Banner
University Medical Center
Tucson

HIGH GRADE B-CELL LYMPHOMA

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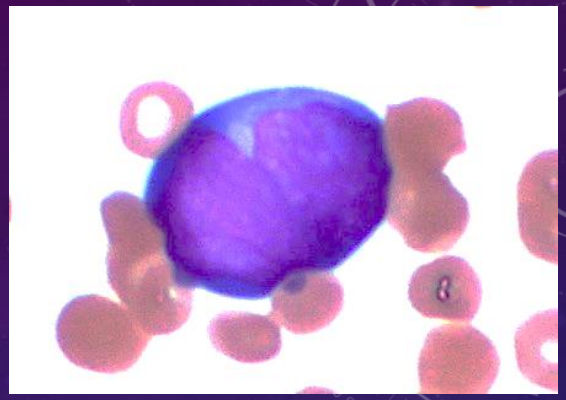
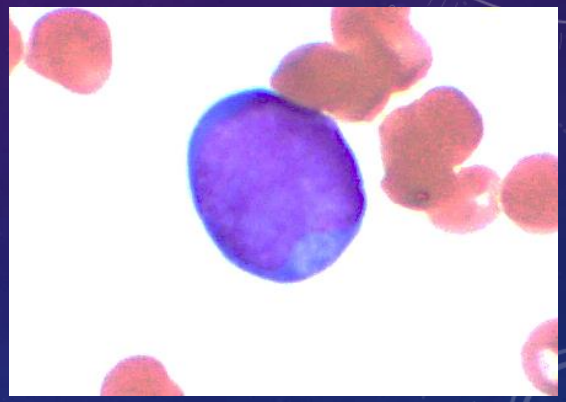
OUTLINE

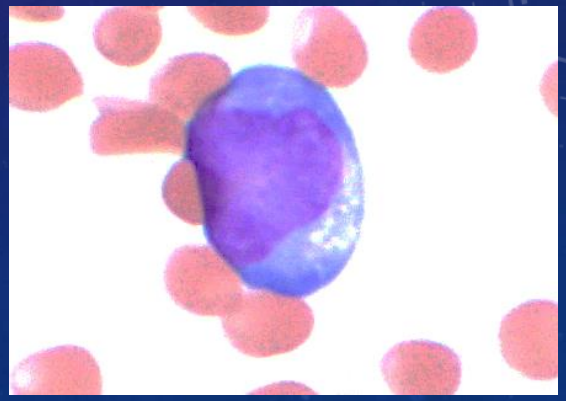
- High grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
  - Patient presentation
  - 2008/2016 WHO classification
  - Epidemiology
  - Clinical features
  - Microscopic features
  - Genetic profile
- High grade B-cell lymphoma, NOS
- HGBL treatment

PATIENT PRESENTATION

- 54 year-old-man with hypertension and diabetes mellitus
  - Night sweats
  - Weight loss
  - Bilateral hip pain
- Primary care physician discovered pancytopenia
  - Anemia
  - Leukopenia
  - Severe thrombocytopenia
- Sent to Emergency Room

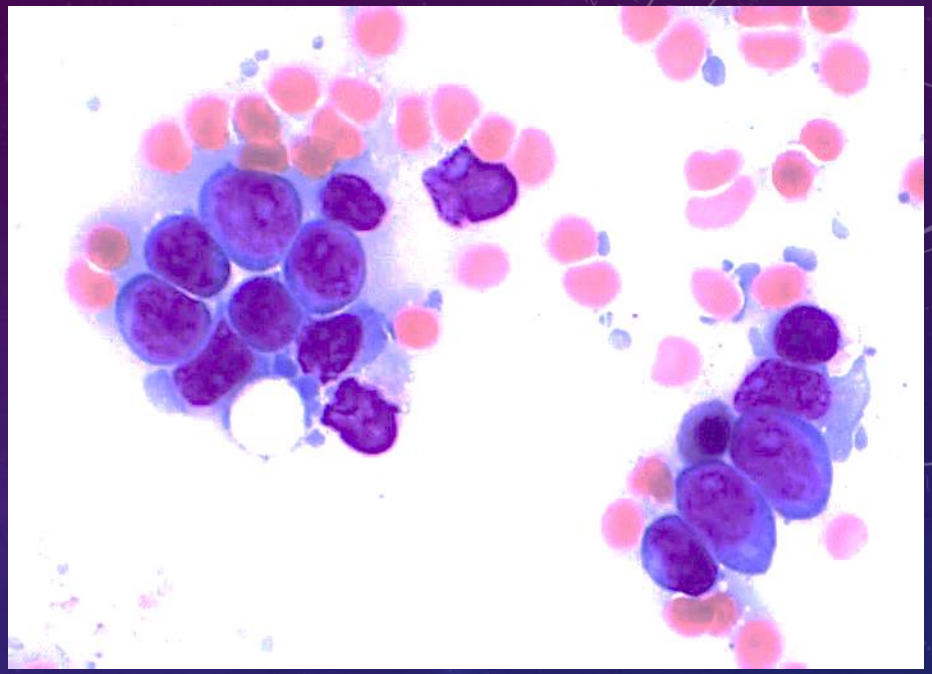


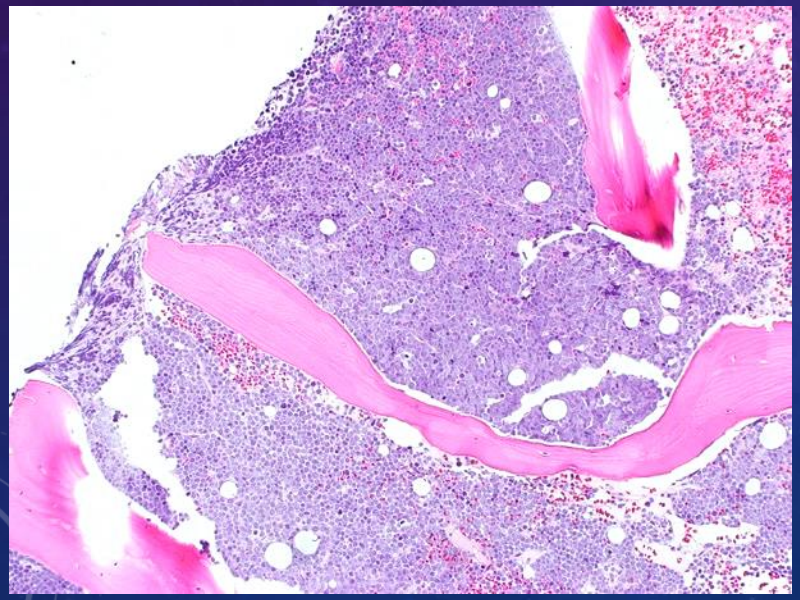


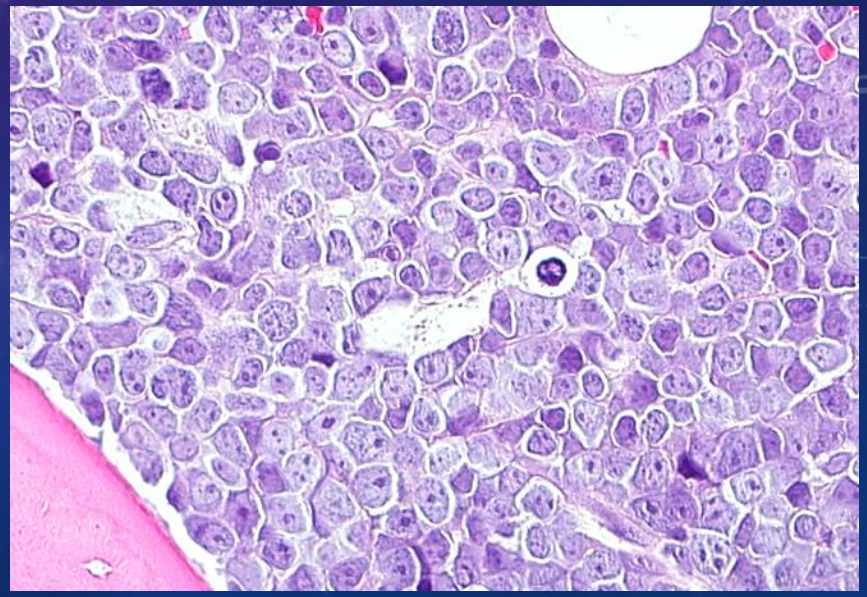


BONE MARROW BIOPSY

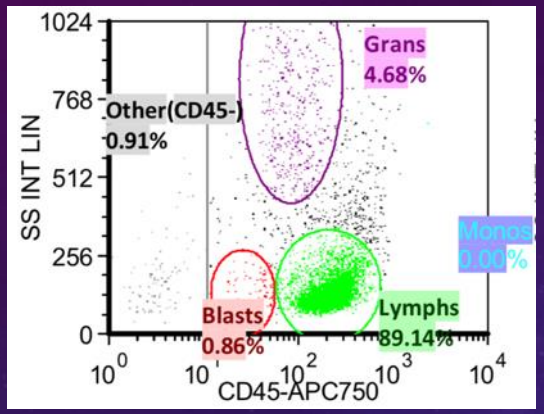
- 87% atypical cells
- 90% cellular

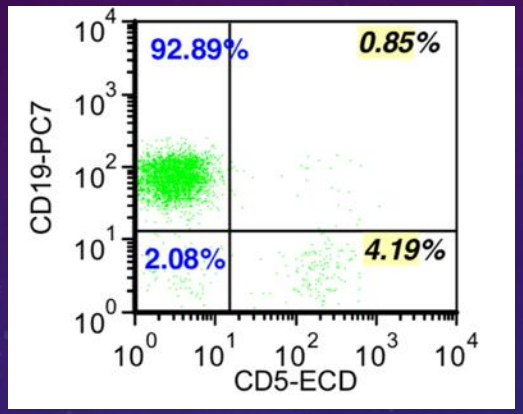


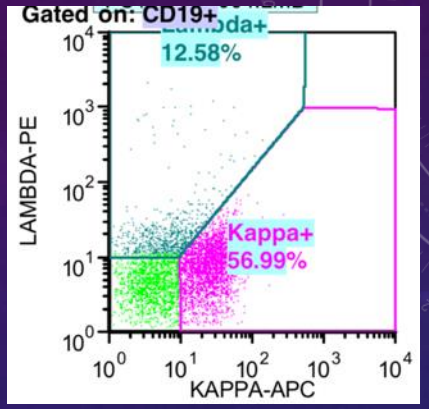


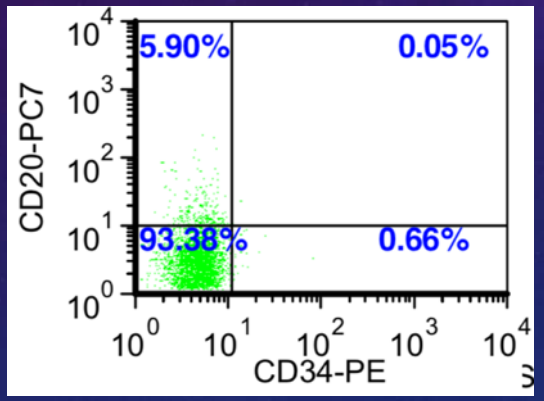


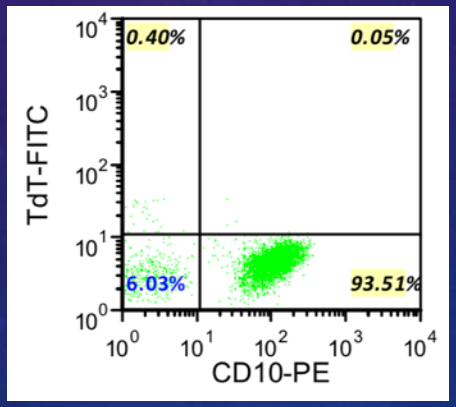
FLOW CYTOMETRY – MATURE B-CELL NEOPLASM, GERMINAL CENTER ORIGIN







