RIMINI 16 aprile 2016

Aula G, Ospedale Infermi

Con il supporto non condizionato di janssen

Linfoma Mantellare

Moderatori: P.P. Fattori, A. Zaccaria

08.30	**Introduzione (Definizione, frequenza, età, sesso, care...)**	*P. Tosi*
09.00	**Aggressivi e indolenti: diagnostica differenziale, morfologica e biomolecolare**	*E. Sabattini*
09.30	**Varietà indolente: approccio terapeutico e risultati**	*C. Pellegrini*
10.00	**Varietà aggressiva: approccio terapeutico e risultati**	*F. Zaja*
10.30	**L'impiego di farmaci target: grandi risultati con scarsa tossicità**	*A. Broccoli*
	Moderatore: S. Tura	
11.00	**Nuovi approcci dell'imaging nel paziente neutropenico febbrile**	*C. Sassi*

"Aggressivi e indolenti: diagnostica differenziale morfologica e biomolecolare"

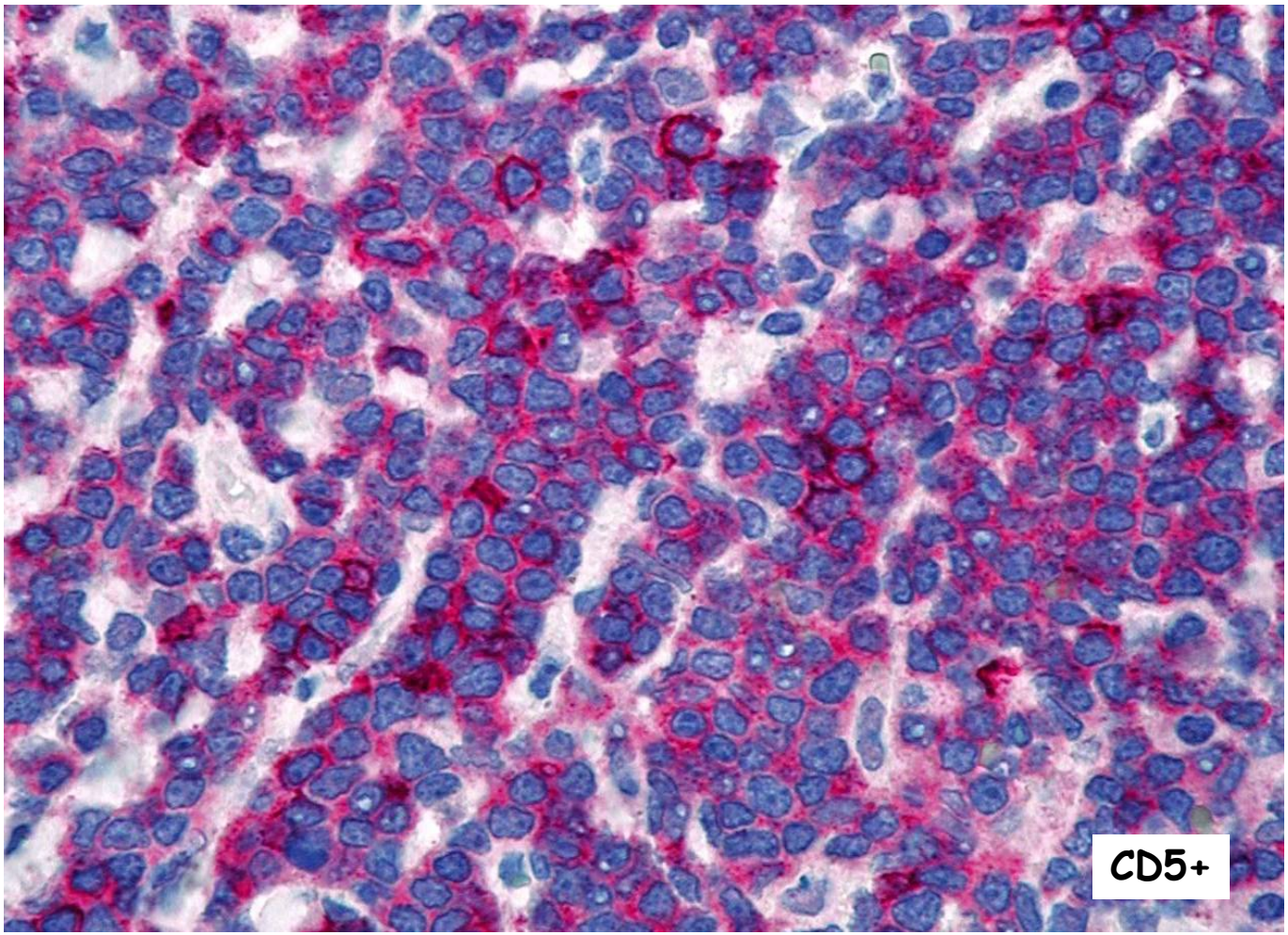
Elena Sabattini

Unità di Emolinfopatologia, Ist.L&A Seragnoli,Bologna

B cell markers+/CD5+
CD23-/CD200-/LEF1- (*vs* B-CLL)
CD10-/Bcl6-(rare cases+) (vs FL)
IRTA1-/MNDA-+ (MZL)
CD21+ FDCs meshwork

diagnosis:

morphology
diagnostic t(11;14)

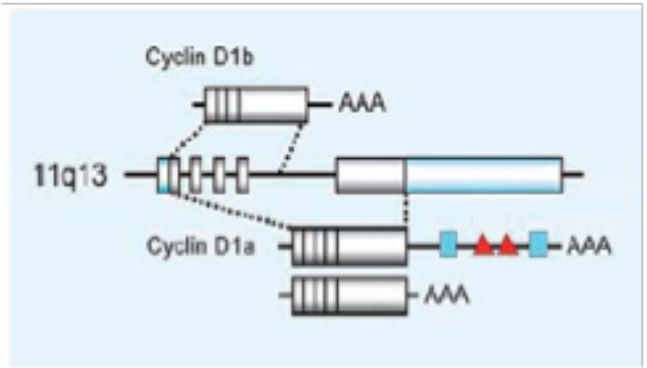


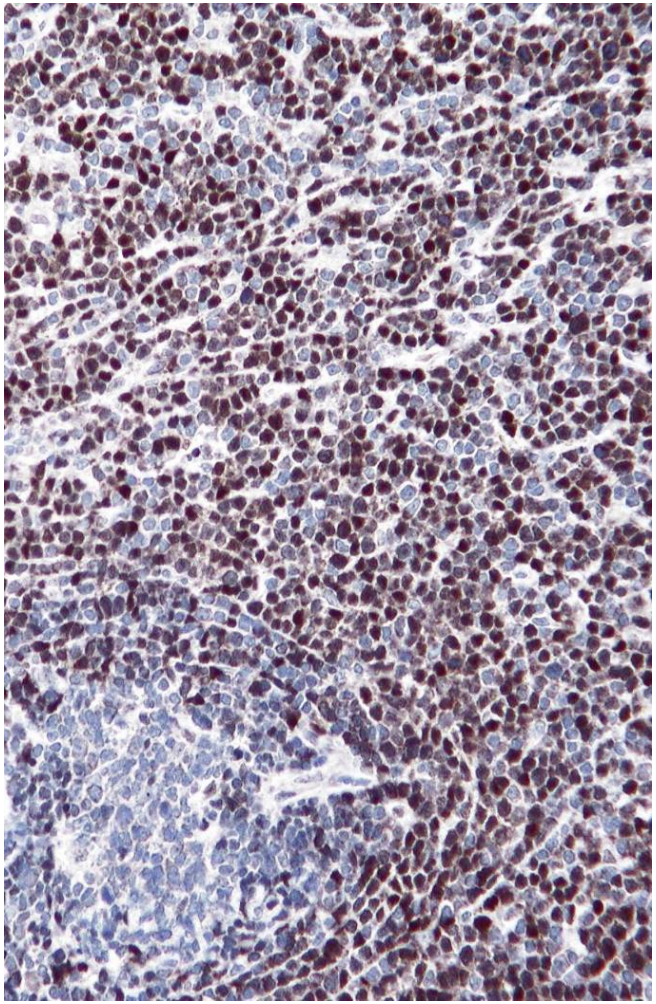
INITIAL/PRIMARY ONCOGENIC EVENT

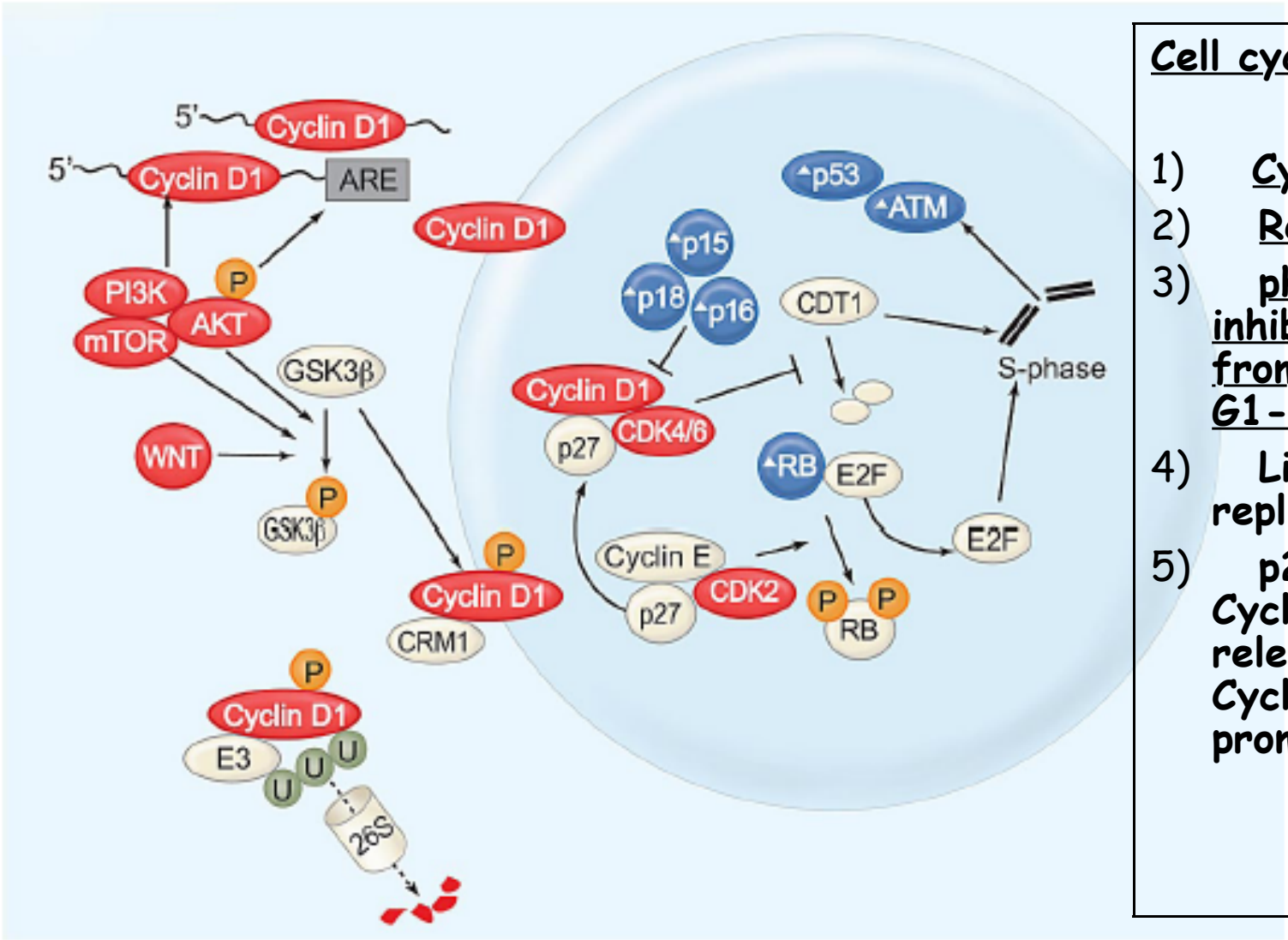
95% t(11;14) (q13;q32) juxtaposes CCND1 gene (11q13) at IGH (14q32)
forces overexpression of cyclin D1 (not detected in normal Bly)

<u>t(11;14) *per se* likely not tranforming</u>
<u>additional mechanisms for cyclin D1 expression</u>

* Mutations in CCND1 at 3'UTR/untranslated region
a) truncated cyclin D1 transcripts with longer half-life
-- potentiated activity +
b) delete area for microRNA15/16 binding no inhibitory effect
* Amplification of the translocated t(11;14) allele







Cell cycle related functions

1) CyclinD1
2) Regulates CDK4&6
3) phosphorilation of RB1 (E2F inhibitor) --- separate pRB1 from E2F --- E2F induces G1-S phase
4) Limits CDT1 (DNA replication limiting)
5) p27 binds to CyclinD1\CDK4CDK6 and is released by cyclindEActivates CyclinE/CDK2 which then promotes cell cycle

CyclinD1 is exported in the cytoplasm by action of GSK3B and degradated E3ligase/ubiquitin/proteasome

Cases with otherwise classic MCL without t(11;14)/Cyclin D1 negative

CCND1 dysregulation is not the only possible initiating event
CCND1- cases have the same GEP signature as CCND1+ and similar secondary chromosomal aberrations

CCND2/IgH in 50% cases

Salaverria I et al. Blood. 2013 Feb 21
Carvajal-Cuenca et al. Mod Pathol 2012,
Gesk et al. Blood 2006

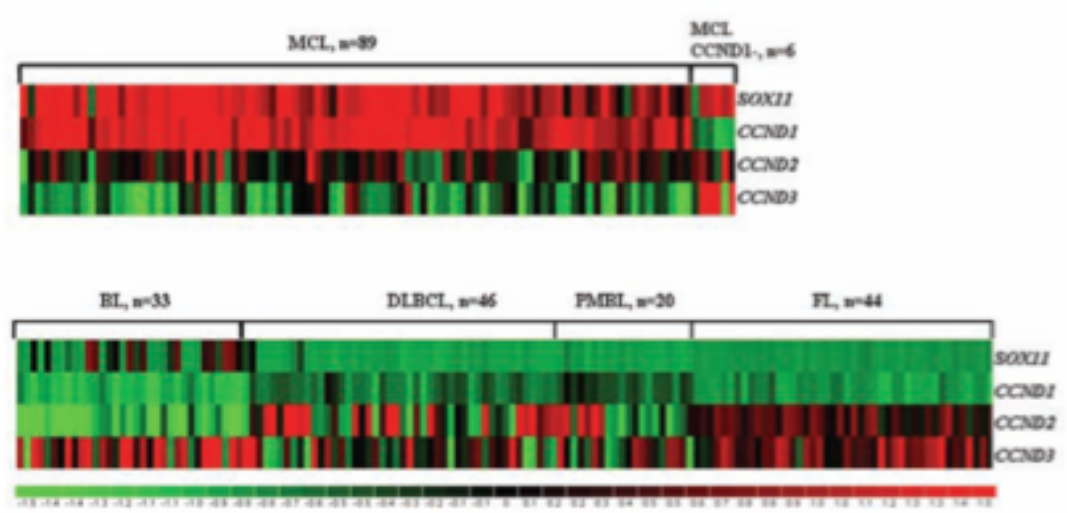
No cyclin gene alteration in 50% cases
No answer (other pathological drivers)

SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype

Ana Mozos,[1] Cristina Royo,[1] El
Dennis D. Weisenburger,[5] Jan
Sandeep Dave,[10] Lisa Rimsza,[1]
Dolors Colomer,[1] Louis M. Sta

Strong lymphoid nuclear expression of *SOX11* transcription factor defines lymphoblastic neoplasms, mantle cell lymphoma and Burkitt's lymphoma

Michael Dictor,[1] Sara Ek,[3] Maria Sundberg,[1] Janina Warenholt,[1] Czabafy György,[1] Sandra Sernbo,[3] Elin Gustavsson,[3] Waleed Abu-Alsoud,[2*] Torkel Wadström,[2] and Carl Borrebaeck[3]



Neuronal transcription factor

Not expressed in other mature lymphomas or lymphocytes
Function in lymphomagenesis not understood

Positive in CCND1pos and CCND1neg cases

good <u>diagnostic biomarker</u>

<u>Possible adjunct in prognostication</u>

Haematologica. 2015 - **Lord M et al.**

The utility of mRNA analysis in defining SOX11 expression levels in mantle cell lymphoma and reactive lymph nodes.

