A monster often ignored: Peripheral T-cell lymphoma

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Presenter Disclosure

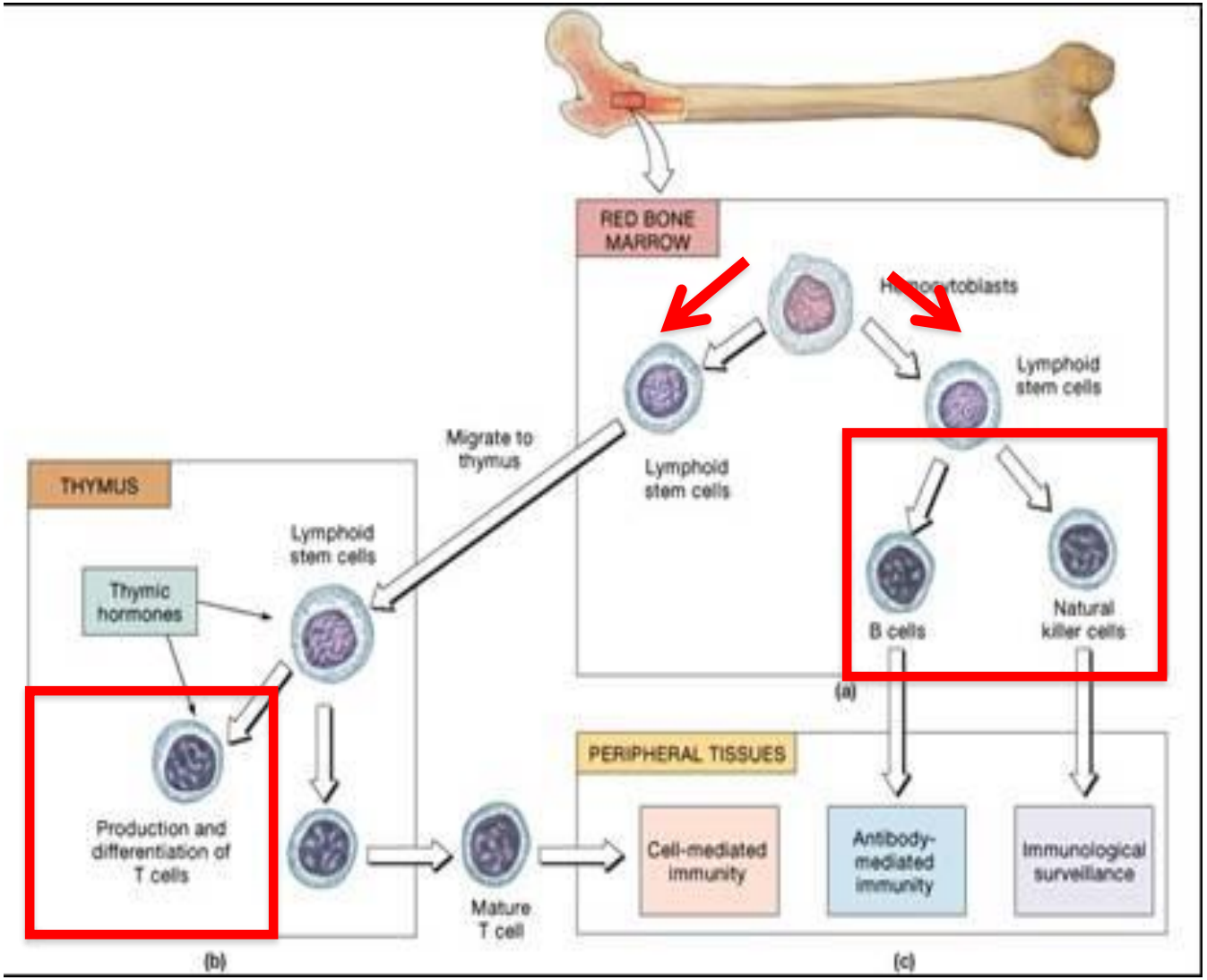
- **Faculty:** Roopesh Kansara

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** Celgene, Lundbeck
  - **Other:** None

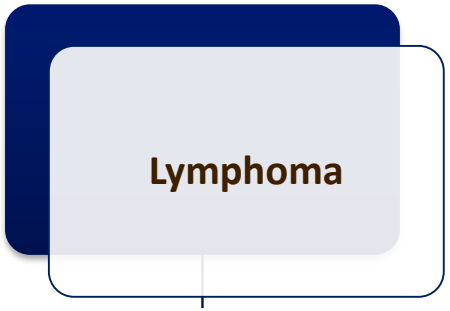
Learning Objectives

- At the end of this session, participants will be able to:
  - ✓Classify T-cell lymphomas
  - ✓Discuss pathophysiology
  - ✓Discuss evidence behind management of Peripheral T-cell
  - ✓Discuss novel approaches to improve the outcomes of patients with Peripheral T-cell lymphoma

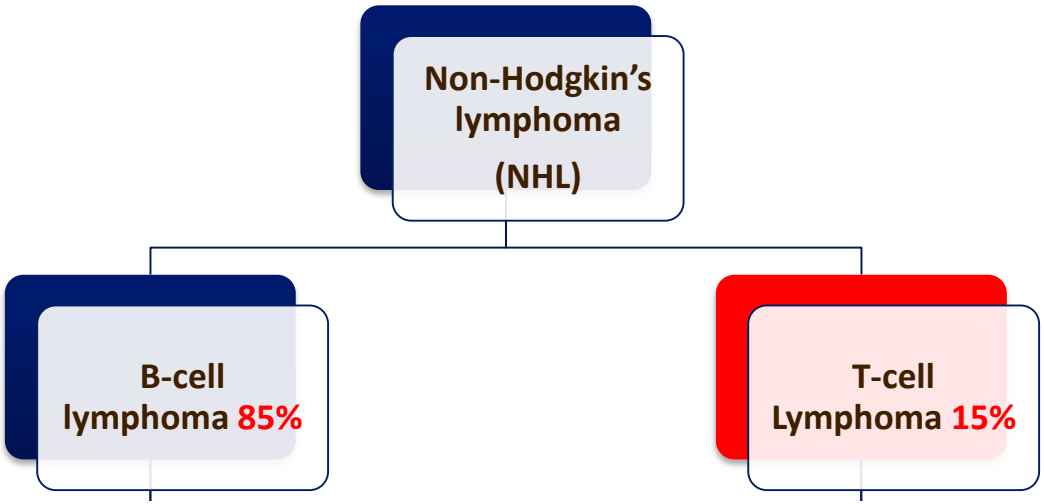
Lymphopoiesis



Classification of Lymphoma



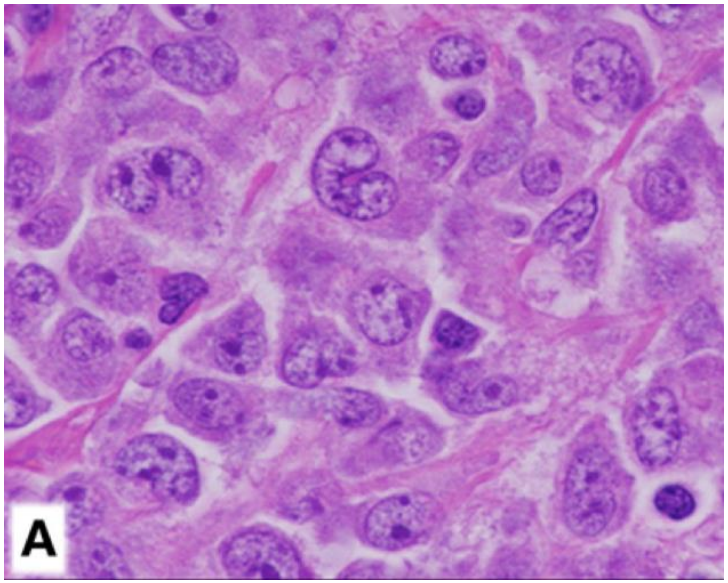
Classification of NHL



WHO 2016 classification

Mature T and NK neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV$^+$ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8$^+$ T-cell lymphoma**
- *Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK$^+$
- Anaplastic large-cell lymphoma, ALK$^-$*
- *Breast implant–associated anaplastic large-cell lymphoma**



Swerdlow S.H. Blood. 2016

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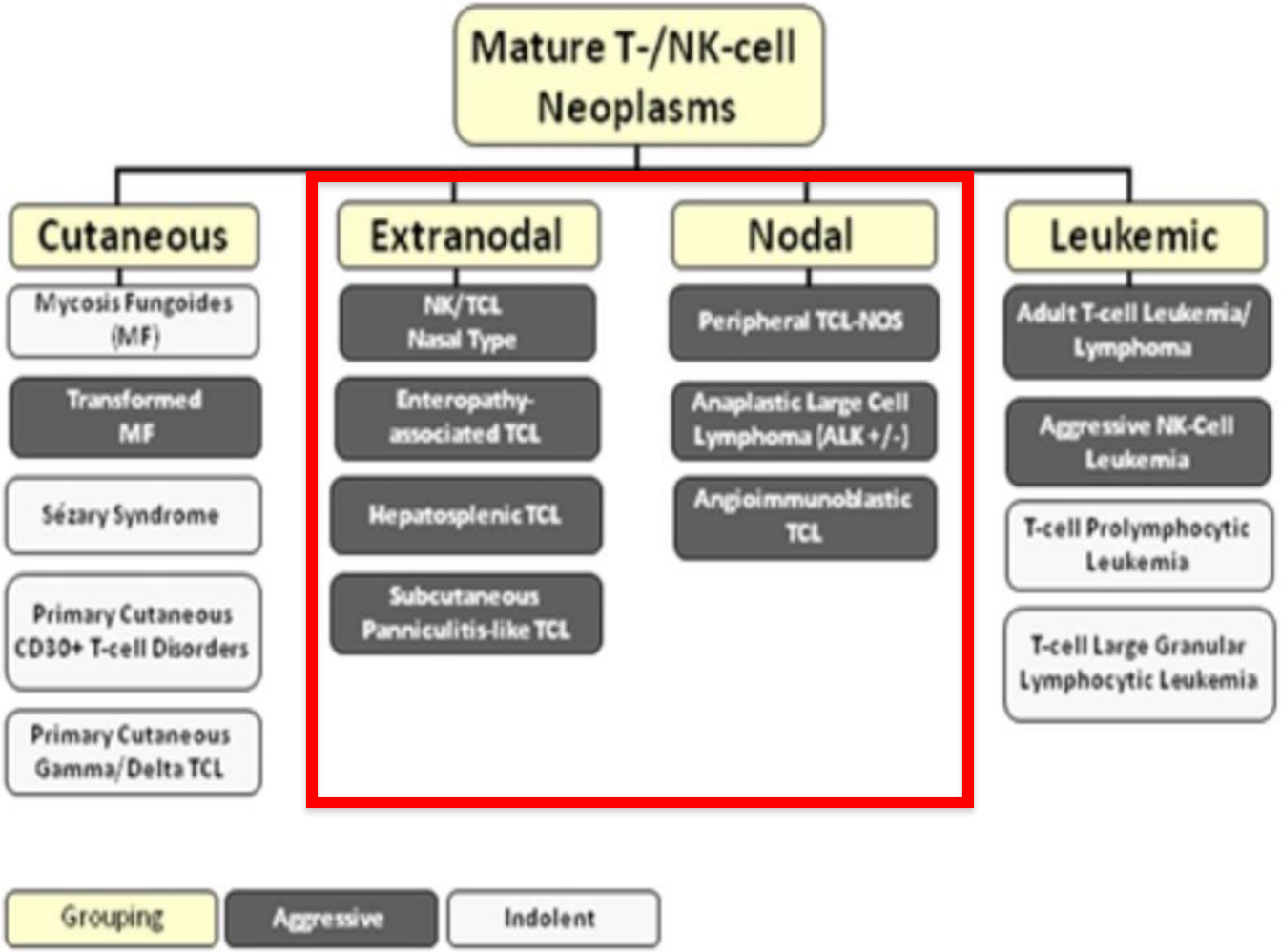


Figure 1 (*adapted from Rodriguez J, et al. Crit Rev Oncol Hematol. 2008*)

Wikipedia.

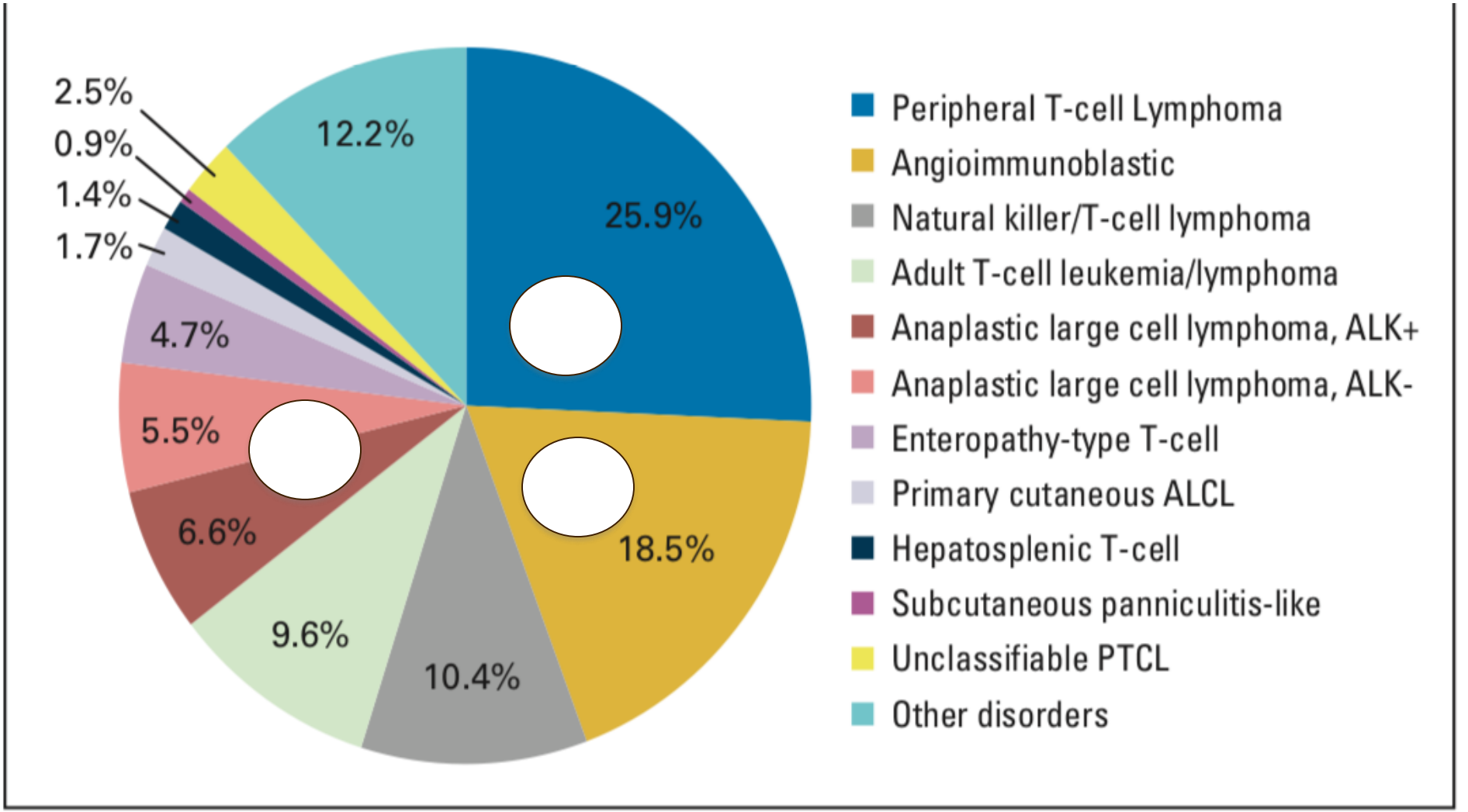


Fig 1. Distribution of 1,314 cases by consensus diagnosis. NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; PTCL, peripheral T-cell lymphoma.

