ANATOMIA PATOLOGICA DEL LINFOMA A CELLULE DEL MANTELLO

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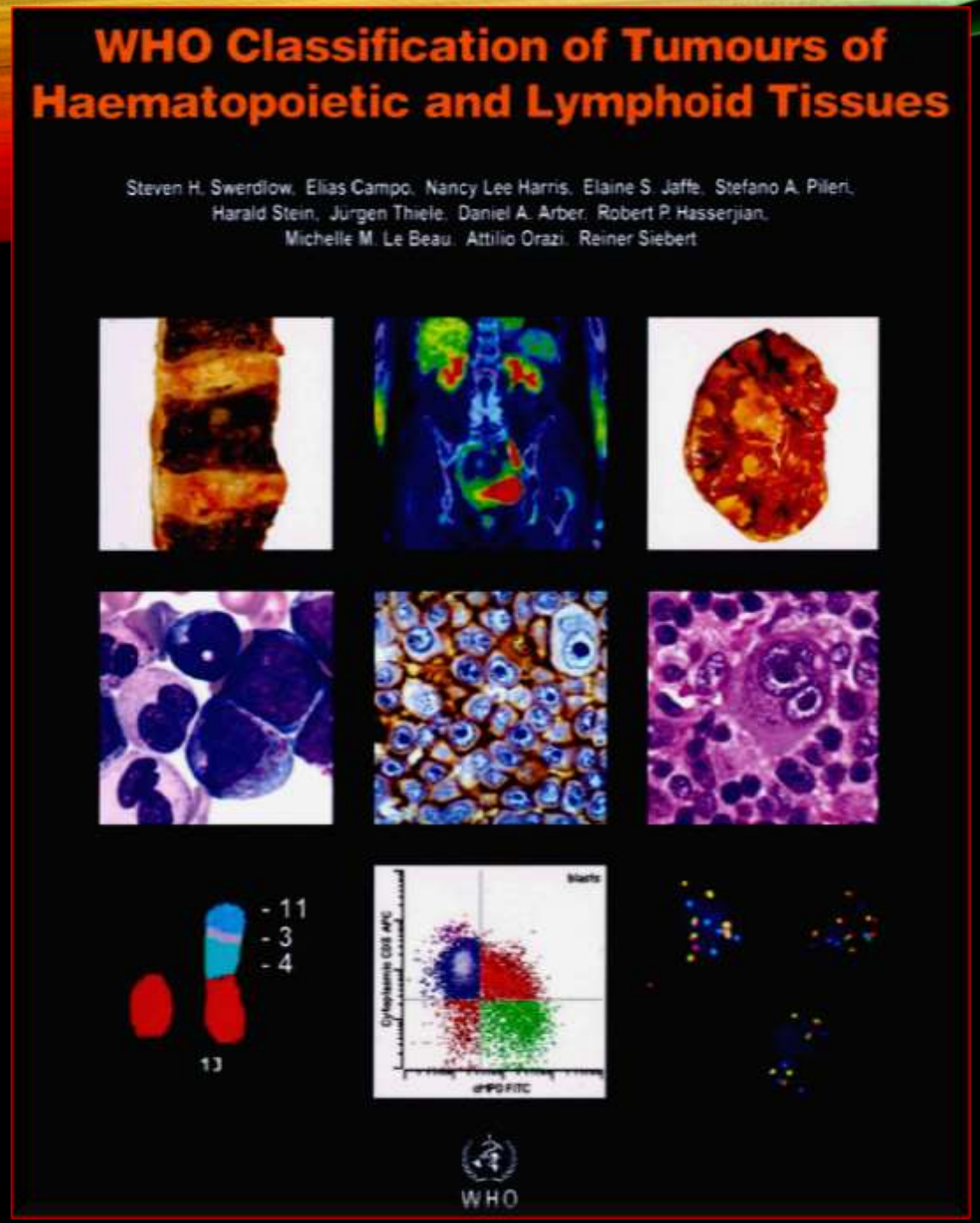
Università di Torino



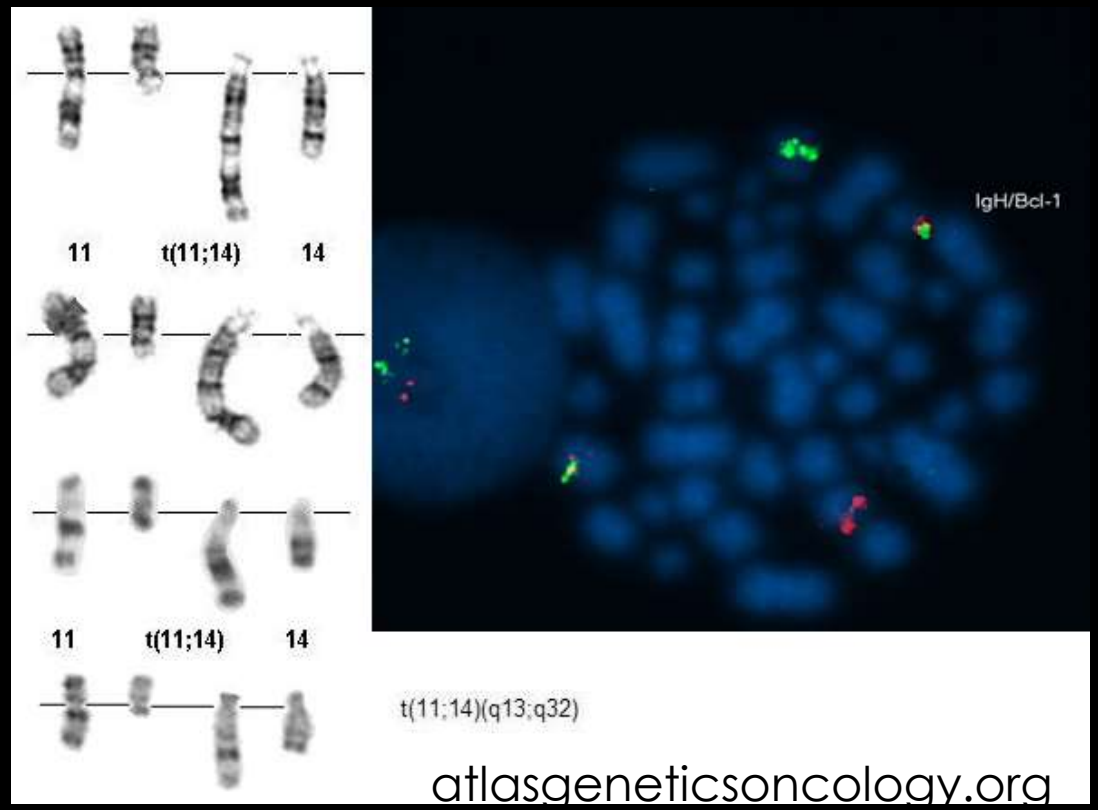
Definition

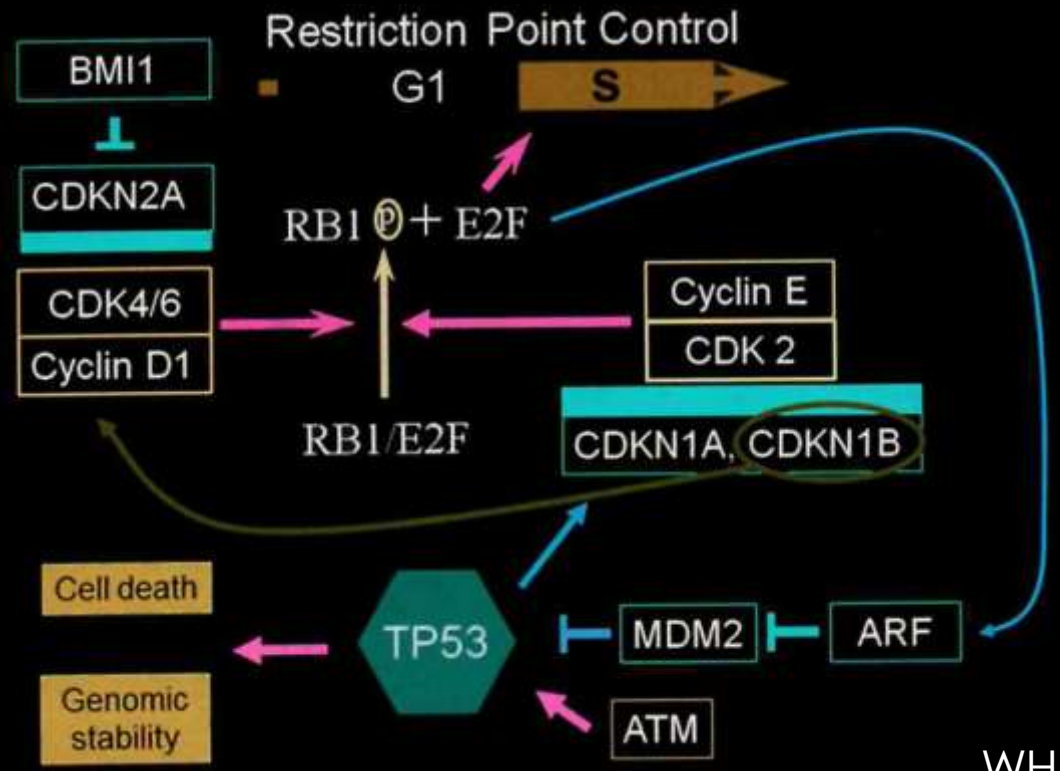
Mantle cell lymphoma is a mature B-cell neoplasm usually composed of monomorphic small to medium-sized lymphoid cells with irregular nuclear contours; in >95% of cases, there is a *CCND1* translocation {245,543,2219,2269,3849, 4018}. Neoplastic transformed cells (centroblasts), paraimmunoblasts, and proliferation centres are absent. Mantle cell lymphoma has traditionally been considered a very aggressive and incurable lymphoma, but more indolent variants, including leukaemic non-nodal mantle cell lymphoma and in situ mantle cell neoplasia, are now also well recognized.

PATOGENESI

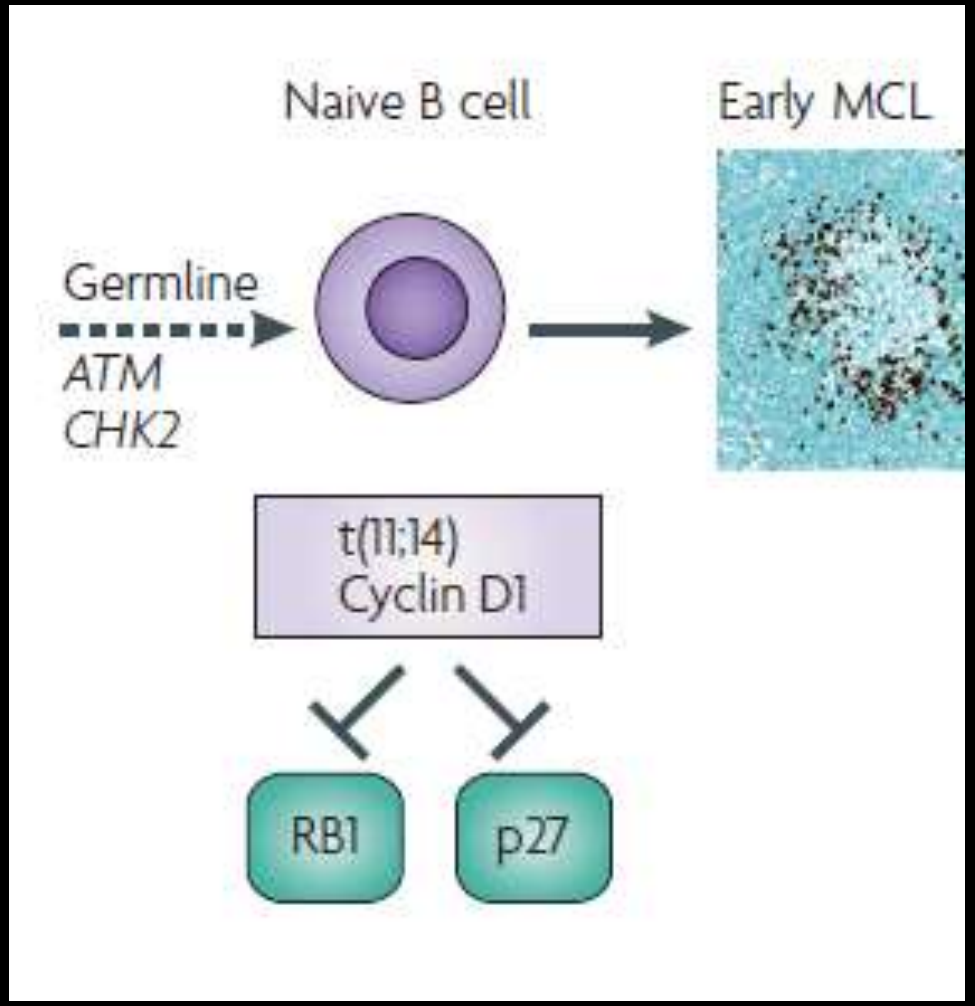
LINFOMA A CELLULE DEL MANTELLO

- Deriva da una cellula pre-B che acquisisce una traslocazione a carico del locus di ciclina D1

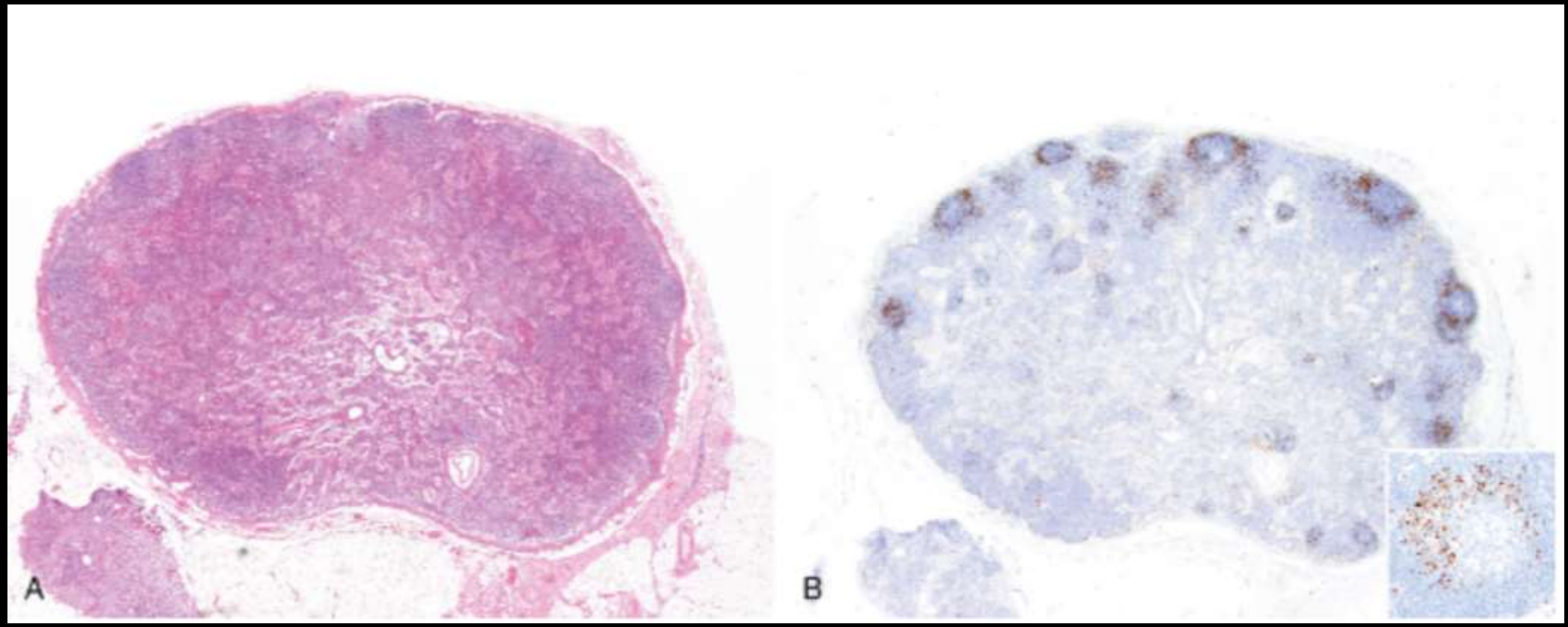




WHO BB


Naive B cell
Early MCL
Germline
ATM
CHK2
t(11;14)
Cyclin D1
RB1
p27

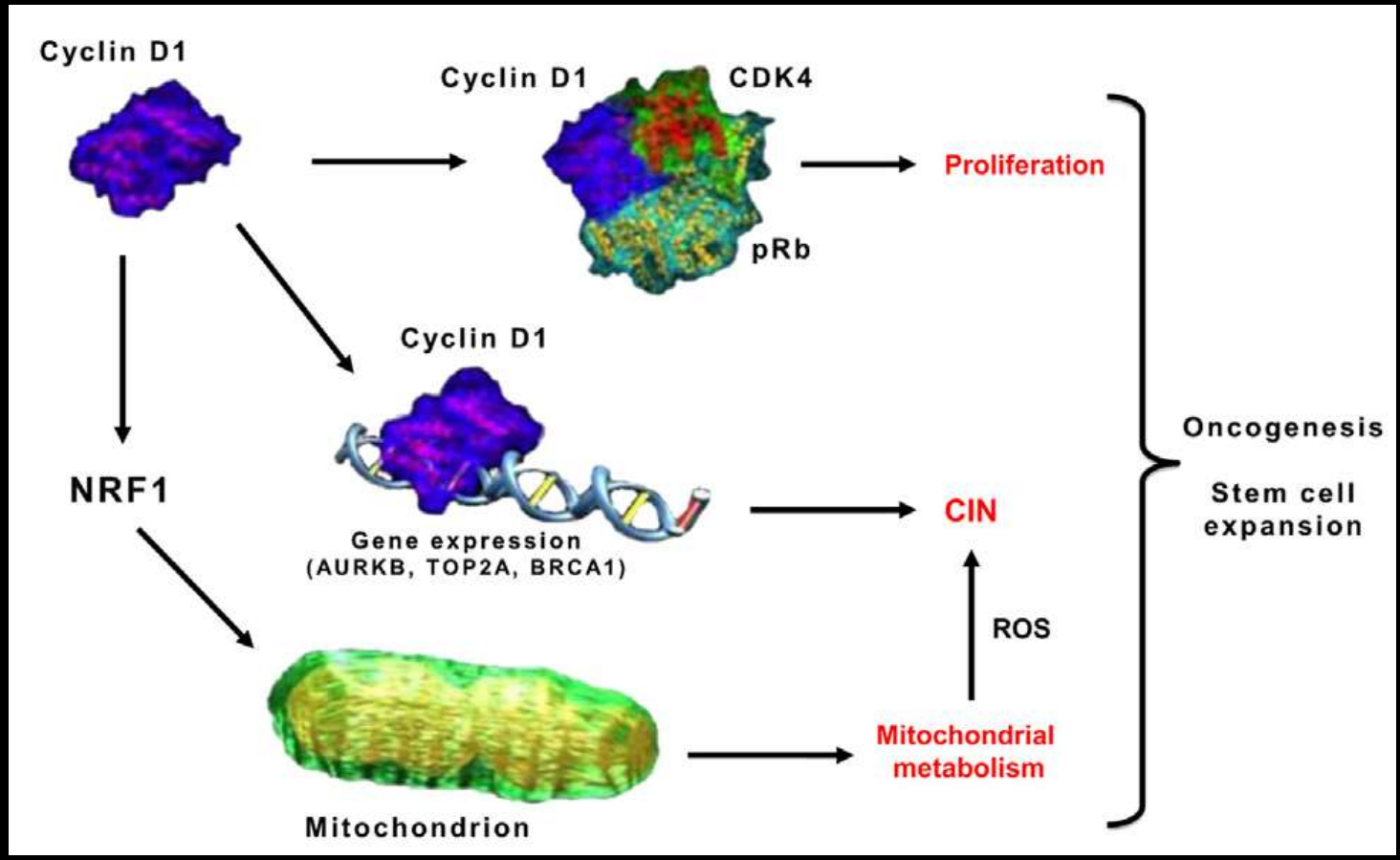
NEOPLASIA MANTELLARE IN SITU



CICLINA D1

- Funzioni classiche
  - Interazione con CDK4/6
- Funzioni alternative
  - Regolazione della trascrizione
  - DNA damage response
  - Inibizione di BAX

