1:15–1:55 PM

T-Cell Lymphoma

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THE 2nd ANNUAL HemOnc Pulse LIVE | AUSTIN 2025

Novel Agents and HCT in Nodal T-cell Lymphomas: Unanswered Questions and Top Research Priorities

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DISCLOSURES

- **Grant support-** Seattle Genetics, Secura Bio, Astra Zeneca, Myeloid, CRSPR, Daiichi Sankyo
- Consultancy- Secura Bio, Citius, Myeloid, Kyowa Kirin
- Speaker Bureau- Kyowa Kirin

KEY CHALLENGES IN TREATING NODAL PERIPHERAL T-CELL LYMPHOMAS

- **Upfront therapy- how to choose the best regimen for my patient**
- Should ASCT be offered in CR1?
- **Relapsed disease – how to optimize treatment options**
- Role of allogeneic stem cell transplant
- **Special populations- elderly, frail**
- Rare subtypes

Current State

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b]

	FIRST-LINE THERAPY[c]
ALCL[d]	**Preferred regimen** • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[e] (category 1) **Other recommended regimens** (alphabetical order) • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) • CHOEP[f] (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) • CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
Other histologies • PTCL-NOS • EATL • MEITL[g] • AITL (WHO4R)/nodal TFH cell lymphoma, angioimmunoblastic type (WHO5) • *Nodal PTCL, TFH* (WHO4R)/nodal TFH cell lymphoma, NOS (WHO5) • FTCL (WHO4R)/nodal TFH cell lymphoma, follicular type (WHO5)	**Preferred regimens** (alphabetical order) • Brentuximab vedotin + CHP for CD30+ histologies[e,h] • CHOEP[f] • CHOP • Dose-adjusted EPOCH **Other recommended regimens** (alphabetical order) • CHOP followed by IVE (ifosfamide, etoposide, and epirubicin) alternating with intermediate-dose methotrexate (Newcastle Regimen; studied only in patients with EATL)[i] • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

FIRST-LINE CONSOLIDATION
• Consider consolidation with autologous HCT

Footnotes on PTCL-B 6 of 8

See Initial Palliative-Intent Therapy (PTCL-B 2 of 8)
See Second-Line and Subsequent Therapy:
• PTCL-NOS; EATL; MEITL; FTCL (PTCL-B 3 of 8)
• AITL, including nodal PTCL, TFH (PTCL-B 4 of 8)
• ALCL (PTCL-B 5 of 8)

Note: All recommendations are category 2A unless otherwise indicated.

Heterogeneity of T-Cell Lymphomas

Primarily Leukemic

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic LPD of NK cells

Adult T-cell leukemia/lymphoma

EBV+ T-/NK-Cell LPDs of Childhood

Severe mosquito bite allergy

Hydroa vacciniform LPD

- Classic and systemic

Severe mosquito bite allergy

Chronic active EBV disease (systemic)

- T-cell and NK-cell phenotypes

Systemic EBV+ T-cell lymphoma of childhood

EBV+ T-/NK-Cell Lymphoma/Leukemia

Extranodal NK/T-cell lymphoma (nasal)

Aggressive NK-cell lymphoma

Primary nodal EBV+ T-/NK-cell lymphoma

Primarily Extranodal Entities

Enteropathy-associated T-cell lymphoma

Type II refractory celiac disease

Monomorphic epitheliotropic intestinal T-cell lymphoma

Indolent clonal T-cell LPD of the GI tract

Indolent clonal T-cell LPD of the GI tract

Hepatosplenic T-cell lymphoma

Primarily Nodal and Anaplastic

PTCL NOS (not otherwise specified)

Follicular helper T-cell lymphoma

- AITL
- Follicular
- NOS

ALCL

- ALK-
- ALK+

Breast implant-associated ALCL

Cutaneous T-Cell LPDs/Lymphomas

Mycosis fungoides

Sezary syndrome

Primary cutaneous CD30+ T-cell LPDs

- Lymphomatoid papulosis
- Primary cutaneous anaplastic large-cell lymphoma

Primary cutaneous small/medium CD4+ T-cell LPD

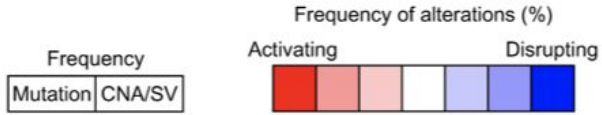
Subcutaneous panniculitis-like T-cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous acral CD8+ T-cell LPD

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

Molecular Heterogeneity of PTCL-NOS



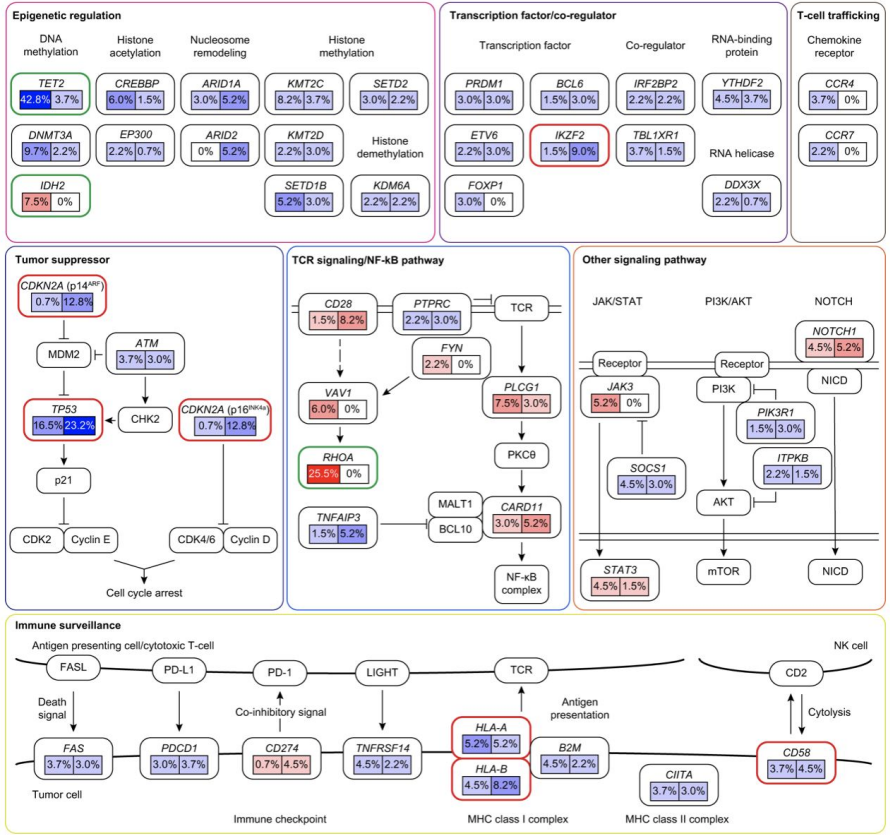
):2159-2170

Most common alterations

- Epigenetic regulation 50/133
- Tumor suppressor 42/133

Significant heterogeneity

- 80% carried ≥ 1 mutation
- 49 “recurrently” altered genes (found in ≥ 3 cases)
- But only 10 were affected in ≥ 5% of the cases



Progress in the Field

1968 T cells described

1974 Kiel /Luke Collins classification lists T cell lymphoma subtypes- morphology

1982 Working formulation

2000 REAL classification described Mature T cand NK cells neoplasms

2008 WHO classification -13 subtypes of T cell lymphoma

2009 - **Pralatrexate** and **Romidepsin** gets approved for relapsed PTCL

2014- **Belinostat** gets approved for RR PTCL- **Chidamide** gets approved for RR PTCL in China - **Mogamulizumab** gets approved for CCR4+ RR PTCL in Japan

