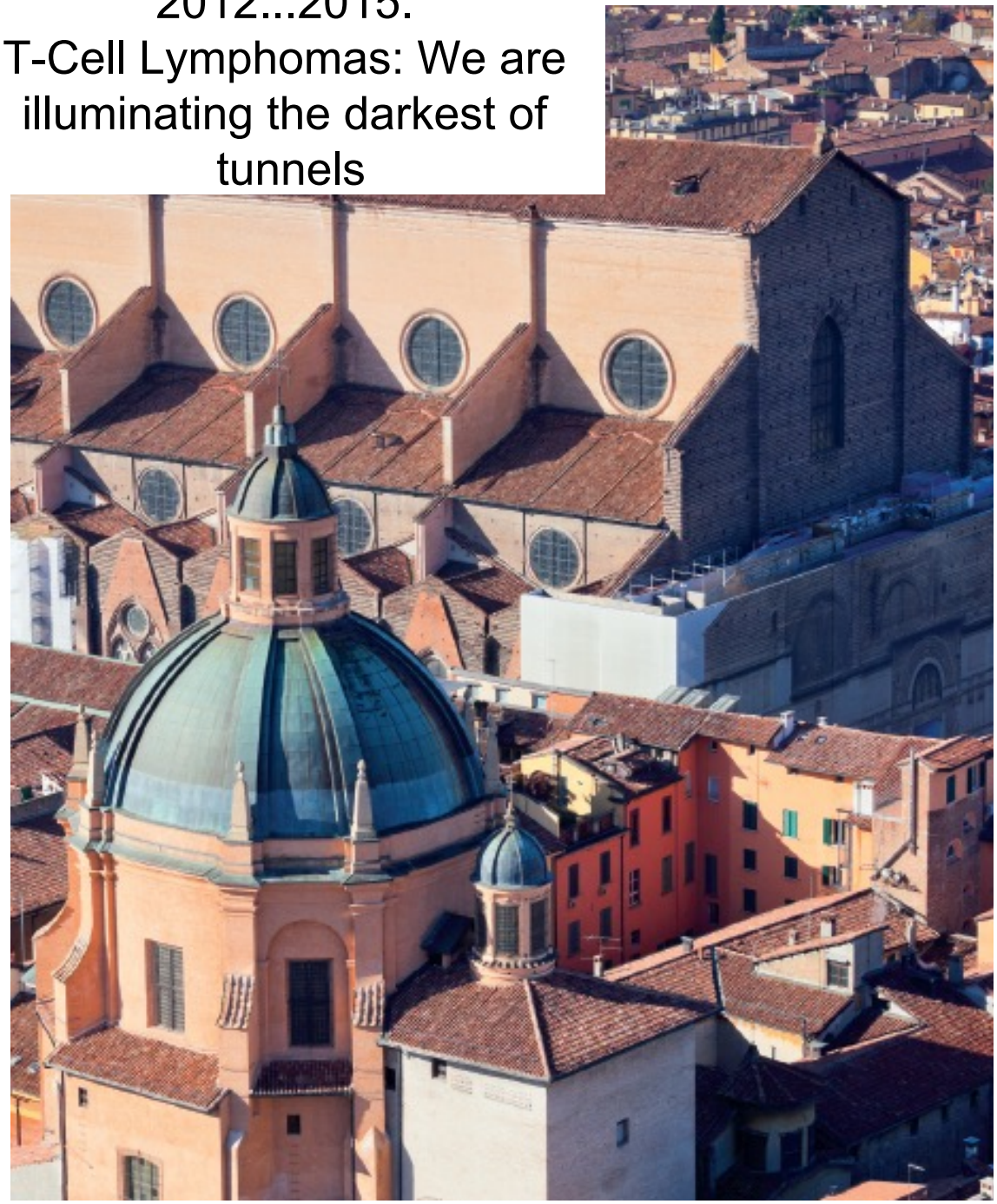
2012...2015.
T-Cell Lymphomas: We are illuminating the darkest of tunnels



Haemolymphopathology Units

Policlinico S.Orsola-Malpighi-Bologna
Elena Sabattini

Istituto Oncologioco Europeo – Milano
Stefano Pileri

introduction topic on

Histology and immune-histology of PTCL NOS

T-Cell Lymphomas in South America and Europe

Rev Bras Hematol Hemoter. 2012

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Carmino Antonio de Sc
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Peripheral T-cell lymphomas are a group of rare neoplasms originating from clonal proliferation of mature post-thymic lymphocytes with different entities having specific biological characteristics

Table 2 - Histologic subtype distribution (%) according to reviewed histology of 737 cases registered in the T-cell project by geographic region

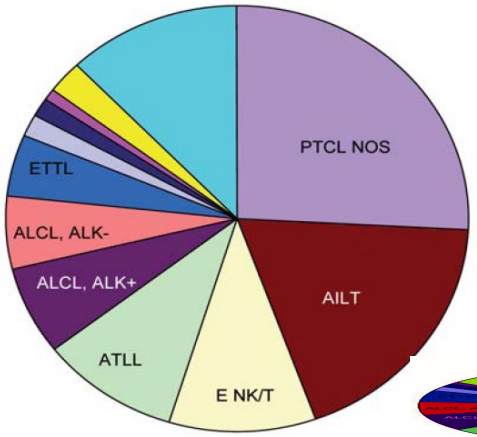
	Overall	Europe	USA	South America	Middle/ Far East
PTCL-NOS	38	40	42	42	26
AITL	17	20	21	8	15
ALCL, ALK$^-$	13	14	9	23	6
ALCL, ALK$^+$	7	6	8	8	4
NK/T nasal, nasal type, lymphoma/leukemia	13	6	9	13	31
Other histologies	12	14	11	6	18

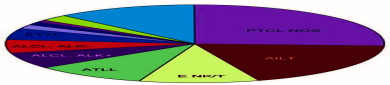
PTCL: Peripheral T-cell lymphomas; NOS: Not otherwise specified; AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large cell lymphomas; ALK: Anaplastic lymphoma kinase; NK: Natural killer

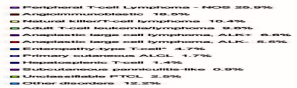
Table 3 - Histologic subtype distribution by country of the 317 cases registered for European sites in the T-cell project

	Overall		Italy		United Kingdom		Others *	
	n	%	n	%	n	%	n	%
PTCL-NOS	127	40	99	41	19	41	9	33
AITL	63	20	47	19	10	22	6	22
ALCL, ALK$^-$	44	14	34	14	9	20	1	4
ALCL, ALK$^+$	21	6	18	8	2	4	1	4
NK/T nasal, nasal type	19	6	13	5	3	7	3	11
Enteropathy-type	22	7	17	7	2	4	3	11
Hepatosplenic	5	2	5	2	-	-	-	-
Other histologies	16	5	11	4	1	2	4	15
Subcutaneous panniculitis-like	4		3		1		-	
Peripheral γδ T-cell lymphomas	3		1		-		2	
Unclassifiable T/NK PTCLs	9		7		-		2	
Total	317		244		46		27	

PTCL: Peripheral T-cell lymphomas; NOS: Not otherwise specified; AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large cell lymphomas; ALK: Anaplastic lymphoma kinase; NK: Natural killer
* Switzerland, Slovakia and Spain







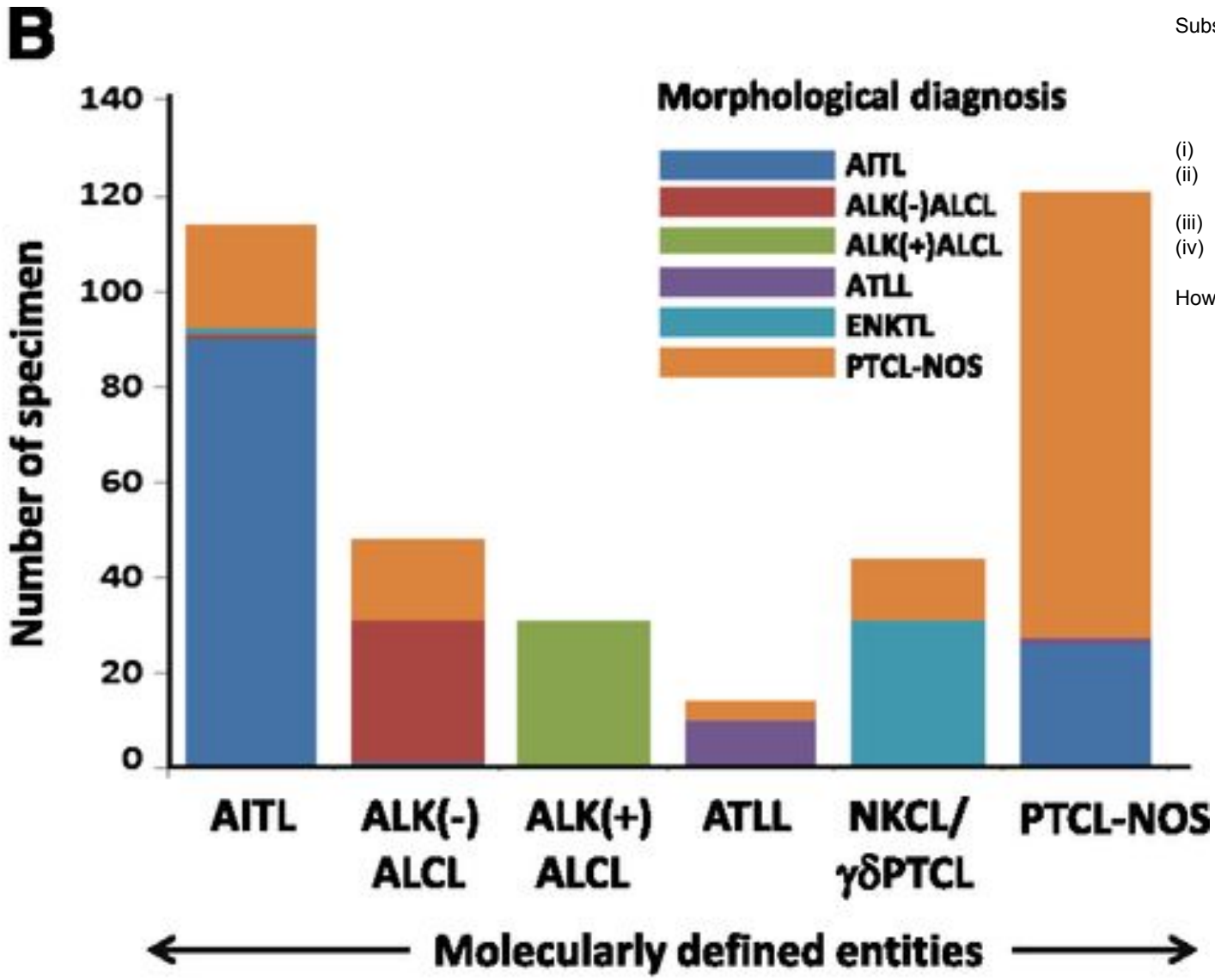
"NOS" category: still diagnosed on "exclusion-criteria" model

not defined by specific immune-morphologic features

Mainly "nodal", but can be extranodal.

In such cases site-specific T-cell lymphoma types should be first excluded

Iqbal J et al. Blood 2014;123:2915-2923



(B)
Pathological vs molecular diagnosis comparison.

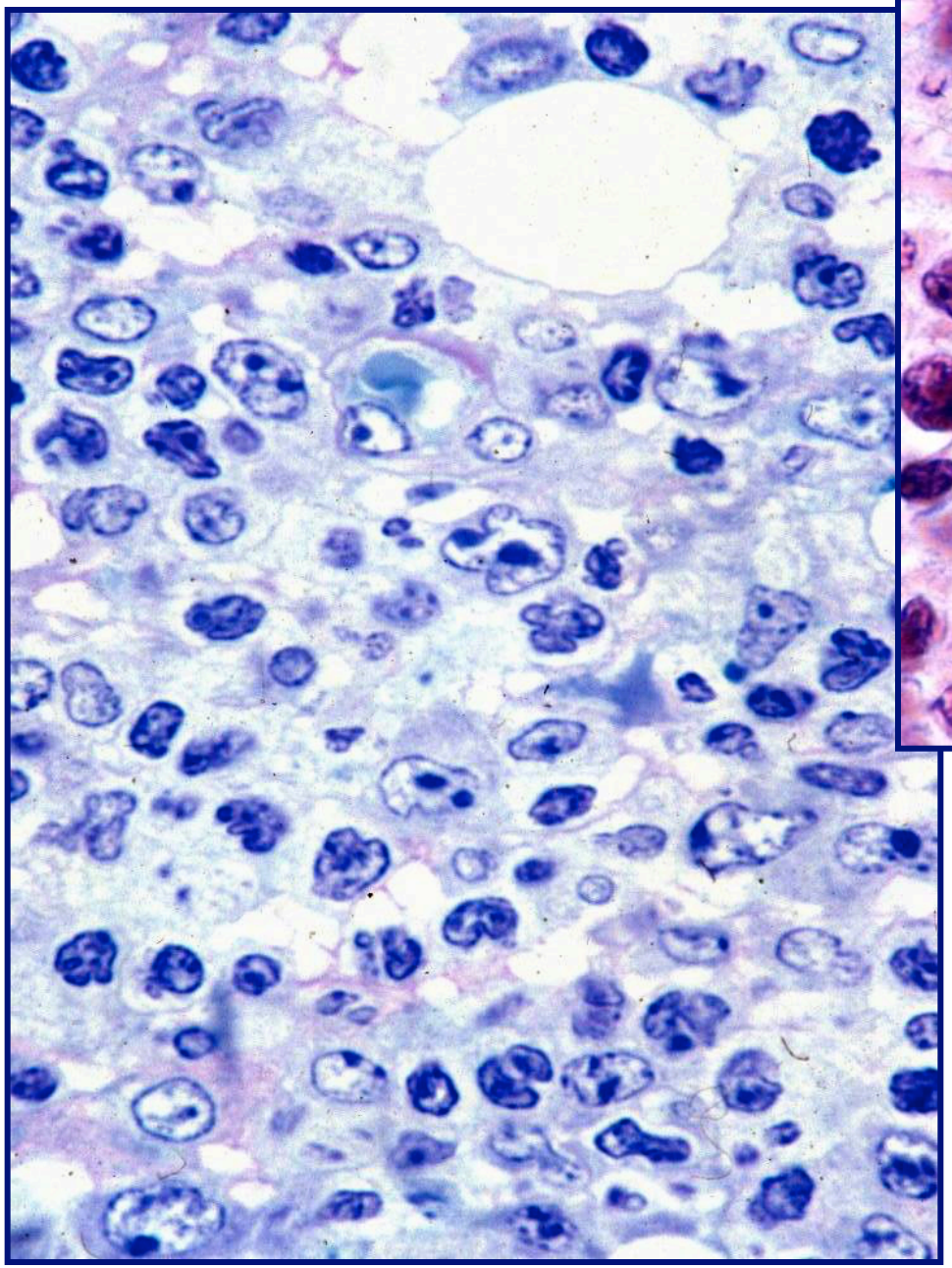
Substantial number of cases from PTCL-NOS were molecularly classified into WHO recognized PTCL subgroups:
(i) AITL (n = 21, 14%);
(ii) ALK(–)ALCL (n = 17, 11%);
(iii) ATLL (n = 4, 3%);
(iv) γδ-PTCL (n = 13, 9%).

