Peripheral T-cell lymphoma (PTCL) and NK cell lymphoma

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18/03/2023

BHS course

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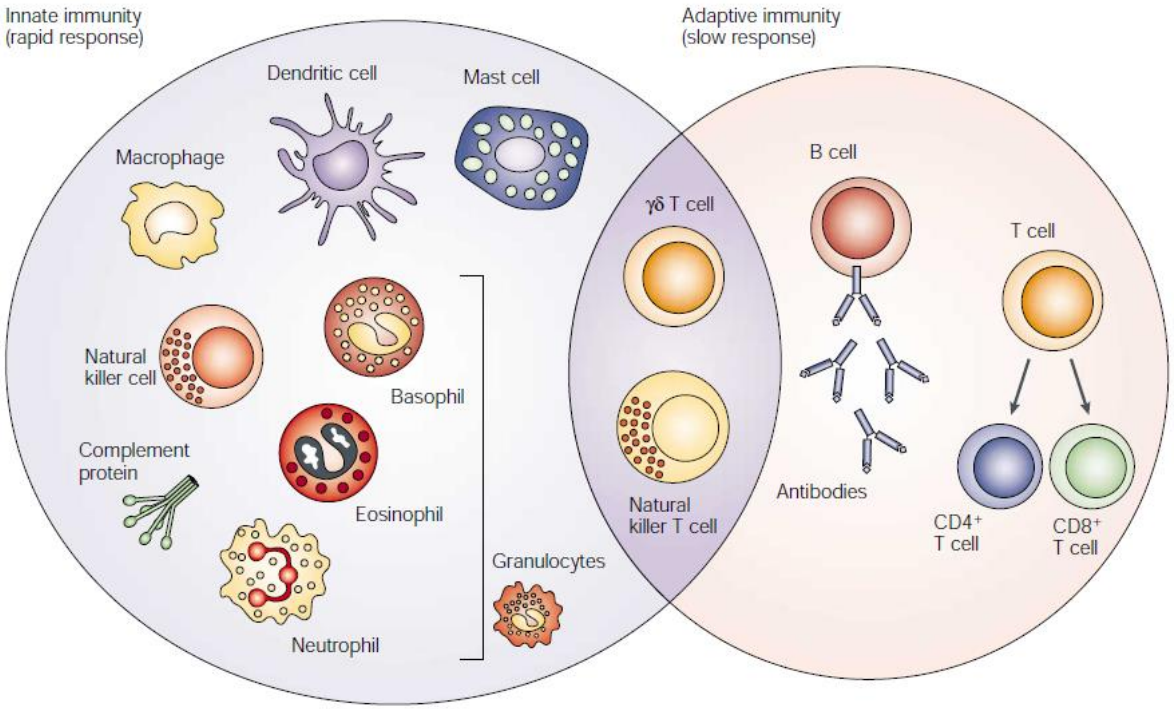
OUTLINE

- Pathophysiology
- WHO/ICC classification
- Diagnosis
- Prognosis
- Clinical characteristics of subtypes
- Treatment
- References

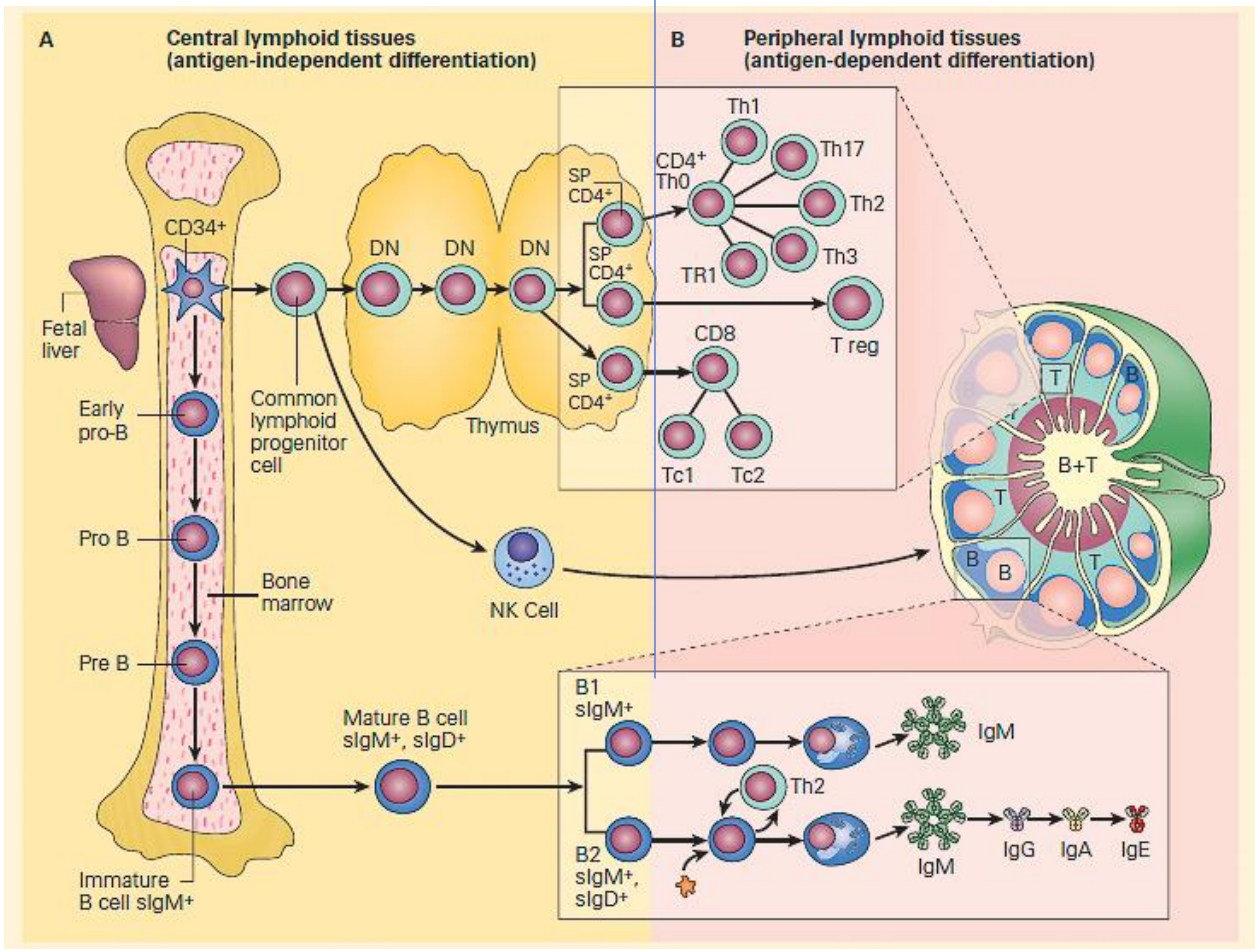
Pathophysiology



Dranoff, Nat.Rev. Cancer, 2004

Immature T-cell malignancies

Mature/post-thymic T-cell malignancies: PTCL



Bellanti, JA Immunology IV: Clinical Applications in Health and Disease.

≈10% of all NH lymphomas > 35 entities (2022)

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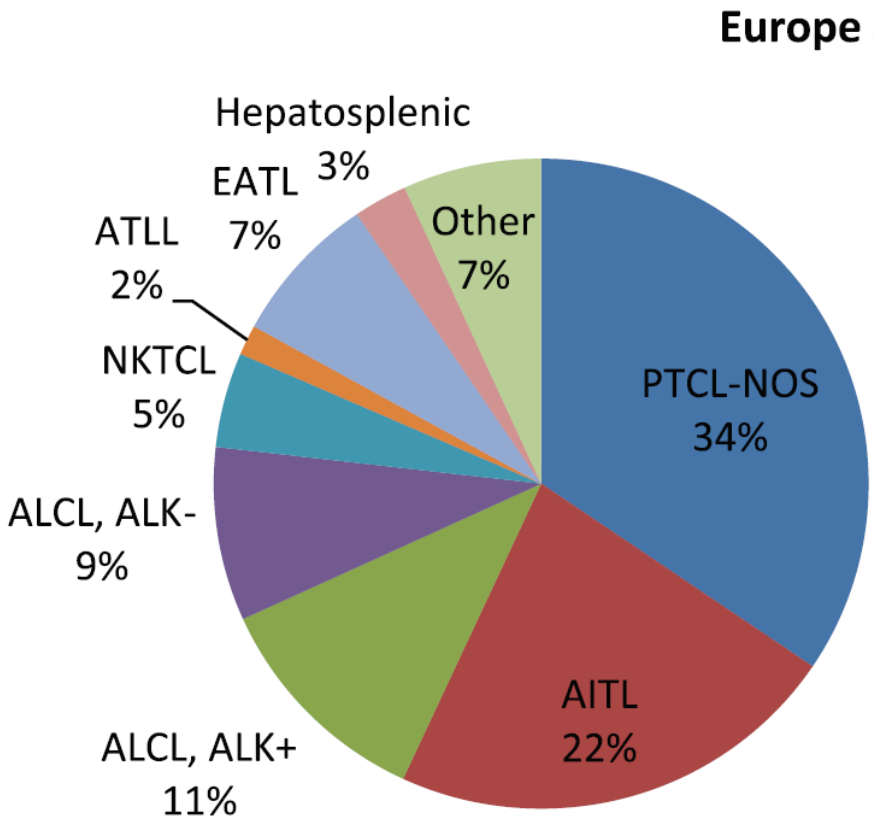
Different entities, different classifications…



Swerdlow et al. Blood 2016; Hildyard et al., Clin Med In: Blood disorders, 2017

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ICD-O	WHO 2017	WHO 2022	ICC 2022
	(nodal) FTH cell lymphoma		
9705/3	AITL	**nTFH cell lymphoma, angioimmunoblastic type**	**TFH cell lymphoma, angioimmunoblastic type (AITL)**
9702/3	follicular TCL	**nTFH cell lymphoma, follicular type**	**TFH cell lymphoma, follicular type**
9702/3	Nodal peripheral TCL with T follic helper phenotype	**nodal TFH cell lymphoma, NOS**	**TFH cell lymphoma, NOS**
9702/3	PTCL, NOS	PTCL, NOS	PTCL, NOS

3 entities, brought together under the umbrella of (nodal) T-follicular helper cell lymphoma with 3 subtypes

Table: Courtesy of Dr. Pascale De Paepe
Based on:
Alaggio et al. WHO Classification of Haematolymphoid tumours, 5th edition, table 2: T and NK cell lymphoid proliferations, Leukemia, June 2022
Campo et al. The international Consensus Classification of Mature Lymphoid Neoplasms: table 4, Blood, June 2022

ICD-O	WHO 2017	WHO 2022	ICC 2022
	EBV + NK/T cell lymphomas		
9702/3		**EBV+ nodal T-and NK cell lymphoma**	**primary nodal EBV+ T-and NK cell lymphoma**
9719/3	extranodal NK/T cell lymphoma, nasal type	extranodal NK/T cell lymphoma	extranodal NK/T cell lymphoma, nasal type
9714/3	ALCL, ALK+	ALK+ ALCL	ALCL, ALK+
9715/3	ALCL, ALK-	ALK- ALCL	ALCL, ALK-
9715/3	BIA-ALCL	BIA-ALCL	BIA-ALCL

Earlier: variant of PTCL, NOS; now provisional entity in ICC, definitive entity in WHO5:
Asia, elderly, often IS, no nasal involvement, CD56-, CD3+CD8+, frequent T> NK derivation, bad prognosis

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Based on:
Alaggio et al. WHO Classification of Haematolymphoid tumours, 5th edition, table 2: T and NK cell lymphoid proliferations, Leukemia, June 2022
Campo et al. The international Consensus Classification of Mature Lymphoid Neoplasms: table 4, Blood, June 2022

ICD-O	WHO 2017	WHO 2022	ICC 2022
9834/3	T-PLL	T-PLL	T-PLL
9831/3	T-LGL	T-cell LGL	T-cell LGL
9831/3	chronic LPD of NK cells	**NK-large granular lymphocytic leukemia**	chronic LPD of NK cells
9827/3	adult T-cell	adult T-cell leukemia/lymphoma	adult T-cell leukemia/lymphoma
9701/3	Sézary syndrome	Sézary syndrome	Sézary syndrome
9948/3	aggressive NK-cell leukemia	aggressive NK-cell leukemia	aggressive NK-cell leukemia
9716/3	hepatosplenic T-cell lymphoma	hepatosplenic T-cell lymphoma	hepatosplenic T-cell lymphoma

Table: Courtesy of Dr. Pascale De Paepe

Based on:

Alaggio et al. WHO Classification of Haematolymphoid tumours, 5th edition, table 2: T and NK cell lymphoid proliferations, Leukemia, June 2022

Campo et al. The international Consensus Classification of Mature Lymphoid Neoplasms: table 4, Blood, June 2022

ICD-O	WHO 2017	WHO 2022	ICC 2022
	Intestinal T/NK cell LPD/lymphomas		
9702/1	indolent T-cell LPD of GI	**indolent T-cell lymphoma of GI**	**indolent clonal T-cell LPD of GI tract**
9702/1		**indolent NK-cell LPD of GI tract**	**indolent NK-cell LPD of GI tract**
9717/3	enteropathy-associated T-cell lymphoma	enteropathy-associated T-cell lymphoma	enteropathy-associated T-cell lymphoma
	(refractory coeliac disease	(refractory coeliac disease (RCD) II)	(type II refractory celiac disease)
9717/3	MEITL	MEITL	MEITL
9717/3	intestinal T-cell lymphoma, NOS	intestinal T-cell lymphoma, NOS	intestinal T-cell lymphoma, NOS

Type II refractory celiac disase is accepted as a precursor of EATL, has been added to the classification

Table: Courtesy of Dr. Pascale De Paepe
Based on:
Alaggio et al. WHO Classification of Haematolymphoid tumours, 5th edition, table 2: T and NK cell lymphoid proliferations, Leukemia, June 2022
Campo et al. The international Consensus Classification of Mature Lymphoid Neoplasms: table 4, Blood, June 2022

Intestinal T/NK-cell LPD/lymphomas

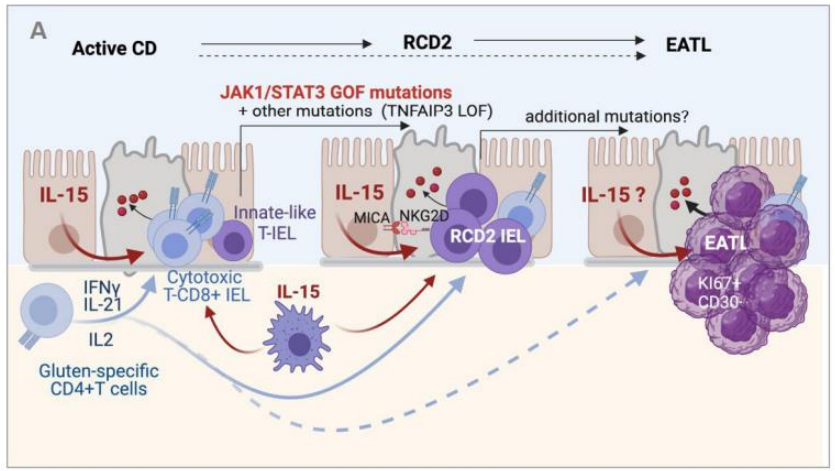

Figure 4 Inflammation-driven lymphomagenesis in coeliac disease (CD). (A) *Left panel*: in active CD

Small intestines

RCD-II → **EATL**

30-40% 5yr progression risk!

colon

Indolent clonal GI T-LPD

Intestinal T cell lymphoma NOS

Indolent NK-LPD

stomach

MEITL

RCD II :
monoclonal TCR,
Often CD8- ,
often partial trisomy of 1q
somatic mutations in 80% of cases:
JAK1/STAT3/TET2/DDX3X/…

Levescot et al. Gut 2022

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Diagnosis and staging

1. Biopsy: Preferably excision/incision biopsy, NO FNAC

    - Immunophenotype
        - CD4 >>, CD8, CD4+CD8+ DP en CD4-CD8- DN also possible
        - Frequent antigenic loss. eg. CD5- and CD7-
        - NK markers (CD56+, …)
        - CD30+? (also therapeutic implications)
        - ALK
        - EBER ISH (EBV) (ENKTL, AITL)
        - **Follicular T helper cell signature** (BCL6, PD-1, CD10, CXCL13, ICOS, …)

    - Genetics and molecular profiling
        - TCR rearrangement (CAVE NK subtypes: can be germinal)
        - Translocation t(2;5): NPM-ALK fusion protein
        - rearrangements of DUSP22, TP63; recurrent mutations in *TET2, DNMT3A, IDH2, RHOA*, …

2. PET-CT /CT
3. Bone marrow biopsy
4. Peripheral blood/biochemistry/ EBV PCR (ENKTL, AITL,…)

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Prognosis

- In general POOR (5yr OS 30-40%)

  Exceptions:

  - ALK positive ALCL
  - Cutaneous forms
- Also correlated to high IPI score at diagnosis

(> 70% IPI > or = 2)

- Poor compared to aggressive B cell lymphoma, especially in the rituximab Era.

» Risk factors for the Definition of the International Prognostic Index (IPI)

General Index	Parameter	Age Adjusted Index
1	Age > 60 years	n.a.
1	PS 2-4	1
1	Stage 3-4	1
1	LDH elevated	1
1	Extra nodal >1 site	non considered
5	**Maximum Score**	**3**

» Risk Groups of the International Prognostic Index

No. of Risk Factors	No. of Risk Factors	IPI Group
0 - 1	0	1 = low
2	1	2 = low intermediate
3	2	3 = high intermediate
4 - 5	3	4 = high

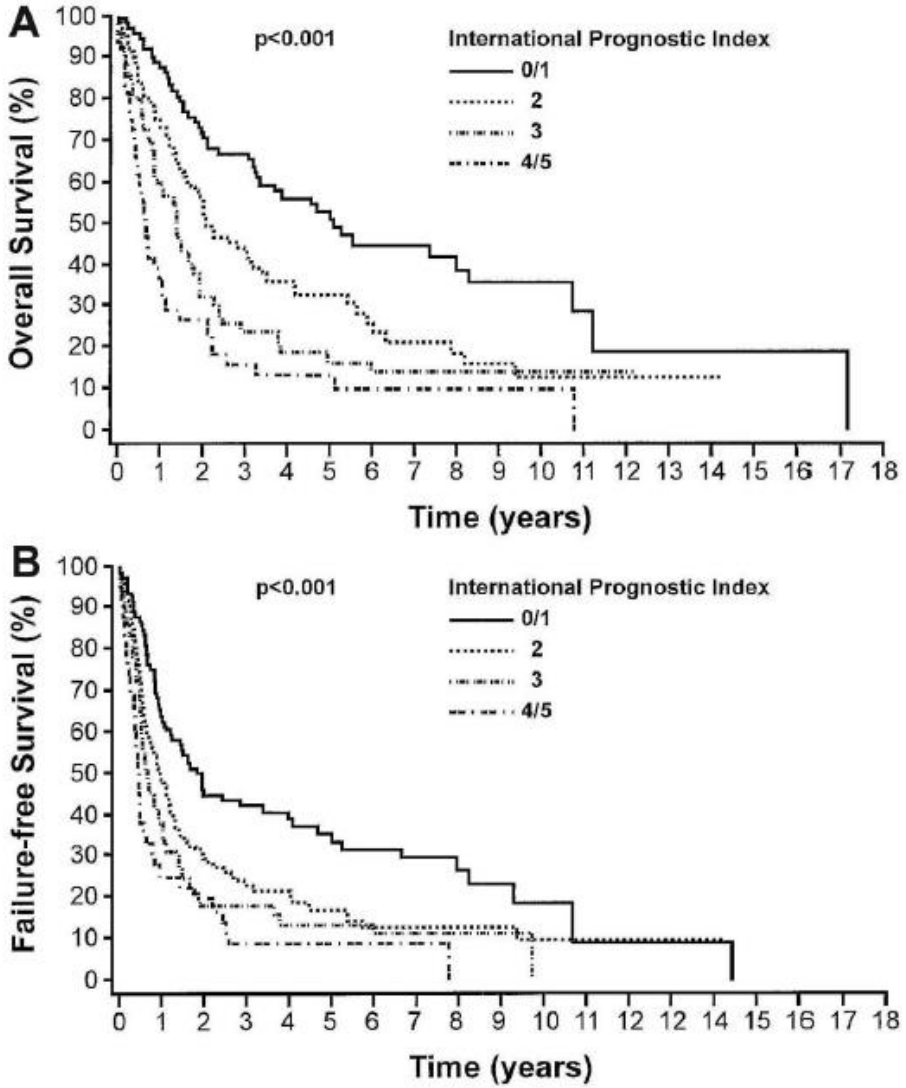

Figure 3. Survival. OS (A) and FFS (B) of patients with PTCL-NOS (n = 315) according to the IPI.