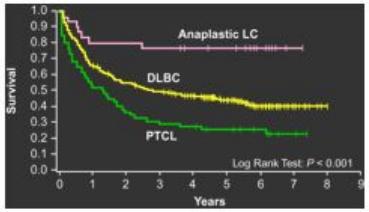
2017- **Brentuximab Vedotin** gets approved for RR ALCL

2016 WHO classification - 22 major subtypes of T cell lymphoma

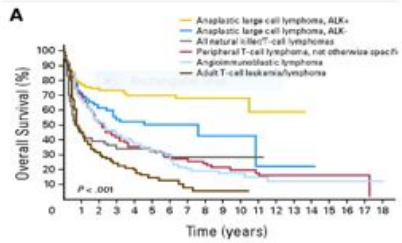
201[illegible] **Brentuximab + CHP** gets FDA approval for first line treatment of CD30+ PTCL

2022- withdrawal of FDA approval for Romidepsin

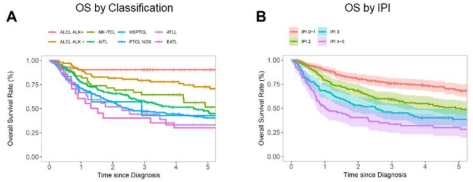
2022- 5th WHO Classification - integration of clinical features, immunophenotype and genetics -over 30 major subtypes



Armitage – Ann of Oncol 2004



Vose et al: JCO 2008



Lymphoma epidemiology of outcomes and molecular epidemiology resource (leo-mer) prospective cohort study (20 years)

Ruan et al. ASH 2022.

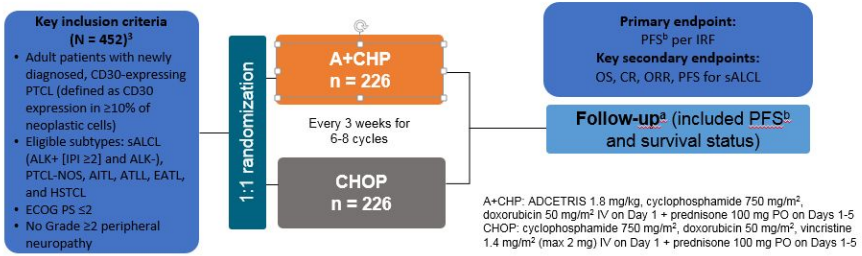
Brentuximab Plus CHP vs CHOP

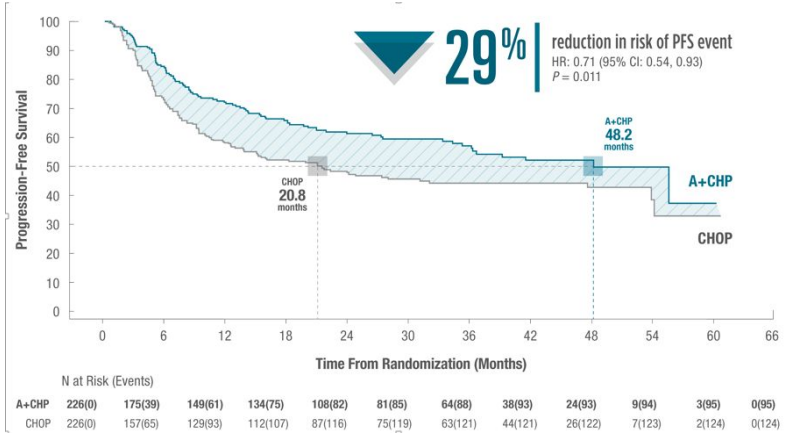
Echelon -2 Frontline treatment with A+CHP vs CHOP for newly diagnosed, CD30-expressing PTCLs demonstrated a 29% reduction in risk of PFS event (HR: 0.71; 95% CI: 0.54-0.93; *P* = 0.011)

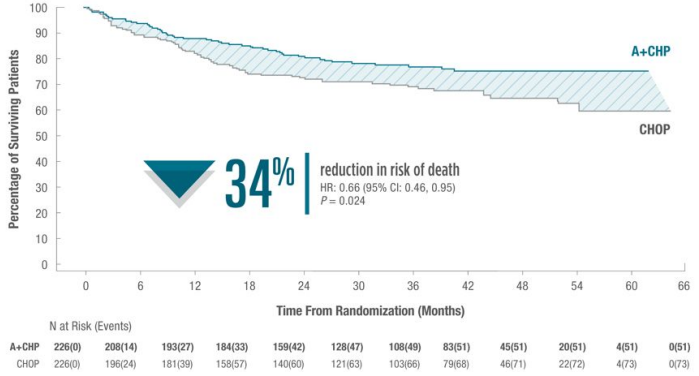
A+CHP more than doubled median PFS vs CHOP (48.2 vs 20.8 months, respectively)

34% reduction in risk of death with A+CHP (HR: 0.66; 95% CI: 0.46-0.95; *P* = 0.024)[1]. Median OS was not reached in either arm

A+CHP has a comparable safety to CHOP







Horwitz et all. *Lancet*. 2019.

Food for Thought

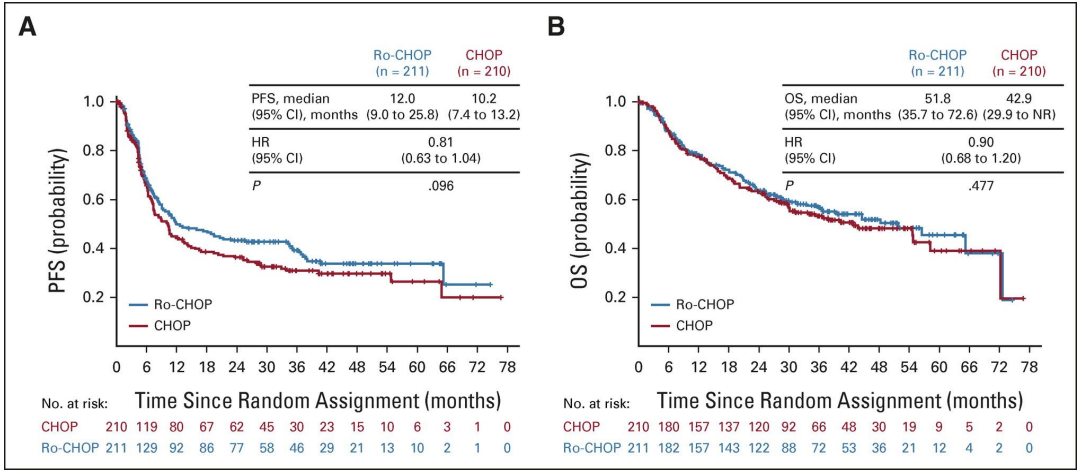
Analysis by Subtypes: Estimated 5-year PFS and OS rates in prespecified subgroups

