NEW AGENTS AND NEW PATHWAYS: THE CHEMO-FREE ERA?

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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						
Dren Bio	X						
Everest Clinical Research							Data Safety Monitoring Commettee

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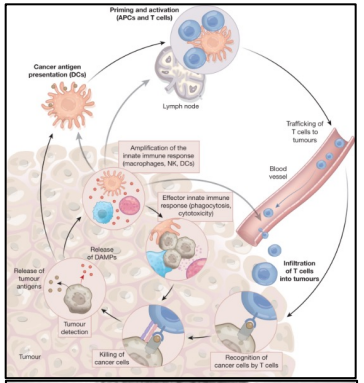
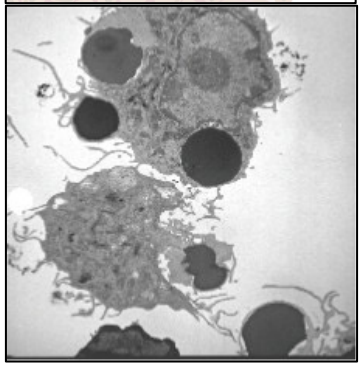
- **The Challenges of Improving Outcome in PTCL**
- Novel Drug Combinations as the backbone to improve outcome
- The Addition of Biologics/Immune Therapeutics: Leveraging the Immune System
- Beyond Immune-Checkpoint Inhibitor: Targeting Necroptosis
- Protein Degrader: Targeting the Jak/STAT Pathway
- Novel Monoclonal antibodies: Targeting Rare Subtypes
- Conclusion

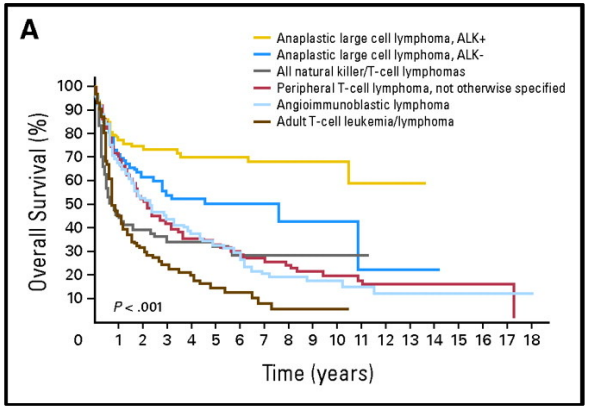


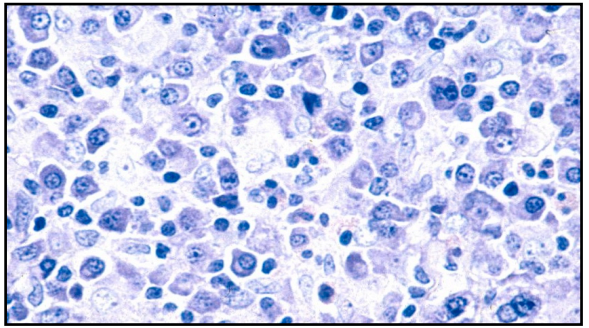


PTCL: Background

- 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 > than 30 different subtypes (WHO 2022; ICC 2022)
- PTCL represent 15% - 20% of **all aggressive** lymphomas
- Except ALK+ ALCL, PTCL subtypes have **poor OS with standard therapies →5 years OS 15-20%**
- **25% patients are primary REFRACTORY to first line**

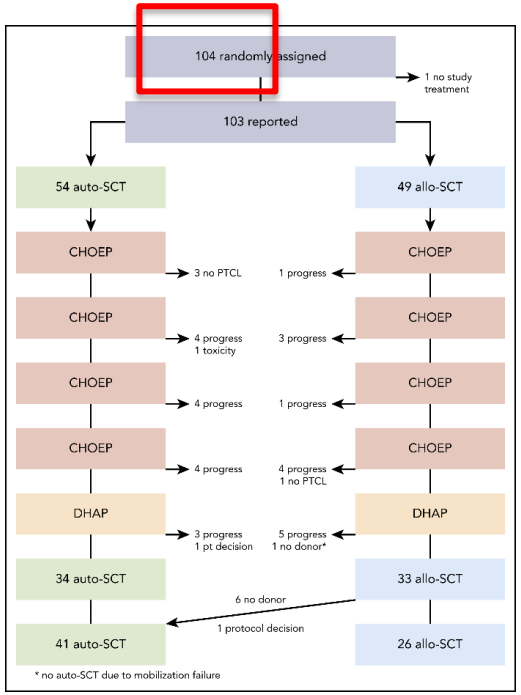
Molecular characterization → to identification of subtypes with different prognoses → development of novel pathway-directed and subtype-specific therapies

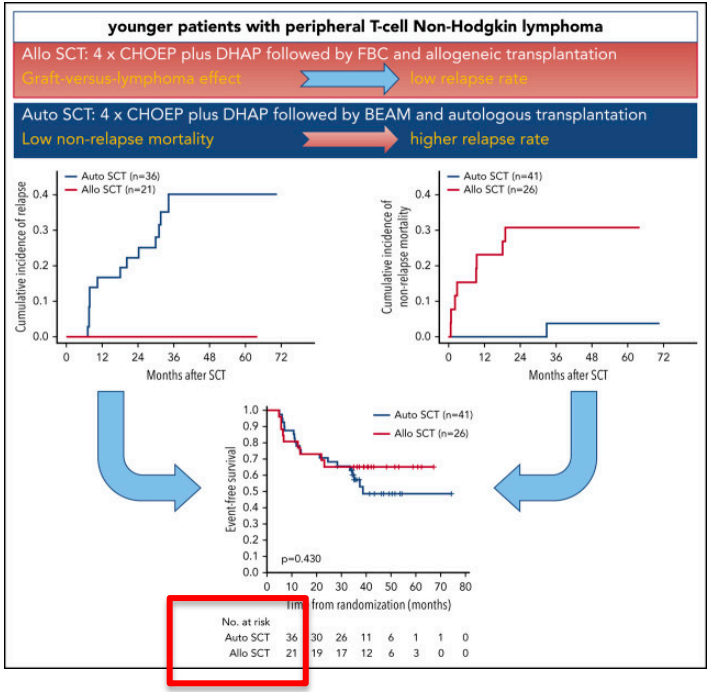




Vose et al; JCO 2008;26:4124.

