10th POSTGRADUATE
Lymphoma
Conference

New targeted agents in PTCL: could the light at the end of the tunnel be near?

Dr.Swami iyer
UT MD Anderson Cancer Center

Venice,
March 12-13, 2026

Hotel Monaco & Grand Canal

President:
P.L. Zinzani

DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
CRISPR	☒					☒	
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SEAGEN/PFIZER	☒					☒	
YINGLI	☒					☒	
ACROTECH	☒					☒	
INNATE	☒						
TRILLIUM/Pfizer	☒						
ASTRA ZENECA	☒						
ONO	☒						
LEGEND	☒						
SALARIUS			☒				
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PTCL: From empirical chemotherapy to biological precision

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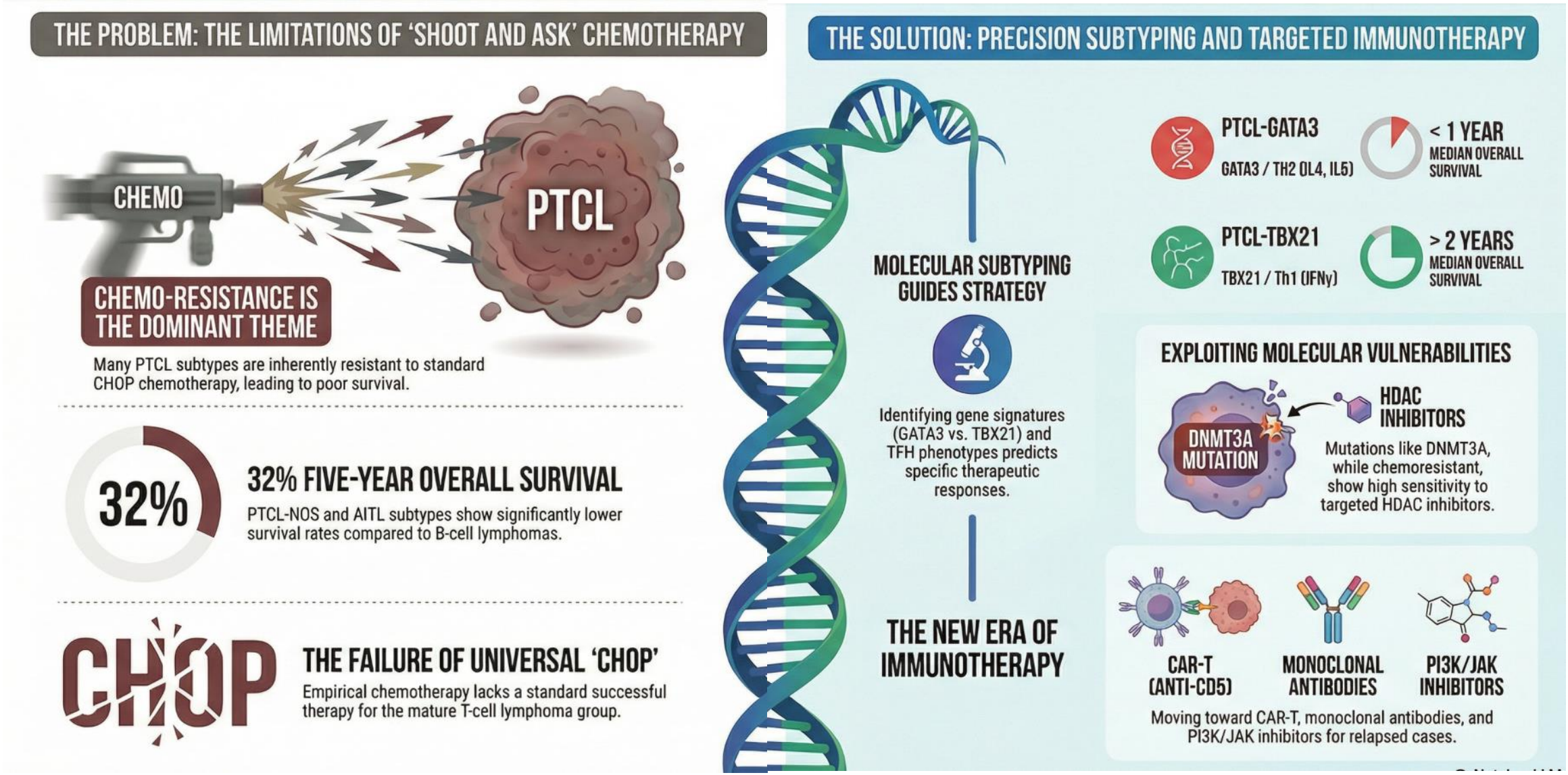

PTCL Treatment Challenge Overview

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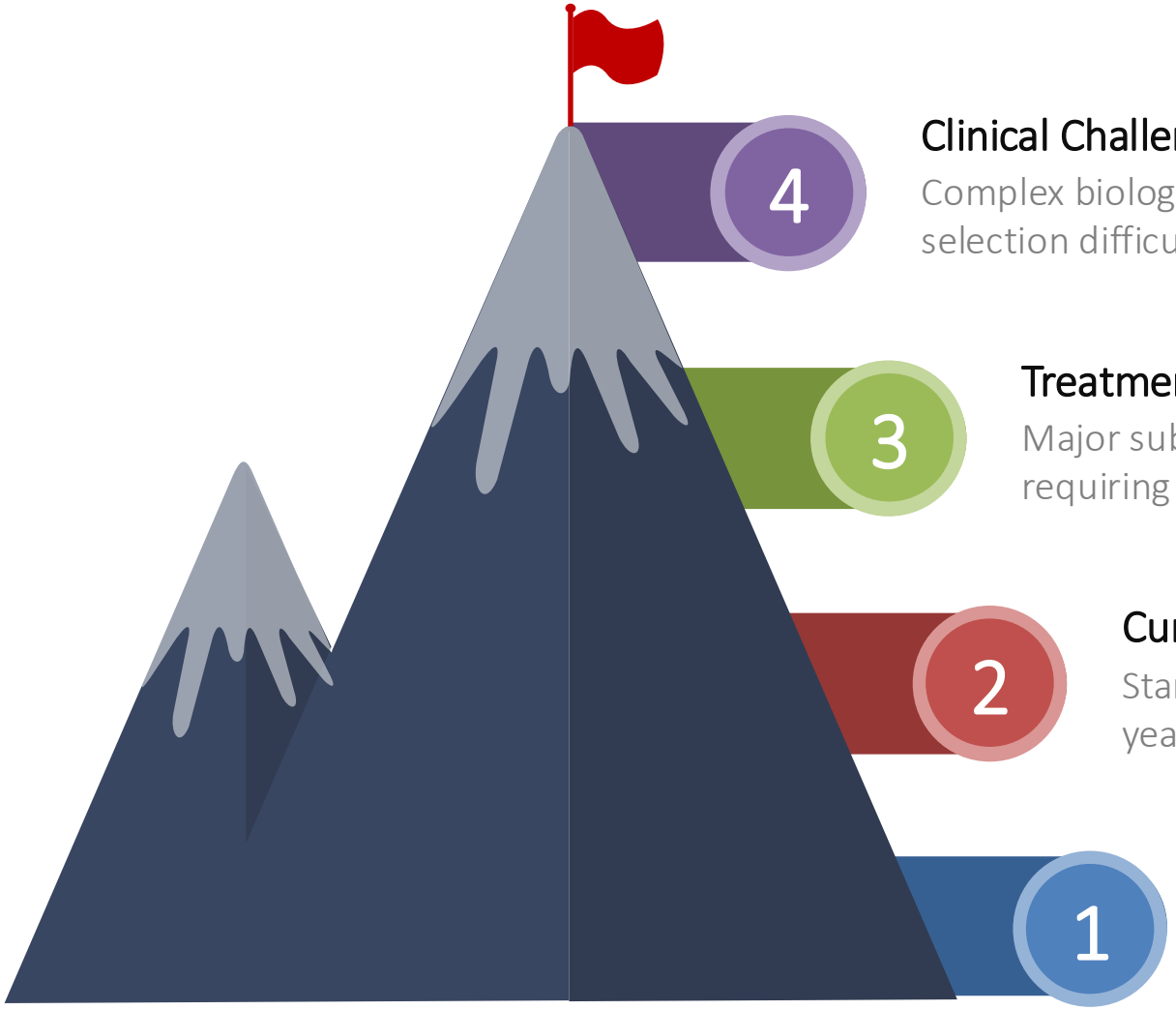

Clinical Challenge

Complex biological heterogeneity creates diagnostic and treatment selection difficulties

Treatment Gap

Major subtypes demonstrate significant chemoresistance requiring innovative therapeutic strategies

Current Limitations

Standard chemotherapy yields poor results with only 32% five-year survival

Disease Definition

Heterogeneous group of aggressive mature post-thymic T/NK-cell neoplasms requiring personalized treatment a

Advances in T cell Lymphoma: From “shoot first” to Precision targeting

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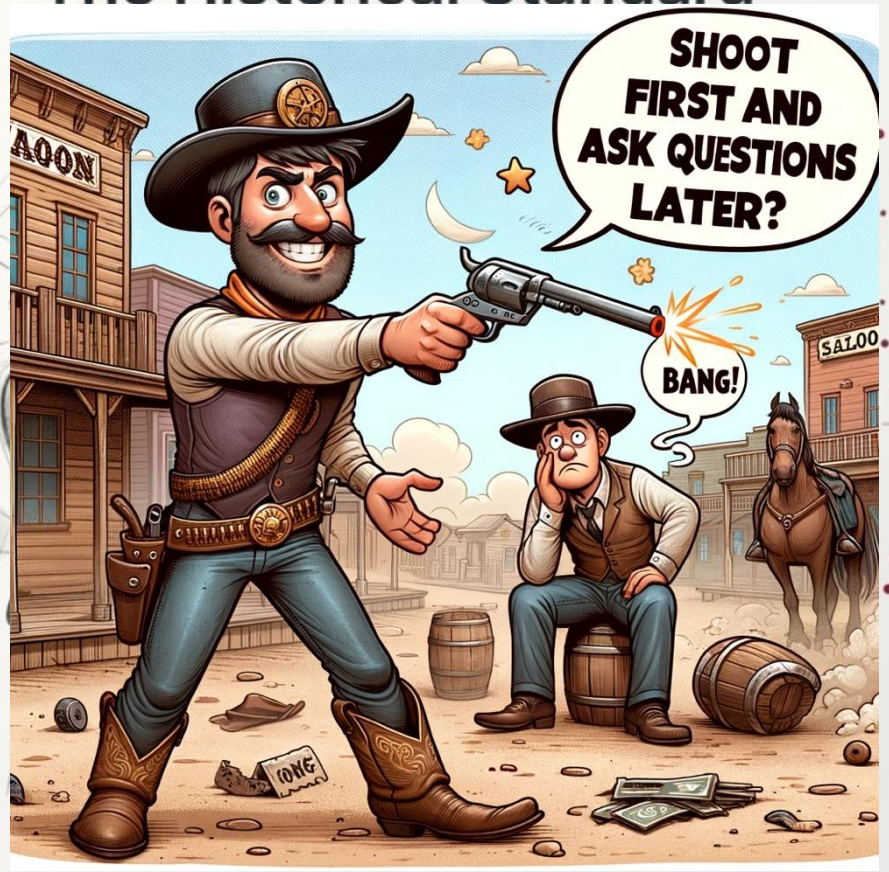
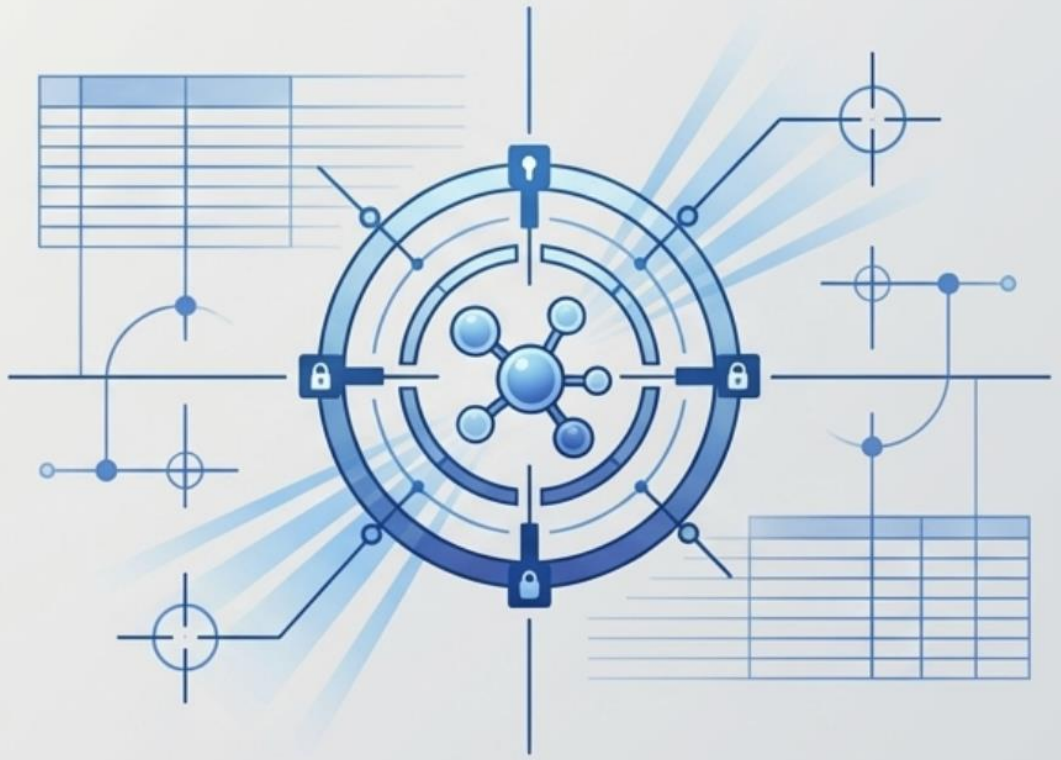
The Historical Standard



The Targeted Era



Patients With Relapsed or Refractory Disease Have an Especially Poor Prognosis

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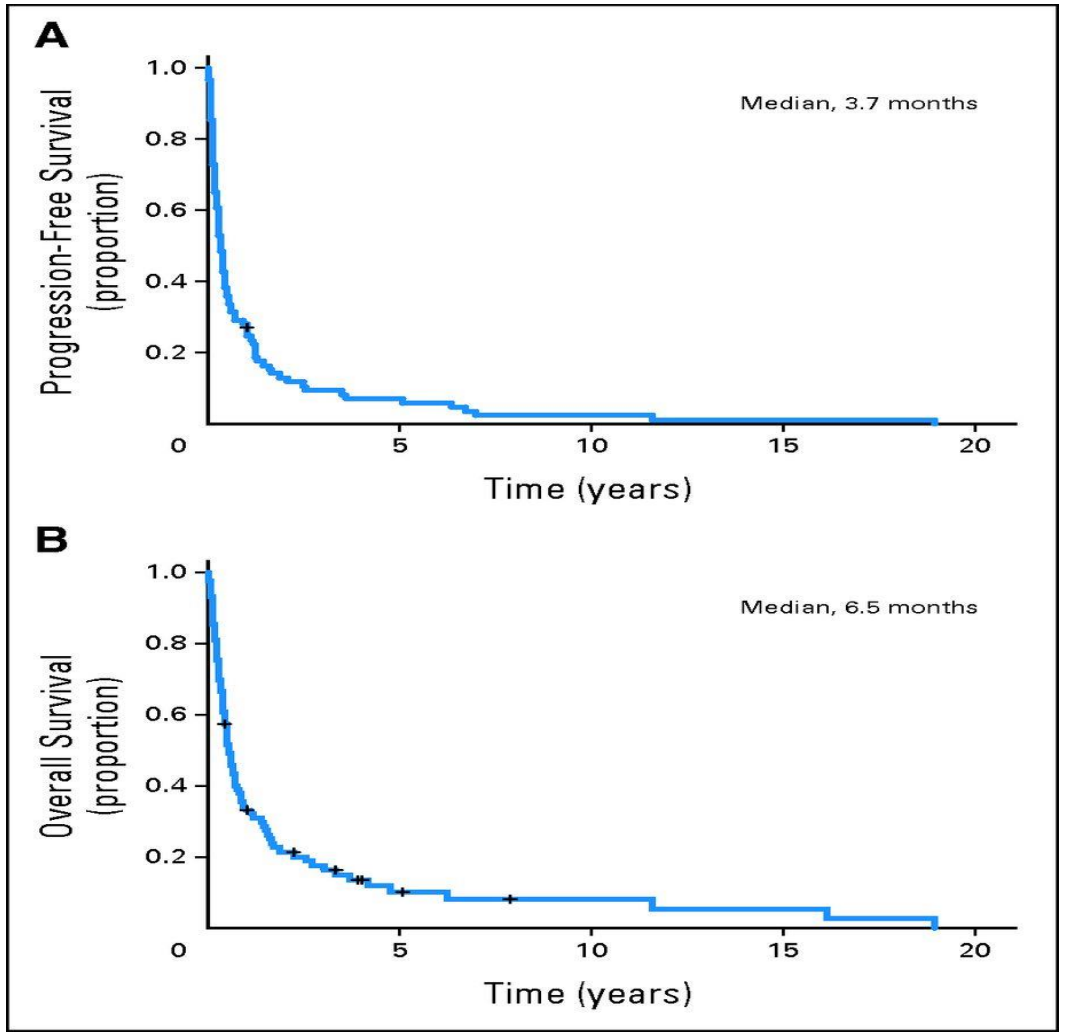

2nd PFS (median, 3.7 months) of patients treated with chemotherapy (n = 89) with R/R PTCL

2nd PFS = 3.7 months

OS (median, 6.5 months) after first relapse or progression of PTCL.

Overall Survival from 2nd Relapse = 6.5 months

Mak et al. 2013

MDACC Outcomes for PTCL

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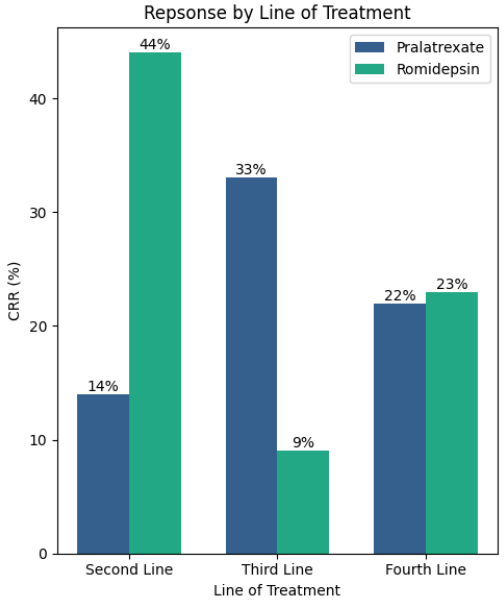
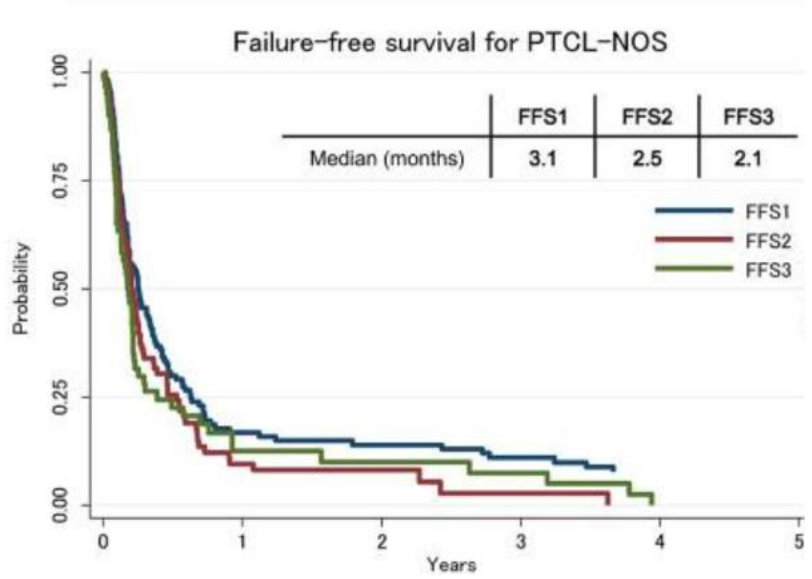
PTCL-NOS, AITL: 321 pts (180 PTCL-NOS, 141 AITL)
PFS1: PFS to front-line therapy
PFS2: PFS to 1st salvage
PFS3: PFS to 2nd salvage
Med OS1, OS2 and OS3 were 47.7, 15.1 and 8.1 mo.

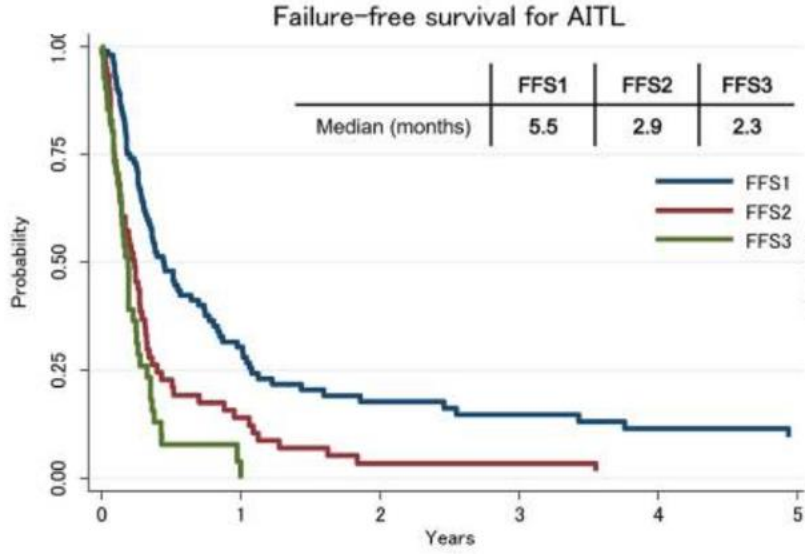
Pralatrexate or Romidepsin at 1st or 2nd salvage TX were not associated with longer PFS2 or PFS3.



	PFS1	PFS2	PFS3
All	10.3	4.1	2.5
PTCL	8.4	3.1	2.5
AITL	13.1	10.9	2.4

Results: Med Mo





Chihara D, et al. Br J Haematol. 2017

Pralatrexate and Belinostat: Primary Efficacy Data Supporting Accelerated Approval

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	PROPEL Study Pralatrexate[1] N = 109	BELIEF Study Belinostat[2] N = 120
Overall response rate (ORR), n (%)	**32 (29%)**	**31 (26%)**
Best overall response		
Complete response (CR)	**11 (10%)**	**13 (11%)**
Complete response unconfirmed (CRu)*	**1 (1%)**	**-**
Partial response (PR)	**20 (18%)**	**18 (15%)**
Duration of response, median (95% CI)	**10.1 months** (3.4–NE)	**13.6 months** (4.5–29.4)
Progression-free survival (PFS), median (95% CI)	**3.5 months** (1.7–4.8)	**1.6** (1.4–2.7)
Overall survival (OS), median (95% CI)	**14.5 months** (10.6–22.5)	**7.9** (6.1–13.9)

1. O'Connor, 2011; 2. O'Connor, 2015

***CRu is a category between CR and PR (ie, does not strictly match either CR or PR); a CRu does not indicate a short-lasting CR**

CD30 as the predictive marker in TCL

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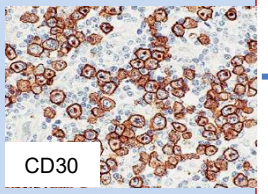
CD30+ Histologies:
PTCL-NOS
AITL (?)
ALK- ALCL
ALK + ALCL



BV + CHP

CR or PR → Complete Rx

CR or PR → ASCT

No response or PD → Rx as r/r PTCL

No response or PD → Rx as r/r PTCL

CD30

PTCL

Salvage therapy/ Clinical trials

PTCL Histologies:
PTCL-NOS
AITL (?)

