Where Science Becomes Hope

IMPACT OF PTCL SUBTYPE ON SELECTION OF FRONT-LINE TREATMENT

Mary Jo Lechowicz, MD

July 26th, 2024

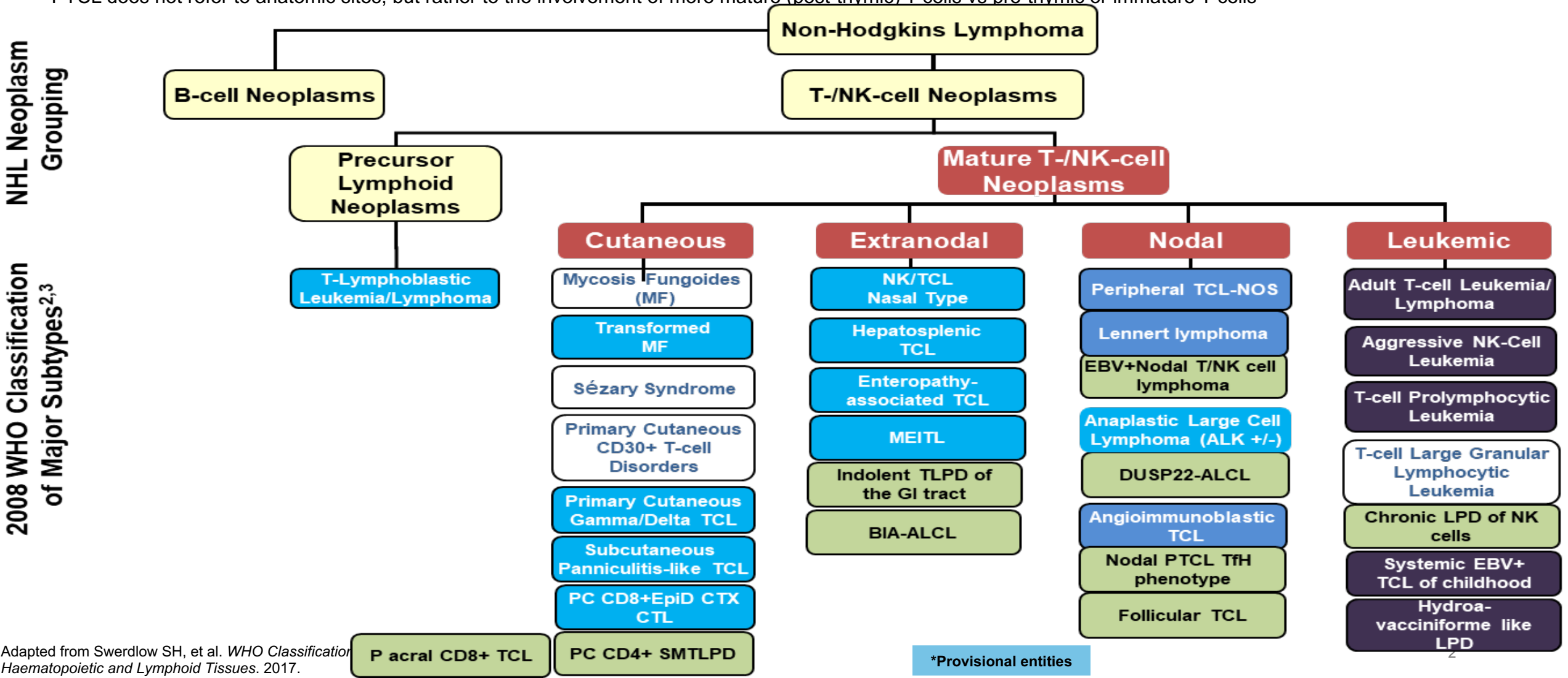
EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

Classification of Peripheral T-cell Lymphoma (PTCL)- WHO do we follow?

PTCL is a heterogeneous group of aggressive mature T-/NK-cell lymphomas

PTCL does not refer to anatomic sites, but rather to the involvement of more mature (post-thymic) T cells vs pre-thymic or immature T cells[1]



Adapted from Swerdlow SH, et al. *WHO Classification of Haematopoietic and Lymphoid Tissues*. 2017.

Table 2. WHO Classification of Haematolymphoid Tumours, 5th edition: T-cell and NK-cell lymphoid proliferations and lymphomas.

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Tumour-like lesions with T-cell predominance	
Kikuchi-Fujimoto disease	*Not previously included*
Indolent T-lymphoblastic proliferation	*Not previously included*
Autoimmune lymphoproliferative syndrome	*Not previously included*
Precursor T-cell neoplasms	
T-lymphoblastic leukaemia/lymphoma	
T-lymphoblastic leukaemia / lymphoma, NOS	T-lymphoblastic leukaemia/lymphoma
Early T-precursor lymphoblastic leukaemia / lymphoma	Early T-cell precursor lymphoblastic leukaemia
(Entity deleted)	NK-lymphoblastic leukaemia/lymphoma
Mature T-cell and NK-cell neoplasms	
Mature T-cell and NK-cell leukaemias	
T-prolymphocytic leukaemia	(Same)
T-large granular lymphocytic leukaemia	T-cell large granular lymphocytic leukaemia
NK-large granular lymphocytic leukaemia	Chronic lymphoproliferative disorder of NK cells
Adult T-cell leukaemia/lymphoma	(Same)
Sezary syndrome	(Same)
Aggressive NK-cell leukaemia	(Same)
Primary cutaneous T-cell lymphomas	
Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder	(Same)
Primary cutaneous acral CD8-positive lymphoproliferative disorder	Primary cutaneous acral CD8-positive T-cell lymphoma
Mycosis fungoides	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma	(Same)
Subcutaneous panniculitis-like T-cell lymphoma	(Same)
Primary cutaneous gamma/delta T-cell lymphoma	(Same)
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	(Same)
Primary cutaneous peripheral T-cell lymphoma, NOS	*Not previously included*

Alaggio et al
Leukemia
2022

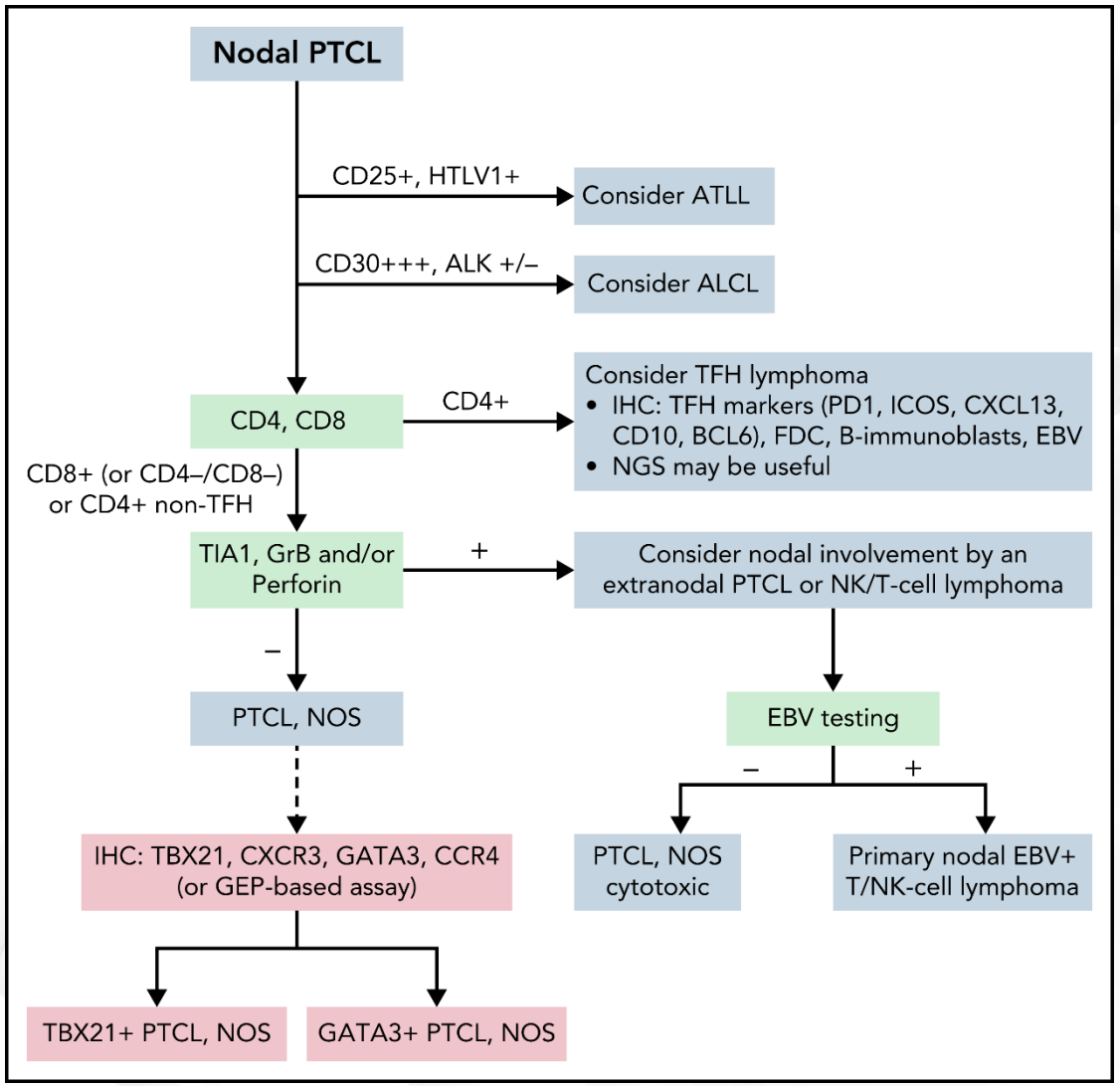
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas	
Indolent T-cell lymphoma of the gastrointestinal tract	Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract	*Not previously included*
Enteropathy-associated T-cell lymphoma	(Same)
Monomorphic epitheliotropic intestinal T-cell lymphoma	(Same)
Intestinal T-cell lymphoma, NOS	(Same)
Hepatosplenic T-cell lymphoma	
Hepatosplenic T-cell lymphoma	(Same)
Anaplastic large cell lymphoma	
ALK-positive anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-positive
ALK-negative anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-negative
Breast implant-associated anaplastic large cell lymphoma	(Same)
Nodal T-follicular helper (TFH) cell lymphoma	
Nodal TFH cell lymphoma, angioimmunoblastic-type	Angioimmunoblastic T-cell lymphoma
Nodal TFH cell lymphoma, follicular-type	Follicular T-cell lymphoma
Nodal TFH cell lymphoma, NOS	Nodal peripheral T-cell lymphoma with TFH phenotype
Other peripheral T-cell lymphomas	
Peripheral T-cell lymphoma, not otherwise specified	(Same)
EBV-positive NK/T-cell lymphomas	
EBV-positive nodal T- and NK-cell lymphoma	*Not previously included*

