
Lymphoma · Leukemia
& Myeloma Congress
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New York City
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Peripheral T-Cell Lymphoma in Practice: Improving Diagnostic Accuracy and Therapeutic Decision-Making

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Disclosures

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Learning Objectives

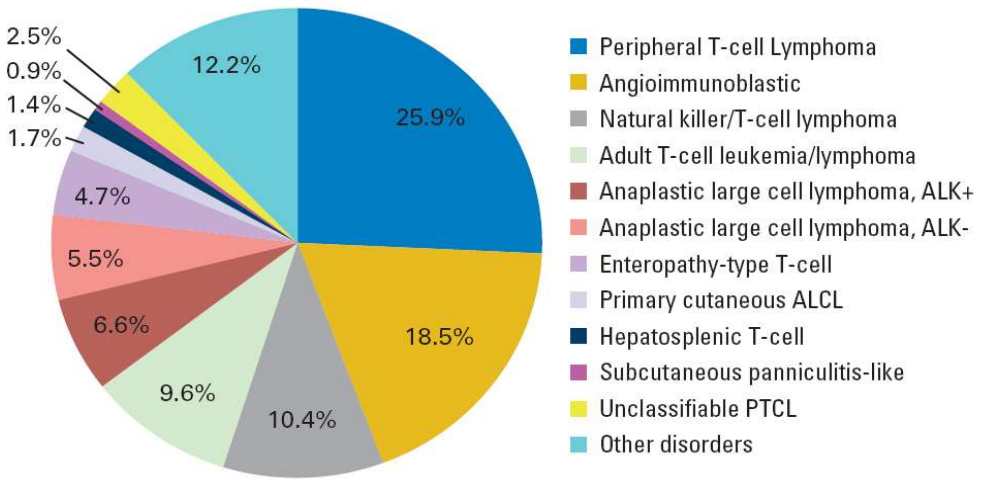
- Identify factors that contribute to delayed or inaccurate diagnosis of PTCL and describe strategies to improve recognition of key subtypes in clinical practice
- Evaluate clinical data supporting newer therapeutic strategies for the management of R/R PTCL across disease subtypes
- Summarize current evidence guiding treatment selection and sequencing R/R PTCL, including considerations related to tolerability and patient quality of life

PTCL = peripheral T-cell lymphoma; R/R = relapsed/refractory.

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Mature NK/T-Cell Lymphomas are Uncommon and Heterogenous

International T-Cell Study (1990-2002)



WHO 5th Edition 2022 update

Nodal

- PTCL, NOS
- Follicular helper T-cell lymphoma
  - *TFH, AITL type*
  - *TFH, follicular type*
  - *TFH, NOS*
- ALCL, *ALK+*
- ALCL, *ALK-*
- *Breast Implant-assoc ALCL*

Extranodal

- NK/T-cell, nasal type
- Enteropathy-associated TCL
- *Monomorphic epitheliotropic intestinal TCL*
- Hepatosplenic TCL

Disseminated

- *T-cell PLL*
- *T-cell LGL*
- *Chronic lymphoproliferative NK cells*
- *Aggressive NK-cell leukemia*
- *ATLL*
- *Systemic EBV+ TCL*

Cutaneous

- *Mycosis fungoides*
- *Sezary syndrome*
- *Primary cutaneous CD30+ LPD*
  - *Primary cutaneous ALCL*
  - *Lymphomatoid papulosis*
- *Subcutaneous panniculitis-like T-cell lymphoma*
- *Primary cutaneous gamma-delta T-cell*
- *Other*

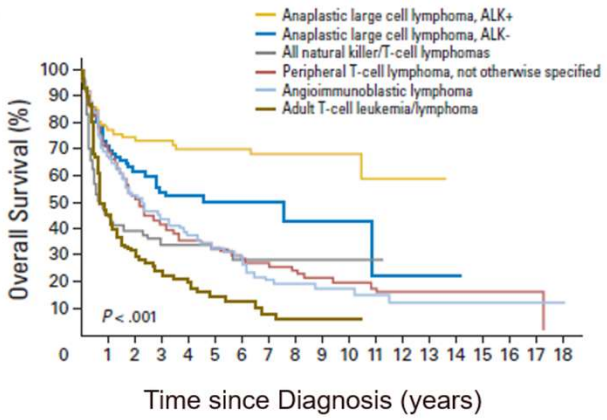
WHO = World Health Organization; ALCL = anaplastic large-cell lymphoma; NOS = not otherwise specified; PLL = prolymphocytic leukemia; LGL = large granular lymphocytic leukemia; ATLL = adult T-cell leukemia/lymphoma; EBV = Epstein-Barr virus; LPD = lymphoproliferative disorder.

Swerdlow SH, et al. *Blood*. 2016;127(20):2375-2390. Vose J, et al. *J Clin Oncol*. 2008;26(25):4124-4130. Alaggio R, et al. *Leukemia*. 2022;36(7):1720-1748.

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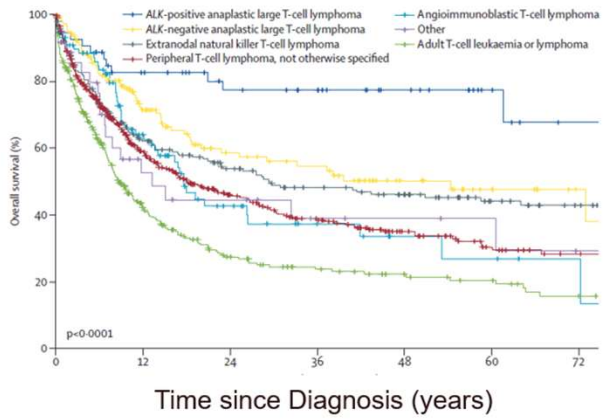
Unmet Need: PTCL Has Poor Outcomes in Most Subtypes

International T-cell Study (Retrospective, 1990-2002)



5-yr OS non-ALCL: ~30%

Latin America T-cell Cohort (Retrospective, 2000-2023)

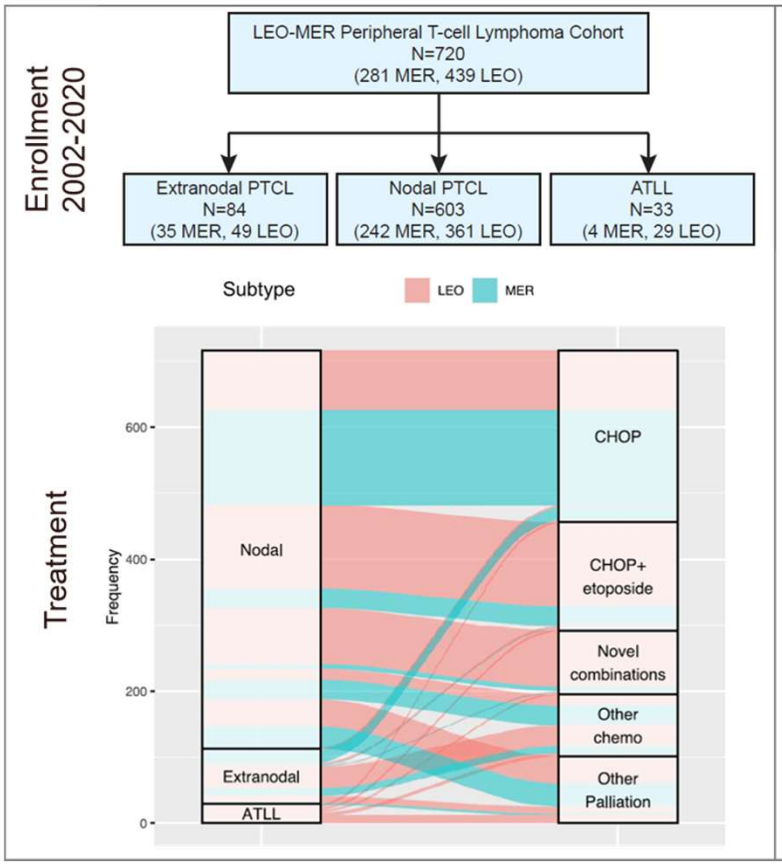


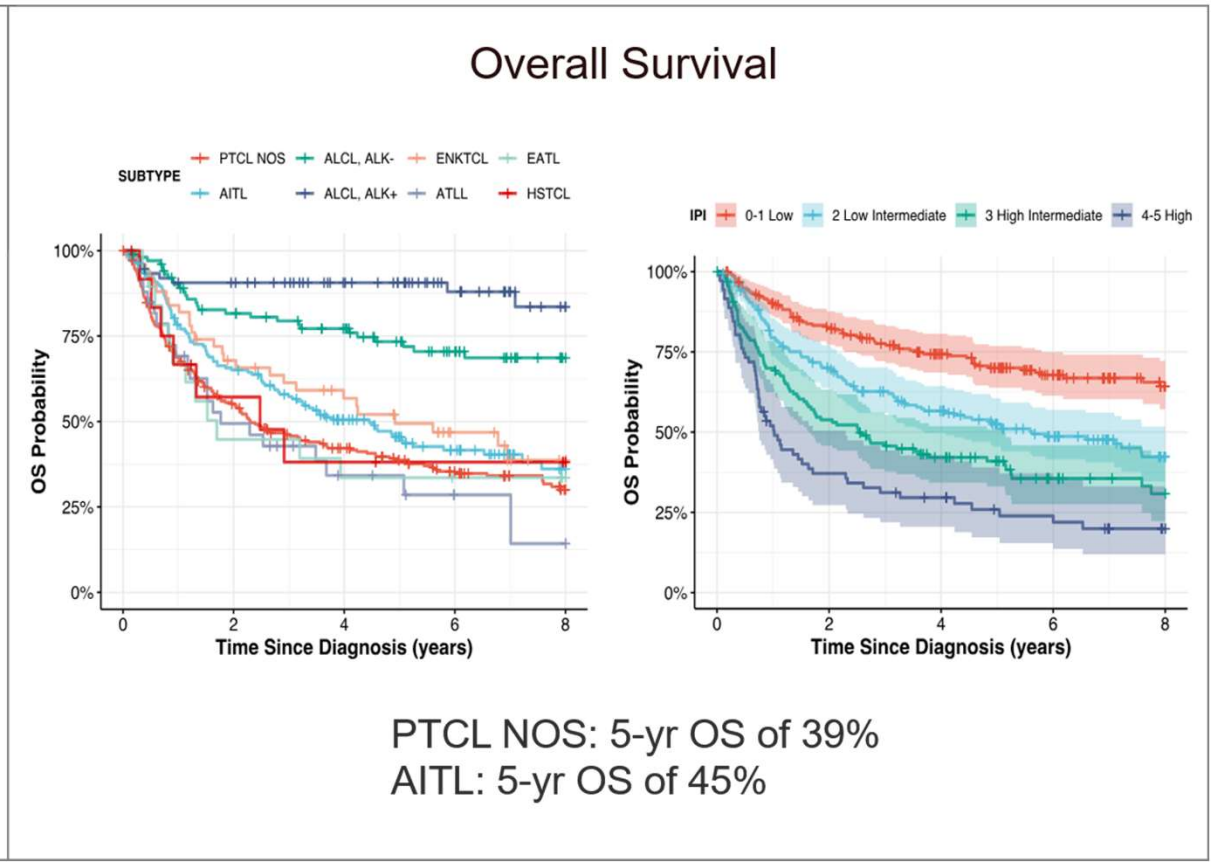
PTCL NOS: 3-yr OS of 39%
AITL: 3-yr OS of 37%

OS = overall survival; AITL = angioimmunoblastic T-cell lymphoma.
Vose J, et al. *J Clin Oncol*. 2008;26(25):4124-4130. Malpica L, et al. *Lancet Haematol*. 2025;12(4):e258-e268.

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The LEO-MER Prospective Cohort Study: Contemporary Benchmark for PTCL





LEO = Lymphoma Epidemiology of Outcomes; MER = Molecular Epidemiology Resource; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone.

Ruan J, et al. *Blood Adv*. 2026;10(10):3480-3493

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PTCL: First-Line CHOP vs CHOEP Is Inadequate for Most Subtypes

CHOP
- ORR 60-80+%, CR 30-40+%
- Durable remissions <20-30%
  - Stratification based on IPI/subtype

Study	N	Outcomes	Ref
DSHNHL (1993-2007)	320 total 144 age≤60	3-yr EFS CHOEP vs CHOP: *ALK+: 91.2% vs 57.1%, p=0.012* *ALK-: 60.7% vs 48.3%, p=0.057*	Schmitz 2010
Swedish registry (2000-2009)	499 total 252 age≤70	PFS CHOEP vs CHOP: HR, 0.84; *p*=0.424; age≤70 HR, 0.49; *p*=0.008; age≤60	Ellin 2014
Netherlands Cancer Registry (1989-2018)	1427 <65	5-yr OS CHOEP vs CHOP: ALK+: 90% vs 61%, p<0.01	Brink 2022

CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; ORR = objective response rate; IPI = International Prognostic Index; EFS = event-free survival.
Schmitz N, et al. *Blood*. 2010;116(18):3418-3425. Ellin F, et al. *Blood*. 2014;124(10):1570-1577. Brink M, et al. *Blood*. 2022;140(9):1009-1019.

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PTCL: Consolidative Autologous Stem Cell Transplant

Study	Phase (N)	ORR	CR	PFS	OS
Reimer et al CHOP	II (83)	66%	56%	3-yr @36%	3-yr @48% (71% vs 11%)
D'Amore et al CHOEP / CHOP	II (160)	82%	50%	5-yr @44%	5-yr @51%
Corradini et al MACOP-B or HDS	II (62)	72%	56%	12-yr @30%	12-yr @34%
CIBMTR Smith et al	40	N/R	N/R	3-yr @58%	3-yr @70%
Swedish registry Ellin et al	128	60%	36%	5-yr @41%	5-yr @48%
Netherlands registry Brink et al	128	N/R	N/R	N/R	5-yr @78%

MACOP-B = methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; HDS = high-dose sequential therapy; CIBMTR = Center for International Blood and Marrow Transplant Research; CR = complete response; PFS = progression-free survival.

