EXPLORING AN IMMUNOLOGIC RATIONALE TO BUILDING NOVEL PLATFORM IN PTCL

Enrica Marchi, M.D., Ph.D.
Assistant Professor of Medicine
Co-Director Program for T-Cell Lymphoma Research
Division Hematology – Oncology, Department of Medicine
NCI-Designated Cancer Center, University of Virginia
Email: EM5YT@hscmail.mcc.virginia.edu

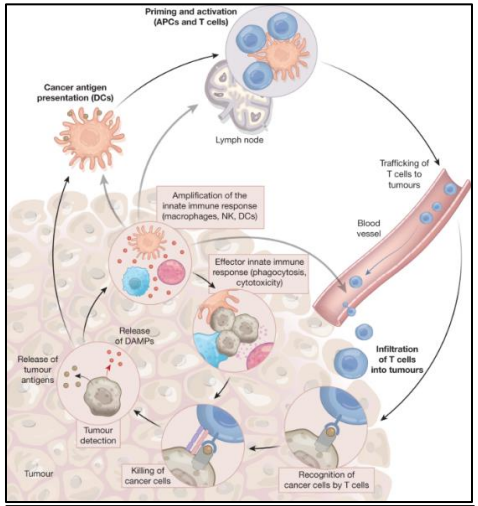
DISCLOSURE

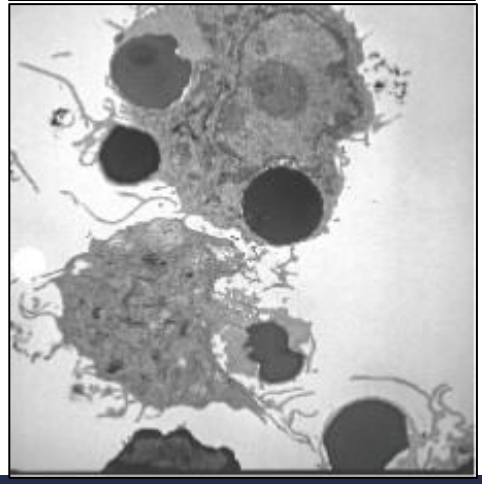
Disclosures of Enrica Marchi, MD, PhD

COMPANY NAME	RESEARCH SUPPORT	EMPLOYEE	CONSULTANT	STOCKHOLDER	SPEAKERS BUREAU	ADVISORY BOARD	OTHER
Merck	X						
Celgene/BMS	X						
Astex Pharmaceutical	X						
Kymera Therapeutics	X						
Myeloid Therapeutics	X						
Daiichi Sankyo			X				
Kyowa Kirin			X				
SecuraBio			X				
Everest Clinical Research							Data Safety Monitoring Commettee

EXPLORING AN IMMUNOLOGIC RATIONALE TO BUILDING NOVEL PLATFORM IN PTCL

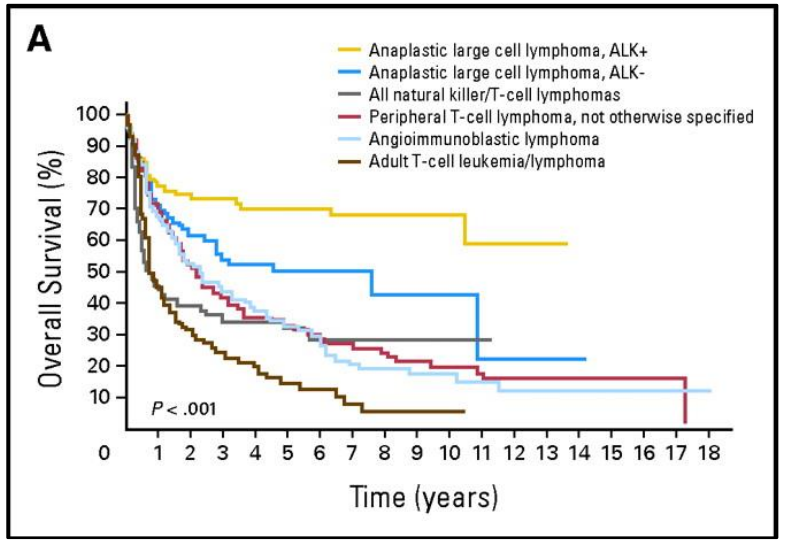
- **The Challenges of Improving Outcome in PTCL**
- Novel Drug Combinations Provide the Rationale for the Addition of Biologics/Immune Therapeutics
- Leveraging ICI in Epigenetic Combinations
- Conclusion

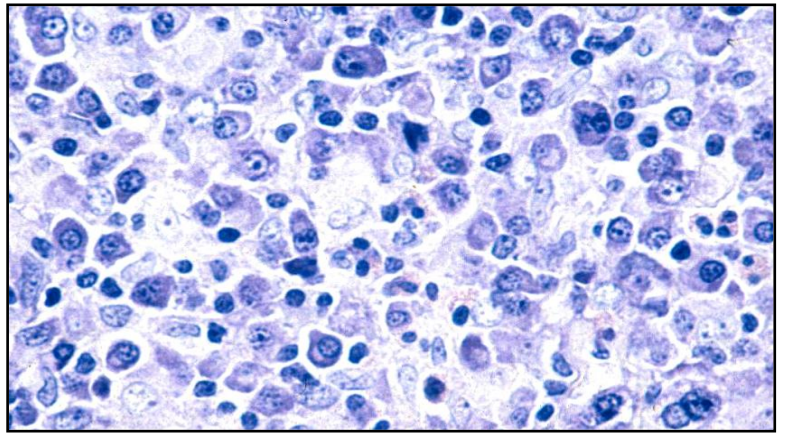




PTCL: Background

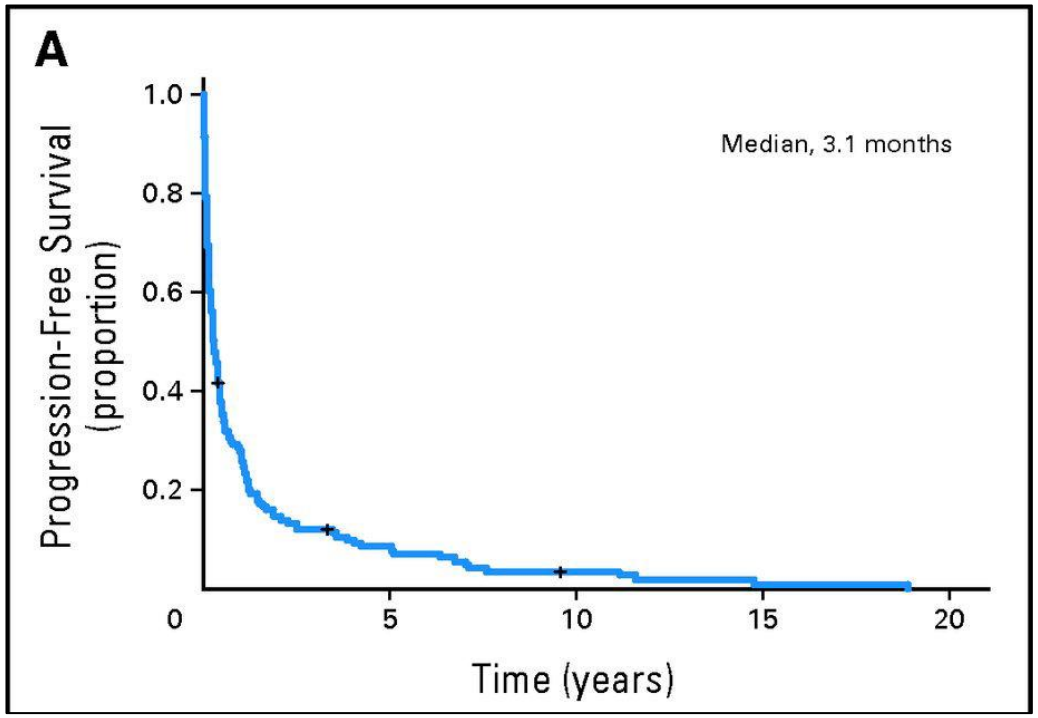
- PTCL is a **rare** and **heterogeneous** group of **mature**, **postthymic**, T-cell, and NK-cell lymphoproliferative disorders
- PTCL account for 6-10% of all NHL cases → 6,000 to 10,000 cases/year and they are very heterogenous with more than 30 different subtypes
- PTCL represent 15% - 20% of **all aggressive** lymphomas
- With the exception of ALK+ ALCL, PTCL subtypes have **poor OS with standard therapies →5 years OS 15-20%**
- Molecular characterization has led to identification of subtypes with different prognoses and is contributing to the development of novel pathway-directed therapies



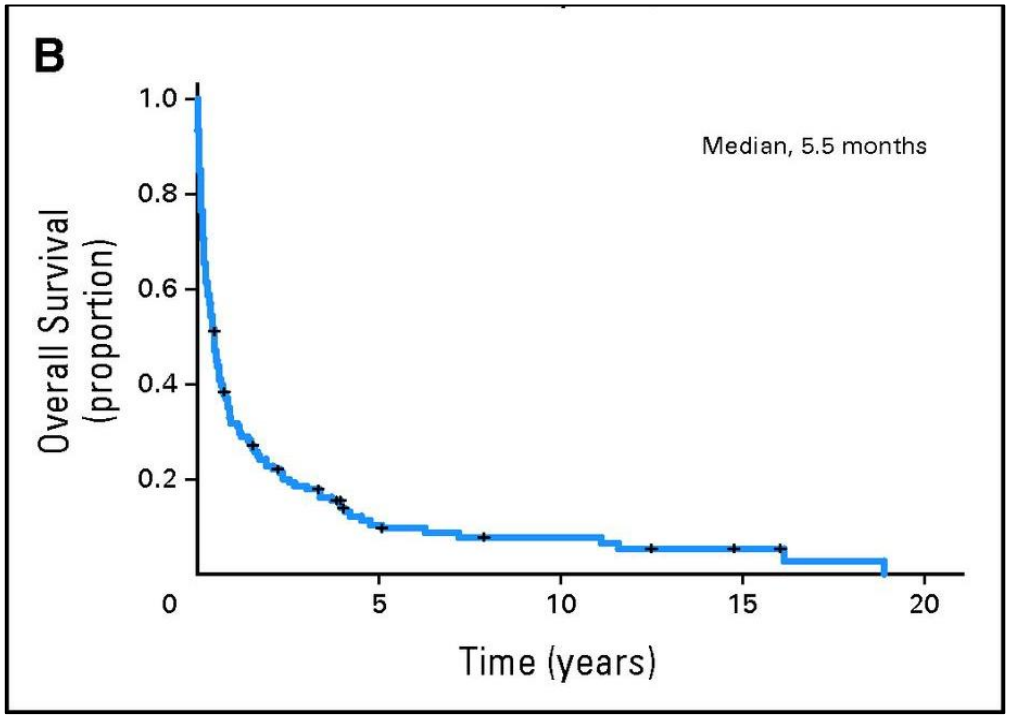


Vose et al; JCO 2008;26:4124.