Table 2. continued

Extranodal NK/T-cell lymphoma	Extranodal NK/T-cell lymphoma, nasal-type
EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood	
Severe mosquito bite allergy	(Same)
Hydroa vacciniforme lymphoproliferative disorder	Hydroa vacciniforme-like lymphoproliferative disorder
Systemic chronic active EBV disease	Chronic active EBV infection of T- and NK-cell type, systemic form
Systemic EBV-positive T-cell lymphoma of childhood	(Same)

Alaggio et al
Leukemia 2022

CLASSIFICATION OF NODAL PERIPHERAL T-CELL LYMPHOMAS



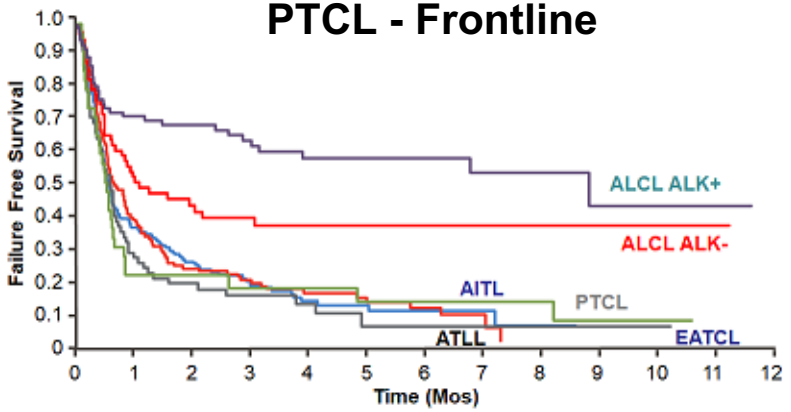
The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Elias Campo et al, Blood, 2022, Figure 5.

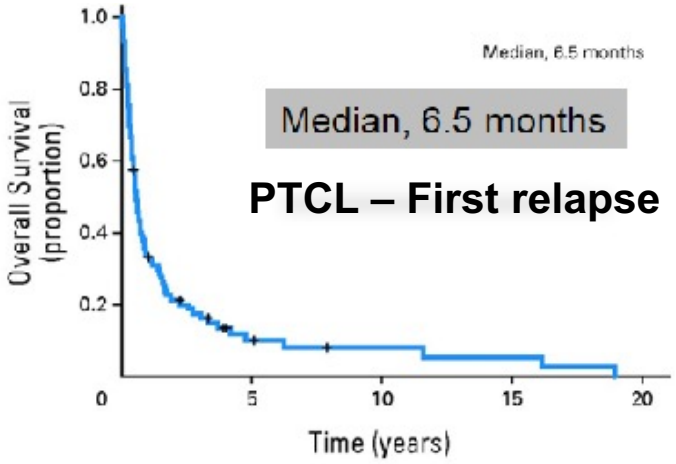
T/NK cell lymphoma: Prognosis by subtype

PTCL - Frontline



PTCL Subtypes: 5-yr OS%

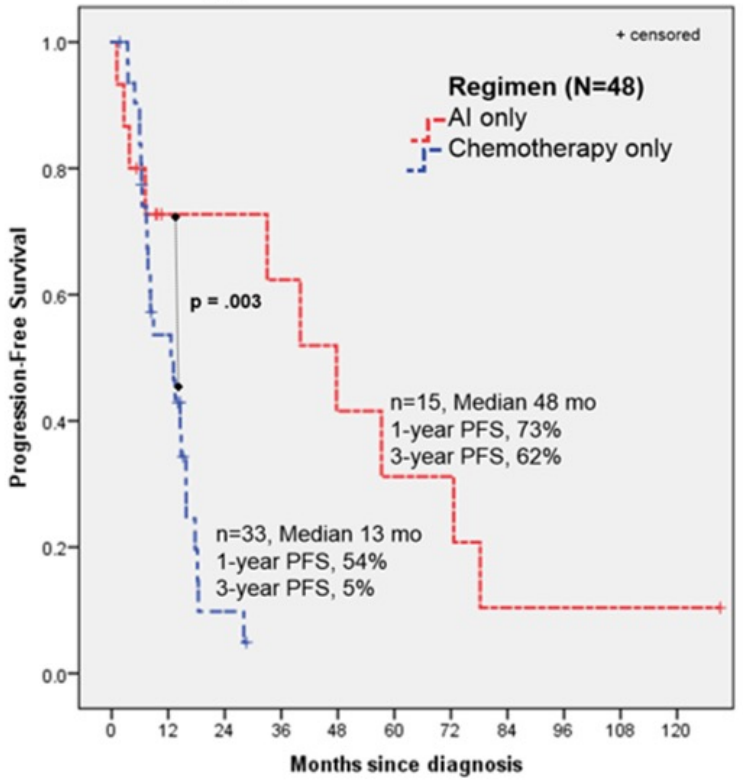
ALK+ ALCL	ALK– ALCL	PTCL-NOS	AITL	NK/TCL	ATLL
70	49	32	32	32	14



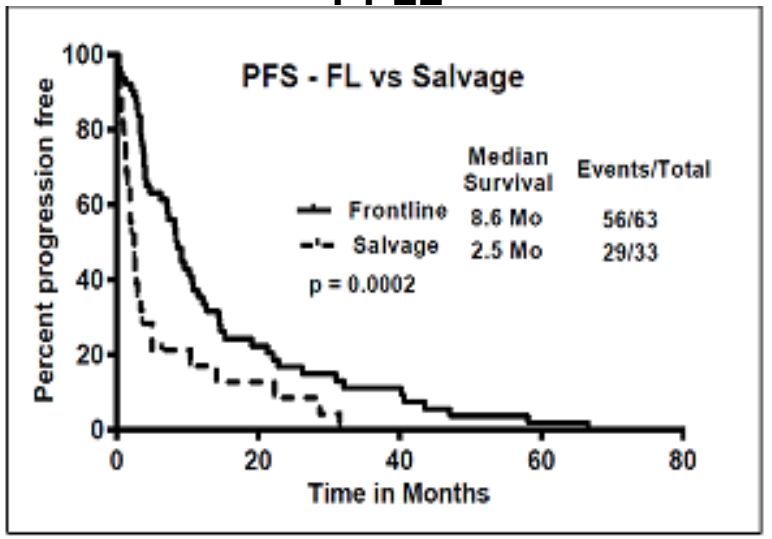
Median, 6.5 months

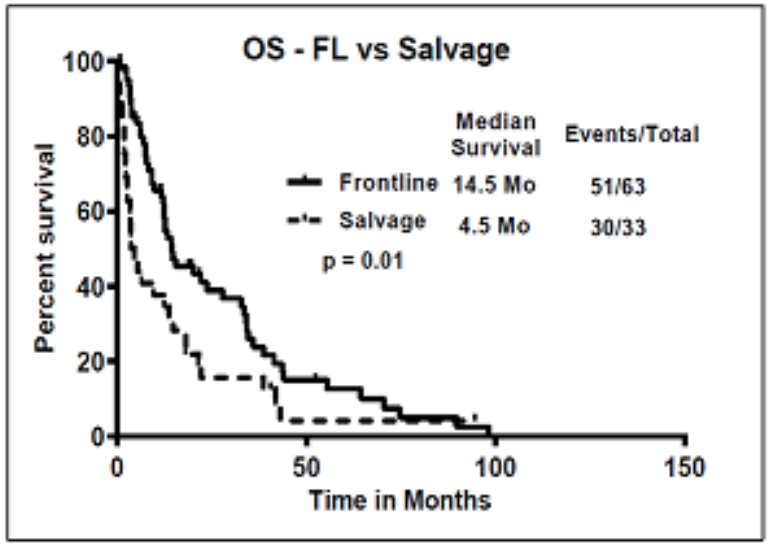
PTCL – First relapse

ATLL



T-PLL





International T-Cell Lymphoma Project. *J Clin Oncol*. 2008;26:4124-4130. [1] Armitage JO, et al. *Ann Oncol.* 2004;15:1447–1449. [2] Savage KJ. *Blood Rev.* 2007;21:201–216. [3] Rüdiger T, et al. *Ann Oncol.* 2002;13:140-149. Katsuya, Blood, 2015; Malpica, Blood Advances, 2018; Malpica, JCO GO, 2021. Jain P, et al. Annals of Oncology 2017

T-CELL LYMPHOMA SUBTYPES BASED ON UTILITY OF CHOP TREATMENT

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Always

Anaplastic large-cell, ALK-1 positive

CHOP variations

Peripheral T-cell lymphoma, NOS

Angioimmunoblastic T-cell lymphoma

Anaplastic large-cell, ALK-1 negative

Enteropathy-type intestinal lymphoma

Subcutaneous panniculitis-like T cell

Hepatosplenic T-cell lymphoma

Adult T-cell leukemia/lymphoma

Never

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30+ disorders

- Anaplastic large-cell lymphoma
- Lymphomatoid papulosis

T-cell large granular lymphocytic

Extranodal NK/T-cell lymphoma, nasal

NK/T-cell leukemia/lymphoma

T-cell prolymphocytic leukemia

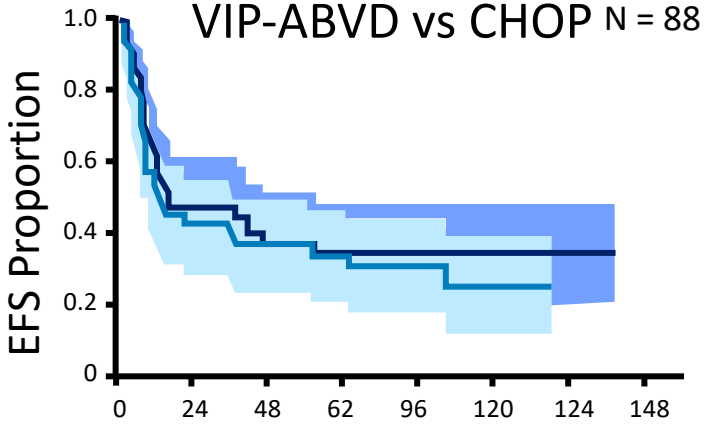
- Is there an R-CHOP?
  - Romidepsin
  - Revlimid
  - Alemtuzumab
  - Brentuximab
  - Etoposide
  - Azacitidine
  - PI3Kγδ inhibitors

With permission from S Iyer

Gallamini A, et al. Blood. 2007;110:2316-2323. Foss F, et al. 2008 ICML. Abstract.