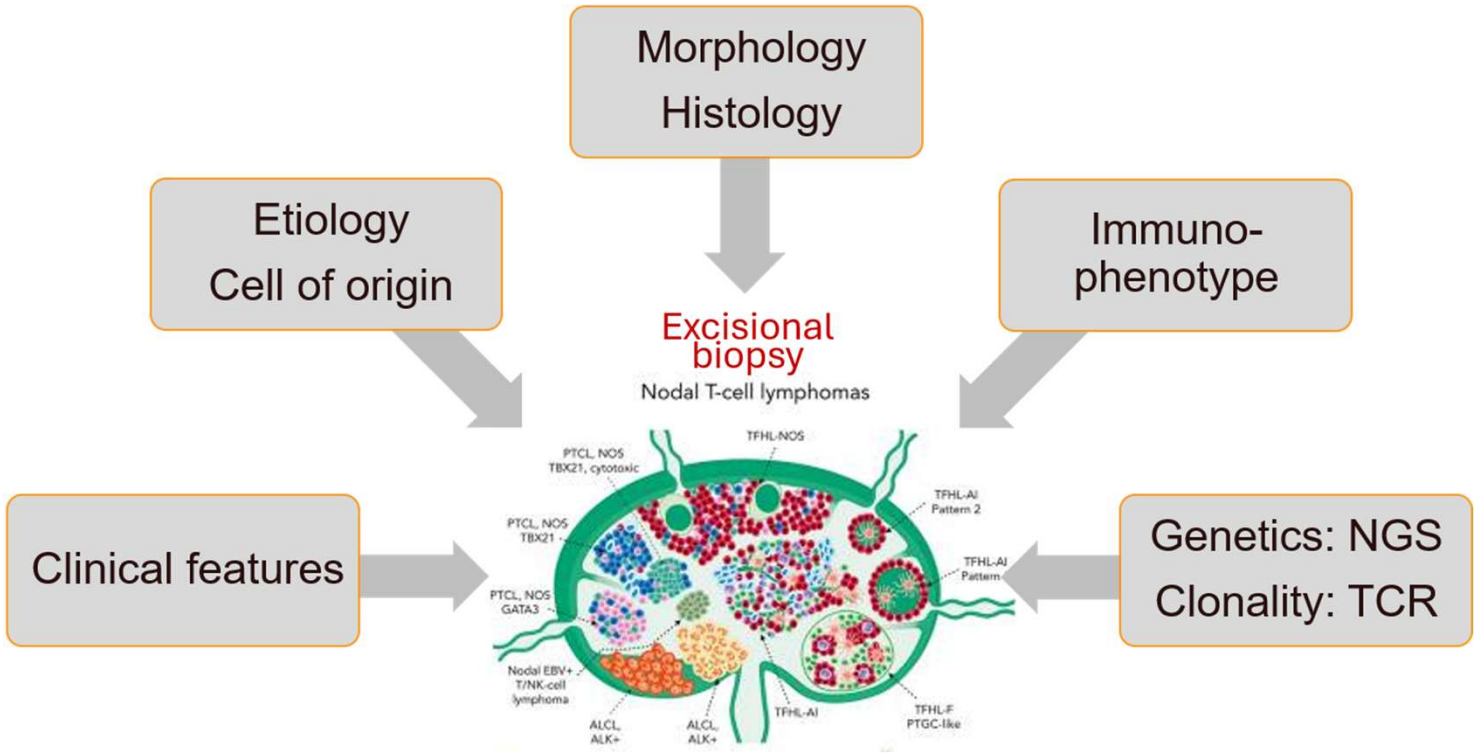
Reimer P, et al. *J Clin Oncol*. 2009;27:106-113. D'Amore F, et al. *J Clin Oncol*. 2012;30:3093-3099. Corradini P, et al. *Leukemia*. 2006;20(9):1533-1538. Smith SM, et al. *J Clin Oncol*. 2013;31(25):3100-3109. Abramson JS, et al. *Ann Oncol*. 2014;25(11):2211-2217. Ellin F, et al. *Blood*. 2014;124(10):1570-1577. Brink M, et al. *Blood*. 2022;140(9):1009-1019.

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Recent advances in the genomic and molecular characterization of PTCL have translated into significant updates in the 2022 classifications of lymphomas for diagnosis and treatment planning.

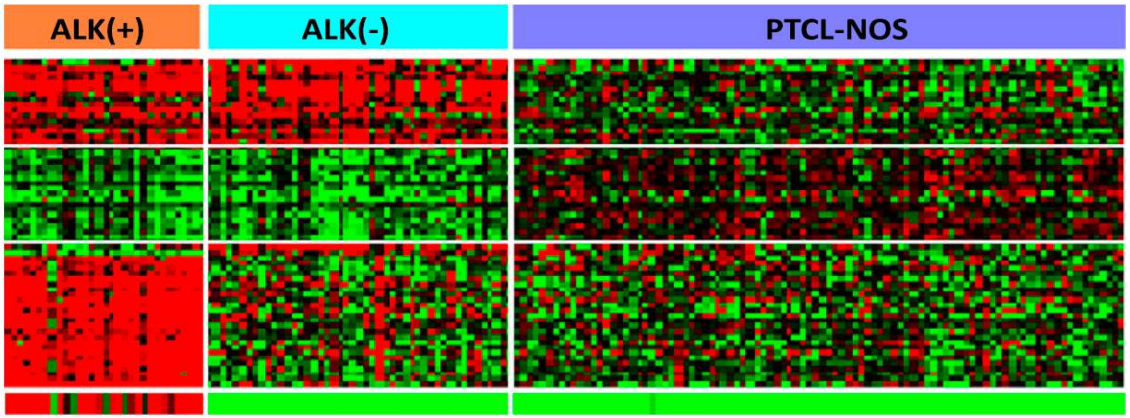
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Improving Diagnostic Accuracy in PTCL

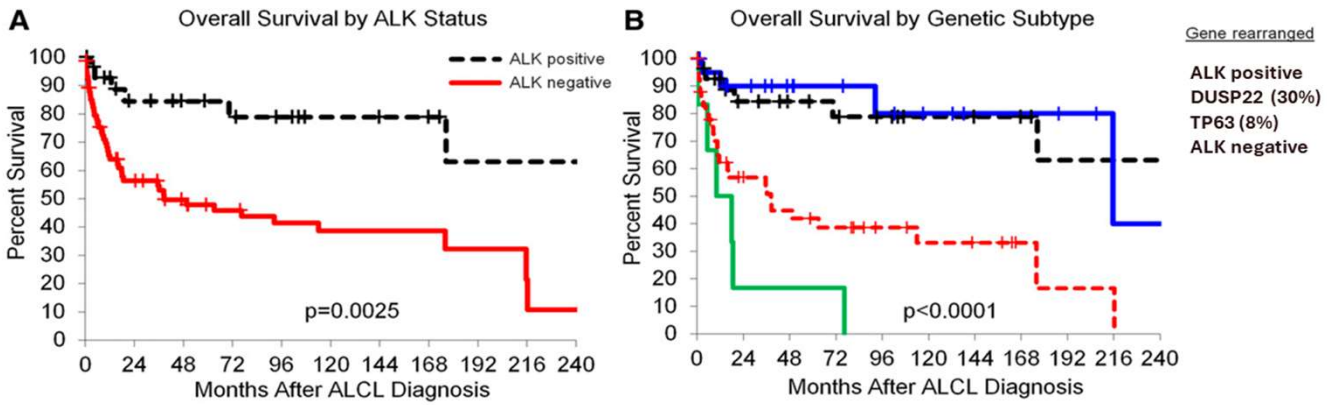


Adapted from de Leval L, et al. *Blood*. 2024;144(18):1855-1872

Molecular Subgroups of PTCL: ALCL



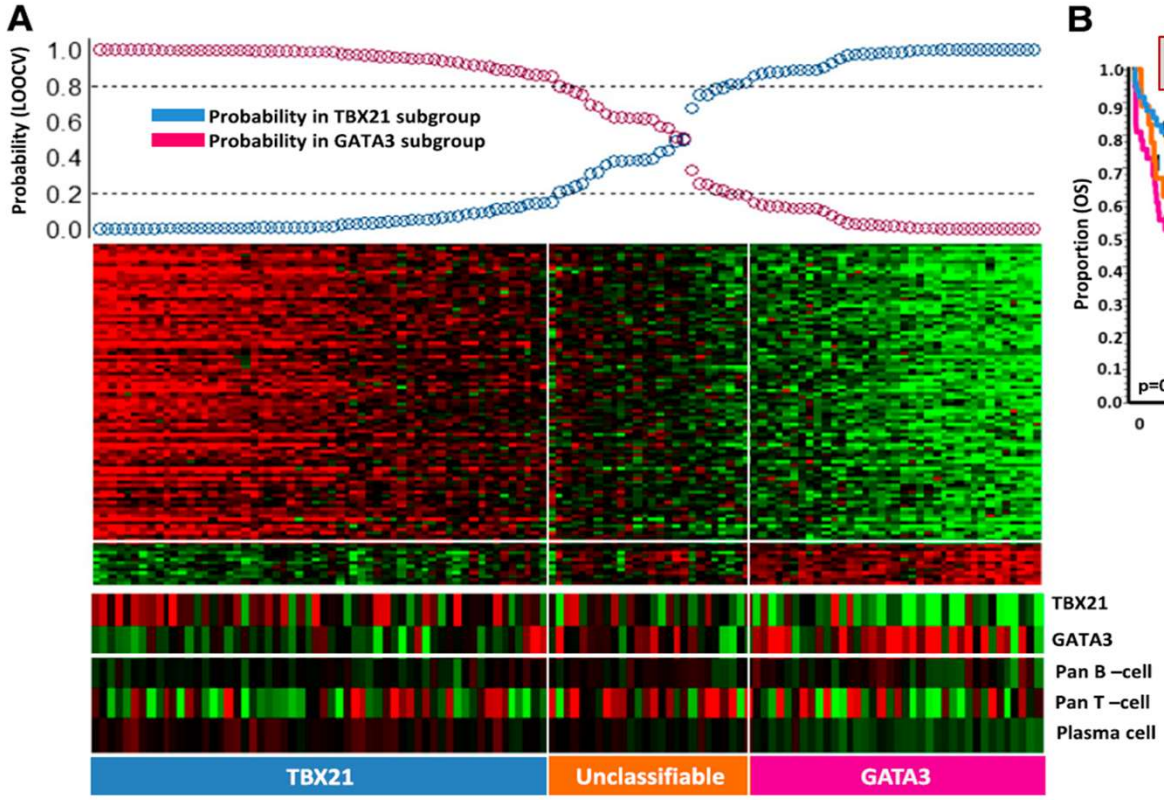
- Uniform CD30+
- JAK/STAT activation
- DUSP22/IRF4
- TP63

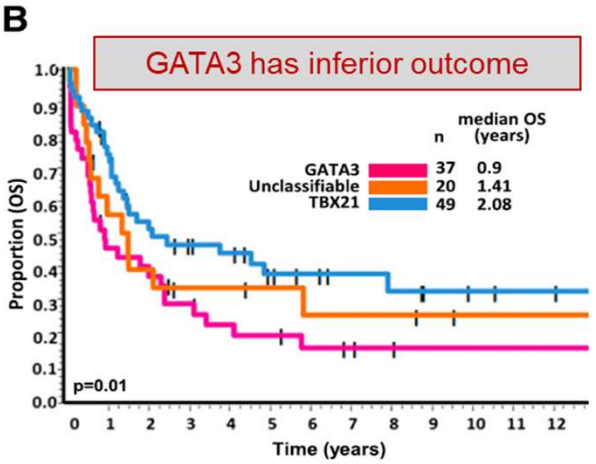


Parrilla Castellar ER, et al. *Blood*. 2014;124(9):1473-1480. Iqbal J, et al. *Blood*. 2014;123(19):2915-2923. Qiu L, et al. *Haematologica*. 2023;108(6):1604-1615.

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Molecular Subgroups of PTCL: PTCL-NOS





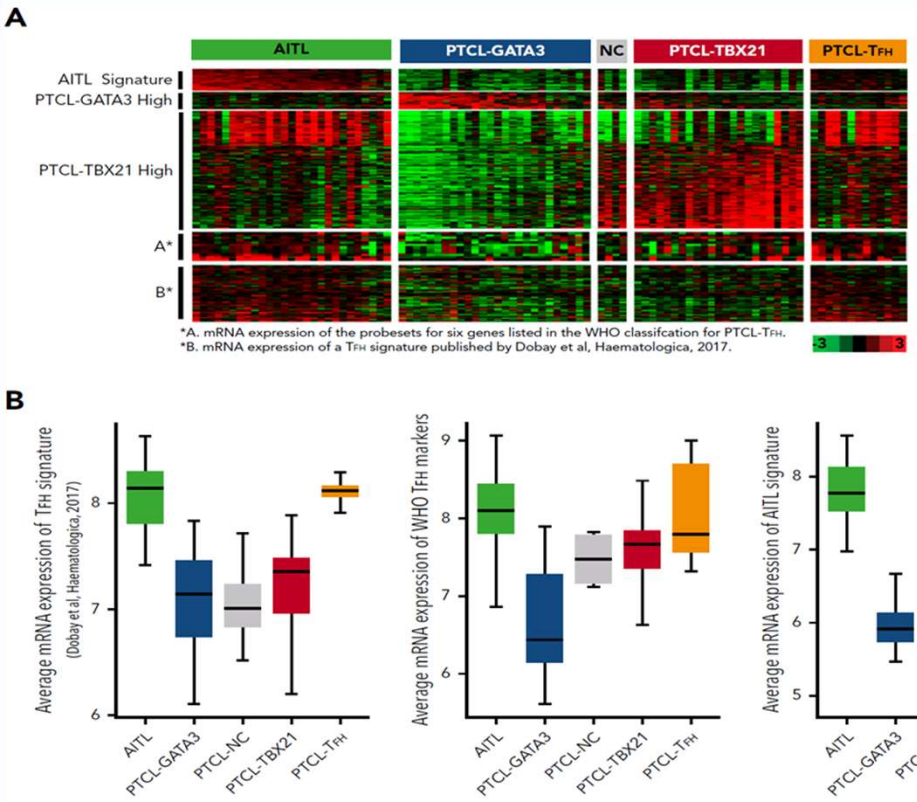
- GATA3: TH2 signature, greater genomic complexity, loss of tumor suppressor genes.
- TBX21: TH1 signature, targeting cytotoxic effectors, enriched in epigenetic regulators.

LOOCV = leave-one-out cross-validation.
Iqbal J, et al. *Blood*. 2014;123(19):2915-2923

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Molecular Subgroups of PTCL: PTCL-TFH

TFH-PTCLs have recurrent mutations in epigenetic modifiers



Epigenetics drivers

- *TET2 (80%)*
- *DNMT3A (25%)*
- *IDH2 (25%)*

Other gene(s)

- *RHOA*

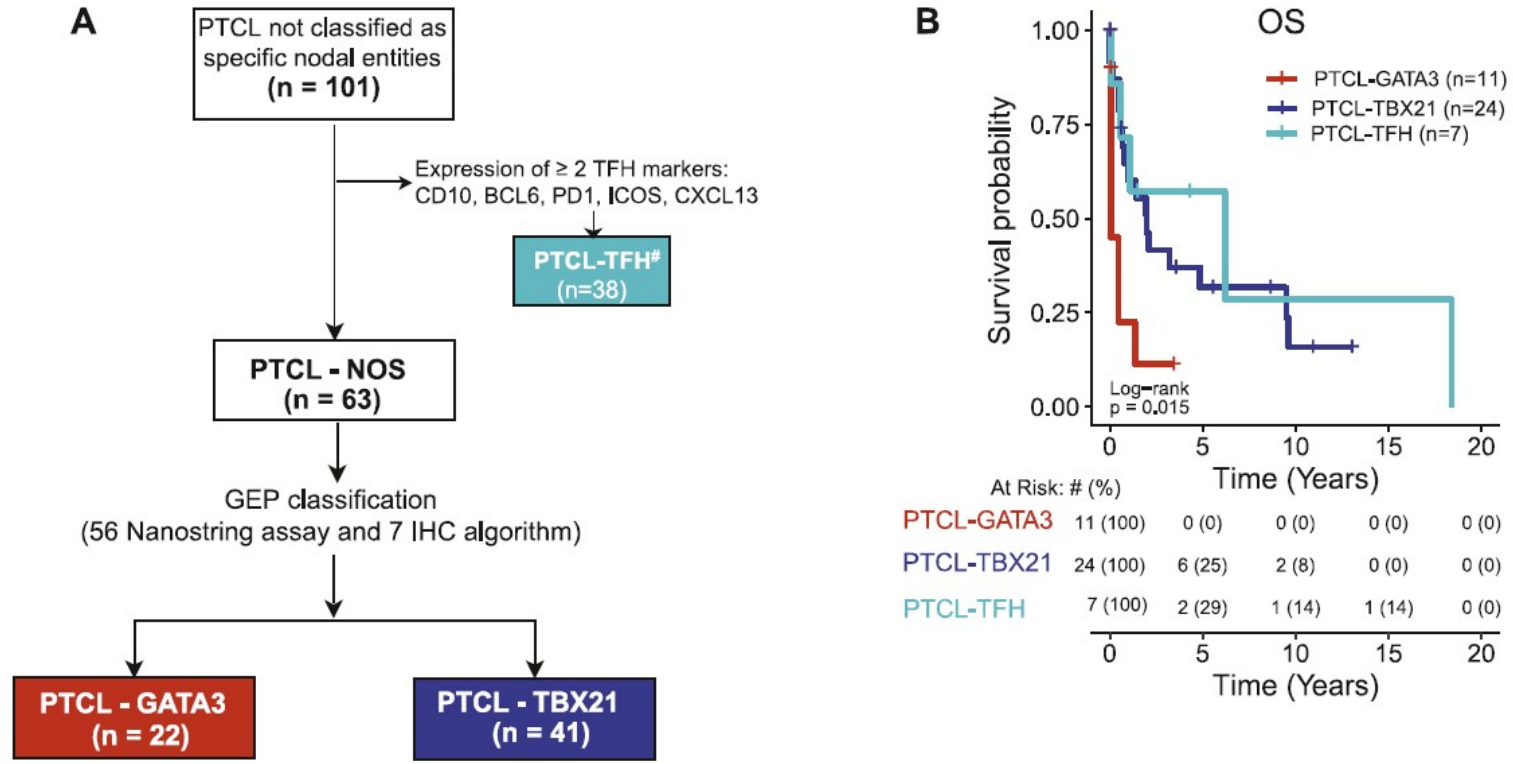
TFH-related genes (IHC)

- *PD1*
- *CD10*
- *BCL6,*
- *CXCL13*
- *ICOS*
- *SAP*
- *CCR5*

TFH = T-follicular helper; IHC = immunohistochemistry.
Heavican TB, et al. *Blood*. 2019;133(15):1664-1676.