PROOF OF INTRINSEC INADEQUACY OF CONVENTIONAL CHEMOTHERAPY



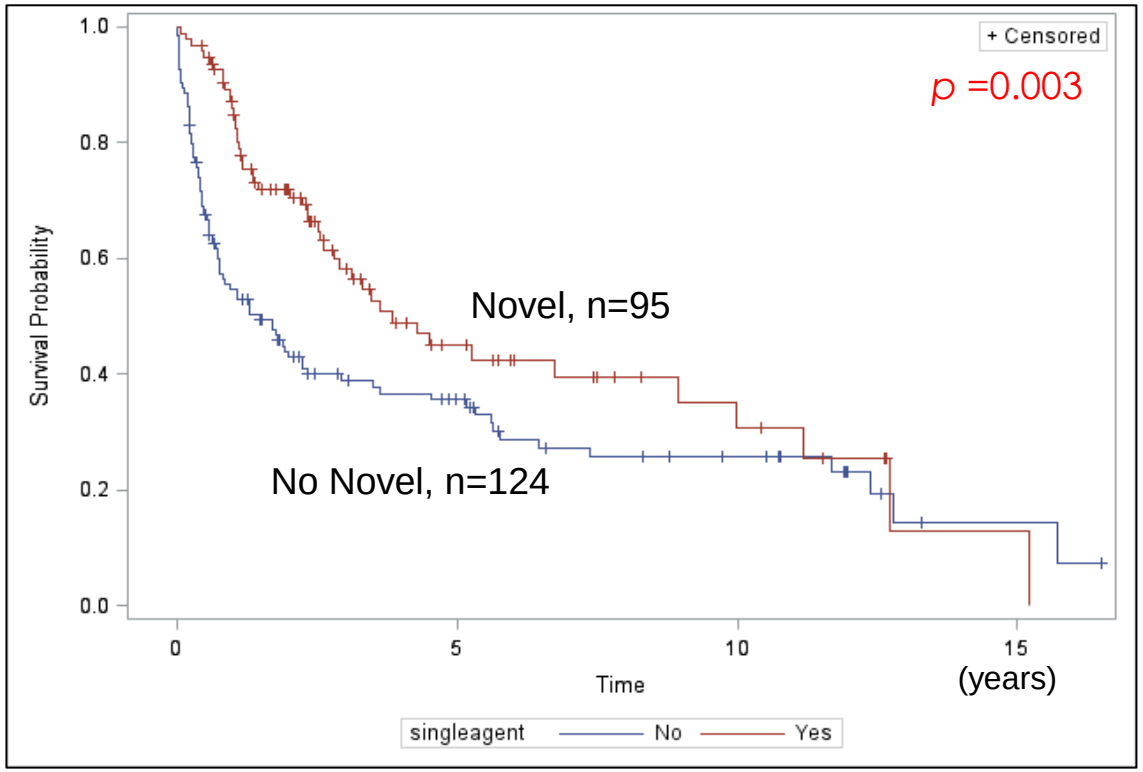
PFS at First Relapse:
3.1 Months

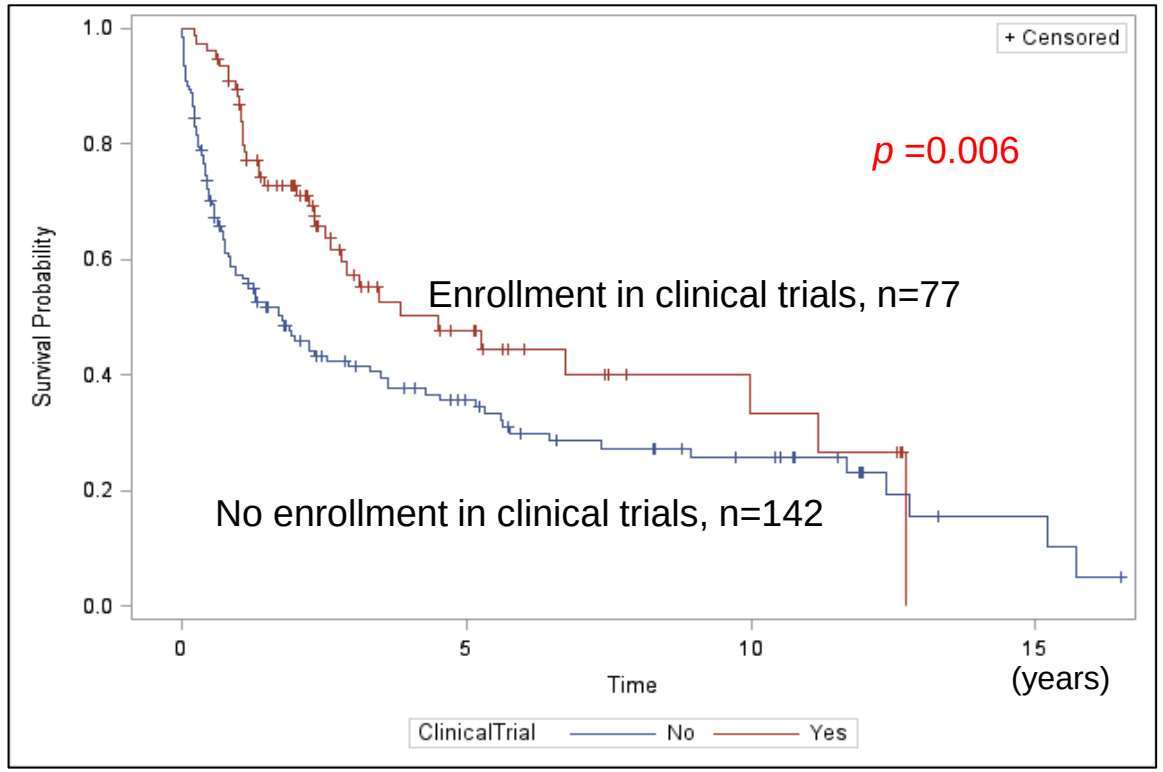


OS at First Relapse:
5.5 Months

Mak V et al. JCO 2013

EXPOSURE TO NOVEL THERAPIES & ENROLLEMENT IN CLINICAL TRIALS IMPROVE SURVIVAL

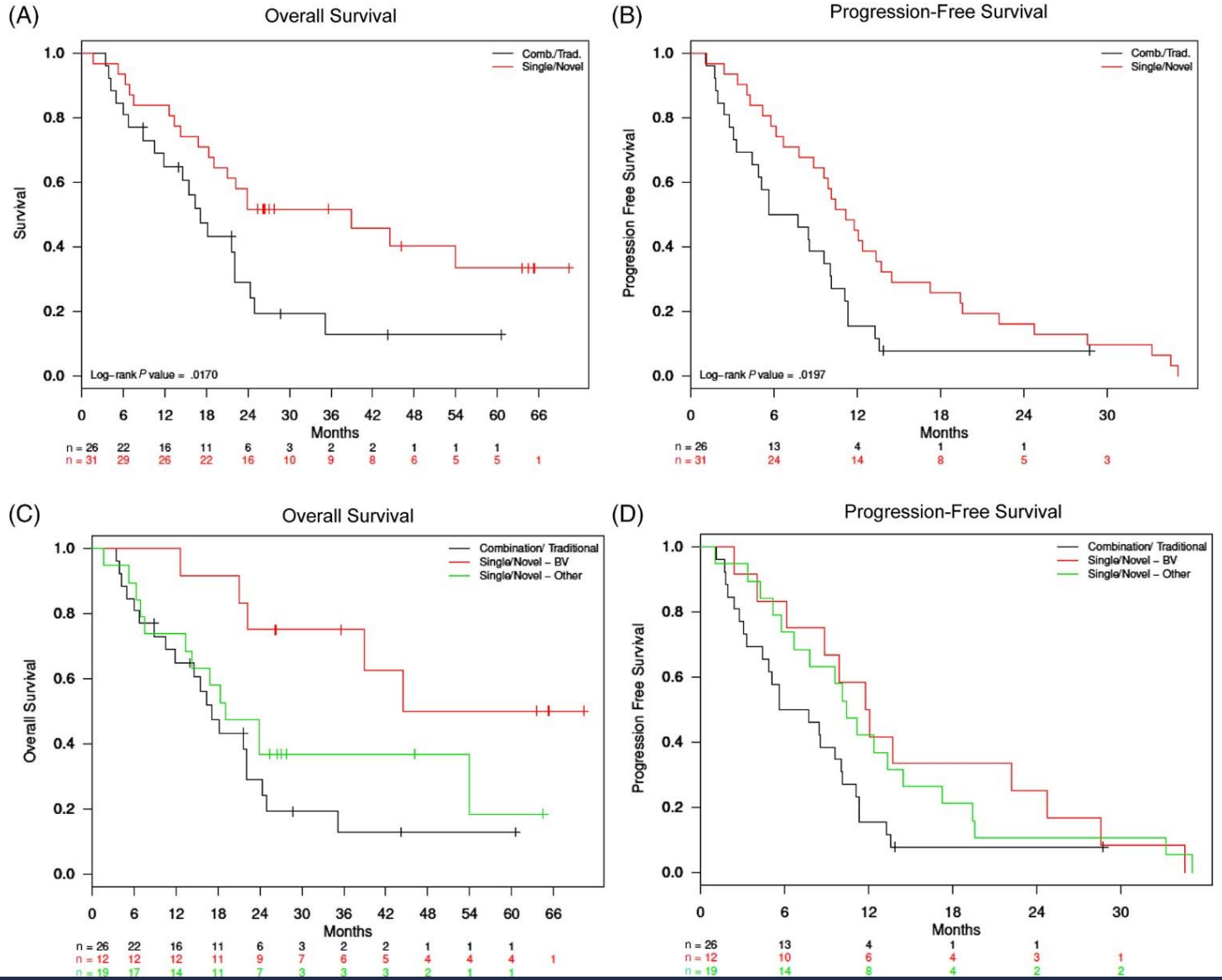




Data from Single Center, Retrospective Analysis of 219 PTCL patients treated from 1994 - 2019

Ma et al; Hematol Oncol 2019

IMPROVED RESPONSE AND SURVIVAL WITH NOVEL AGENTS



Retrospective Data from the COMPLETE Registry

Novel Agents as Bridge to Transplant

Stuver RN et al; et al; Am J Hematol 2019

EXPLORING AN IMMUNOLOGIC RATIONALE TO BUILDING NOVEL PLATFORM IN PTCL

- The Challenges of Improving Outcome in PTCL
- **Novel Drug Combinations Provide the Rationale for the Addition of Biologics/Immune Therapeutics**
- Leveraging ICI in Epigenetic Combinations
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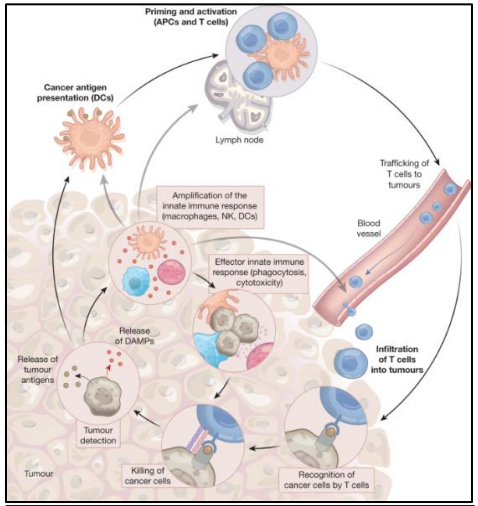
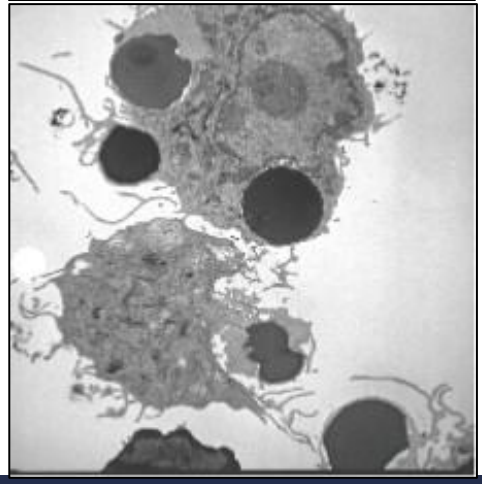
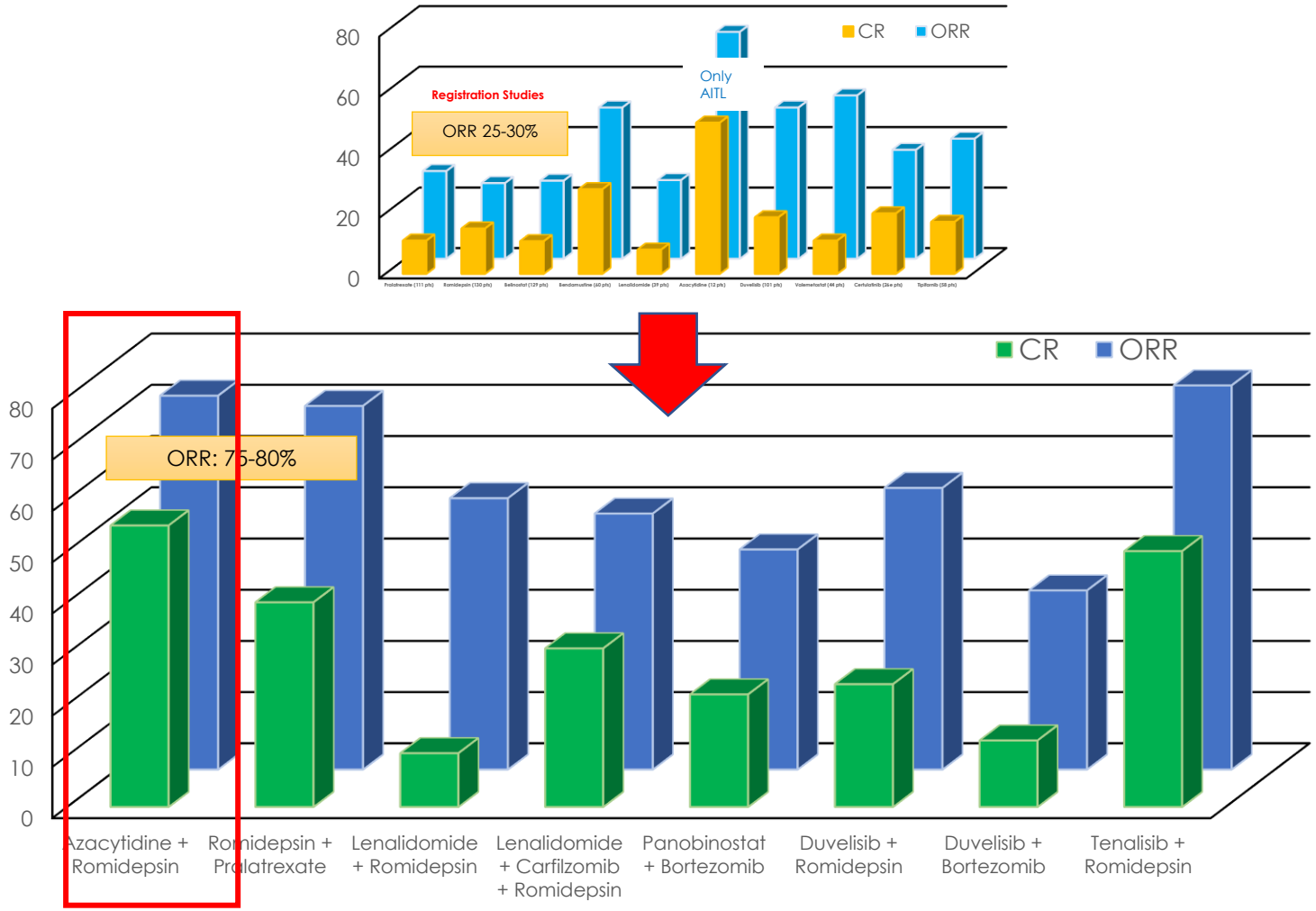




NEW PATHS TO IMPROVE OUTCOME:

