
3rd POSTGRADUATE
Lymphoma
Conference

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

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THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9]

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Blood 2016; 127:2370-2390; 2391-2405.

13.12. Follicular lymphoma

Jaffe E.S.
Harris N.L.
Swerdlow S.H.
Ott G.
Nathwani B.N.
de Jong D.
Yoshino T.
Spagnolo D.
Gascoyne R.D.

Definition

Composed of centrocytes and centroblasts.

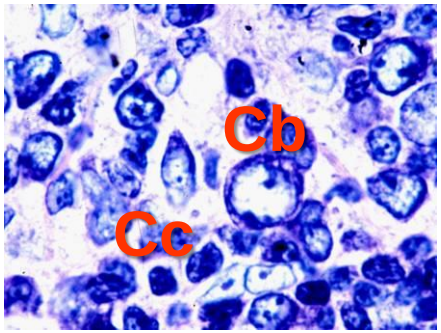
Partially showing a follicular growth pattern.

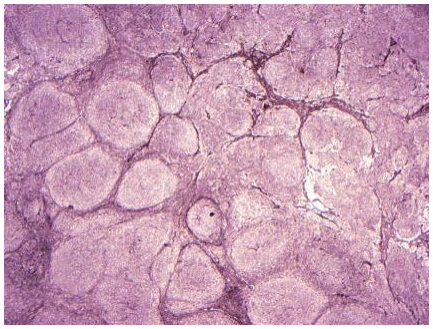
Progression in cytological grade common.

Four variants recognized:
in situ follicular neoplasia (formerly FLIS)
duodenal-type FL
testicular FL
diffuse variant of FL

Pediatric type FL

***Primary cutaneous follicle-centre lymphoma separately classified*.**





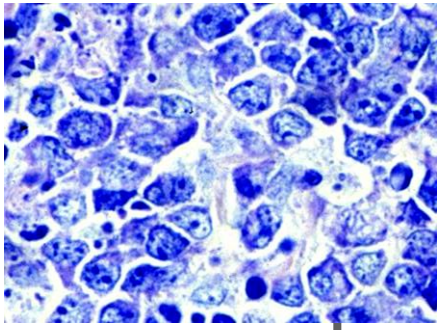


Table 13.17 Follicular lymphoma grading, based on the absolute number of centroblasts per high-power (40 × objective, 0.159 mm^2) microscopic field (HPF)[a]

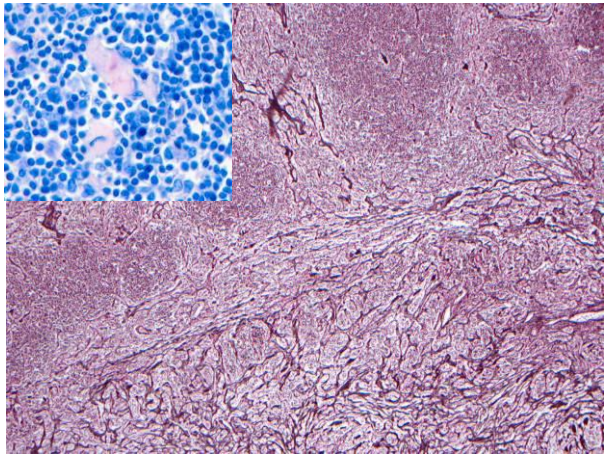
Grading	Definition
Grade 1–2 (low grade)	0–15 centroblasts per HPF
1	0–5 centroblasts per HPF
2	6–15 centroblasts per HPF
Grade 3	>15 centroblasts per HPF
3A	Centrocytes present
3B	Solid sheets of centroblasts
Reporting of pattern	**Proportion follicular**
Follicular	>75%
Follicular and diffuse	25–75%[b]
Focally follicular	<25%[b]
Diffuse	0%[c]

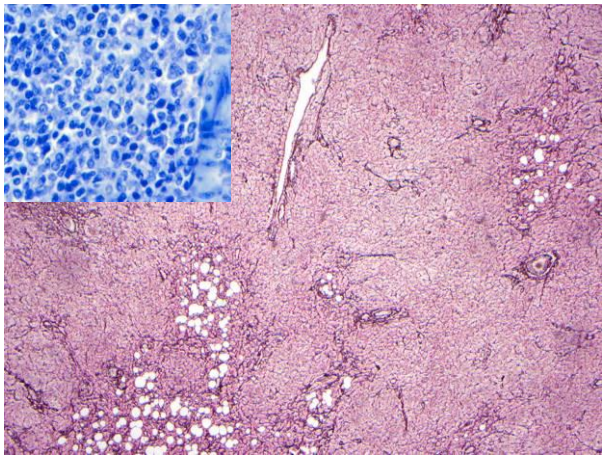
Diffuse areas containing >15 centroblasts per HPF are reported as diffuse large B-cell lymphoma with follicular lymphoma (grade 1–2, grade 3A, or grade 3B)[b].

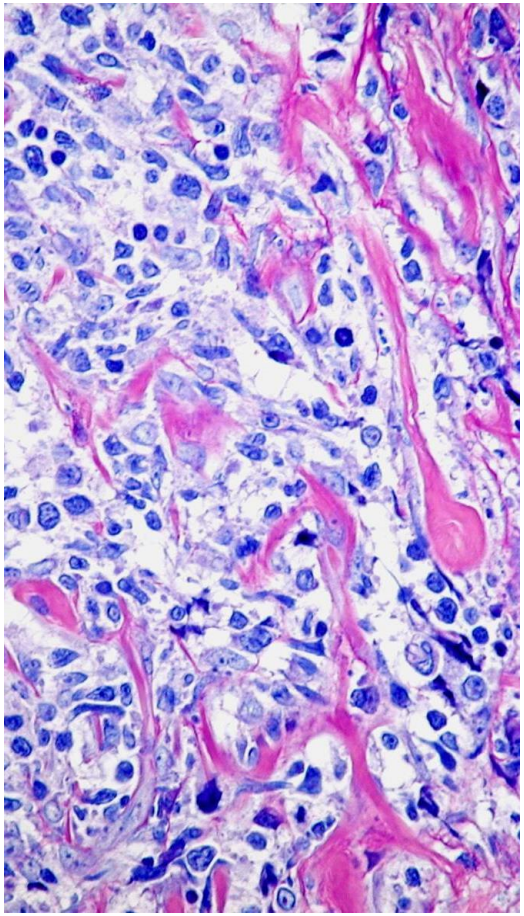
[a] To determine the number of centroblasts per 0.159 mm2 HPF: if using an 18 mm field of view ocular, count the centroblasts in 10 fields and divide by 10; if using a 20 mm field of view ocular, count in 8 fields and divide by 10 or count in 10 fields and divide by 12; if using a 22 mm field of view ocular, count in 7 fields and divide by 10 or count in 10 fields and divide by 15.

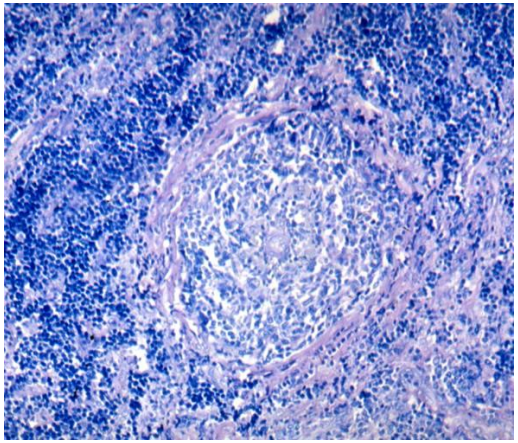
[b] Mention the approximate percentage of each component in the report.

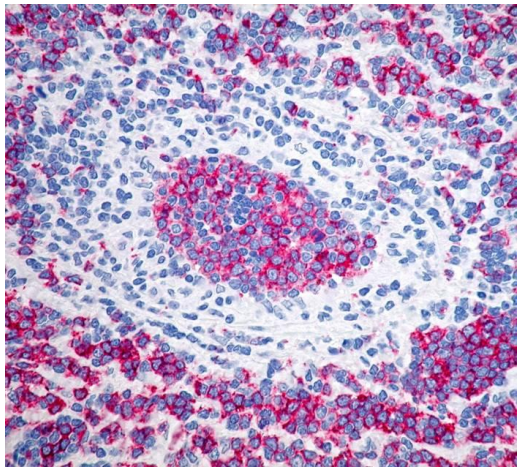
[c] If the biopsy specimen is small, a note should be added that the absence of follicles may reflect sampling error.



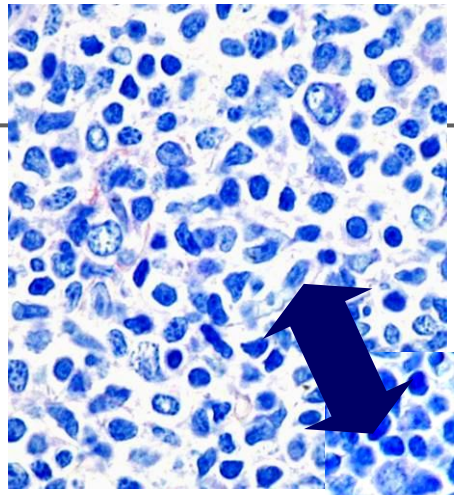




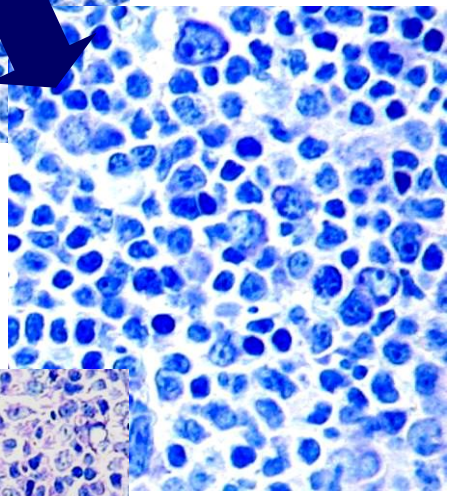




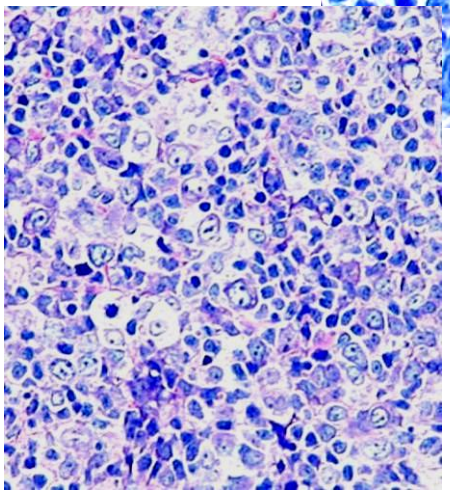
FL



<15 Cb/HPF



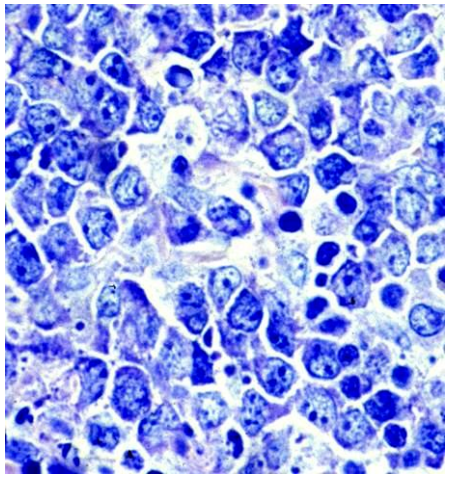
Grades 1-2
Grade 3A



>15 Cb/HPF

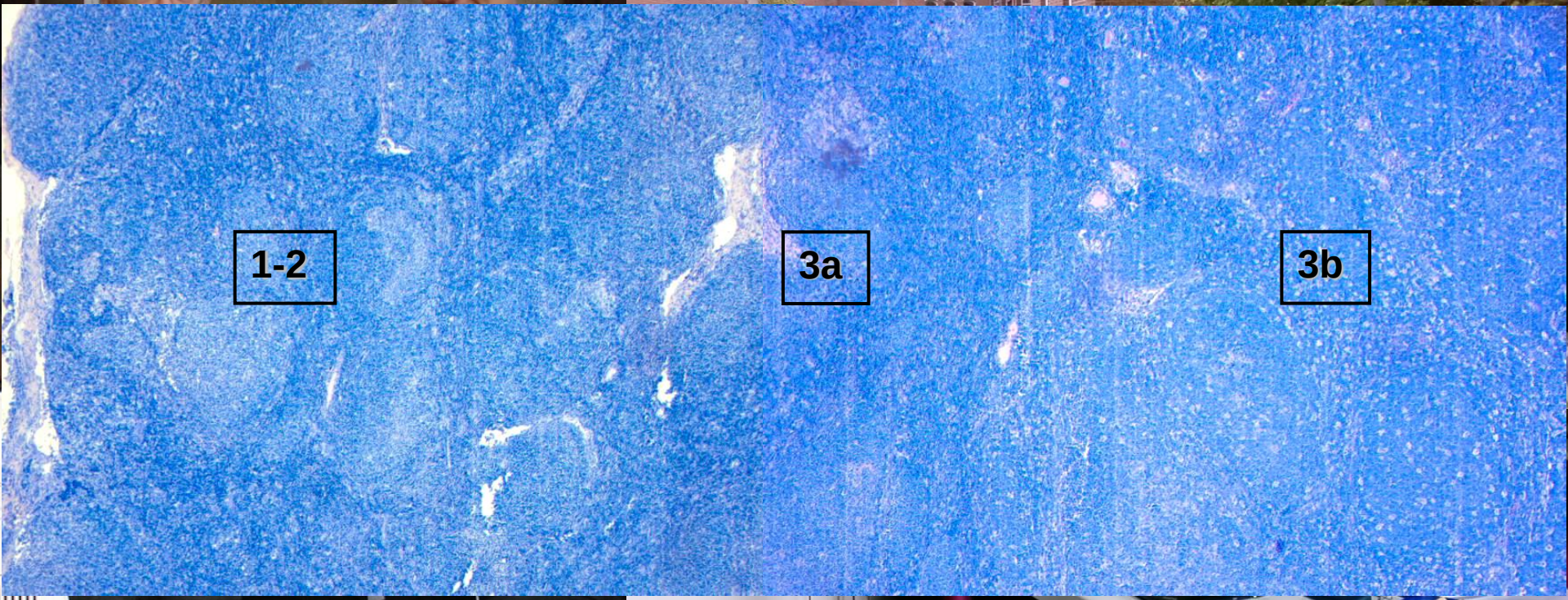
FL

Grade 3B
Follicular!

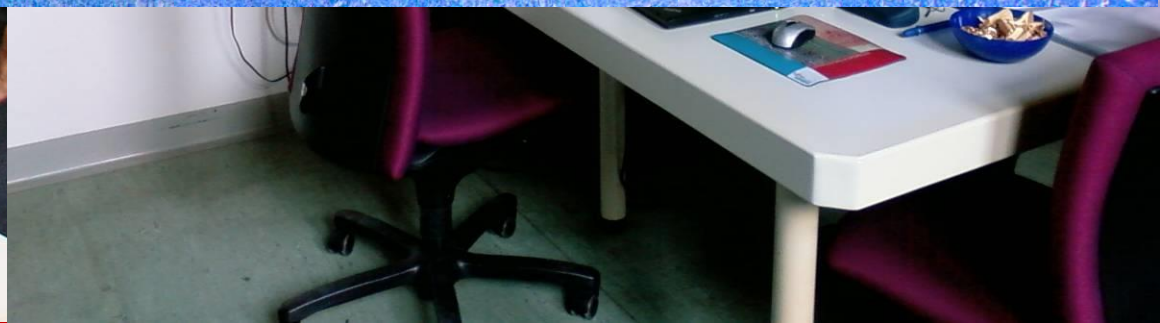


Solid Cb sheets

DLBCL, if diffuse


1-2
3a
3b

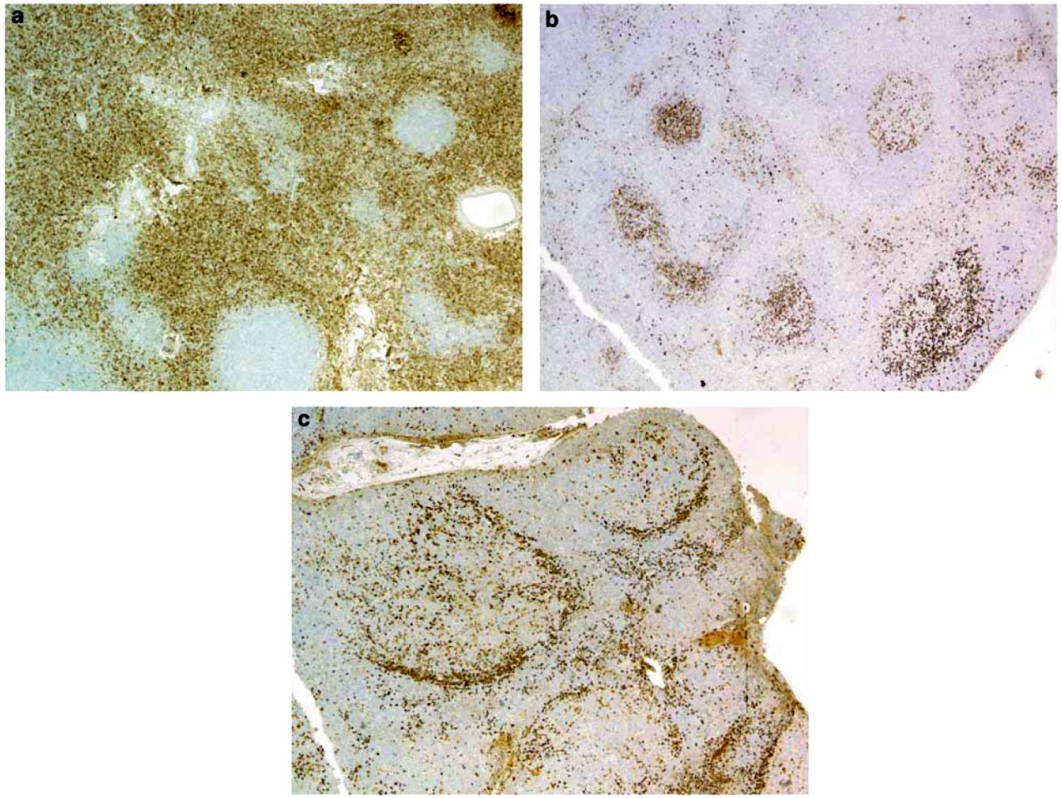

Kiel, 2009



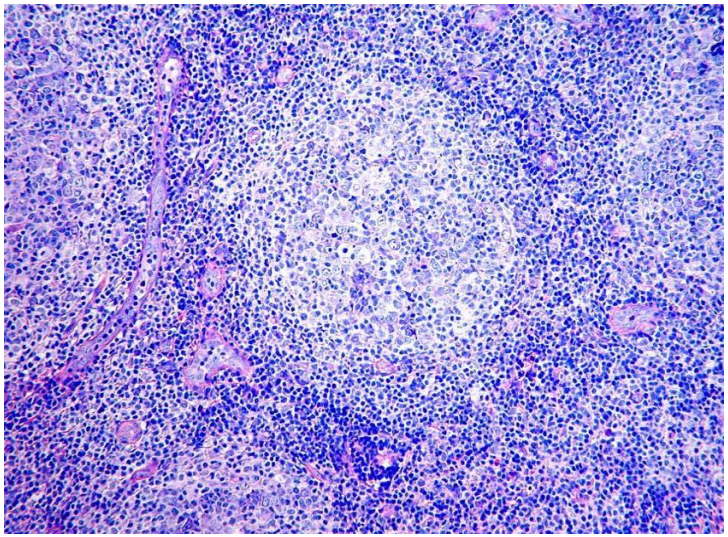
Modern Pathology (2009), 1–9

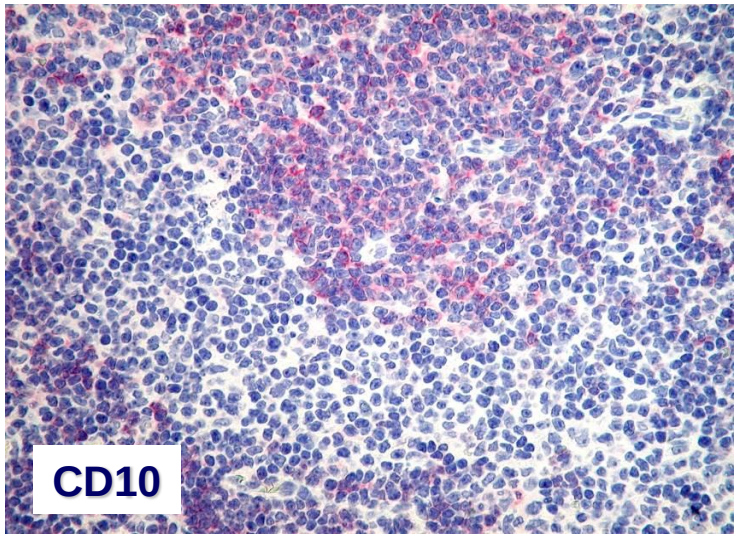
Follicular lymphomas with plasmacytic differentiation include two subtypes

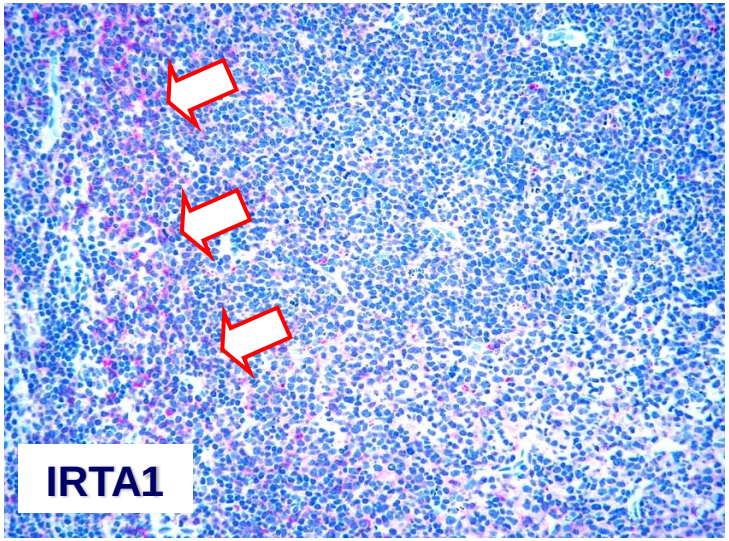
Joel F Gradowski[1], Elaine S Jaffe[2], Roger A Warnke[3], Stefania Pittaluga[2], Urvashi Surti[4], Leena A Gole[5] and Steven H Swerdlow[1,*]