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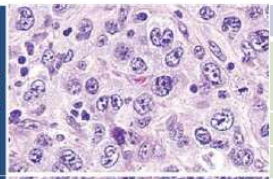
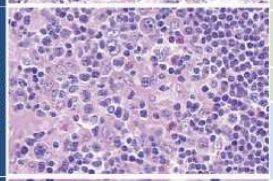
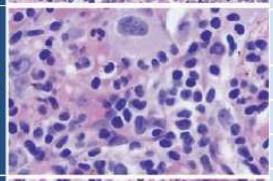
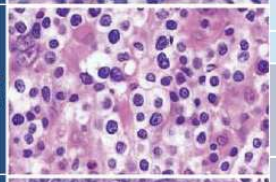
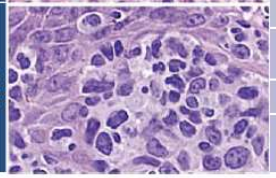
Differentiating Non-ALCL Subtypes: PTCL-NOS vs PTCL-TFH



GEP = gene expression profile.
Amador C, et al. *Mod Pathol*. 2025;38(2):100646

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Recurrent Genetic Mutations in PTCL with Therapeutic Potential

		NK and T-cell neoplasms	Genetic lesions	Mechanism	Potential therapeutic intervention	
ALCL		TFHL, PTCL NOS, CTCL, ATLL	*CD28 FYN CARD11 PLCG1 RHOA* mutations	TCR signaling activation	PI3K inhibitors (duvelisib, copanlisib), mTOR inhibitors (everolimus, temsirolimus), TKI (dasatinib), ITK inhibitor (CPI-818) (a,c)	TCR
		TFHL, CTCL, ATLL	*CD28* fusions	Increased CD28 signaling	CTLA4 blockade (ipilimumab) (*CTLA4::CD28*) (b, c)	
		TFHL, PTCL NOS	*FYN::TRAF3IP2*	NF-kappaB activation	IkB kinase inhibitors (c)	
PTCL-NOS		TFHL	*ITK::SYK*	SYK and JAK3/STAT5 activation	JAK3 inhibitor (tofacitinib), dual SYK and JAK inhibitor (cerdulatinib) (c)	
		ALK- ALCL, PTCL NOS, ATLL	*VAV1* fusions	VAV1 and RAC1 activation	RAC1 inhibitor (azathioprine) (c)	
T-LGLL		T-LGLL, NK-LGLL, T-PLL, MEITL, EATL, HSTL, ENKTCL, ALK- ALCL, BIA-ALCL, PTCL NOS	*JAK1 JAK2 JAK3 STAT3 STAT5B SOCS1* mutations	STAT3 phosphorylation	JAK inhibitors (ruxolitinib, tofacitinib, gandotinib, momelotinib), dual SYK and JAK inhibitor (cerdulatinib) (a, c)	JAK/STAT
		ALK- ALCL, BIA-ALCL, CD30+ PTCL NOS, ITLPD-GI	*JAK2* fusions	STAT5 phosphorylation		
		ALK+ ALCL	*ALK* fusions	STAT3 phosphorylation	ALK inhibitors (crizotinib, alectinib) (a)	
		ALK- ALCL	*FRK* fusions	STAT3 phosphorylation	Kinase inhibitor (dasatinib) (c)	
		PTCL NOS, TFHL-F	*ITK::FER*	STAT3 phosphorylation	JAK3 inhibitor (tofacitinib), kinase inhibitors (c)	
ATL		ALK- ALCL	*ROS1* fusions	STAT3 phosphorylation	ROS1 inhibitor (JNJ-ROS1i-A) (c)	
		ALK- ALCL	*TYK2* fusions	STAT1 phosphorylation	JAK inhibitors, TYK2 inhibitor (deucravacitinib) (c)	
		TFHL, PTCL NOS, CTCL, ATLL	*TET2 DNMT3A IDH2* mutations	DNA hypermethylation Oncometabolite production ($IDH2^{R172}$)	Hypomethylating agents (5-azacytidine, decitabine), histone deacetylase inhibitors (romidepsin, belinostat, chidamide, vorinostat); IDH2 inhibitors (enasidenib) (a, b)	Epigenetics
		MEITL, HSTL	*SETD2* mutations deletions	Loss of H3K36me3	Wee1 inhibitor (adavosertib) (c)	
ATLL		ENKTCL, ATLL	*CD274* CNA or SV	PD-L1 overexpression	Anti-PD1 antibodies (pembrolizumab, nivolumab) (b, c)	Others
		ATLL	*CCR4* mutations	Increased CCR4 expression	Anti-CCR4 antibody (mogamulizumab) (b)	
		ALK- ALCL	*ERBB4* fusions or truncated transcripts	ERBB4 overexpression	Inhibitors of ERBB-family kinases (lapatinib) (c)	

T-LGLL = T-cell large granular lymphocytic leukemia; CTCL = cutaneous T-cell lymphoma; MEITL = monomorphic epitheliotropic intestinal T cell lymphoma; EATL = enteropathy-associated T-cell lymphoma; HSTL = hepatosplenic T-cell lymphoma; ENKTCL = extranodal NK-/T-cell lymphoma; BIA = breast-implant associated; ITLPD-GI = indolent T-cell lymphoproliferative disorder of the gastro-intestinal tract; TFHL-F = follicular-type TFH lymphoma.

de Leval L, et al. *Blood*. 2022;140(21):2193-2227.

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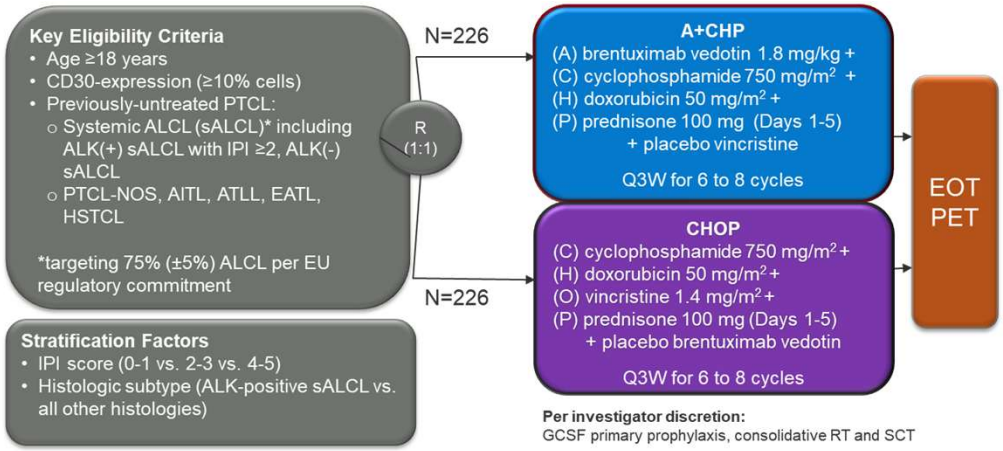
Biomarker-Driven Approach for PTCL

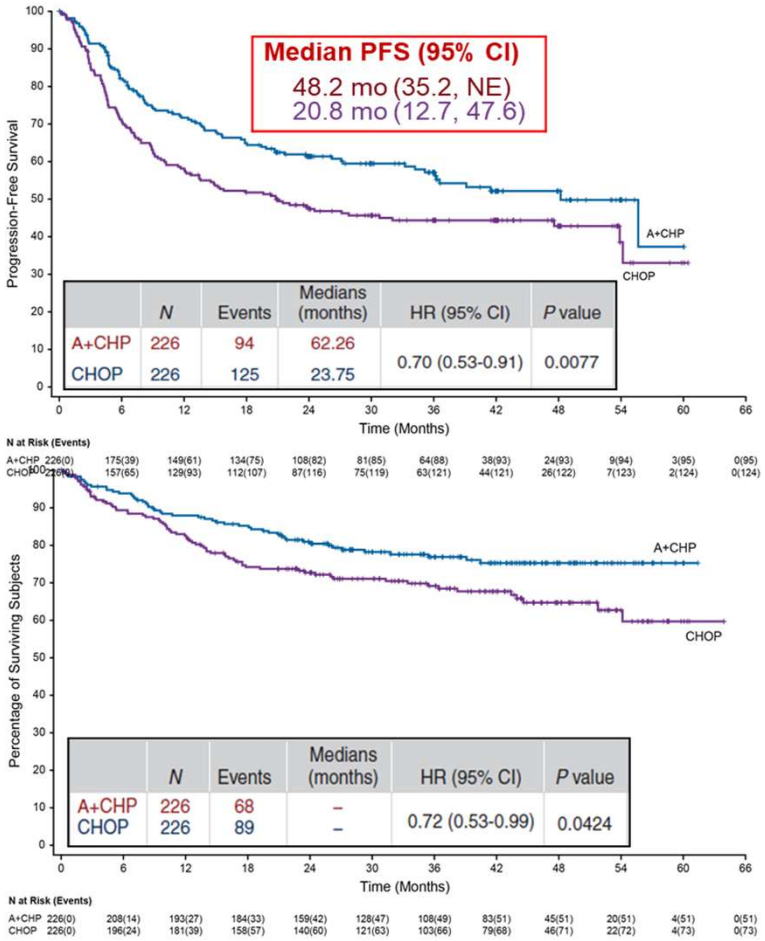
- Stratifying treatment based on diagnosis/prognosis
  - *Surface markers: eg, CD30*
  - *ALK-neg ALCL: e.g. DUSP22/IRF4, TP63*
  - *PTCL NOS: GATA3, TBX21, TCR signaling*
  - *PTCL-TFH: epigenetic modifiers, TCR signaling*
- Incorporating targeted agents in treatment
  - *Improve efficacy of initial therapies*
  - *Develop novel strategies for R/R diseases*

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BV+CHP Improves Survival for CD30+ PTCL

ECHELON-2 established BV-CHP as new standard for CD30+ PTCL





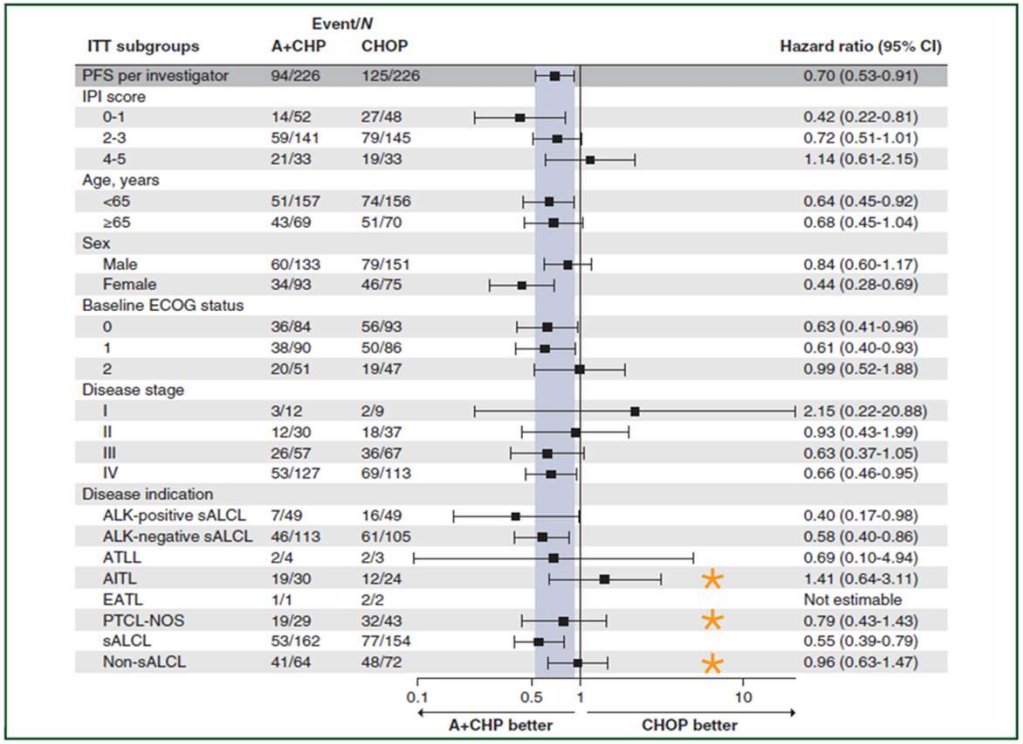
GCSF = granulocyte colony-stimulating factor; EOT = end of treatment; PET = positron emission tomography; A+CHP = brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone.

Horwitz S, et al. *Lancet*. 2019;393(10168):229-240. Horwitz S, et al. *Ann Oncol*. 2022;33(3):288-298.

