What's the Data Supporting The Clinical Merits of Targeting the PTCL Epigenome?

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T-Cell Lymphomas: Finally, Vision and Mission!
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- Just how does targeting the PTCL epigenome kill a malignant cell?
- Next steps, oh so many, but…….Dr. Marchi will highlight epigenetic strategies that may modulate the 'immunome' which may have the strongest logic.

The Null Hypothesis
There is no difference in outcome between conventional chemotherapy and drugs (as +/-) targeting the epigenome.

The Alternative Hypothesis
There is a difference in outcome between conventional chemotherapy and drug targeting the epigenome

THE WORLD OF T-CELL LYMPHOMA

Resolution
Conduct a randomized study of epigenetic targeted drugs against SOC chemotherapy regimens

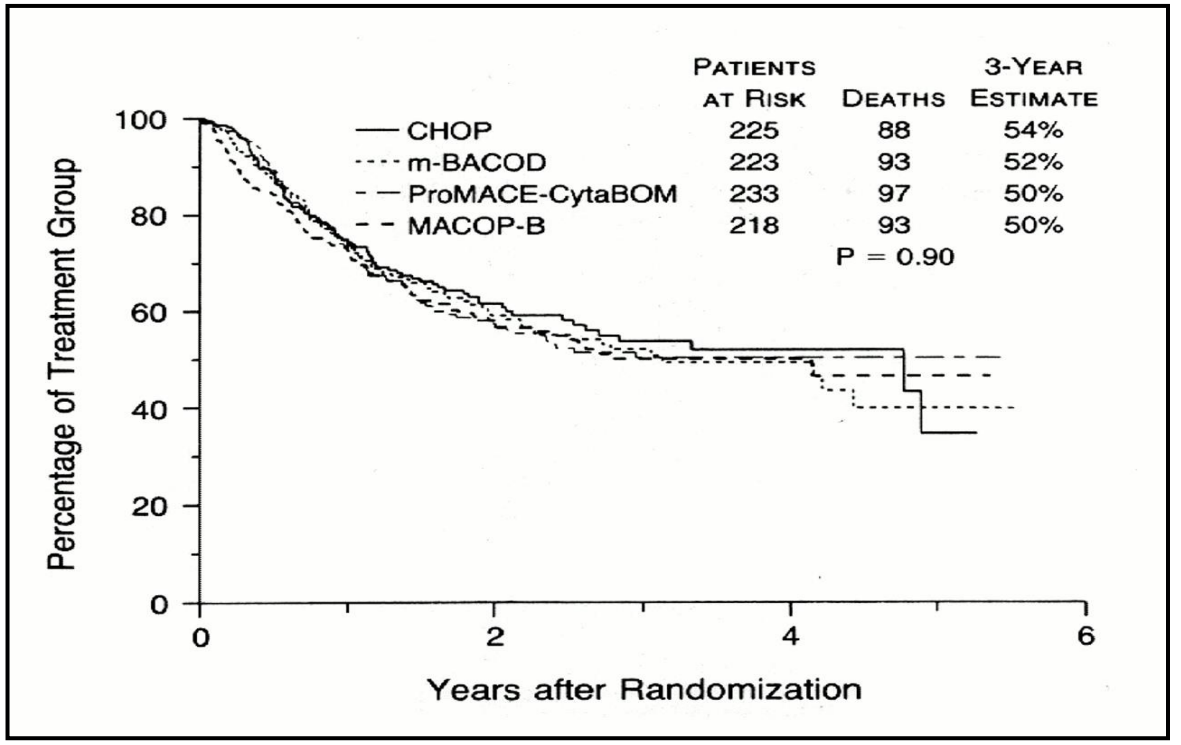
COMPARISON OF A STANDARD REGIMEN (CHOP) WITH THREE INTENSIVE CHEMOTHERAPY REGIMENS FOR ADVANCED NON-HODGKIN'S LYMPHOMA

RICHARD I. FISHER, M.D., ELLEN R. GAYNOR, M.D., STEVE DAHLBERG, M.S., MARTIN M. OKEN, M.D., THOMAS M. GROGAN, M.D., EVONNE M. MIZE, JOHN H. GLICK, M.D., CHARLES A. COLTMAN, JR., M.D., AND THOMAS P. MILLER, M.D.

CHARACTERISTIC	CHOP (N = 225)	m-BACOD (N = 223)	ProMACE-CytaBOM (N = 233)	MACOP-B (N = 218)
Age				
Median (yr)	56	57	54	57
Range (yr)	15–79	18–81	17–81	19–79
≥65 yr (%)	26	25	27	24
Marrow involvement (%)	25	26	27	27
Bulky disease (%)	40	41	41	40
LDH >250 U/liter (%)*	45	43	42	43
Working formulation group (%)†				
D or E	14	15	15	14
F, G, or H	81	82	81	82
J	5	4	4	4

*LDH denotes lactate dehydrogenase.

†These groups were defined according to the system of the Non-Hodgkin's Lymphoma Pathologic Classification Project.[10]



Is This One of the Reasons Why We Get Here?

Anyone Remember This?

Its the Study Population That Led to the SOC in PTCL

The Working Formulation

Low Grade	Intermediate Grad	High Grade
Small lymphocytic (A)	Follicular large cel	Large cell immunoblastic (H)
Follicular small cleaved cell (B)	Diffuse d cell (E)	Lymphoblastic (I)
Follicular small cleaved and large cell (C)	ixed and small and cell (F)	Small non-cleaved cell (Burkitt and non-Burkitt type) (J)
	Diffuse large cell (G)	

So, Where is PTCL?

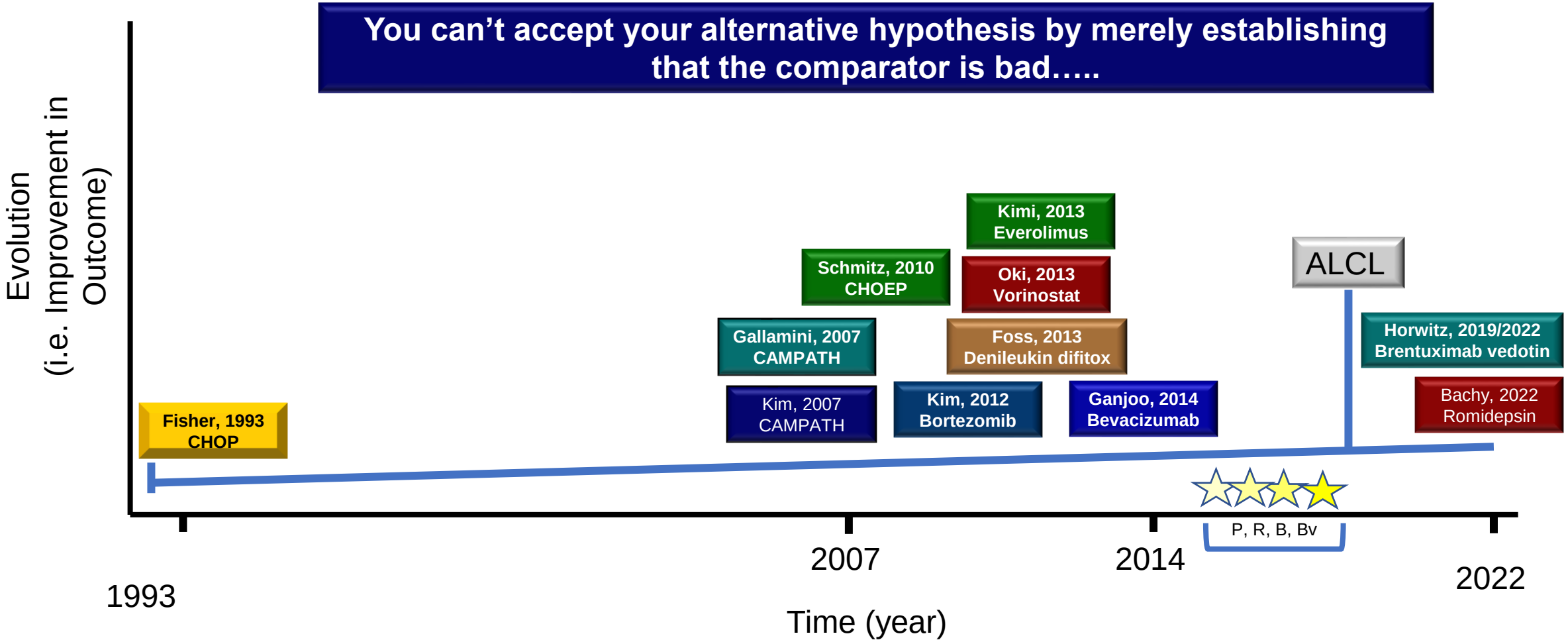
D and E ~ 14-15%

F, G & H ~ 80%

J ~ 4%

THE EVOLUTION OF CHOP AND CHOP-PLUS REGIMENS

3-DECADES OF RELATIVE STAGNATION



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Evidence the PTCL May be a Prototypical Epigenetic Disease

A Non-Exhaustive List of Considerations

Event	Timeline
Inactivating mutations in SWI/SNF complex (chromatin remodeler) SNF5/INI1/BAF47 in T-cell Lymphoma	Yuge et al., *Cancer Genet Cytogenet* 2000
First case report of an HDAC inhibitor (romidepsin) exhibiting activity in CTCL (R. Piekarz and S. Bates)	2001
Vorinostat achieves U.S. FDA approval for R/R/ CTCL	2006
Over-expression of HDAC2 and HDAC4 leading to H4 acetylation reported in CTCL. HDAC 6 prognostic in CTCL	Marquard et al., Hematopathology. 2008
Romidepsin achieves U.S. FDA approval in R/R CTCL	2009
Romidepsin ahieves U.S. FDA approval in R/R PTCL	2011
Mutations in DNMT3 in PTCL Mutations in TET2 in AITL and PTCL Mutations in IDH2 in AITLE and PTCL	Couronne et al., NEJM. 2012 Lemonnier et al., Blood. 2012 Cairns et al., Blood. 2012
Belinostat achieves U.S. FDA approval in R/R PTCL	2014
Chidamide achieves regulatory approval in CHINA in R/R PTCL	2015

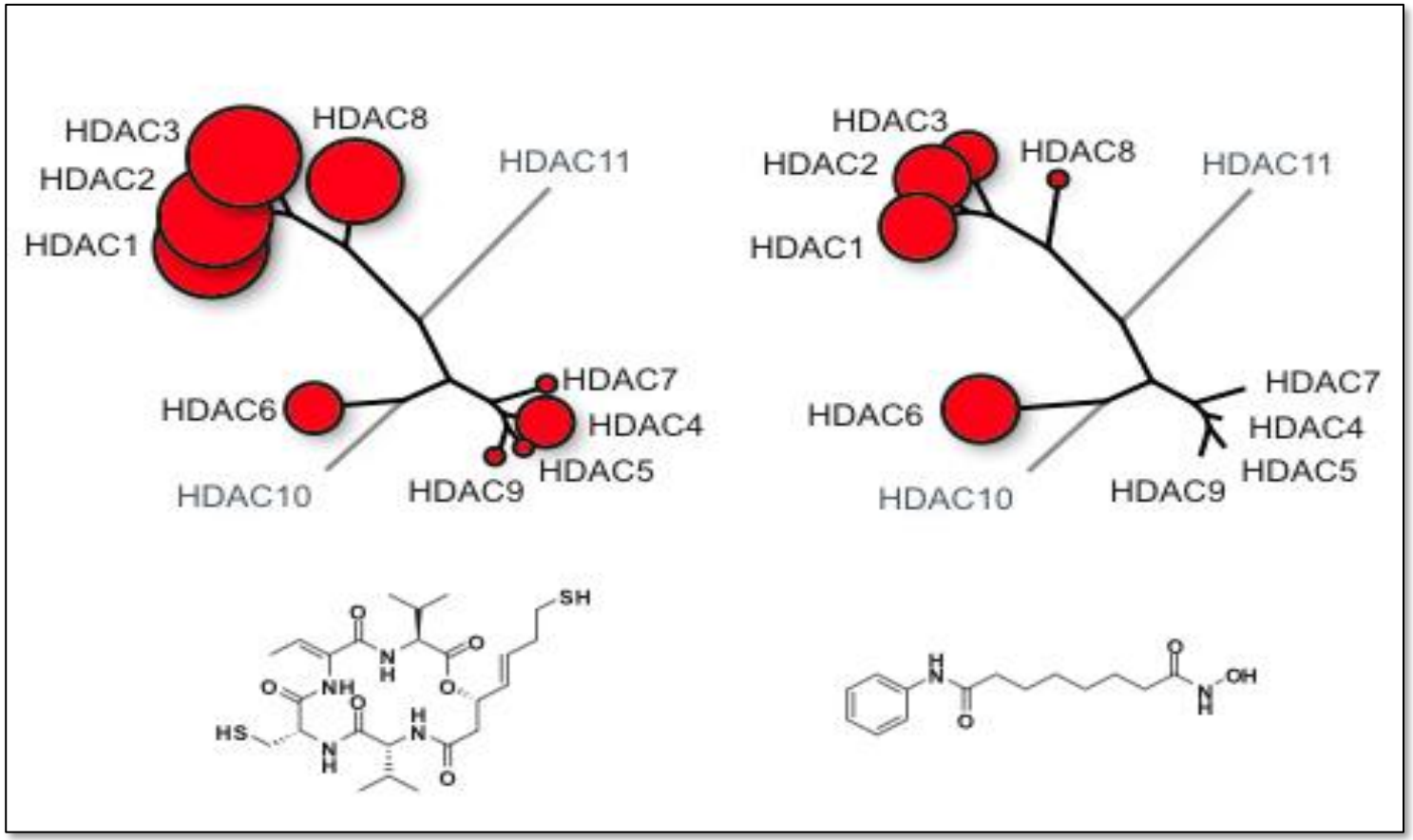
One of the First Big Clues That the PTCL Epigenome is a Valid Target

	Vorinostat	Romidepsin	Belinostat	Chidamide
Approval	CTCL (2006)	CTCL (2009) PTCL (2011)	PTCL (2014)	China Only PTCL (2015)
ORR	30%	25%	26%	28%
CR	1%	15%	11%	14%
PFS	8.5 months	2.6 months	1.6 months	4.3 months
DOR	5.5 months	28 months	13.6 months	9.9 months
Reference(s)	Olson et al. 2007 O'Connor et al. 2006 (FIH)	Coiffier et al., 2014	O'Connor, et al. 2015	Shi et al., 2015

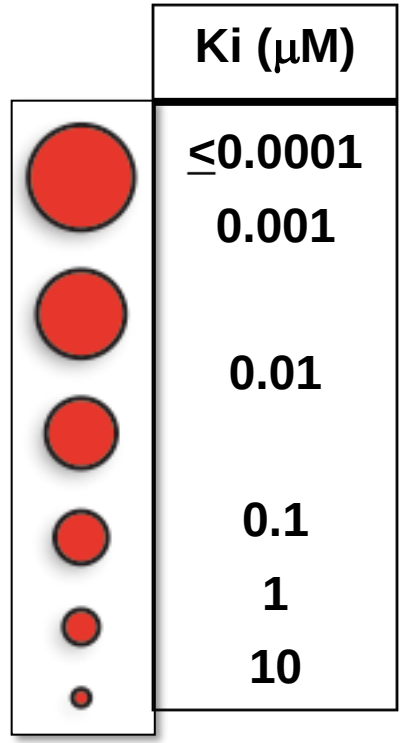
A remarkably consistent 25% of patients respond across PTCL and CTCL

PHYLOGENETIC RELATIONSHIPS BETWEEN VORINOSTANT AND ROMIDEPSIN

(NOT ALL HDACI ARE CREATED EQUALLY)



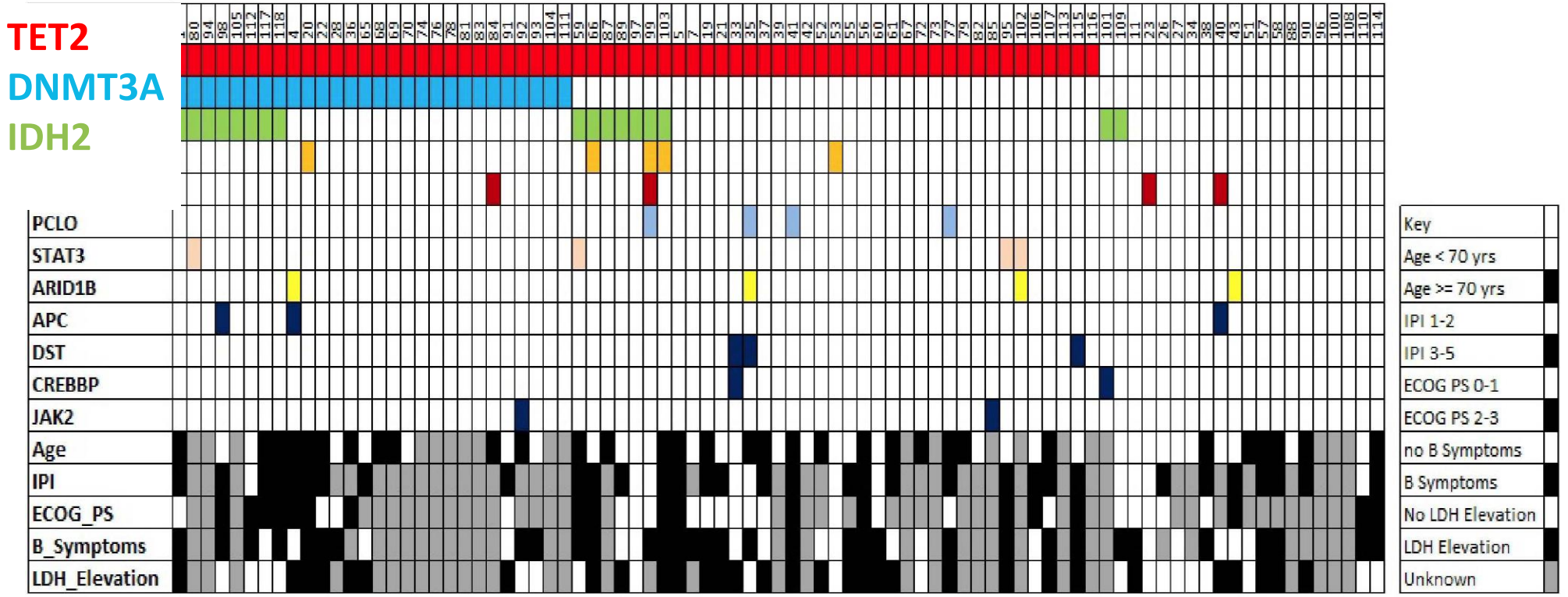
Chemical Phylogenetics Of Histone Deacetylase Inhibitors
Bradner et al. Nature Chem Biol 6:238 – 243, 2010



Just a Few of the Many Established Epigenetic Lesions in the T-Cell Lymphomas

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 Cytogenet* 2000

3 Well Established Paths to Aberrant DNA Methylation



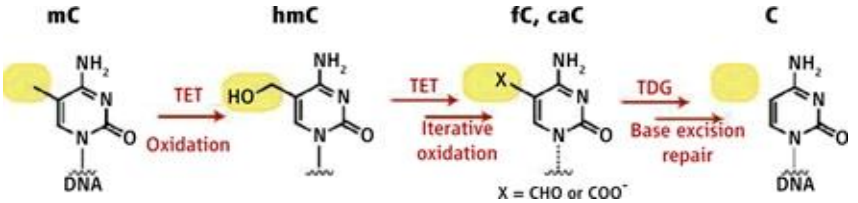
Does this open the door for considering hypomethylating agents?

