3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

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10.40 Pathobiology of nodal peripheral T-cell lymphoma

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ALMA MATER STUDIORUM A.D. 1088

Disclosures of Stefano A. Pileri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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Stemline					+	+	
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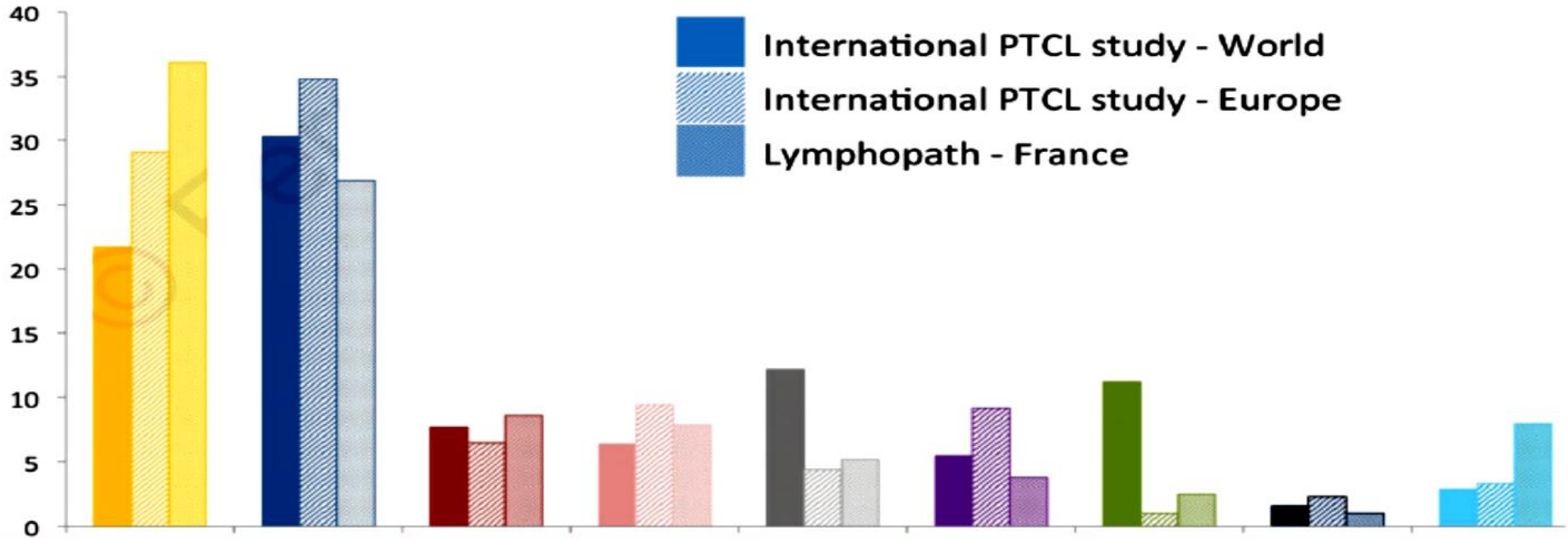
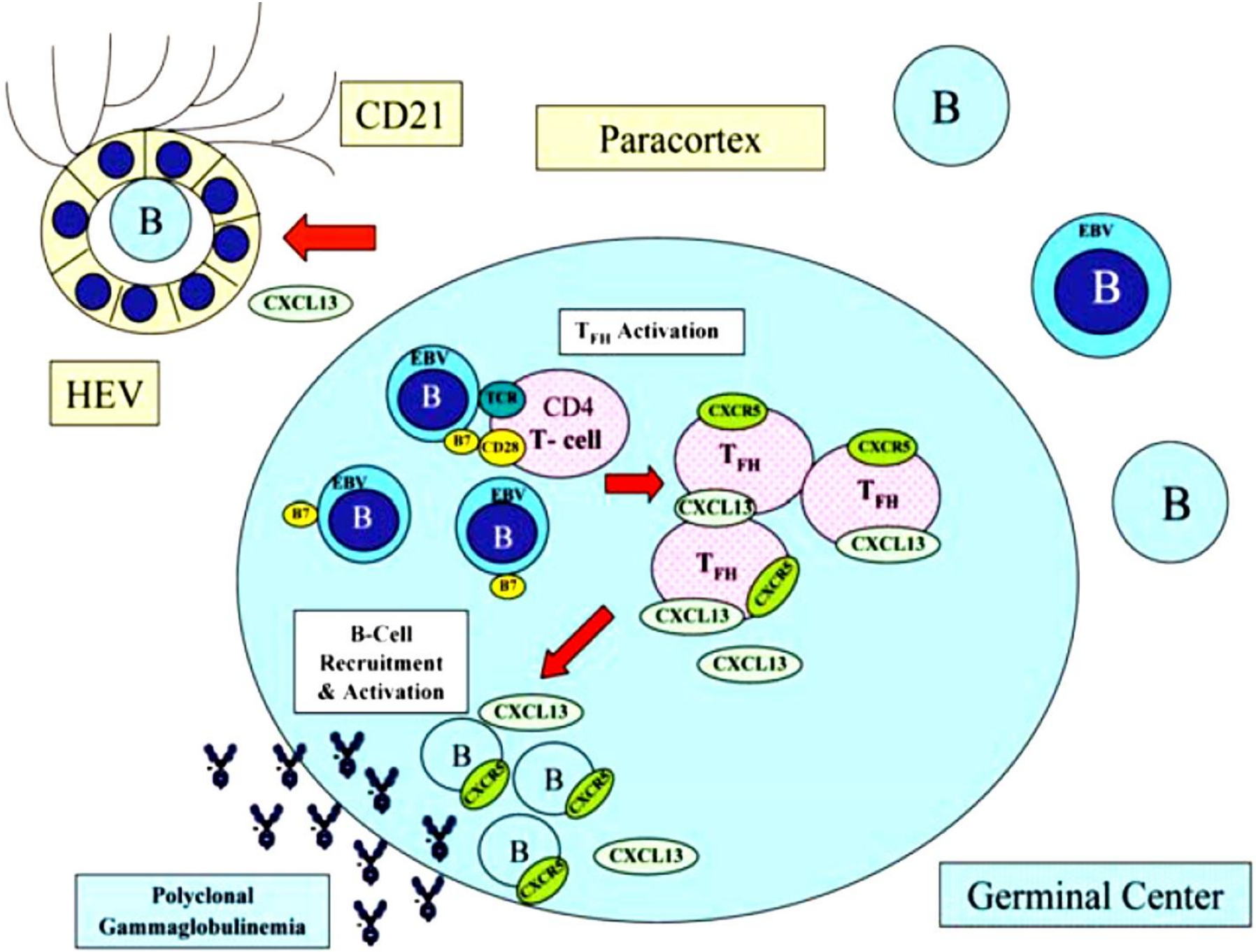
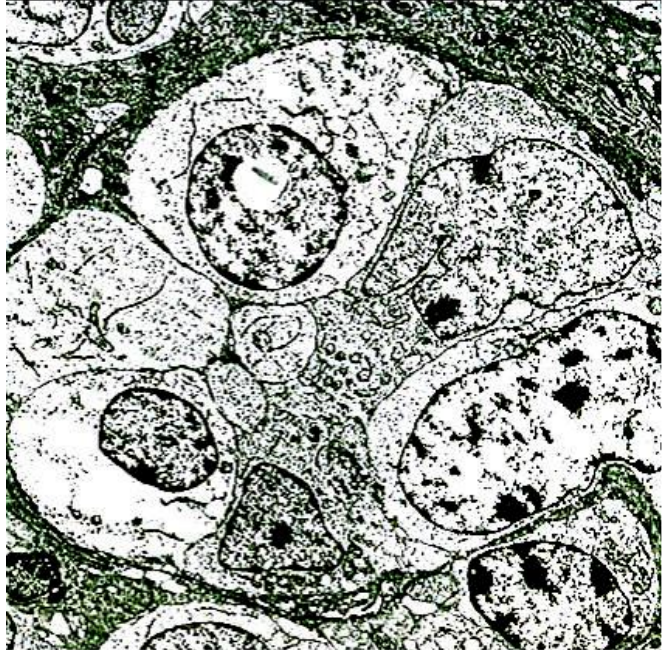
Takeda					+		
Diatech						+	

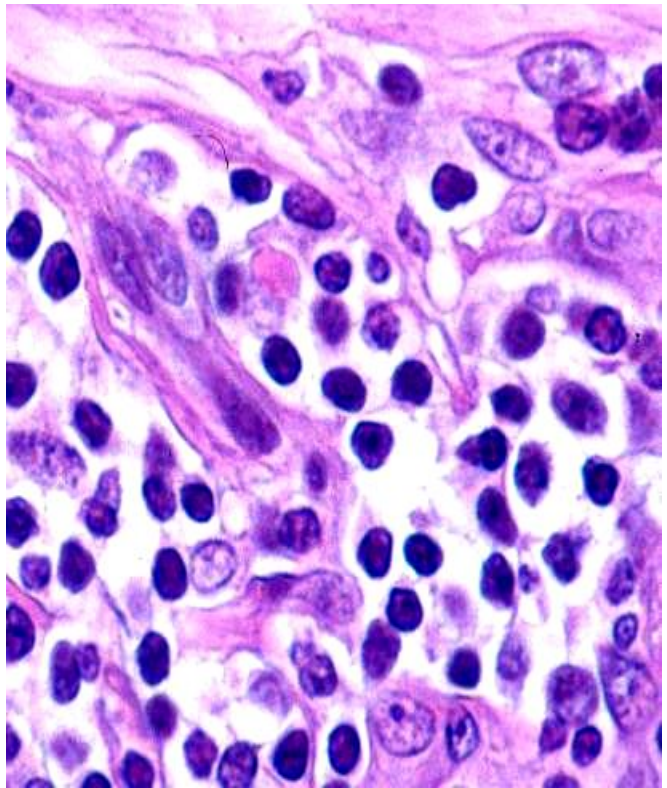


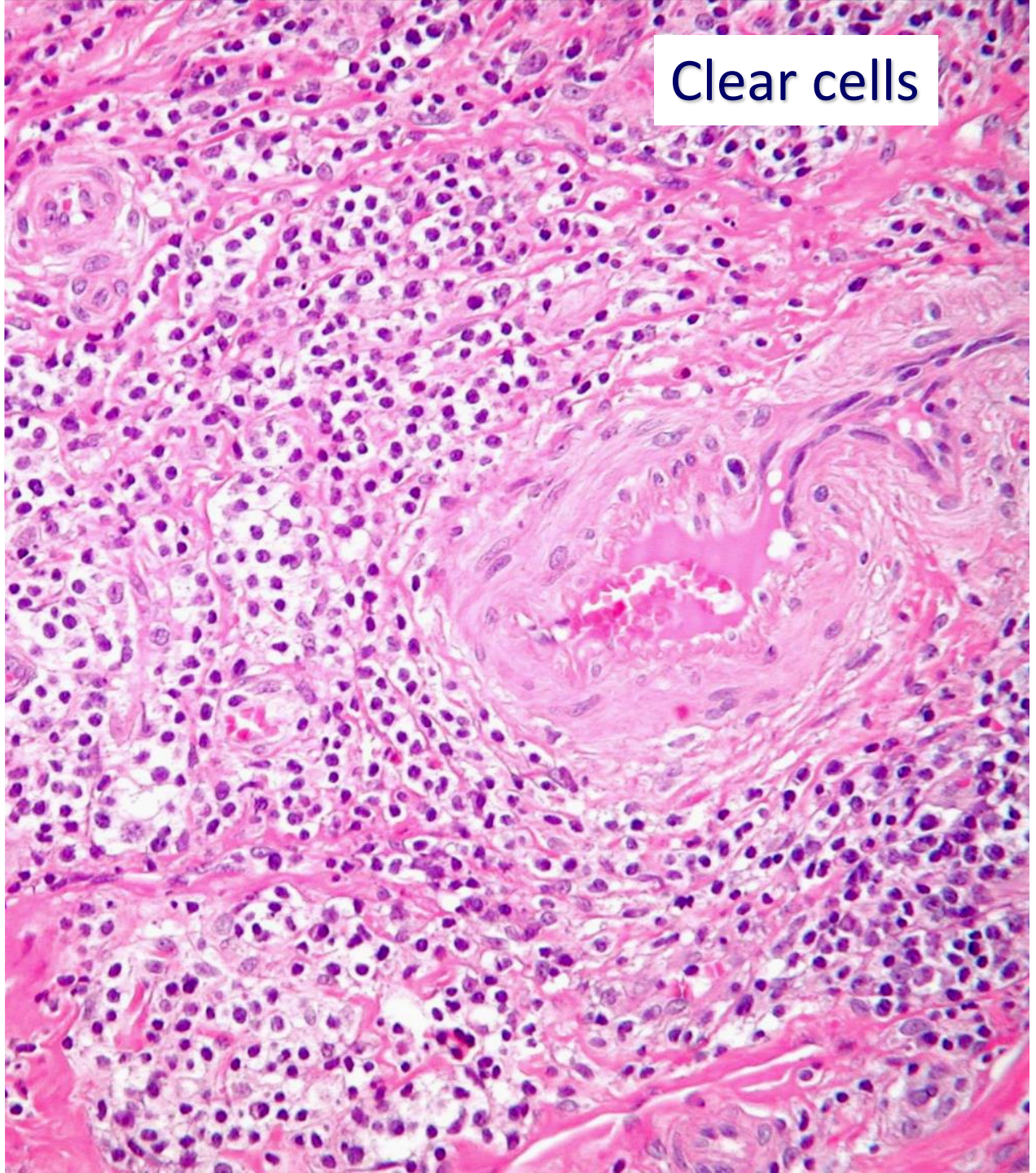
%	AITL	PTCL-NOS	ALK+ ALCL	ALK- ALCL	NKTCL	EATL	ATLL	HSTL	Others
World	21.7	30.4	7.7	6.5	12.2	5.5	11.3	1.6	2.9
Europe	29.1	34.8	6.5	9.5	4.4	9.2	1	2.3	3.3
France	36.1	26.9	8.6	7.9	5.2	3.8	2.5	1	8


CD21
Paracortex
B
HEV
B
CXCL13
EBV
B
T_{FH} Activation
EBV
B
TCR
CD4
T- cell
B7
CD28
CXCR5
T_{FH}
CXCL13
EBV
B
B7
EBV
B
B7
B
B-Cell
Recruitment
& Activation
CXCL13
B
CXCR5
B
CXCR5
B
CXCR5
CXCL13
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 (≥16 g/dl)	23/48 (48%)	2/11 (18%)	4/19 (21%)	0.05



