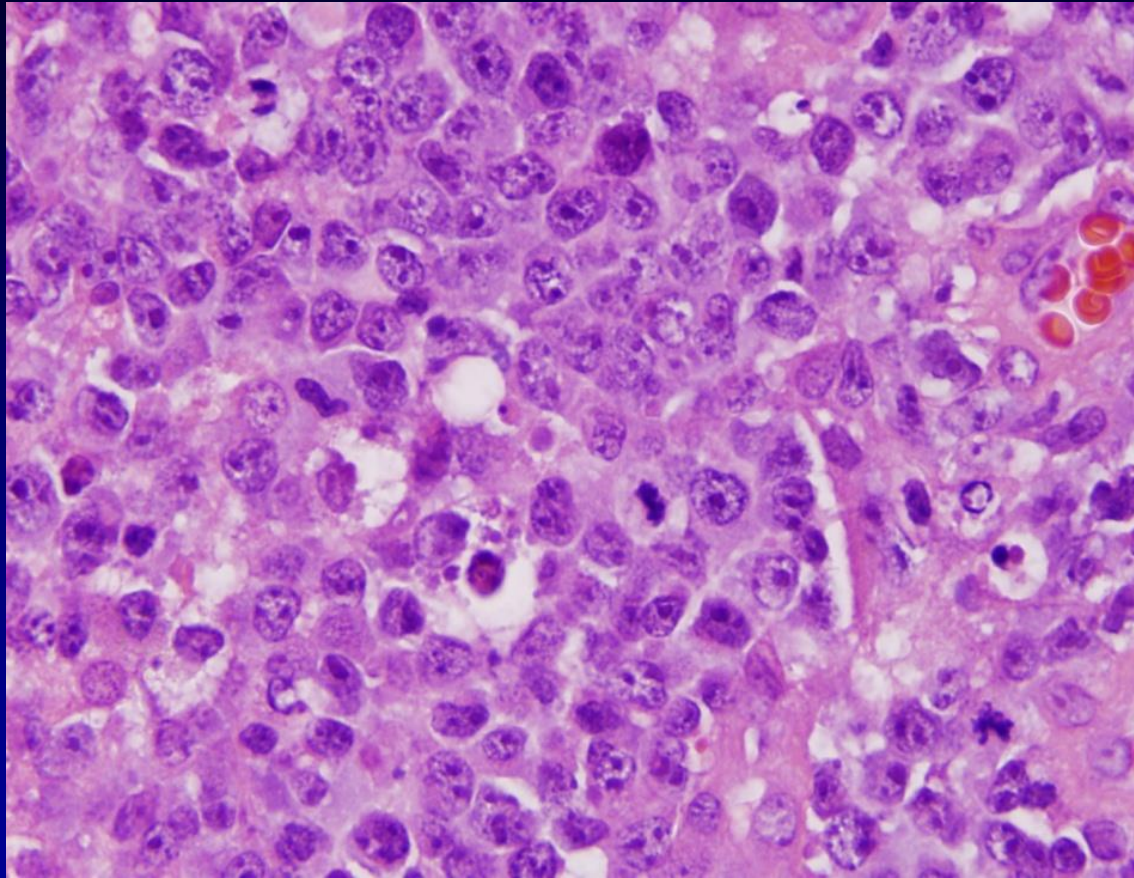


Diffuse Large B-cell Lymphoma



L. Jeffrey Medeiros
MD Anderson Cancer Center

Outline

Introduction and 2016 WHO classification

Features of DLBCL, NOS

Clinical

Morphology

Immunophenotype

Chromosomal translocations

Gene expression profiling

Gene mutations

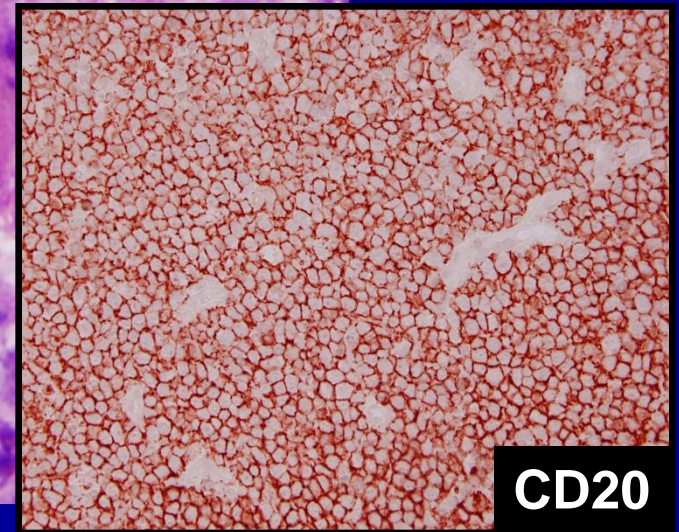
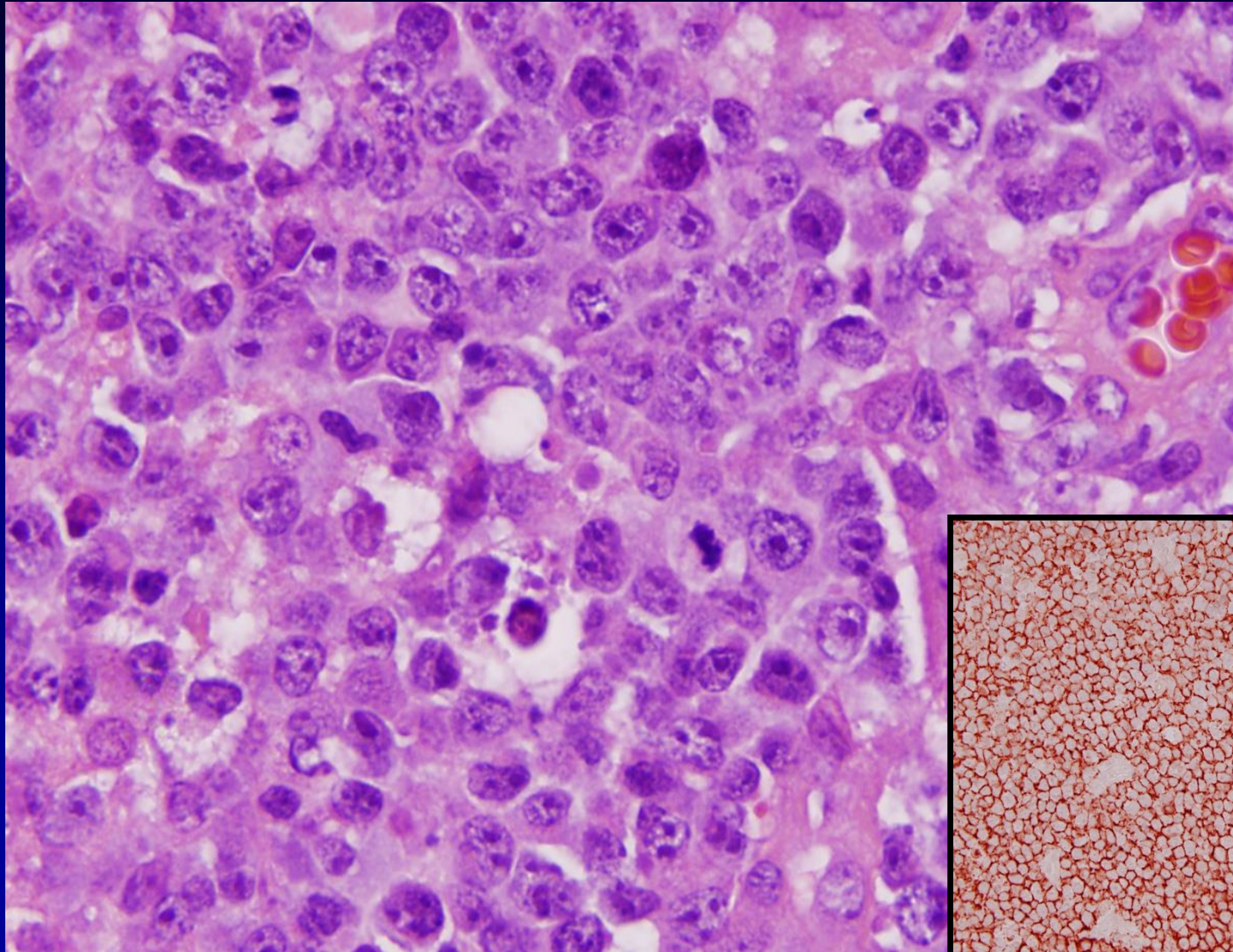
High-grade B-cell lymphoma

Diffuse Large B-cell Lymphoma

Definition

DLBCL is a neoplasm of large B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei that has a diffuse growth pattern

Diffuse Large B-cell Lymphoma, NOS



CD20

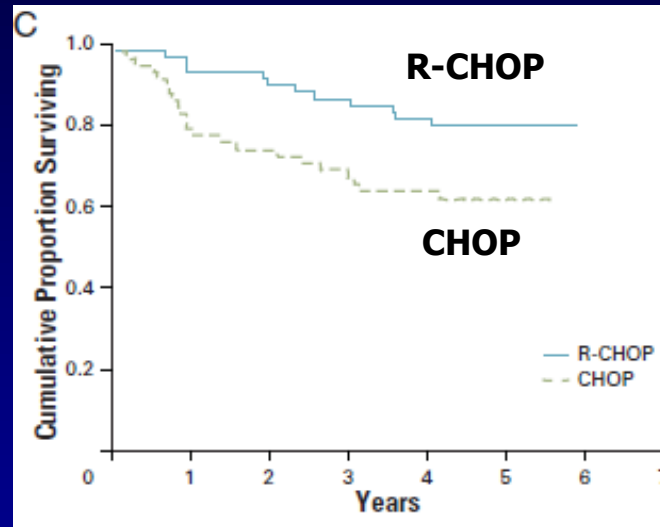
Diffuse Large B-cell Lymphoma

R-CHOP is Standard Frontline Therapy

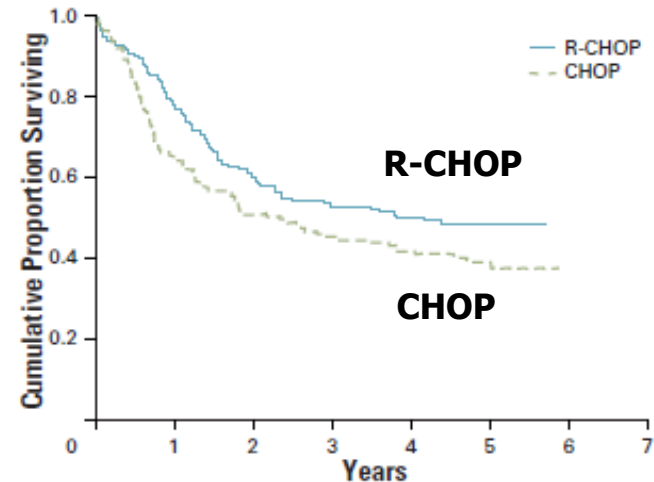


Bertrand Coiffier, MD

Low risk



High risk



Rituximab
Cyclophosphamide
Hydroxydaunorubicin/Adriamycin
Oncovin/vincristine
Prednisone

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

Diffuse large B-cell lymphoma, NOS

GCB versus ABC/non-GCB

CD5

Subtypes

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

Primary DLBCL of the central nervous system

Primary cutaneous DLBCL, leg-type

EBV+ DLBCL

Other lymphomas of large B-cells

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

DLBCL associated with chronic inflammation

Lymphomatoid granulomatosis

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

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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 |

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. Winter¹

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.

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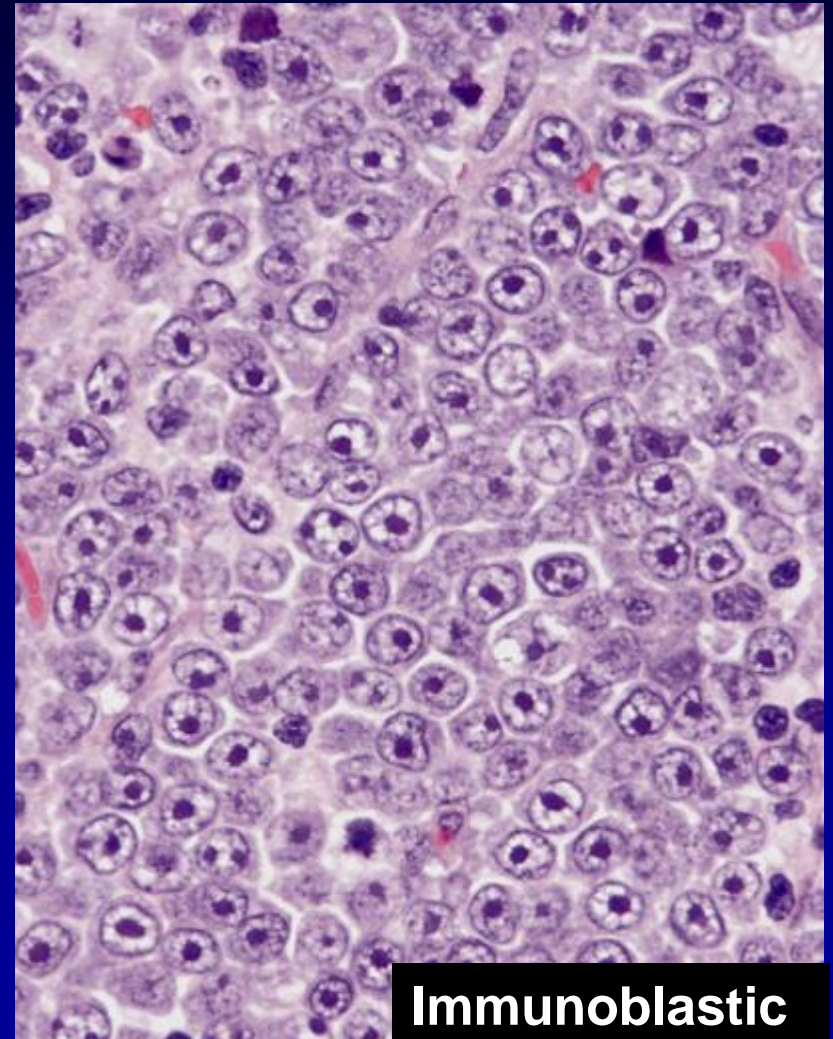
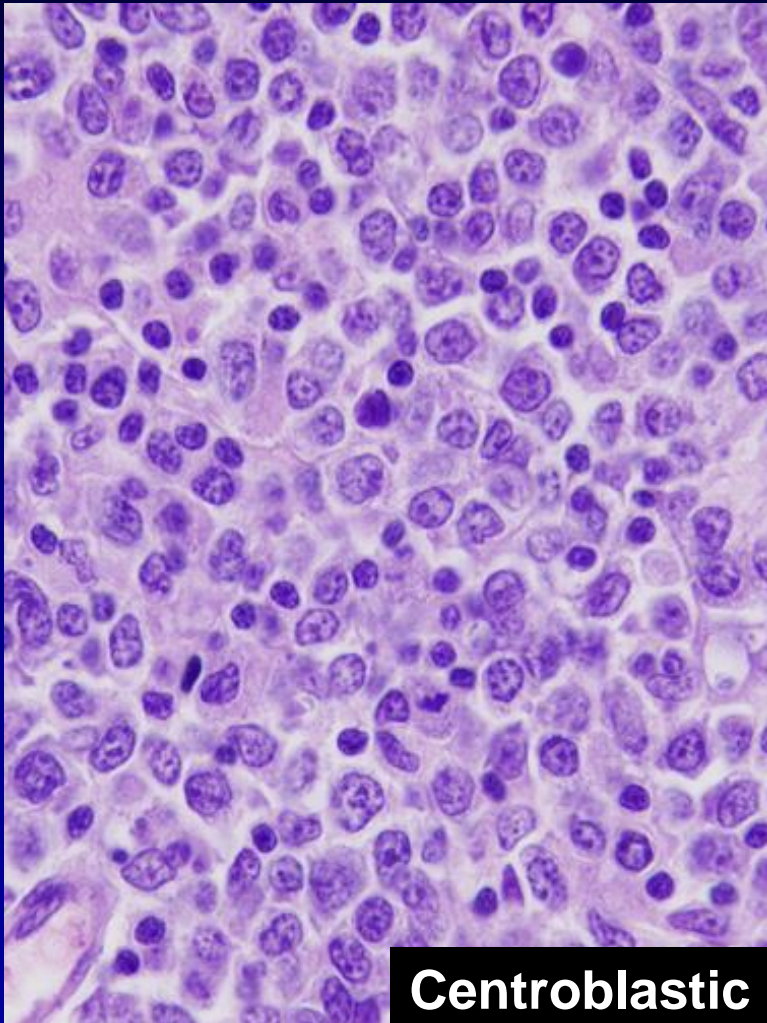
Gene expression profiling