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ECHELON 2: Subgroups

- *BV-CHP improves survival for ALK+ and ALK-ALCL*
- *Non-ALCL subgroups under-powered in ECHELON-2*

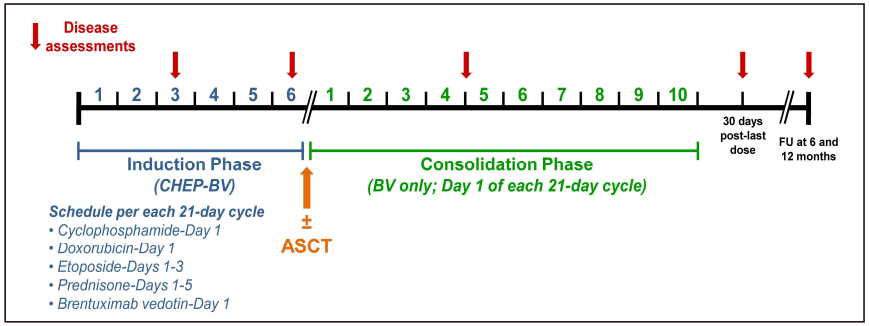


ITT subgroups	Event/*N* A+CHP	CHOP	Hazard ratio (95% CI)
PFS per investigator	94/226	125/226	0.70 (0.53-0.91)
IPI score			
0-1	14/52	27/48	0.42 (0.22-0.81)
2-3	59/141	79/145	0.72 (0.51-1.01)
4-5	21/33	19/33	1.14 (0.61-2.15)
Age, years			
<65	51/157	74/156	0.64 (0.45-0.92)
≥65	43/69	51/70	0.68 (0.45-1.04)
Sex			
Male	60/133	79/151	0.84 (0.60-1.17)
Female	34/93	46/75	0.44 (0.28-0.69)
Baseline ECOG status			
0	36/84	56/93	0.63 (0.41-0.96)
1	38/90	50/86	0.61 (0.40-0.93)
2	20/51	19/47	0.99 (0.52-1.88)
Disease stage			
I	3/12	2/9	2.15 (0.22-20.88)
II	12/30	18/37	0.93 (0.43-1.99)
III	26/57	36/67	0.63 (0.37-1.05)
IV	53/127	69/113	0.66 (0.46-0.95)
Disease indication			
ALK-positive sALCL	7/49	16/49	0.40 (0.17-0.98)
ALK-negative sALCL	46/113	61/105	0.58 (0.40-0.86)
ATLL	2/4	2/3	0.69 (0.10-4.94)
AITL	19/30	12/24	1.41 (0.64-3.11)
EATL	1/1	2/2	Not estimable
PTCL-NOS	19/29	32/43	0.79 (0.43-1.43)
sALCL	53/162	77/154	0.55 (0.39-0.79)
Non-sALCL	41/64	48/72	0.96 (0.63-1.47)

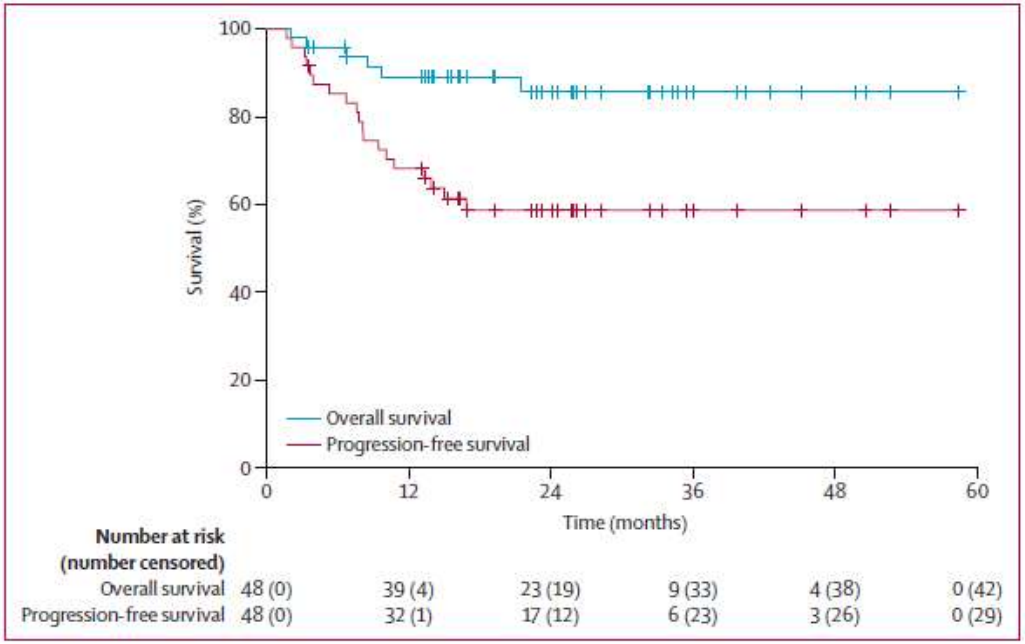
ITT = intention-to-treat; ECOG = Eastern Cooperative Oncology Group.
Horwitz S, et al. *Ann Oncol.* 2022;33(3):288-298.

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BV-CHEP Followed by BV Consolidation Is Safe and Active for CD30+ PTCL



Response	All Pt (n=47)	ALCL (n=15)	Non-ALCL (n=32)	AITL (n=19)	PTCL NOS (n=11)	TFH (n=2)	CD30 1-9% (n=16)	CD30 ≥10% (n=16)
ORR	91%	93%	91%	95%	82%	100%	94%	88%
CR	79%	87%	75%	79%	64%	100%	63%	88%
PR	13%	7%	16%	16%	18%	0	31%	0
SD	0	0	0	0	0	0	0	0
PD	9%	7%	9%	5%	18%	0	6%	13%



AE (grade ≥3): neutropenia (29%), leukopenia 23%, anemia (21%), febrile neutropenia (21%), lymphopenia (19%), and thrombocytopenia (19%).

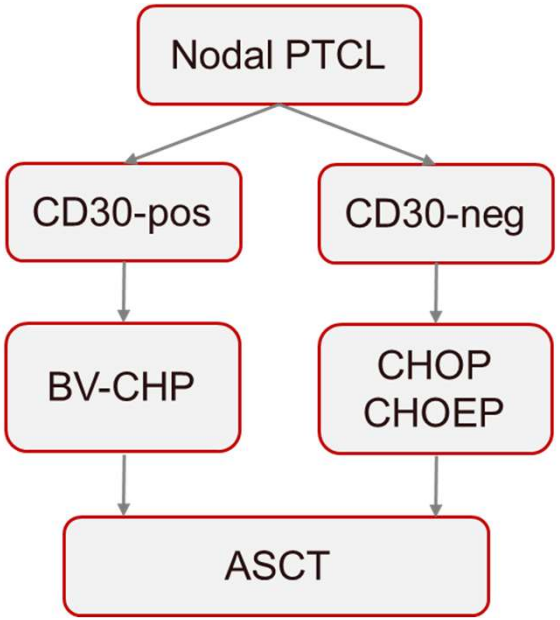
ASCT = autologous stem cell transplant; CHEP = cyclophosphamide, doxorubicin, etoposide, prednisone; AE = adverse event; PR = partial response; SD = stable disease; PD = progressive disease.

Herrera AF, et al. *Lancet Haematol*. 2024;11(9):e671-e681.

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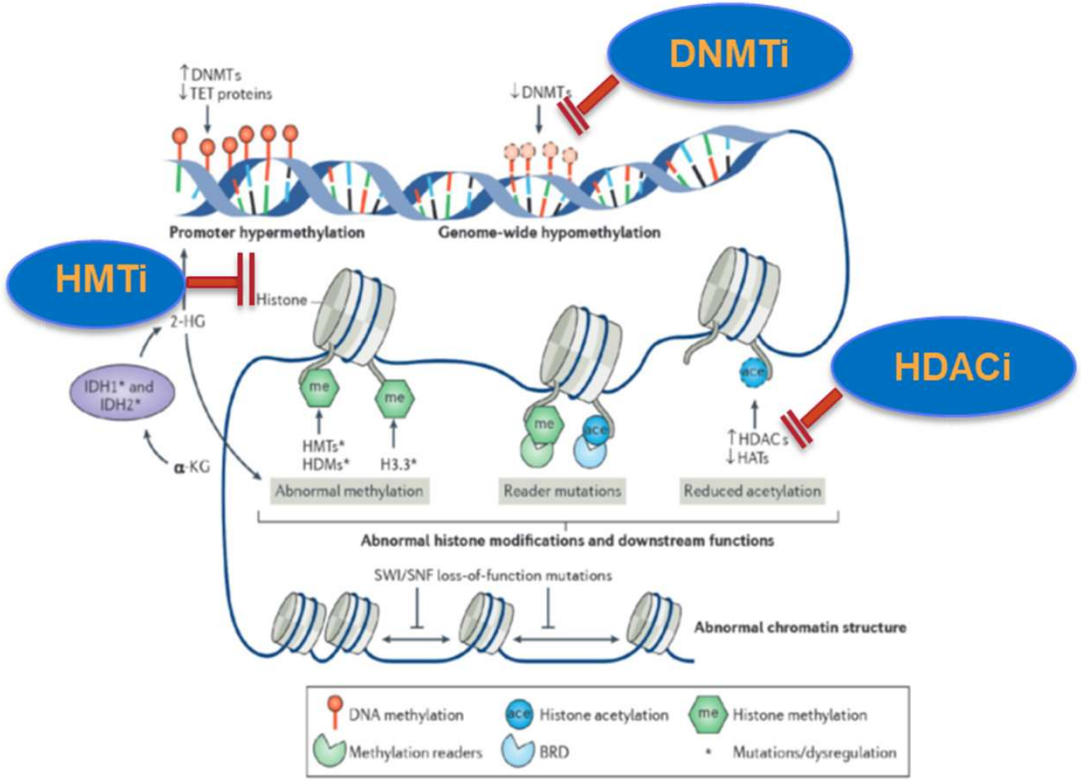
Current Gaps and Unmet Needs

- Peripheral T-cell lymphomas are heterogenous
- CHOP-based regimens have limited efficacy
- BV-CHP improves survival, mostly in ALCL
- Non-ALCL subtypes continue to do poorly
- Relapsed and refractory diseases are common
- Molecular subtypes and biomarkers guide paths for precision medicine



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Targeting Epigenetic Regulators in T-Cell Lymphomas



- Epigenetic alterations, including DNA methylation and histone methylation and acetylation, drive lymphomagenesis in many TCL subtypes.
- HDAC inhibitors are approved agents for T-cell lymphoma
- Clinical trials with demethylating agents are underway
  - DNMTi: e.g. azacitidine
  - HMTi: e.g. valemetostat

i = inhibitor.

Pfister SX, Ashworth A. *Nat Rev Drug Discov*. 2017;16(4):241-263.

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Histone Deacetylase (HDAC) Inhibitors

Agents	Romidepsin	Belinostat		Tucidinostat
Drug class	Class I HDACi	Class I&II HDACi		Class I&IIb HDACi
Dosing	14 mg/m2 IV 4h, weekly 3 of 4 wks	1000 mg/m2 IV 30min, daily x 5, Q3wks		40 mg twice per week Taken orally
PTCL subtypes	PTCL	PTCL	AITL	PTCL
Pt number	130	129	22	46
ORR	25%	26%	45%	46%
CR	15%	11%	18%	11%
DOR	28 months	13.6 months	7.5 months	11.5 months
PFS	4 months	1.6 months	5.8 months	5.6 months
OS	11.3 months	7.9 months	9.2 months	22.8 months
Thrombocytopenia (gr 3/4) Neutropenia (gr 3/4) Anemia (gr 3/4)	24% 20% 11%	7% 6% 11%		38% 35%

DOR = duration of response.

Coiffier B, et al. *J Clin Oncol*. 2012;30(6):631-636. O'Connor OA, et al. *J Clin Oncol*. 2015;33(23):2492-2499. O'Connor OA, et al. *J Clin Oncol*. 2013;31(15 Suppl):8507. Horwitz S, et al. *Hematol Oncol*. 2013;31(Suppl 1):147. Rai S, et al. *Haematologica*. 2023;108(3):811-821.

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Real-World Data: HDACi Is Active in TFH-PTCL

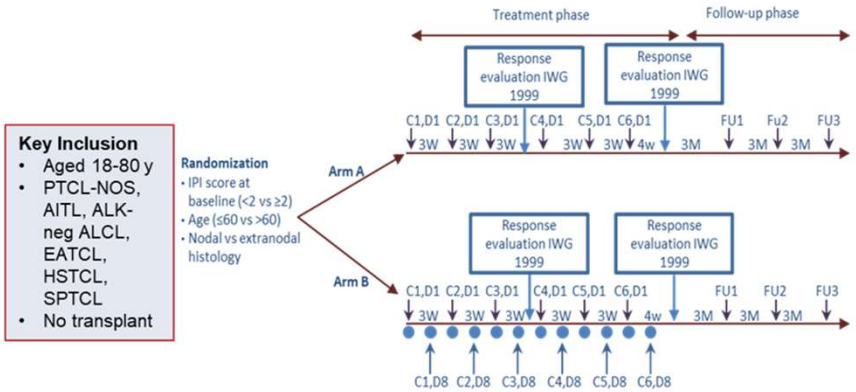
Romidepsin+	TFH (n=76) ORR	TFH (n=76) CR	Non-TFH (n=51) ORR	Non-TFH (n=51) CR	P
Overall (n=127)	56.5%	28.9%	29%	19.6%	0.0035
Single agent (n=97)	54.2%	25.4%	31%	21.0%	0.0371
Combinations (n=30)	61.1%	38.8%	25%	16.6%	0.717

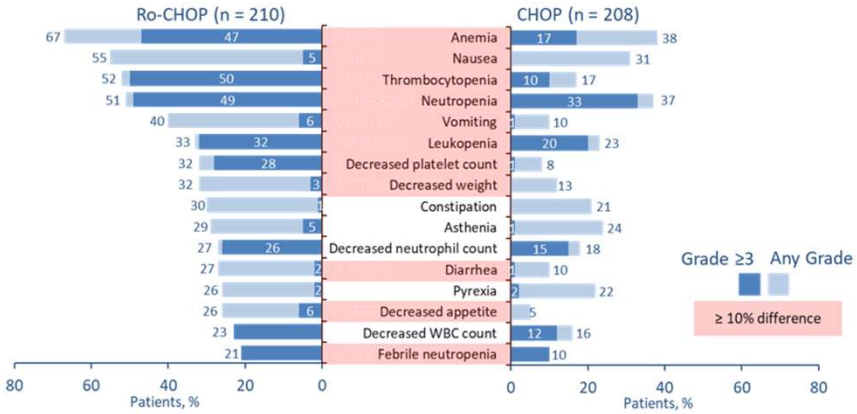
Combinations: romi+len, romi+len+carfilzomib, romi+duvelisib, romi+pralatrexate

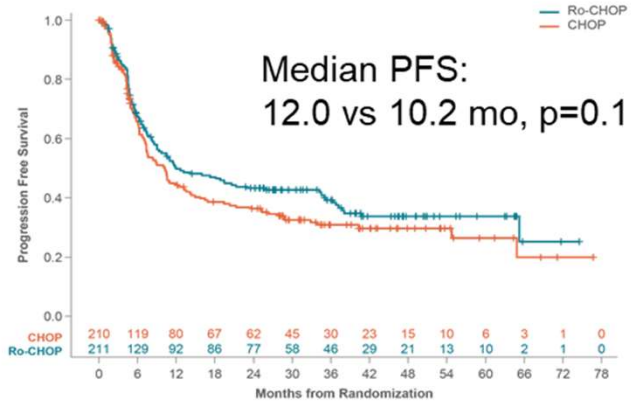
Ghione P, et al. *Blood Adv*. 2020;4(19):4640-4647.

