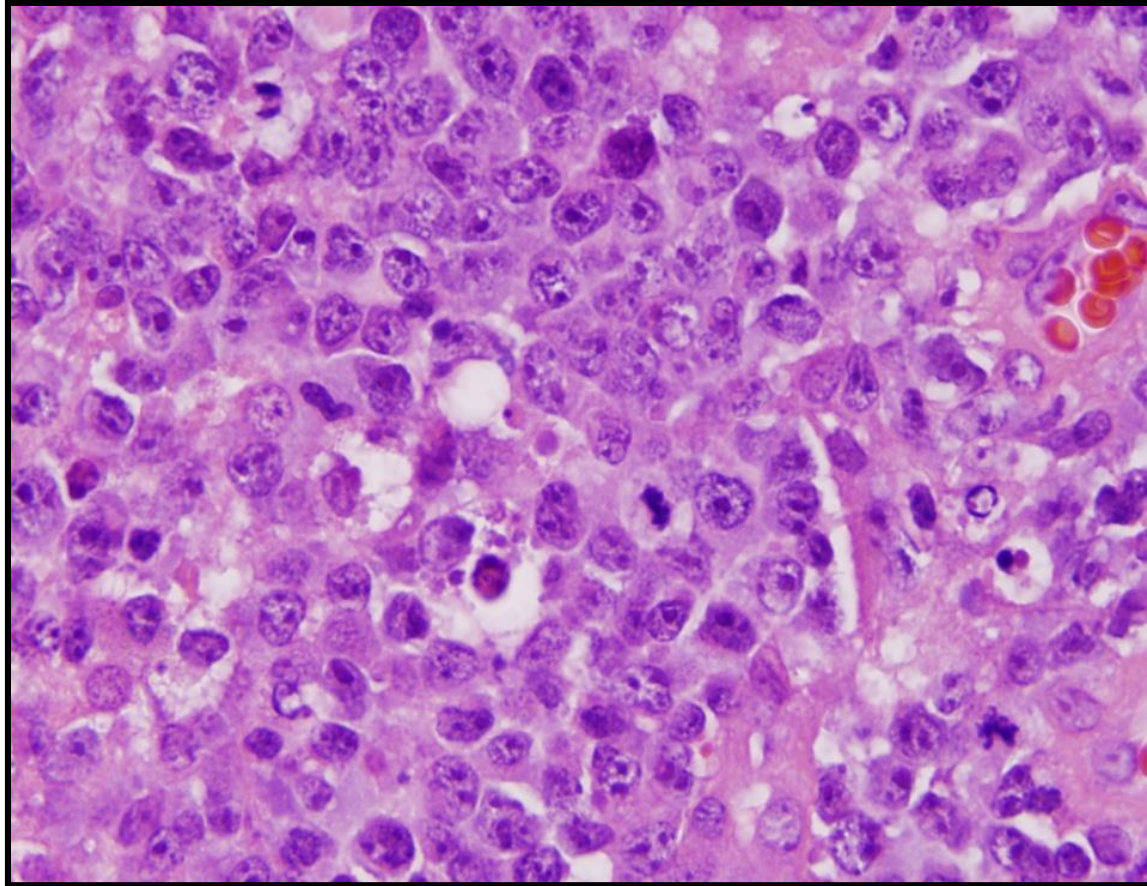


Diffuse Large B-cell Lymphoma



L. Jeffrey Medeiros
MD Anderson Cancer Center

Outline

Diffuse Large B-cell lymphoma (DLBCL), NOS

Introduction/2017 WHO classification

Clinical

Morphology

Immunophenotype

Chromosomal translocations

Cell-of-origin (COO) classification

Gene mutations

Recent studies integrating COO and genetics

High-grade B-cell lymphoma

Not otherwise specified (NOS)

***MYC* and *BCL2* and/or *BCL6* translocations**

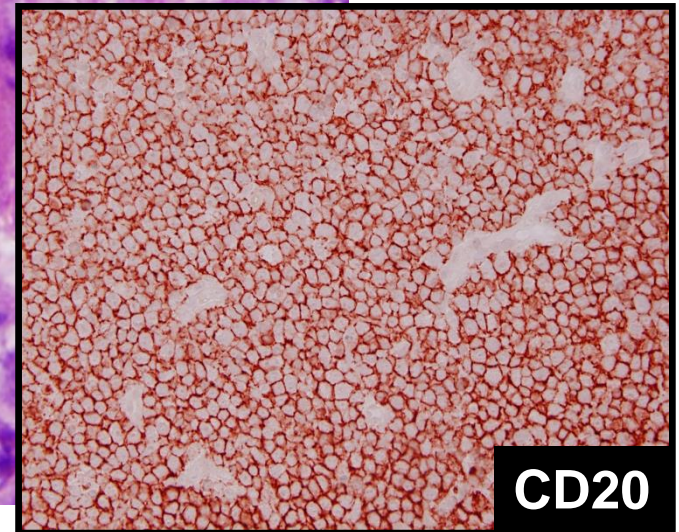
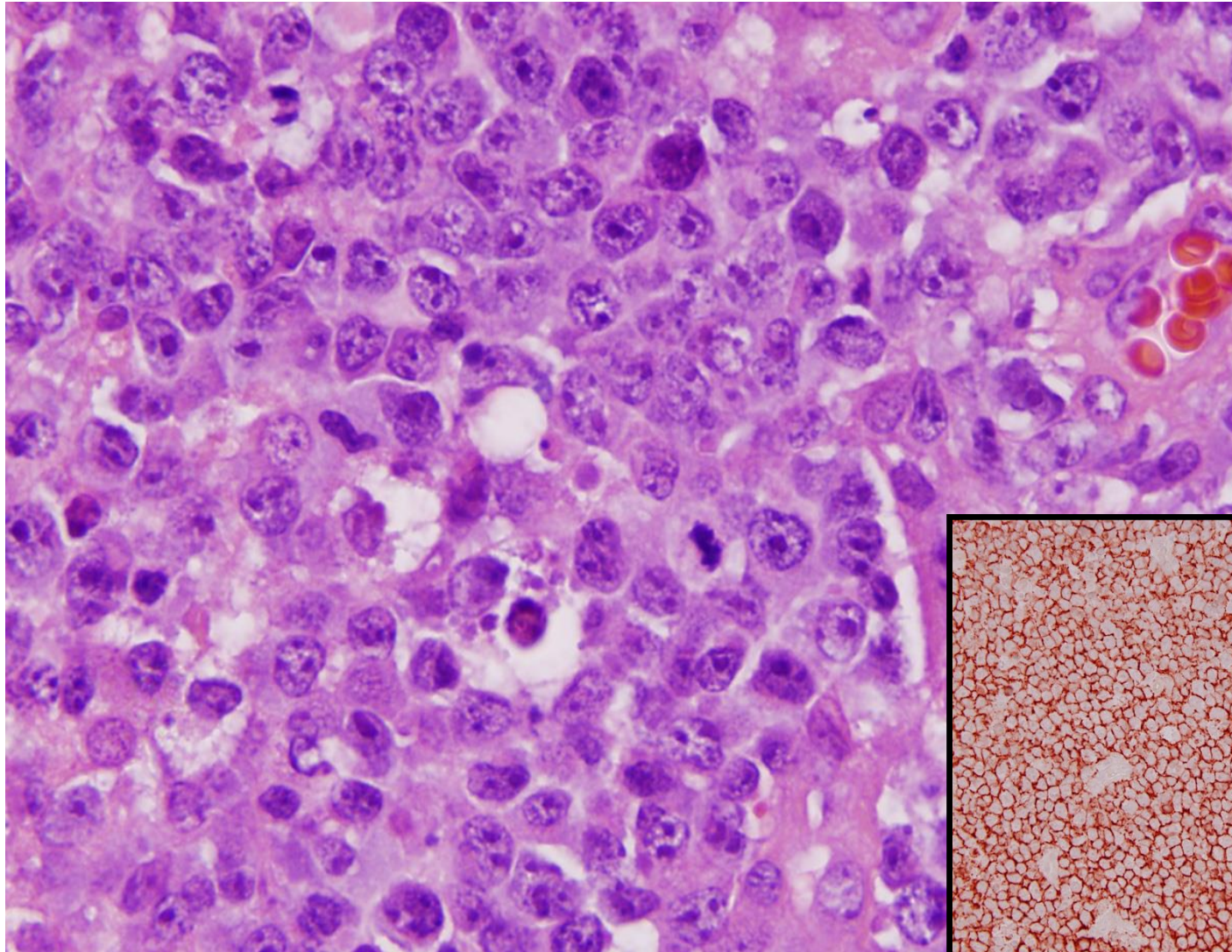
Diffuse Large B-cell Lymphoma

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

Most common type of lymphoma, ~ 33%

Diffuse Large B-cell Lymphoma, NOS



CD20

WHO Classification of Diffuse Large B-cell Lymphoma (2016)

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)

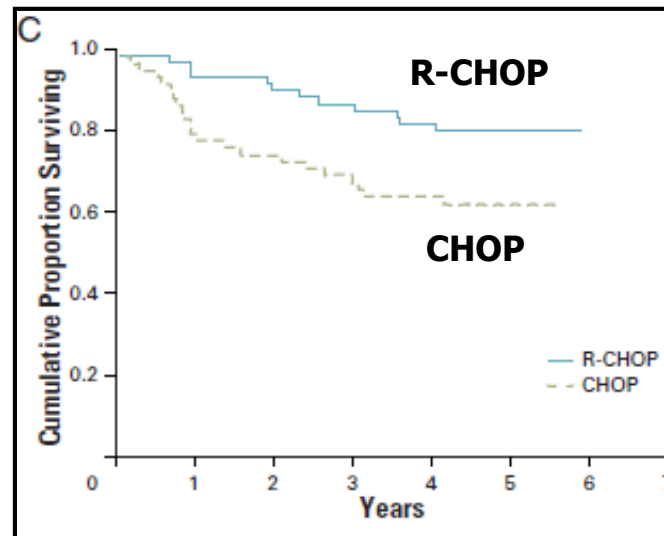
B-cell lymphoma, unclassifiable, intermediate between DLBCL & CHL

Diffuse Large B-cell Lymphoma

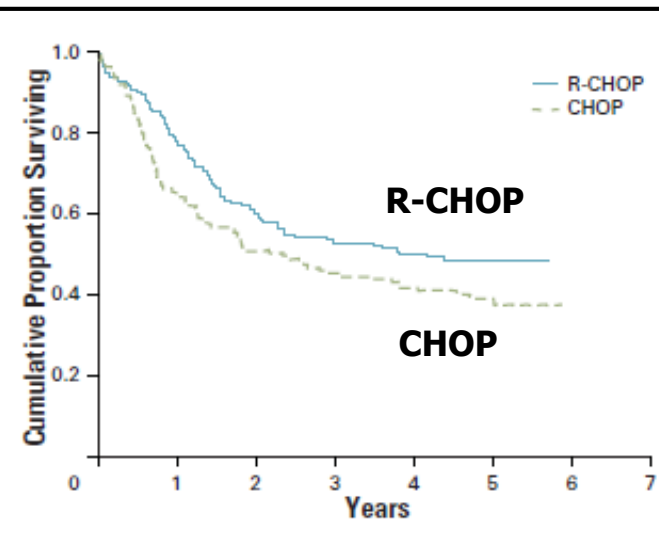


Bertrand Coiffier, MD

Low risk



High risk



Rituximab
Cyclophosphamide
Hydroxydaunorubicin/Adriamycin
Oncovin/vincristine
Prednisone

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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%

Diffuse Large B-cell Lymphoma

International Prognostic Index

A ge	≤ 60 vs. >60 years
P erformance status	0-1 vs. 2-4
L DH	Normal vs elevated
E xtranodal sites	≤ 1 vs >1 site
S tage	I-II vs III-IV

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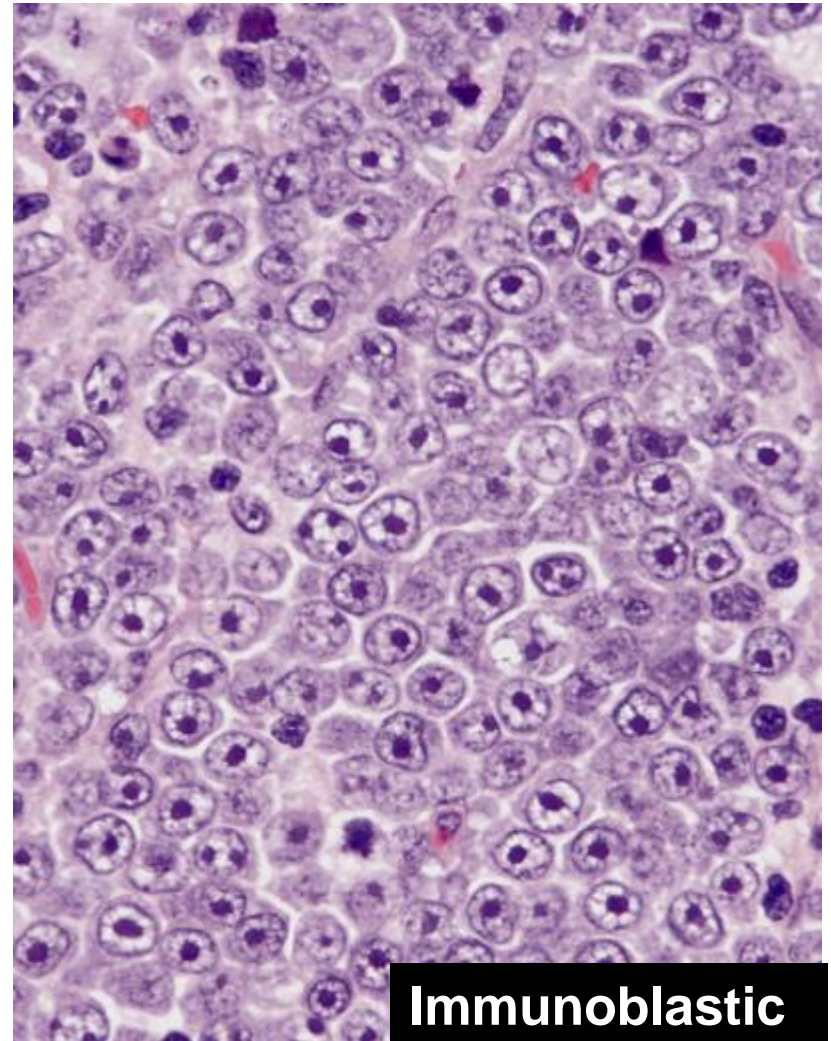
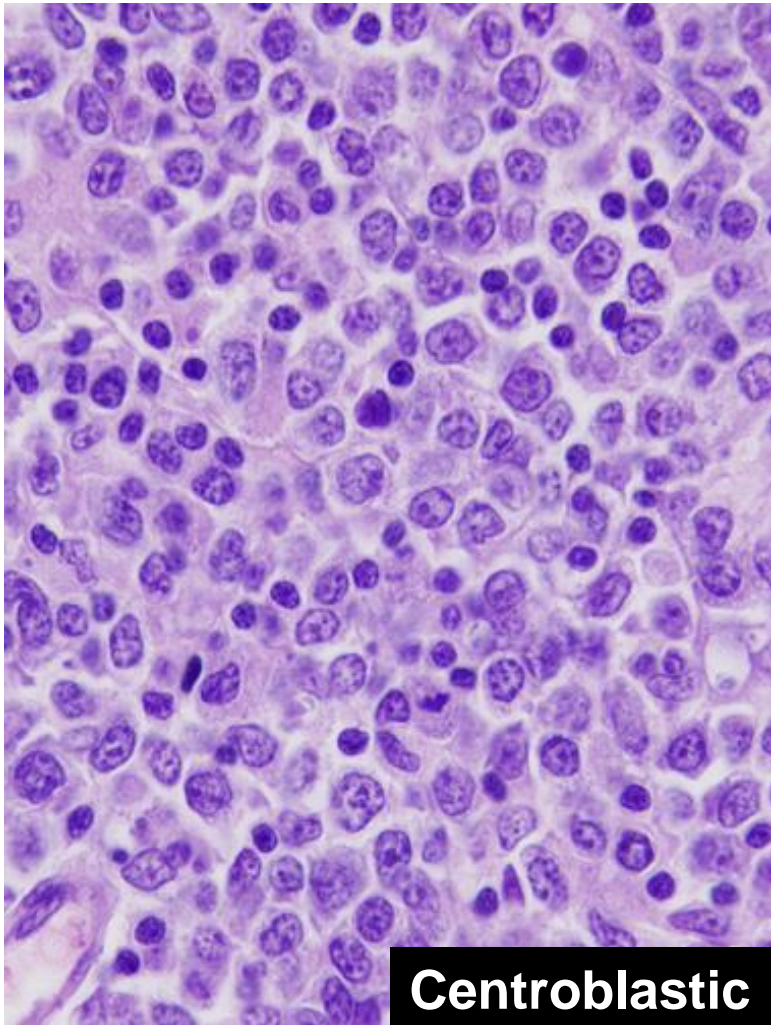
High-grade B-cell lymphoma

Not otherwise specified (NOS)