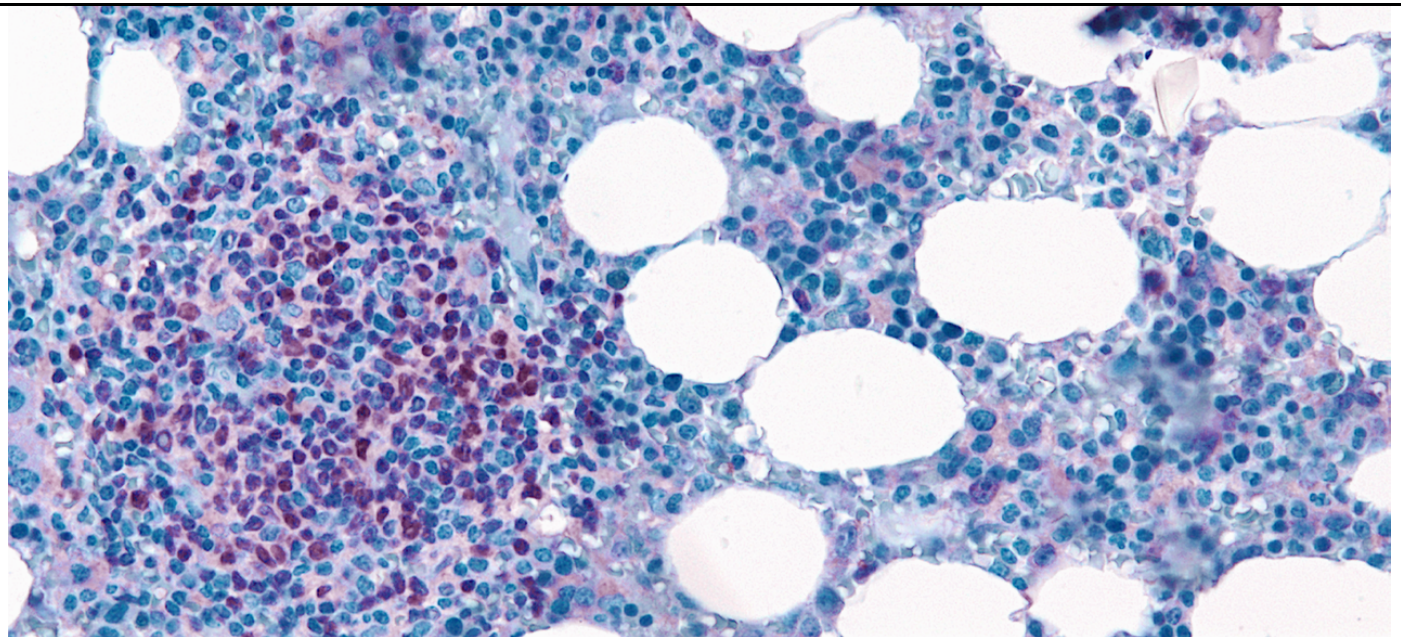
good correlation between SOX11 expression at the mRNA and protein level

both mRNA analysis and ihc could **not identify a natural cut-off** that would identify cases with low expression: MCL can be reliably defined as SOX11 positive (also weak and partial) or negative either by qPCR analysis or by scoring IHC staining

Reproducibility of SOX-11 detection in decalcified bone marrow tissue in mantle cell lymphoma patients.

S. Righi, S. Pileri, C. Agostinelli, F. Bacci, S. Spagnolo, E. Sabattini

SUBMITTED



CLINICAL & PROGNOSTIC VARIABILITY

Martin et al JCO 2009

Blood First Edition Paper, prepublished online March 15, 2016; DOI 10.1182/blood-2016-01-643569

The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms

Steven H. Swerdlow1, Elias Campo2, Stefano A. Pileri, Nancy Lee Harris, Harald Stein, Reiner Siebert, Ranjana Advani, Michele Ghielmini, Gilles A. Salles, Andrew D. Zelenetz, Elaine S. Jaffe

… as an aggressive but incurable small B-cell lymphoma
Classical MCL is usually composed of IGHV unmutated or minimally mutated Bcells that usually express SOX11 and typically involves lymph nodes and other extranodal sites.
Acquisition of additional molecular/cytogenetic abnormalities can lead to even more aggressive blastoid or pleomorphic MCL.

Two types of clinically indolent variants are

Other MCL develop from IGHV mutated SOX11 negative B-cells which leads to, usually involving the peripheral blood, bone marrow and often spleen. These **leukemic non-nodal MCL** cases are frequently clinically indolent but secondary abnormalities, often involving TP53, may occur and lead to aggressive disease.

In situ MCL/neoplasia with a low rate of progression, characterized by cyclin D1+ cells in the inner mantle zones of follicles in lymphoid tissues that do not otherwise suggest the diagnosis of a MCL; often found incidentally, sometimes in association with other lymphomas. They may be disseminated but appear to have a low rate of progression.

Should be distinguished from overt **MCL with a mantle zone growth pattern** or **other classical MCL with a low proliferative fraction** which may also be relatively indolent

BIOLOGICAL PARAMETERS LIKELY INVOLVED IN CLINICAL BEHAVIOUR
SOME DEFINED, SOME ONGOING

MIPI

Histology (cytology and growth pattern)

IgVH Mutational Status

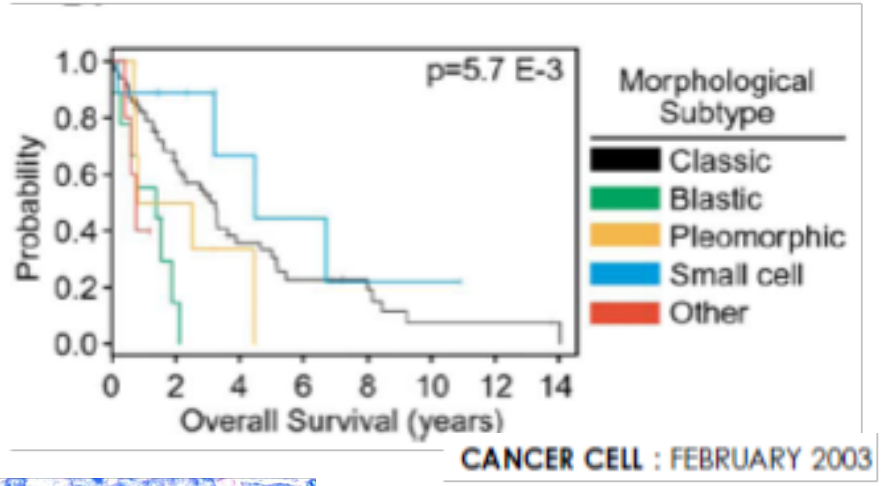
SOX11 expression

Proliferative signature/kinetics

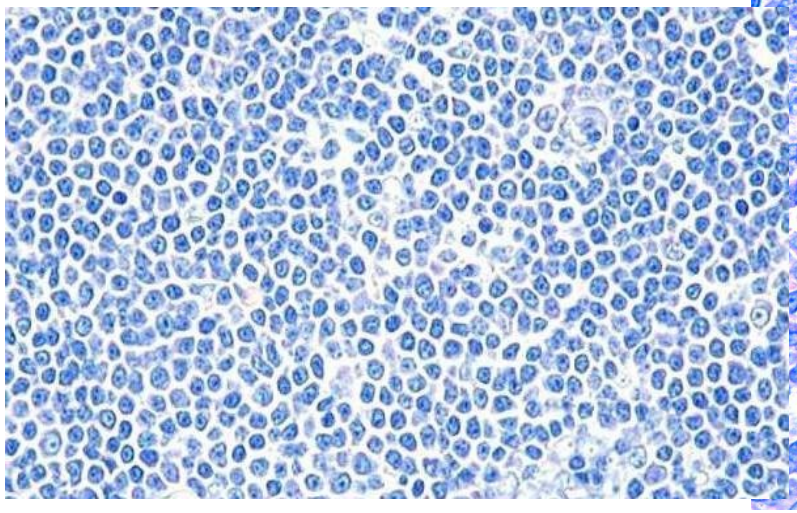
Somatic mutations/genetic aberrations

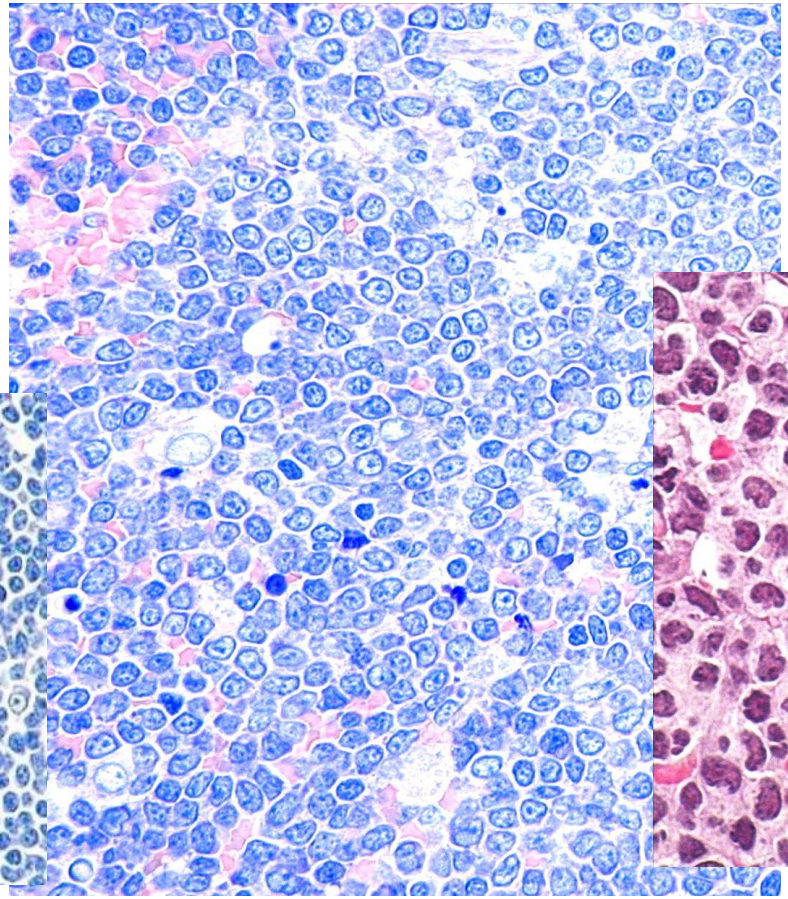
<u>blastoid</u>:
>LDH and >MIPI
(comparable age,PS,WBC)

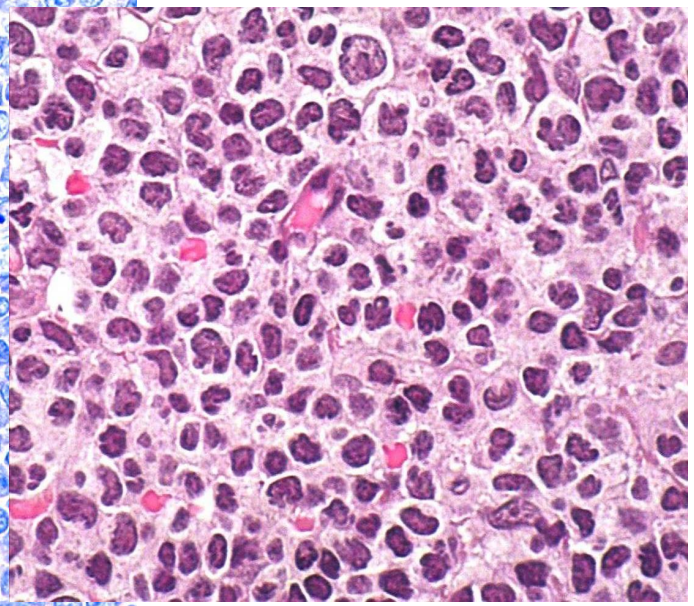
Median Ki-67
blastoid 80%
pleomorphic 39%
Classic/small-cell: 19%

