Beyond B-Cell Thinking: Managing Peripheral & Cutaneous T-Cell Lymphomas

Jonathan Schatz, MD
Professor
Division of Hematology
Department of Medicine

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

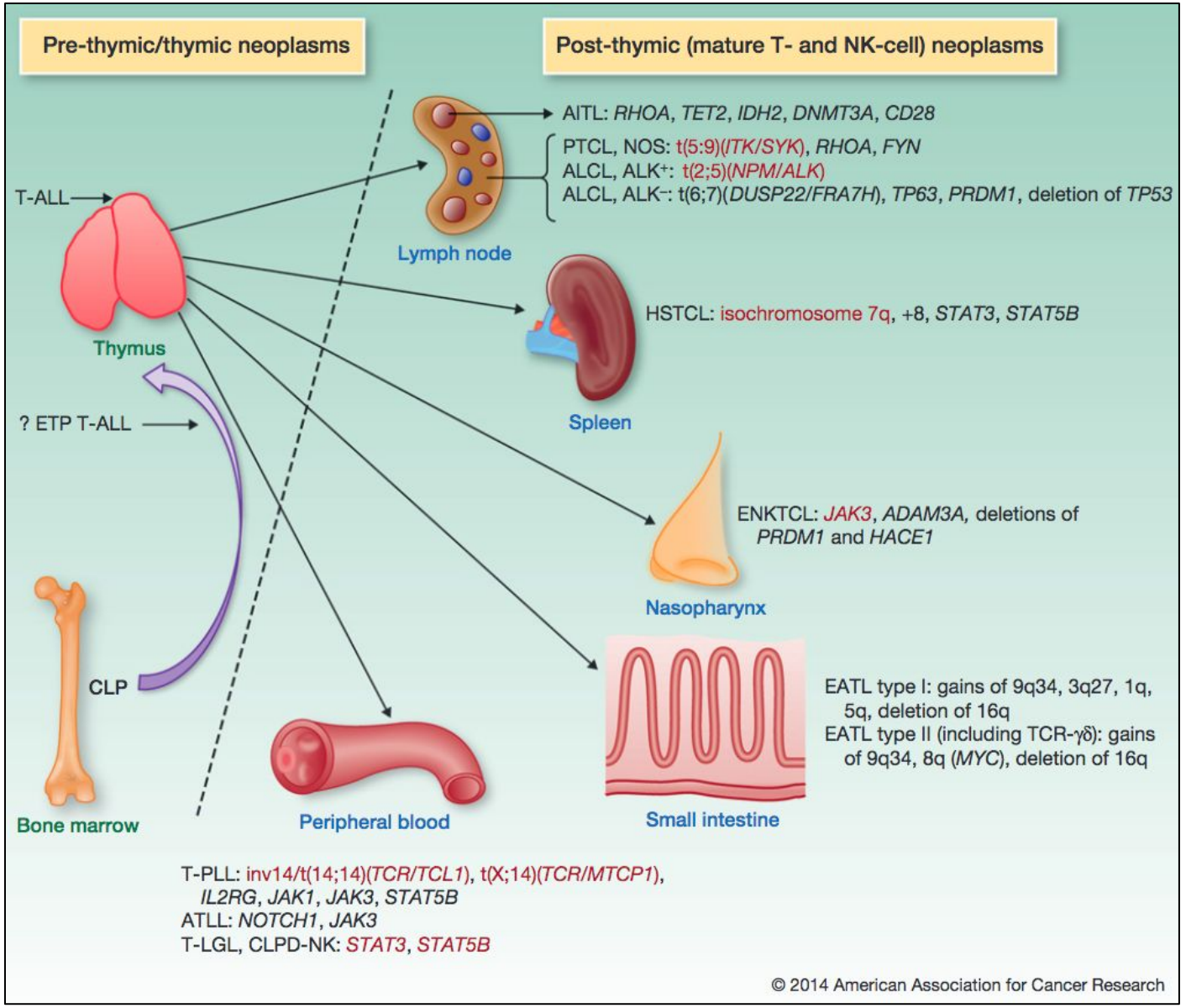
NCI Designated Cancer Center

BEST HOSPITALS U.S.News & WORLD REPORT CANCER 2026-2027

CANCER CENTER of EXCELLENCE Florida HEALTH

Overview

- Mature T-Cell Lymphomas Origin and Biology
- Nodal PTCL: Types and Management
- CTCL: MF/SS Management Across the Stages
- Post-Thymic T Leukemias: T-PLL, T-LGL
- ENKTCL



O'Connor *et al*., Clin Cancer Res, 2014

Post-Thymic T-Cell Lymphoma: 27 established or provisional diagnoses

MATURE T-AND NK-NEOPLASMS

Leukemias
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*

Viral: HTLV-1/2
- Adult T-cell leukemia/lymphoma

- EBV-positive T/NK LPD of childhood*
  - Hydroa vacciniforme LPD
    - Classic
    - Systemic
  - Severe mosquito bite allergy
  - Chronic active EBV disease (T and NK-cell phenotype)
  - Systemic EBV-positive T-cell lymphoma of childhood

Viral: EBV
- Extranodal NK/T-cell lymphoma, nasal type
- Aggressive NK cell leukemia
- *Primary nodal EBV-positive T/NK-cell lymphoma**

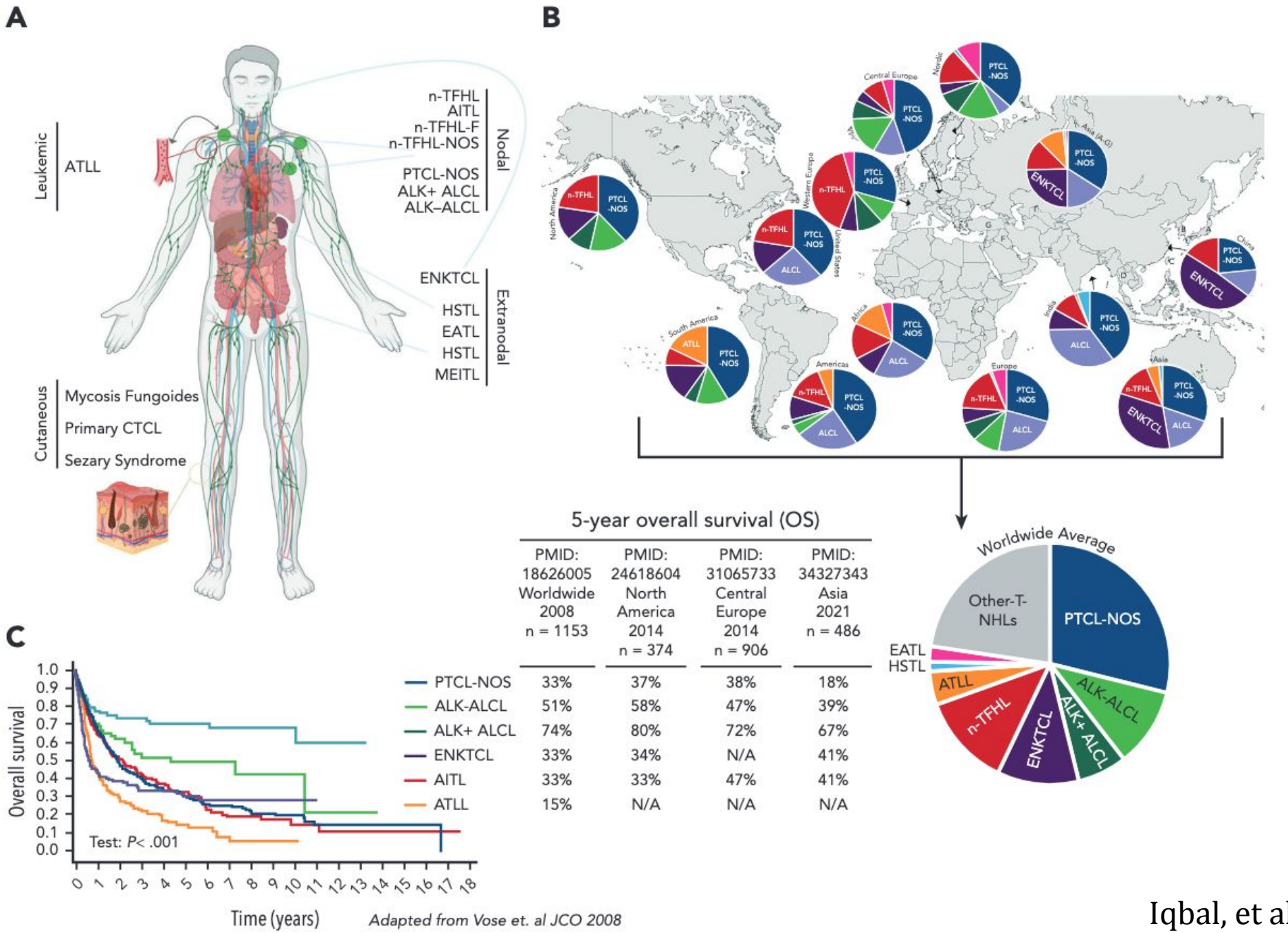
GI Tract
- Enteropathy-associated T-cell lymphoma
  - Type II refractory celiac disease*
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Intestinal T-cell lymphoma, NOS
- Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract*
- Indolent NK cell lymphoproliferative disorder of the gastrointestinal tract*
- Hepatosplenic T-cell lymphoma