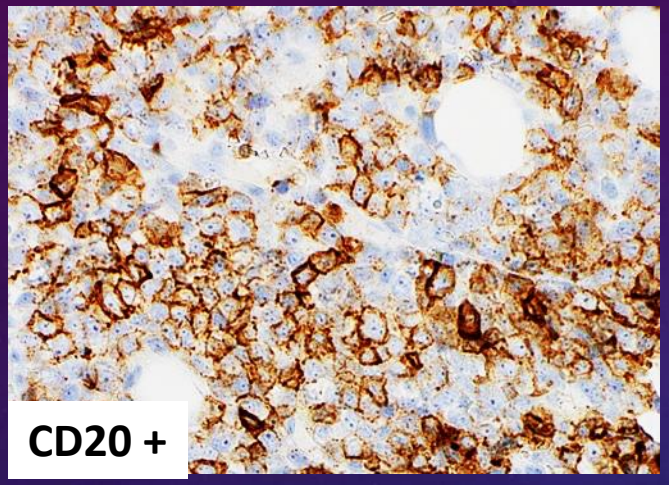


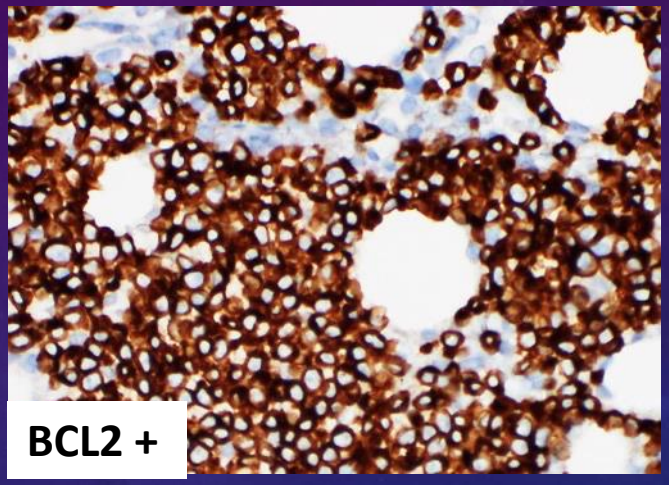


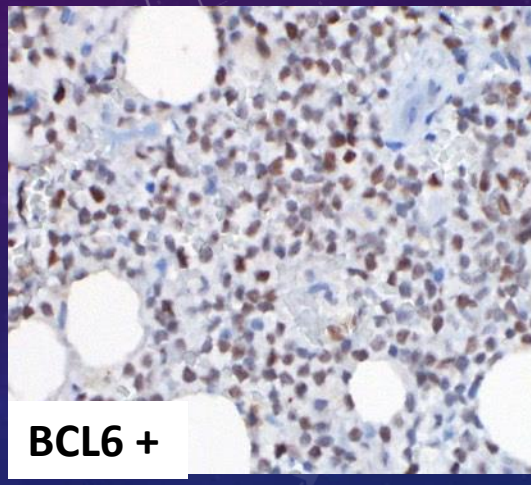
Side scatter	Cytoplasm complexity (granules)
CD45	Leukocyte common antigen
CD5	T-lymphocytes
CD19	All stages of B-lymphocytes
CD20	Mature B-lymphocytes
Kappa/Lambda light chains	Mature B-lymphocytes; shows clonality
CD34	Immature lymphoid/myeloid
CD10	Germinal center B cells
TdT	Immature lymphoid cells

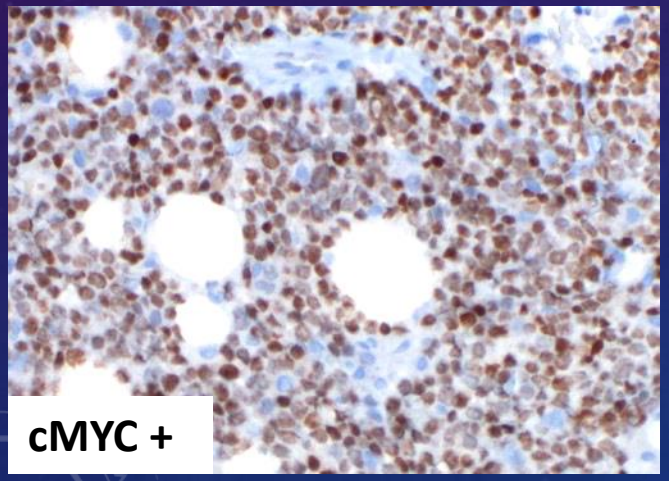
Mature (CD34- Tdt-), monoclonal (Kappa predominant) B-lymphocyte (CD19+, CD20+, CD22+) neoplasm, expressing CD10

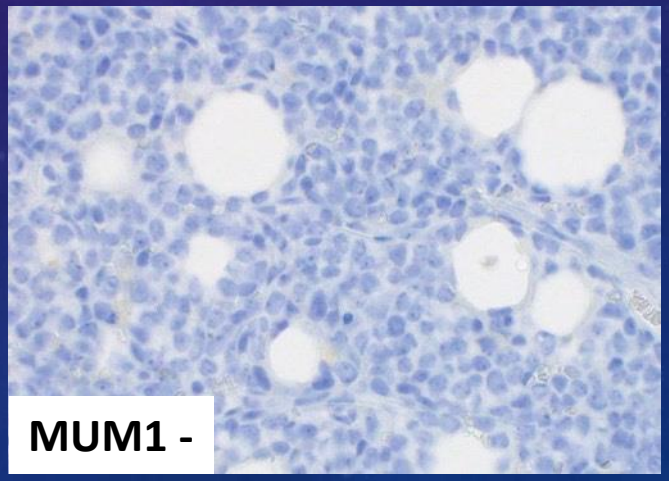
IMMUNOHISTOCHEMISTRY (IHC)