Gene mutations

High-grade B-cell lymphoma

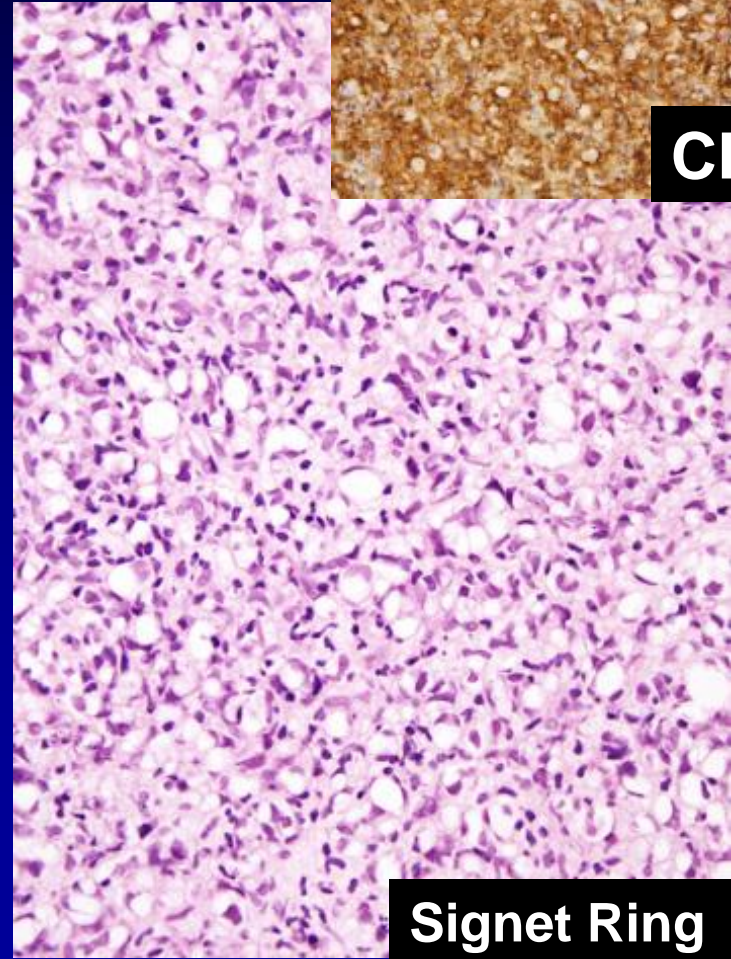
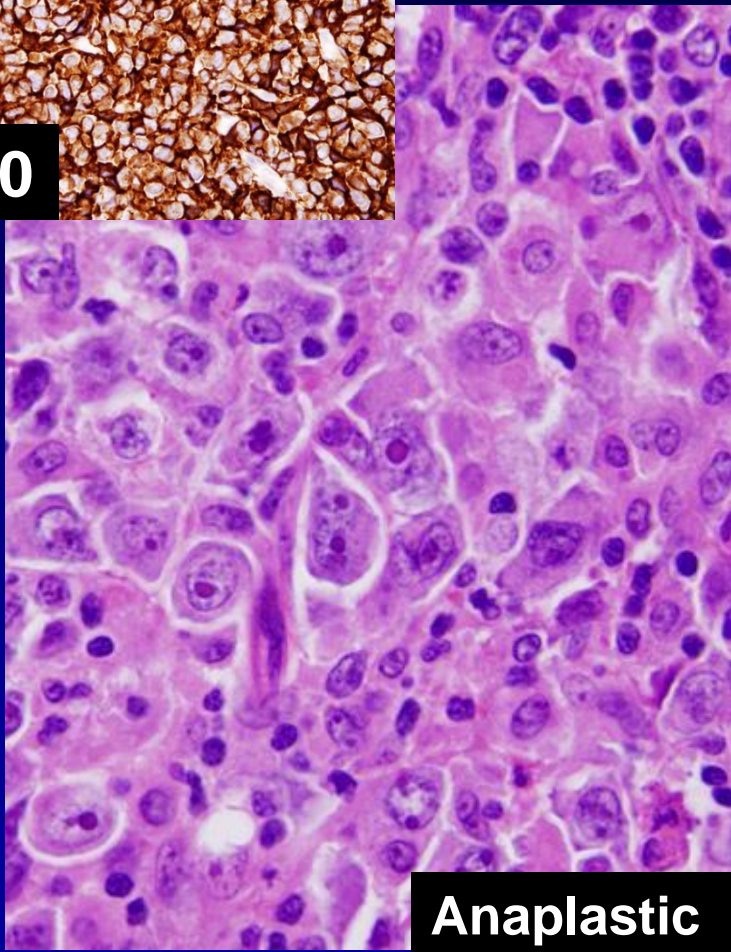
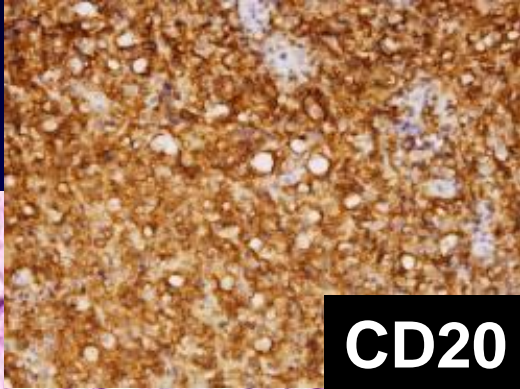
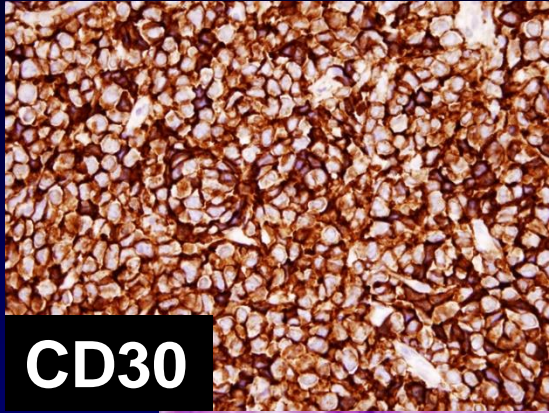
Diffuse Large B-cell Lymphoma NOS

Morphologic Variants



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

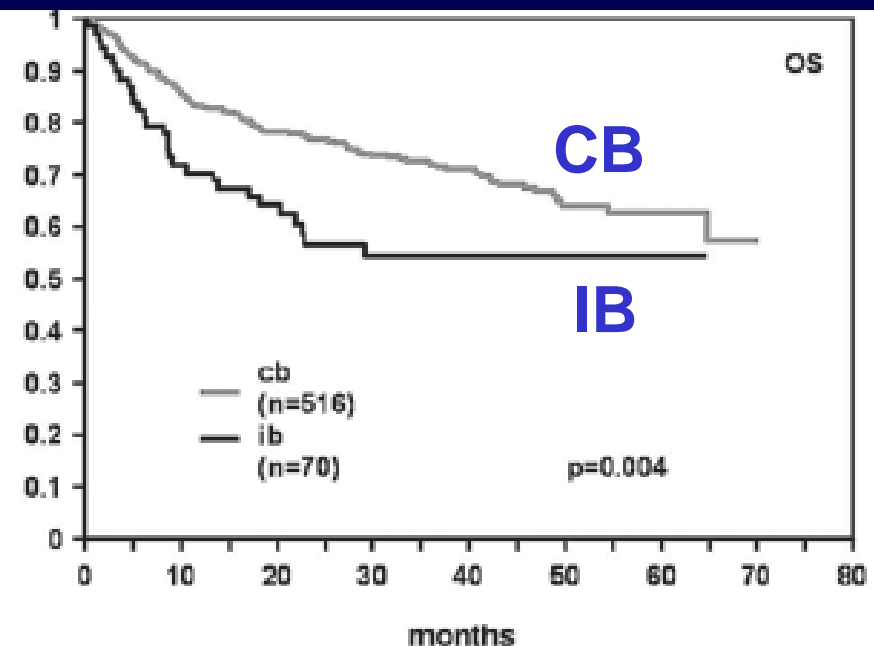
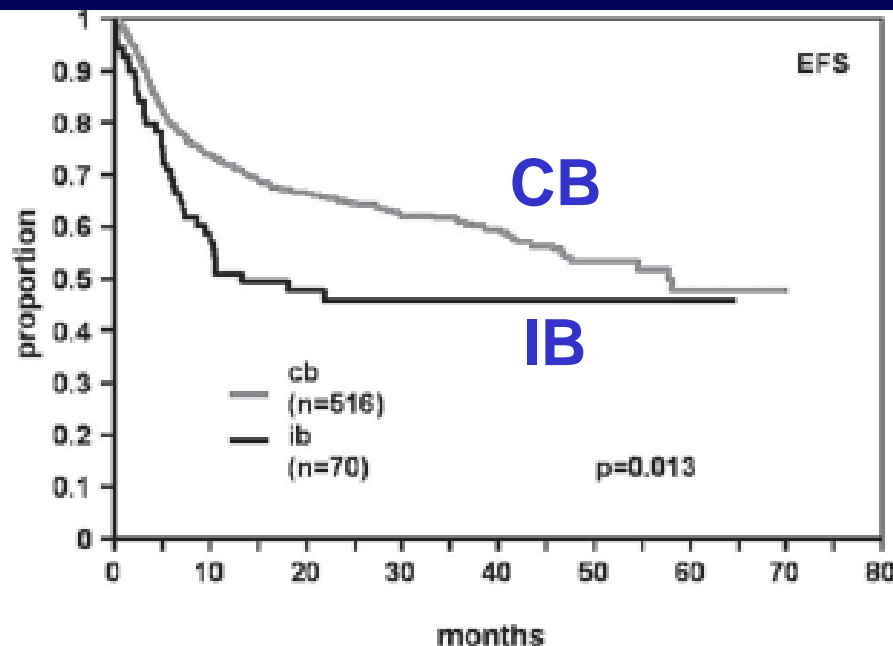
Signet Ring

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



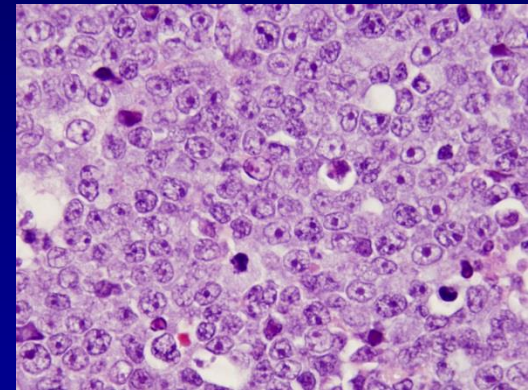
Diffuse Large B-cell Lymphomas of Immunoblastic Type Are a Major Reservoir for *MYC-IGH* Translocations

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**



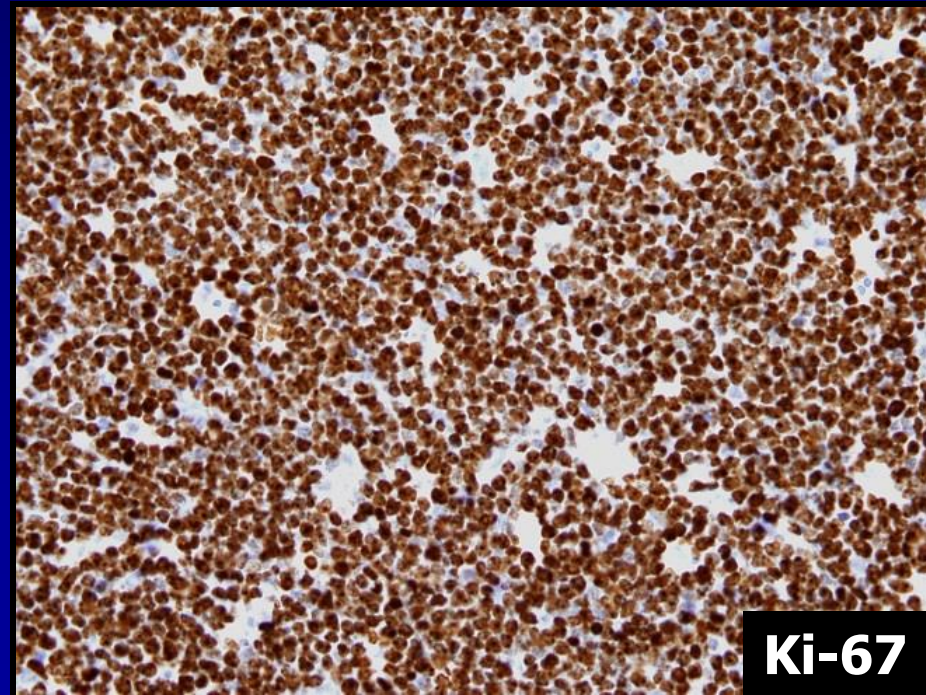
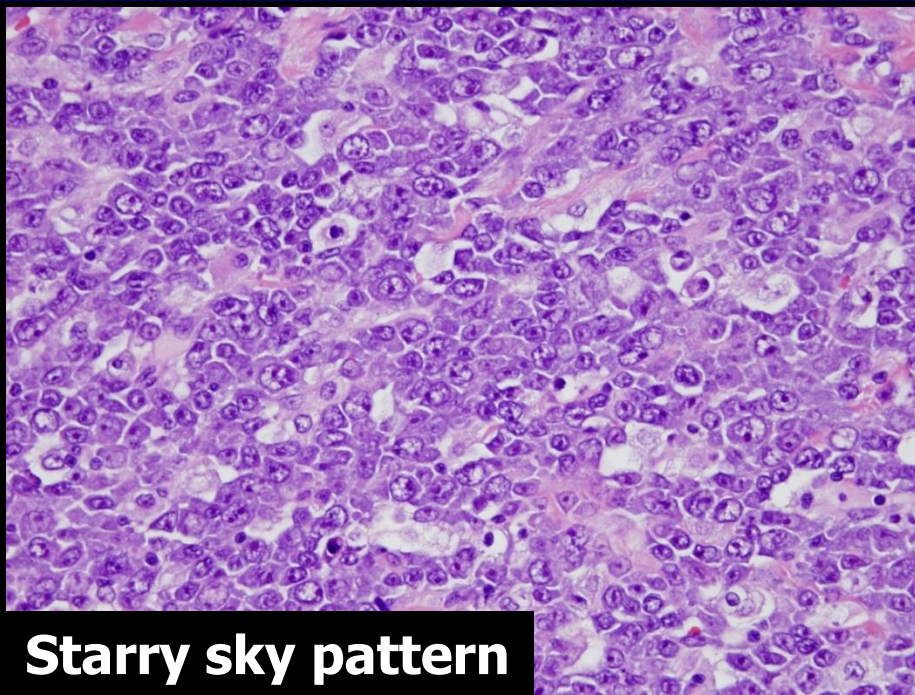
**All immunoblastic DLBCL with *MYC* translocations
had MYC-IGH fusions**

Diffuse Large B-cell Lymphoma

Features that Correlate with Poorer Prognosis

Starry sky pattern

High mitotic / proliferation (Ki-67) rate



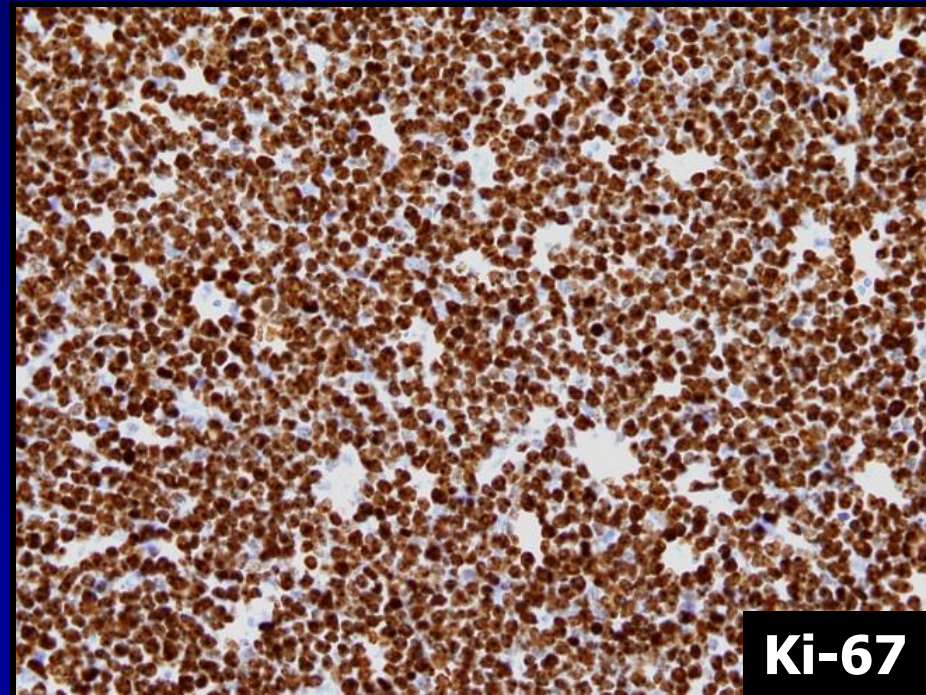
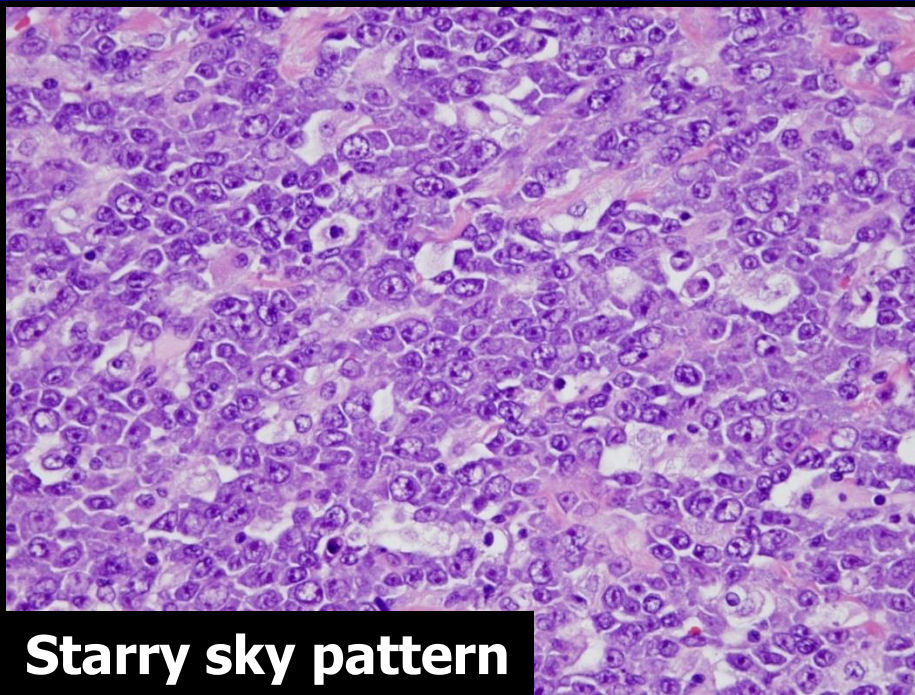
Diffuse Large B-cell Lymphoma

Features that Correlate with Poorer Prognosis

Starry sky pattern

High mitotic / proliferation (Ki-67) rate

Increased frequency of MYC R



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Immunophenotypic Analysis of DLBCL

What Is The Purpose ?