FIRST LINE TREATMENT: ONLY 54% OF A HIGHLY SELECTED PATIENT POPULATION MADE IT TO THE PRIMARY INTERVENTION

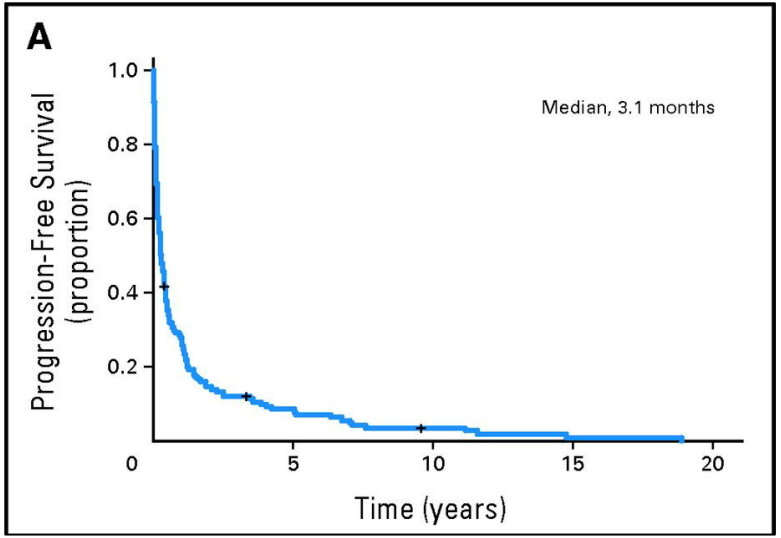




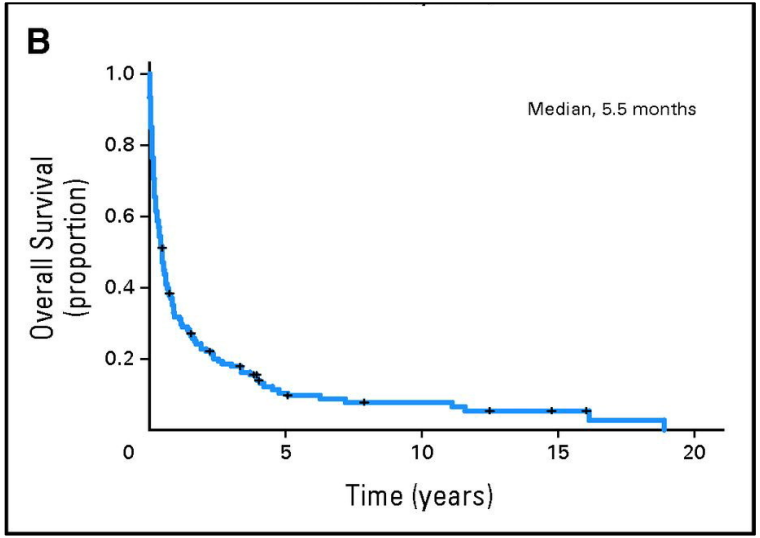
At 3 years	EFS	OS
Allogeneic SCT	43% (no relapses)	57%
Autologous SCT	38% (13/34 relapse)	70%

Schmitz N et al; Blood 2022

RELAPSE/REFRACTORY:
PROOF OF INTRINSEC INADEQUACY OF CONVENTIONAL CHEMOTHERAPY



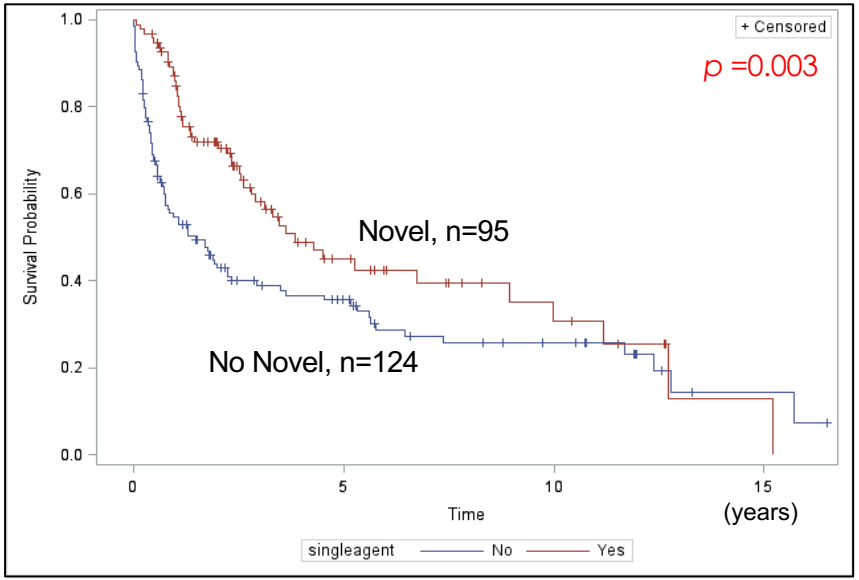
PFS at First Relapse:
3.1 Months

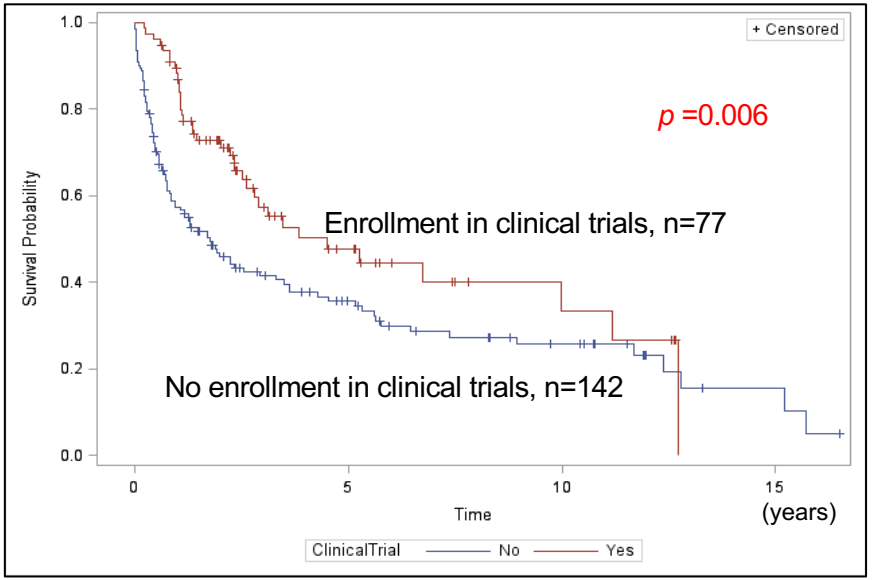


OS at First Relapse:
5.5 Months

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

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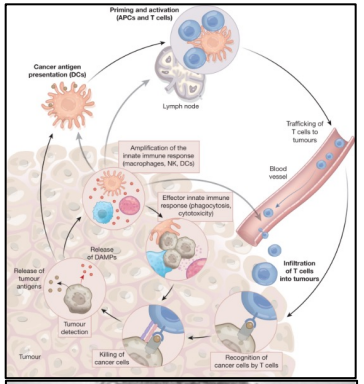
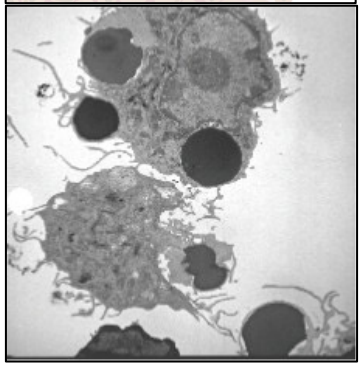
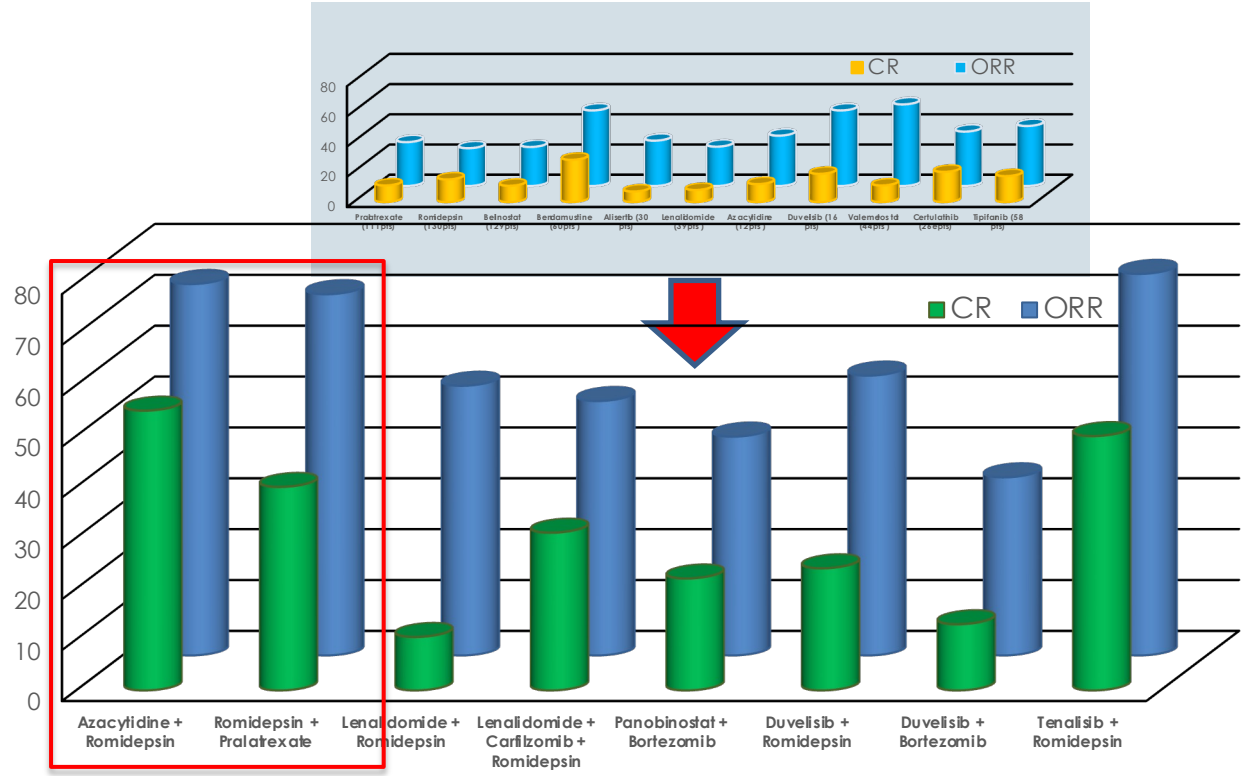




