Società Italiana di Ematologia

Convegno Regionale
SIE
LE NUOVE FRONTIERE NELLA TERAPIA DEL LINFOMA: INNOVAZIONE E FUTURO

30 Marzo 2026
Napoli, *Centro Congressi Federico II*

DELEGAZIONE **CAMPANIA**

Linfomi a grandi cellule

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Disclosures of ELENA SABATTINI

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Menarini Stemline						X	X
Astrazeneca						X	
Recordati Rare Disease						X	x
Kyowa Kyrin							X
Takeda							X

Large cells with B cell phenotype (variation if plasmablastic features) diffuse growth, commonly with high proliferation rate

Site of onset

Cytology

centroblastic/Immunoblastic, plasmoblastic, linfoblastoid, Burkitt-like

Amount of reactive microenvironment

Phenotype

lineage B cell markers; variation if plasmablastic features (CD20, CD79a, Pax5; IRF4, CD138)

functional B-lineage associated markers

Bcl6, CD10, IRF4, cMyc, Bcl2)

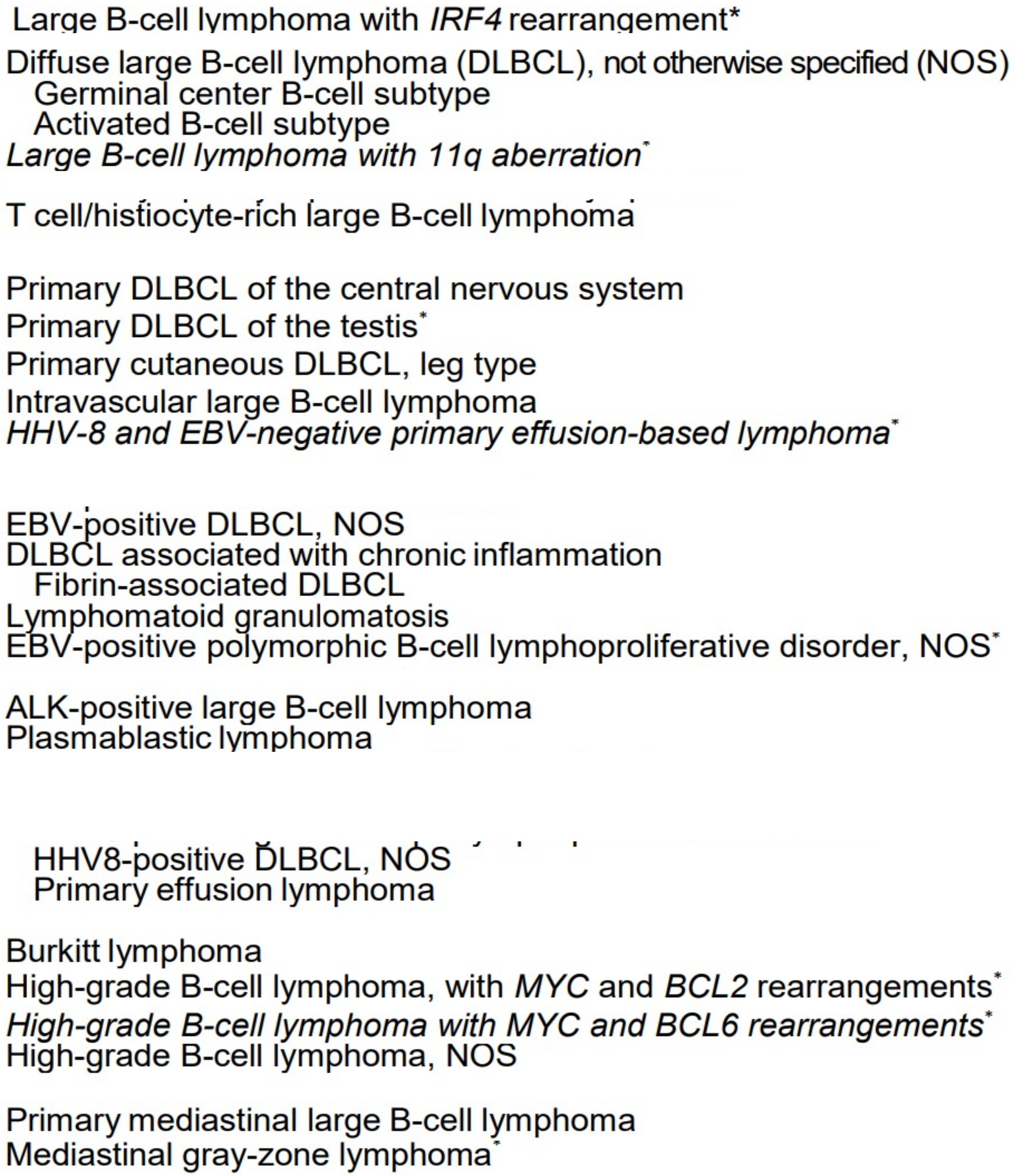
Virus associated

EBV (EBER/LMP1), HHV8

Molecular studies

(FISH, ISH, NGS, other)

ICC



Large B-cell lymphoma with *IRF4* rearrangement*

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
  - Germinal center B-cell subtype
  - Activated B-cell subtype

*Large B-cell lymphoma with 11q aberration**

T cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of the central nervous system
Primary DLBCL of the testis*
Primary cutaneous DLBCL, leg type
Intravascular large B-cell lymphoma
*HHV-8 and EBV-negative primary effusion-based lymphoma**

EBV-positive DLBCL, NOS
DLBCL associated with chronic inflammation
  - Fibrin-associated DLBCL

Lymphomatoid granulomatosis
EBV-positive polymorphic B-cell lymphoproliferative disorder, NOS*

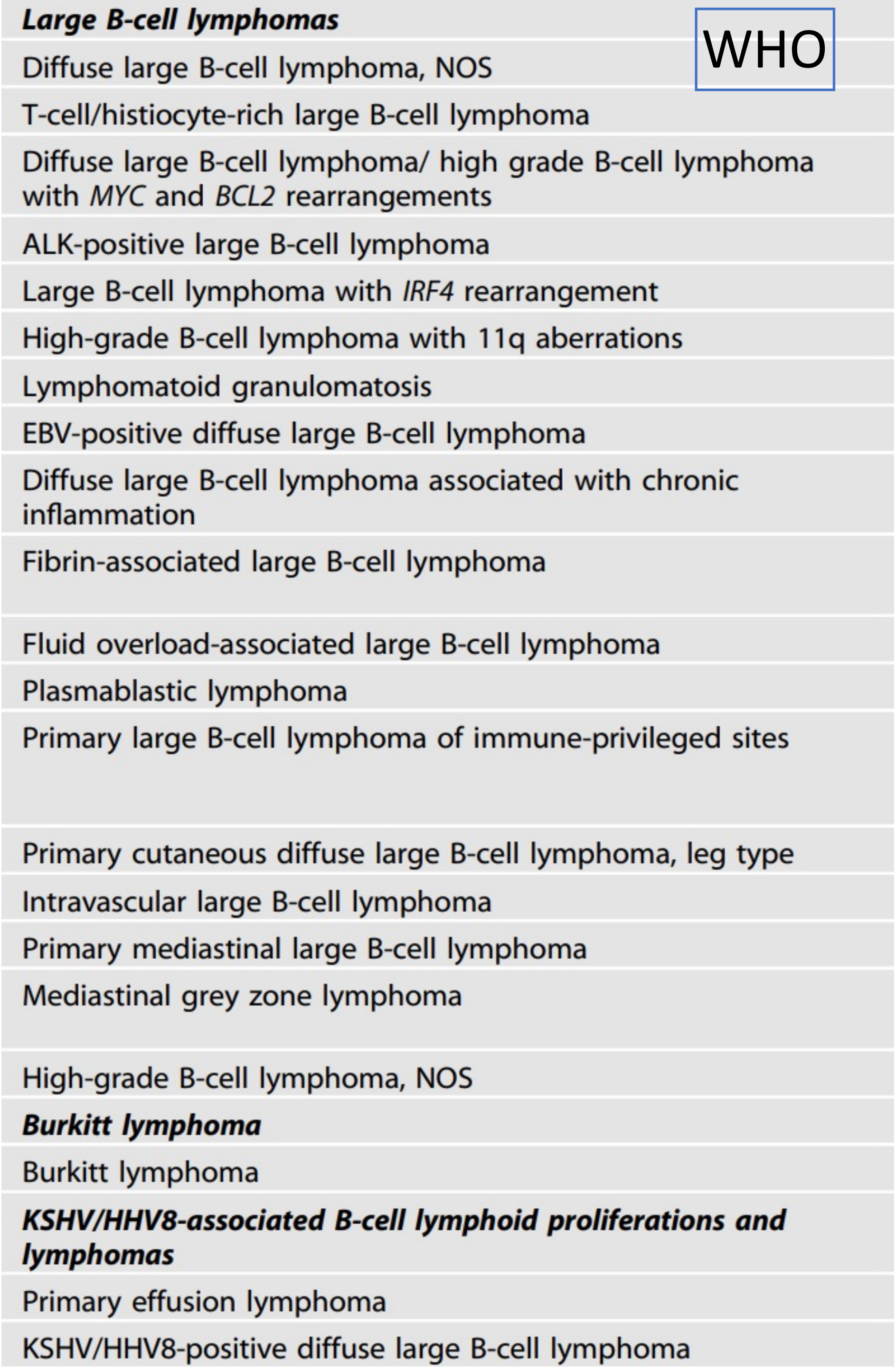
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma

  - HHV8-positive DLBCL, 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
Mediastinal gray-zone lymphoma*

WHO

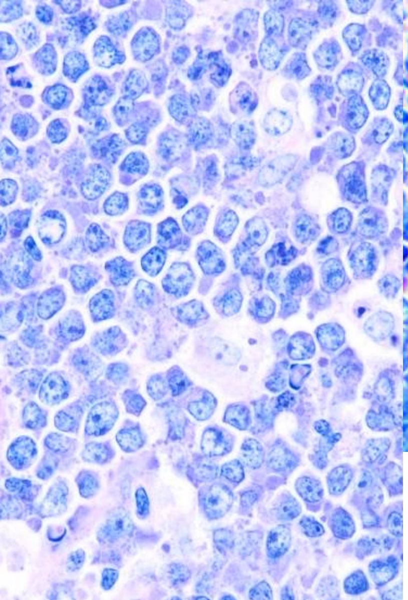


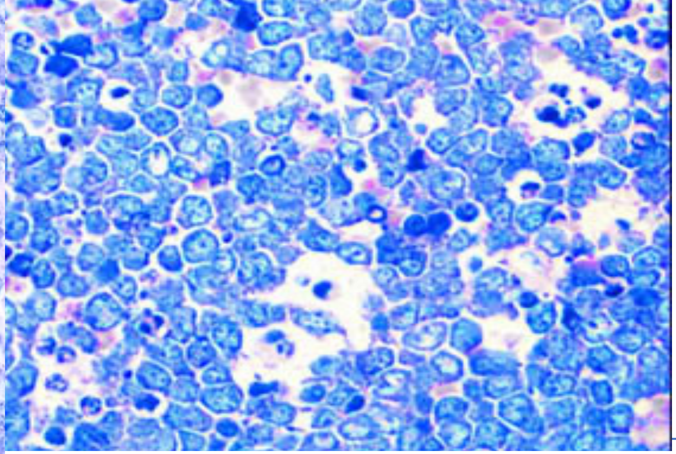
Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with *IRF4* rearrangement
High-grade B-cell lymphoma 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
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas
Primary effusion lymphoma
KSHV/HHV8-positive diffuse large B-cell lymphoma

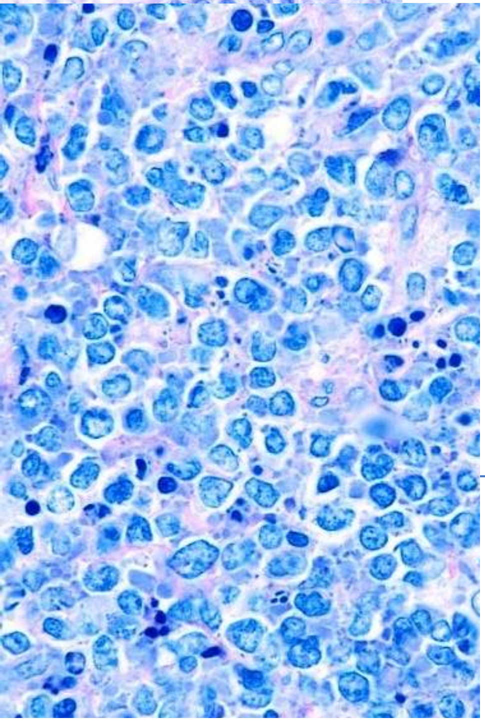
Large cells with B cell lymphomas

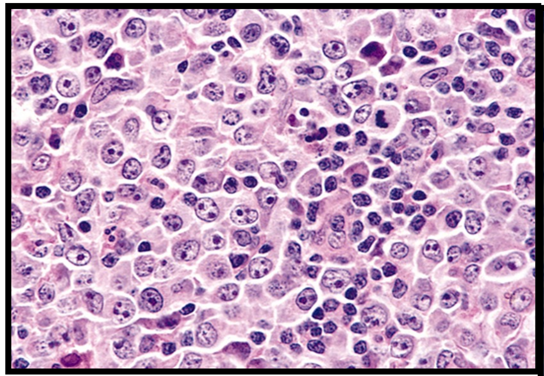
Not site-defined
Not virus-associated
Either nodal or extranodal

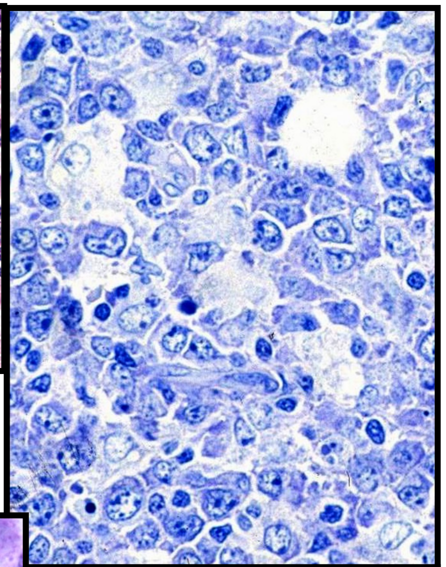
Diffuse Large B cell Lymphoma, NOS
Burkitt Lymphoma
Large B-cell Lymphoma with IRF4 rearrangement
High grade/Large B-cell Lymphoma with MYC and BCL2 rearrangement (MYC/BCL6)
High grade B-cell Lymphoma / Large B-cell lymphoma with 11q aberration

