PTCL: morphology and pathobiology
Anaplastic large cell lymphoma

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MATURE T-CELL AND NK-CELL NEOPLASMS

T-cell prolymphocytic leukaemia	9834/3
T-cell large granular lymphocytic leukaemia	9831/3
Chronic lymphoproliferative disorder of NK-cells	9831/3
Aggressive NK cell leukaemia	9948/3
Systemic EBV positive T-cell lymphoproliferative disease of childhood	*9724/3*
Hydroa vaccineforme-like lymphoma	*9725/3*
Adult T-cell leukaemia/lymphoma	9827/3
Extranodal NK/T cell lymphoma, nasal type	9719/3
Enteropathy-associated T-cell lymphoma	9717/3
Hepatosplenic T-cell lymphoma	9716/3
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Mycosis fungoides	9700/3
Sézary syndrome	9701/3

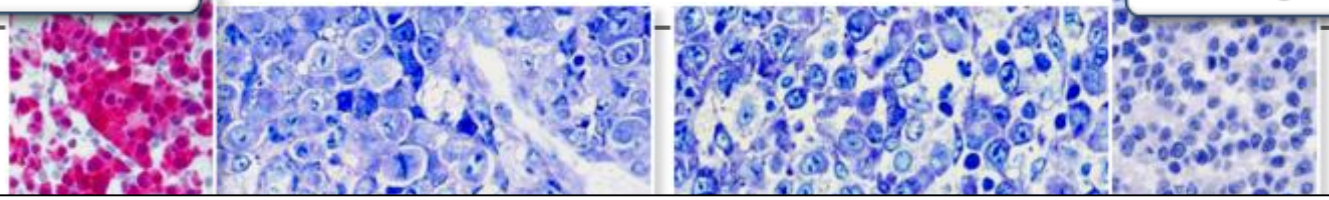
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	
Lymphomatoid papulosis	9718/1
Primary cutaneous anaplastic large cell lymphoma	9718/3
Primary cutaneous gamma-delta T-cell lymphoma	*9726/3*
Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
Primary cutaneous CD4 positive small/medium T-cell lymphoma	9709/3
Peripheral T-cell lymphoma, NOS	9702/3
Angioimmunoblastic T-cell lymphoma	9705/3

Systemic!

Anaplastic large cell lymphoma

ALK-positive

ALK-negative



CD45+/-
EMA +/-
TCM -/+
CD43 +
CM +
PAX5 – (*)
TCR/R

The NEW ENGLAND JOURNAL of MEDICINE

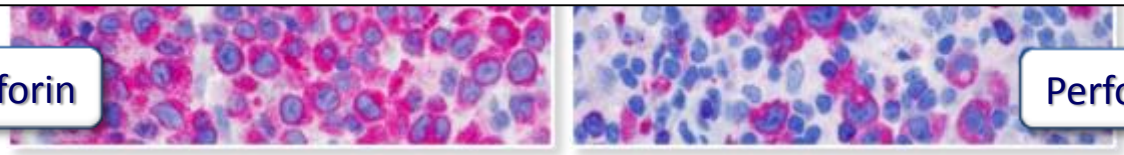
ORIGINAL ARTICLE

Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas

Anas Younes, M.D., Nancy L. Bartlett, M.D., John P. Leonard, M.D., Dana A. Kennedy, Pharm.D., Carmel M. Lynch, Ph.D., Eric L. Sievers, M.D., and Andres Forero-Torres, M.D.

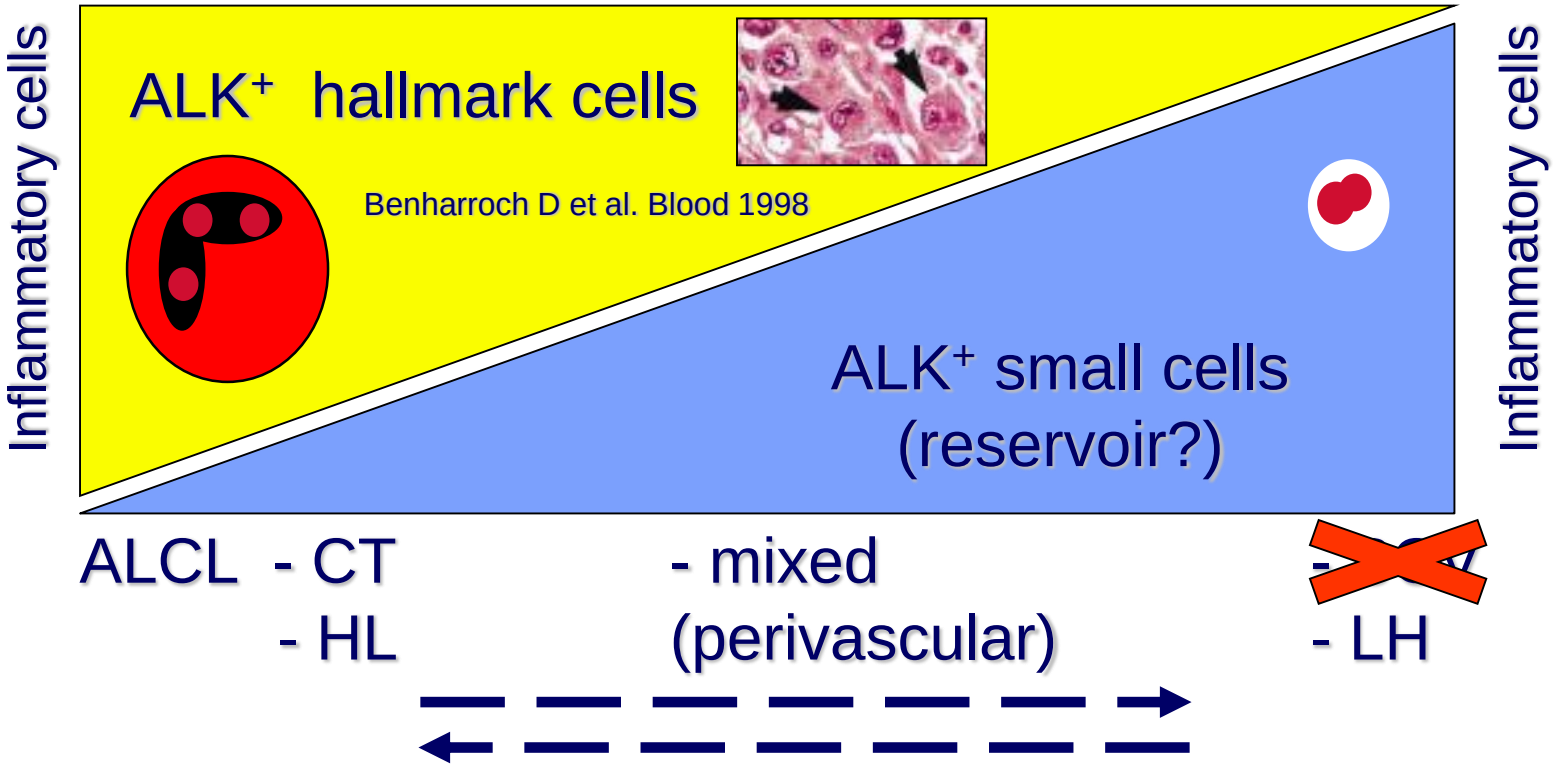
Perforin

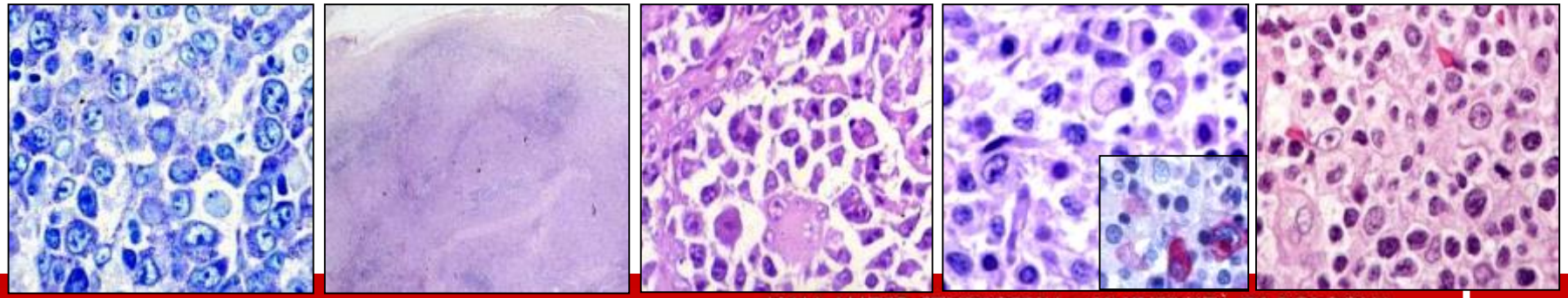
Perforin



(*) Feldman et a., Mod Pathol 2010, 23:593602.

Morphologic spectrum of "ALK+ ALCL



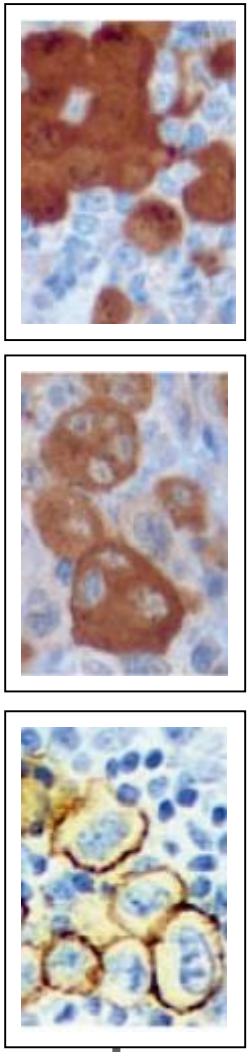


Translocations and fusion proteins involving the ALK gene in ALK+ ALCL

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.

ALK Kinase Domain Mutations in Primary Anaplastic Large Cell Lymphoma: Consequences on NPM-ALK Activity and Sensitivity to Tyrosine Kinase Inhibitors

Federica Lovisa[1]*, Giorgio Cozza[2], Andrea Cristiani[3], Alberto Cuzzolin[3], Alessandro Albiero[4], Lara Mussolin[1,5], Marta Pillon[1], Stefano Moro[3], Giuseppe Basso[1], Angelo Rosolen[1†], Paolo Bonvini[1,5]