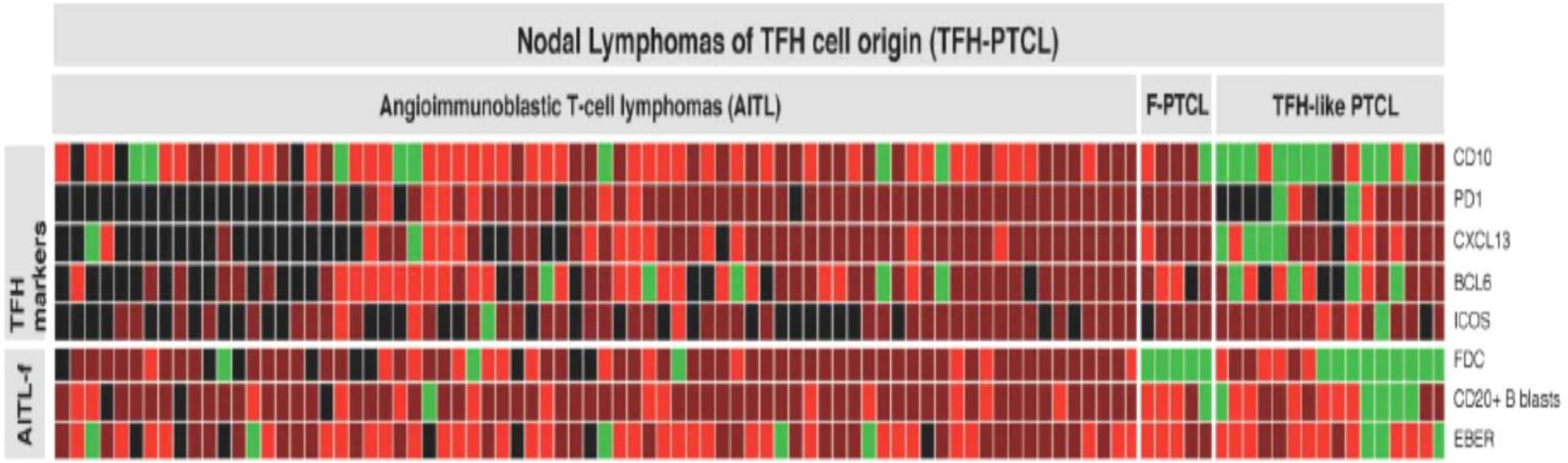



Clear cells

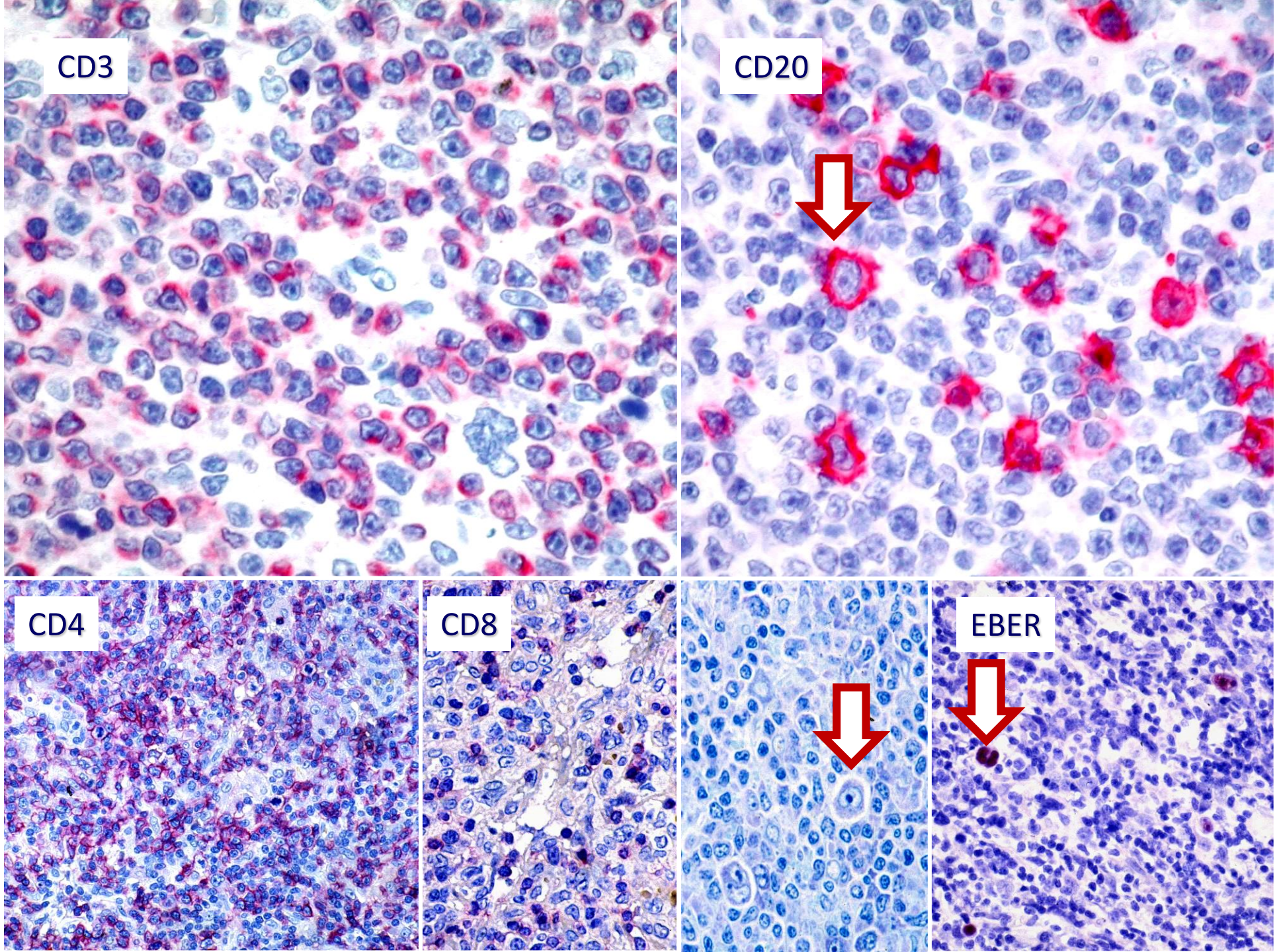
A novel subset of T-helper cells: follicular T-helper cells and their markers

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

Targeting intratumoral B cells with rituximab in addition to CHOP in angioimmunoblastic T-cell lymphoma. A clinicobiological study of the GELA

Marie-Hélène Delfau-Larue,[1,2,3] Laurence de Leval,[4]* Bertrand Joly,[5]* Anne Plonquet,[1,2,3] Dominique Challine,[1,6] Marie Parrens,[7] Alain Delmer,[8] Gilles Salles,[9] Franck Morschhauser,[10] Richard Delarue,[11] Pauline Brice,[12] Reda Bouabdallah,[13] Olivier Casasnovas,[14] Hervé Tilly,[15] Philippe Gaulard,[1,2,16] and Corinne Haioun[1,17]

Conclusions

We report here the results of the first clinical trial targeting both the neoplastic T cells and the microenvironment-associated CD20+ B lymphocytes in angioimmunoblastic T-cell lymphoma, showing no clear benefit of adding rituximab to conventional chemotherapy. A strong relationship, not previously described, between circulating Epstein-Barr virus and circulating tumor cells is highlighted. *(This trial was registered at www.clinicaltrials.gov as NCT00169156.)*

haematologica | 2012; 97(10)

Am J Surg Pathol. 2007 Jul;31(7):1077-88. doi: 10.1097/PAS.0b013e31802d68e9.

Histologic evolution of angioimmunoblastic T-cell lymphoma in consecutive biopsies: clinical correlation and insights into natural history and disease progression

Ayoma Deepthi Attygalle [1], Charalampia Kyriakou, Jehan Dupuis, Karen Lynne Grogg, Timothy Charles Diss, Andrew Charles Wotherspoon, Shih Sung Chuang, José Cabeçadas, Peter Gershon Isaacson, Ming-Qing Du, Philippe Gaulard, Ahmet Dogan

High-dimensional and single-cell transcriptome analysis of the tumor microenvironment in angioimmunoblastic T cell lymphoma (AITL)

Joshua C. Pritchett[1], Zhi-Zhang Yang[1], Hyo Jin Kim[1], Jose C. Villasboas[1], Xinyi Tang[1], Shahrzad Jalali[1], James R. Cerhan[2], Andrew L. Feldman[3] and Stephen M. Ansell[1]✉

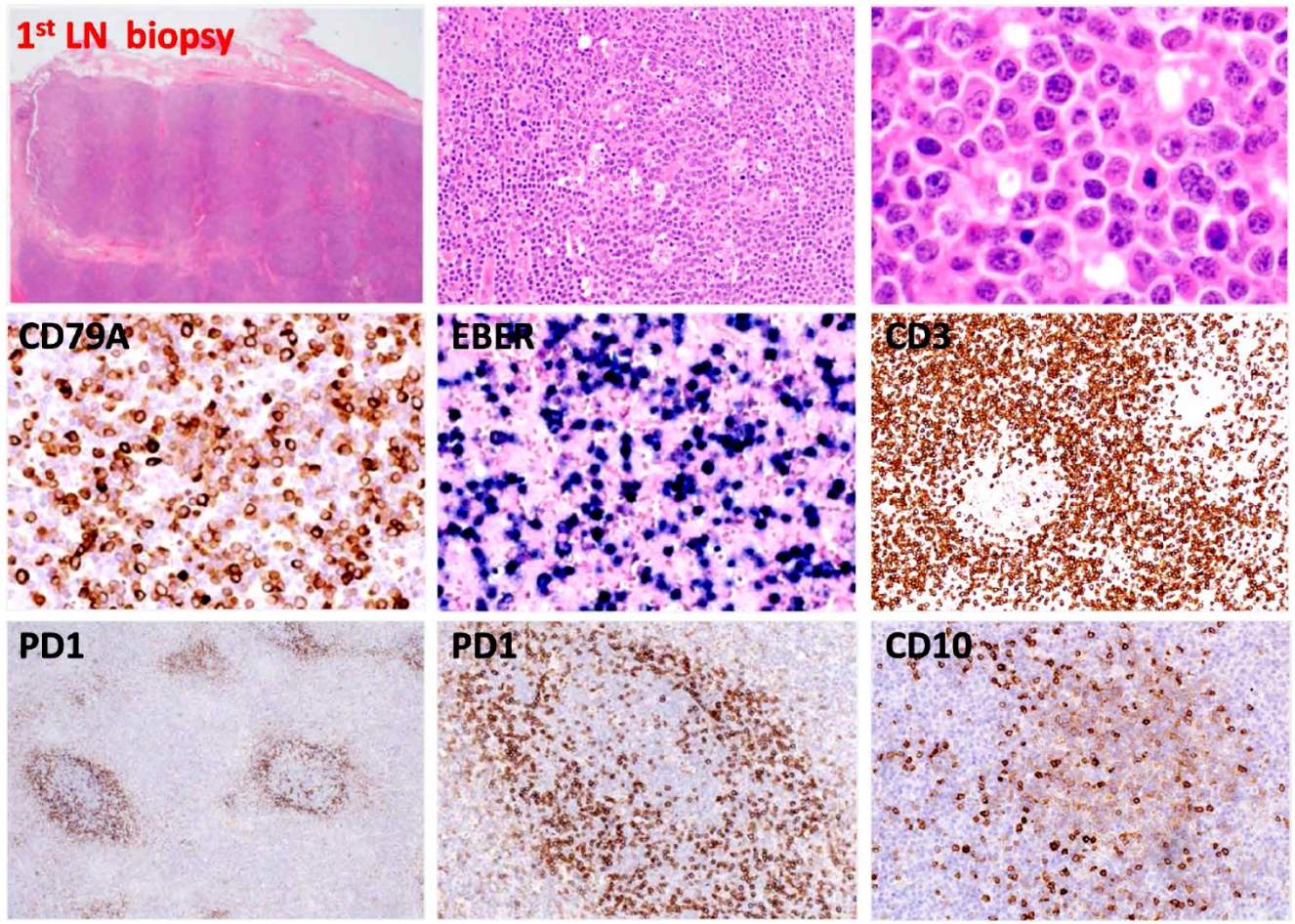
Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive lymphoid malignancy associated with a poor clinical prognosis. The AITL tumor microenvironment (TME) is unique, featuring a minority population of malignant CD4+ T follicular helper (TFH) cells inter-mixed with a diverse infiltrate of multi-lineage immune cells. While much of the understanding of AITL biology to date has focused on characteristics of the malignant clone, less is known about the many non-malignant populations that comprise the TME. Recently, mutational consistencies have been identified between malignant cells and non-malignant B cells within the AITL TME. As a result, a significant role for non-malignant populations in AITL biology has been increasingly hypothesized. In this study, we have utilized mass cytometry and single-cell transcriptome analysis to identify several expanded populations within the AITL TME. Notably, we find that B cells within the AITL TME feature decreased expression of key markers including CD73 and CXCR5. Furthermore, we describe the expansion of distinct CD8+ T cell populations that feature an exhausted phenotype and an underlying expression profile indicative of dysfunction, impaired cytotoxicity, and upregulation of the chemokines XCL2 and XCL1.

Leukemia (2022) 36:165–176; https://doi.org/10.1038/s41375-021-01321-2

Haematologica 2022
Volume 107(2):489-499

Early detection of T-cell lymphoma with T follicular helper phenotype by *RHOA* mutation analysis

Rachel Dobson,[1] Peter Y. Du,[1] Lívia Rásó-Barnett,[2] Wen-Qing Yao,[1] Zi Chen,[1] Calogero Casa,[2] Hesham El-Daly,[2] Lorant Farkas,[2,3] Elizabeth Soilleux,[1,4] Penny Wright,[4] John W. Grant,[4] Manuel Rodriguez-Justo,[5] George A. Follows,[6] Hala Rashed,[7] Margarete Fabre,[6,8] E. Joanna Baxter,[6] George Vassiliou,[6,8] Andrew Wotherspoon,[9] Ayoma D. Attygalle,[9] Hongxiang Liu[2] and Ming-Qing Du[1,4]



Multicenter phase 2 study of oral azacitidine (CC-486) plus CHOP as initial treatment for PTCL

Jia Ruan,[1] Alison Moskowitz,[2] Neha Mehta-Shah,[3] Lubomir Sokol,[4] Zhengming Chen,[1] Nikita Kotlov,[5] Grigorii Nos,[5] Maria Sorokina,[5] Vladislav Maksimov,[5] Andrea Sboner,[1] Michael Sigouros,[1] Koen van Besien,[1] Steven Horwitz,[2] Sarah C. Rutherford,[1] Erin Mulvey,[1] Maria V. Revuelta,[1] Jenny Xiang,[1] Alicia Alonso,[1] Ari Melnick,[1] Olivier Elemento,[1] Giorgio Inghirami,[1] John P. Leonard,[1] Leandro Cerchietti,[1] and Peter Martin[1]

[1]Meyer Cancer Center, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Washington University in St. Louis, St. Louis, MO; [4]Moffitt Cancer Center, Tampa, FL; and [5]BostonGene Corporation, Waltham, MA

KEY POINTS

- **Addition of oral azacitidine to CHOP as initial therapy is safe, and induces high rates of CR in patients with PTCL-TFH.**
- **Integrative analyses suggest that azacitidine priming promotes apoptosis and inflammation within the lymphoma tumor microenvironment.**

Peripheral T-cell lymphomas (PTCL) with T-follicular helper phenotype (PTCL-TFH) has recurrent mutations affecting epigenetic regulators, which may contribute to aberrant DNA methylation and chemoresistance. This phase 2 study evaluated oral azacitidine (CC-486) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as initial treatment for PTCL. CC-486 at 300 mg daily was administered for 7 days before C1 of CHOP, and for 14 days before CHOP C2-6. The primary end point was end-of-treatment complete response (CR). Secondary end points included safety and survival. Correlative studies assessed mutations, gene expression, and methylation in tumor samples. Grade 3 to 4 hematologic toxicities were mostly neutropenia (71%), with febrile neutropenia uncommon (14%). Nonhematologic toxicities included fatigue (14%) and gastrointestinal symptoms (5%). In 20 evaluable patients, CR was 75%, including 88.2% for PTCL-TFH (n = 17). The 2-year progression-free survival (PFS) was 65.8% for all and 69.2% for PTCL-TFH, whereas 2-year overall survival (OS) was 68.4% for all and 76.1% for PTCL-TFH. The frequencies of the *TET2, RHOA, DNMT3A,* and *IDH2* mutations were 76.5%, 41.1%, 23.5%, and 23.5%, respectively, with *TET2* mutations significantly associated with CR (*P* = .007), favorable PFS (*P* = .004) and OS (*P* = .015), and *DNMT3A* mutations associated with adverse PFS (*P* = .016). CC-486 priming contributed to the reprograming of the tumor microenvironment by upregulation of genes related to apoptosis (*P* < .01) and inflammation (*P* < .01). DNA methylation did not show significant shift. This safe and active regimen is being further evaluated in the ALLIANCE randomized study A051902 in CD30-negative PTCL. This trial was registered at www.clinicaltrials.gov as #NCT03542266.

