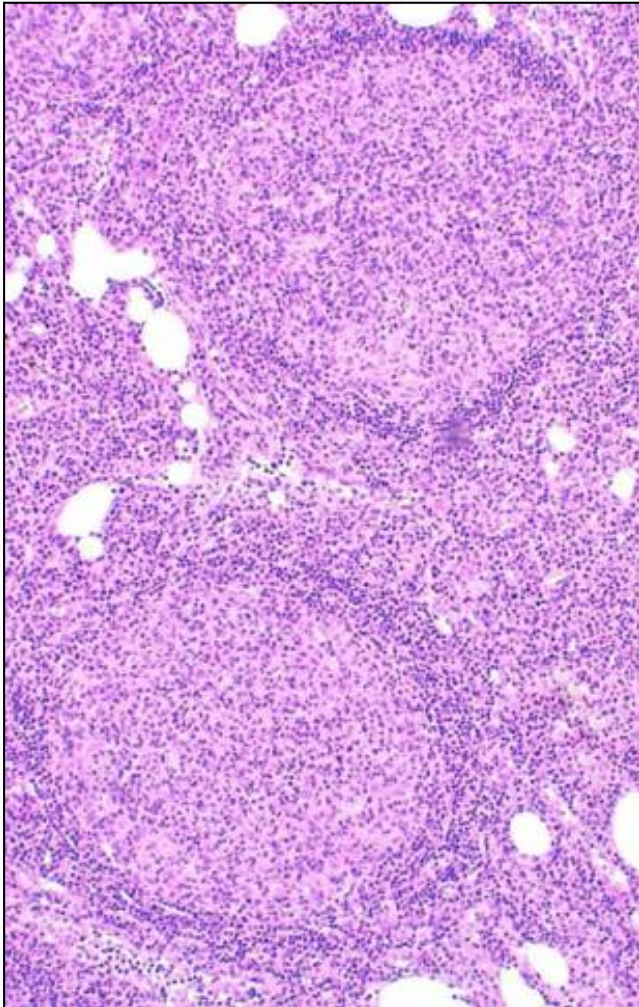


*Follicular Lymphomas
Histological Spectrum*

*Elaine S Jaffe
National Cancer Institute
Bethesda, MD*

Follicular Lymphoma



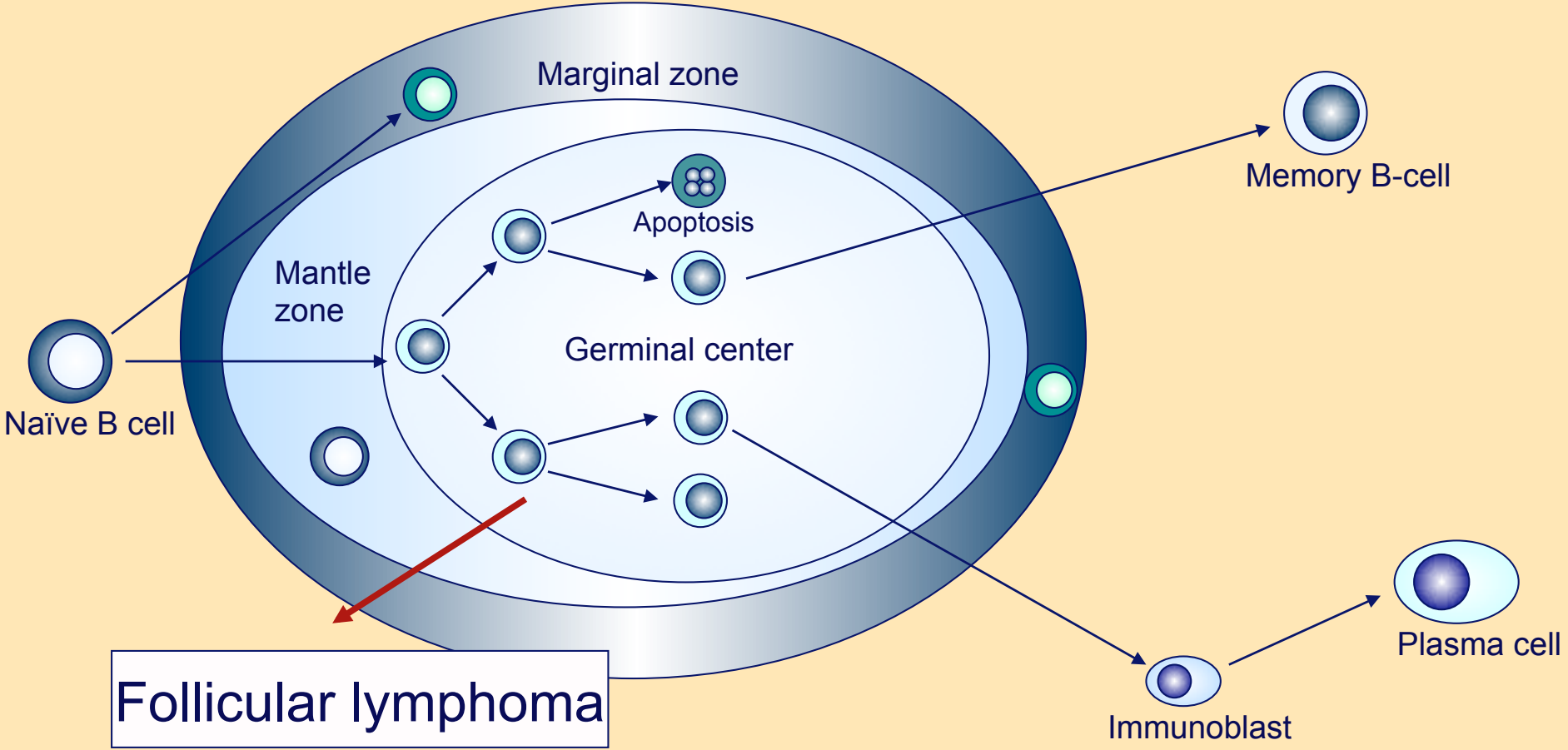
Morphology: Follicular proliferation of centrocytes and centroblasts associated with follicular dendritic cells

Immunophenotype: CD20+, CD19+,
CD79a+
IgM, IgG, IgA
CD10+, CD5-
BCL-2+, BCL-6+

Genetics: *IGH/BCL2* rearrangement
t(14;18); somatic mutations of VH

Clinical: Adults, indolent course but generally incurable
Most patients present with advanced stage disease, III/IV A

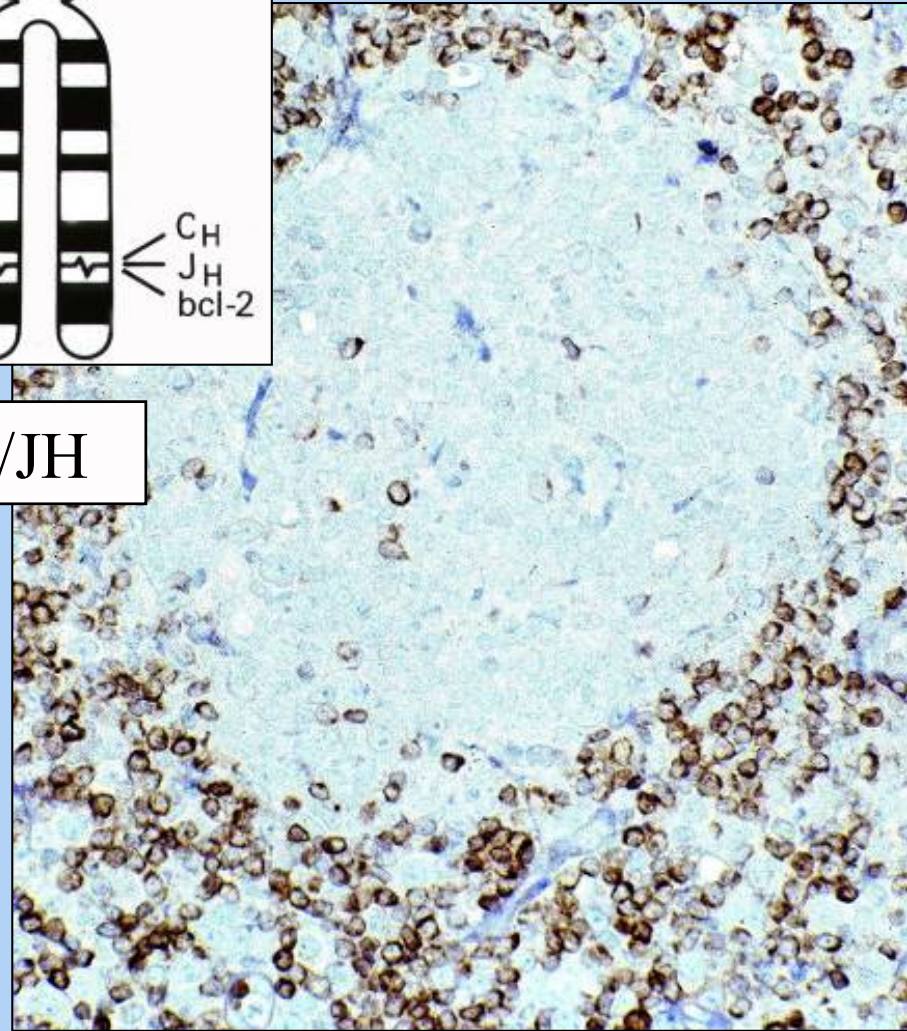
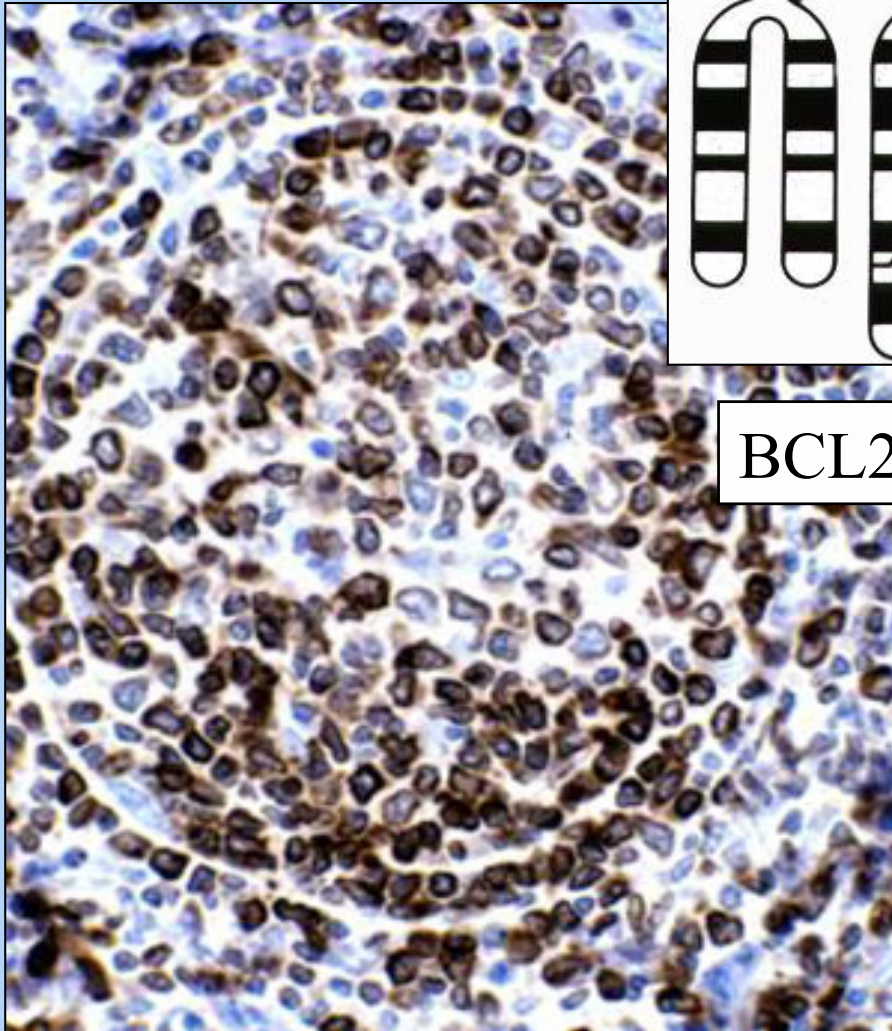
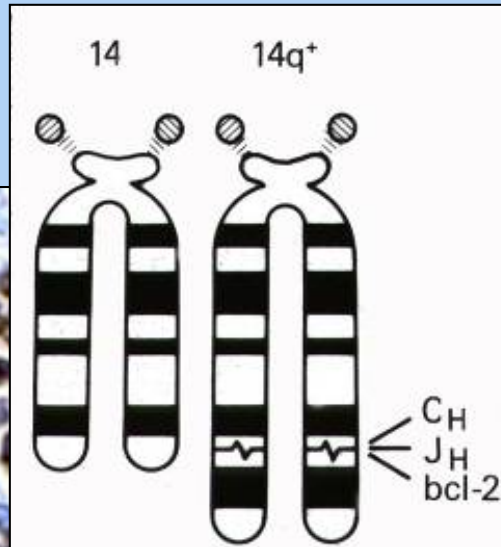
Germinal Center Events in B-cell differentiation



V-gene recombination **Clonal expansion, somatic hypermutation Class switching** Differentiation

