

Aggressive Lymphoma Workshop

Bologna, Royal Hotel Carlton

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Histology of Aggressive B-cell Lymphomas in the International Consensus Classification

Elaine S Jaffe, National Cancer Institute, Bethesda MD, USA

President: **Pier Luigi Zinzani**



ALMA MATER STUDIORUM
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DIPARTIMENTO DI
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POLICLINICO DI
SANT'ORSOLA



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Disclosures

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Elsevier							Author Editor

“Large” B-cell Neoplasms in the ICC (*Blood 2022*)

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

Large B-cell lymphoma with *IRF4* R

(Nodular lymphocyte predominant B-cell lymphoma)

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

Burkitt lymphoma

High-grade B-cell lymphoma, with *MYC* and *BCL2* R

High-grade B-cell lymphoma with MYC and BCL6 R

High-grade B-cell lymphoma, NOS

Primary mediastinal large B-cell lymphoma

Mediastinal gray-zone lymphoma

EBV-positive mucocutaneous ulcer

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-associated lymphoproliferative disorder

 Multicentric Castleman disease

 HHV8- positive germinotropic lymphoproliferative disorder

 HHV8- positive DLBCL, NOS

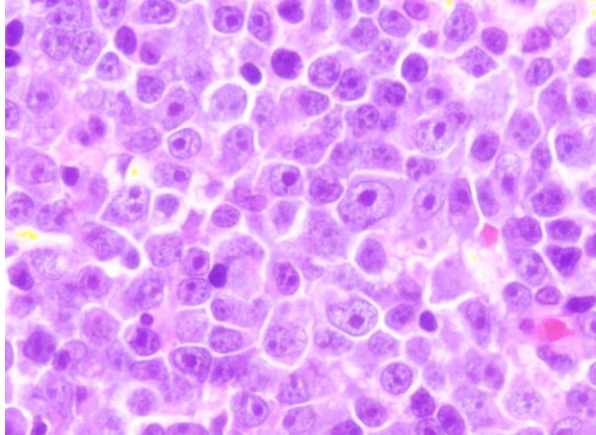
 Primary effusion lymphoma

HHV-8 and EBV-negative primary effusion-based lymphoma

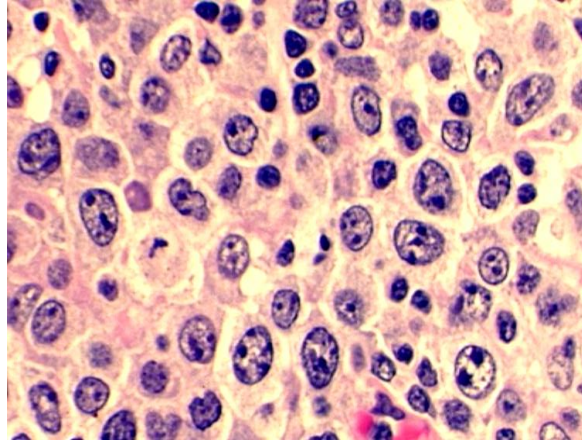
- Disease with changes introduced in the ICC 2022
- *Provisional Entities*

DLBCL: De-emphasize morphologic and phenotypic variants

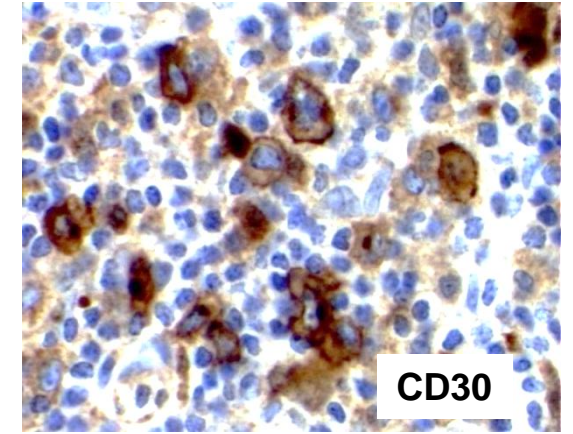
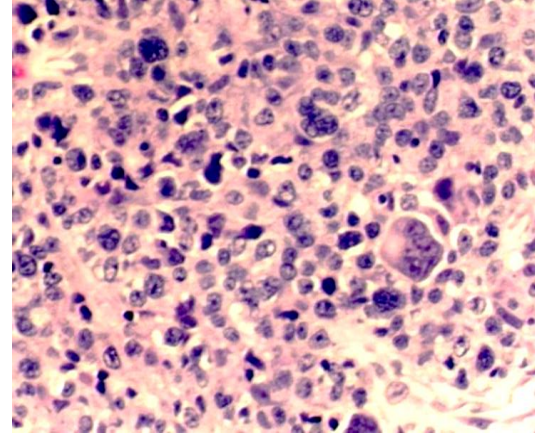
Immunoblastic



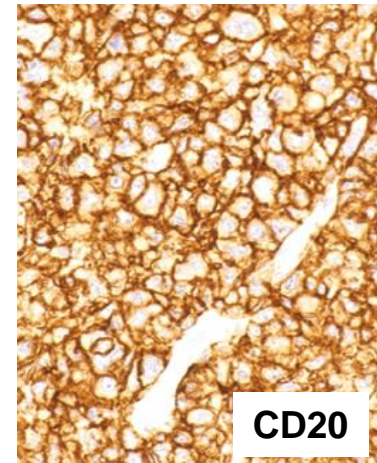
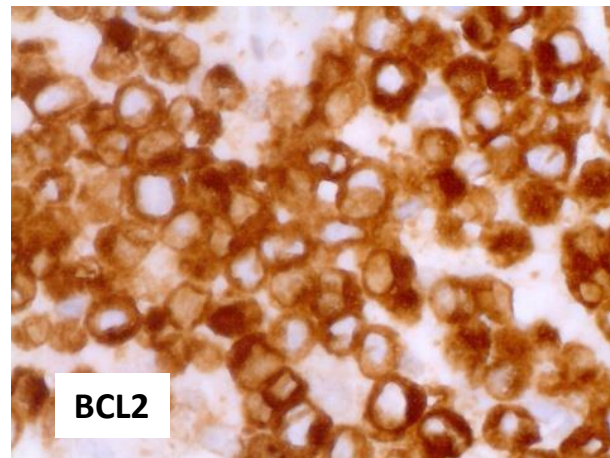
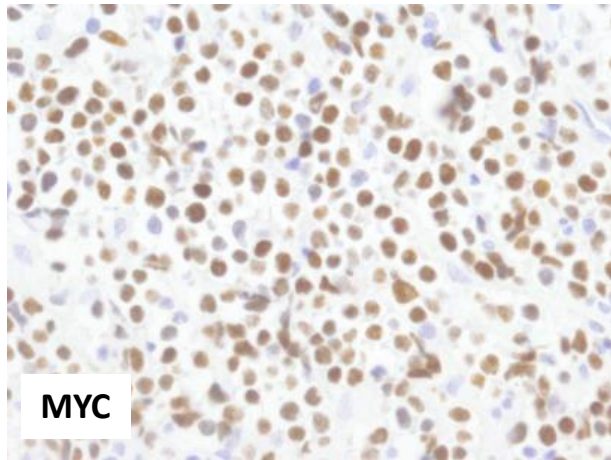
Centroblastic



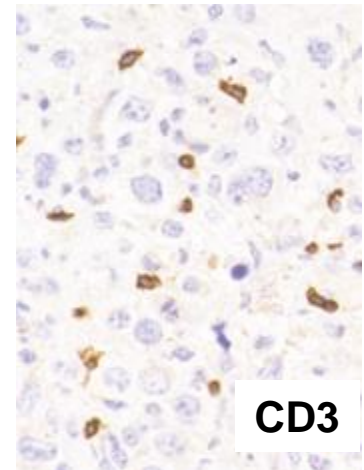
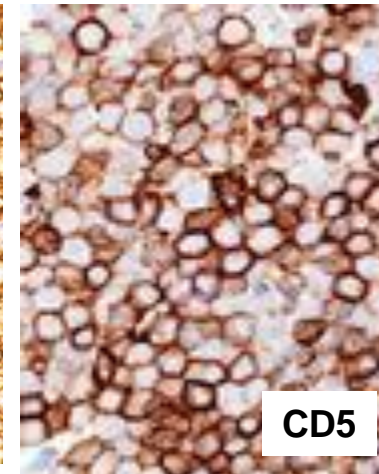
Anaplastic



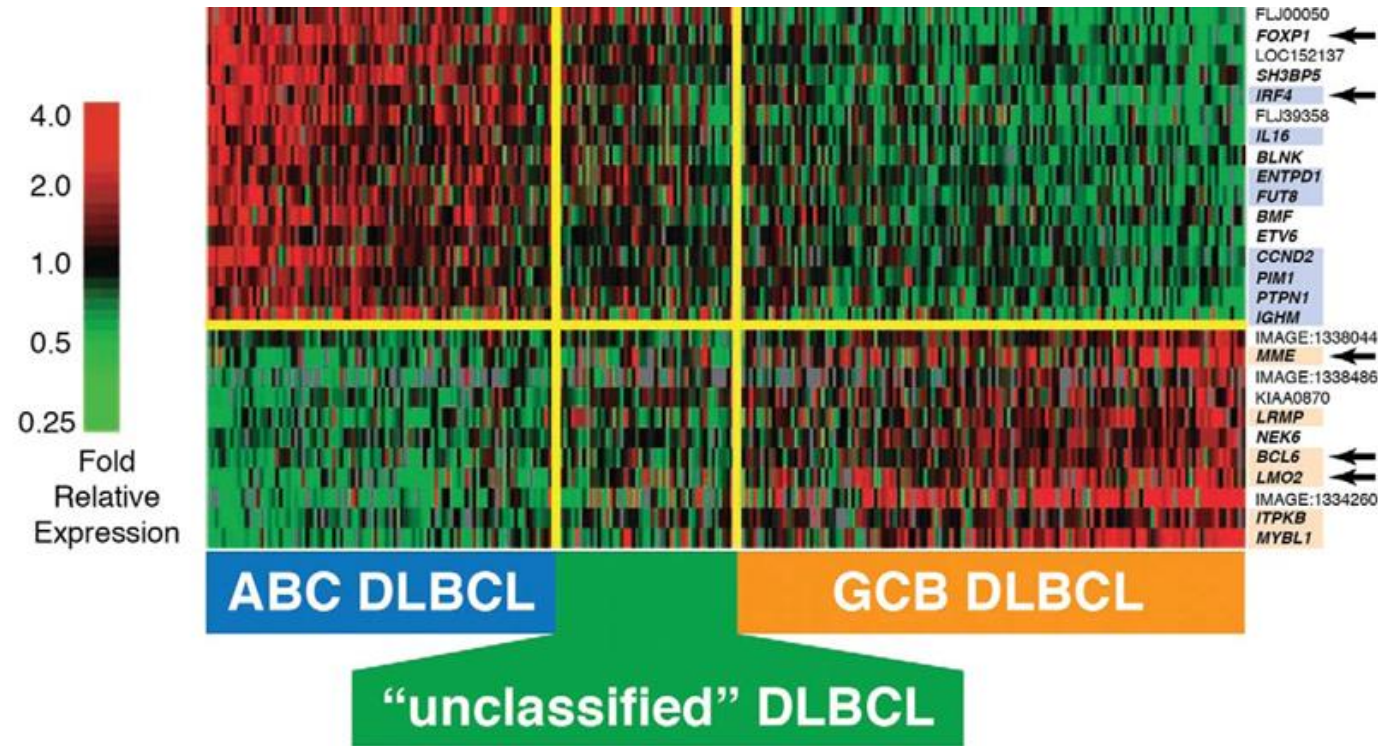
"Double Expressors"



CD5 + DLBCL



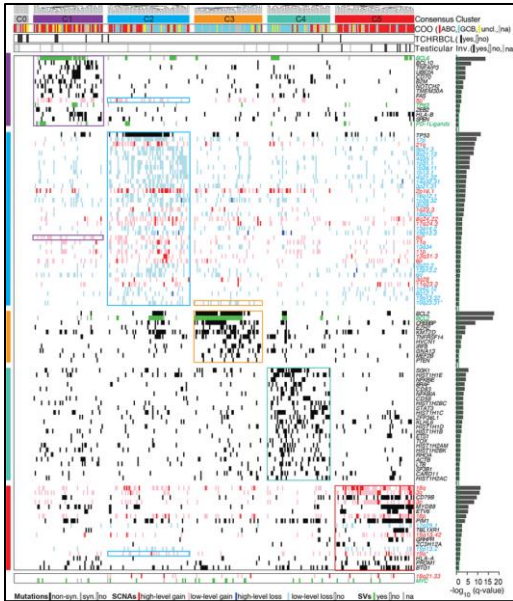
Current Classification of Diffuse Large B-cell Lymphoma



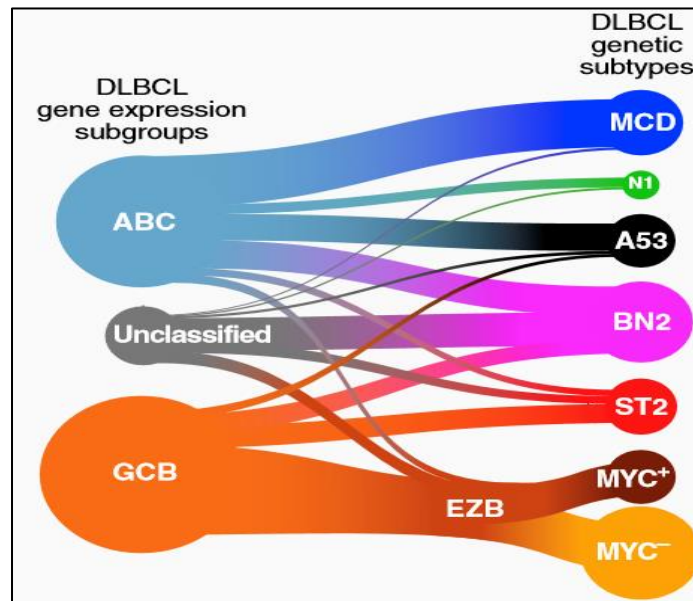
- Cell-of-origin in DLBCL, NOS should be maintained since it reflects a basic biological distinction
- However, this “binary” classification fails to capture the complexity of DLBCL

