## SESSION I

Moderators:
*Antonio Cuneo (Ferrara), Francesco Lanza (Ravenna)*

**8:45**
**Biology of aggressive lymphomas:**
- **Diffuse large B cell lymphoma (DLBCL)**
- **Primary central nervous system lymphoma (PCNSL)**
- **Primary mediastinal B cell lymphoma (PMBCL)**
- **Mantle cell lymphoma**
- **T cell NOS**
- **Angioimmunoblastic T cell lymphoma**
- **Anaplastic T cell lymphoma**

*Elena Sabattini (Bologna)*

**9:45**
**DLBCL Young patients:**
**Therapy for limited stages and IPI < 2**
*Luigi Rigacci (Firenze)*

**10:15**
**DLBCL Young patients:**
**Therapy for High risk IPI ≥ 2**
*Umberto Vitolo (Torino)*

**10:45** *Coffee Break*

**11:00**
**Terapeutic strategies for elderly patients**
*Michael Pfreundschuh (Homburg-DE)*

**11:40**
**Mantle cell lymphoma:**
**Risk adapted strategies and current treatment algorithm**
*Emanuele Zucca (Bellinzona-CH)*

**12:20**
**PMBCL: First line treatment and salvage therapy**
*Maurizio Martelli (Roma)*

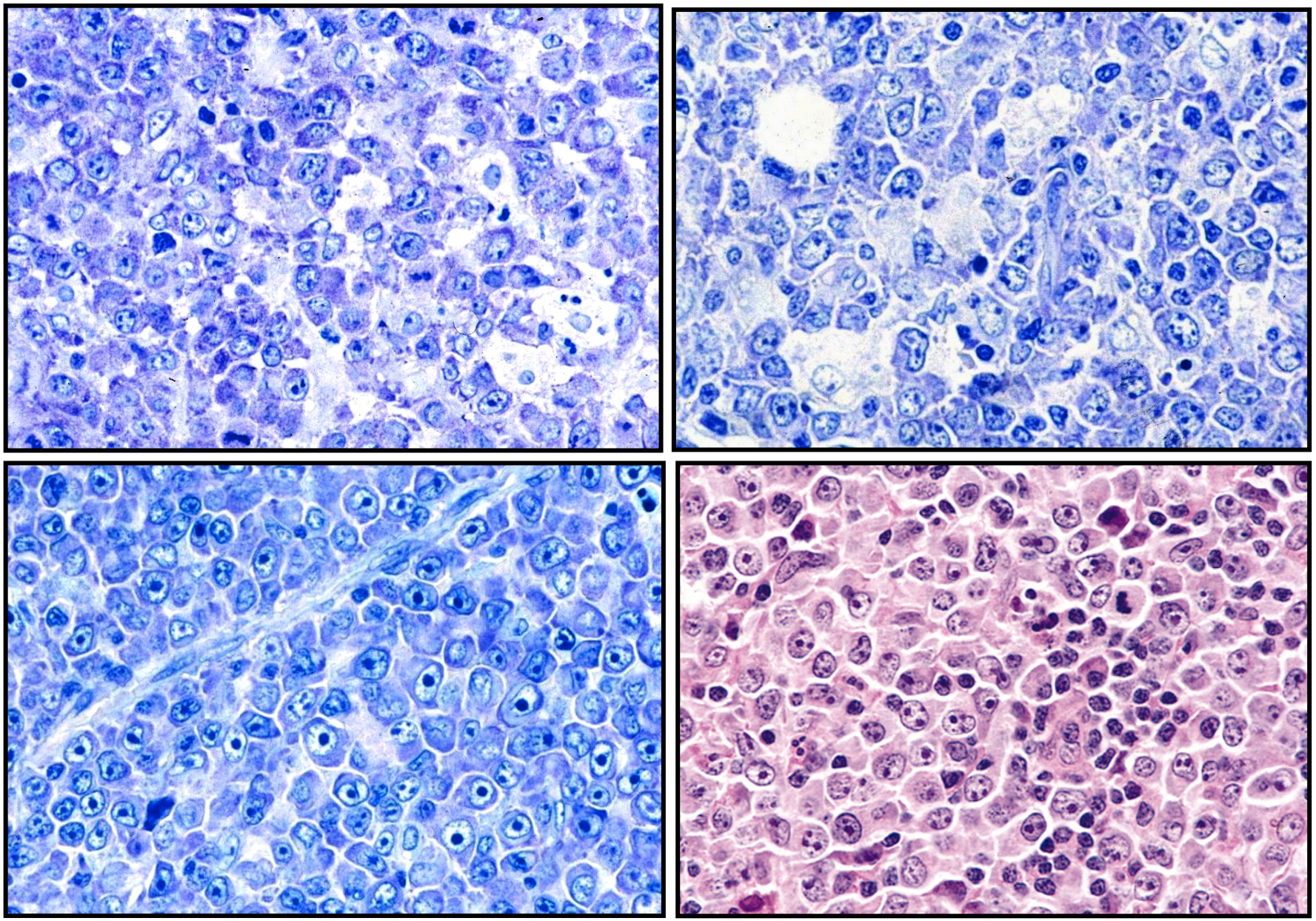
**12:50**
**PCNSL: State of the art**
*Andres J.M. Ferreri (Milano)*

**Unità di Emolinfopatologia**
**Istituto L&A Seragnoli**
**AOU di Bologna**

# AGGRESSIVE LYMPHOMAS

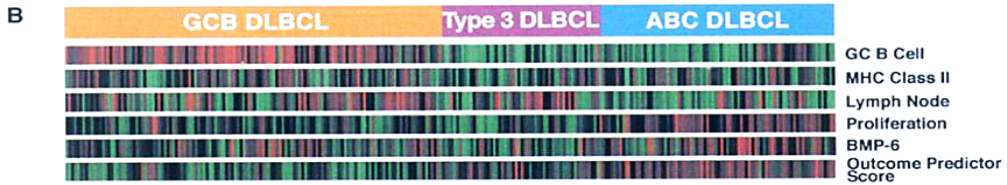
Rimini
20 maggio 2016

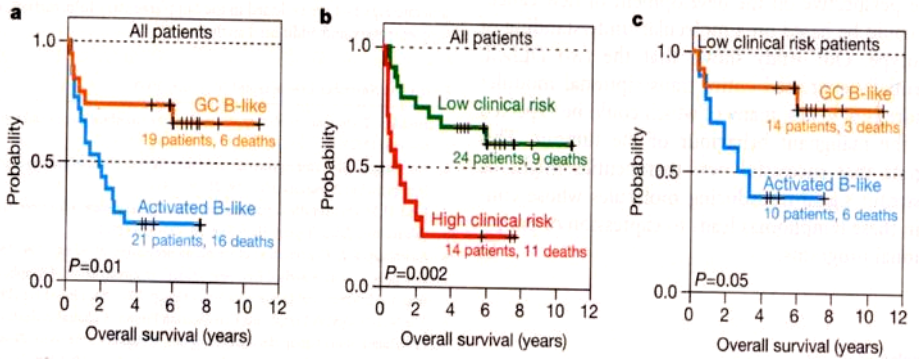
DLBCL: most frequent, made of large lymphocytes positive for B-cell markers, but morphologically, phenotipically, biologically and clinically heterogenous group of malignant diseases; IPI: still the most robust prognostic indicator

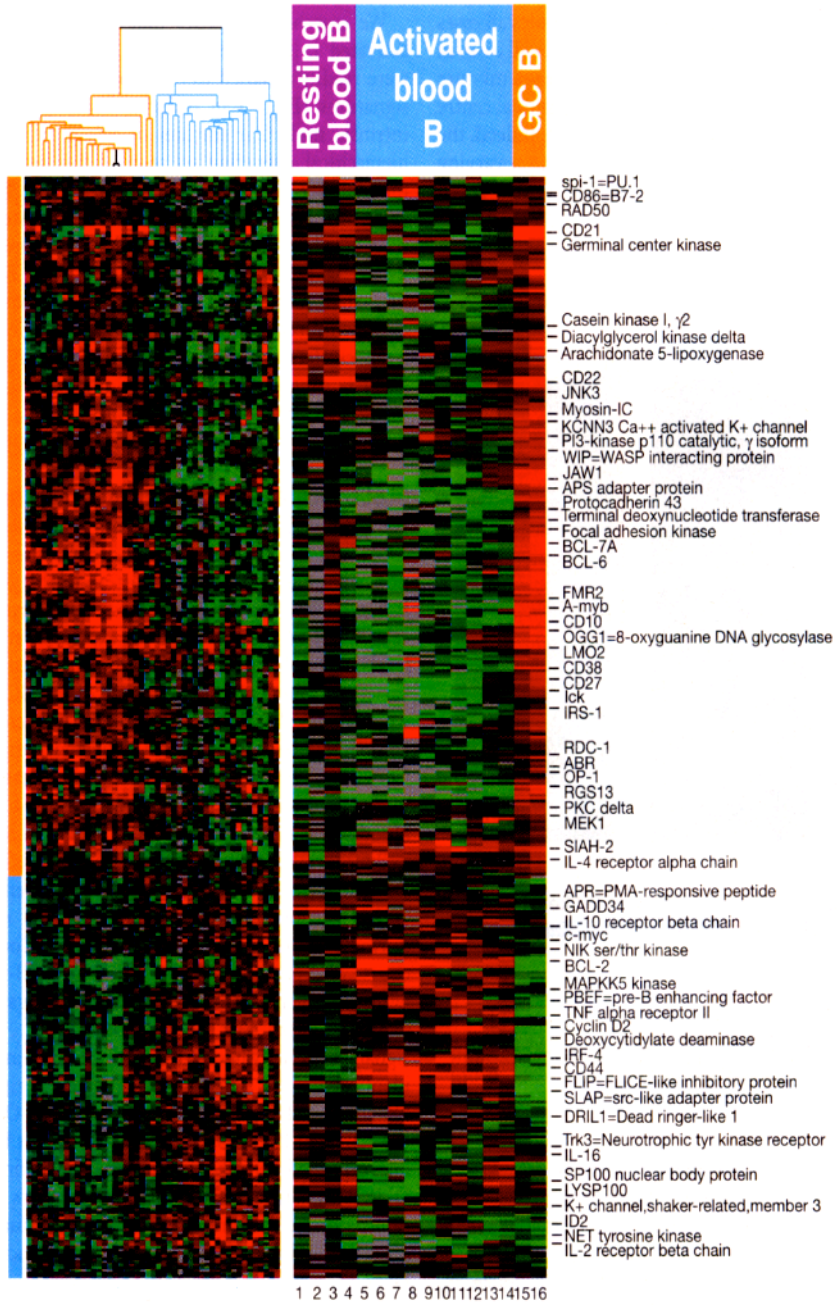


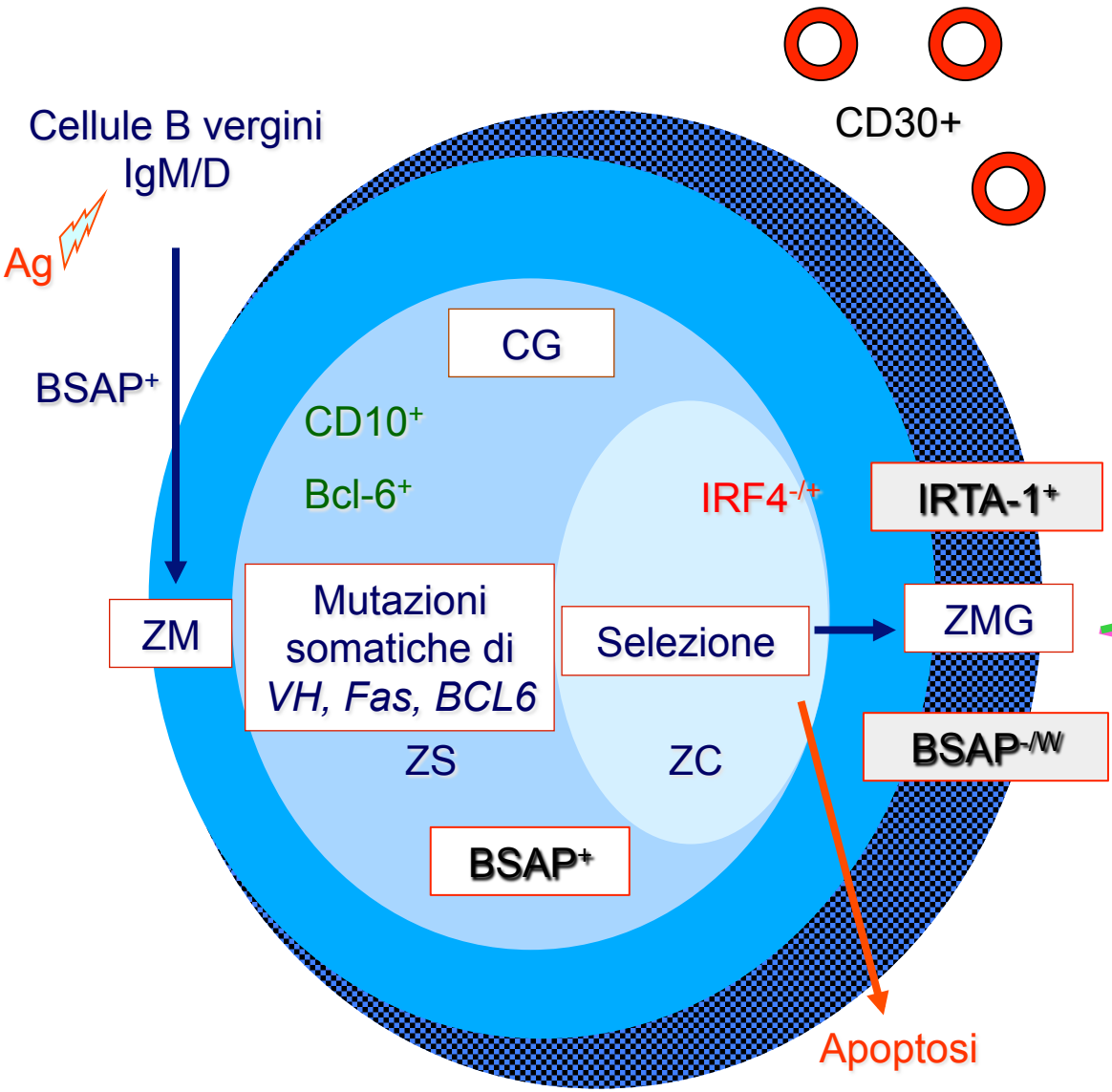
Alizadeh AA et al. Nature 2000, 403: 503-11

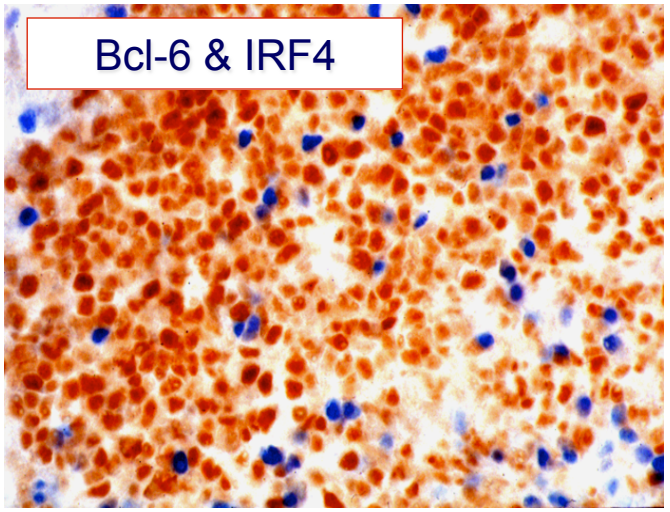
# Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling



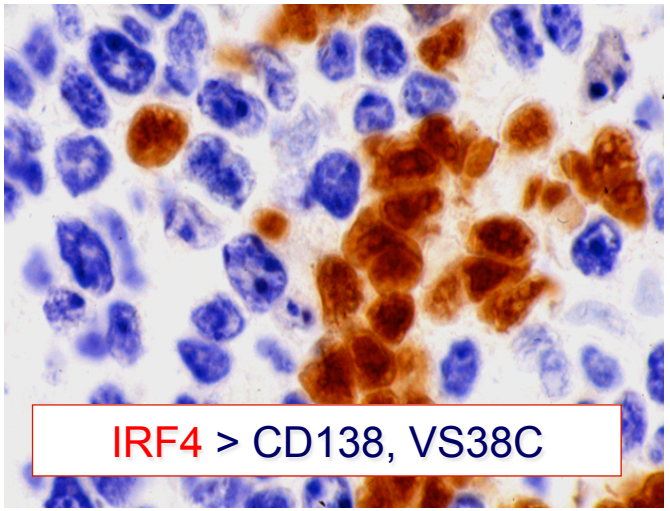


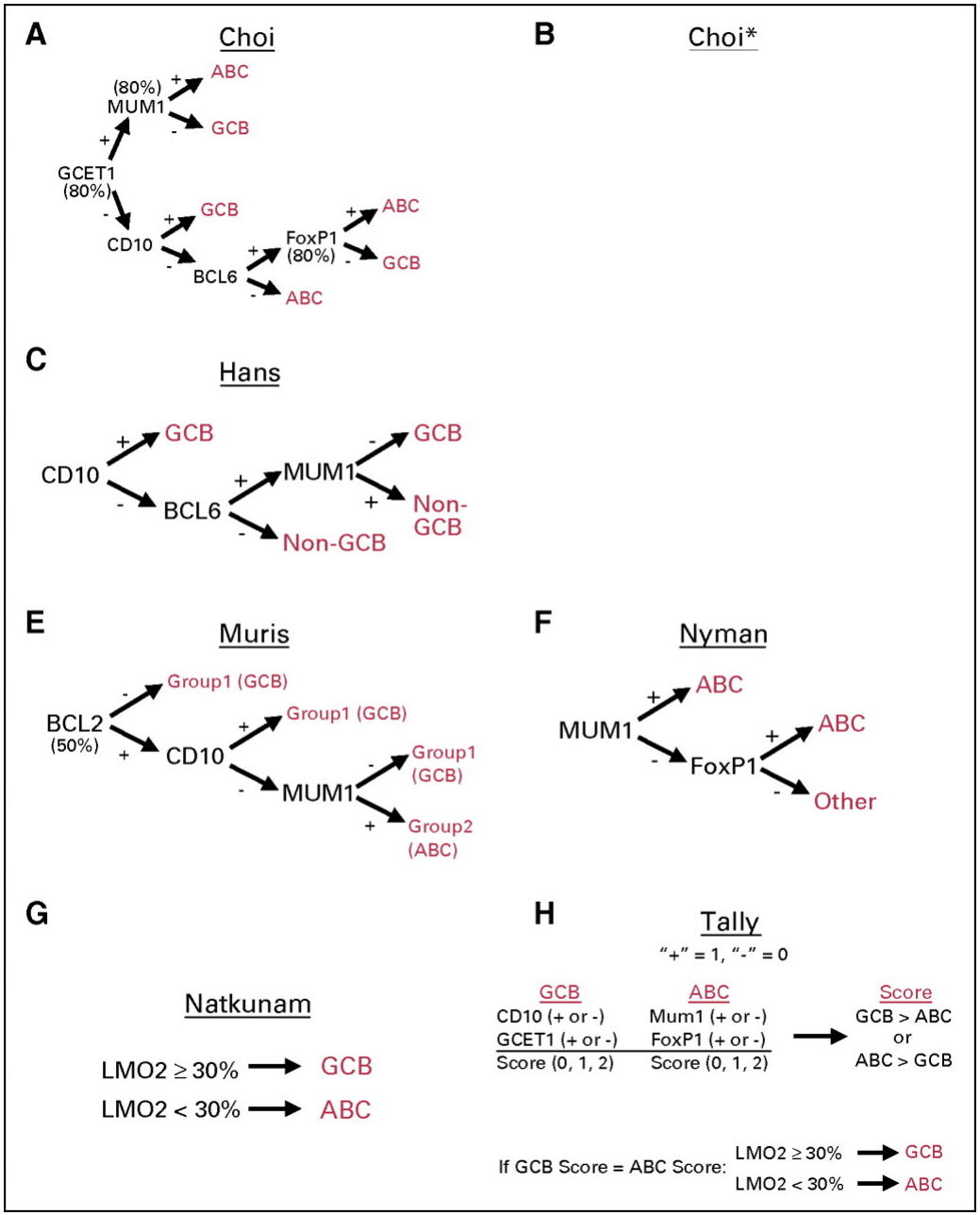

Cellule memoria
IRF4W/CD27

Blimp-1

Plasmacellule
BSAP-



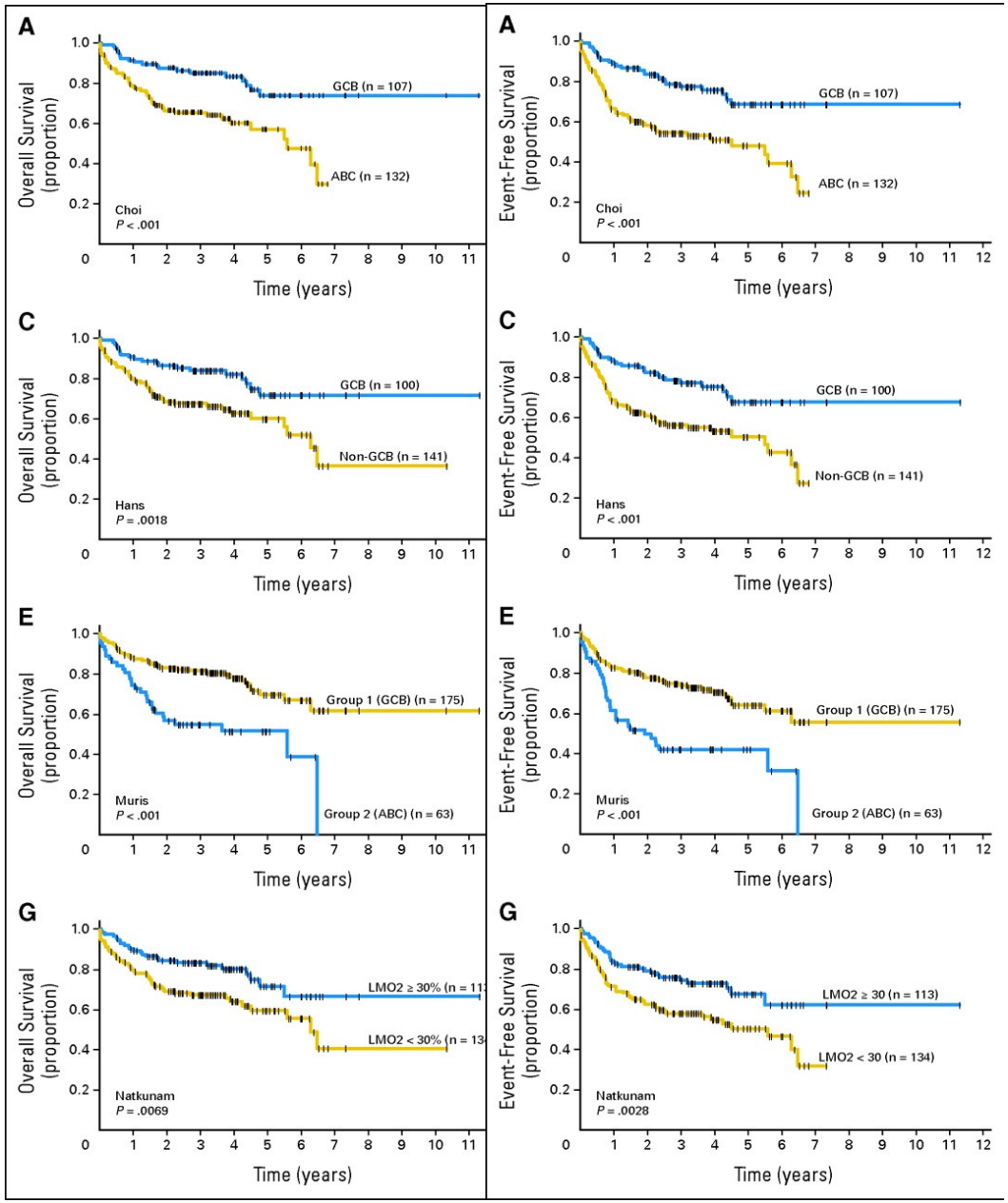
MEYER et al JCO 2011; 262 DLBCL

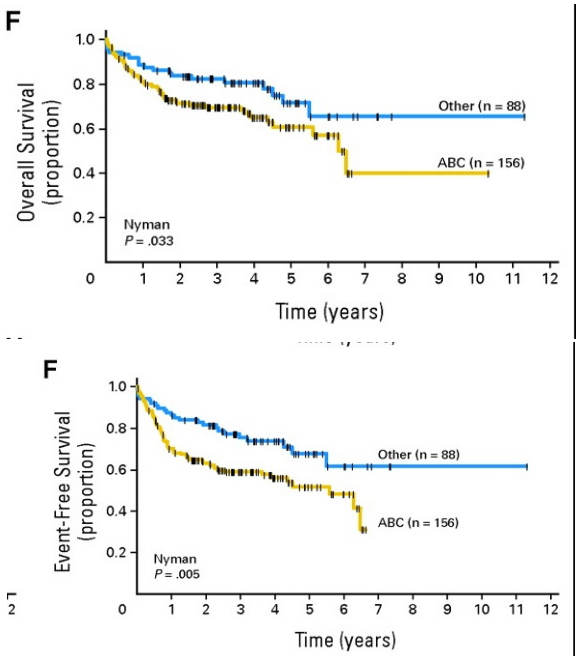



| Algorithm and IPT | No. | Concordance with GEP results(%) |
|---|---|---|
| **Choi** | | |
| GCB | 83 | **87** |
| ABC | 86 | |
| **Hans** | | |
| GCB | 79 | **86** |
| ABC | 90 | |
| **Muris** | | |
| GCB | 122 | **77** |
| ABC | 45 | |
| **Nyman** | | |
| GCB | 62 | **81** |
| ABC | 108 | |
| **Natkunam** | | |
| GCB | 84 | **74** |
| ABC | 86 | |

HIERACHICAL ORDER OF IMMUNE-REACTIVITY
CD10, bcl6, LMO2, GCET1 as GC related
IRF4, FOX1 as ABC related
Bcl2

# Can recognize GCB and non-GCB immunohistochemical subgroups




All algorythms divided cases into groups that predicted OS and EFS independent of the IPI.

More successful ones those compared with GEP

**WHO 2008**
**GEP not available as a routine clinical test**
**issues of reproducibility and reliability of ihc algorithms,**
**DBCL subclassification of DLBCL, NOS was optional**

**availability of target therapies for genes/pathways involved in GCB or non-GCB subsets**

**WHO 2016**
**identification of these two subtypes required**

**But since GEP is still not a routine test**
**IHC algorithms is acceptable (specify which algorithm)**

**(although WHO acknowledges that they do not recognize the 10-15% of tumors unclassified by GEP**

**However, also GEP does not recognize 10-15% cases**

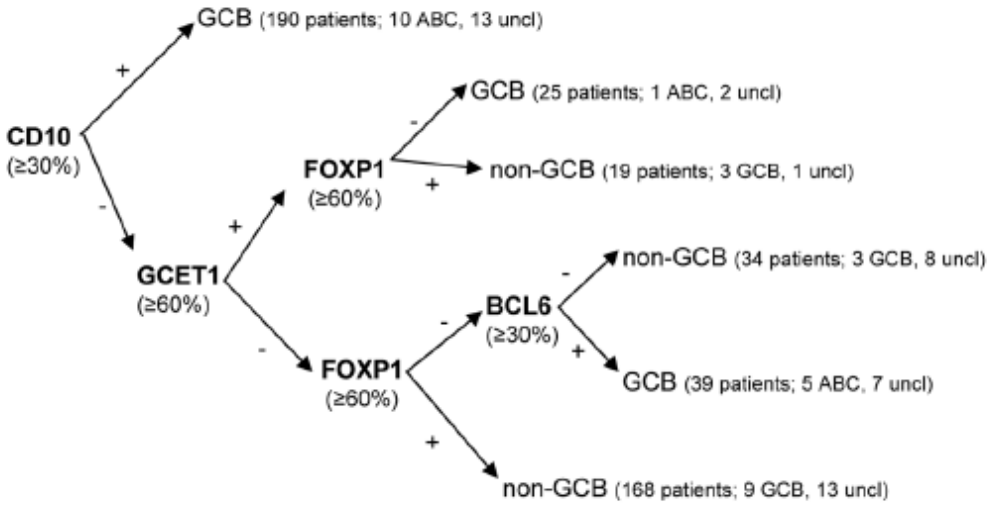
**Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorithm for molecular subtype classification in diffuse large B-cell lymphoma: A report from the International DLBCL Rituximab-CHOP Consortium Program Study**

Leukemia. 2012

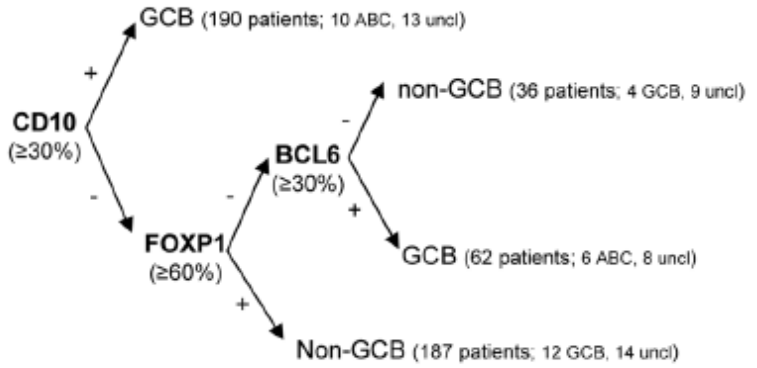
Following B-cell steps of differentiation

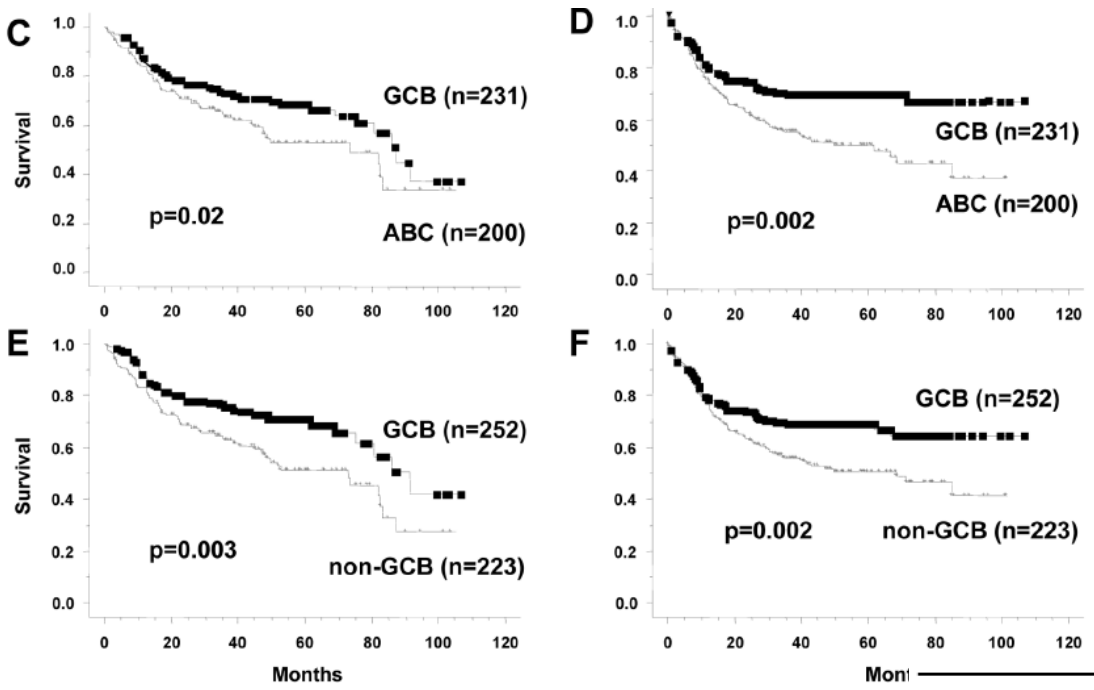
Carlo Visco[1,2], Yan Li[3], Zijun Y. Xu-Monette[1], Roberto N. Miranda[1], Tina M. Green[4], Yong Li[5], Alexander Tzankov[6], Wei Wen[3], Wei-min Liu[3], Brad S. Kahl[7], Emanuele S. G. d'Amore[2], Santiago Montes-Moreno[8], Karen Dybkær[9], April Chiu[10], Wayne Tam[11], Attilio Orazi[11], Youli Zu[12], Govind Bhagat[13], Jane N. Winter[14], Huan-You Wang[15], Stacey O'Neill[16], Cherie H. Dunphy[16], Eric D. Hsi[17], X. Frank Zhao[18], Ronald S. Go[19], William W. L. Choi[20], Fan Zhou[21], Magdalena Czader[22], Jiefeng Tong[23], Xiaoying Zhao[23], J. Han van Krieken[24], Qing Huang[25], Weiyun Ai[26], Joan Etzell[26], Maurilio Ponzoni[27], Andres J. M. Ferreri[27], Miguel A. Piris[8], Michael B. Møller[4], Carlos E. Bueso-Ramos[1], L. Jeffrey Medeiros[1], Lin Wu[3], and Ken H. Young[1,¶]

**A. Four-marker algorithm (Visco-Young algorithm)**




**B. Three-marker algorithm (Visco-Young algorithm)**






GEP data

Visco Young algorythm

## Stratifying diffuse large B-cell lymphoma patients treated with chemoimmunotherapy: GCB/non-GCB by immunohistochemistry is still a robust and feasible marker

**Ana Batlle-López[1], Sonia González de Villambrosía[1], Francisco Mazorra[1], Sefora Malatxeberria[1], Anabel Sáez[2], Carlos Montalban[3], Lydia Sánchez[4], Juan F Garcia[5], Eva González-Barca[6], Andrés López[7], MC Ruiz-Marcellan[7], Manuela Mollejo[8], Carlos Grande[9], KL Richards[10], ED Hsi[11], Alexandar Tzankov[12], Carlo Visco[13], Zijun Y Xu-Monette[14], Xin Cao[14], Ken H Young[14], Miguel Angel Piris[1], Eulogio Conde[1], Santiago Montes-Moreno[1]**