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

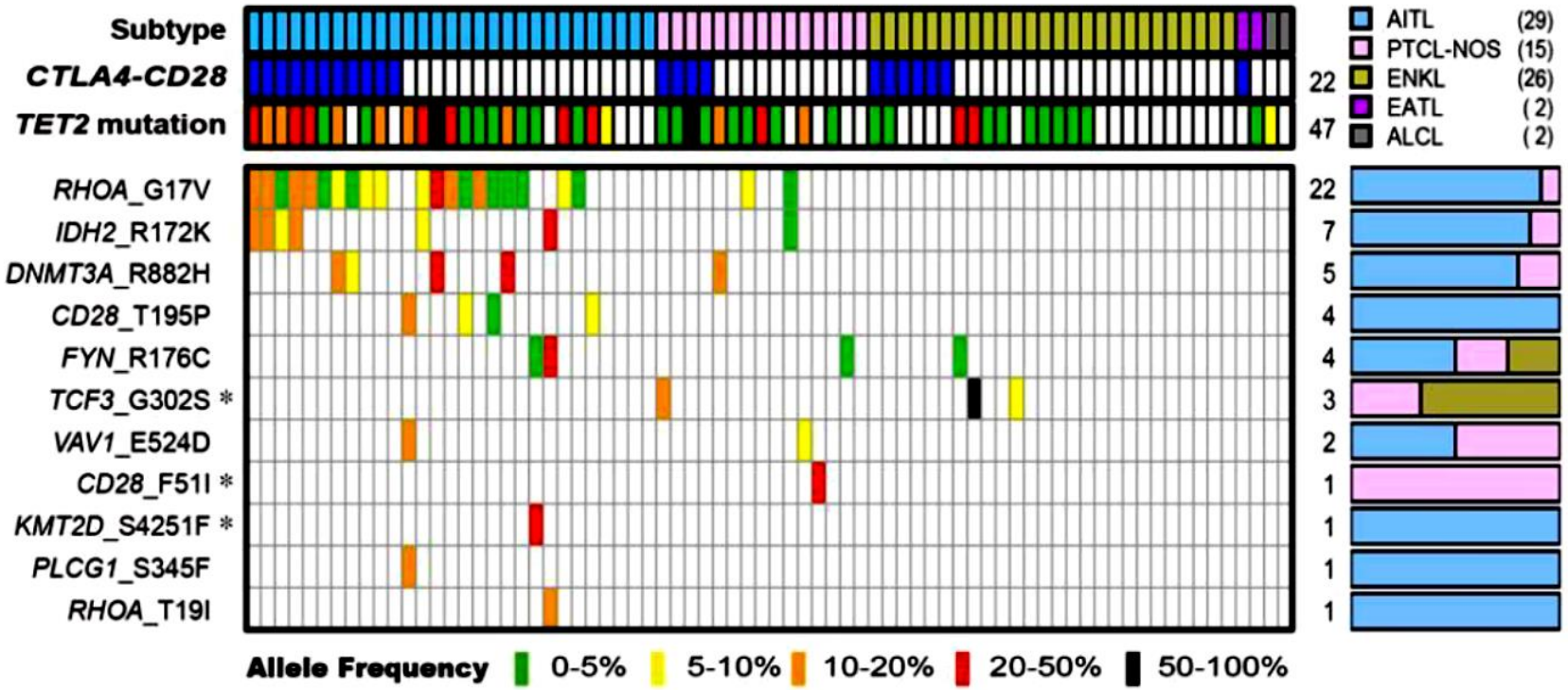
Nature Genetics **46**, 166–170 (2014) doi:10.1038/ng.2873
Received 28 May 2013 Accepted 12 December 2013 Published online 12 January 2014

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.

Frequent CTLA4-CD28 gene fusion in diverse types of T cell lymphoma

Yoo HY, Kim P, Kim WS, Lee SH, Kim S, Kang SY, Jang HY, Lee JE, Kim J, Kim SJ, Ko YH, Lee S.

Haematologica 2016
Volume 101(6):757-763



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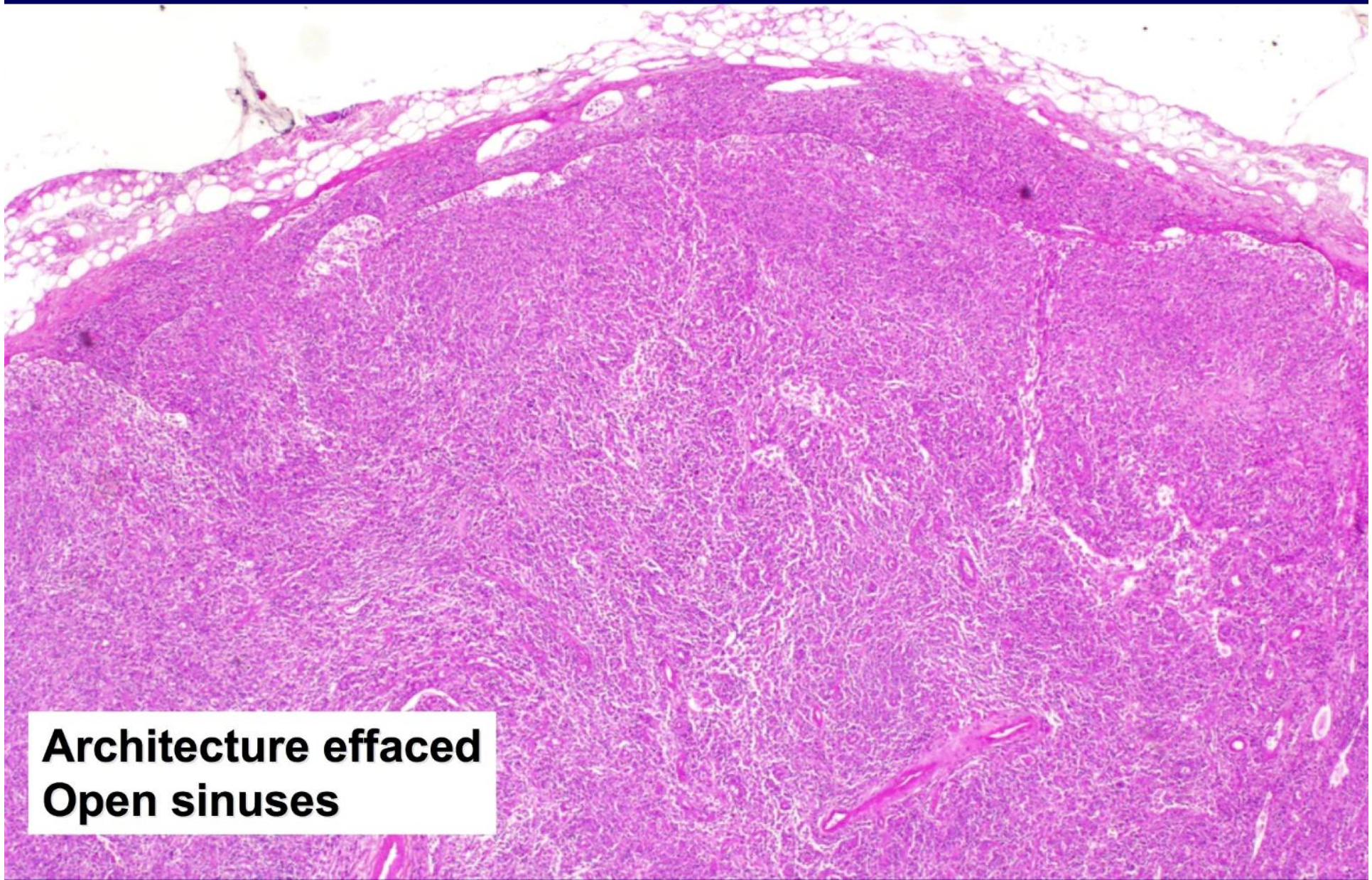
FER and FES tyrosine kinase fusions in follicular T-cell lymphoma

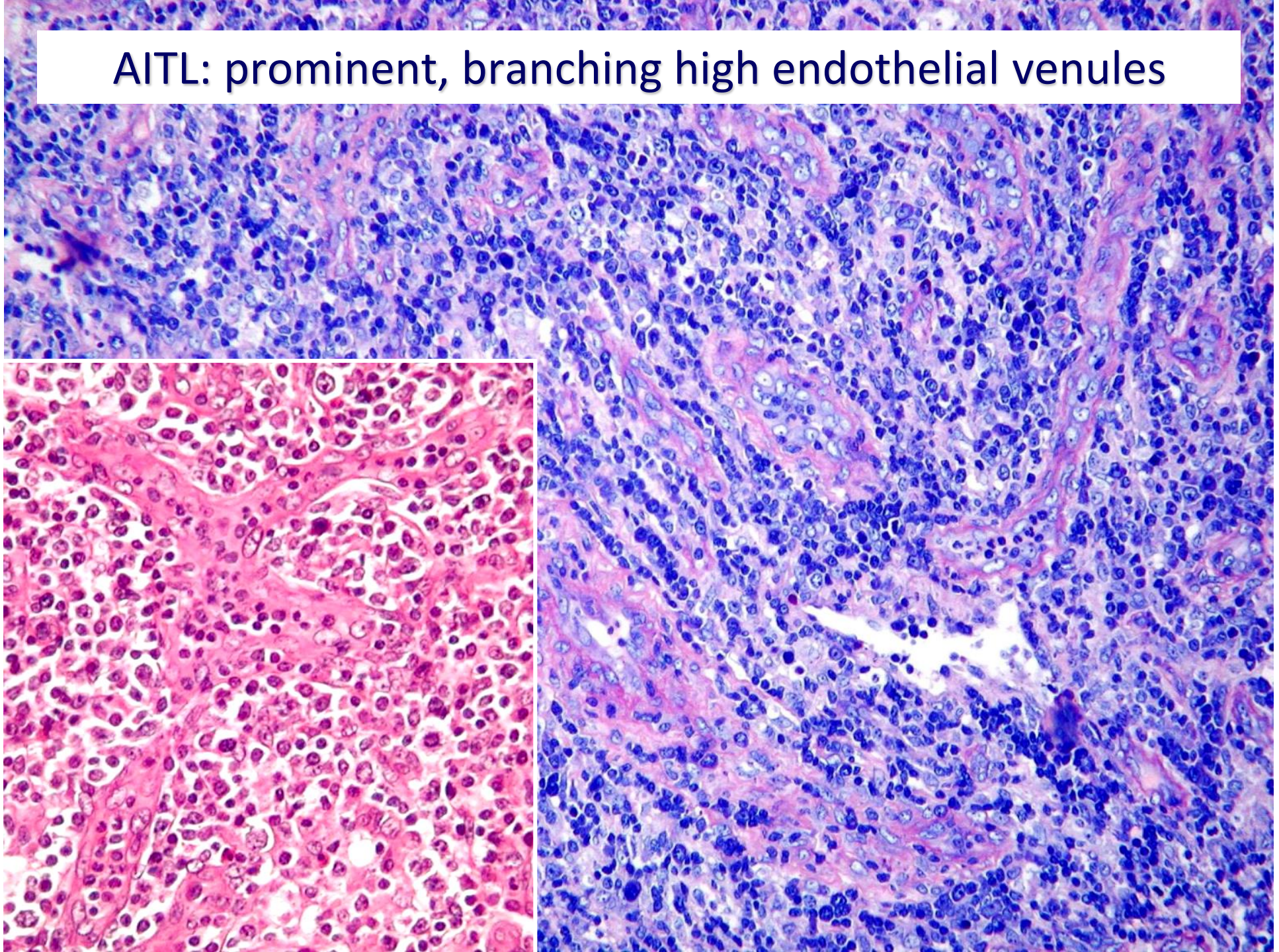
Tracking no: BLD-2019-002401R1

Koen Debackere (KU Leuven - VIB, Belgium) Jo-Anne van der Krogt (KU Leuven, Belgium) Thomas Tousseyn (University Hospitals KU Leuven, Belgium) Julio Finalet Ferreiro (K U Leuven, Belgium) Katrien Van Roosbroeck (KU Leuven, Belgium) Lukas Marcelis (KU Leuven, Belgium) Carlos Graux (CHU UCL Namur - Godinne, Belgium) Daan Dierickx (University Hospitals Leuven, Belgium) Geneviève Ameye (Centre of Human Genetics, University Hospitals Leuven, Leuven, Belgium, Belgium) Peter Vandenberghe (University Hospital Leuven, Belgium) Lucienne Michaux (KULeuven, Belgium) Jan Cools (KU Leuven - VIB, Belgium) Iwona Wlodarska (KU Leuven, Belgium)

