La rivoluzione terapeutica nel **linfoma** e nel **mieloma**

Napoli, Royal Hotel Continental • 14–15 Maggio 2026

DLBCL: Classificazione Istopatologica

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

ICC 2022

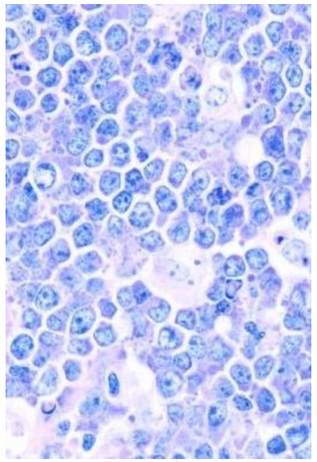
- Diffuse large B-cell lymphoma, NOS
  - Germinal center B-cell subtype
  - Activated B-cell subtype
- *Large B-cell lymphoma with 11q aberration**
- Nodular lymphocyte predominant B-cell lymphoma*
- T cell/histiocyte-rich large B-cell lymphoma
- Primary diffuse large B-cell lymphoma of the central nervous system
- Primary diffuse large B-cell lymphoma of the testis*
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Intravascular large B-cell lymphoma
- *HHV-8 and Epstein-Barr virus–negative primary effusion-based lymphoma**
- Epstein-Barr virus–positive mucocutaneous ulcer*
- Epstein-Barr virus–positive diffuse large B-cell lymphoma, NOS
- Diffuse large B-cell lymphoma associated with chronic inflammation
  - Fibrin-associated diffuse large B-cell lymphoma
- Lymphomatoid granulomatosis
- Epstein-Barr virus–positive polymorphic B-cell lymphoproliferative disorder, NOS*
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- HHV-8–associated lymphoproliferative disorders
  - Multicentric Castleman disease
  - HHV-8–positive germinotropic lymphoproliferative disorder
  - HHV-8–positive diffuse large B-cell lymphoma, NOS
  - Primary effusion lymphoma
- Burkitt lymphoma
- High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements*
- *High-grade B-cell lymphoma with MYC and BCL6 rearrangements**
- High-grade B-cell lymphoma, NOS
- Primary mediastinal large B-cell lymphoma

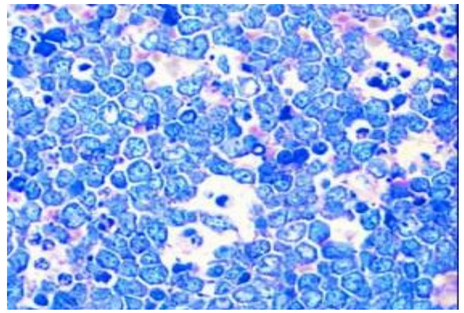
Combination of morphologic and molecular - based classification

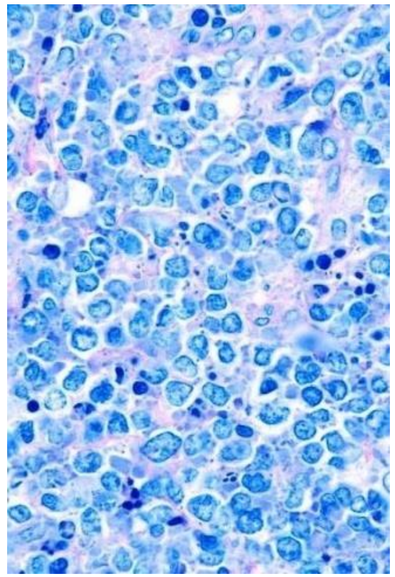
WHO 2022

- ***Large B-cell lymphomas***
- Diffuse large B-cell lymphoma, NOS
- T-cell/histiocyte-rich large B-cell lymphoma
- Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
- ALK-positive large B-cell lymphoma
- Large B-cell lymphoma with *IRF4* rearrangement
- High-grade B-cell lymphoma with 11q aberrations
- Lymphomatoid granulomatosis
- EBV-positive diffuse large B-cell lymphoma
- Diffuse large B-cell lymphoma associated with chronic inflammation
- Fibrin-associated large B-cell lymphoma
- Fluid overload-associated large B-cell lymphoma
- Plasmablastic lymphoma
- Primary large B-cell lymphoma of immune-privileged sites
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Intravascular large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Mediastinal grey zone lymphoma
- High-grade B-cell lymphoma, NOS
- ***Burkitt lymphoma***
- Burkitt lymphoma

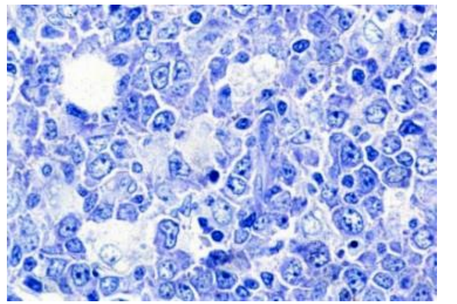
Burkitt - like

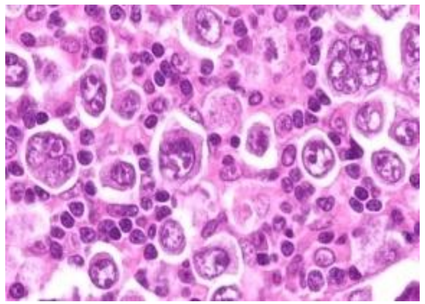


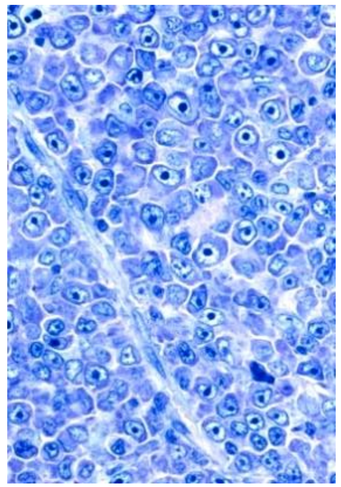


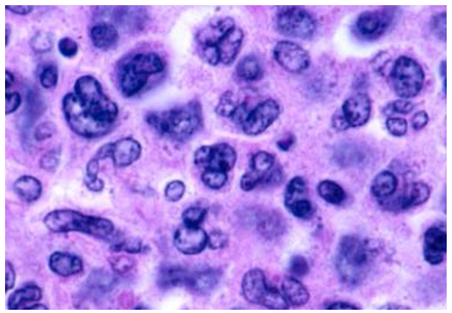


DLCL - like









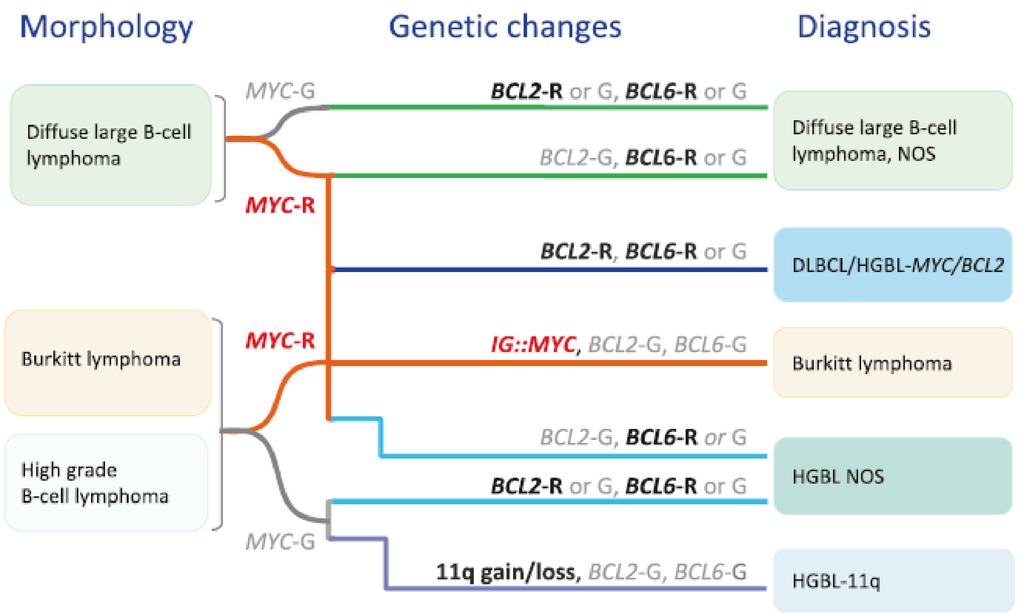
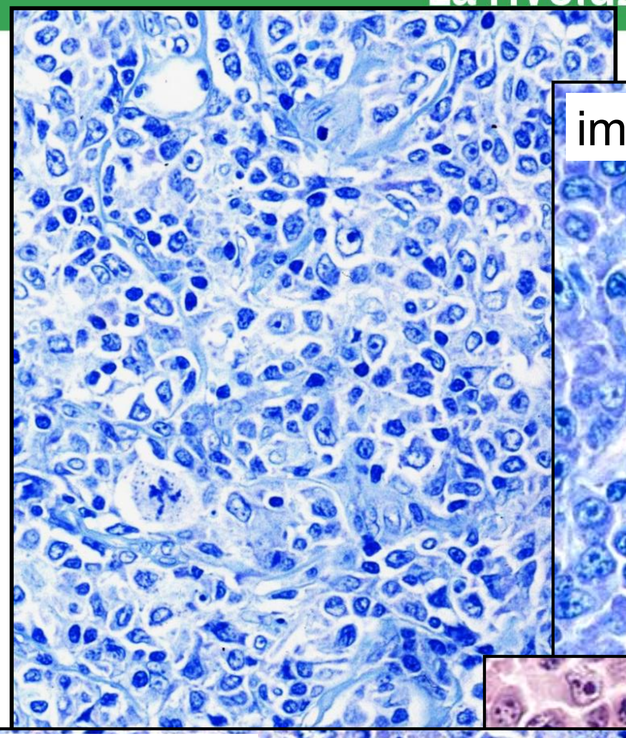
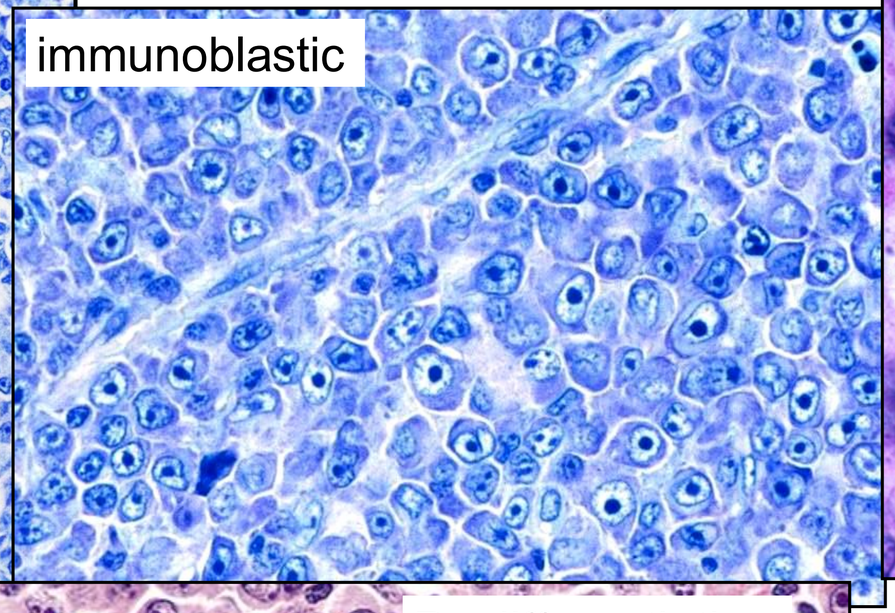
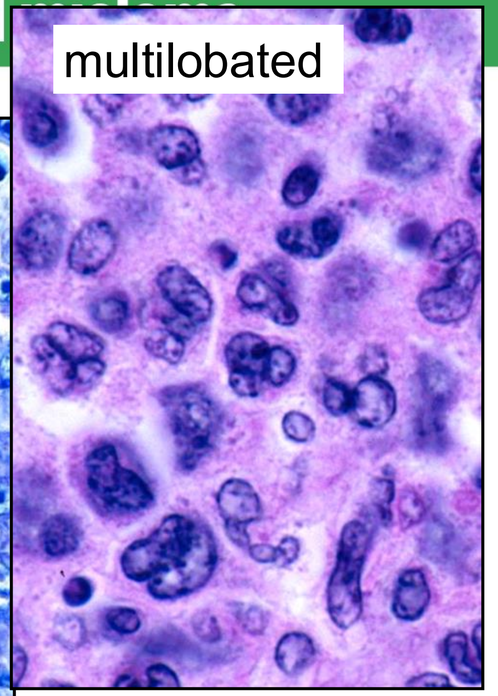


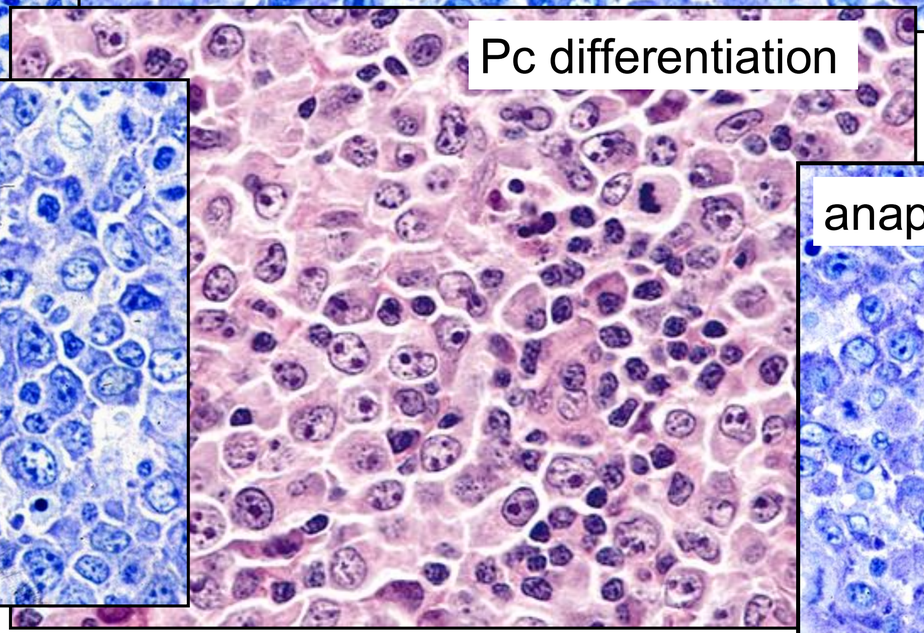
Fig. 4 **Algorithm for classification of aggressive B-cell lymphomas in WHO-HAEM5 in the light of *MYC*, *BCL2* and *BCL6* rearrangement and complex 11q gain/loss patterns.** HGBL high grade B-cell lymphoma, R rearrangement, G germline configuration.