CHOP

No response or PD → Rx as r/r PTCL

CR or PR → Complete Rx

No response or PD → Rx as r/r PTCL

CR or PR → ASCT

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- HOW CAN WE HARNESS THE ADVANCES IN BIOLOGY?

Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma

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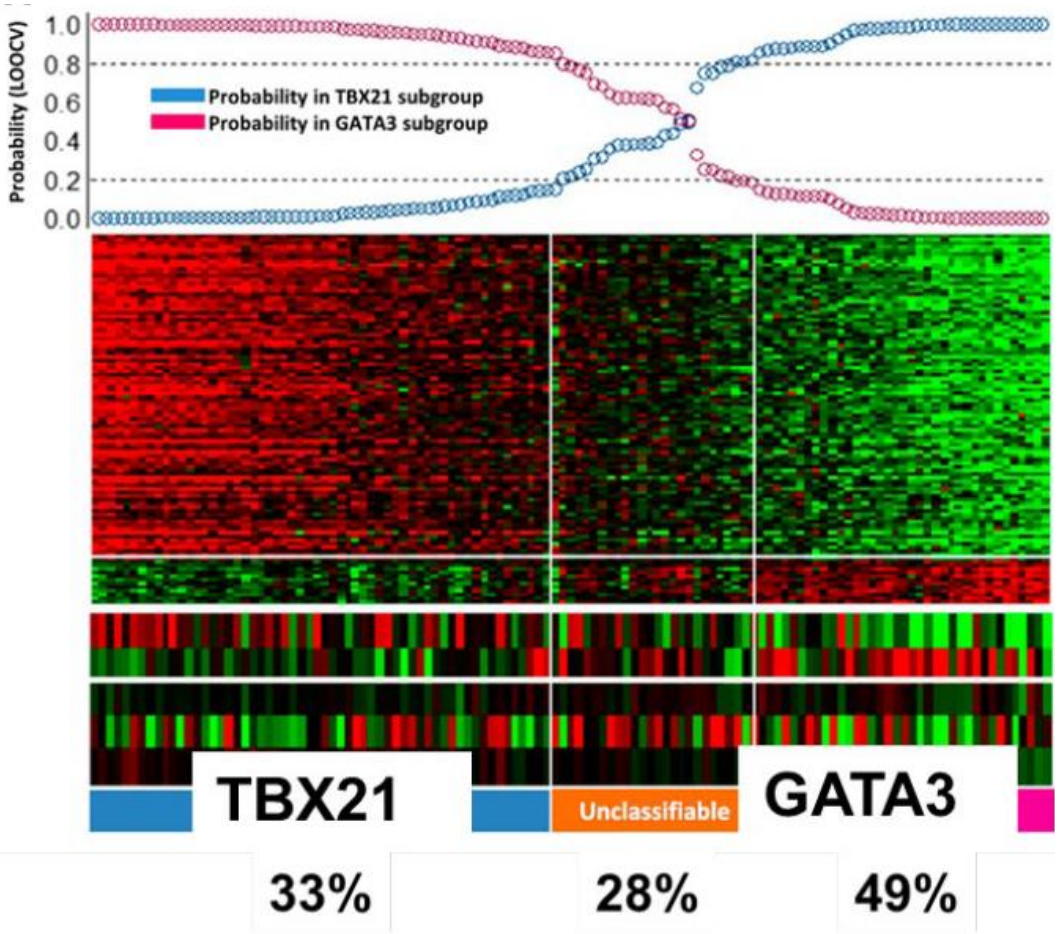
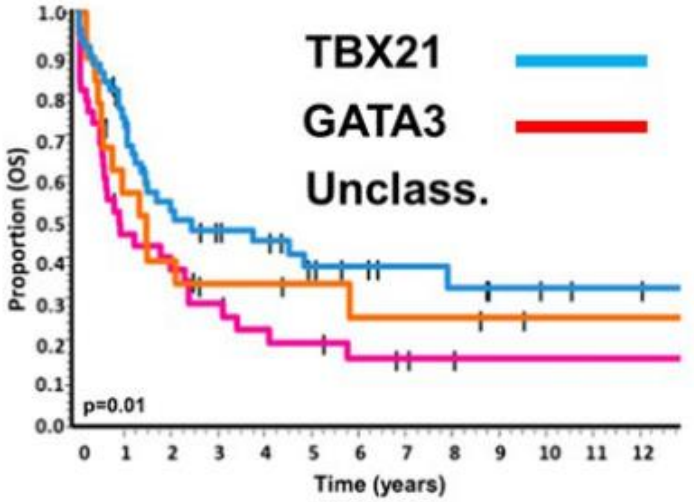


TBX21
GATA3
Pan B-cell
Pan T-cell
Plasma cell



TBX21 Phenotype

Th1 IFNγ signaling through NF-κB pathway with median survival exceeding two years

Therapeutic Implications

Distinct signaling pathways suggest different targeted therapy approaches for subtypes

GATA3 Phenotype

Th2 IL4/IL5 signaling via PI3K-mTOR/MYC pathway with poor one-year survival

Survival Difference

TBX21 subtype demonstrates significantly better prognosis than GATA3 variant

Iqbal et al. Blood 2014; 123;2915-23

Clinical Diagnostic Algorithm Development

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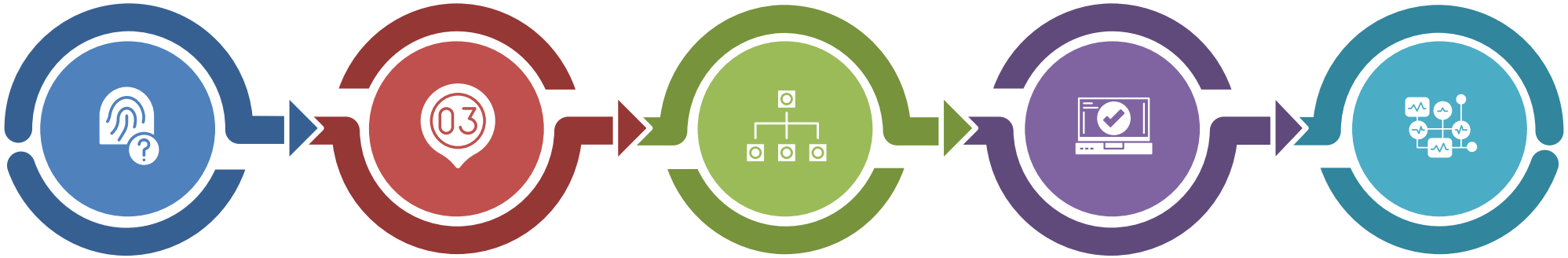
CXCR3 Marker

Secondary CXCR3 positivity (≥20%) supports TBX21 subtype when TBX21 negative

CCR4 Confirmation

CCR4 positivity (≥50%) provides additional GATA3 subtype confirmation when needed



TBX21 Identification

Positive TBX21 immunohistochemistry (≥20%) confirms TBX21 subtype classification

GATA3 Classification

GATA3 immunohistochemistry (≥50%) identifies GATA3 subtype in appropriate cases

Diagnostic Flow

Sequential algorithm enables systematic subtype classification for treatment selection

COO based Diagnosis in PTCL

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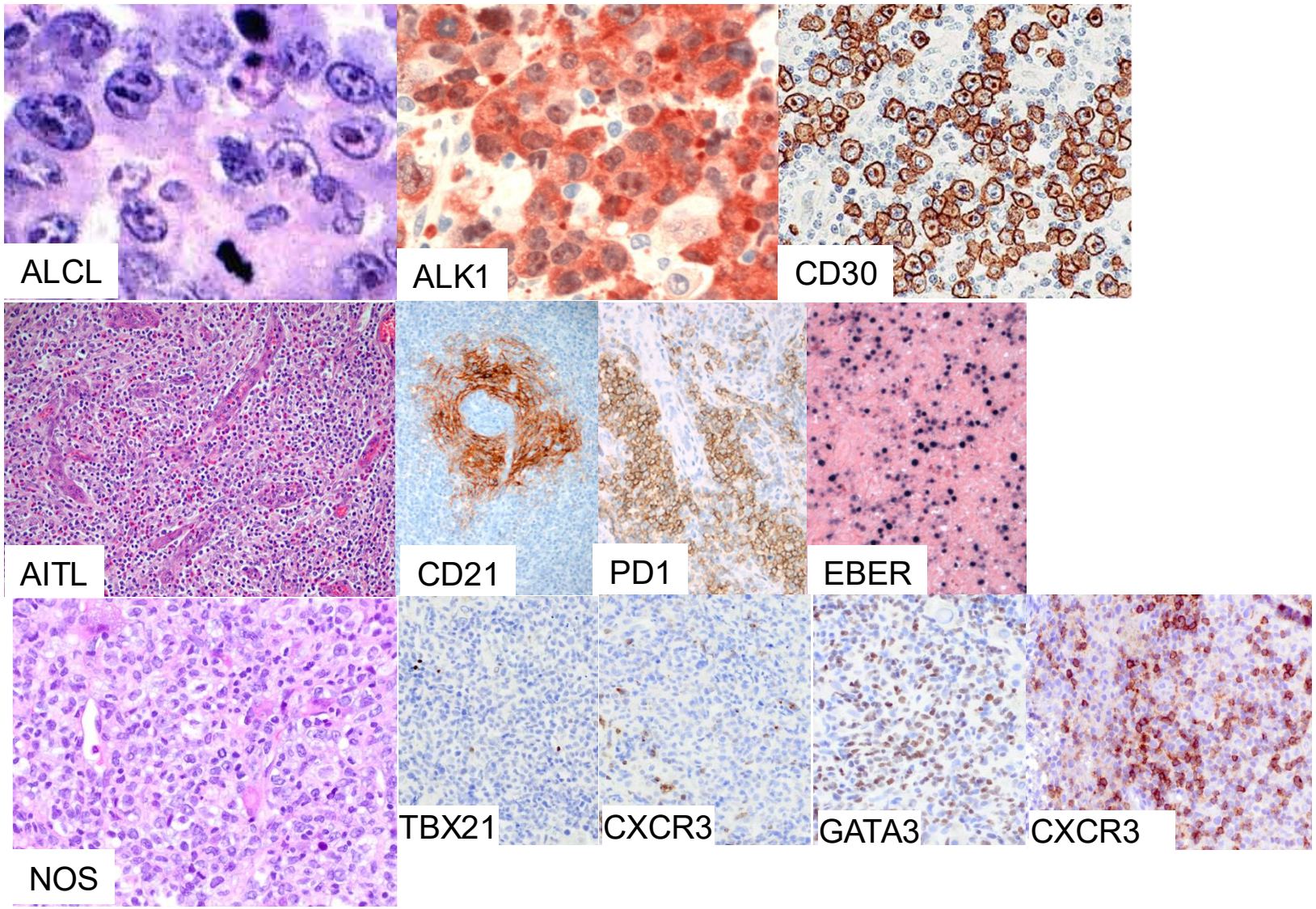

Vega F, EXABS-TCL-052.2020

Therapeutic Options Beyond Chemotherapy: disrupting dysregulated pathways

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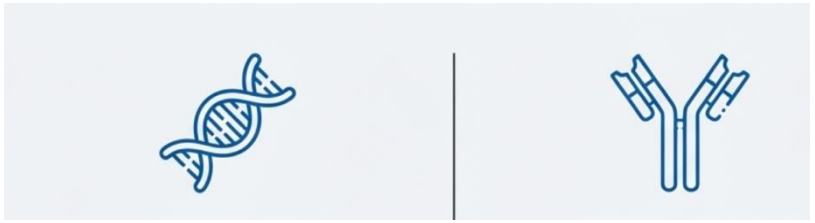

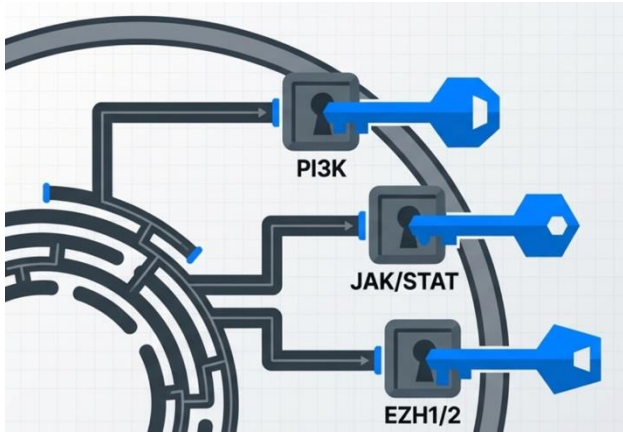

Cellular Therapies

Anti-CD5 CAR-T and anti-CD70 & TRBC1

Monoclonal mAbs/ADCs

Brentuximab vedotin and mogamulizumab provide targeted antibody-drug conjugate therapy. Anti-PD1

Kinase Inhibitors

Valemetostat, crizotinib, Alectinib and PI3K inhibitors (Duvelisib, Linperlisib, Tenalisib), JAK inhibitors (Ruxolitinib, Golidocitinib), Soquelitinib

Epigenetic modulators

Romidepsin, belinostat, and chidamide and Azacytidine target epigenetic dysregulation mechanisms

Immunomodulatory

Lenalidomide, Golcadamide, provide alternative mechanism for immune system activation against tumors

Single-Agent PTCL Treatments Overview

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Single Agent	Therapeutic Class	ORR (%)	CRR (%)	Reference	Year
SGN-30	Monoclonal antibody	17	5	Forero-Torres et al., 2009	2009
Romidepsin	HDAC inhibitor	25	15	Piekarz et al., 2011; Coiffier et al., 2012	2011
Pralatrexate	Anti-metabolite	29	11	O'Connor et al., 2011	2011
Lenalidomide	Immunomodulatory	22	8	Morschhauser et al., 2013; Toumishey et al., 2015	2013
Mogamulizumab	Monoclonal antibody	34	17	Ogura et al., 2014; Ishitsuka et al., 2024	2014
Brentuximab vedotin (BV)	Monoclonal antibody	86	66	Pro et al., 2017; Horwitz et al., 2014	2014
Belinostat	HDAC inhibitor	26	11	O'Connor et al., 2015	2015
Chidamide	HDAC inhibitor	28	14	Shi et al., 2015	2015
Alisertib	Aurora kinase inhibitor	33	18	O'Connor et al., 2019	2019
Cyclosporine	Immunosuppressive agent	86	45	Omoto et al., 2019	2019
Crizotinib	ALK inhibitor	83	58	Bossi et al., 2020	2020
Alectinib	ALK inhibitor	80	60	Fukano et al., 2020	2020
Tenalisib	PI3K δ/γ inhibitor	45	8	Huen..Iyer et al., 2020	2020
Ruxolitinib	JAK 1/2 inhibitor	27	7	Moskowitz et al., 2021	2021
Nivolumab	Immune checkpoint inhibitor	33	17	Bennani et al., 2022	2022
Azacitidine	Hypomethylating agent	33	12	Dupuis et al., 2024	2024
Duvelisib	PI3K γ/δ inhibitor	48	33	Mehta-Shah et al., 2024	2024
Tipifarnib	Farnesyltransferase inhibitor	40	10	Witzig et al., 2024	2024
Cerdulatinib	JAK/SYK inhibitor	36	21	Horwitz et al., 2025	2025
Golidocitinib	JAK1 inhibitor	44	24	Song et al., 2024	2024
Valemetostat	EZH1/2 inhibitor	44	17	Zinzani et al., 2024	2024
Linperlisib	PI3K γ/δ inhibitor	49	33	Iyer et al., 2024	2024
Golcadomide	Immunomodulatory	-	-	Izutsu et al., 2024	2024

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Emerging themes in T cell Lymphomas

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- Epigenetic targeting of Tfh
- Targeting dysregulated pathways: JAK/STAT, PI3K, EZH1/2, ITK
- Immunotherapy: checkpoint blockade and cellular
- Targeting cytotoxic, gamma-delta and NK subtypes
- Pan SIRP inhibitor for LA-HLH

Emerging themes in T cell Lymphomas

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T-Follicular Helper Phenotype Biology

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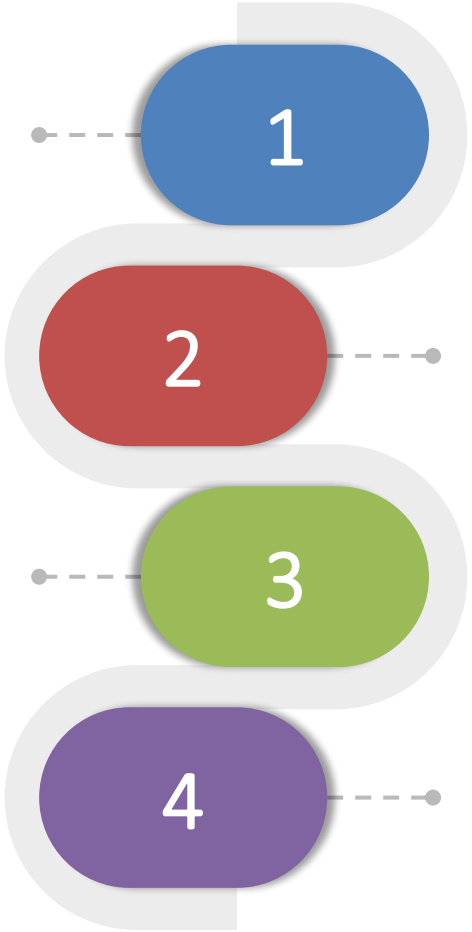
TFH Markers

PD1, ICOS, CXCL13, BCL6, and CD10 define follicular helper phenotype



Lymphoma Origins

Nodal lymphomas of TFH cell origin include AITL and follicular TCL

Common Biology

Identifying cell origin reveals shared biological engine driving distinct classifications

Clinical Significance

TFH phenotype provides framework for understanding disease mechanisms and targeting

Malignant Microenvironment Mechanisms

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Cellular Interactions

Malignant follicular helper T-cells interact with germinal center B-cells

Cytokine Signaling

IL-21 and IL-6 promote B-cell activation and plasma cell differentiation

Immune Checkpoints

PD-1/PD-L1 and ICOS/ICOSL pathways regulate T-cell and B-cell interactions

Vascular Development

High microvessel density supports AITL tumor growth and progression

BCL-6 Expression

Maintains malignant phenotype through transcriptional regulation of target genes

Nodal T-cell lymphomas with TfH phenotype
AITL, PTCL with TfH & Follicular TCL

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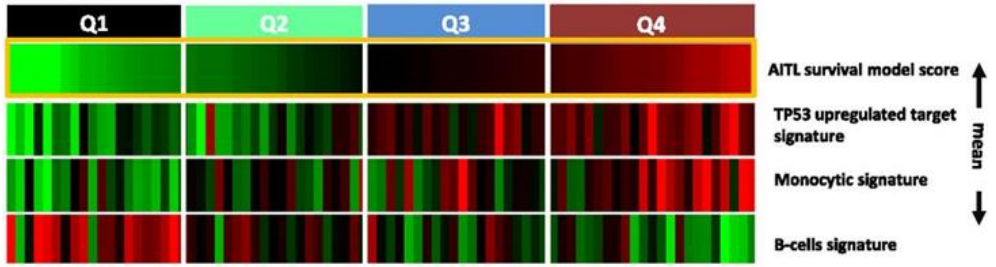
- TFH markers: PD1, ICOS, CXCL13, BCL6 & CD10
- Partial overlapping genetic landscapes

Gene	Freq.
RHOA (G17V)	50-70%
Epigenetic regulators	
TET2	47-83%
DNMT3	20-30%
IDH2 (R172)	20-45%

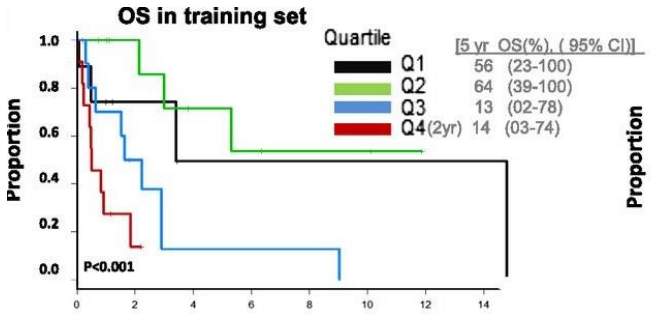
Average expression of prognostic gene signature in AITL

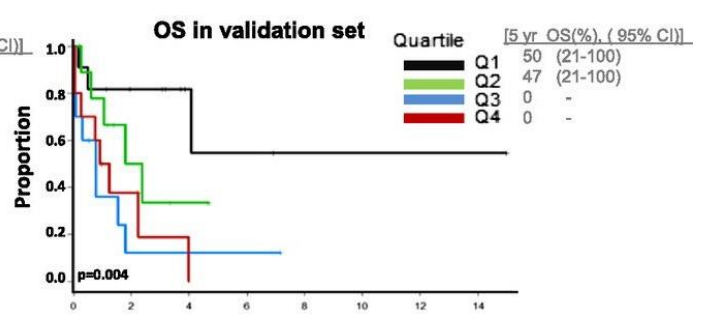


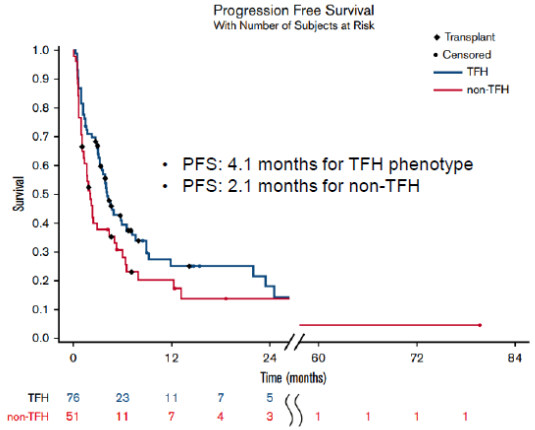
AITL with *RHOA* mutations	Classical clinicopath features
	Higher microvessels density
	More FDC proliferation
	More pronounced THF phenotype
AITL with *IDH2* mutations	Medium to large tumor cells with clear cells Strong CD10 and CXCL13 expression
	Gains of chromosomes 5 and 21

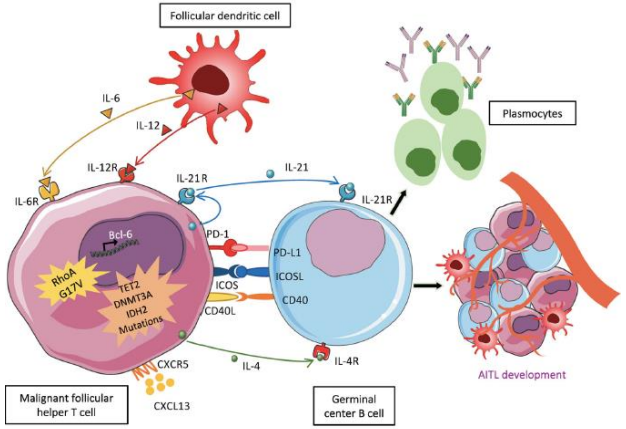
Nodal lymphomas of TFH cell origin (TFH-PTCL)

n=114	AITL	Other TFH-PTCL: TFH-like PTCL	Other TFH-PTCL: F-PTCL*	PTCL-NOS	
Mutations (%)					
TET2	31/64 (48%)	7/11 (64%)	3/4 (75%)	4/24 (17%)	p<0.001
DNMT3A	19/64 (30%)	1/10 (10%)	1/4 (25%)	1/24 (4%)	p<0.05
IDH2	22/66 (33%)	1/11 (10%)	0/5 (0%)	0/23 (0%)	p<0.001
RHOA (G17V)	42/72 (58%)	8/14 (57%)	3/5 (60%)	0/23 (0%)	p<0.001