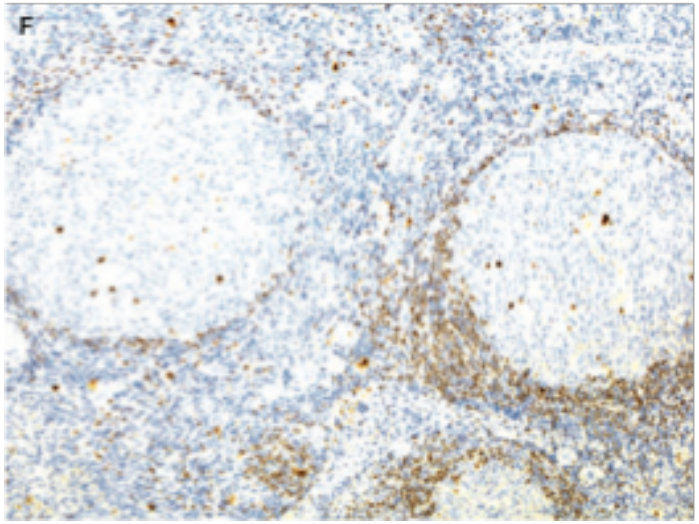


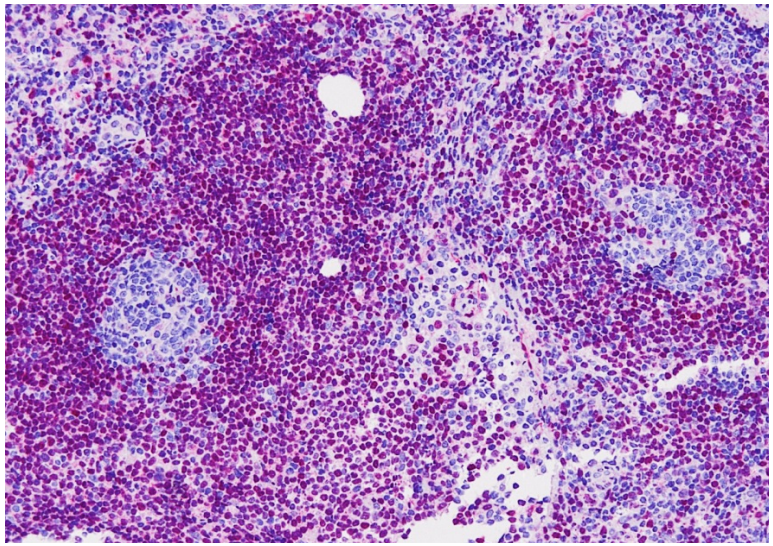
CANCER CELL : FEBRUARY 2003

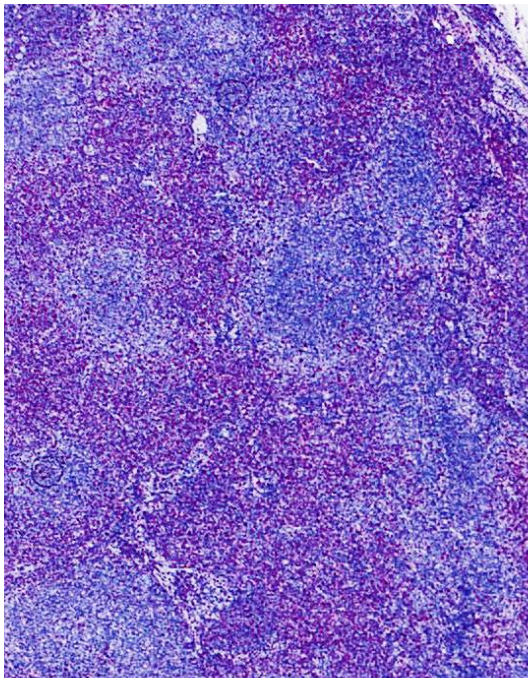










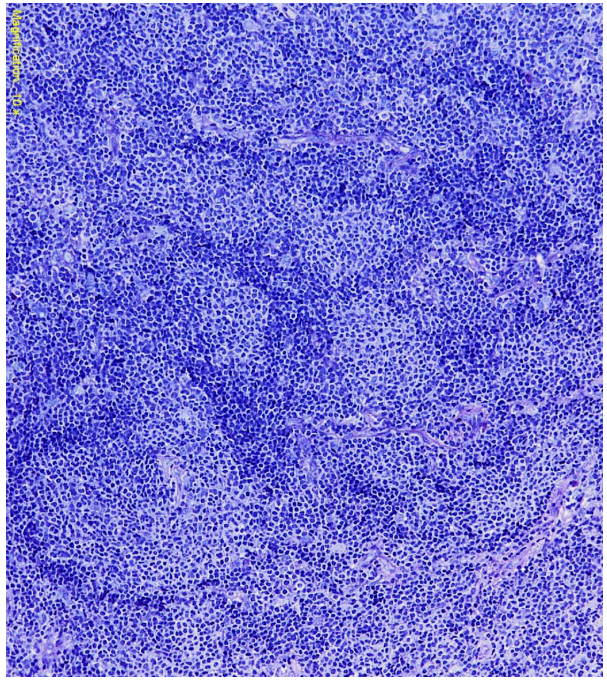


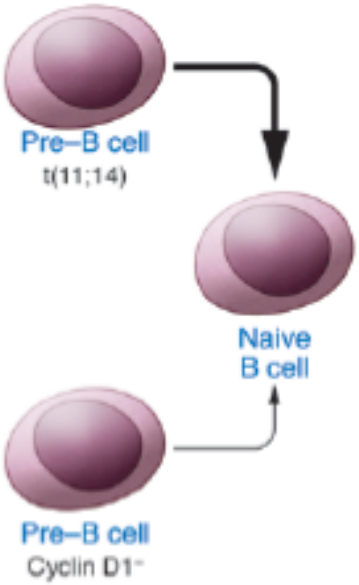
Growth

in situ/ mantle-zone / nodular / diffuse

diffuse: older pts, >MIPI

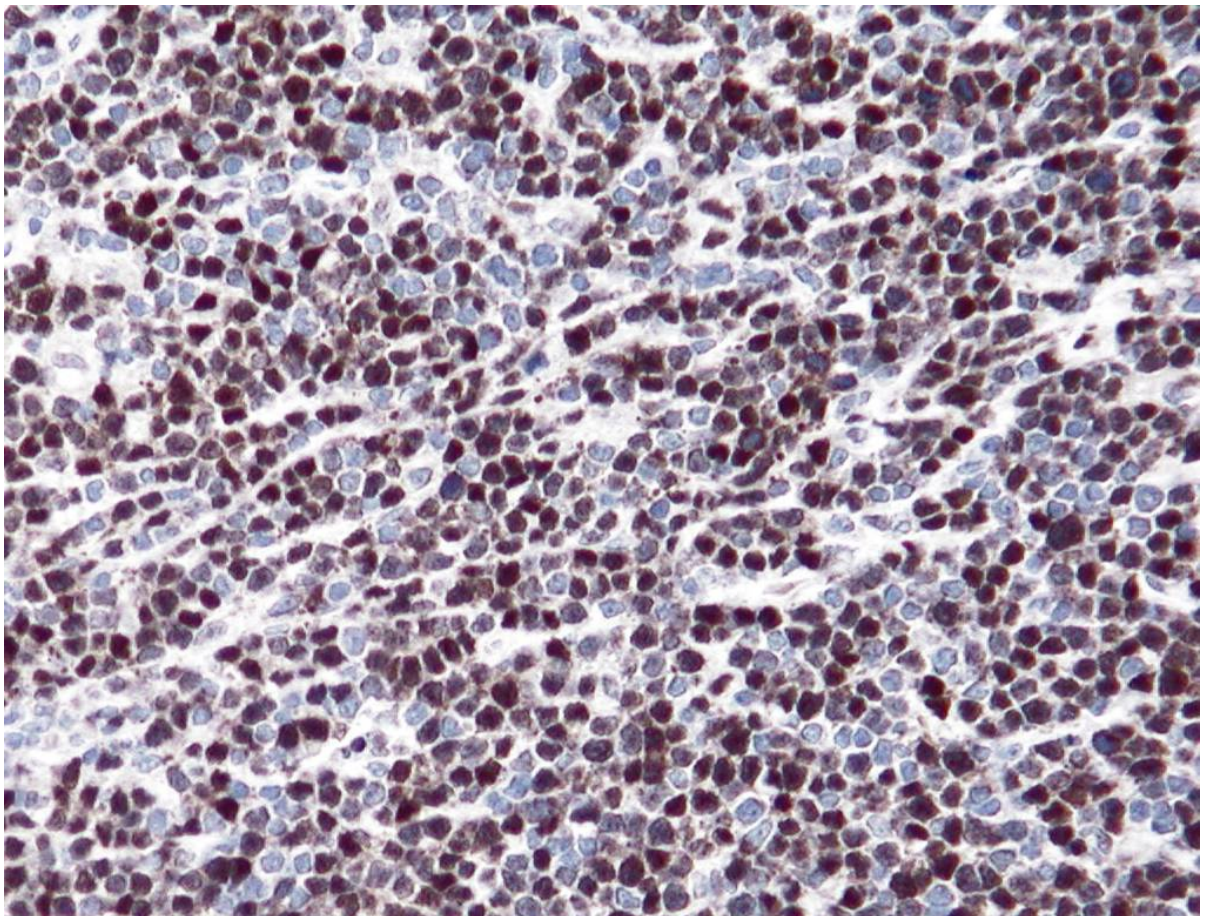
No difference in Ki67 index
(Median Ki67 diffuse 21%, non-diffuse 20%)
BUT: 75% blastoid are diffuse





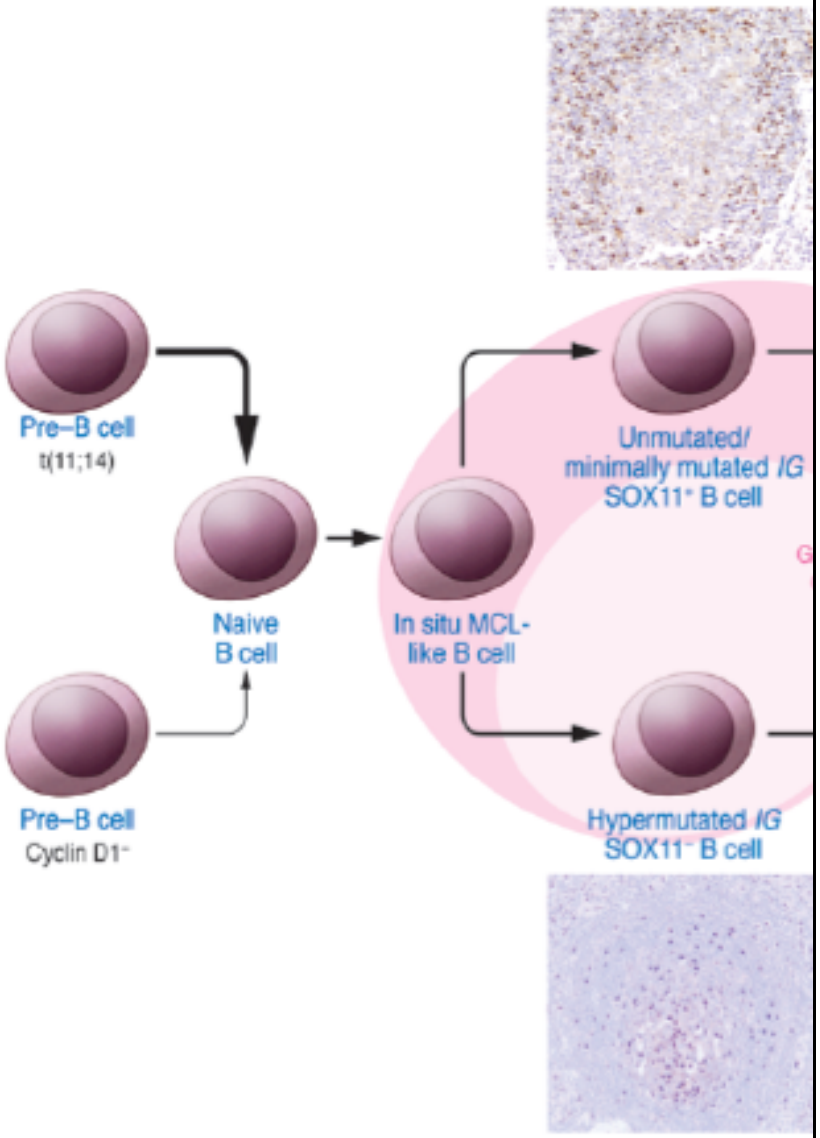
Initial event at pre-B stage in bm during ricombination VDJ (in bone marrow at lymphoblast-stage)

But the tumour is made of mature B ly: the translocated cell is capable of maturing and that full phenotype is acquired at later stages of maturation



Walsh et al. Blood 2003,
Kienle et al. Blood 2003,
Hadzidimitrou A et al. Blood 2011,
Kolar et al. Blood 2007,
Sims et al. Blood 2005

Like in BCLL

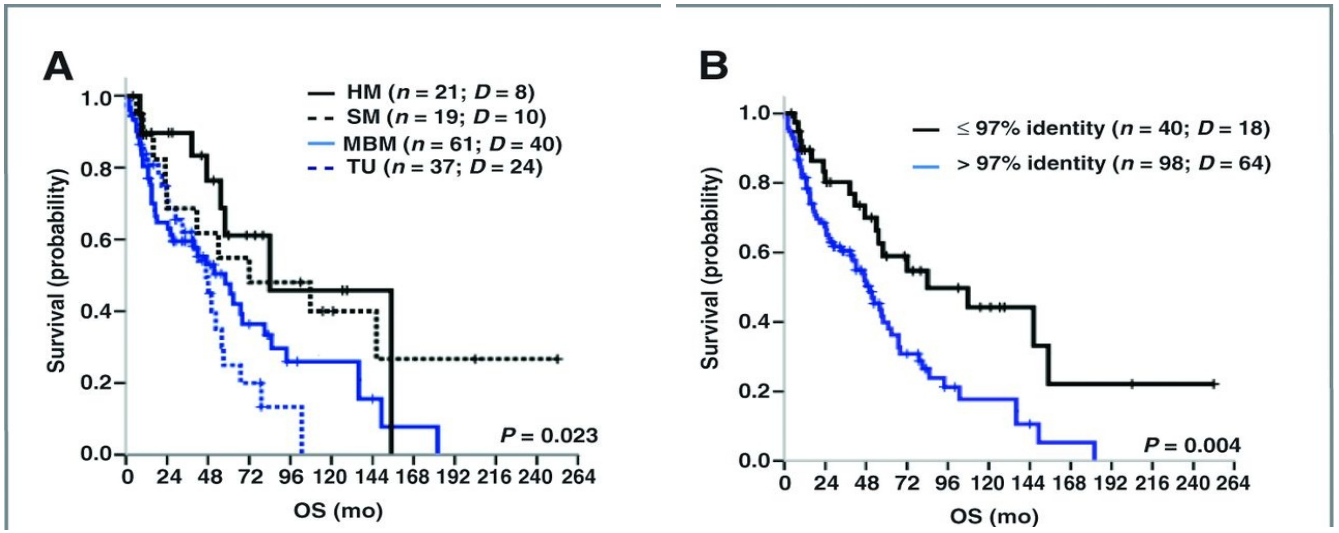


BCR/CDR diversity analysis

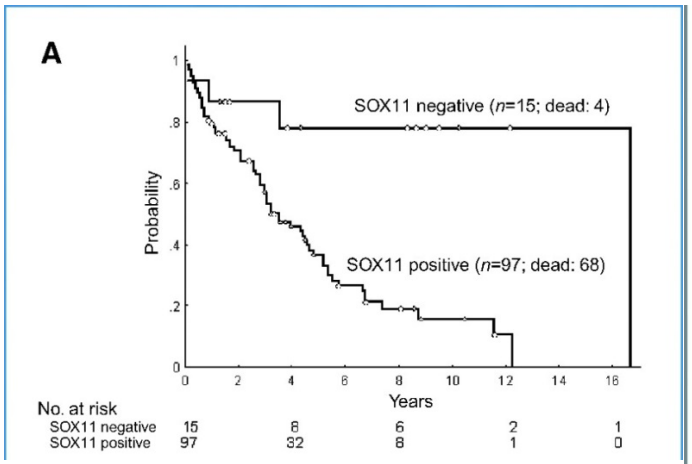
Totally or minimally UNMUTATED IgVH
(likely from naive Bly)

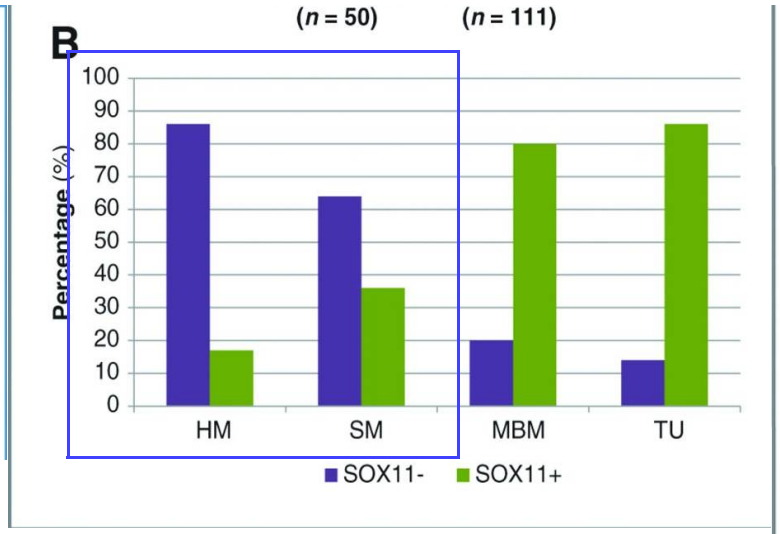
MUTATED IgVH
(with bias in VH repertoire usage
(IGHV 3-21,3-23,4-34,4-59)
=antigen experienced Bly
possible GC/post GC phenotype

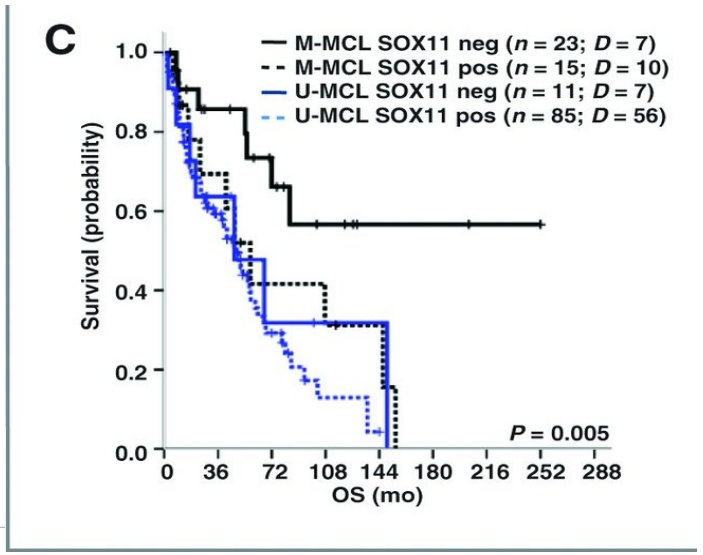
***High mutational load**
likely from cells in the GC
***Low mutational load**
Likely from intermediate cells from naive and CG (marginal zone/like B1 CD5+/AID+ cells)



The mutational status is somehow related to SOX11 expression



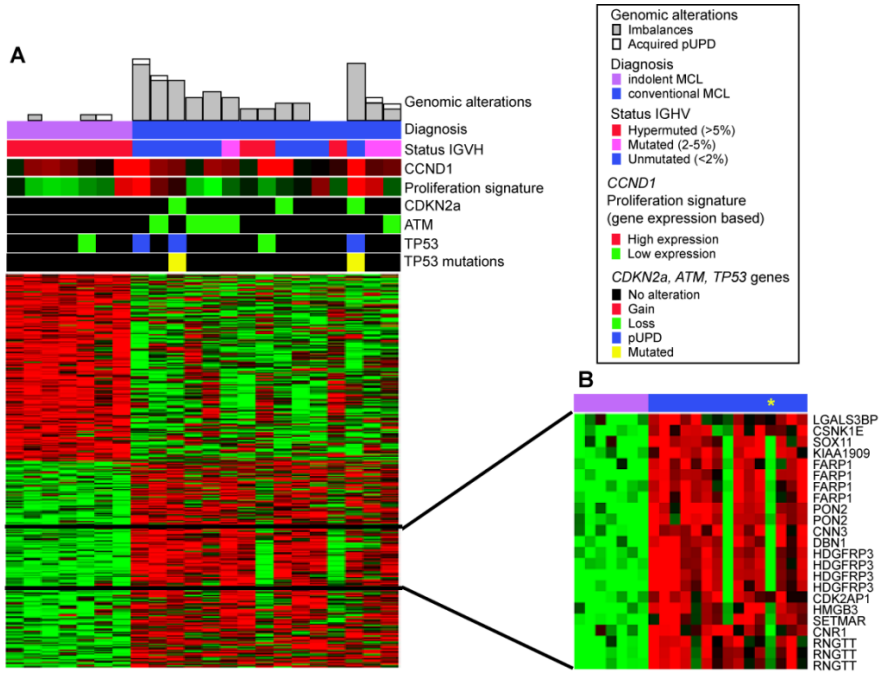




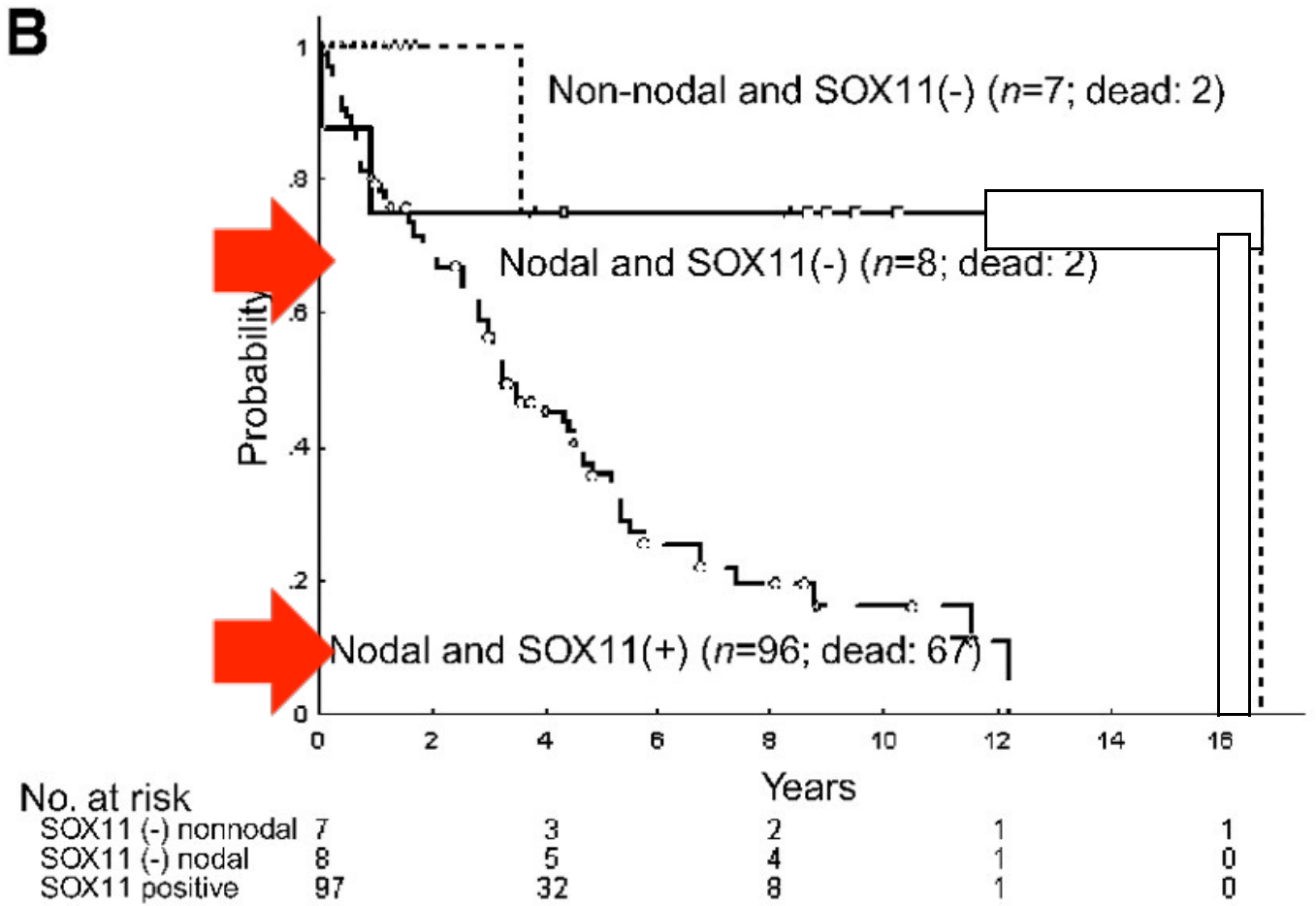
Fernàndez V Cancer Res. 2010, Navarro A et al. Cancer Res 2012

Degree of identity variable : 97% cut-off best for defining UM vs M
(Mutated = highlymutated + somaticallymutated; Umutated: minimally mutated + totally unmutated)

Fernàndez V Cancer Res. 2010, Navarro A et al. Cancer Res 2012



Beyond non-nodal leukemic indolent MCLs, any chance for indolency in nodal MCL?

