Peripheral T-cell lymphomas

- #*Stefano A. Pileri
- #Unit of Haematopathology – European Institute of Oncology, Milan
- *Bologna University School of Medicine, Bologna, Italy

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International Agency for Research on Cancer (IARC)

Revised 4th Edition

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by

Steven H. Swerdlow

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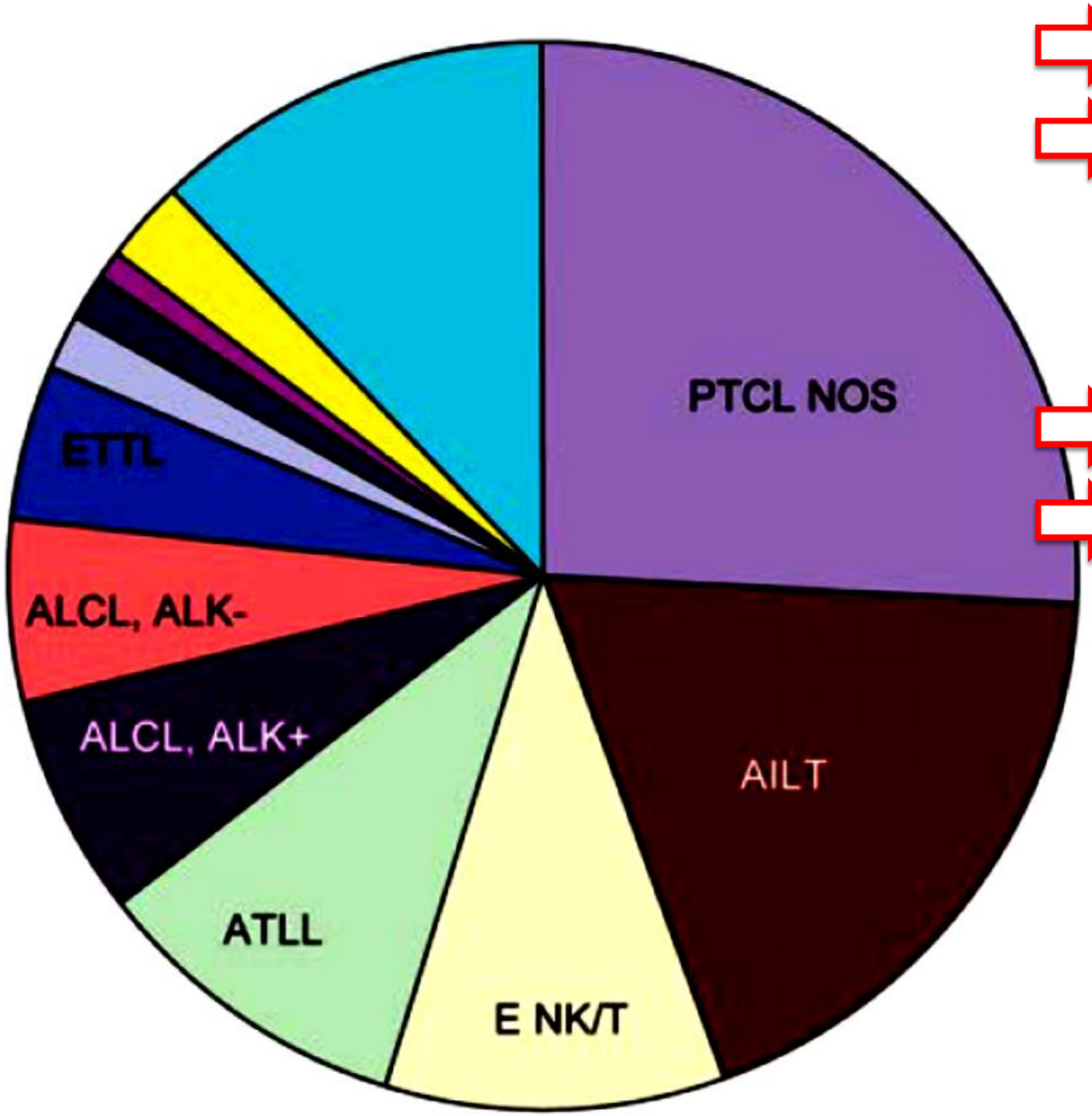
MATURE T-AND NK-NEOPLASMS

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



- Peripheral T-cell Lymphoma - NOS 25.9%
- Angioimmunoblastic 18.5%
- Natural killer/T-cell lymphoma 10.4%
- Adult T-cell leukemia/lymphoma 9.6%
- Anaplastic large cell lymphoma, ALK+ 6.6%
- Anaplastic large cell lymphoma, ALK- 5.5%
- Enteropathy-type T-cell* 4.7%
- Primary cutaneous ALCL 1.7%
- Hepatosplenic T-cell 1.4%
- Subcutaneous panniculitis-like 0.9%
- Unclassifiable PTCL 2.5%
- Other disorders 12.2%

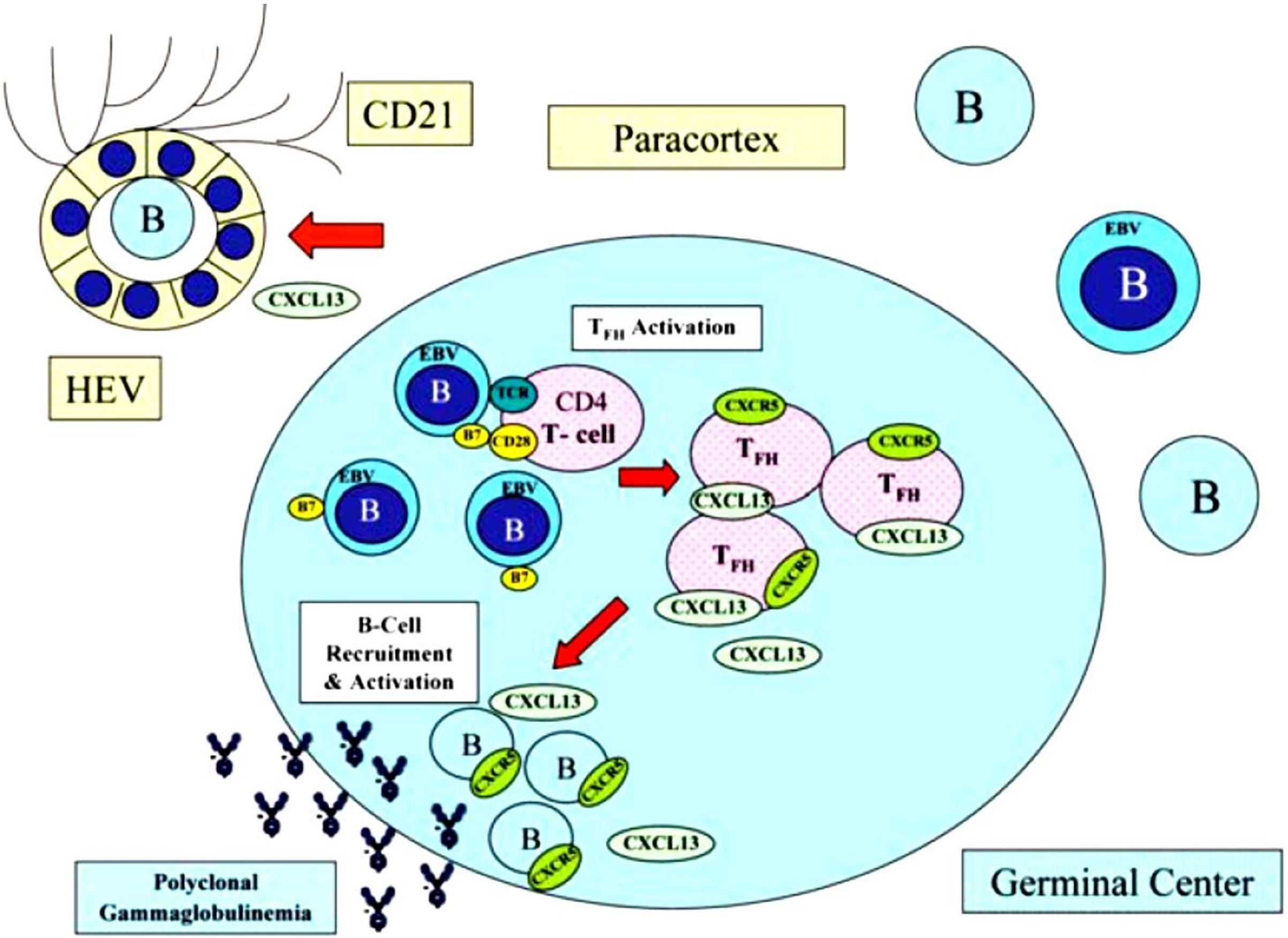
BIOLOGICAL INSIGHTS INTO LYMPHOID TUMORS

Novel insights into the pathogenesis of T-cell lymphomas

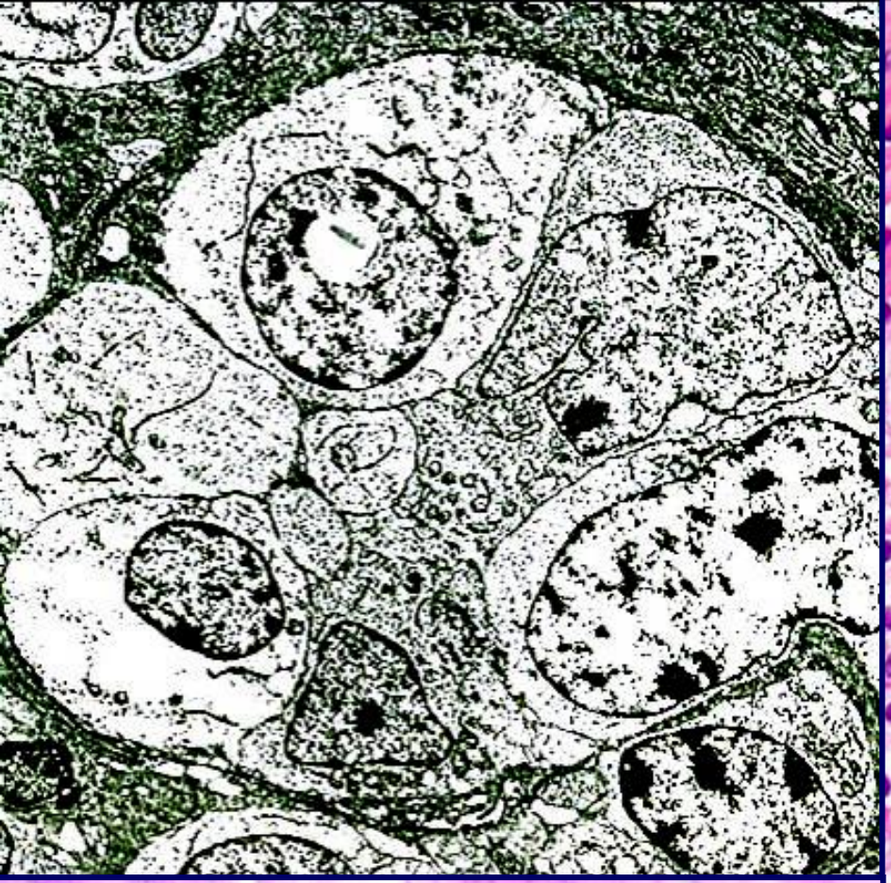
John S. Van Arnam,[1] Megan S. Lim,[1] and Kojo S. J. Elenitoba-Johnson[1,2]

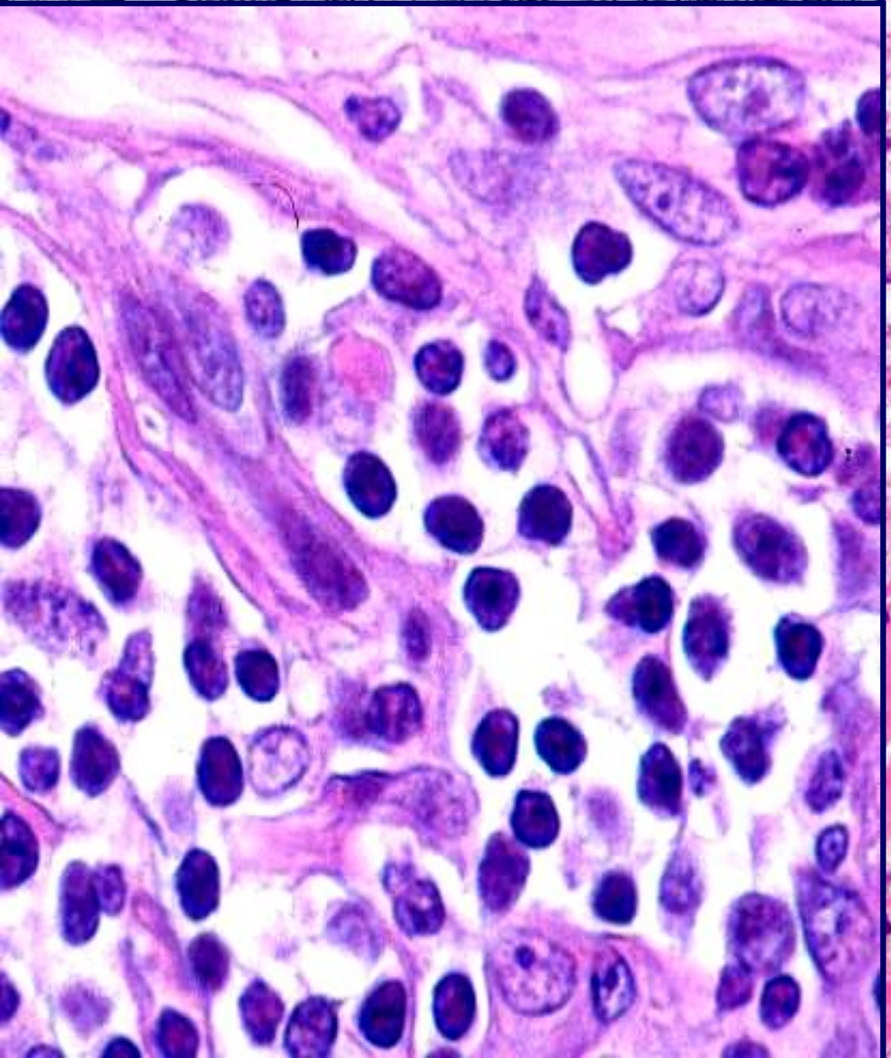
[1]Department of Pathology and Laboratory Medicine and [2]Center for Personalized Diagnostics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

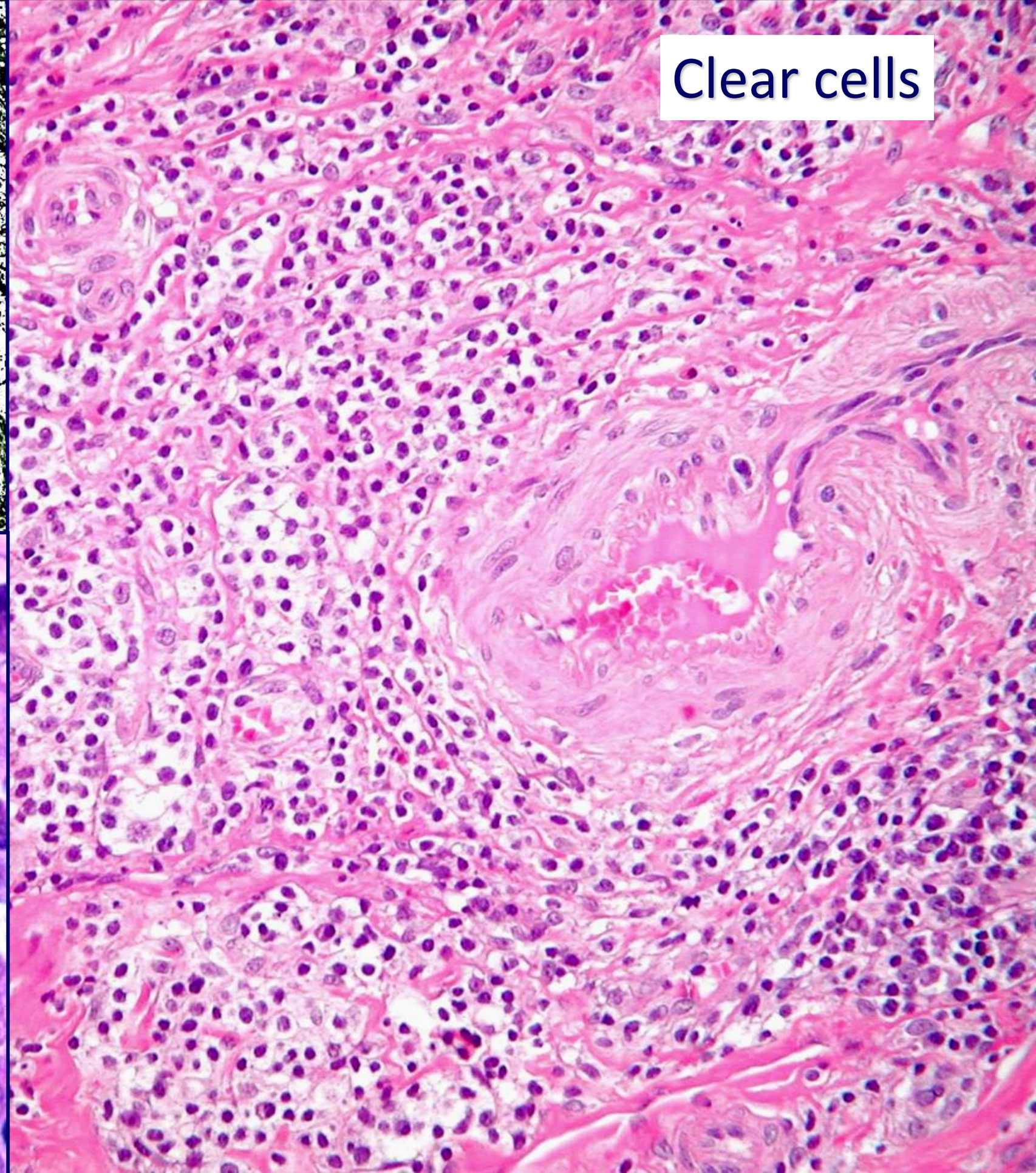
T-cell lymphomas are a heterogeneous group of rare malignancies with overlapping clinical, immunologic, and histologic features. Recent advances in our understanding of T-cell differentiation based on gene expression profiling, next-generation sequencing, and transgenic mouse modeling studies have better elucidated the pathogenetic mechanisms underlying the diverse biology of T-cell lymphomas. These studies show that although genetic alterations in epigenetic modifiers are implicated in all subtypes of T-cell lymphomas, specific subtypes demonstrate enrichment for particular recurrent alterations targeting specific genes. In this regard, *RHOA* and *TET2* alterations are prevalent in nodal T-cell lymphomas, particularly angioimmunoblastic T-cell lymphomas, peripheral T-cell lymphomas (PTCLs) not otherwise specified, and nodal PTCLs with T-follicular helper phenotype. JAK-STAT signaling pathways are mutationally activated in many extranodal T-cell lymphomas, such as natural killer/T-cell and hepatosplenic T-cell lymphomas. The functional significance of many of these genetic alterations is becoming better understood. Altogether these advances will continue to refine diagnostic criteria, improve prognostication, and identify novel therapeutic targets, resulting in improved outcomes for patient with T-cell lymphomas. (*Blood*. 2018; 131(21):2320-2330)


CD21
Paracortex
B
B
CXCL13
HEV
EBV
B
T$_{FH}$ Activation
EBV
B
TCR
CD4
T- cell
B7
CD28
CXCR5
T$_{FH}$
CXCR5
T$_{FH}$
CXCL13
CXCL13
EBV
B
B7
EBV
B
B7
T$_{FH}$
CXCR5
CXCL13
CXCL13
B-Cell
Recruitment
& Activation
CXCL13
B
CXCR5
B
CXCR5
B
CXCR5
CXCL13
B
Polyclonal
Gammaglobulinemia
Germinal Center

	AITL	Other TFH-PTCL	PTCL-NOS	p-value across entities (Fisher test)
Clinical variables				
Median age at diagnosis (years)	67.8	65.2	59.6	NA
Sex (M)	53/94 (56%)	10/19 (53%)	23/34 (68%)	0.4
Stage III-IV	84/85 (99%)	18/19 (95%)	29/34 (85%)	< 0.01
ECOG ≥ 2	67/83 (53%)	7/17 (41%)	11/33 (33%)	0.47
IPI ≥ 3	20/32 (81%)	11/17 (55%)	67/83 (63%)	0.08
Coombs (+)	25/56 (45%)	2/5 (40%)	0/6 (0%)	0.03
Anemia	47/71 (66%)	7/13 (54%)	10/27 (37%)	0.02
Hypergammaglobulinemia ($\geq$16 g/dl)	23/48 (48%)	2/11 (18%)	4/19 (21%)	0.05