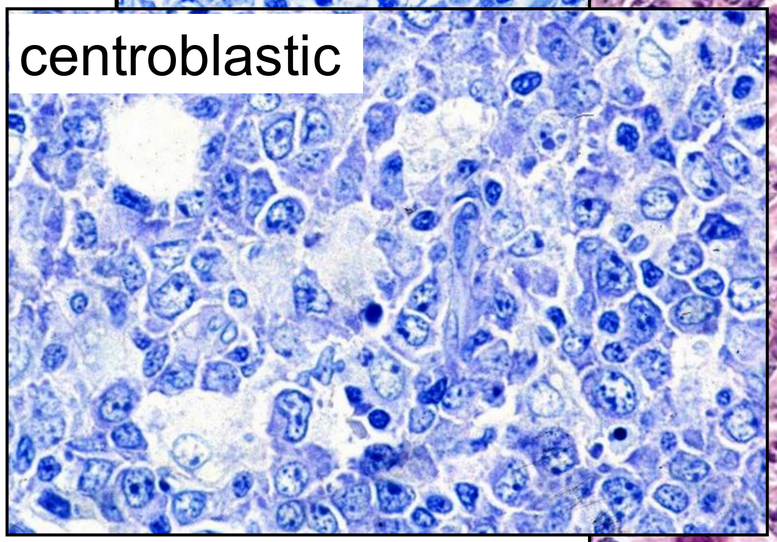
WHO 5th




immunoblastic


multilobated


Pc differentiation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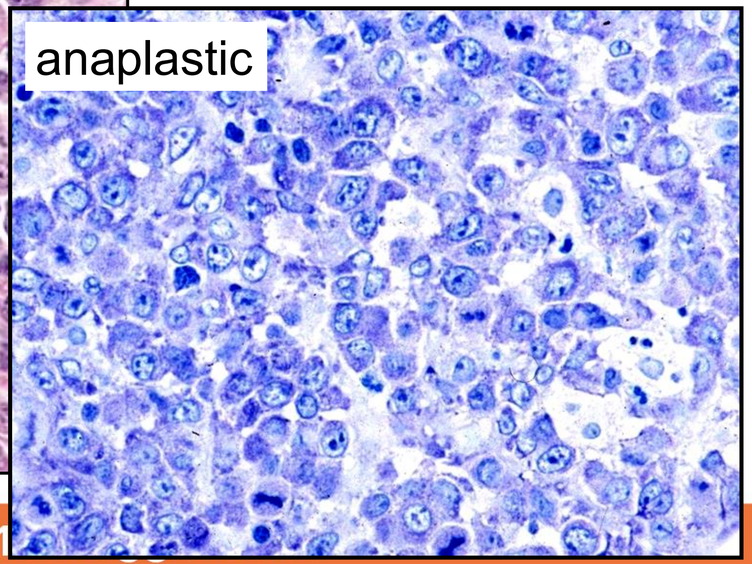
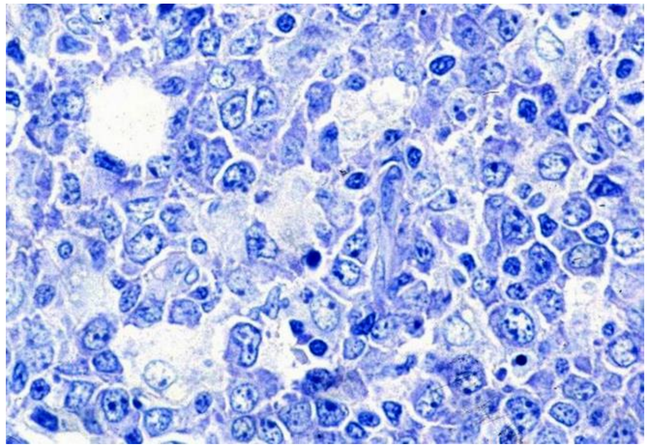
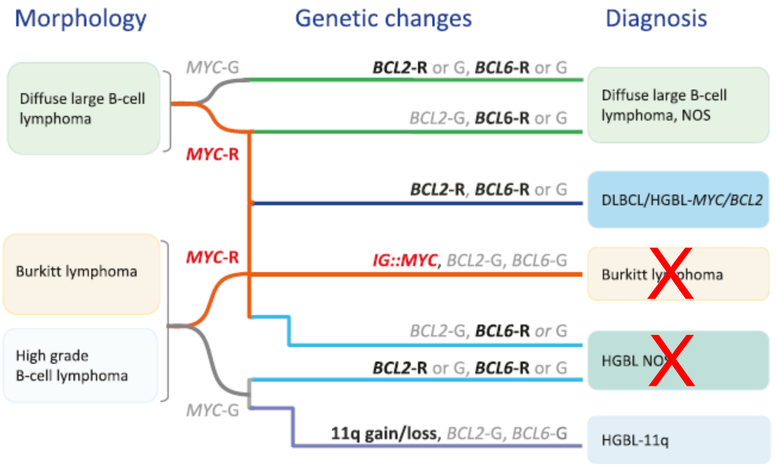

anaplastic





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Lymph2Cx is the gold standard
(20 gene Customized Nanostring-GEP signature on FFPE tissue)
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COO-IHC algorithms acceptable specify which algorithm; 2004 Hans' mostly applied
GCB-cases (high concordance between IHC vs GEP COO)
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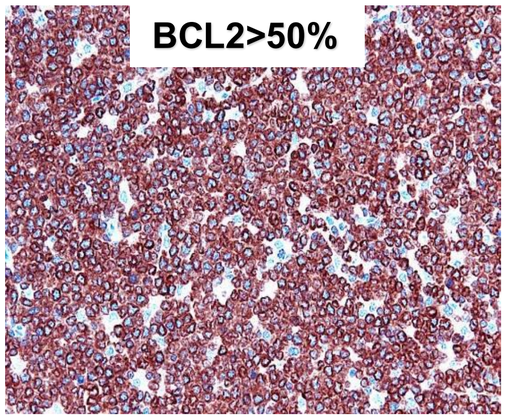
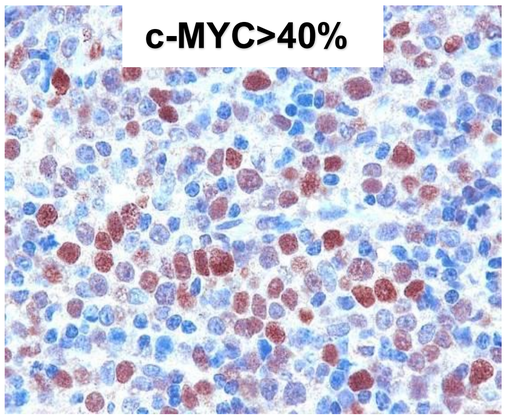




Can include cases with *MYC-R* (reported with worse outcome)
DLBCL-NOS with MYC-R and BCL6-R: excluded in ICC (included into DH category; included in WHO5)

Nanostring

LYMPHOID NEOPLASIA

Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue

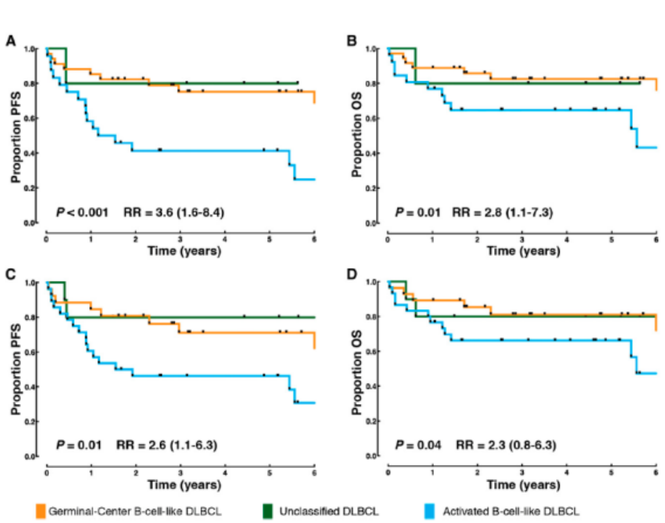
David W. Scott,[1] George W. Wright,[2] P. Mickey Williams,[3] Chih-Jian Lih,[3] William Walsh,[3] Elaine S. Jaffe,[4] Andreas Rosenwald,[5] Elias Campo,[6] Wing C. Chan,[7] Joseph M. Connors,[1] Erlend B. Smeland,[8] Anja Mottok,[1] Rita M. Braziel,[9] German Ott,[10] Jan Delabie,[11] Raymond R. Tubbs,[12] James R. Cook,[13] Dennis D. Weisenburger,[14] Timothy C. Greiner,[7] Betty J. Glinsmann-Gibson,[15] Kai Fu,[7] Louis M. Staudt,[16] Randy D. Gascoyne,[1,17] and Lisa M. Rimsza[15]

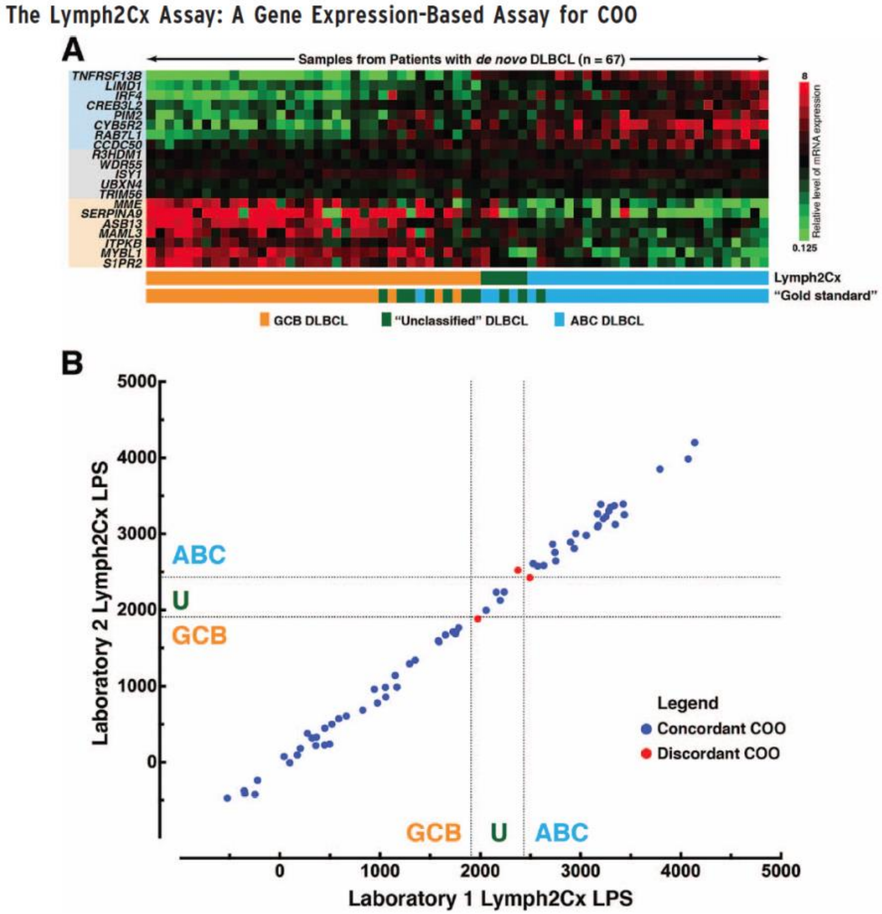
Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies

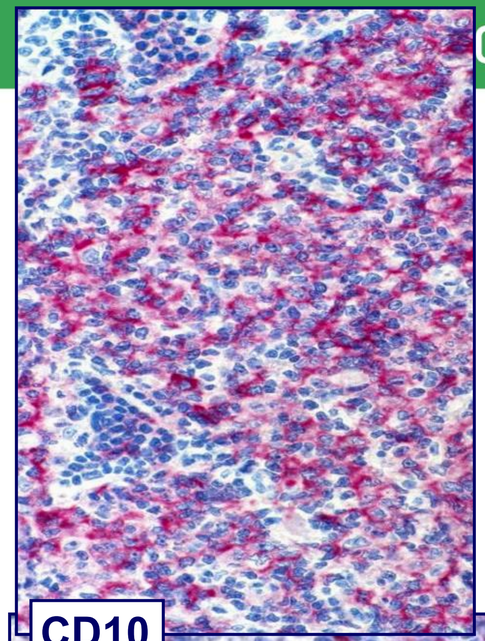
David W. Scott, Anja Mottok, Daisuke Ennishi, George W. Wright, Pedro Farinha, Susana Ben-Neriah, Robert Kridel, Garrett S. Barry, Christoffer Hother, Pau Abrisqueta, Merrill Boyle, Barbara Meissner, Adele Telenius, Kerry J. Savage, Laurie H. Sehn, Graham W. Slack, Christian Steidl, Louis M. Staudt,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

