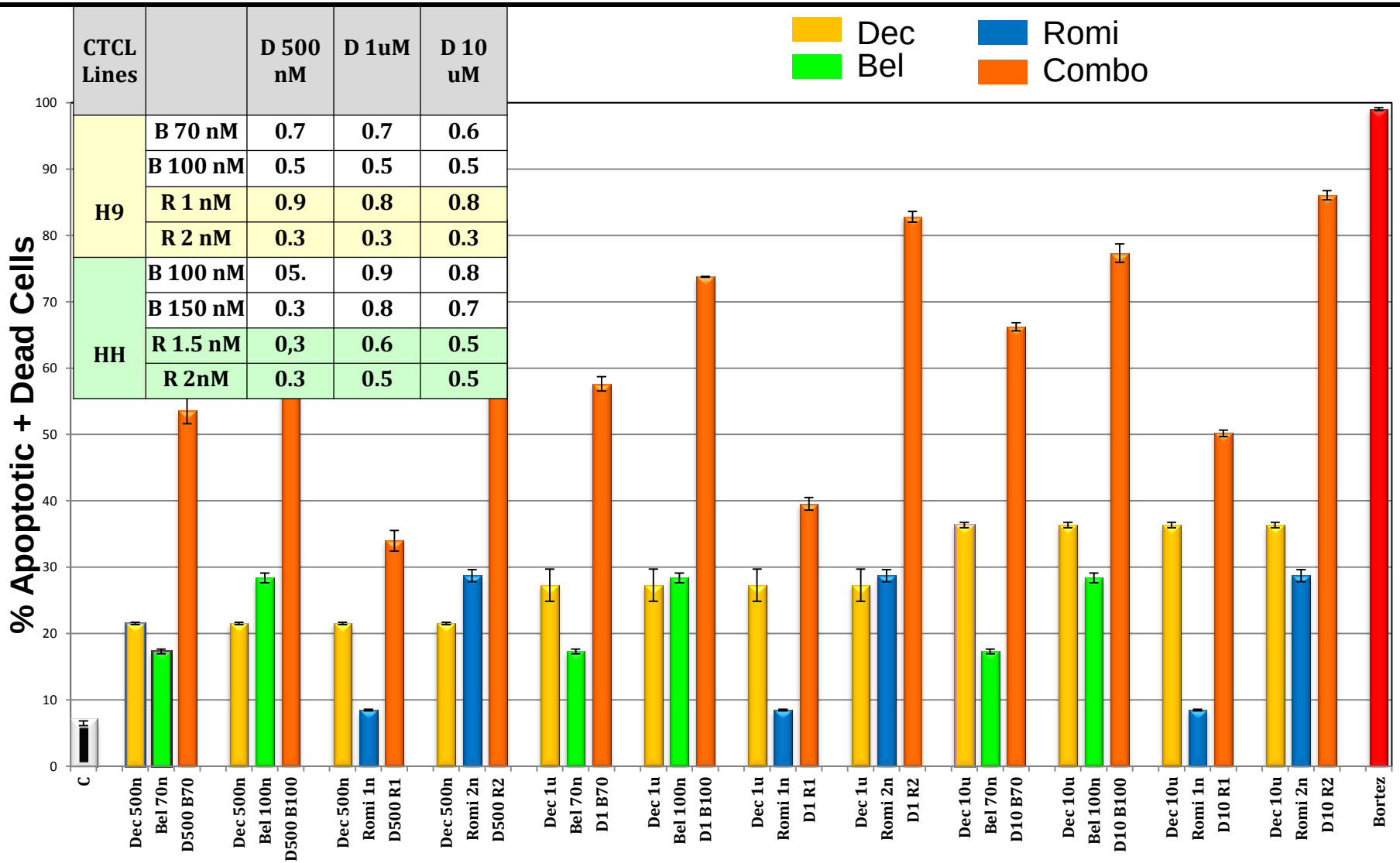
P12	(uM)	
(nM)	D 0.5	D 1
B 70	0.9	0.8
B 100	0.8	0.7
R 1	0.6	0.5
R 2	0.1	0.04
R 3	0.0007	0.01
L 5	0.7	0.5
L 6	0.7	0.4
L 8	0.4	0.2
S 800	0.8	0.9
S 1000	0.7	0.8

PF382	uM	
(nM)	D 0.5	D 1
B 100	0.9	0.9
B 150	0.6	0.5
R 1	0.9	0.8
R 1.5	0.5	0.5
R 2	0.2	0.1
L 4	0.9	0.9
L 5	0.9	0.9
S 600	0.9	0.9
S 800	0.9	0.9

O'Connor et al. ASH, 2013.

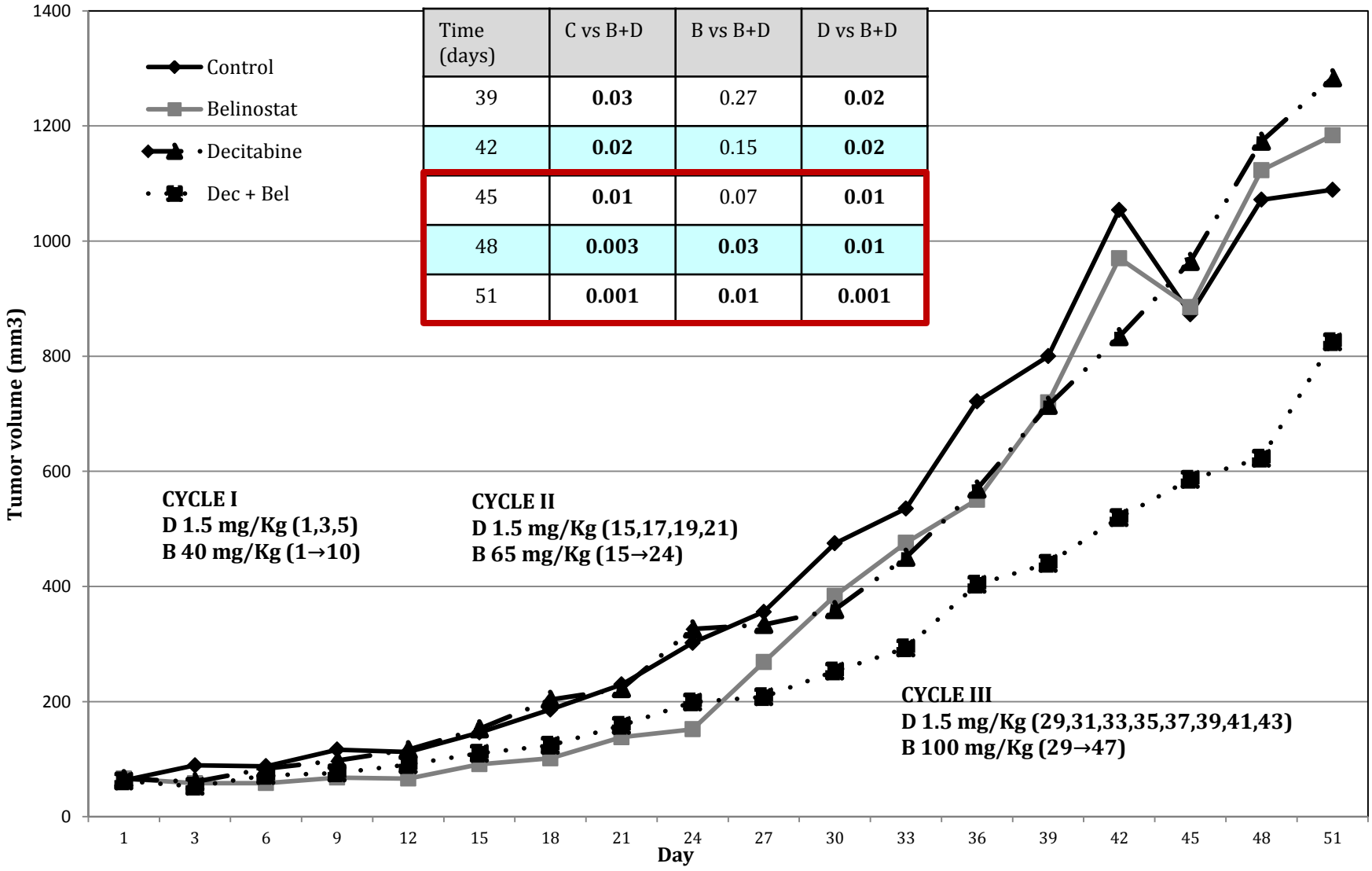
The Combination of HoME and HDAC Inhibitor Synergistically Produces Apoptosis Across Panel of T-Cell Lymphomas: tCTCL H9

CTCL Lines		D 500 nM	D 1uM	D 10 uM
H9	B 70 nM	0.7	0.7	0.6
	B 100 nM	0.5	0.5	0.5
	R 1 nM	0.9	0.8	0.8
	R 2 nM	0.3	0.3	0.3
HH	B 100 nM	05.	0.9	0.8
	B 150 nM	0.3	0.8	0.7
	R 1.5 nM	0,3	0.6	0.5
	R 2nM	0.3	0.5	0.5

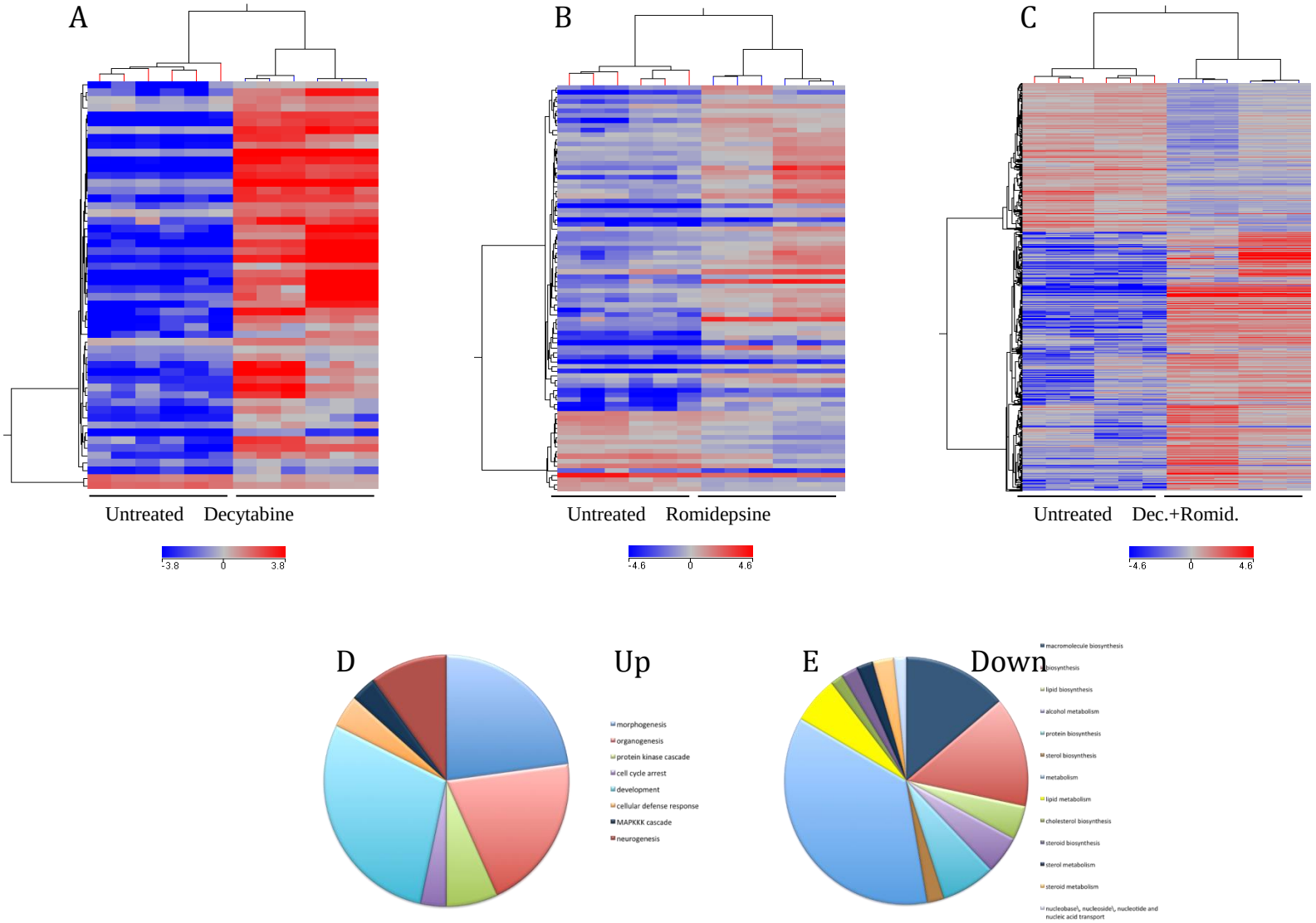


The Combination of Belinostat and Decitabine Produce a Statistically Significant Growth Delay in SCID-Bg Model of HH

Time (days)	C vs B+D	B vs B+D	D vs B+D
39	**0.03**	0.27	**0.02**
42	**0.02**	0.15	**0.02**
45	**0.01**	0.07	**0.01**
48	**0.003**	**0.03**	**0.01**
51	**0.001**	**0.01**	**0.001**