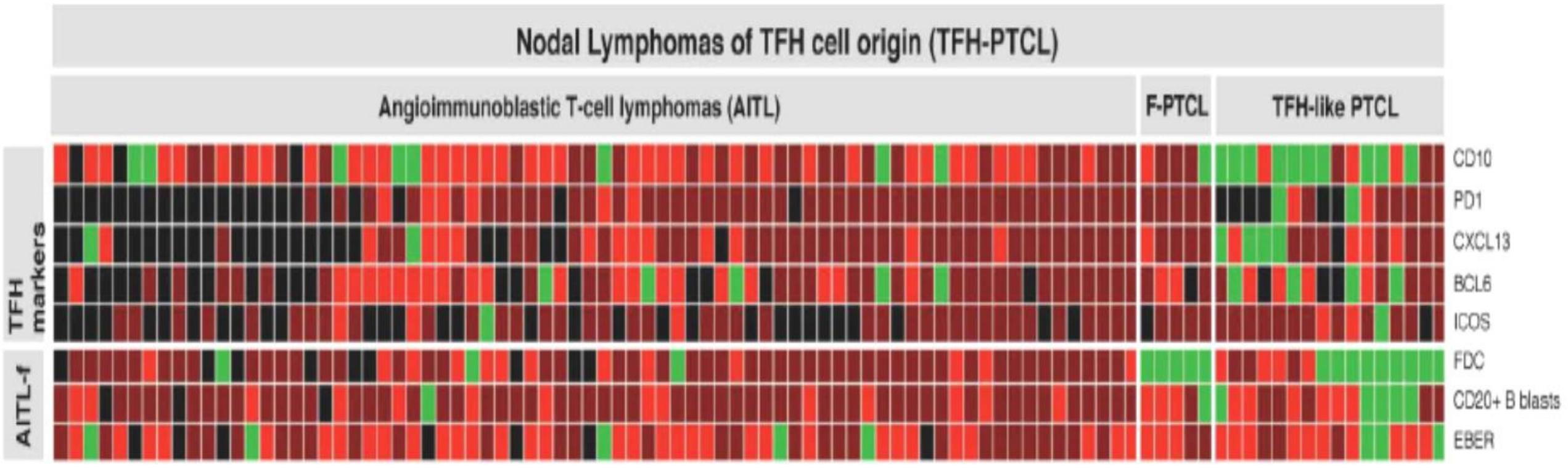


Clear cells

A novel subset of T-helper cells: follicular T-helper cells and their markers

Camille Laurent,[1] Nicolas Fazilleau[2] and Pierre Brousset[3]

[1]INSERM, U.563, Centre de Physiopathologie de Toulouse-Purpan, Toulouse, F-31300 France; [2]Université Paul-Sabatier, Toulouse, F-31400 France; [3]Laboratoire d'Anatomie Pathologique, CHU Purpan, Toulouse,France
E-mail: brousset.p@chu-toulouse.fr. *doi:10.3324/haematol.2009.019133*



BCL6, CD10, PD-1, ICOS, SAP, CXCL13, CCR5

CD3

CD20

CD4

CD8

EBER

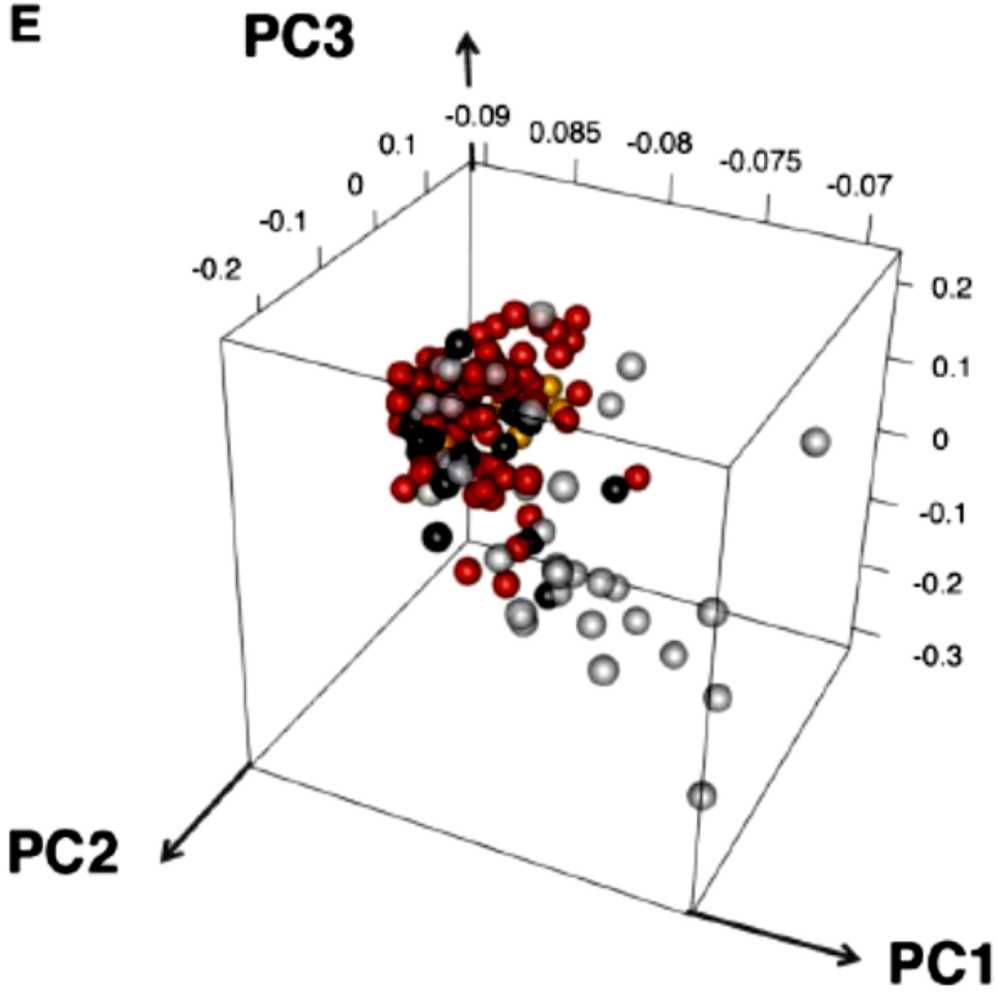
Am J Surg Pathol. 2013 June ; 37(6): 816–826. doi:10.1097/PAS.0b013e3182785610.

Peripheral T-cell lymphomas of follicular T-helper cell derivation with Hodgkin/Reed-Sternberg cells of B-cell lineage: Both EBV-positive and EBV-negative variants exist

Alina Nicolae, MD, PhD[1], Stefania Pittaluga, MD, PhD[1], Girish Venkataraman, MD, PhD[2], Anahi Vijnovich-Baron, MD[3], Liqiang Xi, MD[5], Mark Raffeld, MD, PhD[5], and Elaine S. Jaffe, MD[1,*]

Peripheral T-cell lymphomas (PTCL) are functionally and morphologically complex. EBV-positive B- cells have been reported in angioimmunoblastic T-cell lymphoma (AITL) and other PTCL and may mimic Hodgkin/Reed-Sternberg (HRS) cells, but EBV-negative HRS-like B-cells have not been described. We wished to assess the nature of the PTCL associated with HRS-like cells, and to determine whether EBV-negative HRS-like cells may be seen. We identified 57 PTCL cases reported as containing HRS-like cells. These included 32 AITL, 19 PTCL-NOS, 3 PTCL-NOS, follicular variant, 1 PTCL-NOS, T-zone variant and 2 adult T-cell leukemia/lymphoma (ATLL). All patients were adults, median age, 63, and presented with lymphadenopathy. The male: female ratio was 31:26 (1.2:1). Clonal TRG rearrangement was detected in 46/53 cases. 6/38 cases had a concomitant clonal immunoglobulin gene rearrangement. In 52/57 cases the HRS cells were positive for EBV. Five cases, three classified as AITL and two as PTCL-NOS, follicular variant, contained HRS-like cells negative for EBV. All PTCL with EBV-negative HRS cells had a T_{FH}-immunophenotype. The neoplastic T-cells expressed CD3, CD4, and PD-1, and formed rosettes around the HRS-like cells. The HRS-like cells were positive for CD20 (variable intensity), PAX5, CD30 and CD15 (4/5). We conclude that both EBV positive and EBV negative HRS-like B-cells may occur in the background of PTCL; caution is needed to avoid misdiagnosis as CHL. The close interaction between the HRS-like cells and the rosetting PD-1-positive T-cells suggests a possible pathogenetic role in this phenomenon, and provides new insights into the abnormal B-cell proliferations that occur in the context of T_{FH} malignancies.

E



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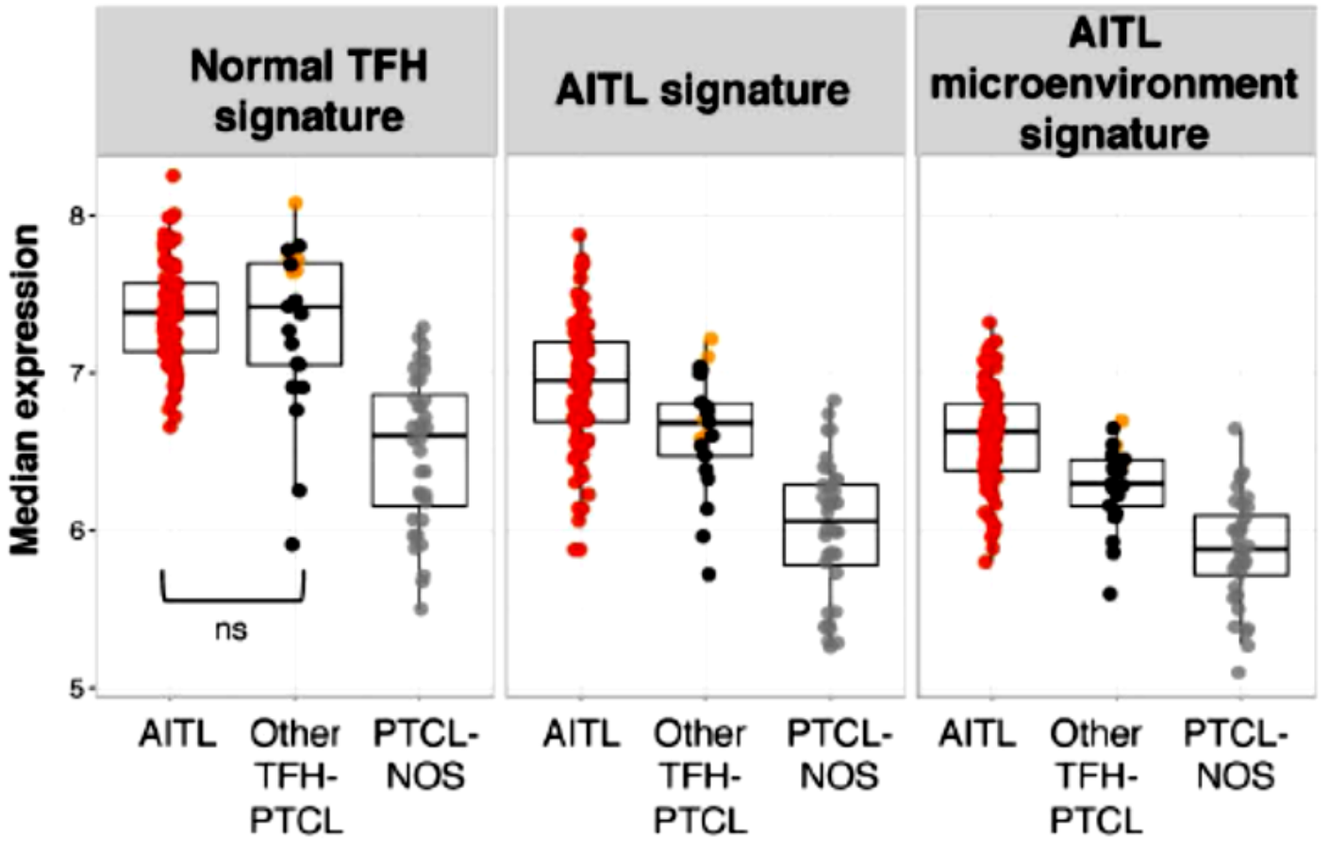

AITL TFH-like PTCL F-PTCL PTCL-NOS

	AITL	Other TFH-PTCL	PTCL-NOS	p-value across entities (Fisher test)
Mutations (%)*				
TET2	31/64 (48%)	10/15 (67%)	4/24 (17%)	$< 1.0 \times 10^{-2}$
DNMT3A	19/64 (30%)	2/14 (14%)	1/24 (4%)	0.02
IDH2	22/66 (33%)	1/16 (6%)	0/23 (0%)	$< 1.0 \times 10^{-3}$
RHOA	45/72 (63%)	11/19 (58%)	4/23 (17%)	$< 1.0 \times 10^{-3}$
Copy number variations				
Events per patient (average)	3.17	3.15	10.8	
Patients with events	23/60 (38%)	5/15 (33%)	17/27 (63%)	0.38
Heavily-rearranged (>10 events) patients	6/60 (8%)	3/15 (20%)	11/27 (41%)	0.03
Patients with homozygous deletions or amplifications	3/60 (5%)	3/15 (20%)	12/27 (44%)	< 0.01

CD4+ T

IL-12

AITL

Wild-type

TET2 single-mutant

IDH2/TET2 double-mutant

212

172

58

48

105

440

- *CXCL12* - *CXCR3*
- *IRF6* - *A2M*
- *MED14* - *IRF1*
- *RUNX2* - *IFIM3*
- *AKT* - *FOXP1*

- *CXCL9* - *IFIT3*
- *CCL2* - *IL17RA*
- *IL2* - *STAT1*
- *RHOJ* - *IL10RA*
- *CXCL10*

- *CCNB1* - *HDAC8*
- *CKD2* - *TOP2A*
- *DHFR* - *CCNB2*
- *IL21* - *CKS2*
- *AURKA* - *CKS1B*
- *CDK1* - *ICOS*

Row Z-Score

−3 0 3

Recurrent mutations in epigenetic regulators, *RHOA* and *FYN* kinase in peripheral T cell lymphomas

Teresa Palomero, Lucile Couronné, Hossein Khiabanian, Mi-Yeon Kim, Alberto Ambesi-Impiombato, Arianne Perez-Garcia, Zachary Carpenter, Francesco Abate, Maddalena Allegretta, J Erika Haydu, Xiaoyu Jiang, Izidore S Lossos, Concha Nicolas, Milagros Balbin, Christian Bastard, Govind Bhagat, Miguel A Piris, Elias Campo, Olivier A Bernard, Raul Rabadan & Adolfo A Ferrando

Nature Genetics **46**, 166–170 (2014) doi:10.1038/ng.2873
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Peripheral T cell lymphomas (PTCLs) are a heterogeneous and poorly understood group of non-Hodgkin lymphomas[1, 2]. Here we combined whole-exome sequencing of 12 tumor-normal DNA pairs, RNA sequencing analysis and targeted deep sequencing to identify new genetic alterations in PTCL transformation. These analyses identified highly recurrent epigenetic factor mutations in *TET2*, *DNMT3A* and *IDH2* as well as a new highly prevalent *RHOA* mutation encoding a p.Gly17Val alteration present in 22 of 35 (67%) angioimmunoblastic T cell lymphoma (AITL) samples and in 8 of 44 (18%) PTCL, not otherwise specified (PTCL-NOS) samples. Mechanistically, the RHOA Gly17Val protein interferes with RHOA signaling in biochemical and cellular assays, an effect potentially mediated by the sequestration of activated guanine-exchange factor (GEF) proteins. In addition, we describe new and recurrent, albeit less frequent, genetic defects including mutations in *FYN*, *ATM*, *B2M* and *CD58* implicating SRC signaling, impaired DNA damage response and escape from immune surveillance mechanisms in the pathogenesis of PTCL.

Leukemia (2016) **30,** 1062–1070

www.nature.com/leu

ORIGINAL ARTICLE

Recurrent activating mutations of CD28 in peripheral T-cell lymphomas

J Rohr[1,2,14], S Guo[3,14], J Huo[4], A Bouska[1], C Lachel[1], Y Li[2], PD Simone[5], W Zhang[1], Q Gong[2], C Wang[1,2,6], A Cannon[1], T Heavican[1], A Mottok[7,8], S Hung[7,8], A Rosenwald[9], R Gascoyne[7,8], K Fu[1], TC Greiner[1], DD Weisenburger[2], JM Vose[10], LM Staudt[11], W Xiao[12], GEO Borgstahl[13], S Davis[4], C Steidl[7,8], T McKeithan[2], J Iqbal[1] and WC Chan[2]

Peripheral T-cell lymphomas (PTCLs) comprise a heterogeneous group of mature T-cell neoplasms with a poor prognosis. Recently, mutations in TET2 and other epigenetic modifiers as well as RHOA have been identified in these diseases, particularly in angioimmunoblastic T-cell lymphoma (AITL). CD28 is the major co-stimulatory receptor in T cells which, upon binding ligand, induces sustained T-cell proliferation and cytokine production when combined with T-cell receptor stimulation. We have identified recurrent mutations in CD28 in PTCLs. Two residues—D124 and T195—were recurrently mutated in 11.3% of cases of AITL and in one case of PTCL, not otherwise specified (PTCL-NOS). Surface plasmon resonance analysis of mutations at these residues with predicted differential partner interactions showed increased affinity for ligand CD86 (residue D124) and increased affinity for intracellular adaptor proteins GRB2 and GADS/GRAP2 (residue T195). Molecular modeling studies on each of these mutations suggested how these mutants result in increased affinities. We found increased transcription of the CD28-responsive genes *CD226* and *TNFA* in cells expressing the T195P mutant in response to CD3 and CD86 co-stimulation and increased downstream activation of NF-κB by both D124V and T195P mutants, suggesting a potential therapeutic target in CD28-mutated PTCLs.

Leukemia (2016) **30,** 1062–1070; doi:10.1038/leu.2015.357

Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell–derived lymphomas

David Vallois,[1,*] Maria Pamela D. Dobay,[2,*] Ryan D. Morin,[3,4] François Lemonnier,[5] Edoardo Missiaglia,[1] Mélanie Juilland,[6] Justyna Iwaszkiewicz,[2] Virginie Fataccioli,[5] Bettina Bisig,[1] Annalisa Roberti,[1] Jasleen Grewal,[3] Julie Bruneau,[7] Bettina Fabiani,[8] Antoine Martin,[9] Christophe Bonnet,[10] Olivier Michielin,[2,11] Jean-Philippe Jais,[12] Martin Figeac,[13] Olivier A. Bernard,[14] Mauro Delorenzi,[2,11,15] Corinne Haioun,[16] Olivier Tournilhac,[17] Margot Thome,[6] Randy D. Gascoyne,[18] Philippe Gaulard,[5,†] and Laurence de Leval[1,†]

[1]Institute of Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [2]SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland; [3]Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada; [4]Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada; [5]INSERM U955, Université Paris-Est, Département de Pathologie, Hôpital Henri-Mondor, Créteil, France; [6]Department of Biochemistry, University of Lausanne, Lausanne, Switzerland; [7]Service d'Anatomie et cytologie pathologiques, Hôpital Necker, Paris, France; [8]Service d'Anatomie et cytologie pathologiques, Hôpital Saint-Antoine, Paris, France; [9]Service d'Anatomie pathologique, Hôpital Avicenne, Bobigny, France; [10]Hématologie clinique, CHU Liège, Liège, Belgium; [11]Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [12]Service de Biostatistiques, GH Necker-Enfants Malades, Paris, France; [13]Plate-forme de Génomique Fonctionnelle et Structurale, Institut Pour la Recherche sur le Cancer de Lille, Lille, France; [14]INSERM U1170, Institut Gustave Roussy, Villejuif, France; [15]Ludwig Center for Cancer Research, University of Lausanne, Epalinges, Switzerland; [16]Hémopathies lymphoides, CHU Henri Mondor, Creteil, France; [17]Hématologie Clinique, CHU Estaing, Clermont-Ferrand, France; and [18]Centre for Lymphoid Cancer, BC Cancer Agency, Vancouver, BC, Canada

Key Points

- A high frequency of diverse activating mutations in costimulatory/TCR-related signaling genes occurs in AITL and other TFH-derived PTCL.
- Deregulated TCR activation may play a role in the pathogenesis of TFH-derived PTCL, paving the way for developing novel targeted therapies.