NEW PATHS TO IMPROVE OUTCOME:

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

ORAL 5-AZACITIDINE & ROMIDEPSIN

SUMMARY CLINICAL EXPERIENCE

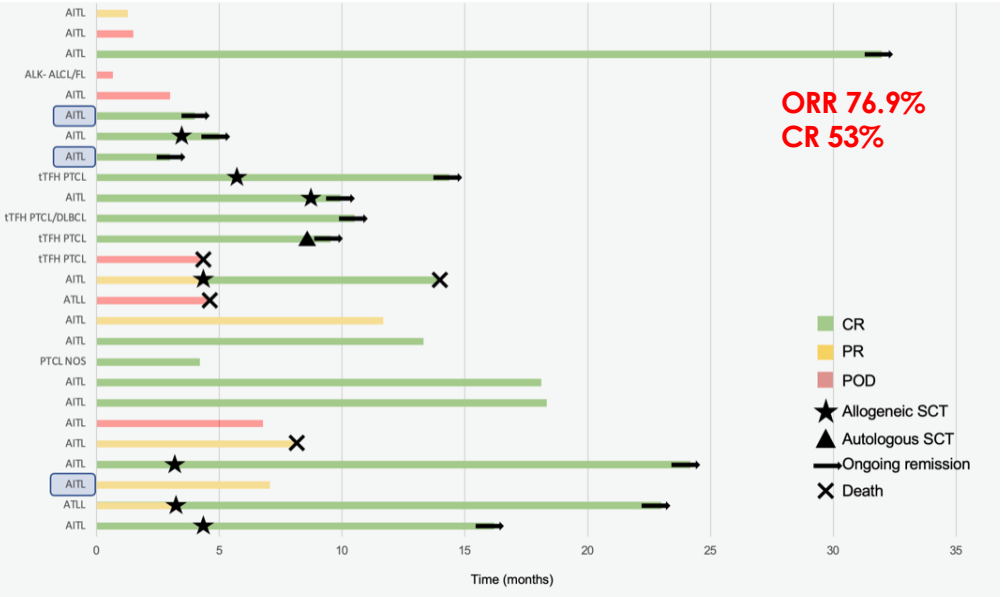
Phase 1: O'Connor et al; Blood 2019

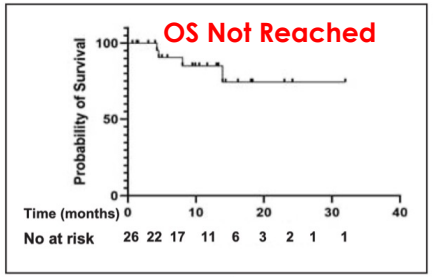
	All (N = 31)	Phase 1 (N = 26)	Expansion (T-cell) (N = 5)	Non-T-Cell (N = 20)	T-Cell (N = 11)
ORR	10 (32%)	6 (23%)	4 (73%)	2 (10%)	**8 (73%)**
CR	7 (23%)	3 (12%)	4 (80%)	1 (5%)	**5 (55%)**
PR	3 (10%)	3 (12%)	0	1 (5%)	**2 (18%)**
SD	7 (23%)	7 (27%)	0	7 (35%)	**0**
POD	11 (35%)	10 (38%)	1 (20%)	9 (45%)	**2 (18%)**
Not Evaluable	3 (10%)	3(12%)	0	2 (10%)	**1 (9%)**

Phase 2: Falchi L. & Ma H. et al; Blood 2020

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

REAL WORLD EXPERIENCE OF AZA-ROMI:
IMPROVED OUTCOME AND DOR





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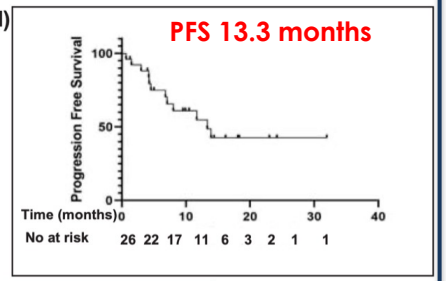

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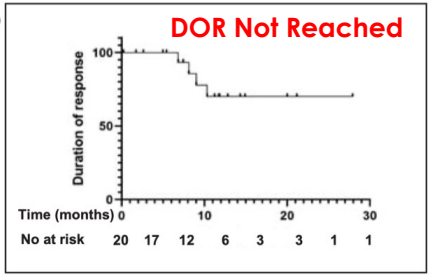

Kalac et al; Blood Adv 2023

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

Tissue (pre- and post-treatment)