SELECTED ATTEMPTS TO IMPROVE UPON CHOP FOR PTCL

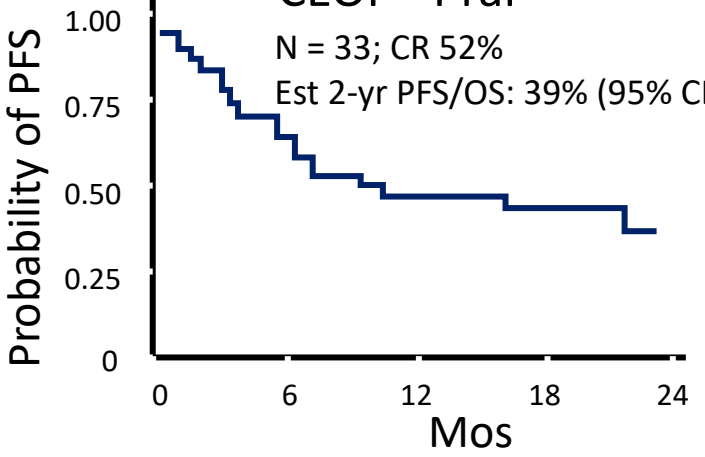
VIP-ABVD vs CHOP N = 88



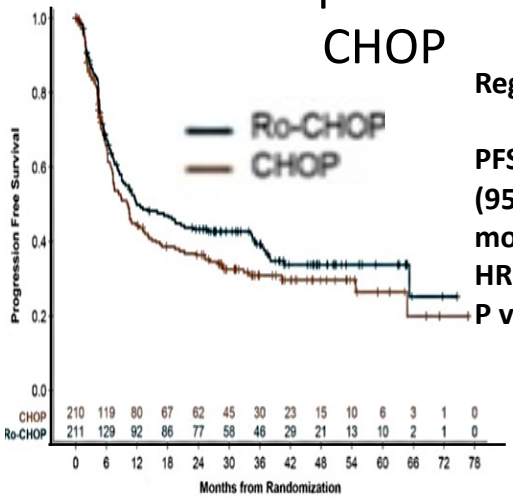
CEOP –Pral

N = 33; CR 52%

Est 2-yr PFS/OS: 39% (95% CI 21-57)

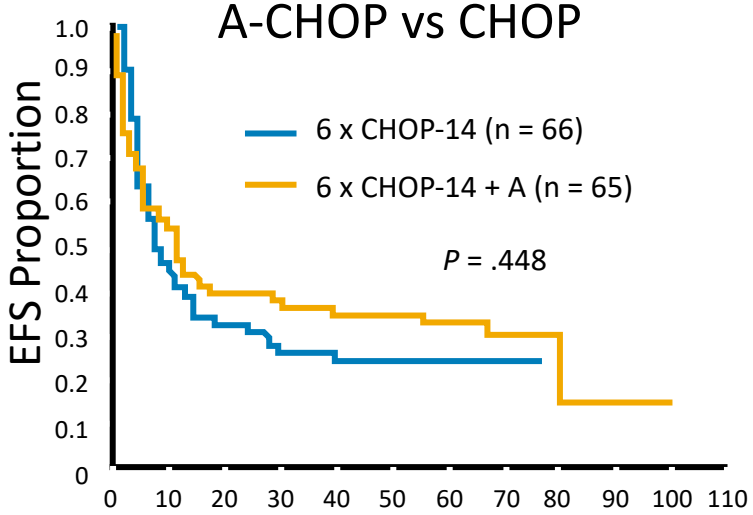


Romidepsin-CHOP vs. CHOP



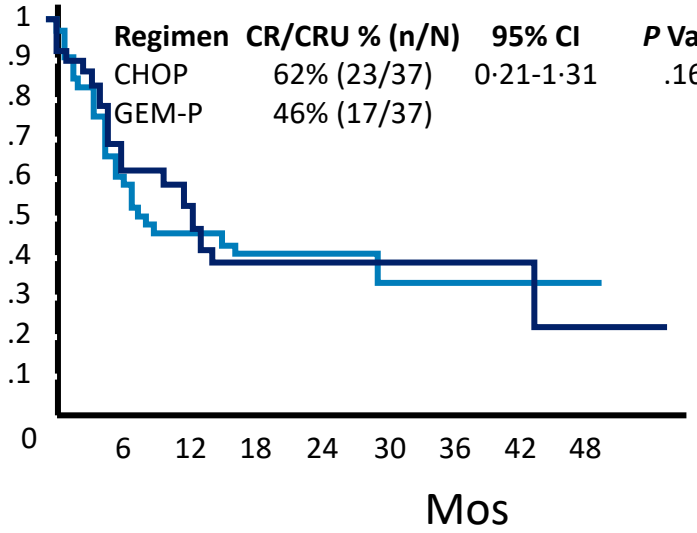
Regimen	Ro-CHOP (n=211)	CHOP (n=230)
PFS median (95% CI), mo	12.0 (9-25.8)	10.2 (7.4-13.2)
HR (95% CI)	0.81 (0.63-1.04)	
P value	0.096	

A-CHOP vs CHOP



CHOP vs GEM-P

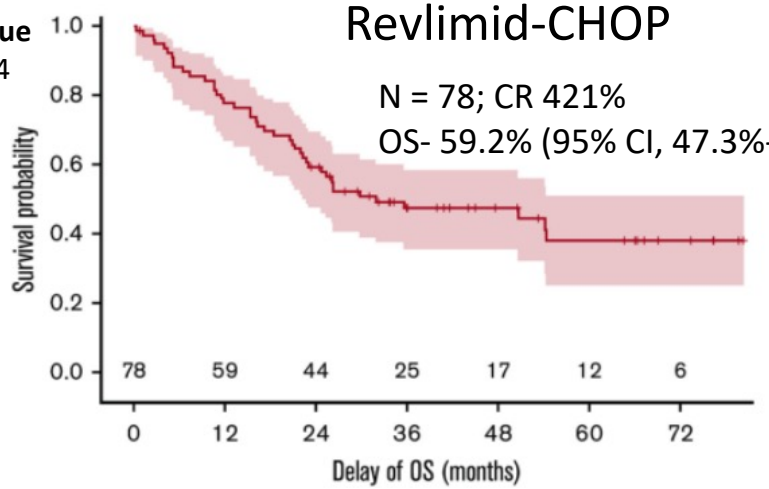
Regimen	CR/CRU % (n/N)	95% CI	*P* Value
CHOP	62% (23/37)	0·21-1·31	.164
GEM-P	46% (17/37)		



Revlimid-CHOP

N = 78; CR 421%

OS- 59.2% (95% CI, 47.3%-69.3%)



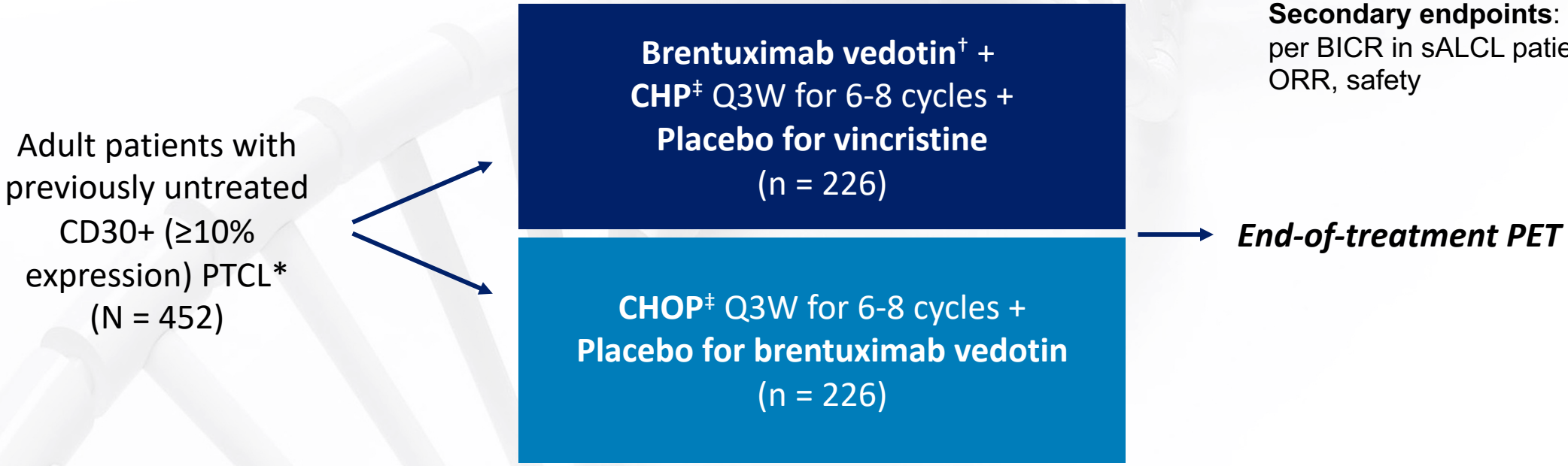
Simon. Br J Haem. 2010. d'Amore. ASH 2018. Advani. Br J Haem. 2016;172:636. Gleeson. Lancet Haem. 2018;5:E190; Bachy et al. Lancet Haem. 2021, Lemmonier et al. Blood Adv, 2021

ECHELON-2: BRENTUXIMAB VEDOTIN + CHP VS CHOP IN UNTREATED CD30+ PTCL

Multicenter, randomized double-blind, double-dummy, active-controlled phase III trial

Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)

Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety



*PTCL includes sALCL (including ALK+ sALCL with IPI ≥2 and ALK- sALCL), PTCL-NOS, AITL, ATLL, EATL, HSTCL. Study targeted 75% (± 5%) ALCL in line with European regulatory commitment. †Brentuximab vedotin 1.8 mg/kg. ‡Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (CHOP only), prednisone 100 mg on Days 1-5. G-CSF primary prophylaxis, consolidative RT, SCT per investigator discretion.