Table 1. Major Lymphoma Subtypes by Geographic Region

Subtype	%		
	North America	Europe	Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	9.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTCL, natural killer/T-cell lymphoma.

Table 2. Patient Characteristics by Histologic Type

Diagnosis	Median Age (years)	% Male	% Stage III/IV	% Marrow Positive	% IPI 0/1	% IPI 2/3	% IPI 4/5
PTCL-NOS	60	66	69	22	28	57	15
Angioimmunoblastic	65	56	89	29	14	59	28
Nasal NKTCL	52	64	27	10	51	47	2
Extranasal NKTCL	44	68	69	18	26	57	17
ATLL	62	55	90	28	19	65	16
ALCL, ALK+	34	63	65	12	49	37	14
ALCL, ALK−	58	61	58	7	41	44	15
Enteropathy-type	61	53	69	3	25	63	13
Primary cutaneous ALCL	55	64	14	0	86	14	0
Hepatosplenic	34	68	95	74	5	47	47
Subcutaneous panniculitis-like	33	75	83	8	42	42	17

Abbreviations: IPI, International Prognostic Index; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; NKTCL, natural killer/T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large-cell lymphoma.

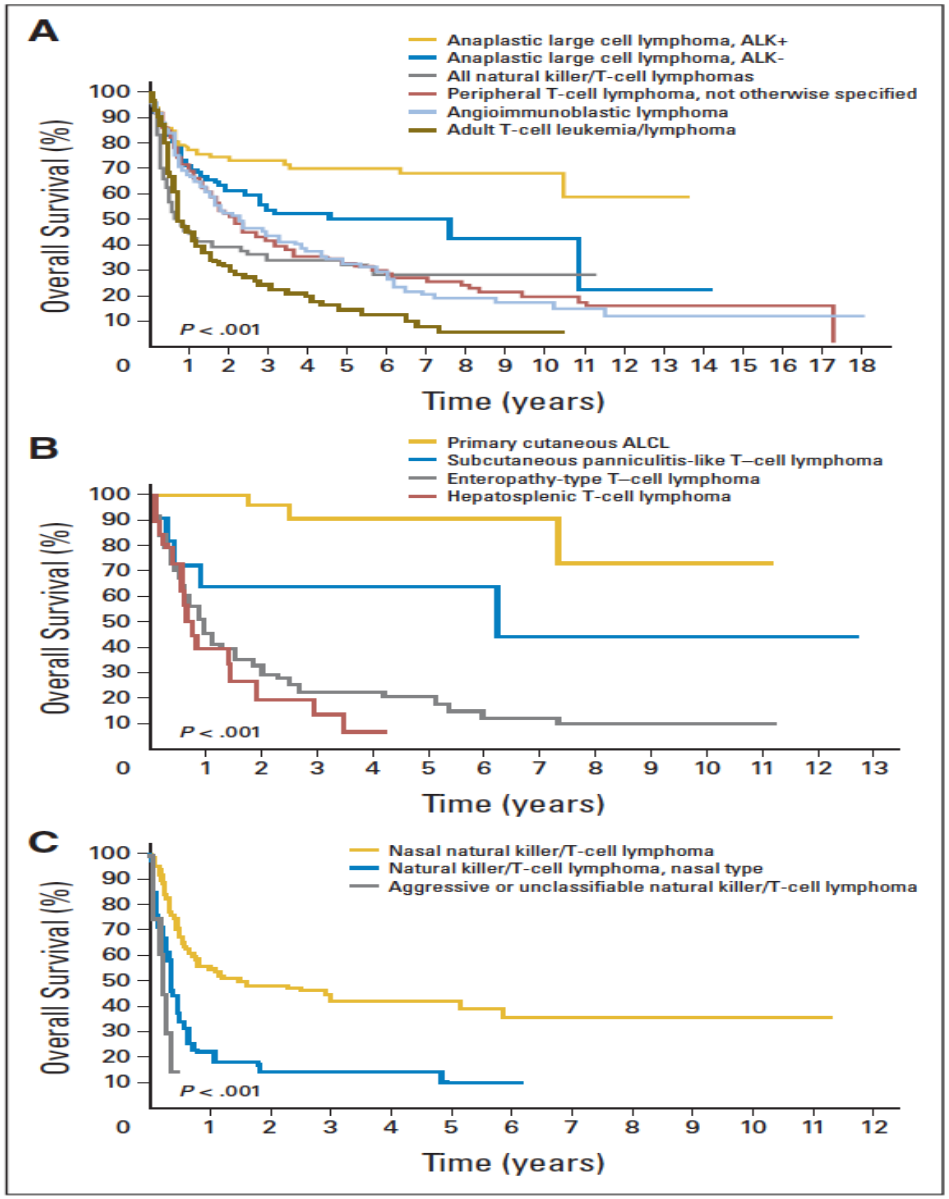


Fig 2. (A) Overall survival of patients with the common subtypes of peripheral T-cell lymphoma (PTCL). (B) Overall survival of patients with the less common subtypes of PTCL. (C) Overall survival of patients with natural killer T-cell lymphoma.

Aggressive T-cell lymphoma

TABLE 3: Immunophenotypic and histochemical markers of T-cell lymphomas/leukemias

Histology	CD3	CD5	CD7	CD4	CD8	CD30	NK16/56	Cytotoxic granules	TCR
T-PLL	+	–	+	+(–)	–(+)	–	–	–	α/β
T-LGL disease*	+	–	+	–	+	–	+/–	+	α/β >> γ/δ
Mycosis fungoides	+	+	+	+	–(+)	–(+)	–	–	α/β
Cutaneous ALCL	+	+(–)	+(–)	+(–)	(–)	++	–(+)/–(+)	+/–	α/β
Primary systemic ALCL^	+(–)	+(–)	+(–)	–(+)	–(+)	++	–	–	α/β
Peripheral T-cell lymphoma, unspecified	+(–)	+(–)	–(+)	+(–)	–(+)	–(+)	–(+)/–(+)	–(+)	α/β > γ/δ
Subcutaneous panniculitis-like T-cell	+	+	+	–(+)	+(–)	–(+)	–/–(+)	+	γ/δ >> α/β
Hepatosplenic T-cell lymphoma	+	–	+	–	–	–	+/+(–)	+	γ/δ >> α/β
Angioimmunoblastic T-cell lymphoma#	+	+	–	+(–)	–(+)	–	–	–	α/β#
Extranodal NK/T-cell lymphoma	S –, C +	–	–(+)	–(+)	–	–	–/+	+	–
Enteropathy-associated T-cell lymphoma	+	+	+	–(+)	+(–)	+(–)	–	+	α/β >> γ/δ
Adult T-cell leukemia/lymphoma&	+	+	–	+(–)	–(+)	+(–)	–	–	α/β

+ = > 90% positive; +(-) = > 50% positive; –(+) = < 50% positive; - = < 10% positive; ALCL = anaplastic large cell lymphoma; C = cytoplasmic; LGL = large granular lymphoproliferative; NK = natural killer; PLL = prolymphocytic leukemia; S = surface; TCR = T-cell–rearranged (molecular)

*Approximately 15% to 20% of LGL cases arise from a NK lineage; they are typically CD56+ and CD16-negative.

^The anaplastic lymphoma kinase (ALK) protein is expressed in 50% to 60% of cases.

#Expanded follicular dendritic cell clusters (CD21+) are present around proliferated venules; Epstein-Barr virus (EBV) genomes are detected in most cases (eg, EBER) and may be present in either T or B cells; in addition, TCR may be negative or oligoclonal in 20% to 25% of cases, whereas B-cell immunoglobulin may be rearranged in 10% of cases.

&Adult T-cell leukemia/lymphoma cases are always associated with the presence of HTLV-I; further, CD25 is expressed in the majority of cases.

Immunophenotype

- AITL –EBV+, Follicular T-helper cell markers (TFH) + (CD10, BCL6,CXCL13,PD-1)
- ALCL ALK+ - t(2;5) ALK-NPM gene (85%) rearrangement, EMA+
- EN NK/T cell lymphoma – EBV+,CD2+
- EATL – HLADQ2+

Gene expression profiling PTCL

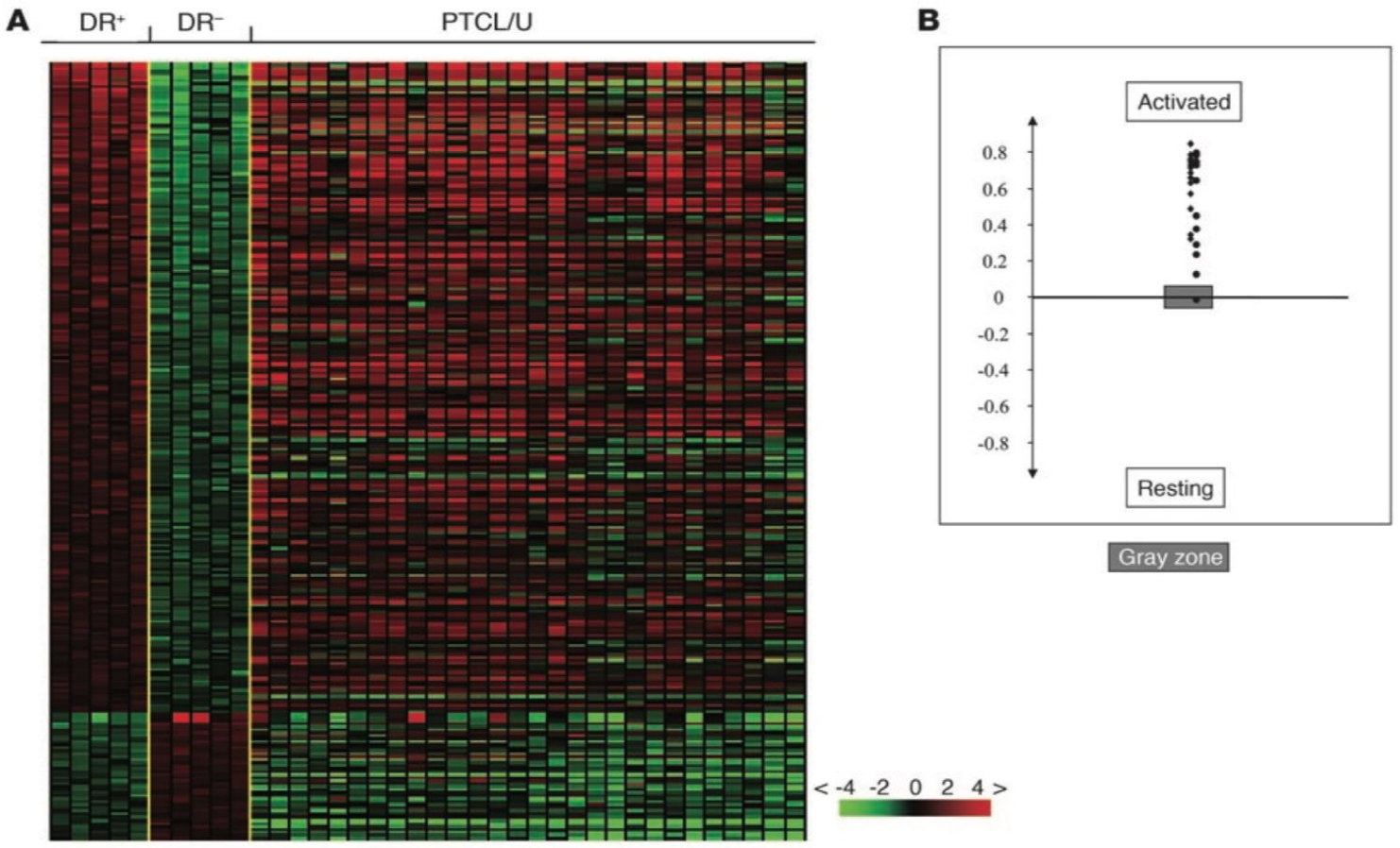


Figure 2
Relatedness of PTCL/U to resting and activated normal lymphocytes. Relatedness of the gene expression profile of PTCL/U to normal T cell populations. (**A**) A supervised analysis was used to identify the genes differentially expressed between 2 groups of samples. HLA-DR+ (activated) T cells are compared with HLA-DR− (resting) T cells. The expression of the selected genes is investigated in PTCLs/U, represented on the right side of the matrix. (**B**) A cell-type classification is used to measure the relatedness of PTCL/U to HLA-DR+ and HLA-DR− T cells. The gray area marks 95% confidence: the *P* value decreases with increasing distance from the *x* axis.