IHC (VECTRA)
GEP
Methylation

Arm B
(Investigator Choice):
Romidepsin
Belinostat
Pralatrexate
Gemcitabine

Mutational analysis
T-cell subpopulation
Cytokines analysis

WGS/WES/RNA Seq
CyTOF
IsoPlexis

Food and Drug Administration
Federal agency

Funded by FDA RO1 Orphan Products Development (OPD) Grant

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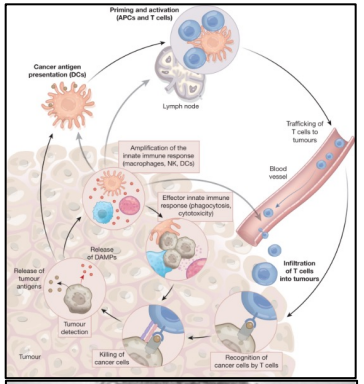
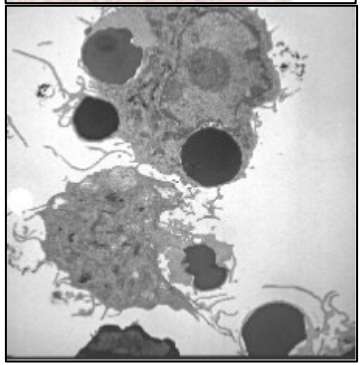
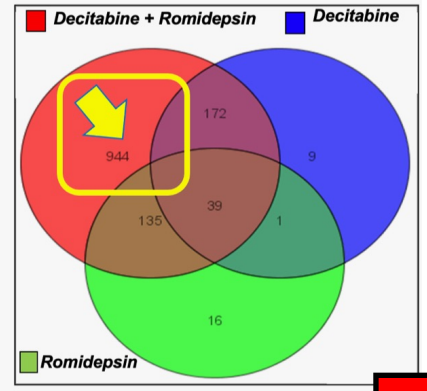
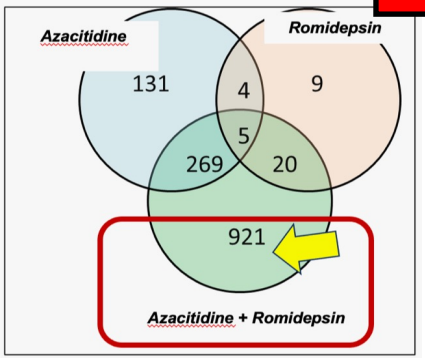
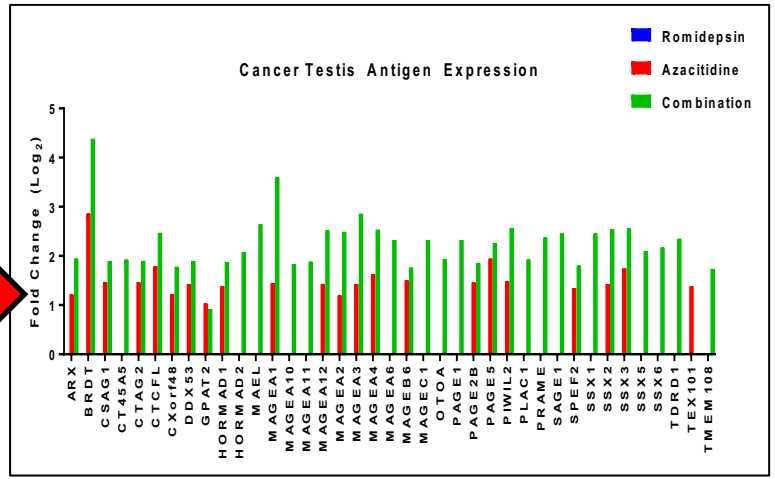


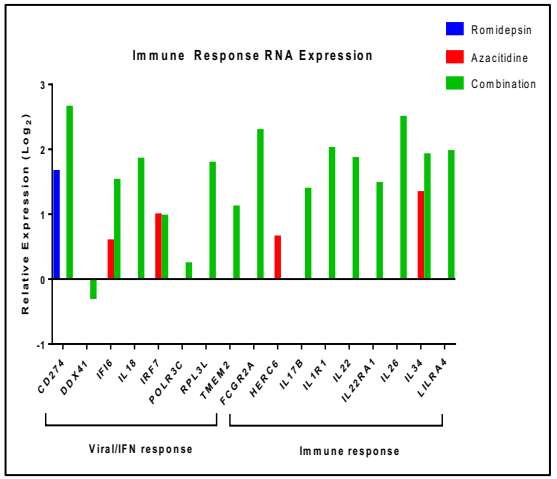


HDACI AND HMA UNIQUELY AFFECTS GEP & INDUCE CANCER TESTIS ANTIGEN AND ENDOGENOUS RETROVIRUS



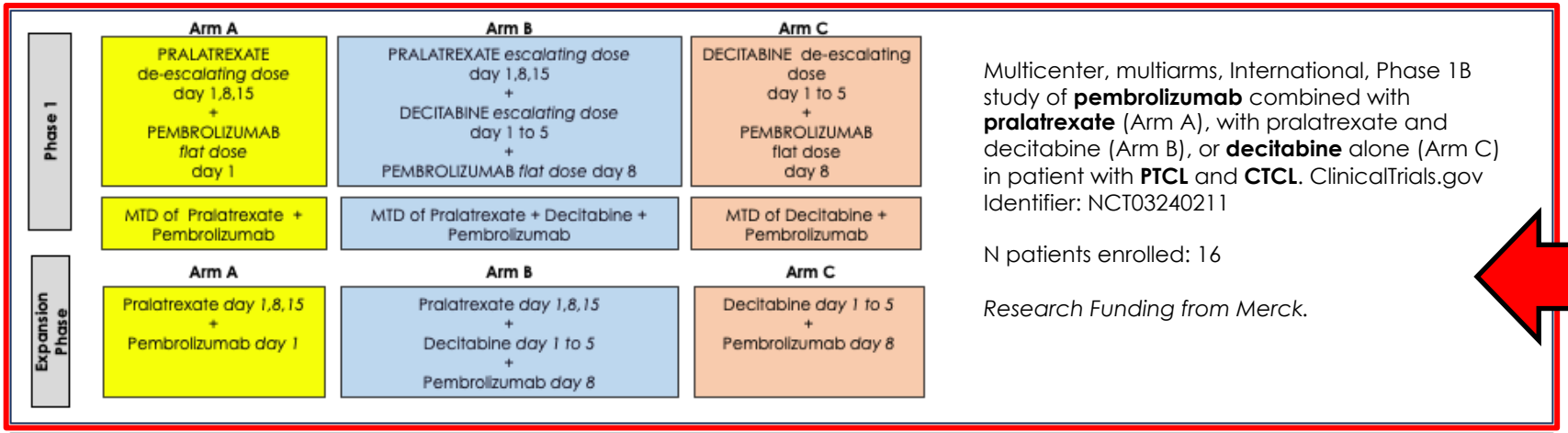






Marchi E. et al; Br J Haematol 2015
Scotto L et al; Mol Cancer Therapeutics 2021

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: 16

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

Arm A	Arm B	Arm C	Arm D
Azacytidine & Romidepsin (MTD) + Durvalumab	Pralatrexate & Romidepsin (MTD) + Durvalumab	Romidepsin + Durvalumab	5-Azacytidine + Durvalumab
MTD of Aza/Romi + Durvalumab	MTD of Romi /PDX + Durvalumab	MTD of Romidepsin + Durvalumab	MTD of 5-Azacytidine + Durvalumab
Romidepsin + Aza + Durvalumab	Romidepsin + PDX + Durvalumab	Romidepsin + Durvalumab	5-Azacytidine + Durvalumab

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

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.