In the past

Diagnosis

Currently

Diagnosis

Prognosis

Identifying targets for therapy

DLBCL Patients Treated with R-CHOP

CD5+ Correlates with Poorer Survival

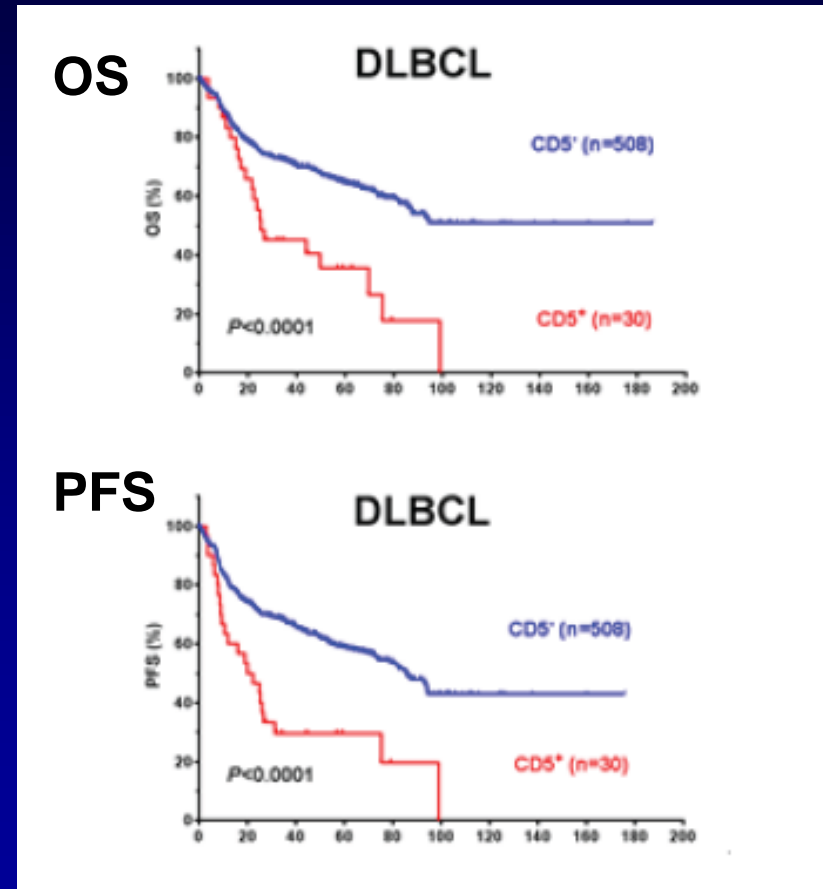
CD5+ in ~6% of DLBCL

Older
Women > men
Poorer performance status
Bulky
Higher frequency BM+ and
CNS relapse
Independent of cell-of-origin
classification



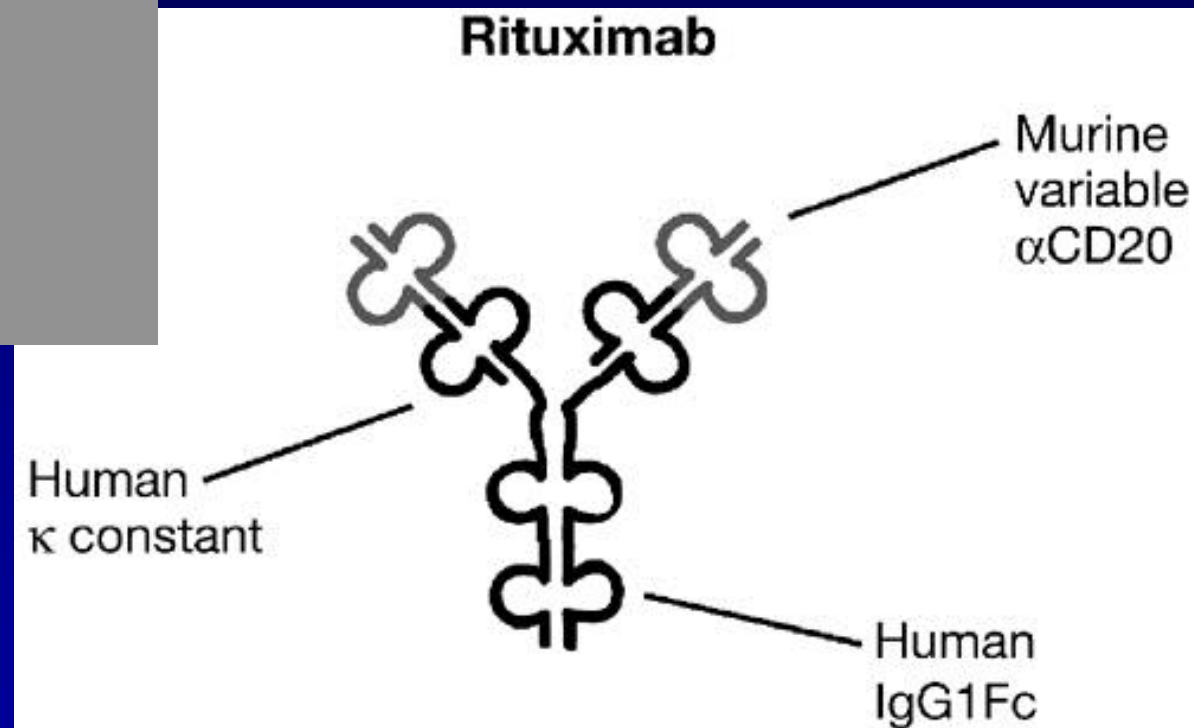
Ken H. Young MD, PhD

CD5+
CD5-



Monoclonal Antibodies and Antibody-Drug Conjugates

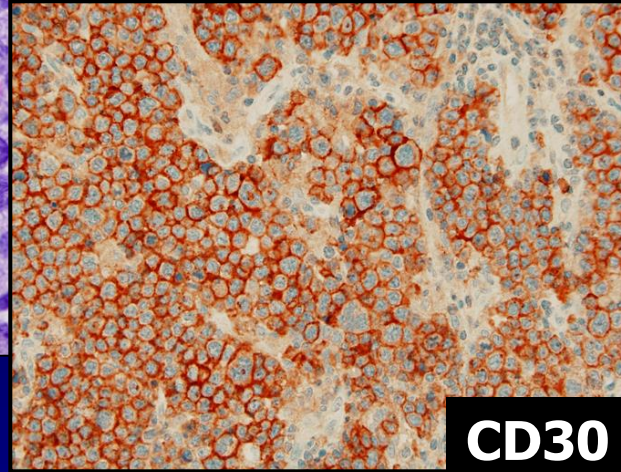
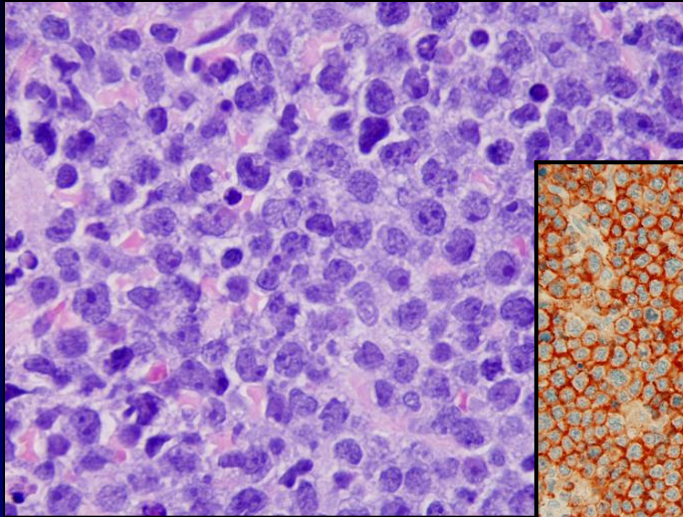
Pan B-cell Antigens



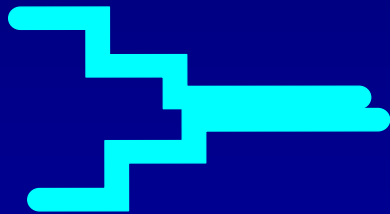
Other agents to:

CD19, CD22

CD30 in Diffuse Large B-cell Lymphoma



**~15% of DLBCL
are CD30+**



Anti-CD30



**Peptide
linker**

**Monomethyl
Auristatin E**

Brentuximab vedotin

Potential Targets Assessable by IHC

| Candidate | Oncogenic Pathway |
|-----------------------|--------------------------------------|
| CD30 | NF-κB |
| CD38 | Signal transduction, adhesion |
| SYK, BTK | B-cell receptor |
| pAKT | PI3K |
| pSTAT3, pSTAT5 | JAK-STAT |
| p65 | NF-κB |
| pERK 1/2 | MAP kinase |
| BCL2 | Apoptosis |
| PD-L1 / PD-L2 | Checkpoint inhibitors |

Genetic basis of *PD-L1* overexpression in diffuse large B-cell lymphomas

Konstantinos Georgiou,¹ Longyun Chen,^{1,2} Mattias Berglund,³ Weicheng Ren,¹ Noel F. C. C. de Miranda,⁴ Susana Lisboa,⁵ Marco Fangazio,⁶ Shida Zhu,² Yong Hou,² Kui Wu,² Wenfeng Fang,⁷ Xianhuo Wang,⁸ Bin Meng,⁸ Li Zhang,⁷ Yixin Zeng,⁷ Govind Bhagat,⁹ Magnus Nordenskjöld,¹⁰ Christer Sundström,¹¹ Gunilla Enblad,¹¹ Riccardo Dalla-Favera,⁶ Huilai Zhang,⁸ Manuel R. Teixeira,⁵ Laura Pasqualucci,⁶ Roujun Peng,⁷ and Qiang Pan-Hammarström¹

PD-L1/PD-L2 locus abnormalities in DLBCL

(n=176 Chinese pats)

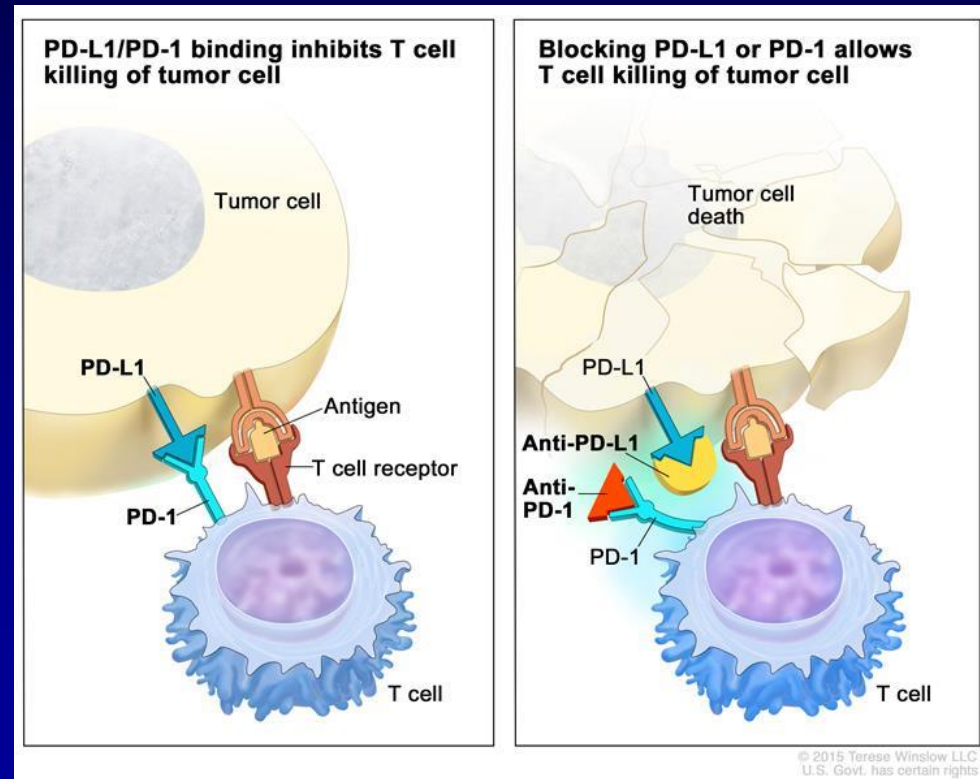
12% Gains

3% Amplifications

4% Translocations

Common in non-GCB type

26% of cases of DLBCL are PD-L1 + by IHC



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Common Translocations in DLBCL

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

BCL6 also partners with other genes

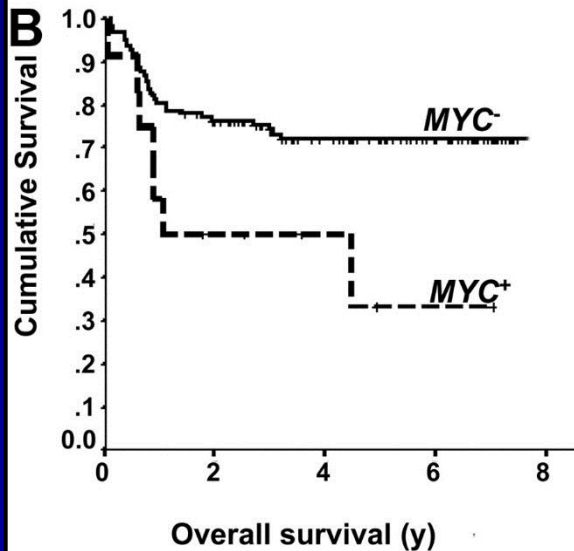
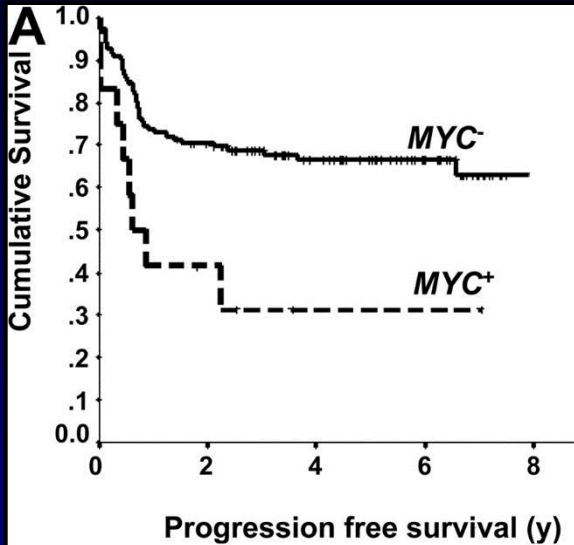
t(14;18)(q32;q21); IGH-BCL2 ~20%

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

MYC also partners with other genes

MYC is Prognostic in DLBCL

R-CHOP Therapy



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**

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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