Odejide et al., December 17, 2013;

THE FREQUENCY OF IDH MUTATIONS IS INCONSISTENT ACROSS SUBTYPES

Disease	IDH1R132	IDH2R172	IDH2R140
Hodgkin lymphoma	0/66	0/66	0/66
Non-Hodgkin B-cell lymphoma	0/14	0/14	0/14
B-cell acute lymphoblastic lymphoma (ALL B) 0	0/32	0/32	0/32
T-cell acute lymphoblastic lymphoma (ALL T) 0/8 0/8	0/8	0/8	0/8
AML	2/8	0/8	0/8
PTCL			
PTCL not otherwise specified (PTCLnos)	0/43	0/43	0/43
Anaplastic large cell lymphoma (ALCL)	0/50	0/50	0/50
Enteropathy type T-cell lymphoma (ETL)	0/8	0/8	0/8
Cutaneous T-cell lymphoma (CTCL)			
Hepatosplenic T-cell lymphoma (HSTCL)	0/10	01/10	01/10
Extranodal NK/T-cell lymphoma (NK/TCL)	0/10	0/10	0/10
AITL	0/79	15/79	1/79
UNMC Patients			
AITL 0/22	0/22	0/22	0/22

- IDH1 (R132) and IDH2 (R140/R172) mutations frequently observed in myeloid malignancies
  - ~15-30% de novo and secondary AML
  - Myelodysplasia and myeloproliferative disorders (~5% chronic phase; ~20% transformed cases)
- IDH1/2 catalyzes interconversion of isocitrate and α-KG
- Mutant IDH1/2 acquires neomorphic enzymatic activity, catalyzing the reduction of α-KG to 2R-HG
- 2HG also inhibit all oxoglutarate dependent dioxygenases including TET enzymes histone demethylases and prolyl hydroxylases
- TET2 mutation → AML hypermethylation phenotype (Levine and Melnick, Cancer Cell 2010)



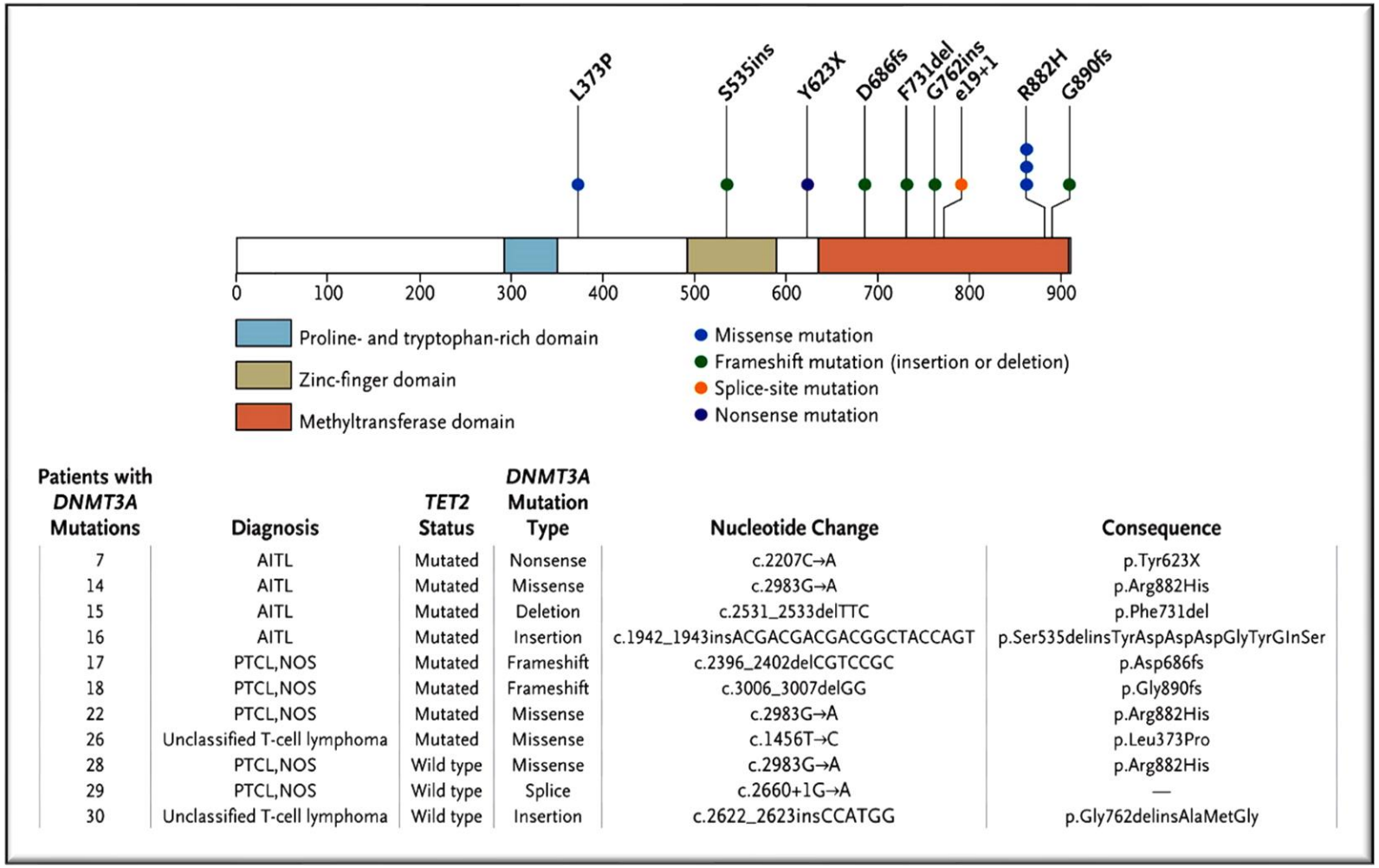
Cairns et al., Blood, 2012

TET2 Mutations Across PTCL Subtypes

Really no Consistent Signal

PTCL entity	TET2 mutation		
	N of disease	N with mut	%
AITL	86	40	47
PTCL NOS*	58	22	38
T_{FH}-like	24	14	58
Others	34	8	24
ALCL	18	0	0
EATL*	10	2	20
Extranodal NK/T	12	0	0
HSTL	6	0	0
Total	**190**	**64**	**34**

DNMT3 Mutations In 96 Patients with T-Cell Lymphoma as Function of TET-2 Status

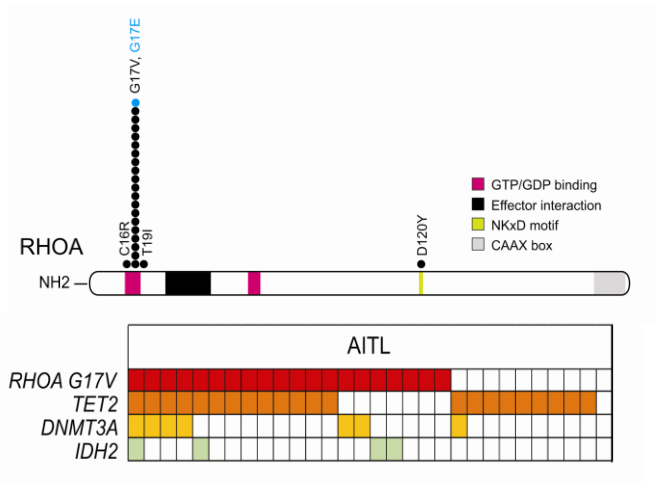


Patients with *DNMT3A* Mutations	Diagnosis	*TET2* Status	*DNMT3A* Mutation Type	Nucleotide Change	Consequence
7	AITL	Mutated	Nonsense	c.2207C→A	p.Tyr623X
14	AITL	Mutated	Missense	c.2983G→A	p.Arg882His
15	AITL	Mutated	Deletion	c.2531_2533delTTC	p.Phe731del
16	AITL	Mutated	Insertion	c.1942_1943insACGACGACGACGGCTACCAGT	p.Ser535delinsTyrAspAspAspGlyTyrGlnSer
17	PTCL,NOS	Mutated	Frameshift	c.2396_2402delCGTCCGC	p.Asp686fs
18	PTCL,NOS	Mutated	Frameshift	c.3006_3007delGG	p.Gly890fs
22	PTCL,NOS	Mutated	Missense	c.2983G→A	p.Arg882His
26	Unclassified T-cell lymphoma	Mutated	Missense	c.1456T→C	p.Leu373Pro
28	PTCL,NOS	Wild type	Missense	c.2983G→A	p.Arg882His
29	PTCL,NOS	Wild type	Splice	c.2660+1G→A	—
30	Unclassified T-cell lymphoma	Wild type	Insertion	c.2622_2623insCCATGG	p.Gly762delinsAlaMetGly

- Unclear if these mutations lead to frank alteration in methylation of the PTCL genome
- Unclear if any of these are truly prognostic
- Unclear what specific genes might be altered
- Unclear if these mutations portend differences in sensitivity to DNMT3 inhibitors;
- But, its another clue….

Couronné L et al. N Engl J Med 2012;366:95-96.

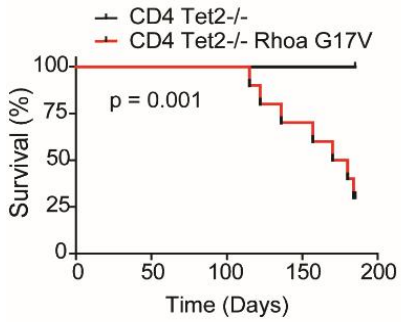
Co-occurring RHOA G17V and TET2 mutations in AITL

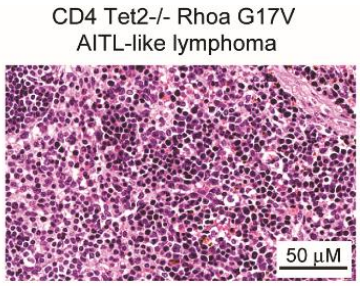


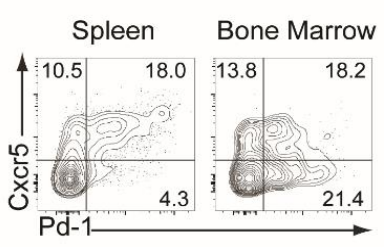
Palomero et al. Nat Genet 2014

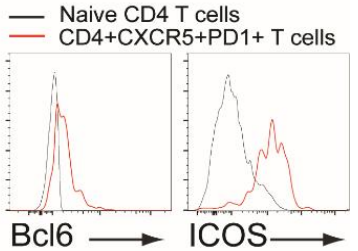
Palomero and colleagues (1 of 3 groups) show that AITL driven by RHOA G17V and loss of Tet2 can recapitulates what looks like human AITL

Expression of Rhoa G17V and loss of Tet2 induces mouse AITL

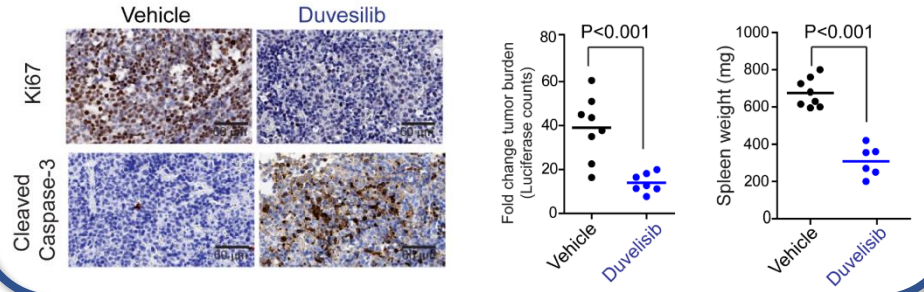






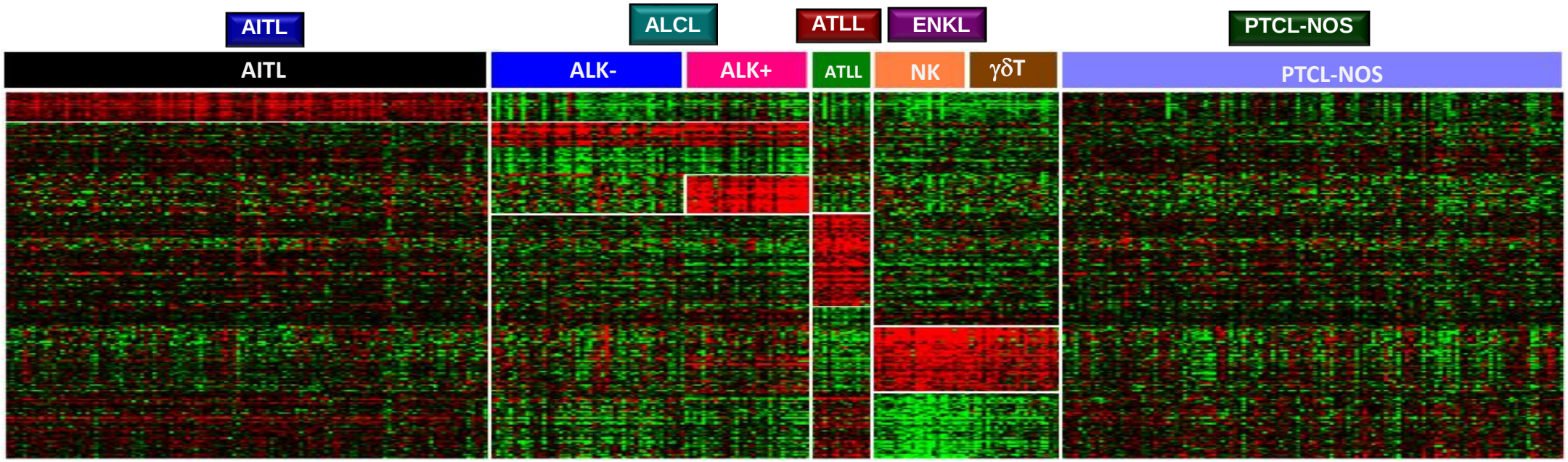


Antitumor effects of PI3K inhibition in Rhoa G17 Tet2-/- mouse induced lymphomas



Therapeutic effects seen with PI3K inhibitors

GEP Reveals Distinct Patterns Across Subtypes, But…. Cannot Unmask Epigenetic Dysregulation



Compelling strategy that could improve classification, but has not to data identified driver events to target across the diversity of the disease, and certainly not epigentic ones

Blood. 2014 May 8;123(19):2915-23.

