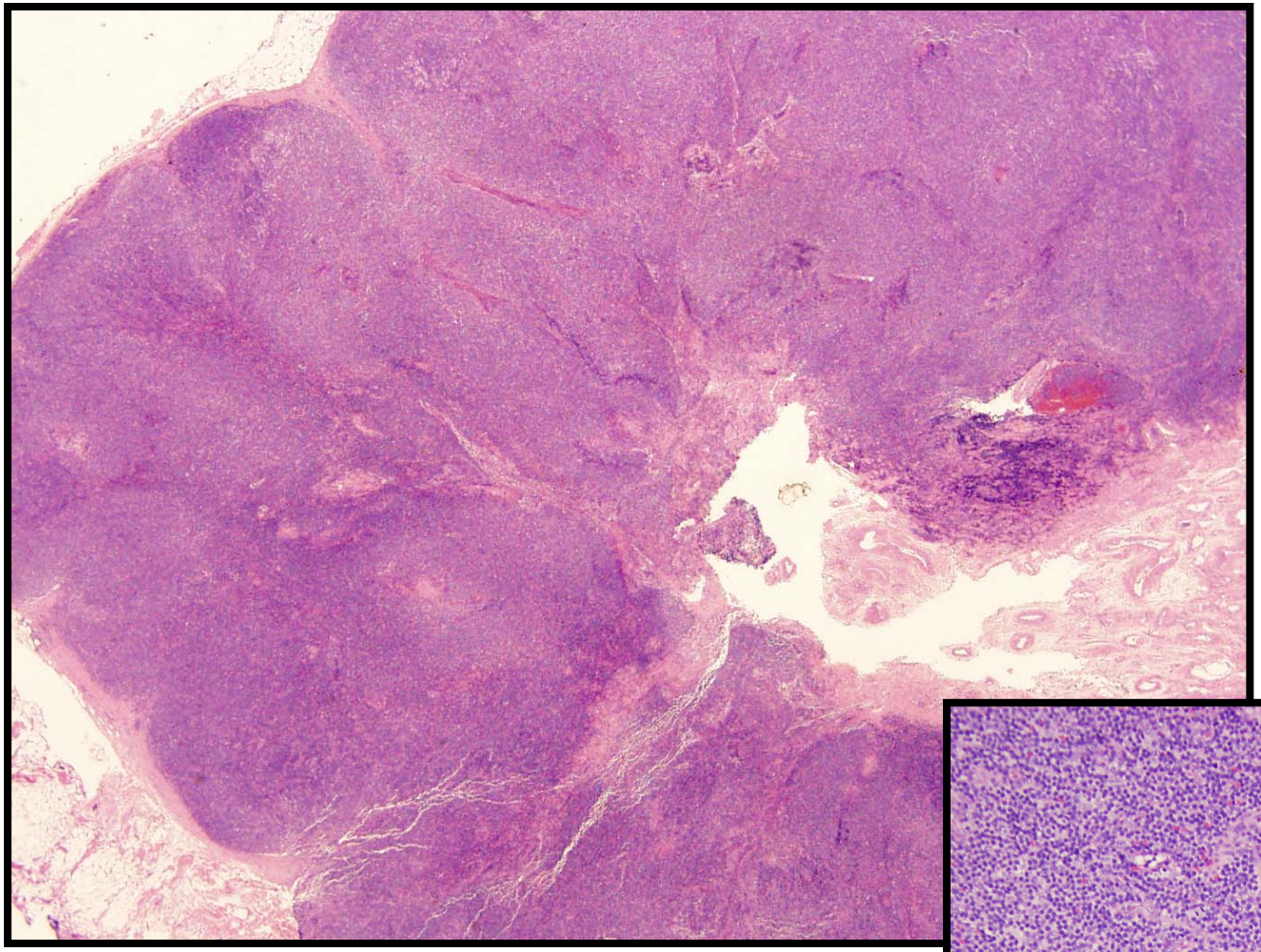
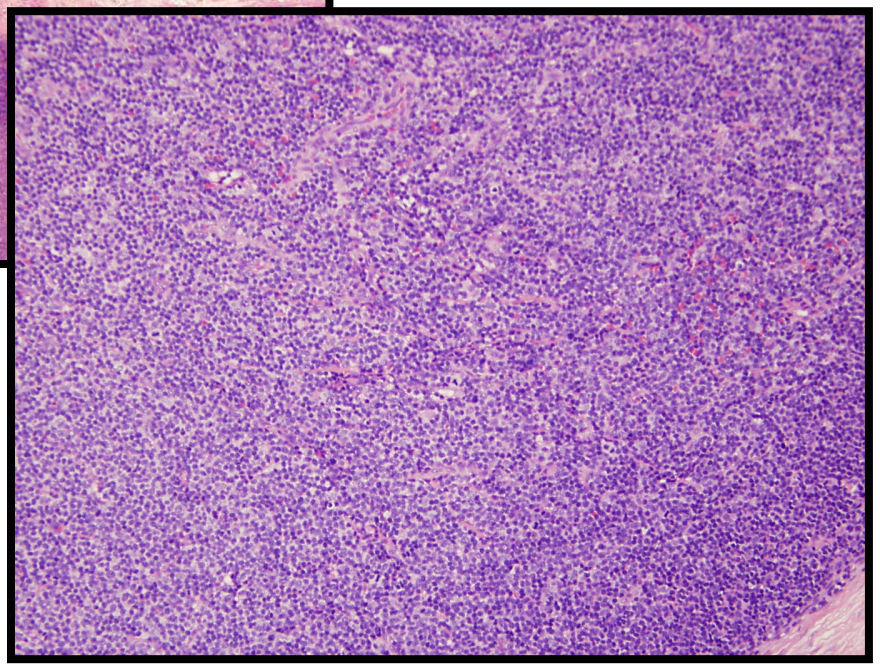
CASE 2

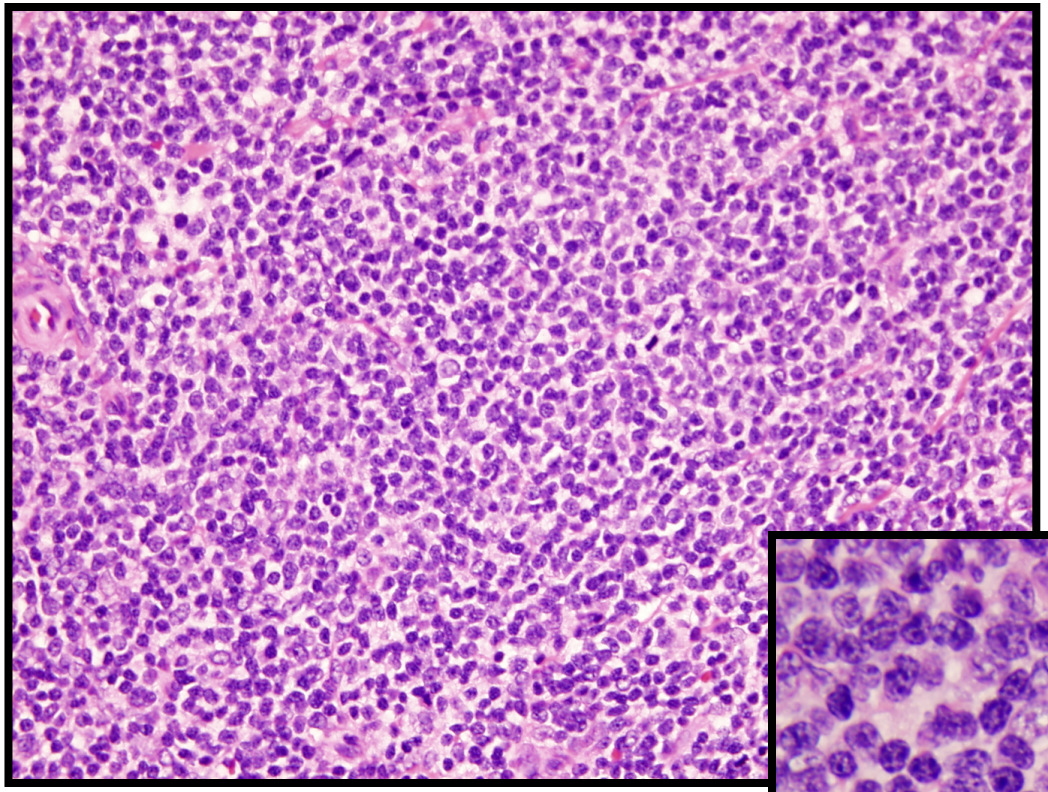
A 38-year-old man developed severe fatigue on mild exertion x 1 month. He also had intermittent night sweats and frontal headache. A CBC showed anemia (Hb, 9.7). CT scans showed bilateral small LNs in the neck, supraclavicular region, mediastinum, and inguinal region. He also had prominent splenomegaly and bulky upper abdominal lymph nodes. This is a biopsy of an inguinal LN.

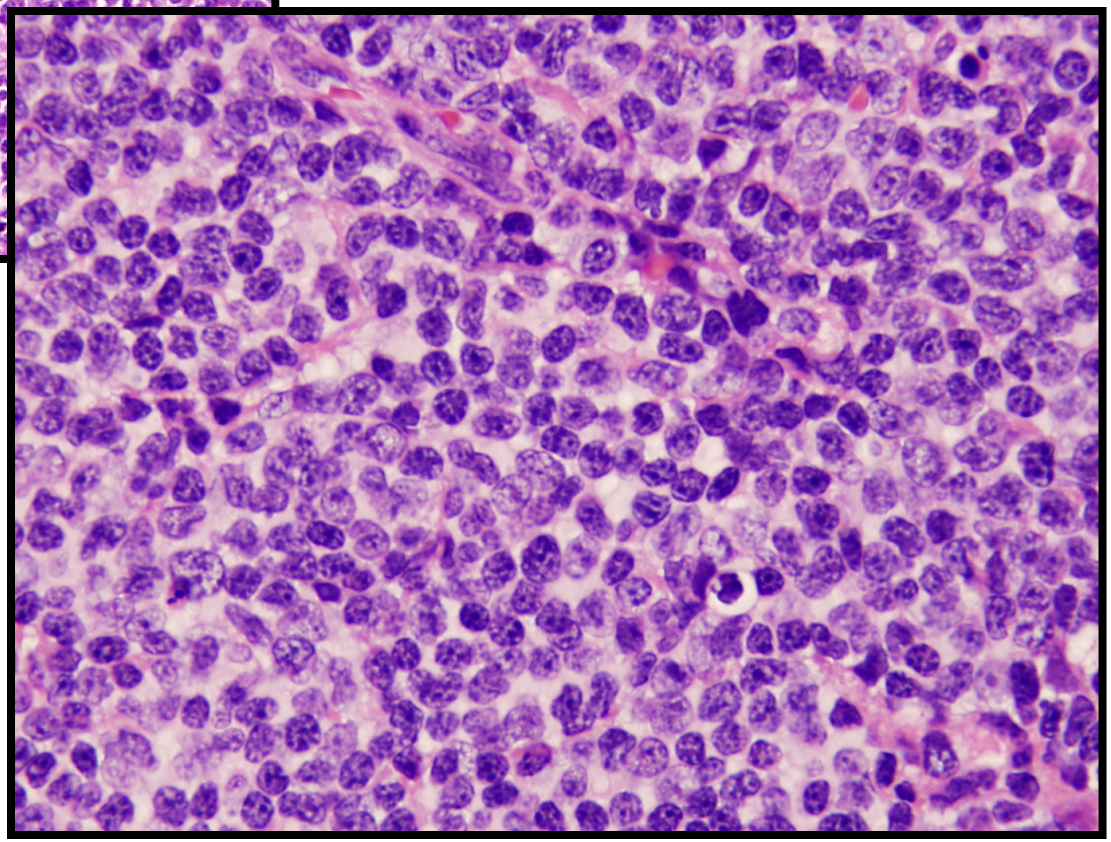
Case 2



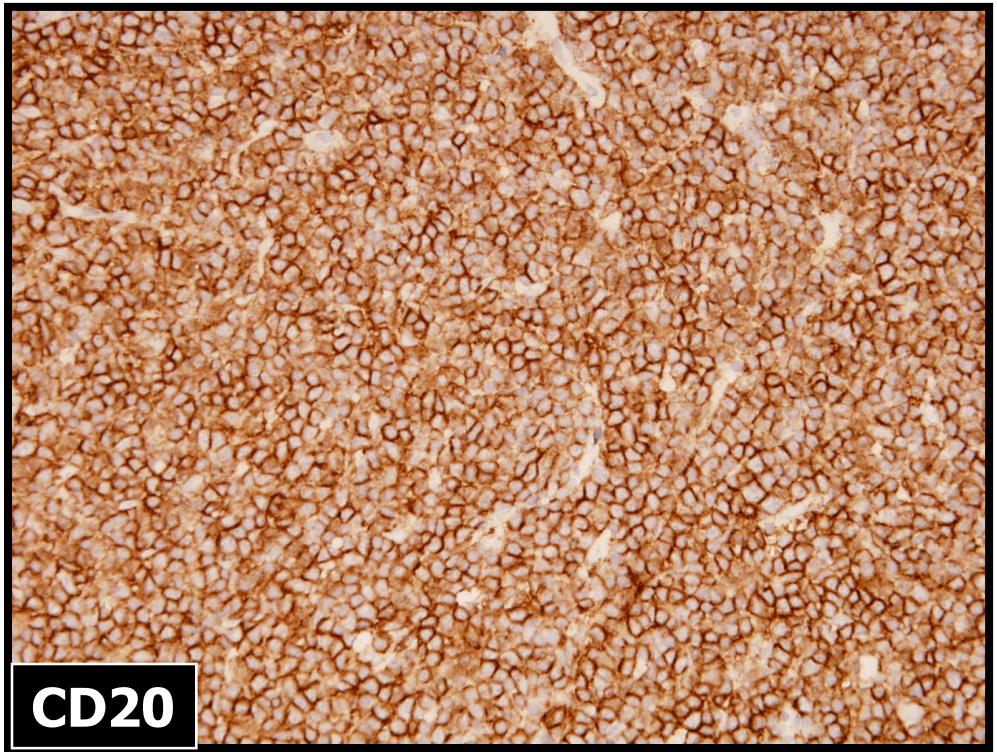


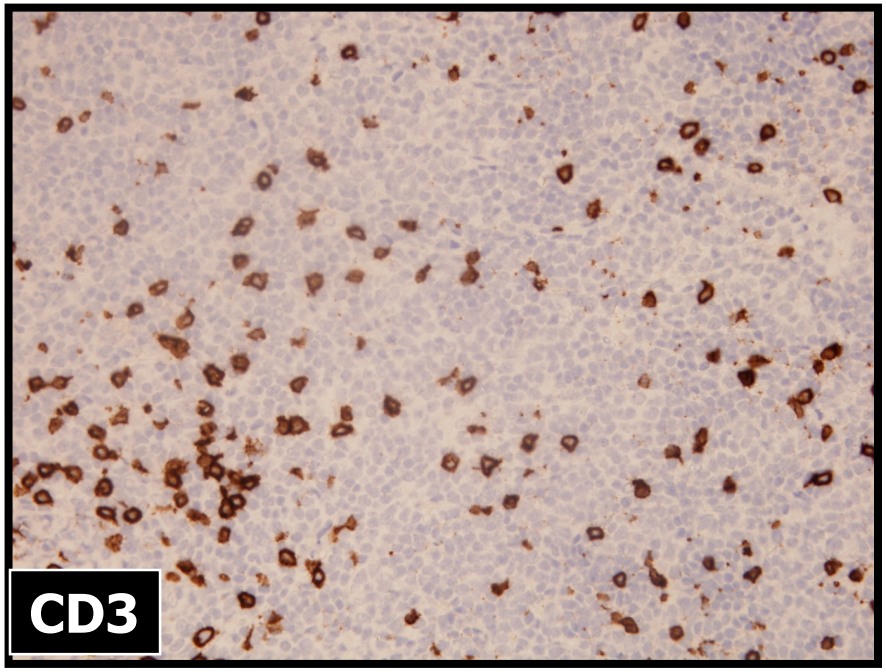
Case 2

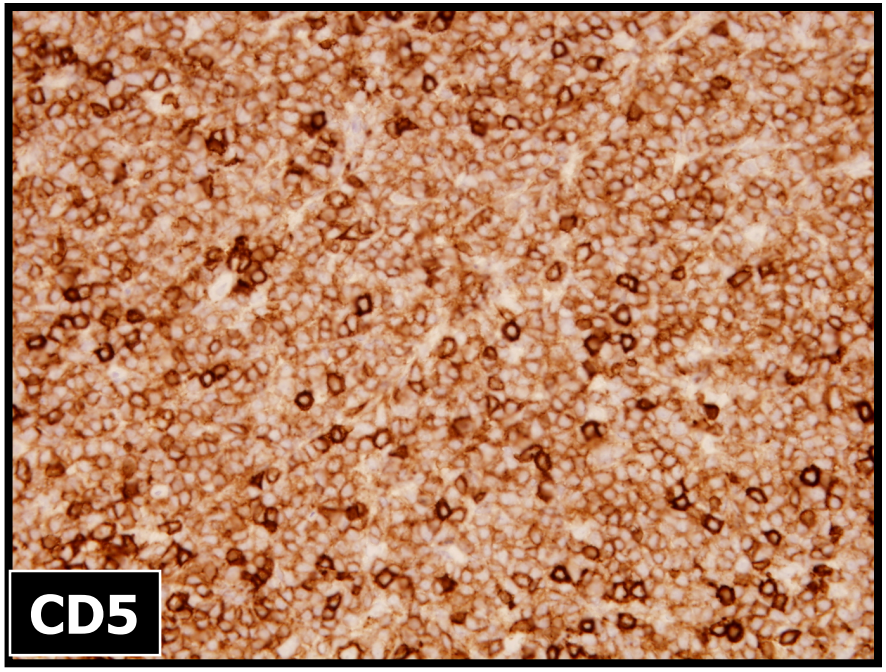




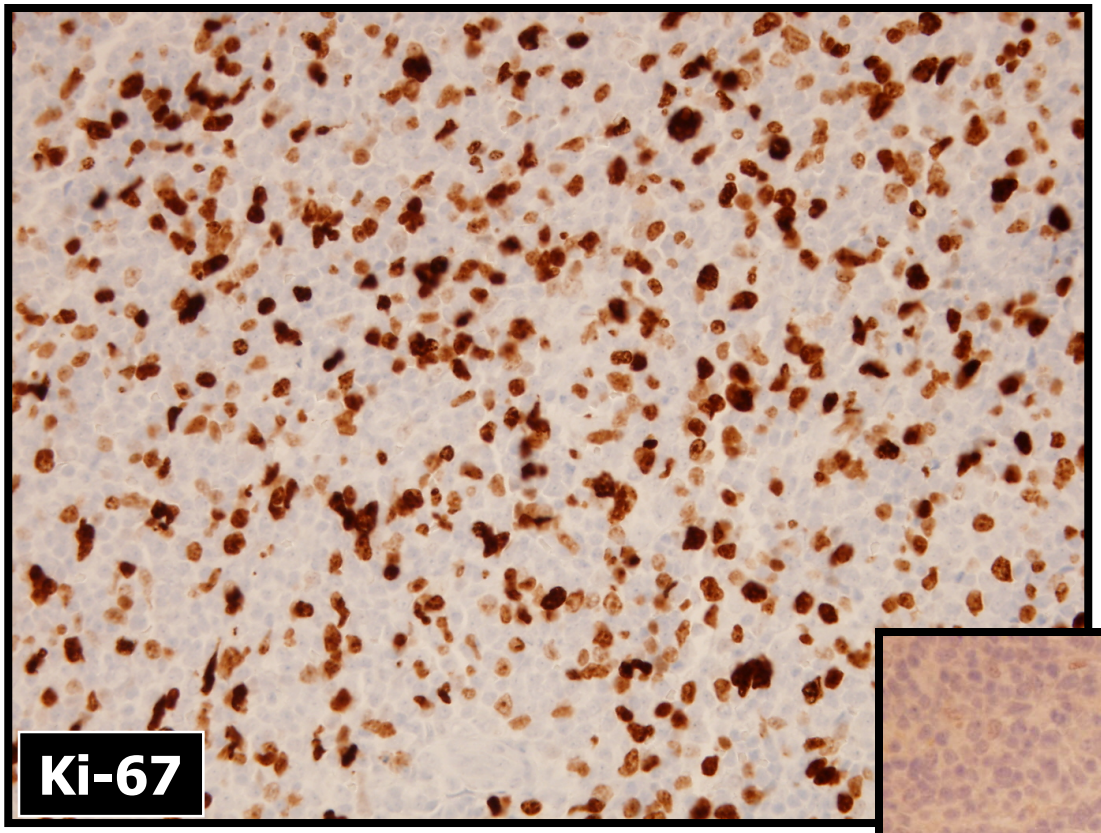
Case 2

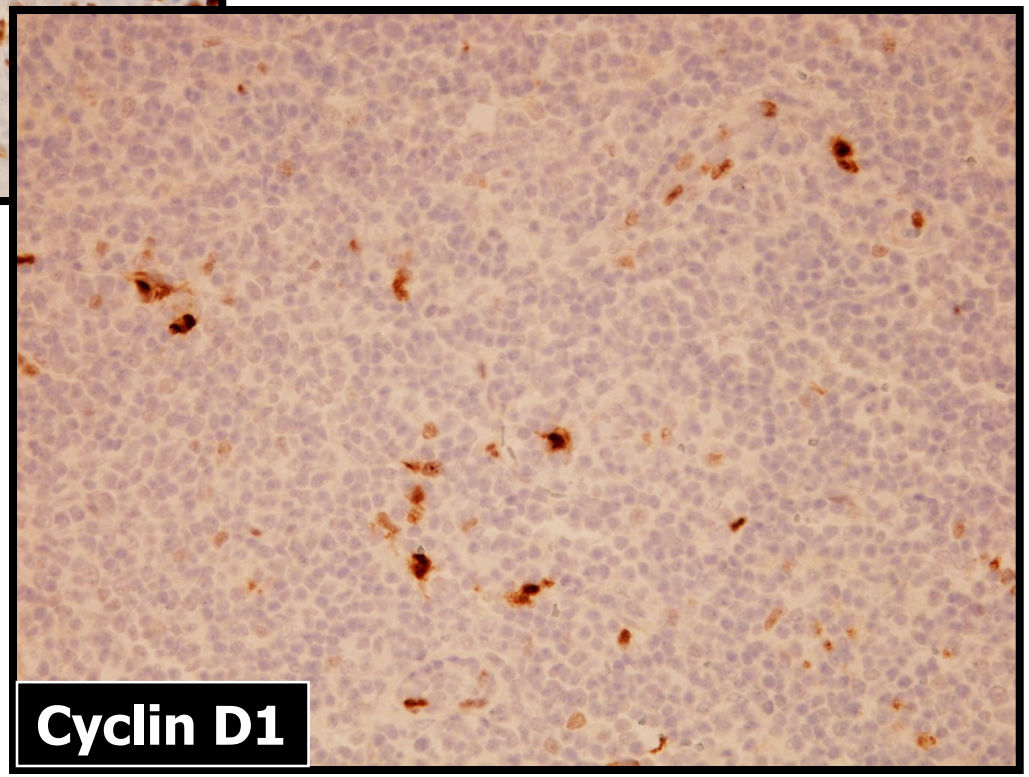




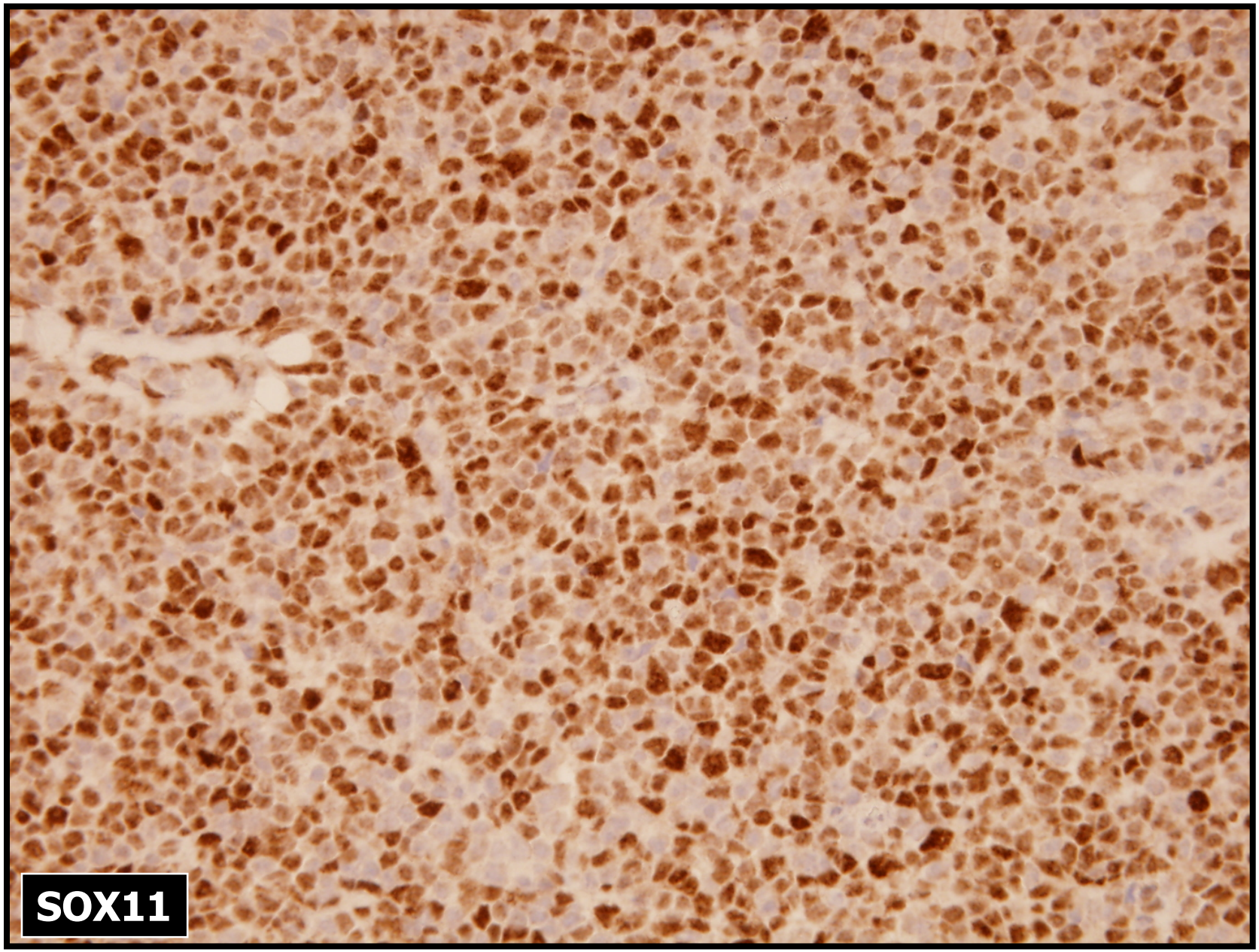


Case 2





Case 2

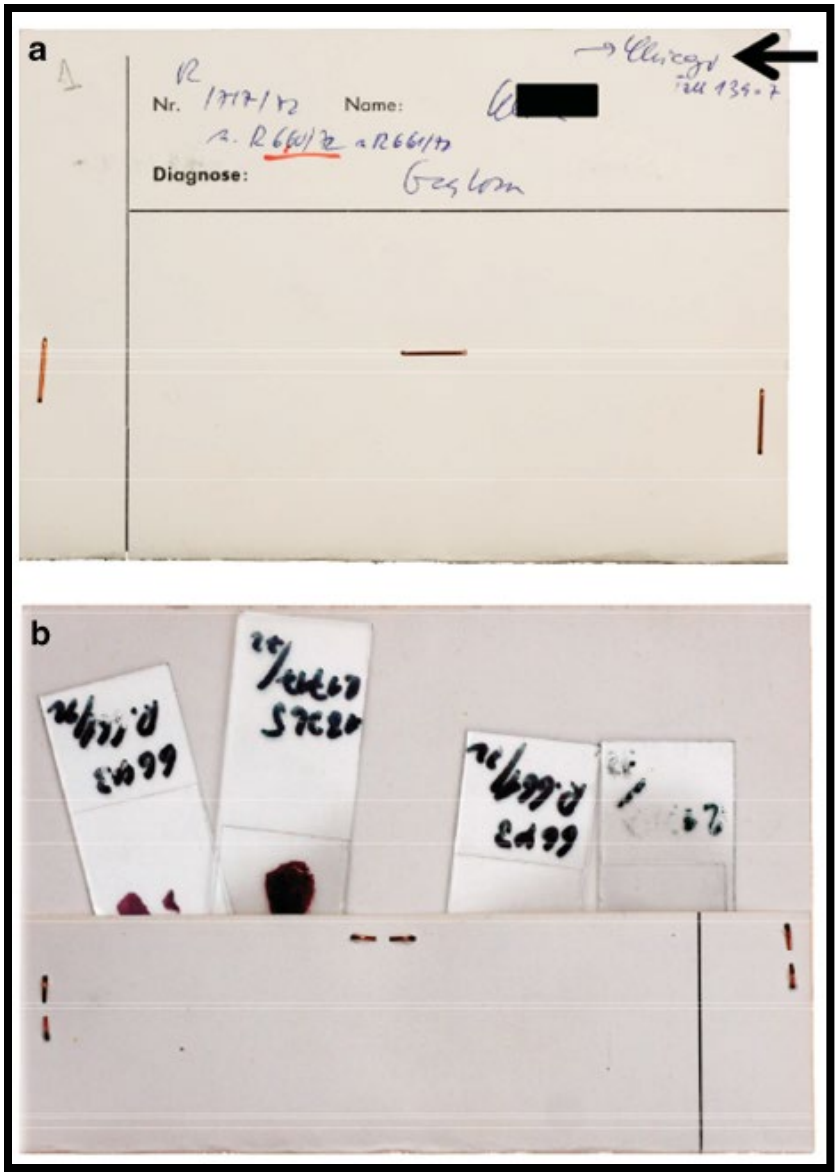


DIAGNOSIS (CASE 2)

Mantle cell lymphoma, cyclin D1 negative

Lymphoma 'type K.'