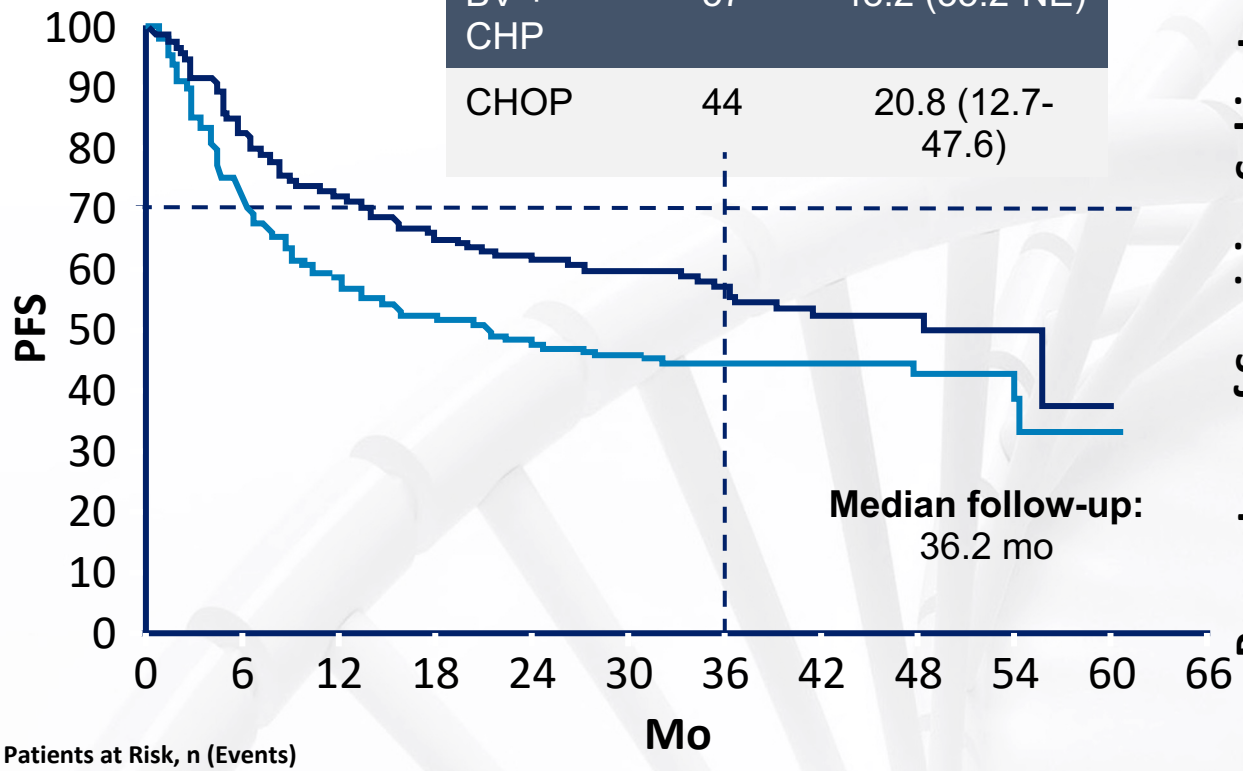
ECHELON-2: BASELINE CHARACTERISTICS

Characteristic	BV + CHP (n = 226)	CHOP (n = 226)
Male, n (%)	133 (59)	151 (67)
Median age, yr (IQR)	58 (45-67)	58 (44-67)
Disease diagnosis, n (%)		
▪ sALCL	162 (72)	154 (68)
• ALK+	49 (22)	49(22)
• ALK-	113 (50)	105 (46)
▪ AITL	30 (13)	24 (11)
▪ PTCL-NOS	29 (13)	43 (19)
▪ ATLL	4 (2)	3 (1)
▪ EATL	1 (0)	2 (1)

Horwitz. Lancet. 2019;393:229.

ECHELON-2: IMPROVED PFS AND OS WITH BRENTUXIMAB VENDOTIN

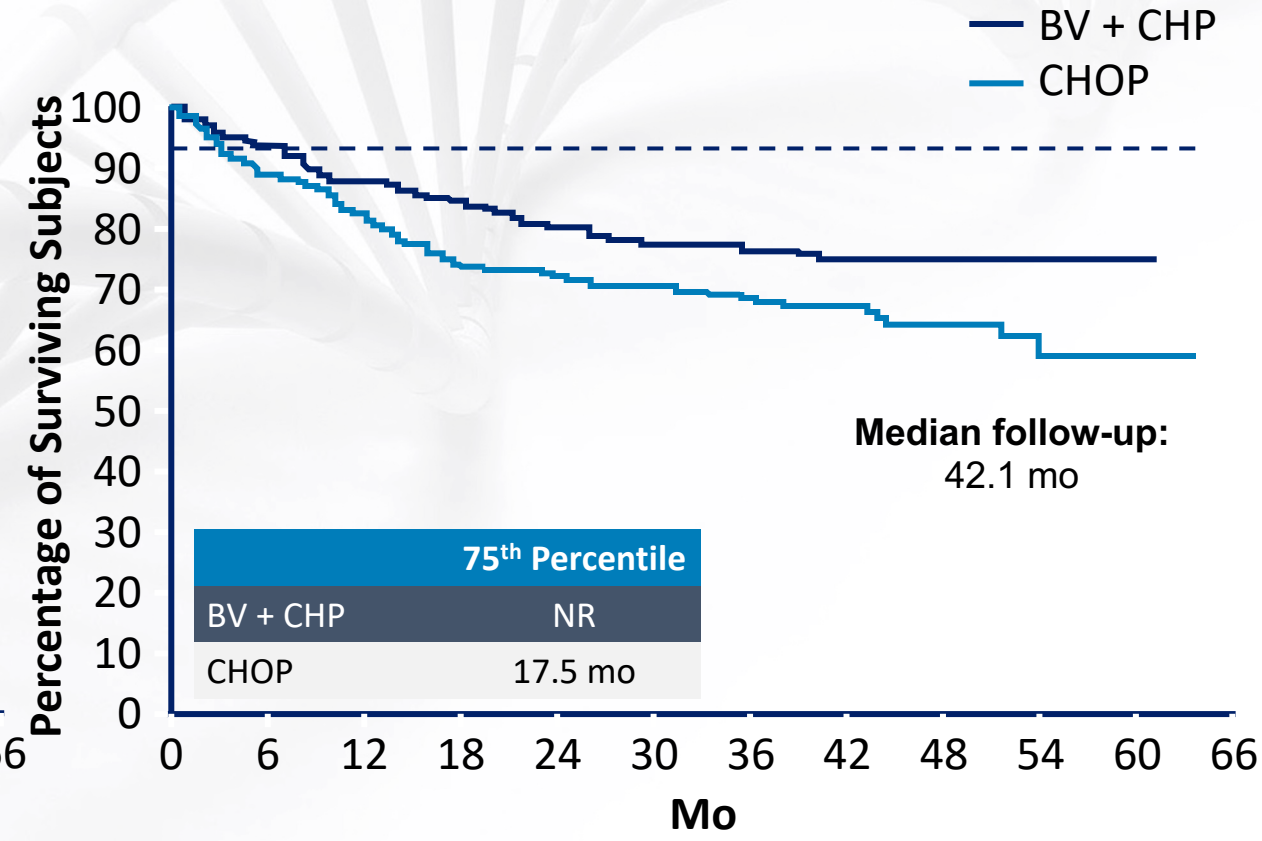
	3-Yr PFS, %	mPFS, Mo (95% CI)
BV + CHP	57	48.2 (35.2-NE)
CHOP	44	20.8 (12.7-47.6)



Patients at Risk, n (Events)

BV + CHP	226 (0)	175 (39)	149 (61)	134 (75)	108 (82)	81 (85)	64 (88)	38 (93)	24 (93)	9 (94)	3 (95)	0 (95)
CHOP	226 (0)	157 (65)	129 (93)	112 (107)	87 (116)	75 (119)	63 (121)	44 (121)	26 (122)	7 (123)	2 (124)	0 (124)

	Events, n (%)	HR (95% CI)	*P* Value
BV + CHP	95 (42)	0.71 (0.54-0.93)	.011
CHOP	124 (55)		



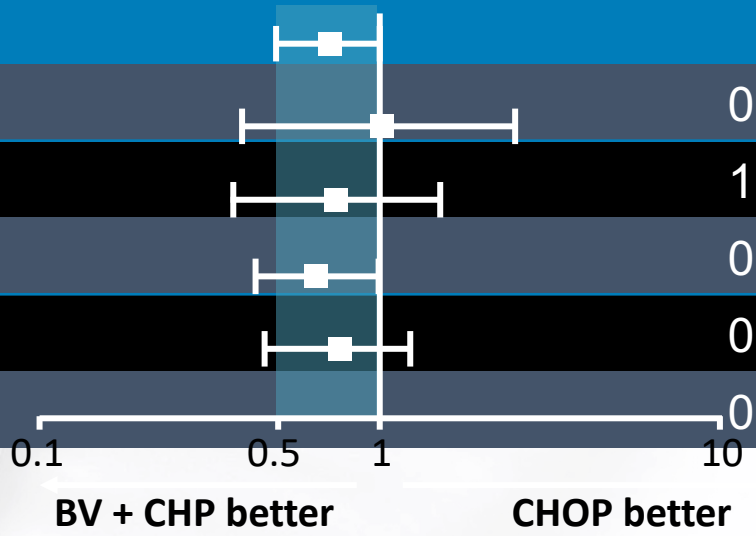
	75th Percentile
BV + CHP	NR
CHOP	17.5 mo