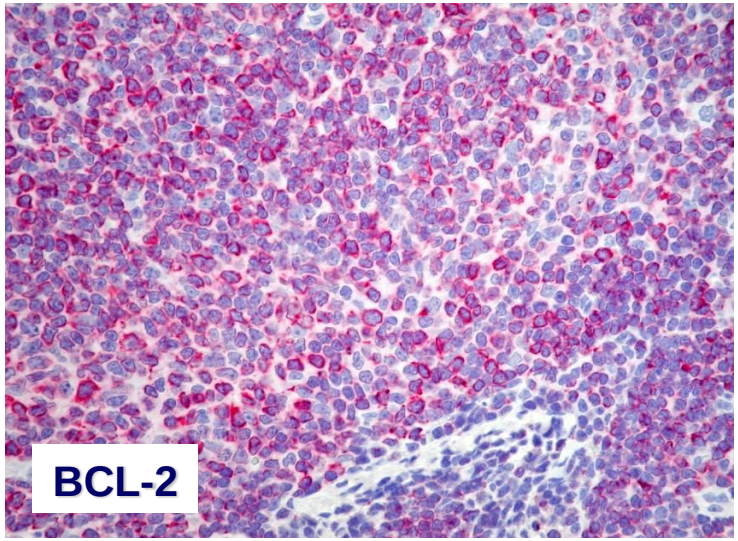


Marginal zone differentiation

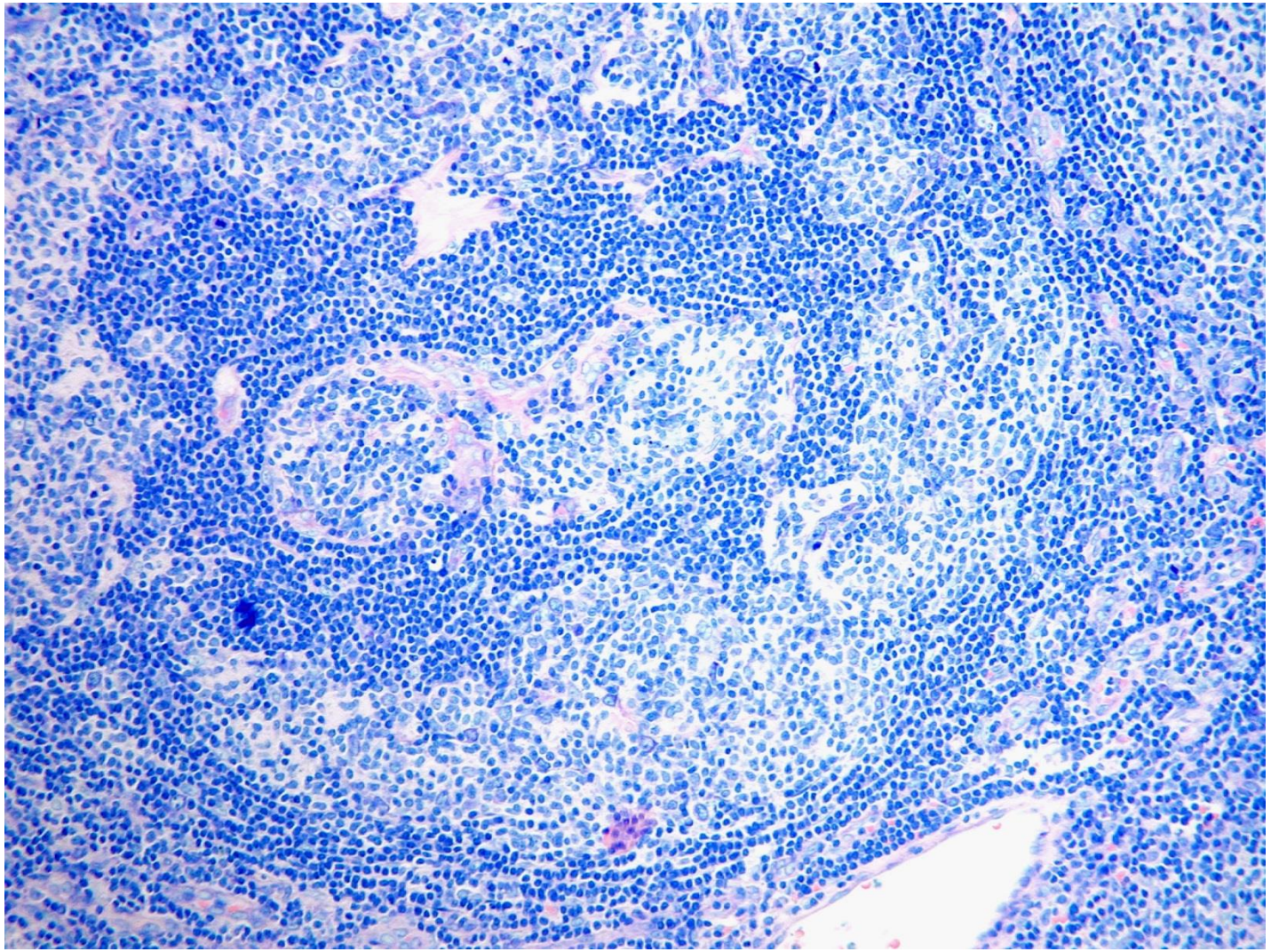




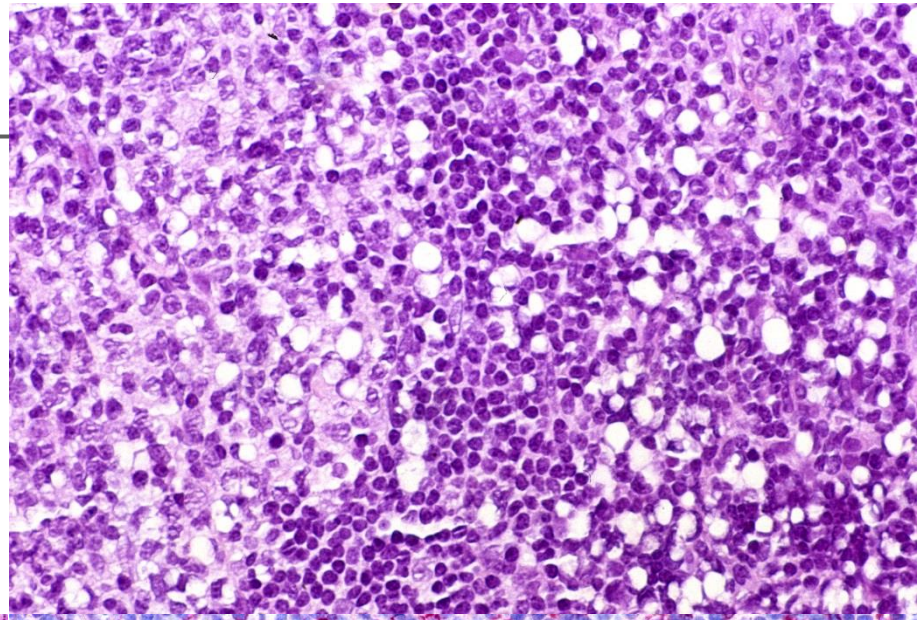


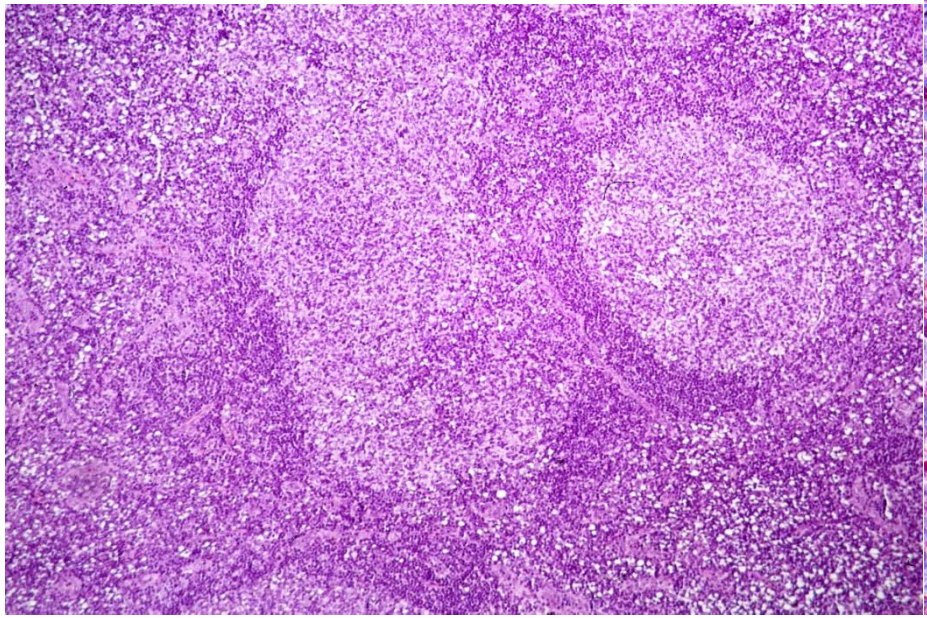


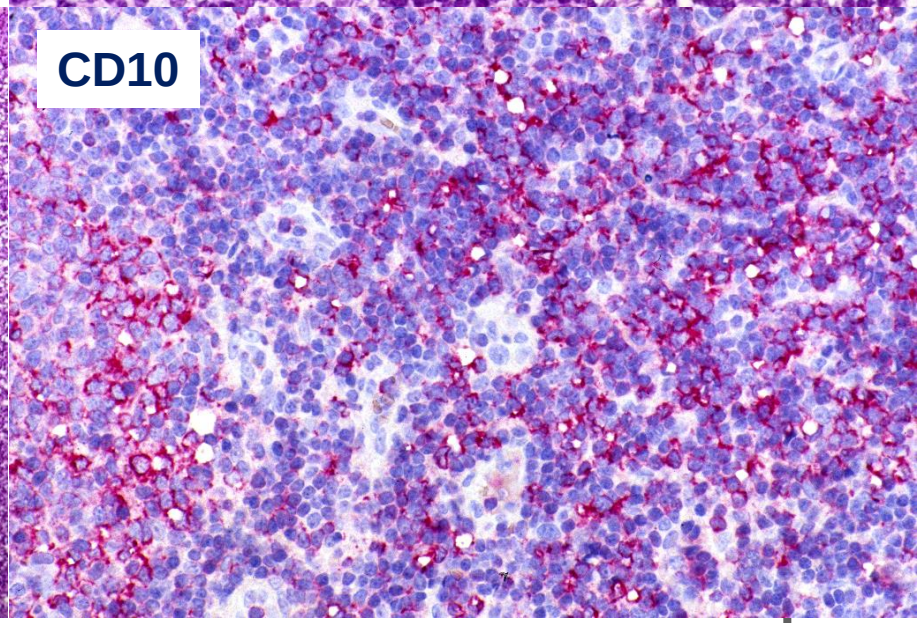
Floral variant



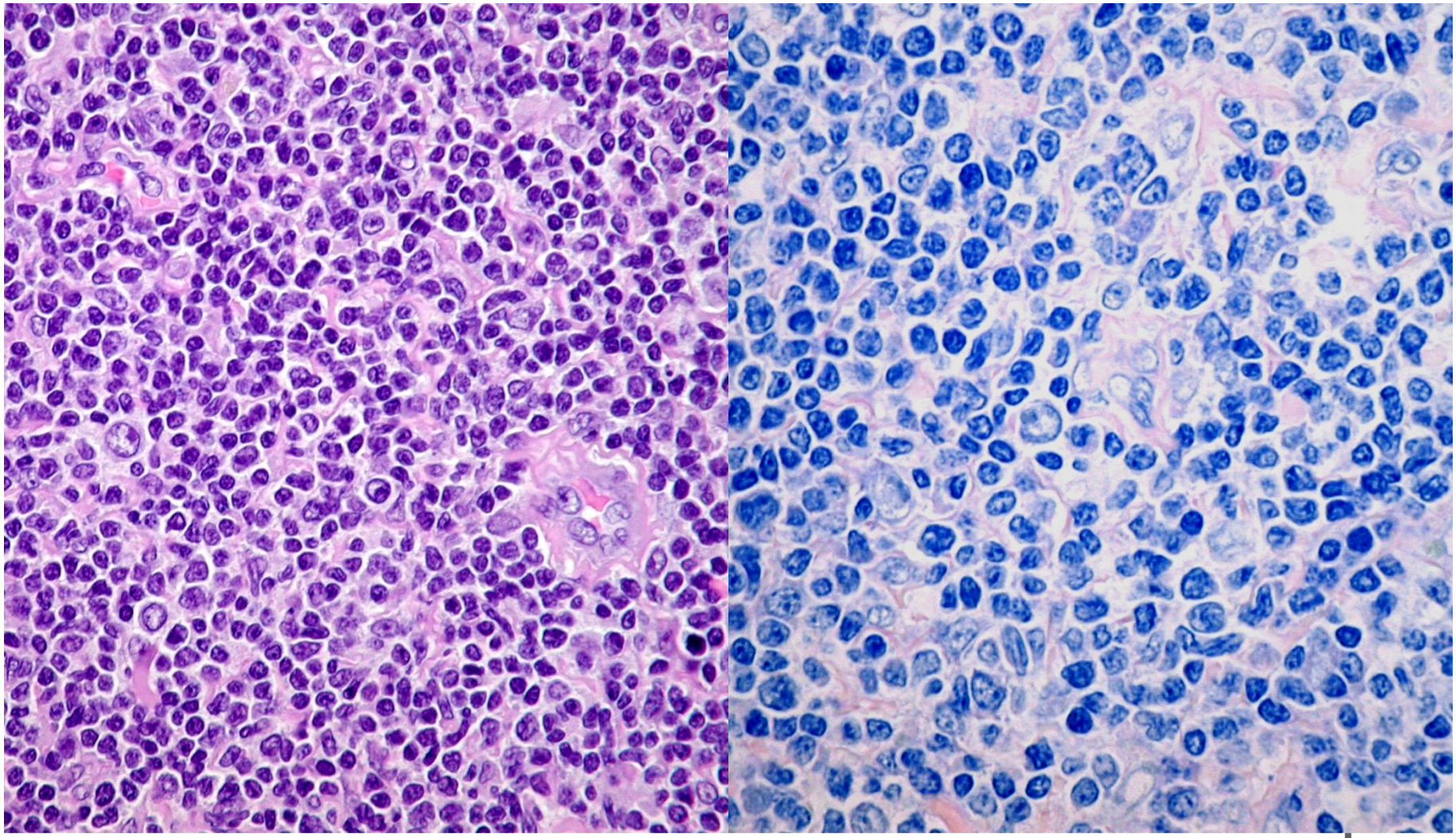
Signet - ring cell FL



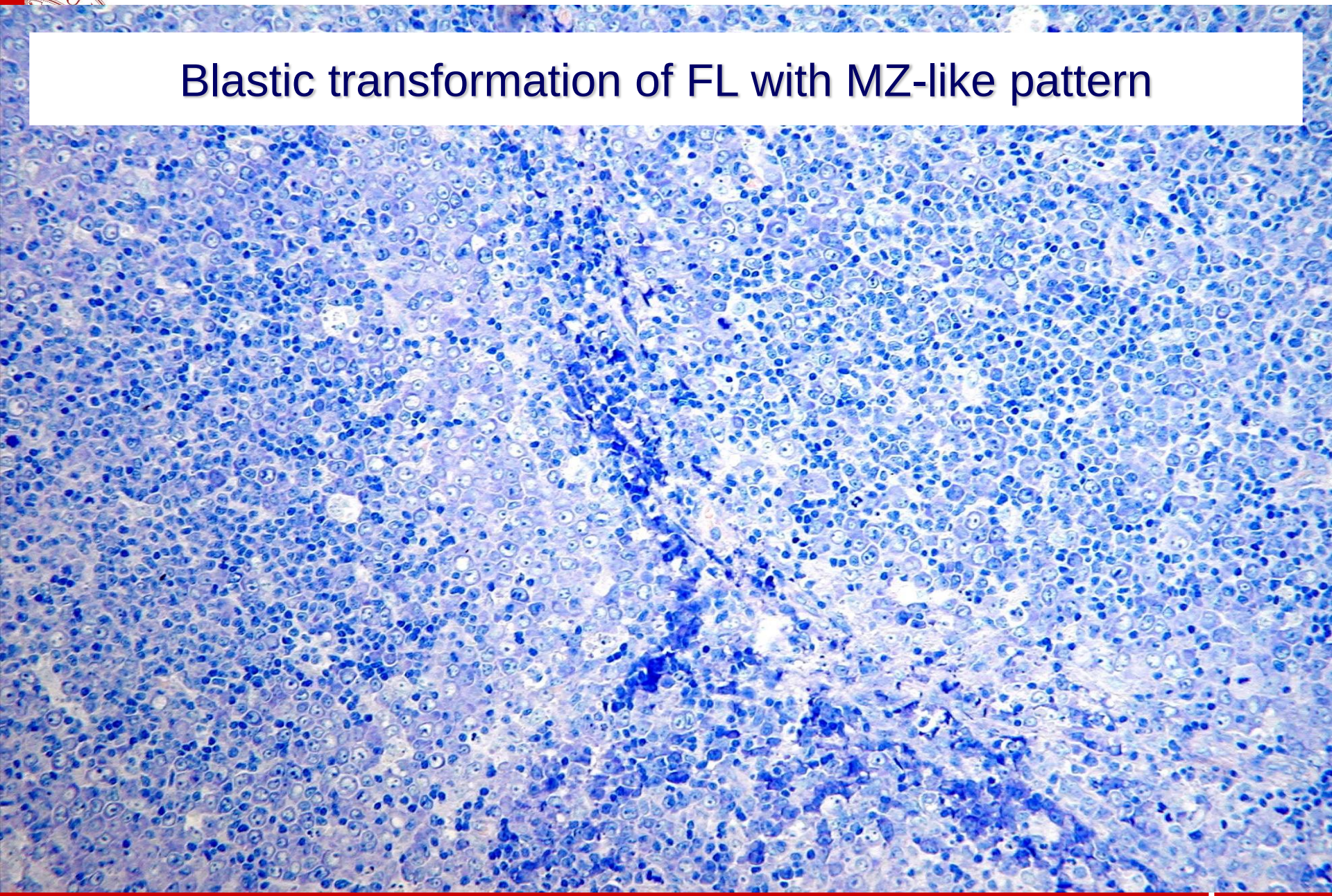


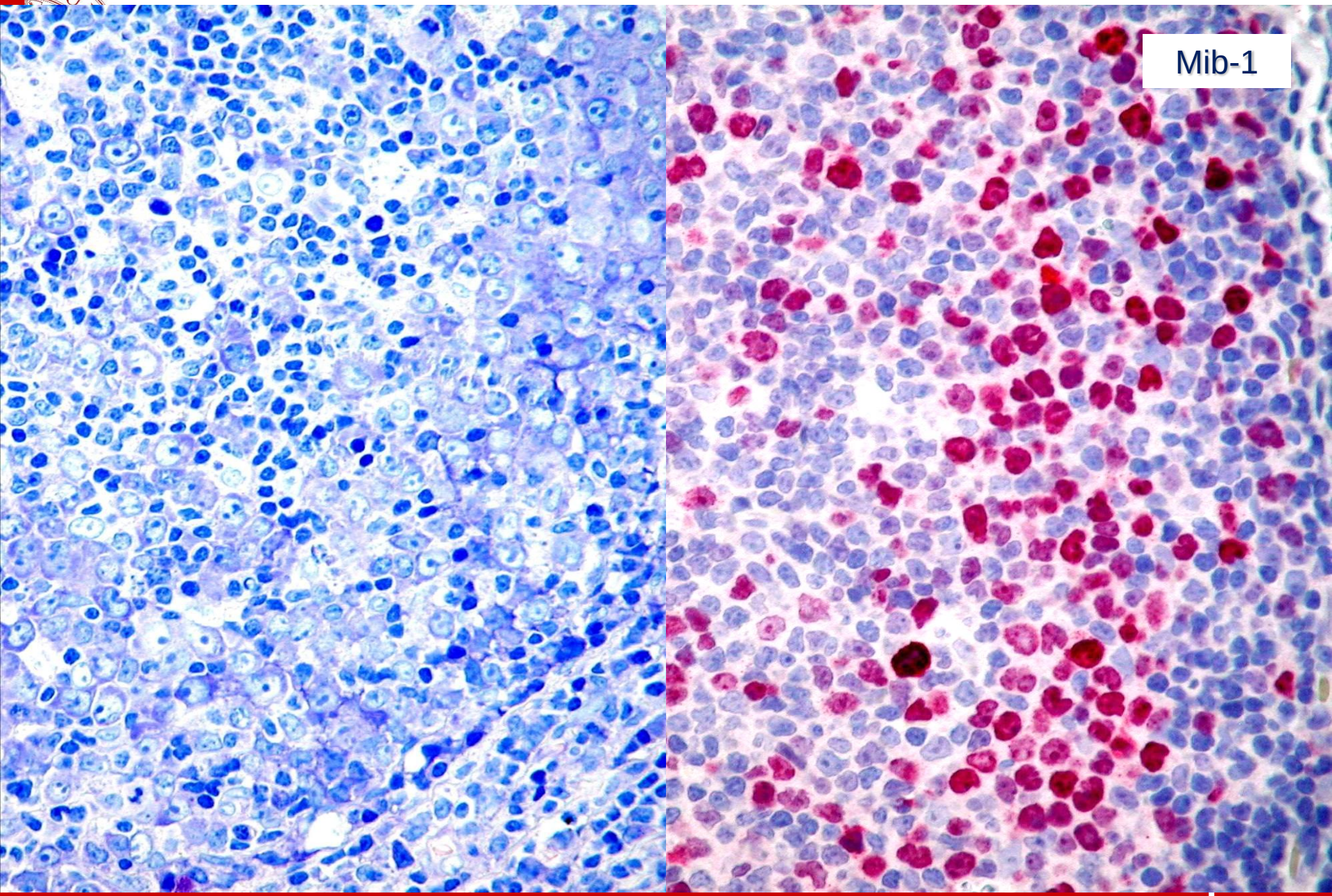


Blastoid variant

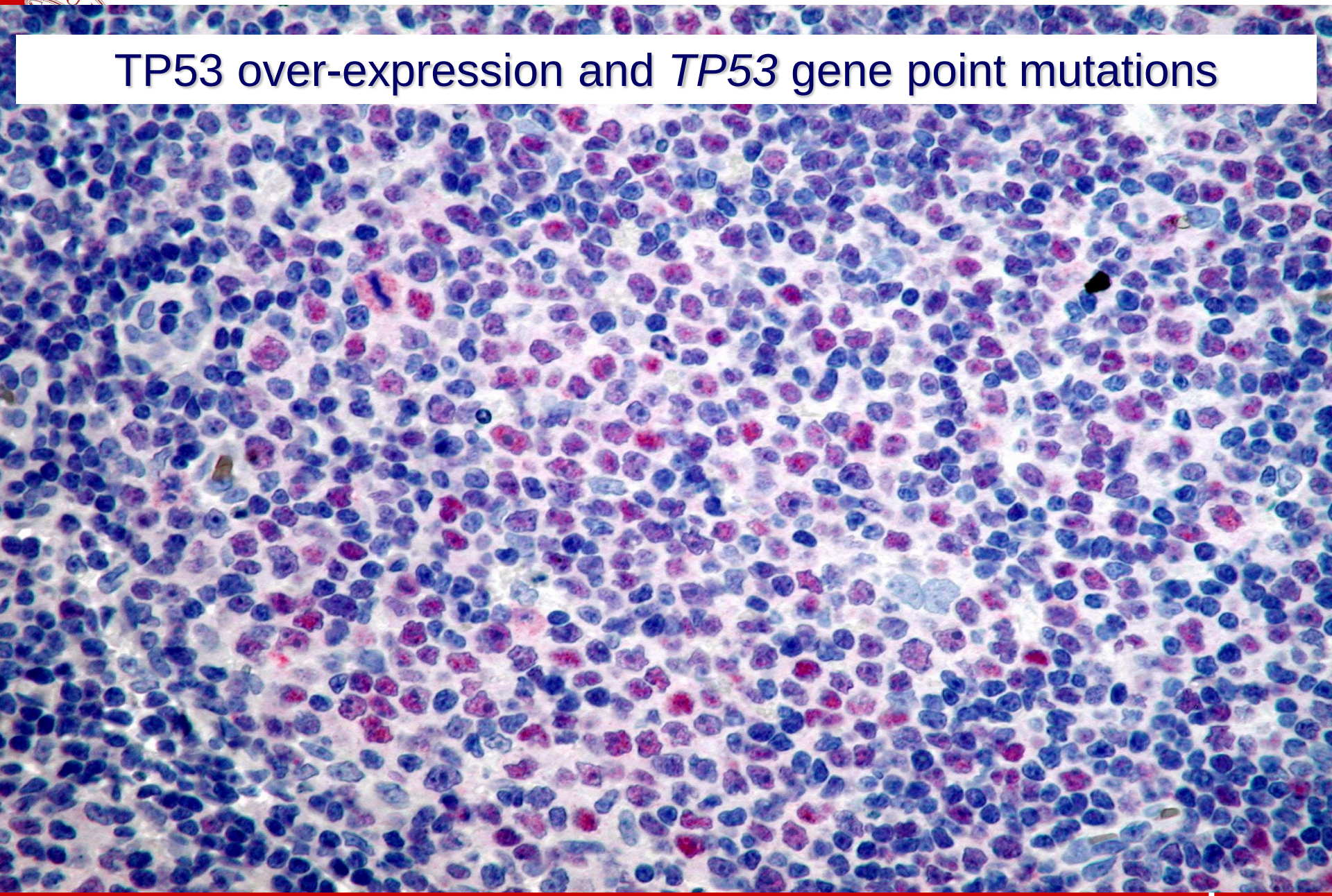


Blastic transformation of FL with MZ-like pattern




Mib-1

TP53 over-expression and *TP53* gene point mutations

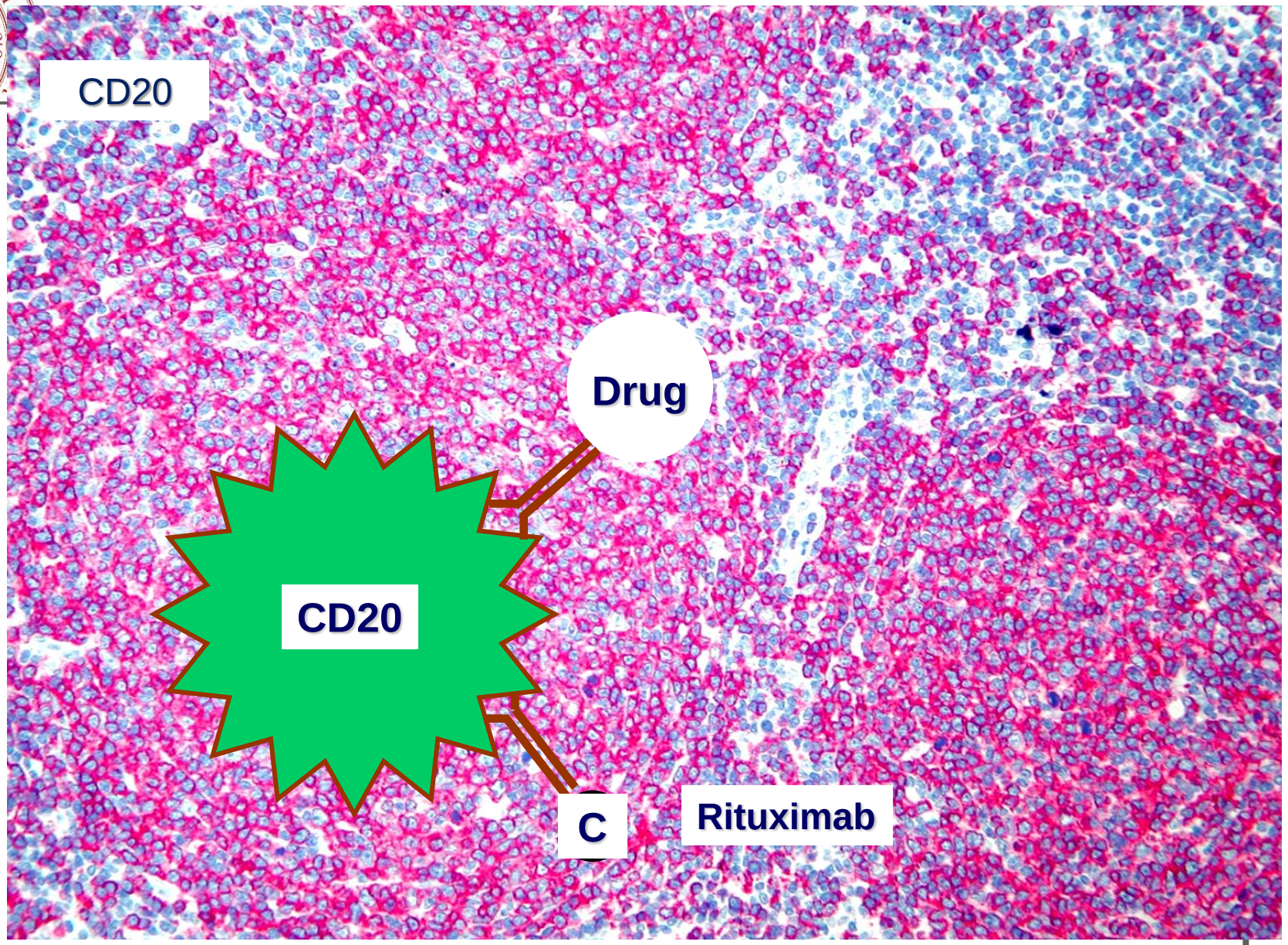


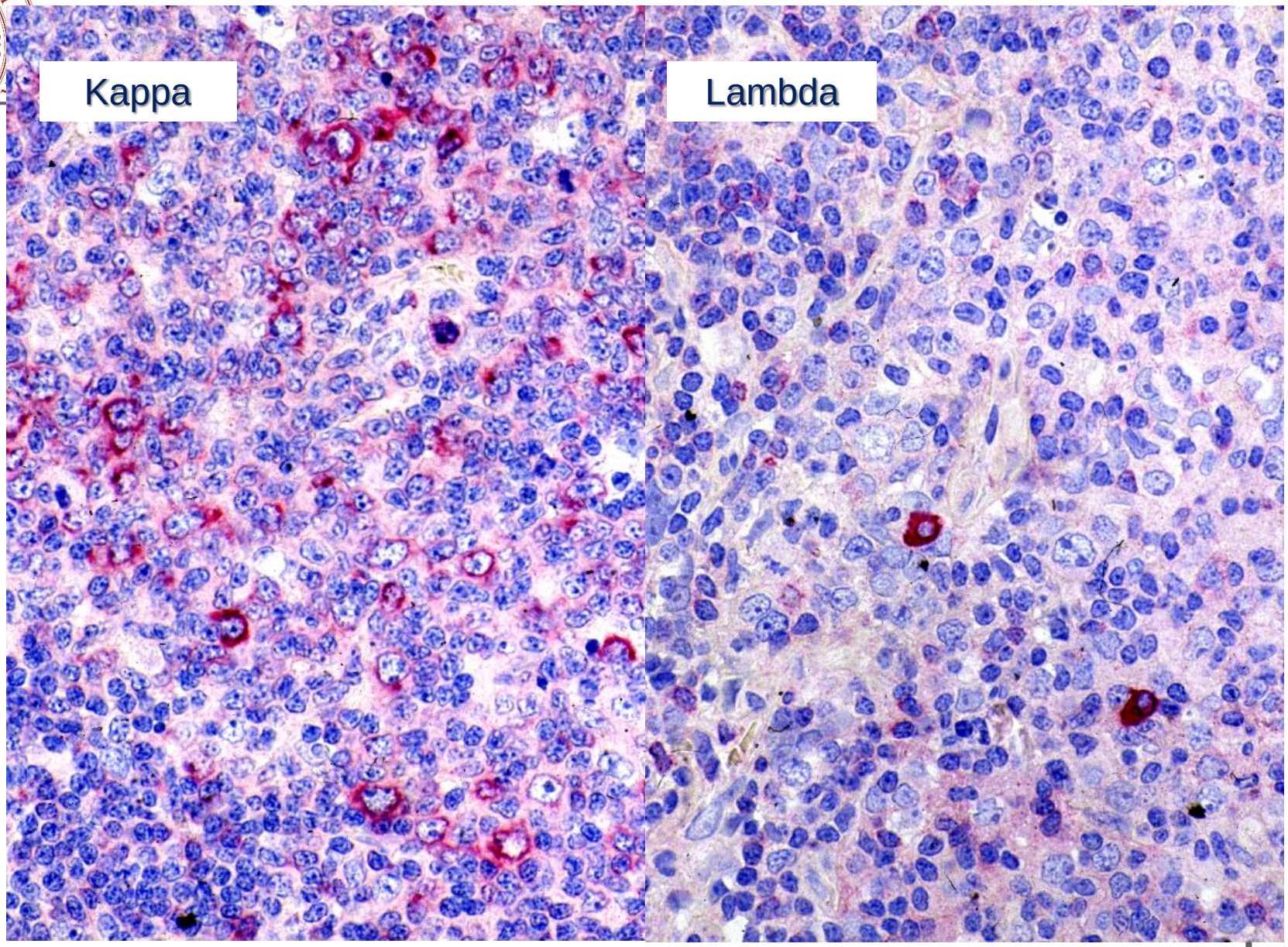
Warning

- FL more often occurs in lymph nodes.
- However, it can also affect extranodal sites or give raise to deep masses.
- Caution should be used in diagnosing needle biopsies, since the spectrum of architectural and cytological features might not be fully representative.

Phenotype

B-cell markers:	**CD19/20/22/79a^{+}**
T-cell markers:	CD5^{rare}
GCC-associated markers:	CD10/AID/Bcl-6^{+}
Transcription factors:	BSAP/Oct1/Oct2/BOB-1^{+}