CTCL
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder*
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma

Nodal PTCL
- Peripheral T-cell lymphoma, NOS
- Follicular helper T-cell lymphoma*
  - Follicular helper T-cell lymphoma, angioimmunoblastic type (Angioimmunoblastic T-cell lymphoma)
  - Follicular helper T-cell lymphoma, follicular type
  - Follicular helper T-cell lymphoma, NOS
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative
- Breast implant-associated anaplastic large cell lymphoma

International Consensus Guidelines, Campo et al., *Blood*, 2022

WHO 5th Edition, Alaggio et al., *Leumemia*, 2022

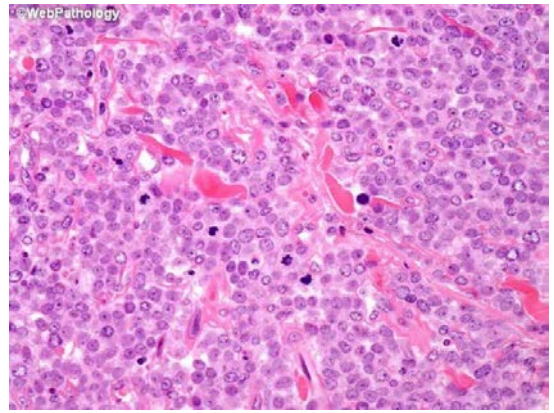


	PMID: 18626005 Worldwide 2008 n = 1153	PMID: 24618604 North America 2014 n = 374	PMID: 31065733 Central Europe 2014 n = 906	PMID: 34327343 Asia 2021 n = 486
PTCL-NOS	33%	37%	38%	18%
ALK-ALCL	51%	58%	47%	39%
ALK+ ALCL	74%	80%	72%	67%
ENKTCL	33%	34%	N/A	41%
AITL	33%	33%	47%	41%
ATLL	15%	N/A	N/A	N/A

Iqbal, et al., *Blood*, 2024

PTCL Types with Uniform Frontline Management Guidelines

- PTCL-NOS
  - GATA3
  - TBX21
- nTFHL
  - Angioimmunoblastic T-Cell Lymphoma (AITL)
  - Follicular helper T-Cell Lymphoma, Follicular Type
  - Follicular helper T-cell Lymphoma-NOS
- Systemic ALCL
  - ALK-Positive
  - ALK-Negative
- Aggressive Intestinal TCLs (Celiac Disease-Associated)
  - Enteropathy Accociated T-Cell Lymphoma (EATL)
  - Monomorphic Epitheliotrphic Intestinal T-Cell Lymphoma (MEITL)

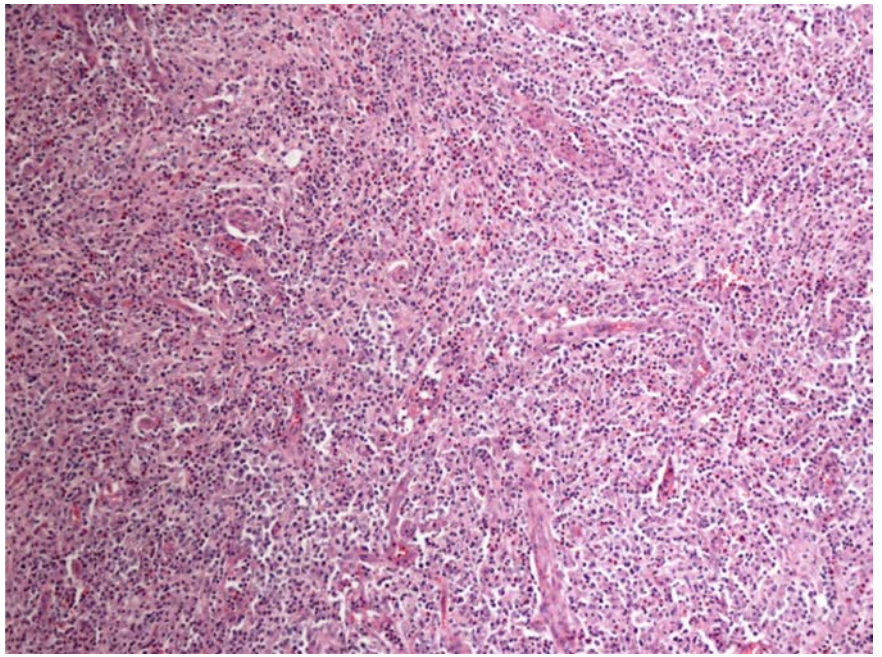


PTCL-NOS

NCCN Clinical Practice Guidelines in Oncology, T-Cell Lymphomas, Version 2.2026

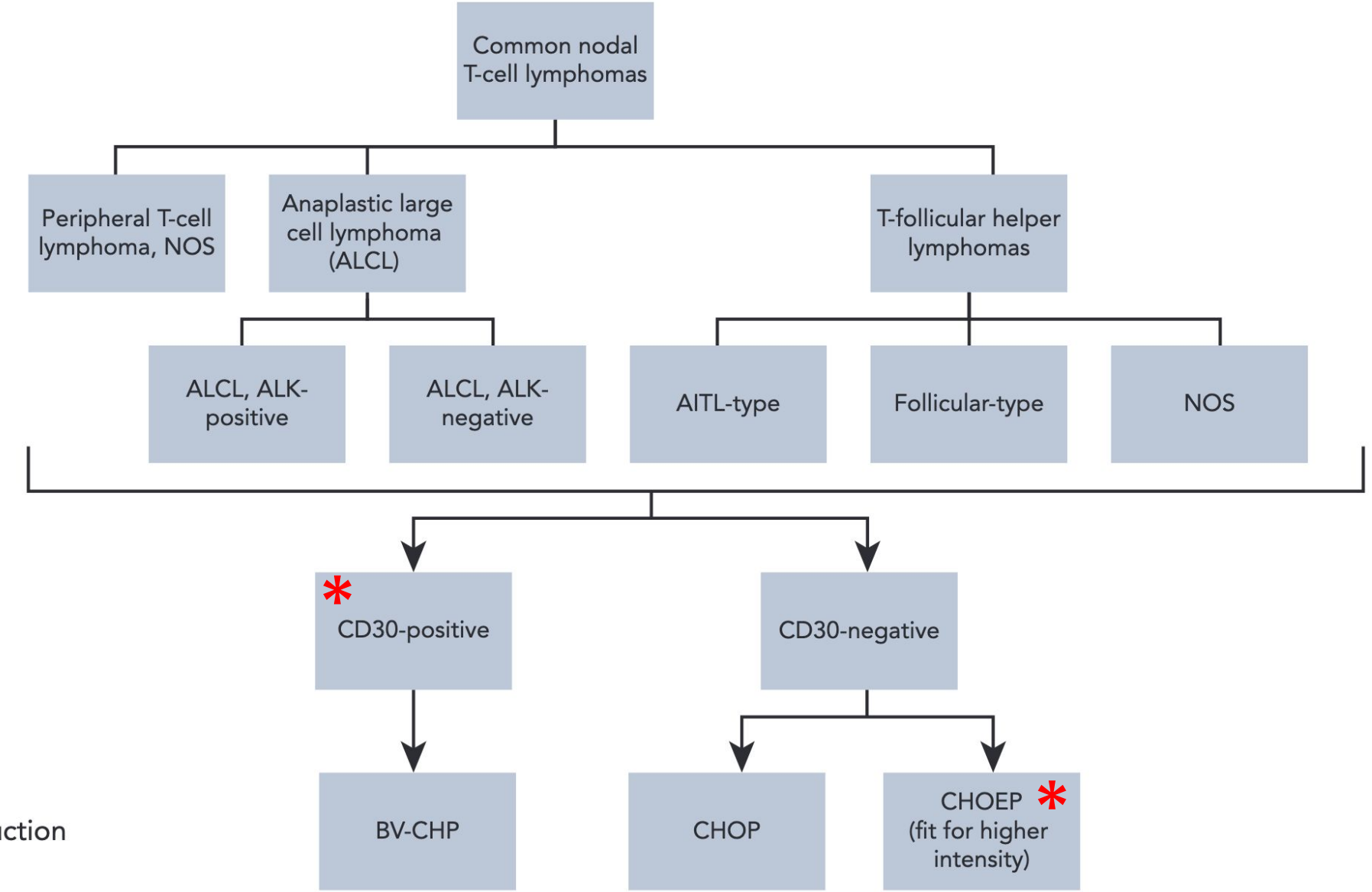
Angioimmunoblastic T-Cell Lymphoma (AITL)