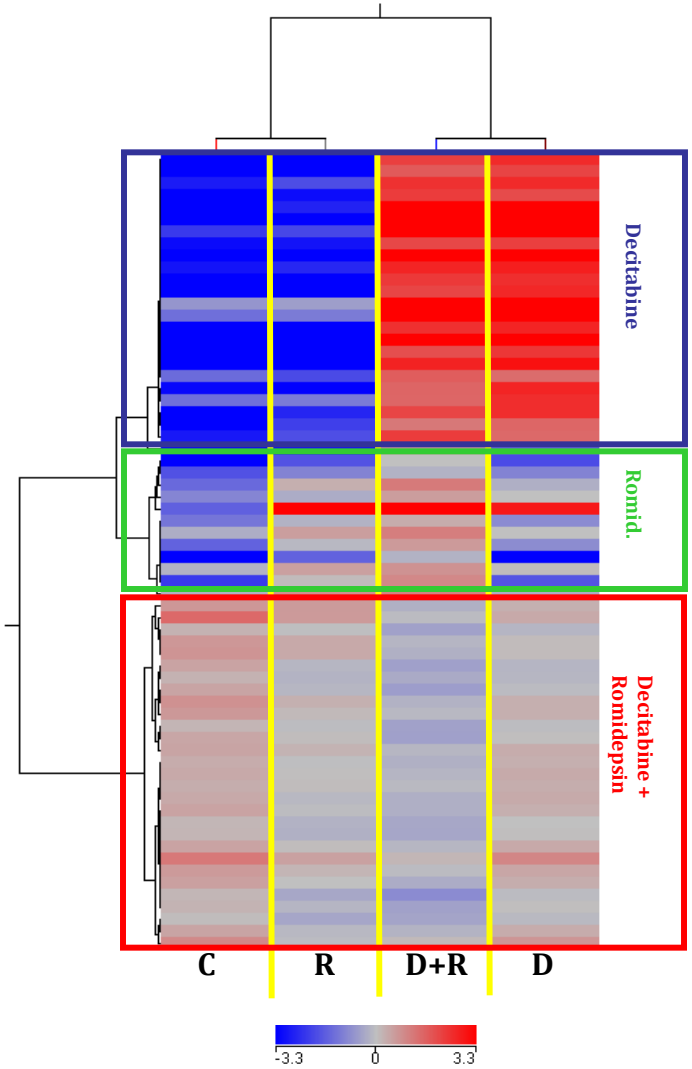


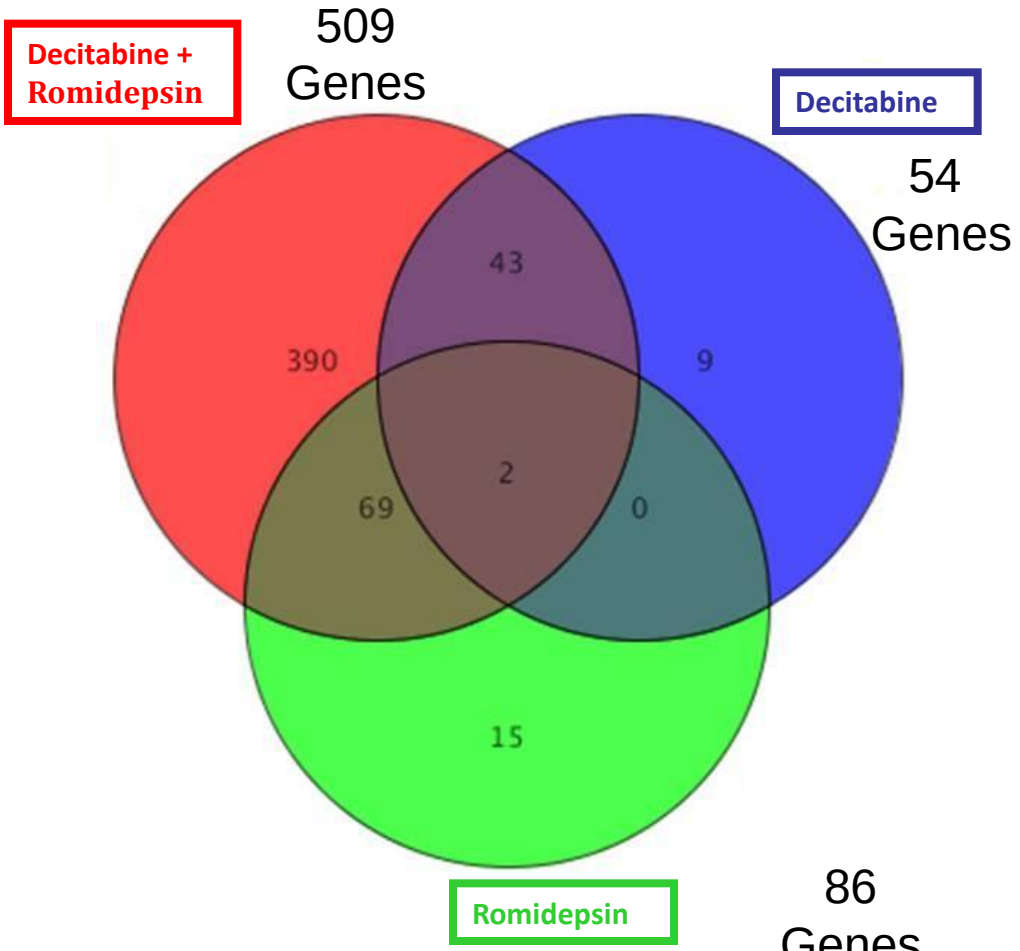
Supervised Hierarchial Clustering Based on GEP
?Reversal of the Malignant Phenotype in PTCL?



O'Connor, O.A. et al. ASH, 2013.

Supervised Hierarchial Clustering of Gene Expression Reveals 390 Unique Genes Modulated by the Combination Romidpesin and Decitabine





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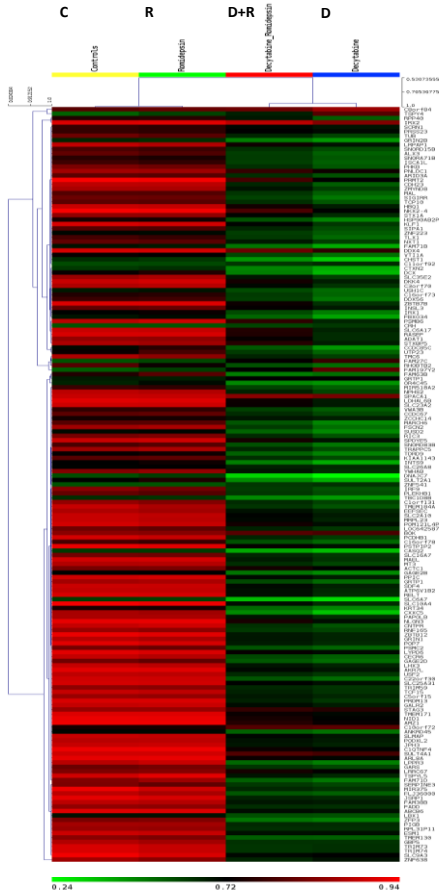

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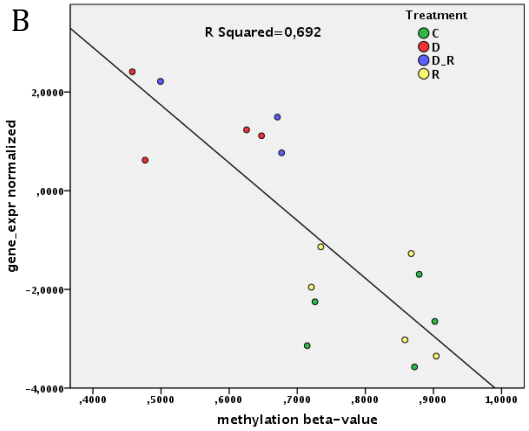

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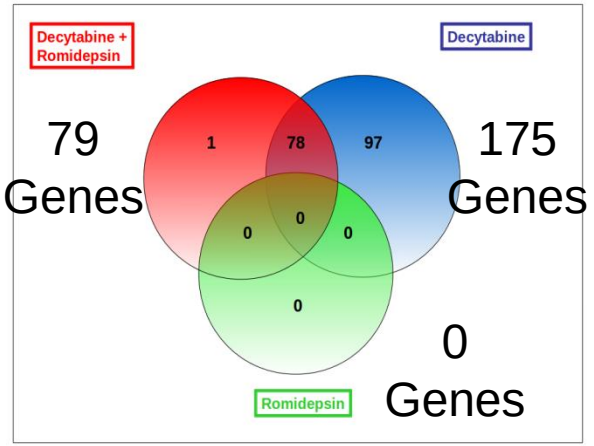

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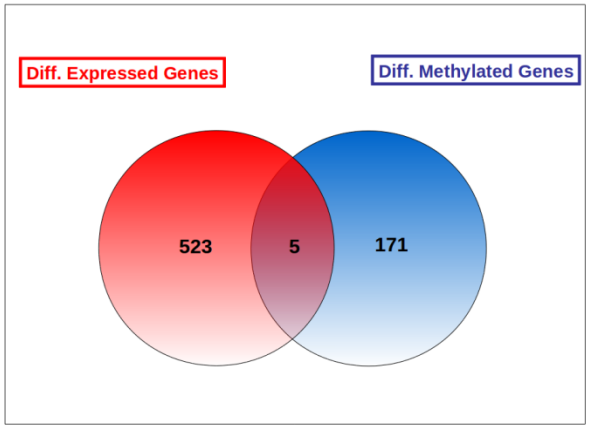

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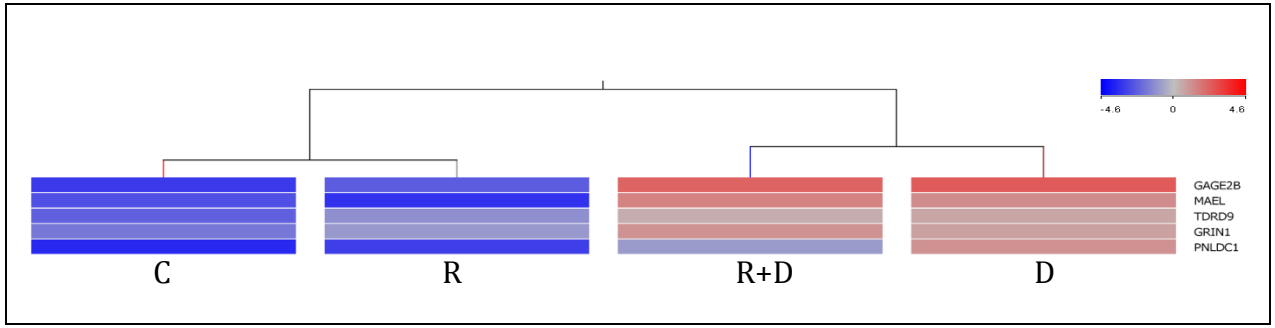


Hierarchical clustering of T-cell Samples According to the Differential Methylation Pattern

- Scatter plot demonstrates inverse relationship between GE and differentially methylated genes in the MP analysis
- The Venn diagram shows the relationship among differentially expressed gene, with 5 common genes

PHASE 1-2 STUDY OF ORAL 5-AZACYTIDINE AND ROMIDEPSIN IN LYMPHOMA

Cohort	Patient	Disease	Prior Treatment	Toxicities	Response
1 **100mg Azacitadine** **Days 1-14 (Q21)** **10mg/m² Romidepsin** **Days 8,15(Q21)**	1	Hodgkin's Lymphoma	12 lines of prior treatment	No DLT	PR
	2	Follicular Lymphoma	4 lines of prior treatment	No DLT	PR
	3	T - Acute Lymphoblastic Lymphoma/Leukemia	3 lines of prior treatment	No DLT	CR
	4	Hodgkin's Lymphoma	11 line of prior treatment	No DLT	POD
	5	CD8+ Cytotoxic Cutaneous T-cell Lymphoma	8 lines of prior treatment	No DLT	PR
	6	Hodgkin's Lymphoma	6 lines of prior treatment	No DLT	POD
2 **200mg Azacitadine** **Days 1-14 (Q21)** **10mg/m² Romidepsin** **Days 8,15(Q21)**	1	Diffuse Large B-Cell Lymphoma	9 lines of prior treatment	Delay of Cycle 2 due to Low Platelets	POD
	2	Diffuse Large B-Cell Lymphoma	2 lines of prior treatment	DLT – Pleural Effusion	NE
	3	Hodgkin's Lymphoma	9 lines of prior treatment	No DLT	SR
3 **200mg Azacitadine** **Days 1-14 (Q28)** **10mg/m² Romidepsin** **Days 8,15(Q28)**	1	Hodgkin's Lymphoma	6 lines of prior treatment	No DLT	POD
	2	Hodgkin's Lymphoma	10 lines of prior treatment	N/A	SD
	3	Hodgkin's Lymphoma	16 lines of prior treatment	N/A	POD

Phase 1-2 Study of Oral 5-Azacytidine and Romidepsin in Lymphoma

4 of 4 Patients with TCL Responding (2 CR)

Cohort	Patient	Disease	Prior Treatment	Toxicities	Response
4 **300mg Azacitadine** **Days 1-14** **10mg/m^2 Romidepsin** **Days 8,15(Q28)**	1	Adult T-Cell Leukemia / Lymphoma	3 lines of prior treatment	No DLT	CR
	2	Hodgkin Lympoma	6 lines of prior treatment	No DLT	POD
	3	Hodgkin Lymphoma	12 lines of prior treatment	No DLT	POD
5 **300mg Azacitadine** **Days 1-14** **14mg/m^2 Romidepsin** **Days 8,15(Q28)**	1	Cutaneous DLBCL (Leg type)	4 lines of prior treatment	No DLT	POD
	2	ALK(-) ALCL	4 lines of prior treatment	No DLT	PR
	3	Mycosis fungoides	9 lines of prior treatment	No DLT	TBD
6 **300mg Azacitadine** **Days 1-14 (Q28)** **14 mg/m^2 Romidepsin** **Days 8,15, 22(Q28)**	1	Hodgkin's Lymphoma	6 lines of prior treatment	TBD	TBD
	2				
	3				
7 **300mg Azacitadine** **Days 1-21 (Q28)** **14 mg/m^2 Romidepsin** **Days 8,15, 22(Q28)**					