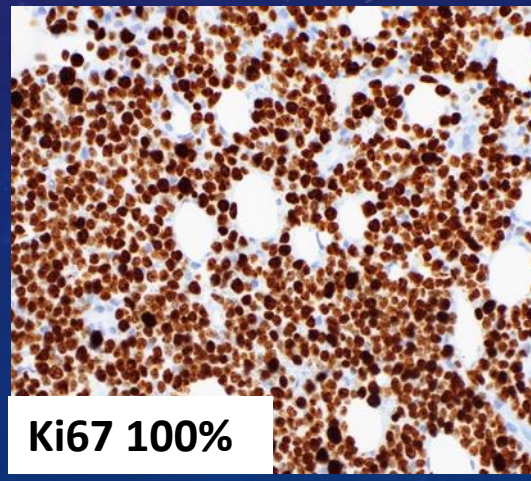




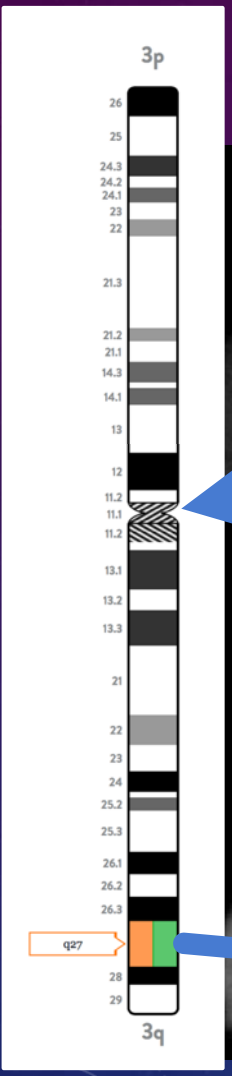


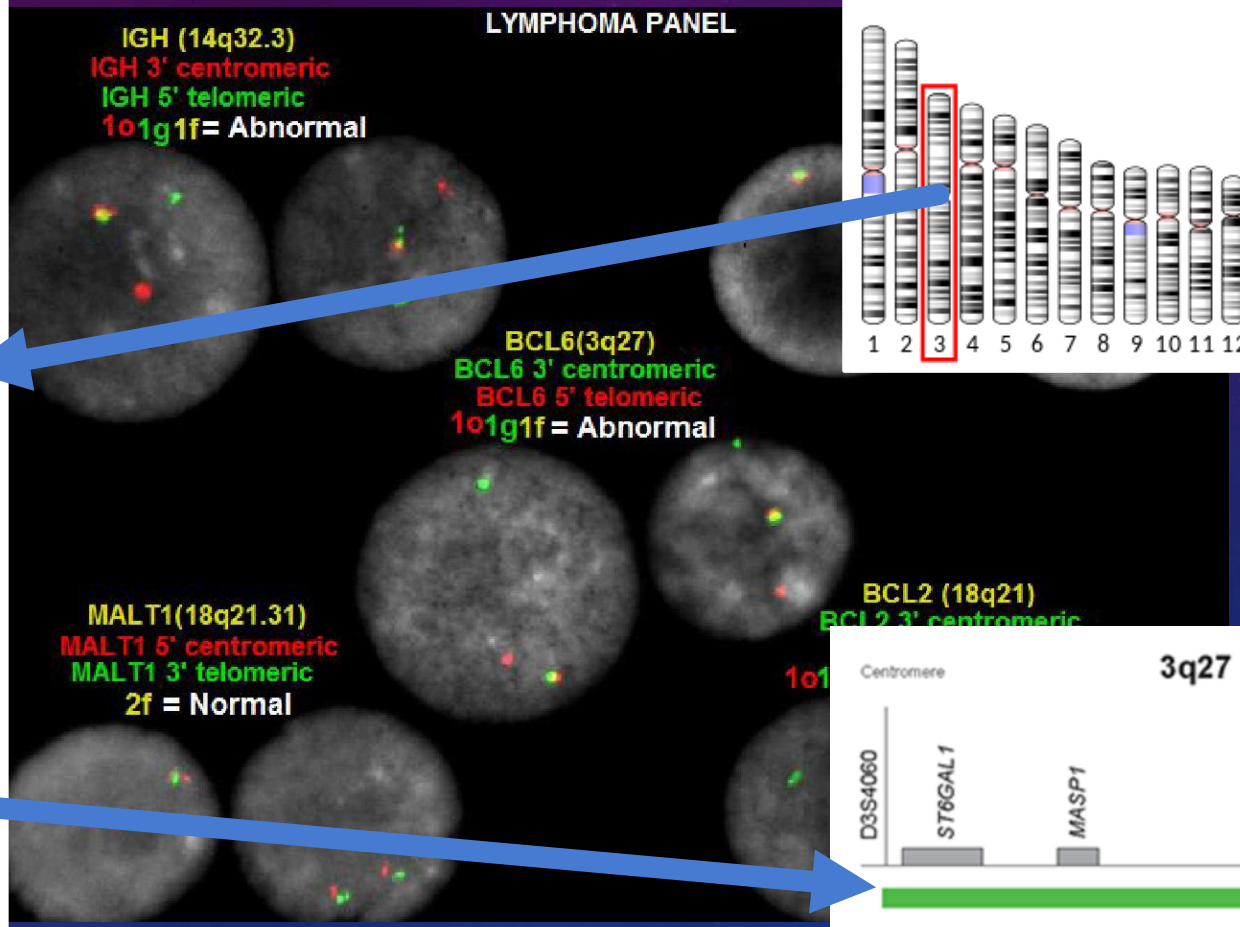


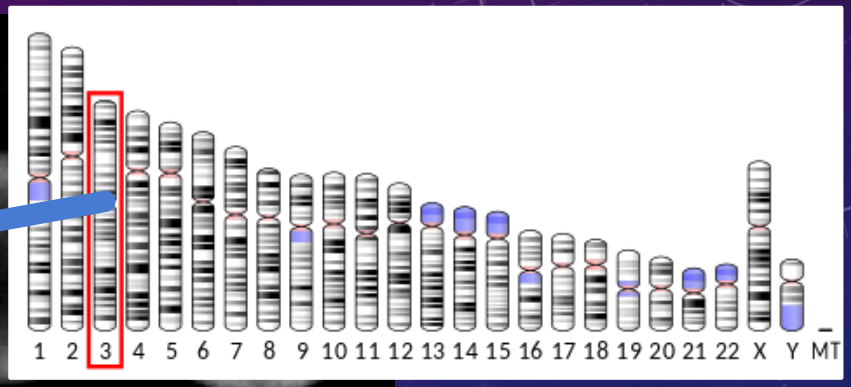


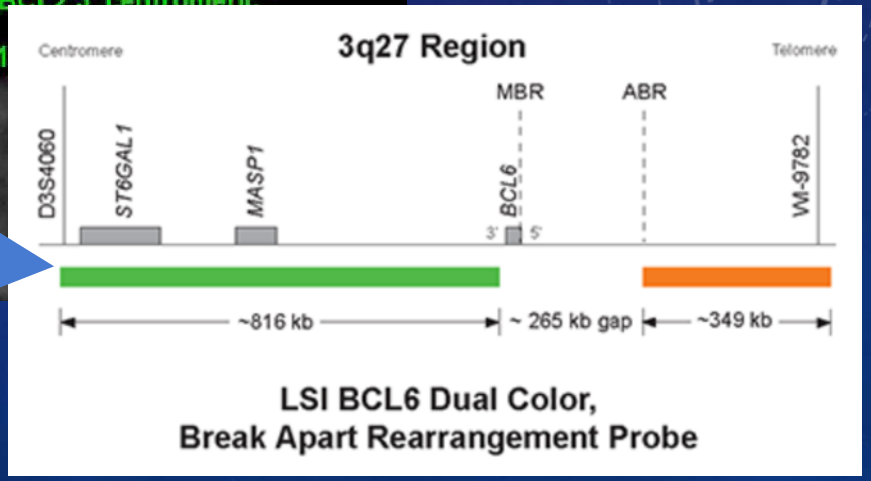


FISH - LYMPHOMA PANEL

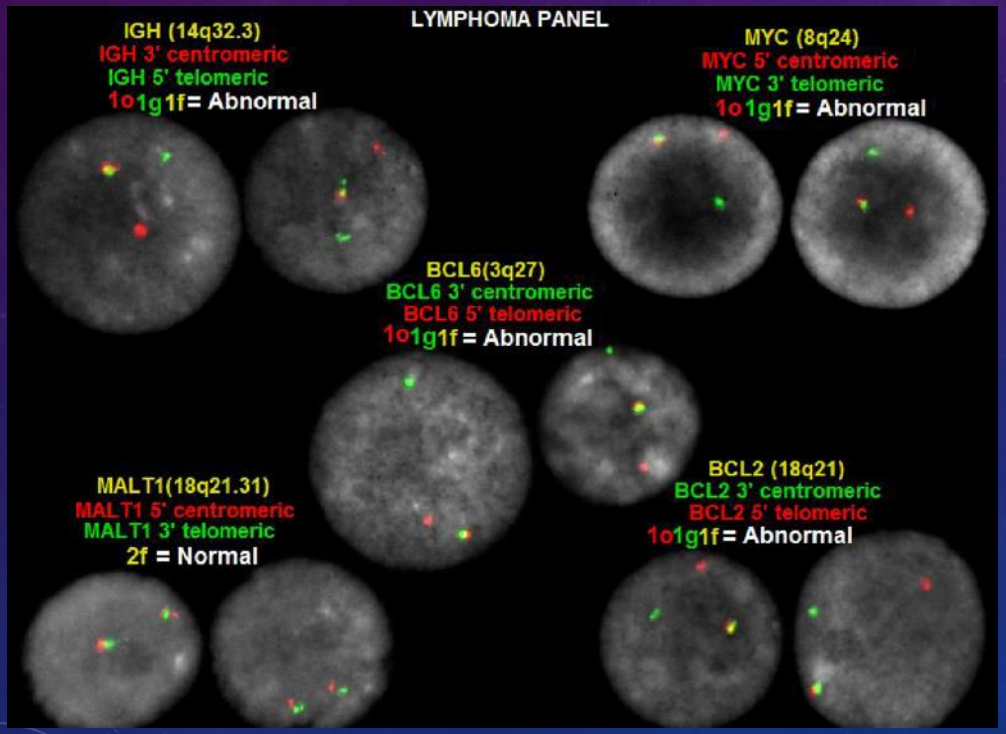








HIGH GRADE B-CELL LYMPHOMA (HGBCL) WITH *MYC* AND *BCL2* AND/OR *BCL6* REARRANGEMENTS



nuc ish

(BCL6x2)(3'BCL6 sep 5'BCL6x1)[198/200],

(MYCx2)(5'MYC sep 3'MYCx1)[196/200],

(IGHx2)(3'IGH sep 5'IGHx1)[198/200],

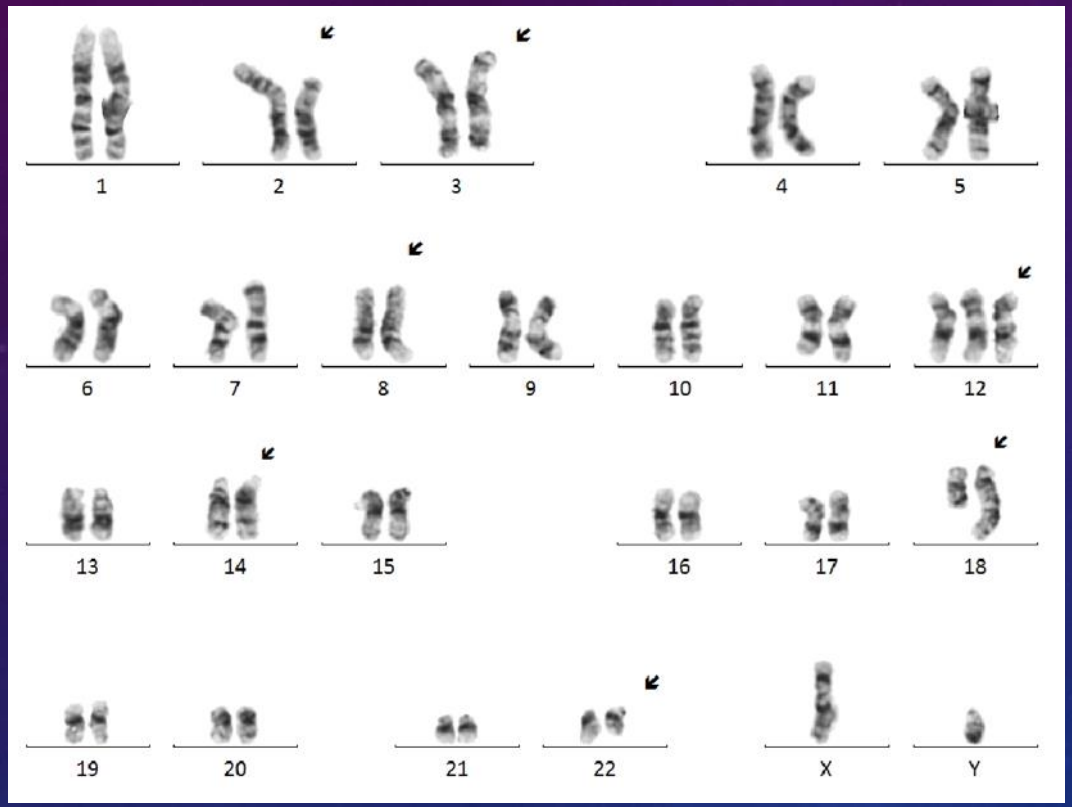
(MALT1x2)[200/200],

(BCL2x2)(3'BCL2 sep 5'BCL2x1)[197/200]

LYMPHOMA PANEL GENES

Gene	Gene Name	Location	Protein
IGH	Immunoglobulin heavy locus	14q32.3	Antibody heavy chain
MYC	Cellular myelocytomatosis	8q24.1	Cell proliferation
BCL2	B cell lymphoma 2	18q21.3	Anti-apoptotic
BCL6	B cell lymphoma 6	3q27	Transcription repressor
MALT1	Mucosa-associated lymphoid tissue lymphoma translocation protein 1	18q21.3	Lymphocyte activator