Gene expression profiling PTCL

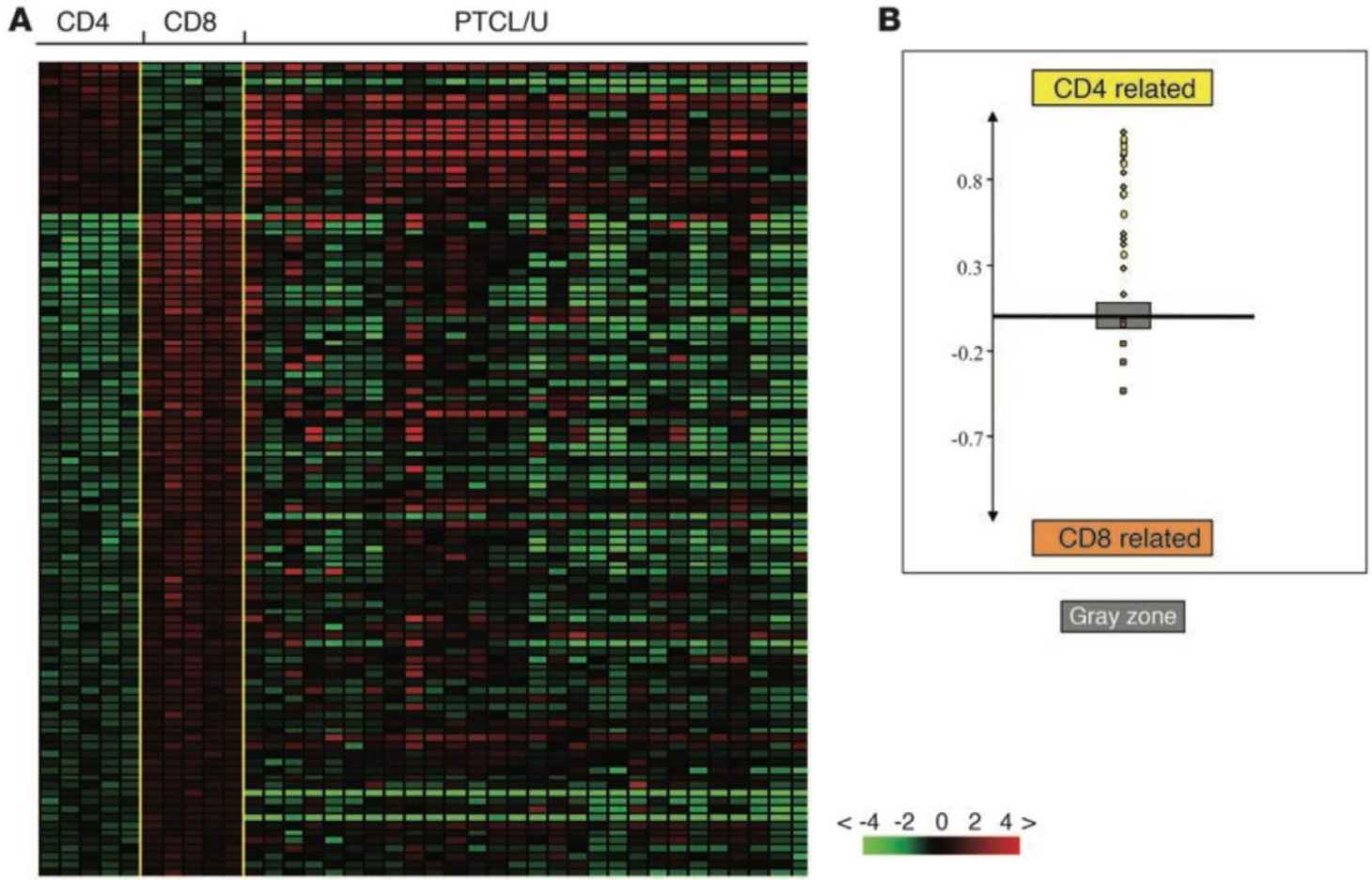
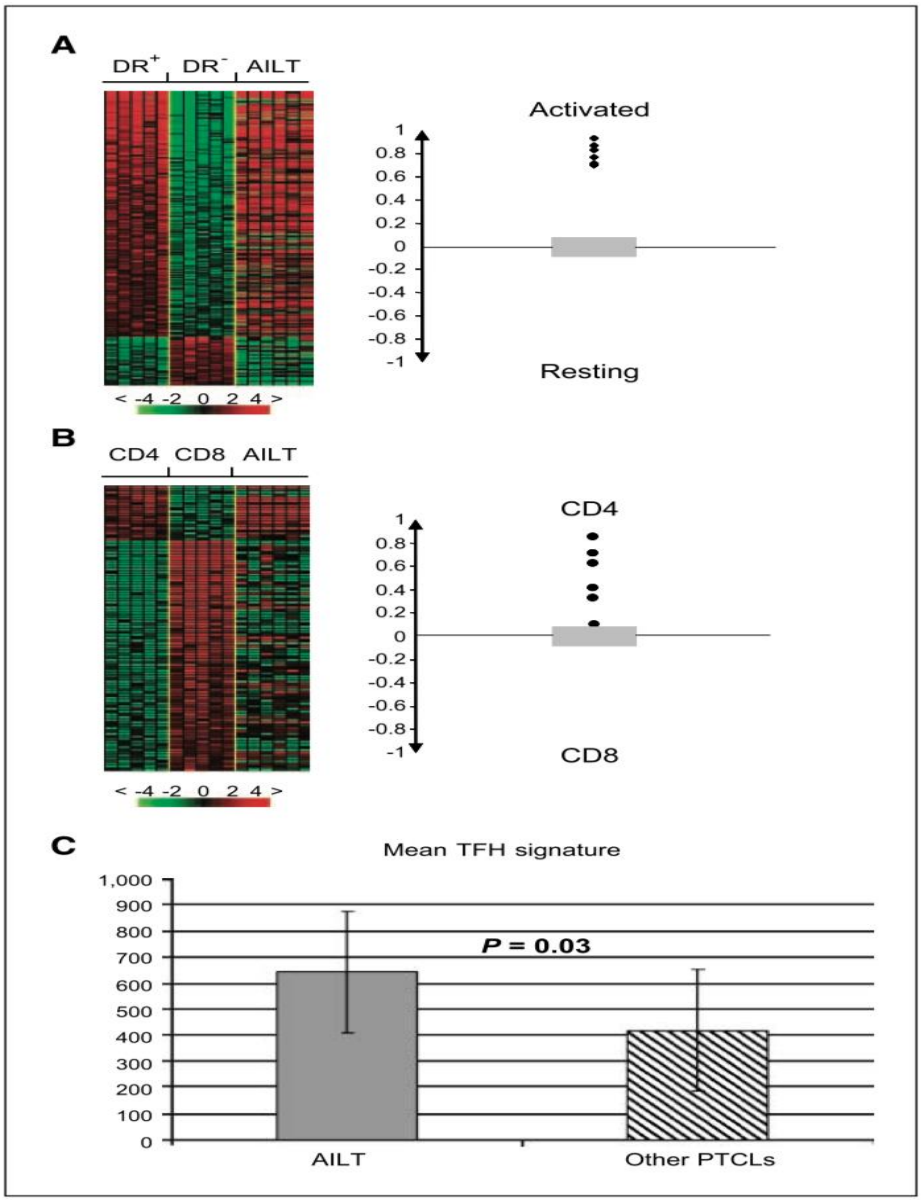
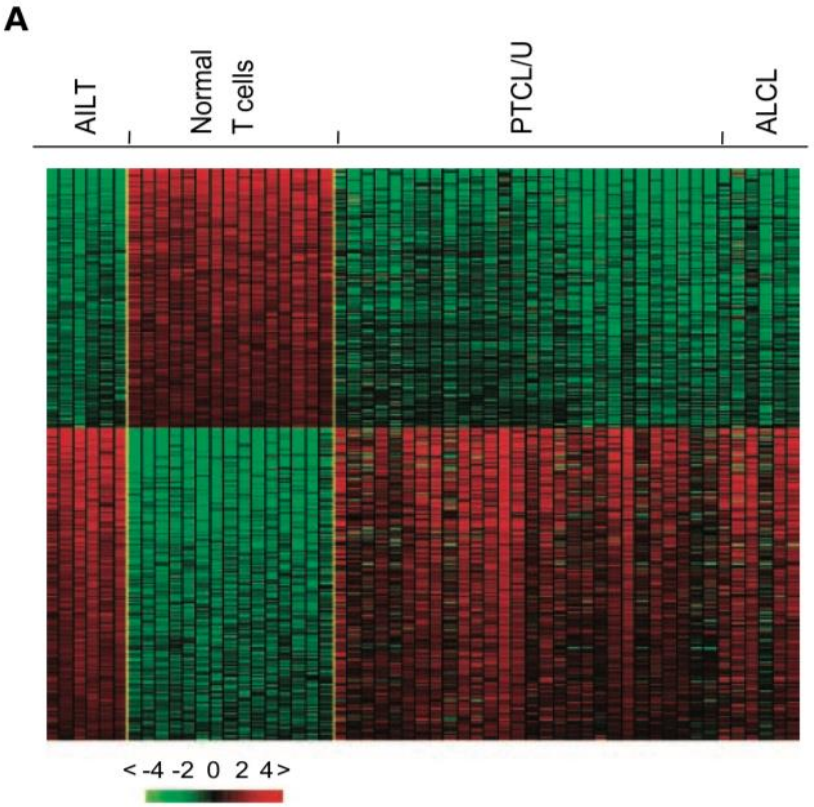


Figure 3

Relatedness of PTCL/U to CD4 and CD8 normal lymphocytes. Relatedness of the gene expression profile of PTCL/U to normal T cell populations. A supervised analysis was used to identify the genes differentially expressed between 2 groups of samples. (**A**) $CD4^+$ T cells are compared with $CD8^+$ T cells. The expression of the selected genes is investigated in PTCLs/U, represented on the right side of the matrix. (**B**) A cell-type classification is used to measure the relatedness of PTCL/U to $CD4^+$ and $CD8^+$ T cells. The gray area marks 95% confidence: the *P* value decreases with increasing distance from the *x* axis.

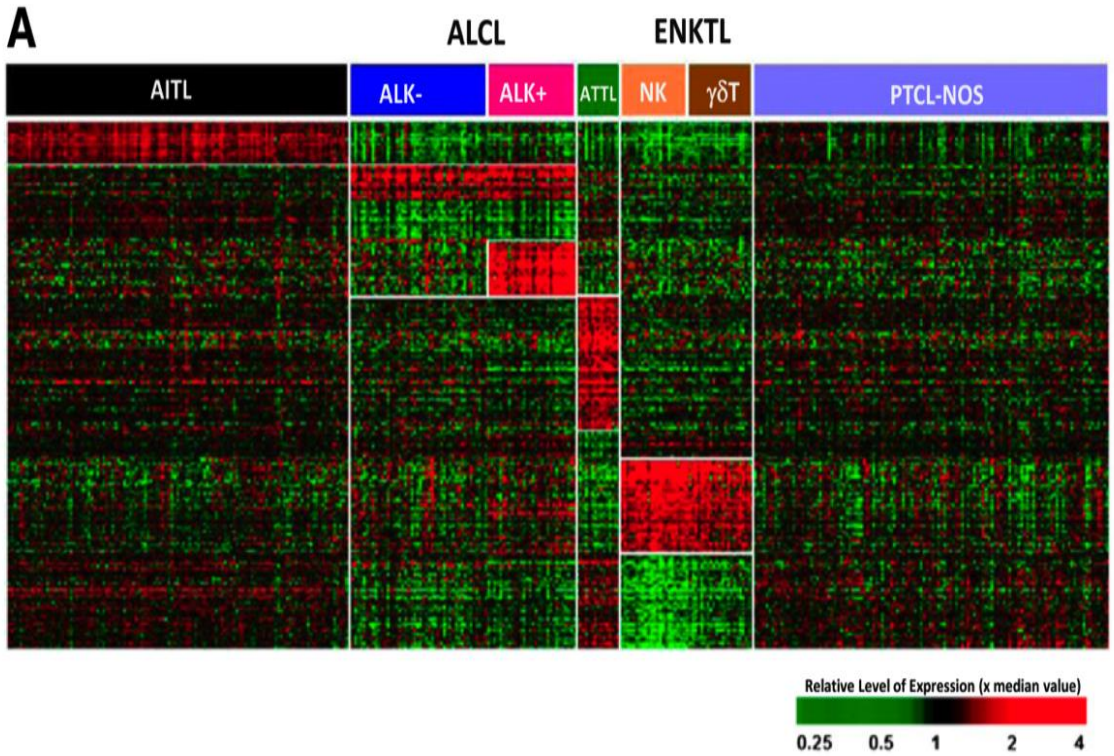
Gene expression profiling AITL





Piccaluga PP. Cancer Res. 2007

Gene expression signature



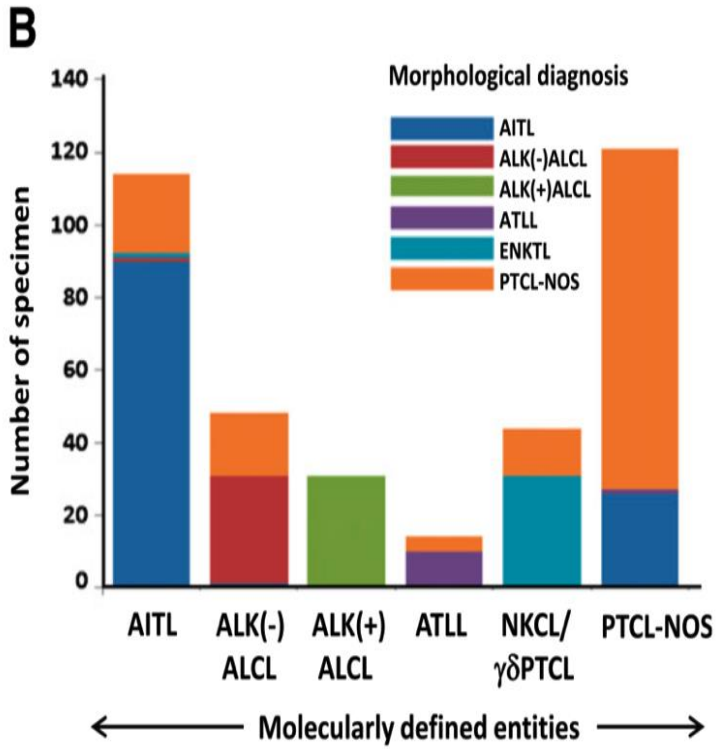
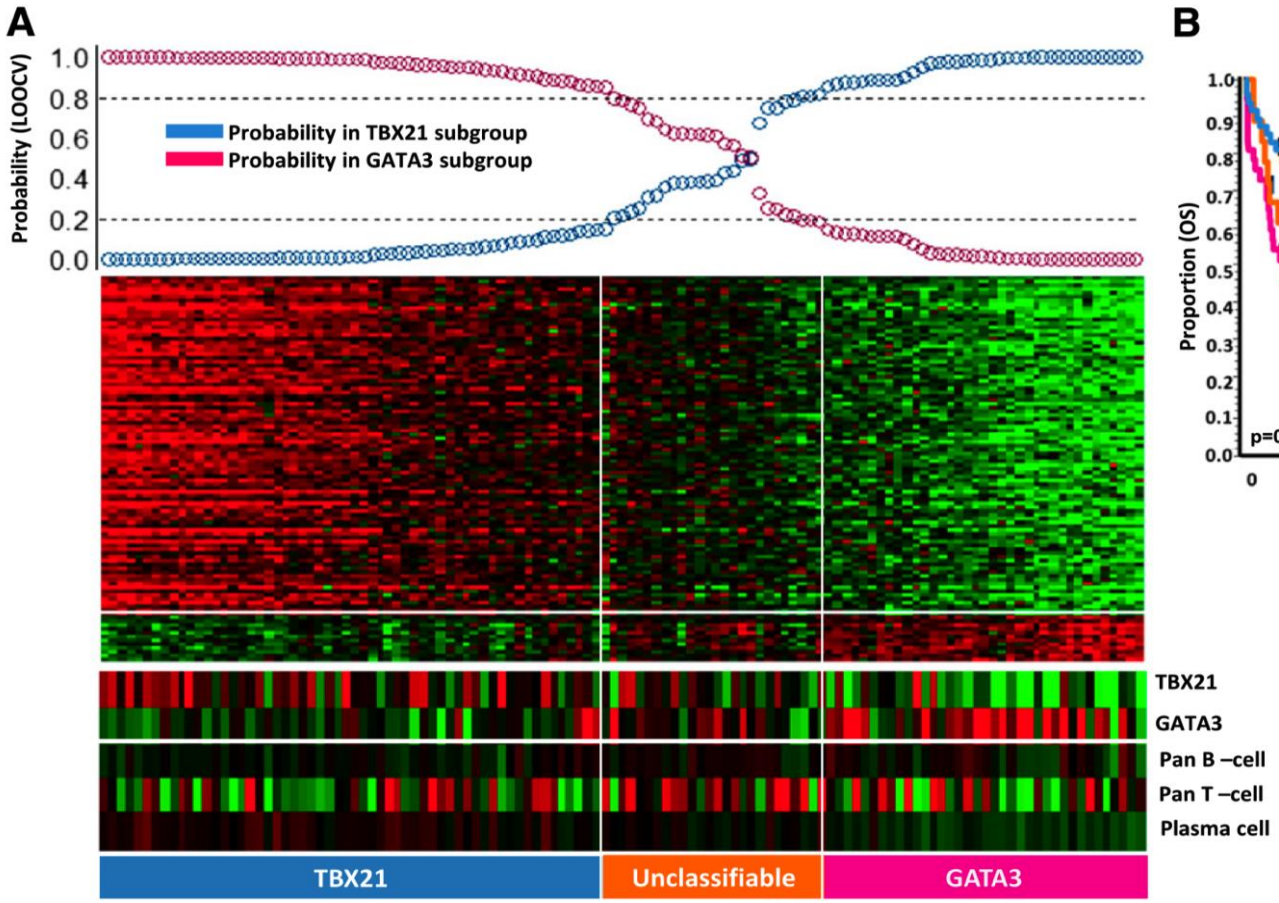


Figure 1. Molecular diagnostic signatures of PTCL subgroups. (A) Unique gene expression signatures were identified for major PTCL entities using compound covariate prediction model (see Materials and methods for details), and the predictor score from top ranking genes for each subtype was used to classify a PTCL patient. ALCL and ENKTL groups are further differentiated into ALK(+)ALCL and ALK(–)ALCL, and NK and γδ T-cell subgroups, respectively. Each column represents a PTCL patient and each row represents a unique gene of the classifier. The relative gene expression scale is indicated below. (B) Pathological vs molecular diagnosis comparison. Substantial number of cases from PTCL-NOS were molecularly classified into WHO recognized PTCL subgroups: (i) AITL (n = 21, 14%); (ii) ALK(–)ALCL (n = 17, 11%); (iii) ATLL (n = 4, 3%); (iv) γδ-PTCL (n = 13, 9%). However, 26 AITL cases (22%) were not molecularly classifiable and changed to PTCL-NOS.