Evidence for Select Emerging Doublets in PTCL

Alisertib

+

Romidepsin

SWOG Phase 2 of Alisertib in PTCL

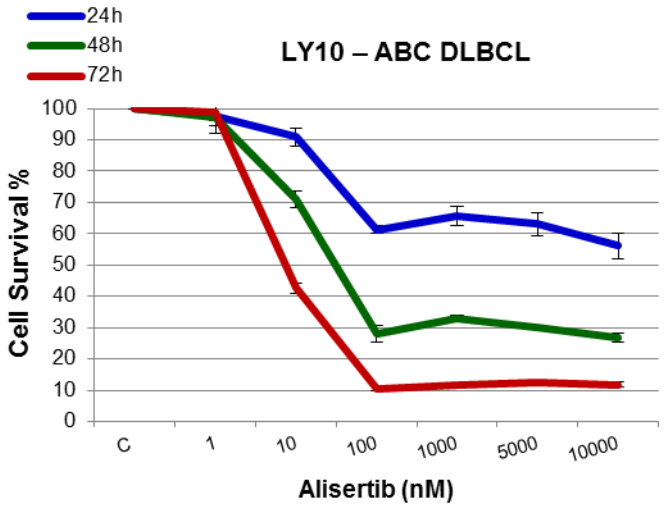
No. of patients	**42 (37 evaluable)**
Median Age	62 (22-86)
Prior therapies	3 (1-18)
Refractory to last Rx	20
ORR	24% (95%CI: 12-41%)
CR Rate	22%

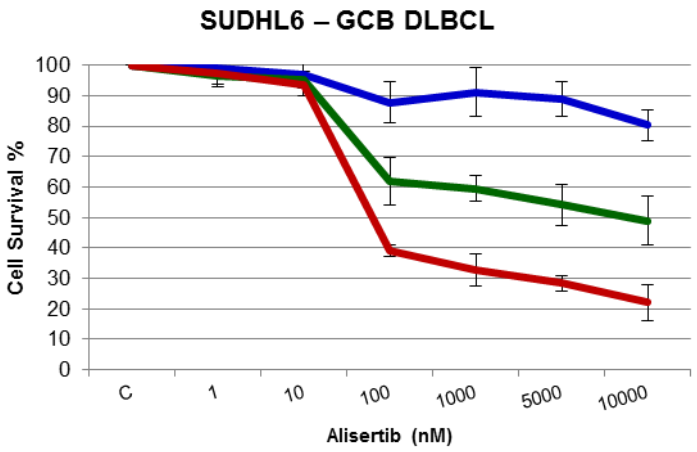
Response	**PTCL-NOS**	**AITL**	**Transformed MF**	**ATLL**	**ALCL**	**NK/T**
N	13	9	7	4	2	2
CR/PR	1/3	0/3	0/0	1/0	0/1	0/0
SD	1	2	2	0	1	1
POD	8	4	5	3	0	1

Omit **Transformed MF** = 33% (CR = 22%)

Barr et al., ASCO 2014

Length of Exposure to Drug is Essential for its Activity



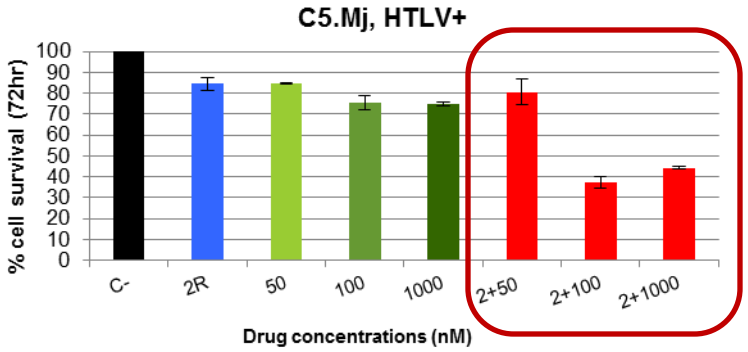


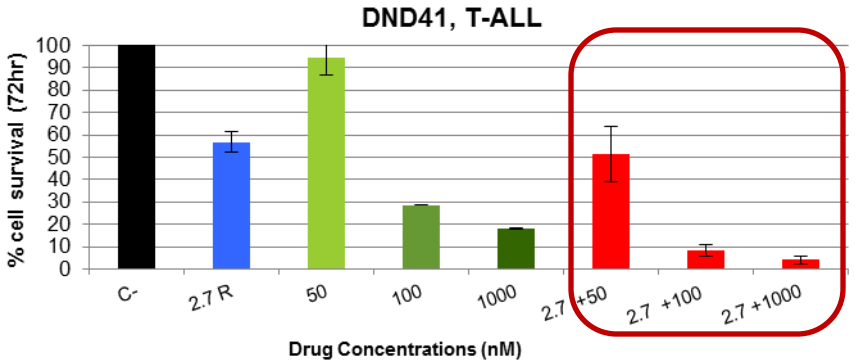
- IC_{50} in B- and T-Cell lymphomas similar & range from 10 – 100 nM at 72 hours

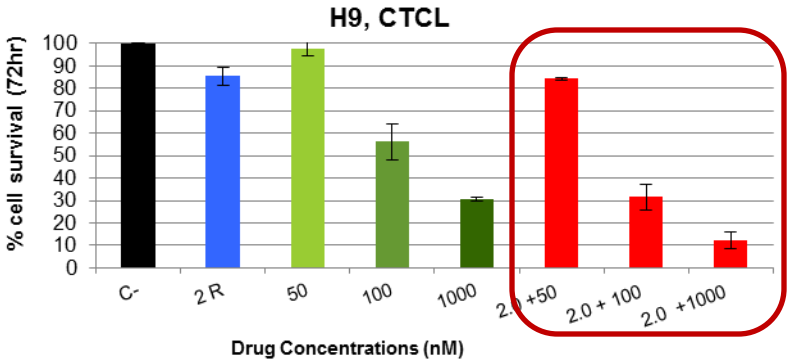
Alisertib IC_{50} Values in B-Cell Lymphoma

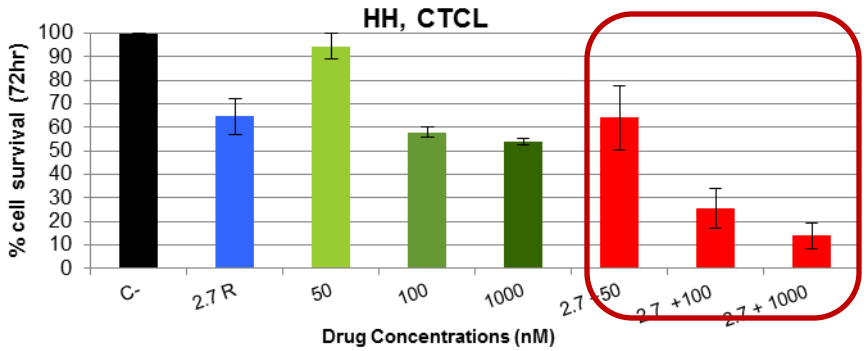
	DLBCL				MCL			
T(hrs)	**Ly10**	**LY7**	**SUDHL-2**	**SUDHL6**	**Jeko-1**	**JVM2**	**Rec-1**	**Z-138**
24h	>1000	N/A	N/A	>1000	N/A	N/A	N/A	N/A
48h	80	180	7.89	>1000	38	30	78	22
72h	10	81	10.12	100	29	10	87	13

Using High-Throughput Screening Techniques Alisertib Found to be HIGHLY Synergistic with Romidepsin……..ONLY in T-Cell Lymphomas







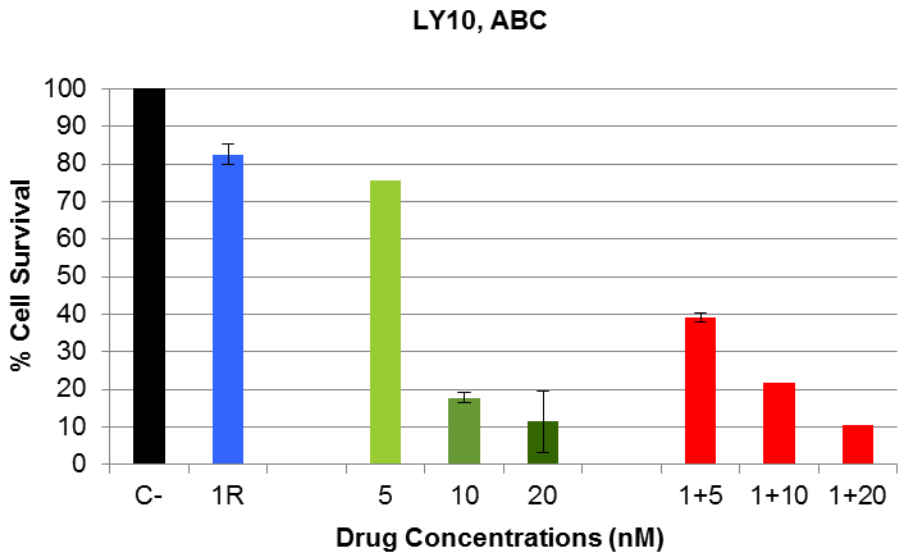


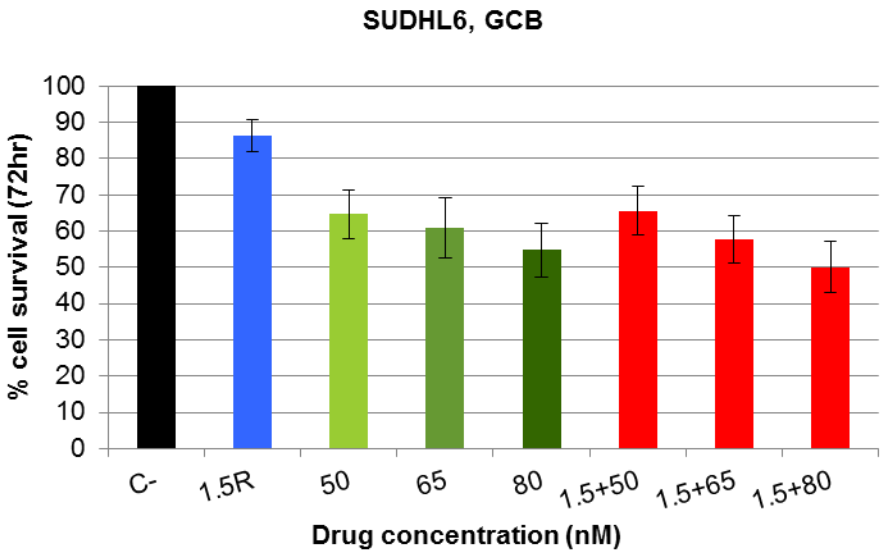
Cell Line	Romidepsin(nM)	50nM Alisertib RRR (Excess over Bliss)	100 nM Alisertib RRR (Excess over Bliss)	1000 nM Alisertib RRR (Excess over Bliss)
C5MJ	2	(-9.05)	(26.54)	(18.89)
DND41	2.7	(1.94)	(7.90)	(6.18)
H9	2	(-0.61)	(16.54)	(14.07)
HH	2.7	(-3.02)	(12.05)	(21.01)

Increasing Synergy

Alisertib Does Not Synergize with Romidepsin in B-Cell Lymphomas

Is This an Example of a Lineage Specific Synergy?