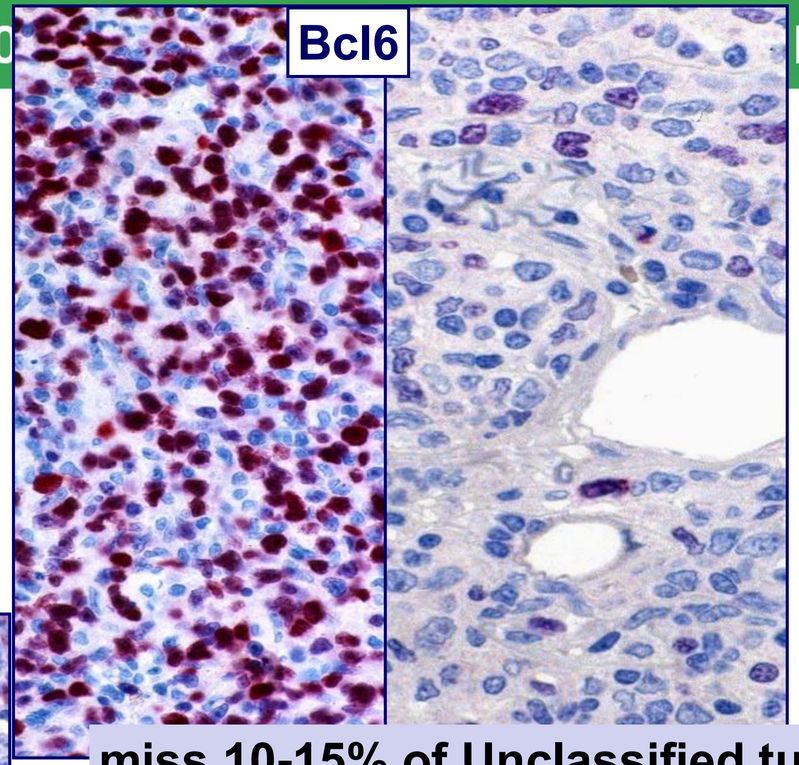
Key Points

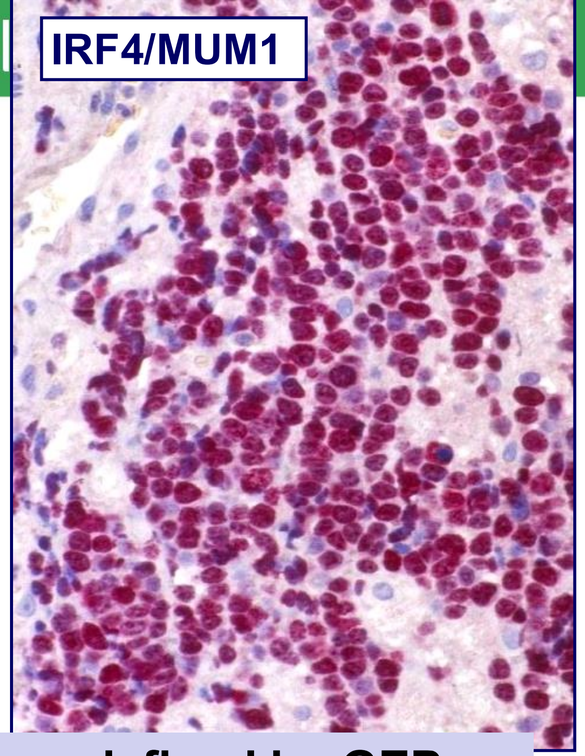
- A 20-gene gene expression-based assay accurately and robustly assigns COO subtypes of DLBCL using formalin-fixed paraffin-embedded tissue.

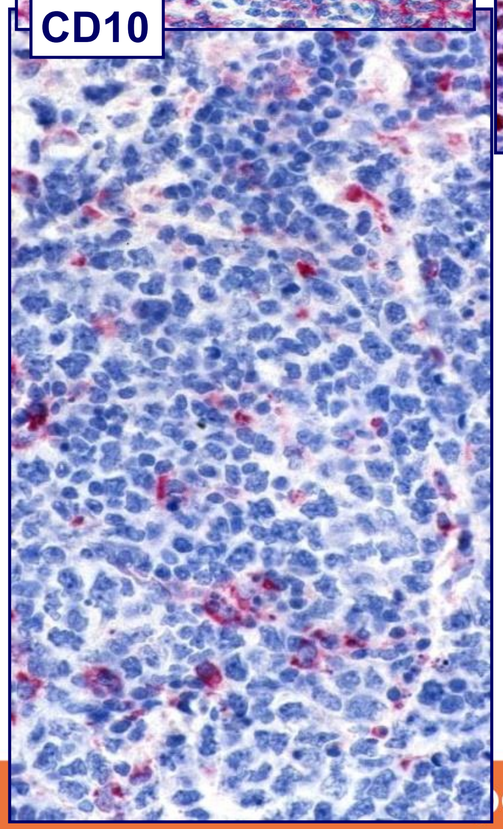




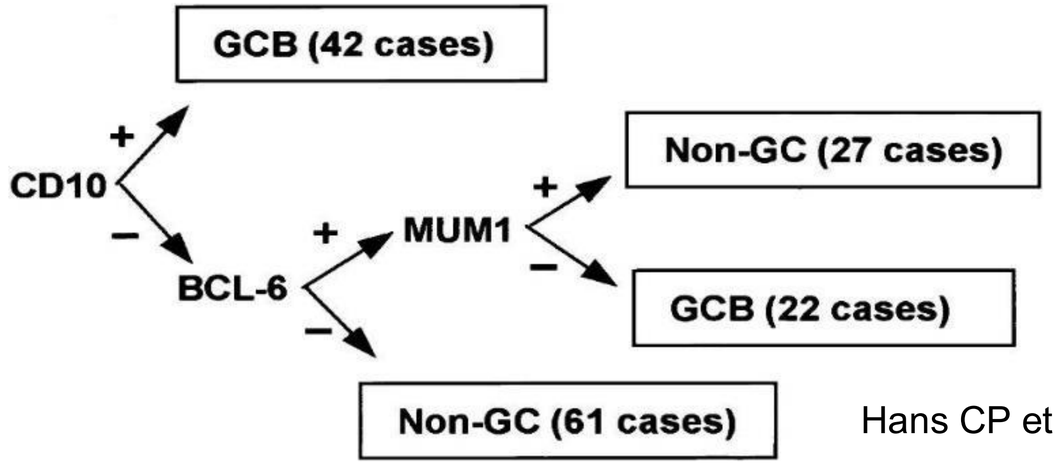




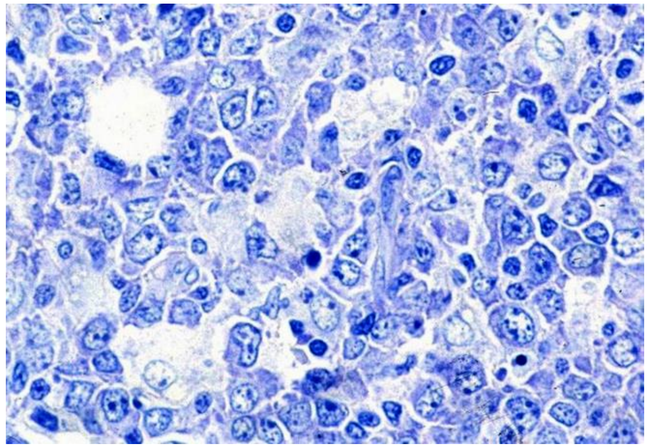


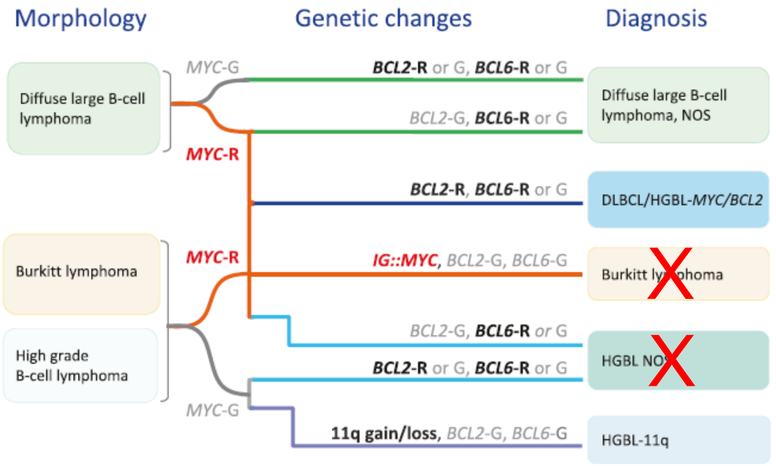


miss 10-15% of Unclassified tumors defined by GEP



Hans CP et al. Blood 2004





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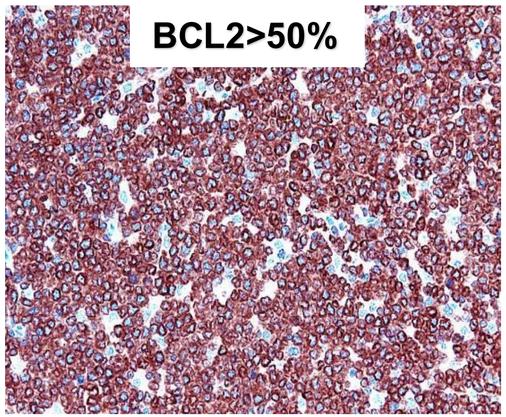

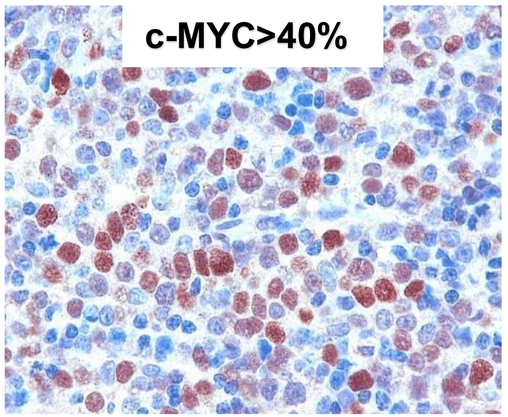

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WHO5: Diffuse large/High grade B-cell Lymphoma with MYC/BCL2-R
ICC: High grade B-cell Lymphoma with MYC and BCL2 rearrangements
ICC: High grade B-cell Lymphoma with MYC and BCL6 rearrangements (provisional)

Molecularly based diagnosis

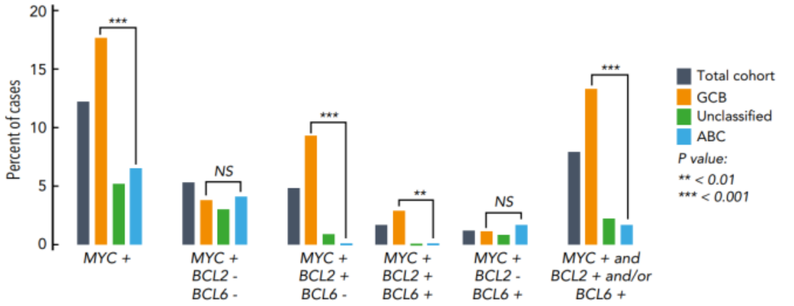
All cytology types: should be reported (DLBCL morphology in about 50% cases significantly better outcome approximately 60% after 5 years vs high grade morphology)

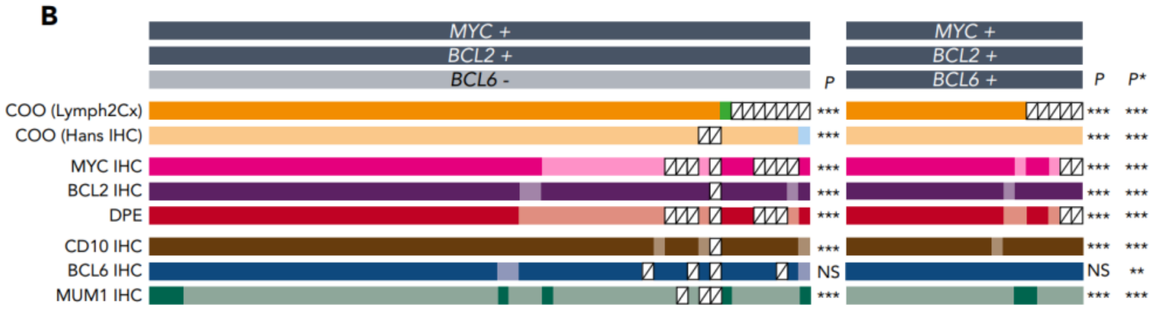
MYC/BCL2

Most cases belong to COO-GCB
Most cases are DE (75%)
IHC: CD10+ (95%), BCL2+ strong (95%)
MUM1 neg (89%), MYC+ (>70% positive cells) (80%)
Subset is transformed FL (presence of DH/TH exclude FL)

HBGL-TH:

1.7% >GCB





1228 biopsies

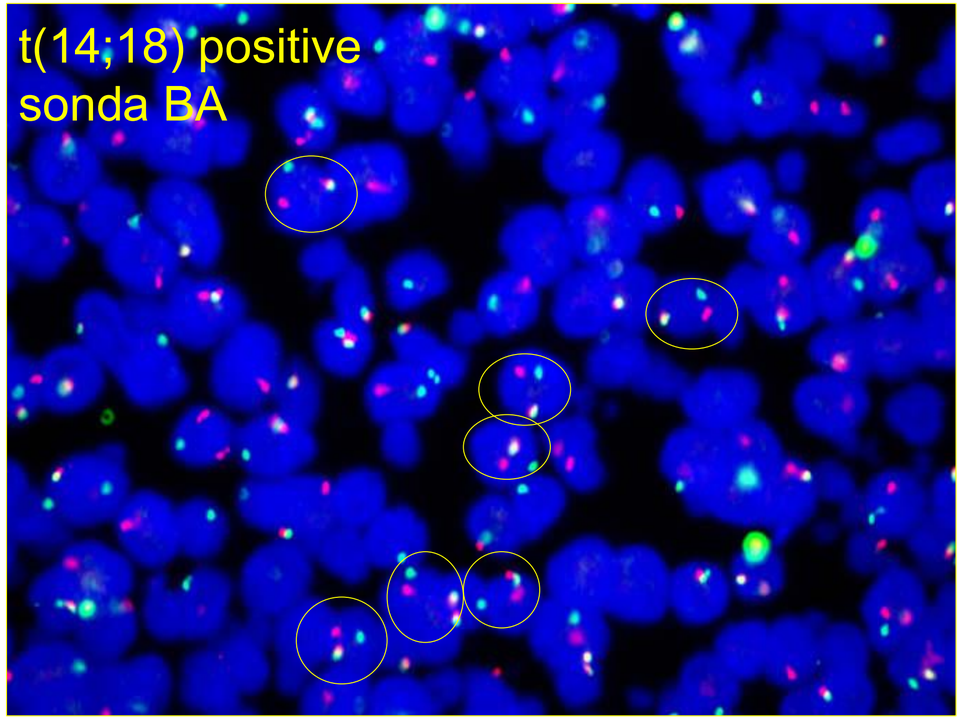
LYMPHOID NEOPLASIA

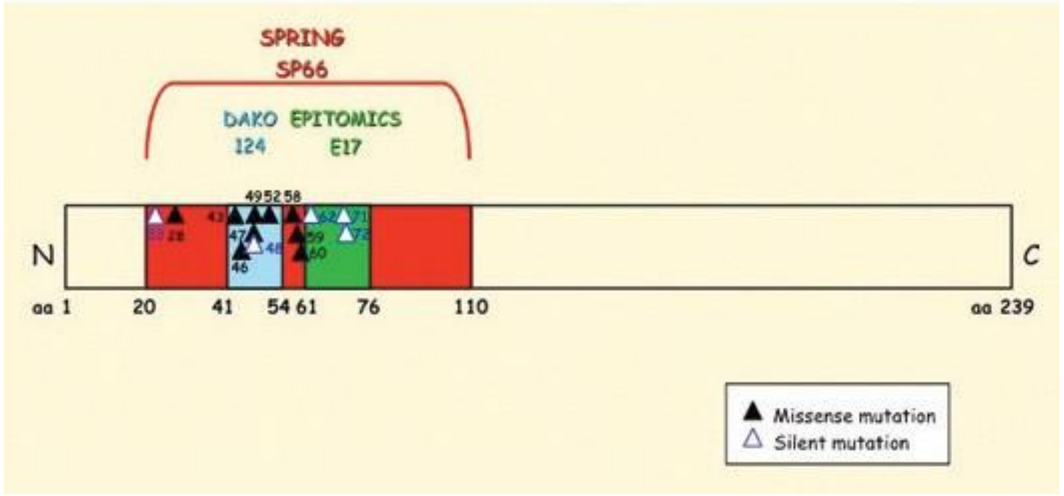
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements with diffuse large B-cell lymphoma morphology