Angioimmunoblastic T-cell lymphoma (AITL) and other lymphomas derived from follicular T-helper cells (TFH) represent a large proportion of peripheral T-cell lymphomas (PTCLs) with poorly understood pathogenesis and unfavorable treatment results. We investigated a series of 85 patients with AITL (n = 72) or other TFH-derived PTCL (n = 13) by targeted deep sequencing of a gene panel enriched in T-cell receptor (TCR) signaling elements. *RHOA* mutations were identified in 51 of 85 cases (60%) consisting of the highly recurrent dominant negative G17V variant in most cases and a novel K18N in 3 cases, the latter showing activating properties in in vitro assays. Moreover, half of the patients carried virtually mutually exclusive mutations in other TCR-related genes, most frequently in *PLCG1* (14.1%), *CD28* (9.4%, exclusively in AITL), *PI3K* elements (7%), *CTNNB1* (6%), and *GTF2I* (6%). Using in vitro assays in transfected cells, we demonstrated that 9 of 10 PLCG1 and 3 of 3 CARD11 variants induced MALT1 protease activity and increased transcription from NFAT or NF-κB response element reporters, respectively. Collectively, the vast majority of variants in TCR-related genes could be classified as gain-of-function. Accordingly, the samples with mutations in TCR-related genes other than *RHOA* had transcriptomic profiles enriched in signatures reflecting higher T-cell activation. Although no correlation with presenting clinical features nor significant impact on survival was observed, the presence of TCR-related mutations correlated with early disease progression. Thus, targeting of TCR-related events may hold promise for the treatment of TFH-derived lymphomas. (*Blood*. 2016;128(11):1490-1502)

Willemsen and Schouten *Biomarker Research* (2017) 5:6
DOI 10.1186/s40364-017-0085-8

Biomarker Research

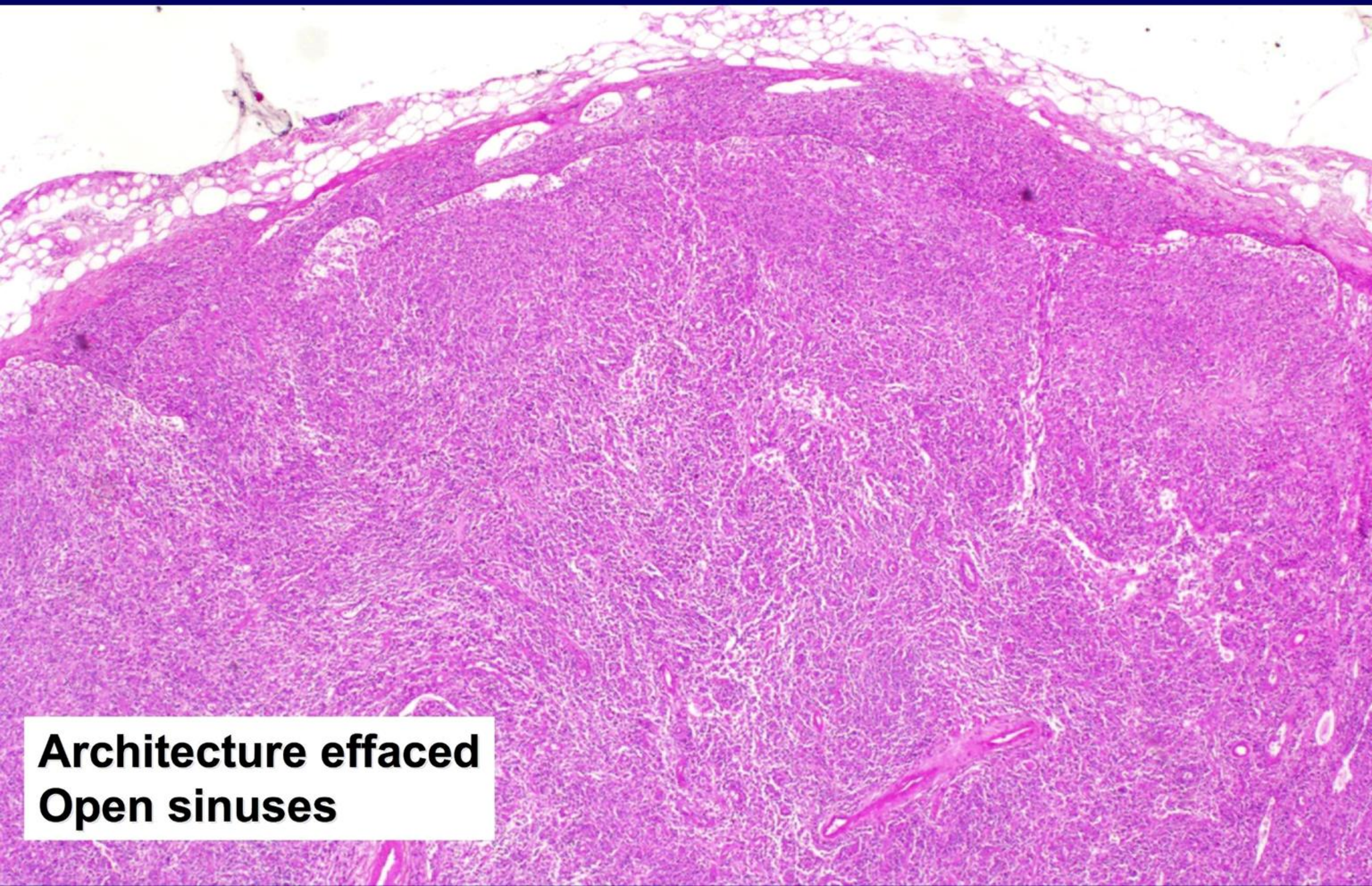
COMMENTARY

Open Access

Inappropriate costimulation and aberrant DNA methylation as therapeutic targets in angioimmunoblastic T-cell lymphoma

Mathijs Willemsen* and Harry C. Schouten

Angioimmunoblastic T-cell lymphoma

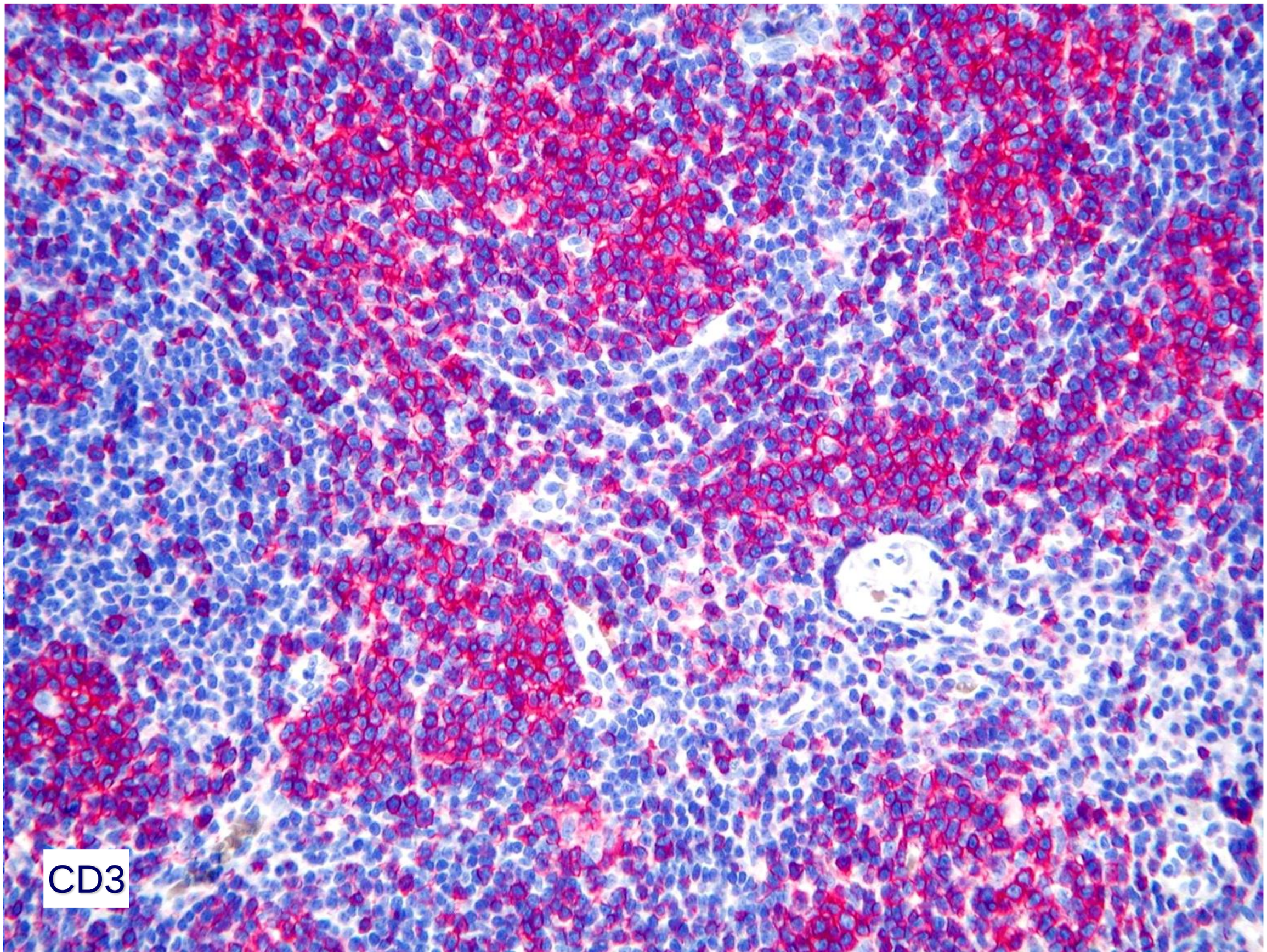


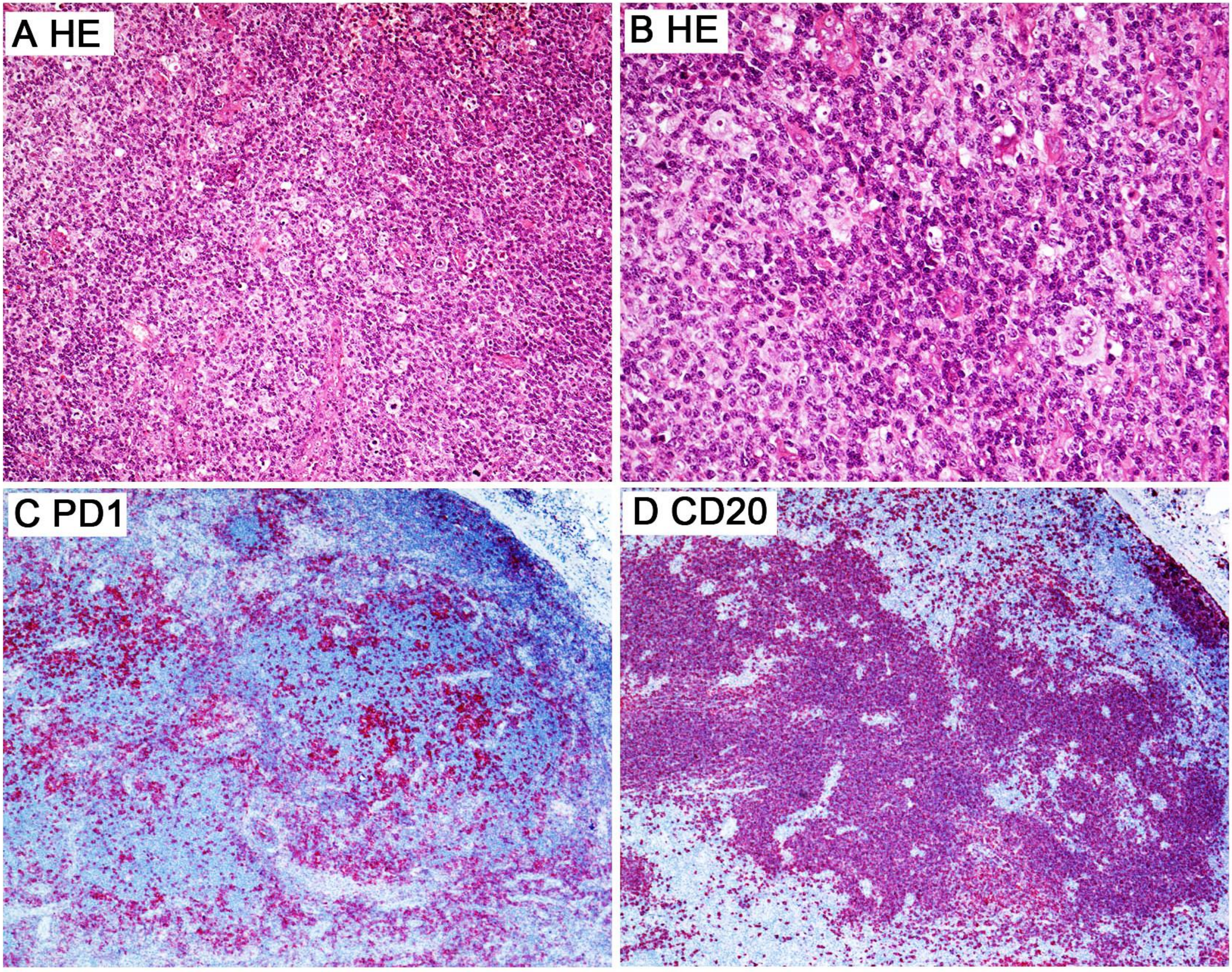
AITL: prominent, branching high endothelial venules

AITL: Follicular dendritic cell hyperplasia

CD21

Follicular peripheral T- cell lymphoma




A HE
B HE
C PD1
D CD20

Nodal PTCL of TFH origin (ex-NOS)

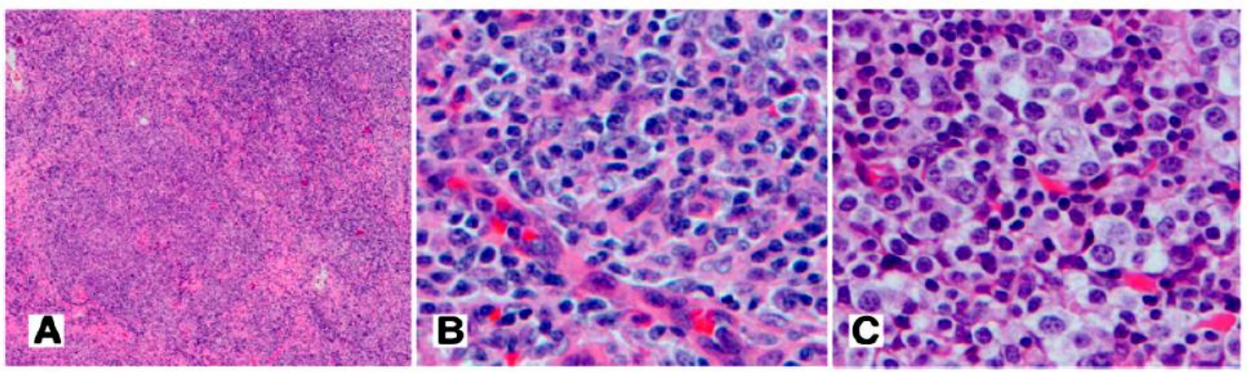
Comment on Wang et al, page 1741

Follicular helper T-cell–related lymphomas

Stefano A. Pileri EUROPEAN INSTITUTE OF ONCOLOGY; BOLOGNA UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Wang et al describe the occurrence and pathogenetic relevance of $IDH2^{R172}$ mutations in angioimmunoblastic T-cell lymphoma (AITL).[1]

A follicular helper T-cell (T_{FH})-related gene signature was for the first time reported in AITL by de Leval et al in 2007.[2] However, these authors found that a small group of peripheral T-cell lymphoma, not otherwise specified (PTCL/NOS) bore a similar signature.[2] Later, an increasing number of antibodies detected T_{FH}-associated molecules (ie, CD10, B-cell lymphoma 6 [BCL6], programmed cell death-1 [PD1], CXC chemokine ligand 13 [CXCL13], CC chemokine receptor 5, signaling lymphocytic activation molecule–associated protein [SAP], and inducible T-cell costimulator [ICOS]), their use possibly surrogating for gene expression profiling (GEP).[2,3] It was agreed that at least 3 of these antibodies should simultaneously be positive to suggest the derivation of a given T-cell neoplasm from T_{FH} cells because a single marker might occur due to cell plasticity.[4] In 2008, the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues, identified a variant of PTCL/NOS, characterized by a follicular growth pattern and sustained by T_{FH}-related cells.[5] It was not lumped with AITL because it lacked hyperplasia of follicular dendritic cells (FDCs) and high endothelial venules (HEVs), that is, the morphologic hallmarks of AITL.[5] In addition, in about 20% of cases, t(5;9) is present, causing the formation of the hybrid gene *ITK/SYK*, found only in these tumors.[5] In 2011, Agostinelli et al found that a wide spectrum of T-cell neoplasms carried the T_{FH} phenotype, morphologically corresponding to AITL and PTCLs/NOS with and without follicular growth pattern.[6] As opposed to the follicular variant, the latter showed a diffuse effacement of the lymph node structure. When compared with AITL, these cases lacked FDC and HEV hyperplasia and did not show a residual open marginal sinus but contained variable amounts of B blasts (either Epstein-Barr virus positive or negative [EBV^+ or EBV^-]) intermingled with neoplastic T cells. In some cases with serial biopsies, transition was observed from 1 pattern to the other (eg, follicular at disease onset, AITL at the time of the first relapse, and PTCL/NOS at the second relapse [see figure]). Such observations, along with the distinctive morphology of neoplastic cells (small-medium size, slightly irregular nuclear profile, and wide rim of clear cytoplasm) and the common phenotype, led to the idea that AITL and T_{FH}-related PTCLs/NOS with and without follicular growth pattern might represent different aspects of the same family of neoplasms.[6] This concept was strengthened by the detection of the same gene mutations in AITL and PTCLs/NOS, although prevalence is different.[7-9] These mutations affected *TET2*, *IDH2*, *DNMT3A*, and *RHOA* among others.[7-9] Last but not least, *ITK/SYK* was also detected in AITL.[10] This array of mutations is relevant for 2 reasons. First, they can play an important role in the process of lymphomagenesis, although, as correctly pointed out by Wang et al,[1] some mutations like those affecting *TET2* and *DNMT3A* may represent early events comparable to *BCL2* rearrangement in the setting of follicular lymphoma. Second, they may have therapeutic implications.[1]



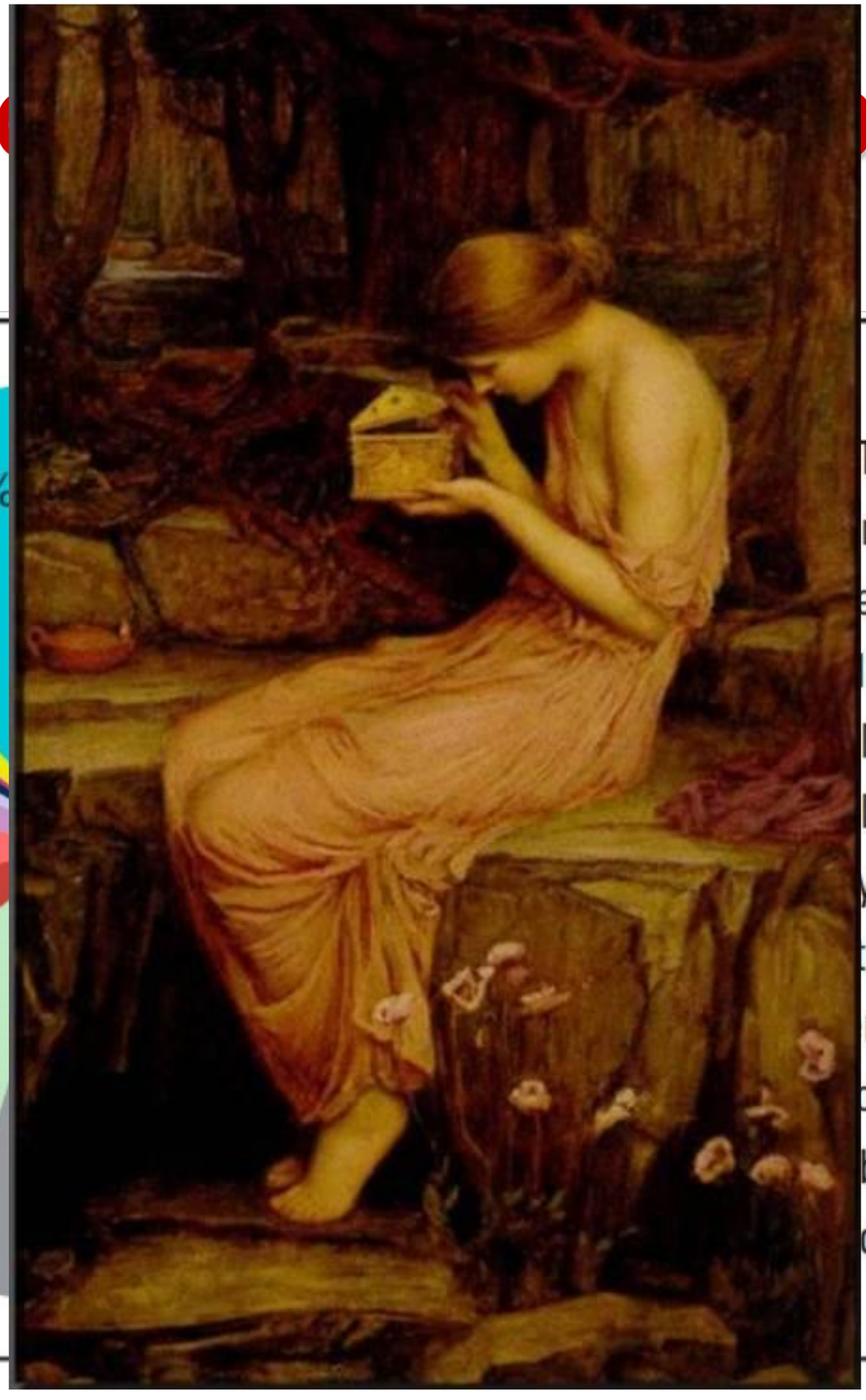
The images referred to the same case at (A) disease onset, (B) first relapse, and (C) second relapse. The tumor consists of cells characterized by a clear rim of cytoplasm and T_{FH} phenotype as defined by the expression of PD1, CXCL13, BCL6, CD10, and ICOS (not shown); in panel A, it has a "follicular" growth pattern (hematoxylin and eosin, ×20), and in panel B, it has the typical "angioimmunoblastic" appearance (please note the hyperplastic HEV and the inflammatory component [hematoxylin and eosin, ×400]). In panel C, the "angioimmunoblastic" characteristics are lost and neoplastic cells acquire at least in part a more blastic appearance (hematoxylin and eosin, ×400).