CICLINA D1 E CIN



Pestell 2013

MCL T(11;14) NEGATIVO

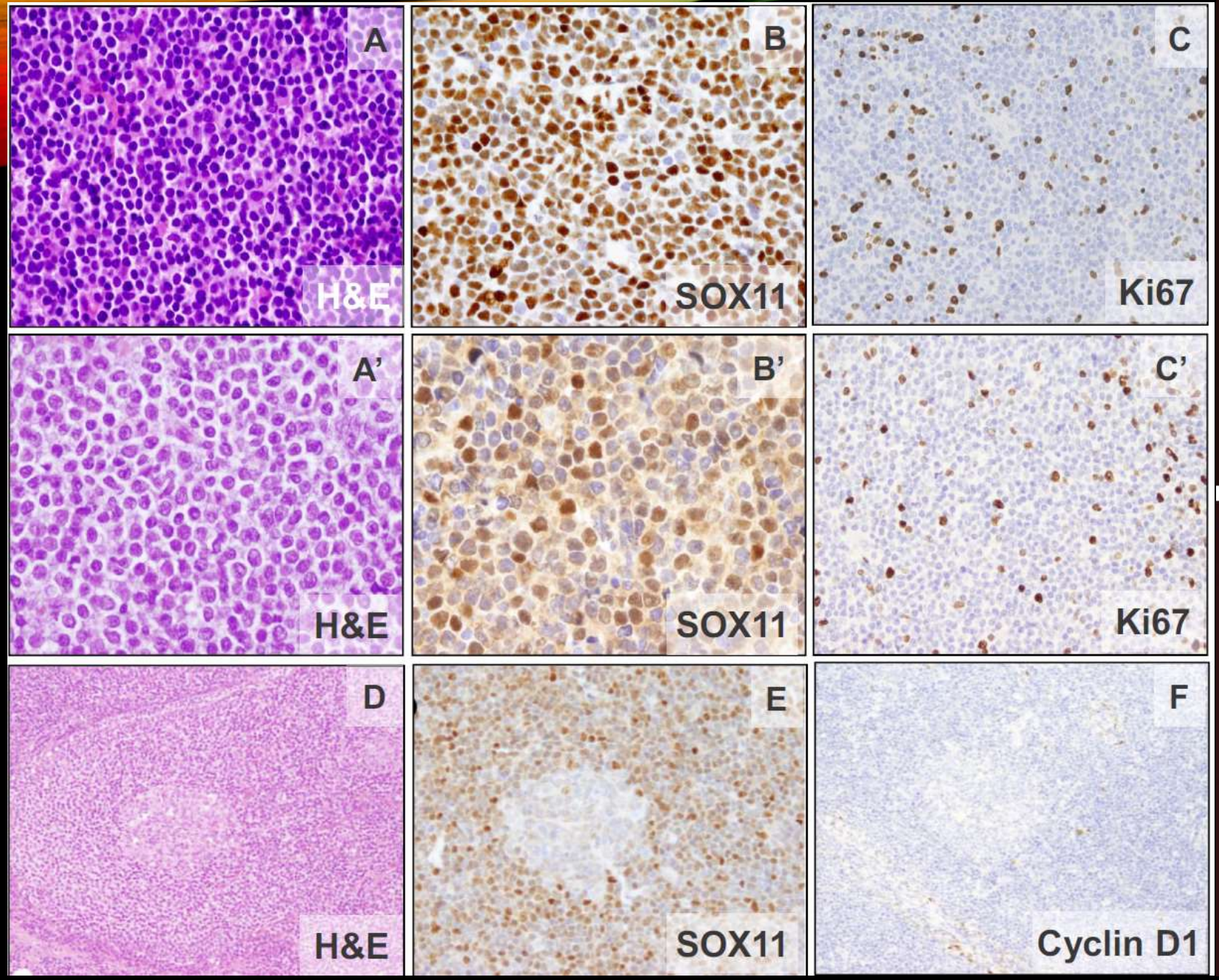
CCND2 rearrangements are the most frequent genetic events in cyclin D1$^-$ mantle cell lymphoma

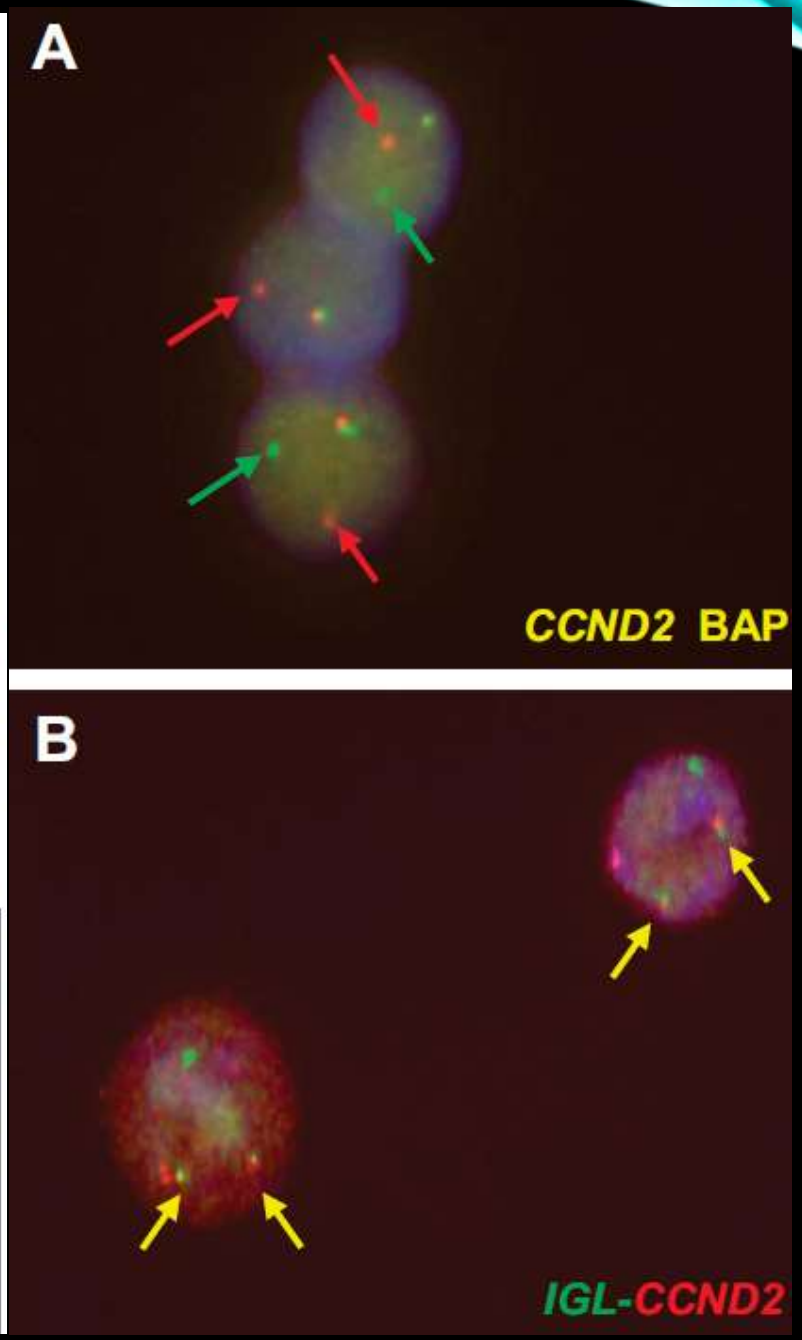
*Itziar Salaverria,[1,2] *Cristina Royo,[1] Alejandra Carvajal-Cuenca,[1] Guillem Clot,[1] Alba Navarro,[1] Alejandra Valera,[1] Joo Y. Song,[3] Renata Woroniecka,[4] Grzegorz Rymkiewicz,[5] Wolfram Klapper,[6] Elena M. Hartmann,[7] Pierre Sujobert,[8] Iwona Wlodarska,[9] Judith A. Ferry,[10] Philippe Gaulard,[8] German Ott,[11] Andreas Rosenwald,[7] Armando Lopez-Guillermo,[12] Leticia Quintanilla-Martinez,[13] Nancy L. Harris,[10] Elaine S. Jaffe,[3] Reiner Siebert,[2] Elias Campo,[1] and Sílvia Beà[1]

BLOOD, 21 FEBRUARY 2013 • VOLUME 121, NUMBER 8

Table 1. Genetic, morphologic, and immunophenotypical parameters of 40 cyclin D1$^-$/SOX11$^+$ MCL patients

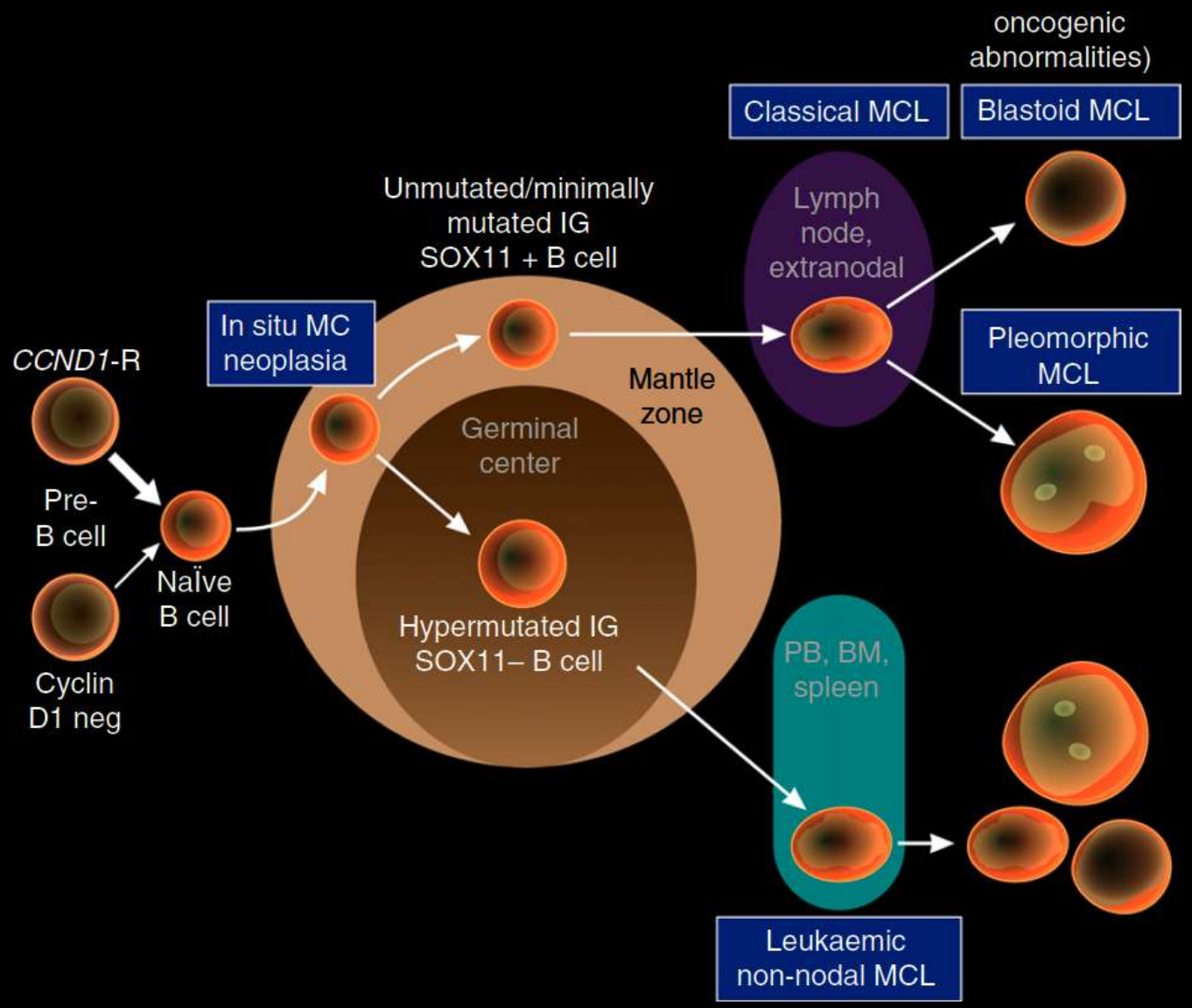
Parameter	n	%
***CCND2* translocation**		
IGH-CCND2	3/40	8
IGK-CCND2	10/40	25
IGL-CCND2	5/40	13
CCND2-break*	2/40	5
CCND2-?†	2/40	5
Negative	18/40	45


A
H&E
B
SOX11
C
Ki67
A'
H&E
B'
SOX11
C'
Ki67
D
H&E
E
SOX11
F
Cyclin D1


A
CCND2 BAP
B
IGL-CCND2

PATOGENESI

- Successivamente due vie patogenetiche
- >> Bypass de centro germinativo (cellule naive)
- < Esperienza del centro germinativo (cellule memoria)



I DUE SOTTOTIPI DIFFERISCONO

- Ipermutazione somatica dei geni delle IG
- Profili di espressione genica
- microRNA
- Pattern di metilazione
- Alterazioni genomiche
- Comportamento clinico

CLASSIFICAZIONE WHO 2016-7

Large B-cell lymphoma with IRF4 rearrangement
Primary cutaneous follicle centre lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal centre B-cell subtype
Activated B-cell subtype

- Two MCL subtypes recognized with different clinicopathological manifestations and molecular pathogenetic pathways: one largely with unmutated/minimally mutated IGHV and mostly SOX11^{+} and the other largely with mutated IGHV and mostly SOX11^{-} (indolent leukemic nonnodal MCL with PB, bone marrow (BM), ±splenic involvement, may become more aggressive).

WHO BB, Swerdlow 2016

MCL TIPO NAIVE

- Più frequente
- Sox11 molto trascritto, proteina elevata
- Geneticamente instabile
- Mutazioni multiple in regolatori del ciclo cellulare, geni del DNA-damage-response, modificatori della cromatina e geni che regolano l'apoptosi

MCL TIPO MEMORY

- Poco frequente
- RNA e proteina di SOX11 bassi
- Geneticamente stabile (inizialmente)
- Ipermutazione somatica IG e non-IG
- Leucemico non-nodale

SOX11

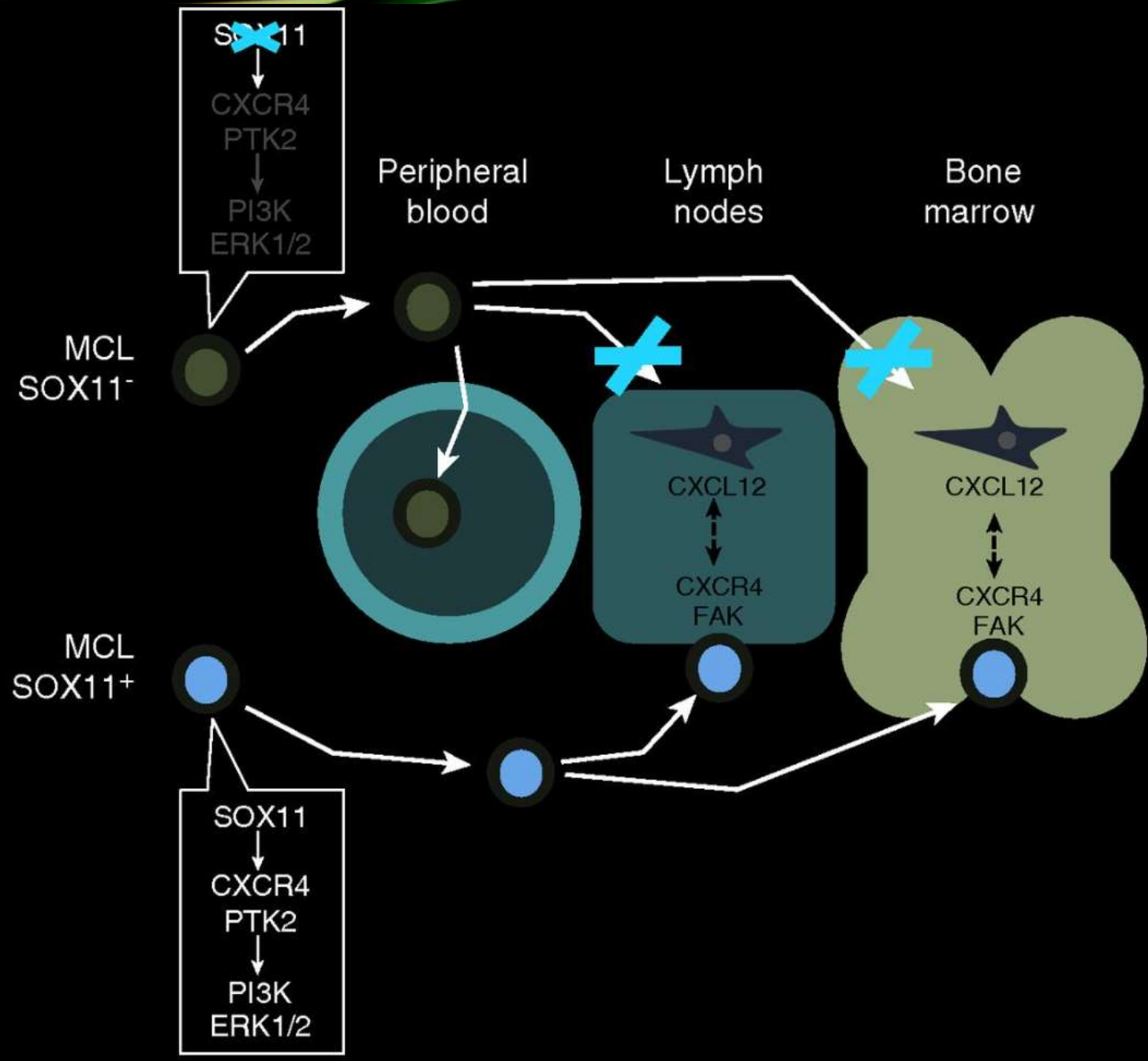
- Fattore di trascrizione
- Assente nelle cellule linfoidi normali
- Espressione nel 25-50% dei linfomi di Burkitt
- Altri linfomi con eccezione del MCL negativi

SOX11

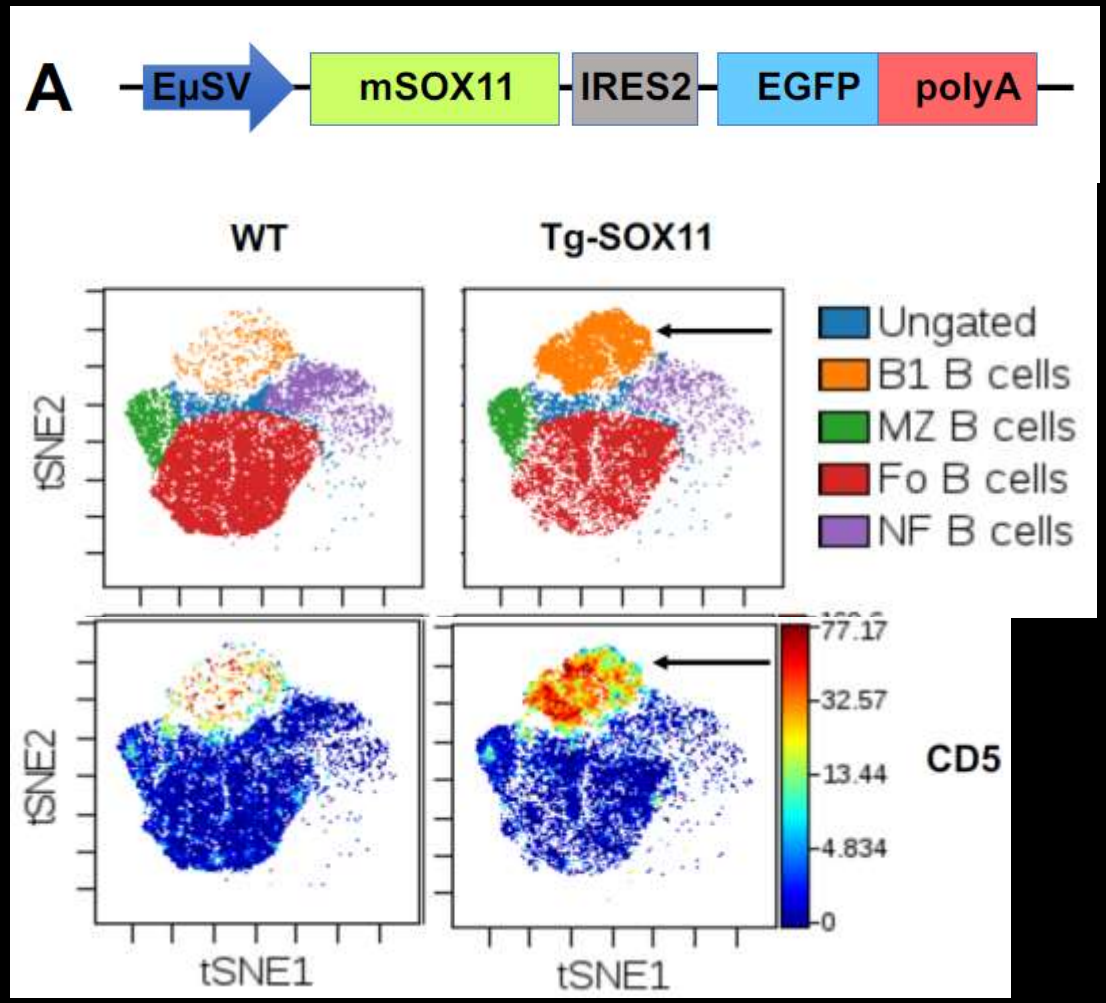
Aumenta la trascrizione di PAX5

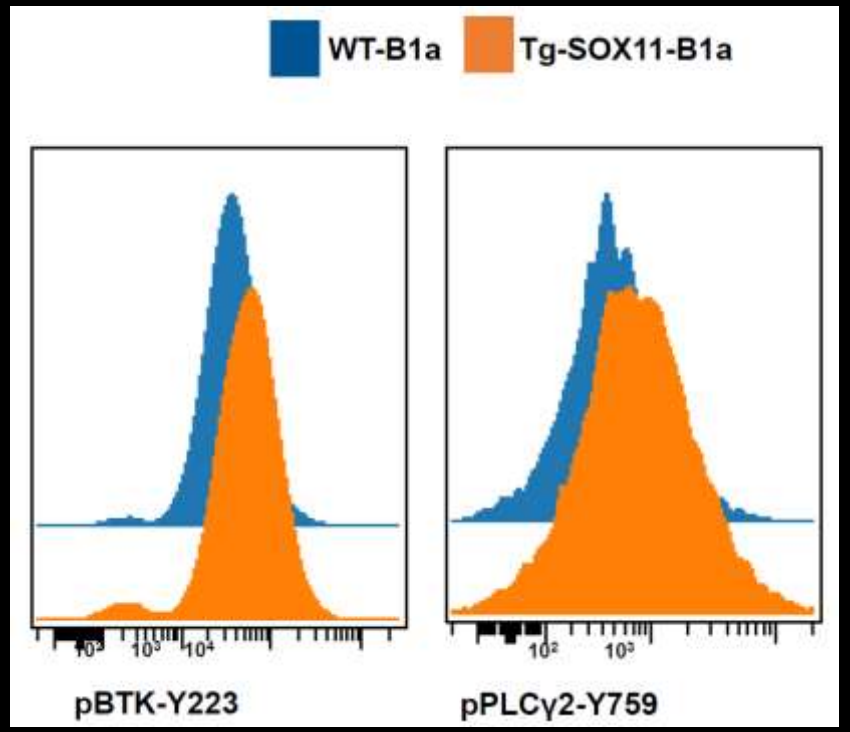
Reprime la trascrizione di BCL6

Regola PDGFA, CXCL4, FAK


SOX11
CXCR4
PTK2
PI3K
ERK1/2
Peripheral blood
Lymph nodes
Bone marrow
MCL SOX11-
CXCL12
CXCR4
FAK
CXCL12
CXCR4
FAK
MCL SOX11+
SOX11
CXCR4
PTK2
PI3K
ERK1/2