- Derived from T follicular helper (TFH) cells
  - Markers: PD1, **CD10, BCL6**, CXCL13, ICOS, SAP, CCR5
  - T-Clonality is key!
- Recurrent Mutations: *TET2, IDH2, DNMT3A, RHOA* (G17V), *CD28*
- B-cell blasts (usually EBV+) may resemble HRS cells, may transform to B-cell lymphomas



- Common systemic symptoms, autoimmune cytopenias, skin involvement

Lunning and Vose, *Blood*, 2017



Moskowitz et al., *Blood*, 2022

Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial

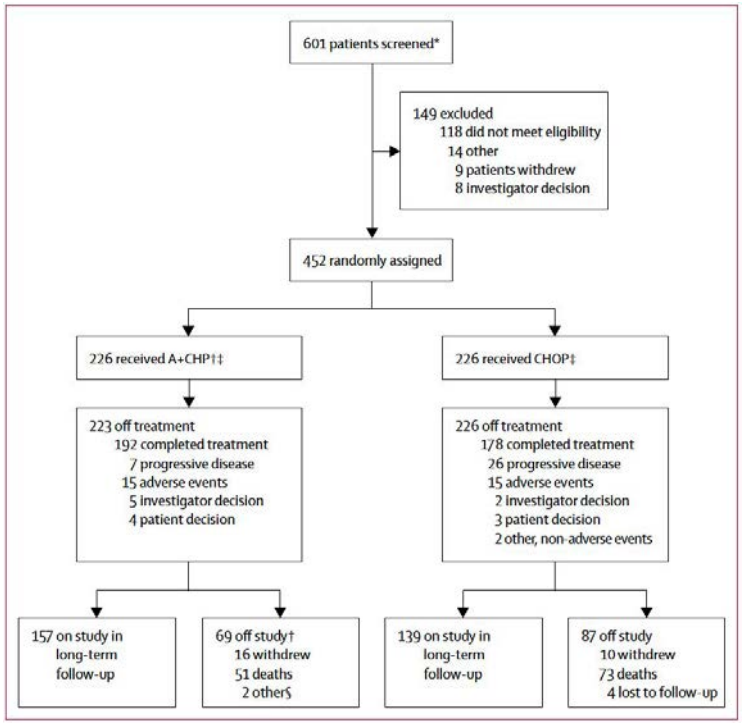
Steven Horwitz, Owen A O'Connor, Barbara Pro*, Tim Illidge*, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper*, for the ECHELON-2 Study Group†*

Summary

Background Based on the encouraging activity and manageable safety profile observed in a phase 1 study, the ECHELON-2 trial was initiated to compare the efficacy and safety of brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (A+CHP) versus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of CD30-positive peripheral T-cell lymphomas.

Lancet 2019; 393: 229–40

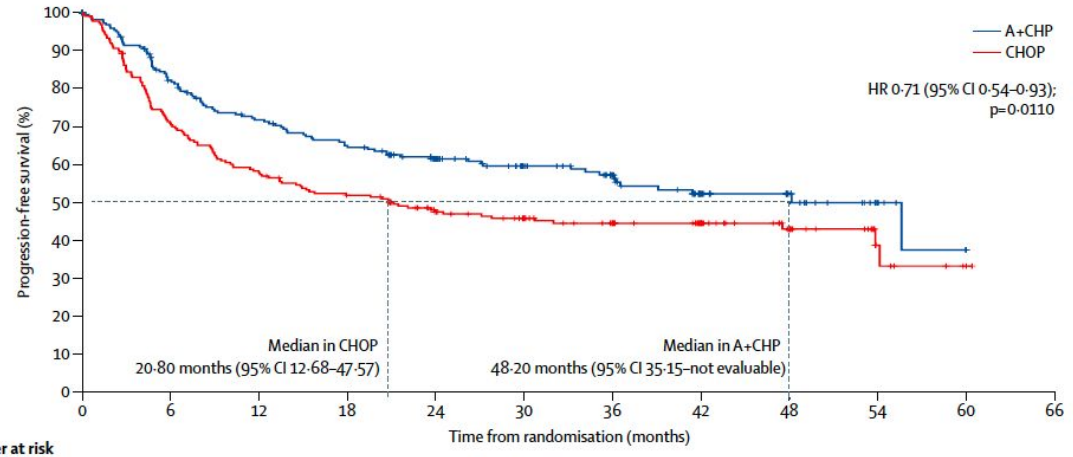
Published Online
December 4, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32984-2



By local assessment, tissue from the diagnostic biopsy was confirmed for CD30 positivity by immunohistochemistry (anti-CD30 BerH2 antibody). The 3 following criteria must have been met to declare CD30 positivity:

1. CD30 detected in 10% or greater of neoplastic cells (in cases where enumeration of neoplastic cells was not possible, total lymphocytes may have been used).
2. CD30 staining at any intensity above background.
3. Membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.

A

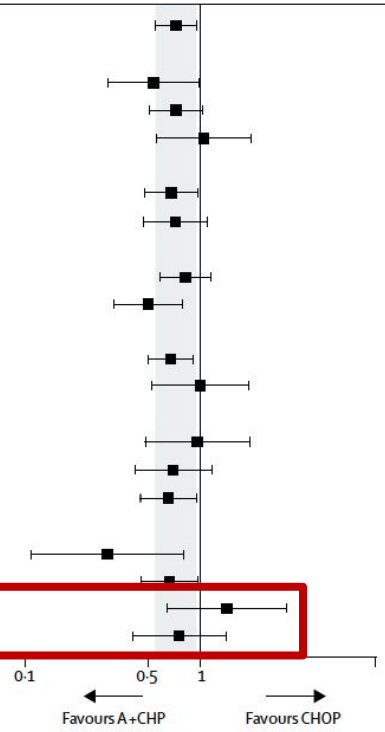


Number at risk (number censored)

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

B

	Event/N		HR (95% CI)
	A+CHP	CHOP	
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)
Sex			
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			
1–2	15/42	19/46	0·95 (0·48–1·88)
3	29/57	35/67	0·69 (0·42–1·14)
4	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)



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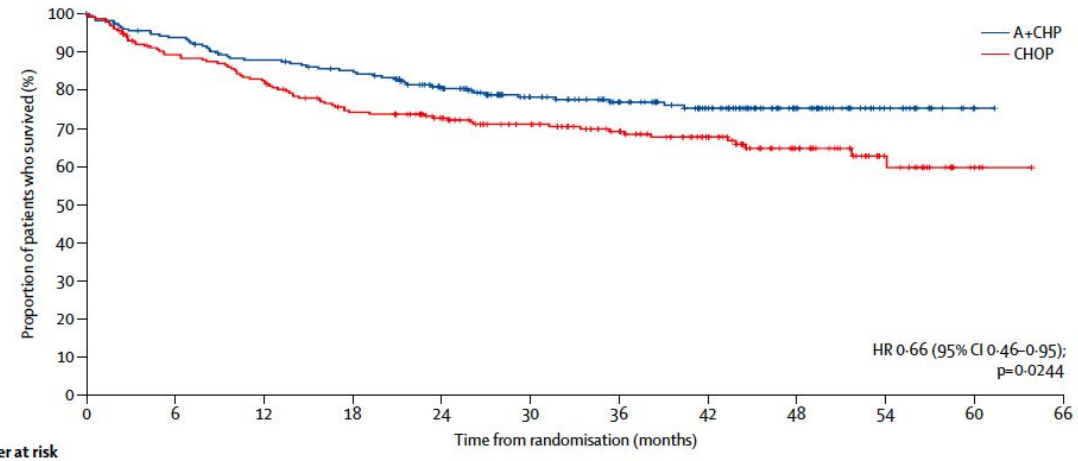
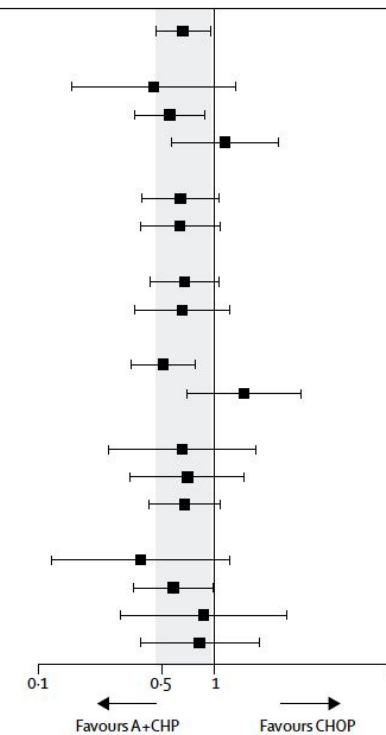