Gene expression signatures



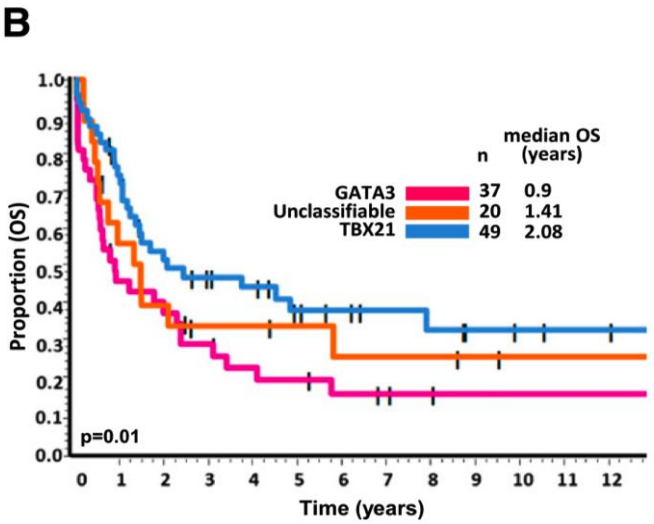


Figure 3. Two major molecular subgroups within PTCL-NOS with biological and overall survival differences. (A) Bayesian predictor for the GATA3 and TBX21 subgroups was derived using cases from hierarchical cluster 1 and cluster 2. LOOCV was used for classification precision. (B) Overall survival (OS) analysis of molecularly-defined GATA3 and TBX21 subgroups showed significant difference in clinical outcome ($P = .01$). A subset of cases mentioned in the text lacked clinical outcome data and are not included in OS analysis. (C) Representative cases in the TBX21 subgroup (H&E) with TBX21 immunostain showed positivity ranging from 40% to 80% of cells, whereas positivity in the GATA3 subgroup was <10%. (D) Representative cases in GATA3 subgroup immunostained with GATA3 showing positivity ranging from 50% to 80% of cells, and were negative for TBX21.

ALCL, ALK+ve vs ALK-ve

Table 3. Cytogenetic abnormalities and molecular features of ALK+ vs ALK− ALCL

ALK+ ALCL	ALK- ALCL
Recurrent translocations involving ALK	Recurrent translocations involving *DUSP22:IRF4*
t(2;5)(p23;25) *ALK:NPM1* (85%)	(6p25.3) (30%)
t(2;v) (15%)	Recurrent translocations involving *TP63* (3q28) 8%
Gains: 7, 17p, 17q	Gains: 1q, 6p, 8q, 12q
Deletions: 4, 11q, 13q	Deletions: 6q, 4q, 13q

v, variant partner[30,38,40]

Hapgood G. Blood. 2015

ALCL, ALK+ve vs ALK-ve

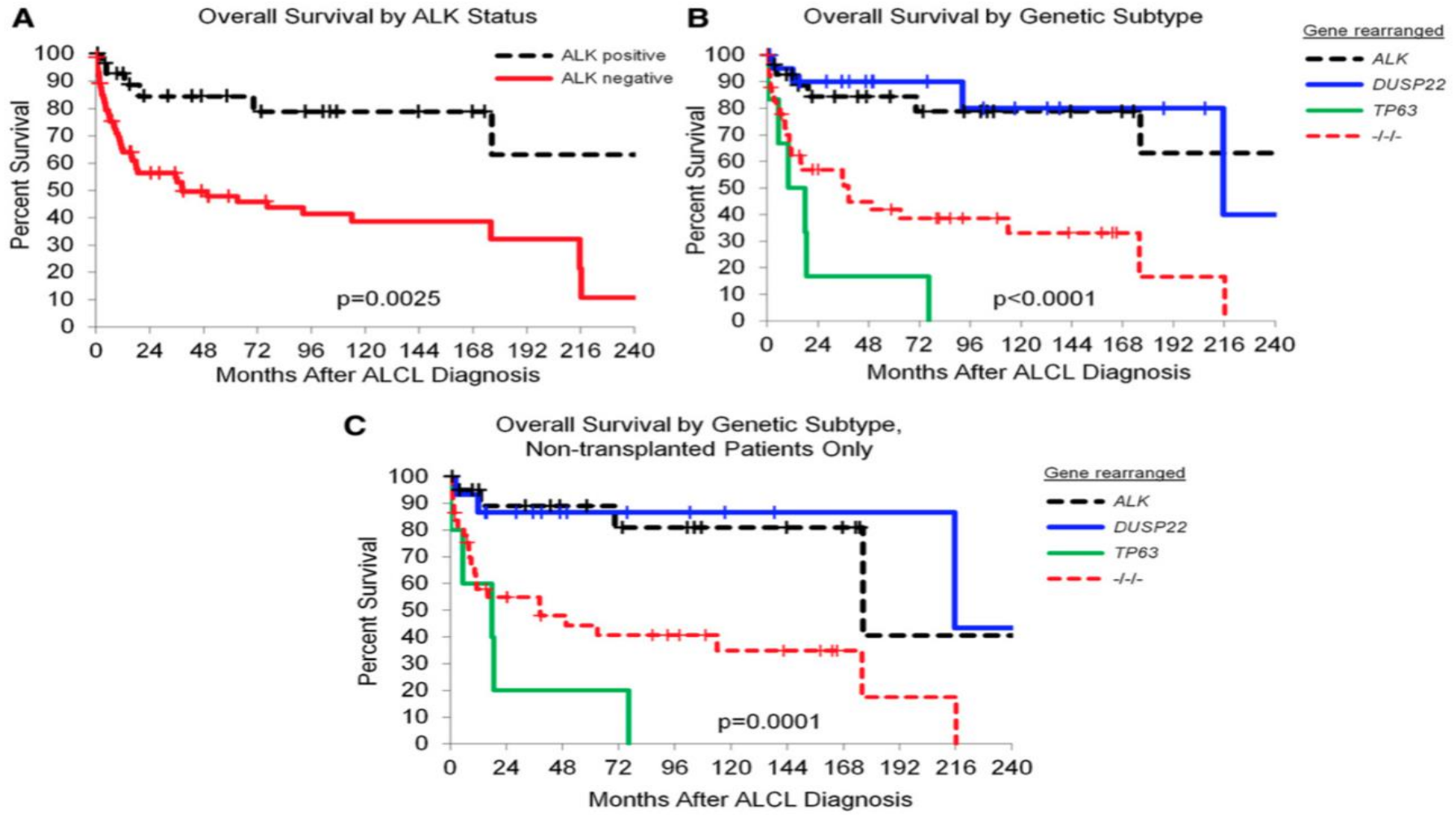


Figure 1. Outcomes in patients with ALCL based on genetic subtype. (A) OS rates in patients with ALCL, stratified by ALK status only (ALK positive, N = 29; ALK negative, N = 67). (B) OS rates in patients with ALCL, stratified by rearrangements of *ALK* (N = 29), *DUSP22* (N = 21), and *TP63* (N = 6). $^{-/-/-}$, triple-negative cases lacking all 3 rearrangements (N = 40). (C) OS rates in patients with ALCL who did not undergo transplantation, stratified by rearrangements of *ALK* (N = 21), *DUSP22* (N = 15), and *TP63* (N = 5). $^{-/-/-}$, N = 34.

Parilla Castellar E. Blood. 2014

Therapy

Is CHOP standard?

- The Past:

NEW WORKING FORMULATION for Clinical Use

Low-Grade
- A. Small lymphocytic (lymphocytic; plasmacytoid)
- B. Follicular, predominantly small cleaved cell
- C. Follicular, mixed, small cleaved and large cleaved cell

Intermediate-Grade
- D. Follicular, predominantly large cell, cleaved and/or non-cleaved
- E. Diffuse, small cleaved cell
- F. Diffuse, mixed, large and small cell
- G. Diffuse, large cell, cleaved or noncleaved

High-Grade
- H. Large cell, immunoblastic -(B- or T-cell type)
- I. Lymphoblastic
- J. Small noncleaved cell (Burkitt's and non-Burkitt's)

Miscellaneous

Is CHOP standard?

- Fisher et conducted Phase III randomized trial.

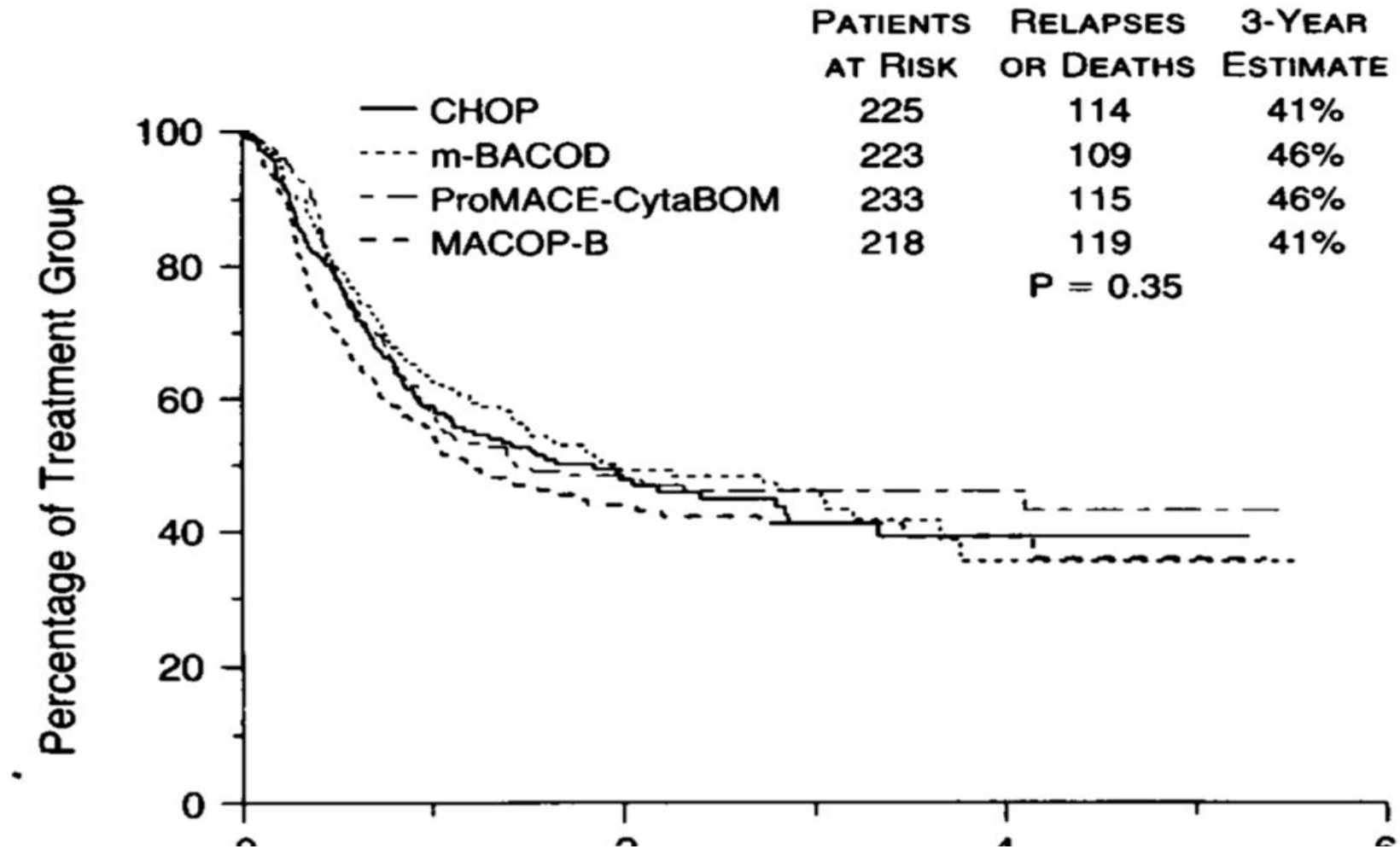
Table 1. Characteristics of the Patients, According to Chemotherapeutic Regimen.

Characteristic	CHOP (N = 225)	m-BACOD (N = 223)	ProMACE-CytaBOM (N = 233)	MACOP-B (N = 218)
Age				
Median (yr)	56	57	54	57
Range (yr)	15–79	18–81	17–81	19–79
≥65 yr (%)	26	25	27	24
Marrow involvement (%)	25	26	27	27
Bulky disease (%)	40	41	41	40
LDH >250 U/liter (%)*	45	43	42	43
Working formulation group (%)†				
D or E	14	15	15	14
F, G, or H	81	82	81	82
J	5	4	4	4

*LDH denotes lactate dehydrogenase.

†These groups were defined according to the system of the Non-Hodgkin's Lymphoma Pathologic Classification Project.[10]

Is CHOP standard?



Fisher R. NEJM. 1993

Annals of Oncology **1**: 45–50, 1990.

Original article

Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: A prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen

B. Coiffier,[1] N. Brou: . Bryon[1] &
J. Diebold[6] for the Gl

[1]*Service d'Hématologie, Ce: tologie Pathologiques, Hôpital*
Necker, Paris; [3]*Service d'A: atomie Pathologique, Hôpital*
Edouard-Herriot, Lyon; [5]*Se: t de Cytologie Pathologiques,*
Hôtel-Dieu, Paris, France

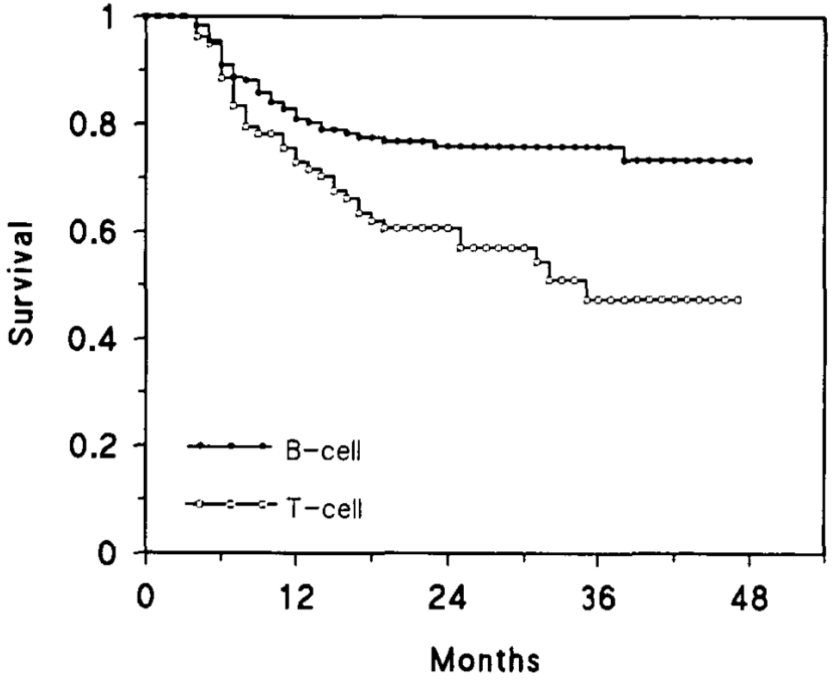


Fig. 2. Freedom-from-relapse survival for B-cell and T-cell malignant lymphoma patients ($X^2 = 9.43$, $p = .002$).