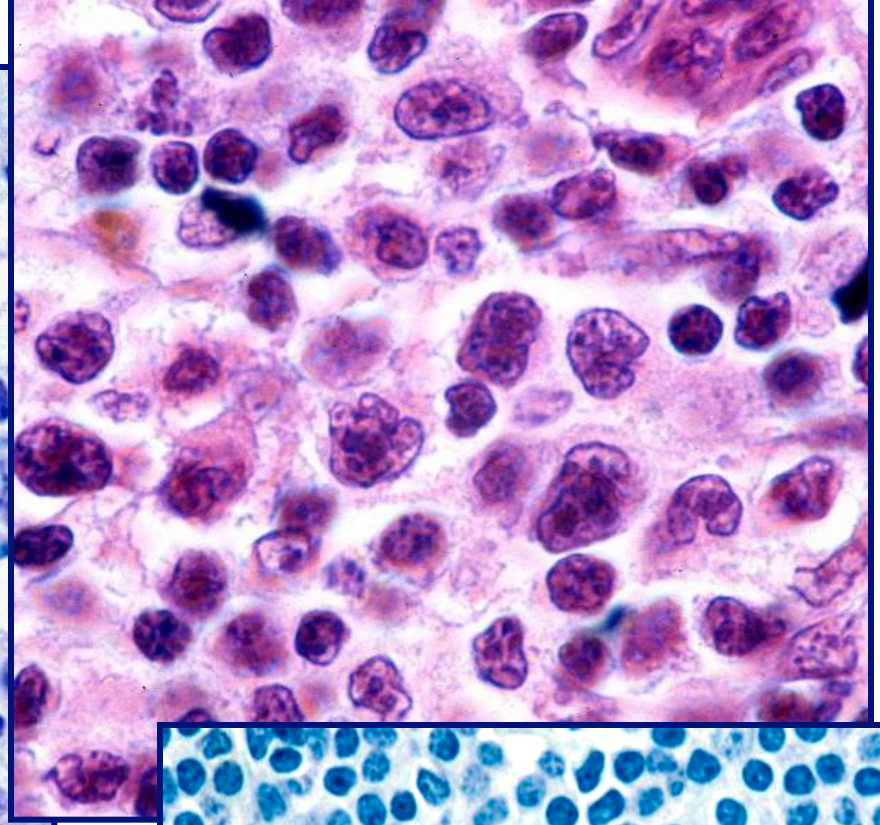
However, 26 AITL cases (22%) were not molecularly classifiable and changed to PTCL-NOS

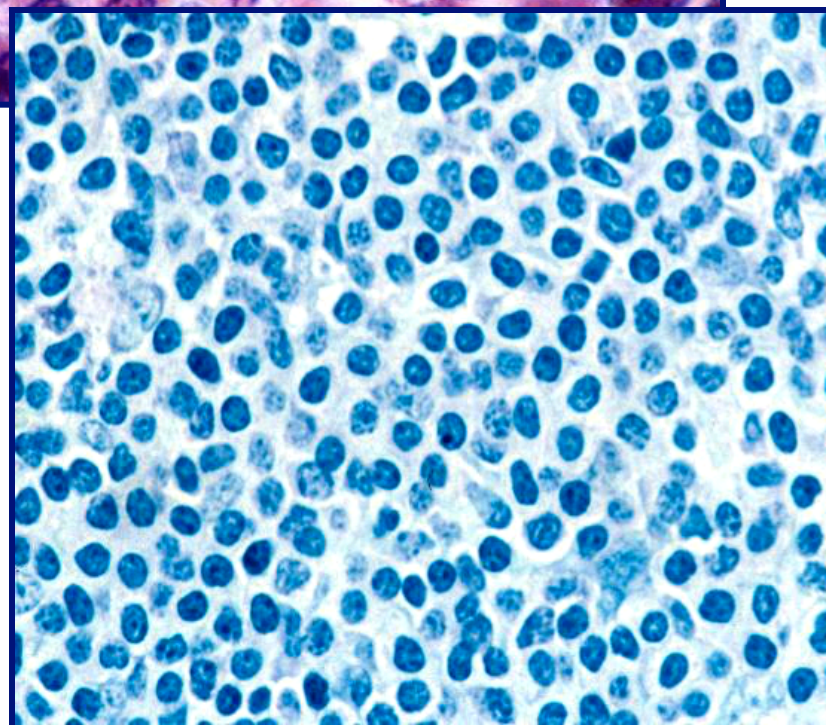
Comparison of Referring and Final Pathology for Patients With T-Cell Lymphoma in the National Comprehensive Cancer Network

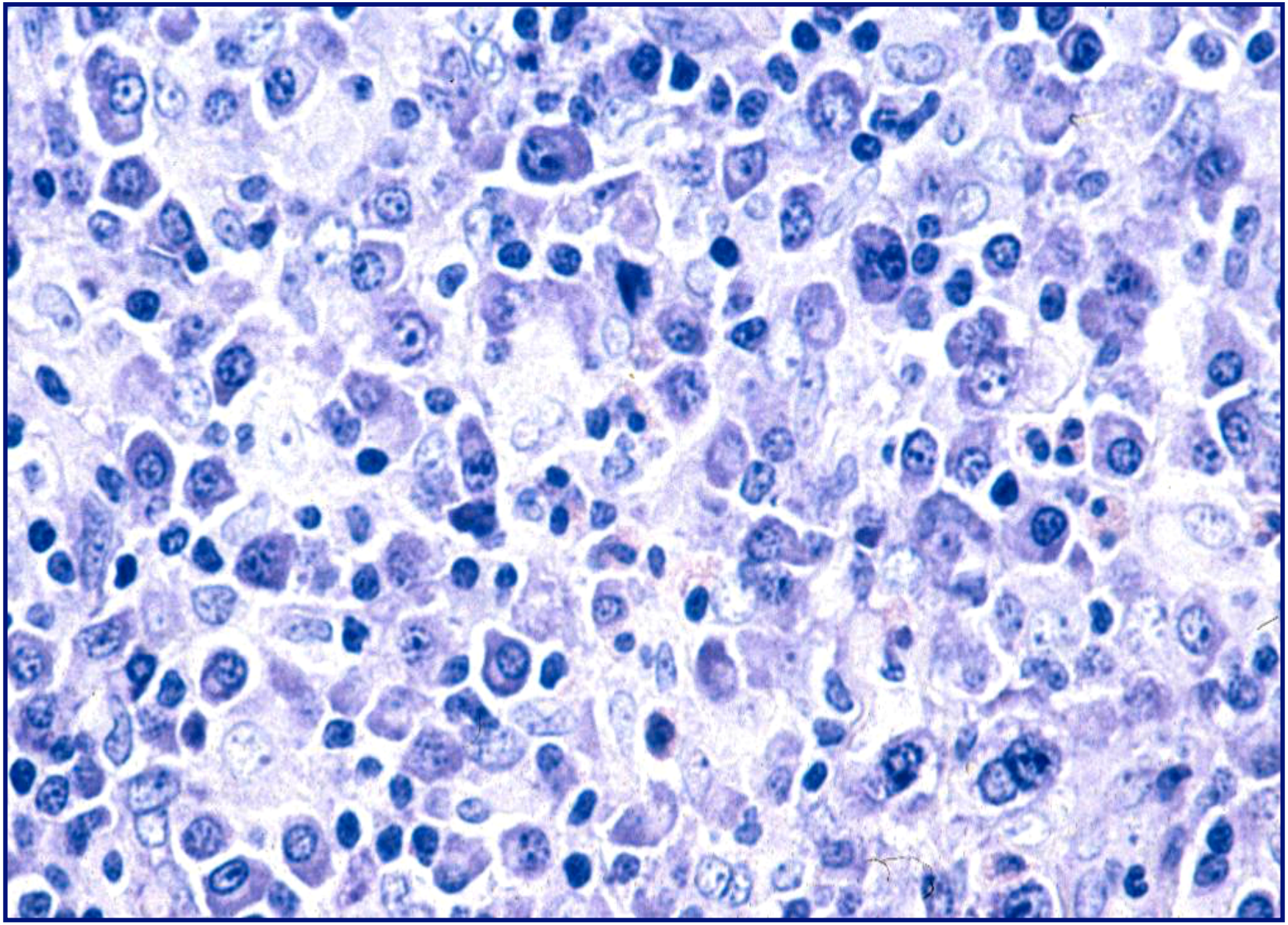
Alex F. Herrera, MD[1]; Allison Crosby-Thompson[2]; Jonathan W. Friedberg, MD[3]; Gregory A. Abel, MD, MPH[1]; Myron S. Czuczman, MD[4]; Leo I. Gordon, MD[5]; Mark S. Kaminski, MD[6]; Michael M. Millenson, MD[7]; Auayporn P. Nademanee, MD[8]; Joyce C. Niland, PhD[8]; Scott J. Rodig, MD, PhD[9]; Maria A. Rodriguez, MD[10]; Andrew D. Zelenetz, MD, PhD[11]; and Ann S. LaCasce, MD[1]

BACKGROUND: T-cell lymphomas (TCLs) are uncommon in the United States. The accurate diagnosis of TCL is challenging and requires morphologic interpretation, immunophenotyping, and molecular techniques. The authors compared pathologic diagnoses at referring centers with diagnoses from expert hematopathology review to determine concordance rates and to characterize the usefulness of second-opinion pathology review for TCL. **METHODS:** Patients in the National Comprehensive Cancer Network non-Hodgkin lymphoma database with peripheral TCL, not otherwise specified (PTCL-NOS), angioimmunoblastic TCL (AITL), and anaplastic lymphoma kinase (ALK)-positive and ALK-negative anaplastic large cell lymphoma (ALCL) were eligible if they had prior tissue specimens examined at a referring institution. Pathologic concordance was evaluated using available pathology and diagnostic testing reports and provider progress notes. The etiology of discordance and the potential impact on treatment were examined. **RESULTS:** Among 131 eligible patients, 57 (44%) had concordant results, totaling 64% of the 89 patients who were referred with a final diagnosis. Thirty-two patients (24%) had discordant results, representing 36% of those who were referred with a final diagnosis. The rates of discordance among patients with of PTCL-NOS, AITL, ALK-negative ALCL, and ALK-positive ALCL were 19%, 33%, 34%, and 6%, respectively. In 14 patients (44% of discordant results), pathologic reclassification could have resulted in a different therapeutic strategy. Forty-two patients (32%) were referred for classification with a provisional diagnosis. **CONCLUSIONS:** In a large cohort of patients with TCL who were referred to National Comprehensive Cancer Network centers, the likelihood of a concordant final diagnosis at a referring institution was low. As current and future therapies target TCL subsets, these data suggest that patients with suspected TCLs would benefit from evaluation by an expert hematopathologist. ***Cancer*** **2014;120:1993–9.** © *2014 American Cancer Society.*