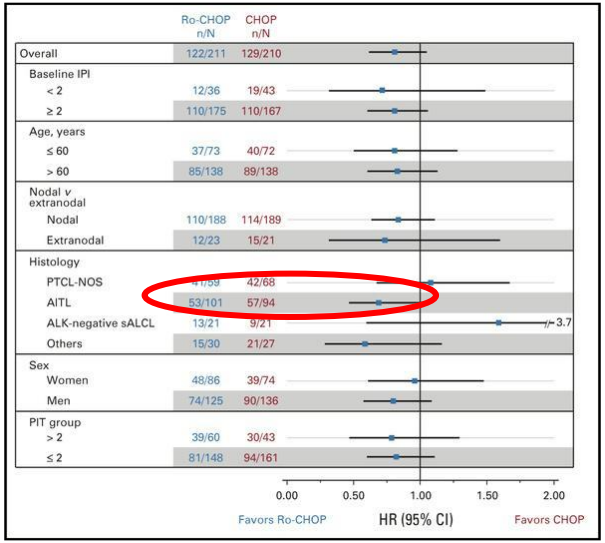
Subgroup	Estimated 5-year PFS rate A+CHP	Estimated 5-year PFS rate CHOP	HR (95% CI)	P-value	Estimated 5-year OS rate A+CHP	Estimated 5-year OS rate CHOP	HR (95% CI)	P-value
PTCL subtype								
PTCL-NOS, % (n)	26.5 (29)	25.7 (43)	0.79 (0.43, 1.43)	0.4	46.2 (29)	35.9 (43)	0.75 (0.37, 1.48)	0.4003
AITL, % (n)	26.6 (30)	48.1 (24)	1.41 (0.64, 3.11)	0.3958	67.8 (30)	62.5 (24)	1.01 (0.40, 2.55)	0.9855
sALCL								
Overall, % (n)	60.6 (162)	48.4 (154)	0.55 (0.39, 0.79)	0.0009	75.8 (162)	68.7 (154)	0.66 (0.43, 1.01)	0.0529
ALK+ % (n)	87 (49)	67 (49)	0.40 (0.17, 0.98)	0.0372	91.5 (26)	79.6 (27)	0.48 (0.16, 1.40)	0.1688
ALK– % (n)	49 (113)	39 (105)	0.58 (0.40, 0.86)	0.0054	68.7 (50)	63.3 (41)	0.71 (0.44, 1.12)	0.1373
sALCL, IPI Score								
0–1, % (n)	59.5 (41)	47.6 (32)	0.42 (0.18, 0.94)	0.0301	87.0 (41)	86.2 (32)	0.73 (0.20, 2.73)	0.6411
2–3, % (n)	68.5 (95)	50.9 (100)	0.57 (0.35, 0.90)	0.0158	80.6 (95)	68.7 (100)	0.57 (0.32, 1.01)	0.0496
4–5, % (n)	27.2 (26)	36.4 (22)	0.73 (0.35, 1.50)	0.3839	38.0 (26)	43.2 (22)	0.89 (0.42, 1.89)	0.7606

ITT, intent-to-treat; IPI, International Prognostic Index

Horwitz et al. ASH 2021.

Romidepsin Plus CHOP vs CHOP





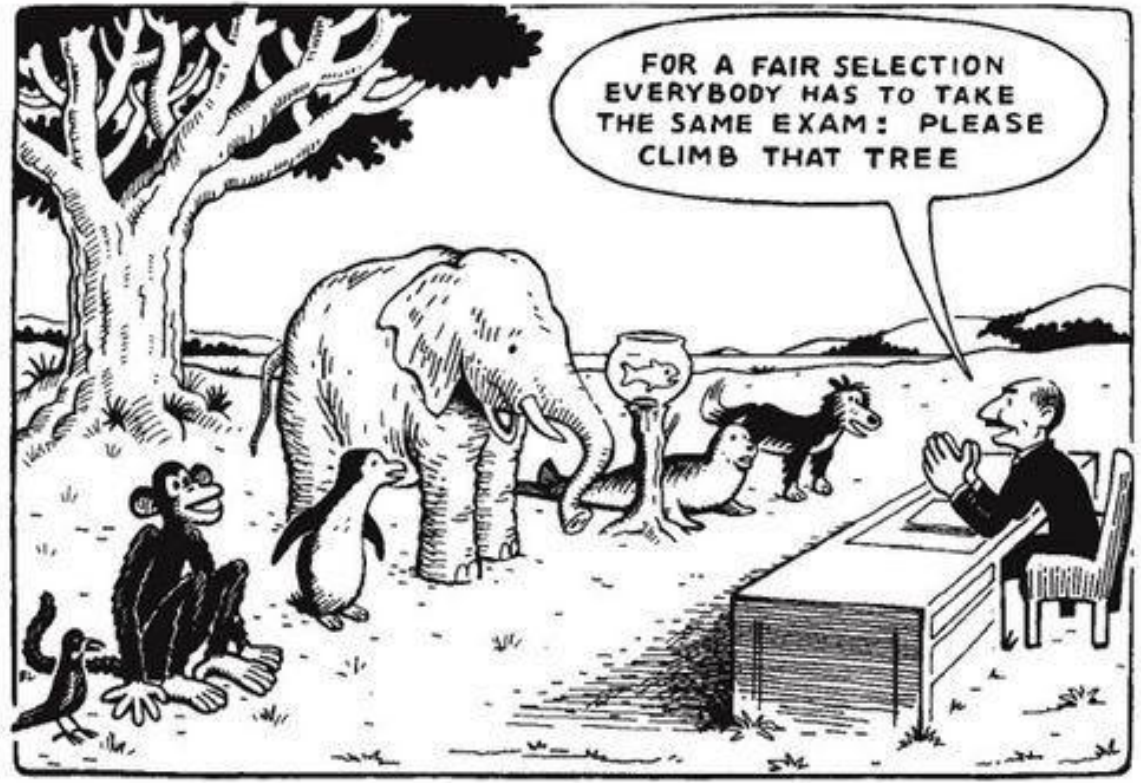
CHOP+ Romidepsin (Ro-CHOP) – Initial results ORR 78% including 66% CR. Randomized phase 3 is negative Romidepsin +CHOEP – did not meet primary end point

.

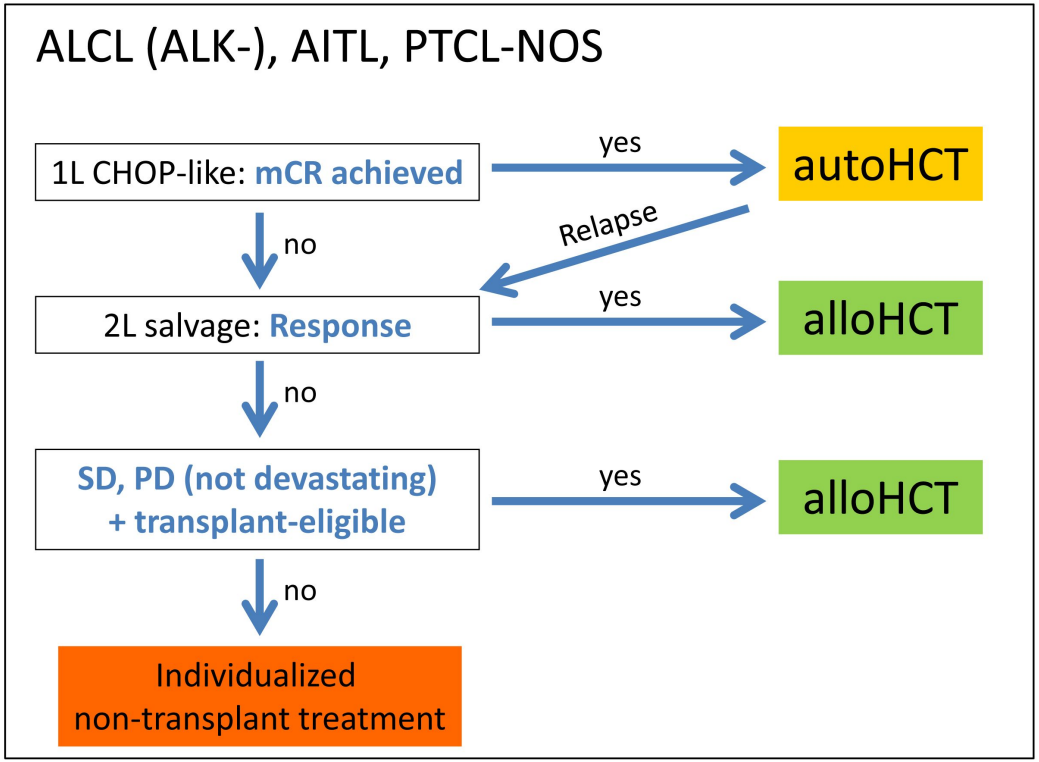
Subgroup analysis showed that prolonged PFS as seen in the TFH subgroup Secondary end point analysis – DOR was longer in the Ro CHOP arm

Bachy et al. *J Clin Oncol*. 2022.