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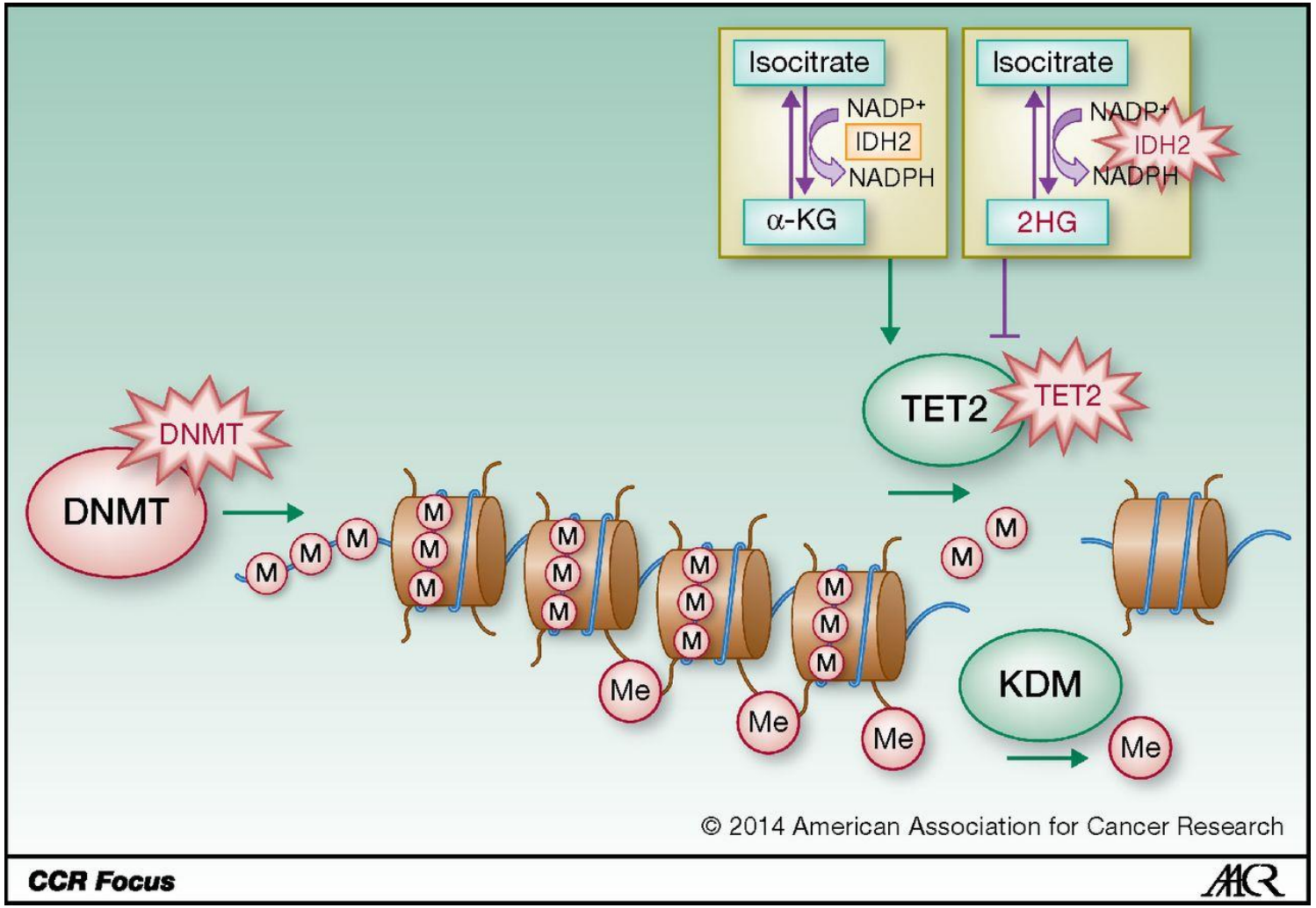
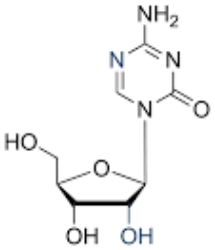
The 3 Recurring Mutations Found in PTCL/AITL All Conspire to Produce Global Hypomethylation of the PTCL Genome

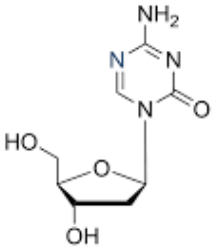
Are DNMT3 inhibitors a cornerstone class of drugs to consider in PTCL?
Or, just in subtypes with the mutation?



Targeted Drugs?



5-azacytidine (azacitibine)

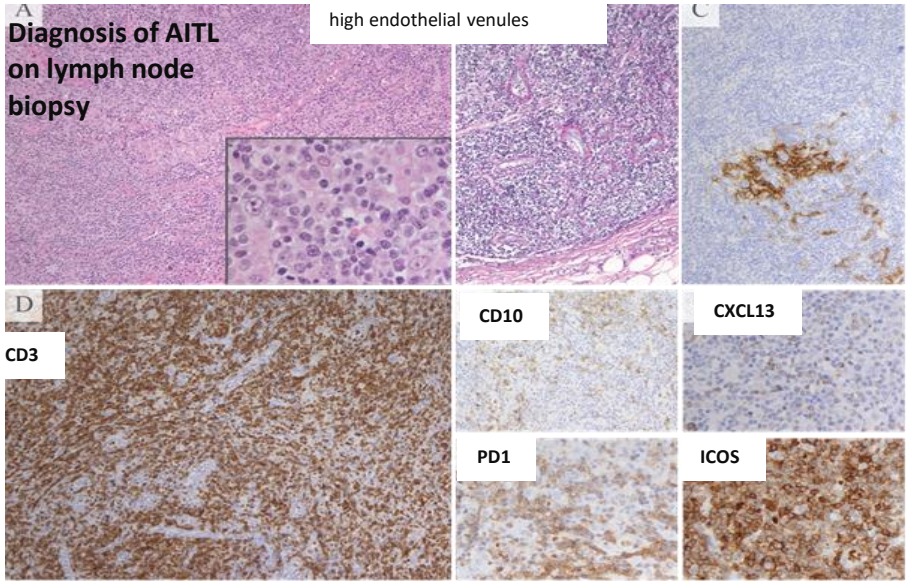


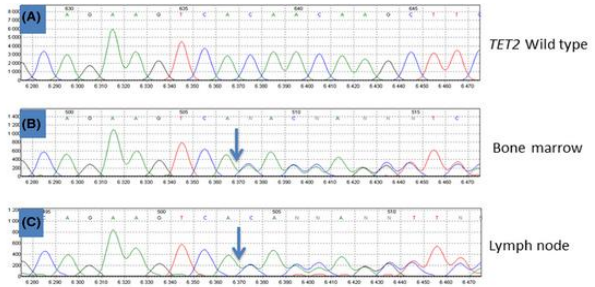
5-aza-2'-deoxycytidine (decitabine)

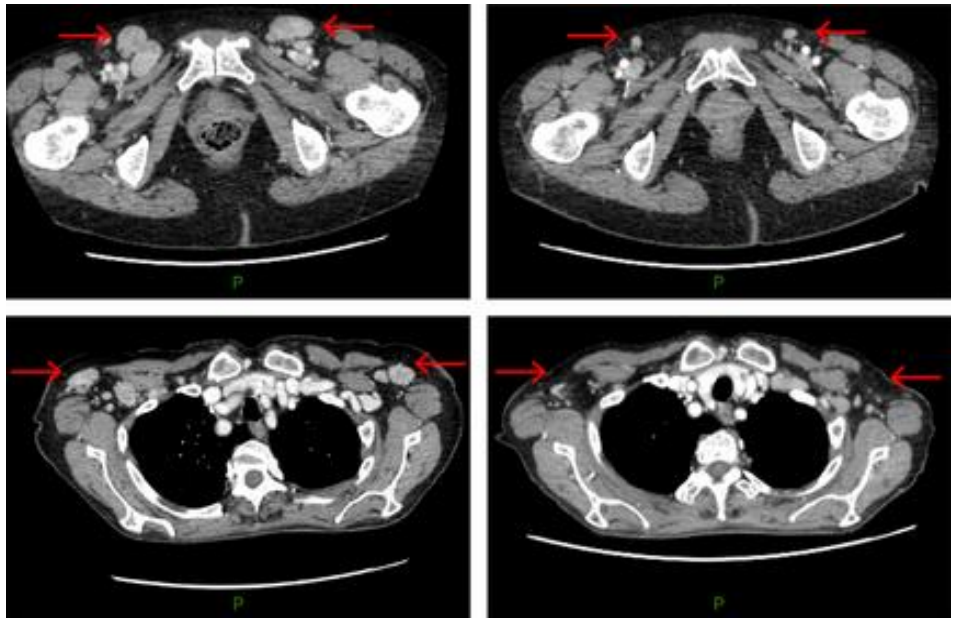
Owen A. O'Connor et al.
Clin Cancer Res 2014;
20:5240-5254

Clinical Cancer Research
AACR American Association for Cancer Research

Early Insights on DNMT3 Inhibitors and Activity in TET2 Mutated AITL





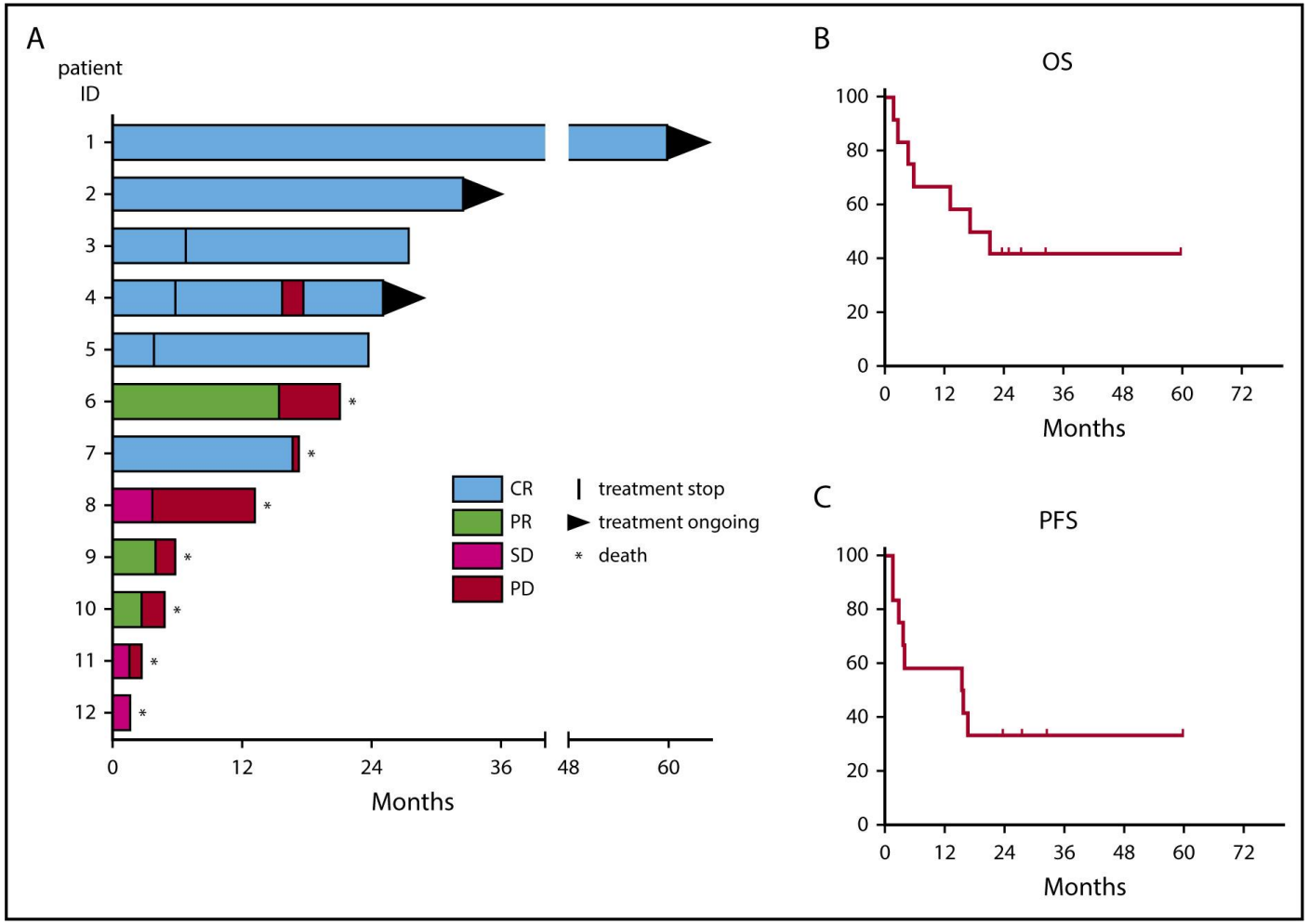


Chemotherapy refractory AITL patient with a TET2 mutation attains a remission following 6 cycles of 5-Aza

Cheminant *et. al* British Journal of Haematology Volume 168, Issue 6, pages 913-916, 2014

5-Azacytidine Exhibits Activity in PTCL, Seemingly Greater in AITL

Phase 3 Data at ASH C☹ming



	AITL	Other PTCL*	p
	12	7	
Median age, y	71 [39 – 85]	59 [32 – 83]	0,09
Male/Female	7/5	5/2	0,65
IPI at diagnosis			1
- 1-2	3	1	
- 3	3	2	
- 4-5	6	4	
PIT at diagnosis			0,62
- <3	3	3	
- 3-4	9	4	
Ann Arbor stage III-IV	12	7	1
LDH level > ULN	9	7	0,26
PS≥2	6	6	0,17
Previous ASCT	2	1	1
Median number of previous therapy	2	3	0,12
TET2 mutation	8/10 (80%)	1/4 (25%)	0,09
ORR	9 (75%)	1 (15%)	0,0198
CR	5 (41%)	0 (0%)	0,106

* ATLL: 3 patients, EATL: 1 patient, PTCL-NOS: 2 patients, transformed MF: 1 patient

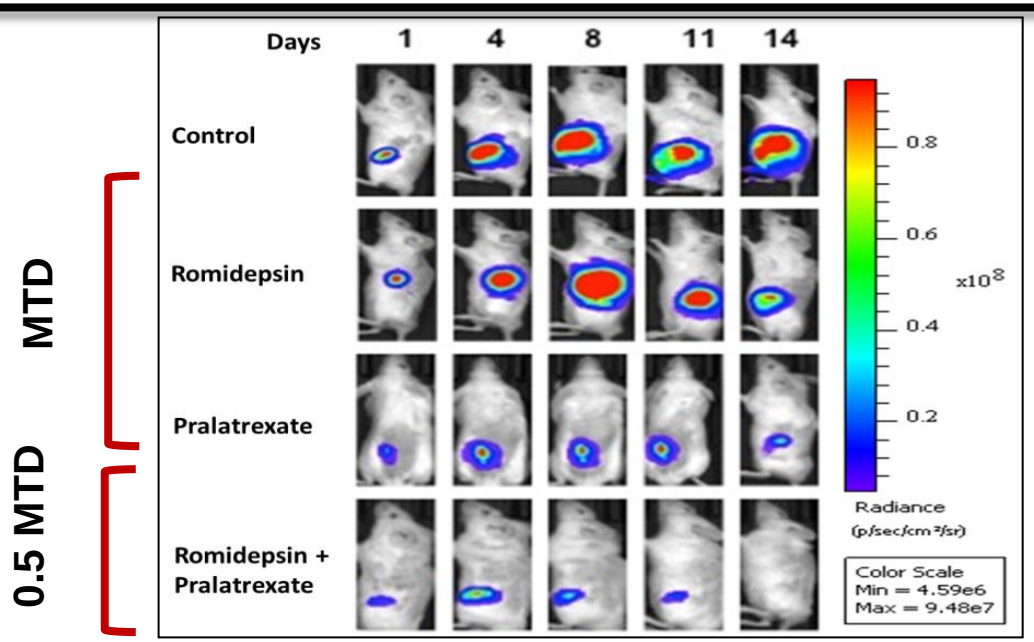
ORR in AILT 9/12 (75%)
ORR in PTCL 1/7 (14%)
ORR Total 10/19 (52%)

Lemonnier, Blood. 2018

Epigenetic Drugs Appear to Synergize with Other Drugs Active in PTCL, but Most Potently with Other Epigenetic Drugs

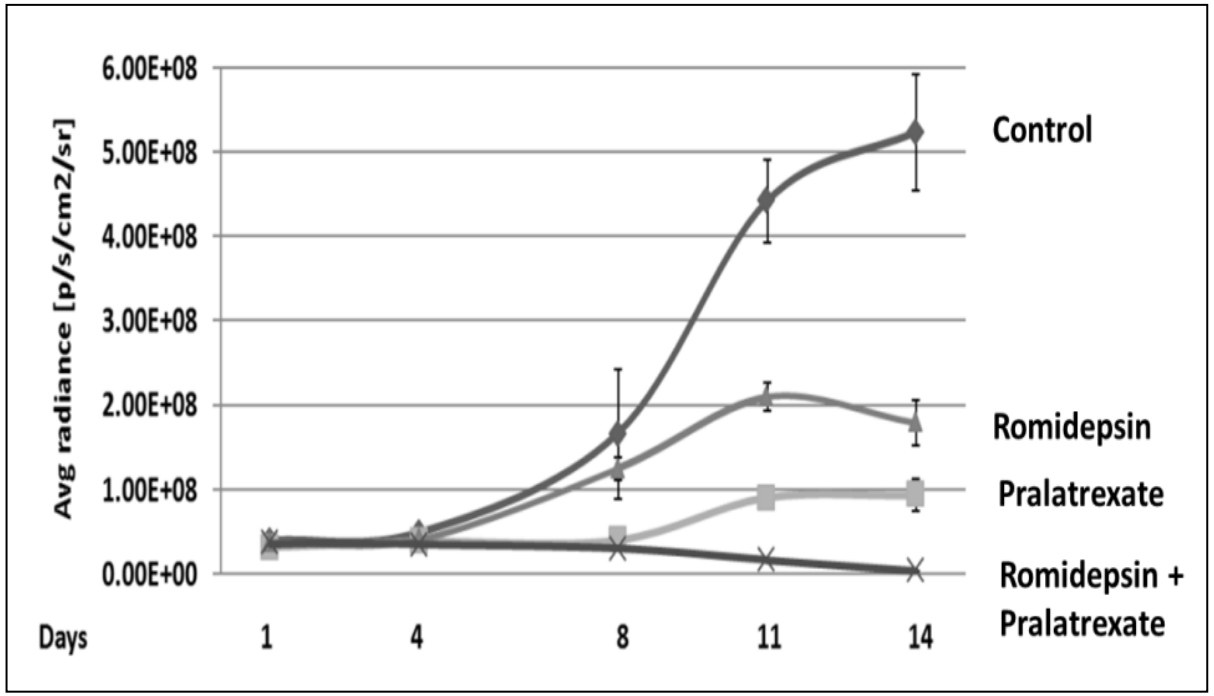
Epigenetic Drug	Alternative Drug	Evidence
Romidepsin	Pralatrexate	Compelling laboratory data, Phase 1 data confirm >70% ORR in PTCL, ~30% in BCL
Romidepsin	5-Azacytidine (epigenetic)	Compelling laboratory, Phase 1 and Phase 2 data, marked improvement in PFS with randomized study underway
Romidepsin	Decitabine (epigenetic)	Laboratory data shows compelling synergy in models of TCL
Panobinostat	Bortezomib	Phase 2 study not compelling to move on to advanced phase
Romidepsin	Duvalisib	Minimal laboratory evidence and early phase data to support at least additive
Romidepsin	Tenalisib	Early phase data support improved activity though short PFS
Decitabine	ASTX660	Compelling laboratory data moving to clinical study soon

Pralatrexate and Romidepsin are Highly Synergistic In Vitro and Across *In Vivo* Models of TCL



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



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

Jain, S. …..O'Connor, O.A.. Clinical Cancer Research, 2015.