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

Roberts N et al., ASH 2022

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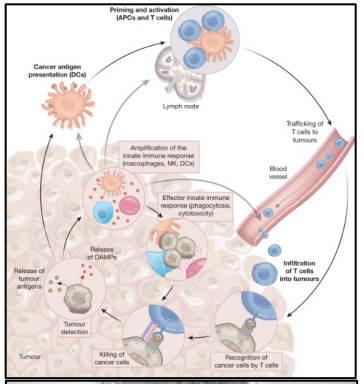
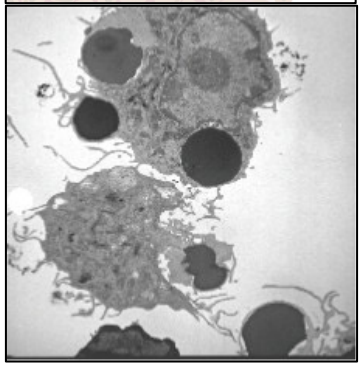
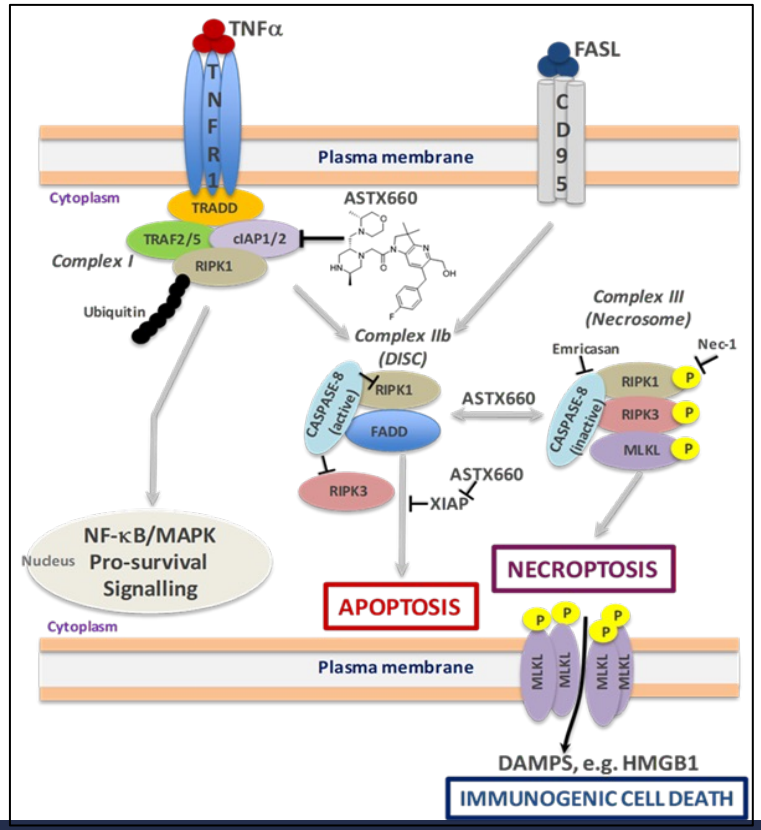




INHIBITORS OF INHIBITORS OF APOPTOSIS PROTEIN (IAP) WITH TOLINOPANT (ASTEX660): TARGETING NECROPTOSIS

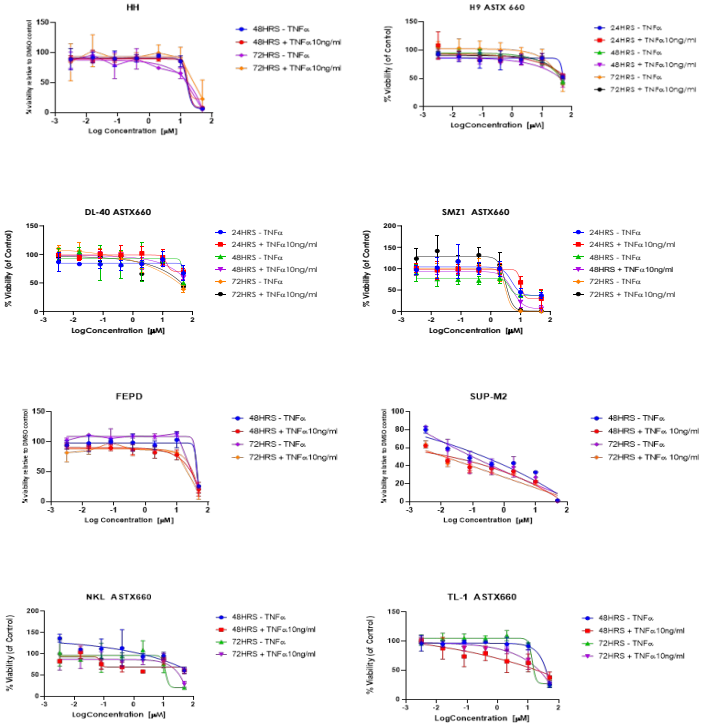


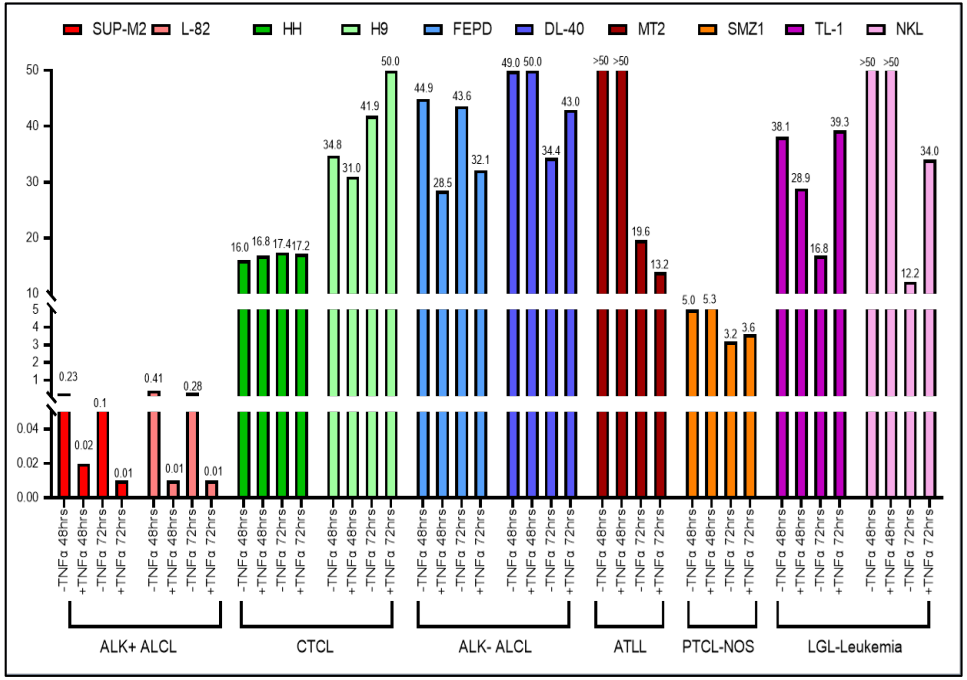
- The inhibitors of apoptosis (IAP) proteins are a family of proteins involved in cell death, immunity, inflammation, cell cycle and migration

- They exert exerts influence on many nodes in a complex biology
  - → Can regulate apoptosis
  - → Can inactivate NF-kB signaling
  - →Can induce necroptosis, or immunogenic cell death

- ASTX660→ Tolinopant is a potent, non-peptidomimetic, small-molecule antagonist of IAPs, discovered by fragment-based drug discovery → showed some preliminary activity in PTCL.

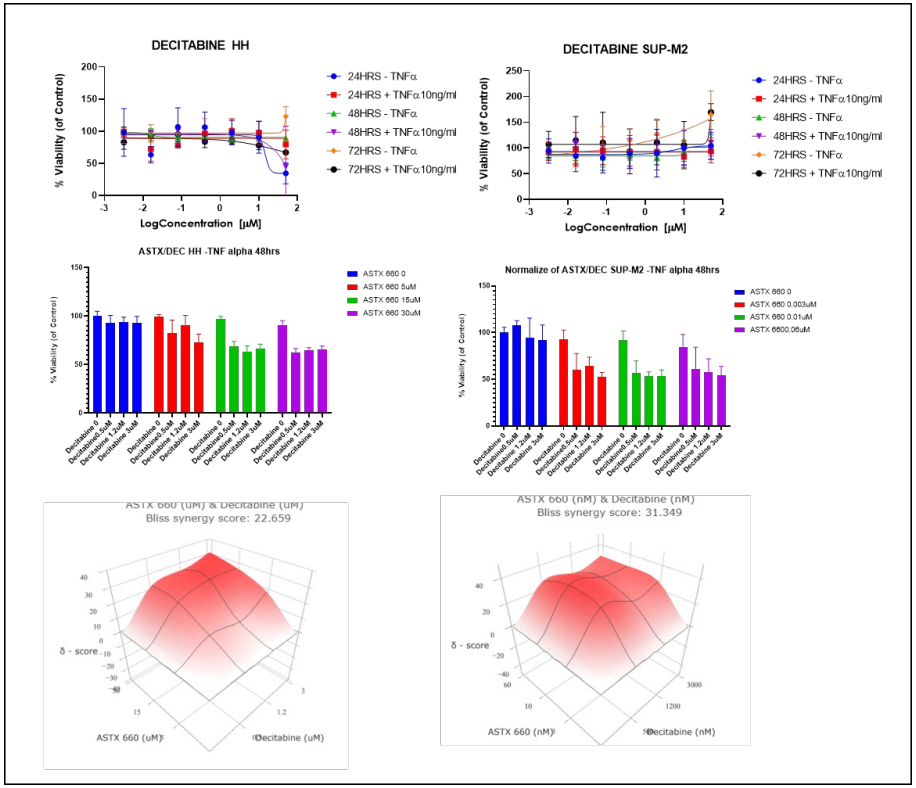
TOLINOPANT EXHIBITS ACTIVITY ACROSS A LARGE PANEL OF TCL, THOUGH SENSITIVITY IS NOT UNIFORMALY CONSISTENT