David W. Scott,[1,2] Rebecca L. King,[3] Annette M. Staiger,[4,5] Susana Ben-Neriah,[1] Aixiang Jiang,[4] Heike Horn,[3] Anja Mottok,[1,7] Pedro Farinha,[1] Graham W. Slack,[1] Daisuke Ennishi,[1] Norbert Schmitz,[6] Michael Pfreundschuh,[6] Grzegorz S. Nowakowski,[10] Brad S. Kahl,[11] Joseph M. Connors,[1,2] Randy D. Gascoyne,[1] German Ott,[4] William R. Macon,[3]* and Andreas Rosenwald[7]*

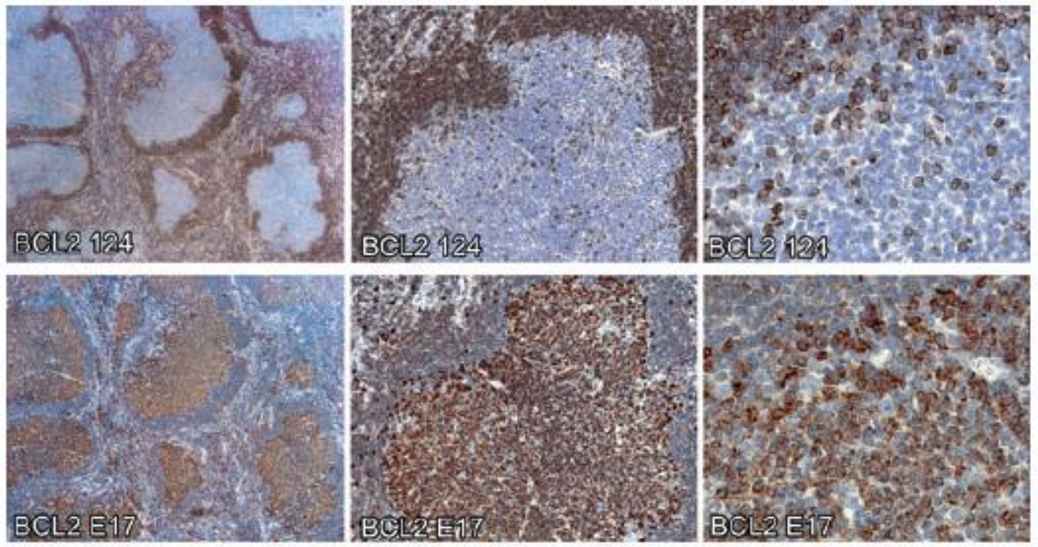
t(14;18) is present but BCL2 gene somatic mutations:

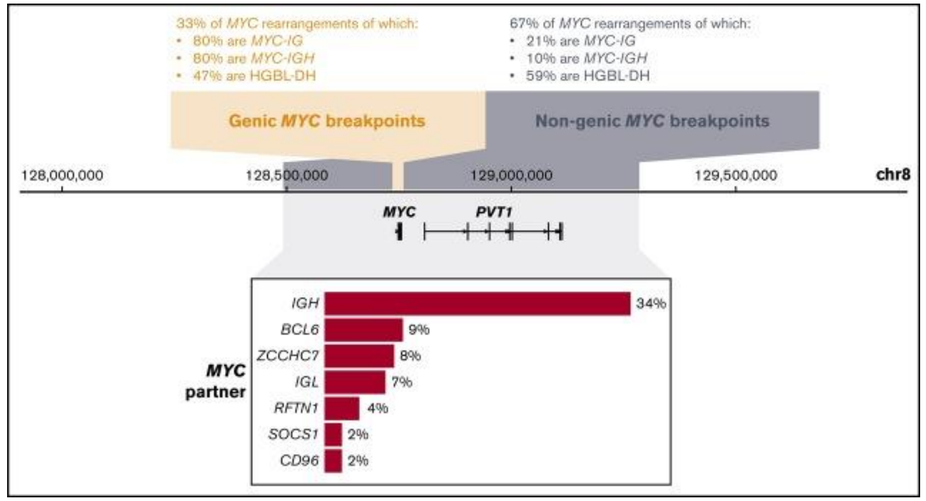
- produce stop codons
- modify epitope

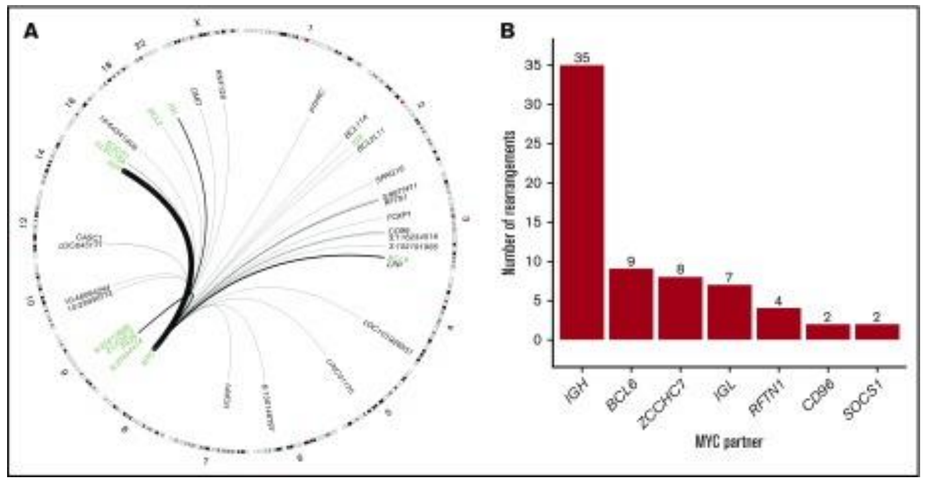




False negative BCL2







Blood Adv . 2018 Oct 23;2(20):2755-2765.

Key Points

- One third of *MYC* rearrangements in DLBCL occur in a cluster upstream of the *MYC* coding sequence and are enriched for *IGH* partners.
- Most *MYC* rearrangements in HGBL-DH patients have non-*IG* partners.

Table 2. Summary of rearrangement partners identified in the *MYC* region using capture sequencing

	Total breakpoints	*IGH* partner	*IGK/IGL* partner	Non-*IG* partner
Genic cluster	35	28 (80)	0 (0)	7 (20)
Other	70	7 (10)	8 (11)	55 (79)
Single-hit	34	14 (41)	3 (9)	17 (50)
HGBL-DH	69	19 (28)	5 (7)	45 (65)
GCB	71	19 (27)	6 (8)	46 (65)
ABC/non-GCB	25	11 (44)	2 (8)	12 (48)

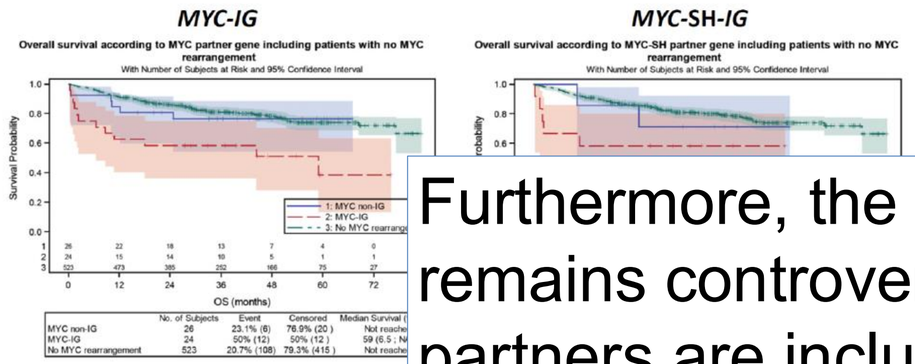
Total counts of rearrangements are shown with percentages in parentheses. Counts include translocations and large intrachromosomal rearrangements (>2 Mb). Rearrangements that failed validation and low-confidence predictions in nonvalidated cases have been omitted.

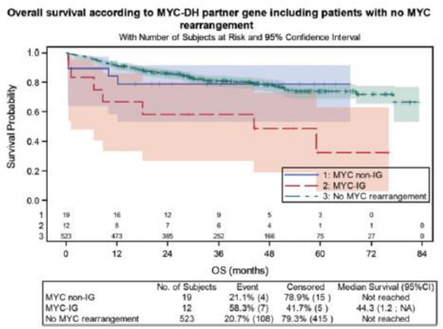
ABC, activated B-cell–like DLBCL.

LYMPHOID NEOPLASIA

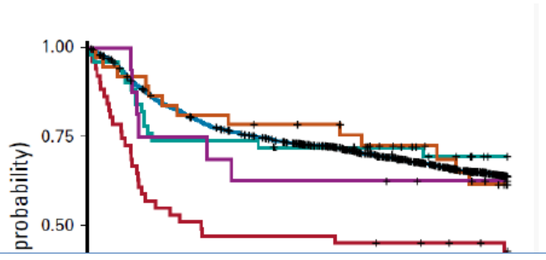
MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study

Christiane Copie-Bergman,[1-3] Peggy Cuillière-Dartigues,[4] Maryse Baia,[3] Josette Briere,[5] Richard Delarue,[6] Danielle Canioni,[7] Gilles Salles,[8] Marie Parrens,[9] Karim Belhadj,[10] Bettina Fabiani,[11] Christian Recher,[12] Tony Petrella,[13] Nicolas Ketterer,[14] Frederic Peyrade,[15] Corinne Haioun,[10] Inga Nagel,[16] Reiner Siebert,[16] Fabrice Jardin,[17] Karen Leroy,[1-3] Jean-Philippe Jais,[18] Herve Tilly,[17] Thierry Jo Molina,[19,*] and Philippe Gaulard[1-3,*]





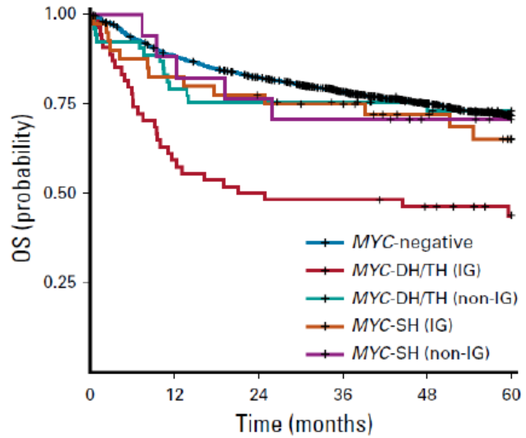
Rosenwald A et al. JCO2019



MYC-DH/TH IG (MYC rearranged with an IG partner) demonstrated inferior outcome

non-IG) and those
G had an
ith those with
(MYC negative)

Furthermore, the significance of the MYC partner gene remains controversial; MYC-R with both IG and non-IG partners are included at present.



effect >evident within 2 yrs after diagnosis

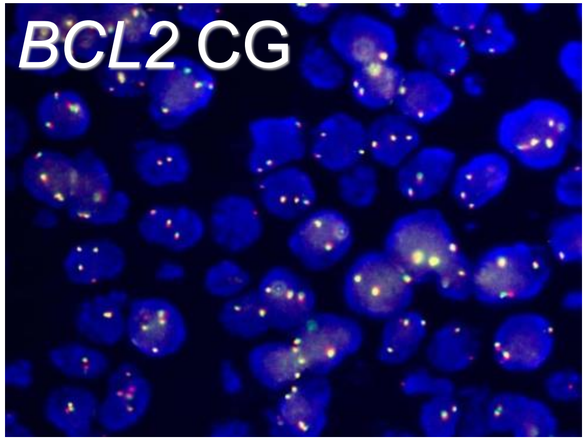
“atypical double hit” category:
Double CNV
1 CNV + 1 translocation

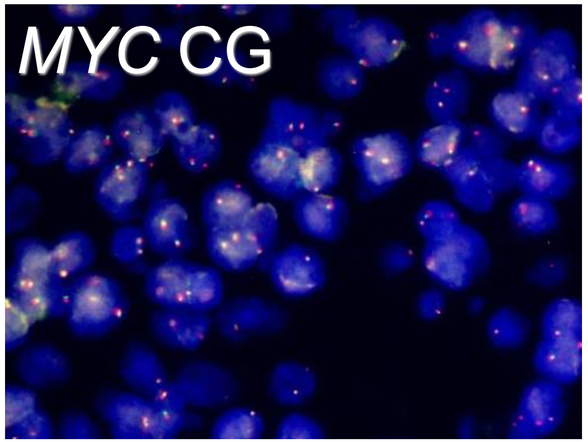
“Therefore, irrespective of prognostic significance, these results strongly support the current WHO classification, whereby only rearrangements are considered in defining HGBL-DH/TH”

Neither copy-number increase, nor amplification, of these genes is sufficient to substitute for rearrangement in these categories….