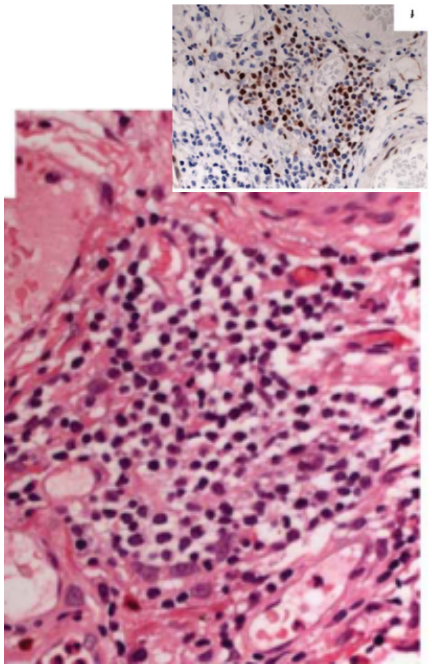


Morphologically reactive tissue taken at least 2 months before MCL diagnosis (Mod pathol 2012 Adam et al)

EARLY-STAGE MCL

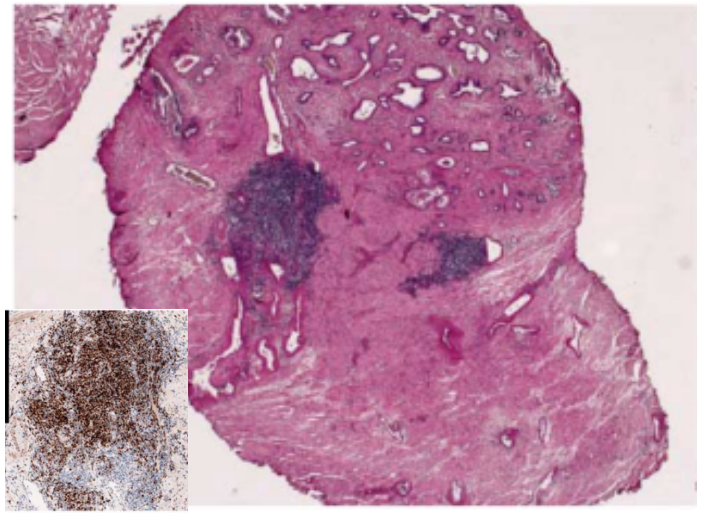
Table 1 Clinical characteristics of MCL patients with a preclinical manifestation

Case	*Age/sex*	*Site*	*MCL diagnostic site*	*Months to MCL diagnosis*
Minimal MCL infiltrations				
1	66/M	Gastric mucosa	Pharynx	23
2	78/M	Colon adenomas	Iliacal lymph node	23
3	84/M	Prostate hyperplasia (TUR)	Bone marrow	61
4	66/M	Leiomyoma of urinary bladder	Bone marrow	59
5	57/M	Papillary urothelial carcinoma low grade pTa	Bone marrow	14
6	69/M	Papillary urothelial carcinoma low grade pTa	Submental lymph node	3
			Median:	23
MCL with mantle zone growth pattern				
7	58/M	Large cell lung cancer	Retroperitoneal mass	86
8	76/M	Appendix, mesenterial lymph nodes	Cervical lymph node	8
9	87/F	Sigma diverticulitis, adnexae	Bone marrow	2
10	75/F	Chronic bursitis	Cervical lymph node	2
			Median:	5



In extranodal dispersed MCL-cells
More marked expansion of mantle zone or follicles with the appearance of primary follicles
Better termed "early MCL" with "mantle-zone" growth or nodular growth MCL

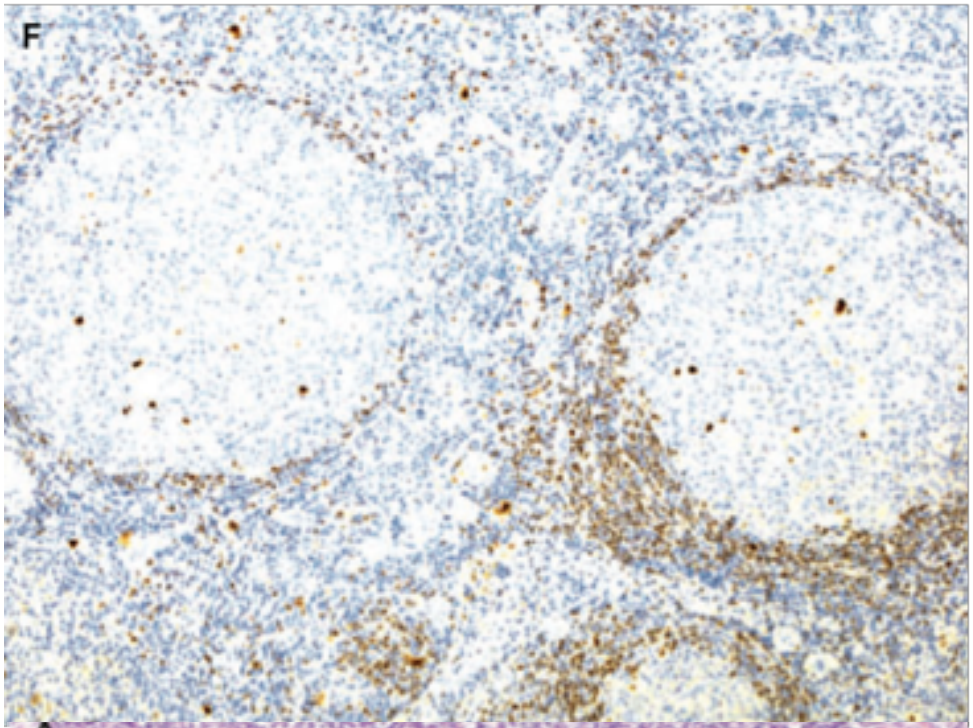
Can be found as preclinical manifestation or in overt diseases
More often SOX11 positive

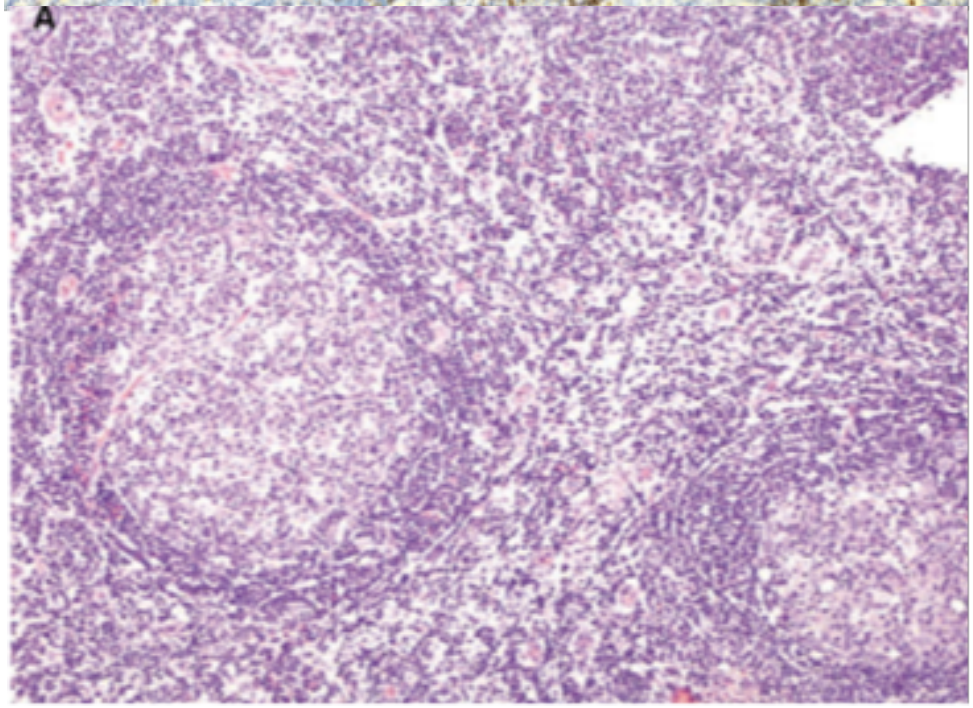


IN MORPHOLOGICALLY NEGATIVE LYMHP NODES
EXCISED FOR OTHER REASONS

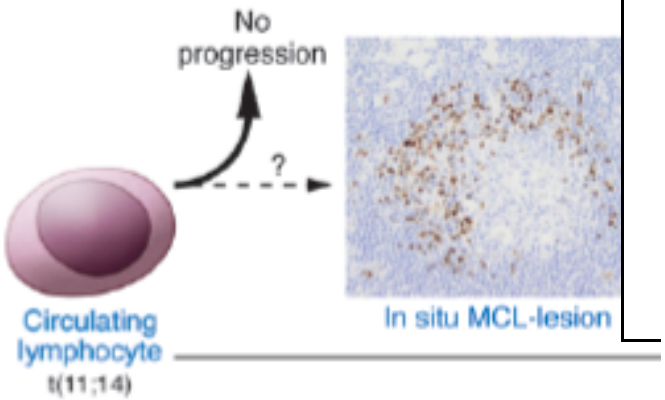
NON EXPANDED MANTLE ZONES; TOTALLY PRESERVED LYMPH NODE ACHITECTURE

IN SITU MANTLE-CELL NEOPLASIA (WHO 2016)





In Situ MCN could be the morphologic counterpart of circulating t(11;14)+ B cells



*B lymphocytes with t(11;14) detected at low levels in pb of healthy individuals (7%) (Hirt et al. Blood 2004)

*Can persist as such for long periods (up to 9 yrs)

*Potential to evolve not defined, likely very low (Lecluse et al Leuk 2009)

*Evolution may require long latency (12 years) (Christian et al. JCO 2012)

Imaging, Diagnosis, Prognosis

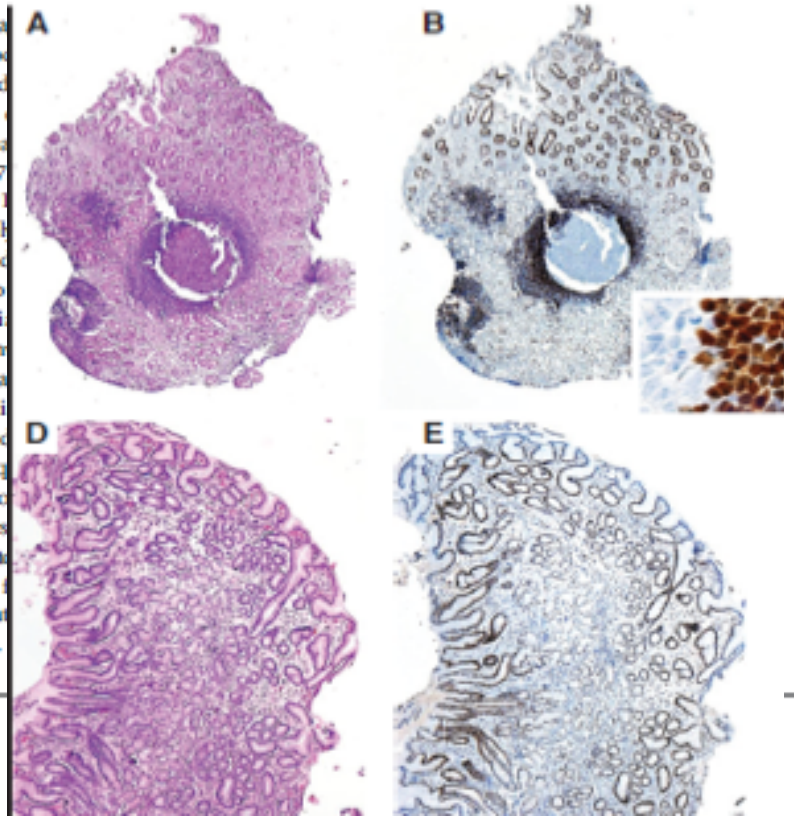
Clinical Cancer Research

Distinction between Asymptomatic Monoclonal B-cell Lymphocytosis with Cyclin D1 Overexpression and Mantle Cell Lymphoma: From Molecular Profiling to Flow Cytometry

Blanca Espinet[1,3], Ana Ferrer[1,3], Beatriz Bellosillo[1,3], Lara Nonell[4], Antonio Salar[2,3], Concepción Fernández-Rodríguez[3], Eulàlia Puigdecanet[4], Javier Gimeno[1], Mar Garcia-Garcia[1,3], Maria Carmen Vela[1], Elisa Luño[11], Rosa Collado[12], José Tomás Navarro[7], Esmeralda de la Banda[8], Pau Abrisqueta[9], Leonor Arenillas[1,3], Cristina Serrano[13], Josep Lloreta[1,3], Belén Miñana[10], Andrea Cerutti[5], Lourdes Florensa[1,3], Alberto Orfao[14], Ferran Sanz[6], Francesc Solé[1,3], David Dominguez-Sola[15], and Sergio Serrano[1,16]

Abstract

Purpose: According to current dia
aggressive variants and rare, nonno
positive (MALD1). We aimed to und
markers for adequate identification
Experimental Design: We compa
MALD1 cases (median follow-up, 7
analysis in five MCL and five MALD
quantitative reverse transcription po
by flow cytometry. Classification an
CD38 and CD200 expression by flo
Results: We found 171 differenti
proliferation signatures in MCL. Con
and inflammatory responses. CD38 a
confirmed by flow cytometry (medi
Assessment of both proteins allowe
unclassified. *SOX11* expression by q
but did not improve the classificatio
Conclusion: We show for the firs
activation and driven by inflammat
distinguish most cases of MALD1
segregated from the current MCL ca
Res; 20(4); 1007–19. ©2013 AACR.



in organs involved in inflammatory processes (in situ/mantle-zone)

could be with or without lymphocytosis (media 6.5)