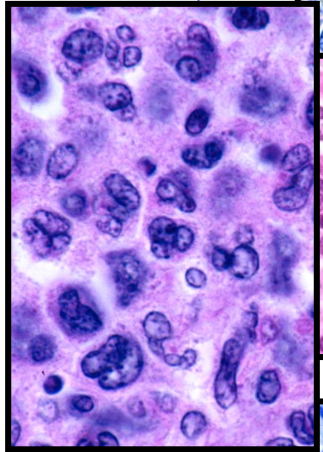


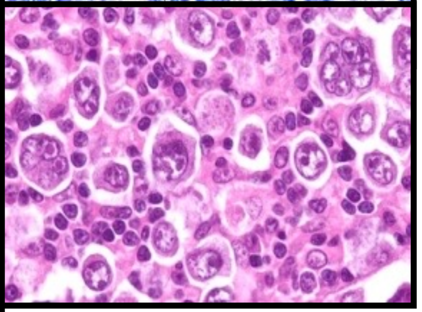


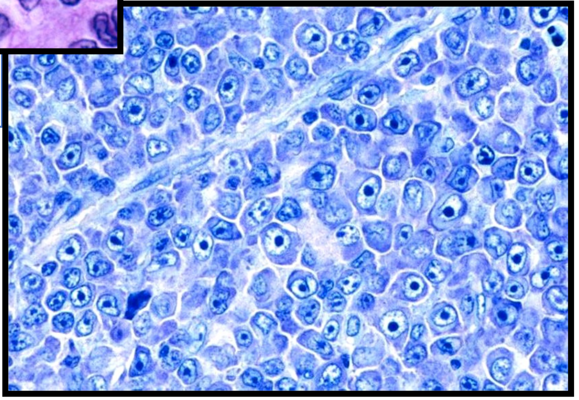


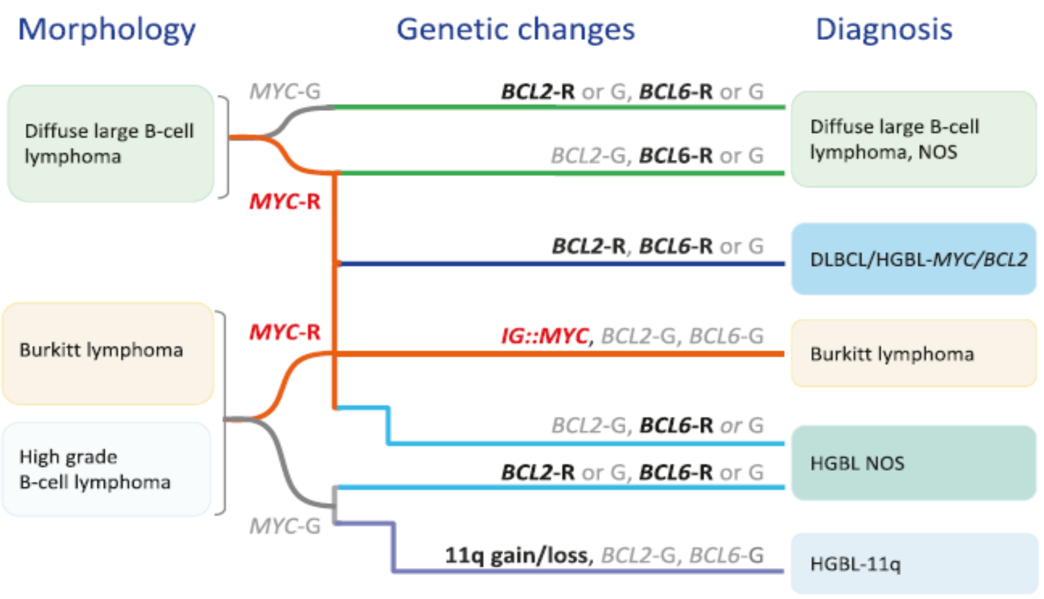












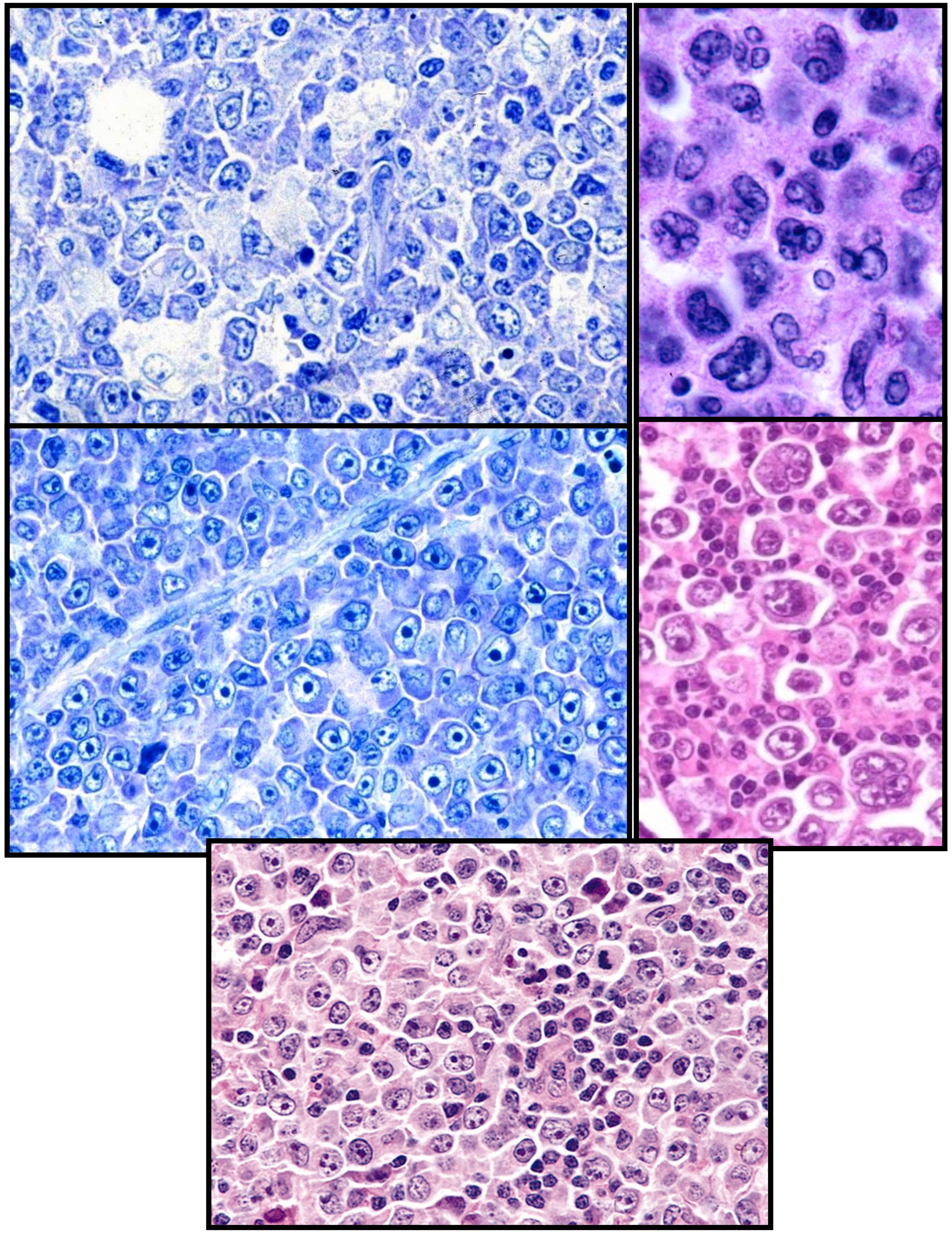
Central pathology review : 44% cases reclassified as DLBCL

13% concordance for assigning blastoid vs BL-like

Nevertheless, morphologic assignement is still required by the WHO-5 and ICC classifications for categorization of HGBLs

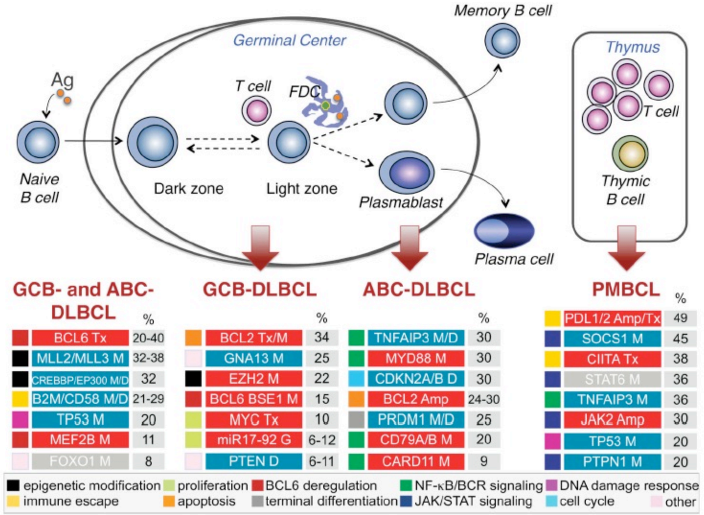
Collinge BJ et al. Hematol Oncol. 2021; 2. Zayac AS et al. Blood Adv. 2023

DLBCL cytology and no double hit (MYC/BCL2-R)



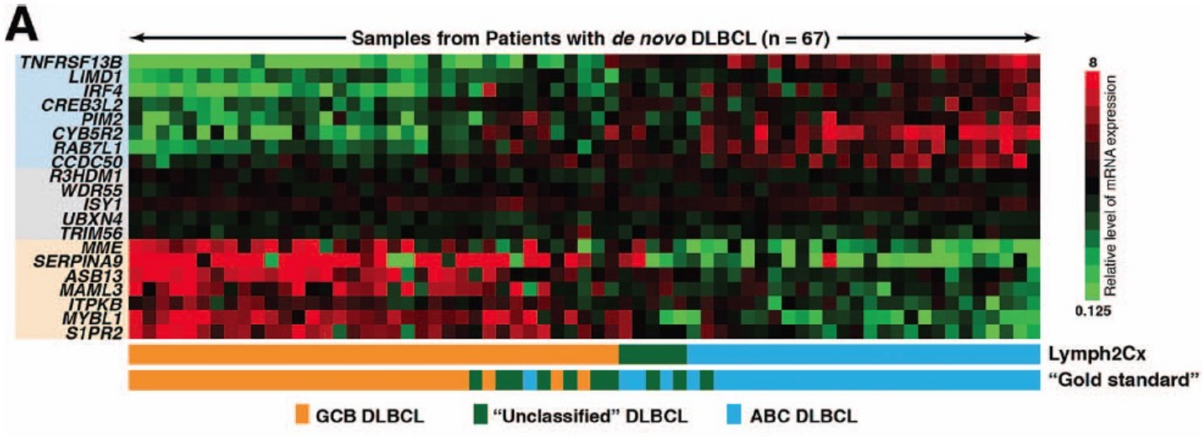
Both WHO and ICC 2022

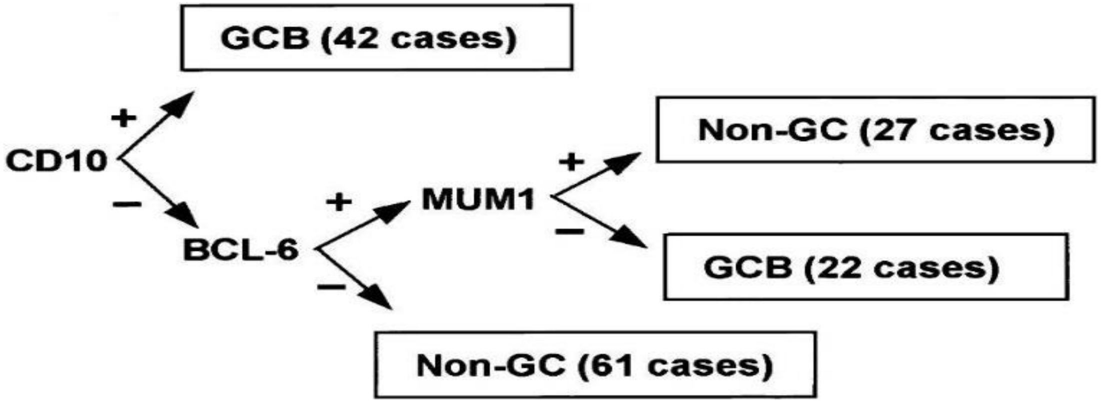
- ➢ Define cell of origin classification requested in both classiifctions
- ➢ Clinical impact
- ➢ **Do not specify in non-NOS LBCL**



GCB- and ABC-DLBCL	%	GCB-DLBCL	%	ABC-DLBCL	%	PMBCL	%
						PDL1/2 Amp/Tx	49
BCL6 Tx	20-40	BCL2 Tx/M	34	TNFAIP3 M/D	30	SOCS1 M	45
MLL2/MLL3 M	32-38	GNA13 M	25	MYD88 M	30	CIITA Tx	38
CREBBP/EP300 M/D	32	EZH2 M	22	CDKN2A/B D	30	STAT6 M	36
B2M/CD58 M/D	21-29	BCL6 BSE1 M	15	BCL2 Amp	24-30	TNFAIP3 M	36
TP53 M	20	MYC Tx	10	PRDM1 M/D	25	JAK2 Amp	30
MEF2B M	11	miR17-92 G	6-12	CD79A/B M	20	TP53 M	20
FOXO1 M	8	PTEN D	6-11	CARD11 M	9	PTPN1 M	20

The Lymph2Cx Assay: A Gene Expression-Based Assay for COO



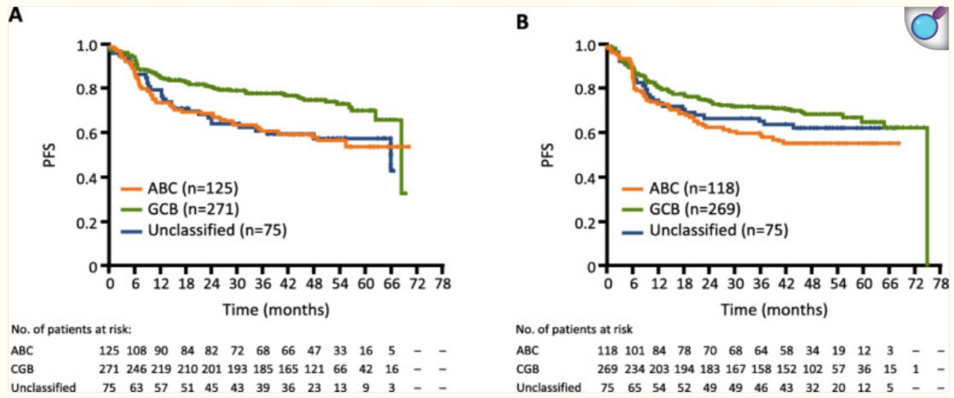


Lymph2Cx is the gold standard but IHC algorithms acceptable (Hans' 2004) specify algorithm
Hans' miss 10-15% of GEP-defined unclassified tumors

Wright G et al. PNA 2003, Lenz G et al NEJM 2008, Rosenwald A et al. NEJM 2002; 100 genes that were most highly differentially expressed; Alduaij et al. Blood 2023; Hans CP et al. Blood 2004; Scott et al. Blood 2014

Unfortunately, clinical studies based on this COO-classification (also GEP) have repeatedly failed to improve the outcome of DLBCL patients (GoYA trial)

this simplified scheme is not sufficiently effective for clinical trial design and define more effective poor-risk criteria for highly aggressive BCL that require different/more intensive therapy approaches



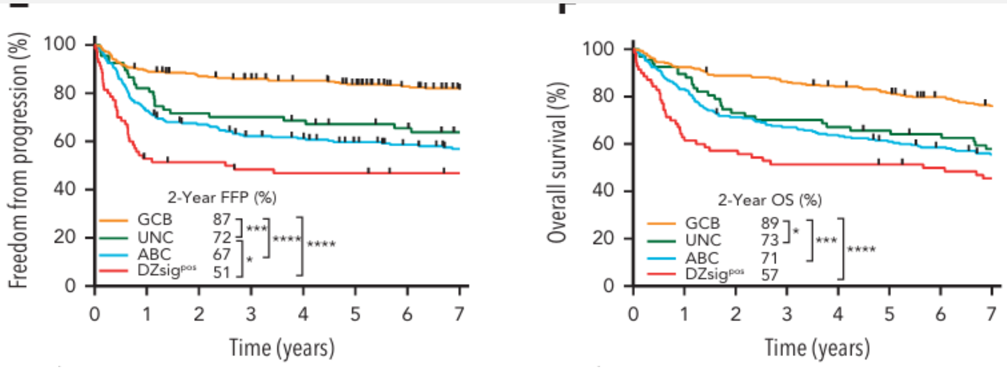
No. of patients at risk:

ABC	125	108	90	84	82	72	68	66	47	33	16	5	–	–
CGB	271	246	219	210	201	193	185	165	121	66	42	16	–	–
Unclassified	75	63	57	51	45	43	39	36	23	13	9	3	–	–

No. of patients at risk

ABC	118	101	84	78	70	68	64	58	34	19	12	3	–	–
CGB	269	234	203	194	183	167	158	152	102	57	36	15	1	–
Unclassified	75	65	54	52	49	49	46	43	32	20	12	5	–	–

A randomized, open-label, Phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-Cell lymphoma: final analysis of GOYA. Sehn et al. JHO 2020