MODELLO TRANSGENICO





Kuo et al. Blood 2018

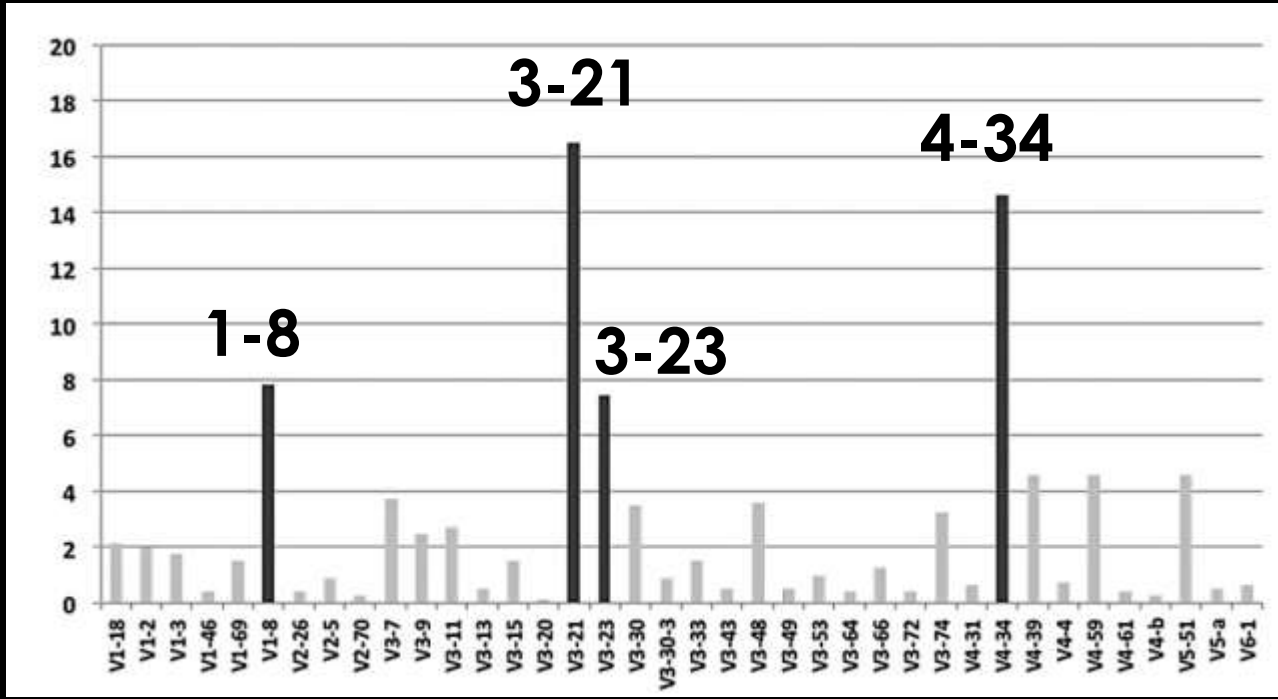
RUOLO DEL B-CELL RECEPTOR

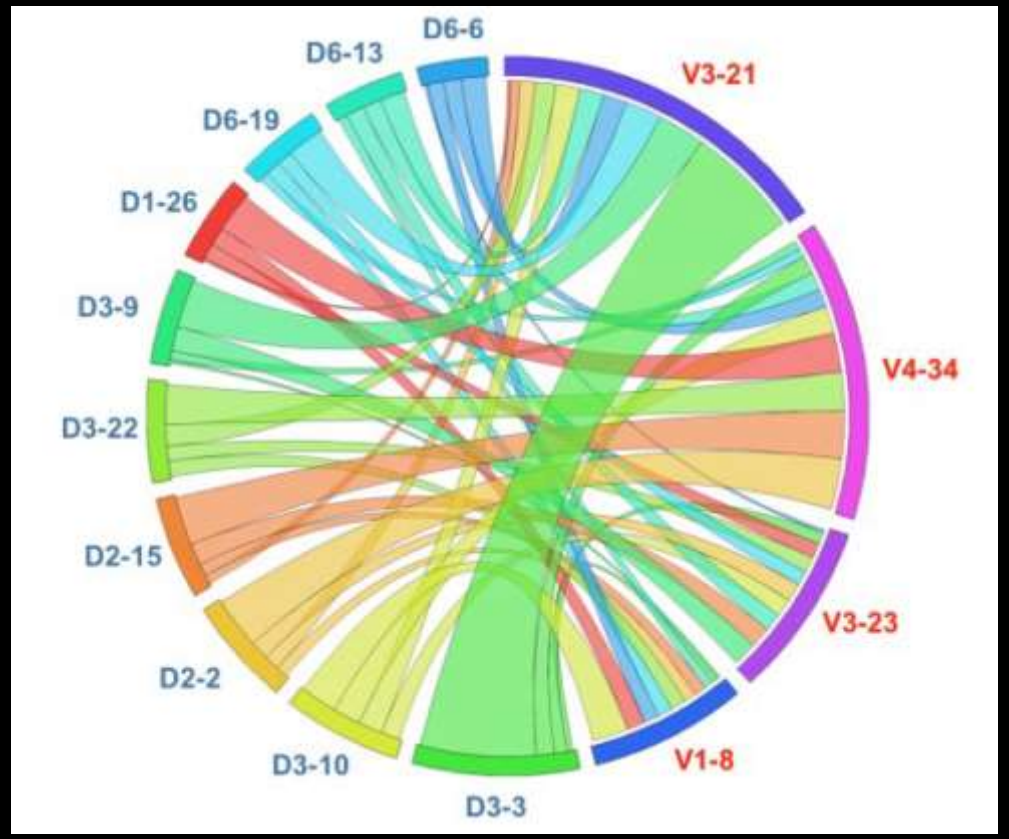
- VH Bias e stereotipi
- Lambda bias
- Attivazione cronica attiva in vitro e in vivo
- Antigeni

Is there a role for antigen selection in mantle cell lymphoma? Immunogenetic support from a series of 807 cases

*Anastasia Hadzidimitriou,[1] *Andreas Agathangelidis,[1-3] Nikos Darzentas,[1] Fiona Murray,[4] Marie-Helene Delfau-Larue,[5,6] Lone Bredo Pedersen,[7] Alba Navarro Lopez,[8] Antonis Dagklis,[9] Paul Rombout,[10] Kheira Beldjord,[11] Arne Kolstad,[12] Martin H. Dreyling,[13] Achilles Anagnostopoulos,[2] Athanasios Tsaftaris,[1] Penelope Mavragani-Tsipidou,[3] Andreas Rosenwald,[14] Maurilio Ponzoni,[15] Patricia Groenen,[10] Paolo Ghia,[9] Birgitta Sander,[16] Theodora Papadaki,[17] Elias Campo,[8] †Christian Geisler,[7] Richard Rosenquist,[4] Frederic Davi,[18] Christiane Pott,[19] and Kostas Stamatopoulos[1,2]

BLOOD, 15 SEPTEMBER 2011 • VOLUME 118, NUMBER 11





10,4% DEI CDR3 SONO STEREOREOTIPATI

A

V3-21/D6-6/J6	V	D6-6	J6
GERMLINE	AR	EYSSSS	YYYYYGMDV
07-5780	..	.....	.....
MC45-2	..	.....	.....
MC57	..	.....T	.....
04-2198	..	.WD...	G.....
MCL-DK-01-0013	..	.....	A.....
MCL-SE-01-0036	..	.....	N.....

V3-21/D3-9/J4	V	N1	D3-9	N2	J4
GERMLINE	AR		YYDILTGYYN		YFDY
06-8174	..	DDT	.....	Y	....
08-9994	..	..R	.....	PD	....
FRA-MCL054	..	EGQ	.....	T.	....
FRA-MCL111	..	.SS	H.....	NS.	....
FRA-MCL139	..	.SR	.....	S.	....

B

V4-34/D2-2/J6	V	N1	D2-2	N2	J6
GERMLINE	AR		DIVVVPAAI		YYYYYYMDV
04-0309	..	G	.....	AVF	.....
05-2890	..	.	.....	LSGF	.....
59812389	..	.	.L.....	G	.....L..
MCL-DK-01-0038	..	DS	.....	KVI	.....
MCL-SE-01-0028	..	.	.....	A	.....
MCL-SE-01-0083	..	.	E.....	S	.....
MCL-SE-01-0113	..	.T	....V..	NS	.....

V4-34/D1-26/J6	V	D1-26	N2	J6
GERMLINE	AR	GIVGAT		YYYYYYMDV
05-2651	.S	.....	TA	.....
07-1996	..	.D....	.	.....D...
MCL-DK-01-0150	..	.E.A..	QS	.....
MCL-DK-01-0158	..	.E....	.A	..F.....

STEREOTIPIA DELLE CATENE LEGGERE

Table IV. LCDR3 alignment of MCL cell lines and published sequences.

Sequence ID	*IGLV* gene	*IGLJ* gene	LCDR3 sequence
MC45-2†	*IGLV3-19*01*	*IGLJ2*01*	CNSRDSSGN-HLVF
MC57†	*IGLV3-19*01*	*IGLJ2*01*	CNSRDSSGN-HVVF
SE-01-0036-L1†	*IGLV3-19*01*	*IGLJ2*01*	CNSRDSSGN-HVVF
Mino	*IGLV3-19*01*	*IGLJ2*01/IGLJ3*01*	CNSRDSSGNPHVVF
Jeko-1	*IGKV3-20*01*	*IGKJ2*01*	CQQYGSSPNTF
UPN-2	*IGKV3-20*01*	*IGKJ4*01*	CQQYGSSP-AF
JVM-2	*IGLV2-14*01*	*IGLJ2*01/IGLJ3*01*	CSSYTSSS-V-VF
JVM-13	*IGLV2-14*01*	*IGLJ2*01/IGLJ3*01*	CSSYTSSSTLMIF

†Data from ref. [18].

Pighi et al. 2013

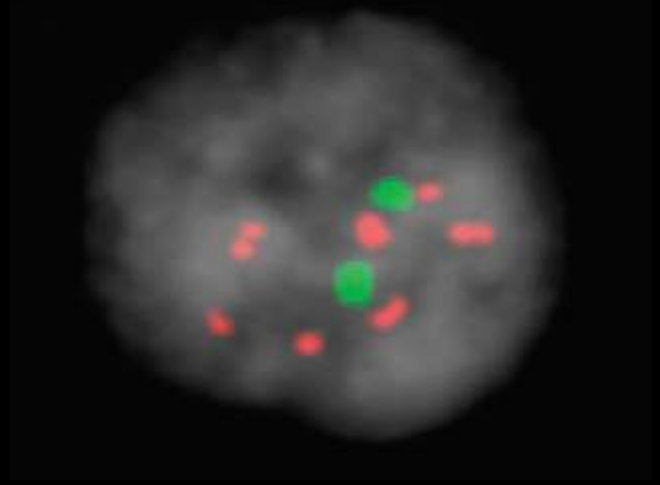
Genomic and expression profiling identifies the B-cell associated tyrosine kinase Syk as a possible therapeutic target in mantle cell lymphoma

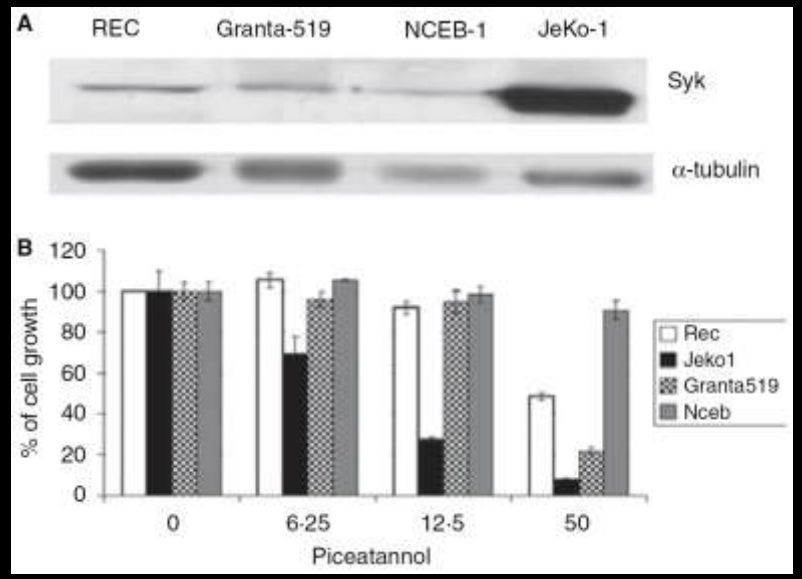
Andrea Rinaldi,[1] Ivo Kwee,[1,2] Monica Taborelli,[1] Cristina Largo,[3] Silvia Uccella,[4] Vittoria Martin,[4] Giulia Poretti,[1] Gianluca Gaidano,[5] Giuseppe Calabrese,[6] Giovanni Martinelli,[7] Luca Baldini,[8] Giancarlo Pruneri,[9] Carlo Capella,[4] Emanuele Zucca,[10] Finbarr E. Cotter,[11] Juan C. Cigudosa,[3] Carlo V. Catapano,[1] Maria G. Tibiletti[4] and Francesco Bertoni[1,11]

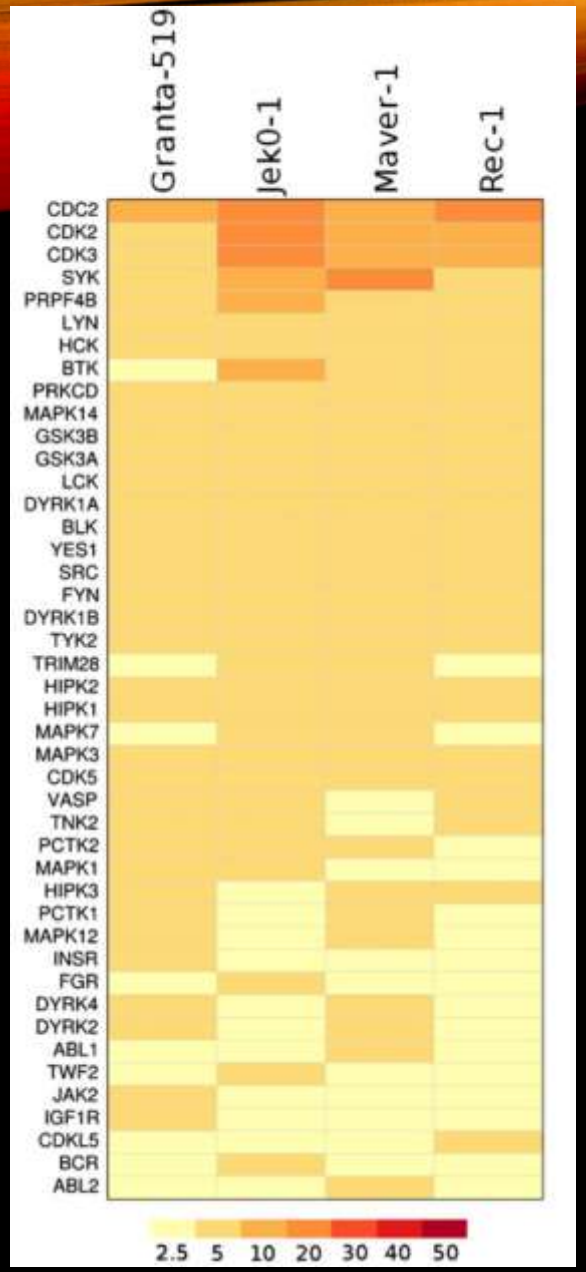
British Journal of Haematology, **132**, 303–316

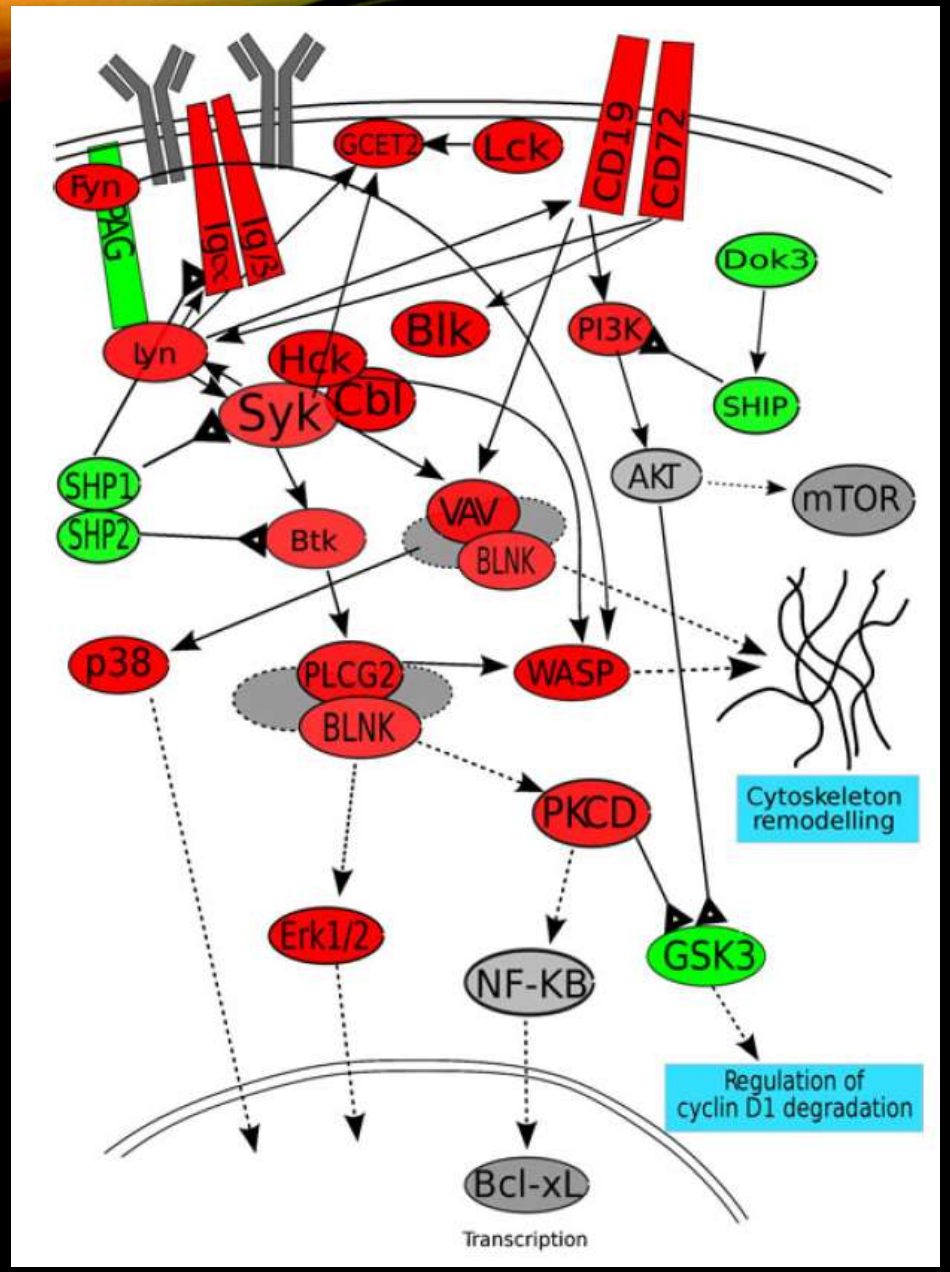
Table II. Genes showing a positive correlation between increased DNA copy number and gene expression in mantle cell lymphoma cell lines.