Clinical Cancer Research

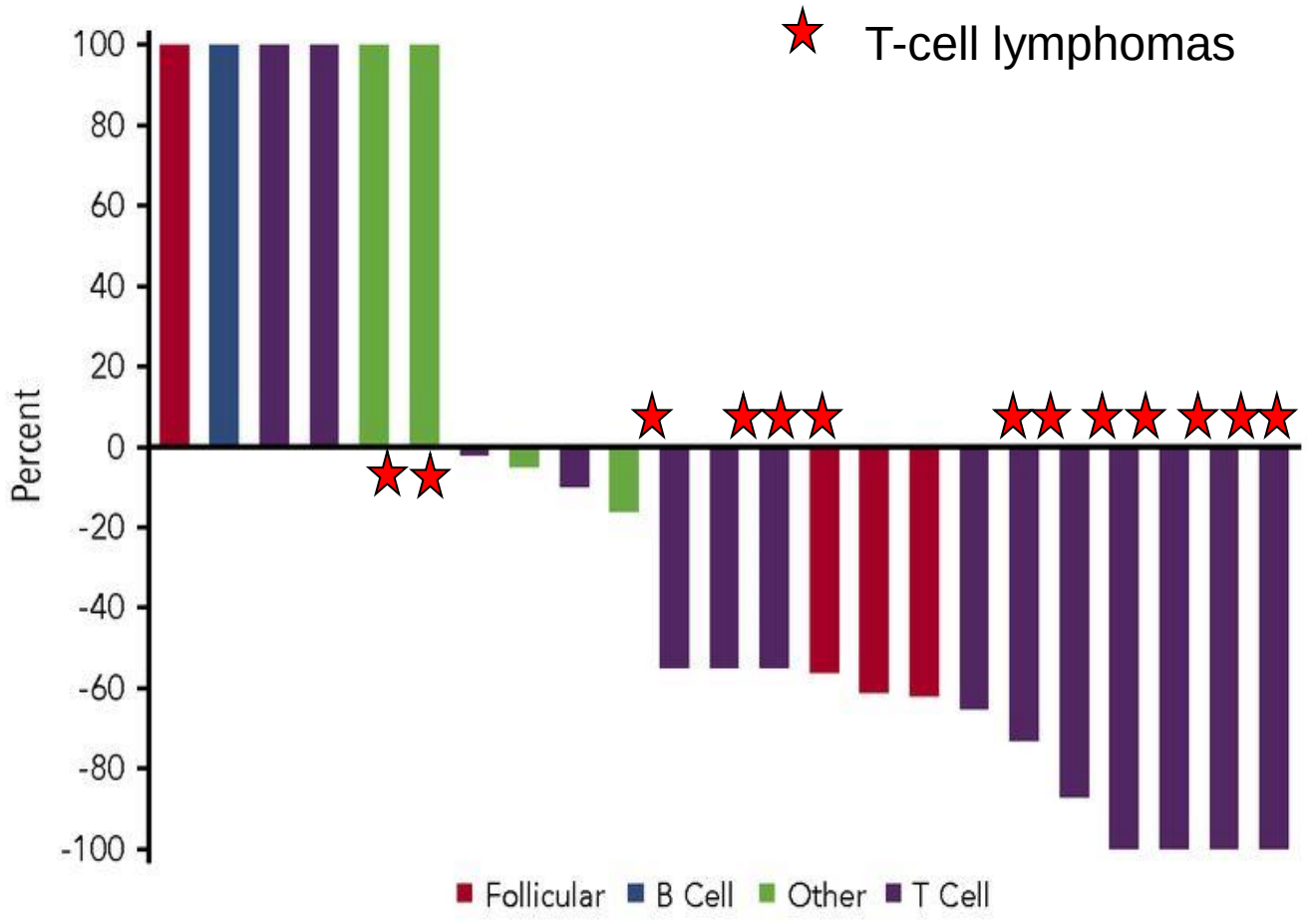
Summary of Response Rates Across Study Population for Patients Treated with Romidepsin and Pralatrexate

blood

A

Parameter	Number
Total # of Patients (evaluable)	29 (23)
All patients ORR	13/23 (57%)
All patients CR	4/23 (17%)
All patients PR	9/23 (39%)
non-TCL ORR	3/9 (33%)
non-TCL CR	0/9 (0%)
non-TCL PR	3/9 (33%)
T-Cell ORR	10/14 (71%)
T-Cell CR	4/10 (40%)
T-Cell PR	6/10 (60%)

B



Dual Targeting of Different Features of the PTCL Epigenome

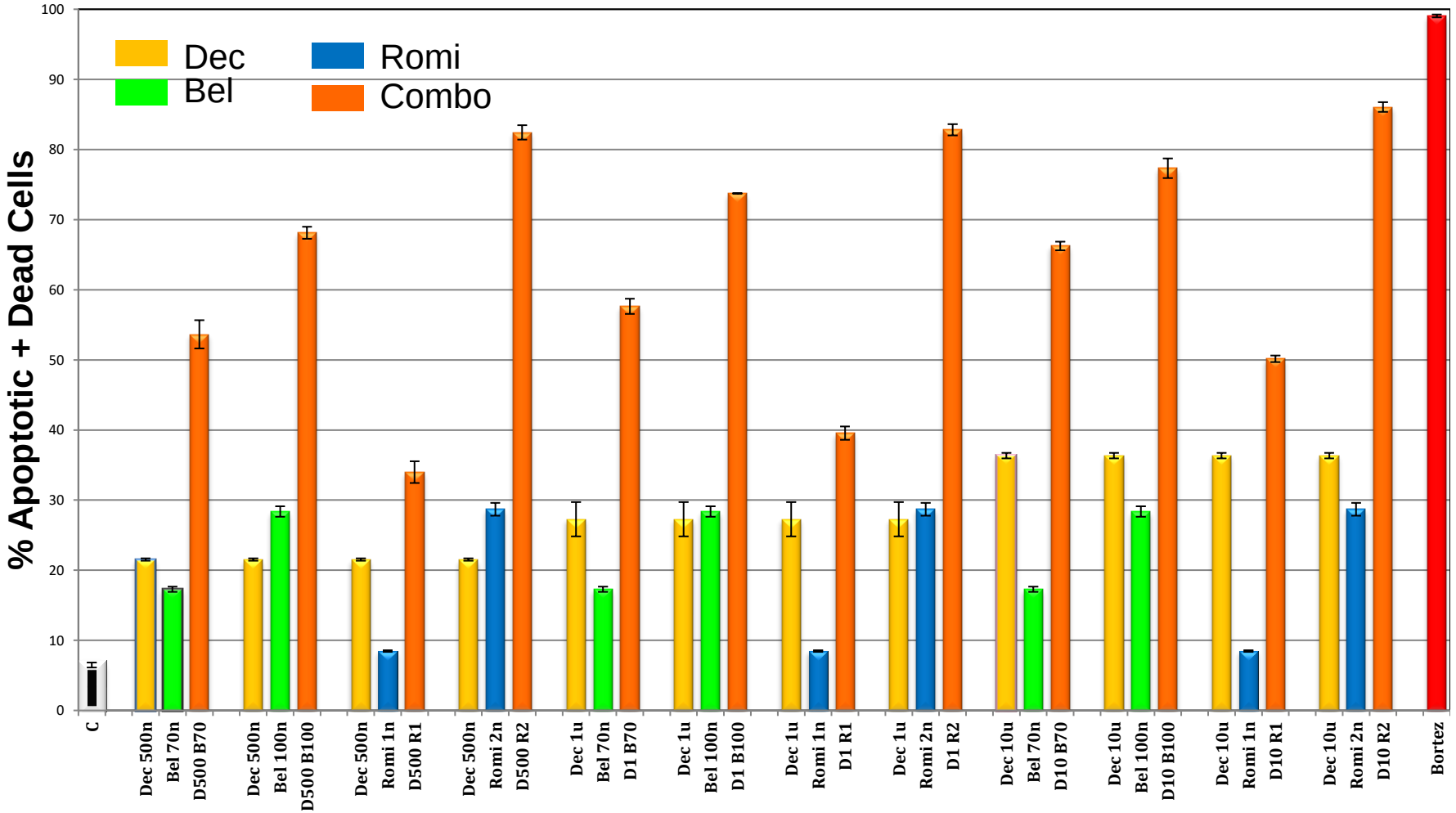
Romidepsin

+

(Oral) 5-Azacytidine

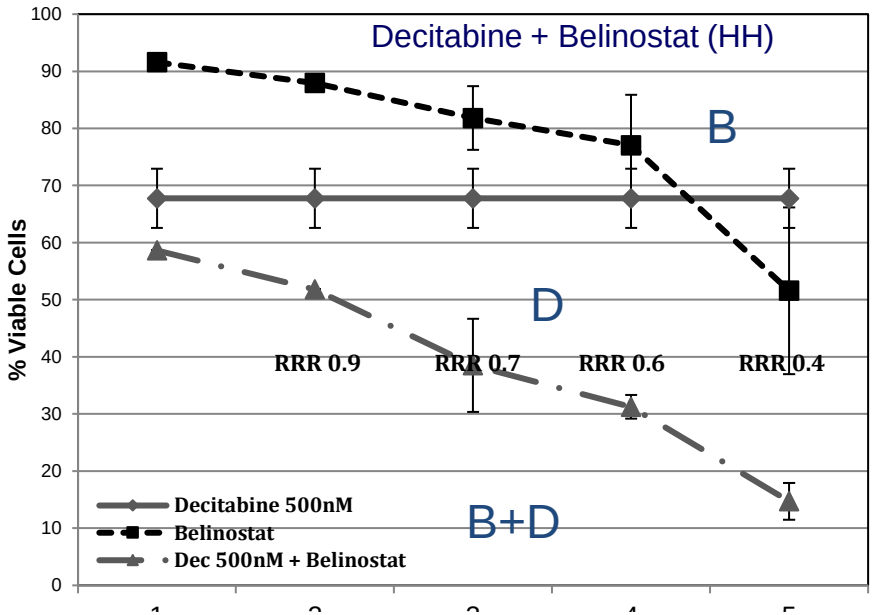
High-Throughput Screening Identifies DNMT3 Inhibitors (& Pralatrexate) as Among the Most Synergistic with HDAC Inhibitors

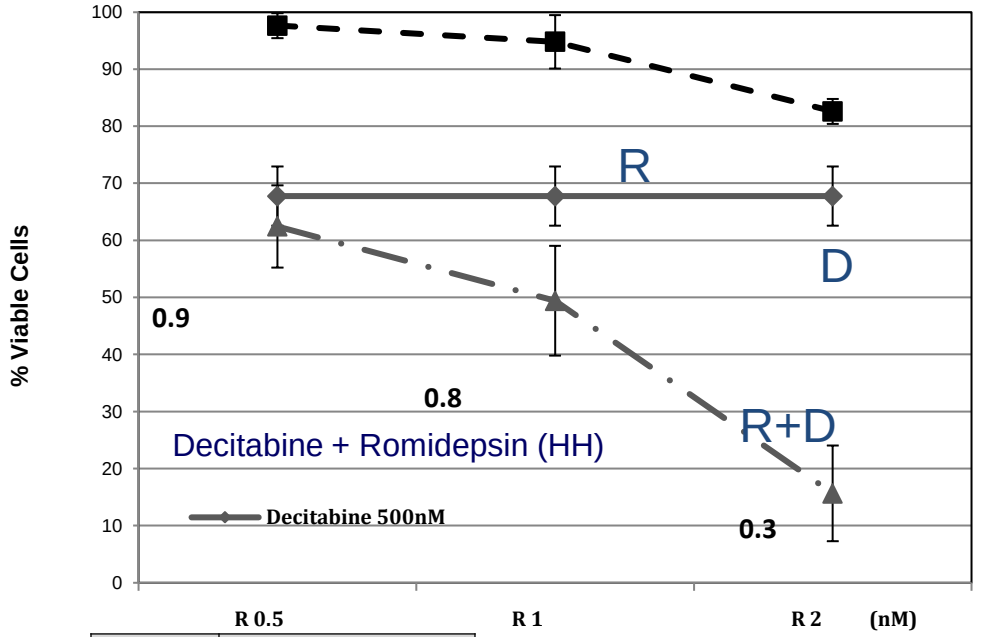
CTCL Lines		D 500 nM	D 1uM	D 10 uM
H9	B 70 nM	0.7	0.7	0.6
	B 100 nM	0.5	0.5	0.5
	R 1 nM	0.9	0.8	0.8
	R 2 nM	0.3	0.3	0.3
HH	B 100 nM	-	0.9	0.8
	B 150 nM	-	0.8	0.7
	R 1.5 nM	-	0.6	0.5
	R 2nM	-	0.5	0.5



Marchi, E ….O'Connor, O.A. 2015.BJH,

DECITABINE PLUS HDAC INHIBITOR MARKEDLY SYNERGISTIC IN PANEL OF TCL





B 10 B 20 B 50

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

B 70 B 100 (nM)

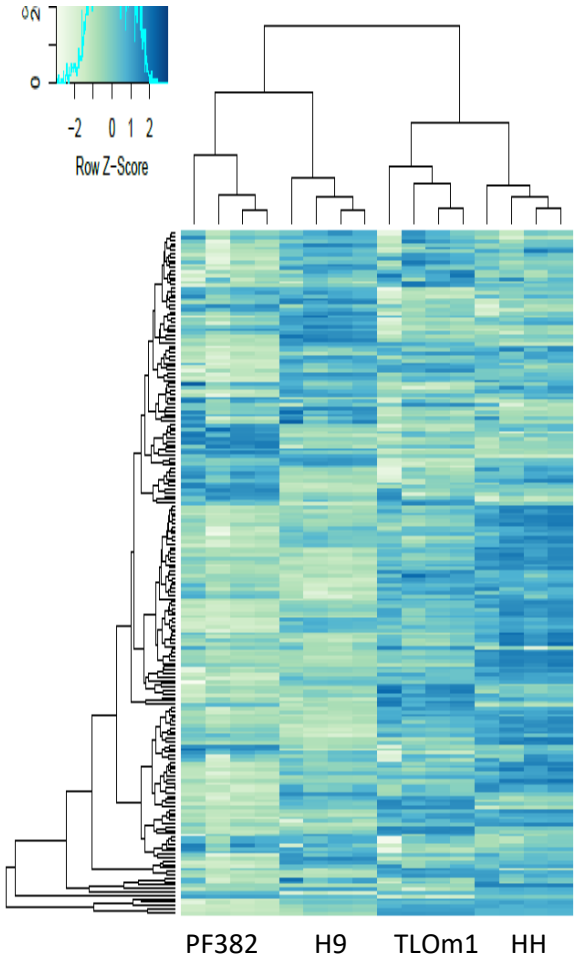
HH	(uM)	
(nM)	D 1	D 10
B 20	>1	0.9
B 50	>1	0.7
B 100	0.8	0.8
R 0.5	>1	0.9
R 1	>1	0.6
R 2	0.6	0.1
L 6	0.8	0.6
L 8	0.7	0.7
L 10	0.5	0.7
S 600	0.8	0.8
S 800	0.8	0.7