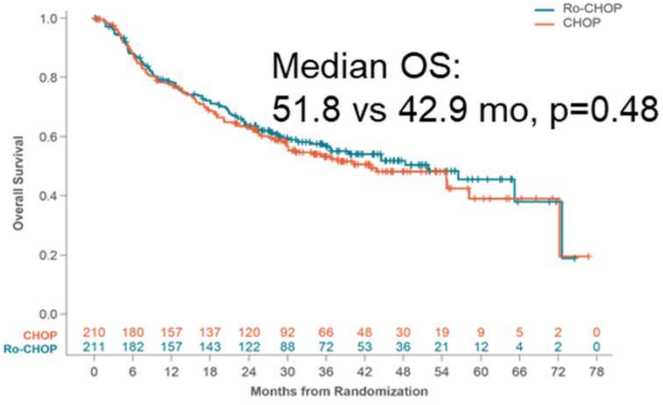
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Phase 3 Romidepsin (Ro)-CHOP vs CHOP







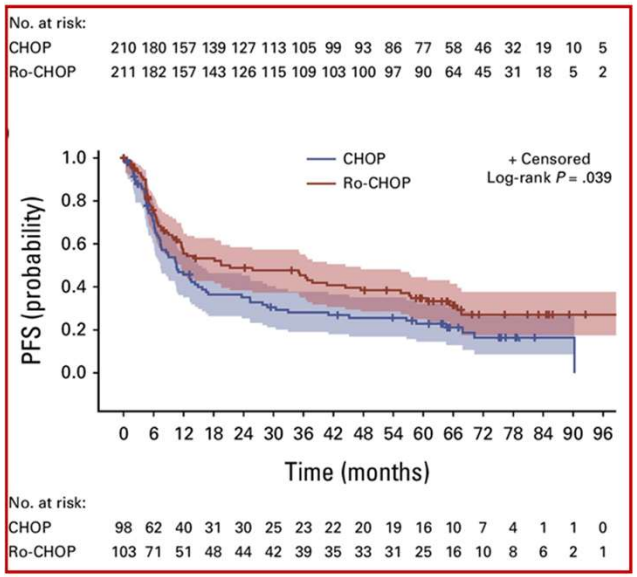


Bachy E, et al. *J Clin Oncol*. 2022;40(3):242-251.

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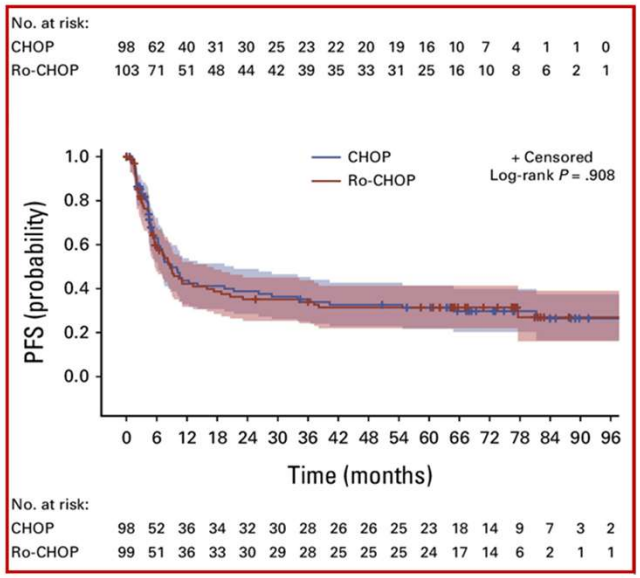
Phase 3 Ro-CHOP vs CHOP: Subgroup Analysis

TFH PTCL



Ro-CHOP:mPFS 19.5 months
CHOP: mPFS 10.6 months
P=0.039

Non-TFH PTCL



Ro-CHOP:mPFS 8.7 months
CHOP: mPFS 9 months
P=0.908

mPFS = median PFS.

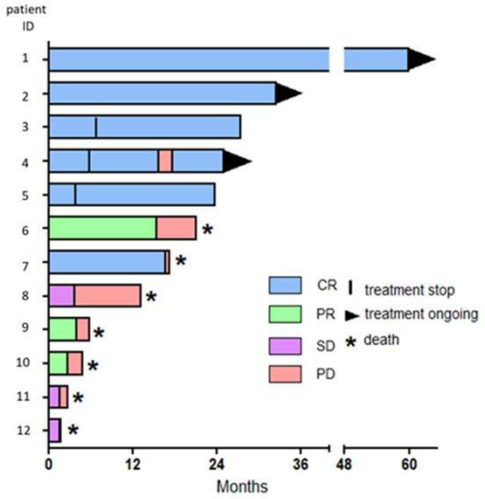
Camus V, et al. *J Clin Oncol*. 2024;42(14):1612-1618.

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DNMTi Azacitidine Is Active in TFH-PTCL

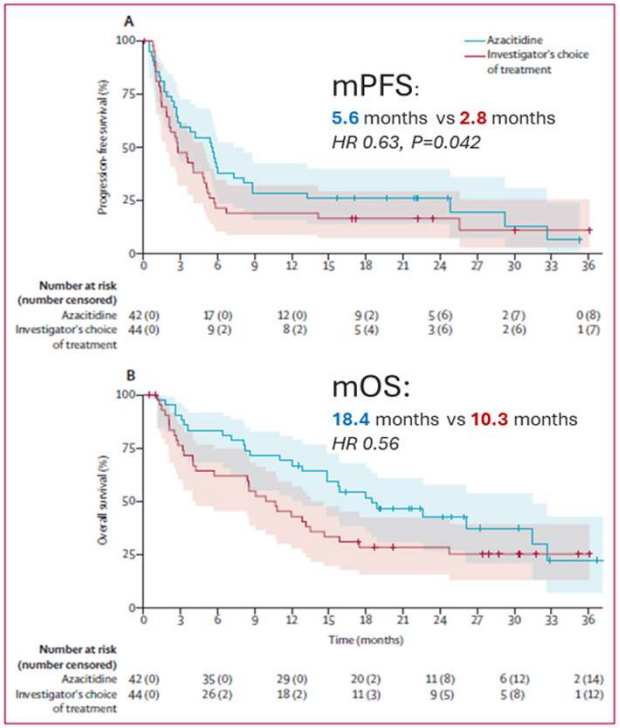
Retrospective AITL cohort (n=12)

- Aza 75 mg/m2 sc daily x 7 q28d
- 12 AITL, median age 71 years
- 5/12 (41%) with MDS/CMML
- ORR 75% ORR and 50% CR/CRu
- mPFS 15 months, mOS 21 months



ORACLE Phase 3 Study (n=86)

Oral aza | IC (gem, benda, romi)



MDS = myelodysplastic syndrome; CMML = chronic myelomonocytic leukemia; CRu = unconfirmed complete response; IC = induction chemotherapy.
Lemonnier F, et al. *Blood*. 2018;132(21):2305-2309. Dupuis J, et al. *Lancet Haematol*. 2024;11(6):e406-e414.

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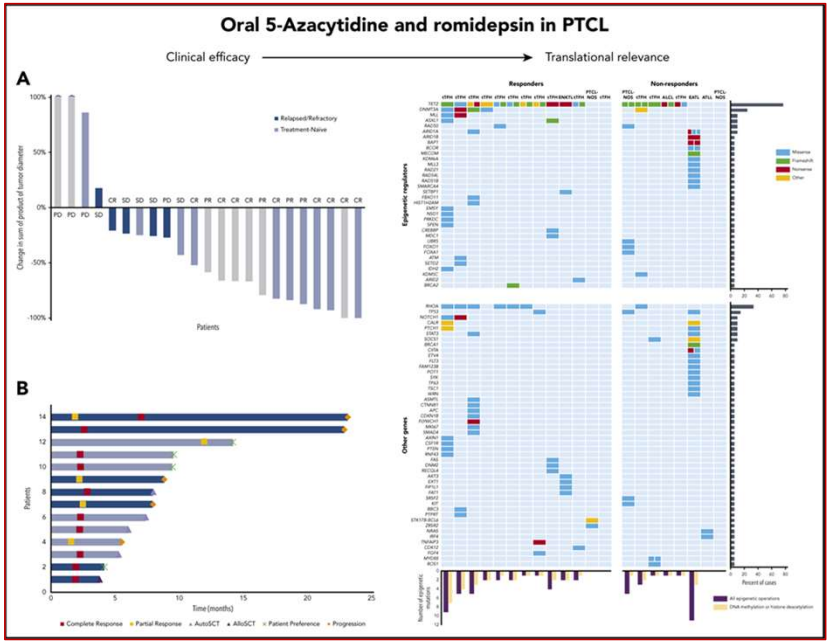
Oral Azacitidine + Romidepsin Is Active in R/R PTCL

Phase 1: MTD and DLT

- MTD—AZA 300 mg (d1-14) and ROMI 14 mg/m2 on d8, 15, and 22, 35-day cycle
- DLTs—grade 4 thrombocytopenia, grade 4 neutropenia, and pleural effusion
- Efficacy: TCL (n=11)—ORR 73%, CR 55%

Phase 2 Efficacy

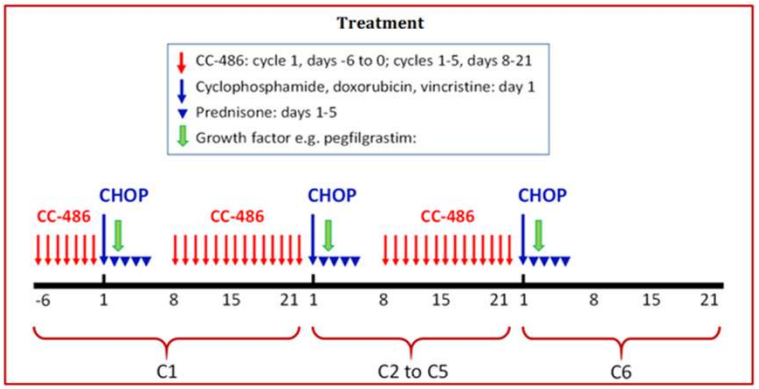
Response	All patients (n=23)	Treatment Naïve (n=10)	Relapsed/ Refractory (n=13)	tTFH (n=15)	Other subtypes (n=8)
Overall response	14 (61%)	7 (70%)	7 (54%)	12 (80%)	2 (25%)
Complete response	10 (43%)	5 (50%)	5 (38%)	9 (60%)	1 (12.5%)
Partial response	4 (17%)	2 (20%)	2 (15%)	3 (20%)	1 (12.5%)
Stable disease	5 (22%)	2 (20%)	3 (23%)	2 (13%)	3 (37.5%)
Progressive disease	4 (17%)	1 (10%)	3 (23%)	1 (7%)	3 (37.5%)



MTD = maximum tolerated dose; DLT = dose-limiting toxicity.
O'Connor, et al. *Blood*. 2019;134(17):1395-1405. Falchi, et al. *Blood*. 2021;137(16):2161-2170.

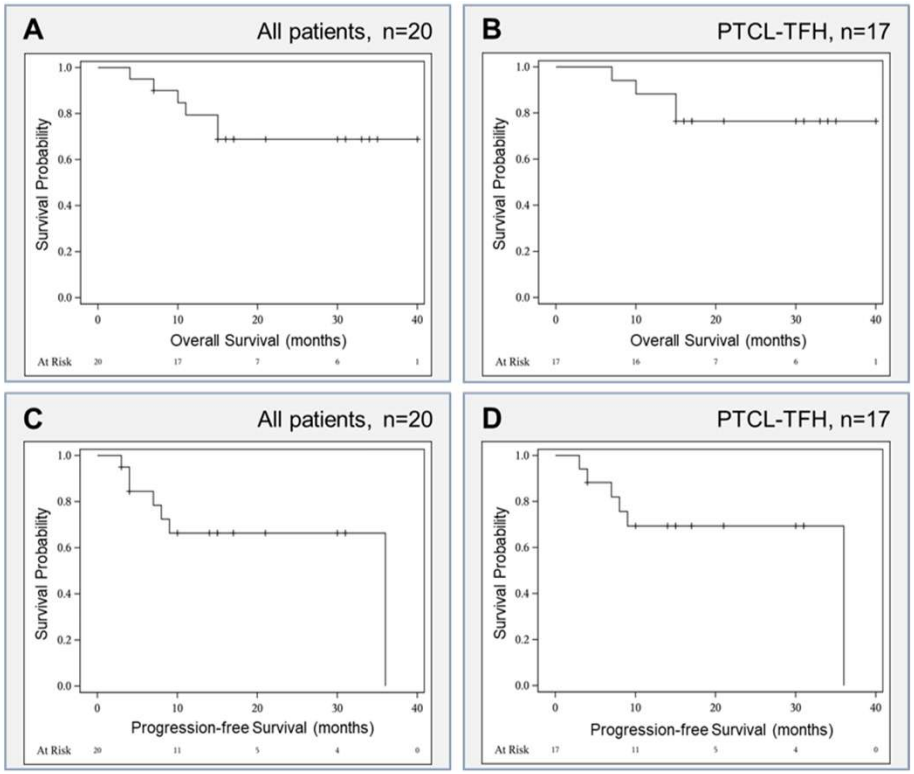
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Oral Azacitidine + CHOP Is an Active and Safe Induction Regimen



EOT Response	Evaluable (n=20)	PTCL-TFH (n=17)
ORR	75%	88%
CR	**75%**	**88%**
PR	0	0
SD	5%	0
PD	10%	6%
Discontinuation	10%	6%

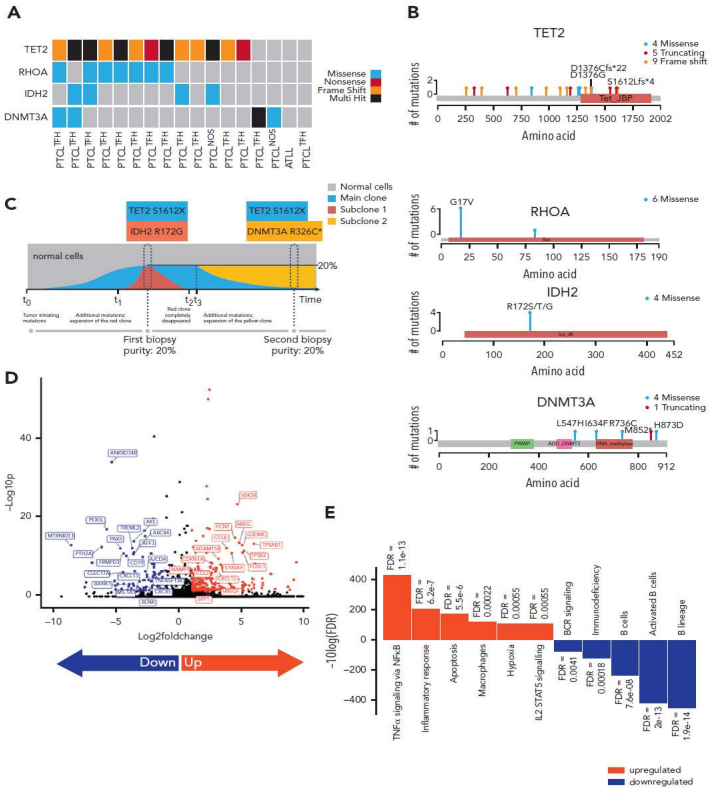
Grade≥3 AEs:
↓ANC
GI symptoms

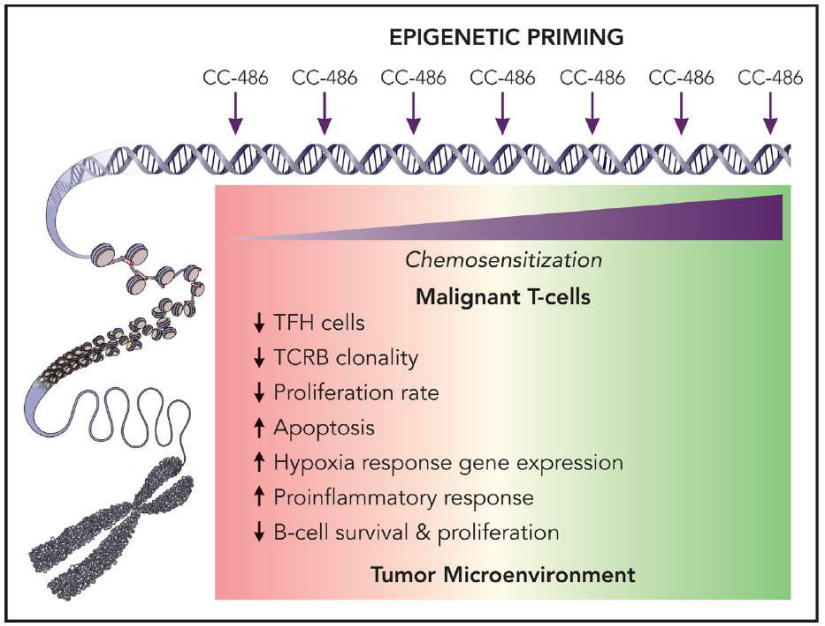


ANC = absolute neutrophil count.
Ruan J, et al. *Blood*. 2023;141(18):2194-2205.