Karl Lennert, MD
1921-2012



Leukemia 27: 519-521, 2013

1970s

Lennert K, Stein H, Kaiserling E. Cytological and functional criteria for the classification of malignant lymphomata. Br J Cancer 31 Suppl II: 29, 1975.

Diffuse germinocytoma/centrocytic lymphoma first proposed at a meeting in Chicago in 1973 (Leukemia 27: 519, 2013)

First published in 1975

Berard CW, Dorfman RF. Histopathology of malignant lymphomas. Clin Haematol 3:39, 1974.

First proposal of concept of lymphocytic lymphoma of intermediate differentiation (IDL)

First Description of t(11;14)(q13;q32)

A NEW CHARACTERISTIC KARYOTYPIC ANOMALY IN LYMPHOPROLIFERATIVE DISORDERS

H. VAN DEN BERGHE, MD, C. PARLOIR, MD, G. DAVID, MD,
J. L. MICHAUX, MD, AND G. SOKAL, MD

A new characteristic chromosome anomaly t(11;14)(q14;q32?) in lymphoproliferative disorders (LPD) is described in 4 cases. The extra material was found on a #14 chromosome (14q+) and belonged to the long arm of one #11 chromosome in 3 cases and to the long arm of a #14 in the other case. These cases confirm that the distal end of chromosome 14q may function as a "receptor site," according to the hypothesis of Kaiser-McCaw *et al.*[12] and also tend to indicate that chromosome #14 may not be unique in showing so-called "donor" and "receptor sites," and that other chromosomes, *in casu* chromosome #11, may behave similarly.

Cancer 44:188–195, 1979.

All 4 cases in BM; all had a complex karyotype

Diagnoses

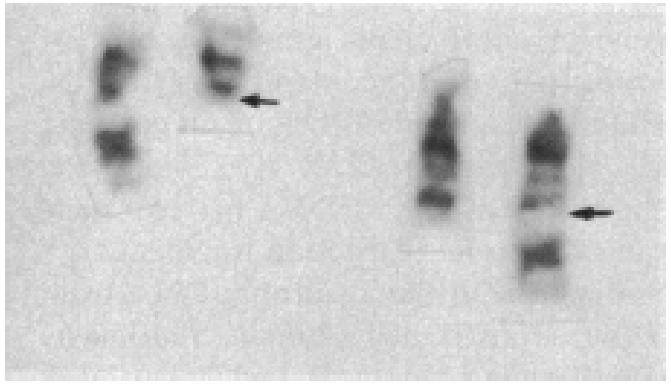
- **Nodular lymphosarcoma**
- **Nodular and diffuse infiltrate of lymphoblasts**
- **Chronic lymphocytic leukemia**
- **Poorly differentiated lymphocytes and lymphoblasts**

RESEARCH ARTICLE

Science 224: 1406, 1984

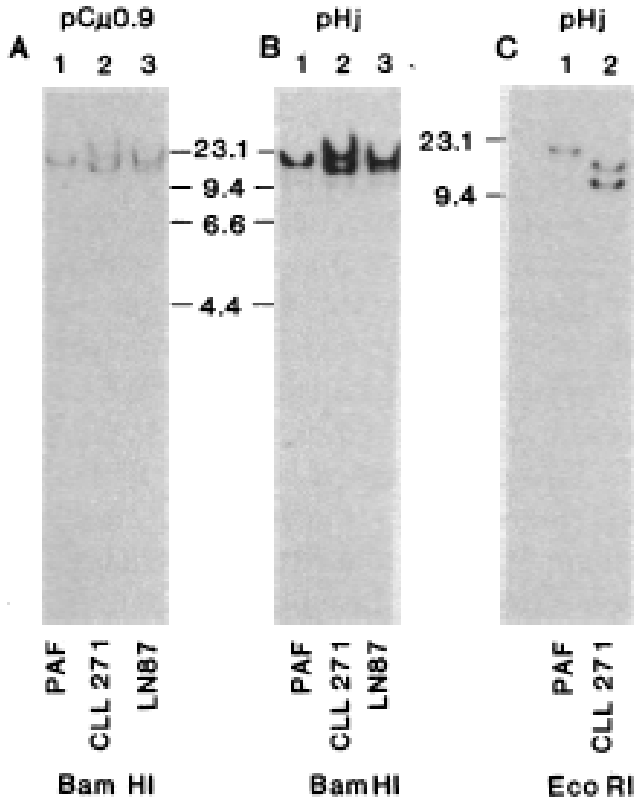
Molecular Cloning of the Chromosomal Breakpoint of B-Cell Lymphomas and Leukemias with the t(11;14) Chromosome Translocation

Yoshihide Tsujimoto, Jorge Yunis, Louise Onorato-Showe
Jan Erikson, Peter C. Nowell, Carlo M. Croce



11 14

Fig. 1 (left). The reciprocal t(11;14) (q13,q32) translocation in the neoplastic cells of a patient with diffuse large cell lymphoma (LN87). Fig. 2 (right). (A to C) Southern blotting analysis of CLL 271 and LN87 DNA's for rearrangements of the C_μ and J_H DNA segments. PAF cells are SV40 transformed human fibroblasts that carry a germ line C_μ gene. In (A) and (B), the rearranged C_μ and J_H bands have the same size in CLL 271 and LN87 DNA's.



Genotypic Characterization of Centrocytic Lymphoma: Frequent Rearrangement of the Chromosome 11 *bcl*-1 Locus

By Michael E. Williams, Cindy D. Westermann, and Steven H. Swerdlow

Centrocytic lymphomas are defined in the Kiel classification as B-cell lymphomas composed exclusively of cells resembling cleaved follicular center cells (FCC). These lymphomas have been shown to be histologically, immunophenotypically, and clinically distinct from other cleaved FCC lymphomas. DNA from 18 centrocytic lymphomas (14 patients) was analyzed using Southern blotting and probes for immunoglobulin heavy (J_H) and kappa light chain (J_K) joining gene, T-cell receptor beta chain constant gene (C_β), *bcl*-1, *bcl*-2, and c-*myc* gene rearrangements. All of the lymphomas had J_H and J_K rearrangements, confirming their B-cell origin. None of the specimens had detectable C_β, *bcl*-2, or c-*myc* rearrangements. However, 4 of 14 patients (28.6%) had rearrangement of the chromosome 11 *bcl*-1 locus. Therefore, centrocytic lymphomas are genotypically distinguishable from the majority of other small cleaved FCC lymphomas by their lack of demonstrable *bcl*-2 rearrangements. This supports the distinct nature of centrocytic lymphomas and suggests the lack of importance for the putative oncogene *bcl*-2 in these cases. Furthermore, the frequent rearrangement of *bcl*-1 suggests a possible role for this locus in the pathogenesis of at least some centrocytic lymphomas.

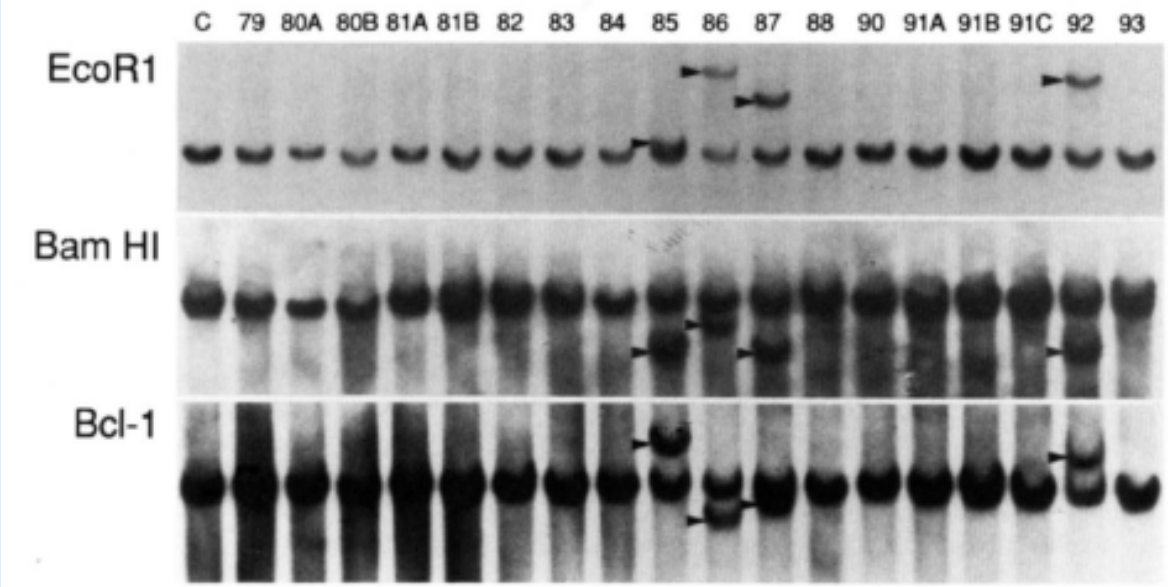


Fig 3. Southern blot autoradiograms demonstrating *bcl*-1 rearrangements (arrowheads) in four centrocytic lymphomas. Lane numbers correspond to case numbers in Table 1. C, placental control DNA. Approximate germline band sizes are: *Eco*R1, 13.5 kb (reference 18); *Bam*HI, 21 kb; and *Bcl*-1, 14 kb (reference 18).

Blood 76: 1387, 1990

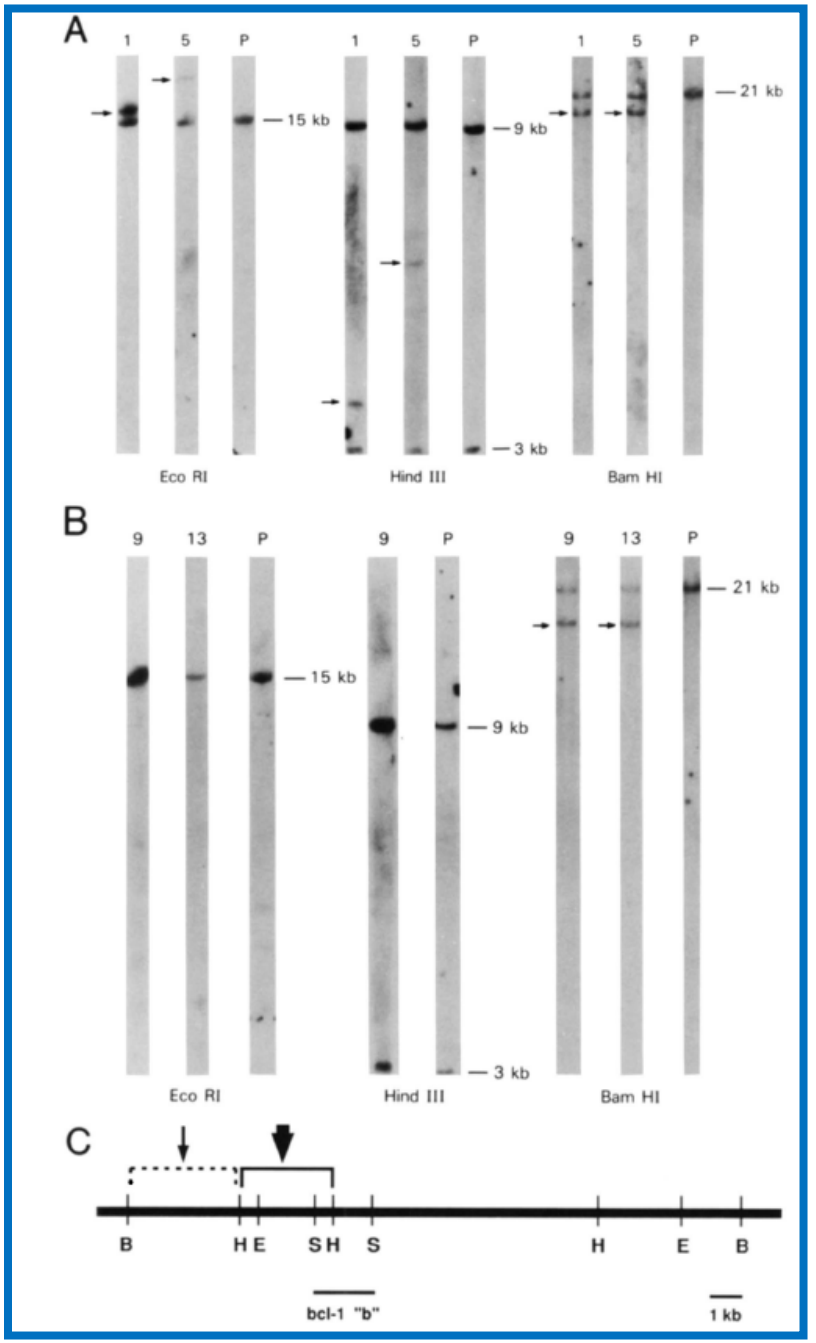
Association of *bcl*-1 Rearrangements With Lymphocytic Lymphoma of Intermediate Differentiation

By L. Jeffrey Medeiros, Johan H. Van Krieken, Elaine S. Jaffe, and Mark Raffeld

Previous studies using classical cytogenetics have demonstrated the presence of the t(11;14) (q13;q32) chromosomal translocation in some cases of lymphocytic lymphoma of intermediate differentiation (IDL), a distinct type of low grade B-cell lymphoma. This finding suggested that the *bcl*-1 region (located at band q13 of chromosome 11) might be involved in this neoplasm. Using a genomic probe from the major breakpoint area of the *bcl*-1 locus, we identified rearrangements of the *bcl*-1 region in 10 of 19 cases, 2 of which comigrated with a rearranged allele of the immunoglobulin heavy chain gene joining region. In contrast, *bcl*-1 rearrangements were not found in other types of low grade B-cell lymphoma, specifically in 36 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and 27 cases of follicular lymphoma (FL). To further assess the molecular pathology of IDL, we analyzed these cases for rearrangements of the *bcl*-2 proto-oncogene, which is associated primarily with follicular lymphomas. None of the 19 cases of IDL had rearrangements. Furthermore, none of the 36 cases of CLL/SLL showed *bcl*-2 rearrangements, whereas, as expected, 21 of 27 cases of FL had rearrangements of the *bcl*-2 locus. Our findings demonstrate an association between a rearranged *bcl*-1 region with approximately 50% of IDLs and suggest that abnormalities of this locus may be important in the pathogenesis of IDL.

Table 1. Summary of Genotypic Results

Case No.	*bcl*-1	JH	*bcl*-2*
1	R+	R	G
2	R+	R	G
3	R+	R	G
4	G	R	G
5	R+	R	G
6	G	R	G
7	G	R	G
8	G	R	G
9	R+ +	R	G
10	G	R	G
11	R+	R	G
12	G	R	G
13	R+ +	R	G
14	R+	R	G
15	G	R	G
16	G	R	G
17	R+	R	G
18	G	R	G
19	R+	R	ND



Blood 76: 2086, 1990

Mantle Cell Lymphoma

A Proposal for Unification of Morphologic, Immunologic, and Molecular Data

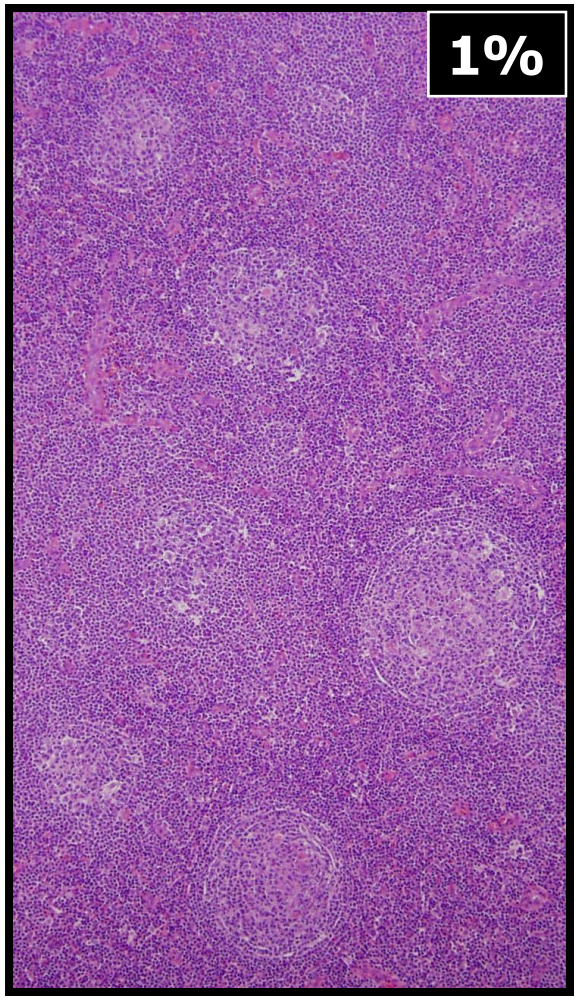
P.M. Banks, M.D., J. Chan, M.D., M.L. Cleary, M.D.,
G. Delsol, M.D., C. De Wolf-Peeters, M.D., K. Gatter, M.D.,
T.M. Grogan, M.D., N.L. Harris, M.D., P.G. Isaacson, M.D.,
E.S. Jaffe, M.D., D. Mason, M.D., S. Pileri, M.D.,
E. Ralfkiaer, M.D., H. Stein, M.D., and R.A. Warnke, M.D.