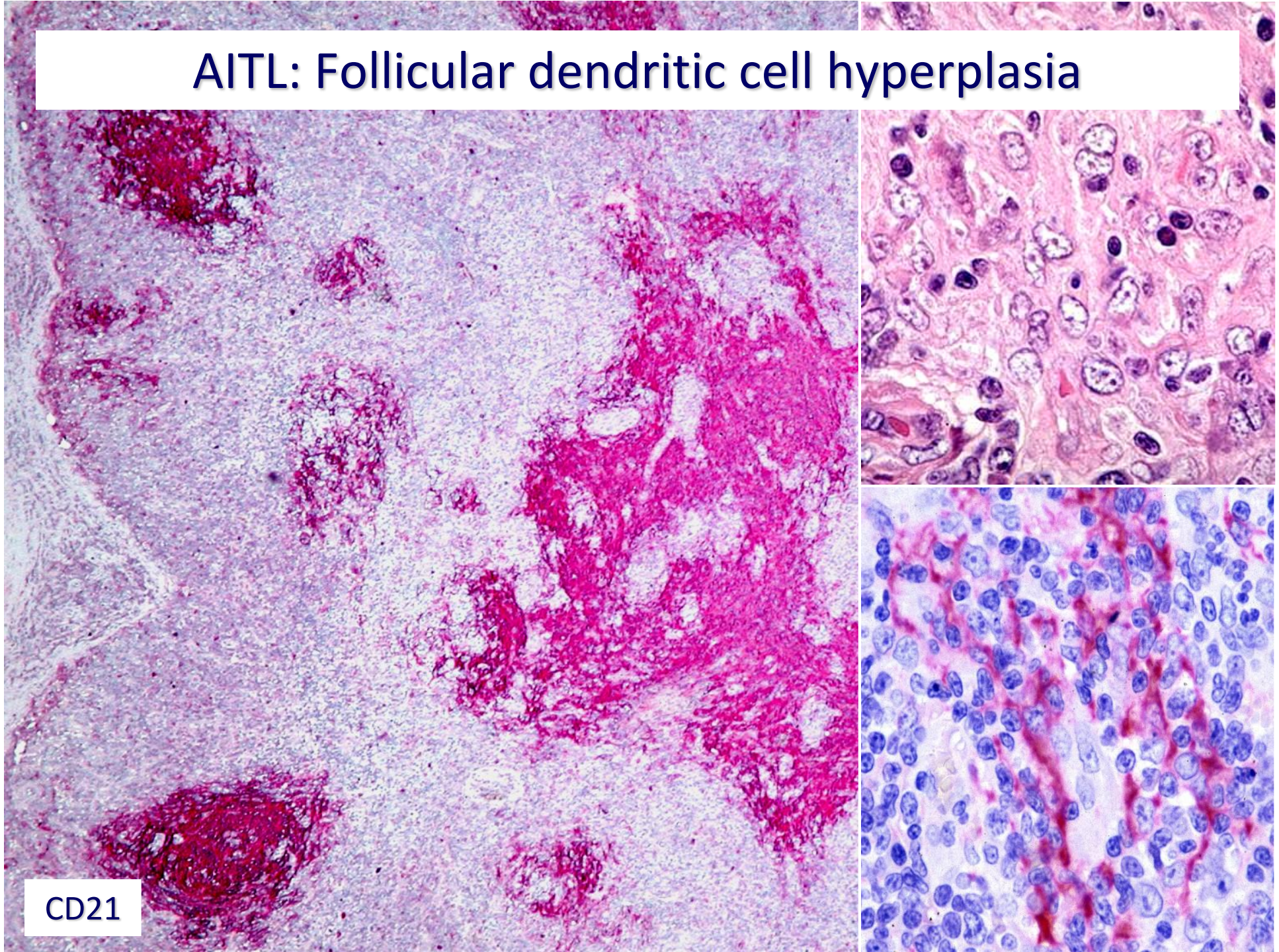
Angioimmunoblastic T-cell lymphoma



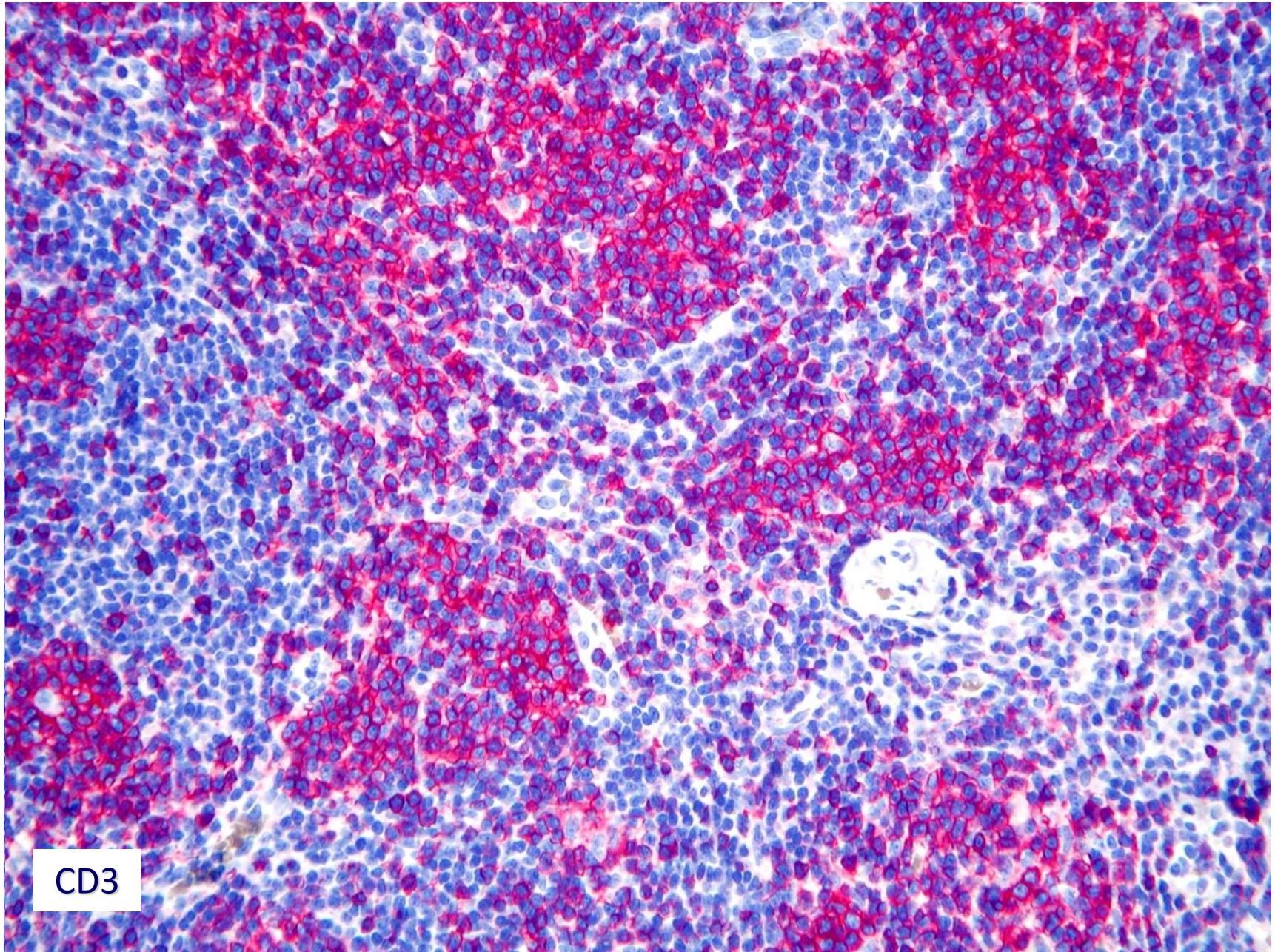
AITL: prominent, branching high endothelial venules

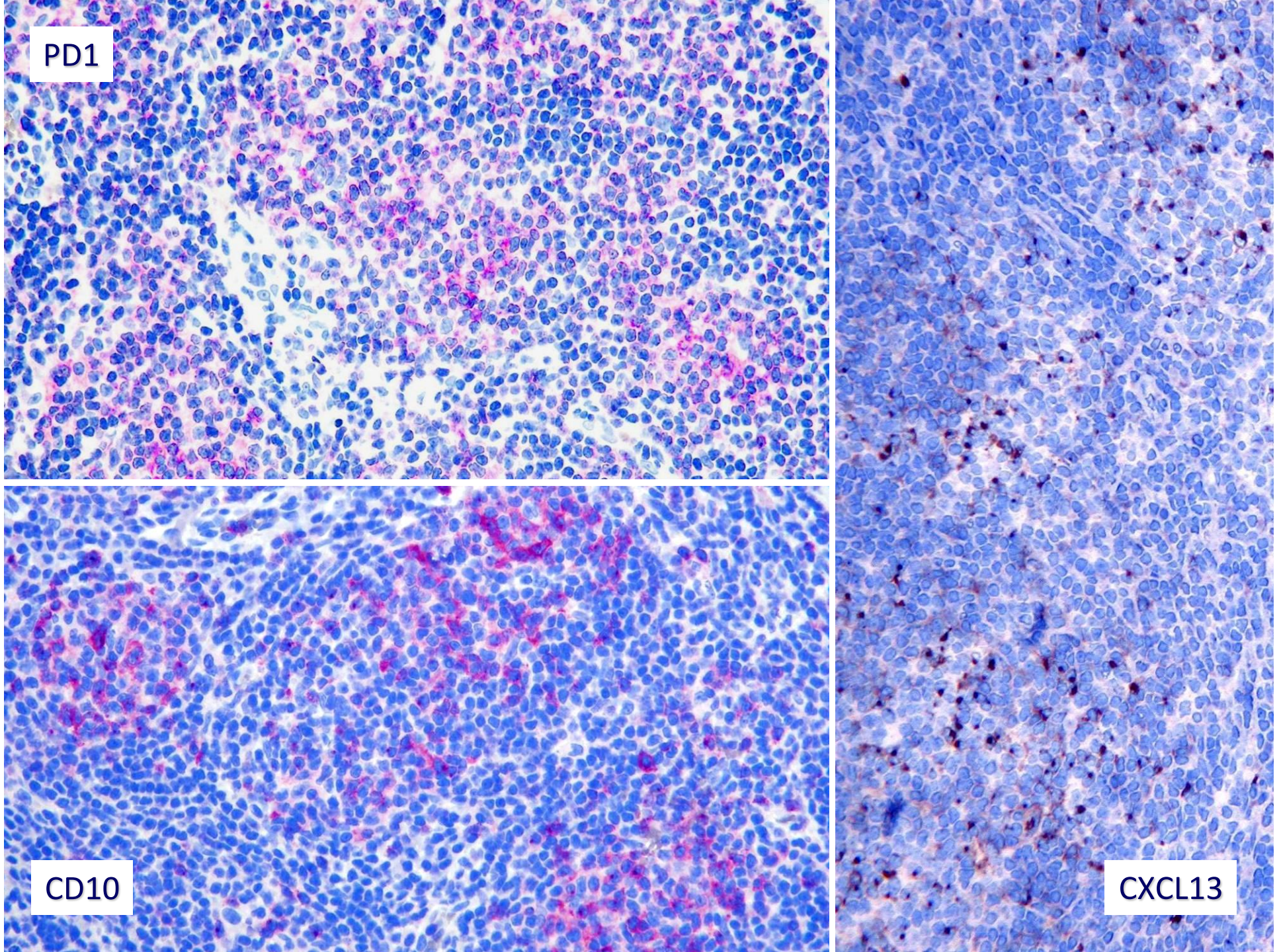


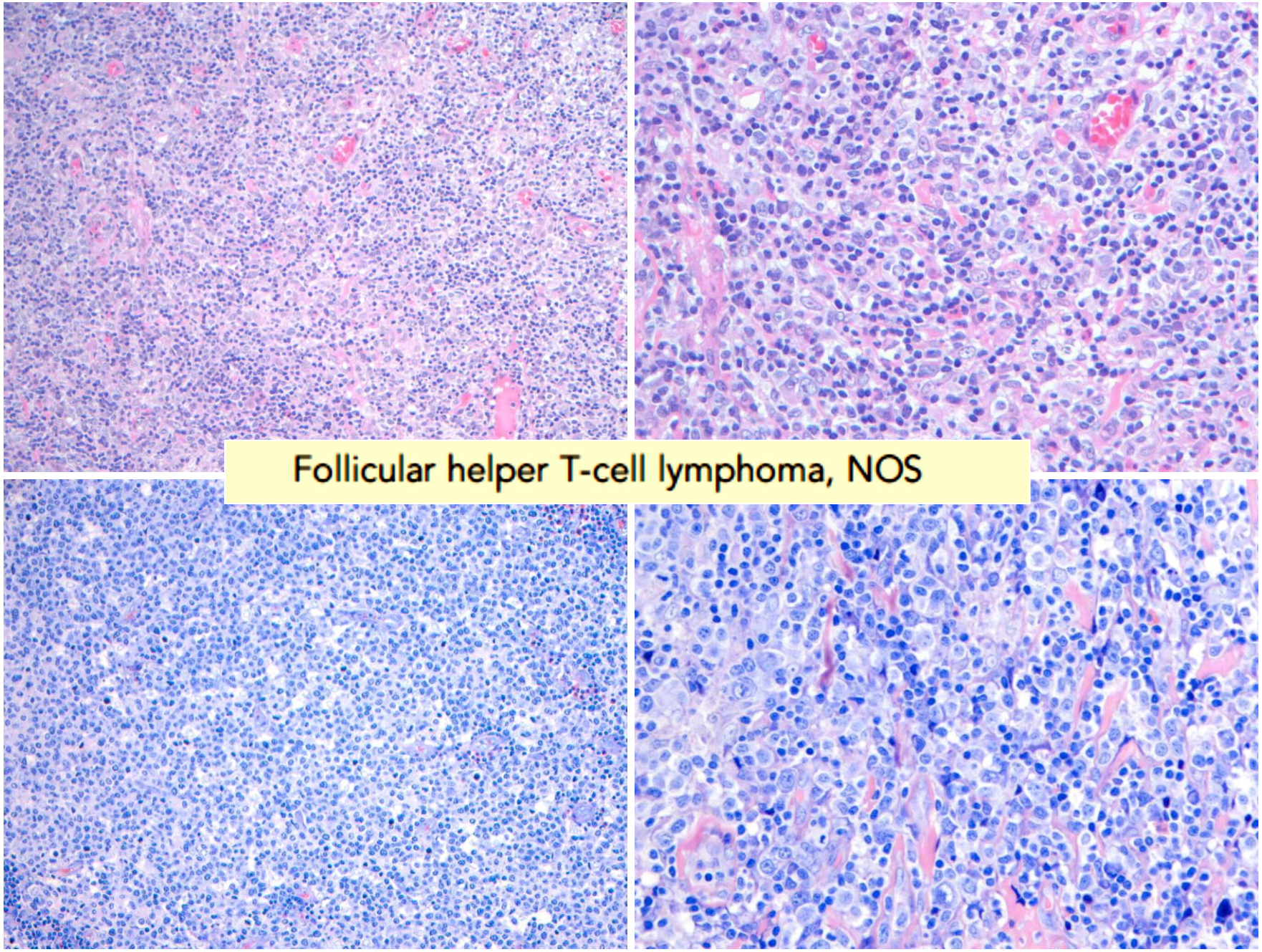
AITL: Follicular dendritic cell hyperplasia



Follicular peripheral T- cell lymphoma



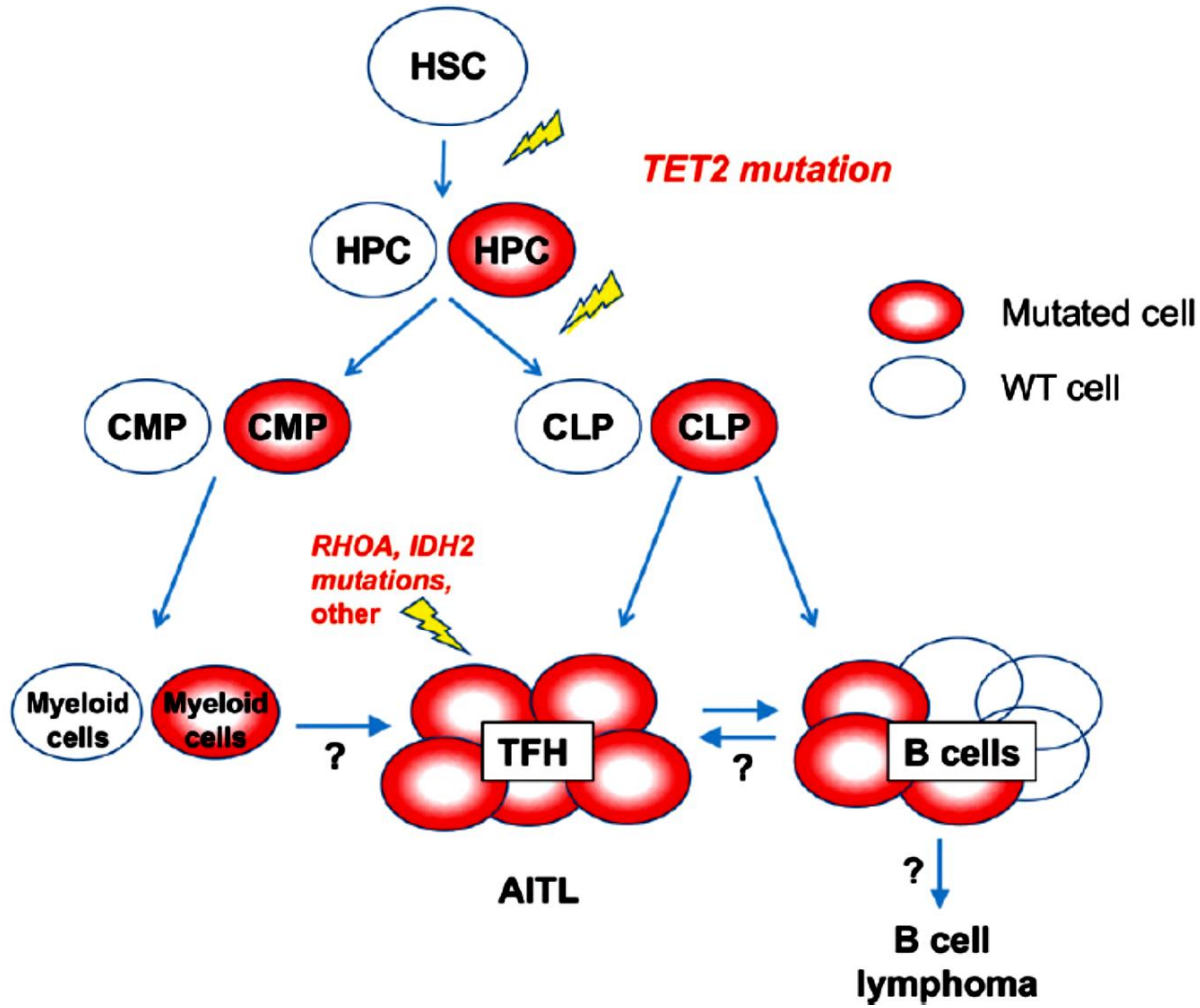

PD1
CD10
CXCL13



Follicular helper T-cell lymphoma, NOS

Angioimmunoblastic T-cell lymphoma: more than a disease of T follicular helper cells†