	IRF4^{-}
Cytoplasmic Ig:	**variable**
FDC meshwork:	CD21/CD23/CD35^{+}
Ki-67/Mib1:	variable
BCL2:	positive in 85-90%

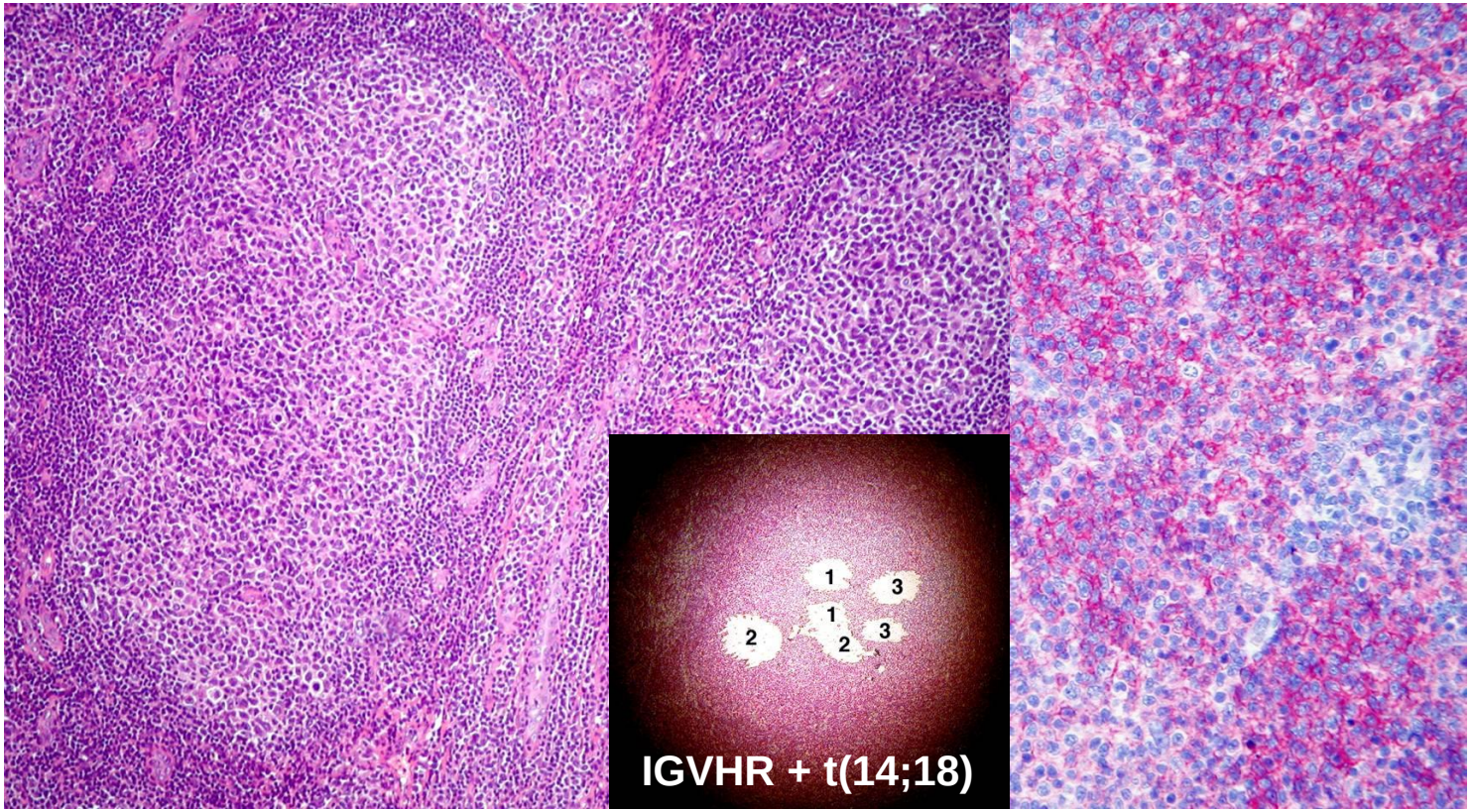

CD20
Drug
CD20
C
Rituximab


Kappa
Lambda

Phenotype

B-cell markers:	CD19/20/22/79a^{+}
T-cell markers:	CD5^{rare}
GCC-associated markers:	CD10/AID/Bcl-6^{+}
Transcription factors:	BSAP/Oct1/Oct2/BOB-1^{+}
	IRF4^{-}
Cytoplasmic Ig:	variable
FDC meshwork:	CD21/CD23/CD35^{+}
Ki-67/Mib1:	variable
BCL2:	positive in 85-90%

CD5+ FL (10 - 15%)



Phenotype

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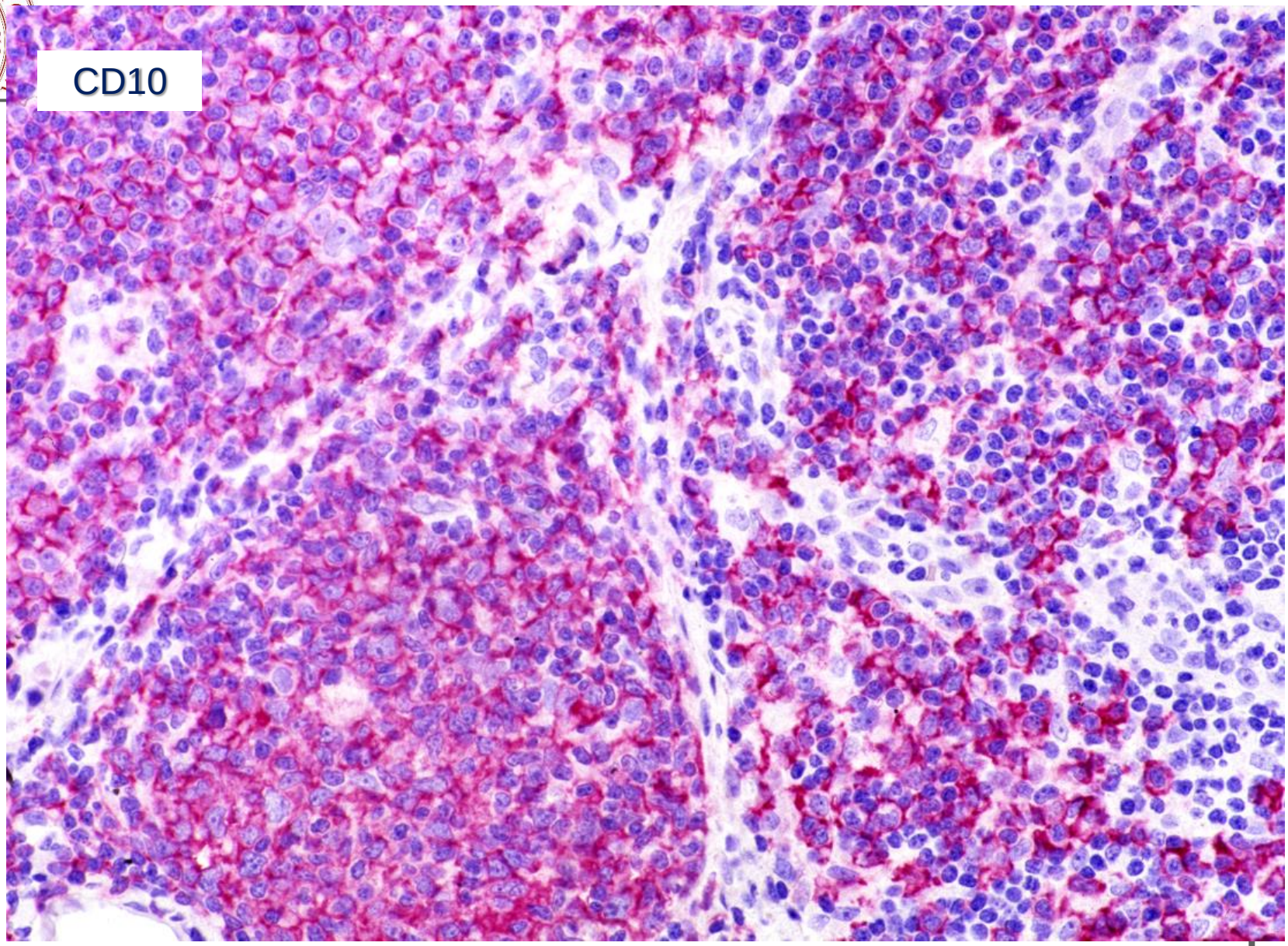
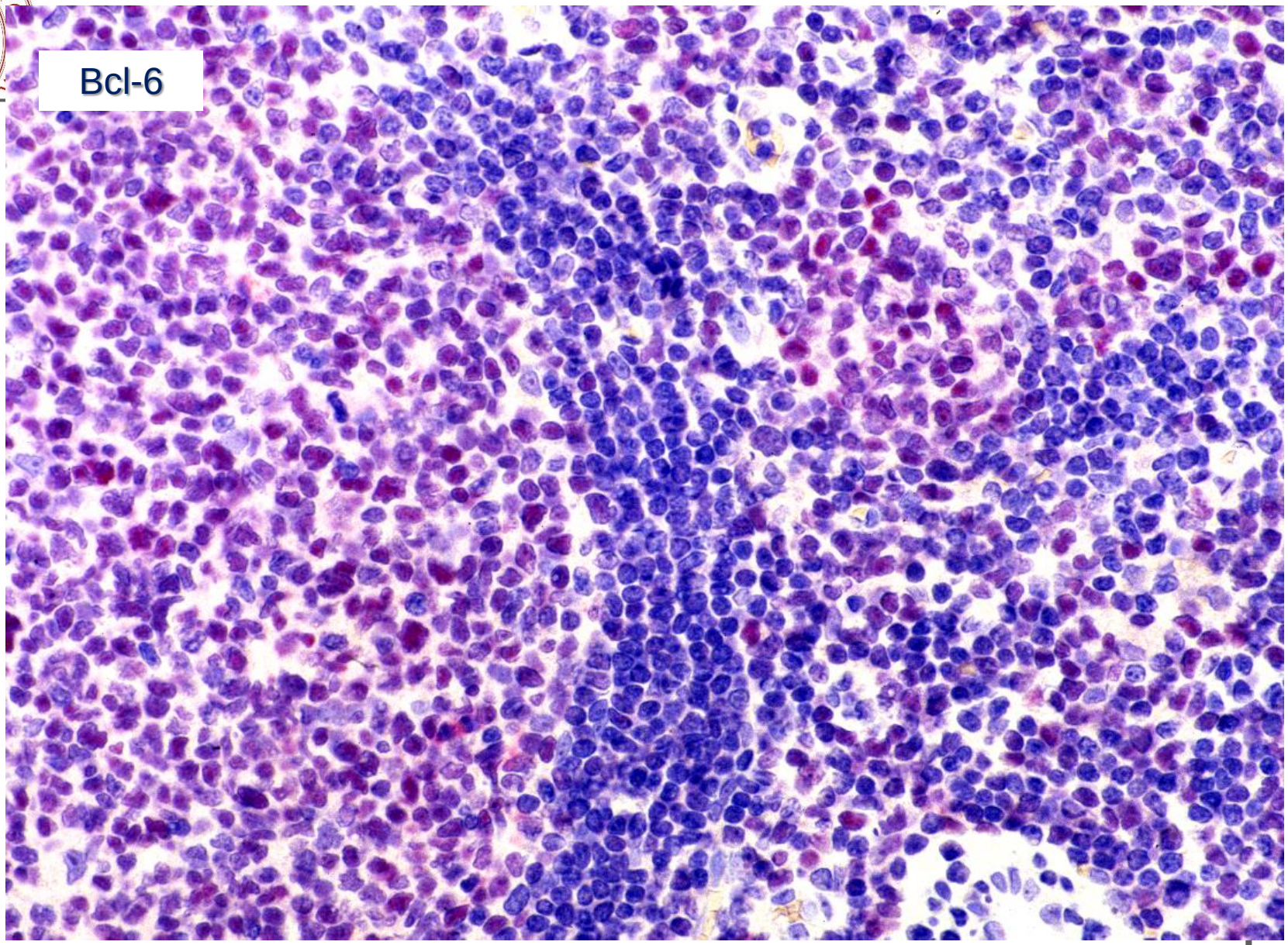
T-cell markers:	CD5^{rare}
GCC-associated markers:	CD10/AID/Bcl-6^{+}
Transcription factors:	BSAP/Oct1/Oct2/BOB-1^{+}
	IRF4^{-}
Cytoplasmic Ig:	variable
FDC meshwork:	CD21/CD23/CD35^{+}
Ki-67/Mib1:	variable
BCL2:	positive in 85-90%

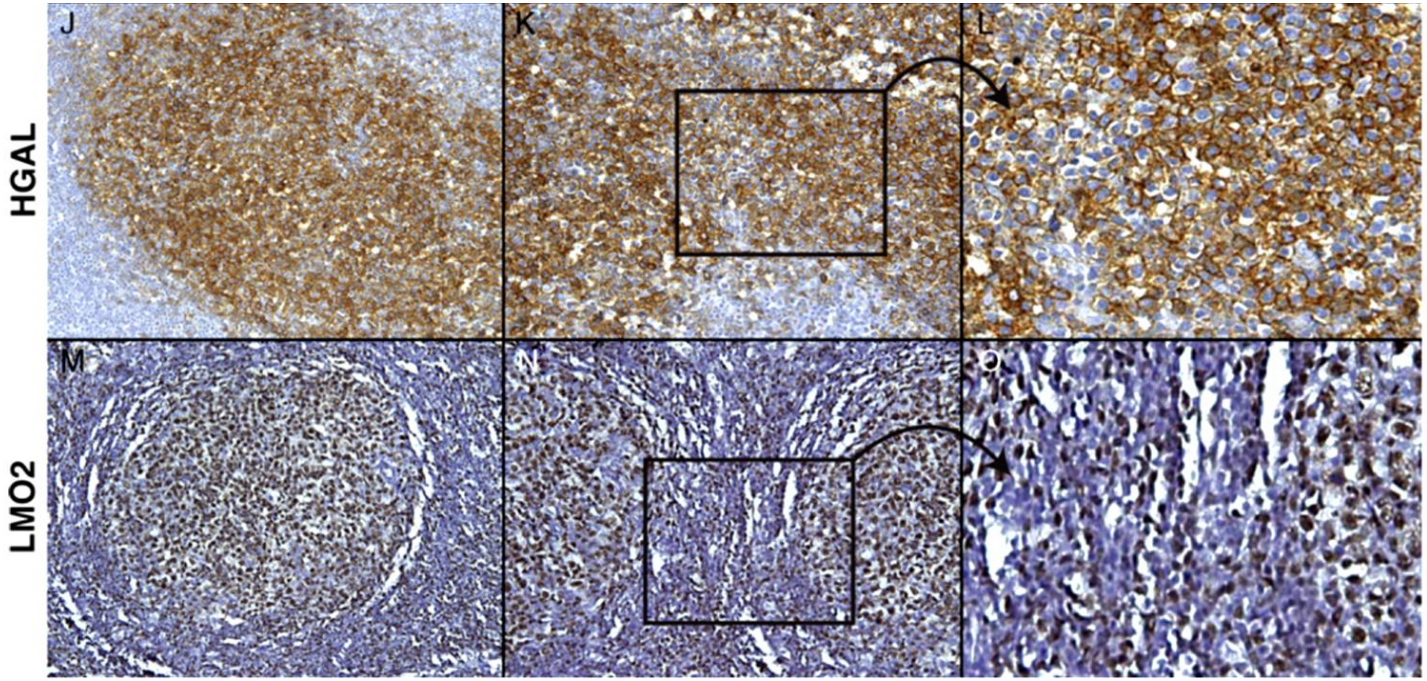

CD10


Bcl-6

Immunoarchitectural Patterns in Follicular Lymphoma: Efficacy of HGAL and LMO2 in the Detection of the Interfollicular and Diffuse Components