Current Classification of Diffuse Large B-cell Lymphoma

- Several studies have identified recurrent genomic subtypes with clinical relevance, **but too early to implement for routine clinical use**
- With current systems, many cases are not assigned to a genetic subtype (~35-40%)



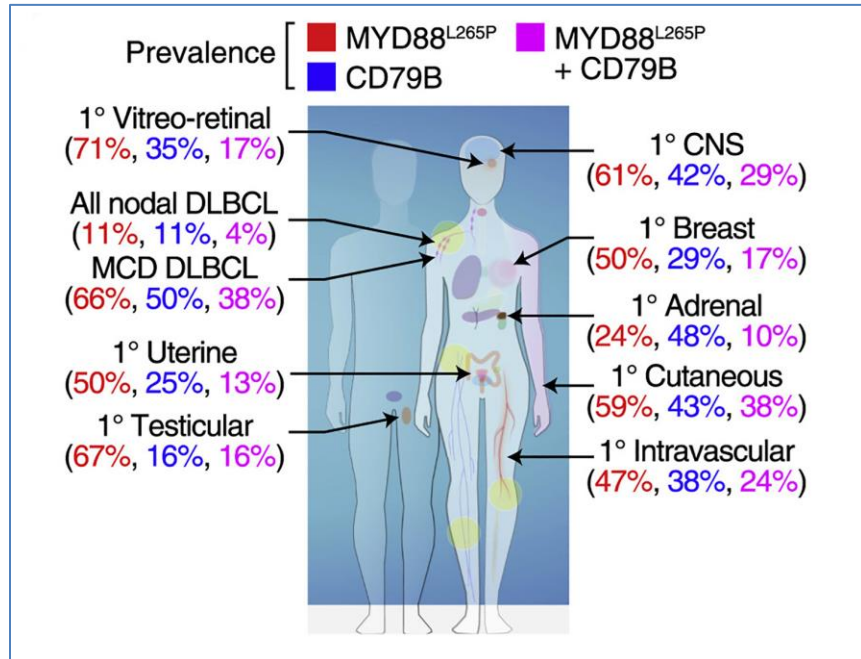
Chapuy



Wright

Wright 2020	Chapuy 2018	Lacy 2020	%
MCD	C5	MYD88	14-21
BN2	C1	NOTCH2	16-19
EZB-MYC-	C3	BCL2	13-18
EZB-MYC+			
A53	C2		7-21
ST2	C4	SOCS1/TET/SGK1	5-17
N1		NEC	3
UNCLASS			37

Is it time to recognize Extranodal DLBCL as a separate entity?



- Many extranodal DLBCL, ABC, share biological features (**MCD/C5**)
- Prototypes include primary CNS and testicular DLBCL
- Some subtypes also defined by their topographic site (IVLBCL)
- Extranodal DLBCL in **other anatomic sites** are more heterogeneous
 - (e.g. Breast, Adrenal, Kidney)

Wright GW et al Cancer Cell 2020

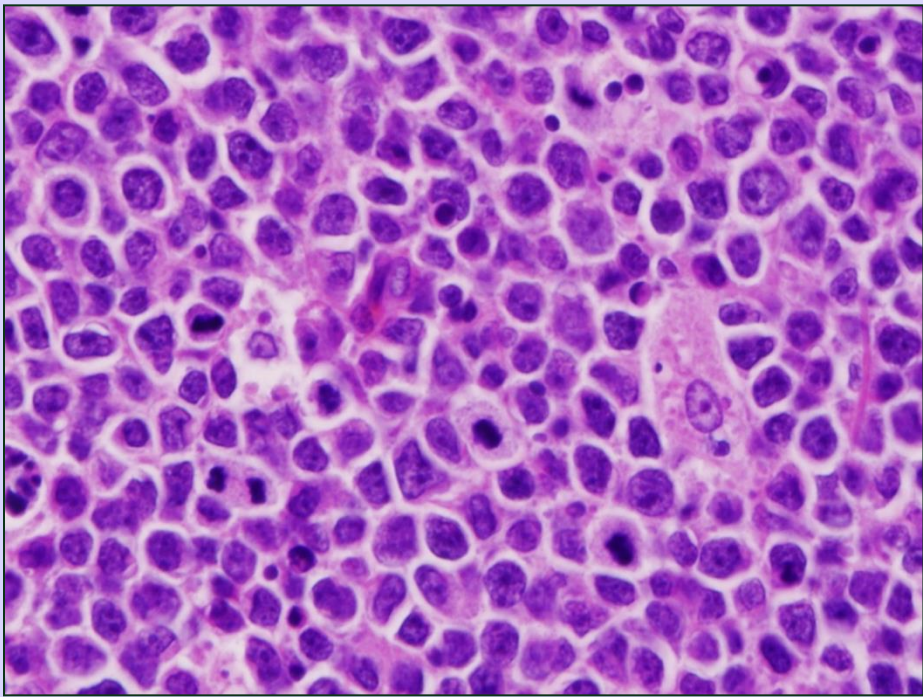
Proposal

- ICC accepts Primary DLBCL of the testis as a specific entity closely related to primary DLBCL of CNS
- Further studies are needed to determine the interrelationships between DLBCL in other extranodal sites
- Unifying features: **CD79B/ MYD88^{L265P}**

Large BCL with 11q aberration (ICC)

- Formerly “Burkitt-like lymphoma with 11q aberration” (WHO 4th Ed)
- Resembles Burkitt lymphoma but favorable prognosis – less intensive Rx required
- High grade BCL with 11q aberration (WHO 5th)
- Mutational profile closer to DLBCL
 - No *ID3*, *TCF3* – Lacks the hallmarks of Burkitt lymphoma
 - *BTG2*, *GNA13* mutations; GCB gene expression profile
 - More appropriate as a variant of DLBCL rather than high grade B-cell lymphoma

(Gonzalez-Farre et al Haematologica, 2019)

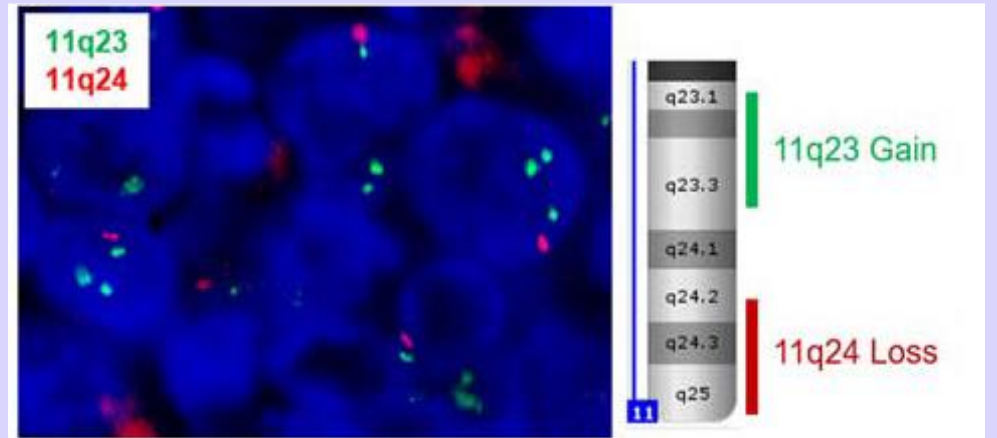
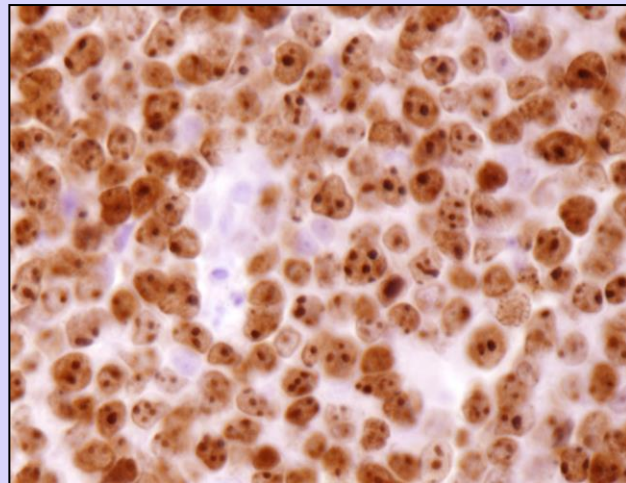
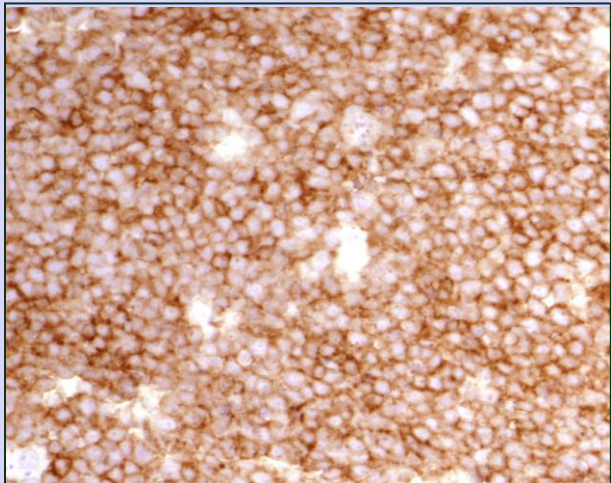


Large B-cell lymphoma with 11q aberration

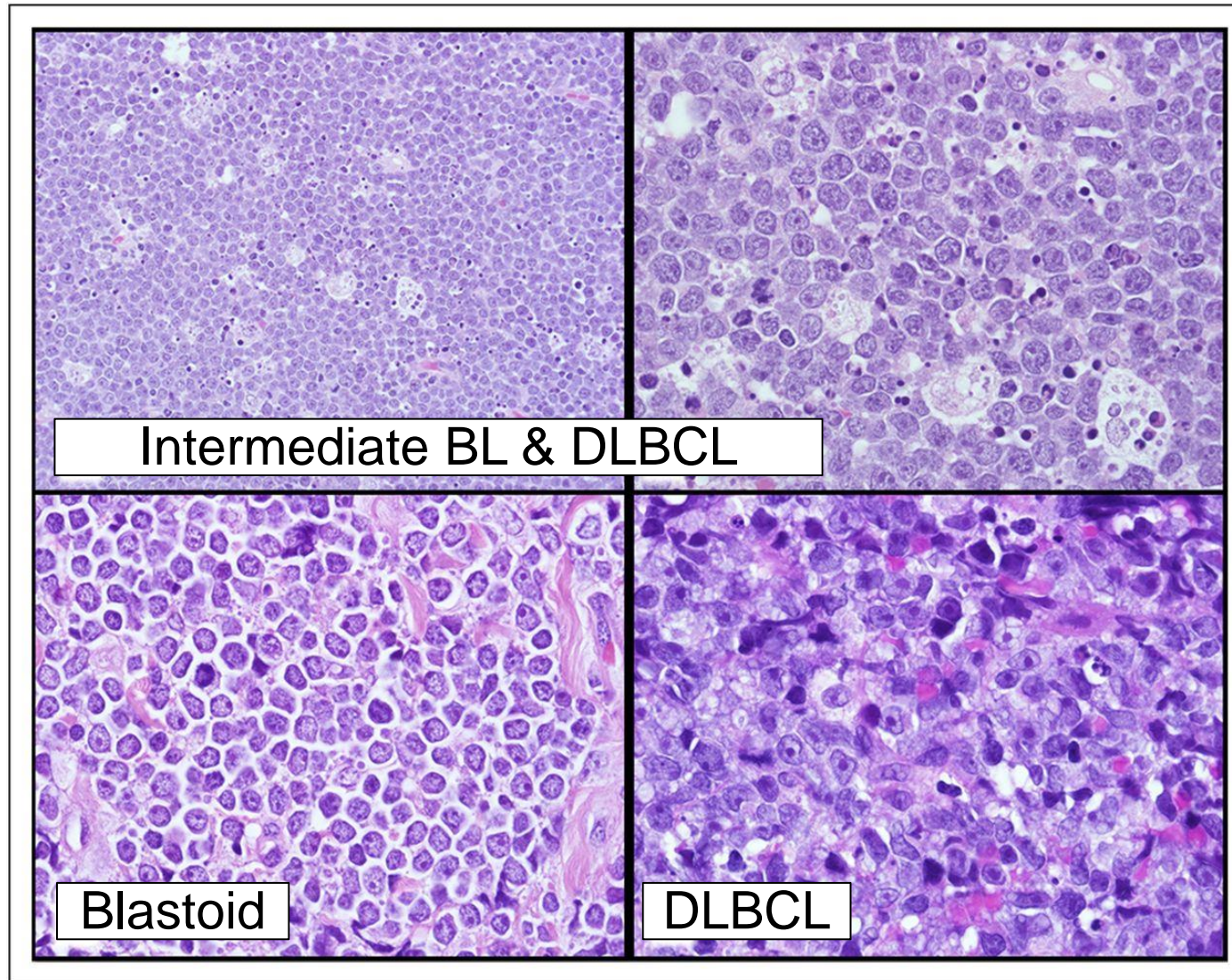
Pediatric, mainly nodal
Starry sky pattern
Negative for MYC R
May have MYC protein
Gains and losses at 11q