Campo et al. Blood 2022: The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee

Double CNV insufficient to produce a HGBCL-DH/TH signature





Double hit MYC/BCL6 ????

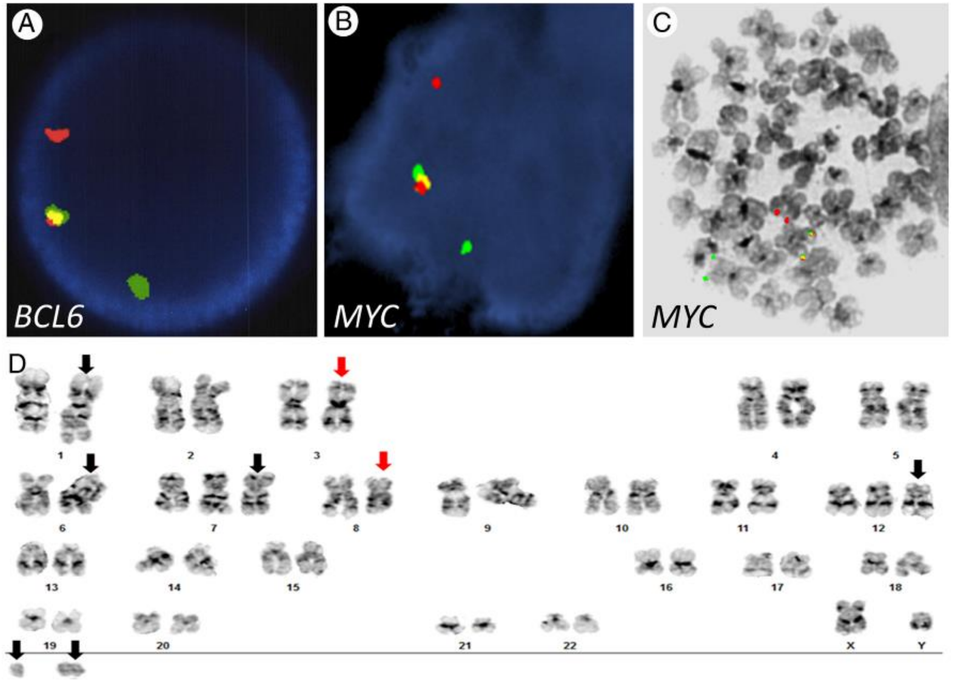
ICC 2022

« Data to support distinct biology in patients with HGBCL-DH-BCL6 are less compelling; however, it has been retainedas a provisional entity to allow for continued study based on the poor outcomes seen in some studies. Although pseudo-DH lymphomas (MYC-R with BCL6 partner) account for up to 30% of patients with HGBCL-DH-BCL6 strategies to identify this are not essential at this time.»

WHO 2022:

« In contrast, lymphoid neoplasms with dual MYC and BCL6 rearrangements represent a more diverse spectrum with variable gene expression profiles and mutational spectra, markedly differing from DLBCL/HGBL-MYC/BCL2. Hence, these cases have been excluded from the DLBCL/HGBL-MYC/BCL2 entity and are now classified either as a subtype of DLBCL, NOS or HGBL, NOS according to their cytomorphological features «

Lymphomas with pseudo–double-hit *BCL6-MYC* translocations due to t(3;8)(q27;q24) are associated with a germinal center immunophenotype, extranodal involvement, and frequent *BCL2* translocations☆,☆☆



DLBCL/HGBCL-DH-BCL2

- typically a complex karyotype, consistent with biological complexity
- frequent mutations in BCL2 (~80%), CREBBP (~50%), EZH2 (~50%) and TNFRSF14 (~45%) typical of follicular and DLBCL GCB
- mutations in ID3 (20-40%), CCND3 (10-20%), also common in BL, and FOXO1 mutations (~25%), known to regulate the dark zone of the germinal center together with CCND3
- TP53 mutations (25-30%)
- FL-like clone as the origin of DLBCL/HGBCL-DH-BCL2 tumors?

HGBCL-DH MYC/*BCL6* :
provisional in ICC2022;
non included into DH in WHO 2022

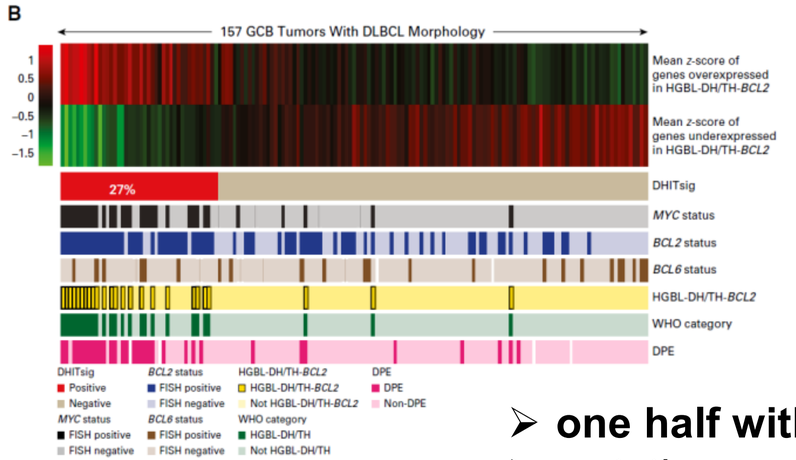
- 1.2% DH;
- do not fall within DH-signature
- mostly non-GCB/ABC
- frequent complex karyotype (92%)
- controversial results about its clinical relevance

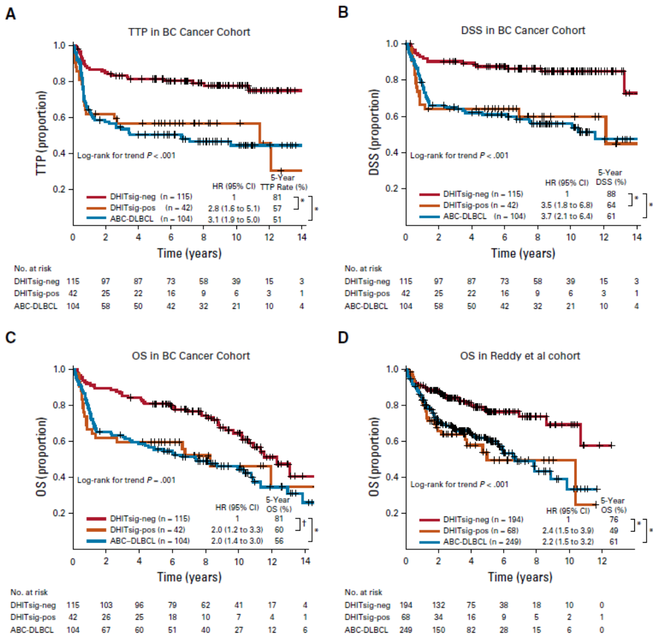
(possibly in view of small cohort sizes)

- could be biologically different from DH/TH-*BCL2*
- Pseudo double Hit-cases (30%)

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

J Clin Oncol 37:190-201. 2018





*«**DH/TH signature**» includes but not exclusively DH/TH conventional cases (means it includes non-DH and/or SH cases and/or HGBCL-NOS)*

- **one half with** MYC and BCL2 rearrangements (HGBL-DH/TH-BCL2)
- putative **non–light zone germinal centre COO:** likley from IZ B cells (transitioning from the LZ to the DZ).
- distinct mutational landscape (**>chromatin modifier genes alterations); cold tumors (**paucity of infiltrating T cells) high incidence of low MHC-I and MHC-II expression; highly metabolically charged (high expression of genes associated with oxidative phosphorylation)
- no **clinical and/or** morphologic differences that distinguished DHITpos and DHITneg tumors

An immunohistochemical germinal center B-cell dark zone signature identifies Burkitt lymphoma and molecular high-grade B-cell lymphomas

Xiaoxian Zhao, PhD[1,•]; Alexandra Balmaceda, MD[1]; Via S. Abiera, BS[1]; Lisa M. Rimsza, MD[2]; Desiree Garber, BS[1]; Lynne S. Rosenblum, PhD[1]; David W. Scott, MBChB, PhD[3]; Eric D. Hsi, MD[1,4,]*

DZ (1 point for each)
AID ≥ 60%
GCSAM ≥ 60%
MYC ≥ 40%

↓

≥2 Points = DZ-positive

Non-DZ (-1 point)
SEMA7a ≥ 40%
STAT3 ≥ 30%

↓

<2 Points = DZ-negative

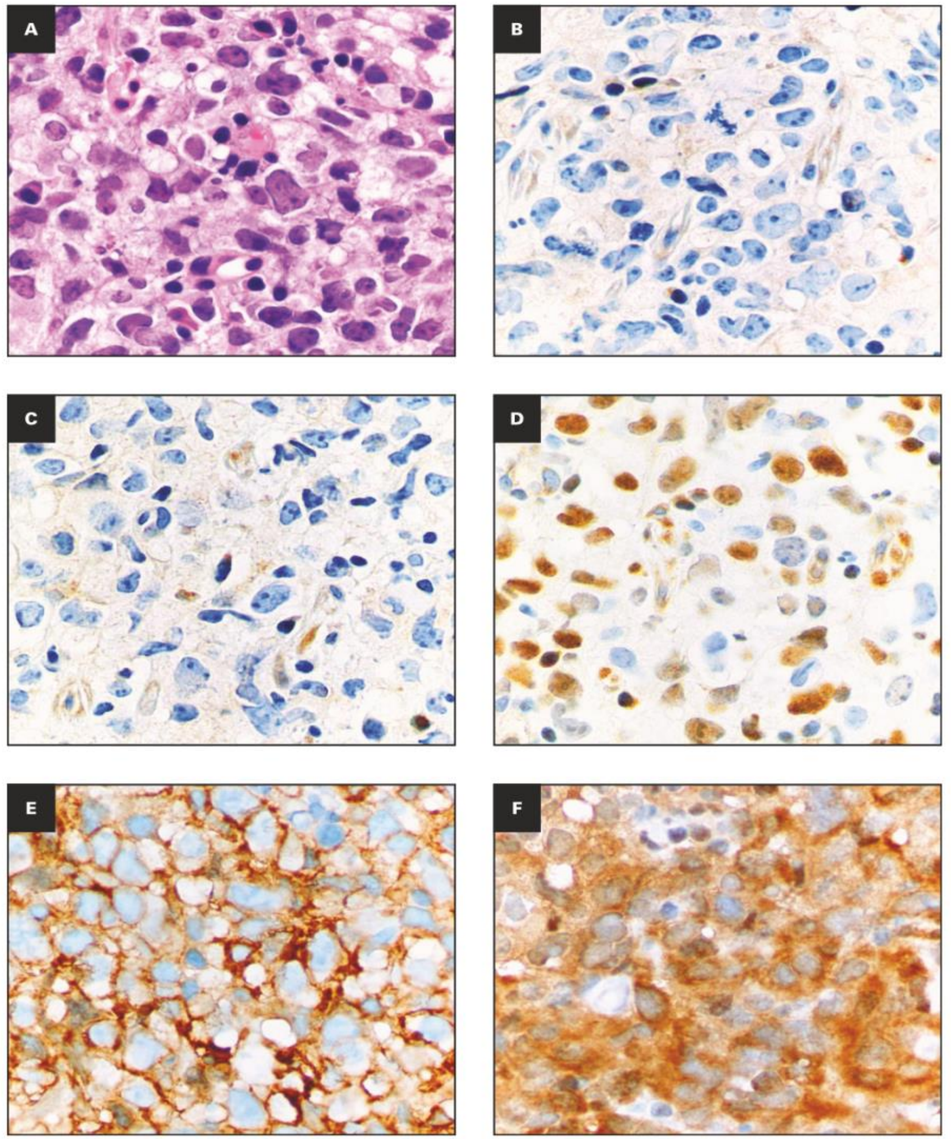
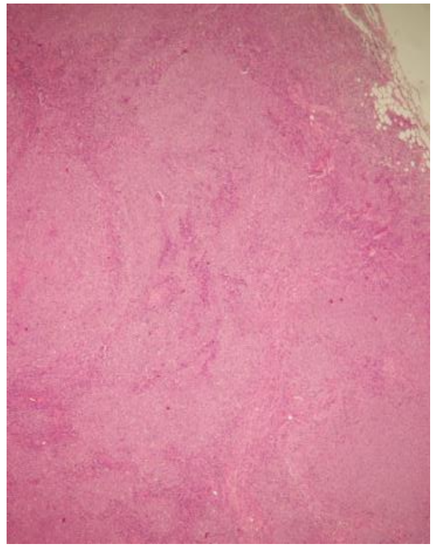
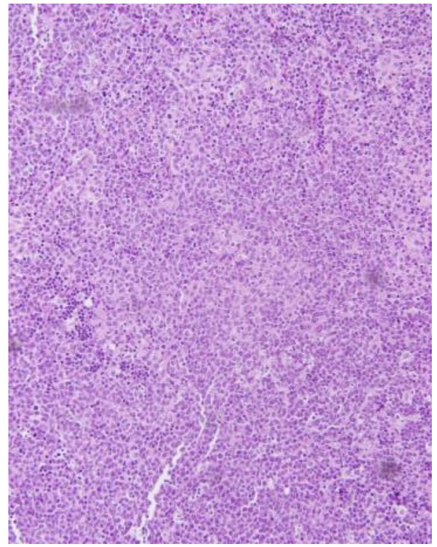


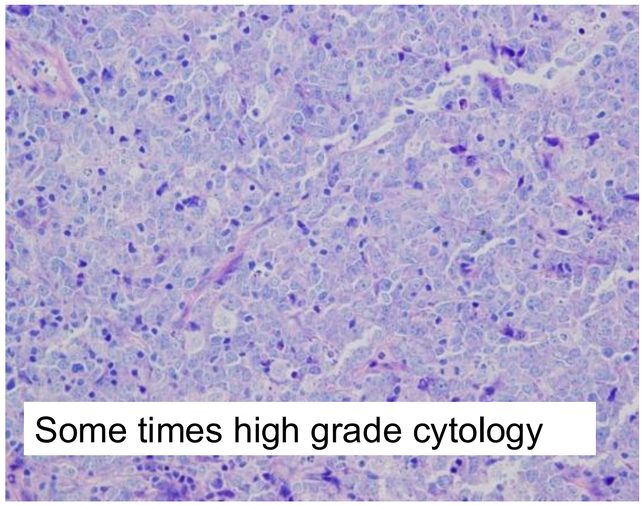
Figure 2 (**A**) Hematoxylin and eosin and (**B-F**) representative immunohistochemical staining of a case of diffuse large B-cell lymphoma, not otherwise specified. No or low expression of dark zone markers of (**B**) AID (0%), (**C**) GCSAM (0%), and (**D**) MYC (40%), while strong expression of light zone markers of (**E**) SEMA7A (100%) and (**F**) STAT3 (80%). AID, activation-induced cytidine deaminase; DZ, dark zone; GCSAM, germinal center–associated, signaling and motility; SEMA7A, semaphorin 7A; STAT3, signal transducer and activator of transcription 3.