ABNORMAL COMPLEX MALE KARYOTYPE

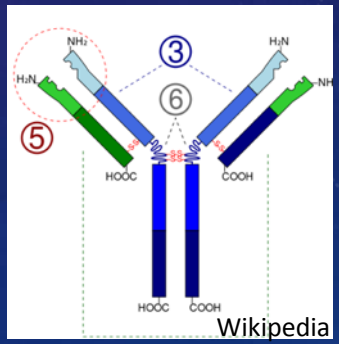


t(2;18)(p11.2;q21.3) IGK + BCL2 → BAD

t(3;14)(q27.3;q32) IGH + BCL6 → BAD

t(8;22)(q24.2;q11.2) IGL + MYC → BAD

+ 12 (~1,000 genes) → Recurrent in double hit lymphomas. Uncertain significance



47, XY, t(2;18)(p11.2;q21.3), t(3;14)(q27.3;q32), t(8;22)(q24.2;q11.2), +12 [14] / 46, XY[6]

PATIENT'S TREATMENT

- Used to treat various aggressive B-cell and T-cell non-Hodgkin lymphomas. [1]
- Shows a promising activity considering double/triple hit, double/triple expressing lymphoma-associated drug resistance. [2]
- Seems to overcome drug resistance associated with *BCL2/MYC/BCL6 overexpression, but not with TP53* deletion. [2]

da EPOCH-R + auto SCT		
Letter	Meaning	Mechanism of Action
d	dose	
a	adjusted	
E	etoposide	Affects cell cycle G2, lysing cells entering mitosis and inhibiting cells from entering prophase
P	prednisone	Inhibits inflammatory cytokines
O	oncovin (vincristine)	Inhibits microtubule formation, arresting mitosis in metaphase
C	cyclophosphamide	Alkylates and crosslinks DNA
H	doxorubicin hydrochloride (hydroxydaunorubicin hydrochloride)	Binds and intercalates DNA, inhibiting nucleic acid and protein synthesis; triggers DNA cleavage by topoisomerase II
R	rituximab	Binds B-lymphocyte CD20 surface antigens

1. NCI Drug Dictionary: https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=38921
2. Grzegorz Rymkiewicz, et al. Blood 2016 128:1754

WHO 2016 NEW LYMPHOMA CATEGORY: HIGH GRADE B-CELL LYMPHOMA WITH *MYC* AND *BCL2* AND/OR *BCL6* REARRANGEMENTS

- So called ”triple hit” lymphoma

- Morphology should be given in the comment, since morphology may indicate behavior of the tumor
  - DLBCL – most cases
  - BL or DLBCL/BL ~50%
  - Blastoid – small portion

- Transformed from_____

World Health Organization 2017 Classification of Tumours of Haematopoeitic and Lymphoid Tissues

2008 WHO CLASSIFICATION OF TUMORS OF HEMATOPOIETIC AND LYMPHOID TISSUES

- “B-cell lymphoma, unclassifiable, with features in between Diffuse Large B-Cell Lymphoma (DLBCL) and Burkitt Lymphoma (BL)”
  - BCLU

- Included
  - Intermediate morphology between DLBCL and BL
  - Burkitt lymphoma with cytologic variation or BCL2 positive
  - ”Double hit” or “triple hit” lymphomas

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

Table 10.18 Morphologic, immunophenotypic, and genetic features that may be useful in distinguishing BL from DLBCL.

Characteristic	BL	Intermediate BL/DLBCL	DLBCL
Morphology			
Only small/medium-size cells	Yes	Common	No
Only large cells	No	No	Common
Mixture	No	Sometimes	Rare
Proliferation (Ki67/MIB1)			
>90% and homogeneous	Yes	Common	Rare
<90% or heterogeneous	No	Sometimes	Common
BCL2 expression			
Negative / weak	Yes	Sometimes	Sometimes
Strong	No	Sometimes	Sometimes
Genetic features			
MYC rearrangement	Yes*	Common	Rare
*IG-MYC***	Yes	Sometimes	Rare
Non *IG-MYC***	No	Sometimes	Rare
BCL2 but no *MYC* rearrangement	No	Rare	Sometimes
BCL6 but no *MYC* rearrangement	No	Rare	Sometimes
Double hit#	No	Sometimes	Rare
MYC-Simple karyotype***	Yes	Rare	Rare
MYC-Complex karyotype***	Rare	Common	Rare

BURKITT LYMPHOMA,

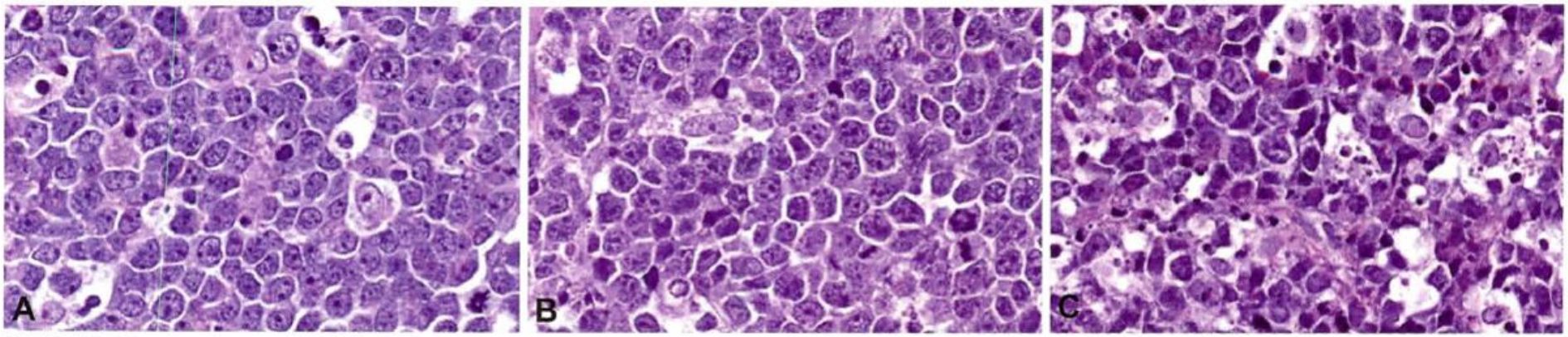


Fig. 10.127 Three lymphomas with t(8;14). **A** Typical BL composed of medium-sized, monomorphous cells with round nuclei, multiple nucleoli, and a moderate amount of cytoplasm, which has a mosaic-like appearance. Prominent apoptosis is evidenced by the presence of macrophages engulfing nuclear debris, creating the "starry-sky" pattern. Nine of 11 experts who reviewed this case independently made a diagnosis of BL; 1 made a diagnosis of atypical BL. **B** Another case with similar overall appearance, but with slightly more variation in size and shape of the cells. Six reviewers called this BL and 5 called it atypical BL. **C** DLBCL with a t(8;14) has a prominent starry-sky pattern. The cells are larger and more pleomorphic than the Burkitt and atypical Burkitt cases. Nine experts called this DLBCL and 2 called it atypical BL. Reproduced from from Harris NL and Horning SJ {896A}.

A) Typical BL B) BL with variation in size and shape of cells C) DLBCL/BL

“DOUBLE HIT” LYMPHOMA WITH FEATURES OF DLBCL AND BL

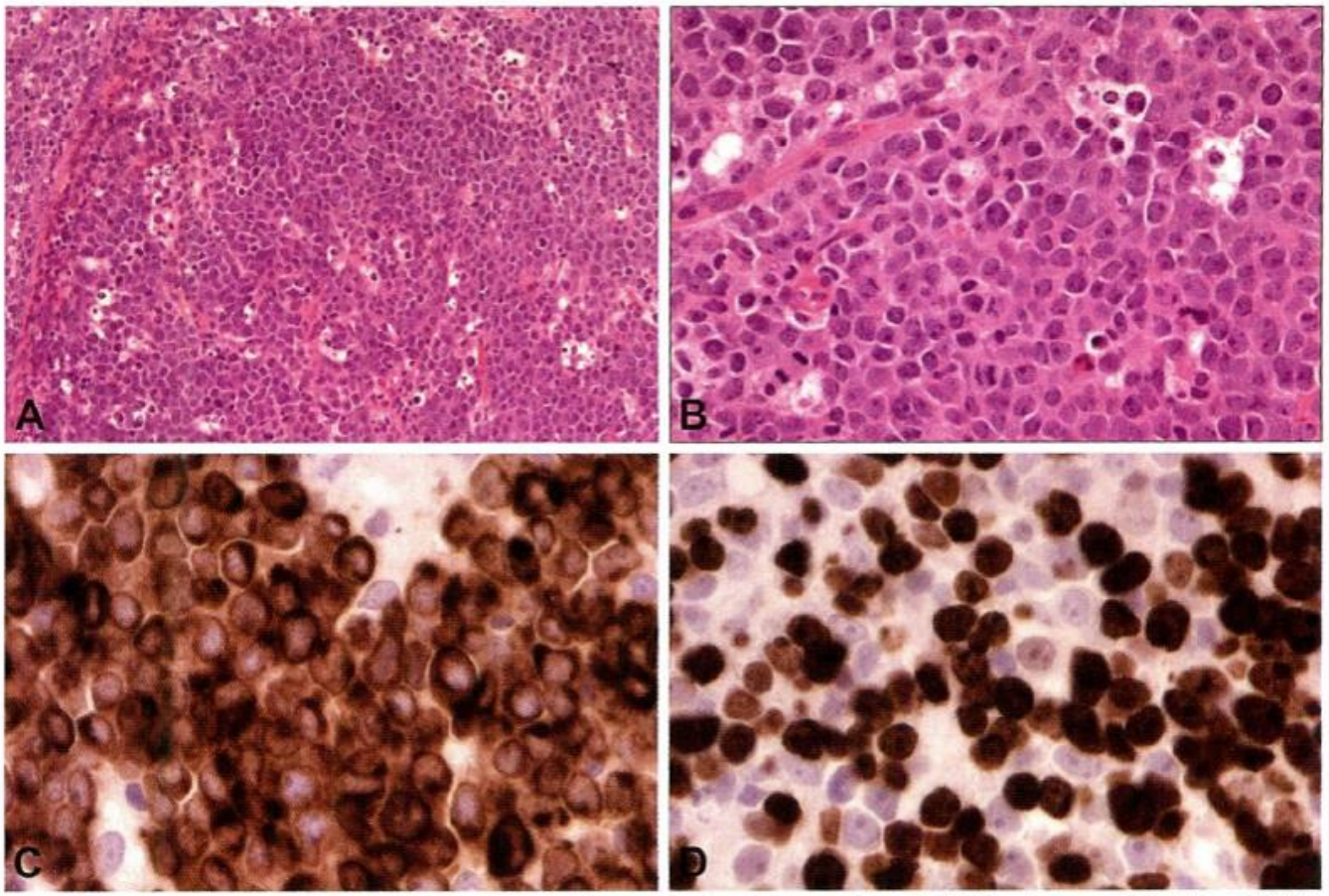
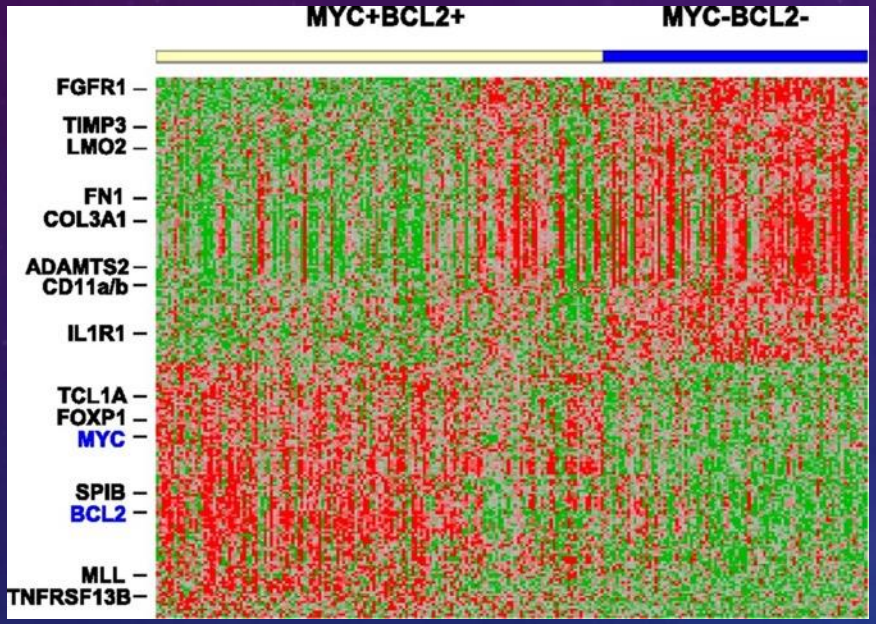
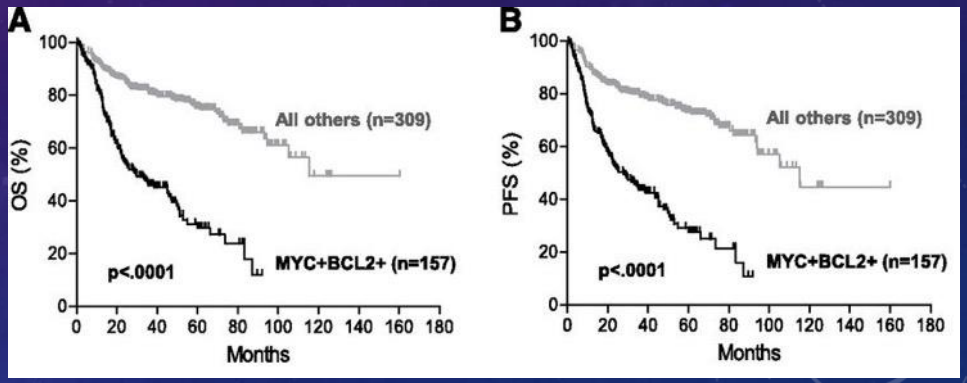