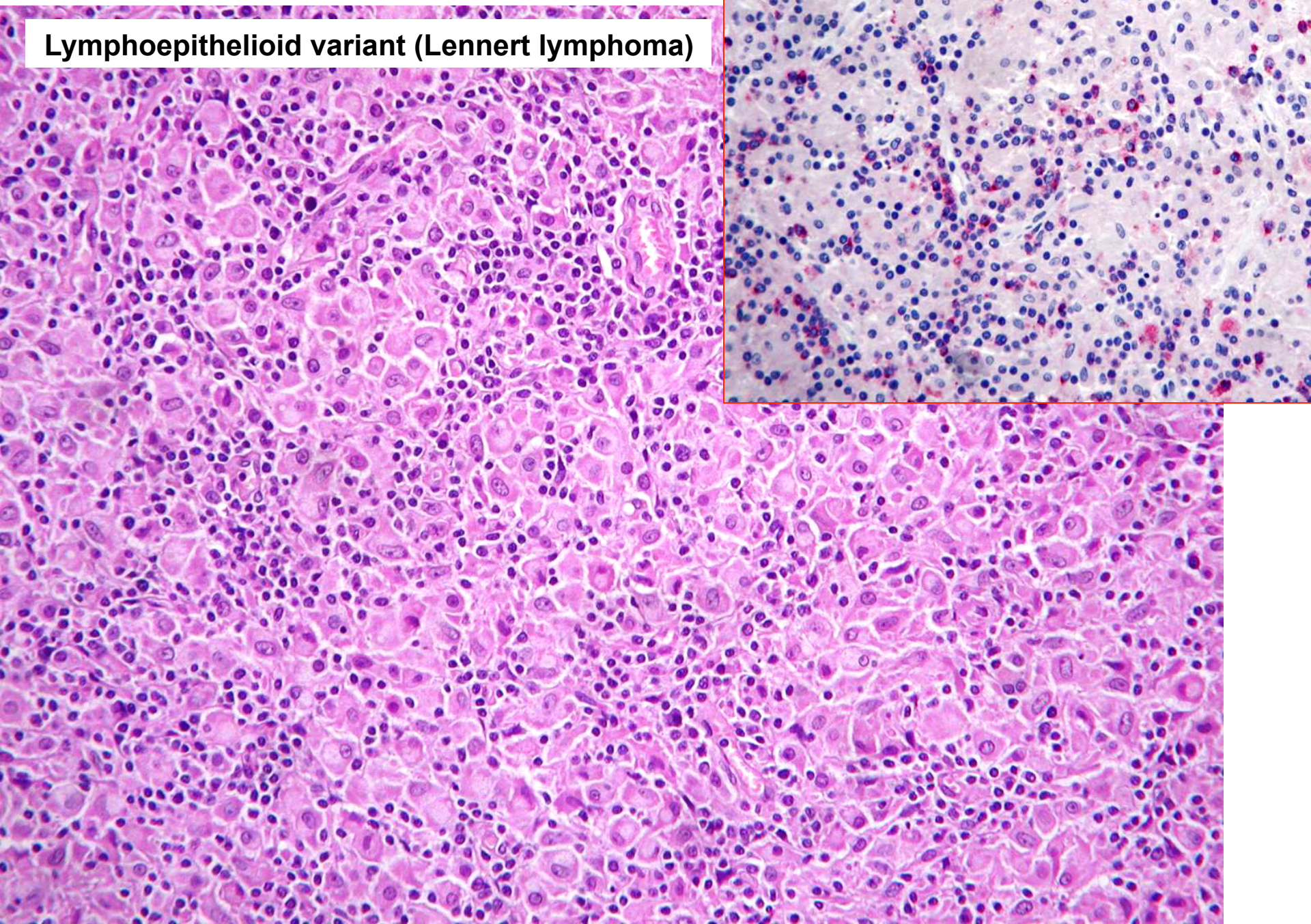


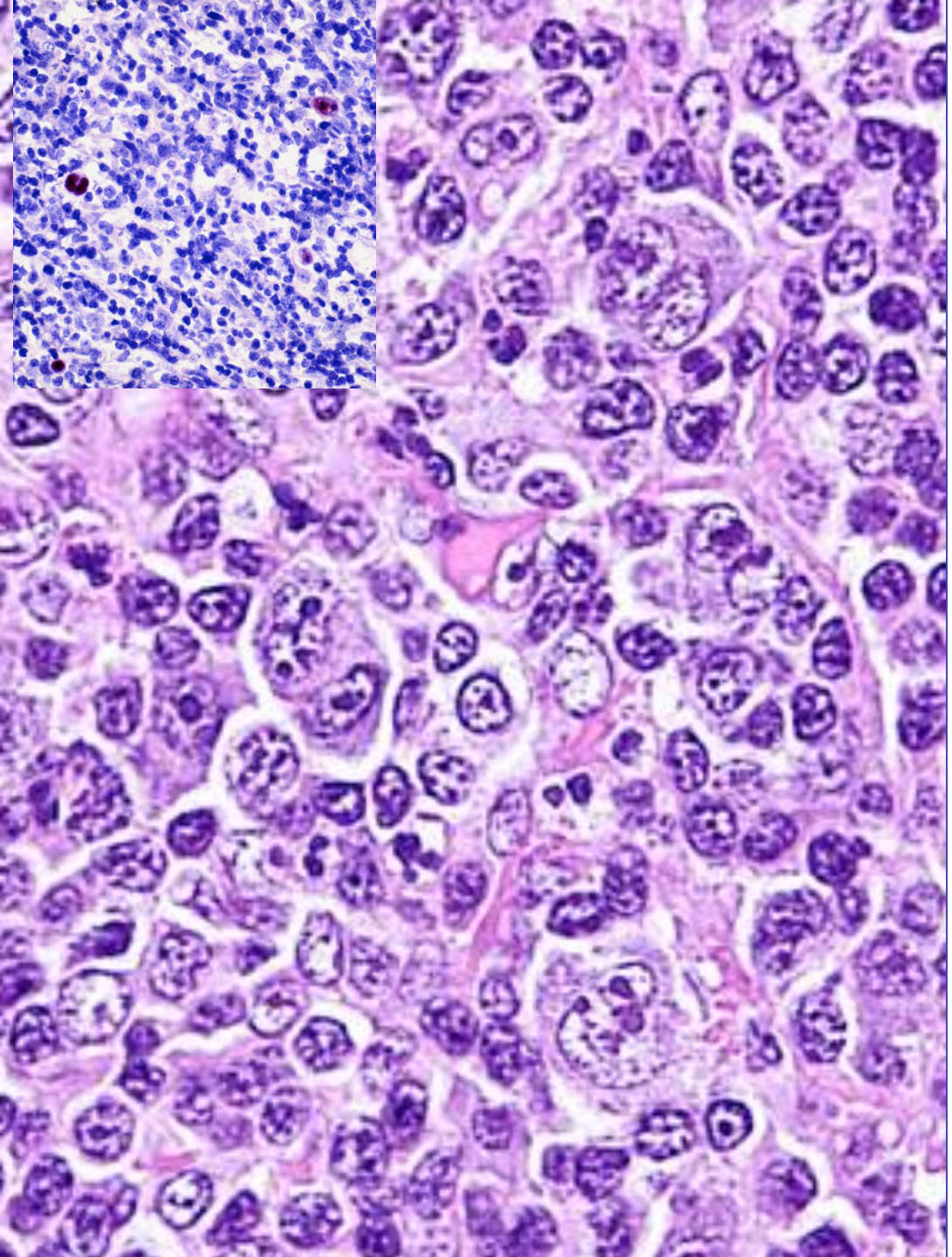




Hartman S et al. Histopathology 2011

Lymphoepithelioid variant (Lennert lymphoma)





HRS cells

Provided with
T-cell phenotype

or B-cell phenotype
either complete or incomplete
possibly EBV+
If CD30+-/CD15+-: dd with HD

Tan BT et al. J Molec Diagnostics 2006

B-cell clonality relatively frequent (35% cases)
> correlated, in part, with the presence of a B-cell proliferation, but not with EBV

Marker Expression in Peripheral T-Cell Lymphoma: A Proposed Clinical-Pathologic Prognostic Score

Philip Went, Claudio Agostinelli, Andrea Gallamini, Pier Paolo Piccaluga, Stefano Ascani, Elena Sabattini, Francesco Bacci, Brunangelo Falini, Teresio Motta, Marco Paulli, Tullio Artusi, Milena Piccioli, Pier Luigi Zinzani, and Stefano A. Pileri

J Clin Oncol 24:2472-2479.

Table 2. Immunophenotypic Features and EBER Expression in a PTCL/AILD TMA

Antigen	PTCL No.	PTCL Positive (%)	AILD No.	AILD Positive (%)
Human TCR βF1	133	97	30	94
CD2	136	70	41	100
CD3	144	86	40	95
CD4	135	46	38	42
CD8	129	15	34	32
CD5	137	20	36	19
CD7	141	19	41	24
CD10	143	1	43	39
CD15	140	4	43	2
CD30	145	3	42	0
CD56	140	6	40	3
CD57	143	10	42	5
TIA-1	138	27	41	34
GB	140	2	40	0
ALK-C	143	0	41	0
EBER	132	5	39	3
Mib-1 high	138	11	40	5
CD20	141	1	42	0
CD79a	142	0	36	0

Abbreviations: EBER, Epstein-Barr virus–associated small RNAs; PTCL, peripheral T-cell lymphoma; AILD, angioimmunoblastic type; TMA, tissue microarray; TCR, T-cell receptor; TIA-1, T-cell intracellular antigen 1; GB, granzyme B; ALK, anaplastic large-cell lymphoma kinase.

CD15 positive in 5 cases (3 with CD30)
CD15 + tended to a shorter survival

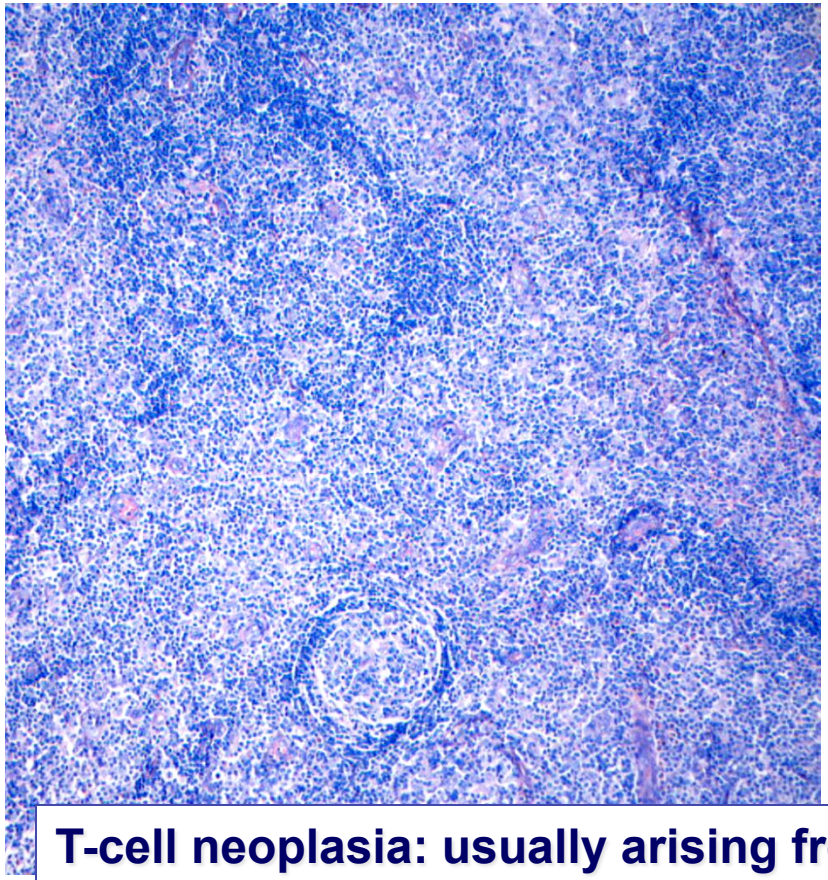
Aberrant T-cell antigen expression in classical Hodgkin lymphoma is associated with decreased event-free survival and overall survival

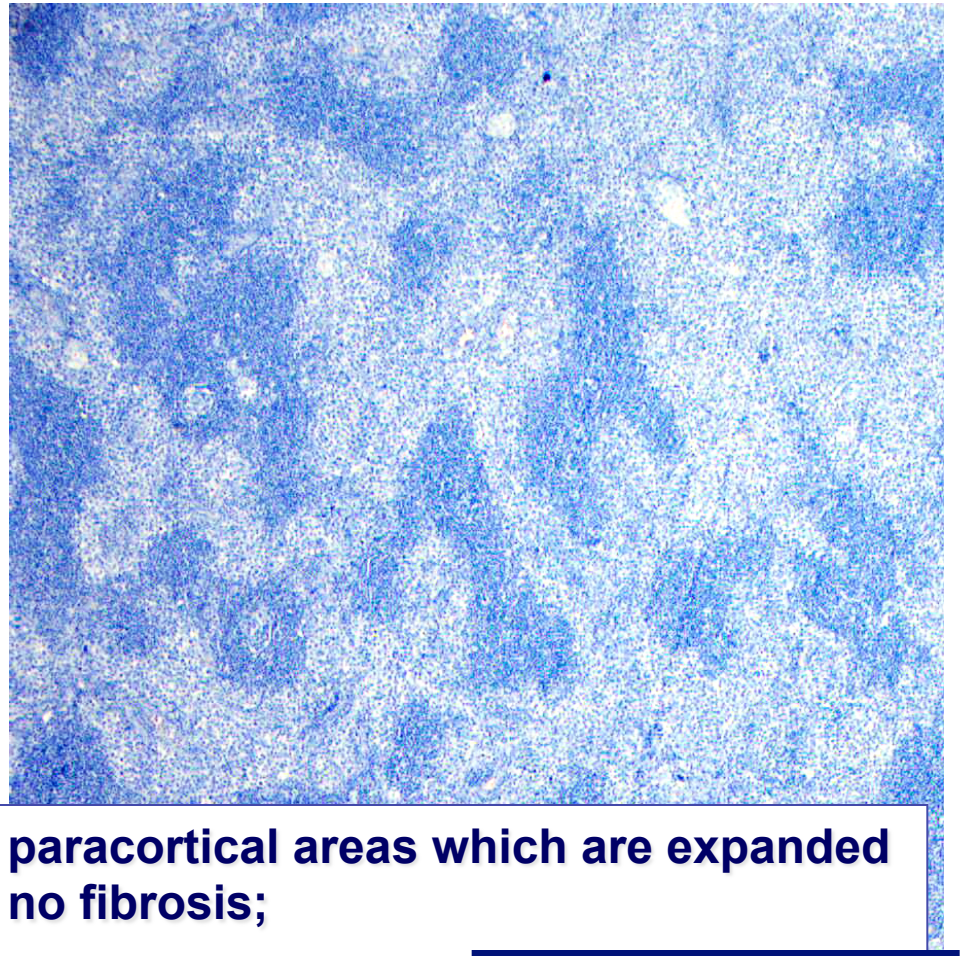
Venkataraman G, Song JY, Tzankov A, Dirnhofer S, Heinze G, Kohl M, Traverse-Glehen A, Eberle FC, Hanson JC, Raffeld MA, Pittaluga S, Jaffe ES.

Blood. 2013

- low stage (stage I/II) > nodular sclerosis
- CD4 and CD2 were most commonly expressed (TCA expression predicted shorter OS)
- TRG@ PCR was negative for clonal rearrangements in 29 of 31 cases.

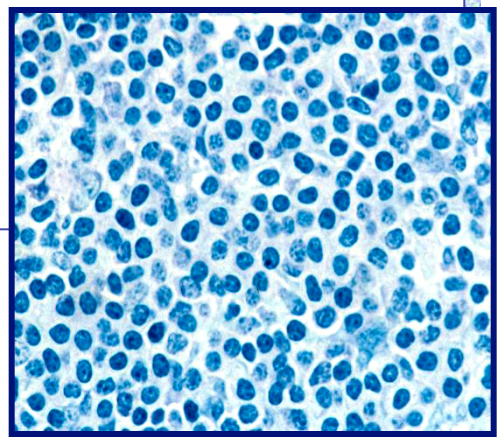
2/10 cases of dissected HRS cells showed monoclonal TCR

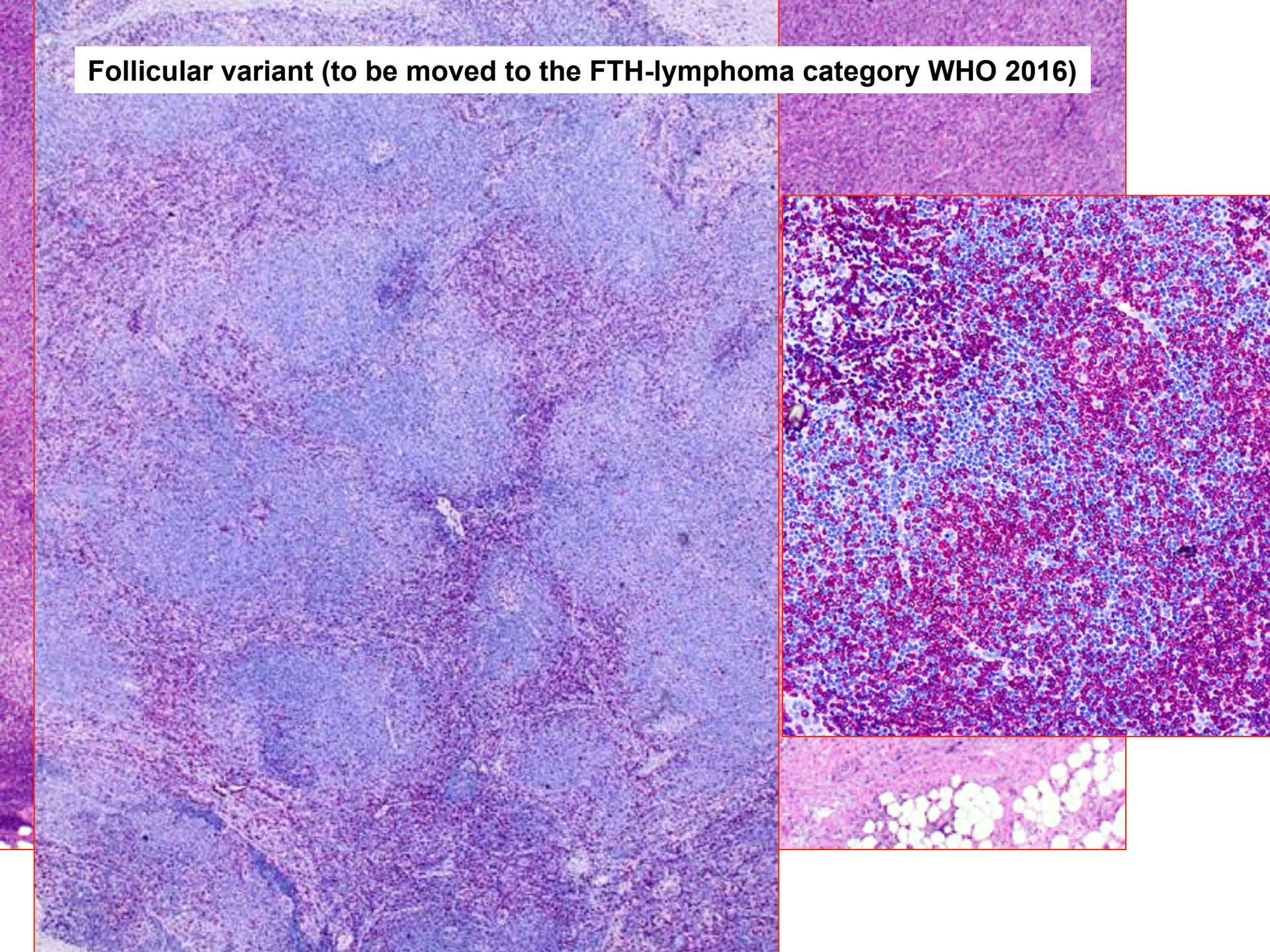




T-cell neoplasia: usually arising from paracortical areas which are expanded with visible residual follicles; usually no fibrosis;