***MYC* and *BCL2* and/or *BCL6* translocations**

Diffuse Large B-cell Lymphoma NOS

Morphologic Variants



Diffuse Large B-cell Lymphoma NOS

Morphologic Variants

Common

Centroblastic (~80%)

Immunoblastic (~10%)

Multilobated (<5%)

Anaplastic (<5%)

Rare

Sinusoidal

Spindled

Myxoid

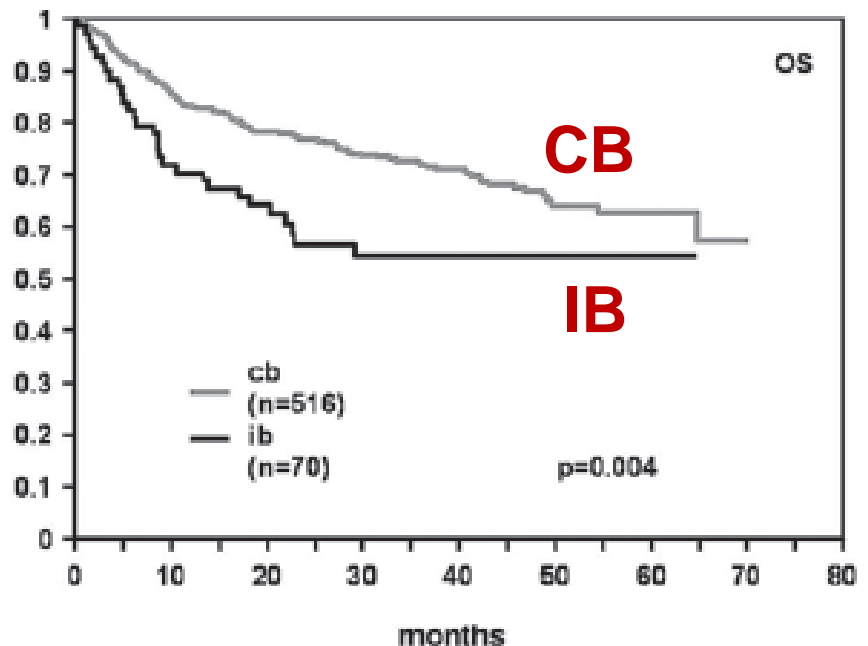
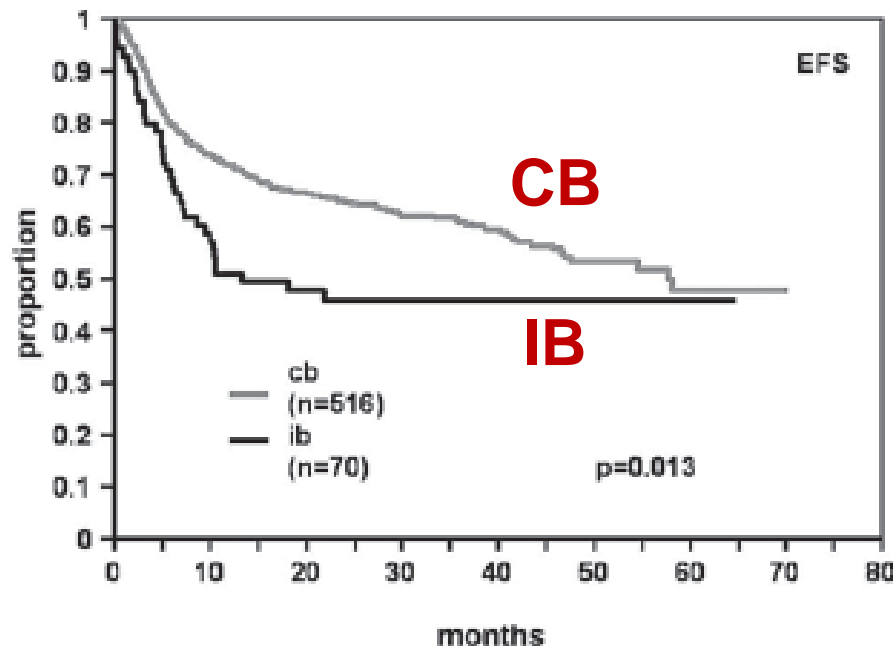
Signet Ring

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 Rosenwald¹



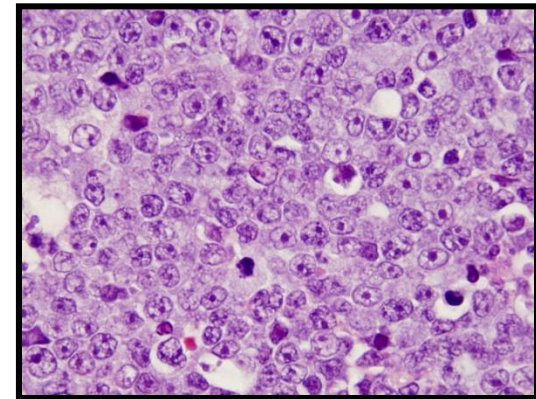
Diffuse Large B-cell Lymphomas of Immunoblastic Type Are a Major Reservoir for *MYC-IGH* Translocations

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**

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***MYC* and *BCL2* and/or *BCL6* translocations**

Immunophenotypic Analysis of DLBCL

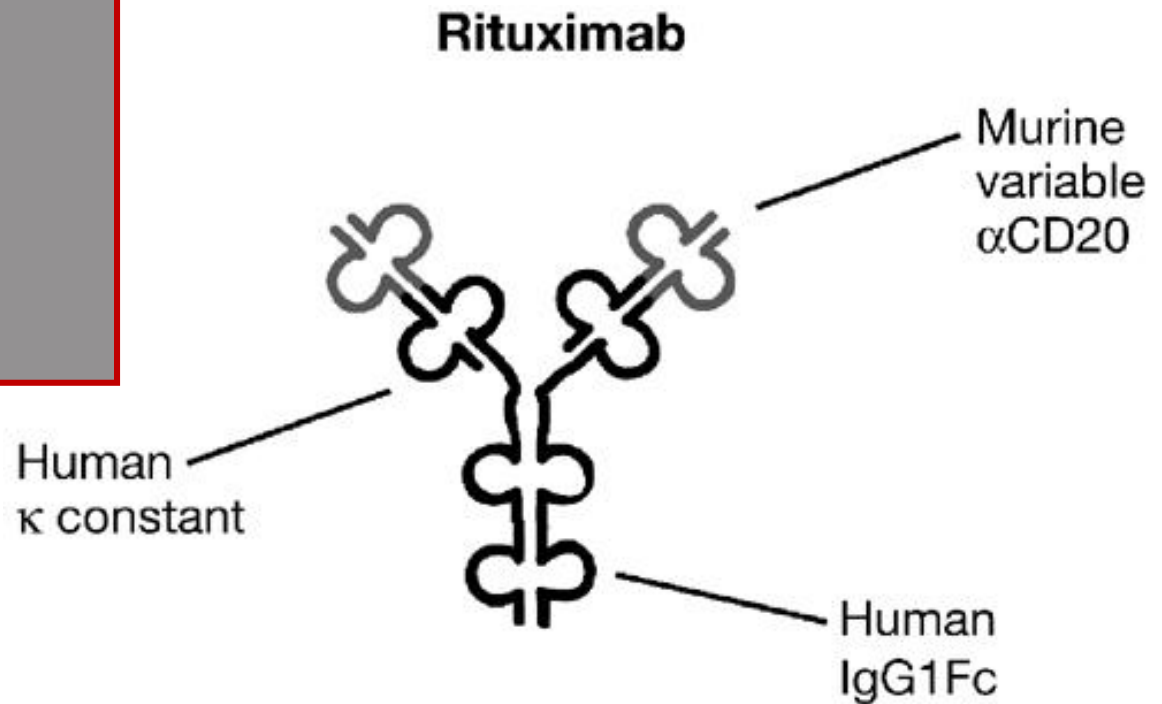
What Is The Purpose ?

In the past
Diagnosis

Currently
Diagnosis
Prognosis
Identifying targets for therapy

Monoclonal Antibodies are a Part of Standard Therapy

CD20 is the Best Example



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
XPO1	Selinexor	Selective inhibitor of nuclear export
BRAF, MEK	Vemurafinib, cobimetinib	MAP kinase
BCL-2	Venetoclax	Apoptosis
PD-L1/L2	Nivolumab, others	Checkpoint inhibitors

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***MYC* and *BCL2* and/or *BCL6* translocations**

Common Translocations in DLBCL

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

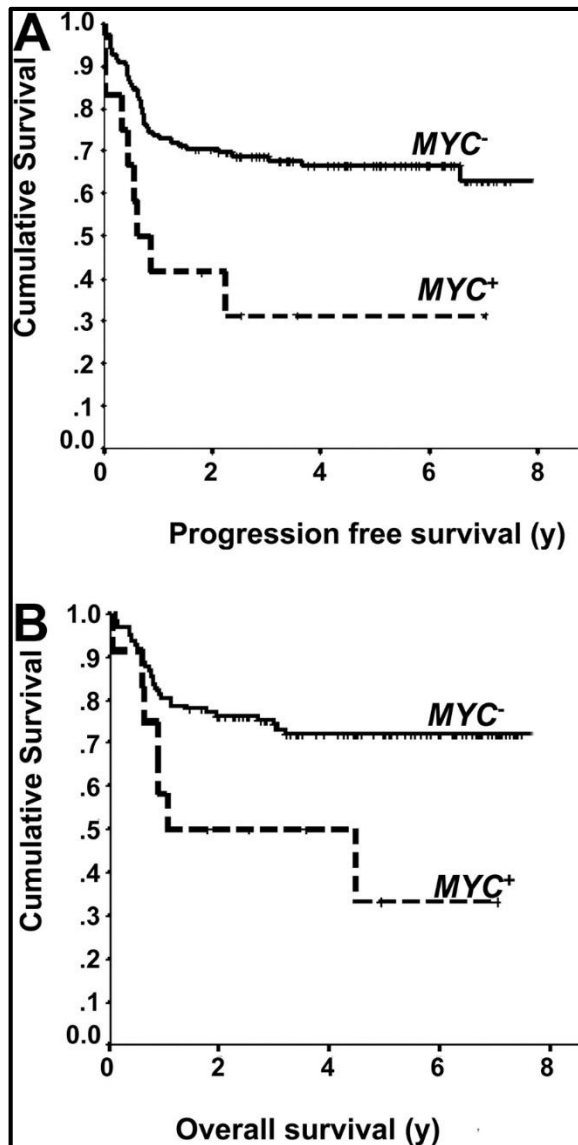
BCL6 also partners with other genes

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

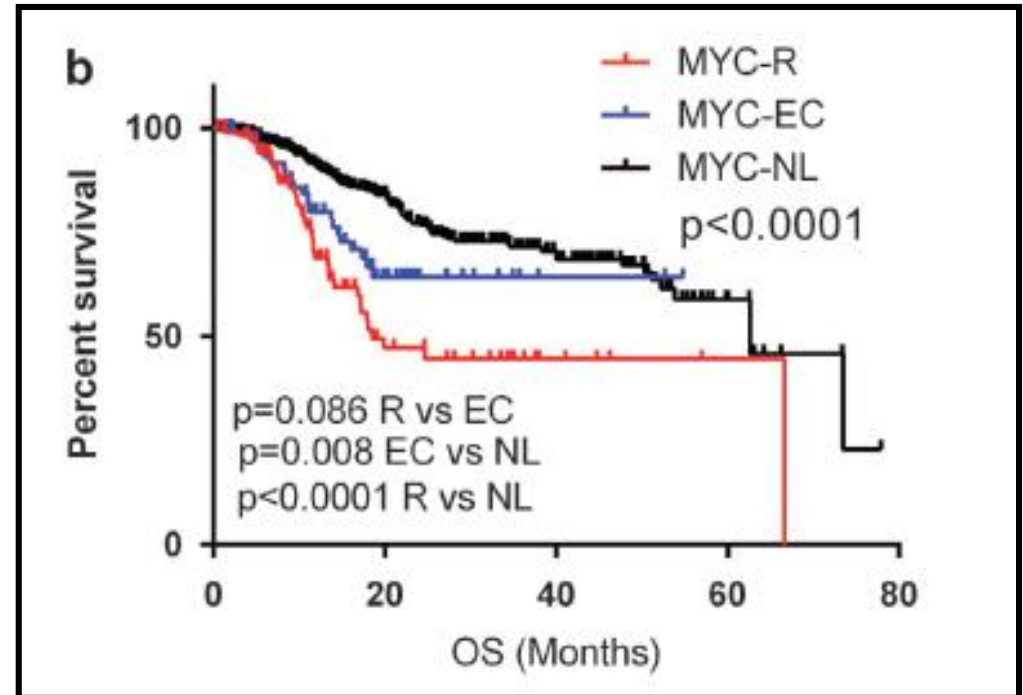
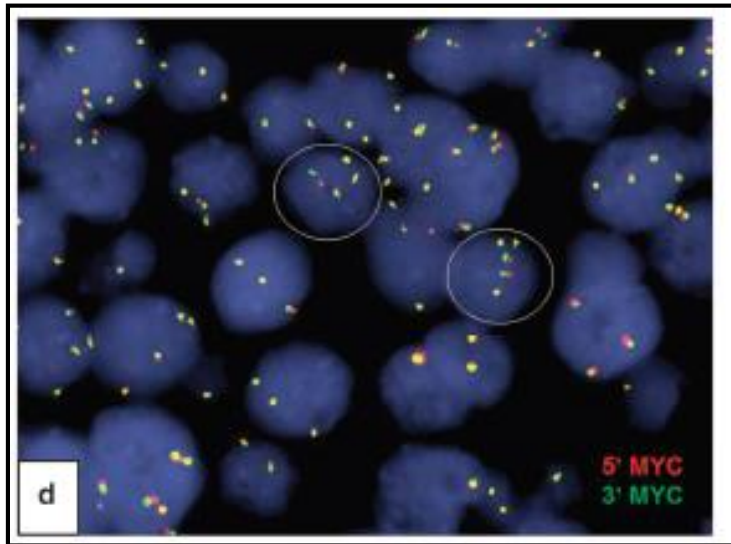
Need viable cells

FISH

IGH and *MYC* probes

MYC breakapart probe

MYC Extra Copies by FISH Predict Poorer Prognosis in DLBCL Patients



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

Andrés E Quesada¹, L Jeffrey Medeiros¹, Parth A Desai¹, Pei Lin¹, Jason R Westin², Huda M Hawsawi¹, Peng Wei³, Guilin Tang¹, Adam C Seegmiller⁴, Nishitha M Reddy⁵, C Cameron Yin¹, Wei Wang¹, Jie Xu¹, Roberto N Miranda¹, Zhuang Zuo¹ and Shaoying Li¹



Andres Quesada, MD

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***MYC* and *BCL2* and/or *BCL6* translocations**