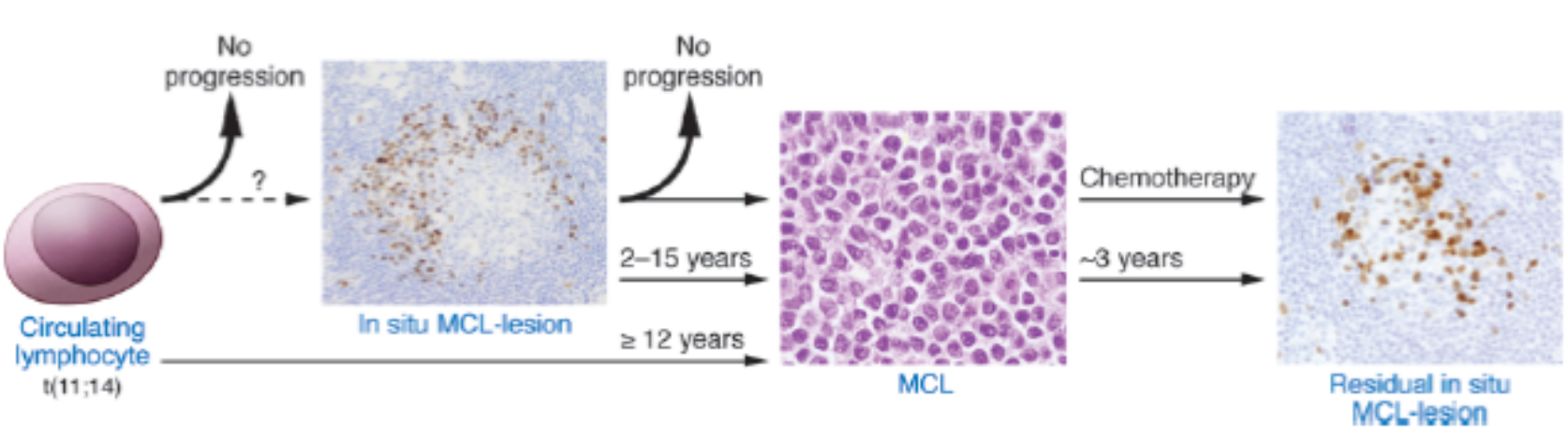
atypical cyclinD1/translocated small lymphocytes

no organomegaly/mild marrow infiltrate

SOX11+- (10/13 cases)
mutated IGHV

GEP different from classic MCL more similar to normal B cells

Flow: CD38-, CD200+;



INMCN: Extremely low prevalence in normal population
(lymph nodes examined for other reasons)
Clinical significance: NOT CLEAR

Very rare cases progress into overt MCL (2-15 years)

But 1/3 full blown MCL with available previous bx have in situ MCL

could be the rule in MCL development?
might represent VERY EARLY STAGE?
RESIDUAL post treatment MCells in lymph nodes of pts in CR?
mostly SOX11 negative

Jader et al. 2012, Adam et al. 2012

Histology (cytology and growth pattern)

IgVH Mutational Status

SOX11 expression

Proliferative signature/kinetics

Somatic mutations/genetic aberrations

Proliferation and clinical behaviour in MCL

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

CANCER CELL : FEBRUARY 2003

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,*]

Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network

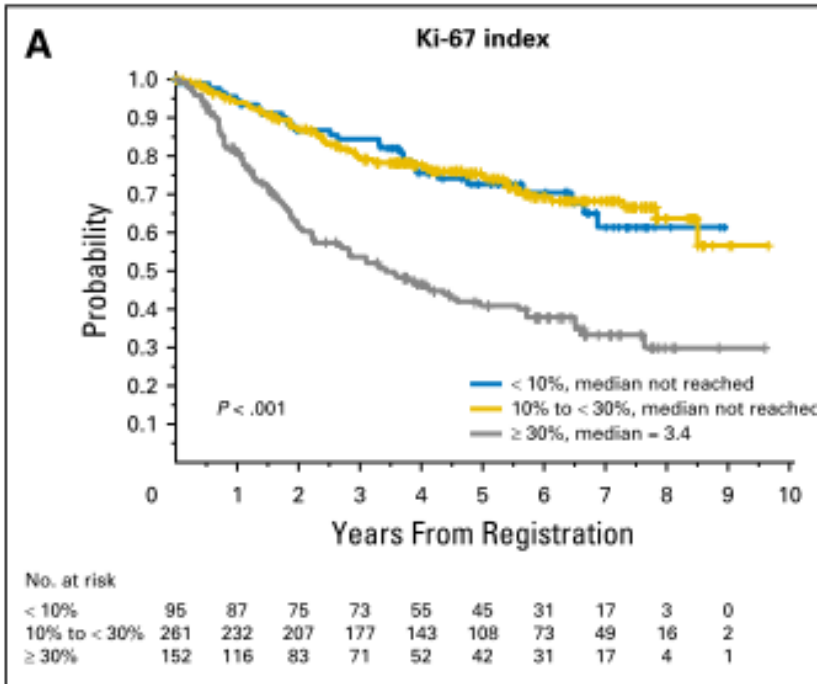
J Clin Oncol 34.

Eva Hoster, Andreas Rosenwald, Françoise Berger, Heinz-Wolfram Bernd, Sylvia Hartmann, Christoph Loddenkemper, Thomas F.E. Barth, Nicole Brousse, Stefano Pileri, Grzegorz Rymkiewicz, Roman Kodet, Stephan Stilgenbauer, Roswitha Forstpointner, Catherine Thieblemont, Michael Hallek, Bertrand Coiffier, Ursula Vehling-Kaiser, Réda Bouabdallah, Lothar Kanz, Michael Pfreundschuh, Christian Schmidt, Vincent Ribrag, Wolfgang Hiddemann, Michael Unterhalt, Johanna C. Kluin-Nelemans, Olivier Hermine, Martin H. Dreyling, and Wolfram Klapper

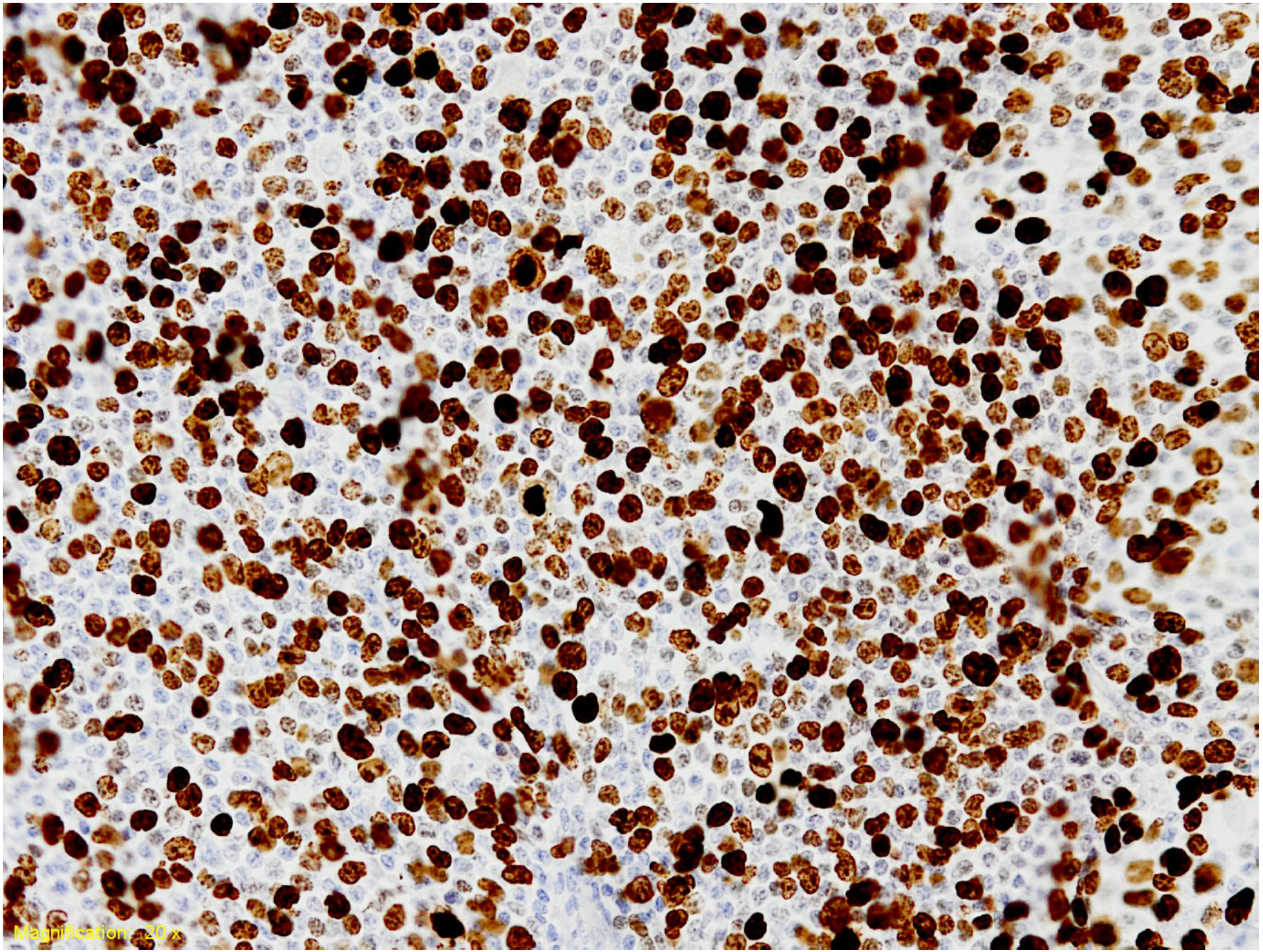
KI67 and OS/PFS

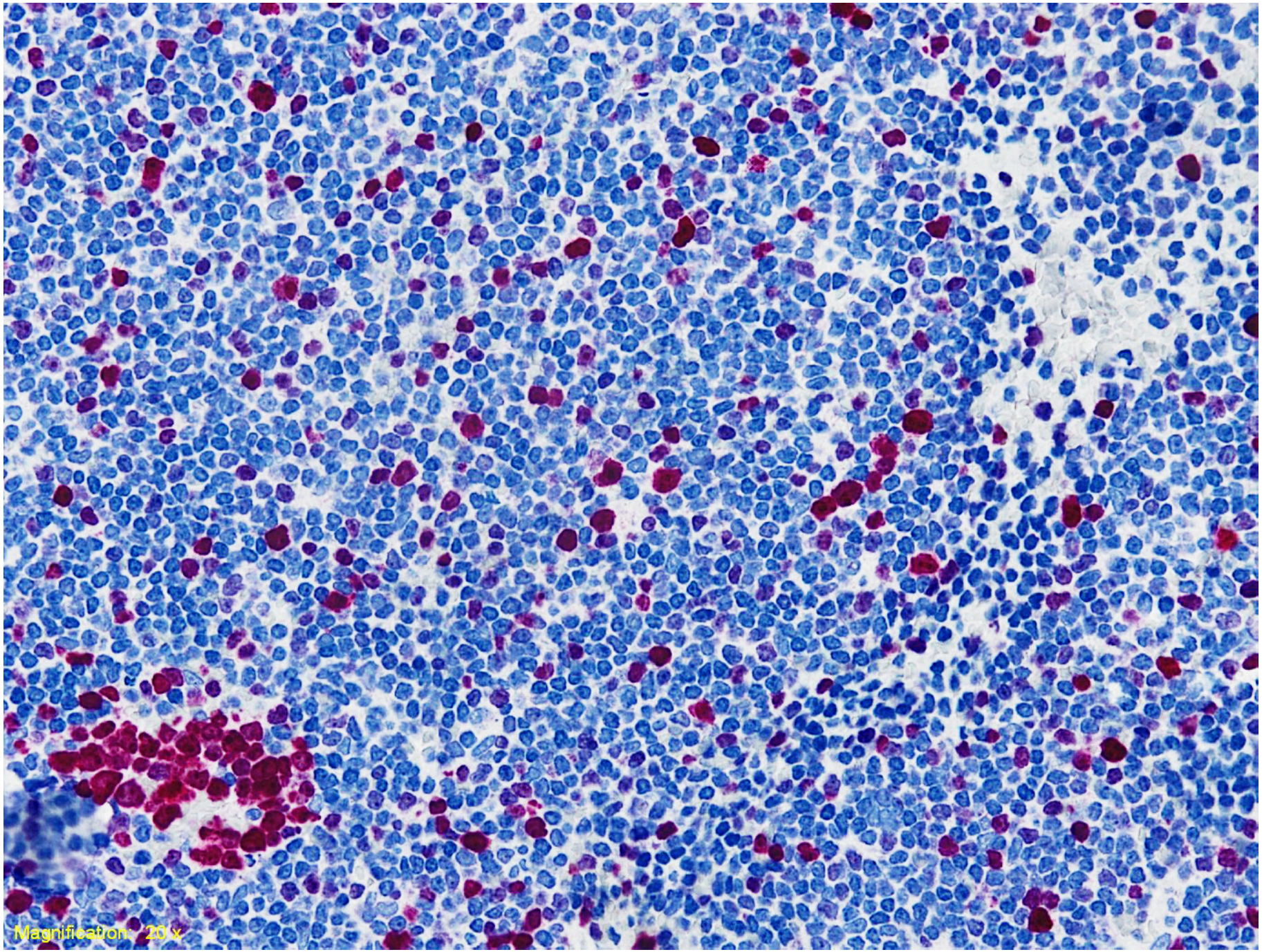
No difference between
<10% or <30% and 40-50% or >50%

So CUT OFF 30%

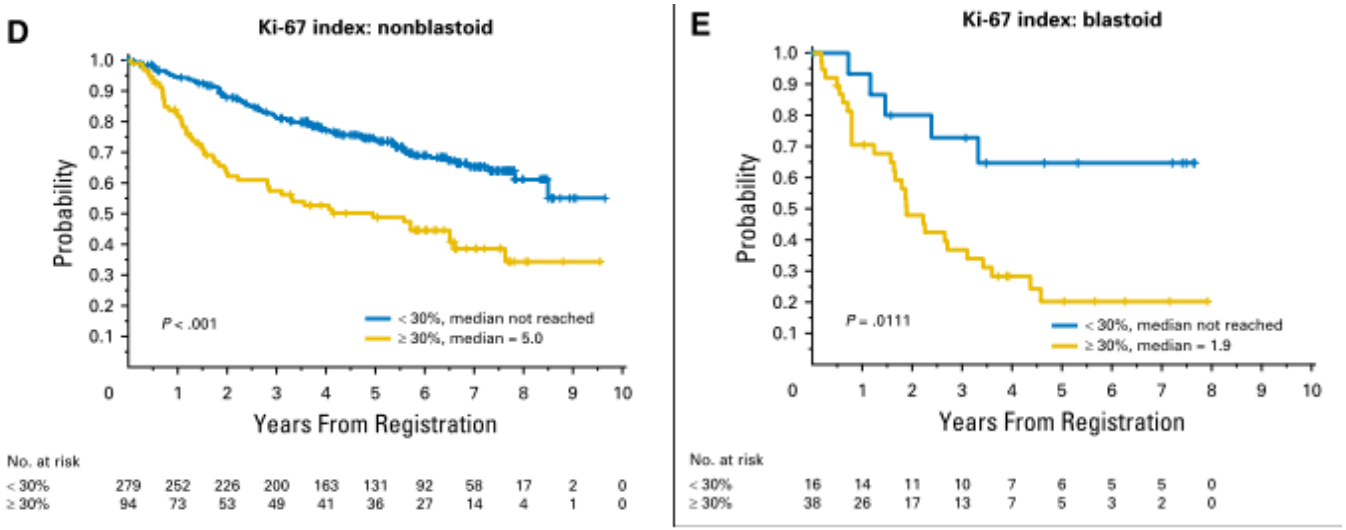


Ki67 and MIPI (MIPI-b)
Ki-67 not correlated with age;
related with PS, LDH, WBC
(low/intermediate MIPI: median ki67 19%
High risk MIPI: median ki67 27%)


Magnification : 20 x


Magnification: 20x

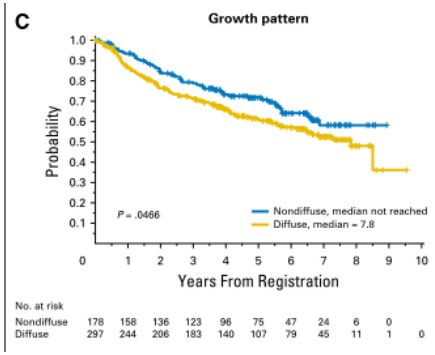
Ki67 and cytology



Median Ki-67

blastoid 80%
pleomorphic 39%
classic/small-cell:19%

Within each cytology subset,a higher Ki-67 index is associated with inferior outcome



No relation with growth

low-risk MIPI
>MC-growth
Ki67 (<30%)

determination of SOX11 & evaluation of mutations in IgVH genes

can be additional parameters to take into cacount for therapy strategy

To segregate other types of "indolent" nodal/extranodal MCL

Histology (cytology and growth pattern)
IgVH Mutational Status
SOX11 expression
Proliferative signature/kinetics
Somatic mutations and other genetic aberrations