PLOS ONE | DOI:10.1371/journal.pone.0121378 April 13, 2015

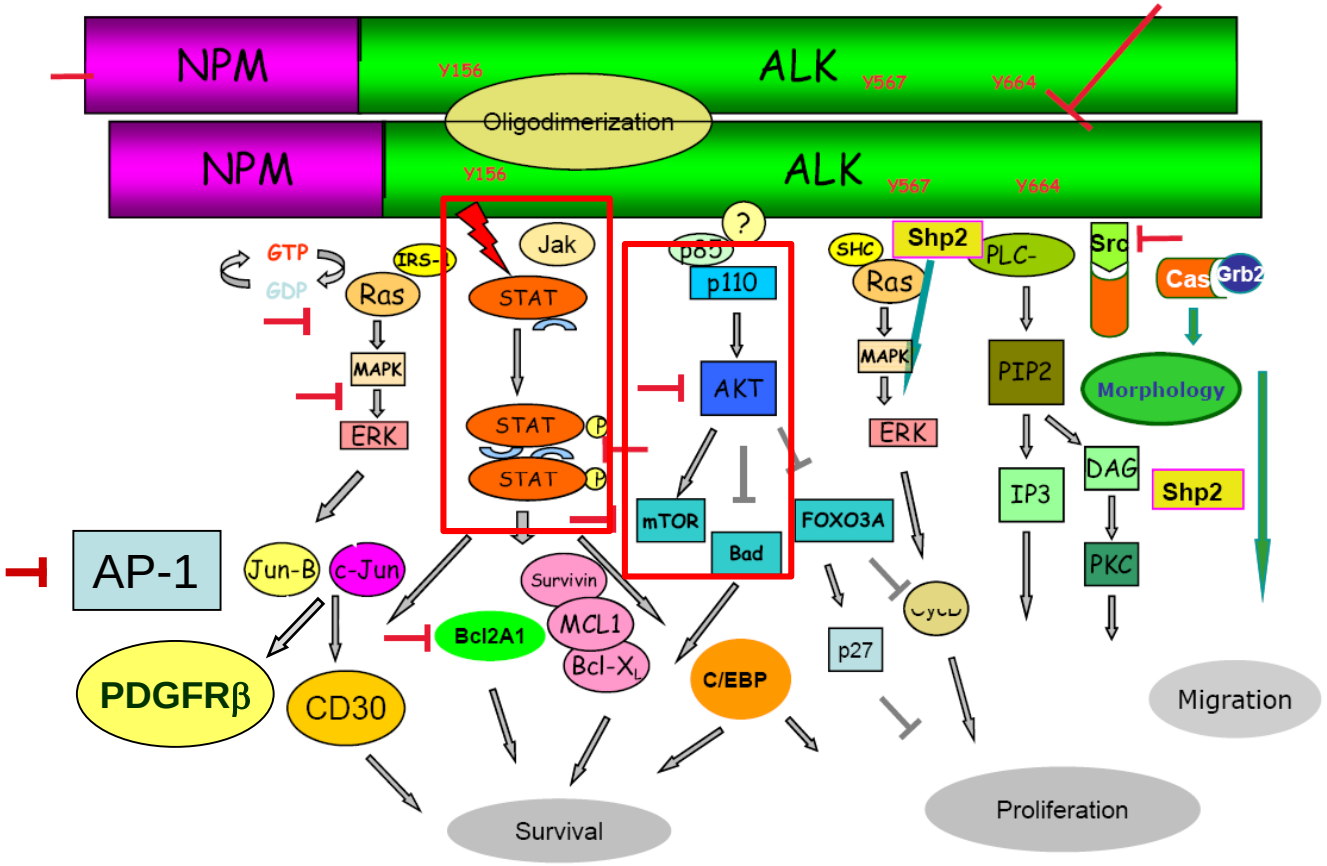
ALK+ ALCL

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

Small Molecule ALK-Tyrosine Kinase Inhibitors



nature medicine

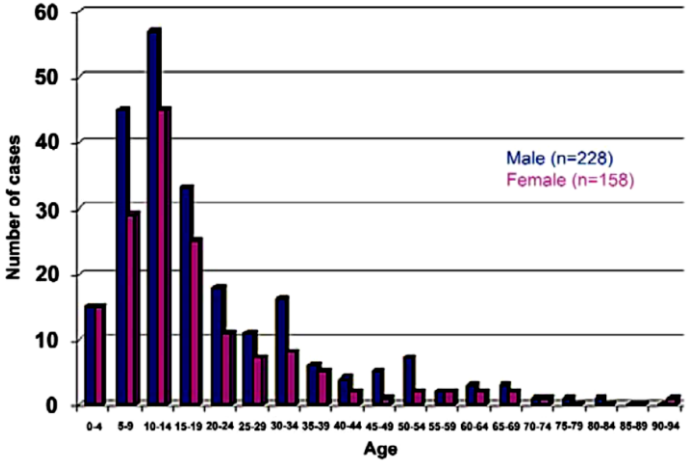
PDGFR blockade is a rational and effective therapy for NPM-ALK–driven lymphomas

Daniela Laimer[1,25], Helmut Dolznig[2,25], Karoline Kollmann[3,25], Paul W Vesely[4,24,25], Michaela Schlederer[5], Olaf Merkel[6,24], Ana-Iris Schiefer[1], Melanie R Hassler[1,7], Susi Heider[1], Lena Amenitsch[1], Christiane Thallinger[7], Philipp B Staber[8,9], Ingrid Simonitsch-Klupp[1], Matthias Artaker[10], Sabine Lagger[10,24], Suzanne D Turner[11], Stefano Pileri[12], Pier Paolo Piccaluga[12], Peter Valent[13,14], Katia Messana[15], Indira Landra[15], Thomas Weichhart[2], Sylvia Knapp[16,17], Medhat Shehata[13], Maria Todaro[15], Veronika Sexl[3], Gerald Höfler[4], Roberto Piva[15,18], Enzo Medico[19,20], Bruce A Ruggeri[21], Mangeng Cheng[21], Robert Eferl[22], Gerda Egger[1], Josef M Penninger[23], Ulrich Jaeger[13], Richard Moriggl[5], Giorgio Inghirami[15,19] & Lukas Kenner[1,5]

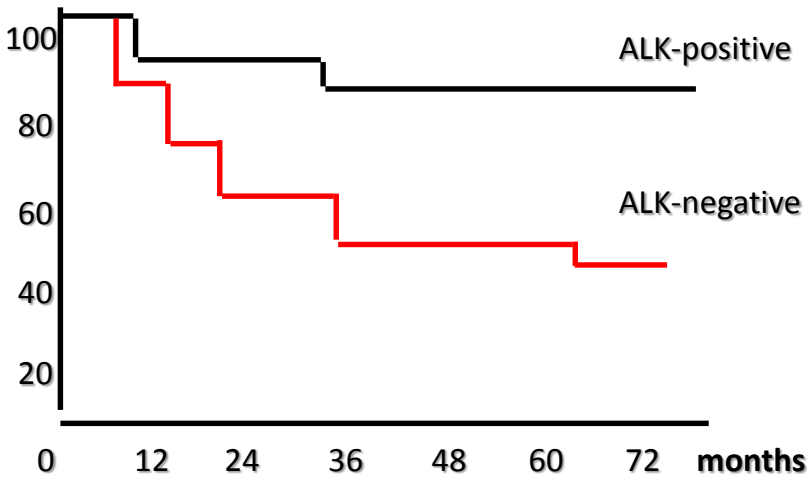
Received 23 July; accepted 10 September; published online 14 October 2012; doi:10.1038/nm.2966

ALCL: ALK-positive and ALK-negative status

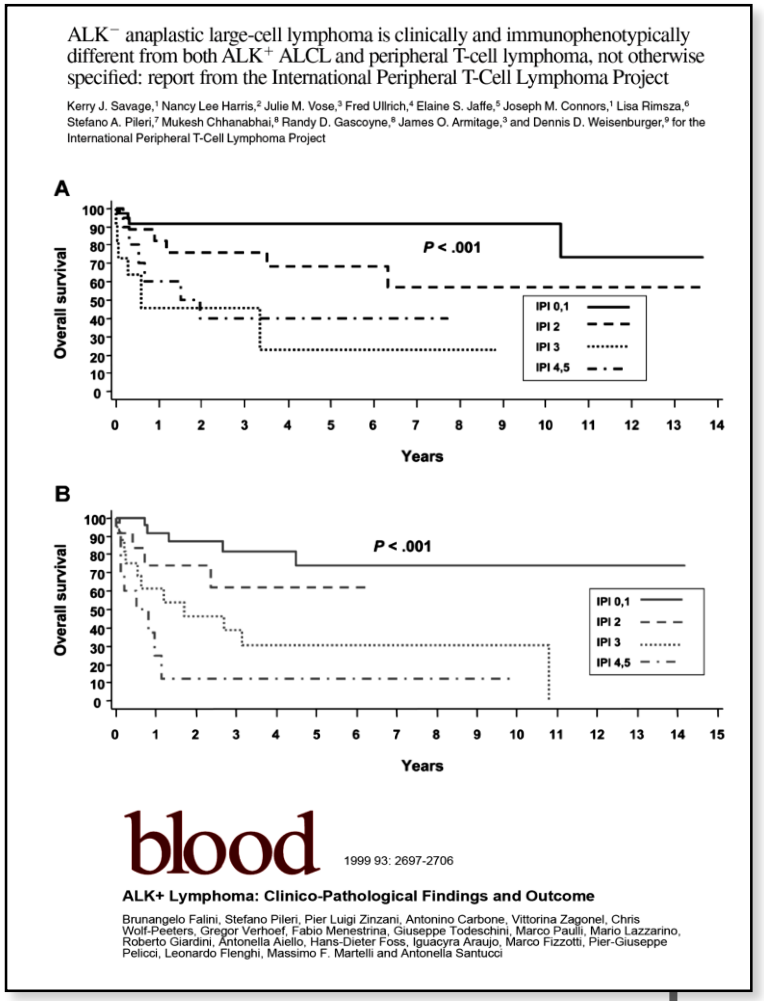
ALK-positive: most frequent in the first three decades of life[1]



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

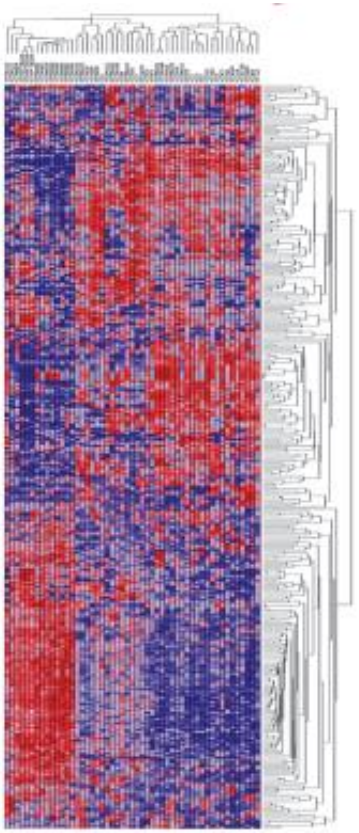
ALK+ Lymphoma: Clinico-Pathological Findings and Outcome

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

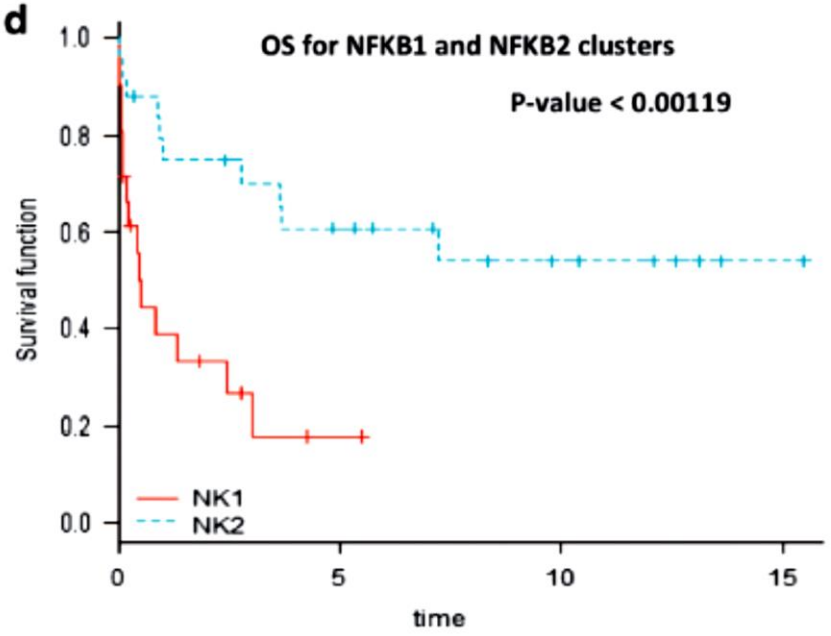
A novel patient-derived tumorgraft model with TRAF1-ALK anaplastic large-cell lymphoma translocation