CD10

MIB-1



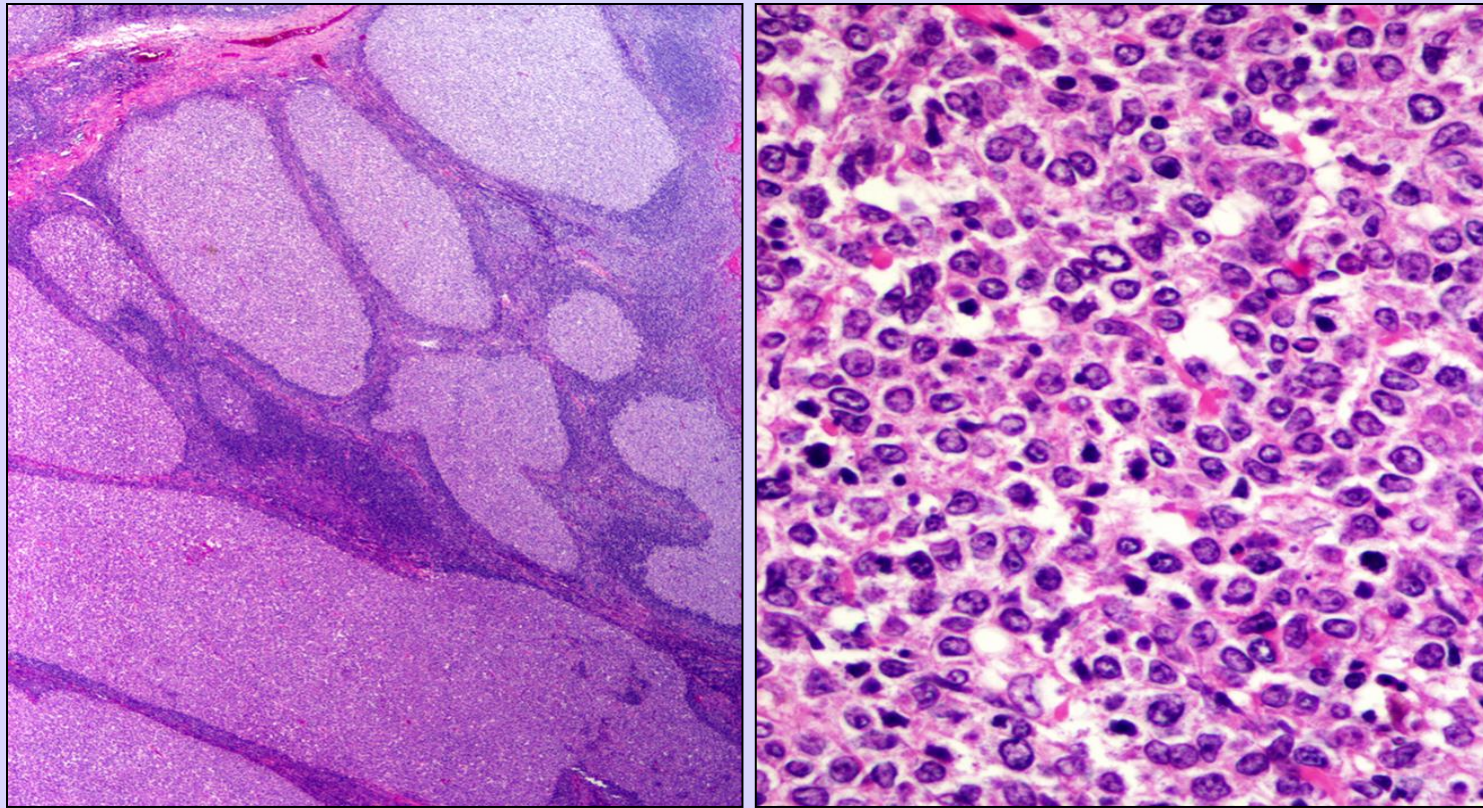
Cytologic spectrum of HGBL, with *MYC* and *BCL2* and/or *BCL6* rearrangements

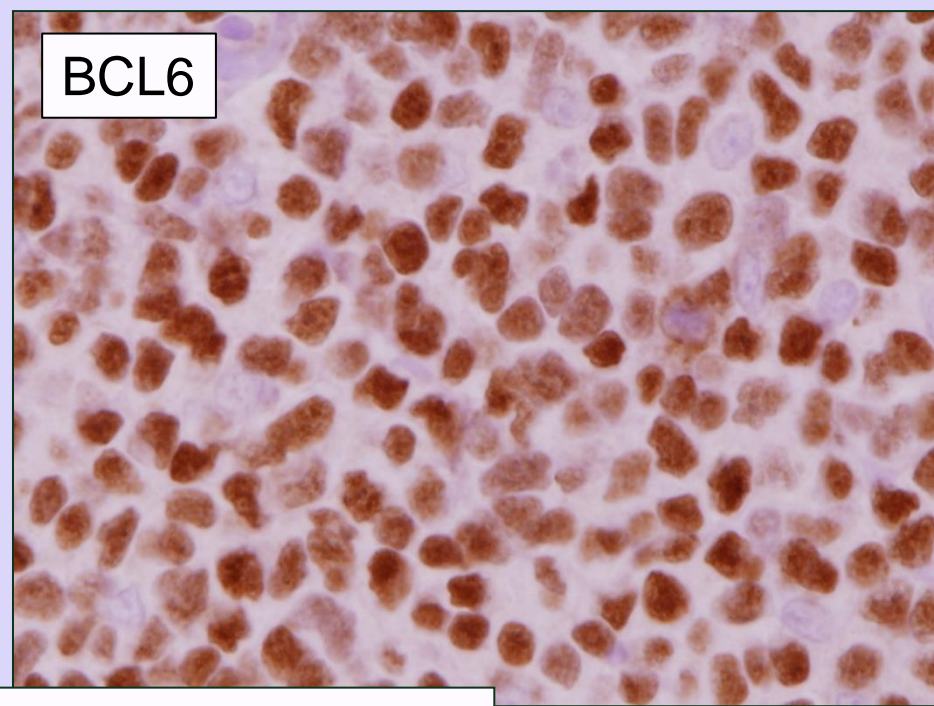
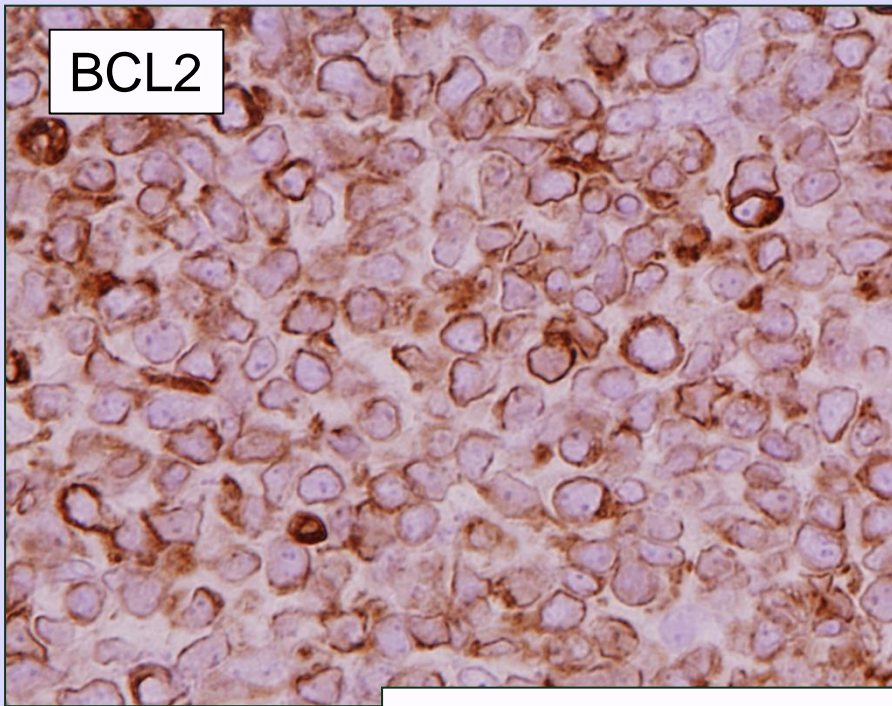


ICC Proposal for high grade B-cell lymphomas

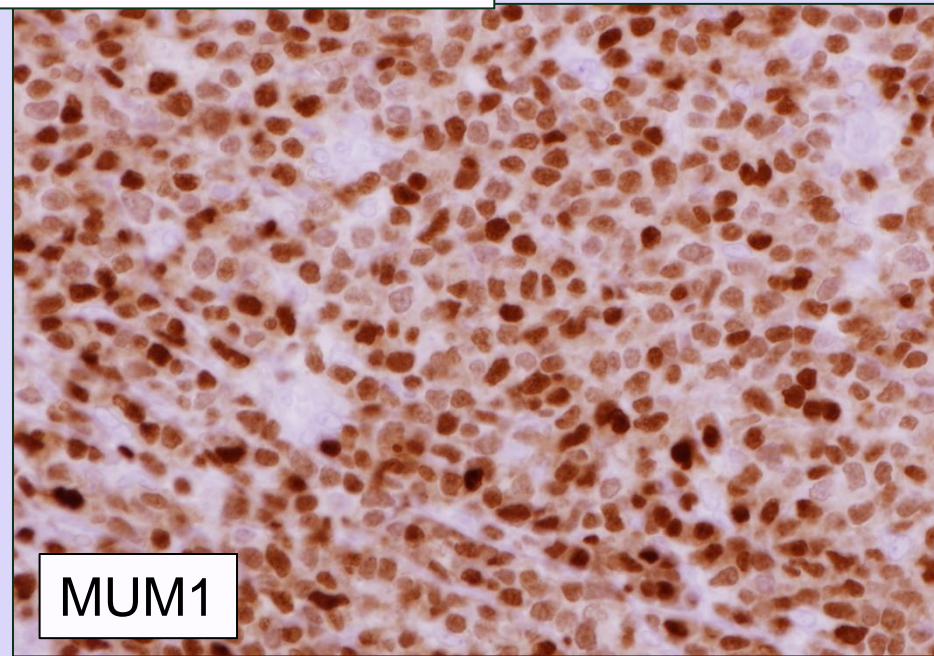
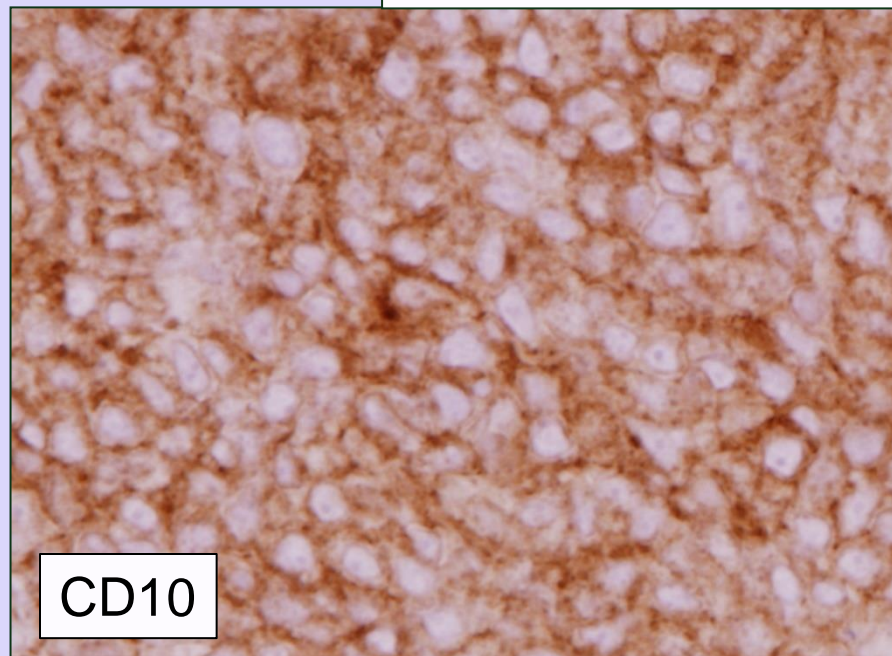
- **High-grade B-cell lymphomas with *MYC* and *BCL2* rearrangements**
 - Broad cytological spectrum, but considered a single entity
 - FISH break apart probes recommended but may miss up to 20% cases (cryptic)
 - Germinal center origin, but may express TDT
 - Gene expression signature of centroblasts in the GC dark zone
 - Mutational profile similar to “aggressive” FL (*BCL2*, ***MYC***, *KMT2D*, *CREBPP*, *TNFRS14*, *EZH2*)
- **High-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements (provisional)**
 - Heterogeneous in cell of origin and mutational profile (less FL –type, *NOTCH2*)
 - 30% may be “pseudo double” hit (*but part of DLBCL by the WHO*)
- **High-grade B-cell lymphoma, NOS**

Large B-cell lymphoma with IRF4 Translocation
Translocation partners include IGH, IGL, and undetermined
Follicular or Diffuse
Waldeyer's Ring in 80%; Median age 12; M=F