Tsujimoto, Croce
Science 1985

Gaulard, Mason
AJP 1992

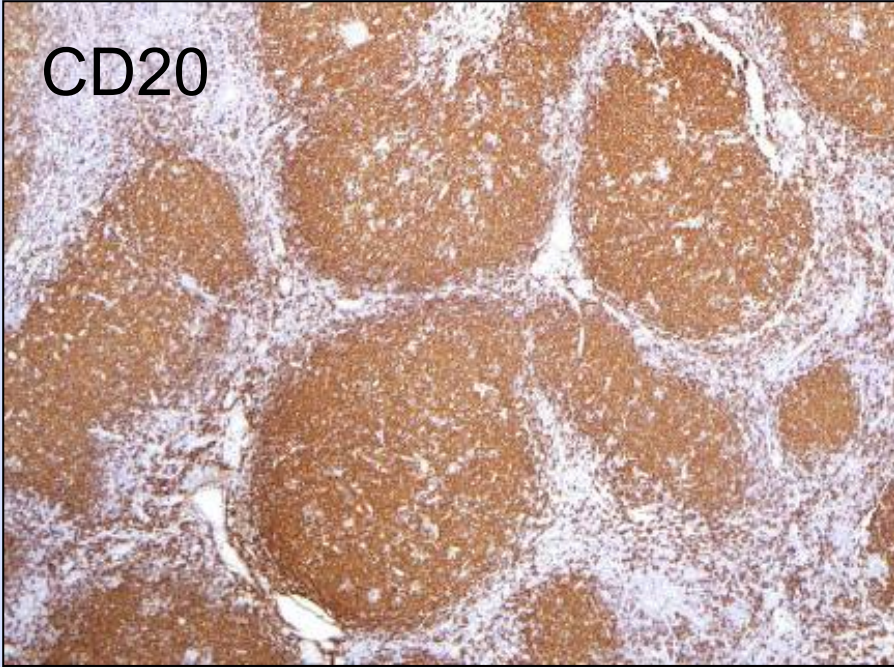


BCL2/JH

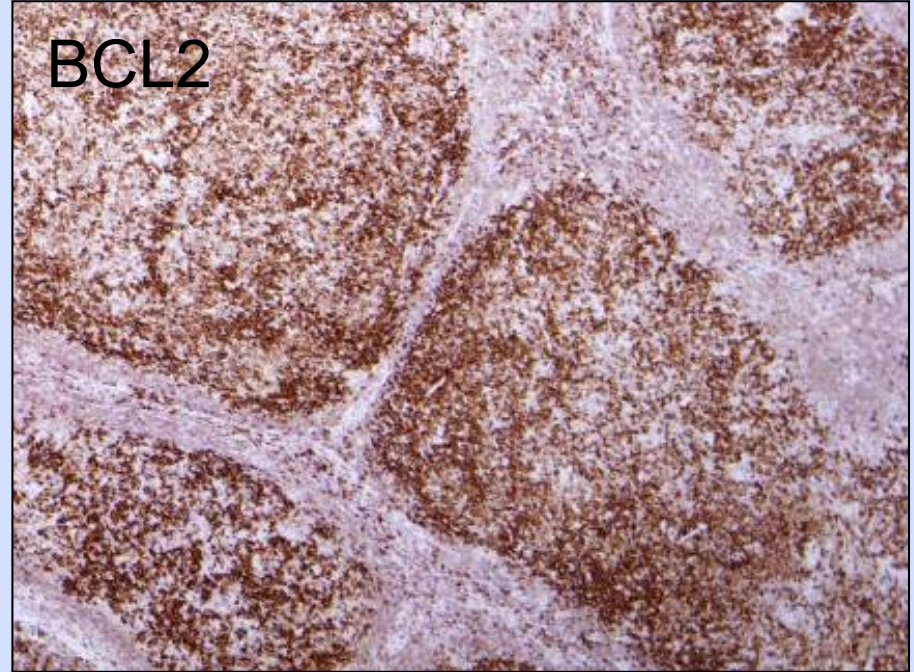
Follicular lymphoma

Germinal Center

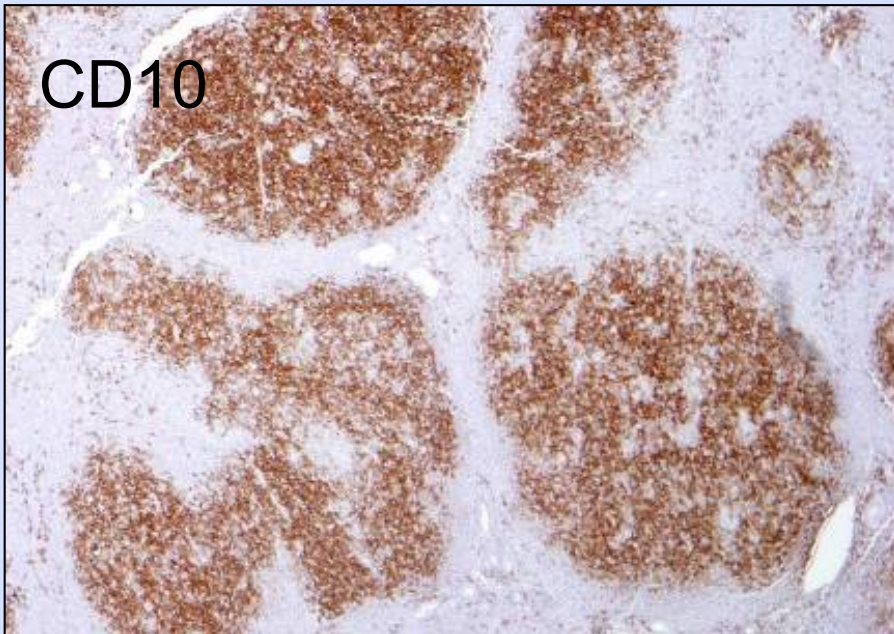
CD20



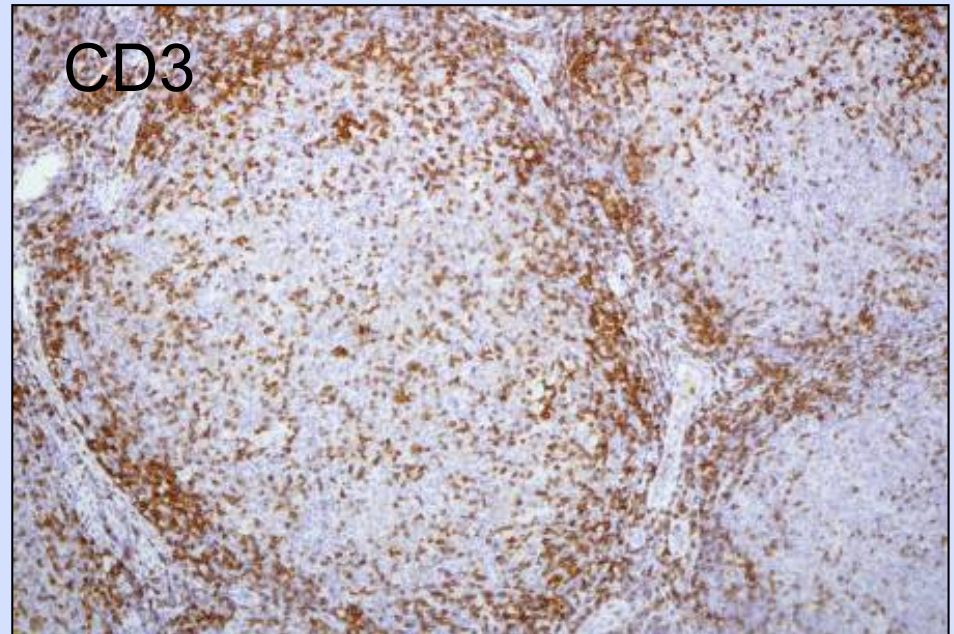
BCL2



CD10



CD3



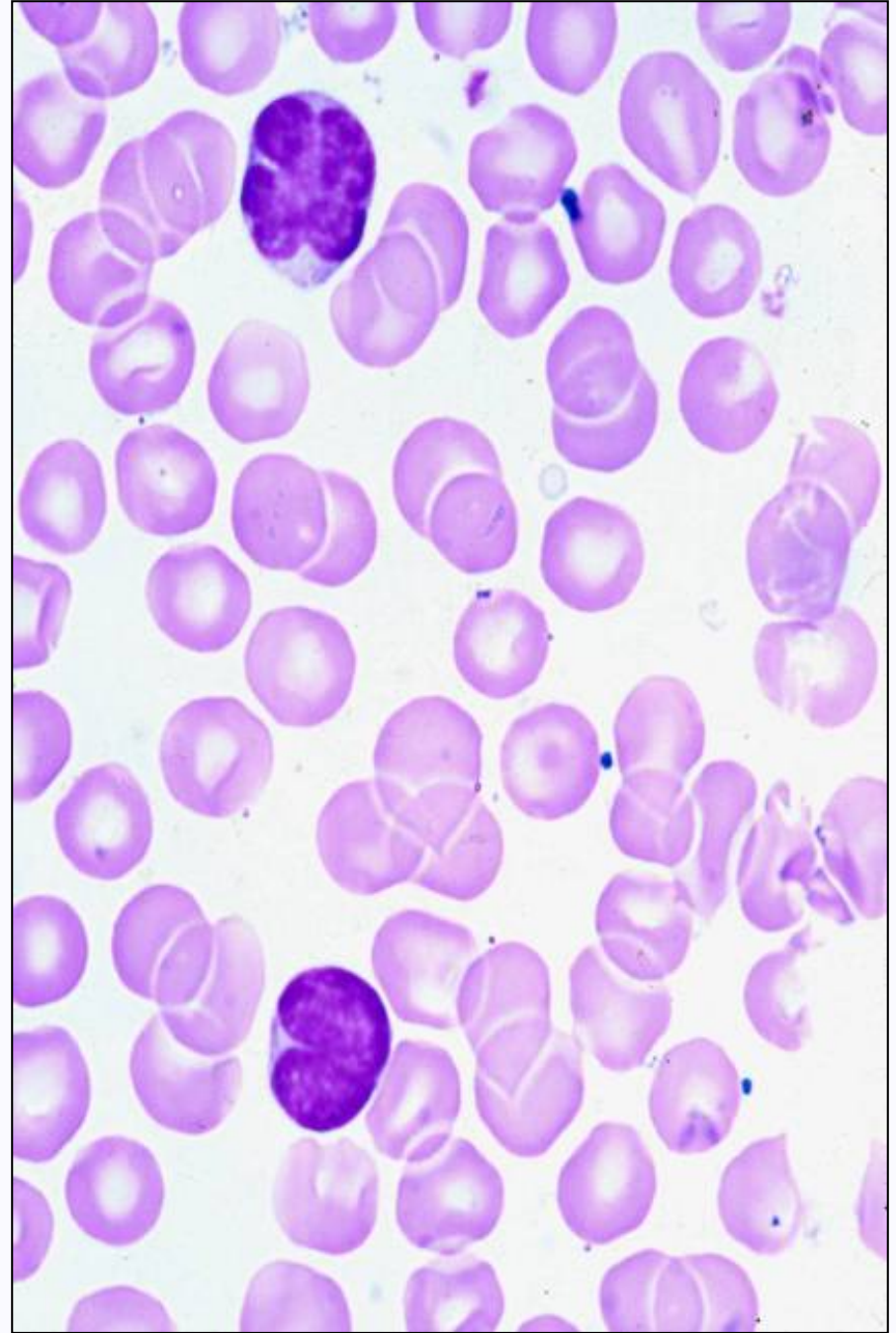
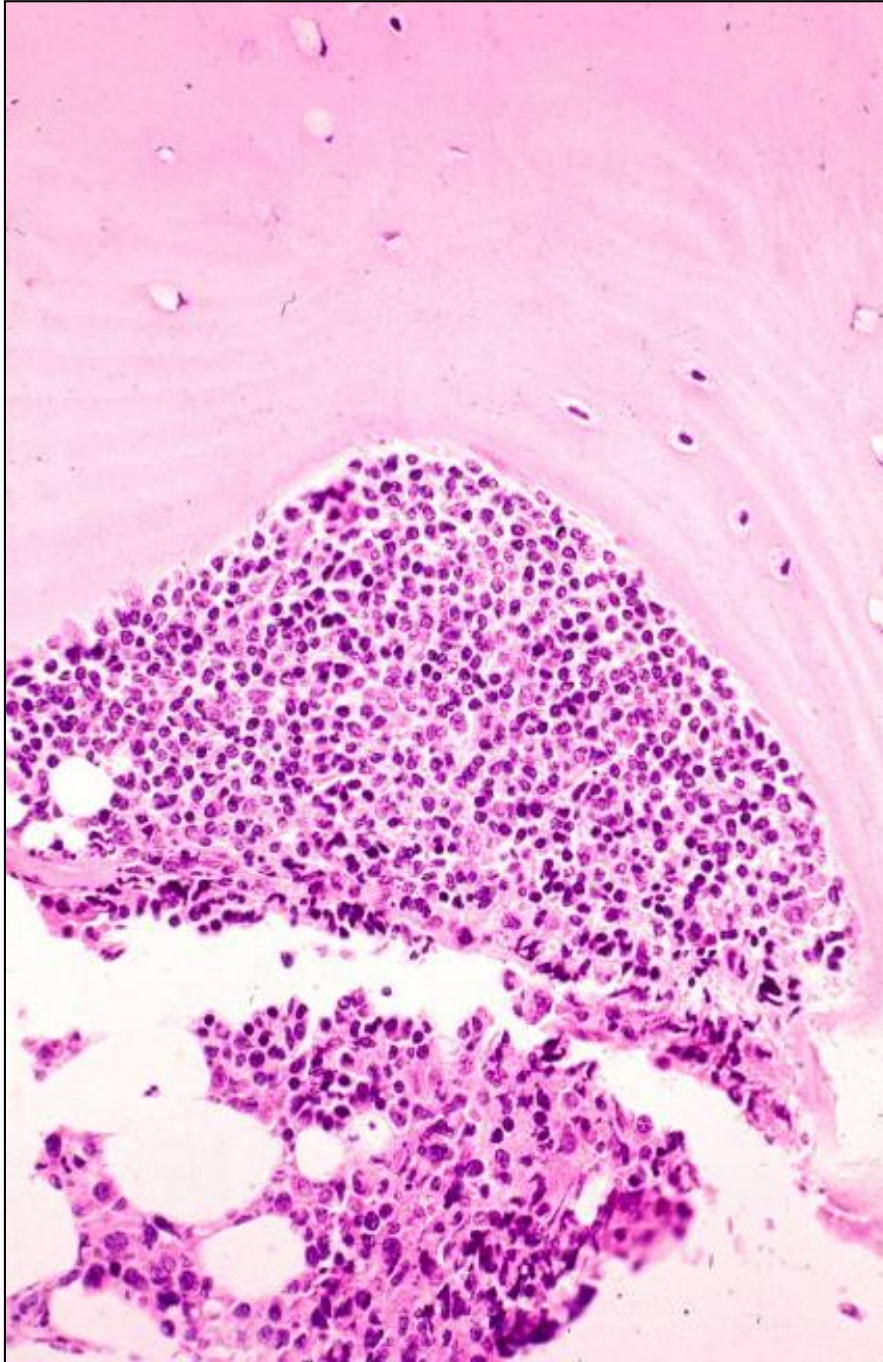


BCL2 IHC negative from mutations in *BCL2* epitope
Use alternative clones: E17, SP66

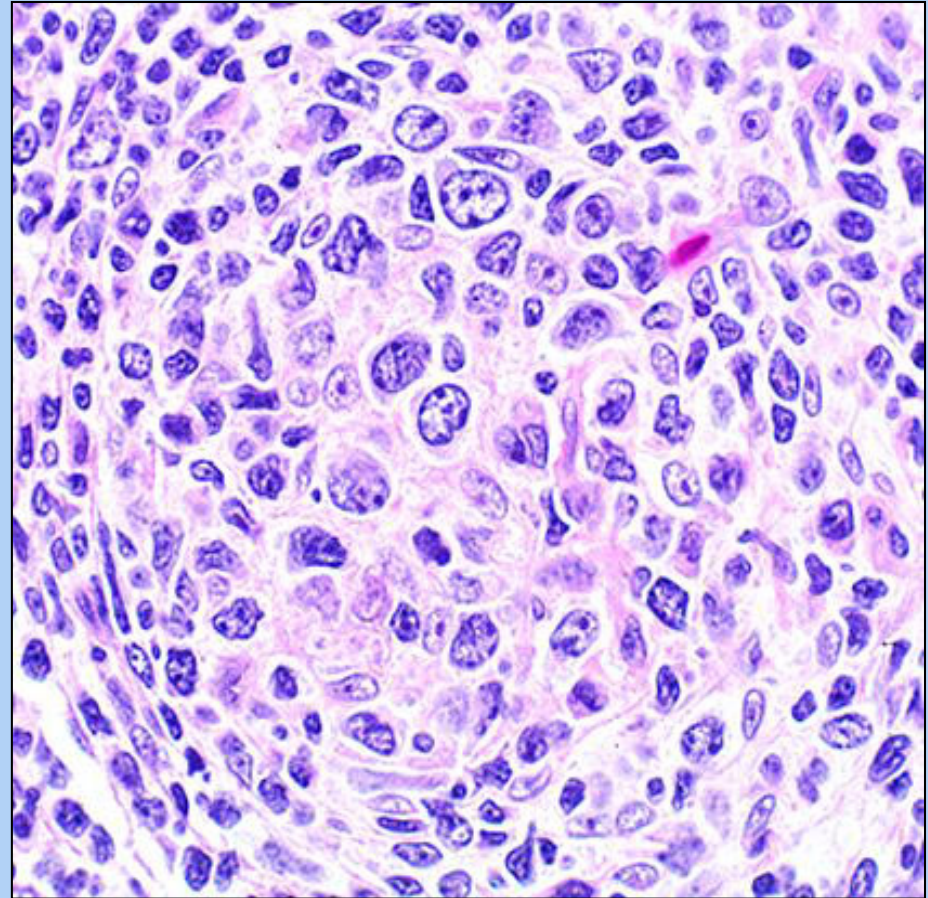
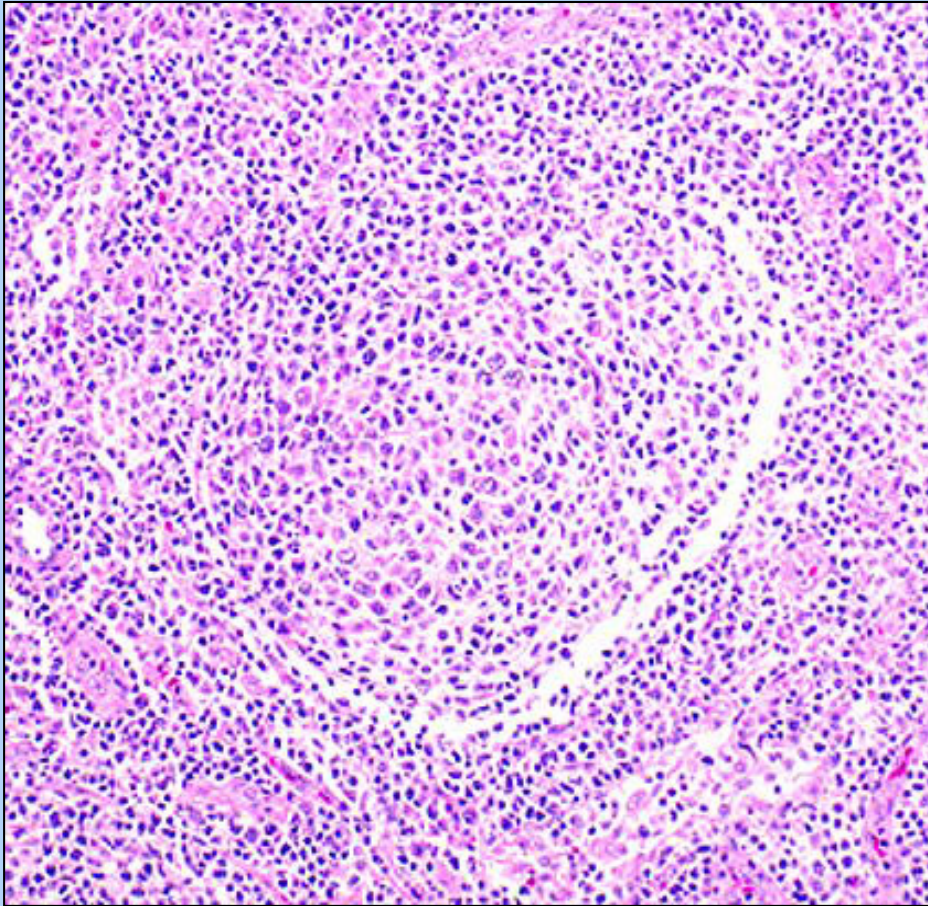