Leukemia (2015), 1–12

F Abate[1,2,3,21], M Todaro[3,21], J-A van der Krogt[4,21], M Boi[3,5], I Landra[3], R Machiorlatti[3], F Tabbò[3], K Messana[3], C Abele[3], A Barreca[3], D Novero[3], M Gaudiano[3], S Aliberti[3], F Di Giacomo[3], T Tousseyn[6], E Lasorsa[3], R Crescenzo[3], L Bessone[3], E Ficarra[1], A Acquaviva[1], A Rinaldi[5], M Ponzoni[7], DL Longo[8], S Aime[8], M Cheng[9,22], B Ruggeri[9], PP Piccaluga[10], S Pileri[10], E Tiacci[11], B Falini[11], B Pera-Gresely[12], L Cerchietti[12], J Iqbal[13], WC Chan[14], LD Shultz[15], I Kwee[5,16,17], R Piva[1,18], I Wlodarska[4], R Rabadan[2], F Bertoni[5,19], G Inghirami[3,18,20] and The European T-cell Lymphoma Study Group[23]



NFKB



	ALK+	ALK-
NFKB1(n=31)	7	24
NFKB2 (n=28)	24	4

P<0.0001

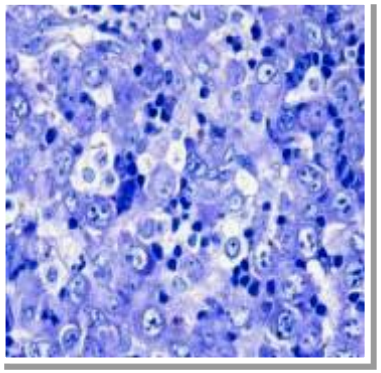
Influence on neoplastic cells and microenvironment

ALCL: ALK-negative

Anaplastic large cell lymphoma, ALK-negative (provisional entity)

D.Y. Mason
N.L. Harris
G. Delsol
H. Stein
E. Campo
M.C. Kinney
E.S. Jaffe
B. Falini

ALK-positive T/null ALCL[1,2]



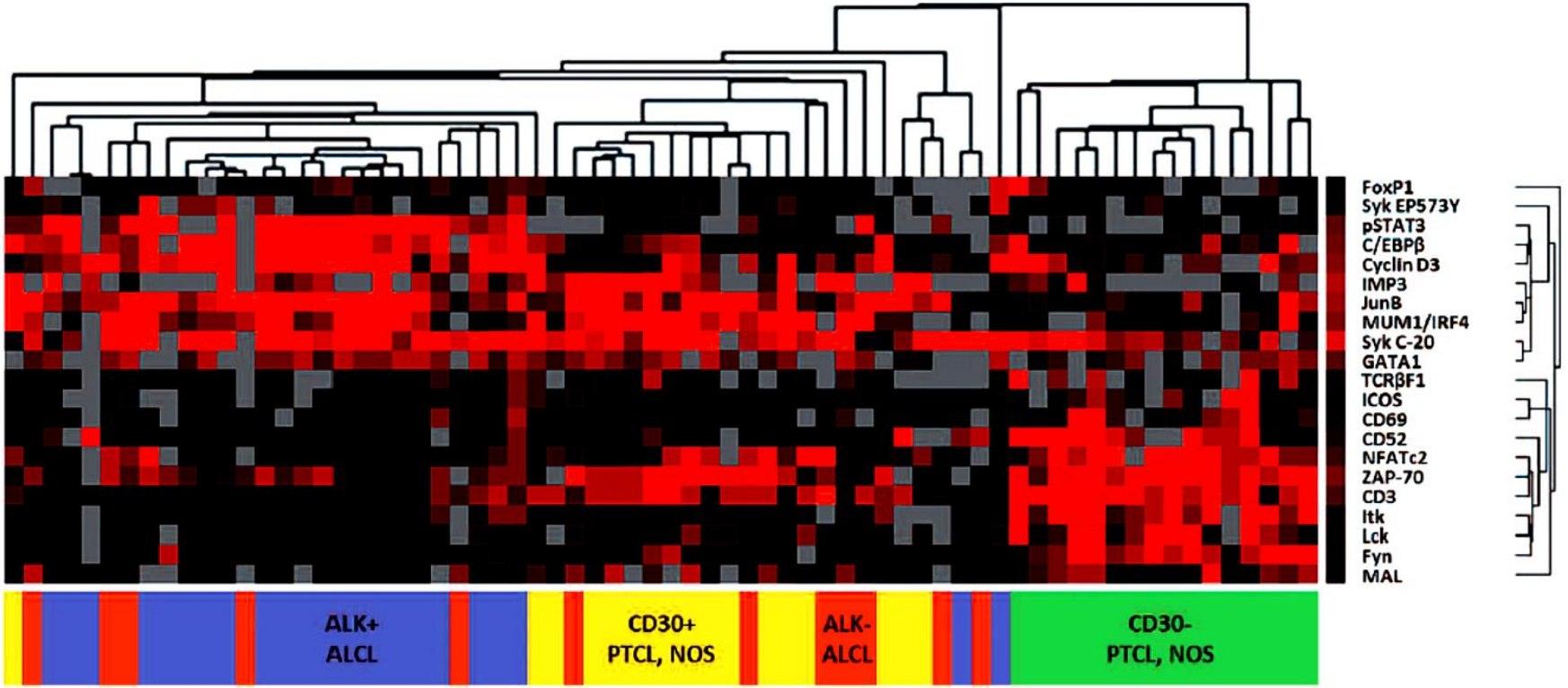
ALK-negative T/null ALCL[1,2]

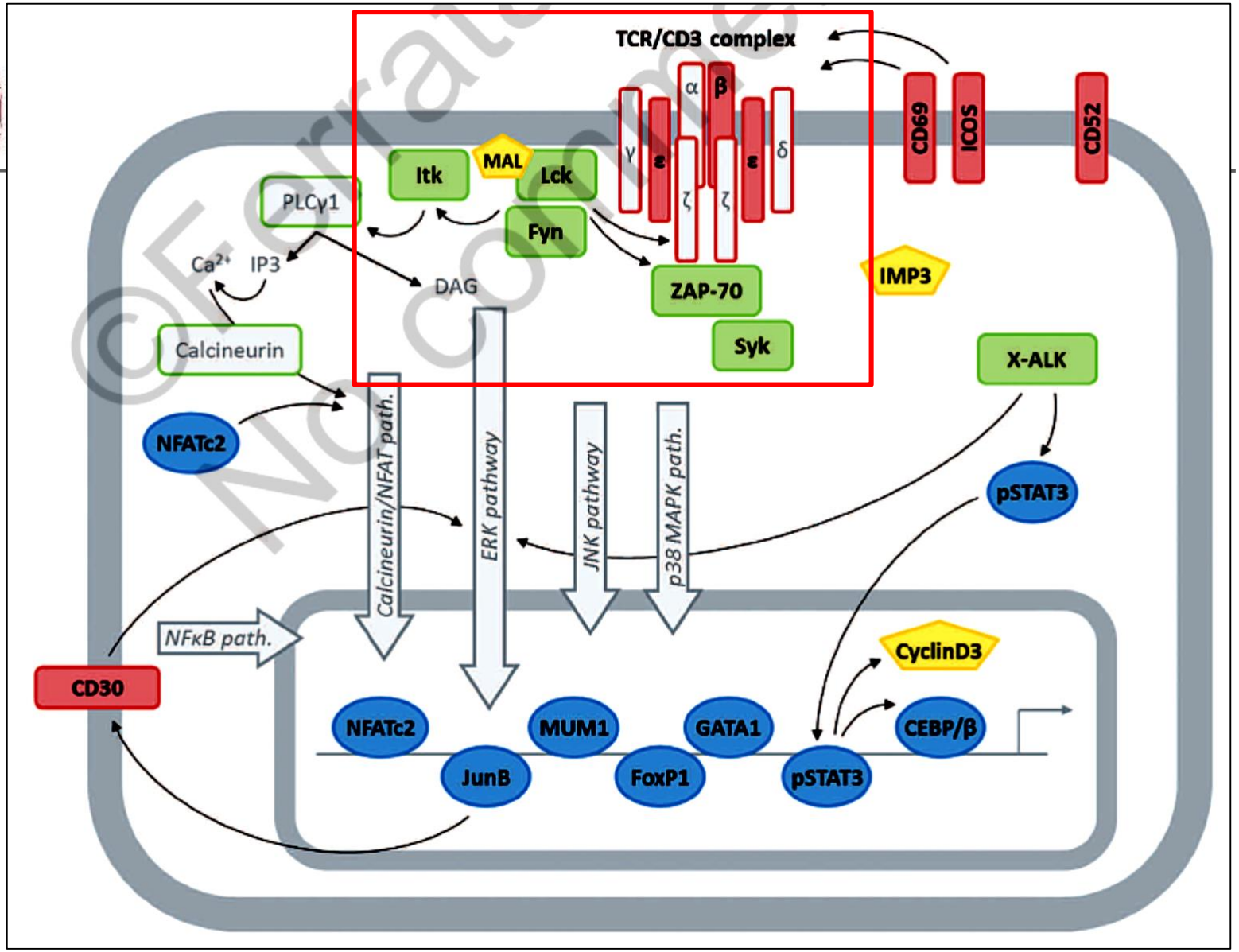
PTCL/NOS[1]

1. Mason D, *et al.* In: Swerdlow SH, *et al.* World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth edition. Lyon, France: IARC Press; 2008, pp. 317;
2. Jaobsen E, The Oncologist 2006, 11:831-840.

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

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





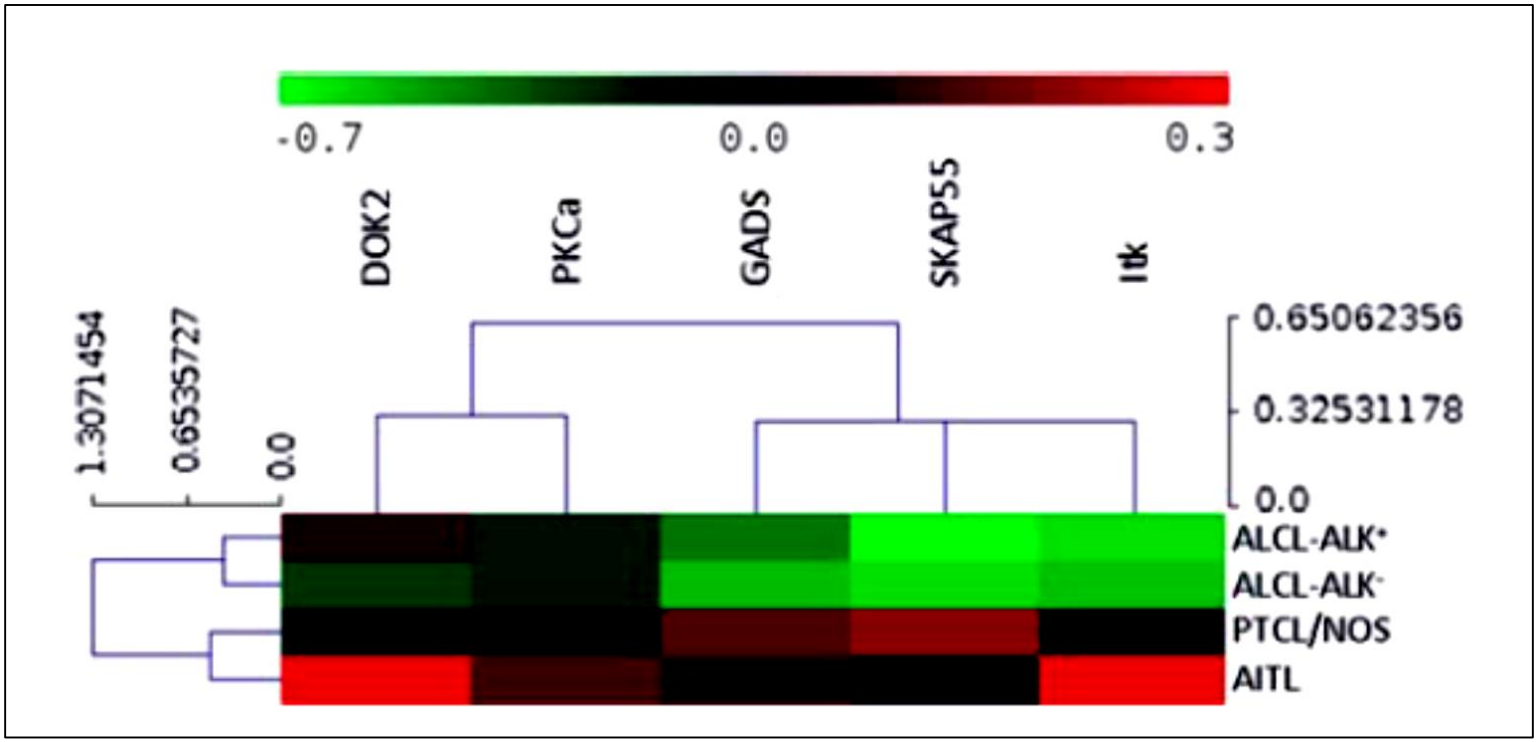
de Leval L and Gaulard P. Haematologica 2013; 95:1627-30.