Gene symbol	Localisation
GYG, SSR3, LAMP3, PLR2H, HES1, EST	3q24–3q29
FGD2, FLJ11236, MRPL2, C6ORF89, MTCH1, EST	6p21-ter
SYK, BICD2, PHF2, PTCH, TGFBR1, SEC61B, TMEFF1, CDW92, ENDOG	9q22–9q31.2
ABAT, CARHSP1, USP7, PROO149, MHC2TA, LOC51760, ESTs	16p12.3–16p13.2
NEDD4L, ZNF532, LMAN1, BCL2, FVT1, VPS4B, TXNDC10, RTTN, SOCS6	18q21–18q22.2

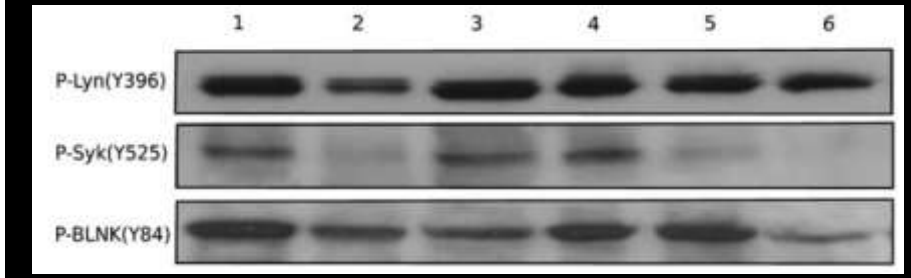


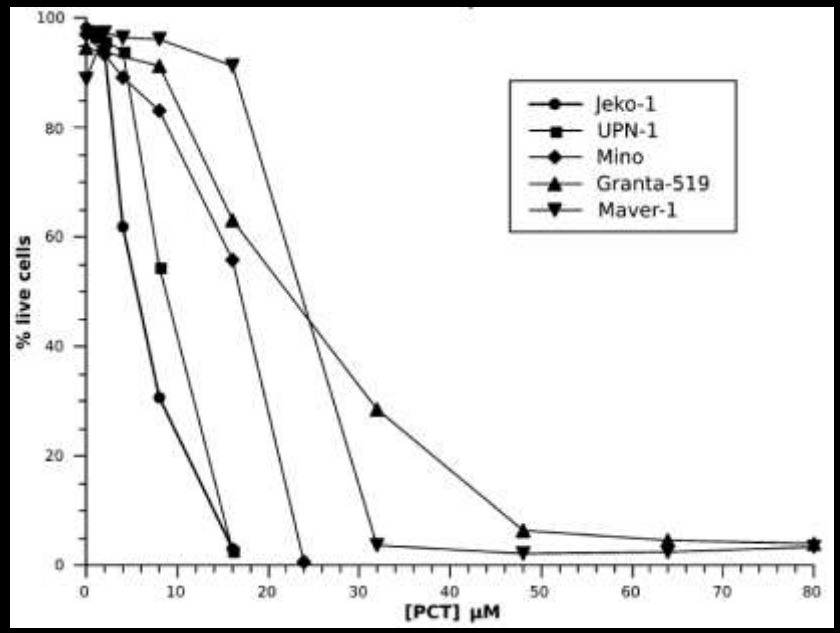






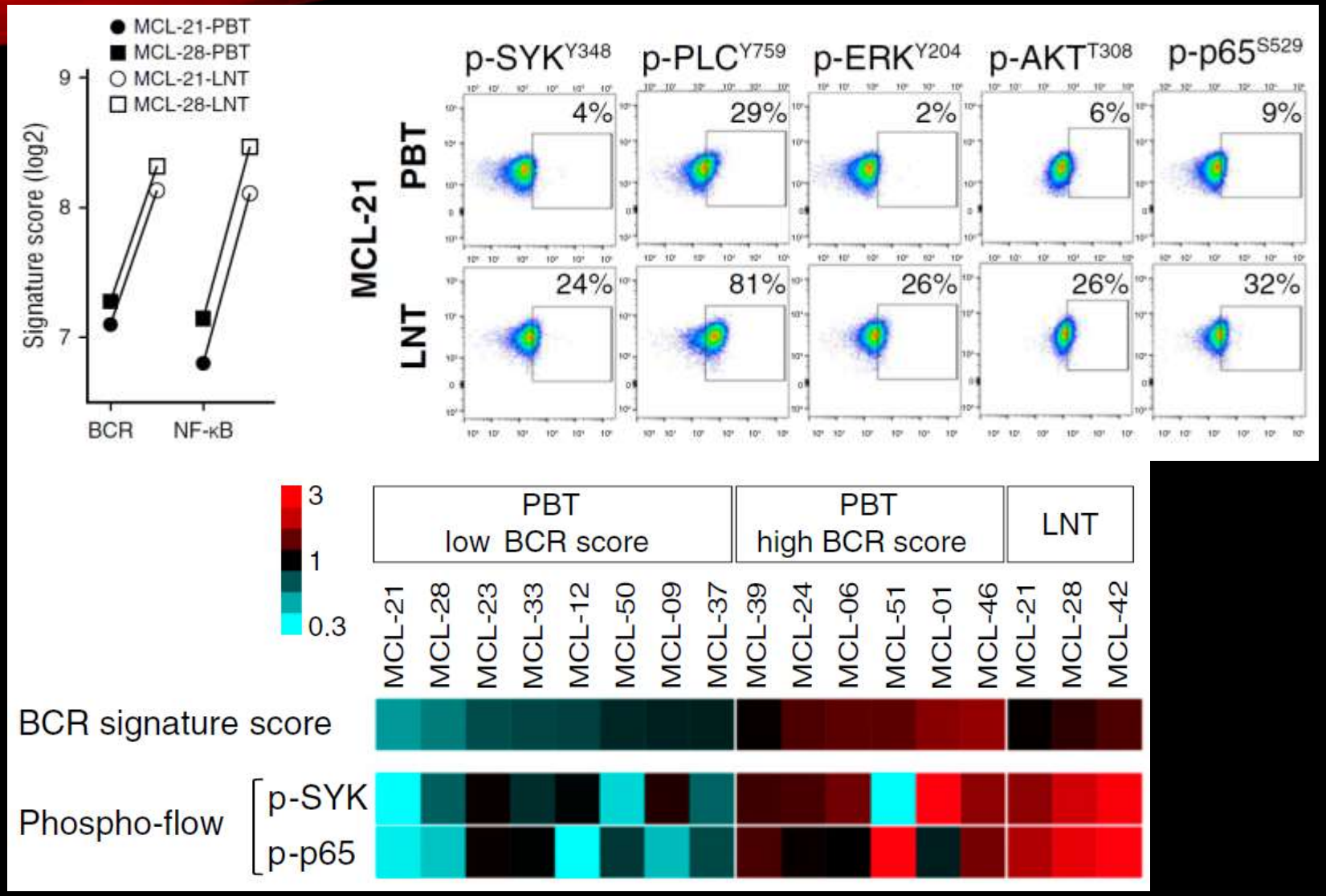
MCL primary tissues





Pighi et al. 2011

Pathogenic role of B-cell receptor signaling and canonical NF-κB activation in mantle cell lymphoma



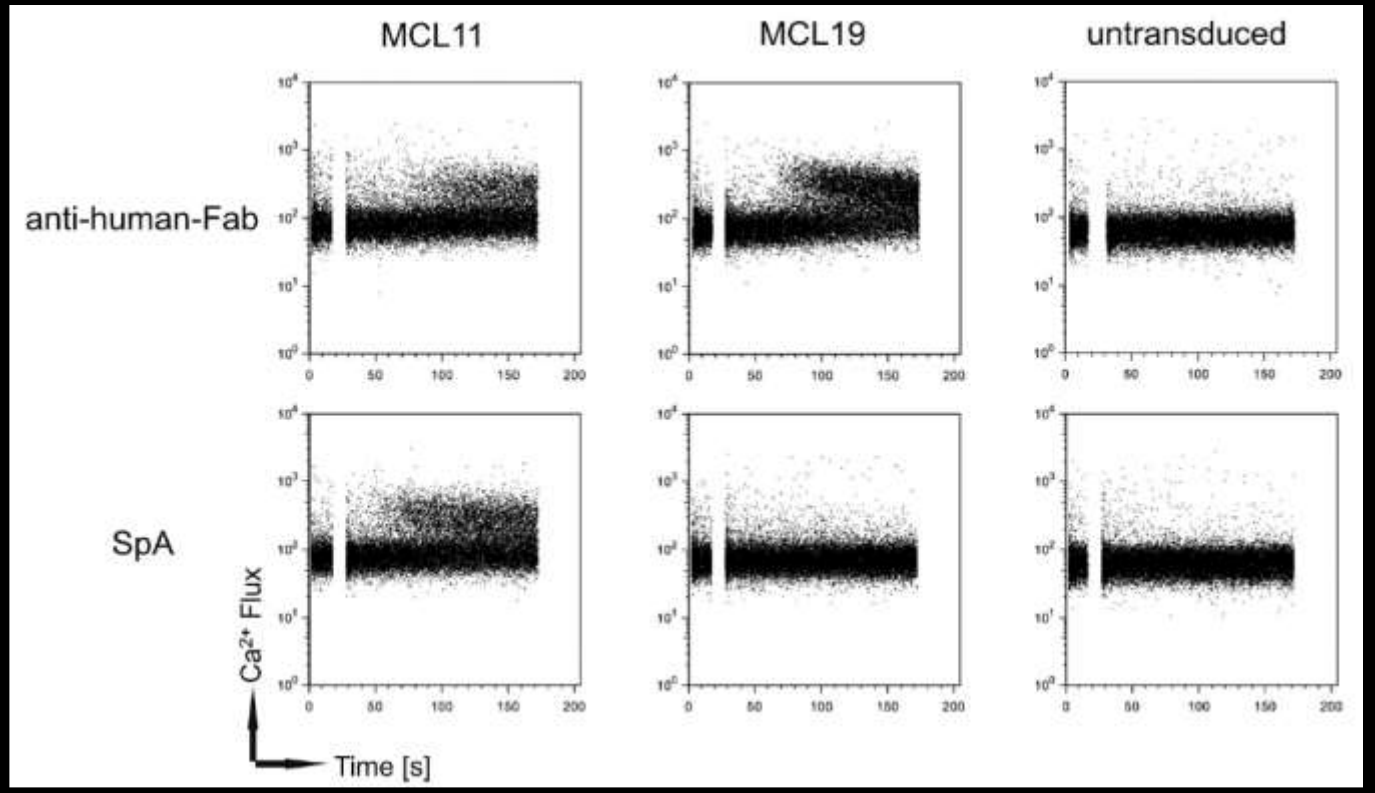
Saba et al.

BLOOD, 7 JULY 2016 • VOLUME 128, NUMBER 1

SUPERANTIGENI – S.AUREUS PROTEIN A MOTIF

A

	Motif	G	S	R/K	K/I/T	Y	K	G	R	T	S	Q	N/G	S
	IGHV-gene	HFR1			HCDR2	HFR3								
Sample	segment	16	18	20	65	67	72	74	75	77	79	90	92	93
MCL23	IGHV3-9	G	S	R	I	Y	K	G	R	T	S	Q	N	S
MCL1	IGHV3-21	G	S	R	I	Y	K	G	R	T	S	Q	N	S
MCL8	IGHV3-21	G	S	R	I	Y	K	G	R	T	S	Q	N	S
MCL11	IGHV3-21	G	S	R	I	Y	K	G	R	T	S	Q	N	S
MCL20	IGHV3-21	G	S	R	I	Y	K	G	R	T	S	Q	N	S
MCL28	IGHV3-21	G	S	R	I	Y	K	G	R	T	S	Q	N	S
MCL2	IGHV3-23	G	S	R	T	Y	K	G	R	T	S	Q	N	S
MCL10	IGHV3-23	G	S	R	T	Y	K	G	R	T	S	Q	N	S
MCL22	IGHV3-30	G	S	R	K	Y	K	G	R	T	S	Q	N	S
MCL13	IGHV3-48	G	S	R	I	Y	K	G	R	T	S	Q	N	S
MCL5	IGHV3-49	G	S	R	T	Y	K	G	R	T	S	Q	N	S
MCL31	IGHV3-74	G	S	R	T	Y	K	G	R	T	S	Q	N	S
FL6	IGHV3-11	G	S	R	T	Y	K	G	R	T	S	Q	N	S
FL10	IGHV3-11	G	S	R	T	Y	E	G	R	F	S	Q	N	N
FL8	IGHV3-11	G	S	R	T	Y	K	G	R	T	S	Q	N	S
FL101	IGHV3-15	G	S	R	T	Y	R	G	R	T	S	H	S	N
FL11	IGHV3-23	G	S	R	T	Y	K	G	R	S	S	H	N	R
FL5	IGHV3-53	G	S	R	T	Y	K	G	R	T	S	Q	N	T
CLL149	IGHV3-7	G	S	R	K	F	K	G	R	S	S	Q	N	S
CLL172	IGHV3-7	G	T	R	K	Y	R	G	R	T	S	Q	N	S
CLL024	IGHV3-9	G	S	R	I	Y	K	G	R	T	S	Q	N	S
CLL83	IGHV3-21	G	S	R	M	Y	K	G	R	T	S	Q	N	S
CLL173	IGHV3-23	G	A	R	T	Y	E	G	R	T	S	Q	N	S
CLL003	IGHV3-30	G	S	R	K	Y	K	G	R	T	S	Q	N	S
CLL145	IGHV3-30	G	S	R	K	Y	K	G	R	T	S	Q	N	S



Fichtner et al. Haematologica. 2016 Sep;101(9):e378-81

LESIONI GENETICHE

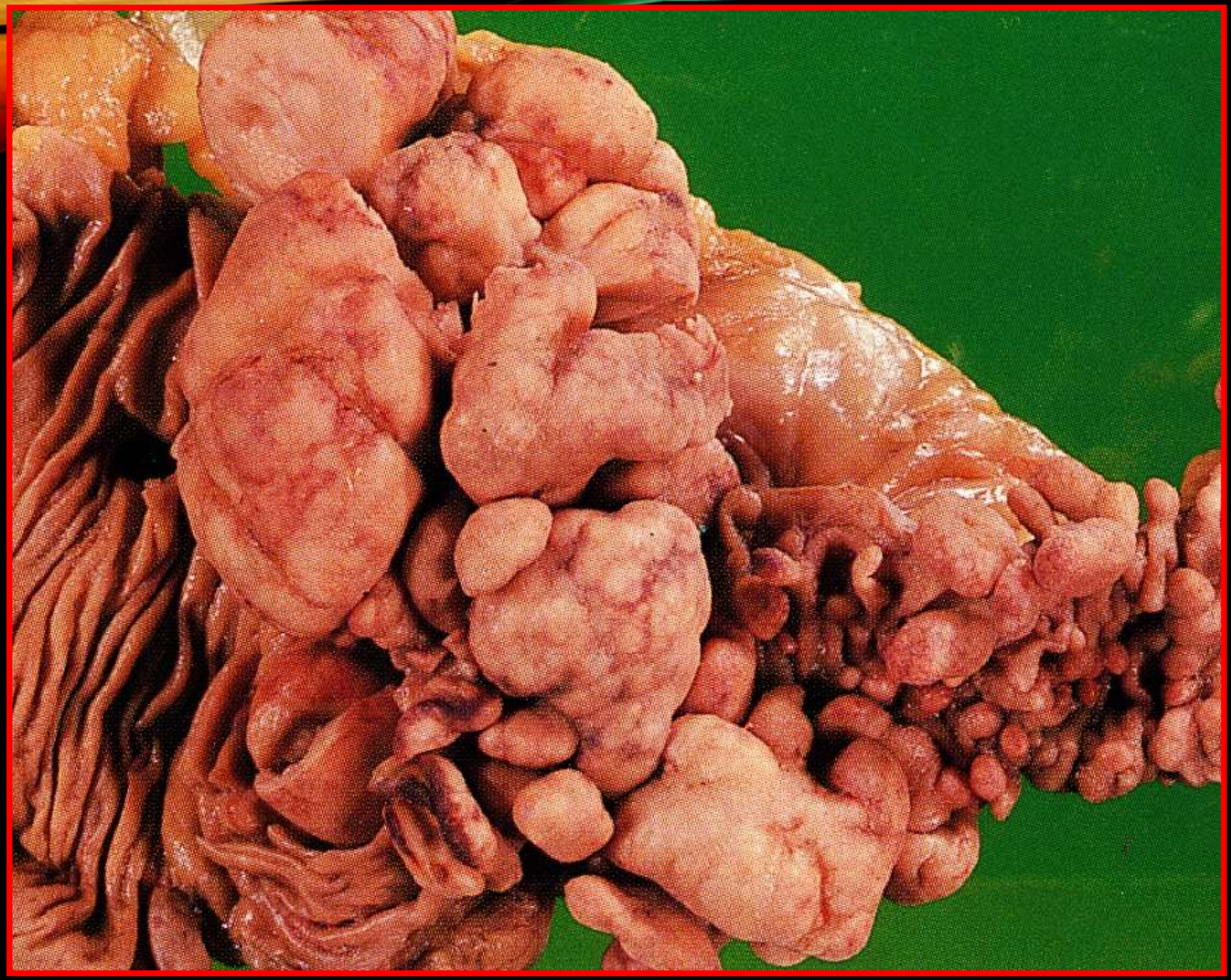
- Elevato numero di lesioni genetiche per caso
- Instabilità genetica
- Frequente cromotripsi/cromoplessia
- Traslocazione di MYC possibile ma rara
- MYC CNA relativamente più frequenti

LESIONI GENETICHE RICORRENTI

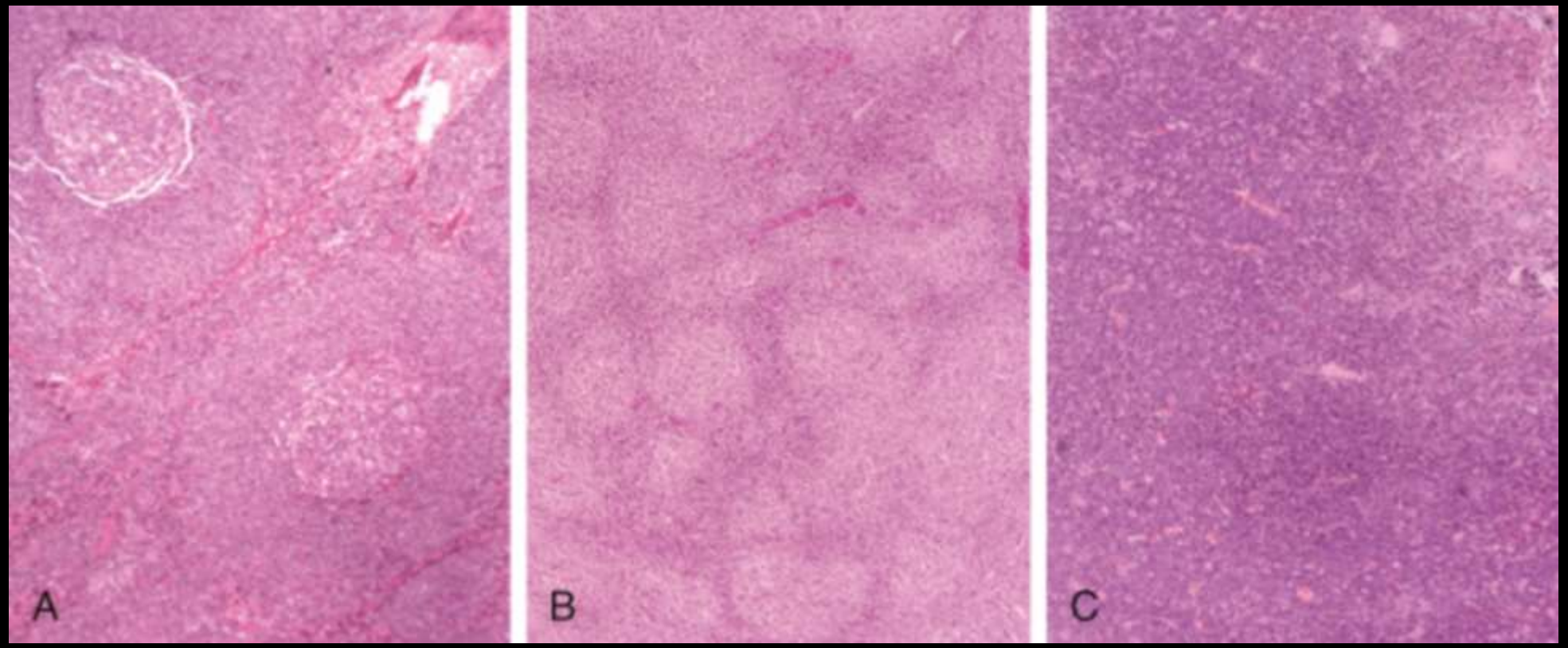
	Naive MCL	Memory MCL
ATM	55%	0%
TP53	25%	25%
CDKN2A deletion	20%	0%
CCND1	18%	**86% (SHM)**
KMT2D	18%	0%
NSD2/WHSC1	15%	0%
UBR5	14%	0%
BIRC3	7%	7%
NOTCH2	6%	4%
NOTCH1	4%	0%
TLR2	0%	**3%**