	226 (0)	208 (14)	193 (27)	184 (33)	159 (42)	128 (47)	108 (49)	83 (51)	45 (51)	20 (51)	4 (51)	0 (51)
	226 (0)	196 (24)	181 (39)	158 (57)	140 (60)	121 (63)	103 (66)	79 (68)	46 (71)	22 (72)	4 (73)	0 (73)

	Deaths, n (%)	HR (95% CI)	*P* Value
BV + CHP	51 (23)	0.66 (0.46-0.95)	.0244
CHOP	73 (32)		

ECHELON-2: PFS AND OS BENEFIT LESS CLEAR IN NON-ALCL

ITT Subgroups	Events/N		HR (95% CI)
	A+CHP	CHOP	
OS	68/226	89/226	0.72 (0.53-0.99)
AITL	12/30	8/24	1.01 (0.40-2.55)
▪ PTCL-NOS	14/29	27/43	0.75 (0.37-1.48)
sALCL	39/162	49/154	0.66 (0.43-1.01)
▪ Non-sALCL	29/64	40/72	0.76 (0.46-1.23)

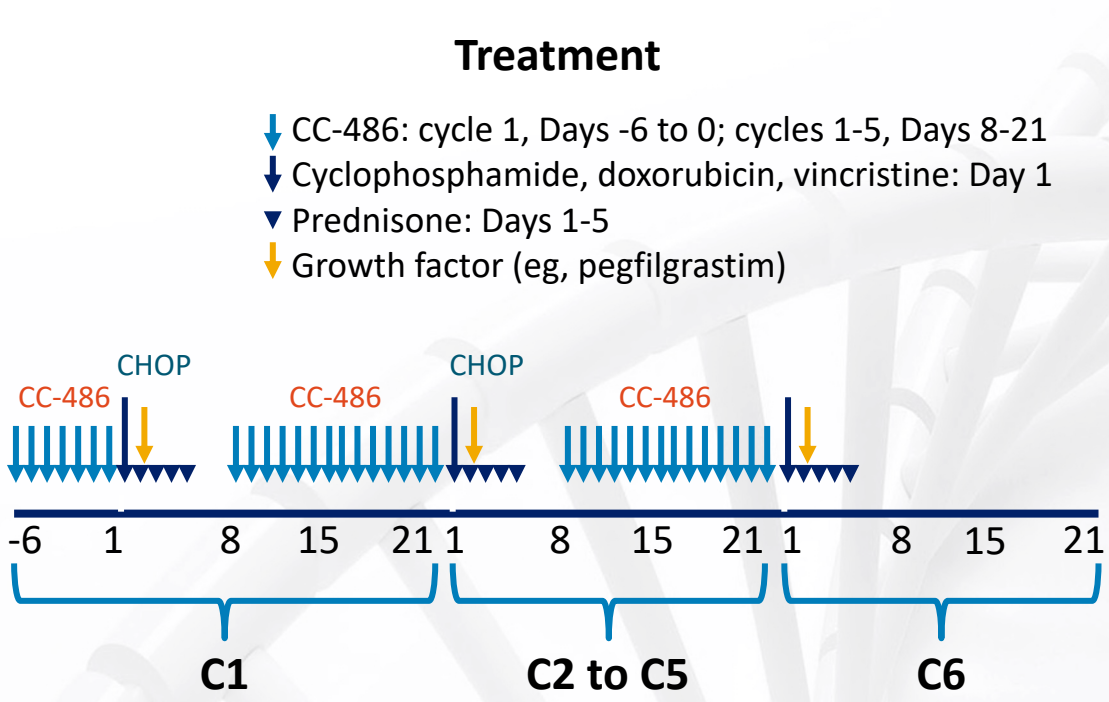


Rate by Treatment, %	ALCL		AITL		PTCL, NOS	
	PFS	5-Yr OS	PFS	5-Yr OS	PFS	5-Yr OS
BV + CHP	60.6	75.8	26.6	67.8	26.5	46.2
CHOP	48.4	68.7	48.1	62.5	25.7	35.9

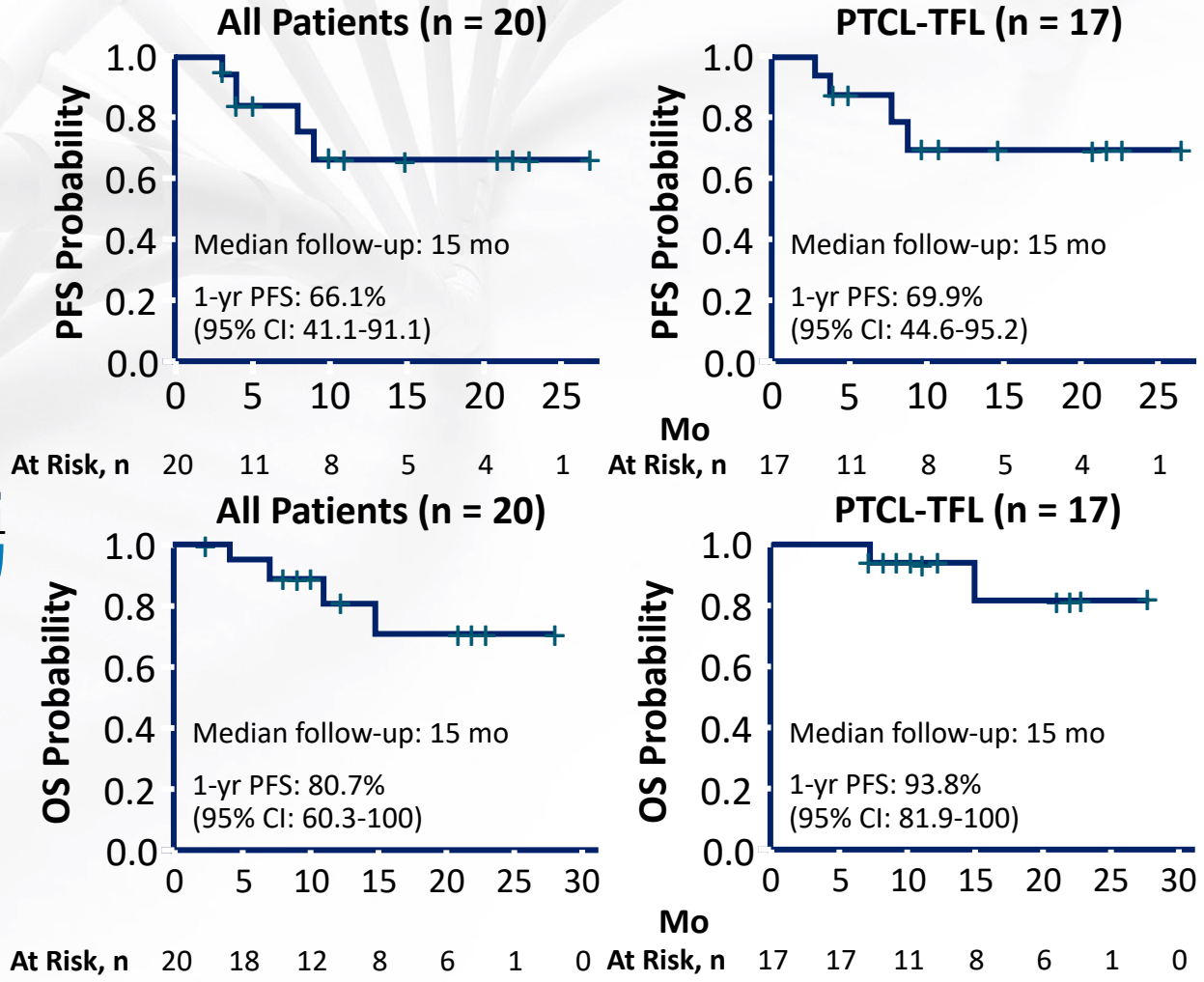
*PFS and OS benefit greatest in patients with sALCL.

Horwitz. Ann Oncol. 2022;33:288.