François Lemonnier[1] and Tak W Mak[1,2]*



cancers

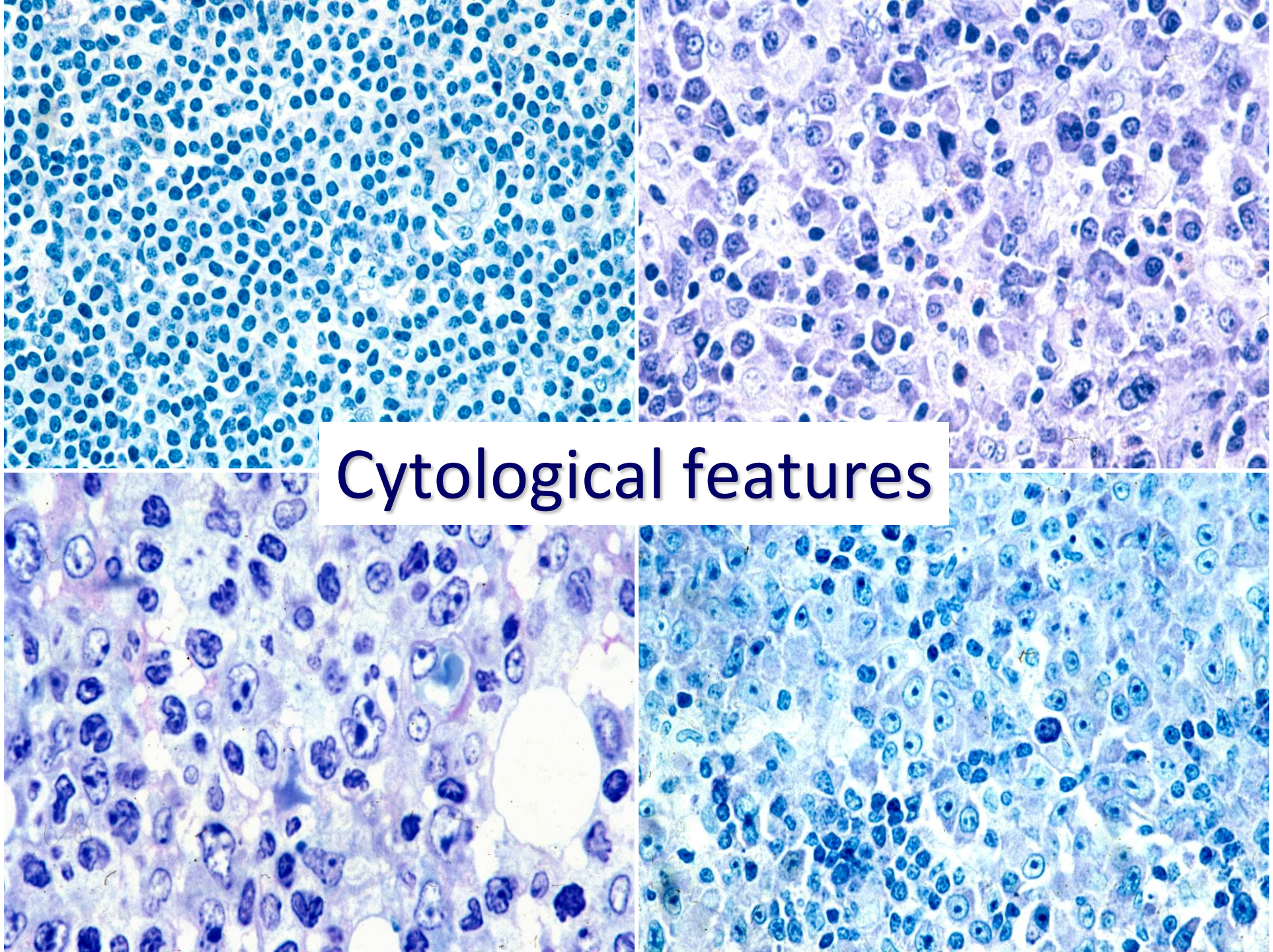
MDPI

Review

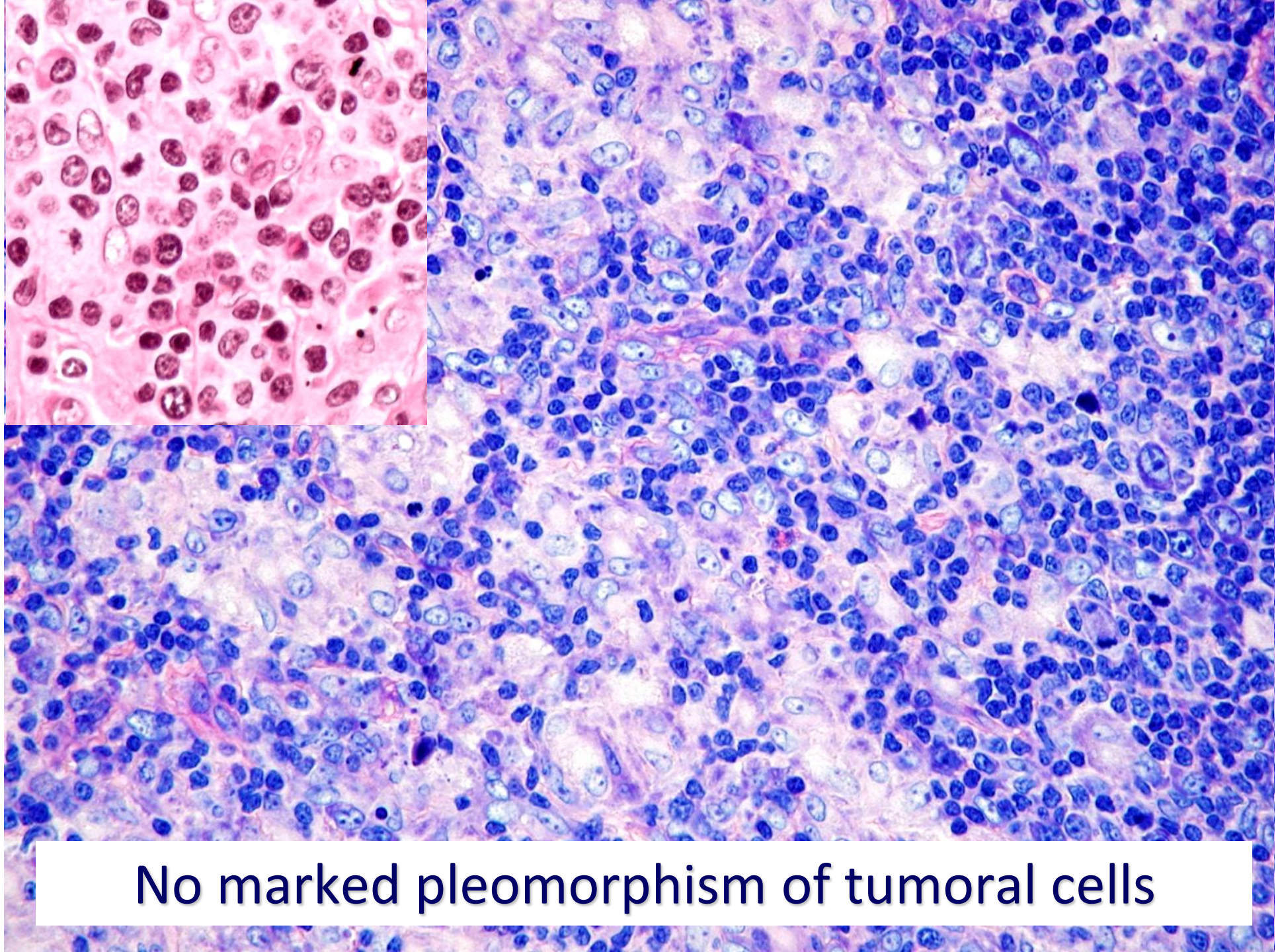
Peripheral T-Cell Lymphoma, Not Otherwise Specified: Clinical Manifestations, Diagnosis, and Future Treatment

Stefano A. Pileri [1,*], Valentina Tabanelli [1], Stefano Fiori [1], Angelica Calleri [1], Federica Melle [1], Giovanna Motta [1], Daniele Lorenzini [1], Corrado Tarella [2,3] and Enrico Derenzini [2,3]

Cancers **2021**, *13*, 4535. https://doi.org/10.3390/cancers13184535



Cytological features

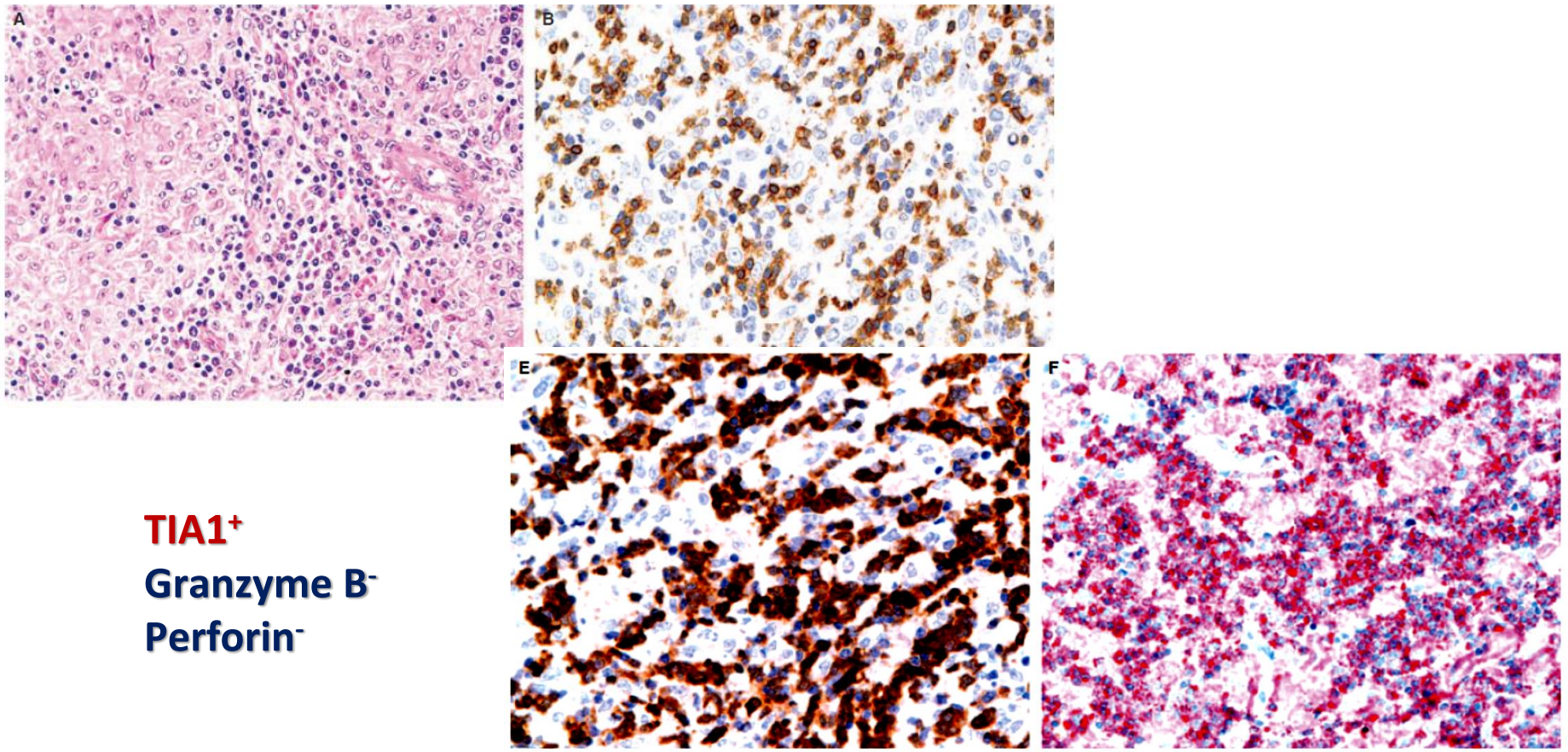


No marked pleomorphism of tumoral cells

Histopathology 2011, 59, 1173–1182. DOI: 10.1111/j.1365-2559.2011.04069.x

Revising the historical collection of epithelioid cell-rich lymphomas of the Kiel Lymph Node Registry: what is Lennert's lymphoma nowadays?

Sylvia Hartmann, Claudio Agostinelli,[1] Wolfram Klapper,[2] Penelope Korkolopoulou,[3] Karoline Koch,[2] Teresa Marafioti,[4] Pier Paolo Piccaluga,[1] Efstratios Patsouris,[3] Stefano Pileri[1] & Martin-Leo Hansmann

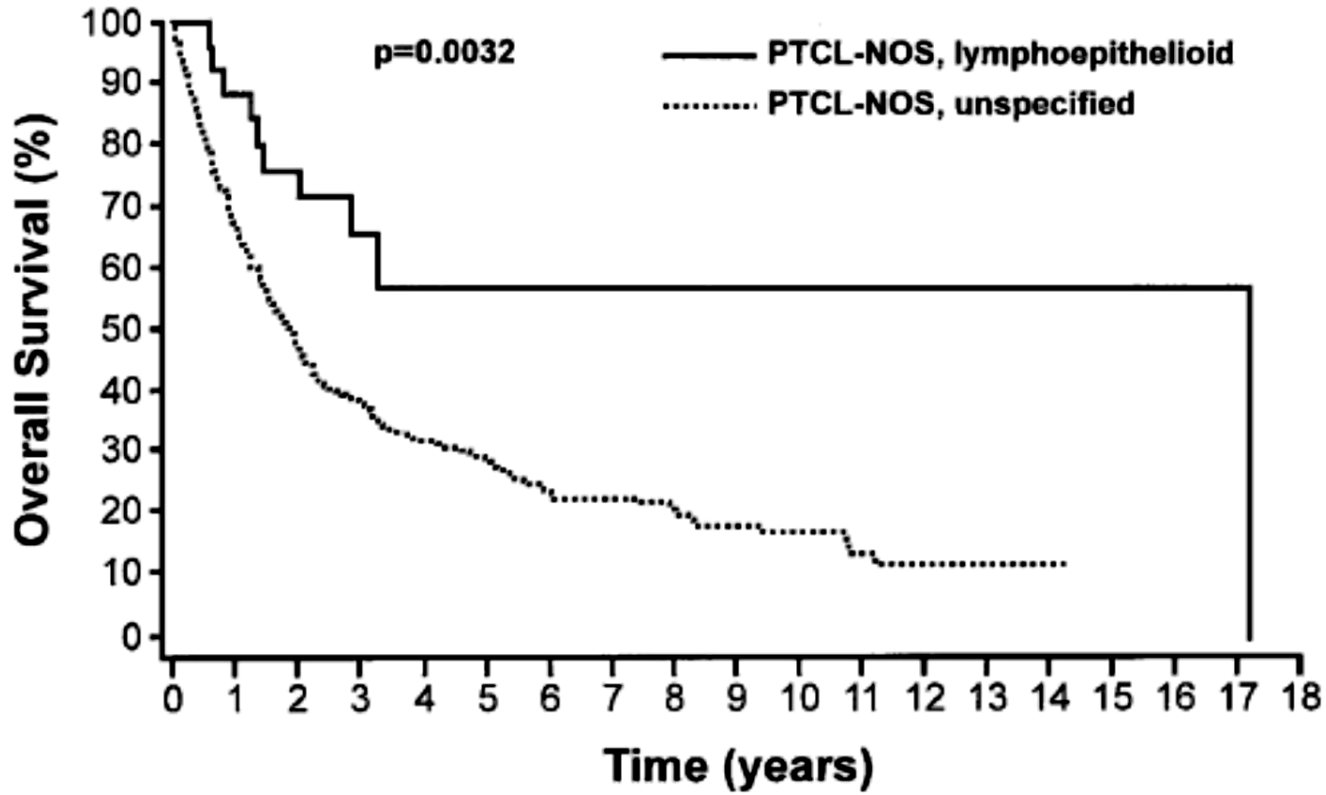


TIA1^{+}
Granzyme B^{-}
Perforin^{-}

Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project

(*Blood*. 2011;117(12):3402-3408)

Dennis D. Weisenburger,[1] Kerry J. Savage,[2] Nancy Lee Harris,[3] Randy D. Gascoyne,[4] Elaine S. Jaffe,[5] Kenneth A. MacLennan,[6] Thomas Rüdiger,[7] Stefano Pileri,[8] Shigeo Nakamura,[9] Bharat Nathwani,[10] Elias Campo,[11] Francoise Berger,[12] Bertrand Coiffier,[13] Won-Seog Kim,[14] Harald Holte,[15] Massimo Federico,[16] Wing Y. Au,[17] Kensei Tobinai,[18] James O. Armitage,[19] and Julie M. Vose,[19] for the International Peripheral T-cell Lymphoma Project



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

12 TMAs from 193 PCTLs

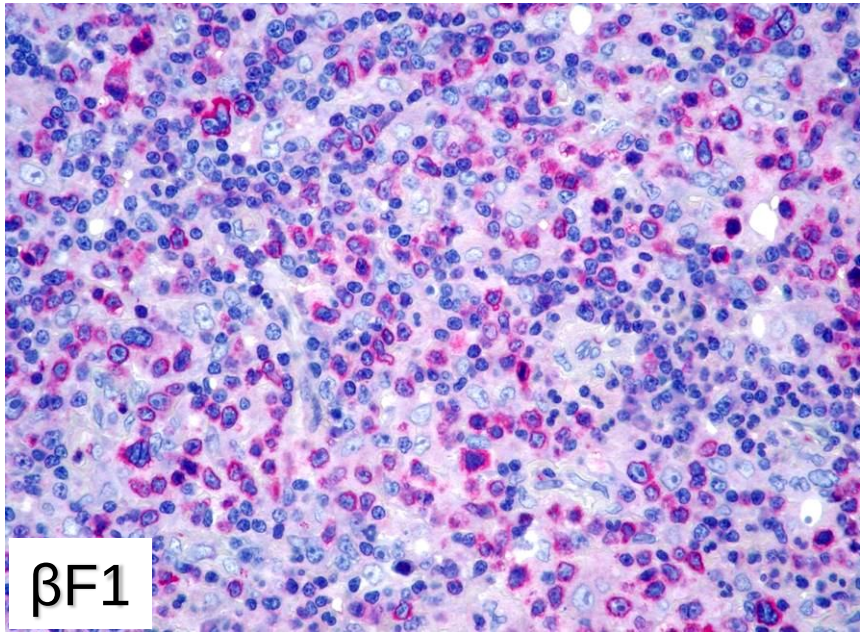


Table 2. Immunophenotypic Features and EBER Expression in a PTCL/AILD TMA

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.