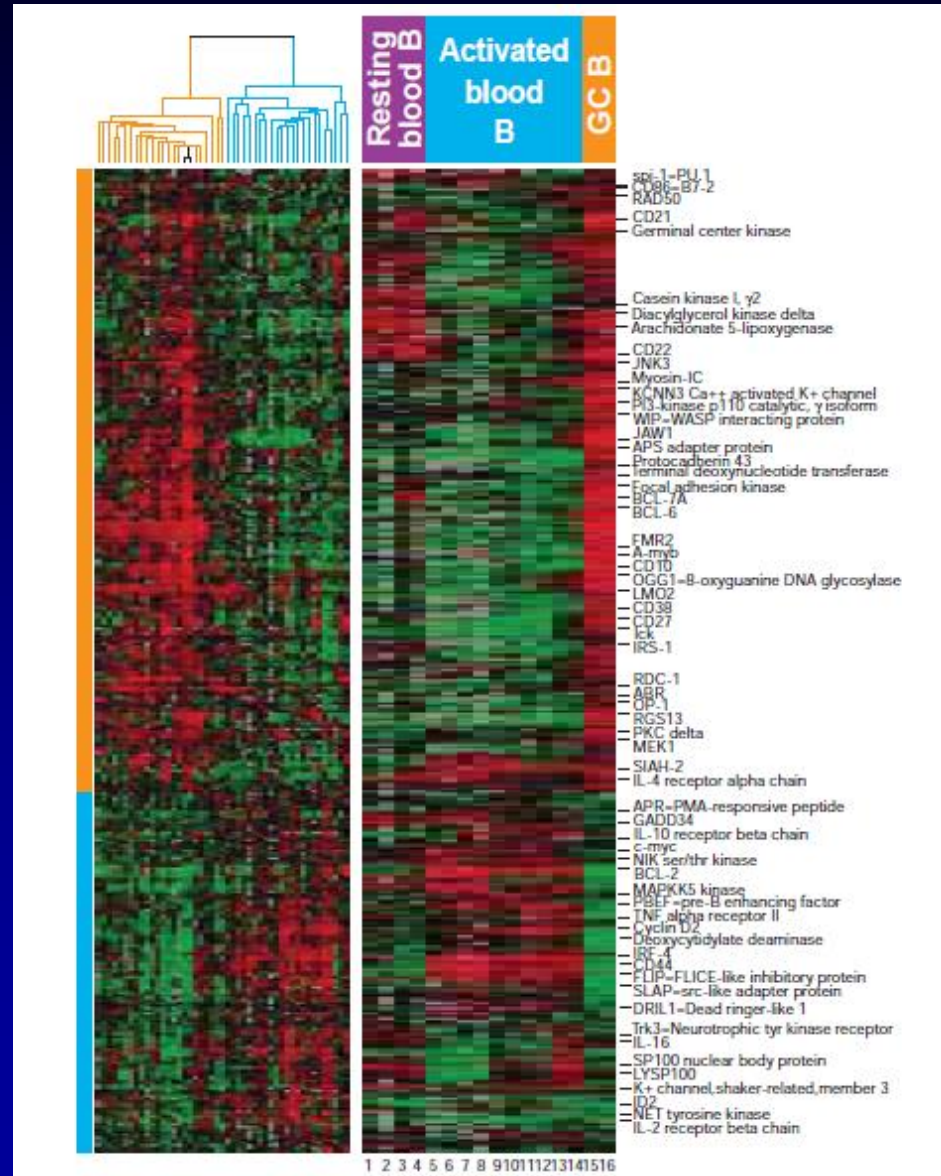


Louis Staudt, MD, PhD

Diffuse Large B-cell Lymphoma

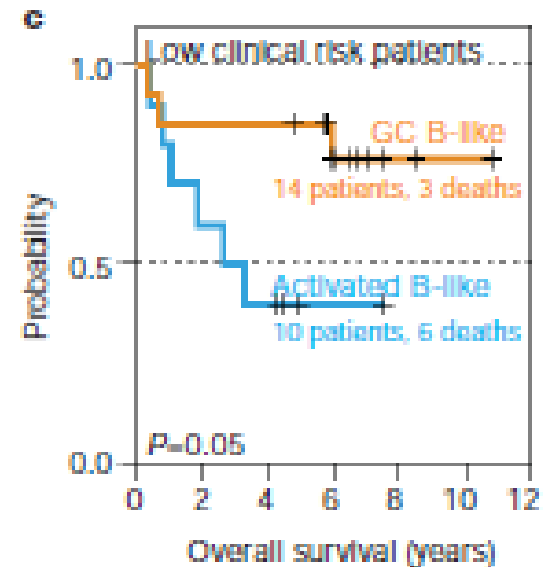
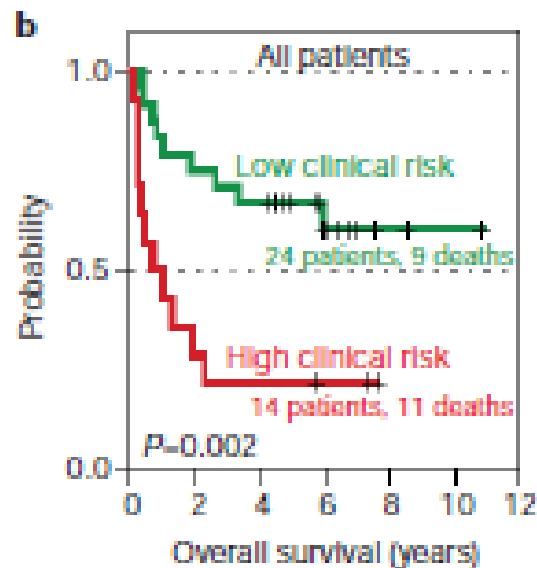
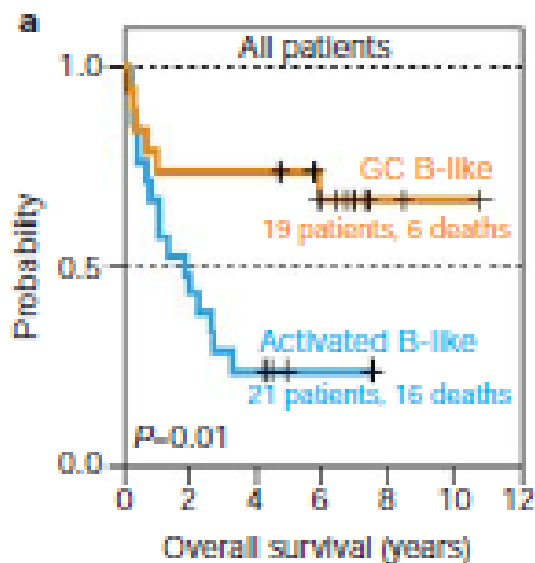
Gene Expression Profiling

GCB
ABC



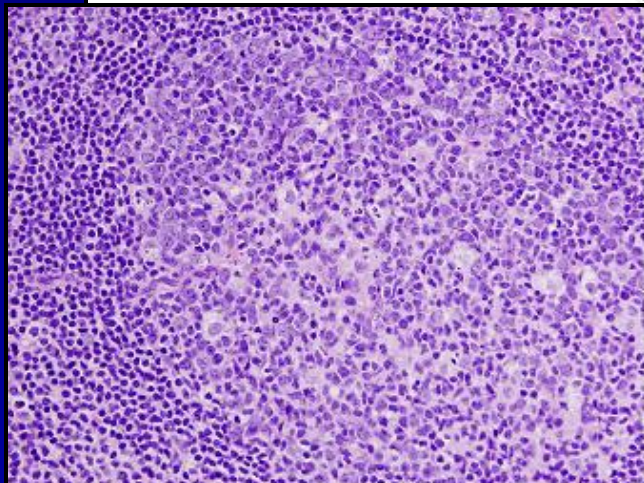
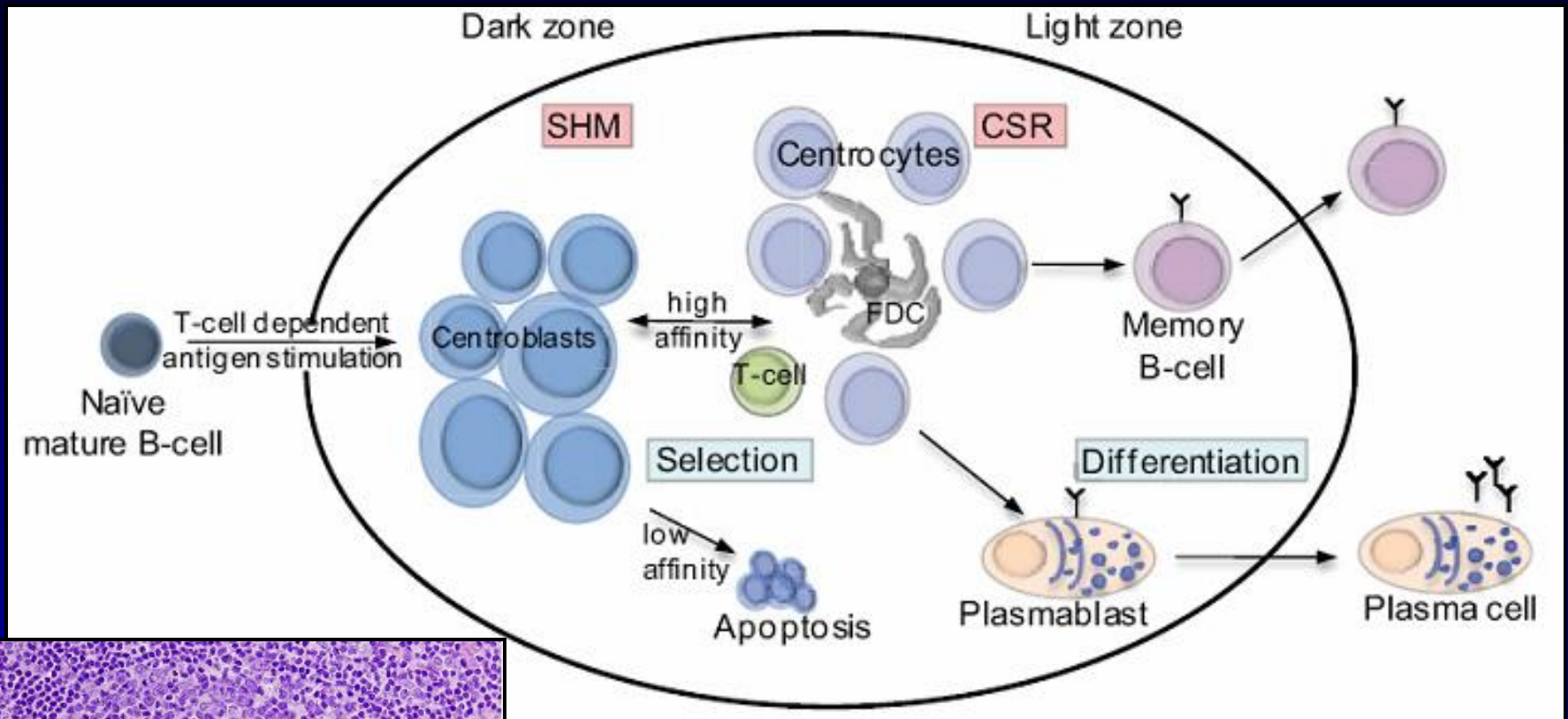
Diffuse Large B-cell Lymphoma

GEP Shows 2 Types that Predict Prognosis



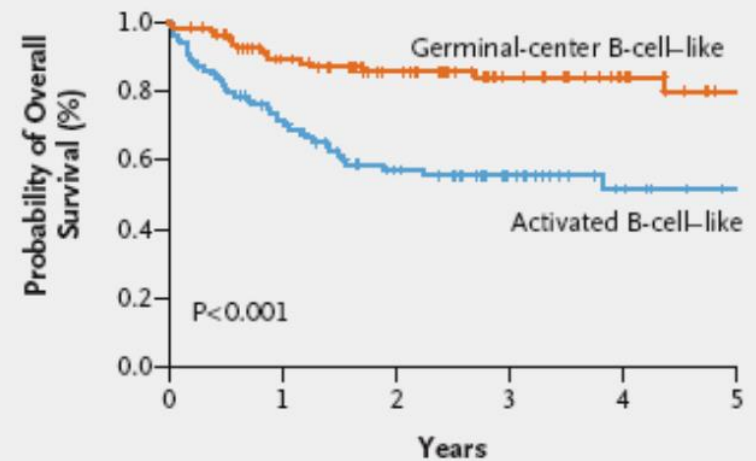
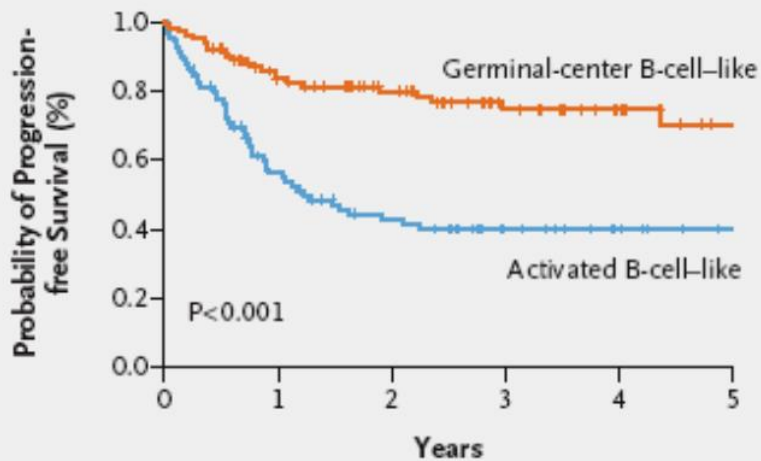
CHOP Therapy

Germinal Center Reaction



Diffuse Large B-cell Lymphoma

GEP is Valid for R-CHOP Treated Patients



No. at Risk

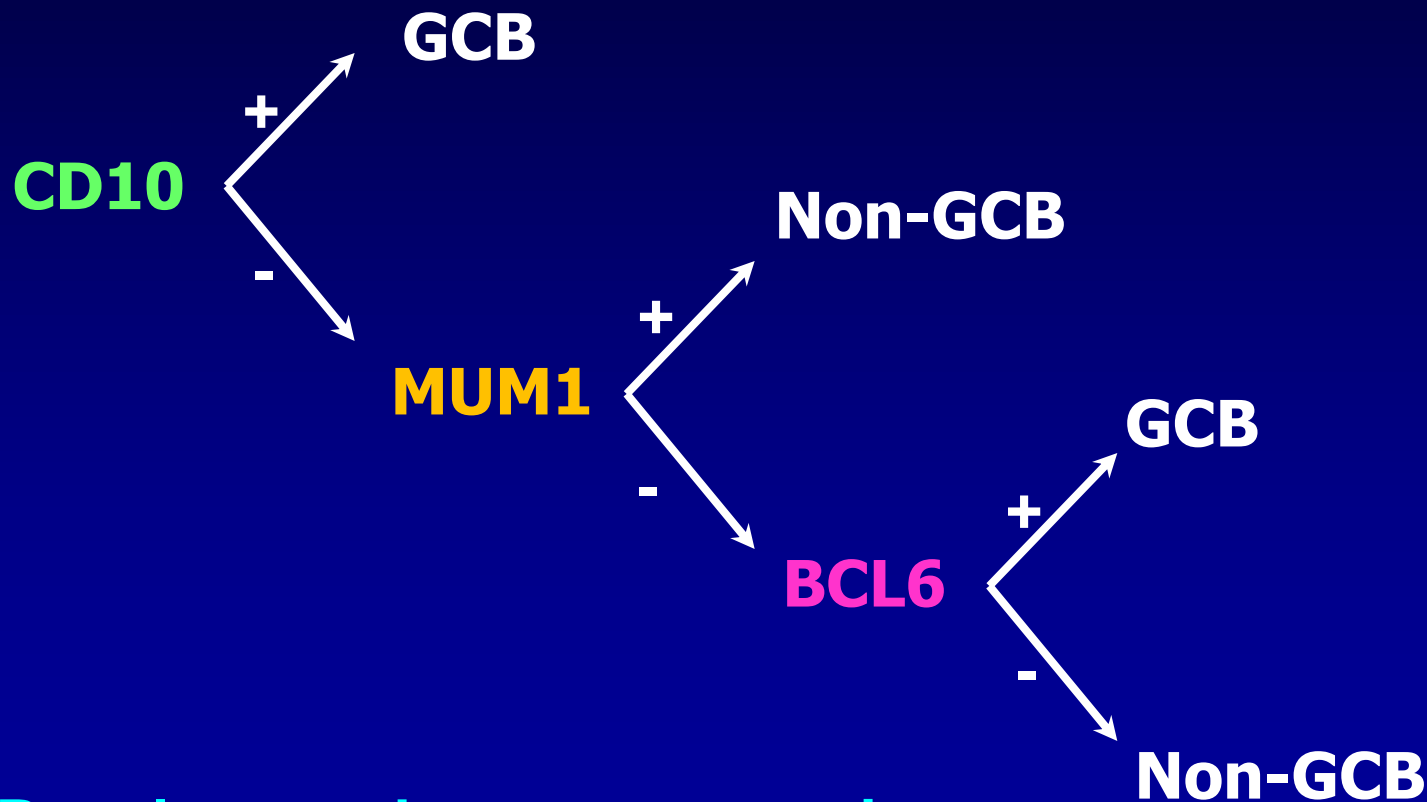
| | | | | | | | | | | | | |
|-----------------------------|-----|----|----|----|----|----|-----|----|----|----|----|----|
| Germinal-center B-cell-like | 107 | 82 | 61 | 39 | 27 | 15 | 101 | 74 | 56 | 35 | 24 | 14 |
| Activated B-cell-like | 93 | 60 | 38 | 23 | 11 | 6 | 90 | 45 | 30 | 17 | 10 | 5 |

Cell-of-Origin Classification

Clinical Relevance for Ibrutinib

| Cell-of-Origin | Overall Response Rate | Complete Remission | Partial Remission |
|------------------------------|-----------------------|--------------------|-------------------|
| ABC (n = 29) | 41% | 8% | 32% |
| GCB (n = 20) | 5% | 0% | 5% |
| Unclassified (n = 16) | 0% | 0% | 0% |

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



Chris Hans, MD

Results match gene expression profile in 76% of cases

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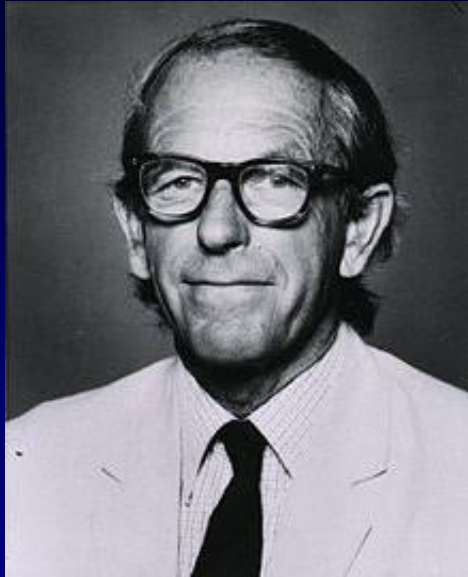
Chromosomal translocations

Gene expression profiling

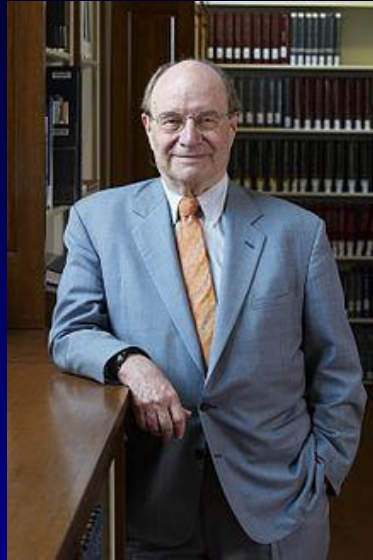
Gene mutations

High-grade B-cell lymphoma

Sanger Sequencing Traditional (dideoxy) Method

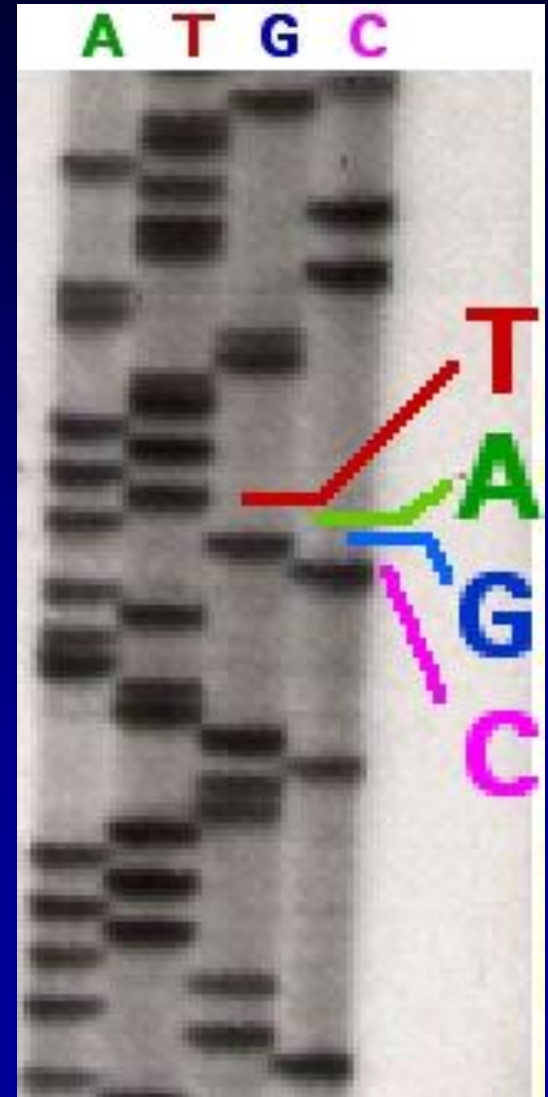


Fred Sanger



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

Next Generation Sequencing Platforms

MDACC Molecular Diagnostics Laboratory

Ion Torrent PGM and Ion Proton

Semiconductor based non optical detection based on change in pH

MiSeq and HiSeq

Flow cell based, 4-color optical imaging of fluorescent labeled nucleotides



Ion Torrent PGM
(3)