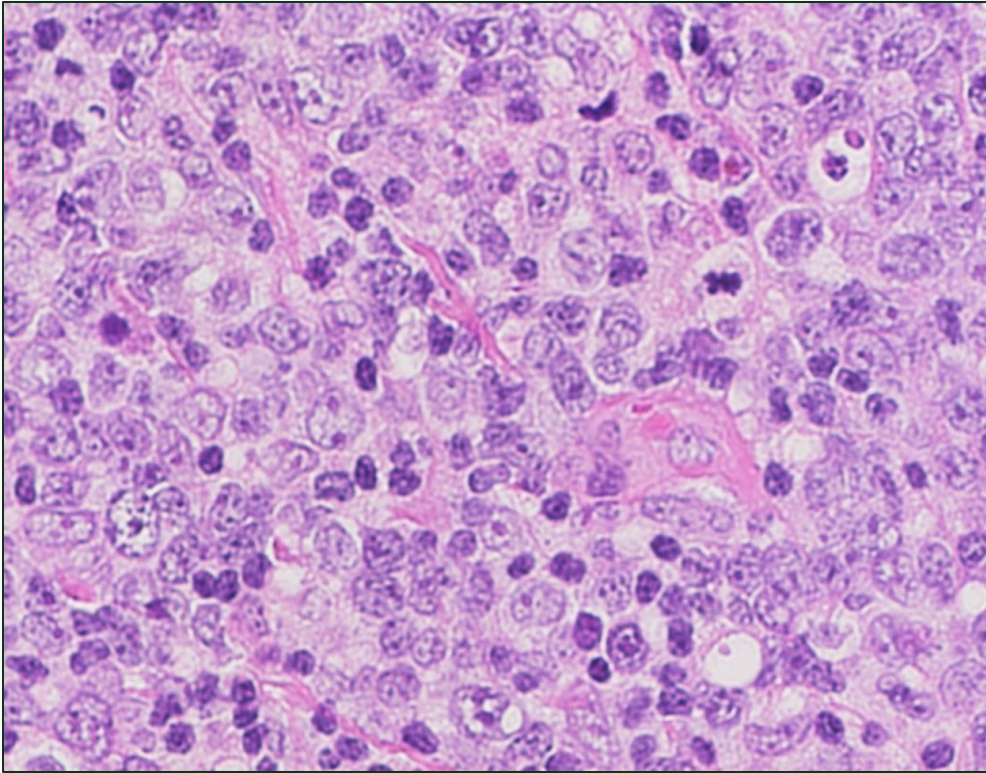




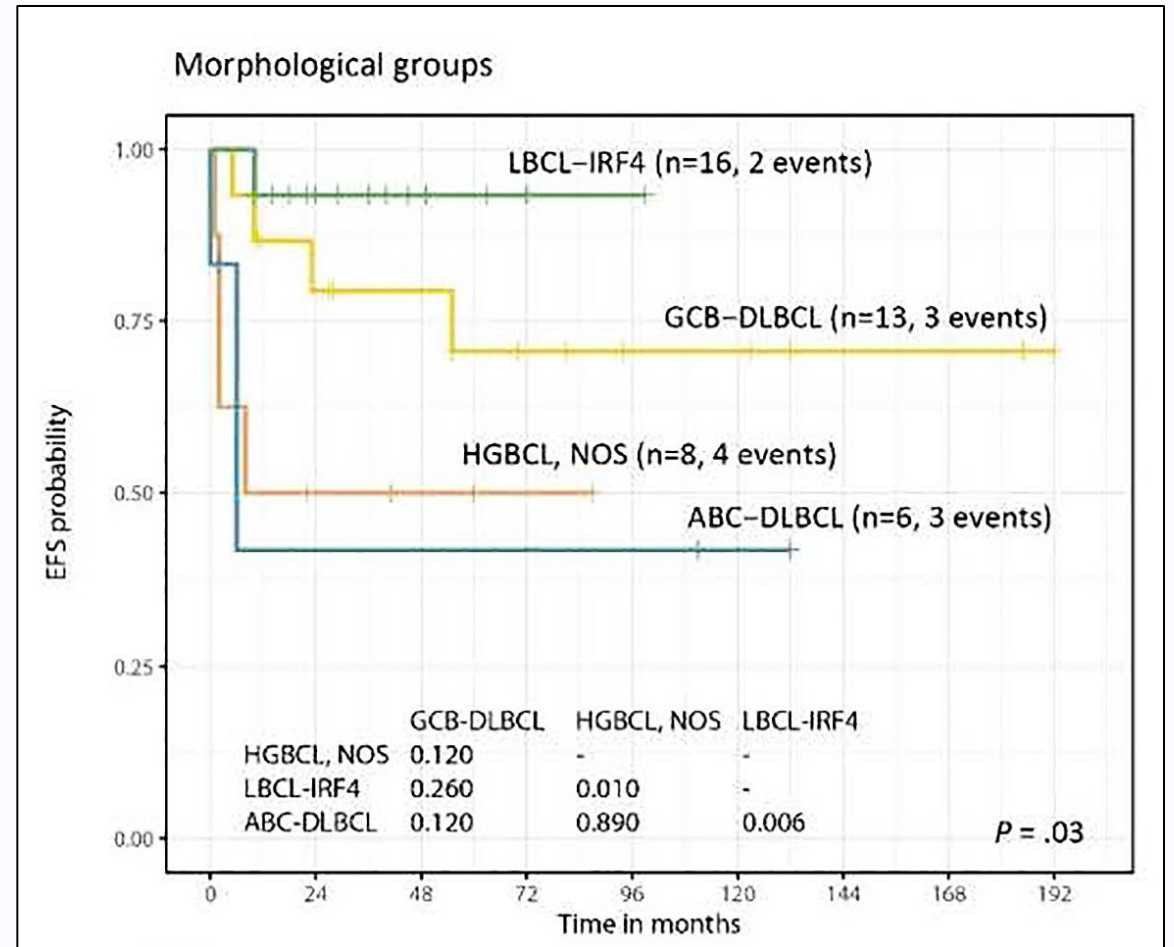
Atypical GCB phenotype, IRF4/MUM1+



IRF4 Large B-cell



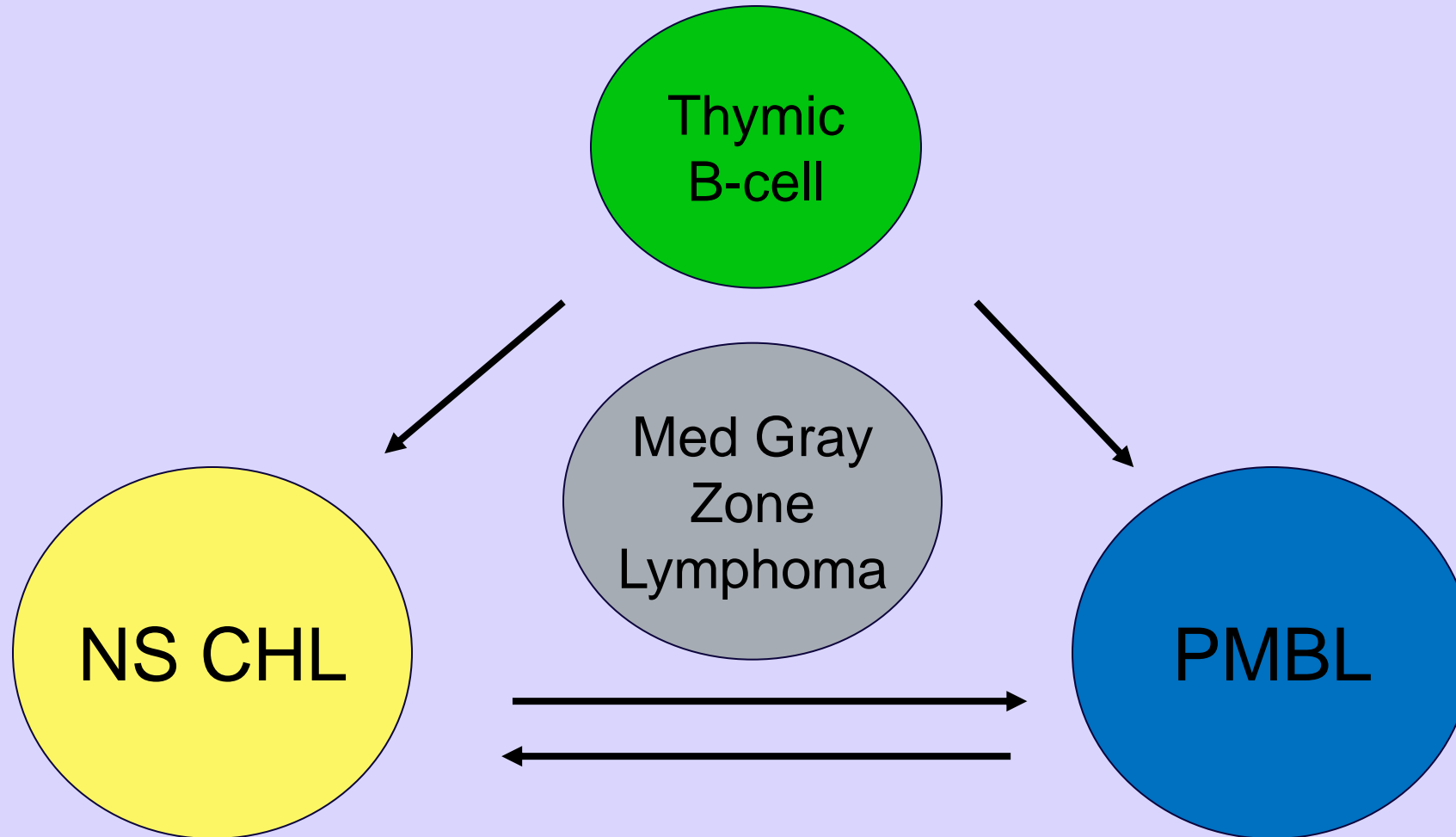
Grouped with follicular lymphoma in ICC based on GEP, architectural features, and good prognosis



Ramis-Zaldivar et al. Blood (2020)
Survival of IRF4 LBCL compared with GCB-DLBCL, ABC-DLBCL, and HGBCL in children and young adults < 25 yrs.

Mediastinal Gray Zone Lymphoma

Arises from a thymic B-cell, related to both NSCHL & PMBL



MGZL

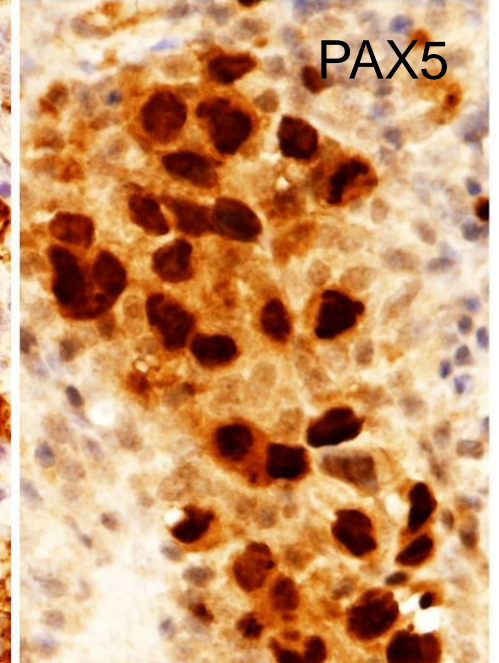
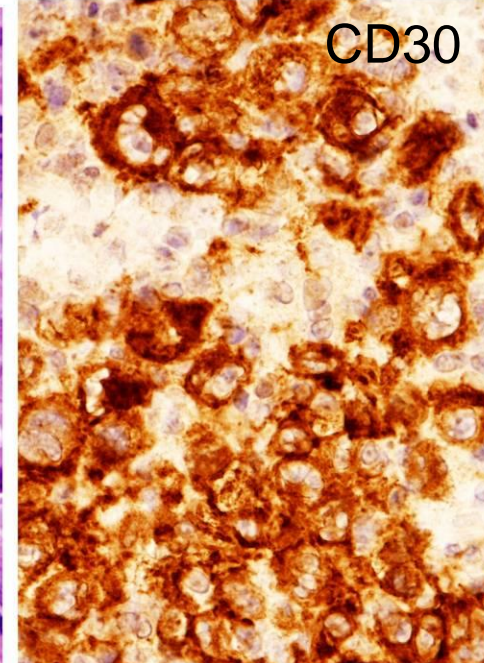
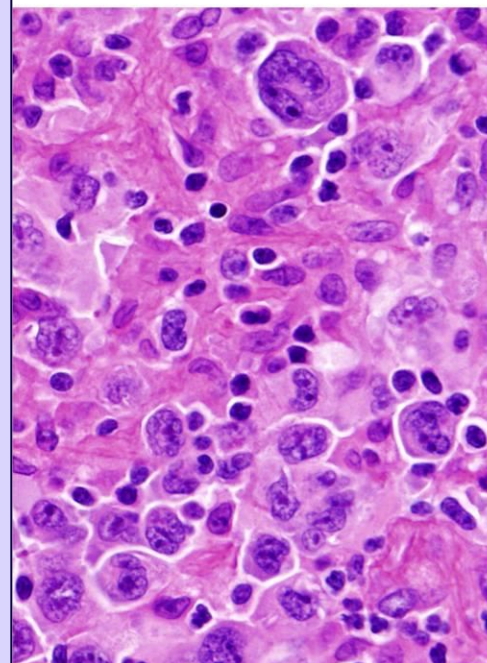
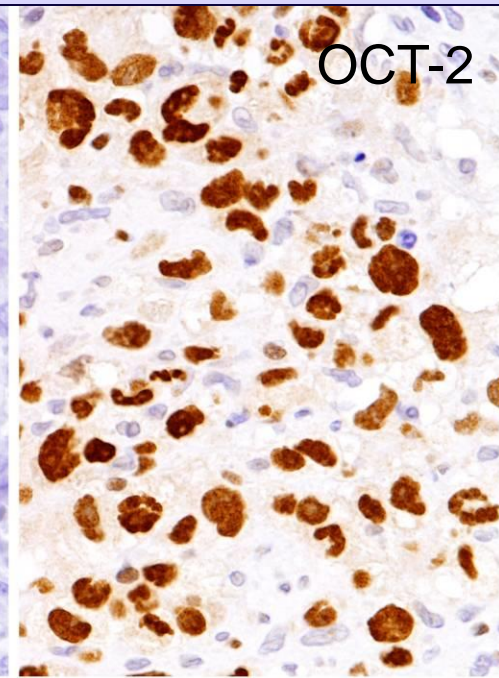
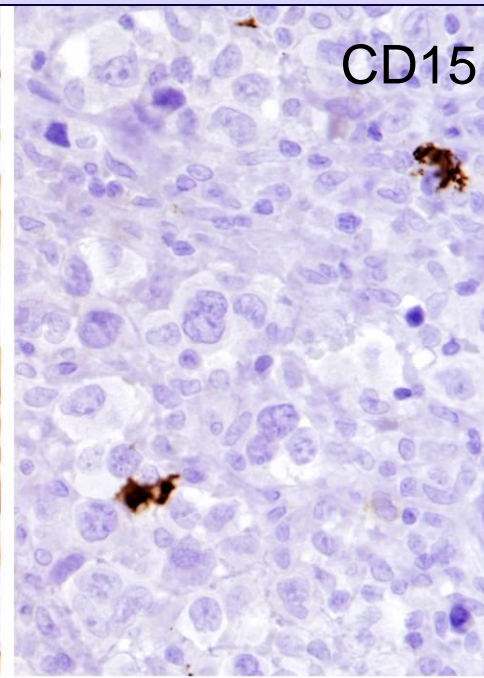
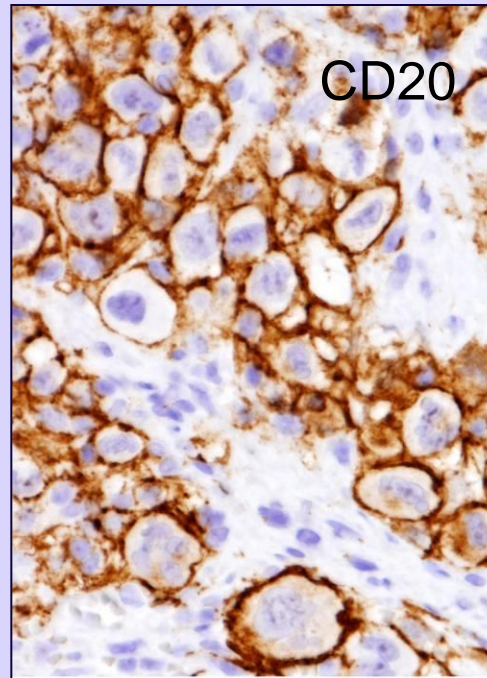
CHL-like
Morphology