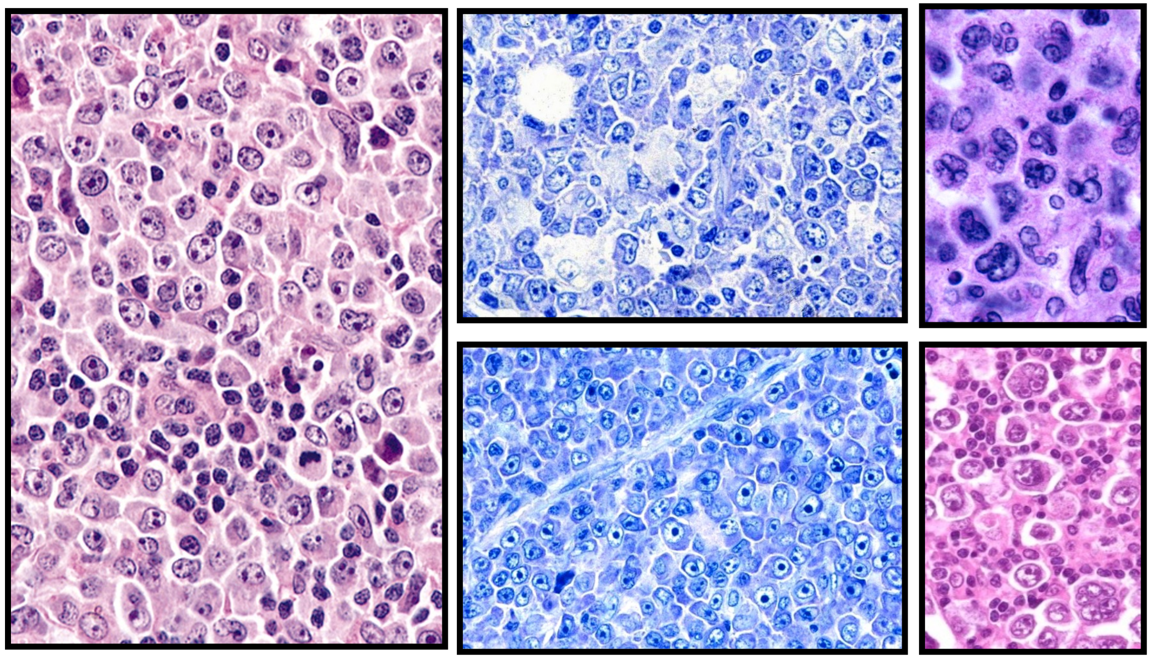


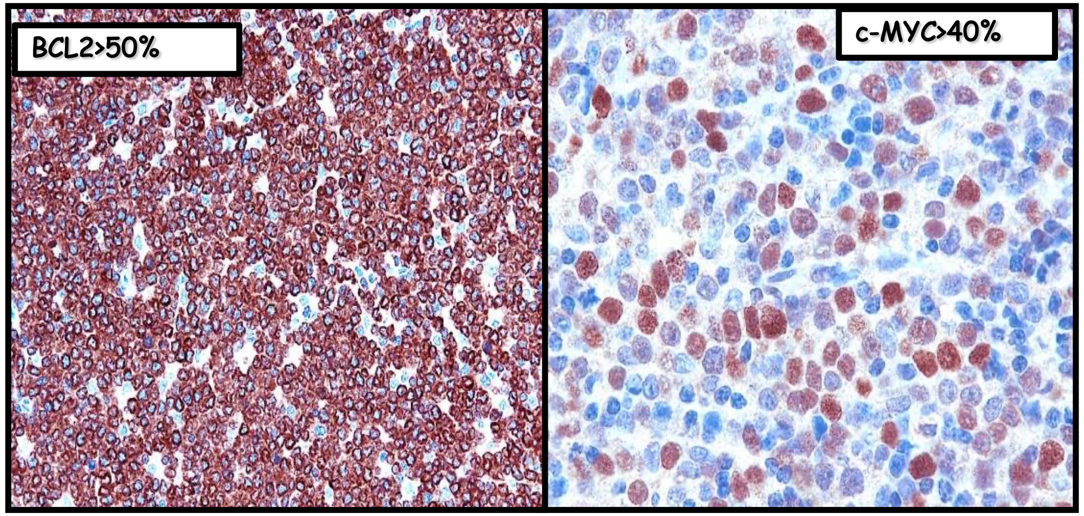
Alduanij et al Blood 2023
Outcome difference between GCB-DLBCL and ABCDLBCL is smaller than previously : COO alone does not account for the heterogenous outcomes following R-CHOP

De-emphasize morphologic variants[1]

De-emphasize double expression of bcl2 and cmyc proteins (bcl2 >50%; cmyc >40%)

can include cases with single hit
-*MYC-R*
reported with worse outcome
or
-*BCL2-R*
likely transformed FL; specified category in the WHO2022

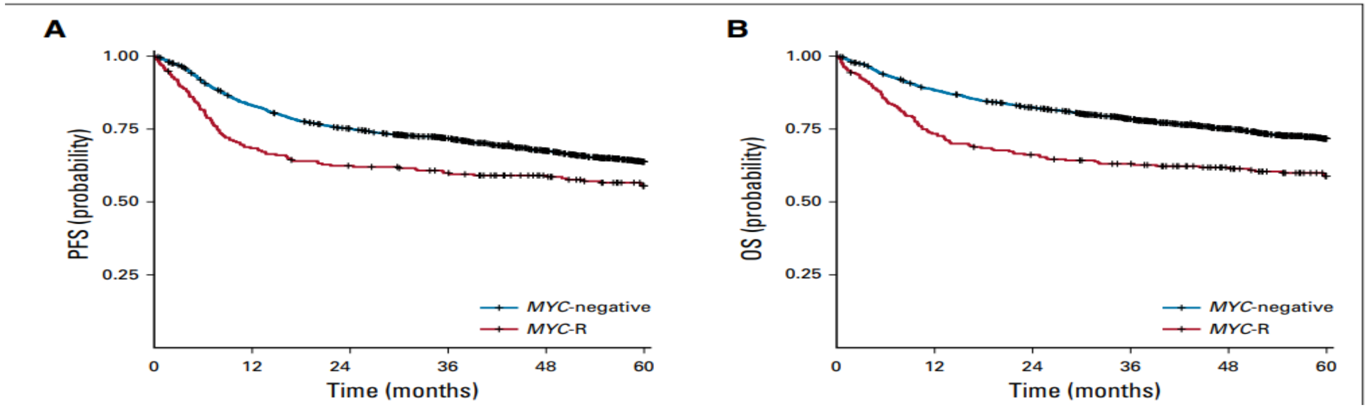


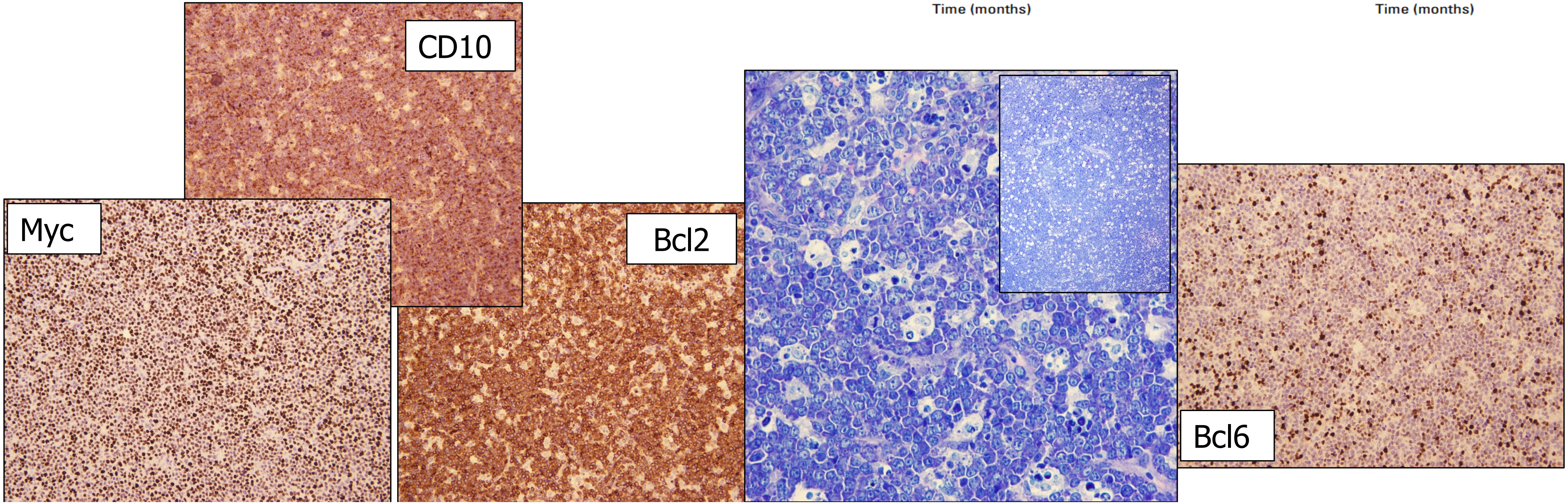


1.Meriranta L et al. Blood Adv. 2020

MYC single hit lymphomas with DLBCL cytology

1) MYC-R negatively affected OS/PFS in DLBCL with an MYC-SH and MYC-DH/TH
2) DLBCL-MYC SH: no reason to change therapeutic approaches (effect negligible)





DLBCL with starry-sky morphology, and/or high proliferation index do not merit recategorization as HGBCL, NOS. They can be MYC-SH

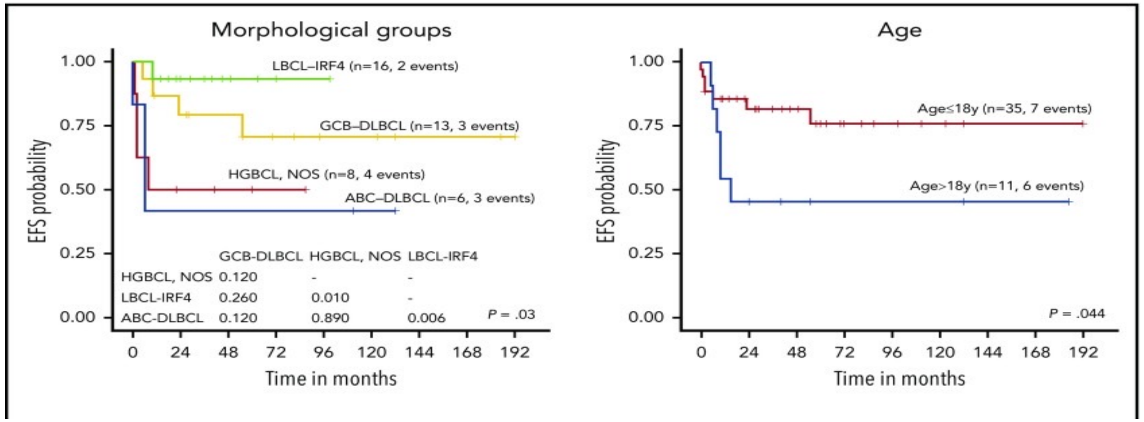
Be careful to

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

- ➢0.05% of DLBCL

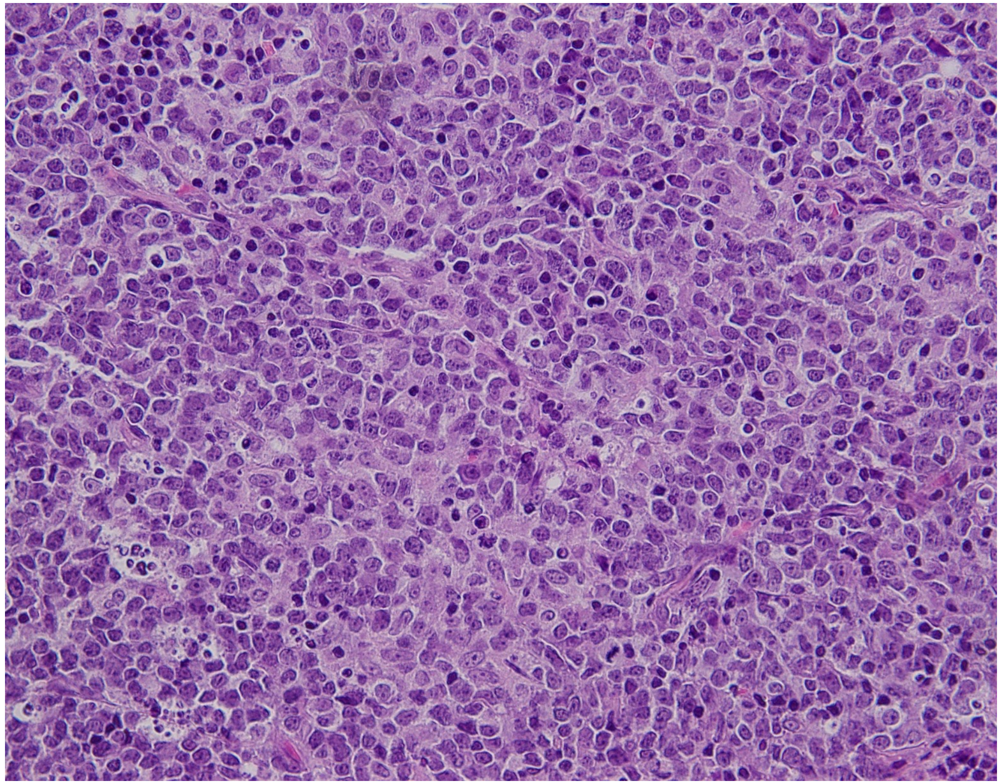
- ➢<u>children and young adults </u>(median 12 yrs; range 4–79 yrs)
- ➢<u>limited stage I-II (>cervical/Waldayer ring</u>; <<subdiaphragm; GI)

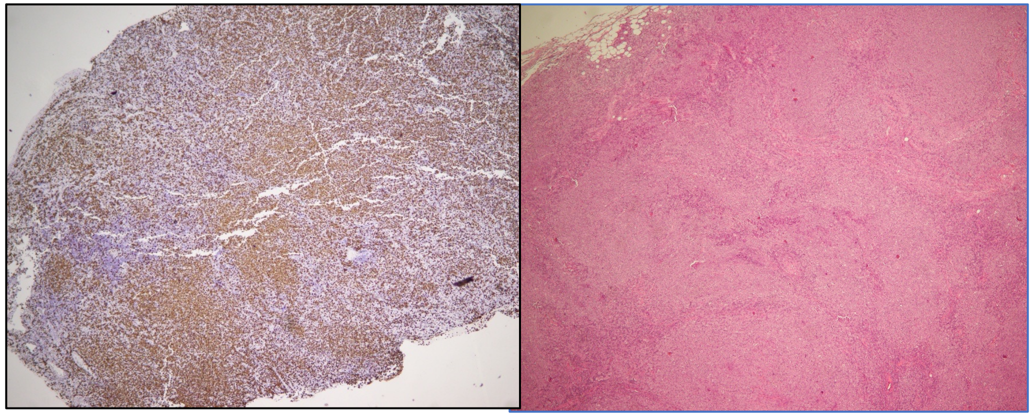
- ➢Aggressive cytology + diffuse>follicular (both) usually no starry sky