In this issue, Wang et al report on a study comparing *TET2*, *IDH2*, and *DNMT3A* mutations with GEP in 90 PTCLs of the AITL, NOS, and anaplastic large-cell lymphoma (ALCL) types.[1] Interestingly, whereas *TET2* and *DNMT3A* mutations assessed by targeted resequencing were observed in all 3 categories, although with different frequencies, *IDH2* detected by Sanger sequencing occurred most frequently in AITL (32.8% vs 5% of NOS and 0% of ALCL). Moreover, the previously reported occurrence of *IDH2* mutations at R172 was confirmed, as was the common co-occurrence with *TET2* mutations. These findings are at variance with acute myeloid leukemia and glioblastoma, in which *IDH2* mutations are at R140 and are mutually exclusive of the *TET2* mutations. In particular, the $IDH2^{R172}$-mutated cases showed a distinct GEP among AITLs and the *IDH2/TET2* double-mutant cases carried upregulation of T_{FH}-associated genes and downregulation of genes associated with T helper 1 (Th1), Th2, and Th17 phenotypes. These double-mutant AITLs were highly enriched for the signature of $CD4^+$ T cells stimulated by interleukin-12, suggesting a more polarized T_{FH} phenotype. Finally, yet importantly, Wang et al provide experimental evidence that IDH^{R172} mutations produce a significant increase in H3K27me3 and DNA hypermethylation of genes involved in T-cell receptor signaling and T-cell differentiation that likely contribute to lymphomagenesis in AITL. In addition, these findings give a strong rationale for the usage of hypomethylating agents in AITL treatment.

The Wang et al article highlights how sequencing analyses can help dissect apparently homogenous neoplasms using conventional techniques. This study provides new insights on the pathogenesis and subclassification of these tumors as well as on the detection of novel and hopefully more effective therapeutic targets.[1] The latter represent a real need because most PTCLs have a dismal prognosis when treated with current therapies.[5]

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

PTCL n ecified

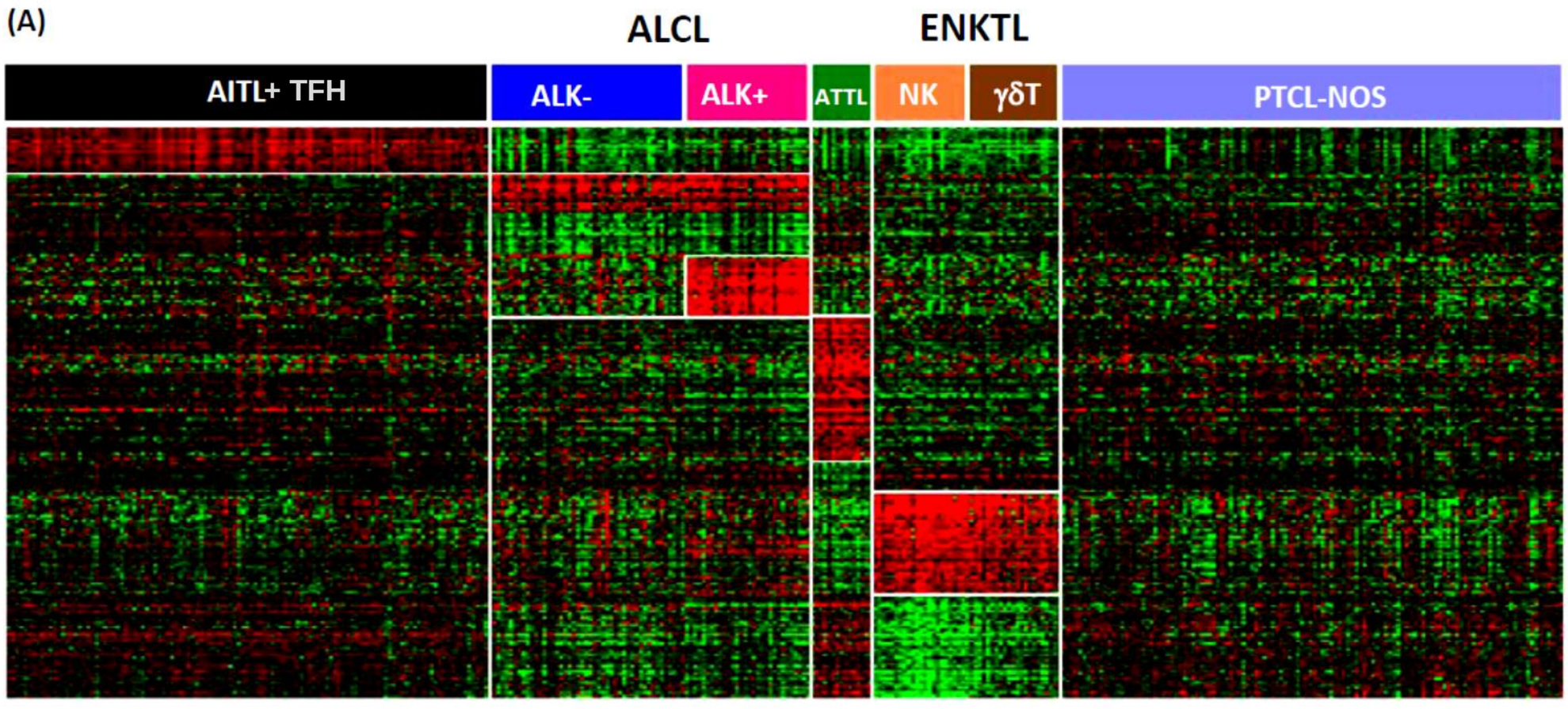


Cytological features

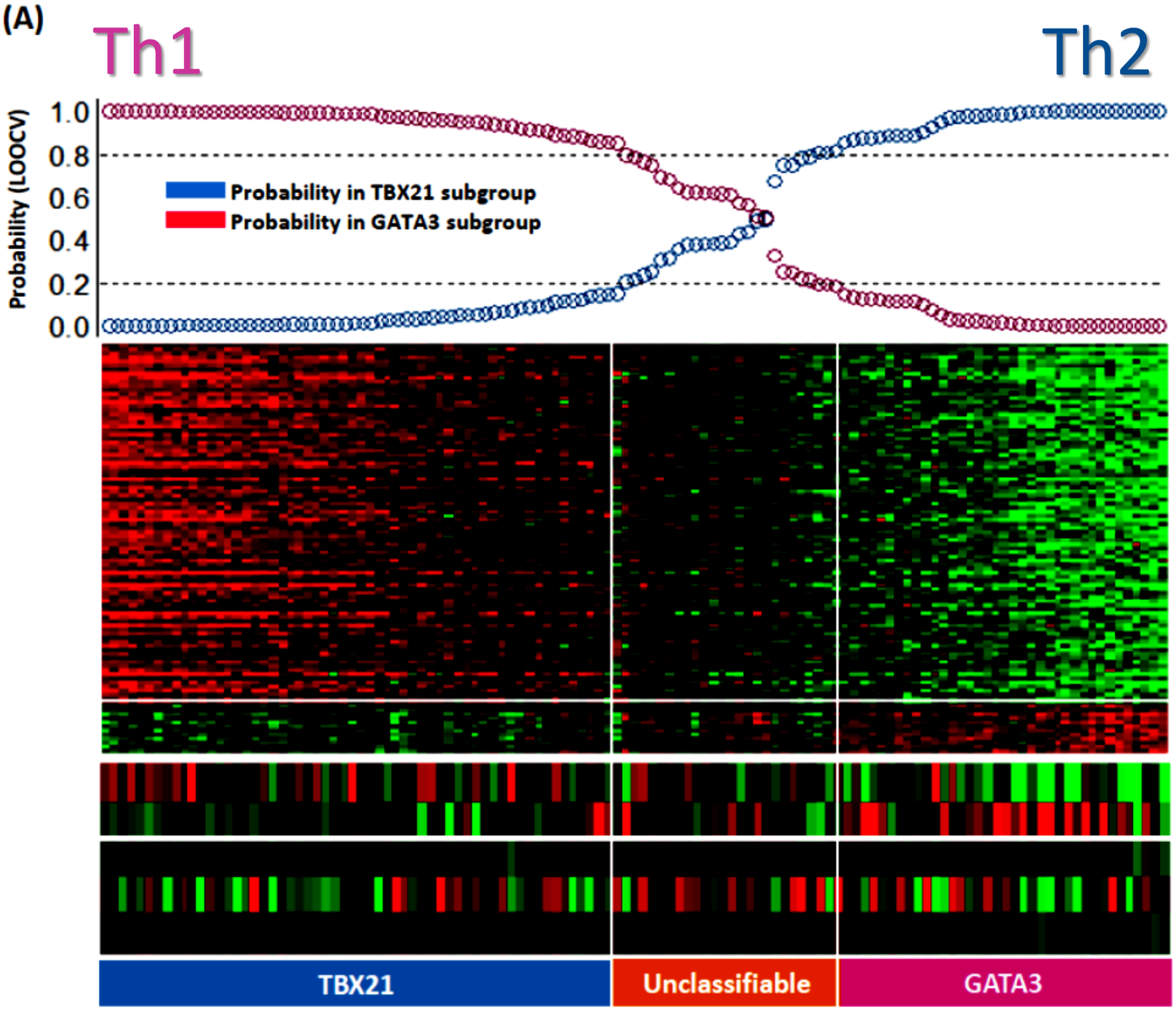
Gene expression signatures delineate biologic and prognostic subgroups in peripheral T-cell lymphoma

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

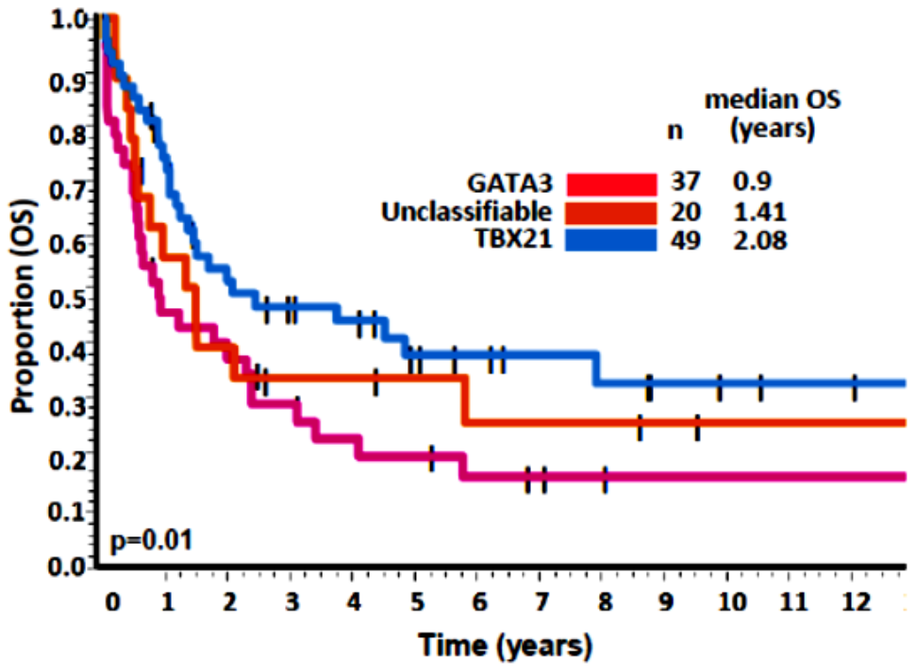
Prepublished online March 14, 2014;
doi:10.1182/blood-2013-11-536359



(A)


Th1
Th2
Probability (LOOCV)
1.0
0.8
0.6
0.4
0.2
0.0
Probability in TBX21 subgroup
Probability in GATA3 subgroup
TBX21
GATA3
Pan B –cell
Pan T –cell
Plasma cell
TBX21
Unclassifiable
GATA3

(B)

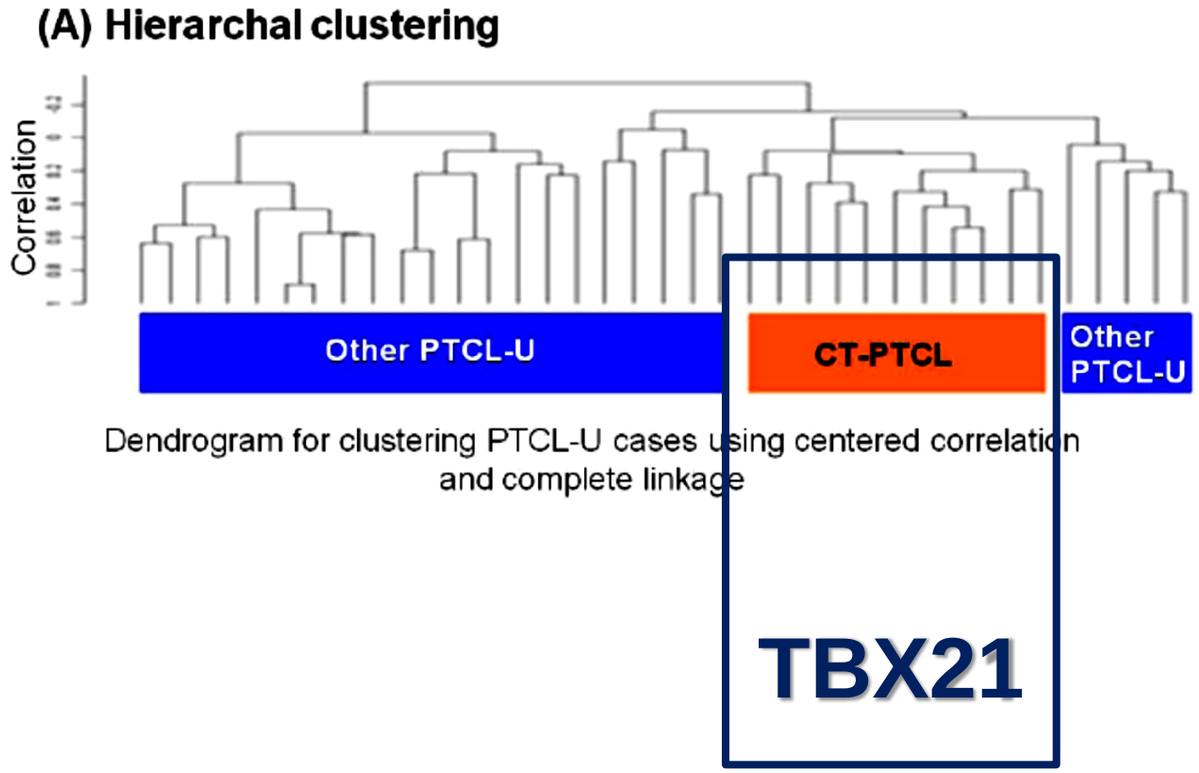

Proportion (OS)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
n
median OS (years)
GATA3 37 0.9
Unclassifiable 20 1.41
TBX21 49 2.08
p=0.01
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (years)

blood

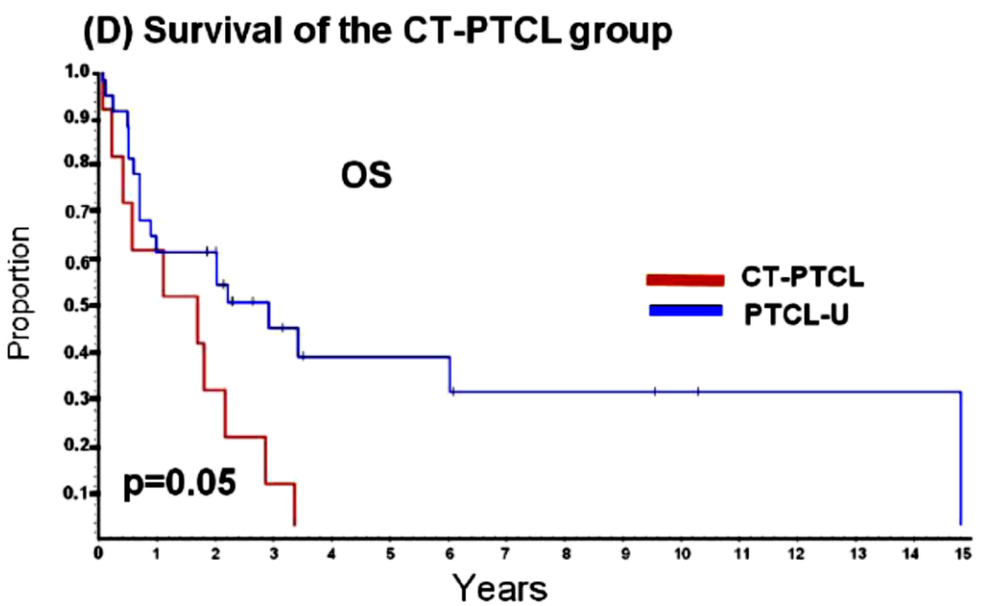
Prepublished online Nov 18, 2009;
doi:10.1182/blood-2009-06-227579

Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma

Javeed Iqbal, Dennis D Weisenburger, Timothy C Greiner, Julie M Vose, Timothy McKeithan, Can Kucuk, Huimin Geng, Karen Deffenbacher, Lynette Smith, Karen Dybkaer, Shigeo Nakamura, Masao Seto, Jan Delabie, Francoise Berger, Florence Loong, Wing Y Au, Young-Hyeh Ko, Ivy Sng, James Olen Armitage and Wing C Chan



Dendrogram for clustering PTCL-U cases using centered correlation and complete linkage



Signatures to be moved to Nanostring

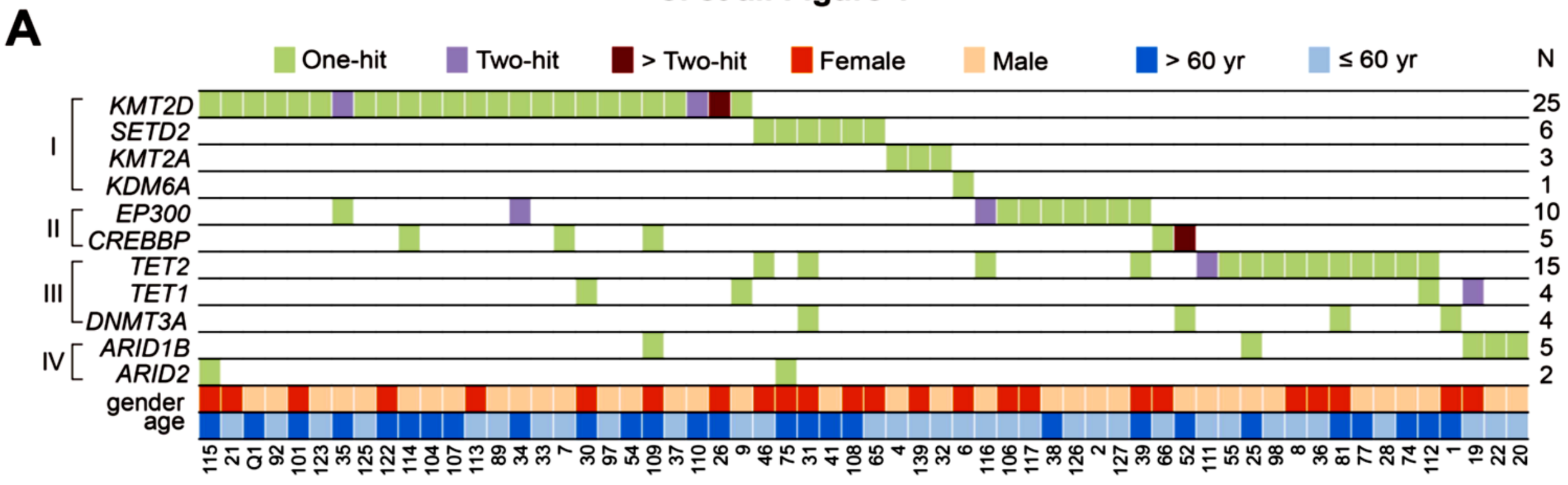
Histone modifier gene mutations in peripheral T-cell lymphoma not otherwise specified