Iqbal et al. Blood 2014; 123;2915-23, Ondrejkaet al. Am J SurgPathol2016: 40:335-41; Nagao R et al. Am J SurgPathol2016; 40:1041-50; Steinhilberet al. Mod Pathol2019; 32:1123-34

Nodal Lymphomas with TFH Phenotype: Role of Epigenetic Modifiers

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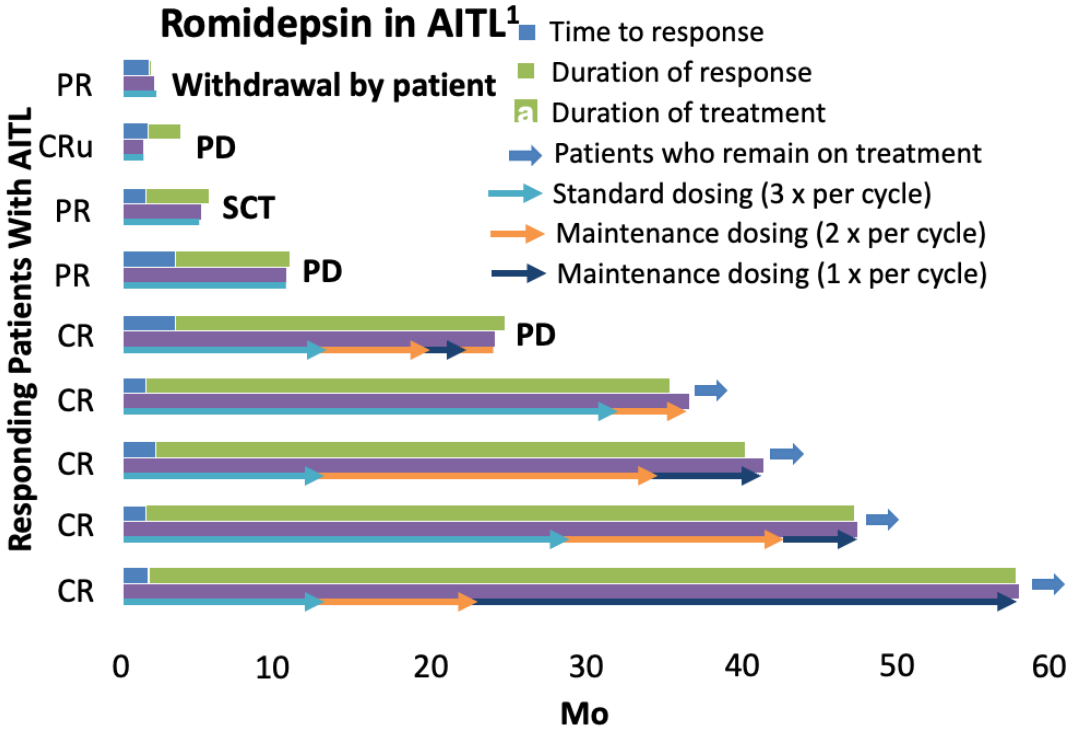

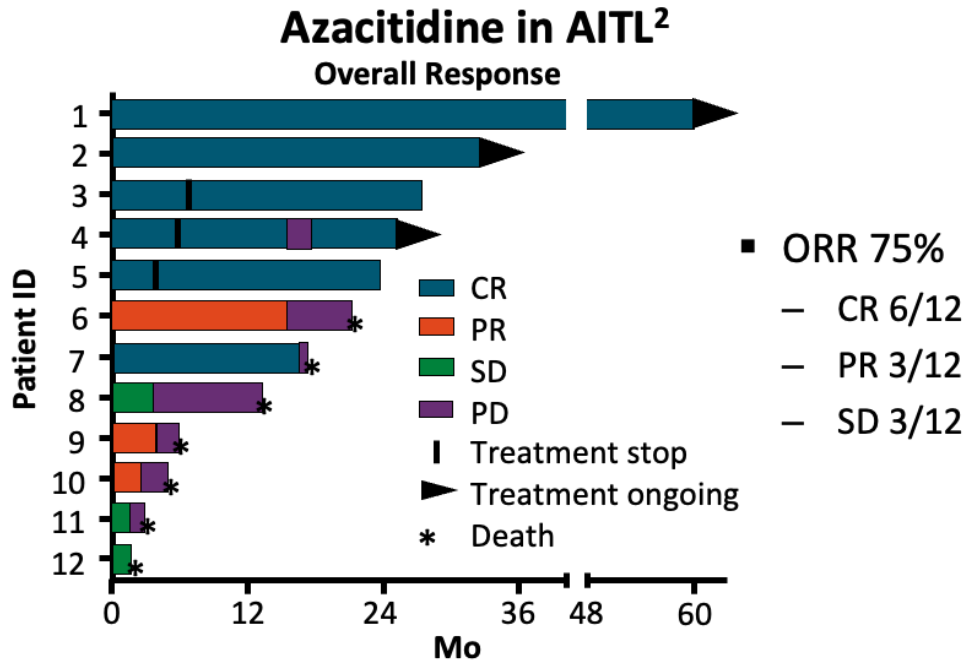

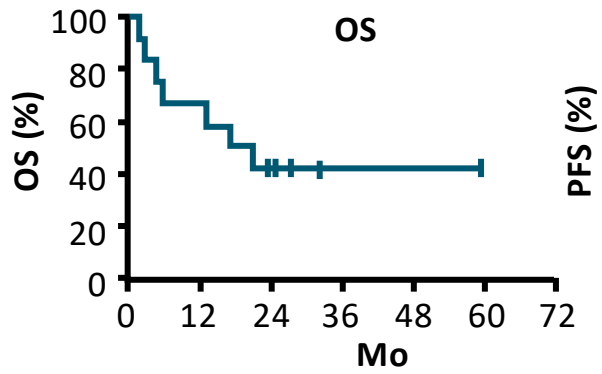

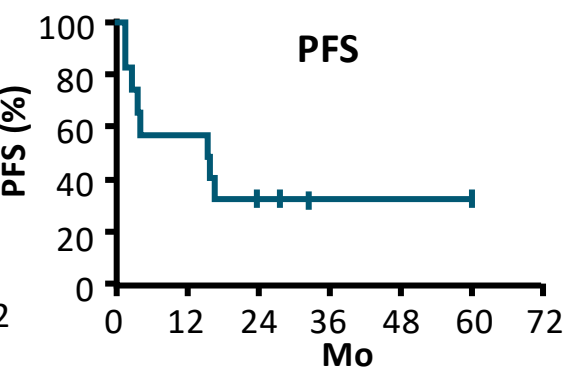

1. Pro. Hematol Oncol. 2017;35:914. 2. Lemonnier. Blood. 2018;132:2305.

ORACLE: Phase III study baseline characteristics

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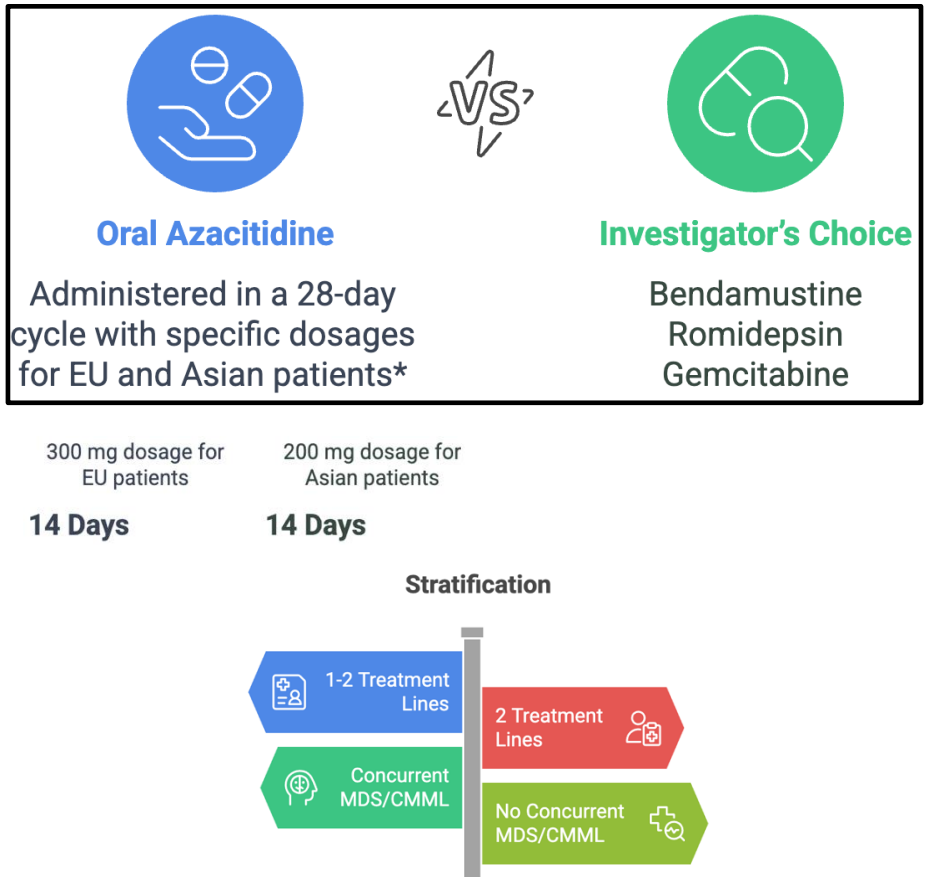

	Azacitidine CC486	Investigator treatment choice	romidepsin	Bendamustine	gemcitabine
N	42	44	4	16	24
median age (IQR)	70.5 (65-77)	68 (58.5-73.5)	68.5 (62.5-71.5)	63.5 (53-68)	72 (64-78)
Sex male	22 (52%)	28 (64%)	3 (75%)	10 (62.5%)	15 (62.5%)
ECOG 2-3	11 (26%)	9 (20%)	0 (0%)	4 (25%)	5 (20%)
Bone marrow involvement	12/37 (32%)	17/40 (42,5%)	1/4 (25%)	8/16 (50%)	8/20 (40%)
Associated MDS/CMML	0	1 (2%)	0	0	1 (4%)
IPI 4-5	13/42 (31%)	14/42 (33%)	0/4	5/15 (33%)	9/23 (39%)
Previous line number					
1-2 vs ≥3	34 (81%) vs 8 (19%)	37 (84%) vs 7(16%)	4 (100%) vs 0 (0%)	14 (88%) vs 2 (12%)	19 (79%) vs 5 (21%)
1	24 (57%)	14 (32%)	4 (100%)	3 (19%)	7 (29%)
2	10 (24%)	23 (52%)	0 (0%)	11 (69%)	12 (50%)
refractory patients	20 (48%)	28 (64%)	1 (25%)	13 (80%)	14 (58%)

Dupuis J et al, ASH 2022 #959

ORACLE – did not meet primary endpoint PFS but OS

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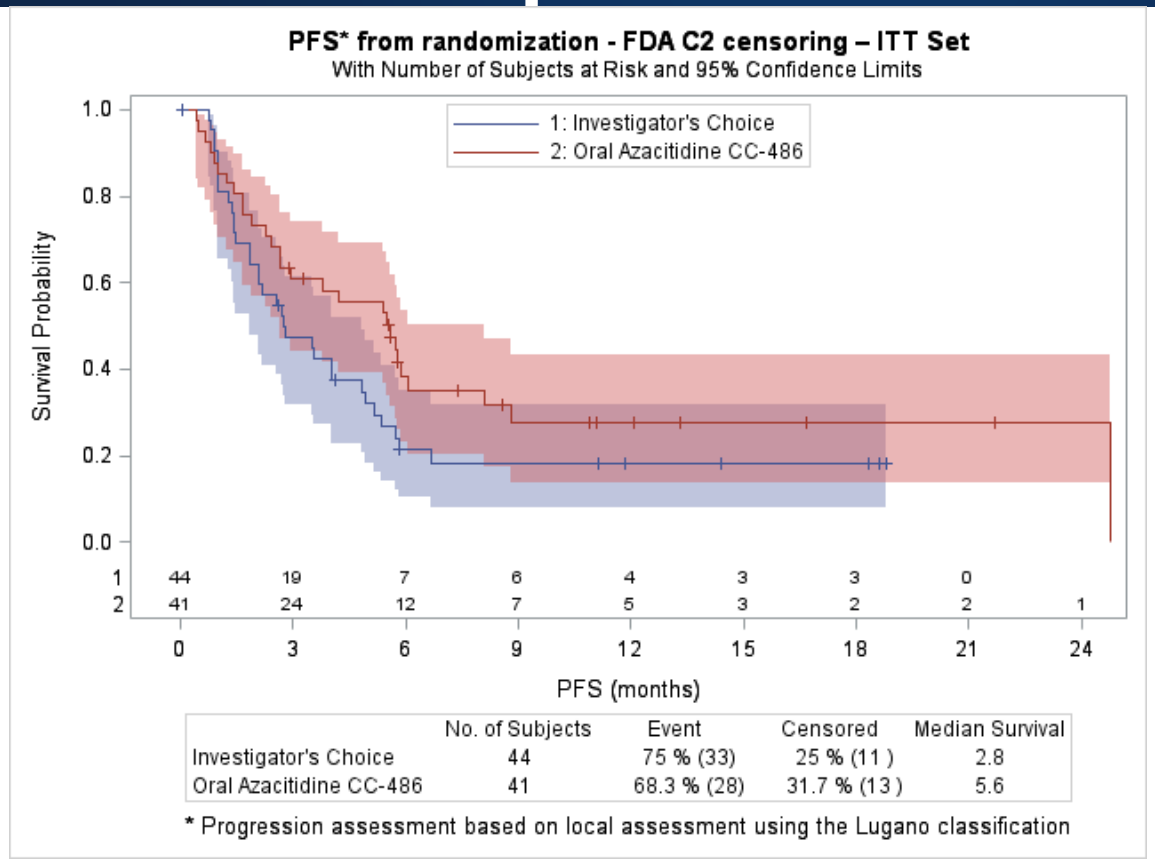

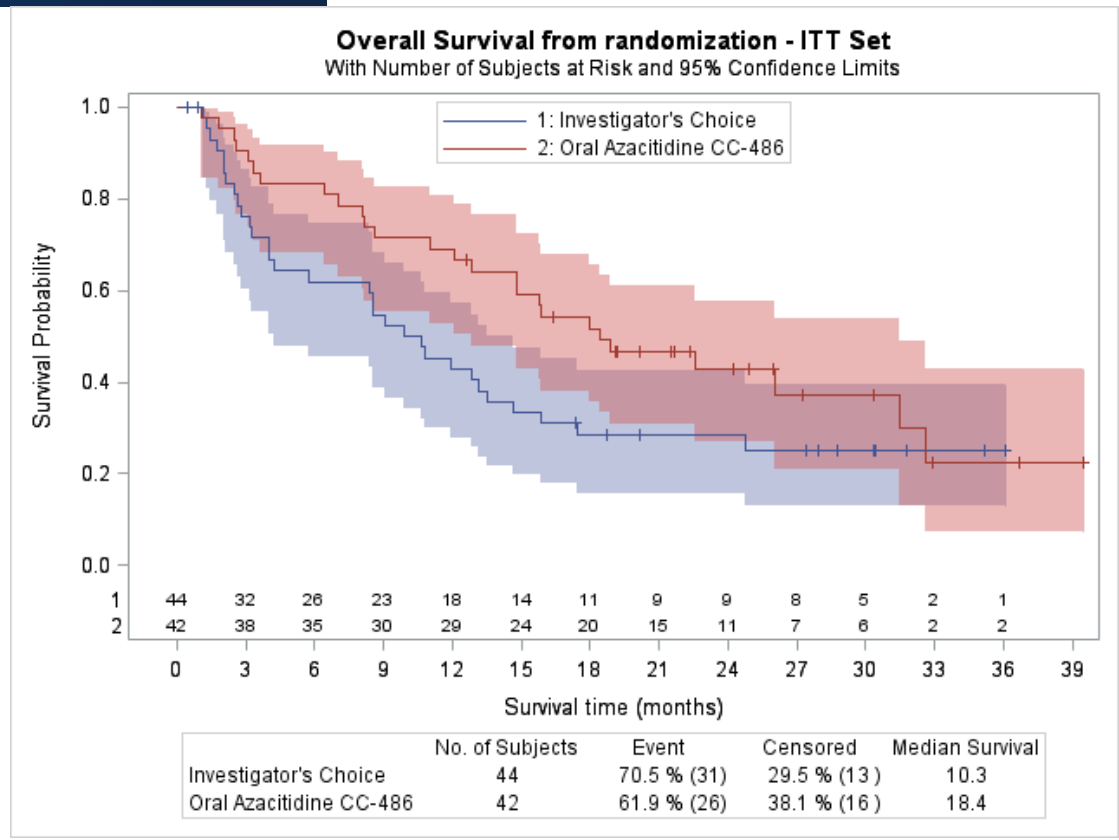

	CC-486	Investigator's choice
median	5.6 months	2.8 months
95% CI	2.7 - 8.1 months	1.9 - 4.8 months
	P=0.0421	>p=0.025

	CC-486	Investigator's choice
median	18.4 months	10.3 months
95% CI	12.9 – 31.5 months	4.2 – 13.5 months
	P=0.0166*	

Dupuis J et al, ASH 2022 #959

* Descriptive p value

Histone modifier gene mutations in peripheral T-cell lymphoma, not otherwise specified.

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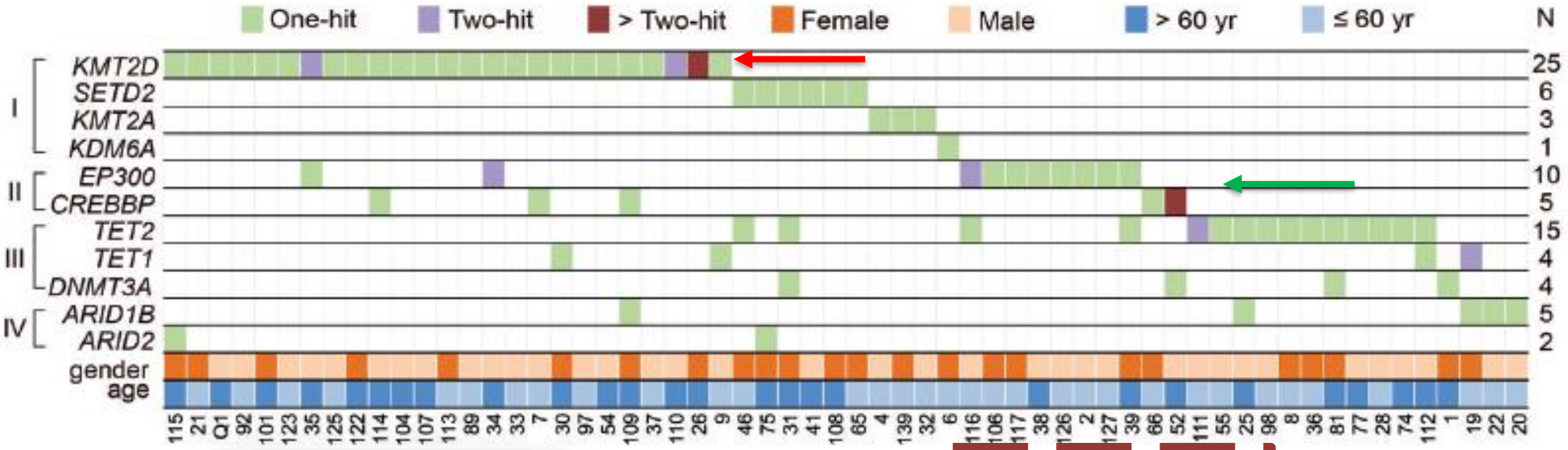
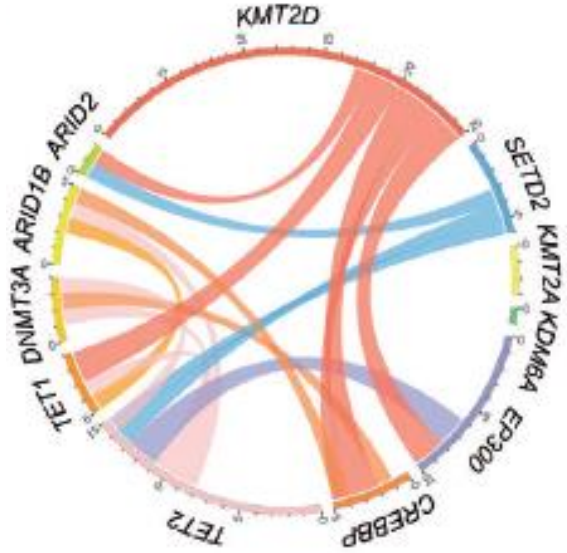
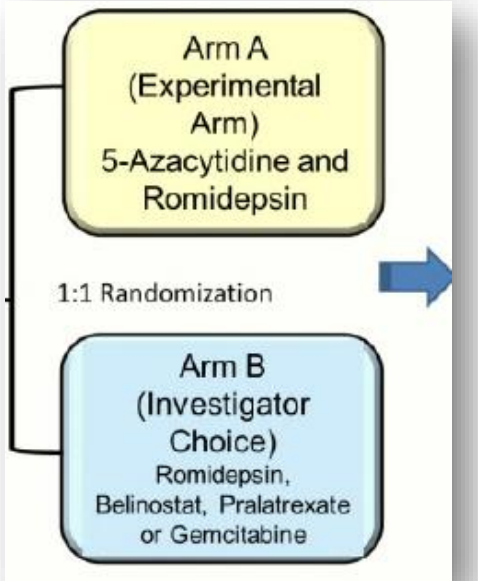
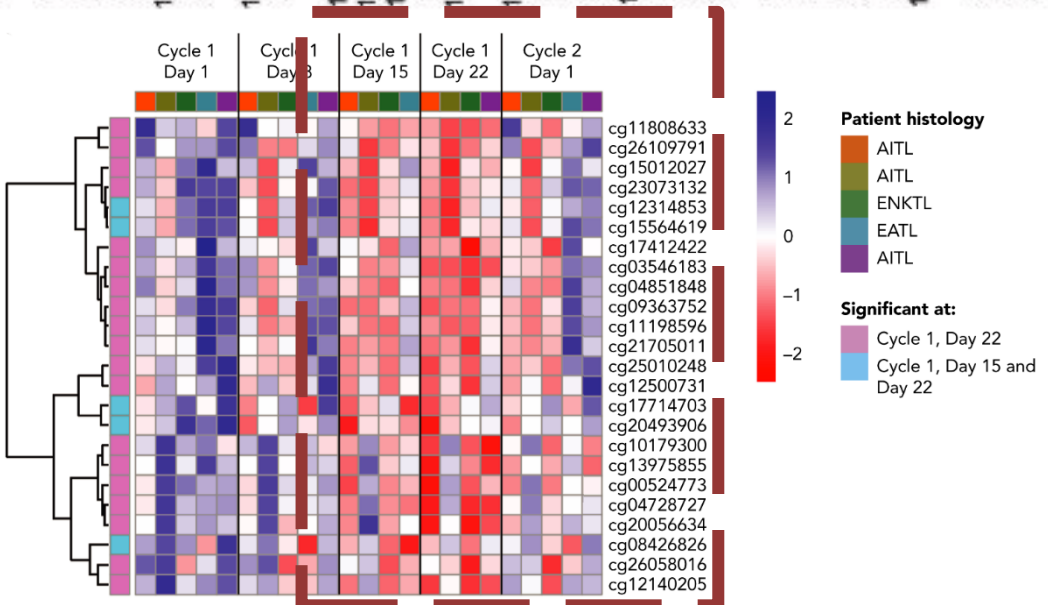
- histone methylation
- histone acetylation
- DNA methylation
- chromatin remodeler