When the perifollicular growth pattern is throughout the lymph node and there is a small cell composition:
T-zone variant




Follicular variant (to be moved to the FTH-lymphoma category WHO 2016)

Annals of Oncology Advance Access published April 9, 2014

SIE-SIES-GITMO guidelines for the management of adult peripheral T- and NK-cell lymphomas, excluding mature T-cell leukemias

P. Corradini[1], M. Marchetti[2], G. Barosi[3], A. Billio[4], A. Gallamini[5], S. Pileri[6], N. Pimpinelli[7], G. Rossi[8], P. L. Zinzani[9], S. Tura[10]

special article

Annals of Oncology 24: 857–877, 2013
doi:10.1093/annonc/mds643
Published online 20 February 2013

ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma

M. Dreyling[1*], C. Thieblemont[2], A. Gallamini[3], L. Arcaini[4], E. Campo[5], O. Hermine[6], J. C. Kluin-Nelemans[7], M. Ladetto[8], S. Le Gouill[9], E. Iannitto[10], S. Pileri[11], J. Rodriguez[12], N. Schmitz[13], A. Wotherspoon[14], P. Zinzani[15] & E. Zucca[16]

List of markers applicable to formalin-fixed, paraffin-embedded tissue sections for the diagnosis of peripheral NK/T cell lymphomas (ESMO/SIE/SIES/GITMO Guidelines).

- T-cell markers: CD2, CD3, CD4, CD5, CD7, CD8, CD52, βF1, TCRγ
- Cytotoxic markers: TIA1, granzyme B, perforin
- FTH markers: CD10, BCL6, PD1, CXCL13, SAP, ICOS, CCR5
- Treg markers: FoxP3
- NK-cell markers: CD16, CD56, CD57
- Activation markers: CD25, CD30
- Proliferation: MIB1/Ki-67
- B-cell markers: CD20, BSAP/PAX5
- Follicular dendritic cells: CD21
- Histiocytes and epithelioid elements: CD68/PG-M1
- EBV: EBER ISH, LMP1, EBNA2
- Others: CCR4, ALK, EMA, CD45

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J Clin Oncol 24:2472-2479.

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CD8	129	15
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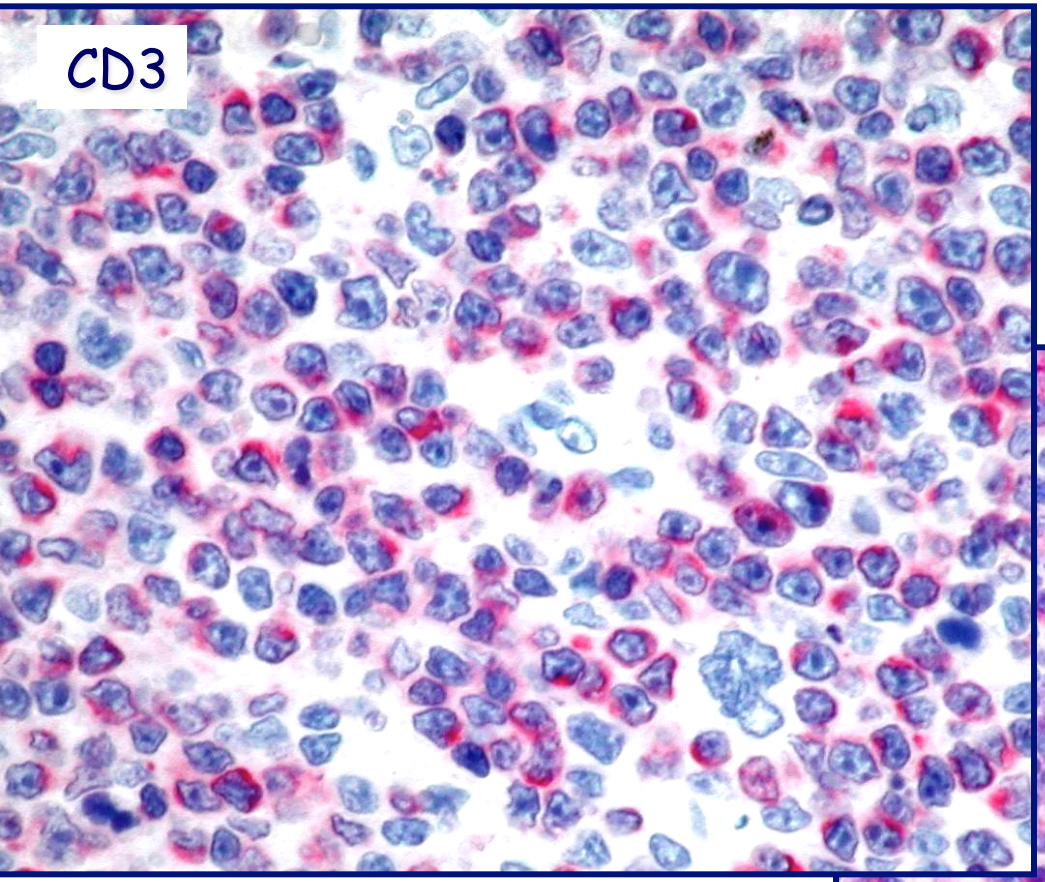
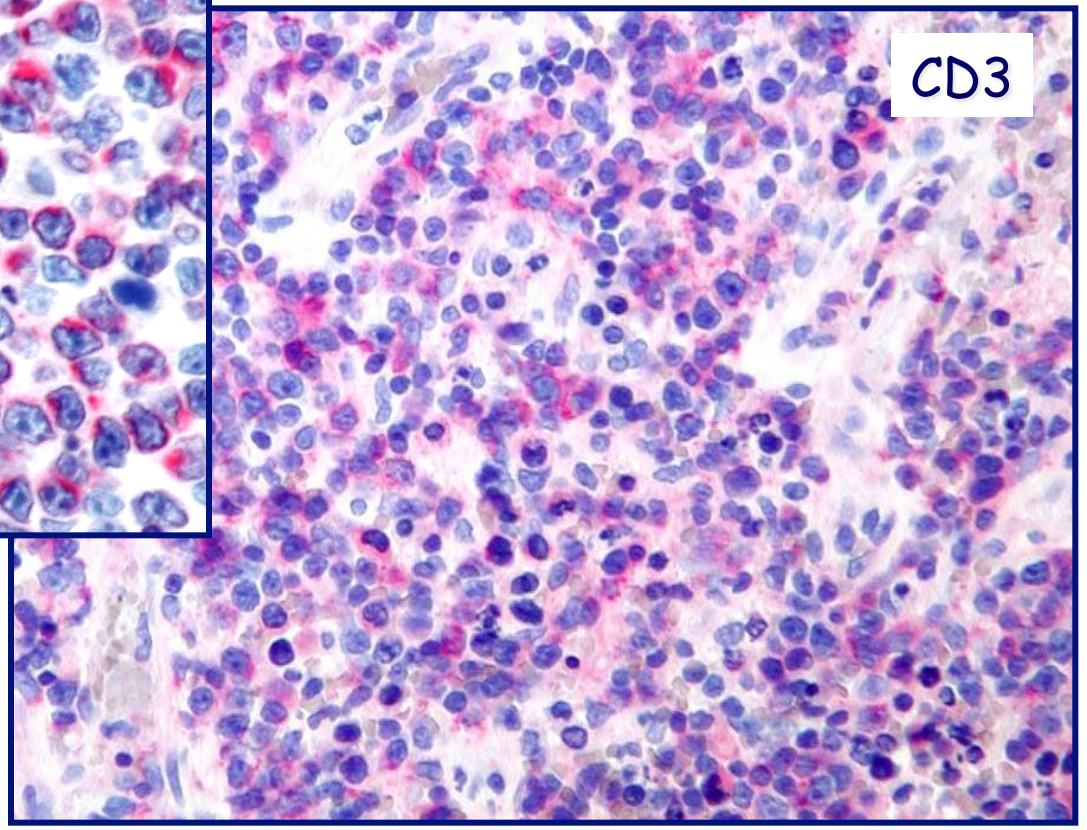
CD7	141	19





148 PTCL, NOS
on TMA

Co-expression of B-cell markers

Table 2. Immunophenotypic Features and EBER Expression in a PTCL/AILD TMA

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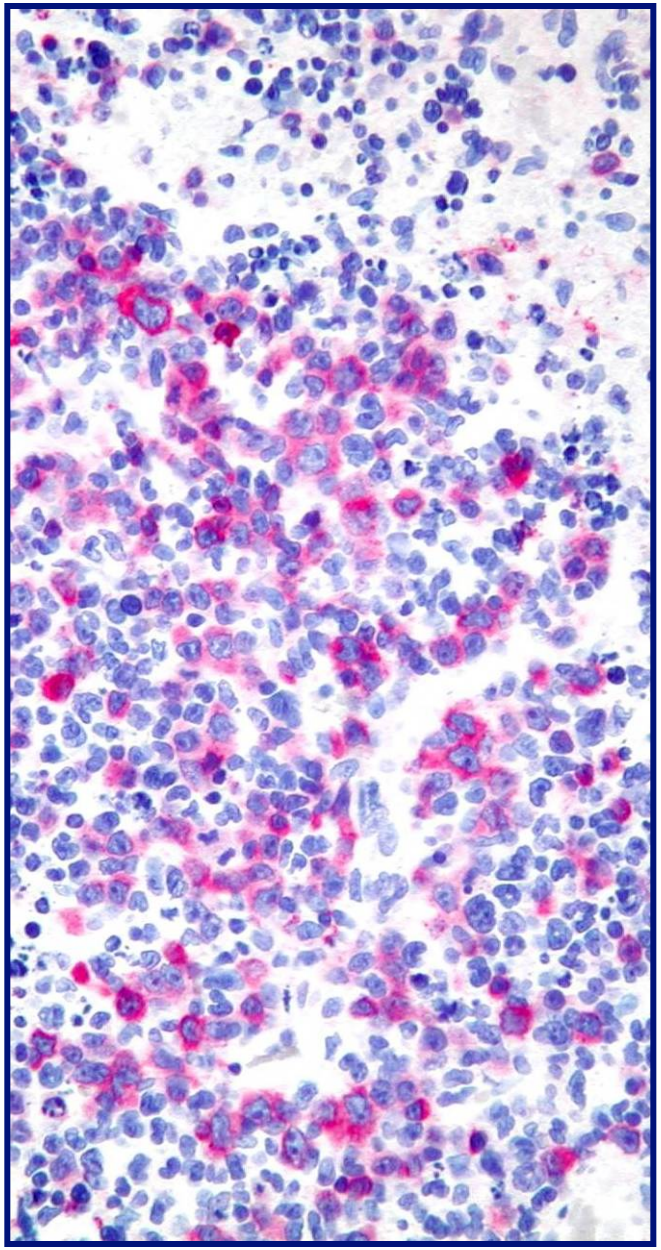
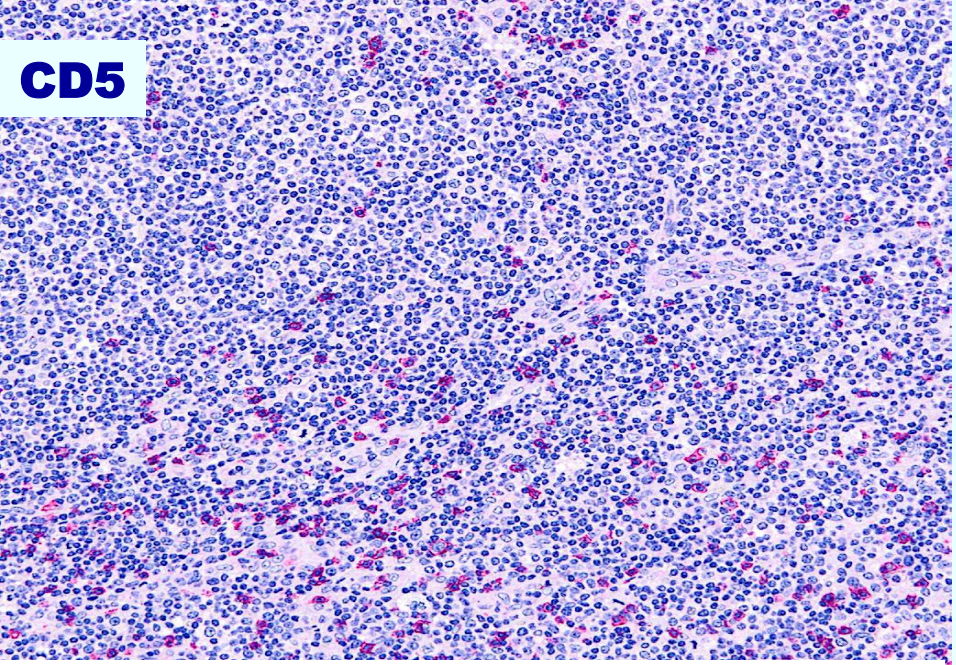
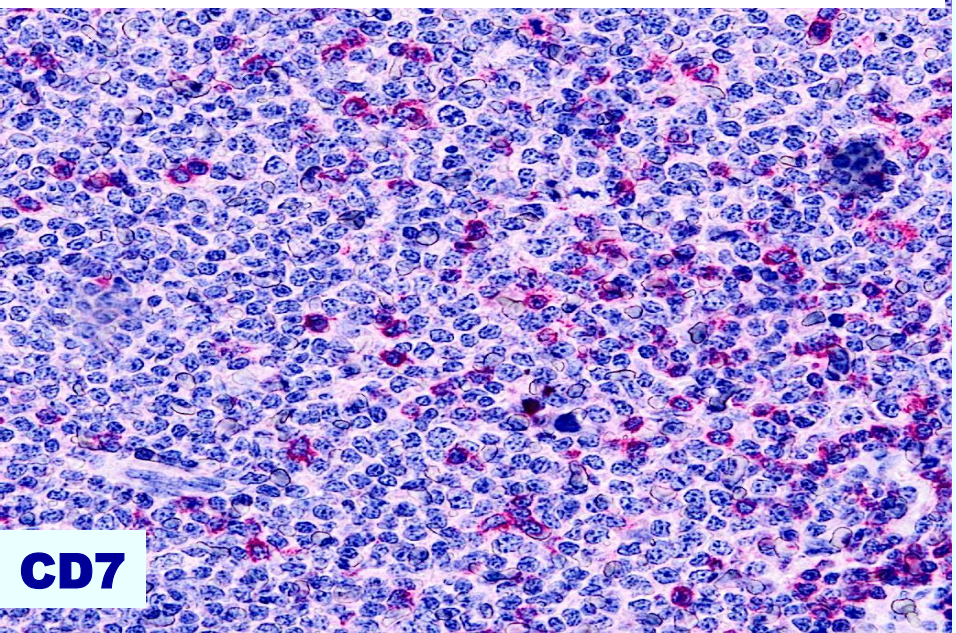


Blakolmer K et al. Immunoreactivity of B-cell markers (CD79a, L26) in rare cases of extranodal cytotoxic peripheral T- (NK/T-) cell lymphomas. Mod Pathol 2000; 13:766-72.
Went P et al. Marker expression in PTCL: a proposed clinico-pathologic score. JCO 2006; 24:2472-9.