Meng-Meng Ji,[1] Yao-Hui Huang,[1] Jin-Yan Huang,[1] Zhao-Fu Wang,[2] Di Fu,[1] Han Liu,[1] Feng Liu,[1] Christophe Leboeuf,[3,4] Li Wang,[1,3] Jing Ye,[3] Yi-Ming Lu,[3] Anne Janin,[3,4] Shu Cheng[1] and Wei-Li Zhao[1,3]

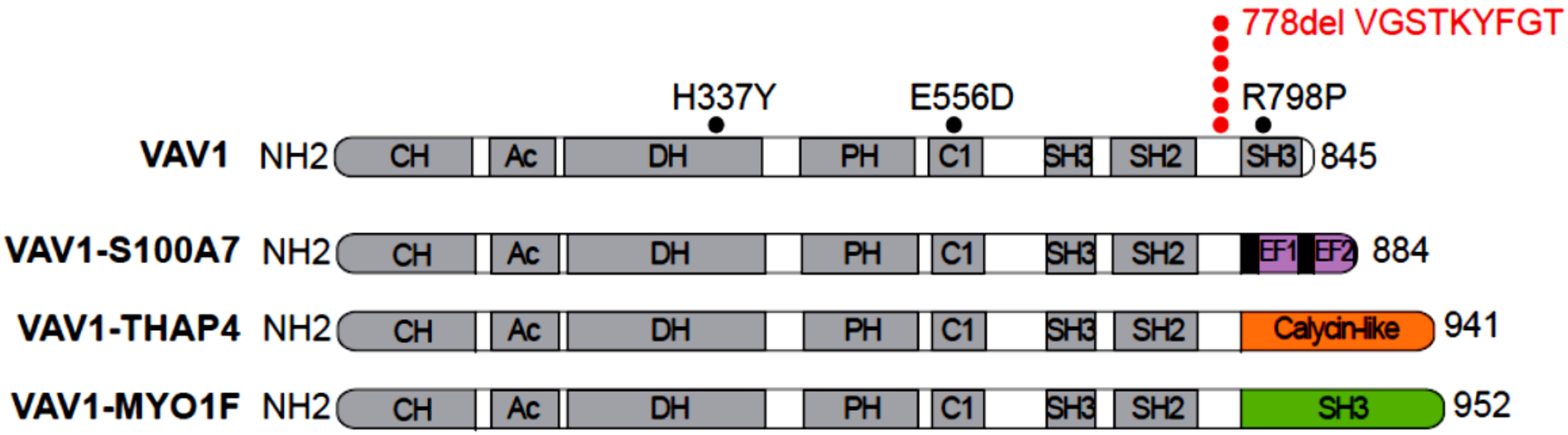
[1]State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology; Shanghai Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, China; [2]Department of Pathology, Shanghai Rui Jin Hospital; Shanghai Jiao Tong University School of Medicine, China; [3]Pôle de Recherches Sino-Français en Science du Vivant et Génomique, Laboratory of Molecular Pathology, Shanghai, China and [4]U1165 Inserm/Université Paris 7, Hôpital Saint Louis, Paris, France

Haematologica 2018
Volume 103(4):679-687

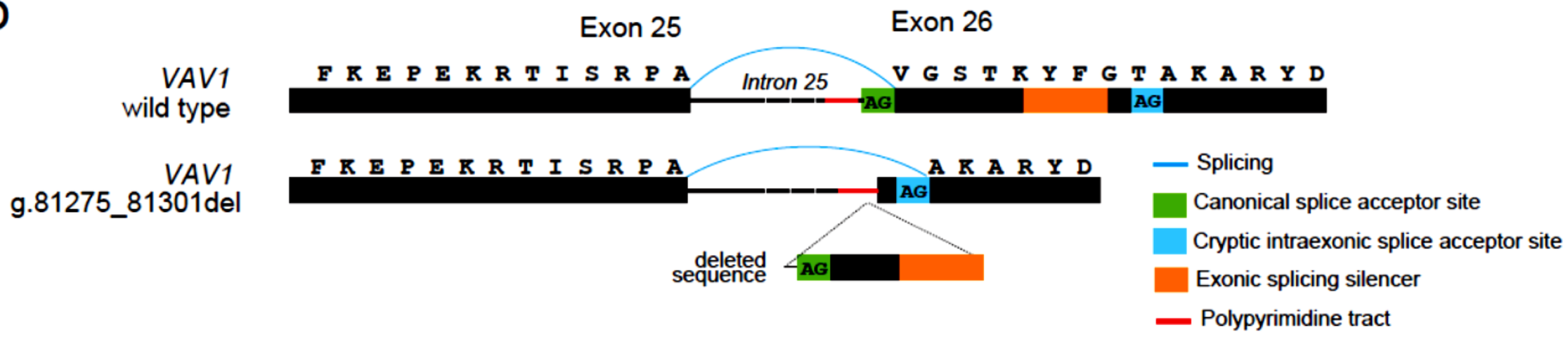
Ji et al. Figure 1



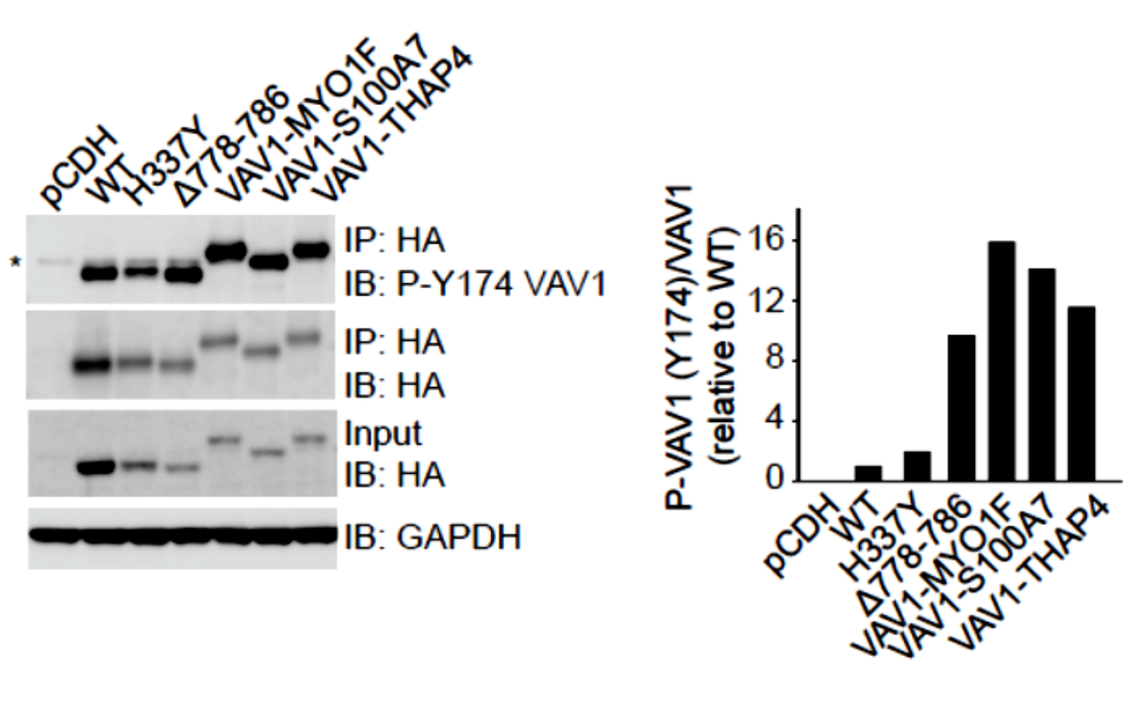
a


778del VGSTKYFGT
H337Y
E556D
R798P
VAV1
NH2
CH
Ac
DH
PH
C1
SH3
SH2
SH3
845
VAV1-S100A7
EF1
EF2
884
VAV1-THAP4
Calycin-like
941
VAV1-MYO1F
SH3
952

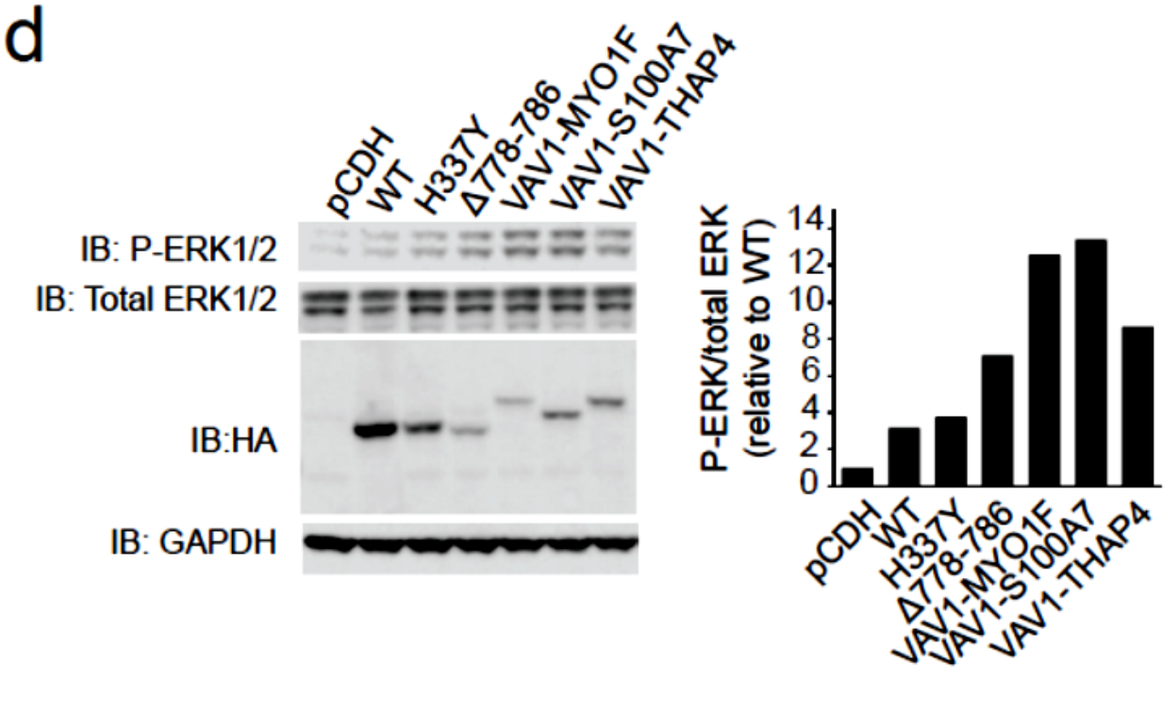
b


Exon 25
Exon 26
VAV1
wild type
F K E P E K R T I S R P A
Intron 25
V G S T K Y F G T A K A R Y D
AG
AG
VAV1
g.81275_81301del
F K E P E K R T I S R P A
A K A R Y D
AG
deleted
sequence
AG
Splicing
Canonical splice acceptor site
Cryptic intraexonic splice acceptor site
Exonic splicing silencer
Polypyrimidine tract

c


pCDH
WT
H337Y
Δ778-786
VAV1-MYO1F
VAV1-S100A7
VAV1-THAP4
IP: HA
IB: P-Y174 VAV1
IP: HA
IB: HA
Input
IB: HA
IB: GAPDH
P-VAV1 (Y174)/VAV1
(relative to WT)
16
12
8
4
0
pCDH
WT
H337Y
Δ778-786
VAV1-MYO1F
VAV1-S100A7
VAV1-THAP4

d


pCDH
WT
H337Y
Δ778-786
VAV1-MYO1F
VAV1-S100A7
VAV1-THAP4
IB: P-ERK1/2
IB: Total ERK1/2
IB:HA
IB: GAPDH
P-ERK/total ERK
(relative to WT)
14
12
10
8
6
4
2
0
pCDH
WT
H337Y
Δ778-786
VAV1-MYO1F
VAV1-S100A7
VAV1-THAP4

Whole Exome Sequencing in PTCL/NOS – Data analysis in cooperation with Francesco Bertoni

Whole Exome Sequencing (WES) (HiScan SQ (Frozen)

Discovery Set

23 PTCLs/NOS (5 matched with saliva of the corresponding patient)

Saliva pool

- **Saliva from the 5 patients with matched PTCL/NOS sample**
- **Saliva from 11 patients with tumors other than PTCL**
- **Saliva from 9 healthy donors**

RNA SEQ data available in 21/23 cases

Targeted Sequencing-MiSeq Platform

Validation Set

23 PTCLs/NOS that underwent WES

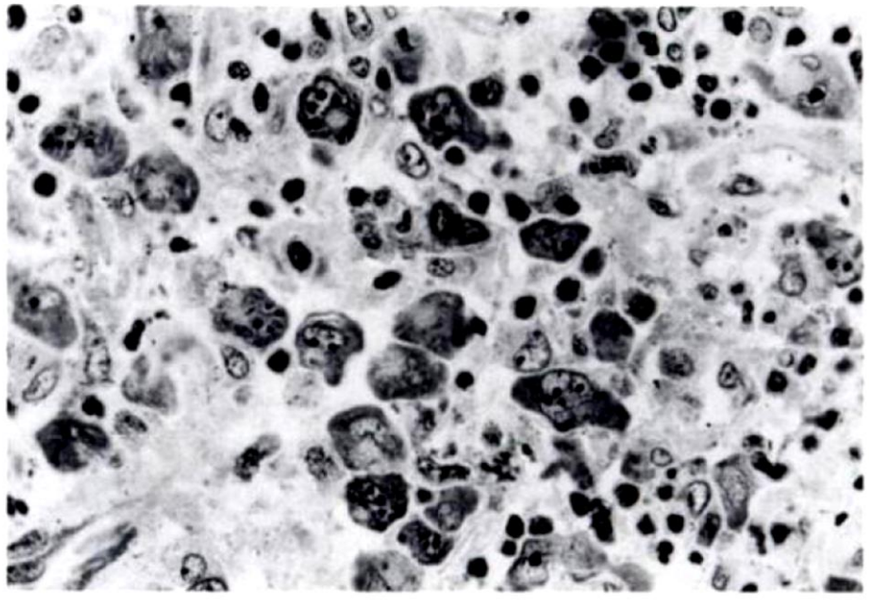
Extension Set

50 FFPE_PTCLs/NOS (8 matched with saliva of the corresponding patient)

9 Cell Lines

Anaplastic large cell lymphoma (ALCL) was first described by Stein et al. (Blood, 66:848-58) in 1985.

The tumour – previously often misdiagnosed as malignant histiocytosis or metastatic involvement by occult carcinoma – was characterised by distinctive morphology, cohesive growth pattern, frequent intra-sinusoidal diffusion, and regular expression of the lymphoid activation molecule Ki-1/CD30.



At that time, no distinction was made among anaplastic large cell lymphoid tumours carrying T, null or B-cell phenotype.

Anaplastic large cell lymphoma, ALK positive

Anaplastic large cell lymphoma, ALK negative (UPGRADED TO DEFINITE ENTITY)

Breast implant-associated ALCL

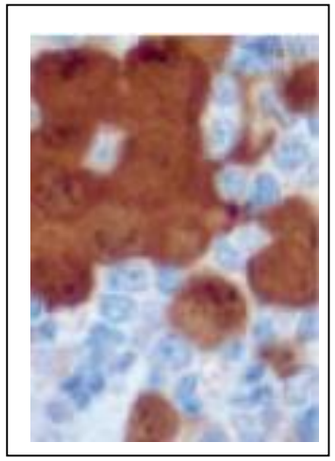
(NEW PROVISIONAL ENTITY)

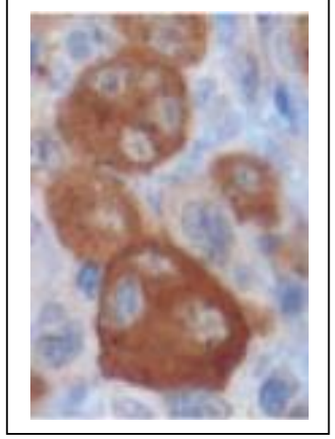
Translocations and fusion proteins involving the ALK gene in ALK$^+$ ALCL

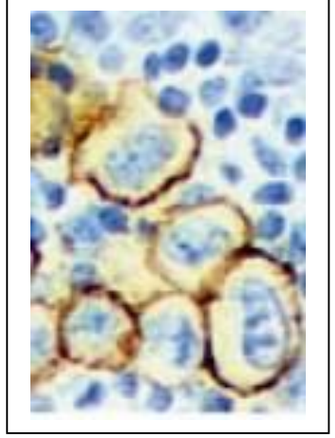
Table 1 Chromosomal translocations involving the ALK gene in human lymphoma

Disease	Chromosomal abnormalities	Fusion protein (kDa)	Partner gene	Frequency (%)	ALK IHC stains	Principal references
ALCL-DLBCL	t(2;5)(p23;q35)	NPM-ALK (80)	*NPM1*	75-80	Cyto/nuclear Nuclear	7, 18
ALCL-IMT	t(1;2)(q25;p23)	TPM3-ALK (104) (104)	*TPM3*	12-18	Cyto	45
ALCL	t(2;3)(p23;q21)	TGF-ALK 113,97.85)	*TFG*	2	Cyto	46, 47
ALCL-IMT	inv(2)(p23;q35)	ATIC-ALK (96)	*ATIC*	2	Cyto	48, 73
ALCL-IMT-DLBCL	t(2;17)(p23;q23)	CLTC1-ALK (250)	*CLTL1*	2	Cyto	49
ALCL	t(2;17)(p23;q25)	ALO17-ALK (ND)	*ALO17*	<1	Cyto	51
ALCL	t(2;X)(p32;q11-12)	MSN-ALK (125)	*MSN*	<1	Cyto	50, 73
ALCL-IMT	t(2;19)(p23;p13)	TPM4-ALK(95-105)	*TPM4*	<1	Cyto	73
ALCL	t(2;22)(p23;q11.2)	MYH9-ALK (220)	*MYH9*	<1	Cyto	52

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase; CLTL1, Clathrin heavy chainlike1; cyto, cytoplasmic; DLBCL, diffuse large B-cell lymphoma; MSN, moesin; NPM, nucleophosmin.







Anaplastic large-cell lymphoma.
Inghirami G and Pileri SA. Sem Diagn Pathol 2011; 28:190-201.