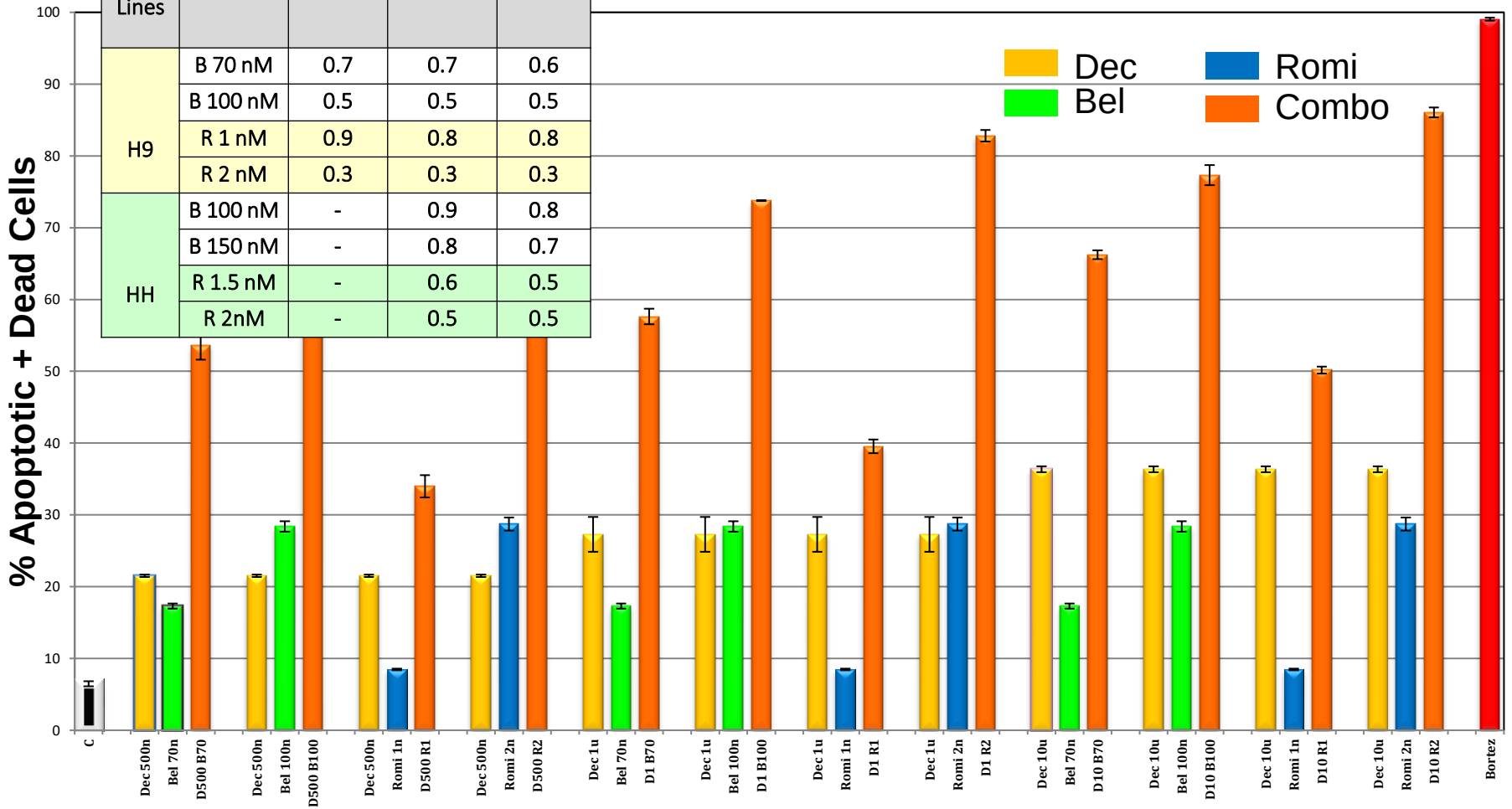
FROM NOVEL AGENTS TO LINEAGE- AND DISEASE-SPECIFIC NOVEL PLATFORMS



Drug Combination	ORR (%)	CR (%)
Azacytidine + Romidepsin *O'Connor et al; Blood 2019* *Falchi & Ma et al; Blood 2021*	73	55
Pralatrexate + Romidepsin *Amengual et al; Blood 2017*	71	40
Lenalidomide + Romidepsin *Mehta-Shah et al; JCO 2015*	53	10.5
Lenalidomide + Carfilzomib + Romidepsin *Mehta-Shah et al; Blood 2016*	50	31
Panobinostat + Bortezomib *Tan et al; Lancet Hem 2015*	43	22
Duvelisib + Romidepsin *Horwitz et al; Blood 2018*	55	24
Duvelisb + Bortezomib *Horwitz et al; Blood 2018*	35	13
Tenalisib + Romidepsin Iyer et al; ASH 2021	75	50

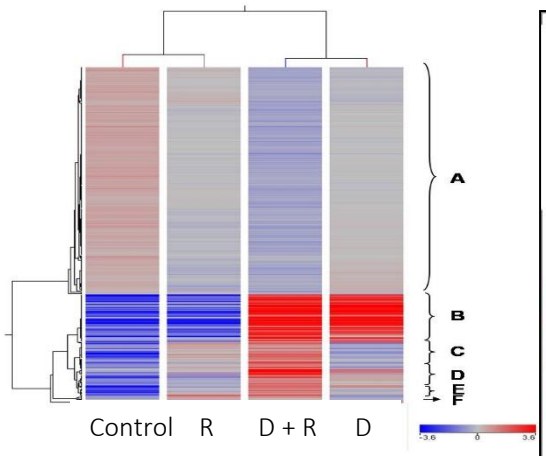
HDACIs SYNERGISTICALLY INDUCE APOPTOSIS IN COMBINATION WITH THE HMA, DECITABINE

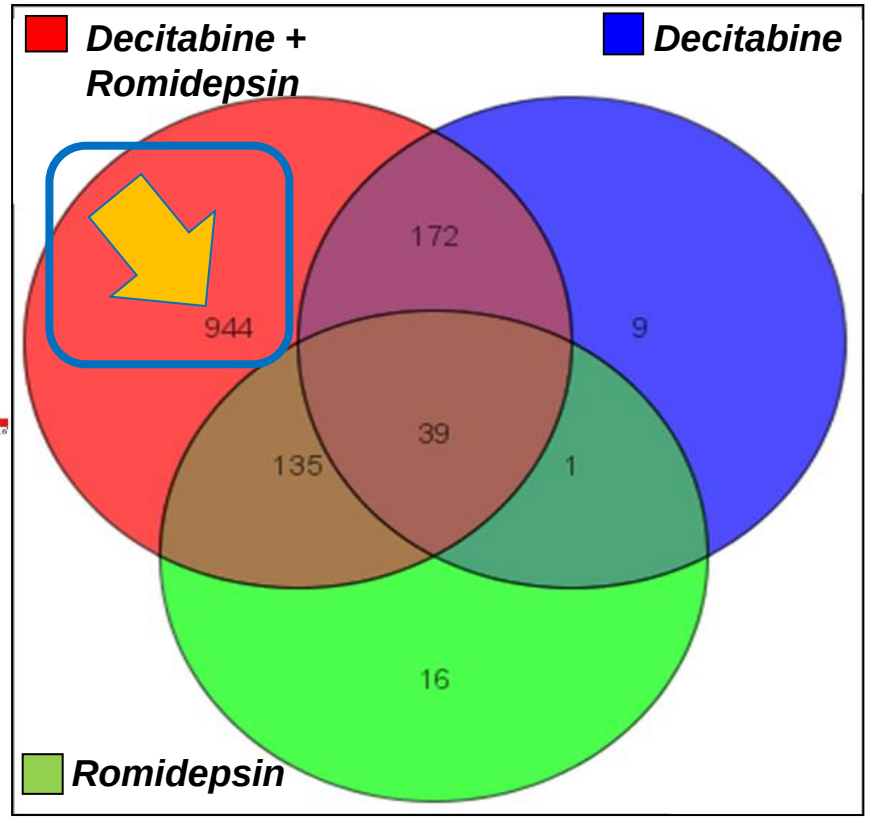
T-cell Lines		D 500 nM	D 1uM	D 10 uM
H9	B 70 nM	0.7	0.7	0.6
	B 100 nM	0.5	0.5	0.5
	R 1 nM	0.9	0.8	0.8
	R 2 nM	0.3	0.3	0.3
HH	B 100 nM	-	0.9	0.8
	B 150 nM	-	0.8	0.7
	R 1.5 nM	-	0.6	0.5
	R 2nM	-	0.5	0.5

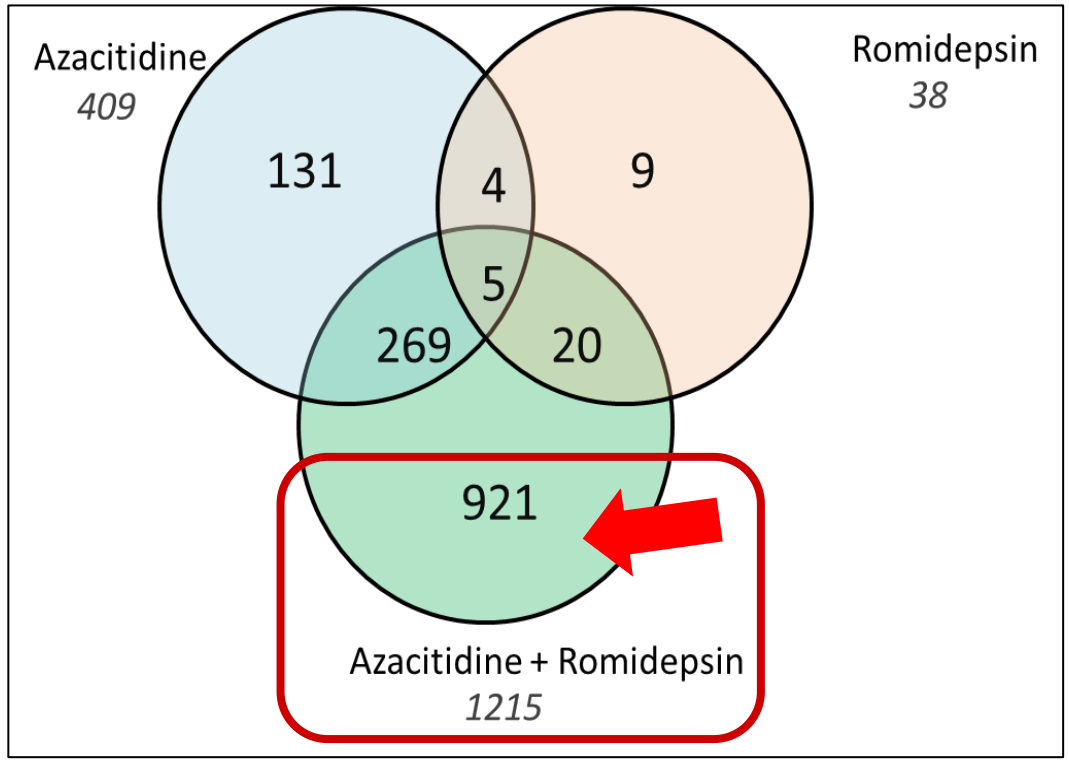


Marchi E. et al; Br J Haematol 2015

THE COMBINATION HDACI AND HMA UNIQUELY AFFECTS GENE EXPRESSION PROFILING







Marchi E. et al; Br J Haematol 2015
Scotto L et al; Mol Cancer Therapeutics 2021

STATISTICAL OVERREPRESENTATION TEST OF DIFFERENTIALLY EXPRESSED GENES

Downregulated genes by the AZA/Romi combo with pvalue<0.05

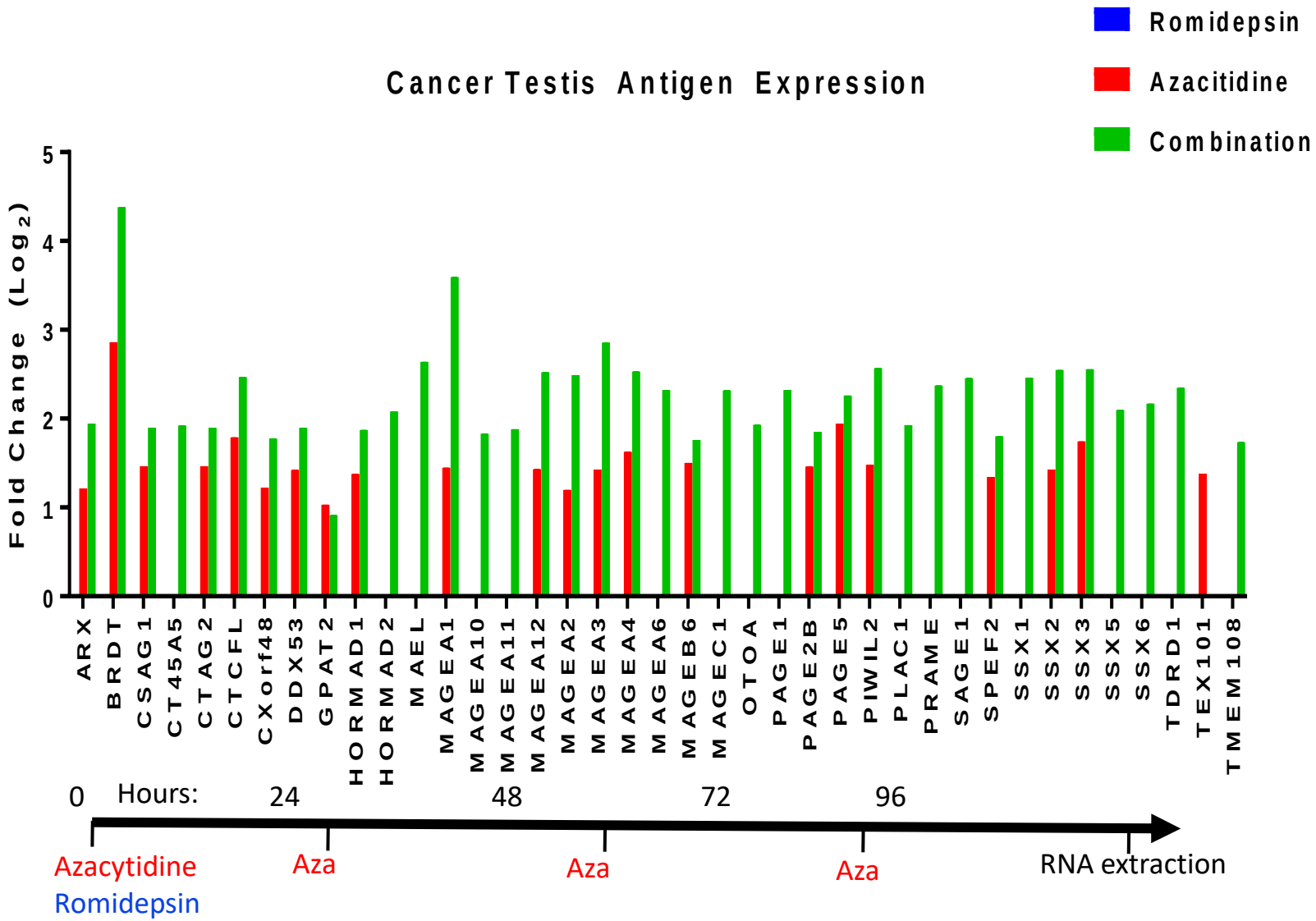
PANTHER GO-Slim Biological Process	#	#	expected	Fold Enrichment	+/-	P value
cholesterol metabolic process	80	8	.91	8.77	+	1.16E-03
↳steroid metabolic process	92	7	1.05	6.68	+	2.51E-02
Unclassified	8633	101	98.38	1.03	+	0.00E00

Upregulated genes by the AZA/Romi combo with pvalue<0.05

PANTHER GO-Slim Biological Process	#	#	expected	Fold Enrichment	+/-	P value
gamete generation	67	16	2.67	5.98	+	5.82E-06
muscle organ development	245	24	9.78	2.45	+	1.85E-02
mesoderm development	412	36	16.44	2.19	+	3.93E-03
ectoderm development	405	34	16.16	2.10	+	1.45E-02
nervous system development	668	49	26.66	1.84	+	1.18E-02
Unclassified	8633	298	344.55	.86	-	0.00E00