Ion Proton (2)

Tests

Tests

CMS 46 (April 2012)

409 gene panel

CMS50 (Sept 2013)



MiSeq (2)

Tests

CMS53 (Oct 2012)

CMS28 (Sept 2013)



HiSeq 2500 (1)

Mostly research

Life Technologies

Illumina

NGS for Hematologic Malignancies at MDACC



Raja Luthra PhD



Keyur Patel, MD, PhD



Rajesh Singh, PhD

Others involved in signout of NGS testing

C. Cameron Yin, MD, PhD

Rashmi Kanagal-Shamanna, MD

Sanam Loghavi, MD

Chi Y. Ok, MD, PhD

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

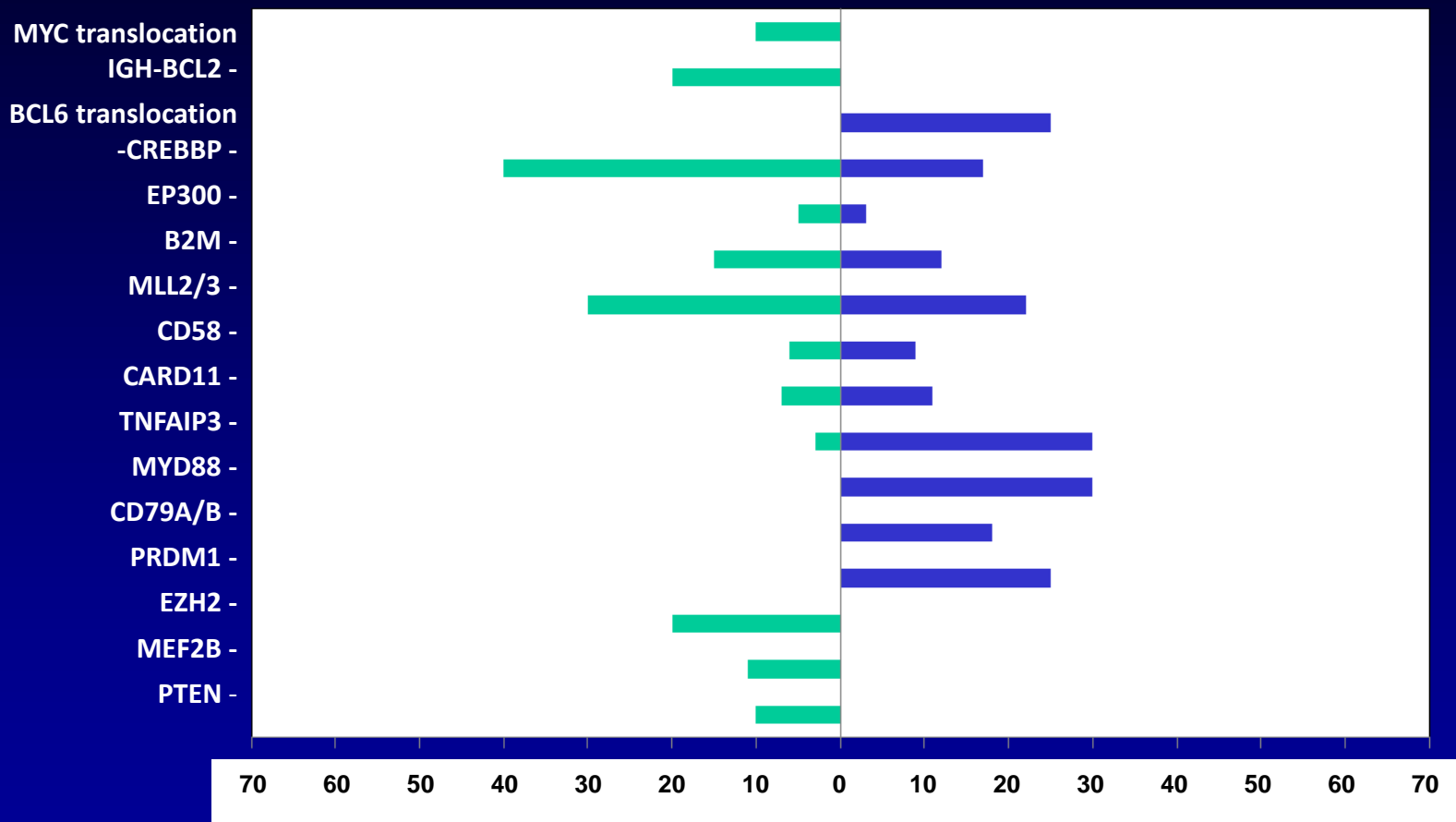
β 2M, CD58

Diffuse Large B-cell Lymphoma, NOS

Mutations correlate with cell-of-origin

GCB

ABC



Frequency of Mutations

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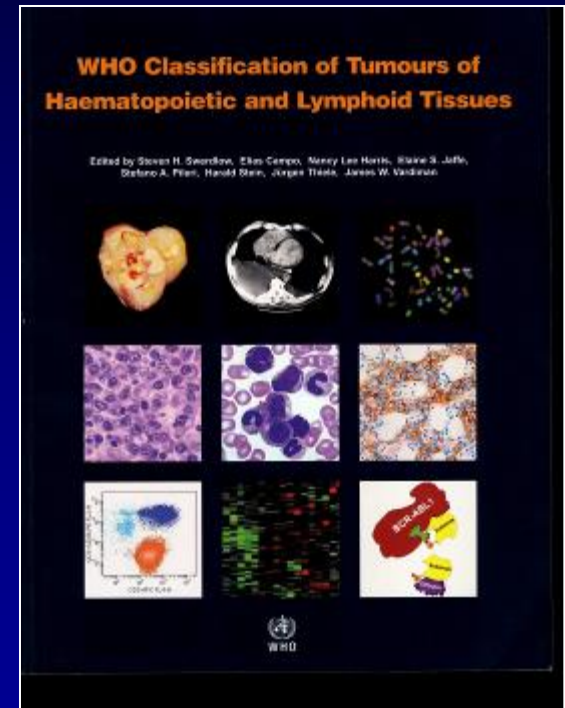
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma

PM Kluijn
N L Harris
H Stein
L Leoncini

M Raphaël
E Campo
E S Jaffe

**Aggressive lymphomas that have
morphological and genetic features of
both DLBCL and BL, but for biological and
clinical reasons should not be included in
these categories.**

**This is a heterogeneous category that is
not considered a disease entity but is
useful in allowing classification of cases
not meeting criteria for BL or DLBCL.**



2016 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 will be

High-grade B-cell lymphoma

Two types

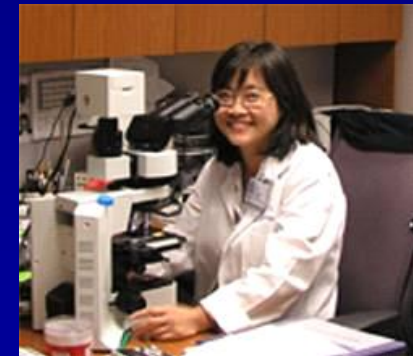
Not otherwise specified (NOS)

Double hit lymphoma (genetic)

High-grade B-cell lymphoma NOS

Previously known as BCLU

| | | |
|---------------------------------|--------------|----------------|
| Age | 57 yo | (18-80) |
| Male | 37/52 | (71%) |
| Stage III/IV | 32/52 | (62%) |
| Performance status >2 | 15/52 | (29%) |
| LDH >2 normal | 18/52 | (35%) |
| IPI ≥ 3 | 28/52 | (54%) |

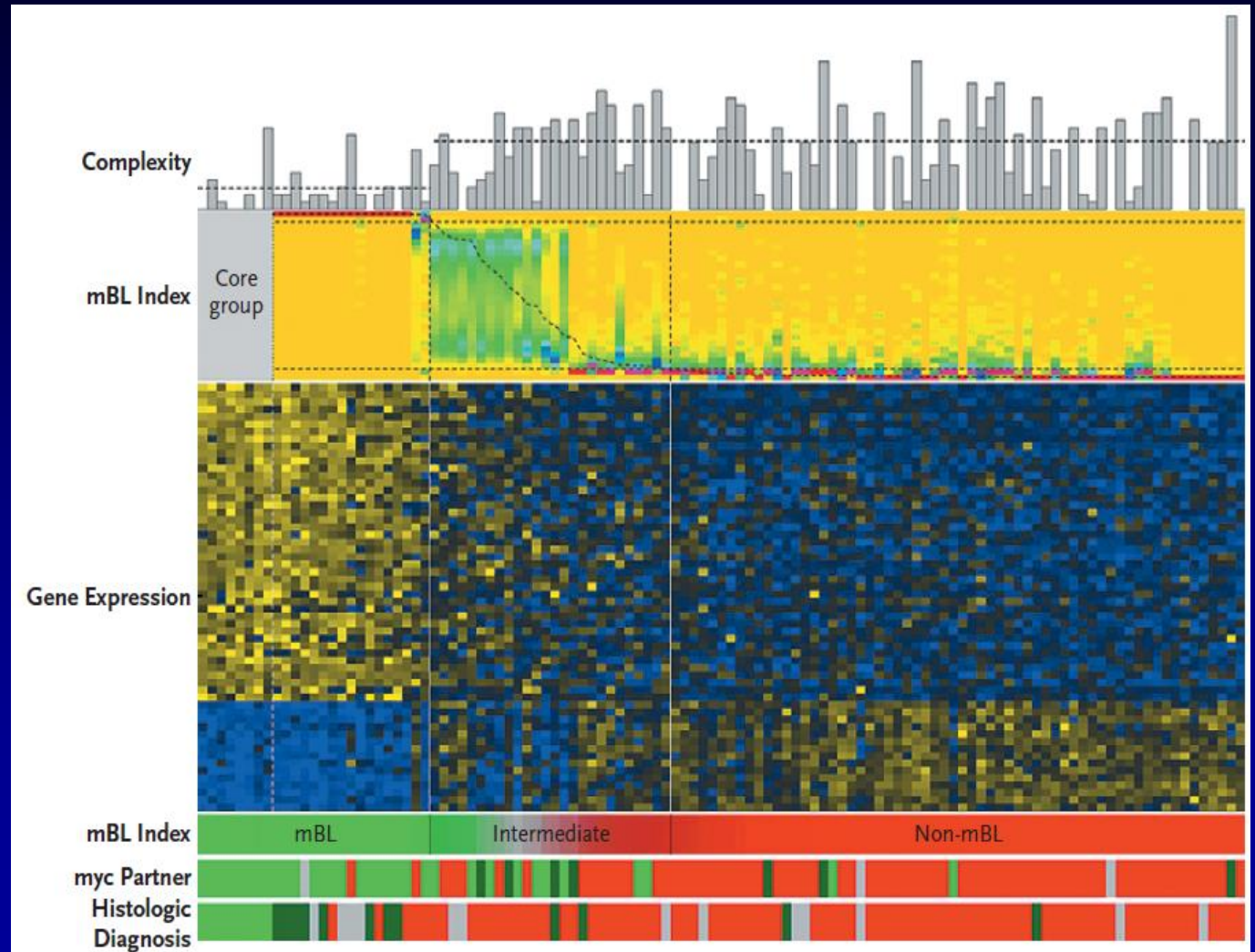


Burkitt Lymphoma and DLBCL

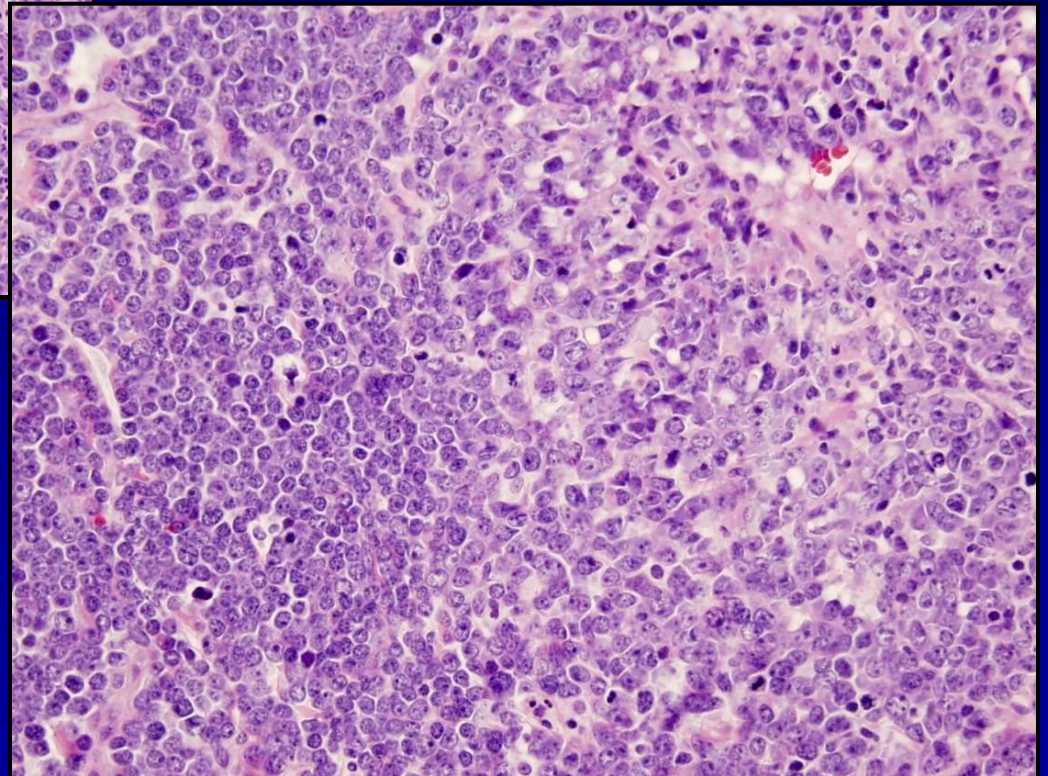
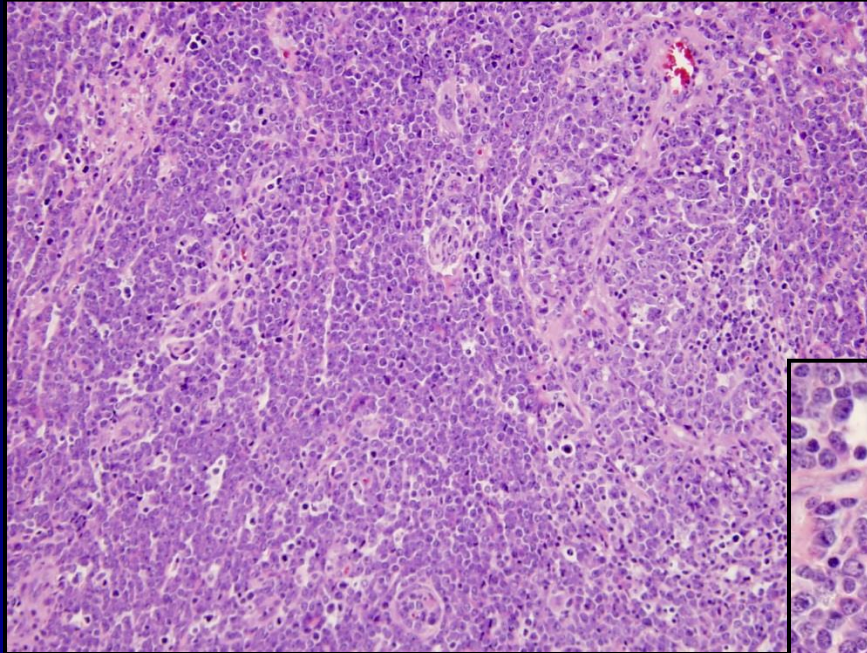
Gene Expression Profiling