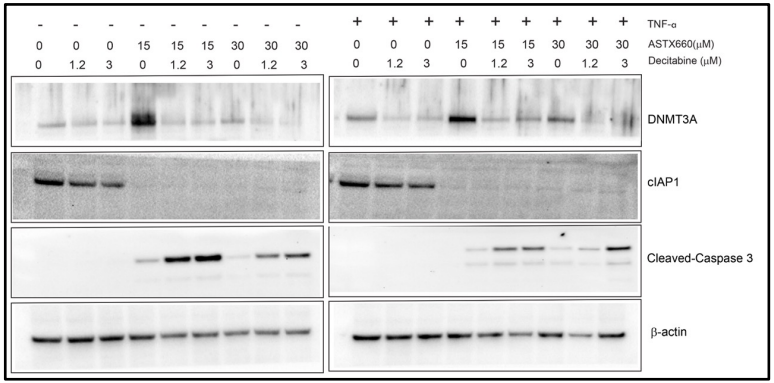


Manavalan JS E et al., EHA 2021

PROFOUND SYNERGY BETWEEN TOLINOPANT & DECITABINE:
PHASE 1-2 TRIAL IS UNDERWAY



		HH	SUP-M2
24HRS	-TNFα	20.86	17.89
	+TNFα	27.08	19.48
48HRS	-TNFα	22.65	31.34
	+TNFα	17.50	22.4
72HRS	-TNFα	12.07	5.51
	+TNFα	1.23	1.4



Manavalan JS E et al., EHA 2021

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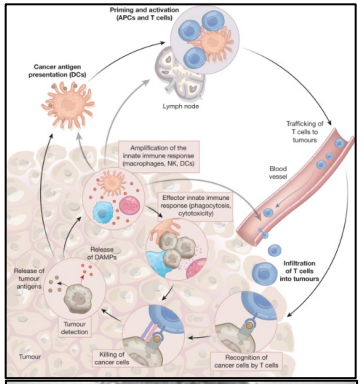
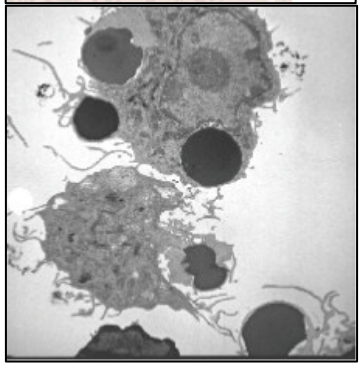
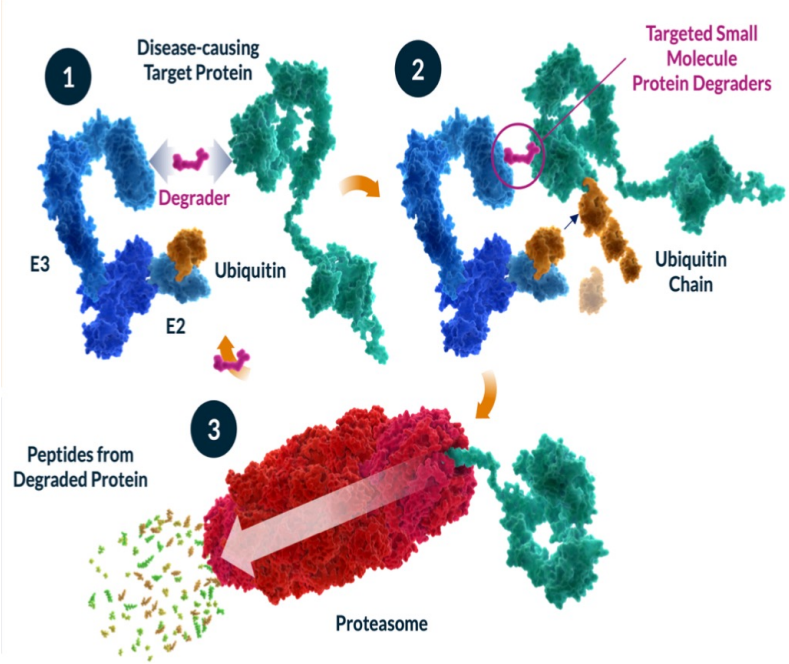




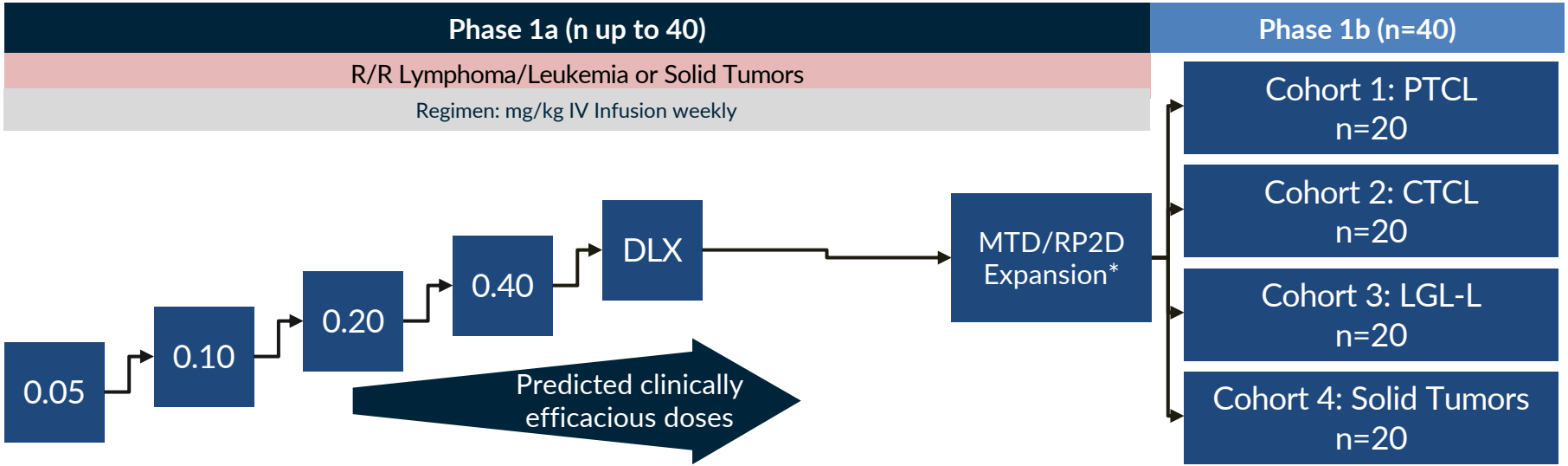
TARGETING THE JAK-STAT PATHWAY IN PTCL : PROTEIN DEGRADER



STAT3 enhances pro-survival signaling essential for T cell expansion → aberrant STAT3 signaling contributes to T cell lymphomagenesis.