S75-647





Cytological Grading of Follicular Lymphoma



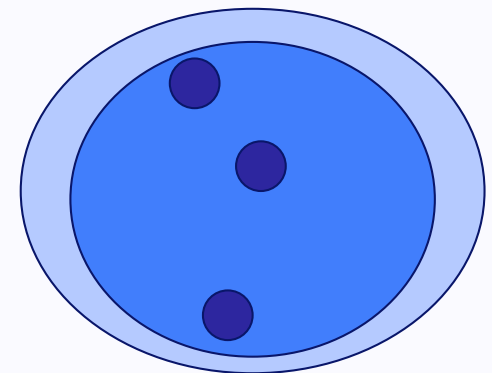
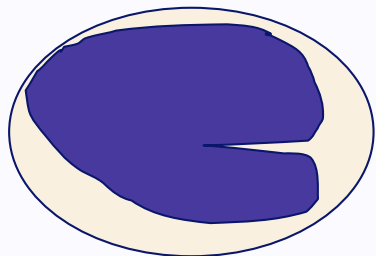
Follicular Lymphoma Grading (WHO 2008/ 2017)

Grade 1 < 5 centroblasts/ hpf
Grade 2 5-15 centroblasts/ hpf

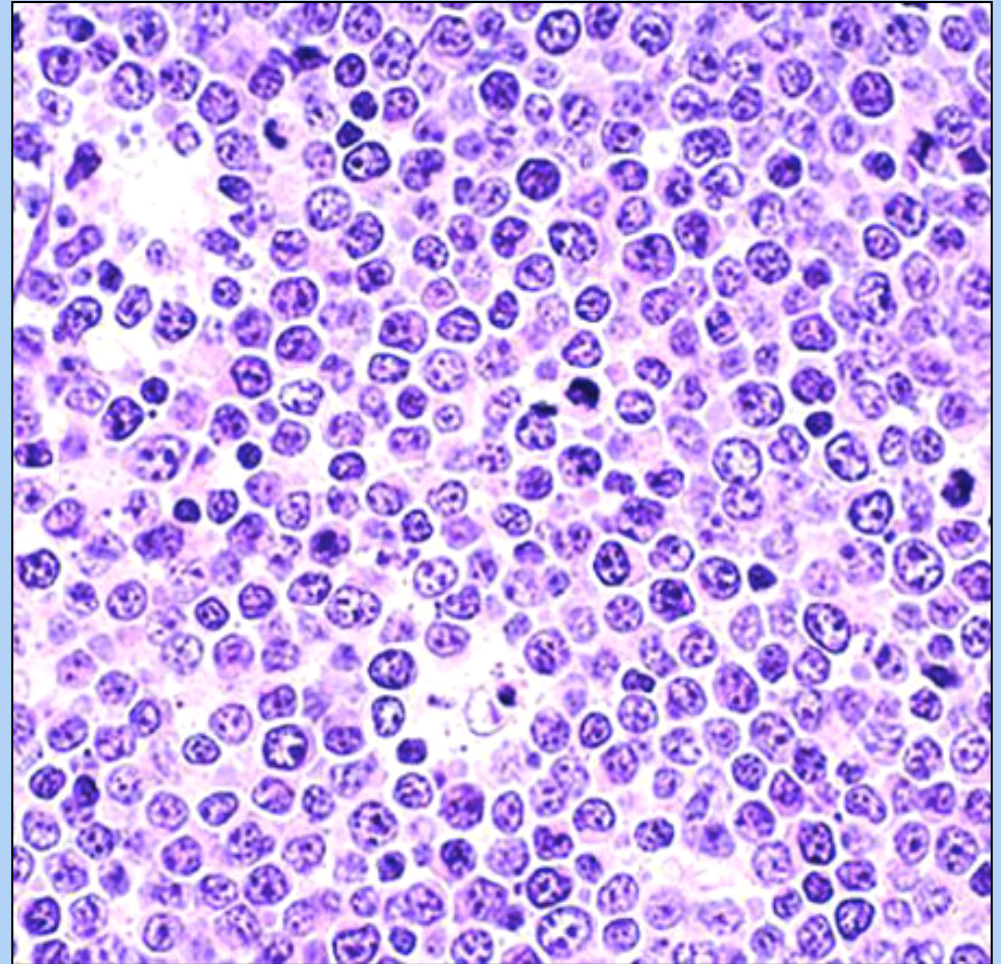
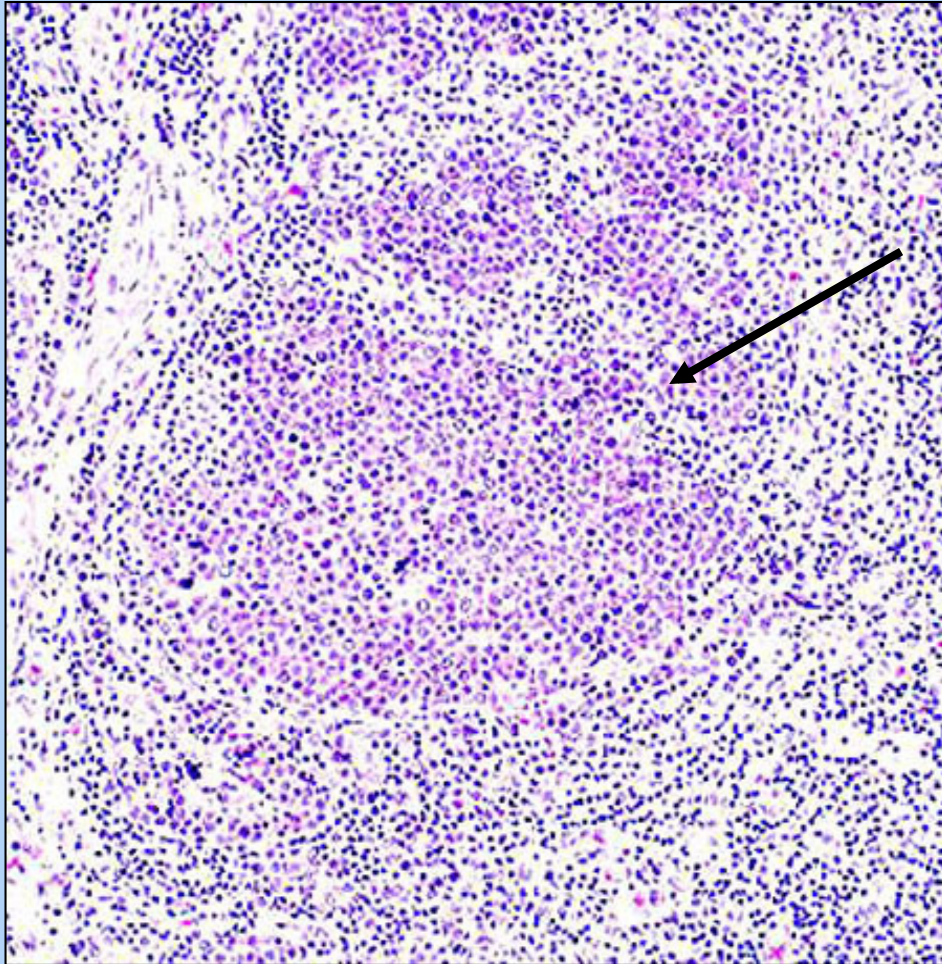
Grade 1-2 need not be distinguished

Grade 3A > 15 centroblasts/ hpf
centrocytes still present

Grade 3B Centroblasts in solid sheets
centrocytes absent



Follicular Lymphoma 3B



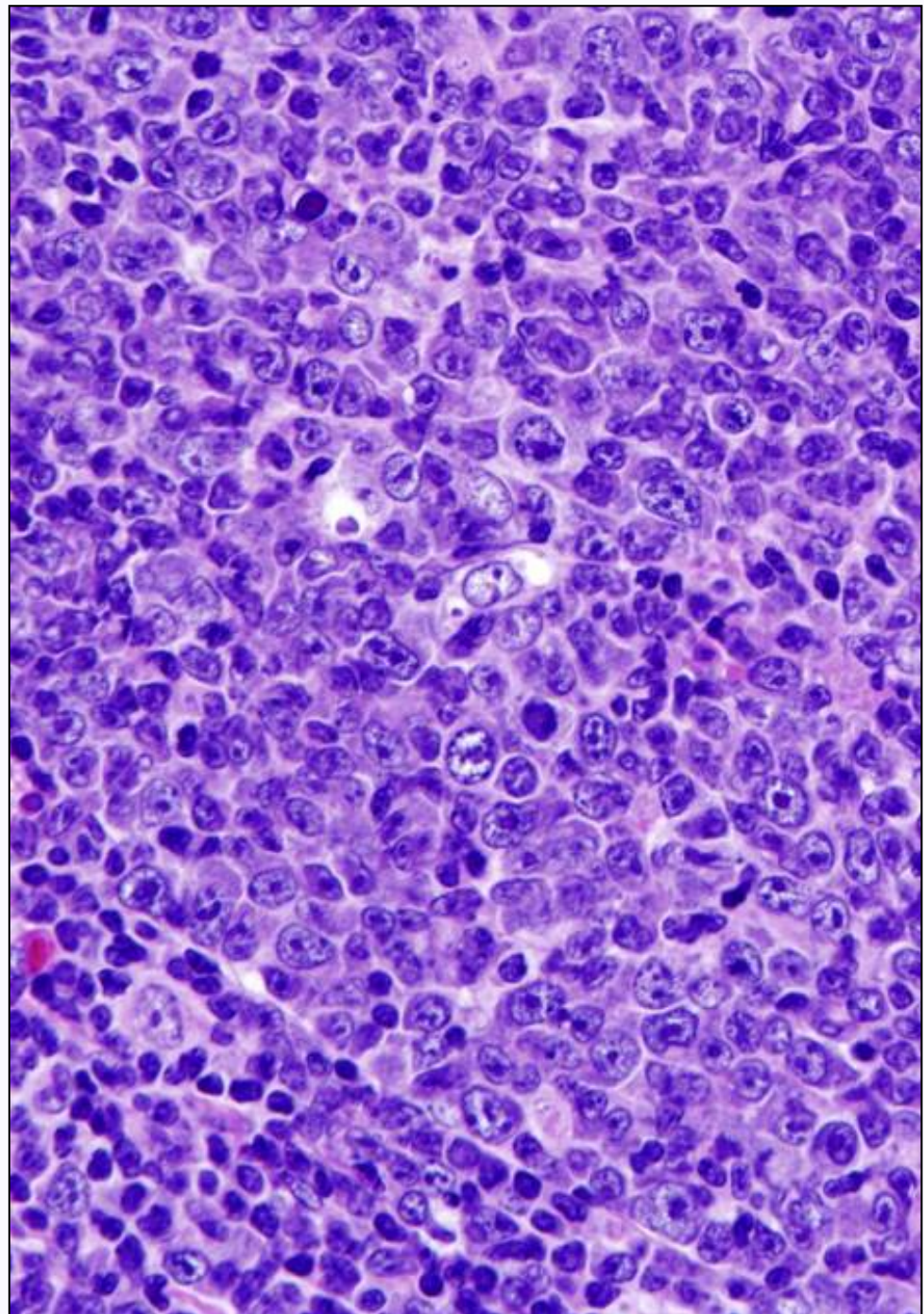
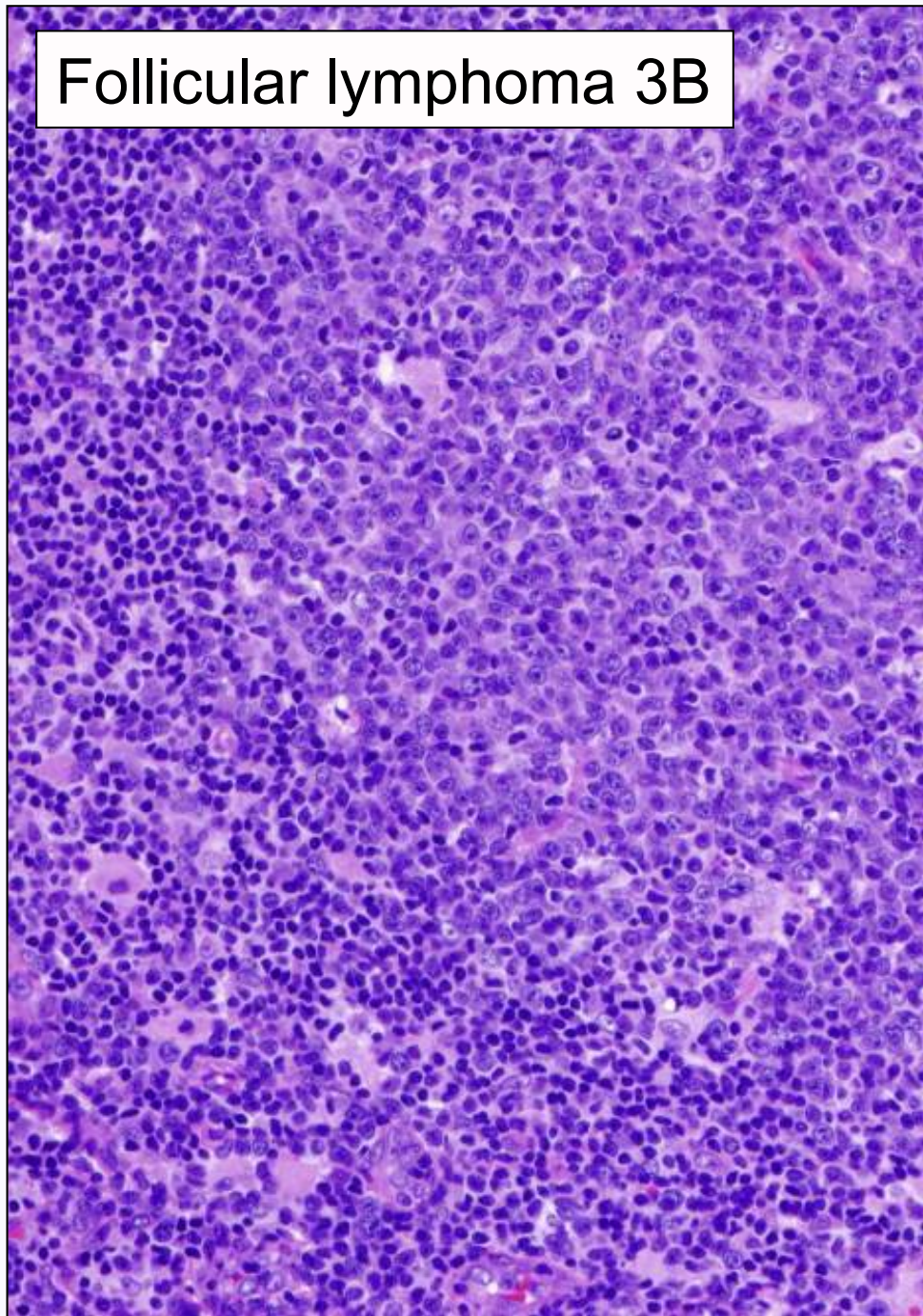
Closely related to DLBCL at the genetic level, .. but for the time being still FL