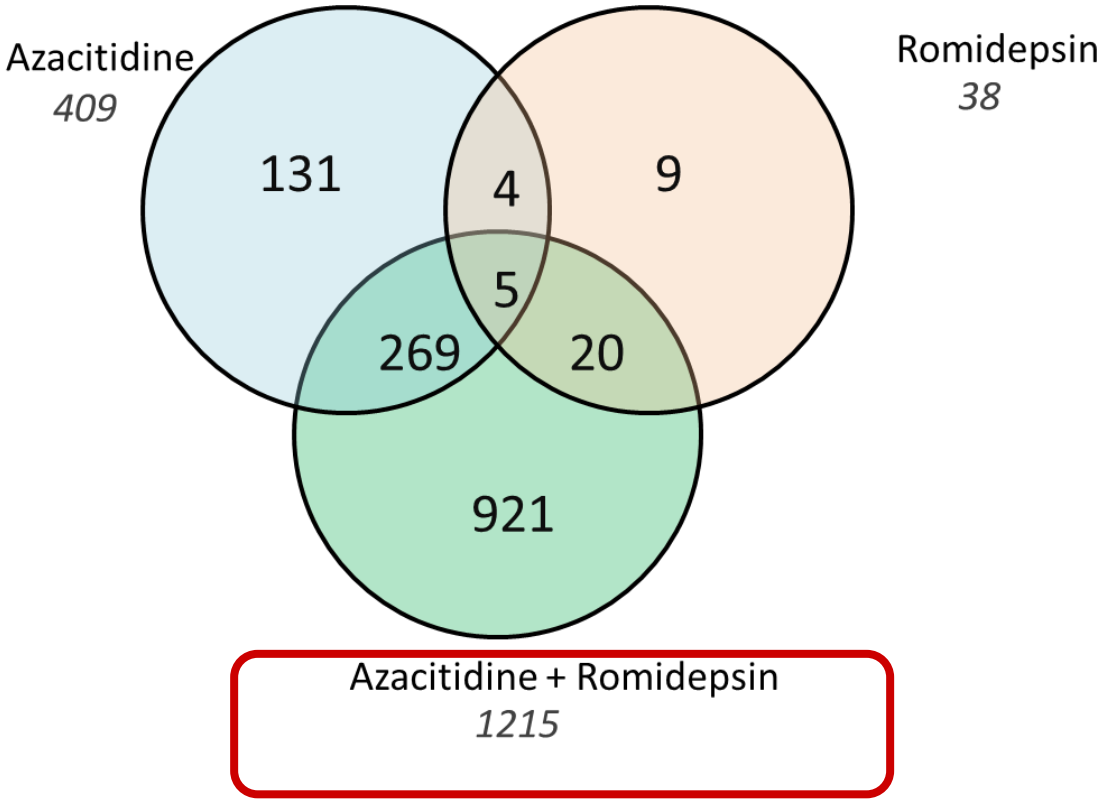
P12	(uM)	
(nM)	D 0.5	D 1
B 70	0.9	0.8
B 100	0.8	0.7
R 1	0.6	0.5
R 2	0.1	0.04
R 3	0.0007	0.01
L 5	0.7	0.5
L 6	0.7	0.4
L 8	0.4	0.2
S 800	0.8	0.9
S 1000	0.7	0.8

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

Marchi et al.
British Journal of Haematology

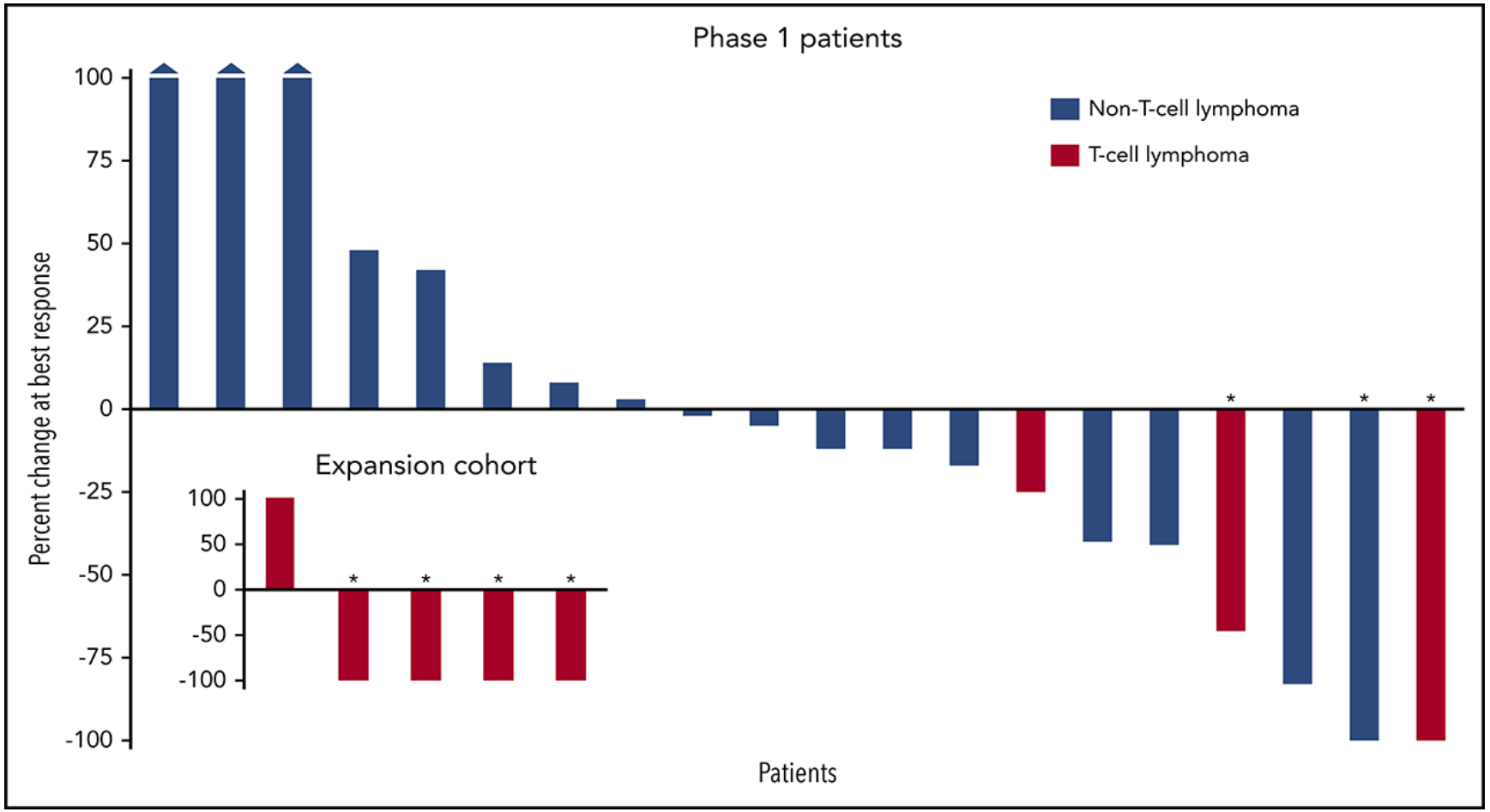
UNSUPERVISED GENE EXPRESSION ANALYSIS OF AZACYTIDINE & ROMIDEPSIN :
MOST UNIQUE PERTURBED GENES IN COMBINATION – IS THIS A NEW DRUG??





The Doublet is Essentially a 'New' Drug

T-Cell Lymphomas are Exquisitely Sensitive to the Combination of Azacytidine and Romidepsin – *Phase 1*



A suggestion B-cell lymphomas less vulnerable – consistent with laboratory observations

O'Connor et al, Blood 2019

Oral 5-Azacytidine and Romidepsin Efficacy

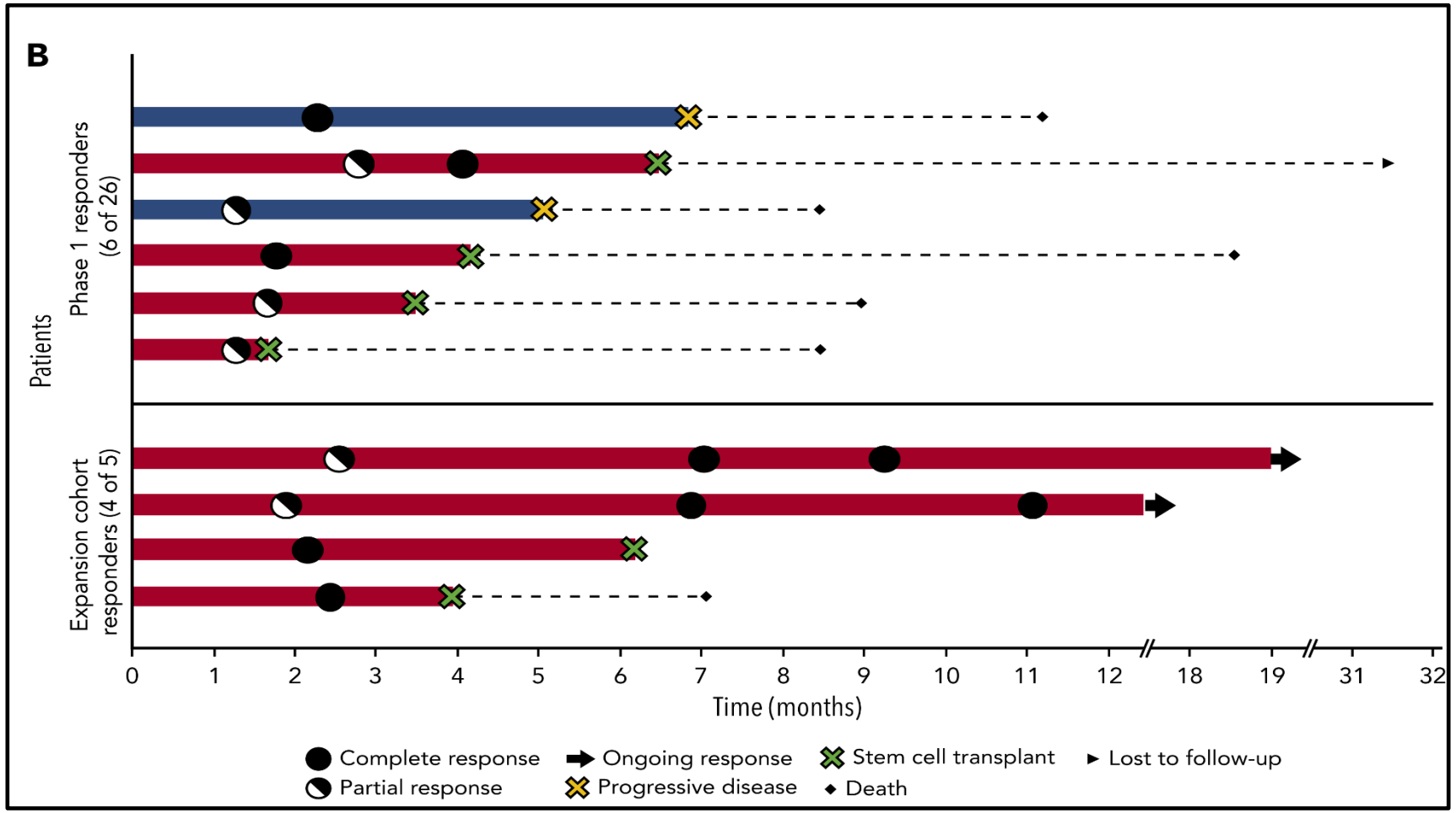
Phase 1 Experience

	All (N = 31)	Phase 1 (N = 26)	Expansion (T-cell) (N = 5)	Non-T-Cell (N = 20)	T-Cell (N = 11)
Overall response	10 (32%)	6 (23%)	4 (73%)80	2 (10%)	**8 (73%)**
Complete response	7 (23%)	3 (12%)	4 (80%)	1 (5%)	**5 (55%)**
Partial response	3 (10%)	3 (12%)	0	1 (5%)	**2 (18%)**
Stable disease	7 (23%)	7 (27%)	0	7 (35%)	**0**
Progressive disease	11 (35%)	10 (38%)	1 (20%)	9 (45%)	**2 (18%)**
Not evaluable	3 (10%)	3(12%)	0	2 (10%)	**1 (9%)**

8 evaluable patients with AITL or PTCL-TFH:
Overall response = 7 (87%); complete response = 4 (50%)

O'Connor et al., Blood 2019

Azacytidine and Romidepsin Produced Durable Responses in PTCL – *Phase 1*

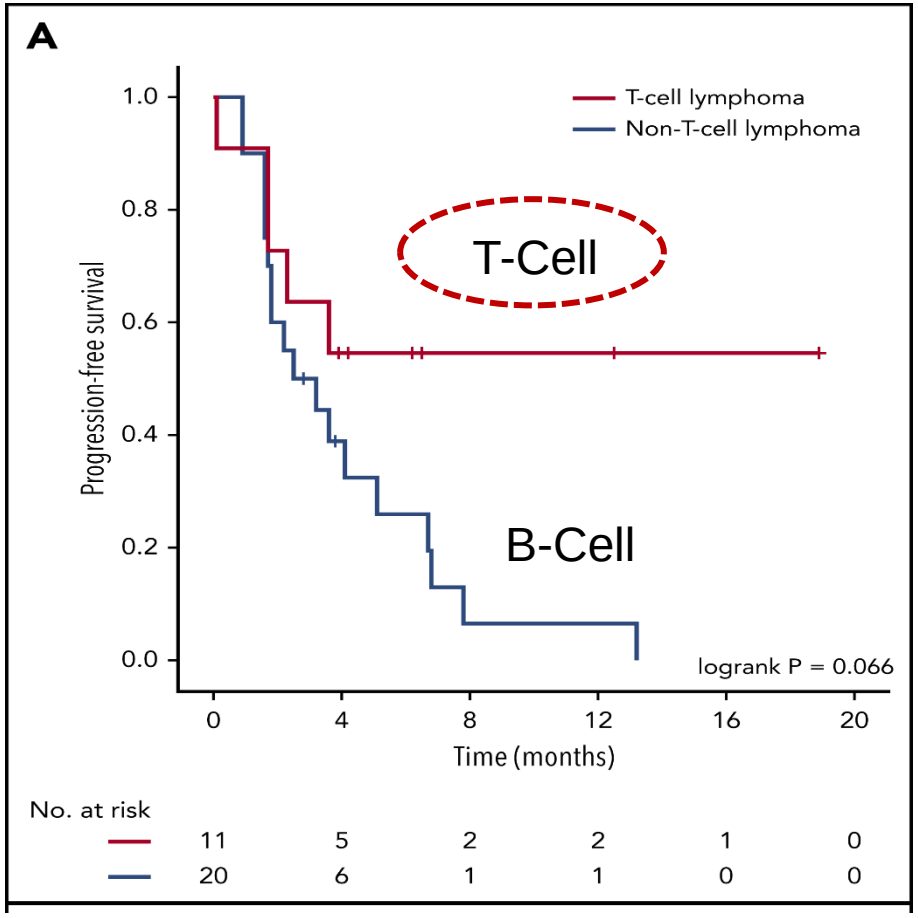


O'Connor et al, Blood 2019

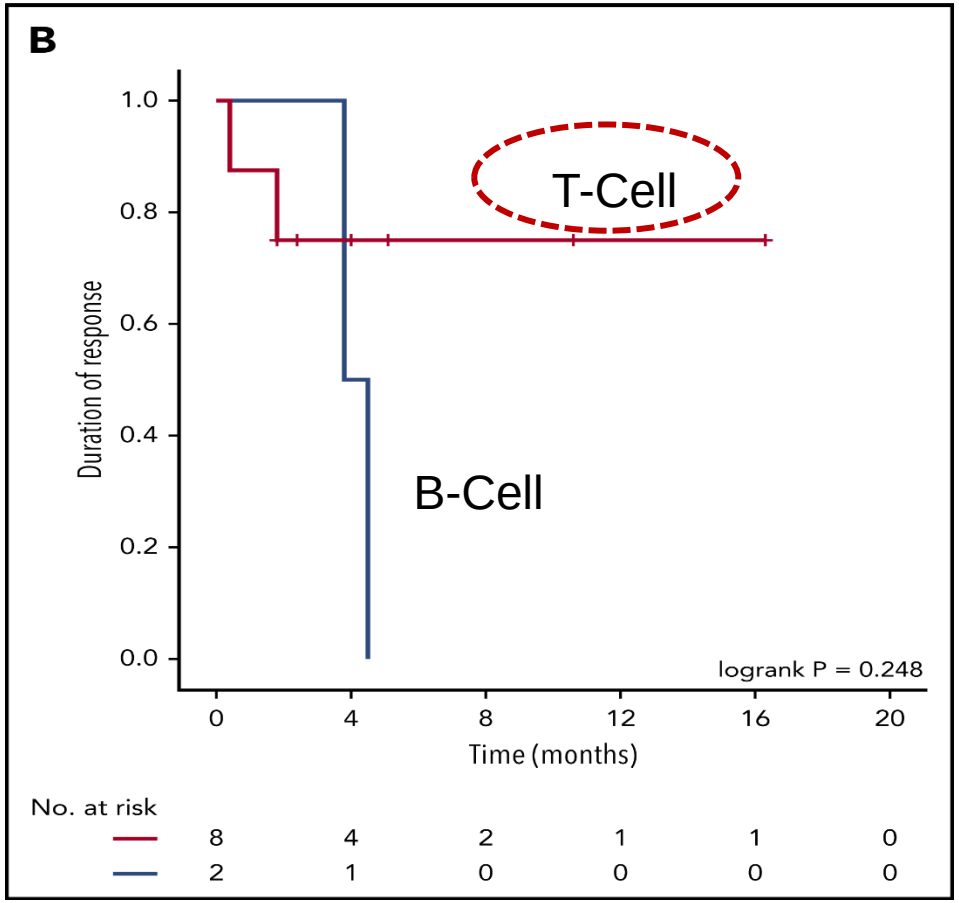
PATIENTS WITH PTCL HAVE LONGER PFS AND DOR