One Size Fits All?



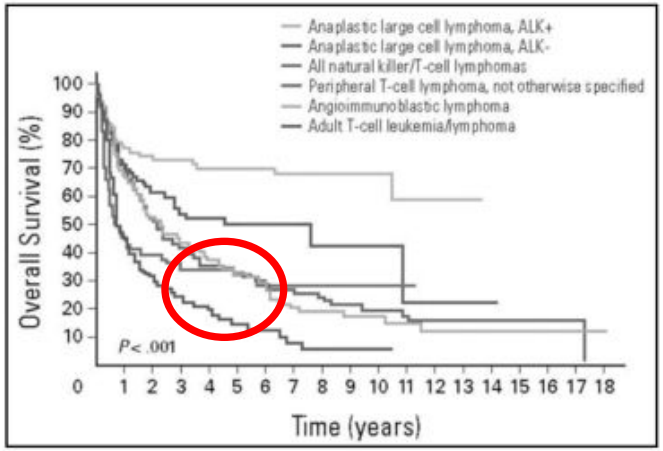
Role of Stem Cell Transplant in T-Cell Lymphoma



Peter Dreger. Am Soc Hematol Educ Program, 2024.

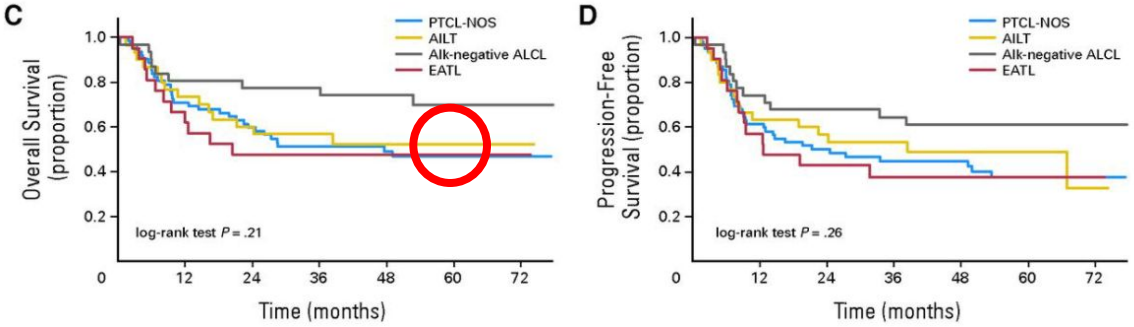
Effect of Upfront Transplant in Nodal PTCL

International T-cell lymphoma project



Vose et al - 2008

Effect of upfront ASCT



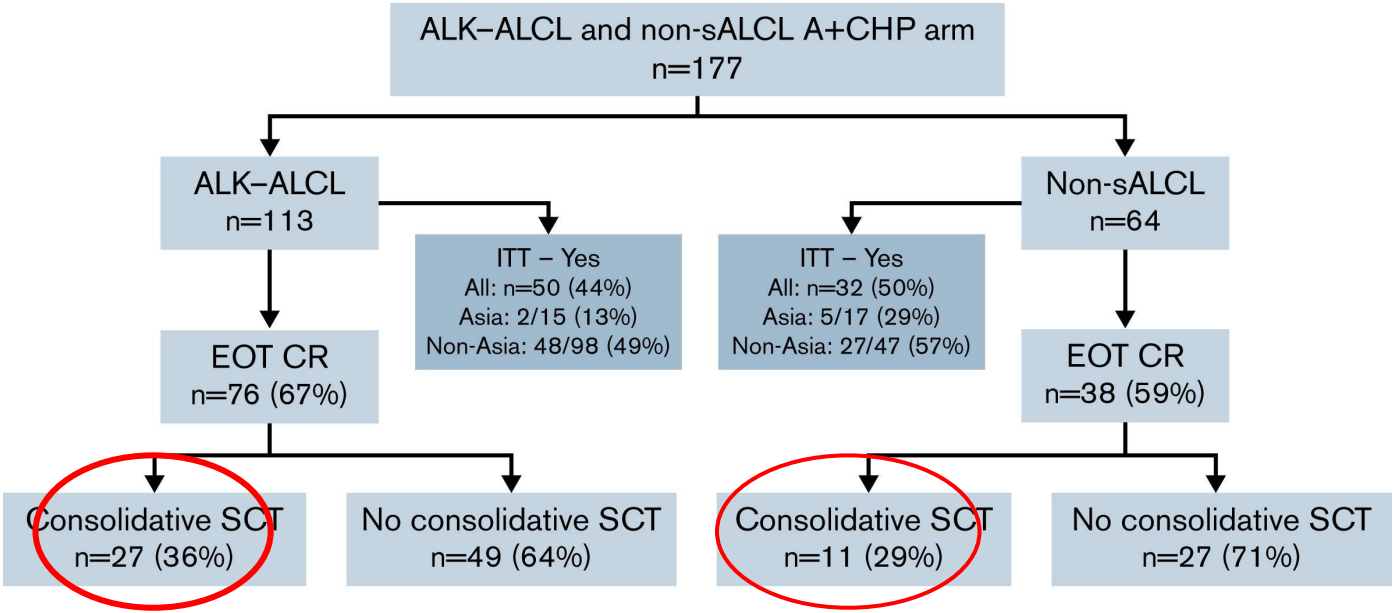
D'Amore et al JCO 2011

	ALCL ALK+	ALCL ALK-	PTCL-NOS	AITL	NK/T
Int T-cell Project	70%	49%	32%	32%	9%
D'Amore et al	Not included	70	47	52	44

Transplant or Not?

- PubMed search for the words “stem cell transplant” and “T-cell lymphoma” showed up 471 ARTICLES IN THE LAST 10 YEARS
- Both NCCN and CIBMTR recommend to consider autologous stem cell transplant as consolidation for initial treatment of nodal T-cell lymphomas- 2 major prospective trials and Echelon 2
- Remains controversial
- No consensus for conditioning regimen

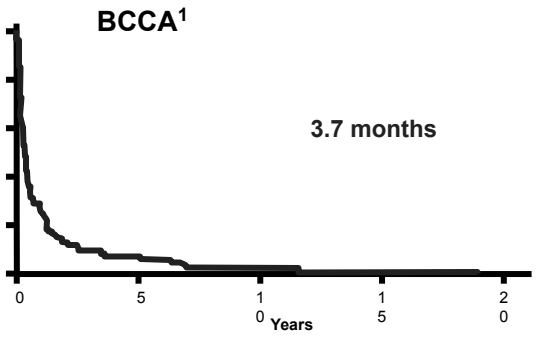
Subanalysis of ECHELON-2: Only a Third of Patients in CR Received a Transplant