Weisenburger, Blood 2011

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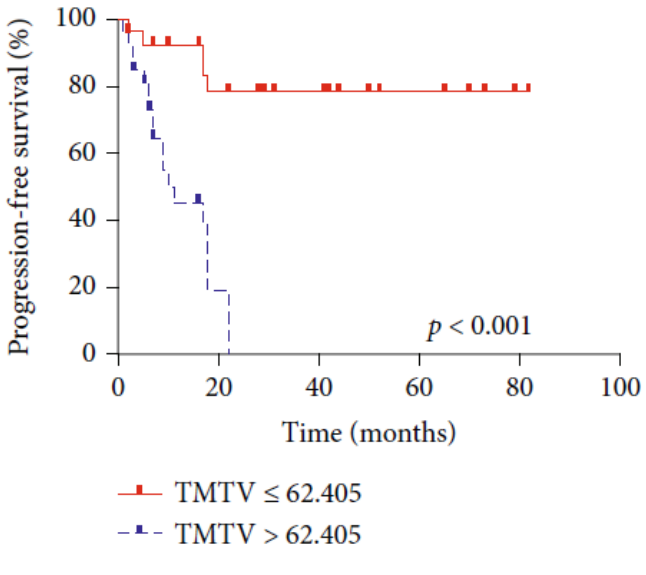
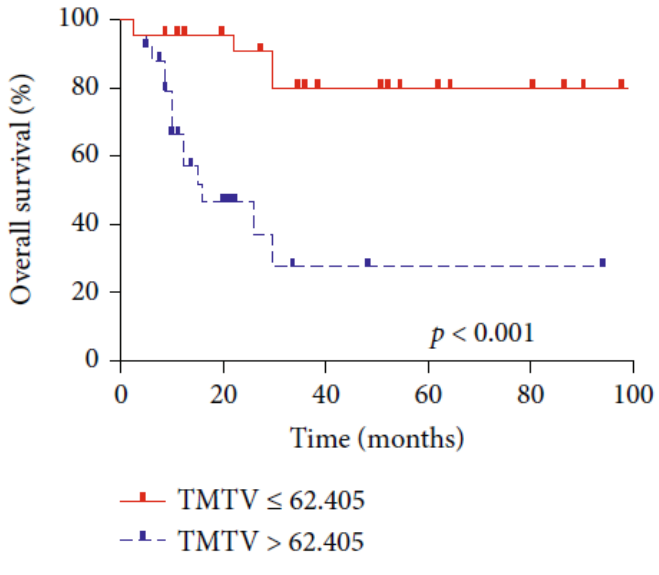
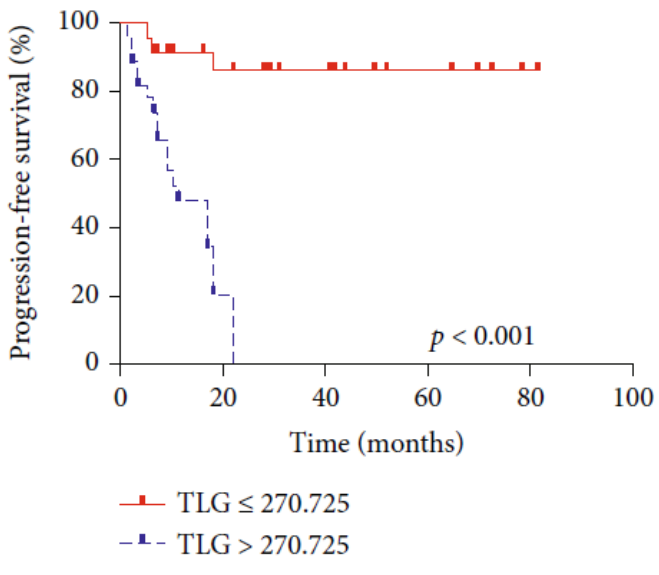
Prognostic value of baseline PET-CT



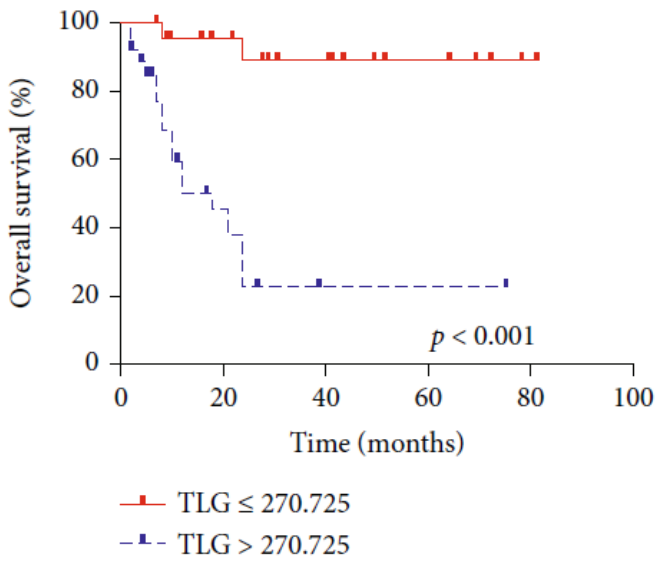
(c)



(d)



(e)



(f)

In a multi-variate analysis baseline
TMTV (Total metabolic Tumor volume) and
TLG (total lesion glycolysis)

were independent predictors of PFS and OS in PTCL

Zhou et al. Bio Med Research International 2020

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Clinical characteristics of important subtypes

1. PTCL, NOS
2. (Nodal) T-follicular helper (TFH) cell lymphoma*: three subtypes
3. Anaplastic large cell lymphoma
4. ENKTL

T cell lymphomas are frequently associated with a hemophagocytic syndrome/ HLH (hemophagocytic lymphohistiocytosis)

*ICC2022: Follicular helper T –cell lymphoma/ WHO2022: nodal T-follicular helper cell lymphoma

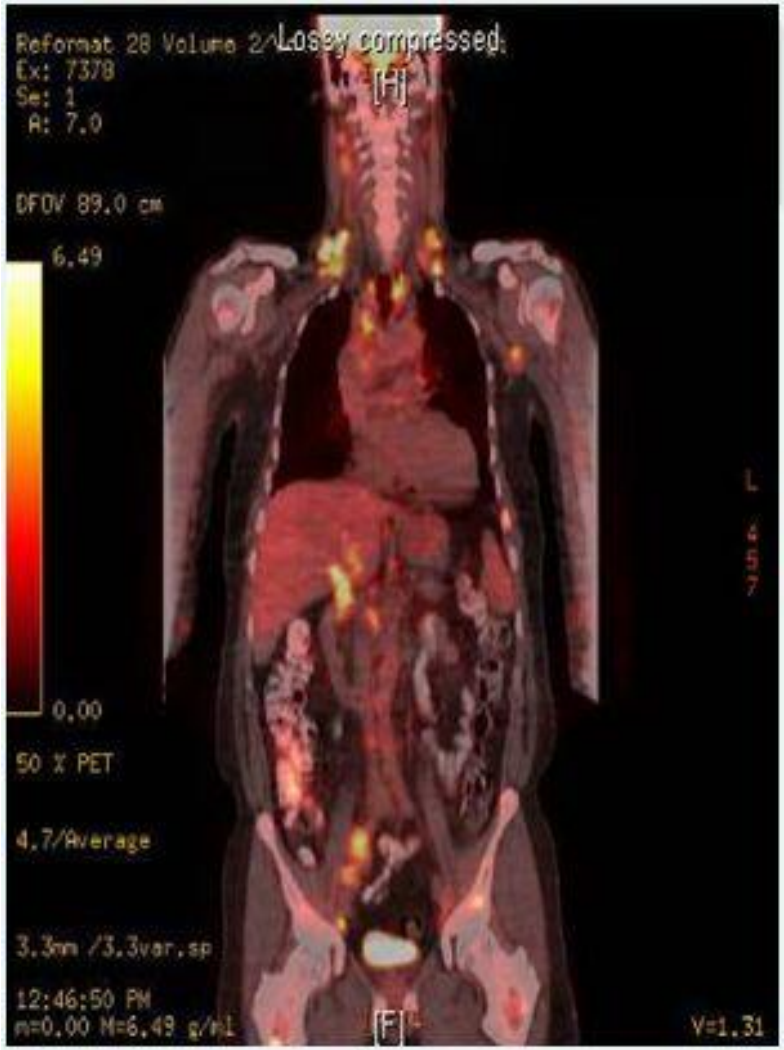
1. Peripheral T-cell lymphoma,NOS (PTCL, NOS)

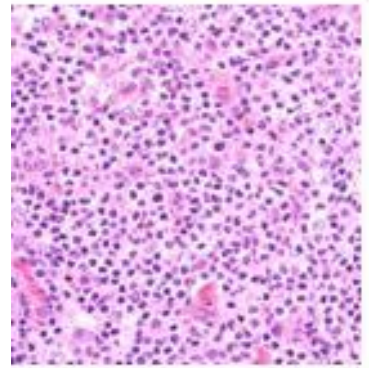
- ✓ Most frequent
- ✓ Often stage III, IV, often extranodal disease
- ✓ Often B symptoms
- ✓ M>F, median age 60 yrs

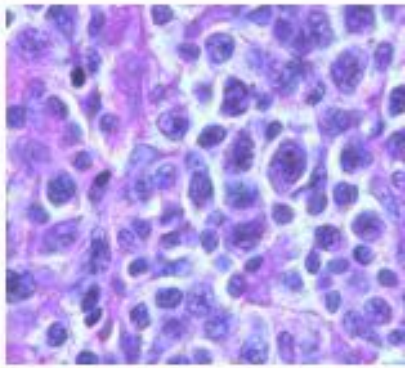
- ✓ Historically: diagnosis of exclusion
  (NOS = Not Otherwise Specified)

2022: Primary nodal EBV+ cases classified separately

- ✓ Molecular profiling studies enable us to distinguish PTCL, NOS from other entities and to identify subtypes.
  - ✓ A proportion of the PTCL,NOS might have a TFH (T follicular helper) signature, and this might influence future treatment strategies.
  - ✓ Two molecular subgroups of bona fide PTCL, NOS







Images Courtesy Dr. A. Shustov (Washington University)

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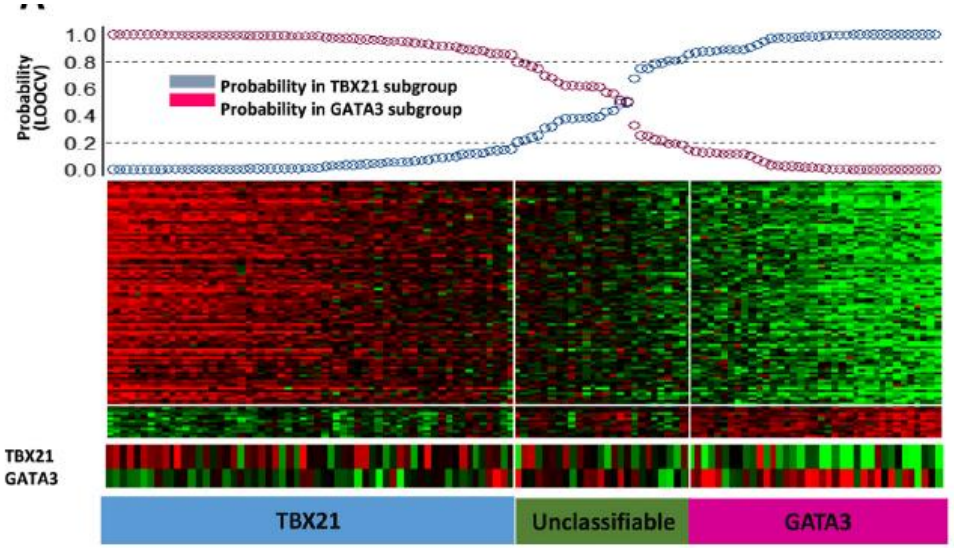
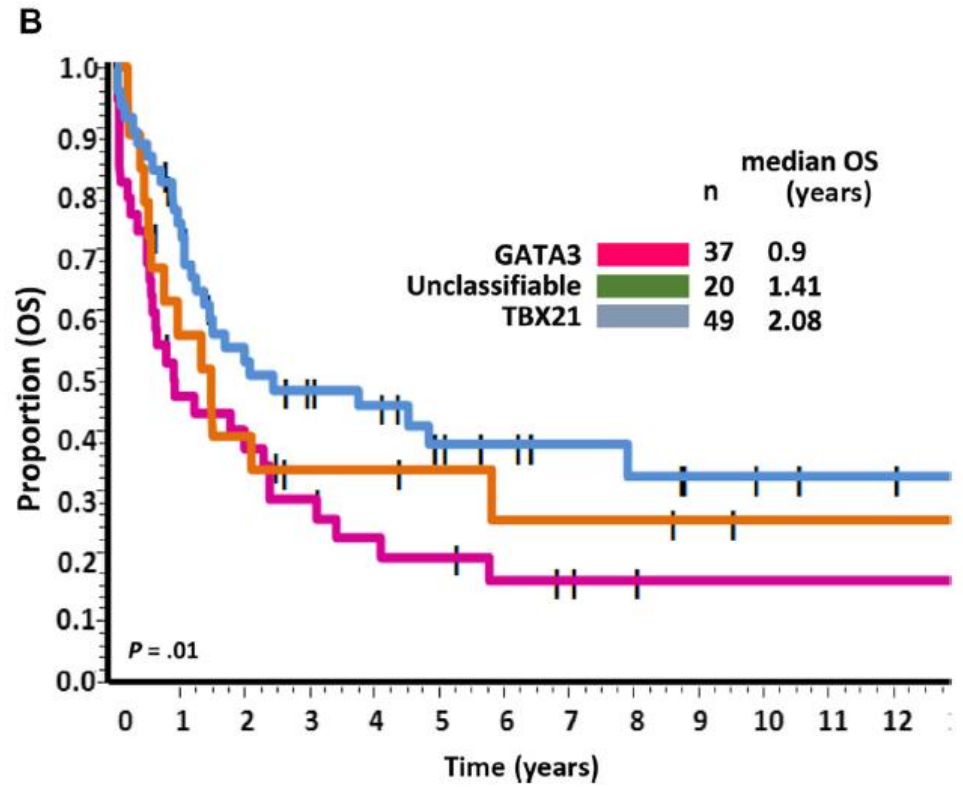
PTCL, NOS

Two major molecular subgroups in GEP studies:

- GATA3 : high expression of GATA3 and its target genes (*CCR4, CXCR7, IK, IL18RA*,…): Th2-like origin, poor prognosis
- TBX21 (“T-BET”): high expression of TBX21 and EOMES and target genes (*IFNg, IL2RB, CXCR3*, …): Th1-like origin, more favorable outcome





38%

19%

Designation of PTCL, NOS according to the molecular subgroups is not routinely incorporated into clinical diagnosis and requires further studies for clinical validation

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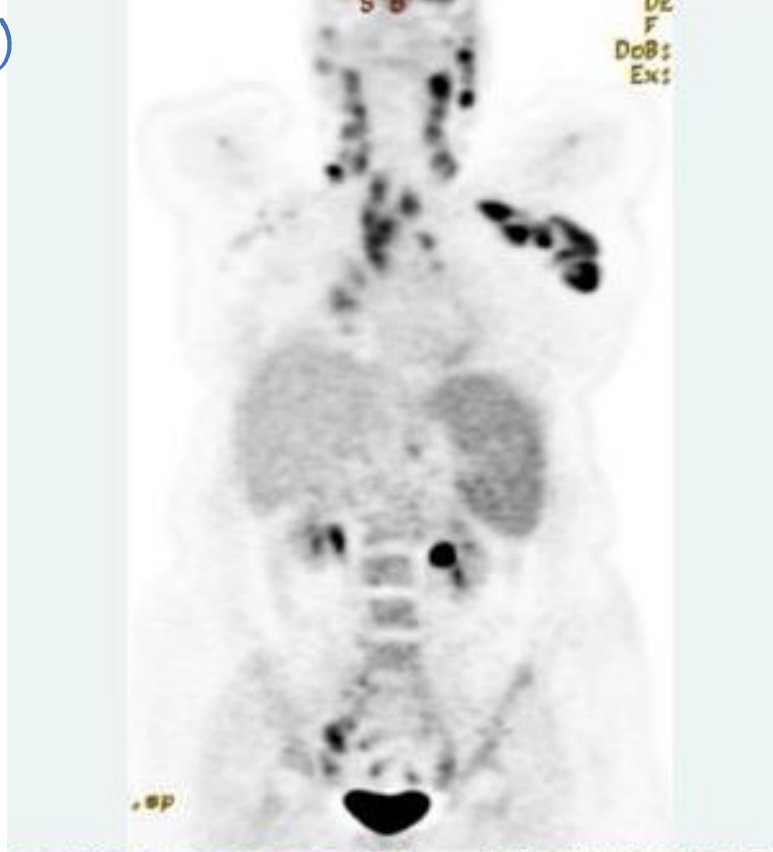
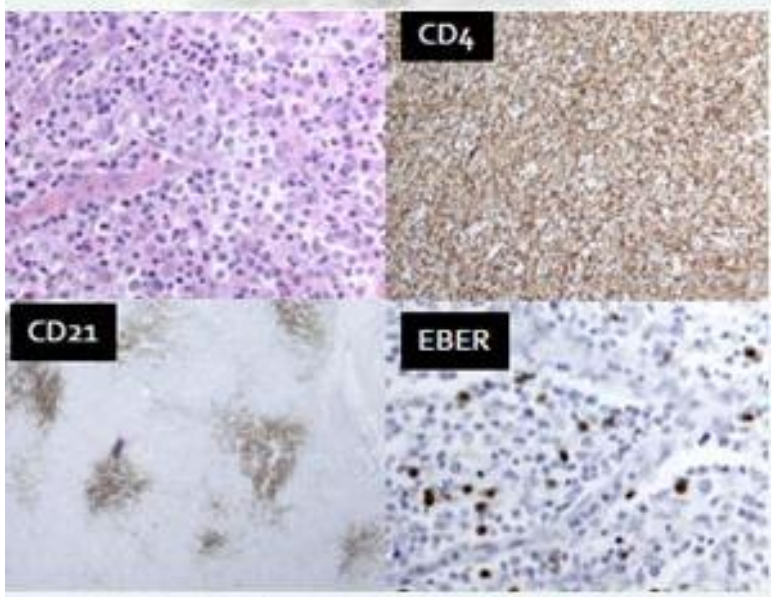
Iqbal et al., Blood 2014
Al-Zahrani and Savage, Hematol Oncol Clin N Am 2017

2. (Nodal) TFH cell lymphoma, Angio-immunoblastic-type (AITL)

- ✓ Often hepatosplenomegaly, stage III or IV
- ✓ Often maculopapular rash, fever
- ✓ Often older age
- ✓ Associated with auto-immunity
- ✓ Associated with a polyclonal hypergammaglobulinemia, eosinophilia
- ✓ Often EBV PCR serum positive

- ✓ Neoplastic cells are admixed with reactive small lymphocytes, eosinophils, plasma cells, and an abundant amount of follicular dendritic cells (CD21+) and endothelial venules/vascular proliferation.
- ✓ Often presence of large scattered CD20+ /EBER + immunoblasts.
- ✓ Specific T_{FH} / **Follicular T helper cell signature:** IHC: BCL6, PD-1, CD10, CXCL13, ICOS, CXCR5…





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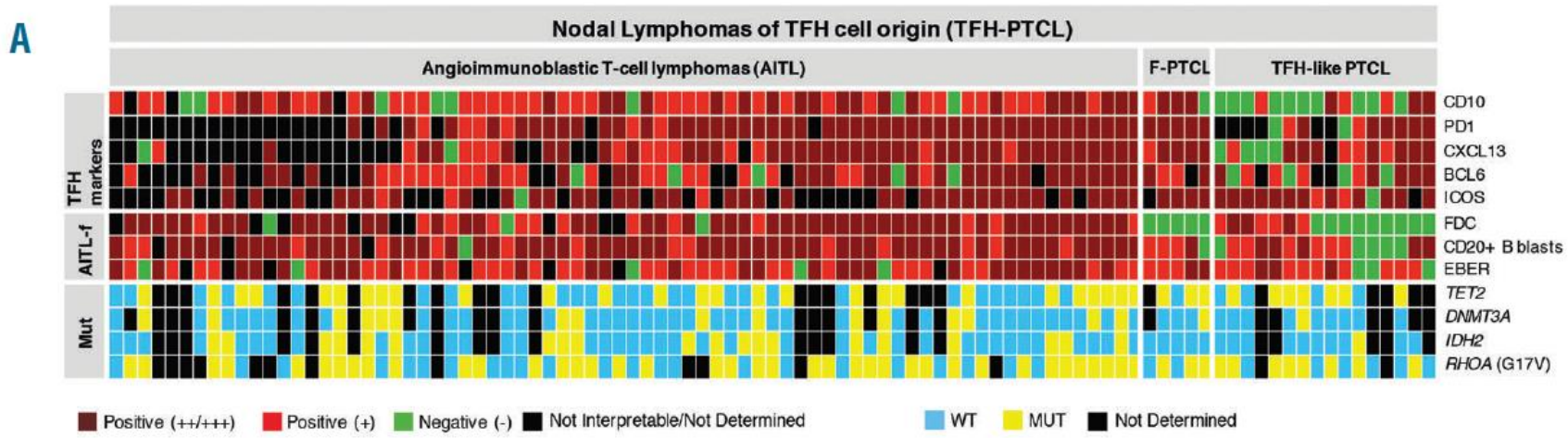
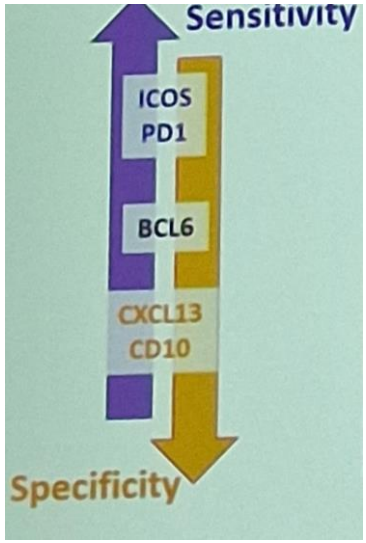
Images Courtesy Dr. A. Shustov (Washington University)
Brocolli A and Zinzani, Hematol Oncol Clin N Am, 2017