Translocations and fusion proteins involving the ALK gene in ALK$^+$ ALCL

The oncogenic role of ALK fusion proteins

- Translocations involving ALK produce fusion proteins with constitutive tyrosine kinase activity in most cases deriving from spontaneous dimerization induced by the different fusion partners
- Transforming ability *in vitro*
- Tumorigenic role in transgenic mouse models
- Engagement of intracellular pathways

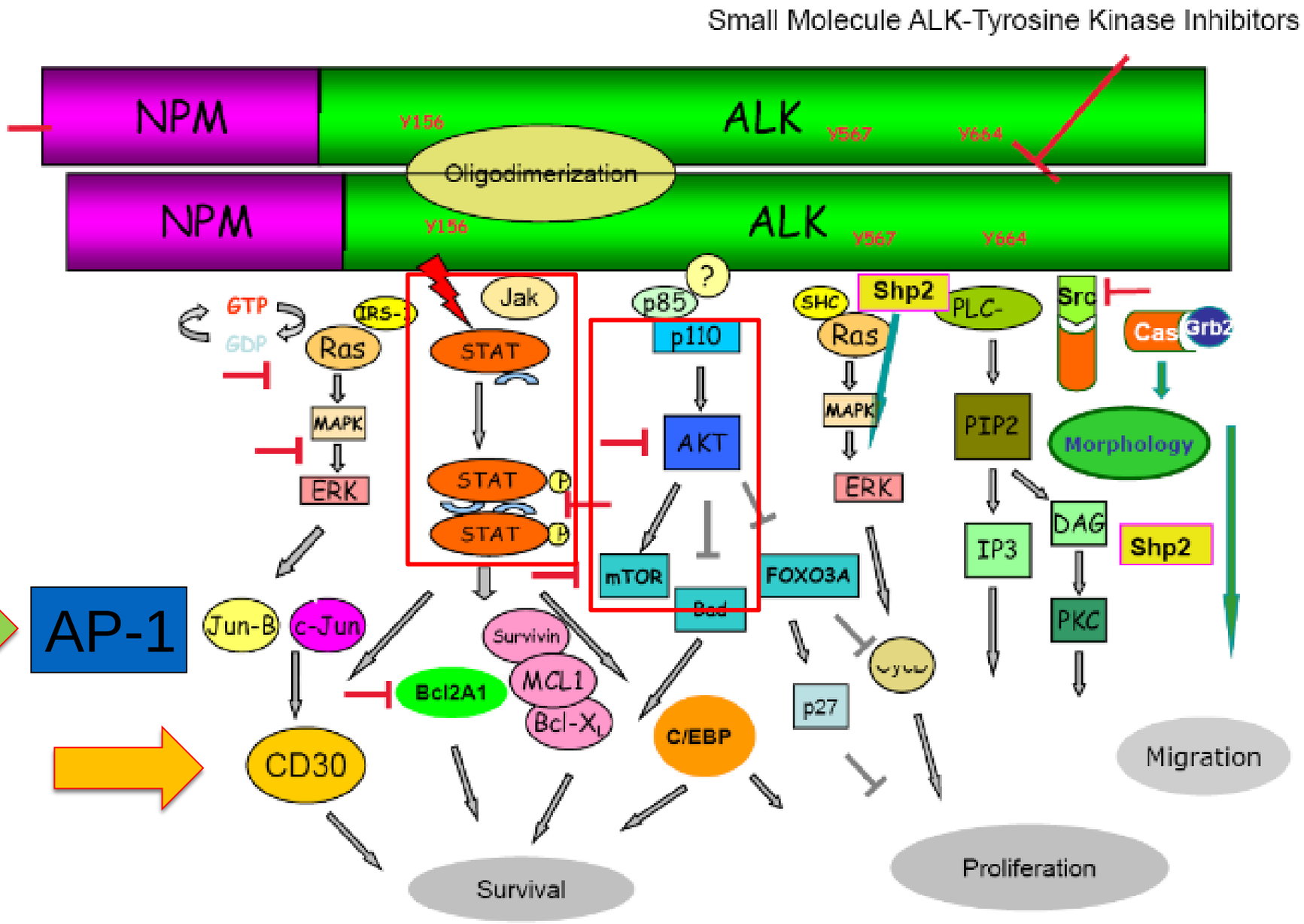
ALK, anaplastic lymphoma kinase.
Chiarle R, *et al.* Nat Rev Cancer 2008;8:11–23.

ALK+ ALCL

Anaplastic large-cell lymphoma

Seminars in Diagnostic Pathology (2011) 28, 190-201

Giorgio Inghirami, MD,[a,b] Stefano A. Pileri, MD,[c] and the European T-Cell Lymphoma Study Group



CLINICAL TRIALS AND OBSERVATIONS

Five-year outcomes for frontline brentuximab vedotin with CHP for CD30-expressing peripheral T-cell lymphomas

Michelle A. Fanale,[1] Steven M. Horwitz,[2] Andres Forero-Torres,[3] Nancy L. Bartlett,[4] Ranjana H. Advani,[5] Barbara Pro,[6] Robert W. Chen,[7] Andrew Davies,[8] Tim Illidge,[9] Mayur Uttarwar,[10] Shih-Yuan Lee,[11] Hong Ren,[10] Dana A. Kennedy,[10] and Andrei R. Shustov[12]

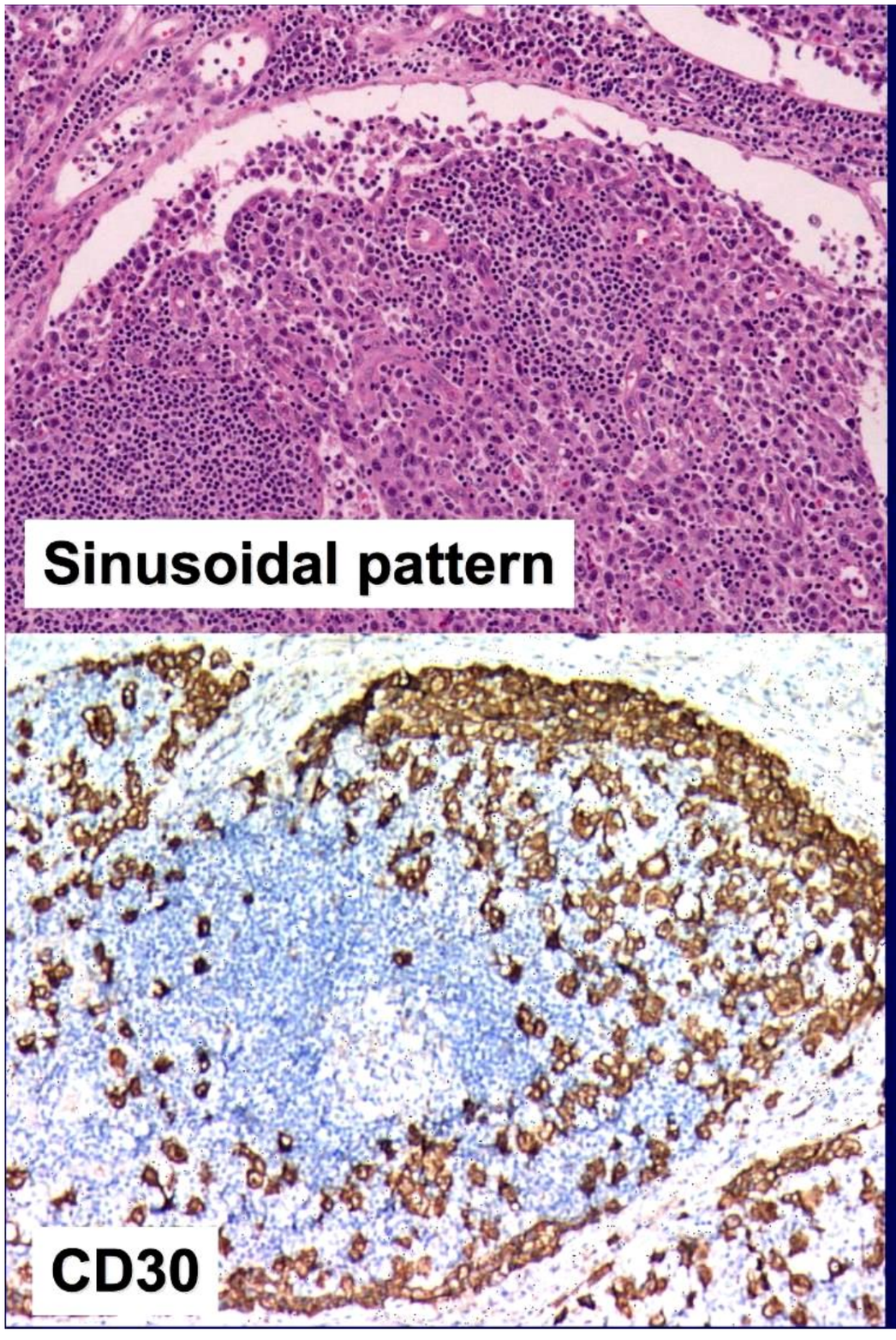
[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL; [4]Washington University School of Medicine, Siteman Cancer Center, St. Louis, MO; [5]Stanford University Medical Center, Palo Alto, CA; [6]Fox Chase Cancer Center, Philadelphia, PA; [7]City of Hope National Medical Center, Duarte, CA; [8]Cancer Research UK Centre, Cancer Sciences Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [9]Christie Hospital NHS, Manchester, United Kingdom; [10]Seattle Genetics, Inc., Bothell, WA; [11]Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceuticals Limited, Cambridge, MA; and [12]University of Washington Medical Center, Seattle, WA

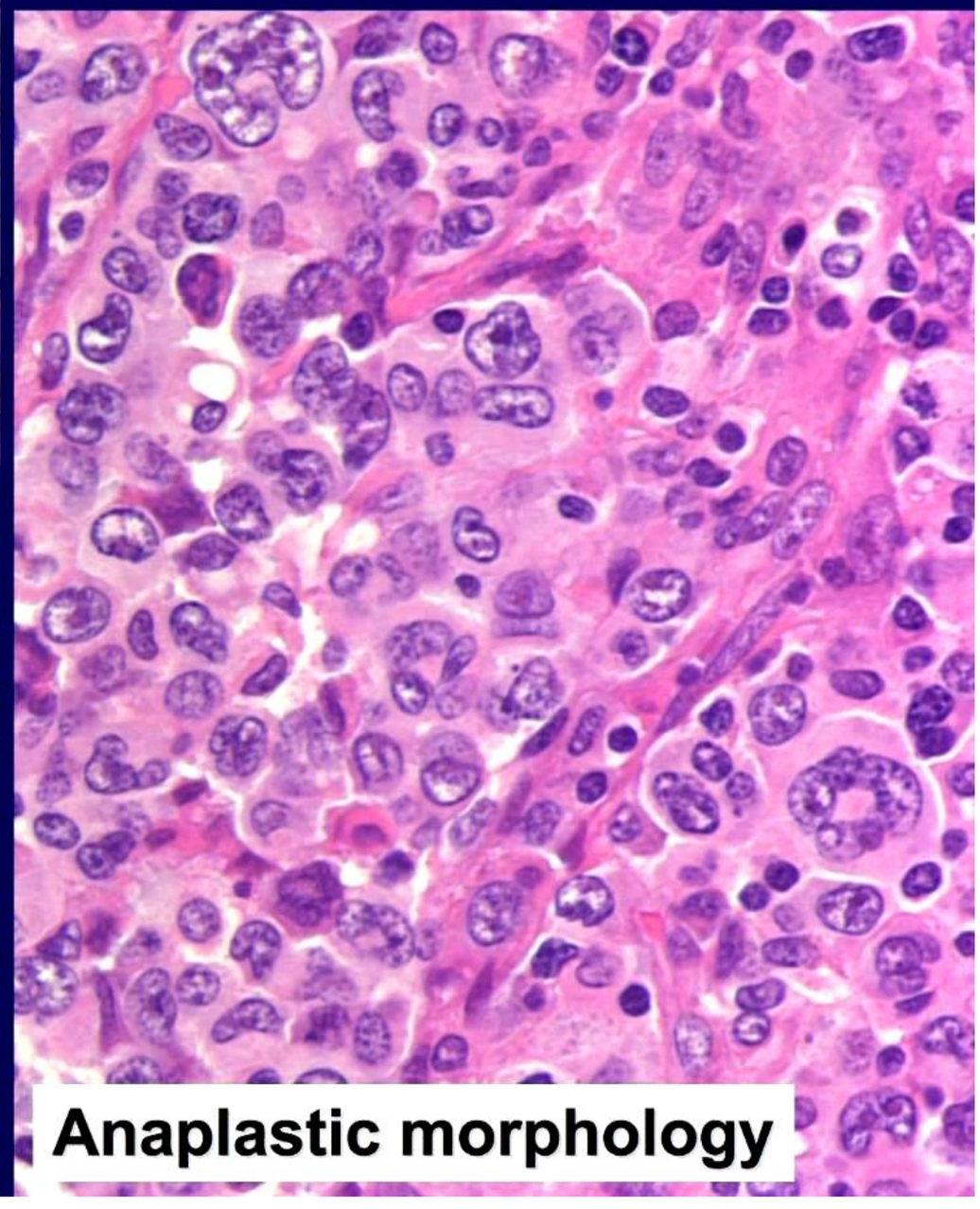
KEY POINTS

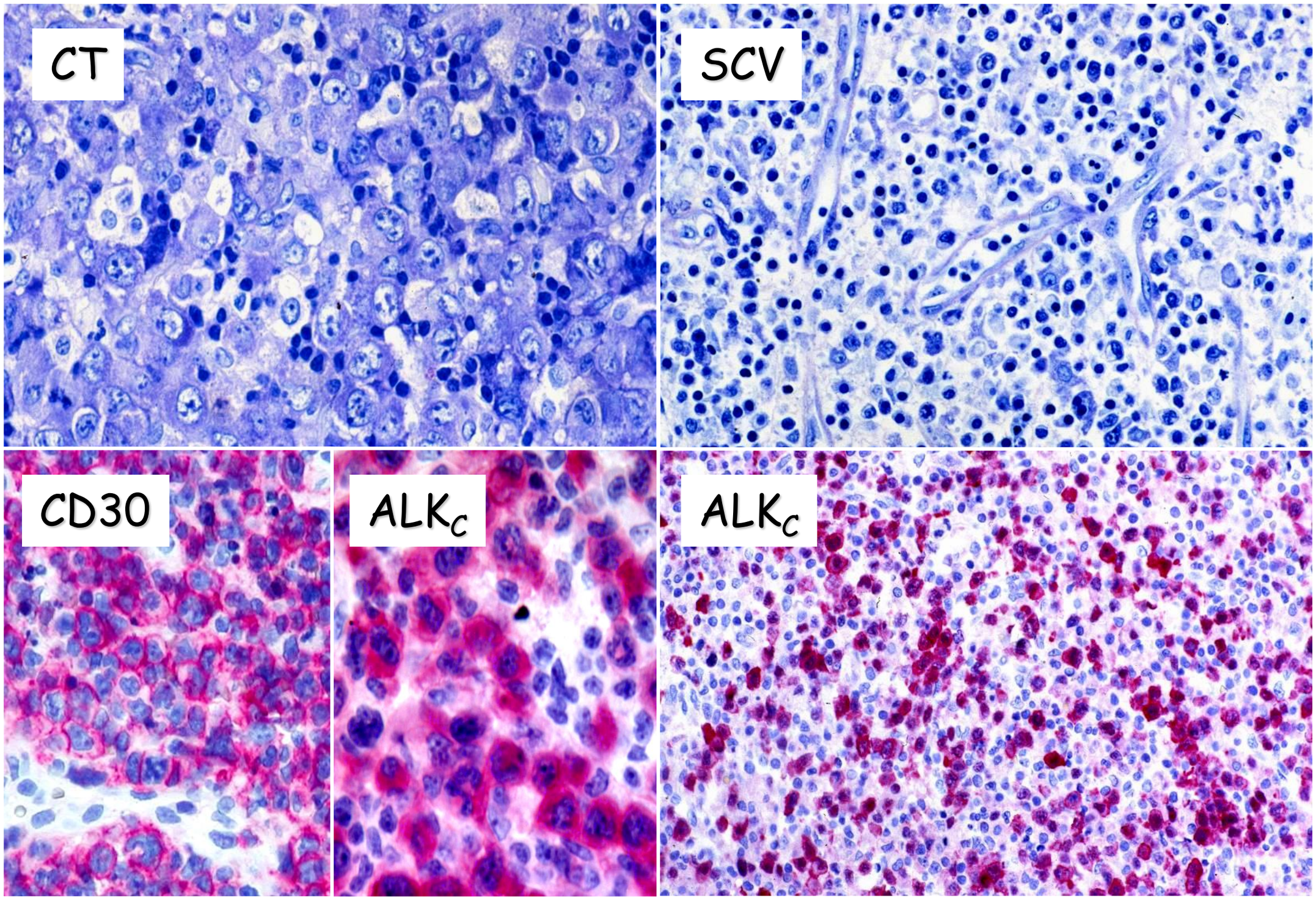
- 100% response rate (92% CR) in 26 patients treated with frontline BV+CHP. After ~5 years, 50% remained in CR (PFS 37.8+ to 66.0+ months).
- 18 of 19 patients (95%) with treatment-emergent PN reported resolution or improvement in symptoms; 9 had resolution of all PN events.

This phase 1 study evaluated frontline brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (BV+CHP; 6 cycles, then up to 10 cycles of brentuximab vedotin monotherapy) in 26 patients with CD30$^+$ peripheral T-cell lymphoma, including 19 with systemic anaplastic large cell lymphoma. All patients (100%) achieved an objective response, with a complete remission (CR) rate of 92%; none received a consolidative stem cell transplant. After a median observation period of 59.6 months (range, 4.6-66.0) from first dose, neither the median progression-free survival (PFS) nor the median overall survival (OS) was reached. No progression or death was observed beyond 35 months. The estimated 5-year PFS and OS rates were 52% and 80%, respectively. Eighteen of 19 patients (95%) with treatment-emergent peripheral neuropathy (PN) reported resolution or improvement of symptoms. Thirteen patients (50%) remained in remission at the end of the study, with PFS ranging from 37.8+ to 66.0+ months. Eight of these 13 patients received the maximum 16 cycles of study treatment. These final results demonstrate durable remissions in 50% of patients treated with frontline BV+CHP, suggesting a potentially curative treatment option for some patients. This trial was registered at www.clinicaltrials.gov as #NCT01309789. (*Blood*. 2018;131(19):2120-2124)

Anaplastic large cell lymphoma







Onset

Relapse

Programmed Death Ligand 1 Is Expressed by Non–Hodgkin Lymphomas and Inhibits the Activity of Tumor-Associated T Cells

David J. Andorsky[1], Reiko E. Yamada[1], Jonathan Said[2], Geraldine S. Pinkus[3], David J. Betting[1], and John M. Timmerman[1]

Abstract

Purpose: Programmed death ligand 1 (PD-L1) is expressed on antigen-presenting cells and inhibits activation of T cells through its receptor PD-1. PD-L1 is aberrantly expressed on some epithelial malignancies and Hodgkin lymphomas and may prevent effective host antitumor immunity. The role of PD-L1 in non–Hodgkin lymphomas (NHL) is not well characterized.

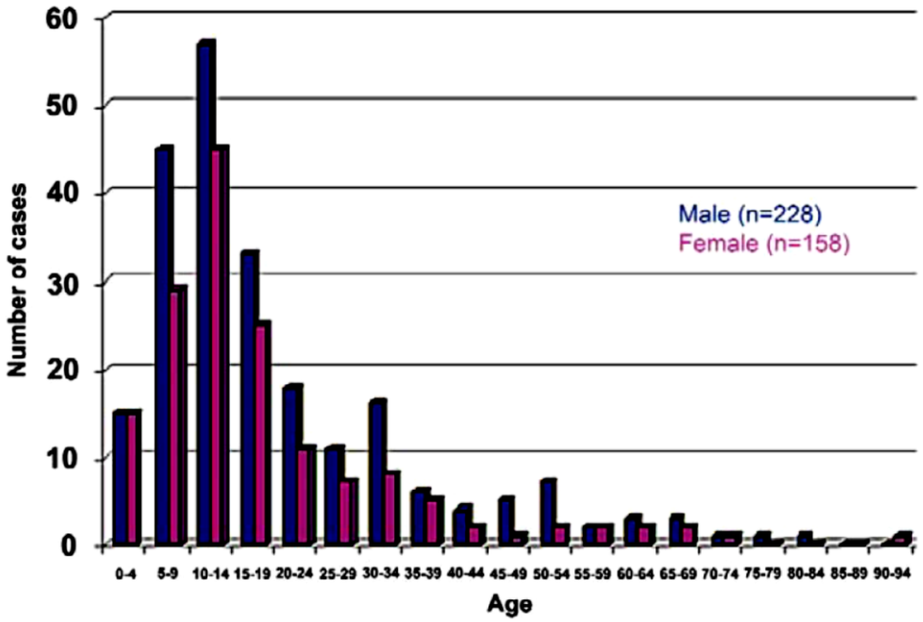
Experimental Design: PD-L1 expression was analyzed in cell lines and lymphoma specimens by using flow cytometry and immunohistochemistry. Functional activity of PD-L1 was studied by incubating irradiated lymphoma cells with allogeneic T cells with or without anti-PD-L1 blocking antibody; T-cell proliferation and IFN-γ secretion served as measures of T-cell activation. Similar experiments were conducted using cultures of primary lymphoma specimens containing host T cells.

Results: PD-L1 was expressed uniformly by anaplastic large cell lymphoma (ALCL) cell lines, but rarely in B-cell NHL, confined to a subset of diffuse large B-cell lymphomas (DLBCL) with activated B-cell features (3 of 28 cell lines and 24% of primary DLBCL). Anti-PD-L1 blocking antibody boosted proliferation and IFN-γ secretion by allogeneic T cells responding to ALCL and DLBCL cells. In autologous cultures of primary ALCL and DLBCL, PD-L1 blockade enhanced secretion of inflammatory cytokines IFN-γ, granulocyte macrophage colony-stimulating factor, interleukin (IL)-1, IL-6, IL-8, IL-13, TNF-α, and macrophage inflammatory protein-1α. In establishing cell lines from an aggressive PD-L1$^+$ mature B-cell lymphoma, we also noted that PD-L1 expression could be lost under certain *in vitro* culture conditions.