	GCB-DLBCL	HGBCL, NOS	LBCL-IRF4
HGBCL, NOS	0.120	-	-
LBCL-IRF4	0.260	0.010	-
ABC-DLBCL	0.120	0.890	0.006

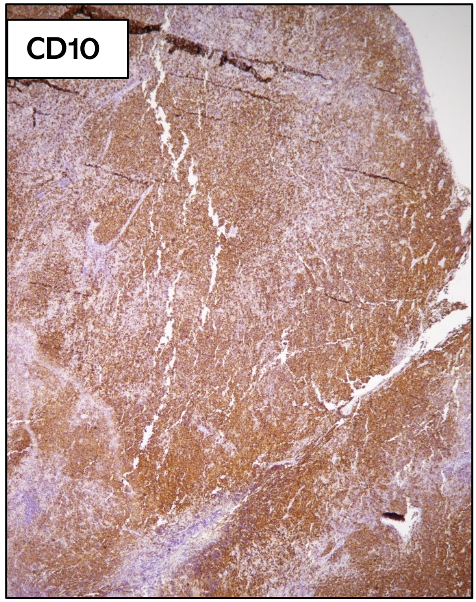
Ramis-Zaldivar Blood 2020

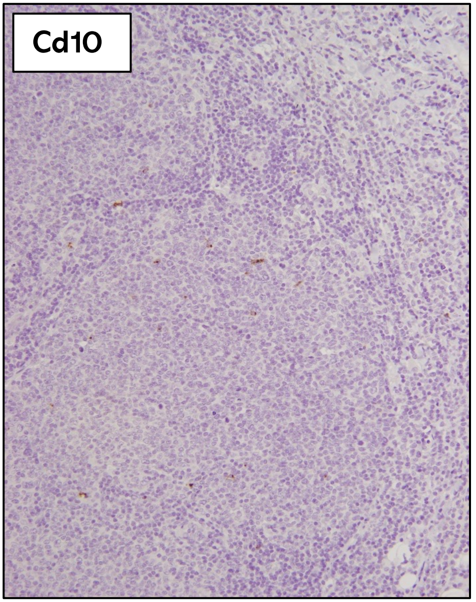


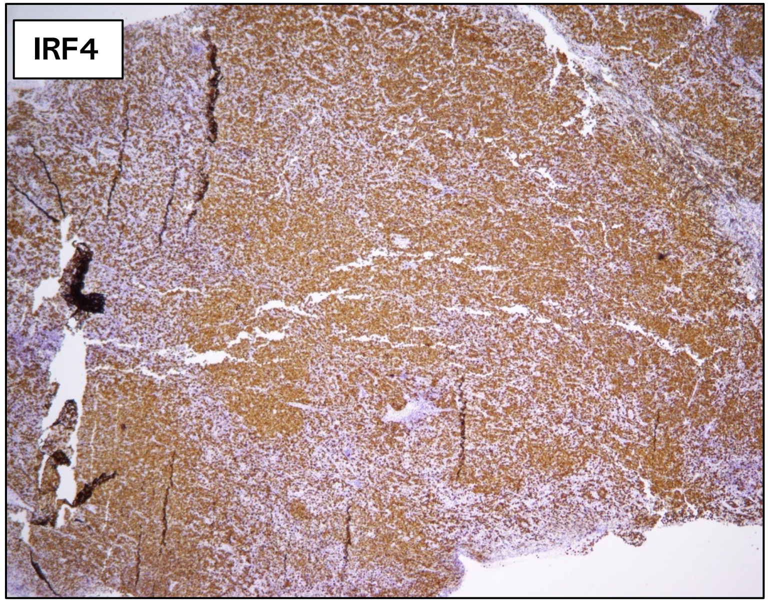


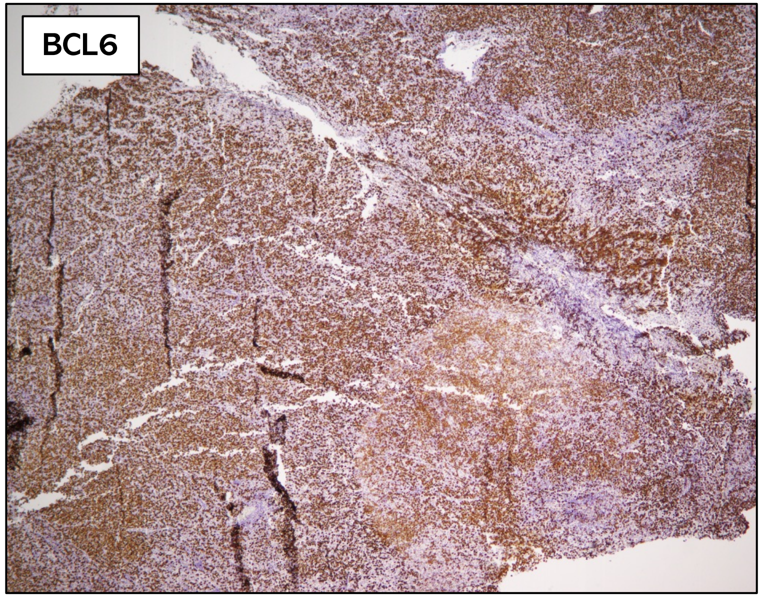
Salavarria et al. 2011 Blood; Ramis-Zaldivar Blood 2020

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







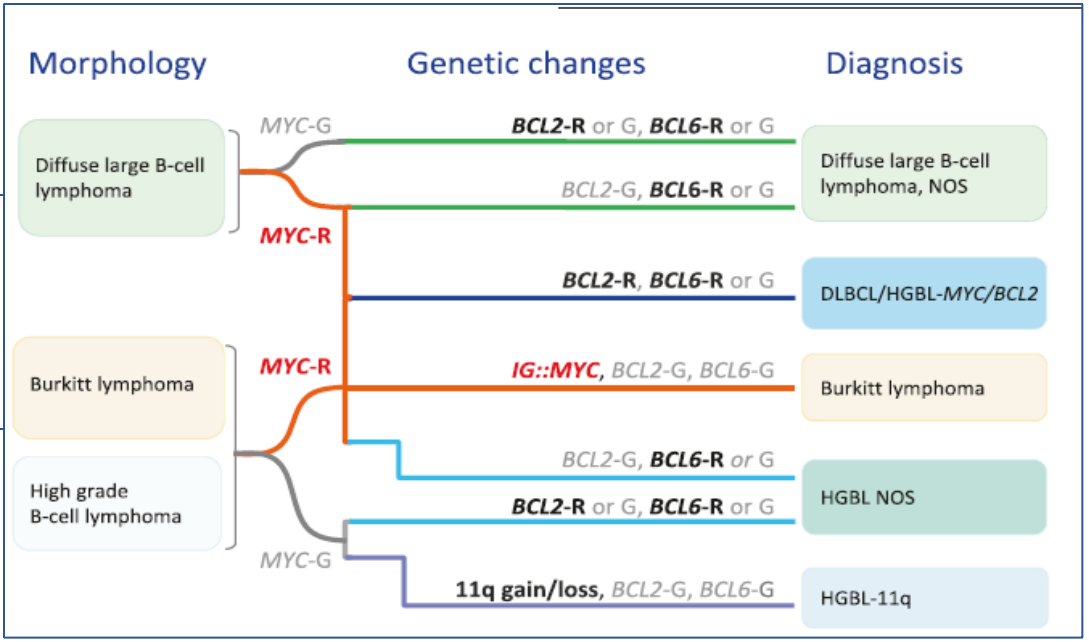


IRF4^{TR}+

- difficult to recognize at conventional karyotyping; often ***IG/IRF4^{TR}***
- possible BCL6^{TR}; no MYC^{TR} no BCL2^{TR}

IRF4 mutations 76% (may support the diagnosis)

MYC R and BCL2 R all cytology types



2022 International Consensus Classification (ICC)
retains the term HGBL with MYC and BCL2 rearrangements regardless of the morphologic appearance; describe the cellular morphology (DLBCL, HG)

Retain High grade B-cell Lymphoma with MYC and BCL6 rearrangements (provisional)

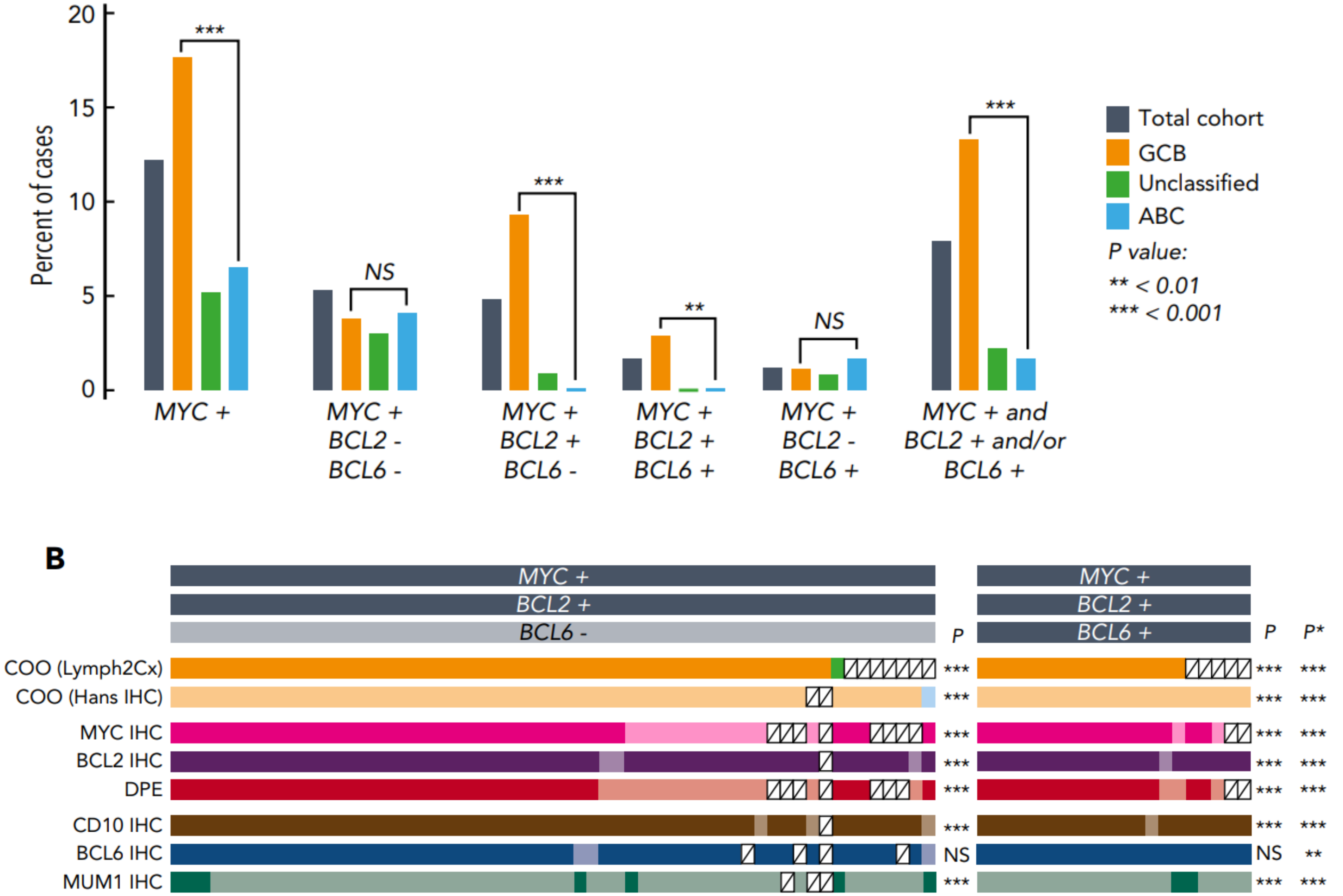
WHO-5
term based on the morphologic appearance (DLBCL or HGBL)
Delete High grade B-cell Lymphoma with MYC and BCL6 rearrangements

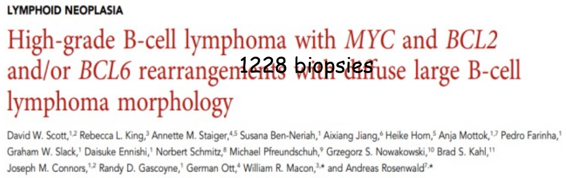
10%
Most cases belong to COO-GCB
CD10+ (95%)
MUM1 neg (89%)Most cases are

DE (75%)
    BCL2+ strong (95%)
    MYC+ (>70%+cells)

Subset is transformed FL
(patients’ history is relevant)

HBGL-TH: 1.7% >GCB

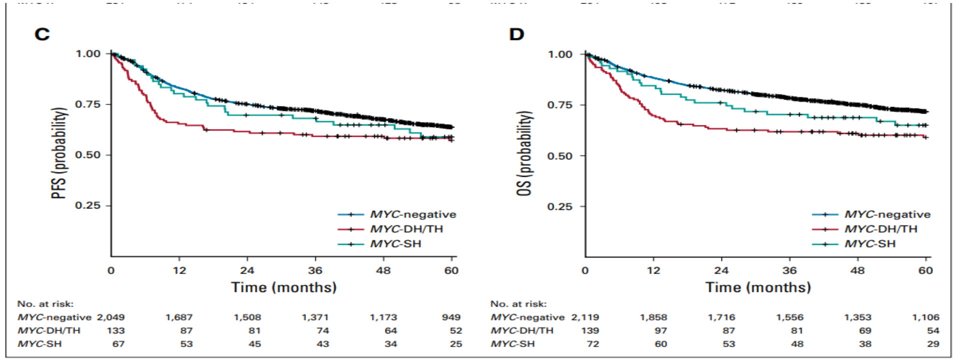



LYMPHOID NEOPLASIA

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

1228 biopsies

David W. Scott,[1,2] Rebecca L. King,[3] Annette M. Staiger,[4,5] Susana Ben-Neriah,[1] Aixiang Jiang,[6] Heike Horn,[5] Anja Mottok,[1,7] Pedro Farinha,[1] Graham W. Slack,[1] Daisuke Ennishi,[1] Norbert Schmitz,[8] Michael Pfreundschuh,[9] 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,*]



No. at risk:

	0	12	24	36	48	60
MYC-negative	2,049	1,687	1,508	1,371	1,173	949
MYC-DH/TH	133	87	81	74	64	52
MYC-SH	67	53	45	43	34	25

No. at risk:

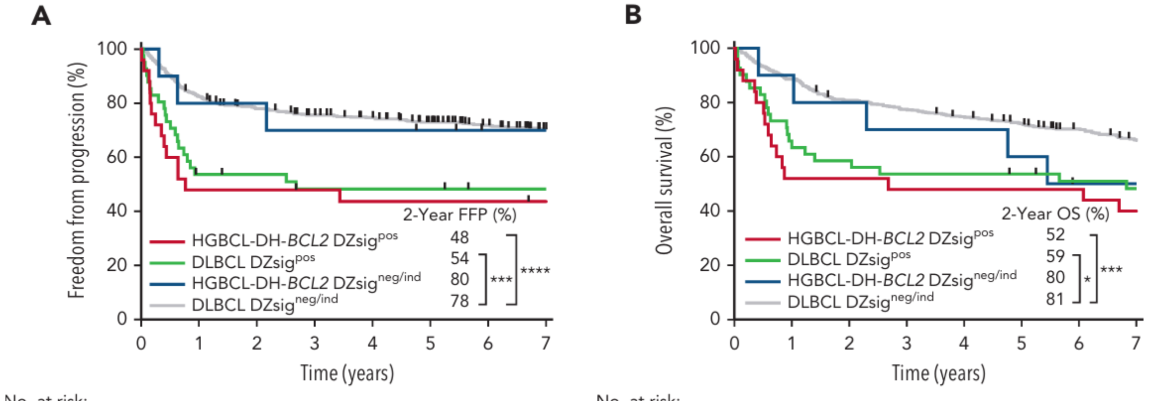
	0	12	24	36	48	60
MYC-negative	2,119	1,858	1,716	1,556	1,353	1,106
MYC-DH/TH	139	97	87	81	69	54
MYC-SH	72	60	53	48	38	29

FIG 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) according to MYC-rearrangement (*MYC*-R); (B) overall survival (OS) according to *MYC*-R; (C) PFS according to *MYC* single-hit (SH), double-hit (DH), or triple-hit (TH) constellation; and (D) OS according to *MYC*-SH, -DH, or -TH constellation.