Fig.10.128 Male patient, 61 years, with a rapidly growing cervical nodal mass. "Double hit" lymphoma with both 8q24/*MYC* and 18q21/*BCL2* breakpoints. **A** Starry sky pattern. **B** Higher magnification showing a mixture of medium/large-sized nuclei with little pleomorphism but prominent nucleoli, absence of granular chromatin and many mitotic figures. **C** Strong BCL2 staining is very unusual for BL. **D** Ki67 staining was heterogeneous but elsewhere there were close to 100% positive cells.

DLBCL WITH MYC/BCL2 CO-EXPRESSION (2013)

THIS SHOWS A DISTINCT GENE EXPRESSION SIGNATURE AND PROGNOSIS

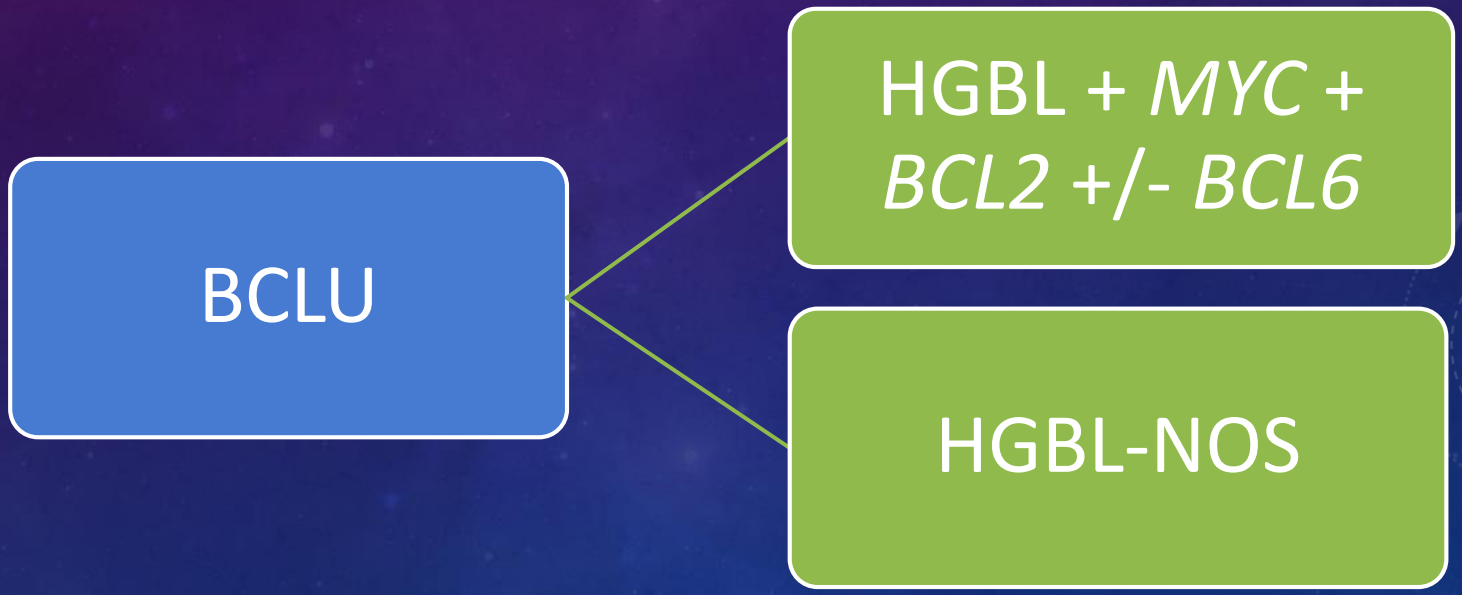




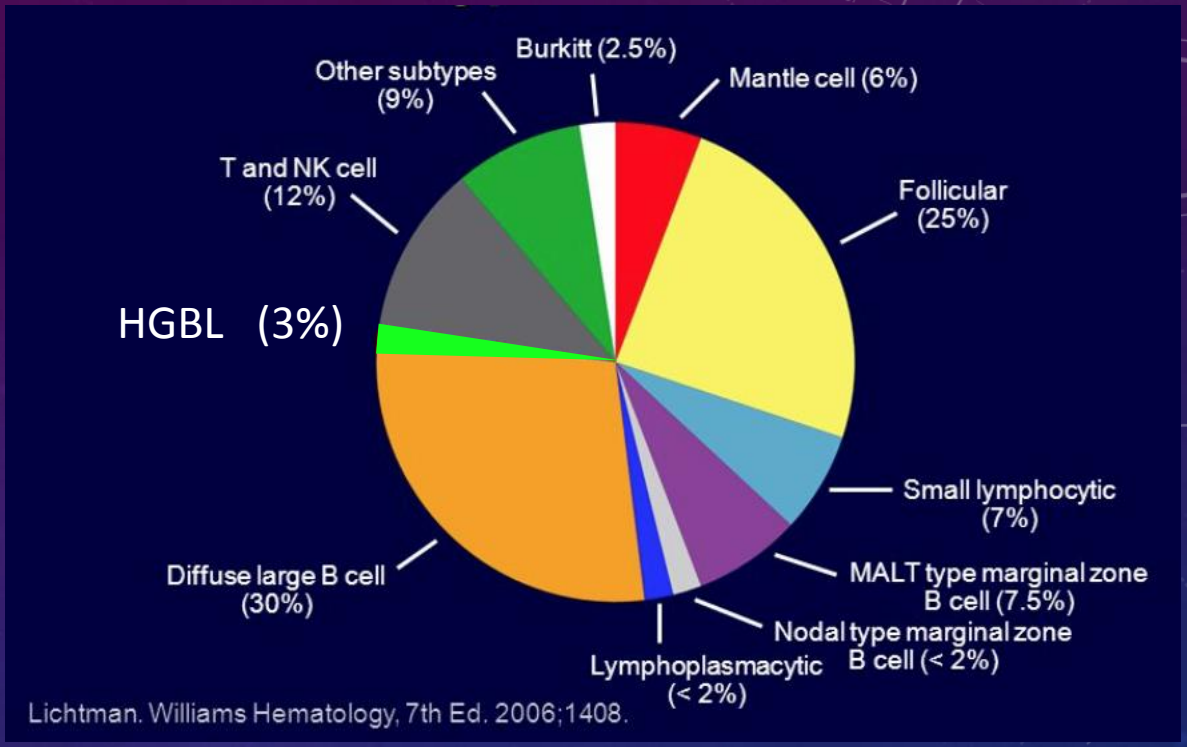
Shimin Hu et al. Blood 2013;121:4021-4031

2008

2016



EPIDEMIOLOGY



- 4-8% of DLBCL are double hit
- Usually in 5th and 6th decades of life
- Youngest cases approximately 30 years old
- Slightly more males than females

World Health Organization 2017 Classification of Tumours of Haematopoeitic and Lymphoid Tissues

ETIOLOGY

- HGBL with *BCL2* rearrangement is from germinal center B-cells (GCB)[1]

- Rearrangement of *MYC* might be secondary
  1. Progression from follicular lymphoma
     - BCL2 rearrangement --> acquires *MYC* rearrangement
  2. De novo disease
     - Some tumors with areas of both *MYC* and *BCL2* rearrangement, other areas only *BCL2*