58 genes

105 cases

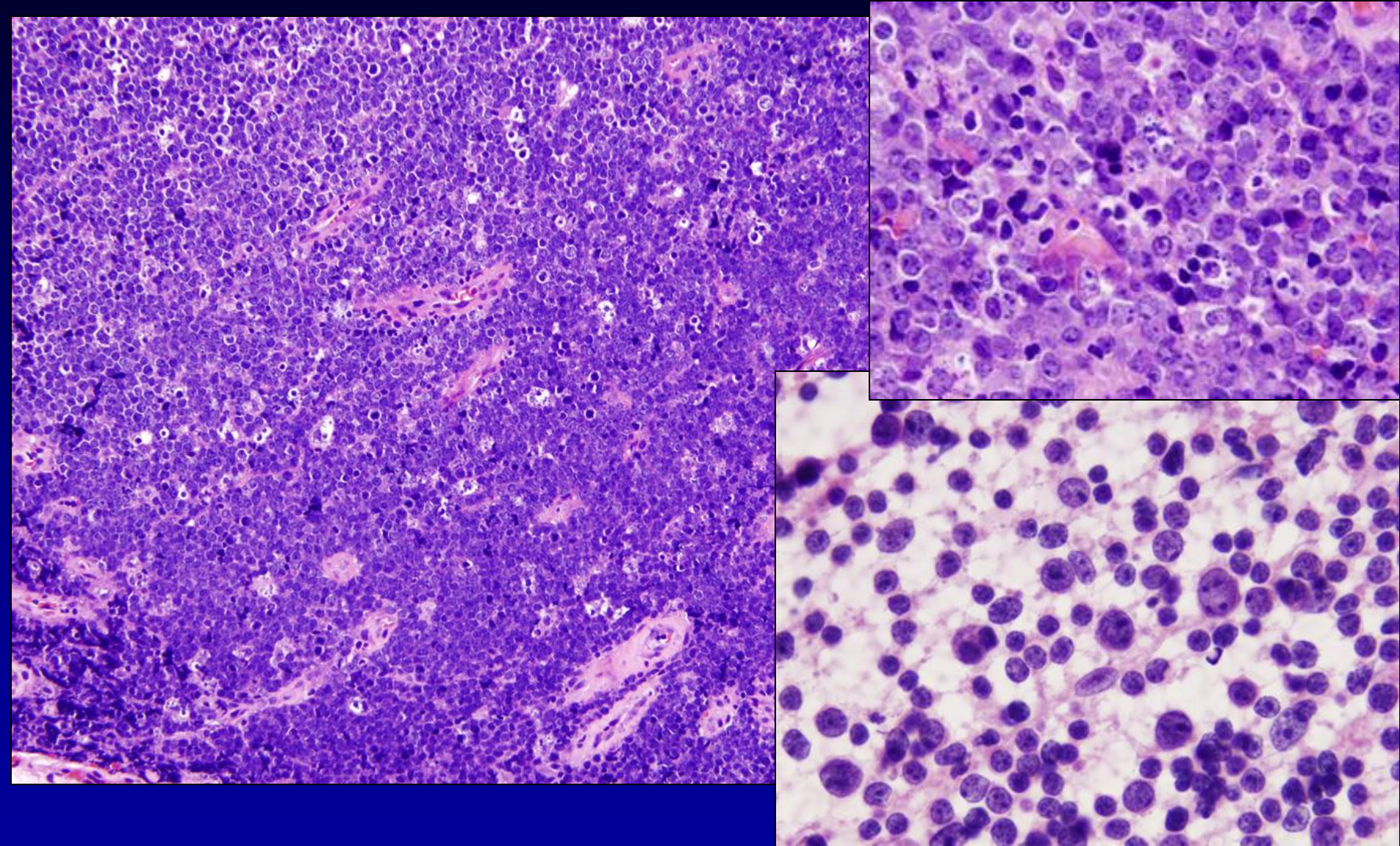


HGBL and DLBCL Morphology in Same Tumor



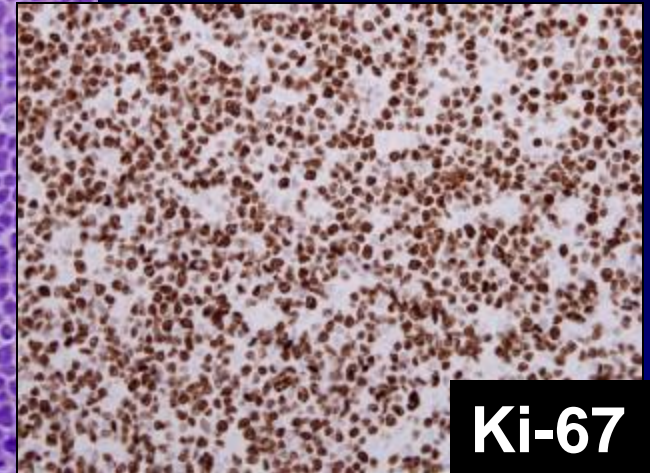
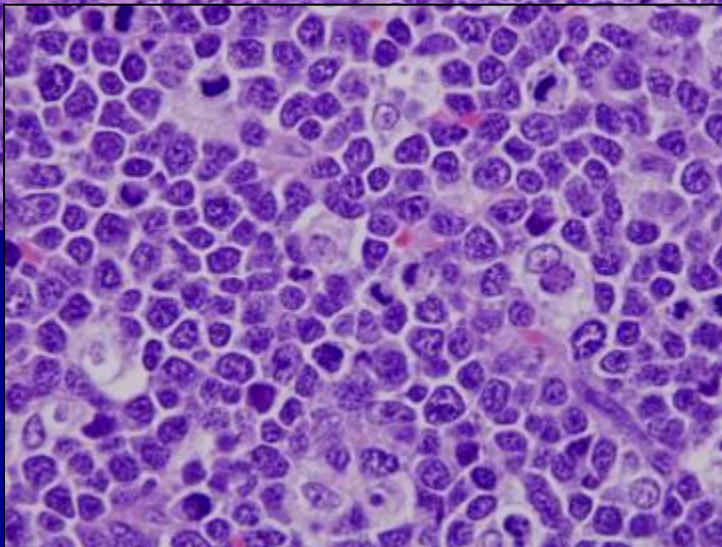
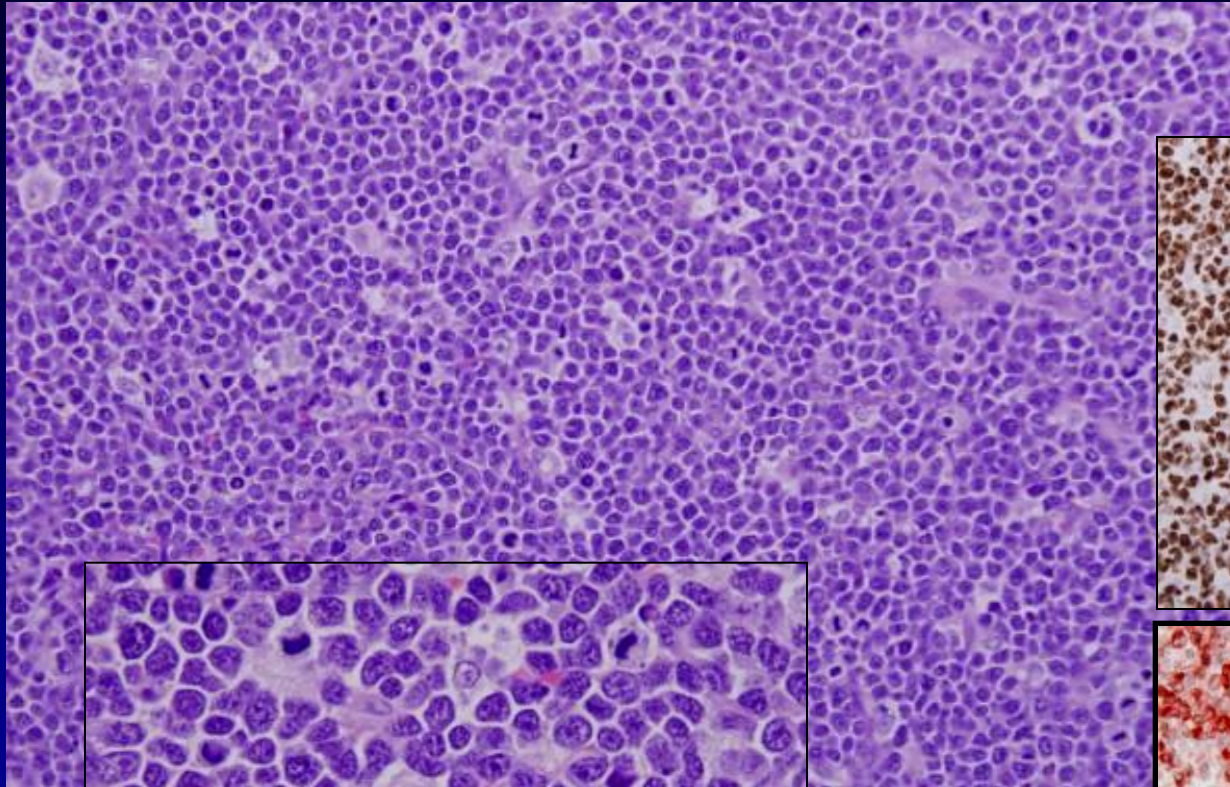
High-grade B-cell Lymphoma

"Type 1"

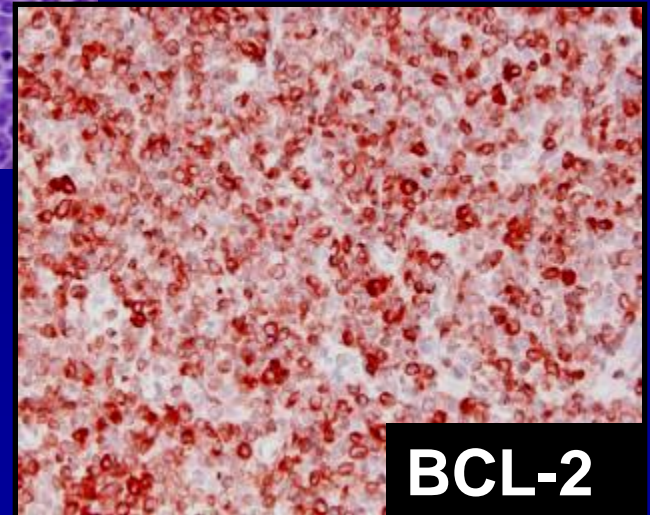


High-grade B-cell Lymphoma

“Type 2”



Ki-67



BCL-2

Double Hit B-cell Lymphoma

Definition

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

MYC + BCL-2

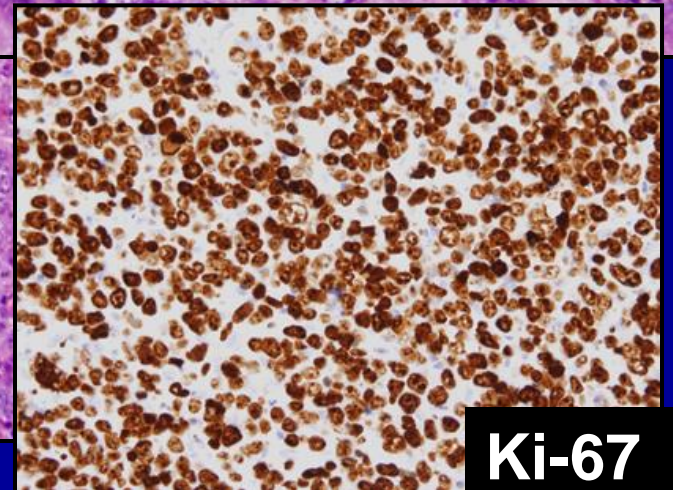
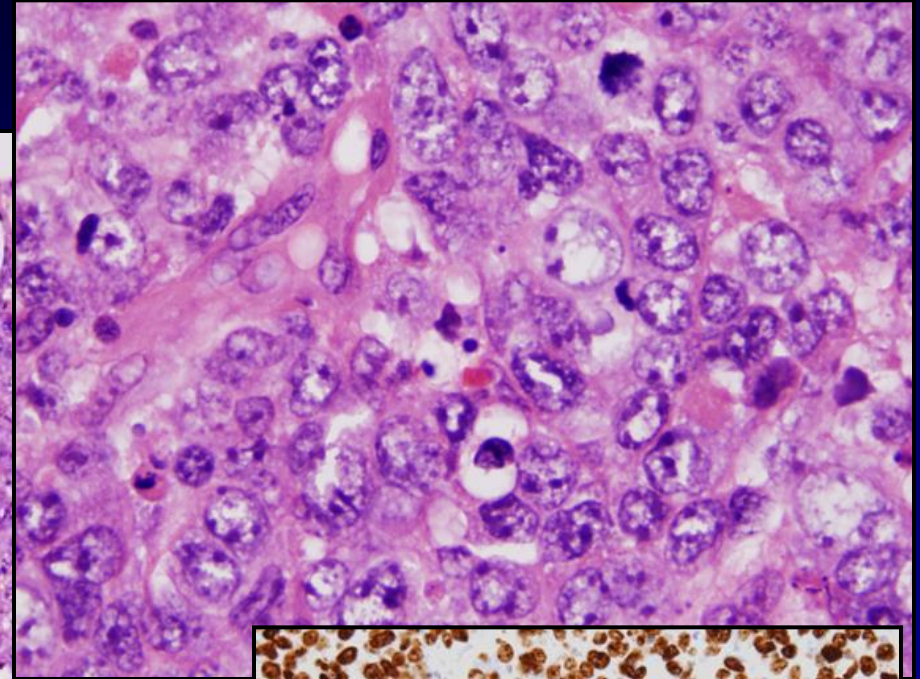
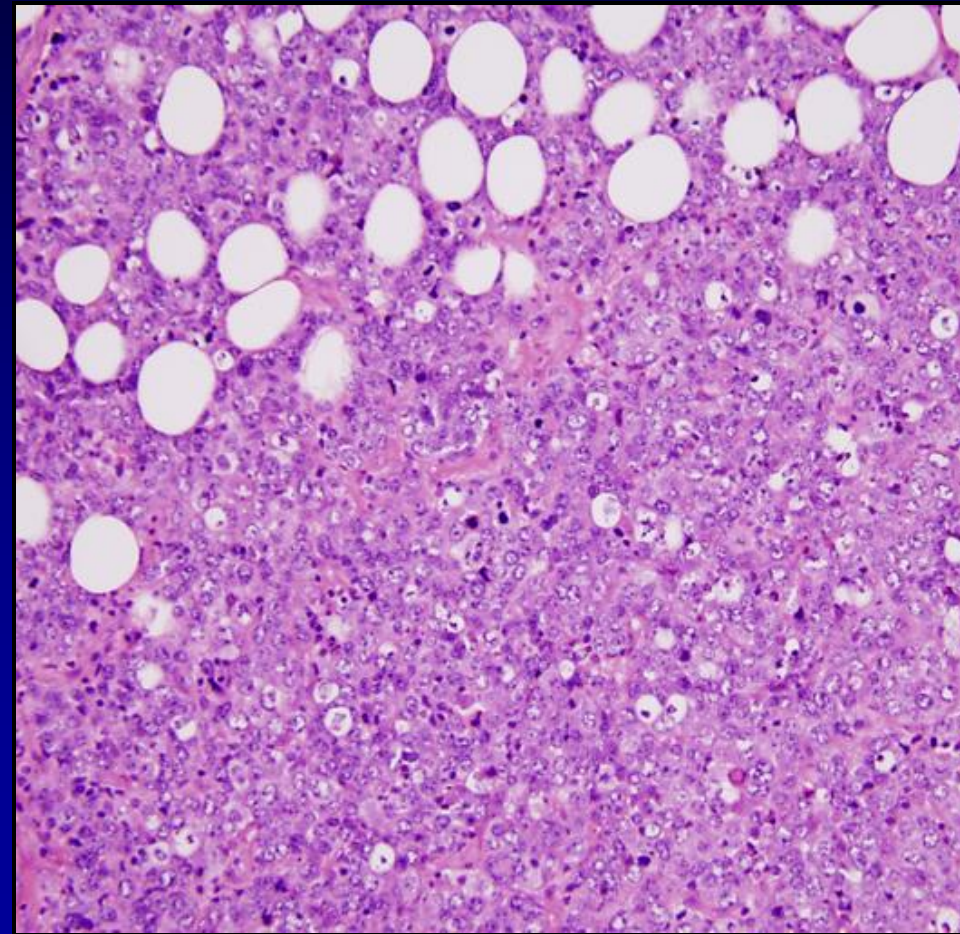
MYC + BCL-6