Intracellular TCR-signaling Pathway

Novel Markers for Lymphoma Diagnosis and Potential Therapeutic Targets

(*Am J Surg Pathol* 2014;38:1349–1359)

Claudio Agostinelli, MD, PhD, Hasan Rizvi, MD,† Jennifer Paterson, MS,† Vishvesh Shende, PhD,† Ayse U. Akarca, MS,† Elena Agostini, MD,* Fabio Fuligni, MS,* Simona Righi, MS,* Sebastiano Spagnolo, BS,* Pier Paolo Piccaluga, MD, PhD,* Edward A. Clark, PhD,‡ Stefano A. Pileri, MD, PhD,* and Teresa Marafioti, MD, PhD†*



Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets

Pier Paolo Piccaluga,[1,2] Claudio Agostinelli,[1] Andrea Califano,[3] Maura Rossi,[1] Katia Basso,[2] Simonetta Zupo,[4] Philip Went,[1,5] Ulf Klein,[2] Pier Luigi Zinzani,[1] Michele Baccarani,[2] Riccardo Dalla Favera,[2,6] and Stefano A. Pileri[1]

JCI, 117:823-34, 2007

Gene expression profiling uncovers molecular classifiers for the recognition of Anaplastic Large Cell Lymphoma within Peripheral T-cell neoplasms

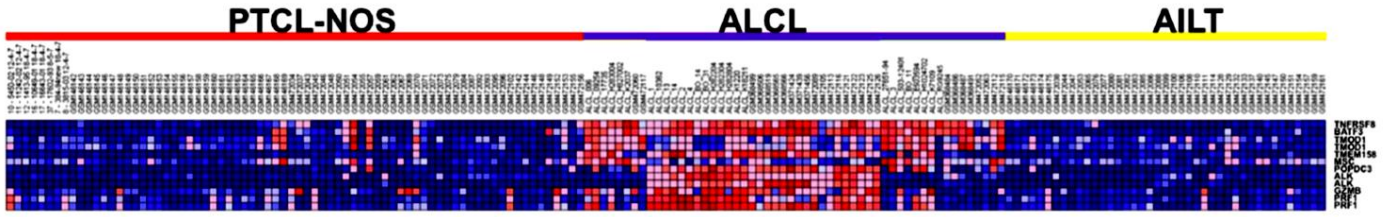
JCO, 2010; 28:1583-90.

Roberto Piva[1,2], Luca Agnelli[3*], Elisa Pellegrino[1*], Katia Todoerti[3], Valentina Grosso[1], Ilaria Tamagno[1], Alessandro Fornari[1], Barbara Martinoglio[4], Enzo Medico[4], Alberto Zamò[5], Fabio Facchetti[6], Maurilio Ponzoni[7], Eva Geissinger[8], Andreas Rosenwald[8], Hans Konrad Müller-Hermelink[8], Cristiane De Wolf-Peeters[9], Pier Paolo Piccaluga[10], Stefano Pileri[10], Antonino Neri[3], Giorgio Inghirami[1,2]

Identification of a three-gene model as a powerful diagnostic tool for the recognition of ALK negative ALCL

Blood, 2012;120:1274-81.

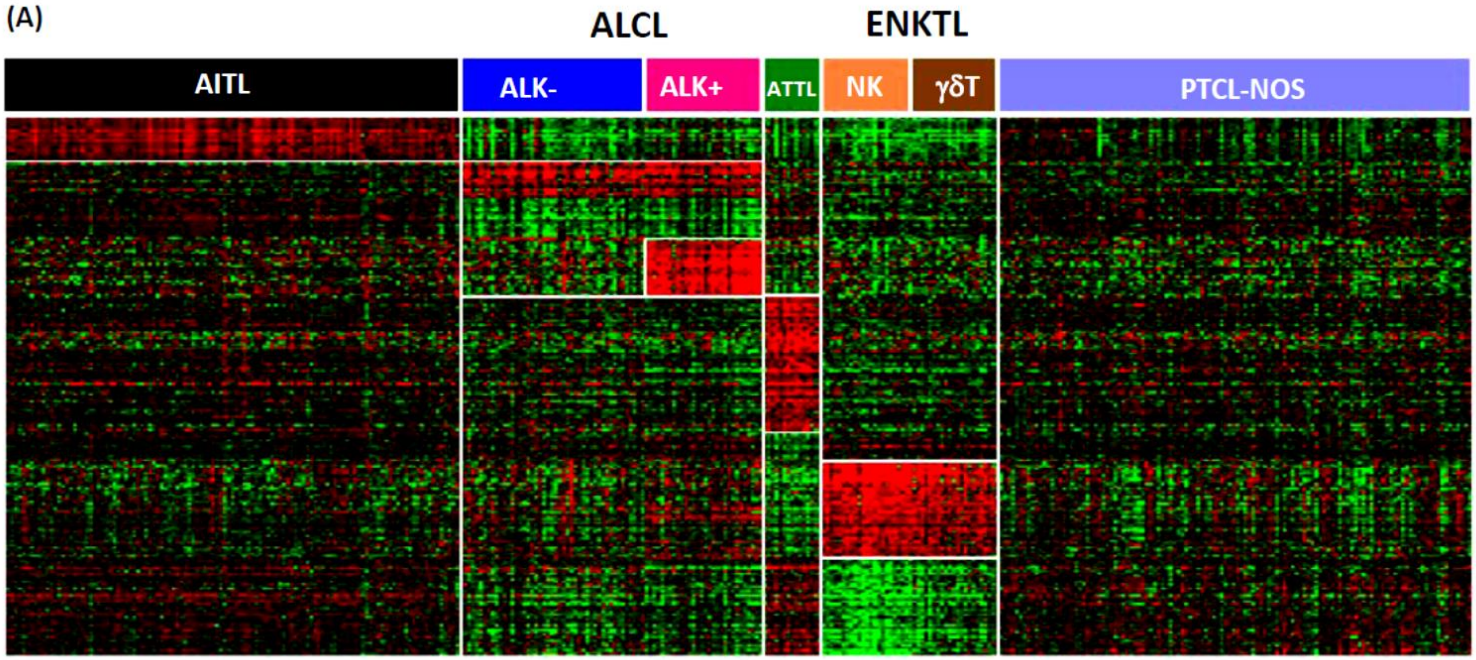
Luca Agnelli, Elisabetta Mereu, Elisa Pellegrino, Tania Limongi, Ivo Kwee, Elisa Bergaggio, Maurilio Ponzoni, Alberto Zamò, Javeed Iqbal, Pier Paolo Piccaluga, Antonino Neri, John C. Chan, Stefano Pileri, Francesco Bertoni, Giorgio Inghirami and Roberto Piva

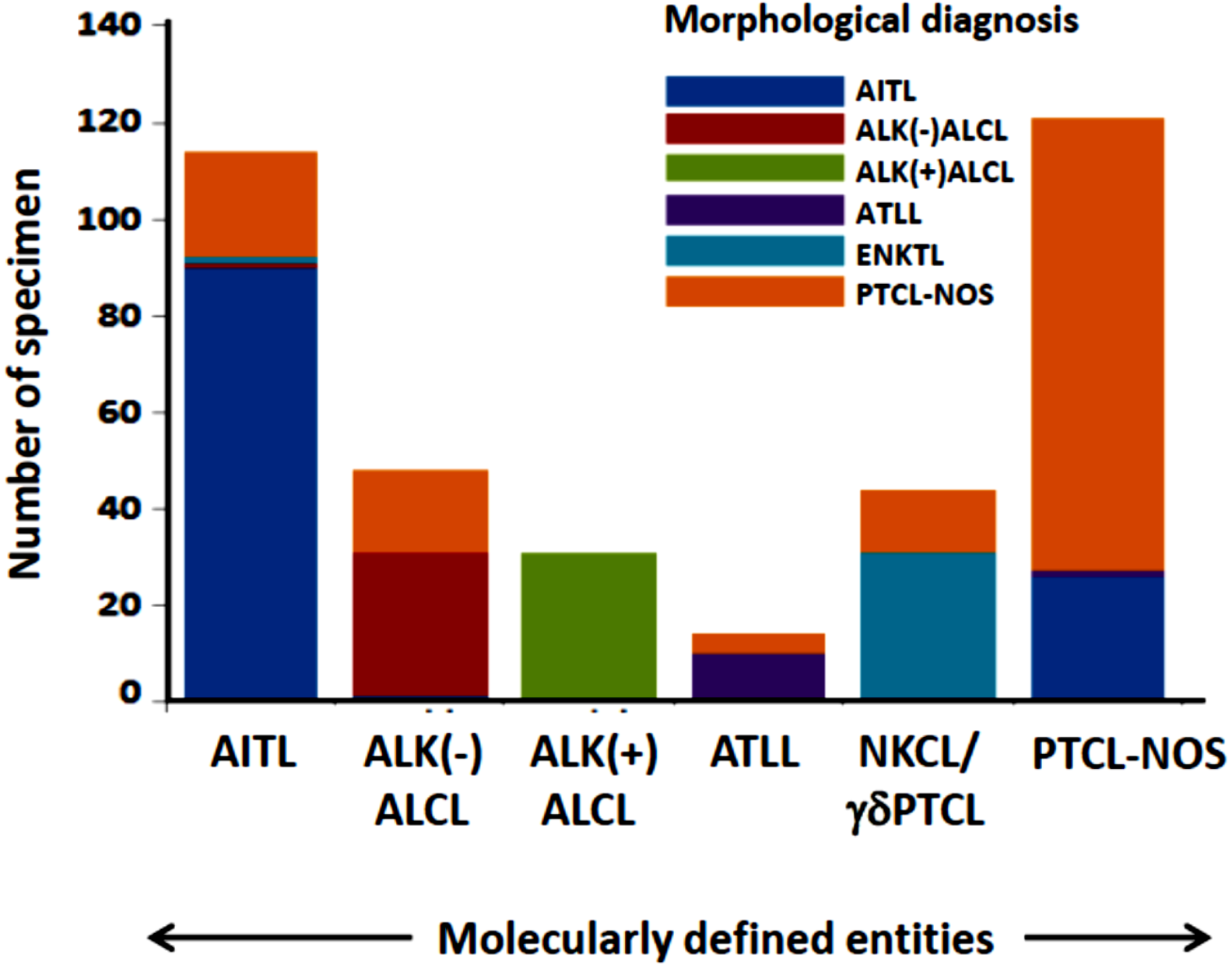


Gene expression signatures delineate biologic and prognostic subgroups in peripheral T-cell lymphoma