Since no clonality immunoistochemical marker is available for TCLs a defective T-cell phenotype is highly indicative of a clonal T cell proliferation



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J Clin Oncol 24:2472-2479. © 2006 by American Society of Clinical Oncology

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CD10	143	1	43	39
CD15	140	4	43	2
CD30	145	3	42	0
CD56	140	6	40	3
CD57	143	10	42	5
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GB	140	2	40	0
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Antigen	PTCL No.	PTCL Positive (%)
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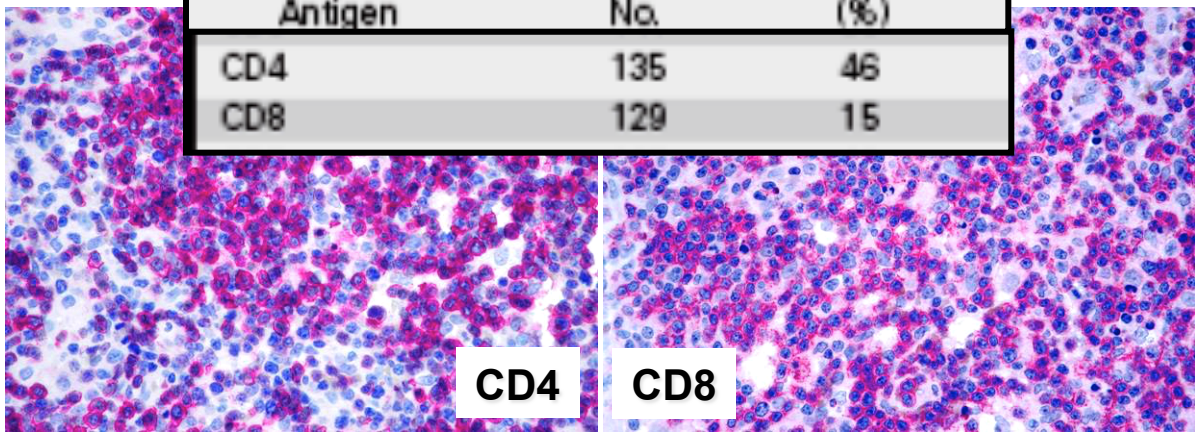
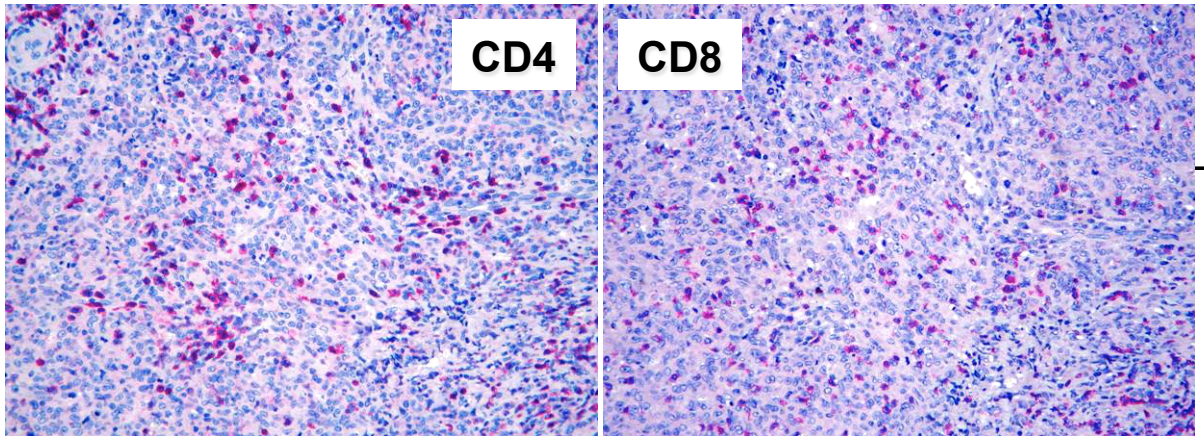
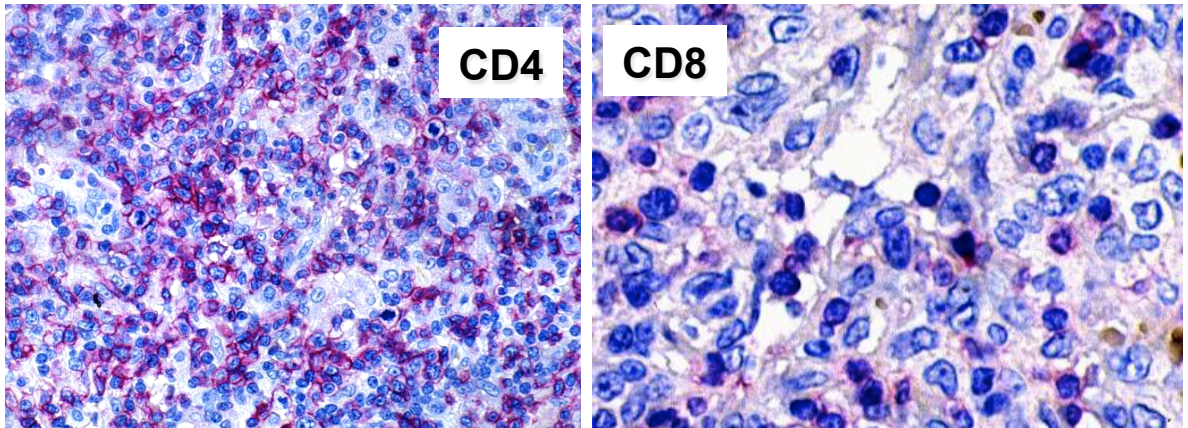
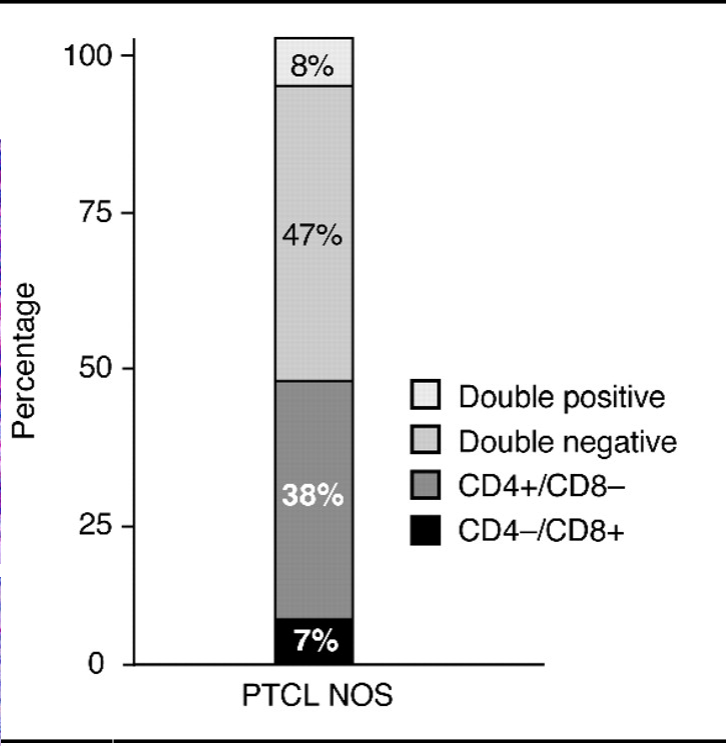
CD8	129	15









No correlation with
•cytotoxic or NK markers
•survival
CD4+/CD8- tended to better outcome (ns)

In vivo administration of anti-CD4 antibodies!

T cell markers expression

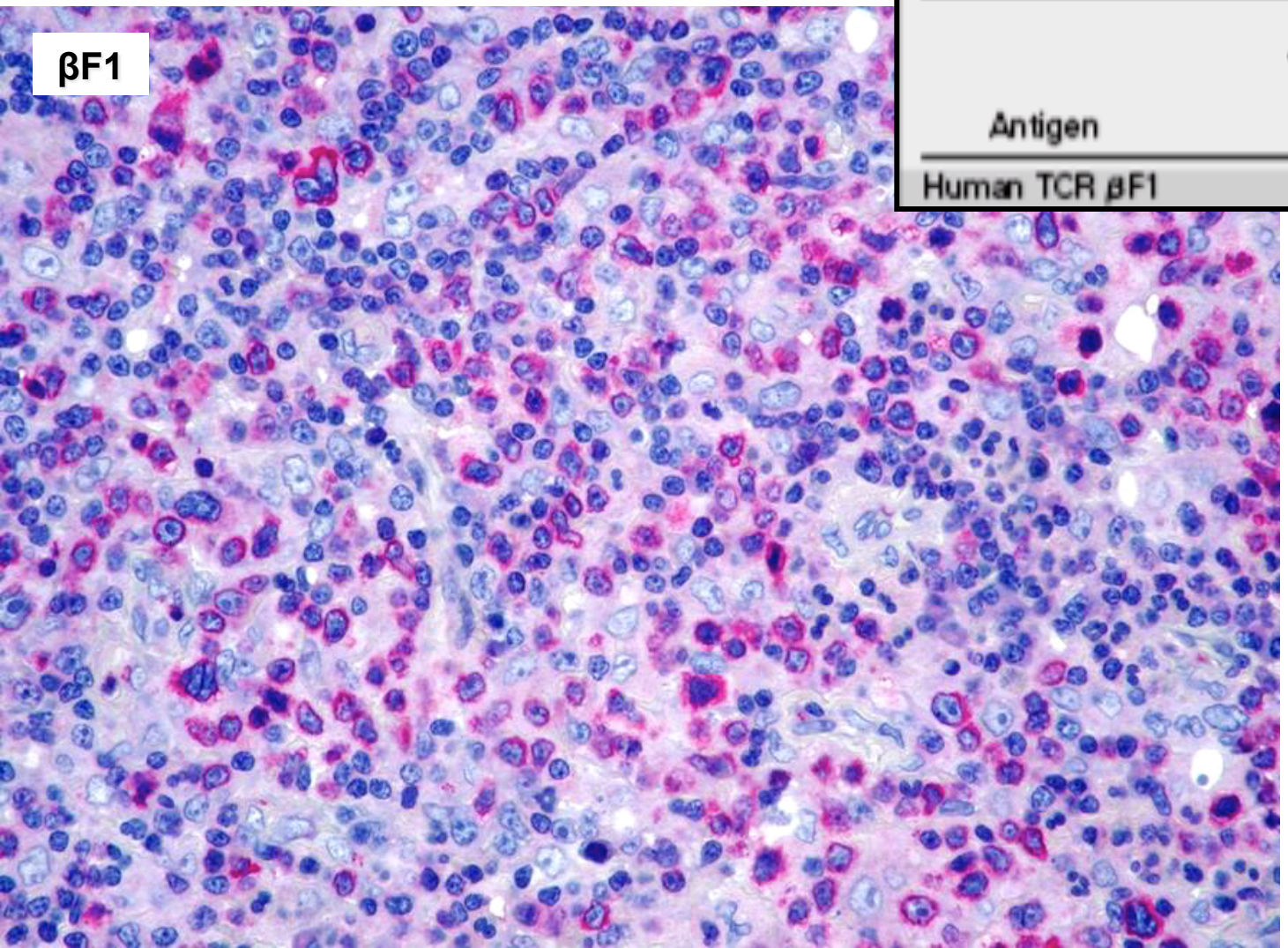
148 PCTL-NOS

Marker Expression in Peripheral T-Cell Lymphoma:
A Proposed Clinical-Pathologic Prognostic Score

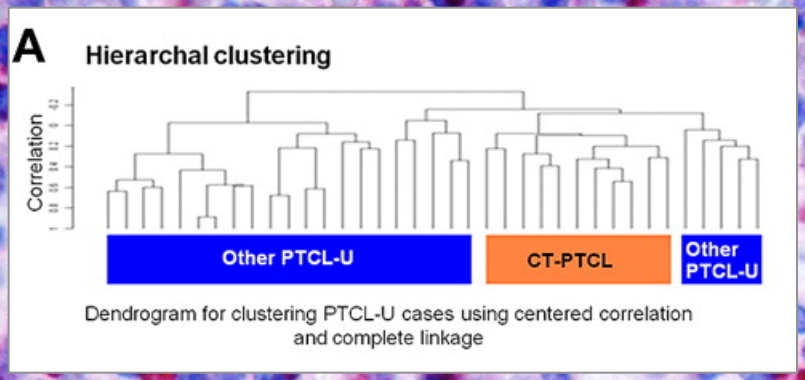
Philip Went, Claudio Agostinelli, Andrea Gallamini, Pier Paolo Piccaluga, Stefano Ascani, Elena Sabattini, Francesco Bacci, Brunangelo Falini, Teresio Motta, Marco Paulli, Tullio Artusi, Milena Piccioli, Pier Luigi Zinzani, and Stefano A. Pileri