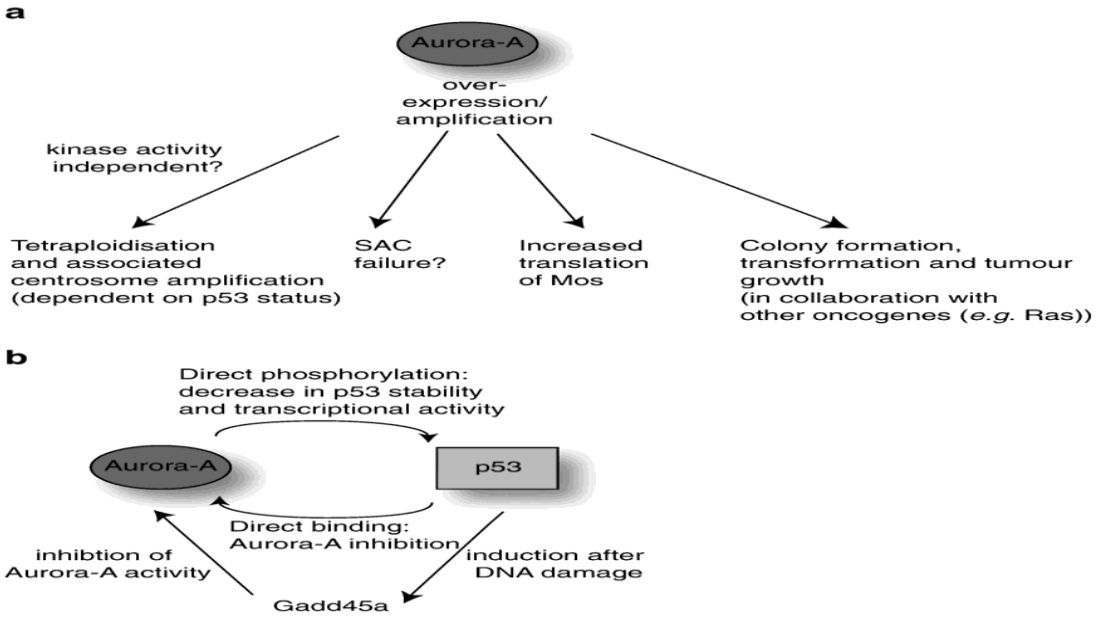


Combination	Synergy Coefficients	Excess over Bliss
1R +5A	0.63	5.83
1R + 10A	1.48	-20.03
1R +20 A	1.10	-1.26

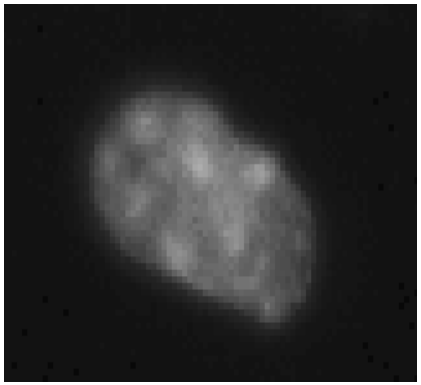
Combination	Synergy Coefficents	Excess over Bliss
1.5R +50A	1.17	-9.70
1.5R + 65A	1.09	-5.01
1.5R +80A	1.05	-2.68

.....Nor did it synergize with pralatrexate and proteasome inhibitors

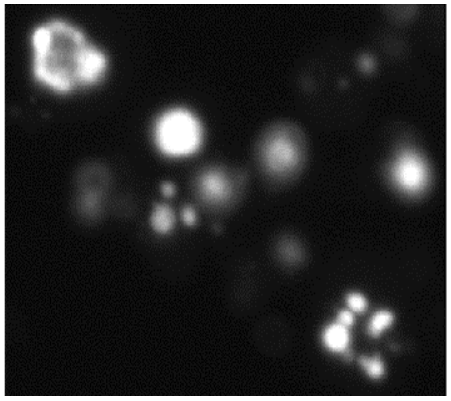
The Combination of Alisertib & Romidepsin Induces Cytokinesis Failure



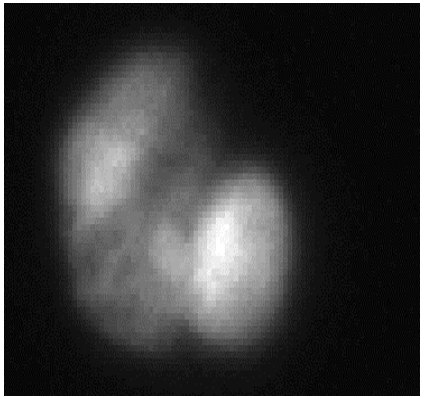
Control 24h



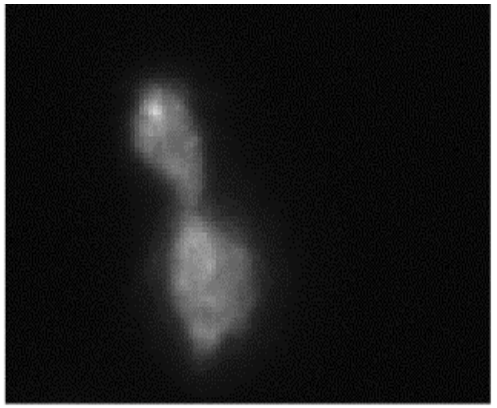
Romidepsin 24h



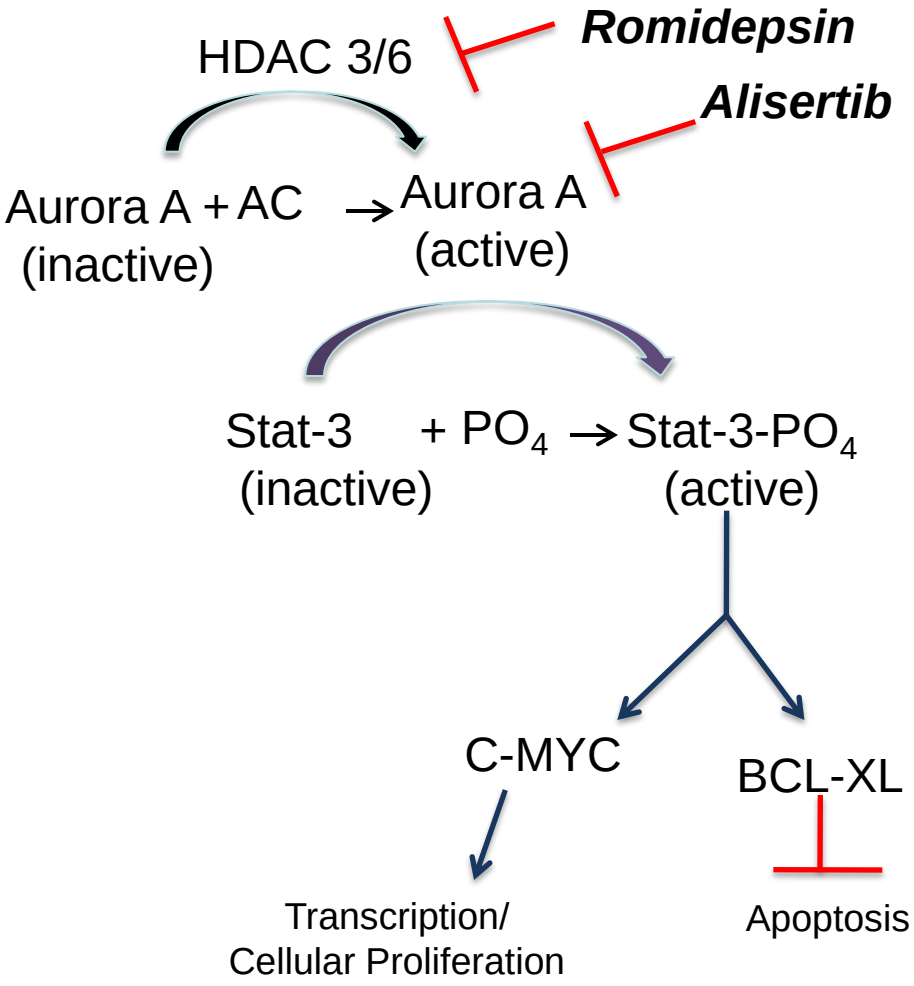
Alisertib 24h



Combo 24h



Working Hypothesis For Romidepsin and Alisertib Synergy



Romidepsin is a potent HDAC3 & 6 Inhibitor

HDAC3 & 6 Deacetylates Aurora A Kinase tagging AAK for Ubiquitination and proteasome degradation

Alisertib Inhibits AAK

AAK Phosphorylates STAT-3 leading to upregulation of c-MYC and BCL-XL(providing a proliferative and antiapoptotic signaling)

Inhibition of AAK blocks the phosphorylation of STAT-3, inhibiting the activation of c-MYC and BCL-XL

Dual Blockade of HDAC3/6 and AAK effectively leads to impaired proliferation and apoptosis

- Minami et al: Leukemia 2013:1-10
- Cha et al: CCR 2009;15(3): 840-850
- Santo et al: CCR 2011;17:3259-3271
- Sommer et al: Leukemia(2004) 18, 1288-1295)
- Darnowski et al: JBC;2006:281:17707-17717
- Hollander et al: Blood(2010); 116:1498-1505

Phase 1 Trial of Alisertib Plus Romidepsin for R/R Aggressive B- and T-Cell Lymphomas Fanale et al. ASH 2014

- 9 patients enrolled with 8 evaluable
- PTCL = 3; DHL = 3; DLBCL = 1; Transformed DLBCL = 1
- Grade 3/4 toxicities included neutropenia, thrombocytopenia, and anemia
- Responses included 1 CR in patient with PTCL in remission x 5 months (1 SD PTCL)
- Ongoing

Development of Novel Backbones in T-Cell Lymphoma

- The T-cell lymphomas may be the protoypical diseases with a vulnerability to epigenetic manipulation

  - 3 HDAC inhibitors approved and only in TCL

- Recurrent genetic lesions exist in multiple pathways leading to epigenetic dysregulation (methylation) in many sub-types of PTCL
- Preliminary data suggests novel doublets have potent preclinical data
- Romidepsin combinations are consistently highly synergistic
- Building beyond ‘doublets’ will take more evidence or better rationale to refine options.
- Whole exome sequencing, methylation and cytokine array conducted on every patient on study…….**biomarker discovery vs combination rationale**

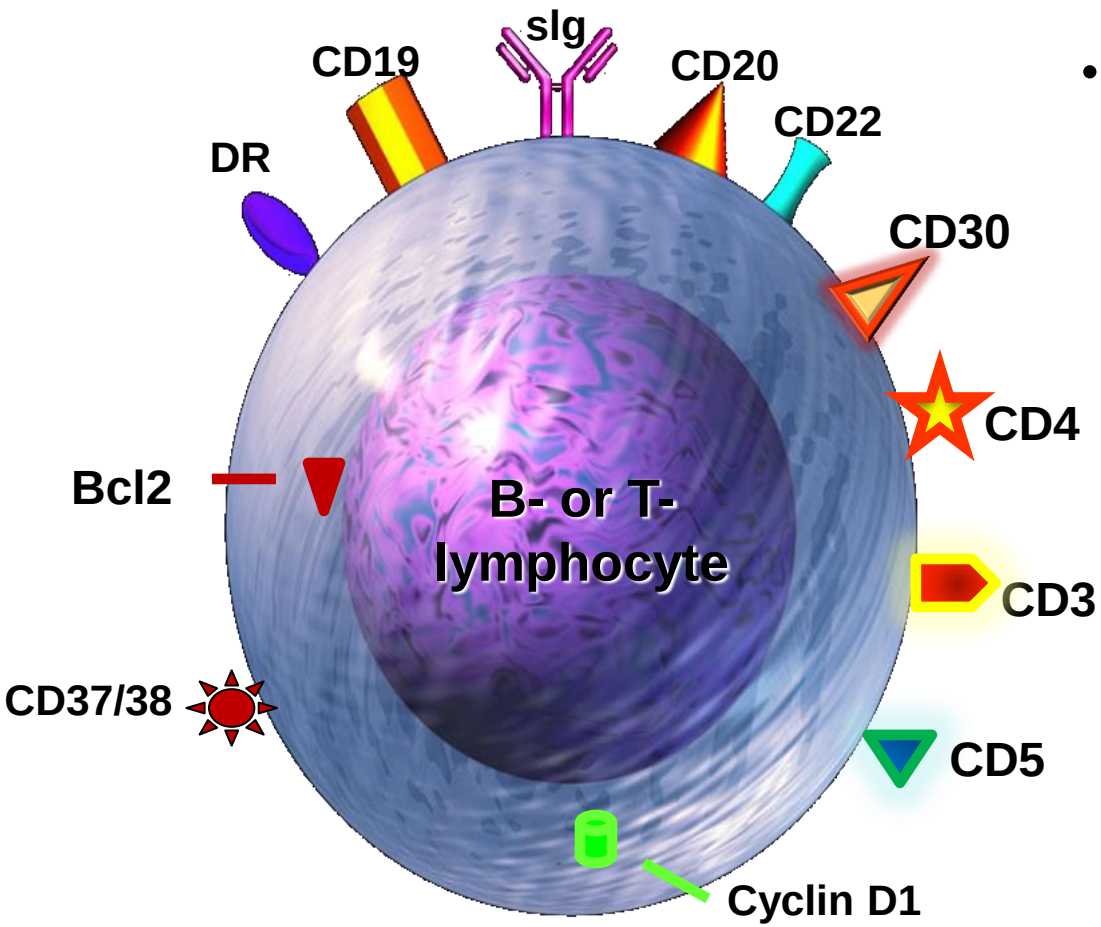
THANK YOU!

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

Finding an R- for PTCL…..Target Epitopes on B- and T- Cell Lymphocytes



- Surface and cytoplasmic proteins targeted by antibodies are:
  - differentially expressed on different types of lymphoma
  - No one epitope has emerged as the optimal T- cell target

Center for Lymphoid Malignancies at Columbia University Medical Center

Physicians

Owen A. O'Connor, M.D., Ph.D.
Jennifer Amengual, M.D.
Changchun Deng, M.D., Ph.D.
Ahmed Sawas, M.D.
Donald Colburn, M.D.
Lauren Geskin, M.D.
(Dermatology / CTCL)

Nurses

Ellen Neylon, NP
Kathleen Maignan, NP
Michael Smith, RN
Emily Lichtenstein,

Administrative Staff

Victoria Serrano, MPH
Joanne Scibilla
Erica Guerva
Chermaine Ford, B.S.
Joanna Duarte.

Research Study Coordinators

Molly Patterson, LMSW
Celeste Rojas, B.S.
Renee Lichtenstein,B.A
Michele Malanga, BA

Laboratory Staff

Luigi Scotto, Ph.D.
Michael Mangone, Ph.D.
Jennifer Amengual, M.D.
Changchun Deng, M.D., Ph.D.
Kelly Zullo, B.S.
Xavier Jirau Serrano, B.S.
Mark Lipstein, B.S.
Maximillian Lombardo, B.S.