Background
inflammatory
cells

Sheeting out
of HRS like
cells

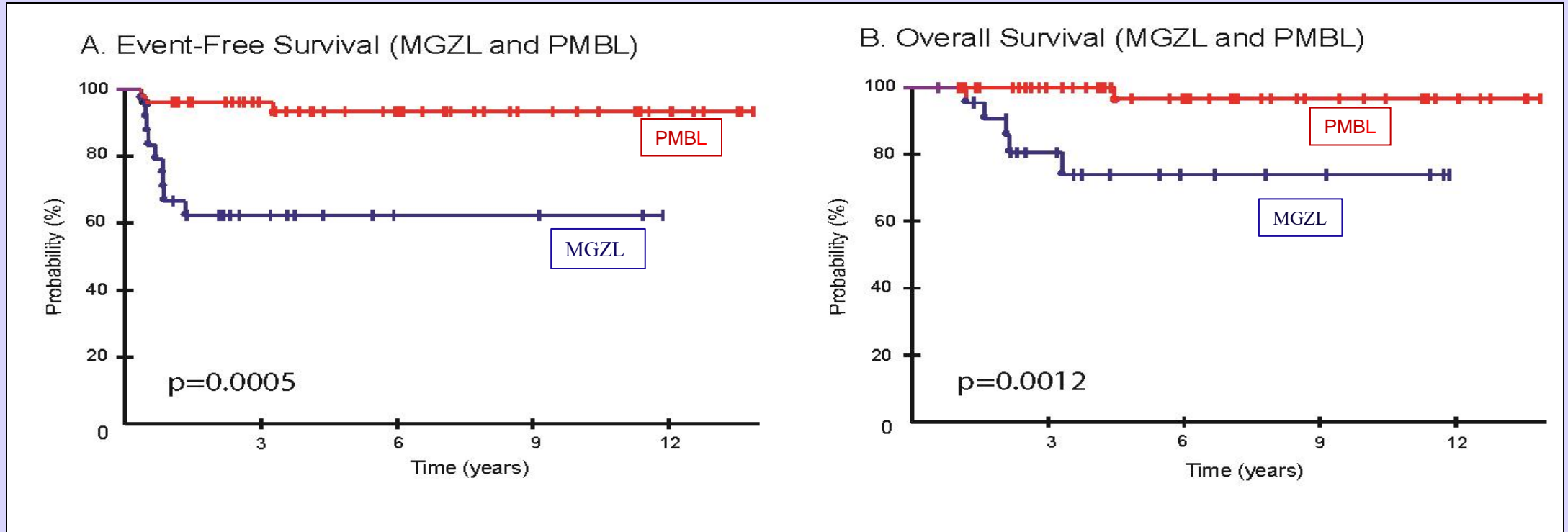
B-cell
program
retained

Most common
pattern
(2/3 of cases)



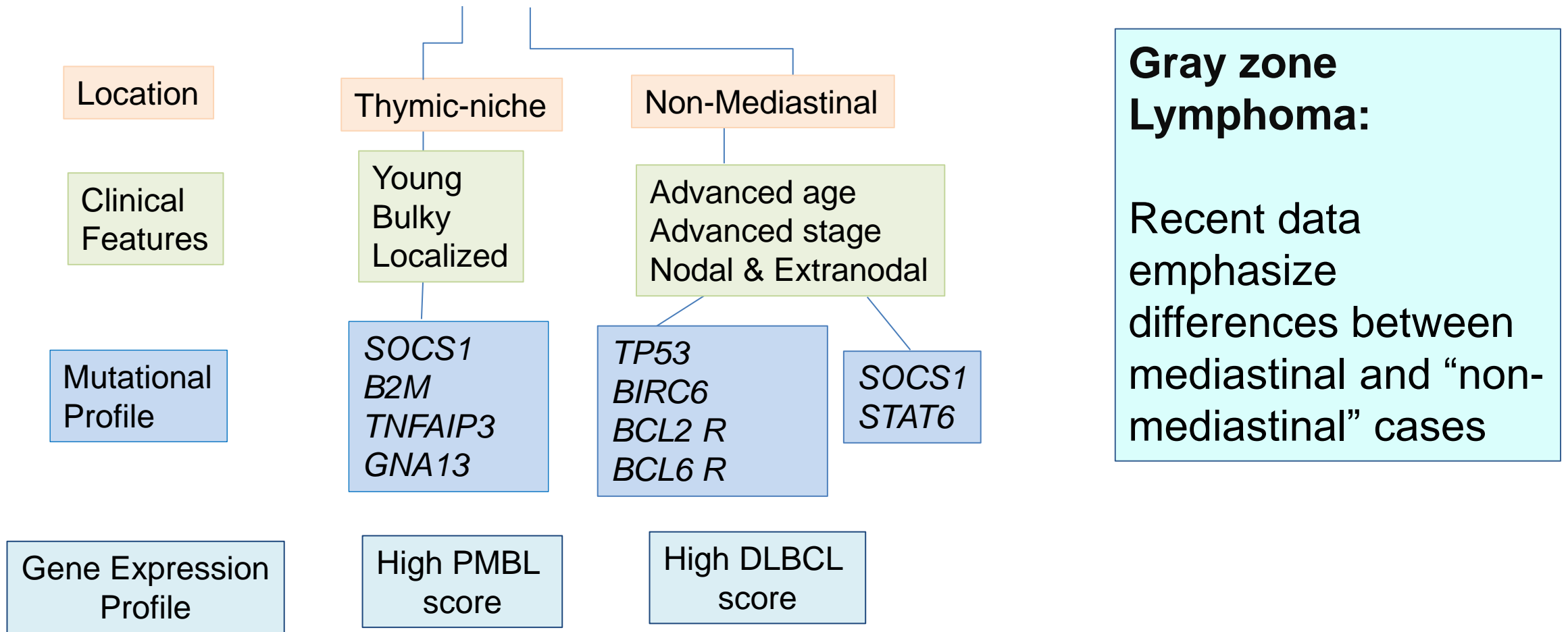
DA-EPOCH R therapy of Mediastinal Gray Zone Lymphoma & comparison with PMBL

Wilson et al. Blood 2014



24 pts with MGZL -- M:F 15:9
Median Age 33 (14-56) ; Bulky mediastinal disease in 50%

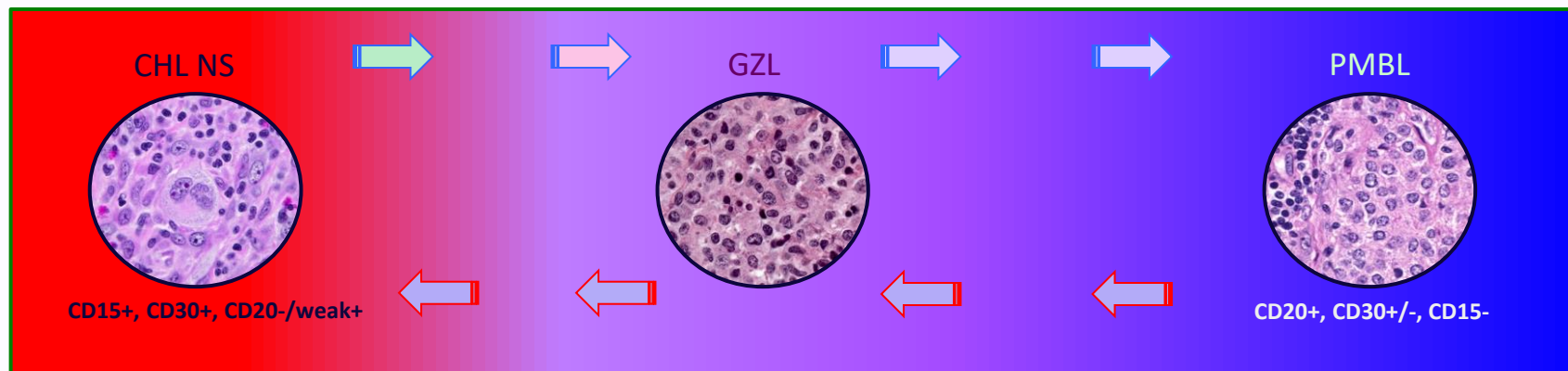
GRAY ZONE LYMPHOMA



Campo E, Jaffe ES. Taking Grey Zone Lymphomas out of the Shadows *Blood*, 2021
Sarkozy C, et al. Mutational Landscape of Grey Zone Lymphoma. *Blood*, 2021

Mediastinal Gray Zone lymphomas (GZL)

- Both ICC & WHO define MGZL as a distinct entity related to PMBL & CHL, nodular sclerosis
- Non mediastinal cases differ in their clinical and genetic features, and are considered a variant of DLBCL
- EBV-positivity in MGZL is rarely seen, and strongly favors a diagnosis of EBV+ DLBCL, NOS
- EBV+ DLBCL with HRS-like cells should not be diagnosed as GZL

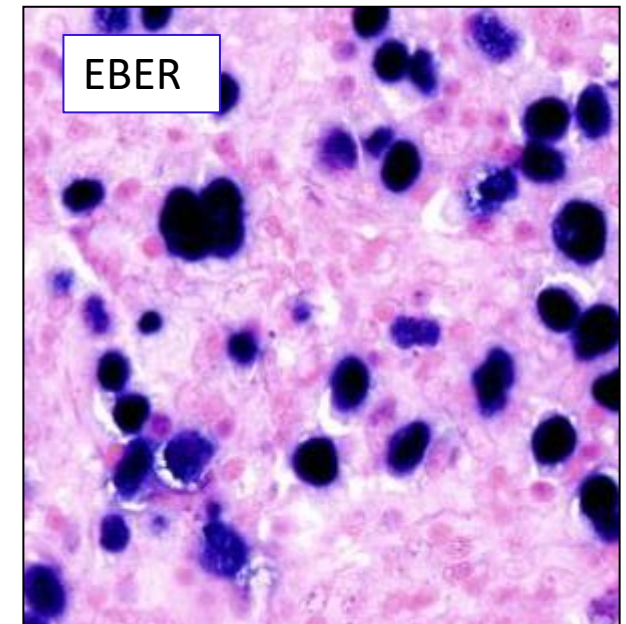
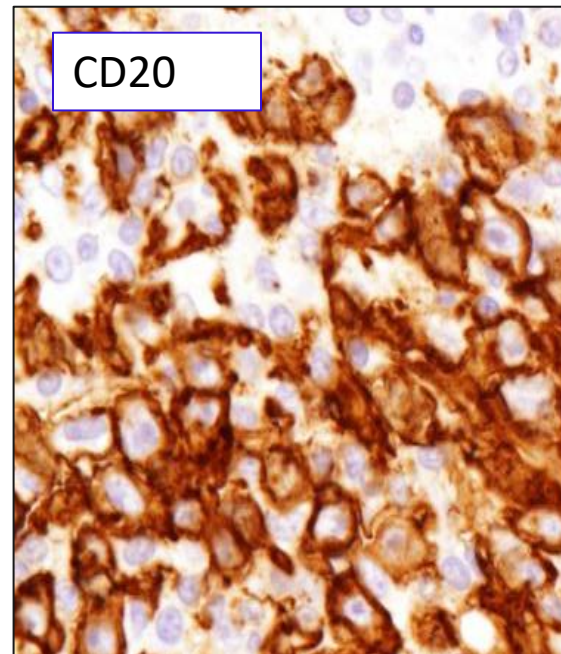
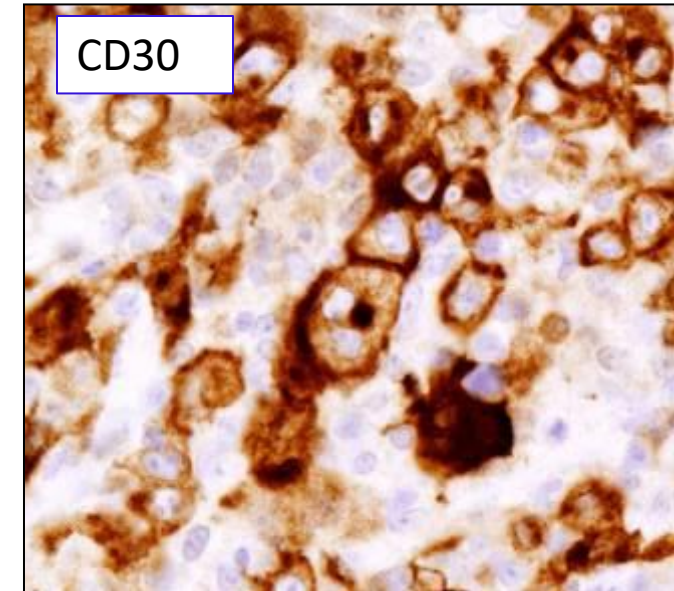
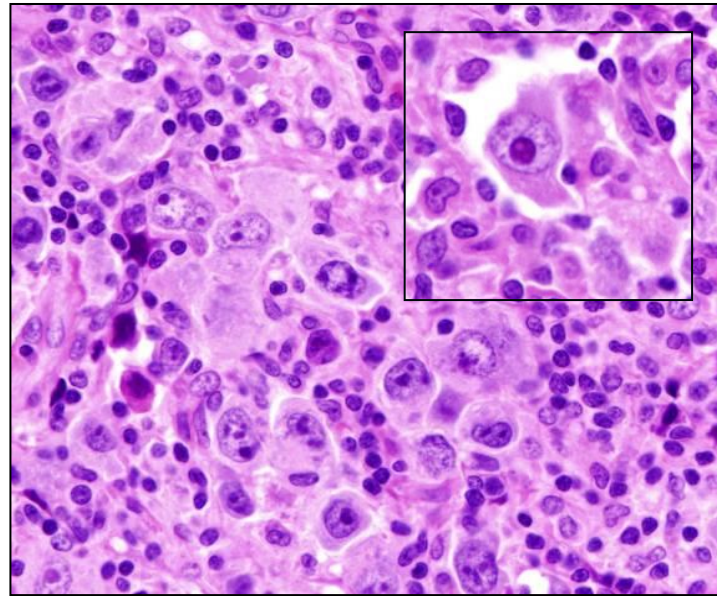