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




Morphological diagnosis
AITL
ALK(-)ALCL
ALK(+)ALCL
ATLL
ENKTL
PTCL-NOS
Number of specimen
140
120
100
80
60
40
20
0
AITL
ALK(-) ALCL
ALK(+) ALCL
ATLL
NKCL/ γδPTCL
PTCL-NOS
Molecularly defined entities

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

JOURNAL OF CLINICAL ONCOLOGY

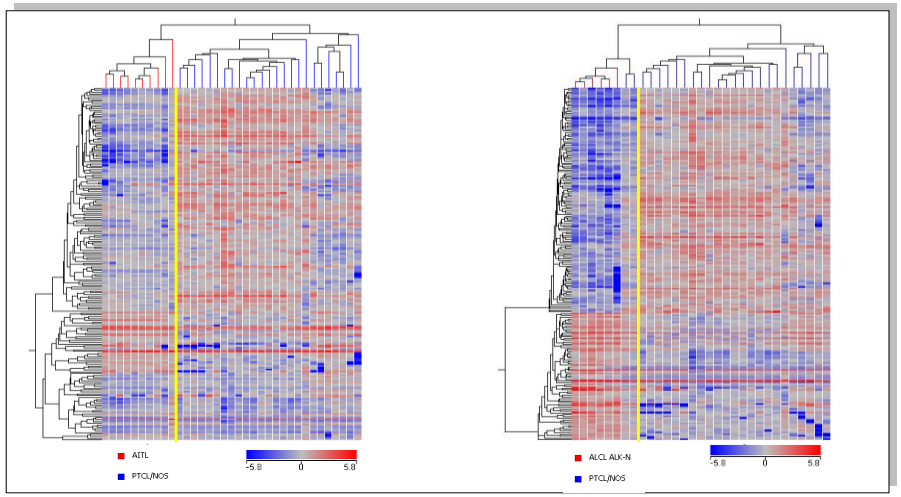
ORIGINAL REPORT

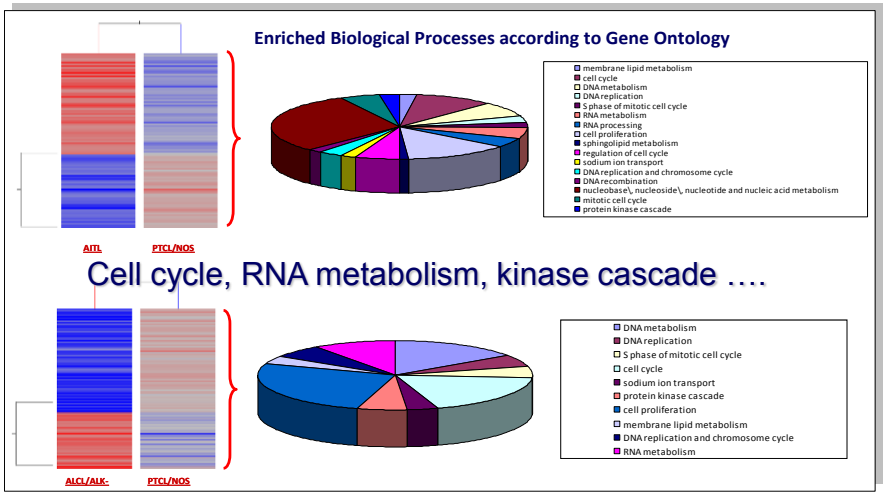
Molecular Profiling Improves Classification and Prognostication of Nodal Peripheral T-Cell Lymphomas: Results of a Phase III Diagnostic Accuracy Study

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

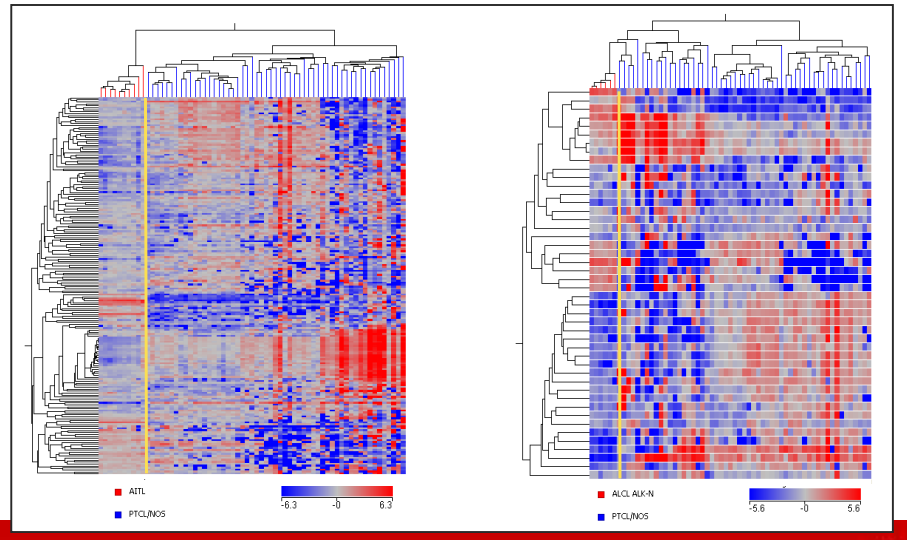
FFPE GEP effective in discriminating PTCL subtypes

Training set





Test set



Discriminant analysis

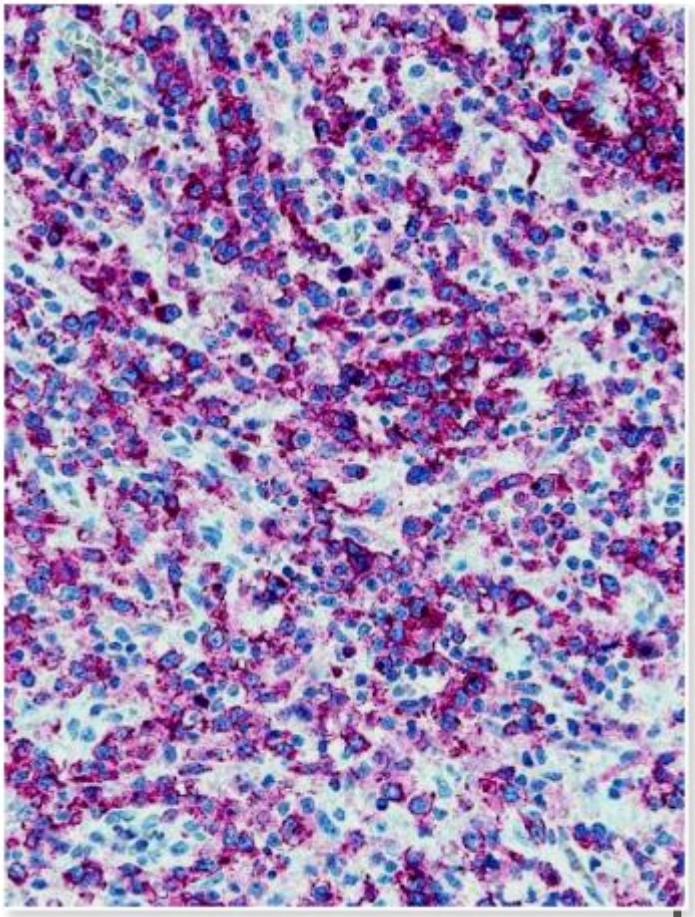
PTCL/NOS *vs.* AITL →38 genes

PTCL/NOS *vs.* ALK$^-$/ALCL →53 genes

CD30-positive PTCL/NOS cases were classified as PTCL/NOS

- CD30-positive PTCL/NOS cases
  - No criteria for ALK-negative ALCL diagnosis
  - 16 cases
- Molecular classifier
  - 16/16 → PTCL/NOS

No ALCL morphology; CD30 >75%

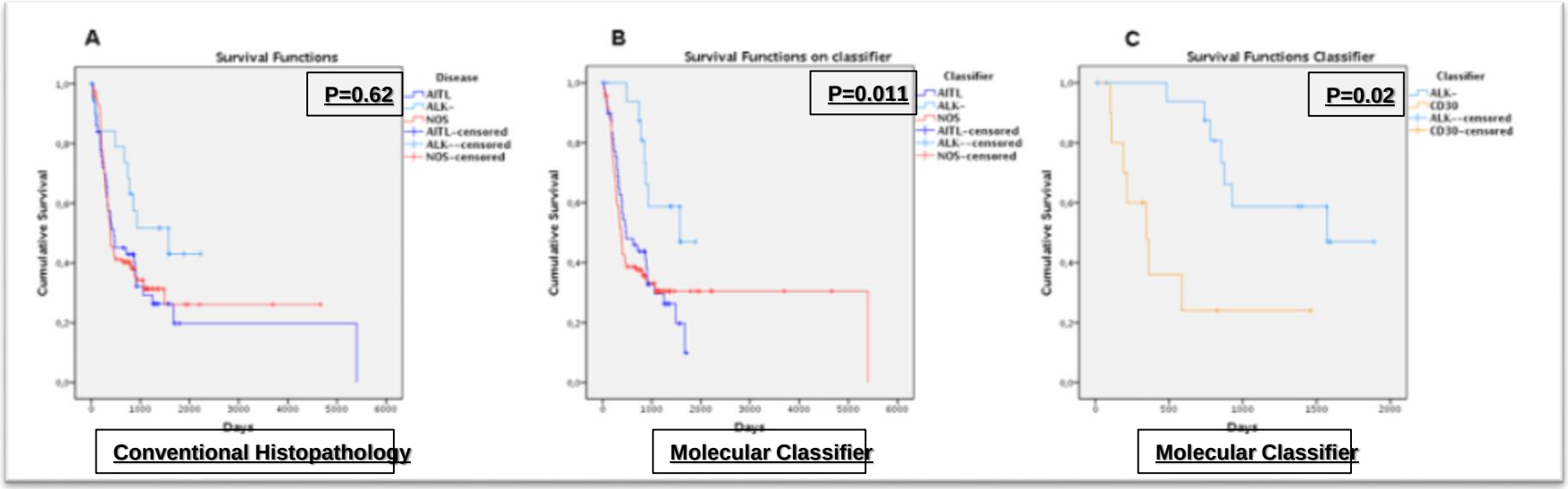


ALK- ALCL vs. CD30+ PTCL/NOS

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

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

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



Conventional Histopathology

Molecular Classifier

Molecular Classifier

microRNA expression profiling identifies molecular signatures associated with anaplastic large cell lymphoma