(Nodal) TFH cell lymphoma, follicular type and NOS



- ✓ Follicular type: follicular dendritic cells associated to the follicles without extrafollicular FDC expansion, positive for most/all TFH markers
- ✓ TFH lymphoma, Not Otherwise specified : lack of typical morphological AITL features (no FDC expansion), but expressing TFH markers (at least 2-3)

Specific T_{FH} / **Follicular T helper cell signature:** IHC: BCL6, PD-1, CD10, CXCL13, ICOS (5 marker panel)



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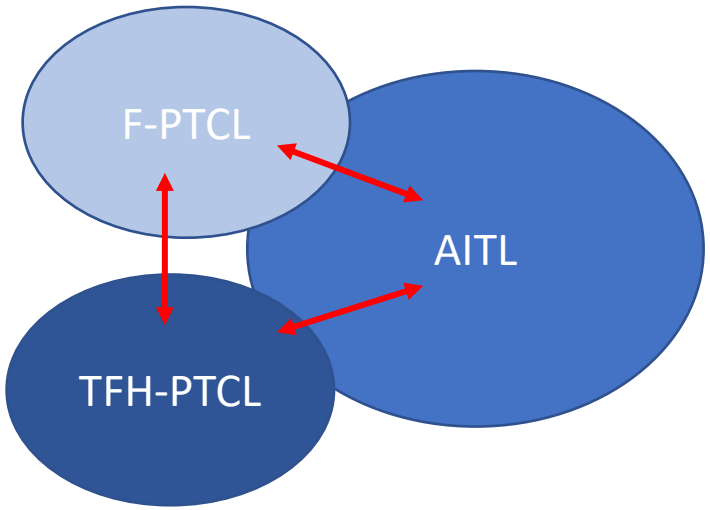
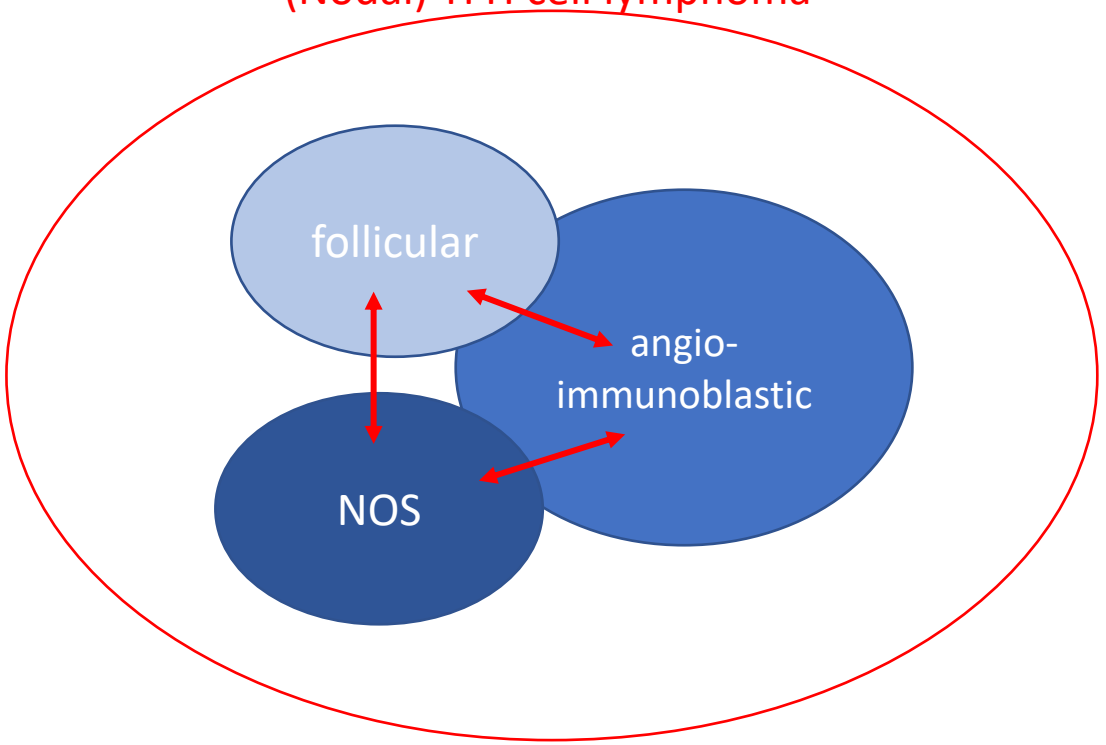
Dobay et al, Haematologica 2017
Swerdlow et al, Blood 2016

(Nodal) TFH cell lymphoma

WHO 4



WHO 5/2022- ICC 2022



- ✓ 2023: there is insufficient evidence that distinction between the 3 subtypes is relevant to clinical management, diagnosis of TFH cell lymphoma is acceptable/ sufficient
- ✓ Per definition: CD4+, systemic

(Nodal) TFH cell lymphoma: recurrent mutations

EPIGENETIC: DNA and histone hypermethylation (tend to co-occur)
TET2 (50-85%)
DNMT3A (20-30%)
IDH2 (30% of AI type/AITL)

TCR SIGNALING: activating
RHOA G17V (50-70%)

And a lot of other mutations …

Conclusion:

- ✓ *Integration of mutational testing / **NGS** in the diagnosis!*
- ✓ *these subtypes might be candidates for epigenetically modifying **therapies** (eg. Hypomethylating agents, HDACi …)*

Lemonnier F et al, 2017, Haematologica

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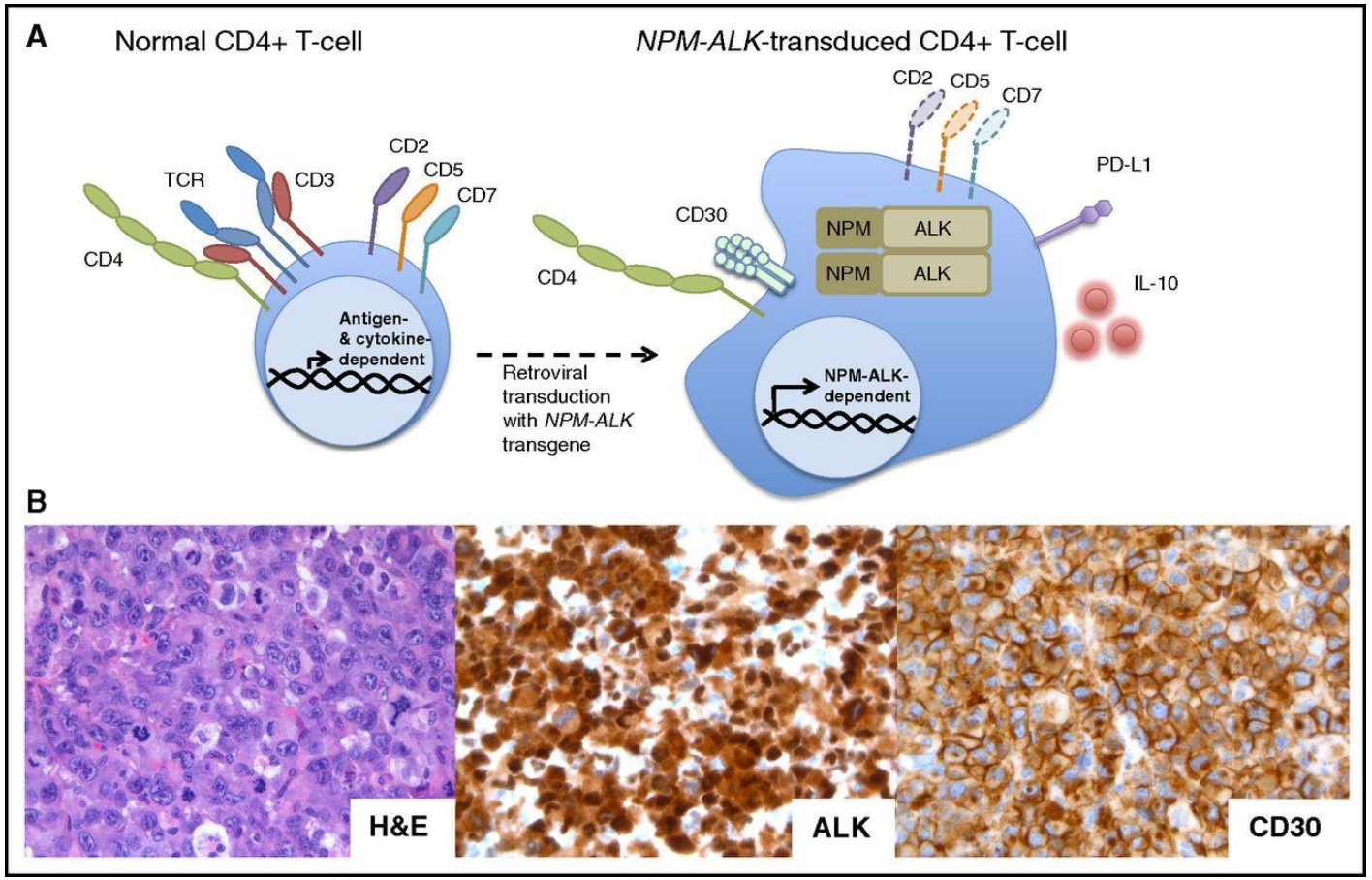
3. Anaplastic large cell lymphoma (ALCL)

- ✓ In general, prognosis better. ALK (Anaplastic lymphoma kinase) +: clearly better prognosis (5yr OS: 65-90% vs 30-50%)
- ✓ Consistently CD30++
- ✓ ALK + (often younger pts) or ALK - (often older pts)
- ✓ Translocation t(2;5) > nucleophosmin (NPM)-ALK fusion protein > NPM-ALK co-opts several intracellular signal transduction pathways, foremost being the STAT3 pathway



Werner et al., Blood 2017

Anaplastic large cell lymphoma (ALCL)

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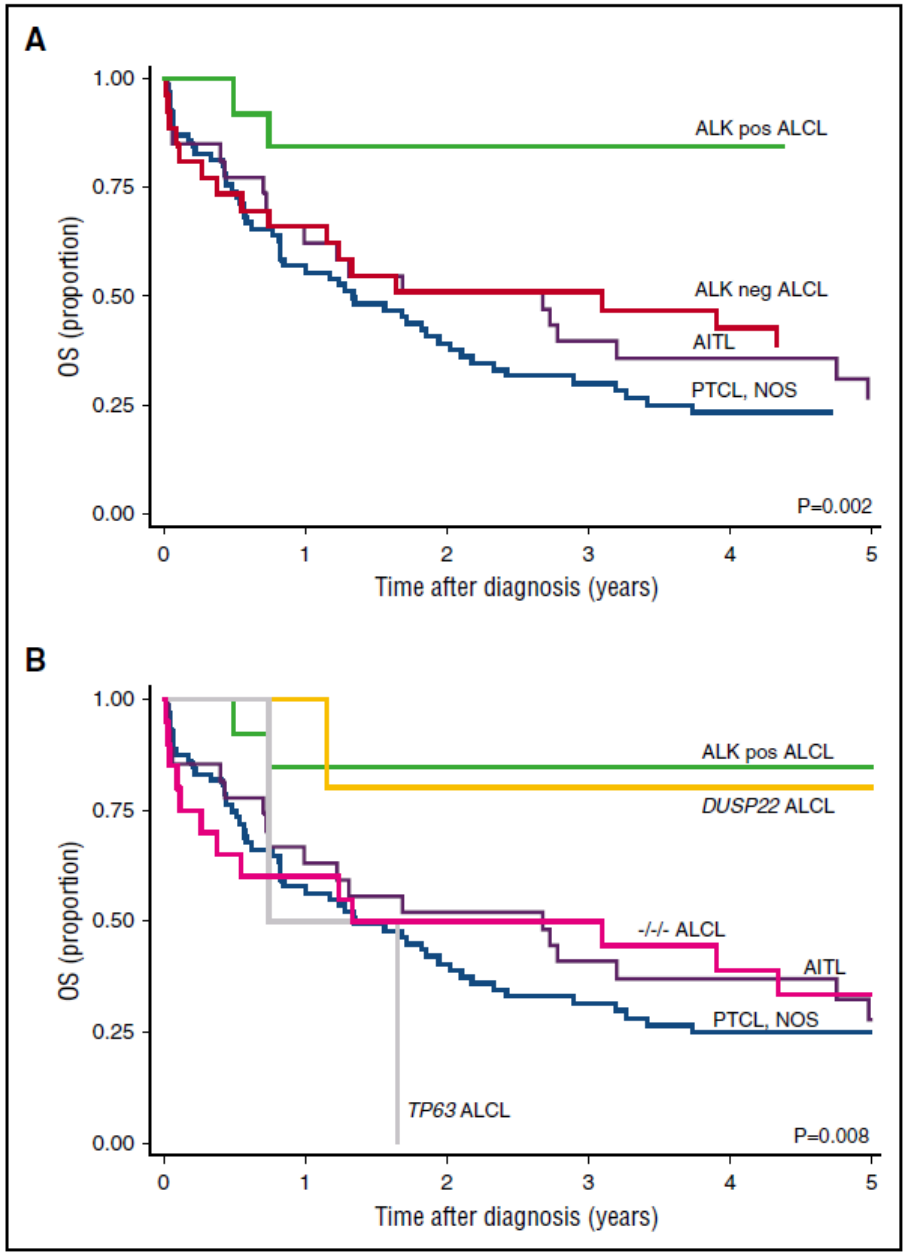


Figure 1. Outcomes in patients with PTCL. (A) Five-year OS rates (Kaplan-Meier estimates) stratified by PTCL subtype and ALK status only (current WHO classification). (B) Five-year OS rates with ALK-negative ALCL stratified by genetic subtype. ALK-pos ALCL, anaplastic lymphoma kinase–positive anaplastic large cell lymphoma; ALK-neg *DUSP22* ALCL, anaplastic lymphoma kinase–negative *DUSP22*-rearranged anaplastic large cell lymphoma; ALK-neg *TP63* ALCL, anaplastic lymphoma kinase–negative *TP63*-rearranged anaplastic large cell lymphoma; −/−/− ALCL, triple-negative anaplastic large cell lymphoma (negative for ALK, *DUSP22*, and *TP63*).

Within systemic ALCL ALK-:

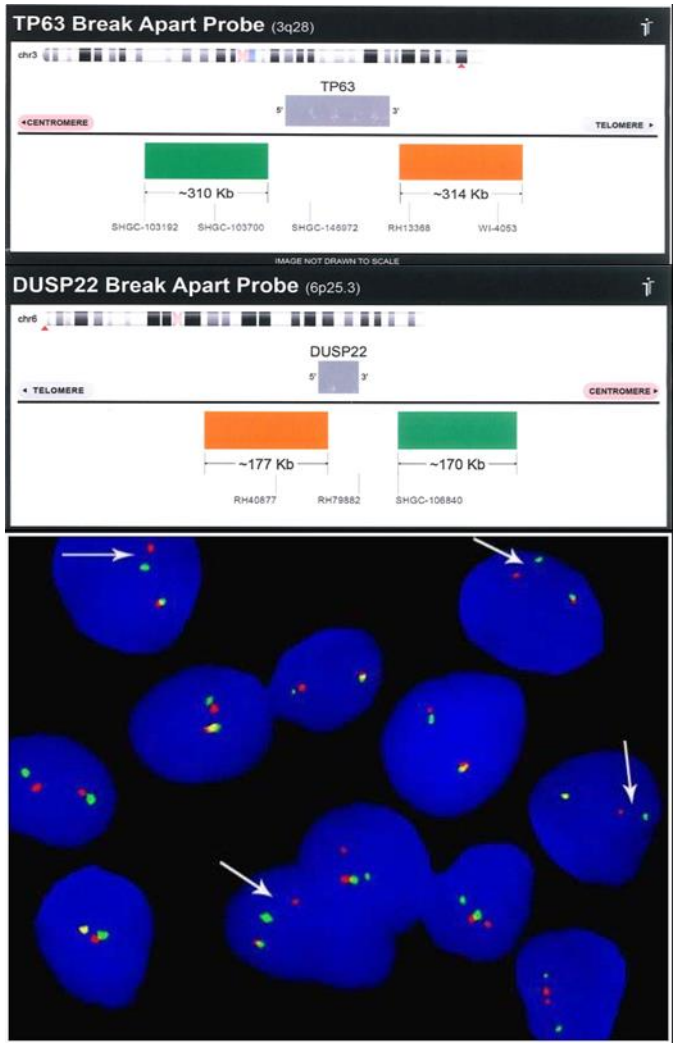
*19-30% *DUSP22-IRF4* rearrangement/ t(6;7): 85-90% OS ?
ICC2022: DUSP22-R ALK- ALCL: genetic subtype

*7-8% *TP63* rearrangement/ inv(3): 7-17% OS

* 2021: 6% JAK2 rearrangements (cave cHL morphology)

Parrilla Castellar et al., Blood 2014
Pedersen MB et al., Blood 2017
Fitzpatrick MJ, et al, Am J Surg Pathol 2021

2022: “FISH recommended”



Breast-implant associated-Anaplastic large cell lymphoma (BIA-ALCL)

- ✓ Definitive entity
- ✓ accumulation of seroma fluid between the implant itself and the surrounding fibrous capsule.
- ✓ median interval from the time of the implant to the lymphoma of about 10 years. Role of micro-textured implants?
- ✓ Register! FAGG and Belgian/French LYSARC Registry (please contact prof Marc André)
- ✓ TNM staging
- ✓ If possible: En bloc capsulectomy

TNM classification	TNM stage			
T: Tumor extent	IA	T1	N0	M0
T1: Confined to seroma or a layer on luminal side of capsule	IB	T2	N0	M0
T2: Early capsule infiltration	IC	T3	N0	M0
T3: Cell aggregates or sheets infiltrating the capsule	IIAb	T4b	N0	M0
T4: Lymphoma beyond the capsule; without (T4b) or with (T4cw) chest wall infiltration	IIAcw	T4cw	N0	M0
N: Lymph node	IIB	T1	N1	M0
N0: No lymph node involvement	IIB	T2	N1	M0
N1: One regional lymph node (+)	IIB	T3	N1	M0
N2: Multiple regional lymph nodes (+)	III	T4	N1	M0
M: Metastasis	III	T4	N2	M0
M0: No distant spread	IV	Any	TN	M1
M1: Spread to other organs/distant sites				

Fig. 5. TNM staging system for BIA-ALCL.

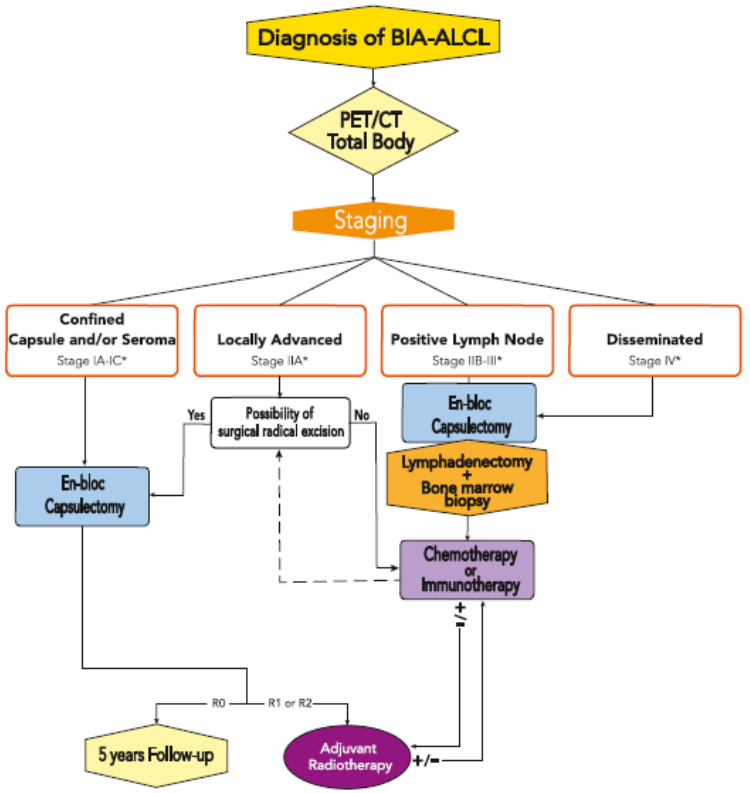


Fig. 3. Diagram showing process flow for confirmed diagnosis of BIA-ALCL.