This was first paper by the International Lymphoma Study Group

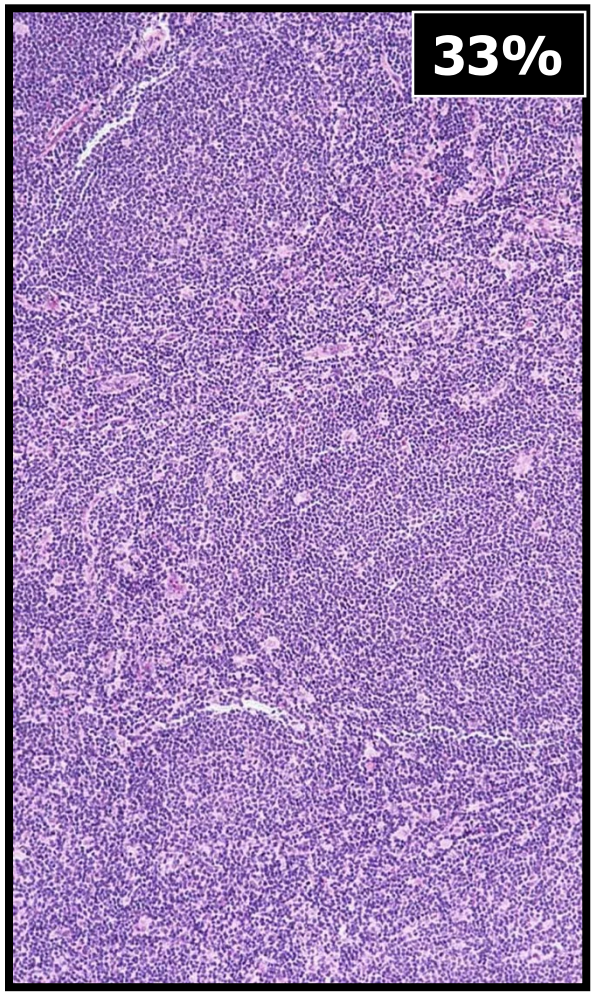
Am J Surg Pathol 16:637, 1992

Mantle Cell Lymphoma

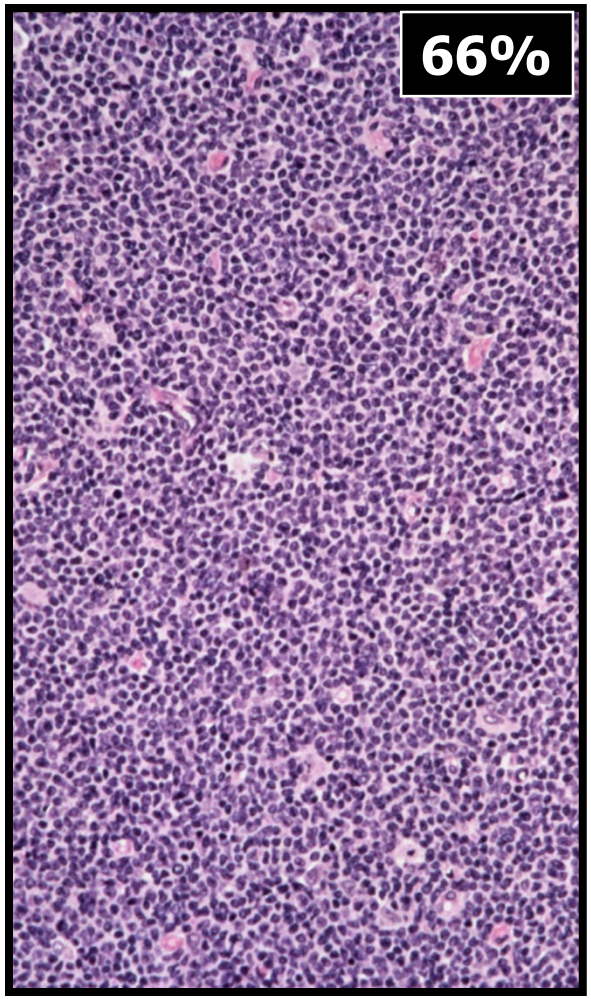
Patterns



Mantle zone

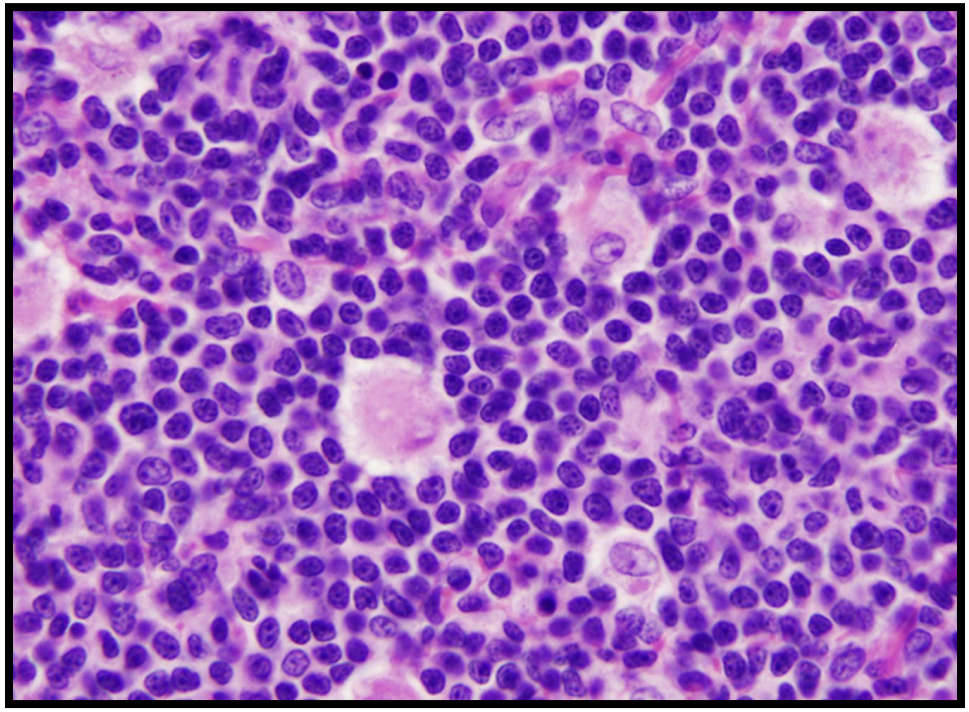


Nodular

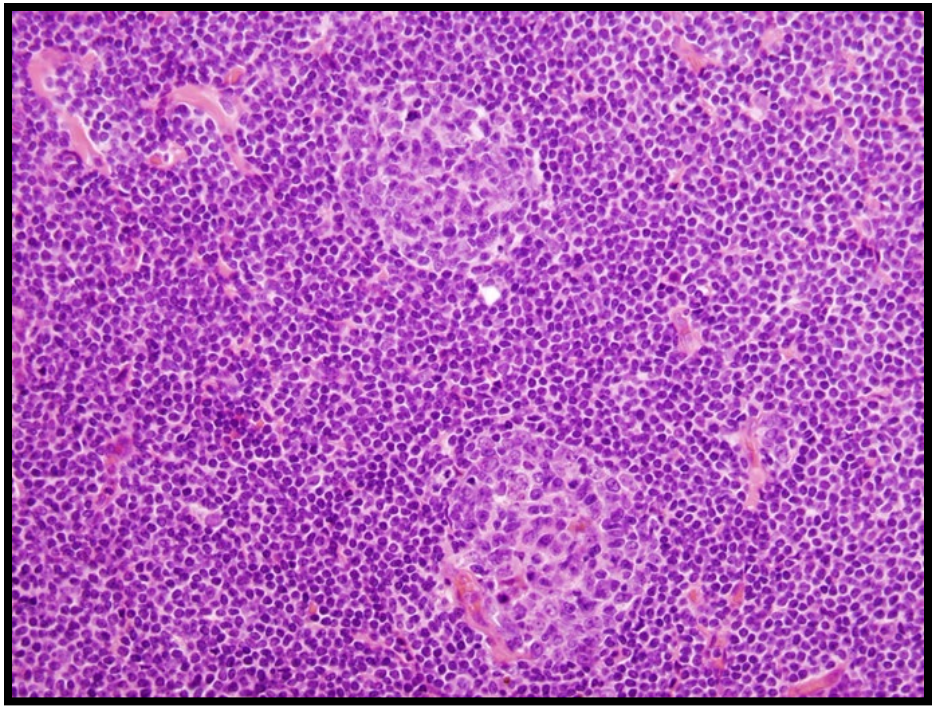


Diffuse

Mantle Cell Lymphoma
Common Features



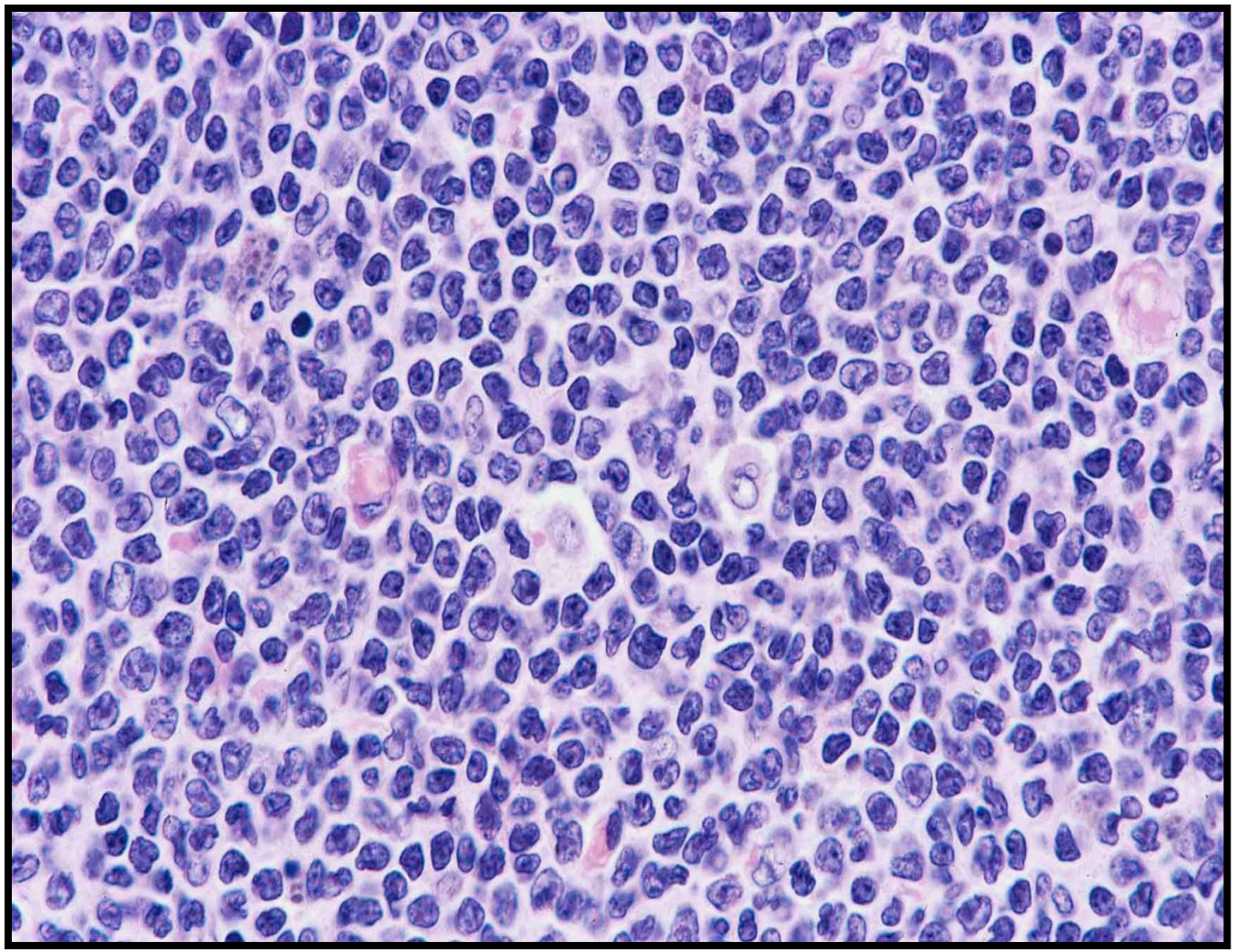
Epithelioid histiocytes



Naked germinal centers

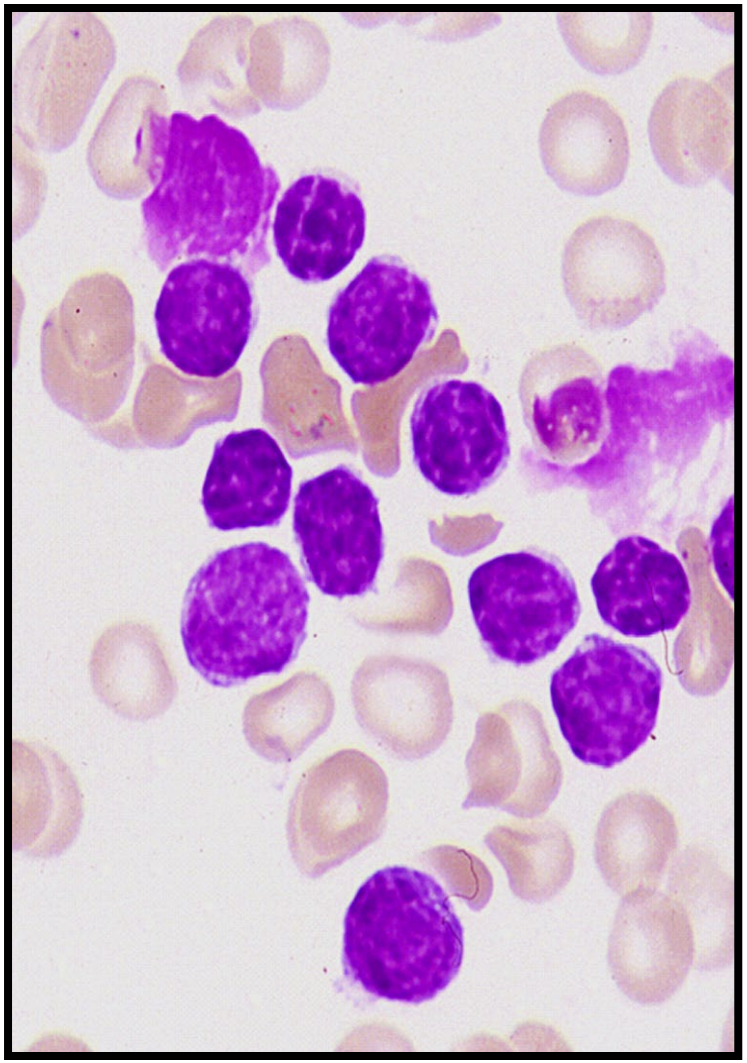
Mantle Cell Lymphoma

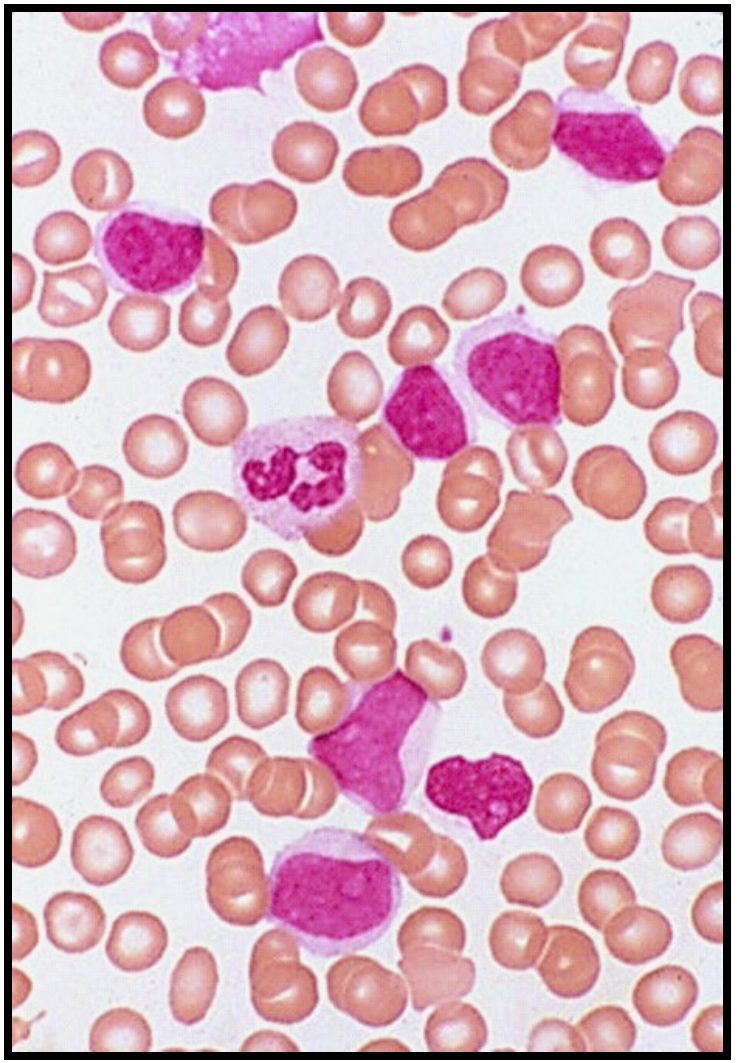
Cytologic Features



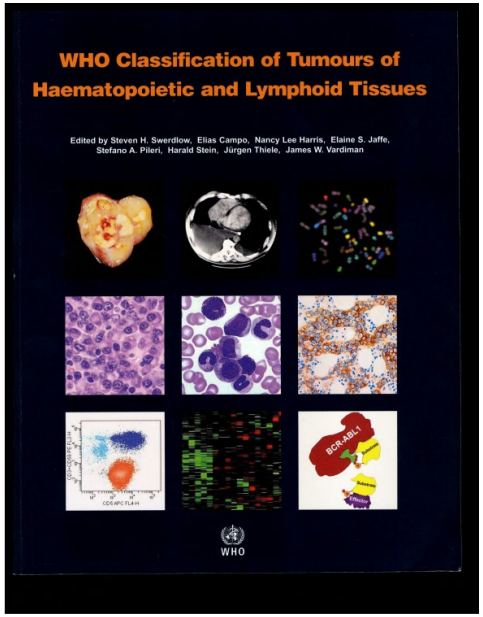
Mantle Cell Lymphoma

Typical Cytology





Mantle Cell Lymphoma
Definition in Current WHO Classification

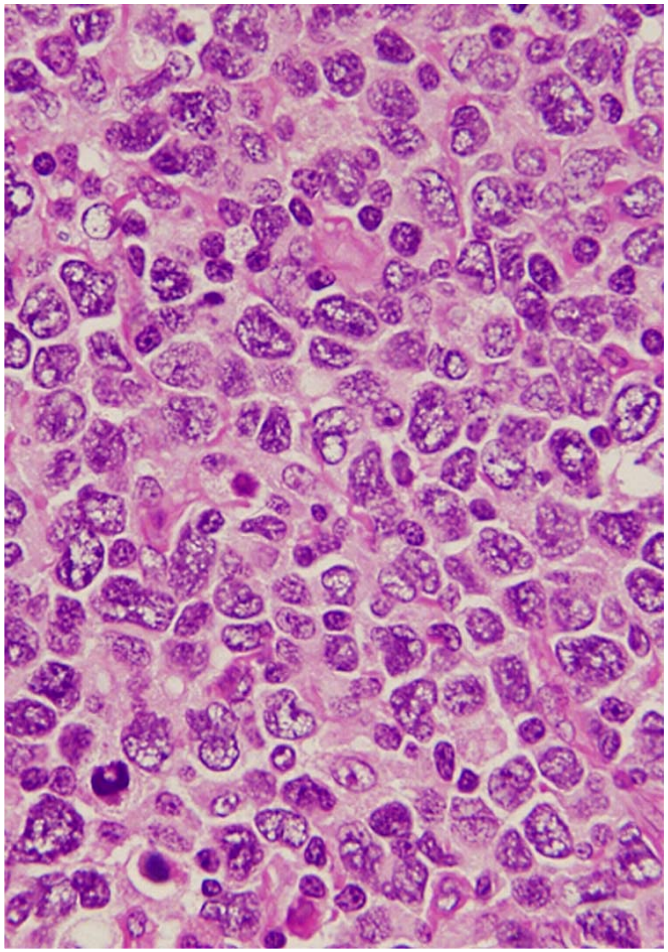


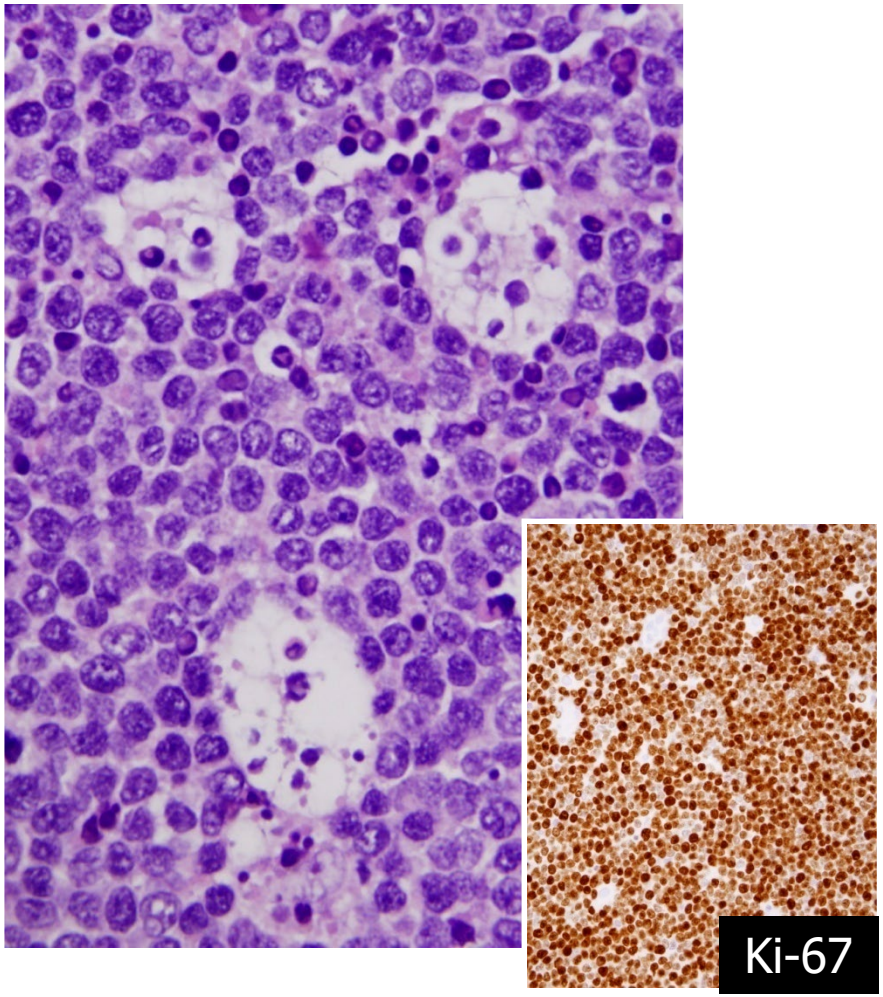
A B-cell neoplasm generally composed of monomorphic small to medium-sized lymphoid cells with irregular nuclear contours and a CCND1 translocation

2017 WHO book, p. 285

Mantle Cell Lymphoma

Aggressive Variants - Two Types





Mantle Cell Lymphoma
Aggressive Variants

Blastoid

Cells resemble lymphoblasts with > 20-30 mitoses/10 hpf

Can mimic lymphoblastic lymphoma

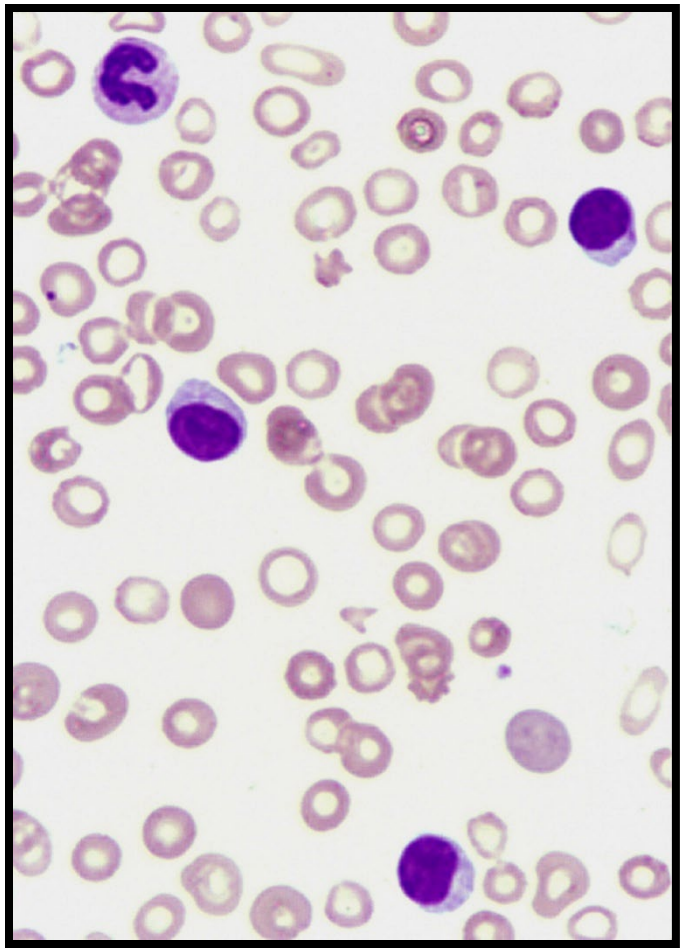
Pleomorphic

Cells with large cleaved or oval nuclei and pale cytoplasm ± prominent nucleoli

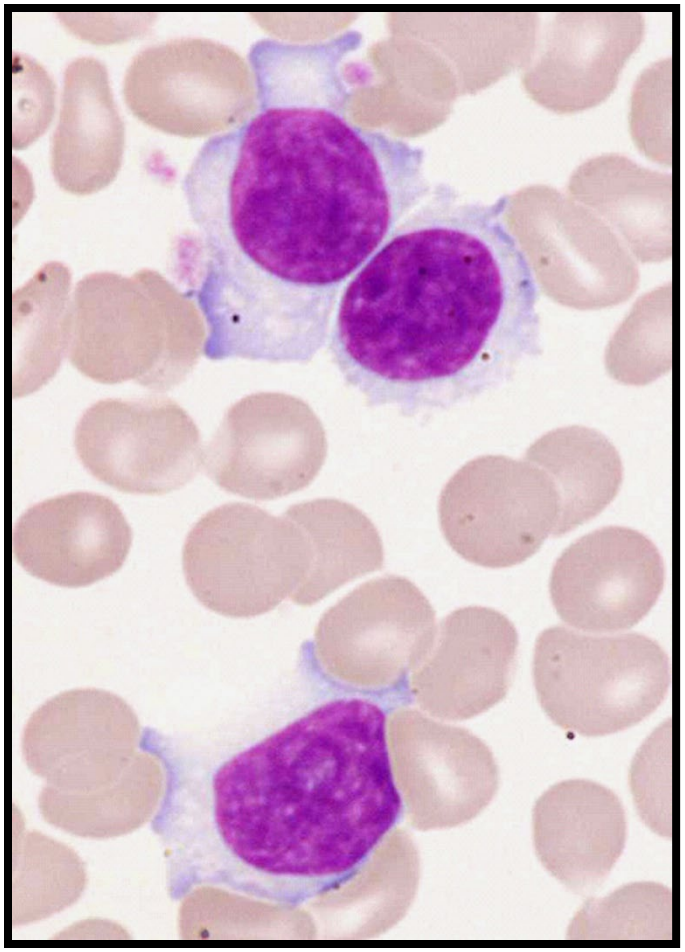
Can mimic diffuse large B-cell lymphoma

2017 WHO book p. 285

Mantle Cell Lymphoma in PB



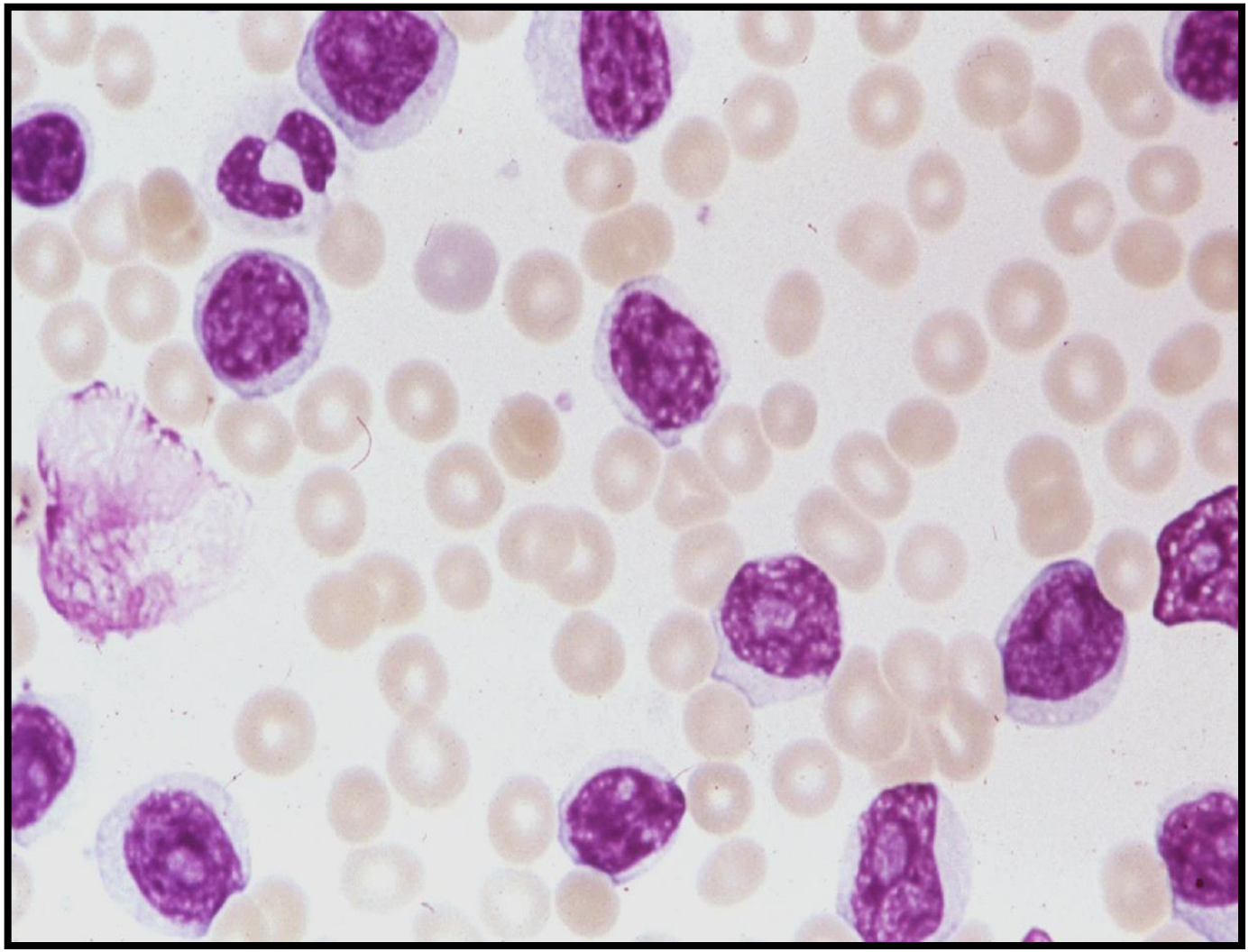
CLL-like



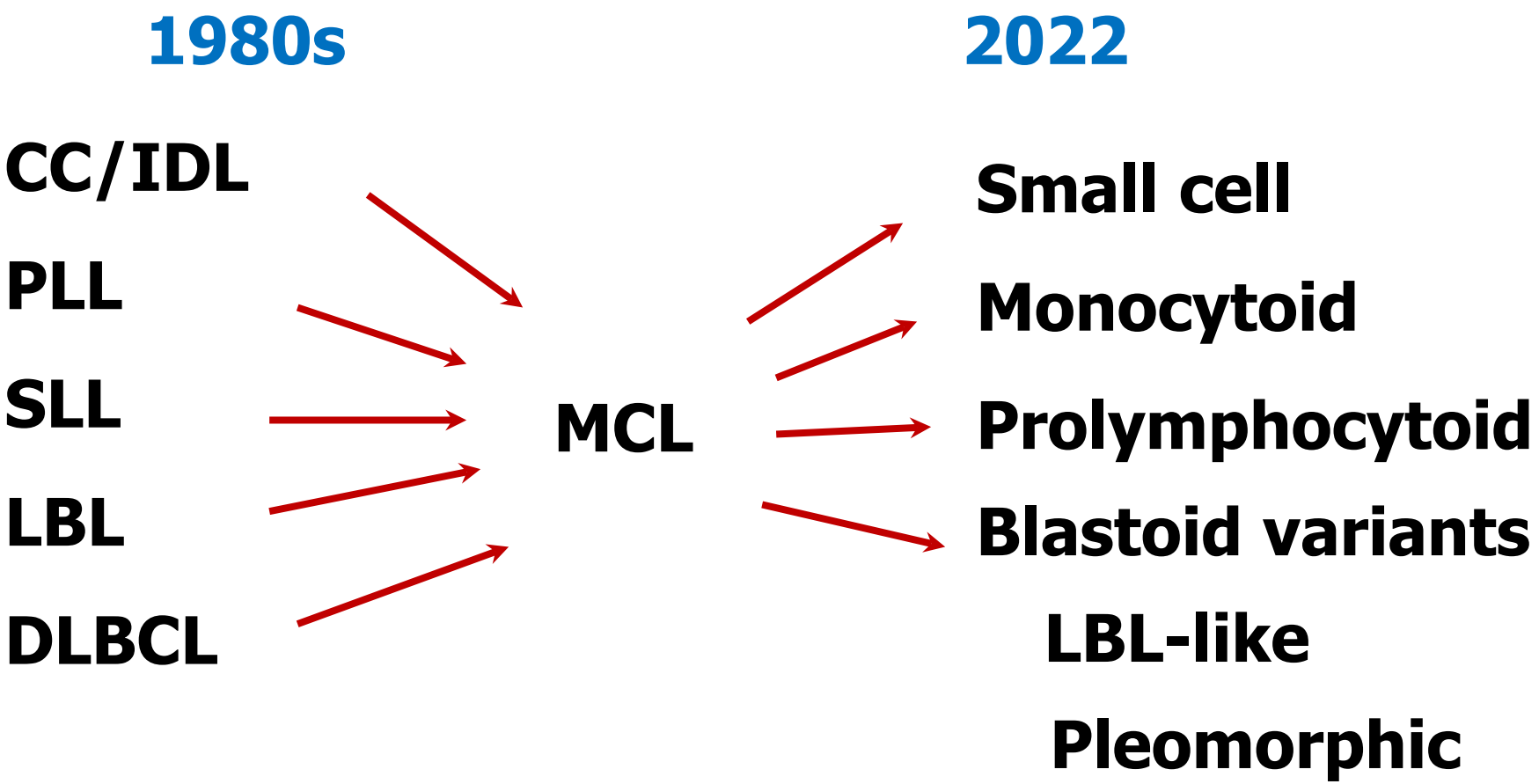
Villous-like

Mantle Cell Lymphoma in PB

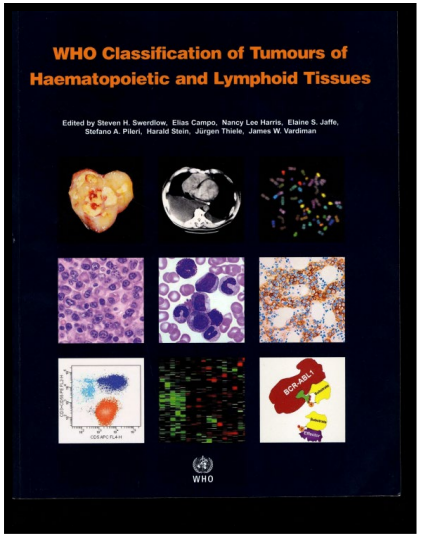
Prolymphocytoid



Mantle Cell Lymphoma



Mantle Cell Lymphoma
Variants Recognized in WHO Classification



Morphologic Variants of MCL

Blastoid
Pleomorphic
Small cell
Marginal zone-like

Other more indolent variants of MCL

Leukemic, non-nodal
In situ mantle cell neoplasia

2017 WHO book, p.285

Mantle Cell Lymphoma

Ancillary Methods for Diagnosis

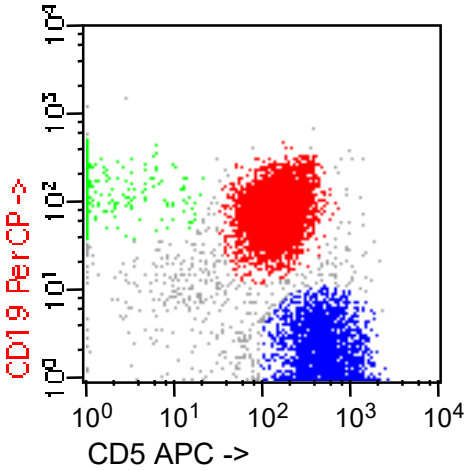
Flow Cytometry

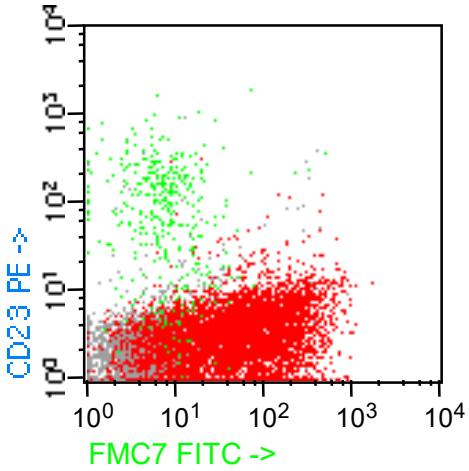
Detection of t(11;14)(q13;q32)

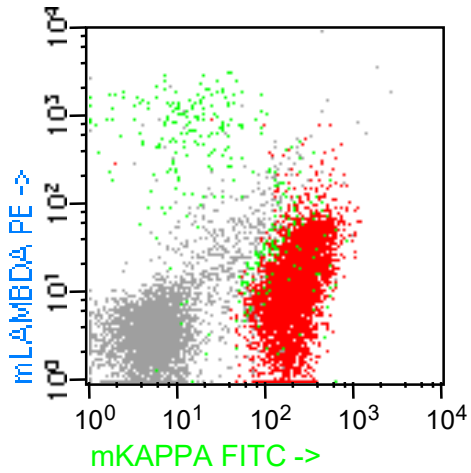
Immunohistochemistry

Mantle Cell lymphoma

Flow Cytometry







sIg +

CD5 +

CD10 -

CD19 +

CD20 +

CD23 –

FMC7 +

Small B-cell Lymphomas
Value of Immunophenotype

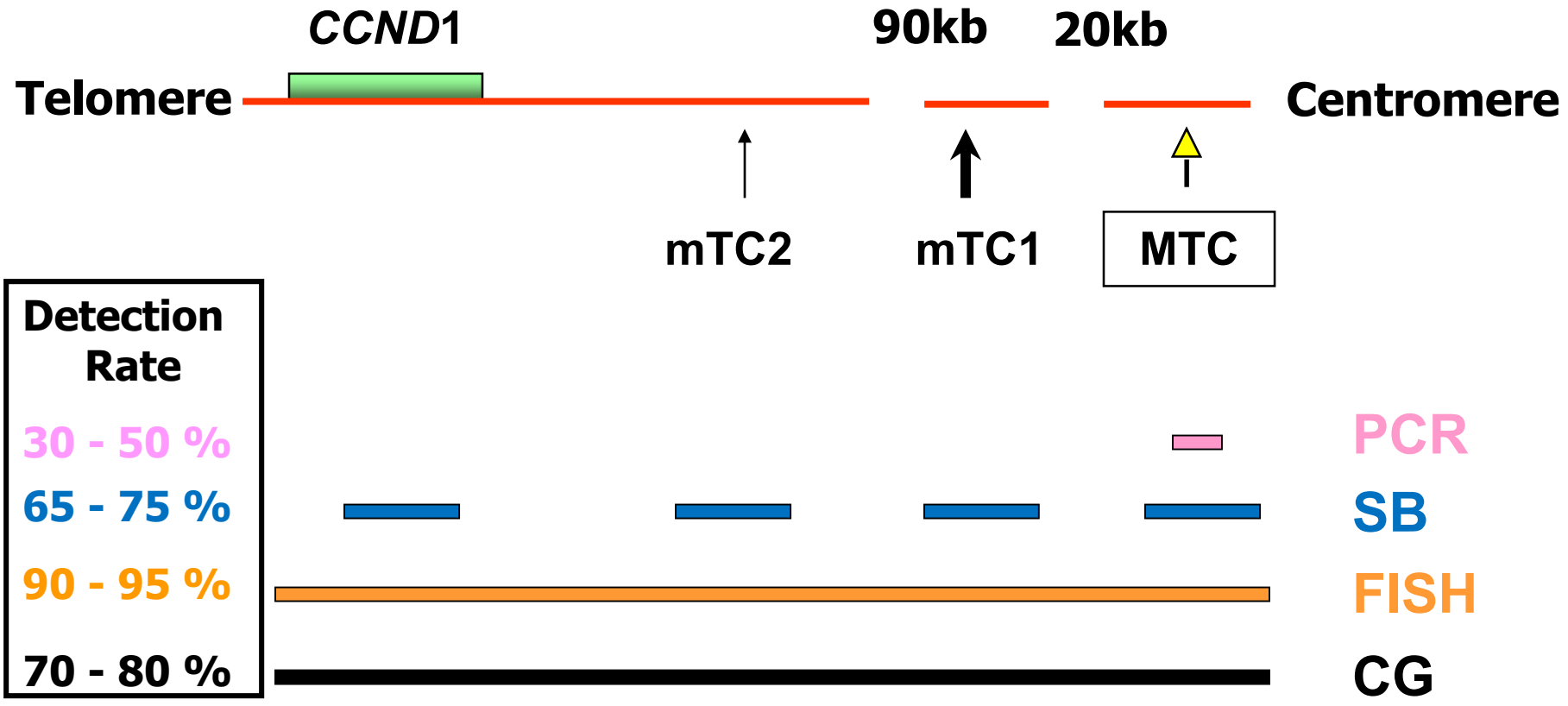
	CLL	MCL	LPL/W	MZL	FL
sIg	+dim	+	+	+	+
CD5	+	+ / -	-	-	-
CD10	-	rare +	-	-	+
CD19	+	+	+	+	+
CD20	+dim	+	+	+	+
CD23	+	- / +	+/ -	- / +	- / +
CD200	+	-/+	+	+/-	+
Cyclin D1	-	+	-	-	-
Bcl-6	-	rare +	-	-	+

t(11;14) in Mantle Cell Lymphoma

Method	Detection Rate
FISH	90 - 95 %
Conventional cytogenetics	70 - 80 %
Southern blot hybridization	65 - 75 %
PCR *bcl*-1 MTC/JH	30 - 50 %