Columbia University Medical Center

Potential Novel Upfront Treatment Paradigms for Patients with PTCL

Conclusions

- Albeit early, preclinical data supports marked activity of many novel : novel drug combinations finding approvals in T-cell lymphoma
- Some appear to exhibit lineage specific synergy, while other combinations appear antagonistic (alisertib + pralatrexate; alisertib + proteasome inhibitor)
- Early Phase 1 clinical data suggests the combinations are well tolerated
- Early clinical activity is being seen is patients with heavily treated PTCL
- Clarifying rationale for a specific third agent or biological agent could pave the way for novel lineage specific platforms

PROPEL Subset: Efficacy as Second-line Treatment Following CHOP Failure
Use FDA Approved Agents in R/R PTCL Earlier!

Efficacy Assessments	Central Review Assessment (n=15), %	Investigator Assessment (n=15), %
Tumour Response		
ORR (CR+CRu+PR)	7 (47)	6 (40)
CR	3 (20)	4 (27)
CRu	0 (0)	1 (7)
PR	4 (27)	1 (7)
SD	4 (27)	4 (27)
PD	4(27)	4 (27)
Not Evaluable	0 (0)	1 (7)
Median DoR	ND*	12.5 months
Median by PFS**	8.1 mths	7.4 months
Median OS	ND*	ND*

Shustov, et al, *Blood* (ASH Annual Meeting Abstracts) 2010 116: Abstract 4882

PROPEL: Prior ICE (n=20)

- ORR (CR + PR): 40%
- CR: 25% by Investigator Assessment
- Median Duration of Response: 16.2 months by Investigator Assessment

Efficacy Assessments	Central Review Assessment (n=20), %	Investigator Assessment (n=20), %
Tumor Response		
ORR (CR+PR)	8 (40)	8 (40)
CR	5 (25)	3 (15)
PR	3 (15)	5 (25)
SD	5 (25)	2 (10)
PD	6 (30)	4 (20)
Not Evaluable	1 (5)	6 (30)
Median DoR	16.2 mths	13.1 mths

Goy A, et al, *Blood* (ASH Annual Meeting Abstracts) 2010 116: Abstract 1753

PRALATREXATE AND ROMIDEPSIN HIGHLY ACTIVE ACROSS IN VIVO MODELS OF TCL

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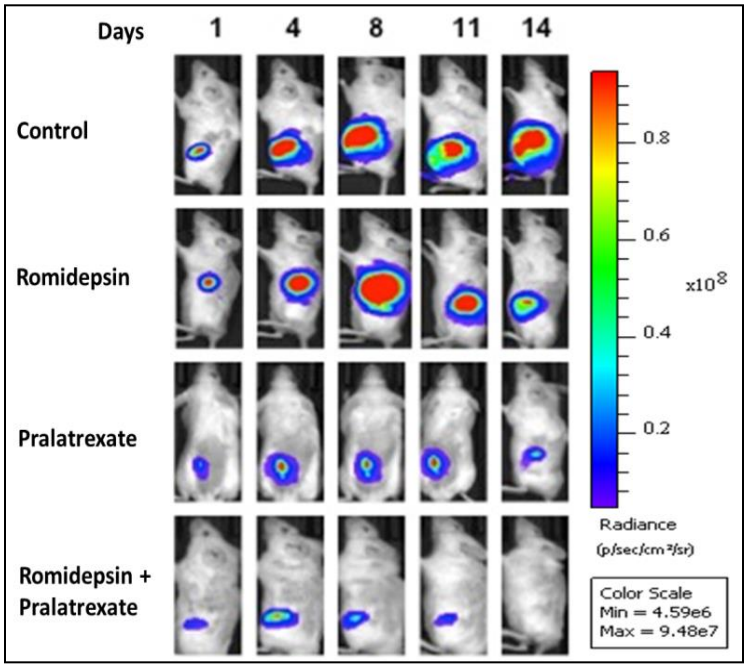

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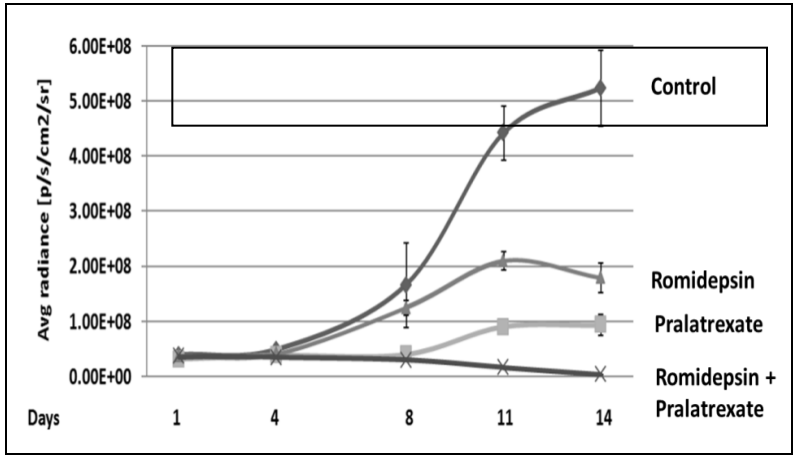


Synergy demonstrated by activity seen at lower doses of each drug compared to MTD of each

C

Treatment group	Estimated log-intensity (p-value)			
	4th day	8th day	11th day	14th day
Control	7.78 (<0.05)	8.09 (<0.05)	8.32 (<0.05)	8.55 (<0.05)
Romidepsin	7.75 (<0.05)	8.00 (<0.05)	8.20 (<0.05)	8.39 (<0.05)
Pralatrexate	7.58 (0.02)	7.74 (<0.05)	7.86 (<0.05)	7.98 (<0.05)
Romidepsin + Pralatrexate	7.49	7.24	7.06	6.87

Hut78 T-cell lymphoma

S. Jain et al. Clin. Cancer Res. 2015; Feb 12

Phase II Trial of Romidepsin in Relapsed or Progressive Peripheral T-Cell Lymphoma Following Prior Systemic Therapy

- **Patient population:**
  - 131 enrolled
  - 130 with confirmed PTCL
  - Failed ≥ 1 prior systemic therapy
- **Treatment regimen: romidepsin 14 mg/m^2, days 1, 8, and 15 q 28 days × 6 cycles; continued beyond 6 cycles in responding patients at investigator and patient discretion**
- **Primary endpoint: CR/CRu by independent review**
- **Secondary endpoints including: ORR, duration of response, TTP, tolerability, and safety**

Coiffier et al. JCO, 2012; 30(6): 631-636

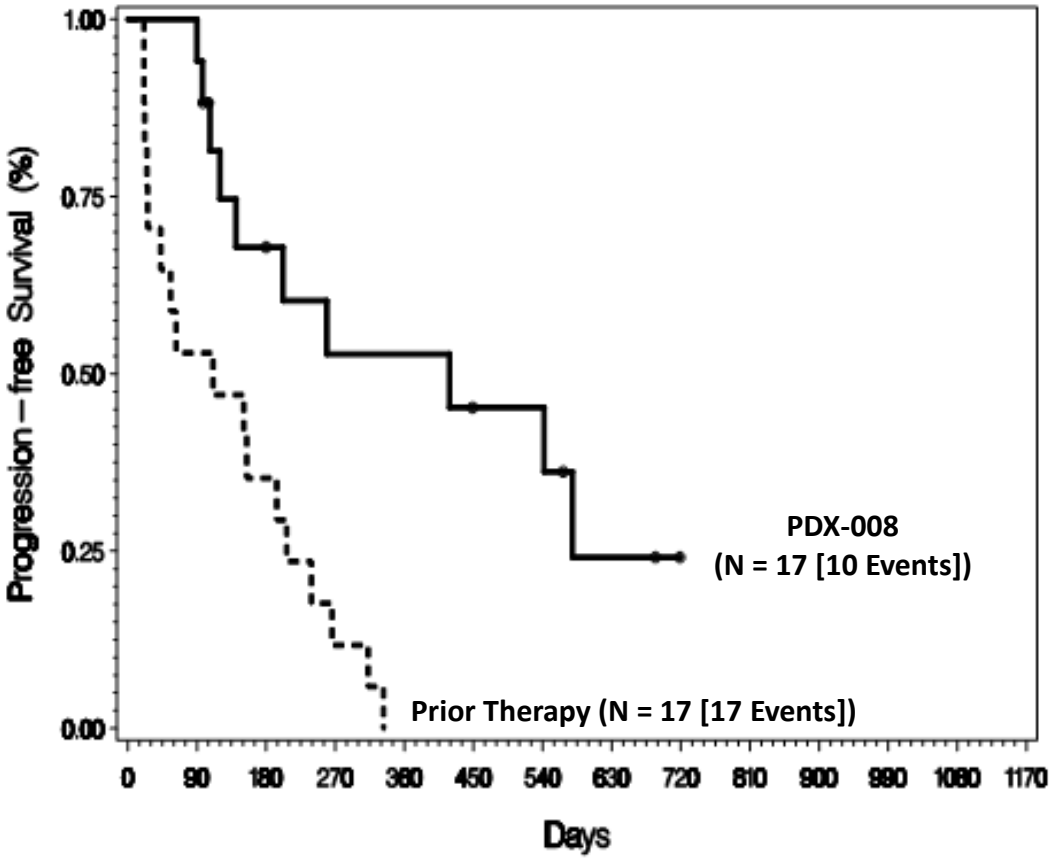
A Comparison of Drugs Evaluated in Clinical Trials in Relapsed/Refractory PTCL

Drug	Disease subtypes	N	ORR/CR (%)	PFS/DOR (months)	Prior Therapies
Pralatrexate	PTCL 53% ALCL 15% AILT 12% (18% tMF,Blastic NK, ATLL)	111	29%/19%	3.5 / 12.4	3 (1-13)
Romidepsin	PTCL 53% AILT 21%	130	25%/15%	4 / 16	2 (1-8)
Brentuximab	PTCL 77% AILT 37%	35	41%/23%	6.7 / 2.6	2 (1-9)
Bendamustine	AILT 53% PTCL 38%	60	50%/28%	3 / 6.6	1 (1-3)
Belinostat	PTCL 64% AILT 18% ALCL 10%	129	25%/10%	1.6 / 13.6	2 (1-8)

Response to Pralatrexate Clearly Associated with Prolonged PFS in Prior Non-Responders

- 69 patients had no response to last prior therapy
  - 17 of 69 (25%) responded to pralatrexate by central review
    - **5 CRs, 12 PRs**
    - **7 patients have response duration > 1 year**
    - **2 of 17 proceeded to SCT and remain in response at 21.6 and 56.5 months**
    - **Median PFS 13.8 months on pralatrexate vs 3.6 months on last prior therapy**

PFS on pralatrexate vs last therapy for pralatrexate responders with no response to prior therapy



Courtesy Spectrum/Mundipharma

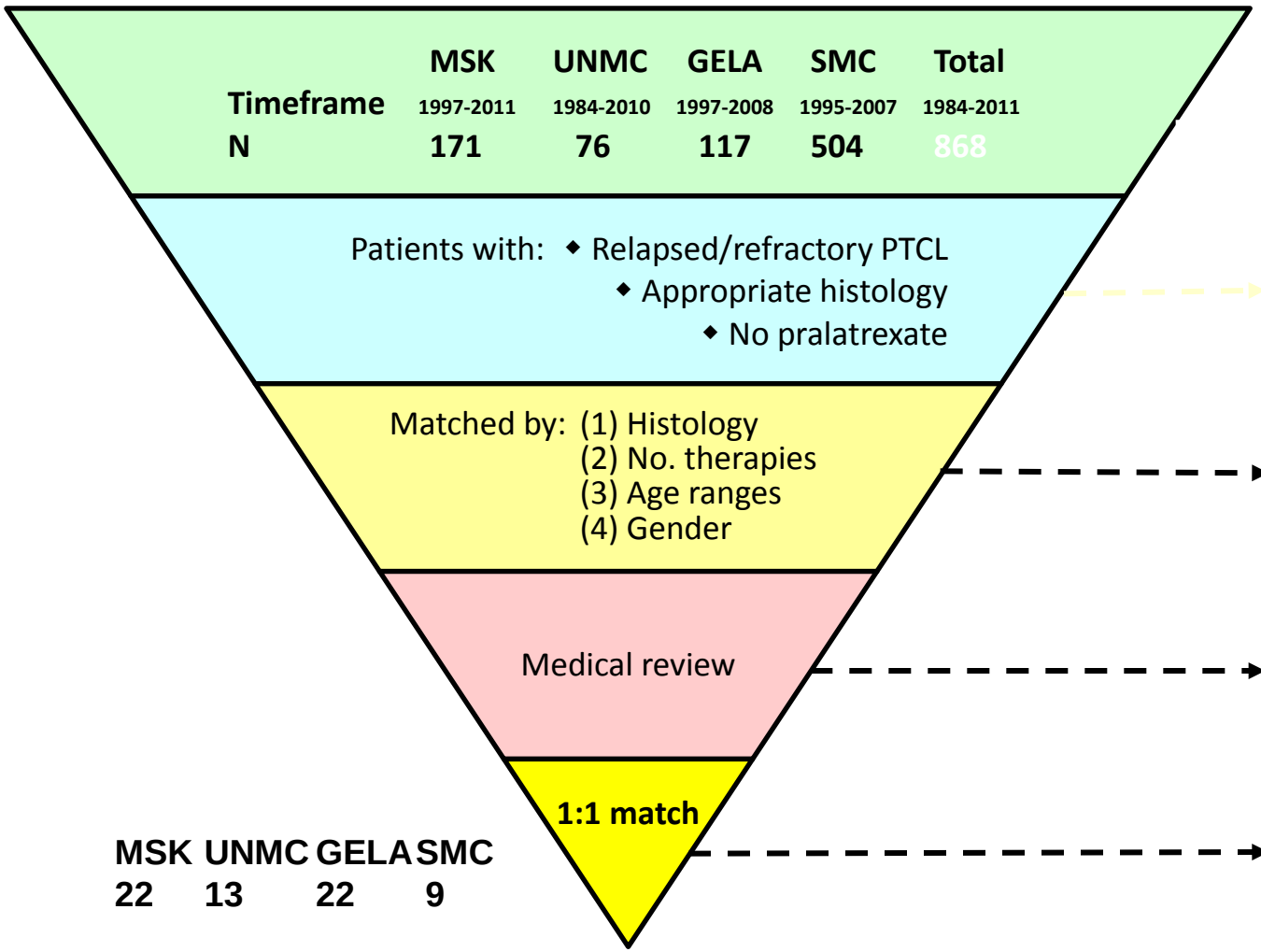
Successfully Matched Control to PDX-008

Matched Variables		PDX-008 (N = 66) %	Historical Control (N = 66) %
Histology, n (%)	ATLL (HTLV 1+)	2	2
	ALCL, primary systemic type	15	15
	AITL	14	14
	PTCL-NOS	67	67
	T/NK-cell lymphoma-nasal	3	3
Prior therapies, n (%)	1	30	30
	2	32	32
	3	27	27
	4	11	11
Gender	Male/Female/Missing	62/38/0	58/29/14
Age at start of matched therapy/ pralatrexate	Median (years)	61.0	60.5
	< 65/≥ 65 years	61/39	61/39
Time from diagnosis to matched therapy/pralatrexate	Median (years)	13.7	11.5