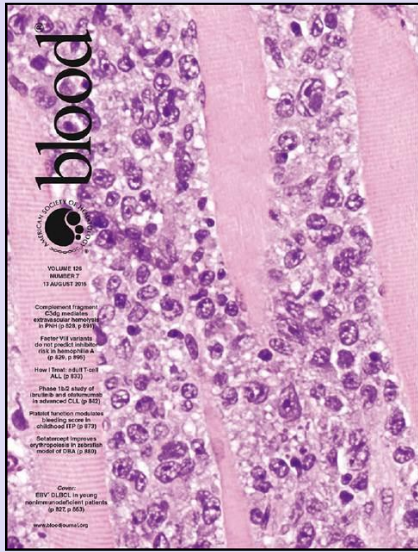
EBV-DLBCL

Non-Mediastinal
Extranodal & Nodal

- Advanced age – immune senescence
- Iatrogenic or congenital immune deficiency
- Aggressive clinical course

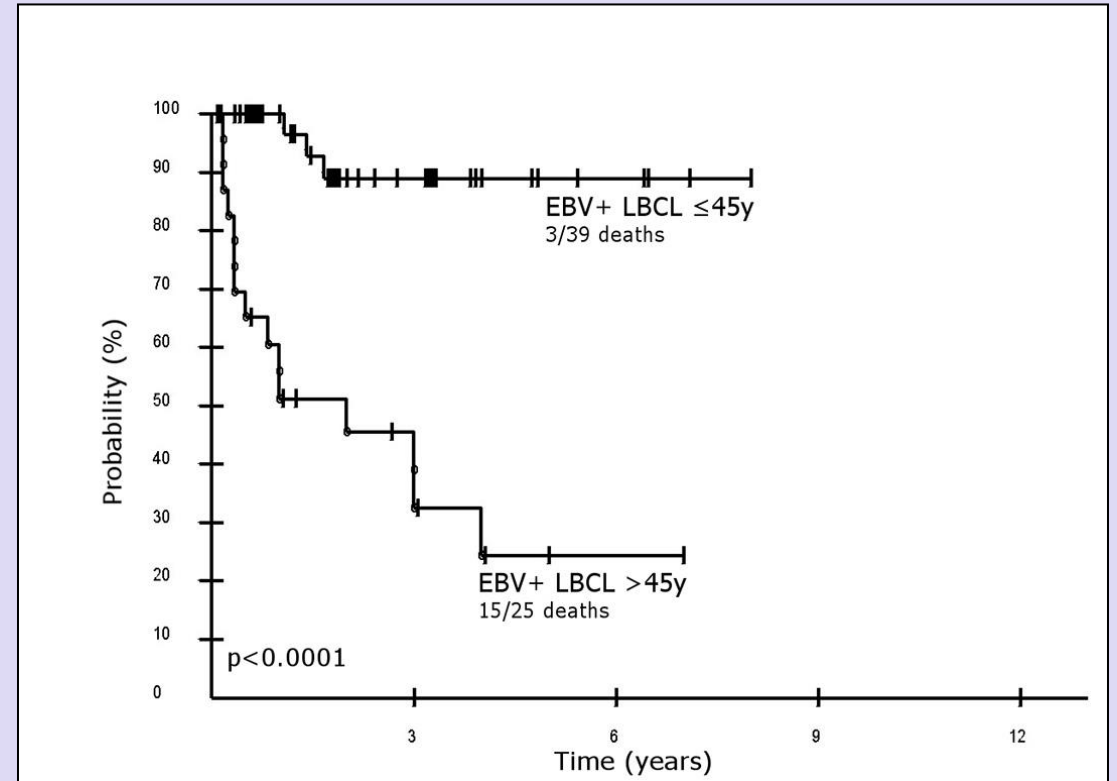
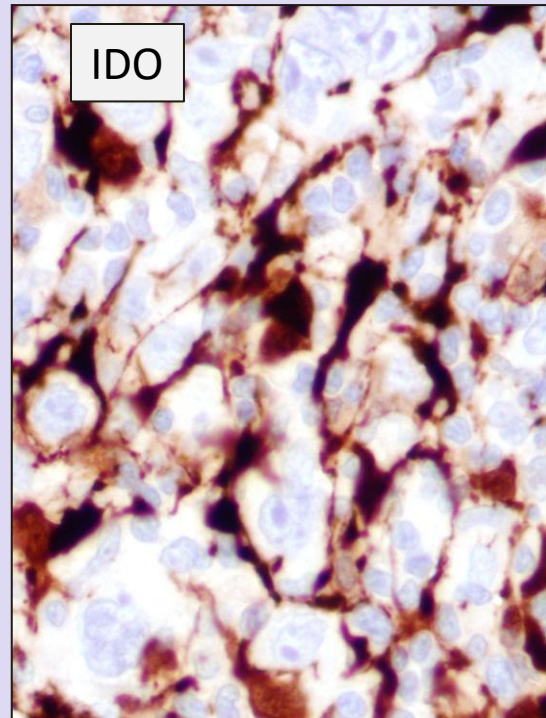
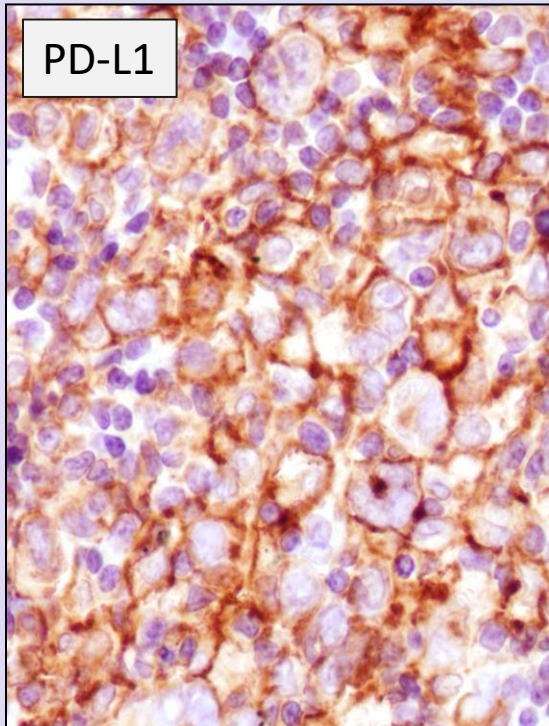
Low mutational burden, but
STAT3 mutations

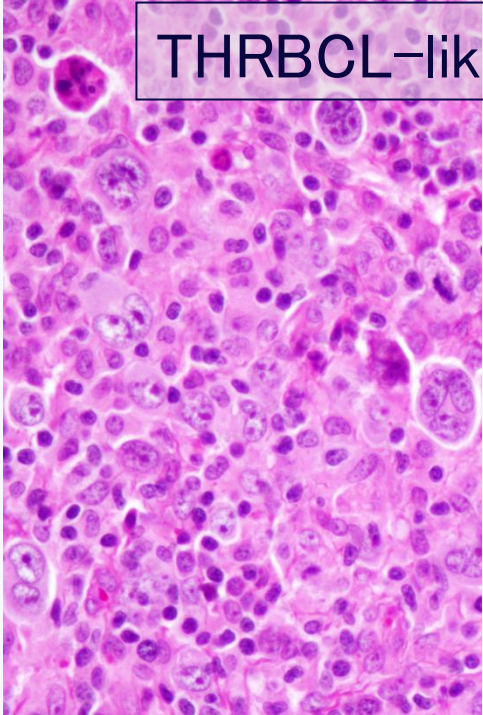
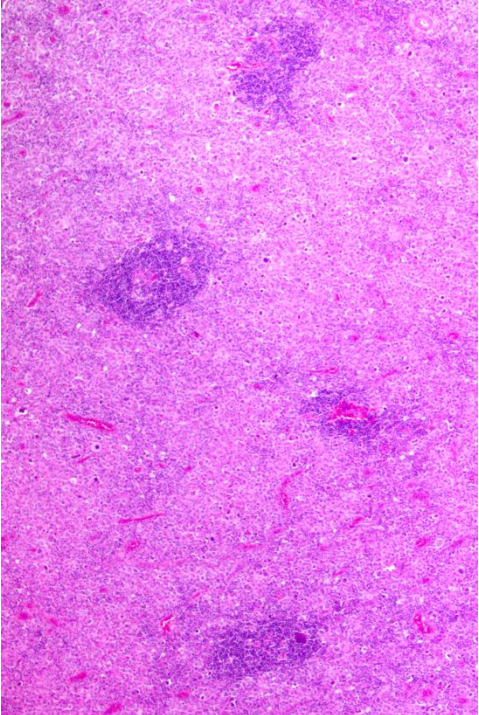




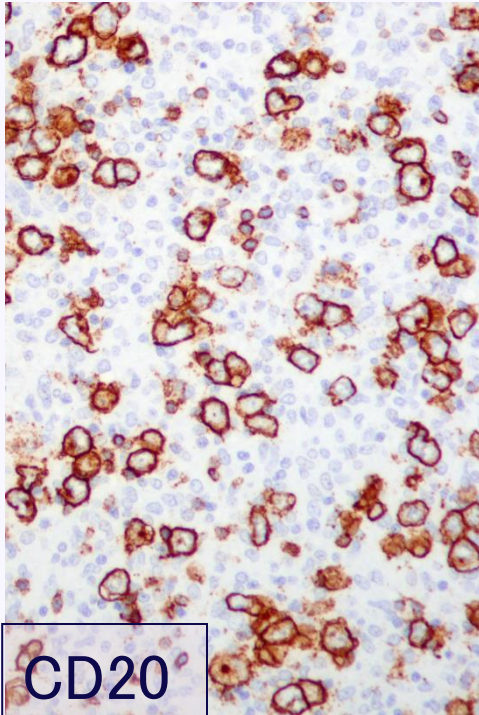
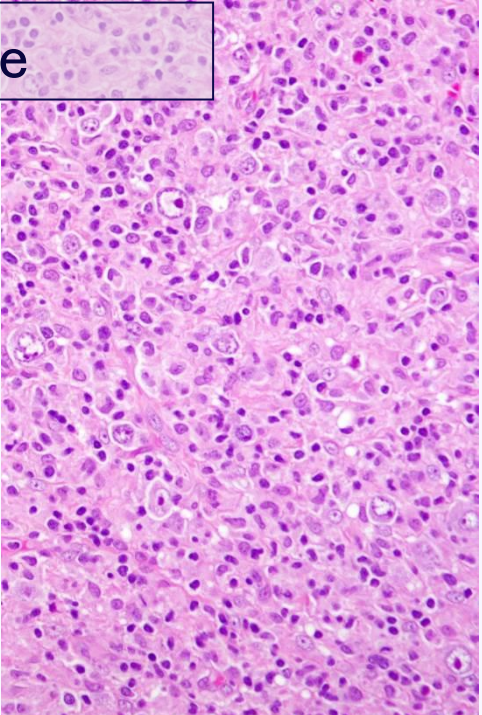
Nicolae et al. (2015)
Blood 126: 863-72

- EBV+ large B-cell lymphoma in patients under age 45
- Nodal disease in 90%
- Evidence of permissive immune environment
- Excellent prognosis – contrasts with elderly