Landscape of somatic mutations and clonal evolution in mantle cell lymphoma

PNAS | November 5, 2013

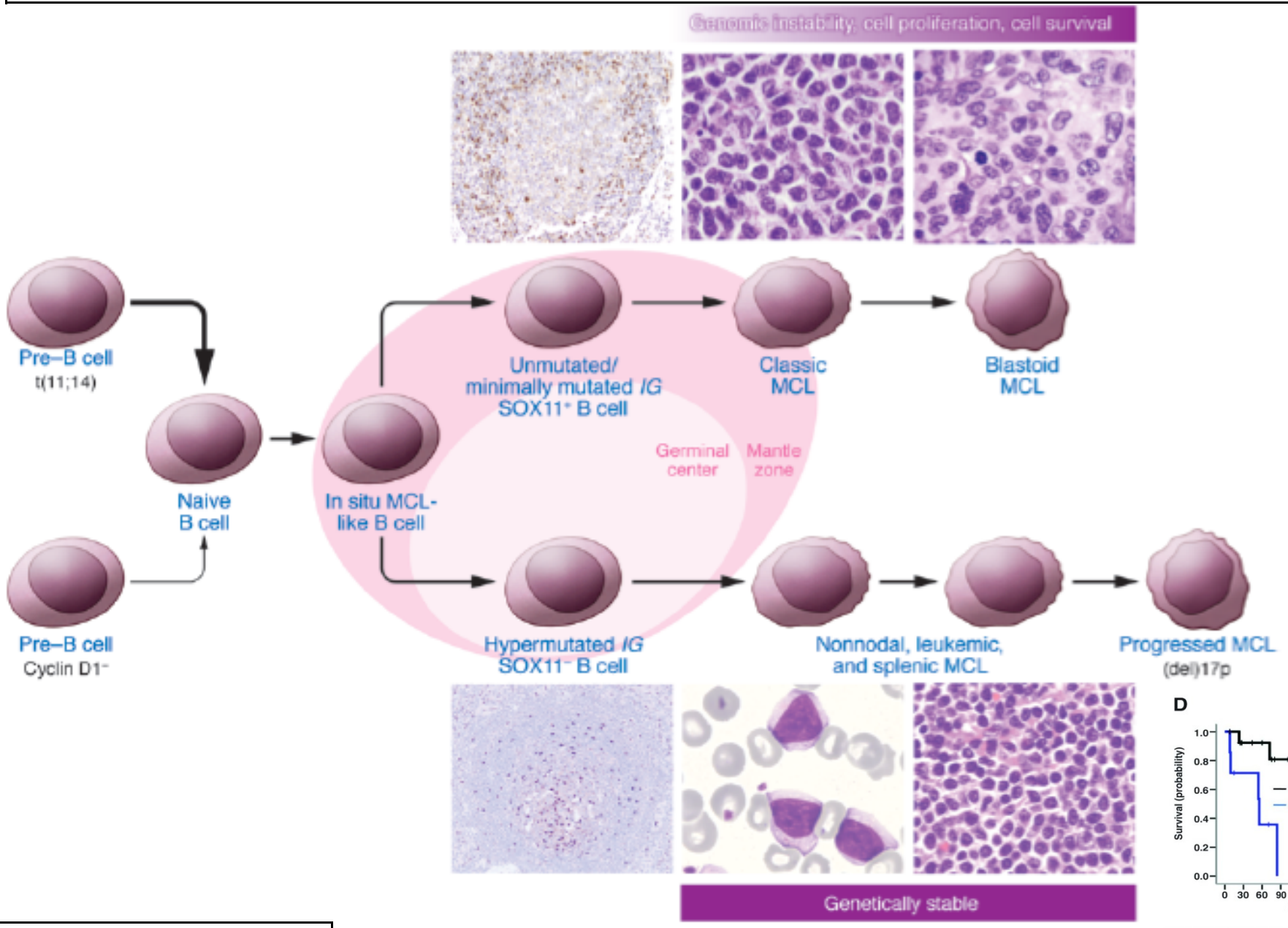
Sílvia Beà[a,1], Rafael Valdés-Mas[b], Alba Navarro[a], Itziar Salaverria[a], David Martín-Garcia[a], Pedro Jares[a], Eva Giné[a], Magda Pinyol[a], Cristina Royo[a], Ferran Nadeu[a], Laura Conde[a], Manel Juan[a], Guillem Clot[a], Pedro Vizán[c], Luciano Di Croce[c], Diana A. Puente[b], Mónica López-Guerra[a], Alexandra Moros[a], Gael Roue[a], Marta Aymerich[a], Neus Villamor[a], Lluís Colomo[a], Antonio Martínez[a], Alexandra Valera[a], José I. Martín-Subero[a], Virginia Amador[a], Luis Hernández[a], Maria Rozman[a], Anna Enjuanes[a], Pilar Forcada[d], Ana Muntañola[d], Elena M. Hartmann[e], María J. Calasanz[f], Andreas Rosenwald[e], German Ott[g], Jesús M. Hernández-Rivas[h], Wolfram Klapper[i], Reiner Siebert[j], Adrian Wiestner[k], Wyndham H. Wilson[l], Dolors Colomer[a], Armando López-Guillermo[a], Carlos López-Otín[b,2], Xose S. Puente[b,1,2], and Elías Campo[a,1,2]

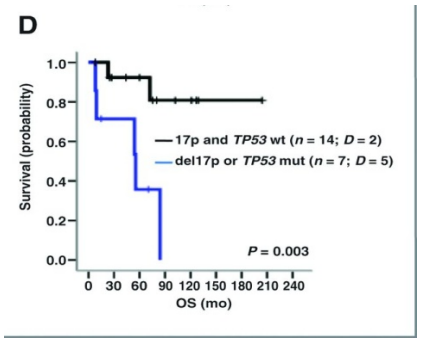
"SECONDARY" ONCOGENIC EVENT

deletions, gains, point mutations

target genes involved in molecular pathways, inducing their constitutive activation

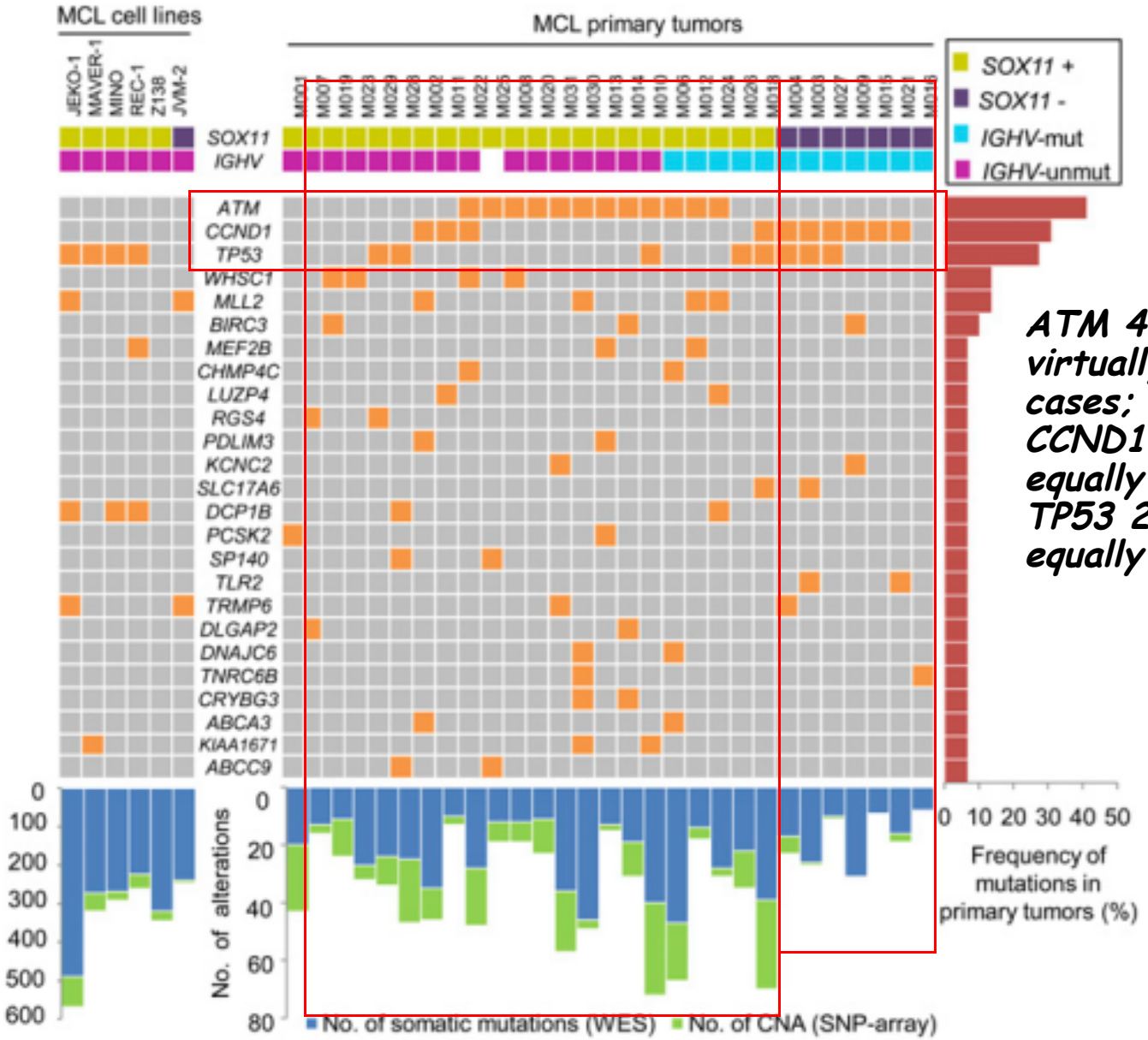
MAY IMPACT ON MCL BIOLOGY AND PROGRESSION





Jared et al. JClinInvest 2012

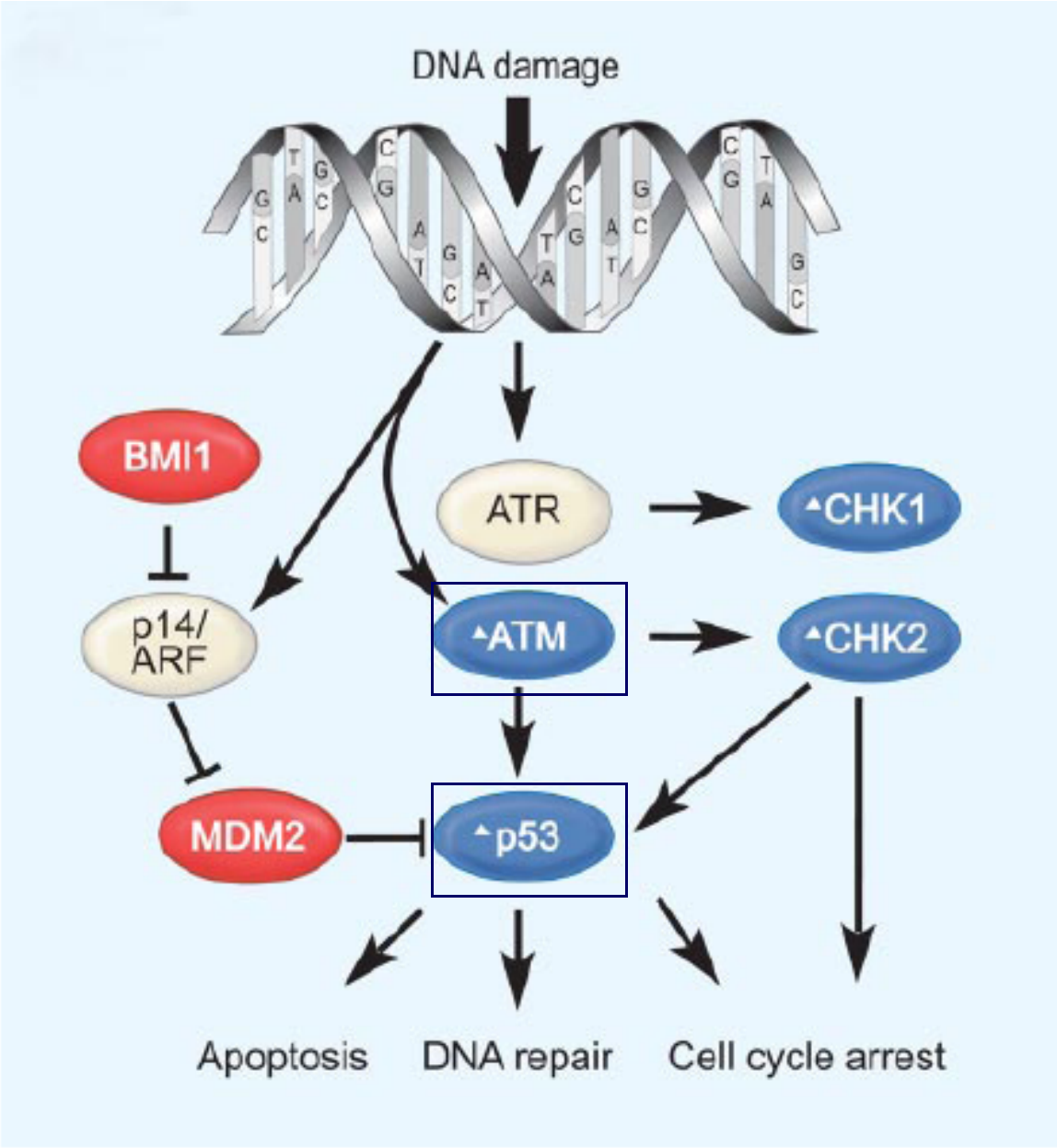
3 MCL gene drivers



ATM 41%
virtually absent in SOX11-/Mutated cases;
CCND1 35%
equally distributed; not defined impact
TP53 28%
equally distributed;

few CNA in SOX11 cases
(not related with muattional status)

ATM (11q21-q23) e TP53: più spesso mutazioni in un allele + delezioni allele wild type (11q e 17p); CCND1: più spesso mutazioni nell'esone 1;



ATM and TP53 involved in DNA repair/damage
via activate kinases
ATR and ATM and TP53
(via CHK1,CHK2)
p14-ARF
Inducing cell cycle arrest/apoptosis

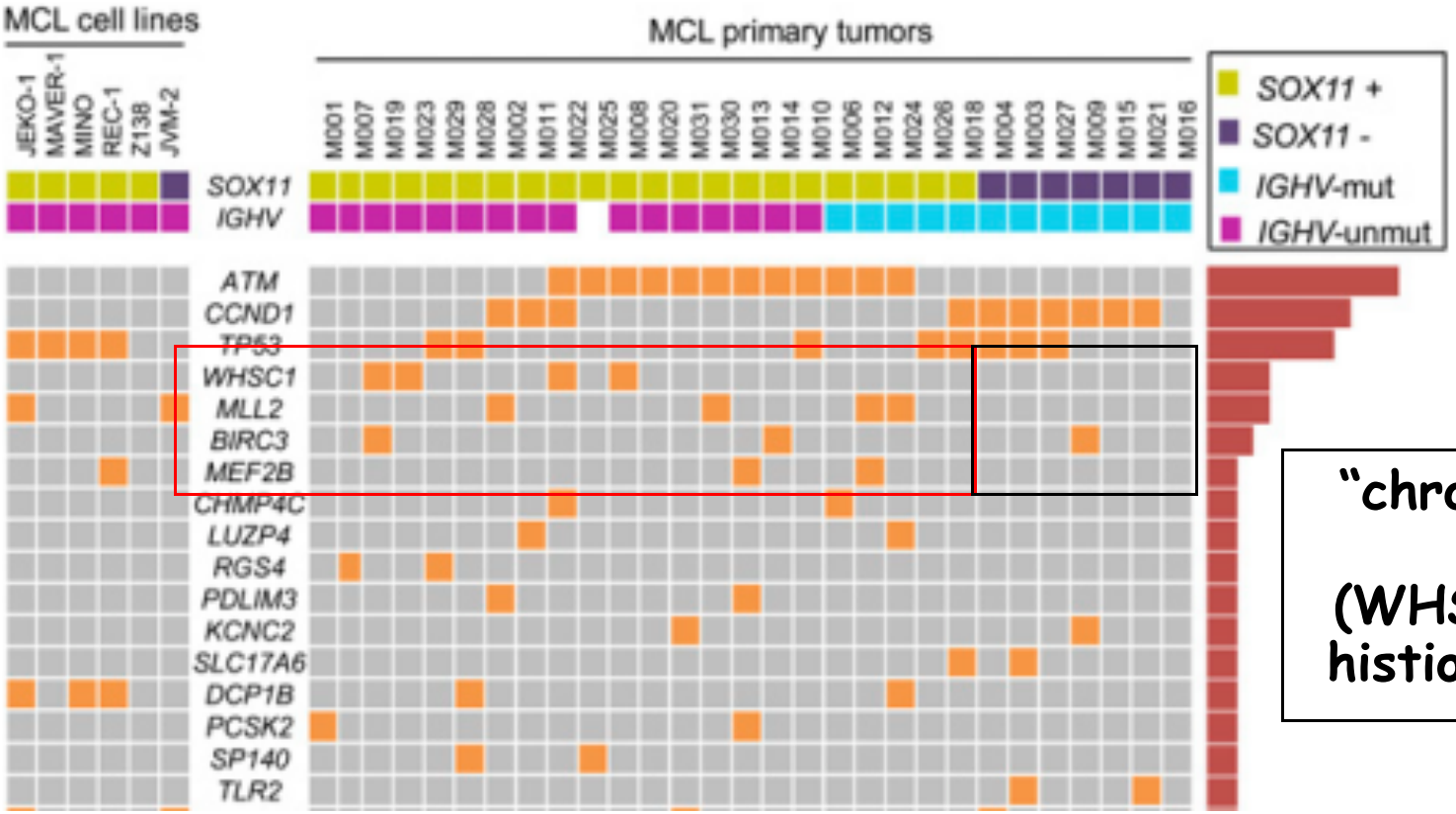
ATM and p53 deletions/mutations

Lead to failure in DNA repair –

Poor outcome

Possible overexpression of MDM2/MDM4

In MCL
BLU: molecules inactivated/downregulated
RED: molecules activated/overexpressed