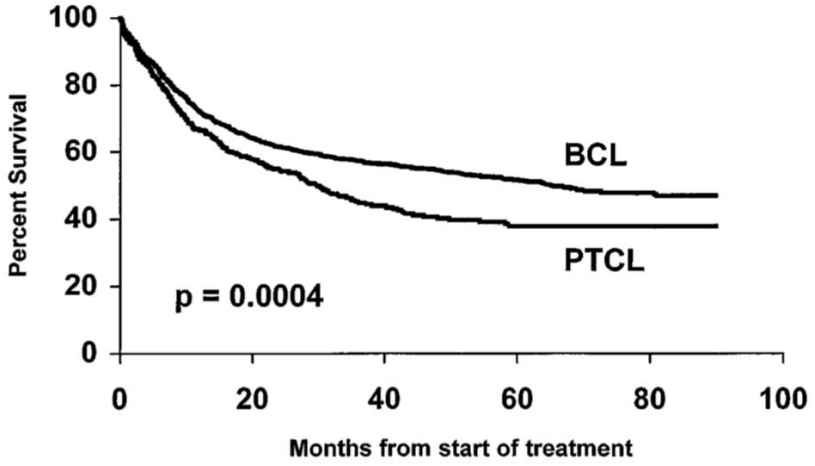


Fig 1. Overall survival of 288 PTCL patients compared with 1,595 diffuse BCL patients.

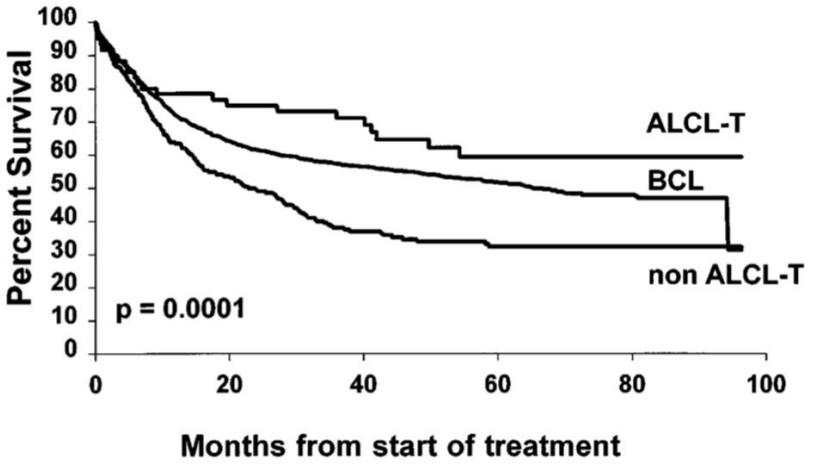


Fig 2. Overall survival of 228 non-ALCL cell and 60 T-ALCL lymphoma patients compared with 1,595 diffuse BCL patients.

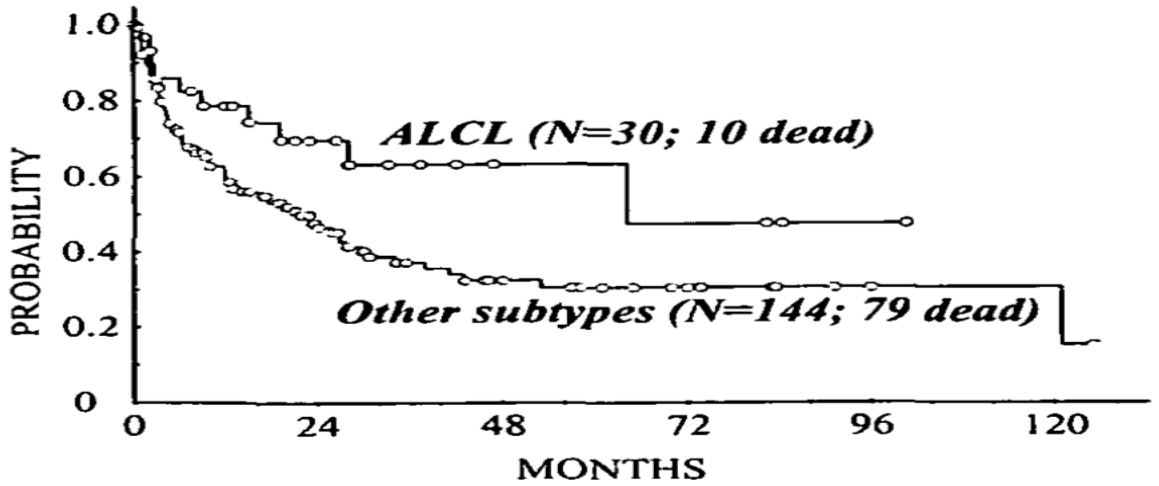


Figure 3. Survival of 174 patients with peripheral T-cell lymphoma (PTCL) according to the histologic subtype: anaplastic large-cell lymphoma Ki-1-positive (ALCL) and the other categories.

Table 3. Response to therapy, overall survival, progression-free survival and overall survival by the International Prognostic Index (IPI)

Histologic subtype	ORR (CR) rate %	5-year OS %	5-year PFS %	5-year OS % by IPI risk[a]		
				Low	Intermediate	High
Favorable						
CUTALCL	100(89)	78	56	NA	NA	NA
Intermediate						
PTCL-US	84(64)	35	29	64	22	22
ALCL	76(55)	43	28	66	16	25
AILT	90(70)	36	13	NA	NA	NA
Unfavorable						
NASAL	80(73)	24	15	38	25	20
ETTL	78(33)	22	22	NA	NA	NA

[a]Overall survival by IPI calculated for histologic subgroups with >10 patients.

CR, complete response; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Improving the CHOP backbone?

Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group

Norbert Schmitz,[1] Lorenz Trümper,[2] Marita Ziepert,[3] Maike Nickelsen,[1] Anthony D. Ho,[4] Bernd Metzner,[5] Norma Peter,[6] Markus Loeffler,[3] Andreas Rosenwald,[7] and Michael Pfreundschuh[8]

[1]Department of Hematology, Oncology and Stem Cell Transplantation, Asklepios Hospital St Georg, Hamburg, Germany; [2]Department of Hematology and Oncology, University of Göttingen, Göttingen, Germany; [3]Institute of Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; [4]Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; [5]Department of Hematology and Oncology, Klinikum Oldenburg, Oldenburg, Germany; [6]Department of Hematology and Oncology, Carl-Thiem Klinikum, Cottbus, Germany; [7]Institute of Pathology, University of Würzburg, Würzburg, Germany; and [8]Department of Internal Medicine I, Saarland University, Homburg/Saar, Germany

- All Nodal and Extra-nodal T-cell lymphoma N= 320
- Treated in prospective trials
  - NHLB1 and NHL-B2 (Comparing CHOP14 vs CHOP21 +/- Etoposide
  - Hi-CHOEP (comparing dose escalating CHOEP-14 vs CHOEP21)
  - MegaCHOEP

Schmitz N. Blood. 2010

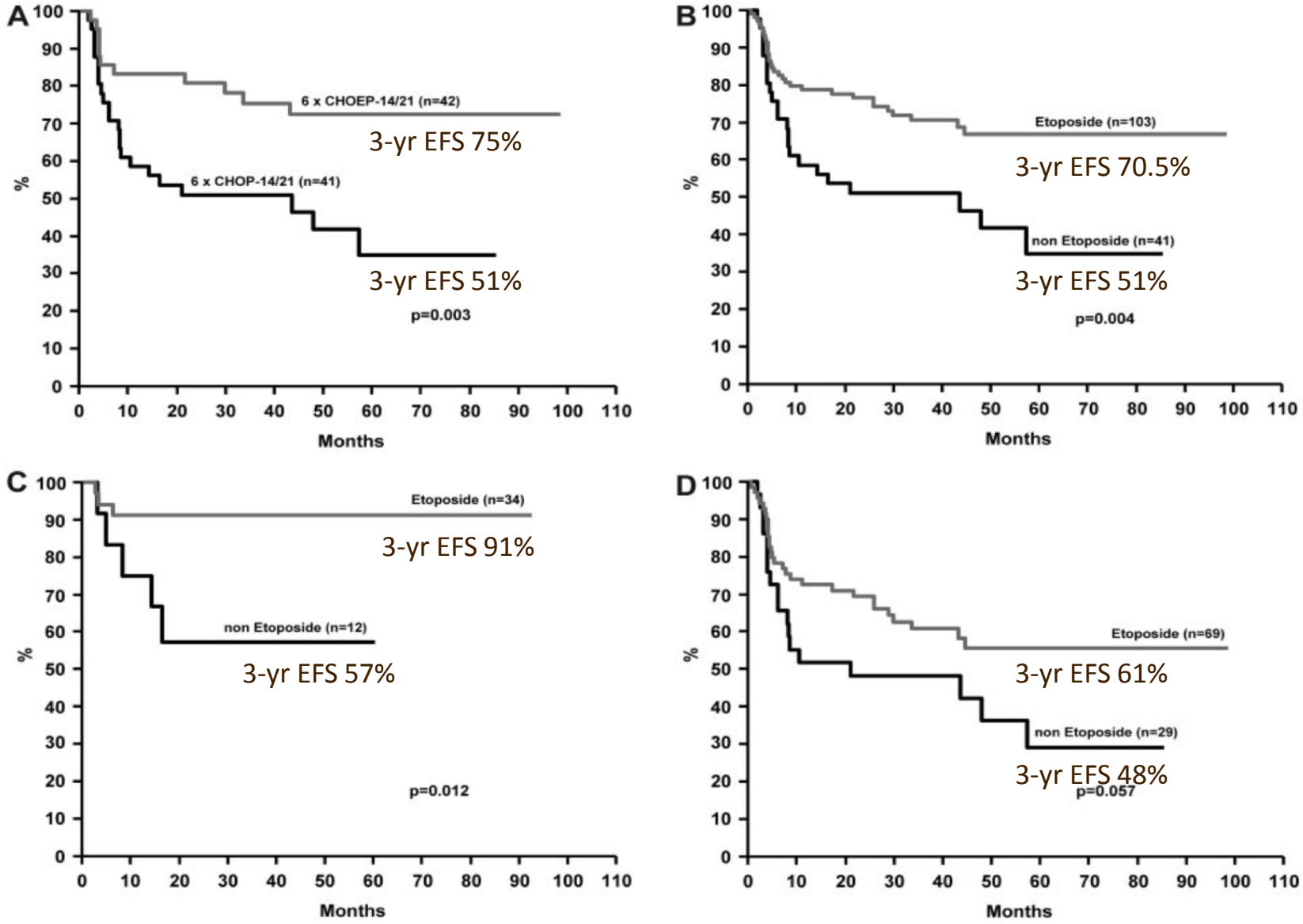


Figure 2. Event-free survival of younger patients (18-60 years, LDH ≤ UNV). Panel A refers to patients treated on the NHL-B1 trial. Panel B refer to patients treated on the NHL-B1 or Hi-CHOEP phase II/III trials. Patients who did or did not receive etoposide plus CHOP (CHOEP) are compared. Panels C and D show the EFS for patients with ALCL, ALK-positive (C), and with other major subtypes (D).

Schmitz N. Blood. 2010

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Improving the CHOP backbone?

Reference	Patients (n)	Treatment	CR	PR	PFS	OS
Kim SJ. Cancer Chemo Phar. 2006	26 (No ALCL ALK+)	CHOP-EG	60%	15%	1yr 50%	1yr 69%
Sung HJ. Br J Heamatol. 2006	52	CEOP-B	17%	46%	5yr 28%	5yr 49%
Gallamini A. Blood 2007	24 (No ALCL ALK+)	CHOP + Alemtuzumab	71%	4%	2yr 48%	2yr 53%
Kim J. Cancer Chemo Phar. 2007	20* (No ALCL ALK+)	CHOP + Alemtuzumab	65%	15%	1yr 43%	1yr 44%
Binder C. Ann Hematol. 2013	46 (No ALCL ALK+)	CHO(E)P + Alemtuzumab	59%	2%	3yr 32%	3yr 62%
Kim SJ. Eur J Cancer.2012	46 (No ALCL ALK+)	CHOP + Bortezomib	65%	11%	3yr 35%	3yr 47%
Foss F. Leuk Lymphoma. 2013	49	CHOP + denileukin diftitox	55%	10%	2yr 43%	2yr 65%
Ganjoo K. Leuk Lymphoma. 2014	39 (No ALCL ALK+)	CHOP + Bevacizumab	49%	41%	3yr 16%	3yr 37%
Kim SJ. Ann Oncol. 2016	30 (No ALCL ALK+)	CHOP + Everolimus	57%	33%	2yr 33%	2yr 70%

Randomized trials compared to CHOP

Reference	Patients (n)	Treatment	CR	PR	PFS	OS
Simon A. Br J Heamatol. 2010	43	CHOP	34%	35%	2yr 41%	2yr 55%
	43	VIP-rABVD	44%	14%	2yr 45%	2yr 55%
Gleeson M. Hemato Oncol. 2017	43	CHOP	57%	-	2yr 36%	2yr 53%
	43	GEM-P	43%	-	2yr 39%	2yr 65%
Li L. Br J Heamatol. 2017	51	CHOP	33%	16%	2yr 35%*	2yr 50%*
	52	GDPT	52%	15%	2yr 57%*	2yr 71%*

A complete different induction?

Reference	Patients (n)	Treatment	CR	PR	PFS	OS
Mahadevan D. Cancer. 2013	33 (No ALCL ALK+)	PEGS	24%	15%	2yr 12%	2yr 31%
Lavoie J. Blood. 2013	34 (No ALCL ALK+)	CHOP-GDP (alternating)	62%	20%	2yr 36%	2yr 64%
Jia B. Hematology. 2016	11	GDP	46%	44%	1yr 46%	1yr 100%

Post induction consolidation?

Study	Number of patients available for analysis	Design of the study	Age	Histology particularities	Response rate after induction	ASCT rate	Survival for the entire cohort	Survival for patients treated with ASCT	Comment on the role of ASCT when a control group of non-transplanted patients in response after induction is available
				Prospective studies					
D'Amore[2] (2012)	160	All eligible patients in response to CHOEP receive ASCT as a consolidation strategy	57	All except CTCL and ALK+ ALCL	CR = 53% PR = 31% PD = 16%	72%	5-y OS = 51% 5-y PFS = 44%	NA	
Rodriguez[5] (2007)	26	All eligible patients in response to Mega CHOP receive ASCT as a consolidation strategy	44	PTCL-NOS, AITL, ALCL ALK-	CR = 46% PR = 27% PD=27%	73% (but 6 patients received salvage therapy before ASCT)	3-y OS = 73% 3-y PFS = 46%	NA	
Mercadal[3] (2008)	41	All eligible patients in response to CHOP/ESHAP receive ASCT as a consolidation strategy	47	All except mycosis fungoides and ALK+ ALCL	CR/CRu= 49% PR = 10% PD = 41%	39%	4-y OS = 39% 4-y PFS = 30% 4-y PFS for patients in CR = 59%	NA	No benefit of ASCT for patients in CR or PR after induction
Wilhelm[6] (2016) & Reimer[4] (2009)	111	All eligible patients in response to CHOP receive ASCT as a consolidation strategy	49	All except ALK+ ALCL and CTCL	CR = 62% PR = 20% PD = 18%	68%	5-y OS = 44% 5-yr PFS = 39%	5-yr OS = 57%	
Corradini[1] (2006)	62	All eligible patients in response HOP/DHAP or MACOP-B receive ASCT as a consolidation strategy	43	ALK+ ALCL included (30%)	CR = 56% PR = 16% PD = 24%	74%	12-yr OS = 34% 12-yr EFS = 30%	NA	

Fossard G. Ann Oncol Supplementary. 2017

Post induction consolidation?