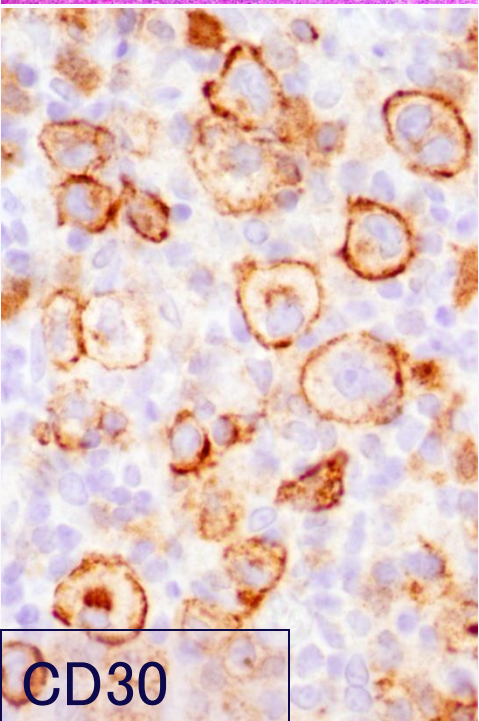




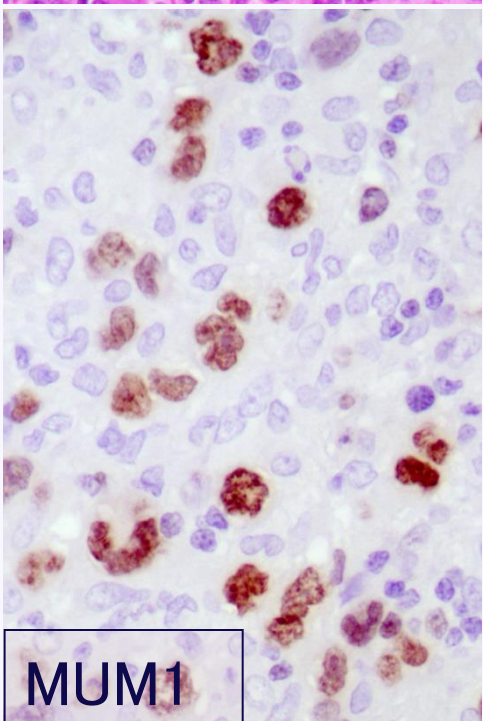
THRBCL-like



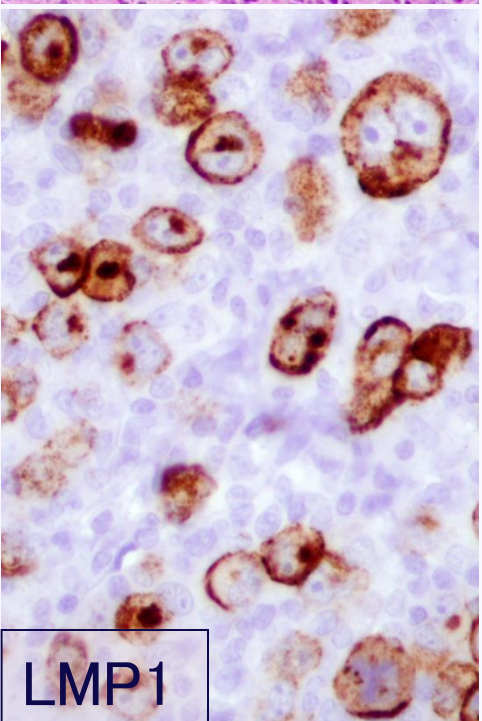
CD20



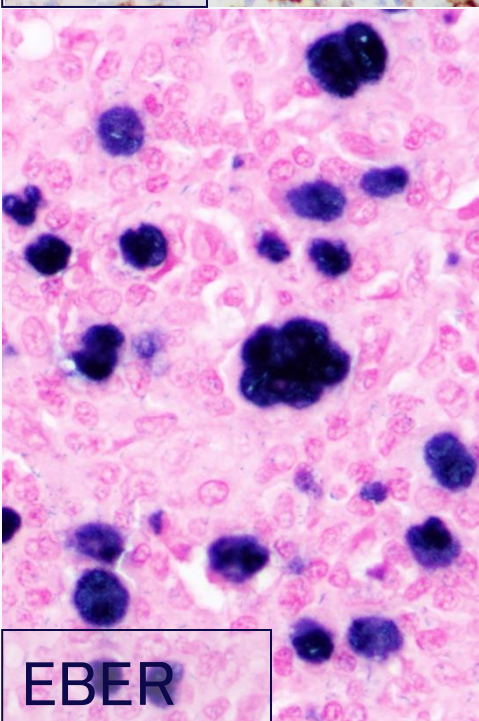
CD30



MUM1



LMP1



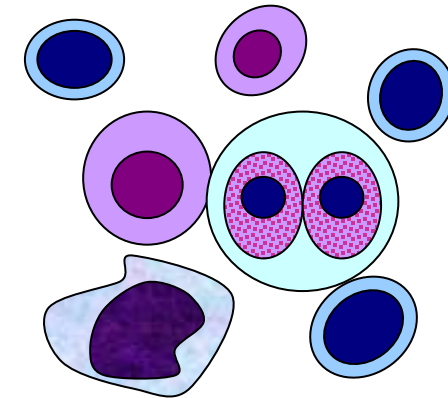
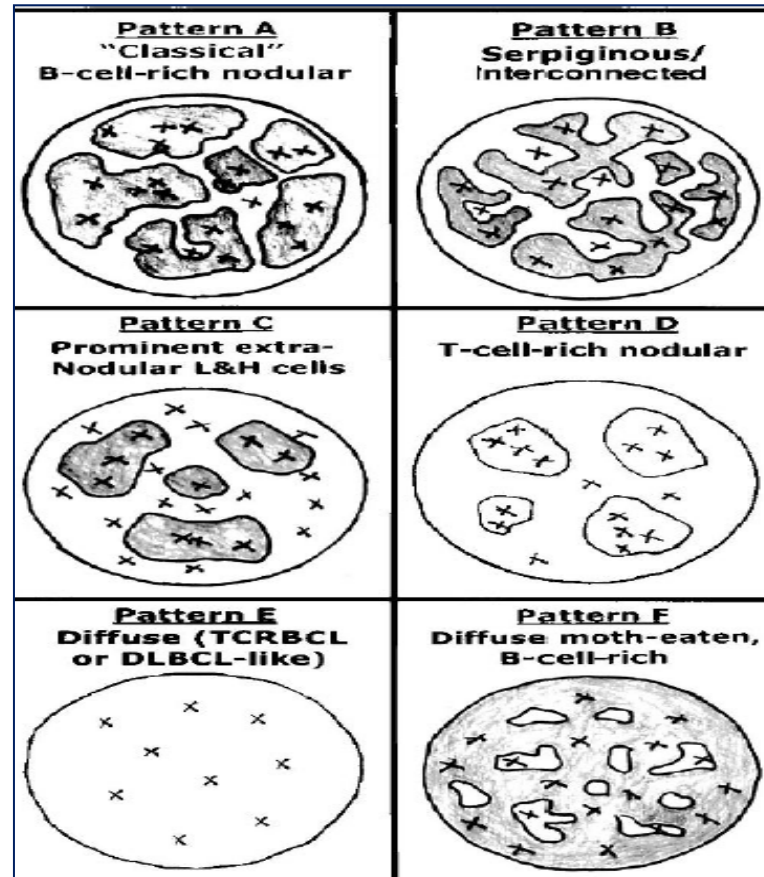
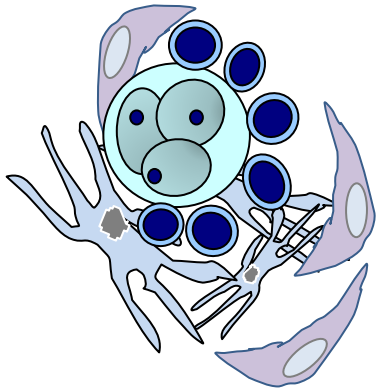
EBER

ICC Proposal: Hodgkin Lymphomas

~~Nodular lymphocyte predominant Hodgkin Lymphoma~~

Nodular Lymphocyte Predominant B-cell lymphoma

Related to THRLBCL – a continuum

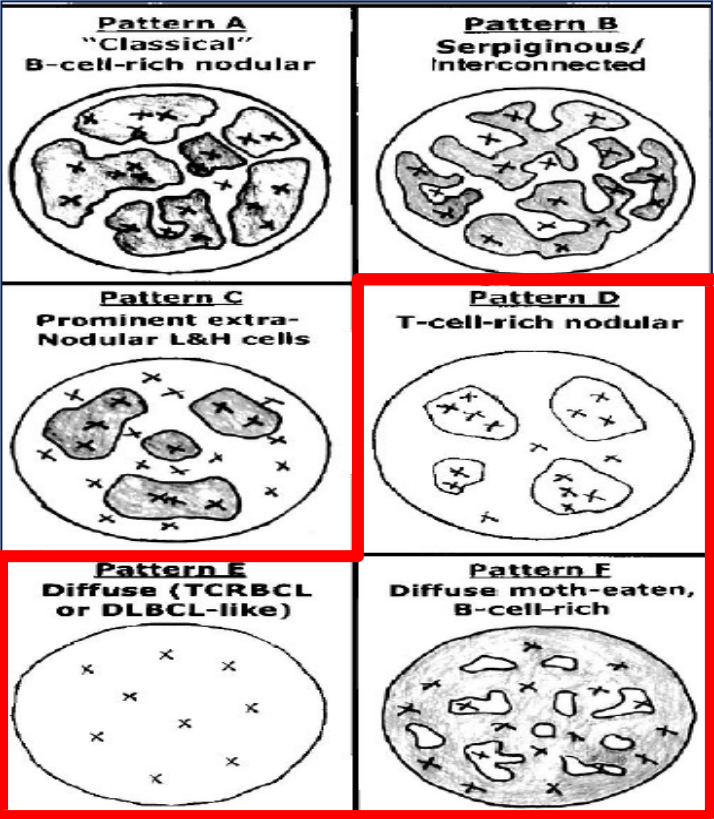
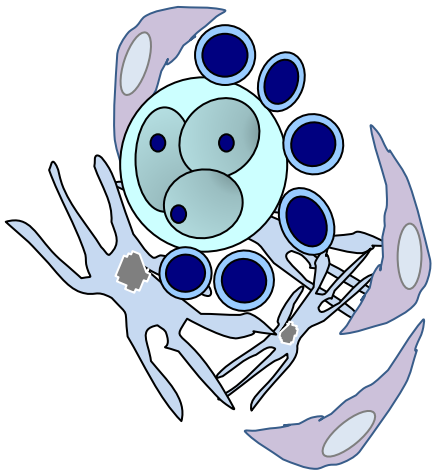


Classical Hodgkin Lymphoma

**Clinical management
distinct from CHL**

ICC Proposal: Hodgkin Lymphomas

~~Nodular lymphocyte predominant Hodgkin Lymphoma~~
Nodular Lymphocyte Predominant B-cell lymphoma
Related to THRLBCL – a continuum



Grade 1: Fan A, B, C

Nodular growth
Relatively rich in B-cells
Often low stage

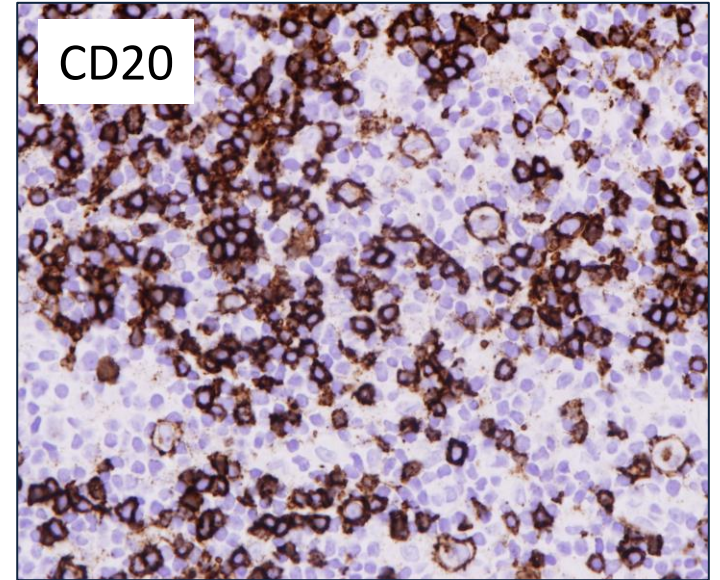
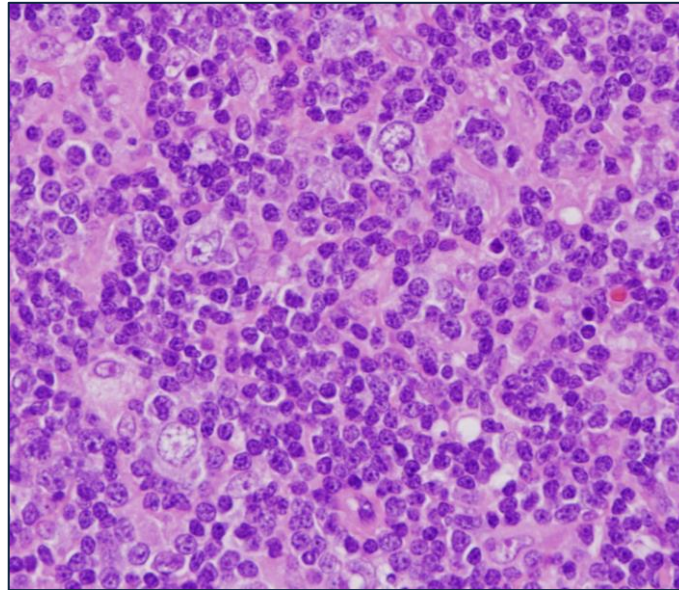


Grade 2: Fan D, E, F

Diffuse component common
Increased T-cells/ TCHRLBCL
Often advanced stage
Rx with DLBCL therapy

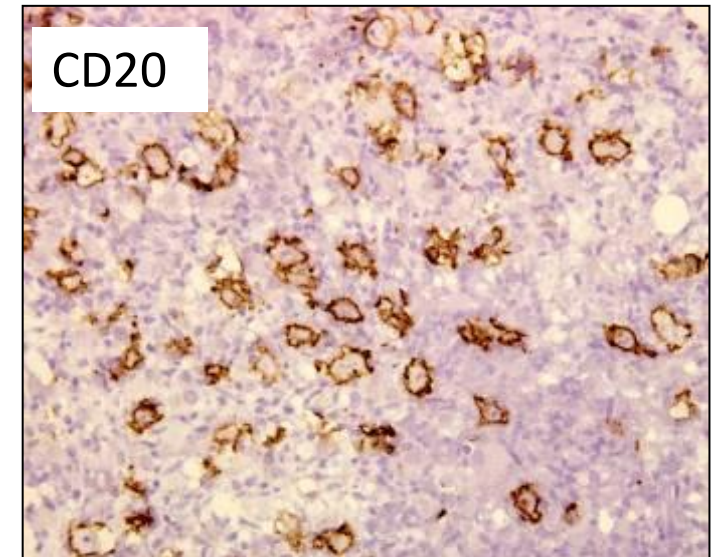
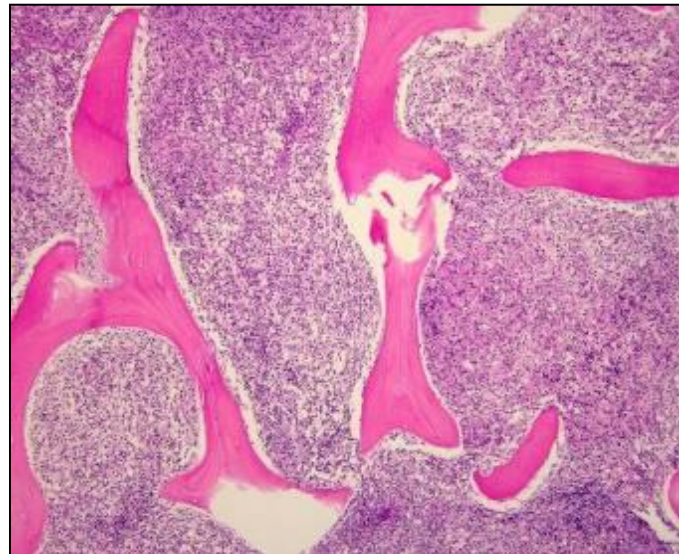
Nodular Lymphocyte
Predominant B-cell lymphoma