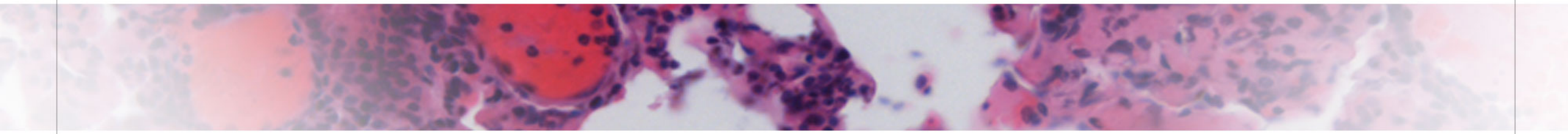
Phase II Study of Oral Azacitidine (CC486) + CHOP in Patients with Previously Untreated PTCL Including TFH



CC486 300 mg daily from Day -6 to 0 for cycle 1 priming, and on Days 8-21 following cycles 1-5
Patients in CR/PR following 6 cycles of treatment have the option to proceed to consolidative HSCT



American Society of Hematology
Helping hematologists conquer blood diseases worldwide



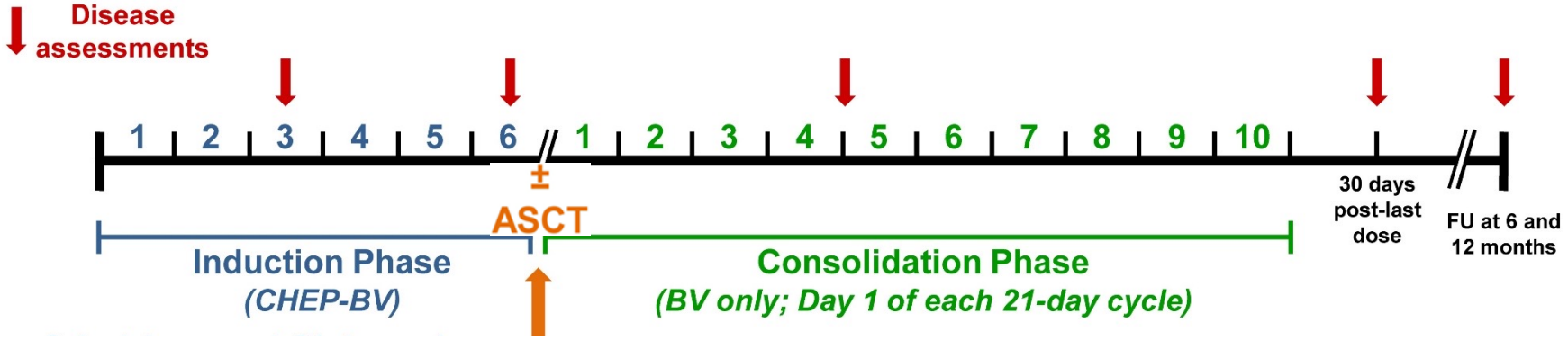
Brentuximab Vedotin Plus Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (CHEP-BV) Followed by BV Consolidation in Patients with CD30-Expressing Peripheral T-cell Lymphomas

Alex F. Herrera[1], Jasmine Zain[1], Kerry J. Savage[2], Tatyana Feldman[3], Jonathan E Brammer[4], Lu Chen[1], Leslie Popplewell[1], L. Elizabeth Budde[1], Matthew Mei[1], Chitra Hosing[5], Ranjit Nair[5], Lori Leslie[3], Lacolle Peters[1], Stephen Forman[1], Steven Rosen[1], Larry Kwak[1], and Swaminathan P. Iyer[5]

[1] Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA, [2] Department of Medical Oncology, BC Cancer, Vancouver, Canada, [3] Lymphoma Division, Hackensack University Medical Center, Hackensack, NJ, [4] Department of Internal Medicine, The Ohio State University, Columbus, OH, [5] Department of Lymphoma and Myeloma, MD Anderson Cancer Center, Houston, TX

CHEP-BV- SCT-BV consolidation

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®



Variable	N (%)
Total	48 (100)
PTCL Subtype	
AITL	18 (37.5)
ALCL	16 (33)
ALK+	13 (27)
ALK-	3 (6)
PTCL NOS	11 (23)
TFH PTCL	2 (4)
ATLL	1 (2)
Male gender	30 (62.5)
Age, median in years	56 (24–79)
CD30 expression	
1-9%	16 (33)
10% or greater	32 (67)
Stage I-II	5 (10)
Stage III-IV	43 (90)

Variable	N (%)
B symptoms	31 (65)
Elevated LDH	27 (56)
Extranodal involvement	31 (65)
ECOG ≥2	7 (15)
IPI score	
0-1	10 (21)
2	19 (40)
3	14 (29)
4-5	5 (10)
Missing	1 (2)
Prior SOC chemotherapy	
No	30 (62.5)
Yes	18 (37.5)
CHOP	8 (17)
CHOEP	4 (8)
EPOCH	1 (2)
BV-CHP	5 (10)

Herrera Blood
ASH 2021

permission from Iyer

Response to CHEP-BV

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

	All Patients (n=46)	
Response	**Interim**	**End of CHEP-BV**
Overall response (ORR)	**44 (96%)**	**42 (91%)**
Complete response (CR)	**27 (59%)**	**37 (80%)**
Partial response (PR)	17	5
Stable disease (SD)	1	0
Progressive disease (PD)	1	4

- Median F/u in surviving pts is 16.1 months (range, 0.9-32.5)
- Overall 18mo PFS and OS were 61% and 89%; 18mo PFS by subgroup: ALCL 81%, non-ALCL 49%, CD30 1-9% 48%, CD30 10+% 67%
- 1y PFS from end of CHEP-BV in responding pts (n=41) was 82% in pts who underwent ASCT vs 48% in pts who did not.

Response	ALCL (n=16)	Non-ALCL (n=30)	AITL (n=17)	PTCL NOS (n=11)	PTCL TFH (n=2)
Overall response (ORR)	**15 (94%)**	**27 (90%)**	**16 (94%)**	**9 (82%)**	**2 (100%)**
Complete response (CR)	**15 (94%)**	**22 (73%)**	**14 (82%)**	**6 (55%)**	**2 (100%)**
Partial response (PR)	0	5	2	3	0
Stable disease (SD)	0	0	0	0	0
Progressive disease (PD)	1	3	1	2	0

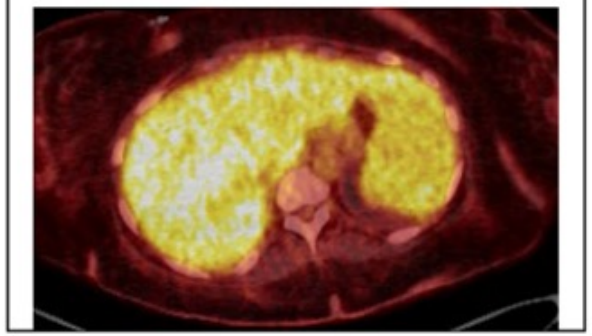
CASE

- 34 yo anesthesiologist comes in for a new consult with moderate pancytopenia and fatigue for 4 months
- Previous work up mild splenomegaly on CT scan and negative bone marrow biopsy
- Now with night sweats and weight loss
- New peripheral blood for flow with “mild clonal T cell population”

Hepatosplenic T-cell Lymphoma

Clinical Presentation

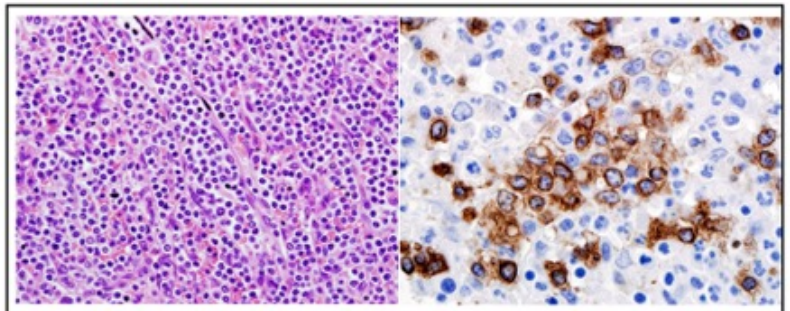
- Cytopenias
- Constitutional symptoms
- Hepatosplenomegaly
- Hemophagocytic syndrome



Treatment

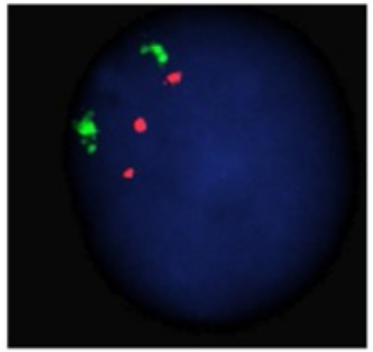
- Induction therapy
- Transplantation in first remission with consideration for allogeneic transplant

Morphology and Immuno-phenotype



- **Morphology:**
  - Sinusoidal pattern
  - Atypical cells, usually small but can resemble blasts
  - Erythrophagocytosis can be seen
- **Phenotype:**
  - 80% γδ T-cell; 20% αβ T-cells
  - CD3+, CD2+, CD5-, CD7+/-,CD4-/CD8-, CD56+, CD57-, TIA+, Perforin-

Genomic Findings



- **Chromosomal Abnormalities:**
  - Isochromosome 7q [i(7q)]
  - trisomy 8
- **Gene mutations:**
  - JAK/STAT pathway: *STAT3* and *STAT5*
  - Chromatin Modifying genes: *SETD2, INO80, TET3, and SMARCA2*

Pro B, et al. *Blood*. 2020;136:2018-2026.

Outcomes in Patients with Enteropathy-Associated T-Cell Lymphoma (EATL) and Hepatosplenic T-Cell Lymphoma (HSTCL): A Population Based Analysis Using the SEER Data

122 pts with HSTCL
Male predominance with 69%
Median age was 38 years (range 4-83)
HSTCL much younger with 79% aged <55 years
Caucasian - 61% and 27% AA
79% pts had stage IV

Median OS 5 months
.