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

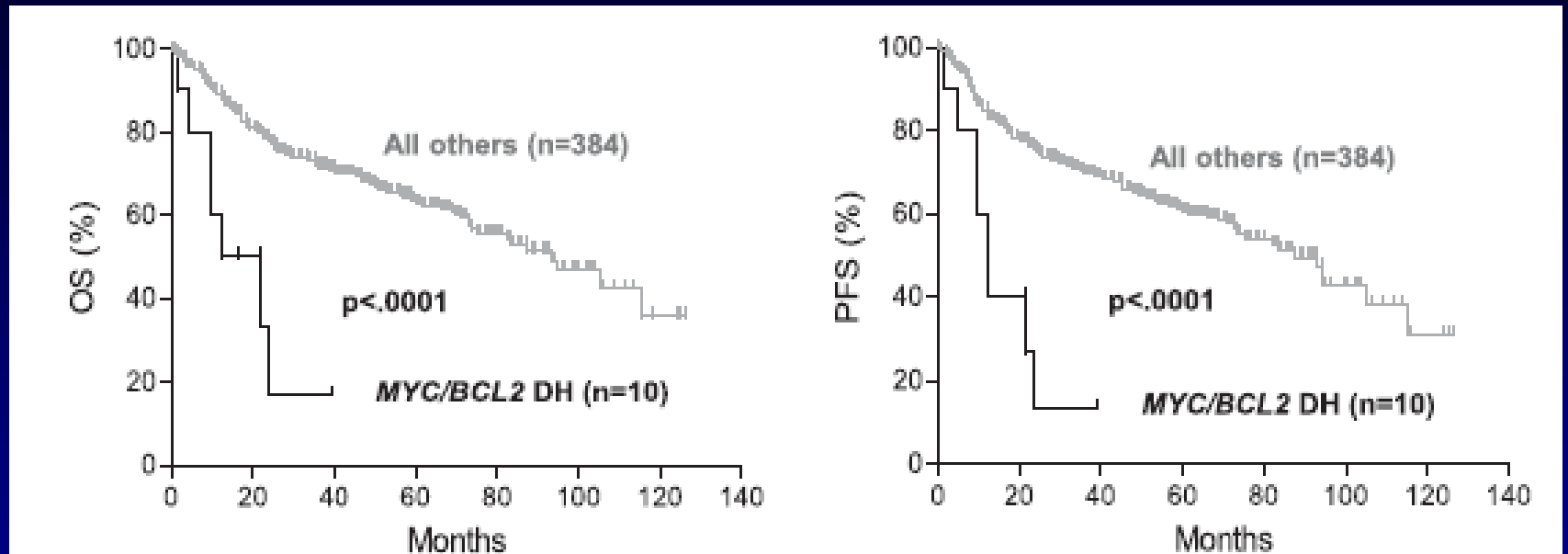
MYC + BCL-3

MYC + CCND1

MYC/BCL2 Double Hit B-cell lymphoma



DLBCL with MYC and BCL2 Translocations A Poor Prognostic Subset



**Pts with double hit lymphoma
have a poor prognosis**

~2-5% of DLBCL

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

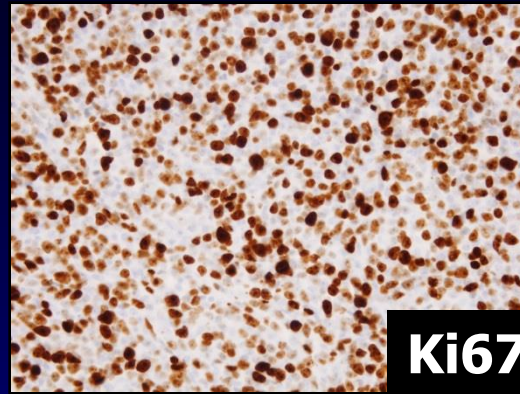
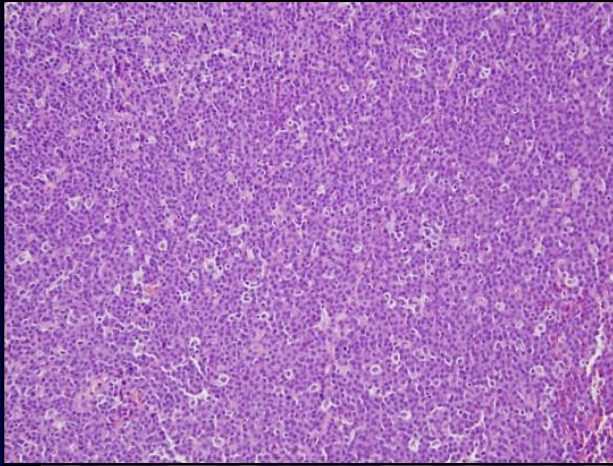
MYC/BCL6 DHL a little different

More often extranodal (liver)

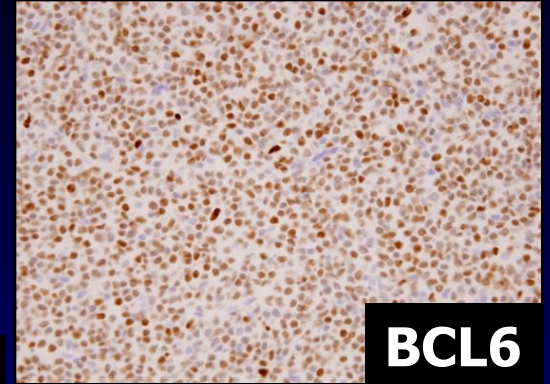
GCB and non-GCB

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

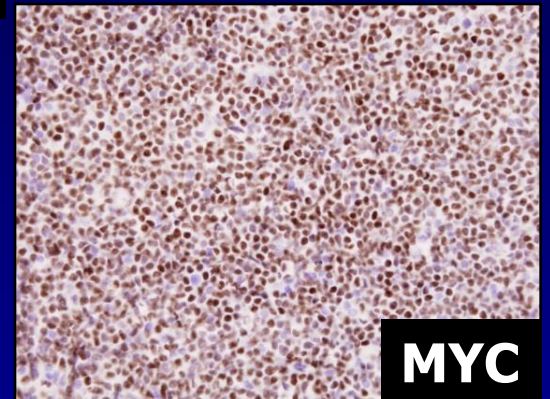
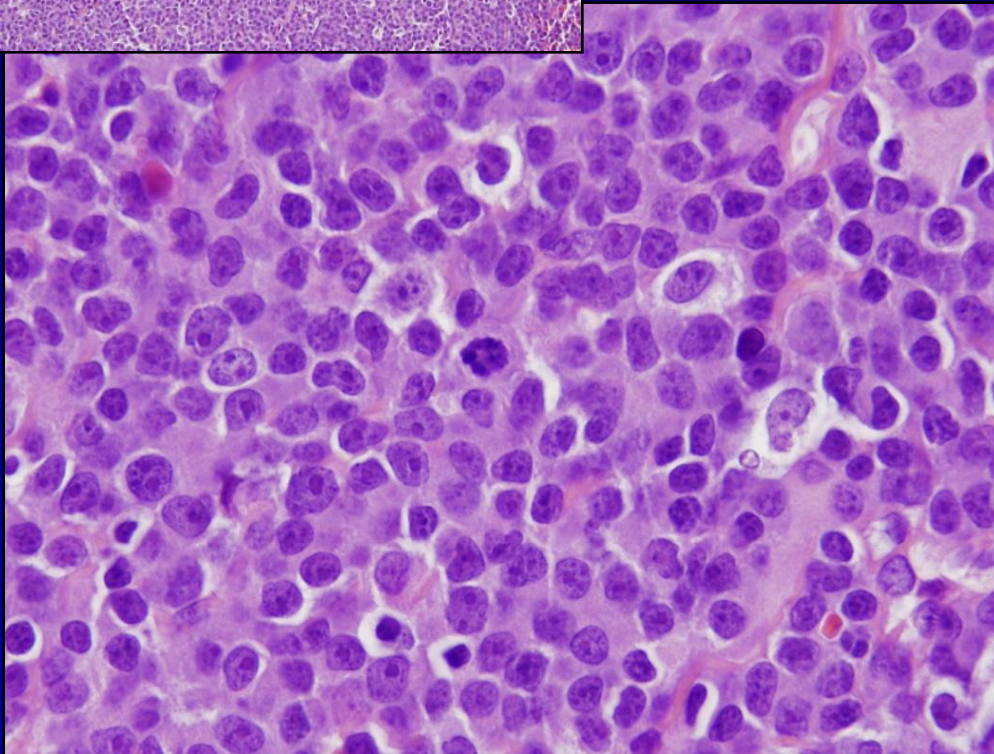
MYC/BCL6 DHL c/w HGBL



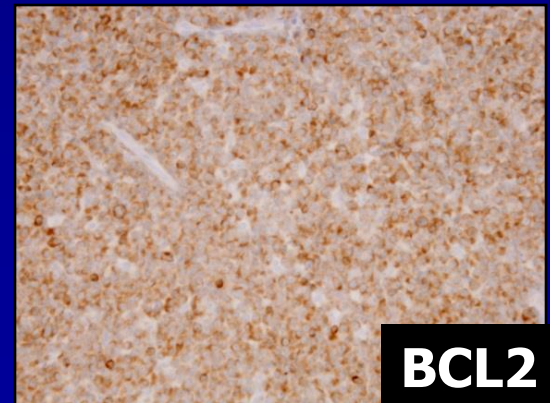
Ki67



BCL6



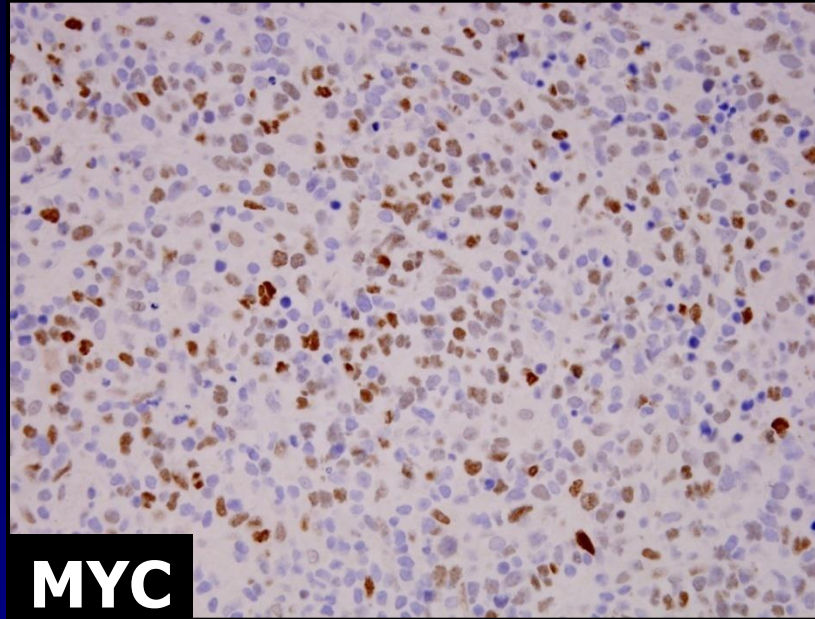
MYC



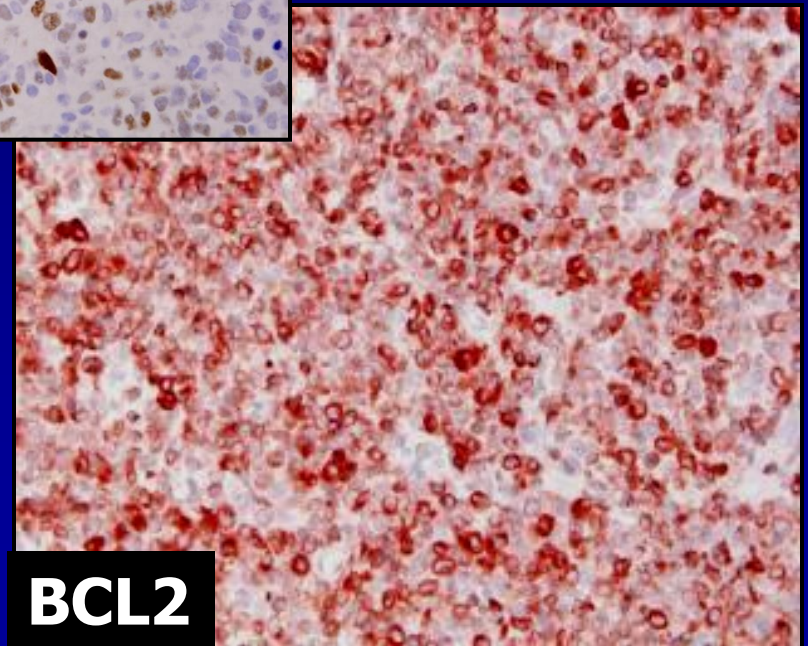
BCL2

MYC and BCL2 IHC

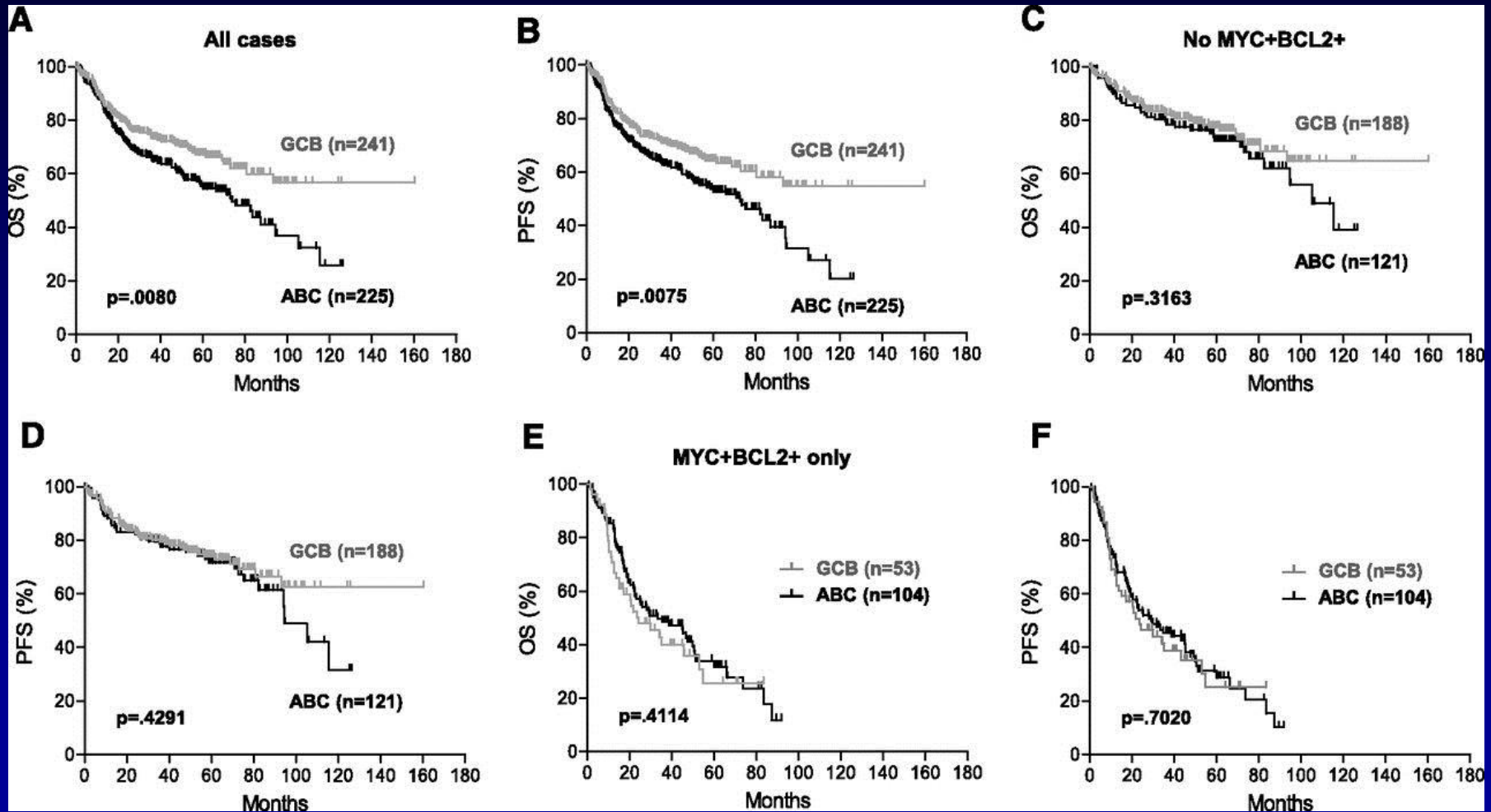
**Epitomics,
MoAb Y69**



**Dako,
MoAB 124**



MYC+ BCL2+ IHC May Explain Poorer Prognosis of ABC Type of DLBCL



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

~ 30% of DLBCL coexpress MYC and BCL2

~ 5% 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

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*†*



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 |

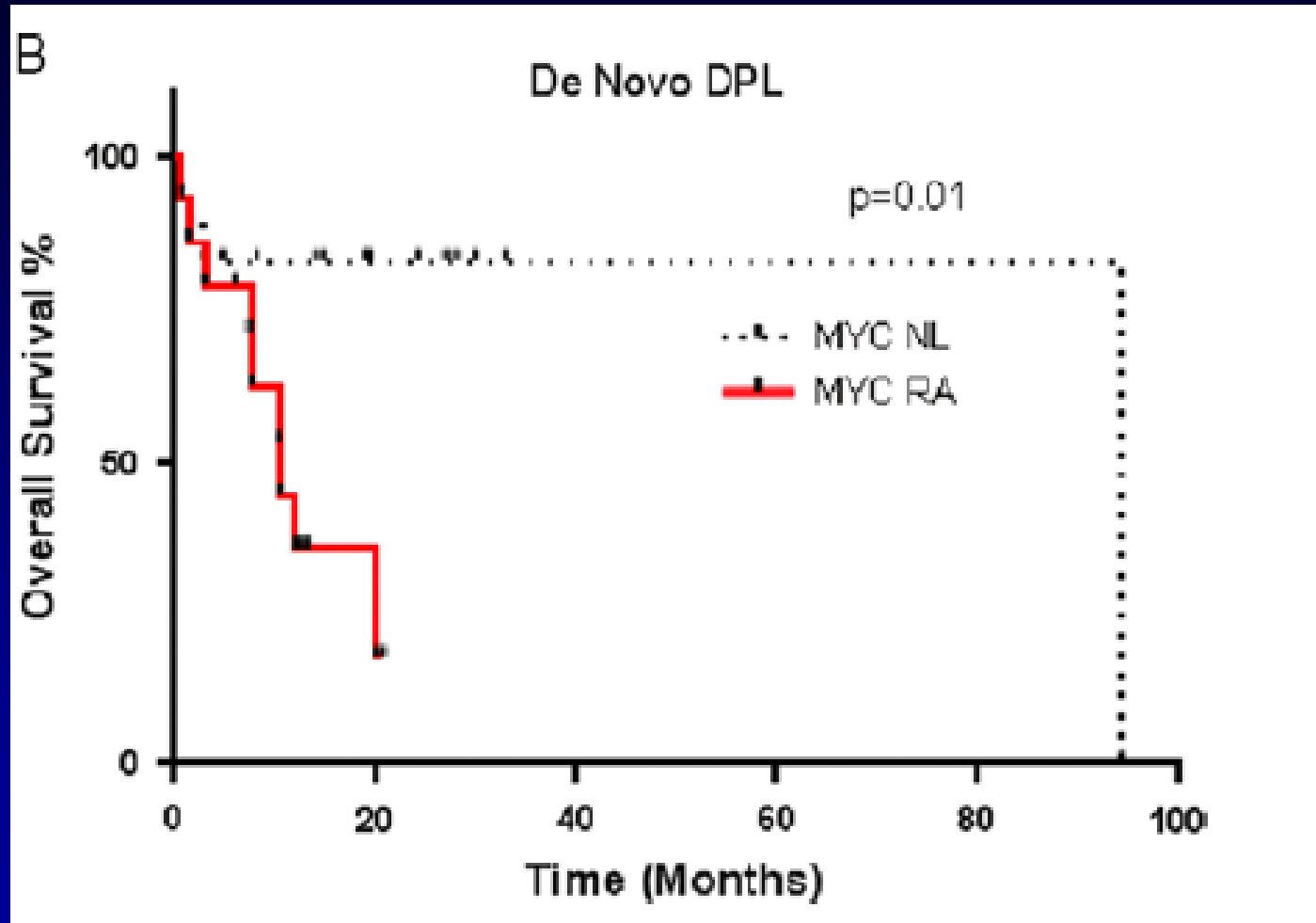
MC indicates multiple copies; RA, rearrangement.