Study	Number of patients available for analysis	Design of the study	Age	Histology particularities	Response rate after induction	ASCT rate	Survival for the entire cohort	Survival for patients treated with ASCT	Comment on the role of ASCT when a control group of non-transplanted patients in response after induction is available
Retrospective studies									
Rodriguez[16] (2007)	74	Study based on patients in CR after induction only		31% of pts with ALCL with no information on ALK status	CR = 100%	100%	5-y OS = 68% 5-y PFS = 63%		
Ellin[17] (2014)	252	Subgroup ITT-based analysis of an initial real-world population of 755 pts	NA	All except CTCL and ALK+ ALCL	No data on this specific subgroup eligible for transplant	51% in ITT	No data on this specific subgroup eligible for transplant	NA	✓ Improved outcome in favor of ASCT but no adjustment on response status at the end of induction
Gui[15] (2014)	45	Patients in first and second remission. Only 26 patients in first response.		All except CTCL (31% of pts with ALK+ or unknown ALK status ALCL)	CR = 69% PR = 31%	100%	For patients in CR1 only: 5-y OS = 89% 5-y OS = 83%		
Han[10] (2017)	52	Only patients in response and receiving ASCT were considered		All except CTCL (4% ALK+ ALCL)	CR = 74% PR = 26%	100%	5-y OS = 71% 5-y PFS = 62%		
Yam[12] (2016)	105	Subgroup comparison of 28 (observation) vs 20 (ASCT) patients in CR after induction		All except CTCL and ALK+ ALCL	CR = 52%	19%	NA	3-y OS = 72%	✗ No benefit in favor of ASCT
Cederleuf[9] (2017)	232	Registry-based study of patients in CR after induction only		ALCL, PTCL-NOS, AITL (19% of ALK+ and 3% of unknown ALK status ALCL)	CR = 100%	36%	2-y OS = ~80% 2-y PFS = 67%	NA	✗ No benefit in favor of ASCT in univariate or multivariate analysis
Abramson[8] (2014)	341	Real-world study of 9 US academic centers		All histology (7% ALK+ ALCL)	CR = 61% PR = 12% PD = 24%	10%	3-yr OS = 49% 3-yr PFS = 29%	3-yr OS = 74% 3-yr PFS = 58%	✗ No benefit in favor of ASCT after adjustment on response status

Fossard G. Ann Oncol Supplementary. 2017

Post induction consolidation?

Role of up-front autologous stem cell transplantation in peripheral T-cell lymphoma for patients in response after induction: An analysis of patients from LYSA centers

G. Fossard[1-3], F. Broussais[1], I. Coelho[4], S. Bailly[5], E. Nicolas-Virelizier[6], E. Toussaint[7], C. Lancesseur[8], F. Le Bras[9], E. Willems[10], E. Tchernonog[11], T. Chalopin[12], R. Delarue[13], R. Gressin[14], A. Chauchet[15], E. Gyan[12], G. Cartron[11], C. Bonnet[10], C. Haioun[9], G. Damaj[8], P. Gaulard[9], L. Fornecker[7], H. Ghesquières[1], O. Tournilhac[5], M. Gomes da Silva[4], R. Bouabdallah[16], G. Salles[1-3], E. Bachy[1-3]

- Retrospective study, 527 pts screened
- 269 pts included
  - < or = to 65
  - In CR or PR
  - At least months in response from induction
- 46% had AITL, 29% PTCL, 25% ALK-ve ALCL
- Intention to treat with ASCT identified
  - 134 ASCT planned
  - 135 no ASCT planned

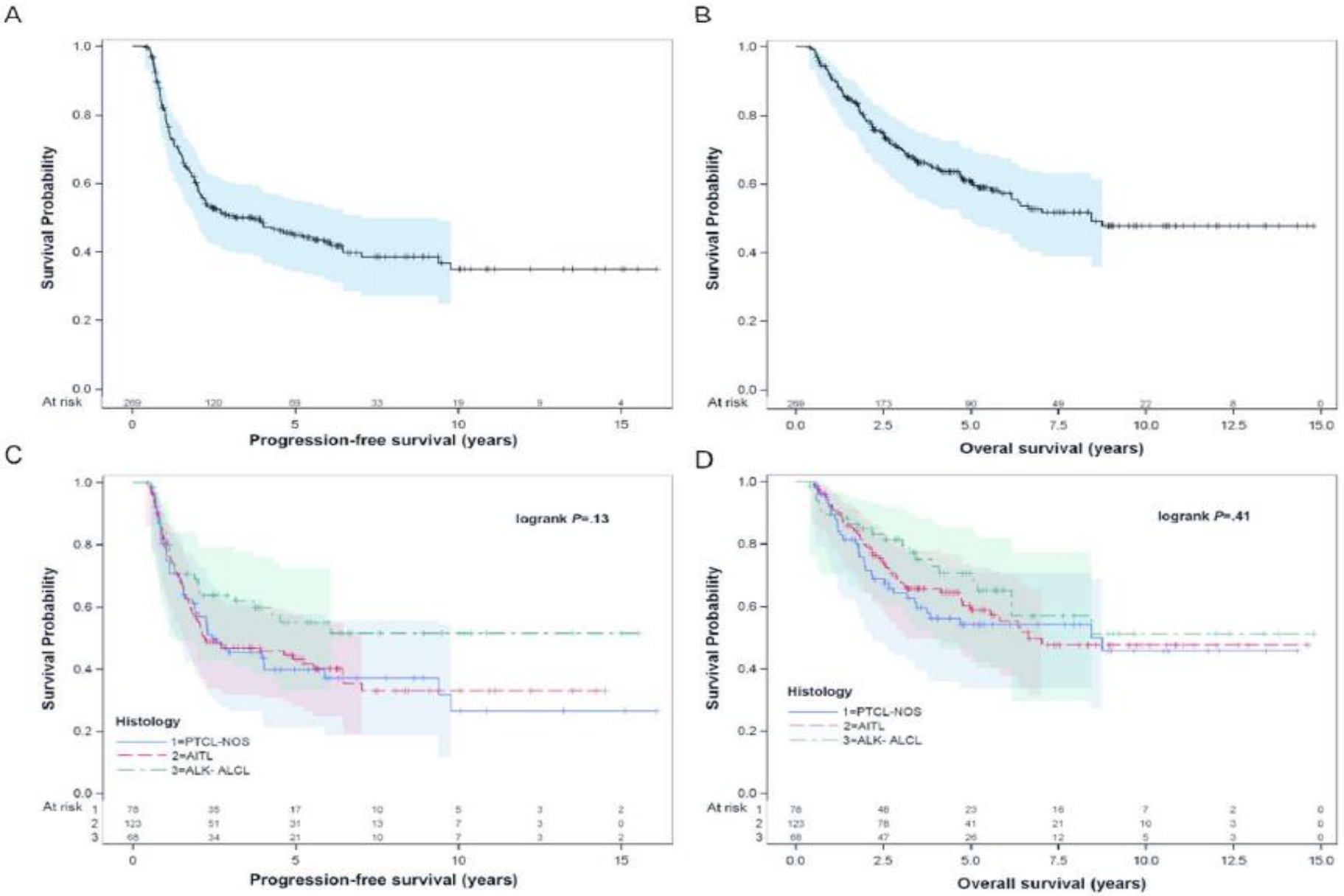
Table 1. Patient characteristics according to ASCT in intention-to-treat

		N (%)*		
	Missing Data (N)	ASCT ITT No (N=135)	ASCT ITT Yes (N=134)	*P*
Age, yrs.	0			0.25
Mean (min-max)		53 (19-65)	52 (19-66)	
Histology	0			0.15
PTCL-NOS		32 (24)	46 (34)	
AITL		66 (49)	57 (43)	
ALK- ALCL		37 (27)	31 (23)	
Sex	0			0.031
Female		48 (36)	65 (48)	
Male		87 (64)	69 (51)	
ECOG score	4			0.39
0-1		105 (80)	100 (75)	
2-4		27 (20)	33 (25)	
B symptoms	18			0.001
no		70 (55)	42 (34)	
yes		58 (45)	81 (66)	
Stage	1			<0.001
I-II		35 (26)	9 (7)	
III-IV		100 (74)	124 (93)	
Bone marrow involvement	4			0.85
no		90 (67)	88 (68)	
yes		45 (33)	42 (32)	
Extranodal involvement	2			0.038
No		62 (46)	45 (34)	
Yes		72 (54)	88 (66)	
LDH	12			0.009
≤UNL		58 (45)	38 (30)	
>UNL		70 (55)	91 (70)	
aaIPI	15			0.002
0-1		62 (49)	38 (30)	
2-3		65 (51)	89 (70)	
PIT	15			0.10
0-1		69 (54)	56 (44)	
2-4		58 (46)	71 (56)	
Response to induction	0			0.028
CR		116 (86)	101 (75)	
PR		19 (14)	33 (25)	
Time from response evaluation to ASCT[V], yrs	0			
Median (min-max)		NA	1.5 (0.2-4.9)	NA
Treatment	0			0.14
CHOP-like or CHOEP[¶]		98 (73)	108 (81)	
ACVBP or COPADM		30 (22)	24 (18)	
Others[§]		7 (5)	2 (1)	

**except for age (mean and range)*

[¶]CHOP every 2 or 3 weeks (n=151), CHOP+rituximab for some patients with AITL (n=21)[30], CHOP+alemtuzumab (n=4) and CHOP+romidepsin (n=6); CHOEP (n=24 patients);

[§]Other regimens are DHAP (aracytine- and platine-based regimen), VIP-rABVD[6], and CVP (CHOP-like regimen without anthracyclines);



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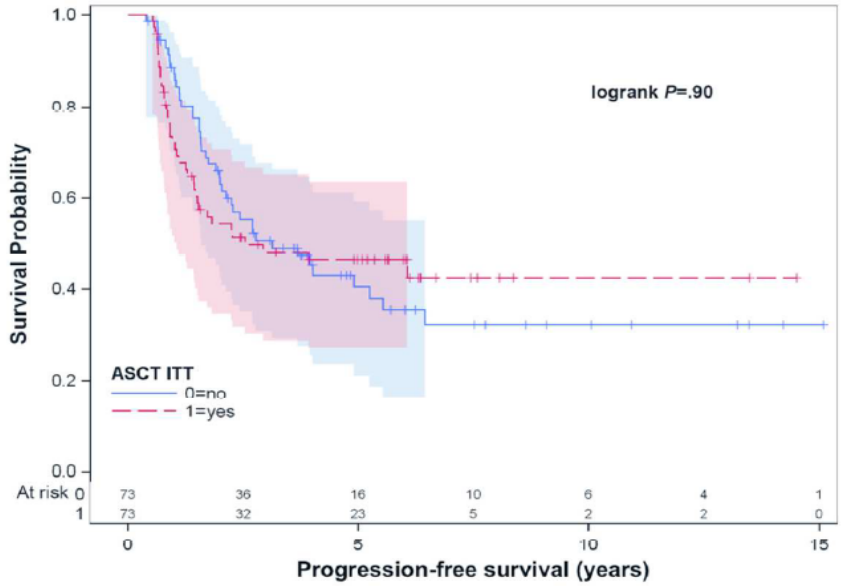

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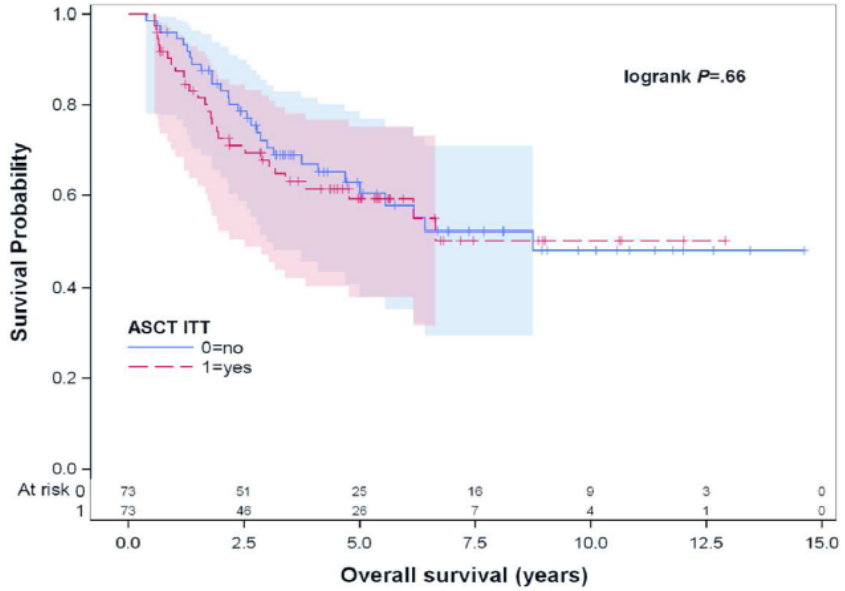


Table 2. Multivariate Cox proportional hazard ratio regression model

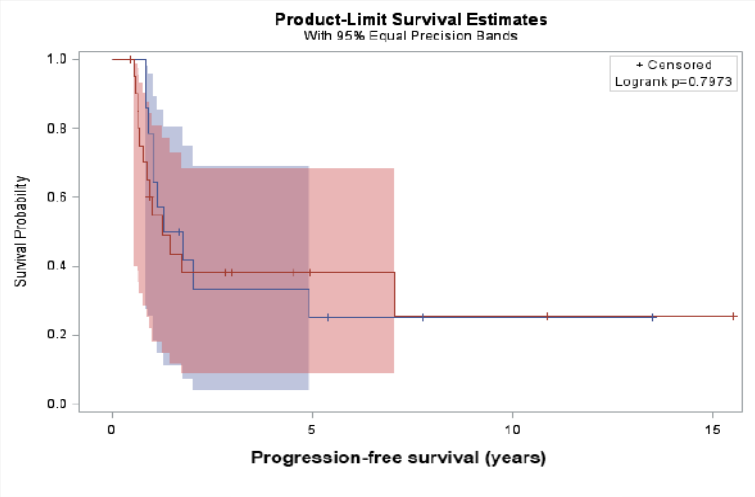
	PFS*			OS*		
	HR	95% CI	P	HR	95% CI	P
B symptoms						
Yes (*vs.* no)	1.18	0.78-1.79	0.41	0.89	0.55-1.44	0.65
Histology						
AITL (*vs.* PTCL-NOS)	0.97	0.62-1.51	0.89	0.97	0.58-1.63	0.92
ALK- ALCL (*vs.* PTCL-NOS)	0.74	0.43-1.25	0.26	0.79	0.43-1.46	0.46
Age, yrs.						
Continuous parameter	0.99	0.97-1.01	0.56	1.01	0.99-1.04	0.15
Sex						
Male (*vs.* female)	1.42	0.97-2.06	0.07	1.21	0.79-1.87	0.37
aaIPI						
1 (*vs.* 0)	1.31	0.61-2.84	0.48	1.27	0.50-3.20	0.60
2 (*vs.* 0)	1.53	0.71-3.29	0.27	1.45	0.57-3.66	0.42
3 (*vs.* 0)	1.72	0.72-4.09	0.21	1.83	0.65-5.13	0.24
Response to induction						
PR (*vs.* CR)	1.86	1.22-2.84	0.003	2.04	1.28-3.25	0.002
ASCT ITT						
Yes (*vs.* no)	1.02	0.69-1.50	0.89	1.08	0.68-1.69	0.74

**Models performed on 240 observations with fully available parameters.*

Abbreviations: PFS, progression-free survival; OS, overall survival; AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; ALK- ALCL, anaplastic large cell lymphoma kinase-negative lymphoma; aaIPI, age-adjusted international prognostic index; PR, partial response; CR, complete response; ASCT ITT, autologous stem cell transplantation in intention-to-treat; HR, hazard ratio; CI, confidence interval; P, p-value.