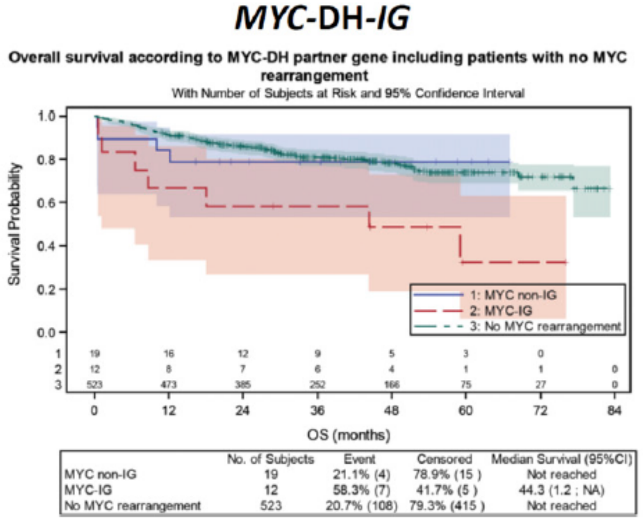
strong negative effect particularly within first 2 yrs after diagnosis: *optimizing first-line treatment approaches to achieve maximum complete response rates because salvage treatment at relapse is not effective*

Additional factors that may influence outcome

more favorable with DLBCL cytology and Dzsignature negative



MYC:IG partner **negative impact**



	No. of Subjects	Event	Censored	Median Survival (95%CI)
MYC non-IG	19	21.1% (4)	78.9% (15)	Not reached
MYC-IG	12	58.3% (7)	41.7% (5)	44.3 (1.2 ; NA)
No MYC rearrangement	523	20.7% (108)	79.3% (415)	Not reached

1. Alduaij et al. Blood 2023, McPhail ED et al. Haematologica. 2018, Copie-Bergman C et al. Blood. 2015; 2. Rosenwald A et al. J Clin Oncol 2019; 3. *Rosenwald A et al. J Clin Oncol. 2019*; Petrich AM et al. Blood. 2014; Dunleavy K et al. Hematology Am Soc Hematol Educ Program. 2021; Moore EM et al. Am J Surg Pathol. 2017; 4. Alduanij et al. 2023

MYC R and BCL6 R: all cytology types

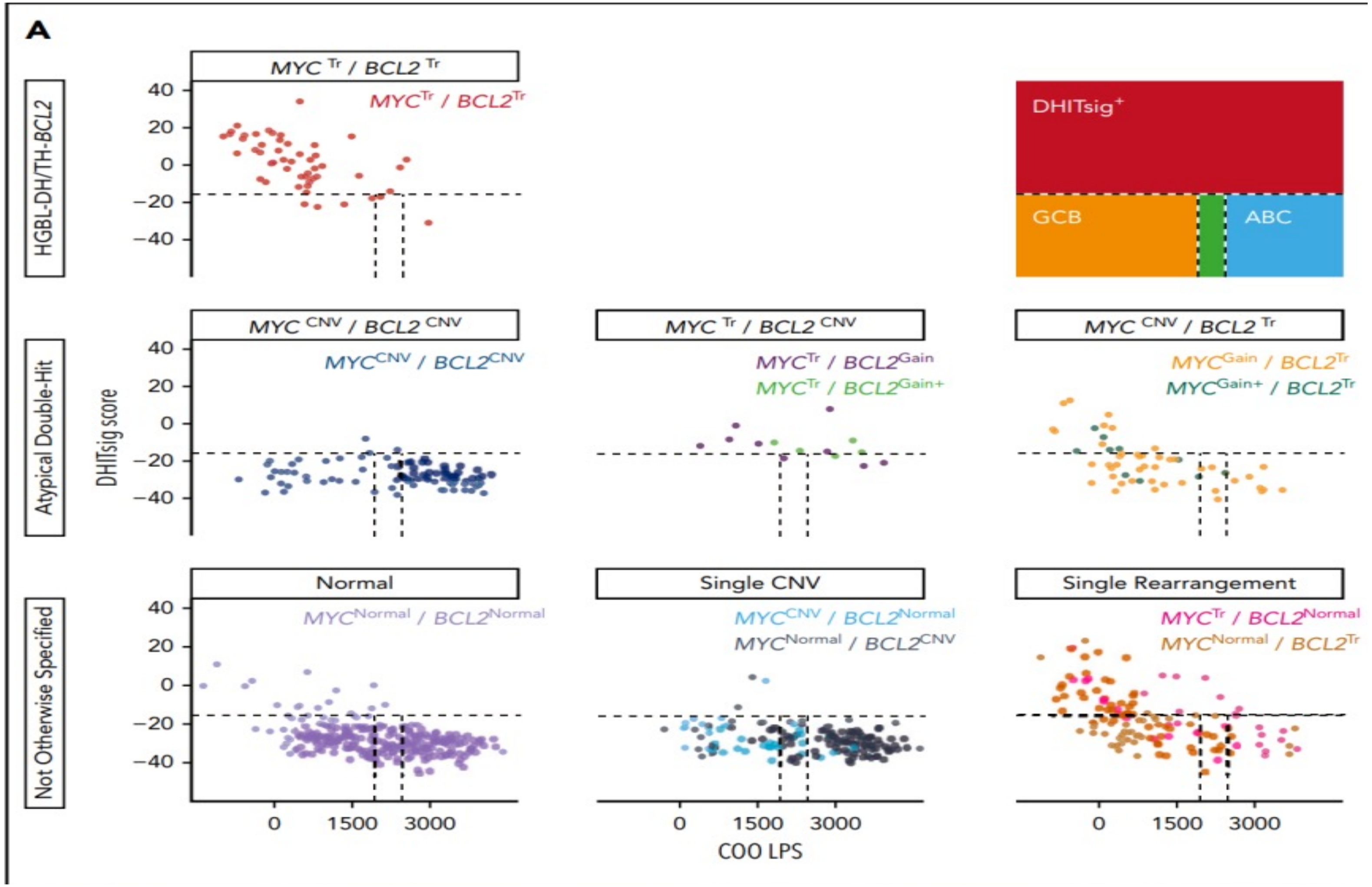
<50% are GCB
complex karyotype
MYC translocation partner may be an IG or non-IG gene

“pseudo-double hit” t(3;8)(q27;q24), which fuses the BCL6 and MYC loci
indistinguishable from conventional MYC and BCL6 “double hits” at BA-FISH
Still undetermined if pseudo-double hits have clinical and biological features distinct from DH-BCL6 with IG gene partners.

genetically more heterogeneous than DH-BCL2
mutations in genes associated with BCL2-rearranged lymphomas but at lower frequencies (KMT2D 18%, CREBBP 12%, BCL2 8%, TNFRSF14 8%, EZH2 50%). some mutational overlap with BL (mutations in CCND3 27%, ID3 13%, FOXO1 13%; approximately 20% show DZ/MHG signature
with LymphGen molecular classifier : cases fall in various groups (EZB, BN2, other groups or unclassified)

double MYC and BCL2 aberrancies (no double translocation)

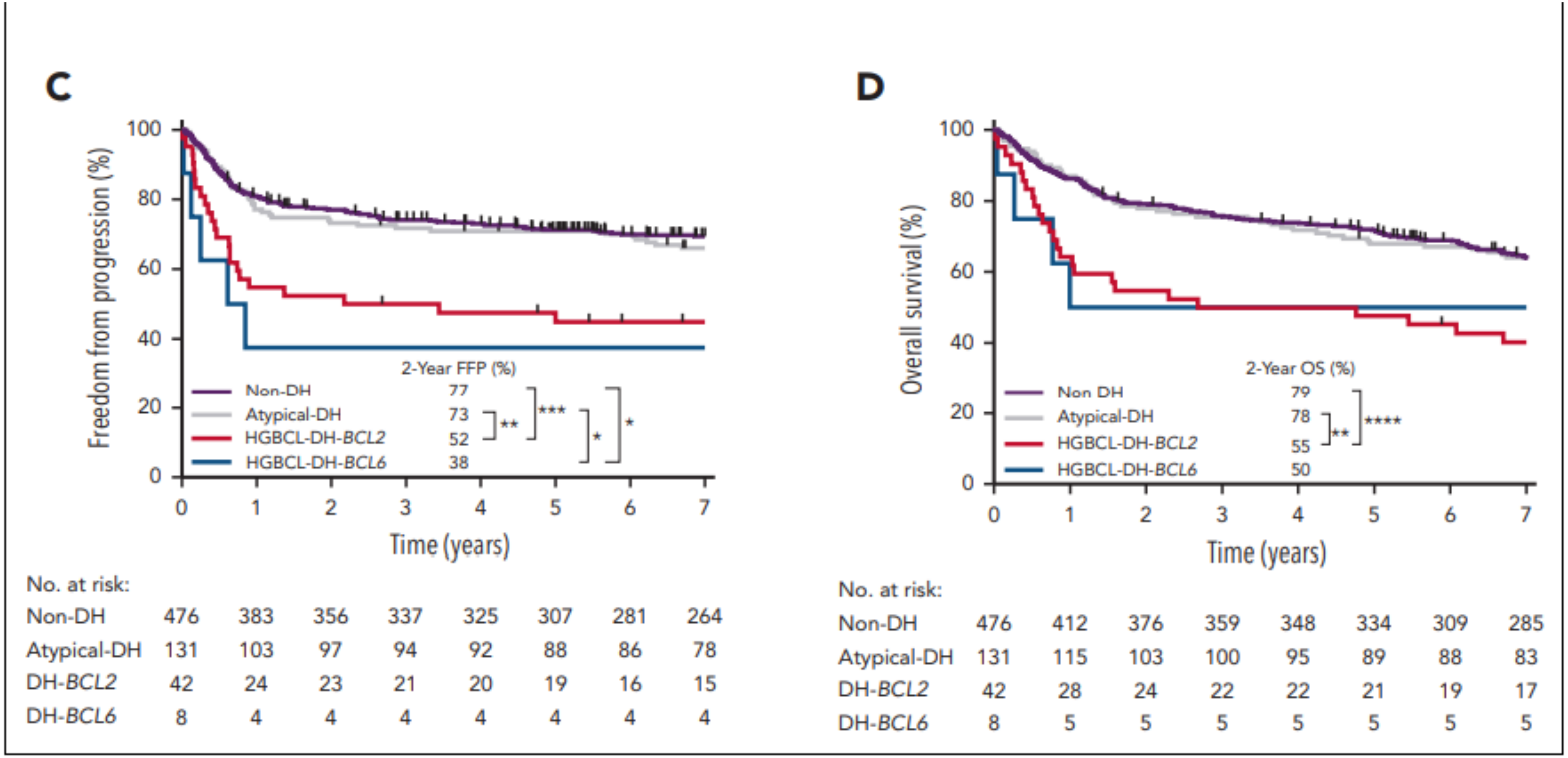
$MYC^{CNV}/BCL2^{CNV}$ 12%, $MYC^{CNV}/BCL2^{TR}$ 8%, $BCL2^{CNV}/MYC^{TR}$ 2%



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

802 de novo tumors of DLBCL morphology: SV detected by FISH

Collinge et al. Blood 2021



No. at risk:

Non-DH	476	383	356	337	325	307	281	264
Atypical-DH	131	103	97	94	92	88	86	78
DH-*BCL2*	42	24	23	21	20	19	16	15
DH-*BCL6*	8	4	4	4	4	4	4	4

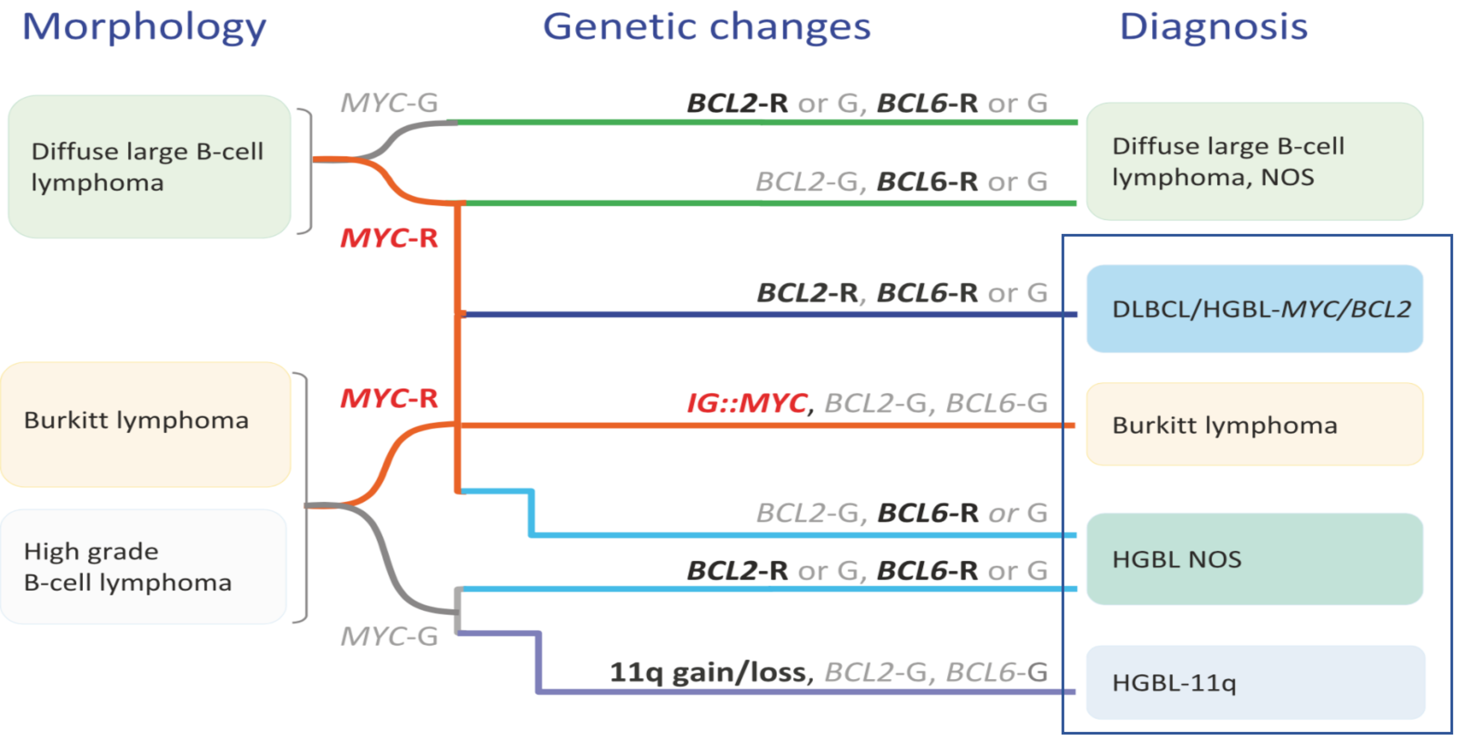
No. at risk:

Non-DH	476	412	376	359	348	334	309	285
Atypical-DH	131	115	103	100	95	89	88	83
DH-*BCL2*	42	28	24	22	22	21	19	17
DH-*BCL6*	8	5	5	5	5	5	5	5