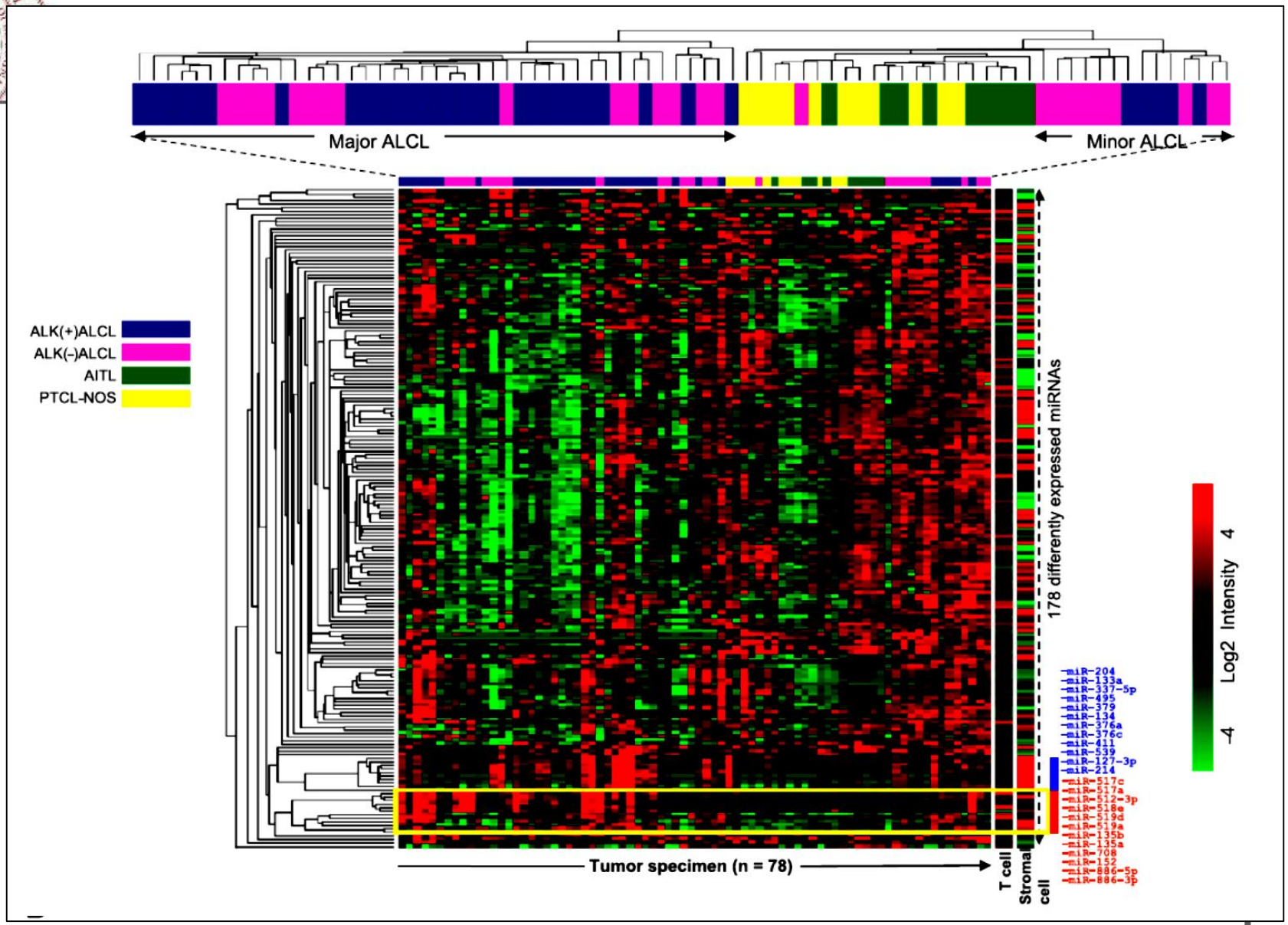
Cuiling Liu,[1,2] Javeed Iqbal,[1] Julie Teruya-Feldstein,[3] Yulei Shen,[1] Magdalena Julia Dabrowska,[4] Karen Dybkaer,[4] Megan S. Lim,[5] Roberto Piva,[6] Antonella Barreca,[6] Elisa Pellegrino,[6] Elisa Spaccarotella,[6] Cynthia M. Lachel,[1] Can Kucuk,[1] Chun-Sun Jiang,[1] Xiaozhou Hu,[1] Sharathkumar Bhagavathi,[1] Timothy C. Greiner,[1] Dennis D. Weisenburger,[1] Patricia Aoun,[1] Sherrie L. Perkins,[7] Timothy W. McKeithan,[1] Giorgio Inghirami,[6] and Wing C. Chan[1]

[1]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE; [2]Department of Pathology, Peking University Health Science Center, Beijing, People's Republic of China; [3]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY; [4]Department of Hematology, Aalborg Hospital, University of Aarhus, Aarhus, Denmark; [5]Department of Pathology, University of Michigan Health System, Ann Arbor, MI; [6]Department of Molecular Biotechnology and Health Sciences, and Center for Experimental Research and Medical Studies, University of Torino, Torino, Italy; and [7]Department of Pathology, University of Utah, Salt Lake City, UT

Key Points

- Anaplastic large-cell lymphoma has a unique miRNA signature.
- The miR-17~92 is an important downstream effector of ALK oncogenic pathway.

Anaplastic large-cell lymphomas (ALCLs) encompass at least 2 systemic diseases distinguished by the presence or absence of anaplastic lymphoma kinase (ALK) expression. We performed genome-wide microRNA (miRNA) profiling on 33 ALK-positive (ALK[+]) ALCLs, 25 ALK-negative (ALK[−]) ALCLs, 9 angioimmunoblastic T-cell lymphomas, 11 peripheral T-cell lymphomas not otherwise specified (PTCLNOS), and normal T cells, and demonstrated that ALCLs express many of the miRNAs that are highly expressed in normal T cells with the prominent exception of miR-146a. Unsupervised hierarchical clustering demonstrated distinct clustering of ALCL, PTCL-NOS, and the AITL subtype of PTCL. Cases of ALK(+) ALCL and ALK(–) ALCL were interspersed in unsupervised analysis, suggesting a close relationship at the molecular level. We identified an miRNA signature of 7 miRNAs (5 upregulated: miR-512-3p, miR-886-5p, miR-886-3p, miR-708, miR-135b; 2 downregulated: miR-146a, miR-155) significantly associated with ALK(+) ALCL cases. In addition, we derived an 11-miRNA signature (4 upregulated: miR-210, miR-197, miR-191, miR-512-3p; 7 downregulated: miR-451, miR-146a, miR-22, miR-455-3p, miR-455-5p, miR-143, miR-494) that differentiates ALK(–) ALCL from other PTCLs. Our in vitro studies identified a set of 32 miRNAs associated with ALK expression. Of these, the miR-17~92 cluster and its paralogues were also highly expressed in ALK(+) ALCL and may represent important downstream effectors of the ALK oncogenic pathway.
(*Blood*. 2013;122(12):2083-2092)

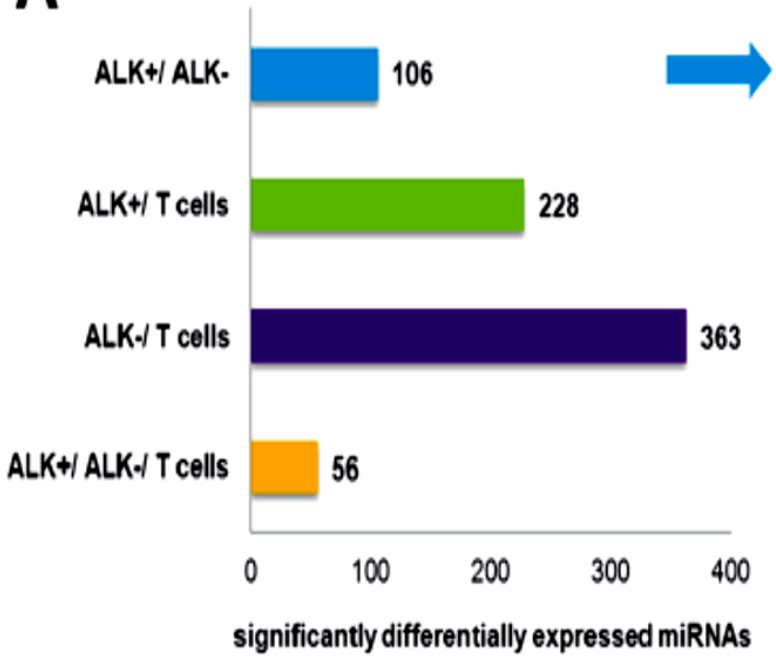

Major ALCL
Minor ALCL
ALK(+)ALCL
ALK(–)ALCL
AITL
PTCL-NOS
178 differently expressed miRNAs
miR-204
miR-133a
miR-337-5p
miR-495
miR-379
miR-134
miR-376a
miR-376c
miR-411
miR-539
miR-127-3p
miR-214
miR-517c
miR-517a
miR-512-3p
miR-518e
miR-519d
miR-519a
miR-135b
miR-135a
miR-708
miR-152
miR-886-5p
miR-886-3p
Tumor specimen (n = 78)
T cell
Stromal cell
Log2 Intensity
4
–4

Next-Generation Sequencing Identifies Deregulation of MicroRNAs Involved in Both Innate and Adaptive Immune Response in ALK+ ALCL

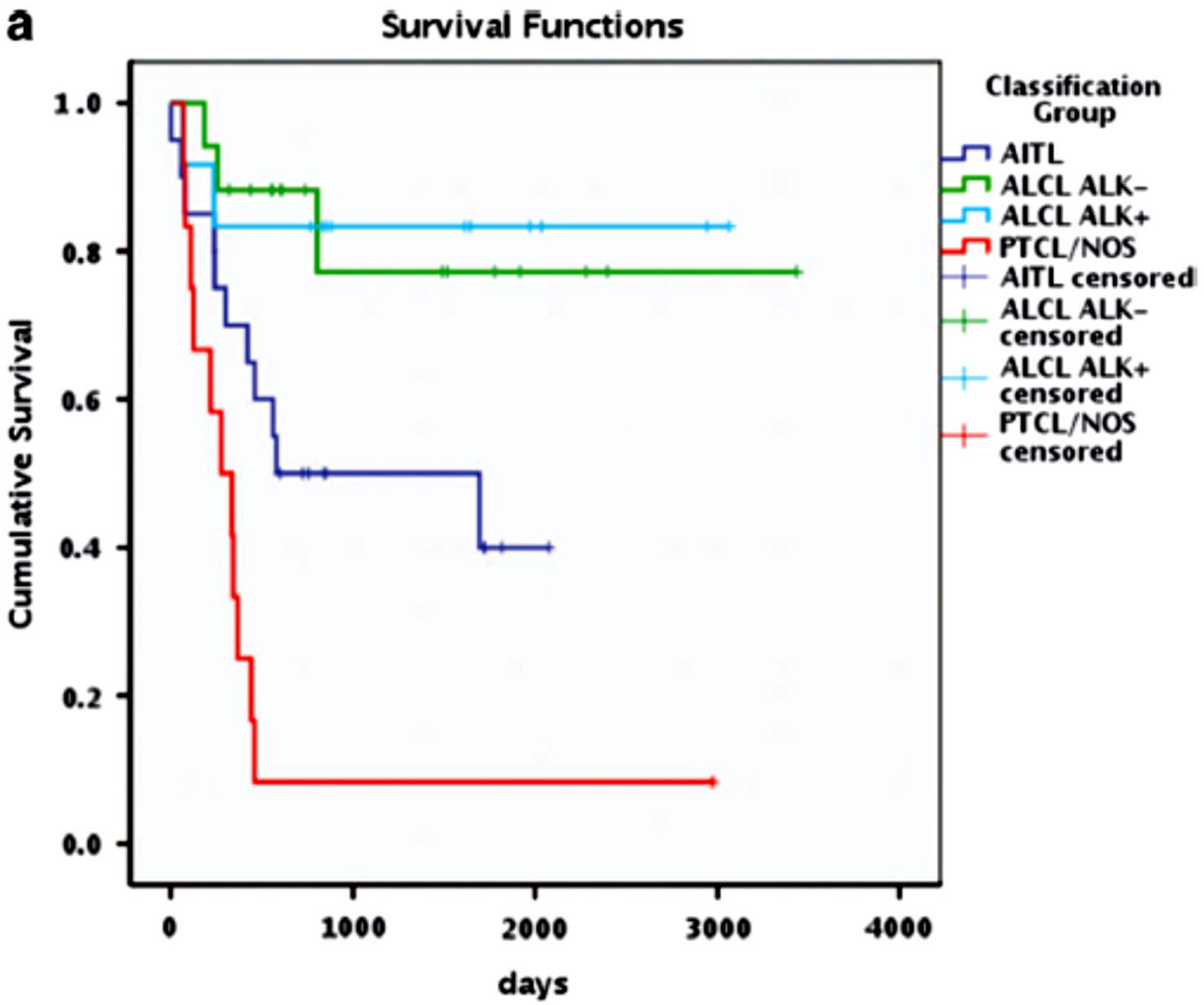
PLOS ONE | DOI:10.1371/journal.pone.0117780 February 17, 2015