COMPARED TO B-CELL LYMPHOMAS – PHASE 1

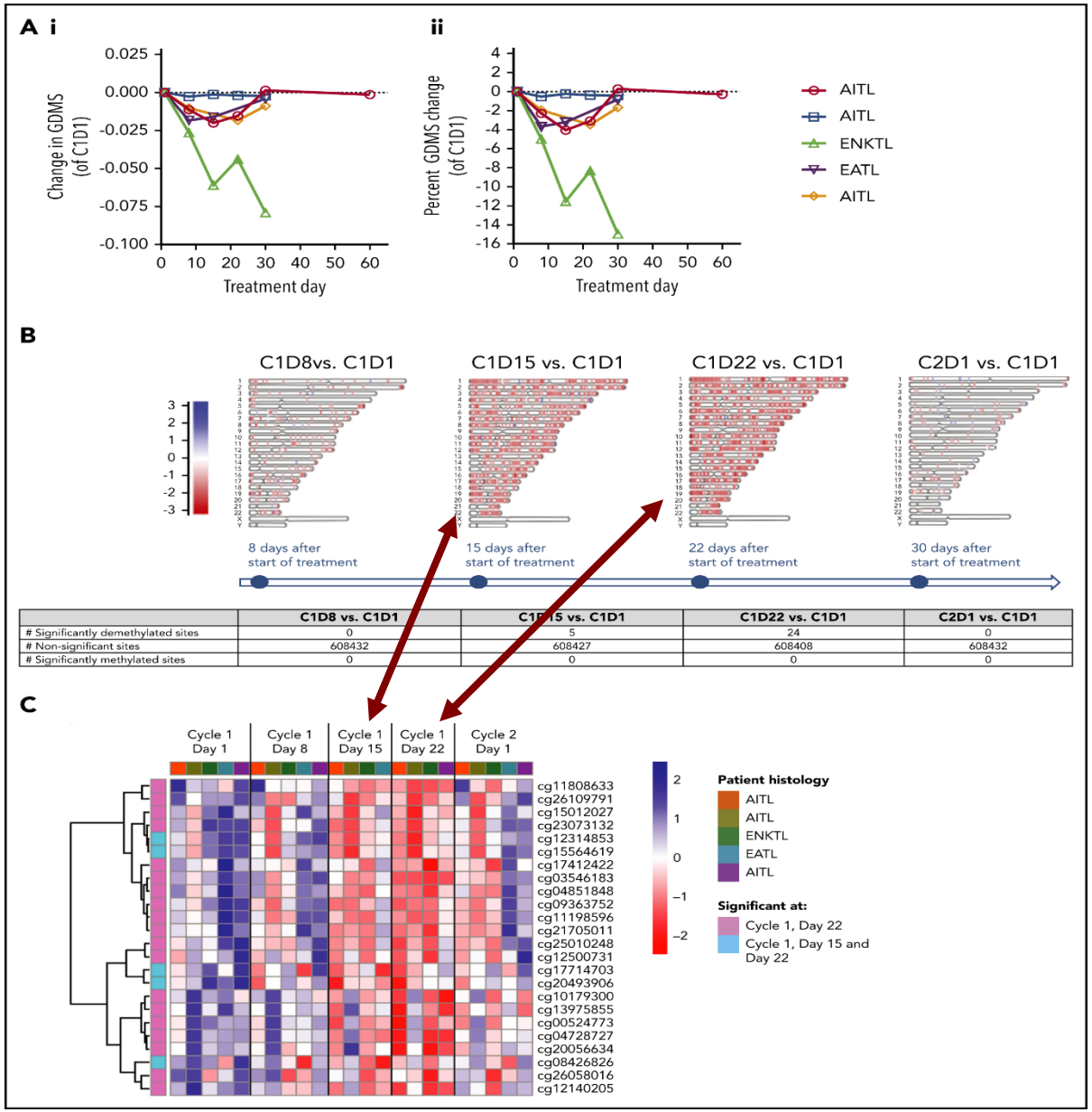
PFS



DOR



O'Connor et al. Blood 2019



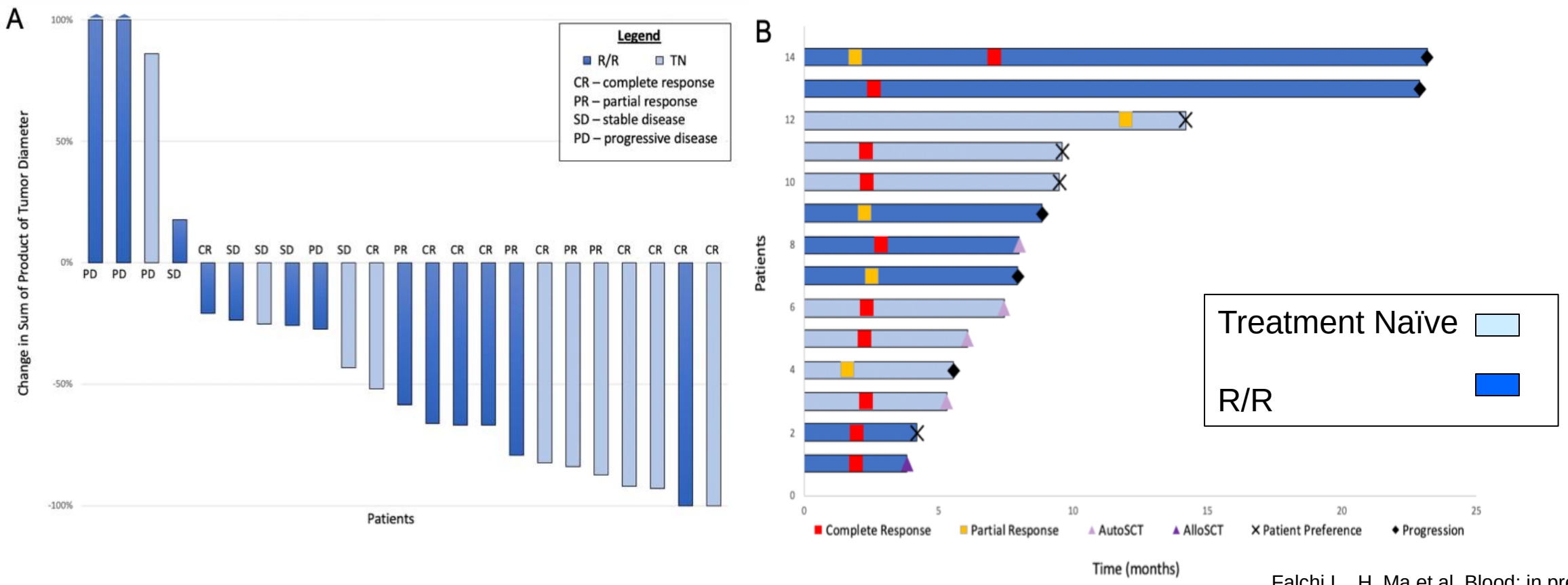
	C1D8 vs. C1D1	C1D15 vs. C1D1	C1D22 vs. C1D1	C2D1 vs. C1D1
# Significantly demethylated sites	0	5	24	0
# Non-significant sites	608432	608427	608408	608432
# Significantly methylated sites	0	0	0	0

- Global Demethylation Score (GDMS) recapitulates what has been seen for SQ/IV azacytidine
- All 4 patients with AITL responded (3/4 had low GDMS)
- Kinetics of demethylation shows effect maximal Day 15-22 (azacytidine given D 0-14)
- Heatmap depicts gene expression changes that coincide with the methylation patterns above (see arrows)
- Red indicates maximal demethylation, blue less demethylation – Suggests similar patterns across the PTCL subtypes.
- No obvious correlation with response

AZA/ROMI EFFICACY ACROSS PTCL – *PHASE 2*

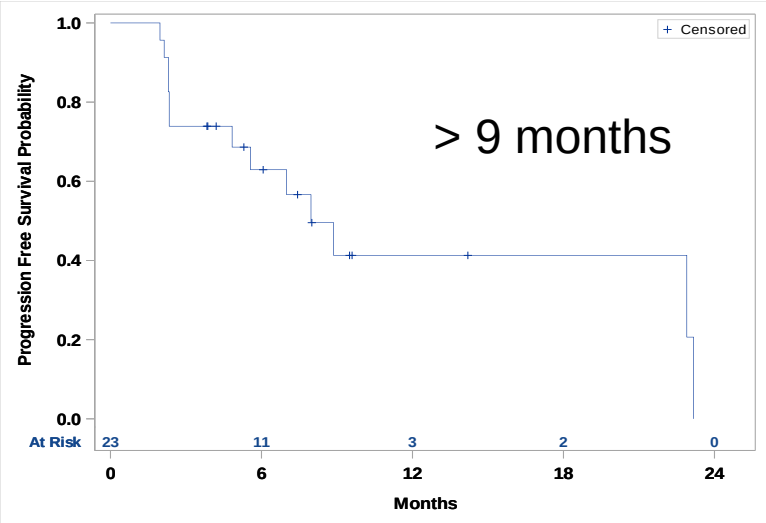
Response	All Patients (N=23)	Treatment Naïve (N=10)	Relapsed/ Refractrory (n=13)	tTFH (N=15)	Other Subtypes (N=8)
Overall Response	14 (61%)	7 (70%)	7 (54%)	12 (80%)	2 (25%)
Complete Response	10 (43%)	5 (50%)	5 (38%)	9 (60%)	1 (12.5%)
Partial Response	4 (17%)	2 (20%)	2 (15%)	3 (20%)	1 (12.5%)
Stable Response	5 (22%)	2 (20%)	2 (23%)	2 (13%)	3 (37.5%)
Progression of Disease	4 (17%)	1 (10%)	2 (23%)	1 (7%)	3 (37.5%)
Not Evaluable	3	2	0	2	0

Treatment Naïve PTCL Patients Have a High Overall Response Rate – *Phase 2*

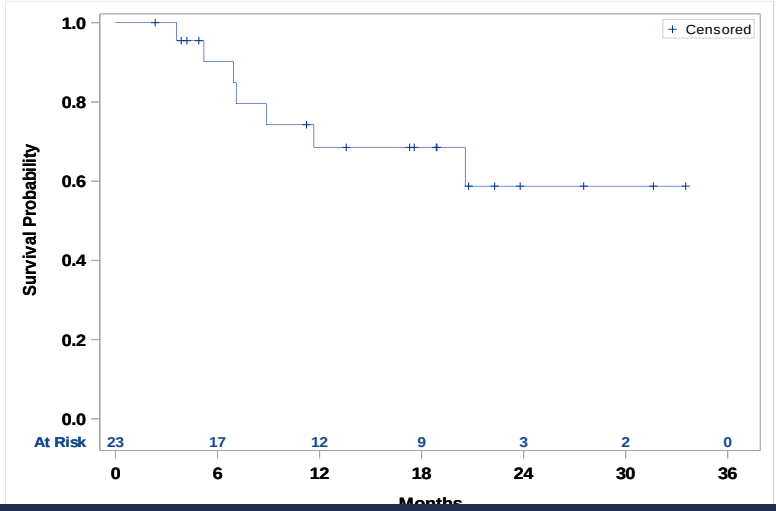


Falchi L., H. Ma et al, Blood; in press

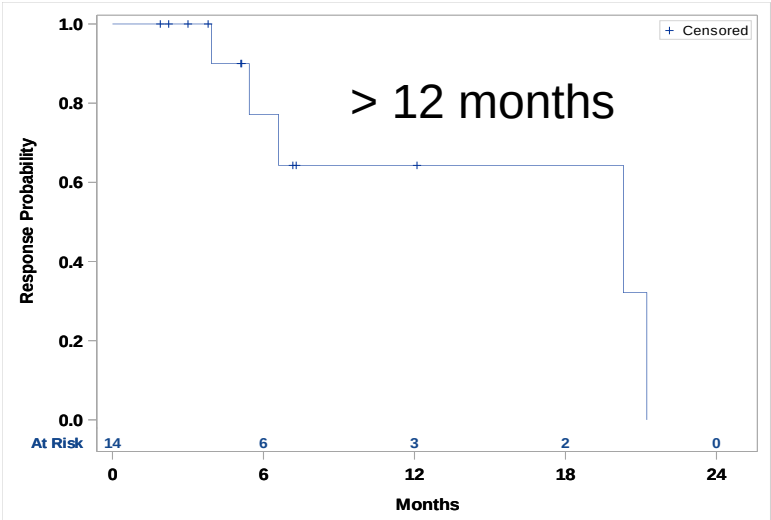
Azacytidine and Romidepsin Produce Durable Responses and Prolonged Survival Compared to Historic Controls - *Phase 2*