Alduaij et al. Blood 2023

High grade cytology

fish is mandatory



Morphology

Genetic changes

Diagnosis

Diffuse large B-cell lymphoma

Burkitt lymphoma

High grade B-cell lymphoma

MYC-G

MYC-R

MYC-R

MYC-G

***BCL2*-R** or G, ***BCL6*-R** or G

BCL2-G, ***BCL6*-R** or G

***BCL2*-R**, ***BCL6*-R** or G

IG::MYC, *BCL2*-G, *BCL6*-G

BCL2-G, ***BCL6*-R** or G

***BCL2*-R** or G, ***BCL6*-R** or G

11q gain/loss, *BCL2*-G, *BCL6*-G

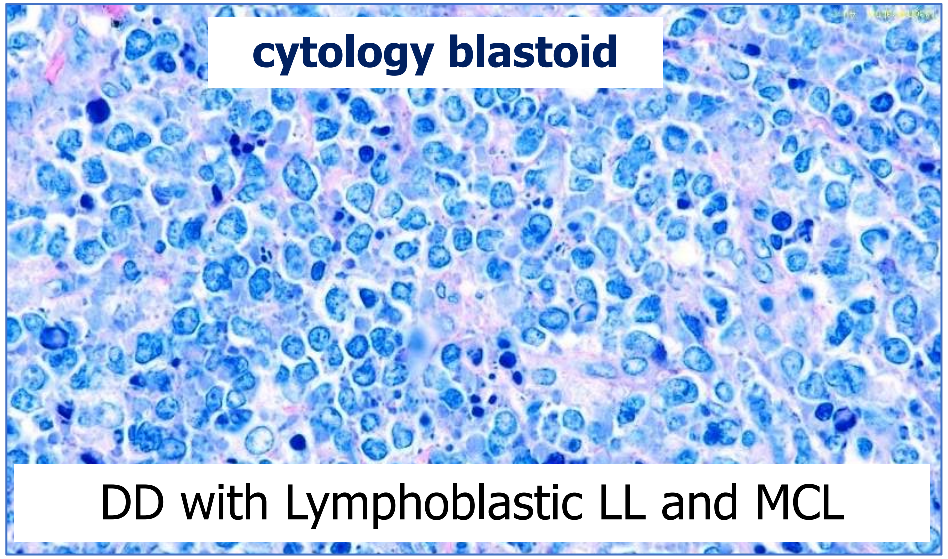
Diffuse large B-cell lymphoma, NOS

DLBCL/HGBL-*MYC/BCL2*

Burkitt lymphoma

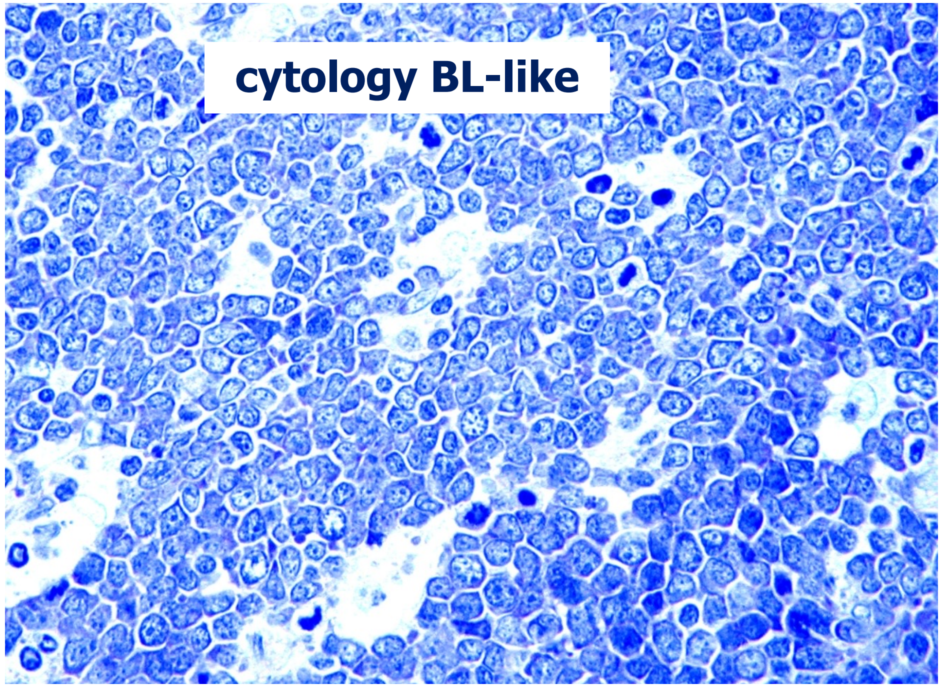
HGBL NOS

HGBL-11q



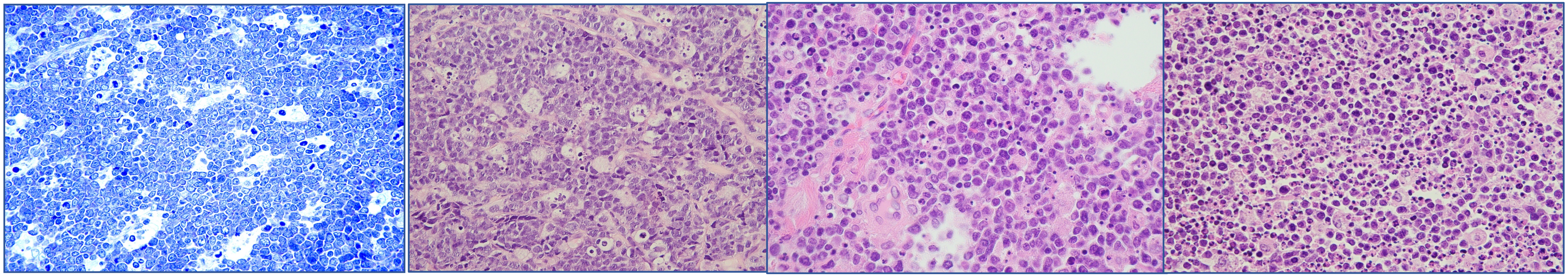
cytology blastoid

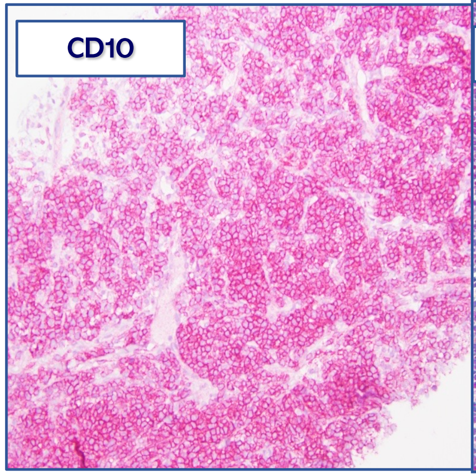
DD with Lymphoblastic LL and MCL

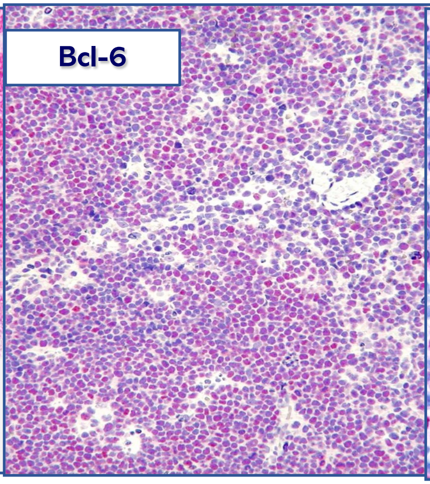


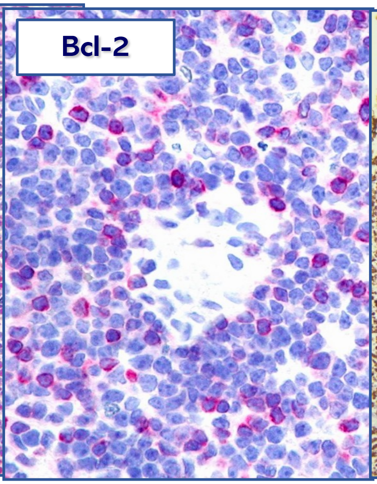
cytology BL-like

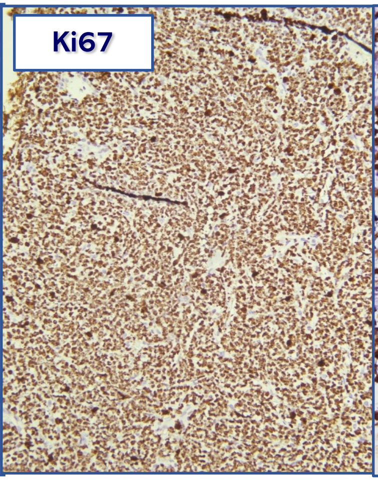
HG cytology Burkitt/Burkitt-like

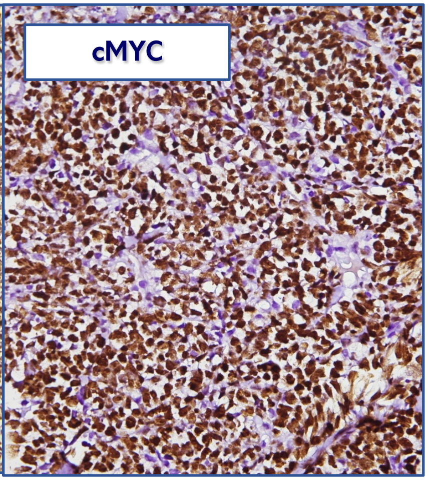


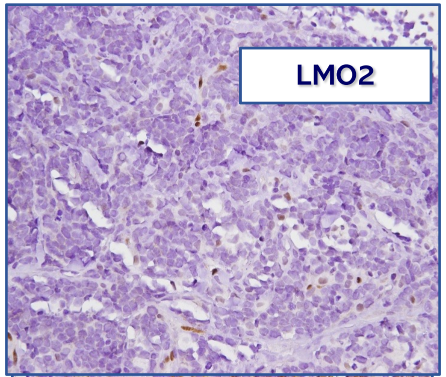

CD10

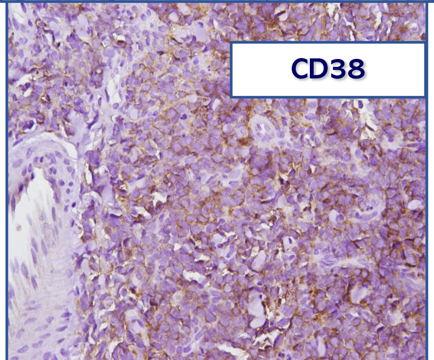

Bcl-6


Bcl-2


Ki67


cMYC

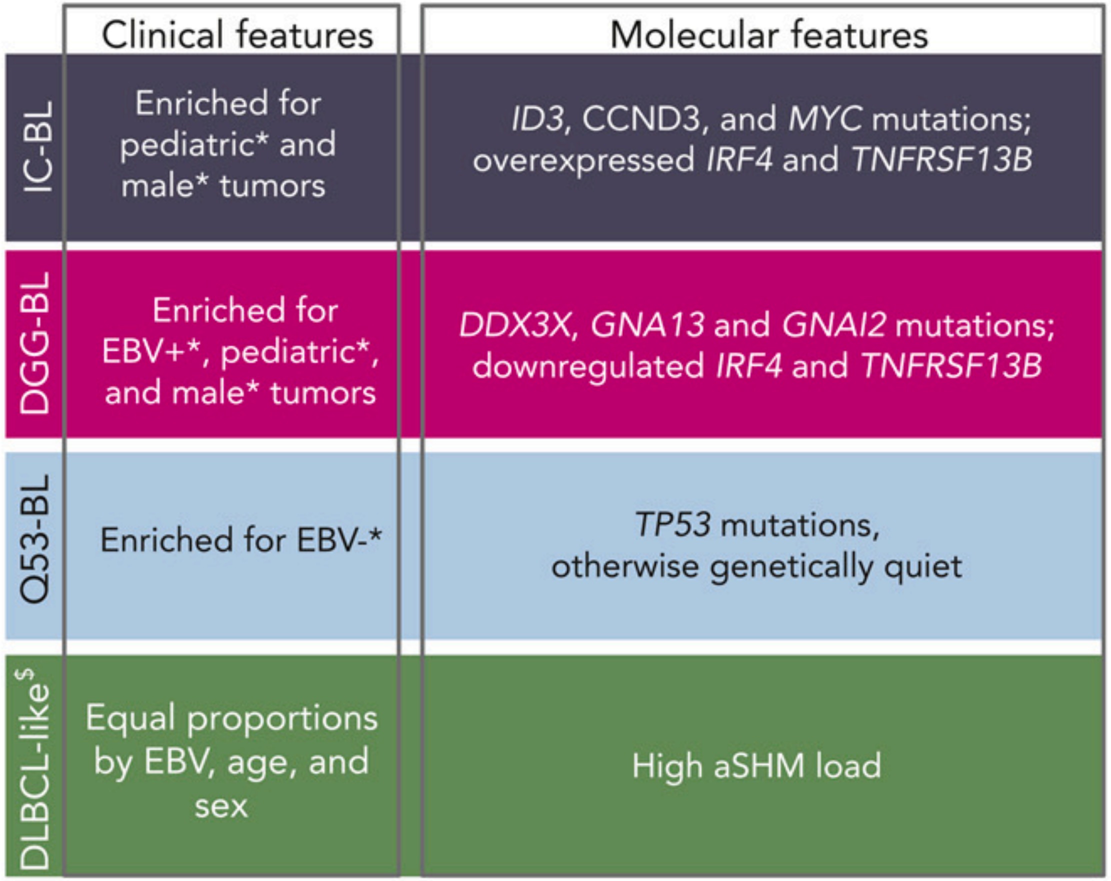

LMO2


CD38

MYC translocation / No BCL2^{TR}/BCL6^{TR}
IGH MYC translocation partner in 80% cases (IGK in 15% and IGL in 5% cases)
Rare BLs (cryptic insertions of MYC into IGH) are not detectable with standard FISH probes 24

MYC^{TR}does not drive BL lymphomagenesis in isolation
low complexity (40% of cases harboring the IG::MYC as the sole cytogenetic alteration)

Recurrent alterations in genes involved in
BCR/PI3K signaling (**ID3**, **TCF3**, FOXO1, PTEN),
MYC regulation (MYC, SIN3A, DDX3X, and TFAP4),
apoptosis and cell cycle regulation (TP53, USP7, CDKN2A, **CCND3***),
epigenetic regulation (ARID1A, SMARCA4, KMT2D, HIST1H1E, CHD8, FBXO11, and BCL7A),
G protein-coupled receptor signaling (GNA13, RHOA, and P2RY8).



	Clinical features	Molecular features
IC-BL	Enriched for pediatric* and male* tumors	*ID3*, CCND3, and *MYC* mutations; overexpressed *IRF4* and *TNFRSF13B*
DGG-BL	Enriched for EBV+*, pediatric*, and male* tumors	*DDX3X*, *GNA13* and *GNAI2* mutations; downregulated *IRF4* and *TNFRSF13B*
Q53-BL	Enriched for EBV-*	*TP53* mutations, otherwise genetically quiet
DLBCL-like$^{\$}$	Equal proportions by EBV, age, and sex	High aSHM load

Thomas N et al. Blood. 2023

Roschewski M et al. N Engl J Med. 2022; Boerma EG et al. Leukemia. 2009*; López C. Nat Commun. 2019;* Grande BM et al. Blood. 2019; *also as protein expressed; 70% sBL/ID-related BL, 40% endemic BL similar to Burkitt but not all fits

B-cell lymphoma with 11q aberration (molecularly defined category)

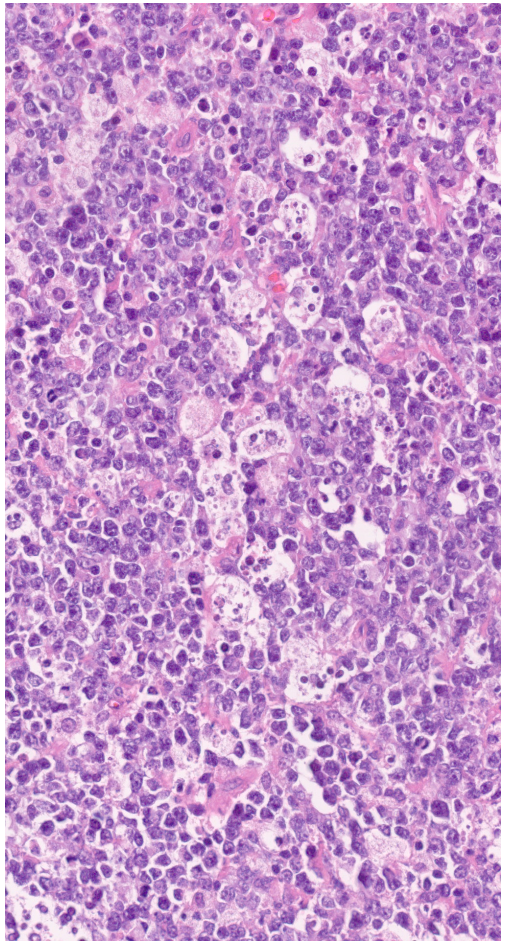
ICC2022: Large B-cell lymphoma
provisional entity (genetically distinct from BL)
WHO-HAEM5: High grade B-cell Lymphoma

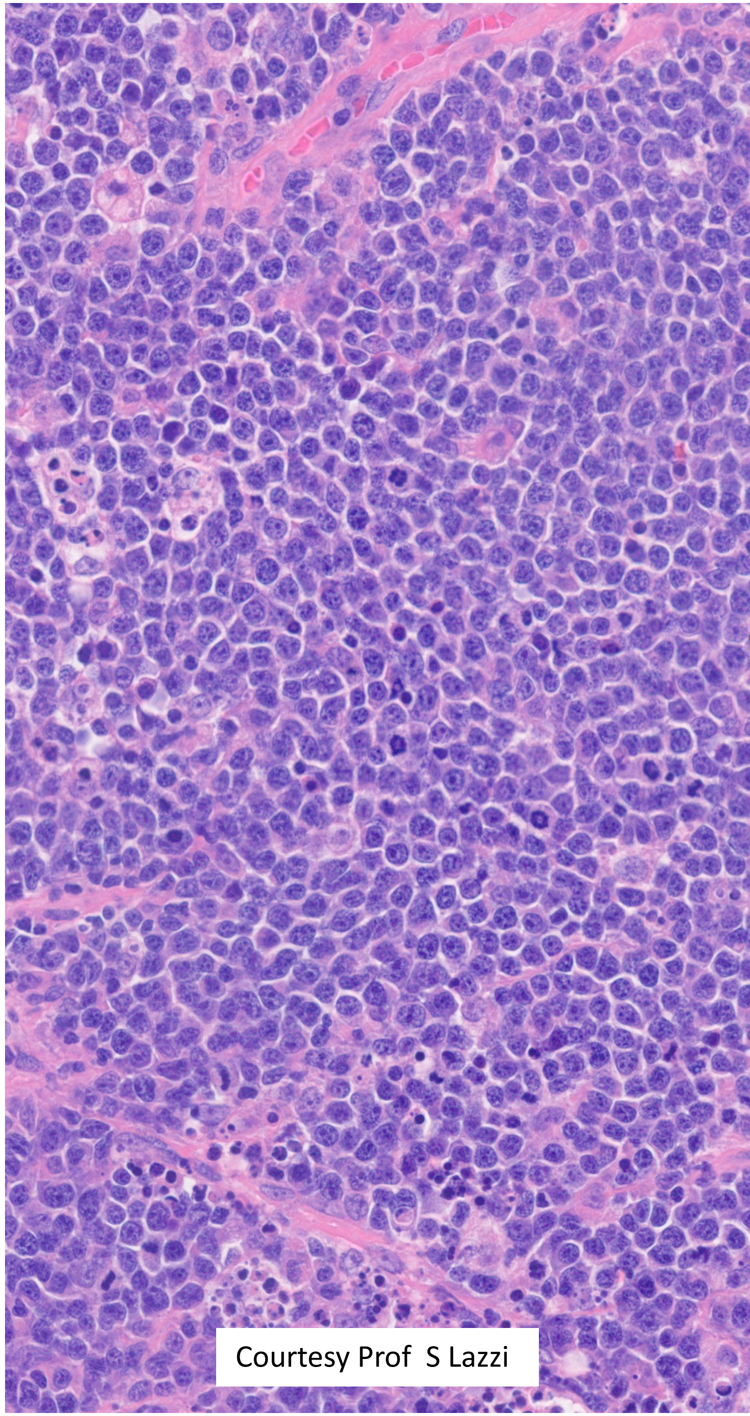
> DLBCL features: more cell pleomorphism than BL
high debris-full histiocytes
diffuse>follicular (>paediatric), in ID patients

no/minimal/little MYC protein expression

Residual phenotype BL-like
>CD10+/Bcl6+/Bcl2 >neg (GCB-COO)
LMO2 >strongly pos (BL mostly negative)