Courtesy Charlie Morris

Case Matching Procedures Using 4 Databases From 3 Continents

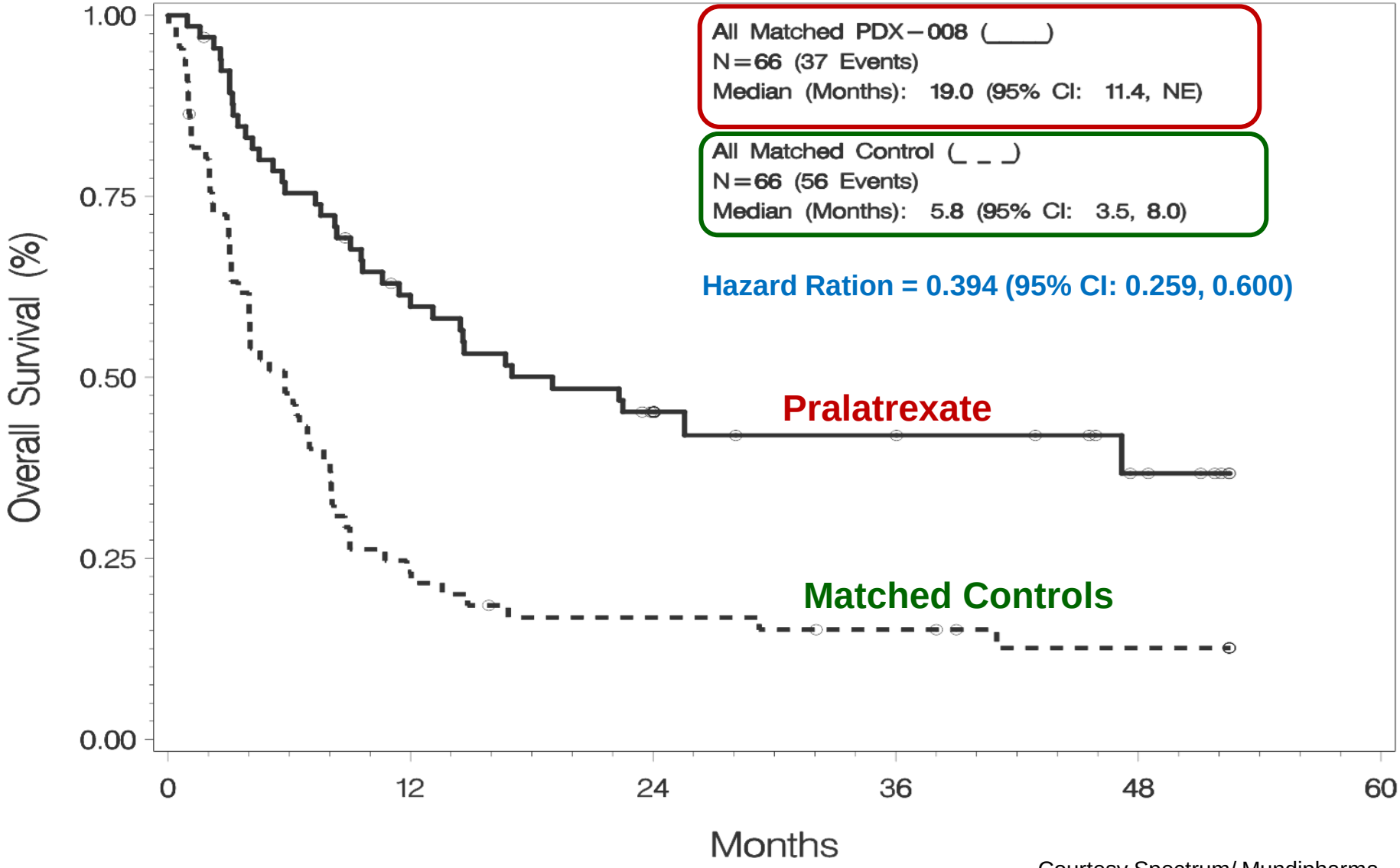
Very Closely Matched Patients Populations



Historical control N	PROPEL N
868	-
390	109
280	75
92	75
66	**66**

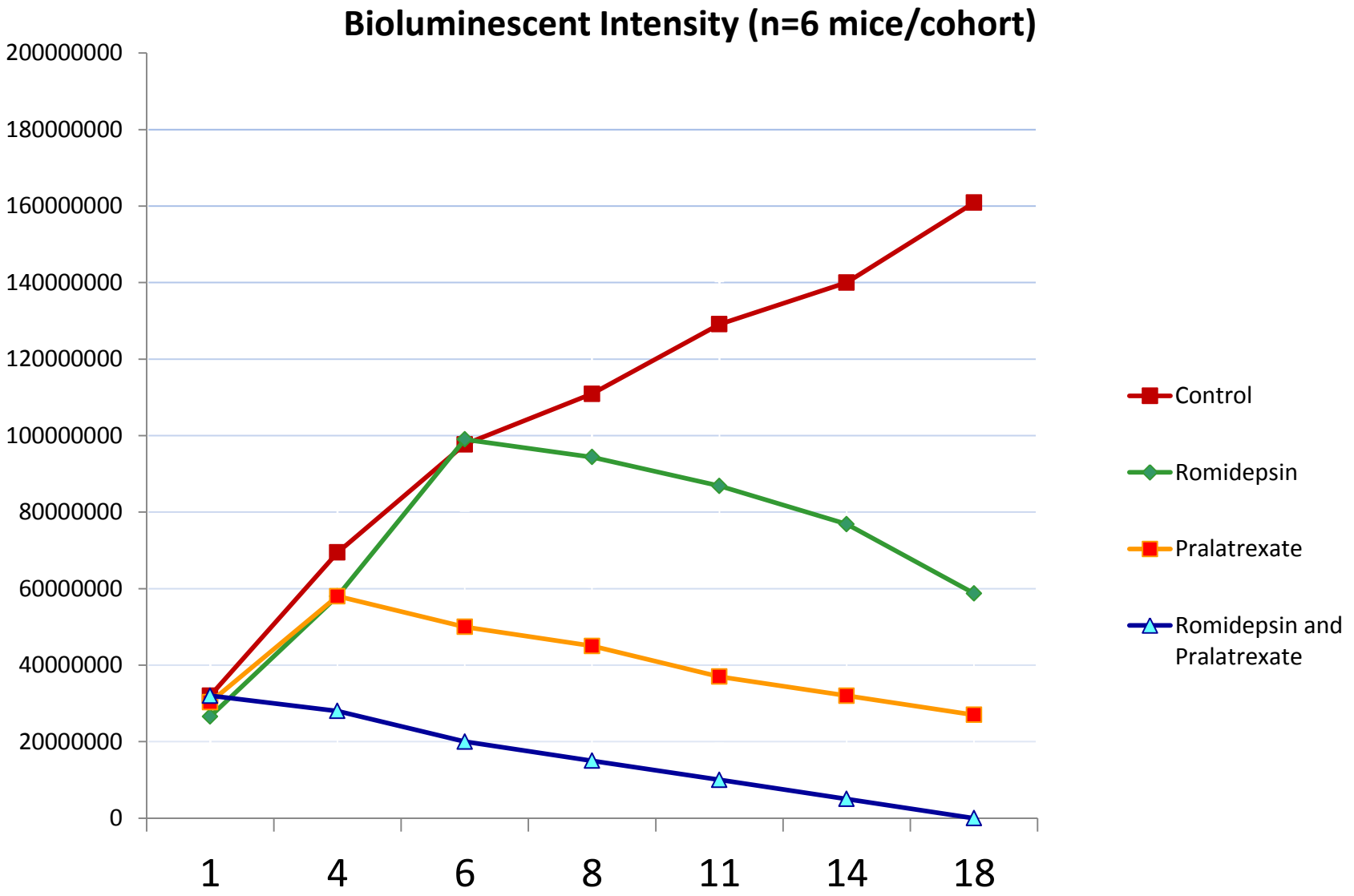
Courtesy Spectrum/Mundipharma

Significant Improvement in Overall Survival vs Matched Controls



Courtesy Spectrum/ Mundipharma

The Combination of Romidepsin and Pralatrexate Produces Complete Remission in T-Cell Lymphoma Not Seen with the Single Agents



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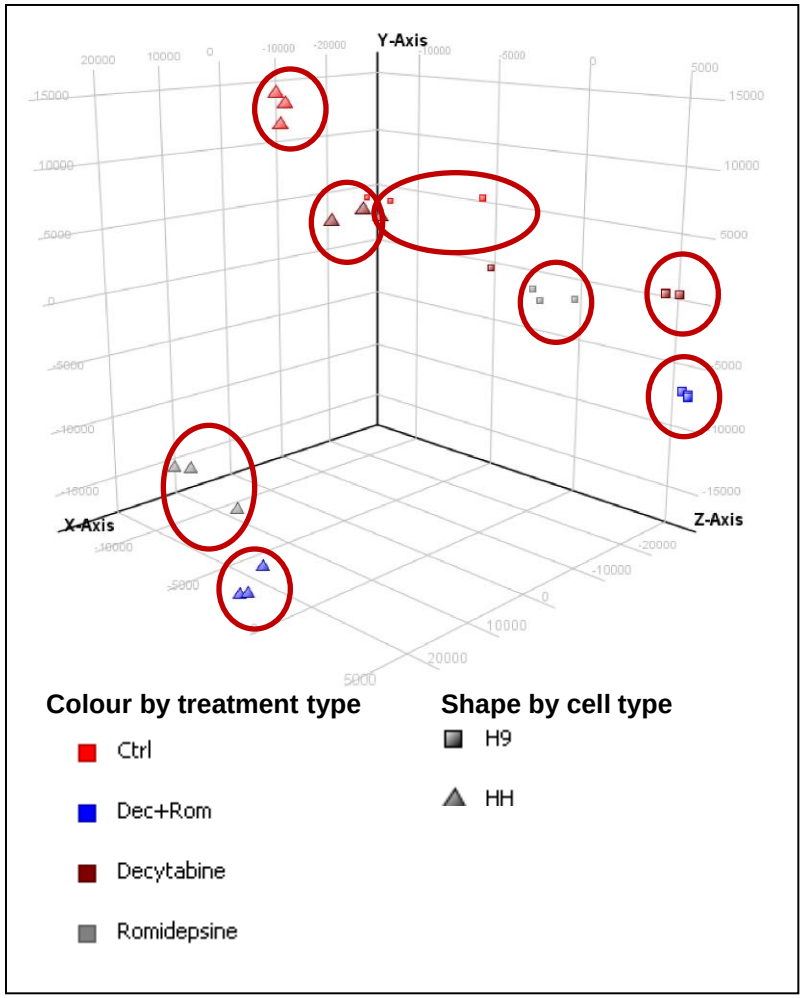