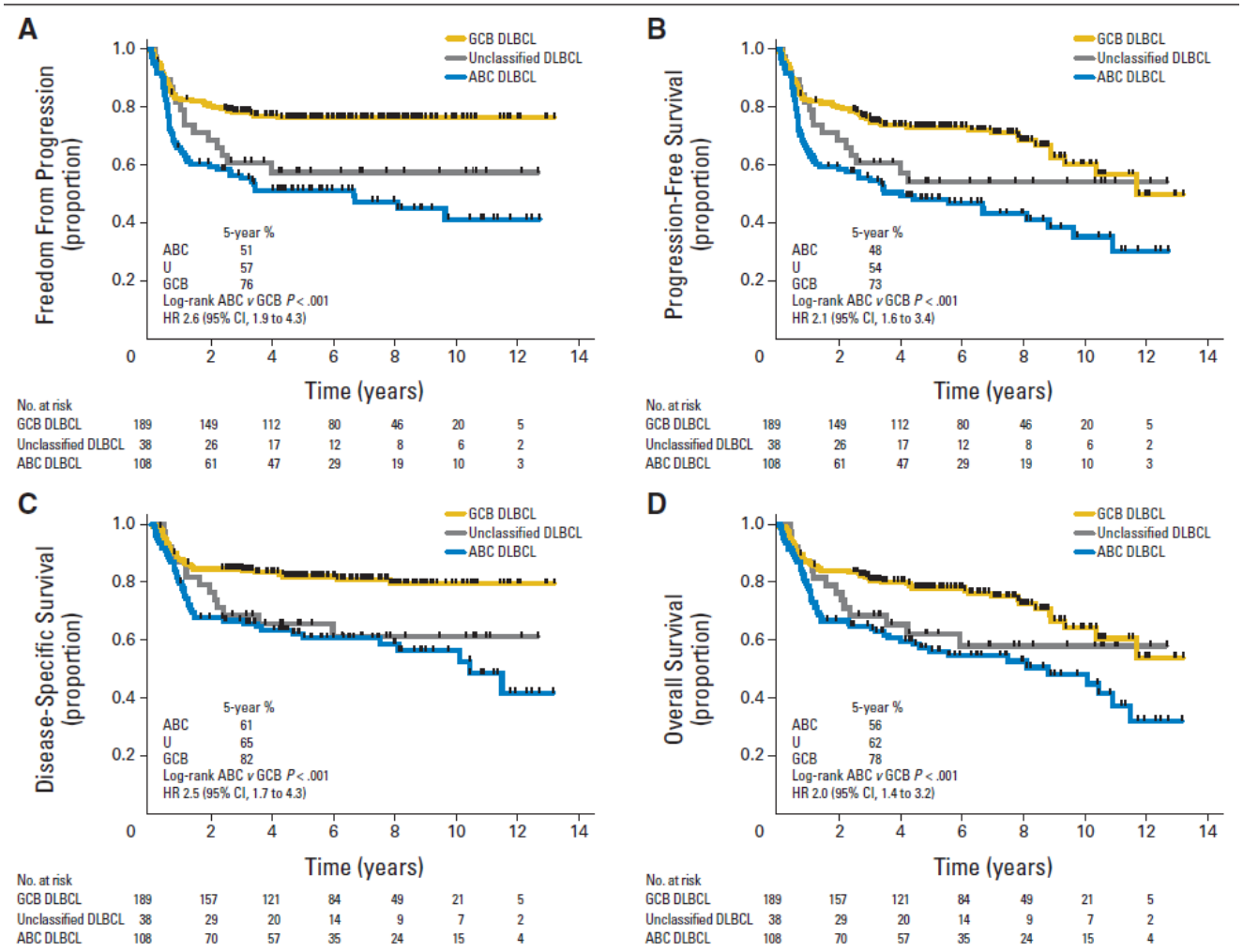
| | GEP analysis | | |
|---|---|---|---|
| **Algorithms** | **GCB (231)** | **ABC (200)** | ***Concordance (%)*** |
| **Three-marker algorithm (Visco-Young Algorithm)** | | | |
| GCB | 215 | 16 | 93.1 |
| Non-GCB | 16 | 184 | 92.0 |
| **Four-marker algorithm (Visco-Young Algorithm)** | | | |
| GCB | 216 | 16 | 93.2 |
| Non-GCB | 15 | 184 | 92.5 |
| **Choi algorithm** | | | |
| GCB | 216 | 28 | 88.6 |
| Non-GCB | 15 | 172 | 91.9 |
| **Hans algorithm** | | | |
| GCB | 209 | 33 | 86.3 |
| Non-GCB | 22 | 167 | 88.3 |

**Geiss et al. Nat Biotechnol 2008, Scott et al Blood 2014, Scott et al. JCO 2015**

GEP from RNA extracted from on **FFPE** (LymphC2x (20 gene probes and Nanostring Techology, Seattle USA), so more applicable in routine tissue

Defines/confirms the *ABC* and *GCB* groups, but **maintains unclassifiable group**
Roughly 32%, 56%, 11%

*ABC cases showed greater stage III/IV and high IPI scores*



## OTHER PHENOTYPIC AND/OR GENOTYPIC/MOLECULAR FEATURES HAVE TO BE CONSIDERED

Cytogenetically most frequent rearranged genes

**BCL6/3q27**: 30-40%
**BCL2/18q21:** 20-30%, mostly as t(14;18)(p32;q21)
**MYC/8q24:** 7-15%

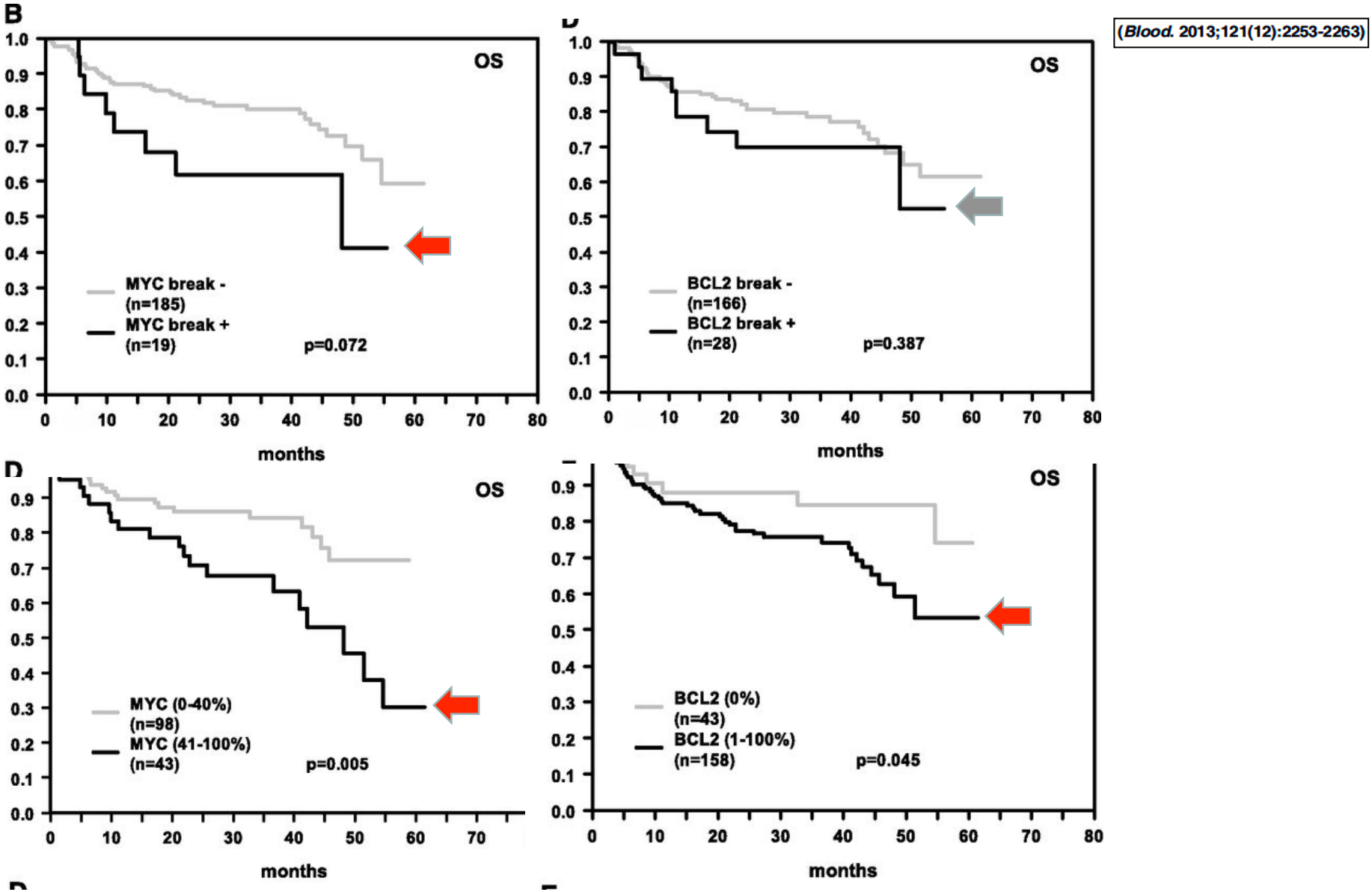
**Usually as single gene abnormalities which lead to protein overexpression**

but data on their prognostic impact are not unanimous

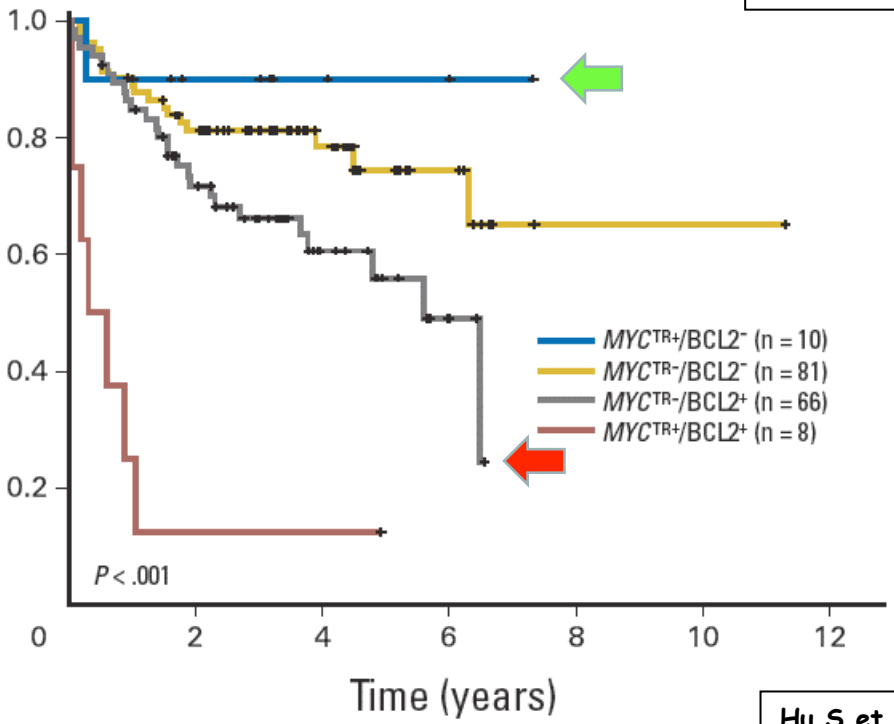
## As single abnormality: impact is more debated among publications; BCL6 no impact;

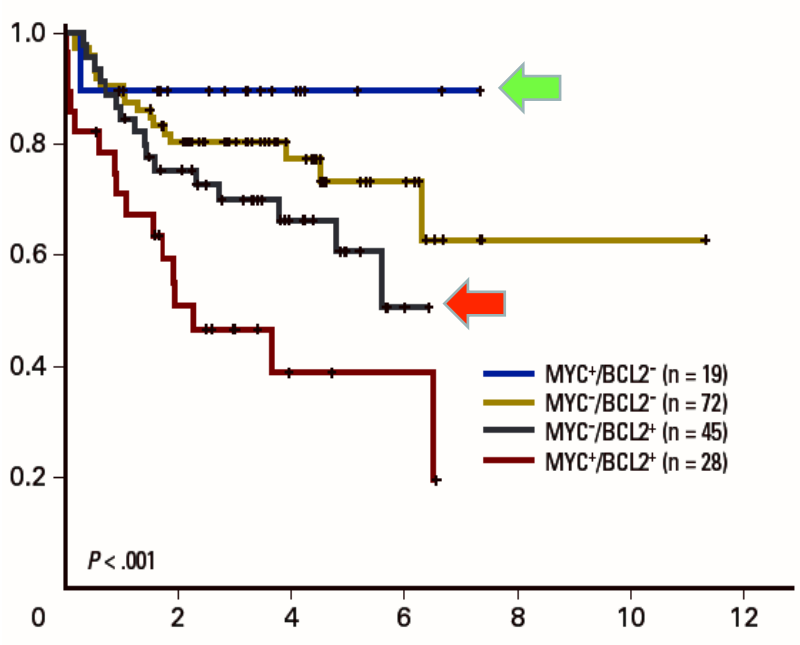
Horn et al.

(*Blood.* 2013;121(12):2253-2263)

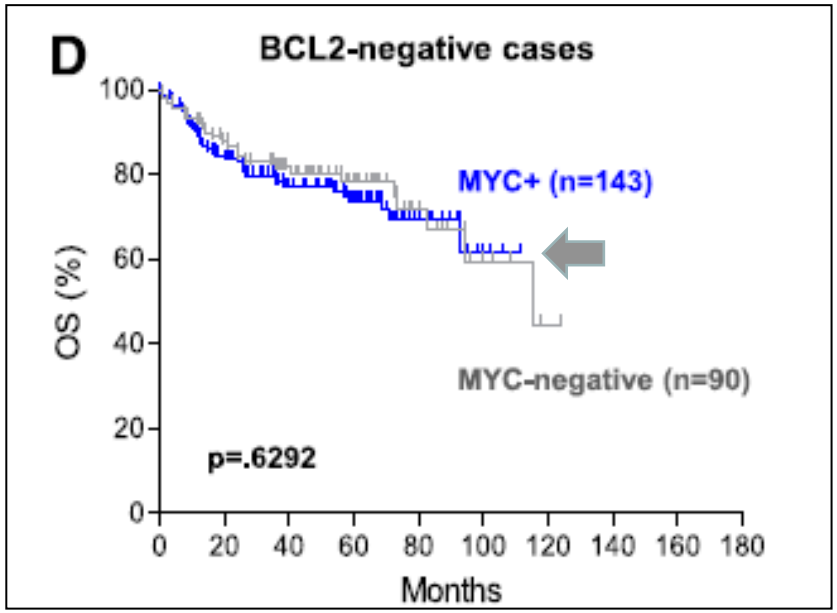


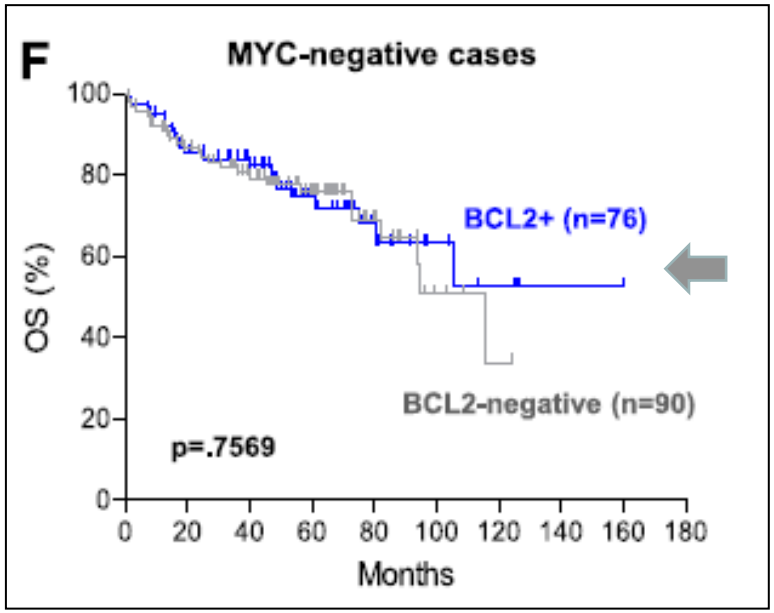
Johnson et al.JCO 2012




Hu S et al.Blood 2013



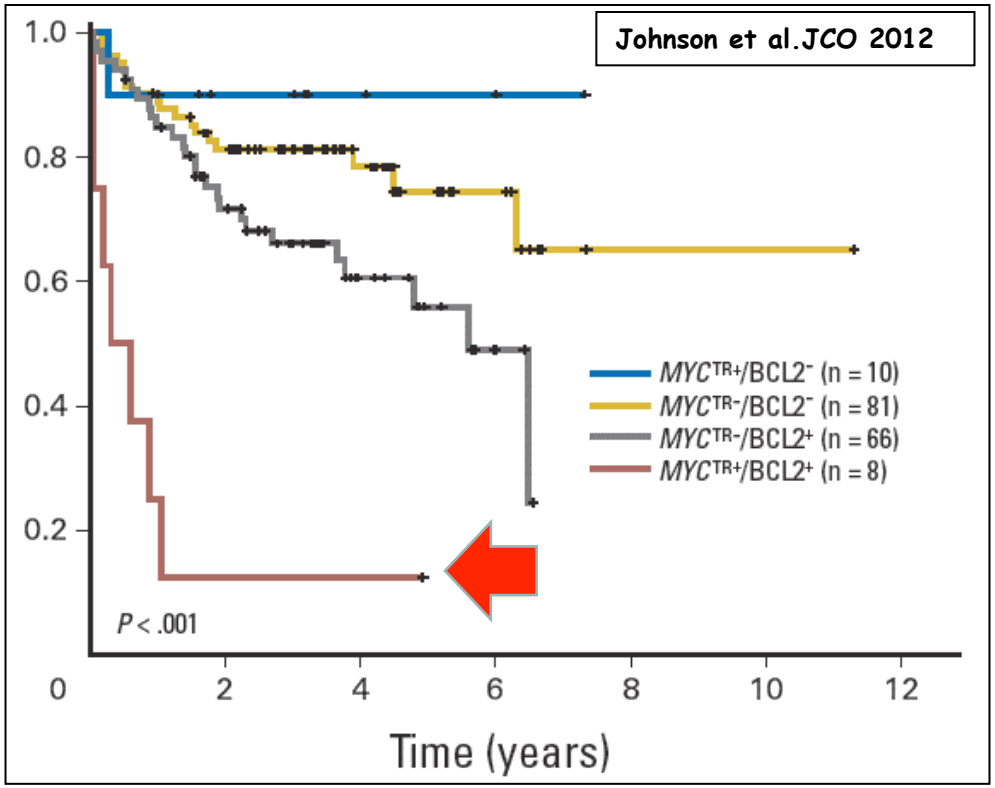
**If events are concurrent prognostication is more definite**

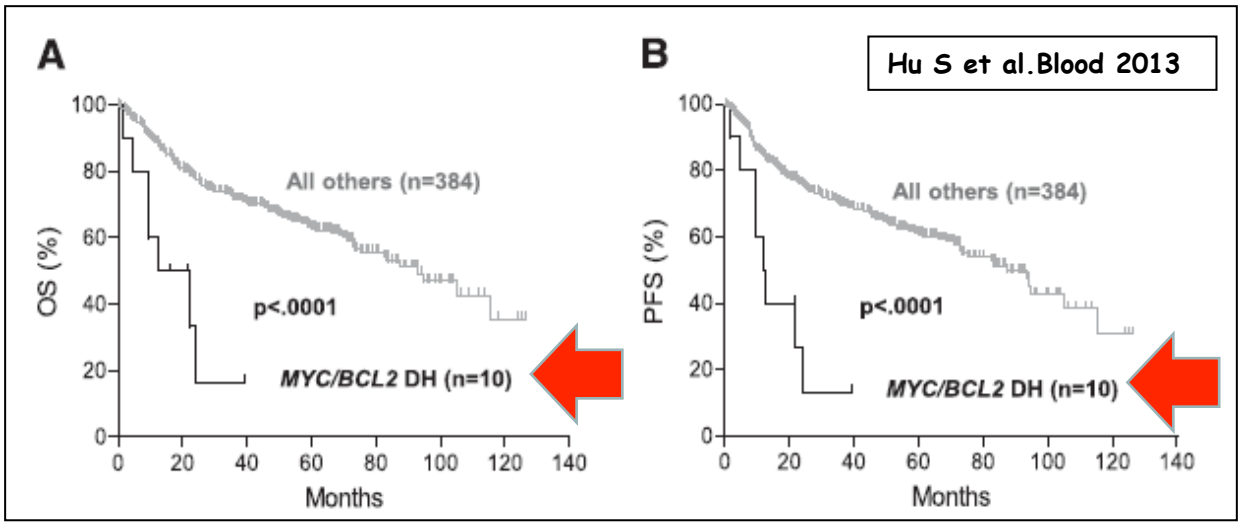
## Double Hit LBCLs

poor outcome
7-15% of LBCL cases
**Most have MYC/bcl2/bcl6 proteins highly expressed**

**MYC/BCL2: more common**
**90% in GCB-type**

**MYC/BCL6**
**less common**,
mainly extranodal,
IRF4+/BCL6+/CD10-
50% GCB-type
clinically



**WHO 2016**

•All LBCL with MYC and BCL2 and/or BCL6 rearrangements will be included in a single category designated

**High Grade B-cell Lymphoma, with MYC and BCL2 and/or BCL6 rearrangements**,

The morphologic appearance should be noted in a comment.

**•B-Cell LYMPHOMA UNCLASSIFIABLE will be eliminated.**

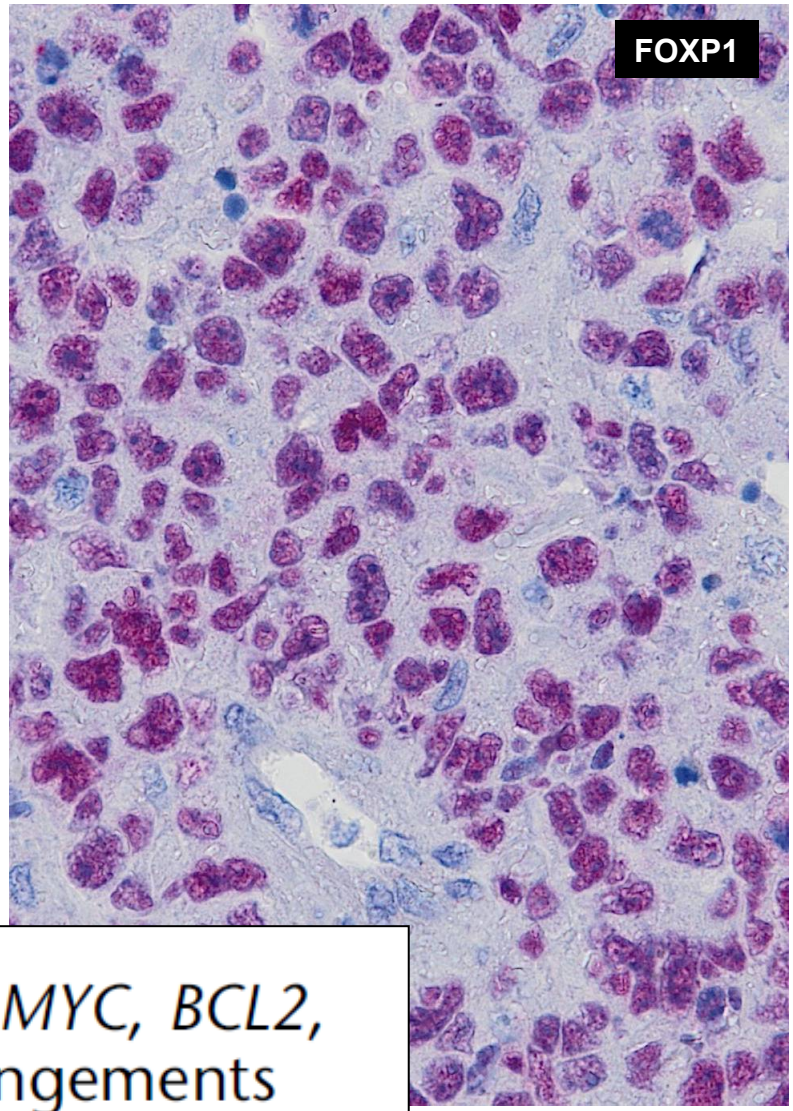
•Cases that appear blastoid or morphologically intermediate between DLBCL and BL but which lack a MYC and BCL2 and/or BCL6 rearrangement, will be placed in the category of HGBL, NOS.

This category include also TRIPLE HIT DLBCLs: very rare, few reports

**Translocations partners**
BCL2/IGH,
BCL6/MYC, IGH, Igk, IG lambda, other
MYC/IGH, IGLambda, BCL6

**CD10+/FOXP1+/BCL2+**
(more similar to MYC/BCL2 DHL)
MYC+- (60%), BCL6+- (70%), IRF4 50%
**Mostly GCB-type**

**Very aggressive course**




Triple-hit B-cell Lymphoma With *MYC*, *BCL2*, and *BCL6* Translocations/Rearrangements

*Clinicopathologic Features of 11 Cases*

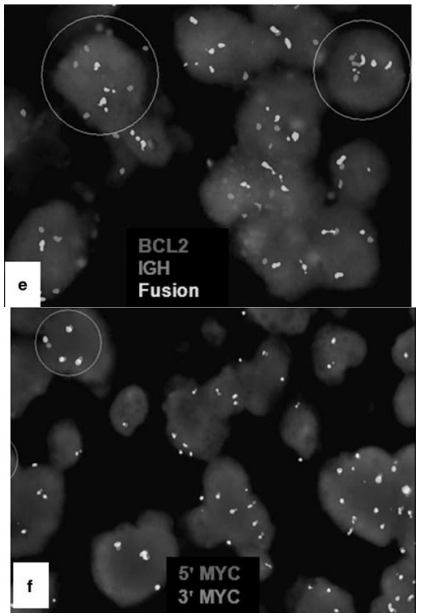
*Wei Wang, MD, PhD, Shimin Hu, MD, PhD, Xinyan Lu, MD, PhD, Ken H. Young, MD, PhD, and L. Jeffrey Medeiros, MD*

(*Am J Surg Pathol* 2015;39:1132–1139)

# What the WHO 2016 does **not include**, are the"atypical DH-LBCLs"

**B-cell lymphomas with concurrent *MYC* and *BCL2* abnormalities other than translocations behave similarly to *MYC/BCL2* double-hit lymphomas** MODERN PATHOLOGY (2015) 28, 208–217

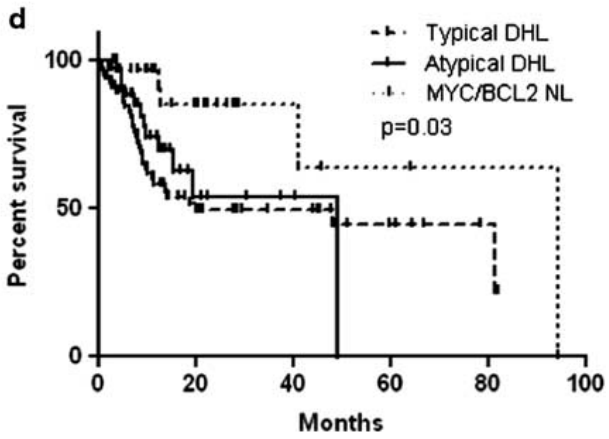
Shaoying Li[1], Adam C Seegmiller[1], Pei Lin[2], Xuan J Wang[1], Roberto N Miranda[2], Sharathkumar Bhagavathi[3] and L Jeffrey Medeiros[2]




MYC translocated + BCL2 amplified: 3 cases
**MYC amplified + BCL2 translocated**: 22 cases
**MYC amplified + BCL2 amplified**: 15 cases

Clinical features compared to non DHL
higher presence of

- Tranformed (from low grade >FL)
- Positive bone marrow and > 2 extranodal sites (40%)
- Complex karyotype
- Same immunophenotypic features and OS as typical DHL and worse than non-DH LBCLs




The number of gene copies does not impact (≥3)
More often belong to GCB-type
Not all "atypical DHL" are dual expressors

**High Grade B-cell Lymphoma, with MYC and BCL2 and/or BCL6 Rearrangements (ex-D/THLs) represent a minority of DLBCLs**

**Shall pathologists have to "fish" all DLBCLs (all types, all ages)?**

A **consensus has not yet been reached** to provide specific guidelines as to which LBCL should have FISH studies

Some believe that all DLBCL should have genetic studies for the detection of DHL, while others would limit them, for example, to cases with a GCB phenotype and/or high grade morphology or to cases with >40% MYC+ cells.