Number at risk (number censored)

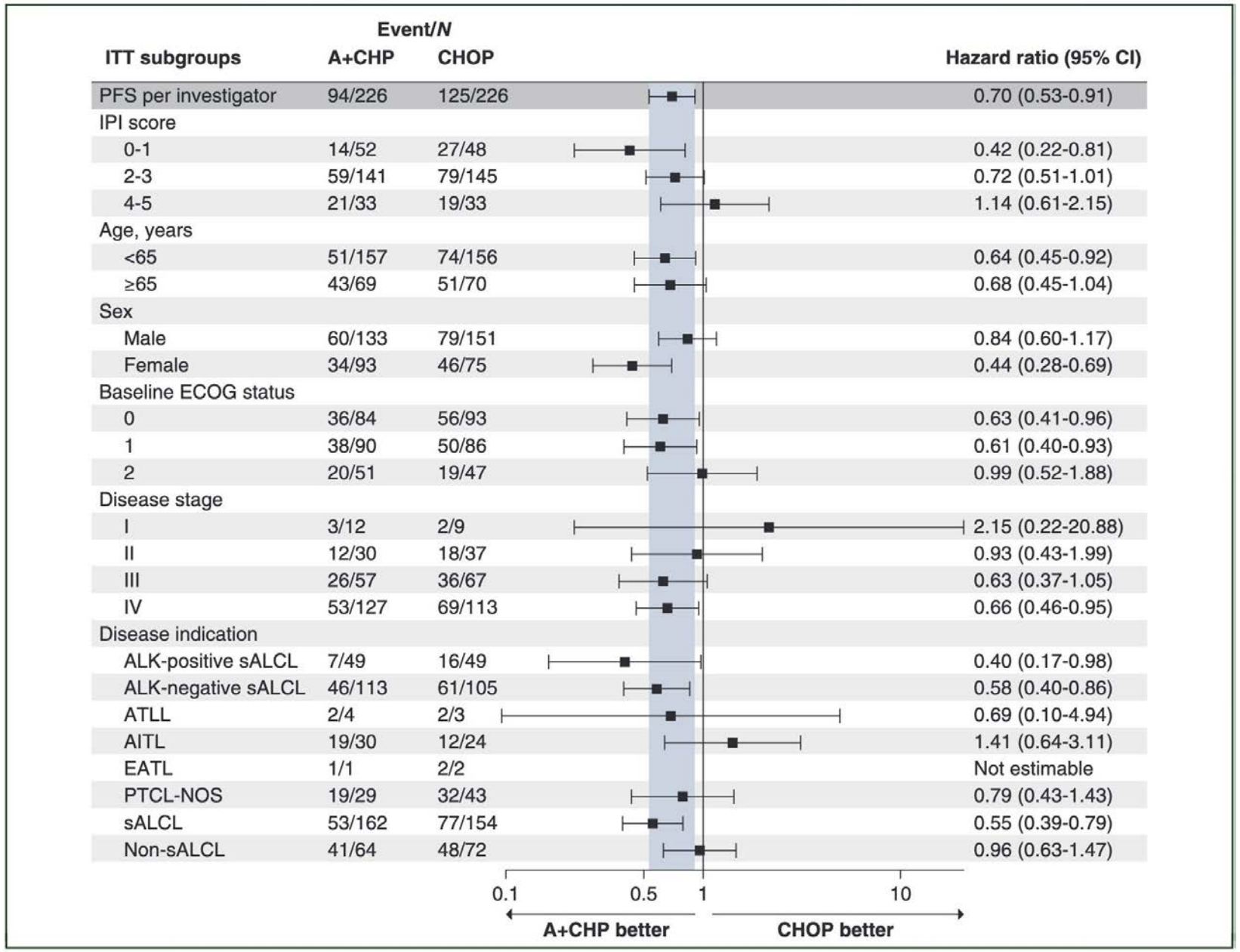
A+CHP	226 (0)	208 (14)	193 (27)	184 (33)	159 (42)	128 (47)	108 (49)	83 (51)	45 (51)	20 (51)	4 (51)	0 (51)
CHOP	226 (0)	196 (24)	181 (39)	158 (57)	140 (60)	121 (63)	103 (66)	79 (68)	46 (71)	22 (72)	4 (73)	0 (73)

B

	Event/N		HR (95% CI)
	A+CHP	CHOP	
Overall	51/226	73/226	0·66 (0·46–0·95)
IPI Score			
0–1	5/52	10/48	0·46 (0·16–1·33)
2–3	29/141	48/145	0·56 (0·35–0·89)
4–5	17/33	15/33	1·15 (0·58–2·31)
Age			
<65 years	26/157	37/156	0·64 (0·39–1·06)
≥65 years	25/69	36/70	0·64 (0·38–1·08)
Sex			
Male	32/133	49/151	0·68 (0·43–1·06)
Female	19/93	24/75	0·66 (0·36–1·22)
Baseline ECOG status			
0–1	34/174	61/179	0·51 (0·34–0·78)
2	17/51	12/47	1·48 (0·70–3·11)
Disease stage			
1–2	7/42	12/46	0·66 (0·25–1·71)
3	13/57	17/67	0·71 (0·33–1·49)
4	31/127	44/113	0·68 (0·43–1·07)
Disease indication			
ALK-positive sALCL	4/49	10/49	0·38 (0·12–1·22)
ALK-negative sALCL	25/113	34/105	0·58 (0·35–0·98)
AITL	8/30	6/24	0·87 (0·29–2·58)
PTCL-NOS	11/29	20/43	0·83 (0·38–1·80)



ECHELON-2: Five Year Results

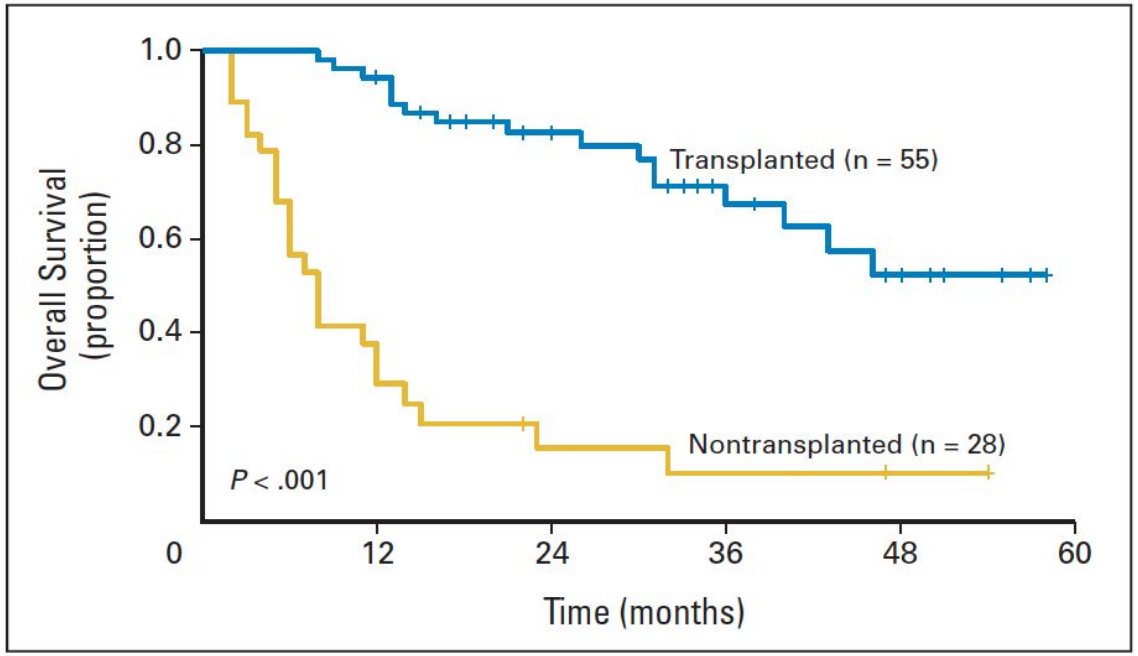


ITT subgroups	Event/*N* A+CHP	Event/*N* CHOP	Hazard ratio (95% CI)
PFS per investigator	94/226	125/226	0.70 (0.53-0.91)
IPI score			
0-1	14/52	27/48	0.42 (0.22-0.81)
2-3	59/141	79/145	0.72 (0.51-1.01)
4-5	21/33	19/33	1.14 (0.61-2.15)
Age, years			
<65	51/157	74/156	0.64 (0.45-0.92)
≥65	43/69	51/70	0.68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