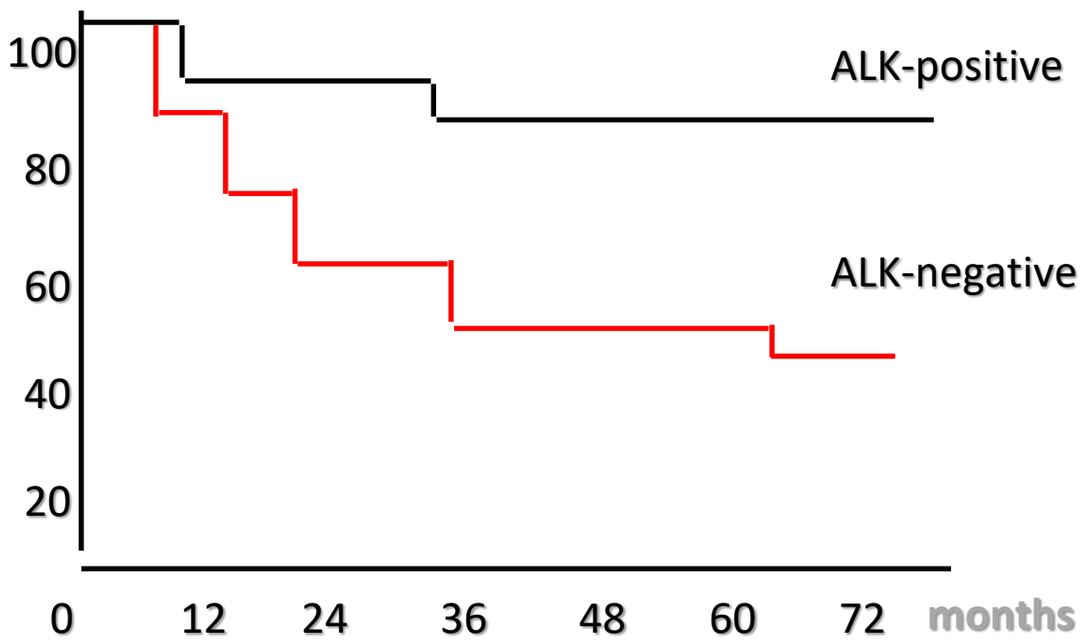
Conclusions: PD-L1 may thwart effective antitumor immune responses and represents an attractive target for lymphoma immunotherapy. *Clin Cancer Res; 17(13); 4232–44. ©2011 AACR.*

ALCL: ALK-positive and ALK-negative status

ALK-positive: most frequent in the first three decades of life[1]



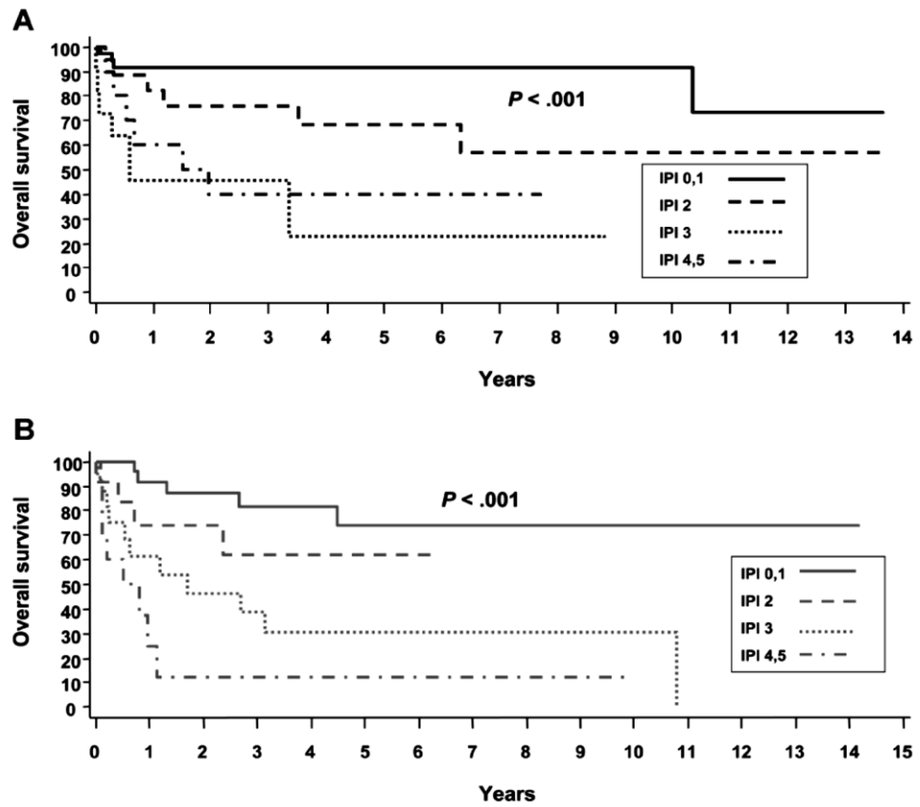
ALCL: overall survival[3]



Overall survival of systemic ALK according to ALK status[2]

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] and Dennis D. Weisenburger,[9] for the International Peripheral T-Cell Lymphoma Project



blood 1999 93: 2697-2706

ALK+ Lymphoma: Clinico-Pathological Findings and Outcome

Brunangelo Falini, Stefano Pileri, Pier Luigi Zinzani, Antonino Carbone, Vittorina Zagonel, Chris Wolf-Peeters, Gregor Verhoef, Fabio Menestrina, Giuseppe Todeschini, Marco Paulli, Mario Lazzarino, Roberto Giardini, Antonella Aiello, Hans-Dieter Foss, Iguacyra Araujo, Marco Fizzotti, Pier-Giuseppe Pelicci, Leonardo Flenghi, Massimo F. Martelli and Antonella Santucci

Anaplastic large cell lymphoma, ALK positive

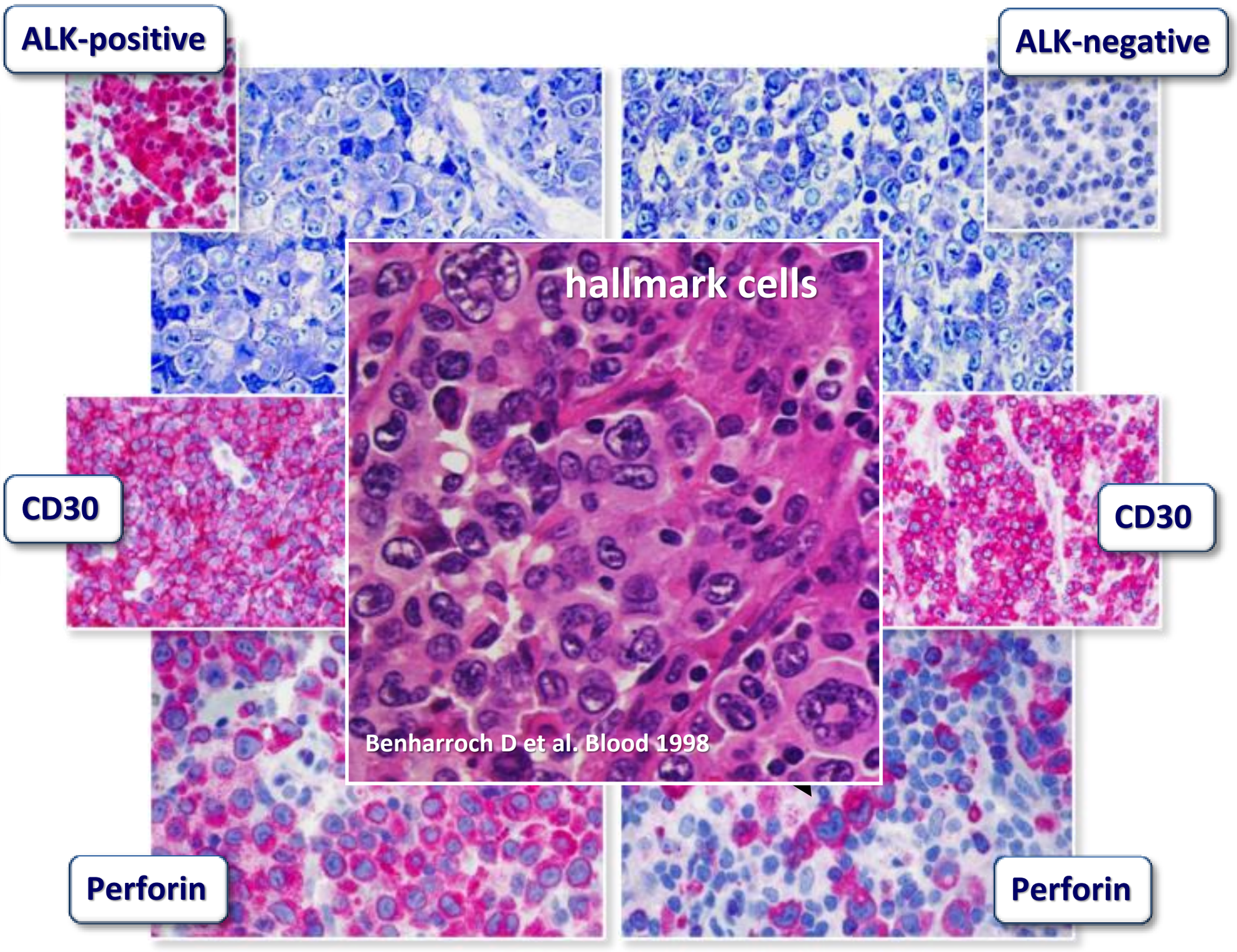
Anaplastic large cell lymphoma, ALK negative
(UPGRADED TO DEFINITE ENTITY)

Breast implant-associated ALCL

(NEW PROVISIONAL ENTITY)

Anaplastic large cell lymphoma

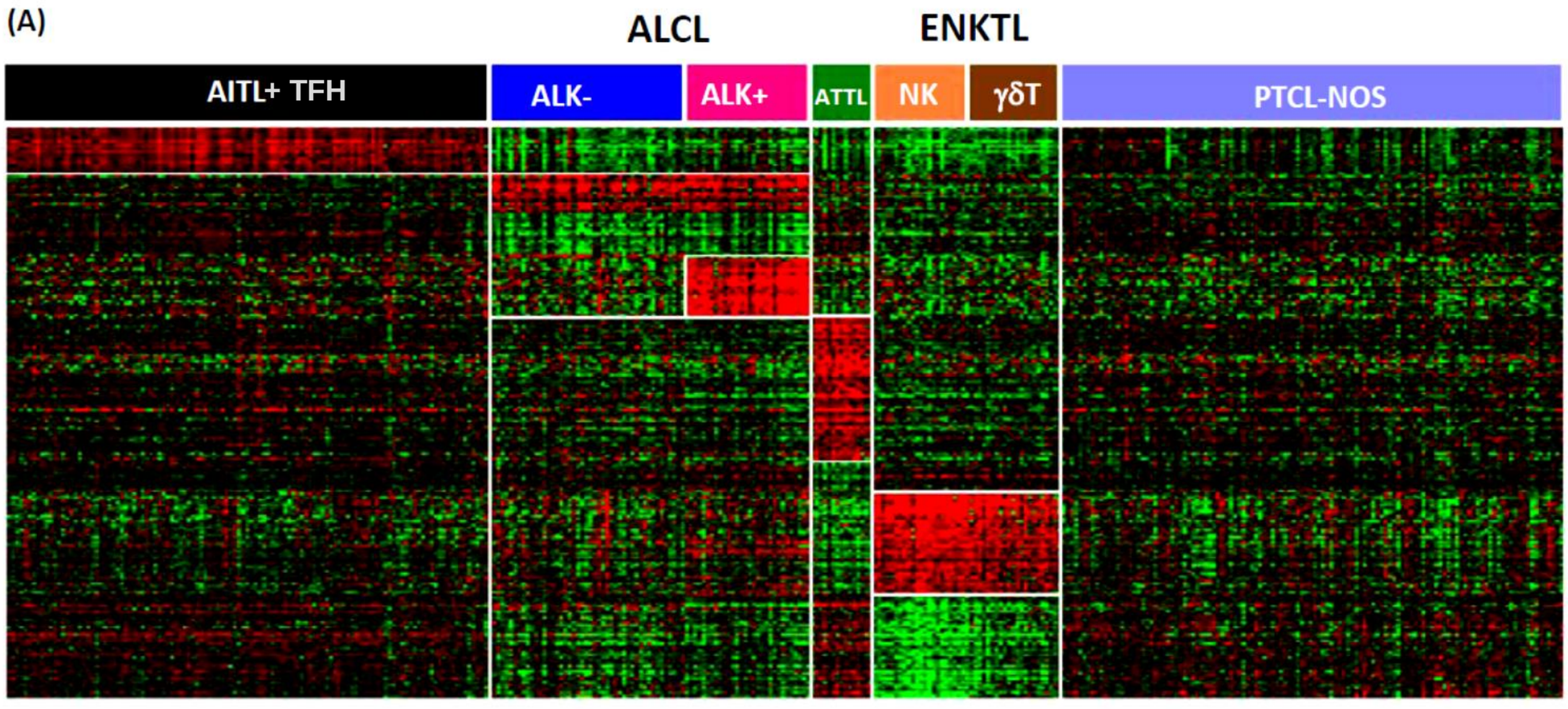
CD45+/-
EMA+/-
TCM-/+
CD43+
CM+
PAX5 –
PD-L1+/-
TCR/R



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

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

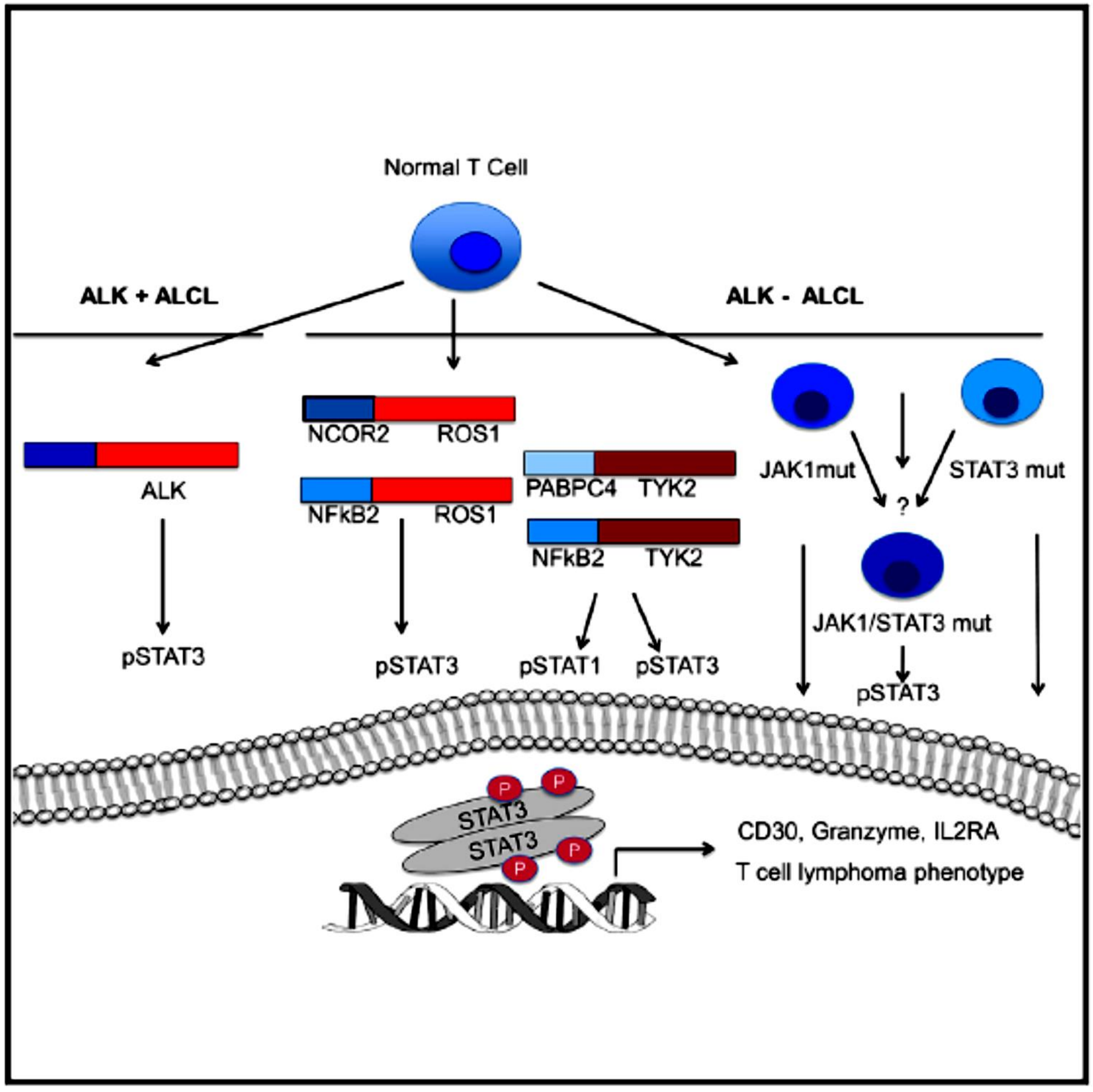


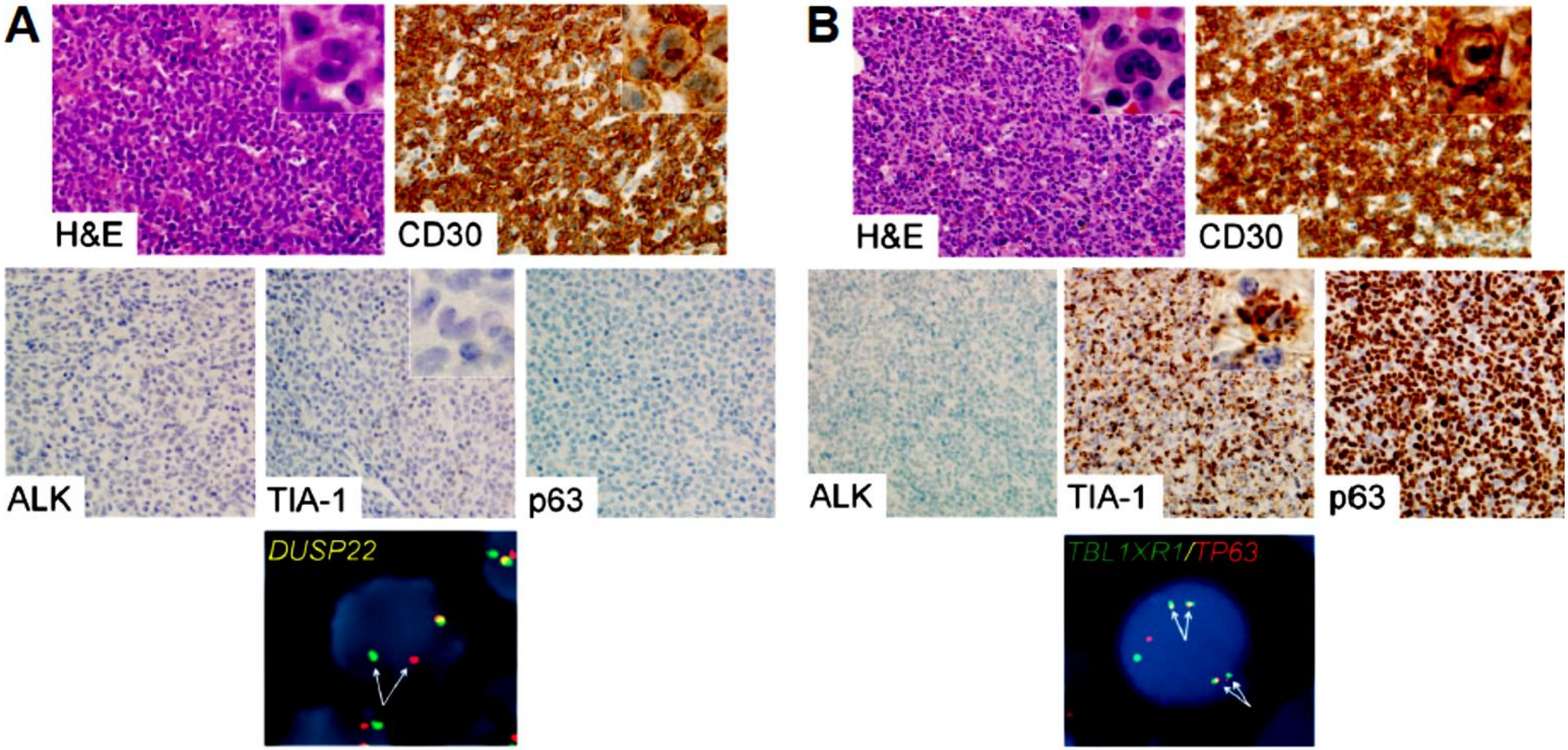
Convergent Mutations and Kinase Fusions Lead to Oncogenic STAT3 Activation in Anaplastic Large Cell Lymphoma

Ramona Crescenzo,[1,2,27] Francesco Abate,[1,3,4,27] Elena Lasorsa,[1,27] Fabrizio Tabbo',[1,2] Marcello Gaudiano,[1,2] Nicoletta Chiesa,[1] Filomena Di Giacomo,[1] Elisa Spaccarotella,[1] Luigi Barbarossa,[1] Elisabetta Ercole,[1] Maria Todaro,[1,2] Michela Boi,[1,2] Andrea Acquaviva,[3] Elisa Ficarra,[3] Domenico Novero,[5] Andrea Rinaldi,[6] Thomas Tousseyn,[7] Andreas Rosenwald,[8] Lukas Kenner,[9] Lorenzo Cerroni,[10] Alexander Tzankov,[11] Maurilio Ponzoni,[12] Marco Paulli,[13] Dennis Weisenburger,[14] Wing C. Chan,[14] Javeed Iqbal,[15] Miguel A. Piris,[16] Alberto Zamo',[17] Carmela Ciardullo,[18] Davide Rossi,[18] Gianluca Gaidano,[18] Stefano Pileri,[19,20] Enrico Tiacci,[21] Brunangelo Falini,[21] Leonard D. Shultz,[22] Laurence Mevellec,[23] Jorge E. Vialard,[24] Roberto Piva,[1,25] Francesco Bertoni,[6,26] Raul Rabadan,[4,*] Giorgio Inghirami,[1,2,25,*] and The European T-Cell Lymphoma Study Group, T-Cell Project: Prospective Collection of Data in Patients with Peripheral T-Cell Lymphoma and the AIRC 5xMille Consortium "Genetics-Driven Targeted Management of Lymphoid Malignancies"

516 Cancer Cell 27, 516–532, April 13, 2015

A systematic characterization of the genetic alterations driving ALCLs has not been performed. By integrating massive sequencing strategies, we provide a comprehensive characterization of driver genetic alterations (somatic point mutations, copy number alterations, and gene fusions) in ALK$^-$ ALCLs. We identified activating mutations of *JAK1* and/or *STAT3* genes in ~20% of 155 ALK$^-$ ALCLs and demonstrated that 38% of systemic ALK$^-$ ALCLs displayed double lesions. Recurrent chimeras combining a transcription factor (*NFkB2* or *NCOR2*) with a tyrosine kinase (*ROS1* or *TYK2*) were also discovered in WT JAK1/STAT3 ALK$^-$ ALCL. All these aberrations lead to the constitutive activation of the JAK/STAT3 pathway, which was proved oncogenic. Consistently, JAK/STAT3 pathway inhibition impaired cell growth in vitro and in vivo.