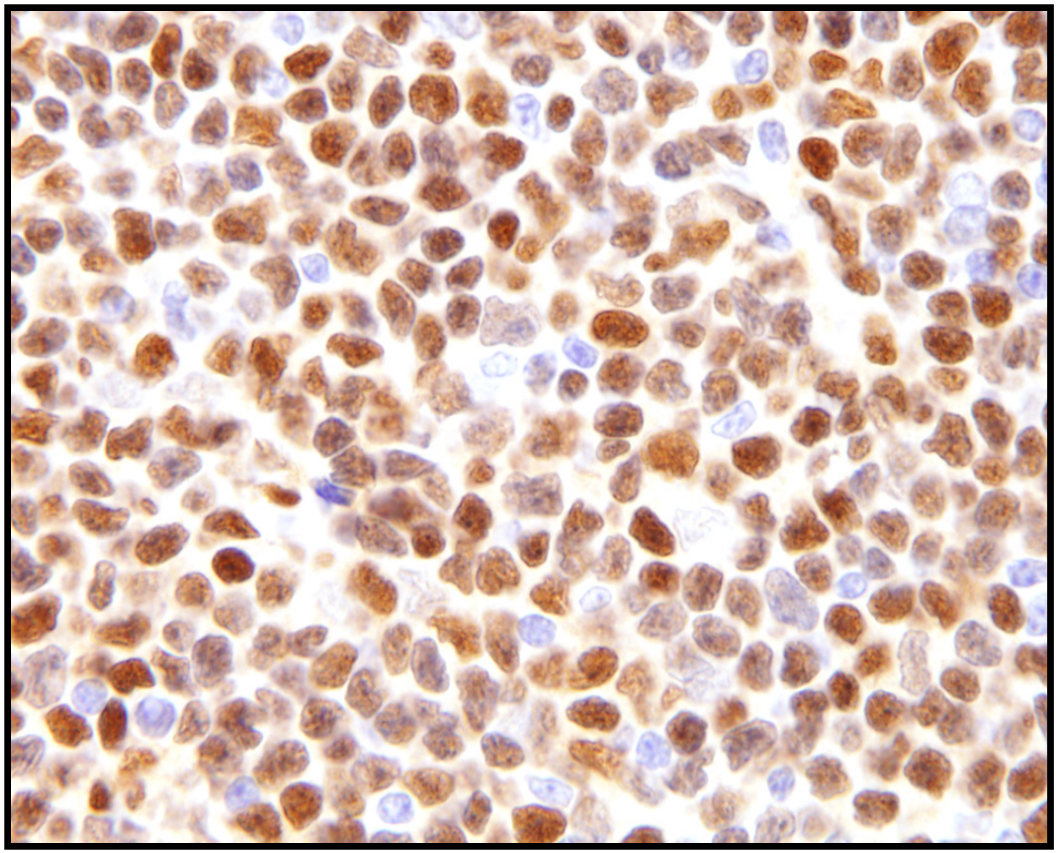
11q13 in Mantle Cell Lymphoma

Breakpoint Detection



Mantle Cell Lymphoma

Cyclin D1 is a surrogate for the t(11;14



Not specific for MCL

Other tumors that can be cyclin D1 +

- **Hairy cell (50%)**
- **Myeloma (33%)**
- **DLBCL (~5%)**
- **CLL/SLL +/- (PCs)**

We use clone EP12 from Leica currently

Mantle Cell Lymphoma
Gene Expression Profiling

101 cases of mantle cell lymphoma

cDNA microarrays (Lymphochip, 12,196 genes)

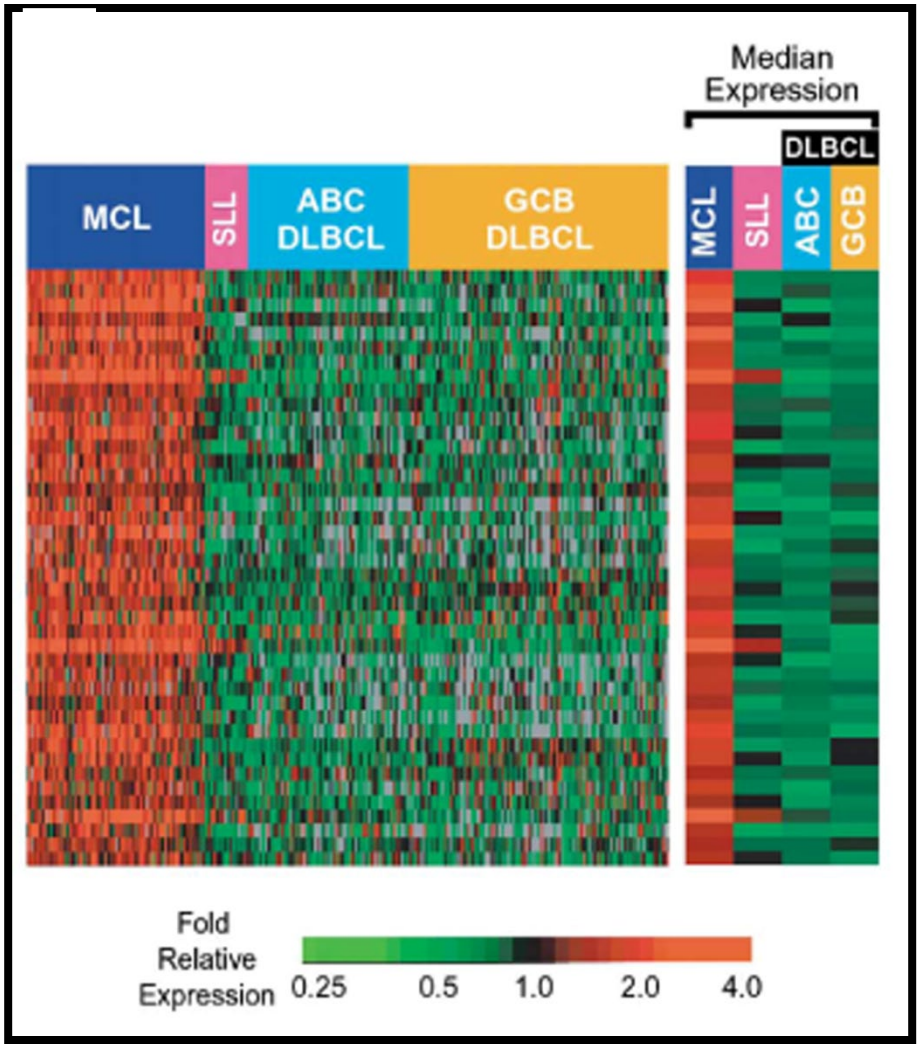
42 genes distinguish MCL from other lymphomas

A group of 20 genes comprise a distinctive proliferation signature

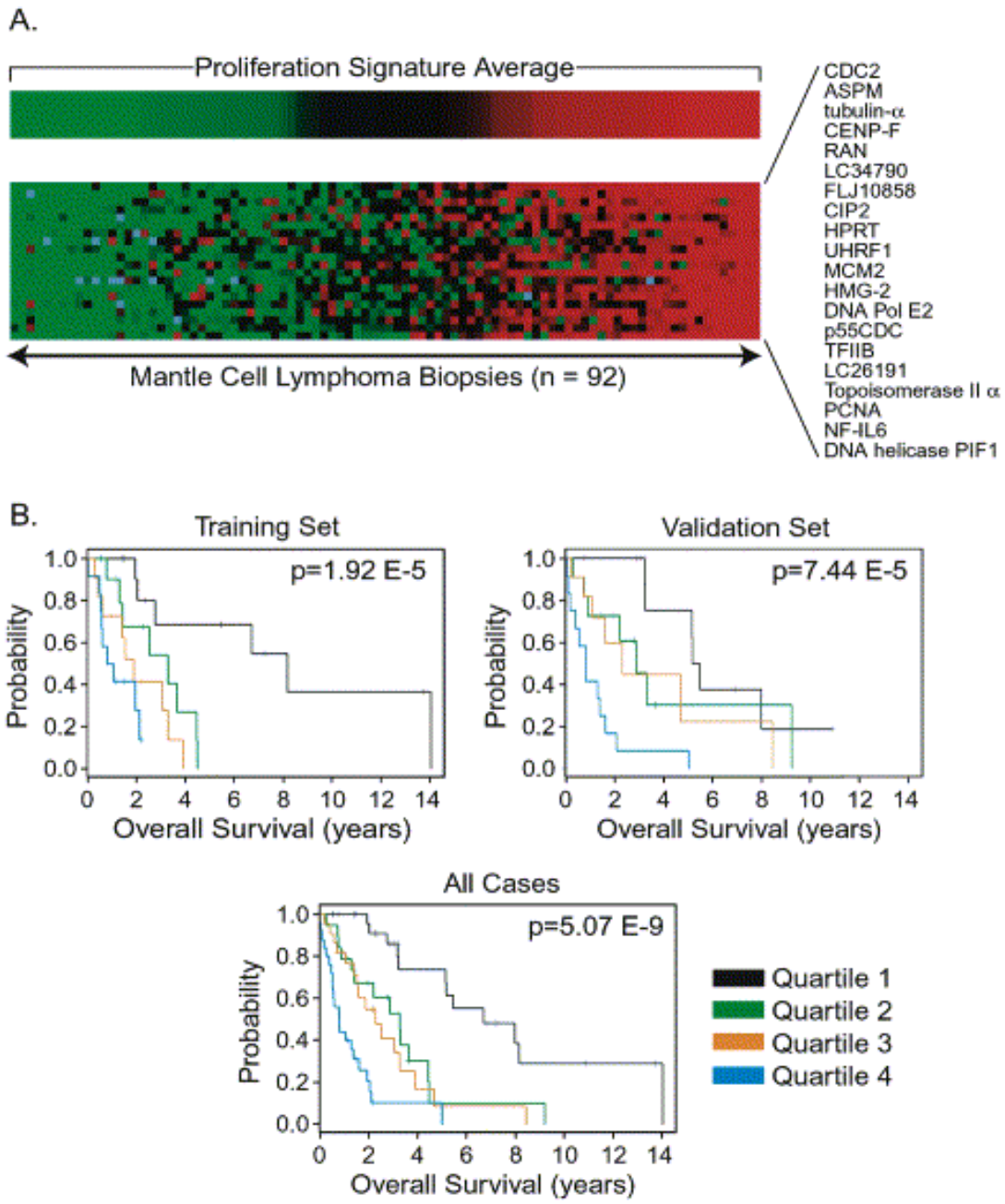
Rosenwald et al. Cancer Cell 3: 185, 2003

Mantle Cell Lymphoma

42 Gene Signature



Cancer Cell 3: 185, 2003



Cancer Cell 3: 185-197, 2003

Mantle Cell Lymphoma
Gene Expression Profiling

Study Group: 101 tumors with MCL histology

92 cyclin D1 +

7 cyclin D1 –

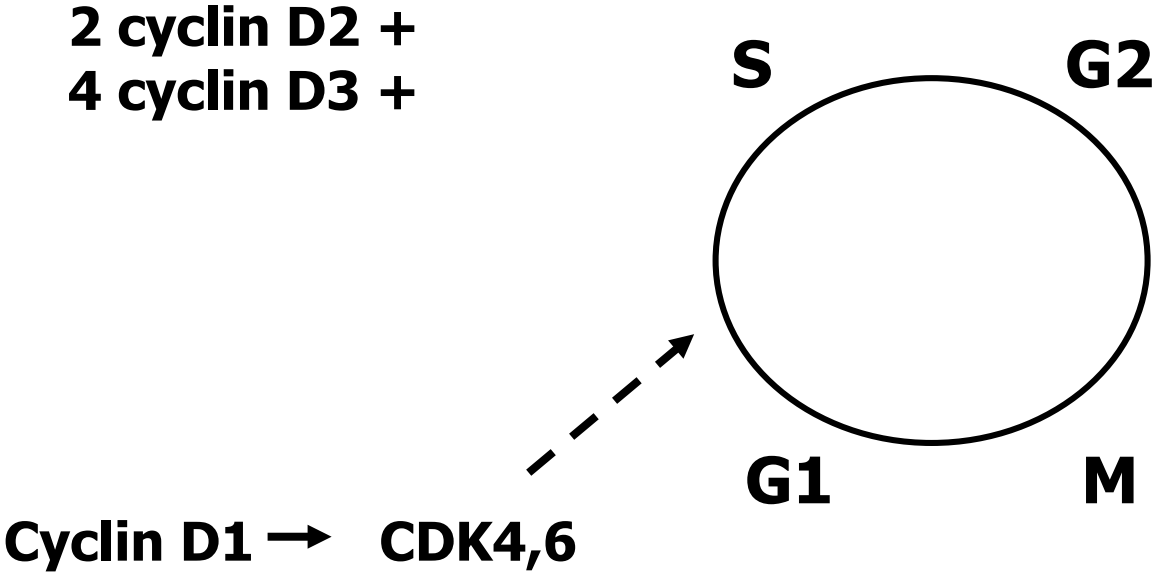
2 reclassified
(both were cyclin D1-)

Cancer Cell 3: 185, 2003

Cyclin D1–negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling

Kai Fu, Dennis D. Weisenburger, Timothy C. Greiner, Sandeep Dave, George Wright, Andreas Rosenwald, Michael Chiorazzi, Javeed Iqbal, Stefan Gesk, Reiner Siebert, Daphne De Jong, Elaine S. Jaffe, Wyndham H. Wilson, Jan Delabie, German Ott, Bhavana J. Dave, Warren G. Sanger, Lynette M. Smith, Lisa Rimsza, Rita M. Braziel, H. Konrad Müller-Hermelink, Elias Campo, Randy D. Gascoyne, Louis M. Staudt, Wing C. Chan and for the Lymphoma/Leukemia Molecular Profiling Project

Tumors look and immunophenotype like MCL but cyclin D1-

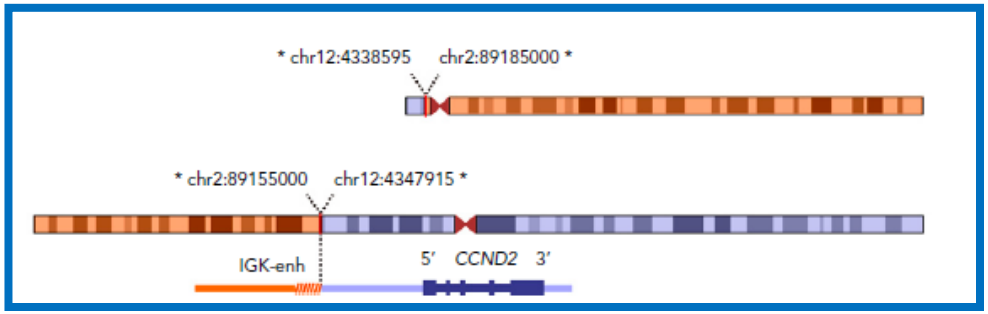


Blood 106:4315, 2006

LYMPHOID NEOPLASIA

CCND2 and *CCND3* hijack immunoglobulin light-chain enhancers in cyclin D1⁻ mantle cell lymphoma

David Martín-Garcia,[1,2,*] Alba Navarro,[1,2,*] Rafael Valdés-Mas,[3] Guillem Clot,[1,2] Jesús Gutiérrez-Abril,[3] Miriam Prieto,[1,2] Inmaculada Ribera-Cortada,[4] Renata Woroniecka,[5] Grzegorz Rymkiewicz,[6] Susanne Bens,[7,8] Laurence de Leval,[9] Andreas Rosenwald,[10,11] Judith A. Ferry,[12] Eric D. Hsi,[13] Kai Fu,[14,15] Jan Delabie,[16,17] Dennis Weisenburger,[18] Daphne de Jong,[19] Fina Climent,[20] Sheila J. O'Connor,[21] Steven H. Swerdlow,[22] David Torrents,[23,24] Sergi Beltran,[25] Blanca Espinet,[26,27] Blanca González-Farré,[2,28] Luis Veloza,[28] Dolors Costa,[2,28] Estella Matutes,[28] Reiner Siebert,[7,8] German Ott,[29,30] Leticia Quintanilla-Martinez,[31] Elaine S. Jaffe,[32] Carlos López-Otín,[2,3] Itziar Salaverria,[1,2] Xose S. Puente,[2,3,†] Elias Campo,[1,2,28,33,†] and Sílvia Beà[1,2,†]



56 cases of cyclin D1- and SOX11+ MCL

39 (70%) with CCND2 rearrangements

No cases with CCND3 rearrangements

10 with cryptic insertion of IGK or IGL enhancers nearby CCND2 (n=4) or CCND3 (n=6)

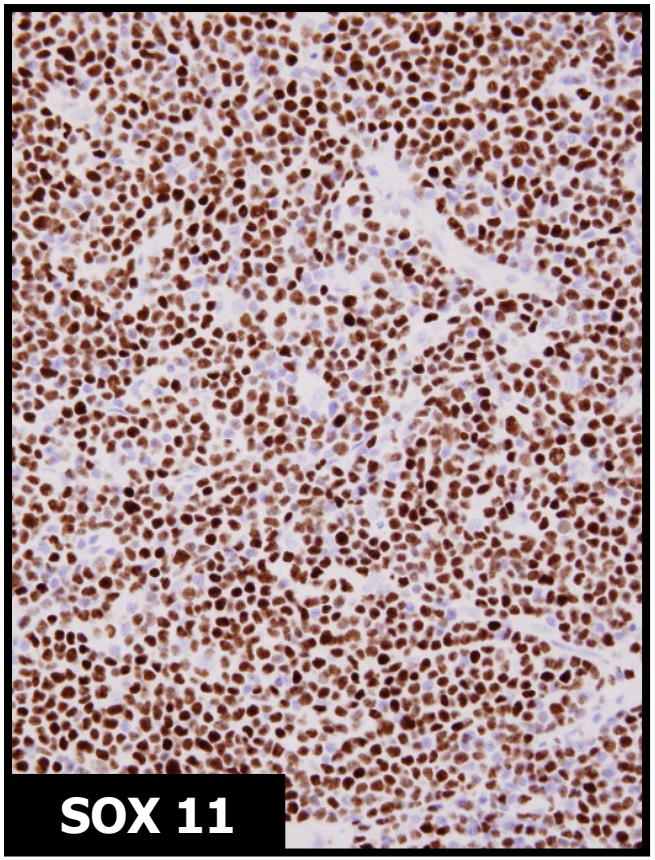
Diagnosis of cyclin D1- MCL can be established using morphology, immunophenotype, and SOX11+

Blood 133:940, 2019

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]

Typical MCL	**50/54 (93%)**
D1- MCL	**12/12 (100%)**
CLL/SLL	**0/12**
Nodal MZL	**0/11**
Splenic MZL	**0/9**
FL	**0/22**



Haematologica 94:1555, 2009

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]

Typical MCL	50/54 (93%)
D1- MCL	12/12 (100%)
B lymphoblastic	1/1 (100%)
Burkitt lymphoma	2/8 (25%)
Classical Hodgkin	1/36 (3%)
T lymphoblastic	5/5 (100%)
T-PLL	2/3 (67%)

Haematologica 94:1555, 2009

Mantle Cell Lymphoma

A Proposal for Unification of Morphologic, Immunologic, and Molecular Data

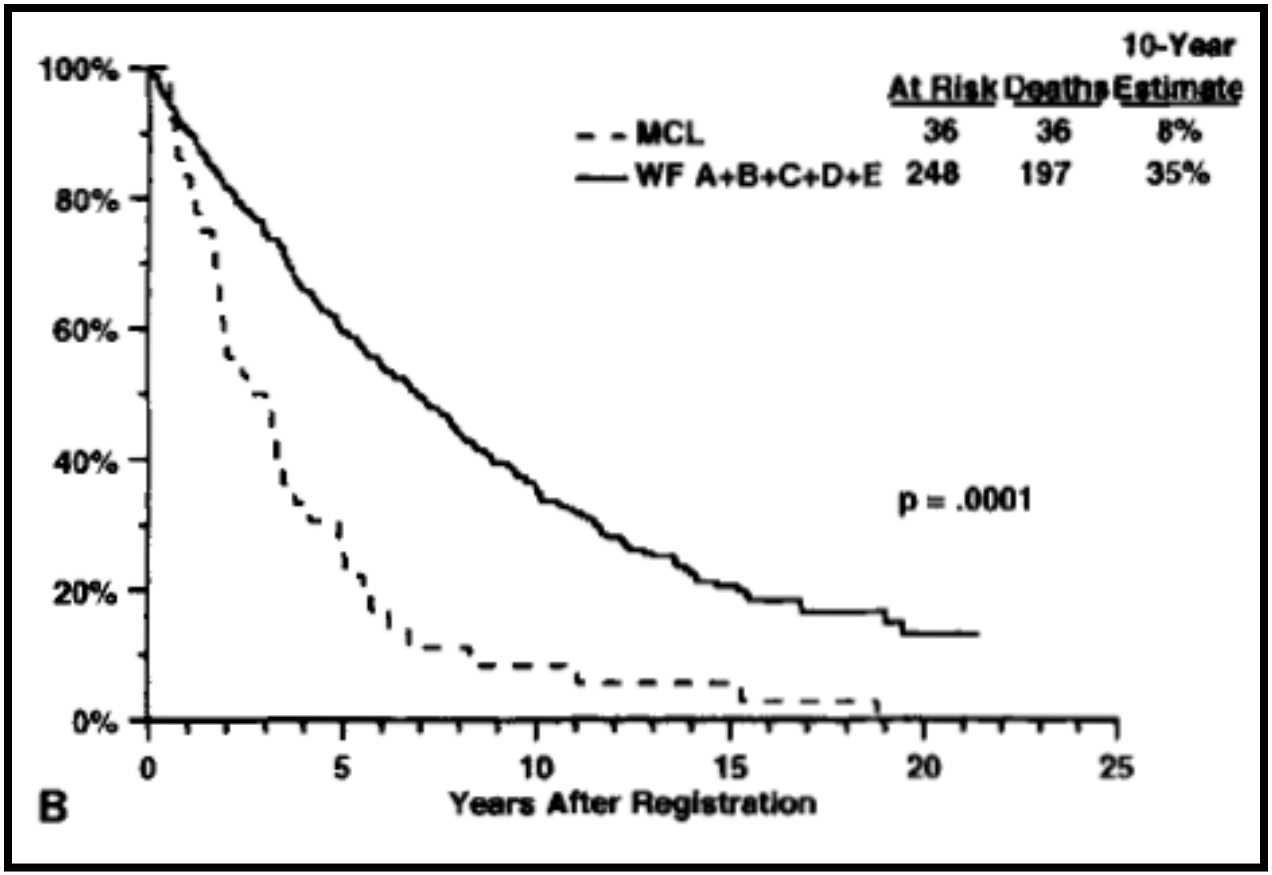
P.M. Banks, M.D., J. Chan, M.D., M.L. Cleary, M.D.,
G. Delsol, M.D., C. De Wolf-Peeters, M.D., K. Gatter, M.D.,
T.M. Grogan, M.D., N.L. Harris, M.D., P.G. Isaacson, M.D.,
E.S. Jaffe, M.D., D. Mason, M.D., S. Pileri, M.D.,
E. Ralfkiaer, M.D., H. Stein, M.D., and R.A. Warnke, M.D.