No ASCT (ITT)
ASCT (ITT)

A



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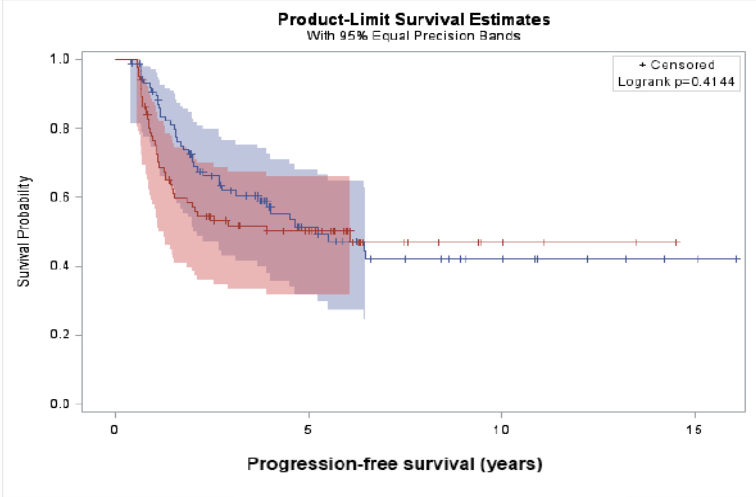

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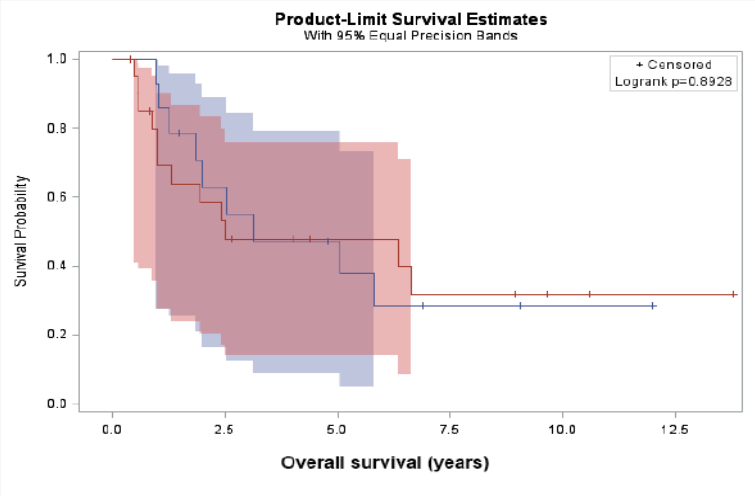

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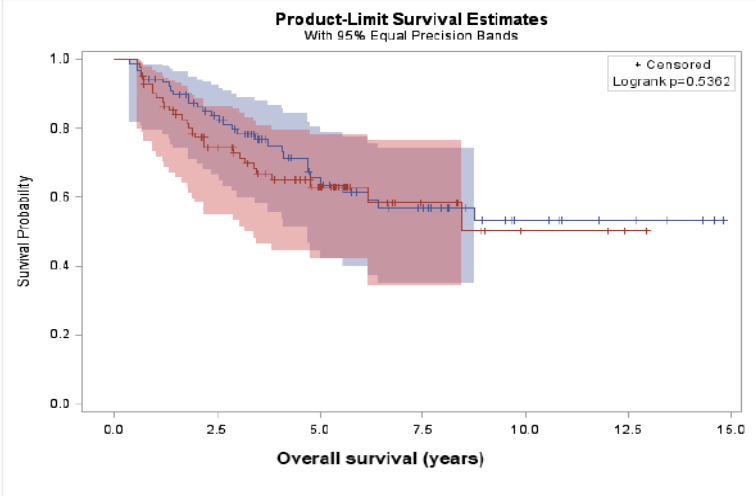
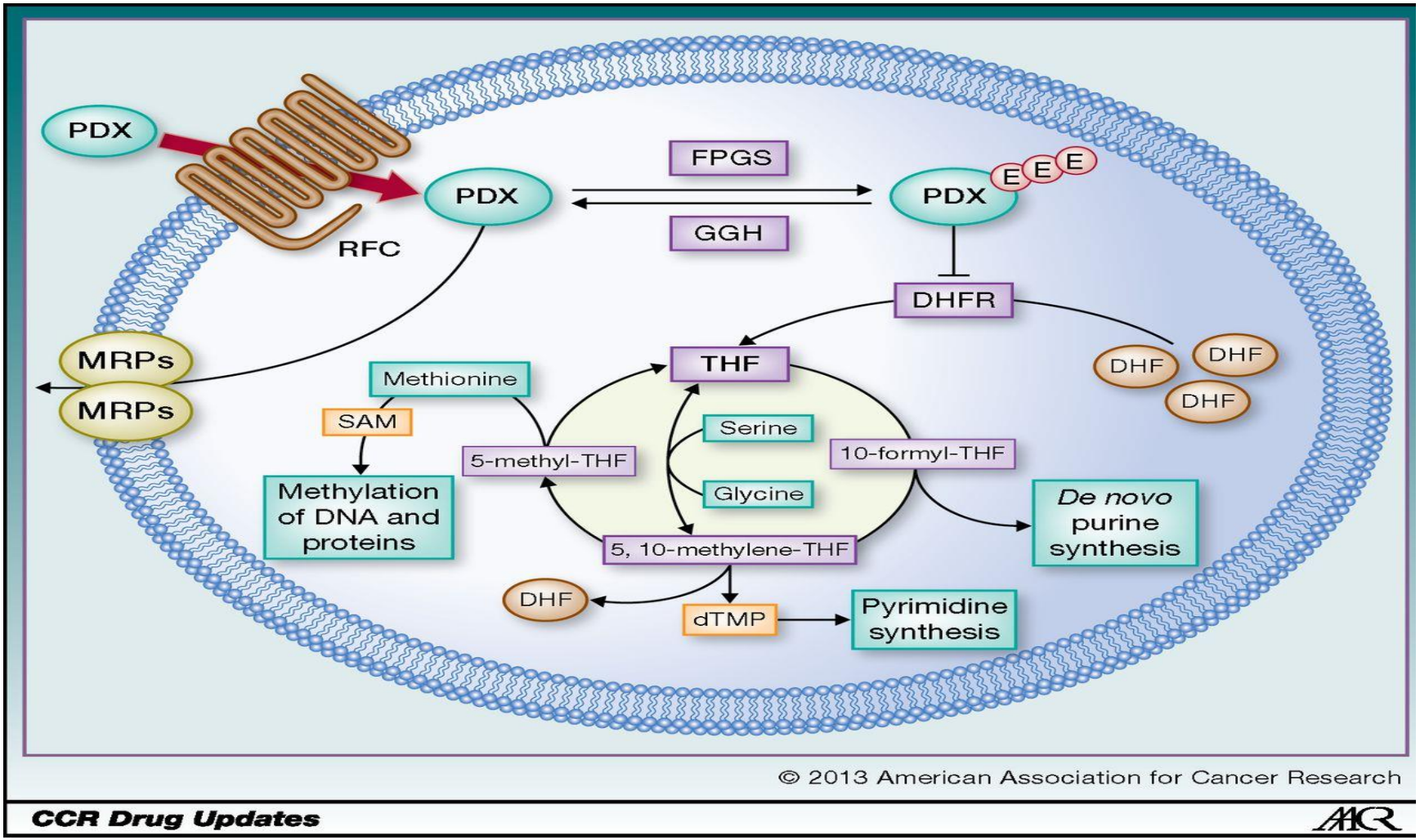


AlloSCT upfront?

Reference	Patients (n)	Treatment	CR	PR	PFS	OS
Loirat M. Ann Oncol. 2014	49 (No ALCL ALK+)	CHOP + AlloSCT	35%	43%	2yr 51%	2yr 55%
Corradini P. Leukemia. 2014	61 (No ALCL ALK+)	CHOP-Al + HD + Allo (23)/auto (14)	54%	11%	4yr 44% 4yr 69% (Allo) 4yr 70% (Auto)	4yr 49% 4yr 69% (Allo) 4yr 92% (Auto)
	25	CHOP-AL	60%	12%	4yr 26%	31%

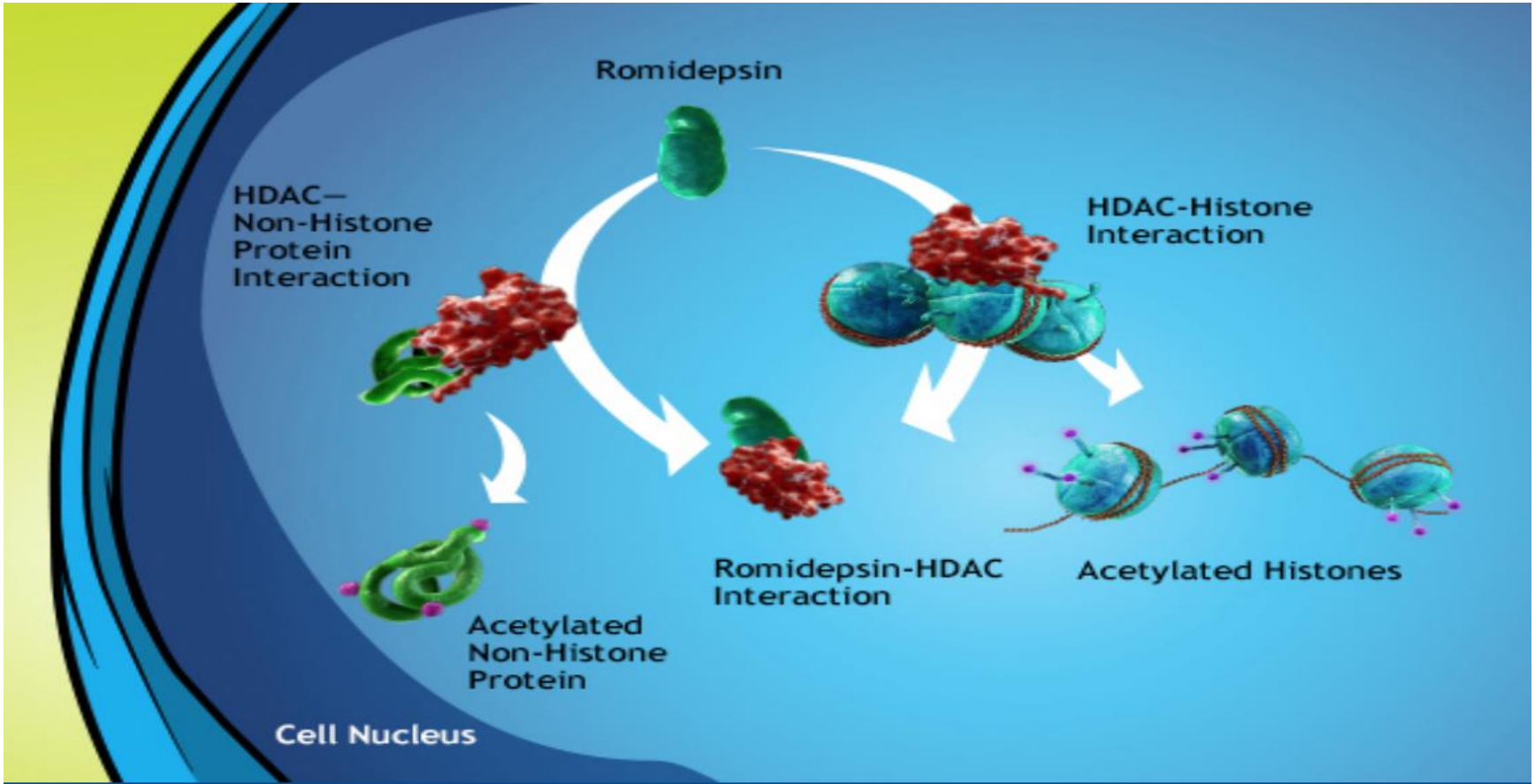
Back to square one

Novel Agents: Pralatrexate



Treatment	Author, year Trial type	Pts.	Subtypes[‡] (Pts.)	ORR, %	CR, %	Median DOR, mos	Median OS, mos	Median PFS, mos	Ref.
Pralatrexate	O'Connor, 2011 Phase 2 Multicenter	111	All patients[§] PTCL-NOS (59) ALCL (17) AITL (13) Other PTCL (8)	29[§§] 32 35 8 38	11 – – – –	10.1	14.5	3.5	[16]

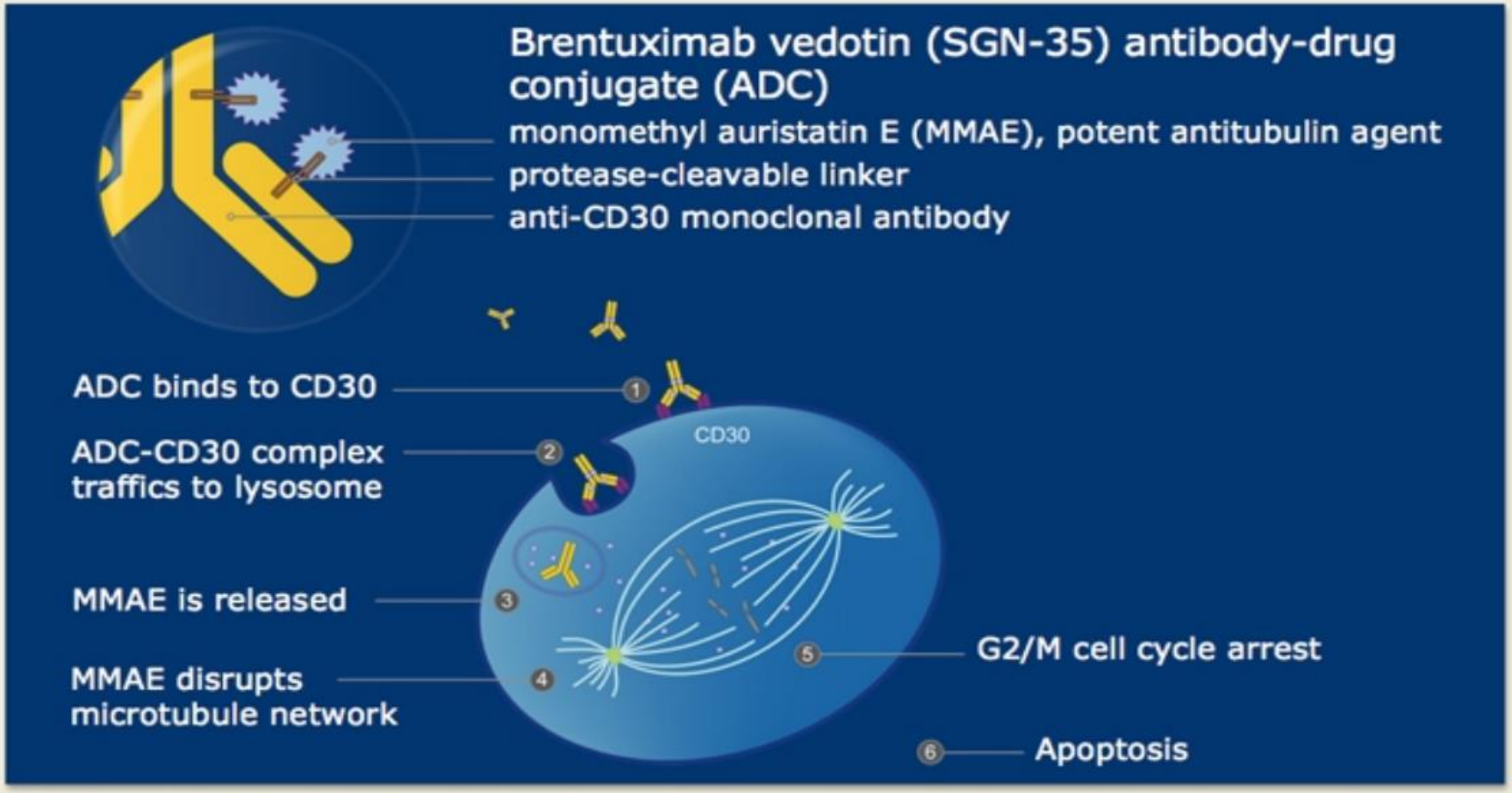
Novel Agents: Romidepsin



In vitro, ISTODAX causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC_{50} values in the nanomolar range.[1]