CD30 expression in PTCL

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

	CD30 IHC score					
	0	1+	2+	3+	4	Score ≥ 2+
PTCL-NOS, n (%) (N = 87)	31 (35.63)	11 (12.64)	18 (20.69)	11 (12.64)	16 (18.39)	45 (51.72)
AITL, n (%) (N = 42)	24 (51.14)	9 (21.42)	5 (11.90)	4 (9.52)	–	9 (21.42)
ENTL, n (%) (N = 10)	2 (20.00)	1 (10.00)	3 (30.00)	1 (10.00)	3 (30.00)	7 (70.00)
MF, n (%) (N = 32)	13 (40.63)[a]	15 (46.88)[b]	2 (6.25)[c]	–	2 (6.25)[d]	4 (12.50)
Transformed MF, n (%) (N = 9)	–	–	3 (33.33)	6 (66.67)	–	9 (100.00)
EATL type 1, n (%) (N = 9)	–	–	2 (22.22)	–	7 (77.78)	9 (100.00)
EATL type 2, n (%) (N = 3)	3 (100)	–	–	–	–	–
All types, n (%) (N = 192)	73 (38.02)	36 (18.75)	33 (17.18)	17 (8.85)	28 (14.58)	83 (43.22)

[a] 2 cases in tumoural phase. [b] 1 case in tumoural phase. [c] Folliculotropic variant. [d] Pagetoid reticulosis sybtype.
AITL, angioimmunoblastic T-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma;
ENTL, extranodal NK/T-cell lymphoma, nasal type; MF, mycosis fungoides.

Sabattini E, et al. Haematologica. 2013;98:e81-2.

Brentuximab vedotin in the treatment of CD30$^+$ PTCL

Stefan K. Barta,[1] Jerald Z. Gong,[2] and Pierluigi Porcu[3]

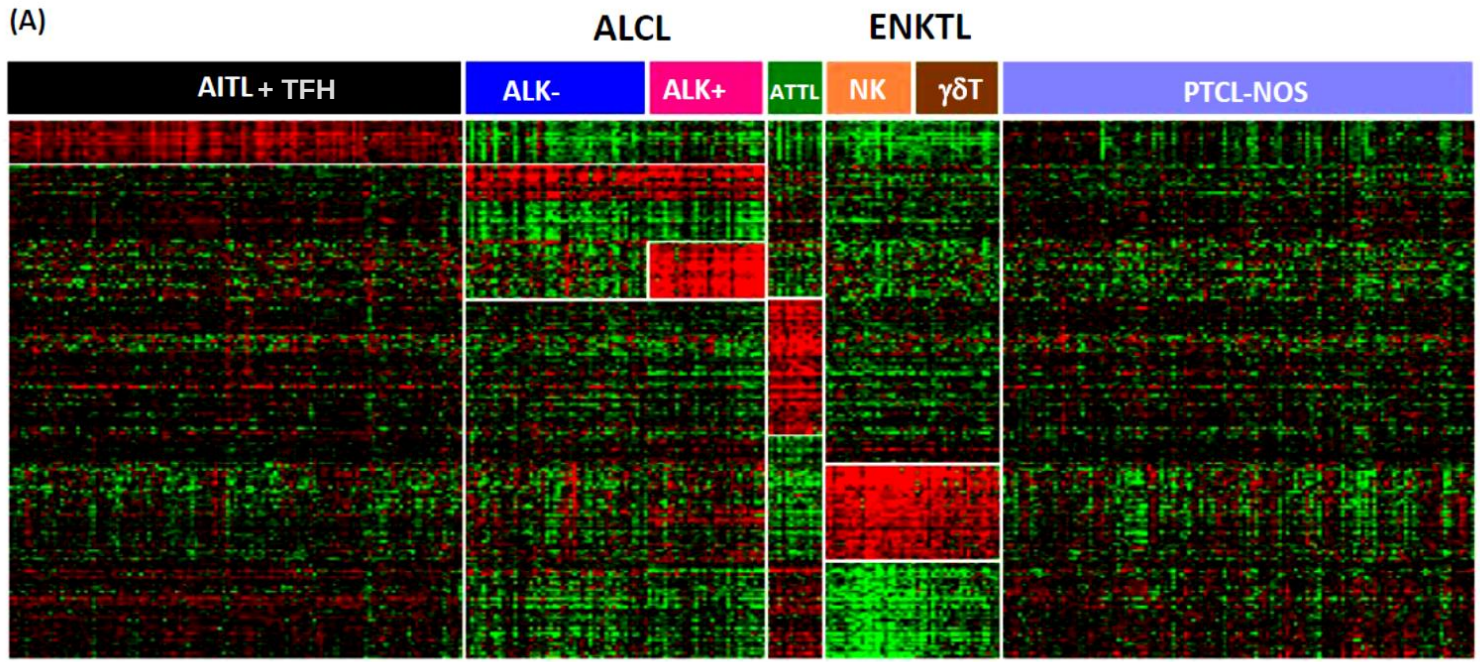
[1]Division of Hematology-Oncology, Perelman School of Medicine, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [2]Division of Hematopathology, Department of Pathology, Thomas Jefferson University, Philadelphia, PA; and [3]Division of Hematologic Malignancies and Hematopoietic Stem Cell Transplantation, Department of Medical Oncology, Sidney Kimmel Cancer Center, Philadelphia, PA

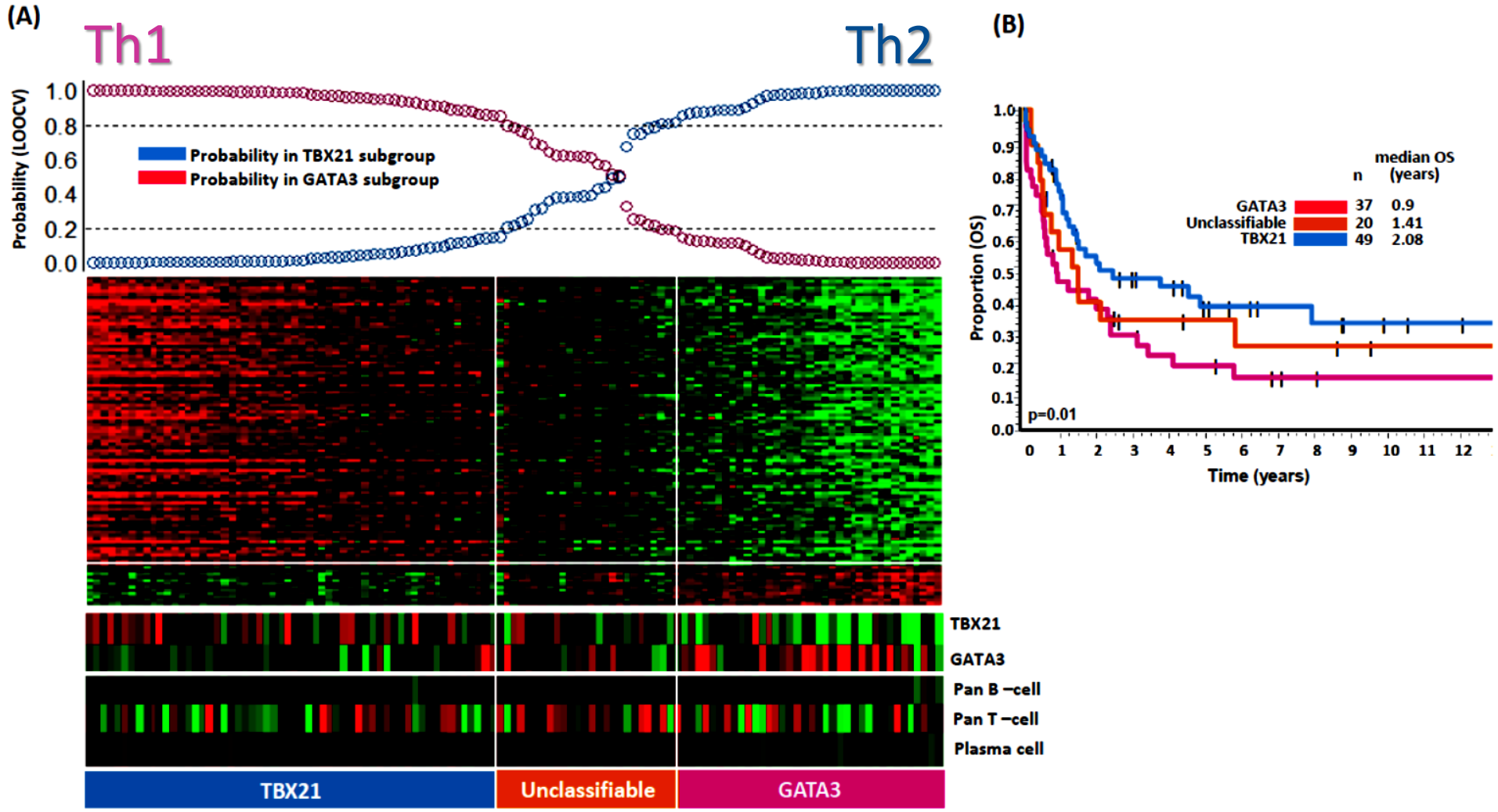
The development of brentuximab vedotin has opened a new era in the management of peripheral T-cell lymphomas (PTCLs). The improved outcomes with brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin, and prednisone (BV-CHP) vs cyclophosphamide, doxorubicin, vincristine, and prednisone in the ECHELON-2 trial are practice changing for common nodal CD30$^+$ PTCLs. Questions regarding the optimal cutoff of CD30 expression for BV-CHP therapy and the efficacy and safety of BV-CHP in less common subtypes of CD30$^+$ PTCL subtypes await clarification. (*Blood*. 2019;134(26):2339-2345)

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

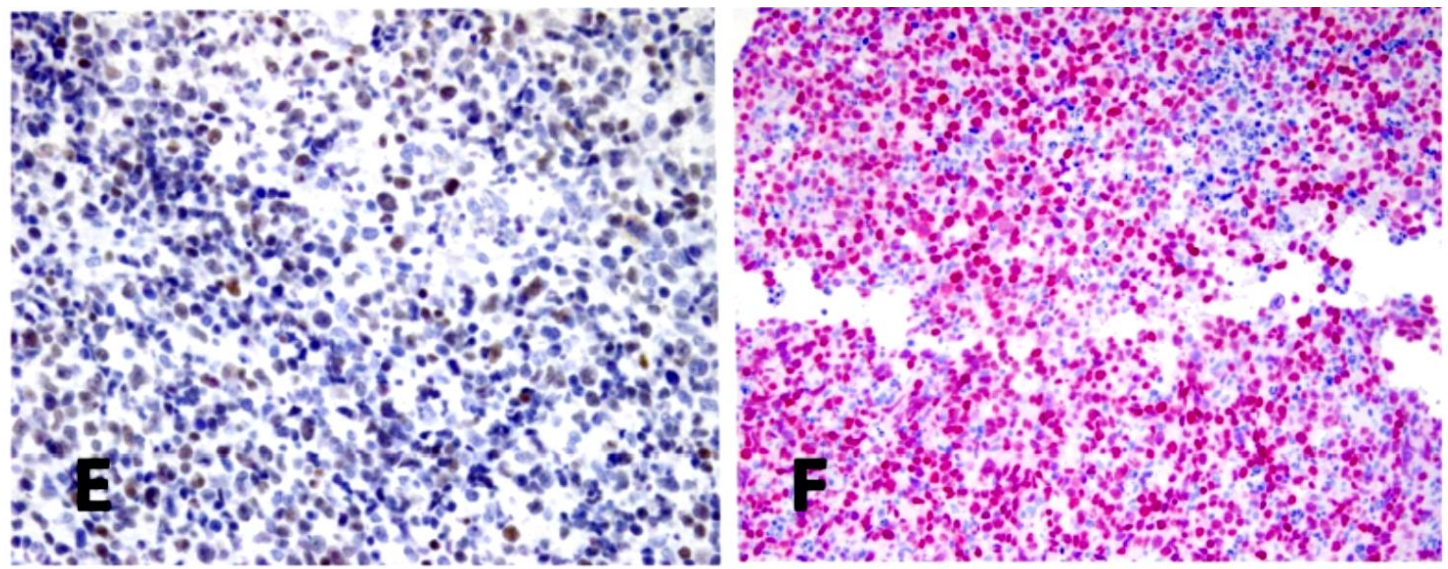



(A)
Th1
Th2
Probability (LOOCV)
1.0
0.8
0.6
0.4
0.2
0.0
Probability in TBX21 subgroup
Probability in GATA3 subgroup
TBX21
GATA3
Pan B –cell
Pan T –cell
Plasma cell
TBX21
Unclassifiable
GATA3
(B)
Proportion (OS)
median OS
n (years)
GATA3 37 0.9
Unclassifiable 20 1.41
TBX21 49 2.08
p=0.01
Time (years)

LYMPHOID NEOPLASIA

DNMT3A mutations define a unique biological and prognostic subgroup associated with cytotoxic T cells in PTCL-NOS

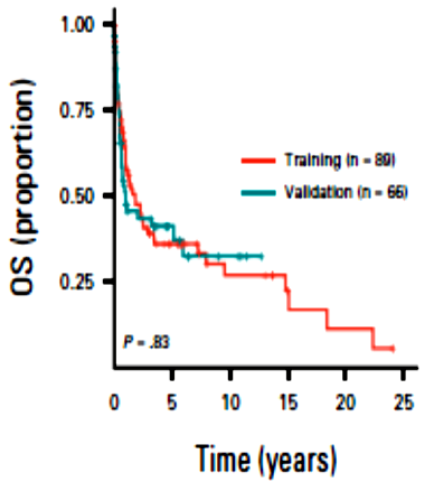
Tyler A. Herek,[1] Alyssa Bouska,[1] Waseem Lone,[1] Sunandini Sharma,[1] Catalina Amador,[1] Tayla B. Heavican,[2] Yuping Li,[3] Qi Wei,[3] Dylan Jochum,[1] Timothy C. Greiner,[1] Lynette Smith,[4] Stefano Pileri,[5] Andrew L. Feldman,[6] Andreas Rosenwald,[7] German Ott,[8] Soon Thye Lim,[9] Choon Kiat Ong,[9] Joo Song,[3] Elaine S. Jaffe,[10] Gang Greg Wang,[11,12] Louis Staudt,[13] Lisa M. Rimsza,[14] Julie Vose,[15] Francesco d'Amore,[16] Dennis D. Weisenburger,[3] Wing C. Chan,[3] and Javeed Iqbal[1]


E
F

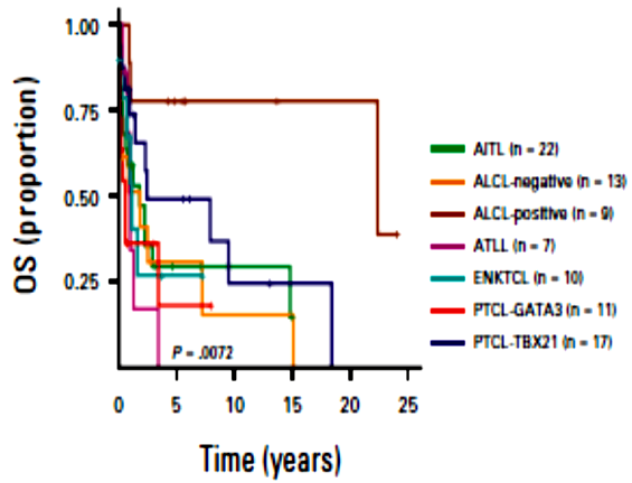
Gene Expression Signatures for the Accurate Diagnosis of Peripheral T-Cell Lymphoma Entities in the Routine Clinical Practice