1. Scott DW, *et al.* 2018. Blood.

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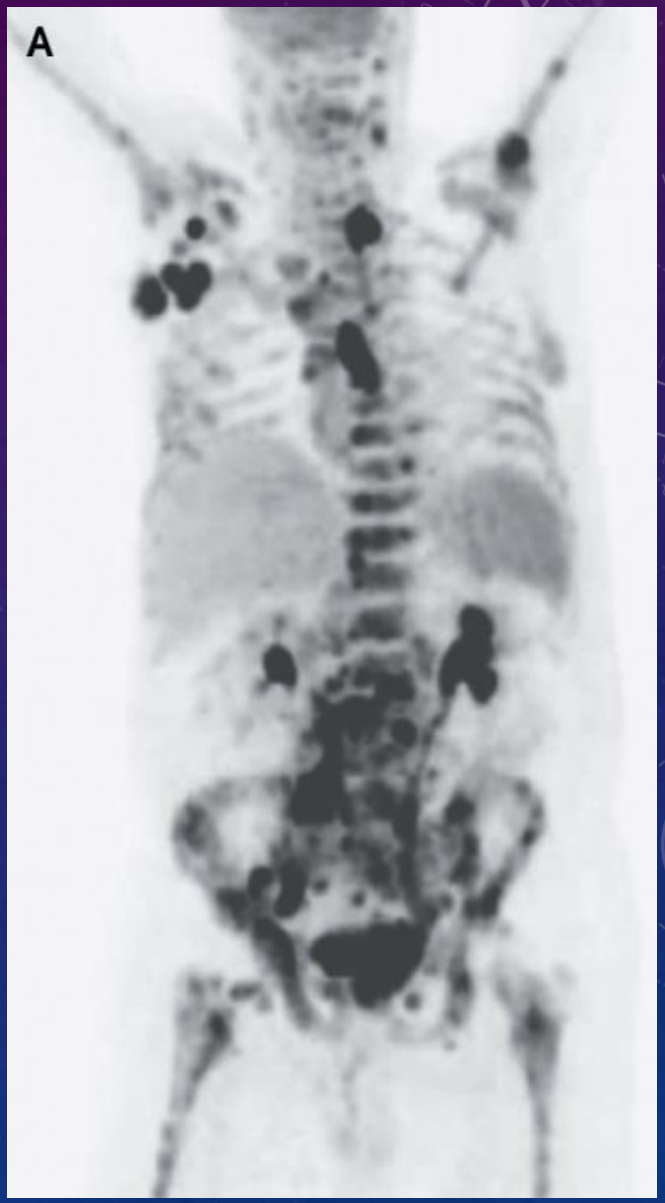
LOCALIZATION

- More than half of patients present with widespread disease, including outside of the lymph nodes.
- More than one extra-nodal site (30-88%)
- Bone marrow (59-94%)
- CNS (up to 45%)



Barnes JA, *et* al. 2013. n engl j med 369;20.

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CLINICAL FEATURES

- Most patients (70-100%) present with advanced disease (stage IV)

- High international prognostic index (IPI)
  - Age greater than 60 years
  - Stage III or IV disease
  - Elevated serum LDH
  - ECOG/Zubrod performance status of 2, 3, or 4 (bedridden)
  - More than 1 extranodal site

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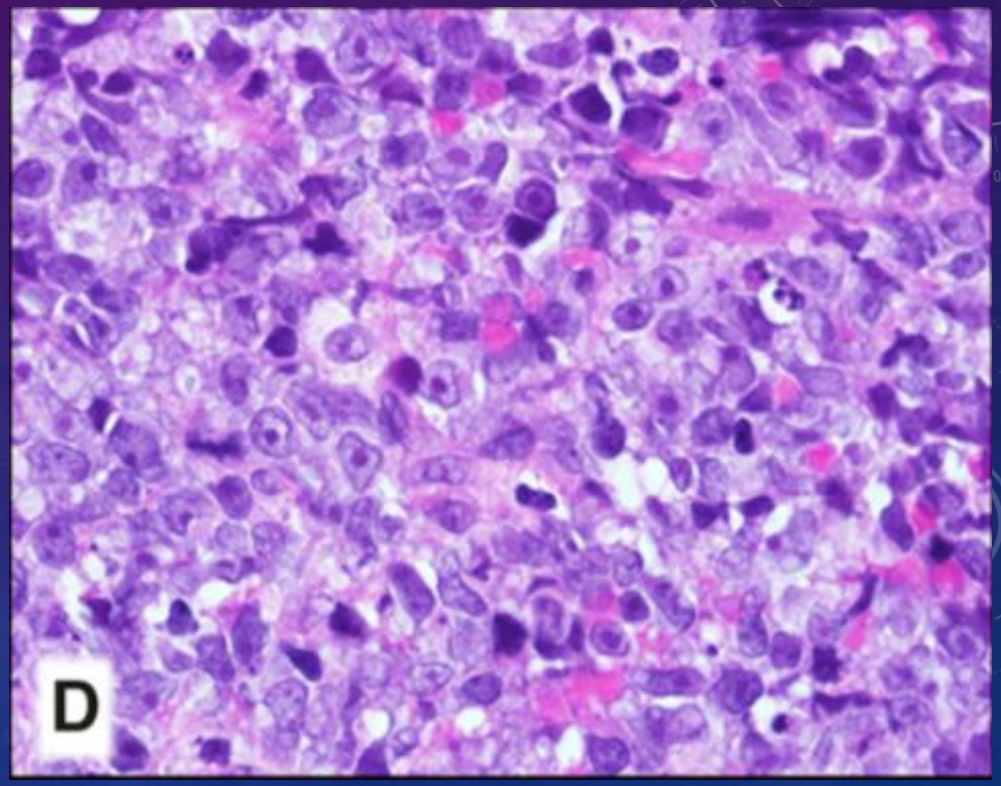
MICROSCOPIC FEATURES

- Most have morphology of DLBCL
- All cases with morphology of DLBCL should be tested for rearrangements
- Medium-size to large cells, abundant cytoplasm, irregular nuclear contours



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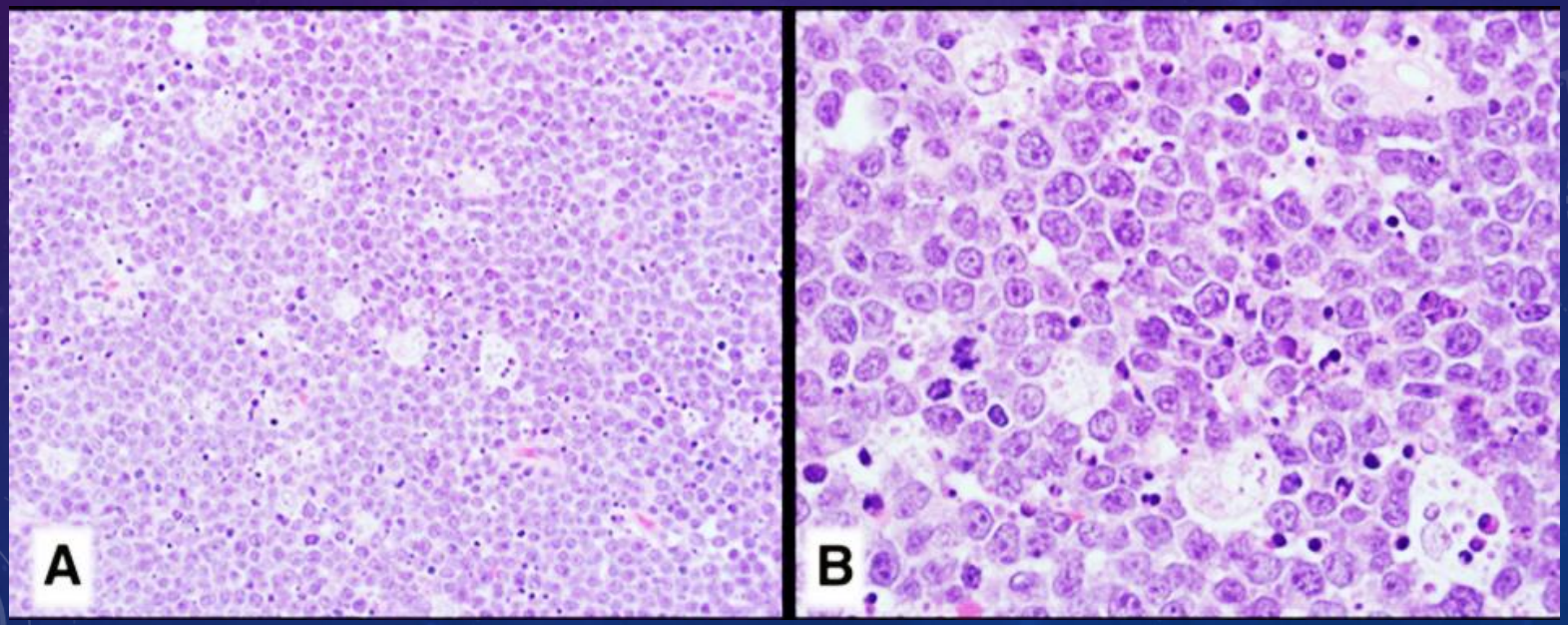
MICROSCOPIC FEATURES

- ~50% have morphology of Burkitt Lymphoma or intermediate between DLBCL and BL
- Medium-size to large cells with large nuclei, monomorphic and with starry sky macrophages
- DLBCL/BL larger cells with less basophilic cytoplasm



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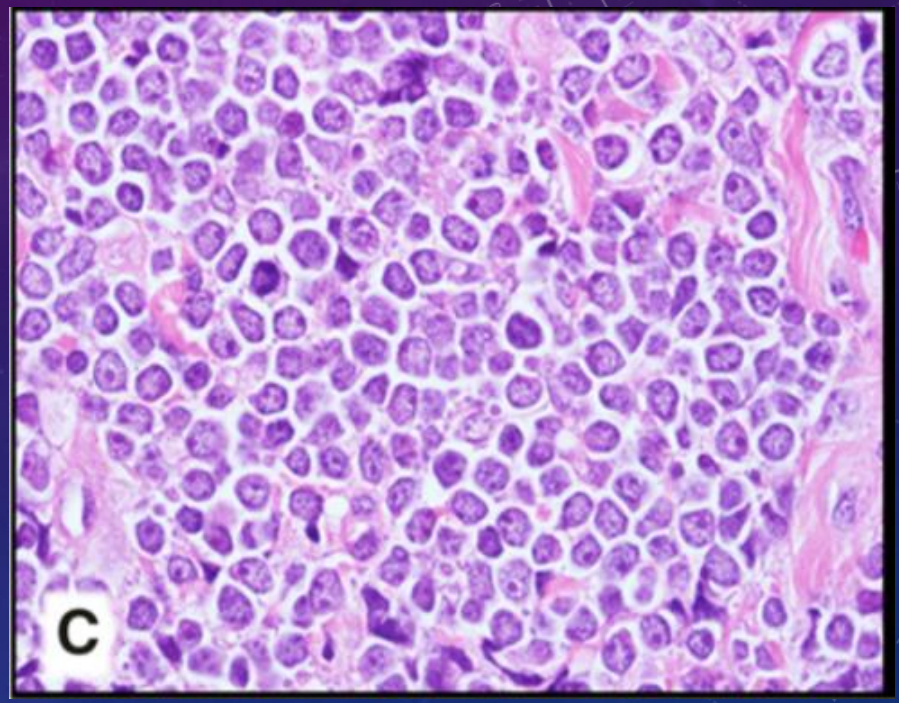
MICROSCOPIC FEATURES