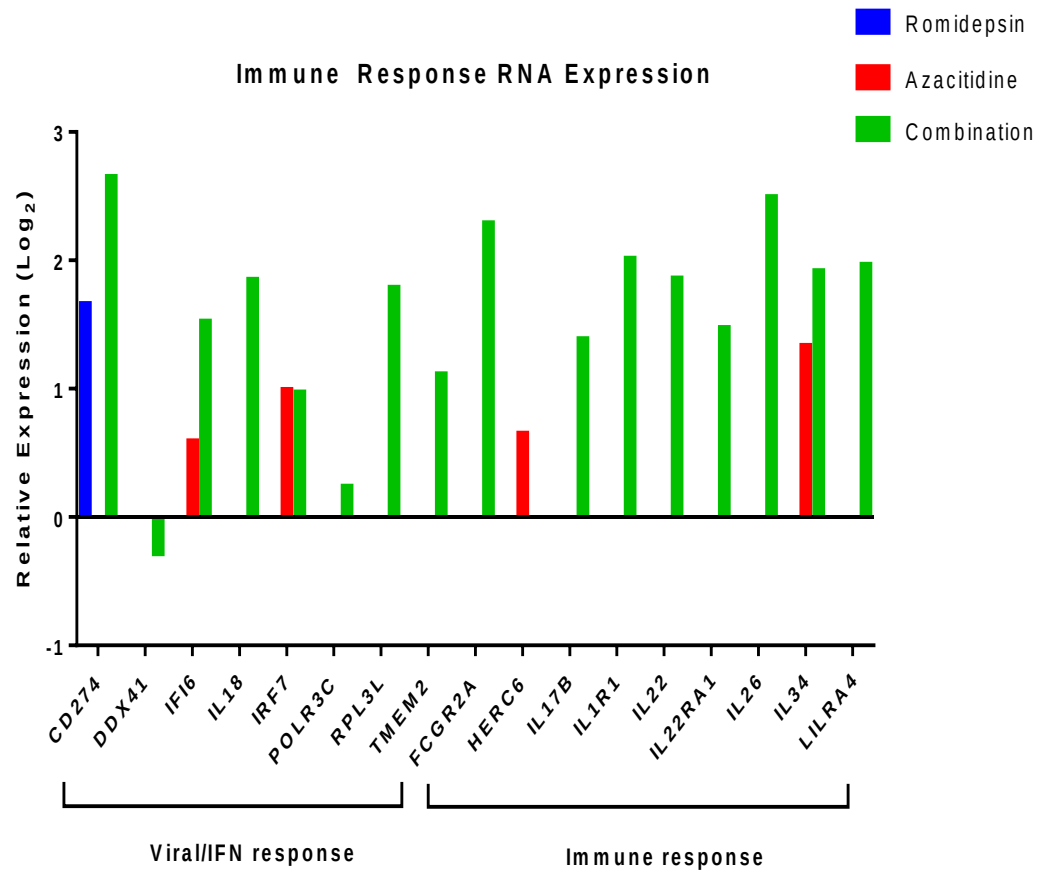
Scoffo L et al; Mol Cancer Therapeutics 2021

CTA EXPRESSION AS A FUNCTION OF TREATMENT



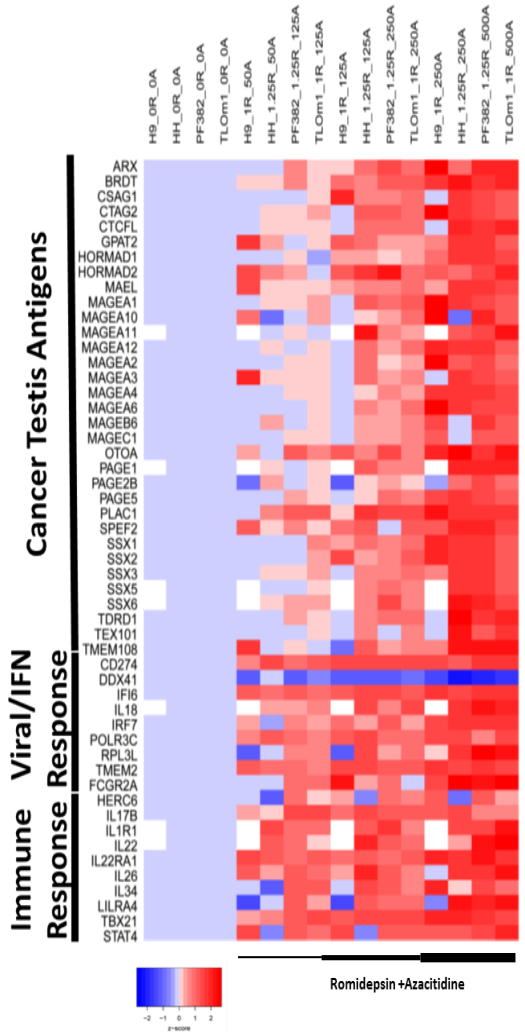
Scotto L. et al; Mol Cancer Ther 2021

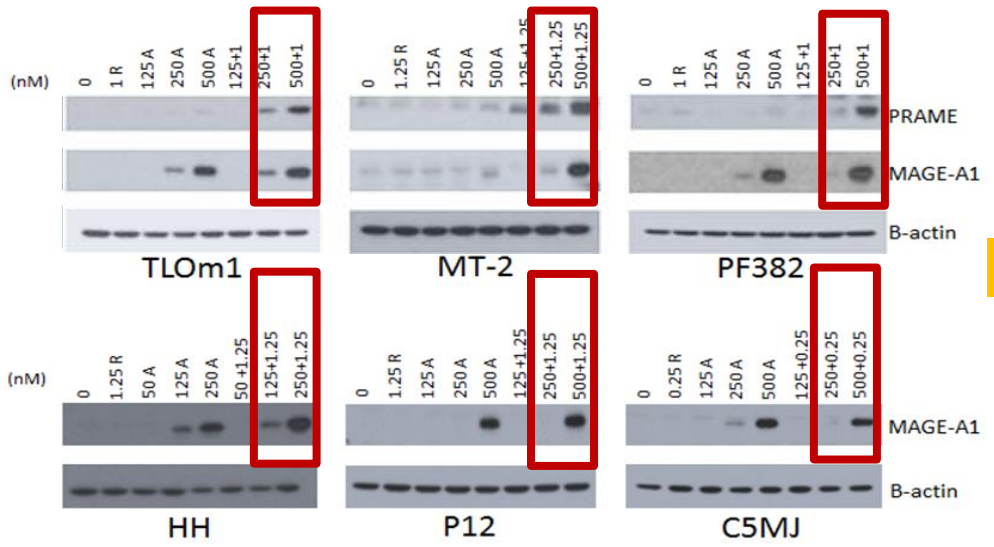
ENDOGENEOUS RETROVIRUS & IMMUNE EXPRESSION AS A FUNCTION OF TREATMENT



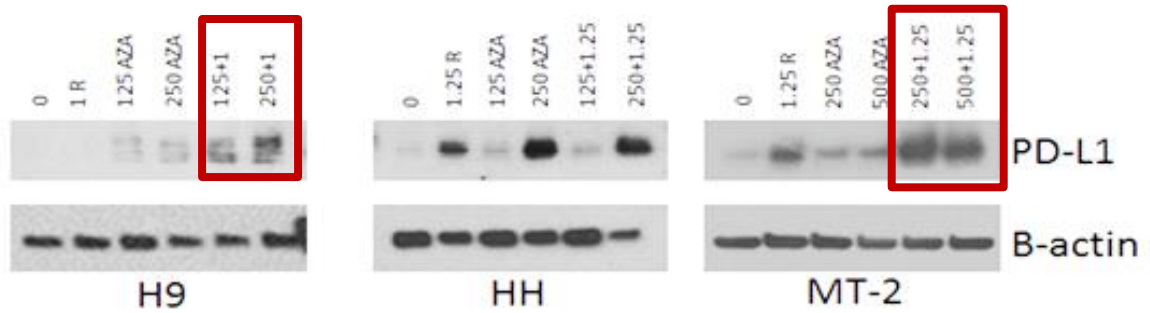
Gene	Protein Function
CD274/PDL-1	Immune check point
DDX41	Cytoplasmic DNA sensor
IFI6	IFNα inducible protein 6
IL18	IFNγ inducing factor
IRF7	IFN regulator factor 7, transcriptional activation of virus inducible cellular genes
POLR3C	Nuclear and cytosolic dsDNA sensor
RPL3L	Ribosomal protein L3 – like. Involved in the viral mRNA translation
TMEM2	Transmembrane protein 2. Interferon-mediated antiviral function in humans through activation of the JAK STAT signaling pathway
FCGR2A	Ig-Fc receptor family. Involved in the process of phagocytosis and clearance of immune complexes
HERC6	Herc ubiquitin ligase, implicated in MCH-I Ag presentation
IL26	Trigger the production type I IFN response. Induced rapid phosphorylation of STA1 and STA3

SUPERVISED ANALYSIS OF CANCER TESTES ANTIGENS AND IMMUNE RESPONSE GENES CONFIRMED BY WESTERN BLOT





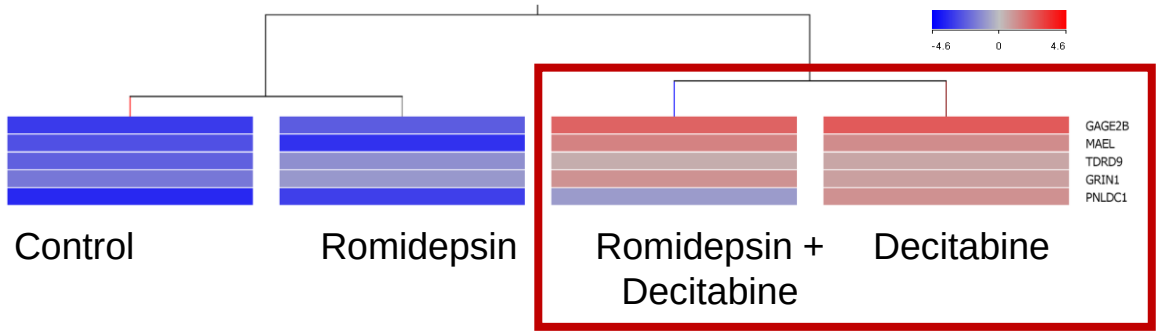
Cancer Testes Antigens

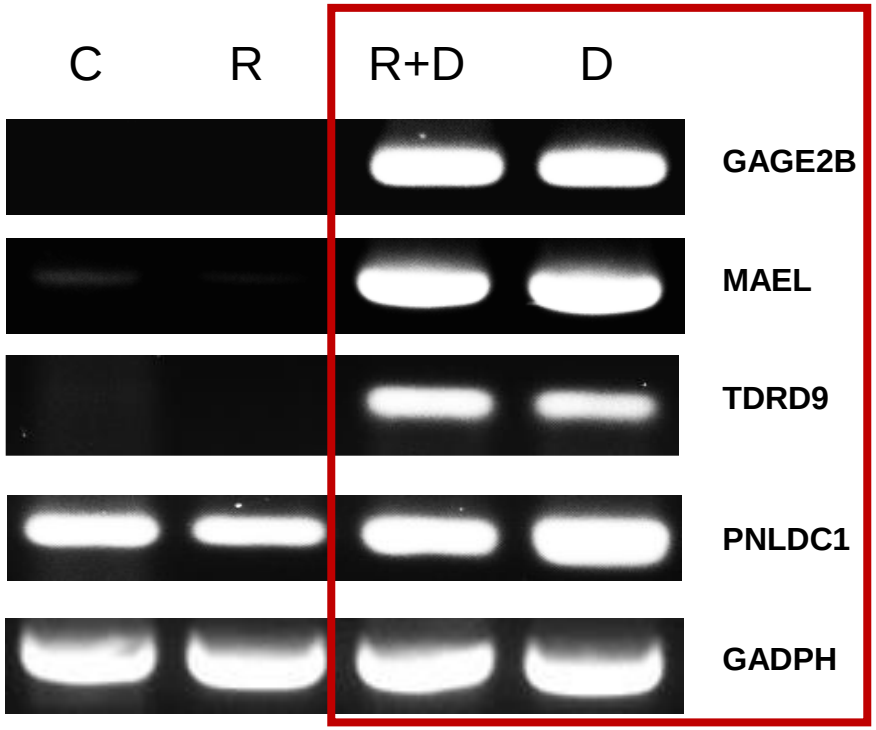


PD-L1 Increased by Doublet

Aza alone effect

EPIGENETIC PRIMING WITH DECITABINE





PCR Validation of the 5 Common Genes Modulated by Gene Expression and Methylation:

CANCER TESTES ANTIGENS

Marchi E. et al; Br J Haematol 2015

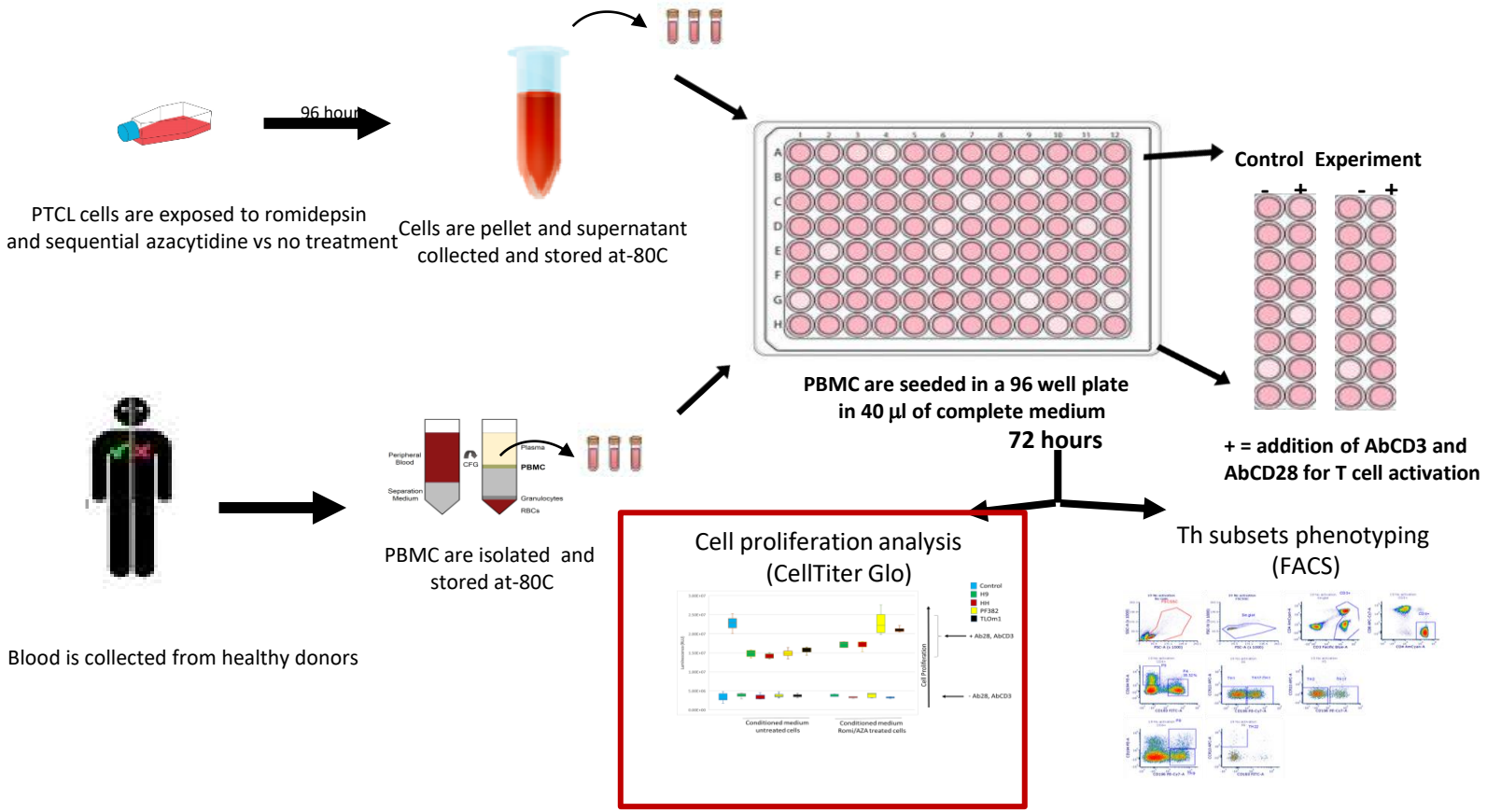
AZA-ROMI INDUCES A TH-1 PHENOTYPE OF LYMPHOCYTES

CONDITIONED-MEDIUM CELL PROLIFERATION AND DIFFERENTIATION ASSAY

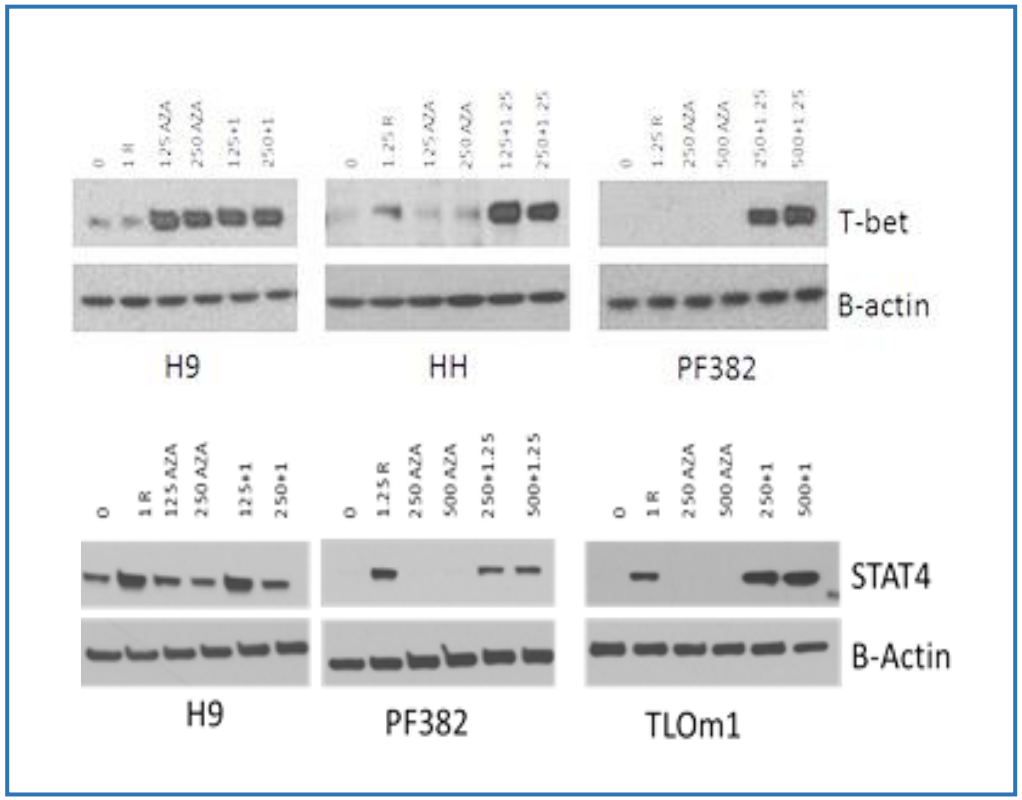
Control : 80 µl of complete medium are added to each well.

Experiment 1: 80 µl of supernatant (conditioned medium) collected from untreated cells are added to each well.

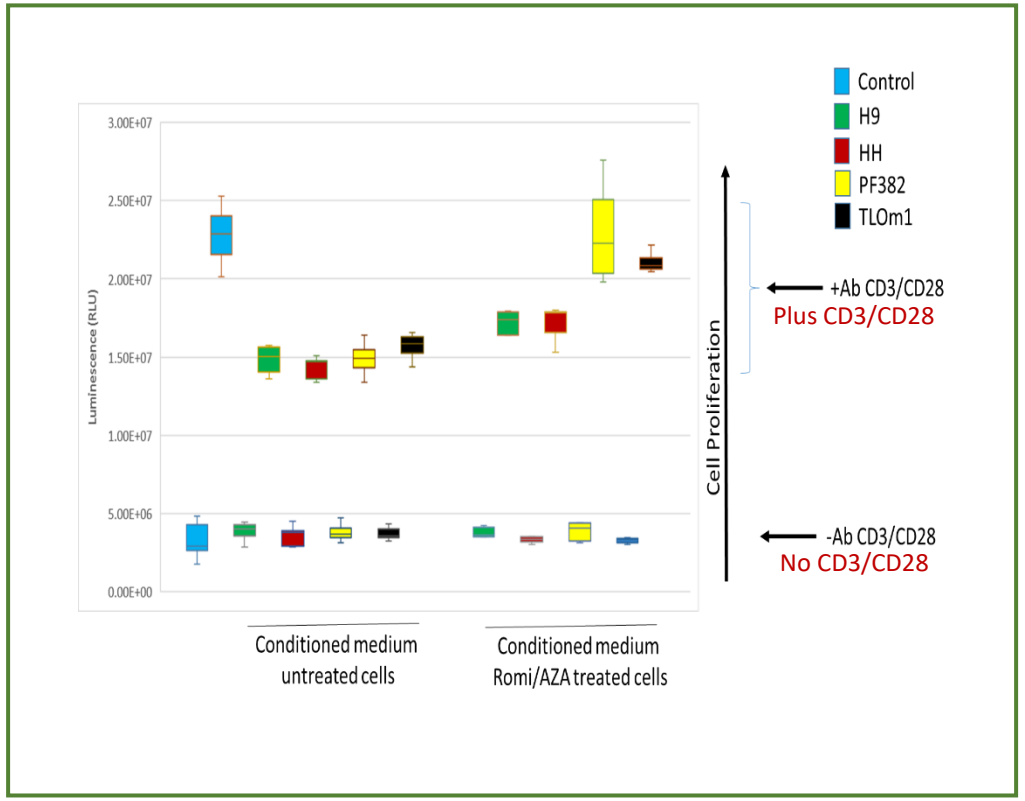
Experiment 2: 80 µl of supernatant (conditioned medium) collected from Romi/AZA treated cells are added to each well.



INDUCTION OF TH1-LIKE PHENOTYPE BY AZA-ROMI IN T-CELL LINES

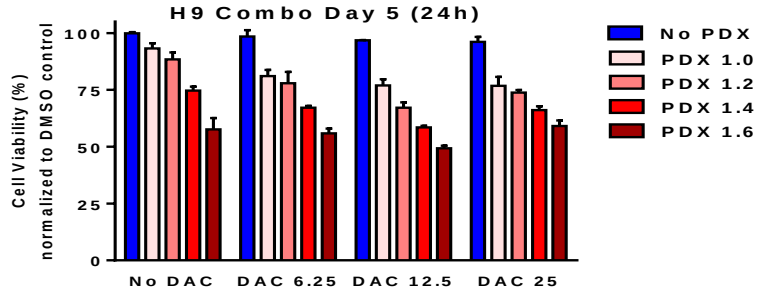


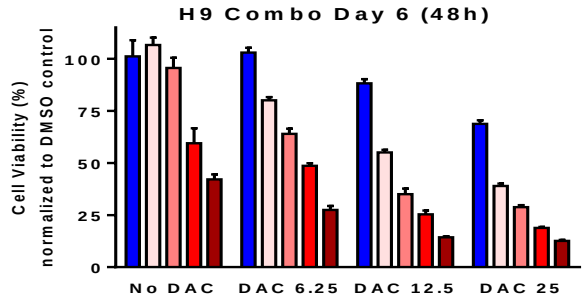
Induction of T-bet and STAT4 in TCL panel by 5-Aza-Romi

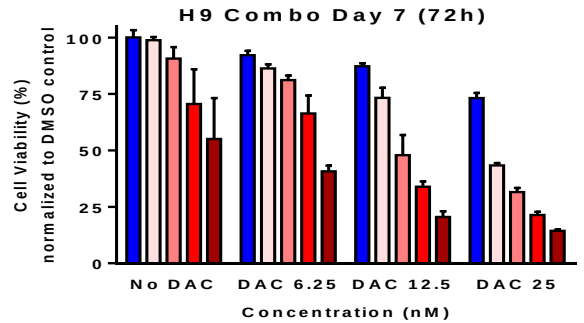


CD3/CD28 induces T-cell proliferation → augmented when supplemented by supernatants from 5-Aza/Romi treated healthy donor

PRALATREXATE SYNERGIZES WITH DECITABINE IN VITRO







Excess Over Bliss (EOB)

24 hours

Conditions (nM)	PDX-1	PDX-1.2	PDX-1.4	PDX-1.6
DAC-6.25	10.9	9.4	6.5	1.0
DAC-12.5	13.5	18.6	13.9	6.6
DAC-25	13.0	11.4	5.8	-3.7

48 hours

Conditions (nM)	PDX-1	PDX-1.2	PDX-1.4	PDX-1.6
DAC-6.25	20.8	31.3	10.7	14.5
DAC-12.5	32.8	47.9	26.3	22.2
DAC-25	29.5	35.8	21.4	15.9

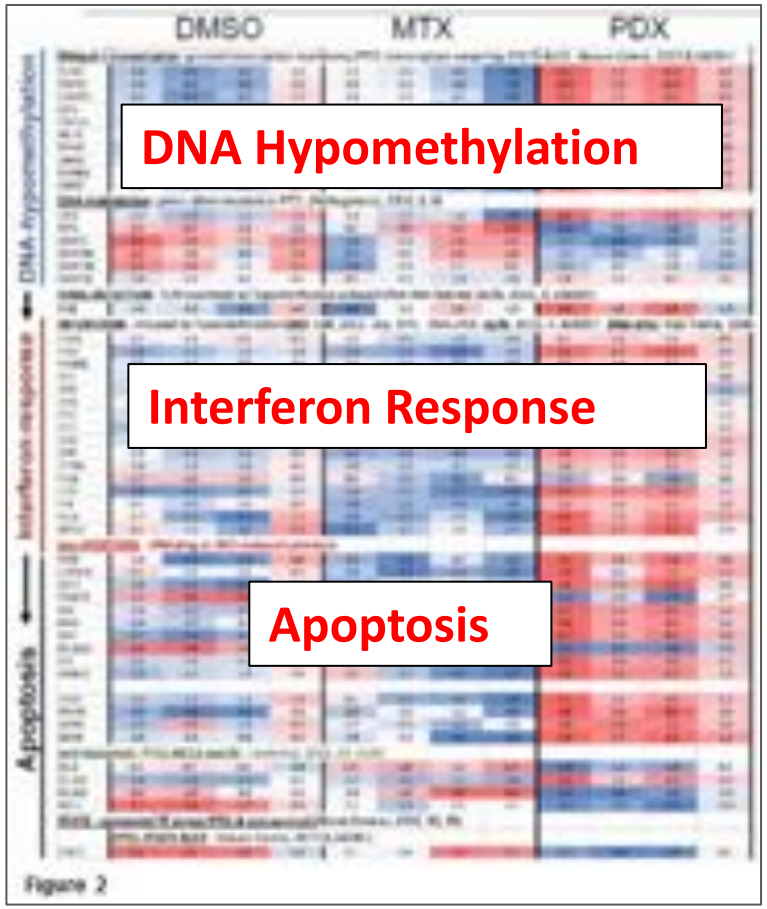
72 hours

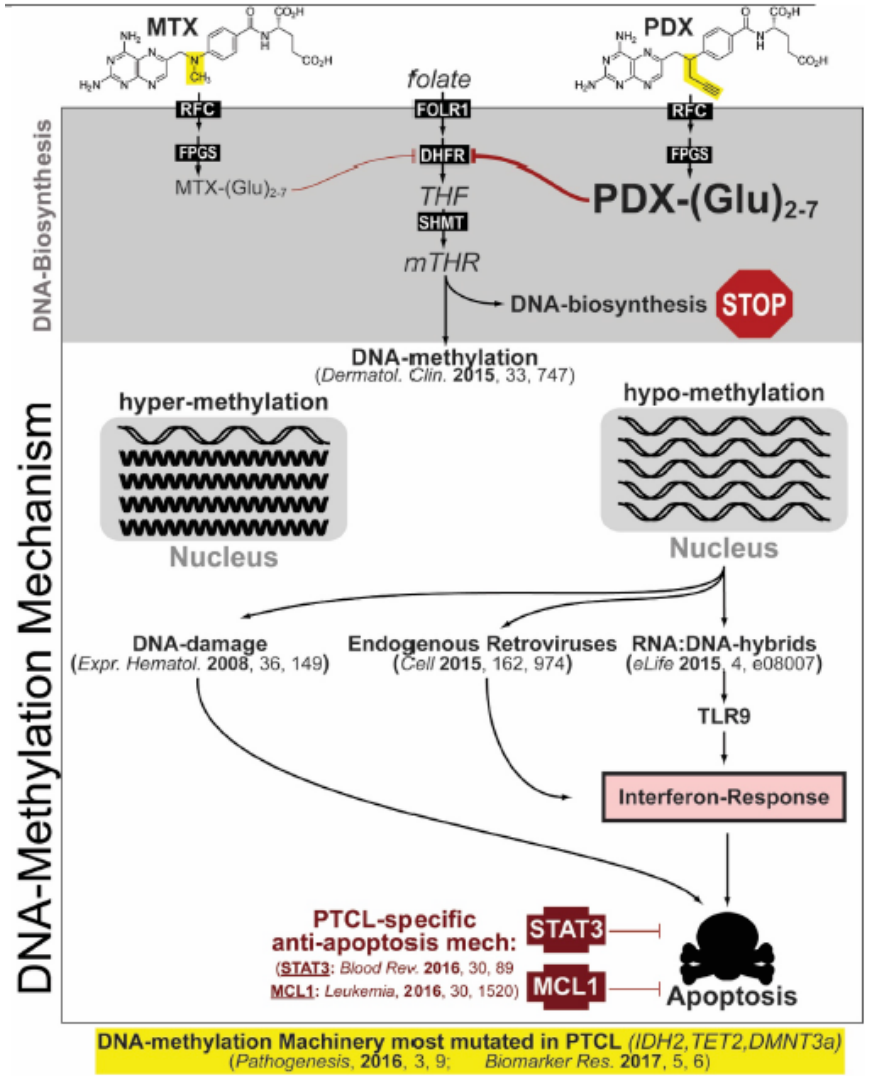
Conditions (nM)	PDX-1	PDX-1.2	PDX-1.4	PDX-1.6
DAC-6.25	4.7	2.4	-1.3	9.9
DAC-12.5	12.9	31.1	27.6	27.4
DAC-25	28.9	34.8	30.2	25.9