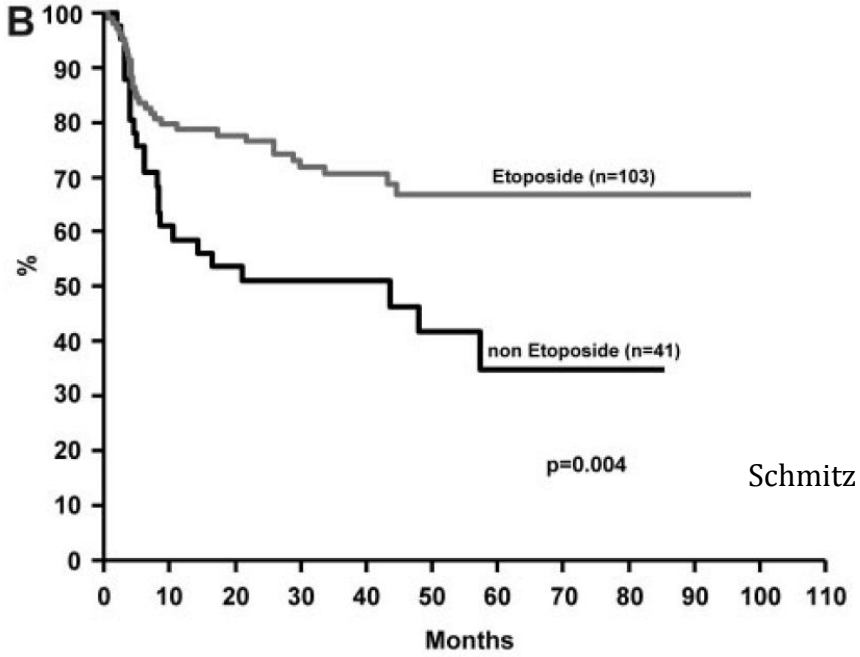
Horwitz et al., Annals of Oncology, 2022

CD30-Negative PTCL Frontline Treatment

- CHOP or CHOP-like is standard frontline: CHOEP, dose-adjusted EPOCH
- Retrospective Data Suggested Benefit of Auto Consolidation and to Include Etoposide



Reimber et al., *JCO*, 2009



Schmitz et al., *Blood*, 2010

EFS, Patients ≤ 60, n=144

VOLUME 30 · NUMBER 25 · SEPTEMBER 1 2012

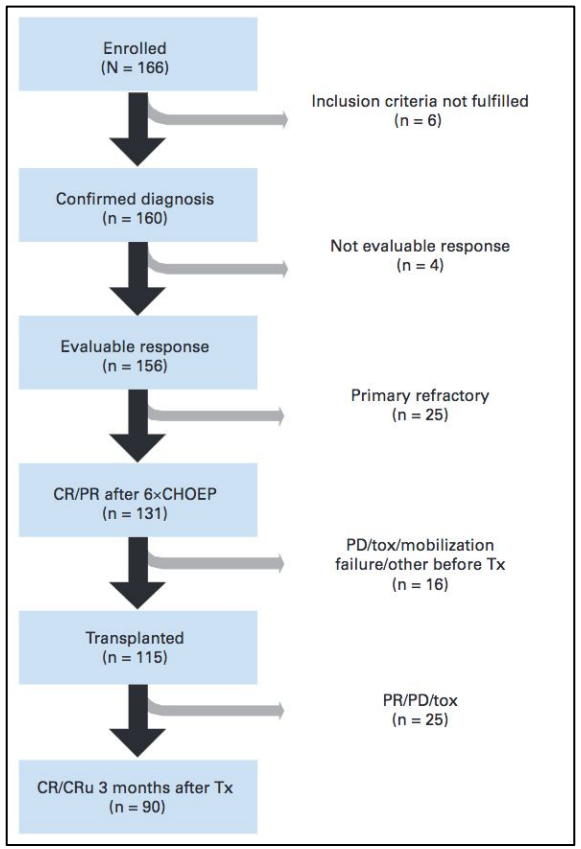
JOURNAL OF CLINICAL ONCOLOGY

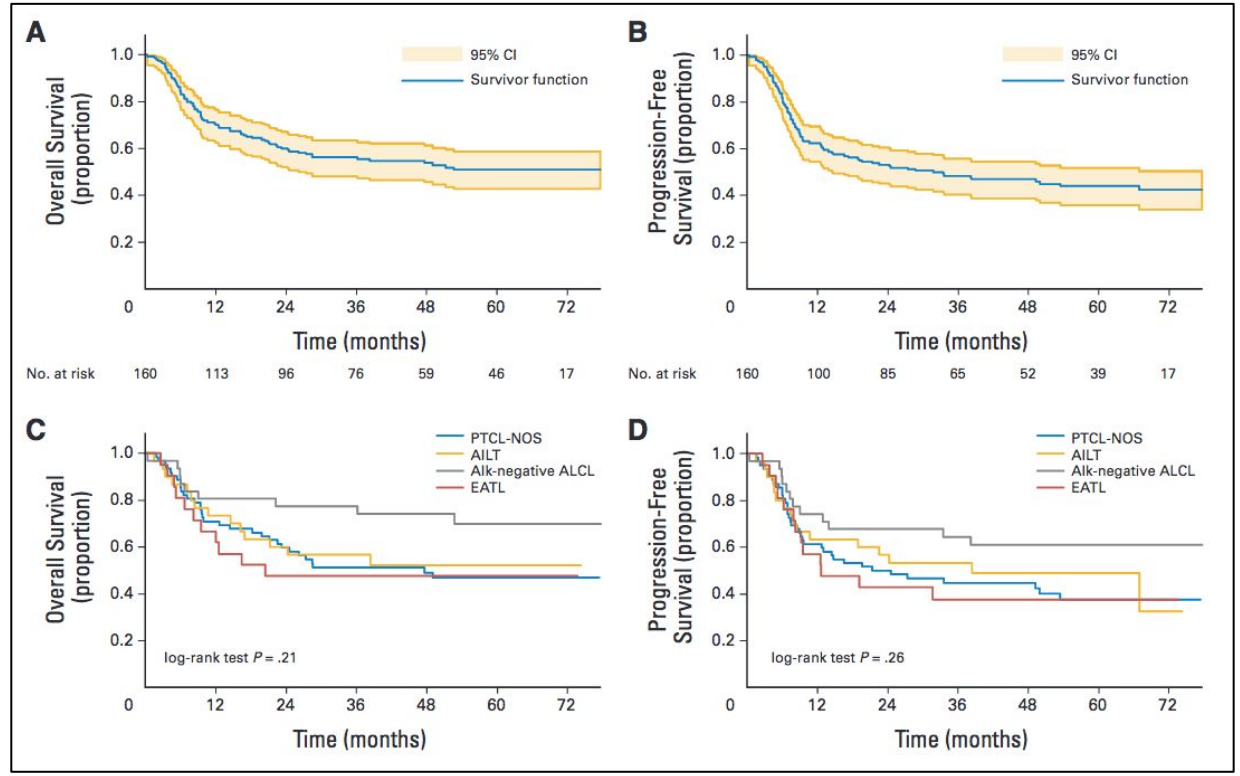
ORIGINAL REPORT

Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01

Francesco d'Amore, Thomas Relander, Grete F. Lauritzsen, Esa Jantunen, Hans Hagberg, Harald Anderson, Harald Holte, Anders Österborg, Mats Merup, Peter Brown, Outi Kuittinen, Martin Erlanson, Bjørn Østenstad, Unn-Merete Fagerli, Ole V. Gadeberg, Christer Sundström, Jan Delabie, Elisabeth Ralfkiaer, Martine Vornanen, and Helle E. Toldbod

Histologic subtype	
PTCL-NOS	62
ALK-negative ALCL	31
AILT	30
EATL	21
Panniculitis like	6
T/NK nasal type	5
Hepatosplenic	5





The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, International T-Cell Project

Monica Bellei,[1] Francine M. Foss,[2] Andrei R. Shustov,[3] Steven M. Horwitz,[4] Luigi Marcheselli,[1] Won Seog Kim,[5] Maria E. Cabrera,[6] Ivan Dlouhy,[7] Arnon Nagler,[8] Ranjana H. Advani,[9] Emanuela A. Pesce,[1] Young-Hyeh Ko,[10] Virginia Martinez,[6] Silvia Montoto,[11] Carlos Chiattone,[12] Alison Moskowitz,[4] Michele Spina,[13] Irene Biasoli,[14] Martina Manni[1] and Massimo Federico;[1] on behalf of the International T-cell Project Network