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

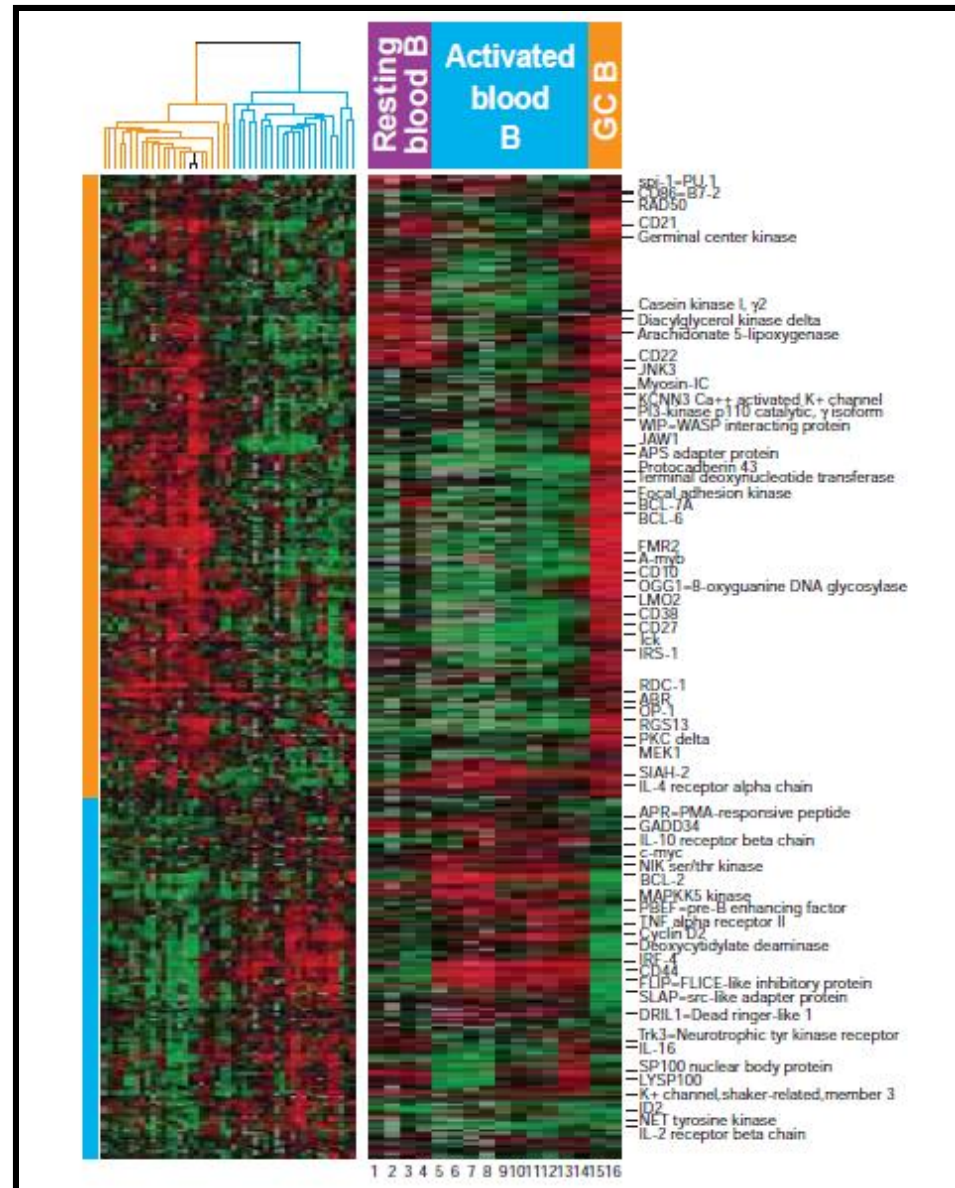
3,186 Activated lymphocyte genes



Louis Staudt, MD, PhD

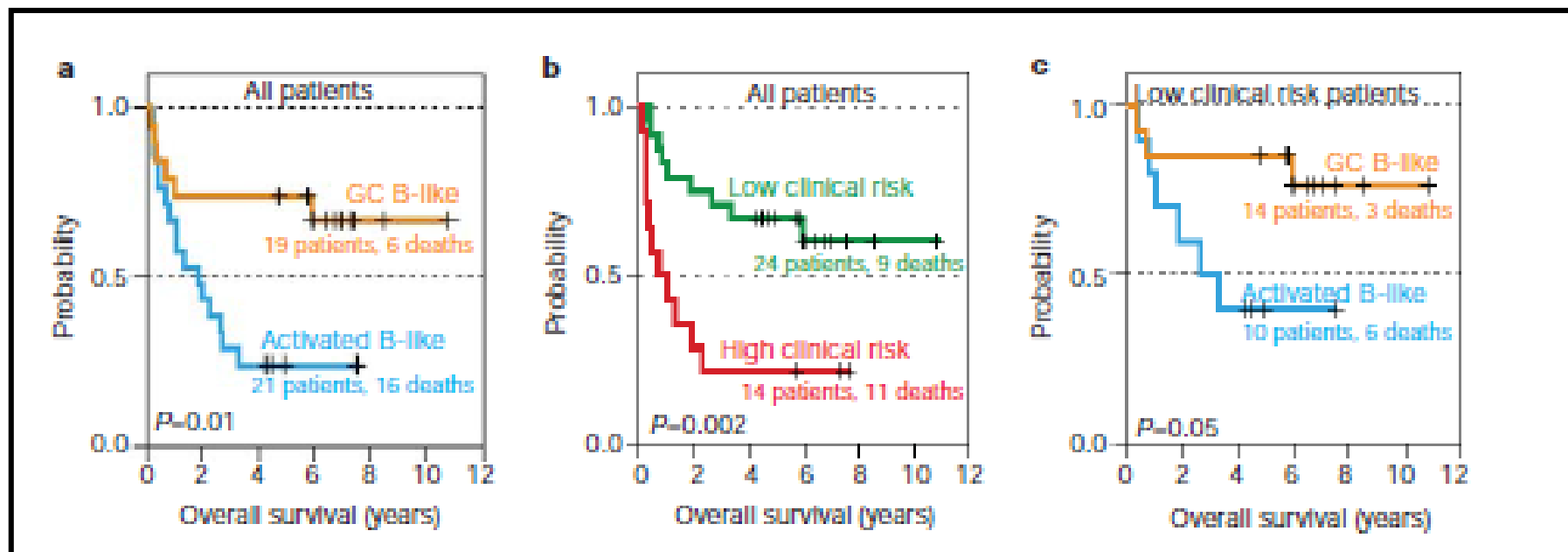
Diffuse Large B-cell Lymphoma

GCB
ABC



Diffuse Large B-cell Lymphoma

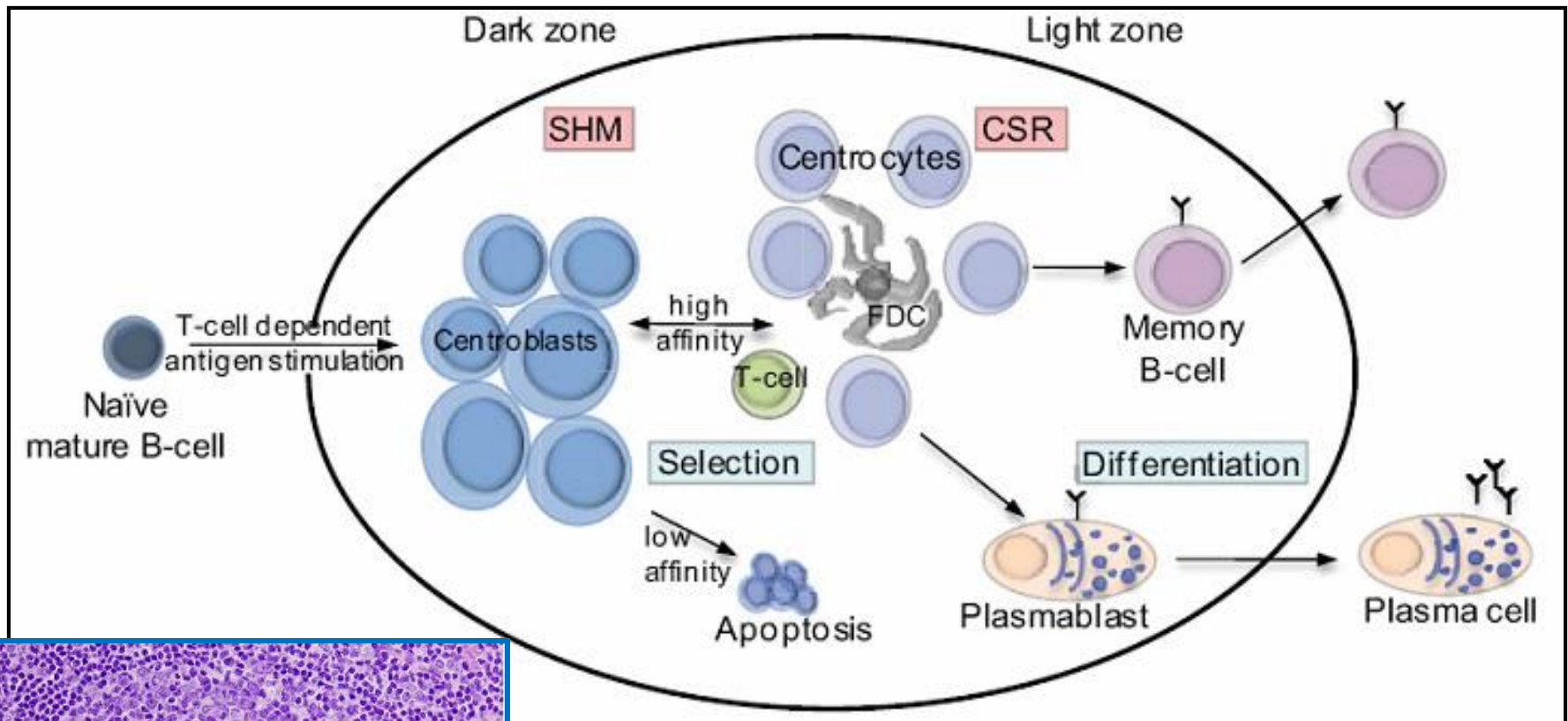
GEP Shows 2 Types that Predict Prognosis



CHOP Therapy

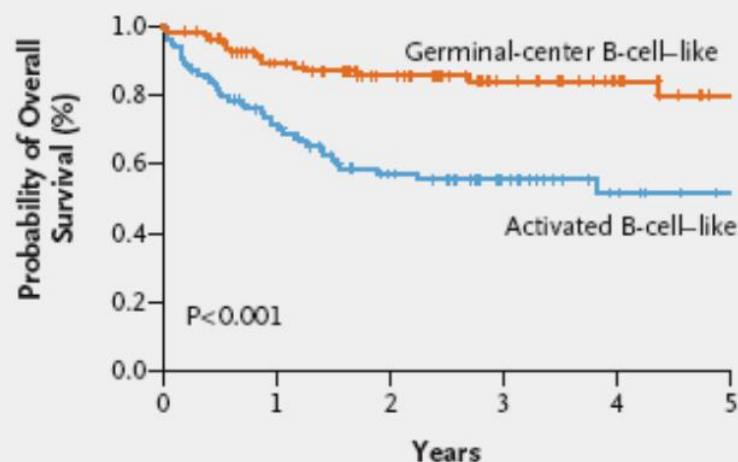
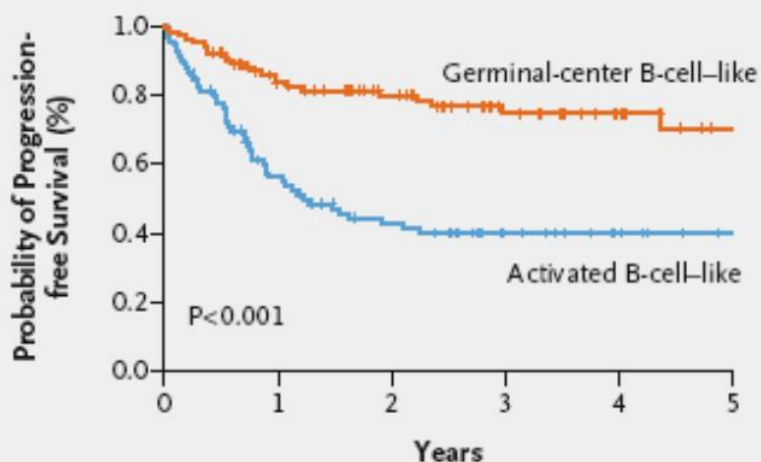
Nature 403: 503, 2000

Germinal Center Reaction



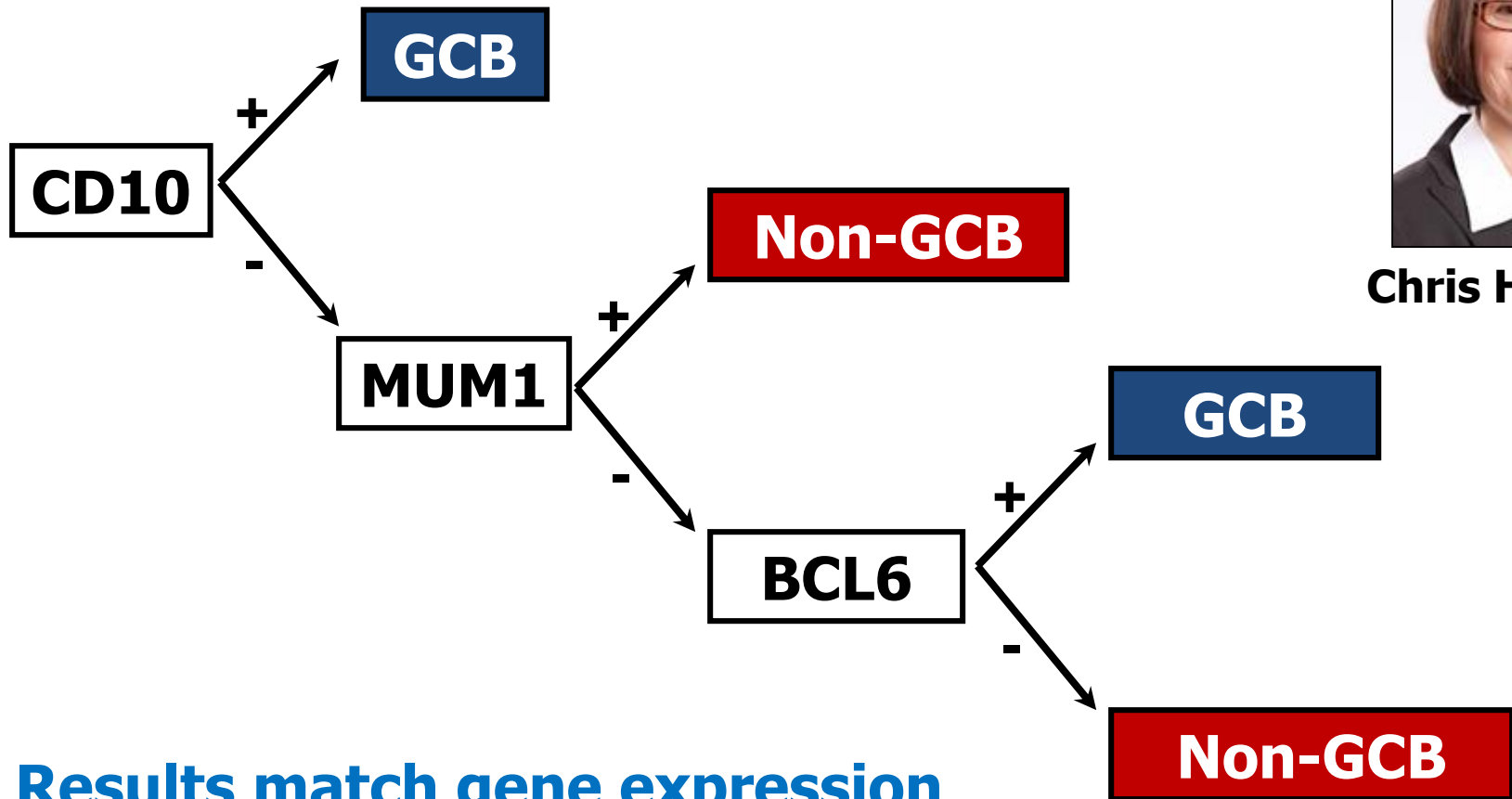
Diffuse Large B-cell Lymphoma

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

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



Chris Hans, MD

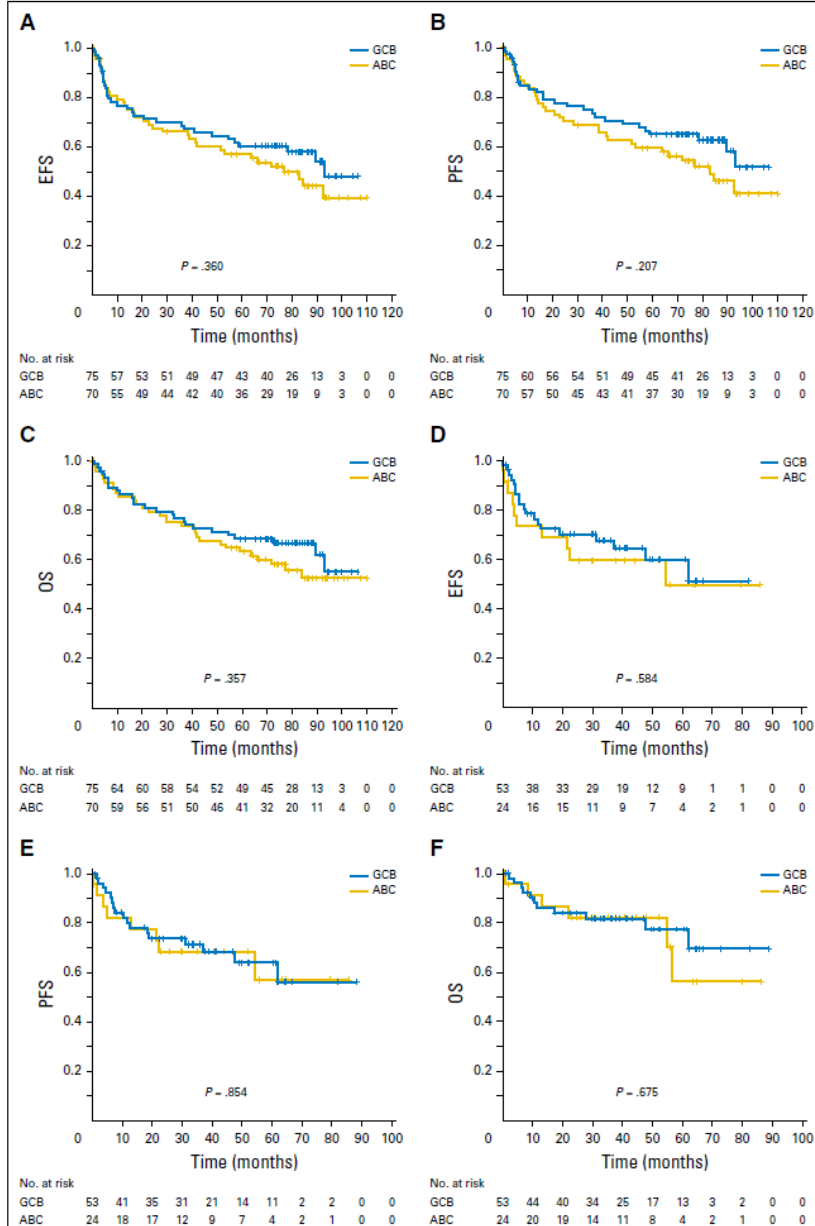
Results match gene expression profile in ~80% of cases