J Clin Oncol 24:2472-2479. © 2006 by American Society of Clinical Oncology

	PTCL	
Antigen	No.	Positive (%)
Human TCR βF1	133	97

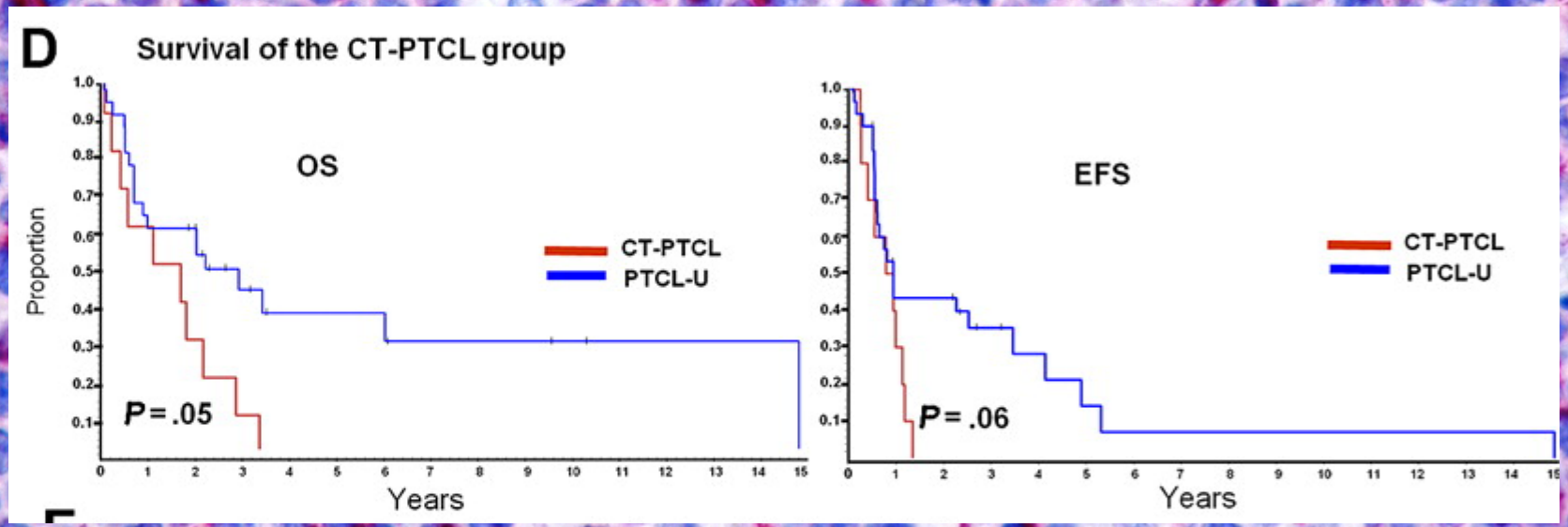


Very important in the dd with ALK-ALCL



Antigen	No.	Positive (%)
TIA-1	138	27
GB	140	2
CD56	140	6
CD57	143	10

Iqbal J et al. Blood 2009



Only 3/8 CD56+ cases were cytotox/BetaF1

Clinicopathologic and Prognostic Significance of Cytotoxic Molecule Expression in Nodal Peripheral T-Cell Lymphoma, Unspecified

Naoko Asano, MD,§ Ritsuro Suzuki, MD,*† Yoshitoyo Kagami, MD,‡ Fumihiro Ishida, MD,§ Kunio Kitamura, MD,‖ Hisashi Fukutani, MD,¶ Yasuo Morishima, MD,‡ Kengo Takeuchi, MD,# and Shigeo Nakamura, MD**

(*Am J Surg Pathol* 2005;29:1284–1293)

41 among 100
younger onset age
poorer performance status
more frequent B-symptoms
higher serum LDH,
extranodal involvement
(particularly bone marrow)
more frequent Epstein-Barr virus integration
higher distribution of the IPI and PIT
lower complete remission rate

Feldman A et al . Leuk 2009
Recurrent translocations involving the IRF4 oncogene locus in PTCL

2 cases PTCL-U showed t(6;14) (p25;q11.2)(IRF4 locus & TCRalpha locus)
Cytotoxic phenotype, IRF4+, CD30-+
Bone marrow+, skin+, without lymphadenopathies
aggressive course

Histopathology

Histopathology 2012, 61, 186–199. DOI: 10.1111/j.1365-2559.2012.04199.x

Nodal cytotoxic molecule (CM)-positive Epstein–Barr virus (EBV)-associated peripheral T cell lymphoma (PTCL): a clinicopathological study of 26 cases

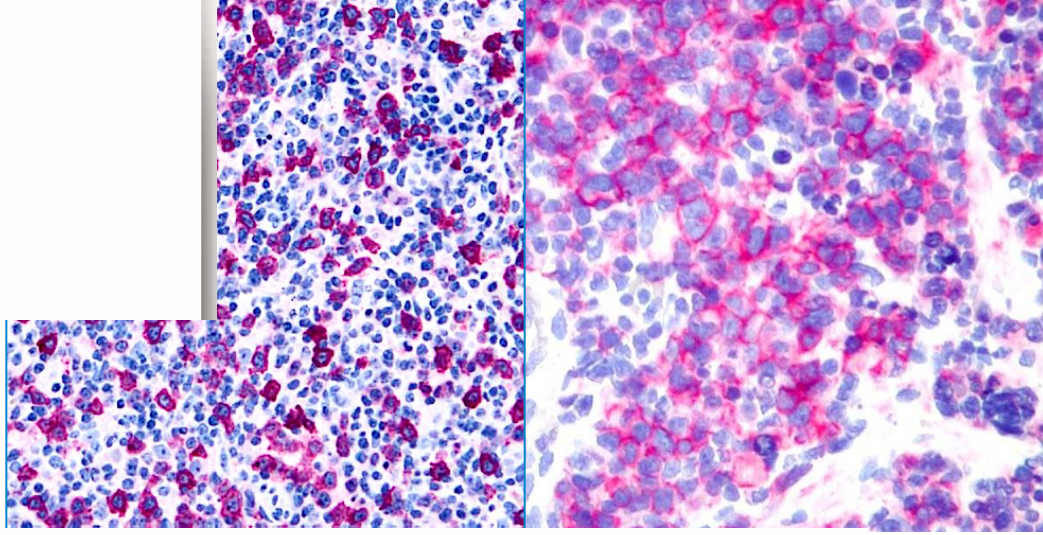
Seiichi Kato, Emiko Takahashi,[1] Naoko Asano,[2] Tsutomu Tanaka,[3] Nirmeen Megahed, Tomohiro Kinoshita[4] & Shigeo Nakamura

high CD8(+), CD56(-) pattern
aggressive clinical course (median, 6.6 months)
Thrombocytopenia in 11 (50%) patients & strongest prognostic indicator

CD30 expression in peripheral T-cell lymphoma

by Elena Sabattini, Marco Pizzi, Valentina Tabanelli, Pamela Baldin, Carlo Sagramoso Sacchetti, Claudio Agostinelli, Pier Luigi Zinzani, and Stefano Pileri

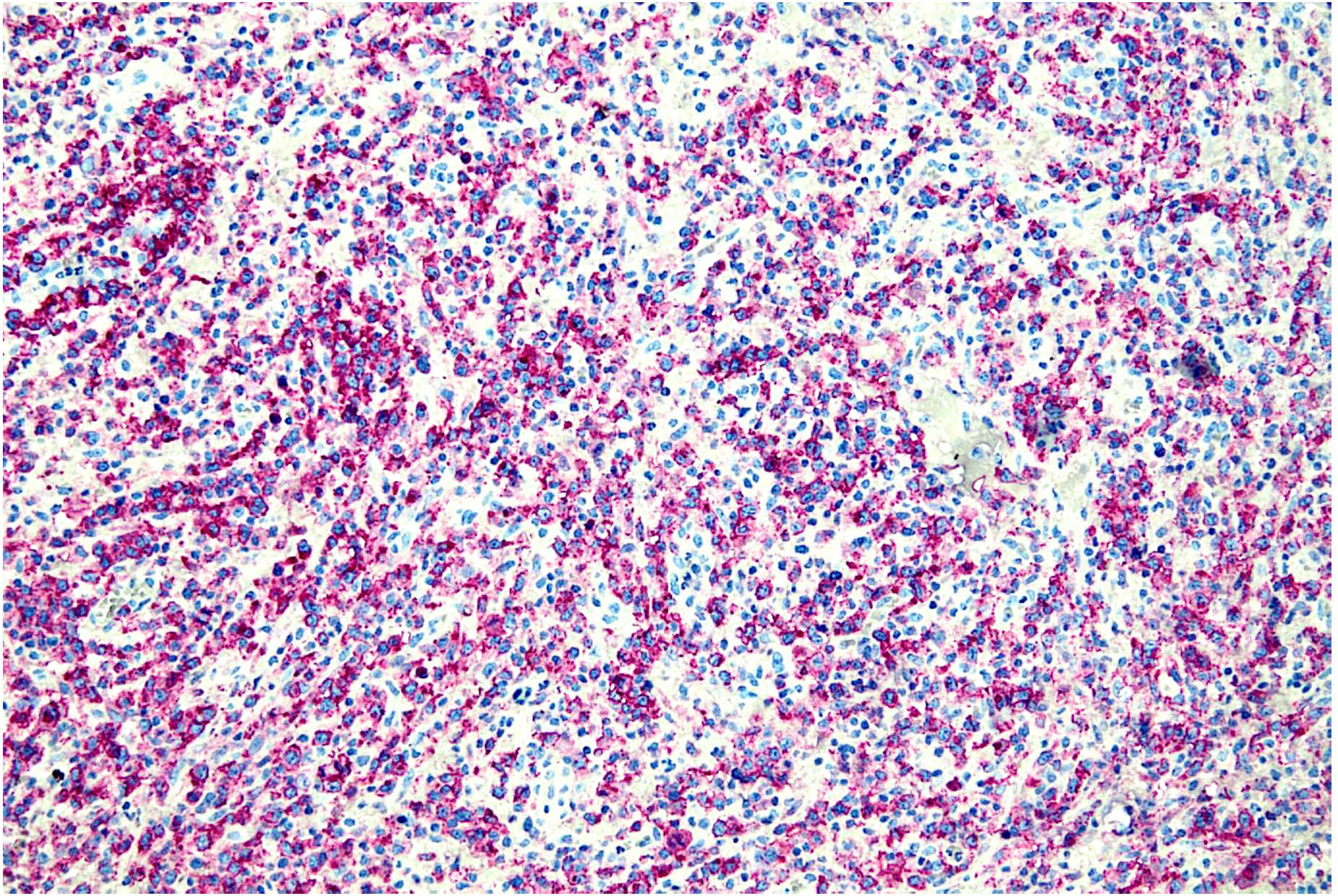
Haematologica 2013 [Epub ahead of print]



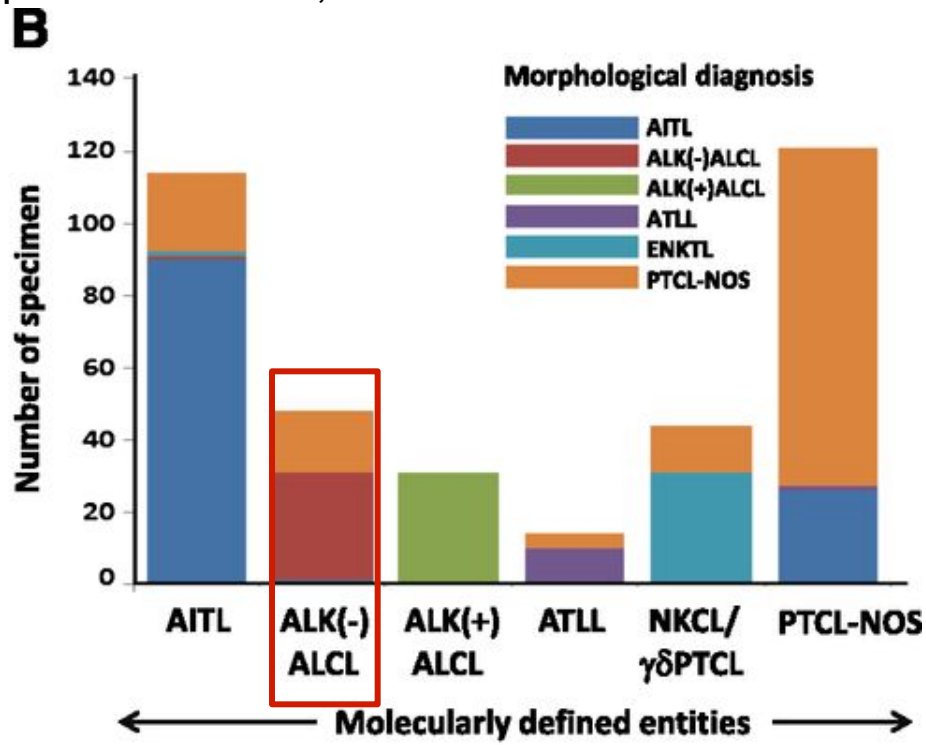
	CD30 IHC SCORE					
	0	1+	2+	3+	4	Score ≥2+
PTCL, NOS (87 cases)	31 (35.63%)	11 (12.64%)	**18 (20.69%)**	**11 (12.64%)**	**16 (18.39%)**	**45/87 (51.72%)**
AITL (42 cases)	24 (51.14%)	9 (21.42%)	**5 (11.90%)**	**4 (9.52%)**	-	**9/42 (21.42%)**
ENTL (10 cases)	2 (20.00%)	1 (10.00%)	**3 (30.00%)**	**1 (10.00%)**	**3 (30.00%)**	**7/10 (70.00%)**
MF (32 cases)	13* (40.63%)	15** (46.88%)	**2[§] (6.25%)**	-	**2[§§] (6.25%)**	**4/32 (12.50%)**
Transformed MF (9 cases)	-	-	**3 (33.33%)**	**6 (66.67%)**	-	**9/9 100%**
EATL type 1 (9 cases)	-	-	**2 (22.22%)**	-	**7 (77,78%)**	**9/9 (100,00%)**
EATL type 2 (3 cases)	3 (100%)	-	-	-	-	-
All types (192 cases)	73 (38.02%)	36 (18.75%)	**33 (17.18%)**	**17 (8.85%)**	**28 (14.58%)**	**83/192 (43.22%)**

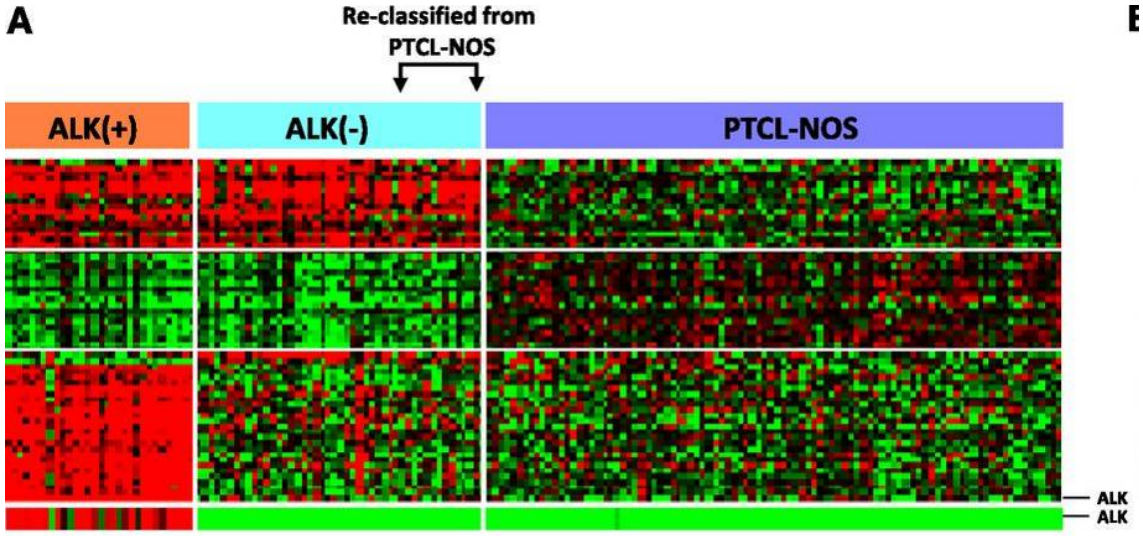
CD30 > 75% cells: PTCL-NOS CD30pos vs ALK neg ALCL