Puente, Jares and Campo 2018

MORFOLOGIA

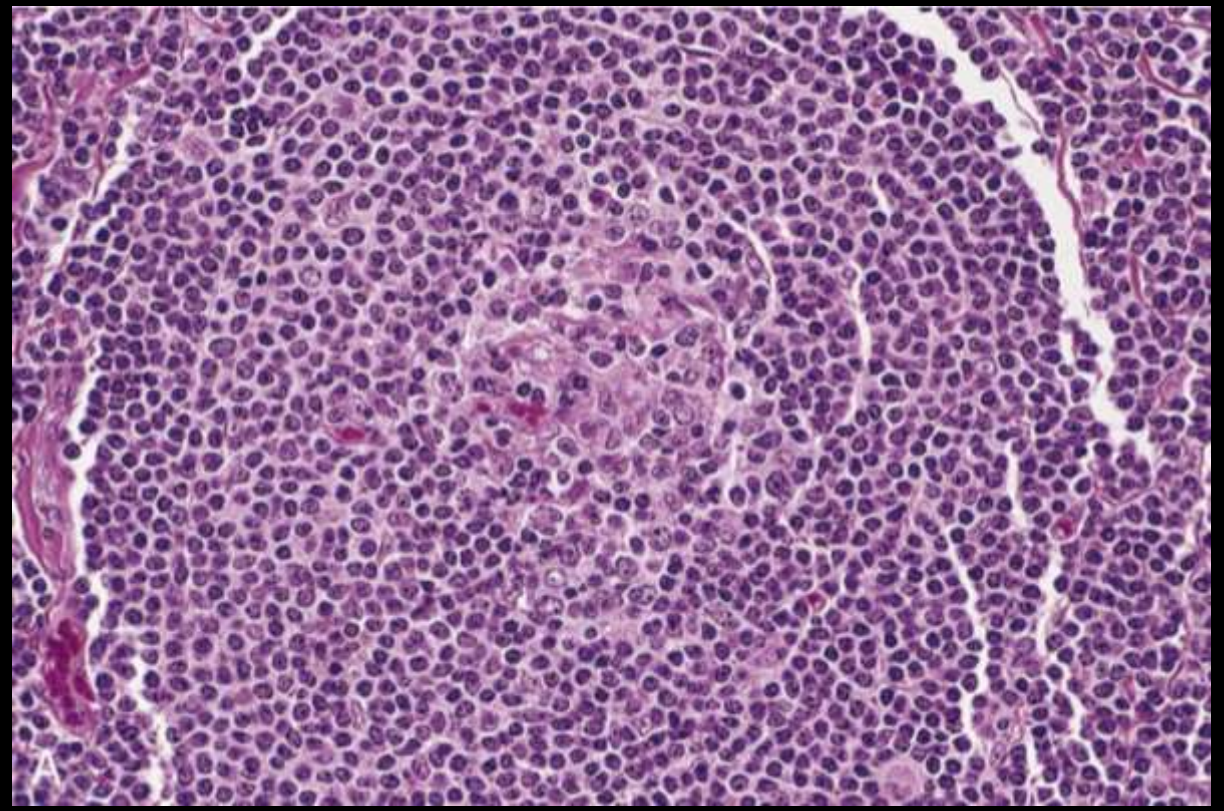


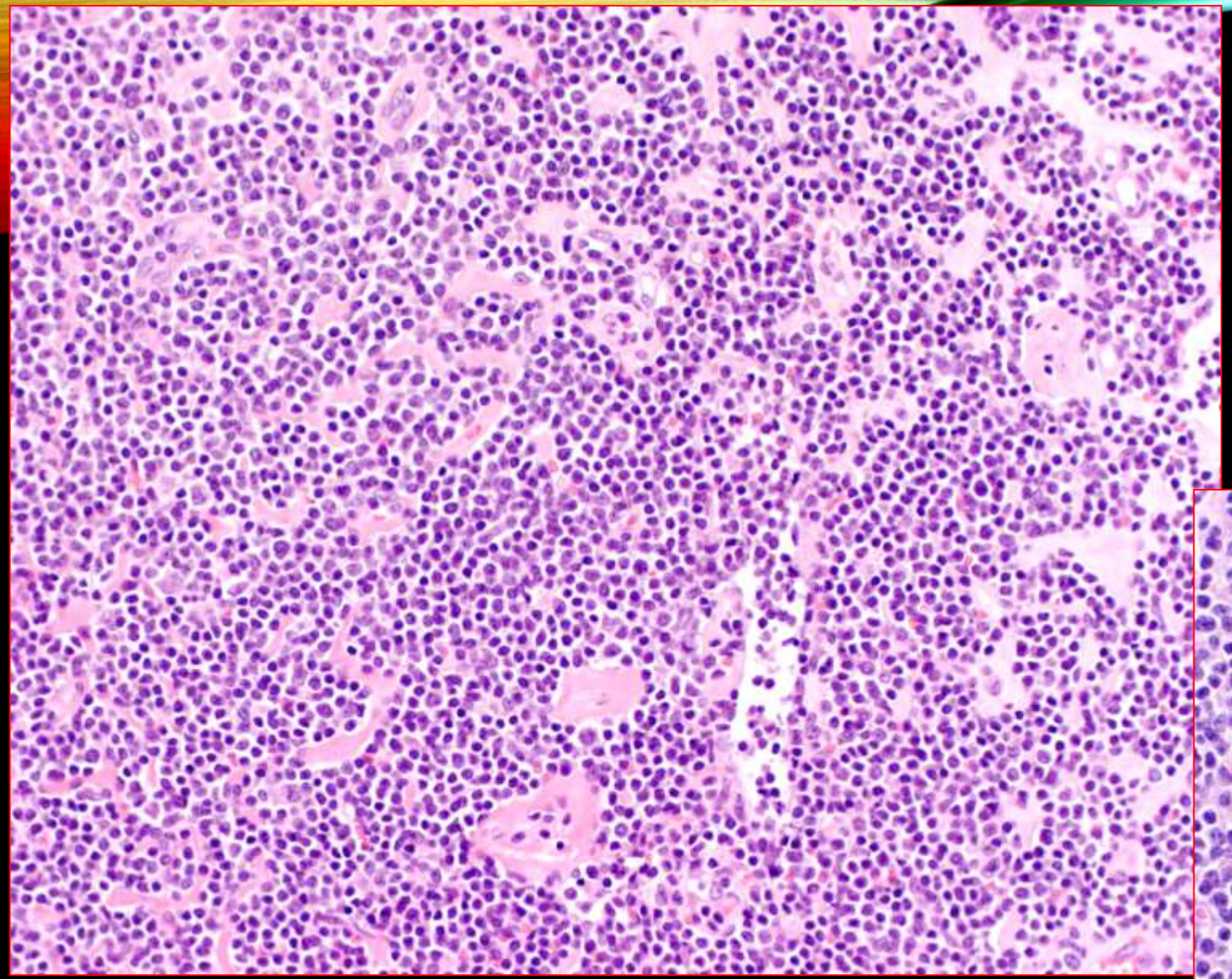
PATTERN LINFONODALI

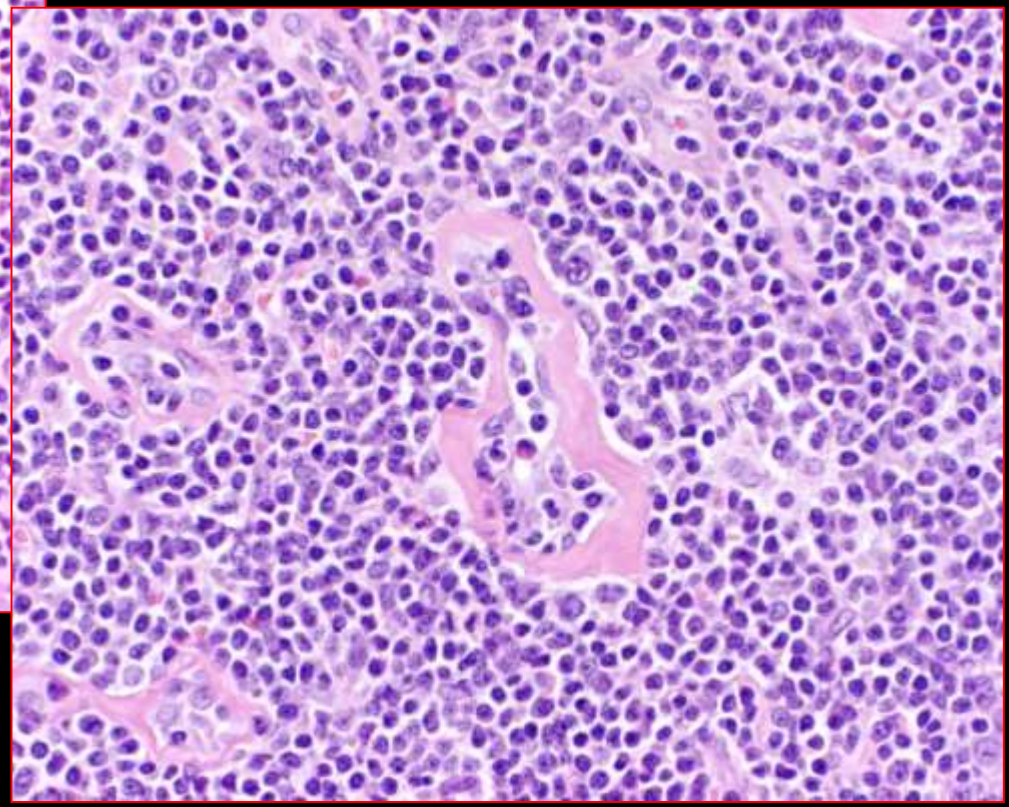


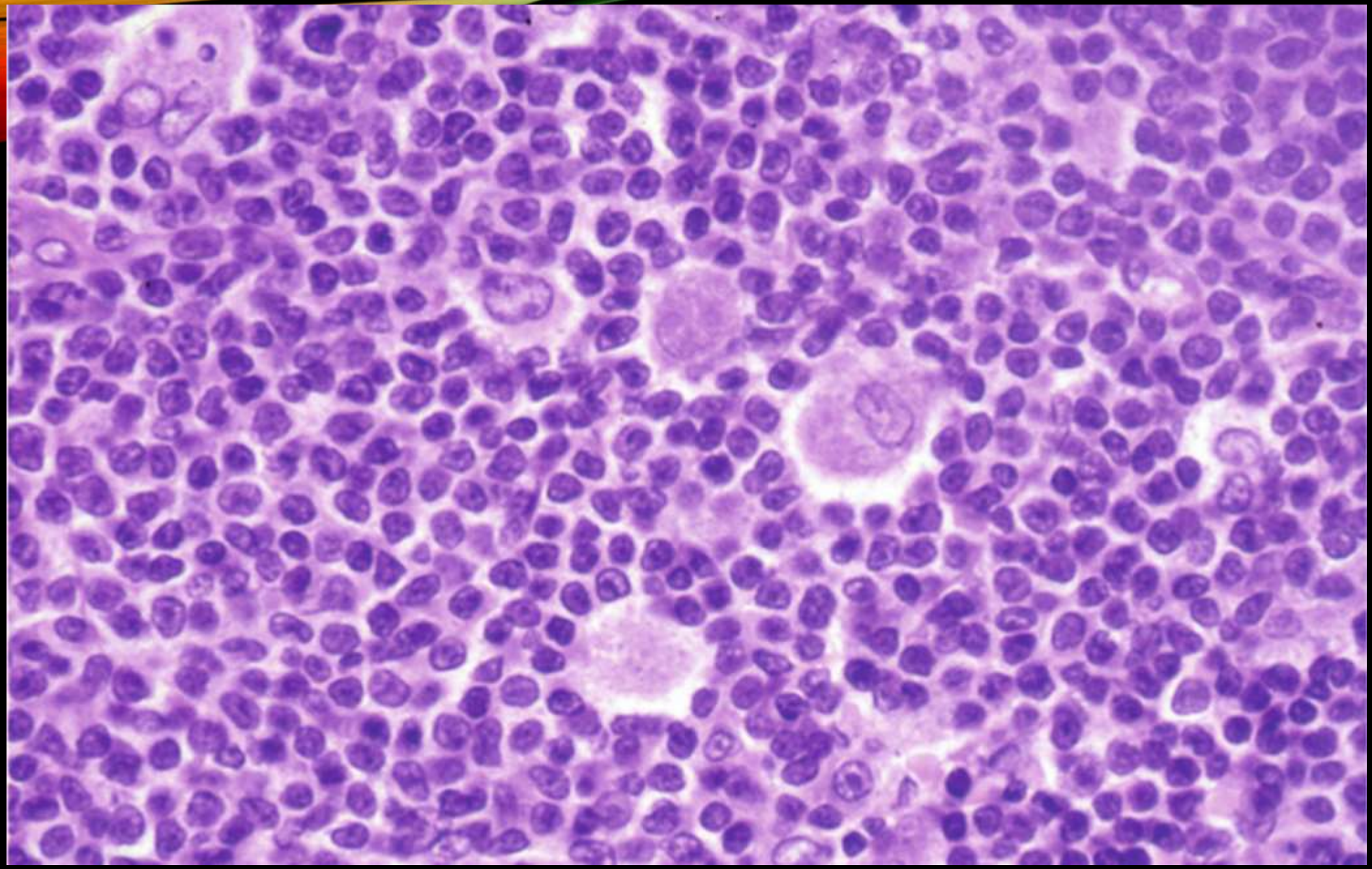
MORFOLOGIA CLASSICA

- Proliferazione nodulare o diffusa
- Elementi medio-piccoli, monotoni



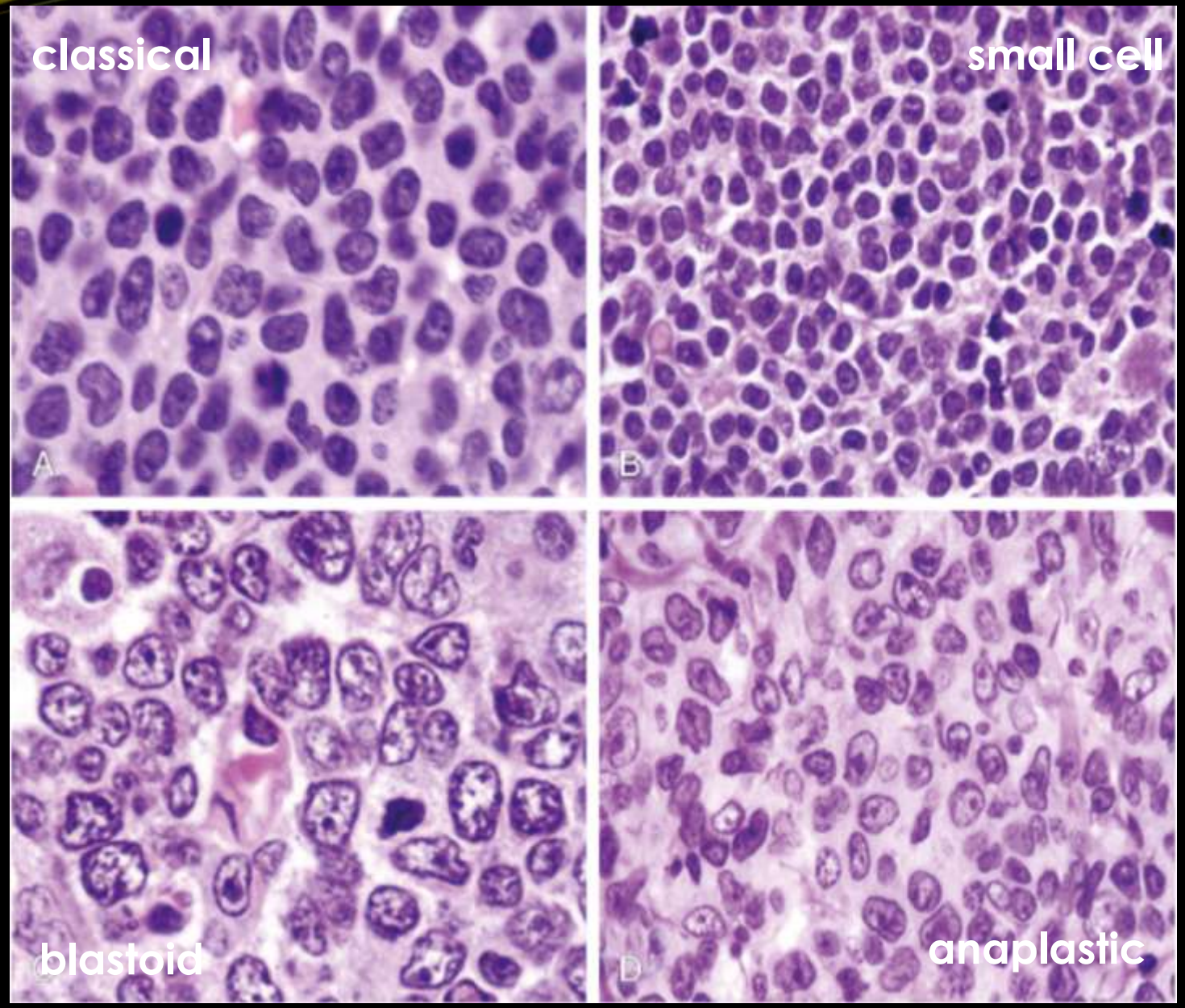






MORFOLOGIA VARIANTE

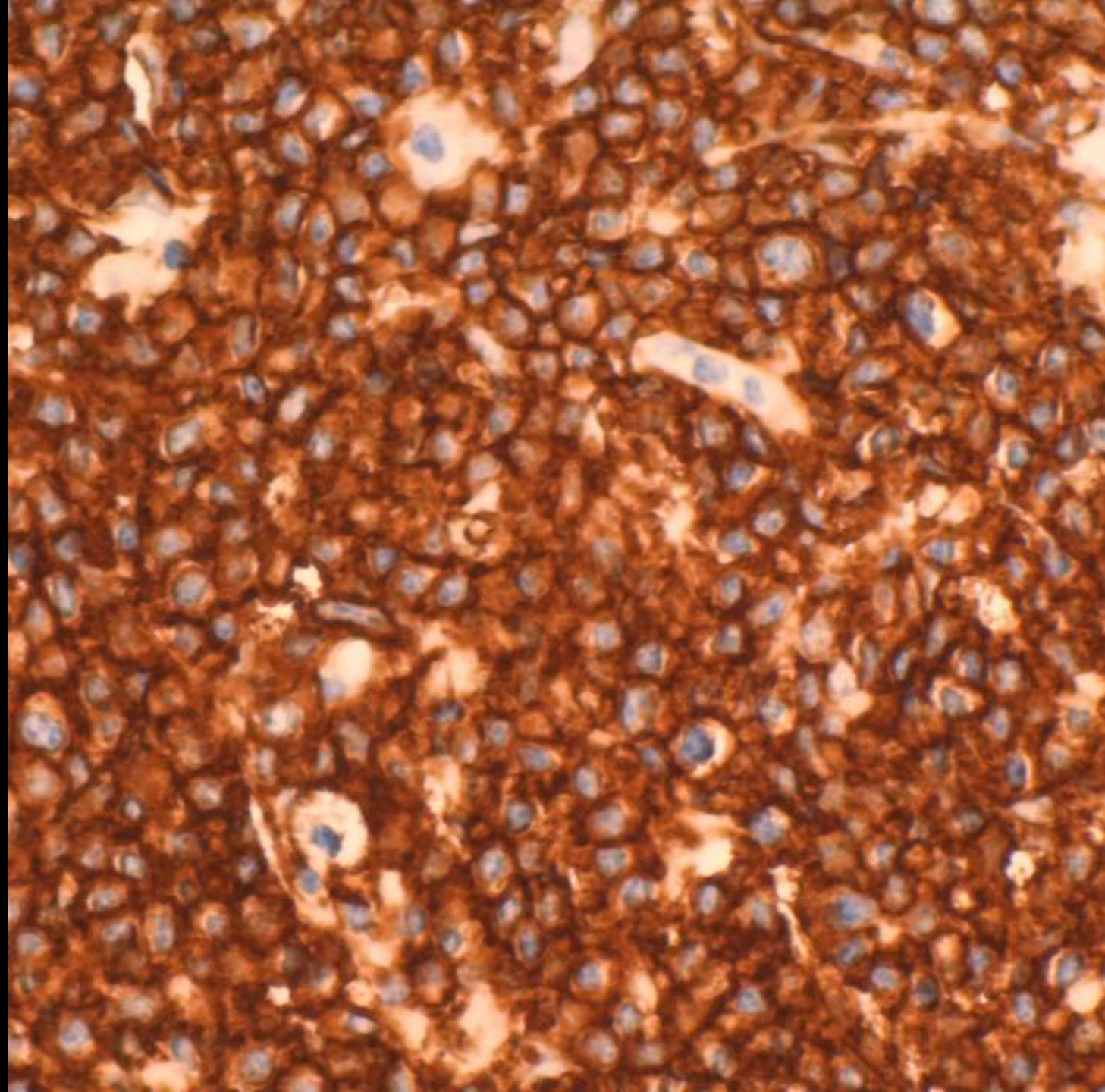
- Piccole cellule
- Blastoide
- Anaplastico
- (Monocitoide)



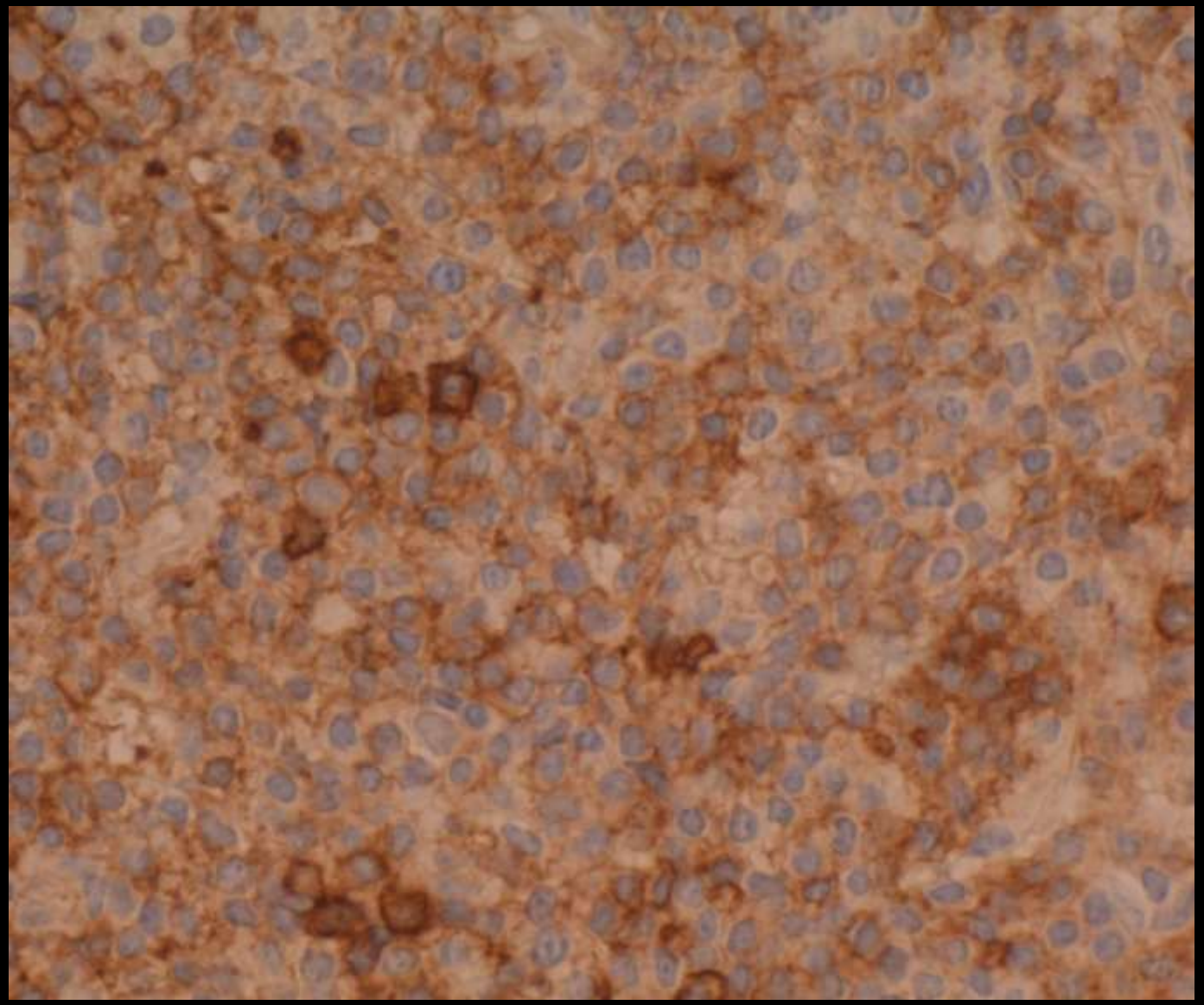
IMMUNOFENOTIPO

- Marcatori B positivi (alta intensità in citometria a flusso)
- CD5 positivo
- Ciclina D1 positivo (90%)
- SOX11 positivo (marcatore più specifico)
- LEF1-negativo (DD B-CLL)