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-Léo 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

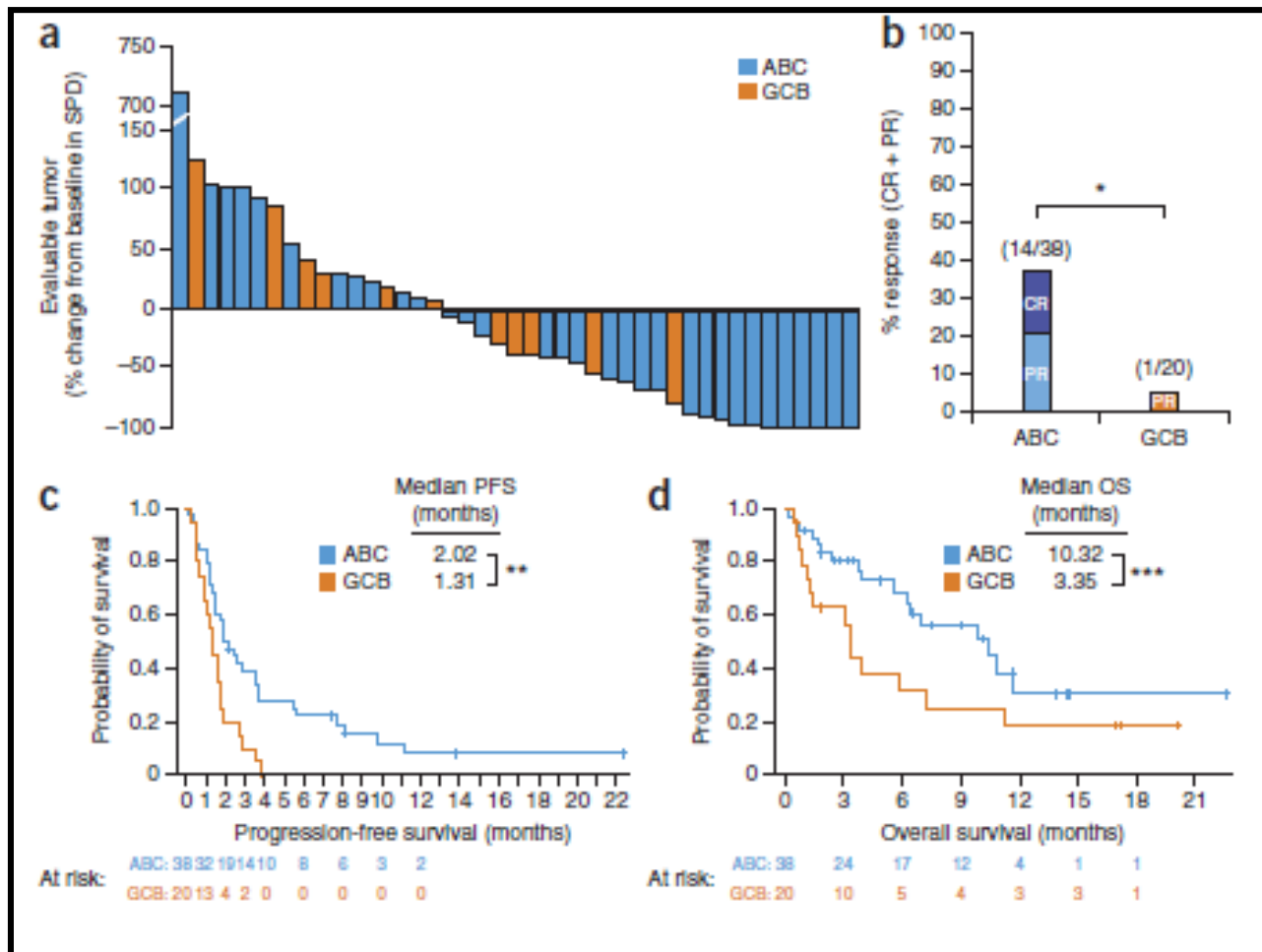
A,C,E. RICOVER-60 trial
B,D,F. R-MegaCHOEP trial

Cell-of-origin classification did not correlate with prognosis



Therapy of Patients with DLBCL

Impact of GCB versus ABC



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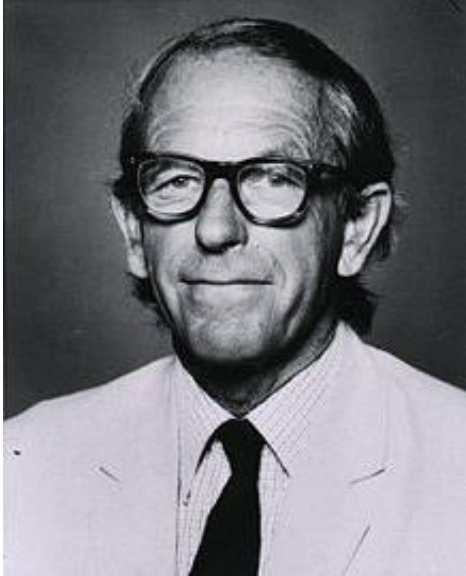
Recent studies integrating COO and genetics

High-grade B-cell lymphoma

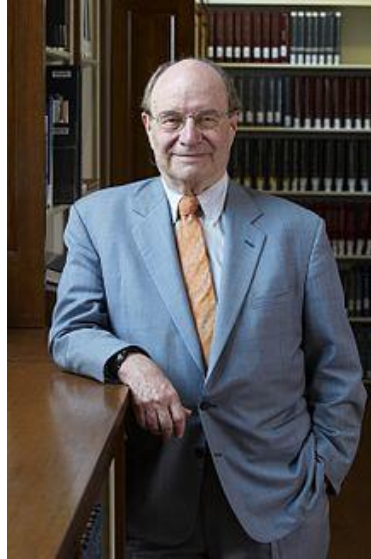
Not otherwise specified (NOS)

***MYC* and *BCL2* and/or *BCL6* translocations**

Sanger Sequencing Traditional (dideoxy) Method

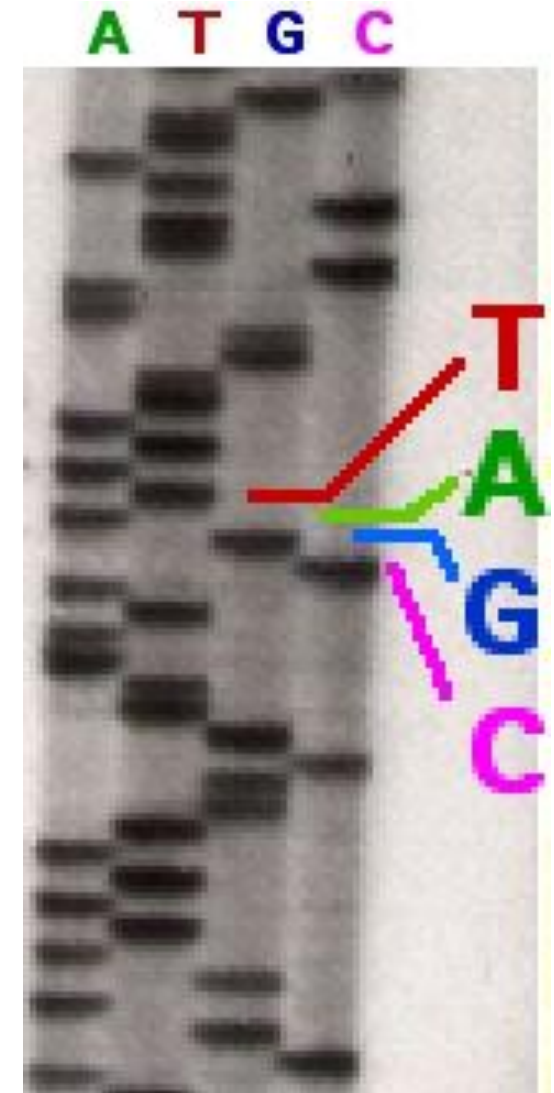


Fred Sanger



Walter Gilbert

**Nobel Prize in 1980
(with Paul Berg)**



Sanger sequencing vs Next Gen Sequencing

Sanger sequencing (1st generation)

One amplicon at a time

One or more amplicons per exon

Genes with many exons

High cost per gene; laborious

Sample limitations

Next-generation sequencing

Instead of one gene in many tubes, one can analyze many genes in one tube

Currently expensive but cost dropping

Mutations in Pathways Involved in DLBCL

B-cell receptor signaling

CD79A, CD79B, CARD11

Toll-like receptor signaling

MYD88

NF- κ B

Lymphocyte differentiation

TNFAIP3/A20, TRAF3, BIRC3, IKK β

DNA repair and transcriptional regulation

p53

Lymphocyte activation

STAT6, BCL10

DNA methylation

EZH2, MLL2

DNA acetylation

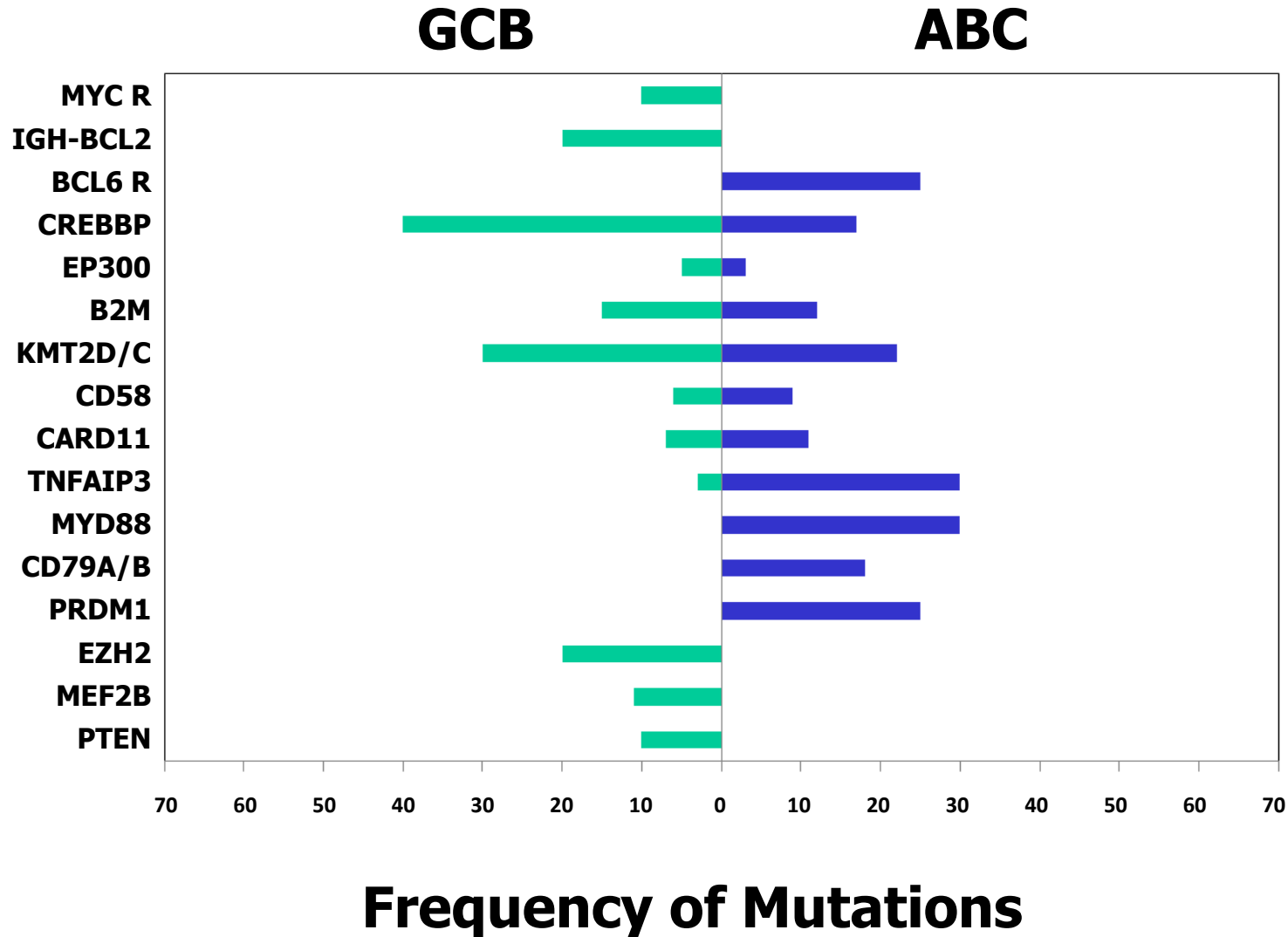
CREBBP, MEF2B

Immune surveillance

β 2M, CD58

Diffuse Large B-cell Lymphoma, NOS

Mutations correlate with cell-of-origin



Diffuse Large B-cell Lymphoma

Molecular Testing

Current NGS Assay for B-cell Neoplasms

29-gene Panel on Illumina MiSeq

ATM	CD79A	DDX3X	LRP1B	PLCG2	TGM7
BIRC3	CD79B	EZH2	MAPK1	PLEKHG5	TP53
BTK	CHD2	FAT1	MUC2	POT1	XPO1
CALR	CSMD3	FBXW7	MYD88	SF3B1	ZMYM3
CARD11	CXCR4	KLHL6	NOTCH1	SPEN	

● CLL
 ● MCL
 ● DLBCL
 ● WM/LPL

Fresh specimens (PB/PB/FNA): ✓
FFPE specimens: ✗



Upcoming EndLymphoma Assay v1

162-Gene Panel on Illumina NextSeq

Partial Gene-List Related to DLBCL

ARID1A	CD79B	HIST1H1E	NF1	STAT6
BCL2	CDKN2A	IRF4	NOTCH2	TBL1XR1
BCL6	CDKN2B	ITPKB	PIK3CA	TNFAIP3
BIRC3	CHEK2	KMT2D	PIK3R1	TNFRSF14
CARD11	CREBBP	KRAS	PIM1	TP53
CCND3	EP300	MEF2B	PRDM1	TRAF3
CD58	EZH2	MYC	PTEN	XPO1
CD79A	FOXO1	MYD88	SOC51	

Fresh specimens (PB/PB/FNA): ✓
FFPE specimens: ✓



Upcoming Cell of Origin Assay

RNA Expression on HTG EdgeSeq+ MiSeq

ACTB	RPL4	BCL6	CD274	CD70	EZH2
DDX5	RPL6	BTX	CD276	CD79A	FCER2
EEF1G	RPS29	CASP7	CD37	CD86	FCGR3A
EIF4A1	TBP	CCND1	CD3D	CD8A	FOXP1
GAPDH	AKT1	CCND2	CD4	CDK16	FUT4
PPIA	BAG5	CCT7	CD47	CDKN1B	FUT8
PRKG1	BAK1	CD19	CD5	CTLA4	GRB2
RPL19	BCL2	CD22	CD68	ENTPD1	HLA-DRA
IL13	MAL	NCAM1	POU2AF1	SPN	TRAF1
IL16	MAP2K7	NCOA1	POU2F2	SREBF1	TYMS
IL4I1	MAP3K13	NF2	PTPRC	STAT3	VDAC1
IRF4	MKI67	PAX5	REL	STAT6	ZHX2
ITPKB	MME	PAX5	RRM2	SUV39H2	
LAG3	MSA41	PDCD1	SERPINA9	TCF3	
LMO2	MYBL1	PDCD1LG2	SMS	TCL1A	
LRMP	MYC	PIM1	SPI1	TNFRSF8	

Fresh specimens (PB/PB/FNA): ✓
FFPE specimens: ✓



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Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

R. Schmitz, G.W. Wright, D.W. Huang, C.A. Johnson, J.D. Phelan, J.Q. Wang, S. Roulland, M. Kasbekar, R.M. Young, A.L. Shaffer, D.J. Hodson, W. Xiao, X. Yu, Y. Yang, H. Zhao, W. Xu, X. Liu, B. Zhou, W. Du, W.C. Chan, E.S. Jaffe, R.D. Gascoyne, J.M. Connors, E. Campo, A. Lopez-Guillermo, A. Rosenwald, G. Ott, J. Delabie, L.M. Rimsza, K. Tay Kuang Wei, A.D. Zelenetz, J.P. Leonard, N.L. Bartlett, B. Tran, J. Shetty, Y. Zhao, D.R. Soppet, S. Pittaluga, W.H. Wilson, and L.M. Staudt