Haematologica, 2018

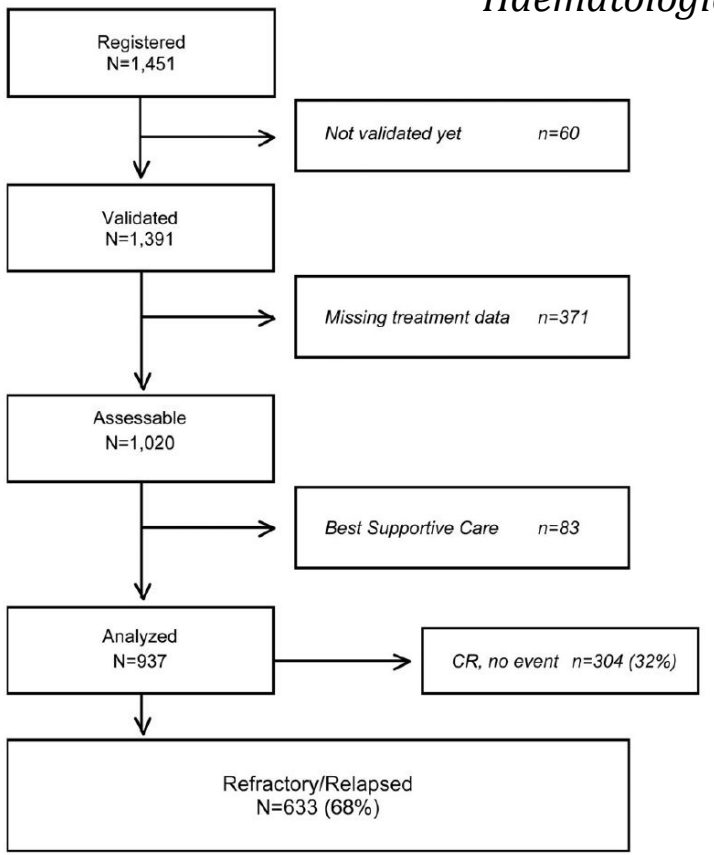
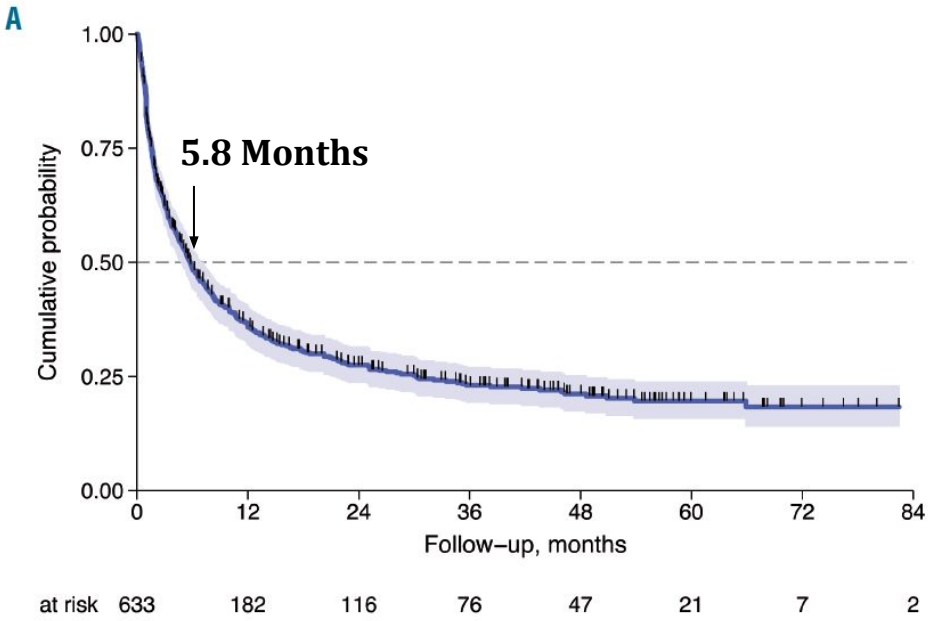
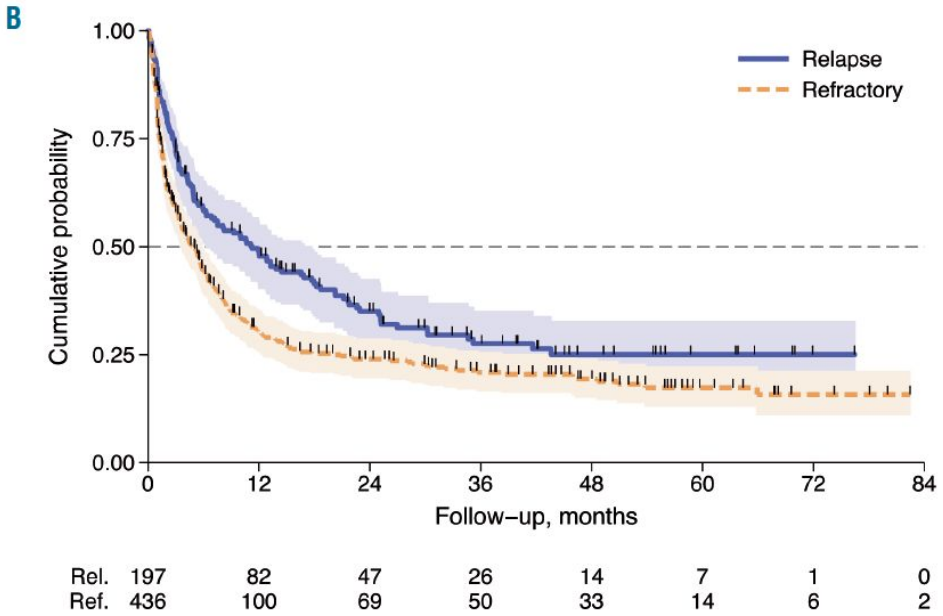


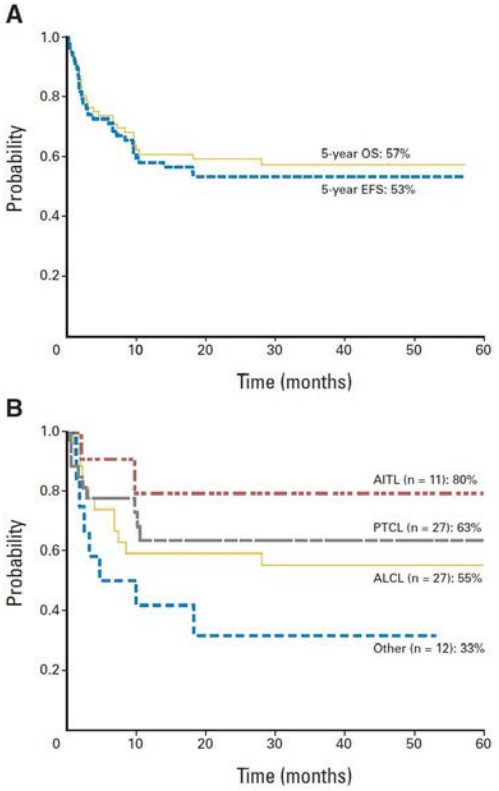
Figure 1. Flow chart of patients included in the analysis. CR: complete remission.





Allogeneic transplant in rel/ref PTCL

- French data: 77 Patients (NOS, AITL, ALCL ALK+/-, others)
- Dana Farber: 52 Patients (Nodal and skin)
- MSKCC: 34 Patients (All mature T and NK/T types)



Le Gouill et al, *JCO*, 2008

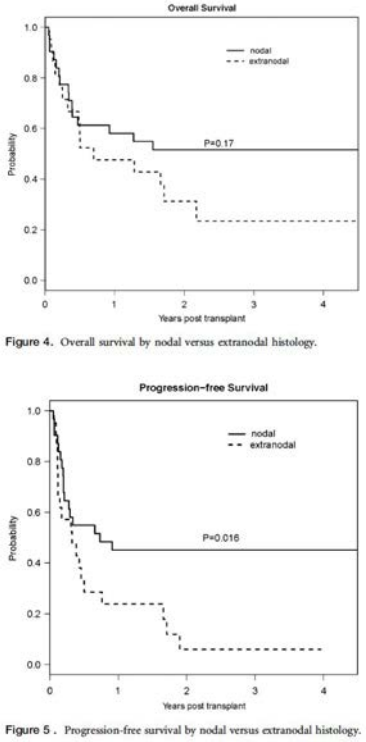


Figure 4. Overall survival by nodal versus extranodal histology.

Figure 5. Progression-free survival by nodal versus extranodal histology.