Catalina Amador, MD[1]; Alyssa Bouska, PhD[1]; George Wright, MA, PhD[2]; Dennis D. Weisenburger, MD[3]; Andrew L. Feldman, MD[4]; Timothy C. Greiner, MD[1]; Waseem Lone, PhD[1]; Tayla Heavican, PhD[1]; Lynette Smith, MS, PhD[5]; Stefano Pileri, MD, PhD[6]; Valentina Tabanelli, MD[6]; German Ott, MD[7]; Andreas Rosenwald, MD[8]; Kerry J. Savage, MS, MD[9]; Graham Slack, MD[9]; Won Seog Kim, PhD[10]; Young Hyeh, MD, PhD[10]; Yuping Li, PhD[3]; Gehong Dong, MD[11]; Joo Song, MD[3]; Sarah Ondrejka, DO[12]; James R. Cook, MD, PhD[12]; Carlos Barrionuevo, MD[13]; Soon Thye Lim, MBBS[14]; Choon Kiat Ong, PhD[14]; Jennifer Chapman, MD[15]; Giorgio Inghirami, MD[16]; Philipp W. Raess, MD, PhD[17]; Sharathkumar Bhagavathi, MD[18]; Clare Gould, MBBS[19]; Piers Blombery, MBBS[19]; Elaine Jaffe, MD[20]; Stephan W. Morris, MD[21]; Lisa M. Rimsza, MD[22]; Julie M. Vose, MD, MBA[23]; Louis Staudt, MD, PhD[24]; Wing C. Chan, MD[3]; and Javeed Iqbal, MS, PhD[1]

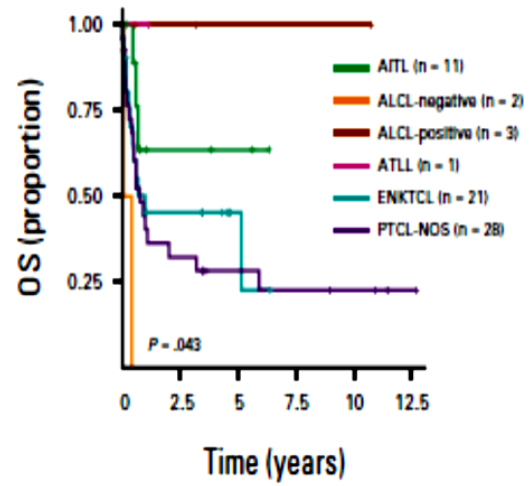
J Clin Oncol 00.



No. at risk:						
Training	89	19	8	4	2	0
Validation	66	10	4	0	0	0



No. at risk:						
AITL	22	3	2	0	0	0
ALCL-negative	13	3	1	1	0	0
ALCL-positive	9	5	3	2	2	0
ATLL	7	0	0	0	0	0
ENKTCL	10	1	0	0	0	0
PTCL-GATA3	11	1	0	0	0	0
PTCL-TBX21	17	6	2	1	0	0



No. at risk:						
AITL	11	3	2	0	0	0
ALCL-negative	2	0	0	0	0	0
ALCL-positive	3	2	1	1	1	0
ATLL	1	0	0	0	0	0
ENKTCL	21	8	2	0	0	0
PTCL-NOS	28	8	5	4	3	1

REGULAR ARTICLE

blood advances

Microenvironmental immune cell signatures dictate clinical outcomes for PTCL-NOS

Takeshi Sugio,[1] Kohta Miyawaki,[1] Koji Kato,[1] Kensuke Sasaki,[1] Kyohei Yamada,[2] Javeed Iqbal,[3] Toshihiro Miyamoto,[1] Koichi Ohshima,[2] Takahiro Maeda,[4] Hiroaki Miyoshi,[2] and Koichi Akashi[1,4]

[1]Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Pathology, School of Medicine, Kurume University, Kurume, Japan; [3]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE; and [4]Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan

Key Points

- Microenvironmental immune cell signatures stratify PTCL-NOS patients into clinically meaningful disease subtypes.
- Immune-checkpoint inhibitors represent potential therapeutic options for a PTCL-NOS patient subgroup.

nCounter system

Assess mRNA leveles of
120 immune-cell related genes

Peripheral T-cell lymphoma (PTCL), not otherwise specified (PTCL-NOS) is among the most common disease subtypes of PTCL, one that exhibits heterogeneous clinicopathological features. Although multiple disease-stratification models, including the cell-of-origin or gene-expression profiling methods, have been proposed for this condition, their clinical significance remains unclear. To establish a clinically meaningful stratification model, we analyzed gene-expression signatures of tumors and tumor-infiltrating immune cells using the nCounter system, which enables accurate quantification of low abundance and/or highly fragmented transcripts. To do so, we assessed transcripts of 120 genes related to cancer or immune cells using tumor samples from 68 newly diagnosed PTCL-NOS patients and validated findings by immunofluorescence in tumor sections. We show that gene-expression signatures representing tumor-infiltrating immune cells, but not those of cancerous T cells, dictate patient clinical outcomes. Cases exhibiting both B-cell and dendritic cell (DC) signatures (BD subgroup) showed favorable clinical outcomes, whereas those exhibiting neither B-cell nor DC signatures (non-BD subgroup) showed extremely poor prognosis. Notably, half of the non-BD cases exhibited a macrophage signature, and macrophage infiltration was evident in those cases, as revealed by immunofluorescence. Importantly, tumor-infiltrating macrophages expressed the immune-checkpoint molecules programmed death ligand 1/2 and indoleamine 2, 3-dioxygenase 1 at high levels, suggesting that checkpoint inhibitors could serve as therapeutic options for patients in this subgroup. Our study identifies clinically distinct subgroups of PTCL-NOS and suggests a novel therapeutic strategy for 1 subgroup associated with a poor prognosis. Our data also suggest functional interactions between cancerous T cells and tumor-infiltrating immune cells potentially relevant to PTCL-NOS pathogenesis.

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]

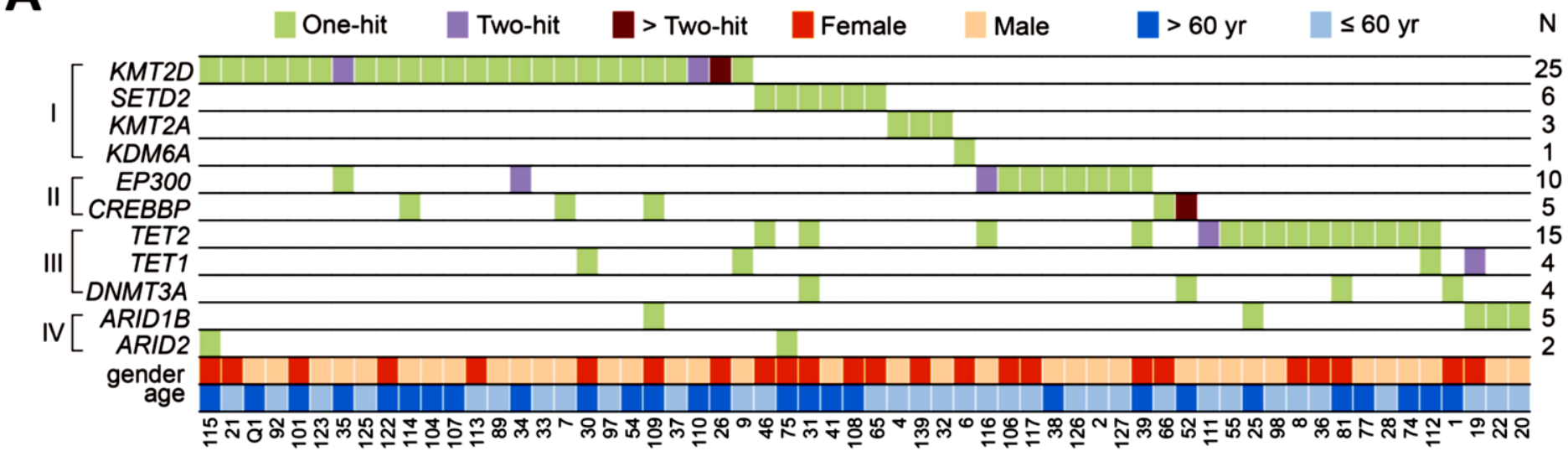
[1]State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology; Shanghai Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, China; [2]Department of Pathology, Shanghai Rui Jin Hospital; Shanghai Jiao Tong University School of Medicine, China; [3]Pôle de Recherches Sino-Français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

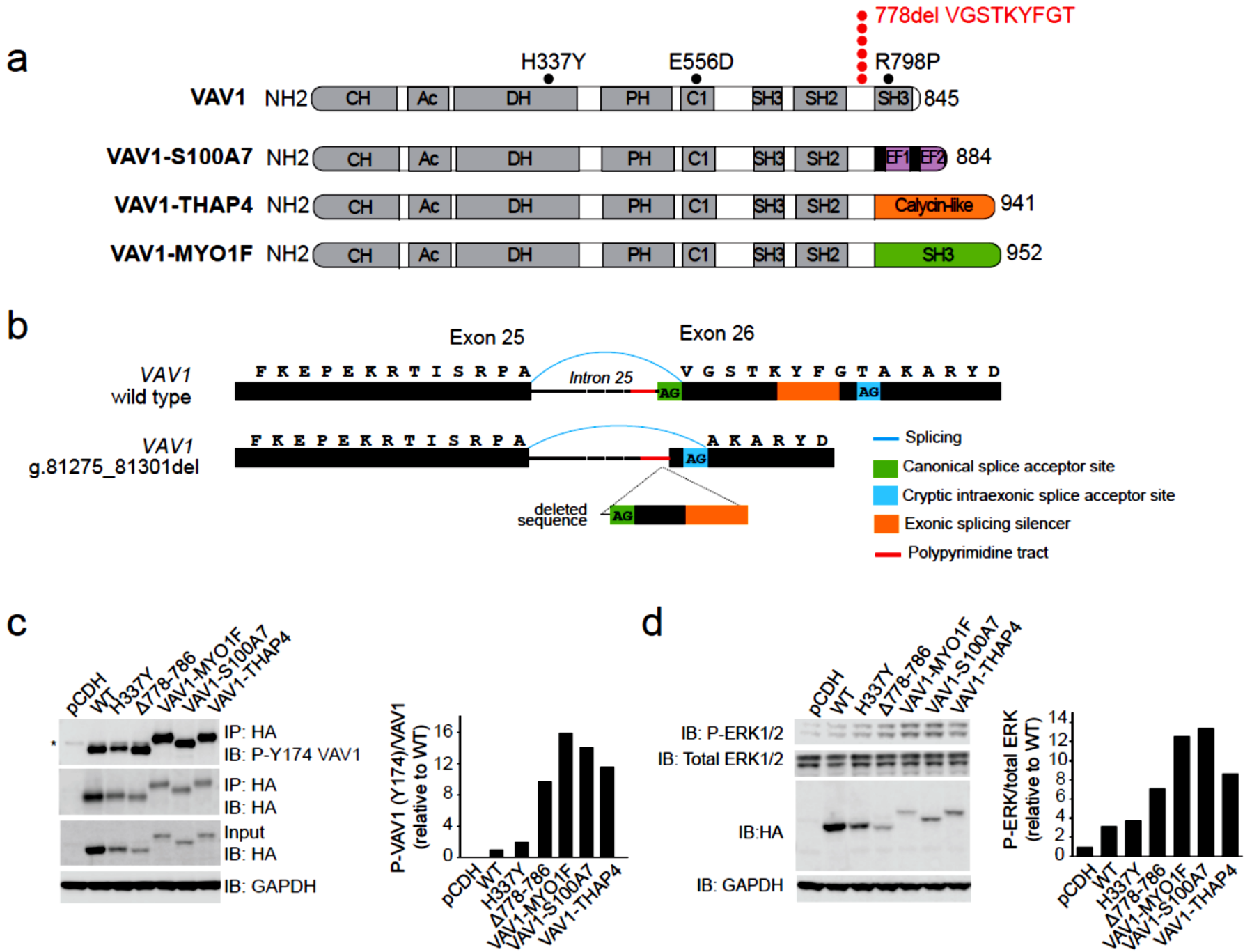
EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

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 NH2 CH Ac DH PH C1 SH3 SH2 EF1 EF2 884
VAV1-THAP4 NH2 CH Ac DH PH C1 SH3 SH2 Calycin-like 941
VAV1-MYO1F NH2 CH Ac DH PH C1 SH3 SH2 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
VAV1 g.81275_81301del
deleted sequence
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)
d
IB: P-ERK1/2
IB: Total ERK1/2
IB:HA
IB: GAPDH
P-ERK/total ERK (relative to WT)

Modern Pathology
https://doi.org/10.1038/s41379-019-0279-8

ARTICLE

Whole exome sequencing reveals mutations in *FAT1* tumor suppressor gene clinically impacting on peripheral T-cell lymphoma not otherwise specified

Maria Antonella Laginestra[1] · Luciano Cascione[2] · Giovanna Motta[3] · Fabio Fuligni[4] · Claudio Agostinelli[1] · Maura Rossi[1] · Maria Rosaria Sapienza[1] · Simona Righi[1] · Alessandro Broccoli[1] · Valentina Indio[5] · Federica Melle[3] · Valentina Tabanelli[3] · Angelica Calleri[3] · Domenico Novero[6] · Fabio Facchetti[7] · Giorgio Inghirami[8] · Elena Sabattini[1] · Francesco Bertoni[2] · Stefano A. Pileri[3]