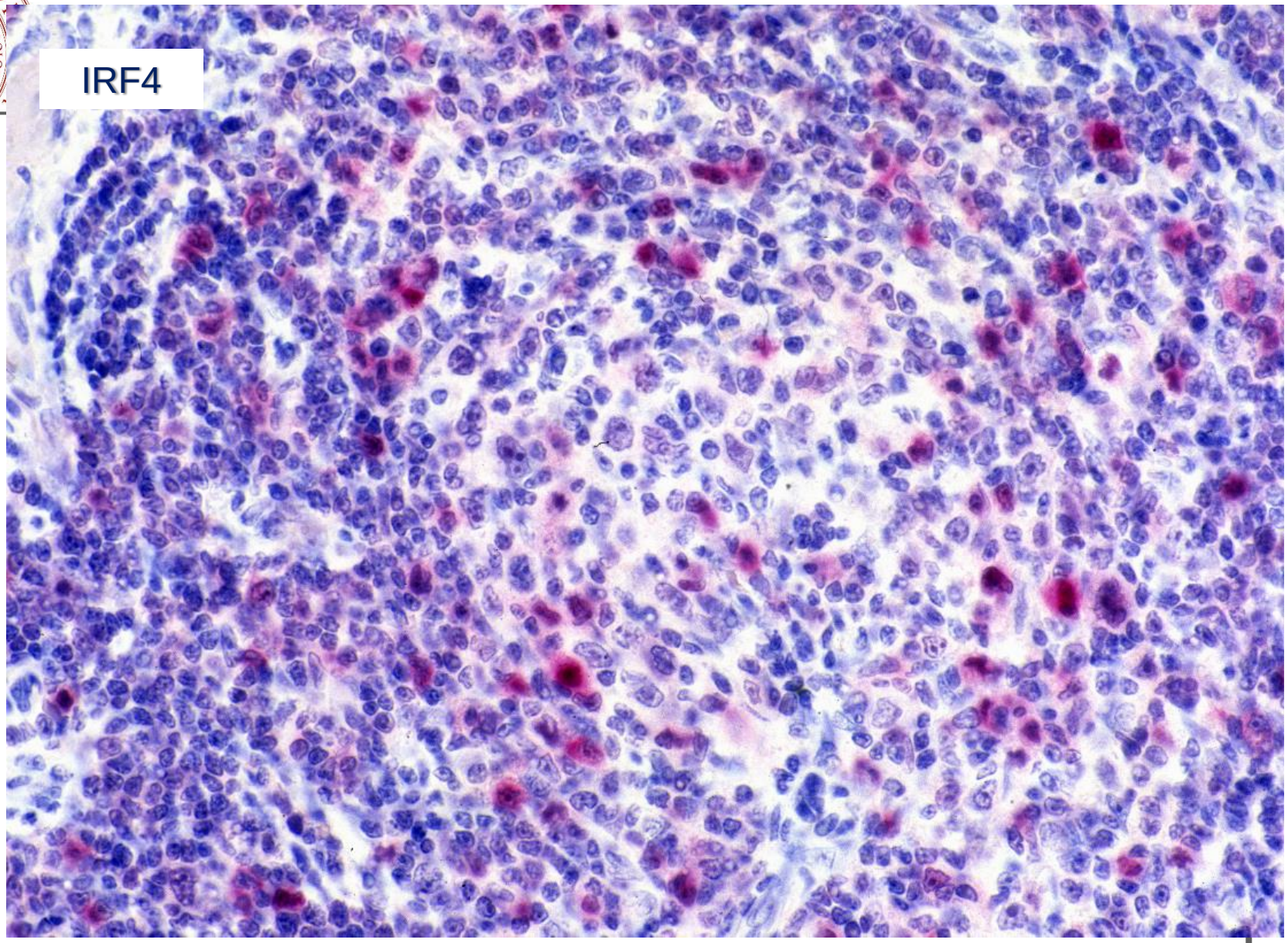
Sheren F. Younes, MD, Andrew H. Beck, MD,* Izidore S. Lossos, MD,† Ronald Levy, MD,‡ Roger A. Warnke, MD,* and Yasodha Natkunam, MD, PhD**

(*Am J Surg Pathol* 2010;34:1266–1276)



Phenotype

B-cell markers:	CD19/20/22/79a^{+}
T-cell markers:	CD5^{rare}
GCC-associated markers:	CD10/AID/Bcl-6^{+}
Transcription factors:	BSAP/Oct1/Oct2/BOB-1^{+}
	IRF4^{-}
Cytoplasmic Ig:	variable
FDC meshwork:	CD21/CD23/CD35^{+}
Ki-67/Mib1:	variable
BCL2:	positive in 85-90%


IRF4

Follicular Lymphoma Grade 3: Review and Updates

Gayatri Vaidyanathan, Myron S. Czuczman

Clinical Lymphoma, Myeloma & Leukemia December 2014 | 431

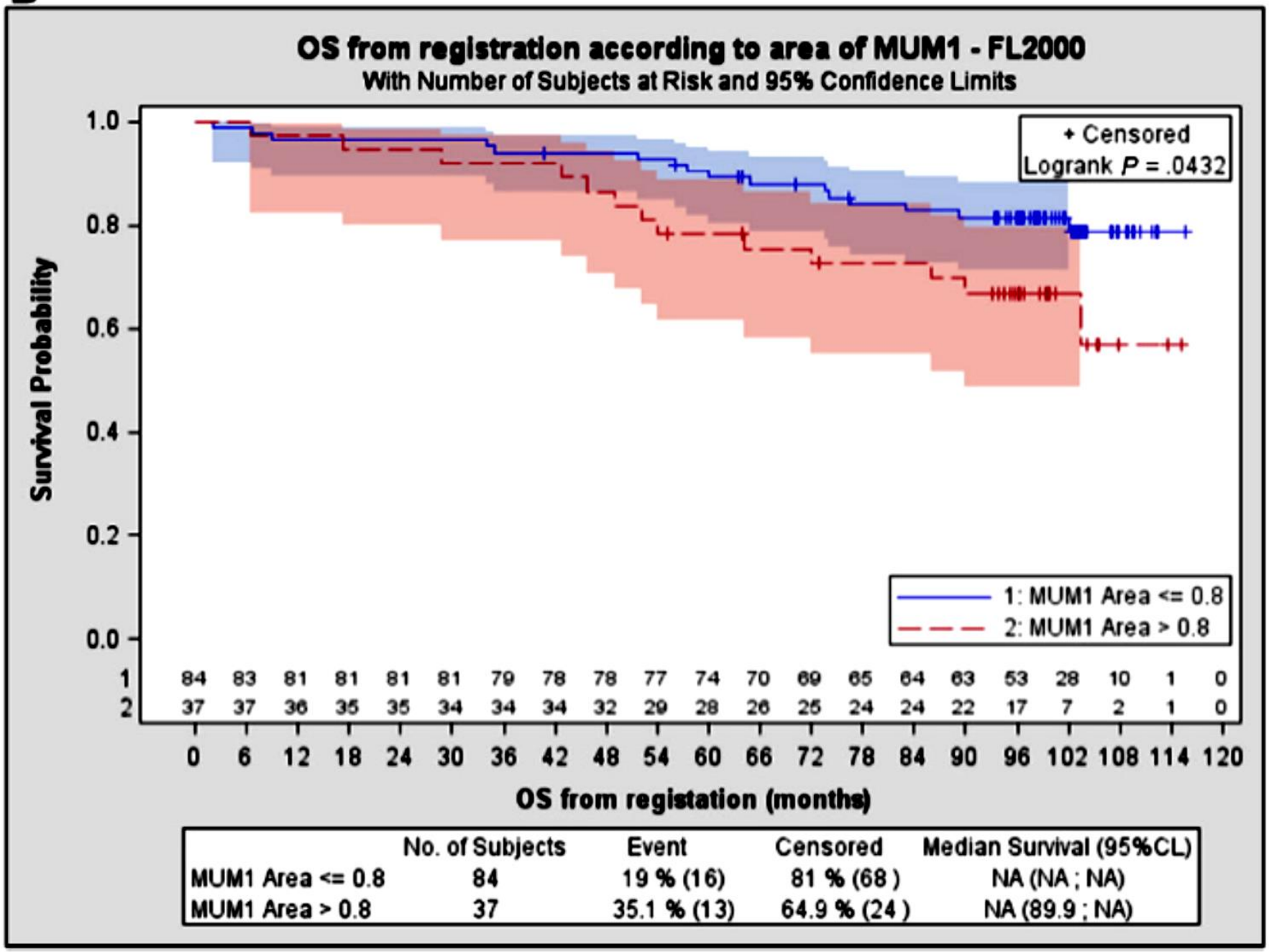
Characteristics	FL (1-3a)	FL (3b)	DLBCL
IHC	CD10+/bcl-6+/MUM1/IRF4-	CD10±/bcl-6+/MUM1/IRF4+	CD10±/bcl-6±/MUM1/IRF4±
Morphology	Follicular pattern	Common diffuse component	Diffuse architecture with large cells
Age	Mainly in adults	Also present in children	Also present in children
Genetics	• Mainly t(14;18) positive • Commonly bcl-6 transl neg • Bcl-6 ABR breakpoint region • IGH Sγ transl common • Common gains of chr 7	• Frequently t(14;18) neg • Frequently bcl-6 transl neg • Bcl-6 ABR breakpoint region - ?transl • Sometimes no gain of chr 7	• Commonly t(14;18) neg • Commonly 3q27/bcl-6 transl positive • Bcl-6 MBR breakpoint region • IGH Sμ transl common • Rare gains of chr 7
Prognosis	Favorable prognosis (except 3a)	Generally bad prognosis	Generally bad prognosis

FL3B with IRF4/MUM1 Expression

- Karube: CD10^{-}, IRF4^{+} FL
  - 91% FL3A/B; 55% with DLBCL
  - 5% BCL2-R (1 case)
  - 73% M, 67y (med), poor prognosis
- Horn: FL3B +/- DLBCL CD10^{-}, IRF4^{+}
  - 42% of FL3B (0 FL1-3A)
  - 63% of FL3B+DLBCL
  - Variable expression of BCL2
  - 0 *IRF4* or *BCL2-R*
  - All adults (44-86); no follow-up information

Courtesy Prof. N.L. Harris

Karube Blood 2007; Horn Haematol 2011



	No. of Subjects	Event	Censored	Median Survival (95%CL)
MUM1 Area <= 0.8	84	19 % (16)	81 % (68)	NA (NA ; NA)
MUM1 Area > 0.8	37	35.1 % (13)	64.9 % (24)	NA (89.9 ; NA)

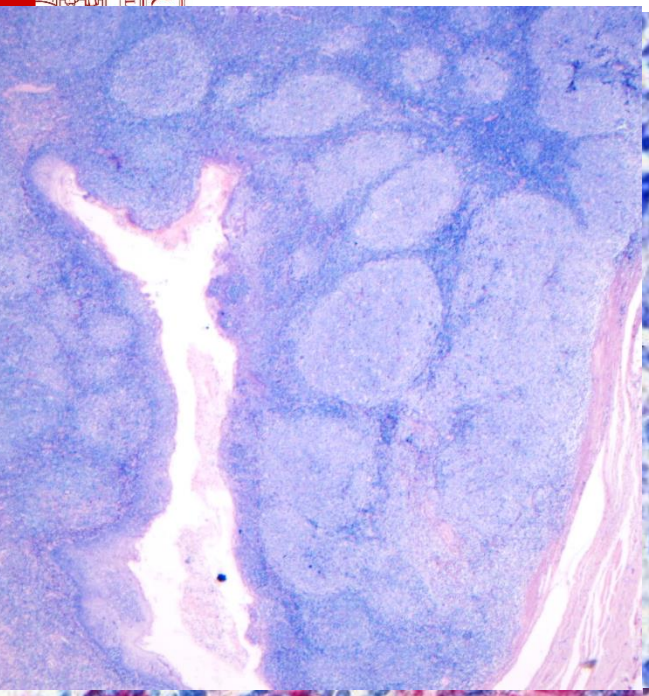
Large B-cell lymphoma with *IRF4 (6p25)* breaks

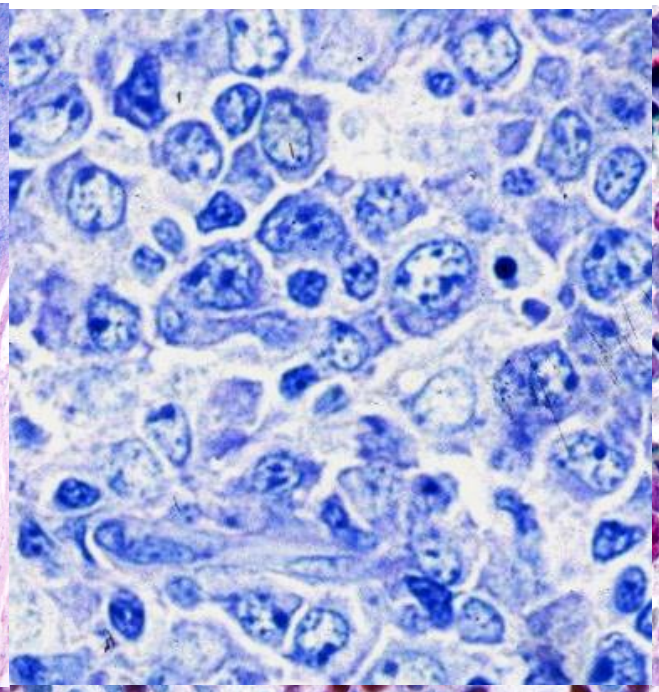
- Morphology
  - FL3B (at times with a DLBCL component)
- Immunophenotype
  - IRF4^{+}, BCL6^{+}, CD10^{+} (60%), BCL2^{+} (60%), CD5^{+} (30%)
  - High proliferation index (>50%)
- Genetics
  - *IGH*: clonally rearranged; *IG/IRF4* fusion
  - *BCL6* breaks occasionally present (30%)
  - *BCL2* rearrangements absent
- Clinical
  - Often pediatric/young adult but may be >40yr
  - Waldeyer's ring, Stage I-II
  - Good response to systemic chemotherapy

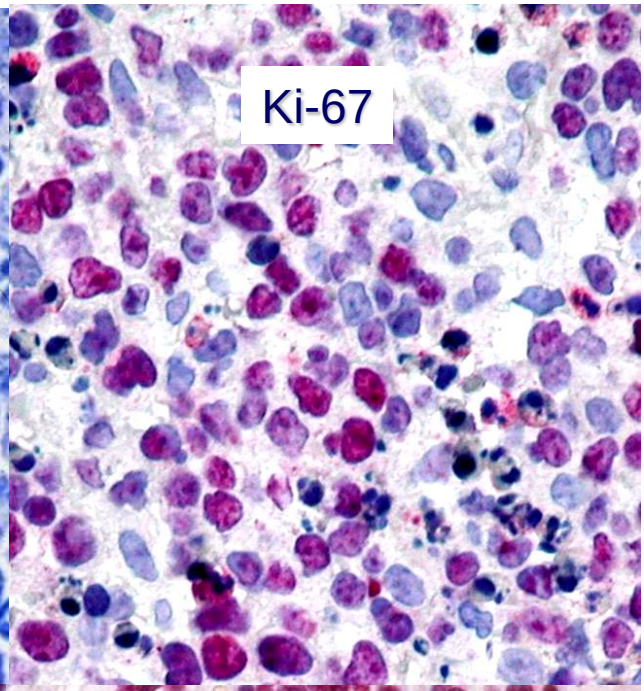
Courtesy Prof. N.L. Harris

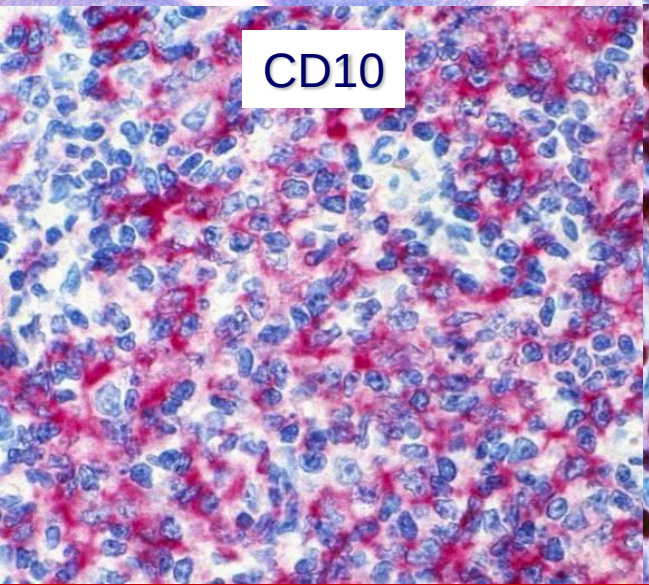
Salaverria et. al, Blood 2011; Liu et. al, AJSP 2013

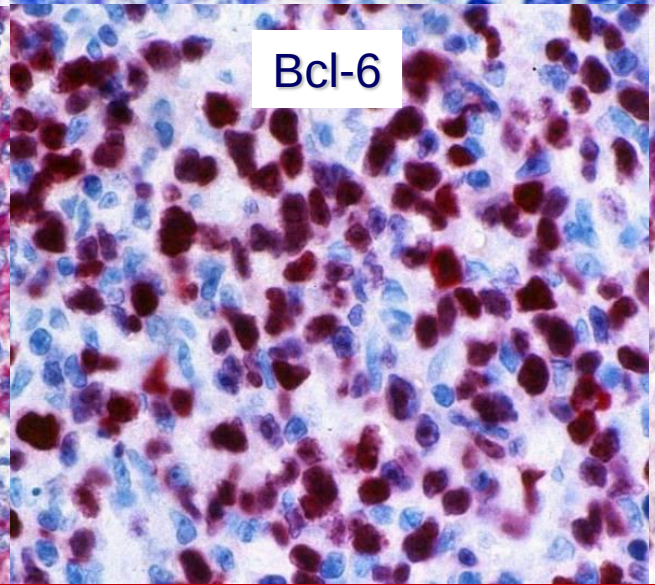
LBCL with *IRF4* Break: male 19-yr-old, tonsil