Julia Steinhilber[1,2], Michael Bonin[3], Michael Walter[3], Falko Fend[1,2], Irina Bonzheim[1,2]*‡, Leticia Quintanilla-Martinez[1,2]*‡

A



miRNA	ALK- ALCL	ALK+ ALCL	fold change	padj
hsa-miR-196b	186	0	0,0006	2.48E-43
hsa-miR-155	44475	1205	0,0271	8.56E-35
hsa-miR-340	0	1538	3660,0000	8.56E-35
hsa-miR-146a	2525	29	0,0114	3.34E-27
hsa-miR-203	0	316	751,0000	1.19E-23
hsa-miR-135b	2	405	172,0000	1.07E-21
hsa-miR-424	1875	98	0,0525	3.22E-21
hsa-miR-135b*	0	119	562,0000	1.67E-18
hsa-miR-503	343	22	0,0645	1.14E-16
hsa-miR-424*	910	78	0,0856	7.64E-15
hsa-miR-182	672	17849	26,6000	3.79E-14
hsa-miR-183	51	1473	28,7000	3.79E-14
hsa-miR-542-3p	413	38	0,0912	1.40E-13


a
Survival Functions
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
days
Classification Group
AITL
ALCL ALK-
ALCL ALK+
PTCL/NOS
AITL censored
ALCL ALK- censored
ALCL ALK+ censored
PTCL/NOS censored

(*Blood*. 2014;124(9):1473-1480)

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

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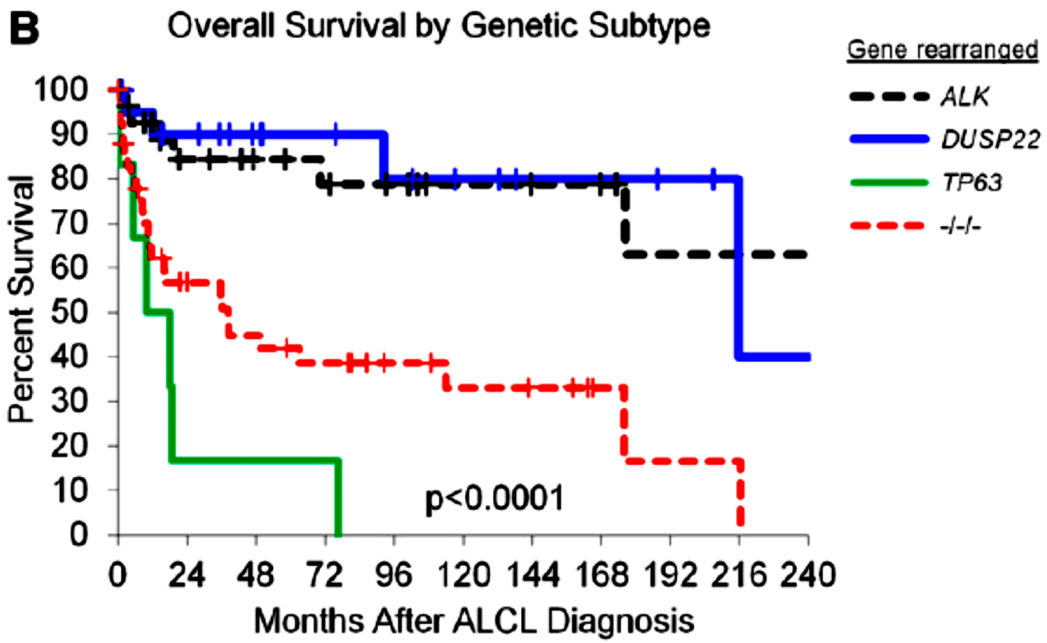
Key Points

- ALK-negative ALCLs have chromosomal rearrangements of *DUSP22* or *TP63* in 30% and 8% of cases, respectively.
- *DUSP22*-rearranged cases have favorable outcomes similar to ALK-positive ALCLs, whereas other genetic subtypes have inferior outcomes.



DUSP22-IRF4 locus

PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma

Michela Boi,[1] Andrea Rinaldi,[1] Ivo Kwee,[1-3] Paola Bonetti,[1] Maria Todaro,[4] Fabrizio Tabbò,[4] Roberto Piva,[4,5] Paola M. V. Rancoita,[1,2] András Matolcsy,[6] Botond Timar,[6] Thomas Tousseyn,[7] Socorro Maria Rodríguez-Pinilla,[8] Miguel A. Piris,[8] Sílvia Beà,[9] Elias Campo,[9] Govind Bhagat,[10] Steven H. Swerdlow,[11] Andreas Rosenwald,[12] Maurilio Ponzoni,[13] Ken H. Young,[14] Pier Paolo Piccaluga,[15] Reinhard Dummer,[16] Stefano Pileri,[15] Emanuele Zucca,[17] Giorgio Inghirami,[4,5] and Francesco Bertoni[1,17]

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Key Points

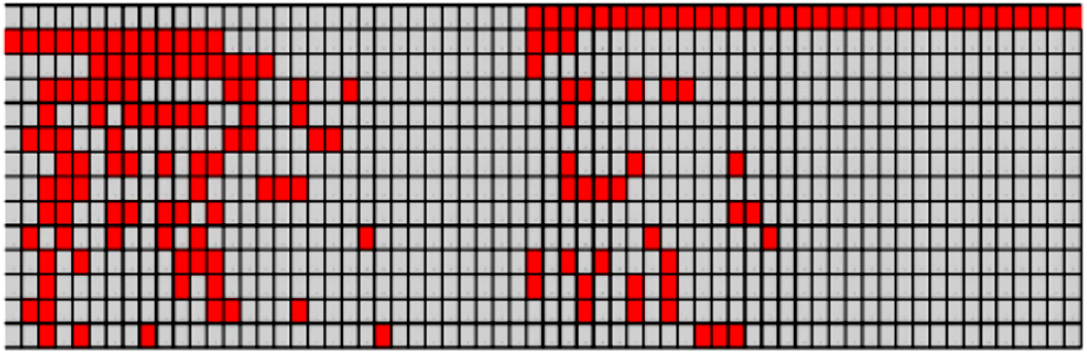
- The commonest lesions in anaplastic large cell lymphomas are losses at 17p13 and at 6q21, concomitant in up to one-quarter of the cases.
- *PRDM1* (BLIMP1) gene (6q21) is inactivated by multiple mechanisms and acts as a tumor suppressor gene in anaplastic large B-cell lymphoma.

Anaplastic large cell lymphoma (ALCL) is a mature T-cell lymphoma that can present as a systemic or primary cutaneous disease. Systemic ALCL represents 2% to 5% of adult lymphoma but up to 30% of all pediatric cases. Two subtypes of systemic ALCL are currently recognized on the basis of the presence of a translocation involving the anaplastic lymphoma kinase *ALK* gene. Despite considerable progress, several questions remain open regarding the pathogenesis of both ALCL subtypes. To investigate the molecular pathogenesis and to assess the relationship between the ALK^+ and ALK^- ALCL subtypes, we performed a genome-wide DNA profiling using high-density, single nucleotide polymorphism arrays on a series of 64 cases and 7 cell lines. The commonest lesions were losses at 17p13 and at 6q21, encompassing the *TP53* and *PRDM1* genes, respectively. The latter gene, coding for BLIMP1, was inactivated by multiple mechanisms, more frequently, but not exclusively, in ALK^-ALCL. In vitro and in vivo experiments showed that that *PRDM1* is a tumor suppressor gene in ALCL models, likely acting as an antiapoptotic agent. Losses of *TP53* and/or *PRDM1* were present in 52% of ALK^-ALCL, and in 29% of all ALCL cases with a clinical implication. (*Blood*. 2013;122(15):2683-2693)

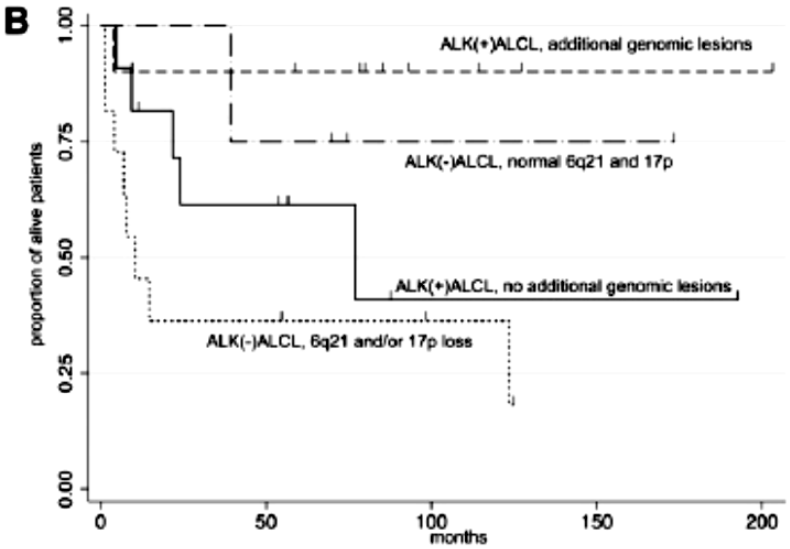
17p13 (TP53) – 6q21 (PRDM1)*

A

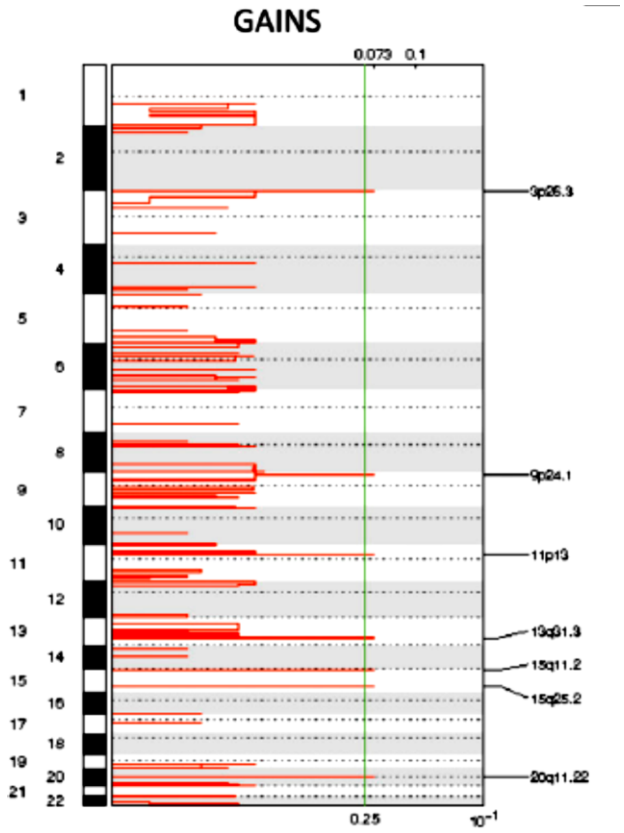
Lesion	freq	freq ALK(+)	freq ALK(-)
ALK translocation	52%	100%	0%
17p13.3-p12 loss	25%	9%	42%
6q21 loss	19%	3%	35%
1q gain	23%	15%	32%
16q23.1-q23.2 loss	16%	3%	29%
1p13.3-p12 loss	11%	0%	26%
13q32.2-q33.3 loss	16%	9%	23%
8q24.22 gain	17%	12%	23%
10p11.23-p11.22 loss	14%	6%	23%
1p36.33-p36.32 loss	13%	6%	19%
7q gain	14%	12%	16%
7p gain	11%	12%	10%
12p13.33-p13.31 gain	13%	9%	16%
2p25.3-p25.2 gain	11%	9%	13%