Treatment	Author, year Trial type	Pts.	Subtypes[‡] (Pts.)	ORR, %	CR, %	Median DOR, mos	Median OS, mos	Median PFS, mos	Ref.
Pralatrexate	O'Connor, 2011 Phase 2 Multicenter	111	All patients[§] PTCL-NOS (59) ALCL (17) AITL (13) Other PTCL (8)	29[§§] 32 35 8 38	11 – – – –	10.1	14.5	3.5	[16]
Romidepsin	Piekarz, 2011 Phase 2 Multicenter	47	All patients PTCL-NOS (27) AITL (7) ALK + ALCL (2) ALK⁻ ALCL (2) Other PTCL (9)	38 41 17 100 – –	18 19 – – – –	8.9	NA (*)	NA (*)	[24]
	Coiffier, 2012 Phase 2 Multicenter	130	All patients[§] PTCL-NOS (69) AITL (27) ALK⁻ ALCL (21) Other PTCL (13)	25[§§] 29 30 24 0	15 14 19 19 0	28.0 (**)	11.3 (**)	4.0	[26]

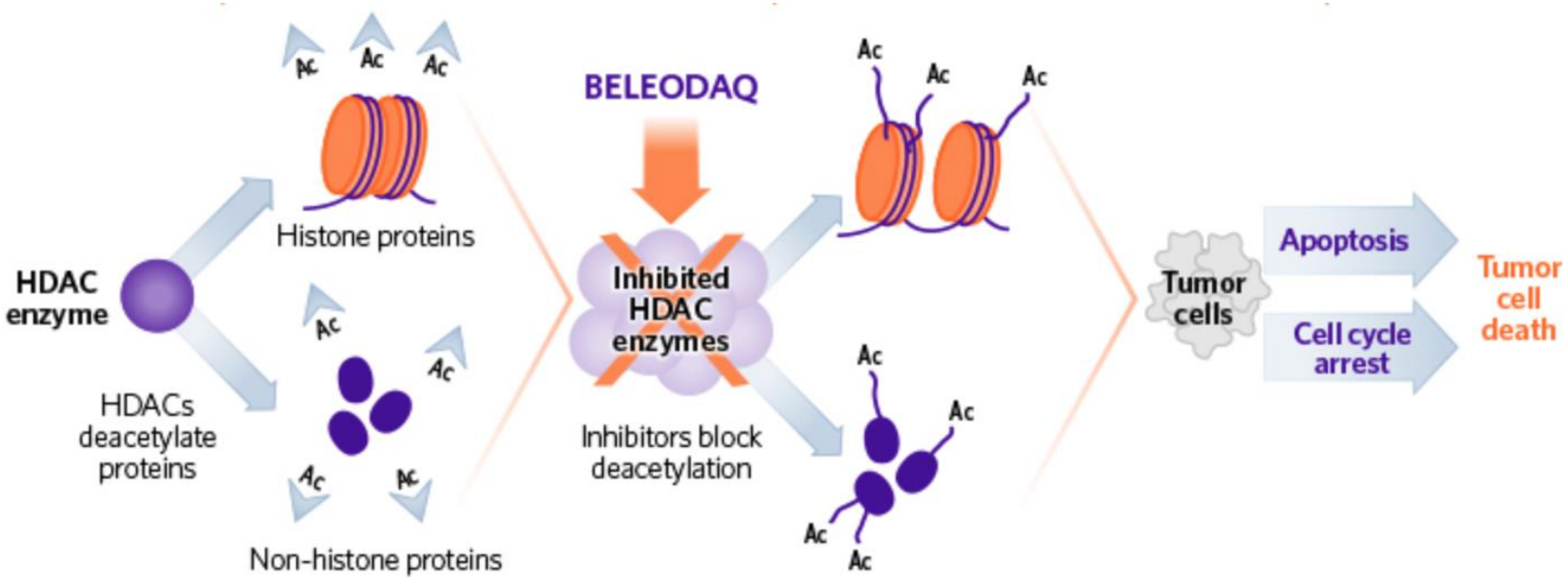
Novel Agents: Brentuximab Vedotin



With permission from Chen R et al. *Proc ASH* 2010;Abstract 283.

Treatment	Author, year Trial type	Pts.	Subtypes[‡] (Pts.)	ORR, %	CR, %	Median DOR, mos	Median OS, mos	Median PFS, mos	Ref.
Pralatrexate	O'Connor, 2011 Phase 2 Multicenter	111	All patients[§] PTCL-NOS (59) ALCL (17) AITL (13) Other PTCL (8)	29[§§] 32 35 8 38	11 – – – –	10.1	14.5	3.5	[16]
Romidepsin	Piekarz, 2011 Phase 2 Multicenter	47	All patients PTCL-NOS (27) AITL (7) ALK + ALCL (2) ALK$^-$ ALCL (2) Other PTCL (9)	38 41 17 100 – –	18 19 – – – –	8.9	NA (*)	NA (*)	[24]
	Coiffier, 2012 Phase 2 Multicenter	130	All patients[§] PTCL-NOS (69) AITL (27) ALK$^-$ ALCL (21) Other PTCL (13)	25[§§] 29 30 24 0	15 14 19 19 0	28.0 (**)	11.3 (**)	4.0	[26]
Brentuximab vedotin	Pro, 2012 Phase 2 Multicenter	58	ALCL[§]	86[§]	57	13.2	Not reached (***)	13.3	[35]
	Horwitz, 2014 Phase 2 Multicenter	34	All patients PTCL-NOS (21) AITL (13)	42 33 54	24 14 38	7.6 7.6 5.5	NA (*)	2.6 1.6 6.7	[37]
	Zinzani, 2015 Review[‡]	23	ALCL	75	74	NA (*)	NA (*)	NA (*)	[36]
	Lamarque, 2016 Named Patient Program[††]	38	All patients ALK$^-$ ALCL (15) PTCL-NOS (11) ALK$^+$ ALCL (9) AITL (1) Other PTCL (2)	47 53 27 78 0 0	45 53 18 78 0 0	NA (*)	NA (*)	ALCL 10.5 Non-ALCL 1.4	[38]

Novel Agents: Belinostat



Treatment	Author, year Trial type	Pts.	Subtypes[‡] (Pts.)	ORR, %	CR, %	Median DOR, mos	Median OS, mos	Median PFS, mos	Ref.
Pralatrexate	O'Connor, 2011 Phase 2 Multicenter	111	All patients[§] PTCL-NOS (59) ALCL (17) AITL (13) Other PTCL (8)	29[§§] 32 35 8 38	11 – – – –	10.1	14.5	3.5	[16]
Romidepsin	Piekarz, 2011 Phase 2 Multicenter	47	All patients PTCL-NOS (27) AITL (7) ALK + ALCL (2) ALK$^-$ ALCL (2) Other PTCL (9)	38 41 17 100 – –	18 19 – – – –	8.9	NA (*)	NA (*)	[24]
	Coiffier, 2012 Phase 2 Multicenter	130	All patients[§] PTCL-NOS (69) AITL (27) ALK$^-$ ALCL (21) Other PTCL (13)	25[§§] 29 30 24 0	15 14 19 19 0	28.0 (**)	11.3 (**)	4.0	[26]
Brentuximab vedotin	Pro, 2012 Phase 2 Multicenter	58	ALCL[§]	86[§]	57	13.2	Not reached (***)	13.3	[35]
	Horwitz, 2014 Phase 2 Multicenter	34	All patients PTCL-NOS (21) AITL (13)	42 33 54	24 14 38	7.6 7.6 5.5	NA (*)	2.6 1.6 6.7	[37]
	Zinzani, 2015 Review[†]	23	ALCL	75	74	NA (*)	NA (*)	NA (*)	[36]
	Lamarque, 2016 Named Patient Program[††]	38	All patients ALK$^-$ ALCL (15) PTCL-NOS (11) ALK$^+$ ALCL (9) AITL (1) Other PTCL (2)	47 53 27 78 0 0	45 53 18 78 0 0	NA (*)	NA (*)	ALCL 10.5 Non-ALCL 1.4	[38]
Belinostat	Foss, 2015 Phase 2 Multicenter	24	All patients PTCL-NOS (13) ALCL (3) AITL (3) Other PTCL (5)	25 – – – –	8 – – – –	3.6	NA (*)	NA (*)	[40]
	O'Connor, 2015 Phase 2 Multicenter	129	All patients[§] PTCL-NOS (77) AITL (22) ALK$^-$ ALCL (13) ALK$^+$ ALCL (2) EATL (2) ENKTCL (2) HSTCL (2)	23[§§] 23 46 15 0 0 50 0	9 – – – – – – –	13.6	7.9	1.6	[41]

Treatment	Author, year Trial type	Pts.	Subtypes[‡] (Pts.)	ORR, %	CR, %	Median DOR, mos	Median OS, mos	Median PFS, mos	Ref.
Gemcitabine	Arkenau, 2007[†] Retrospective Single center	16	All patients AITL (5) ALCL (3) PTCL-NOS (2) EATL (2) Other PTCL (2)	69 80 100 0 100 50	19 40 0 0 50 0	NA (*)	Not reached (**)	4.1 (***)	[44]
	Zinzani, 2010 Retrospective Single center	20	PTCL-NOS	55	30	28.0	NA (*)	NA (*)	[43]
Bendamustine	Damaj, 2013 Phase 2 Multicenter	58	All patients AITL (32) PTCL-NOS (23) ALCL (2) EATL (1)	50 – – – –	28 – – – –	3.5	6.3	3.6	[46]
Lenalidomide	Zinzani, 2011 Phase 2 Multicenter	10	PTCL-NOS	30	30	NA (*)	NA (*)	NA (*)	[48]
	Morschhauser, 2013 Phase 2 Multicenter	54	All patients AITL (26) PTCL-NOS (20) ALCL (3) ENKTCL (1)	22 31 20 – –	11 15 – – –	3.6	NA (*)	2.5	[49]
	Toumishey, 2015 Phase 2 Multicenter	39 (****)	All patients PTCL-NOS (14) ALCL (10) AITL (9) Other PTCL (6)	26 43 10 33 0	8 14 0 11 0	13.0	12.0	4.0	[50]
Duvelisib	Horwitz, 2014 Phase 1	15	All patients PTCL-NOS (6) AITL (3) ALCL (2) Other PTCL (5)	53 – – – –	13 – – – –	NA (*)	8.4	8.3	[51]
Copanlisib	Dreyling, 2013 Phase 2 Multicenter	4	All patients (PTCL)	50	25	NA (*)	NA (*)	NA (*)	[52]
Alisertib	Barr, 2015 Phase 2 Multicenter	37	All patients PTCL-NOS (13) AITL (9) ALK$^-$ ALCL (2) ENKTCL (2)	24 31 33 50 0	5 8 0 0 0	3.0	8.0	3.0	[55]
Mogamulizumab	Ishida, 2012 Phase 2 Multicenter	26	ATLL (*****) Acute disease Chronic disease Lymphoma phase	50[§] 33 83 33	31 – – –	NA (*)	13.7	5.2	[59]
	Ogura, 2014 Phase 2 Multicenter	29	All patients (*****) PTCL-NOS (16) AITL (12) ALK$^-$ ALCL (1)	34[§] 19 50 100	17 6 25 100	NA (*)	14.2	2.0	[58]
	Zinzani, 2016 Phase 2 Multicenter	35	All patients PTCL-NOS (15) AITL (13) ALK$^-$ ALCL (4) ALK$^+$ ALCL (1)	11 13 17 0 0	3 7 0 0 0	2.8	NA (*)	2.1	[61]

The future

Table 2
Novel therapies under investigation for relapsed/refractory peripheral T-cell lymphomas

Single-Agent Trials	Mechanism of Action	Phase	ClinicalTrial.gov ID
Endostar	Angiogenesis inhibitor	II	NCT02520219
E7777	Diphtheria Toxin Fragment-Interleukin-2 Fusion protein	II	NCT02676778
Selinexor	Selective inhibitor of nuclear export	II	NCT02314247
Tipifarnib	Farnesyltransferase inhibitor	II	NCT02464228
Darinaparsin	Organic arsenic compound	II	NCT02653976
Ixazomib	Proteasome inhibitor	II	NCT02158975
Forodesine	PNP inhibitor	I/II	NCT01776411
Ruxolitinib	JAK inhibitor	II	NCT01431209
Temsirolimus	mTOR inhibitor	I	NCT01614197
Carfilzomib	Proteasome inhibitor	I	NCT01336920
Panobinostat	Pan-deacetylase inhibitor	II	NCT01261247
Clofarabine (completed)	DNA synthesis inhibitor	I/II	NCT00644189
MK2006 (completed)	AKT inhibitor	II	NCT01258998
Sorafenib (completed)	Multikinase inhibitor	II	NCT00131937
Alefacept	Immunosuppressive dimeric fusion protein	I	NCT00438802
Pembrolizumab	PD-1 antibody	II	NCT02535247
Fenretinide	Synthetic retinoid derivative	II	NCT02495415
MEDI-570	Anti-ICOS monoclonal antibody	I	NCT02520791
EDO-S101	Alkylating HDAC inhibitor	I	NCT02576496
ALRN-6924	MDM2/MDMX antagonist	I/II	NCT02264613
MLN9708	Proteasome inhibitor	II	NCT02158975

The future

Combination Trials	Mechanism of Action	Phase	ClinicalTrial.gov ID
Chidamide + CHOP	HDAC inhibitor	I	NCT02809573
Pralatrexate + CHOP	DHFR/thymidylate synthase inhibitor	I	NCT02594267
Chidamide + Cyclophosphamide + Thalidomide	HDAC inhibitor	II	NCT02879526
Romidepsin + CHOEP	HDAC inhibitor	I/II	NCT02223208
Romidepsin + CHOP ←	HDAC inhibitor	III	NCT01796002
Romidepsin + ICE	HDAC inhibitor	I	NCT01590732
Romidepson + Lenalidomide	HDAC inhibitor	II I/II	NCT02232516 NCT01742793
Chidamide + ICE	HDAC inhibitor	II	NCT02856997
CPI-613 + Bendamustine	Antimitochondrial metabolism agent	I	NCT02168140
Belinostat + Carfilzomib	HDAC inhibitor + proteasome inhibitor	I	NCT02142530
Brentuximab vedotin + Rituximan	α-CD30 linked to auristatin (antitubulin agent)	I/II	NCT01805037
Brentuximab vedotin + CHP ←	α-CD30 linked to auristatin (antitubulin agent)	III	NCT01777152
Brentuximab vedotin + Bendamustine	α-CD30 linked to auristatin (antitubulin agent)	II	NCT02499627
Pralatrexate + Romidepson	DHFR/thymidylate synthase inhibitor + HDAC inhibitor	I/II	NCT01947140
Romidepsin + 5-Azacitadine	HDAC inhibitor	I/II	NCT01998035

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Conclusion

- T-cell lymphoma portends a poorer prognosis
- CHOP is adequate for ALCL, ALK +ve
- CHOEP should be considered for patients <60 and normal LDH
- Role of transplant (Auto or Allo) is controversial
- Efforts to improve outcome continues

Questions?