Longo et al. The Breast 2022

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4. ENKTL: extra-nodal NK/T cell lymphoma (ICC 2022: nasal type)

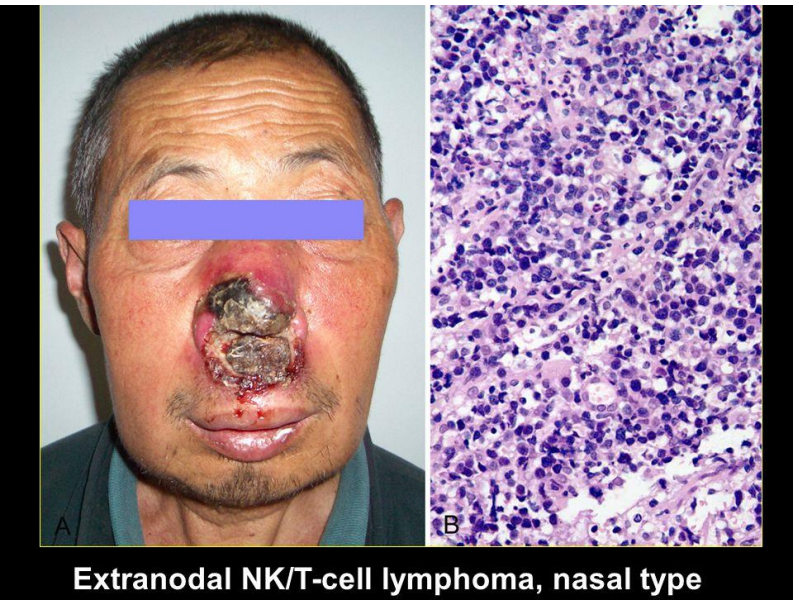
- EBV-driven
- Separate treatment schemes

Staging:

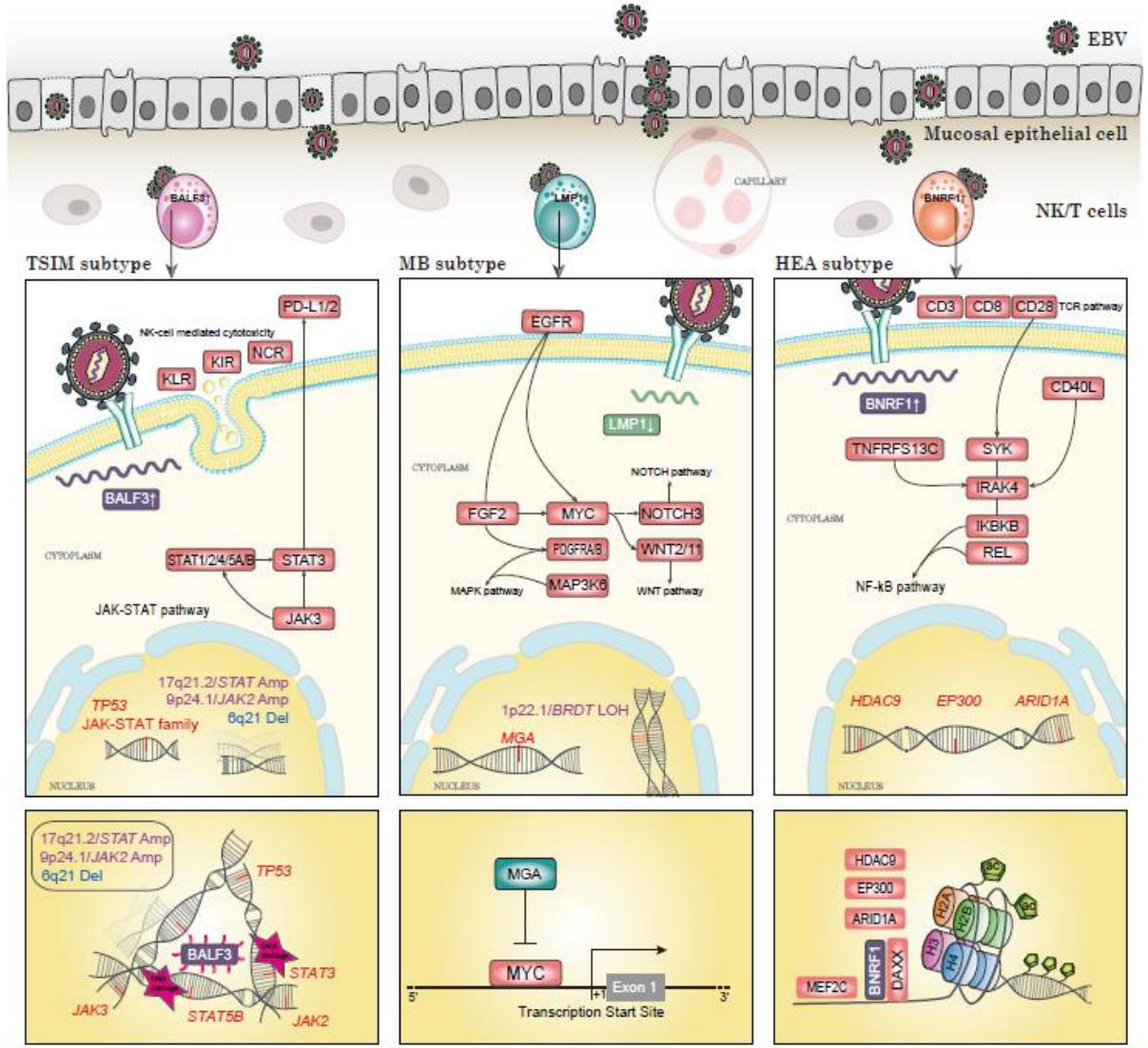
- IE: nasal site (nasopharynx/paranasal sinus/orbita)
- IIE : same + cervical lnn

For treatment decisions 3 groups:

- Nasal type, localised (IE, IIE)
- Nasal type, advanced (IV)
- Non-nasal type (I-IV)



Extranodal NK/T-cell lymphoma, nasal type



- Good prognosis
- Checkpoint-inhibitor?

- bad prognosis
- MYC aberrations> MYC-inhibiton?

- Aberrant Histone acetylation
- HDACi?

Xiong et al. Cancer Cell 2020

OUTLINE

- Pathophysiology
- WHO/ICC classification
- Diagnosis
- Prognosis
- Clinical characteristics of subtypes
- Treatment
- References

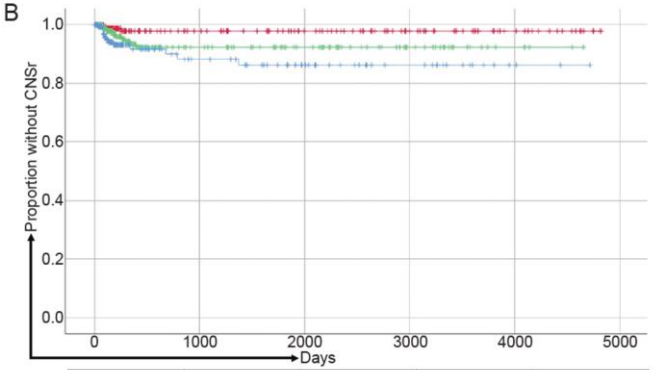
First-line treatment: in general

- CHOP remains gold standard for most subtypes
- Role of interim PET-CT?
  - cfr no/slow response: try to escalate? (DHAP, gemcitabine-containing?)
  - No RCT on PET-driven treatment strategies
- Importance of clinical trials!!!
- CNS prophylaxis? Probably cfr DLBCL/CNS-IPI? CITI score?
- CAVE: Low-risk IPI: reduced therapy is not validated

A

Factor	Coefficient (weight)	Hazard Ratio
TCL Histology		
PTCL-NOS	0.97	2.64
ALCL Alk+	-0.58	0.56
EATL (incl. MEITL and EATL)	1.07	2.92
SPTCL (incl. abSPTCL and PCGD-TCL)	-0.15	0.86
LDH > ULN	0.1	1.1
Stage III or IV	0.04	1.04
B-symptoms	0.14	1.15
2+ sites of EN involvement (incl. BM/PB)	0.98	2.66

B

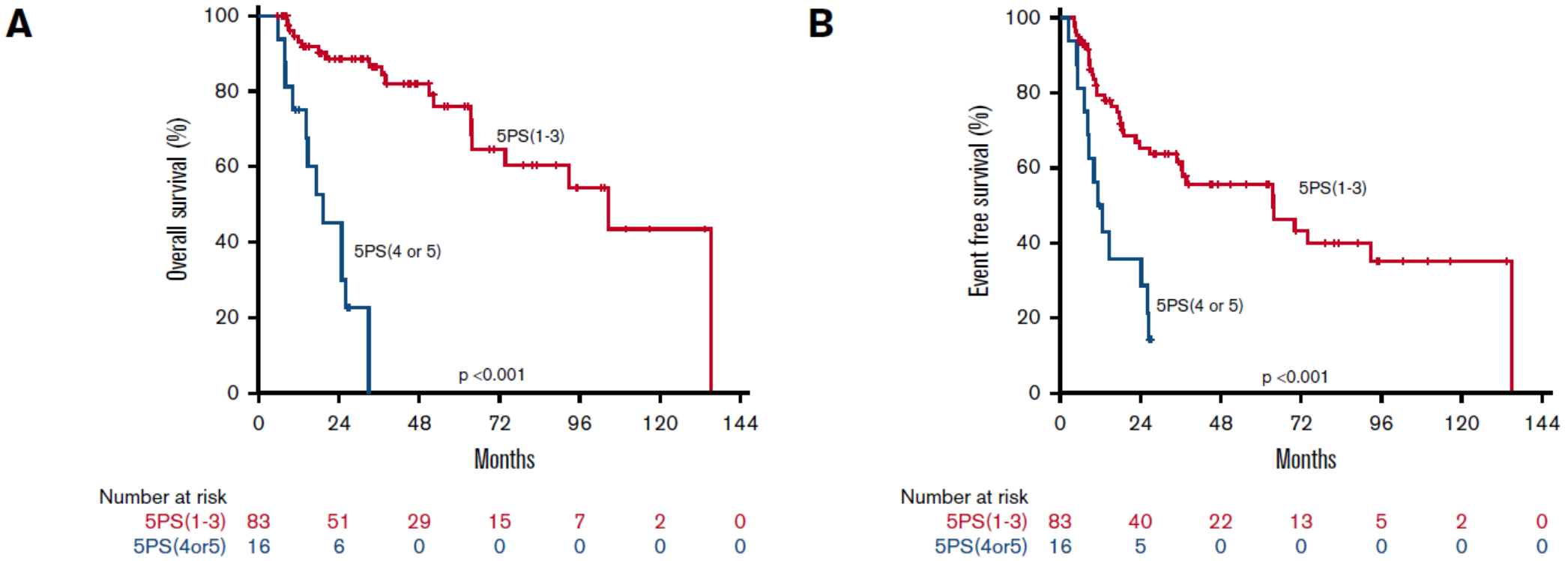


Risk	Cumulative incidence	Hazard ratio	95% CI	p-value
Low	1.9%	Reference	N/a	N/a
Intermediate	4.9%	3.35	0.93-12.02	p=0.057
High	7.3%	5.72	1.64-19.95	p=0.002

Figure 1. Predictive risk factors associated with CNS relapse in T-cell lymphoma.
(A) Using a LASSO Cox regression, several histologic and clinical risk factors were found to correlate with the risk of CNS. Hazard ratios and coefficients (weights) for scoring are shown. Abbreviations - TCL: T- and NK-cell lymphoma; PTCL, NOS: Peripheral T-cell lymphoma, not otherwise specified; ALCL Alk+: ALK+ Anaplastic large cell lymphoma; EATL: Enteropathy-associated T-cell lymphoma; MEITL: Monomorphic epitheliotropic intestinal T-cell lymphoma; abSPTCL: Alpha/beta subcutaneous panniculitis-like T-cell lymphoma; PCGD-TCL: Primary cutaneous gamma/delta T-cell lymphoma; LDH: Lactate dehydrogenase; ULN: Upper limit of normal; EN: Extranodal; BM: Bone marrow; PB: Peripheral blood.
(B) Kaplan-Meier plot shows the proportion of patients in the validation set with CNSr stratified by low-, intermediate-, or high-risk based on cutoffs from the training set. Panel key denotes risk category and risk of CNSr (cumulative incidence) along with hazard ratios, which were calculating in comparison to the low-risk group as a reference.

CNS Relapse in T-Cell Lymphoma Index: A Risk Score to Predict Central Nervous System Relapse in Patients with T-Cell Lymphomas
Bhansali et al. ASH 2022, *Blood* (2022) 140 (Supplement 1): 1481–1484.

Role of interim PET-CT?



Mehta-Shah et al. Blood Advances, 2019

Retrospective study

interim PET= after 4 cycles CHOP or CHOEP (+ intention to treat with ASCT in all CR1)

Conclusion: Deauville 5PS= independent prognostic factor in multivariate analysis for OS/EFS

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Strategies to improve on first line treatment?

1. Intensification of induction chemotherapy

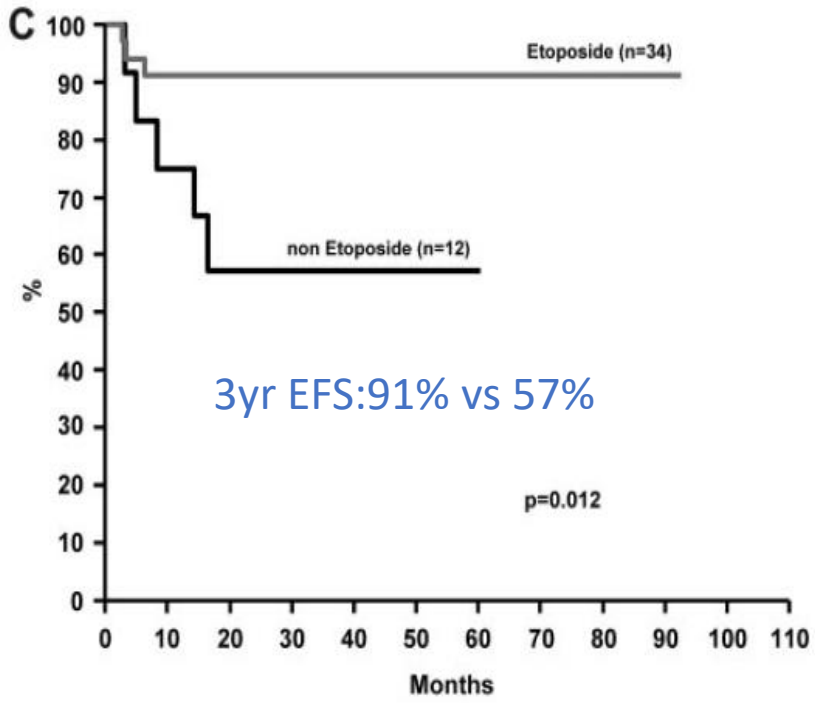
2. Consolidation by stem cell transplantation

3. Combination of chemotherapy with new molecules

1.Intensification of induction chemotherapy: CHOEP

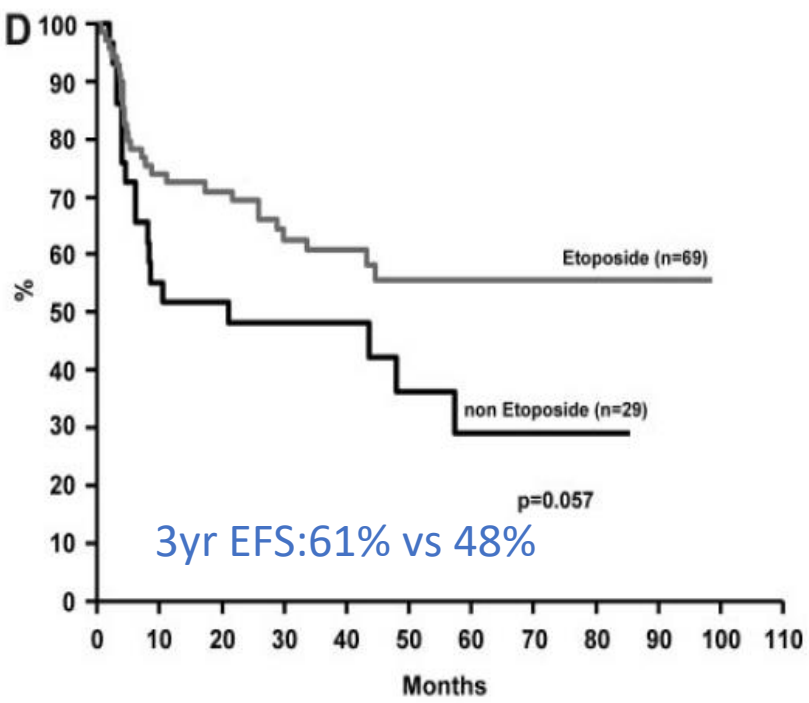
=CHOP
+etoposide d1-3
100 mg/m² IV

ALCL, ALK-positive, nl LDH, <60yr



3yr EFS:91% vs 57%

Other subtypes, nl LDH, < 60 yr



3yr EFS:61% vs 48%

Schmitz et al., Blood 2010

No large Phase III RCTs (**retrospective** data)
Subanalysis: Benefit only in LDH nl, < 60yr pts: EFS advantage: Only statistically significant ALCL ALK +, no OS difference
Cave: more toxicity in elderly: NOT > 60 yr

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1. Intensification of induction chemotherapy: DA-EPOCH

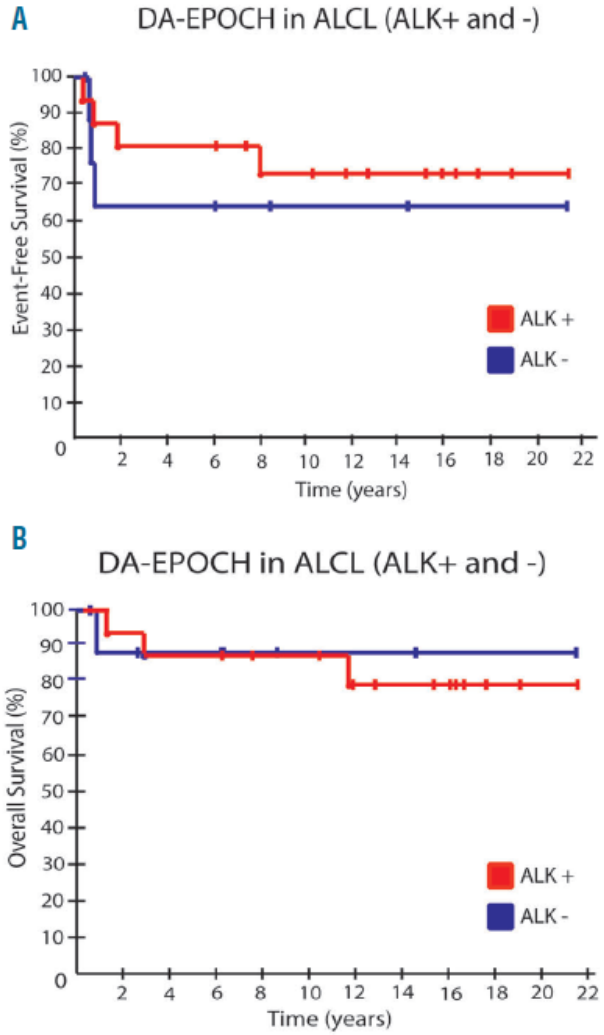


Figure 1. Outcome of 24 patients (15 ALK positive and 9 ALK negative) following DA-EPOCH. (A) Event-free survival (EFS) of ALK positive *versus* ALK negative patients. (B) Overall survival of ALK positive *versus* negative cases.