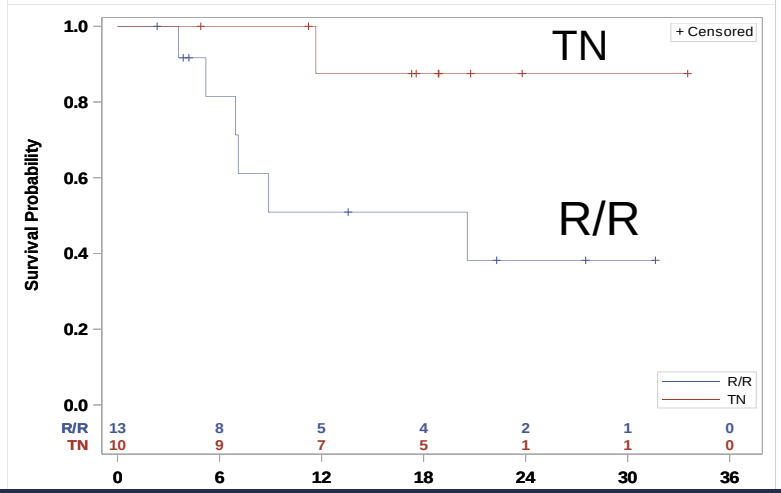
PFS All Patients



OS All Patients

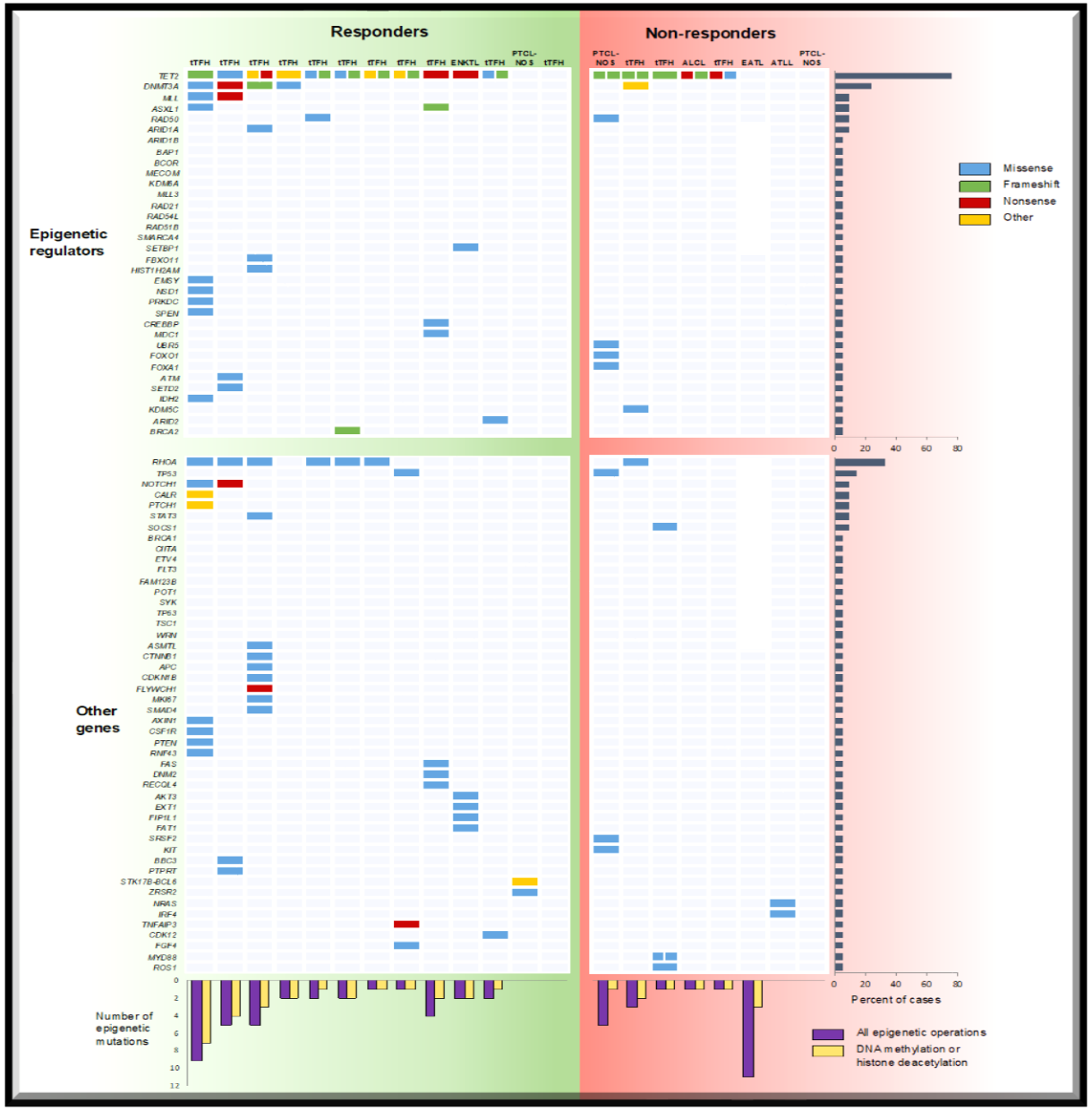


DOR All Patients



OS in TN and R/R Patients

Falchi et al, Blood; in press

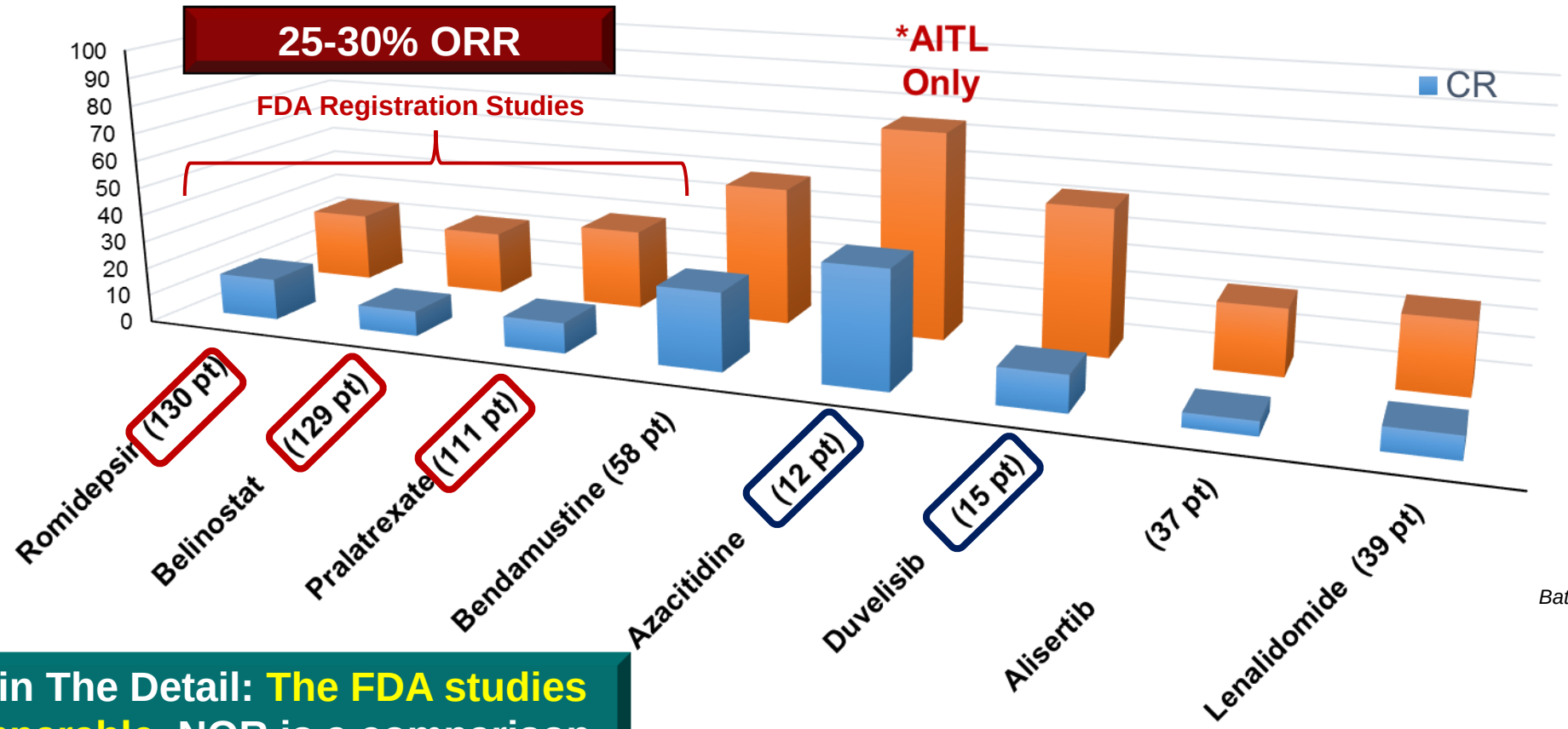


Responders Have a Higher Number of Mutations in Genes Involved in Epigenetic Regulation – Its more complicated than TET2, IDH2 and DNMT3

Falchi et al, Blood; in press

Single Agent Activity of 'T-Cell Active' Drugs

No Home Runs Here……

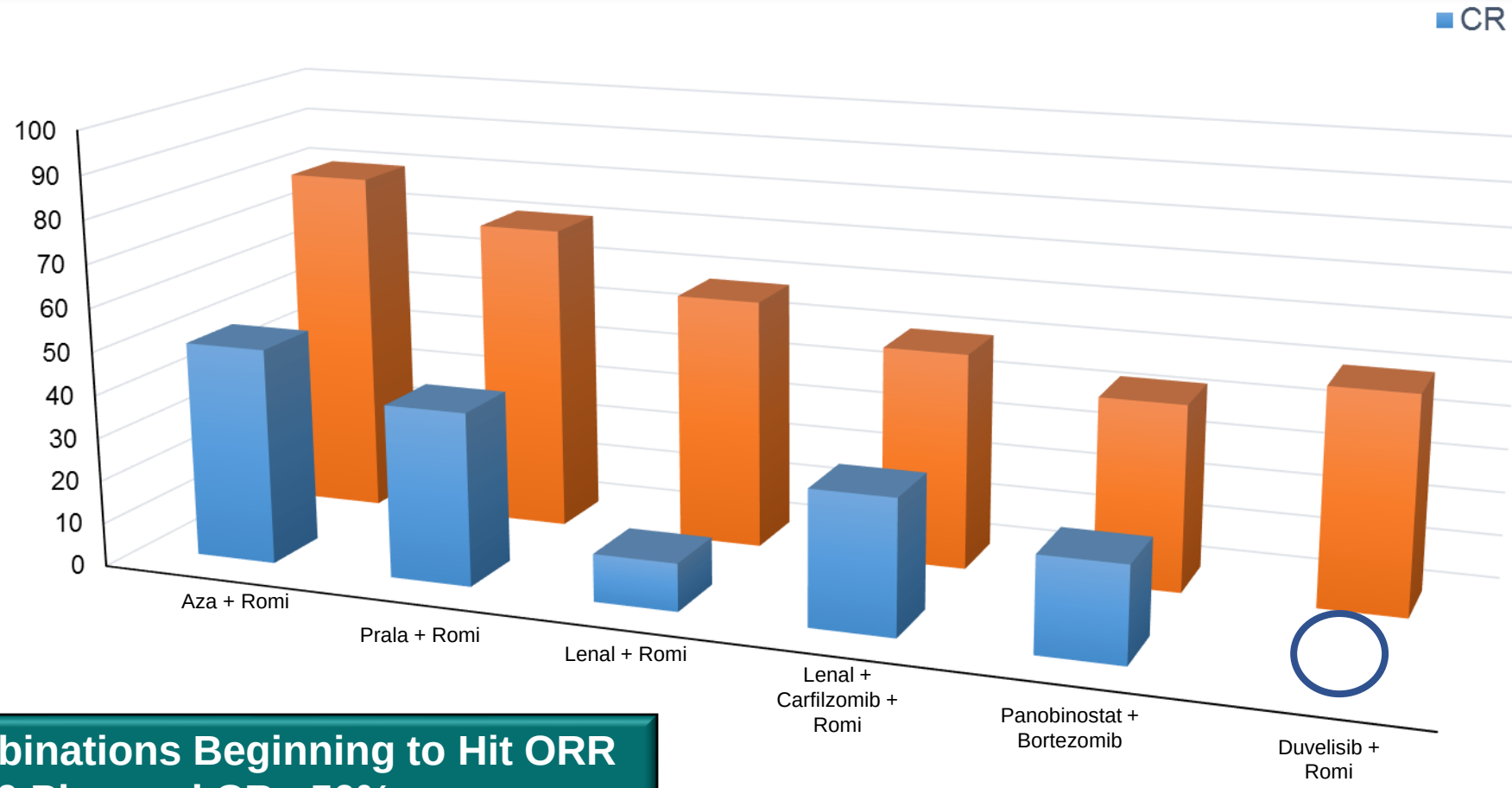


Coiffier et al; JCO 2012
Bates et al; Br J Haematol 2015
O'Connor et al; JCO 2015
O'Connor et al; JCO 2011
Delarue et al; Blood 2016
Horwitz et al; Blood 2014
Barr et al; JCO 2015
Toumishey et al; Cancer 2015

The Devil is in The Detail: The FDA studies are NOT comparable, NOR is a comparison with small non-FDA directed trial

Combinations of Novel : Novel T-Cell Active Drugs

The Basis for a T-Cell Tailored Approach?



Amengual et al; Blood 2017
O'Connor et al; in progress
Mehta-Shah et al; JCO 2015
Mehta-Shah et al; Blood 2016
Tan et al; Lancet Haematology 2015

The Combined Phase 1-2 Experience with Aza/Romi (N=34) ORR = 65% CR = 44%

2- Drug Combinations Beginning to Hit ORR 70 Plus and CR ~50%

ROMIDEPSIN:
A BRIEF REVIEW OF ITS 25 YEAR JOURNEY

1997 - Phase 1 studies of romidepsin (FK228, FR901228)

2001 - First case report by Pierkaz and Bates establishes romidepsin as active in CTCL (Blood, 98(9): 2865.

2004 - Received Fast Track approval from U.S. FDA

2009 – Piekarz et al. publish CTCL results (JCO, 27(32) : 510.)

2009 - U.S. FDA approved romidepsin in CTCL

2011 – Piekarz et al publish PTCL results (Blood, 117(22): 5827)

2011 - FDA grants Accelerated Approval for the treatment of patients with PTCL who received one line of prior therapy in 2011

2021 - * BMS withdrew the approval romidepsin for patients with R/R PTCL based on negative CHOP vs Ro-CHOP Phase 4

BMS Pulls Istodax in Lymphoma After Trial Fails to Show Progression-Free Survival

Published: Aug 03, 2021 By Vanessa Doctor, RN

Failed trial nixes another FDA approval, this time for BMS' Istodax

August 4, 2021

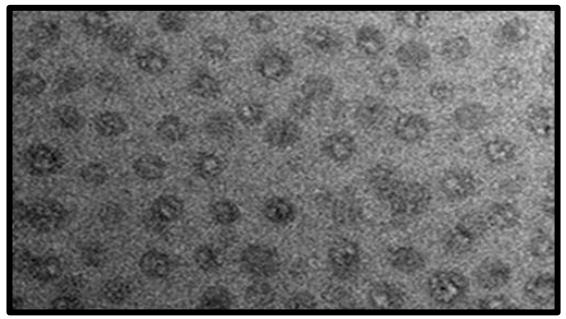
Bristol-Myers Squibb's HDAC inhibitor Istodax has been on the US market for a decade as a treatment for peripheral T-cell lymphoma (PTCL), but will now be withdrawn from sale after a failed phase 3 trial.

BMS withdraws Istodax as a treatment for peripheral T-cell lymphoma

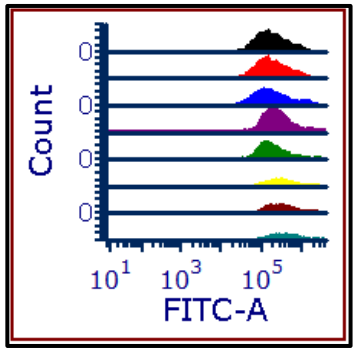
4th August 2021

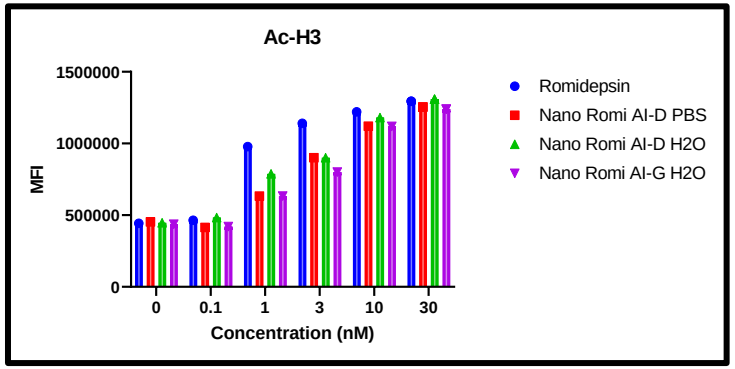
NANO-ROMIDEPSIN IS SAFE AND HIGHLY EFFECTIVE IN MODELS OF PTCL AND LGL

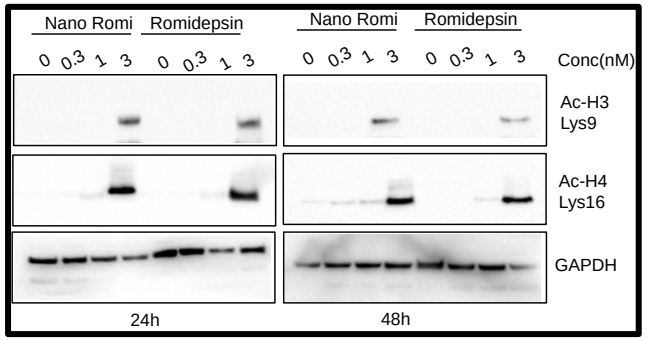
Nano-ROMIDEPSIN (~M.Wt 5K:10K)-H_2O Scanning EM



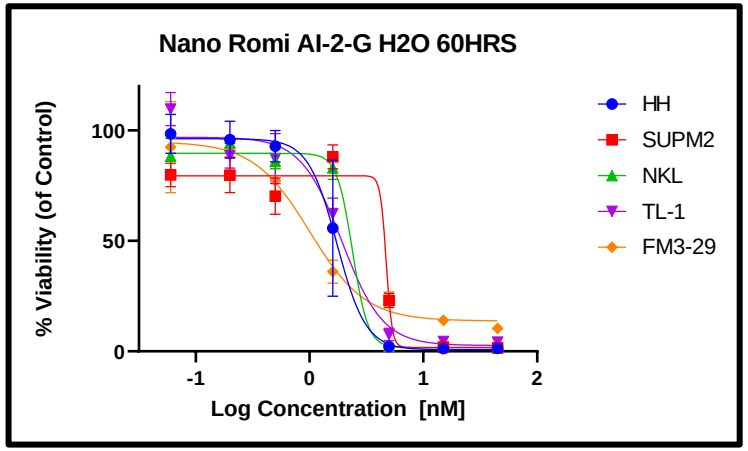
Acetylation of Histone by Nano-ROMIDEPSIN Identical to Naked Romidepsin