Ji MM et al. Haematologica 2018;103(4):679-687;

Pembrolizumab and Romidepsin in r/r PTCL: Outcomes

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Lead in Phase I

R/R CTCL (n=3-6)

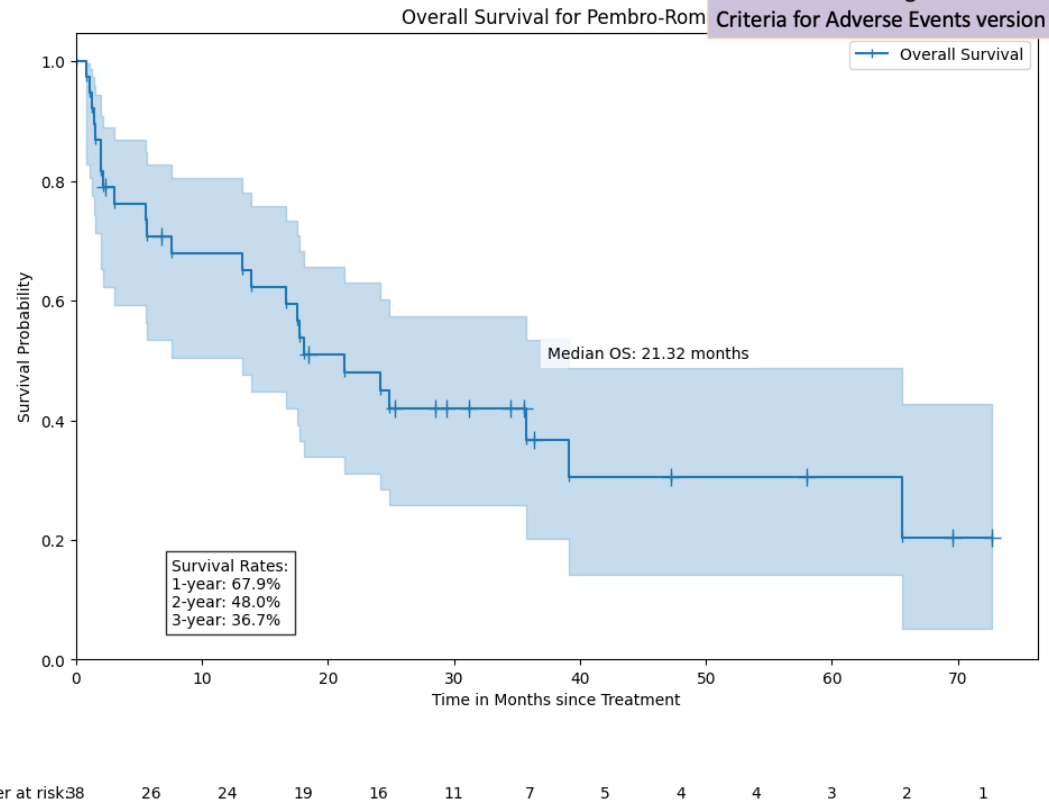
R/R PTCL (n=12)

Phase II: Expansion Phase

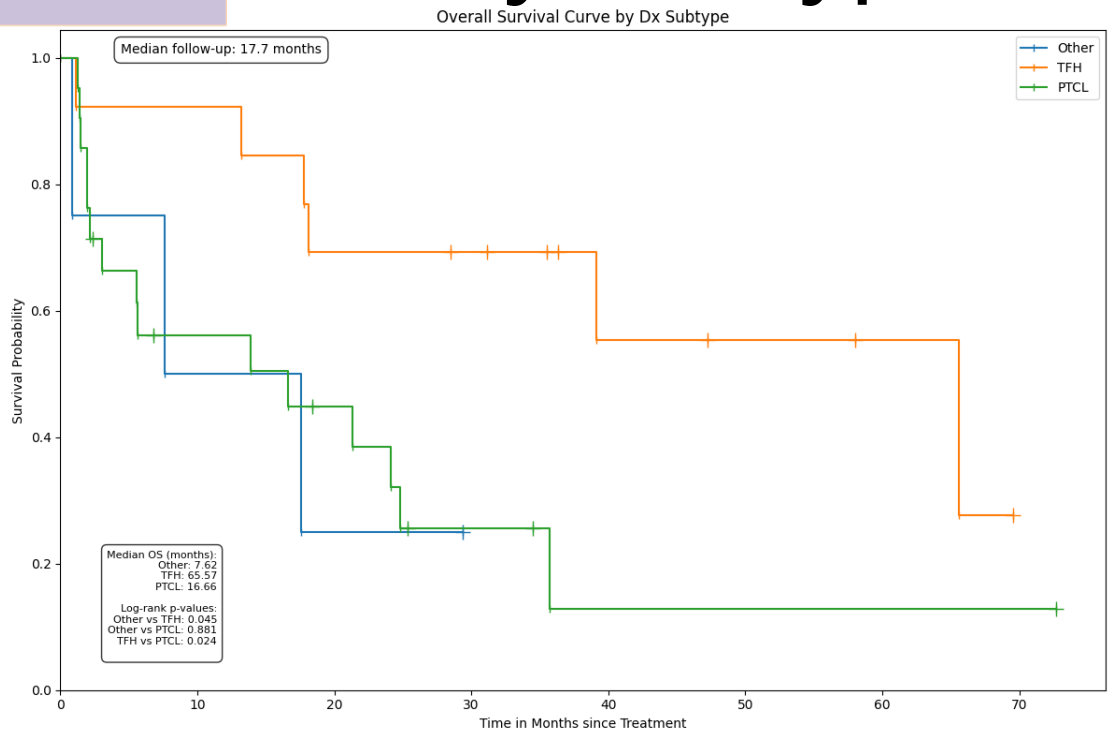
Primary end points: Safety, tolerability and ORR
Secondary end points: CRR, PFS, OS and DoR

AEs monitored and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 guidelines

OS



OS by subtype



CODEX analysis of the immune landscape in responders versus non-responders 12/14.

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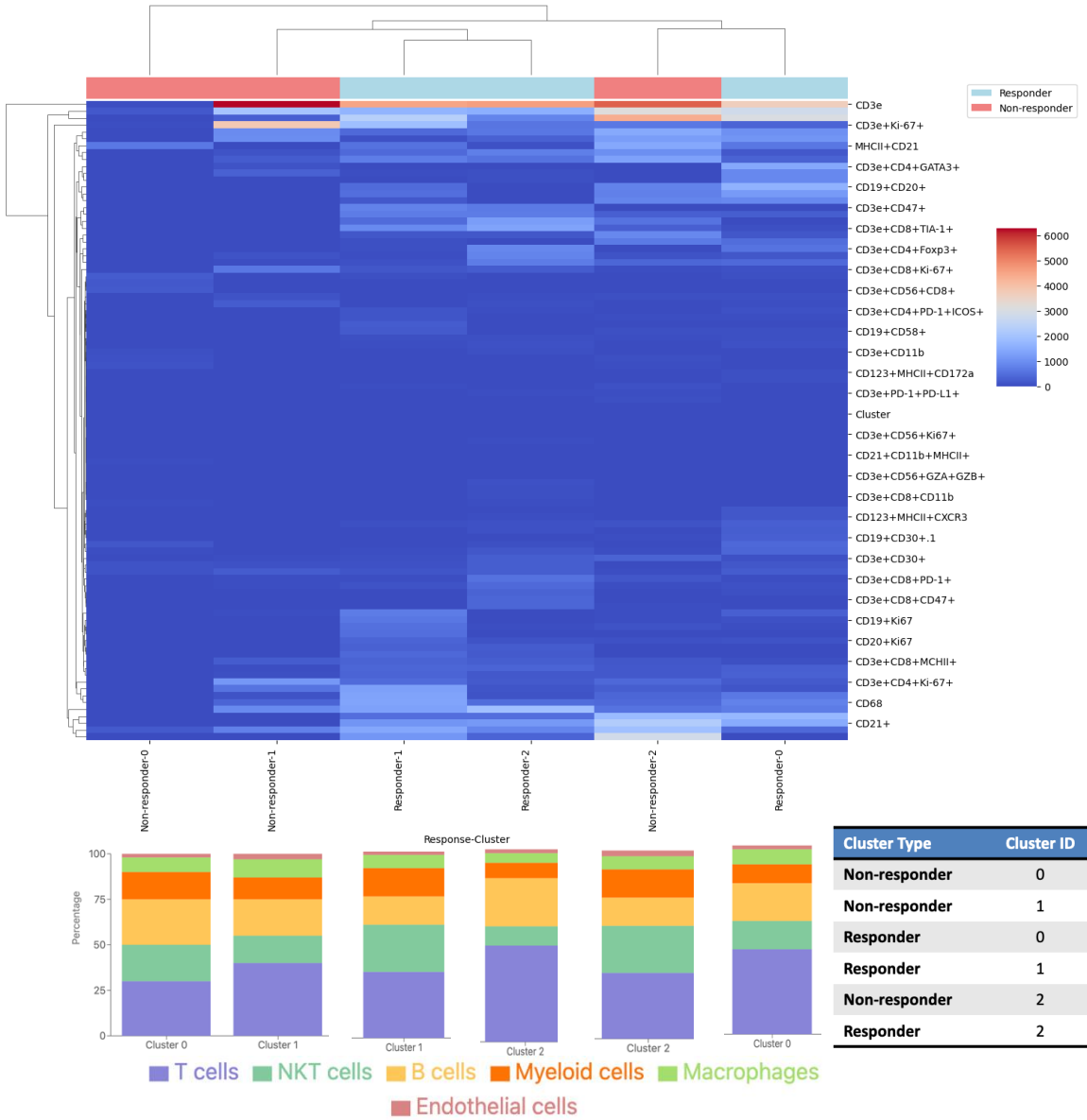

Cluster Type	Cluster ID	Diagnostic Subtypes
Non-responder	0	EATL
Non-responder	1	PTCL1, PTCL2
Responder	0	AITL4, Tfh5
Responder	1	AITL3, AITL6, AITL7
Non-responder	2	AITL2
Responder	2	AITL1

Cell Type	Total Markers	Significant Markers	Trend	Description
T cells	46	15 (32.6%)	↑	Higher in responders
NKT cells	13	6 (46.2%)	↑	Higher in responders
B cells	24	8 (33.3%)	−	No significant difference
Myeloid cells	9	5 (55.6%)	↓	Higher in non-responders
Macrophages	12	8 (66.7%)	↓	Higher in non-responders
Endothelial cells	3	1 (33.3%)	−	No significant difference

Parallel architecture of immune aggregates: AITL TME vs. Cancer Tertiary Lymphoid Structure.

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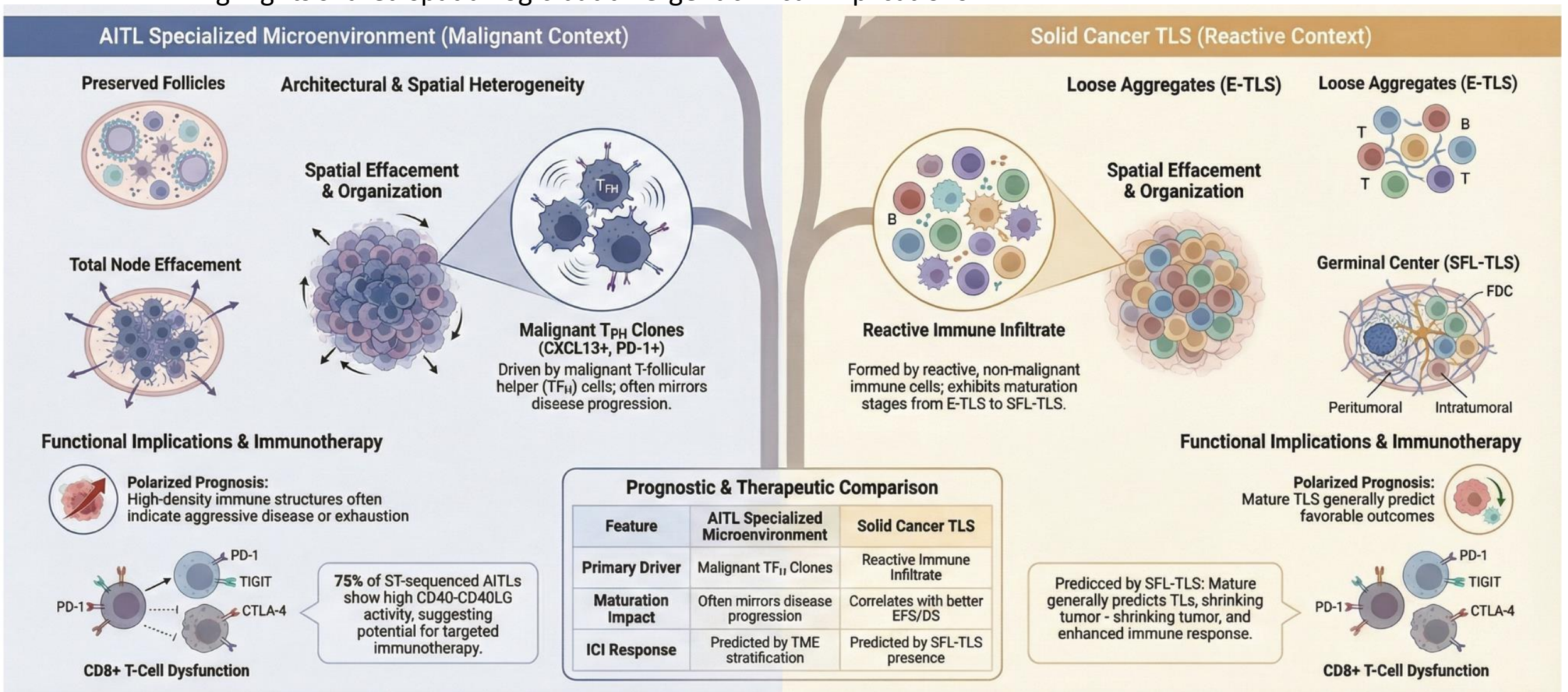
Highlights shared spatial logic but divergent clinical implications



Prognostic & Therapeutic Comparison

Feature	AITL Specialized Microenvironment	Solid Cancer TLS
Primary Driver	Malignant TFH Clones	Reactive Immune Infiltrate
Maturation Impact	Often mirrors disease progression	Correlates with better EFS/DS
ICI Response	Predicted by TME stratification	Predicted by SFL-TLS presence

Zhang, X., Sun, Y., Wu, D., et al. (2026). *Cell Death & Disease.* Schumacher, T. N., & Thommen, D. S. (2022). *Science.* Gu-Trantien, C., et al. *Cell*. Pritchett, J. C., Yang, Z. Z., Kim, H. J., et al. (2022). *Leukemia*. Zhu, M., Li, N., Fan, L., et al. (2024). *Blood*.

Global Differentiation Between Responders and Non-responders

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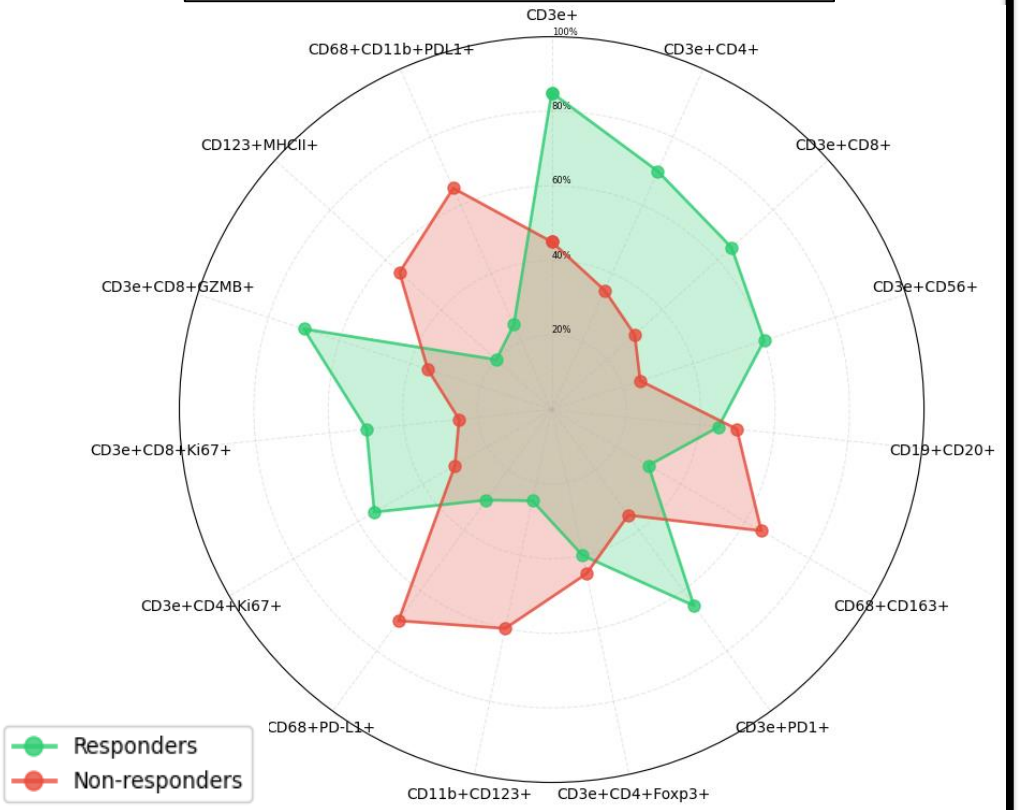
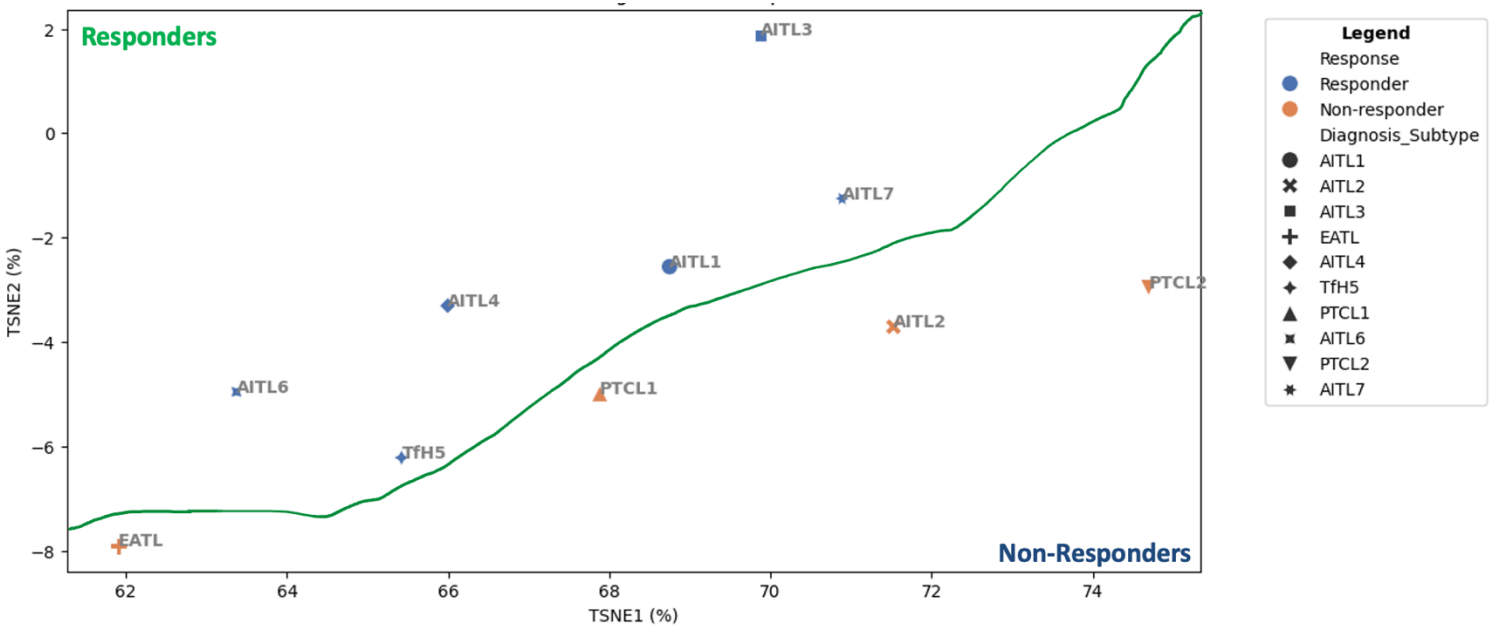
RADAR Plot of responses



Higher immune cell infiltration or activation of CD3e+ as a marker of response

t-SNE of cellular subtypes and responses



Grouping of diagnostic subtypes based on response status, suggests that certain subtypes have a higher likelihood of responding to treatment.