Normal T Cell
ALK + ALCL
ALK - ALCL
ALK
NCOR2
ROS1
NFkB2
ROS1
PABPC4
TYK2
NFkB2
TYK2
JAK1mut
STAT3 mut
?
JAK1/STAT3 mut
pSTAT3
pSTAT3
pSTAT1
pSTAT3
pSTAT3
P
P
STAT3
STAT3
P
P
CD30, Granzyme, IL2RA
T cell lymphoma phenotype


A
H&E
CD30
ALK
TIA-1
p63
DUSP22
B
H&E
CD30
ALK
TIA-1
p63
TBL1XR1/TP63

Expression of p63 protein in anaplastic large cell lymphoma: implications for genetic subtyping☆,☆☆

Xueju Wang MD, PhD[a,b,1], Rebecca L. Boddicker PhD[a,1], Surendra Dasari PhD[c], Jagmohan S. Sidhu MD[d], Marshall E. Kadin MD[e], William R. Macon MD[a], Stephen M. Ansell MD, PhD[f], Rhett P. Ketterling MD[a], Karen L. Rech MD[a], Andrew L. Feldman MD[a,*]

Human Pathology (2017) **64**, 19–27

Summary Anaplastic large cell lymphomas (ALCLs) are CD30-positive T-cell non-Hodgkin lymphomas that bear chromosomal rearrangements of the *TP53* homologue *TP63* in a subset of cases that demonstrate aggressive clinical behavior. In the present study, we examined the relationship between p63 protein expression by immunohistochemistry and the results of fluorescence in situ hybridization using *TP63* probes in 116 ALCLs. We also determined the relative expression of full-length TAp63 and truncated ΔNp63 isoforms (eg, p40) in ALCL cell lines and a subset of clinical cases. Overall, 35.3% of ALCLs were positive for p63 protein. Primary cutaneous and anaplastic lymphoma kinase–negative ALCLs were positive more frequently than anaplastic lymphoma kinase–positive ALCLs ($P = .0034$). As previously reported, cases with *TP63* gene rearrangements expressed p63 uniformly. p63 expression in nonrearranged cases was associated with extra copies of *TP63* on 3q28 ($P < .0001$). Extra copies of *TP63* correlated with extra copies of the *DUSP22* locus on 6p25.3 ($P < .0001$). Results of immunohistochemistry, Western blotting, and RNA sequencing indicated that p63 expression in nonrearranged cases was entirely attributable to TAp63 isoforms. Taken together, these findings indicate that ALCLs without *TP63* rearrangements may express TAp63 isoforms of p63 and that this expression is associated with extra copies of *TP63*, probably due to widespread genomic copy number abnormalities rather than focal gains. Immunohistochemistry for p63 in ALCL is not specific for *TP63* rearrangements but is useful clinically as a screening test to select cases

Histopathology 2015, **66**, 846–855. DOI: 10.1111/his.12529

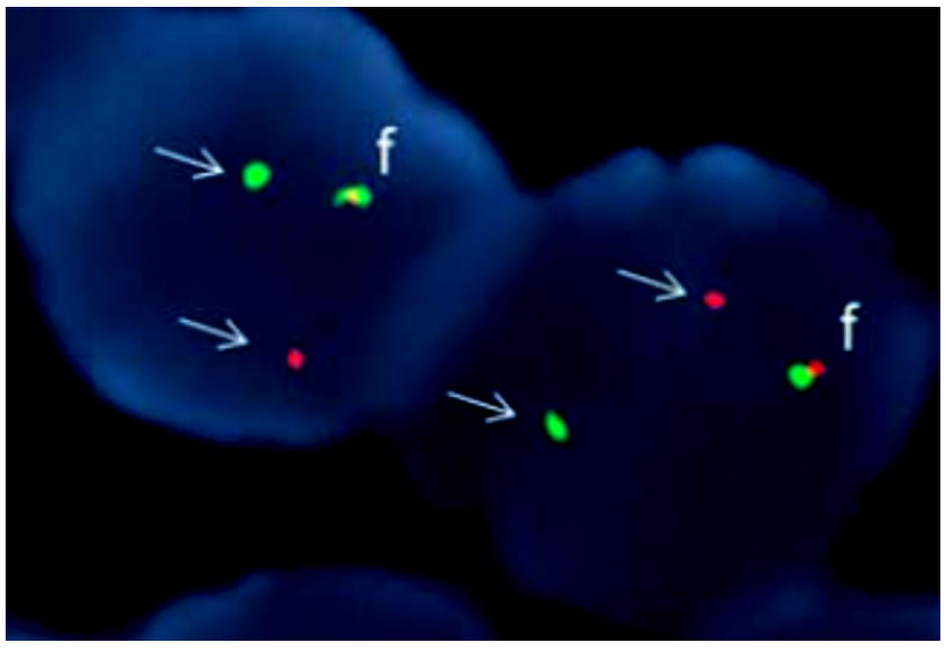
Primary cutaneous anaplastic large cell lymphomas with 6p25.3 rearrangement exhibit particular histological features

Arantza Onaindia,[1] Santiago Montes-Moreno,[1] Socorro M Rodríguez-Pinilla,[2] Ana Batlle,[3] Sonia González de Villambrosía,[3] Antonio M Rodríguez,[4] Víctor Alegre,[5] Glenda M Bermúdez,[1] Carmen González-Vela[1] & Miguel A Piris[1]

Chromosomal Rearrangements of 6p25.3 Define a New Subtype of Lymphomatoid Papulosis

Laszlo J. Karai, MD,† Marshall E. Kadin, MD,‡ Eric D. Hsi, MD,§ Jason C. Sluzevich, MD,‖ Rhett P. Ketterling, MD,¶ Ryan A. Knudson, BS,¶ and Andrew L. Feldman, MD¶*

(*Am J Surg Pathol* 2013;37:1173–1181)



ALK^{-} ALCL with *DUSP22* rearrangement shows:

- lack of STAT3 activation,
- over-expression of immunogenic cancer-testis antigen genes,
- marked DNA hypomethylation,
- minimal expression of PD-L1,
- high expression of CD58 and HLA class II.

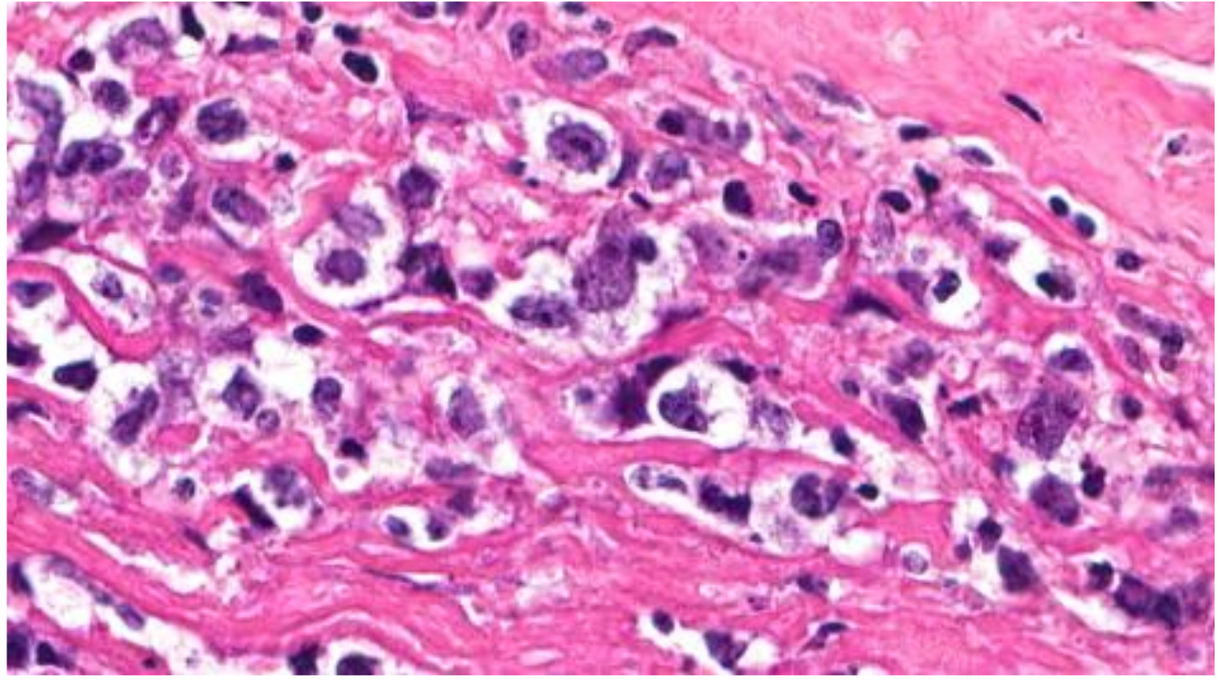
Luchtel RA et al., 2018 Blood, e-pub ahead of print

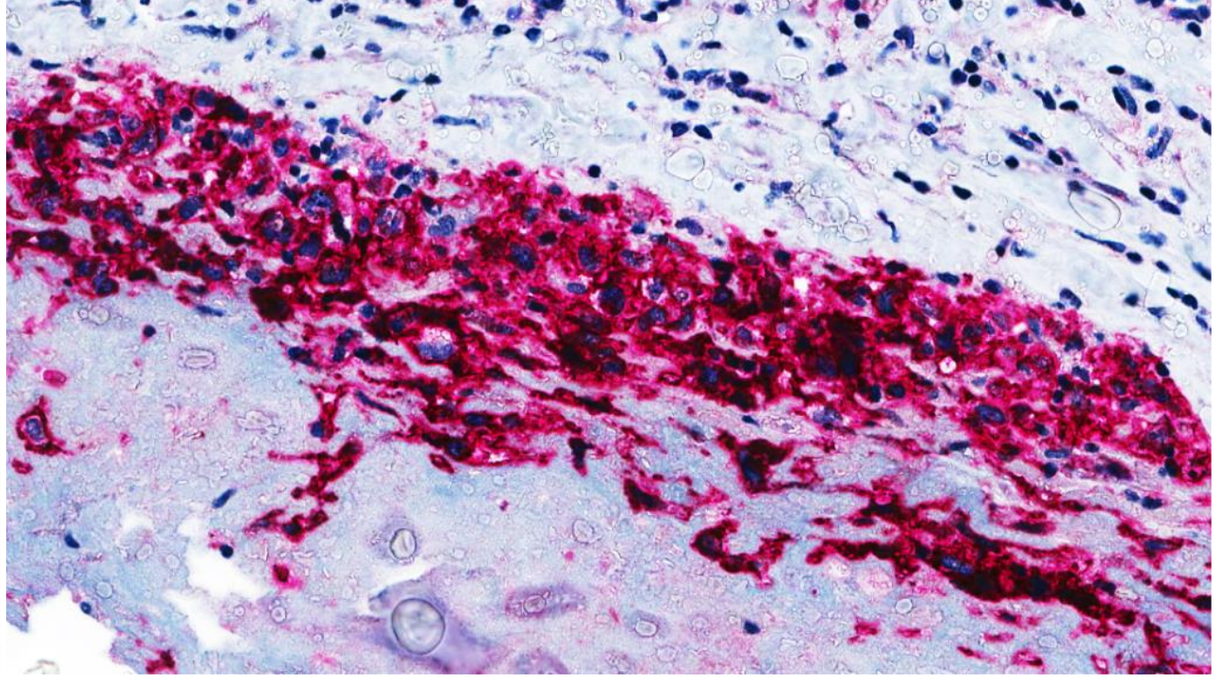
Anaplastic large cell lymphoma, ALK positive

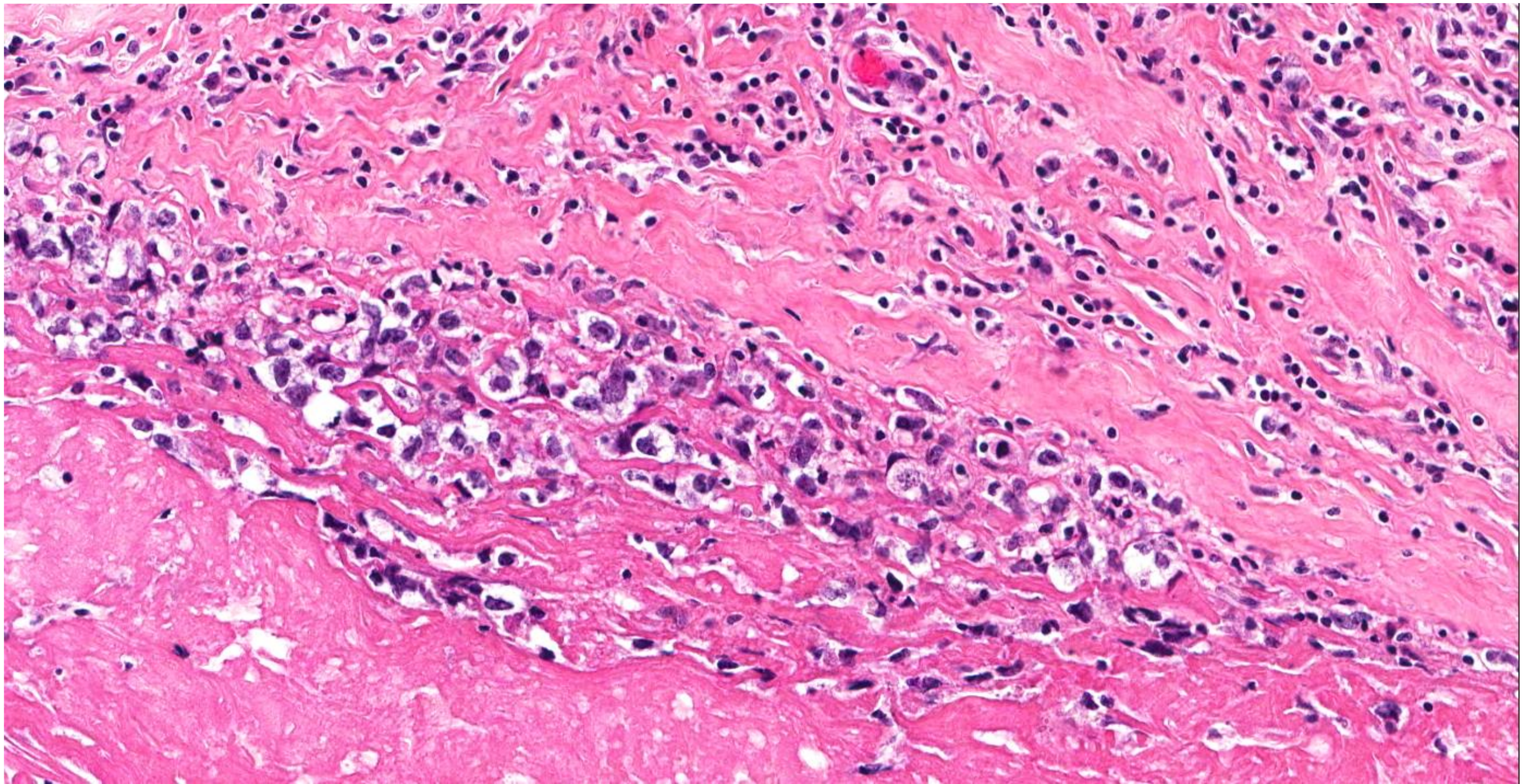
Anaplastic large cell lymphoma, ALK negative
(UPGRADED TO DEFINITE ENTITY)

Breast implant-associated ALCL

(NEW PROVISIONAL ENTITY)







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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant–Associated Anaplastic Large-Cell Lymphoma

Mark W. Clemens, L. Jeffrey Medeiros, Charles E. Butler, Kelly K. Hunt, Michelle A. Fanale, Steven Horwitz, Dennis D. Weisenburger, Jun Liu, Elizabeth A. Morgan, Rashmi Kanagal-Shamanna, Vinita Parkash, Jing Ning, Aliyah R. Sohani, Judith A. Ferry, Neha Mehta-Shah, Ahmed Dogan, Hui Liu, Nora Thormann, Arianna Di Napoli, Stephen Lade, Jorge Piccolini, Ruben Reyes, Travis Williams, Colleen M. McCarthy, Summer E. Hanson, Loretta J. Nastoupil, Rakesh Gaur, Yasuhiro Oki, Ken H. Young, and Roberto N. Miranda

Genetic subtyping of breast implant–associated anaplastic large cell lymphoma

Naoki Oishi,[1,2] Garry S. Brody,[3] Rhett P. Ketterling,[1] David S. Viswanatha,[1] Rong He,[1] Surendra Dasari,[4] Ming Mai,[1] Hailey K. Benson,[1] Christopher A. Sattler,[1] Rebecca L. Boddicker,[1] Ellen D. McPhail,[1] N. Nora Bennani,[5] Christin A. Harless,[6] Kuldeep Singh,[6] Mark W. Clemens,[7] L. Jeffrey Medeiros,[8] Roberto N. Miranda,[8,*] and Andrew L. Feldman[1,*]

Parameter	No. positive/ no. studied	Percent positive
Capsular infiltration (T3*)	4/33	12
Mass/infiltration beyond capsule (T4)	10/33	30
Lymph node involvement†	4/30	13
ALK (IHC‡)	0/36	0
DUSP22 rearrangement (FISH)	0/36	0
TP63 rearrangement (FISH)	0/36	0
pSTAT3^{Y705} (IHC)	27/27	100
JAK1 mutation (NGS)	1/15	7§
JAK3 mutation (NGS)	0/15	0
STAT3 mutation (NGS)	3/15	20
STAT5A mutation (NGS)	0/15	0
STAT5B mutation (NGS)	0/15	0

thank you
ngiyabonga
рахмат
danke
謝謝
spas
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
dank je
misaotra
paldies
grazzi
спасибі
biagodaram
matondo
gracias
хвала
kiitos
dankie
nanni
nandri
dhanyavad
mauruuru
asante
manana
bedankt
hvala
koszonom
aciu
obrigada
bayarlalaa
gracie
dankon
murakoze
tenki
enkosi
djiere dieuf
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mochchakkeram
akun
дякую
mamnun
dziękuję
chnorakaloutioun
gracies
sulpay
go raibh maith agat
sobodi
dekuji
sagolun
sukriya
kop khun krap
taiku
obrigado
arigatô
takk
dakujem
trugarez
mèsi
ありがとう
tanemirt
grazie
didi madloba
najis tuke
terima kasih
rahmet
shukriya
merce
мерси
kam sah hamnida
rahmat
dhanyavadagalu
diolch
ευχαριστώ
xiexie
merci
감사합니다