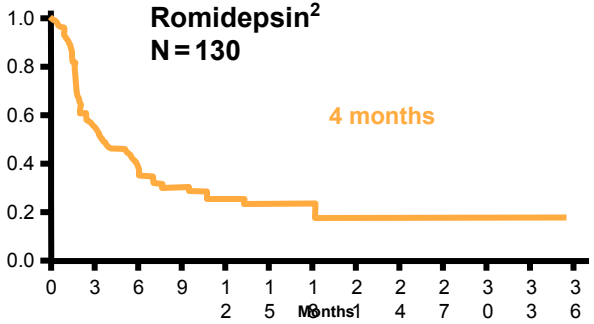


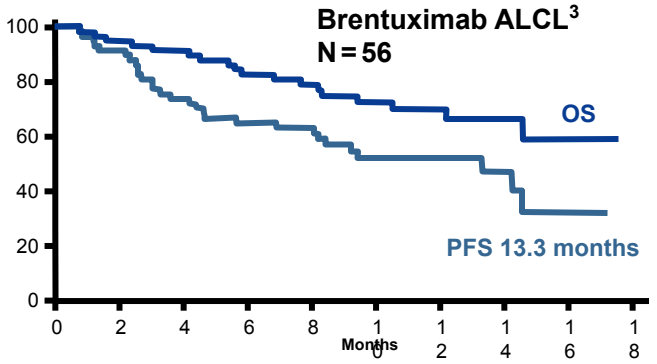
ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; CR = complete response; EOT = end of treatment; ITT = intention to transplant; sALCL = systemic ALCL; SCT = stem cell transplant

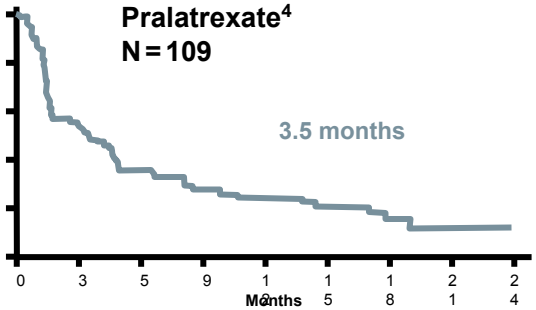
Savage KJ. *Blood Adv*. 2022.

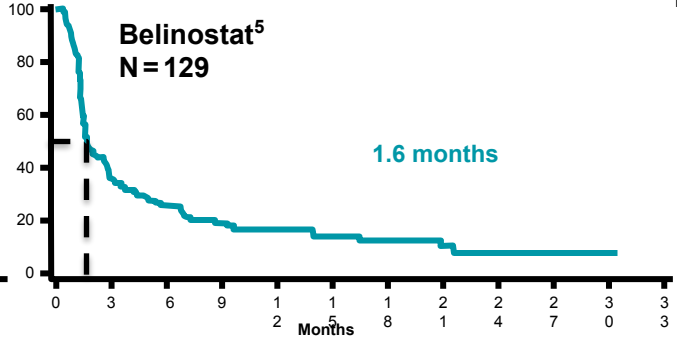
PFS of Relapsed/Refractory PTCL

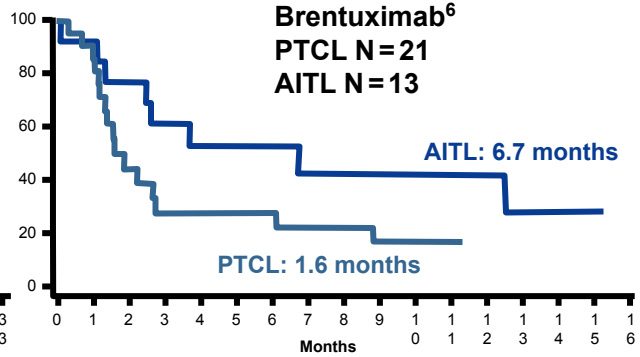






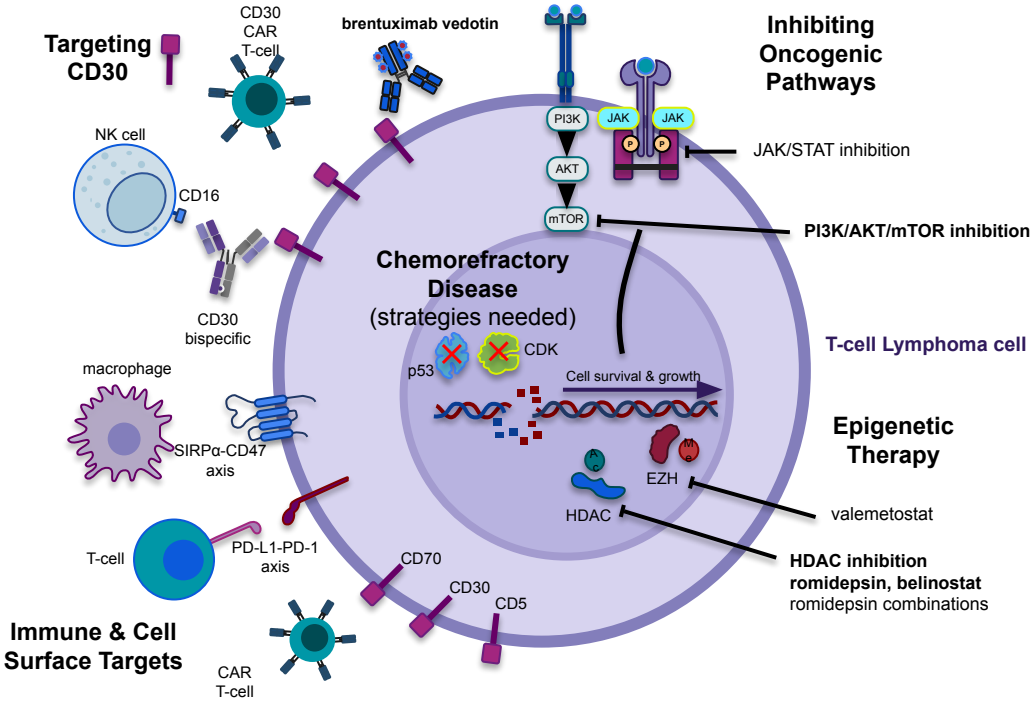






Mak V et al. *J Clin Oncol*. 2013.
Coiffier B et al. *J Clin Oncol*. 2012.
Pro B et al. *J Clin Oncol*. 2012.
O'Connor OA et al. *J Clin Oncol*.
O'Connor OA et al. *J Clin Oncol*. 2015.
Horwitz SM et al. *Blood*. 2022

Therapeutic Targets in T-Cell Lymphomas



Stuver R. *Cancers (Basel)*. 2023.

Duvelisib Monotherapy: Response by Subtype

	PTCL-NOS (n = 52)	AITL (n = 30)	ALCL (n = 15)
ORR by baseline histology, n (%)	25/52 (**48.1**)	20/30 (**66.7**)	2/15 (**13.3**)
Best overall response, n (%)			
Complete response, n (%)	14/52 (26.9)	16/30 (53.3)	2/15 (13.3)
Partial response, n (%)	11 (21.2)	4 (13.3)	NC
Median PFS by IRC, mo (95% CI)	3.4 (1.8, 8.1)	9.1 (6.2, NC)	1.5 (0.7, 1.7)
Median OS, mo (95% CI)	10.9 (5.1, NC)	15.5 (9.5, 18.0)	4.8 (1.7, 15.7)
Median time to response (range)	1.7 (1.7, 0.5)	1.8 (1.9, 0.5)	2.6 (2.6, 1.3)
Median DOR by IRC, mo (95% CI)	5.5 (2.0, 9.2)	8.8 (7.7, NC)	1.9 (1.9, 2.0)
Median DOR for pts achieving CR	7.4 (6.4, NC)	7.9 (3.3, NC)	1.9 (1.9, 2.0)