TfH as the predictive marker in TCL: Lessons from Ro-CHOP Phase III

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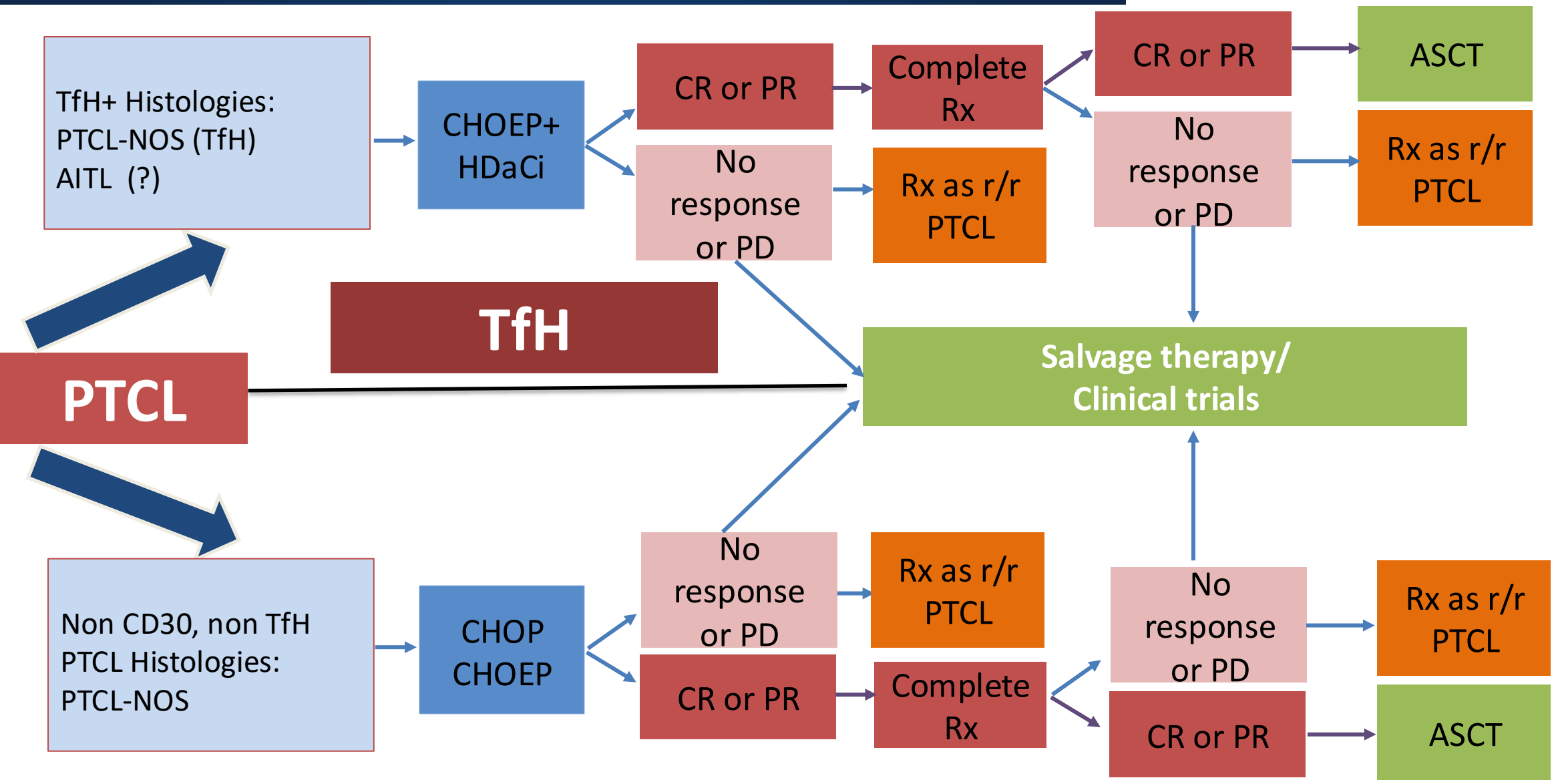

Phase II Trial: Azacitidine + CHOP as Initial Therapy for PTCL

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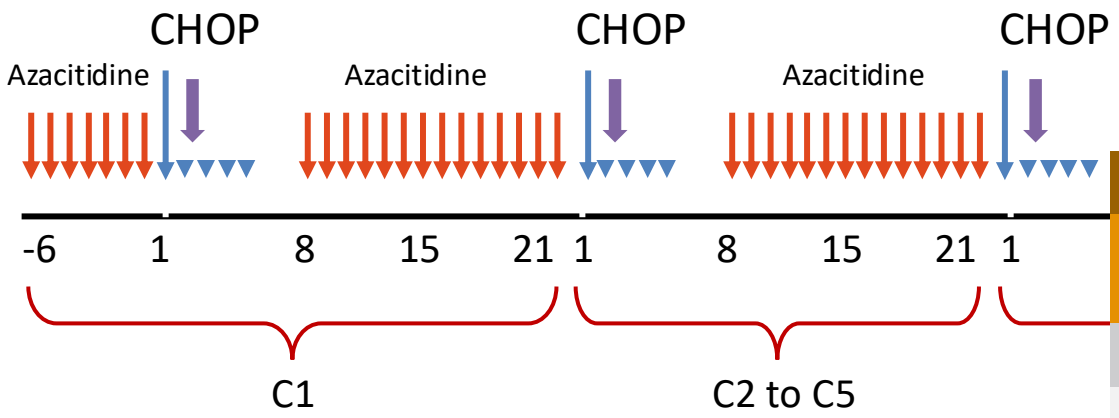
Treatment

- Azacitidine: cycle 1, days -6 to 0; 1-5 days, days 8-21
- Cyclophosphamide, doxorubicin, vincristine: day 1
- Prednisone: days 1-5
- Growth factor e.g., pegfilgrastim:



- Azacitidine dosing: 300 mg/day, d-6 to 0, then D8-2
- Patients in CR/PR after 6 cycles can receive consolic

Patients with untreated PTCL (N = 20)

- **Nodal TCL w/TFH phenotype (per WHO 2016)**
  - **AITL**
  - **Follicular TCL**
  - **PTCL-NOS, TFH variant**
- **PTCL-NOS**
- **ALCL, ALK neg**
- **ALCL, ALK pos w/IPI >2**
- **Adult T-cell lymphoma/leukemia**

Response	Interim			EOT		
	n	Evaluable, % (n = 20)	PTCL-TFH, % (n = 17)	n	Evaluable, % (n = 20)	PTCL-TFH, % (n = 17)
ORR	17	85	94	15	75	88
CR	11	55	59	15	75	88
PR	6	30	35	0	0	0
SD	2	10	0	1	5	0
PD	1	5	6	2	10	6
Discontinued	0	0	0	2	10	6
Median FU, mo	15 (range: 9-23)					

Ruan. ASH 2020. Abstr 40.

Emerging themes in T cell Lymphomas

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- Targeting dysregulated pathways: JAK/STAT, PI3K, EZH1/2, ITK

Emerging themes in T cell Lymphomas

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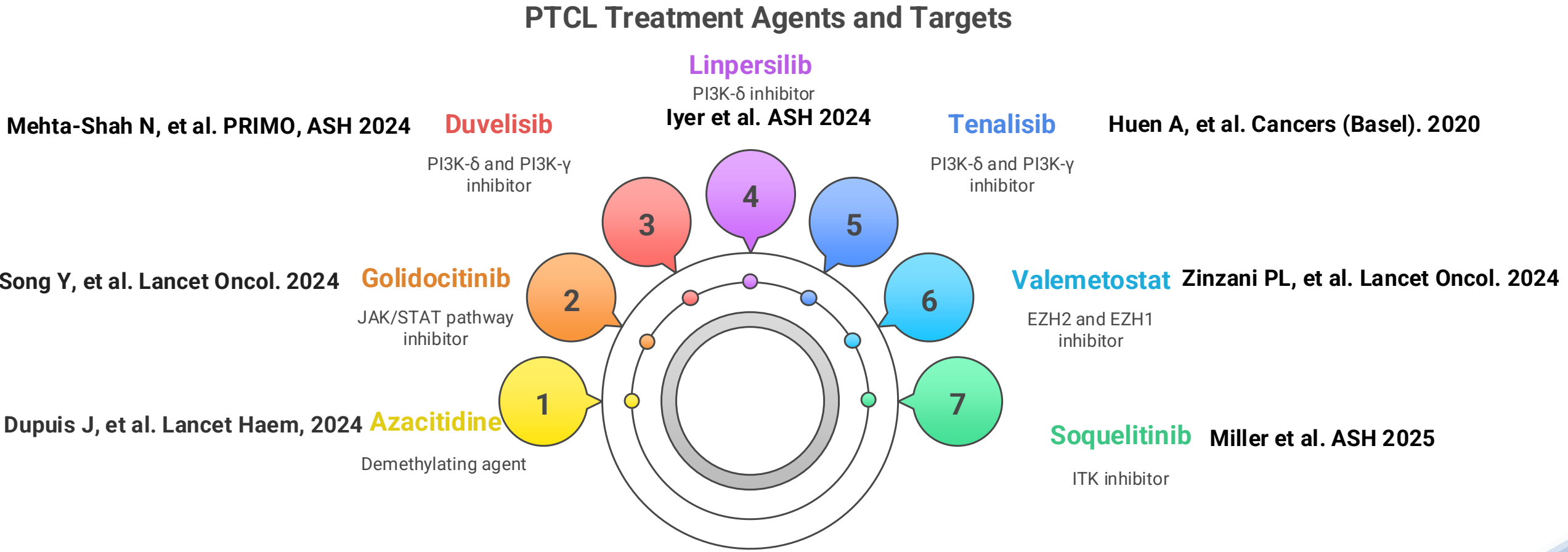
Targeting dysregulated pathways: JAK/STAT, PI3K, EZH1/2, ITK



Efficacy of Novel agents

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Name of Agent	Target / Pathway	N (Patients)	Median Prior Lines (Range)	ORR (Best Overall Response)	CR (Complete Response)	Median F/U	PFS (if available)	Author / Study Reference
Golidocitinib	JAK / STAT pathway (JAK1 selective inhibitor)	104 (Enrolled) / 88 (Efficacy)	2 (1–3)	44.3% (IRC-assessed)	23.9% (IRC-assessed)	NA (Data cut-off Aug 31, 2023)	NA (PFS secondary endpoint)	Song Y, et al. Lancet Oncol. 2024
Duvelisib	Dual PI3K inhibitor (PI3K-δ / PI3K-γ)	123 (All PTCL)	2 (1–9)	48.0% (IRC-assessed)	33.3%	Median PFS: 6.24 months	3.45 months (95% CI: 1.84–3.94)	Mehta-Shah N, et al. PRIMO, ASH 2024
Linperlisib (YY-20394)	PI3K-δ inhibitor	35 (PTCL FAS)	≥1 prior therapy	45.7% (Investigator-assessed)	31.4%	≥6 months follow-up	6-month PFS rate: 40.4% (95% CI: 23.5–56.8)	Iyer et al. ASH 2024
Valemetostat	Dual EZH2 / EZH1 inhibitor	133 (Enrolled) / 119 (Efficacy)	2.0 (1–12)	52.1% (BICR, CT-based)	14.3% (PET-CT based)	NA	NA	Zinzani PL, et al. Lancet Oncol. 2024
Soquelitinib (CPI-818)	ITK inhibitor	19 (Dose-escalation total)	1–18 (range across cohorts)	37%	16%	NA	NA (PFS primary endpoint in Phase 3)	Phase 1 Dose Escalation

Responses in AITL

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Name of Agent	Target / Pathway	N (AITL / TfH Subtype)	Subtype Context / Cohort	Median Prior Lines (Range)	ORR	CR
Valemetostat	Dual EZH2 / EZH1 inhibitor	53 (AITL: 42; Nodal PTCL-TfH: 8; FTL: 3)	ORR 52.1% overall in efficacy-evaluable (N=119);	≥1	52.1%	—
Golidocitinib	JAK / STAT pathway (JAK1 selective inhibitor)	16 (AITL)	15.4% of cohort were AITL; overall ORR 44.3%,	≥1	44.3%)	—
Soquelitinib (CPI-818)	ITK inhibitor	7 (AITL)**	AITL & TFH-NOS eligible in Phase 3; enrolled in dose-escalation; no subtype-specific ORR reported	≥1		—
Linperlisib (YY-20394)	PI3K-δ inhibitor	Not specified for AITL subset*	Conducted in PTCL (including AITL); follow-up ≥6 months	≥1	65%	48%
Duvelisib	Dual PI3K inhibitor (PI3K-δ / PI3K-γ)	37			62.2%	51.4%

Adverse events of Novel agents

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Name of Agent	Grade 3/4 Adverse Events (≥10%)	Special AEs / Key Toxicities	Discontinuation Due to AEs	Related Deaths
Golidocitinib(N = 104)	Any TRAE ≥ Grade 3: 59.6%.Most common: ↓ platelets, ↓ WBC, ↓ neutrophils, ↓ lymphocytes.	TRAE 24.0%; primarily hematologic toxicities.	8.7%	1.0% (1 patient)
Duvelisib(Phase 2 PRIMO, N = 123)	ALT ↑ (21.1%), neutrophils ↓ (17.9%), AST ↑ (17.1%).	Transaminase elevation (ALT/AST) most common special AE; Grade ≥ 3 diarrhea 9.8%.	Not explicitly stated (intolerance criteria).	Cryptococcosis (1), EBV-LPD (1), pneumonitis (1), sepsis (1).
Linperlisib(Phase 2 US & EU, N = 98)	Neutropenia (32%), pneumonia (14%), leukopenia (10%).	Pneumonia (11%) most frequent drug-related SAE; immune-related ≥ G3 TRAEs (ALT/AST ↑, diarrhea, colitis, rash) < 5%.	9.2% (9 patients); dose reductions 22.4%.	Not detailed for N = 98 cohort.
Valemetostat(N = 133)	Thrombocytopenia (23.3%).	Cytopenias common; thrombocytopenia most frequent any grade (49.6%) and G3+ TEAE; 2 secondary AML cases.	9.8% (due to any TEAE).	2 patients with secondary AML (discontinued).
Soquelitinib (CPI-818)(Phase 1 Dose Escalation, N = 45 safety pop.)	Any TEAE ≥ G3: 53.3%. Most common TRAE ≥ G3: neutropenia (11.1%).	Serious TRAE 8.9%; non-hematologic G3+ TRAEs included pneumonia (4.4%) and rash (4.4%).	Not stated.	No treatment-related deaths.

ASH 2026 Oral Presentations

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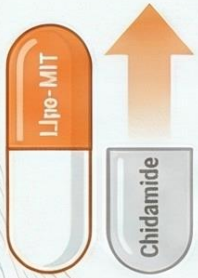
DR-01 in Large Granular Lymphocytic Leukemia (LGLL)

60%
Overall Response Rate
Observed in patients receiving the secondary induction regimen (DR-01 on C1D1/D8/D15).

Favorable Safety Profile
Most adverse events were grade 1-2; no deaths or dese·limiting toxicities occurred.

Durable Responses Observed
Longest onguing response lasted over 15 months in a heavily pretreated patient.

Liposomal Mitoxantrone (Lipo-MIT) vs. Chidamide in R/R PTCL



Lipo-MIT Superior in Progression-Free Survival (PFS)
Lipo-MIT nearly tripled the median PFS compared to chidamide.

Higher Response Rates with Lipo-MIT
The overall response rate was significantly higher for Lipo-MIT than chidamide.

Efficacy Endpoint Comparison

Efficacy Endpoint	Lipo-MIT	Chidamide
Median PFS (months)	7.5	2.6
Overall Response Rate (DBR)	36.1%	18.8%
Overall Survival (DS, months)	14.0	8.8

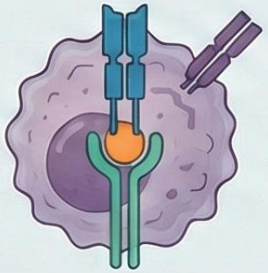
Ulviprubart in T-Cell LGLL (T-LGLL)

53%
Response Rate for Neutropenia
More than half of patients with neutropenia showed improvement with G4W dosing.

22%
Response Rate for Anemia
A notable portion of patients with anemia had increased hemoglotim levels.

Generally Well Tolerated
The treatment was active in depleting cytotoxic T cells with a good safety profile.

MB-105 (CD5.CAR T) in Relapsed/Refractory TCL



100%
ORR in Early Cohort
All 4 assessed patients in the primary cobort achieved a response (3 CR, 1 PR).

Acceptable Safety Profile
Adverse events were mainly Grade 1, with no neurotoxicity reported.

Robust CAR T-Cell Expansion
MB-185 cells expanded significantly and persisted past day 28 in most patients.

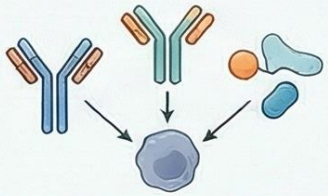
Soquelitinib (SQL) in Relapsed/Refractory TCL

39%
Response Rate
Observed in patients with 1-3 prior theraples at the 200mg BID dose.

18.5 Months
Median Duration of Response
Patients with 1-3 prior therapies showed durable responses.

Well Tolerated
Grade 3+ adverse events were reported in 29% of patients.

Combination Therapy in Relapsed/Refractory PTCL



Triple Combination Therapy
Anti-P01 antibody combined with lenalidomide and azacitidine.

62.1%
Overall Response Rate
Included a complete remission rate of 37.9% in avaluable patients.

73.4%
Estimated 2-Year Overall Survival
The regimen showe potential for long-term survival benefits.

SOQUELITINIB: Phase 1 Subject Enrollment and Patient Characteristics

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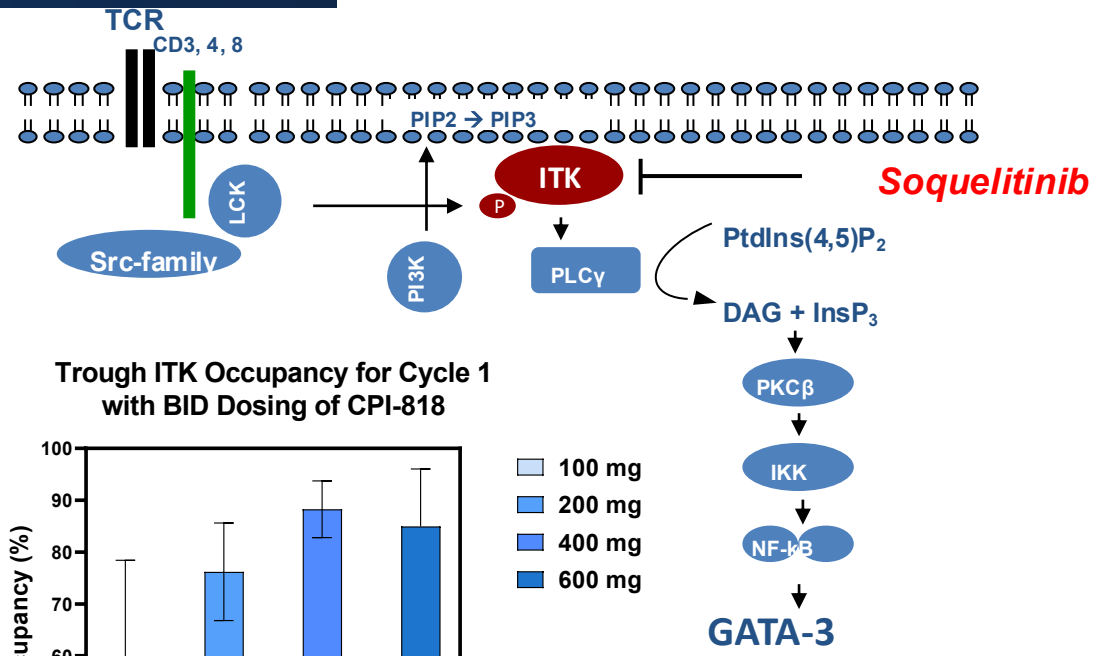
Enrollment in US, AUS, KOR and China (n=60)

31 patients enrolled at 200 mg BID

Patient Characteristics	100 mg (N=4)	200 mg (N=31)	400 mg (N=9)	600 mg (N=16)
Age (yrs.), median (range)	51 (29, 75)	60 (29, 81)	69.0 (41, 80)	63.5 (34, 84)
Gender, male N (%)	3 (75)	14 (45.2)	6 (66.7)	8 (50)
No. of prior therapies, median (range)	3.5 (2, 4)	3 (1,18)	5 (2, 15)	5 (1, 9)
Histologies				
PTCL-NOS	1	13	2	9
AITL	1	4	2	0
ALCL	1	3	0	0
CTCL Sezary	0	2	4	1
CTCL Mycoses	0	5	1	5
Other	1	4	0	1

Data: 18 May 2023



- Good occupancy achieved at 200 mg BID and beyond
- Excellent correlation between PBMC and tissue occupancy in both LN core and skin punch samples
- Conclusion: Occupancy in PBMCs = Occupancy in Lymph nodes = Occupancy in Skin

SOQUELITINIB: a selective ITK inhibitor skews the immune response to enhance anti-tumor activity

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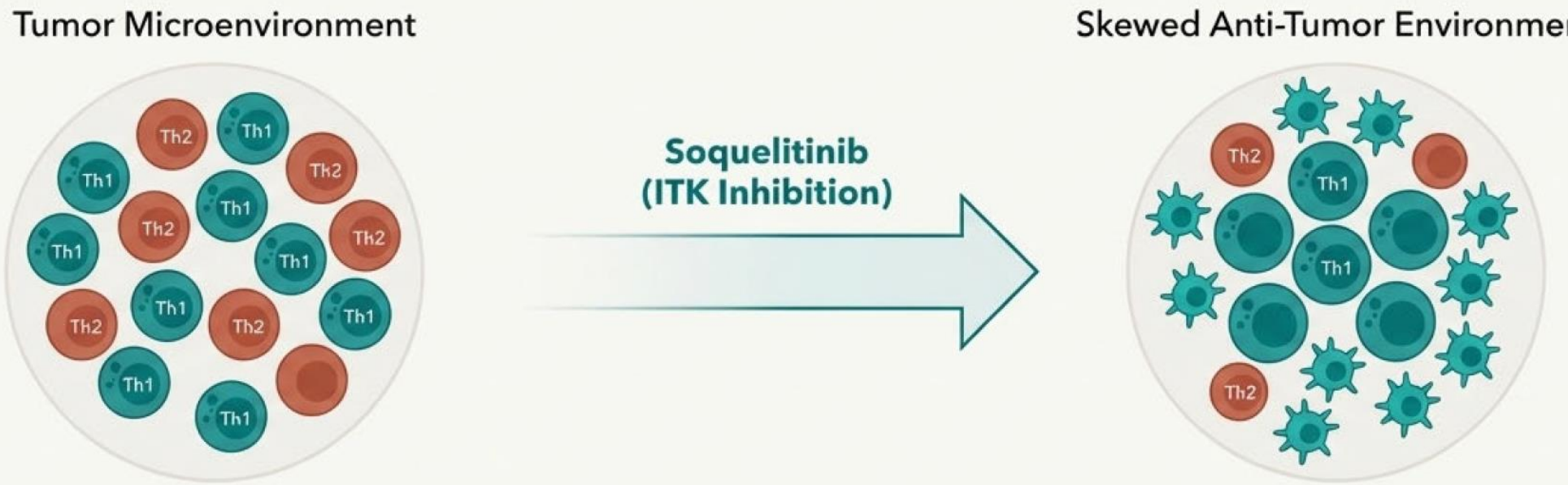
Agent & Mechanism of Action

- **Agent:** Soquelitinib (SQL), an oral, covalent inhibitor of Interleukin-2-inducible T cell kinase (ITK).
- **Mechanism:** ITK is involved in TCR signaling. SQL suppresses the Th2 response while sparing Th1 function. This 'Th1 skewing' is hypothesized to have both direct effects on tumor cells and an indirect effect by inducing a host anti-tumor immune response.
- **Biomarker Rationale:** ITK inhibition reduces GATA3 expression, a master regulator of Th2 cells. The GATA3+ subtype of PTCL is associated with poor prognosis.

***Study:** Phase 1 dose escalation and expansion cohort trial (NCT03952078). **Population:** 75 patients with R/R TCL. **Median** 3 prior therapies. **Dose Focus:** 200mg BID selected as it achieved complete target occupancy.*



SOQUELITINIB shows durable responses in less heavily pre-treated patients

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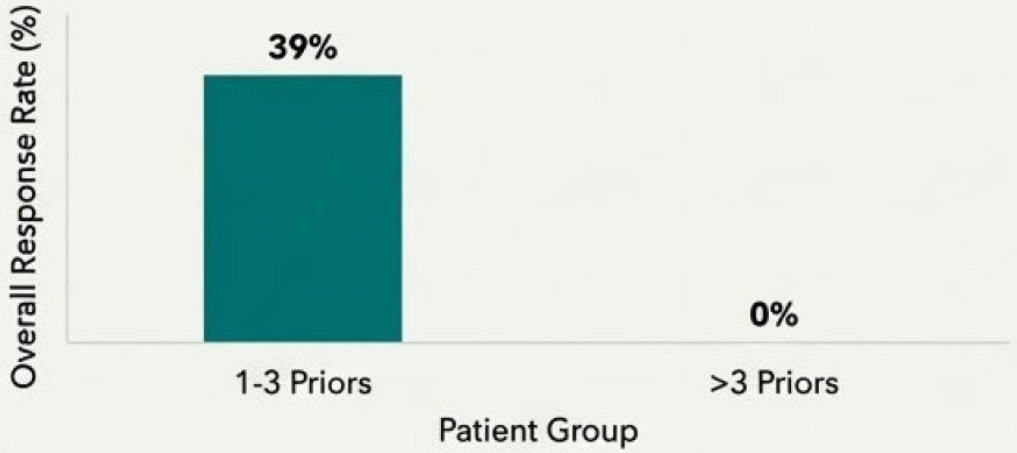
Efficacy is Dependent on Prior Lines of Therapy (200mg BID dose)

1-3 Prior Lines (n=23)
39% ORR

>3 Prior Lines (n=14)
0% ORR



Key Implication: The mechanism requires a baseline level of immunocompetence that may be lost after extensive prior therapy.

Durability and Survival in Patients with 1-3 Prior Lines

- Median Duration of Response: **18.5 months**
- Median Progression-Free Survival: **6.2 months**
- Median Overall Survival: **28.1 months**

Safety and Biomarkers

- **Safety:** Well tolerated; Grade 3+ AEs reported in 29% of patients.
- **Biomarkers:** All 11 patients with available tissue were GATA3+ by IHC. Treatment increased Th1/TEMRA cells and reduced T-cell exhaustion markers (LAG3, TIM3).