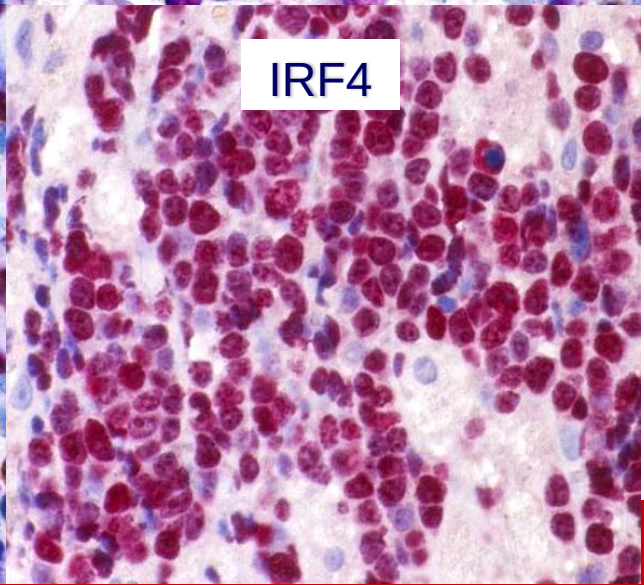






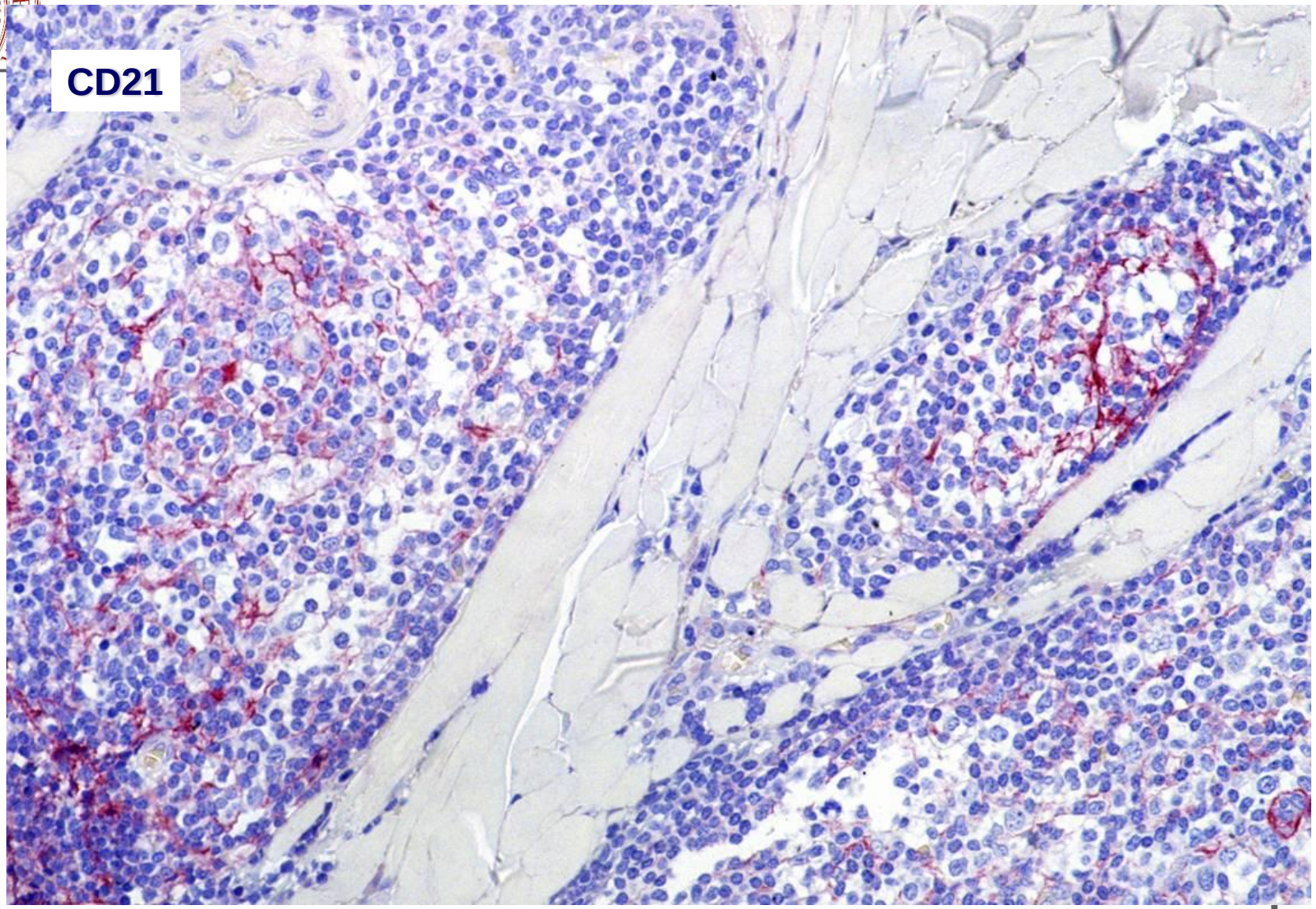




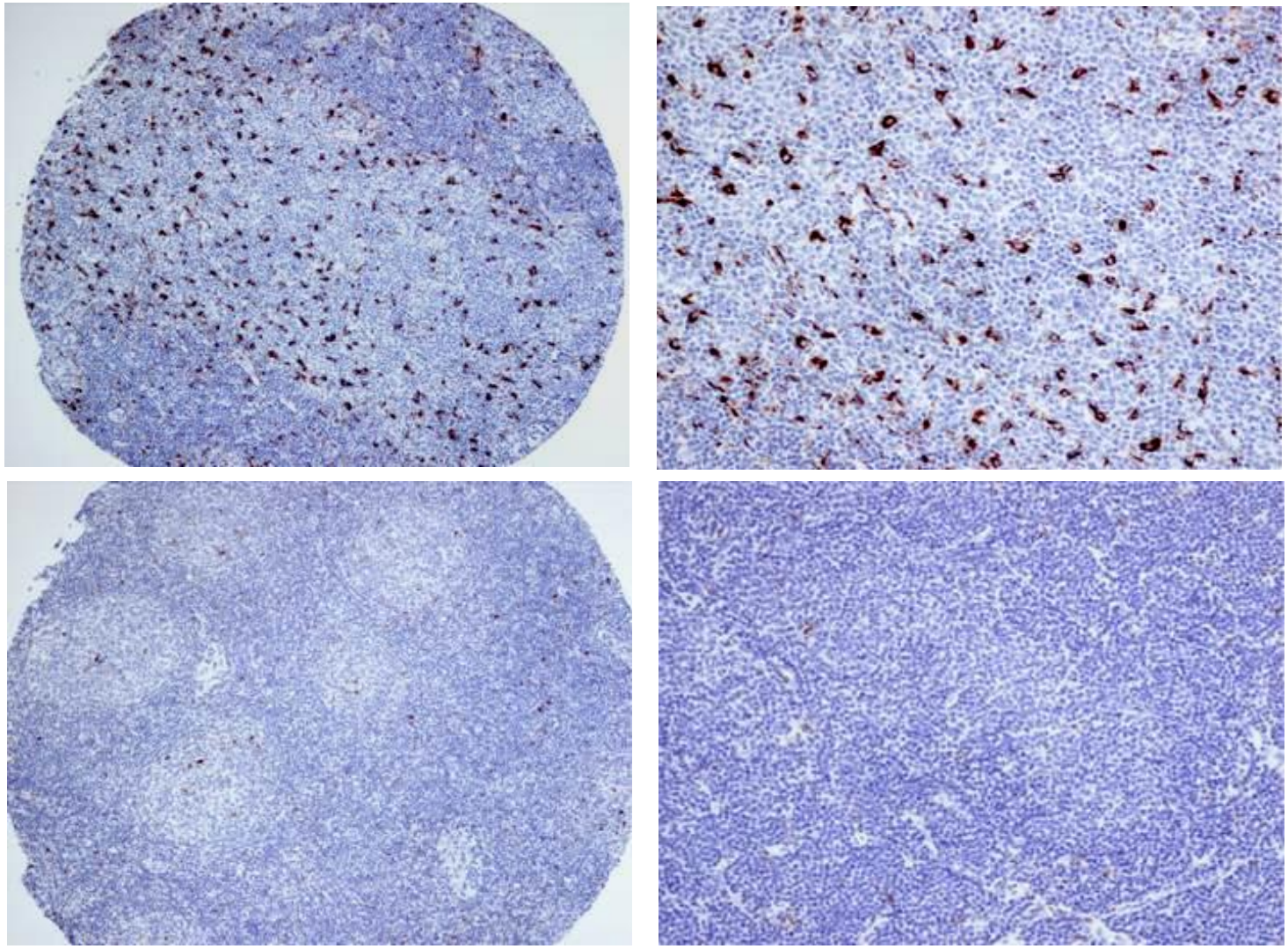


Phenotype

B-cell markers:	CD19/20/22/79a^{+}
T-cell markers:	CD5^{rare}
GCC-associated markers:	CD10/AID/Bcl-6^{+}
Transcription factors:	BSAP/Oct1/Oct2/BOB-1^{+}
	IRF4^{-}
Cytoplasmic Ig:	variable
FDC meshwork:	CD21/CD23/CD35^{+}
Ki-67/Mib1:	variable
BCL2:	positive in 85-90%


CD21

Other reactive components: TFH, Treg-cells, macrophages



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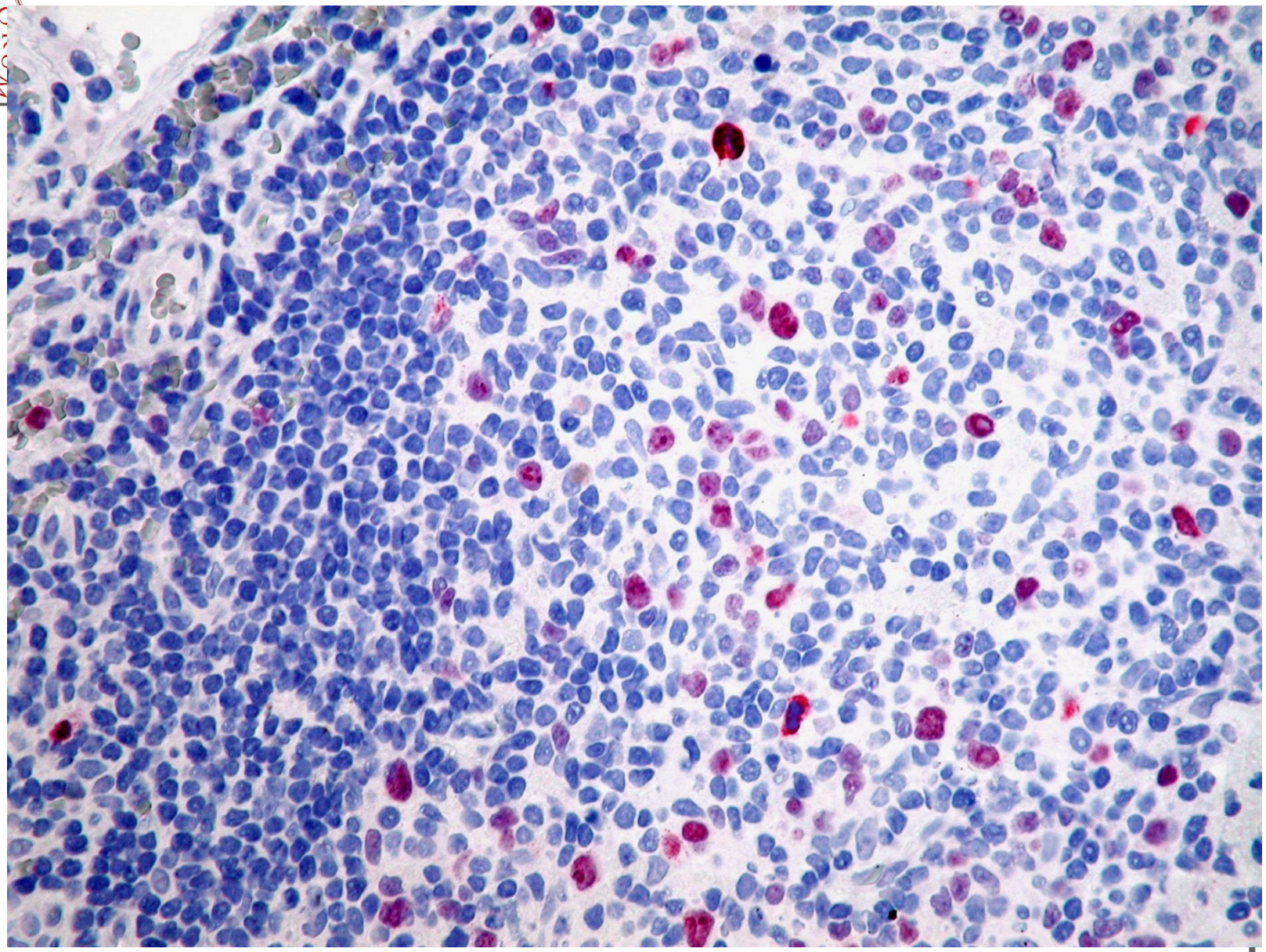
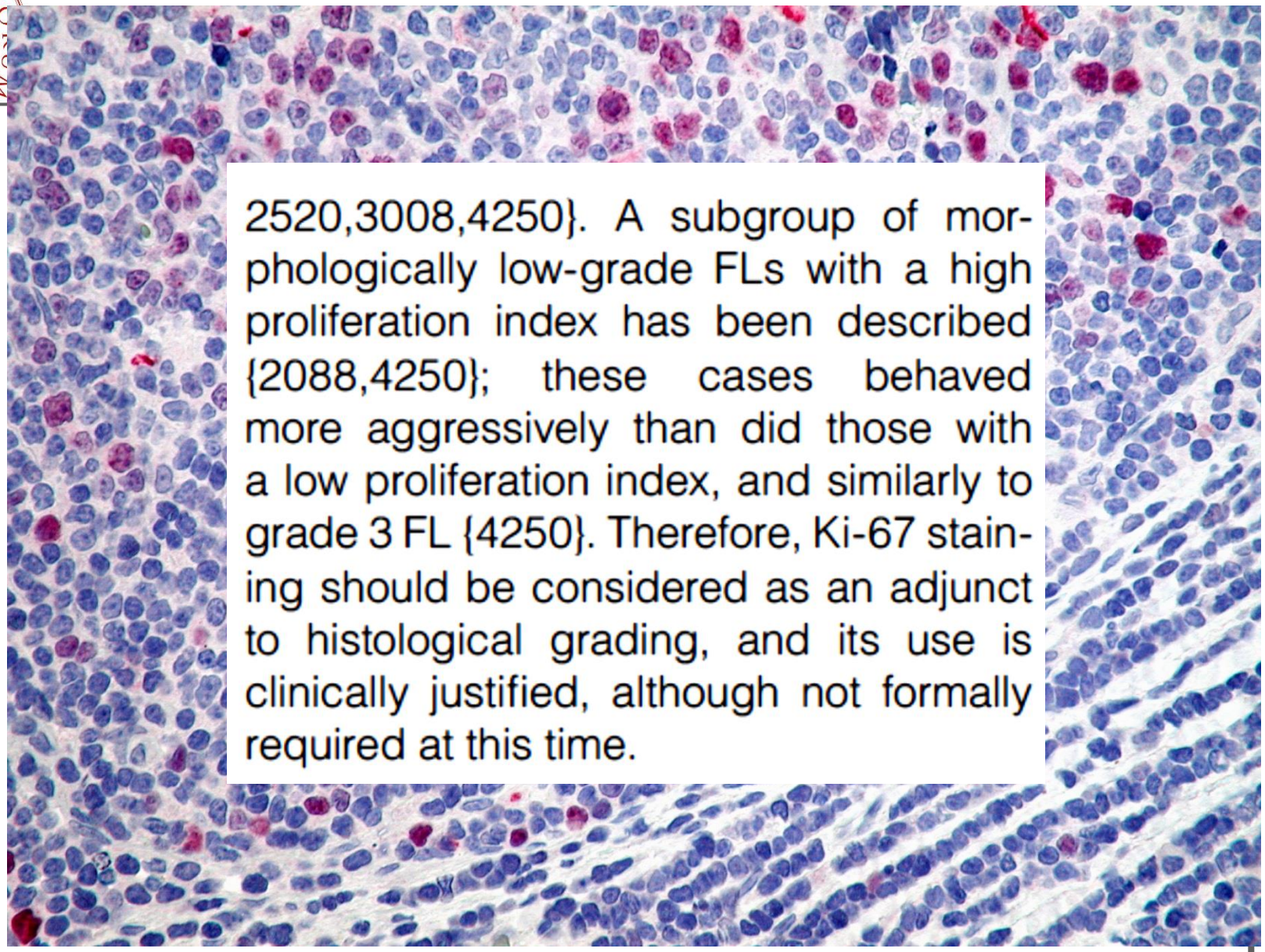
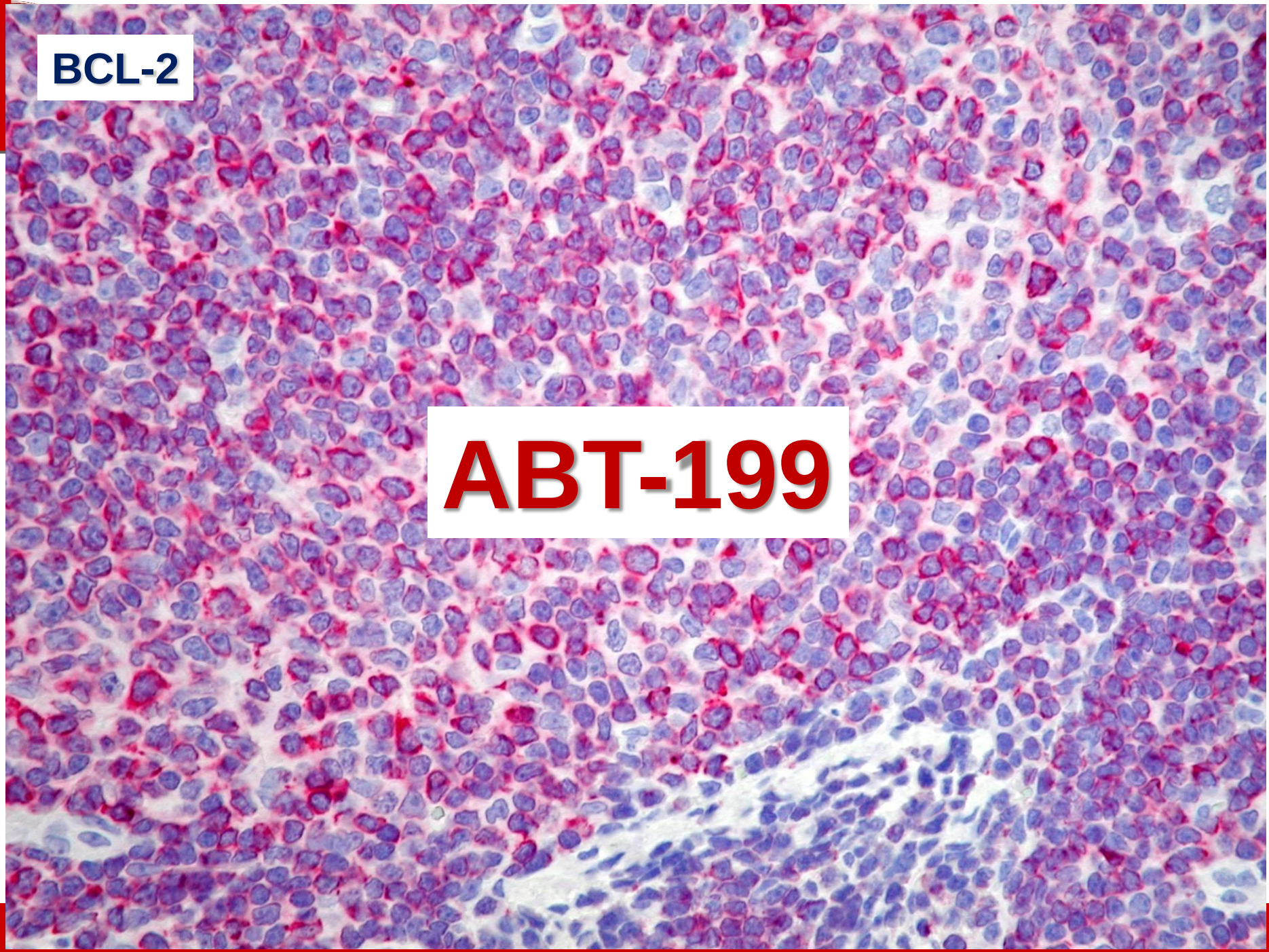
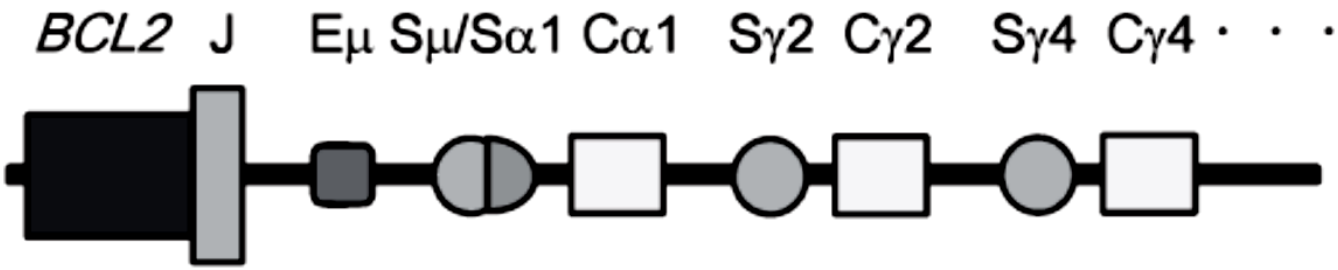



2520,3008,4250}. A subgroup of morphologically low-grade FLs with a high proliferation index has been described {2088,4250}; these cases behaved more aggressively than did those with a low proliferation index, and similarly to grade 3 FL {4250}. Therefore, Ki-67 staining should be considered as an adjunct to histological grading, and its use is clinically justified, although not formally required at this time.

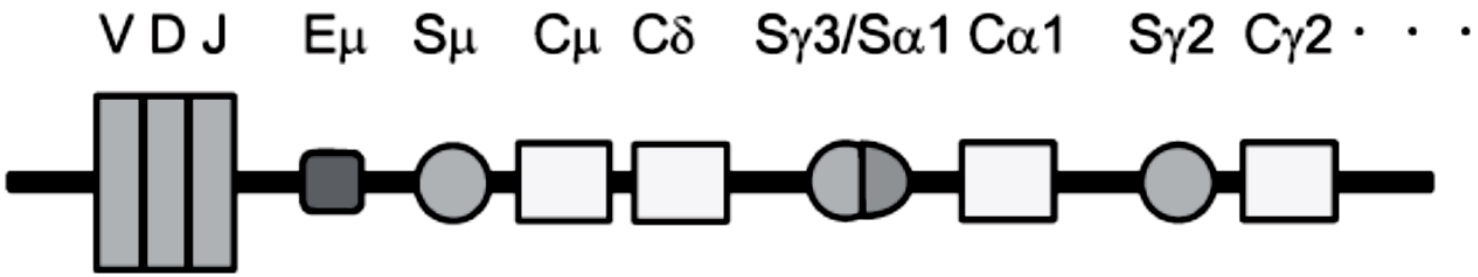

BCL-2
ABT-199

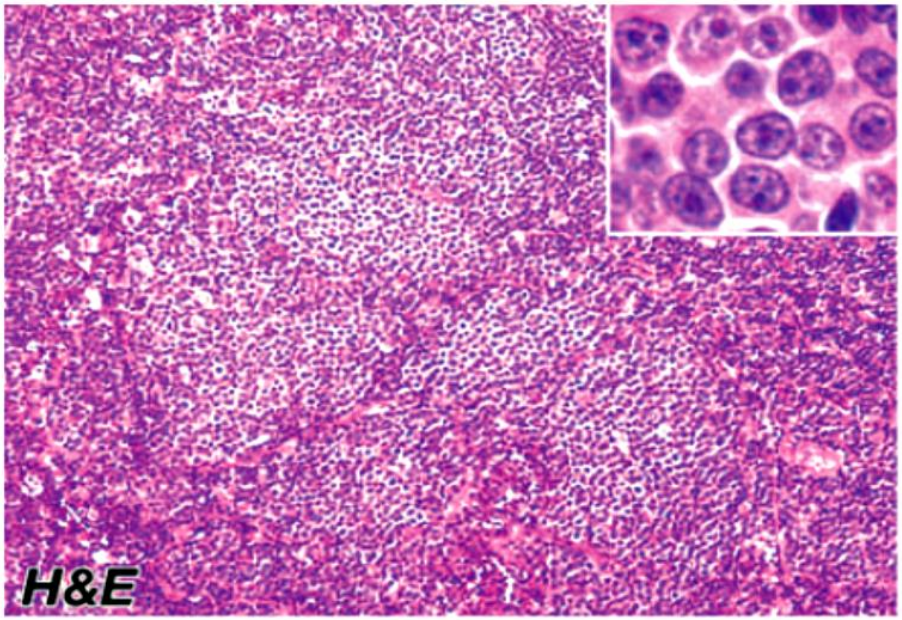
t(14;18)(q32;q21) in 85-90% of FLs

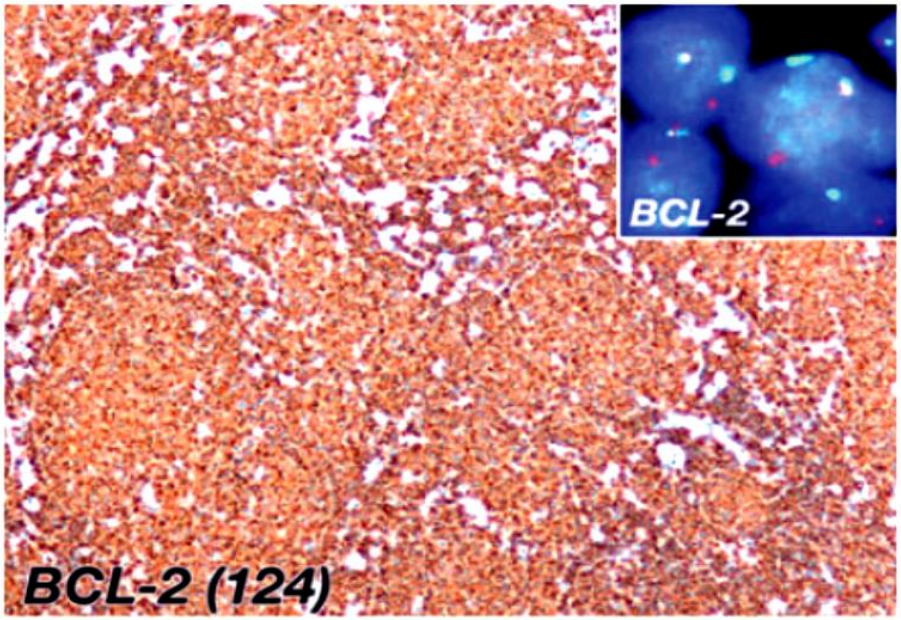
BCL2/ IGH (translocated, non-functional allele)

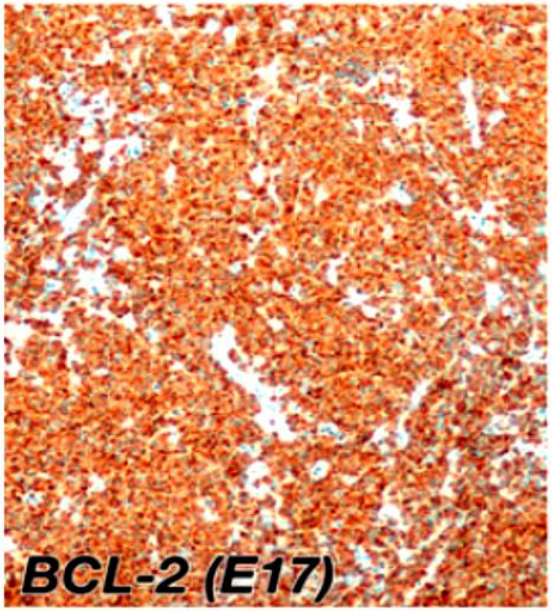


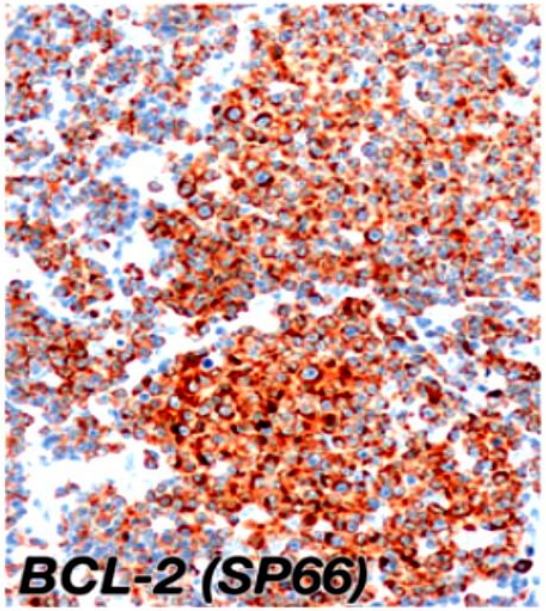
IGH (coding allele)

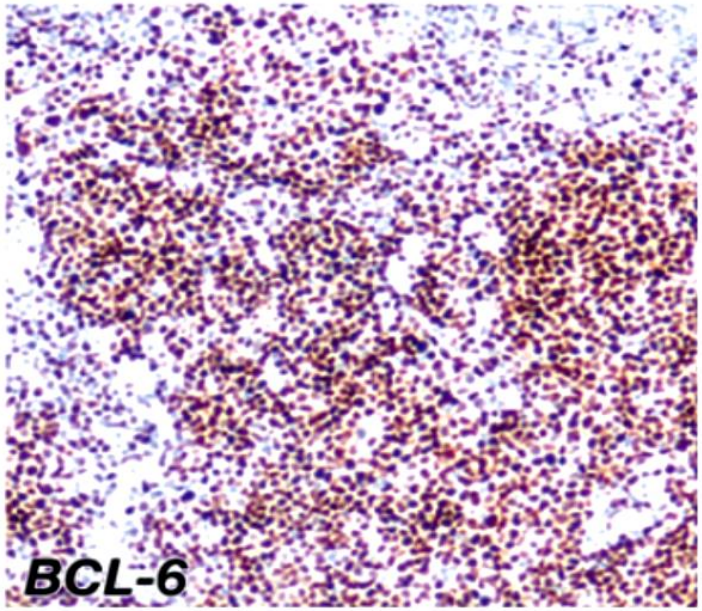



H&E


BCL-2
BCL-2 (124)


BCL-2 (E17)


BCL-2 (SP66)


BCL-6

DD with follicular hyperplasia

Leukemia (2003) 17, 2257–2317

www.nature.com/leu

LEADING ARTICLE

Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: Report of the BIOMED-2 Concerted Action BMH4-CT98-3936

JJM van Dongen[1], AW Langerak[1], M Brüggemann[2], PAS Evans[3], M Hummel[4], FL Lavender[5], E Delabesse[6], F Davi[7], E Schuuring[8,9], R García-Sanz[10], JHJM van Krieken[11], J Droese[2], D González[10], C Bastard[12], HE White[5], M Spaargaren[13], M González[10], A Parreira[14], JL Smith[5], GJ Morgan[3], M Kneba[2] and EA Macintyre[6]

FL pathobiology

N ENGL J MED 356;7 www.NEJM.ORG FEBRUARY 15, 2007

CLINICAL IMPLICATIONS OF BASIC RESEARCH

A Closer Look at Follicular Lymphoma

Louis M. Staudt, M.D., Ph.D.