**THIS BRINGS US TO THE ISSUE OF MYC/BCL2 PROTEIN-EXPRESSION**

# Dual Expressor-LBCLS

- MYC and BCL2 proteins
  (by ihc: cut off MYC >40%, BCL2 >50%)

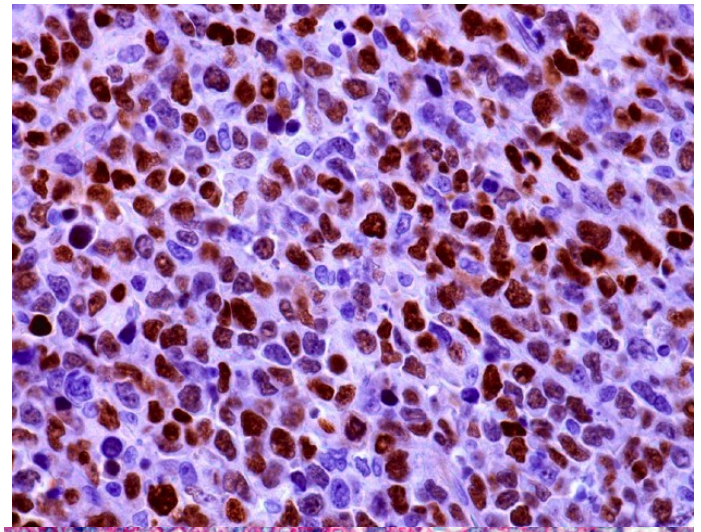
- **DHL are DE** (with high percentage of positive cells) but **few DE are DHL** (3%)
  coexpression regardless the mechanism
  Inactivation of p53, Increased protein instability, activation of pathways upstream to MYC (NF-Kb), loss of immunity, microRNA profiles which may influence MYC expression

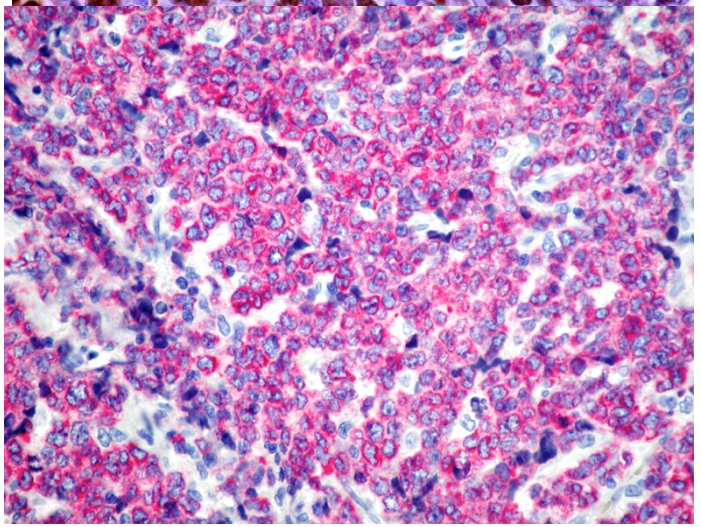
- Approximately **30%** DLBCLs

- **ABC subset** (differently from DHL)

- **GEP**: unique cell adhesion and cell proliferation signature

- Such cases unfavourably impact on outcome





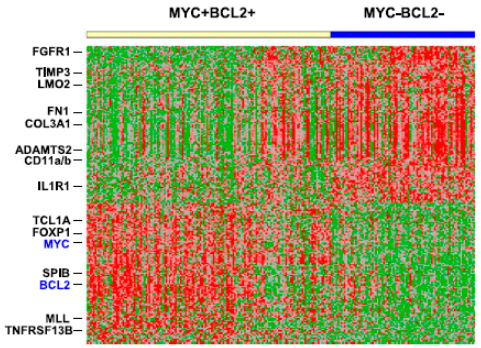
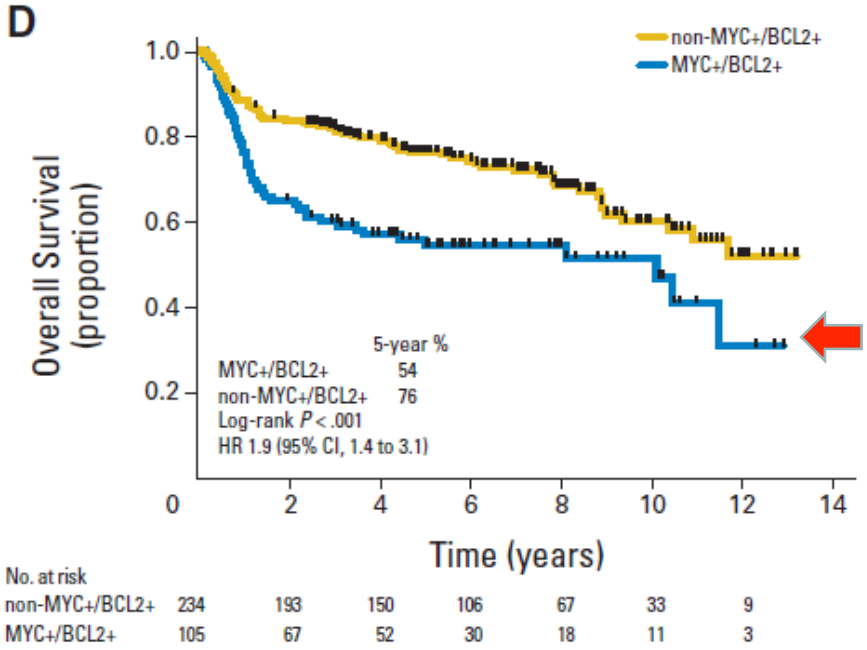


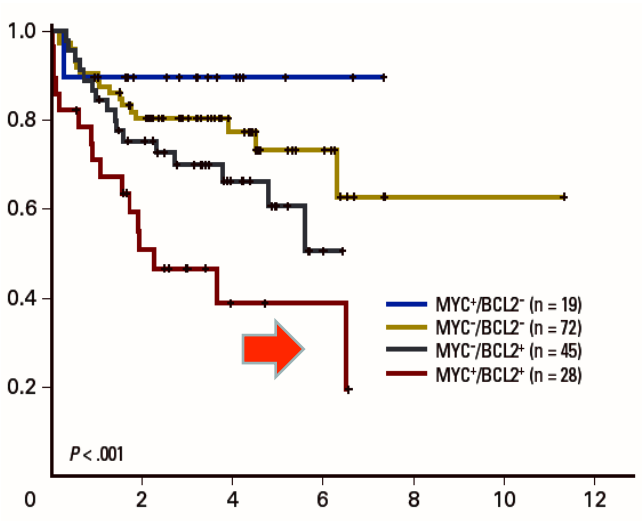

Table 3. Differentially expressed genes in MYC$^+$BCL2$^+$ de novo DLBCL

| Gene functional categories | No. of genes | Representative genes |
|---|---|---|
| **Downregulated genes** | | |
| ECM, ECM production and remodeling | 33 | *COL3A1, VCAN, TNS1, FN1, THBS2, TIMP3, SPARC, SULF1, SPINK2, MMP2, ADAM12, FGFR1, FAP* |
| Cell adhesion and cytoskeletal organization | 21 | *CD11A/CD11B, CD58, THY1, RFTN1, ANTXR1, RHOB, MICAL2* |
| Cell growth regulation | 16 | *LM02, TRAF1, CDK14, SGK1, RGS1, NBL, PDE4D* |
| Others, including unknown | 18 | *PSAP, LYZ, LOC115110, ZNF662* |
| **Upregulated genes** | | |
| Cell proliferation | 20 | *MYC, BCL2, TCL1A, MLL, FOXP1, SPIB, TCF4, TNFRSF13B, PMDAIP1, GAB1, PLOR3G* |
| Cell metabolism | 5 | *DCTPP1, CYB5R2, HK2, TMEM97, CYB5R2* |
| Miscellaneous cell functions | 13 | *PPIL1, PIGW, FUT8, SPINK5* |
| Unknown | 27 | *KIAA0664, C9orf91, ZNF107* |

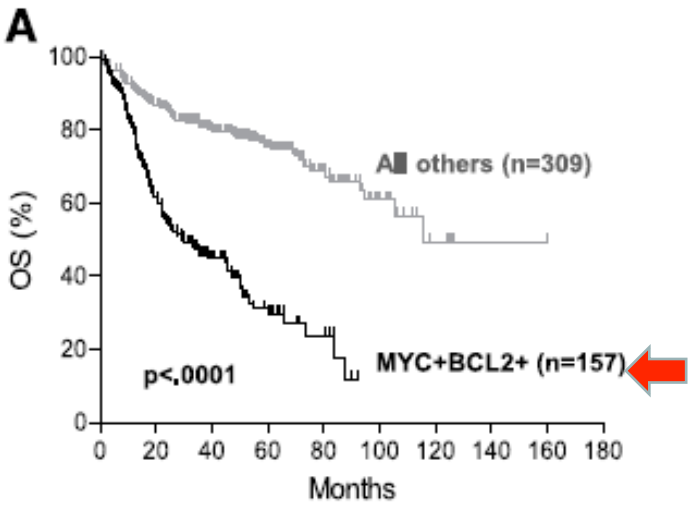
Scott et al.JCO 2015

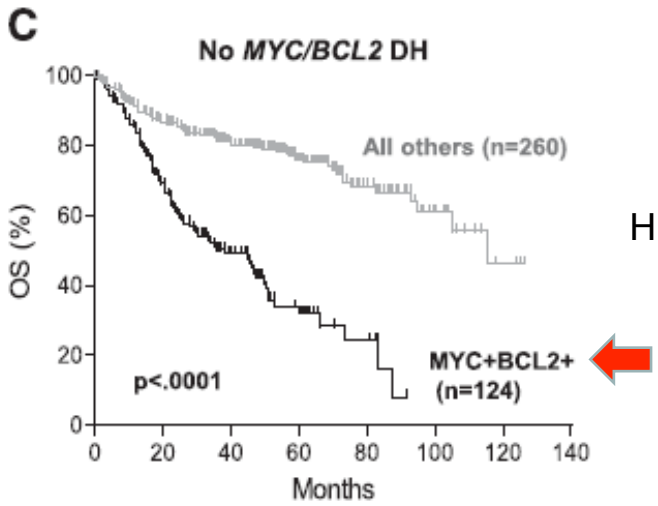



Johnson et al.JCO 2012

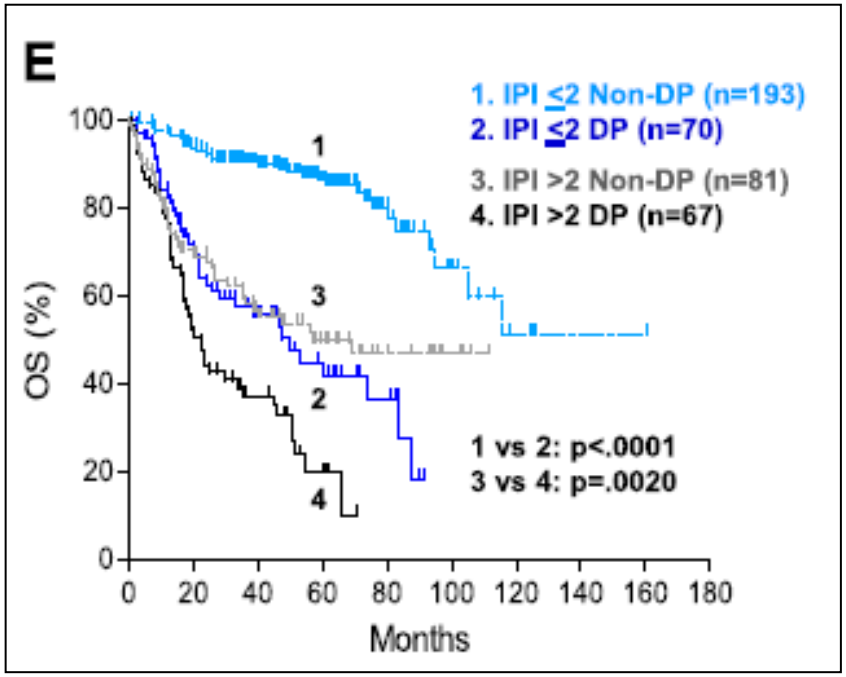


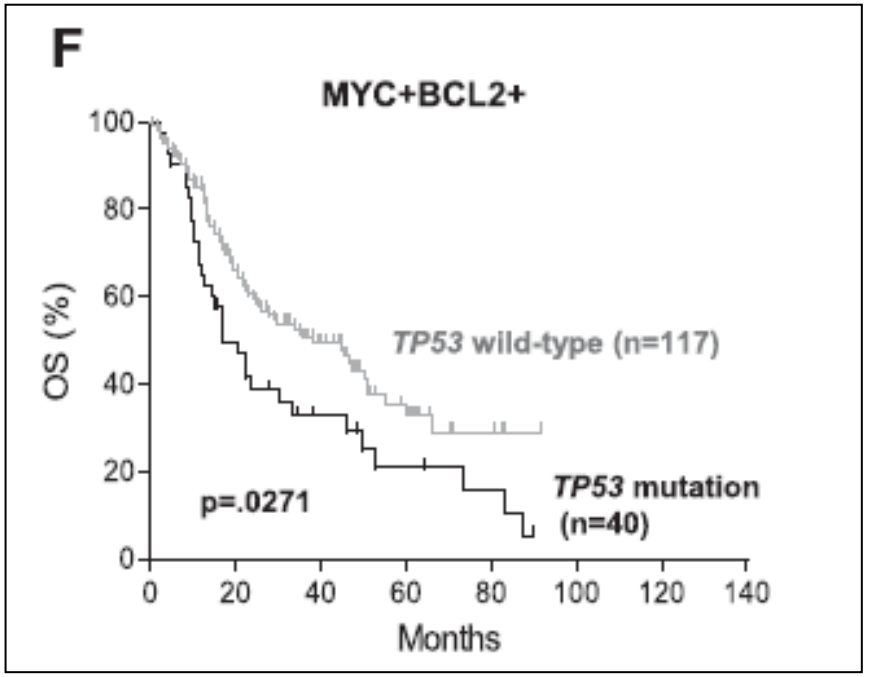

**Unanimous agreement on their unfavourable impact on outcome**




Hu et al. Blood 2013



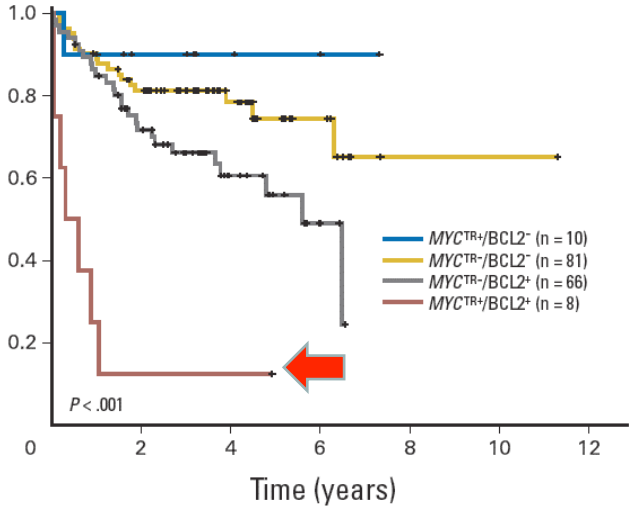



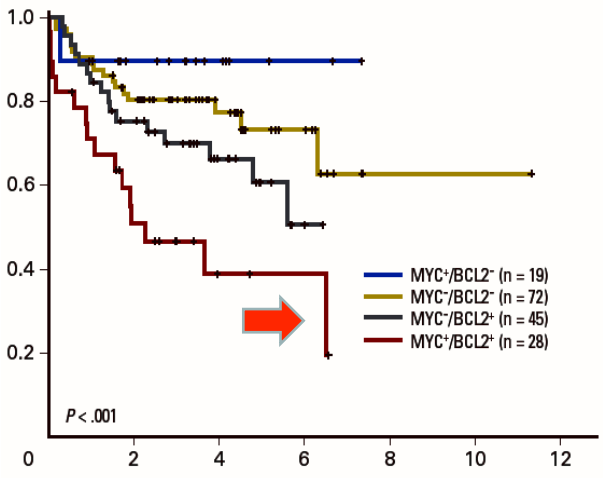

..maintained within IPI category and TP53 mutated pts

## WHO 2016

**Though poorly behaving DE-LBCL, NOS are not as aggressive as the DHL/THL**

**… considered a <u>prognostic indicator</u> in DLBCL,NOS but not a separate category**




Since DHL fell within GCB and DE fell within ABC
is there a relationship between COO and MYC/BCL2 overexpression?

# no definite data

**MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program**

Shimin Hu,[1] Zijun Y. Xu-Monette,[1] Alexander Tzankov,[2] Tina Green,[3] Lin Wu,[4] Aarthi Balasubramanyam,[4] Wei-min Liu,[4] Carlo Visco,[5] Yong Li,[6] Roberto N. Miranda,[1] Santiago Montes-Moreno,[7] Karen Dybkaer,[8] April Chiu,[9] Attilio Orazi,[10] Youli Zu,[11] Govind Bhagat,[12] Kristy L. Richards,[13] Eric D. Hsi,[14] William W. L. Choi,[15] Xiaoying Zhao,[16] J. Han van Krieken,[17] Qin Huang,[18] Jooryung Huh,[19] Weiyun Ai,[20] Maurilio Ponzoni,[21] Andrés J. M. Ferreri,[21] Fan Zhou,[22] Graham W. Slack,[23] Randy D. Gascoyne,[23] Meifeng Tu,[24] Daina Variakojis,[25] Weina Chen,[26] Ronald S. Go,[27] Miguel A. Piris,[7] Michael B. Møller,[3] L. Jeffrey Medeiros,[1] and Ken H. Young[1]

(*Blood.* 2013;121(20):4021-4031)

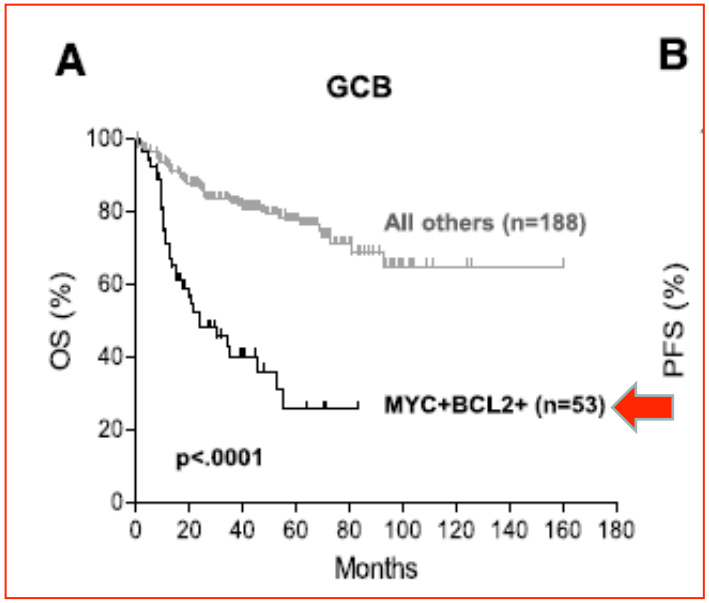
893 cases

344 cases

Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies

*David W. Scott, Anja Mottok, Daisuke Ennishi, George W. Wright, Pedro Farinha, Susana Ben-Neriah, Robert Kridel, Garrett S. Barry, Christoffer Hother, Pau Abrisqueta, Merrill Boyle, Barbara Meissner, Adele Telenius, Kerry J. Savage, Laurie H. Sehn, Graham W. Slack, Christian Steidl, Louis M. Staudt, Joseph M. Connors, Lisa M. Rimsza, and Randy D. Gascoyne*

*J Clin Oncol 33:2848-2856. © 2015*

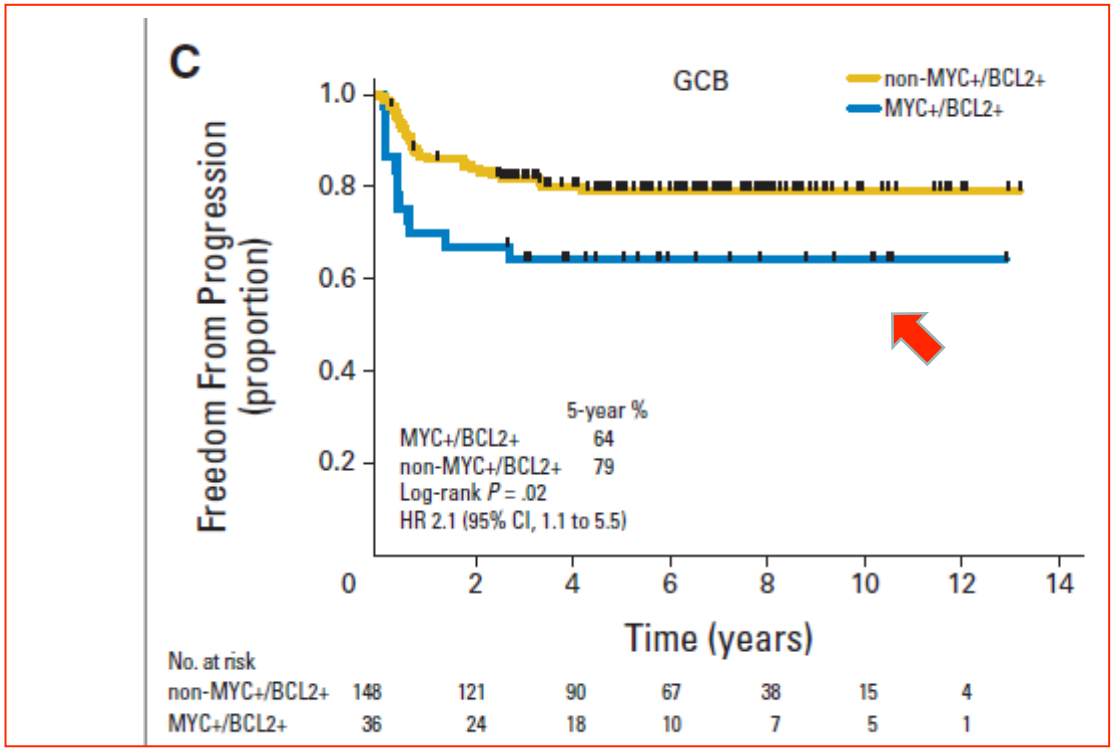


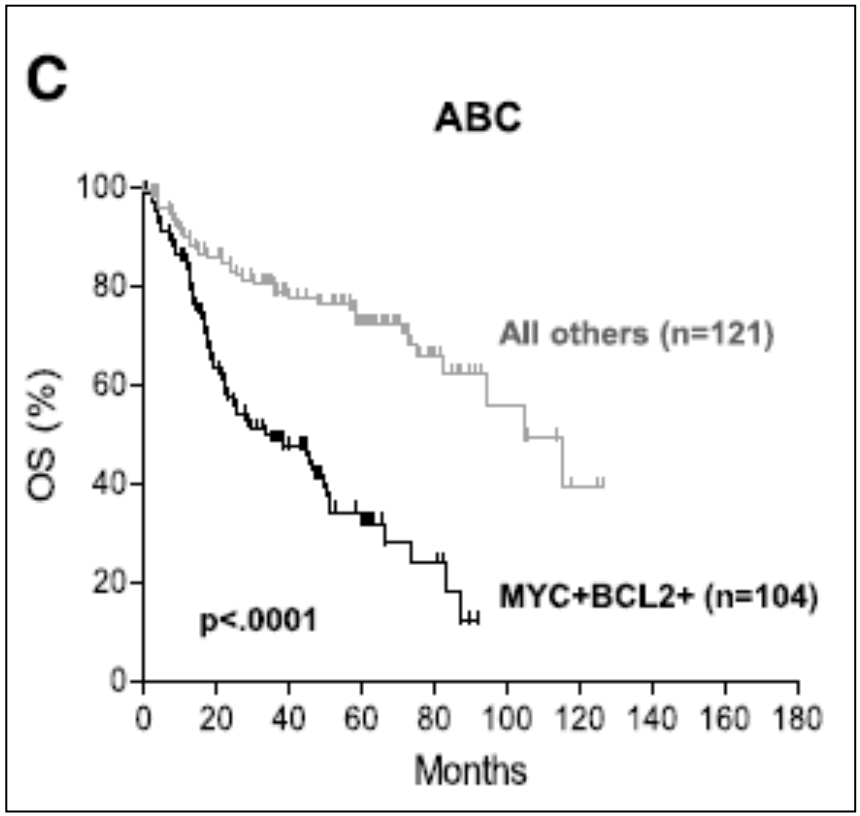

Hu et al. Blood 2013

**Within GCB cases**
**DE impact on outcome**

**(but many are DHL!!)**

Scott et al.JCO 2015

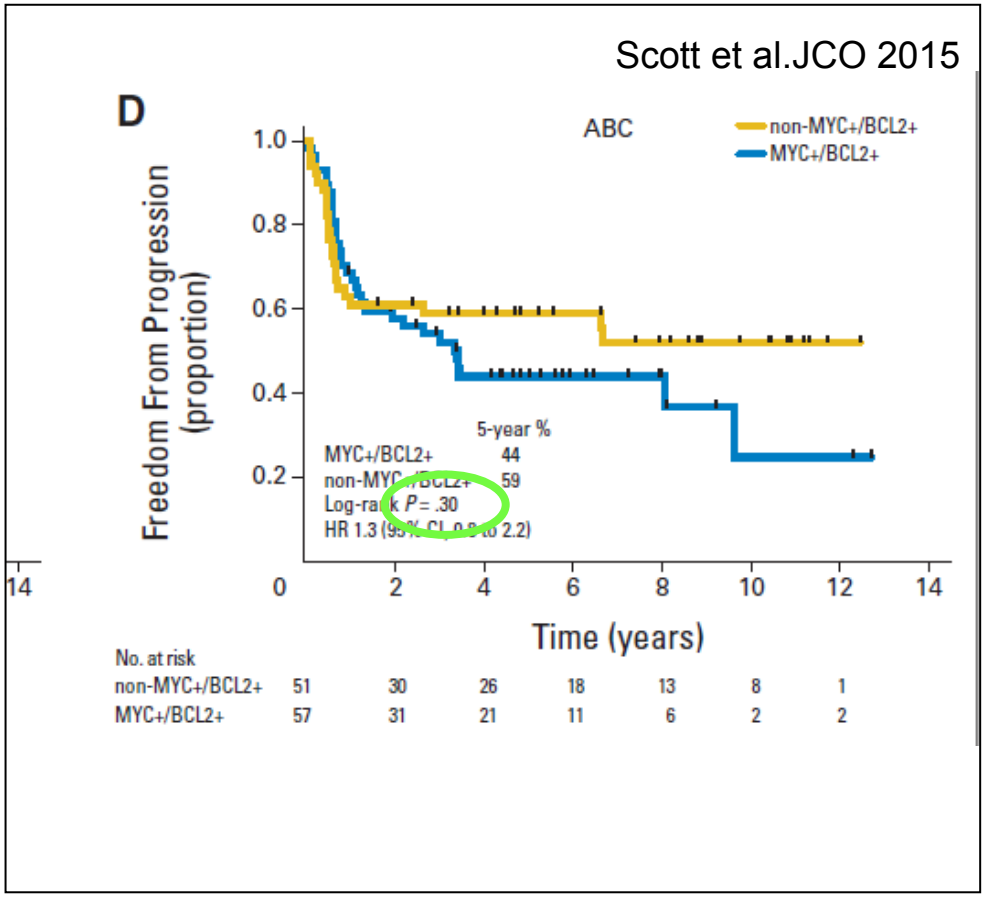




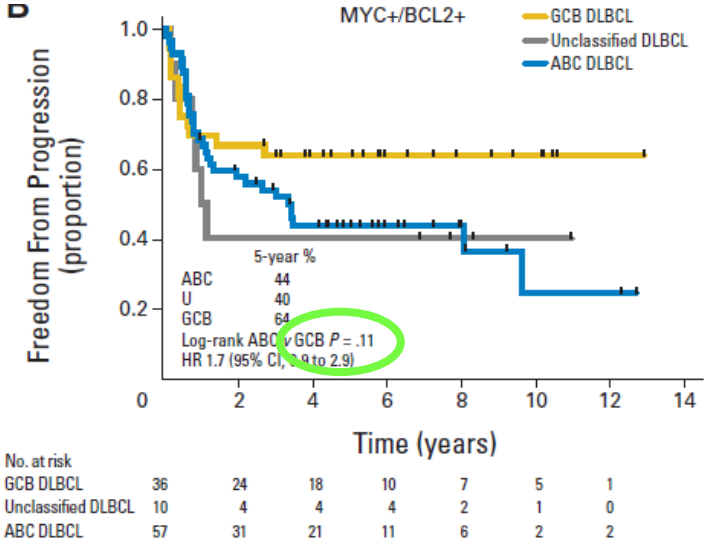

Hu et al. Blood 2013

Within **non-GCB** cases
DE impact is controversial

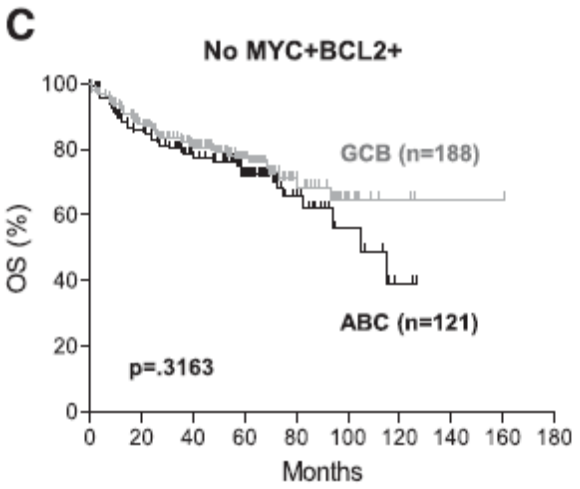
Scott et al.JCO 2015



Scott et al.JCO 2015

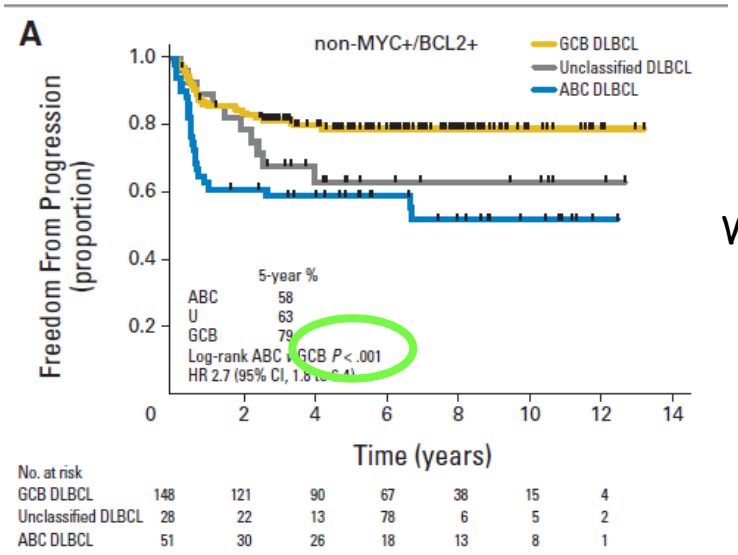



Hu et al. Blood 2013




However in the same cohort, when only DE are considered, COO does not reach significance consistently with data from Hu et at. 2013 as if it was the MYC/BCL2+ that defined poor prognosis independently on COO

Which seems to be indirectly shown by graphs on non-DE where COO defines the difference




Which is reached when non-DE are considered

These persisting uncertainties may explain the lack of guidelines for FISHING cases

A consensus has not yet been reached to provide specific guidelines as to which LBCL should have FISH studies

Some believe that all DLBCL should have genetic studies for the detection of DHL,

while others would limit them, for example, to cases with a **GCB phenotype and/or high grade morphology or to cases with >40% MYC+ cells.**

## in addition to COO, MYC/BCL2: SOMATIC MUTATIONS

= in all DLBCL, ≠ in GCB and ABC

**common in both DLBCL subtypes**

inactivating mutations of **TP53** and genes involved in immunosurveillance (B2M, CD58), alterations in **epigenetic regulators** (CREBBP/EP300, KMT2D/C [MLL2/3], MEF2B), oncogenic activation of **BCL6**.

**GCB-DLBCL**

histone methyl transferase **EZH2**, **BCL2 translocations**, mutations in the cell motility regulator GNA13

**ABC-DLBCL**

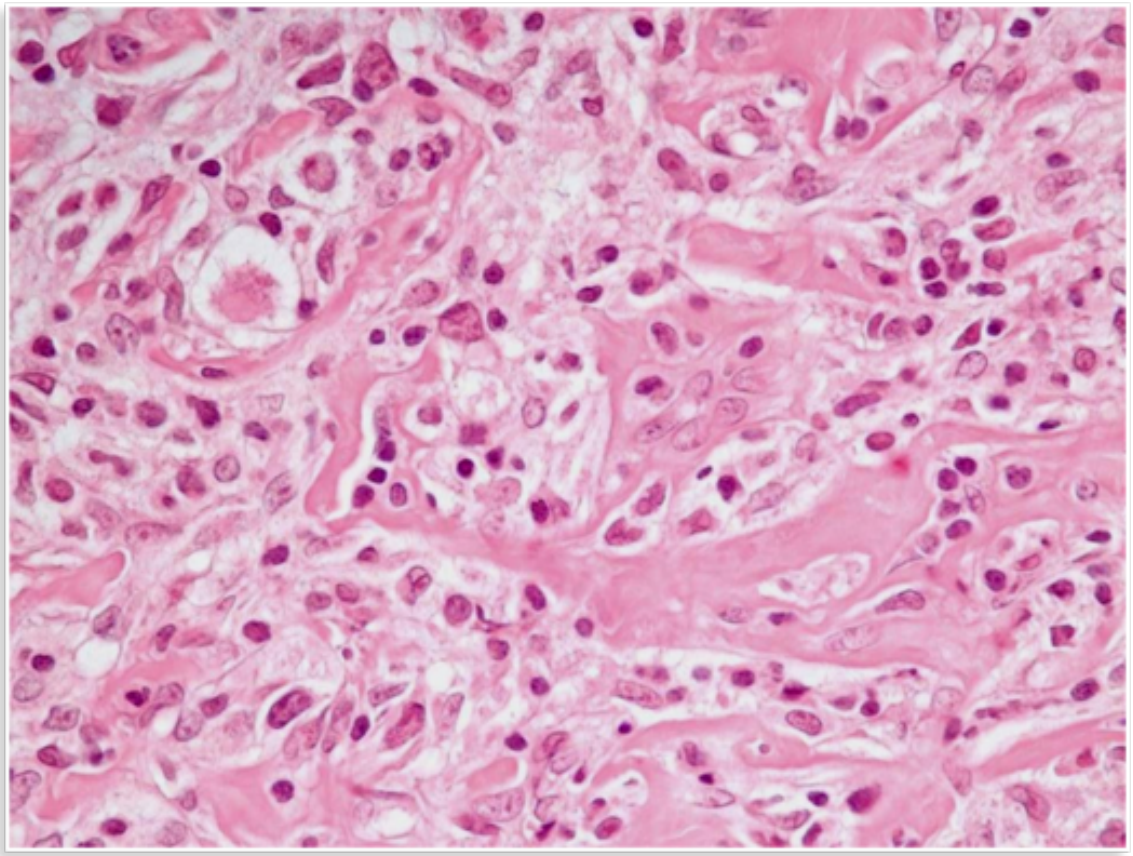
activating the **BCR/TLR** and **NFKB pathways** (MYD88, CD79A, CARD11, TNFAIP3)

clinical implications not fully understood, but likely necessary for guiding targeted therapies in the future

# Primary Mediastinal LBCL

Primary Mediastinal B-Cell Lymphoma

*High Frequency of BCL-6 Mutations and Consistent Expression of the Transcription Factors OCT-2, BOB.1, and PU.1 in the Absence of Immunoglobulins*




Thymic medullary B cell,

**full B cell phenotype, CD30+, BCL6+/IRF4+; low light chain immunoglobulin expression, defective surface MHC class II molecules**

Molecular signature clearly different from other DLBCL, with similarites with cHL

# The molecular pathogenesis of primary mediastinal large B-cell lymphoma

Christian Steidl[1] and Randy D. Gascoyne[1]

(*Blood*. 2011;118(10):2659-2669)

[1]Department of Pathology and Experimental Therapeutics, British Columbia Cancer Agency, University of British Columbia, Vancouver, BC

**most common chromosomal alterations in PMBCL**

translocations/amplifications/rearrangement of

## EVASION FROM IMMUNE RESPONSE

Class II TransActivator gene/gene complex

gains at 9p (genes JAK2, PDL1, PDL2, JMJD2C)

## SIGNALING PATHWAYS

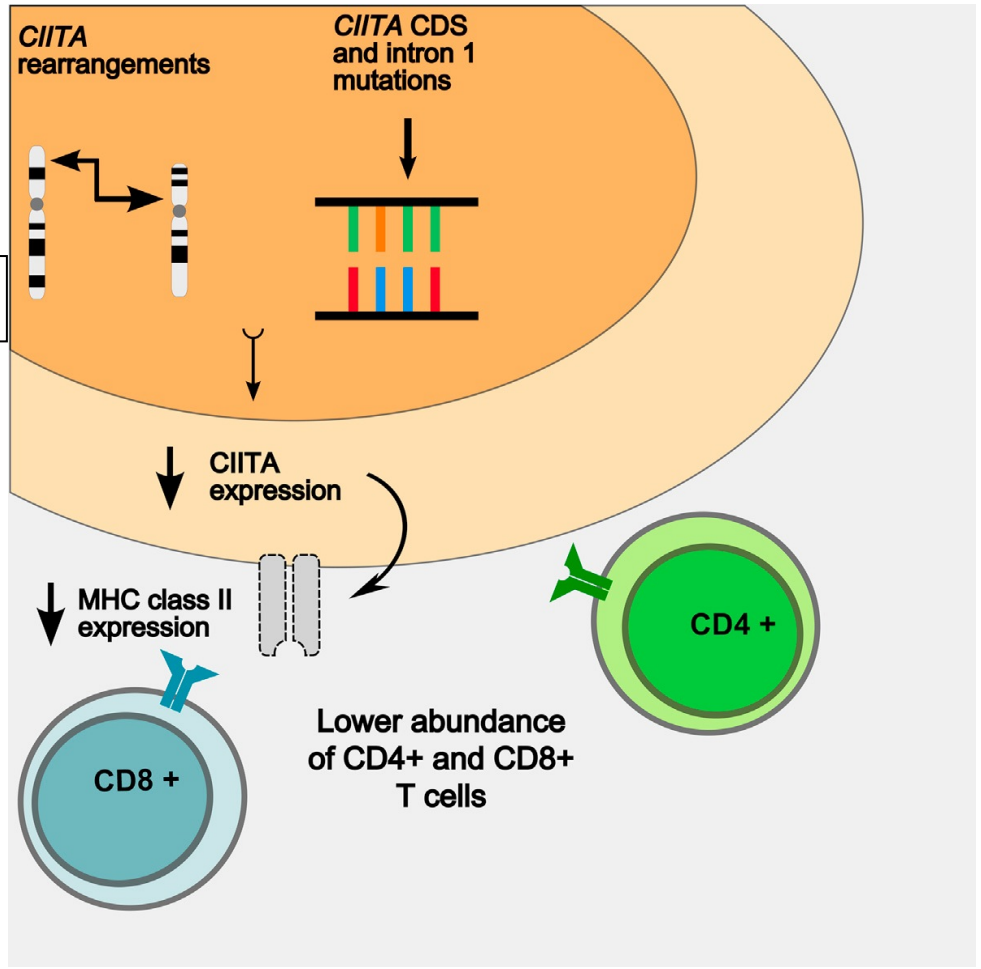
JAK/STAT and NFKb pathways

SOCS1 mutations/deletions, STAT6 mutations, A20 mutations

CIITA locus (16p13.13) : deletions, translocations or CDS (coding sequence) mutations were found in **71%** of PMBCL cases