Jacobsen et al, *Ann Onc*, 2011

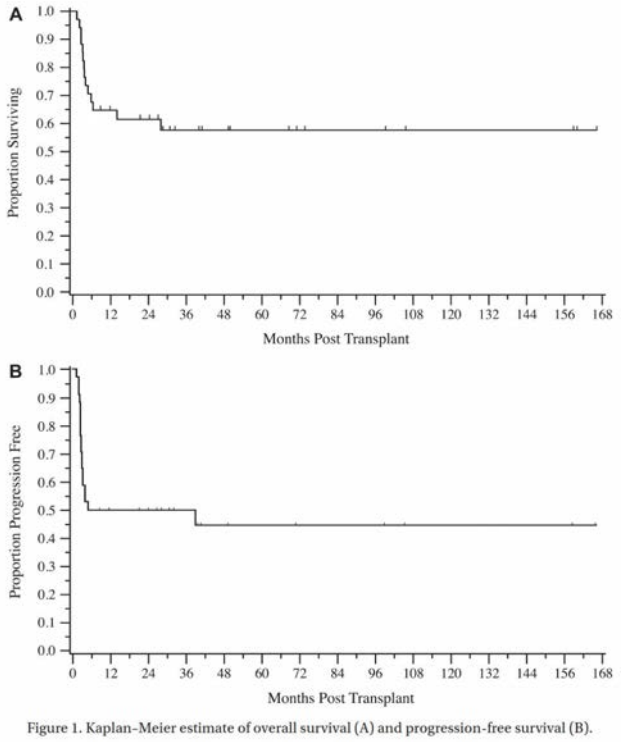


Figure 1. Kaplan–Meier estimate of overall survival (A) and progression-free survival (B).

Goldberg et al, *Leukemia & Lymphoma*, 2011

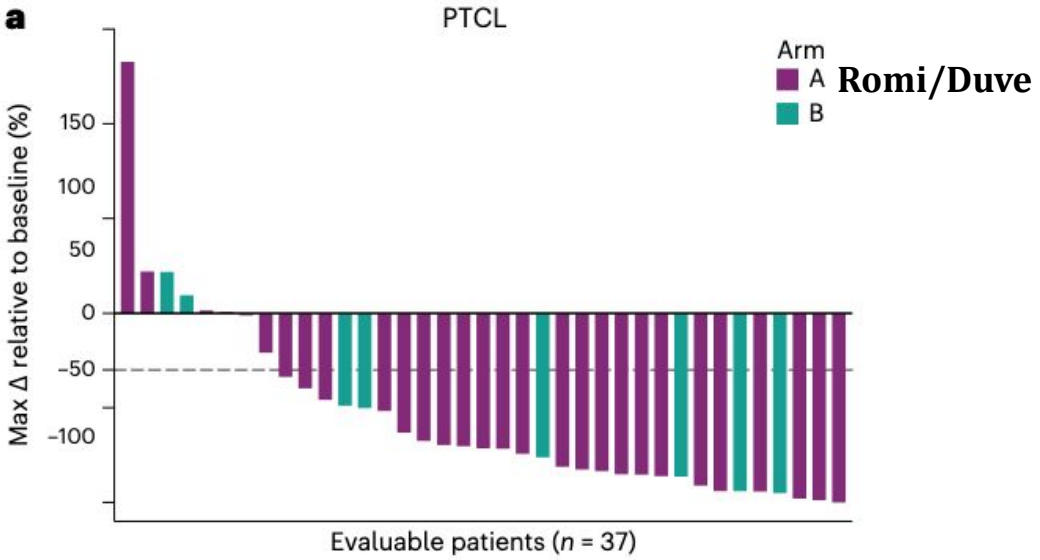
Rel/Ref PTCL: Transplant Eligible

- Salvage Chemo:
  - High-dose AraC containing plus platinum (DHAP/X, ESHAP/X)
  - ICE (Ifosfamide, Carboplatin, Etoposide)
  - Gemcitibine containing (GDP, GemOx)
- Single Agents (less used initially):
  - Labeled in PTCL: Belinostat, Pralatrexate
  - Off-Label: BV (in rel/ref), Duvelisib, Romidepsin (lost PTCL label)

Brink, et al., *Blood Advances*, 2024

Active Off-Label Combinations

Drug	Target	n	ORR, CR rate	PTCL, NOS	ALCL	AITL/TFH
Selected novel combinations						
Romidepsin plus azacytidine[25] Falchi et al., *Blood*, 2021	Epigenetic modification	13	ORR 54% CR 38%	NR	NR	n = 15* ORR 80% CR 60%
Romidepsin plus duvelisib[26] Horwitz et al., *Nature Medicine*, 2024	HDAC and PI3K-δ,γ	53	ORR 58% CR 42%	n = 19 ORR 53% CR 32%	n = 3 ORR 100% CR 67%	n = 19 ORR 68% CR 58%
Romidepsin plus lenalidomide[27] Mehta-Shah et al., *Am J Hematology*, 2021	HDAC and immune modulatory	15	ORR 53%, CR 13%	n = 5 ORR 40% CR 0	NR	n = 2 ORR 100% CR 50%



Palliative/Non-Tranplant: Single Agents

OFF-LABEL

Drug	Target	n	ORR, CR rate	PTCL, NOS	ALCL	AITL/TFH
FDA approved or NCCN compendium listed						
Belinostat[10]	HDAC	120	ORR 25.8% CR 10.8%	n = 77 ORR 23.3%	n = 15 ORR 13.3%	n = 22 ORR 45.5%
Romidepsin[11]	HDAC	130	ORR 25% CR 15%	n = 69 ORR 29% CR 14%	n = 21 ORR 24% CR 19%	n = 27 ORR 30% CR 19%
Pralatrexate[12]	Folate	109	ORR 29% CR 11%	n = 59 ORR 32%	n = 17 ORR 35%	n = 13 ORR 8%
Brentuximab vedotin[13,14]	CD30	n/a	n/a	n = 22 ORR 33% CR 14%	n = 50 ORR 86% CR 57%	n = 13 ORR 54% CR 38%
Duvelisib[15]	PI3K-δ,γ	101	ORR 49% CR 34%	n = 52 ORR 48.1% CR26.9%	n = 15 ORR 13.3% CR 13.3%	n = 30 ORR 66.7% CR 53.3%
Ruxolitinib[16]	JAK1/2	53	ORR 25% CR 6%	n = 12 ORR 18% CR 9%	n = 4 ORR 25% CR 25%	n = 9 ORR 33% CR 11%
Lenalidomide[17]	Various	39	ORR 26% CR 8%	n = 14 ORR 43% CR 14%	n = 10 ORR 10% CR 0	n = 9 ORR 33% CR 11%
Bendamustine[18]	Various	60	ORR 50% CR 28%	n = 23 NR	n = 2 NR	n = 32 NR
Gemcitabine[19]	Various	20	ORR 55% CR 30%	NR	NR	NR
Crizotinib[20]	ALK	n/a	n/a	n/a	ALK-pos n = 26 ORR 83%-90% CR 80%-83%	n/a
Alectiinib[21]	ALK	n/a	n/a	n/a	ALK-pos n = 10 ORR 80% CR 60%	n/a

Moskowitz et al., *Blood*, 2024

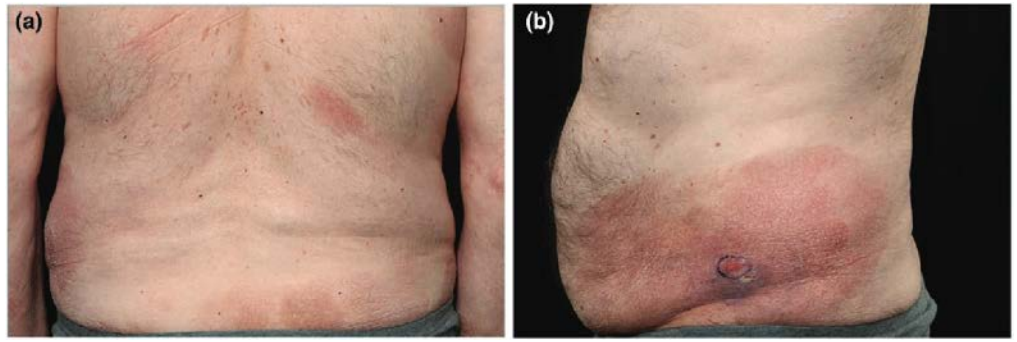
CTCL: Mycosis Fungoides/Sezary Syndrome

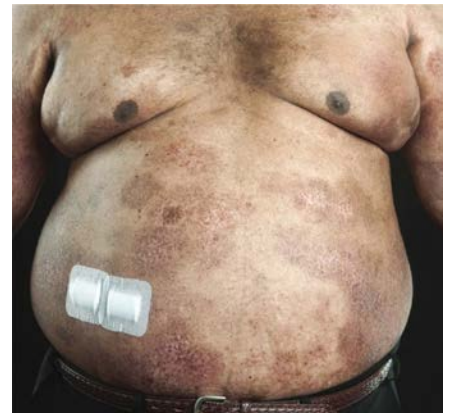
- Named in the 1800s for mushroom-like growths from skin (i.e. tumor-stage skin disease)
- Multidisciplinary approach: Med-Onc, Derm, Pathology, Radiation Oncology
- Diagnosis: Skin biopsy with expert hemepath review
- Staging: Scans not mandatory at Dx, PET at progression
  - Flow cytometry of peripheral blood, not “Sezary Count”
    - B0<250, B1 250-1000, B2 > 1,000 clonal T cells matching skin/μL
- A lifelong disease, rarely if ever cured by allo transplant
- Avoid burning through treatment options early

Johnson et al., *Skin Health and Disease*, 2026; Stuver and Horwitz, *Hematology*, 2025

Stage I Mycosis Fungoides: Skin-Directed

- Stage IA: <10% body surface area
  - Corticosteroids (triamcinolone, betamethasone for face)
  - Mechlorethamine (nitrogen mustard, use with caution)
  - Topical retinoids (Bexarotene)
  - Imiquimod (off-label)
- Stage IB: ≥10% body surface area
  - UV light therapy instead or in addition





Patch-Stage MF

Sheern, *Clinical and Experimental Dermatology*, 2025

Medical Therapies: When to Use?