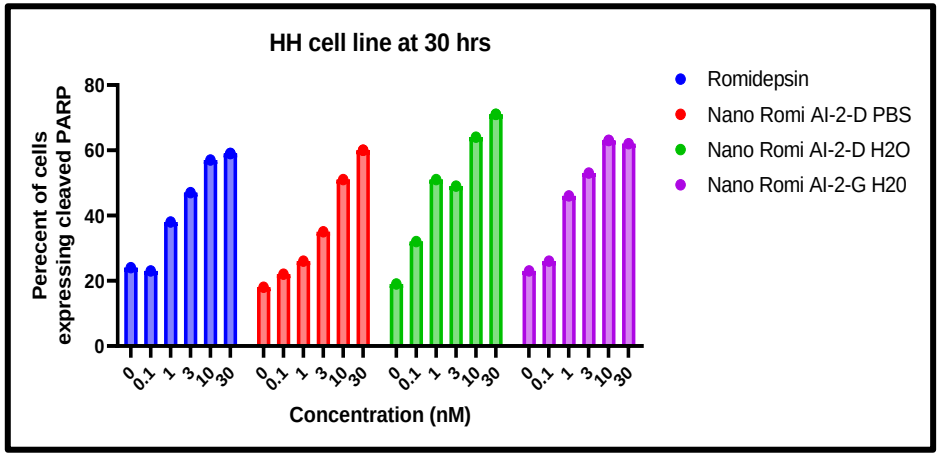




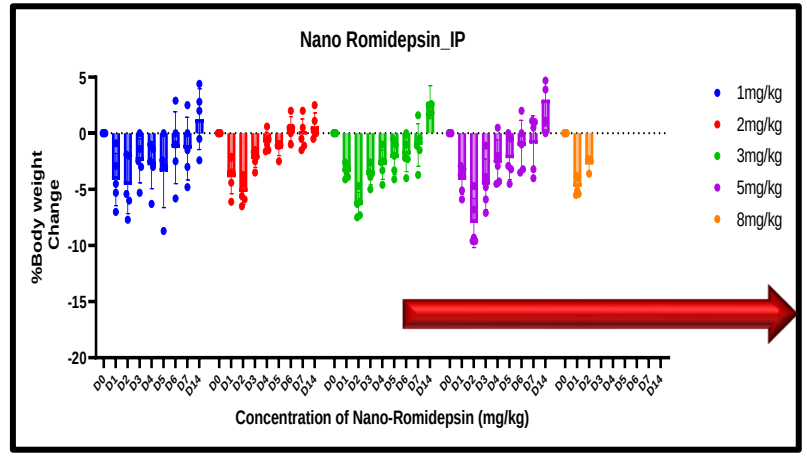


Cytotoxicity of Nano-ROMIDEPSIN Identical to Better Than Naked Romidepsin





In Vivo Safety of Nano-ROMIDEPSIN Equivalent or Better Than Naked Romidepsin



A Randomized, Phase IIB, Multicenter, Trial of Oral Azacytidine Plus Romidepsin versus Investigator's Choice in Patients with Relapse or Refractory Peripheral T-cell Lymphoma (PTCL)

Screening

1:1 Randomization

Arm A
(Experimental Arm):
5-Oral Azacytidine
&
Romidepsin

Investigator Choice):
Romidepsin
Belinostat
Pralatrexate
Gemcitabine

Tissue (pre- and post-treatment)

IHC (VECTRA)
GEP
Methylation

Mutational analysis
T-cell subpopulation
Cytokines analysis

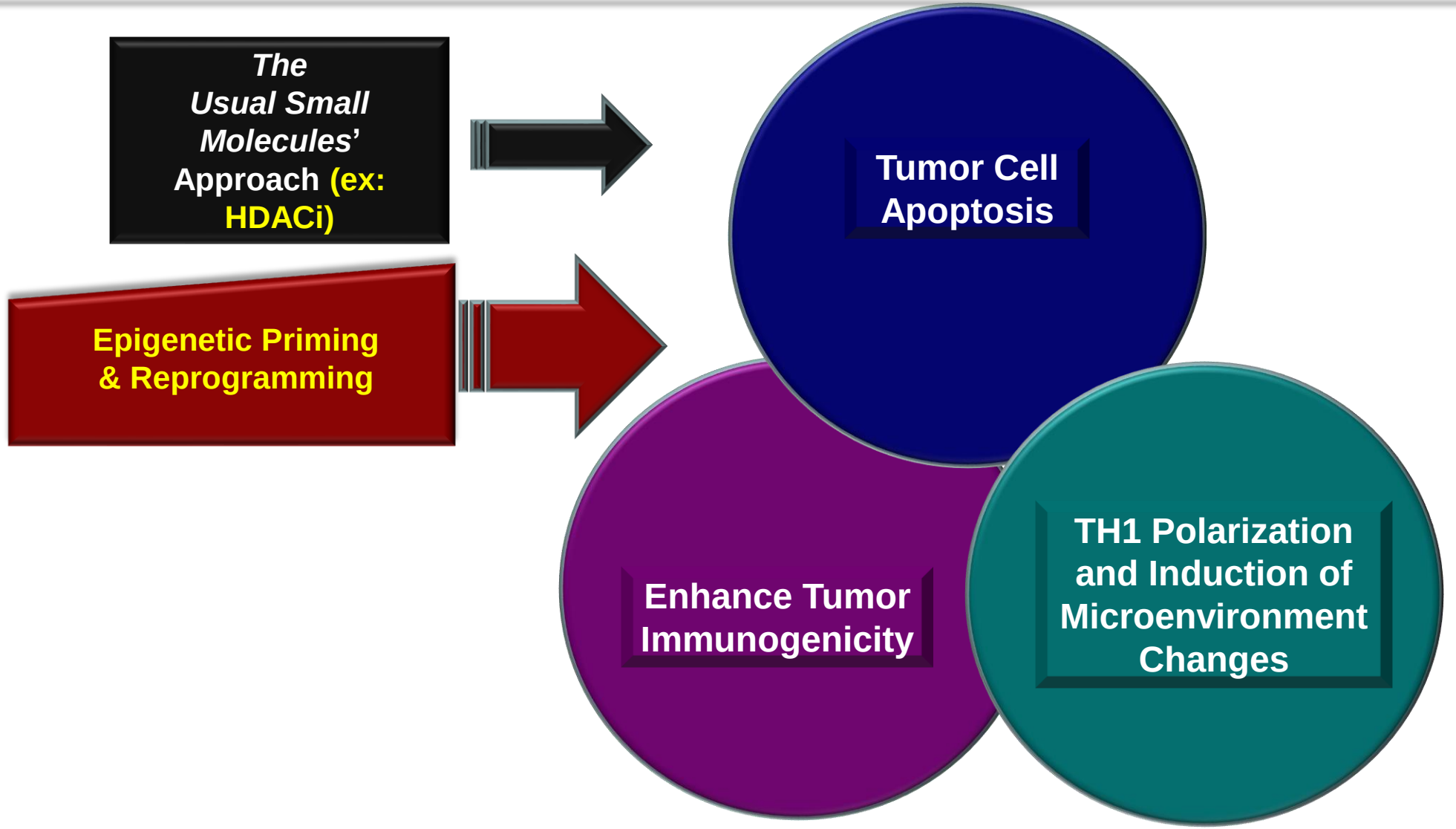
WGS/WES/RNA Seq
CyTOF
IsoPlexis

RO1 Orphan Products Development (OPD) Grant

Food and Drug Administration
Federal agency

FDA

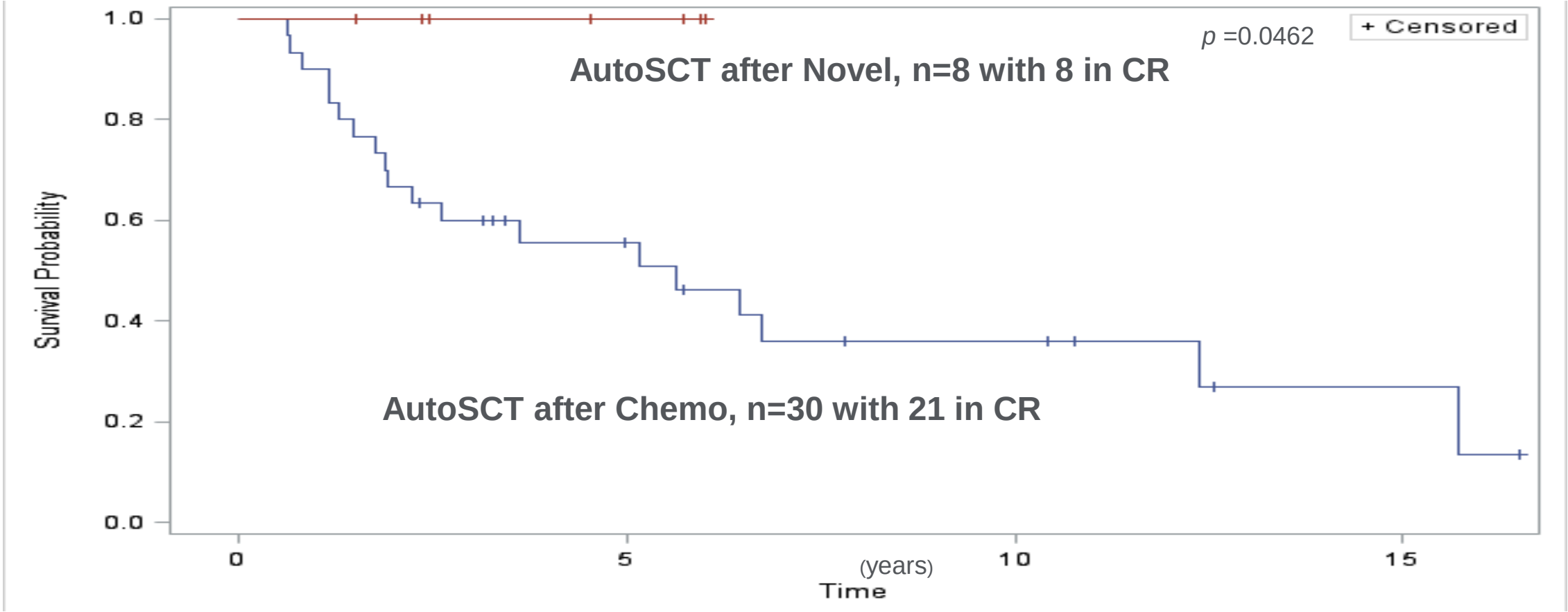
The Complex Mechanisms of Action of Epigenetic Drugs Targeting the PTCL Epigenome: Priming of the Immune Microenvironment



Is This an Example of Epigenetic Priming…?

Novel Here Implies Epigenetic Alone or in Combination

Ma et al., 2020. Hematol Oncol



What's the Data Supporting The Clinical Merits of Targeting the PTCL Epigenome?

- We are short on randomized data to demonstrate that any one therapy is better than another in PTCL, save Lumiere (no difference between alisertib and DC and Echelon 2, only showing advantage for ALCL);
- Molecular data set the stage for targeting the PTCL epigenome, but do not suggest that all PTCL subtypes are created equally with regard to the well characterized mutations (TET2, IDH2 and DNMT3);
- Clinical data suggest that as single agents epigenetic drugs (Phase 3 5-Aza vs DC at ASH) are probably no better than other non-epigenetic targeted drugs, but…
- Robust preclinical laboratory data have identified rational combinations with other epigenetic drugs in combination may be the most promising;
- Strategies exploring CHOP-plus epigenetic Rx approaches are likely not going to follow the fate of other CHOP-plus trials.

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Todd E Fox, PhD
Mark Kester, PhD

Translational Orphan Blood Cancer Research Initiative @ UVA

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SAVE THE DATE

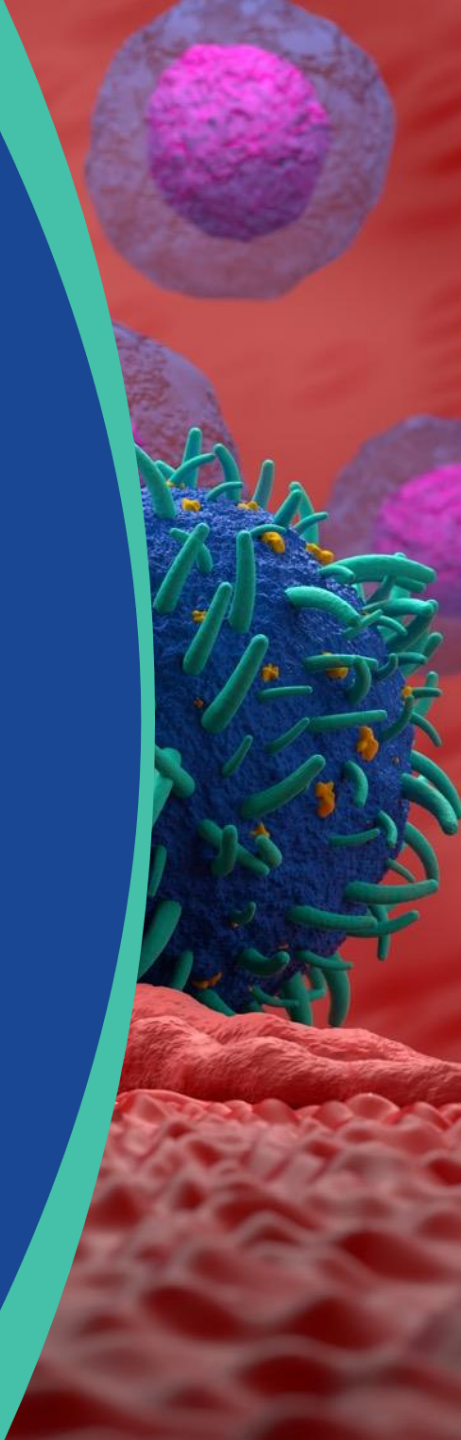
FEBRUARY 2–4, 2023

LA JOLLA, CALIFORNIA

HYBRID EVENT

15th ANNUAL

T-CELL LYMPHOMA FORUM



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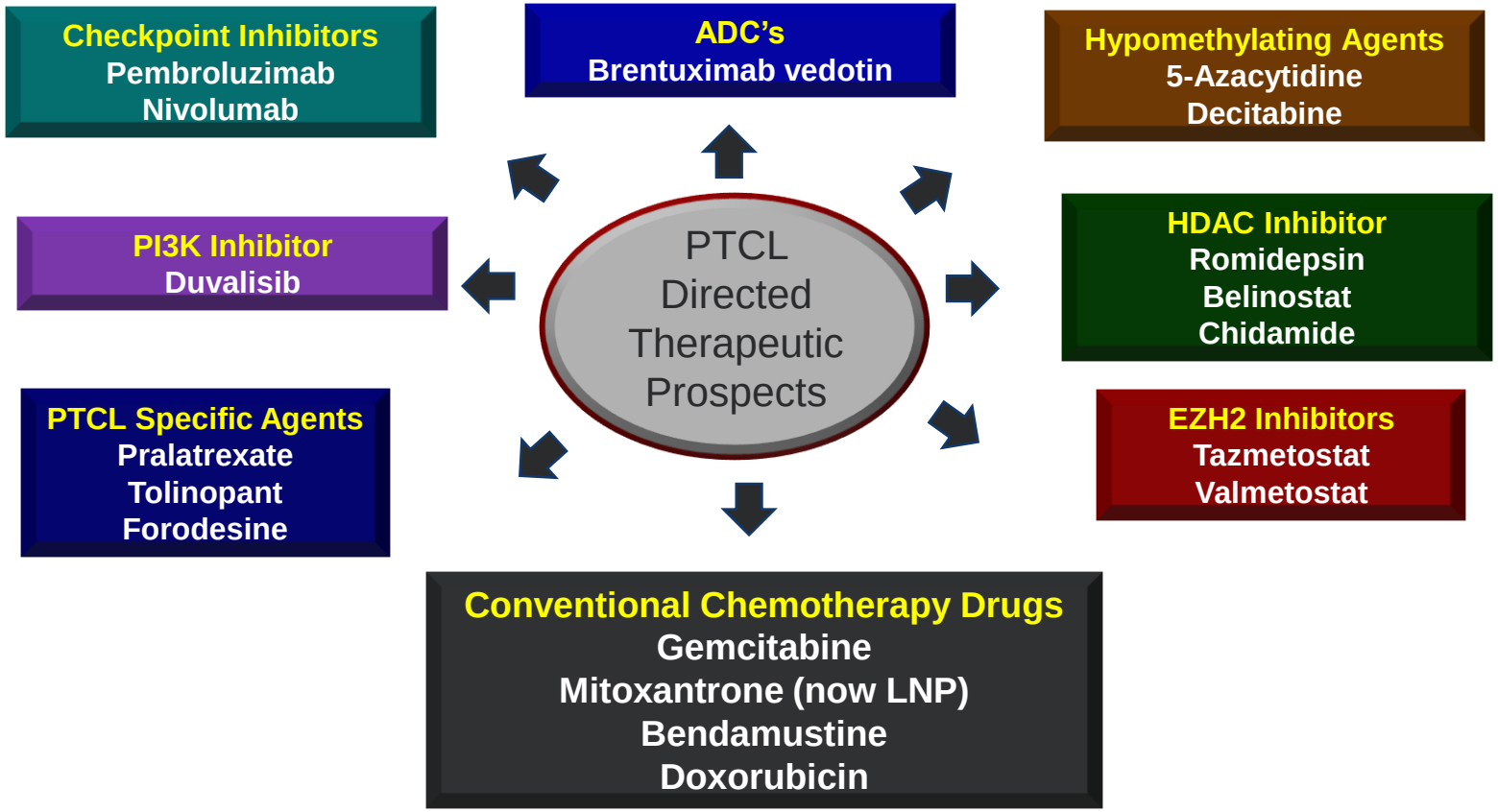
Establishing a New Combination Drug Development Paradigm in PTCL:
The Opportunity is Essentially Infinite



A Combinatorics Approach to Innovative PTCL Therapies

Assume **15 agents** (one each from all categories except **count 1 chemo drug each** and all **3 in PTCL Specific Class**)

# of Doublets	= 105
# of Triplets	= 455
# of Quadruplets	= 1,365

Our combinatorial opportunities would be limitless,,,,