EOB scale: -1 10 30

Mangone M. et al; Unpublished Data 2017

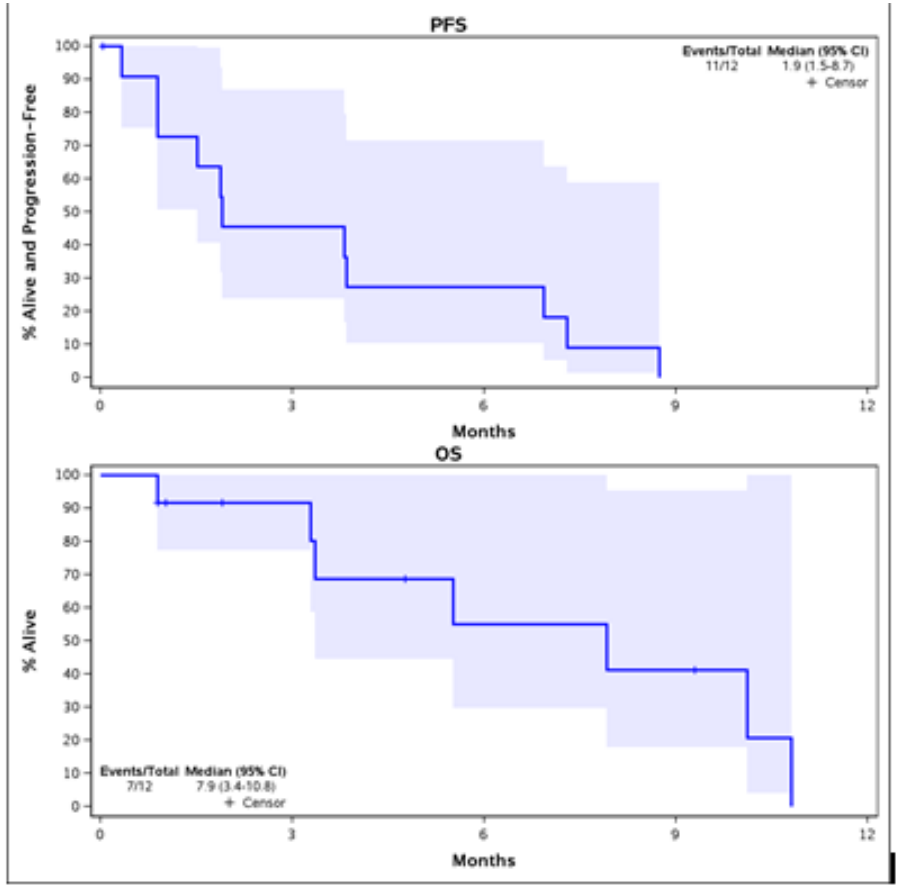
PRALATREXATE ACTS AS IMMUNOMODULATORY AGENT





Marchi E, Douglass E, Scotto L, O'Connor OA, Califano A. et al; Unpublished data 2017

THE DOUBLE SWORD OF ICI:
A STEP BACK TO LEARN UPON



CORRESPONDENCE

Rapid Progression of Adult T-Cell Leukemia–Lymphoma after PD-1 Inhibitor Therapy

95 Citing Articles Letters

TO THE EDITOR:

Adult T-cell leukemia–lymphoma (ATLL) is an aggressive clonal T-cell cancer caused by human T-cell leukemia virus type 1 (HTLV-1).[1] Responses to interferon, zidovudine, arsenic, or mogamulizumab are generally short-lived.[1] Genomic analysis has shown a higher mutation rate in ATLL than in other hematopoietic cancers. These changes include the T-cell receptor, nuclear factor κB, and immune surveillance pathways, including overexpression of the programmed cell death 1 ligand (PD-L1) gene.[2]

May 17, 2018
N Engl J Med 2018; 378:1947-1948
DOI: 10.1056/NEJMc1803181
Metrics

Related Articles

CORRESPONDENCE AUG 16, 2018
PD-1 Inhibitor Therapy in Adult T-Cell Leukemia–Lymphoma

Phase II Study of Nivolumab in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma: halt accrual.

Ratner L. et al; NEJM 2018
Bennani N et al, ASH 2019

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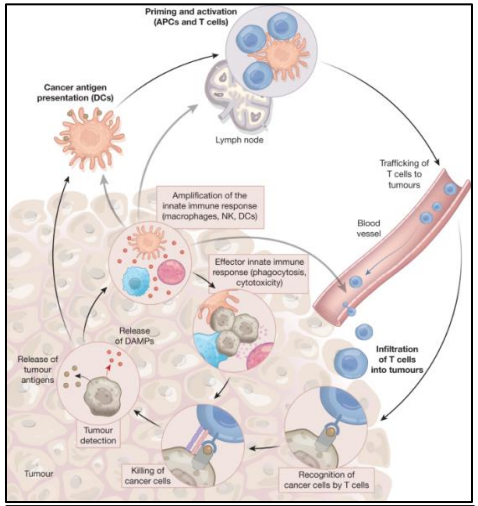
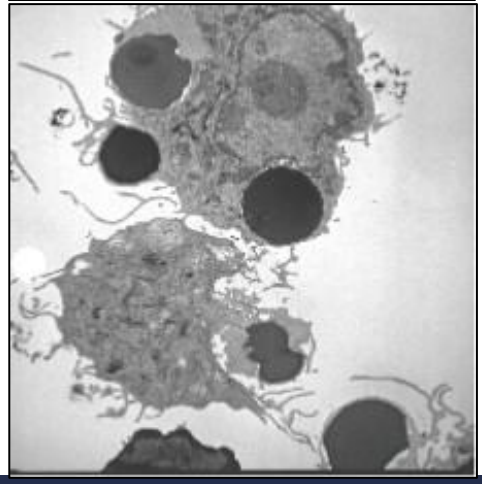
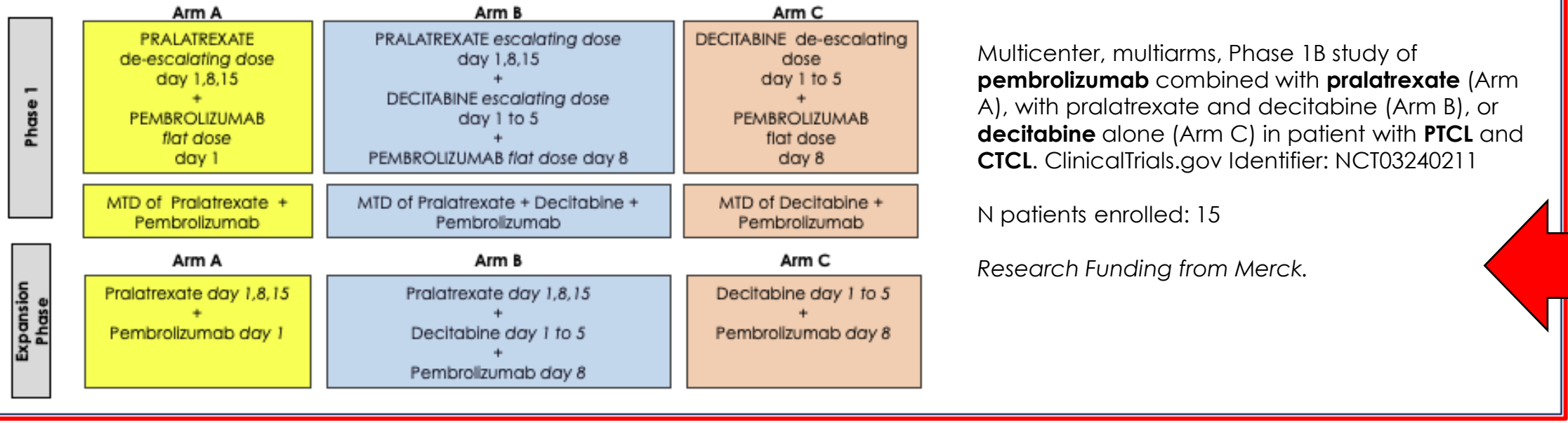




NOVEL IMMUNO-EPIGENETIC PLATFORMS



Multicenter, multiarms, Phase 1B study of **pembrolizumab** combined with **pralatrexate** (Arm A), with pralatrexate and decitabine (Arm B), or **decitabine** alone (Arm C) in patient with **PTCL** and **CTCL**. ClinicalTrials.gov Identifier: NCT03240211

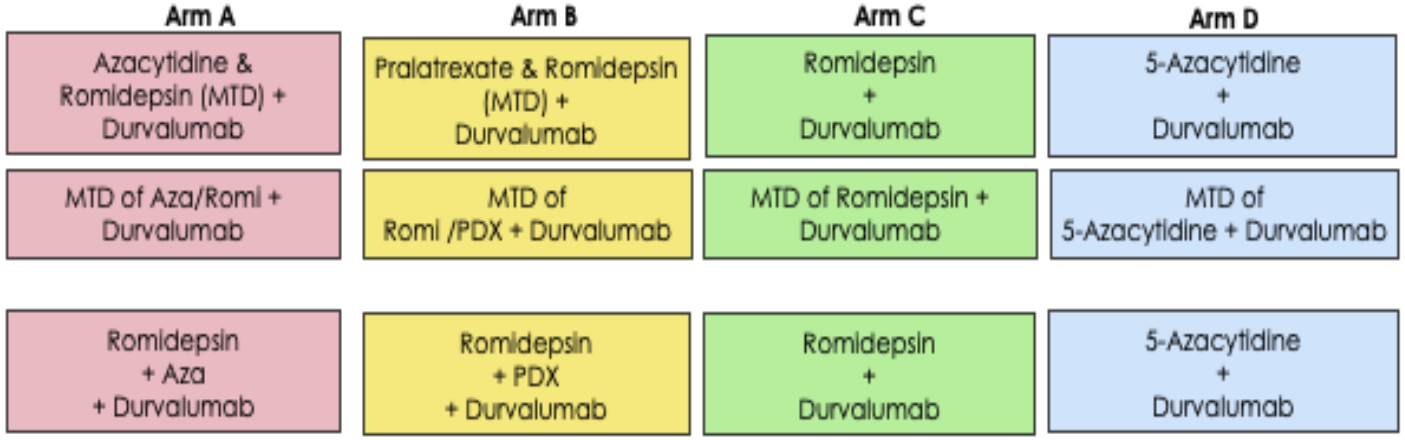
N patients enrolled: 15

Research Funding from Merck.

Phase 1/2A study of durvalumab combined with oral 5-azacytidine + romidepsin (Arm A), pralatrexate + romidepsin (Arm B), romidepsin alone (Arm C), or oral 5-azacytidine alone (Arm D) for the treatment of patients with PTCL. ClinicalTrials.gov Identifier: NCT03161223