Axillary LN

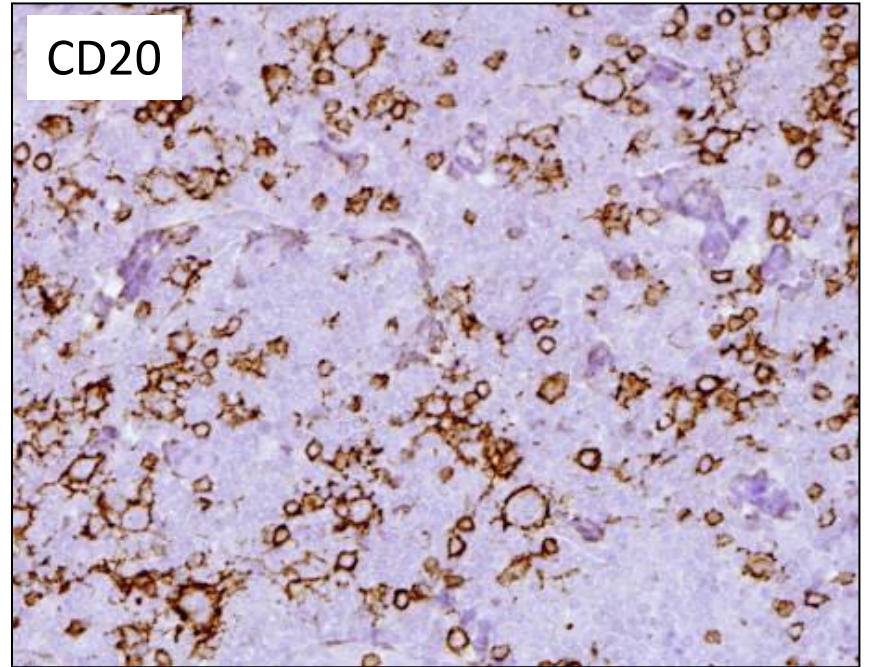
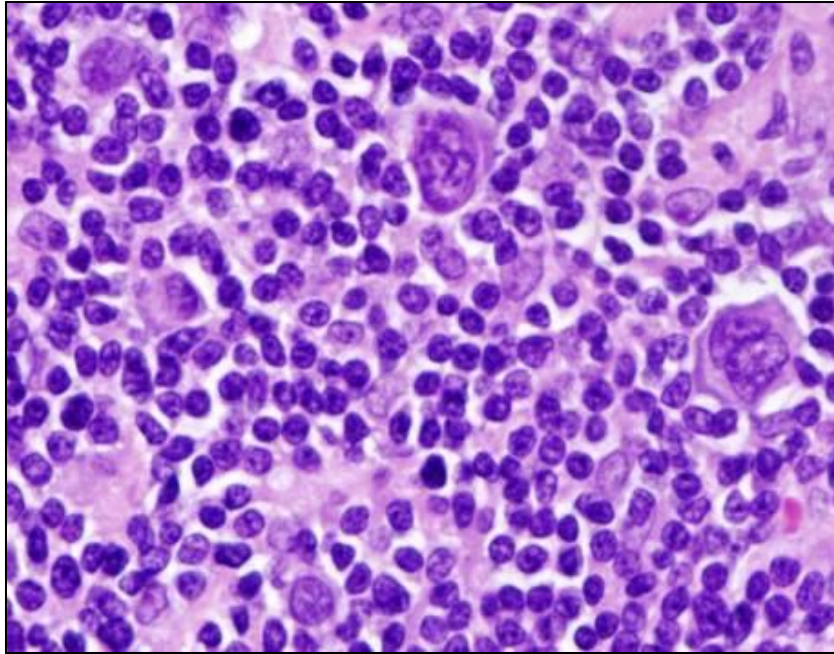


“T-cell/ histiocyte-rich
Large B-cell lymphoma”

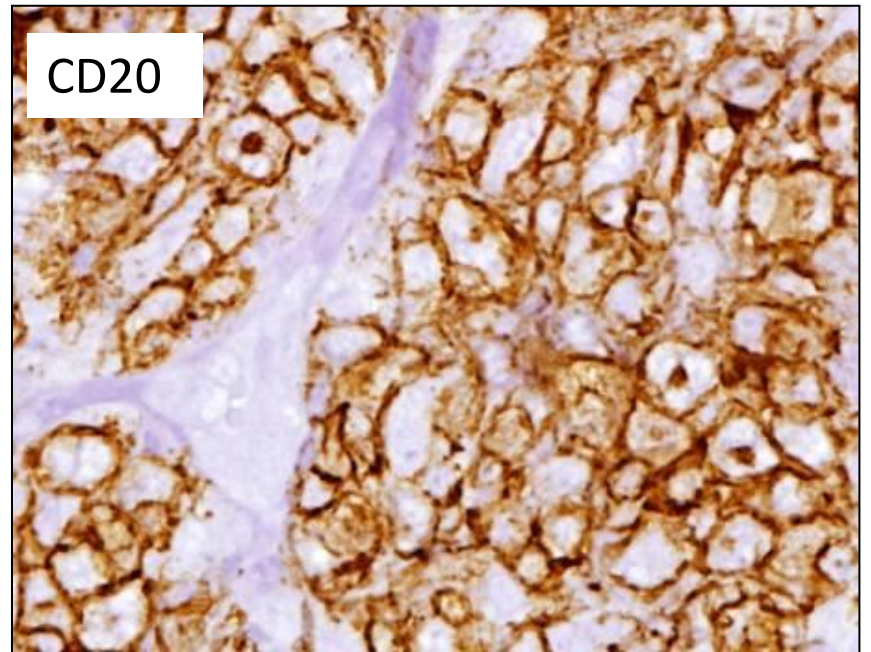
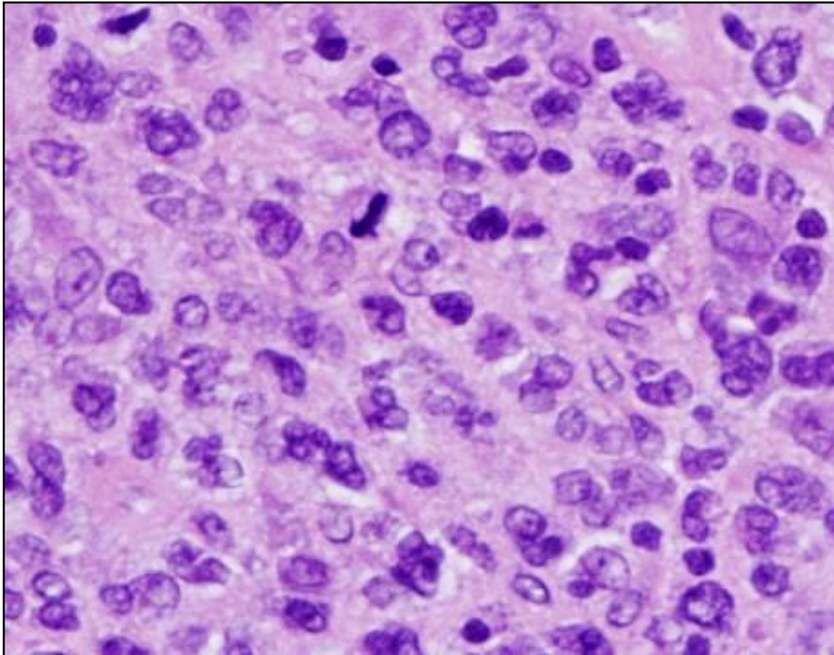
Bone marrow



NLP B-cell lymphoma



DLBCL

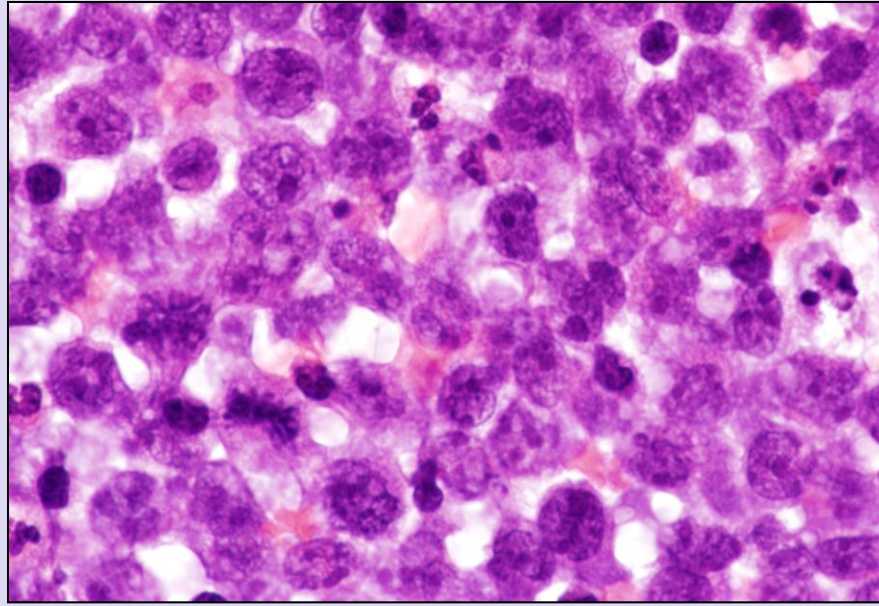
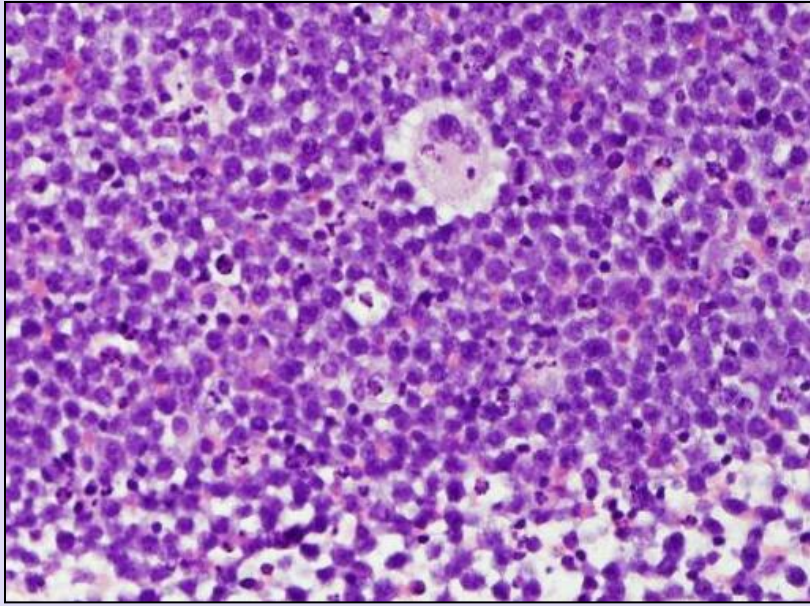


HHV-8 and EBV-negative primary effusion-based lymphoma

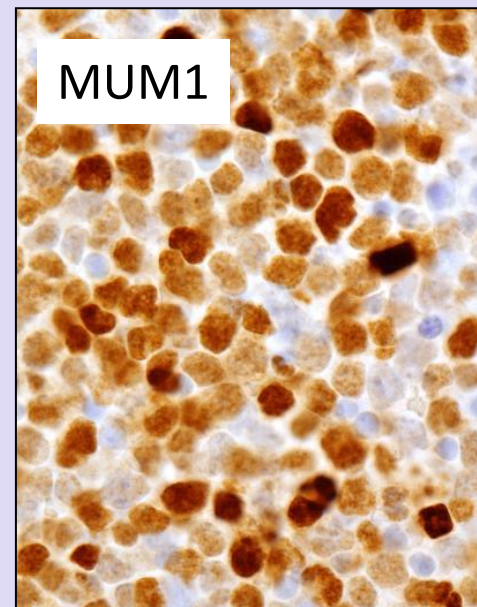
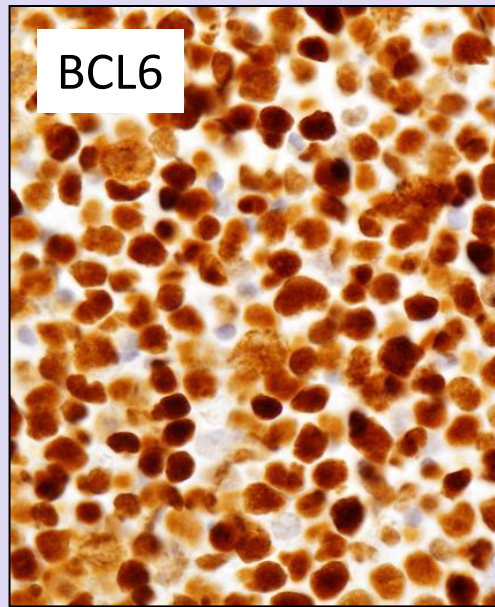
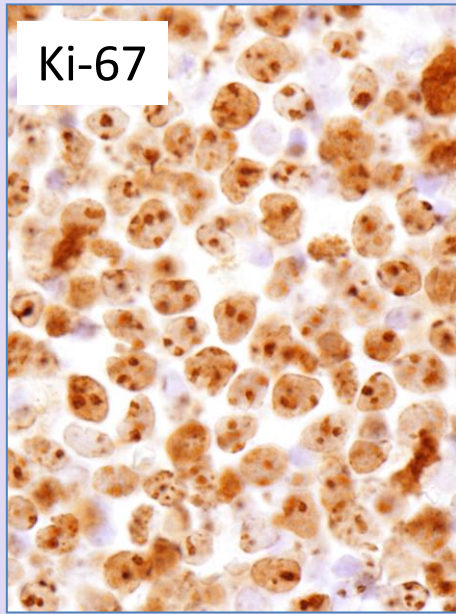
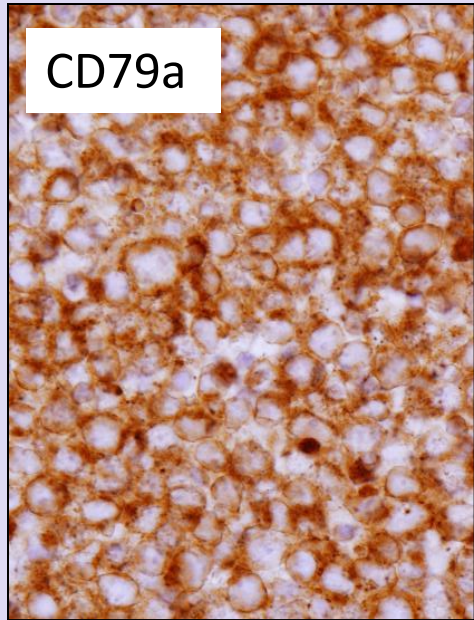
Alexanian et al. Am J Surg Pathol, 2013

Kaji et al. Blood Advances, 2020

- Elderly patients, Median age 70
 - More common in females (~40%) than PEL, Not associated with HIV
- Often associated with fluid overload, cardiac failure
- HCV associated in ~25%, with or without cirrhosis
- Good prognosis; superior to PEL
 - CR 70%; PR 82%
- EBV + large B-cell lymphomas can present as effusions, and are excluded from this category by the ICC
- WHO 5th accepts EBV+ but excluded by ICC as they are clinically more aggressive
- Added as a provisional entity by the ICC



- 88 y.o. female
- Isolated pleural effusion
- CR after R-CHOP with reduced dosing due to cardiac failure



Flow Chart for the Diagnosis of Aggressive B-cell Lymphomas (2023)