Follicular Lymphoma expressing MUM1/ IRF4 & lacking CD10

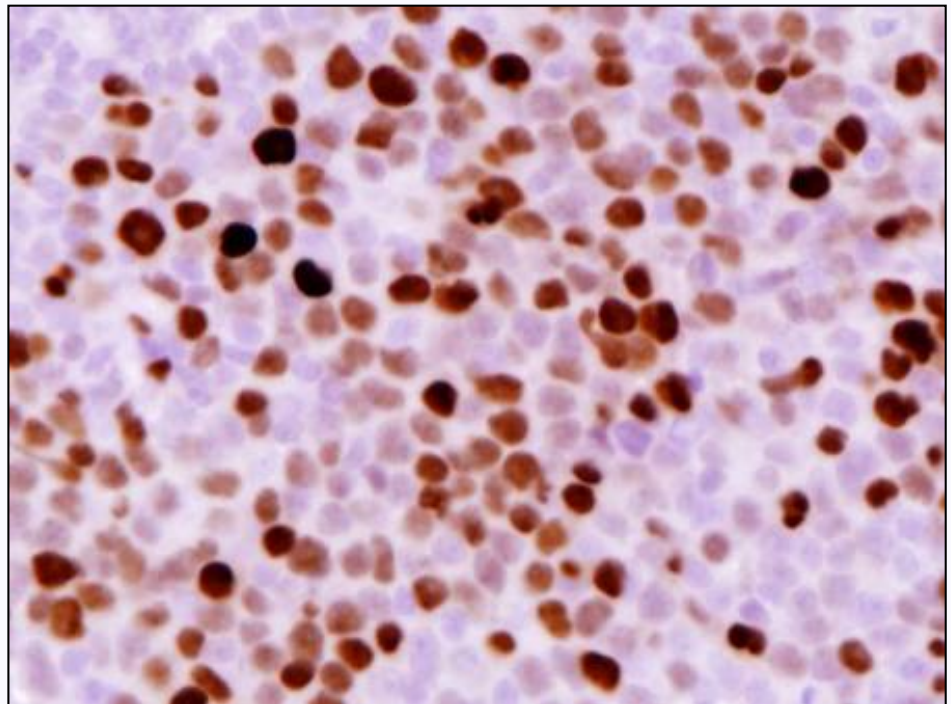
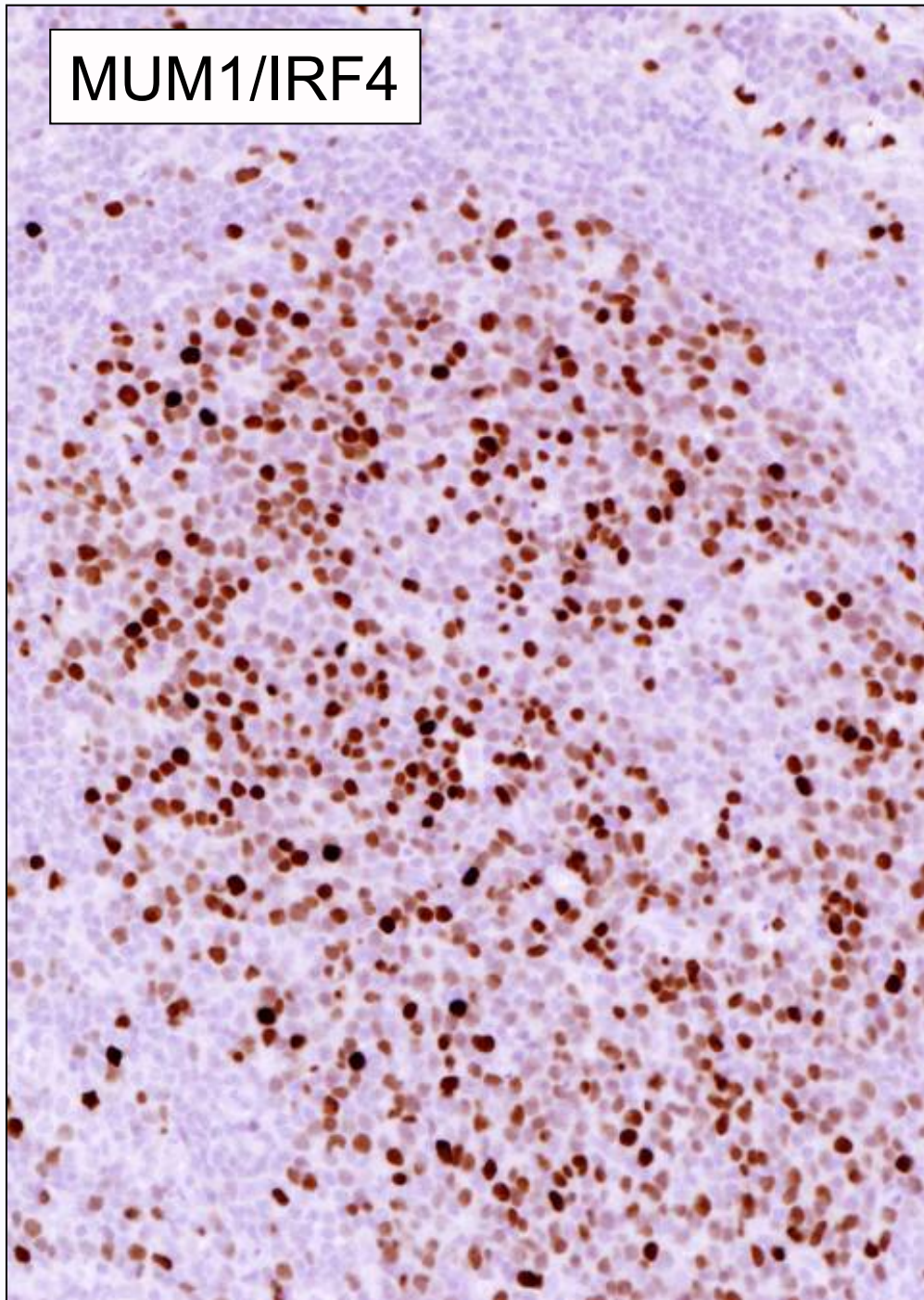
Karube et al. 2007, 2008

- Usually high grade, Grade 3A or 3B
- Negative for *IGH/BCL2* (only 5%)
- *BCL6* translocation or amplification common
- Often with diffuse areas
- More aggressive clinical course, patients are frequently elderly

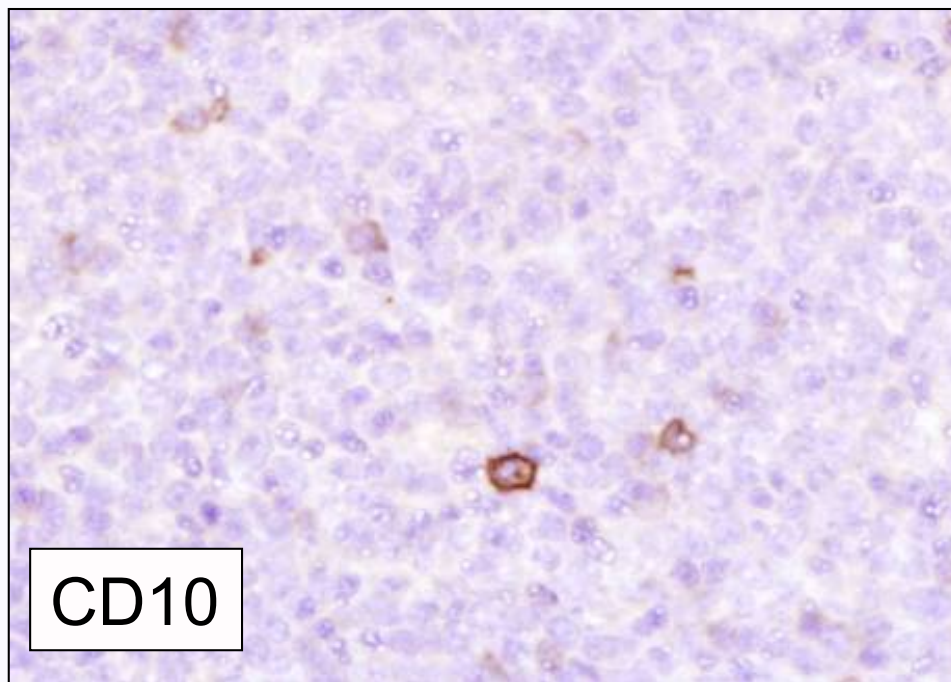
Follicular lymphoma 3B



MUM1/IRF4



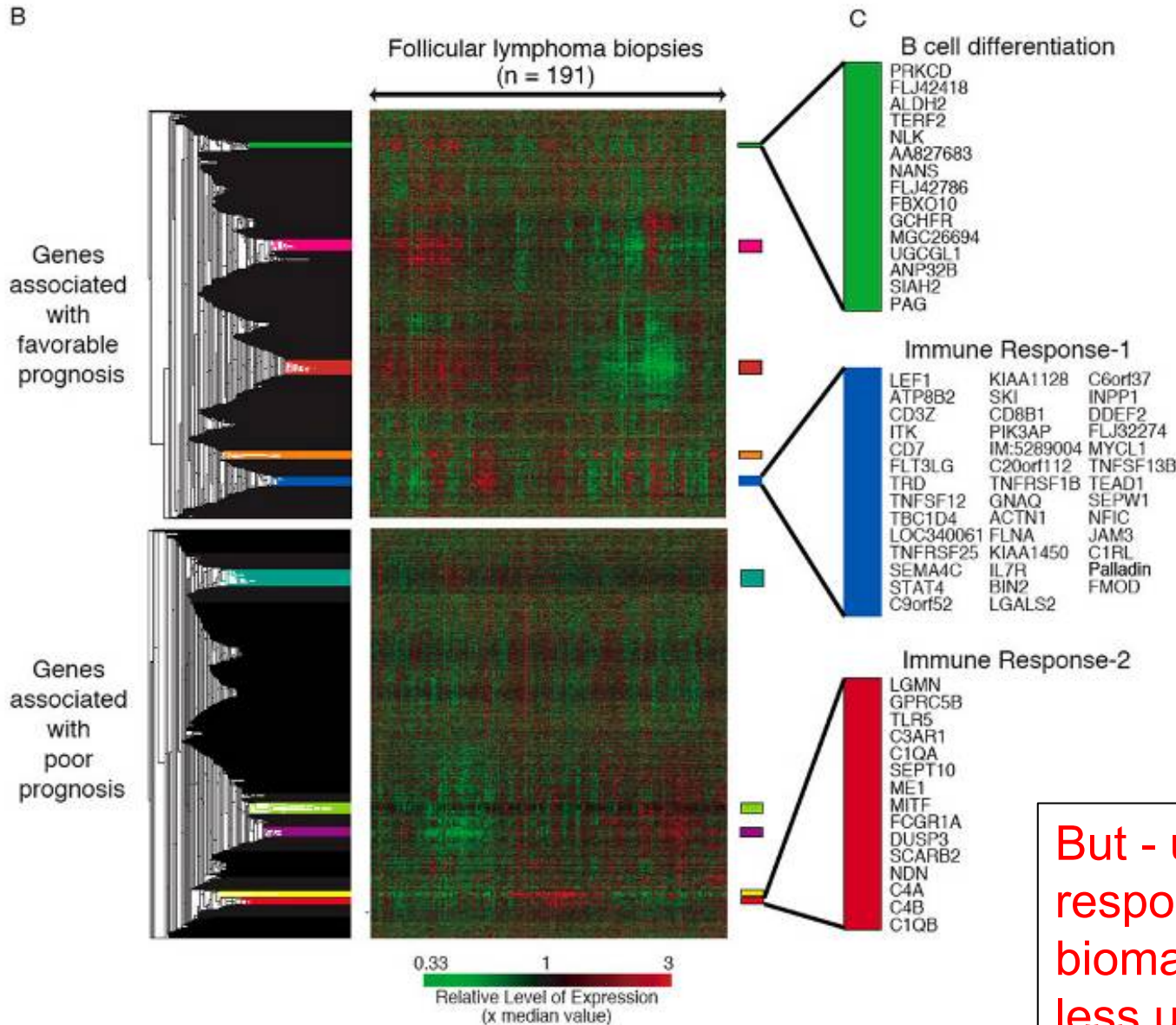
CD10



Historical Evidence for the Importance of the Host Immune Response in FL

- Follicular lymphoma waxes and wanes
- Spontaneous remissions observed, sometimes after acute viral illness
- Rapid and sometimes lasting responses seen after vaccine therapy
- Evidence of an immune response in responders rx with anti-idiotypic, but not in non-responders

Impact of the Microenvironment on Survival in FL



Immune response 1 associated with good prognosis is enriched for genes expressed in PB T-cells

Immune response 2 associated with poor prognosis is enriched for genes expressed in PB monocytes

But - use of immune response signatures & biomarkers have been less useful in daily practice !

Dave et al. N Engl J Med, 2004



Prognosis in follicular lymphoma is multifactorial ...