-Small Phase II study, n = 24
- Only ALCL (15 ALK+)
- age: < 69 yr

Dunleavy et al, Haematologica, 2016

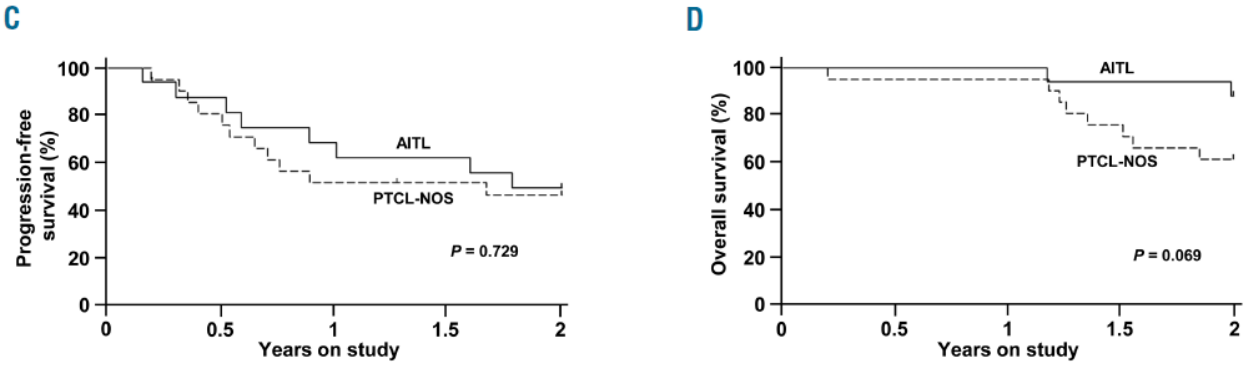
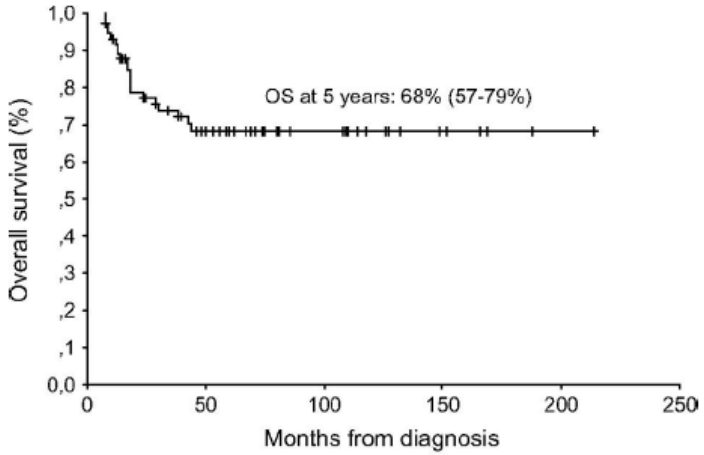


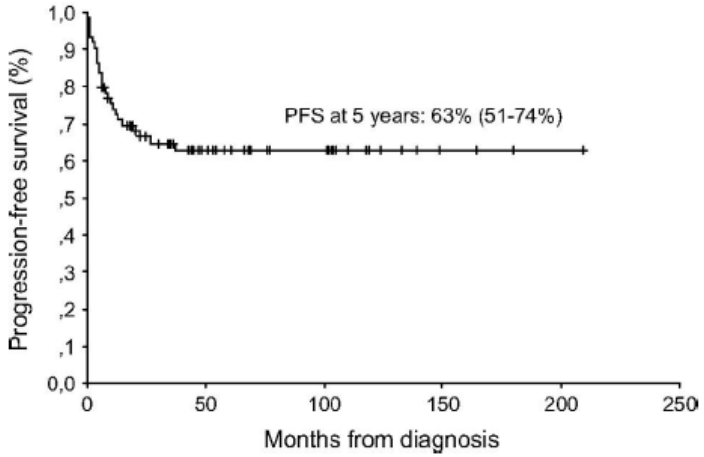
Figure 2. Kaplan-Meier estimates of progression-free and overall survival of patients with peripheral T-cell lymphomas (PTCLs) receiving dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) (DA-EPOCH). Analysis of progression-free survival (PFS) and overall survival (OS) for all patients in this study (A) and younger patients (≤ 60 years old) (B). PFS (C) and OS (D) of angioimmunoblastic T-cell lymphoma (AITL) and PTCL-not otherwise specified (PTCL-NOS) patients.

-Small Phase II study, n = 41
- mainly: AITL (17), PTCL,NOS (21)
- < 60 yr 2 yr PFS: 62%
- > 60 yr 2 yr PFS: 47%
- NB : + 70 yr: -20% starting dose

Maeda et al, Haematologica, 2017

2.Consolidation by ASCT





"OS 68% at 5 years??"

However:

- Retrospective??? (selection bias)
- Young patients (median 46 yr),>> low PIT/IPI score
- ALCL (ALK?) included

Rodriguez, Ann Oncol 2004

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A total of 499 patients with PTCL were enrolled in COMPLETE over a period of 4 years between February 2010 and February 2014 from 56 academic and community centers. The characteristics of the patients enrolled in COMPLETE have been reported previously and are comparable to those of patients from the Surveillance, Epidemiology, and End Results program.[19] The histology reports were reviewed by 5 independent hematopathologists.[20] Before the start of the initial treatment, 18 patients were removed from the study, most commonly because they were lost to follow-up or did not meet the eligibility criteria. Of the remaining patients, 213 achieved CR after frontline therapy and had the required locked records to be included in the analysis. Sixty-four patients (30%) underwent HSCT, whereas 149 patients (70%) were treated without transplantation in CR1. The current analysis focused on 119 patients with nodal PTCL, which was defined as ALK-negative ALCL, AITL, or PTCL NOS, in CR1. Thirty-six patients underwent consolidative ASCT (the ASCT group) whereas 83 were treated without HSCT (the non-ASCT group). The base-

N = 499

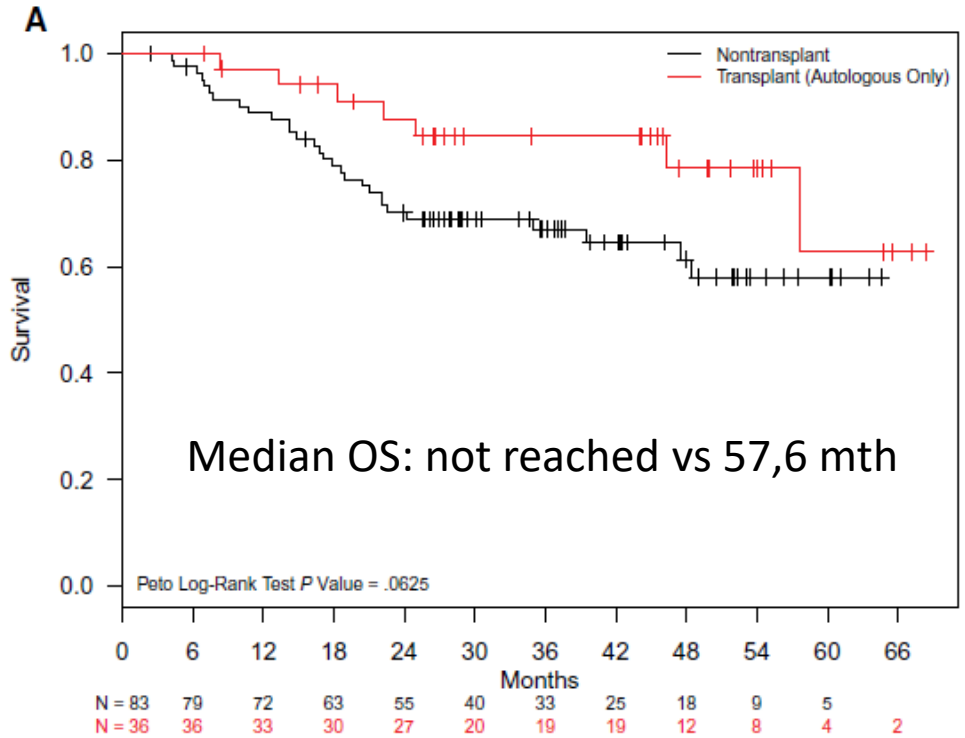
- 213 CR after first line treatment and eligible for analysis
- 30% ASCT, 70% no ASCT
- Not randomized!

The Role of Autologous Stem Cell Transplantation in Patients With Nodal Peripheral T-Cell Lymphomas in First Complete Remission: Report From COMPLETE, a Prospective, Multicenter Cohort Study

Steven I. Park, MD[1]; Steven M. Horwitz, MD[2]; Francine M. Foss, MD[3]; Lauren C. Pinter-Brown, MD[4]; Kenneth R. Carson, MD, PhD[5]; Steven T. Rosen, MD[6]; Barbara Pro, MD[7]; Eric D. Hsi, MD[8]; Massimo Federico, MD[9]; Christian Gisselbrecht, MD[10]; Marc Schwartz[11]; Lisa A. Bellm, MIM[12]; Mark Acosta, PharmD[13]; Ranjana H. Advani, MD[14]; Tatyana Feldman, MD[15]; Mary Jo Lechowicz, MD[16]; Sonali M. Smith, MD[17]; Frederick Lansigan, MD[18]; Anil Tulpule, MD[19]; Michael D. Craig, MD[20]; John P. Greer, MD[21]; Brad S. Kahl, MD[5]; Joseph W. Leach, MD[22]; Neil Morganstein, MD[23]; Carla Casulo, MD[24]; and Andrei R. Shustov, MD[25] for the COMPLETE Investigators

2 yr OS if CR1 :75,3% (ASCT + no ASCT)
2 yr OS if no CR1: 41,9%

Cancer 2019



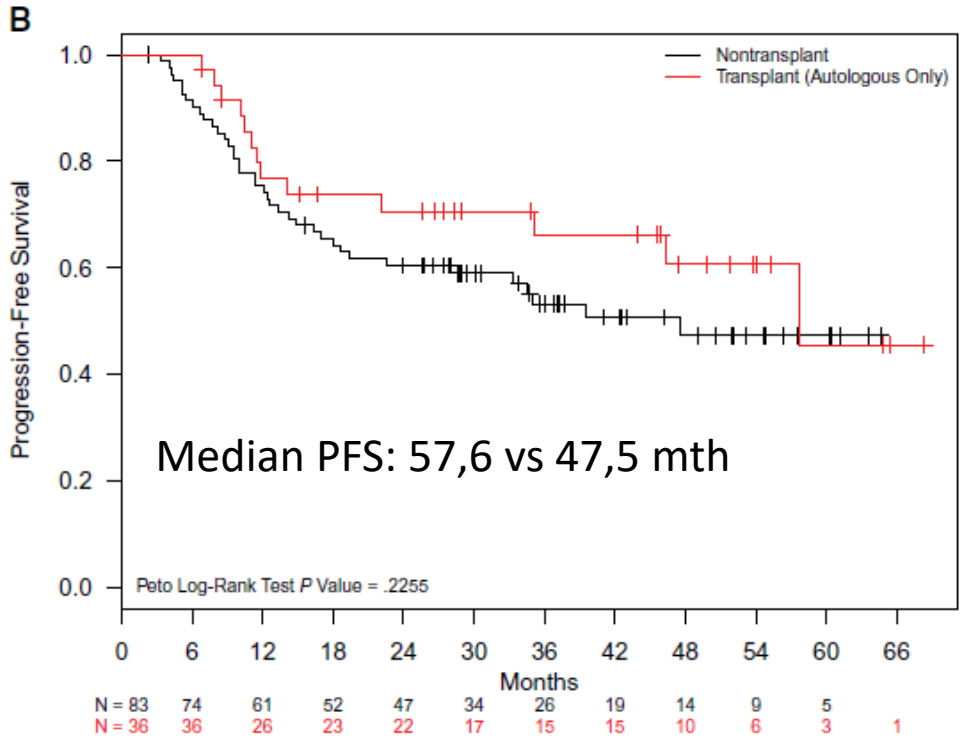


Figure 2. (A) Overall survival and (B) progression-free survival for first complete remission patients with nodal peripheral T-cell lymphoma: ASCT versus non-ASCT. ASCT indicates autologous stem cell transplantation.

Autologous SCT in CR1:

- No Proof of superiority in RCTs (bias…)
- Often problem of eligibility: age/ECOG/**chemo-refractory disease**!
- Belgian Guidelines: Consider (CO) … in young patients with initial high-intermediate/ high IPI (> or = 2)

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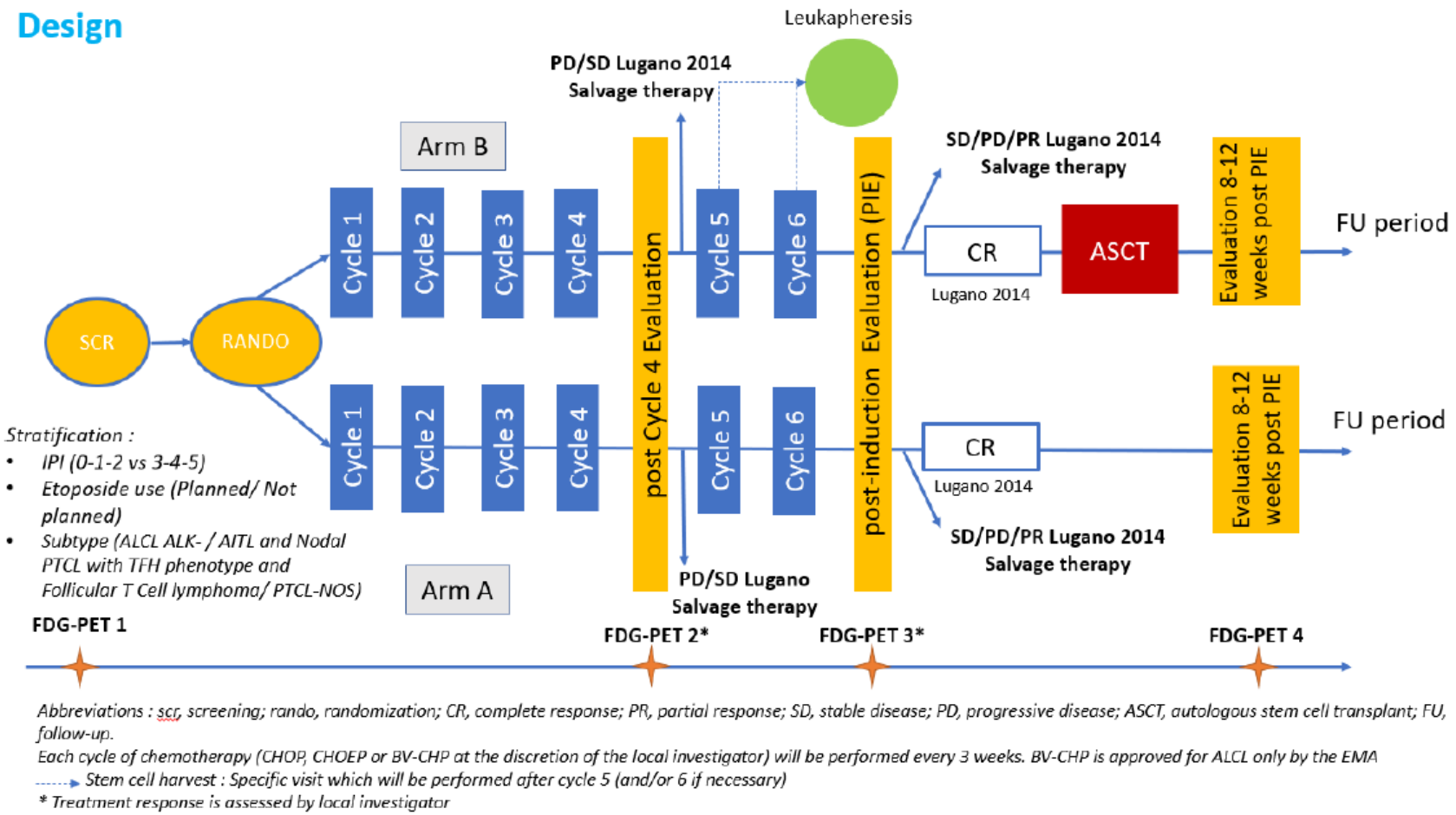
TRANSCRIPT: first RCT investigating the role of ASCT in CR1 in PTCL: recruiting



Abbreviations : scr, screening; rando, randomization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ASCT, autologous stem cell transplant; FU, follow-up.

Each cycle of chemotherapy (CHOP, CHOEP or BV-CHP at the discretion of the local investigator) will be performed every 3 weeks. BV-CHP is approved for ALCL only by the EMA

Stem cell harvest : Specific visit which will be performed after cycle 5 (and/or 6 if necessary)

** Treatment response is assessed by local investigator*

Primary Endpoint: mPFS of patients in CR after 6 cycles of CHOP/CHOEP or BV-CHP with or without ASCT for patients with TFH lymphoma, PTCL, NOS or ALCL, ALK negative.

Source: LYSARC

2.Consolidation by Allo-SCT

RCTs?

The **DSHNHL 2006-1A (AATT) protocol** in which younger patients with PTCL (excluding stage I with IPI 0) received a common induction with four cycles of CHOEP-14 and one cycle of DHAP, and were then randomised between BEAM/ASCT or allo-SCT after FBC (fludarabine 125 mg/m2 , busulfan 12 mg/kg, cyclophosphamide 120 mg/kg) was **prematurely stopped**, based on an interim-analysis which estimated that it was highly unlikely that the primary objective, namely a 25% improvement of PFS at 3 y for allo-SCT, would be reached.

Allogeneic SCT in CR1:

- **No Proof** of superiority in RCTs
- Suggestion of curability/plateau…
- Often problem of eligibility: age/ECOG/how to obtain remission…

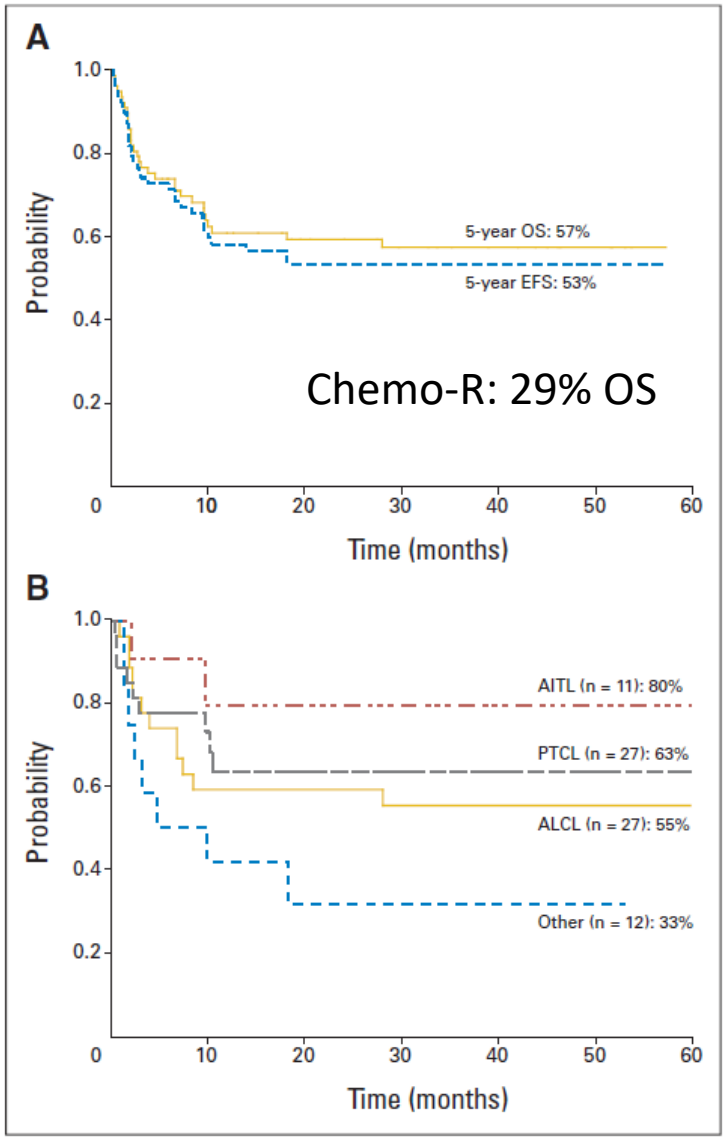


Fig 1. (A) Overall survival (OS) and event-free survival (EFS) after transplantation for all 77 patients. (B) Five-year overall survival according to histopathologic subtypes. PTCL, peripheral T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; other histopathologic subtypes are classified as "other."