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Phase II Frontline Study of Oral Azacitidine + CHOP: Possible MOA



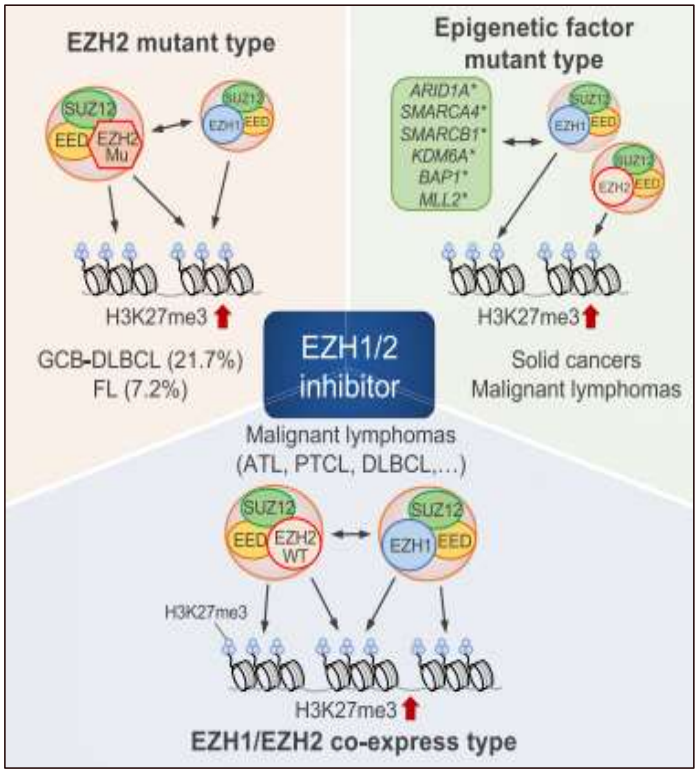


MOA = mechanism of action.

Ruan J, et al. *Blood*. 2023;141(18):2194-2205. Barta SK et al, *Blood*. 2023;141(18):2161-2163.

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EZH1/2 Inhibitor: Valemetostat



Phase 1 Study in R/R PTCL

(NCT02732275)

	PTCL[b] (N = 55)	AITL (n = 22)	PTCL, NOS (n = 26)	ATLL (N = 14)
ORR	**55%** **[40.6, 68.0]**	**64%** [40.7, 82.8]	**50%** [29.9, 70.1]	**64%** **[35.1, 87.2]**
CR	**17 (31)**	10 (45)	7 (27)	**4 (29)**
PR	**13 (24)**	4 (18)	6 (23)	**5 (36)**
Median TTR	**1.8** **(1.0–5.6)**	1.9 (1.0–3.8)	1.8 (1.6–5.6)	**1.9** **(1.7–19.4)**
Median DOR	**21.9** **[10.2, NR]**	21.9 [1.9, 21.9]	NR [4.0, NR]	**21.2** **[1.4, 38.7]**

AE (all-grade): cytopenia, dysgeusia, alopecia
AE (≥grade 3): neutropenia (17%), lymphopenia (11%), thrombocytopenia (14%)

TTR = time to response.
Yamagishi M, et al. *Cell Rep*. 2019;29(8):2321-2337.e7. Maruyama D, et al. *Lancet Oncol*. 2024;25(12):1589-1601.

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EZH1/2 Inhibitor: Valemetostat

Phase 2 Study: VALENTINE-PTCL01 *(NCT04703192)*

Response	AITL (n = 42)	PTCL, NOS (n = 41)	PTCL TFH (n = 8)	ALCL (*ALK*-positive or *ALK*-negative) (n = 9)	Other[a] (n = 19)	All (N = 119)
ORR (CR or PR), n (%)	23 (54.8)	13 (31.7)	4 (50)	3 (33.3)	9 (47.4)	52 (43.7)
95% CI[b]	38.7–70.2	18.1–48.1	15.7–84.3	7.5–70.1	24.4–71.1	34.6–53.1
CR, n (%)	8 (19.0)	4 (9.8)	1 (12.5)	1 (11.1)	3 (15.8)	17 (14.3)
95% CI[b]	8.6–34.1	2.7–23.1	0.3–52.7	0.3–48.2	3.4–39.6	8.5–21.9
PR, n (%)	15 (35.7)	9 (22.0)	3 (37.5)	2 (22.2)	6 (31.6)	35 (29.4)
95% CI[b]	21.6–52.0	10.6–37.6	8.5–75.5	2.8–60.0	12.6–56.6	21.4–38.5
DOR[c], median (range), months	11.9 (1.6–14.9+)	7.9 (0+–14.9+)	NE (5.1–11.1+)	3.8 (3.7–12.0+)	9.2 (3.7–9.5+)	11.9 (0+–14.9+)
95% CI[d]	10.8–NE	3.7–NE	5.1–NE	3.7–NE	3.7–NE	7.8–NE
DOCR[e], median (range), months	NE (0+–12.0+)	11.2 (2.7+–11.2)	5.1 (5.1–5.1)	NE (8.3+–8.3+)	NE (6.5+–9.5+)	11.2 (0+–12.0+)
95% CI[d]	1.7–NE	4.2–NE	NE–NE	NE–NE	NE–NE	4.2–NE

Grade 3-4 AEs: thrombocytopenia 23%, anemia 19%, neutropenia 17%

DOCR = duration of complete response.

Zinzani PL, et al. *Lancet Oncol* 2024;25(12):1602-1613.

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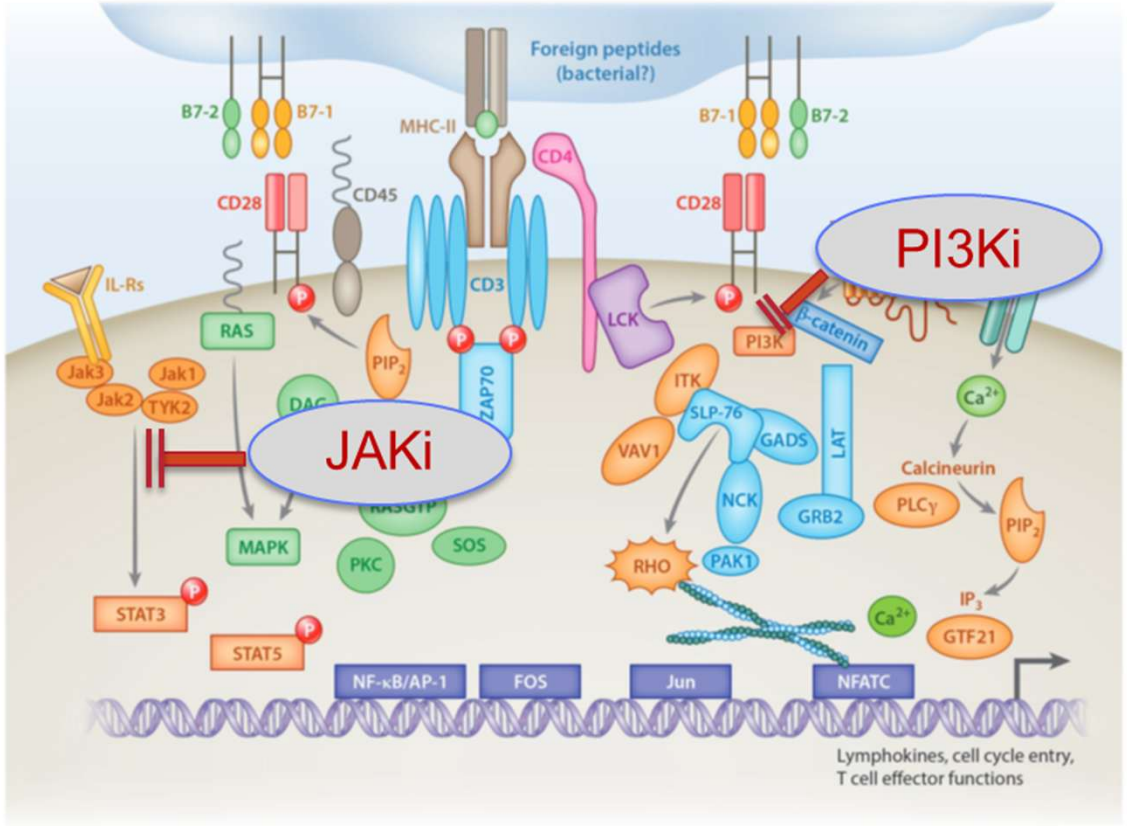
EZH1/2 Inhibitors in PTCL

Agents	SHR2554 (TLN254)	HH2853	Valemetostat
Drug class	EZH2	EZH1/2	EZH1/2
Phase	Phase 2	Phase 1b	Phase 2
Dosing	350 mg twice daily	400 mg twice daily	200 mg daily
PTCL subtypes	PTCL	PTCL	PTCL
Pt number	67	34	133
ORR	64%	67.6%	44%
CR	33%	29.4%	14%
DOR/PFS	mDOR 19m, mPFS 10m	mDOR 14.8m	mDOR 11.9 months
Gr 3/4 AEs	Thrombocytopenia 28%, neutropenia 27% anemia 24%	Thrombocytopenia 24%, neutropenia 24%, anemia 12%	Thrombocytopenia 23%, anemia 19%, neutropenia 17%

Song Y, et al. *Clin Cancer Res*. 2024;30(7):1248-1255. Song Y, et al. *Hematol Oncol.* 2025;43(Suppl 3):63. Hong et al, J Hematol Oncol 18, 50 (2025); Zinzani PL, et al. *Lancet Oncol* 2024;25(12):1602-1613.

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Targeting T-Cell Signaling Pathways



- Dysregulation and activation of PI3K/AKT/mTOR promotes T-cell lymphomagenesis.
  - PI3Ki: duvelisib, tenalisib, linperlisib, etc
- Activating mutations in JAK1, JAK2, JAK3, STAT 3 and STAT5B are common in many TCL subtypes.
  - JAKi: ruxolitinib, golidocitinib cerdulatinib, DZD4205, etc

Pizzi M, et al. *Annu Rev Pathol*. 2018;13:293-320.

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Phosphatidylinositol 3-Kinase Inhibitors

Agents	Duvelisib	Linperlisib	
Isoform target	PI3K δγ	PI3K δ	
Study	Phase 2	Phase 1b	Phase 2
Dosing	75 mg BID -> 25 mg BID maintenance	80 mg QD (40 mg QD maintenance in US study)	
PTCL subtypes	PTCL	PTCL (China)	PTCL (US, Italy)
Pt number	123	43	35
ORR	48%	60.5%	48.5%
CR	33%	35%	33.3%
DOR/PFS	mPFS 3.5m, mDOR 7.9m	mPFS 11.8m, mDOR 11m	mPFS 3.6m, mDOR 5.8m
Gr 3/4 AEs	AST/ALT elevation 24%, rash (11%), neutropenia (18%), infection 13%, diarrhea 10%	Neutropenia 21%, pneumonia 11%, hypertriglyceridemia 7%	Neutropenia 9%, rash 4% transaminitis 2%, hypertriglyceridemia 2%
Phase 3 study	TERZO: DUV vs IC in nTFHL	Planned: Linperlisib vs IC	

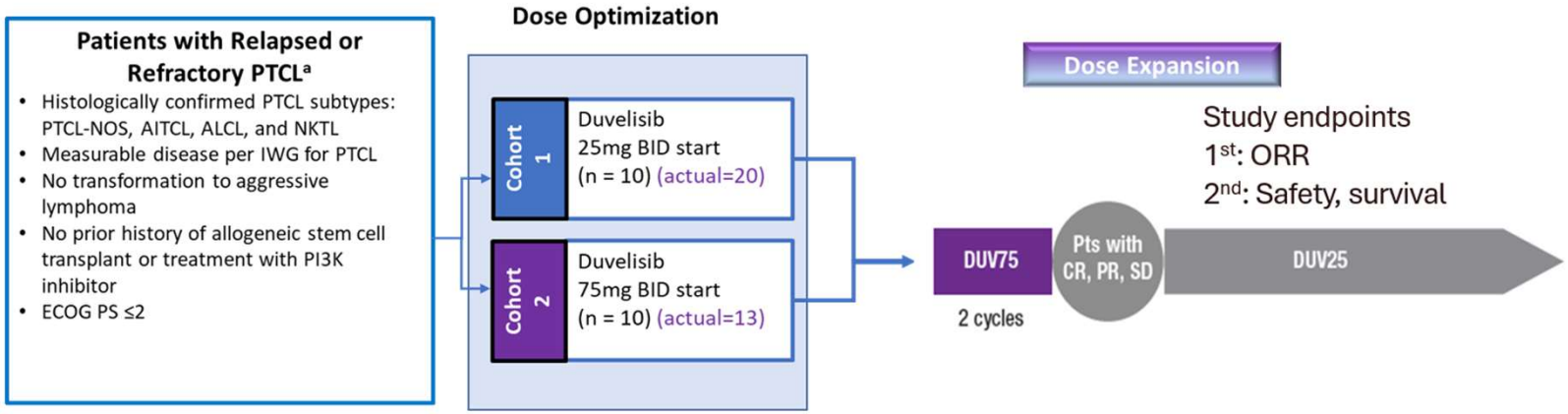
nTFHL = nodal TFHL; AST = aspartate transaminase; ALT = alanine transaminase.

Mehta-Shah N, et al. *Blood*. 2024;144(Suppl 1):3061. Jin J, et al. *Clin Cancer Res*. 2024;30(20):4593-4600. Iyer SP, et al. *Blood*. 2024:144(Suppl 1):4449.