- Upregulation of the STAT3 cytokine signaling pathway → key driver of CTCL pathogenesis
- Somatic activating mutation of JAK1/STAT3 → constitutive activation of the STA3 pathway in about 50% ALK- ALCL
- STAT3 mutations → 30-40% of T-LGL leukemia, leading to STAT3 pathway activation.
- New First in class STAT-3 degrader with pre-clinical activity in many T-cell lymphoma models → KT-333

PHASE 1, MULTICENTER, DOSE-ESCALATION AND EXPANSION TRIAL TO EVALUATE KT-333 IN PATIENTS WITH PTCL, CTCL, LGL-L, AND SOLID TUMORS



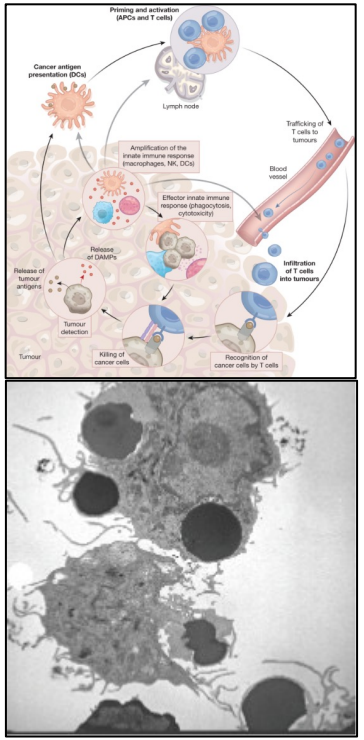
Key Objectives	Phase 1a	Phase 1b
Primary	• Safety/Tolerability and MTD and RP2D	• Safety/Tolerability at RP2D in Patients with Lymphoma/Leukemia and Solid Tumors
Secondary	• PK Parameters of KT-333 • Preliminary Estimates of Activity	• Preliminary Clinical Activity (ORR, DoR, PFS, DCR, OS) • PK Parameters of KT-333
Exploratory	• PD Effects of KT-333	• PD Effects of KT-333

MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose. ORR: Overall Response Rate

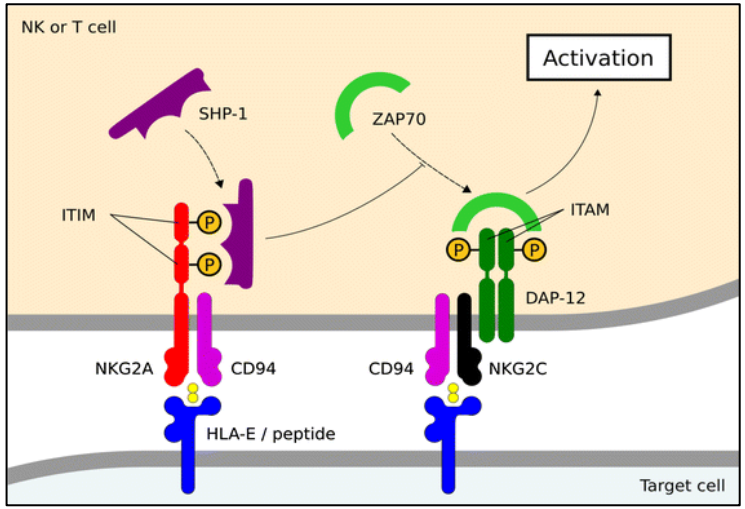
Courtesy of Kymera Therapeutics

NEW AGENTS AND NEW PATHWAYS: THE CHEMO-FREE ERA?

- The Challenges of Improving Outcome in PTCL
- Novel Drug Combinations as the backbone to improve outcome
- The Addition of Biologics/Immune Therapeutics to doublet
- Beyond Immune-Checkpoint Inhibitor: Targeting Necroptosis
- Targeting the Jak-STAT Pathway: Protein Degrader
- Targeting rare subtypes: Novel Monoclonal antibodies
- Conclusion

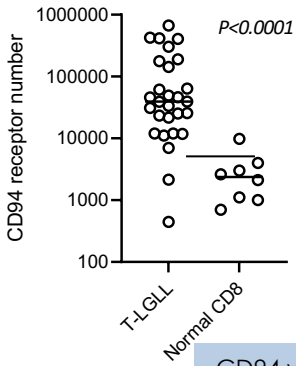


CD94 IS A SCAFFOLD PROTEIN FOR NKG2 RECEPTORS

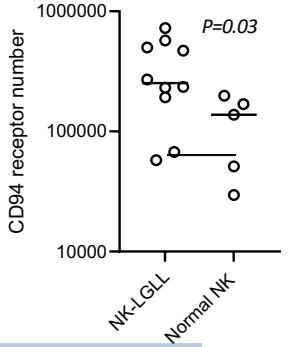


Adapted from Iwaszko 2011

CD94 expression is higher on T-LGLL than on normal CD8 T cells



CD94 expression is higher on NK-LGLL than on normal NK cells



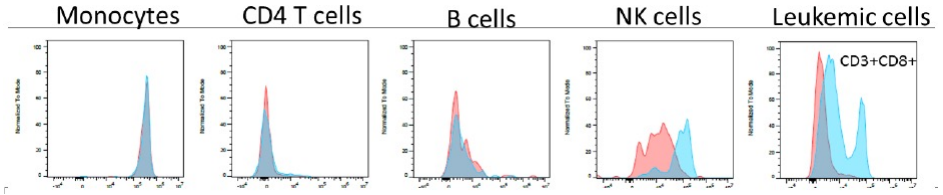
CD94 was identified on all 38 LGLL patient samples screened

CD94 receptor serves as a scaffold to stabilize NKG2, a hallmark of activated cytotoxic cells, and is upregulated on leukemic cells and express in a number of CD8 + lymphoid malignancies.

Courtesy of Dren Bio

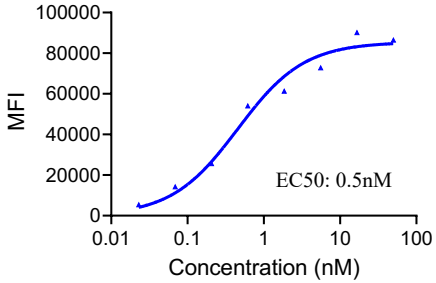
DR-01 IS A NON-FUCOSYLATED ANTIBODY WITH HIGH AFFINITY BINDING TO NORMAL HUMAN AND CYNOMOLGUS NK CELLS AND LGLL CELLS

DR-01 binding to LGLL PBMCs:

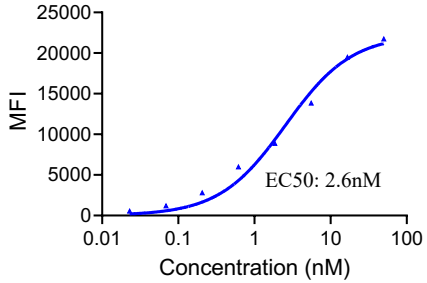


Red= Isotype control
Blue= DR-01

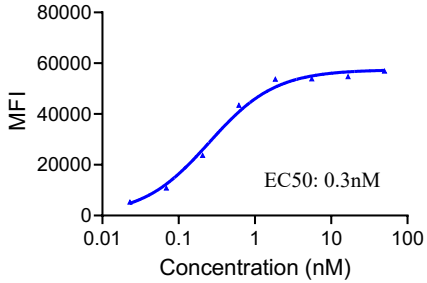
Binding to normal human NK cells



Binding to normal cynomolgus NK cells



Binding to LGLL cells

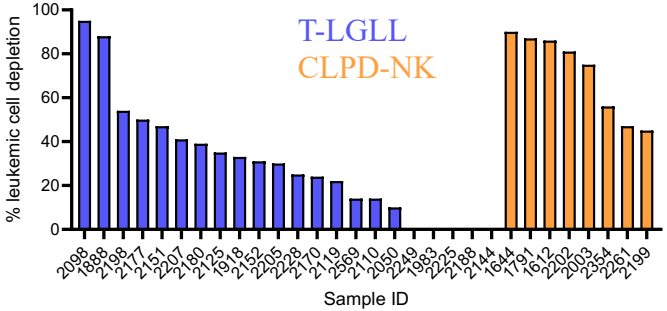


- DR-01 selectively binds to human and cynomolgus NK cells and LGLL cells with high affinity (EC50: 0.3-2.6nM)