- Other morphology is blastoid: medium sized cells with high nucleus/cytoplasm ratio, small rim of cytoplasm and fine chromatin with inconspicuous nucleoli
  - Similar to centroblasts

- Tdt stain should be performed on every case to rule out a precursor neoplasm (B-lymphoblastic leukemia/lymphoma)



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IMMUNOPHENOTYPE

- Mature B-cell lymphoma with
  - CD19
  - CD20
  - CD79a
  - PAX5
  - No TdT
  - No CD34
  - No Cyclin D1
  - Bright CD45

- Some lack surface Ig, possibly due to rearrangement involving Ig loci
  - Should not be interpreted as immature

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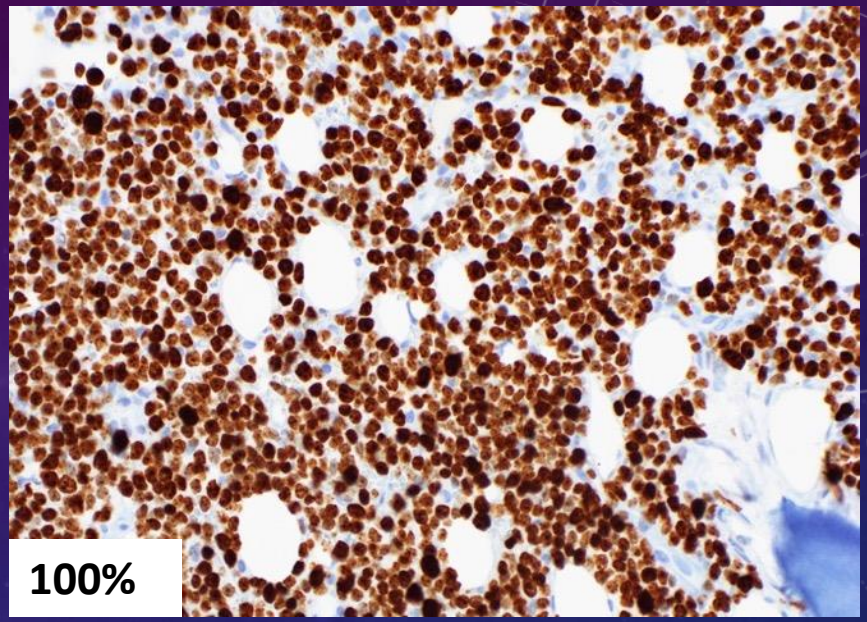
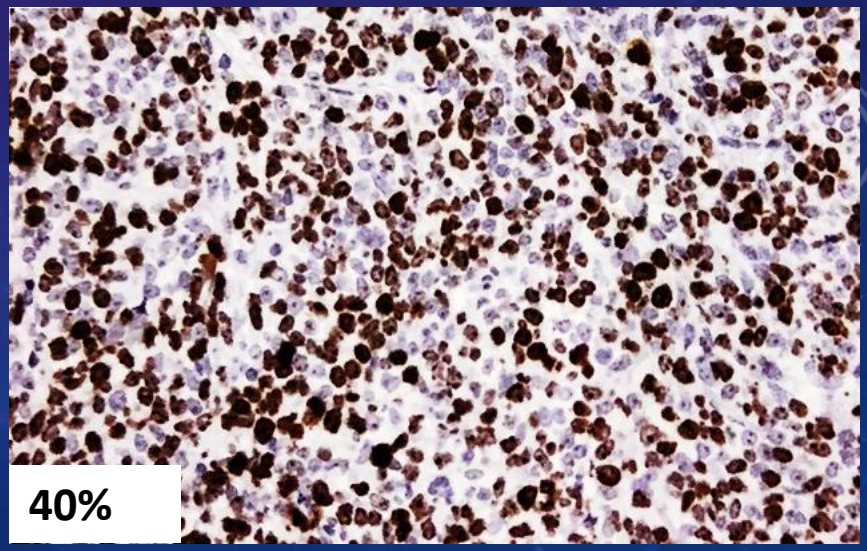
PROLIFERATION

- Ki67 index can be variable
- Ki67 should NOT be used to screen for cases to perform molecular testing





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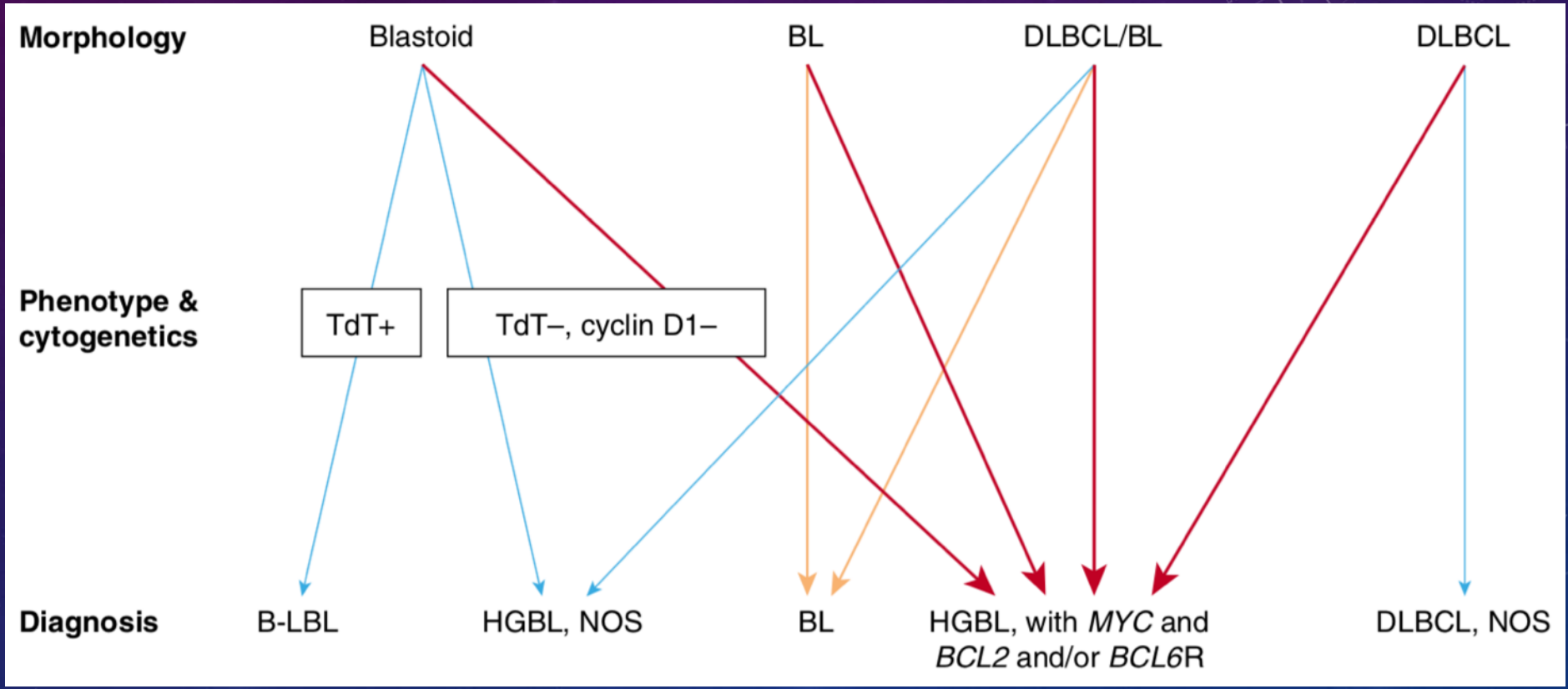
GENETIC PROFILE – *MYC* AND *BCL2* AND/OR *BCL6*

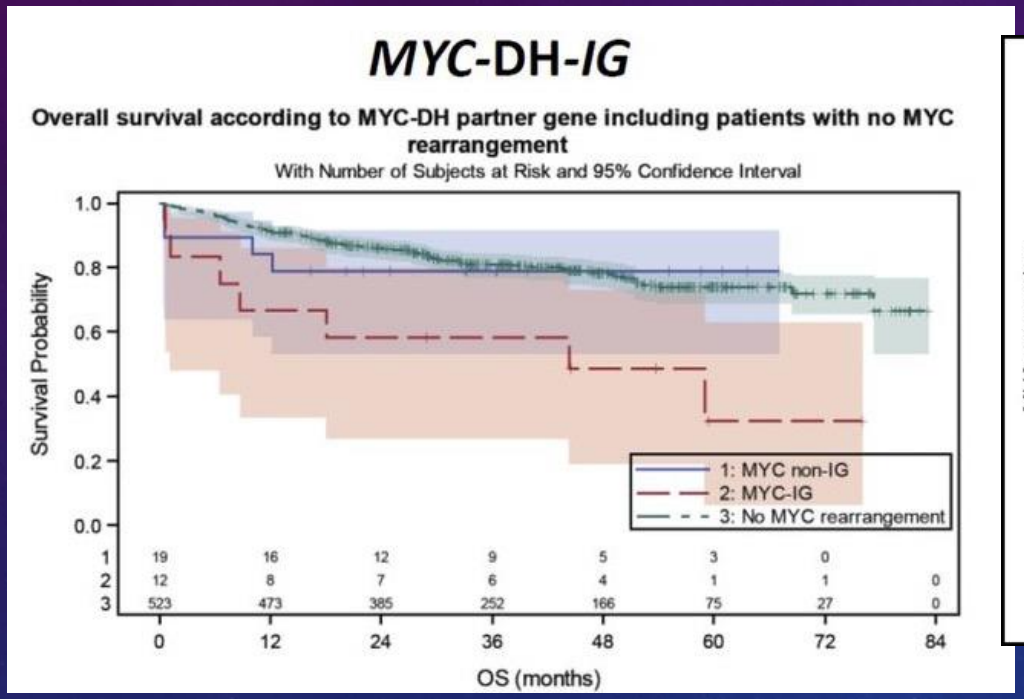
- Rearrangement in *MYC*
  - When paired with IG, this is more aggressive
- Also rearrangements involving *BCL2* and/or *BCL6*
- *MYC* paired with other gene rearrangements (*BCL3* or others) are not included in this diagnostic category
- *BCL2* or *BCL6* copy number increase or amplification not enough (must be rearrangement)
- Many other structural and numerical abnormalities
  - *TP53* frequently mutated
  - *MYD88* sometimes mutated
  - *ID3* hemizygous mutations
  - Usually a complex karyotype

World Health Organization 2017 Classification of Tumours of Haematopoeitic and Lymphoid Tissues