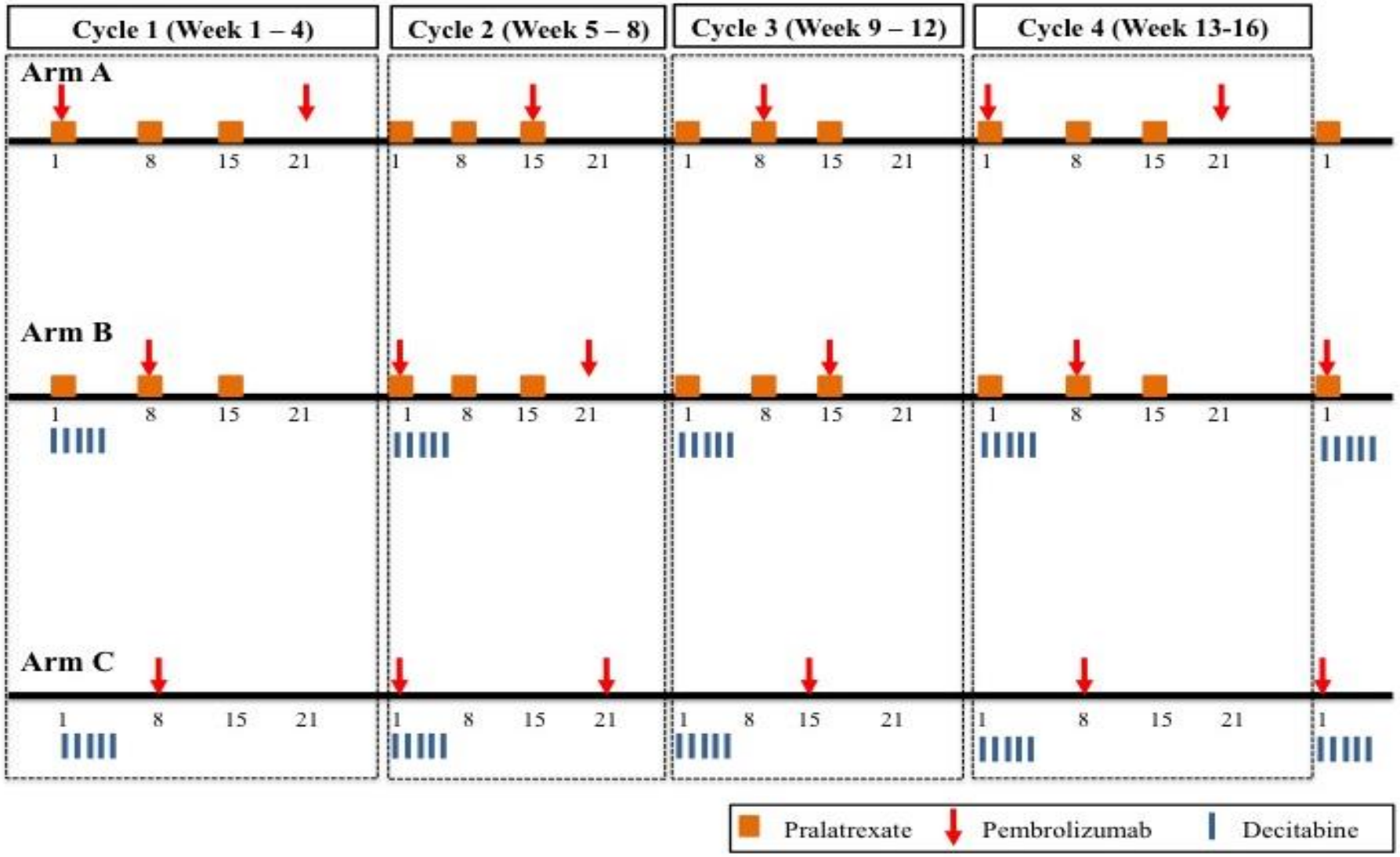
N patients enrolled: 5

Research funding from Celgene



Marchi E et al., AACR 2020
Marchi E et al., ASCO 2020
Roberts N et al., TCLF 2022
Roberts N et al., ASH 2022

TRIAL SCHEMA



EMBOLDEN Trial: Patient Characteristics

Preliminary Result (n=15)

Median age, years (range)	66 (38 - 77)
Sex, n (%) Male Female	 7 (46.7) 8 (53.3)
Race, n (%) White/Non-Hispanic White/Hispanic Black Asian	 8 (53.3) 1 (6.7) 4 (26.7) 2 (13.3)
Histology, n (%) PTCL, NOS AITL Mycosis Fungoides ATLL Sezary Syndrome PCAECTL	 6 (40) 3 (20) 3 (20) 1 (6.7) 1 (6.7) 1 (6.7)
Stage at diagnosis, n (%) I II III IV Tumor Stage	 1 (13.3) 2 (13.3) 5 (33.3) 5 (33.3) 1 (6.7)
Median number of prior therapies (range)	3 (1-5)

EMBOLDEN Trial: Grade 3/4 Toxicities

Preliminary Result (n=15)

Adverse Event	Grade 3/4, n (%)
Thrombocytopenia	2 (14.3)
Neutropenia	4 (28.6)
Anemia	1 (7.1)
Fatigue	1(7.1)
Vomiting	1(7.1)
Immune related adverse event	1(7.1)
Hyponatremia	1(7.1)
Rash	1(7.1)

- One DLT each was observed arms A and B for prolonged grade 3 thrombocytopenia (PLT <50,000 – 25,000/mL) and febrile neutropenia (ANC < 1,000/mL with single temperature >38.3 C), respectively.
- Three DLTs were observed in arm C including one patient with grade 3 hyponatremia and rash; one patient with grade 4 thrombocytopenia, neutropenia, and anemia; and one patient with grade 4 neutropenia.
- There were no treatment-related deaths.

EMBOLDEN Trial: Clinical Response

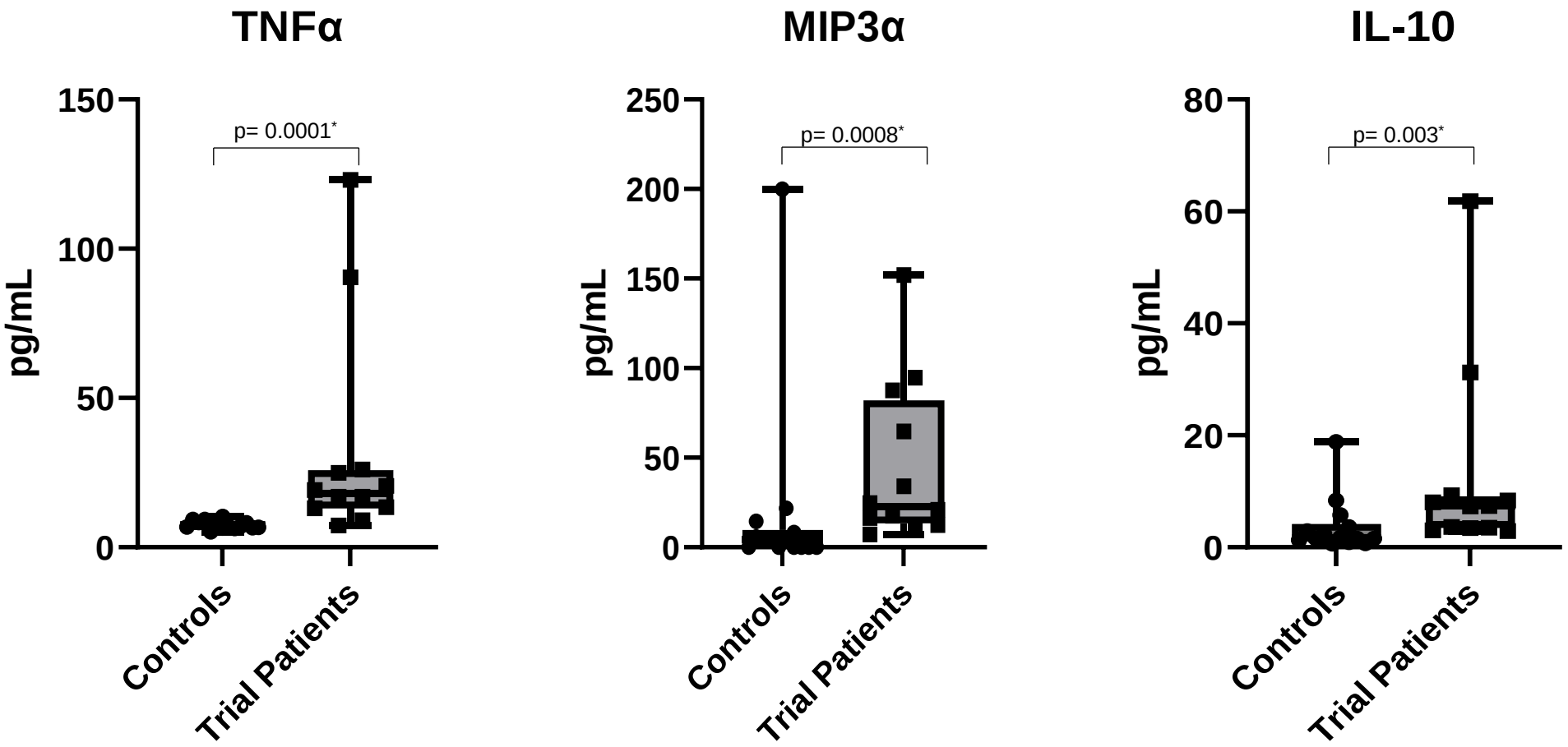
Preliminary Result (n=15)

Response	Number of Patients
Not evaluable	6/15 (40%)
Evaluable	9/15 (60%)
Overall Response (ORR)	3/9 (33.3%)
Complete response (CR)	1/9 (11%)
Partial response (PR)	2/9 (22.2%)
Stable disease (SD)	1/9 (11%)
Progression of disease (POD)	6/9 (66.6%)

Arm (evaluable/total)	CR	PR	SD	PD
Arm A (3/5)	0	1	0	2
Arm B (3/4)	1	1	0	1
Arm C (3/5)	0	0	1	2

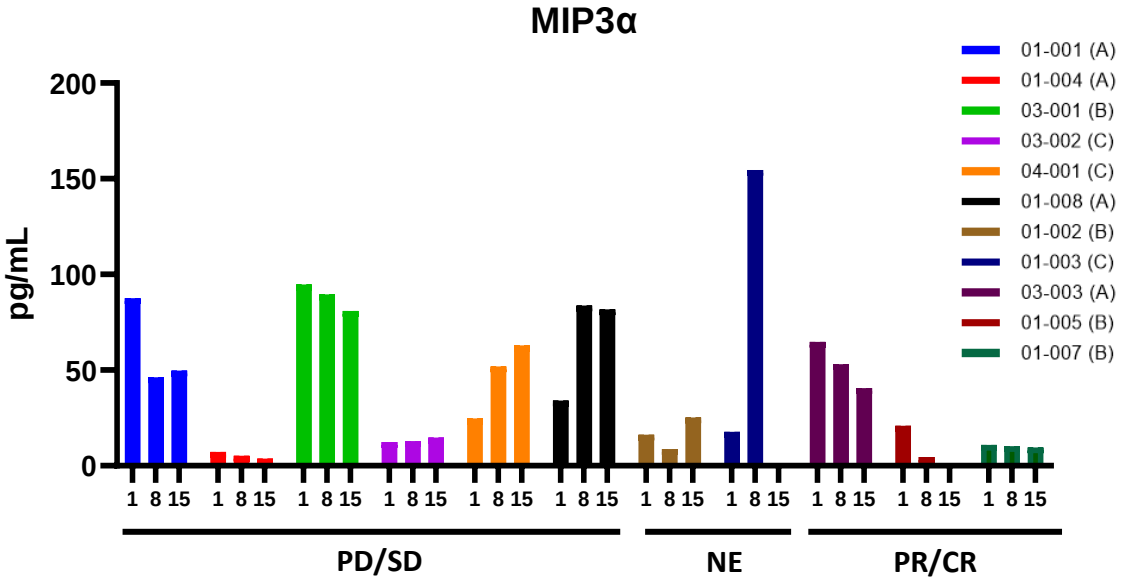
INCREASED CYTOKINES LEVEL IN PTCL PATIENTS

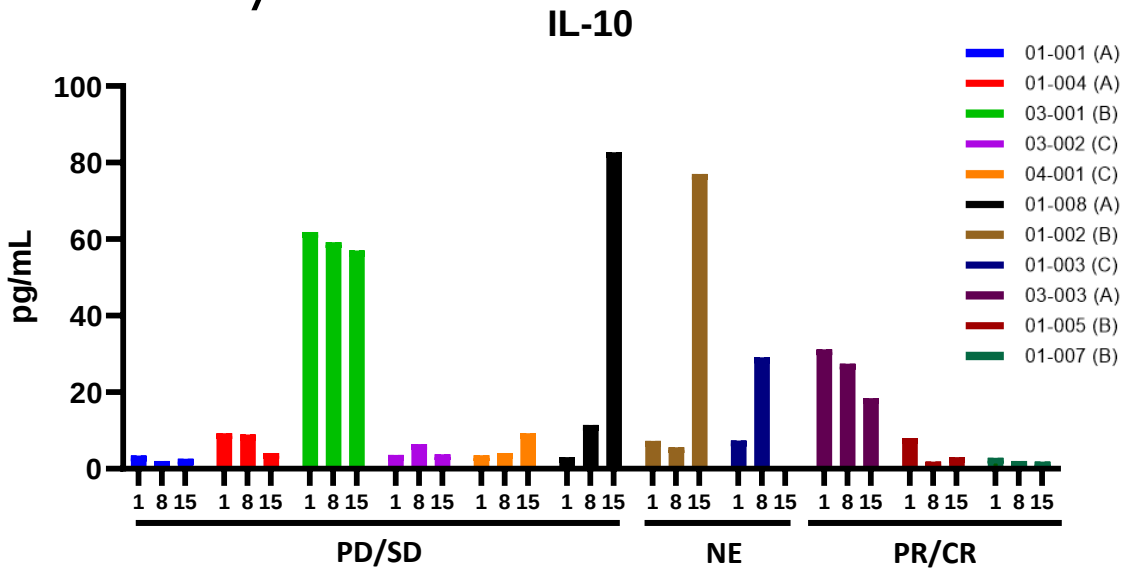
Preliminary Result

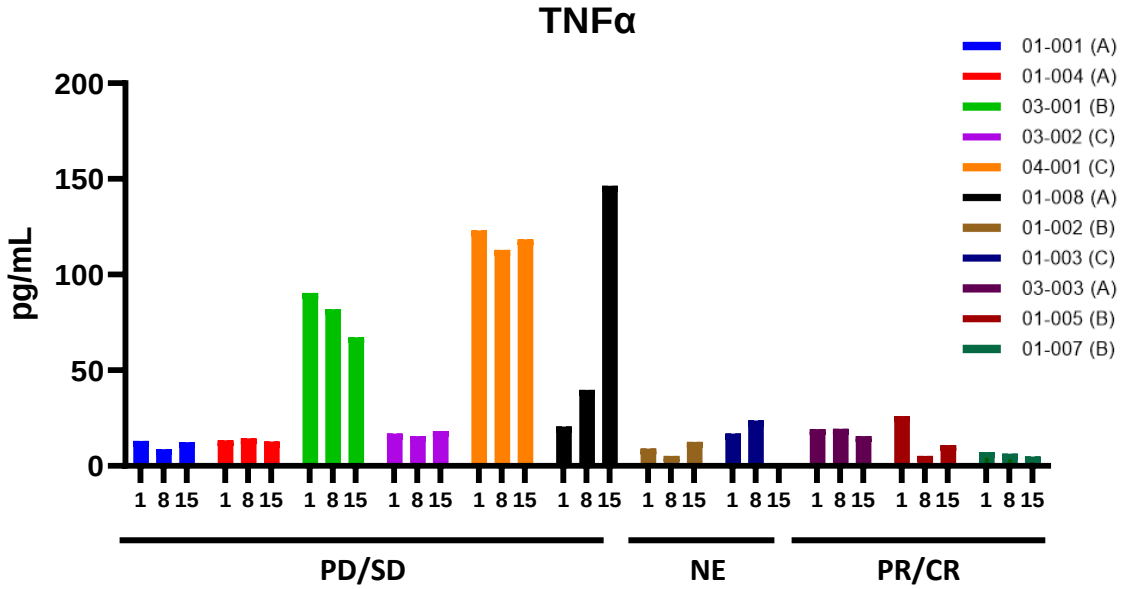


- Baseline (pre-infusion C1D1) levels of select cytokines assessed via Luminex assay in patients enrolled in PTCL-002 ("Trial Patients", n=12) compared with "healthy" age and sex-matched controls (n=14). *Statistical significance assessed via Mann-Whitney U test.