80% sensitive with 40% cutoff

Am J Surg Pathol 39: 1250, 2015

MYC TRANSLOCATION IN DOUBLE POSITIVE DLBCL

Translocation Predicts Poorer Survival



MYC Has Many Cellular Functions

Functions

Growth

Proliferation

Metabolism

Differentiation

Apoptosis

c-Myc Is a Universal Amplifier of Expressed Genes in Lymphocytes and Embryonic Stem Cells

Zuqin Nie,^{1,6} Gangqing Hu,^{2,6} Gang Wei,² Kairong Cui,² Arito Yamane,³ Wolfgang Resch,³ Ruoning Wang,⁴ Douglas R. Green,⁴ Lino Tessarollo,⁵ Rafael Casellas,³ Keji Zhao,^{2,*} and David Levens^{1,*}

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³Genomics and Immunity Section, NIAMS, Bethesda, MD 20892, USA

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⁵Neural Development Section, NCI, FNL, Frederick, MD 21702, USA

⁶These authors contributed equally to this work

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<http://dx.doi.org/10.1016/j.cell.2012.08.033>

SUMMARY

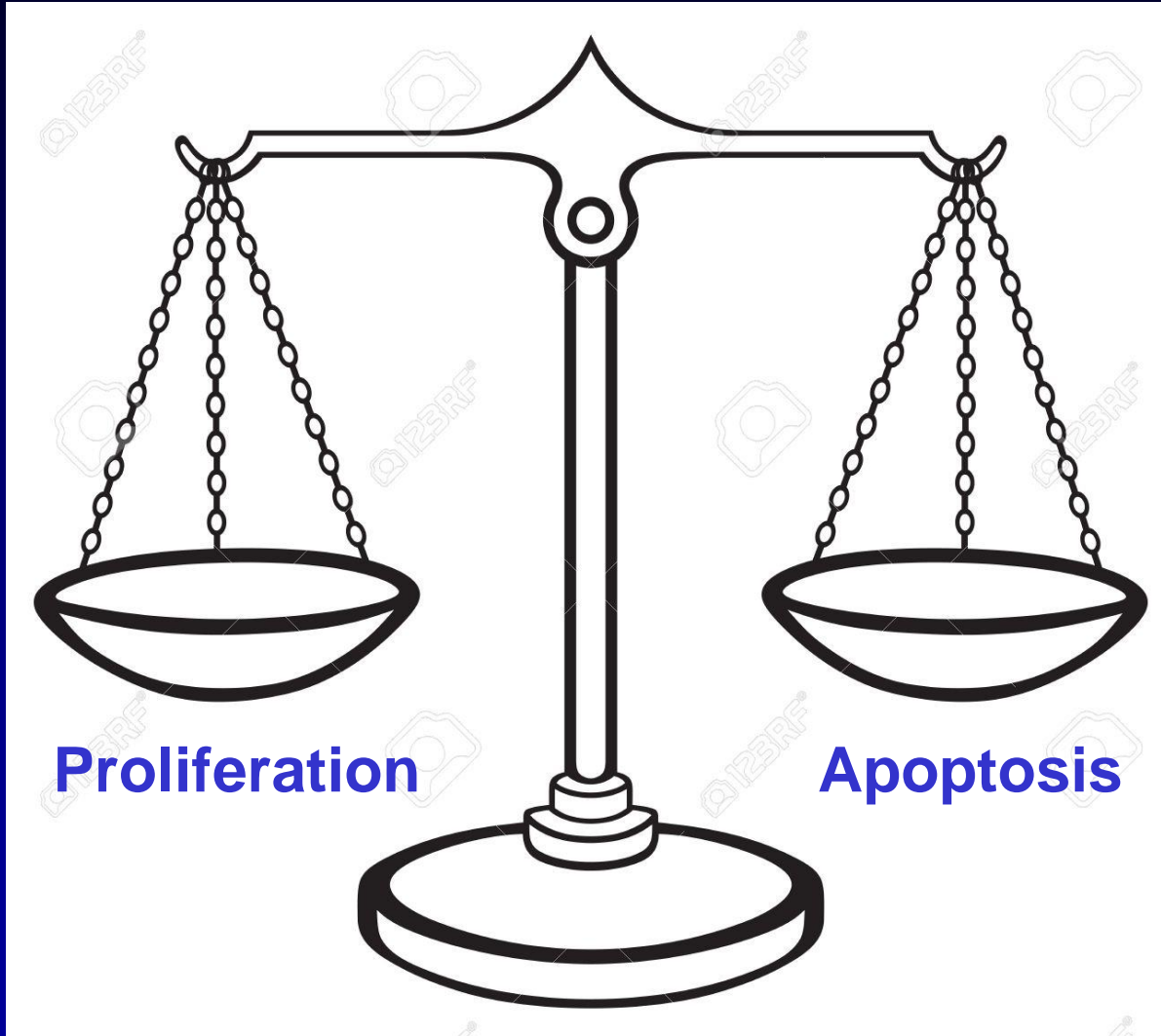
The c-Myc HLH-bZIP protein has been implicated in physiological or pathological growth, proliferation, apoptosis, metabolism, and differentiation at the cellular, tissue, or organismal levels via regulation of numerous target genes. No principle yet unifies Myc action due partly to an incomplete inventory and functional accounting of Myc's targets. To observe Myc target expression and function in a system where Myc is temporally and physiologically regulated, the transcriptomes and the genome-wide distributions of Myc, RNA polymerase II, and chromatin modifications were compared during lymphocyte activation and in ES cells as well. A remarkably simple rule emerged from this quantitative analysis: Myc is not an on-off specifier of gene activity, but is a nonlinear amplifier of expression, acting universally at active genes, except for immediate early genes that are strongly induced before Myc. This rule of Myc action explains the vast majority of Myc biology observed in literature.

between systems, has further confounded the expected discrete, linear pathway(s) for Myc-driven neoplasia.

Myc is often associated with cell activation. Typical of Myc is induced starting from a very low basal level, the G0-G1 transition or in response to numerous stresses (Rabbitts et al., 1985). Thereafter, in steady-state cycling cells, *c-myc* output is stably maintained. In some cells, a second Myc peak ensues 12–24 hr later (Kobayashi et al., 1983; Nepveu et al., 1987; Tonini et al., 1987). The relationship between Myc targets in these primary and secondary systems has not been investigated. Although Myc pathology has been extensively studied in lymphoid neoplasms, including lymphoma, large cell lymphoma, multiple myeloma, and sarcoma, Myc action in primary lymphocytes, has not been studied making it difficult to compare the physiological and pathological Myc networks. Because most cancer lineages do not recapitulate the physiologic regulation of Myc expression (Levens, 2010), we decided to investigate Myc function in primary lymphocytes by using a mouse line that expresses endogenous Myc to enhanced green fluorescent protein. The Myc network was then interrogated in related but physiologically distinct situations, and the profiles of global gene expression and of Myc binding to its target genes were determined. The genome-wide patterns of Myc recruitment, RNA p

MYC - a universal amplifier of other gene functions ?

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

Niklas Gebauer¹, Veronica Bernard¹, Wolfgang Gebauer², Christoph Thorns¹, Alfred C. Feller¹ & Hartmut Merz¹

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

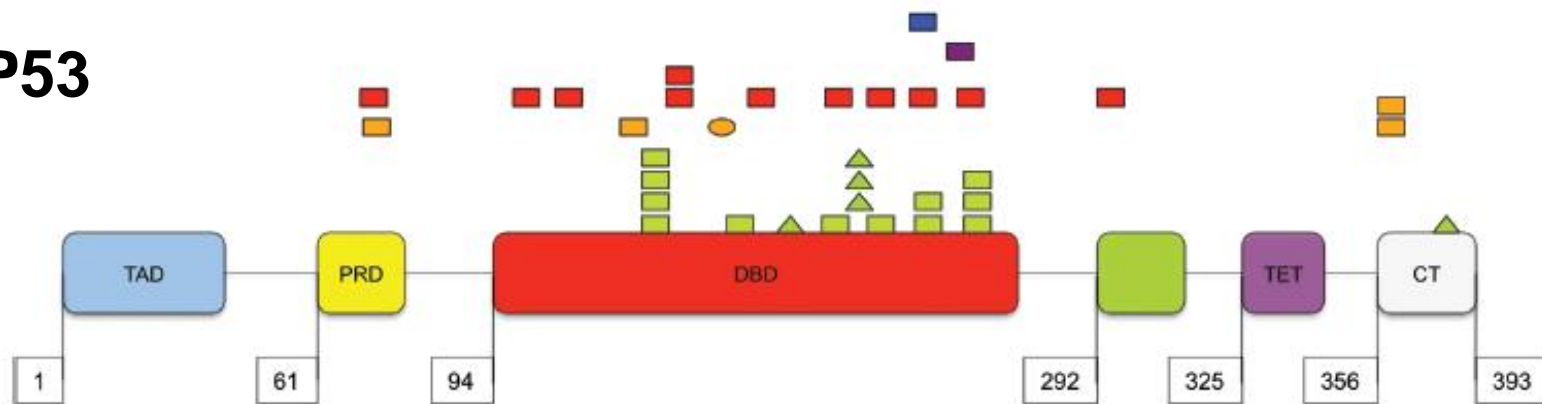
Leuk Lymphoma 56: 179, 2015

TP53 mutations in exons 4-11 detected by NGS

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

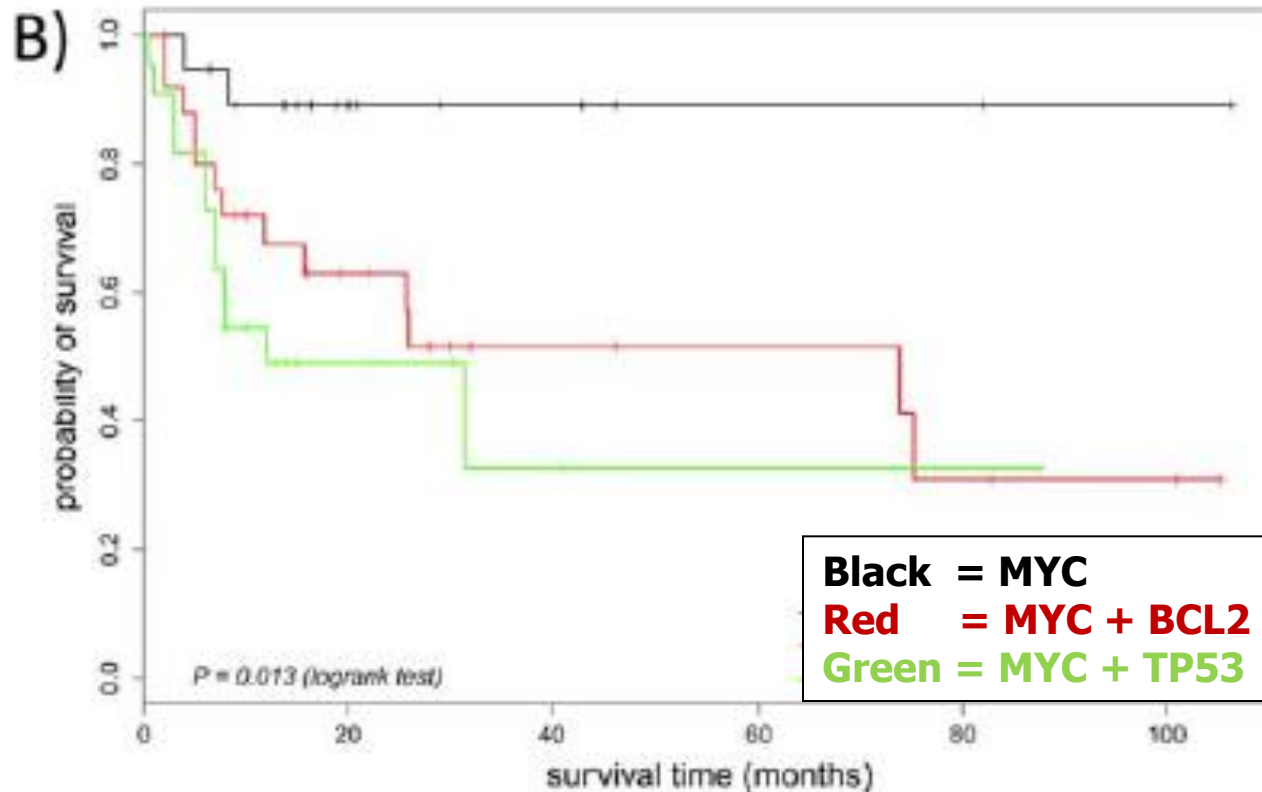
■ = missense
○ = nonsense
▲ = frameshift

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 Womillow,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

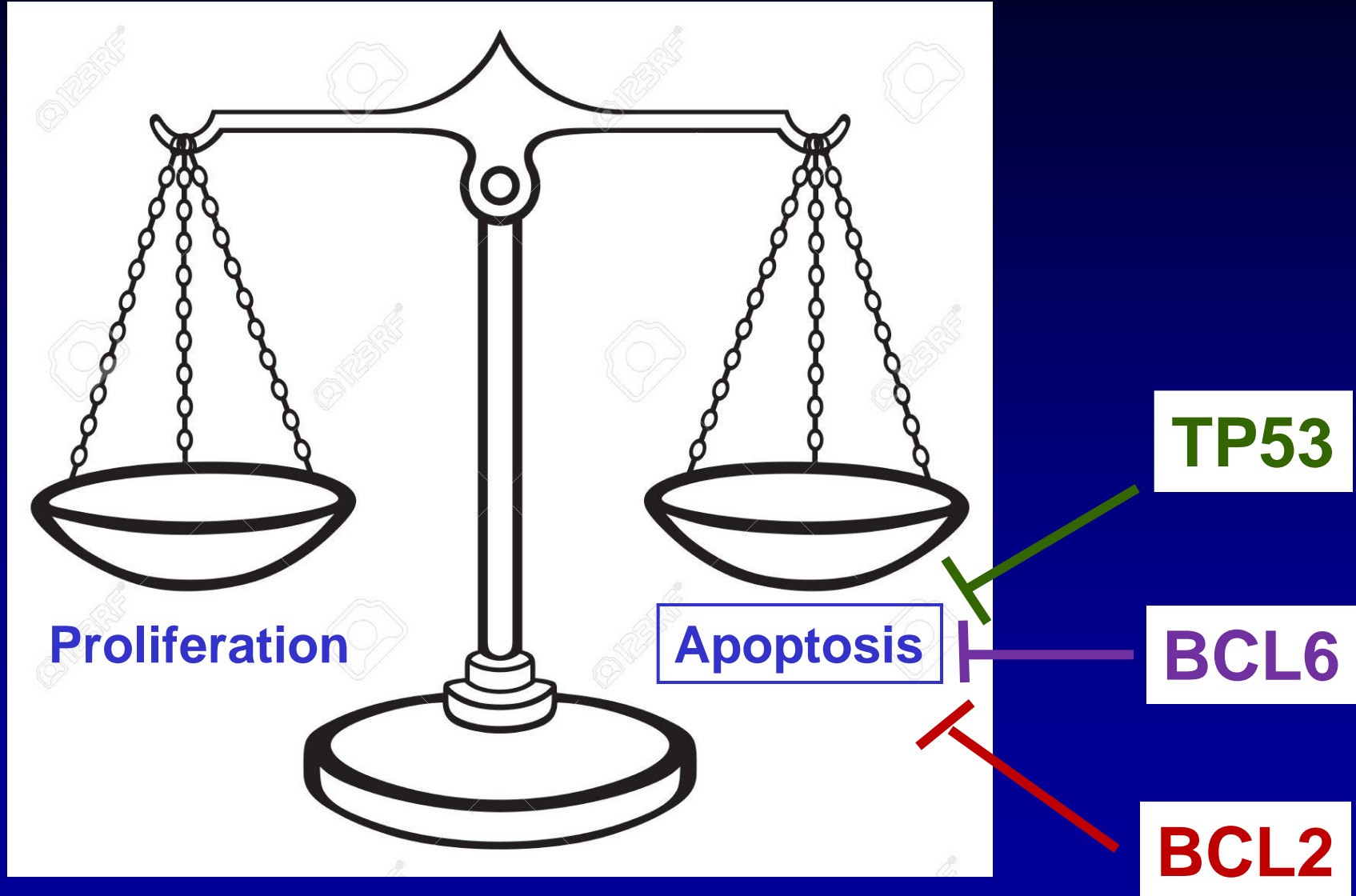
Another type of double hit lymphoma?

P53+ \geq 50% by IHC highly correlates with mutation

We suggest adding p53 to IHC panel

Molecular testing to confirm

MYC INDUCES PROLIFERATION AND APOPTOSIS



Diffuse Large B-cell Lymphoma

What Should be the Workup?

We need to include data for dx and prognosis

Include history (e.g. location, immune status)

Immunophenotype (GCB vs non-GCB)

Prognostic markers (Ki-67, MYC, BCL-2, P53)

Assess for viral infection (EBV, HHV8)

FISH/aCGH/conventional cytogenetics

Next generation sequencing

TP53, MYD88, EZH2, CARD11, CD79A/B

We need to assess for therapeutic targets

CD20, CD30, PD-L1, pAKT, pSTATs, p65, etc.