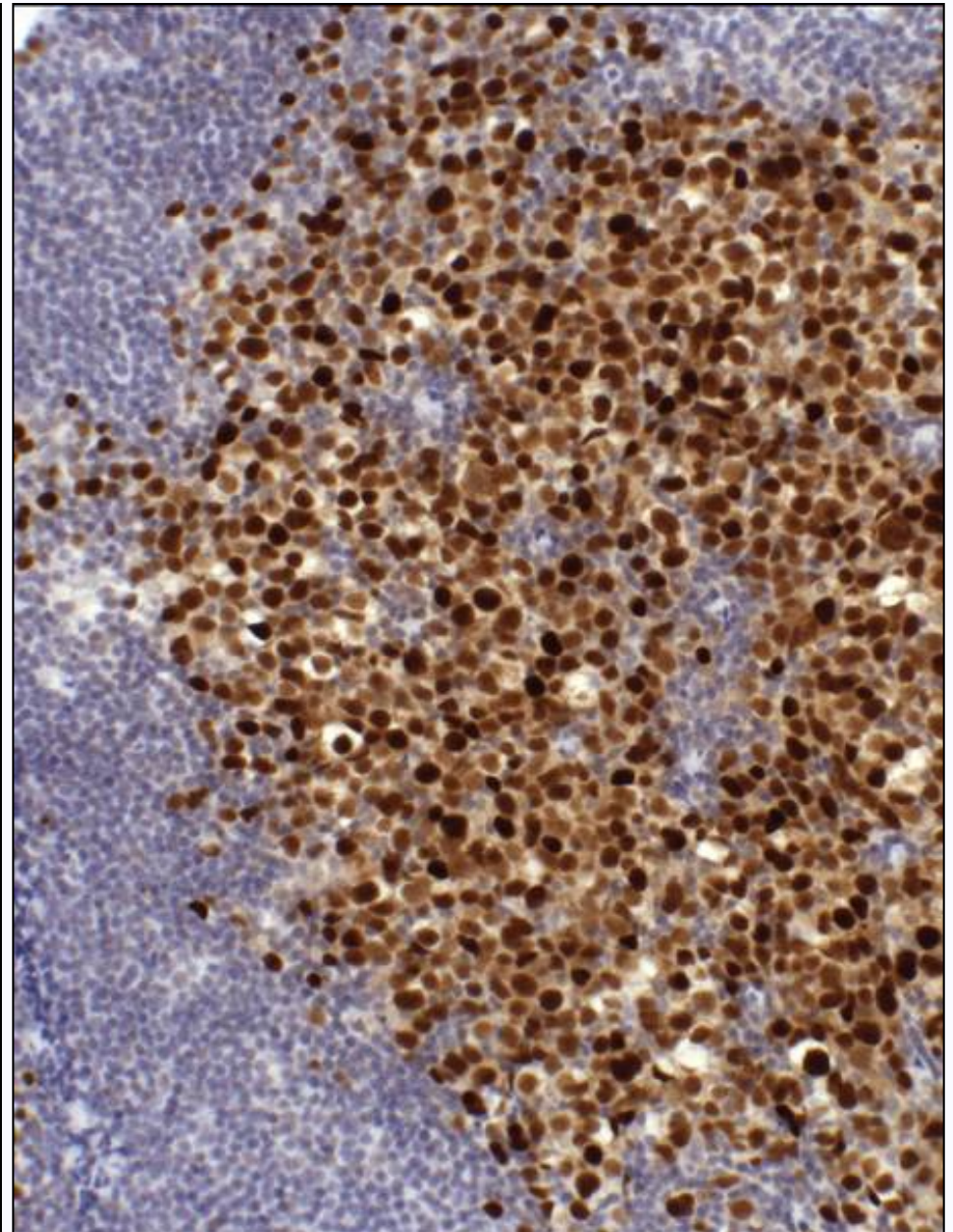
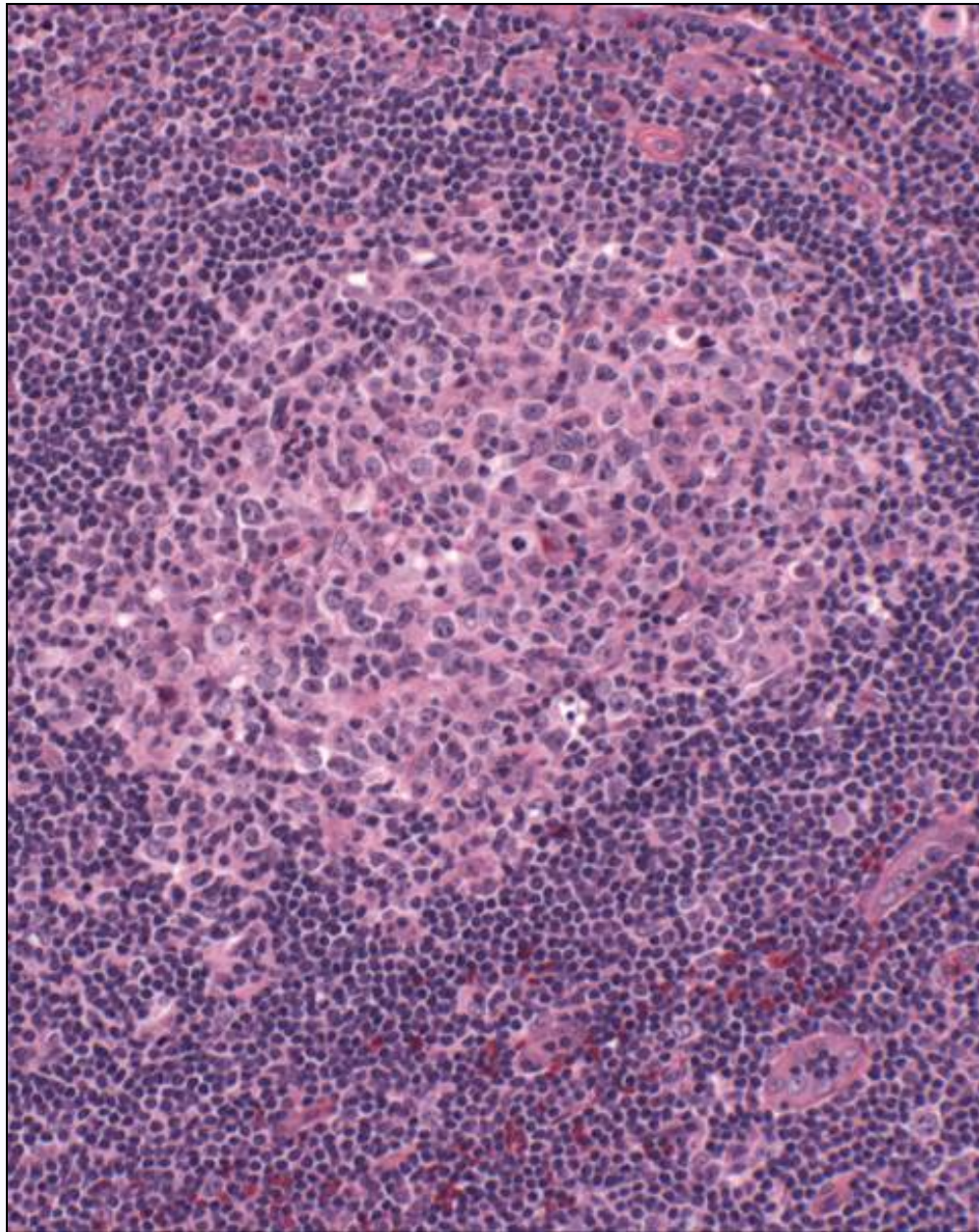
Like the weather, use
all available data to assess risk

- Proliferation index/ grade
- Stage/ FLIPI
- Host immune response / microenvironment
- More recently mutational profile (m7-FLIPI)

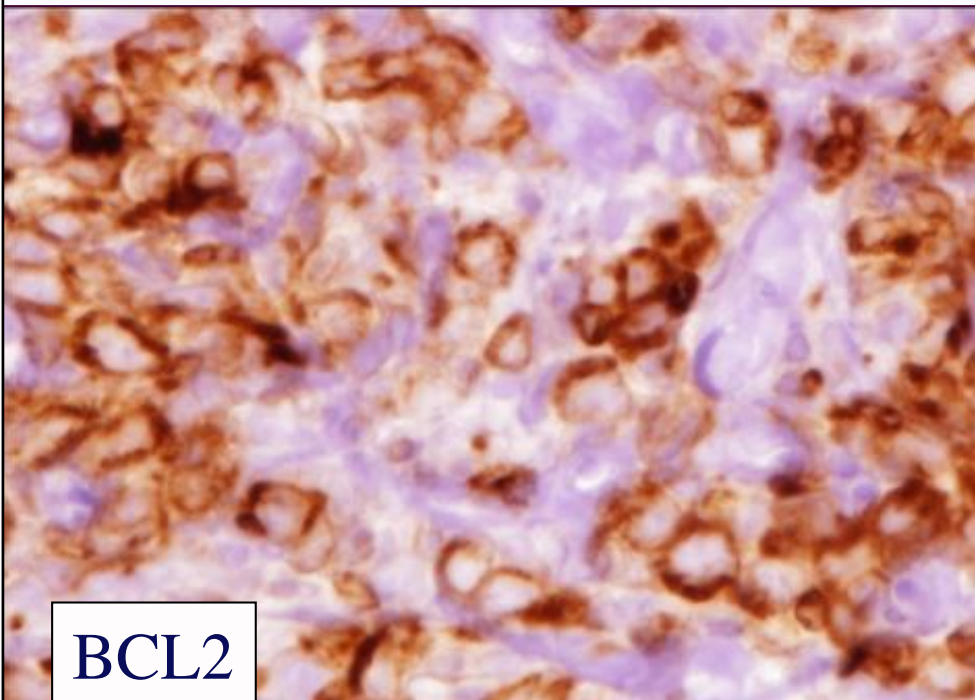
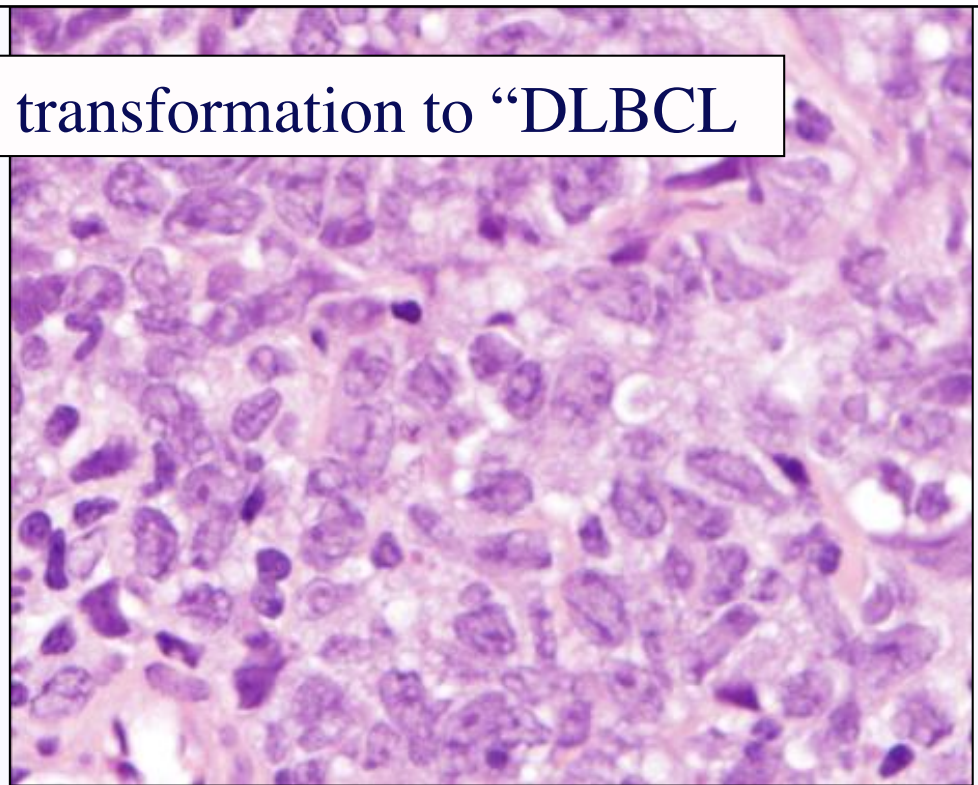
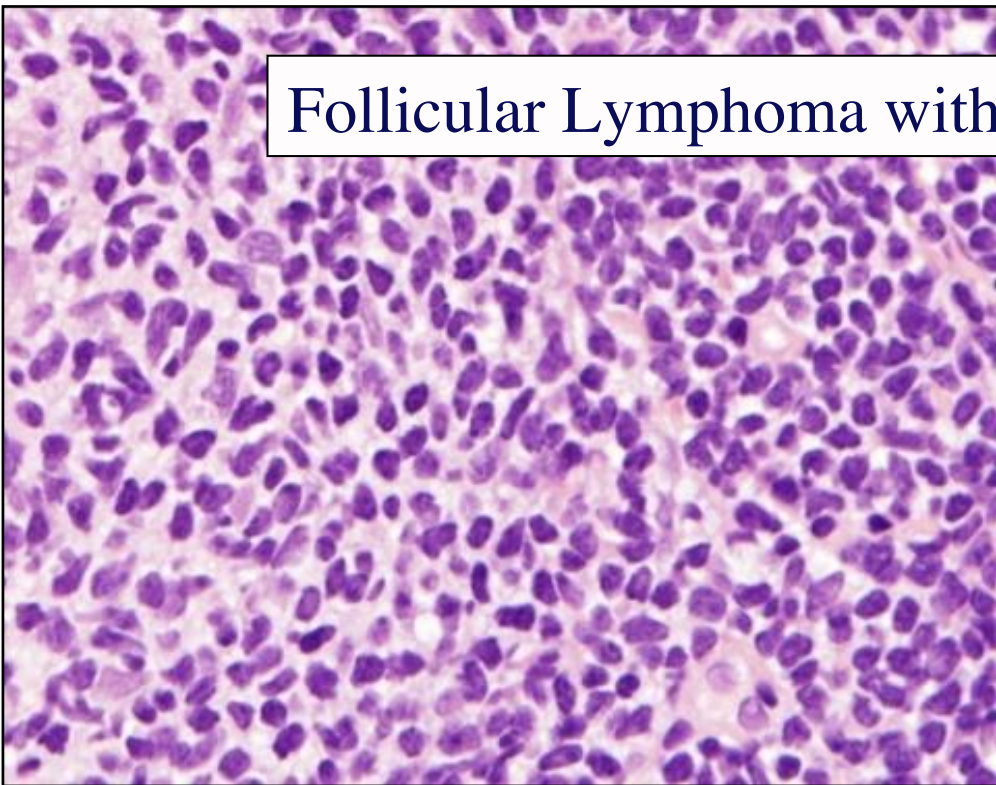
Histological Progression in Follicular Lymphoma –
2° events lead to diverse histologies and phenotype
- all with *BCL2R* & clonally related to FL

- Diffuse large B-cell lymphoma (most common)
- “High Grade B-cell lymphoma” with MYC and BCL2 or BCL6 (so-called double hit lymphomas)
- Pre-B lymphoblastic lymphoma leukemia
- Classical Hodgkin’s lymphoma
- Histiocytic / dendritic cell sarcoma

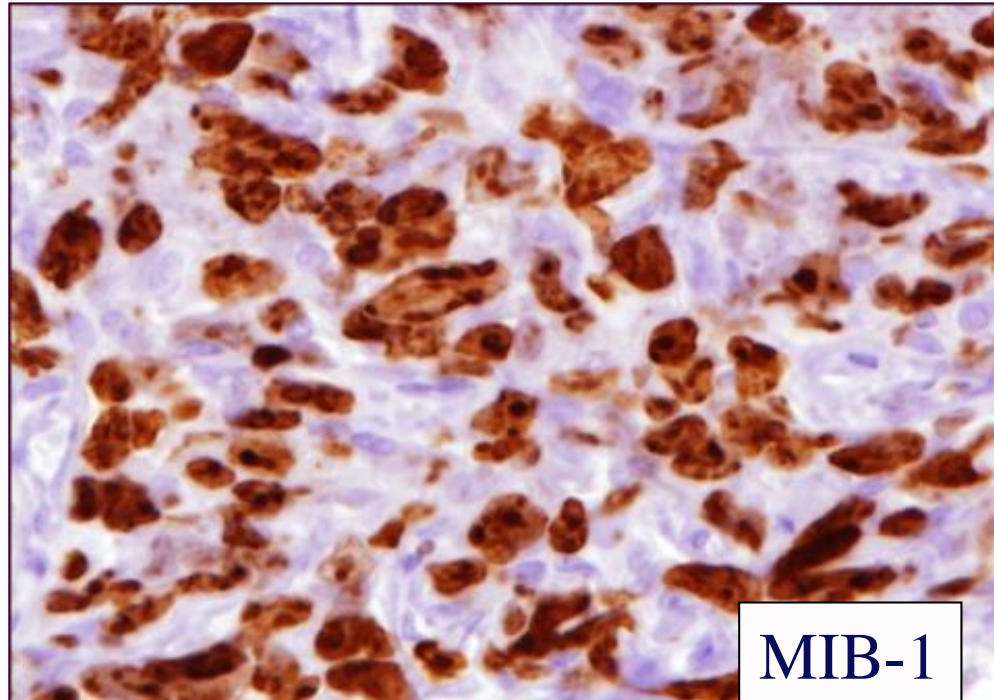
TP53 mediated transformation of follicular lymphoma