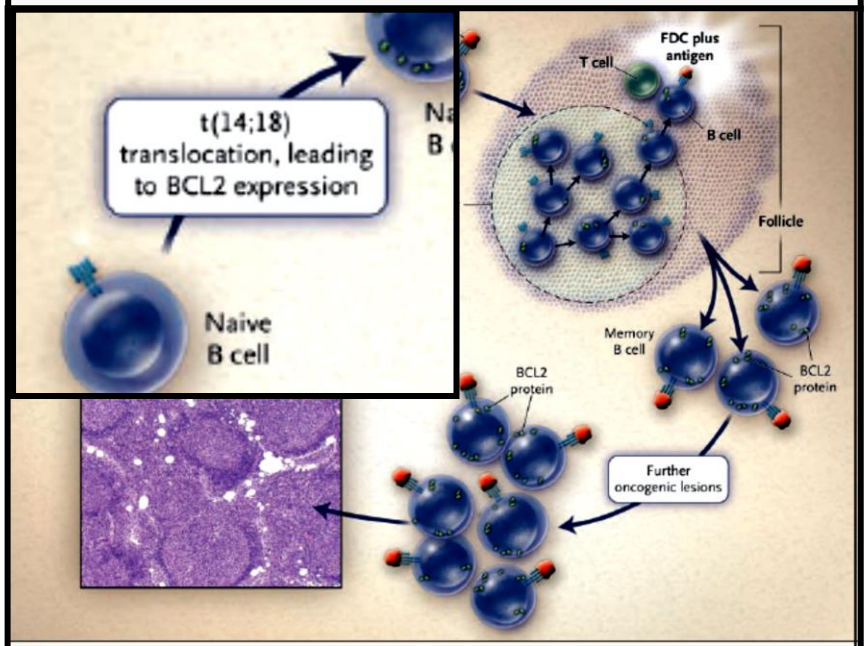


Figure 1. A New Take on Follicular Lymphoma.

The t(14;18) translocation is likely to occur in a naive B cell. A recent study by Roulland et al.[3] suggests that this B cell, if stimulated by an exogenous antigen such as a virus or autoantigen, may enter into a germinal-center reaction. There, on stimulation by an antigen on the surface of a follicular dendritic cell (FDC), together with a T cell, it may differentiate into a memory B cell, which can still be stimulated by antigen. This type of cell represents the majority of the t(14;18)-positive cells in the blood of normal persons. One of these cells may sustain further oncogenic lesions, leading to full transformation to follicular lymphoma, which may retain dependence on antigenic stimulation.

Nature and importance of follicular lymphoma precursors

Emilie Mamessier,[1,2,3] Florence Broussais-Guillaumot,[3,4,*] Bruno Chetaille,[3,5,*] Reda Bouabdallah,[3,4] Luc Xerri,[3,5] Elaine S. Jaffe,[6] and Bertrand Nadel[1,2,3]

Haematologica 2014; 99:802-10

50-70% of healthy individuals show circulating B-lymphocytes carrying the t(14;18)

t(14;18) Translocation: A Predictive Blood Biomarker for Follicular Lymphoma

Sandrine Roulland, Rachel S. Kelly, Ester Morgado, Stéphanie Sungalee, Philippe Solal-Celigny, Philippe Colombat, Nathalie Jouve, Domenico Palli, Valeria Pala, Rosario Tumino, Salvatore Panico, Carlotta Sacerdote, José R. Quirós, Carlos A. Gonzáles, Maria-José Sánchez, Miren Dorronsoro, Carmen Navarro, Aurelio Barricarte, Anne Tjønneland, Anja Olsen, Kim Overvad, Federico Canzian, Rudolf Kaaks, Heiner Boeing, Dagmar Drogan, Alexandra Nieters, Françoise Clavel-Chapelon, Antonia Trichopoulou, Dimitrios Trichopoulos, Pagona Lagiou, H. Bas Bueno-de-Mesquita, Petra H.M. Peeters, Roel Vermeulen, Göran Hallmans, Beatrice Melin, Signe Borgquist, Joyce Carlson, Eiliv Lund, Elisabete Weiderpass, Kay-Tee Khaw, Nick Wareham, Timothy J. Key, Ruth C. Travis, Pietro Ferrari, Isabelle Romieu, Elio Riboli, Gilles Salles, Paolo Vineis, and Bertrand Nadel

Author affiliations appear at the end of this article.

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P.V. and B.N. contributed equally to this work.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/14/3213w-1347w/$20.00

DOI: 10.1200/JCO.2013.52.8190

ABSTRACT

Purpose

The (14;18) translocation constitutes both a genetic hallmark and critical early event in the natural history of follicular lymphoma (FL). However, t(14;18) is also detectable in the blood of otherwise healthy persons, and its relationship with progression to disease remains unclear. Here we sought to determine whether t(14;18)-positive cells in healthy individuals represent tumor precursors and whether their detection could be used as an early predictor for FL.

Participants and Methods

Among 520,000 healthy participants enrolled onto the EPIC (European Prospective Investigation Into Cancer and Nutrition) cohort, we identified 100 who developed FL 2 to 161 months after enrollment. Prediagnostic blood from these and 218 controls were screened for t(14;18) using sensitive polymerase chain reaction–based assays. Results were subsequently validated in an independent cohort (65 case participants; 128 controls). Clonal relationships between t(14;18) cells and FL were also assessed by molecular backtracking of paired prediagnostic blood and tumor samples.

Results

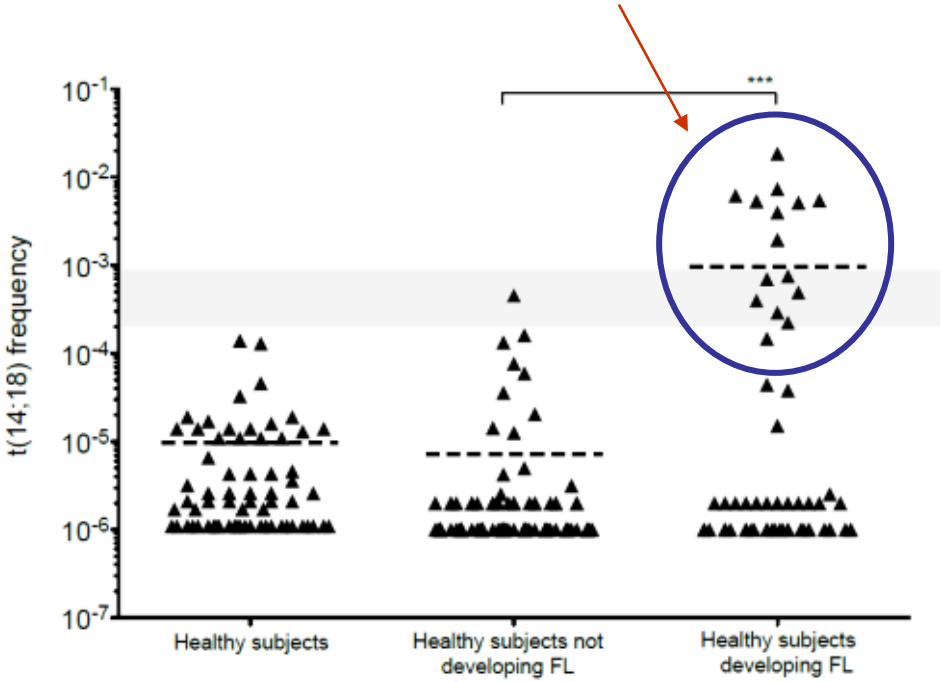
Clonal analysis of t(14;18) junctions in paired prediagnostic blood versus tumor samples demonstrated that progression to FL occurred from t(14;18)-positive committed precursors. Furthermore, healthy participants at enrollment who developed FL up to 15 years later showed a markedly higher t(14;18) prevalence and frequency than controls ($P < .001$). Altogether, we estimated a 23-fold higher risk of subsequent FL in blood samples associated with a frequency $> 10^{-4}$ (odds ratio, 23.17; 95% CI, 9.98 to 67.31; $P < .001$). Remarkably, risk estimates remained high and significant up to 15 years before diagnosis.

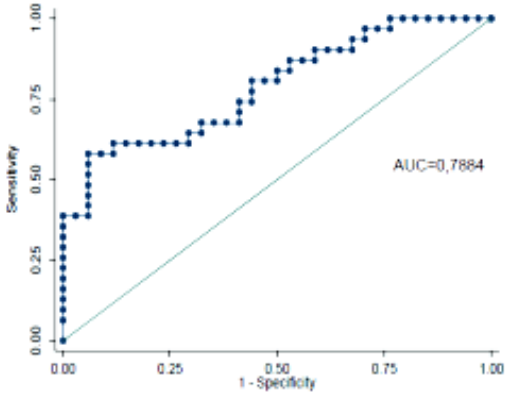
Conclusion

High t(14;18) frequency in blood from healthy individuals defines the first predictive biomarker for FL, effective years before diagnosis.

t(14;18) frequency, a predictive biomarker of risk (Tellier J et al., Blood 2014)

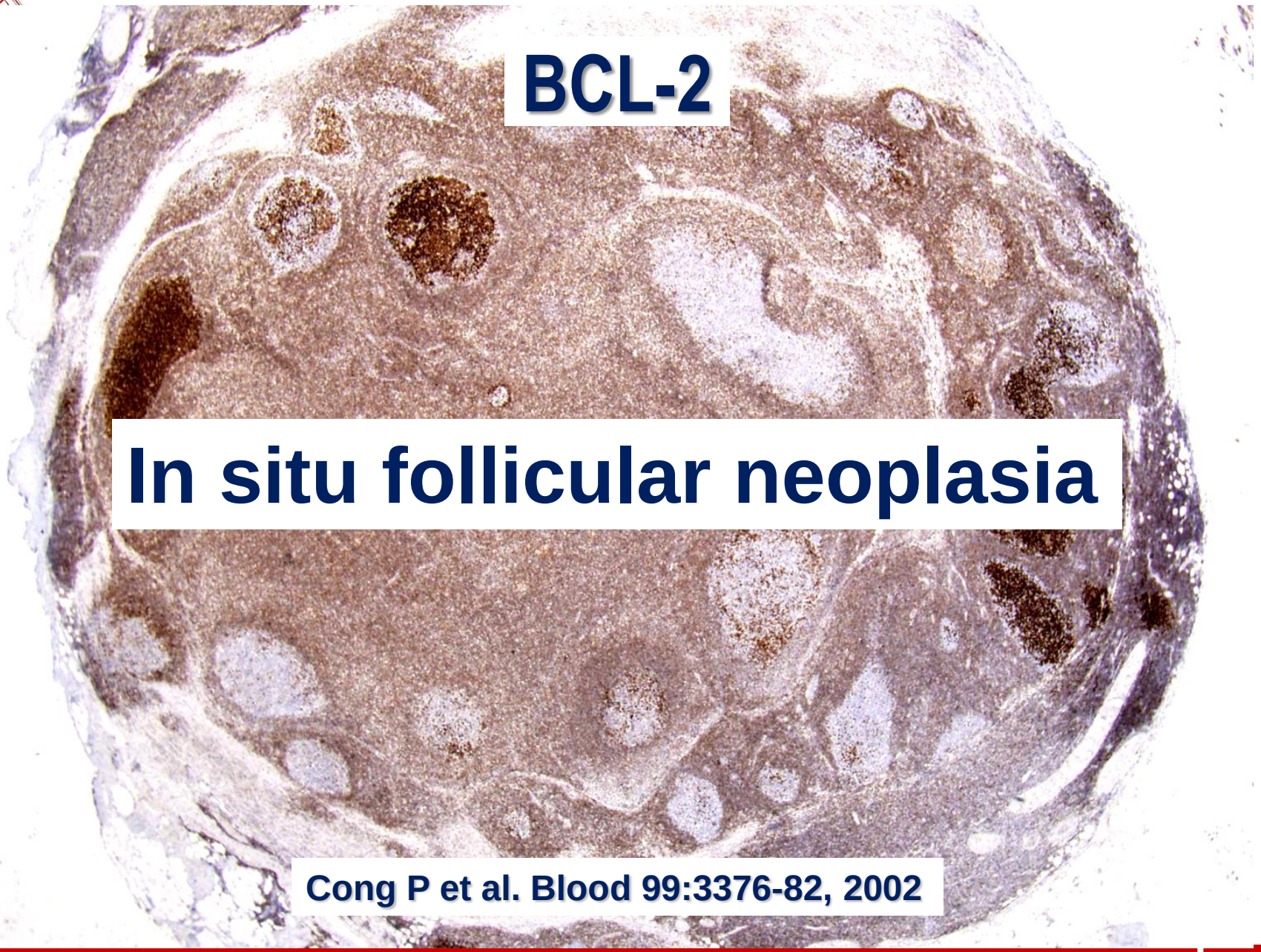
frequencies never observed before in healthy individuals !!





→ **Significant increase in t(14;18) frequency among prediagnostic FL samples**

→ **16-fold higher risk of FL development above 10^{-4}**



In situ follicular neoplasia

Cong P et al. Blood 99:3376-82, 2002

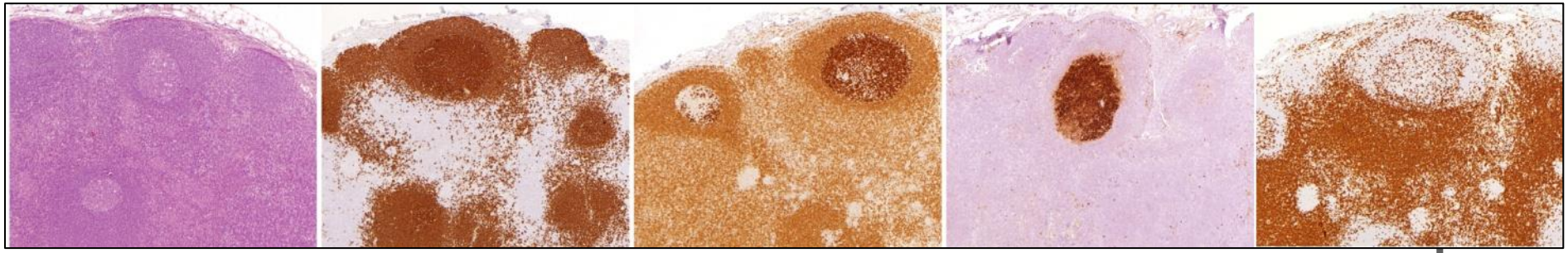
Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma

*Armin G. Jegalian,[1] *Franziska C. Eberle,[1] Svetlana D. Pack,[1] Mariya Mirvis,[1] Mark Raffeld,[1] Stefania Pittaluga,[1] and Elaine S. Jaffe[1]

[1]Laboratory of Pathology, National Cancer Institute, Bethesda, MD

Follicular lymphoma in situ (FLIS) was first described nearly a decade ago, but its clinical significance remains uncertain. We reevaluated our original series and more recently diagnosed cases to develop criteria for the distinction of FLIS from partial involvement by follicular lymphoma (PFL). A total of 34 cases of FLIS were identified, most often as an incidental finding in a reactive lymph node. Six of 34 patients had prior or concurrent FL, and 5 of 34 had FLIS composite with another lymphoma. Of patients with negative staging at diagnosis and available follow-up (21 patients), only one (5%) developed FL (follow-up: median, 41 months; range, 10-118 months). Follow-up was not available in 2 cases. Fluorescence in situ hybridization for BCL2 gene rearrangement was positive in all 17 cases tested. PFL patients were more likely to develop FL, diagnosed in 9 of 17 (53%) who were untreated. Six patients with PFL were treated with local radiation therapy (4) or rituximab (2) and remained with no evidence of disease. FLIS can be reliably distinguished from PFL and has a very low rate of progression to clinically significant FL. FLIS may represent the tissue counterpart of circulating t(14;18)-positive B cells. (*Blood*. 2011;118(11): 2976-2984)

CD20 BCL2 CD10 CD3



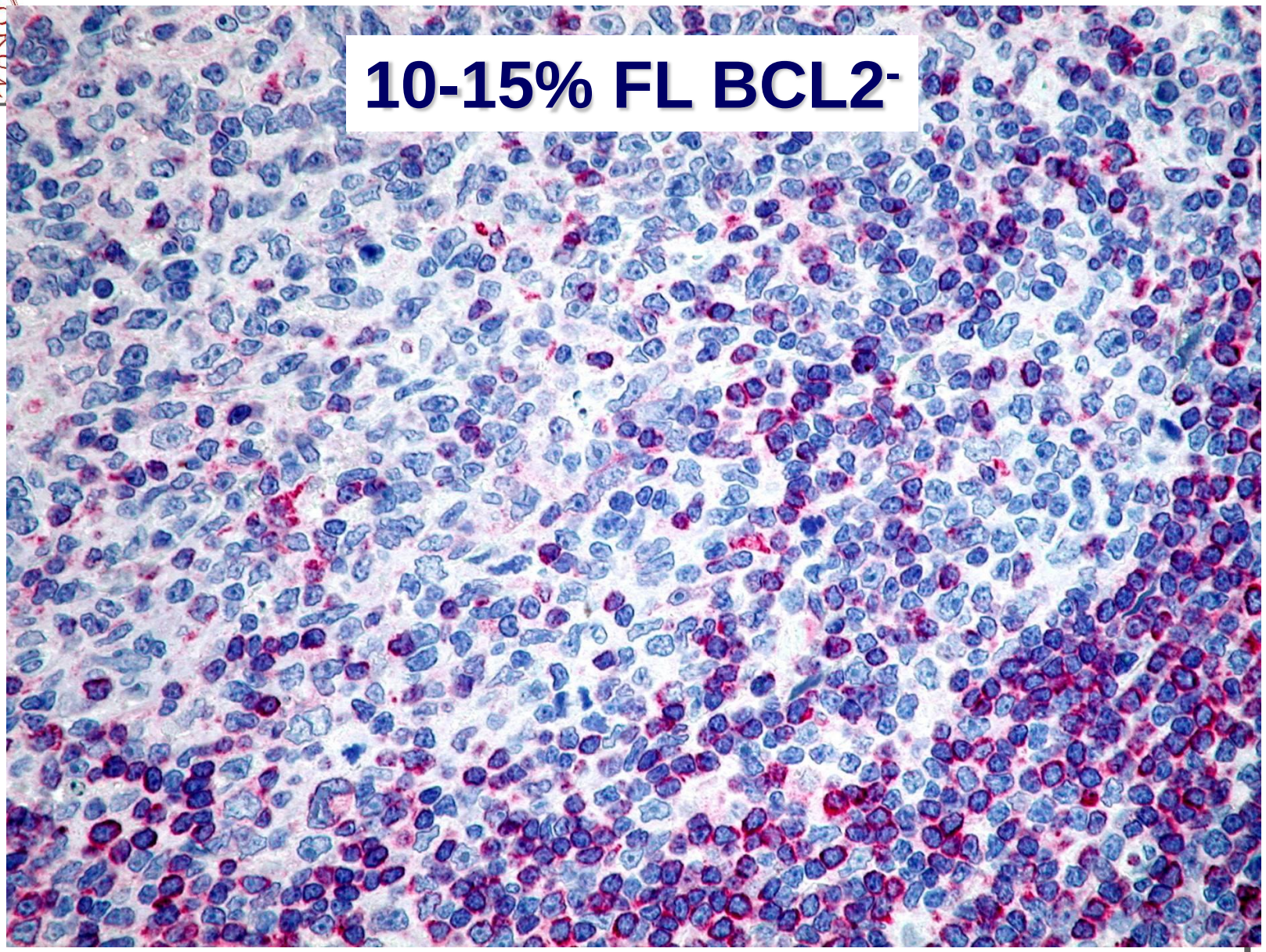
“In Situ” Lesion (ex-FLIS)

- This is the tissue equivalent of peripheral blood lymphocytes carrying t(14;18) translocations.
  - It represents an incidental finding without well documented risk of developing FL.
    - Need to exclude systemic lymphoma in other nodes.