Duvelisib is not FDA approved for PTCL
Mehta-Shah N, et al. *Hemasphere*. 223

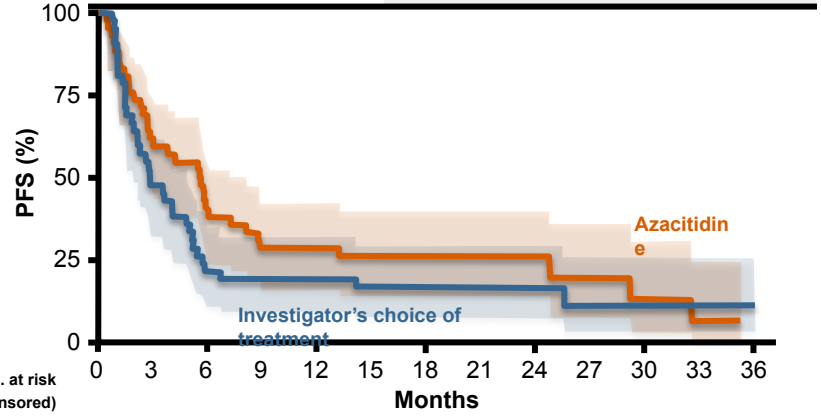
Other PI3K Inhibitor Monotherapies Under Investigation

	Linperlisib[1]	Tenalisib [2]
Target	PI3Kd	PI3K δ/γ
Trial (Phase)	NCT04108325 (1b)	NCT02567656 (1/1b)
ORR/CR, %	60%/35%	46.7%/20% (PTCL subset)
mDoR	15 months (95%CI, 6.9–NE)	6.5 months (95% CI, 2.9–14.9) (PTCL subset)
mPFS	10 months (95%CI, 3.7– NE)	NR
AEs	• TRAEs: 39 of 43 pts (91%) • Most common grade ≥ 3 were neutropenia (21%), pneumonia (12%), and hypertriglyceridemia (7%)	• Most frequently reported TEAEs were fatigue (45%), AST increase (36%), ALT increase (35%), and diarrhea (33%) • Most common grade ≥ 3 TEAEs were transaminase elevations (21%), anemia (8.6%), neutropenia (6.9%), and hyponatremia (6.9%) • Grade 4 related TEAEs included two events of ALT increase and one event of sepsis

Qiu et al. *Blood* 2022, Huen A, et al. *Cancers (Basel)*. 2020

Phase 3 ORACLE Study: Oral Azacitidine vs Investigator's Choice

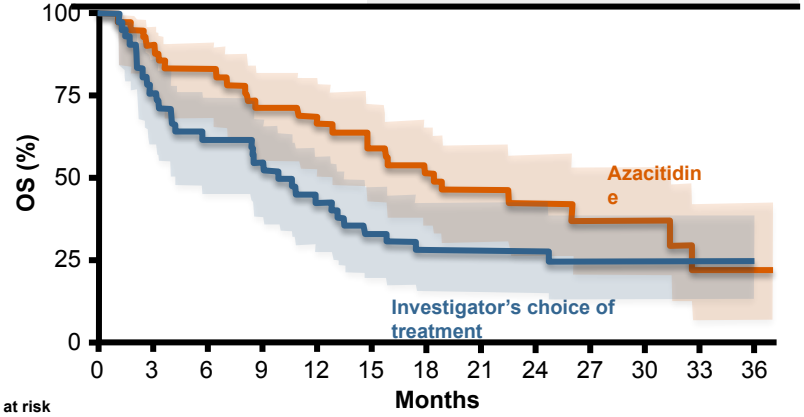
	Azacitidine	Investigator's choice
Median PFS, months (95% CI)	**5.6** (2.7–8.1)	**2.8** (1.9–4.8)
HR (95% CI)	**0.63** (0.38–1.07) 1-sided *P*=0.042	



No. at risk (no. censored)							
Azacitidine	42 (0)	17 (0)	12 (0)	9 (2)	5 (6)	2 (7)	0 (8)
Investigator's choice of treatment	44 (0)	9 (2)	8 (0)	5 (4)	3 (6)	2 (6)	1 (7)

Primary end point: PFS based on local assessment

	Azacitidine	Investigator's choice
Median OS, months (95% CI)	**18.4** (12.9–31.5)	**10.3** (4.2–13.5)
HR (95% CI)	**0.56** (0.32–0.96)	



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Dupuis J, et al. *Lancet Haematol*. 2024;11(6):e406-e414.

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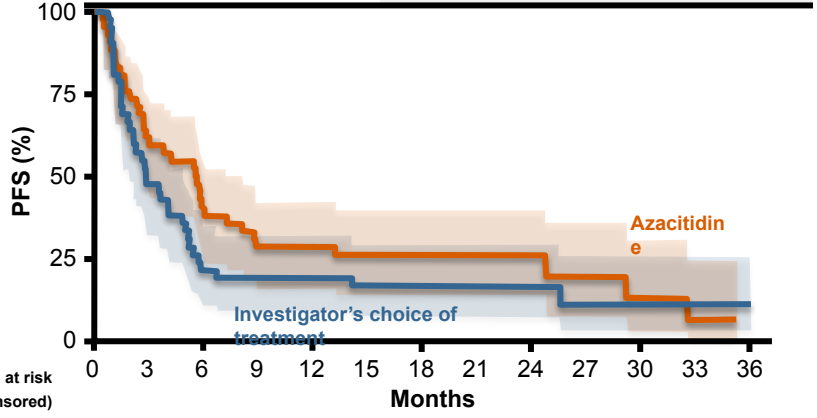

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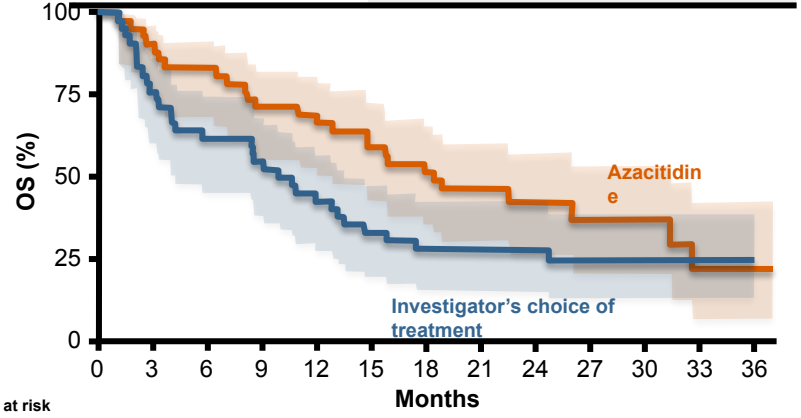
Investigator's choice of treatment	44 (0)						

Primary end point: PFS based on local assessment
Superiority would be claimed if 1 sided stratified *P* value was less than 0.025

	Azacitidine	Investigator's choice
Median OS, months (95% CI)	**18.4** (12.9–31.5)	**10.3** (4.2–13.5)
HR (95% CI)	**0.56** (0.32–0.96)	

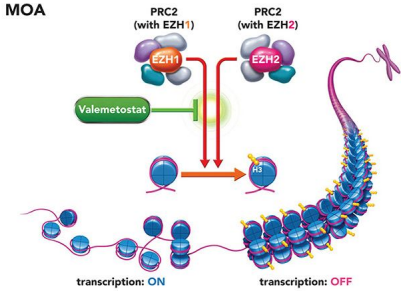


No. at risk (no. censored)							
Azacitidine	42 (0)	35 (0)	29 (0)	20 (2)	11 (8)	6 (12)	2 (14)
Investigator's choice of treatment	44 (0)	26 (2)	18 (2)	11 (3)	9 (5)	5 (8)	1 (12)