	Group		p value
Variable	**HSTCL (n=122)**	**EATL (n=163)**	
Age (years), %			**<0.001***
≤55	79	26	
>55	21	74	
Gender, %			**0.07**
Male	69	58	
Female	31	42	
Race, %			**0.0002***
White	61	77	
African American	27	9	
Other	12	14	
Diagnosis year, %			
1996-2008	47	55	
2008-2014	53	45	
Ann Arbor Stage, %			**<0.0001***
I	11	3	
II	6	32	
III	2	26	
IV	79	6	
Marital Status, %			**<0.0001***
Single (never married)	47	12	
Married	35	66	
Separated	2	2	
Divorced	7	7	
Widowed	0	12	
Unmarried/Domestic partner	2	0	
Unknown	7	2	
Radiation, %			**0.0257***
Received	10	3	
Chemotherapy, %			**<0.0001***
Received as first course of therapy	83	55	
None	17	45	
Surgery, %			**<0.0001***
Received	43	70	

Table 1. Demographic and treatment related characteristics of patients with HSTCL and EATCL

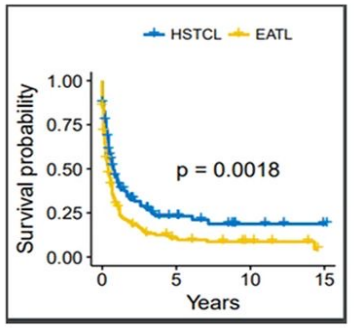


Figure 1A: Comparison of survival for EATL and HSTCL

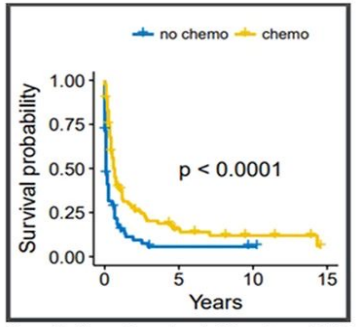


Figure 1B: Comparison of survival in patients with EATL based on chemotherapy administration

Mukhija Dhruvika,Tomas Radivoyevitch, PhD,Brian T. Hill, MD PhD,Robert M. Dean, MD,Brad Pohlman, MD,Deepa Jagadeesh, MDMPH, Outcomes in Patients with Enteropathy-Associated T-Cell Lymphoma (EATL) and Hepatosplenic T-Cell Lymphoma (HSTCL): A Population Based Analysis Using the SEER Data, Blood, 2017,

INTENSIVE INDUCTION THERAPY COMPARED WITH CHOP FOR HEPATOSPLENIC T-CELL LYMPHOMA

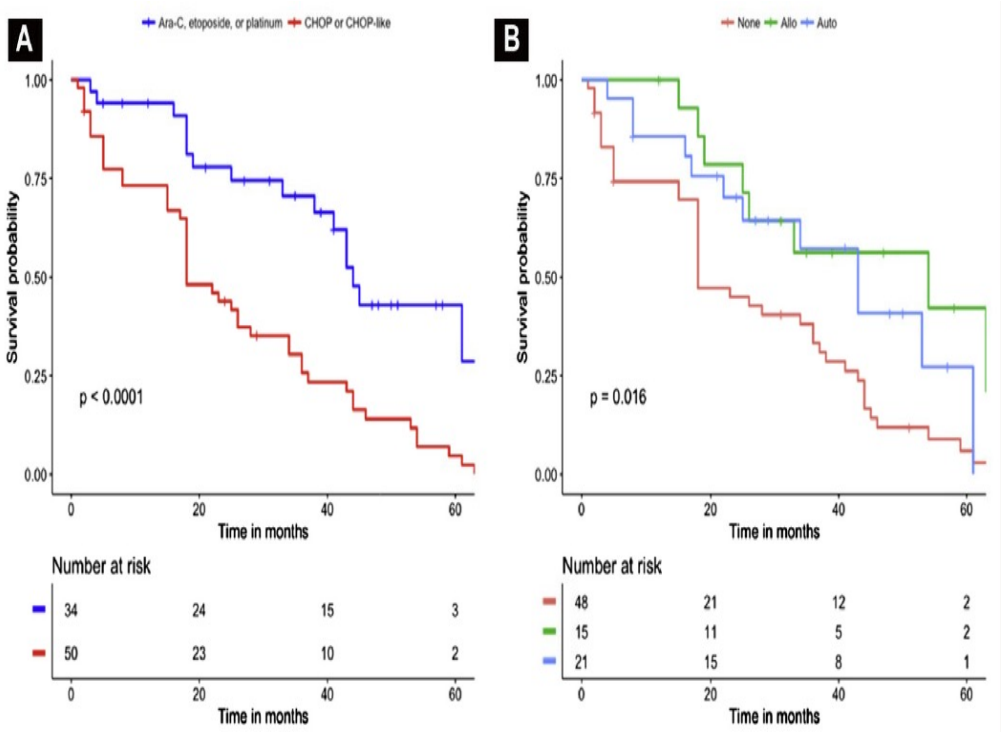
Daniella Klebaner et al

Table 1 Patient Characteristics

	N	PR, n (%)	Response Rate			Survival		
			CR, n (%)	Unadjusted OR (95% CI) (CR/PR vs. NR)	*P* Value	Median OS, mos[b]	HR (95% CI)	*P* Value
Treatment								
CHOP/CHOP-like[a] (reference)	50	7 (14)	19 (38)			18		
Cytarabine/etoposide/platinum-containing	34	9 (26)	19 (56)	4.31 (1.59-13.16)	**.006**[c]	36.5	0.33 (0.19-0.58)	**.00014**
Age, y								
4-34 (reference)	38	8 (21)	14 (37)			31		
35-69	37	8 (22)	18 (49)	1.72 (0.67-4.55)	.27	24	0.89 (0.53-1.52)	.68
Missing	9	0	6 (67)			8		
Gender								
Male (reference)	57	12 (21)	22 (39)			23		
Females	18	4 (22)	10 (56)	2.37 (0.74-9.17)	.17	33.5	0.52 (0.27-1.02)	.056
Missing	9	0	6 (67)			8		
Bone marrow involvement								
No (reference)	13	3 (23)	8 (62)			35		
Yes	46	7 (15)	21 (46)	0.28 (0.041-1.21)	.13	20	1.65 (0.72-3.77)	.23
Missing	25	6 (24)	9 (36)			25		
TCR expression								
γδ (reference)	64	12 (19)	27 (42)			18.5		
αβ	5	0	3 (60)	0.96 (0.15-7.69)	.97	18	1.06 (0.38-2.97)	.90
Missing	15	4 (27)	8 (53)			41		

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CI = confidence interval; CR = complete response; HR = hazard ratio; NR = no response; OR = odds ratio; OS = overall survival; PR = partial response; TCR = T-cell receptor.
[a]CHOP-like = CHOP + bleomycin or CHOP-derived.
[b]Survival time from induction was calculated as one of the following: (1) Number of months from induction, (2) Ability to calculate number of months from induction given detailed information on intervening time periods, or (3) Survival from diagnosis with no reported delay between diagnosis and induction.
[c]*P* values in bold indicate significance at $\alpha = 0.05$.

Klebaner. Clin Lymphoma Myeloma Leuk. 2020



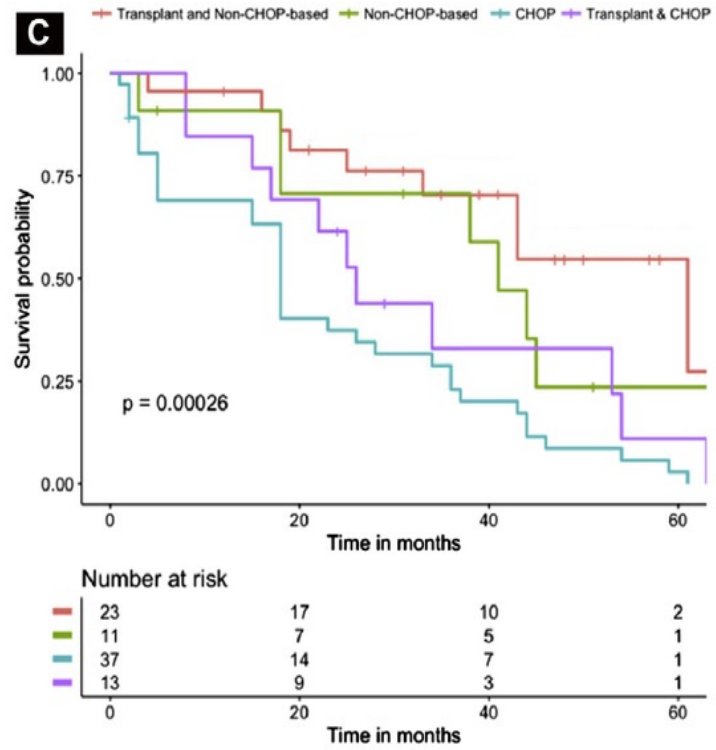


Figure 2 OS From Induction by Induction Treatment Group: OS = 36.5 months for Non-CHOP-based, 18 months for CHOP/CHOP-like (A); by Transplant Status: OS = 33 months for Allo-HSCT, 27 months for Auto-HSCT, and 18 Months for No Transplant (B); by Induction and Transplant Status: OS = 35 months for Non-CHOP-based and Transplant, 38 months for Non-CHOP-based Only, 25 months for CHOP and Transplant, and 18 months for CHOP Only (C)

Klebaner. Clin Lymphoma Myeloma Leuk. 2020

CASE

- 58 yo for second opinion
  - Noted to have fatigue and viral syndrome last Fall
  - Mild weight loss
  - Fatigue continued ? “long hauler COVID”
  - Labs done following March with Wbc 23K with moderate lymphocytosis
  - Sent to Heme/Onc Wbc 43K six weeks later
  - Scans mild splenomegaly
  - Bone marrow CD 4 + and cytogenetics Abnormalities of 14q32
  - Comes in with his wife with a little more fatigue
  - Critical lab calls wbc count 164K

T - PROLYMPHOCYTIC LYMPHOMA

T-PLL represents 2% of chronic leukemias for adults

Clinical presentation:

- **B-symptoms**
- **hepato-splenomegaly**
- **usually excessive lymphocytosis above 100,000.**
- **Nodal and extranodal presentation including skin, pleural or peritoneal effusions in around 25% of patients**
- **CNS involvement in less than 10% of patients**

Staber Blood 2019

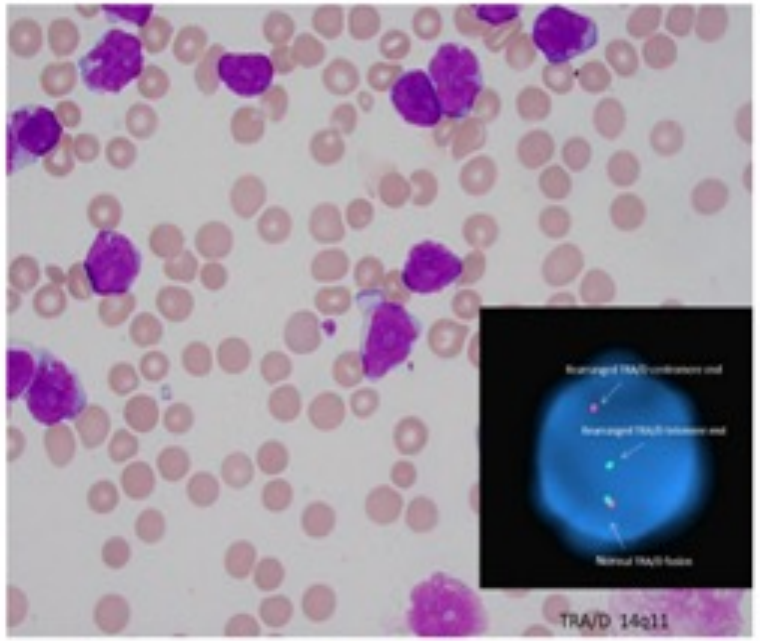


FIGURE 1 T-cell prolymphocytic leukemia. Peripheral blood smear demonstrates a lymphocytosis with numerous prolymphocytes with high nuclear: cytoplasmic ratio and prominent nucleoli (Wright-Giemsa, original magnification ×1000). Insert: Fluorescence in situ hybdrization shows a chromosome 14q11 rearrangement (insert image courtesy of Dr Julie Neidich, Department of Pathology and Immunology, Washington University School of Medicine)