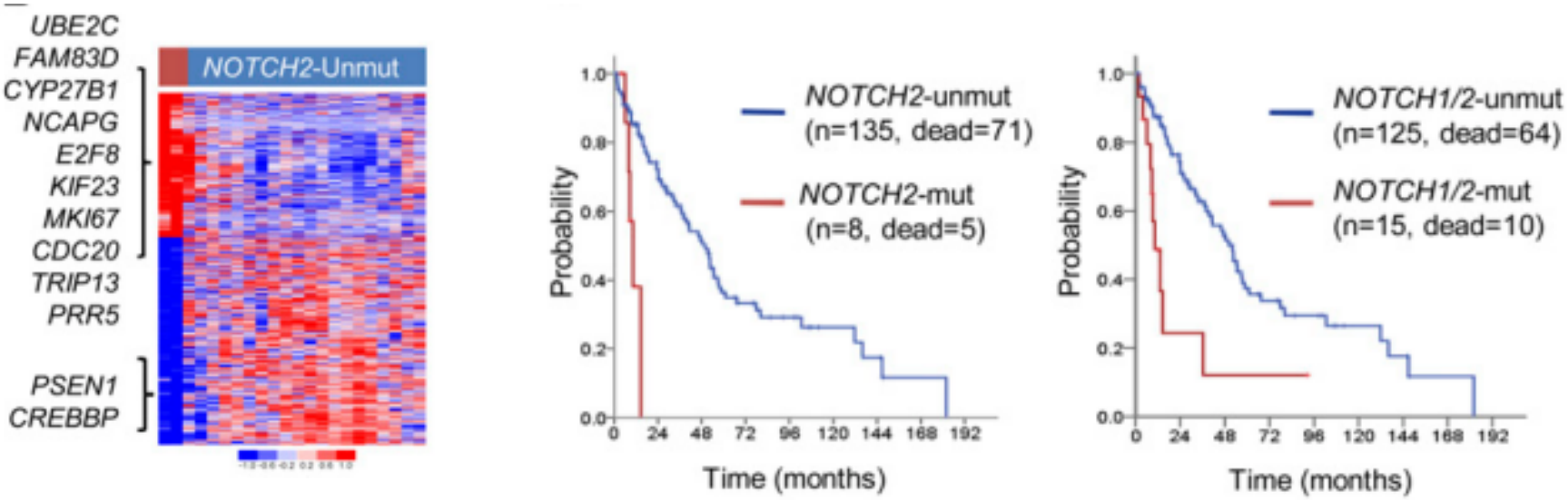
"chromatin modifiers" genes

(WHSC1 and MLL2 code for histione-methyltransferases)

WHSC1 10%
MLL2 14%
MEF2B 3%

VIRTUALLY ABSENT IN SOX11 NEGATIVE CASES

BIRC3	6 (11/173)	7 (7/95)	9 (9/97)



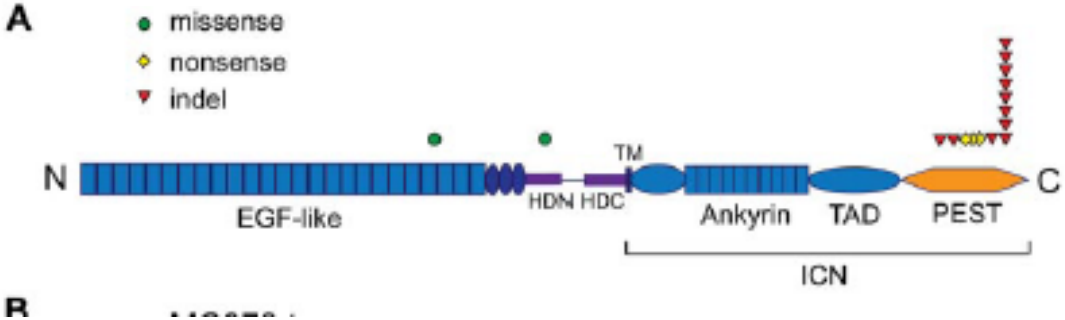
9.5% cases present NOTCH1 (4.7%) or NOTCH2 (5.2%) mutations
Usually alone, not together

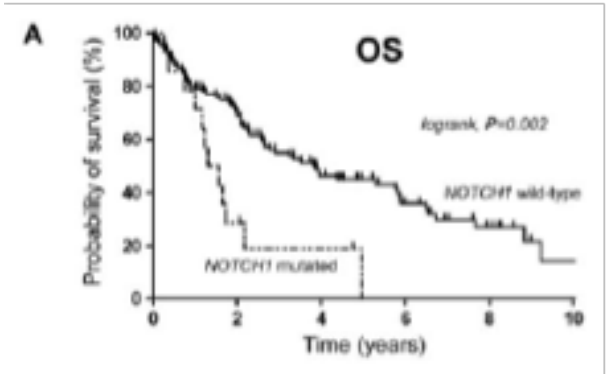
Adverse biological features (blastoid/pleomorphic) & shorter OS

Jared et al. JClinInvest 2012

NOTCH1 mutations: 12%

Usually single nucleotide substitution in PEST DOMAIN





No differences with non mutated cases as for stage, IPI, histology
NOTCH1+ not related with progression (≠BCLL Richter)
Possible link with MYC alteration

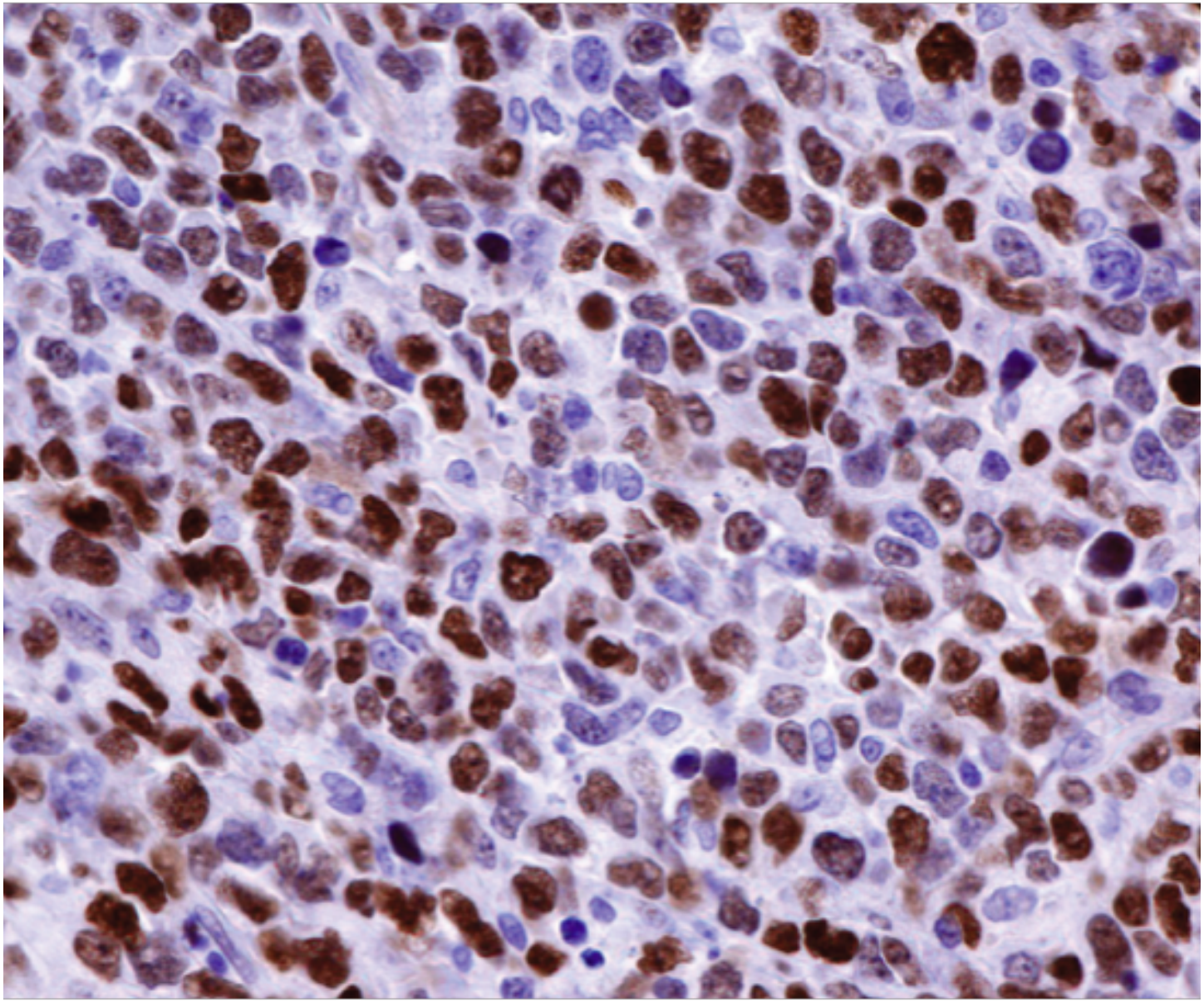
Worse OS (not PFS):
NOTCH1 as independent negative biomarker

Whole transcriptome sequencing reveals recurrent *NOTCH1* mutations in mantle cell lymphoma

Robert Kridel,[1,2] Barbara Meissner,[1] Sanja Rogic,[1] Merrill Boyle,[1] Adele Telenius,[1] Bruce Woolcock,[1] Jay Gunawardana,[1,2] Christopher Jenkins,[3] Chris Cochrane,[3] Susana Ben-Neriah,[1] King Tan,[1] Ryan D. Morin,[4] Stephen Opat,[1] Laurie H. Sehn,[1] Joseph M. Connors,[1] Marco A. Marra,[4] *Andrew P. Weng,[3] *Christian Steidl,[1,2] and *Randy D. Gascoyne[1,2]

(*Blood*. 2012;119(9):1963-1971)

MYC



Oberley MJ, et al. Histopathology. 2013 Immunohistochemical evaluation of MYC expression in mantle cell lymphoma.

… **showed that MYC IHC score is an independent predictor** of progression-free survival and overall survival…

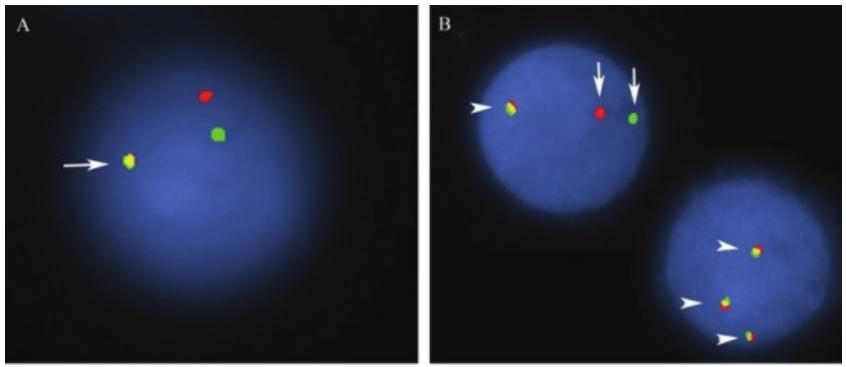
*MYC alterations usually as secondary events

All cases were **blastoid MCL,
with **high WBC** count,
bm involvement
splenomegaly
elevated LDH
***Complex karyotype**
very aggressive
(few reach CR which is short; BL-like regimens

High incidence of MYC and BCL2 abnormalities in MCL, although only MYC abnormality predicts poor survival
Yi S et al. Oncotarget. 2015

Myc overexpression correlates with MYC amplification or translocation and is associated with poor prognosis in MCL
Choe JY et al. Histopat 2016

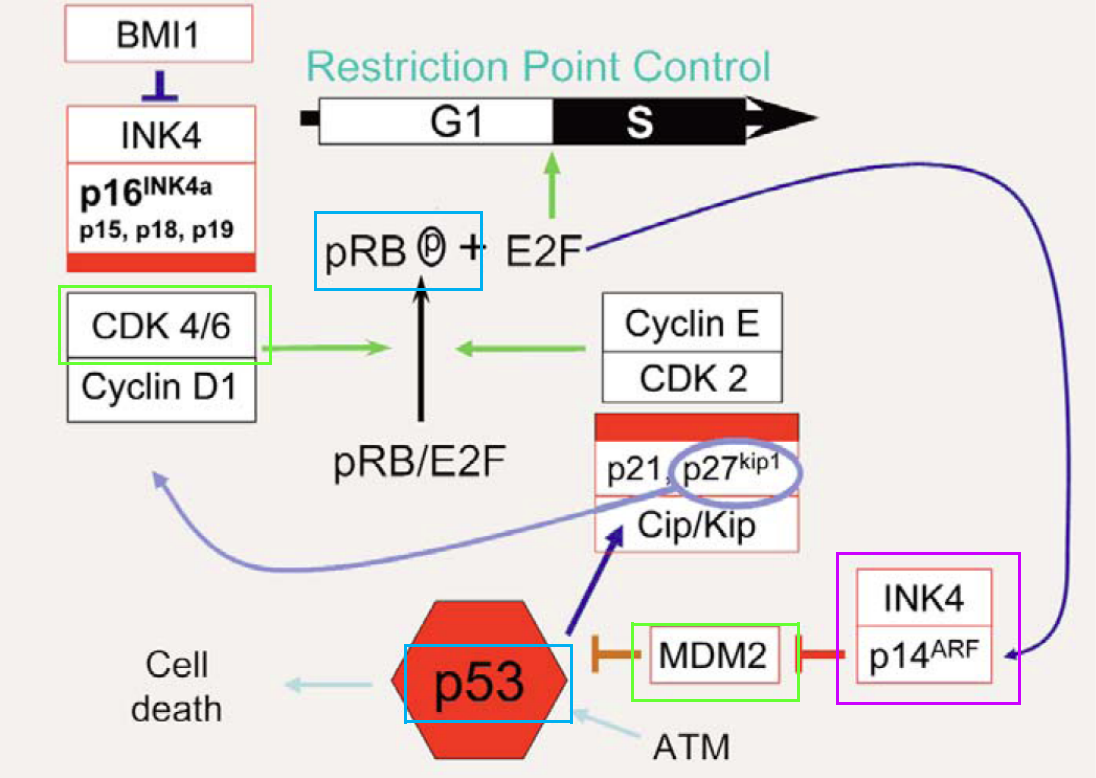
An aggressive B cell lymphoma with rearrangement of MYC and CCND1 genes: a rare subtype of double hit lymphoma
Durot E et al. Leuk Lymph 2013



Double-hit mantle cell lymphoma with MYC gene rearrangement or amplification: a report of four cases and review of the literature Int J Clin Exp Pathol 2013;

Reza Setoodeh[1,2], Stuart Schwartz[3], Peter Papenhausen[3], Ling Zhang[1,2], Elizabeth M Sagatys[1,2], Lynn C Moscinski[1,2], Haipeng Shao[1,2]

targeting CELL CYCLE genes

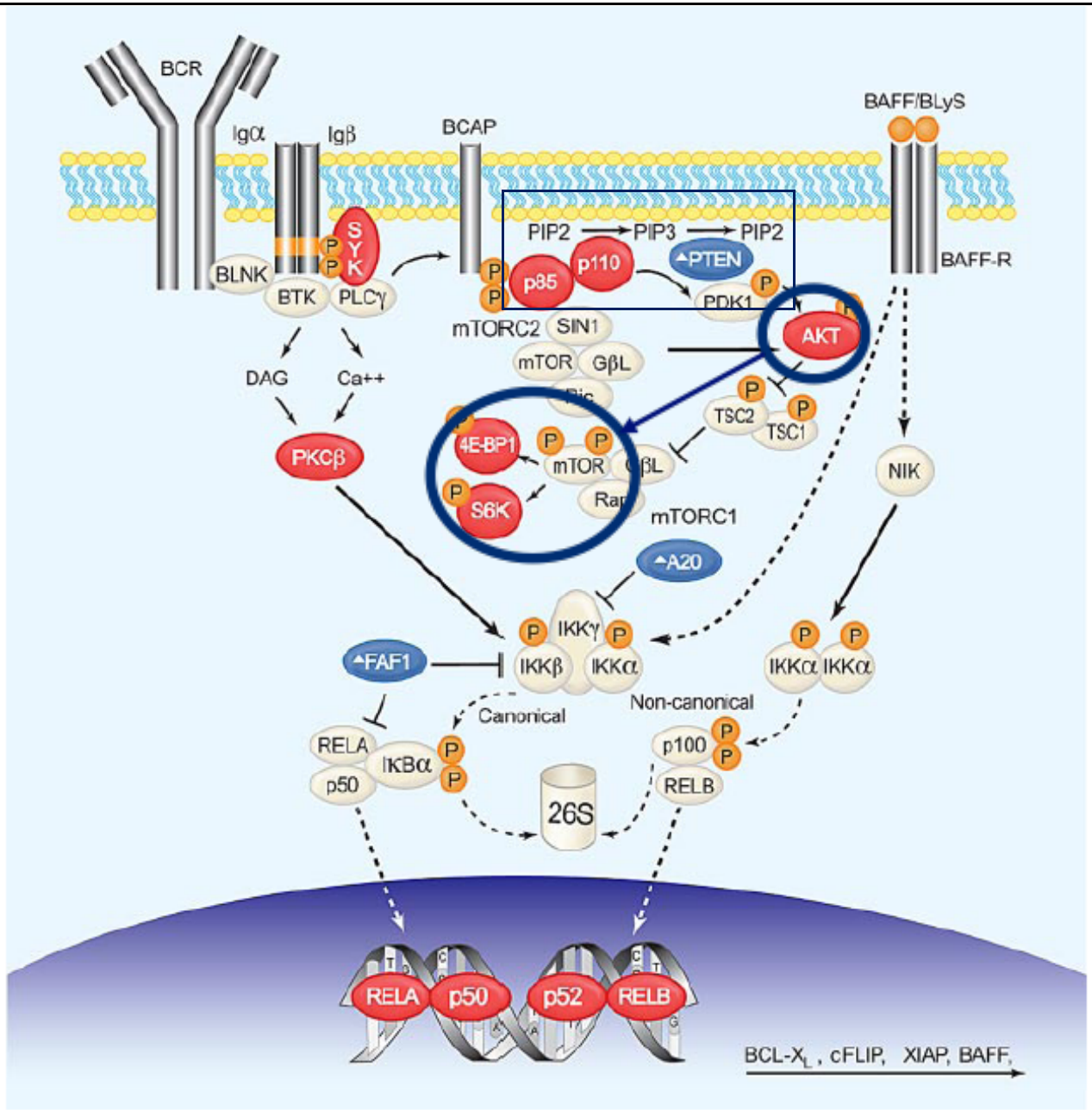


Point mutations/deletions RB1 activated E2F

Amplification of CDK4 or MDM2

Deletion of CDKN2A (9p21) which encodes for INK4/p16 (CDK inhibitor) and ARF/p14 (positive p53 regulator and MDM2 inhibitor): CDK are not inhibited and p53 is not activated --- aggressive MCL