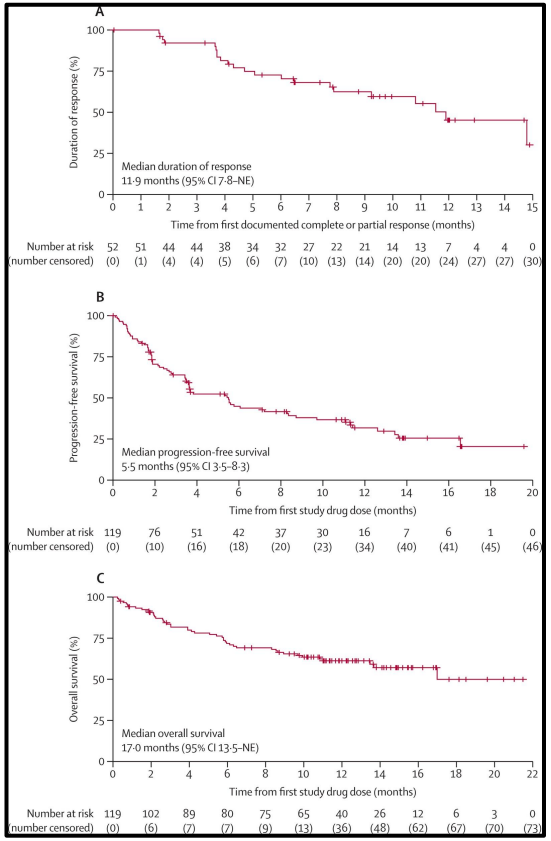
5-Azacitidine is not FDA approved for PTCL
Dupuis J, et al. *Lancet Haematol*

Targeting the Histone Methylation

- Valemetostat
- Targets EZH1 and EZH2
- Prevents methylation of lysine 27 on H3 (H3K27)



	N=119	AITL n=42	PTCL-TFH n=8	PTCL-nos n=41	ALCLn =9	Other n=19
ORR	52 (43.7%)	54%	50%	31%	33%	47%
CR	14%	18%	12%	10%	11%	16%
SD	17%	24%	13%	20%	11%	5%
DOR	11.9 months	11.9 months		7.9 months	3.8 months	9.2 months



Zinzani et al. *Lancet*. 2024.

Targeting the Jak/STAT Pathway

Response by Cohort

Cohorts	Total treated, n	Total evaluable for response, n	ORR n (%)	CBR n (%)
Cohort 1	21	21	**7 (33%)**	10 (48%)
Cohort 2	15	14	**4 (29%)**	5 (36%)
Cohort 3	17	17	**2 (12%)**	3 (18%)
Total	53	52	**13 (25%)**	18 (35%)
P (cohorts 1 & 2 vs 3)			***P*=0.2**	*P*= 0.073

Response by Subtype

Subtype	Evaluable for response, n	ORR n (%)	CBR n (%)
PTCL-NOS	11	**2 (18%)**	2 (18%)
T-PLL	8	**3 (38%)**	4 (50%)
AITL/TFH	9	**3 (33%)**	4 (44%)
T-LGL	5	**2 (40%)**	4 (80%)
ALCL	4	**1 (25%)**	1 (25%)
ATLL	3	**0**	0
CTCL	7	**1 (14%)**	1 (14%)
G/D TCLs	4	**1 (25%)**	1 (25%)
SPTCL	1	**0**	1 (100%)

- Adverse events were consistent with the known side effect profile of ruxolitinib and primarily involved cytopenias
- Treatment-related SAEs included herpes simplex virus-1 stomatitis (n = 1), spontaneous bacterial peritonitis (n = 1), febrile neutropenia (n = 3), anemia (n = 1), and herpes zoster (n = 1)

Ruxolitinib is not FDA approved for PTCL
Moskowitz AJ, et al. *Blood*. 2021

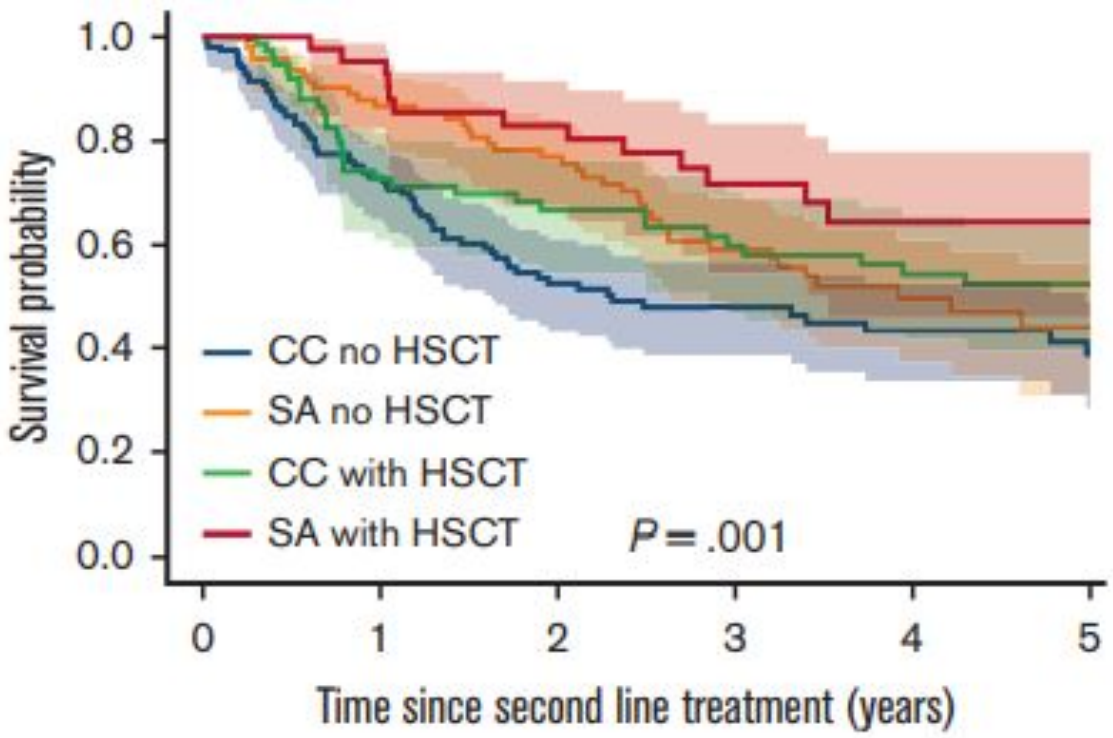
Phase 2 JAKPOT08 Study: Golidocitinib for R/R PTCL

	n = 88	
Tumor response	**By IRC**	**By investigator**
ORR, n (%)	39 (44.3)	33 (37.5)
Overall response, n (%)		
Complete response	21 (23.9)	11 (12.5)
Partial response	18 (20.5)	22 (25.0)
Stable disease	17 (19.3)	17 (19.3)
Progressive disease	20 (22.7)	27 (30.7)
Not evaluable	12 (13.6)	11 (12.5)

Histology subtypes*	Total number of subjects, n** (%)	ORR*** n (%)	CRR*** n (%)
PTCL-NOS	50 (56.8)	23 (46.0)	14 (28.0)
AITL	16 (18.2)	9 (56.3)	4 (25.0)
ALCL	10 (11.4)	1 (10.0)	0
NKTCL	3 (3.4)	2 (66.7)	1 (33.3)
Others	9 (10.2)	4 (44.4)	2 (22.2)

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

Prognosis for R/R Mature T-Cell and NK Cell Lymphomas: Results From the PETAL Consortium