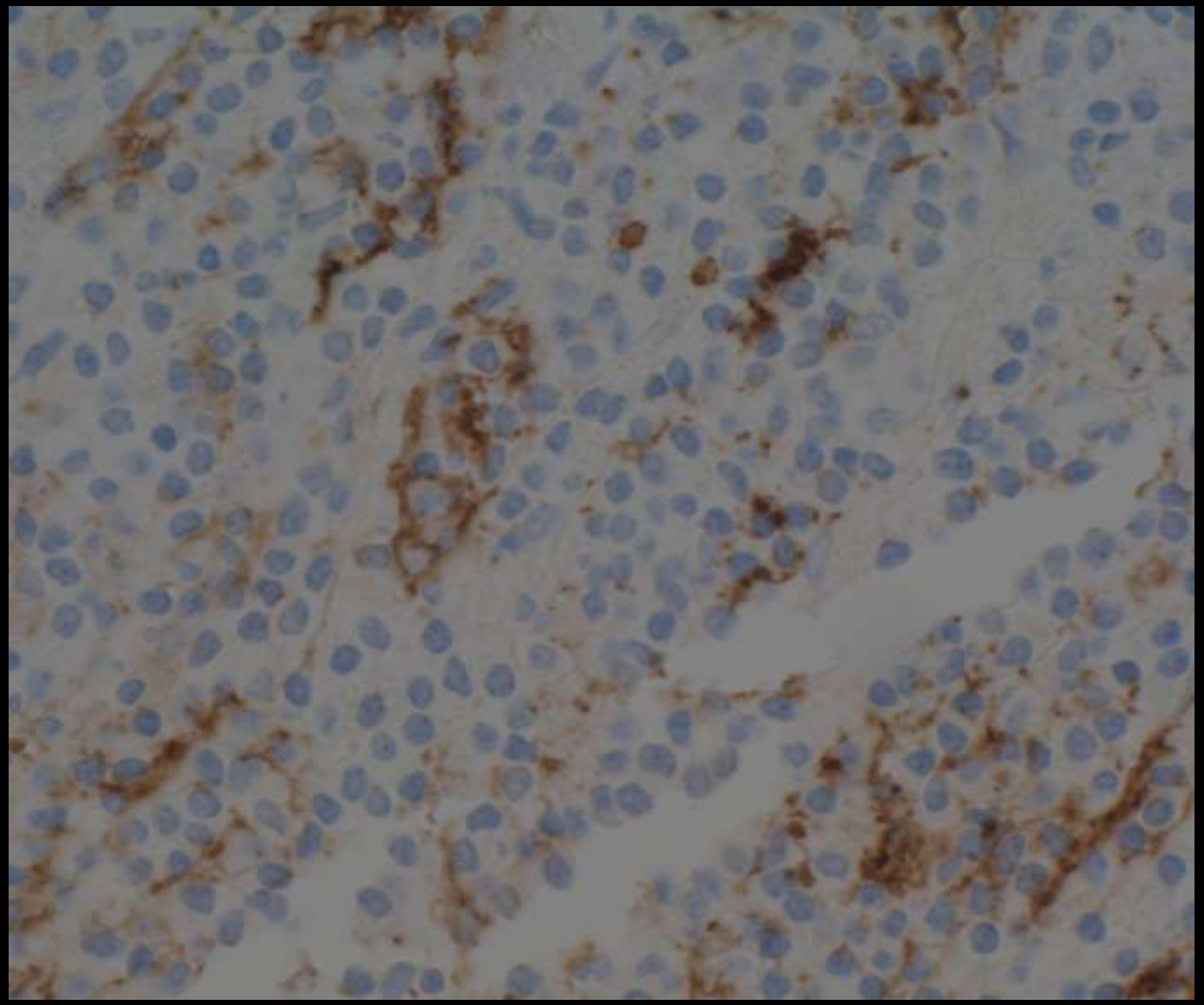
CD20



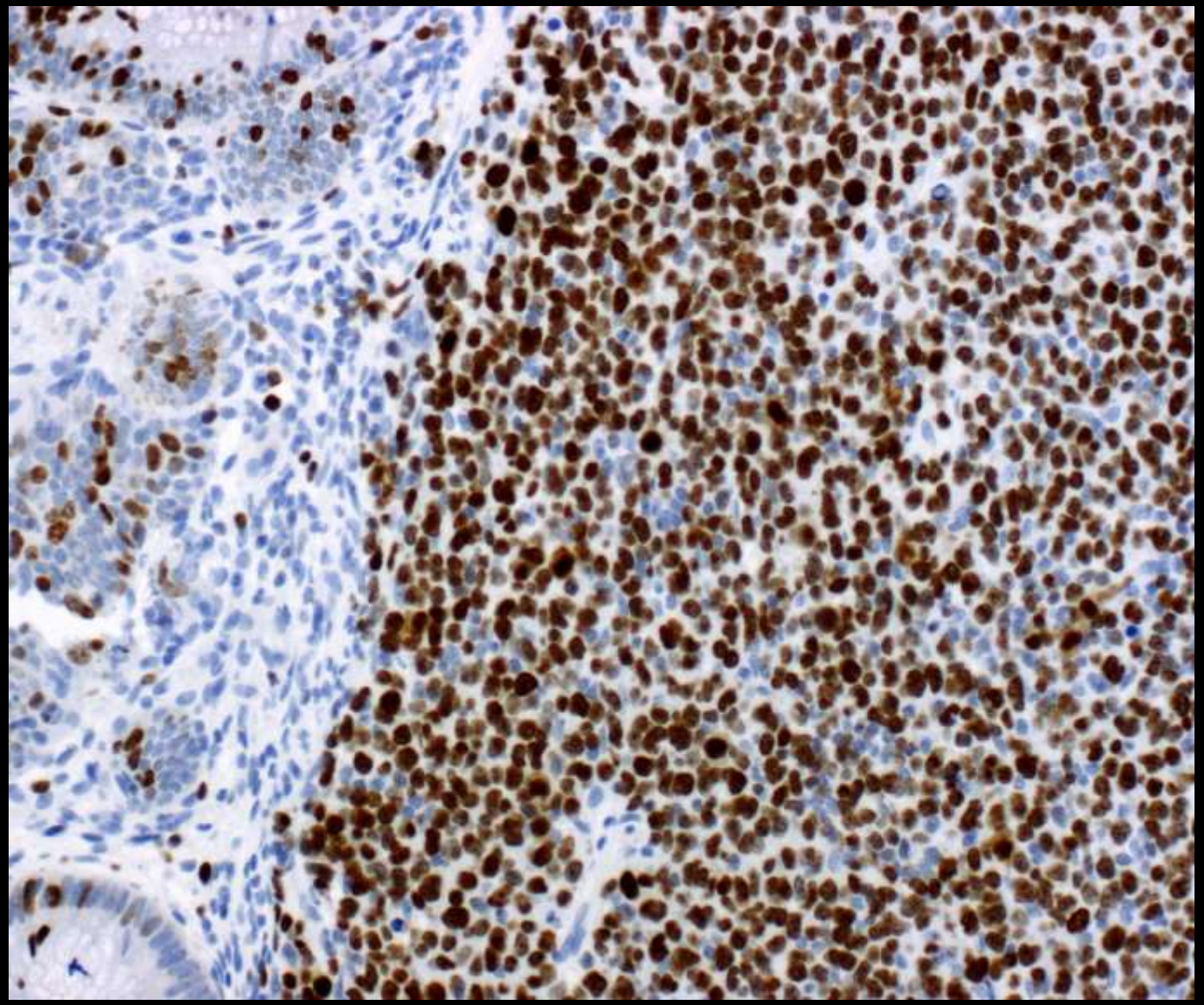
CD5



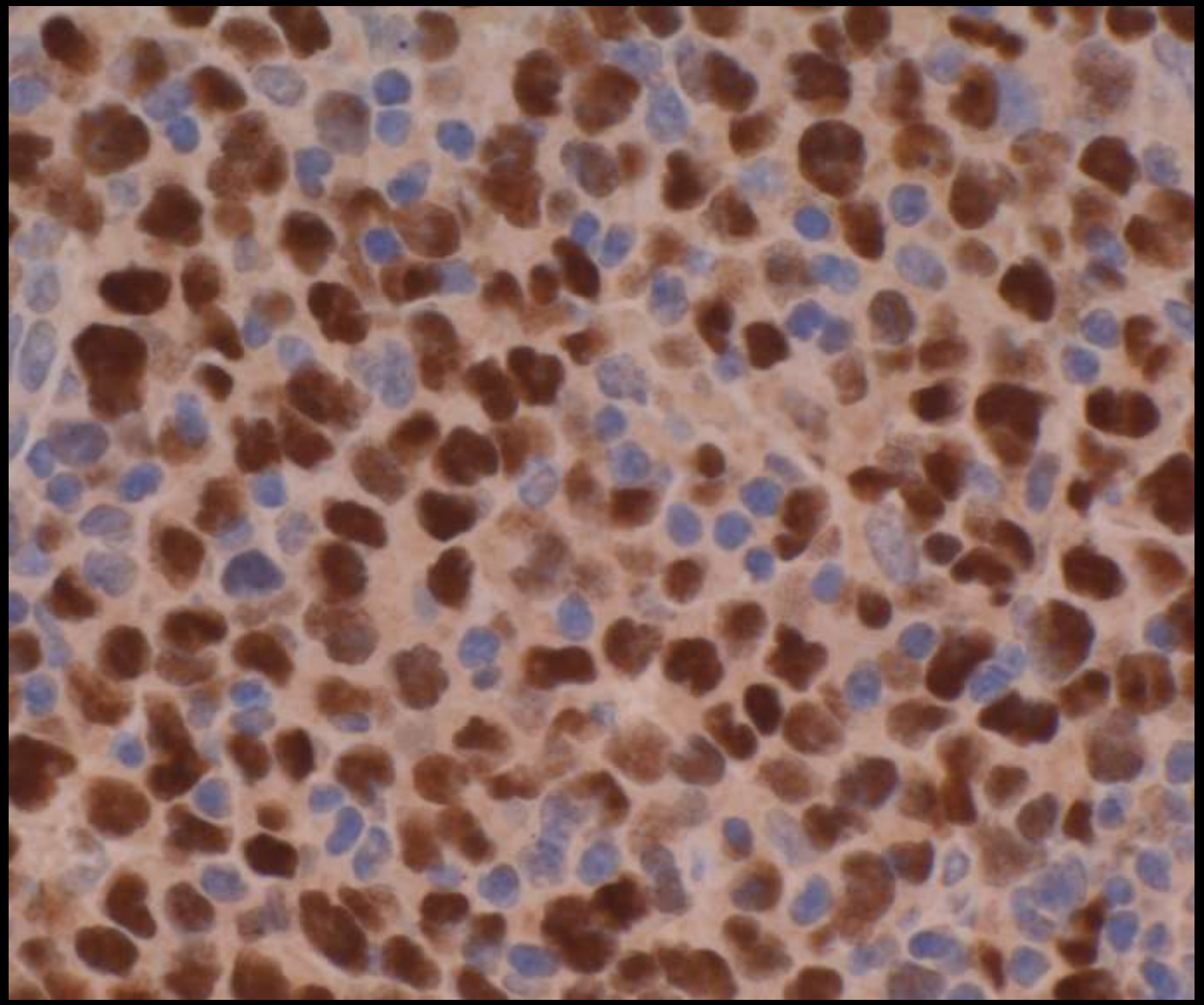
CD23



CCND1



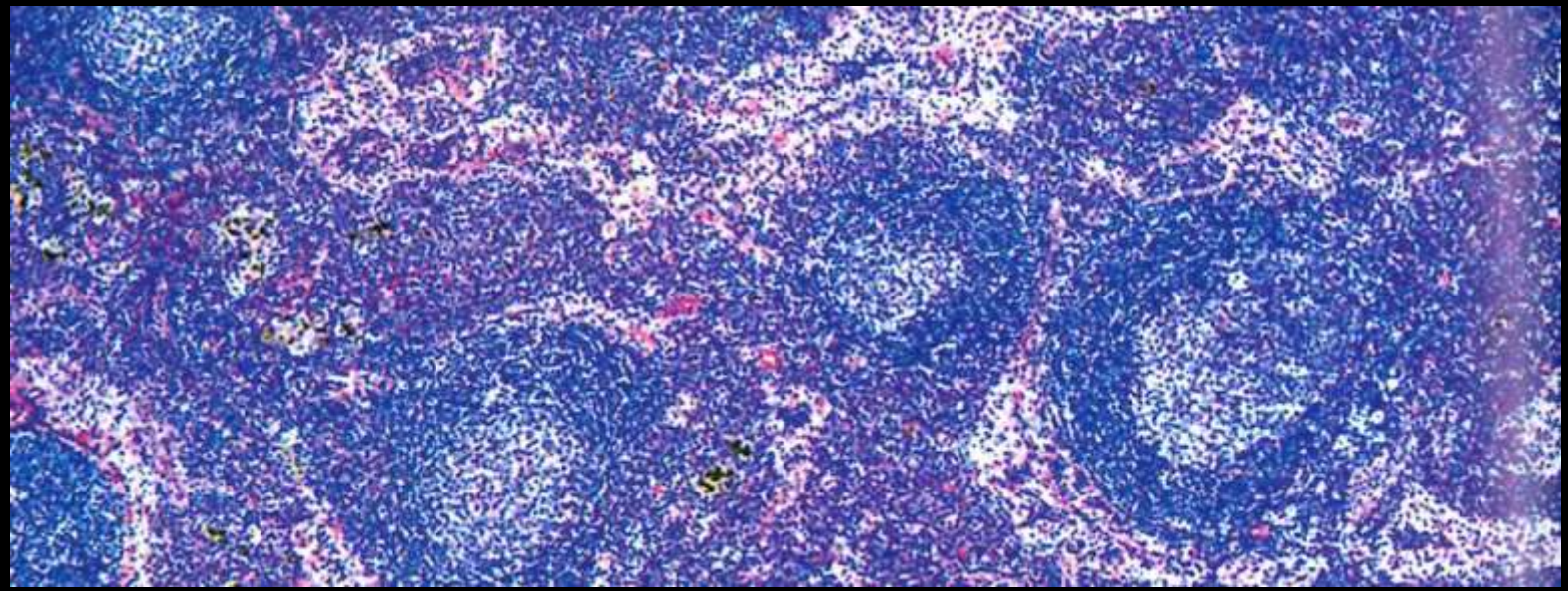
SOX11



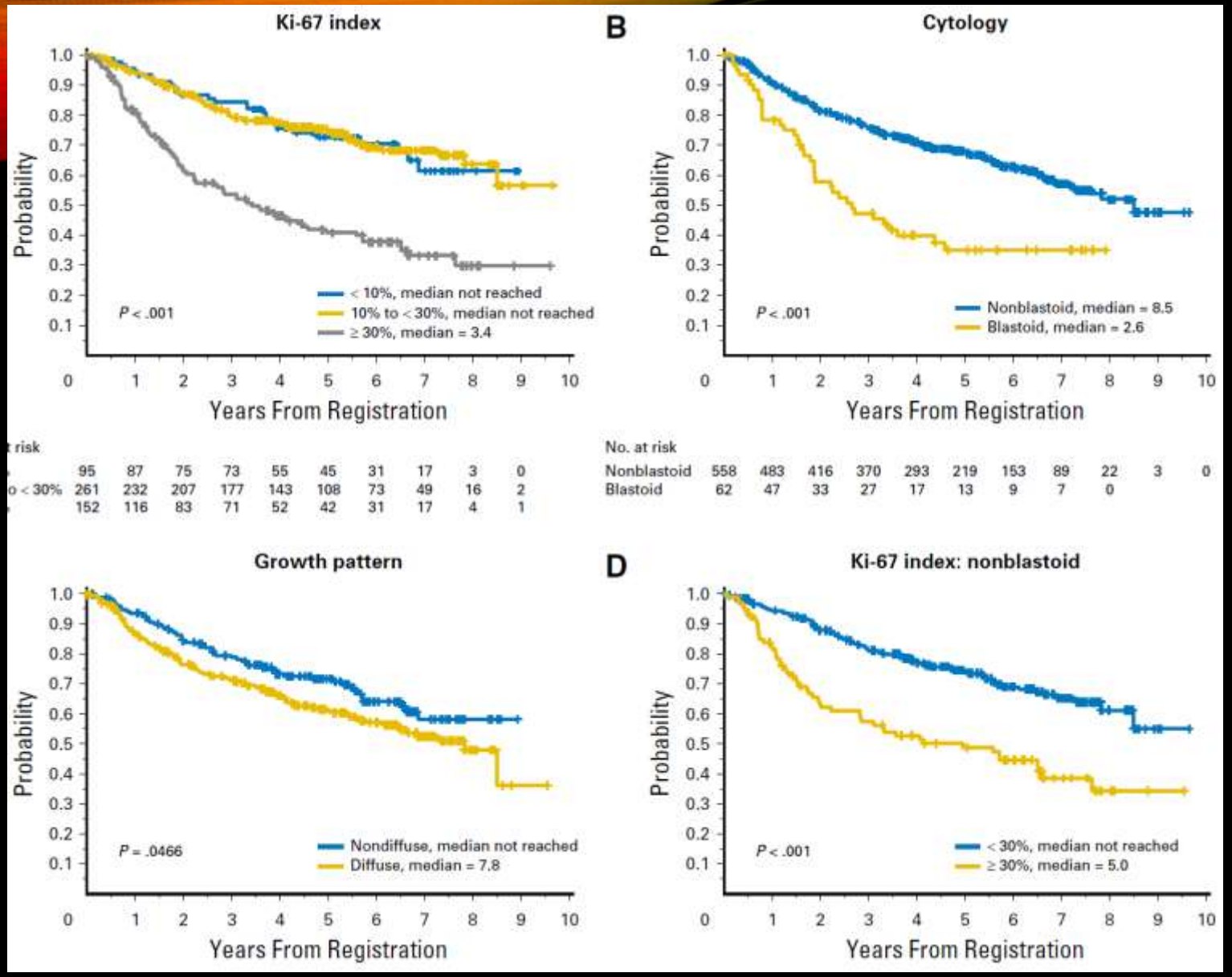
FATTORI PROGNOSTICI PATOLOGICI

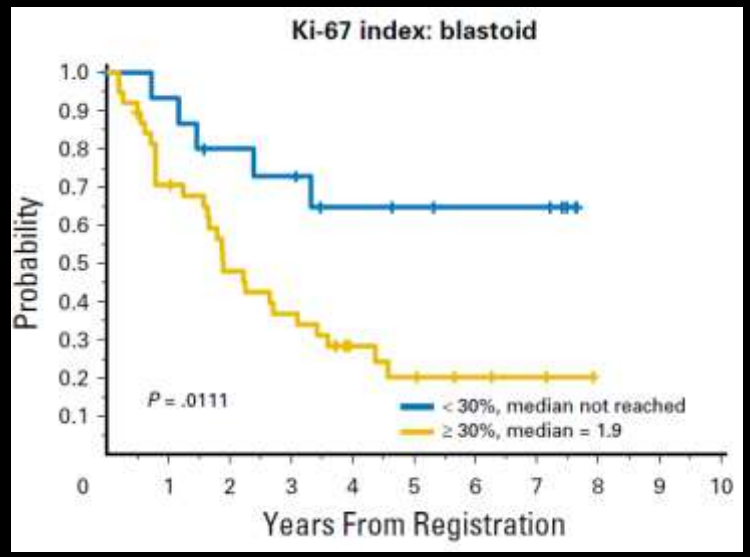
VARIANTI MORFOLOGICHE

- Blastoide (prognosi peggiore, forse non indipendente)
- A piccole cellule (migliore, correlata a variante leucemica non-nodale)
- Pattern mantellare (migliore)



KI-67

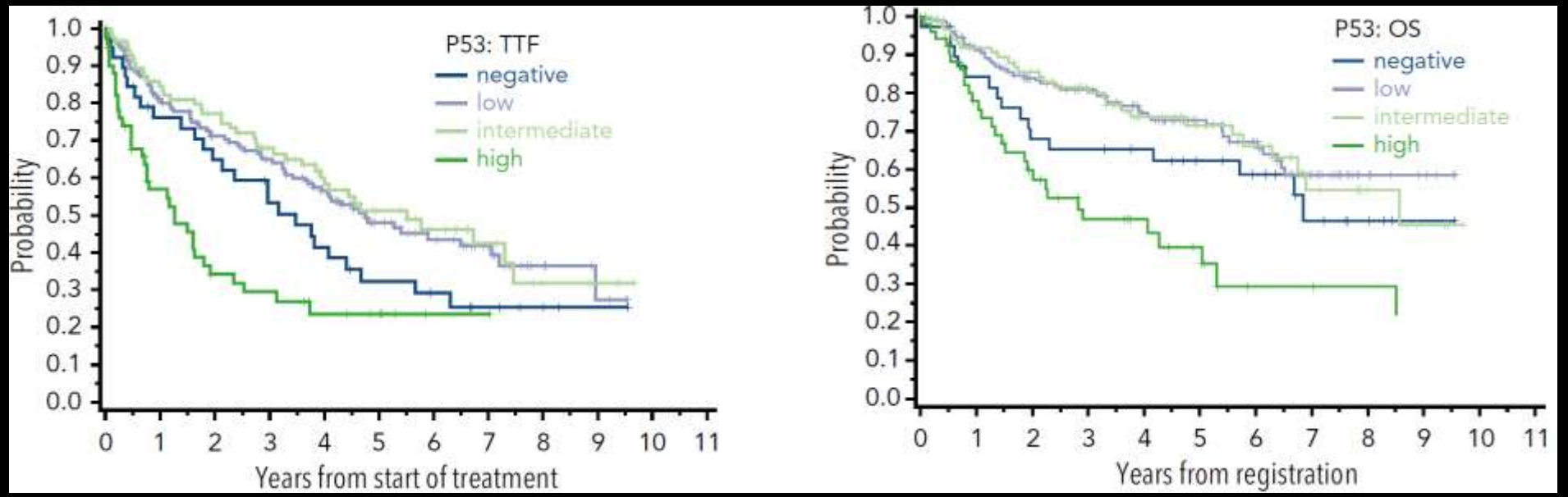




Hoster et al.