This was first paper by the International Lymphoma Study Group

Am J Surg Pathol 16:637, 1992

A Clinical Analysis of Two Indolent Lymphoma Entities: Mantle Cell Lymphoma and Marginal Zone Lymphoma (Including the Mucosa-Associated Lymphoid Tissue and Monocytoid B-Cell Subcategories): A Southwest Oncology Group Study

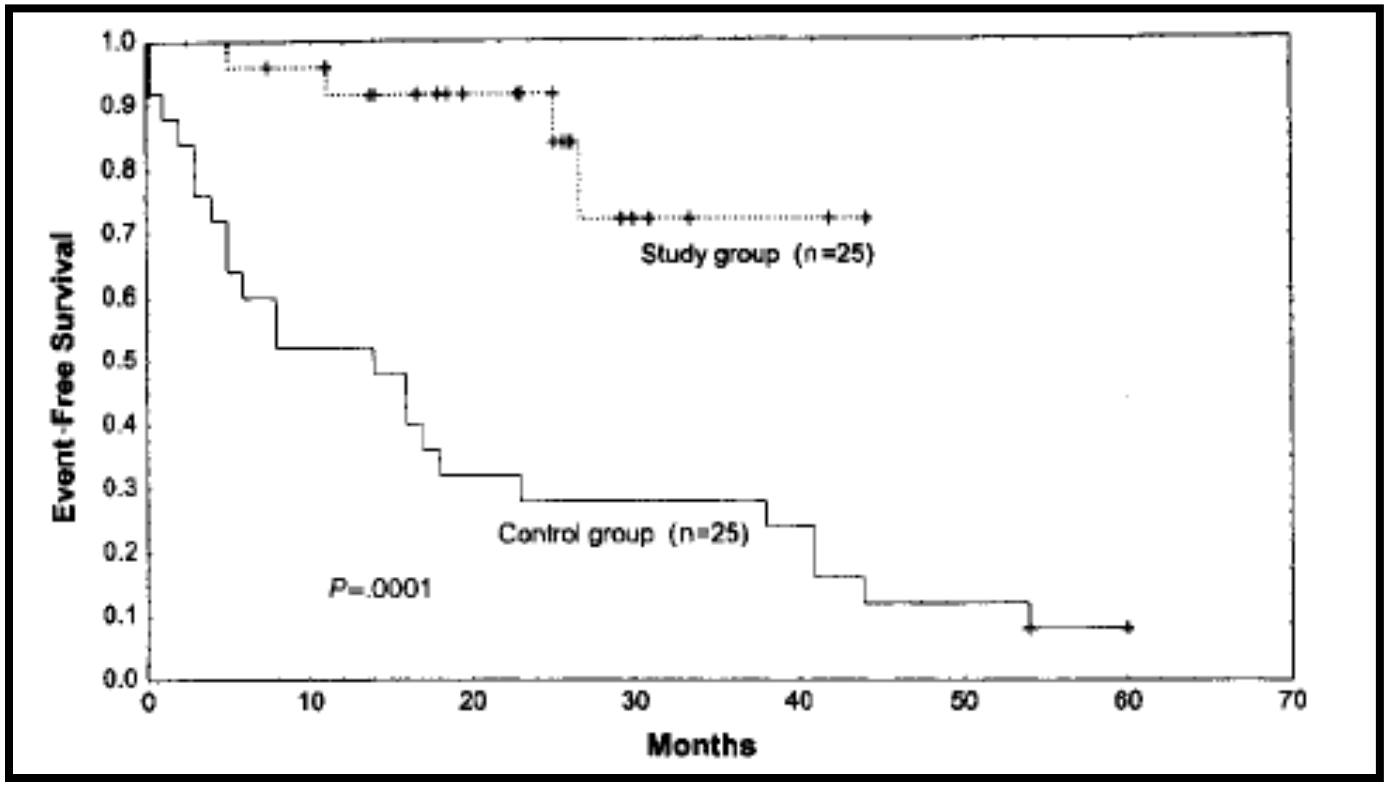
By Richard I. Fisher, Steve Dahlberg, Bharat N. Nathwani, Peter M. Banks, Thomas P. Miller, and Thomas M. Grogan



Blood 85: 1075-1082, 1995

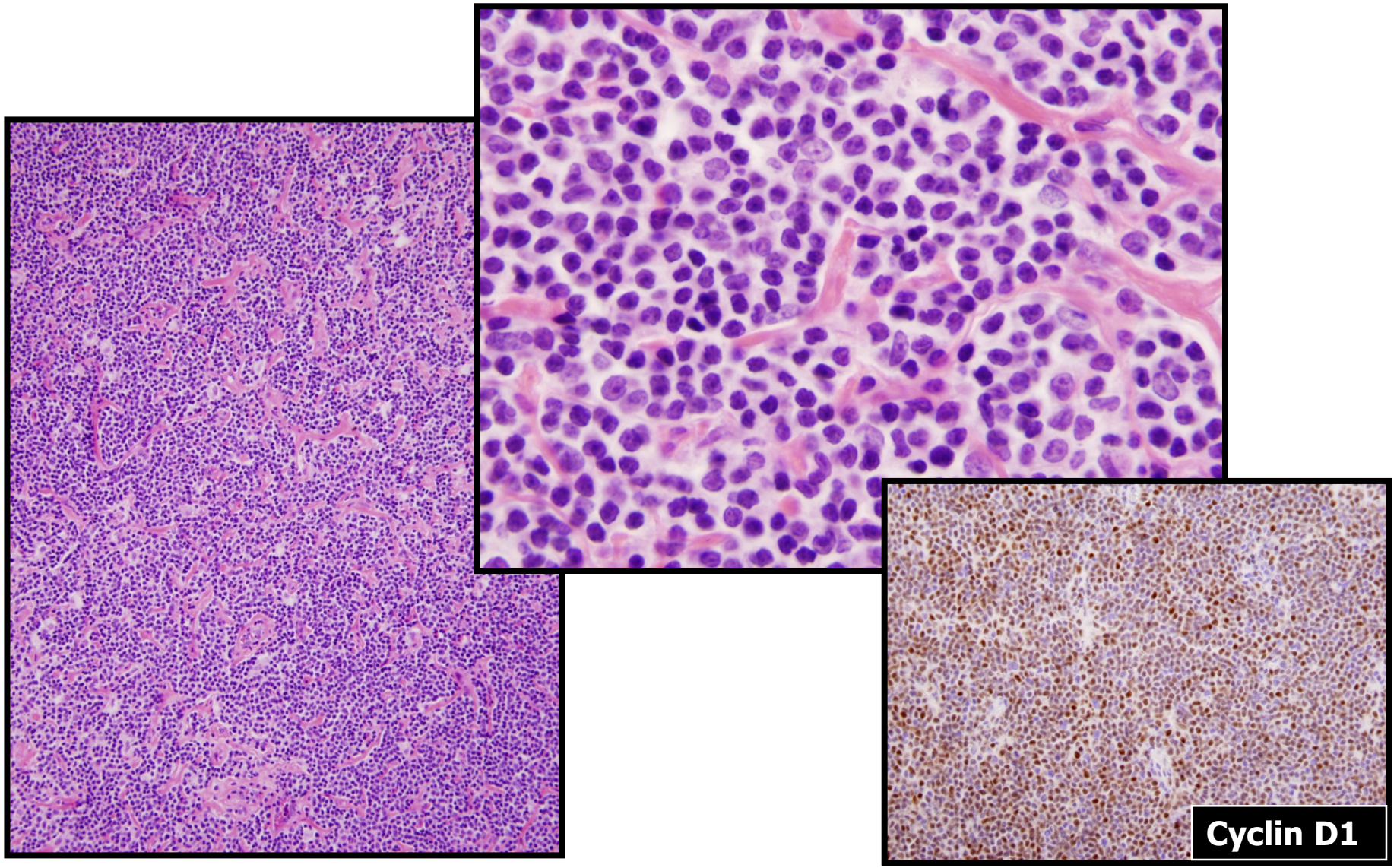
Hyper-CVAD and High-Dose Methotrexate/Cytarabine Followed by Stem-Cell Transplantation: An Active Regimen for Aggressive Mantle-Cell Lymphoma

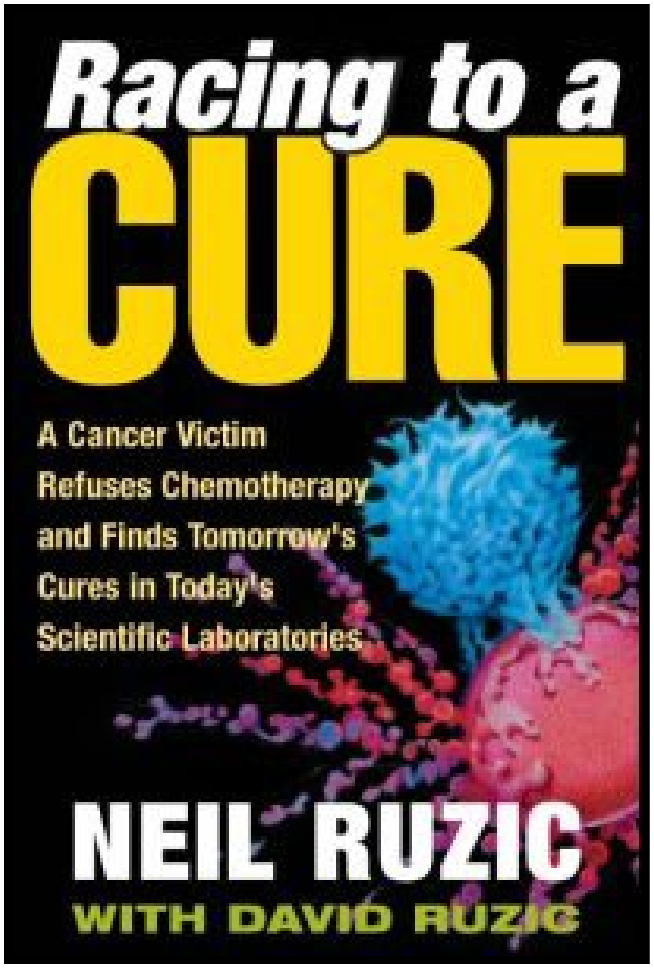
By Issa F. Khouri, Jorge Romaguera, Hagop Kantarjian, J. Lynn Palmer, William C. Pugh, Martin Korbling, Fredrick Hagemeister, Barry Samuels, Alma Rodriguez, Sergio Giralt, Anas Younes, Donna Przepiorka, David Claxton, Fernando Cabanillas, and Richard Champlin



J Clin Oncol 16: 3803, 1998

68-year-old man with splenomegaly and abdominal lymphadenopathy





Neil P. Ruzic

He lived 7 years after refusing therapy

Therapy for Mantle Cell Lymphoma
There are now many options

Ki-67 < 30%

Watchful waiting

Bortezomib

Ibrutinib and rituximab

Ki-67 ≥ 30%

Aggressive chemotherapy (HyperCVAD, others)

Autologous stem cell transplant

Relapse

Investigational agents in trials

Mantle Cell Lymphoma
Risk Stratification is Essential

MCL International Prognostic Index (MIPI)

Age, performance status, LDH, WBC

MIPI Biologic (MIPIb)

MIPI plus Ki-67 (30% cutoff)

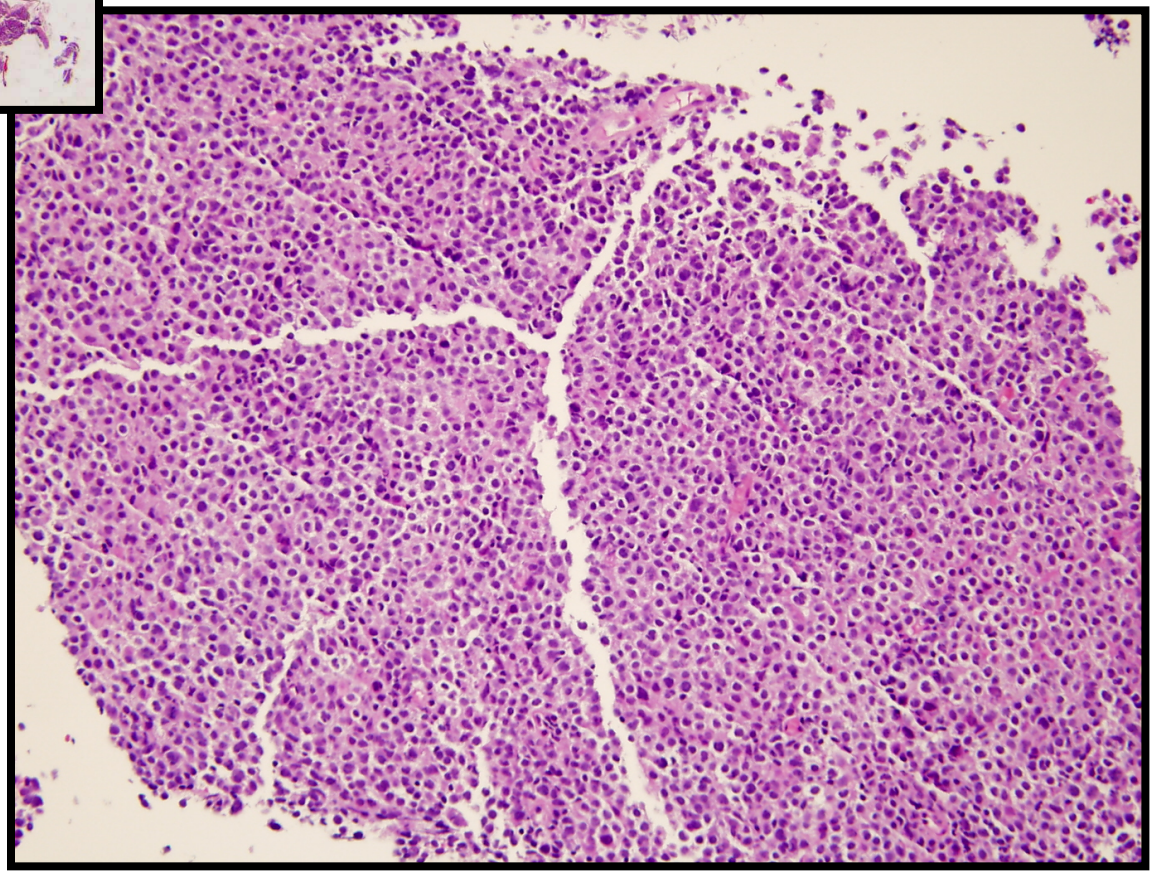
Genetic Biomarkers

TP53
NOTCH 1/2
Truncated cyclin D1 transcripts
MYC **rearrangement**

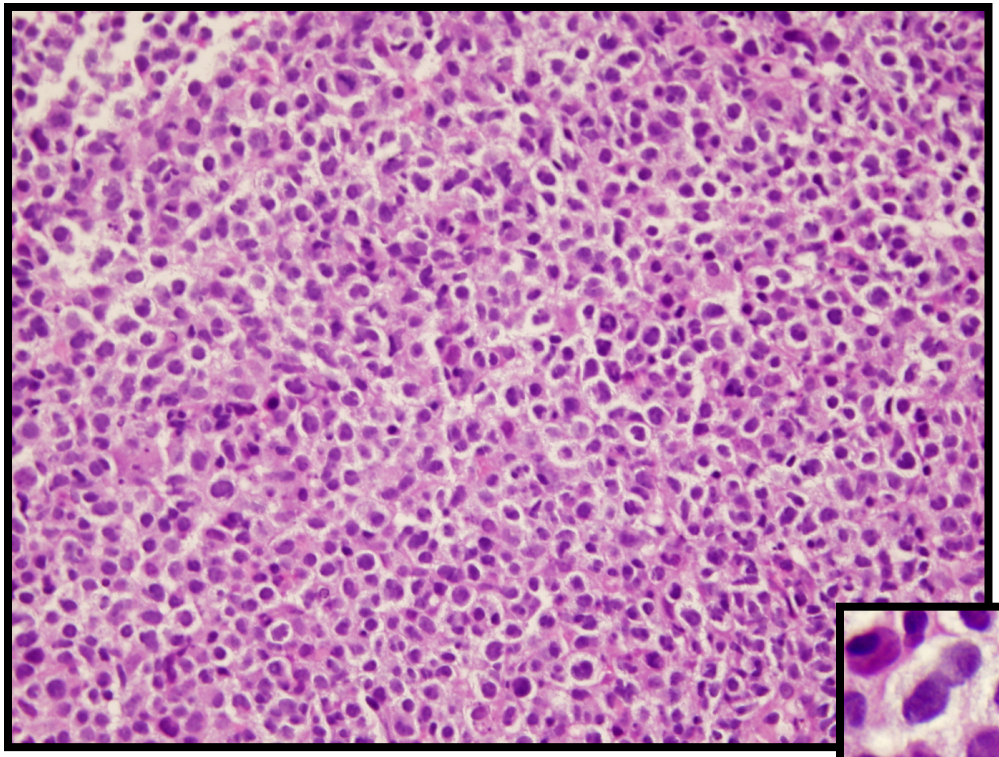
CASE 4

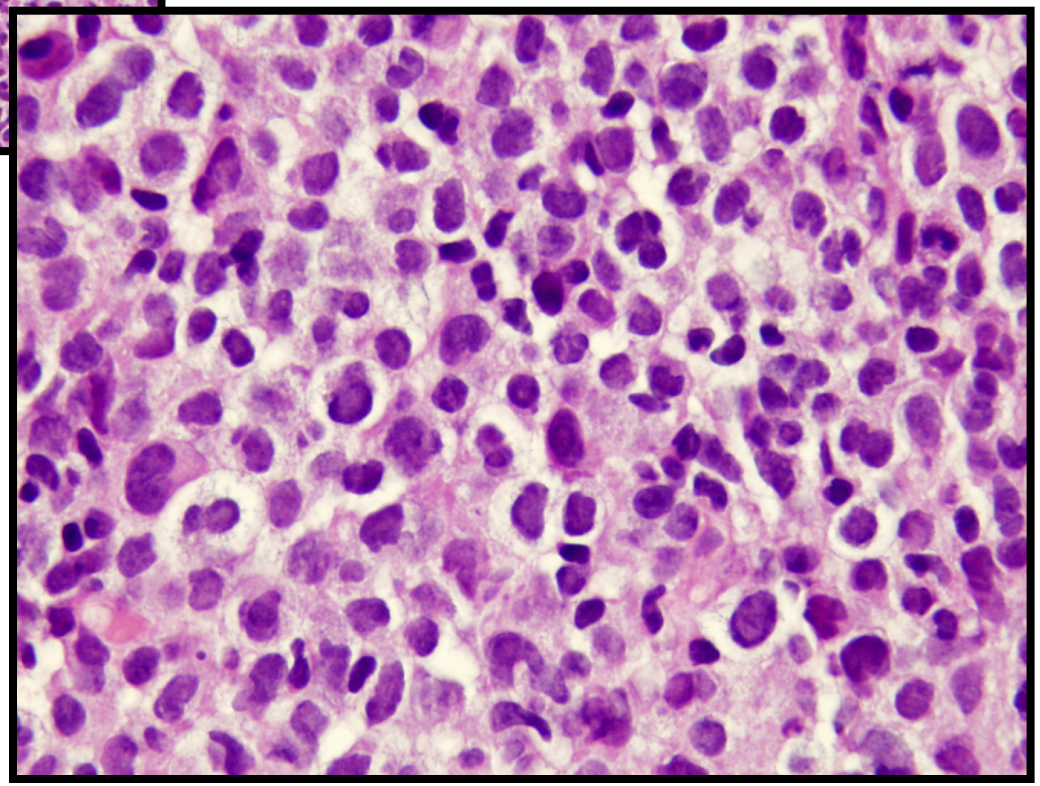
A 70-year-old woman with a history of diabetes, hypertension and kidney failure presented with acute onset of fatigue and dizziness. Physical examination showed B-type symptoms. Laboratory evaluation showed hypercalcemia. PET/CT showed lymphadenopathy, splenomegaly and bone lesions. This is a right axillary lymph node needle biopsy.

Case 4

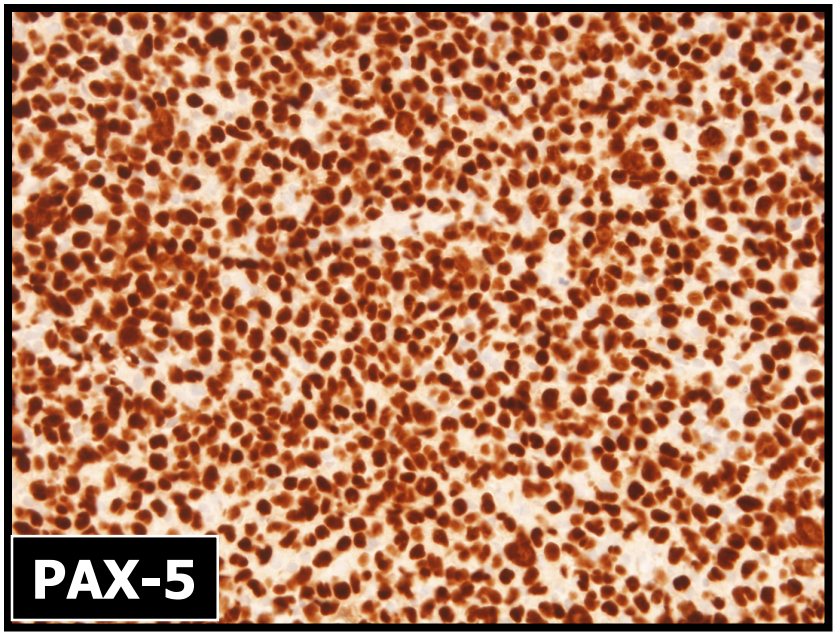


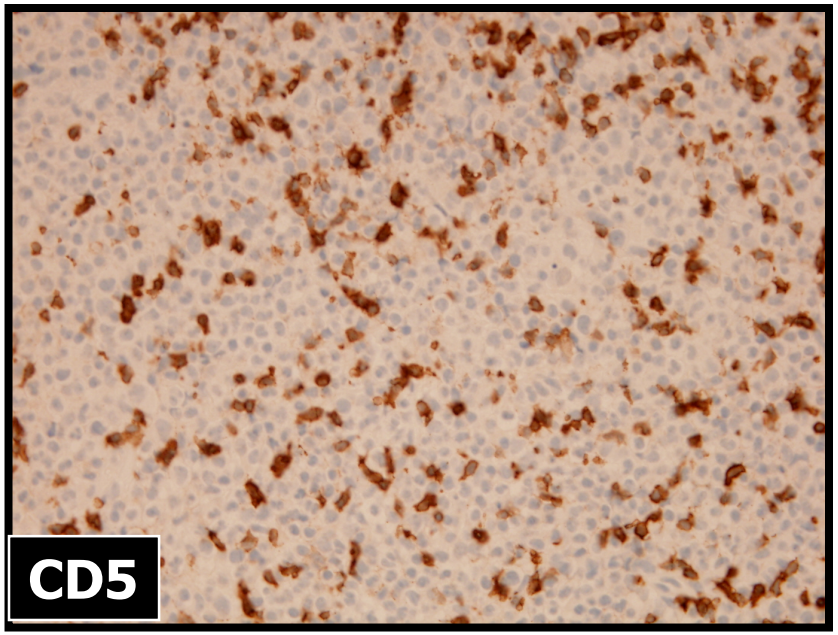
Case 4

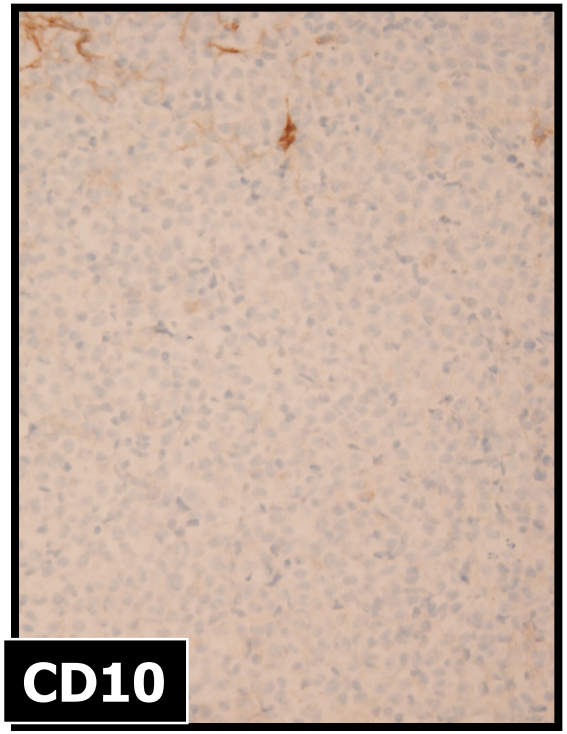


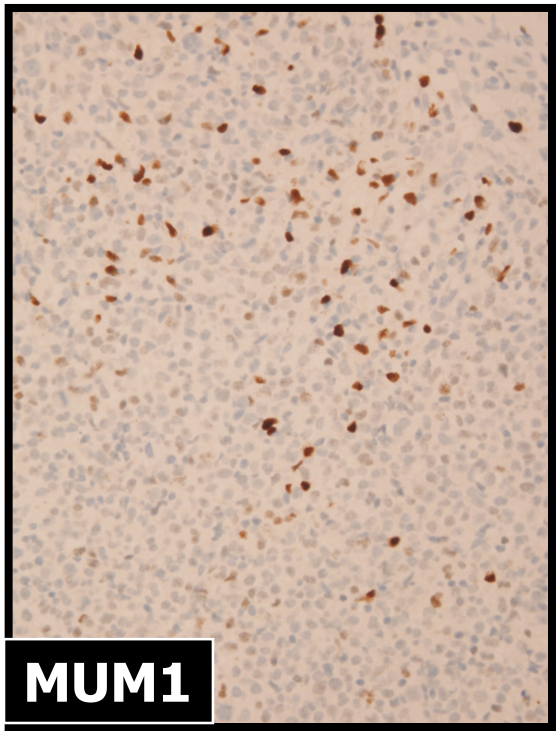


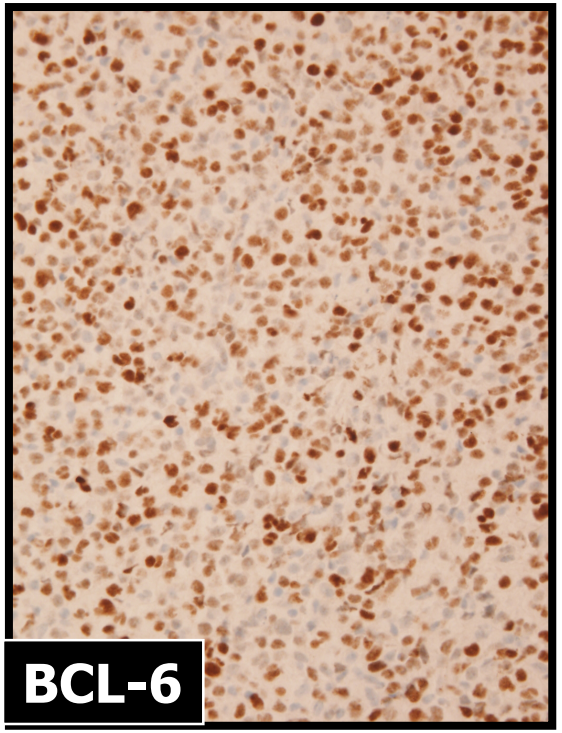
Case 4

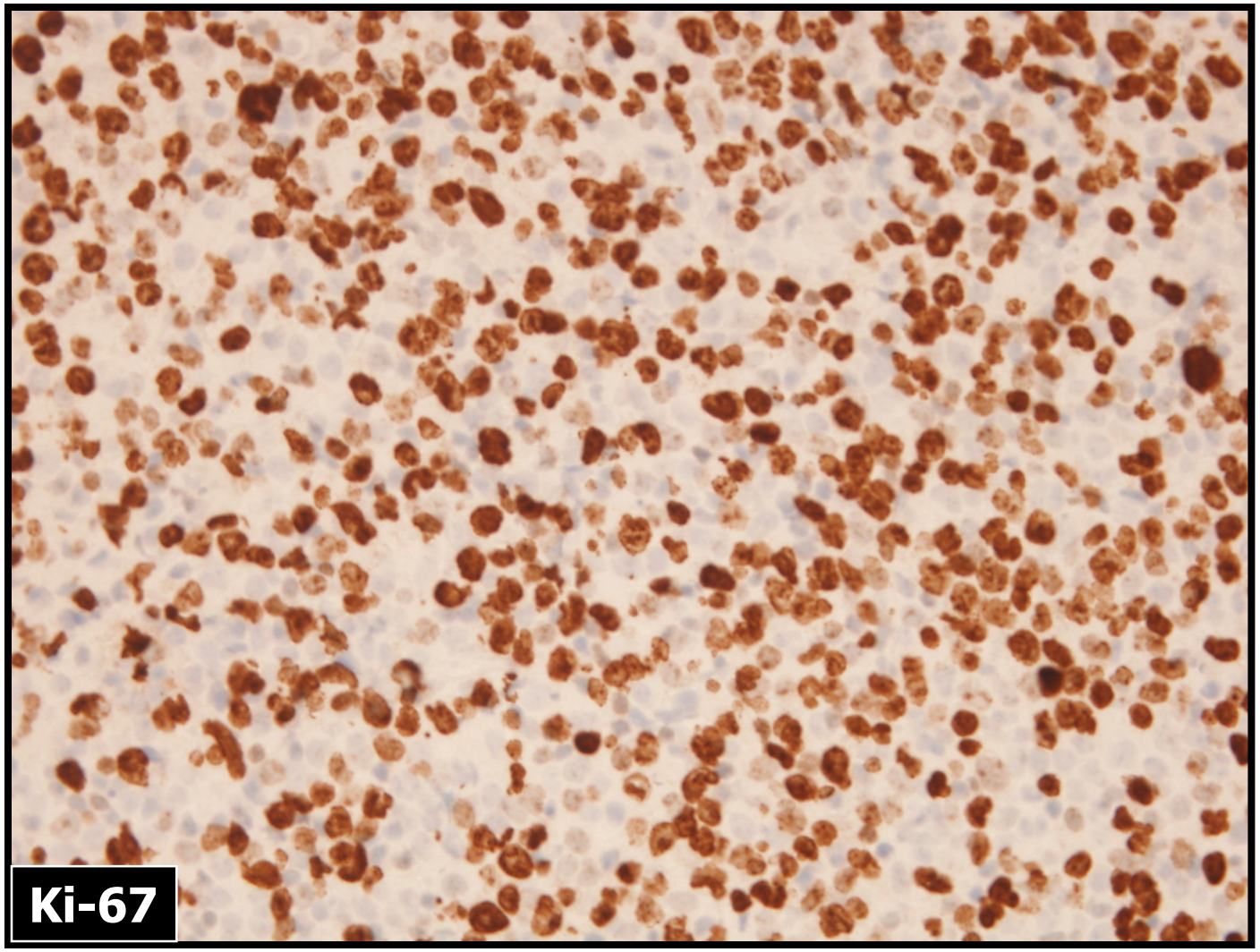




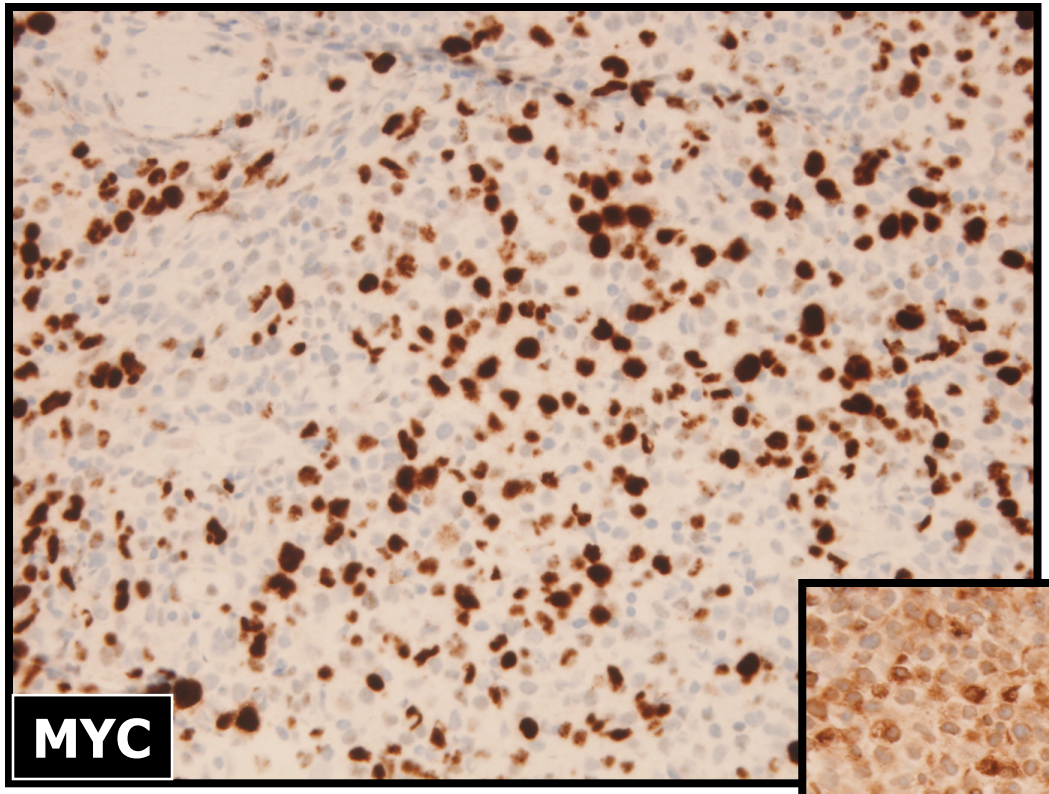


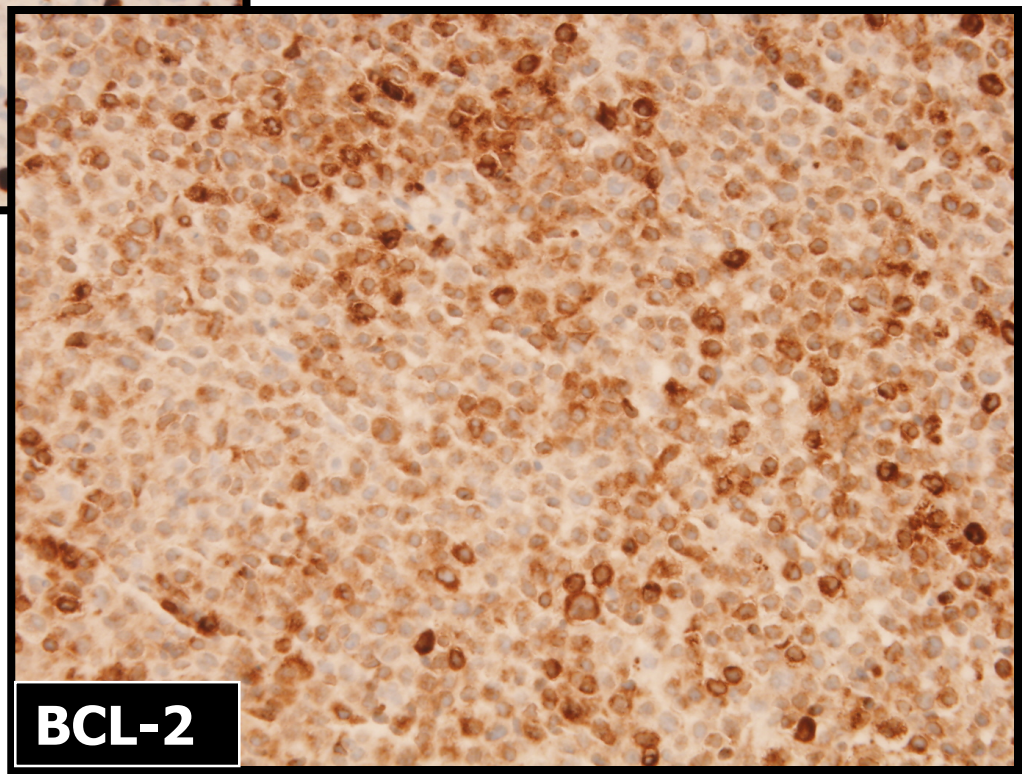





Ki-67

Case 4





DIAGNOSIS (CASE 4)