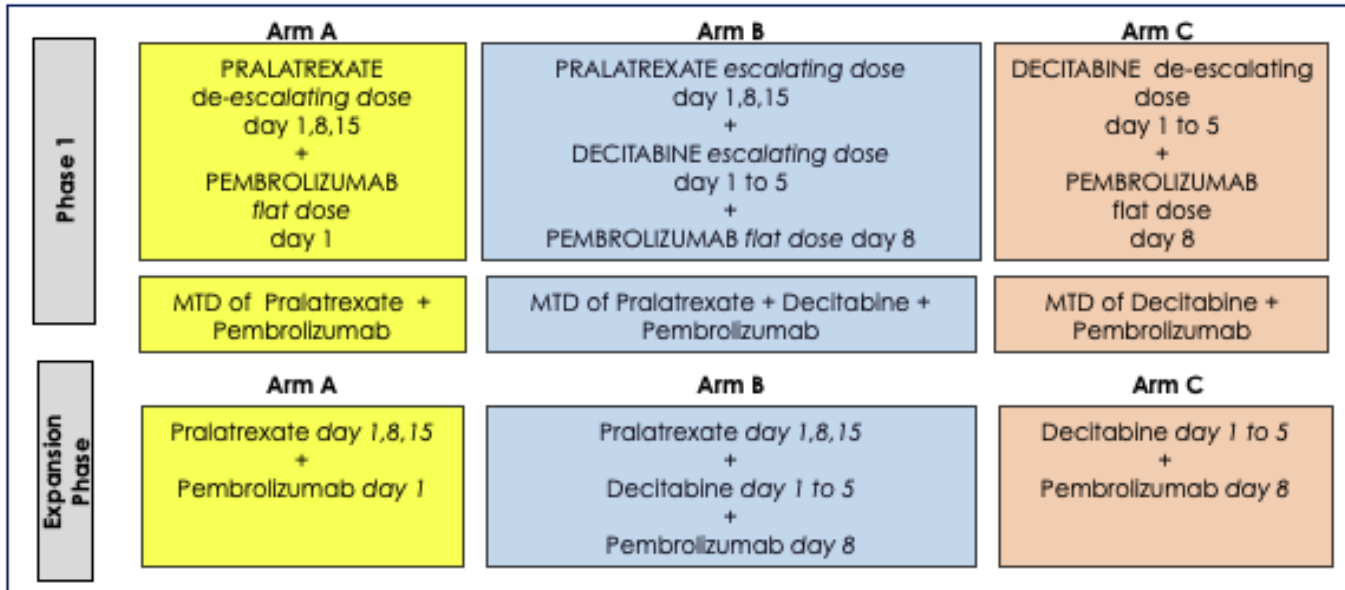
DECREASE IN CYTOKINE LEVELS APPEARS TO CORRELATE WITH DISEASE RESPONSE: Preliminary Result







NOVEL IMMUNO-EPIGENETIC PLATFORMS



Multicenter, multiarms, International, Phase 1B study of **pembrolizumab** combined with **pralatrexate** (Arm A), with pralatrexate and decitabine (Arm B), or **decitabine** alone (Arm C) in patient with **PTCL** and **CTCL**. ClinicalTrials.gov Identifier: NCT03240211

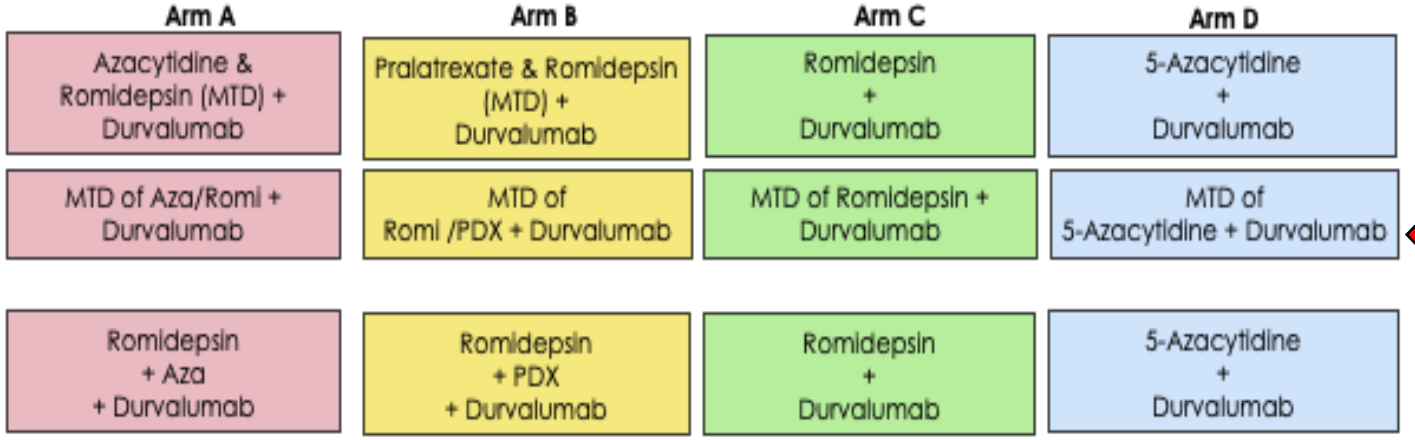
N patients enrolled: 13

Research Funding from Merck.

Phase 1/2A study of durvalumab combined with oral 5-azacytidine + romidepsin (Arm A), pralatrexate + romidepsin (Arm B), romidepsin alone (Arm C), or oral 5-azacytidine alone (Arm D) for the treatment of patients with PTCL. ClinicalTrials.gov Identifier: NCT03161223

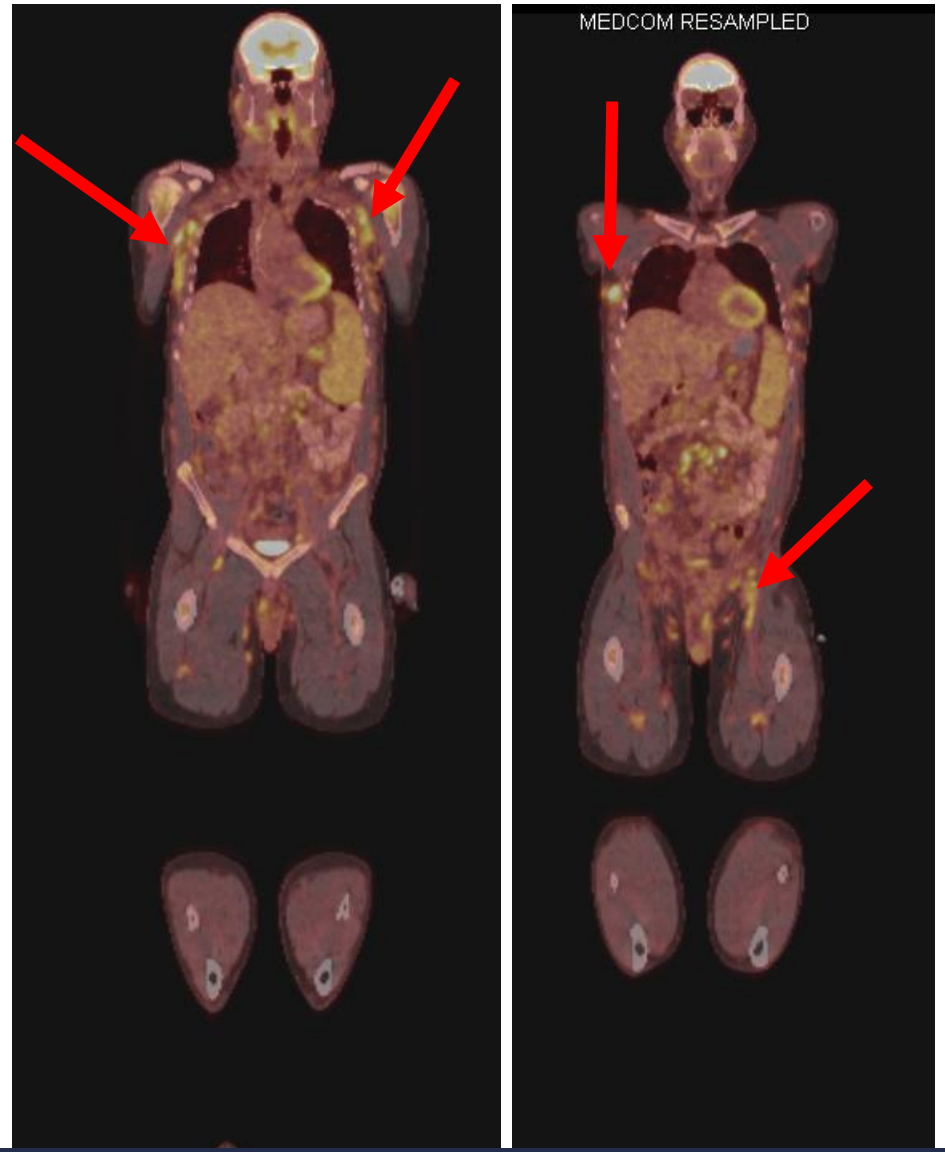
N patients enrolled: 5

Research funding from Celgene



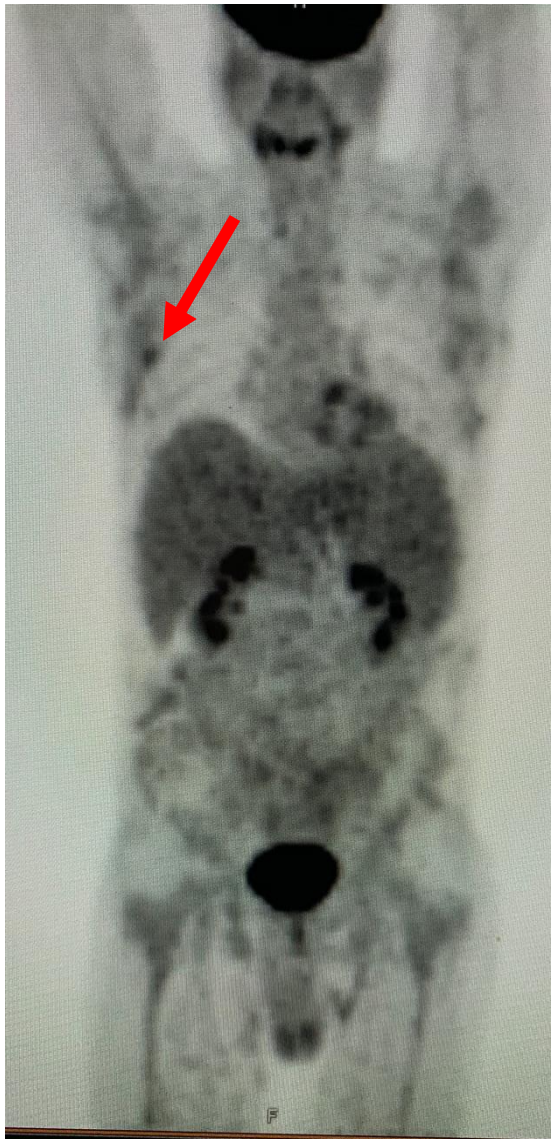
Marchi E et al., AACR 2020
Marchi E et al., ASCO 2020
Roberts N et al., TCLF 2022
Roberts N et al., ASH 2022

AZA-ROMI & PD-L1 IN PRIMARY REFRACTORY PTCL NOS PATIENT



Oral Azacitidine x 8 days →
day 8 Romidepsin & Durvalumab →

→ CRS → near CR that lasted for > 4 months w/o additional treatment

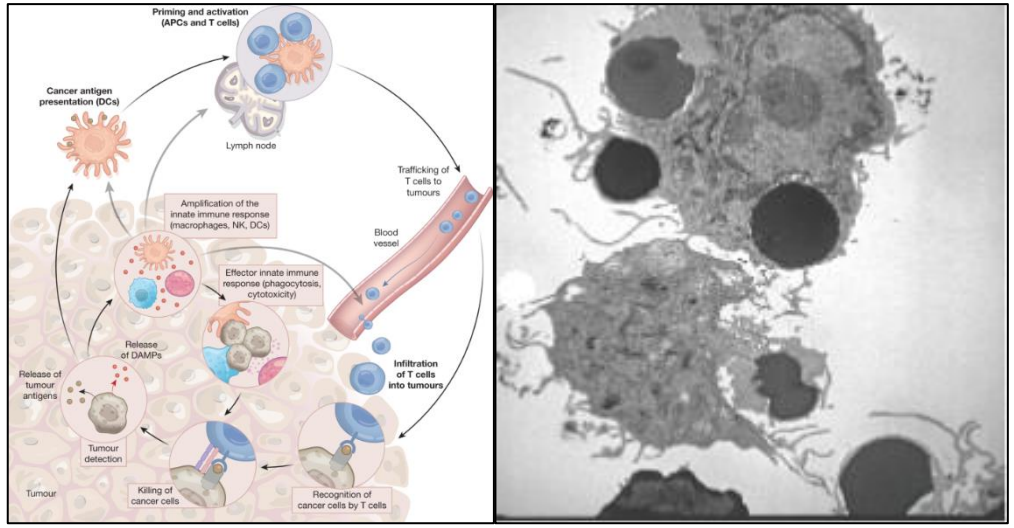


CONCLUSION

- Nothing is easy in T-cell lymphoma: ICIs are not for all but…. maybe for some and likely in combination with other active drug combinations

- Therapeutic strategies that work sensitizing the immune-system could leverage the innate and adaptive immune response provide a backbone to add on biologics

- Multiple questions remain unanswered:
  - Which biologics?
  - Which combination?
  - Which sequence?



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Administrative & Clinical Research Staff
Kim Bullock, PhD
Cara Harby
Marian Abdelmalek
Justin Alicea
Lori J. Elder, RN BSN, CCRA
Tammy Battaglia
Aishling Rada, RN

Laboratory Staff and Collaborators
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All Our PATIENTS and THEIR FAMILIES

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Mount Sinai

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

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