J Clin Oncol 34:1386-1394. © 2016

TP53 EXPRESSION



Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network

Sietse M. Aukema,[1,*] Eva Hoster,[2,3,*] Andreas Rosenwald,[4,5] Danielle Canoni,[6] Marie-Hélène Delfau-Larue,[7-9] Grzegorz Rymkiewicz,[10] Christoph Thorns,[11] Sylvia Hartmann,[12] Hanneke Kluin-Nelemans,[13] Olivier Hermine,[14,15] Martin Dreyling,[2,*] and Wolfram Klapper[1,*]

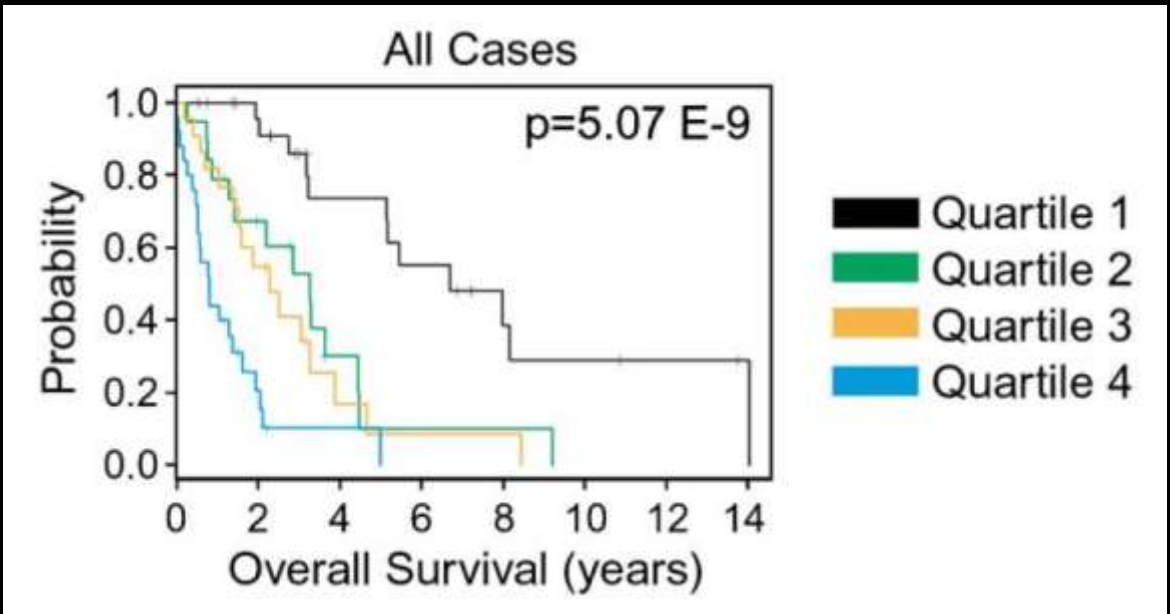
blood® 25 JANUARY 2018 | VOLUME 131, NUMBER 4

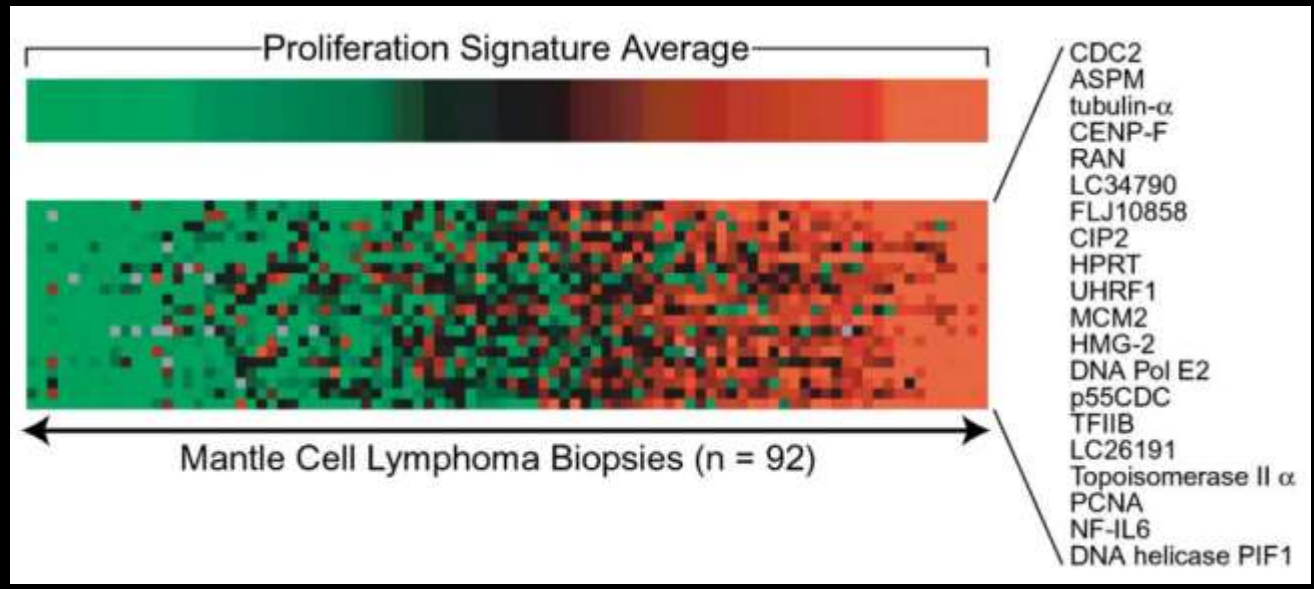
FATTORI PROGNOSTICI MOLECOLARI

PROLIFERATION SIGNATURE

The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma

Andreas Rosenwald,[1,2] George Wright,[1,5] Adrian Wiestner,[1,2] Wing C. Chan,[1,9] Joseph M. Connors,[1,18] Elias Campo,[1,8] Randy D. Gascoyne,[1,18] Thomas M. Grogan,[1,13,17] H. Konrad Muller-Hermelink,[1,19] Erlend B. Smeland,[1,22] Michael Chiorazzi,[1,2] Jena M. Giltnane,[1,2] Elaine M. Hurt,[1,2] Hong Zhao,[1,2] Lauren Averett,[1,2] Sarah Henrickson,[1,2] Liming Yang,[1,7] John Powell,[1,7] Wyndham H. Wilson,[1,3] Elaine S. Jaffe,[1,4] Richard Simon,[1,5] Richard D. Klausner,[1,6] Emilio Montserrat,[1,8] Francesc Bosch,[1,8] Timothy C. Greiner,[1,9] Dennis D. Weisenburger,[1,9] Warren G. Sanger,[1,10] Bhavana J. Dave,[1,9] James C. Lynch,[1,11] Julie Vose,[1,12] James O. Armitage,[1,12] Richard I. Fisher,[1,16,17] Thomas P. Miller,[1,14,17] Michael LeBlanc,[1,15,17] German Ott,[1,19] Stein Kvaloy,[1,20] Harald Holte,[1,20] Jan Delabie,[1,21] and Louis M. Staudt[1,2,*]





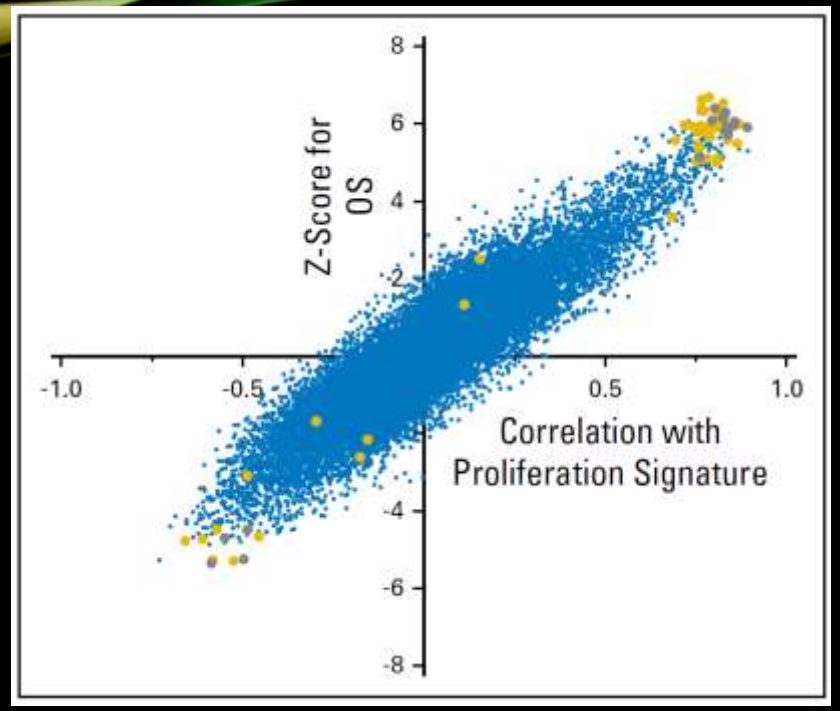
CANCER CELL : FEBRUARY 2003 · VOL. 3

VOLUME 35 · NUMBER 15 · MAY 20, 2017

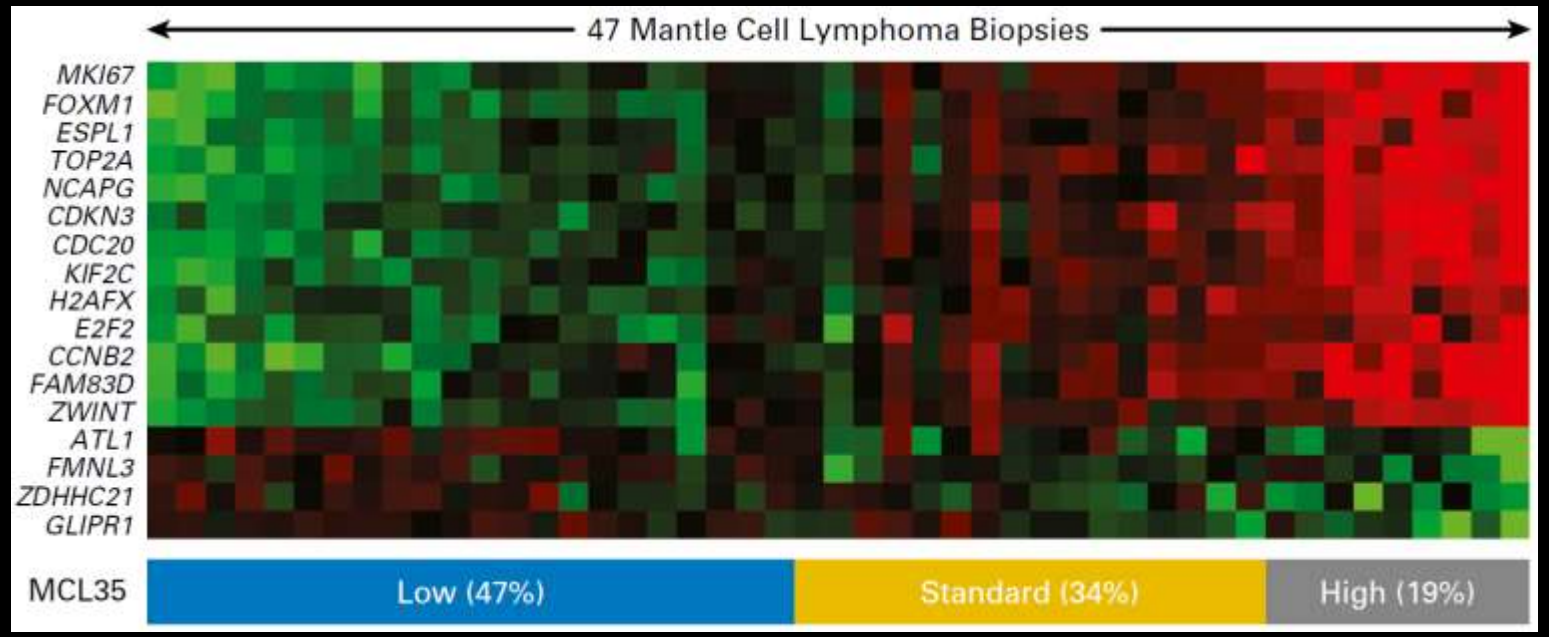
JOURNAL OF CLINICAL ONCOLOGY

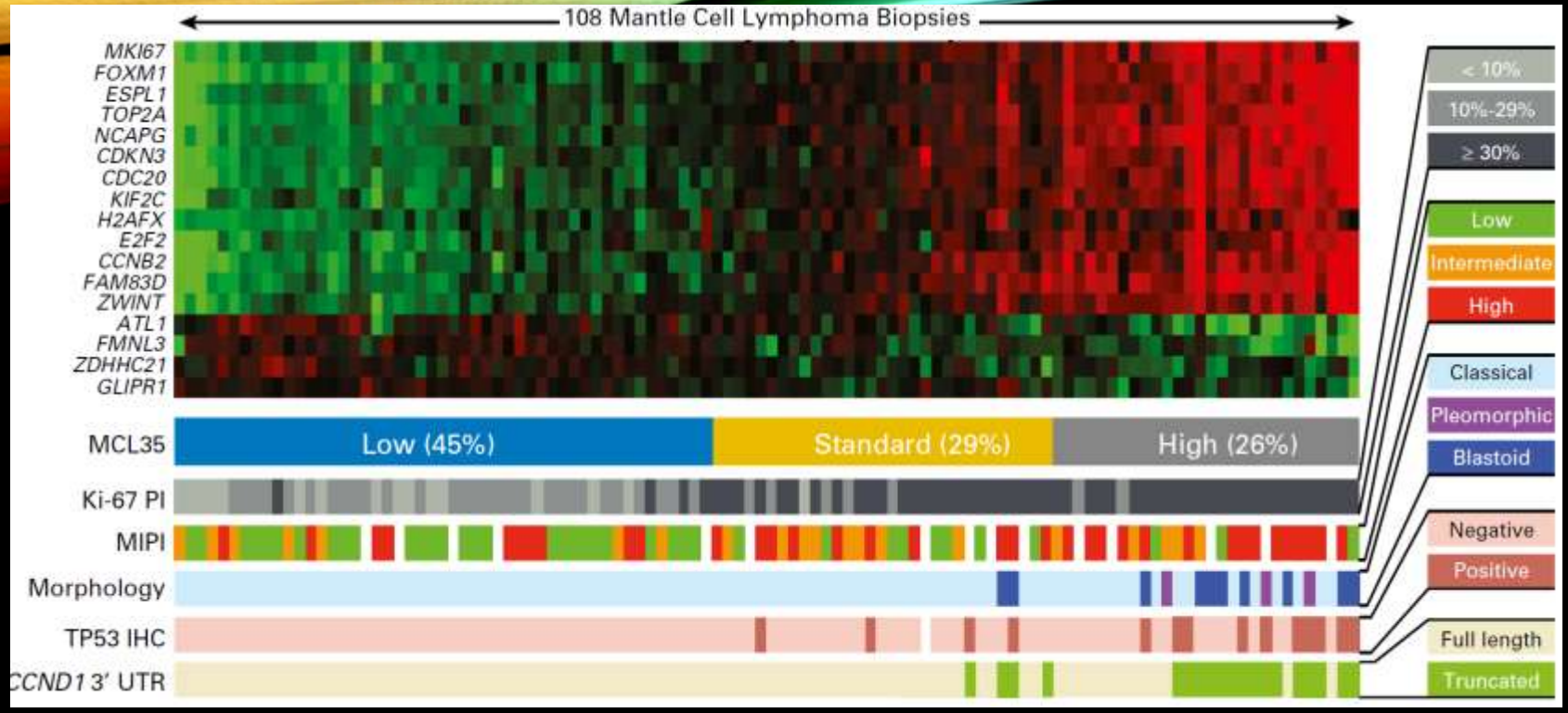
New Molecular Assay for the Proliferation Signature in Mantle Cell Lymphoma Applicable to Formalin-Fixed Paraffin-Embedded Biopsies

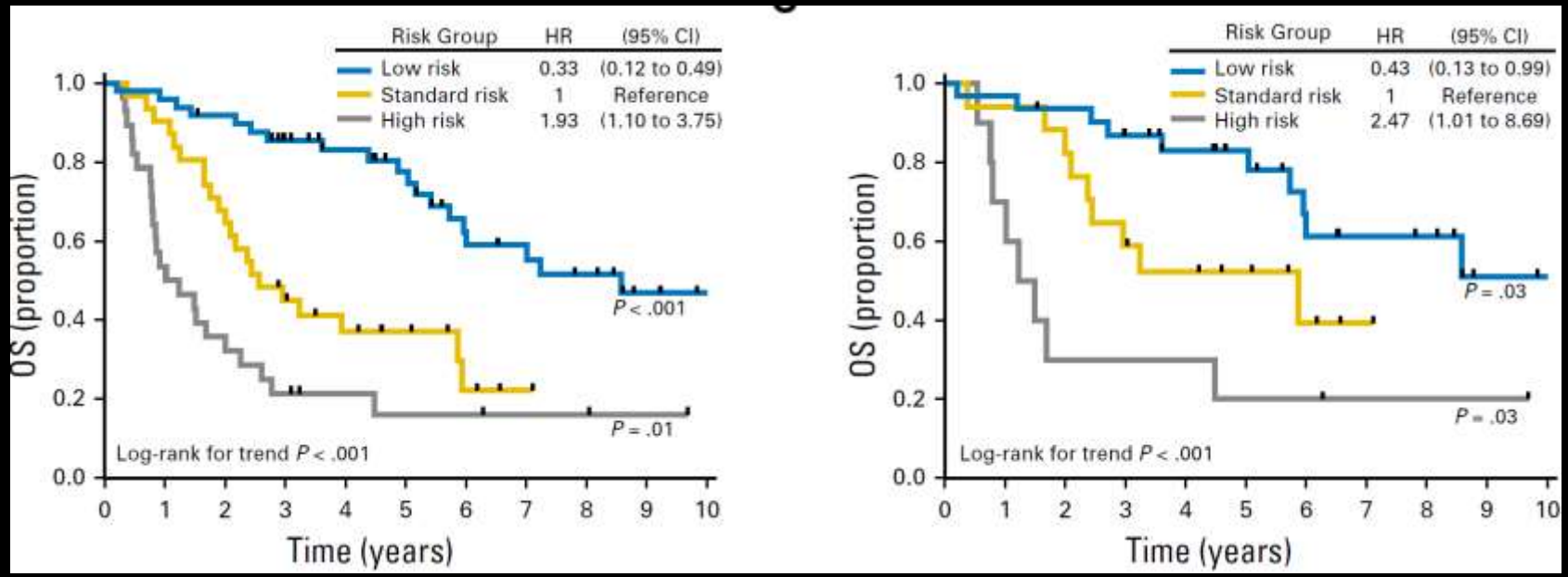
David W. Scott, Pau Abrisqueta, George W. Wright, Graham W. Slack, Anja Mottok, Diego Villa, Pedro Jares, Hilka Rauert-Wunderlich, Cristina Royo, Guillem Clot, Magda Pinyol, Merrill Boyle, Fong Chun Chan, Rita M. Braziel, Wing C. Chan, Dennis D. Weisenburger, James R. Cook, Timothy C. Greiner, Kai Fu, German Ott, Jan Delabie, Erlend B. Smeland, Harald Holte, Elaine S. Jaffe, Christian Steidl, Joseph M. Connors, Randy D. Gascoyne, Andreas Rosenwald, Louis M. Staudt, Elias Campo, and Lisa M. Rimsza, for the Lymphoma/Leukemia Molecular Profiling Project