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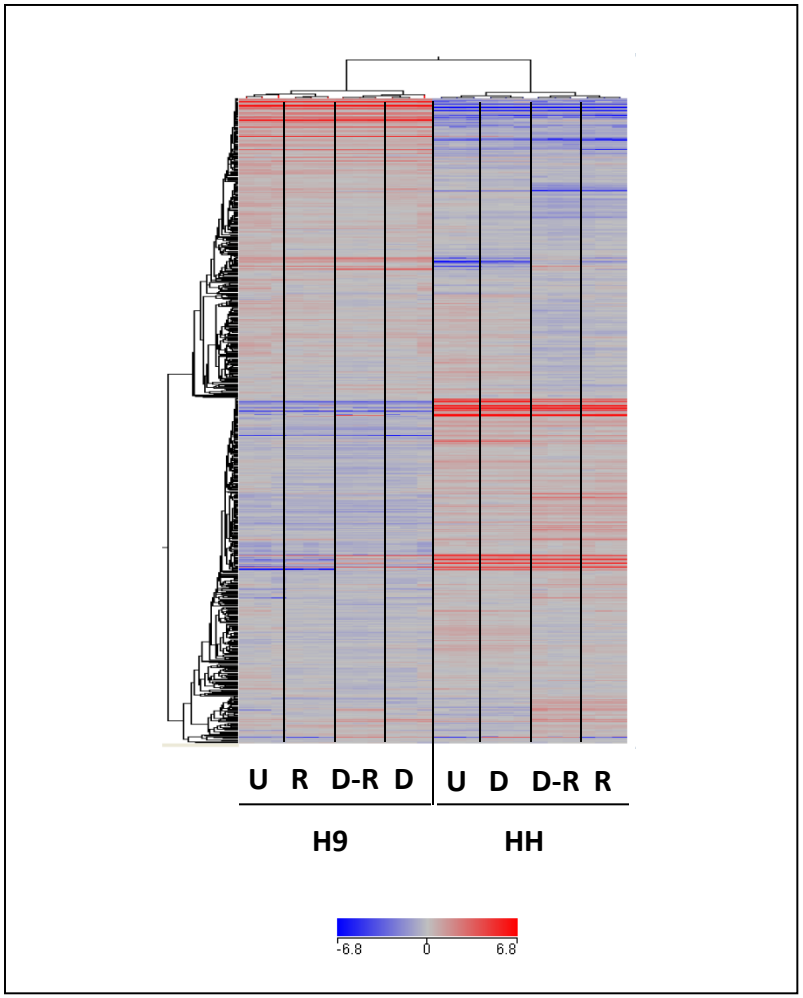
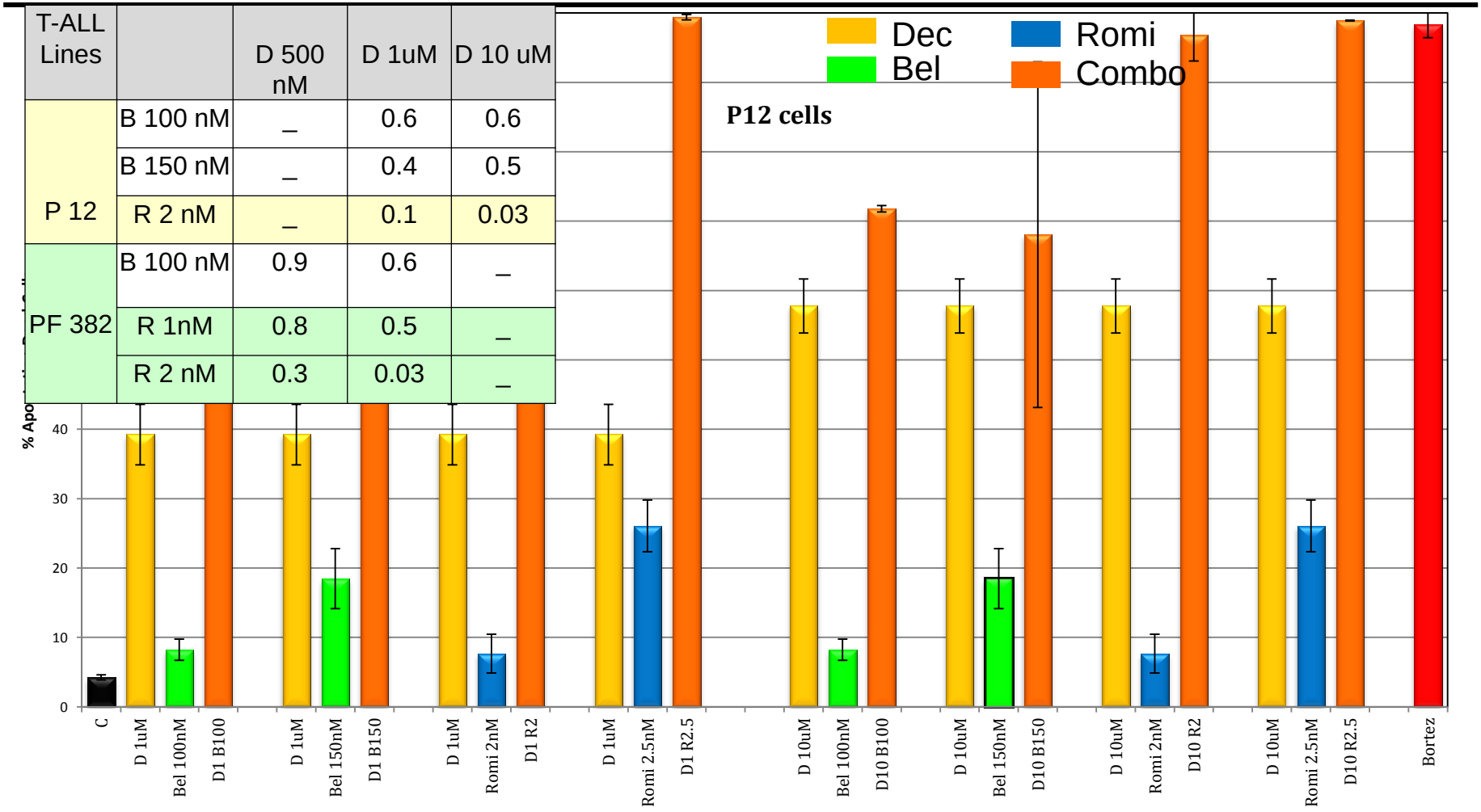


Cumulative variance=73.63%

Principle Component Analysis (PCA) Demonstrates Clear Distinction and Unsupervised Hierarchial Clustering Divided Samples According to Cell Type and Treatment

The Combination of HoME and HDAC Inhibitor Synergistically Produces Apoptosis Across Panel of T-Cell Lymphomas: P12 T-ALL

T-ALL Lines		D 500 nM	D 1uM	D 10 uM
P 12	B 100 nM	_	0.6	0.6
	B 150 nM	_	0.4	0.5
	R 2 nM	_	0.1	0.03
PF 382	B 100 nM	0.9	0.6	_
	R 1nM	0.8	0.5	_
	R 2 nM	0.3	0.03	_



CD30 is Higly Expressed Across Most PTTCL Sybtypes: International PTCL Study

Subtype (n)	CD30 Expression (%)			
	0-5%	6-49%	50-80%	>80%
PTCL-NOS (168)	54	32	7	7
AITL (167)	55	42	2	1
EATL (27)	74	11	4	11
ATLL (120)	50	37	8	5
Nasal NK/T (73)	53	34	6	7
Extranasal NK/T (30)	27	27	23	23

Courtesy Dennis Weisberger, University of Nebraska

Brentuximab vedotin in Relapsed / Refractory ALCL: Key Response Results Summary

	N=58
Objective response rate (95% CI)	86% (75, 94)
Median duration of OR (95% CI)	12.6 mo (5.7, –)
CR rate (95% CI)	57% (43, 70)
Median duration of response in patients with CR (95% CI)	13.2 mo (10.8, –)
Median PFS (95% CI)	13.3 mo (6.9, –)
Median OS	Not reached

Pro et al. JCO, 2012: 30(18): 2190

Brentuximab vedotin in Relapsed PTCL (Non-ALCL PTCL)

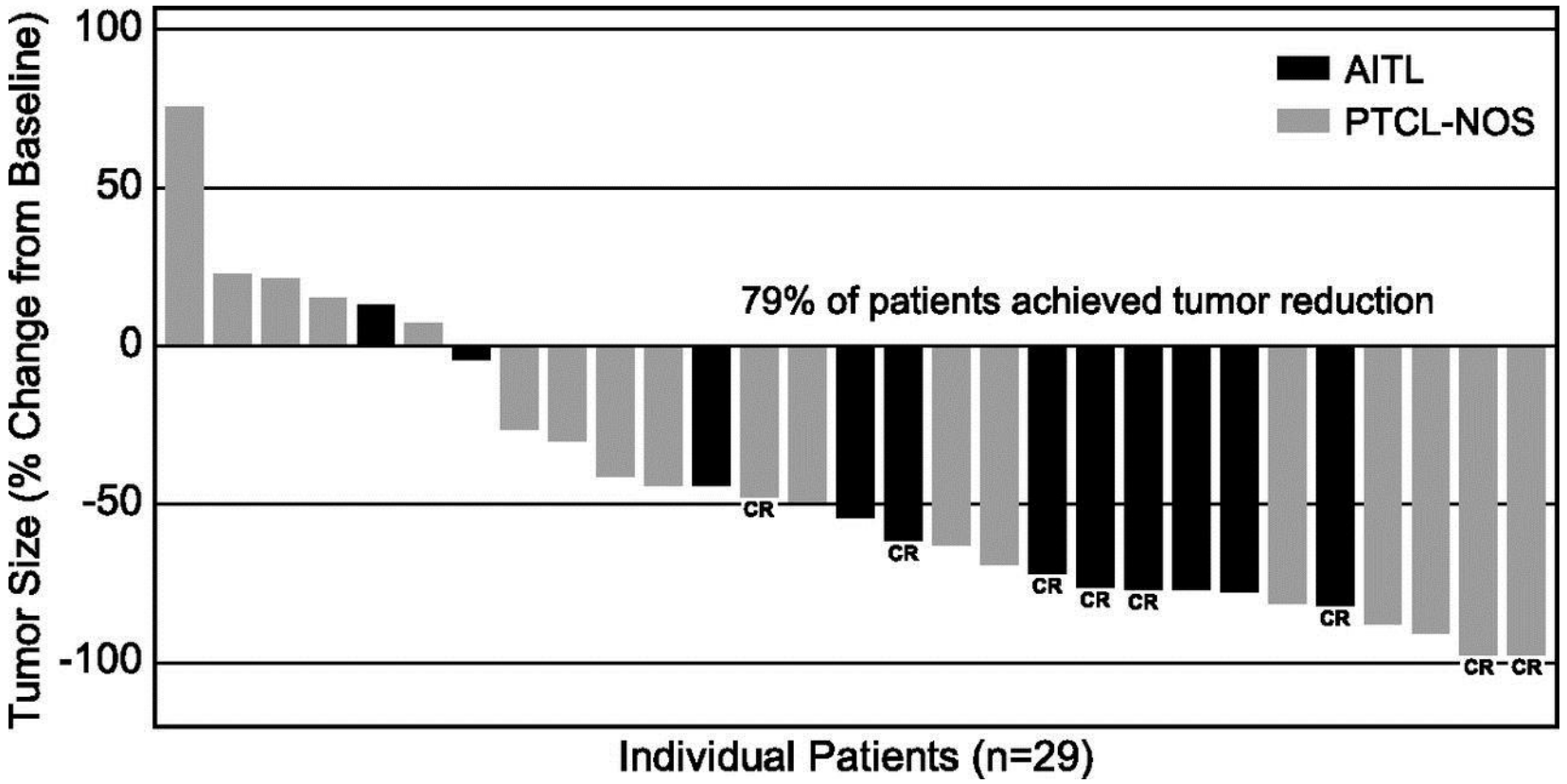
	AITL (n=13)	PTCL-NOS (n=21)	Total (n=34)
ORR	7 (54%)	7 (33%)	14 (41%)
Complete remission	5 (38%)	3 (14%)	8 (24%)
Partial remission	2 (15%)	4 (19%)	6 (18%)
Stable disease	3 (23%)	3 (14%)	6 (16%)
Progressive Disease	3 (23%)	11 (52%)	14 (41%)
Progression free survival	6.74 mo	1.61 mo	2.6 mo

- Comparatively restricted patient population
- Short duration of PFS compared to other agents
- Not a heavily treated patient population

Horwitz et al. Blood, 2012; 123(20):3095-3100

Brentuximab vedotin in Relapsed PTCL (Non-ALCL PTCL)

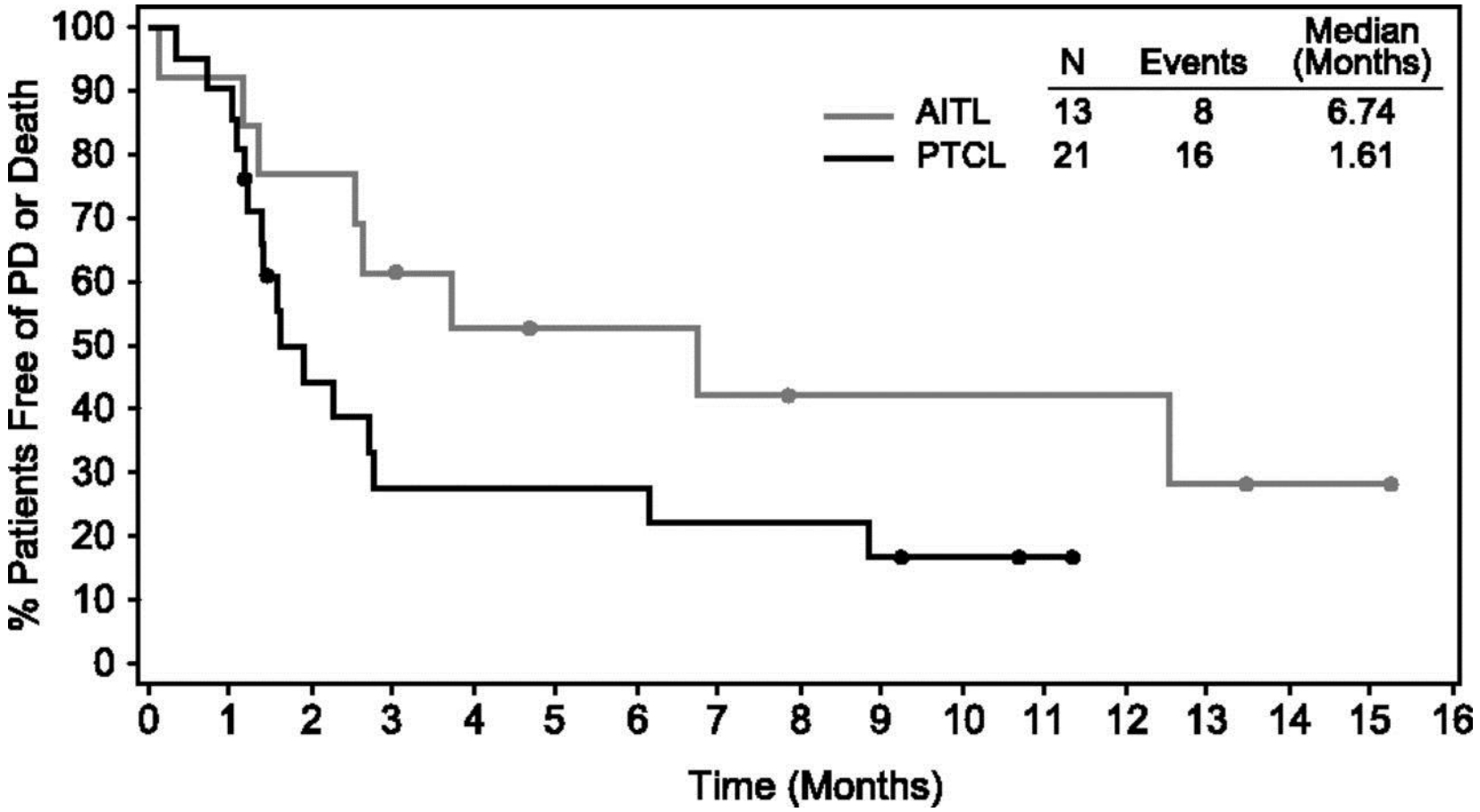
Maximum Tumor Size Reduction from Baseline