Immunophenotype are not strictly differentiating, but no ALCL morphology;



Iqbal J et al. Blood 2014;123:2915-2923



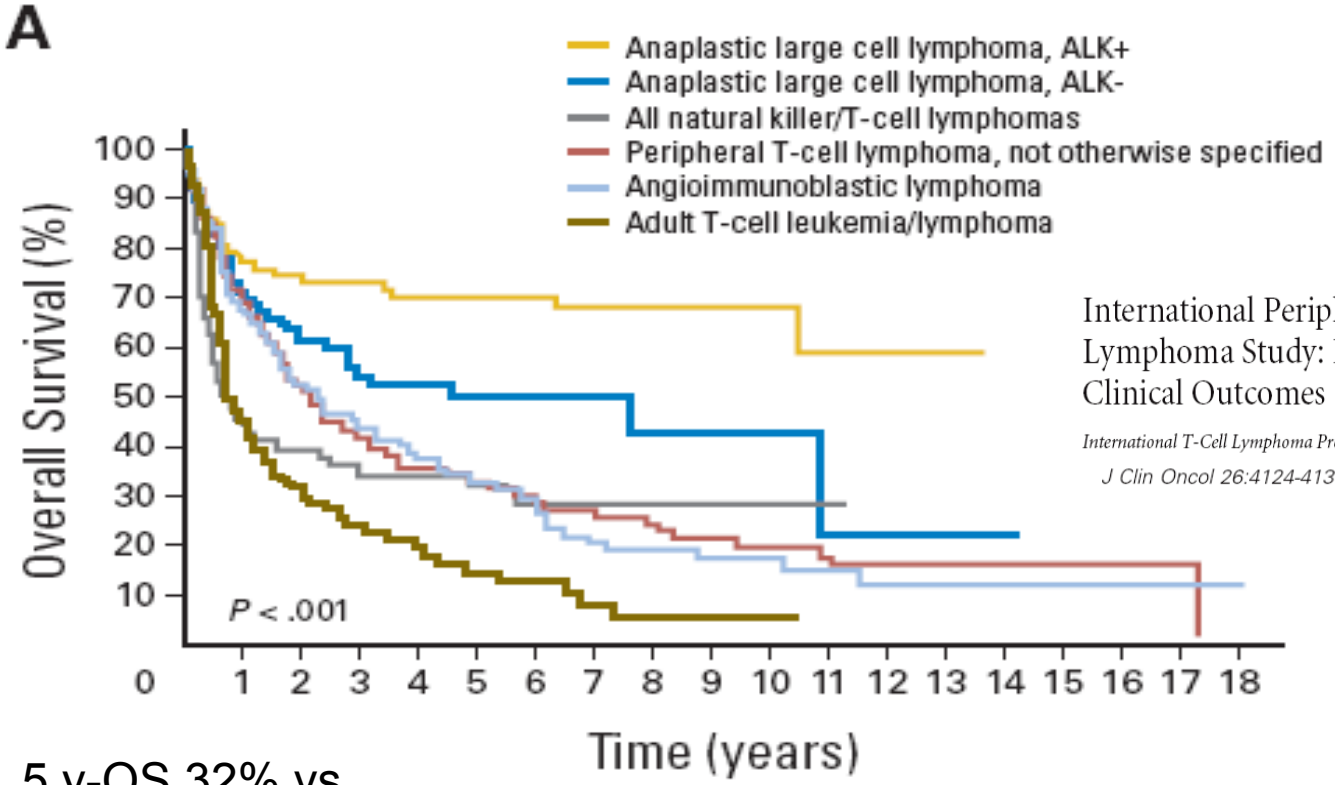


(B)
Pathological vs molecular diagnosis comparison.

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



International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes

International T-Cell Lymphoma Project

5 y-OS 32% vs 51%

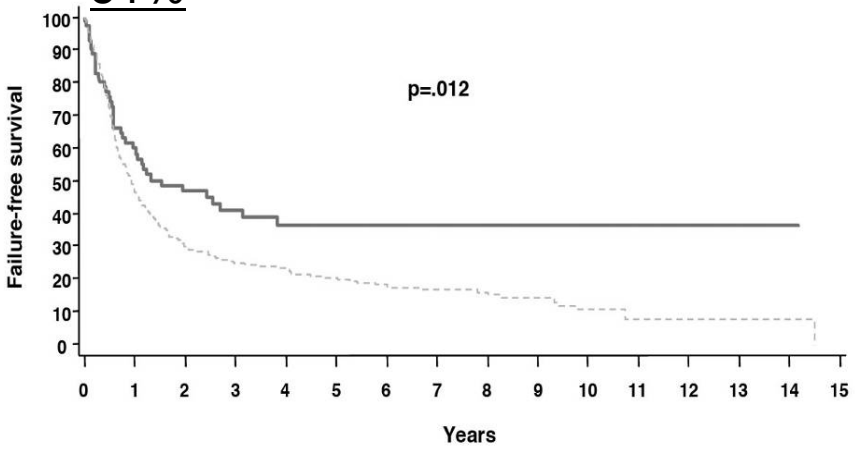


Figure 3a. Failure-free survival of ALK-neg ALCL and PTCL-NOS

Blood, 15 June 2008, Vol. 111, No. 12, pp. 5496-5504.

ALK⁻ anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK + ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project

Kerry J. Savage[1], Nancy Lee Harris[2], Julie M. Vose[3], Fred Ullrich[4], Elaine S. Jaffe[5], Joseph M. Connors[1], Lisa Rimsza[6], Stefano A. Pileri[7], Mukesh Chhanabhai[8], Randy D. Gascoyne[8], James O. Armitage[3], Dennis D. Weisenburger, for the International Peripheral T-Cell Lymphoma Project[9]

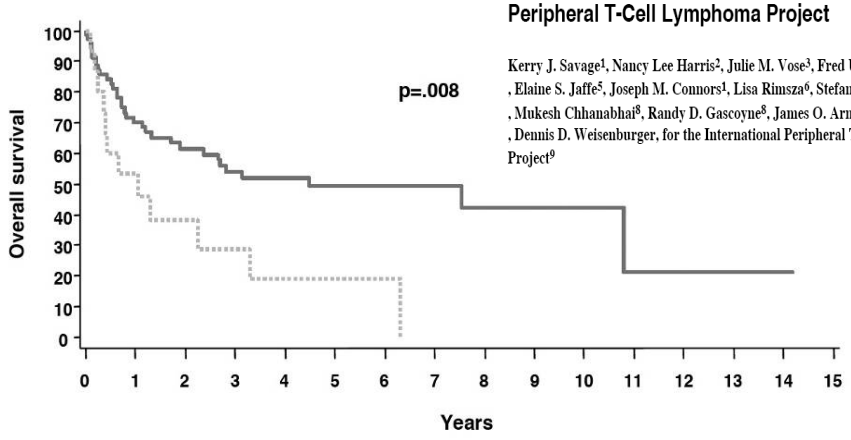
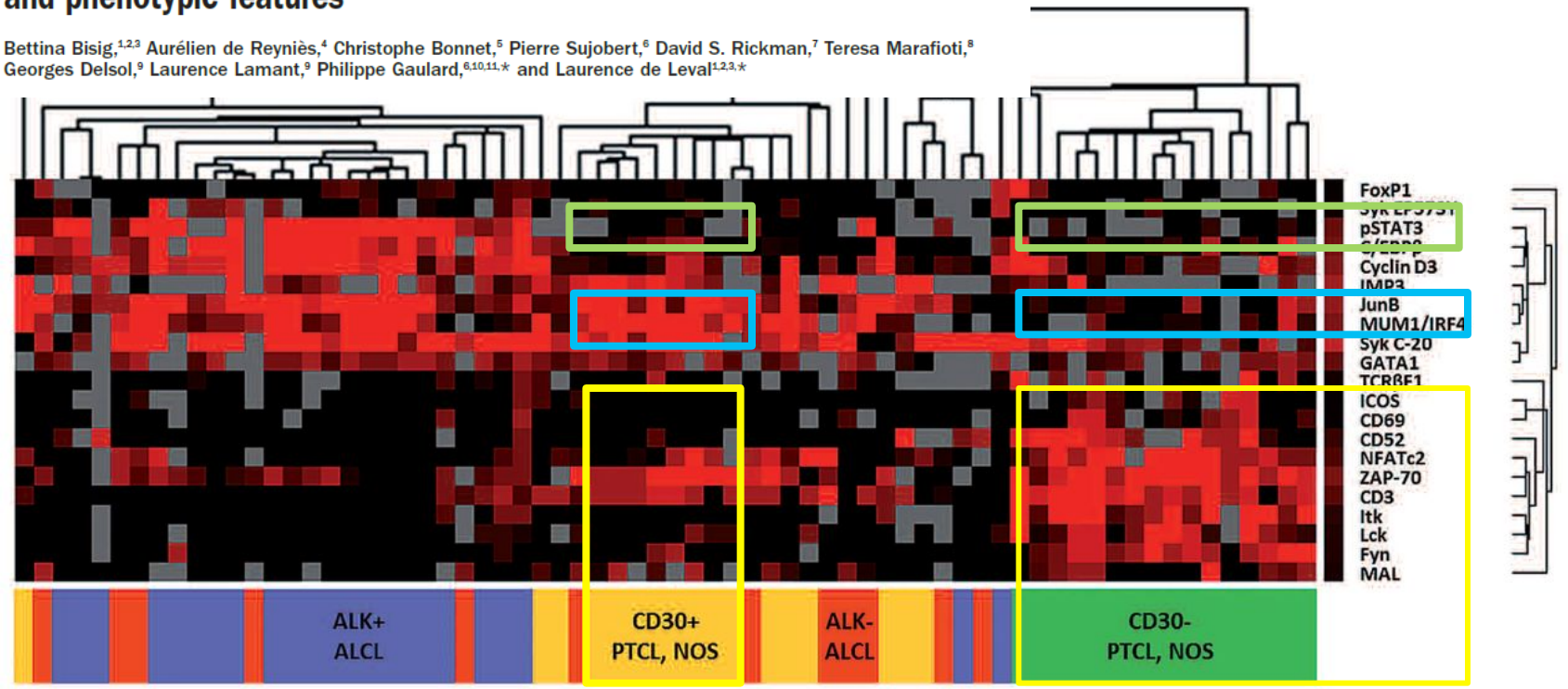


Figure 3d. Overall survival of ALK-neg ALCL and PTCL-NOS (CD30+ >80% cells)

CD30-positive peripheral T-cell lymphomas share molecular and phenotypic features

Bettina Bisig,[1,2,3] Aurélien de Reyniès,[4] Christophe Bonnet,[5] Pierre Sujobert,[6] David S. Rickman,[7] Teresa Marafioti,[8] Georges Delsol,[9] Laurence Lamant,[9] Philippe Gaulard,[6,10,11,*] and Laurence de Leval[1,2,3,*]



downregulation of
1) TCR differentiation/activation (CD52, CD69, ICOS, CD28)
2) Transcription factor NFATc2
3) Proximal TCR signaling (Lck, Itk, Fyn; ZAP70 exception)

Upregulate CD30+/ALK independent associated signature
JunB+, IRF4+

ALCL associated signature
pSTAT3 up & CD3 down

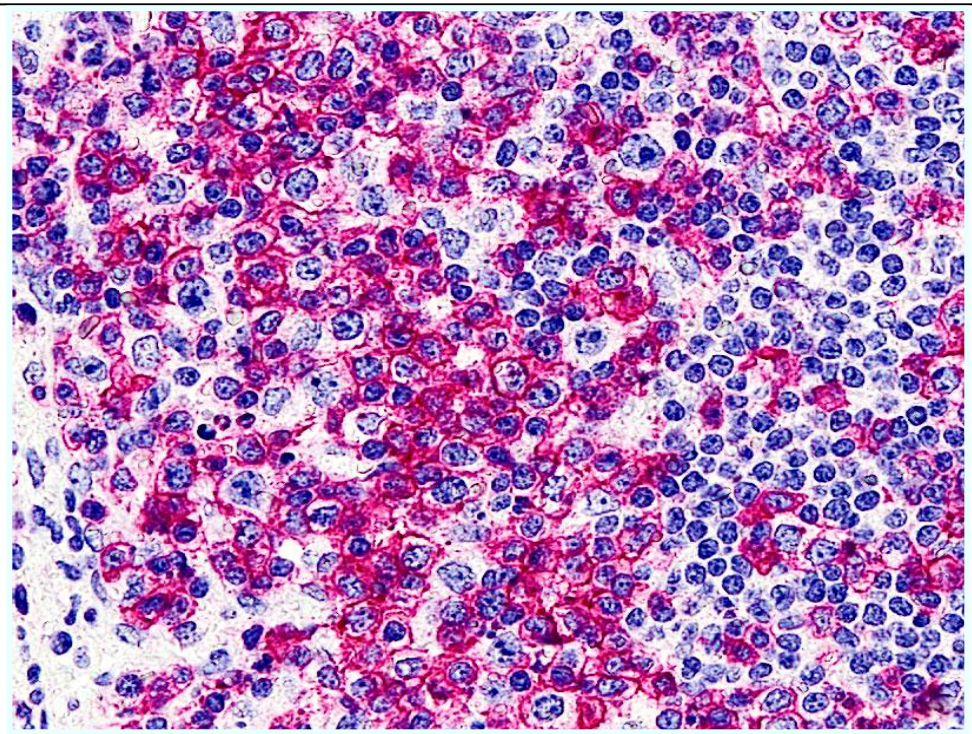
CD30+PTCLNOS
1) Share common features with ALCL (both ALK+/ALK-) due to a common CD30 signature
2) Cluster as a group close to ALK-ALCL

FOLLICULAR HELPER T CELL MARKERS

CXCL13, programmed cell death-1 (PD1/CD279) and inducible costimulator (ICOS), CD200, Bcl6, CD10, adaptor molecule SAP

About 25-30% of PTCL NOS cases express FTH markers without the morphological features of AITL

Some cluster with "FTH gene signature"cases; will be moved to TFH-lymphoma (Who 2016)



Published Ahead of Print on July 15, 2013 as 10.1200/JCO.2012.42.5611
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.42.5611

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

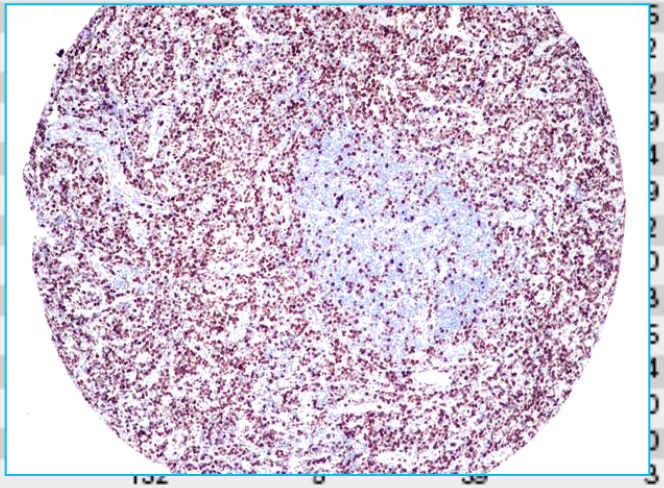
Molecular Profiling Improves Classification and Prognostication of Nodal Peripheral T-Cell Lymphomas: Results of a Phase III Diagnostic Accuracy Study