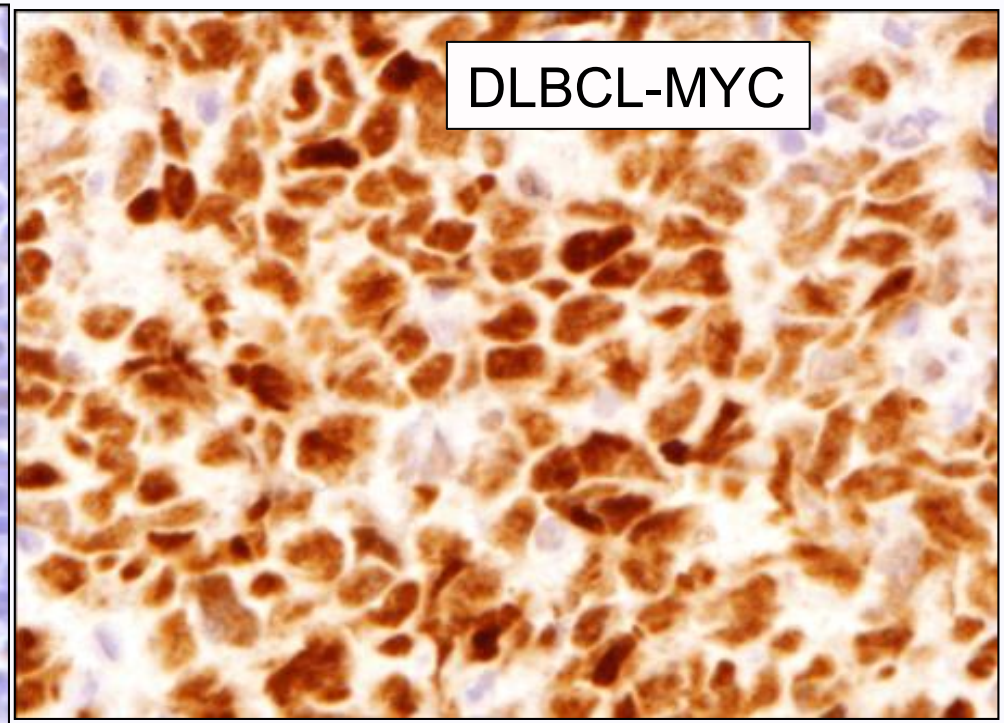
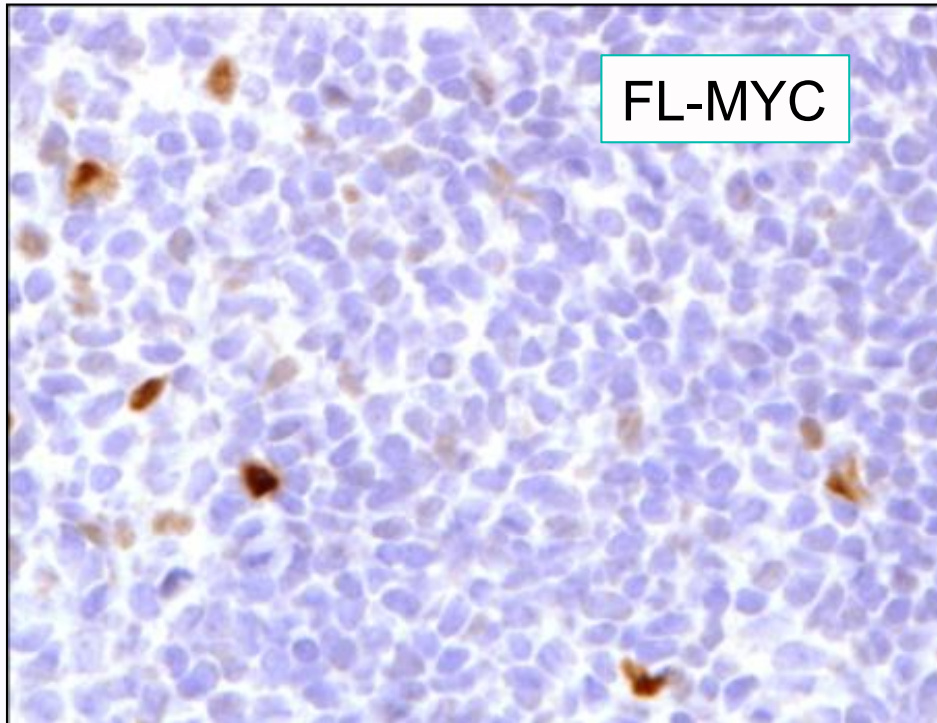
Follicular Lymphoma with transformation to "DLBCL



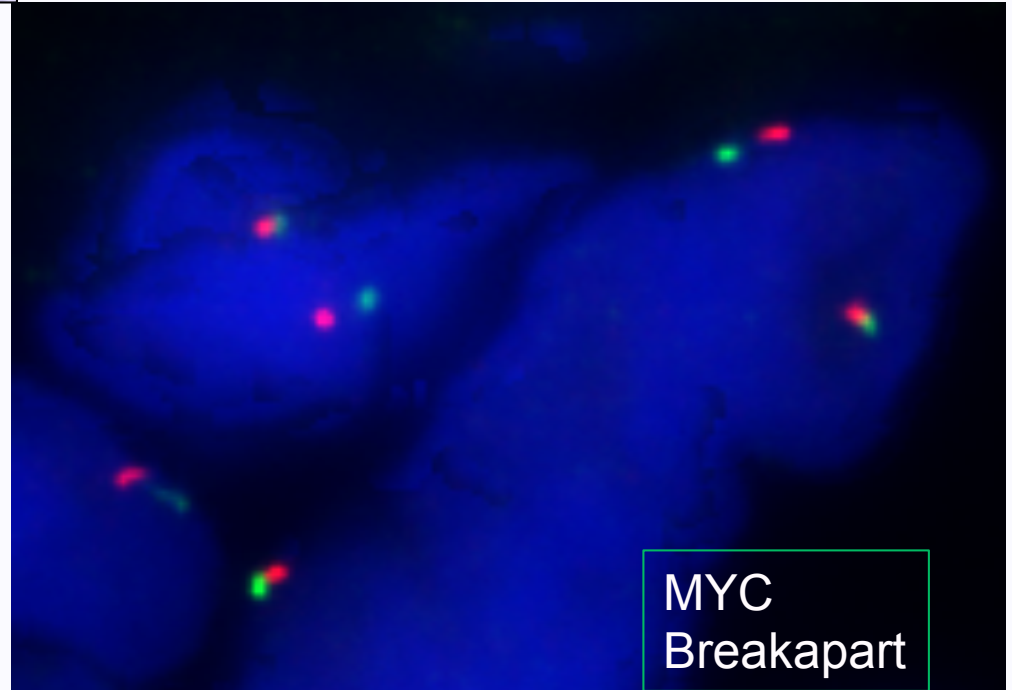
BCL2



MIB-1



- Only DLBCL positive for MYC protein
- Only DLBCL has *C-MYC* R
- Both FL and DLBCL have *BCL2* R
- Presence of both *BCL2* and *MYC* rearrangement indicates diagnosis of “high grade B-cell lymphoma” (double hit)

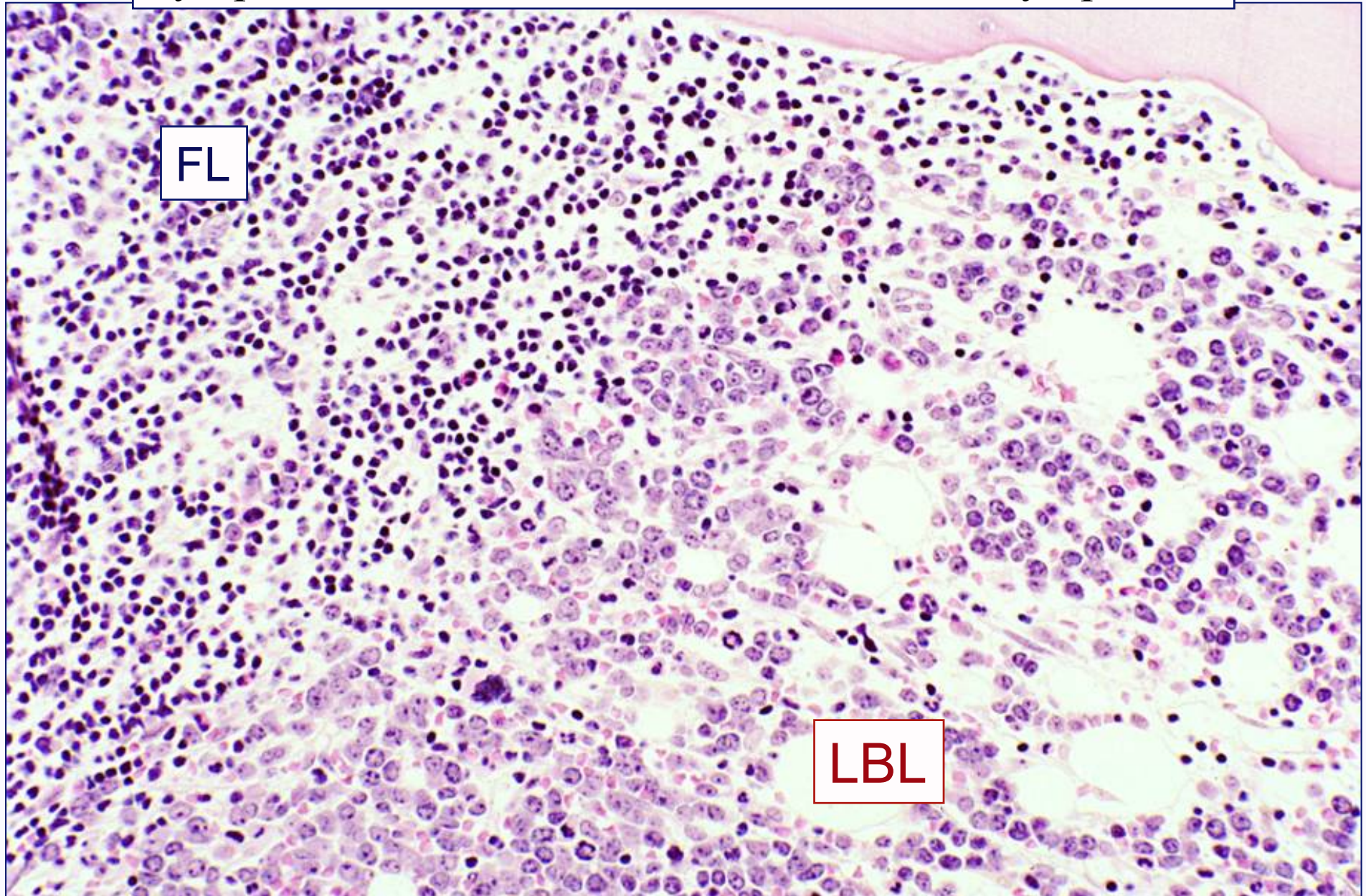


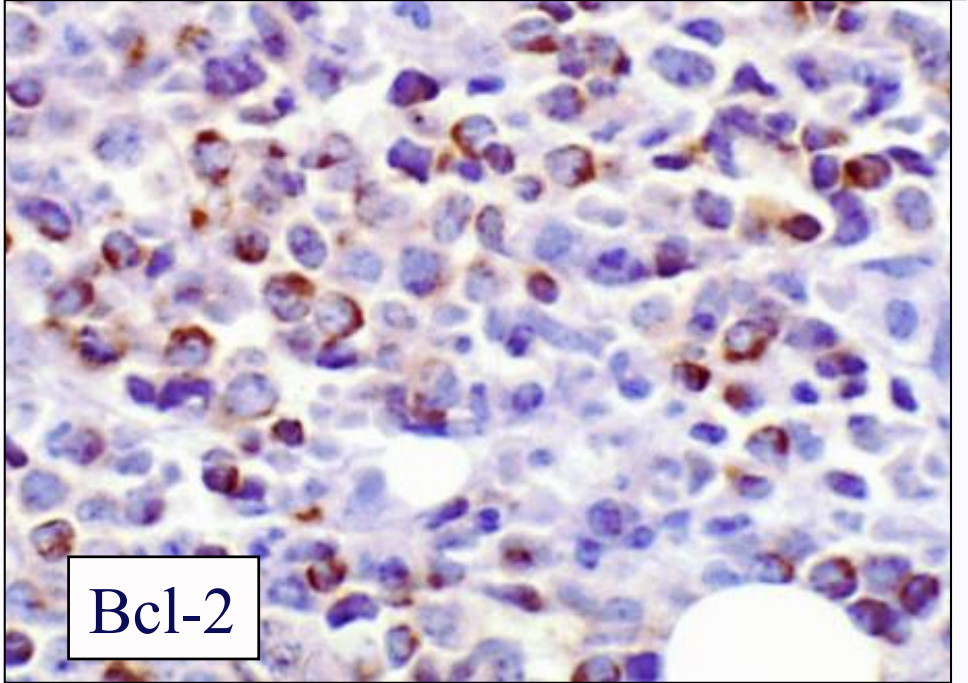
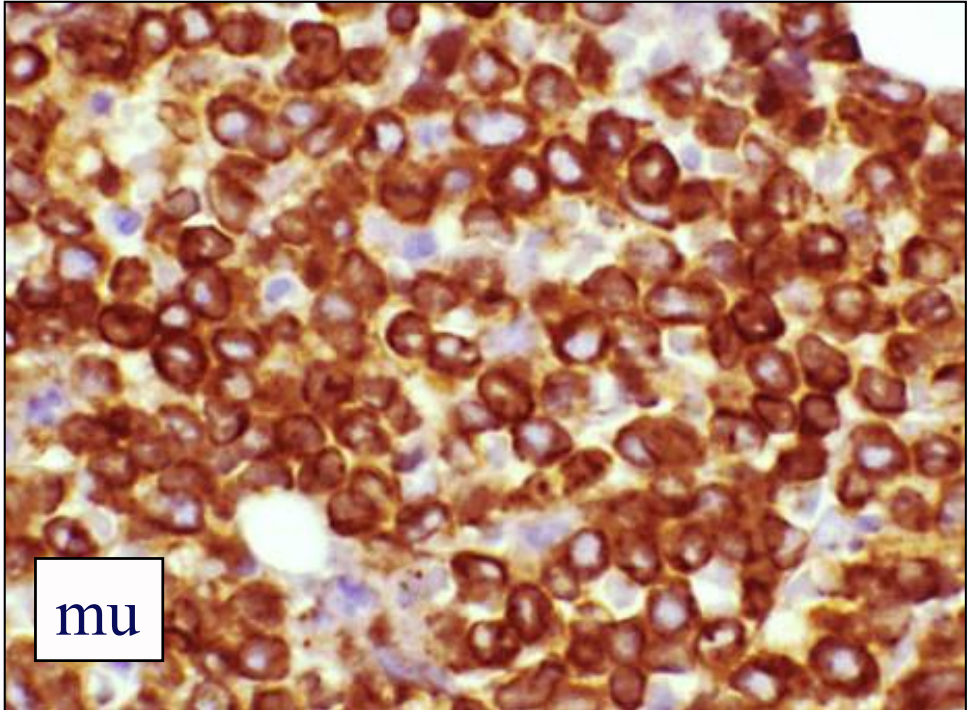
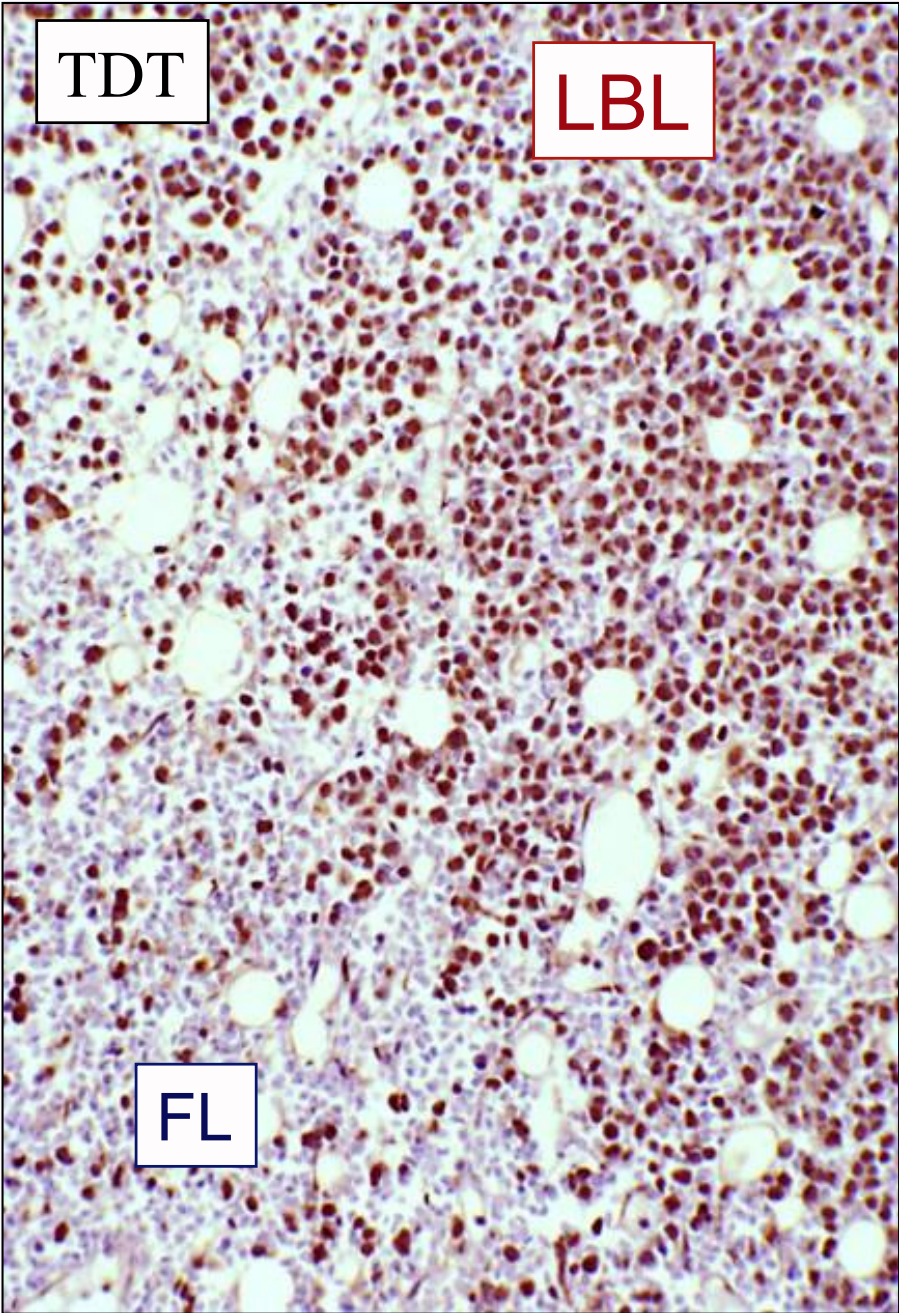
Lymphoblastic Transformation of FL