Le Gouill, JCO 2008 (CAVE most patients R/R and young (med age 36!, n = 77, TRM 34%,mostly MAC)

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T cell lymphoma	Autologous SCT	Allogeneic SCT	
PTCL, NOS / AITL / ALK $^{-}$ ALCL			
CR1/PR1	CO/II	NGR/II	
Primary refractory (Ch-R)	NGR/II	CO/II	
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II	
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II	
ALK $^{+}$ ALCL			
CR1/PR1	CO if high-risk disease/II	NGR/III	HR: IPI >2
Primary refractory (Ch-R)	NGR/II	CO/II	
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II	
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II	
ENKTL			
CR1/PR1	NGR in limited - CO in advanced/II	NGR/III	
Primary refractory (Ch-R)	NGR/II	CO/II	
First relapse	SC (if Ch-S)/II	CO/II	
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II	

Belgian guidelines on transplant in lymphoma. Snauwaert et al. 2019 Belgian Journal of Hematology

3. Combination of chemotherapy with new molecules

a) CHP + brentuximab vedotin (immunoconjugate): phase III ECHELON-2

b) CHOP + alemtuzumab (anti-CD52): DSHNHL2006-1B/ACT-2 trial

c) CHOP + romidepsine (HDAC-I): phase III RO-CHOP LYSARC

d) CHOP + pralatrexate: no clear benefit

e) CHOP + chidamide and azacitidine: no clear benefit

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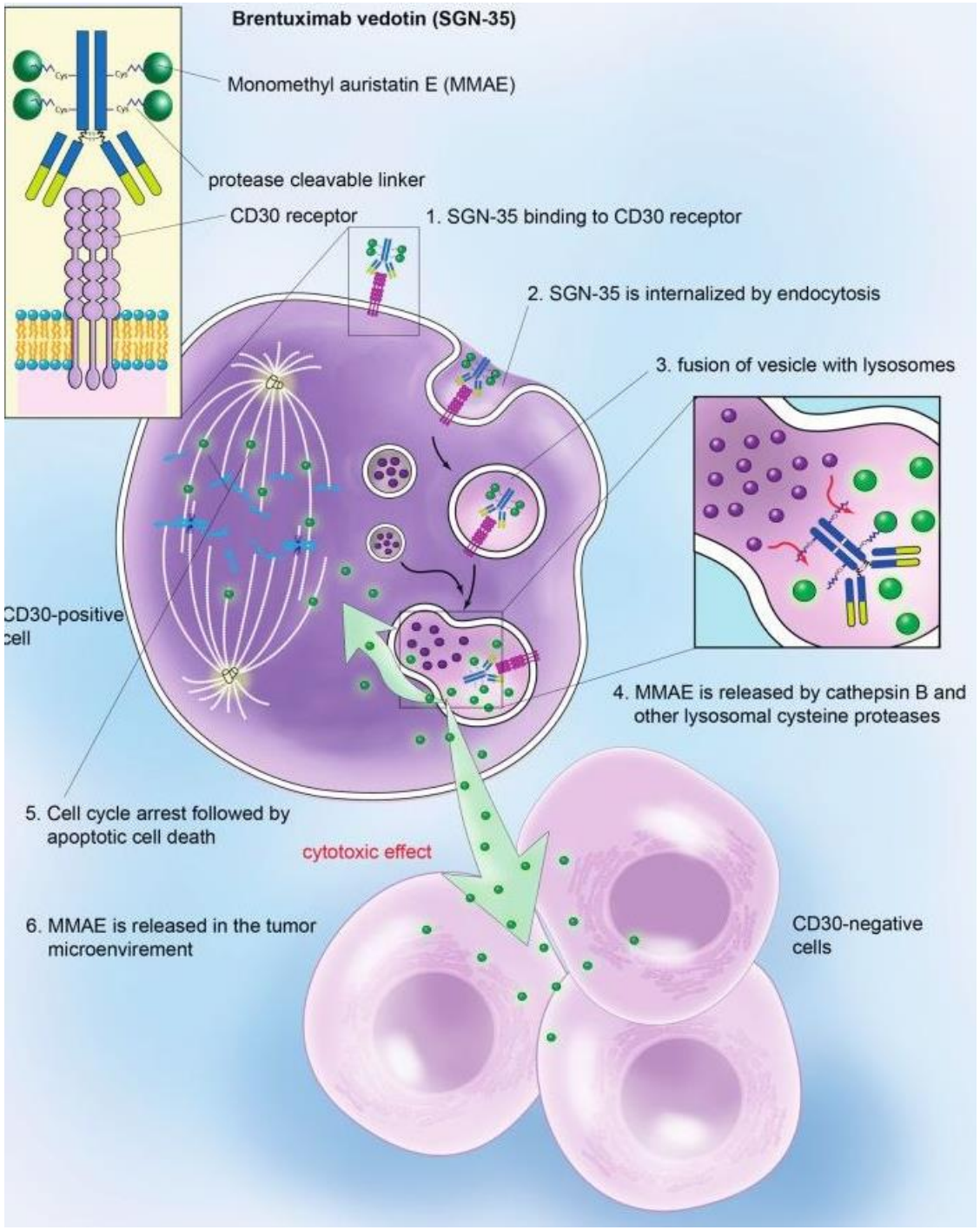

Brentuximab vedotin

an antibody–drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule disrupting drug monomethyl auristatin E.

subtype	% CD30+ (> 10%)
ALCL	+/-100%
PTCL, NOS	30-60%
AITL	43-63%

Horwitz, Lancet 2018

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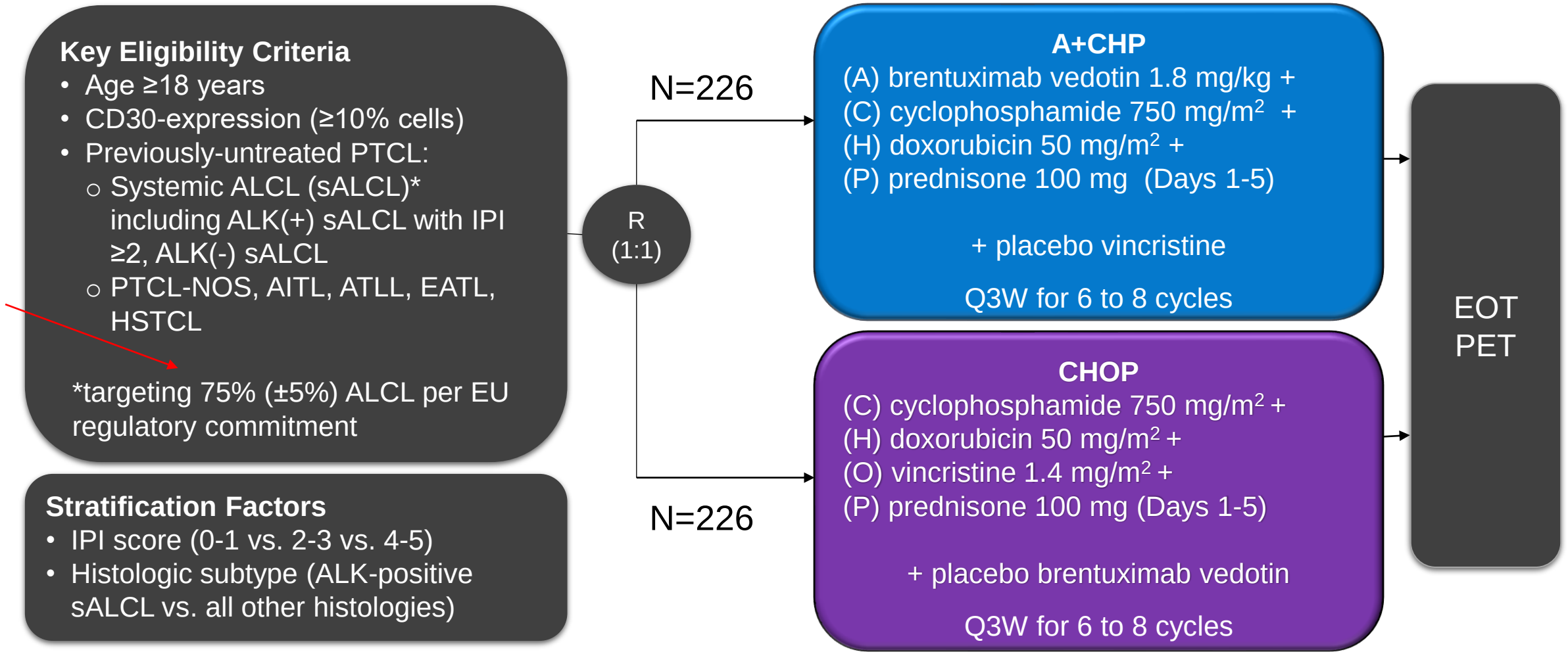
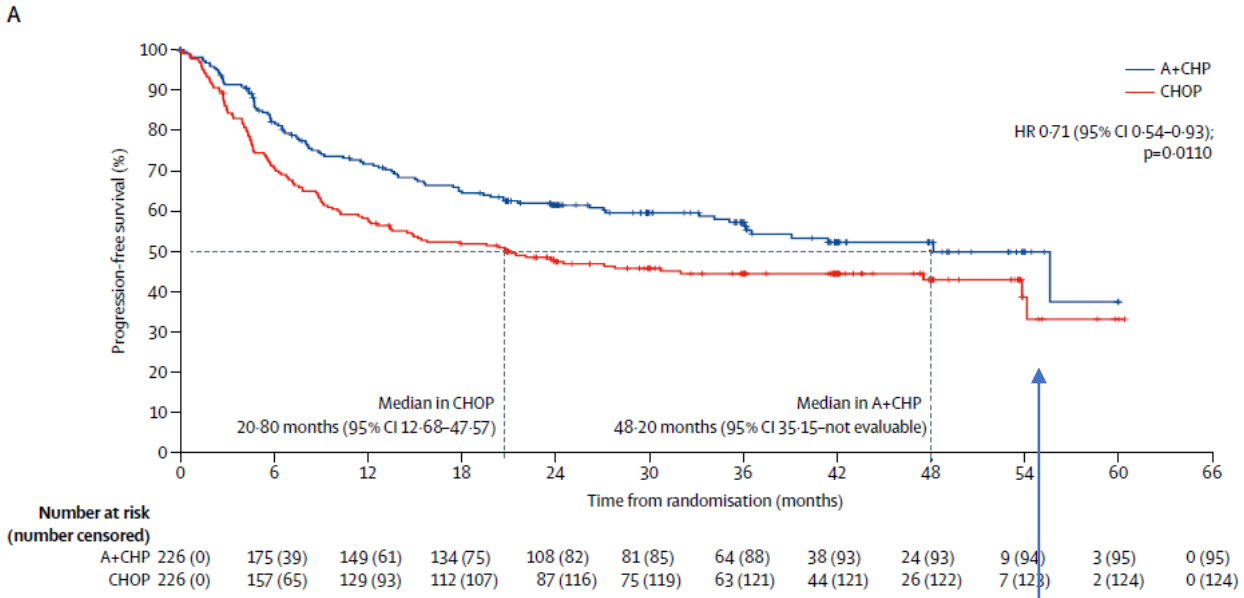
ECHELON-2 Study Design (NCT01777152)

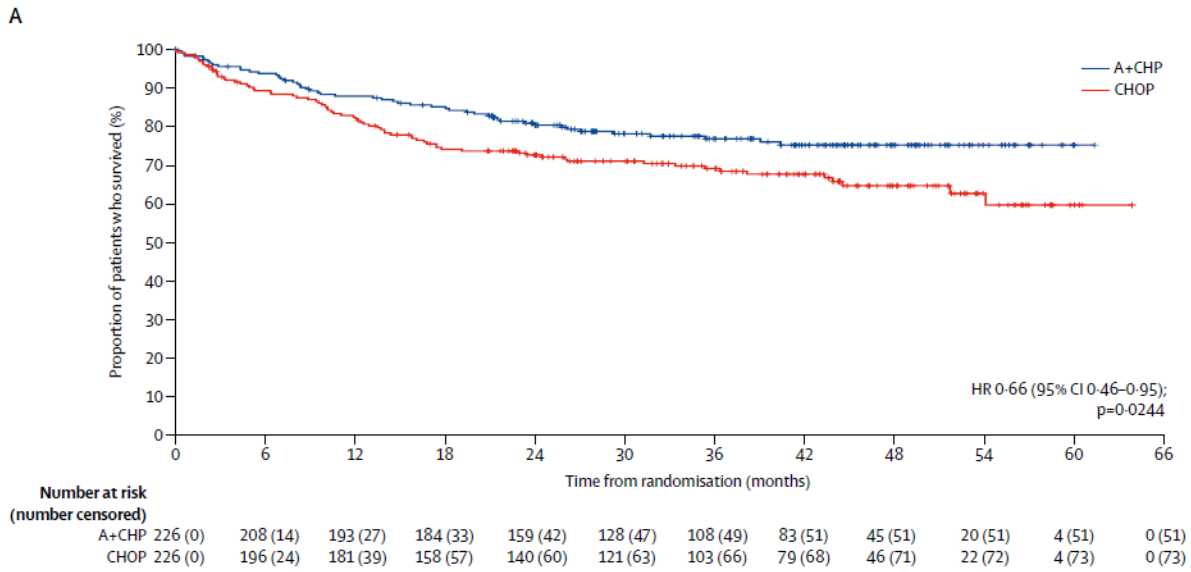


AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukaemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; GCSF, granulocyte-colony stimulating factor; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index

Per investigator discretion:
GCSF primary prophylaxis, consolidative RT and SCT

Horwitz, Lancet 2019





3-yr PFS:
A+ CHP: 57,1%
CHOP: 44,4%

Med PFS:
A + CHP: 48 mths
CHOP 20,8 mths

No plateau?

Med OS:
A + CHP: NR mths
CHOP NR mths
HR: 0,66

3-yr OS:
High for T cell lymphoma? > 70% : ALCL…
(22% of total n= ALCL ALK+)

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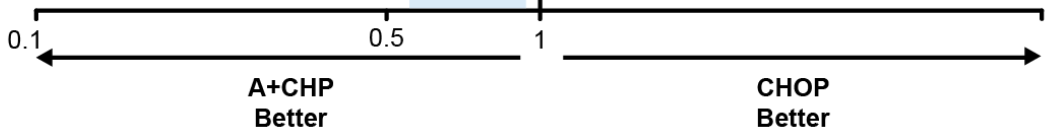
Prespecified Subset Analyses: PFS

Belgium: reimbursement only in ALCL, ALK- or ALCL ALK+ and IPI ≥ 2.

ITT Subgroups	Event/N A+CHP	Event/N CHOP	Hazard Ratio (95% CI)
Overall	95/226	124/226	0.71 (0.54, 0.93)
IPI Score			
0–1	18/52	27/48	0.53 (0.29, 0.97)
2–3	56/141	77/145	0.71 (0.50, 1.00)
4–5	21/33	20/33	1.03 (0.55, 1.92)
Age			
<65 years	54/157	75/156	0.67 (0.47, 0.95)
≥65 years	41/69	49/70	0.70 (0.46, 1.08)
Gender			
Male	59/133	80/151	0.80 (0.57, 1.13)
Female	36/93	44/75	0.49 (0.31, 0.78)
Baseline ECOG Status			
0/1	76/174	105/179	0.66 (0.49, 0.89)
2	19/51	19/47	0.98 (0.51, 1.87)
Disease Stage			
I/II	15/42	19/46	0.95 (0.48, 1.88)
III	29/57	35/67	0.69 (0.42, 1.14)
IV	51/127	70/113	0.64 (0.45, 0.93)
Disease Indication			
ALK-positive sALCL	5/49	16/49	0.29 (0.11, 0.79)
ALK-negative sALCL	50/113	60/105	0.65 (0.44, 0.95)
AITL	18/30	13/24	1.40 (0.64, 3.07)
PTCL-NOS	19/29	31/43	0.75 (0.41, 1.37)
PFS (PD, Death)	84/226	103/226	0.75 (0.56, 1.00)



3.Combination of chemotherapy with new molecules

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d) CHOP + pralatrexate: no clear benefit
e) CHOP + chidamide and azacitidine: no clear benefit

"Alemtuzumab added to CHOP increased response rates, but did not improve survival due to treatment-related toxicity "

Wulf et al. Leukemia 2020

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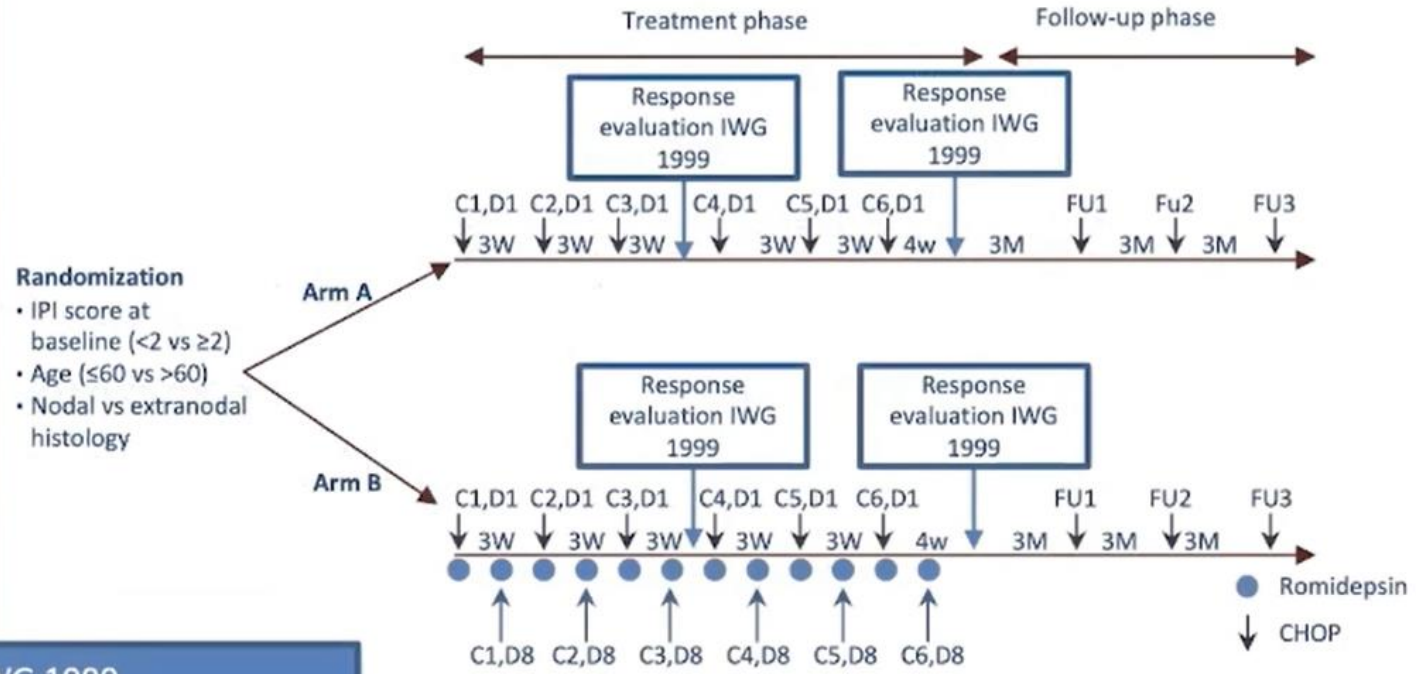
Ro-CHOP: Study Design

Key Inclusion Criteria

- Aged 18-80 y
- Histologically proven PTCL according to WHO classification: PTCL-NOS, AITL, ALK-neg ALCL, EATCL, HSTCL, SPTCL
- Ann Arbor stage I-IV
- ECOG PS 0-2
- Life expectancy ≥ 3 mo

Key Exclusion Criteria

- Other subtypes of PTCL
- Previous treatment for PTCL except for short-term corticosteroids (≤ 8 d)
- Autologous or allogeneic transplant planned as consolidation
- CNS or meningeal involvement
- Abnormal renal, hepatic, and marrow function unless related to lymphoma



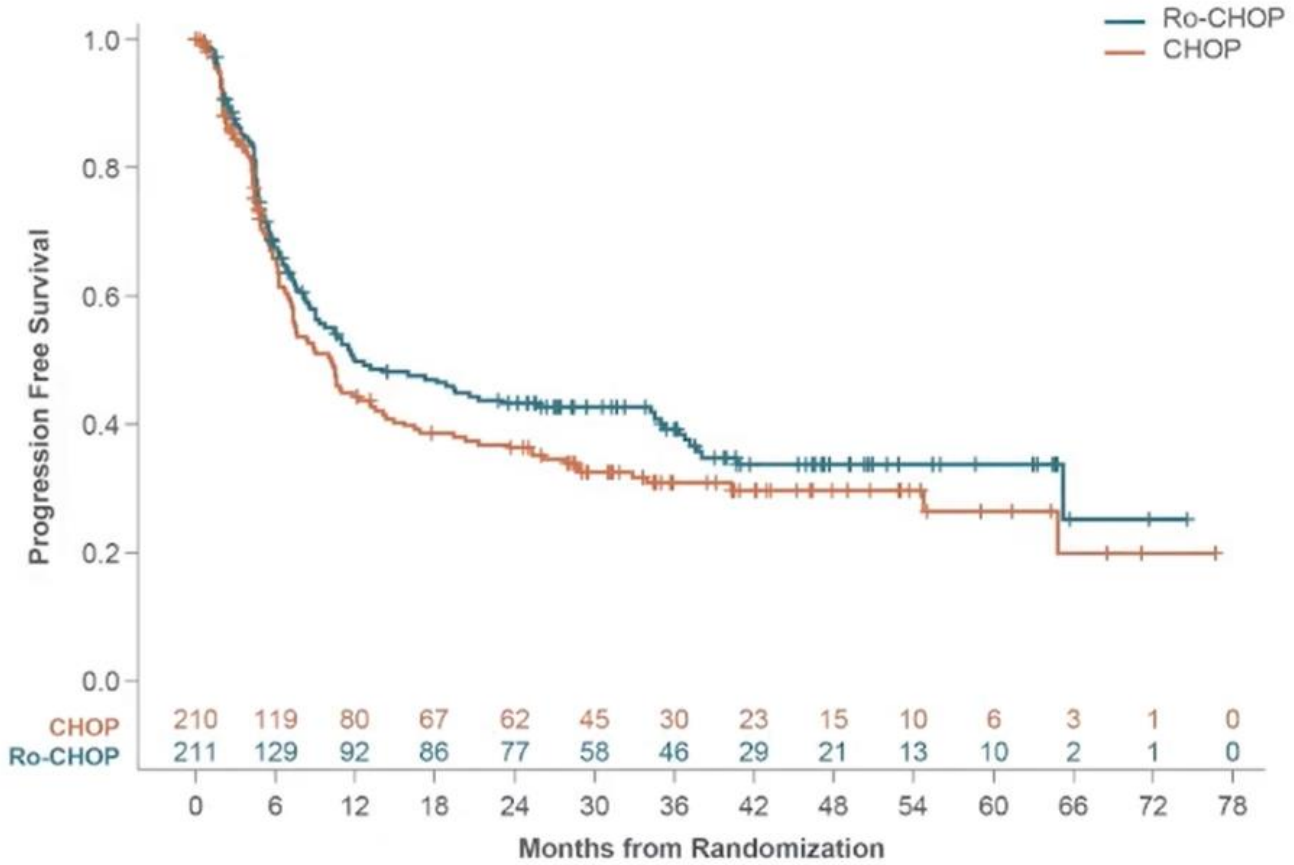
Primary end point: PFS by RAC assessment according to IWG 1999

- Hypothesis: Median PFS of 12 mo (control) vs 16.8 mo (experimental)

Secondary end points: OS, response rate, DOR, TTP, TTF, safety, QOL

NCT01796002. AITL, angioimmunoblastic T-cell lymphoma; ALK-neg ALCL, anaplastic lymphoma kinase-negative anaplastic large cell lymphoma; C, cycle; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CNS, central nervous system; D, day; EATCL, enteropathy-associated T-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow-up; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index; IWG, international working group; OS, overall survival; PFS, progression-free survival; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; QOL, quality of life; RAC, response adjudication committee; Ro, romidepsin; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; TTF, time to treatment failure; TTP, time to progression; W, week; WHO, World Health Organization.