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PRIMO: Phase 2 Study of Duvelisib Monotherapy in R/R PTCL

MOA: Direct inhibition of tumor cells, modulation of immune cells



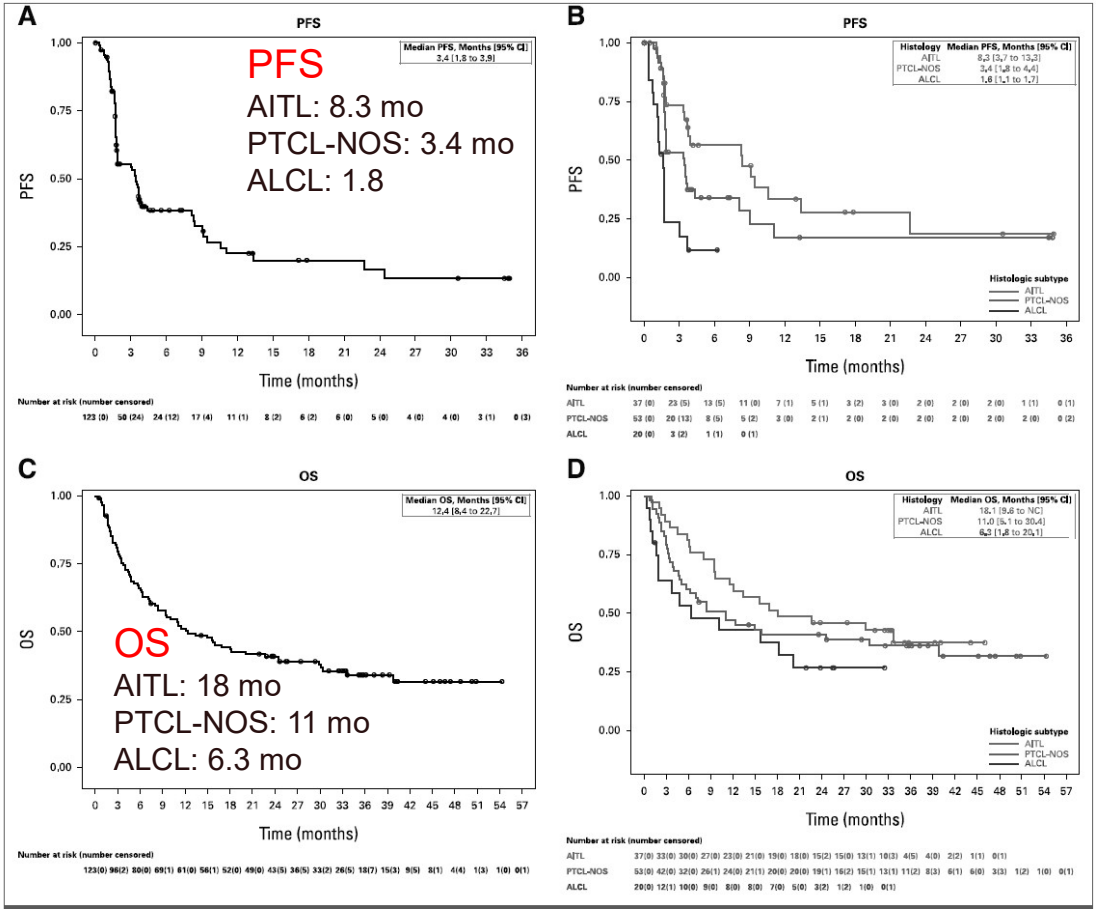
Grade ≥3 AE:
ALT increase 21%
AST increase 17%
Neutropenia 18%

Dose Expansion			
Outcome (n=123)	PTCL-NOS (n=53)	AITL (n=37)	ALCL (n=20)
ORR (CR)	48% (33%)	62% (51%)	13.3% (13.3%)
mDOR	7.9 months	11.3 months	1.9 months
mPFS	3.4 months	8.3 months	1.5 months
mOS	12.4 months	18.1 months	4.8 months

IWG = International Working Group; ECOG PS = ECOG performance status.
Pro B, et al. Presented at: 62nd American Society of Hematology (ASH) Annual Meeting & Exposition; 2020. Abstract 44. Mehta-Shah N, et al. *J Clin Oncol*. 2026;44(20):1889-1898.

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PRIMO: Phase 2 Study of Duvelisib Monotherapy in R/R PTCL

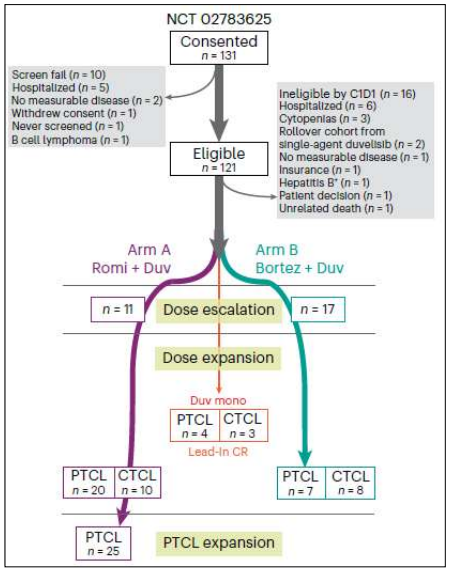


Pro B, et al. Presented at: 62nd ASH Annual Meeting & Exposition; 2020. Abstract 44. Mehta-Shah N, et al. *J Clin Oncol*. 2026;44(20):1889-1898

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Duvelisib and Romidepsin Combination Is Active in R/R PTCL

Phase 1 Study Schema



MTD
D 75mg BID
R 10 mg/m2 on days 1, 8, 15
28-day cycle

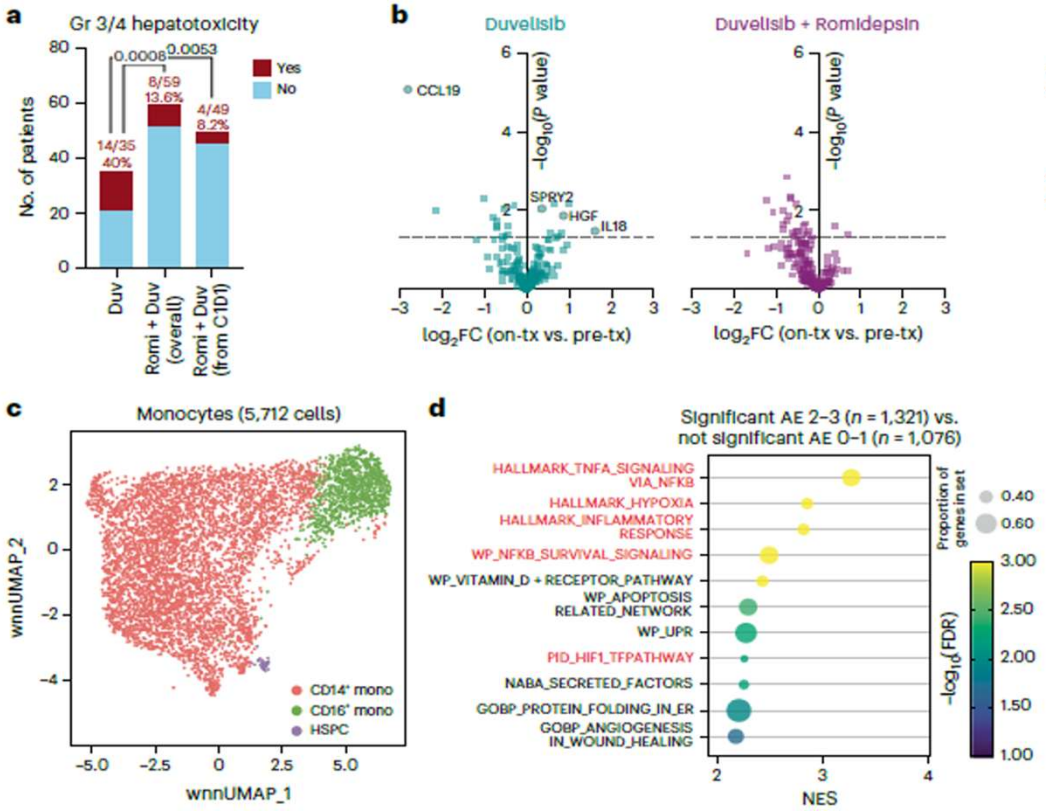
Histology	Treated	Evaluable	ORR N (%)	CR N (%)	Bridged to Allo SCT N (%)
PTCL	**55**	**53**	**31 (58)**	**22 (42)**	**15 (28)**
PTCL NOS	20	19	10 (53)	6 (32)	3 (16)
AITL/TFH	19	19	13 (68)	11 (58)	7 (37)
PC γδ	3	3	1 (33)	1 (33)	1 (33)
ALCL	3	3	3 (100)	2 (67)	2 (66)
HSTCL	2	2	1 (50)	0	1 (50)
Aggr epidermotropic CD8+	2	2	1 (50)	1 (50)	0
Other TCL	6	5	2 (40)	1 (20)	1 (20)
CTCL	**11**	**11**	**4 (36)**	**0**	**0**
MF	7	7	2 (29)	0	0
LCT	*3*	*3*	*0*	*0*	*0*
SS	4	4	2 (50)	0	0
LCT	*1*	*1*	*0*	*0*	*0*
Overall	**66**	**64**	**35 (55)**	**22 (34)**	**15 (23)**

MF = Mycosis fungoides; SS = Sézary syndrome; HSTCL = hepatosplenic T-cell lymphoma.

Horwitz SM, et al. *Nat Med.* 2024;30(9):2517-2527. Horwitz SM, et al. Presented at: 16th Annual International Conference on Malignant Lymphoma (ICML); 2021. Abstract 56.

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Duvelisib and Romidepsin Combination: Phase 1 Data Summary



- Romi attenuates duvelisib-driven hepatotoxicity
- Grade >3 AEs
  - Transaminases: 8%
  - Diarrhea (12%)
  - Rash (6%)
  - Neutropenia (39%)
  - Infection (12%)

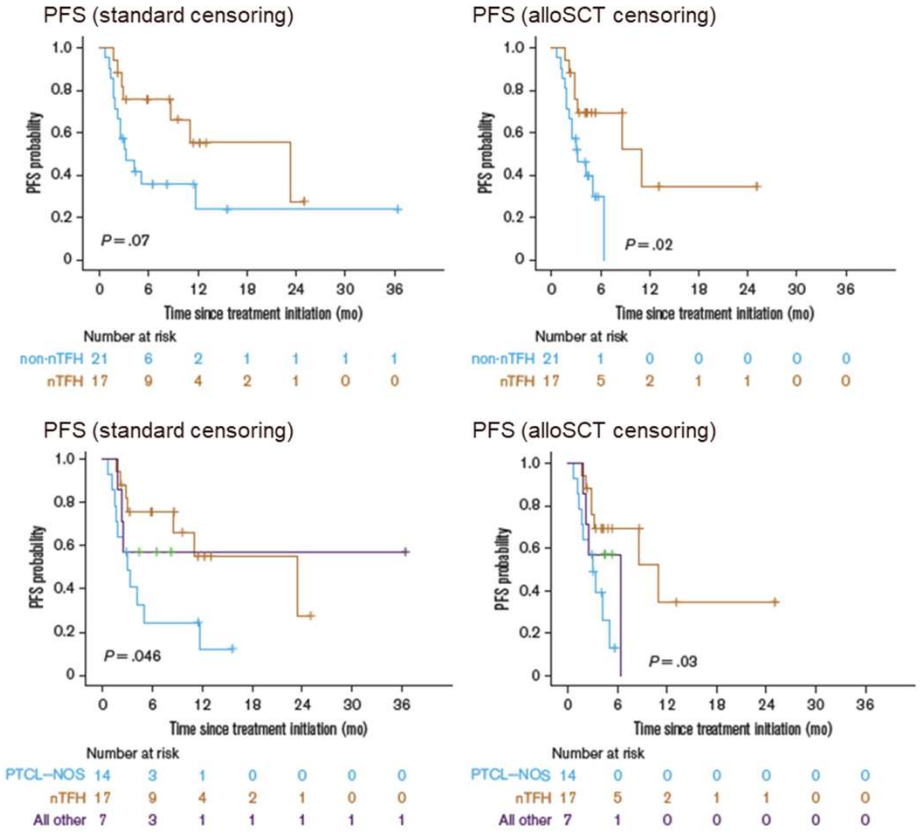
Horwitz SM, et al. *Nat Med*. 2024;30(9):2517-2527. Horwitz SM, et al. Presented at:16th Annual ICML; 2021. Abstract 56.

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Duvelisib and Romidepsin Combination: Real-World Experience

Romi+Duv	Response		Survival	
	ORR	CR	mPFS	mOS
Overall (n=38)	61%	47%	5 m	9.7 m
TFH (n=17)	82%	71%	11 m	16 m
Non-TFH (n=21)	43%	29%	3.3 m	8.3 m

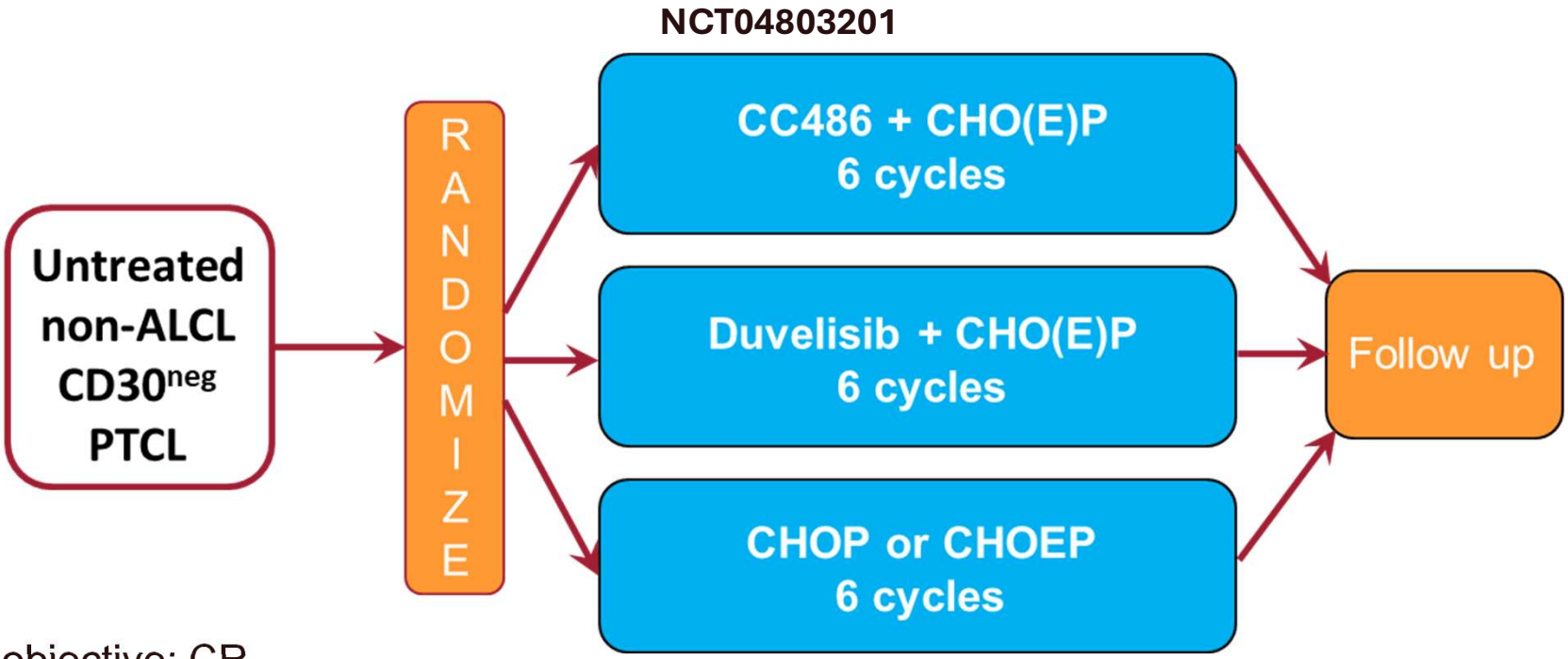
*11 patients (29%) bridged to alloSCT



alloSCT = allogeneic SCT.
Ford J, et al. *Blood Adv*. 2025;9(16):4286-4305.

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US Intergroup Study ALLIANCE A051902 Schema



- 1st objective: CR
- 2nd objectives: safety and efficacy (ORR, survival)

National Cancer Institute (NCI) [www.cancer.gov]. Accessed Oct 7, 2024. https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCT04803201.