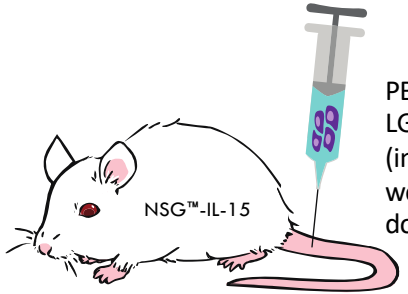
Courtesy of Dren Bio

DR-01 DEPLETES LGLL CELLS IN PATIENT PBMC & HUMANIZED MOUSE MODEL OF LGLL

Maximum LGLL cell depletion ex vivo



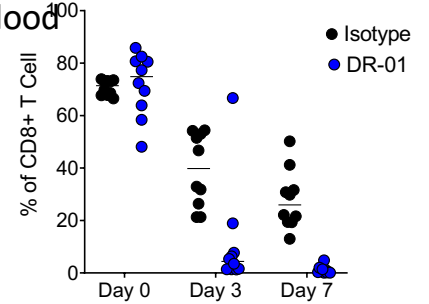
LGLL in vivo model



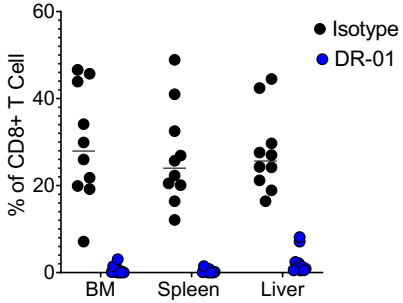
PBMCs from LGLL patients (injected 3 weeks prior to dosing)

Image adapted from Walsh 2017

*Depletion CD8+CD94+ cells in blood



Depletion CD8+CD94+ cells in tissue

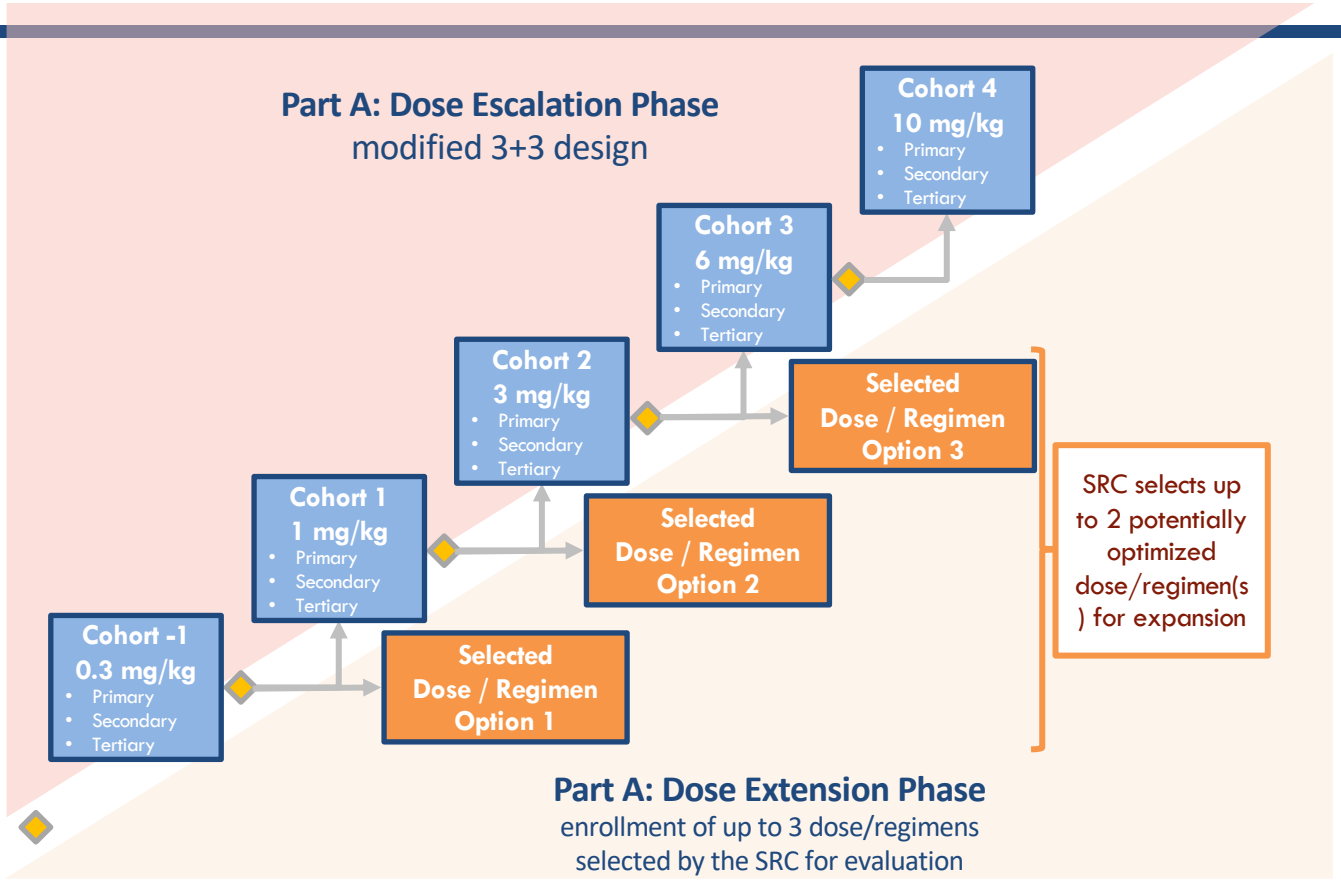


*A decline in CD8 engraftment was observed

- DR-01 depleted LGLL cells ex vivo in 25/30 samples tested
- There was no apparent correlation between CD94 expression and degree of leukemic cell depletion

- LGLL disease model was established using humanized NSG-hIL-15 mice engrafted with LGLL patient splenocytes
- >90% depletion of CD94+ leukemic cells in blood and tissues was observed with a single 5 mg/kg dose of DR-01

OVERALL STUDY DESIGN FOR DR-01-ONC-001



2 study populations

Leukemic:

T-LGLL and NK-CLPD

CD8+/NK- Lymphoma

ENKTL
ANKL
Subcutaneous Paniculitis type TCL
ɤ/∂ -T-cell lymphoma
Primary cutaneous CD8+ TCL
HSTCL
EATL
MEITL
CD8+ EBV+ TCL

Clinicaltrials.gov: NCT05475925

Courtesy of Dren Bio

CONCLUSION

- Treatment of PTCL is struggling to move away from chemotherapy but more chemo is not the answer

- Therapeutic strategies that work sensitizing the immune-system could leverage the innate and adaptive immune response and provide the rationale to build novel platform

- There are multiple pathways that could be targeted in PTCL and a growing number of novel agents and therapeutic approaches

- Multiple questions remain unanswered:
  - Which agents should be prioritized?
  - Which combinations?
  - How do we become more effective in enrolling patients into clinical trials?

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