➢ **In situ follicular neoplasia (ISFN)**

ISFN vs. Partial Involvement

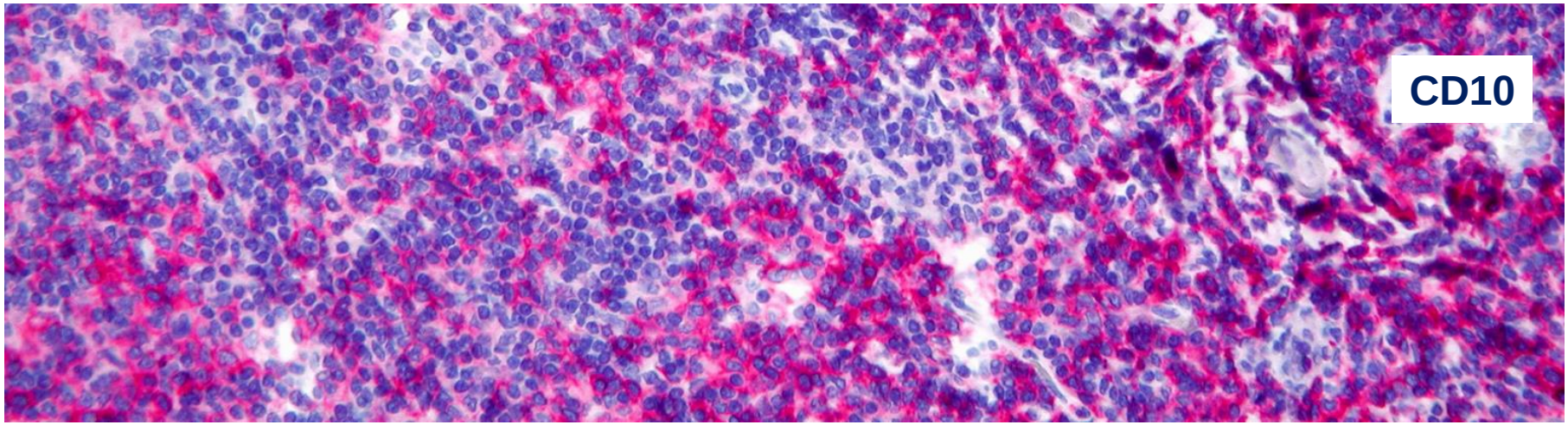
ISFN	Partial involvement by FL
Nodal architecture intact	Altered architecture evident on H&E staining
Follicle size normal	Follicle size often expanded
Involved follicles widely scattered	Involved follicles grouped together
Mantle cuff intact, with sharp border to germinal centre	Mantle cuff often attenuated or with blurred border to germinal centre
BCL2 and CD10 immunostaining very strongly positive	BCL2 and CD10 immunostaining more variable in intensity
Composed almost exclusively of centrocytes	Composed of centrocytes and few centroblasts
Atypical cells confined to the germinal centre	Atypical cells (CD10+, BCL2+) may be found outside the germinal centre


10-15% FL BCL2-

Follicular lymphoma grade 3B is a distinct neoplasm according to cytogenetic and immunohistochemical profiles

Heike Horn,[1] Christopher Schmelter,[2] Ellen Leich,[2] Itziar Salaverria,[3] Tiemo Katzenberger,[4] M. Michaela Ott,[5] Jörg Kalla,[1] Monica Romero,[6] Reiner Siebert,[3] Andreas Rosenwald,[2] and German Ott[1]

Subgroup	*BCL2* Break	*BCL6* Break	*MYC* Break	BCL2$^+$	CD10$^+$	IRF4/MUM1$^+$	clg$^+$
FL1/2	88% 22/25	0 0/25	0 0/25	96% 24/25	100% 25/25	0 0/25	13% 2/16
FL/LCC	78% 7/9	22% 2/9	22% 2/9	78% 7/9	78% 7/9	0 0/9	33% 3/9
FL3A	58% 7/12	17% 2/12	0 0/12	50% 6/12	83% 10/12	0 0/5	45% 5/11
FL3B	9% 2/23	17% 4/23	22% 5/23	45% 9/20	43% 9/21	42% 8/19	57% 12/21
FL3U	40% 6/15	13% 2/15	13% 2/15	53% 8/15	43% 6/14	14% 2/14	13% 2/15
DLBCL/FL3B	13% 2/16	50% 8/16	19% 3/16	44% 7/16	31% 5/16	63% 10/16	25% 4/16


CD10

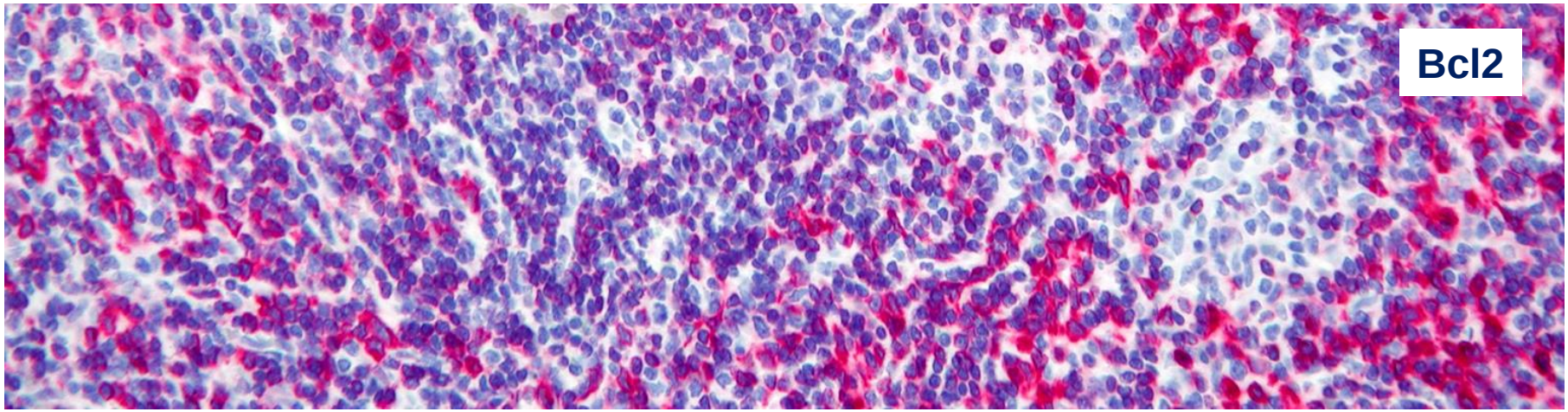

Bcl2

Table 13.18 Frequency of genetic alterations in follicular lymphoma at diagnosis

Gene	Frequency of alterations (%)[a]	Predominant type zof alteration
BCL2	85–90	Translocation, SNV
KMT2D (also called *MLL2*)	85	SNV
TNFRSF14	45–65	Deletion, SNV
EZH2	60	Recurrent SNV (Y641)
EPHA7	70	SNV
CREBBP	33	Deletion, SNV
BCL6	45	Translocation, SNV
MEF2B	15	SNV
EP300	10	Deletion, SNV
TNFAIP3 (also called *A20*)	20	Deletion, SNV
FAS	5	SNV
TP53	< 5	Deletion, SNV
MYC	< 5	Translocation, gain

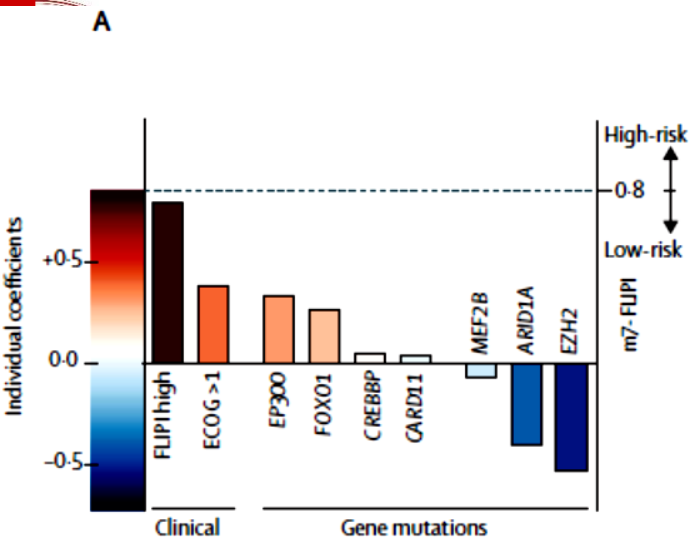
SNV, single/small nucleotide variant.

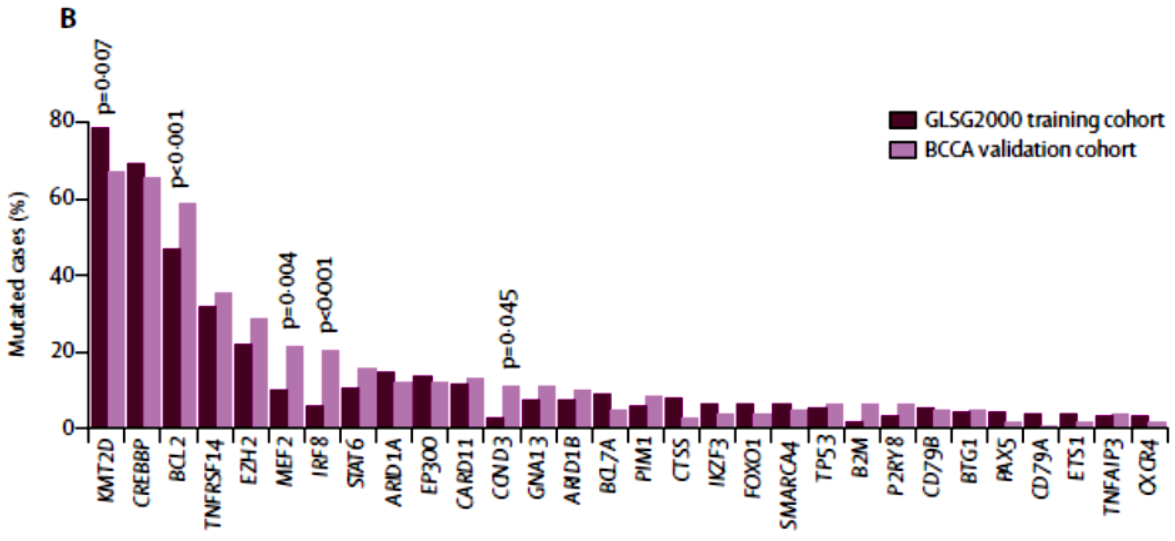
[a] Approximate frequency of alterations; some alterations may be subclonal.

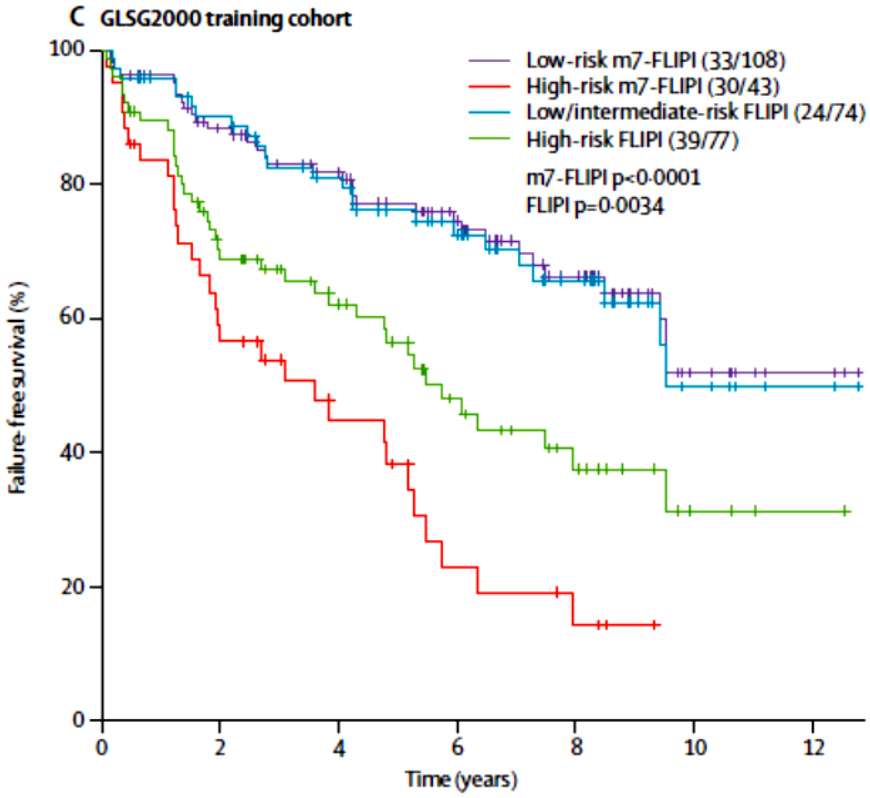
Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry

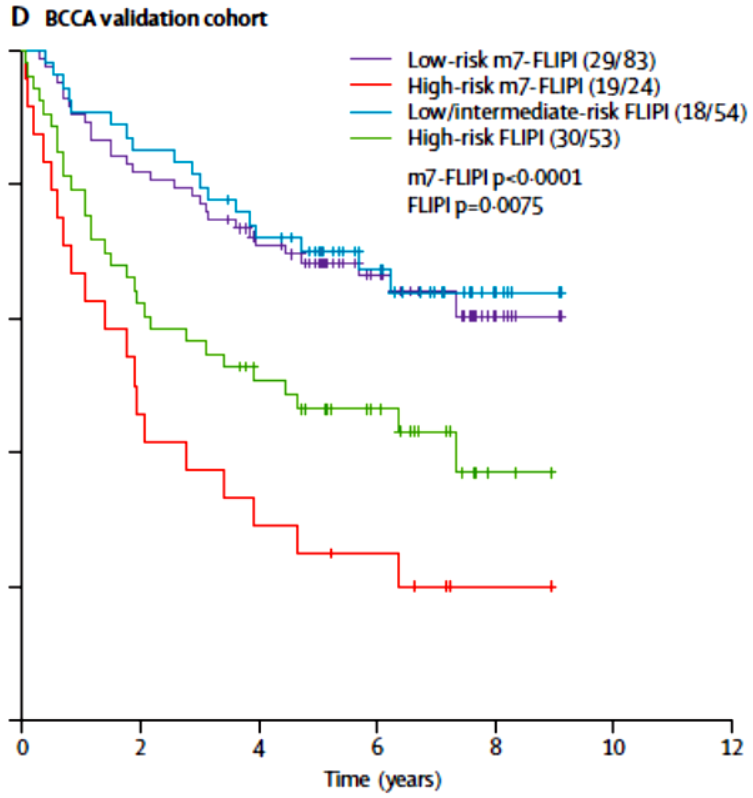
Alessandro Pastore, Vindi Jurinovic*, Robert Kridel*, Eva Hoster*, Annette M Staiger, Monika Szczepanowski, Christiane Pott, Nadja Kopp, Mark Murakami, Heike Horn, Ellen Leich, Alden A Moccia, Anja Mottok, Ashwini Sunkavalli, Paul Van Hummelen, Matthew Ducar, Daisuke Ennishi, Hennady P Shulha, Christoffer Hother, Joseph M Connors, Laurie H Sehn, Martin Dreyling, Donna Neuberg, Peter Möller, Alfred C Feller, Martin L Hansmann, Harald Stein, Andreas Rosenwald, German Ott, Wolfram Klapper, Michael Unterhalt, Wolfgang Hiddemann, Randy D Gascoyne*, David M Weinstock*, Oliver Weigert**

Lancet Oncol 2015; 16: 1111–22


A
Individual coefficients
+0·5
0·0
−0·5
FLIPI high
ECOG >1
EP300
FOXO1
CREBBP
CARD11
MEF2B
ARID1A
EZH2
High-risk
0·8
Low-risk
m7-FLIPI
Clinical
Gene mutations


B
Mutated cases (%)
p=0·007
p<0·001
p=0·004
p<0·0001
p=0·045
GLSG2000 training cohort
BCCA validation cohort
KMT2D
CREBBP
BCL2
TNFRSF14
EZH2
MEF2
IRF8
STAT6
ARID1A
EP300
CARD11
CCND3
GNA13
ARID1B
BCL7A
PIM1
CTSS
IKZF3
FOXO1
SMARCA4
TP53
B2M
P2RY8
CD79B
BTG1
PAX5
CD79A
ETS1
TNFAIP3
CXCR4


C GLSG2000 training cohort
Failure-free survival (%)
Low-risk m7-FLIPI (33/108)
High-risk m7-FLIPI (30/43)
Low/intermediate-risk FLIPI (24/74)
High-risk FLIPI (39/77)
m7-FLIPI p<0·0001
FLIPI p=0·0034
Time (years)


D BCCA validation cohort
Low-risk m7-FLIPI (29/83)
High-risk m7-FLIPI (19/24)
Low/intermediate-risk FLIPI (18/54)
High-risk FLIPI (30/53)
m7-FLIPI p<0·0001
FLIPI p=0·0075
Time (years)

Genetics of follicular lymphoma transformation

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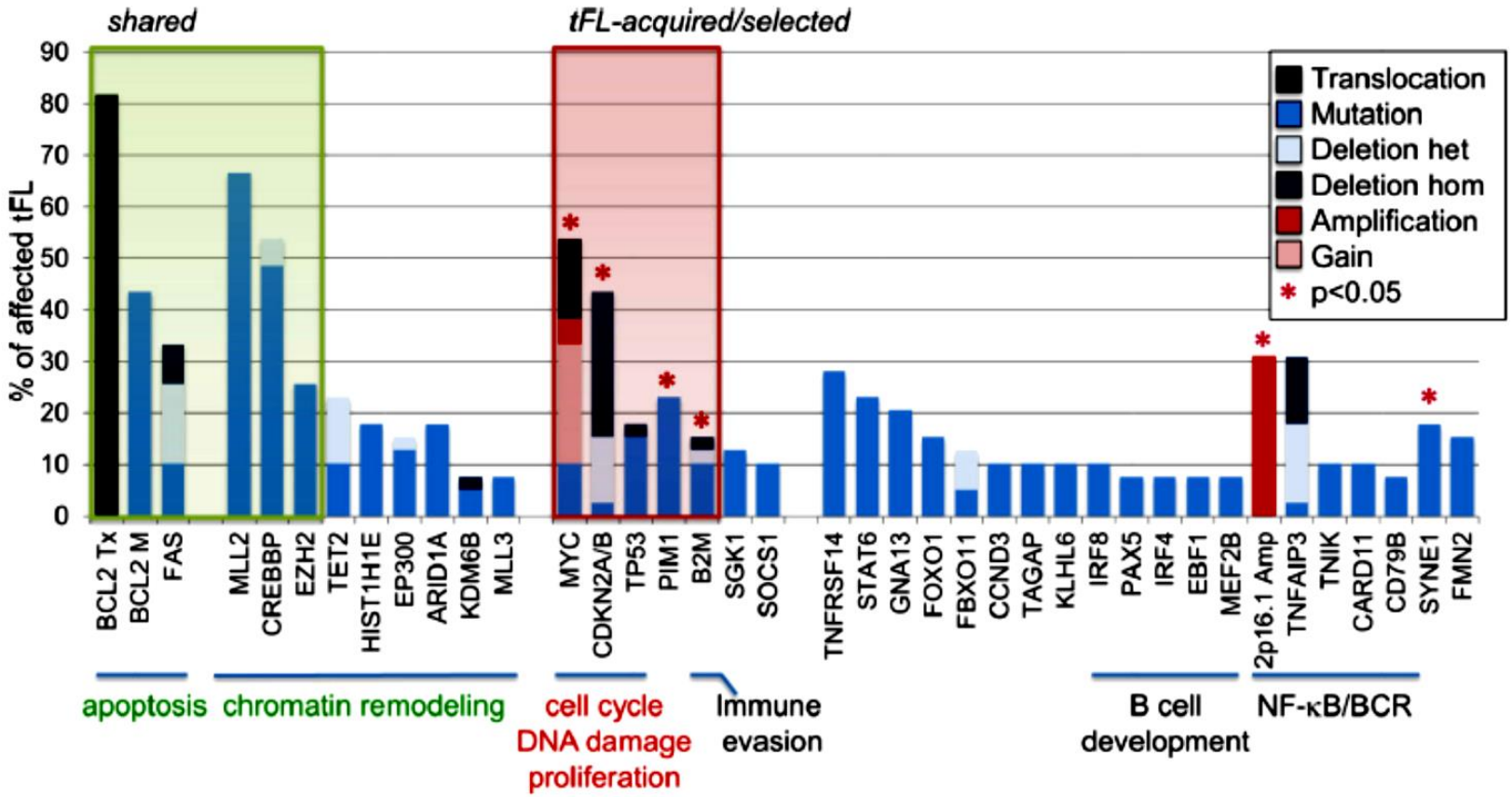
Cell Rep. 2014 January 16; 6(1): 130–140.

FL and tFL arise from a common mutated precursor clone by divergent evolution

Epigenetic modifiers and anti-apoptotic genes are mutated in the common precursor

Biallelic disruption of CDKN2A/B and deregulation of MYC are specific to tFL

tFL displays a unique genomic profile with only partial similarity to DLBCL

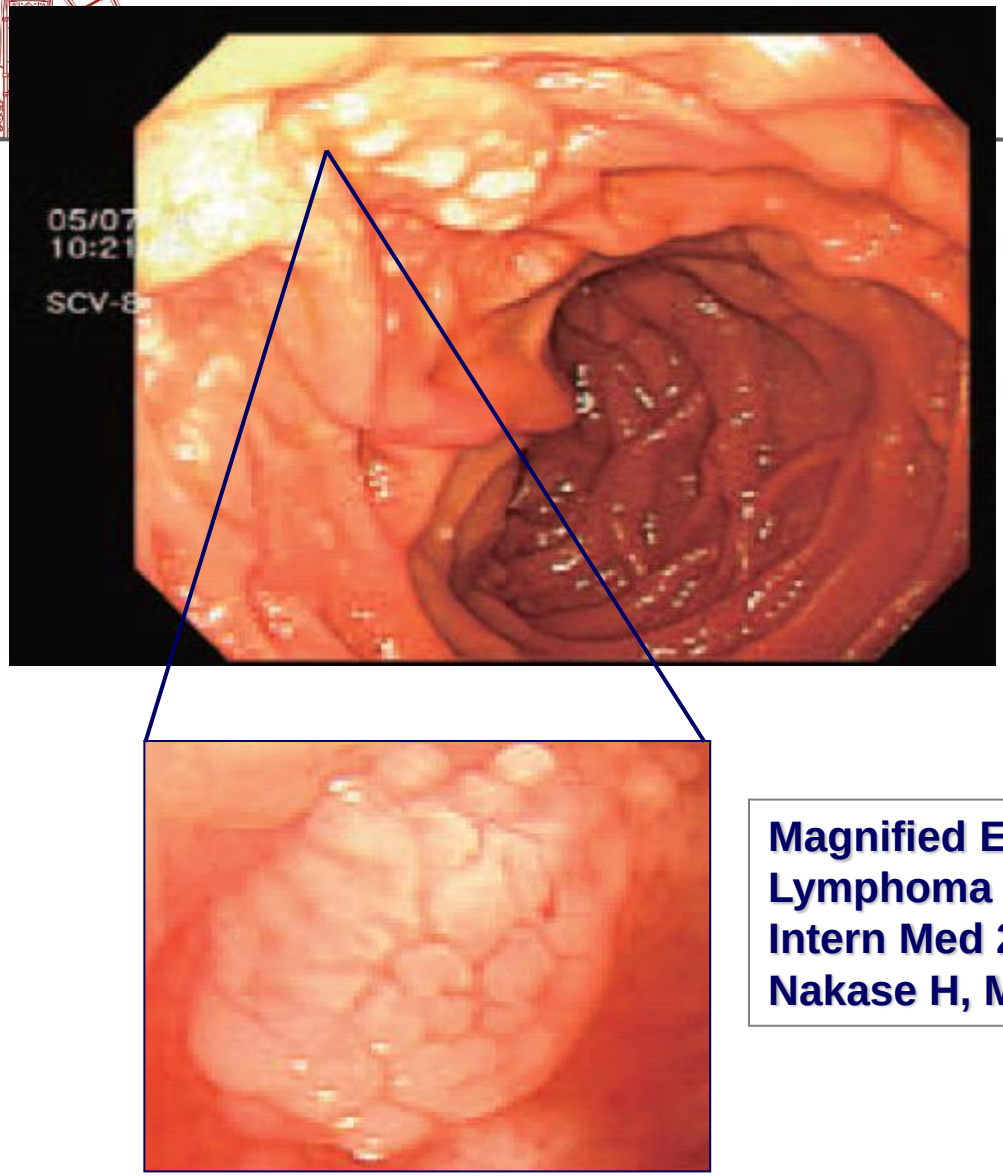

shared
tFL-acquired/selected
% of affected tFL
90
80
70
60
50
40
30
20
10
0
Translocation
Mutation
Deletion het
Deletion hom
Amplification
Gain
* p<0.05
BCL2 Tx
BCL2 M
FAS
MLL2
CREBBP
EZH2
TET2
HIST1H1E
EP300
ARID1A
KDM6B
MLL3
MYC
CDKN2A/B
TP53
PIM1
B2M
SGK1
SOCS1
TNFRSF14
STAT6
GNA13
FOXO1
FBXO11
CCND3
TAGAP
KLHL6
IRF8
PAX5
IRF4
EBF1
MEF2B
2p16.1 Amp
TNFAIP3
TNIK
CARD11
CD79B
SYNE1
FMN2
apoptosis
chromatin remodeling
cell cycle
DNA damage
proliferation
Immune
evasion
B cell
development
NF-κB/BCR