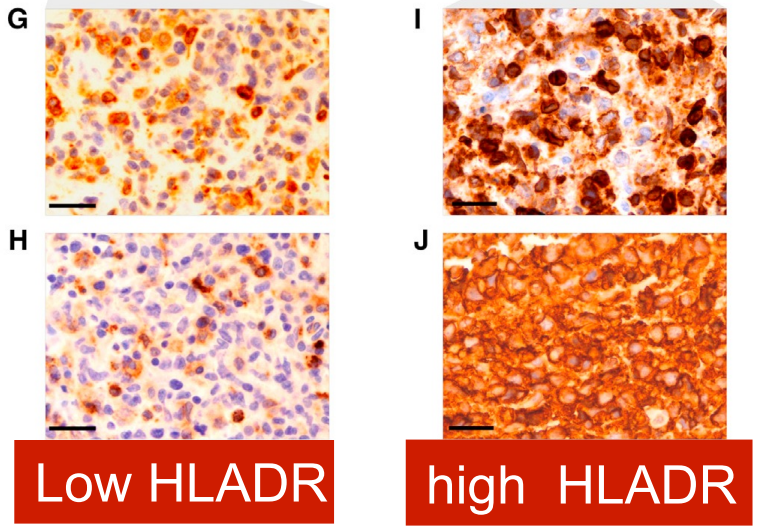
## Reduced CIITA protein expression

deficient CIITA protein not capable of inducing HLA-DR surface expression (diminished HLA-DR/DP/DQ protein)




CIITA low/rearr

CIITA high/not rearr



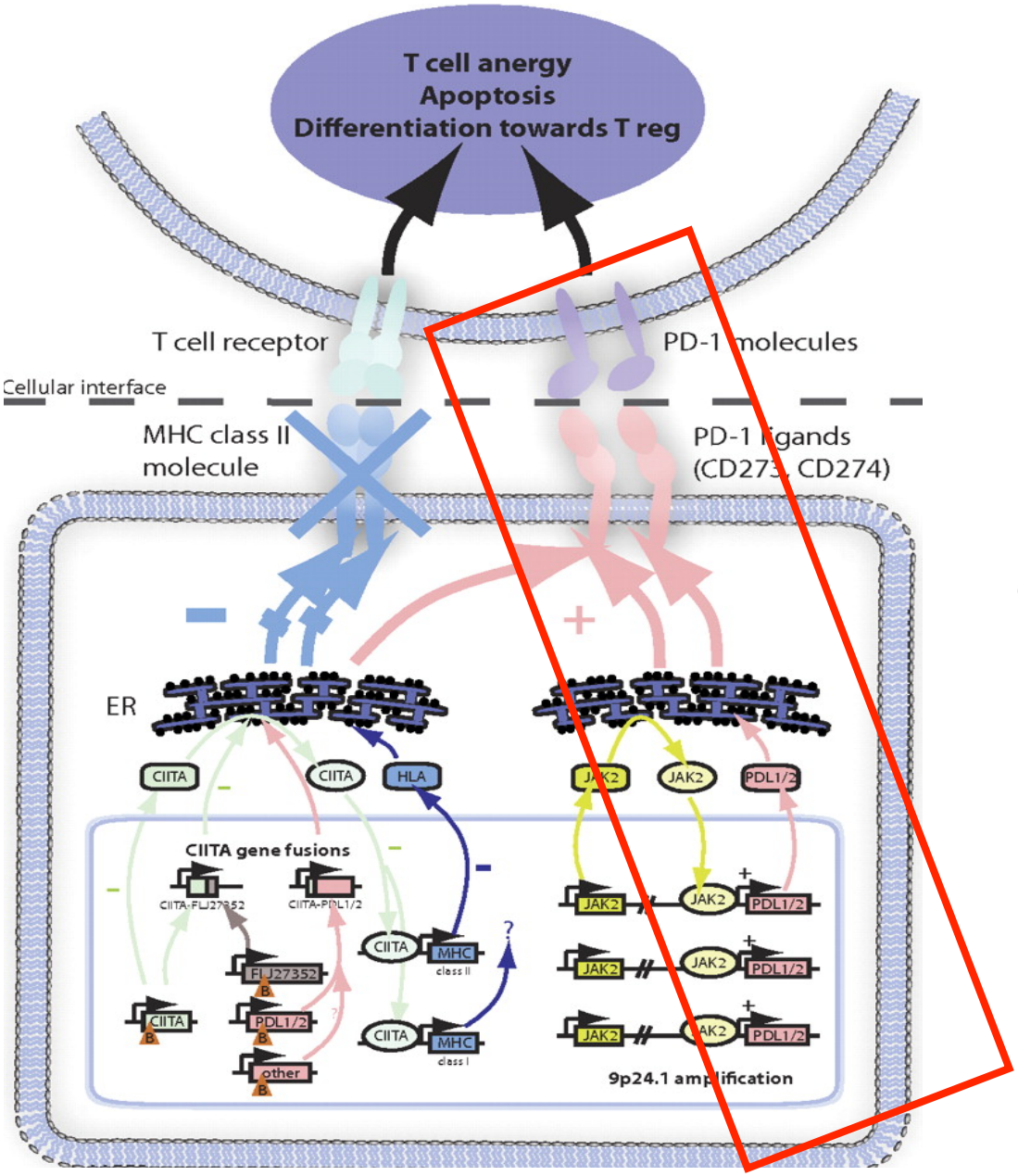

Low HLADR

high HLADR

**Reduced T cells**

**Easier immune evasion**

Most cases with CIITA-PDCD1LG2 (DEV)




**PDL1 (CD274) and PDL2 (PDCD1LG2/PDL affinity receptor)** on 9p24.1 translocation or amplification 30% cases **transcripts are elevated in both rearranged & NON rearranged cases** (alternative mechanisms such as epigenetic and microRNA regulatory factors)

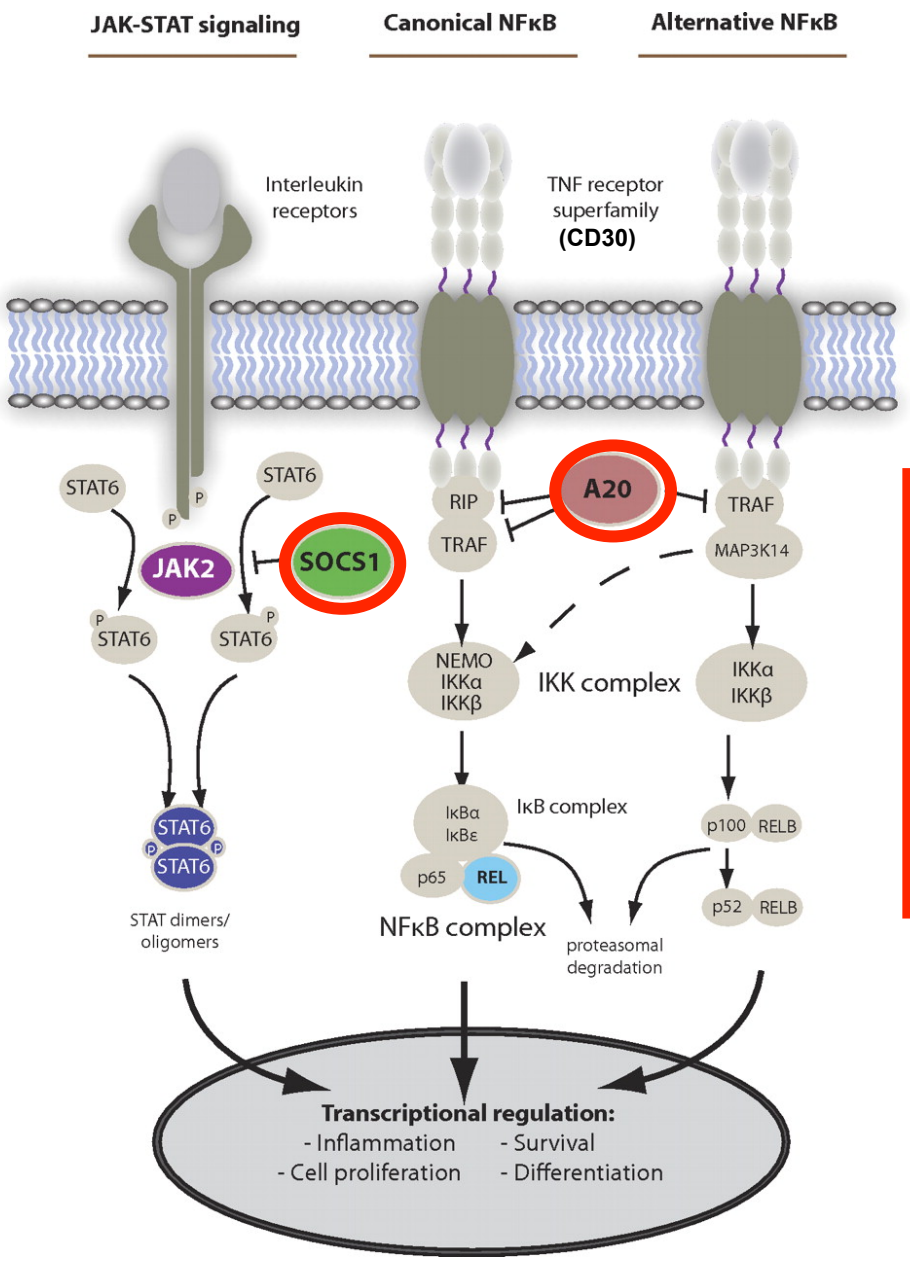
**·INDUCE IMMUNE T-CELL ANERGY, AND TO T-REGS**

No difference between arranged and non-rearranged cases for clinical parameters and survival

**SOCS1 Mutations or deletions**
Loss of its inhibitory role on JAK2/STAT6 pathway

**JAK2 gene gains at 9p**

**STAT6 activating mutations**




**A20 mutations**
30% cases

Loss of its inhibitory role on NFKb pathway
NF-κB signaling through TNFR superfamily

blood

A significant pathogenetic role of a constuitutively activated **NFKb** pathway is a feature of **Primary Central Nervous System Lymphoma**

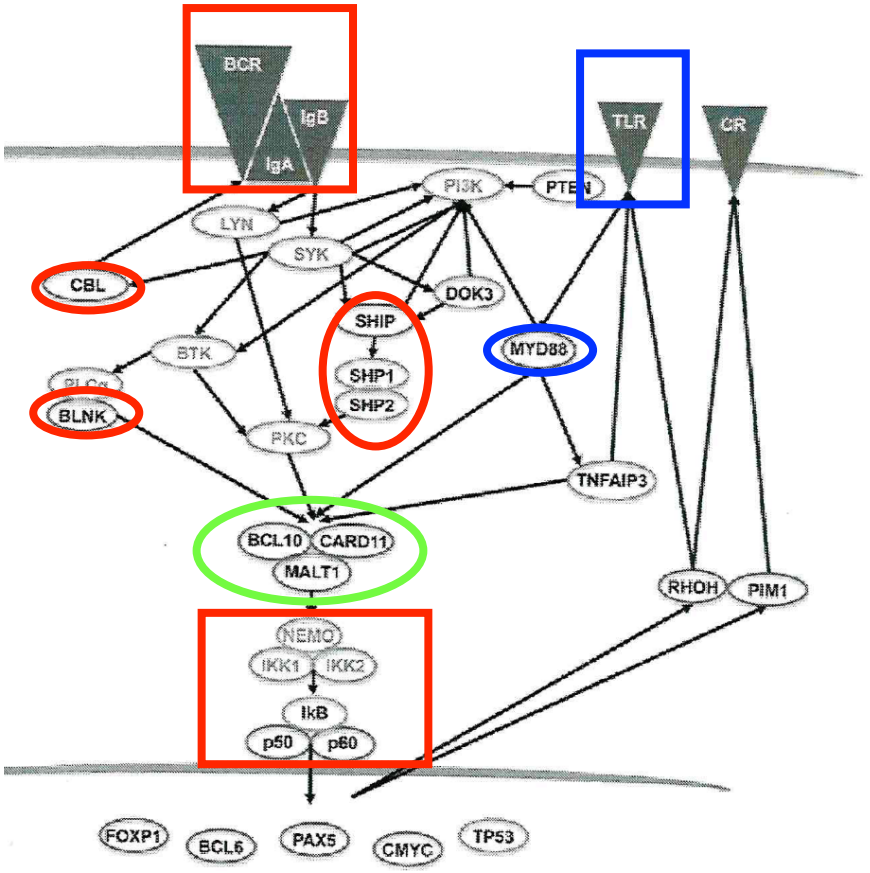
due to aberrancies in many KFKb upstream genes/proteins

acting in combination and sinergy

- **40% cases BCR** signaling cascade altered by somatic mutations (SHIP, CBL, BLNK)

-- activating mutations or amplification of the BCM compex (BCL10, CARD11 and MALT1)

- **50% cases** TollLikeReceptor pathway altered *via* **MYD88** mutations (Leucine265Proline)



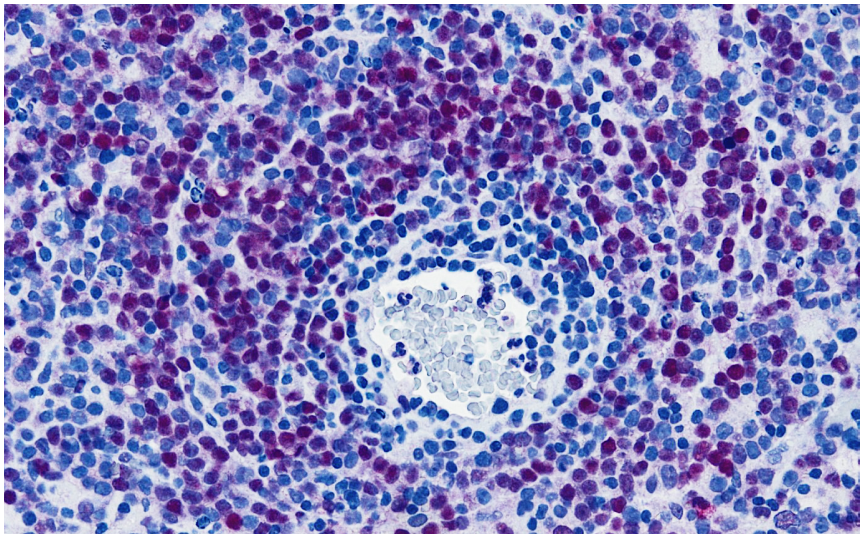
PCNSL: large B cell lymphoma confined to the CNS, an organ normally devoid of classical lymphatic dreinage system which tend to remain confined to CNS;
Excluded are lymphomas of the dura, intravascular LBCL, lymphomas with simultaneous systemic involvement and immune-deficiency associated lymphomas; EBV negative

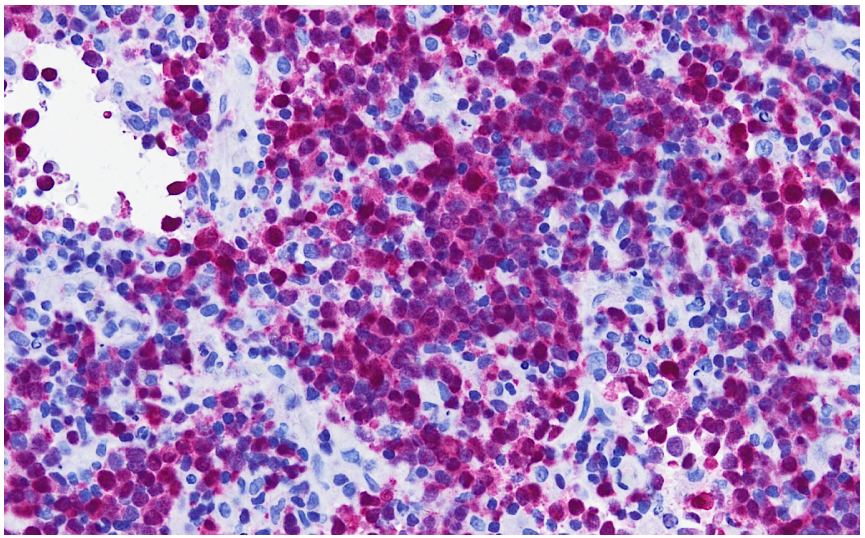
**late germinal centre exit B cell**
**«permanent *GC*-stage»**

IgM/IgD, BCL6+
**SHM/aSHM**: in Ig, BCL6 gene, and in tumour suppressor genes such as PAX5, PIM1 and CMYC
**25-30% cases BCL6 translocation** (>Ig)

**but with impaired terminal differentiation**

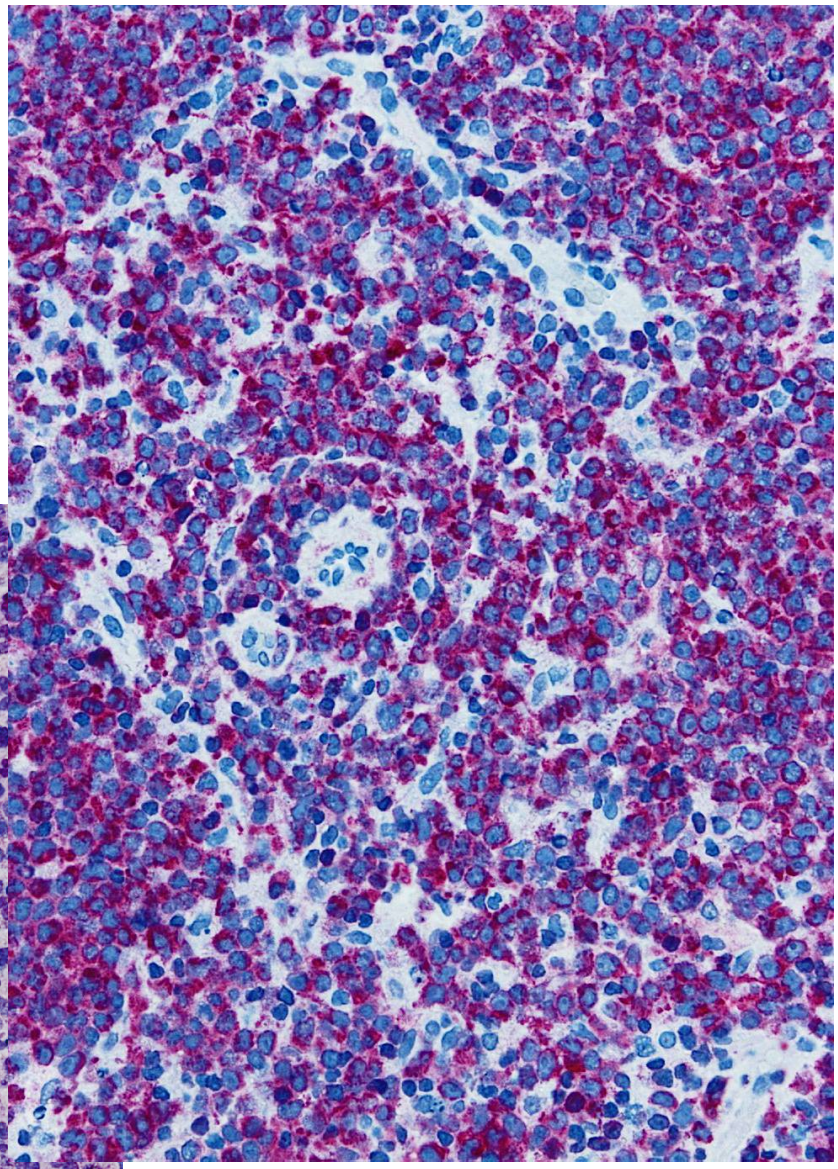
**IRF4+** (target of NFKb pathway)
negative plasmacellular markers

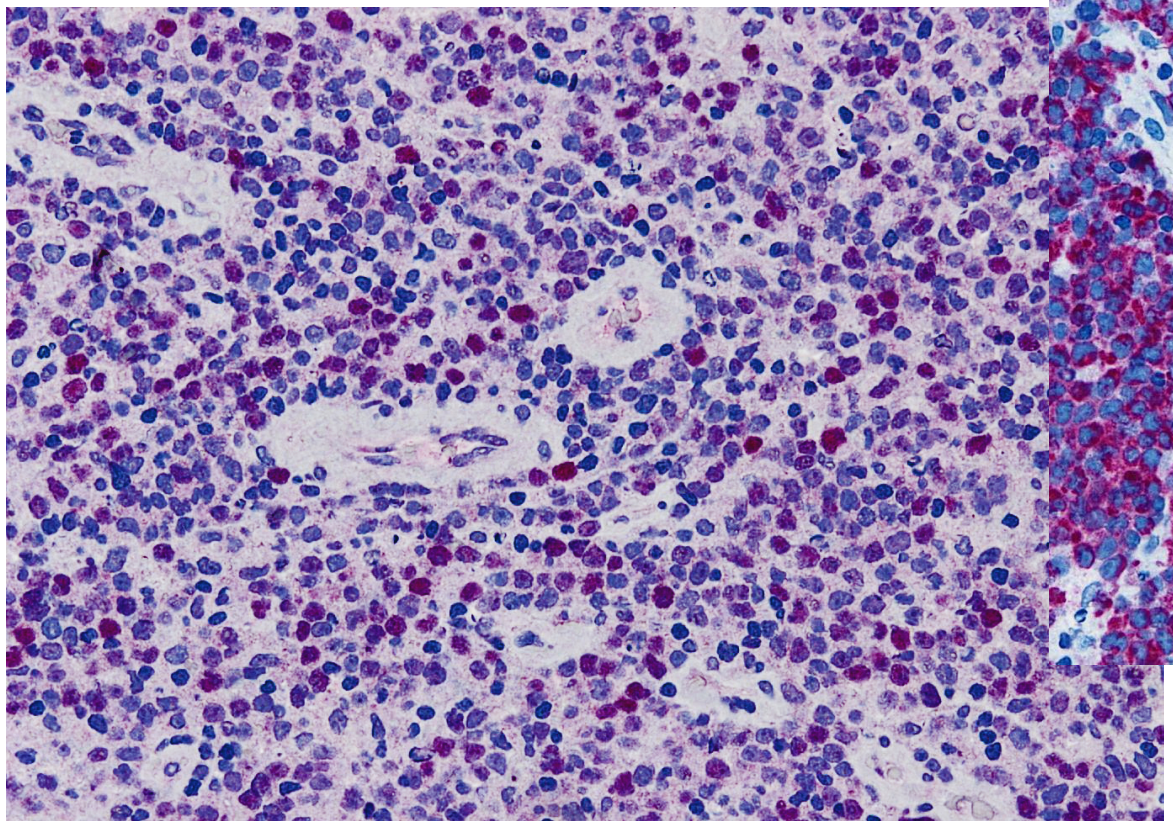




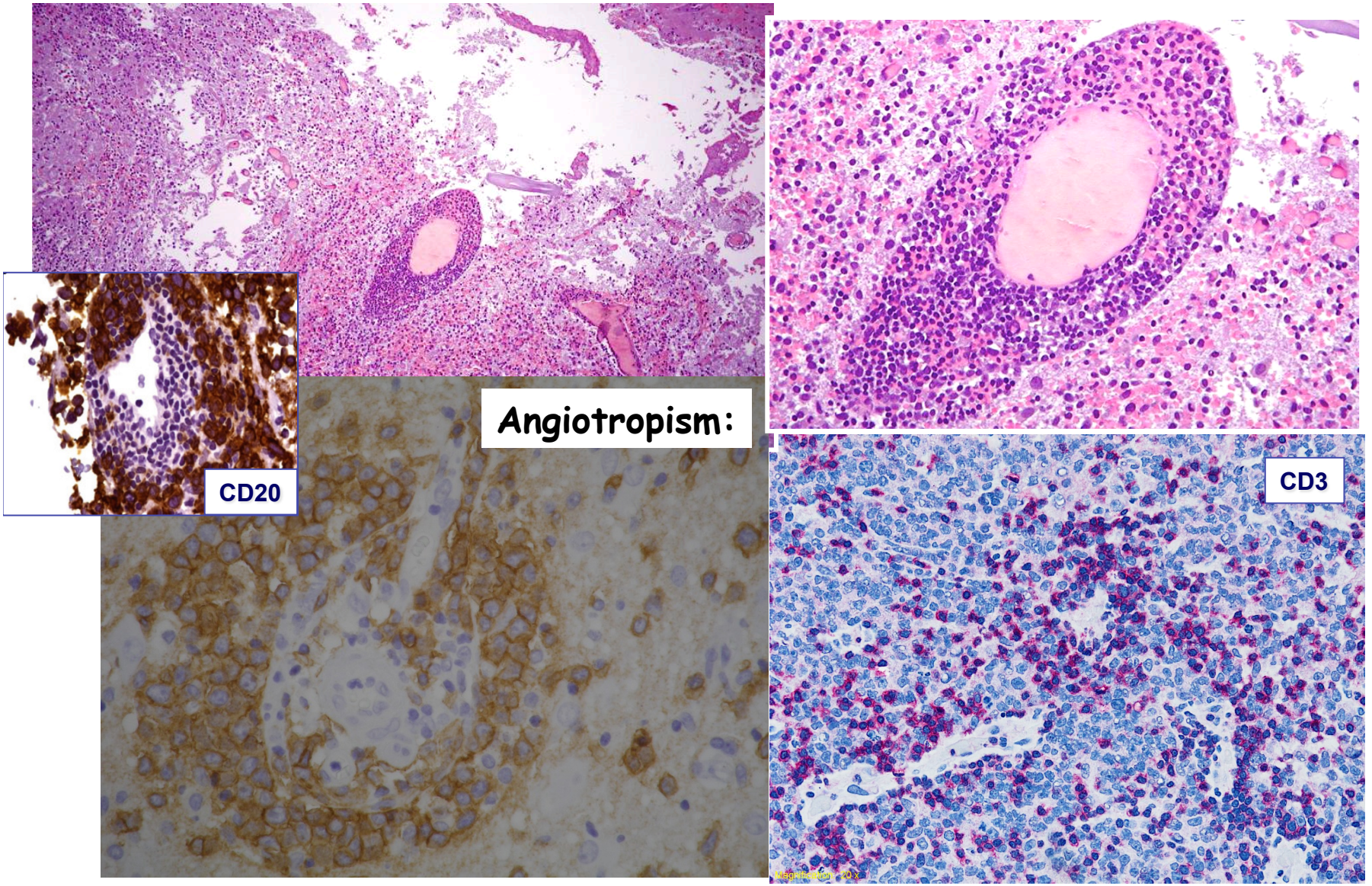
**Dual expressor**
**MYC+/BCL2+ in 85% cases**

- higher than non CNS-LBCLs
almost no dual negative cases
- but only 8% are MYC
translocated





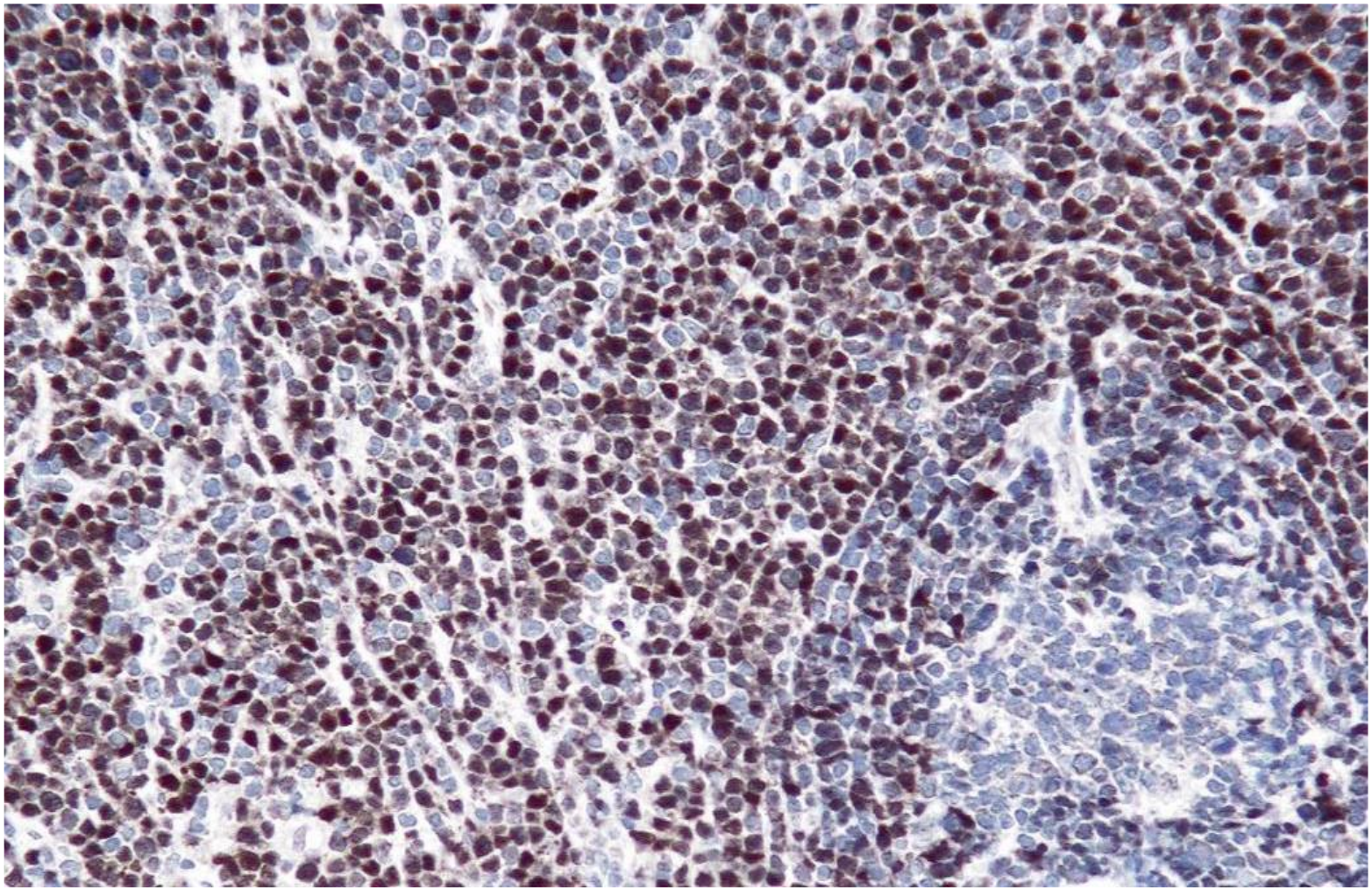
chemokine-mediated intercellular play between neoplastic B-cells and endothelia, T cells (CD4+/CD8+), macrophages and APC all located at perivascular spaces: fertile micromilieu which maintains proliferation and survival in a permanent BCL6-activated state (CXCR4 and CXCL12)



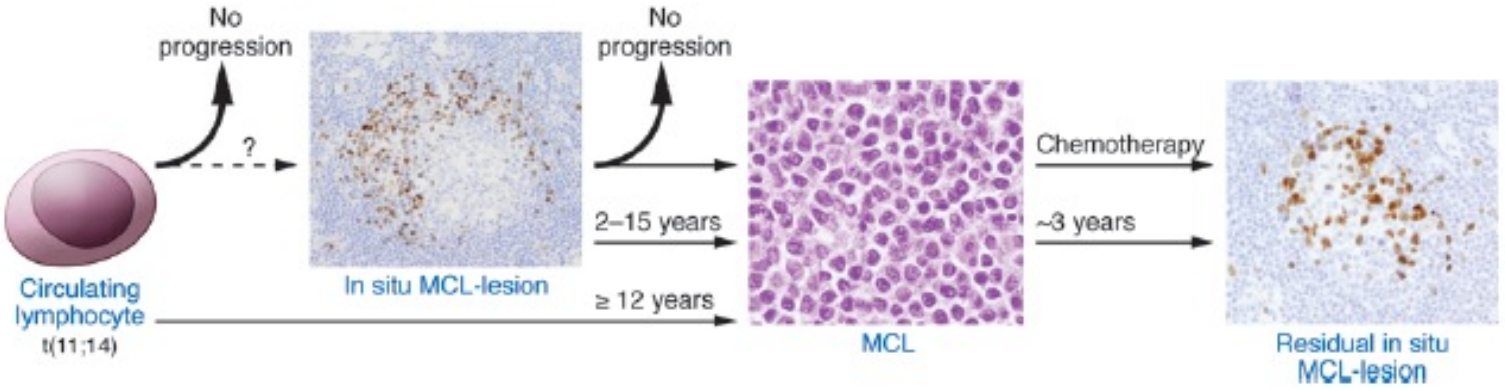

Immune evasion could be enhanced by the defective HLADR expression on neopalstic cells & by alteration of the cytokine milieu induced by BCL6 and MYD88 anomalies