PI3K/AKT/mTOR: activation of key proteins



PI3K (reverted by PTEN)

↓

activates AKT
(AKT is activated by complexTORC2)

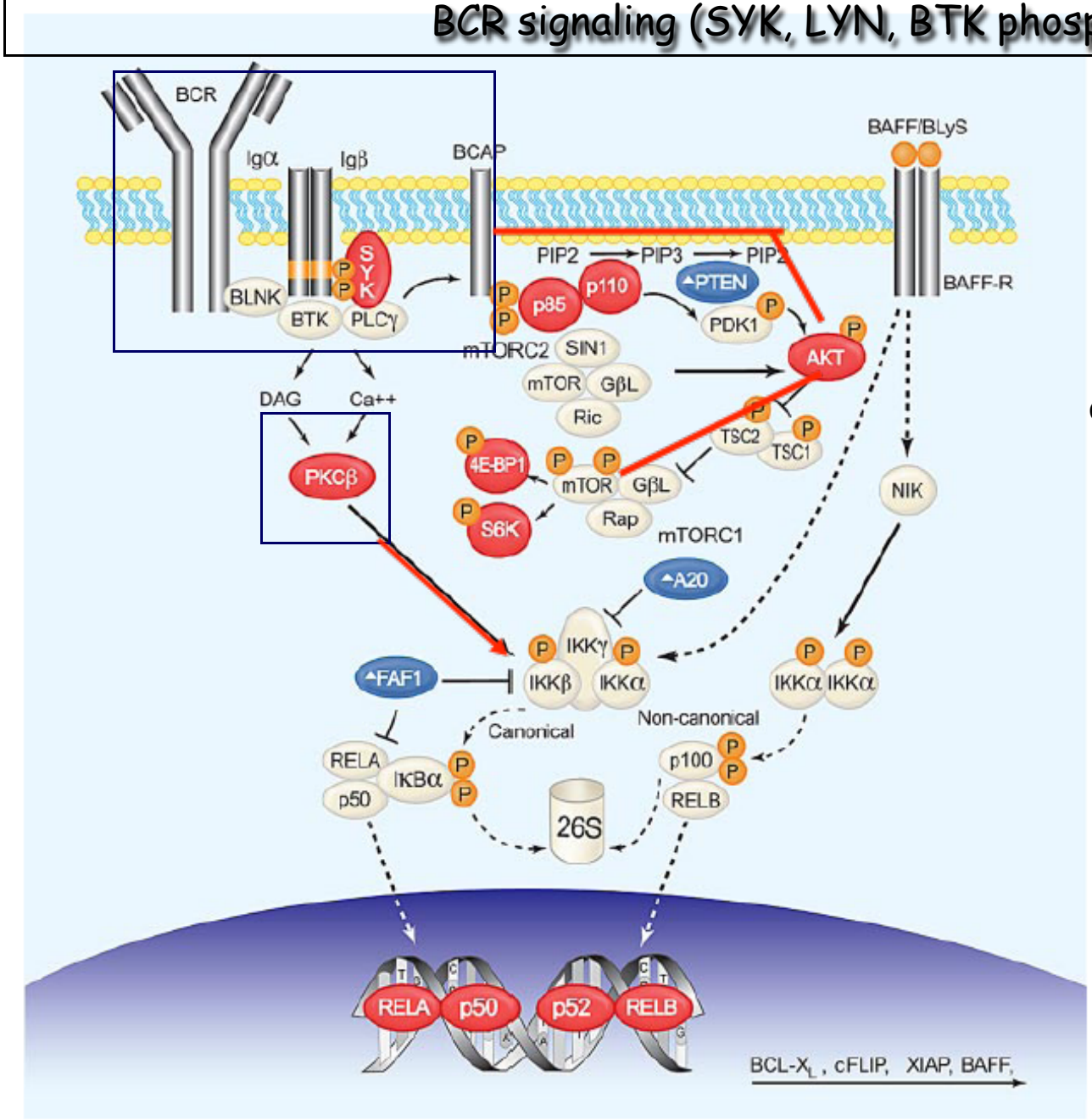
↓

activates mTOR
(complexTORC1)

↓

Increase translation of cyclinD1,MYC

BCR signaling (SYK, LYN, BTK phosphorilated)

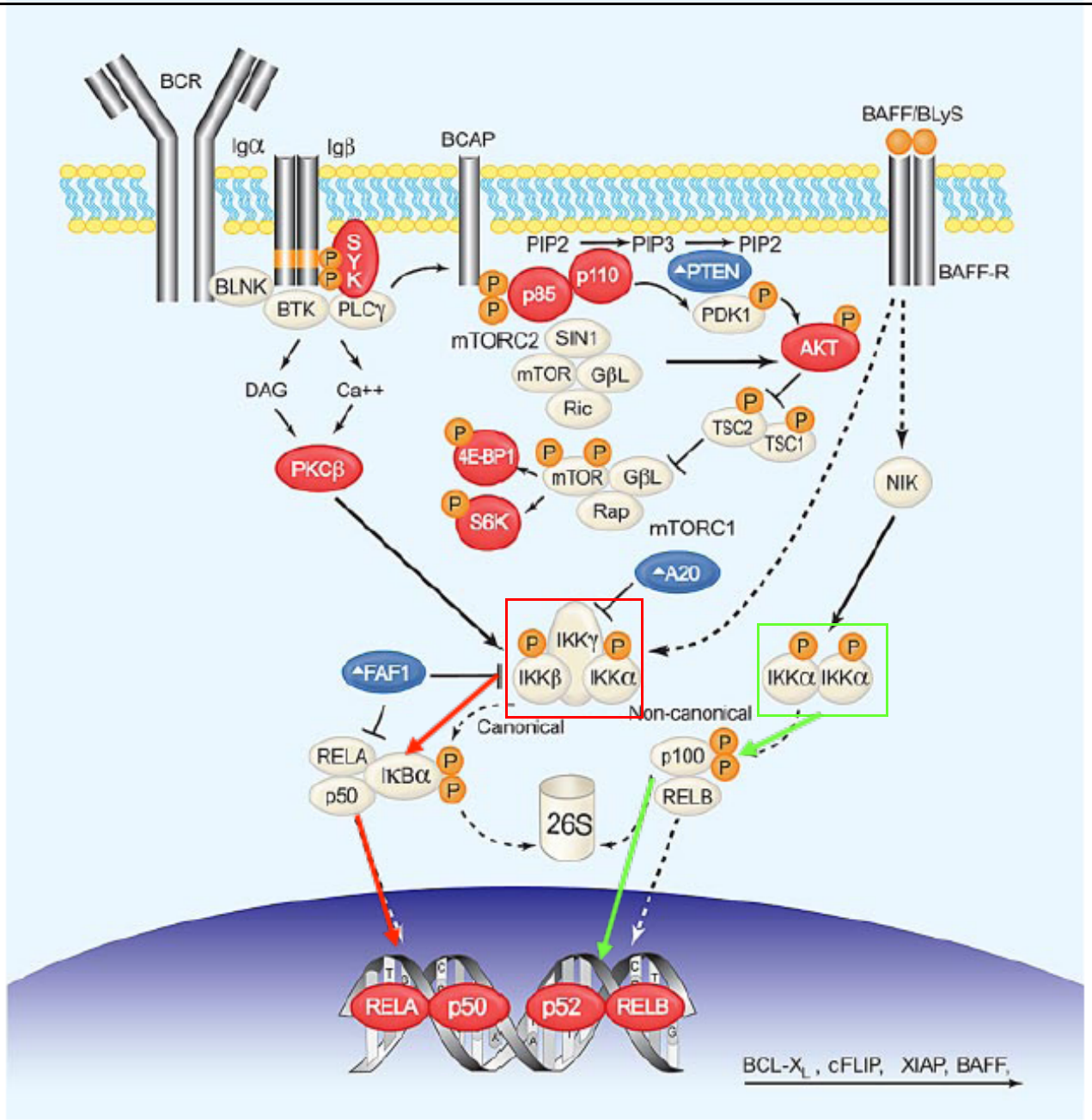


BCR and SYK BTK kinases

amplify PI3K/AKT/mTOR pathway through SYKinase

Or
Activate NF-kappa B through PKCbeta

NFkb classic / NFkb alternative



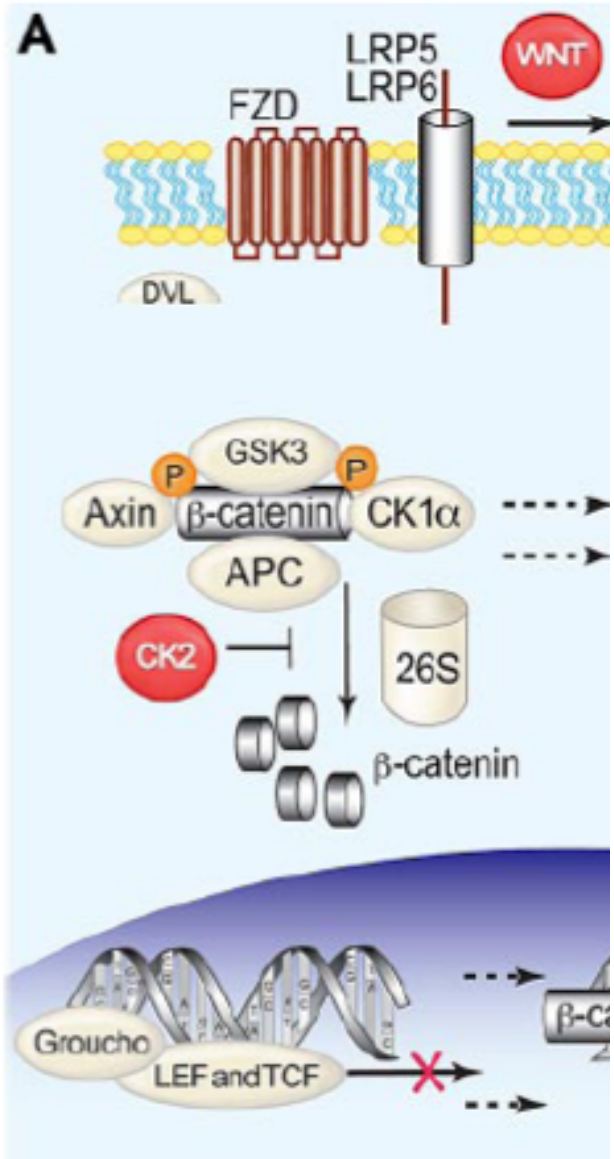
CLASSIC
Phosphorilation of IKK complex – phosphorilate/degradation of IKBa (inhibitor) with release of RELA/p50 which move to nucleus

ALTERNATIVE
Phosphorilation of IKKa— phosphorilation of p100 – proteosomal generation of p52/RELB

Either way end is positive signals for SURVIVAL, PROLIFERATION, APOPTOSIS

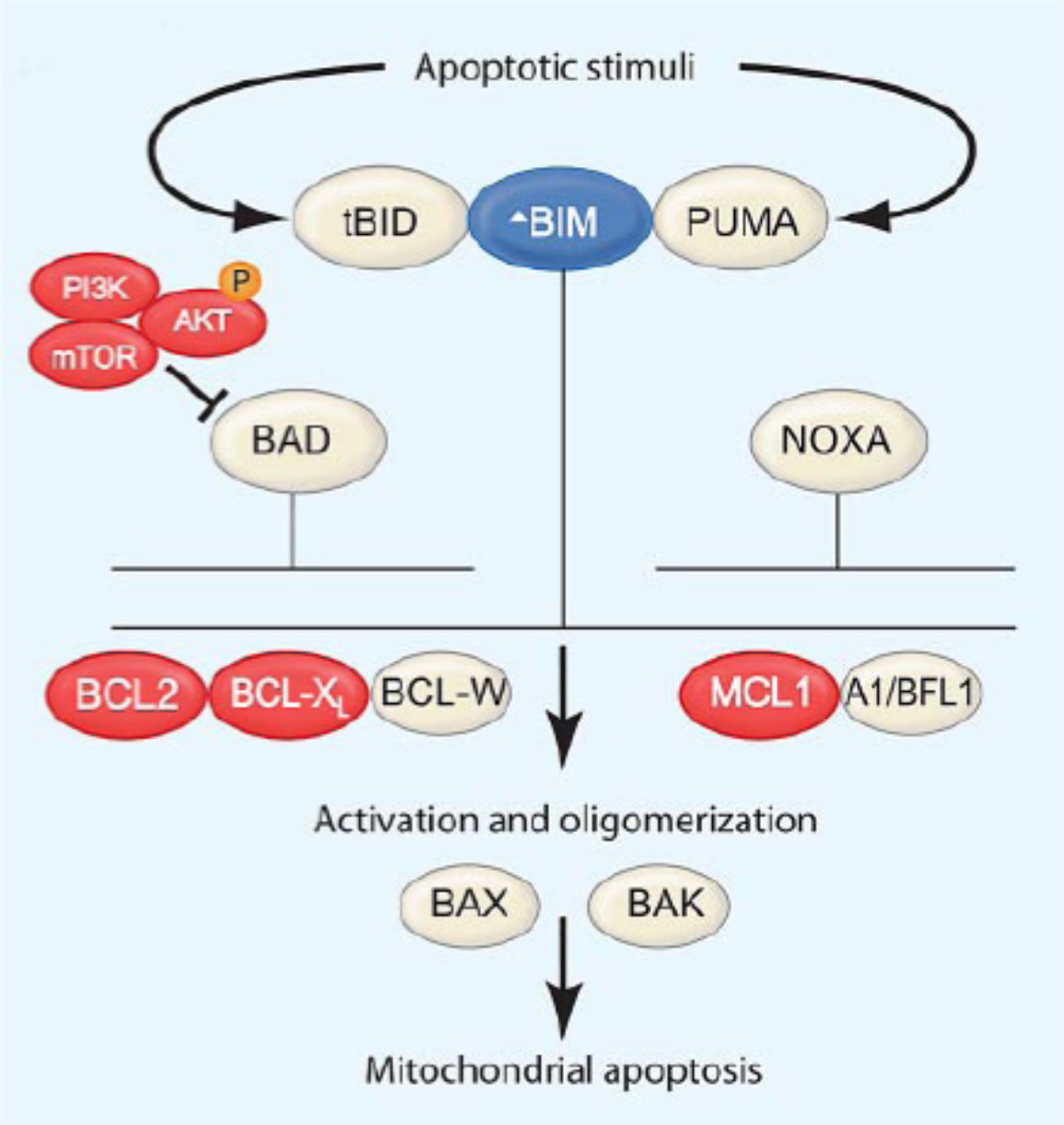
WNT/beta catenin

When WNT is not linked to its receptor B catenin is usually degradated by GSK3 (+ other proteins degradation box)



In MCL

WNT is linked to its receptor, B catenin is not degradated and go to the nucleus activating LEF and TCF



In MCL

- **Propapoptotic BIM/BCL2L11/ 2q13: frequently with homozygous deletion**
- **Antiapoptotic molecules BCL2 (18q21): often amplified**
- **PI3K\AKT\mTOR inhibits the proapoptotic BAD**

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COMMON MOLECULAR FEATURES AMONG B-CELL LYMPHOMAS BUT ALSO RELEVANT DIFFERENCES

BCLL: NOTCH1, ATM, BIRC3

no NOTCH2, MLL2, MEFB2, WHSC1

SMZL: NOTCH2

no NOTCH1, WHSC1

DLBCL/FL: MLL2, MEFB2

no ATM, BIRC3, WHSC1

MCL: NO MYD88, CARD11, EXH2, SF3B1