Next Steps

Now being evaluated vs. standard therapy in a randomized Phase 3 trial (NCT06561048) in PTCL patients with 1-3 prior therapies.

Clinical Results in Optimum Dose Cohort

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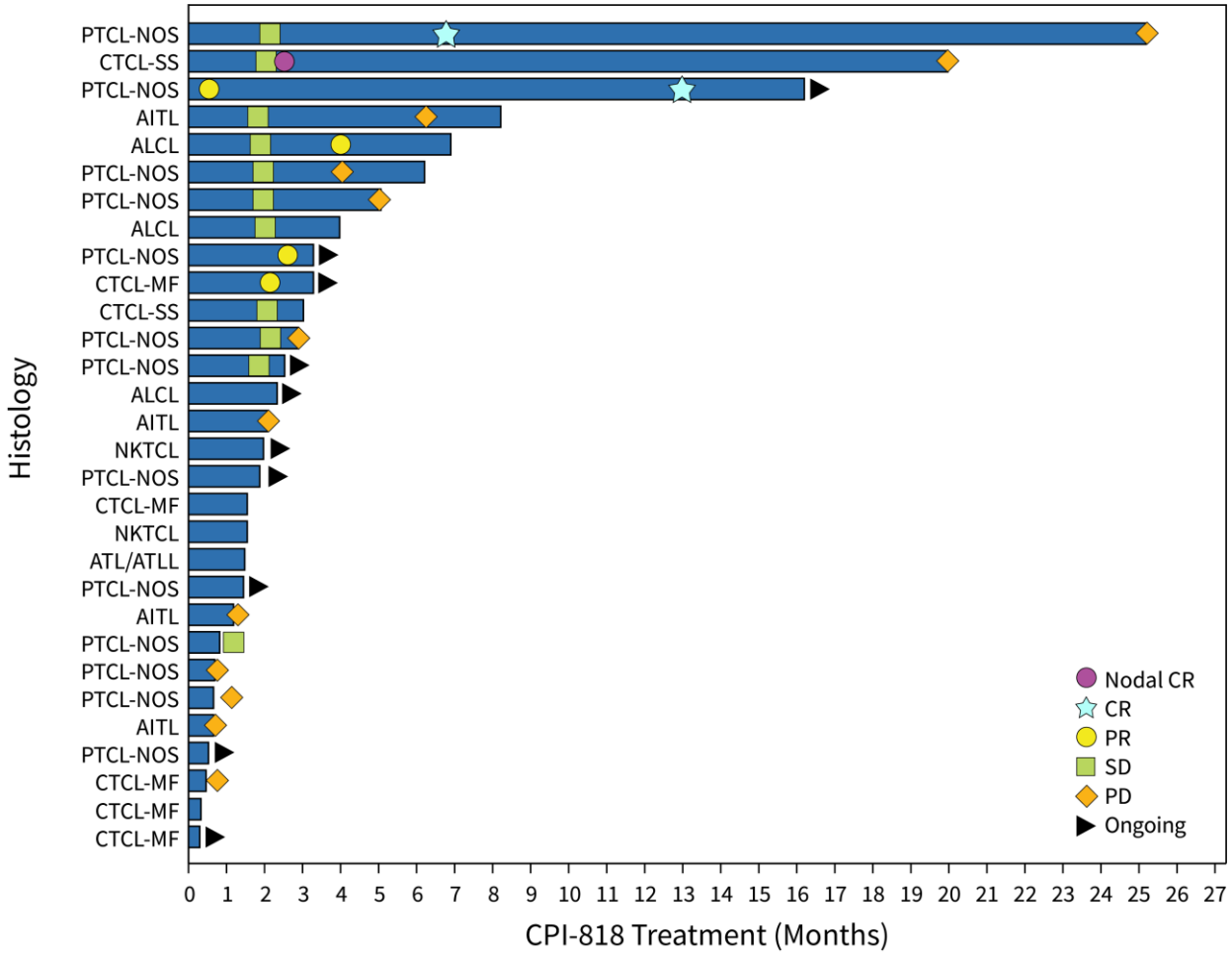

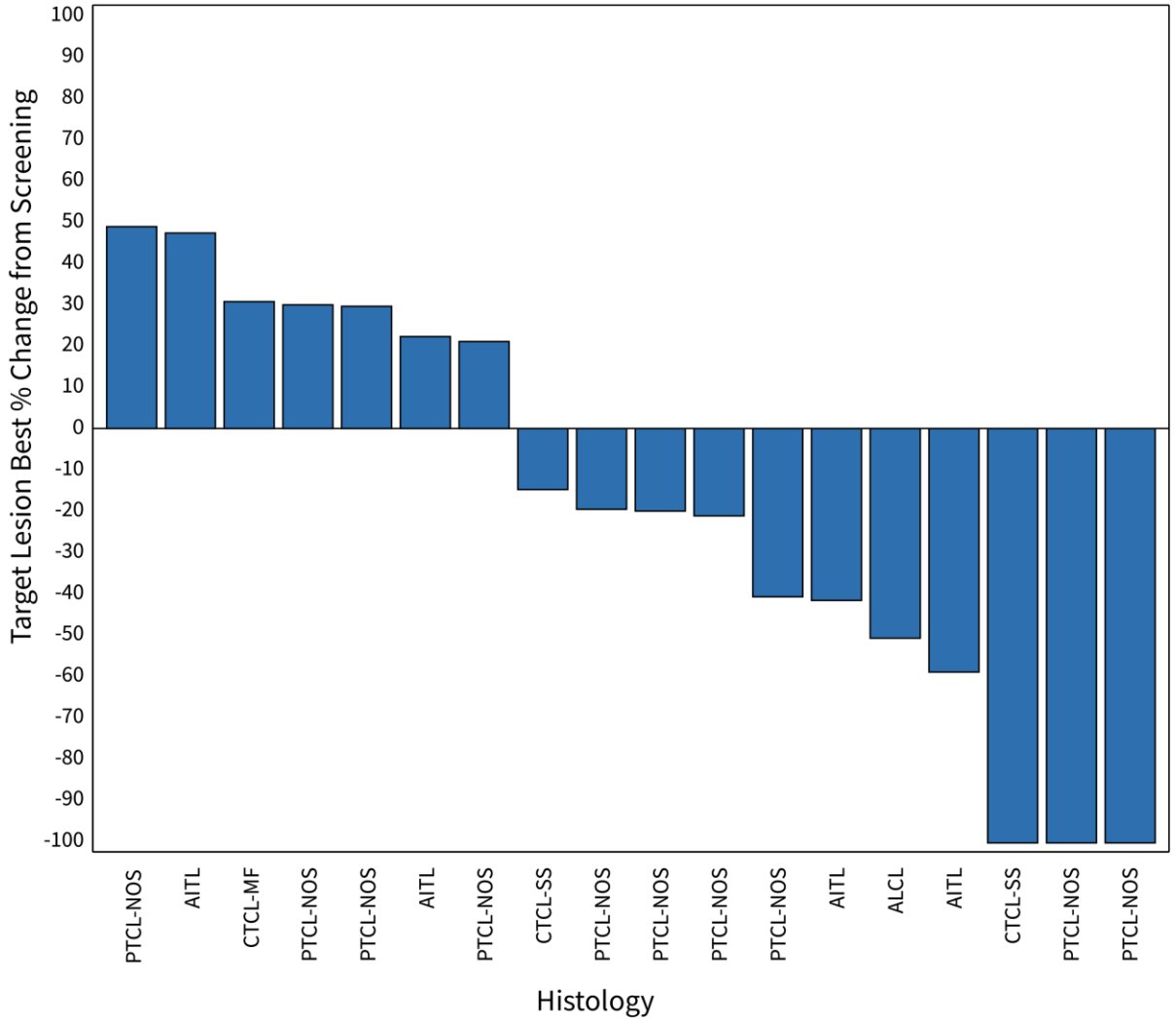

Data: 18 May 2023

Randomized Phase 3 Trial

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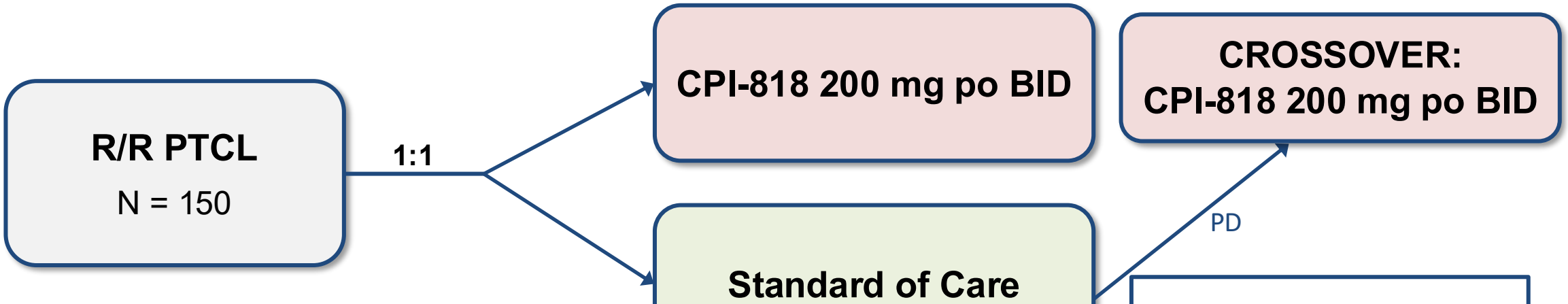

Eligibility

- >1 and ≤3 prior therapies
- PTCL-NOS, ALCL, AITL, FHTCL-NOS, or FHTCL-Follicular

Endpoints

- Primary: PFS
- Secondary:
  - ORR
  - OS
  - DOR

Emerging themes in T cell Lymphomas

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- Epigenetic targeting of Tfh
- Targeting dysregulated pathways: JAK/STAT, PI3K, EZH1/2
- Targeting cytotoxic, gamma-delta and NK subtypes
- Immunotherapy: checkpoint blockade and cellular

DR-01 Targets Cytotoxic Lymphomas (CTLs): Rare with High Unmet Need

CTLs

- Group of rare lymphoma subtypes (3%–6% of non-Hodgkin lymphoma)[1]
- Characterized by cytotoxic cells expressing CD94
- Few CTL patients are represented in randomized studies

Outcomes are poor

- Median overall survival (mOS) < 1 year in newly diagnosed HSTCL, EATL, and ENKTL patients[2]
- mOS of only ~3 months in R/R ENKTL[3]

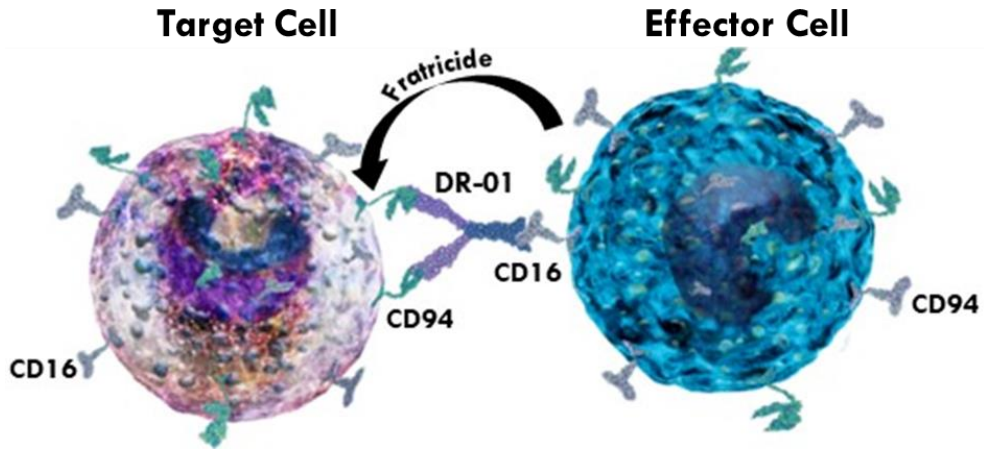
DR-01 (non-fucosylated antibody)

- Engages Fc-γ receptors, such as CD16a
- Triggers antibody-dependent cellular cytotoxicity (ADCC) by effector cells or fratricide, resulting in target cell depletion

Cytotoxic Lymphoma Histologies

ENKTL, nasal type	ET-CTCL
EATL	ANKL
MEITL	HVLPD
HSTCL	PTCL-NOS*
SPTCL	Cutaneous PTCL-NOS*
PCγδTCL	

**Selected patients with a cytotoxic phenotype*



[1]*Leukemia and Lymphoma Society 2024;* [2]*Vose et al. JCO 2008 ;* [3]*Bellei M et al. Haematologica 2018*

Promising Response Rate, including CRs, in CTL Patients During Dose Escalation in Majority of Histologies

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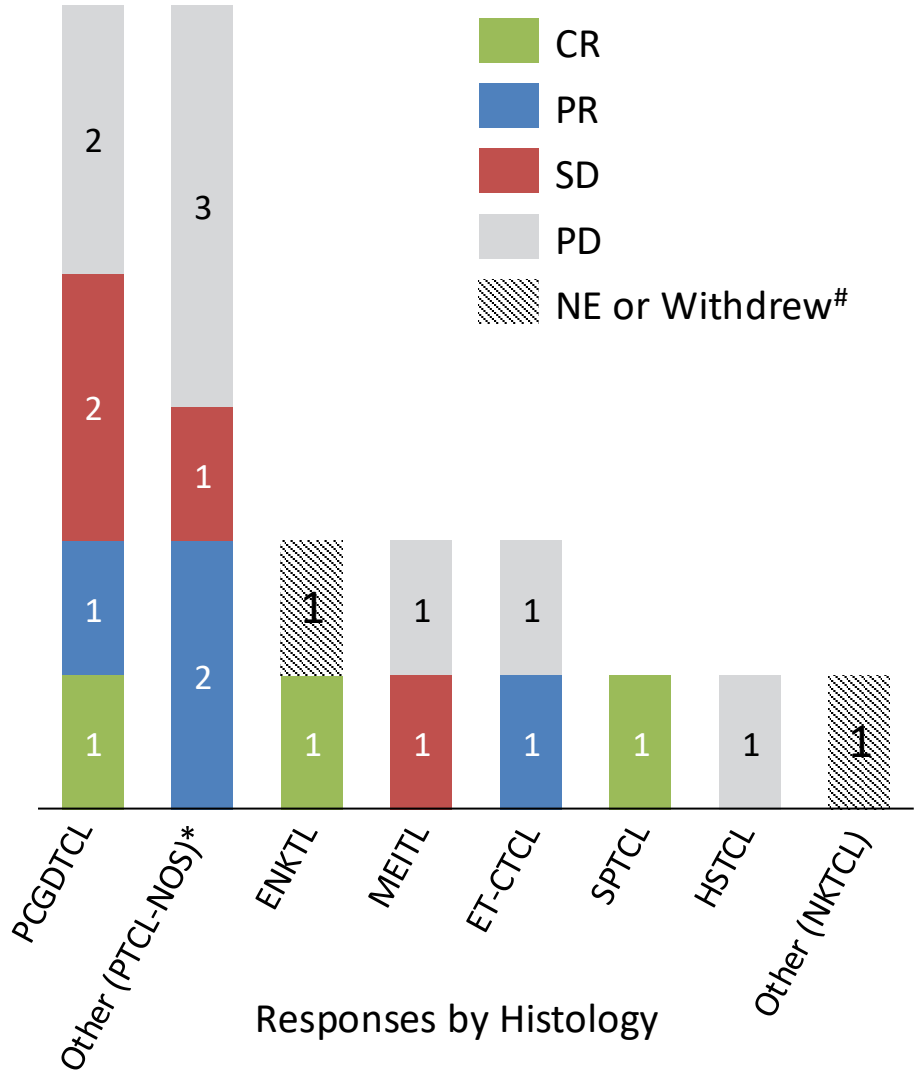
	Dose Level (mg/kg)					
	0.3 (N=1)	1 (N=6)	3 (N=4)	6 (N=5)	10 (N=3)	Total (N=19)#
ORR, n (%)	0	4 (67)	1 (25)	2 (40)	9	7 (37)
CR	0	3 (50)	0	0	0	3 (16)
PR	0	1 (17)	1 (25)	2 (40)	0	4 (21)
SD	0	0	1 (25)	2 (40)	1 (33)	4 (21)
PD	1 (100)	2 (33)	2 (50)	1 (20)	2 (67)	8 (42)

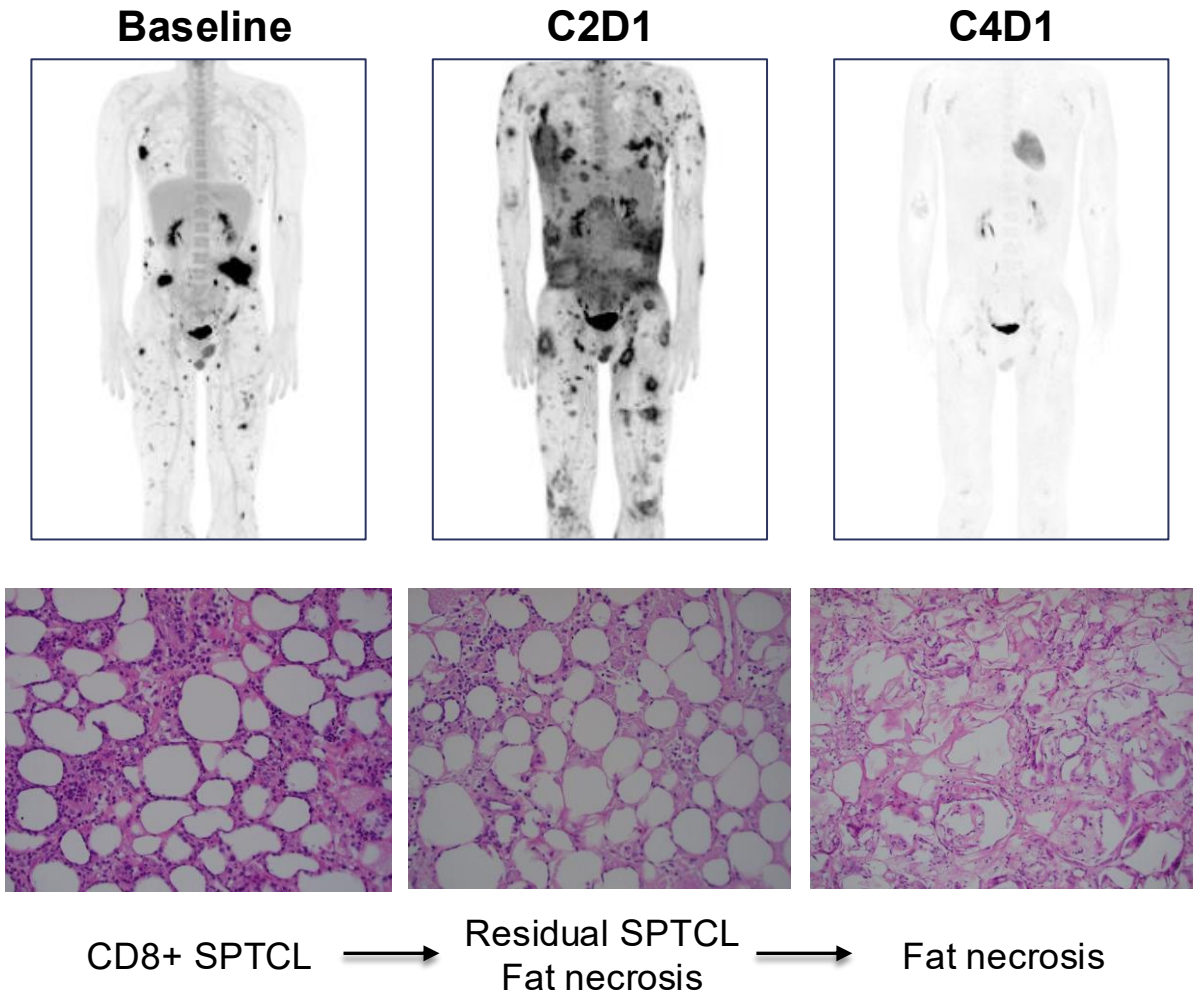


One unrelated AE withdrawal and one PI withdrawal without assessment
*Includes cutaneous subtypes

Zain J, Iyer S et al. Abstract 980: DR-01 in R/R Cytotoxic Lymphomas

Case Study: R/R Subcutaneous Panniculitis-like TCL

- 24-year-old M with stage IV SPTCL who received 3 prior lines of therapy (corticosteroids, romidepsin, and cyclosporine)
- At C2D1 response assessment:
  - PET scan showed increased FDG-avid lesions which was possibly related to inflammatory response
  - Biopsy of nodule showed residual SPTCL, some fat necrosis and decreased Ki-67
- At C4D1 response assessment:
  - Resolution of FDG-avid lesions
  - Achievement of CR



Images: courtesy of Dr. Christiane Querfeld (City of Hope)

Choosing the right targets: expression of CD markers on T lineage and mature T αβ cells

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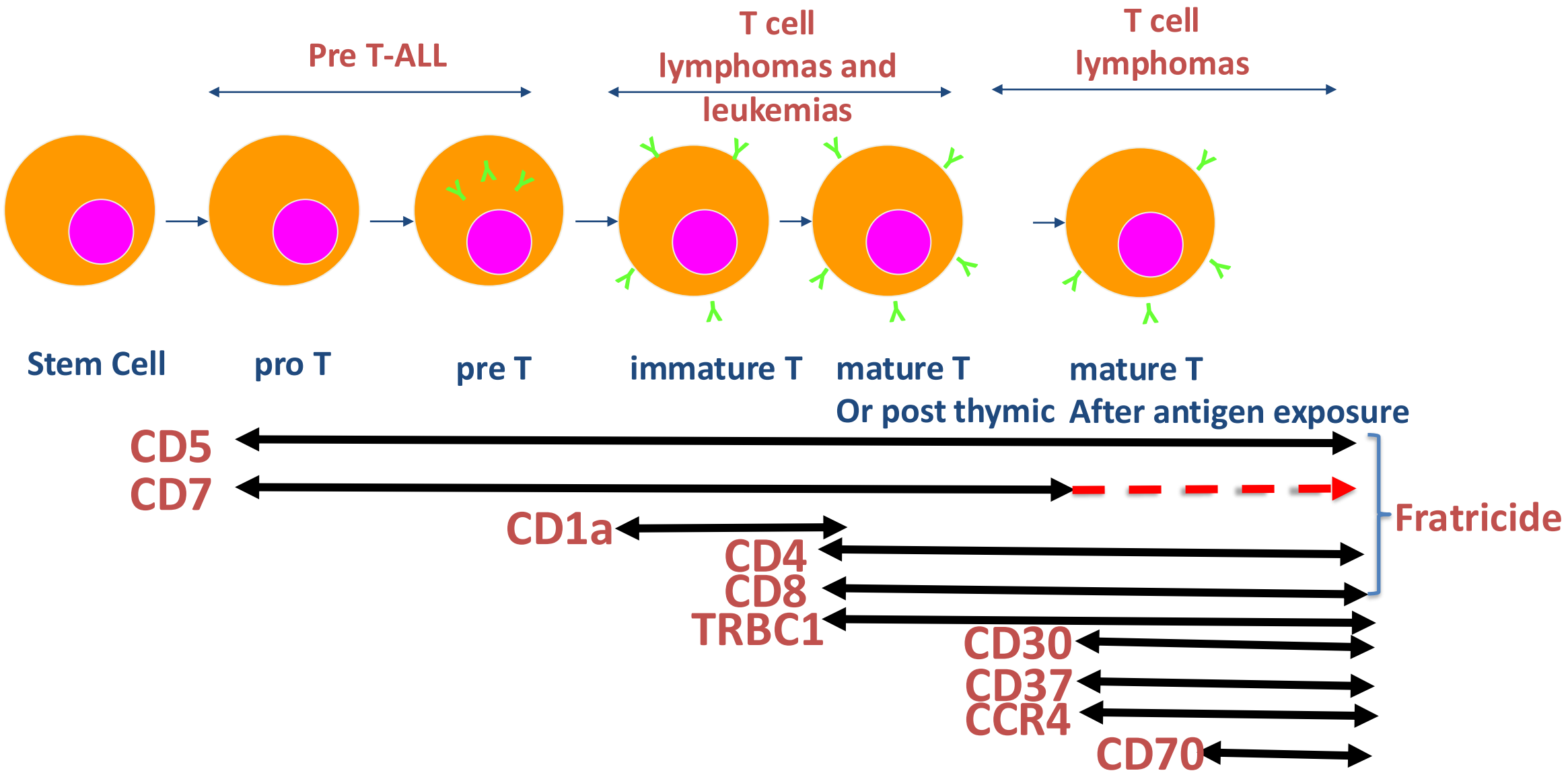