# Mantle Cell Lymphoma

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



# *per se* likely not tranforming




detected at low levels in pb of healthy individuals (7%) (Hirt et al. Blood 2004)

additional mechanisms needed to develop lymphoma

* Mutations in CCND1 at 3'UTR/untranslated region ---truncated cyclin D1 transcripts with longer half-life -- potentiated activity

b) delete area for microRNA15/16 binding no inhibitory effect

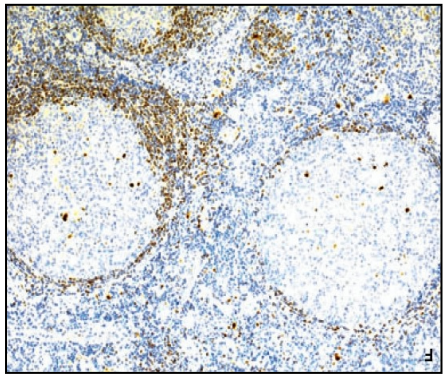
* Amplification of the translocated t(11;14) allele

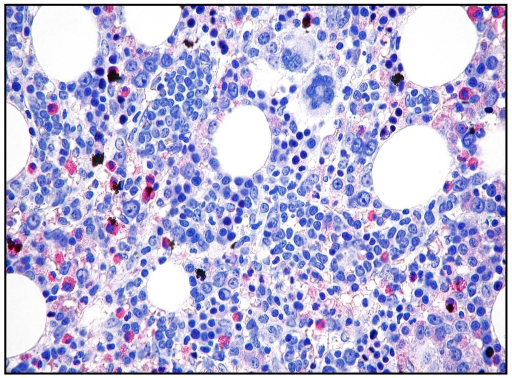
Jader et al. 2012, Adam et al. 2012

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Two types of clinically indolent variants are

**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:** 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.



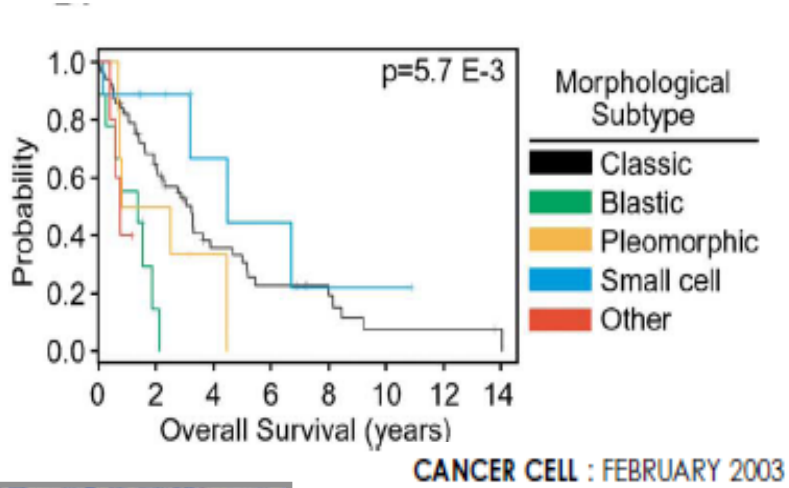


Should be distinguished from overt MCL with a mantle zone growth pattern or other classical MCL with a low proliferative fraction which may also be relatively indolent

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

# CYTOLOGY :

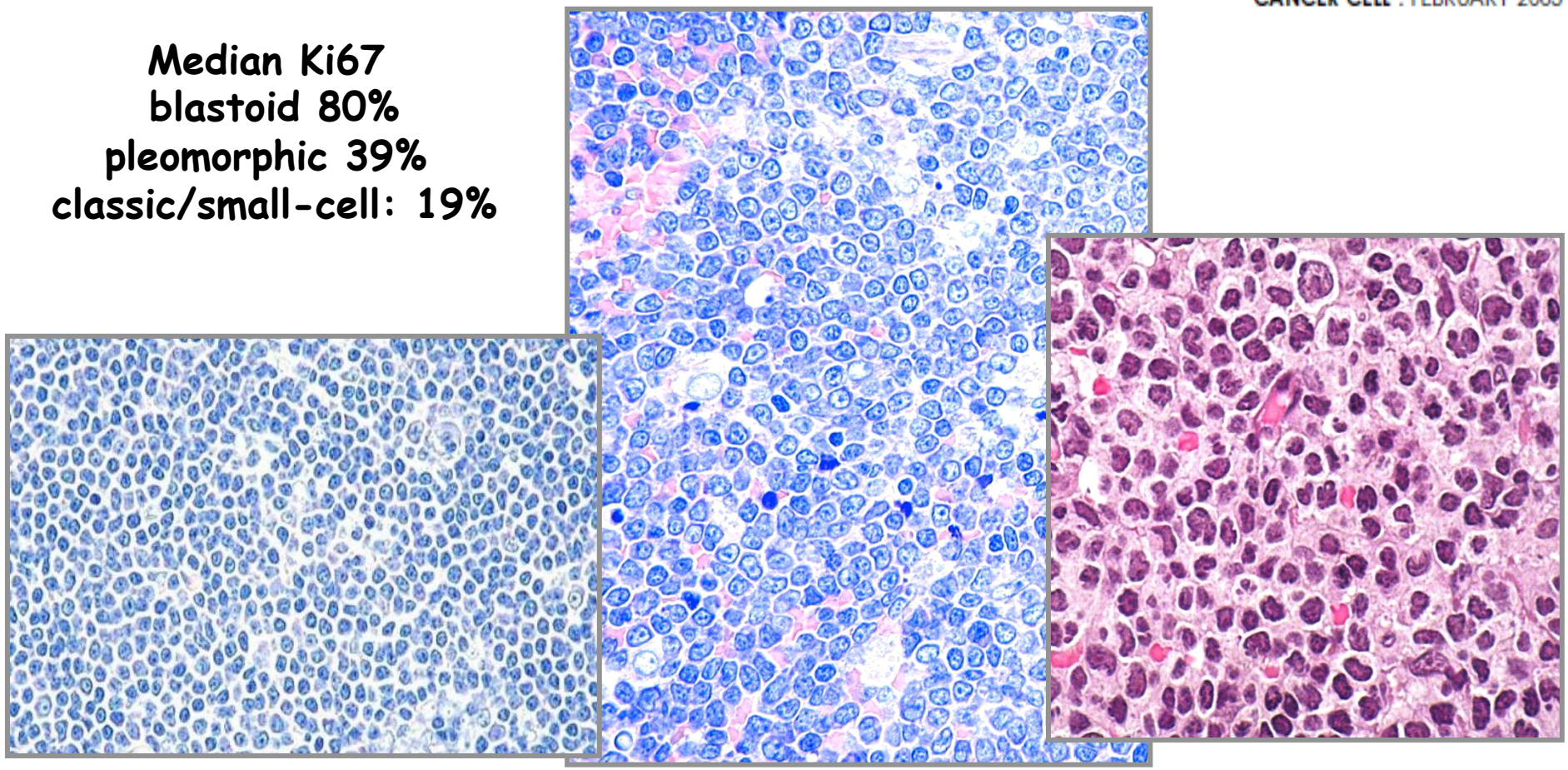
## small cell,classic, pleomorphic, blastoid

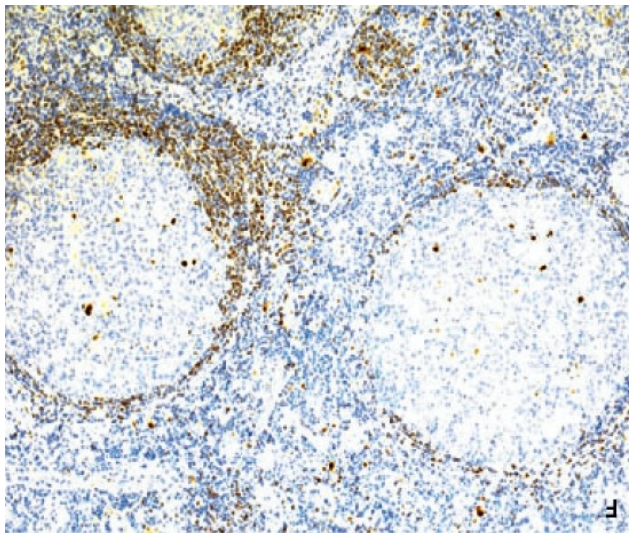


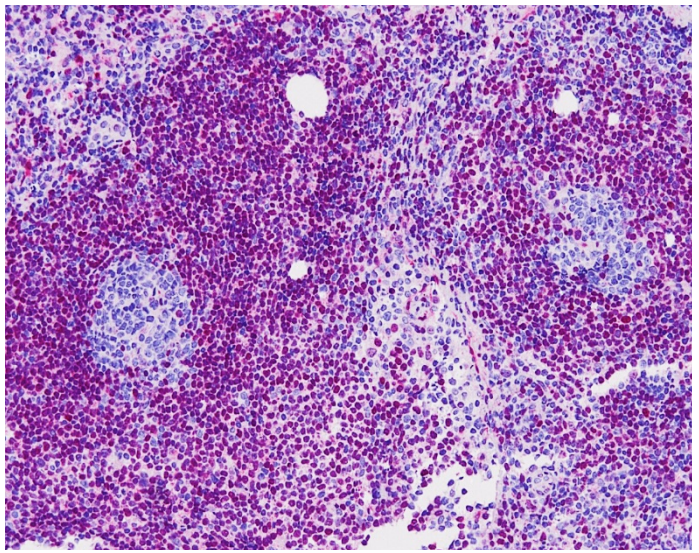

CANCER CELL : FEBRUARY 2003

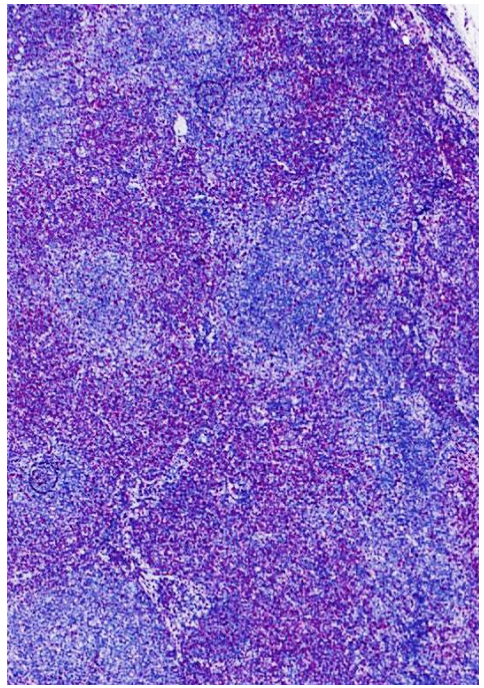
**blastoid**
**>LDH and >MIPI**
**(comparable age,PS,WBC)**

**Median Ki67**
**blastoid 80%**
**pleomorphic 39%**
**classic/small-cell: 19%**







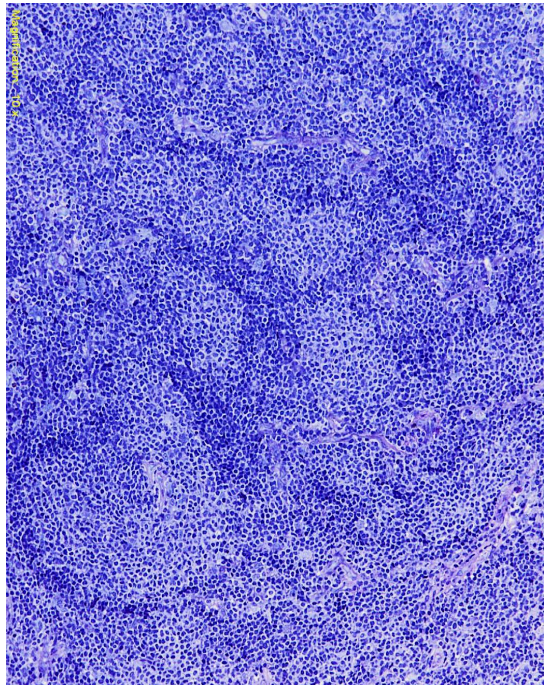


**Growth**

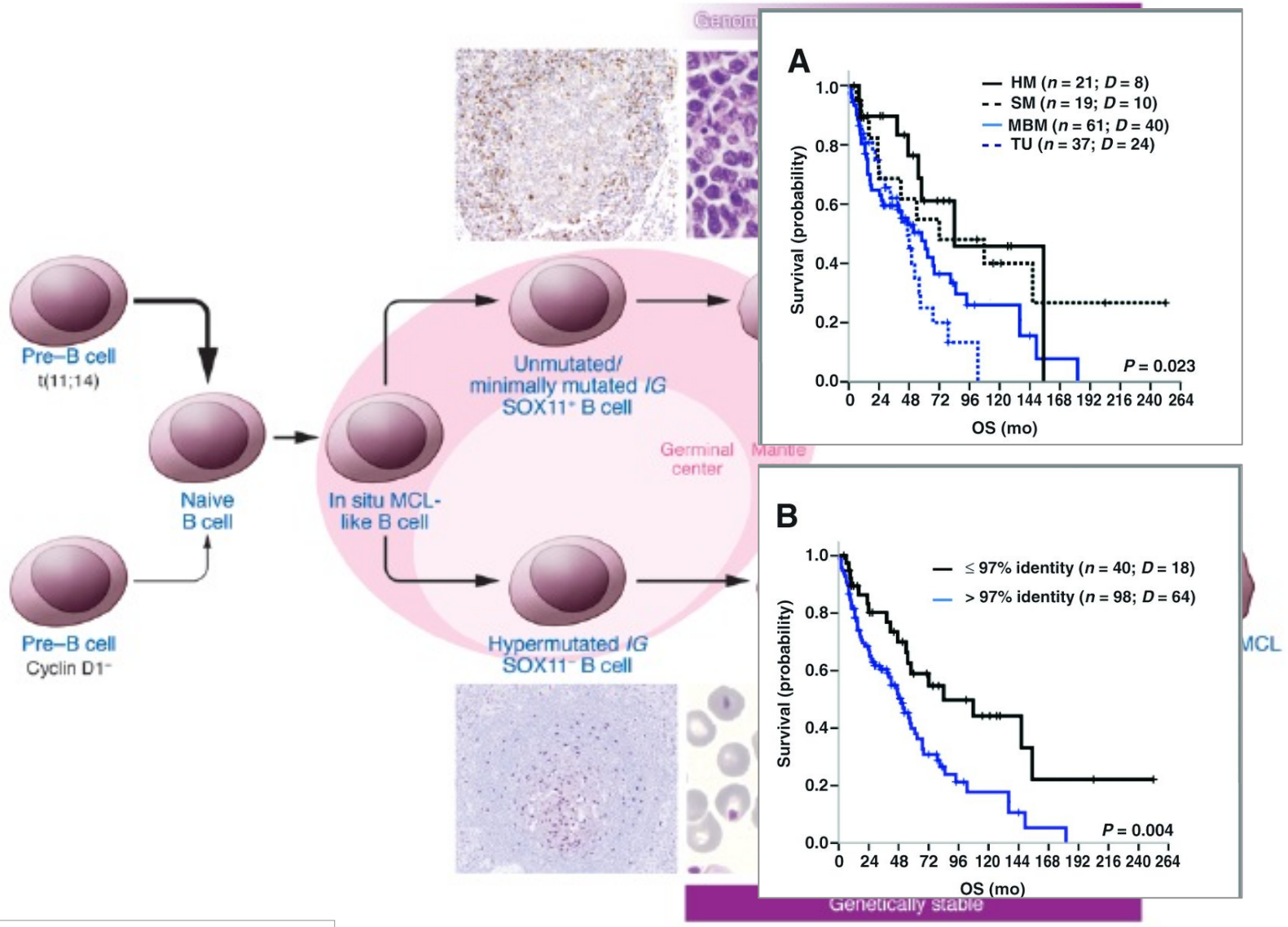
in situ/ mantle-zone / nodular / diffuse

diffuse: older pts, >MIPI

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



# Start point: mutational status; additional aberrancies follow for progression



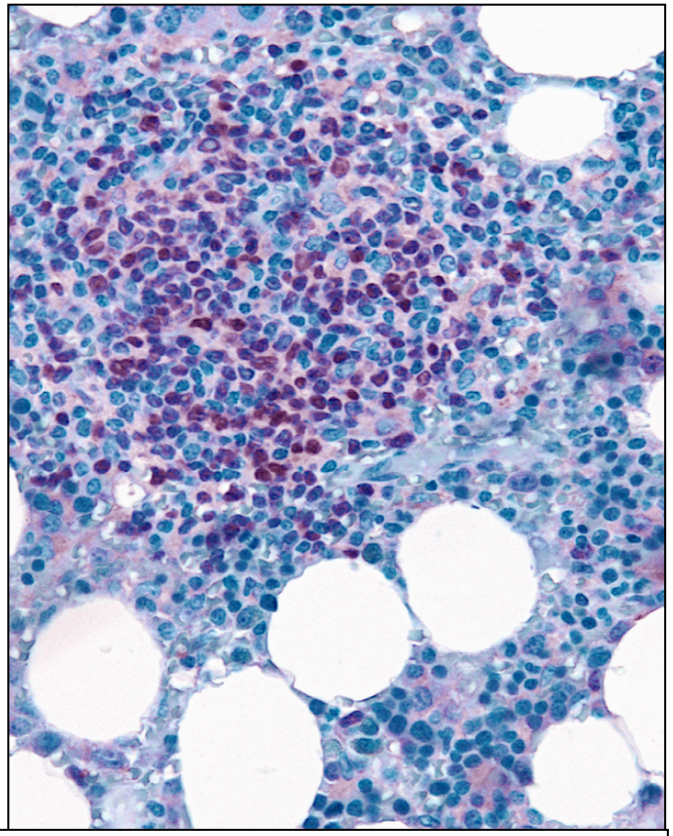

Jared et al. JClinInvest 2012

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

Ana Mozos,[1] Cristina Royo,[1] Elena Hartmann,[2] Daphne De Jong,[3] Cristina Baró,[4] Alexandra Valera,[1] Kai Fu,[5] Dennis D. Weisenburger,[5] Jan Delabie,[6] Shih-Sung Chuang,[7] Elaine S. Jaffe,[8] Carmen Ruiz-Marcellan,[9] Sandeep Dave,[10] Lisa Rimsza,[11] Rita Braziel,[12] Randy D. Gascoyne,[13] Francisco Solé,[4] Armando López-Guillermo,[1] Dolors Colomer,[1] Louis M. Staudt,[8] Andreas Rosenwald,[14] German Ott,[14] Pedro Jares,[1] and Elias Campo[1]

## 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**

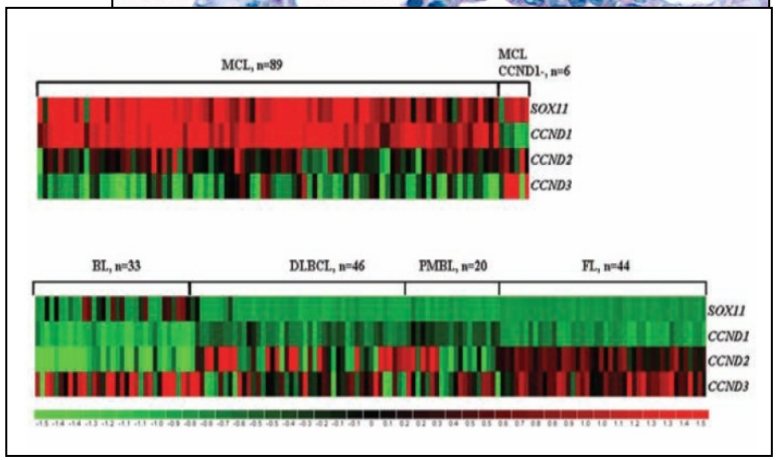
**Not expressed in other mature lymphomas or lymphocytes**

**Function in lymphomagenesis not understood**

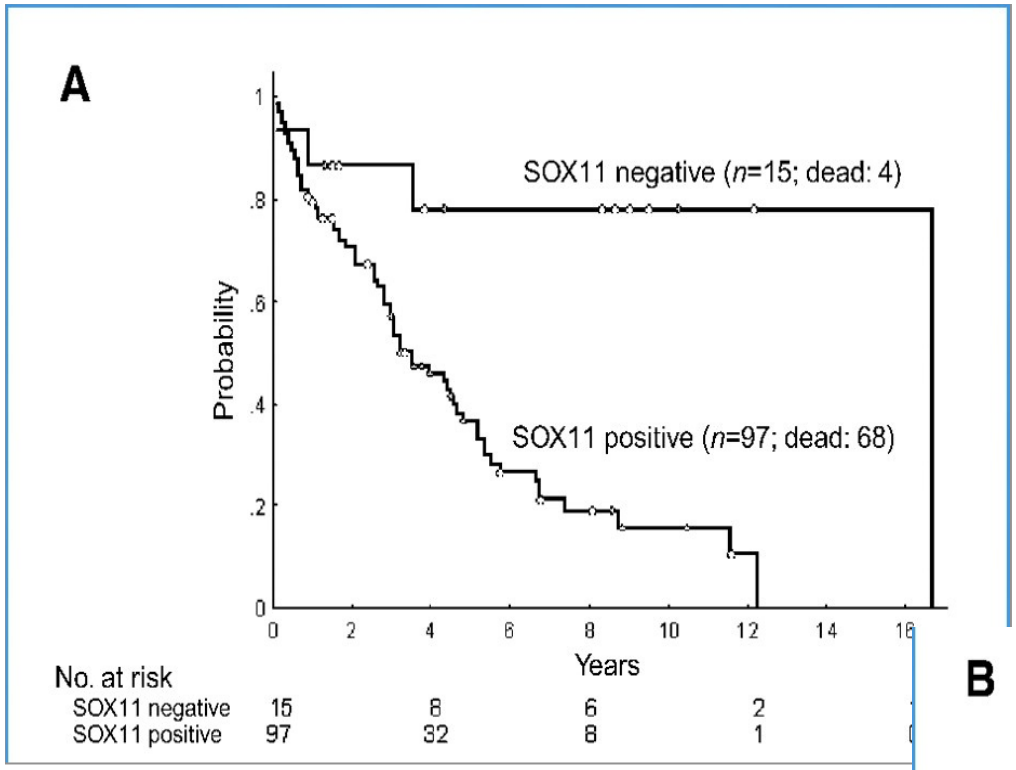
**Positive in CCND1pos and CCND1neg cases**

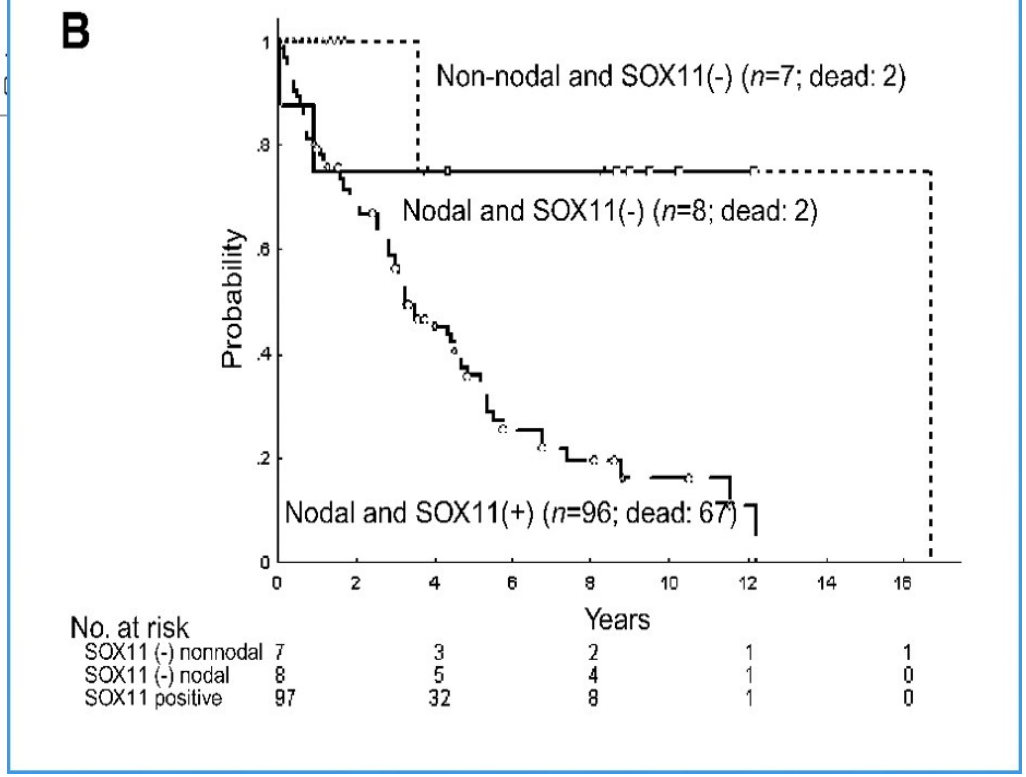
**good <u>diagnostic biomarker</u>**

**<u>Possible adjunct in prognostication</u>**

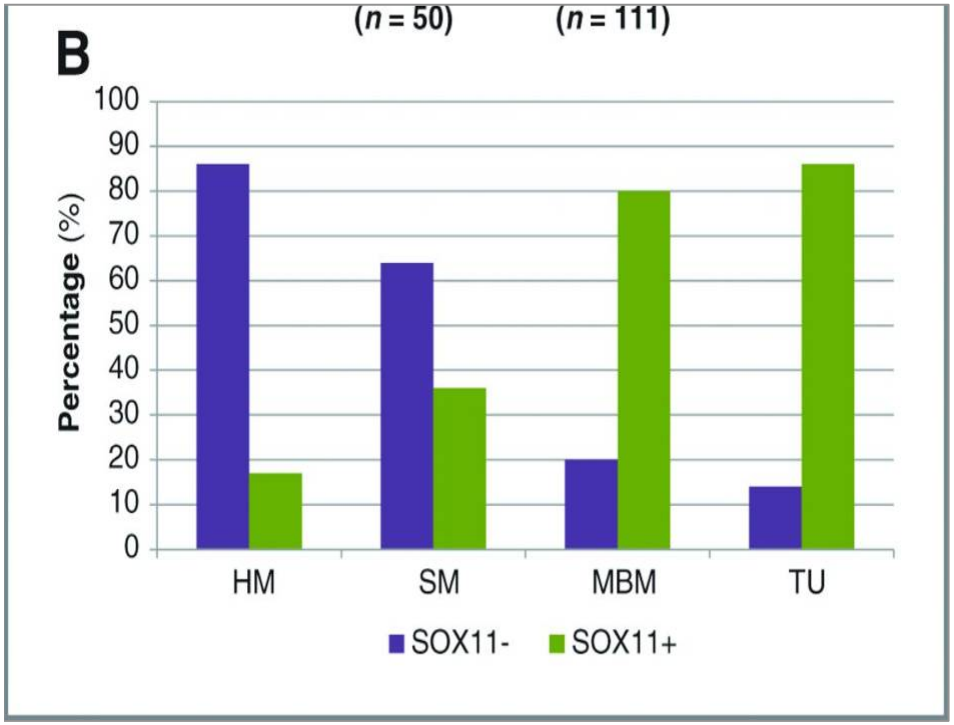


**Fernàndez V Cancer Res. 2010**
**Navarro A et al. Cancer Res 2012**

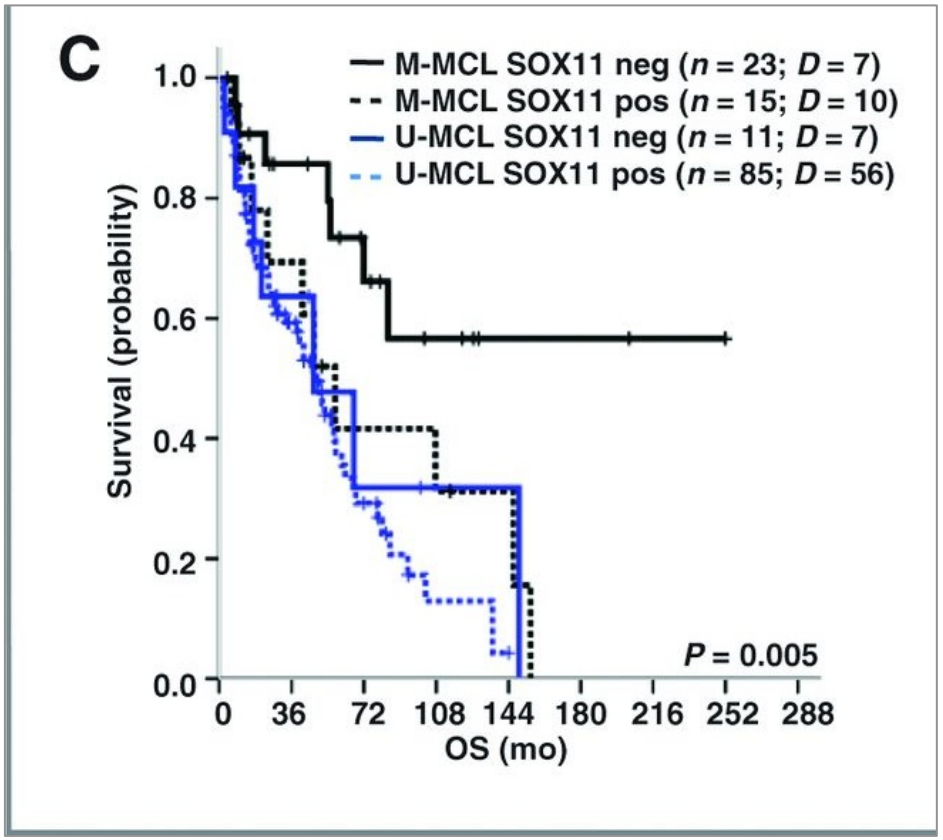


# The mutational status is somehow related to SOX11 expression




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



# Proliferation and clinical behaviour in MCL

## 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. © 2016 by American Society of Clinical Oncology*

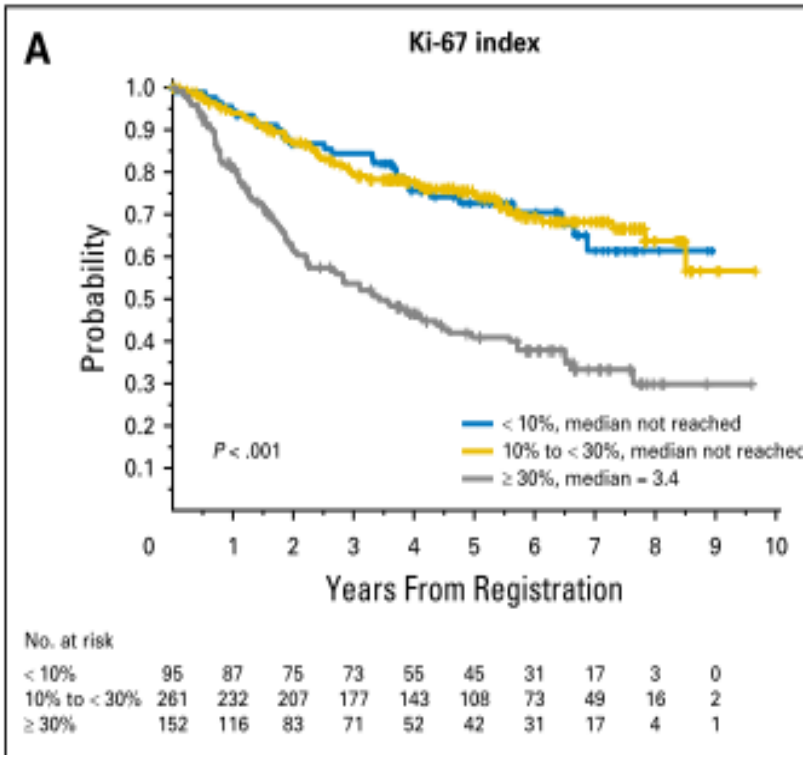
*Eva Hoster, Andreas Rosenwald, Françoise Berger, Heinz-Wolfram Bernd, Sylvia Hartmann, Christoph Loddenkemper, Thomas F.E. Barth, Nicole Brousse, Stefano Pileri, Grzegorz Rymkiewicz, Roman Kodet, Stephan Stilgenbauer, Roswitha Forstpointner, Catherine Thieblemont, Michael Hallek, Bertrand Coiffier, 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*

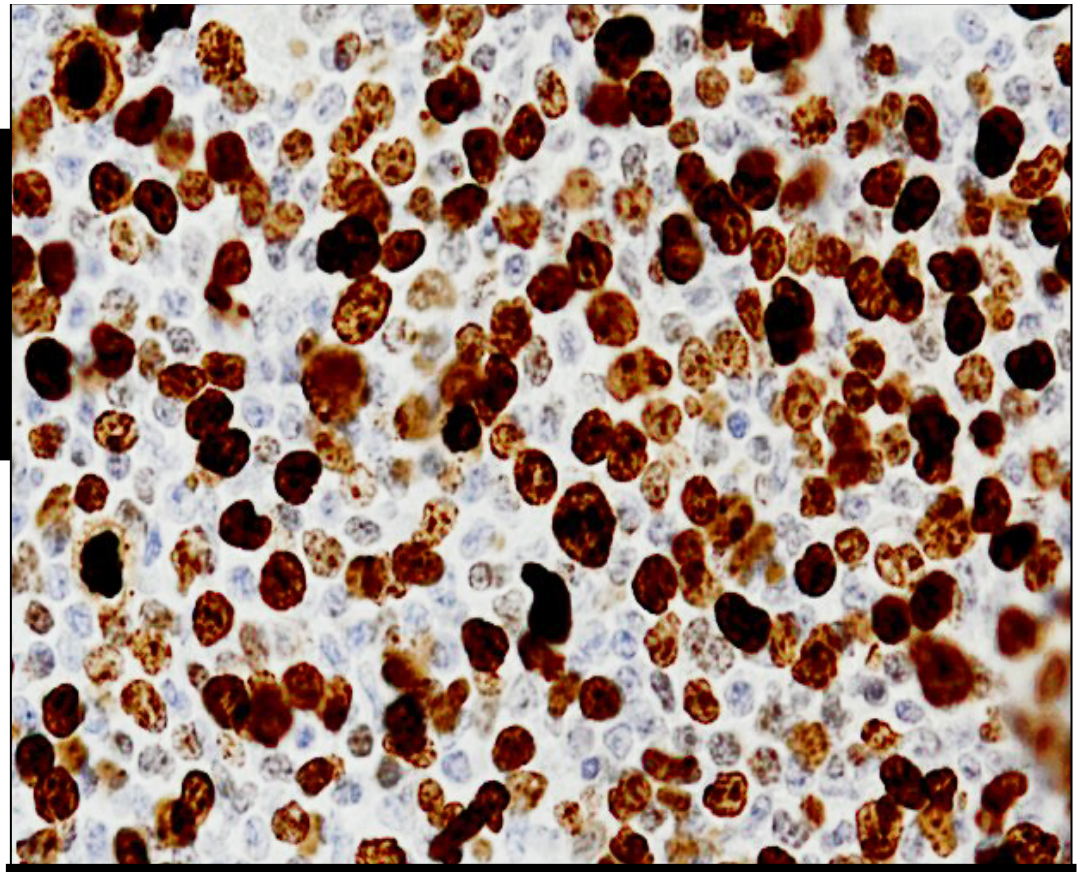
## The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma

**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,*]

KI67 and OS/PFS
No difference between
<10% or <30% and 40-50% or >50%
So CUT OFF 30%



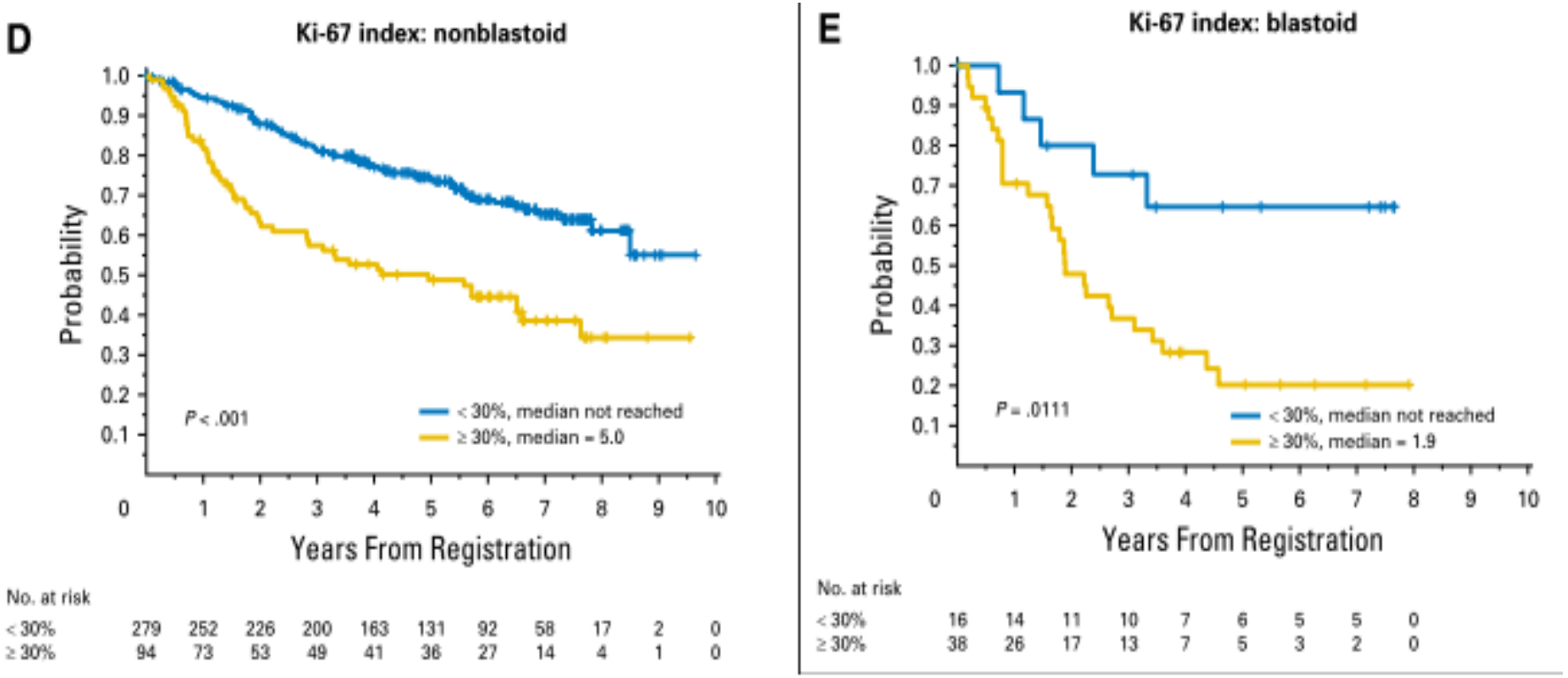
Ki67 and MIPI (MIPI-b)
Ki-67 not correlated with age but with PS, LDH, WBC

low/intermediate MIPI:
median ki67 19%

high risk MIPI
median ki67 27%

blastoid MCL (median 80%)

# Ki67 and cytology




**Within each cytology subset higher Ki-67 index relates with worse outcome**

- 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

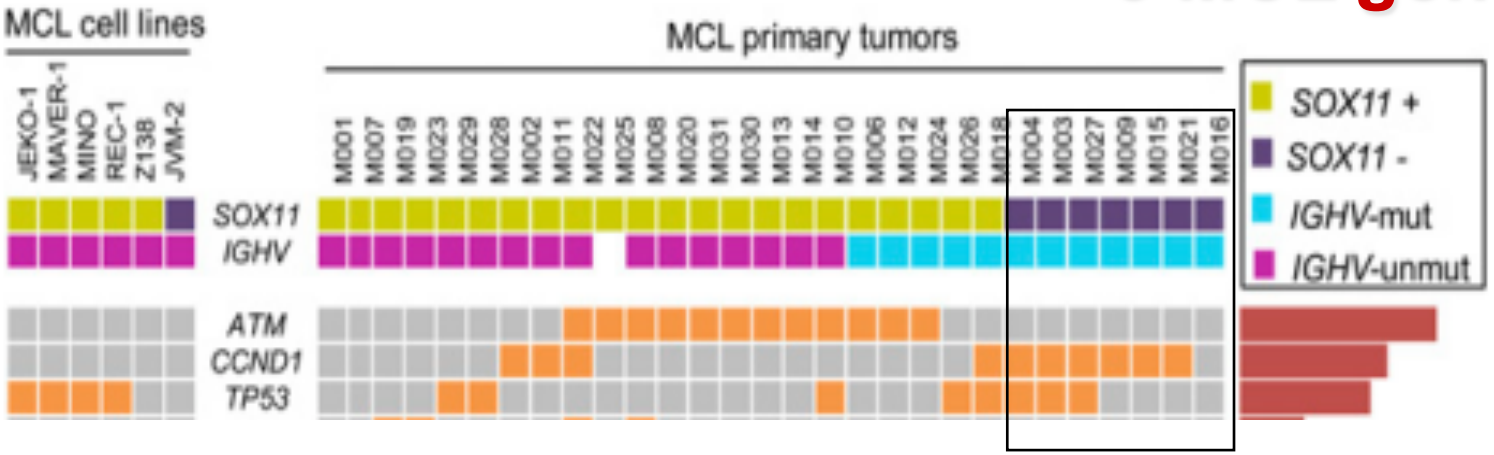
PNAS | November 5, 2013

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 EVENTS

- one of the most "rearranged" lymphoma
- deletions, gains, point mutations
- target genes involved in molecular pathways, inducing their constitutive activation
- Usually secondary, but subclones can be present at onset and expand later
- Impact on progression (of both classic and indolent forms)

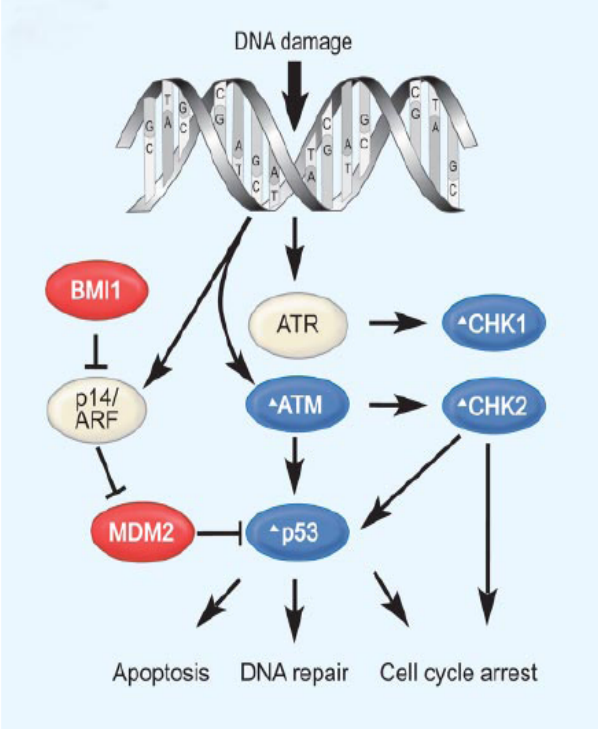
# 3 MCL gene drivers



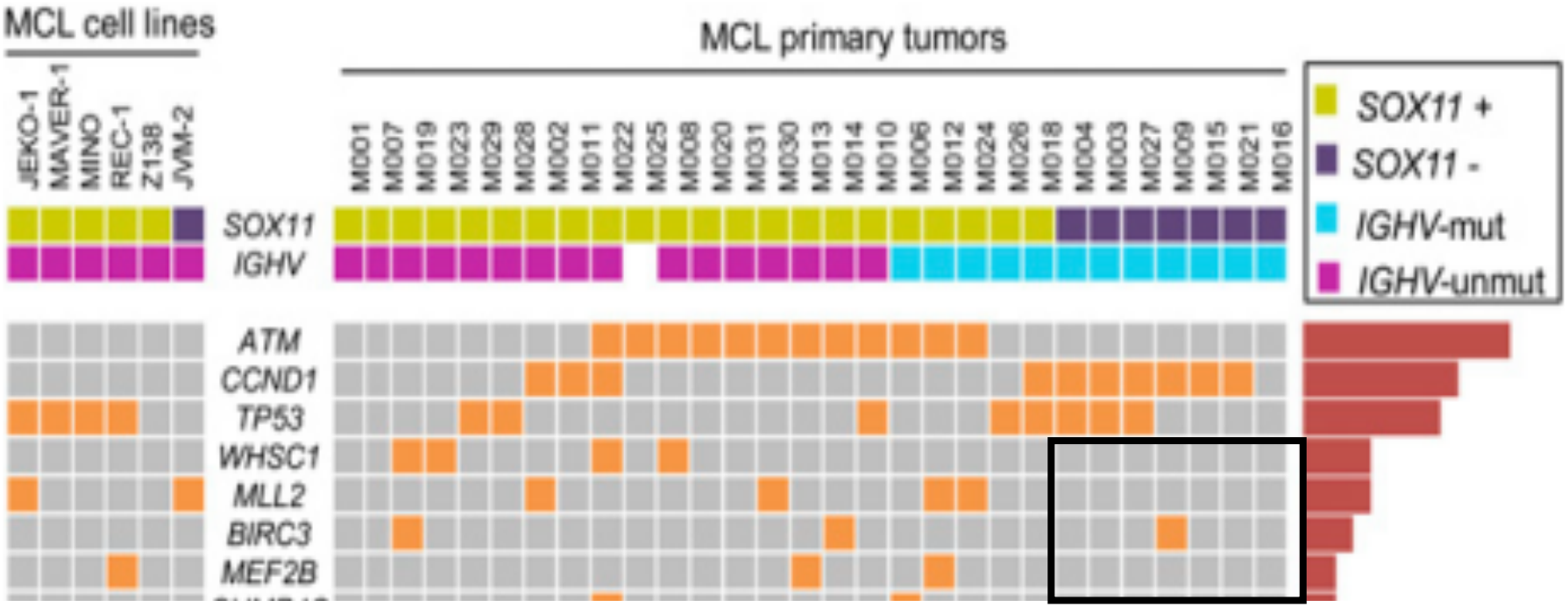

***ATM 41% virtually absent in SOX11-/ Mutated cases; worse impact***

***CCND1 35% : equally distributed; not defined impact***

***TP53 28% : equally distributed; worse impact; specific aberrancy in indolent cases***




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;



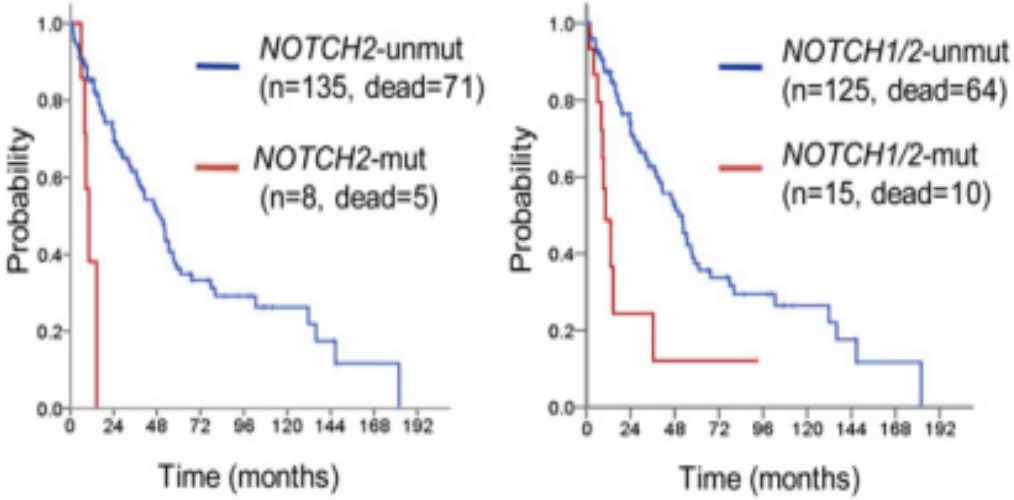

**"chromatin modifiers" genes**

**(WHSC1 and MLL2 code for histione-methyltransferases)**

**WHSC1 10%**
**MLL2 14%**
**MEF2B 3%**

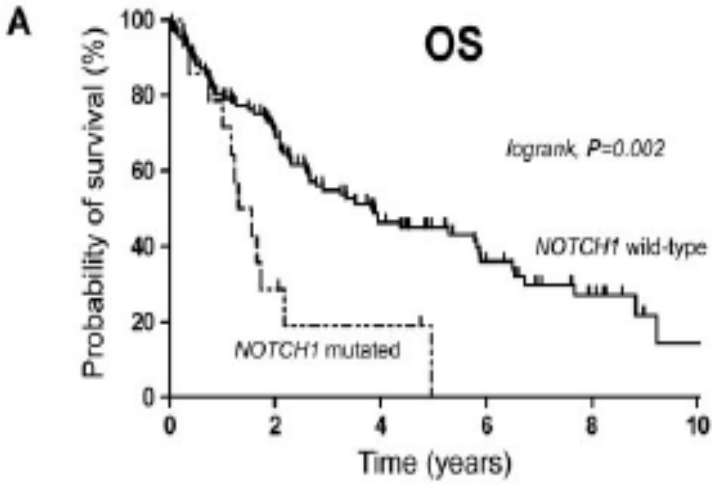
**VIRTUALLY ABSENT IN SOX11-/MUTATED CASES**

Jared et al. JClinInvest 2012




NOTCH1 (4.7%)
NOTCH2 (5.2%)
Usually alone, not together

**Adverse biological features (blastoid/ pleomorphic) & shorter OS**



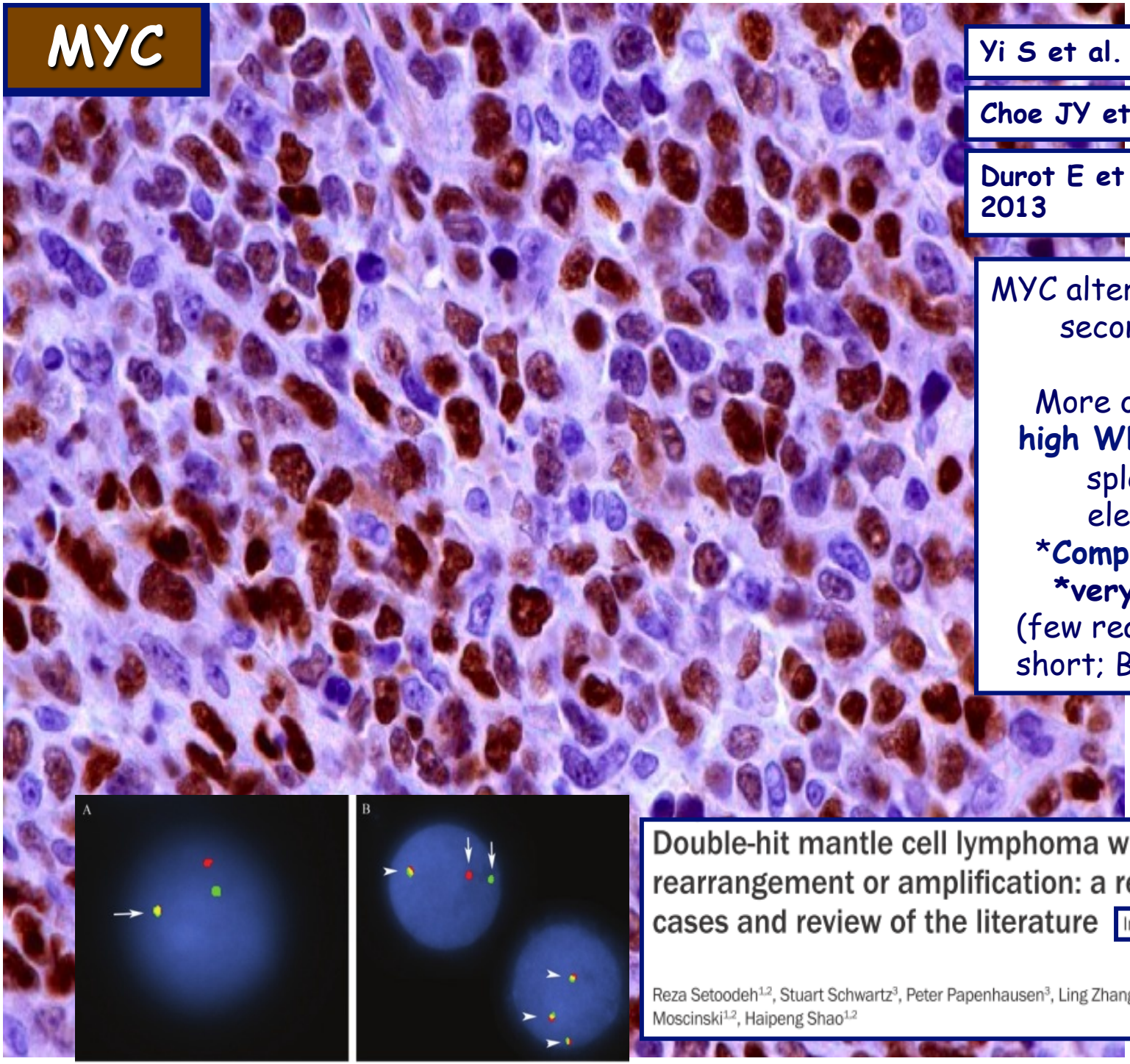

NOTCH1 12%
No differences with non mutated cases as for stage, IPI, histology

Not related with progression (≠BCLL Richter)

**Worse OS (not PFS)**

Kridel et al. Blood 2912

# MYC



Yi S et al. Oncotarget. 2015

Choe JY et al. Histopat 2016

Durot E et al. Leuk Lymph 2013

MYC alterations usually as secondary events

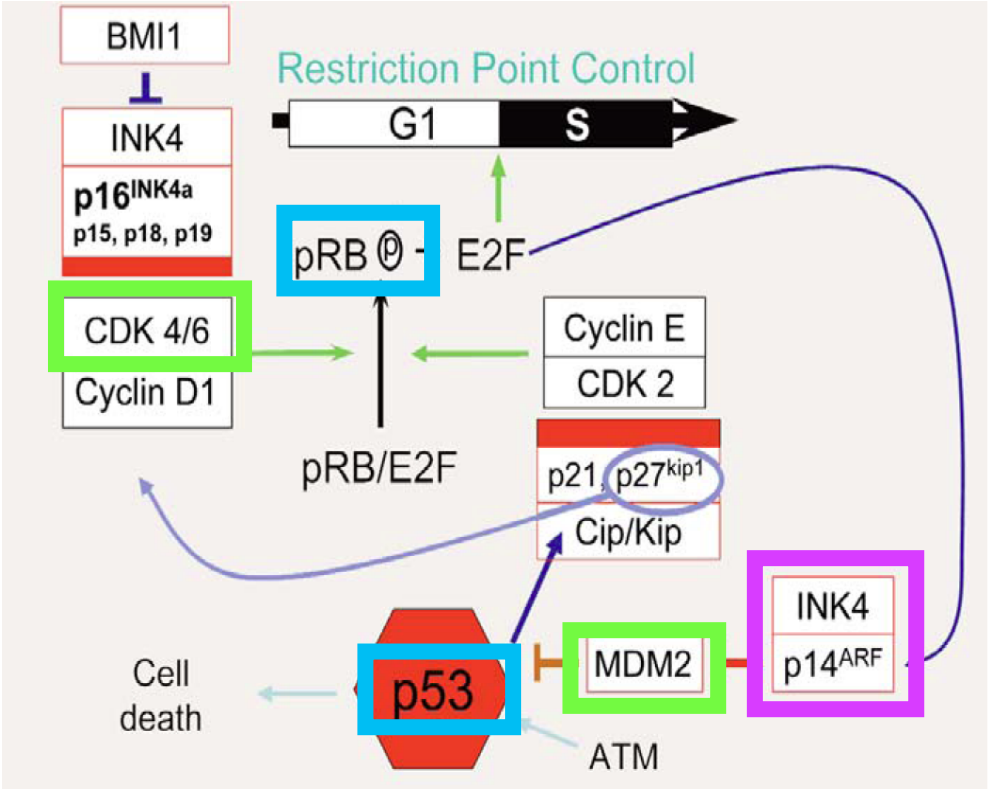
More often **blastoid**
**high WBC** count/**bm+**
splenomegaly
elevated LDH
***Complex karyotype**
***very aggressive**
(few reach CR which is short; BL-like regimens




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]

# aberrancies in CELL-CYCLE genes




EFFECT

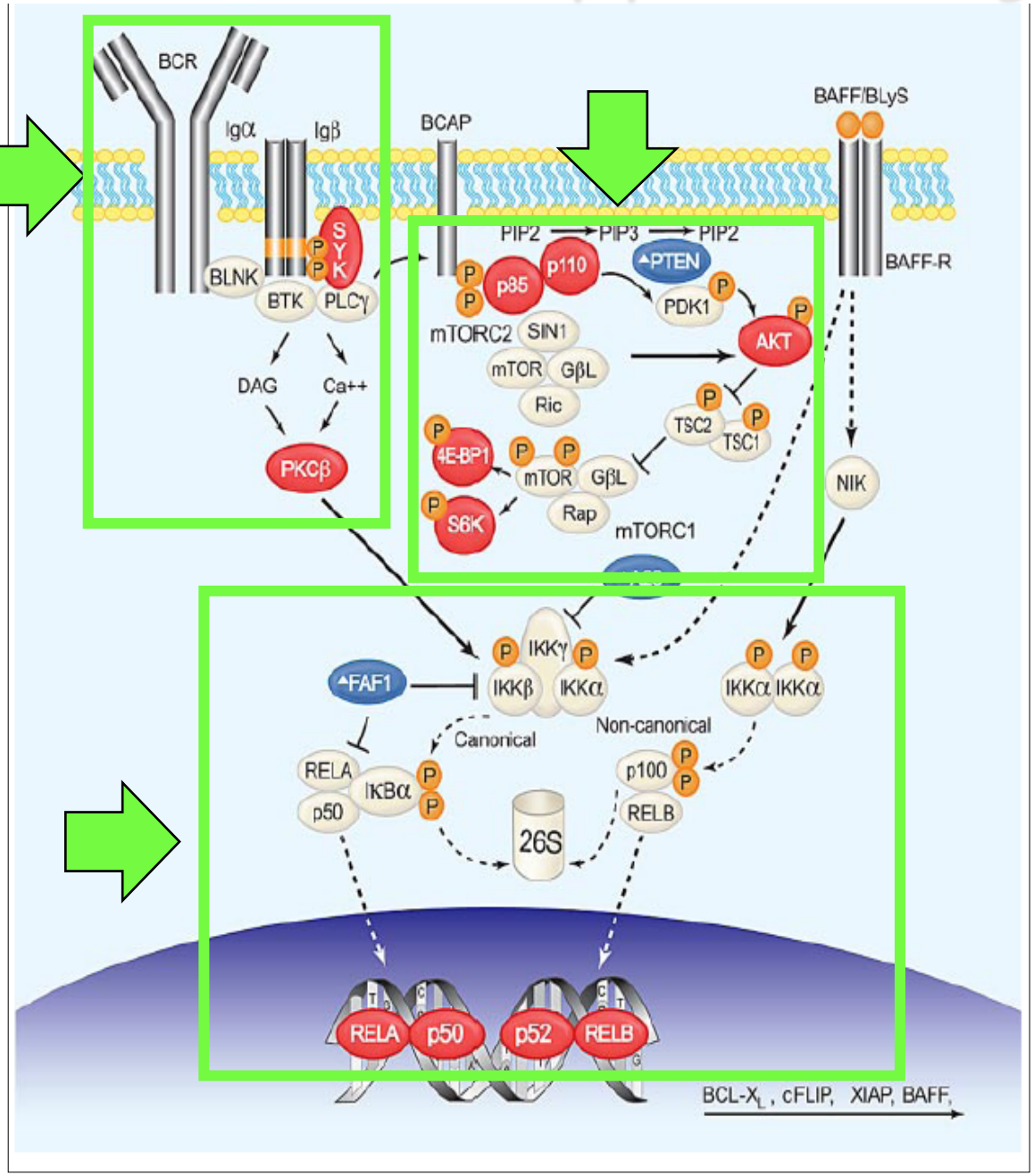
- CONTINUOUS ACTIVATION OF CYCLINS OR CYCLIN MEDIATED PROTEINS INDUCING PROLIFERATION
- INHIBITION OF P53

Point mutations/deletions RB1 activates E2F

Deletion of CDKN2A (9p21

Amplification of CDK4 or MDM2

# activation of key proteins of signaling pathways



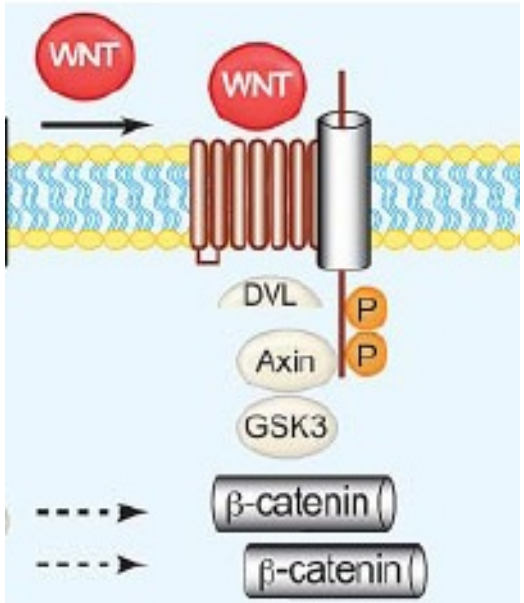

PI3K/AKT/mTOR

BCR signaling (SYK, LYN, BTK phosphorilated)

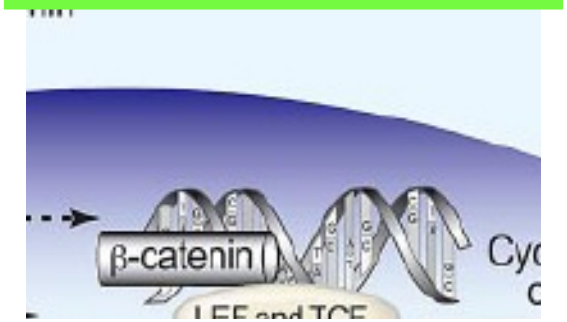
NFkb classic
NFkb alternative

# activation of key proteins of signaling pathways

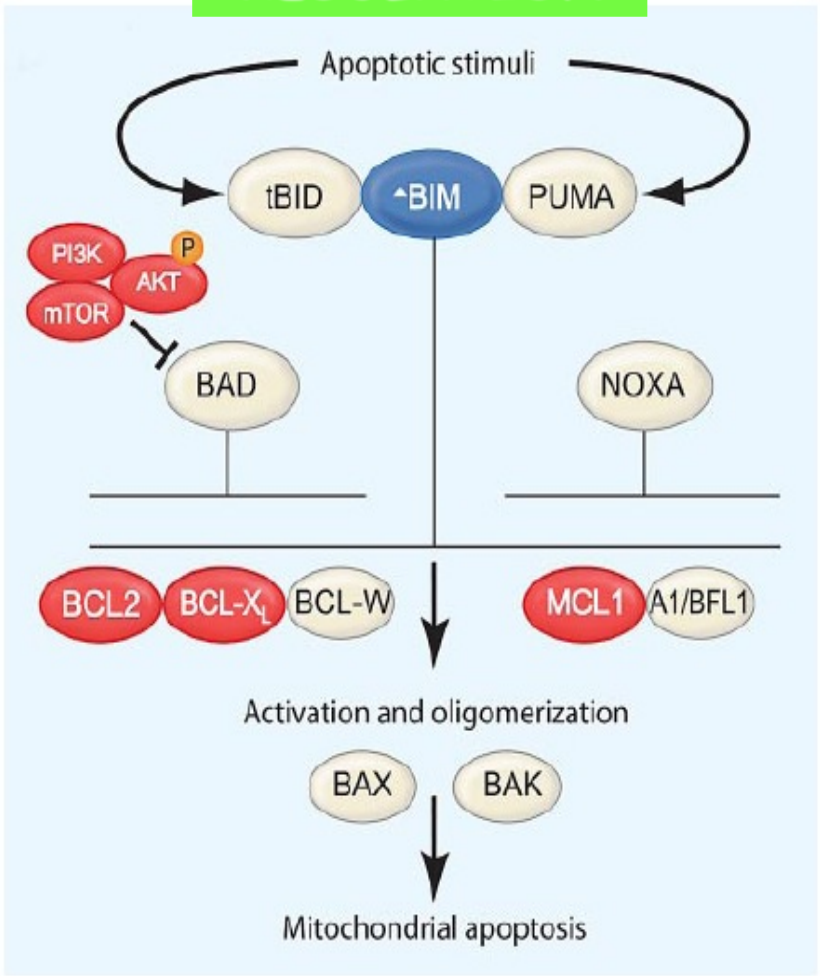
WNT is linked to its receptor, B catenin is not degradated and go to the nucleus activating LEF and TCF




## WNT/beta catenin




## APOPTOSIS REGULATION




- Deletion of proapoptotic genes (BIM/ BCL2L11)
- amplification of anti apoptotic genes (BCL2
- PI3K\AKT \mTOR inhibits the pro apoptotic BAD

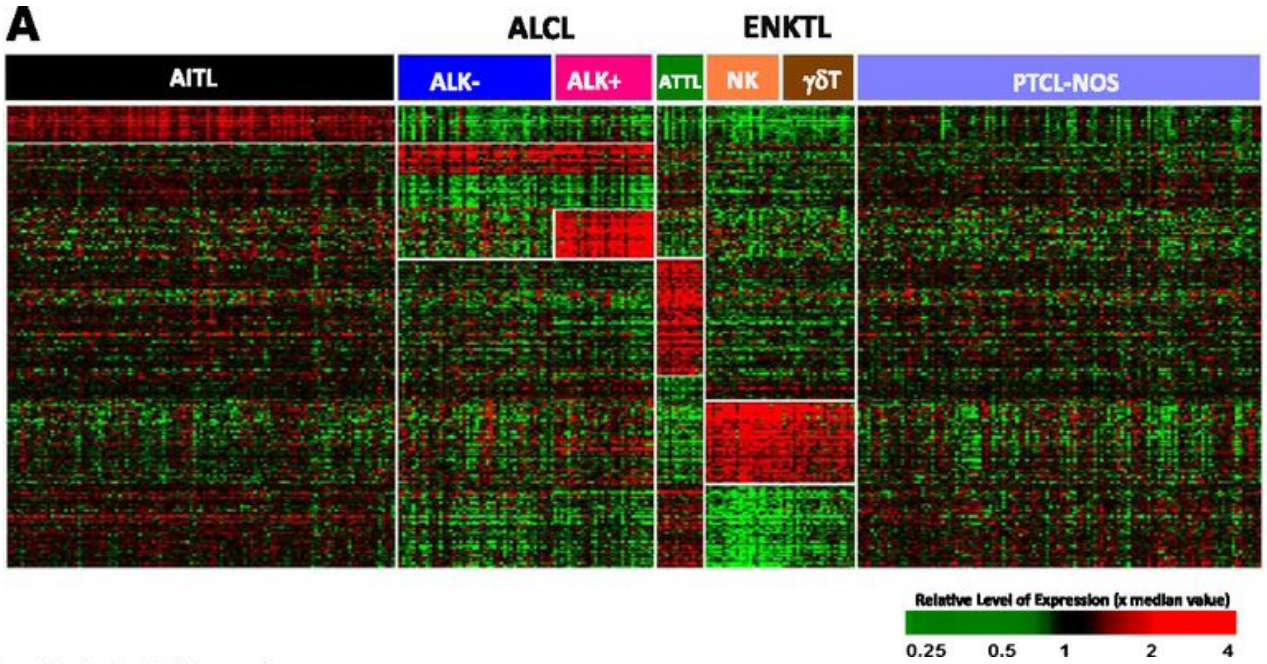
# Peripheral T-cell lymphomas

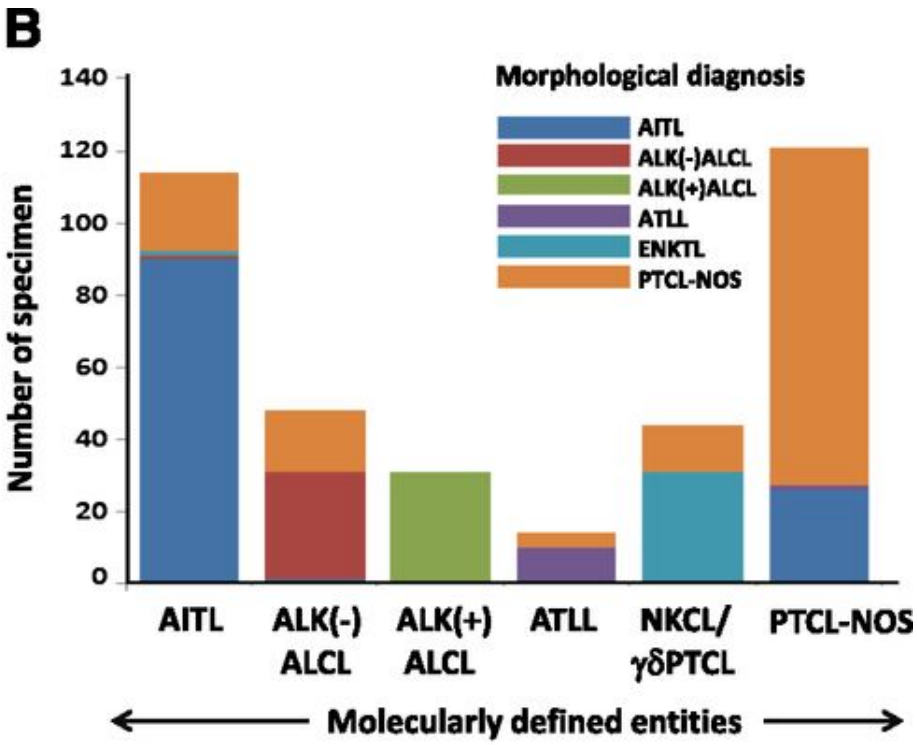
**Published data in the recent years have improved our knowledge also for PTCL and have had impact on their COO-classification and on their prognostic stratification which will be included in the 2016 WHO**

Iqbal J et al. Blood 2014

·PTCL: molecular classification and morphology and behaviour

·PTCLnos is the category more heterogeneously diagnosed




(B)
Pathological vs molecular diagnosis comparison.