«Large B-cell lymphoma with IRF4 rearrangement»(sole abnormality) now definite entity

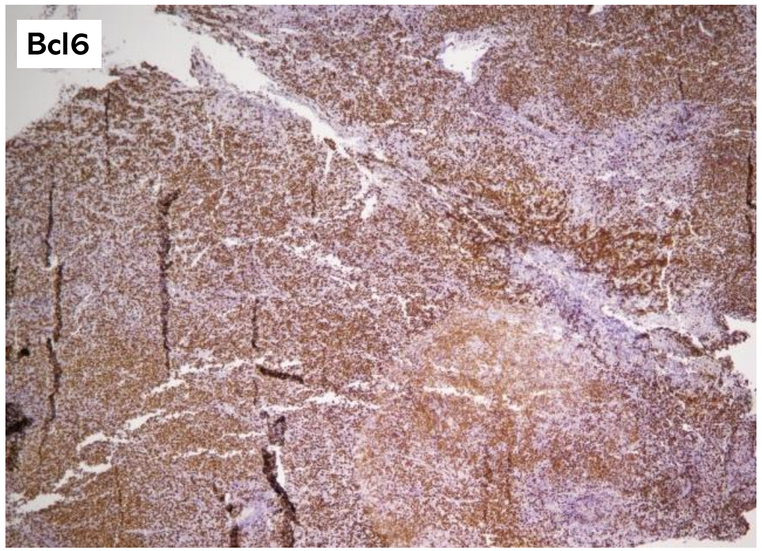
- 0.05% of DLBCL;
- **children and young adults** (median 12 yrs; range 4–79 yrs);
- **> cervical/Waldayer ring**; few cases subdiaphragm; GI tract
- **limited stage I-II**
- growth pattern: follicular (FL3B; usually no starry sky)
  or follicular/diffuse or diffuse
- follicular cases: >indolent disease excellent prognosis following excision; chemotherapy may not be needed (DD: pediatric type FL; usually no starry sky pattern in follicular areas)
  purely diffuse : often require chemotherapy

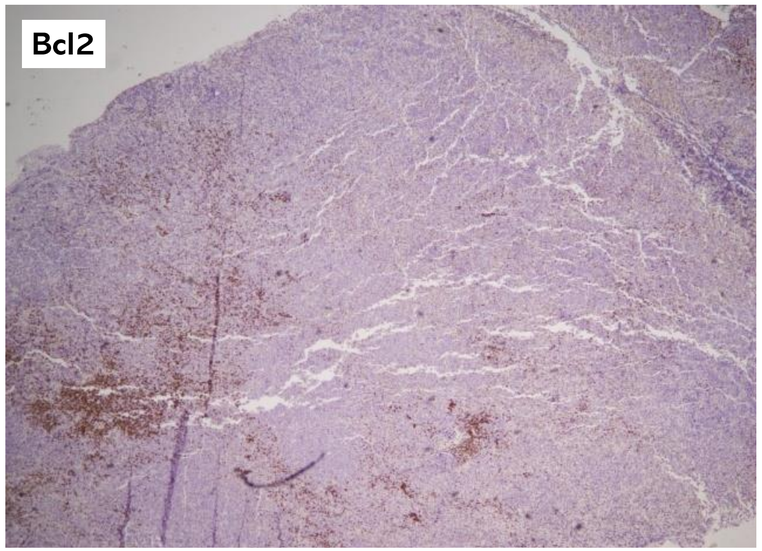


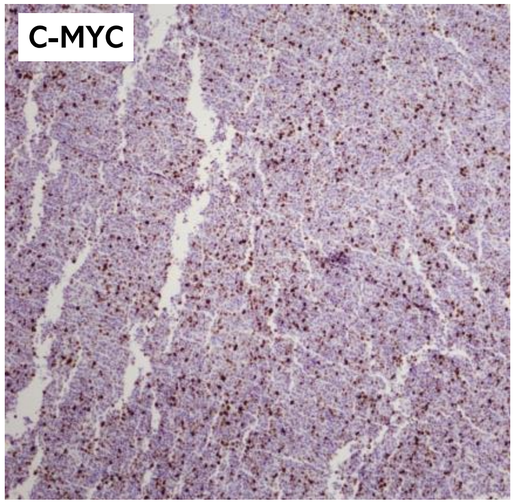




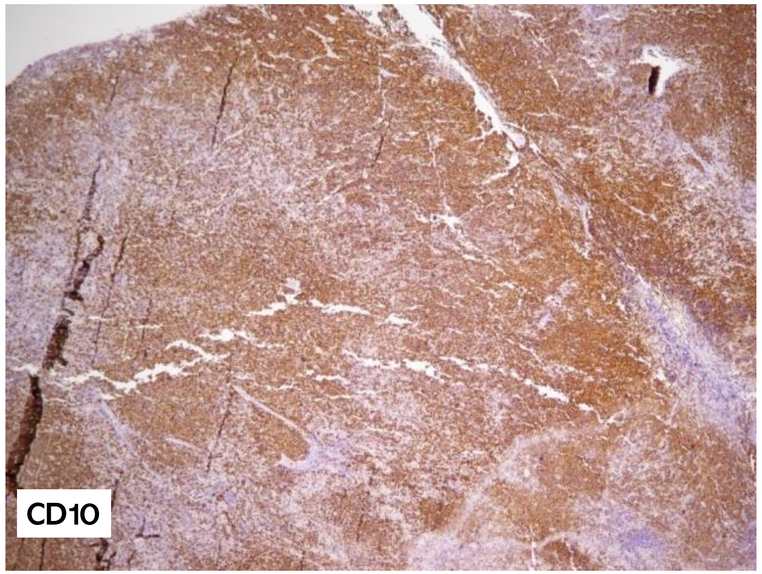
Salavarria et al. 2011 Blood; Ramis-Zaldivar Blood 2020

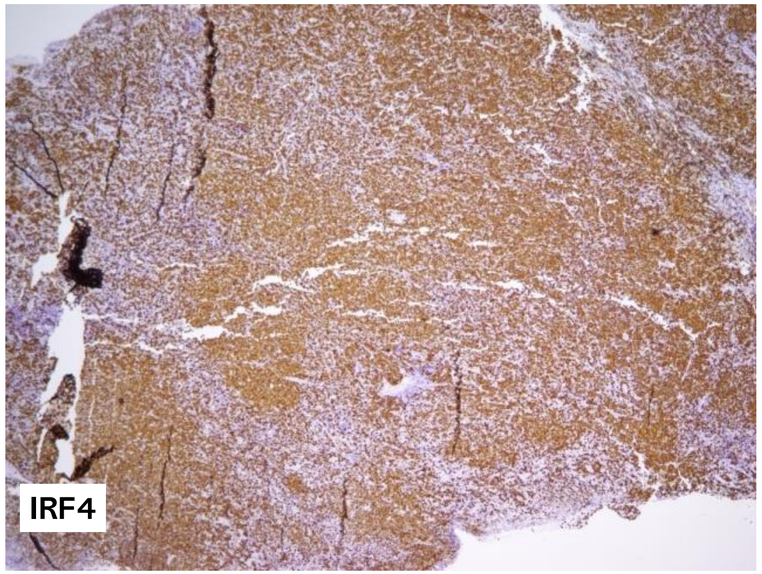


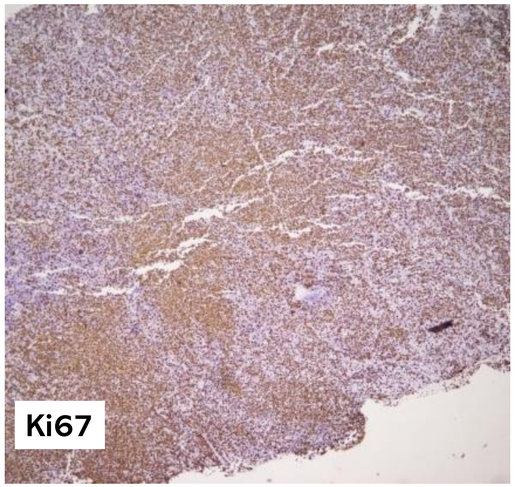




IRF4+ strong/Bcl6+, CD10+ or - (triple or dual positive) ; GCB or nonGCB with Hans, but have GCB type biology; Bcl2+ (60%)







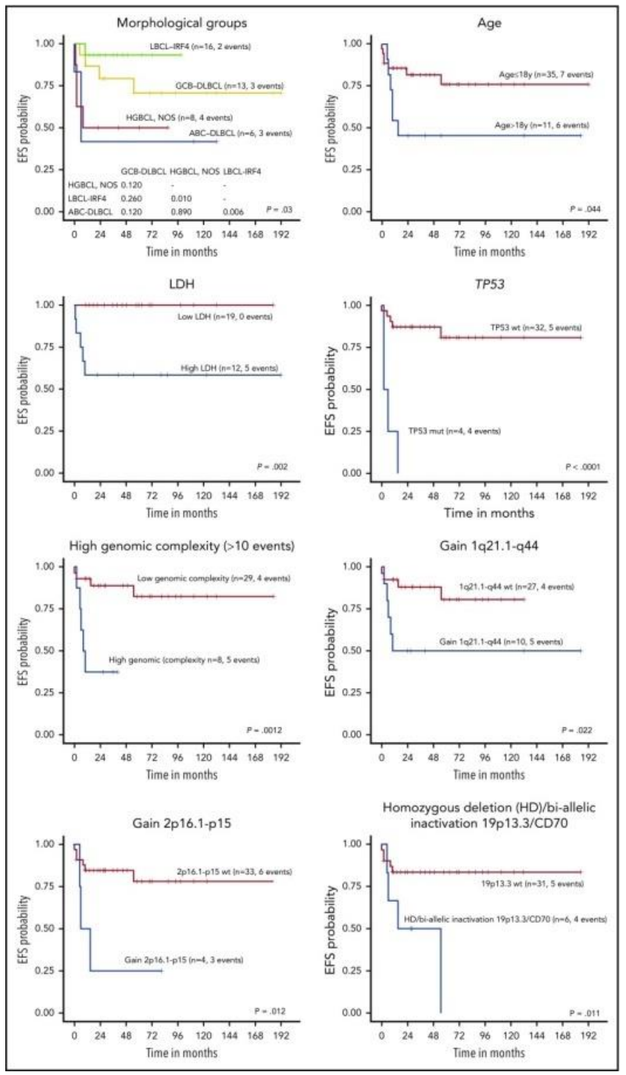
- **IRF4^{TR}+**
- difficult to recognize at conventional karyotyping;
- often *IG/IRF4^{TR}*
- possible BCL6^{TR}; no MYC^{TR} no BCL2^{TR}
- In cases lacking demonstrable rearrangements (10%),break in IGH or IGL/K locus (in absence of IRF4, MYC, BCL6, BCL2 R) could support the diagnosis
- If IRF4 rearrangement cannot be performed : is all pathologic features and clinical setting are consistent : LBCL with IRF4R “not molecularly defined”
- IRF4 mutations 76% (may support the diagnosis)

CARD11 (mutations in NFkB related genes CARD11 35% only in diffuse patterns>CD79a>MYD88; CCND3 in 24%

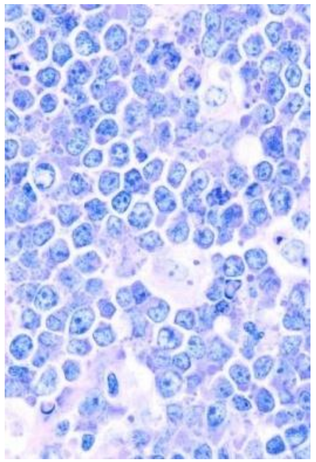
MAP2K1 in follicular patterns only

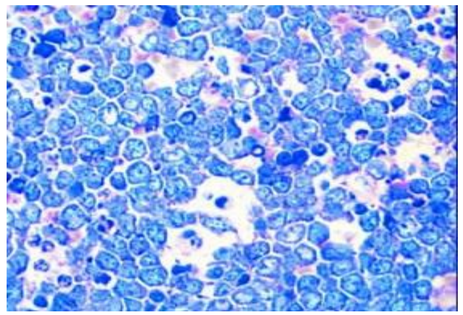
•Globally favourable prognosis, but variability upon age and presence/absence of genetic features