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

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

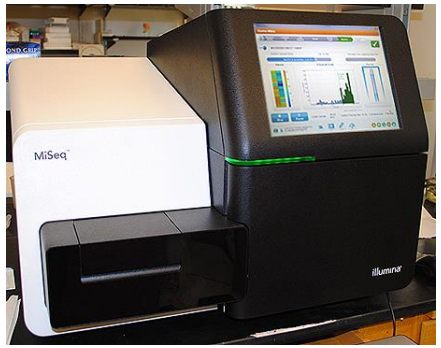
Discovery Set

21 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 21/21 cases



Targeted Sequencing-MiSeq Platform

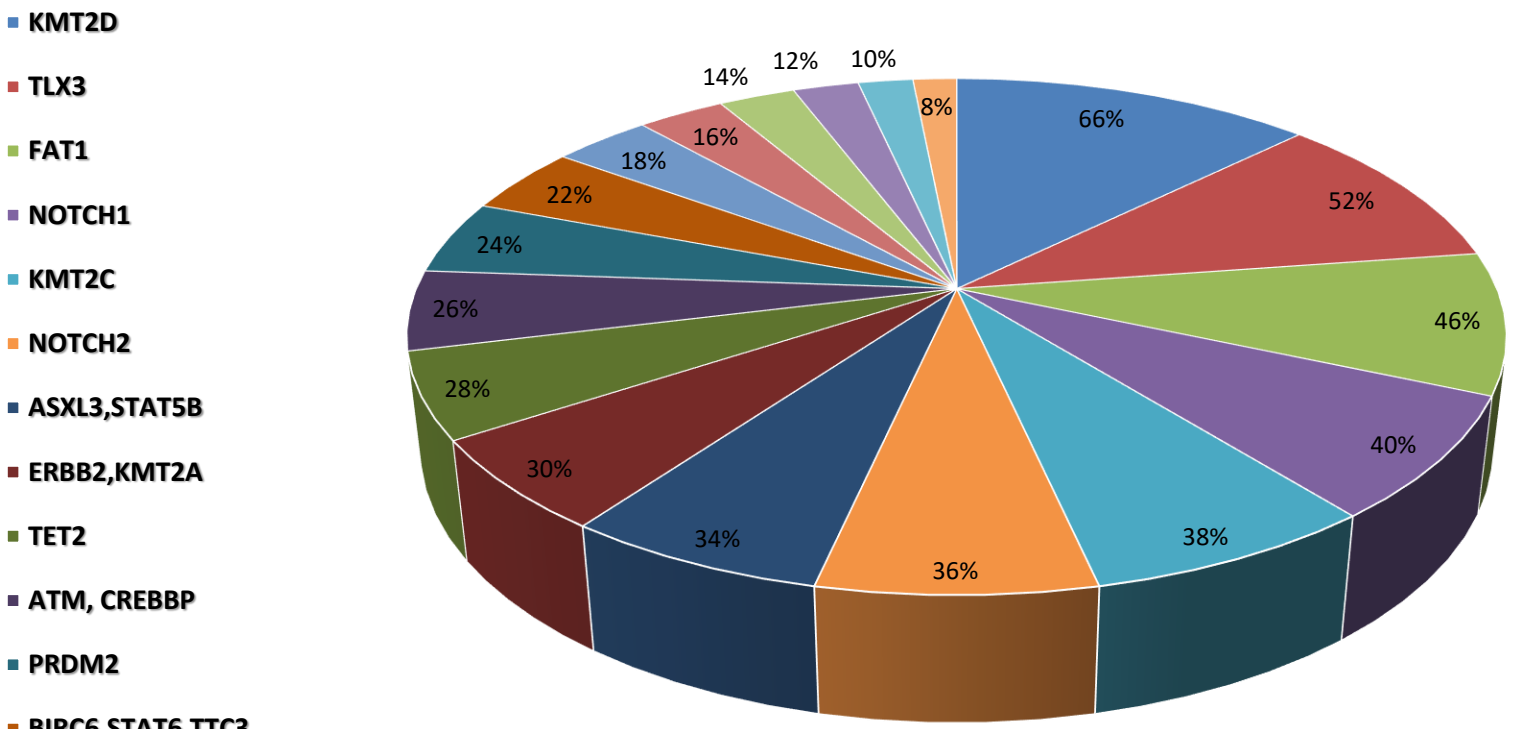
Validation Set

21 PTCLs/NOS that underwent WES

Extension Set

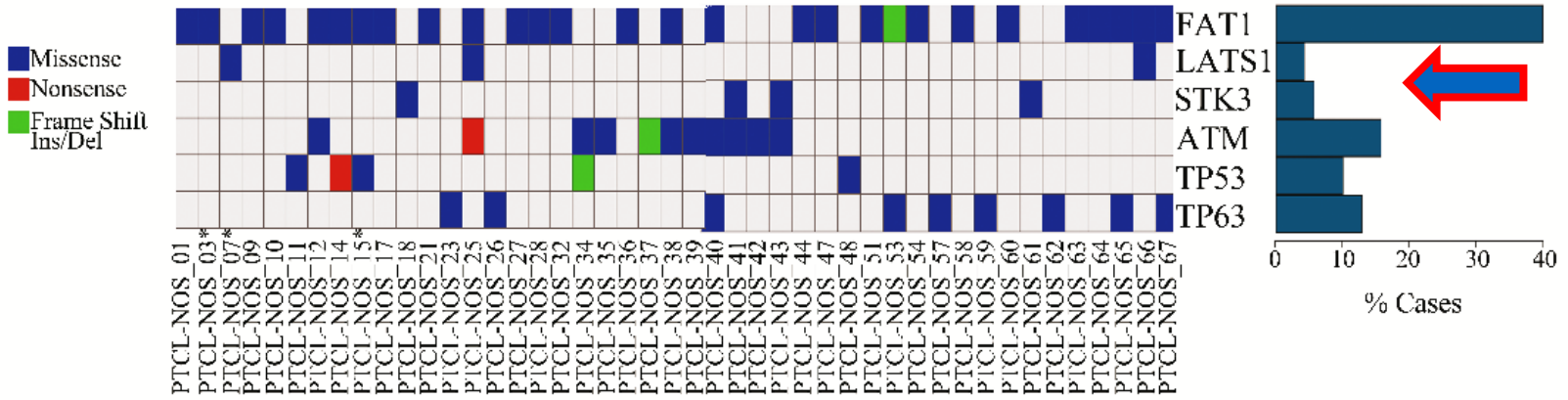
50 FFPE_PTCLs/NOS (8 matched with saliva of the corresponding patient)

9 Cell Lines



Genes involved in epigenetic regulation and chromatin remodeling: *KMT2D* (32%), *TET2* (22%), *CREBBP* (16%) *KMT2A* (11%), *SETD2* (10%) and *CHD1* (7%), *DNMT3A*, *ASXL3*, *MBD4* (8%, each).

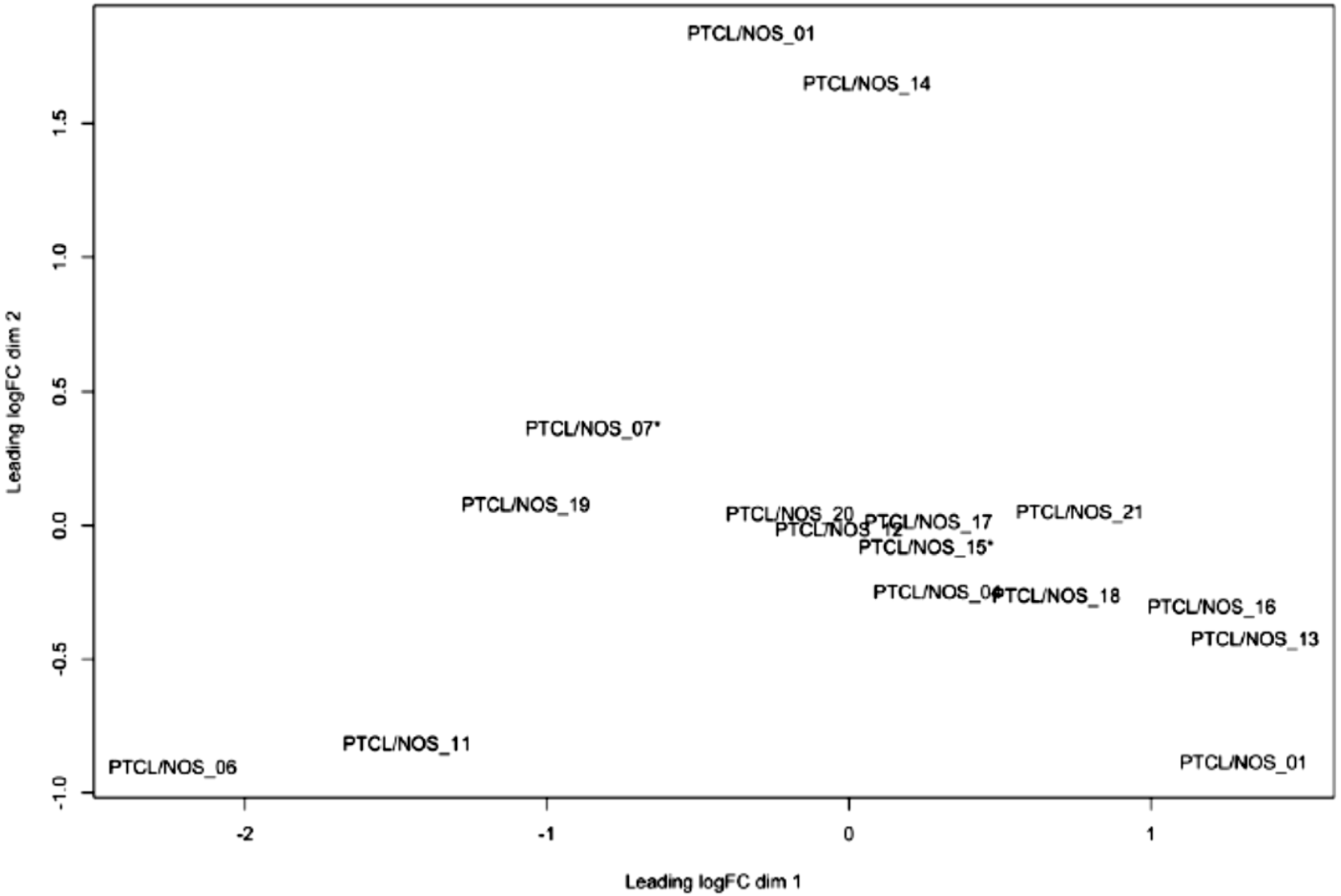
Genes involved in NOTCH1/NOTCH2 and JAK/STAT pathways: *NOTCH1* (22%), *NOTCH2* (19%), *JAK3* (7%), and *STAT6* (3%).



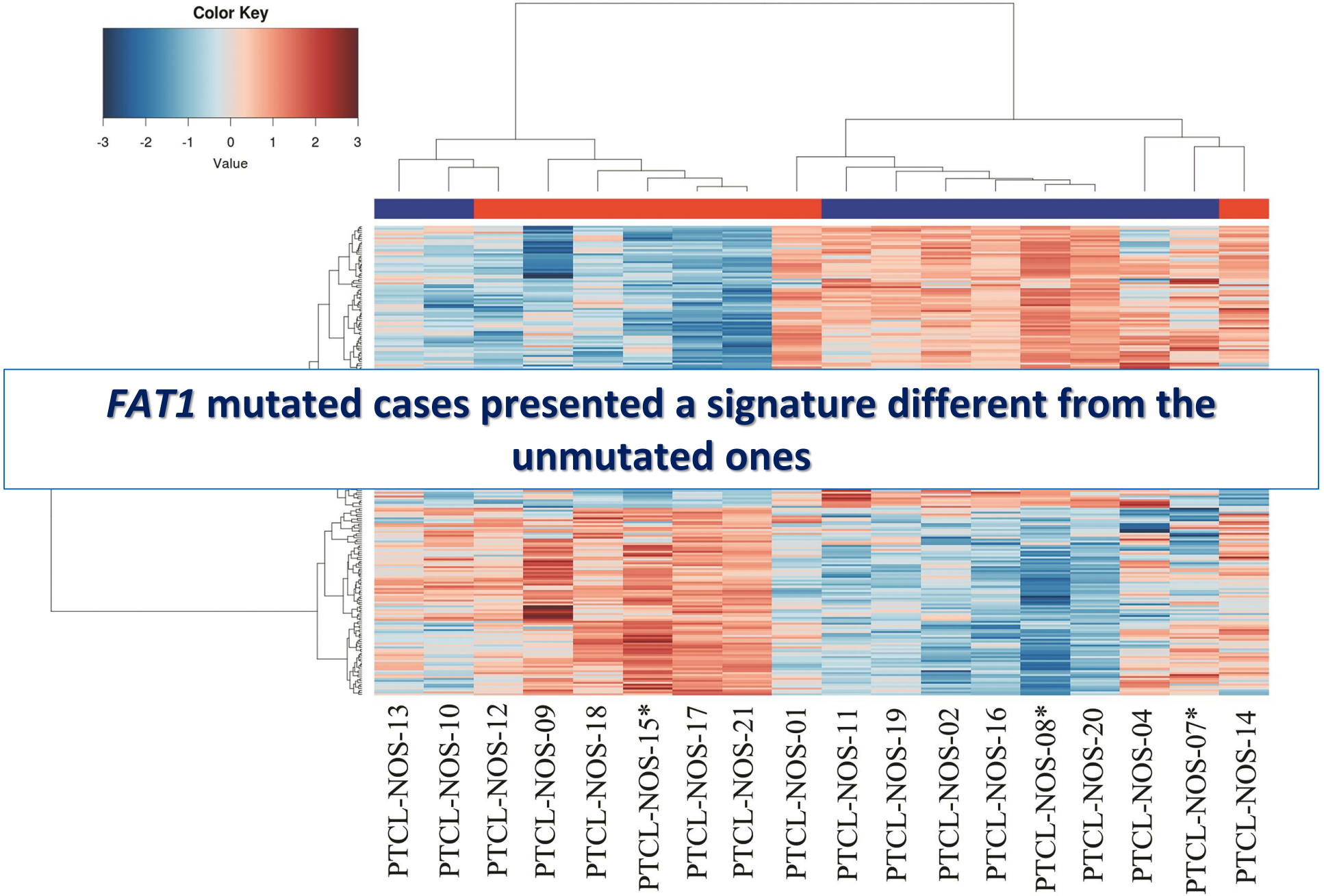
Recurrent mutations of *FAT1* in 28/71 patients (39.7%).

FAT1 **encodes the homologous protein (atypical cadherin type 1a), which acts as an adhesion molecule and/or signaling receptor during development and communication processes. It has been reported to potently suppress cancer cell growth by binding beta-catenin and antagonizing the nuclear localization.**

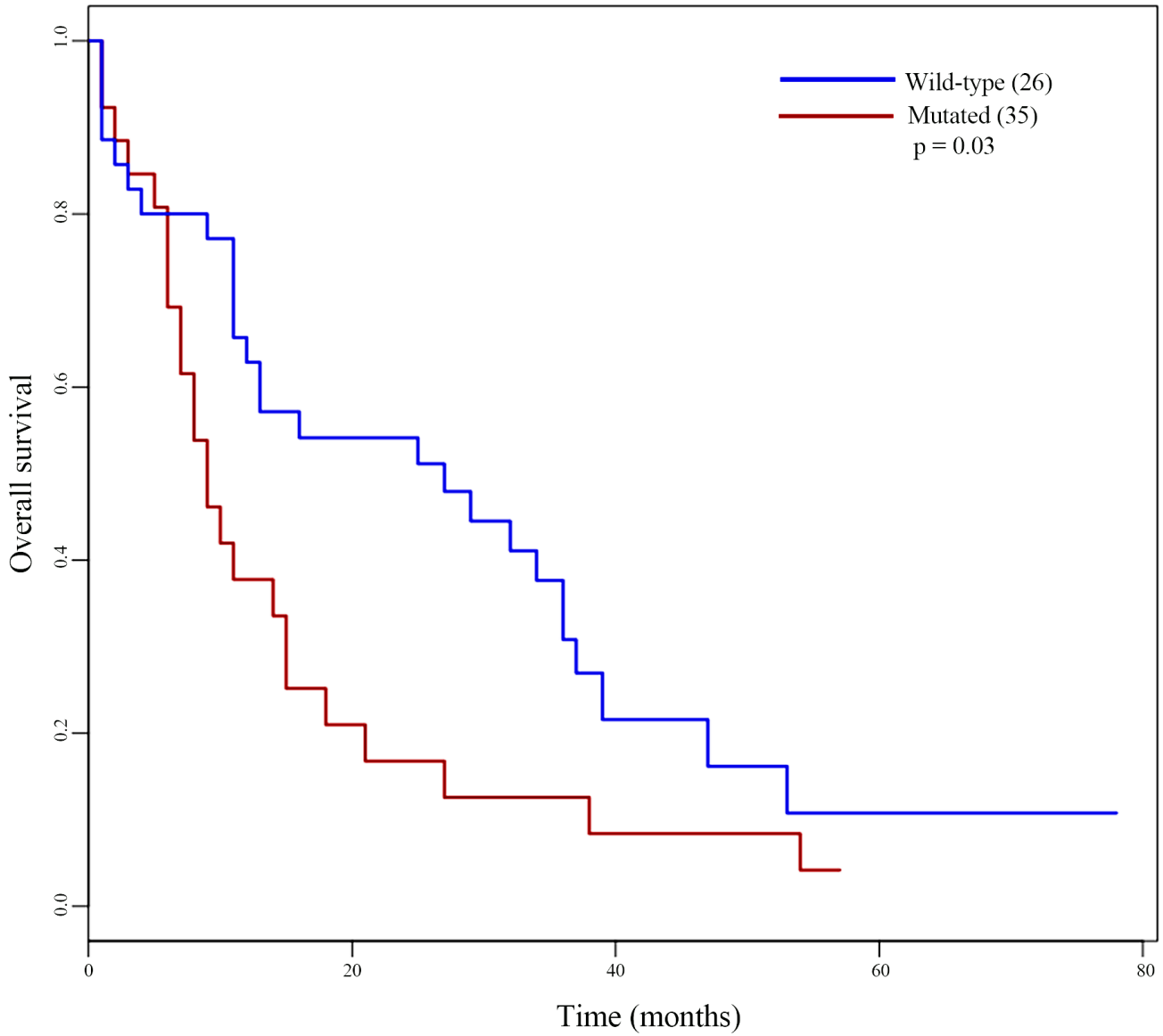
FAT1 is also involved in the assembly and activation of the Hippo signalome leading to phosphorylation and inactivation of YAP1.



Irrespective of the subtype of PTCL/NOS (with a TBX21 or GATA3-related signature)



***FAT1* mutated cases presented a signature different from the unmutated ones**


Wild-type (26)
Mutated (35)
p = 0.03
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
Time (months)

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