Horwitz S M et al. Blood 2014;123:3095-3100

blood

Brentuximab vedotin in Relapsed PTCL (Non-ALCL PTCL)
PFS by Histology Subtype

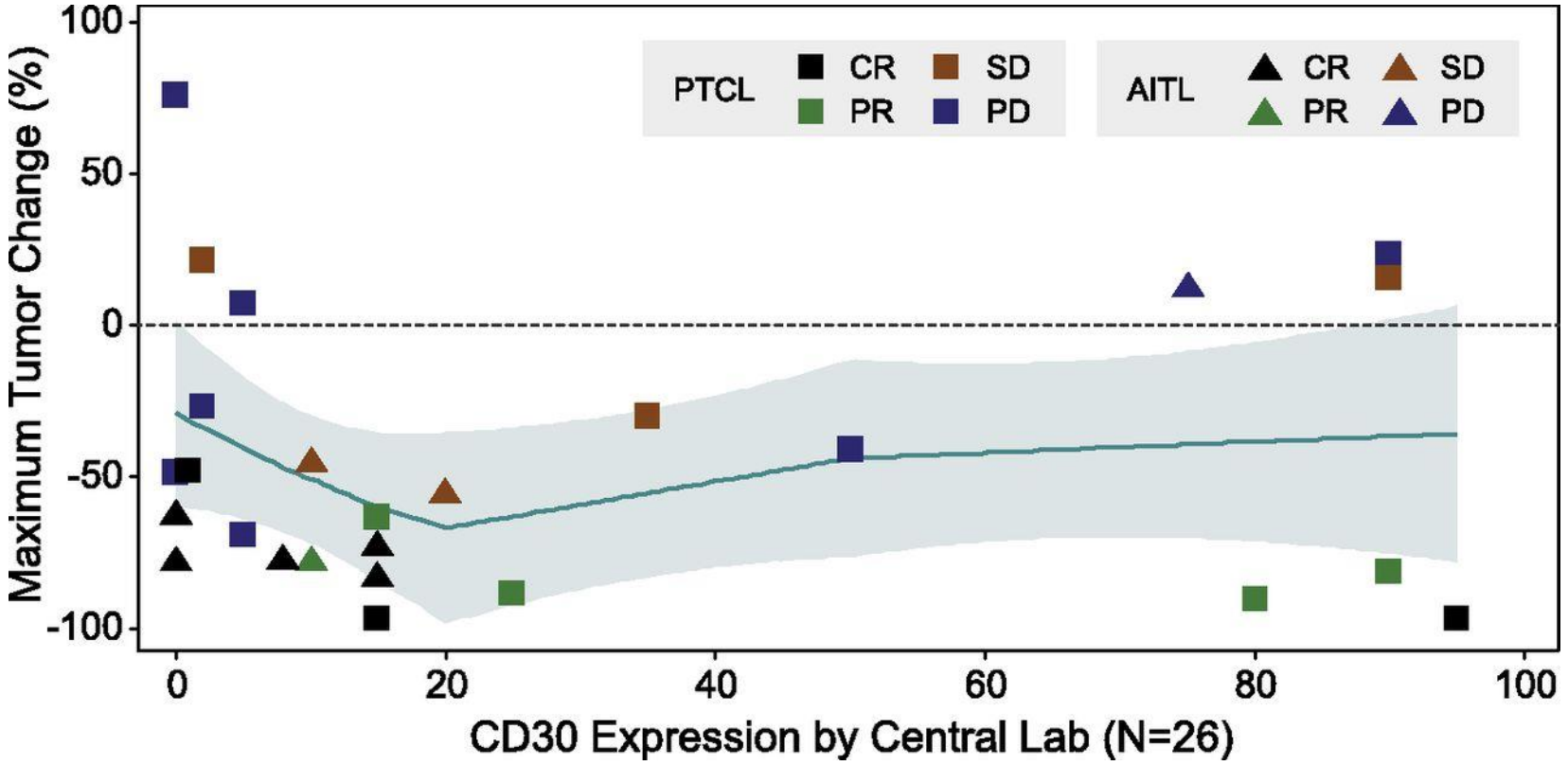


Horwitz S M et al. Blood 2014;123:3095-3100

blood

Brentuximab vedotin in Relapsed PTCL (Non-ALCL PTCL)

Maximum Tumor Size Decrease by Quantitative CD30 Expression



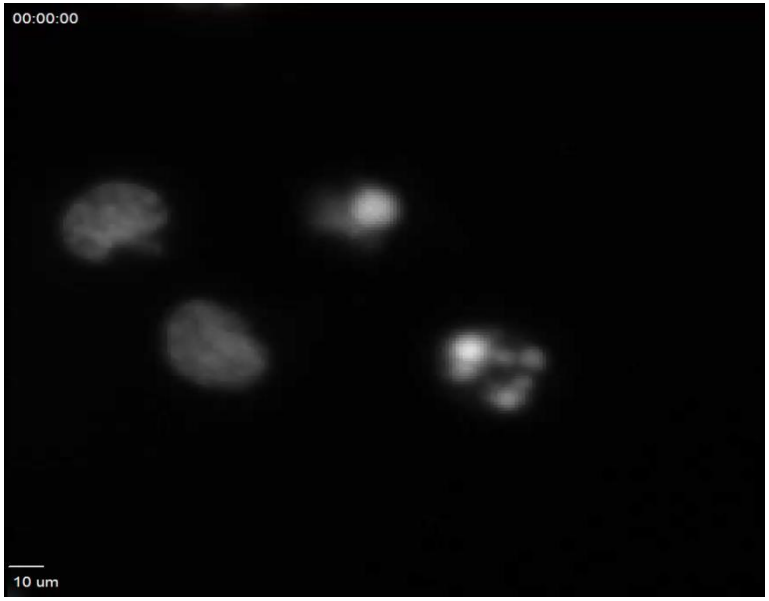
Level of CD30 Expression Does not Correlate with Response

Horwitz S M et al. Blood 2014;123:3095-3100

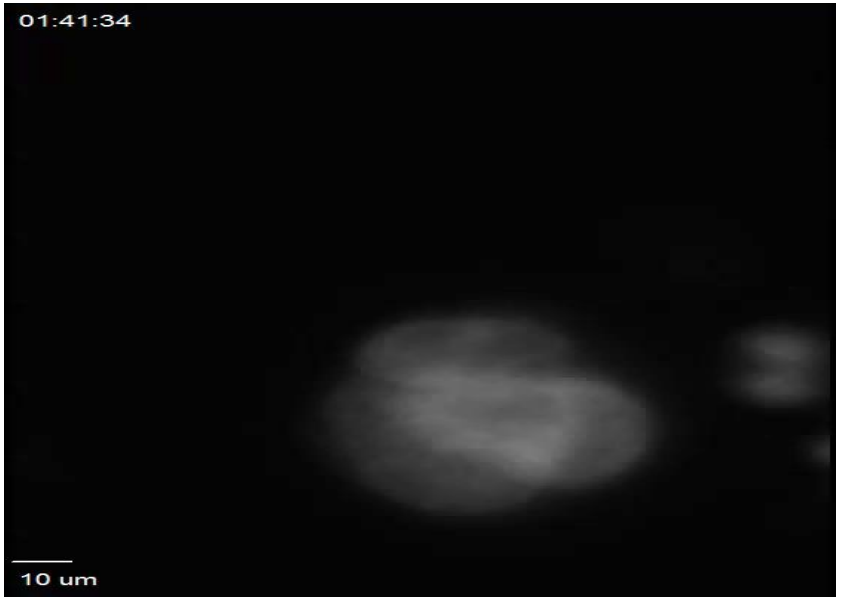
blood

We Developed the First Live Cell Imaging of Lymphoma Cells in Culture

Untreated Cells



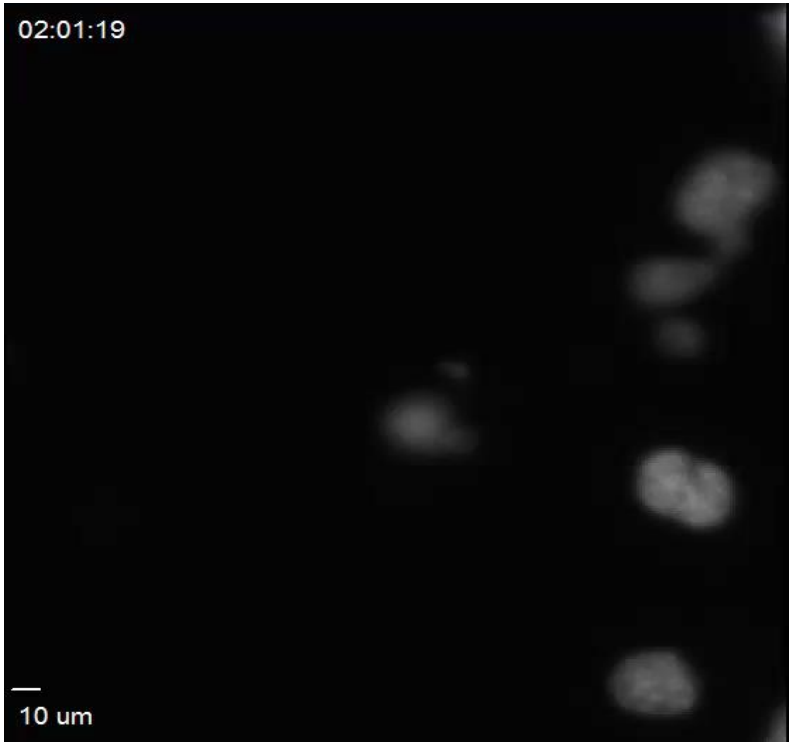
Alisertib



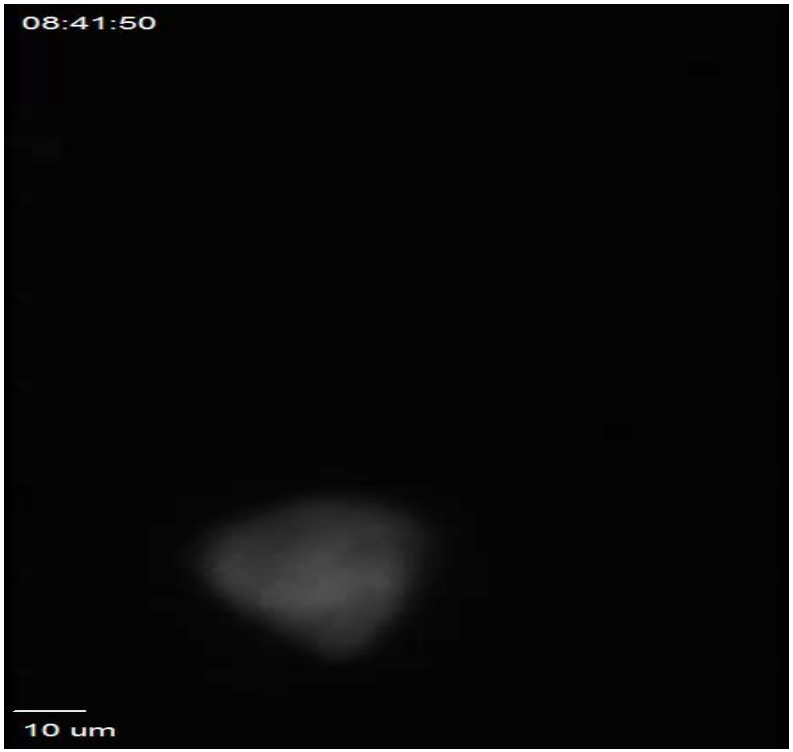
- Untreated cells divide and replicate on a roughly every 24 hour basis
- Alisertib treated cells accumulate in mitosis (appearing as two conjoined cells)

Live Cell Imaging of Lymphoma Cells Treated with the Combination Demonstrates Greater Inhibition of Growth

Romidepsin cells



Alisertib in combination with Romidepsin cells



This Powerful Technique Allows Us to Directly Visualize and Understand What Happens to a Lymphoma Cell Following Treatment with New Drugs