CTX130: An ”off the shelf” CAR-T Cell therapy for TCL

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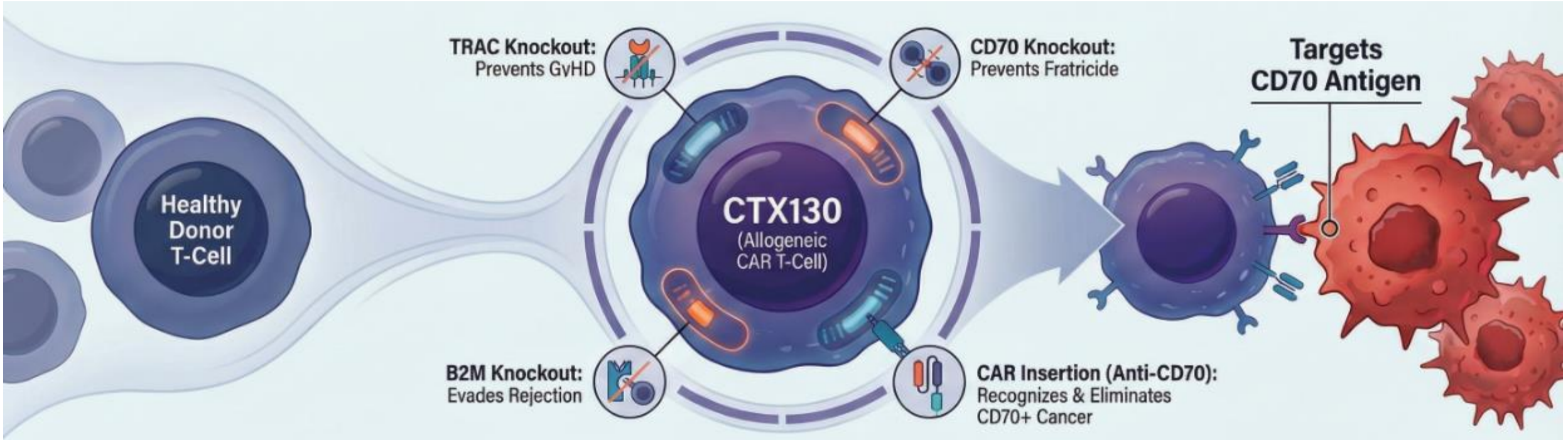


THE EVIDENCE: Preclinical & Clinical Results

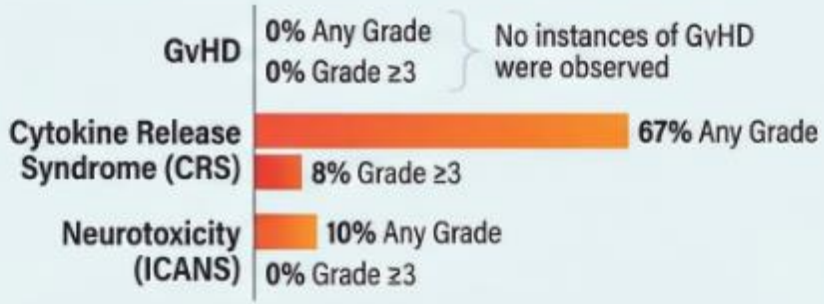
Preclinical Models

Complete Tumor Regression
(Xenograft Models)

Phase 1 COBALT-LYM Clinical Trial (N=39)

Objective Response Rate
in T-Cell Lymphoma Patients

Favorable and Manageable Safety Profile



MF/SS: Response trends

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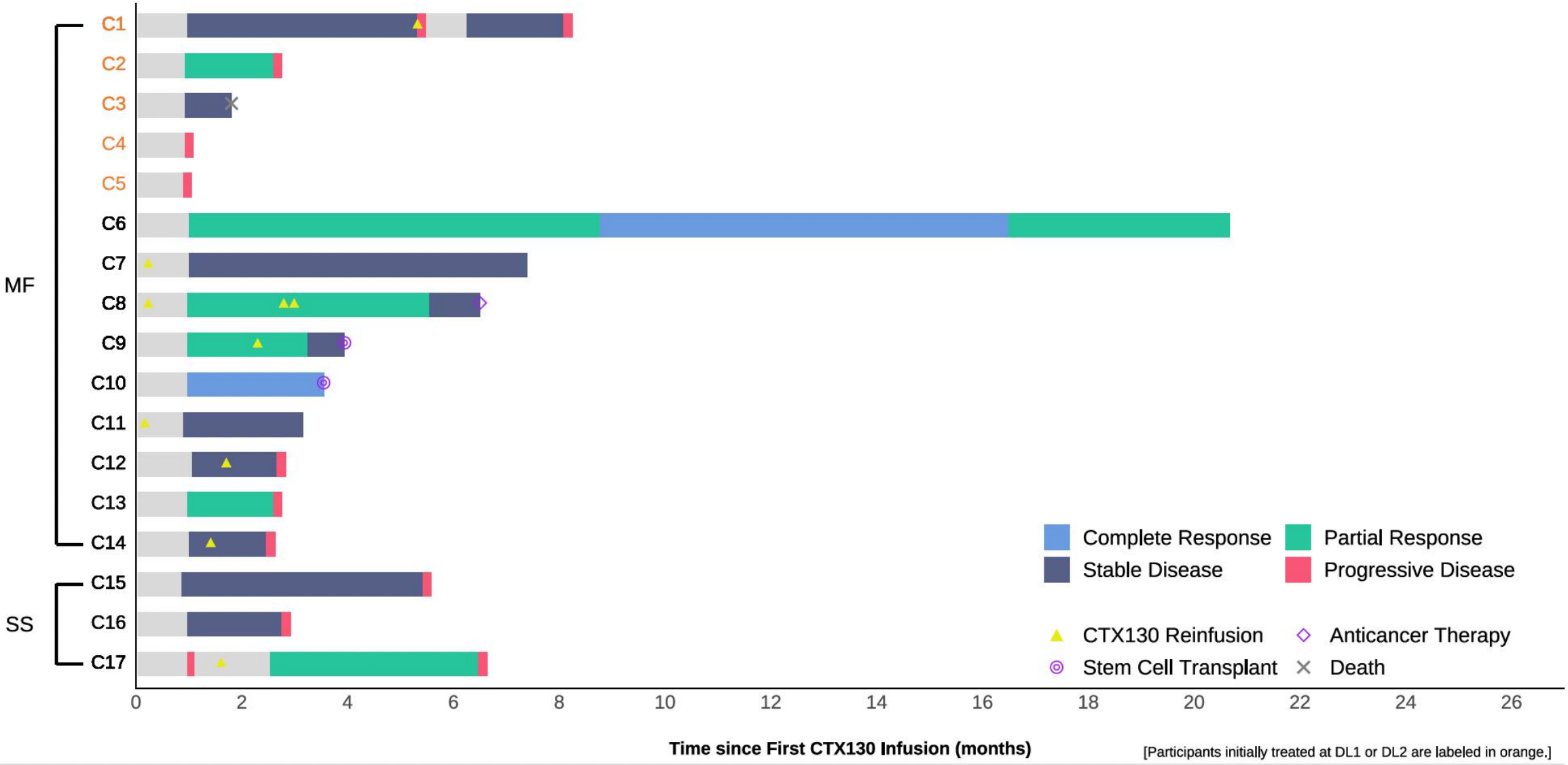
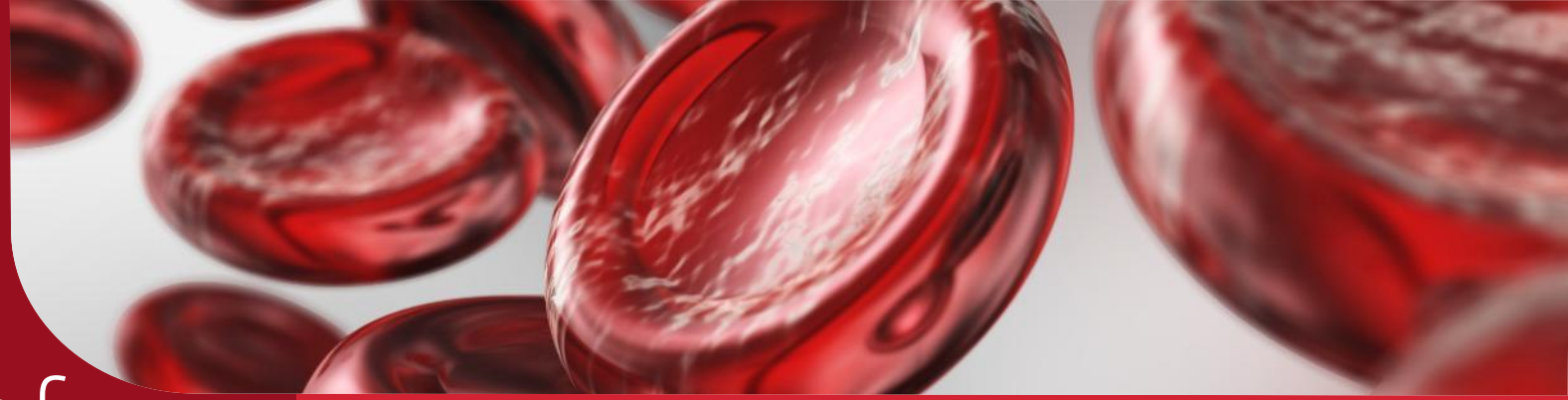


[Participants initially treated at DL1 or DL2 are labeled in orange.]

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Interim analysis of safety and efficacy in a Phase 2 study of MB-105, a CD5.CAR-T therapy for patients with relapsed/refractory T cell lymphoma

8 December 2025 | **Swaminathan Iyer**
Salvia Jain, Aaron Goodman, Julie Vose, Eric Mou, LaQuisa Hill, Steven Horwitz, Natalie Grover, Anne Beaven, Aleksandr Lazaryan, Malcolm Brenner, Sarah Hein, Federica Giordano, Eric Smith, Robert Michel, Ah-Reum Jeong, Michael Tees, Andy Chen, Shashank Cingam, Maksim Mamonkin, Alice Bexon

MB-105 evades fratricide without additional engineering

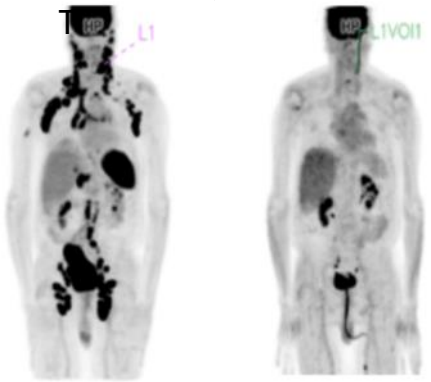
CD5 protein is internalized and degraded in optimized CD5.CAR-T cells

CD5 expression in T cell lymphoma

- CD5 is a surface receptor expressed in T cells
- Expressed in ~70% of peripheral and cutaneous TCL
- Highly expressed in PTCL-NOS and TFH-like lymphomas
- Expression retained in relapsed/refractory disease

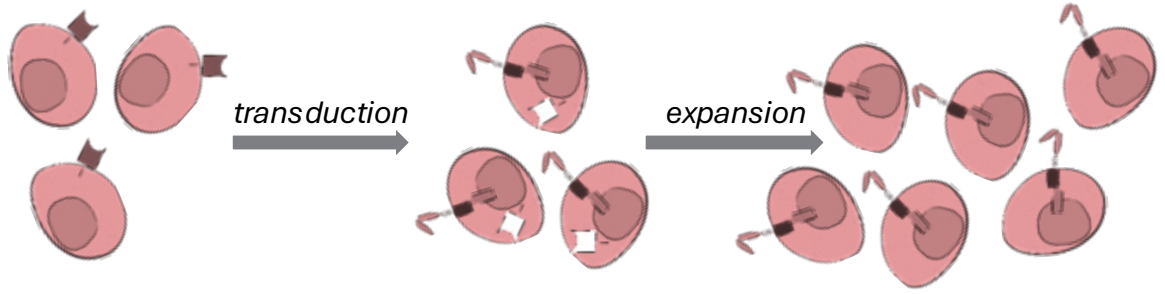
Phase 1 trial Responses in TCL

Pre-CD5 CAR T ➡ CR at 4 weeks



CR in 4/11 patients
2/4 CR patients alive >6 years

Self degradation of CD5 reduces cost and complexity of MB-105 CAR-T production



Selected T cells

Internalization and degradation of CD5

Robust expansion of CAR-T cells without fratricide

Hill, L. C., et al. (2023). Blood. https://doi.org/10.1182/blood.2023022204 | Mamonkin et al. Blood (2015) | Ma et al. Cell Reports Medicine (2024)

Demographics and baseline characteristics

Characteristic, n (%)	Treated patients (n=7)
Age (years)	
Median (range)	70 (60-76)
Sex female	3 (43)
Race	
White	5 (71)
Black	1 (14)
Other	1 (14)
Karnofsky 90-100	5 (71)
Karnofsky 70-80	2 (29)
Type of lymphoma	
PTCL	5 (71)
PTCL-NOS	3 (43)
AITL	2 (29)
CTCL (all MF)	2 (29)

Lymphoma history, CD5 expression and prior treatments

Characteristic: median (range)*	Treated patients (n=7)
Baseline CD5 expression	
Percent CD5	98 (15-100)
H-score	286 (43-300)
$CD5_{low}$ n (%)	1 (14)
Months since diagnosis	43 (13-109)
NCCN-IPI at initial diagnosis (PTCL)	2 (1-4)
TNMB at initial diagnosis (CTCL)	T2N0M0B0-1
Months since last relapse	4 (1-19)
Prior lines of systemic therapy	3 (2-7)
Prior transplants, n (%)	5 (71)
Autologous	4 (45)
Allogeneic	1 (18)
Baseline LDH	243 (172-267)

* Unless otherwise stated

Treatment-emergent adverse events in >1 patient

Hematologic TEAEs (n=7)		
Preferred Term n (%)	Grade 3-4	All
Anaemia	3 (43)	5 (71)
Neutropenia	2 (29)	4 (57)
Neutrophil count decreased	3 (43)	3 (43)
Thrombocytopenia	3 (43)	3 (43)
Platelet count decreased	1 (14)	2 (29)
Blood creatinine increased	0	2 (29)
Hypokalaemia	0	3 (43)

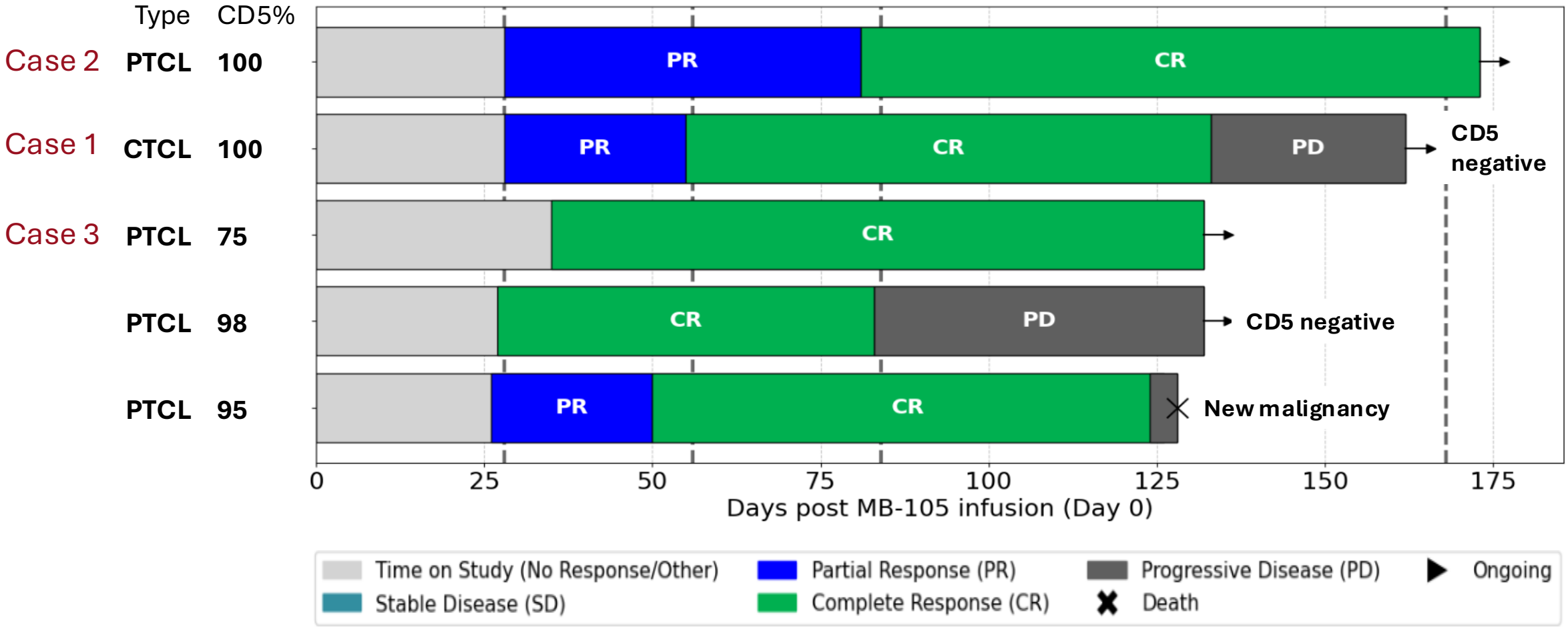
Non-hematologic TEAEs (n=7)		
Preferred Term n (%)	Grade 3-4	All
Cytokine release syndrome	**0**	**4 (57)**
Fatigue	0	4 (57)
Dizziness	0	3 (43)
Hypotension	2 (29)	3 (43)
Pyrexia	0	3 (43)
Deep vein thrombosis	2 (29)	3 (43)
Oedema peripheral	0	2 (29)
Constipation	0	2 (29)
Dehydration	0	2 (29)
Dry mouth	0	2 (29)
Febrile neutropenia	2 (29)	2 (29)
Polyomavirus viraemia	0	2 (29)
Pruritus	0	2 (29)

All MB-105-related treatment emergent AEs

Preferred Term n (%)	Treated patients (n=7)				
	G1	G2	G3	G4	All
Cytokine release syndrome	4 (57)	-	-	-	4 (57)
Diffuse large B-cell lymphoma	-	-	-	-	1 (14)*
Neutrophil count decreased	-	-	1 (14)	-	1 (14)
Epstein-Barr virus	-	1 (14)	-	-	1 (14)
Fatigue	-	1 (14)	-	-	1 (14)
Headache	-	1 (14)	-	-	1 (14)
Rash	-	1 (14)	-	-	1 (14)
Arthritis (hand)	1 (14)	-	-	-	1 (14)

*Death due to DLBCL on study day 128

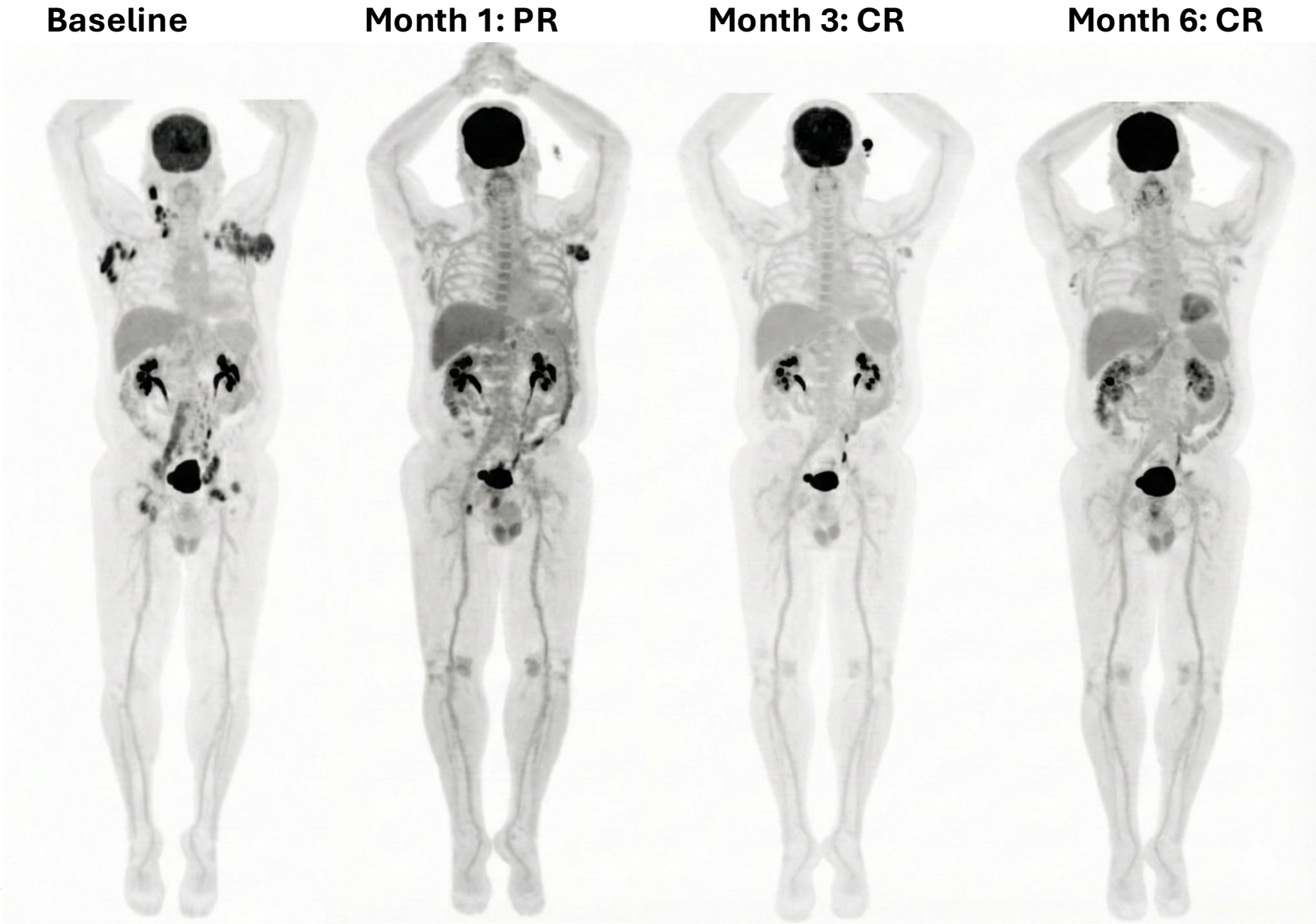
Efficacy: swimmer plot



Includes evaluable patients who received the full dose of 50 million MB-105 cells (data cut 14Nov2025)
Two patients are excluded from the efficacy population (1 underdosed, 1 had baseline CD5 expression <50%); both best response PD