(de Jong et al 1988; Kobrin et al 2006; Geyer et al. 2015)

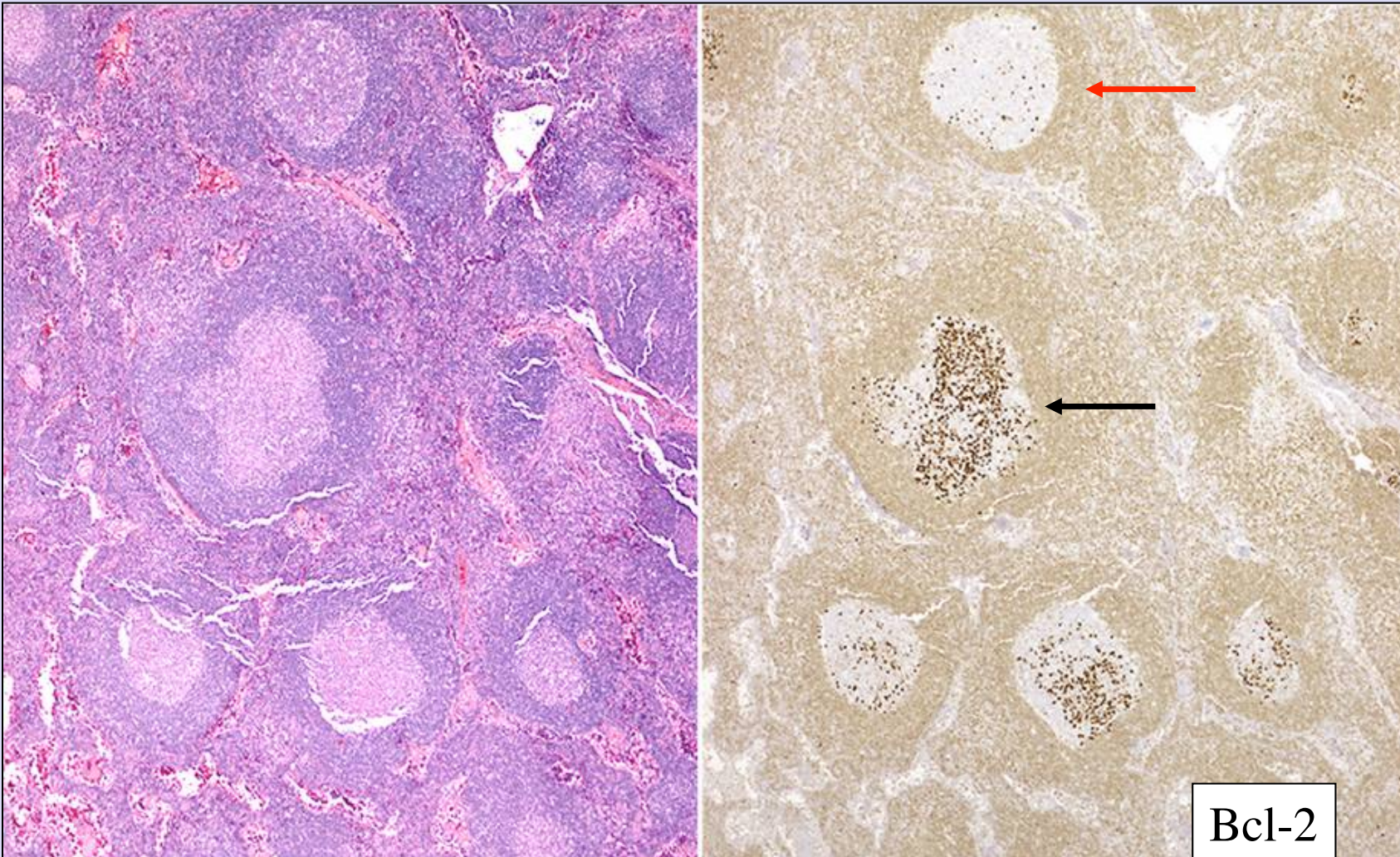
- Precursor B-cell phenotype, TdT +
 - Bone marrow and PB involved with clinical picture of ALL
- Clonally related to original FL t(14;18)
- Usually have a *C-MYC* rearrangement, but not included in WHO “double hit” category
- Follicular lymphoma (low grade) may persist focally in BM or LNs

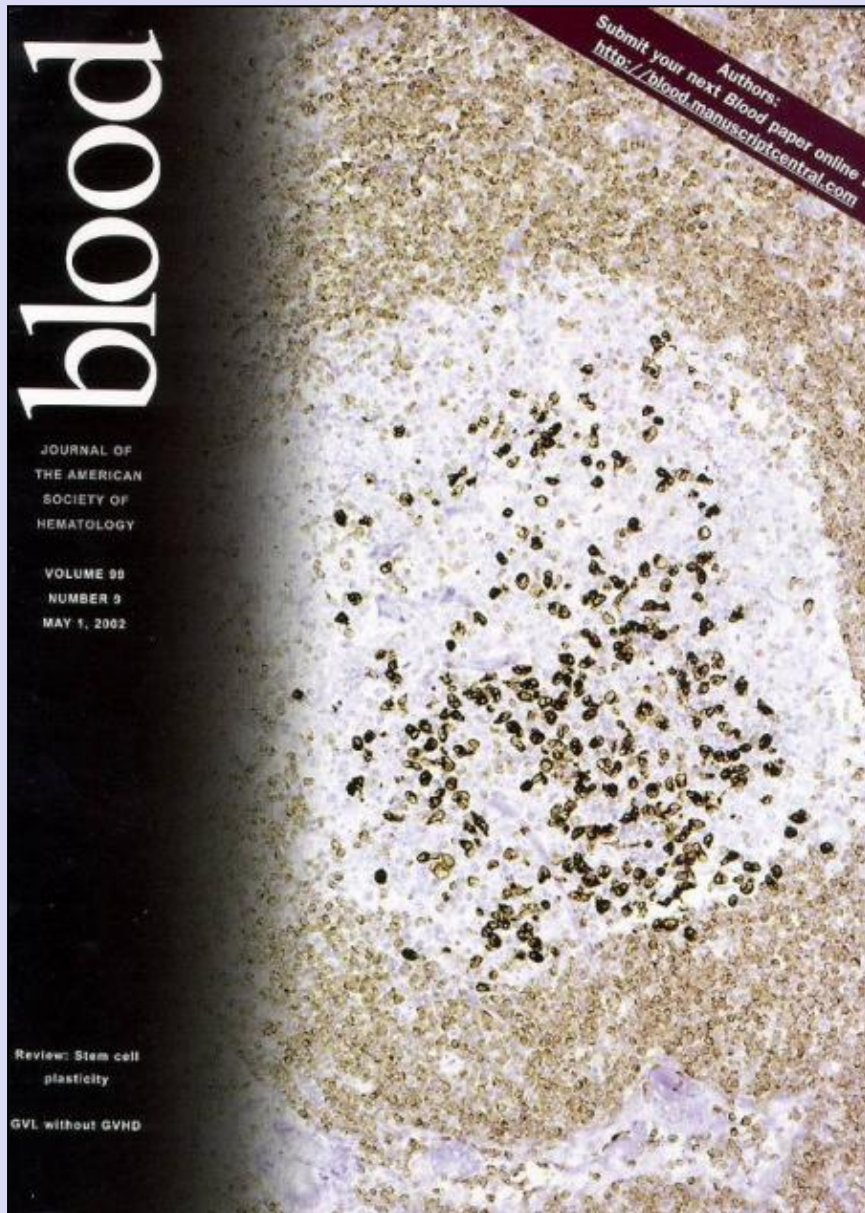
Lymphoblastic Transformation of Follicular Lymphoma





FL In situ (FLIS) (Cong et al. Blood 2002)
In Situ Follicular Neoplasia (WHO 2017)



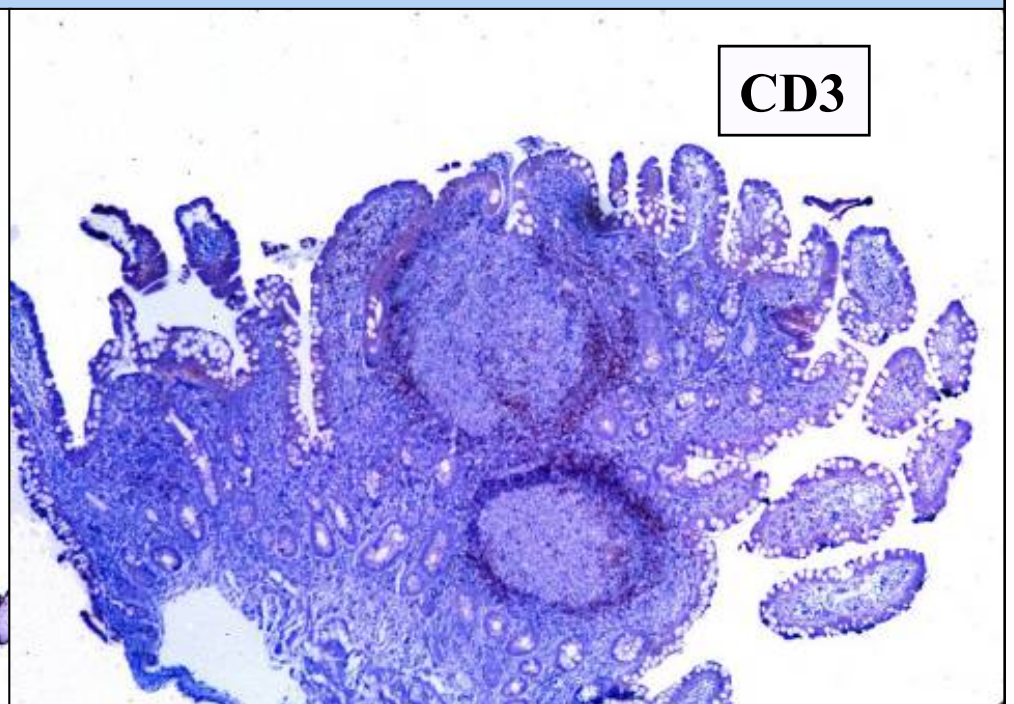
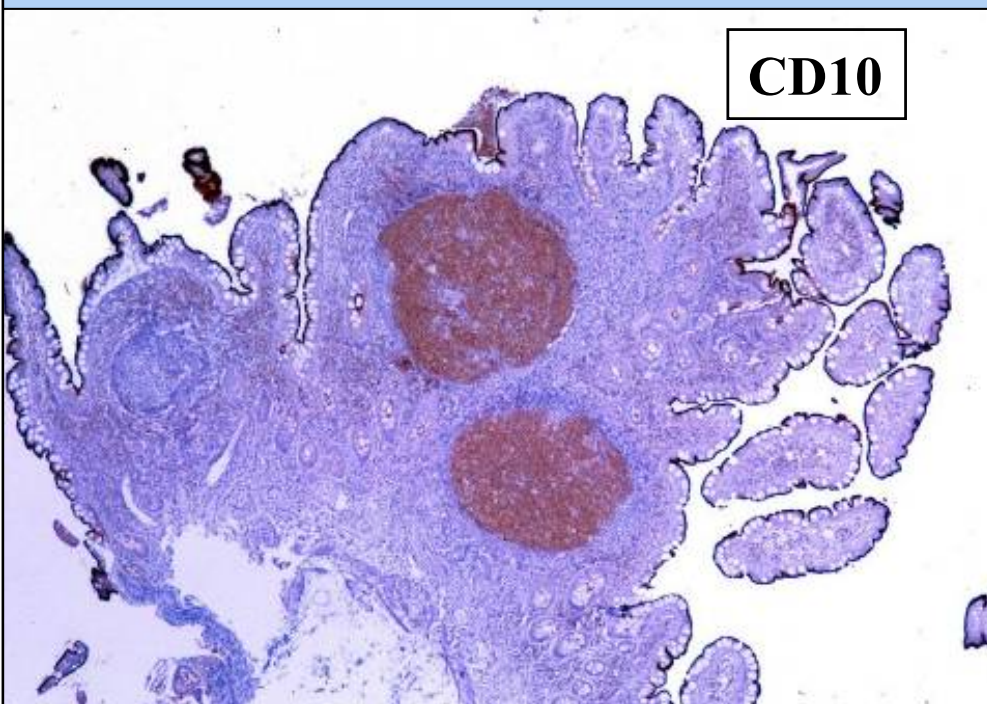
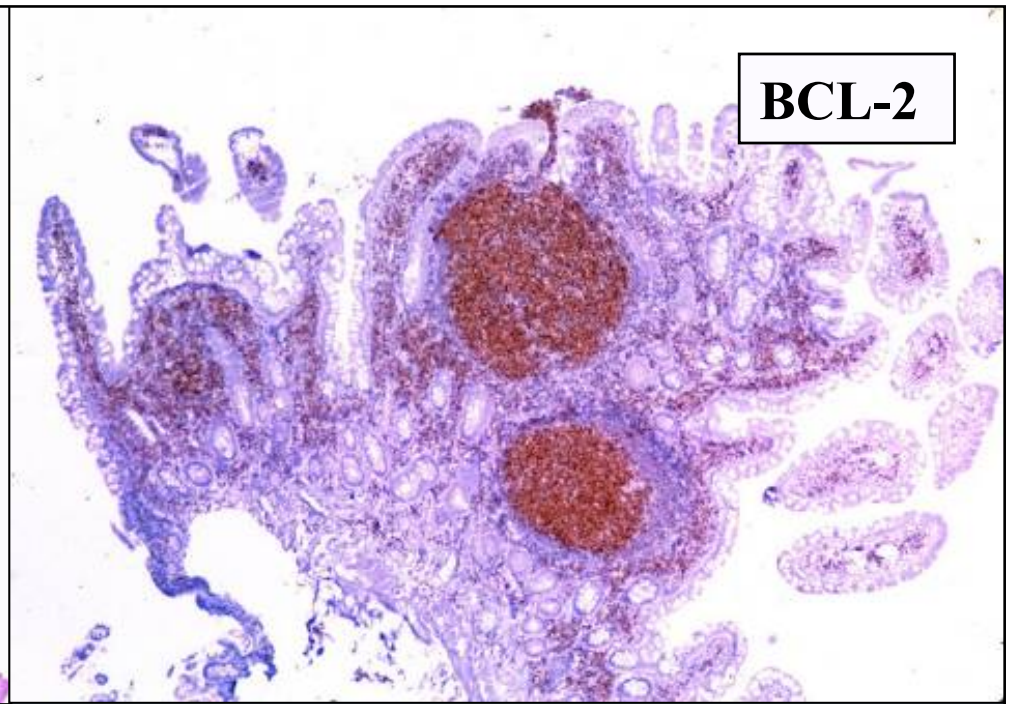
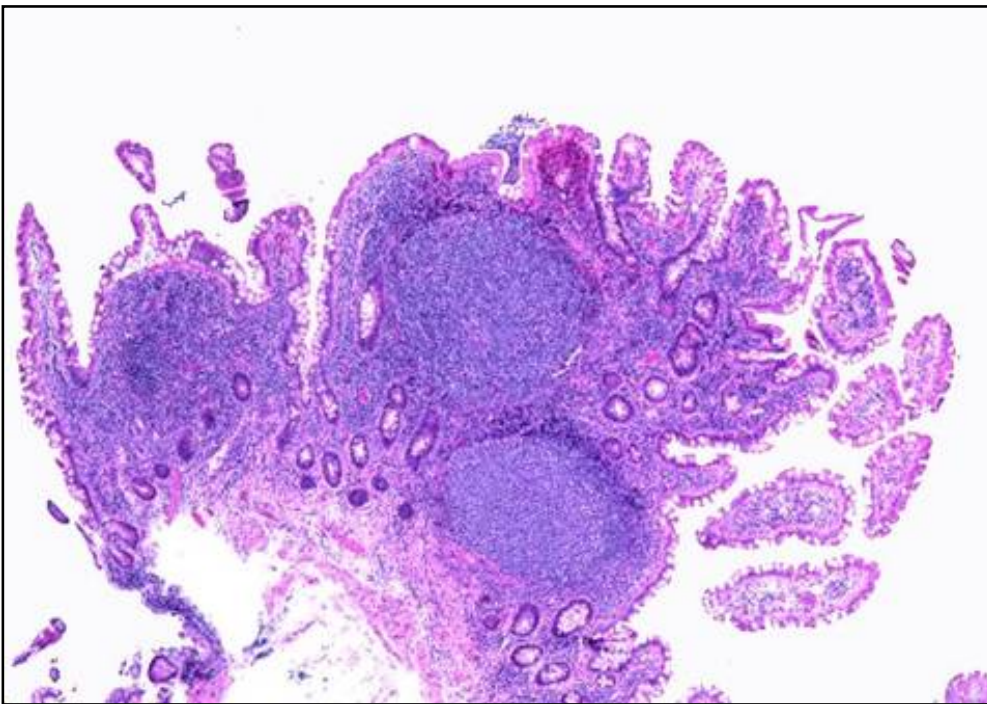