Substantial number of cases from PTCL-NOS were molecularly classified into WHO recognized PTCL subgroups:

(i) AITL (n = 21, 14%);
(ii) ALK(–)ALCL (n = 17, 11%);
(iii) ATLL (n = 4, 3%);
(iv) γδ-PTCL (n = 13, 9%).

However, 26 AITL cases (22%) were not molecularly classifiable and changed to PTCL-NOS

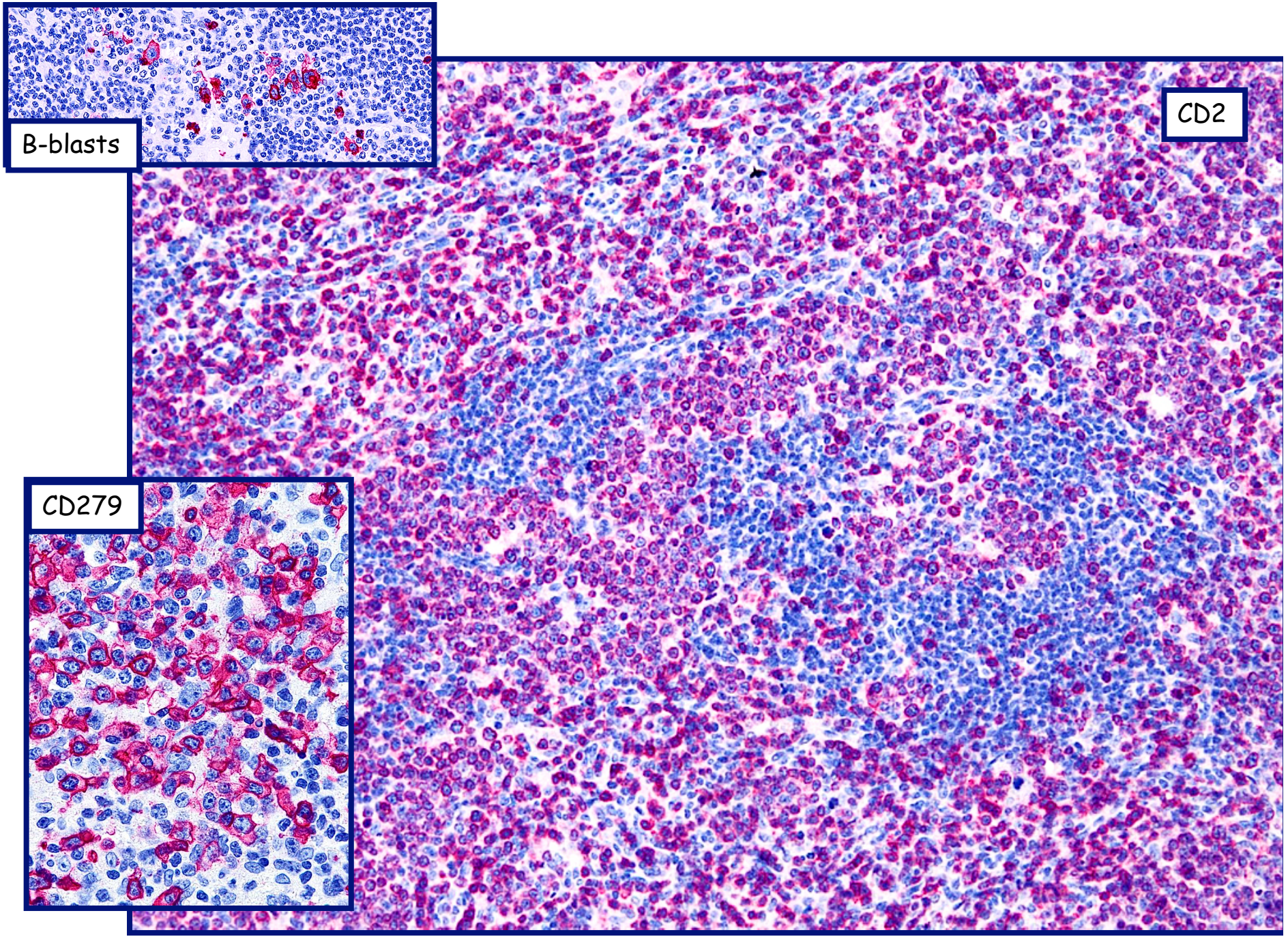
# PTCL, with FOLLICULAR HELPER T-CELL PHENOTYPE

CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP and CCR5
at least two or preferably three antigens are required

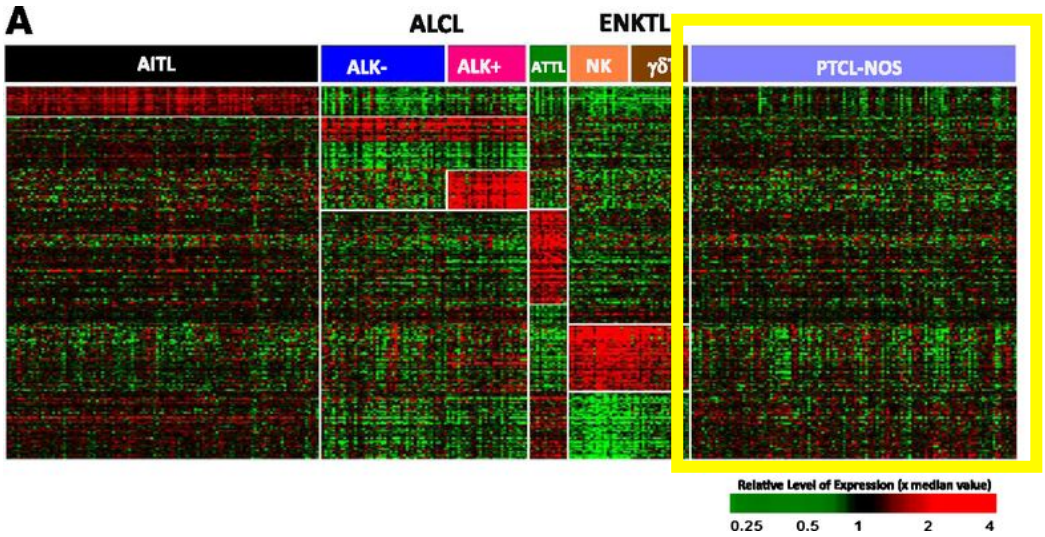
ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA
FOLLICULAR VARIANT OF PTCL, NOS
NODAL PTCL, NOS, with FHT-CELL PHENOTYPE

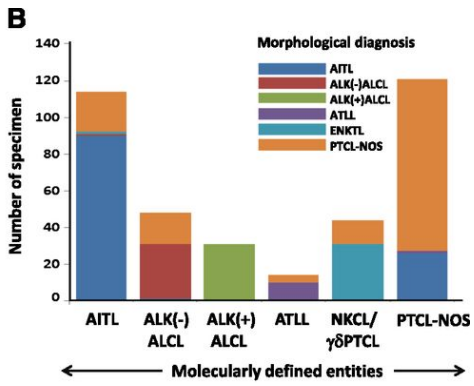
- Share similar signature at GEP (FTH related signature)

- Recurrent genetic abnormalities (TET2, IDH2, DNMT3A, RHOA, CD28 mutations, gene fusions ITK-SYK or CTLA4-CD28)
- Possible targeted (e.g. epigenetic modifiers)
- May contain B-cell blasts, often EBV-positive, sometimes resembling Hodgkin-Reed Sternberg cells (leading to HL misdiagnosis)
- Possible progression to EBV-positive LBCL (more rarely EBV-negative)
- Due to clinical/genetic differences definition of the subtype is required

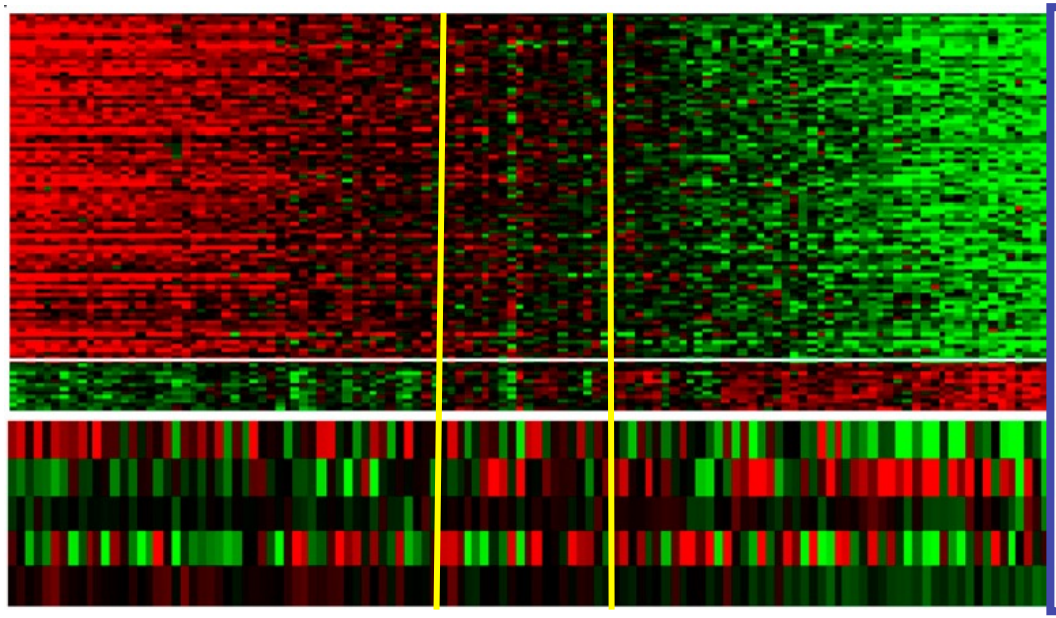

B-blasts
CD2
CD279

Iqbal J et al. Blood 2014;123:2915



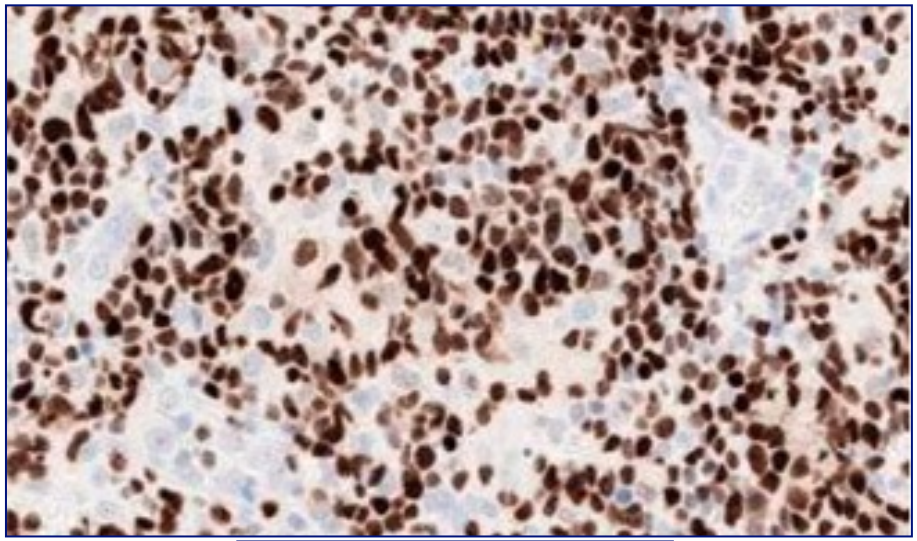




~ 50% cases
+TBX21
+EOMES
+target genes
(IFNg CXCR3, IL2RB,CCL3,)
Enriched in signatures of IFN a/b/g, CD8+ T cells, NF-kB

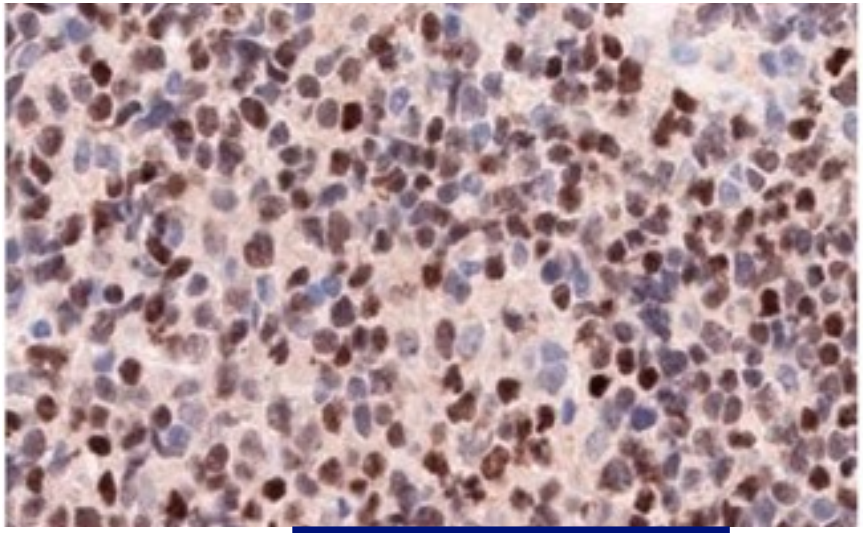


TBX21 uncl GATA3

~30% cases
GATA3+
target genes
(CCR4, IL18RA, CXCR7, IK).
Enriched in signatures of mTOR-, MYC, PI3Kinase, b-catenin



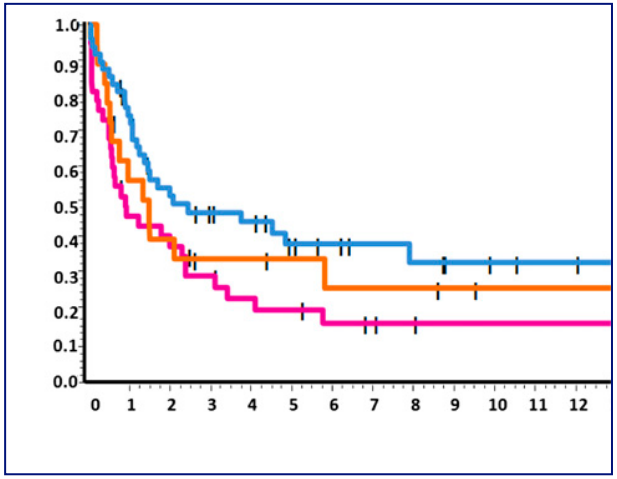
Tbet



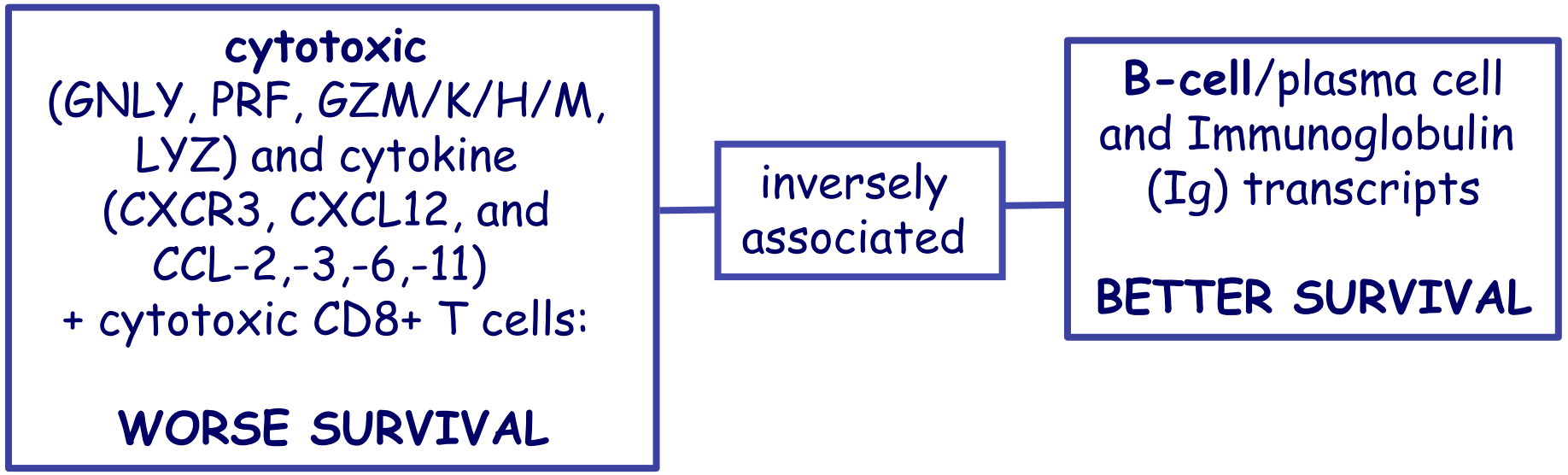
Gata 3

good correspondence with IHC; no correlation with CD4 and CD8

5-ys OS 33%




5-ys OS 19%



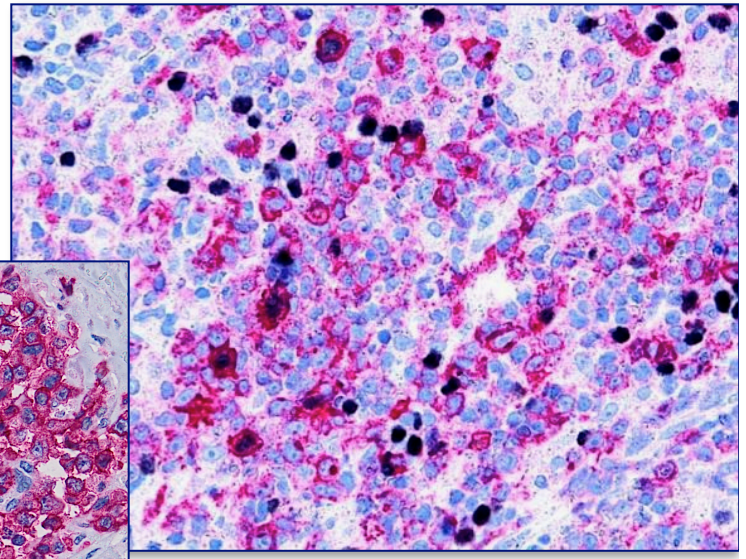

**good correspondence with IHC**

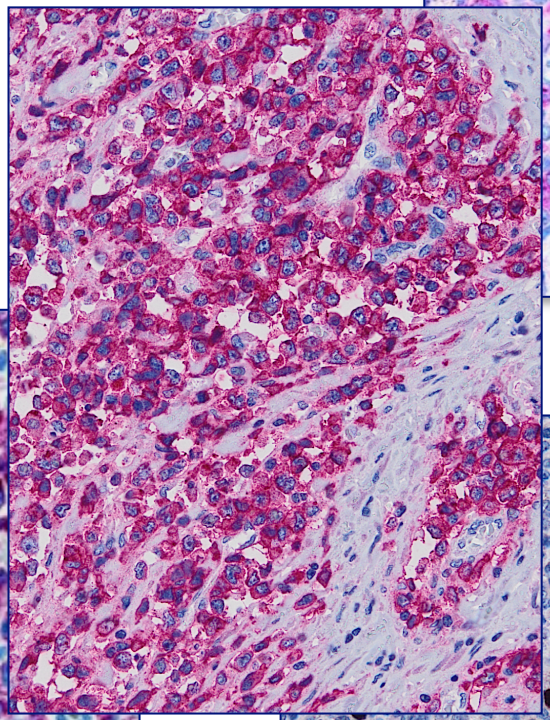
**T-cell markers +**
**TFH-related markers**
**GATA3/Tbet**
**Cytotoxic markers / B cell markers**
**CD30**

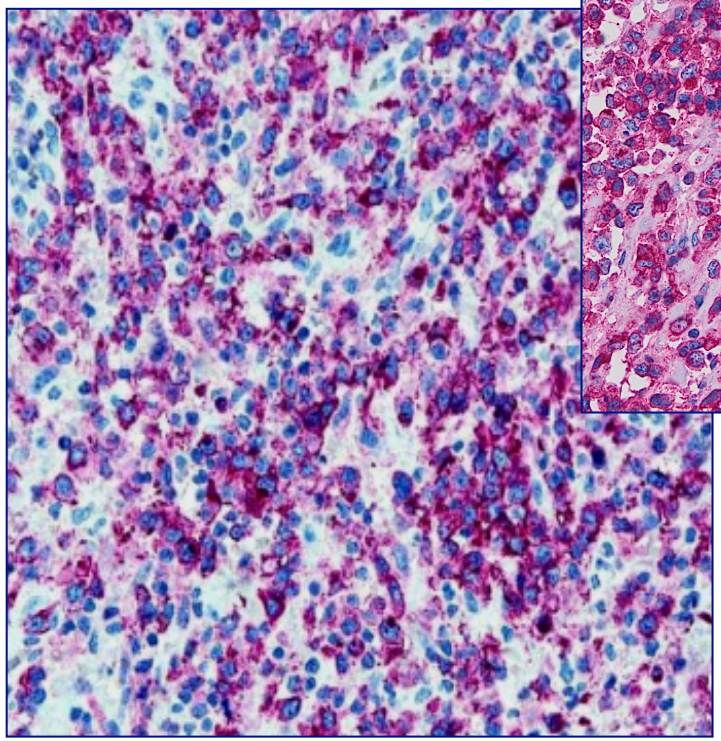
25 - >75% cells
in 46% of PTCLs

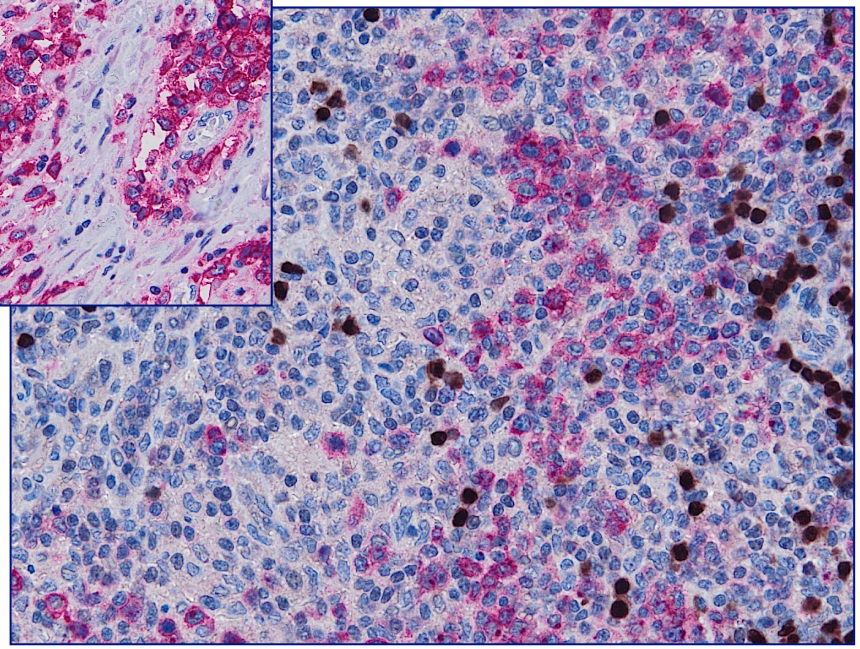
100% ALCL (ALK- & ALK+)
50% PTCL,NOS
27% AITL
70% in ENKTCL
70% type1 EATL
40% MF

Sabattini E, *et al.*
Haematologica 2013

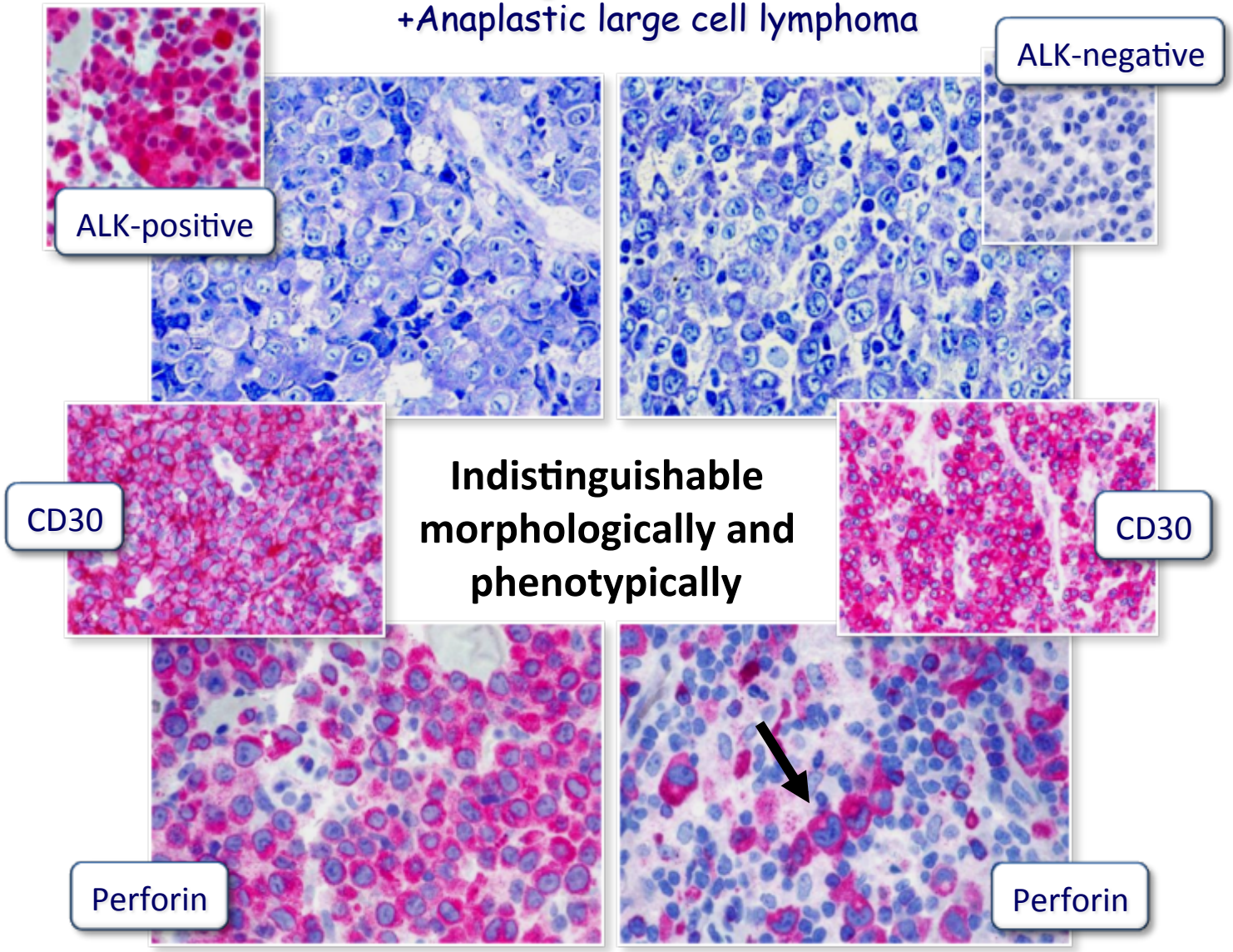




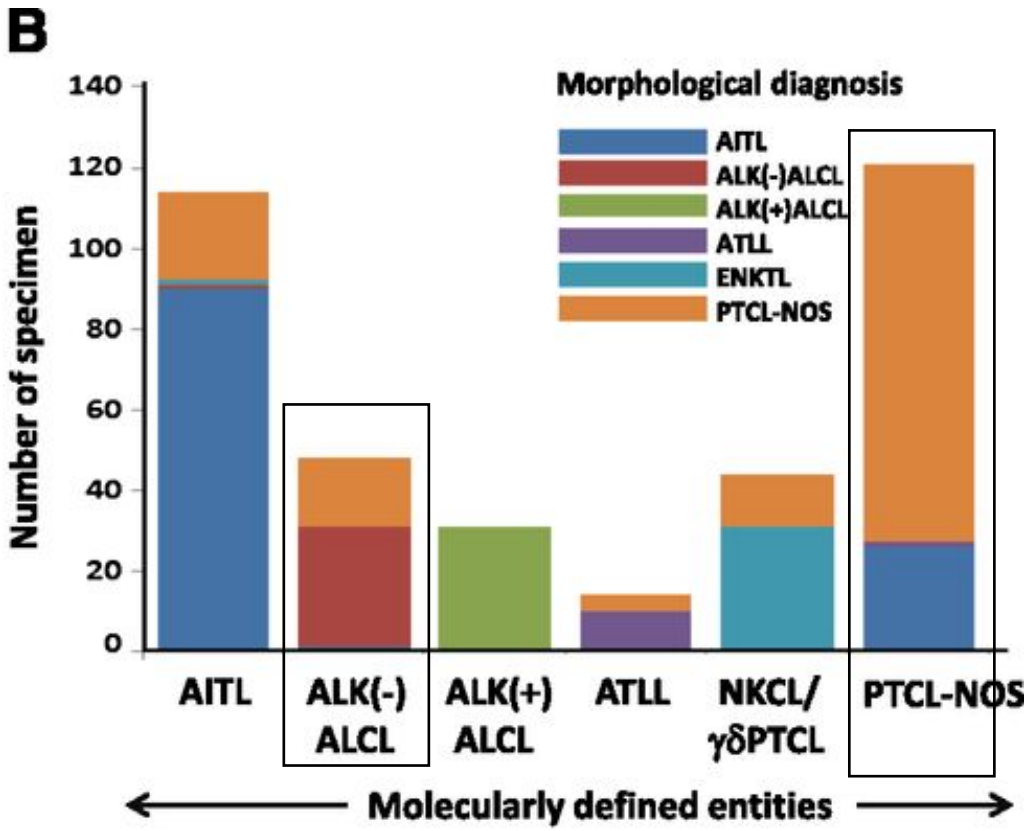


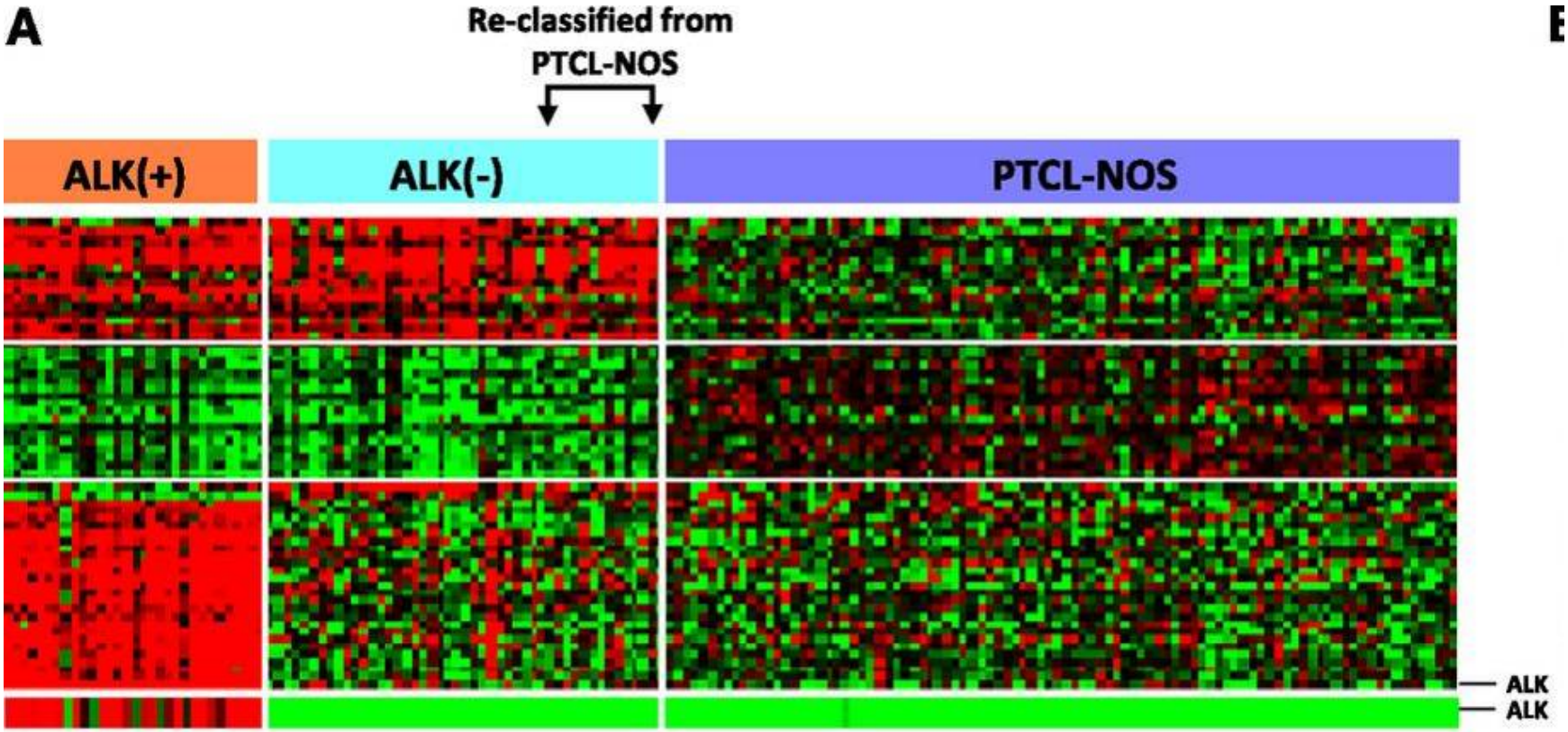


CD30 diagnostic molecule in ALK +Anaplastic large cell lymphoma




CD45+/-, EMA +/-, TCM -/+, CD43+, Cytotoxic Markers +, PAX5-


B
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

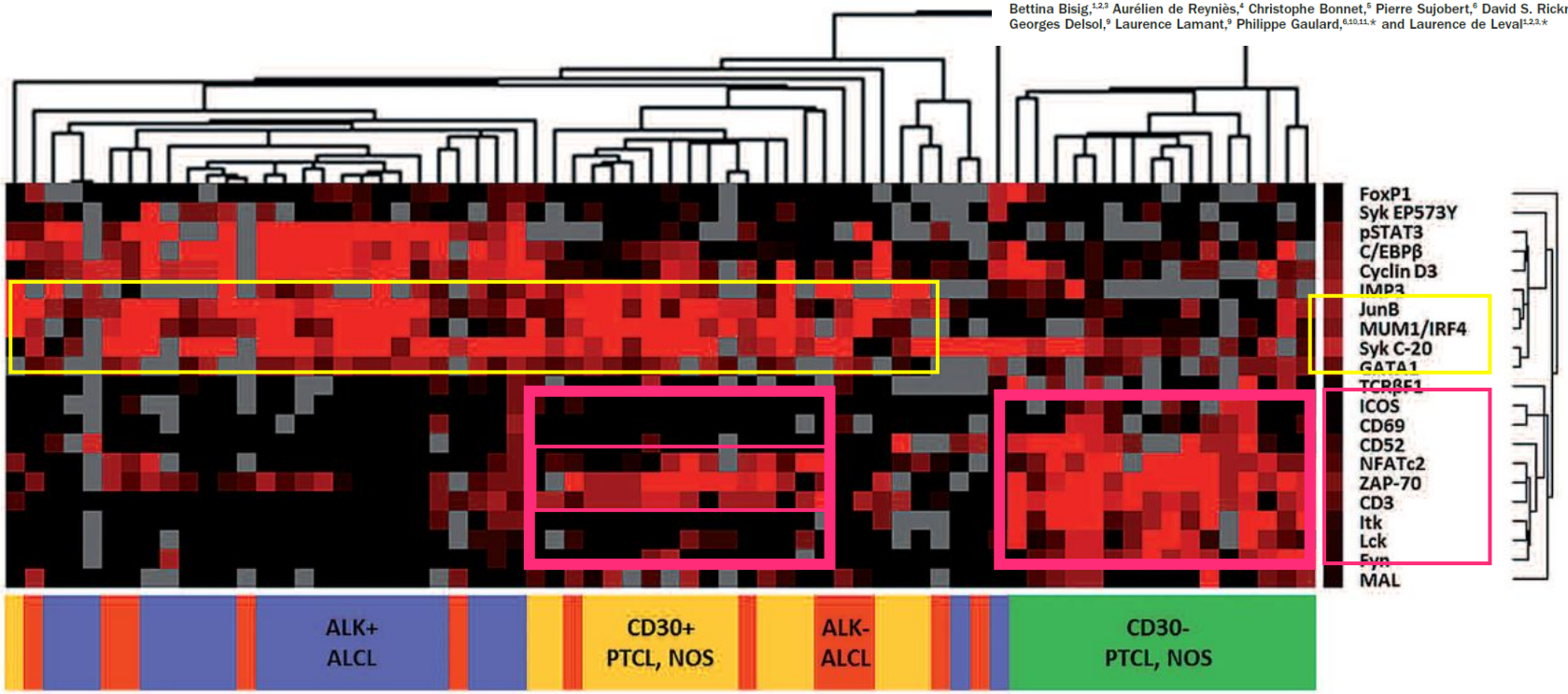



PTCLNOS cases reclassified as ALCL were all

**ALK-, CD30 strongly expressed,**
**Large cell, Anaplastic morphology**
**Cytotoxic markers expressed**
**Lower TCR associated markers**