Case 2 – 60 y.o. male, PTCL - NOS

- NCCN IPI score 1
- B-symptoms (fever)
- 26 months since diagnosis
- 5 prior regimens, including allo-SCT

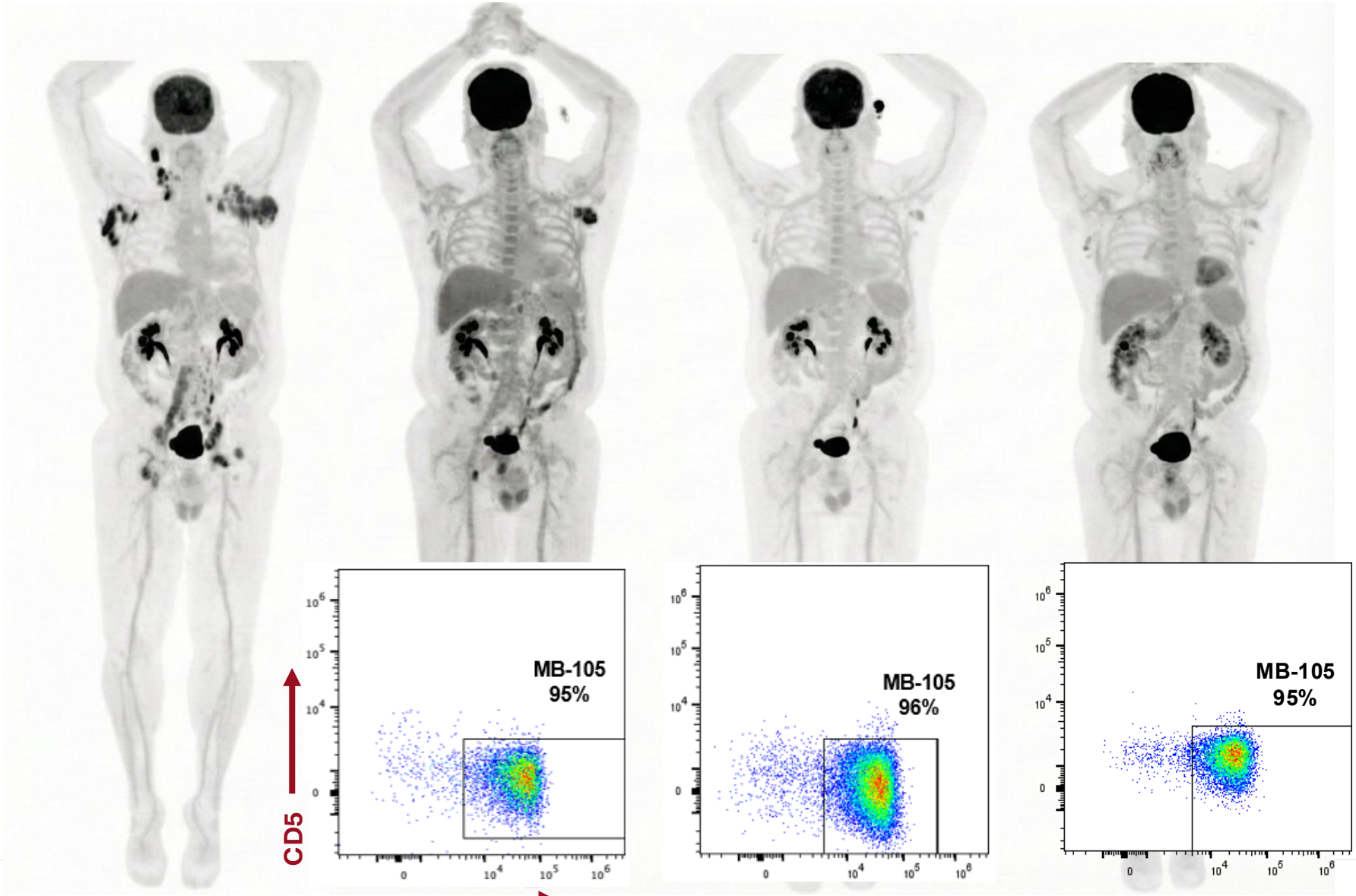


Data cut 14 Nov 2025

Case 2 – 60 y.o. male, PTCL - NOS

- NCCN IPI score 1
- B-symptoms (fever)
- 26 months since diagnosis
- 5 prior regimens, including allo-SCT

Baseline **Month 1: PR** **Month 3: CR** **Month 6: CR**



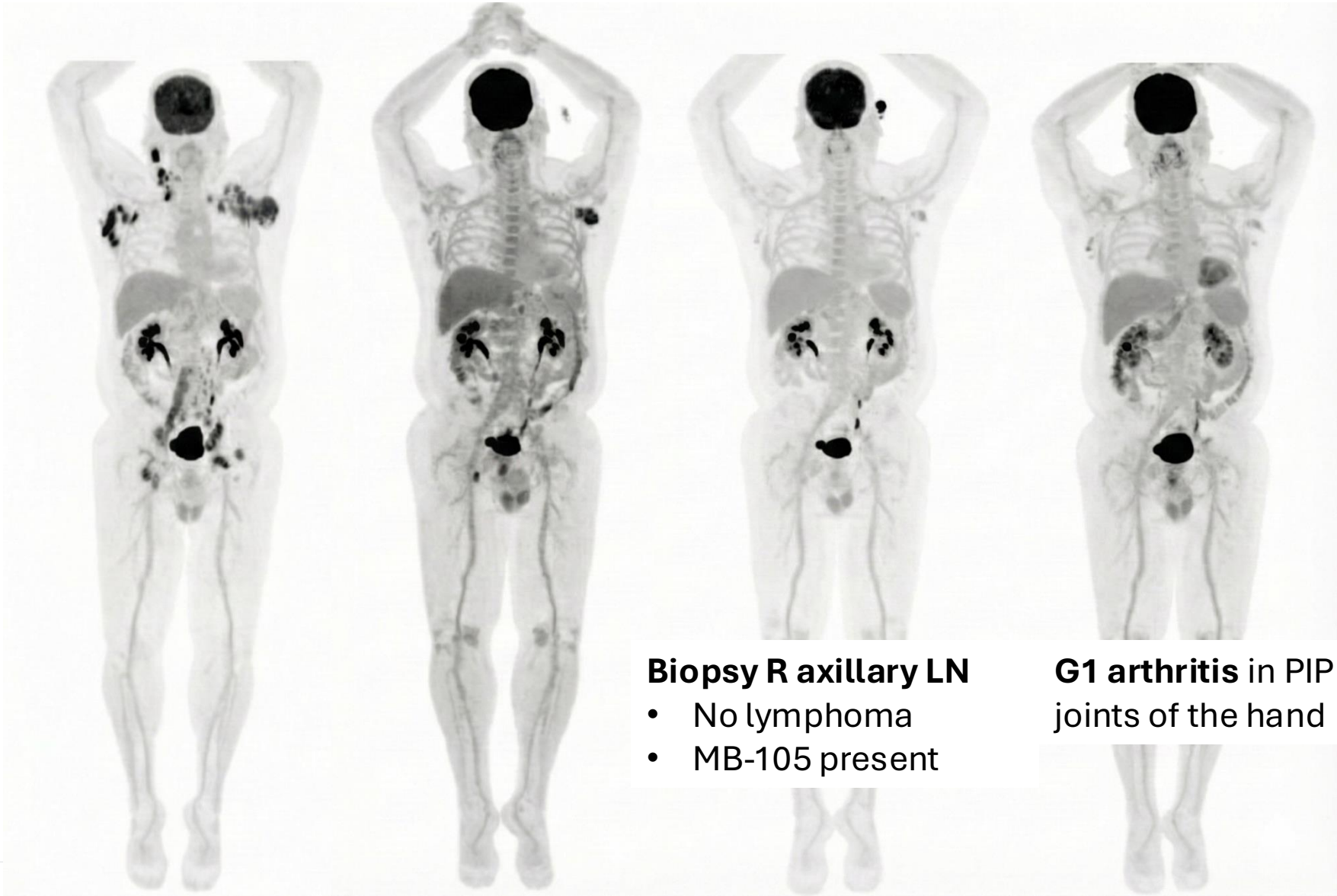
MB-105 Flow

Data cut 14 Nov 2025

Case 2 – 60 y.o. male, PTCL - NOS

- NCCN IPI score 1
- B-symptoms (fever)
- 26 months since diagnosis
- 5 prior regimens, including allo-SCT

Baseline | **Month 1: PR** | **Month 3: CR** | **Month 6: CR**



Biopsy R axillary LN
- No lymphoma
- MB-105 present

G1 arthritis in PIP joints of the hand

Data cut 14 Nov 2025

Cytokine Storm

ORAL
ASH 2024

ELA026 TARGETING OF SIRP(+) IMMUNE CELLS RESULTS IN A HIGH RESPONSE RATE AND IMPROVED 2-MONTH SURVIVAL OF TREATMENT-NAÏVE MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A PHASE 1 STUDY

Abhishek Maiti, Naval Daver, William Johnson, Gaurav Goyal, Catherine M Broome, Satyen Gohil, JAM van Laar, Francisco Javier Lopez Jimenez, David McCall, Hayley Lane, Benjamin Kim, Sandip Panicker, Gary Patou, Stephen Moore, Brian Mangal, Kelly Covert, Graham Parry, Kathy Dong, Kim-Hien Dao, Carl Allen, Swaminathan Iyer

(LB3442)

June 16, 2024
EHA2024 Hybrid Congress
Late-Breaking Oral Session
Abstract LB3442

ELA026 Is a First-In-Class, Clinical Stage mAb Targeting SIRPa/b/g

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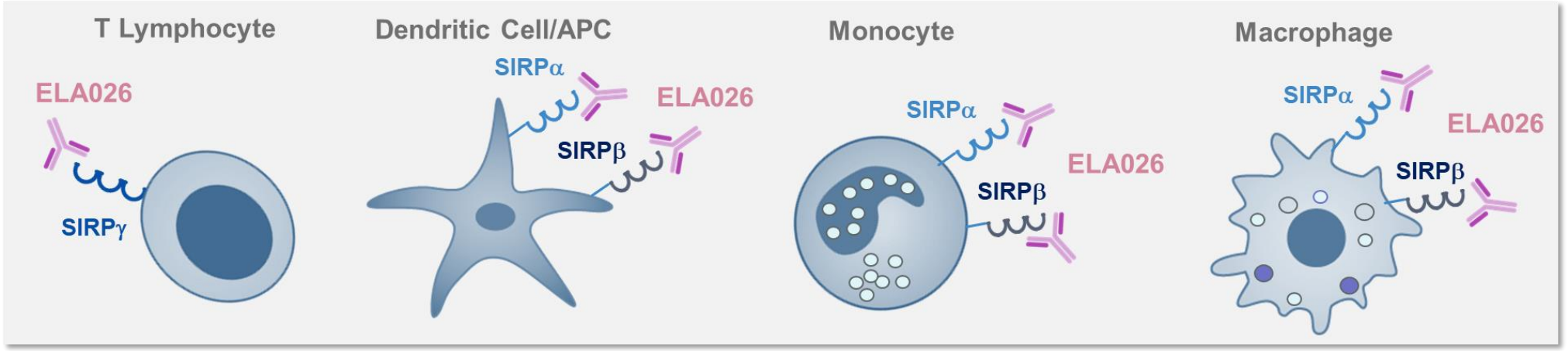
Hypothesis: Targeting depletion of multiple pathogenic immune cells may rapidly control the cytokine storm in sHLH

- ELA026 is a fully human IgG1 monoclonal antibody targeting SIRPα/β on myeloid cells and SIRPγ on T lymphocytes
- Mediates ADCC and ADCP *in vitro*, with potent depletion of myeloid cells and T lymphocytes demonstrated in non-human primates



Overall Study Response and Survival

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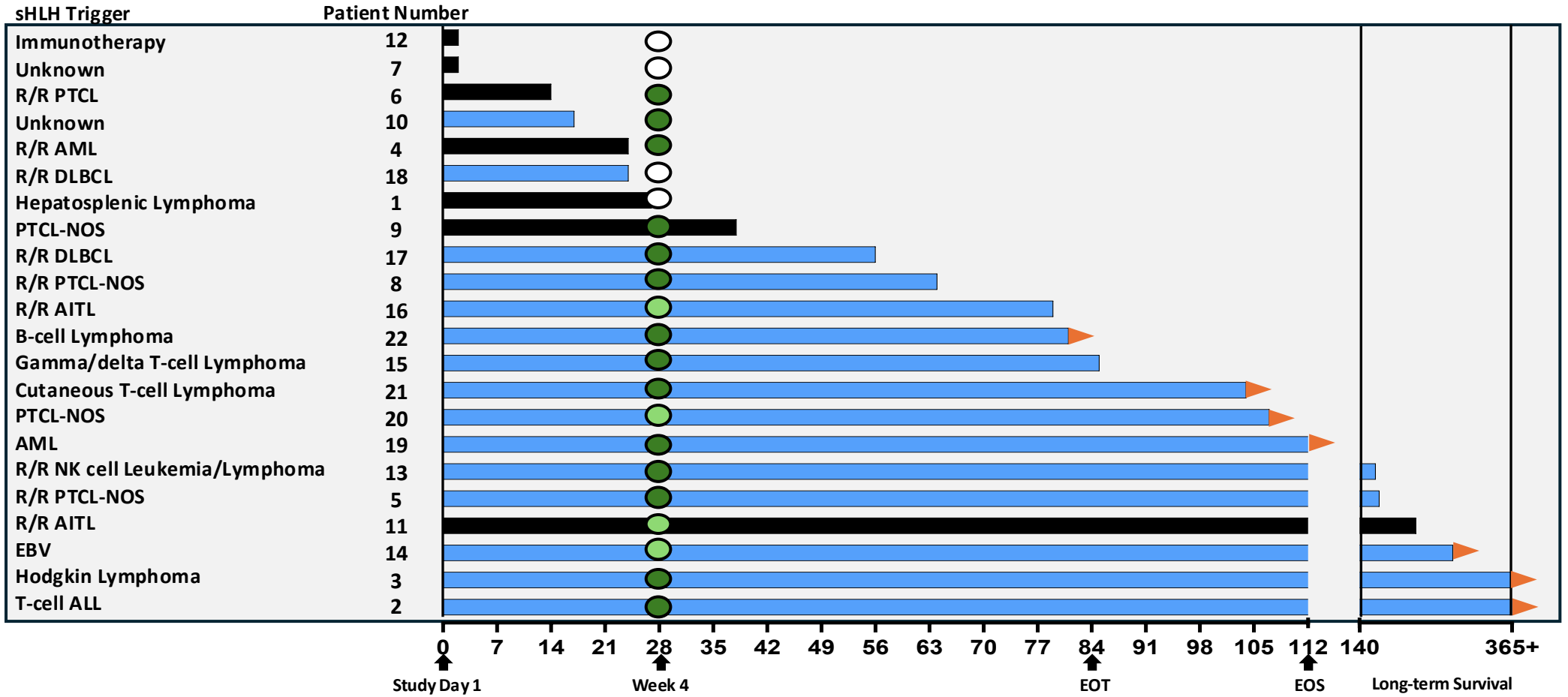

Beware of PFS threshold in r/r PTCL

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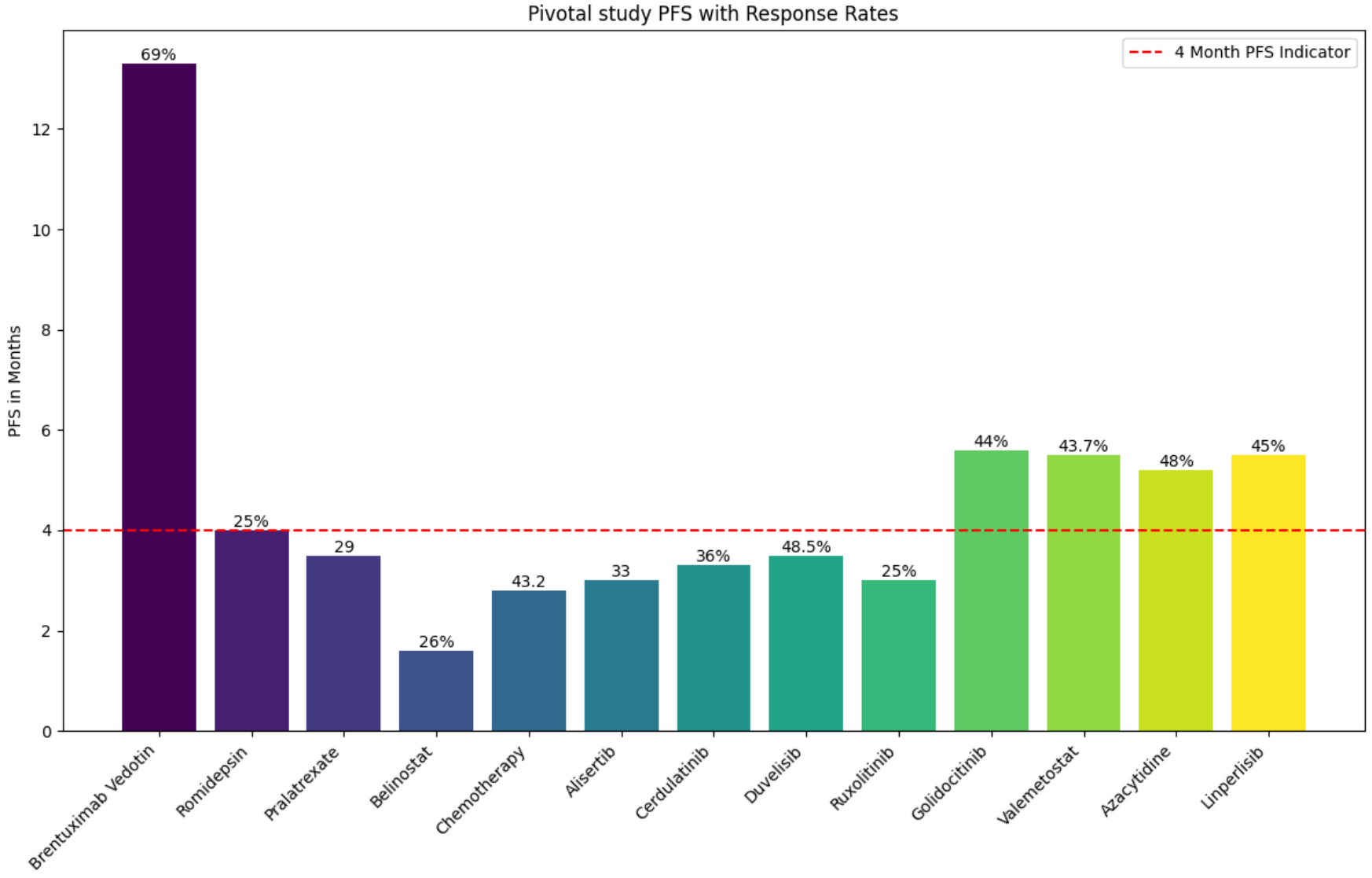

Iyer S- unpublished-Modified from pivotal studies

A modern paradox in R/R PTCL: short PFS, improving OS

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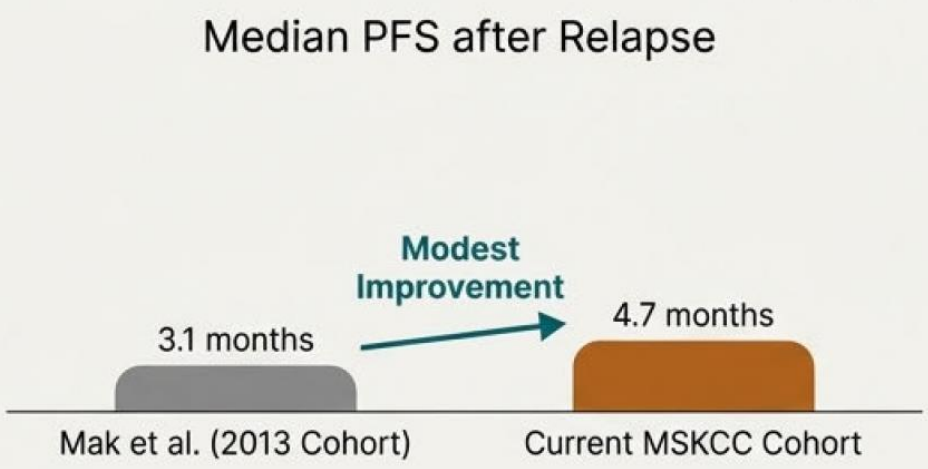
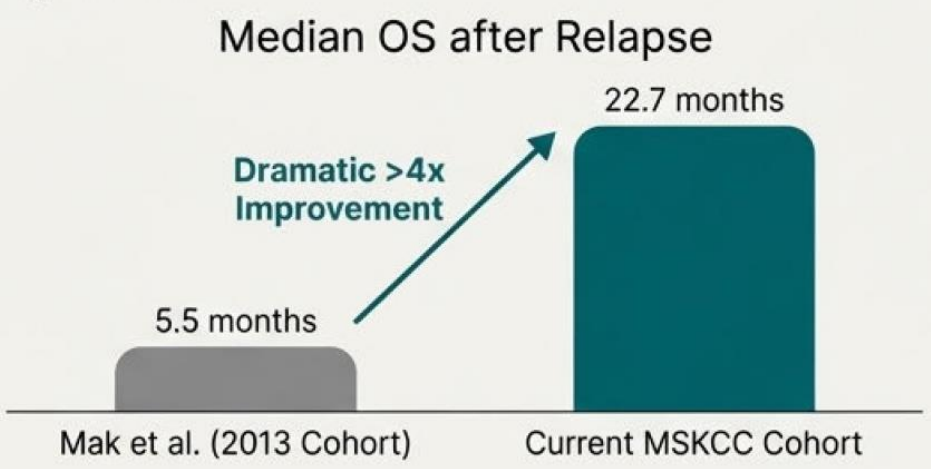
A large analysis of 2L therapy for R/R PTCL reveals a striking disconnect: while the PFS remains short, OS has improved dramatically

Study: Epstein-Peterson et al. | **N=212** R/R PTCL patients initiating 2L therapy (2012-2025) | 57% received novel agents.

Survival Metric Comparison





Interpretation of the Disconnect

- The modest PFS improvement suggests no single 2L therapy is a panacea.
- The dramatic OS improvement suggests the **availability of multiple, mechanistically diverse options** allows for effective sequencing.
- Increased use of consolidative allogeneic transplant also contributes.

Conclusions: Yes, we see the light

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- **Synthesis:** Recent therapeutic breakthroughs conclusively signify a turning poing in TCL
- **Core takeaway:**
  - We cannot fully abandon the generic chemo but must leverage precise epigenetic and pathway inhibitors.
  - Demand rigorous baseline diagnostic algorithms for the major subtypes

- Impact size of treatment: higher response rate (RR) generally has higher impact- intensification is reasonable
- Current paradigm of single agent approval followed by combination approaches
- For rare disease and promising drug- potential benefit is assumed to exist until proven otherwise
  - Preclinical and early phase studies are promising
  - However, aim for realistic PFS in front line and relapsed/refractory settings
  - Humbling lessons point to an incremental approach that can get drugs approved (eg in Lung Cancer)
  - Targeting disease subtypes
  - Naysayers and data pundits who don't treat patients
  - They analyze data and perform a watchdog function
  - We should be given the benefit of the doubt to get drugs approved
- ODAC meeting was reality check on FDA views
  - An exceptional case was made for PTCL approval
  - This is unlikely to happen again in PTCL or other diseases

T Cell Lymphoma Group

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Collaborators:

- Statisticians

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- Dr.Simrit Parmar
- Dr.Kumar Pappa
- Dr.Pavan Bachireddy

Thank you very much!

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Bloodbytes @DrSwami_Iyer