- FL-like B-cells home to GC environment
- 2-3% of all lymph node biopsies; sometimes coincidental with other B-cell lymphomas
- Low level of genetic aberrations beyond *BCL2R*
- Low risk of progression to FL < 5%
- No therapeutic intervention required

Duodenal-type Follicular Lymphoma

(Schmatz JCO 2011; Takata 2013)

- Phenotypically and genetically similar to nodal FL (*BCL2/IGH*), but usually IgA+
- Low level of genetic aberrations beyond *BCL2R*
- Commonly present in duodenum
 - other sites in distal small bowel
- Superficial polypoid lesions in mucosa
- Express homing receptor found on intestinal lymphocytes ($\alpha4\beta7$ integrin)
- Lack AID activity
- Local recurrences without dissemination
 - *self-limited course*



Pediatric Follicular Lymphoma

WHO 2008

Rare subtype in children (1-2%)

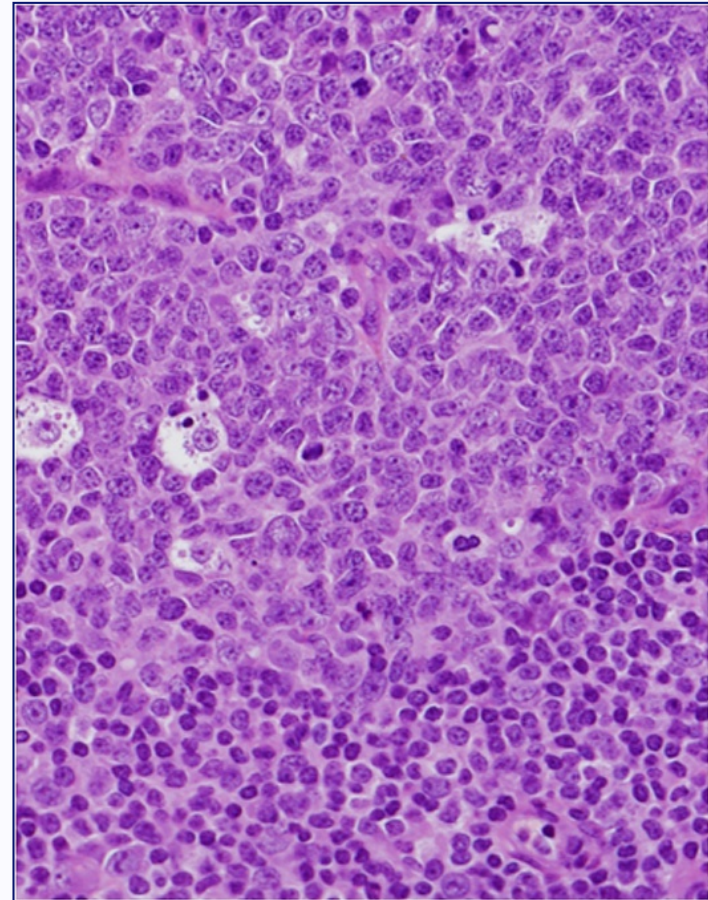
Tonsils, nasopharynx, GI tract,
testis, lymph nodes

Typically “high grade” (3A/3B)

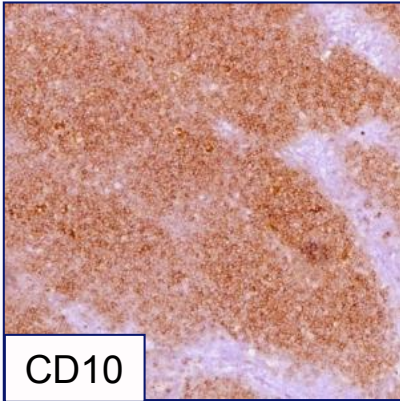
Male >> Female

85% localized, Stage I or II

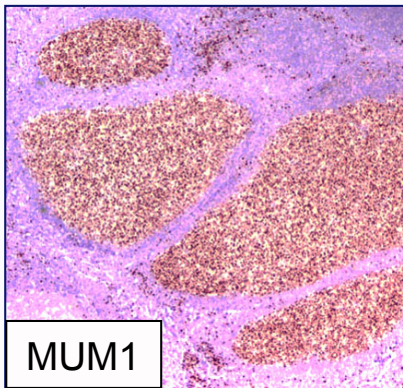
- Not clearly defined as an entity
- Nodal and extranodal forms not clearly distinguished



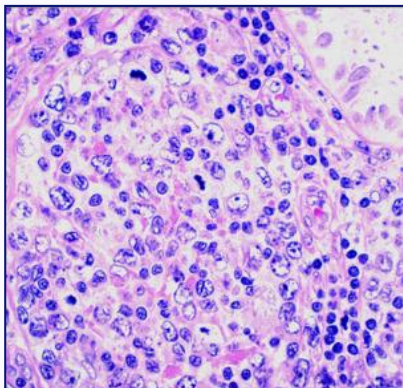
Pediatric Follicular Lymphomas WHO 2017



Nodal, Usually Head and Neck, Stage I
M >>F, BCL2R / BCL6R negative
CD10+, BCL6+, BCL2-, MUM1-



Tonsil/ Waldeyer's ring; M=F
Co-expression of MUM1, BCL6, often CD10
Frequent IRF4 breaks (6p25)
IRF4 + large B-cell lymphoma – provisional entity in revised WHO



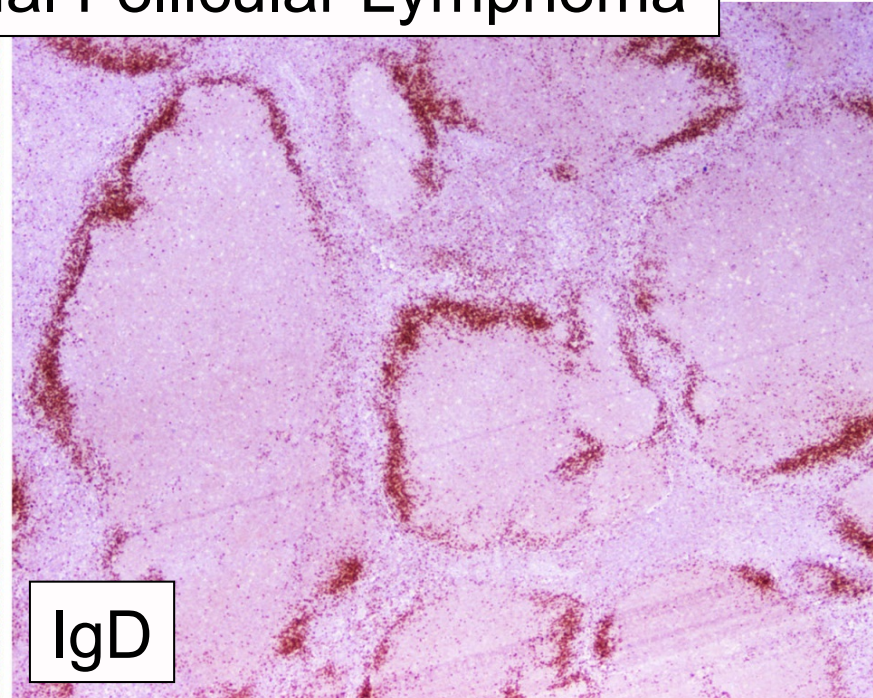
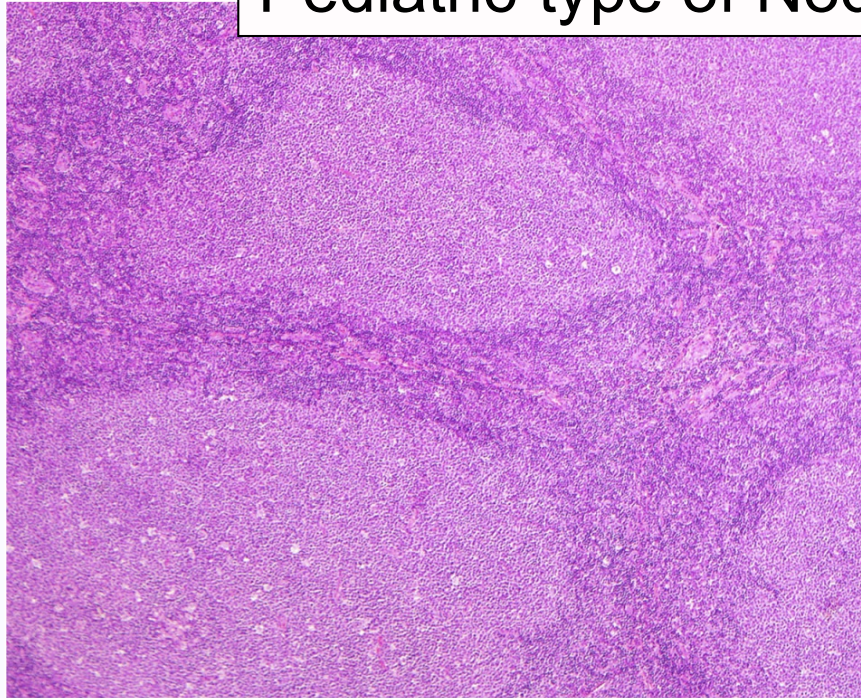
Testicular, Stage I, good prognosis
CD10+, BCL6+, BCL2-, MUM-
Occasional BCL6 breaks

Pediatric-type Follicular Lymphoma

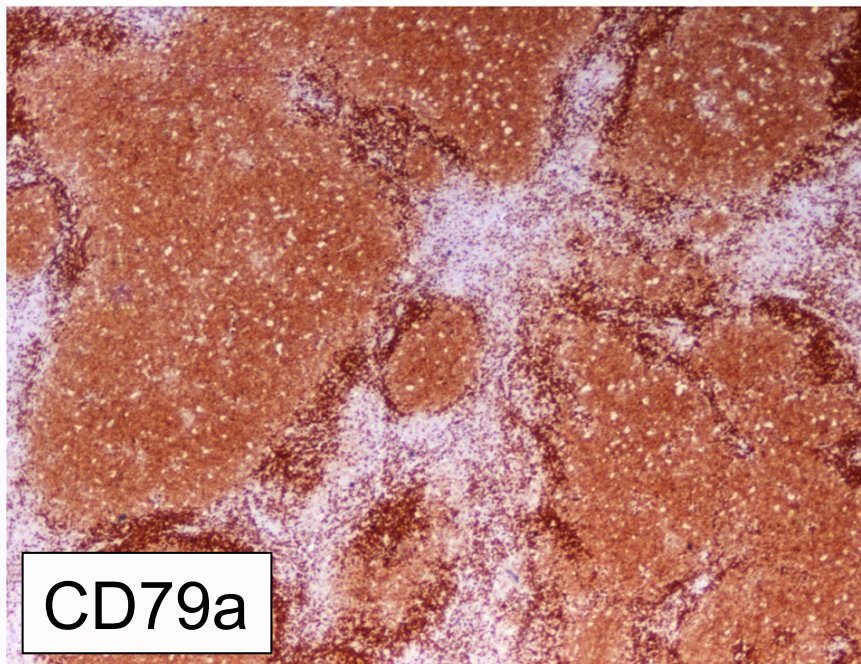
(Louissaint et al, 2012; Liu et al 2013)

- A clonal germinal center B-cell proliferation of undetermined malignant potential
- Median age, 15-18 yrs, uncommon over age 40
- Marked male predominance (~10:1)
- Clonal CD10+ B-cells by flow; IG PCR+
- No genetic aberrations for BCL2, BCL6, IRF4
- Many patients in continuous CR following surgical excision and no further treatment – conservative approach recommended

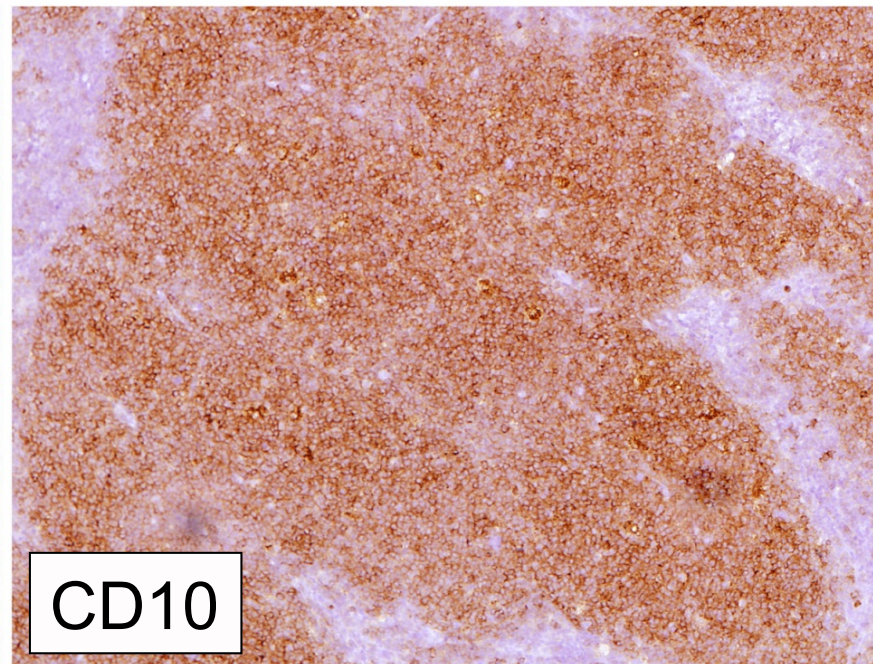
Pediatric-type of Nodal Follicular Lymphoma



IgD



CD79a



CD10

Pediatric-type Nodal Follicular Lymphoma

(Schmidt et al., Blood 2016; 2017; Louissaint et al, Blood 2016)

- Genome wide analysis shows recurrent mutations
 - Mutations in *TNFRSF14* with frequent copy-number neutral loss of 1p36; region affected in > 50% of cases
 - *KMT2D* (MLL2) mutations seen in 16%
- Above genes can be altered in “usual” FL, but with different frequencies*
- Frequent mutations involving the MAPK pathway
 - *MAP2K1* (~50%); more rarely *RRAS*; *MAPK1*



Follicular Lymphoma (WHO 2017)

Follicular lymphoma

Grades 1-2, 3A, 3B

Variants: *BCL2R-*, CD10-/IRF4/MUM1+

In situ follicular neoplasia

Duodenal-type follicular lymphoma

Pediatric-type follicular lymphoma

IRF-4 large B-cell lymphoma

Primary cutaneous follicle center lymphoma