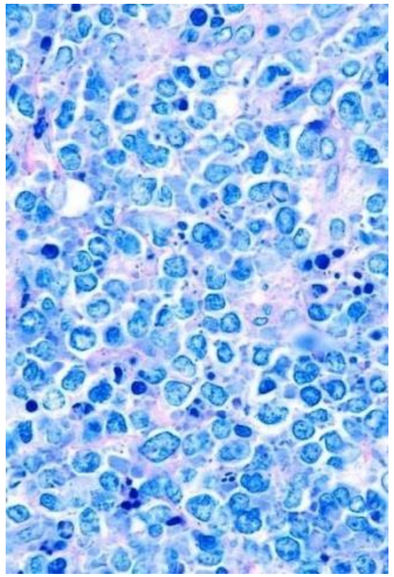
Ramis-Zaldivar Blood 2020



Burkitt - like







High grade cytology

IHC: CD10/BCL6/BCL2/IRF4/CMYC

Fish for MYC/BCL2/BCL6

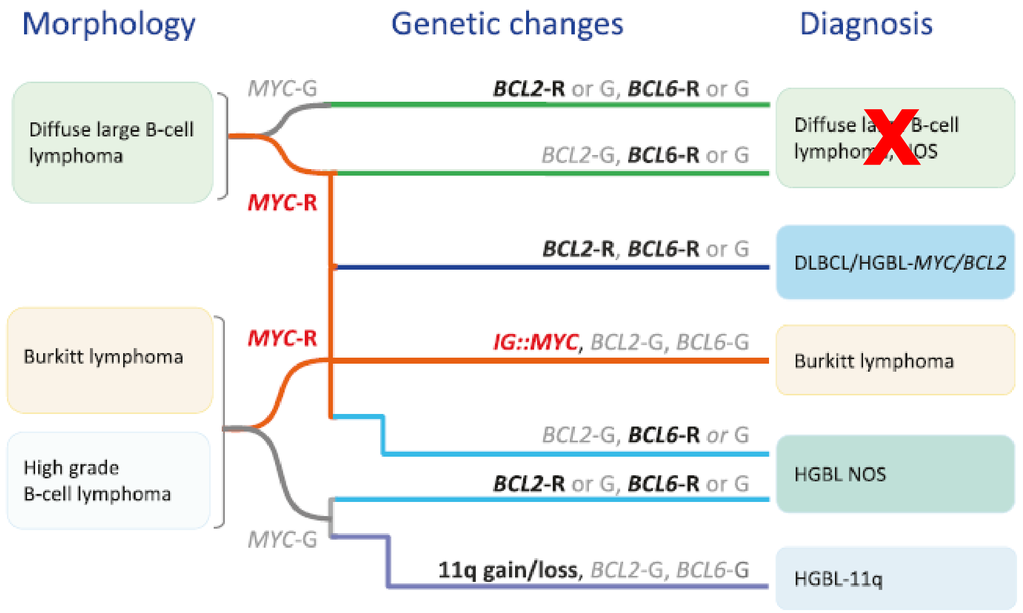
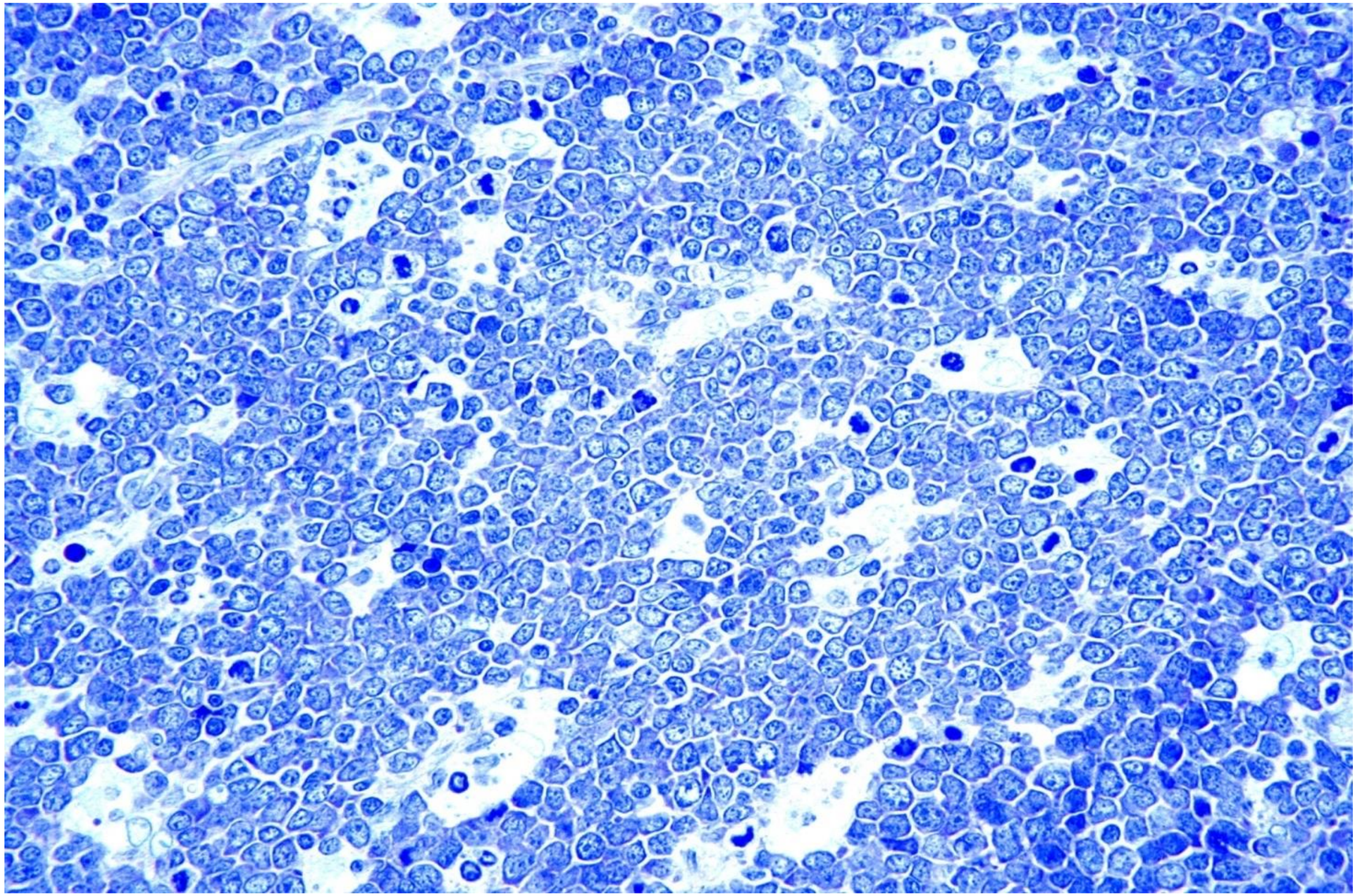
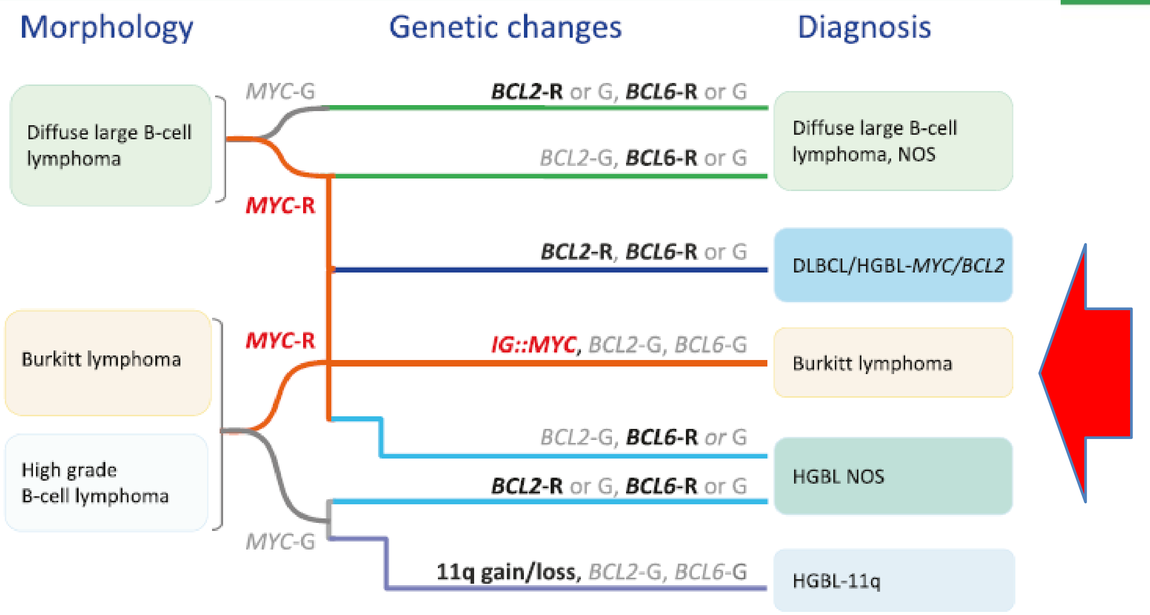


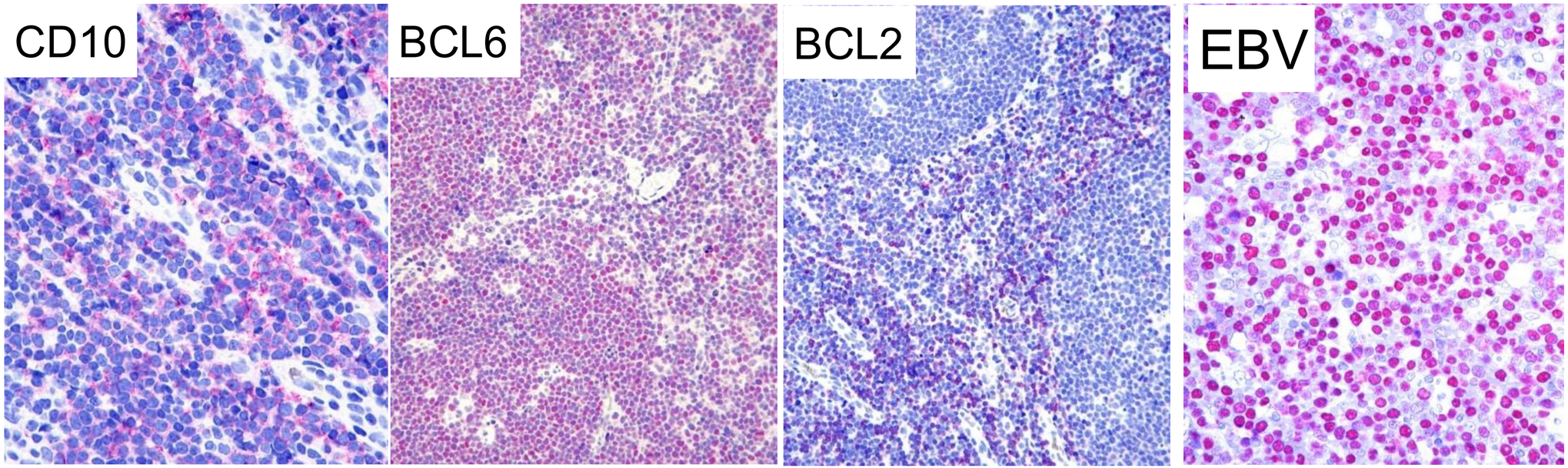
Fig. 4 Algorithm for classification of aggressive B-cell lymphomas in WHO-HAEM5 in the light of *MYC*, *BCL2* and *BCL6* rearrangement and complex 11q gain/loss patterns. HGBL high grade B-cell lymphoma, R rearrangement, G germline configuration.

BURKITT-LIKE

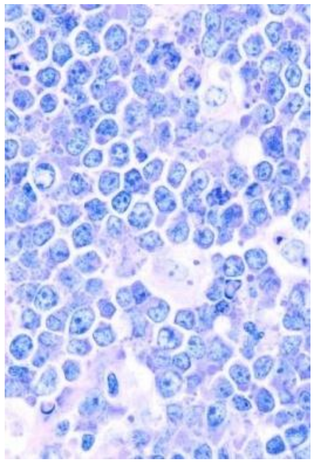


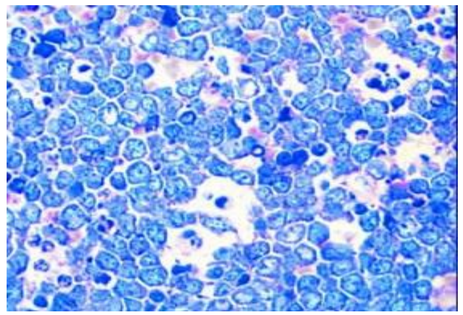
exclude
Burkitt

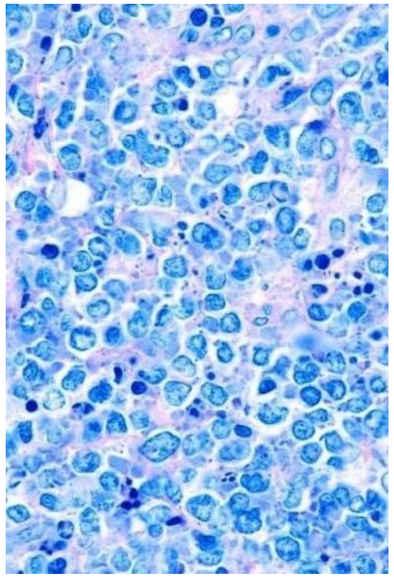




Burkitt - like







High grade cytology

IHC: CD10/BCL6/BCL2/IRF4/CMYC

Fish for MYC/BCL2/BCL6

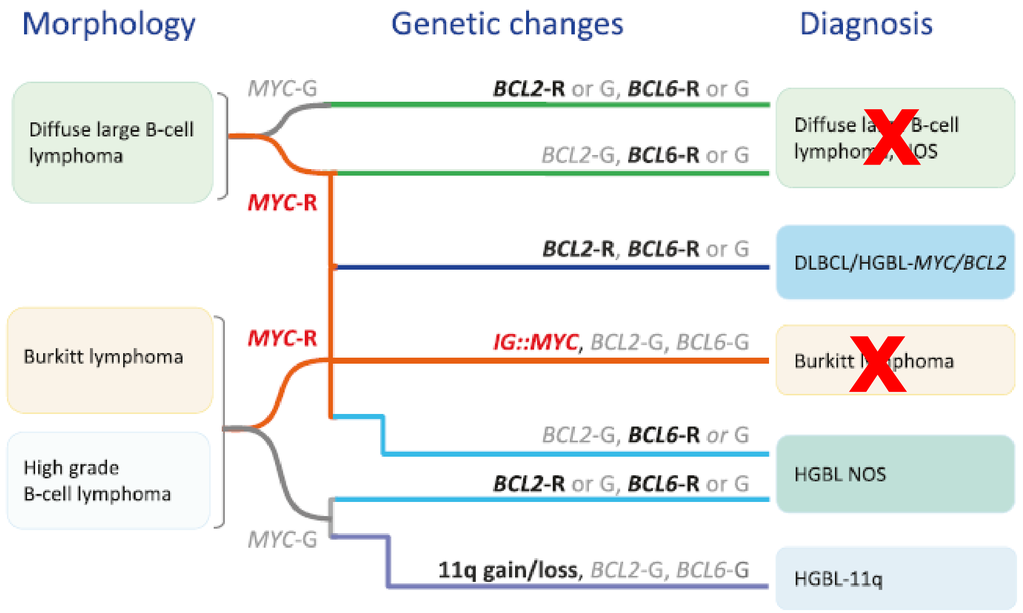


Fig. 4 Algorithm for classification of aggressive B-cell lymphomas in WHO-HAEM5 in the light of *MYC*, *BCL2* and *BCL6* rearrangement and complex 11q gain/loss patterns. HGBL high grade B-cell lymphoma, R rearrangement, G germline configuration.