Diffuse large B-cell lymphoma

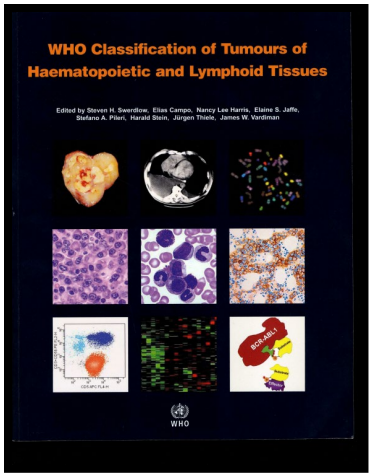
The neoplasm also has:

Germinal center B-cell immunophenotype
Double expressor immunophenotype
Ki-67 ~70%
***MYC* not rearranged**
***BCL6* rearranged**
***BCL2* not rearranged**

Diffuse Large B-cell Lymphoma

Definition

DLBCL is a neoplasm with a diffuse growth pattern composed of medium or large B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei, or more than twice the size of normal lymphocyte nuclei



2017 WHO book, p. 291

WHO Classification of Diffuse Large B-cell Lymphoma (2017)

Diffuse large B-cell lymphoma, NOS

GCB versus ABC/non-GCB

CD5

Other lymphomas of large B-cells

T-cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of the central nervous system

Primary cutaneous DLBCL, leg-type

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

DLBCL associated with chronic inflammation

Lymphomatoid granulomatosis

EBV+ diffuse large B-cell lymphoma

ALK+ large B-cell lymphoma

Plasmablastic lymphoma

HHV8+ lymphoproliferative disorders

Primary effusion lymphoma

Borderline cases

High-grade B-cell lymphoma (NOS versus double hit)

B-cell lymphoma, unclassifiable, intermediate between DLBCL & CHL

Diffuse Large B-cell Lymphoma
R-CHOP is Standard Frontline Therapy

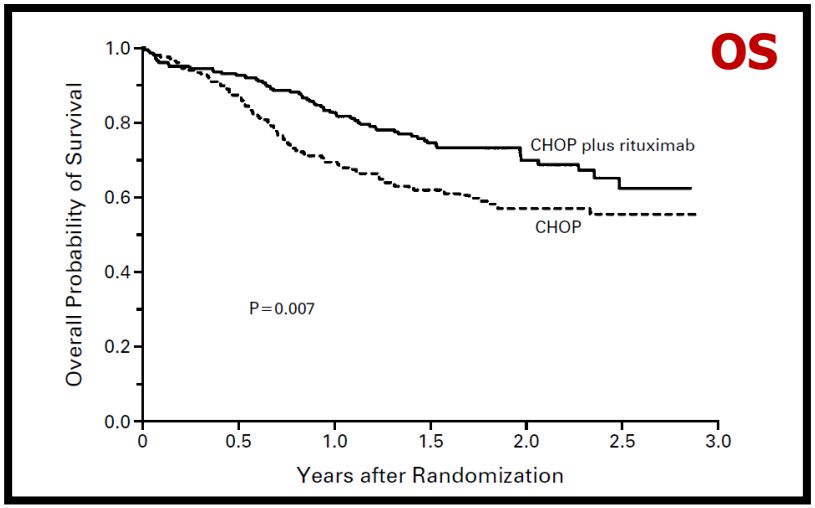
Rituximab
Cyclophosphamide
Hydroxydaunorubicin/Adriamycin
Oncovin/vincristine
Prednisone

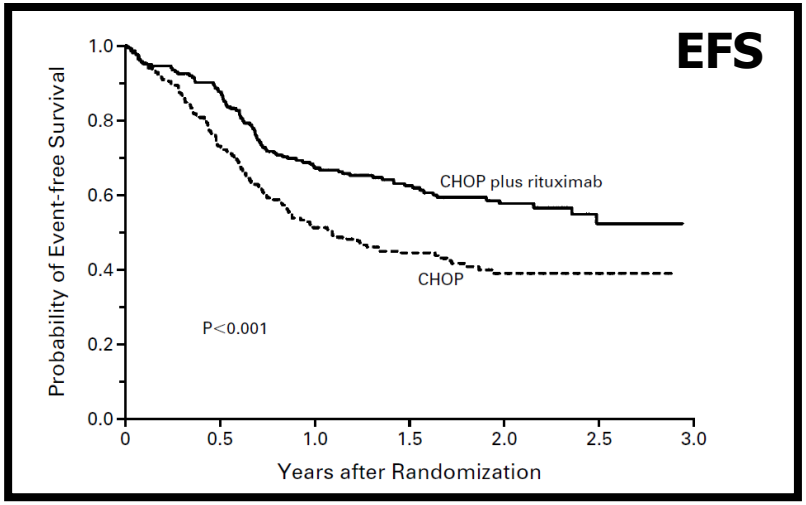
Bertrand Coiffier, MD

CHOP CHEMOTHERAPY PLUS RITUXIMAB COMPARED WITH CHOP ALONE IN ELDERLY PATIENTS WITH DIFFUSE LARGE-B-CELL LYMPHOMA

BERTRAND COIFFIER, M.D., ERIC LEPAGE, M.D., PH.D., JOSETTE BRIÈRE, M.D., RAOUL HERBRECHT, M.D., HERVÉ TILLY, M.D., REDA BOUABDALLAH, M.D., PIERRE MOREL, M.D., ERIC VAN DEN NESTE, M.D., GILLES SALLES, M.D., PH.D., PHILIPPE GAULARD, M.D., FELIX REYES, M.D., AND CHRISTIAN GISSELBRECHT, M.D.

N Engl J Med 346: 235, 2002





Diffuse Large B-cell Lymphoma NOS

Clinical Findings

Median age	64 y (wide range)
Male	55%
Stage I-II	54%
III-IV	46%
B symptoms	33%
BM involved	16%
IPI 0-1	35%
2-3	46%
4-5	19%

Nebraska NHL Classification Project

Diffuse Large B-cell Lymphoma
International Prognostic Index

Age	≤ 60 vs. >60 years
Performance status	0-1 vs. 2-4
LDH	Normal vs elevated
Extranodal sites	≤ 1 vs >1 site
Stage	I-II vs III-IV

N Engl J Med 329: 987, 1993

An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era

Zheng Zhou,[1] Laurie H. Sehn,[2] Alfred W. Rademaker,[1] Leo I. Gordon,[1] Ann S. LaCasce,[3] Allison Crosby-Thompson,[3] Ann Vanderplas,[4] Andrew D. Zelenetz,[5] Gregory A. Abel,[3] Maria A. Rodriguez,[6] Auayporn Nademanee,[7] Mark S. Kaminski,[8] Myron S. Czuczman,[9] Michael Millenson,[10] Joyce Niland,[4] Randy D. Gascoyne,[2] Joseph M. Connors,[2] Jonathan W. Friedberg,[11] and Jane N. Winter[1]

Table 3. The NCCN-IPI

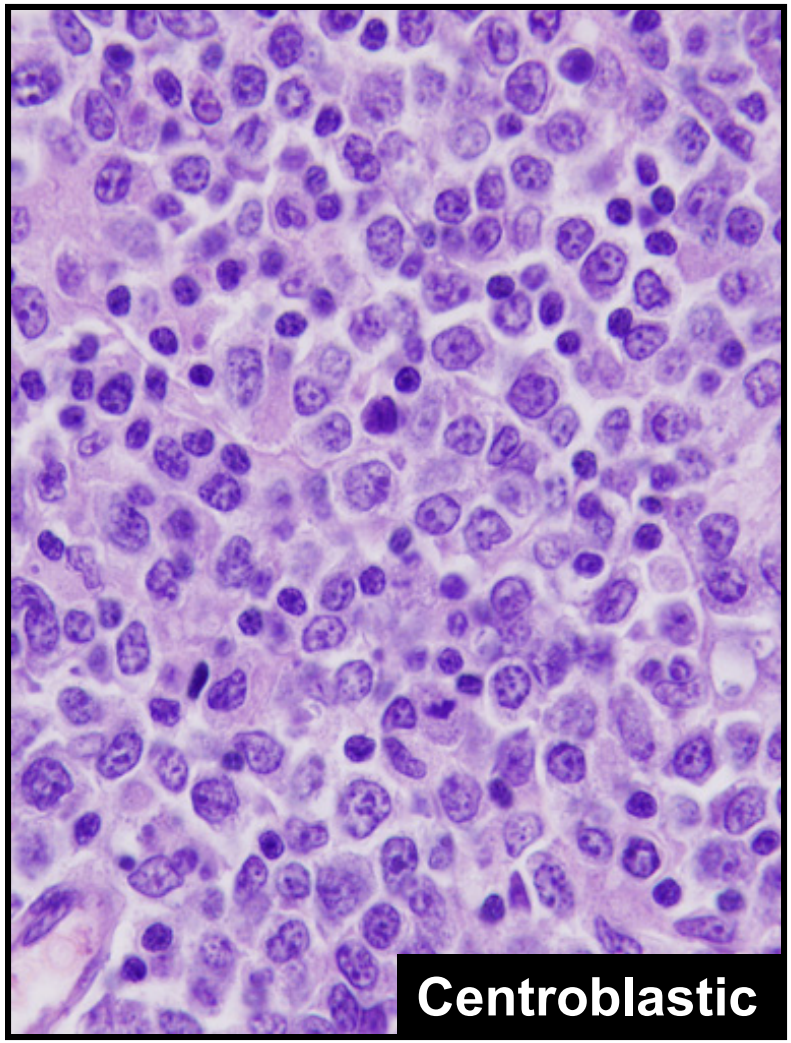
NCCN-IPI	Score
Age, y	
>40 to ≤60	1
>60 to ≤75	2
>75	3
LDH, normalized	
>1 to ≤3	1
>3	2
Ann Arbor stage III-IV	1
Extranodal disease*	1
Performance status ≥2	1

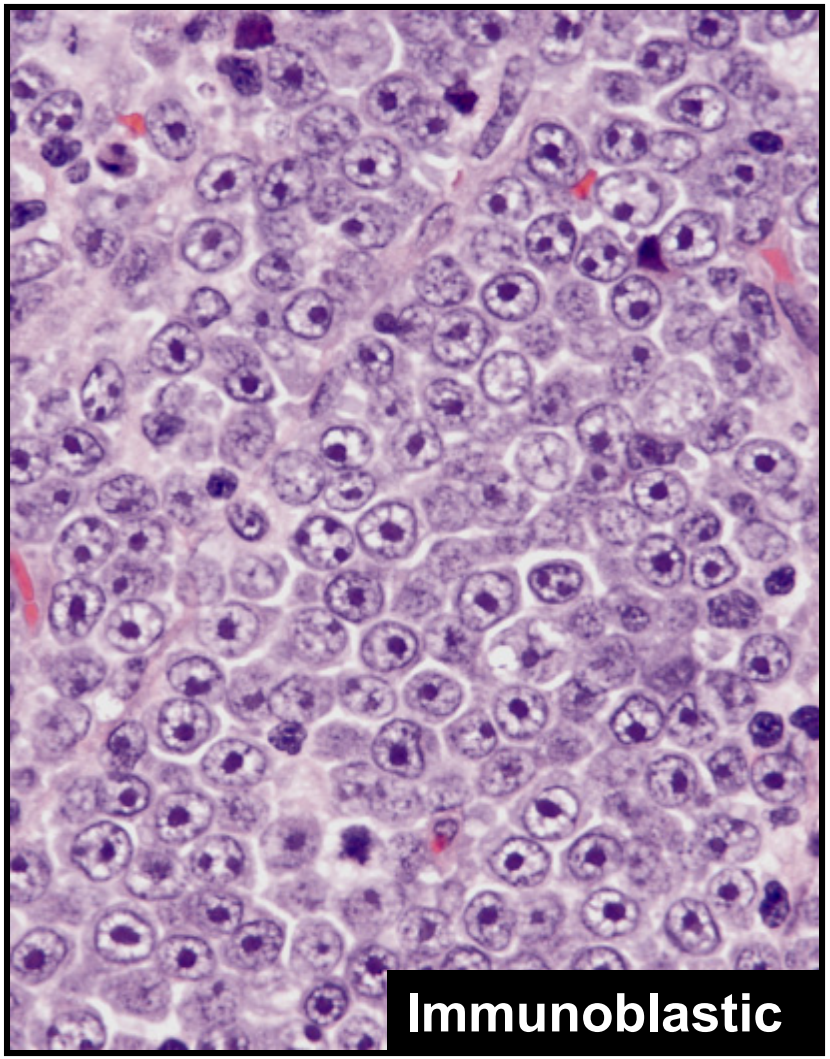
*Disease in bone marrow, CNS, liver/GI tract, or lung.