MCL35



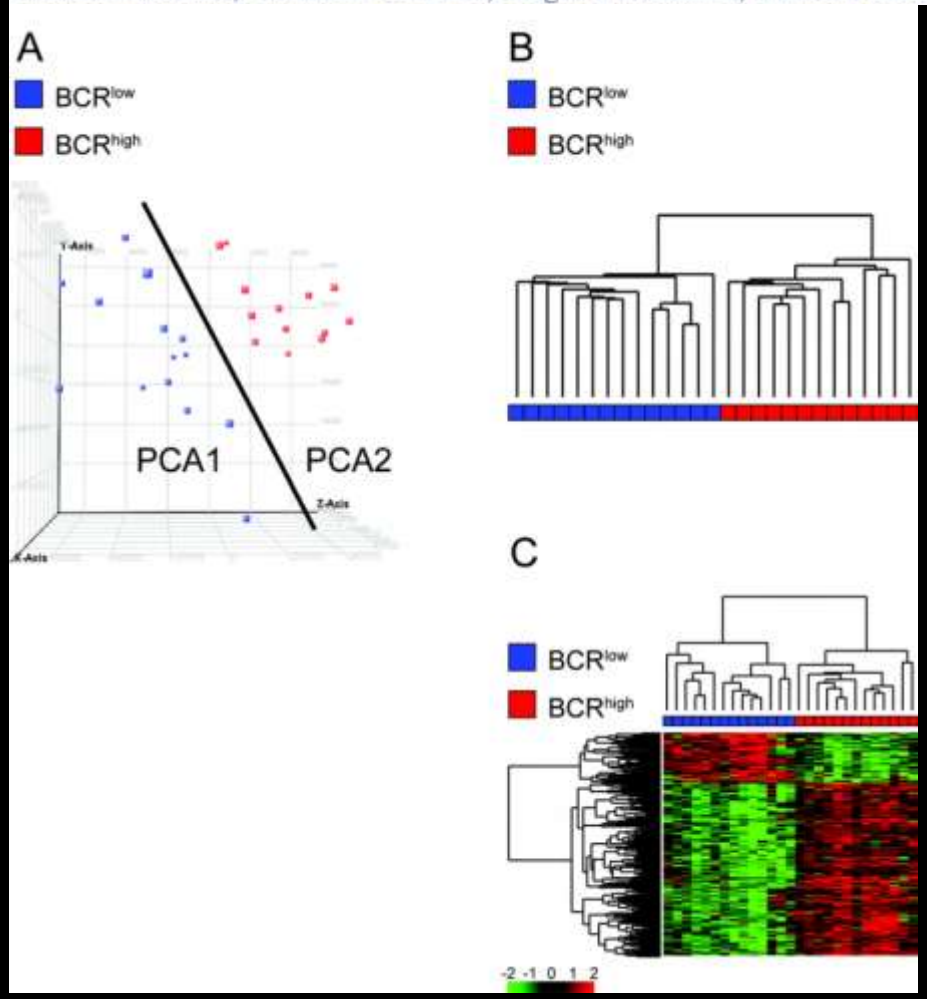

108 Mantle Cell Lymphoma Biopsies
MKI67
FOXM1
ESPL1
TOP2A
NCAPG
CDKN3
CDC20
KIF2C
H2AFX
E2F2
CCNB2
FAM83D
ZWINT
ATL1
FMNL3
ZDHHC21
GLIPR1
MCL35
Low (45%)
Standard (29%)
High (26%)
Ki-67 PI
MIPI
Morphology
TP53 IHC
CCND1 3′ UTR
< 10%
10%-29%
≥ 30%
Low
Intermediate
High
Classical
Pleomorphic
Blastoid
Negative
Positive
Full length
Truncated


Risk Group HR (95% CI)
Low risk 0.33 (0.12 to 0.49)
Standard risk 1 Reference
High risk 1.93 (1.10 to 3.75)
OS (proportion)
P < .001
P = .01
Log-rank for trend P < .001
Time (years)
Risk Group HR (95% CI)
Low risk 0.43 (0.13 to 0.99)
Standard risk 1 Reference
High risk 2.47 (1.01 to 8.69)
OS (proportion)
P = .03
P = .03
Log-rank for trend P < .001
Time (years)

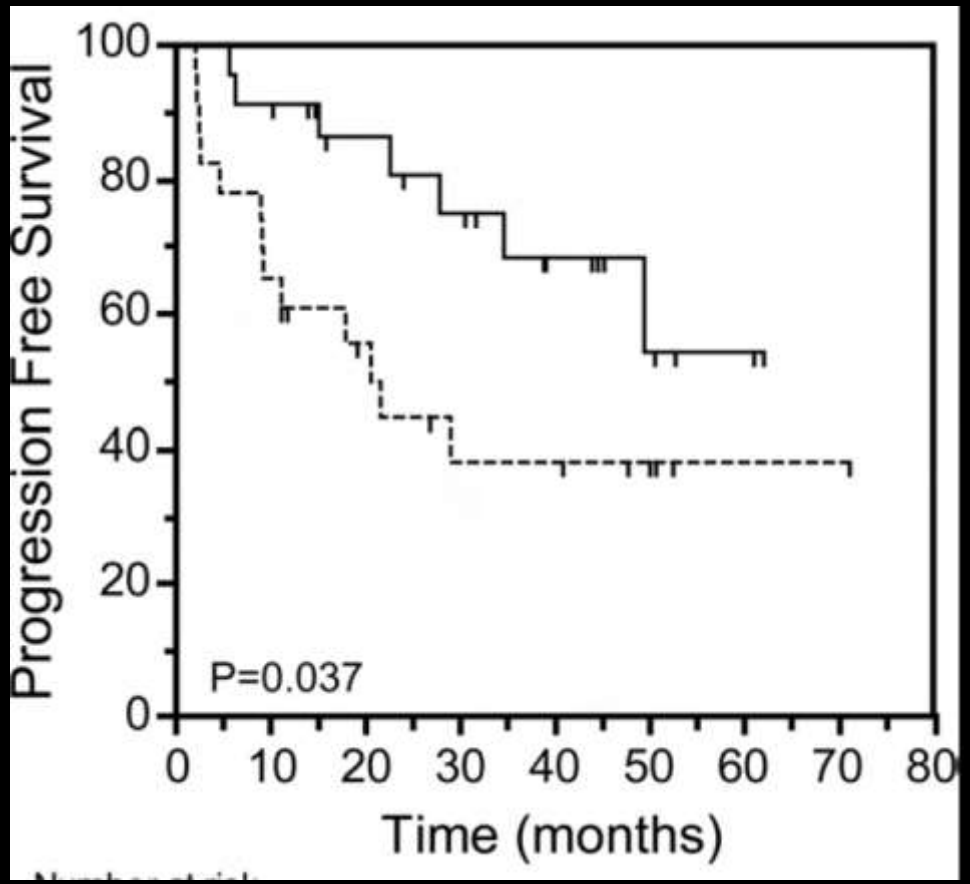
A B-cell receptor-related gene signature predicts survival in mantle cell lymphoma: results from the "Fondazione Italiana Linfomi" MCL-0208 trial

by Riccardo Bomben, Simone Ferrero, Tiziana D'Agaro, Michele Dal Bo, Alessandro Re, Andrea Evangelista, Angelo Michele Carella, Alberto Zamò, Umberto Vitolo, Paola Omedè, Chiara Rusconi, Luca Arcaini, Luigi Rigacci, Stefano Luminari, Andrea Piccin, Delong Liu, Adrien Wiestner, Gianluca Gaidano, Sergio Cortelazzo, Marco Ladetto, and Valter Gattei

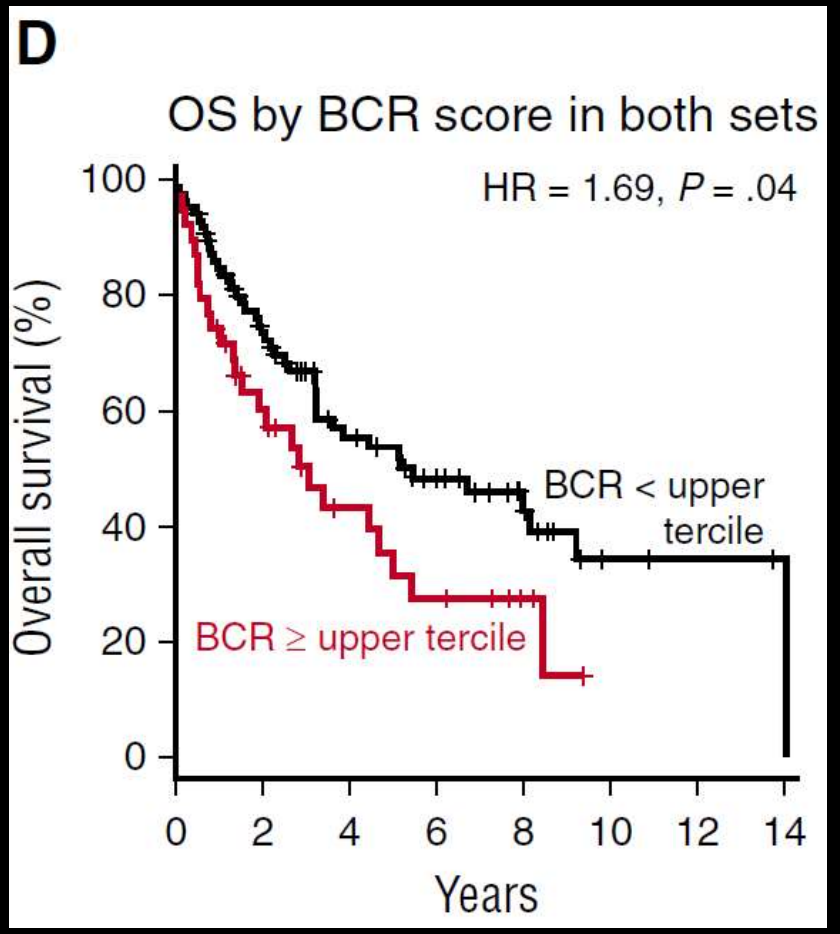
Haematologica 2018 [Epub ahead of print]



BCR INDEX



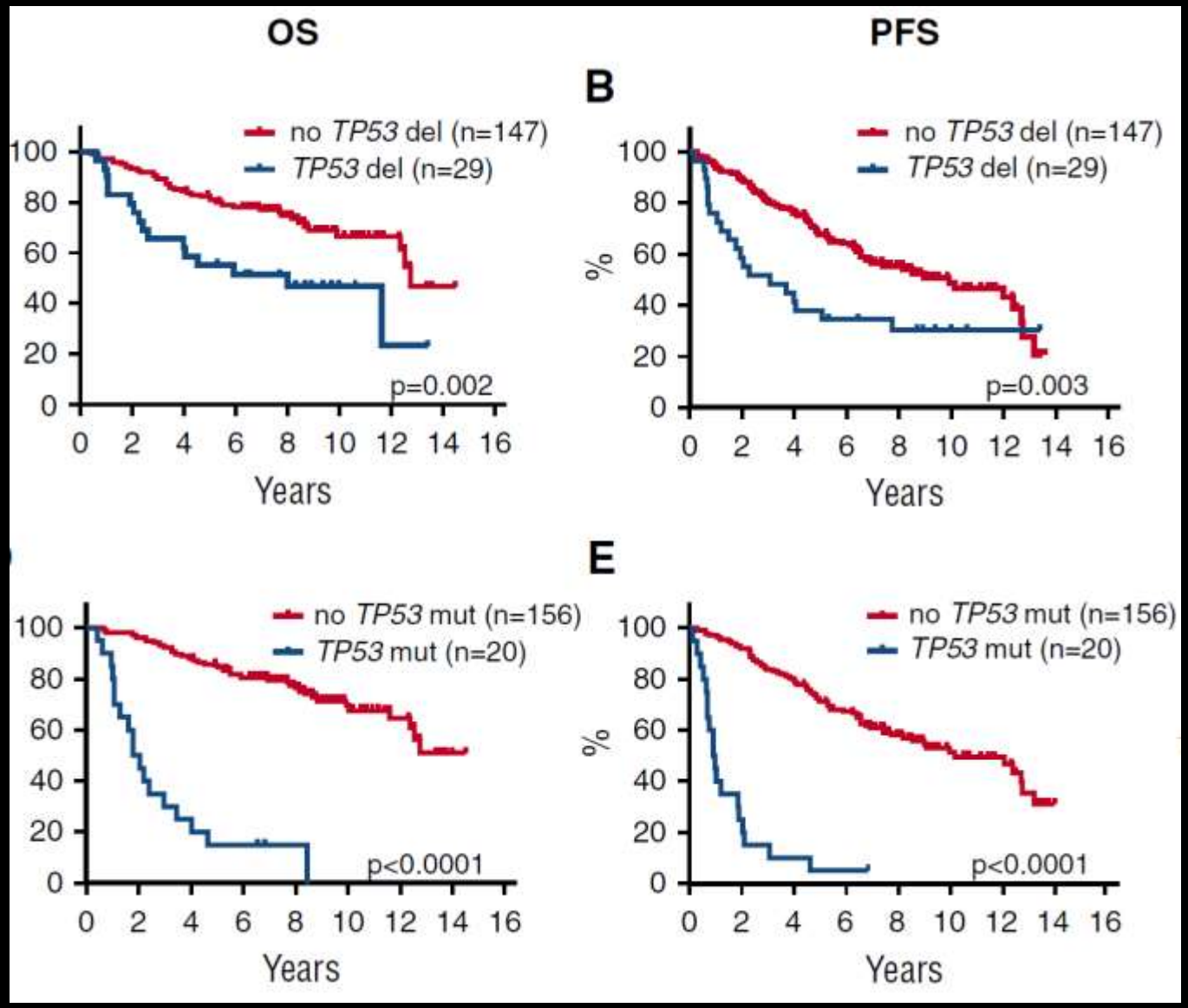
BCR SCORE



Saba et al. 2016

MUTAZIONI/DELEZIONI DI TP53

Eskelund et al., Blood. 2017 Oct 26;130(17):1903-1910

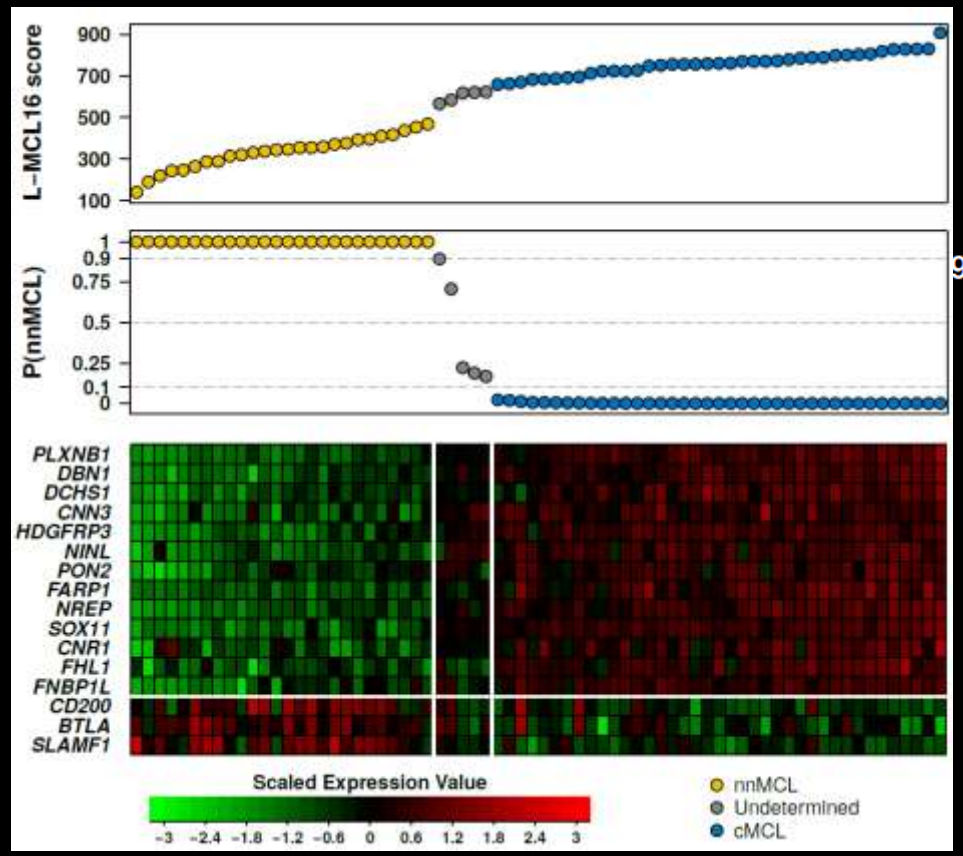


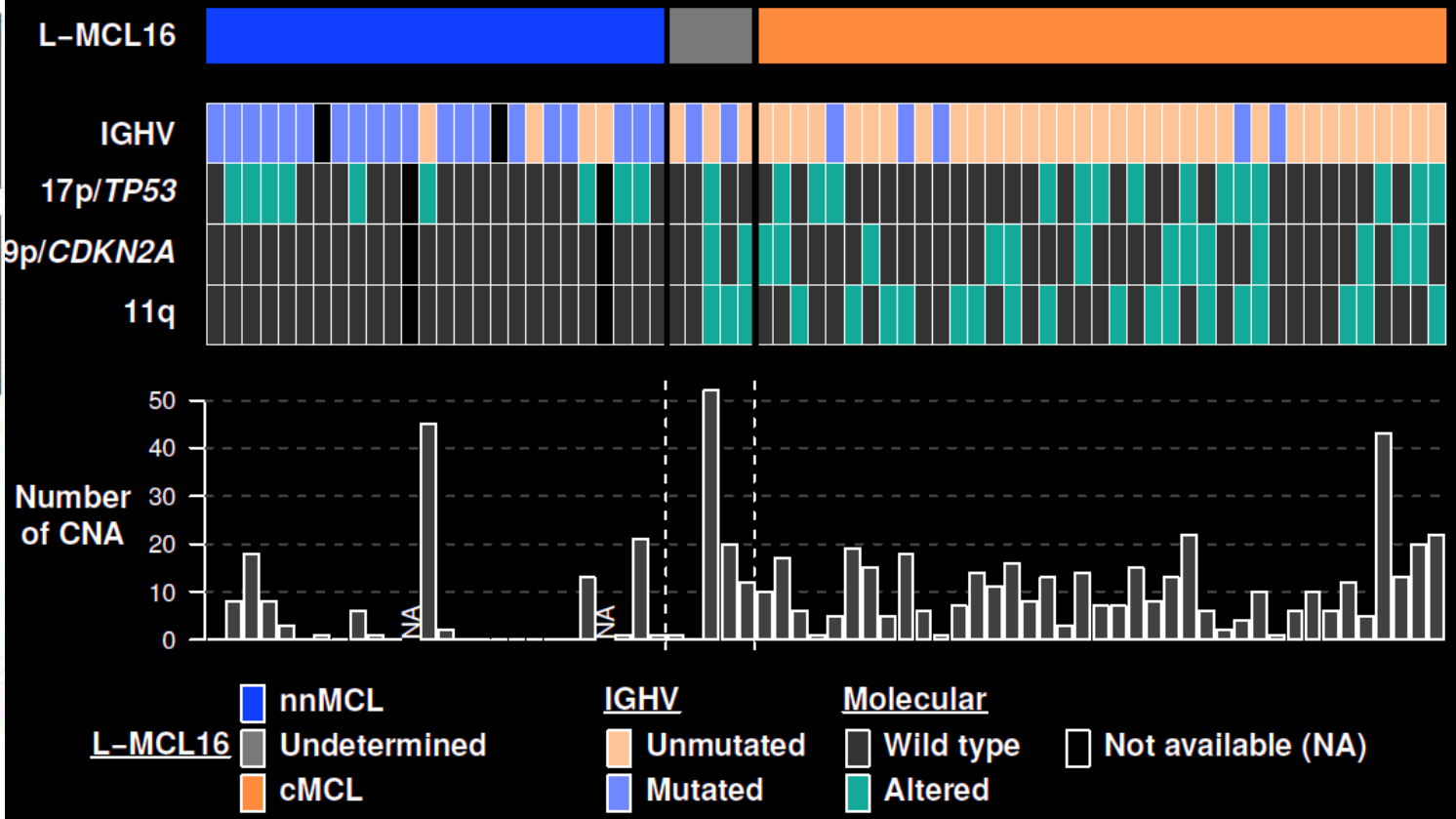
Blood. 2018 May 16. pii: blood-2018-03-838136. doi: 10.1182/blood-2018-03-838136. [Epub ahead of print]

A new molecular assay and genomic complexity predict outcome in conventional and leukemic non-nodal mantle cell lymphoma.

Clot G[1], Jares P[2], Giné E[3], Navarro A[1], Royo C[1], Pinyol M[1], Martín-Garcia D[1], Demajo S[1], Espinet B[4], Salar A[4], Ferrer A[4], Muntañola A[5], Aymerich M[6], Rauert-Wunderlich H[7], Jaffe ES[8], Connors JM[9], Gascoyne RD[9], Delabie J[10], López-Guillermo A[1], Ott G[11], Wright GW[8], Staudt LM[8], Rosenwald A[7], Scott DW[9], Rimsza LM[12], Beà S[1], Campo E[13].

L-MCL16





WHAT'S IN THE FUTURE?

- Separazione del MCL "memory"
- Signatures molecolari
- Sequenziamento genico/CNA