Ro-CHOP: Progression-Free Survival by Independent RAC (ITT Population)*

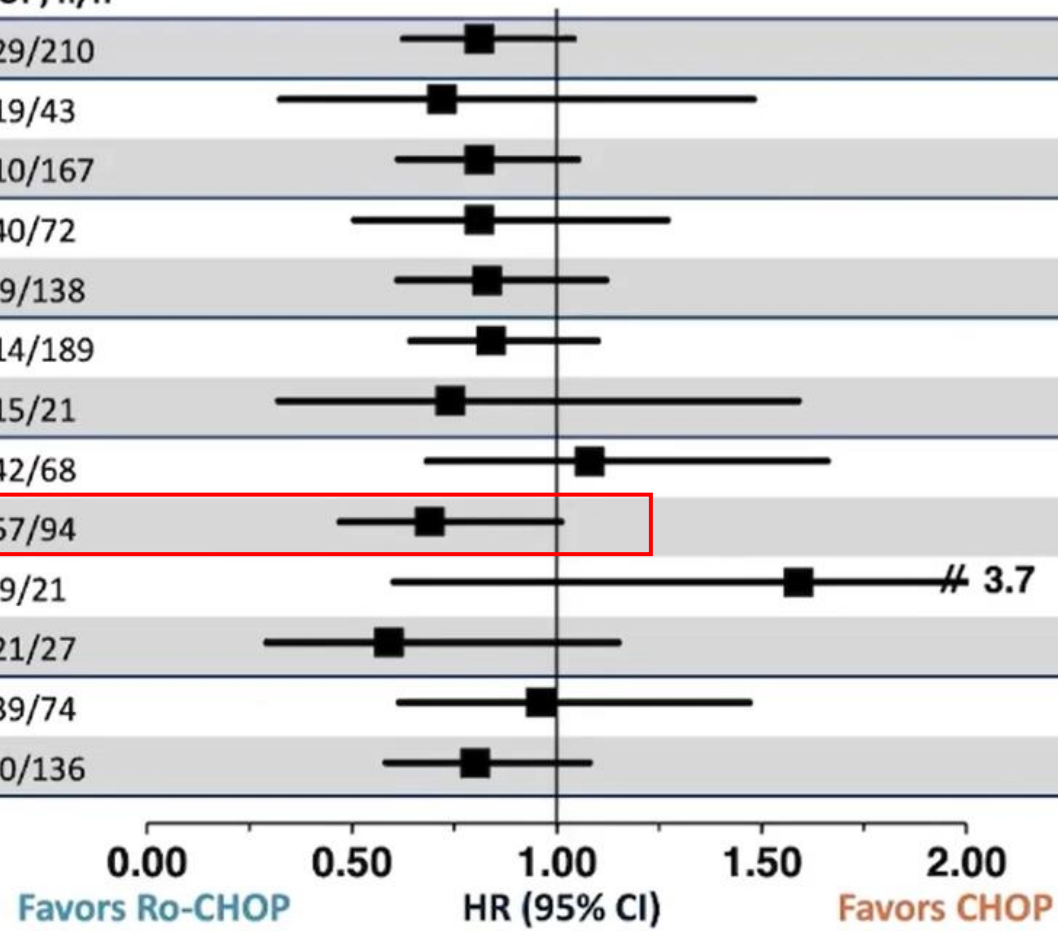


	Ro-CHOP (n = 211)	CHOP (n = 210)
PFS, median (95% CI), mo	12.0 (9.0-25.8)	10.2 (7.4-13.2)
HR (95% CI)	0.81 (0.63-1.04)	
P-value	0.096	

Data cutoff 13Dec2019.
HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival; RAC, response adjudication committee.
*According to IWG 1999 criteria.

Ro-CHOP: Subgroup Analysis of PFS (ITT Population)

		Ro-CHOP, n/n	CHOP, n/n
Overall		122/211	129/210
Baseline IPI	<2	12/36	19/43
	≥ 2	110/175	110/167
Age	≤ 60 y	37/73	40/72
	> 60 y	85/138	89/138
Nodal vs Extranodal	Nodal	110/188	114/189
	Extranodal	12/23	15/21
Histology	PTCL-NOS	41/59	42/68
	AITL	53/101	57/94
	ALK-neg sALCL	13/21	9/21
	Other	15/30	21/27
Sex	Women	48/86	39/74
	Men	74/125	90/136



Data cutoff 13Dec2019.
AITL, angioimmunoblastic T-cell lymphoma; ALK-neg sALCL, anaplastic lymphoma kinase-negative systemic anaplastic large cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; IPI, international prognostic index; intention-to-treat; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; Ro, romidepsin.

3.Combination of chemotherapy with new molecules

a) CHP + brentuximab vedotin (immunoconjugate): ECHELON-2
b) CHOP + alemtuzumab (anti-CD52): DSHNHL2006-1B/ACT-2 trial
c) CHOP + romidepsine (HDAC-I): phase III RO-CHOP LYSARC

d) CHOP + pralatrexate: no clear benefit
e) CHOP + chidamide and azacitidine: no clear benefit (phase III, non-RCT, ASH 2022, abstract 2922)

Relapse/refractory disease

Salvage therapy is palliative (med OS < 6 mths) OR bridge to transplant

- Discussion : Consolidation by ASCT or alloSCT?
  - High dose chemotherapy and ASCT
    - If no ASCT in CR1 AND chemo-S?
  - Allo-SCT
    - “more advised in young/fit than ASCT in relapsed setting”? Moskowitz et al. Blood 2014

- Even more challenging: how to reach a remission?
  - Salvage **chemotherapy**
    - DHAP, gemcitabine containing regimens, ICE, bendamustine, …
  - (combinations of) **new molecules**+/- chemotherapy
  - Importance of inclusion in **clinical trials**!

- Best supportive care, palliative radiotherapy

1. Consolidation by Allo-SCT in R/R PTCL

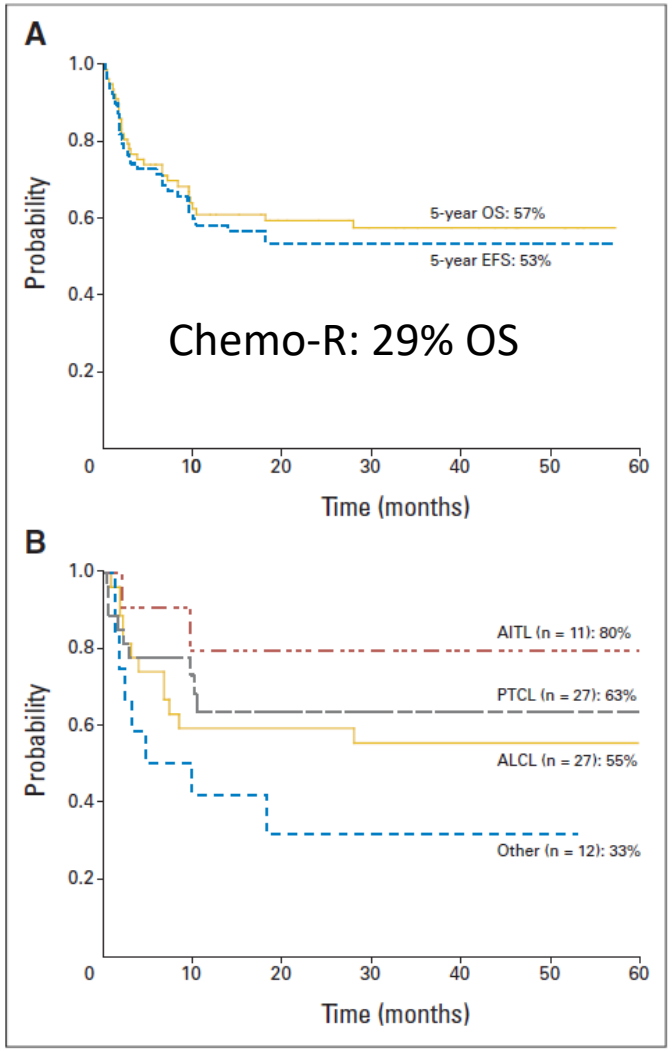


Fig 1. (A) Overall survival (OS) and event-free survival (EFS) after transplantation for all 77 patients. (B) Five-year overall survival according to histopathologic subtypes. PTCL, peripheral T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; other histopathologic subtypes are classified as "other."

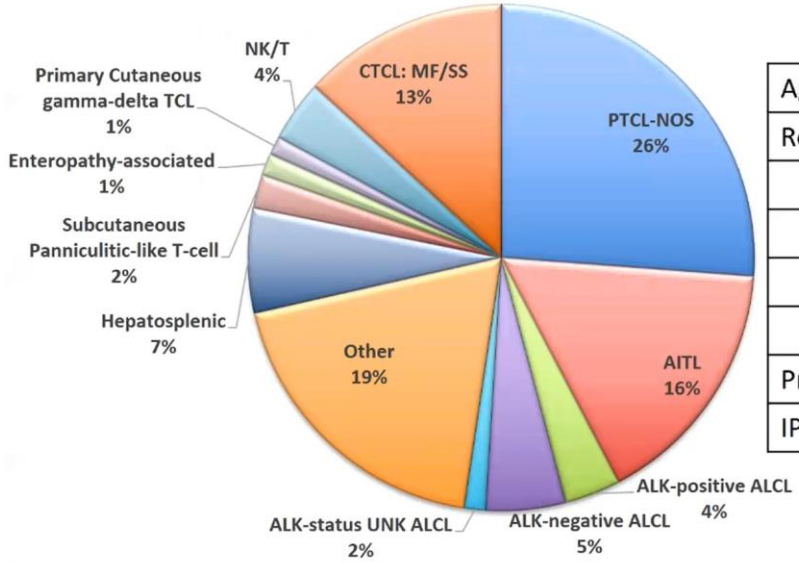
Le Gouill, JCO 2008 (most patients R/R and young (med age 36!, n = 77, TRM HIGH 34%,mostly MAC)

1. Consolidation by Allo-SCT in R/R PTCL

- Multicentric American retrospective analysis of R/R T-cell lymphoma
- Very heterogenous group of T cell lymphoma subtypes
- Highly susceptible to selection bias
- Conclusion:

"Eligible patients with R/R T cell lymphoma should be considered for alloSCT"

Patient Characteristics (n=508)



Age (median, Range)	51 (16-72)
Remission Status	
CR	254 (54.4%)
PR	168 (37.2%)
SD	23 (5.0%)
PD	16 (3.2%)
Prior Auto	78 (15.5%)
IPI (median, range)	2 (0-5)

American Society *of* Hematology

Mehta-Shah N et al. (group of S. Horwitz, ASH 2020, Abstract 41

1. Consolidation by Allo-SCT in R/R PTCL

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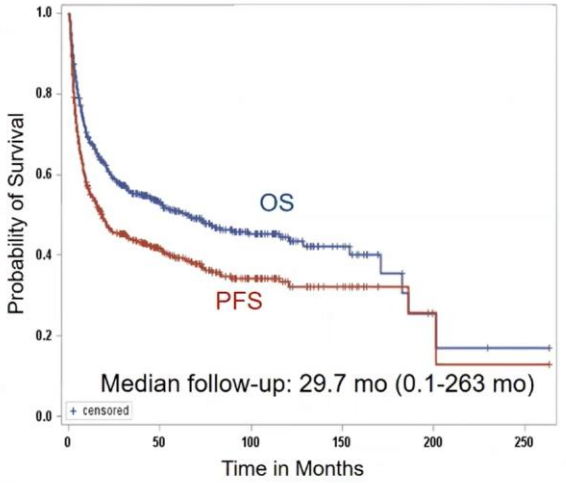
Overall Survival (OS) and Progression Free Survival (PFS)



Overall Survival (OS)

- **2 years: 59.1%** (95%CI: 54.6-63.3%)
- **5 years: 50.8%** (95%CI: 46.1-55.3%)

Progression Free Survival (PFS)

- **2 years: 45.8%** (95%CI: 41.3-50.2%)
- **5 years: 39.4%** (95%CI: 34.9-43.9%)

Median time from relapse to death post Allo:

- 10.2 mo (0-158.4 mo)

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Mehta-Shah N et al. (group of S. Horwitz, ASH 2020, Abstract 41

2. How to obtain a remission?

Crizotinib: ALK inhibitor:
small studies: 90-100 % ORR
Oktober 2022: Xalkori:
EMA approved
no RIZIV/INAMI reimbursement (age 6-18 yr)

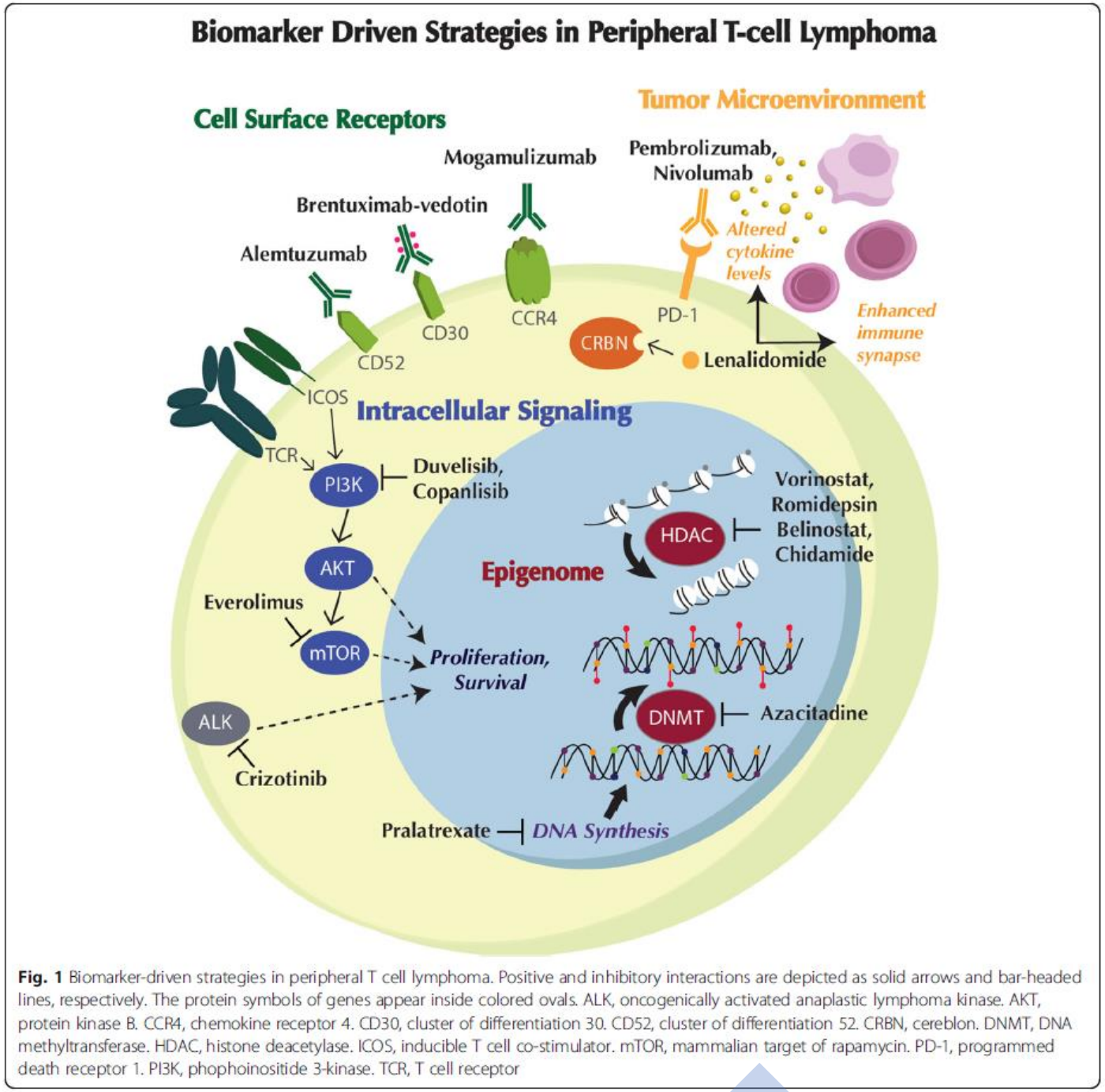


Fig. 1 Biomarker-driven strategies in peripheral T cell lymphoma. Positive and inhibitory interactions are depicted as solid arrows and bar-headed lines, respectively. The protein symbols of genes appear inside colored ovals. ALK, oncogenically activated anaplastic lymphoma kinase. AKT, protein kinase B. CCR4, chemokine receptor 4. CD30, cluster of differentiation 30. CD52, cluster of differentiation 52. CRBN, cereblon. DNMT, DNA methyltransferase. HDAC, histone deacetylase. ICOS, inducible T cell co-stimulator. mTOR, mammalian target of rapamycin. PD-1, programmed death receptor 1. PI3K, phophoinositide 3-kinase. TCR, T cell receptor

Mulvey and Ruan. Journal of hematology and oncology 2020

FDA approved:

Belgium:

- Only Brentuximab vedotin

In R/R ALCL

2. How to obtain a remission?

FDA

Table 1
Summary of clinical trial data for recently approved drugs for anaplastic large cell lymphoma

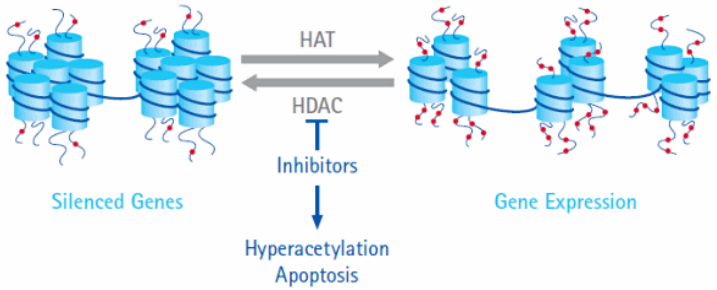
	All PTCLs	ALK + ALCL	ALK − ALCL	ALCL	Refs.
Brentuximab Vedotin					
ORR	—	81%	88%	86%	Pro et al,[34] 2012;
CR rate	—	69%	52%	57%	Pro et al,[35] 2015
Median PFS	—	25.5 mo	20.0 mo	20.0 mo	
Median OS	—	—	—	4-y: 64%	
Pralatrexate					
ORR	29%	—	—	35%	O'Connor et al,[39] 2011
CR rate	11%	—	—	—	
Median PFS	3.5 mo	—	—	—	
Median OS	14.5 mo	—	—	—	
Romidepsin					
ORR	25%	—	24%	—	Coiffier et al,[40] 2012;
CR rate	15%	—	19%	—	Coiffier et al,[41] 2014
Median PFS	4.0 mo	—	—	—	
Median OS	11.3 mo	—	—	—	
Belinostat					
ORR	26%	0%	15%	—	O'Connor et al,[43] 2015
CR rate	11%	—	—	—	
Median PFS	1.6 mo	—	—	—	
Median OS	7.9 mo	—	—	—	