MUM1 >neg
EBER negative





Courtesy Prof S Lazzi

- **DEFINITION**

in keeping with the convention to call high grade on BL-like morphology)

- **MOLECULAR FEATURES**

- 11q deletion/insertion FISH positive
  (11q23 gain/11q24-qter loss; only 11q loss may be acceptable)
  specific FISH probes (>sufficient); CN array studies: ideal in FISH false-negative cases*

- MYC^{TR} negative (recommended wide MYC-R studies including BA, fusion probes)

- Distinct profile from MYC^{TR}BL
- more complex genetic aberrations (gains in chr 5q,12p, 18q, deletions 6q)
- typical BL mutations (TCF3 and ID3) absent; harbor GNA13 mutations (not found in BL but in GCB-DLBCL)

*particularly in the rare cases with copy-neutral loss of heterozygosity at 11q24-qter) ; *Horn H et al. Am J Surg Pathol. 2021*

BUT BEWARE THAT

- 11q alterations can associate with MYC-R (in Burkitt and HGBCL-NOS)
- HGBCLNOS wityh MYC and 11q rearrangements show features resembling BL

- So, in routine diagnostics if MYC-TR is positive in a HGBCL no need to search for 11q aberrancies, since it would not change the classification of the disease

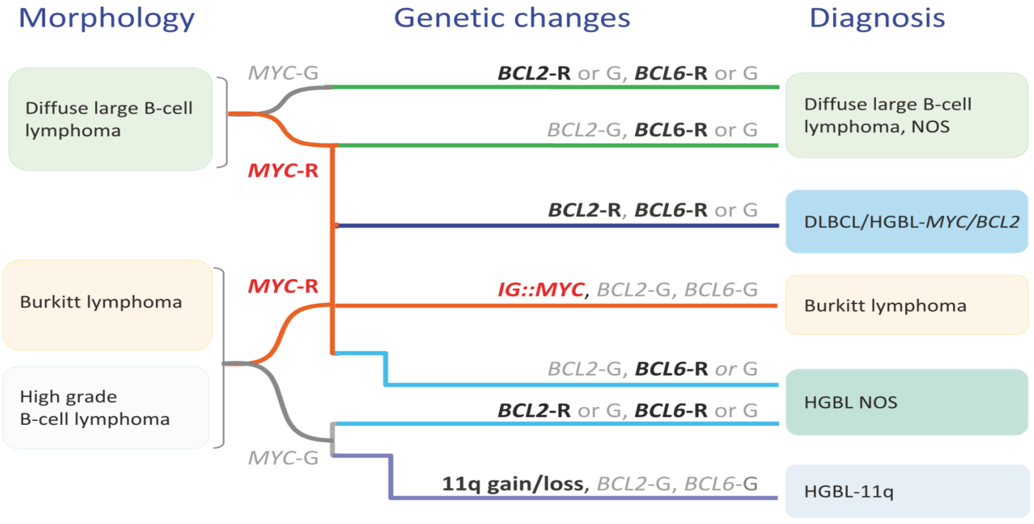
High grade B-cell lymphoma, NOS

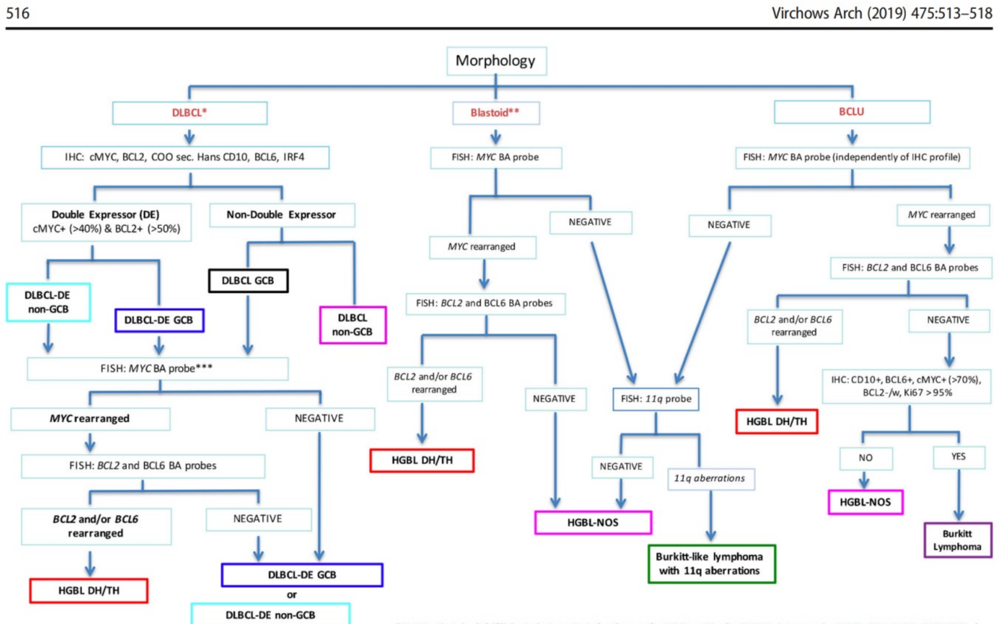
>**older** individuals; median age 7th decade, male predominance; **rare/not recognized in pediatric** age

often widespread, **advanced-stage** (III/IV) disease, extranodal/bone marrow involvement common

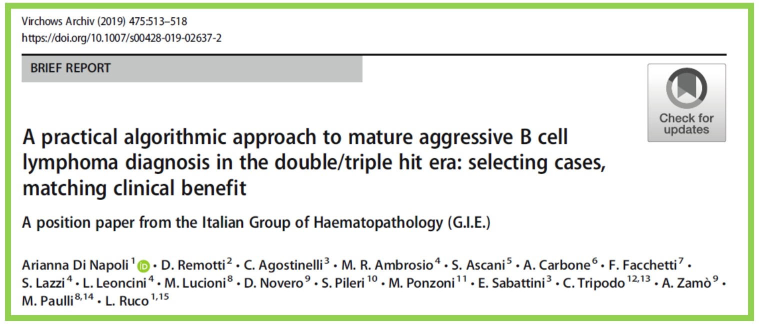
Survival outcomes are less favorable than DLBCL, NOS (2-year PFS 55.2%; OS 68.1%)

genetically heterogeneous
most commonly of **GCB origin** by GEP (57% reported in 1 study)
complex karyotype
MYC-TR in one-third of cases (>IG gene partner)
59% display a DZ signature; GEP more closely overlaps HGBL/DLBCL-DH than GCB-derived DLBCL, NOS
>unclassified by the LymphGen algorithm (small subsets into EZB (13%), MCD (9%), ST2 (7%), BN2 (4%)
Recurrent mutations in KMT2D, TP53, CXCR4, TET2.





*DLBCLs that don't fulfill the inclusion criteria for the specific DLBCL entities (i.e. PMBCL, intravascular DLBCL, EBV+ DLBCL, TCRHRBCL...)
** Lymphoblastic lymphomas and mantle cell lymphomas are excluded
*** Discussion with the referring hematologist is highly recommended before proceeding with FISH analyses


Virchows Archiv (2019) 475:513–518
https://doi.org/10.1007/s00428-019-02637-2

BRIEF REPORT

A practical algorithmic approach to mature aggressive B cell lymphoma diagnosis in the double/triple hit era: selecting cases, matching clinical benefit

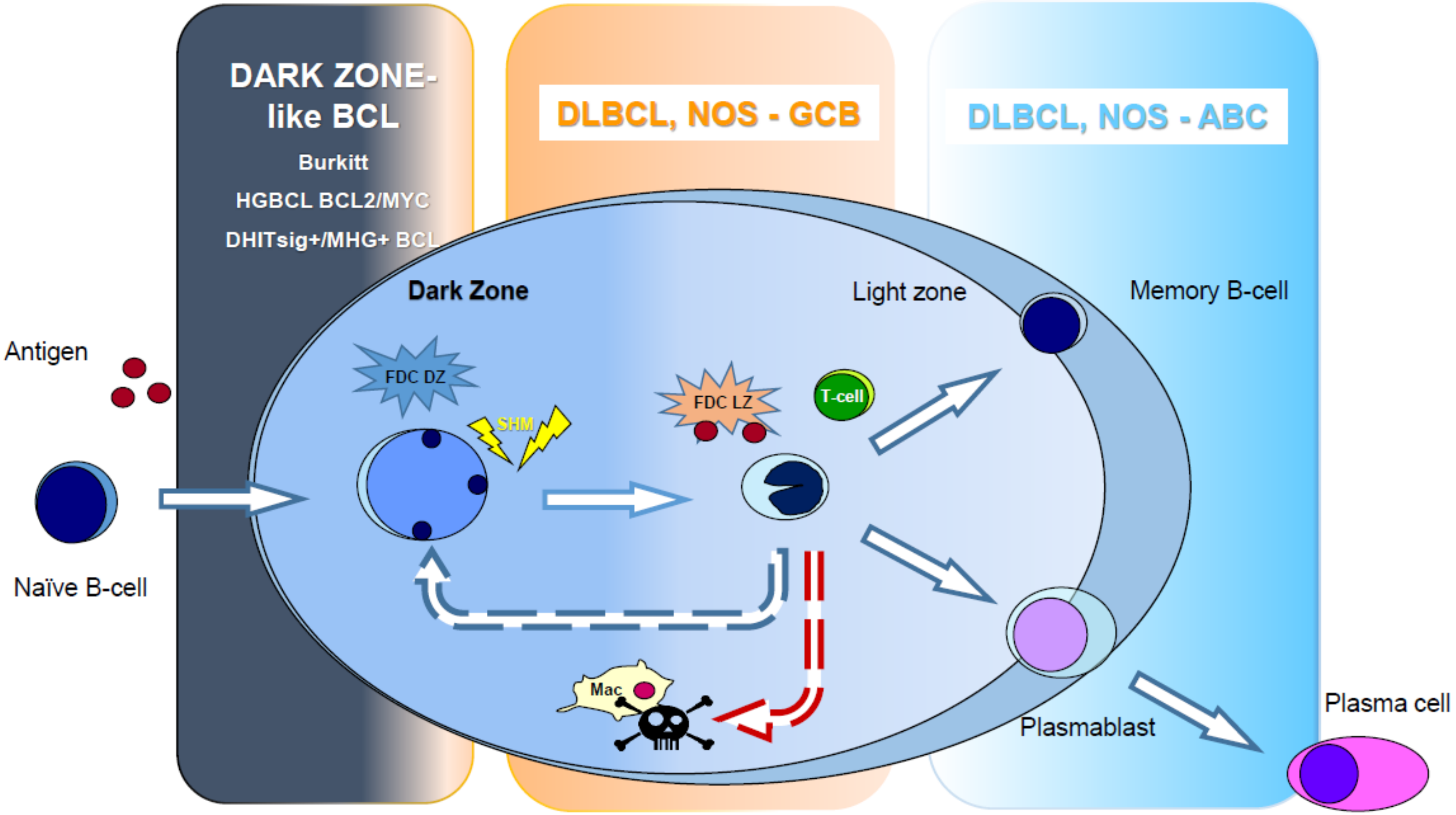
A position paper from the Italian Group of Haematopathology (G.I.E.)

Arianna Di Napoli[1] · D. Remotti[2] · C. Agostinelli[3] · M. R. Ambrosio[4] · S. Ascani[5] · A. Carbone[6] · F. Facchetti[7] · S. Lazzi[4] · L. Leoncini[4] · M. Lucioni[8] · D. Novero[9] · S. Pileri[10] · M. Ponzoni[11] · E. Sabattini[3] · C. Tripodo[12,13] · A. Zamò[9] · M. Paulli[8,14] · L. Ruco[1,15]

- **BL/high grade cytology** :
FISH-MYC mandatory

- **DLBCL cytology**:
COO GCB (high correspondence between Hans and Lymph2Cx)
MYC protein expression: cutoff >70% may guide, almost always present in MYC rearranged cases
If limited resources or optimizable: discuss with the hematologist (to verify patient's fitness and potential eligibility to undergo intensified therapy for HGBL DH/TH)