Frater. Int J Lab Hematol. 2020

T CELL LYMPHOCYTOSIS

TABLE 3 Comparison of the major features of benign and malignant T-cell disorders involving the blood

Name	Cytomorphology	Immunophenotype	Genetics	Other helpful features
Reactive lymphocytosis	Predominant population of Downey type II cells (majority of cases)	CD2+, CD3+, CD4 < CD8, CD5+, CD7+	Polyclonal TCR	Monospot positive (EBV), History of physiologic stress (stress lymphocytosis)
T-cell prolymphocytic leukemia	Prolymphocyte (most cases)	CD2+, CD5+, CD7+, CD4+ (majority), CD4/CD8+ (~25% of cases), CD4−/CD8+ (~15% of cases), TCL1+	Chromosome 14q11-21 rearrangements (~80% of cases), monoclonal TCR	Leukemic presentation and splenomegaly > lymphadenopathy
Adult T-cell leukemia/lymphoma	Flower cells (mature chromatin, irregular nuclear contours)	CD2+, CD3+, CD4 > CD8, CD5+, CD7−/+	Monoclonal TCR	HTLV-1 serology + in most cases, hypercalcemia
T lymphoblastic leukemia/lymphoma	Blasts	CD45dim, CD1a+, cCD3+, CD4/CD8+ (25% of cases)	*TR* gene loci on chromosome 14q11.2, 7q35, 7p14-15	Large mediastinal mass in many cases
Sézary syndrome	Sézary cells (mature chromatin, deep cerebriform nuclear grooves) ≥1000/μL blood	CD2+, CD3+, CD5+/1, CD7− CD4:CD8 ratio ≥ 10:1, CD25+	Monoclonal TCR	Generalized erythroderma and pruritus (many cases)
Disseminated peripheral T-cell lymphoma, NOS	Medium-sized to large lymphocytes (variable)	CD2, CD3, CD5+/−, CD7+/−, CD4 > CD8	Monoclonal TCR	Peripheral lymphadenopathy common
T-large granular lymphocytic leukemia	Large granular lymphocytes > 2×10^9/L in blood, >6-mo duration	CD2+, CD3+, CD5+/−, CD7+/−, CD8+/CD57+	Monoclonal TCR	Cytopenias and splenomegaly common

For details regarding cytomorphology, immunophenotype, and genetic features, see text.

Abbreviations: EBV, Epstein-Barr virus; HTLV-1, Human T-cell leukemia virus, type 1; TCR, T-cell receptor gene rearrangement studies.

Frater. Int J Lab Hematol. 2020

Frater 2020\

Table 2. Requirements to establish the diagnosis of T-PLL

Major criteria	Minor criteria (at least 1 required)
• >5 × 10⁹/L cells of T-PLL phenotype in peripheral blood or bone marrow	• Abnormalities involving chromosome 11 (11q22.3; *ATM*)
• T-cell clonality (by PCR for TRB/TRG, or by flow cytometry)	• Abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q
• Abnormalities of 14q32 or Xq28 OR expression of *TCL1A/B*, or *MTCP1**	• Abnormalities in chromosome 5, 12, 13, 22, or complex karyotype
	• Involvement of T-PLL specific site (eg, splenomegaly, effusions)

*Cases without TCL1A, TCL1B, or MTCP1 rearrangement or their respective overexpression are collected as TCL1-family negative T-PLL.

Table 4. Criteria for staging and indication of treatment in T-PLL

Staging: at least 1 criterion defines active T-PLL (= indication for treatment)		
Disease-related constitutional symptoms	Significant fatigue: ECOG ≥2	
	Unintentional weight loss of >10% of normal body weight in ≤6 mo	
	Drenching night sweats, without evidence of infection	
	Fever greater than 38°C, without evidence of infection	
Symptomatic bone marrow failure	Hemoglobin	<10 g/dL
	Platelet count	<100 × 10⁹/L
Rapidly enlarging lymph nodes, spleen, and liver	>50% in 2 mo; diameter doubling <6 mo	
	Symptomatic enlarged lymph node, spleen, or liver	
Increasing lymphocytosis	If >30 × 10⁹/L: >50% in 2 mo; lymphocyte doubling time <6 mo	
Extranodal involvement	Organ infiltration; peritoneal or pleural effusion, central nervous system involvement	

Staber Blood 2019

Table 6. Summary of most relevant clinical studies on T-PLL

Regimen	Trial	Disease status	n	ORR, %	CR, %	PR, %	PFS, mo	OSa, mo	Reference
Pentostatin	Single center, retrospective	Pretreated	56	45	9	36	6	9	55
Alemtuzumab, IV	Single center, retrospective	Pretreated	15	73	60	13	6	8	46
Alemtuzumab, IV	Multicenter, prospective	Pretreated	39	76	60	16	7	10	47
Alemtuzumab, IV	Multicenter, retrospective	Untreated	4	75	75	0	4.5	7.5	52
		Pretreated	72	50	37.5	12.5			
Pentostatin + alemtuzumab, IV	Single center, prospective	Pretreated	13	69	62	8	7.8	10.2	56
Alemtuzumab, IV	Single center, prospective	Untreated	32	91	81	10	(67%) 12 mo	(37%) 48 mo	4
Alemtuzumab, sc		Untreated	9	33	33	0	(67%) 12 mo	(33%) 48 mo	
Alemtuzumab, IV		Pretreated	45	74	60	14	(26%) 12 mo	(18%) 48 mo	
FMC + alemtuzumab, IV	Multicenter, prospective	Untreated	16	92	48	44	11.5	17.1	5
		Pretreated	9						
Bendamustine	Multicenter, retrospective	Untreated	6	55.3	20	33.3	5	8.7	7
		Pretreated	9						
Alemtuzumab, IV	Single center, retrospective	Untreated	42	81	61	20	11	15	15
Alemtuzumab, IV + pentostatin		Untreated	13	82	73	9	4.3	10.4	
Alemtuzumab, IV		Pretreated	15	46	46	—	3	15	
Alemtuzumab, IV + pentostatin		Pretreated	5	75	50	25	2.6	2.6	
FMC + alemtuzumab, sc	Multicenter, prospective	Untreated	13	68.7	25.8% CR, 6.25% CRi	36.6	7.5	11.5	8
		Pretreated	5						

sc, subcutaneous.

Staber Blood 2019

ALLO TRANSPLANT IN T-PLL

Multivariant analysis:

- RIC/NMA conditioning regimen longer DFS (hazard ratio [HR], 1.86; 95% CI, 1.32 to 2.61; P = .0004) and OS (HR, 2.18; 95% CI, 1.53 to 3.09; P < .0001)
- KPS <90 both inferior DFS (HR, 1.51; 95% CI, 1.12 to 2.05; P = .0075) and inferior OS (HR, 1.53; 95% CI, 1.12 to 2.08; P = .0073)
- Age >60 years (HR, 1.41; 95% CI,1.03 to 1.93 [P = .0337] and 1.61; 95% CI, 1.15 to 2.24 P = .0053], respectively).

H.S. Murthy et al. / Transplantation and Cellular Therapy 28 (2022) 187.e1–187.e10

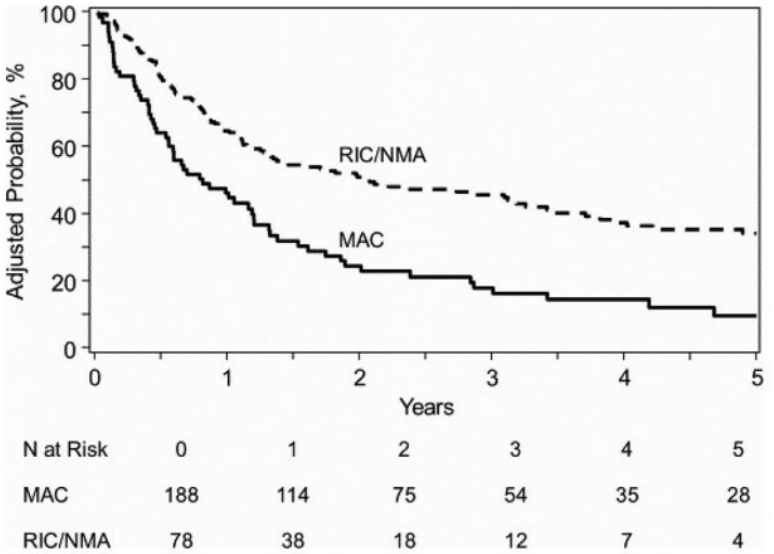


Figure 1. Adjusted OS by conditioning intensity ($P < .0001$).

Murthy 2022

SUMMARY

We are making strides with classifications of PTCL

BV-CHP increases OS and PFS with decrease in deaths, powered for sALCL and possible signaling in PTCL

Response to BV and BV combinations may not be determined by quantitative expression ? Other mechanisms

There are subtypes of Mature T cell diseases where CHOP/CHOP-like regimens are not upfront standards

Clinical trials remain important

ACKNOWLEDGEMENTS

Special Thanks to Pamela Allen and S Iyer
The patients and their families
The Organizers
Our Emory Lymphoma Team
Research Team
Division of Hematology
My family