**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,*]




**CD30+/ALK independent associated signature**
**downregulation of**
1) TCR differentiation/activation (CD52, CD69, ICOS, CD28) →
2) Transcription factor NFATc2
3) Proximal TCR signaling (Lck, Itk, Fyn; ZAP70 exception)
**Upregulation of:** JUNB+, IRF4+ →

**these upregulated in CD30 neg PTCL NOS**

**these downregulated in CD30 neg PTCL NOS**

**ALCL associated signature:** pSTAT3 up & CD3 down
**ALK+ associated signature:** CEBPbeta, Cyclin D3

**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**

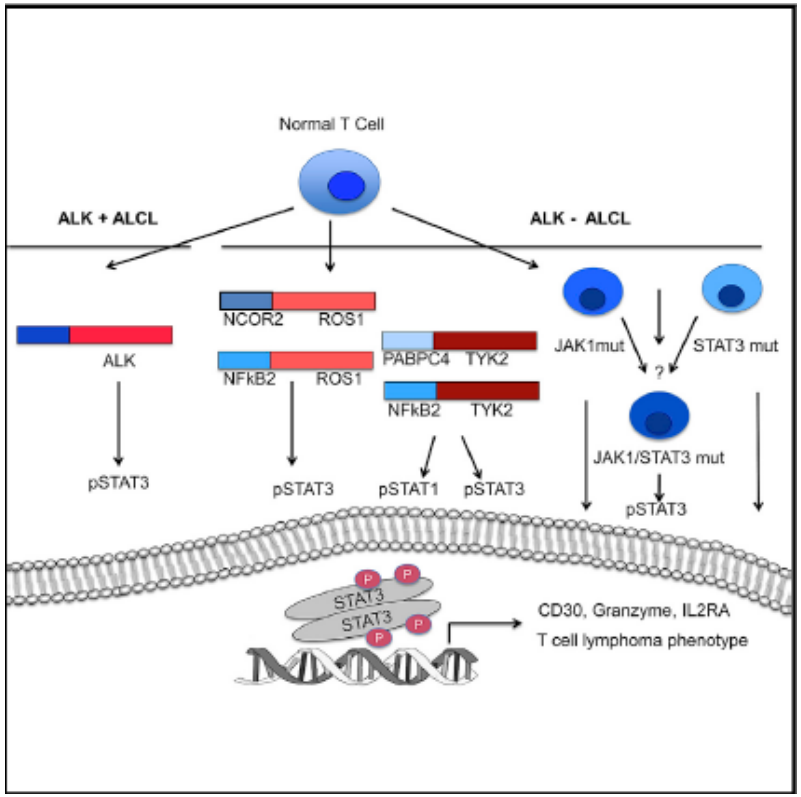
**Blood, 2012;120:1274-81.**

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

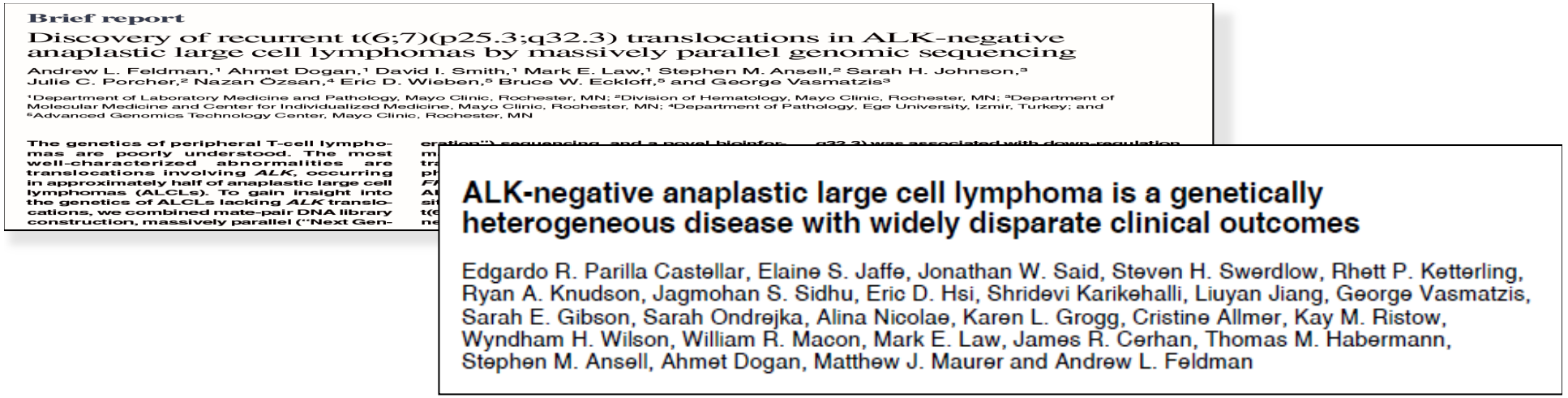
**Cancer Cell**

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

**ALK-negative ALCL is no longer considered provisional**




However there are differences that can be assessed and impact on prognosis



Brief report

Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing

Andrew L. Feldman,[1] Ahmet Dogan,[1] David I. Smith,[1] Mark E. Law,[1] Stephen M. Ansell,[2] Sarah H. Johnson,[3] Julie C. Porcher,[2] Nazan Ozsan,[4] Eric D. Wieben,[5] Bruce W. Eckloff,[5] and George Vasmatzis[3]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [2]Division of Hematology, Mayo Clinic, Rochester, MN; [3]Department of Molecular Medicine and Center for Individualized Medicine, Mayo Clinic, Rochester, MN; [4]Department of Pathology, Ege University, Izmir, Turkey; and [5]Advanced Genomics Technology Center, Mayo Clinic, Rochester, MN

The genetics of peripheral T-cell lymphomas are poorly understood. The most well-characterized abnormalities are translocations involving *ALK*, occurring in approximately half of anaplastic large cell lymphomas (ALCLs). To gain insight into the genetics of ALCLs lacking *ALK* translocations, we combined mate-pair DNA library construction, massively parallel ("Next Gen-

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

Edgardo R. Parilla Castellar, Elaine S. Jaffe, Jonathan W. Said, Steven H. Swerdlow, Rhett P. Ketterling, Ryan A. Knudson, Jagmohan S. Sidhu, Eric D. Hsi, Shridevi Karikehalli, Liuyan Jiang, George Vasmatzis, Sarah E. Gibson, Sarah Ondrejka, Alina Nicolae, Karen L. Grogg, Cristine Allmer, Kay M. Ristow, Wyndham H. Wilson, William R. Macon, Mark E. Law, James R. Cerhan, Thomas M. Habermann, Stephen M. Ansell, Ahmet Dogan, Matthew J. Maurer and Andrew L. Feldman

**DUSPP22 (Dual-Phosphatase 22, close to IRF4 gene) translocation: 30%**

absent in ALK+ALCLs; more classic ALCL morphology; CD30+ALCL skin (Wada DA et al.2011)

Not definable on ihc, **Cytotoxic neg, EMA neg, T-cell markers pos**

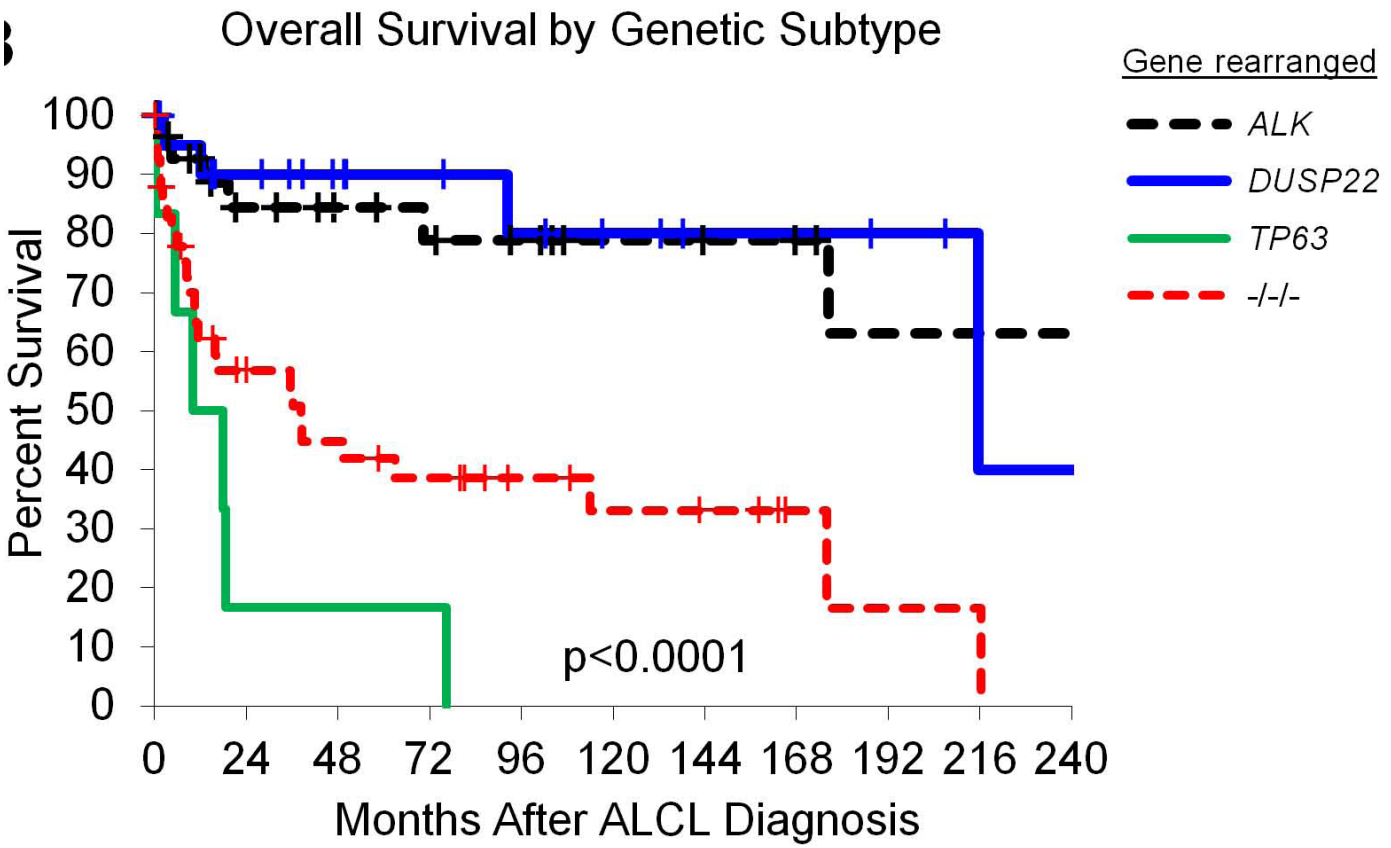
**Rearranged/translocated TP63 (TP53 homologue) on 3q28: 8%**

Less anaplastic morphology than in DUSP22 cases

**All cases are P63+ at ihc (useful in iHC)**

No other phenotypic original features, but **usually EMA-**

DUSP22 –IRF4 locus on 6p25.3 which leads to decreased expression of DualSpecificityPhoshatase-22);




Five-year overall survival rates were 85% for ALK-positive ALCLs,
**90% for DUSP22-rearranged ALCLs**,
17% for TP63-rearranged ALCLs, and
42% for cases lacking all three genetic markers ($p<0.0001$).

Possible therapy as ALK+
(only CHOP with no high dose BEAM like followed by AST?)

# 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]

[1]Lymphoma and Genomics Research Program, IOR Institute of Oncology Research, Bellinzona, Switzerland; [2]Dalle Molle Institute for Artificial Intelligence (IDSIA), Manno, Switzerland; [3]SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland; [4]Department of Pathology and Center for Experimental Research and Medical Studies (CeRMS), University of Turin, Turin, Italy; [5]Department of Pathology and NYU Cancer Center, New York University School of Medicine, New York, NY; [6]Semmelweis University, Budapest, Hungary; [7]Translational Cell and Tissue Research, KU Leuven, Leuven, Belgium; [8]Hospital Universitario Marques de Valdecilla, Santander, Spain; [9]Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [10]Herbert Irving Comprehensive Cancer Center, Department of Pathology and Cell Biology, Columbia University Medical Center and New York Presbyterian Hospital, New York, NY; [11]Department of Pathology, Division of Hematopathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [12]Institute of Pathology, University of Wuerzburg, Wuerzburg, Germany; [13]Unit of Lymphoid Malignancies, Department of Onco-Haematology, San Raffaele Scientific Institute, Milan, Italy; [14]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX; [15]S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [16]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; and [17]Lymphoma Unit, IOSI Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

**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)

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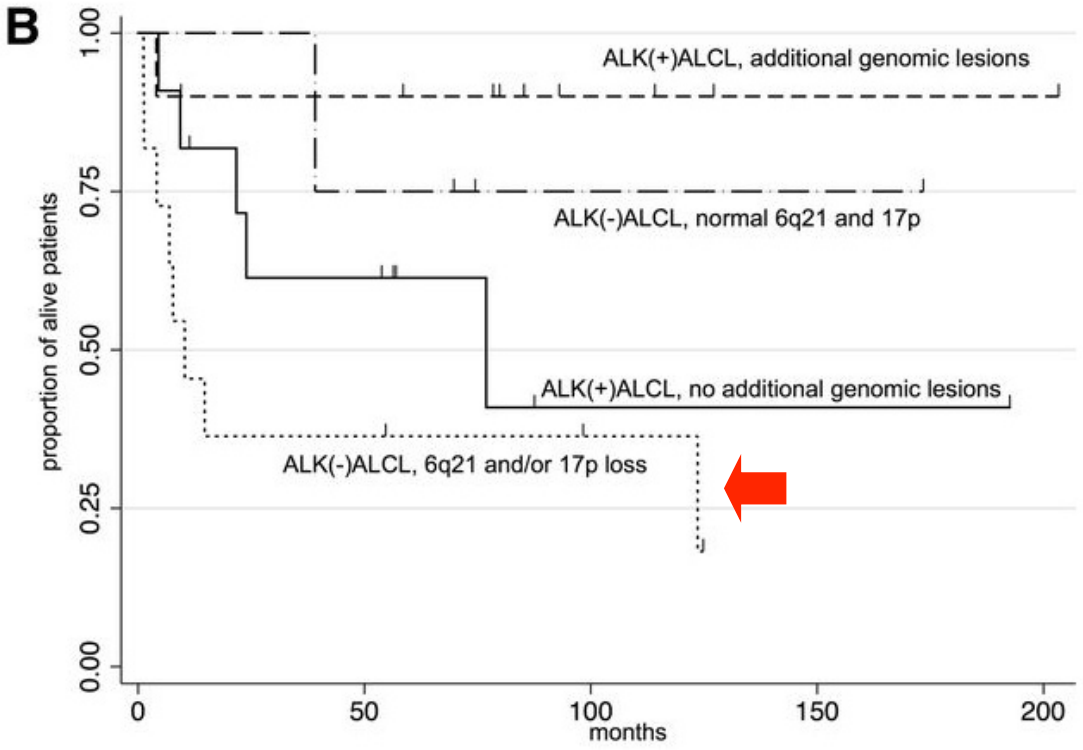
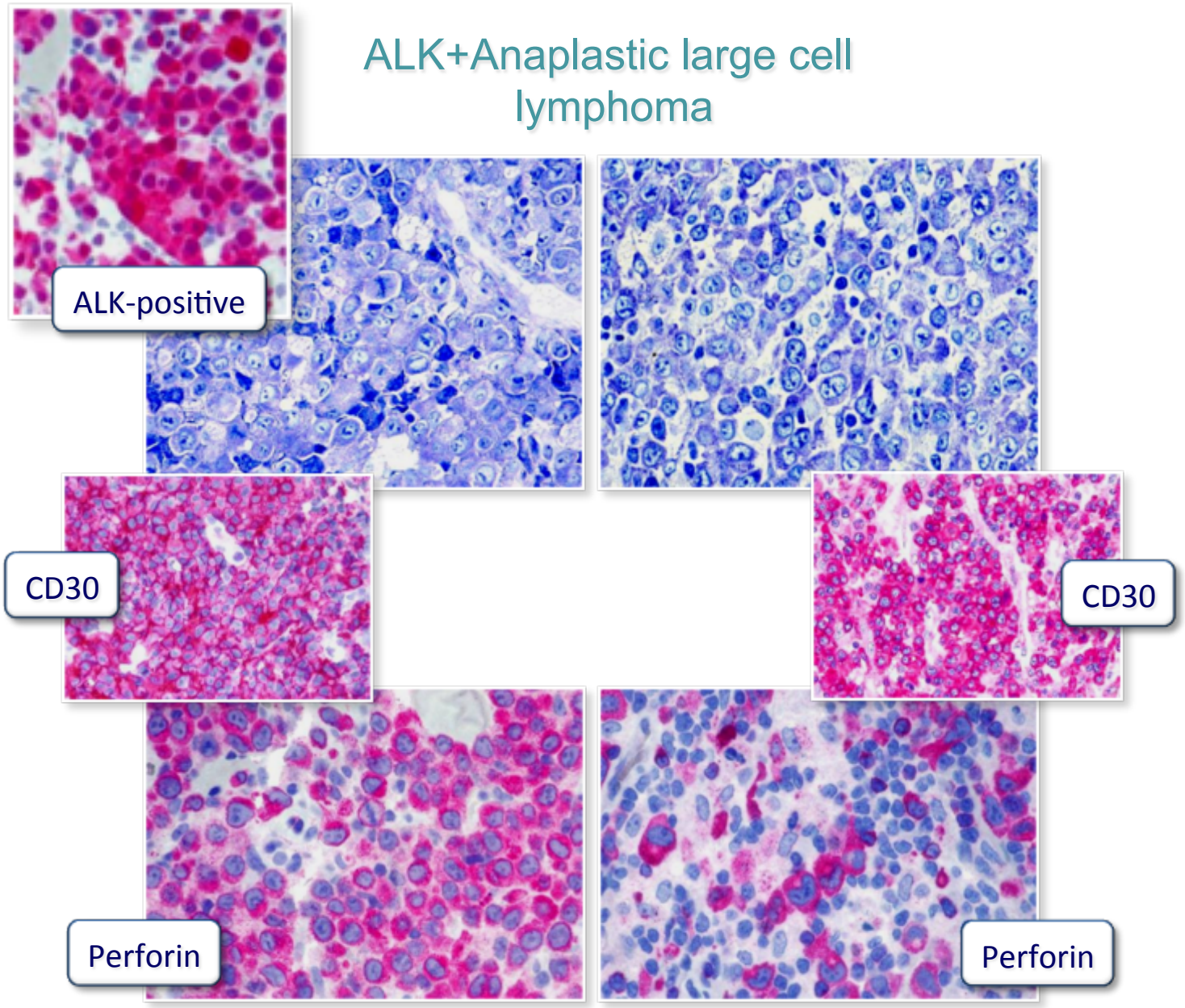



much higher in ALK- than ALK+ ALCL
not related to ihc

# ALK+Anaplastic large cell lymphoma



**ALCL signature (both ALK+ and ALK-)**

•Common signature

unique origin & common genes are ALK independent

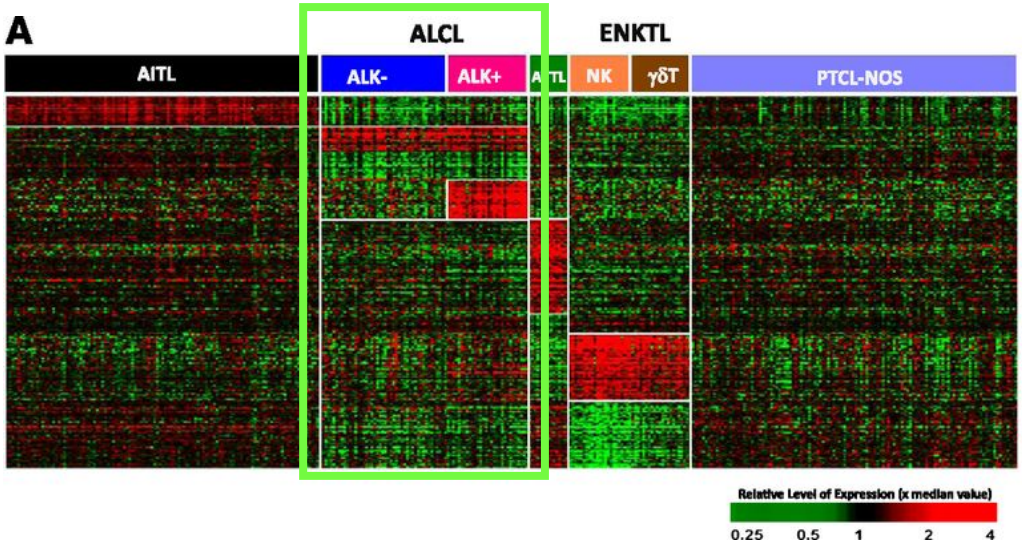
•Differentiate from PTCL NOS

•Roughly 30 genes

•Upregulated in ALCL independent of ALK:

•**TNFRSF8(CD30)**, SNFT, PERP2, **BATF3**, GGT1, LGALS1,

•**low TCR related activation genes** (LCK, FYB, CSK1)




**ALK signature (from ALK+ALCL cell lines)**

•Mainly related to ALK/STAT signaling

•Genes that mostly correlated with ALK+ (PRF1, GAS1; IL1RAP, CCDN3, BCL3)

**ALKnegALCL signature:**

**3 gene-classifier: TNFRSF8, BATF3, TMOD1**

## Anaplastic large-cell lymphoma

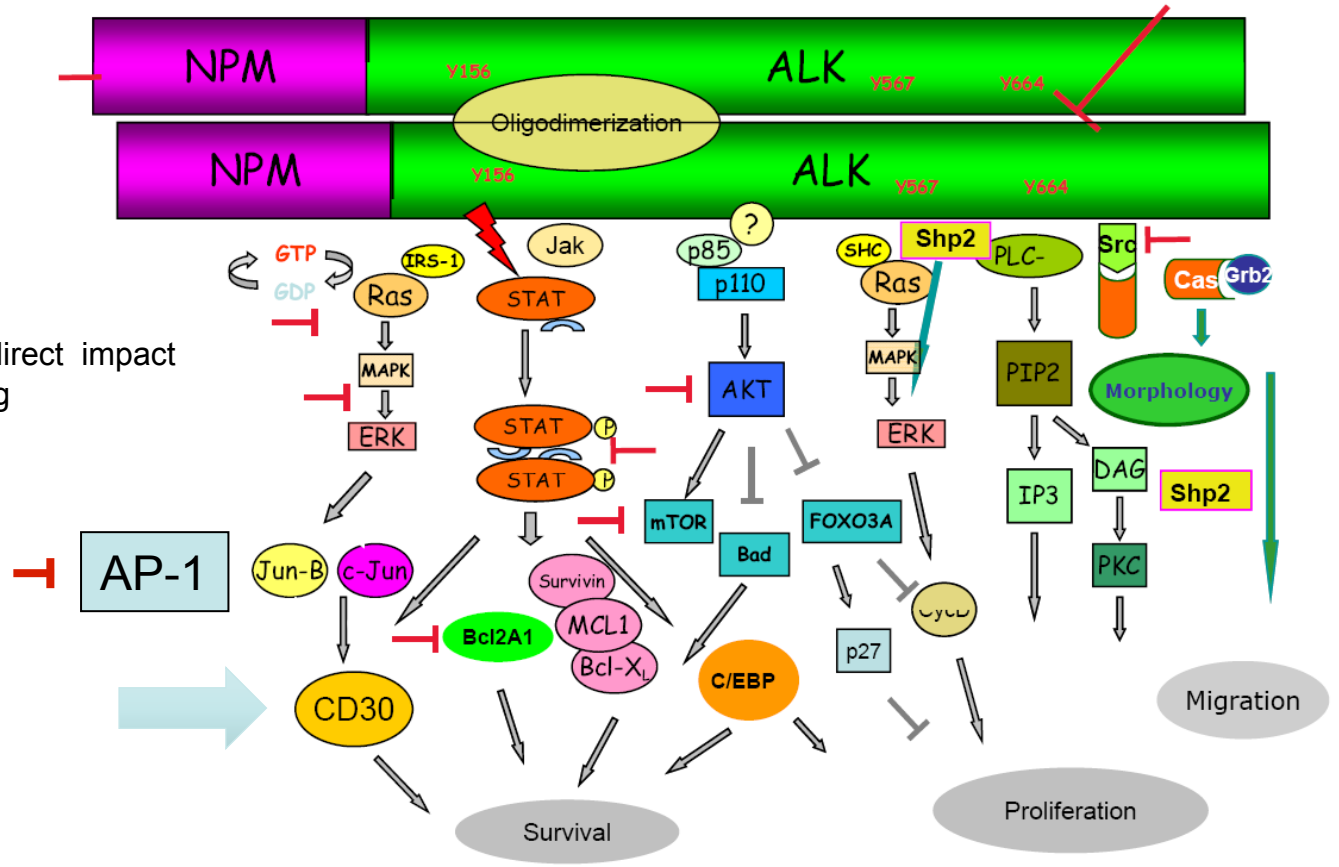
Seminars in Diagnostic Pathology (2011) 28, 190-201

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

# The oncogenic role of ALK fusion proteins

RAS/ERK
JAK/STAT
AKT/mTOR

NPM-ALK has indirect impact on CD30 signaling



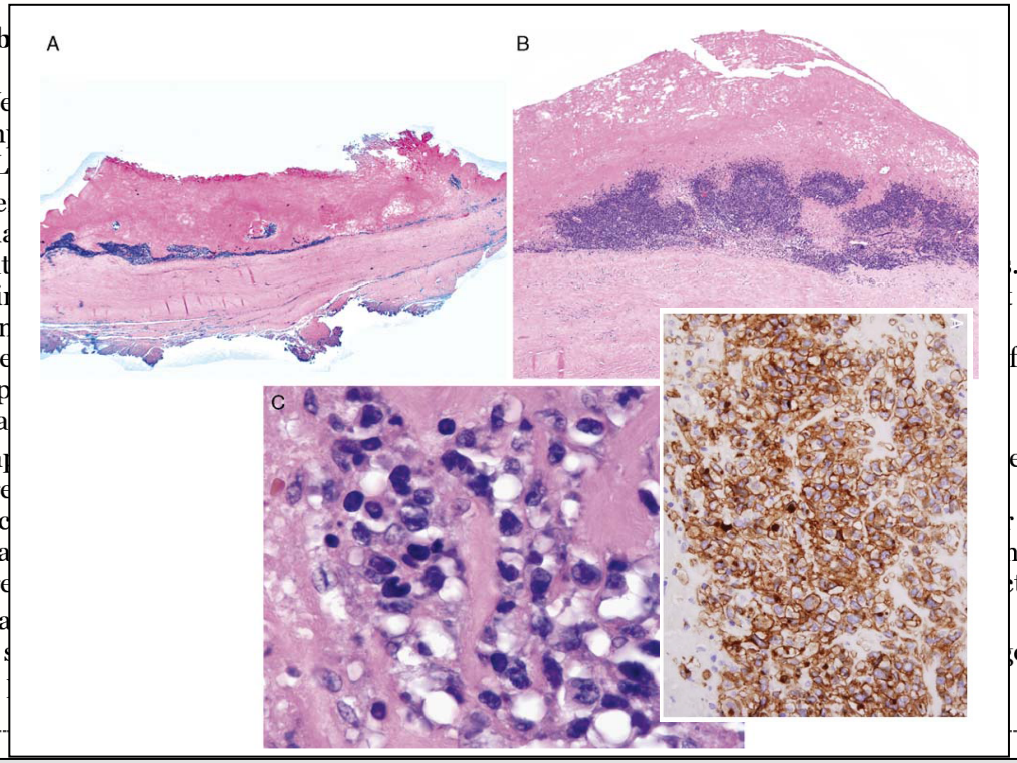

ALK is necessary and sufficient to induce transformation (impact of anti-ALK drugs- crizotinib)

Translocations involving ALK produce fusion proteins with constitutive tyrosine kinase activity
engagement of intracellular pathways

American Journal of Surgical Pathology:
July 2012 - Volume 36 - Issue 7 - p 1000–1008
doi: 10.1097/PAS.0b013e31825749b1
Original Articles

# Anaplastic Large Cell Lymphoma Associated With Breast Implants: A Report of 13 Cases

**Aladily, Tariq N. MD[*]; Medeiros, L. Jeffrey MD[*]; Amin, Mitual B. MD[†]; Haideri, Nisreen MD[‡]; Ye, Dongjiu MD[§]; Azevedo, Sergio J. MD[□]; Jorgensen, Jeffrey L. MD, PhD[*]; de Peralta-Venturina, Mariza MD[¶]; Mustafa, Eid B. MD[#]; Young, Ken H. MD, PhD[*]; You, M. James MD, PhD[*]; Fayad, Luis E. MD[**]; Blenc, Ann Marie MD[†]; Miranda, Roberto N. MD[*]**




**WHO 2016**

Both saline and silicone filled implants
median interval from implant 10 years

Neoplastic cells confined to the seroma fluid, without invasion of the capsule: conservative management recommended (removal of the implant and capsule)
With invasion through the capsule: risk of lymph node involvement and systemic spread, warrant chemotherapy