Integration of gene expression profiling, copy number alterations, and mutations

4 Subgroups of DLBCL

EZB

***EZH2* mutations and *BCL2* translocations**

BN2

***BCL6* fusions and *NOTCH2* mutations**

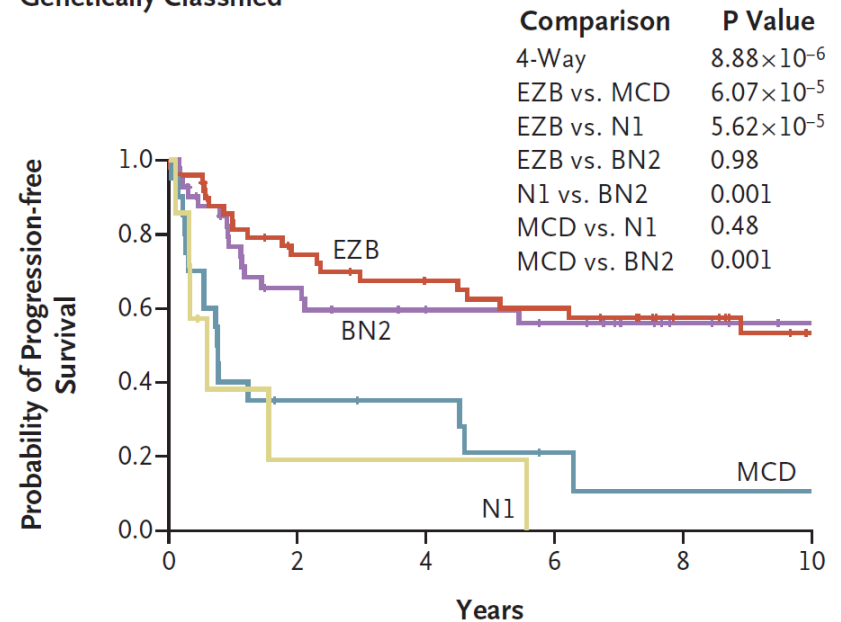
MCD

***MYD88* and *CD79B* mutations**

N1

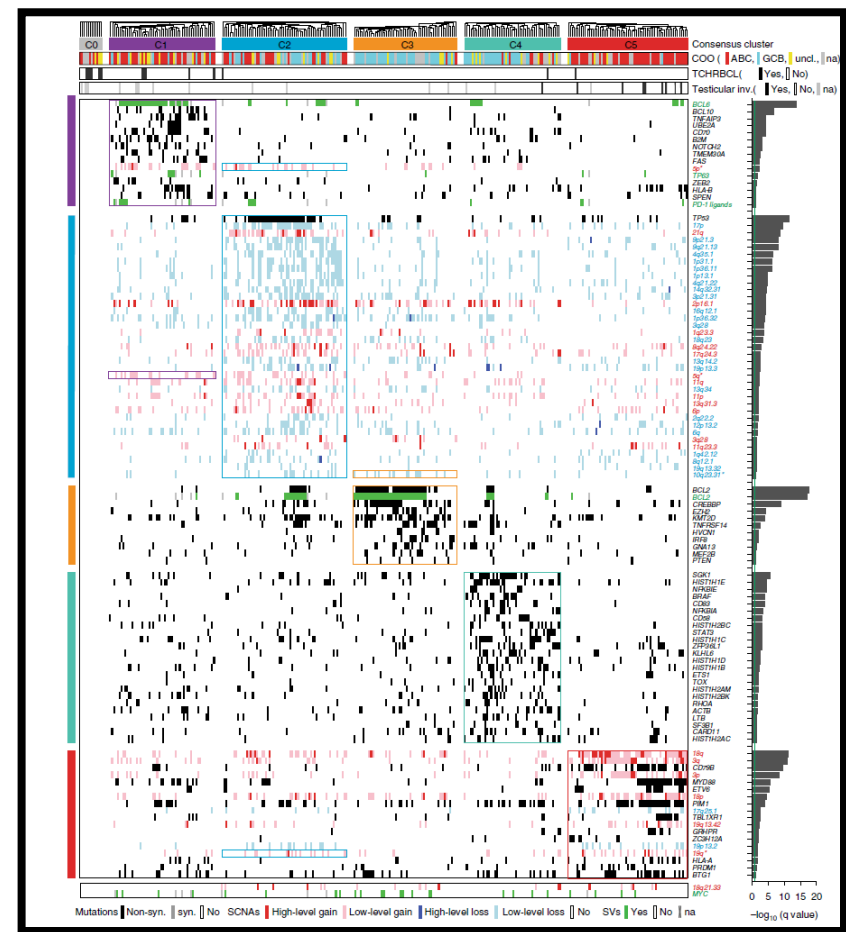
***NOTCH1* mutations**

Progression-free Survival among Patients Whose Tumors Were Genetically Classified



Bjoern Chapuy^{1,2,18}, Chip Stewart^{3,18}, Andrew J. Dunford^{3,18}, Jaegil Kim³, Atanas Kamburov³, Robert A. Redd⁴, Mike S. Lawrence^{2,3,5}, Margaretha G. M. Roemer¹, Amy J. Li⁶, Marita Ziepert⁷, Annette M. Staiger^{8,9}, Jeremiah A. Wala¹⁰, Matthew D. Ducar¹⁰, Ignaty Leshchiner¹⁰, Ester Rheinbay³, Amaro Taylor-Weiner³, Caroline A. Coughlin¹, Julian M. Hess³, Chandra S. Pedamallu³, Dimitri Livitz¹⁰, Daniel Rosebrock³, Mara Rosenberg³, Adam A. Tracy³, Heike Horn⁸, Paul van Hummelen¹⁰, Andrew L. Feldman¹⁰, Brian K. Link¹², Anne J. Novak¹¹, James R. Cerhan¹¹, Thomas M. Habermann¹¹, Reiner Siebert¹³, Andreas Rosenwald¹⁴, Aaron R. Thorner¹⁰, Matthew L. Meyerson^{2,3}, Todd R. Golub^{2,3}, Rameen Beroukhi^{2,3}, Gerald G. Wulf¹⁵, German Ott⁹, Scott J. Rodig^{2,16}, Stefano Monti⁶, Donna S. Neuberg^{2,4}, Markus Loeffler⁷, Michael Pfreundschuh⁷, Lorenz Trümper¹⁵, Gad Getz^{2,3,5,19*} and Margaret A. Shipp^{1,2,19*}

Integration of gene expression profiling, copy number alterations, and mutations



C1 *BCL6* translocations, NOTCH2 pathway, NF- κ B (n=56)

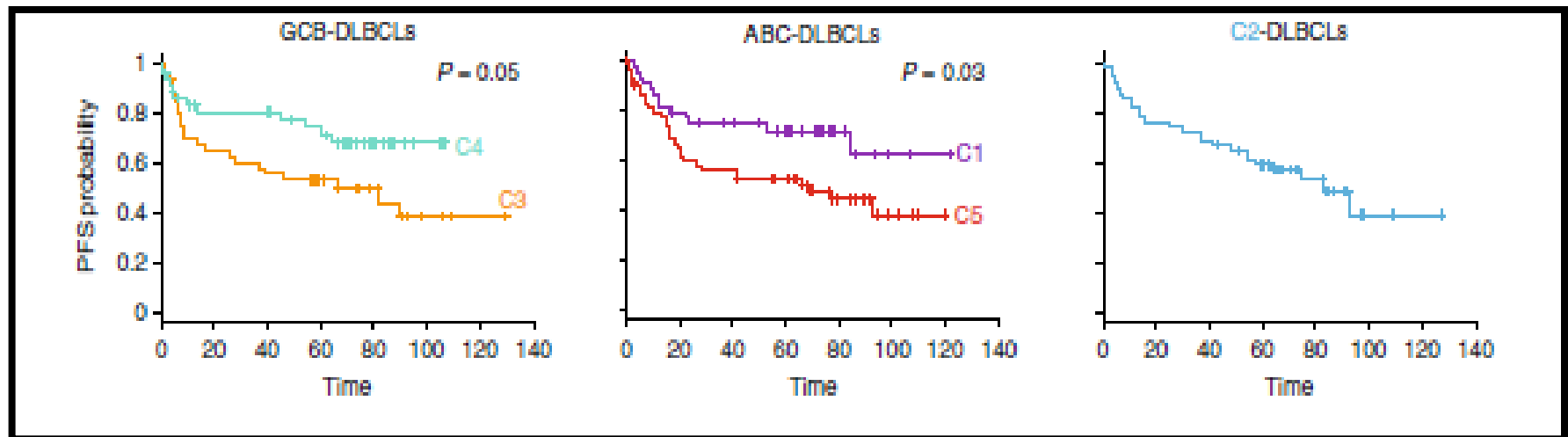
C3 *BCL2* translocations, chromatin modifier gene mutations (n=55)

C5 *CD79B*, *MYD88*, 18q/ *BCL2* gains, other genes (n=64)

Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes

Bjoern Chapuy^{1,2,18}, Chip Stewart^{3,18}, Andrew J. Dunford^{3,18}, Jaegil Kim³, Atanas Kamburov³, Robert A. Redd⁴, Mike S. Lawrence^{2,3,5}, Margaretha G. M. Roemer¹, Amy J. Li⁶, Marita Ziepert⁷, Annette M. Staiger^{8,9}, Jeremiah A. Wala³, Matthew D. Ducar¹⁰, Ignaty Leshchiner³, Ester Rheinbay³, Amaro Taylor-Weiner³, Caroline A. Coughlin¹, Julian M. Hess³, Chandra S. Pedamallu³, Dimitri Livitz³, Daniel Rosebrock³, Mara Rosenberg³, Adam A. Tracy³, Heike Horn⁸, Paul van Hummelen¹⁰, Andrew L. Feldman¹¹, Brian K. Link¹², Anne J. Novak¹¹, James R. Cerhan¹¹, Thomas M. Habermann¹¹, Reiner Siebert¹³, Andreas Rosenwald¹⁴, Aaron R. Thorner¹⁰, Matthew L. Meyerson^{2,3}, Todd R. Golub^{2,3}, Rameen Beroukhi^{2,3}, Gerald G. Wulf¹⁵, German Ott⁹, Scott J. Rodig^{2,16}, Stefano Monti⁶, Donna S. Neuberg^{2,4}, Markus Loeffler⁷, Michael Pfreundschuh¹⁷, Lorenz Trümper¹⁵, Gad Getz^{2,3,5,19*} and Margaret A. Shipp^{1,2,19*}

Nat Med 24:679, 2018



C1 Good ABC (marginal zone origin)

C2 Poor prognosis; no association with COO

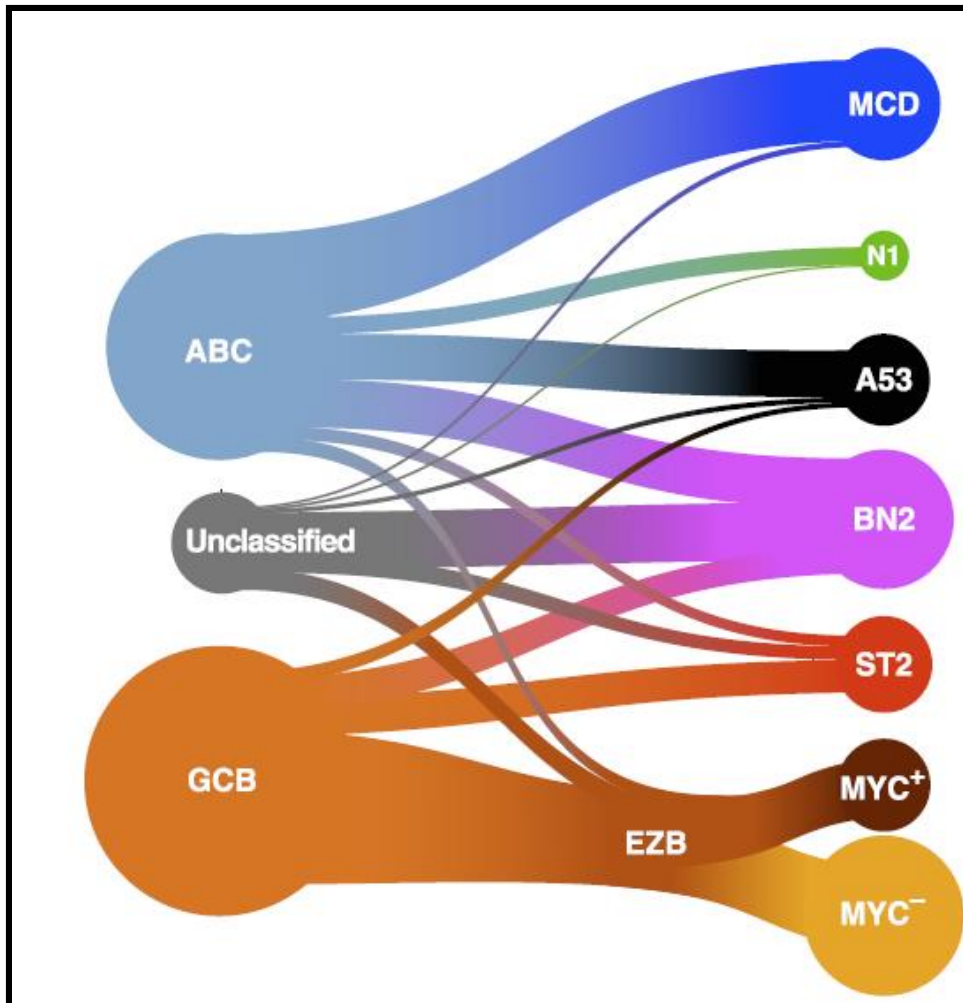
C3 Bad GCB (t(14;18)+/follicular lymphoma origin)

C4 Good GCB

C5 Bad ABC

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

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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

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

2017 Update of WHO Classification

Term “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma” will be discontinued

The new name for these tumors is

High-grade B-cell lymphoma

Two types

Not otherwise specified (NOS)

Double hit lymphoma (genetic)

MYC R + BCL2 R +/- BCL6 R

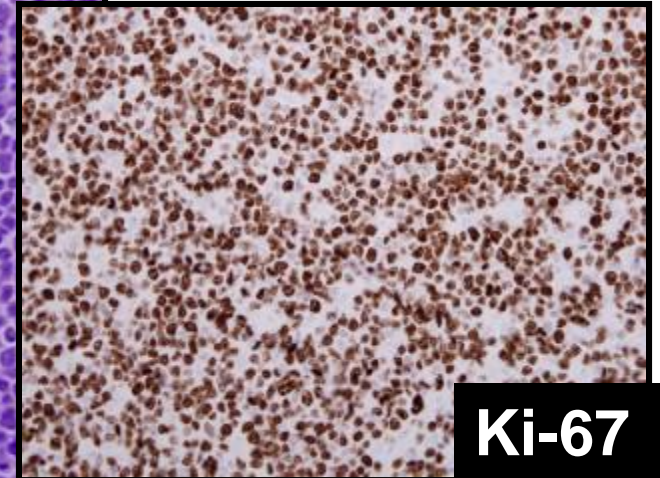
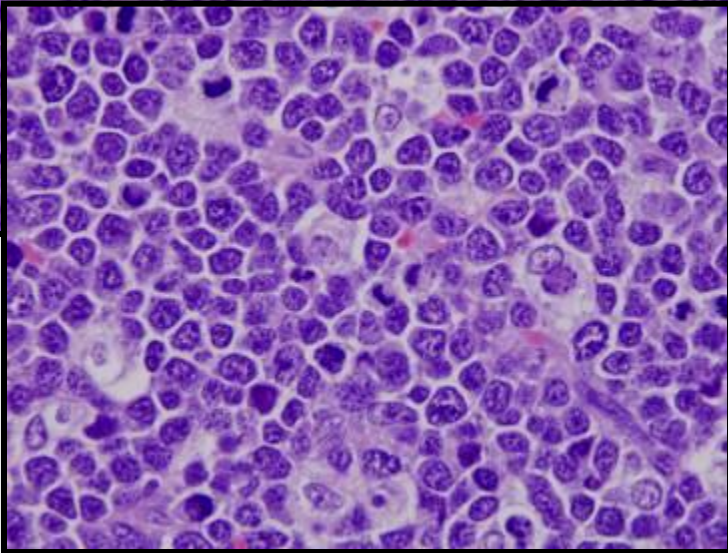
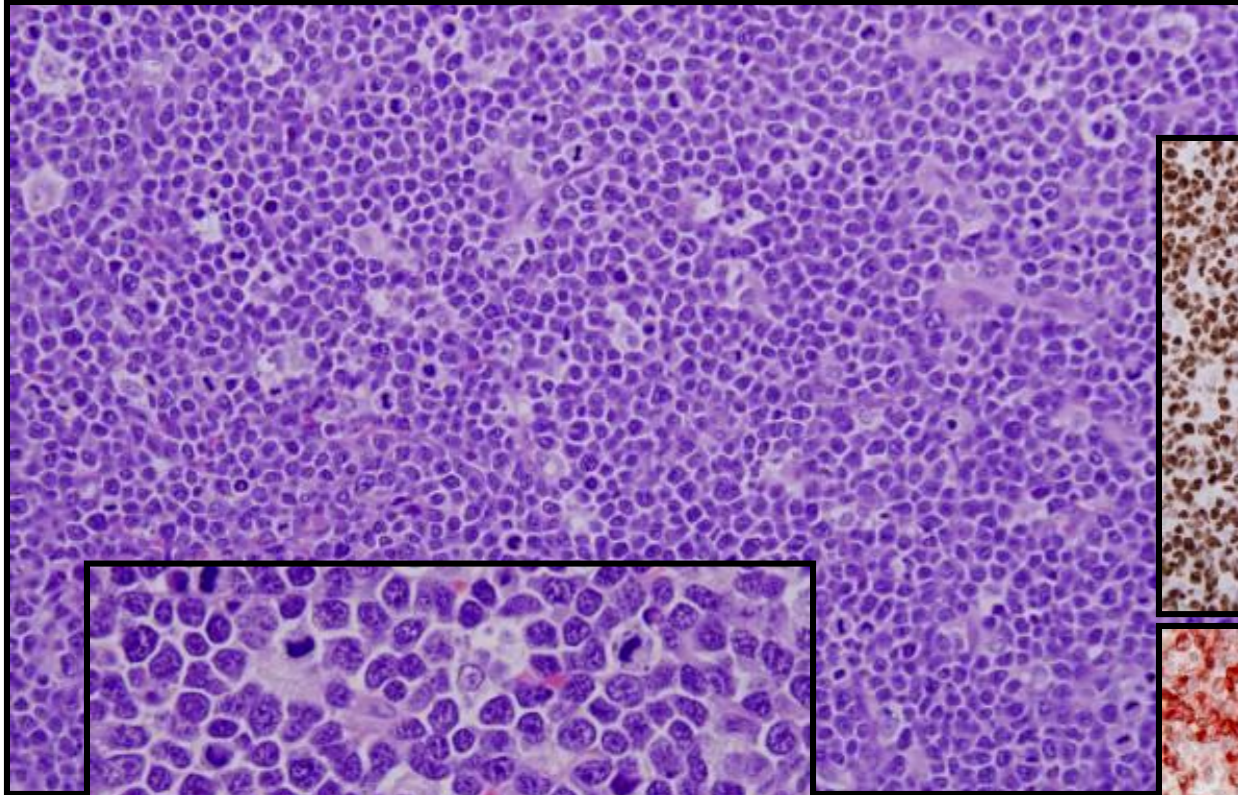
High-grade B-cell Lymphoma