Significance

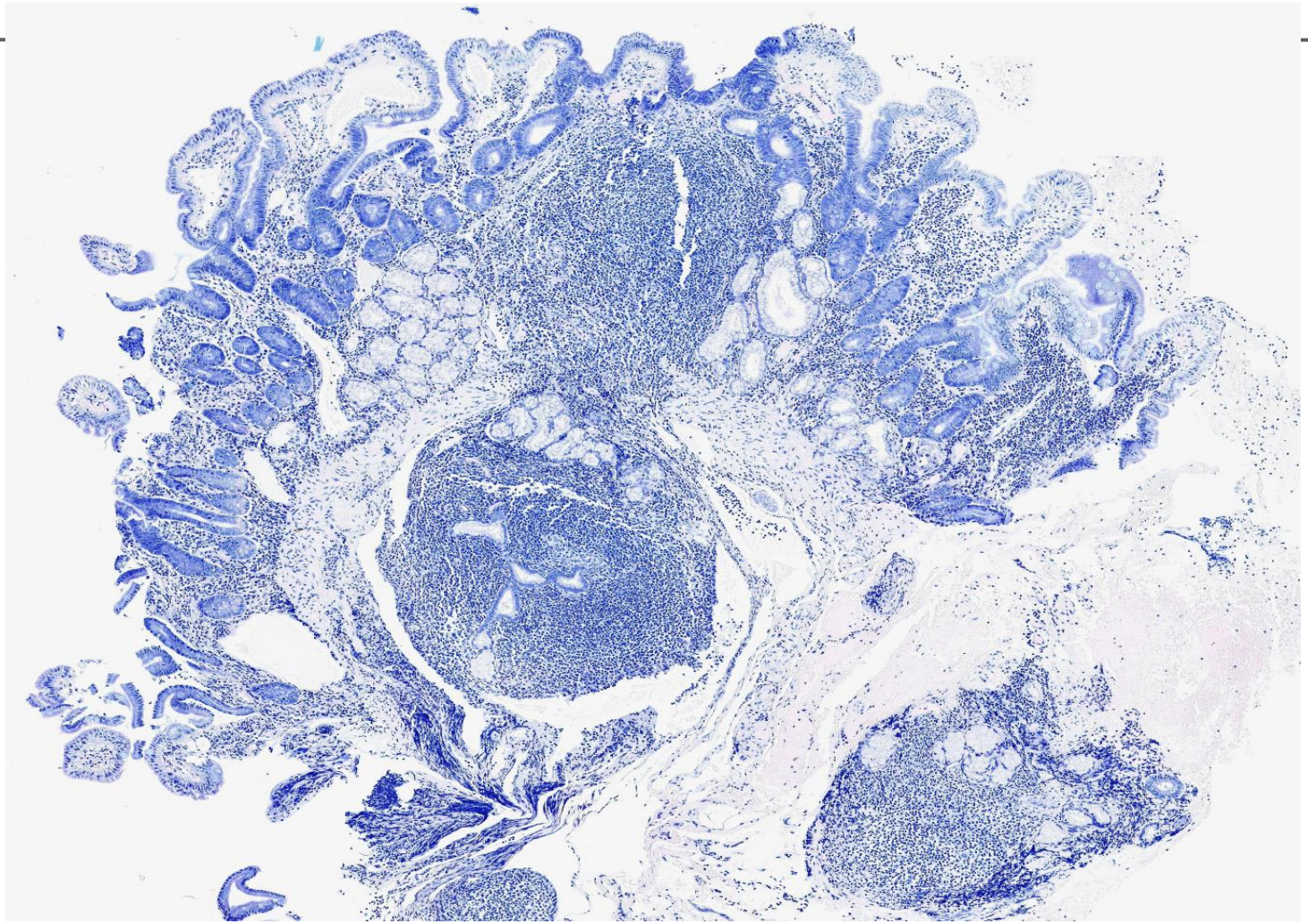
Follicular lymphoma (FL) is a disease characterized by multiple relapses that are linked by a common progenitor bearing only a subset of the mutations found within the tumor that presents clinically. Inability to cure this disease may therefore be linked to the failure of current therapies to clear these early tumor-propagating clones. Here we further define the genetic hallmarks of this disease and model the steps in evolution through phylogenetic analysis of serial tumor biopsies. This identified ***CREBBP*** mutations as early events in genome evolution that are enriched within tumor cell progenitors and provided evidence that these mutations act by allowing immune evasion. This highlights ***CREBBP*** mutations as an attractive therapeutic target in FL and provides insight into their pathogenic mechanism.

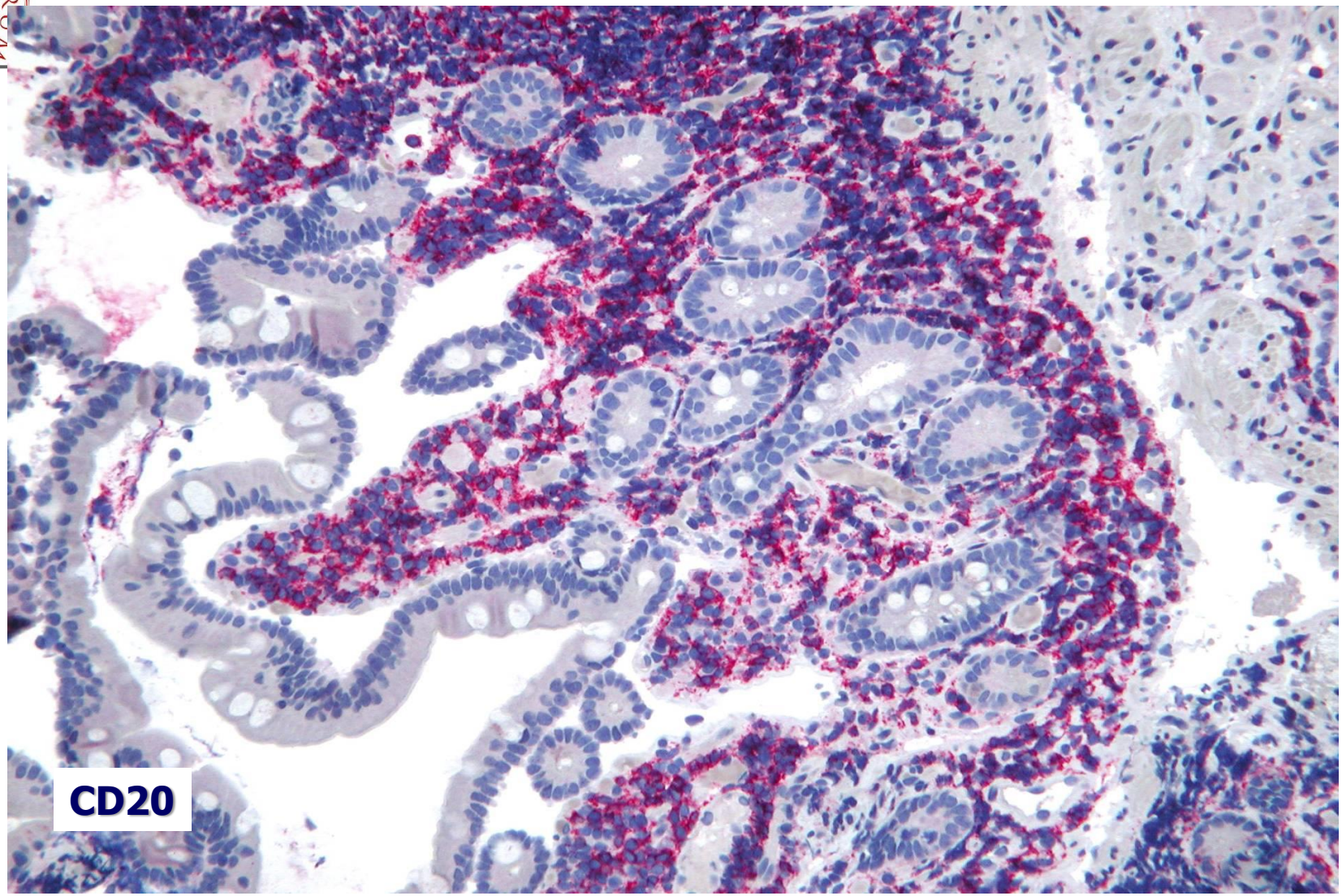
Duodenal-type FL

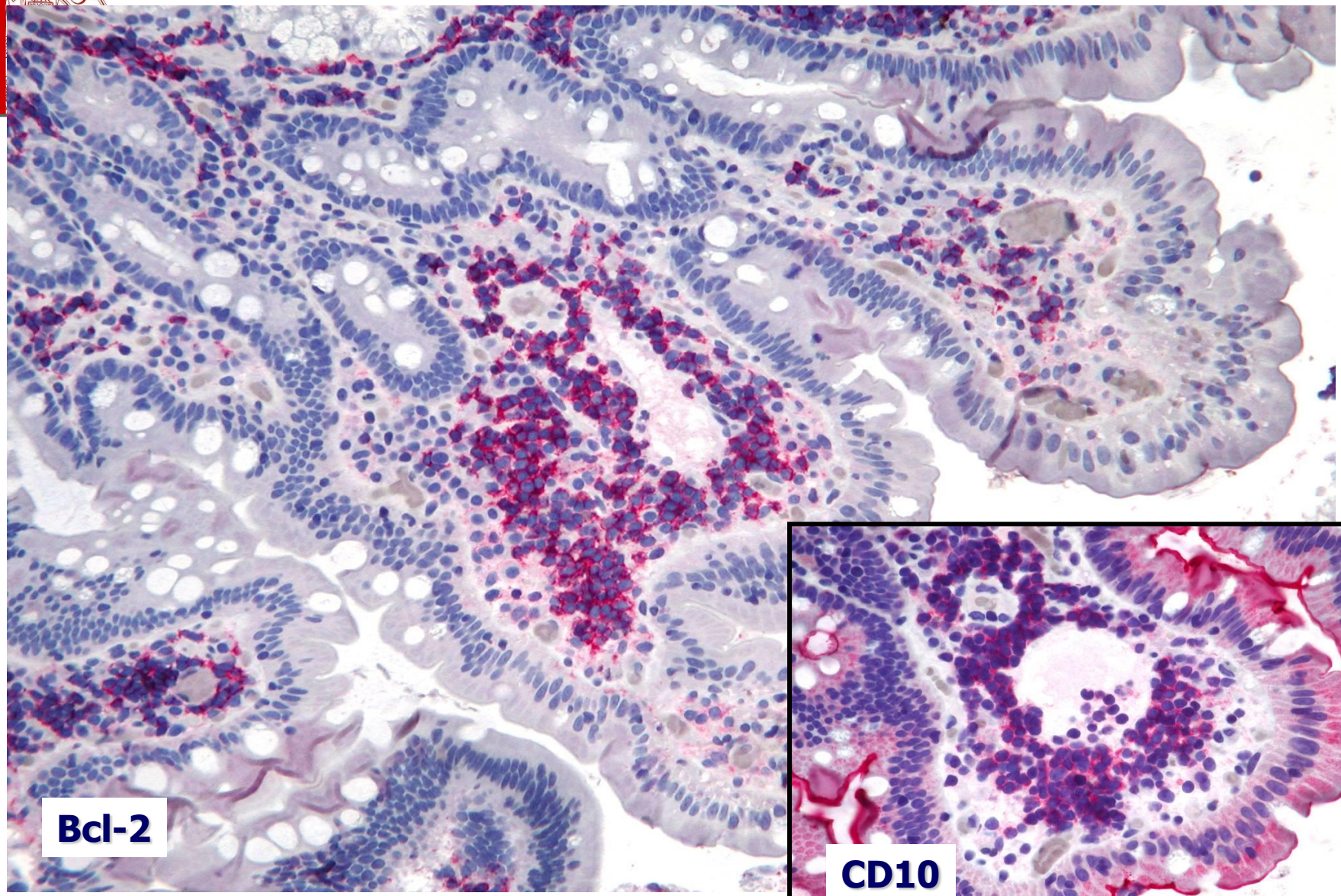
- Occasional finding during endoscopy.
- Tendency to remain localized.
- Possible involvement of other tracts of the intestine.
- Excellent prognosis (RXT, CVP, Rituximab)

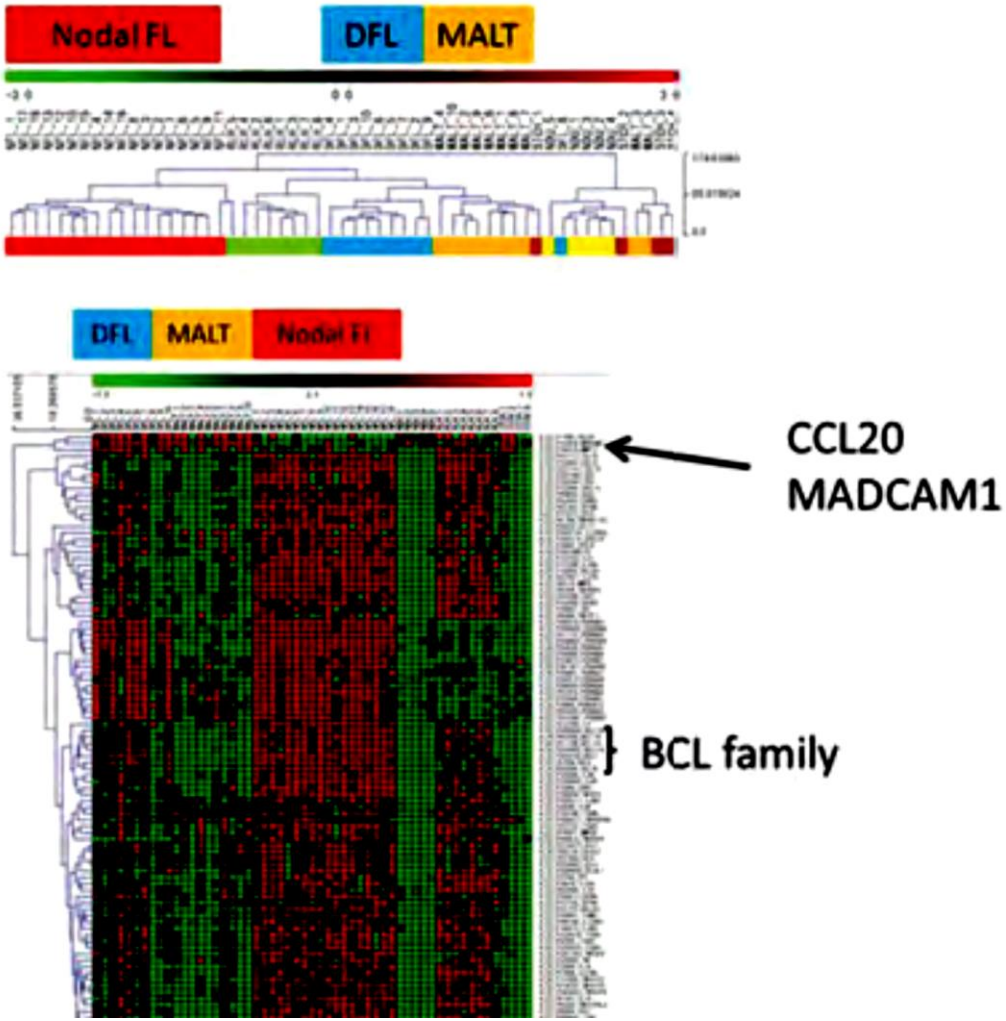


Magnified Endoscopic View of Primary Follicular Lymphoma at the Duodenum Papilla
Intern Med 2007; 46: 141-142
Nakase H, Matsuura M, Mikami S, and Chiba T




CD20


Bcl-2
CD10


Nodal FL
DFL
MALT
DFL
MALT
Nodal FL
CCL20
MADCAM1
BCL family

Paediatric type follicular lymphoma

Table 13.20 Primary diagnostic criteria for paediatric-type follicular lymphoma (PTFL)

Morphology	At least partial effacement of nodal architecture (required) Pure follicular proliferation (required)[a] Expansile follicles[b] Intermediate-sized so-called blastoid cells (not centrocytes)[b]
Immunohistochemistry (required)	BCL6 positivity BCL2 negativity or weak positivity High proliferative fraction (> 30%)
Genomics (required)	No BCL2, BCL6, IRF4, or aberrant IG rearrangement No BCL2 amplification
Clinical features	Nodal disease (required) Stage I–II disease (required) Patient age < 40 years[b] Marked male predominance

[a] The presence of any component of diffuse large B-cell lymphoma or advanced-stage disease excludes PTFL
[b] These are common features of PTFL, but not required for diagnosis.

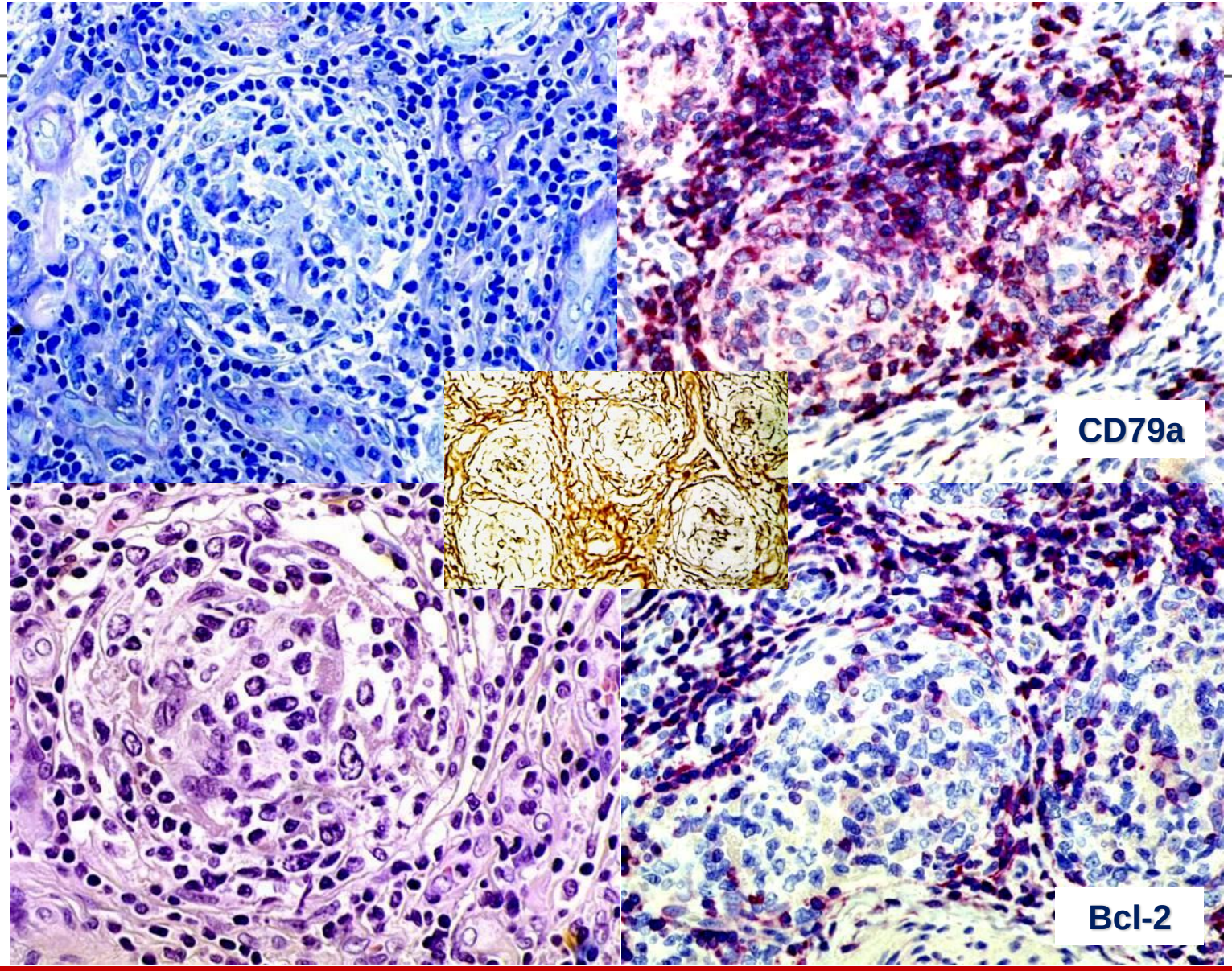
Genetic Analysis of Pediatric Lymphoma

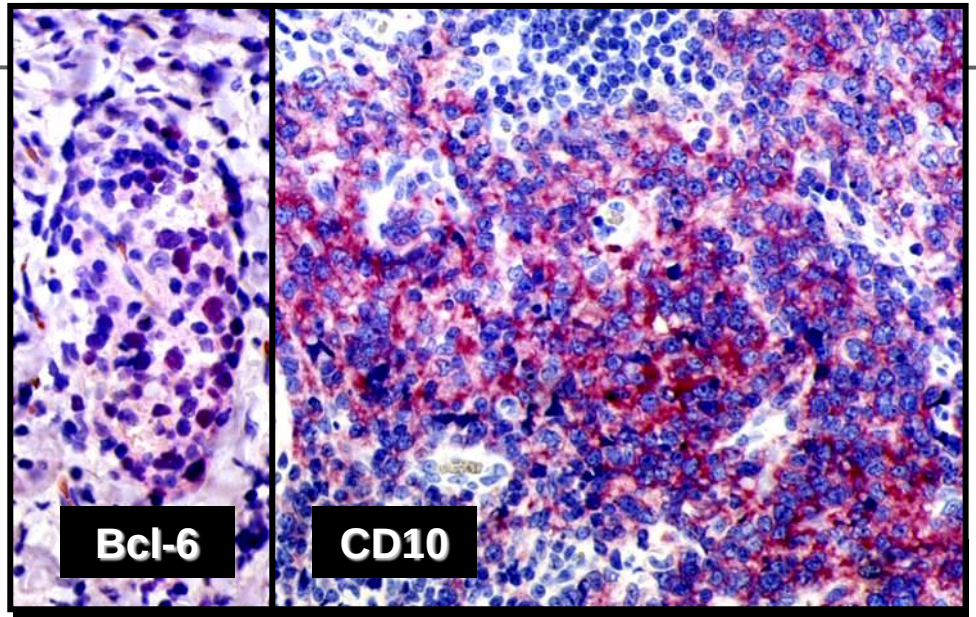
- Any genetic abnormality (50%)
  - TNFRSF14 mutation/deletions (1p36) (40%)
  - EZH2 mutation (10%)

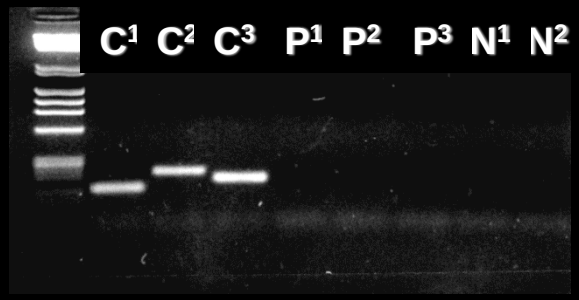
- All patients treated with systemic therapy; no difference in outcome based on genetic abnormalities

Martin-Guerrero, Haematologica 2013

Testicular FL







BCL-2


рахмат
danke
謝謝
ngiyabonga
spas
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
tack
mahalo
tapadh leat
спасибо
faafetai lava
dank je
misaotra
paldies
grazzi
matondo
спасибі
thank you
gracias
kiitos
dankie
nanni
nandri
dhanyavad
mauruuru
хвала
asante
manana
bedankt
bayarlalaa
gracie
hvala
köszönöm
aciu
dankon
akun
obrigada
murakoze
tenki
enkosi
djiere dieuf
tau
mochchakkeram
дякую
mamnun
dziękuję
chnorakaloutioun
gracies
sulpay
taiku
go raibh maith agat
sobodi
dėkuji
obrigado
sagolun
sukriya
kop khun krap
arigatô
takk
dakujem
trugarez
mèsi
didi madloba
najis tuke
ありがとう
tanemirt
grazie
terima kasih
rahmet
ευχαριστώ
diolch
dhanyavadagalu
shukriya
merce
мерси
kam sah hamnida
rahmat
감사합니다
xiexie
merci