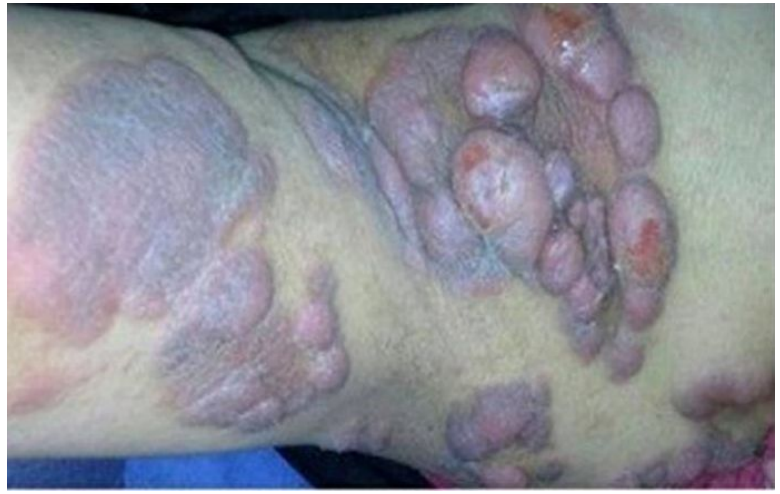
- Inadequate Response to Skin-Directed
  - **PO Methotrexate (first choice)**
  - Retinoids: PO Bexarotene
  - IV: mogamulizumab, romidepsin, vorinostat
  - Off-label: gemcitibine, liposomal doxorubicin, Interferon Alpha
- Nodal and/or visceral
  - Single agents above
  - Consider Multiagent Chemo if Allo-Eligible
- Non-Isolated Large-Cell Transformation (=PTCL?)

Plaque-Stage MF

Sheern, *Clinical and Experimental Dermatology*, 2025

Potential Roles for Radiation

- Unilesional Presentation
- Skin large-cell transformation (limited)
- Tumor-Stage Skin Disease
- Total-Skin Electon Beam (TSEB): Great but Short-Lived Responses
  - Erythrodermic disease (stage III-IV)
  - Consolidate Remission Pre-Allo

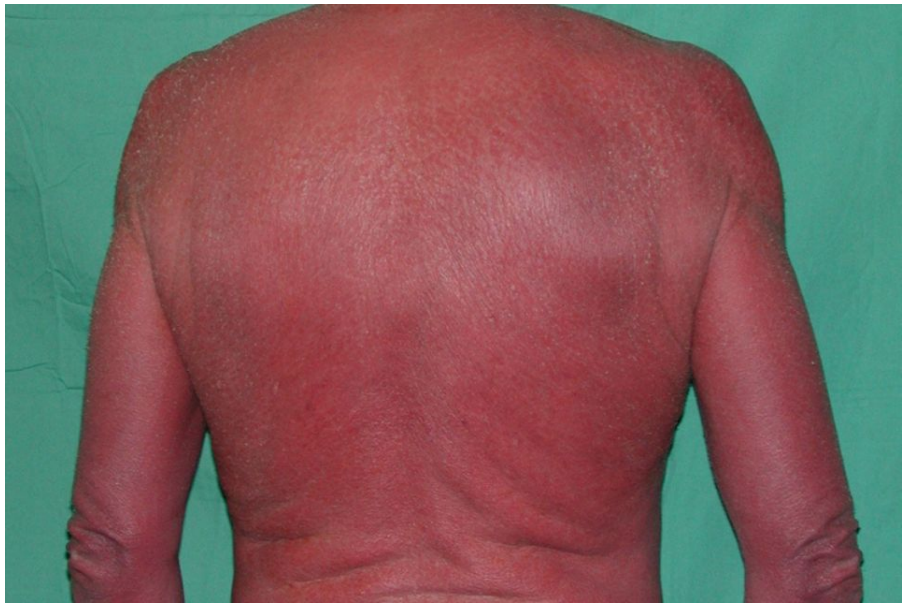


Tumor-Stage MF

Hoppe, *Dermatologic Therapy*, 2003
Schiavone, et al., *Dermatology Reports,* 2024

Sezary Syndrome: >1,000/µL

- Assess Transplant Eligibility
- Extracorporeal Photophoresis (ECP)
  - Consider adding for any B+ disease
- Mogamulizumab
- Romidepsin
- Consider Multi-Agent Chemo/TSEB Conslidation pre-Allo

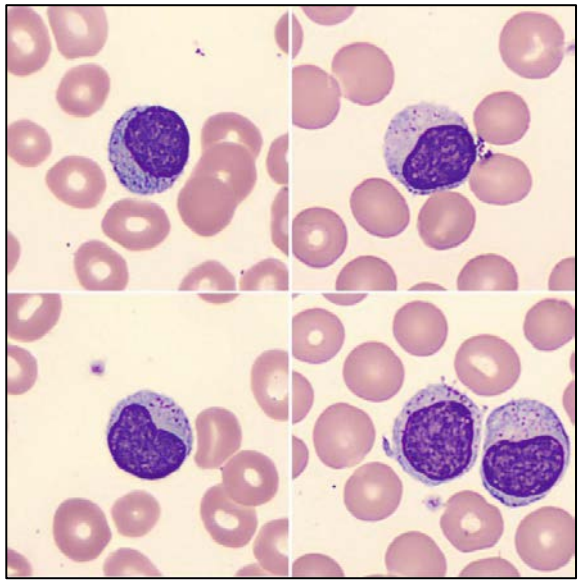


Erythrodermic MF/SS

Damaj et al., *Bone Marrow Transplantation*, 2025
Campbell, et al., *British Journal of Haematology,* 2024

Post-Thymic T-Cell Leukemias

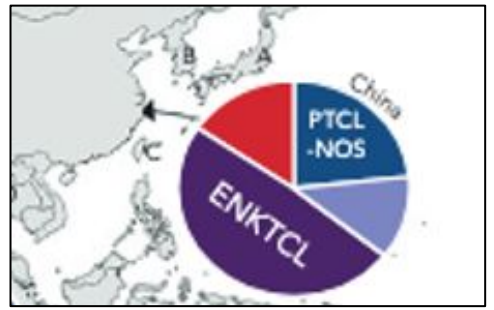
- T-Cell Prolymphocytic Leukemia (T-PLL)
  - May mimic CLL on a smear, T cells by flow
  - Alemtuzumab +/- pentostatin (off-label)
  - Refer for allo workup ASAP
- T-Cell Large Granular Leukemia (T-LGL)
  - Check smear, flow, and NGS on blood (*STAT3, STAT5B* mutations)
  - Indolent and may often be observed at diagnosis
  - Treat for cytopenias. Neutropenia <500 most common reason
  - PO MTX is first choice and needs time to work
  - Subsequent line (off-Label): PO cyclophosphamide, cyclosporine



T-LGL

van Jan, *Blood*, 2024; Lamy, et al., *Blood,* 2017

Extranodal NK/T-Cell Lymphoma



- Increased incidence: Asia and South America
- Presentation in nasal/upper aerodigestive tract most common, others possible: skin, testes, GI tract
- EBV+ in tumor; Quant EBV in whole blood tracks tumor burden
- Diagnosis typically by ENT, Stage with PET
- **Treatment: Concurrent or Sequential Chemo and RT is Required; Either Alone is Inadequate**
- Unique combinations (e.g. mSMILE: Dexamethasone, MTX, Ifos., PEG-asparaginase, etoposide). Most include asparaginase.
- Auto consolidation: No clear role
- Relapsed/Refractory: Aggressive salvage and allo if possible

van Doesum et al., *HemoSphere,* 2021