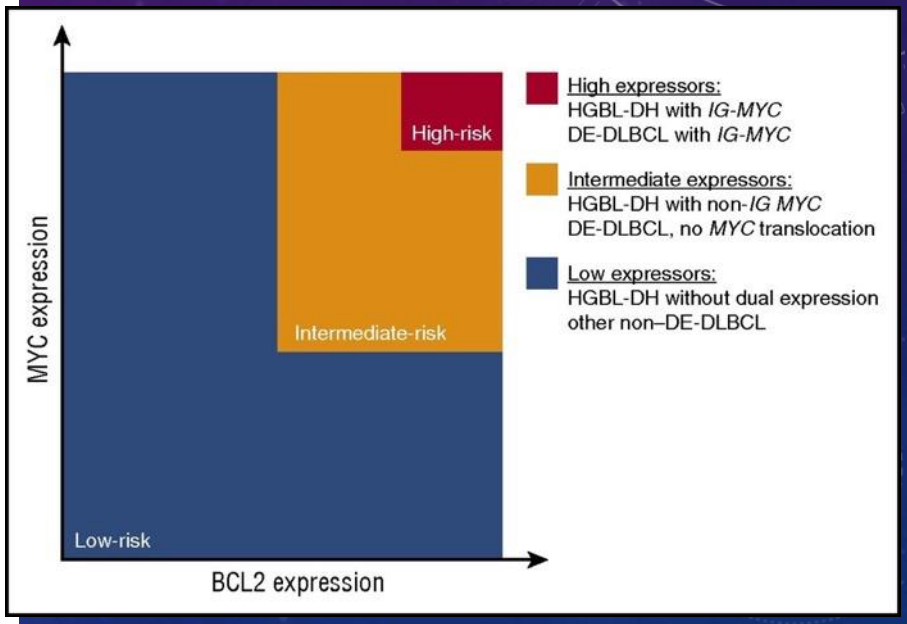
DIAGNOSTIC CATEGORIES



MYC REARRANGEMENT PARTNER MATTERS

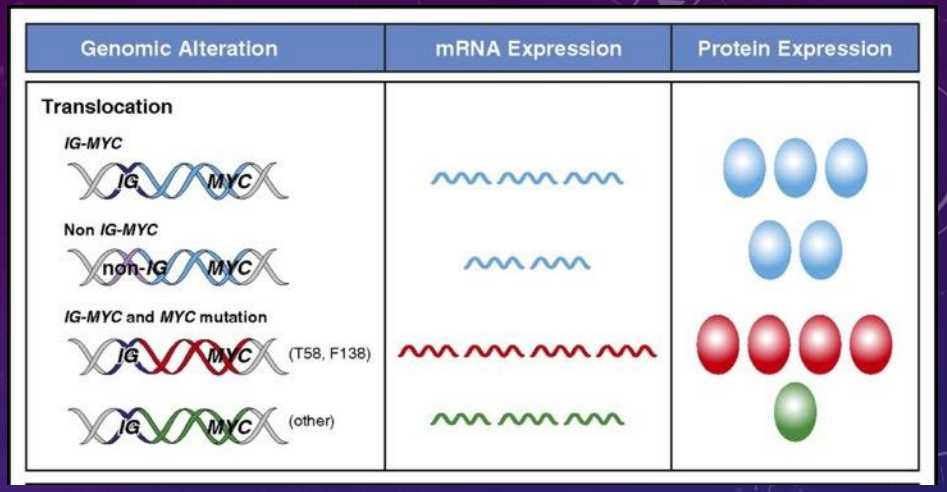


Christiane Copie-Bergman et al. Blood 2015;126:2466-2474



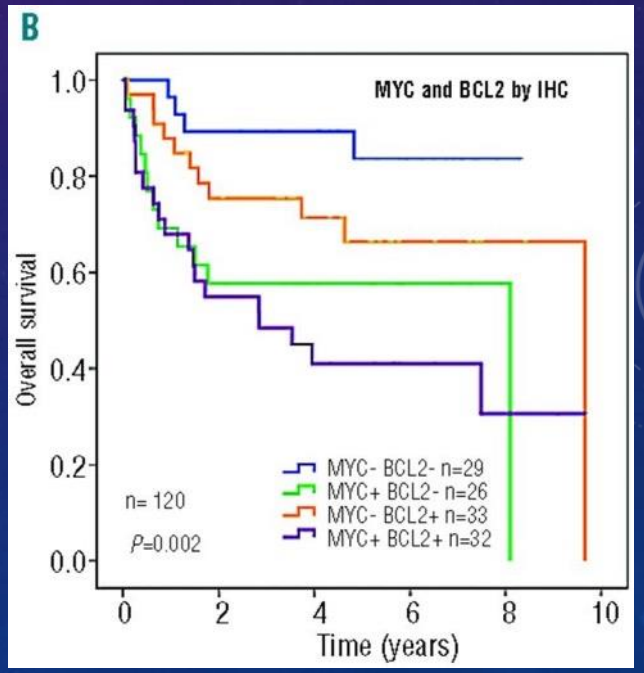
Pierre Sesques, and Nathalie A. Johnson Blood 2017;129:280-288

DOUBLE/TRIPLE-HIT VS DOUBLE/TRIPLE-EXPRESSOR



Pierre Sesques, and Nathalie A. Johnson Blood 2017;129:280-288

- MYC + BCL2 expression is synergistic
- *MYC* rearrangement to IG worse than others
- Without rearrangements, cannot include in this diagnosis
  - Would be DLBCL with double expression

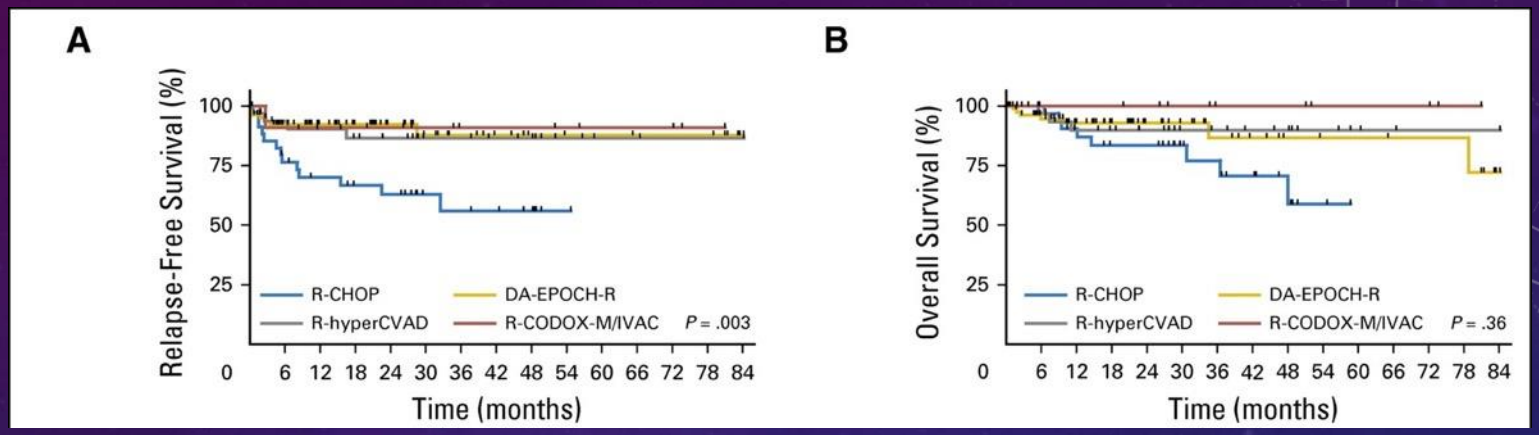


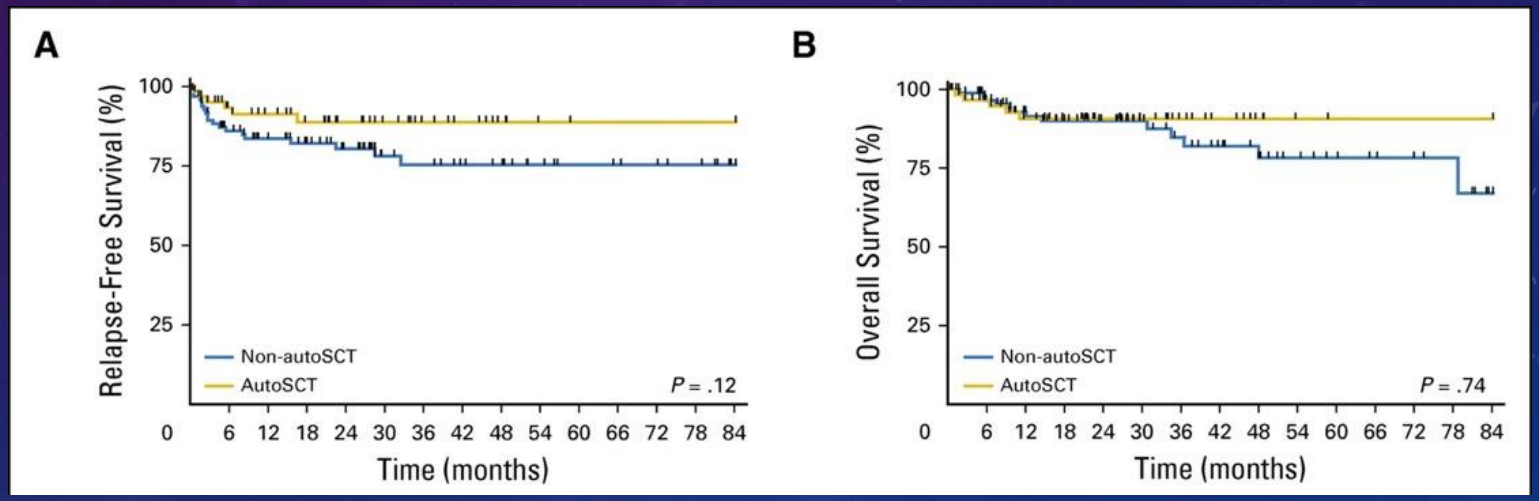
Alexandra Valera et al. Haematologica 2013;98:1554-1562

HIGH GRADE B-CELL LYMPHOMA, NOS

- Heterogeneous category
- Aggressive mature B-cell lymphomas that lack *MYC* plus *BCL2* and/or *BCL6* rearrangements
- Blastoid-appearing mature B-cell lymphomas (not mantle cell type)
- Rare, to be used only when truly unable to classify as DLBCL or BL
- Affects the elderly; males and females affected almost equally
- Poor outcome, though slightly better than those with double-hit HGBL

HGBL TREATMENT





Daniel J. Landsburg, Xavier Rivera, Daniel O. Persky, et al. *JCO* **2017,** 35, 2260-2267.

- R-CHOP is inadequate induction therapy
- Future therapies may target MYC and BCL2[1]

1. Dr. David Scott. 2015. Update on Molecular Classification of DLBCL. ASCO.

SUMMARY

- B-cell lymphoma, unclassifiable is now
  - High grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HG-DH/TH)
  - High grade B-cell lymphoma, NOS (HG-NOS)
- Treatment should be more aggressive