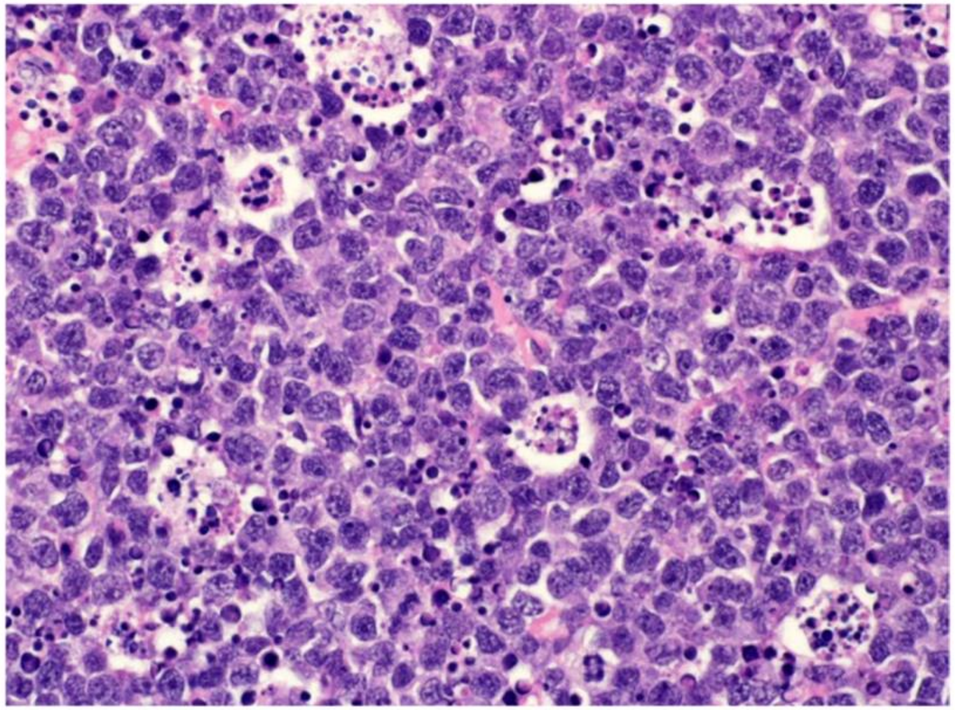
ICC 2022
This provisional entity has now been renamed **"large B-cell lymphoma with 11q aberration"** Chromosome 11q gains and losses

ICC 2022
High-grade B-cell lymphoma with 11q aberration (HGBL- 11q)

Aggressive B cell lymphoma lacking MYC-R and with 11q aberration

- children and young adults
- >nodal, extranodal (head, neck, tonsil 60%); GI tract 30%
- May occur in ID-settings

- Morphology: intermediate/BL-like (morphologically not distinguishable) > DLBCL
  peculiar starry sky pattern (high debris-full histiocytes)
- diffuse>follicular (>paediatric)
- **Phenotype BL-like:** CD10+/Bcl6+/Bcl2- (GCB-COO)
  cMYC variable: > negative; some partial weak/moderate; rare full/intense
  LMO2 >strongly pos (BL mostly negative)
  EBER negative



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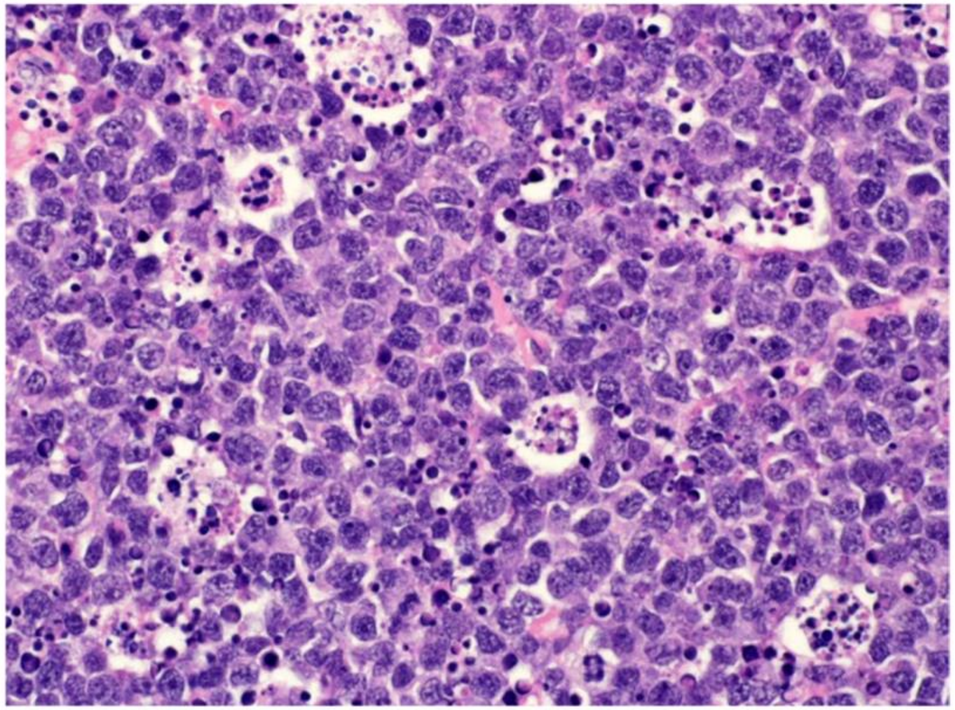


FISH defining cytogenetic event:
- **MYC^{TR} negative, BCL2R/BCL6R negative**
- **11q deletion/insertion FISH positive (11q23 gain/11q24-qter loss)**

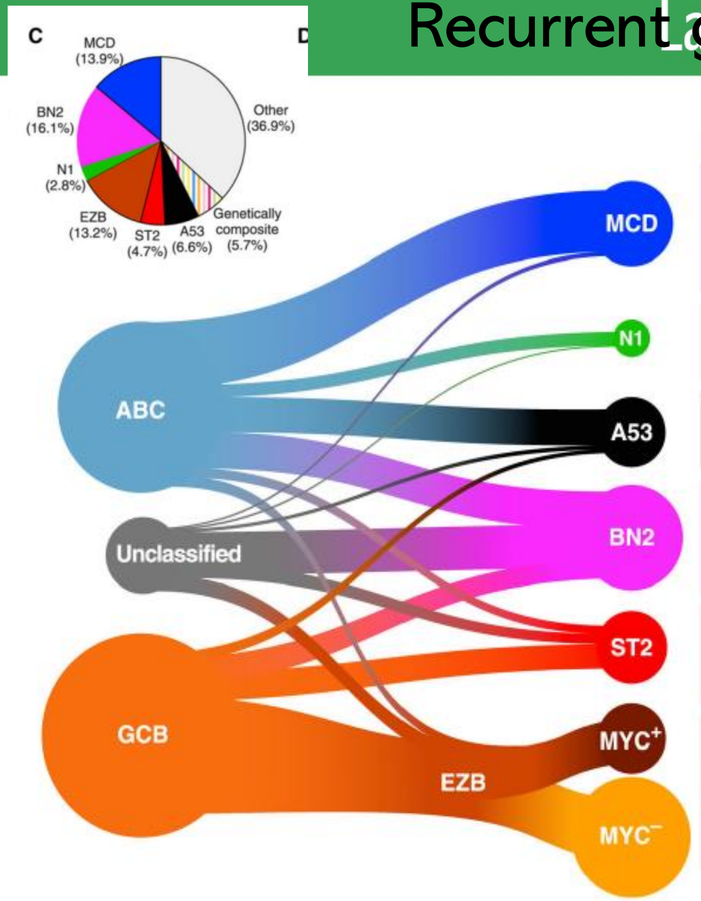
Distinct molecular profile from MYC^{TR}BL
- more complex genetic aberrations (gains in chr 5q,12p, 18q, deletions 6q)
- recurrent mutations in BTG2, DDX3X, ETX1, NFRKB, EP300 and GNA13, but BL-typical mutations, such as ID3, TCF3 or CCND3 are missing supporting the idea that these tumors are closer to DLBCL GCB than Burkitt lymphoma.

Prognosis uncertain:
pediatric patients good prognosis: receive BL-like therpay;
adults: more controversial and heterogenous: DLBCL-therapy worse

HGBCL-NOS

- Category created in WHO 2016
- typically intermediate-sized cells, often with blastoid or Burkitt-like cytology
- The identification of HGBCL, NOS is subjective and not always reproducible (important quality of the histological preparation)
- Data on HGBCL, NOS remain scarce and heterogeneous
- **54% of HGBCL NOS have DHITsig profile**
- Patients appear to be older adults (average age 70 years), many with advanced disease
- Response rates to standard therapy for DLBCL-like patients remain difficult to ascertain due to the recent adoption of this category
- Some studies suggest superior outcomes with more aggressive treatment regimens

Recurrent genomic subtypes with clinical relevance



Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF-κB Immune evasion-MHC class I Cell survival - *BCL2* expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	Primary extranodal DLBCL Transformed WM	B cell activation NF-κB IRF4 Myc Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2-BCLX$_L$-MCL1 JAK1 IRAK4 IRF4
1.7%	27% (All) 22% (ABC)	NOTCH1 signaling Altered B cell differentiation BCR: IgM > IgG	NOTCH1-mutant CLL	NOTCH Quiescence Plasma cell T cell-myeloid-FDC	NOTCH1 Immune checkpoints
5.8%	63% (All) 33% (ABC) 100% (GCB)	*TP53* inactivation/DNA damage Aneuploidy Immune evasion - *B2M* loss BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	–	p53 Immune low	BCR-dep. NF-κB
13.3%	67% (All) 76% (ABC) 100% (GCB) 38% (UC)	NOTCH2 signaling Altered B cell differentiation BCR-dependent NF-κB Immune evasion - *CD70* loss Proliferation - Cyclin D3 BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	MZL Transformed MZL	B cell activation NF-κB NOTCH Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2 NOTCH2
6.4%	84% (All) 81% (GCB)	JAK/STAT3 signaling NF-κB activation *P2RY8 – GNA13* inactivation Altered B cell differentiation BCR: IgG >> IgM	NLPHD THRLBCL	GC B cell PI3K signaling JAK2 signaling Glycolysis Stromal	PI3 kinase JAK2
5.9% (MYC^+) 17.6% (MYC^-)	48% (MYC^+) 82% (MYC^-)	Chromatin modification Anti-apoptosis PI3 kinase signaling *S1PR2 – GNA13* inactivation Altered T_{FH} interactions MYC (EZB-MYC^+) BCR: IgG > IgM	FL Transformed FL BL (EZB-MYC^+)	GC LZ (MYC^-) GC IZ (MYC^+) BCL6 (MYC^+) TCF3 (both) T_{FH} cells (MYC^-) Stromal (MYC^-) Immune low (MYC^+)	PI3 kinase mTORC1 EZH2 BCL2-MCL1

MCD/C5; >ABC-type poor prognosis
contain the majority of primary CNS lymphomas, primary testicular lymphoma

A53/2 showing aneuploidy and frequent TP53 abnormalities.

BN2/1 NOTCH2 and BCL6 mutation ; no obvious association with COO; mutational similarities to marginal zone lymphoma

EZB(MYC+MYC-)/C3 GCB-type
mutational profile overlapping FL; BCL2 R; favorable prognosis but DH/TH cases are includes with adverse outcome

Recurrent genomic subtypes with clinical relevance (Chapuy Nat Med 2018; Wright NEJM 2018; Lacy 2020; at present not included in routine clinical use; **35-40% of cases are not currently assigned to a genetic subtype**

LymphGen	Modified HMRN	Harvard	Main Genetic Alterations	COO	Clinical Outcome	Related Lymphoma
MCD	**MYD88**	**C5**	*$MYD88^{L265P}$, CD79B, PIM1, ETV6, CDKN2A*	ABC	Poor	Primary CNS lymphoma, Primary testis lymphoma
EZB	**BCL2**	**C3**	*BCL2*-R, *EZH2, CREBBP, KMT2D, TNFRSF14*	GCB	Good	Follicular lymphoma
EZB-MYC+	**BCL2-MYC**				Poor	Double hit lymphoma
BN2	**NOTCH2**	**C1**	*BCL6*-R, *NOTCH2, BCL10, SPEN, CD70, TNFAIP3*	ABC, GCB, UC	Intermediate	Marginal zone lymphoma
ST2	**TET2/SGK1**	**C4**	*TET2, SGK1, KLHL6, BRAF*	GCB	Good	Nodular lymphocyte predominant Hodgkin lymphoma
	SOCS1/SGK1		*SOCS1, SGK1, CD83, NFKBIA, NFKBIE, STAT3*	GCB	Very good	Primary mediastinal B cell lymphoma
Other	NEC	**C0**				
N1	**NOTCH1**	NA	*NOTCH1, ID3*	ABC	Poor	Chronic lymphocytic leukaemia
A53	NA	**C2**	*TP53*, aneuploidy	Mixed	Intermediate	


Thanks
Thank you very much
I really appreciate it
You are the best
I owe you one
I owe you big time
You re great
You re awesome
You re too kind
You re a life saver
Please accept my best thanks
You ve saved my life
You re a dear
You made my day
Thanks a lot
I don t know what to say!
Thank you for everything
It s very kind of you
I thank you from the bottom of my heart
Thanks a bunch
Thanks a million
How can I ever thank you enough
I do not know what I would do without you
I thank you most warmly
I m so grateful
You are an angel
Thanks so much
Thanks for everything
Many thanks
I couldn t have done it without you
I really want to thank you for your help
I wish to thank everyone who pitched in
Thanks a ton
I humbly thank you
You saved my day
I can t thank you enough
It was so awesome of you
All I can say is, Thanks!
I cannot express my appreciation
Words can t describe how thankful I am
I really appreciate your help
I appreciate your time