Blood 123: 837, 2014

Diffuse Large B-cell Lymphoma NOS

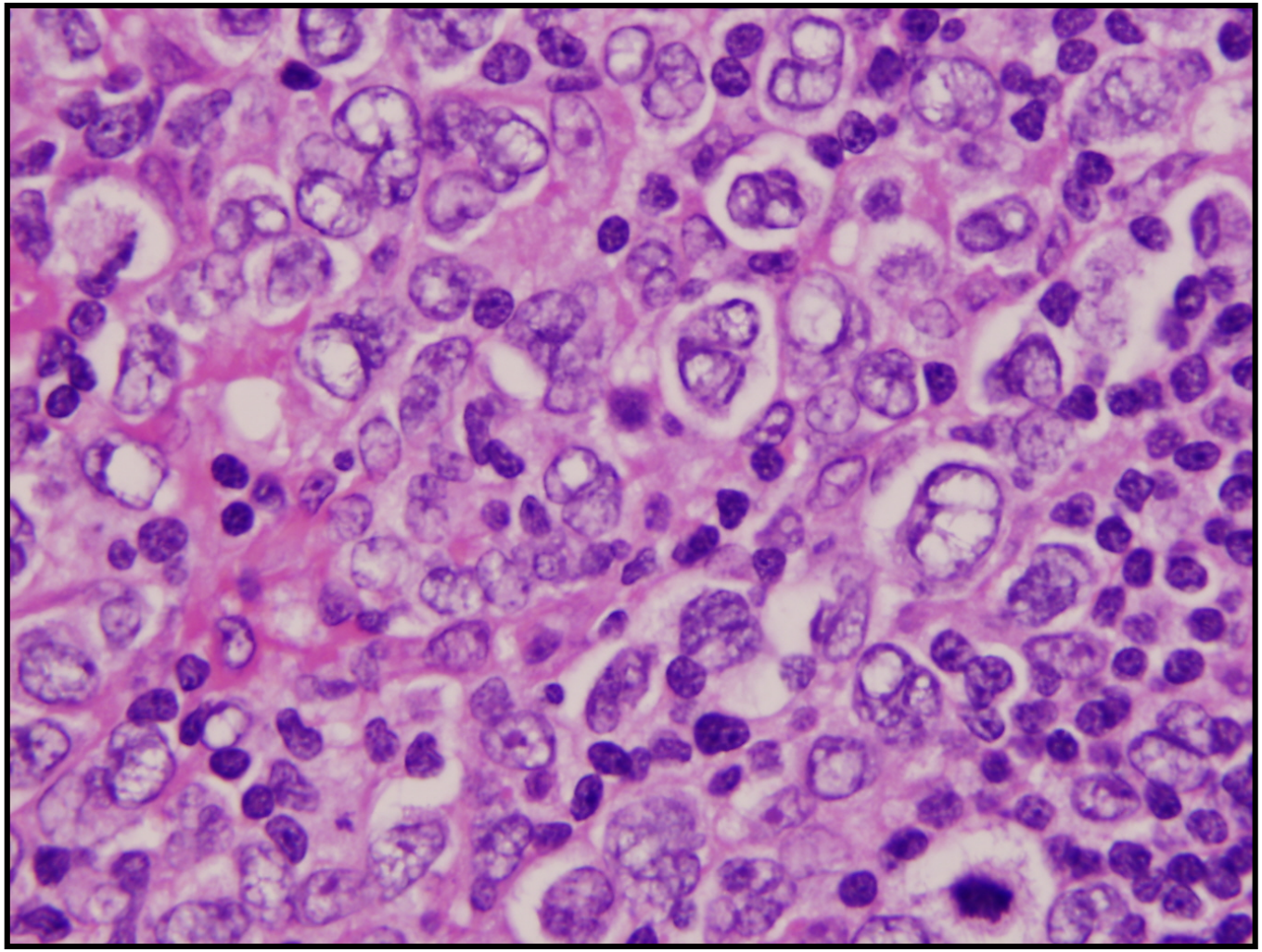
Morphologic Variants





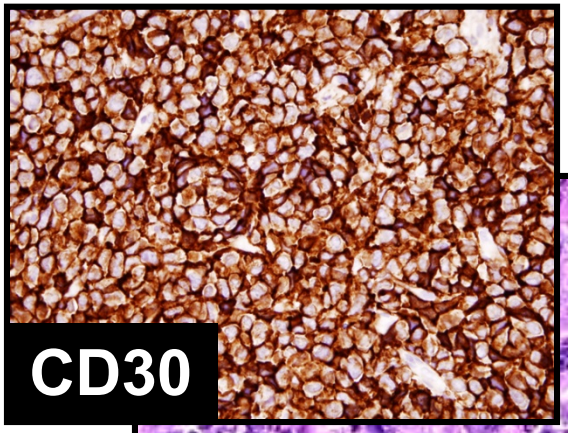
Diffuse Large B-cell Lymphoma NOS

Multilobated Variant

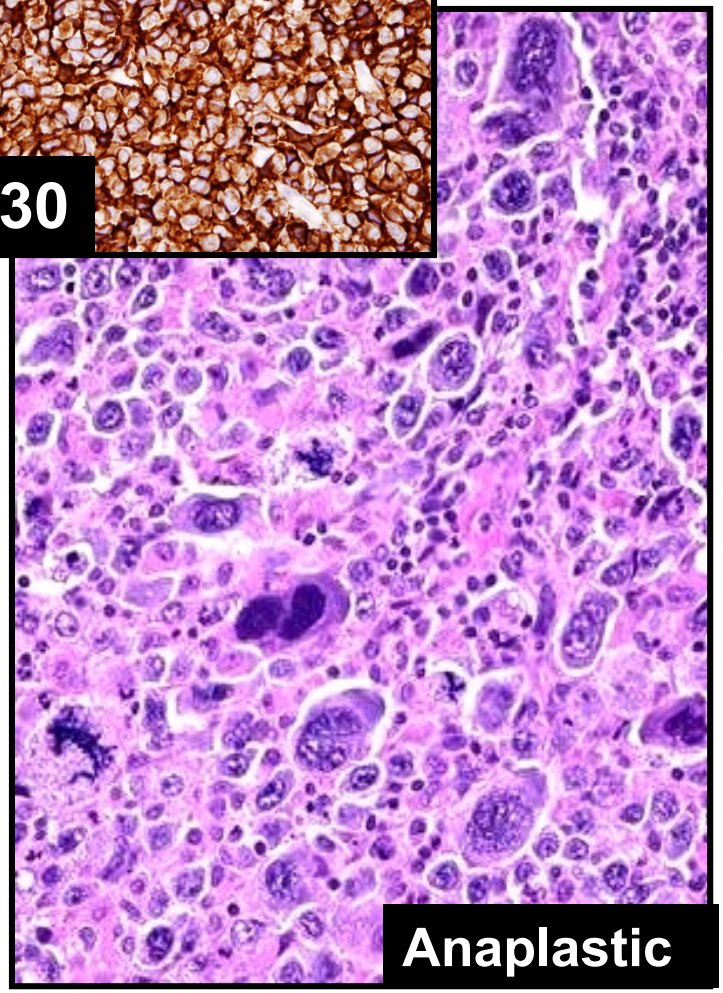


Diffuse Large B-cell Lymphoma NOS

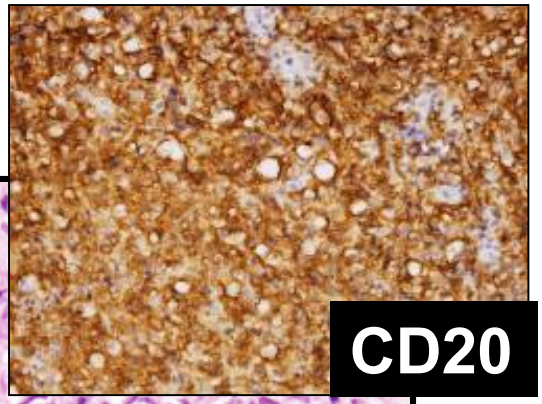
Morphologic Variants



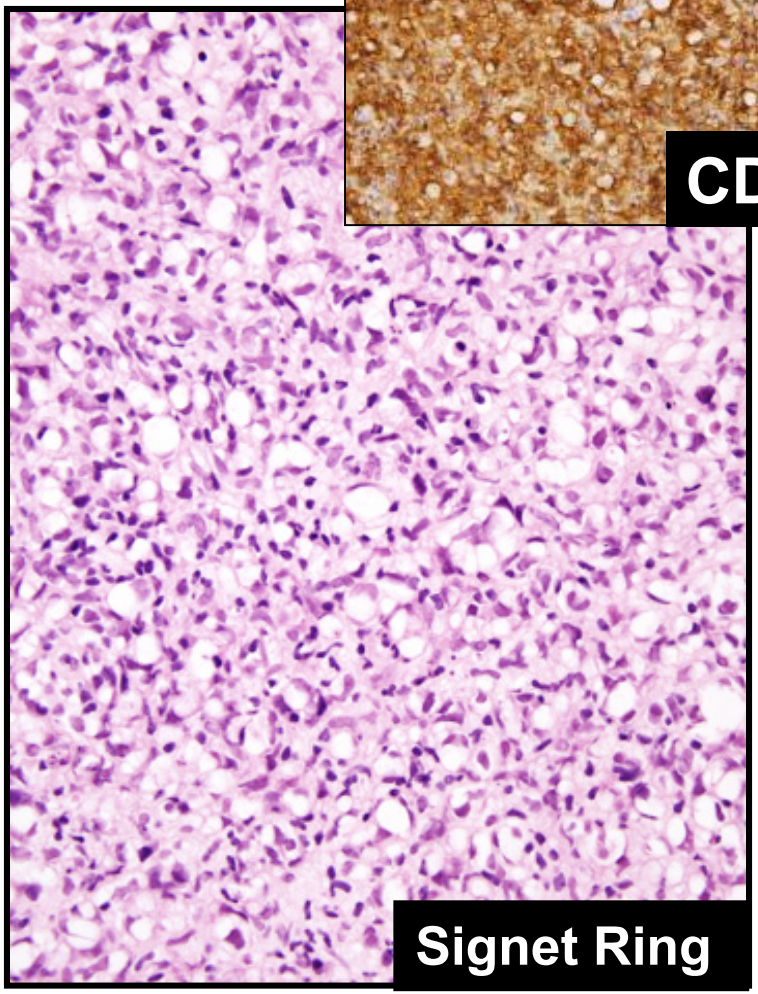
CD30



Anaplastic



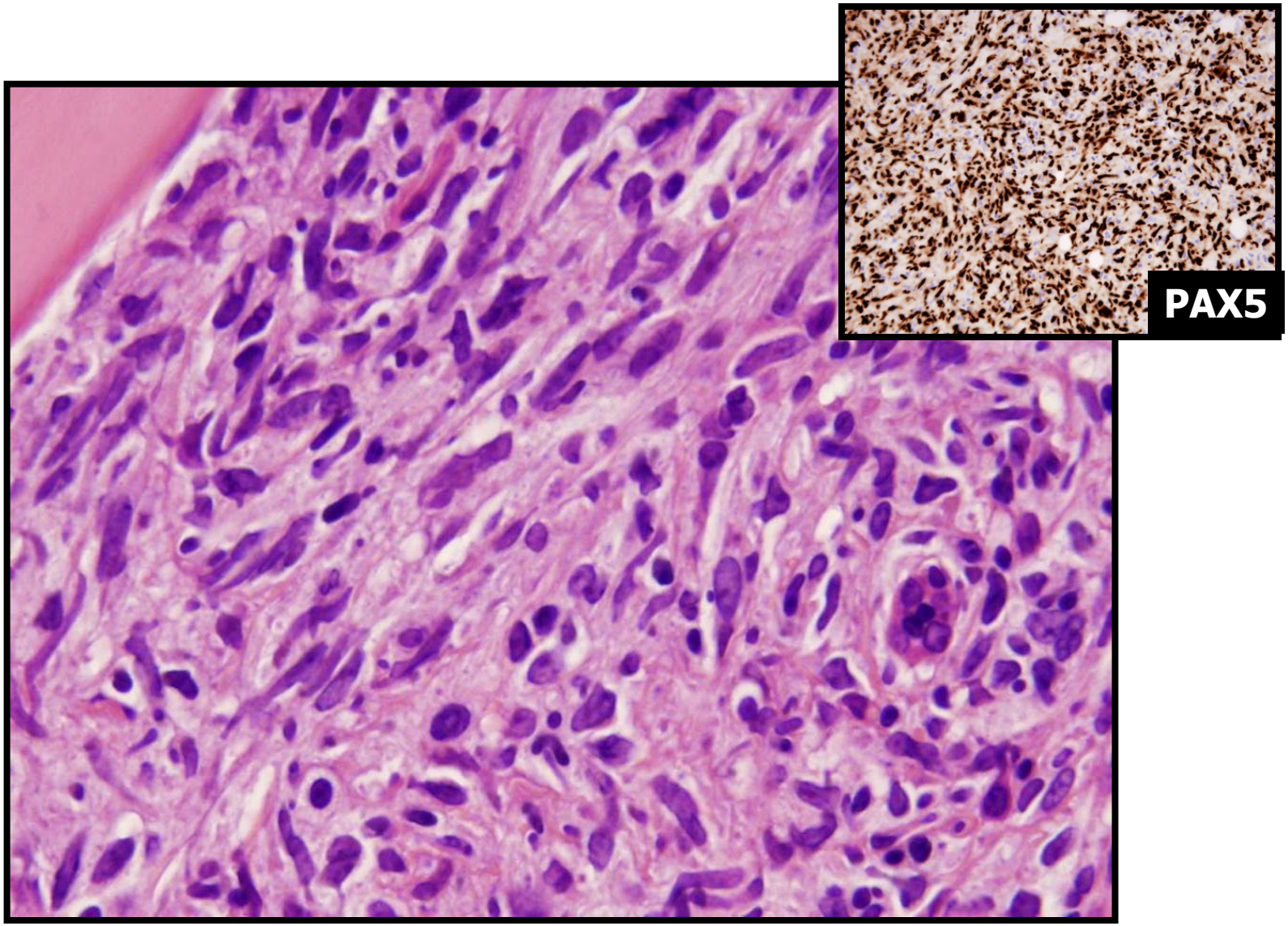
CD20



Signet Ring

Diffuse Large B-cell Lymphoma NOS

Spindle Cell Variant



Diffuse Large B-cell Lymphoma NOS

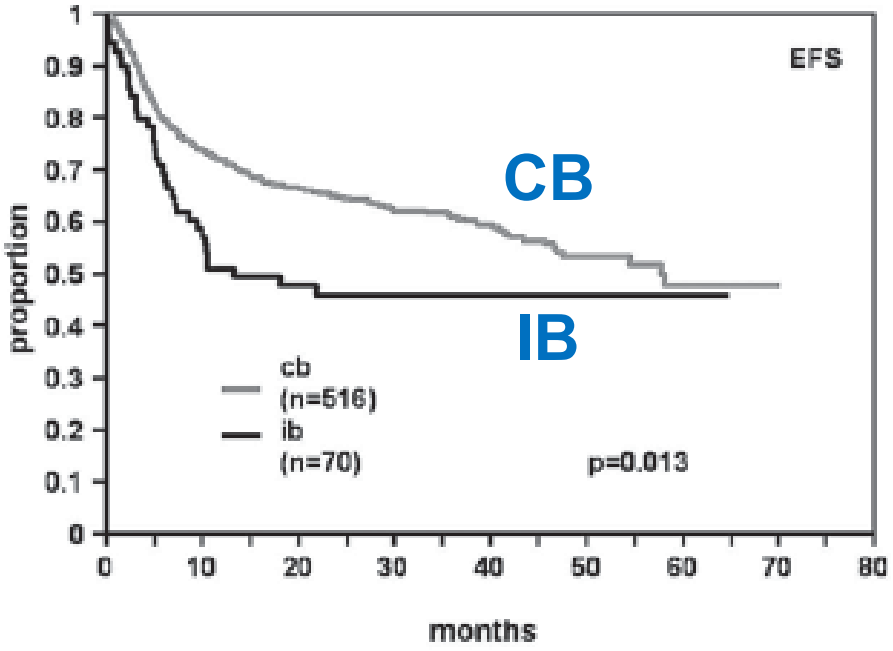
Morphologic Variants

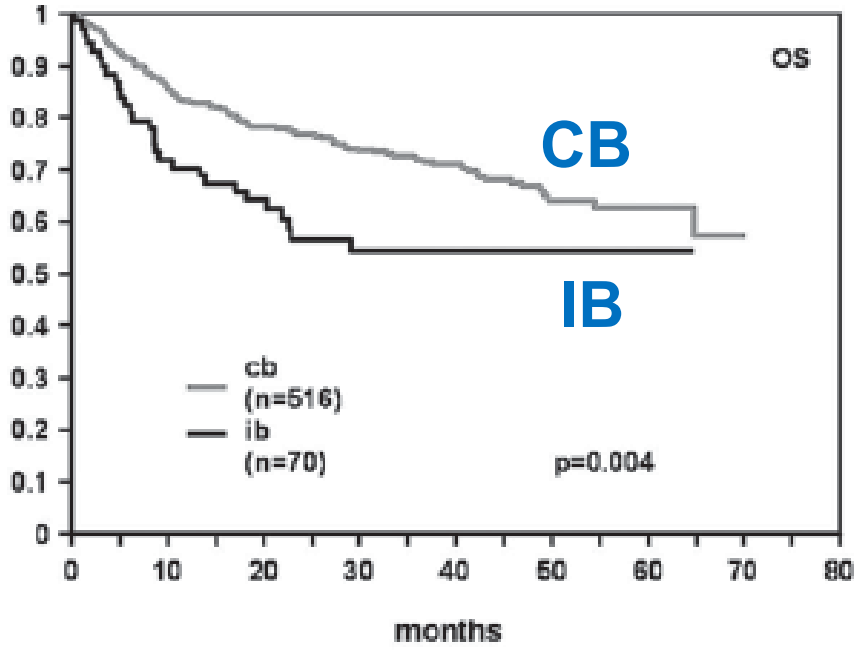
Common	Rare
Centroblastic (~80%)	Sinusoidal
Immunoblastic (~10%)	Spindled
Multilobated (<5%)	Myxoid
Anaplastic (<5%)	Signet Ring
	Rosettes

Does morphology correlate with prognosis ?

Immunoblastic morphology but not the immunohistochemical GCB/nonGCB classifier predicts outcome in diffuse large B-cell lymphoma in the RICOVER-60 trial of the DSHNHL

German Ott,[1,2] Marita Ziepert,[3] Wolfram Klapper,[4] Heike Horn,[2] Monika Szczepanowski,[4] Heinz-Wolfram Bernd,[5] Christoph Thorns,[5] Alfred C. Feller,[5] Dido Lenze,[6] Michael Hummel,[6] Harald Stein,[6] Hans-Konrad Müller-Hermelink,[1] Matthias Frank,[7] Martin-Leo Hansmann,[7] Thomas F. E. Barth,[8] Peter Möller,[8] Sergio Cogliatti,[9] Michael Pfreundschuh,[10] Norbert Schmitz,[11] Lorenz Trümper,[12] Markus Loeffler,[3] and Andreas Rosenwald[1]





Blood 116: 4916, 2010

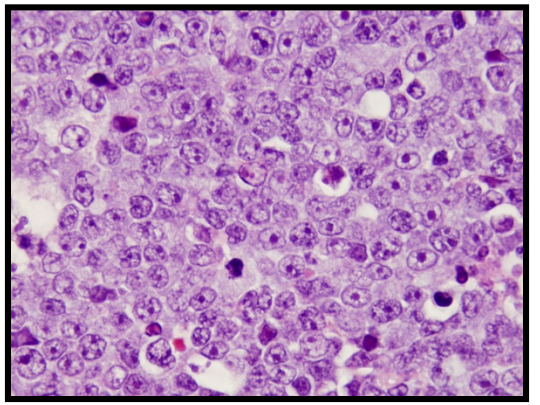
Diffuse Large B-cell Lymphomas of Immunoblastic Type Are a Major Reservoir for *MYC-IGH* Translocations

Heike Horn, PhD, Annette M. Staiger, MSc,* Matthias Vöhringer, MD,† Ulrich Hay, MD,‡ Elias Campo, MD,§ Andreas Rosenwald, MD,‖ German Ott, MD,* and M. Michaela Ott, MD¶*

The authors assessed 107 DLBCL using FISH with MYC breakapart and *MYC-IGH* fusion probes

***MYC* translocations detected in**

13 / 39 (33%) immunoblastic
5 / 68 (7%) centroblastic



All immunoblastic DLBCL with *MYC* translocations had *MYC-IGH* fusions

Am J Surg Pathol 39: 61, 2015

Immunophenotyping of DLBCL
What Is The Purpose ?

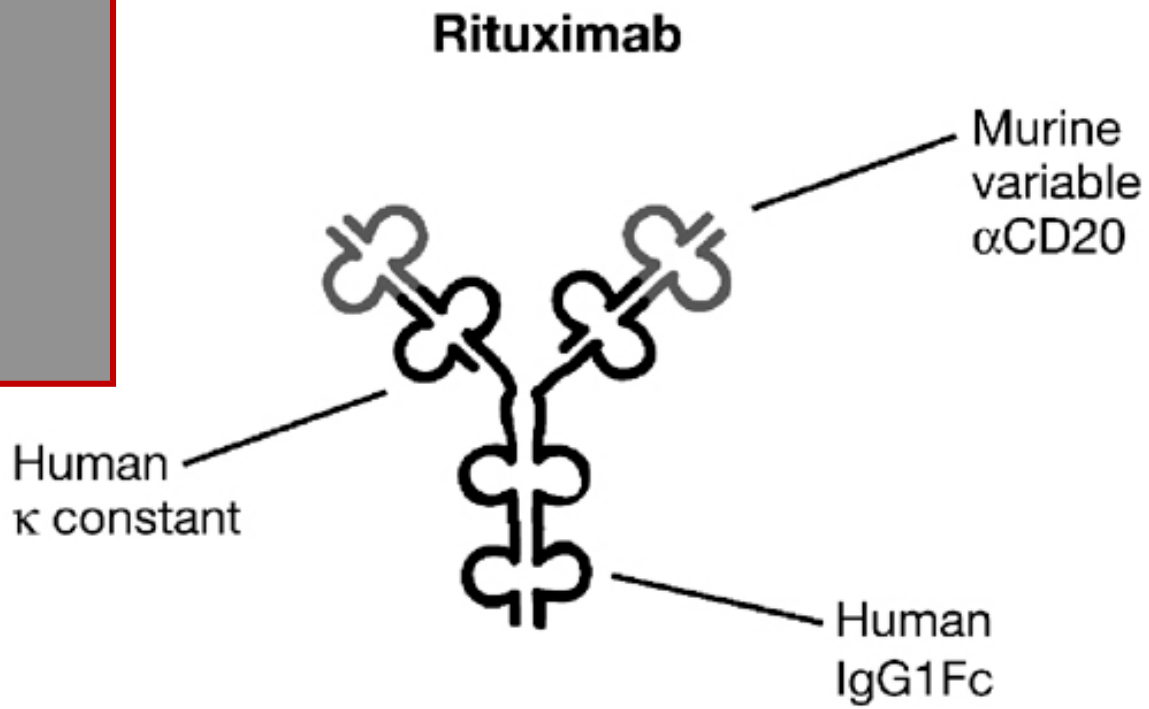
In the past

- Diagnosis

Currently

- Diagnosis
- Prognosis
- Identifying targets for therapy

Monoclonal Antibodies are Being Added to Standard Therapy



CD20 is used for diagnosis and is a therapeutic target

Potential Targets Assessable by IHC

Target	Drug	Pathway
CD19	Tafasitamab	B-cell receptor signaling
CD30	Brentuximab vedotin	NF-κB
CD38	Daratumumab	Cell migration, adhesion, signaling
CD79A	Polatuzumab vedotin	B-cell receptor signaling
BTK	Ibrutinib	B-cell receptor signaling
XPO1	Selinexor	Selective inhibitor of nuclear export
BRAF, MEK	Vemurafinib, cobimetinib	MAP kinase
BCL-2	Venetoclax	Apoptosis
PD-L1/L2	Nivolumab, others	Checkpoint inhibitors

Common Translocations in DLBCL

t(3;14)(q27;q32); ***BCL6::IGH*** **~25%**

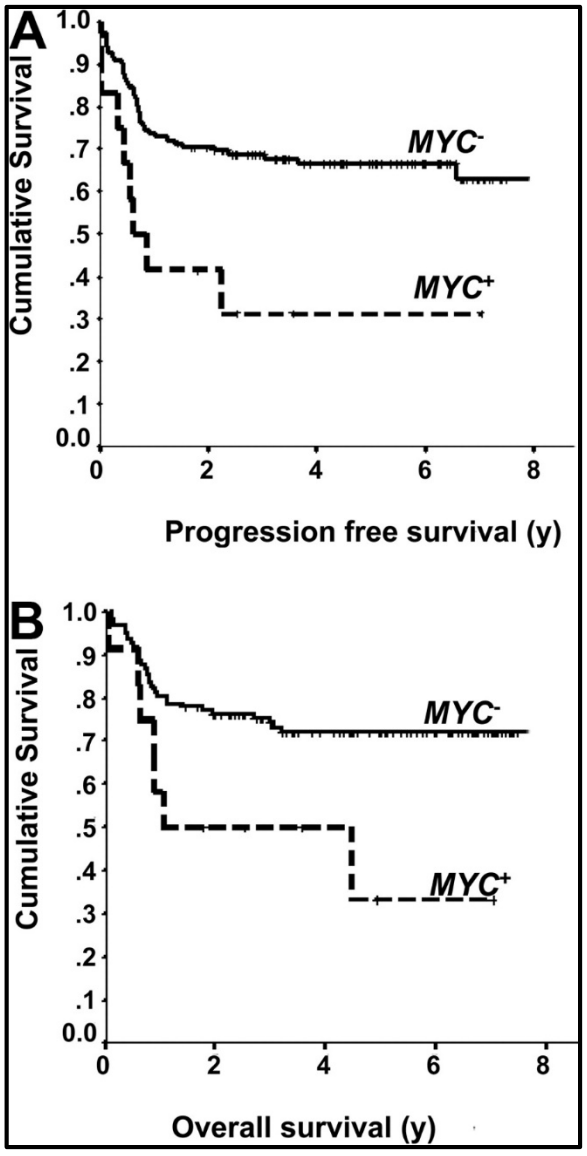
BCL6 also partners with other genes

t(14;18)(q32;q21); ***IGH::BCL2*** **~20%**

t(8;14)(q24;q32); ***MYC::IGH*** **~10%**

MYC also partners with other genes

MYC Rearrangment is Prognostic in DLBCL



t(8;14)(q24;q32) - *IGH* (80%)
t(8;22)(q24;q11) - *IGλ* (15%)
t(2;8)(p11;q24) - *IGκ* (5%)

Diagnostic tests

Conventional cytogenetics

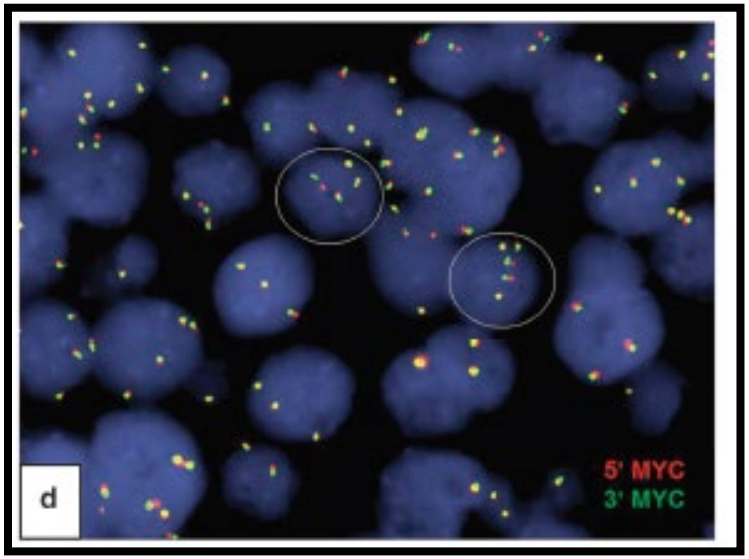
- **Need viable cells**

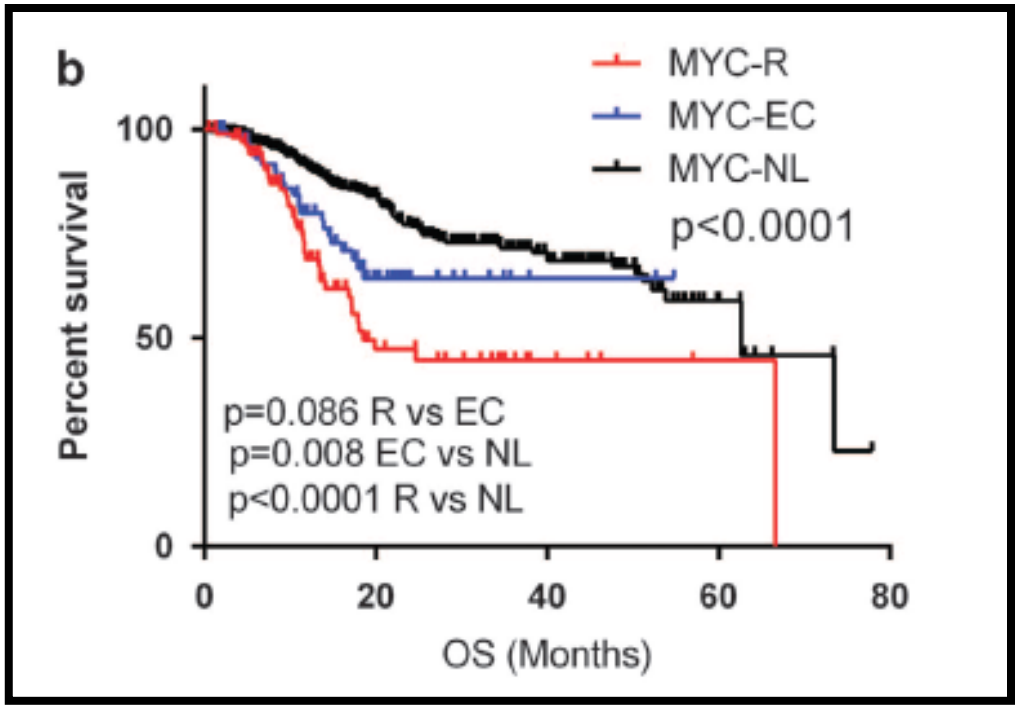
FISH

- ***IGH* and *MYC* probes**
- ***MYC* breakapart probe**

Blood 114:3533, 2009

MYC Extra Copies by FISH Predict Poorer Prognosis in DLBCL





Andres Quesada, MD

Increased *MYC* copy number is an independent prognostic factor in patients with diffuse large B-cell lymphoma

Andrés E Quesada[1], L Jeffrey Medeiros[1], Parth A Desai[1], Pei Lin[1], Jason R Westin[2], Huda M Hawsawi[1], Peng Wei[3], Guilin Tang[1], Adam C Seegmiller[4], Nishitha M Reddy[5], C Cameron Yin[1], Wei Wang[1], Jie Xu[1], Roberto N Miranda[1], Zhuang Zuo[1] and Shaoying Li[1]

Mod Pathol 30: 1688, 2017

Diffuse Large B-cell Lymphoma

Gene Expression Profiling Using DNA Microarrays

Ash Alizadeh, MD, PhD

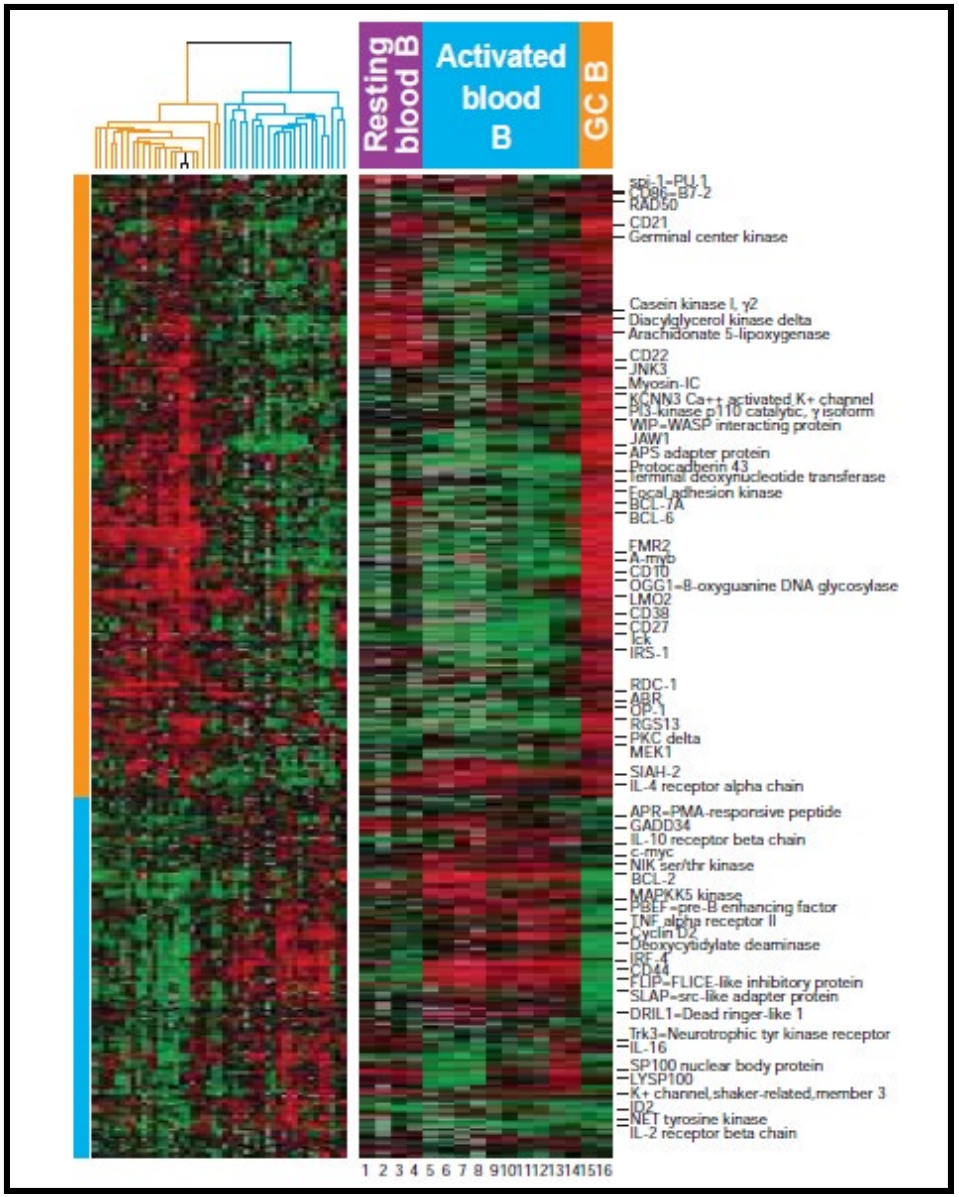
Lymphochip with 17,856 cDNA clones	
12,069	Germinal center B-cell genes
2,338	B-cell NHL genes
3,186	Activated lymphocyte genes

Louis Staudt, MD, PhD

Nature 403: 503, 2000

Diffuse Large B-cell Lymphoma

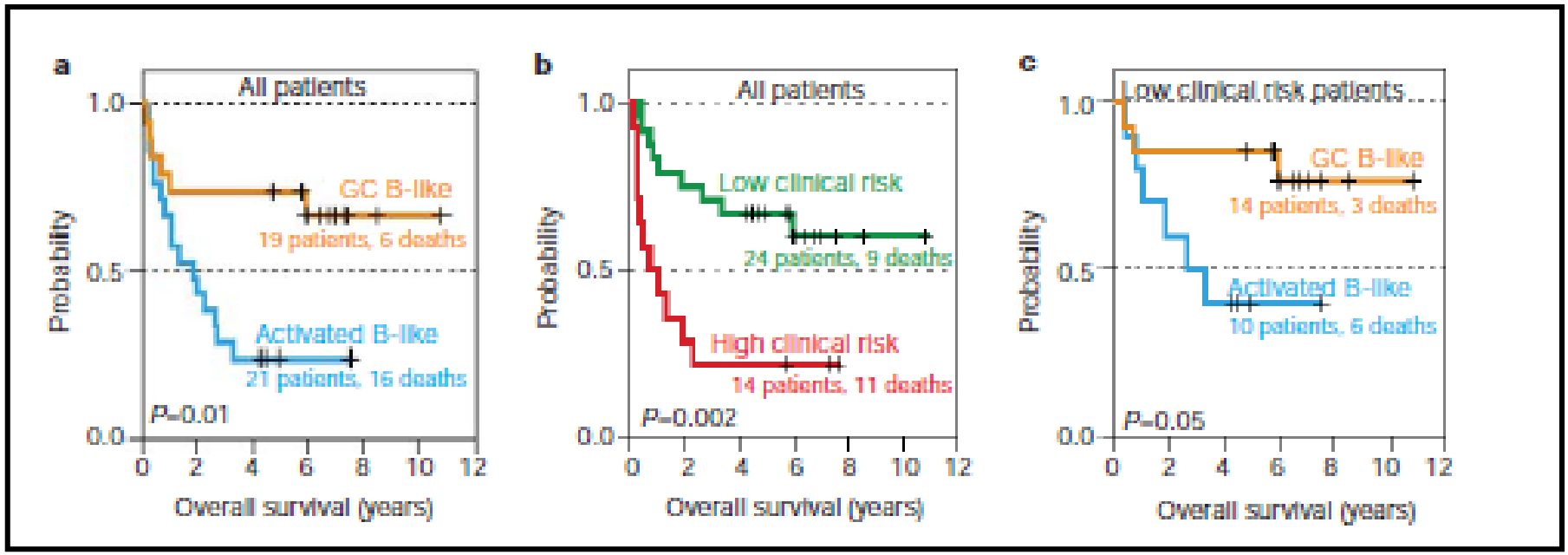
GCB
ABC



Nature 403: 503, 2000

Diffuse Large B-cell Lymphoma

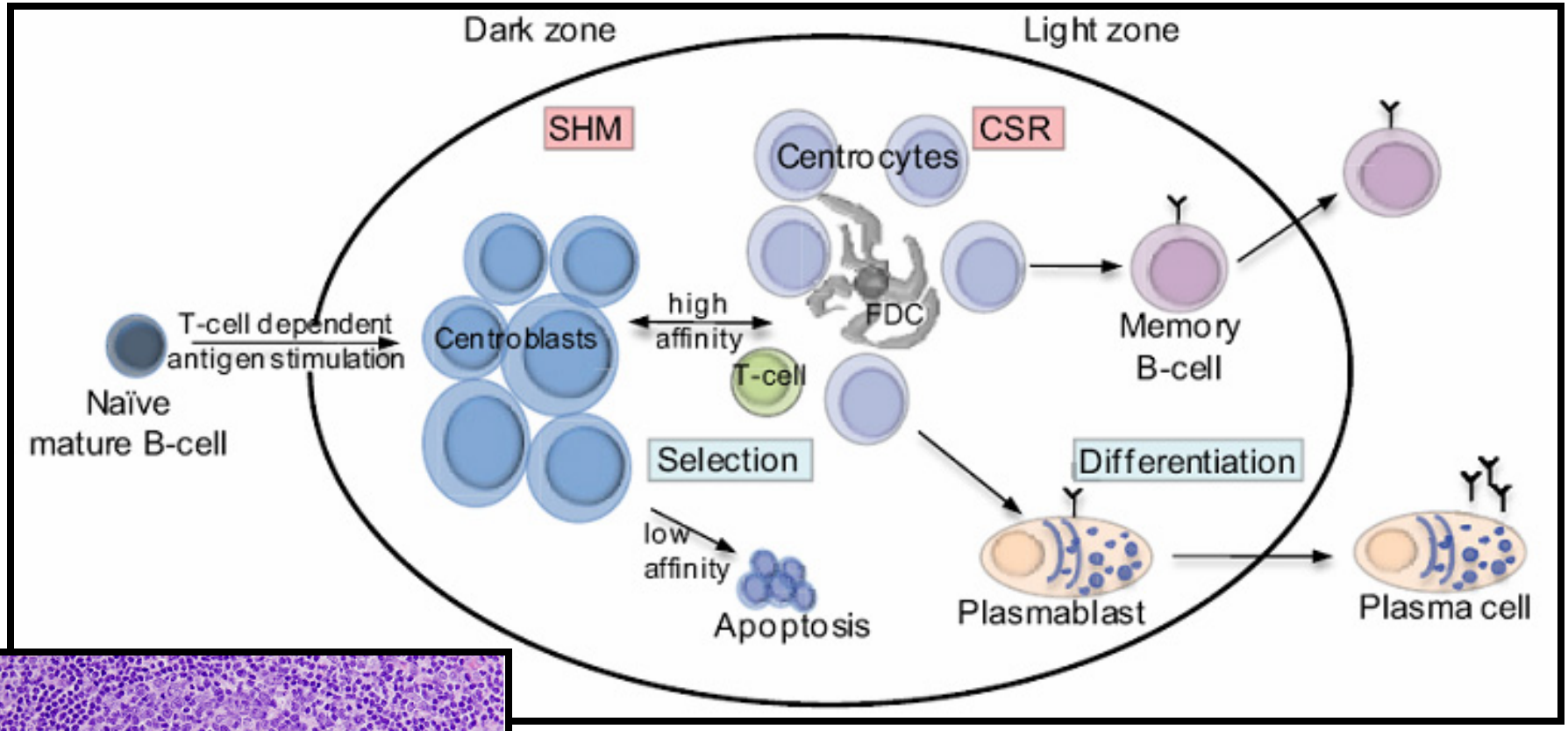
GEP Shows 2 Types that Predict Prognosis