Burkitt-like

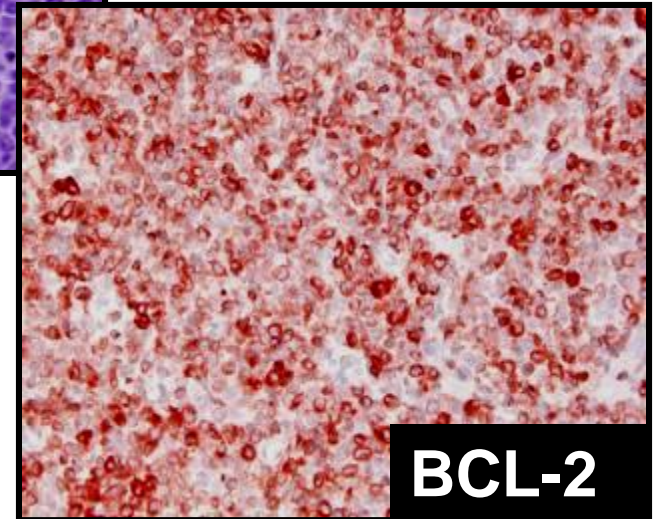


High-grade B-cell Lymphoma

Close mimic of Burkitt



Ki-67

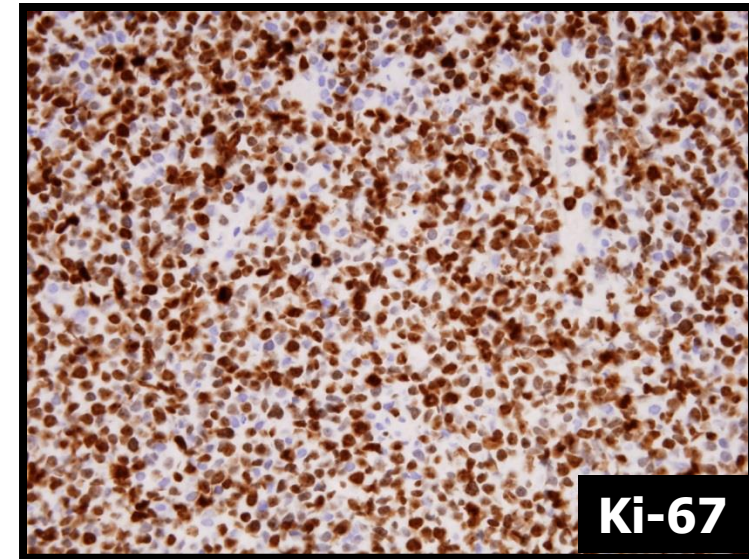
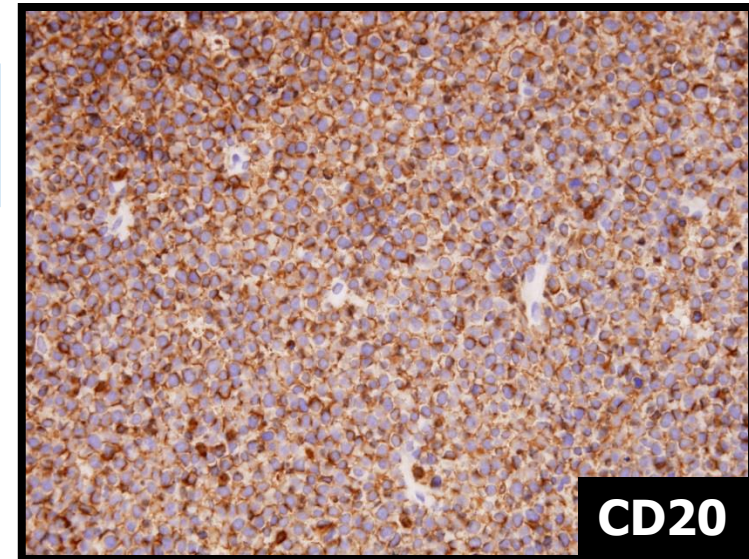
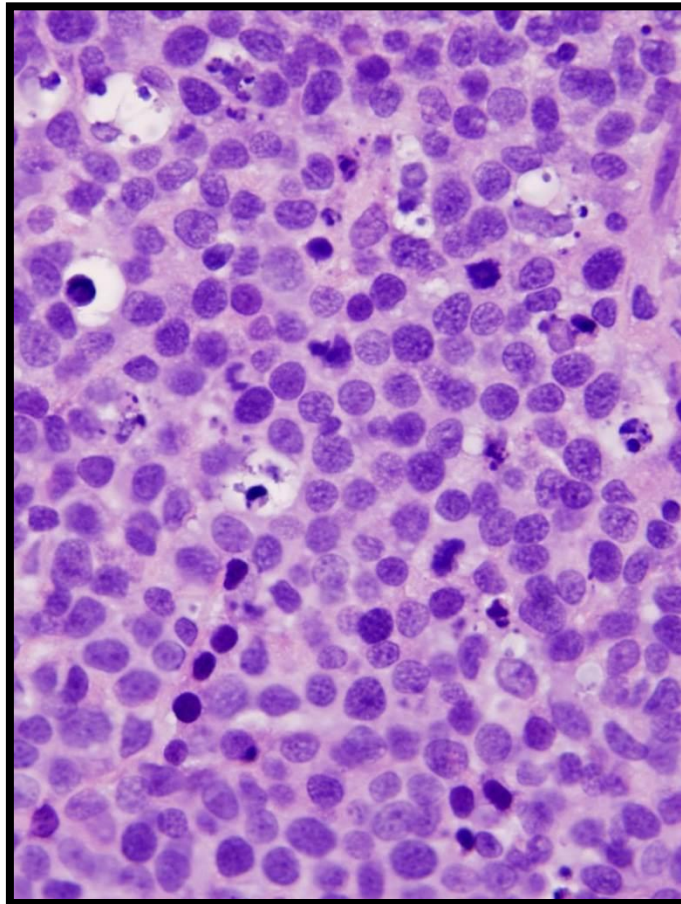


BCL-2

HIGH-GRADE B-CELL LYMPHOMA

Blastoid

Looks like lymphoblastic lymphoma but
negative for TdT or other immature markers



Rashmi Kanagal Shamanna, MD

High-grade B-cell Lymphoma

Morphologic Spectrum

Burkitt-like lymphoma

**Burkitt lymphoma but bcl-2+
Lymphoblastoid**

Diffuse large B-cell lymphoma

Double Hit B-cell Lymphoma

Definition

**Lymphomas with recurrent chromosomal breakpoints activating multiple oncogenes
- one of which is MYC**

MYC + BCL-2

MYC + BCL-6

MYC + BCL-2 + BCL-6 (triple hit)

MYC + BCL-3

MYC + CCND1

High-grade B-cell Lymphoma with Double Hit Genetics Morphologic Spectrum

Burkitt-like lymphoma

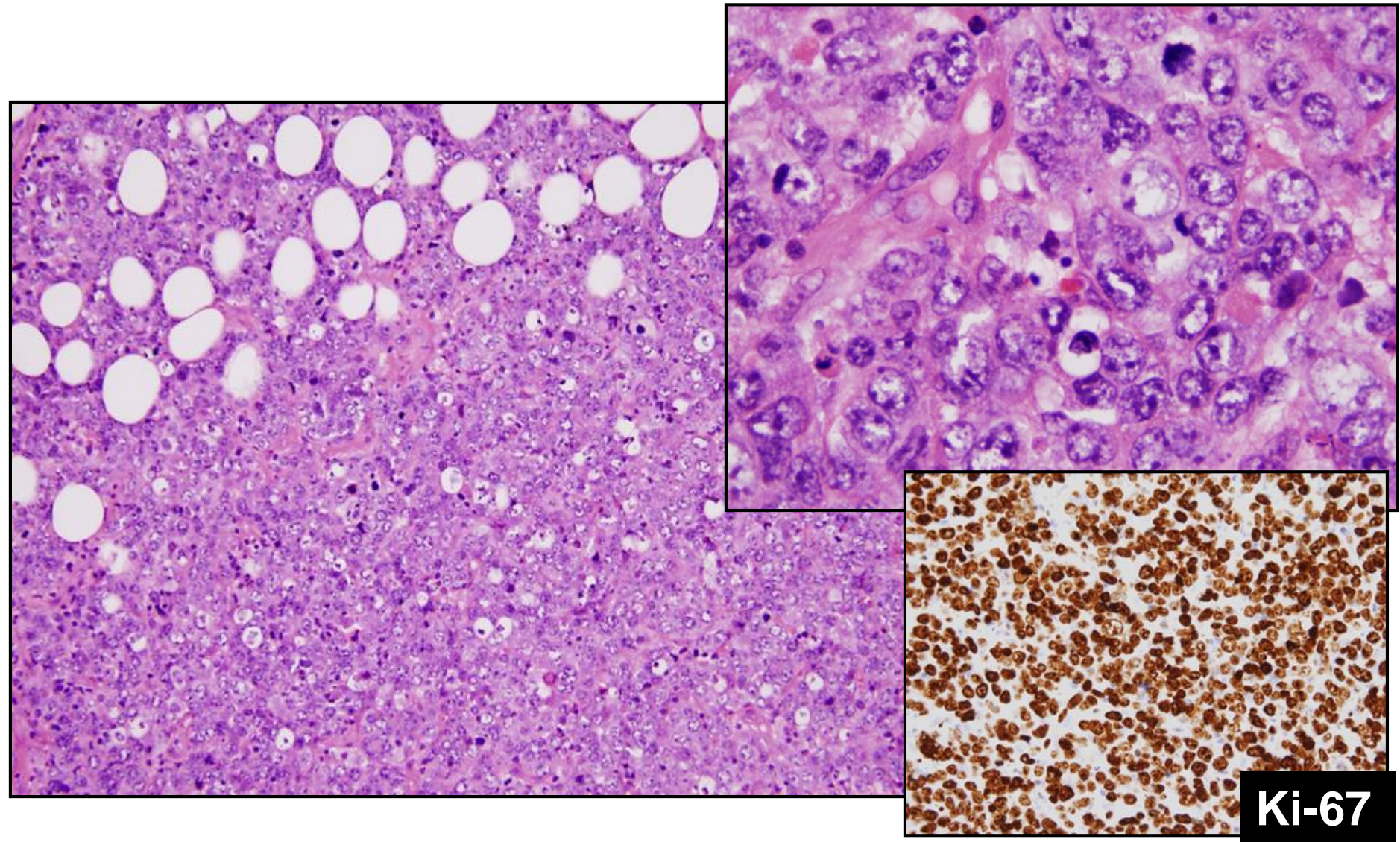
Burkitt lymphoma but bcl-2+

Lymphoblastoid

Diffuse large B-cell lymphoma

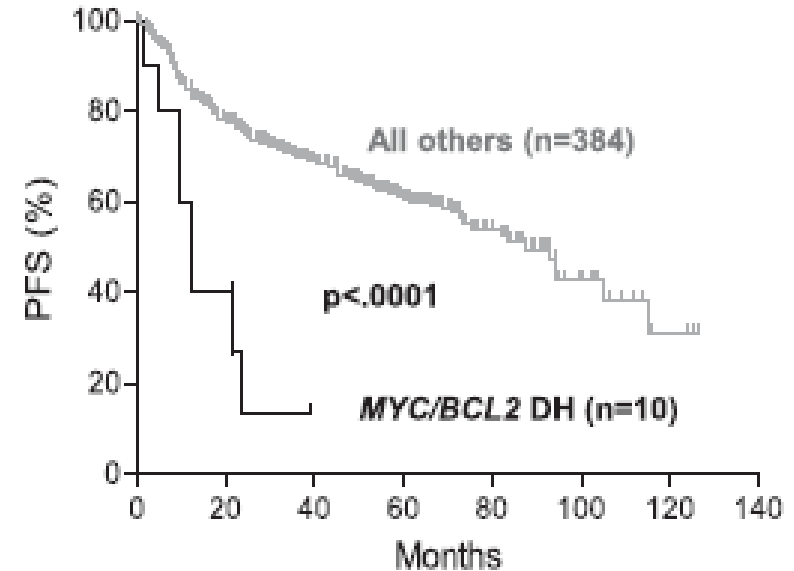
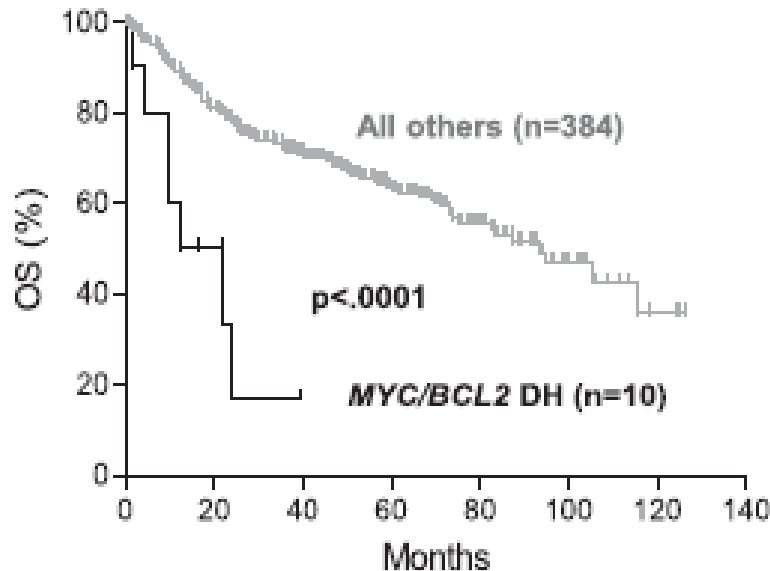
DLBCL morphology is most common