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JAK Inhibitors

Agents	Ruxolitinib	Golidocitinib
Molecular target	JAK1/2	JAK1
Study	Phase 2	Phase 2
Dosing	20 mg BID	150 mg Daily
PTCL subtypes	PTCL, MF *Cohort 1: JAK/STAT mutations* *Cohort 2: pSTAT3 expression ≥30%* *Cohort 3: Neither*	PTCL *PTCL-NOS (57%), AITL (18%)* *ALAC (11%)*
Pt number	45 (PTCL), 7 (MF)	88
ORR	25%	44.3%
CR	6%	24%
Clinical benefit	35%	
DOR/PFS	mDOR 8.4 months	mDOR 20.7 months
Gr 3/4 AEs	Cytopenia	Cytopenia

Moskowitz AJ, et al. *Blood*. 2021;138(26):2828-2837. Song Y, et al. *Lancet Oncol*. 2024;25(1):117-125.

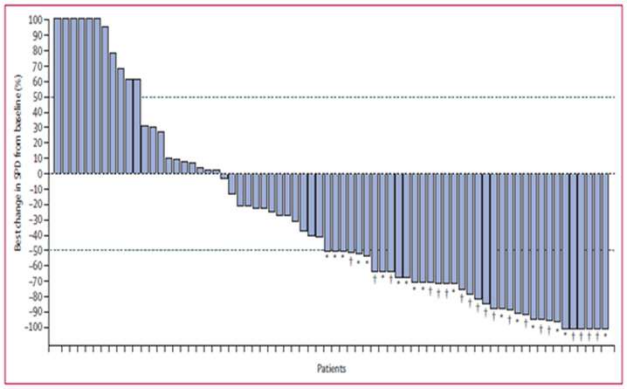
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Golidocitinib in Pts with R/R PTCL: JACKPOT8 Part B

Golidocitinib 150 mg once daily

	Patients (n=88)
Best tumour response	
Complete response	21 (24%)
Partial response	18 (20%)
Stable disease	17 (19%)
Progressive disease	20 (23%)
Not evaluable	12 (14%)
Objective response rate	**39 (44%)**
Complete response rate	**21 (24%)**

Data are n (%), unless otherwise indicated. *Excluding five patients with radiological complete response who did not have a post-treatment bone marrow biopsy sample available for confirmation, and so were determined to have partial responses.



Grade 3-4 AEs: neutropenia (29%), thrombocytopenia (20%)

	Grade 1–2	Grade 3	Grade 4	Grade 5
All	34 (33%)	49 (47%)	12 (12%)	1 (1%)
Blood and lymphatic system disorders	40 (38%)	12 (12%)	0	0
Anaemia	34 (33%)	9 (9%)	0	0
Neutropenia	4 (4%)	2 (2%)	0	0
Splenic infarction	0	1 (1%)	0	0
Metabolism and nutrition disorders	40 (38%)	3 (3%)	2 (2%)	0
Hypertriglyceridaemia	15 (14%)	2 (2%)	0	0
Hyperuricaemia	11 (11%)	0	0	0
Hyperkalaemia	3 (3%)	0	1 (1%)	0
Hypokalaemia	3 (3%)	1 (1%)	0	0
Metabolic acidosis	0	0	1 (1%)	0
Investigations	35 (34%)	40 (38%)	12 (12%)	0
Platelet count decreased	44 (42%)	15 (14%)	6 (6%)	0
White blood cell count decreased	33 (32%)	24 (23%)	3 (3%)	0
Neutrophil count decreased	29 (28%)	22 (21%)	8 (8%)	0
Aspartate aminotransferase increased	27 (26%)	3 (3%)	0	0
Alanine aminotransferase increased	23 (22%)	3 (3%)	0	0
Blood creatinine increased	18 (17%)	1 (1%)	0	0
Blood lactate dehydrogenase increased	16 (15%)	1 (1%)	0	0
Blood fibrinogen decreased	14 (13%)	3 (3%)	0	0
Blood creatine phosphokinase increased	12 (12%)	1 (1%)	0	0
Lymphocyte count decreased	10 (10%)	18 (17%)	4 (4%)	0
γ-Glutamyltransferase increased	7 (7%)	1 (1%)	0	0
Blood bilirubin increased	3 (3%)	1 (1%)	0	0
Fibrin D-dimer increased	1 (1%)	1 (1%)	0	0
Gastrointestinal disorders	26 (25%)	4 (4%)	1 (1%)	0
Stomatitis	6 (6%)	2 (2%)	0	0
Gastrointestinal haemorrhage	0	1 (1%)	1 (1%)	0
Intestinal perforation	0	1 (1%)	0	0
General disorders and administration site conditions	25 (24%)	2 (2%)	0	0
Pyrexia	12 (12%)	1 (1%)	0	0
Fatigue	4 (4%)	1 (1%)	0	0
Infections and infestations	19 (18%)	8 (8%)	0	1 (1%)
Pneumonia	7 (7%)	0	0	1 (1%)
Herpes zoster	5 (5%)	5 (5%)	0	0
Upper respiratory tract infection	5 (5%)	1 (1%)	0	0
Febrile infection	2 (2%)	1 (1%)	0	0
Tonsillitis	1 (1%)	1 (1%)	0	0
Viral infection	0	1 (1%)	0	0

Song Y, et al. *Lancet Oncol*. 2024;25(1):117-125.

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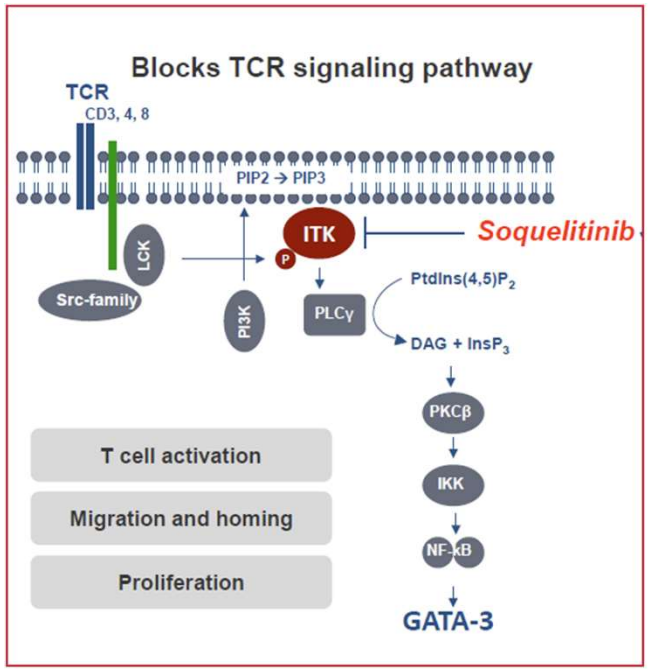
Dual Targeted Therapy with Ruxolitinib plus Duvelisib

- Phase 1 study in PTCL, CTCL, T-PLL
  - Part I: MTD ruxolitinib 20 mg BID plus duvelisib 25 mg BID
  - Part II: dose expansion cohorts
    - 1) Cohort A: with JAK/STAT activation mutations
    - 2) Cohort B: without JAK/STAT activation mutations
- Grade ≥ AEs
  - Neutropenia 38%, anemia 16%, thrombocytopenia 12%
  - Transaminitis 4%, diarrhea 2%, mucositis 2%
- Efficacy
  - Overall: ORR 41%, CR 24%
  - Cohort A: ORR 52%, CR 29%
  - Cohort B: ORR 14%, CR 14%
  - TFH-PTCL: ORR 79%, CR 64%
  - T-PLL: ORR 60%, CR 0%

Moskowitz A, et al. *Blood*. 2024;144(Suppl 1):463.

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ITK Inhibitor Soquelitinib (CPI-818): Phase 3 Trial



Registration Trial: NCT06561048

Eligibility

- Relapsed / refractory PTCL
  - PTCL-NOS
  - AITL
  - FHTCL-NOS
  - FHTCL-Follicular
  - ALCL
- ≥1 and ≤3 prior therapies

N = 150

Clinical Trial

1:1 randomization to

- Soquelitinib 200 mg po BID
- Standard of care chemotherapy:
  - Belinostat
  - Pralatrexate

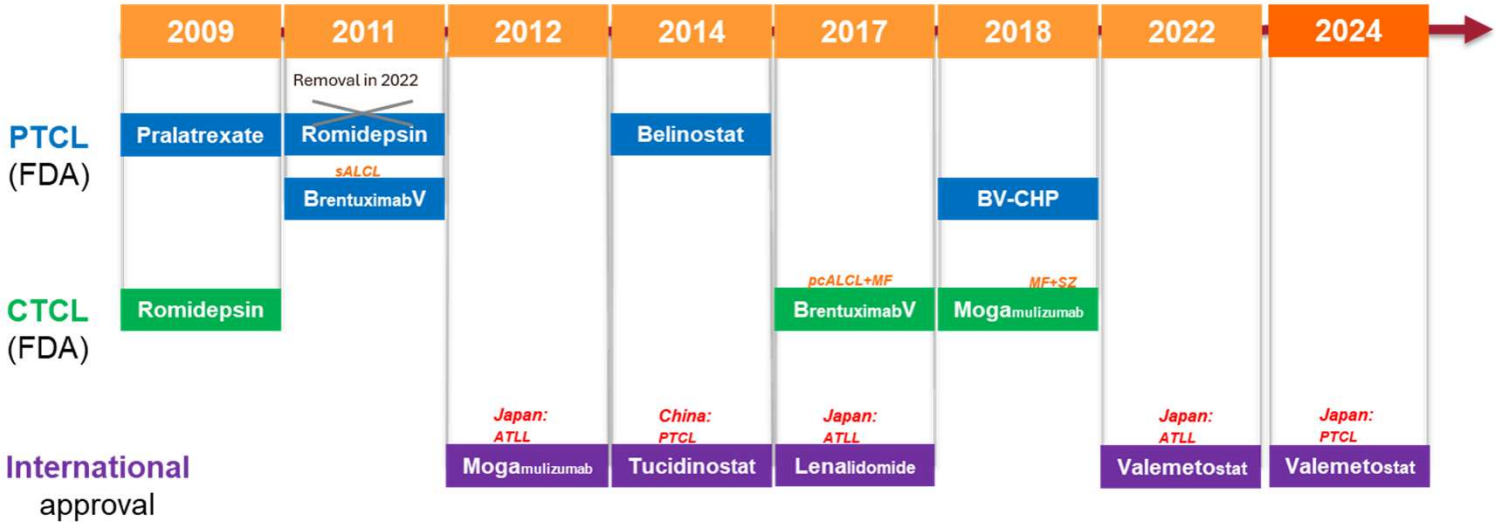
Endpoints

- Primary: Progression free survival
- Secondary:
  - Overall response rate
  - Overall survival
  - Duration of response

Miller RA, et al. *Blood*. 2026;blood.2026034704 [Epub ahead of print].

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Novel Agents in TCL Therapy



Experimental Agents

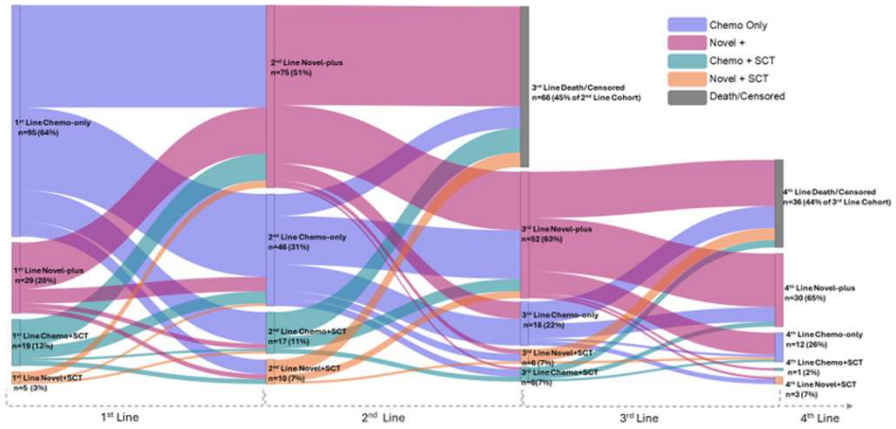
- **PI3K inhibitors**
  - Duvelisib
  - Linperlisib
- **HDAC inhibitors**
  - Tucidinostat
- **HMA**
  - Azacitidine
  - Valemetostat
  - SHR2554 (TLN254)
- **JAK inhibitors**
  - Ruxolitinib
  - Golidocitinib
- **ITK inhibitor**
  - Soquelitinib
- ADC
- BiTE
- CAR-T
- **Combinations**

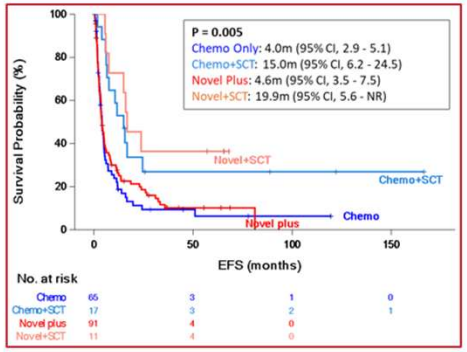
BiTE = bispecific T-cell engager.

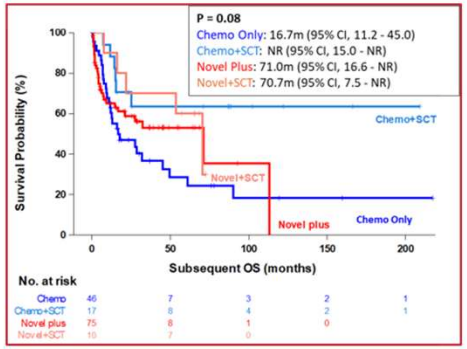
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Sequencing of Novel Agents May Improve Outcomes in R/R PTCL

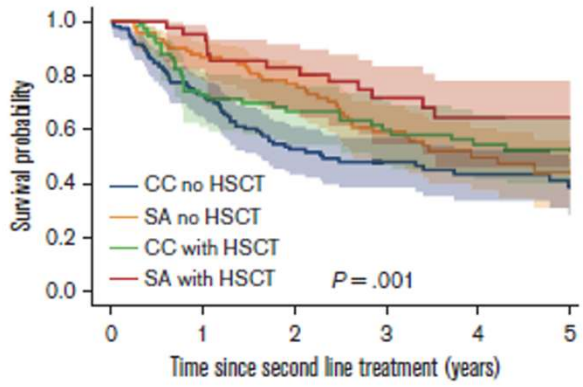
Weill Cornell / Columbia Experience (1998-2021, n=184)







PETAL Consortium Novel Agents in 2nd line favorably impacted outcomes



Older or transplant-ineligible individuals with R/R PTCL may benefit from individualized single-agent therapy based on prior treatment, efficacy, tolerability, and quality of life considerations

CC = cytotoxic chemotherapy; SA = single agent.

Tolu SS, et al. *Leuk Lymphoma*. 2025:66(13):2437-2447. Han J, et al. *Blood Adv*. 2025;9(3):583-602.

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Key Learning Points



- Clinical management of PTCL remains challenging
  - Heterogenous, uncommon and high-risk diseases
  - Diagnosis often delayed and inaccurate
- Genomic and molecular characterization of PTCL have contributed to biomarker-driven classifications to guide diagnosis and treatment planning
- Integrate knowledge of PTCL biology and novel agents into evidence-informed decision-making for patients with R/R or high-risk PTCL
- Novel agents and combinations are promising options for R/R diseases
  - Surface targets
    - Anti-CD30 directed therapies
  - Targeting epigenetics
    - HDAC, DNMT, EZH1/2 inhibitors
  - Targeting signaling pathways
    - PI3Ki, JAKi, ITKi
  - Promising combinations
    - Romi+aza, romi+duv, rux+duv

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Q&A Session