Pier Paolo Piccaluga, Fabio Fuligni, Antonio De Leo, Clara Bertuzzi, Maura Rossi, Francesco Bacci, Elena Sabattini, Claudio Agostinelli, Anna Gazzola, Maria Antonella Laginestra, Claudia Mannu, Maria Rosaria Sapienza, Sylvia Hartmann, Martin L. Hansmann, Roberto Piva, Jaweed Iqbal, John C. Chan, Denis Weisenburger, Julie M. Vose, Monica Bellei, Massimo Federico, Giorgio Inghirami, Pier Luigi Zinzani, and Stefano A. Pileri

De Leval L et al Blood 2007
Dupuis J et al Am J Surg pathol 2006
Dorfman DM et al Am J Surg pathol 2011
Rogdriguez justo M et al Mod Pathol 2009
Rogriguez-Pinilla e al Am J Surg Pathol 2008
Iqbal J et al Blood 2009
Gaulard P et al Semin Diagn Pathol 2011
Hartmann S et al Histopathology 2011
Zhan HQ et al J Clin Pathol 2011
Agostinelli C et al. Histopathology 2011

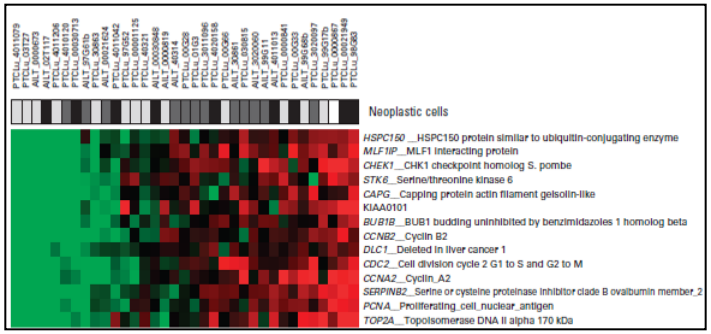
Table 2. Immunophenotypic Features and EBER Expression in a PTCL/AILD TMA

Antigen	PTCL No.	PTCL Positive (%)	AILD No.	AILD Positive (%)
Human TCR βF1	133	97	30	94
CD2	136	70	41	100
CD3				
CD4				
CD8				
CD5				
CD7				
CD10				
CD15				
CD30				
CD56				
CD57				
TIA-1				
GB				
ALK-C				
EBER				
Mib-1 high	138	11	40	5
CD20	141	1	42	0
CD79a	142	0	36	0

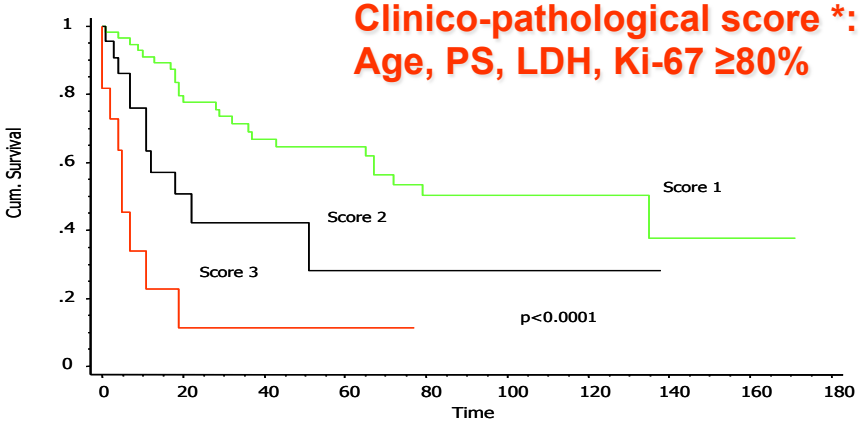


Abbreviations: EBER, Epstein-Barr virus–associated small RNAs; PTCL, peripheral T-cell lymphoma; AILD, angioimmunoblastic type; TMA, tissue microarray; TCR, T-cell receptor; TIA-1, T-cell intracellular antigen 1; GB, granzyme B; ALK, anaplastic large-cell lymphoma kinase.

Cuadros, JCO, 2007



Went et al, JCO, 2006



*found to be more robust than PIT (P = .0043) in the present series (Gutierrez-Garcia: Ann. Oncol: 2010) .

EBV adverse prognostic factor

Marker Expression in Peripheral T-Cell Lymphoma: A Proposed Clinical-Pathologic Prognostic Score

Philip Went, Claudio Agostinelli, Andrea Gallamini, Pier Paolo Piccaluga, Stefano Ascani, Elena Sabattini, Francesco Bacci, Brunangelo Falini, Teresio Motta, Marco Paulli, Tullio Artusi, Milena Piccioli, Pier Luigi Zinzani, and Stefano A. Pileri

J Clin Oncol 24:2472-2479. © 2006 by American Society of Clinical Oncology

EBER in 5% cases (7/148 cases)

NEOPLASIA

Prognostic significance of Epstein-Barr virus in nodal peripheral T-cell lymphoma, unspecified: a Groupe d'Etude des Lymphomes de l'Adulte (GELA) study

Jehan Dupuis, Jean-François Emile, Nicolas Mounier, Christian Gisselbrecht, Nadine Martin-Garcia, Tony Petrella, Reda Bouab, Françoise Berger, Alain Delmer, Bertrand Coiffier, Félix Reyes, and Philippe Gaulard

EBER in 41% cases (but few cells in most cases)
5-yr-OS 11% in positive cases

Histopathology

Histopathology 2012, 61, 186–199. DOI: 10.1111/j.1365-2559.2012.04199.x

Nodal cytotoxic molecule (CM)-positive Epstein–Barr virus (EBV)-associated peripheral T cell lymphoma (PTCL): a clinicopathological study of 26 cases

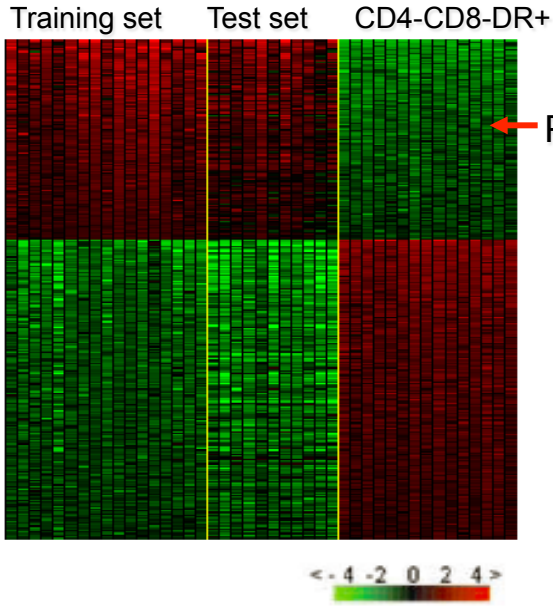
Seiichi Kato, Emiko Takahashi,[1] Naoko Asano,[2] Tsutomu Tanaka,[3] Nirmeen Megahed, Tomohiro Kinoshita[4] & Shigeo Nakamura

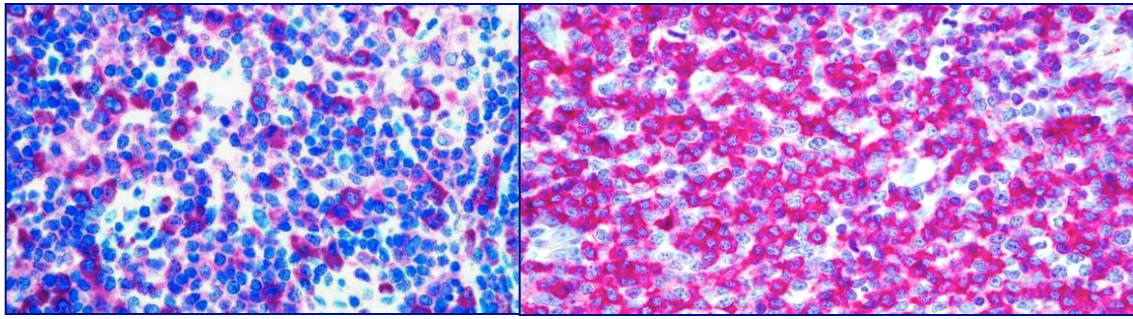
high CD8(+), CD56(-) pattern
aggressive clinical course (median, 6.6 months)
Thrombocytopenia in 11 (50%) patients & strongest prognostic indicator

List of markers applicable to formalin-fixed, paraffin-embedded tissue sections for the diagnosis of peripheral NK/T cell lymphomas (ESMO/SIE/SIES/GITMO Guidelines)

- T-cell markers: CD2, CD3, CD4, CD5, CD7, CD8, CD52, βF1, TCRγ
- Cytotoxic markers: TIA1, granzyme B, perforin
- FTH markers: CD10, BCL6, PD1, CXCL13, SAP, ICOS, CCR5
- Treg markers: FoxP3
- NK-cell markers: CD16, CD56, CD57
- Activation markers: CD25, CD30
- Proliferation: MIB1/Ki-67
- B-cell markers: CD20, BSAP/PAX5
- Follicular dendritic cells: CD21
- Histiocytes and epithelioid elements: CD68/PG-M1
- EBV: EBER ISH, LMP1, EBNA2
- Others: ALK, EMA, CD45, GATA3, TBX21, PDGFRα, VEGFR

PDGFR a and b in PTCL NOS





TCL subtype	cases included in TMA	PDGFRα	p-PDGFRα	PDGF-A	PDGF-B
PTCL/NOS	156	128/141	105/110	74/86	85/92

Piccaluga et al. Lancet Oncology 2005, Leukaemia 2014

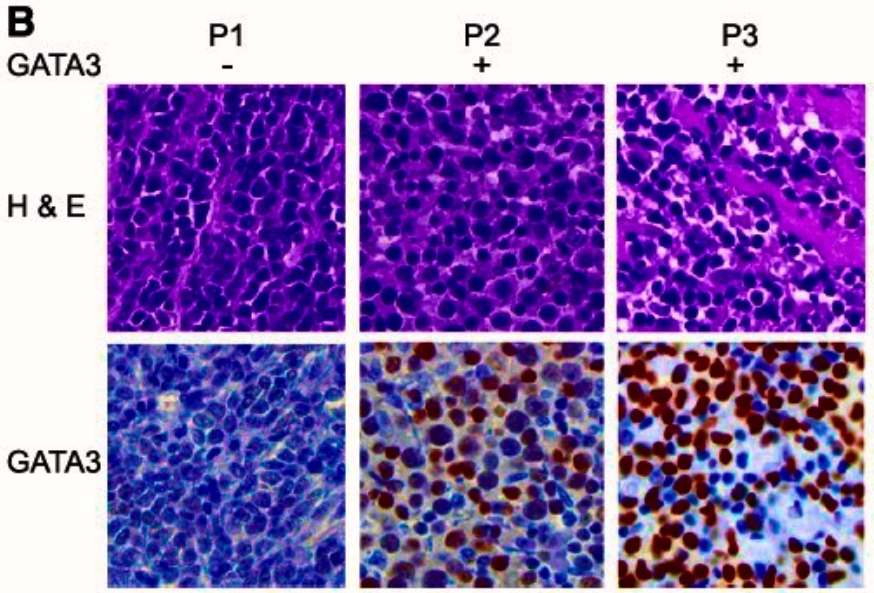
Tyrosine kinase inhibitor PDGFRa is expressed and activated in virtually all PTCL NOS
(by autocrine stimulation)
and PDGFRs blockade can be an effective strategy in PTCL-U
(Roncolato et al. Exper Rev Hematol 2011, Turner SD. Leukaemia 2013)
as in other PTCL (Leimer D Nat Med 2012)

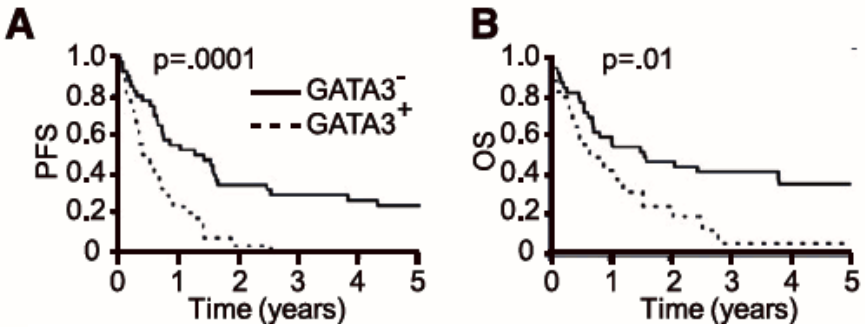
PTCL-DASA01 (CA180-548) "Open Label, Phase IIa Multicenter Pilot Study of Dasatinib in the Treatment of Patients with Peripheral T-Cell Lymphoma (PTCL) Relapsed/Refractory or not Amenable to Conventional Therapy" EudraCT 2013-005240-28

GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features

Tianjiao Wang,[1] Andrew L. Feldman,[2] David A. Wada,[3] Ye Lu,[1] Avery Polk,[1] Robert Briski,[1] Kay Ristow,[4] Thomas M. Habermann,[4] Dafydd Thomas,[5] Steven C. Ziesmer,[4] Linda E. Wellik,[4] Thomas M. Lanigan,[6] Thomas E. Witzig,[4] Mark R. Pittelkow,[7] Nathanael G. Bailey,[5] Alexandra C. Hristov,[5] Megan S. Lim,[5] Stephen M. Ansell,[4] and Ryan A. Wilcox[1]

(*Blood*. 2014;123(19):3007-3015)





blood

Prepublished online March 14, 2014;
doi:10.1182/blood-2013-11-536359

Gene expression signatures delineate biologic and prognostic subgroups in peripheral T-cell lymphoma

Javeed Iqbal, George Wright, Chao Wang, Andreas Rosenwald, Randy D. Gascoyne, Dennis D. Weisenburger, Timothy C. Greiner, Lynette Smith, Shuangping Guo, Ryan A. Wilcox, Bin Tean Teh, Soon Thye Lim, Soon Yong Tan, Lisa M. Rimsza, Elaine S. Jaffe, Elias Campo, Antonio Martinez, Jan Delabie, Rita M. Braziel, James R. Cook, Raymond R. Tubbs, German Ott, Eva Geissinger, Philippe Gaulard, Pier Paolo Piccaluga, Stefano A. Pileri, Wing Y. Au, Shigeo Nakamura, Masao Seto, Francoise Berger, Laurence de Leval, Joseph M. Connors, James Armitage, Julie Vose, Wing C. Chan and Louis M. Staudt

T cell lineage as important factor for PTCL NOS biology
TBX21/Tbet and other Th1-related transcripts
GATA3 and other Th2-related transcripts (poorer prognosis)

This is what we routinely do to reach a hopefully correct diagnosis of PTCL-U

The recent molecular data published on a PTCL NOS subclassification as well as the mutational aberrancies discovered with NGS techniques will likely identify cellular pathways and additional molecules useful for both diagnosis and therapy in PTCL-U