Han et al. *Blood Adv*. 2025. – PETAL consortium

How to Make Sense of All These Data for Relapsed/Refractory PTCL

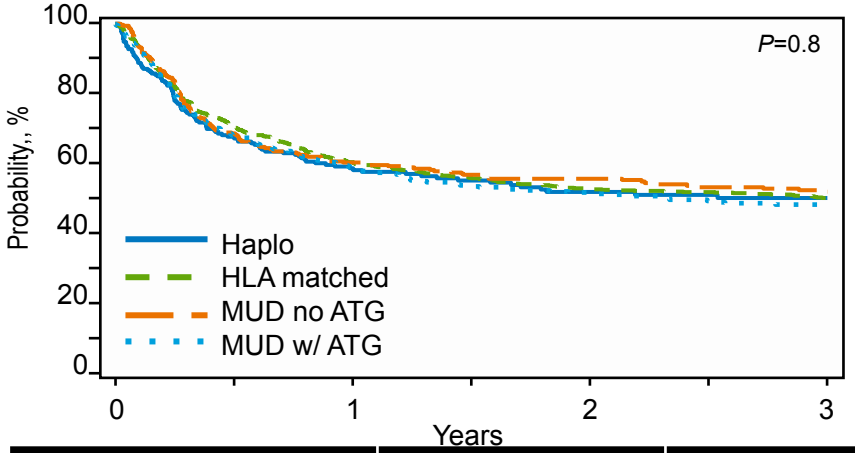
- Clinical trial – novel agents in study – CDK9 inhibitors, EZH2 inhibitors
- Send for mutation analysis if possible
- For TFH subtypes – prefer
  - Epigenetic therapies – romidepsin alone or in combination– (5 aza, lenalidomide)
  - Duvelisib
- ALCL- alk+
  - Alk inhibitors
  - BV- can try again if not previously refractory
  - Pralatrexate
- ALCL- alk –ve
  - BV- can try again if not previously refractory, BV + bendamustine
  - Pralatrexate
- PTCL-nos
  - Duvelsib
  - Epigenetic therapy
  - Pralatrexate

Allogeneic stem cell transplant in eligible patients

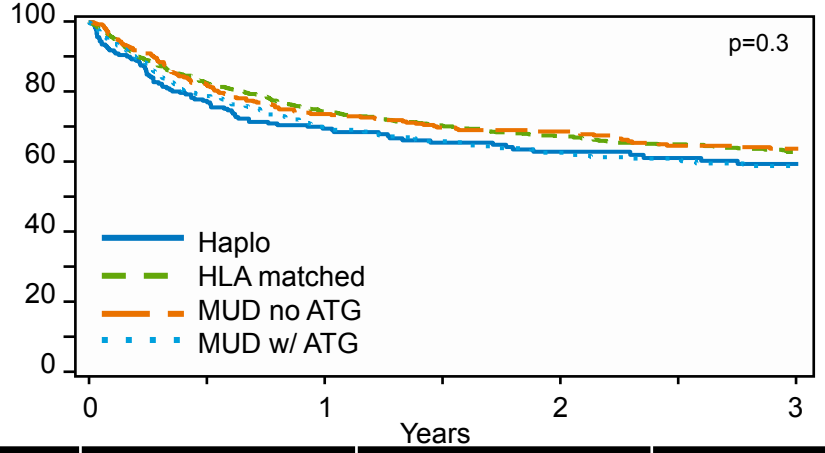
If transplant ineligible, consider maintenance strategies

Allogeneic HCT Can Provide Durable Control in Mature T-cell Lymphomas

Progression-Free Survival



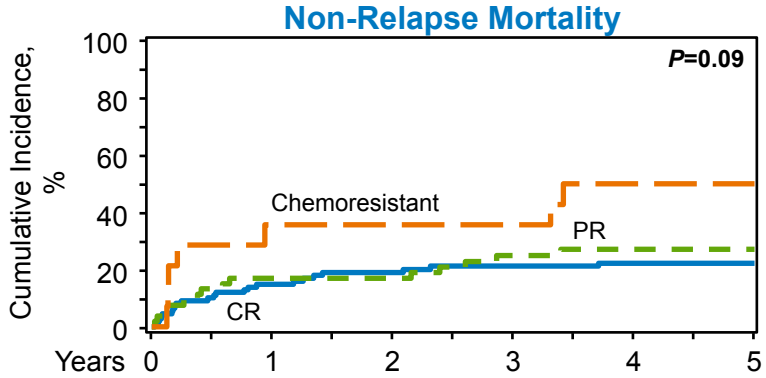
Overall Survival

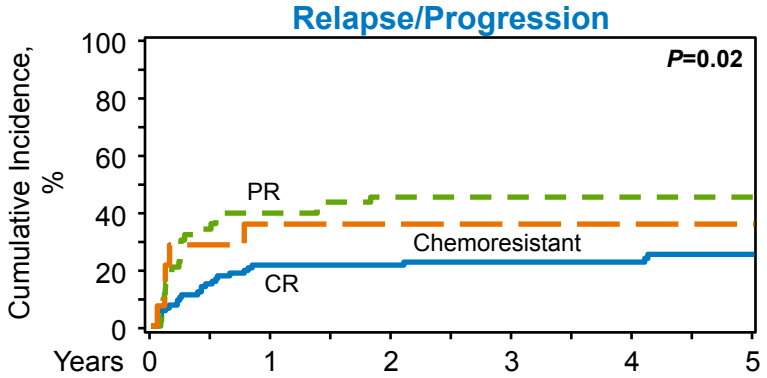


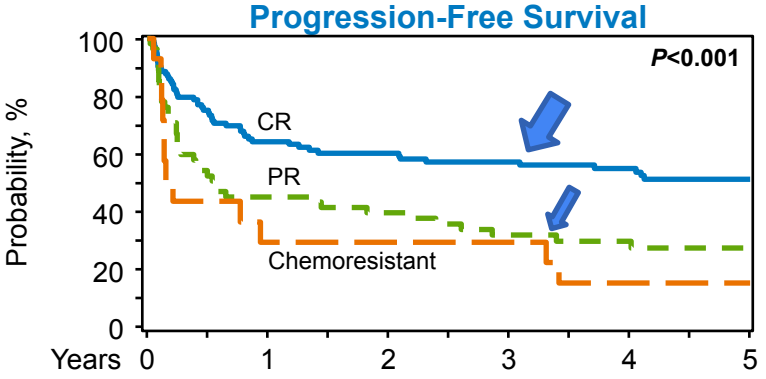
Outcomes	Haplo	Match Sibling	MUD w ATG	MUD w/o ATG	*P* Value
3-year PFS	50% (43-57)	50% (47-54)	48% (43-53)	52% (46-58)	0.80
3-year OS	60% (52-66)	63% (59-66)	59% (54-64)	64% (58-69)	0.30

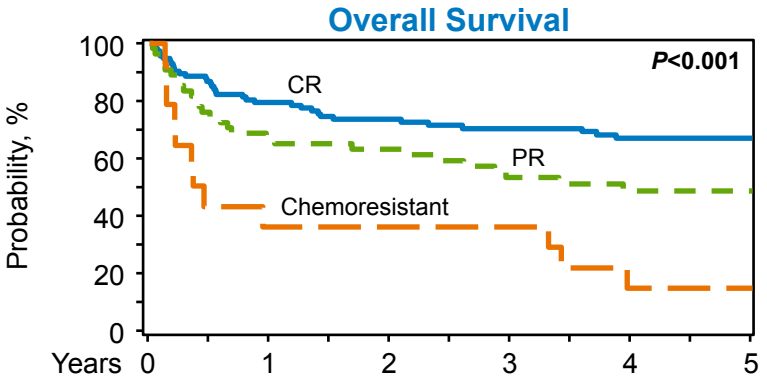
Hamadani M et al. *Blood Adv*. 2022;6(3):920-930.

Impact of Remission Status









Furqan F et al. *Br J Haematol*. 2023;200(1):54-63.

Conclusions

- R/R PTCL lacks a uniform standard-of-care approach[1,2]
  - Overall survival (OS) in R/R setting without allogeneic hematopoietic stem cell transplantation is less than 1 year
- Studies have usually taken a “one size fits all” approach with wide variations in outcomes for R/R PTCL
- Heterogeneous outcomes result from variations: subtypes, treatment approaches, and access to alloSCT
- Standard treatments for PTCL in the R/R setting include newer non-chemotherapeutic agents, combinations

THANK YOU

PANEL DISCUSSION

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