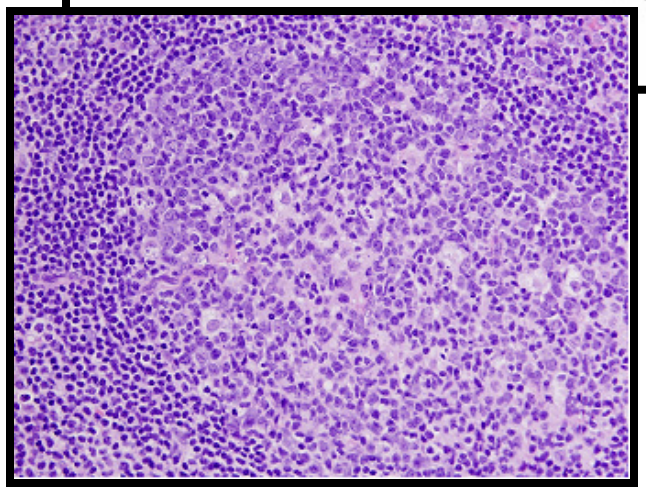


CHOP Therapy

Nature 403: 503, 2000

Germinal Center Reaction

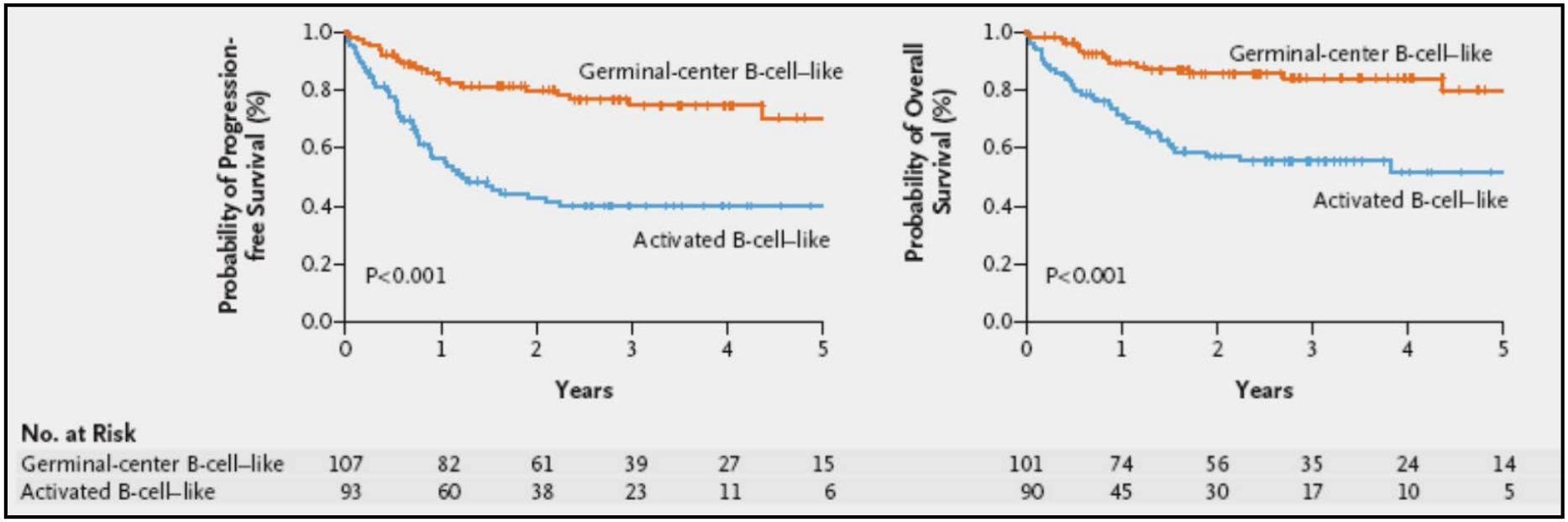




Sem Diagn Pathol 28: 167, 2011

Diffuse Large B-cell Lymphoma

GEP is Valid for R-CHOP Treated Patients



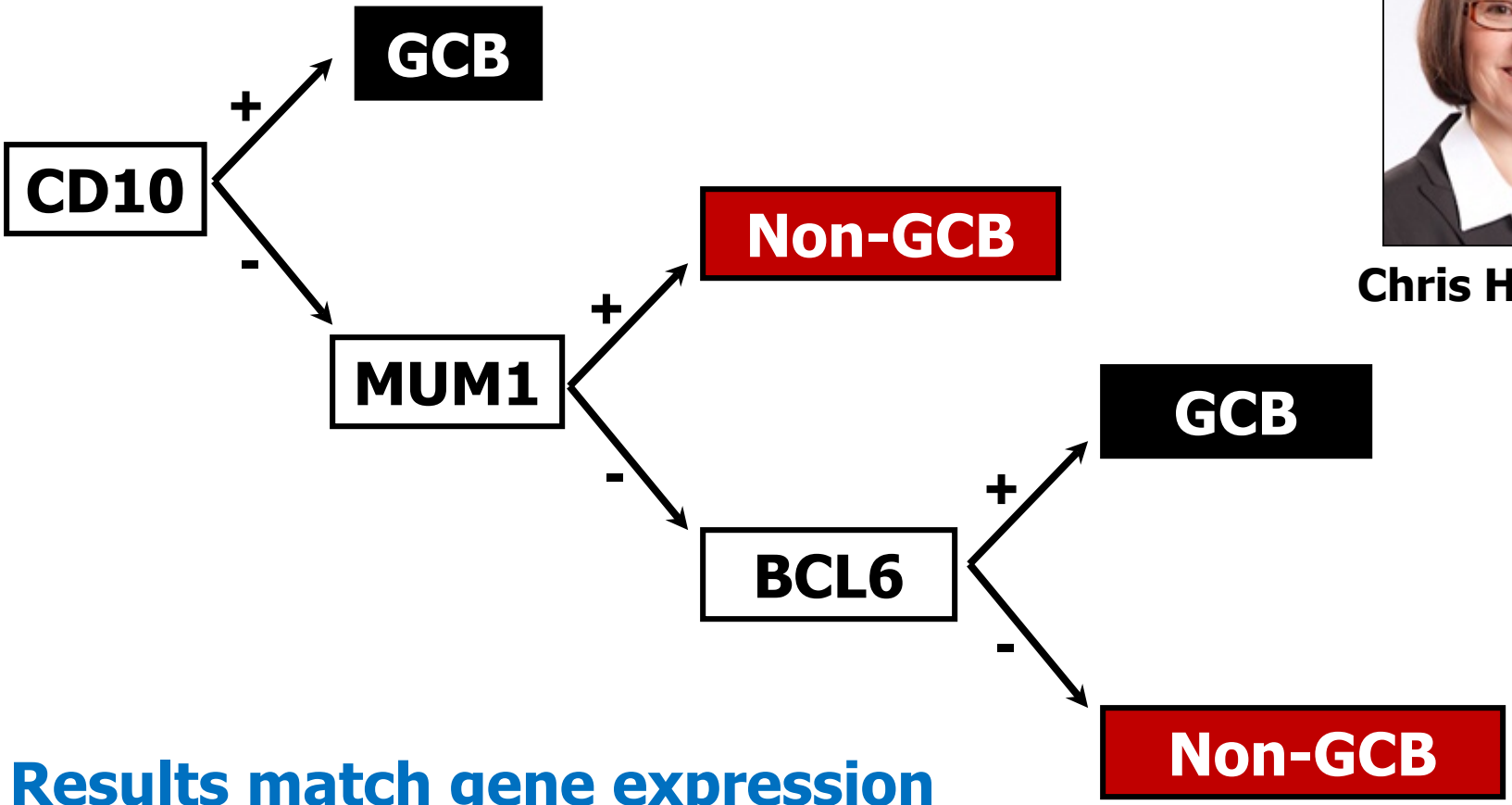
No. at Risk

Germinal-center B-cell–like	107	82	61	39	27	15	101	74	56	35	24	14
Activated B-cell–like	93	60	38	23	11	6	90	45	30	17	10	5

N Engl J Med 359: 2317, 2008

Can Immunohistochemistry be used as a Surrogate for GEP in DLBCL?

Chris Hans, MD



Results match gene expression profile in ~80% of cases

Blood 106: 275, 2004

VOLUME 35 · NUMBER 22 · AUGUST 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

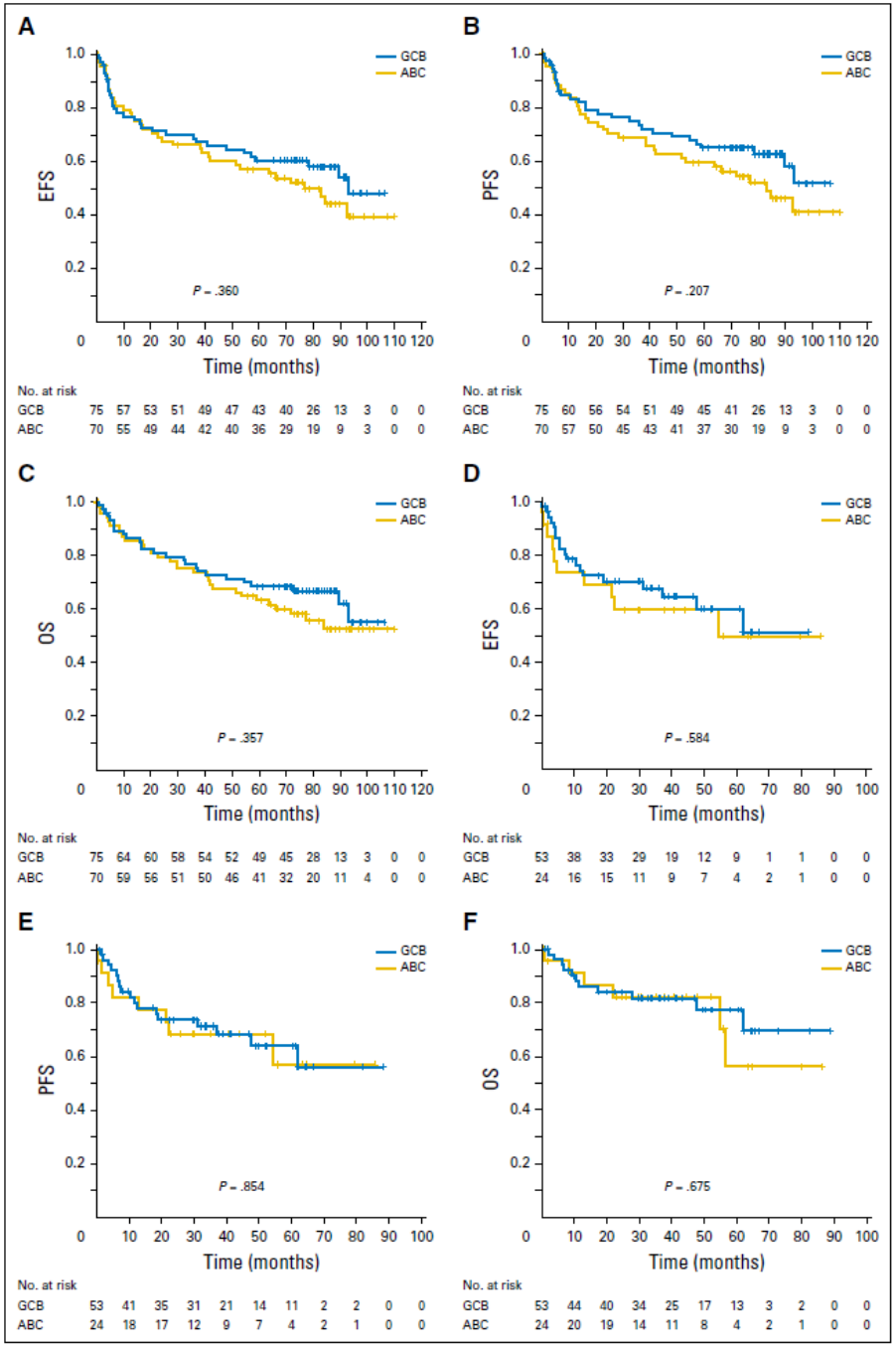
ORIGINAL REPORT

Clinical Impact of the Cell-of-Origin Classification and the *MYC*/*BCL2* Dual Expresser Status in Diffuse Large B-Cell Lymphoma Treated Within Prospective Clinical Trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group

Annette M. Staiger, Marita Ziepert, Heike Horn, David W. Scott, Thomas F.E. Barth, Heinz-Wolfram Bernd, Alfred C. Feller, Wolfram Klapper, Monika Szczepanowski, Michael Hummel, Harald Stein, Dido Lenze, Martin-Leo Hansmann, Sylvia Hartmann, Peter Möller, Sergio Cogliatti, Georg Lenz, Lorenz Trümper, Markus Löffler, Norbert Schmitz, Michael Pfreundschuh, Andreas Rosenwald, and German Ott for the German High-Grade Lymphoma Study Group

A,C,E. RICOVER-60 trial
B,D,F. R-MegaCHOEP trial

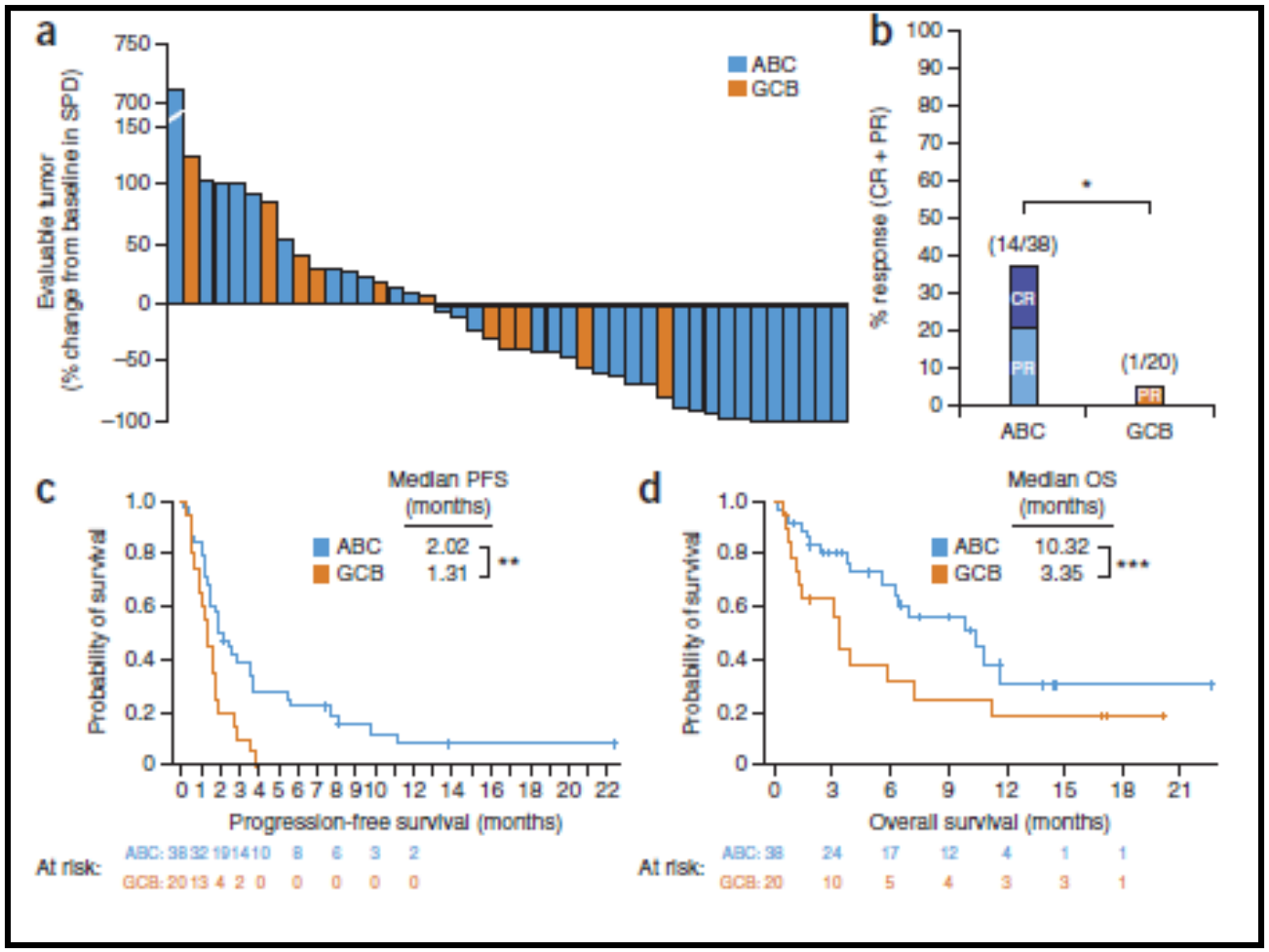
Cell-of-origin classification did not correlate with prognosis



J Clin Oncol 35:2515, 2017

R-CHOP+Ibrutinib for DLBCL

Impact of GCB versus ABC



Nat Med 21: 922, 2015

Mutations in Pathways Involved in DLBCL

B-cell receptor signaling

CD79A, CD79B, CARD11

Toll-like receptor signaling

NF-κB

MYD88

Lymphocyte differentiation

TNFAIP3/A20, TRAF3, BIRC3, IKKβ

DNA repair and transcriptional regulation

p53

Lymphocyte activation

STAT6, BCL10

DNA methylation

EZH2, MLL2

DNA acetylation

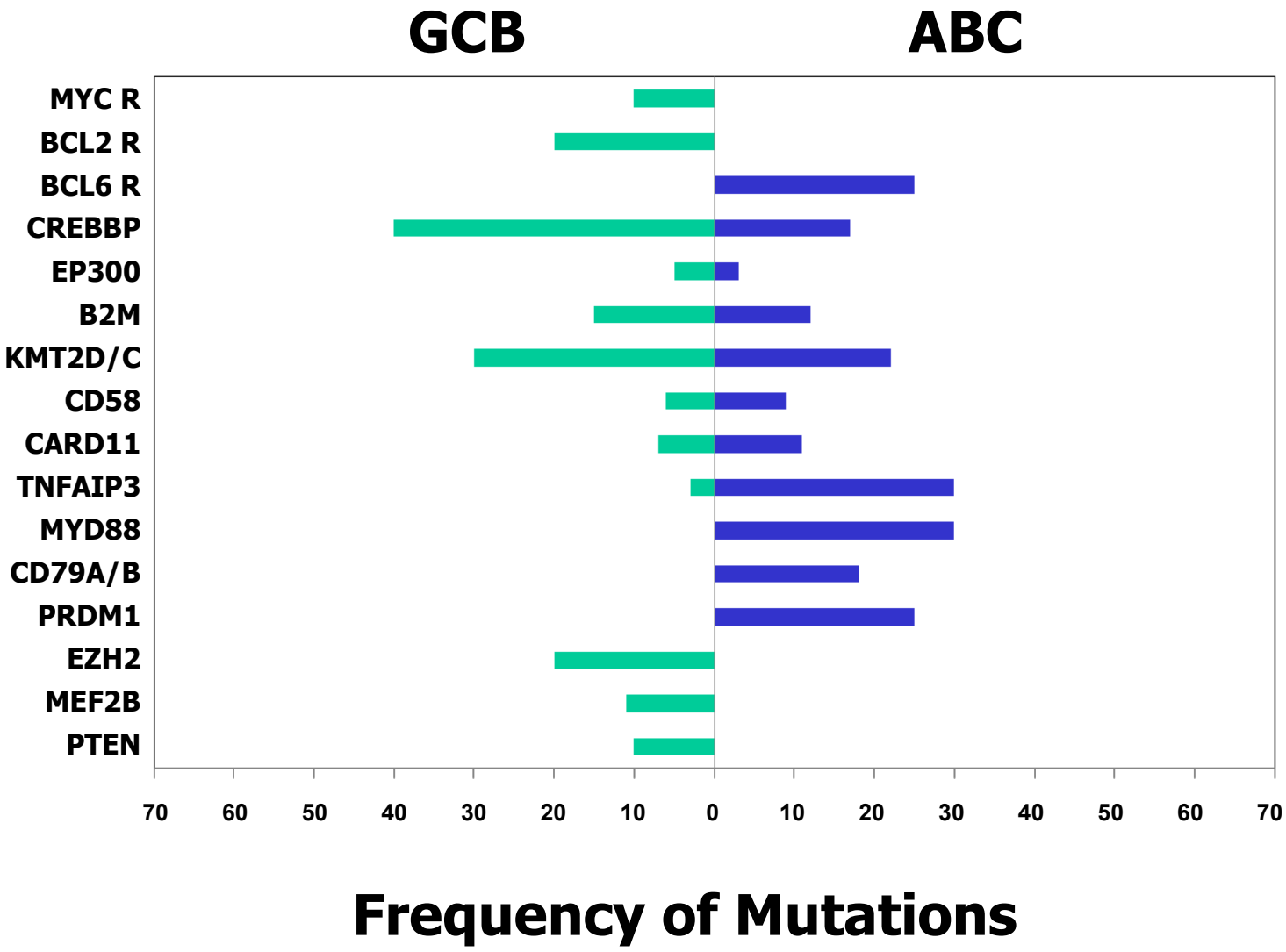
CREBBP, MEF2B

Immune surveillance

β2M, CD58

Diffuse Large B-cell Lymphoma, NOS

Rearrangements and mutations correlate with COO



Comparison of Three Systems

LymphGen	Modified HMRN	Harvard	Main gene mutations	COO	Outcome	Related Lymphoma
MCD	MYD88	C5	*MYD88^{L265P}, CD79B, PIM1*	ABC	Poor	Primary CNS Lymphoma, Primary Testicular Lymphoma
EZB	BCL2	C3	*BCL2, EZH2, CREBBP, KMT2D*	GCB	Good	Follicular Lymphoma
EZB-MYC+	BCL2-MYC				Poor	Double-hit Lymphoma
BN2	NOTCH2	C1	*NOTCH2, BCL10, SPEN, CD70, BCL6*	ABC, GCB, UC	Intermediate/ Good	Marginal Zone Lymphoma
ST2	TET2/SGK1	C4	*TET2, SGK1, KLHL6, BRAF, MAP2K1, KRAS*	GCB	Good	Nodular Lymphocyte Predominant Hodgkin Lymphoma
	SOCS1/SGK1		*SOCS1, SGK1, CD83, NFKBIA, HIST1H1E, STAT3*	GCB	Very Good	Primary Mediastinal B-Cell Lymphoma
N1	NOTCH1		*NOTCH1, ID3*	ABC	Poor	Chronic Lymphocytic Leukaemia
A53		C2	*TP53*, aneuploidy	Mixed	Intermediate	
Other	NEC	C0		ABC, GCB, UC	Intermediate	

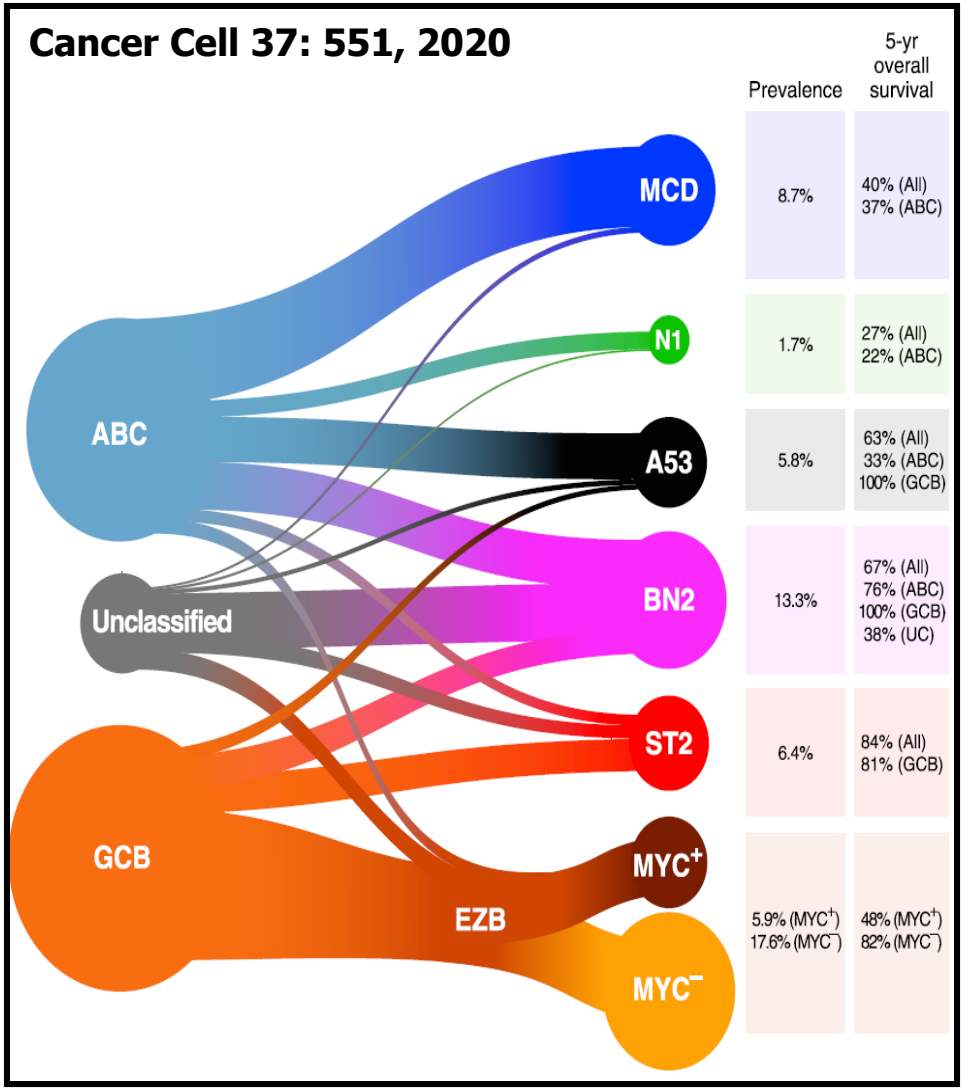
Wright **Chapuy**

Courtesy of Daniel Hodson, MD
Cambridge, UK

Cancer Cell
Article

A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications

George W. Wright,[1] Da Wei Huang,[2] James D. Phelan,[2] Zana A. Coulibaly,[2] Sandrine Roulland,[2] Ryan M. Young,[2] James Q. Wang,[2] Roland Schmitz,[2] Ryan D. Morin,[3] Jeffrey Tang,[3] Aixiang Jiang,[3] Aleksander Bagaev,[4] Olga Plotnikova,[4] Nikita Kotlov,[4] Calvin A. Johnson,[5] Wyndham H. Wilson,[2] David W. Scott,[6] and Louis M. Staudt[2,7,*]



LymphGen Classifier

DLBCL Subgroups

MCD
MYD88 + *CD79B* **mutations**

N1
NOTCH1 **pathway**

A53
Aneuploidy + TP53 mutations

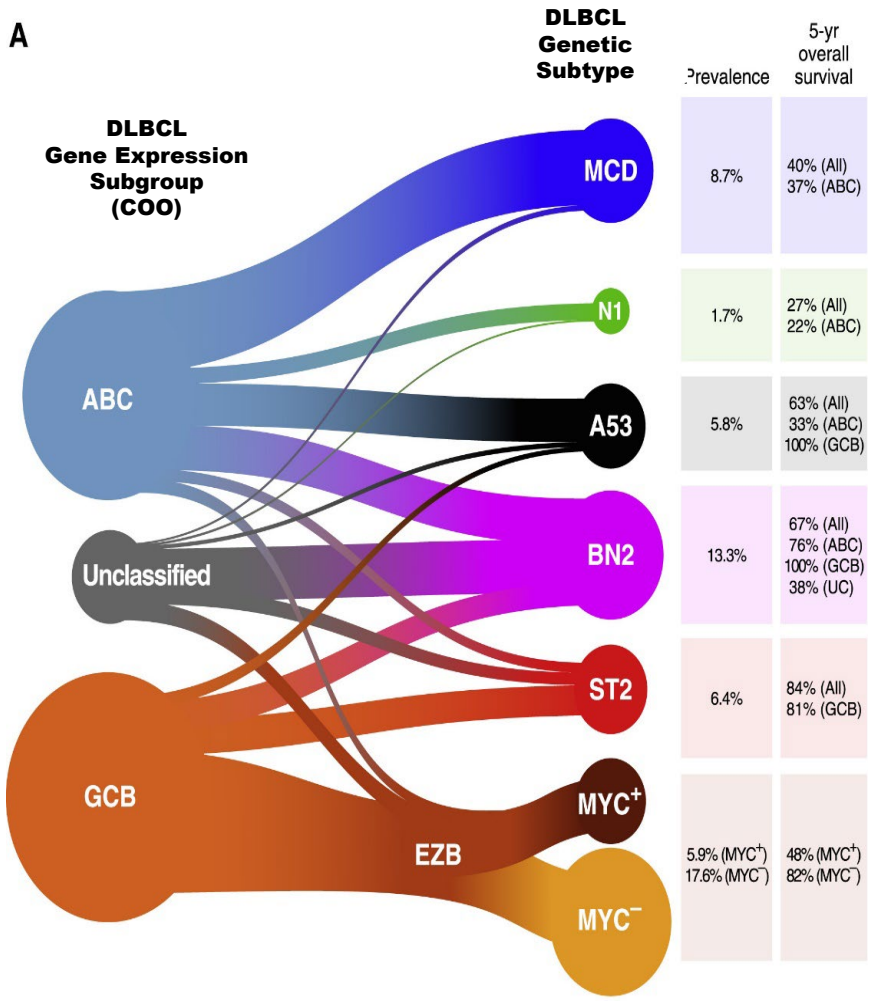
BN2
BCL6 **fusions** + *NOTCH2* **mutations**

ST2
SGK1 **and** *TET2* **mutations**

EZB
EZH2 **mutations +**
BCL2 **translocations**

DLBCL Genetic Subtypes

Implications for Pathogenesis and Therapy



Potential drug targets

MCD
BTK, PI3K, BCL2, JAK

N1

A53

BN2
BTK, PI3K, BCL2

ST2
PI3K, JAK

EZB
EZH2, PI3K, BCL2

Cancer Cell 37: 551, 2020

Take Home Points

The traditional cell-of-origin model (GCB vs ABC) is not sufficiently granular to predict prognosis or to plan therapy

For now, we will need to keep using this model, but only until a better, more practicable system becomes available

A new model may not lead to optimal therapy currently, but it will lead to design of clinical trials and evaluation of therapies

However, this new system needs to be practical