NB: CD30+ PTCLs not ALCL: ORR: 33-54%

New antifolate

HDACi

HDACi



Chihara D and Fanale M, Hematol Oncol Clin N Am 2017

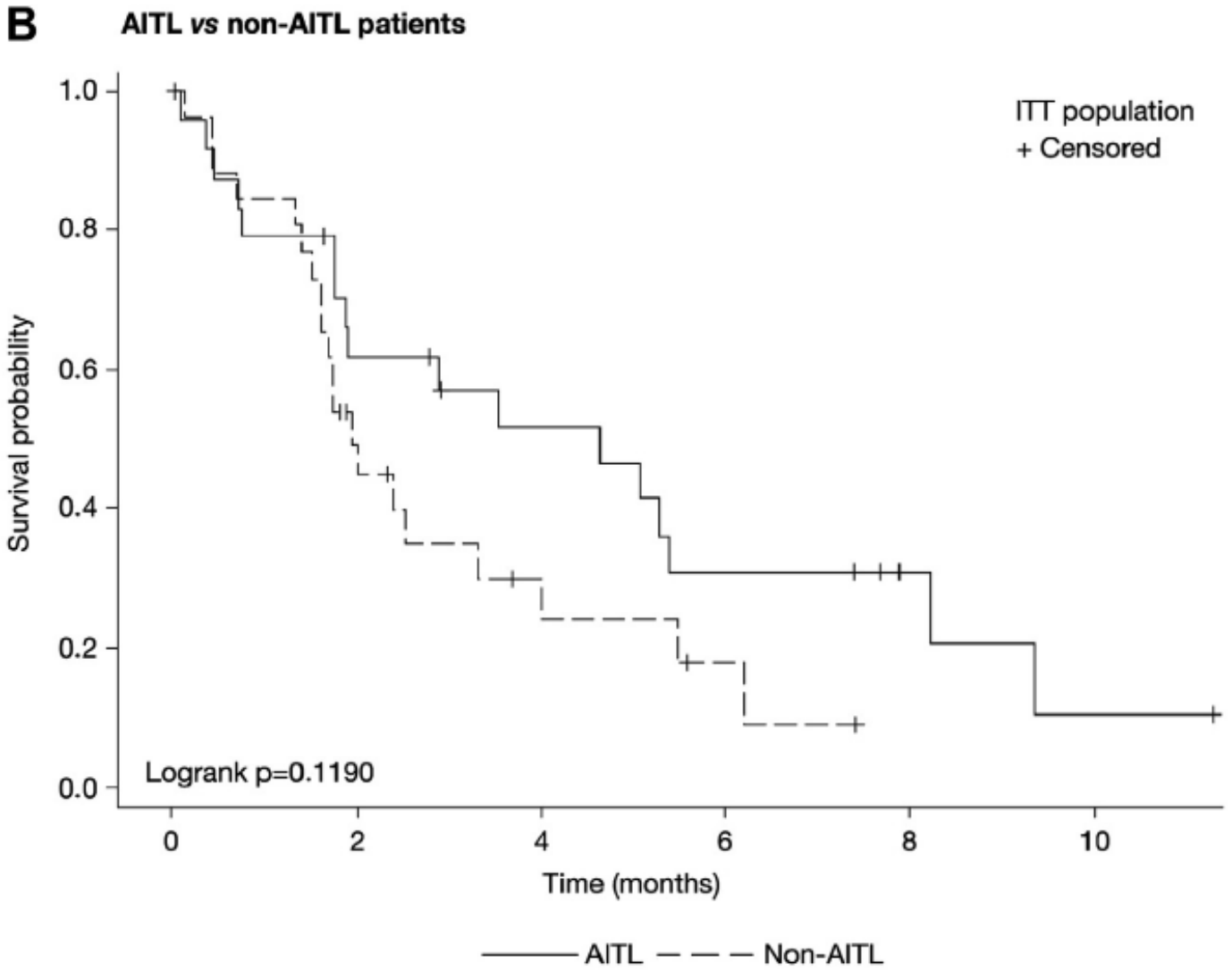
az sint-jan
brugge - oostende av

Lenalidomide

In conclusion, lenalidomide has demonstrable single-agent activity in heavily pre-treated patients with poor prognostic PTCL, but comparison with competitor agents suggests further evaluation should be particularly focused in patients with AITL

ORR 22%, 11% CR mostly in AITL

Expect Trial, Morshhauser F, et al, Eur J of Cancer 2013



	No. of patients	Event	Censored	Median survival	(95% CI)
AITL	26	17 (65%)	9 (35%)	4.6	(1.8–8.2)
Non-AITL	28	20 (71%)	8 (29%)	1.9	(1.6–3.3)

Fig. 1. Kaplan–Meier estimates of PFS with lenalidomide in patients with PTCL.

Brentuximab + gemcitabine (TOTAL trial)

Figure 1A (n=71)

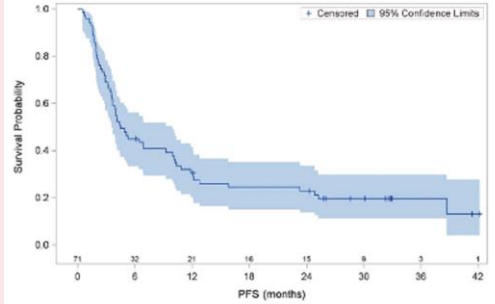


Figure 1B (non ALCL pts)

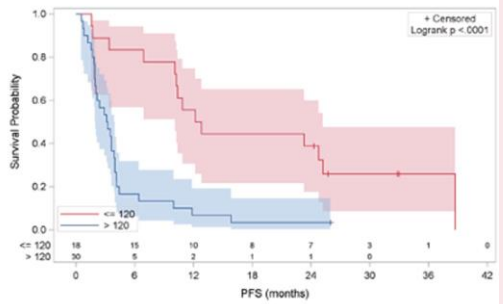


Table 1 CD30 evaluation in non-ALCL pts

	Baseline serum sCD30 (ELISA) (n=48)		p	CD30 on tumor cells (IHC) (n=44)		p
	≤120 ng/mL	>120 ng/mL		≤10%	>10%	
n	18	30		13	31	
ORR	77.8%	13.3%	*<0.001*	46.2%	38.7%	*0.65*
PFS	12.5 m (10.1-25.2)	3.2 m (2.0-4.0)	*<0.001*	4.1 m (1.7-10.3)	4.1 m (3.1-10.9)	*0.53*
OS	29.6 m (13.4-39.3)	7.3 m (3.9-10.8)	*<0.001*	9.0 m (5.0-25.5)	13.4 m (7.3-29.6)	*0.44*
n	14	4		6	12	
DOR	24.0 m (10.4-38.7)	10.9 m (6.4-15.8)	*0.019*	10.3 m (4.9-NA)	17.7m (10-25.2)	*0.32*

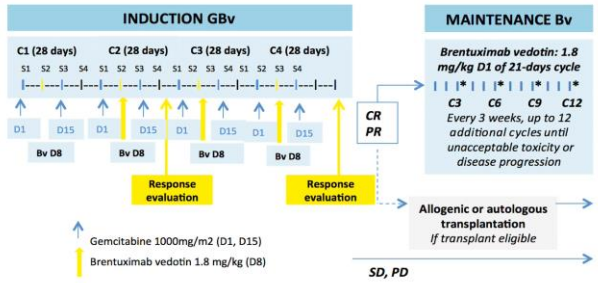
NA : non achieved, m : months

we did not find a clear impact of CD30 expression on tumor cells, however we demonstrate that baseline serum sCD30 at treatment initiation was strongly correlated with both response and outcome.

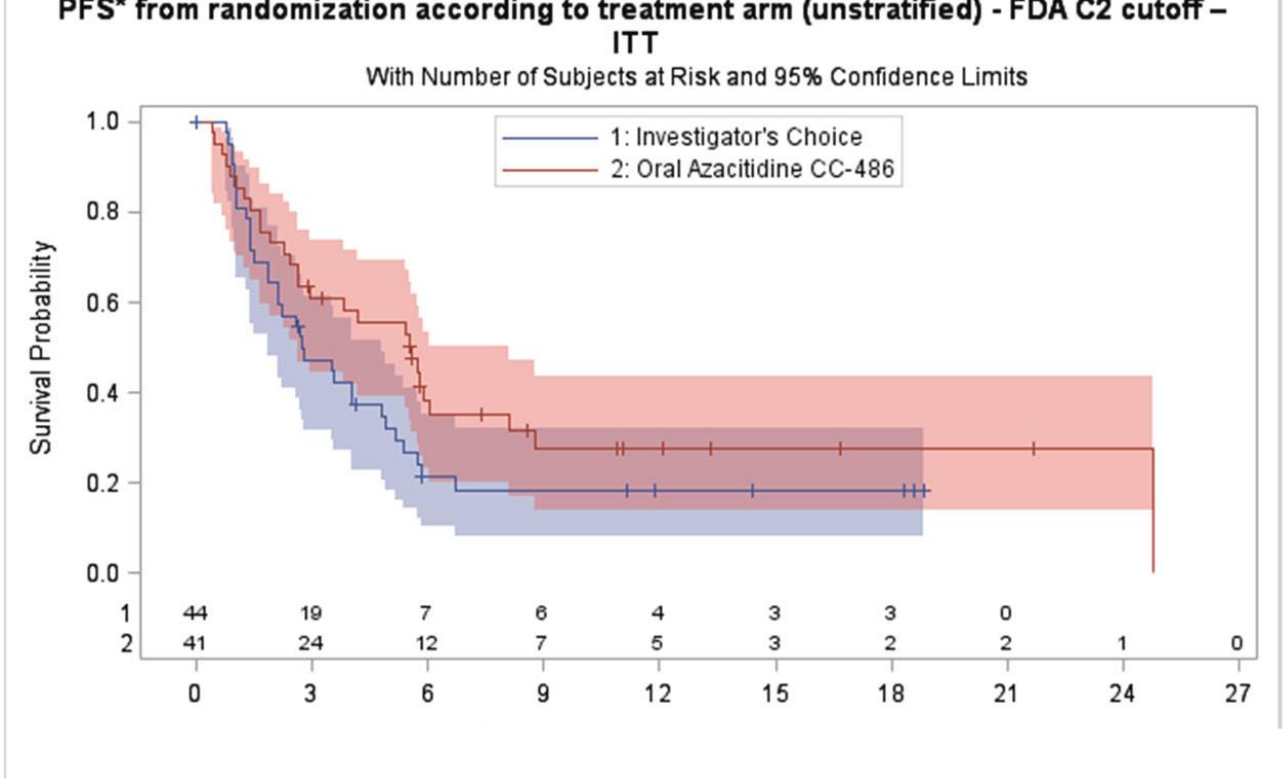
Conclusion

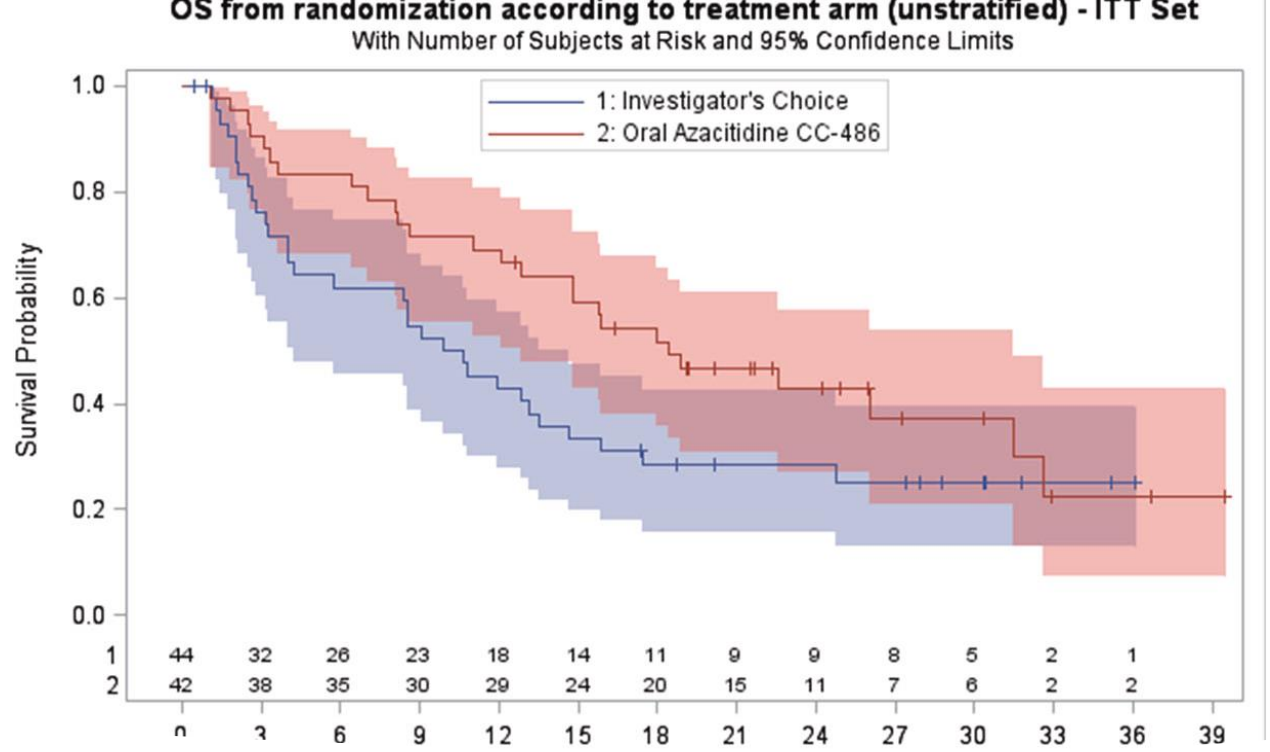
- The addition of Brentuximab vedotin to Gemcitabine produced an ORR of 47.9% with 19.7% CR in relapsed or refractory CD30+ PTCL.
- This combination was generally well tolerated.
- Initial data on OS and duration of response are encouraging for this patient population but PFS remains short and a longer FU is mandatory.

Study objective and methods



O. Tournilhac et al. Blood (2022) 140 (Supplement 1): 2302–2305.





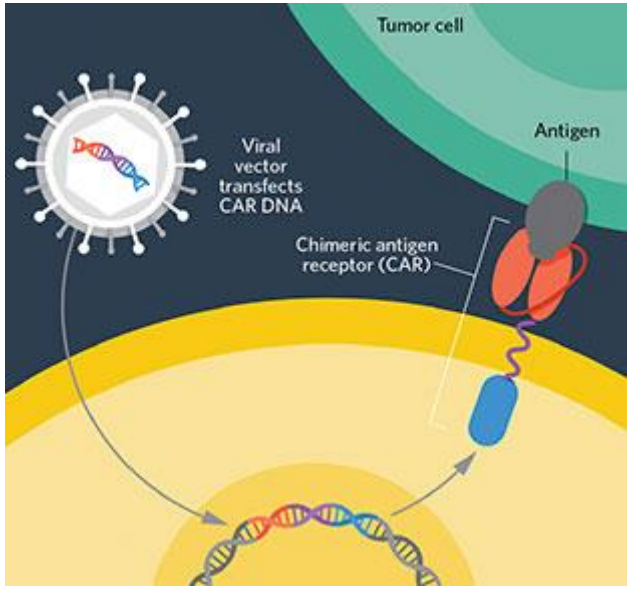
Oracle trial

CONCLUSION: The study did not meet the primary endpoint, likely because of a lack of power. However, CC-486 was associated with prolonged survival and a favorable safety profile. These results support the development of combinations based on 5-azacytidine in the treatment of TFH lymphomas

Jehan Dupuis,Kunihiro Tsukasaki,Emmanuel Bachy,Franck Morschhauser,Guillaume Cartron,Noriko Fukuhara,Nicolas Daguindau,René-Olivier Casasnovas,Sylvia Snauwaert,Rémy Gressin,Christopher P. Fox,Francesco Annibale d'Amore,Philipp B. Staber,Argyrios Gkasiamis,Mitsufumi Nishio,Luc-Matthieu Fornecker,Marie-Helene Delfau,Nouhoum Sako,Sebastien Mule,Laurence De Leval,Philippe Gaulard,Francois Lemonnier, Oral Azacytidine in Patients with Relapsed/Refractory Angioimmunoblastic T-Cell Lymphoma: Final Analysis of the Oracle Phase III Study, Blood, 2022, Figure 1

Others

- ITK targeting (BTK homologue)
- JAK/STAT targeting (ruxolitinib)
- SYK inhibitors
- mTOR inhibitors
- (PI3K-inhibitors: duvelisib, tenalisib,…)
- Anti-CD30 CAR-T cells (phase II trial in R/R PTCL ongoing)
- AUTO4, TRBC1-Targeting CAR T-Cell Therapy (first in human trials ongoing)
- (Anti-CD25 antibody conjugate (ADCT-301))
- Anti-CD47 antibodies
- EZH1/2 inhibitors
- IDH2 inhibitors
- CD38 mAb (ENKL)
- BCL2-inhibitor (TFH PTCL)
- AMF13: BiTE: CD30-CD16A
- Combination of romidepsin and azacitidine
- Checkpoint inhibitors
- …



Anti-CD30 CAR-T cel

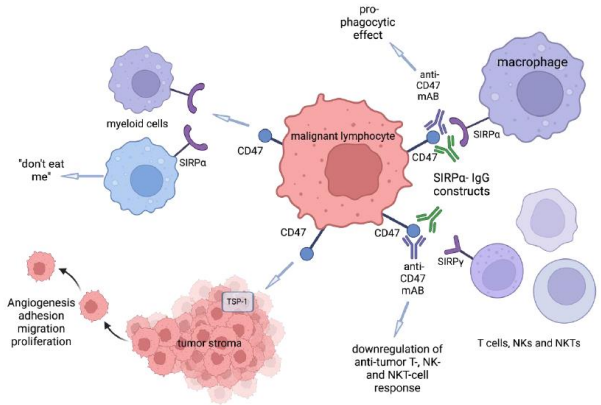


Figure 1. Anti-CD47 mAb boosts tumor phagocytosis by macrophages but dampens the anti-tumor T-cell response due to nonspecific blockage of SIRPα and SIRPγ.

Targeting the CD47-SIRPα axis

Xiao A et al. Cells 2022

Checkpoint-inhibitors

- **Monotherapy** seems to be associated with "hyperprogression".
- Use : "only recommended in the setting of clinical trial"
- Best responses in ENKL

- **Combination trials ongoing**:
  - NIVEAU trial (LYSARC): Gemcitabine/oxaliplatine (GEMOX) + Nivolumab: ongoing
    - No hyperprogression, well tolerated. Encouraging results/but preliminary (ASH 2020, Houot et al. Abstract 2081)
  - Embolden trial: pembro + epigenetic therapy (ASH 2022, Roberts et al. Abstract 4242): n = 15; safe and active
  - Pembrolizumab + romidepsin: Phase II: 2 hyperprogressions, n= 20, ORR 50%: encouraging but preliminary

Table 1. Ongoing trials of PD-1/PD-L1 inhibition in TCL

Study name	Study no.	Study phase
Study of pembrolizumab in patients with early-stage NK/T-cell Lymphoma, nasal type	NCT03728972	2
Pembrolizumab and pralatrexate in treating patients with relapsed or refractory peripheral T-cell lymphomas	NCT03598998	1/2
Pembrolizumab in relapsed or refractory extranodal NK/T-cell lymphoma, nasal type and EBV-associated diffuse large B-cell lymphomas	NCT03586024	1/2
A trial assessing the effect of pembrolizumab combined with radiotherapy in patients with relapsed, refractory, specified stages of cutaneous T-cell lymphoma (CTCL) mycosis fungoides (MF)/Sézary syndrome (SS) (PORT)	NCT03385226	2
Study of pembrolizumab (MK-3475) in combination with romidepsin	NCT03278782	1/2
Study of pembrolizumab combined with decitabine and pralatrexate in PTCL and CTCL	NCT03240211	1
Pembrolizumab and external beam radiation therapy in treating patients with relapsed or refractory non-Hodgkin lymphoma	NCT03210662	2
Phase 2 trial of nivolumab for pediatric and adult relapsing/ refractory ALK^+ anaplastic large cell lymphoma, for evaluation of response in patients with progressive disease (cohort 1) or as consolidative immunotherapy in patients in complete remission after relapse (cohort 2) (NIVO-ALCL)	NCT03703050	2
Nivolumab with standard of care chemotherapy for peripheral T-cell lymphomas	NCT03586999	1/2
Durvalumab in different combinations with pralatrexate, romidepsin and oral 5-azacitidine for lymphoma	NCT03161223	1/2
Durvalumab with or without lenalidomide in treating patients with relapsed or refractory cutaneous or peripheral T-cell lymphoma	NCT03011814	1/2
PARCT: Trial of atezolizumab in relapsed/refractory cutaneous T-cell lymphoma (CTCL) (PARCT)	NCT03357224	2
Avelumab in relapsed and refractory peripheral T-cell lymphoma (AVAIL-T)	NCT03046953	2

ASH 2020, Houot et al. Abstract 2081; ASH 2020, Iyer et al. Abstract 645; Neuwelt A. et al. Blood advances 2020

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

T-Cell Lymphomas, Version 2.2022

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