Who dlbcl ATTENZIONE



C3/EZB MYCpos BCL2

C3/EZB MYCneg BCL2

C4/ST2 SOCS1

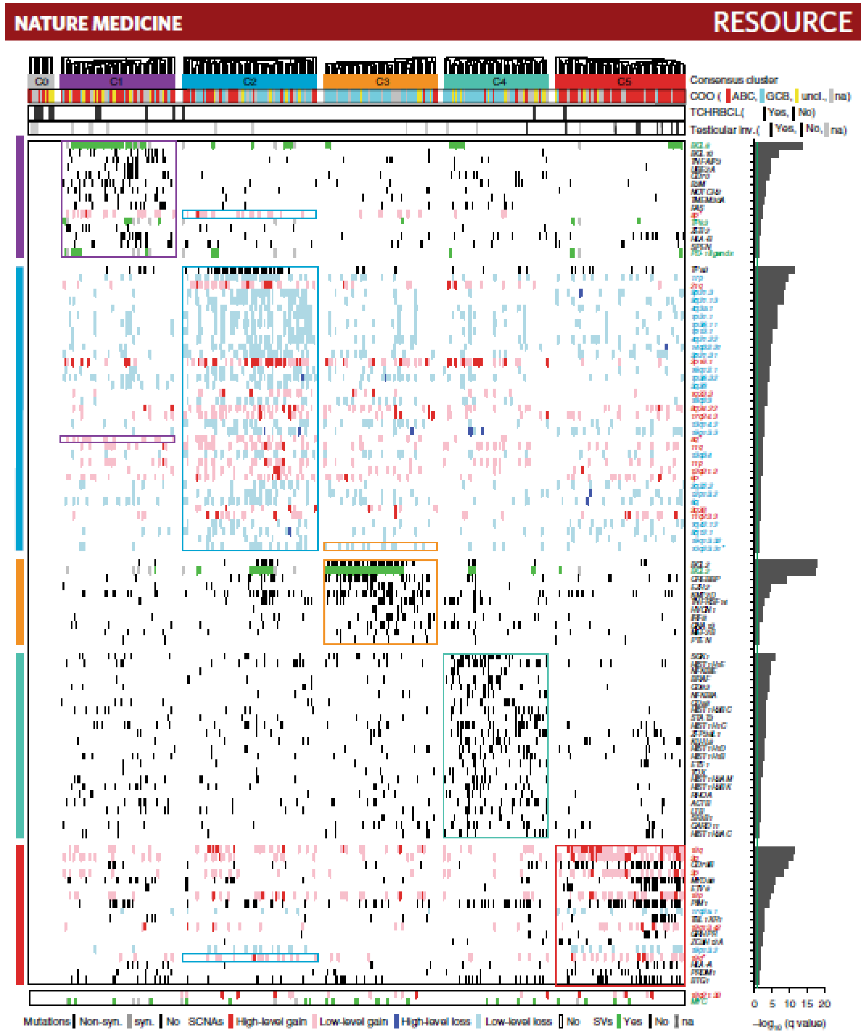
C1/BN2 NOTCH2

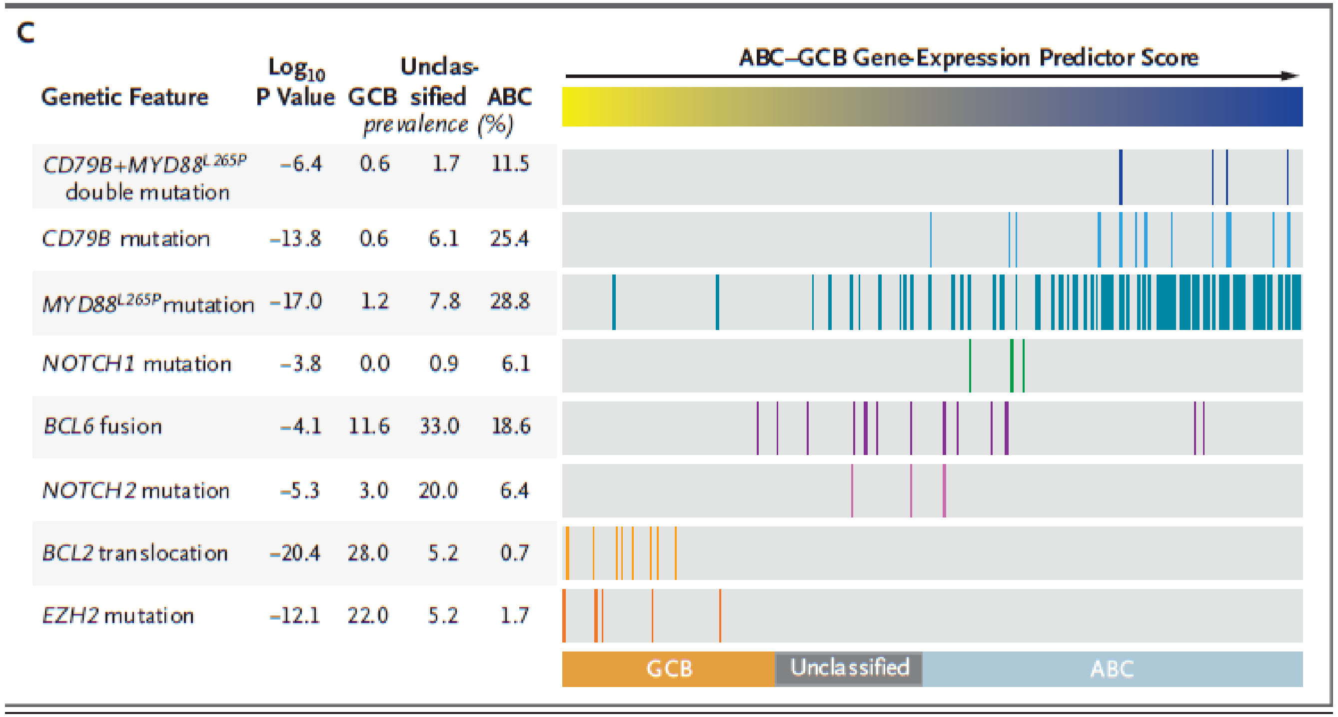
C2/A53

N1 NOTCH1

C5/MCD MYD88

multiplatform genomic studies revealed the existence of genetic subtypes of **DLBCL** using clustering methodologies (WES)





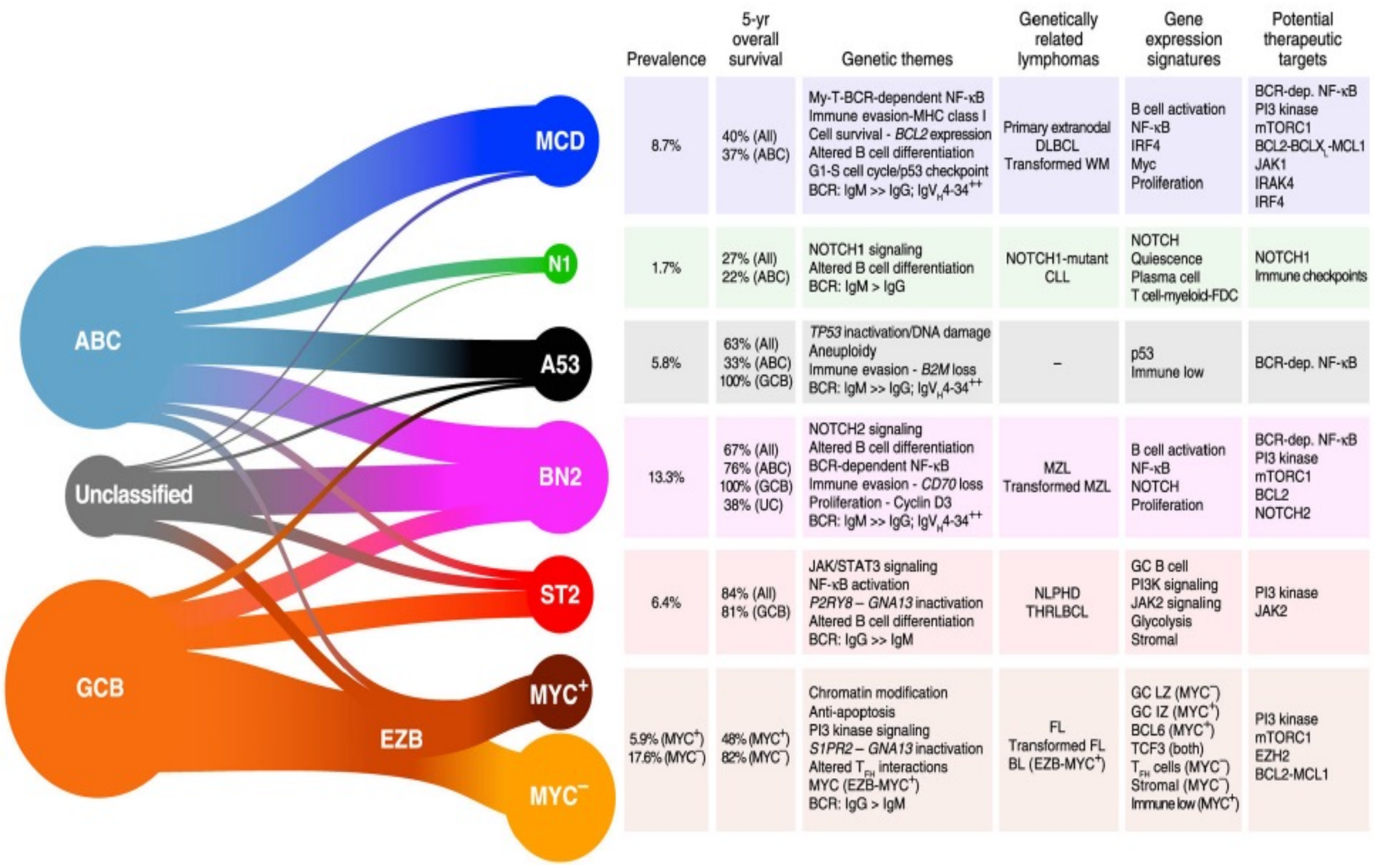
Genetic Feature	Log_{10} P Value	GCB	Unclassified	ABC
		prevalence (%)		
CD79B+MYD88^{L265P} double mutation	−6.4	0.6	1.7	11.5
CD79B mutation	−13.8	0.6	6.1	25.4
MYD88^{L265P} mutation	−17.0	1.2	7.8	28.8
NOTCH1 mutation	−3.8	0.0	0.9	6.1
BCL6 fusion	−4.1	11.6	33.0	18.6
NOTCH2 mutation	−5.3	3.0	20.0	6.4
BCL2 translocation	−20.4	28.0	5.2	0.7
EZH2 mutation	−12.1	22.0	5.2	1.7

at present not included in routine clinical use

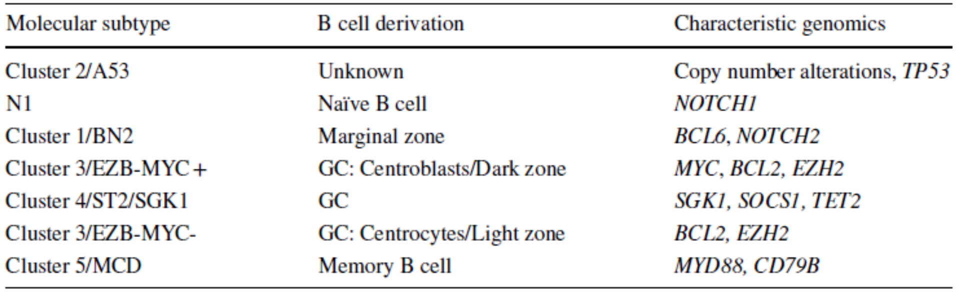
Recurrent genomic subtypes with clinical relevance (Chapuy Nat Med 2018; Wright NEJM 2018; Lacy 2020; at present not included in routine clinical use; 35-40% of cases are not currently assigned to a genetic subtype

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

Cancer Cell. 2020 Wright



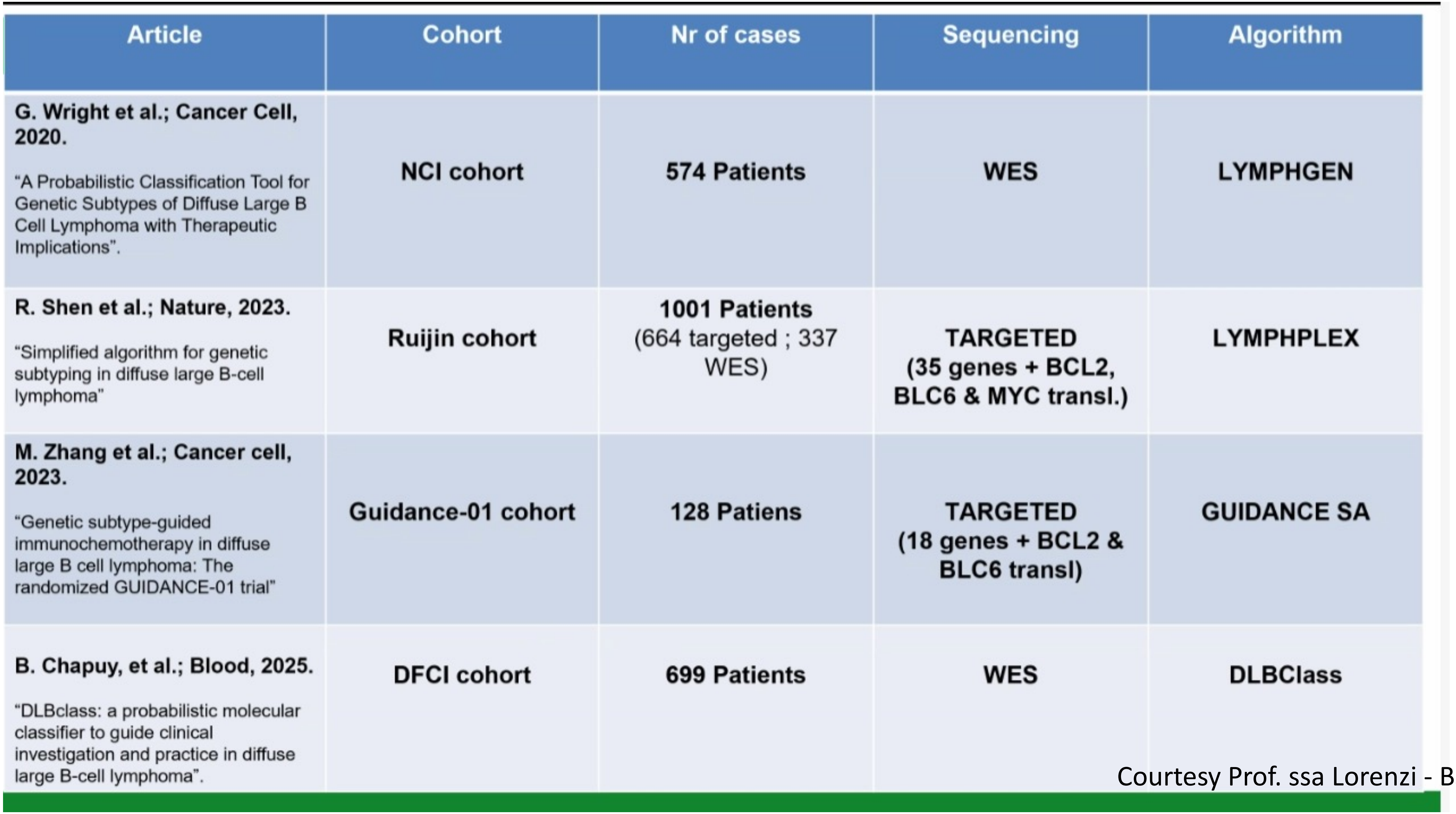
	Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
MCD	8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF-κB Immune evasion-MHC class I Cell survival - *BCL2* expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; $\text{IgV}_\text{H}\text{4-34}^{++}$	Primary extranodal DLBCL Transformed WM	B cell activation NF-κB IRF4 Myc Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 $\text{BCL2-BCLX}_\text{L}\text{-MCL1}$ JAK1 IRAK4 IRF4
N1	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
A53	5.8%	63% (All) 33% (ABC) 100% (GCB)	*TP53* inactivation/DNA damage Aneuploidy Immune evasion - *B2M* loss BCR: IgM >> IgG; $\text{IgV}_\text{H}\text{4-34}^{++}$	–	p53 Immune low	BCR-dep. NF-κB
BN2	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; $\text{IgV}_\text{H}\text{4-34}^{++}$	MZL Transformed MZL	B cell activation NF-κB NOTCH Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2 NOTCH2
ST2	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
EZB	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



Molecular subtype	B cell derivation	Characteristic genomics
Cluster 2/A53	Unknown	Copy number alterations, *TP53*
N1	Naïve B cell	*NOTCH1*
Cluster 1/BN2	Marginal zone	*BCL6, NOTCH2*
Cluster 3/EZB-MYC+	GC: Centroblasts/Dark zone	*MYC, BCL2, EZH2*
Cluster 4/ST2/SGK1	GC	*SGK1, SOCS1, TET2*
Cluster 3/EZB-MYC-	GC: Centrocytes/Light zone	*BCL2, EZH2*
Cluster 5/MCD	Memory B cell	*MYD88, CD79B*

LymphGen algorithm

- publicly accessible at https://llmpp.nih.gov/lymphgen/index.php
- unifies two recent genetic profiling studies (Chapuy et al., 2018; Schmitz et al., 2018) and was also evident in the independent BCC cohort (3 cohorts of data); 54% of the cases are assigned



Article	Cohort	Nr of cases	Sequencing	Algorithm
G. Wright et al.; Cancer Cell, 2020. "A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications".	**NCI cohort**	**574 Patients**	**WES**	**LYMPHGEN**
R. Shen et al.; Nature, 2023. "Simplified algorithm for genetic subtyping in diffuse large B-cell lymphoma"	**Ruijin cohort**	**1001 Patients** (664 targeted ; 337 WES)	**TARGETED (35 genes + BCL2, BLC6 & MYC transl.)**	**LYMPHPLEX**
M. Zhang et al.; Cancer cell, 2023. "Genetic subtype-guided immunochemotherapy in diffuse large B cell lymphoma: The randomized GUIDANCE-01 trial"	**Guidance-01 cohort**	**128 Patiens**	**TARGETED (18 genes + BCL2 & BLC6 transl)**	**GUIDANCE SA**
B. Chapuy, et al.; Blood, 2025. "DLBclass: a probabilistic molecular classifier to guide clinical investigation and practice in diffuse large B-cell lymphoma".	**DFCI cohort**	**699 Patients**	**WES**	**DLBClass**

Courtesy Prof. ssa Lorenzi - BS

Società Italiana di Ematologia

Convegno Regionale

SIE

LE NUOVE FRONTIERE NELLA TERAPIA DEL LINFOMA: INNOVAZIONE E FUTURO

30 Marzo 2026

Napoli, *Centro Congressi Federico II*

DELEGAZIONE **CAMPANIA**

Grazie per la attenzione

SSD di Emolinfopatologia – IRCCS Bologna
Elena Sabattini
Claudio Agostinelli, Clara Bertuzzi, Carlo Alberto Sagramoso Sacchetti