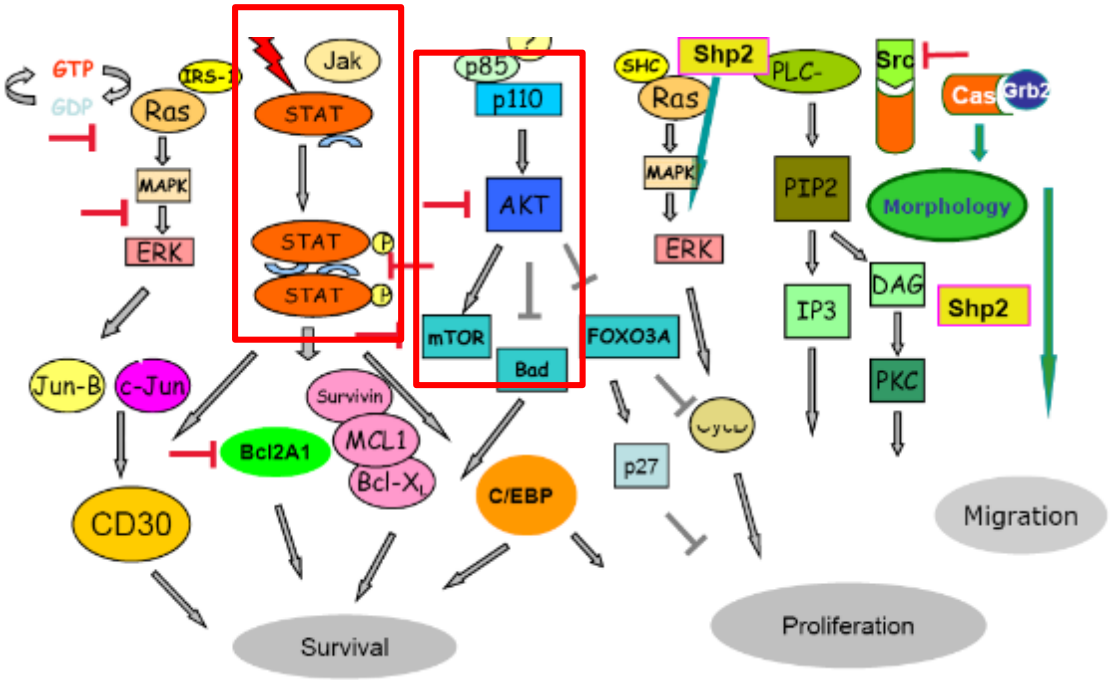


B



Gains of 9p24.1 (*JAK*) and 13q31.3 (*MIR17HG*)



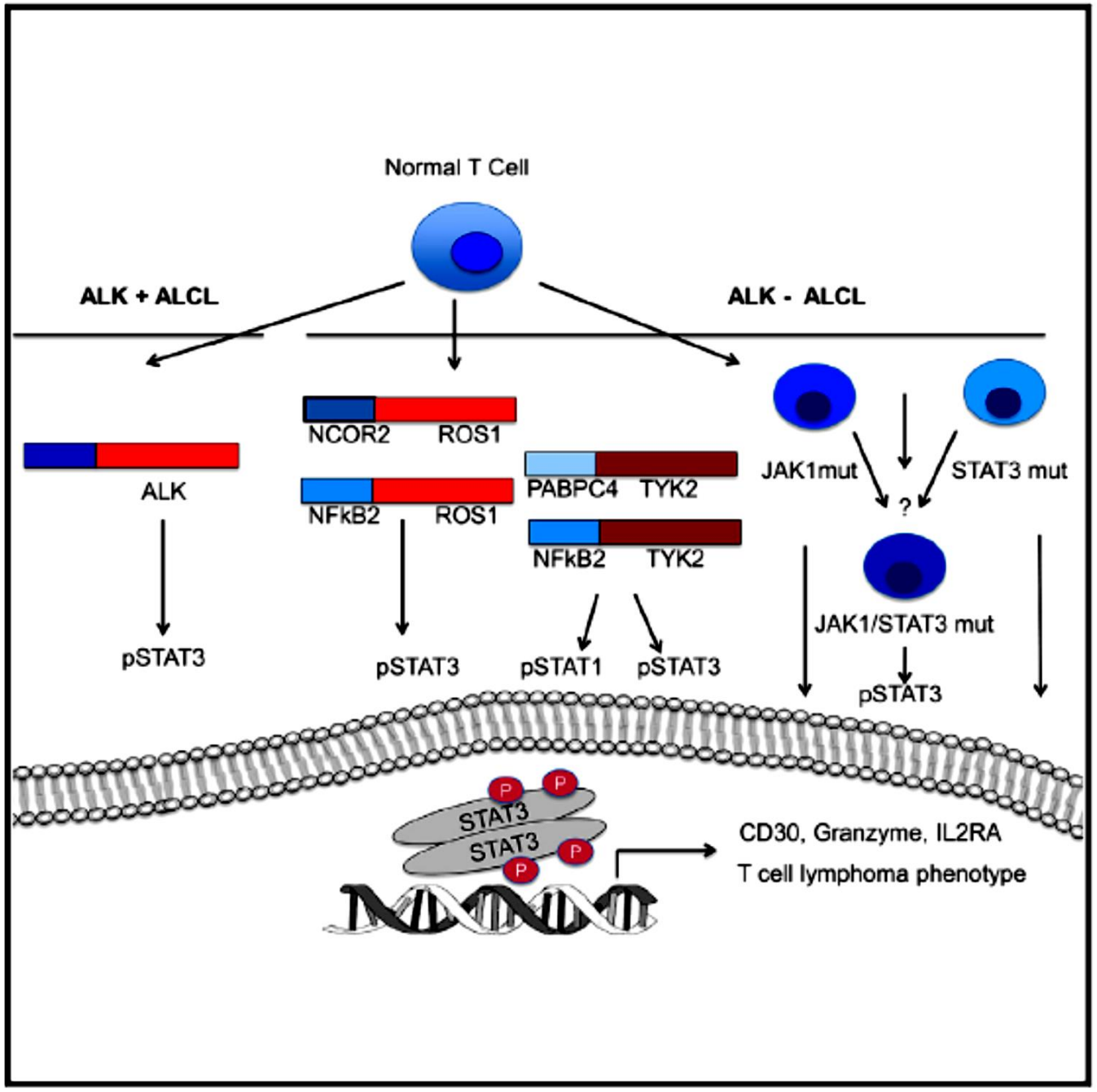


Convergent Mutations and Kinase Fusions Lead to Oncogenic STAT3 Activation in Anaplastic Large Cell Lymphoma

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

Clinical Advisory Committee Meeting
WHO Classification Update
Chicago March 31 – April 1, 2014

In the updated WHO Classification

ALK^{-} ALCL

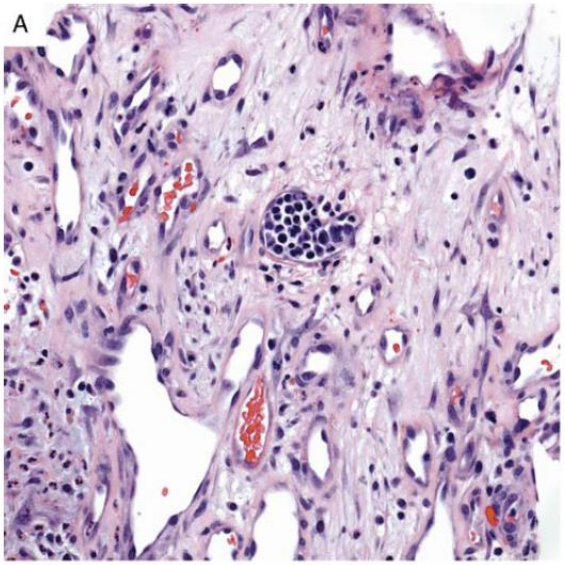
Distinct entity!

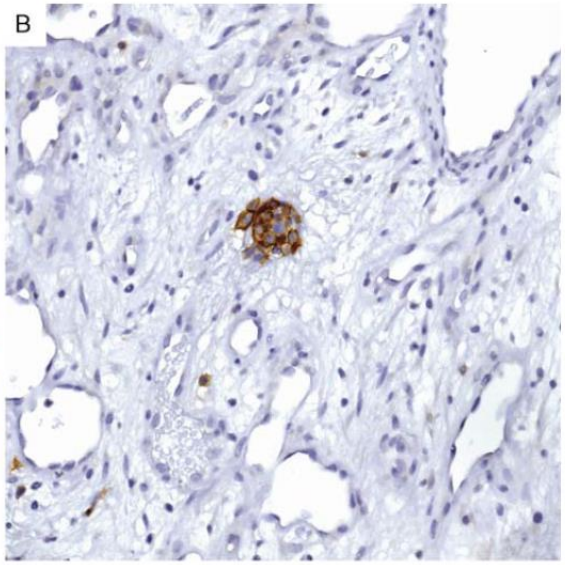
(*Am J Surg Pathol* 2014;38:1203–1211)

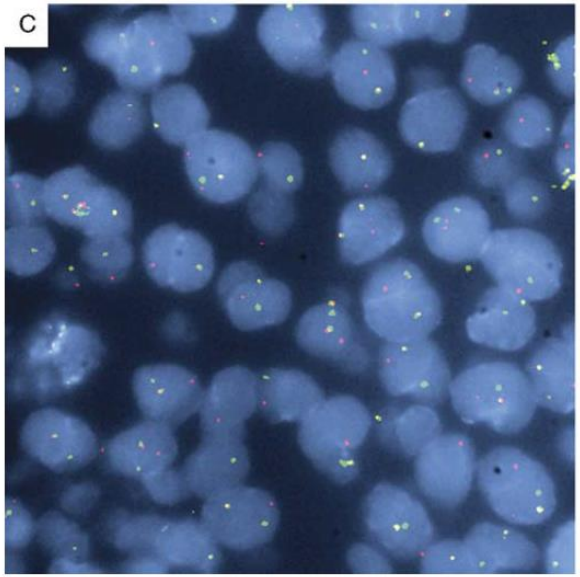
Intralymphatic Cutaneous Anaplastic Large Cell Lymphoma/Lymphomatoid Papulosis

Expanding the Spectrum of CD30-positive Lymphoproliferative Disorders

Mark A. Samols, MD, Albert Su, MD,† Seong Ra, MD,†‡ Mark A. Cappel, MD,§ Abner Louissant, Jr, MD,‖ Ryan A. Knudson, CG(ASCP)CM,¶ Rhett P. Ketterling, MD,¶ Jonathan Said, MD,† Scott Binder, MD,† Nancy Lee Harris, MD,‖ Andrew L. Feldman, MD,¶ Jinah Kim, MD, PhD,* Youn H. Kim, MD,# and Dita Gratzinger, MD, PhD**







Thank you very much for your attention!