MYC/BCL2 Double Hit B-cell lymphoma



DLBCL with *MYC* and *BCL2* Translocations

A Poor Prognostic Subset



Pts with MYC/BCL2 double hit lymphoma have very poor prognosis

~8-10% of tumors that are DLBCL-like
~20-30% of tumors that are Burkitt-like

Frequency of Double Hit Lymphoma Types

Multi-institutional study of 117 cases

MYC/BCL2 65%

MYC/BCL2/BCL6 21%

MYC/BCL6 14%



Dan Landsburg, MD
Univ of Penn

Prognosis poor for all types

MYC/BCL2 DHL and triple hit cases similar

Landsburg et al. Cancer 122:559, 2016

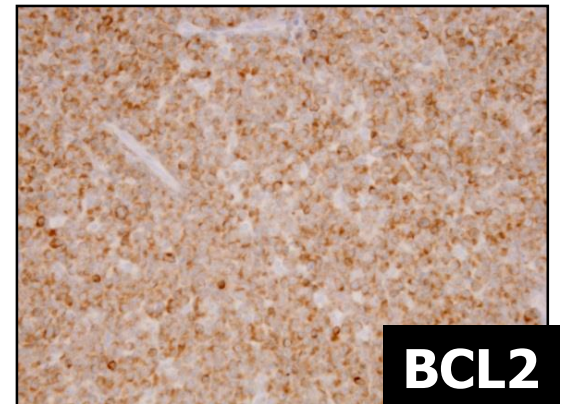
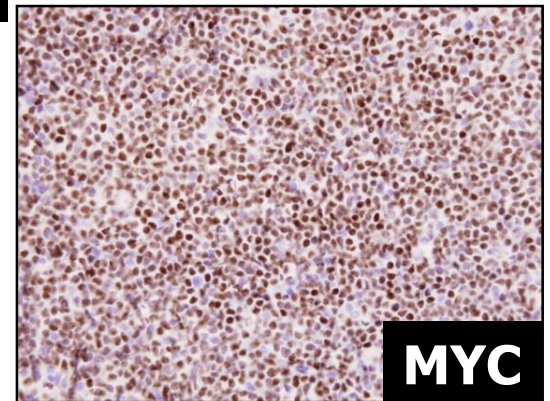
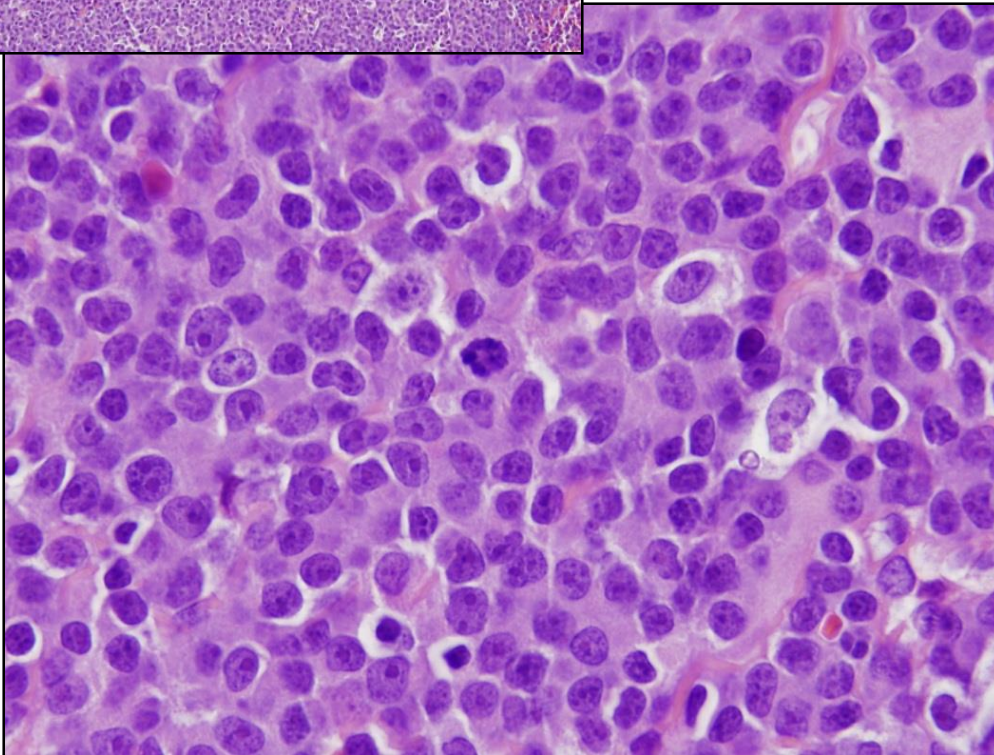
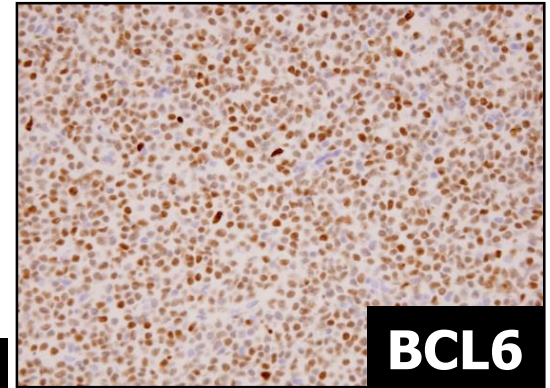
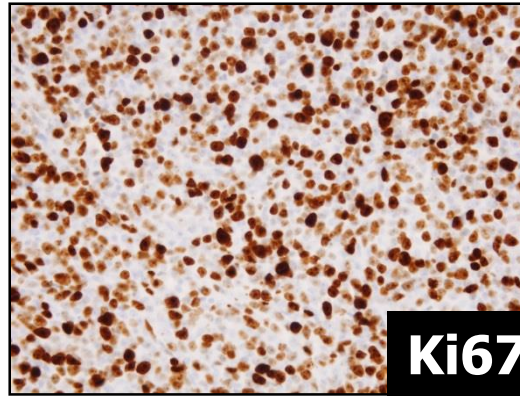
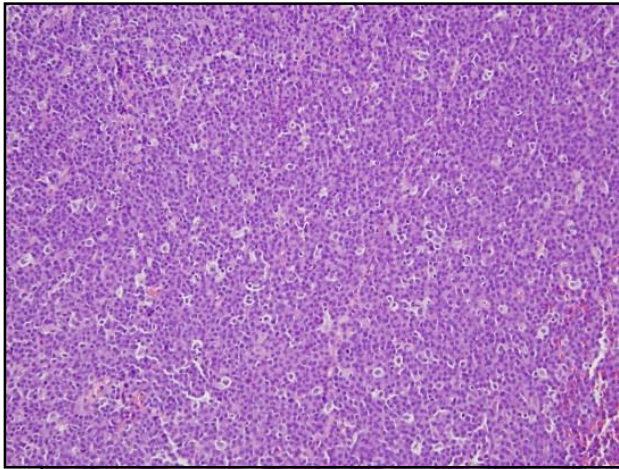
MYC/BCL6 DHL a little different

More often extranodal (liver)

GCB and non-GCB

Pillai et al. Am J Surg Pathol 37:323, 2013
Turakhia et al. Am J Clin Pathol 142: 339, 2014

MYC/BCL6 DHL c/w HGBL



Double-Hit Gene Expression Signature Defines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma

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Methods

J Clin Oncol 37: 190, 2019

157 GCB DLBCL cases

RNA sequencing

25 cases of *MYC/BCL2* double hit lymphoma (DHL)

New Tool

104 gene expression signature for *MYC/BCL2* DHL

Results

42 had DHL signature

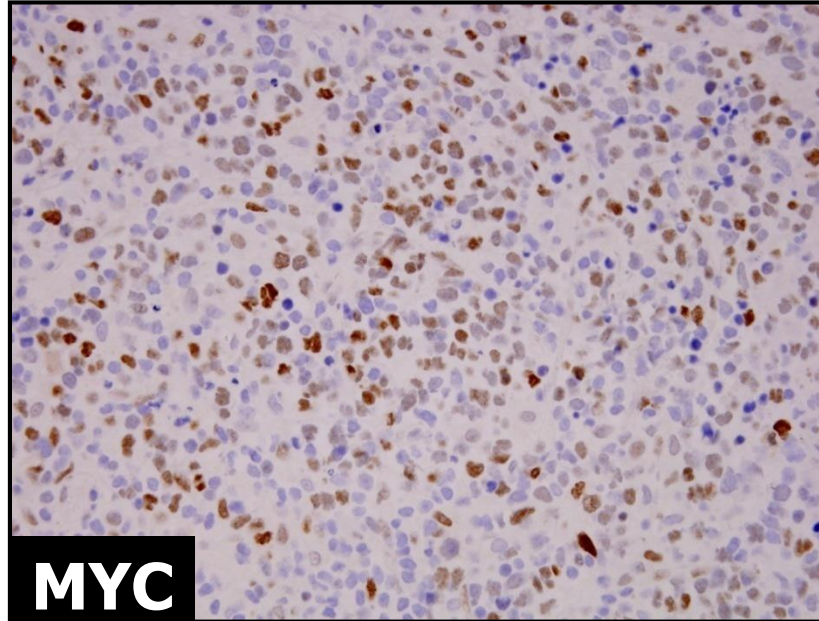
22/25 (77%) *MYC/BCL2* DHLs tested by FISH

115 did not have DHL signature

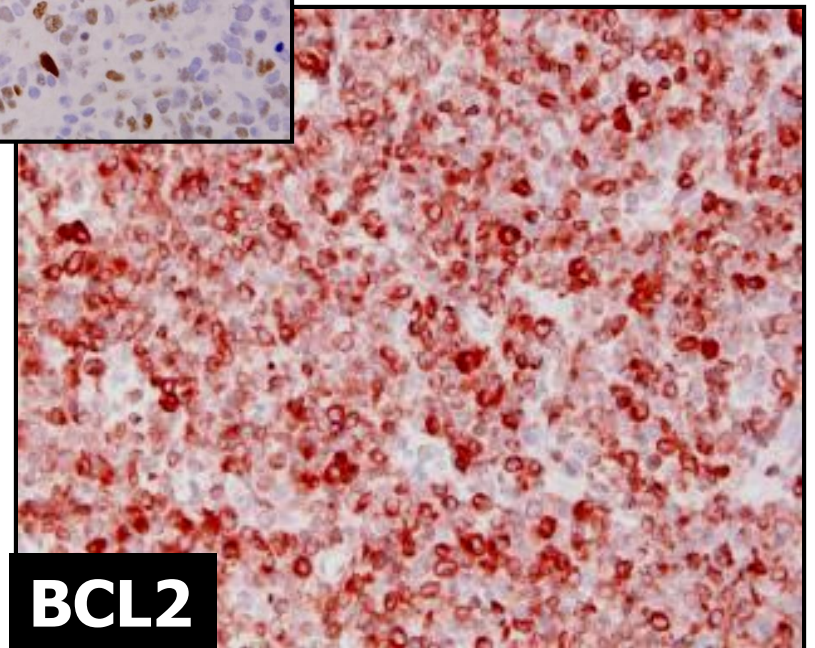
3/25 (13%) *MYC/BCL2* DHLs tested by FISH

MYC and BCL2 IHC

**Epitomics,
MoAb Y69**



**Dako,
MoAB 124**



Can MYC and BCL2 IHC Serve as Surrogates for Genetic Studies?

~ 30% of DLBCL coexpress MYC and BCL2

~ 5-10% of DLBCL have rearrangements of *MYC* and *BCL2* (double hit)

>95% all cases of DHL lymphoma express BCL2 by IHC

MYC IHC is the challenge

Not specific

Not completely sensitive



Shaoying Li, MD

MYC Cytogenetic Status Correlates With Expression and Has Prognostic Significance in Patients With MYC/BCL2 Protein Double-positive Diffuse Large B-cell Lymphoma

Xuan Julia Wang, MD, L. Jeffrey Medeiros, MD,† Pei Lin, MD,† C. Cameron Yin, MD, PhD,† Shimin Hu, MD, PhD,† Mary Ann Thompson, MD, PhD,* and Shaoying Li, MD*†*

TABLE 2. Sensitivity and Specificity of Using MYC Protein Expression by Immunohistochemistry to Detect MYC Cytogenetic Abnormalities

MYC IHC ⁺		MYC FISH Abnormality Detected by IHC						
% Cutoff	Total No.	MYC-RA (n = 32)	MYC-RA (Sensitivity) (%)	MYC-RA (Specificity) (%)	MYC-MC (n = 34)	MYC-MC (Sensitivity) (%)	MYC-(MC + RA) (Sensitivity) (%)	MYC-(RA + MC) Specificity (%)
90	14	13	41	99	0	0	20	98
80	19	16	84	97	0	0	24	95
70	27	18	56	91	3	9	32	91
60	42	21	66	79	10	29	47	83
50	56	25	78	69	13	38	58	72
40	65	26	81	61	17	50	65	66
30	95	28	88	32	22	65	76	31
20	106	29	91	22	23	68	79	18
10	116	31	97	14	28	82	89	14
0	131	32	100	0	34	100	100	0

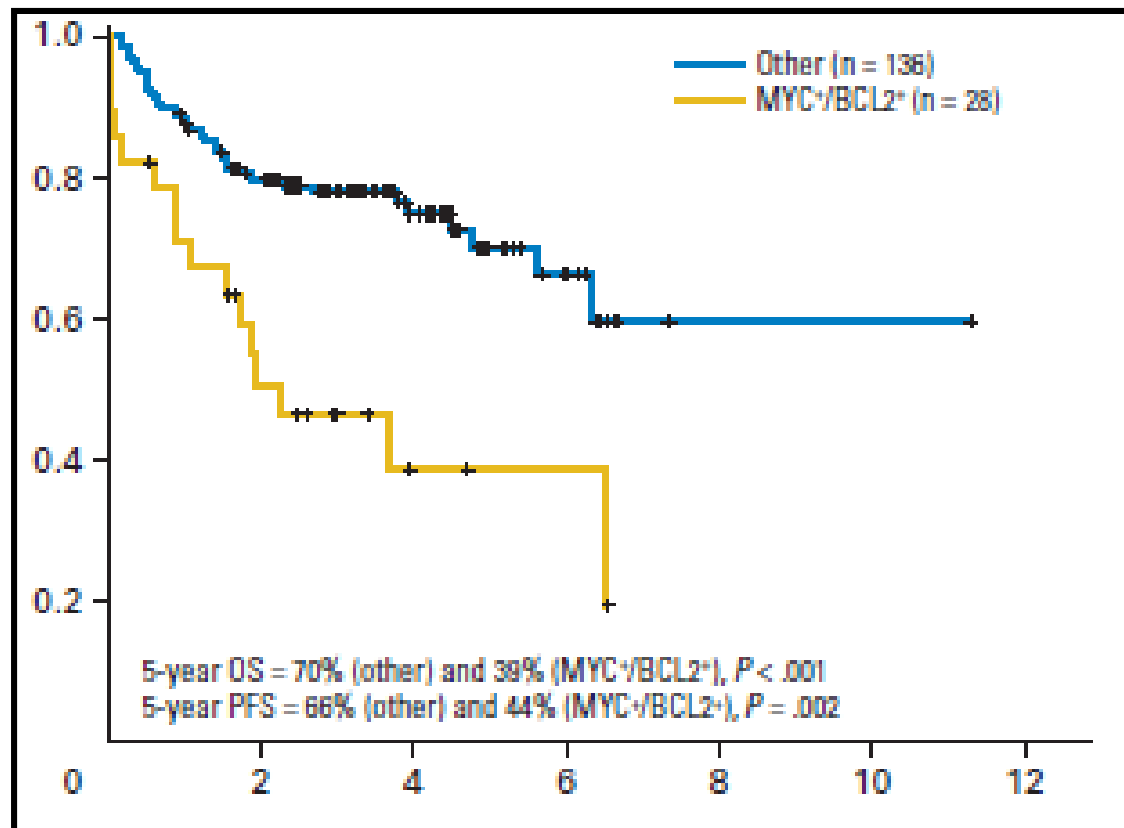
MC indicates multiple copies; RA, rearrangement.

80% sensitive with 40% cutoff

Am J Surg Pathol 39: 1250, 2015

MYC+ BCL2+ DLBCL By IHC

Patients Have a Poorer Prognosis



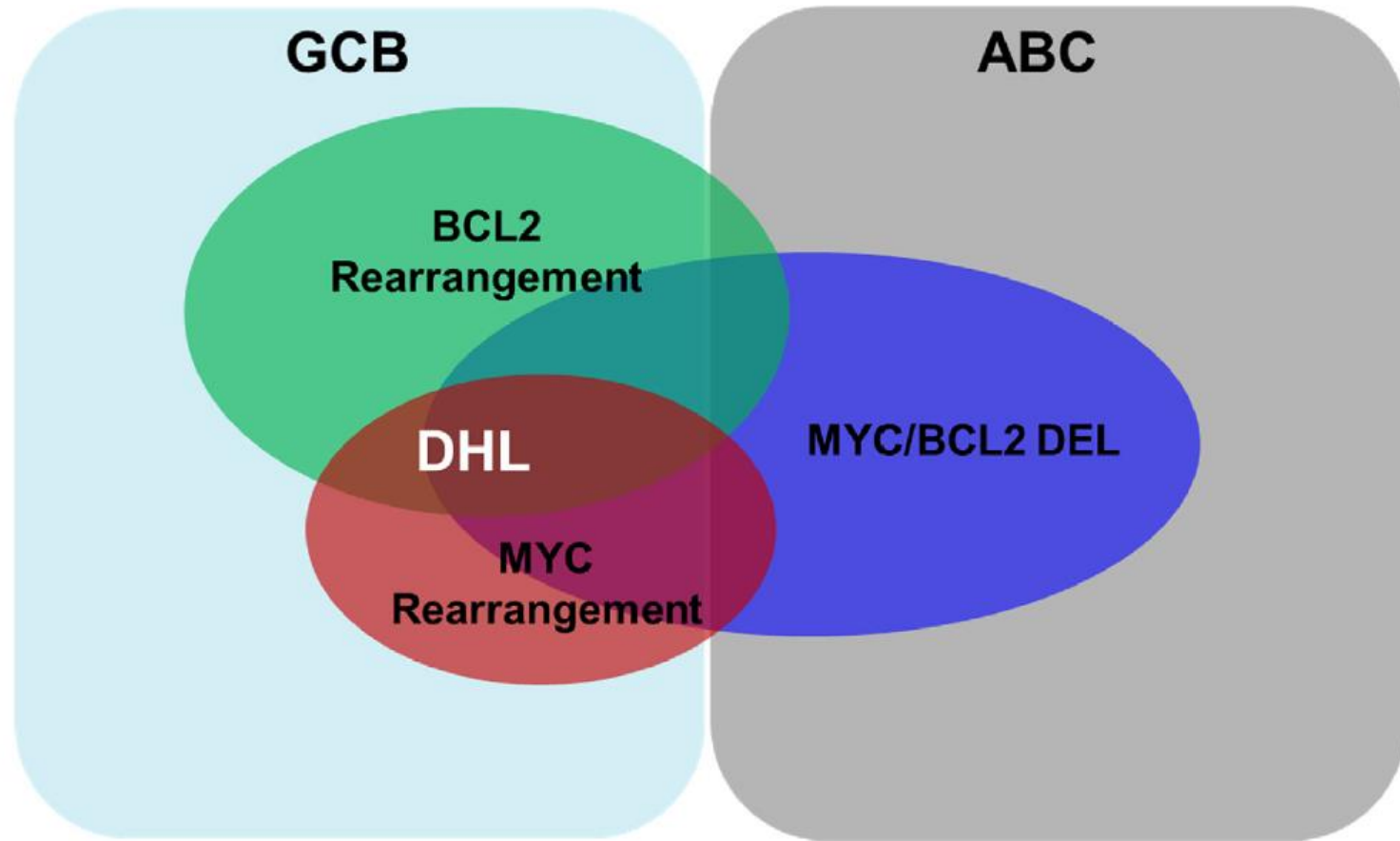
Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

Nathalie A. Johnson, Graham W. Slack, Kerry J. Savage, Joseph M. Connors, Susana Ben-Neriah, Sanja Rogic, David W. Scott, King L. Tan, Christian Steidl, Laurie H. Sehn, Wing C. Chan, Javeed Iqbal, Paul N. Meyer, Georg Lenz, George Wright, Lisa M. Rimsza, Carlo Valentino, Patrick Brunhoeber, Thomas M. Grogan, Rita M. Brazier, James R. Cook, Raymond R. Tubbs, Dennis D. Weisenburger, Elias Campo, Andreas Rosenwald, German Ott, Jan Delabie, Christina Holcroft, Elaine S. Jaffe, Louis M. Staudt, and Randy D. Gascoyne

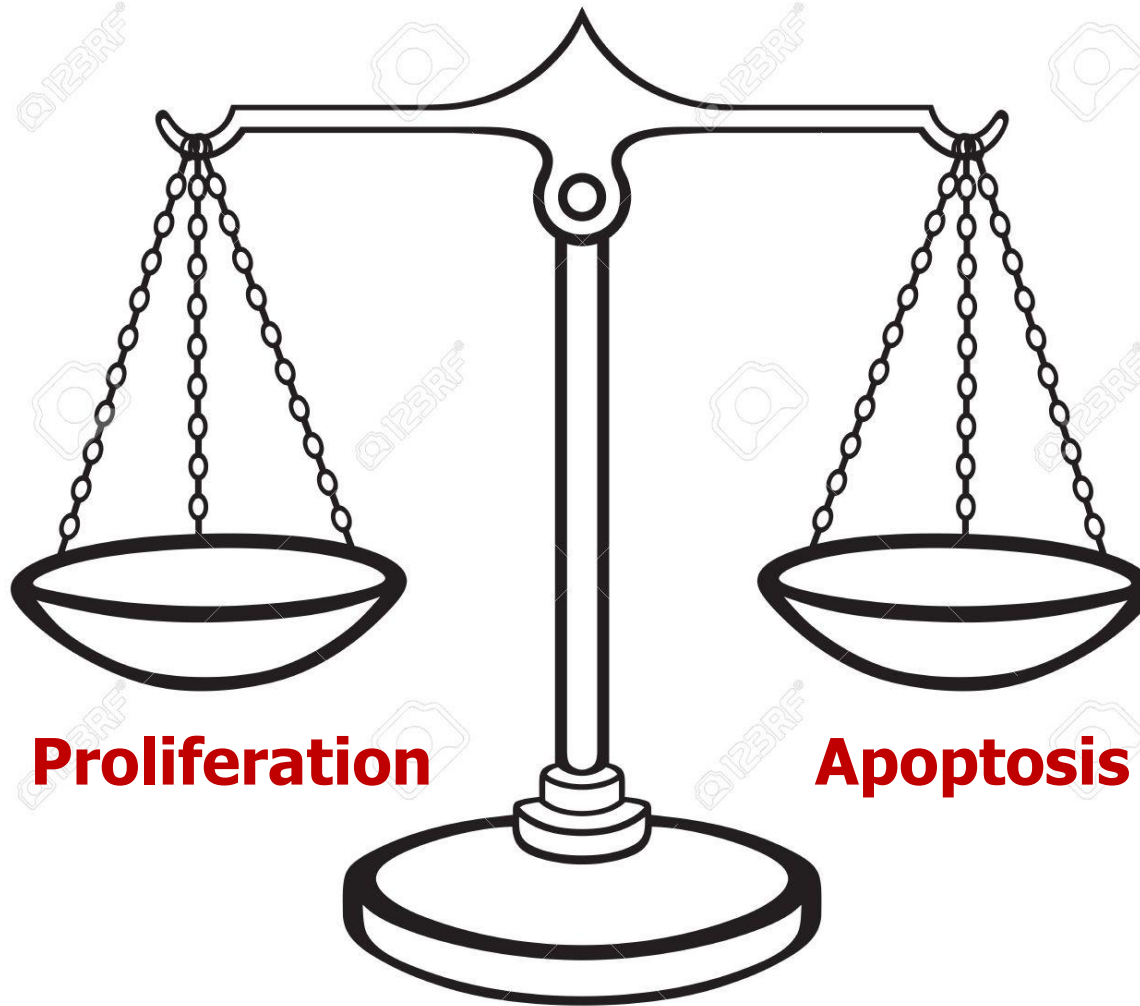
Double expressor lymphoma

J Clin Oncol 30: 3452, 2012

Double Hit vs Double Expressor



MYC INDUCES PROLIFERATION AND APOPTOSIS



***TP53* mutations are frequent events in double-hit B-cell lymphomas with *MYC* and *BCL2* but not *MYC* and *BCL6* translocations**

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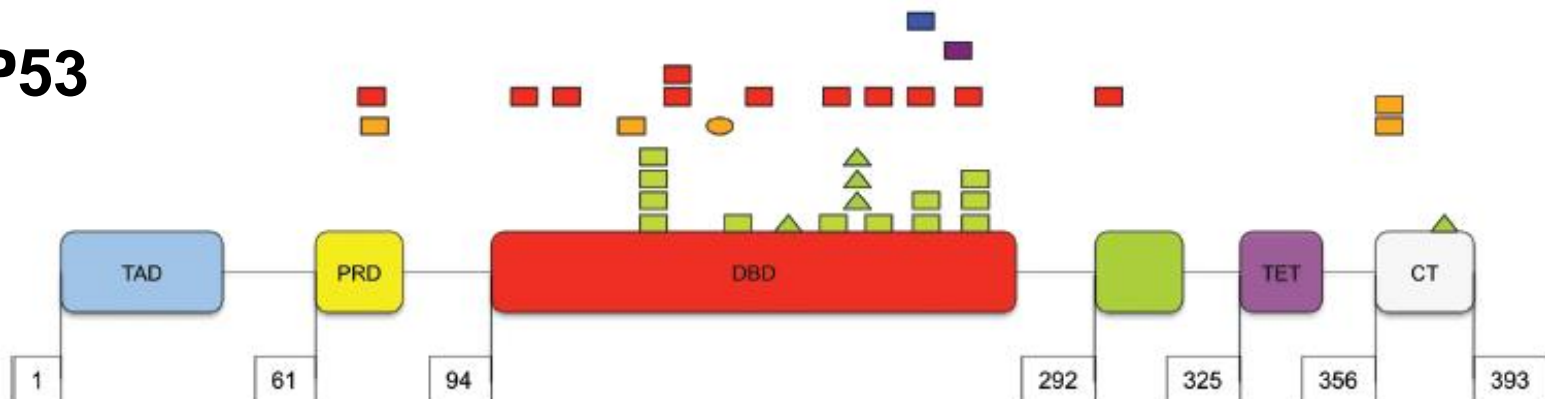
¹Department of Pathology, Reference Center for Lymph Node Pathology and Hematopathology, University Hospital of Schleswig-Holstein, Luebeck, Germany and ²German Red Cross Blood Transfusion Service, Institute Oldenburg, Oldenburg, Germany

Leuk Lymphoma 56: 179, 2015

10/18 (56%) Burkitt,
6/17 (35%) MYC/BCL2 DHL
3/20 (15%) DLBCL
1/16 (6%) MYC/BCL6 DHL

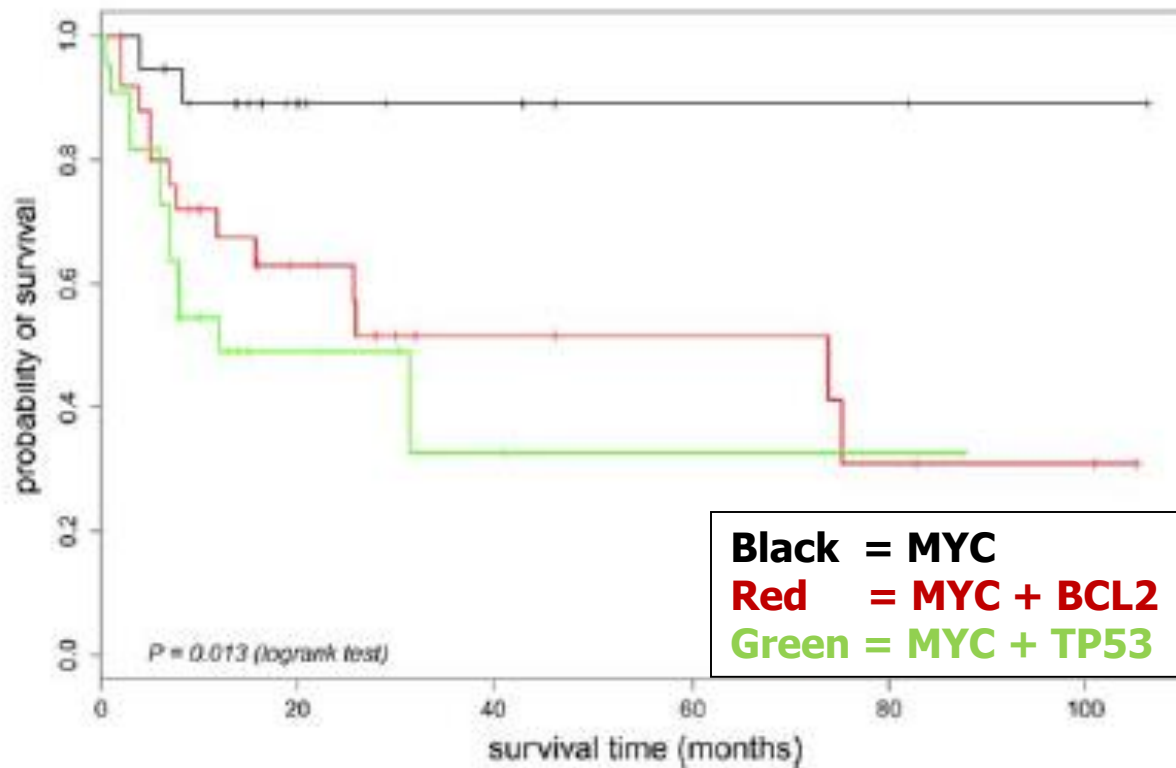
□ = missense
○ = nonsense
△ = frameshift

TP53



The prognosis of *MYC* translocation positive diffuse large B-cell lymphoma depends on the second hit

Alexandra Clipson,¹ Sharon Barrans,² Naiyan Zeng,¹ Simon Crouch,³ Nicholas F Grigoropoulos,^{1,4} Hongxiang Liu,⁵ Sylvia Kocialkowski,¹ Ming Wang,¹ Yuanxue Huang,¹ Lisa Worrillow,² John Goodlad,⁶ Jenny Buxton,⁷ Michael Neat,⁸ Paul Fields,⁹ Bridget Wilkins,¹⁰ John W Grant,⁵ Penny Wright,⁵ Hesham El-Daly,⁴ George A Follows,⁴ Eve Roman,³ A James Watkins,⁴ Peter W M Johnson,¹¹ Andrew Jack² and Ming-Qing Du^{1,5*}



MYC TRANSLOCATION AND TP53 MUTATION

Patients have a poor outcome

As bad as MYC/BCL2 DHL

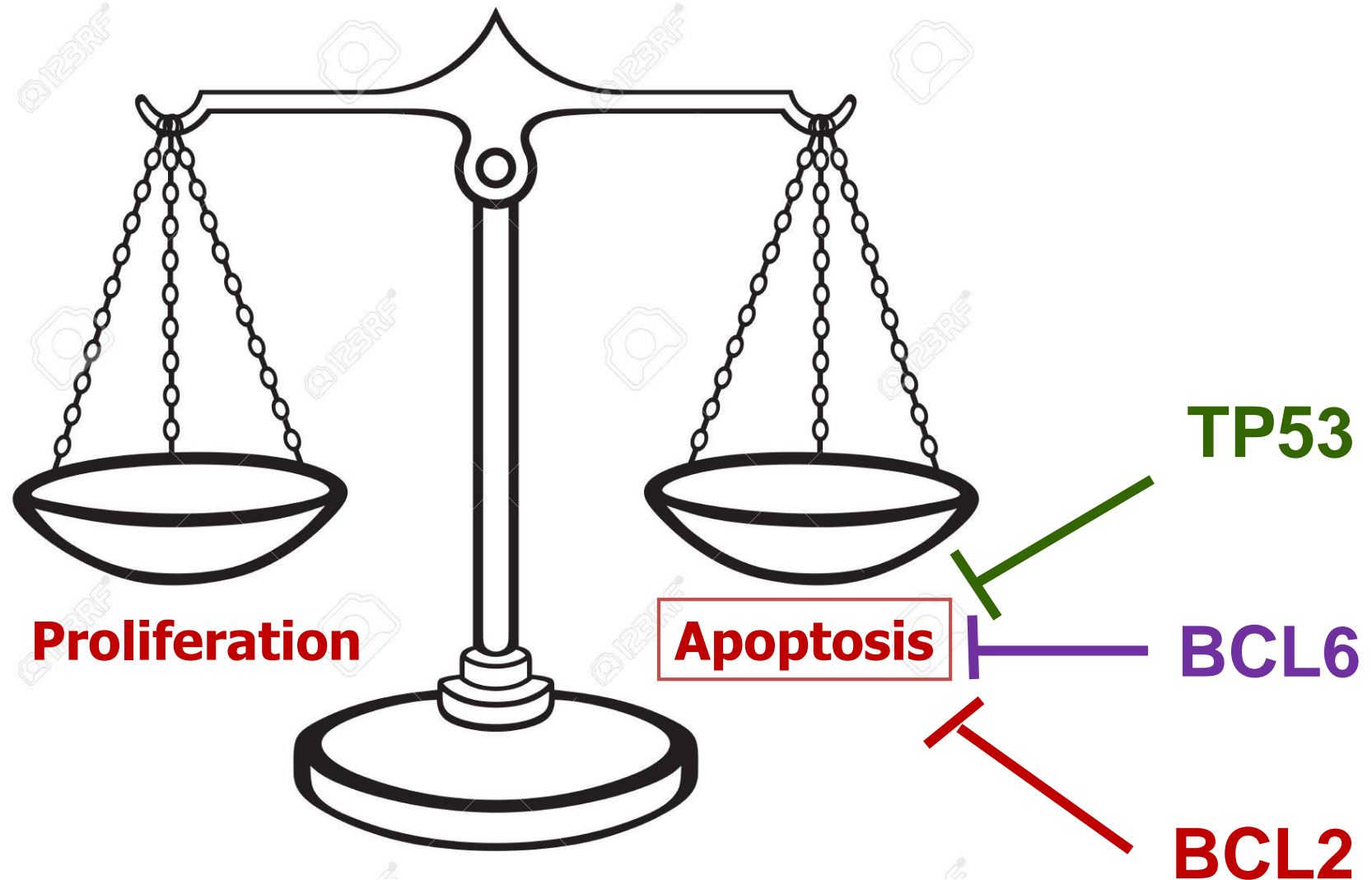
Another type of double hit lymphoma?

P53 IHC \geq 50% highly correlates with mutation

We suggest adding p53 to IHC panel

Molecular testing to confirm

MYC INDUCES PROLIFERATION AND APOPTOSIS



Outline

Diffuse Large B-cell lymphoma (DLBCL), NOS

Introduction/2017 WHO classification

Clinical

Morphology

Immunophenotype

Chromosomal translocations

Cell-of-origin (COO) classification

Gene mutations

Recent studies integrating COO and genetics

High-grade B-cell lymphoma

Not otherwise specified (NOS)

***MYC* and *BCL2* and/or *BCL6* translocations**

Diffuse Large B-cell Lymphoma

References

Pathology (January 2018) 50(1), pp. 74–87

REVIEW: 50TH ANNIVERSARY ISSUE

Diffuse large B-cell lymphoma

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Pathology (January 2020) 52(1), pp. 68–77

LYMPHOMA 2020: AN UPDATE

High-grade B-cell lymphoma: a term re-purposed in the revised WHO classification

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