OTTIMIZZAZIONE DIAGNOSTICA

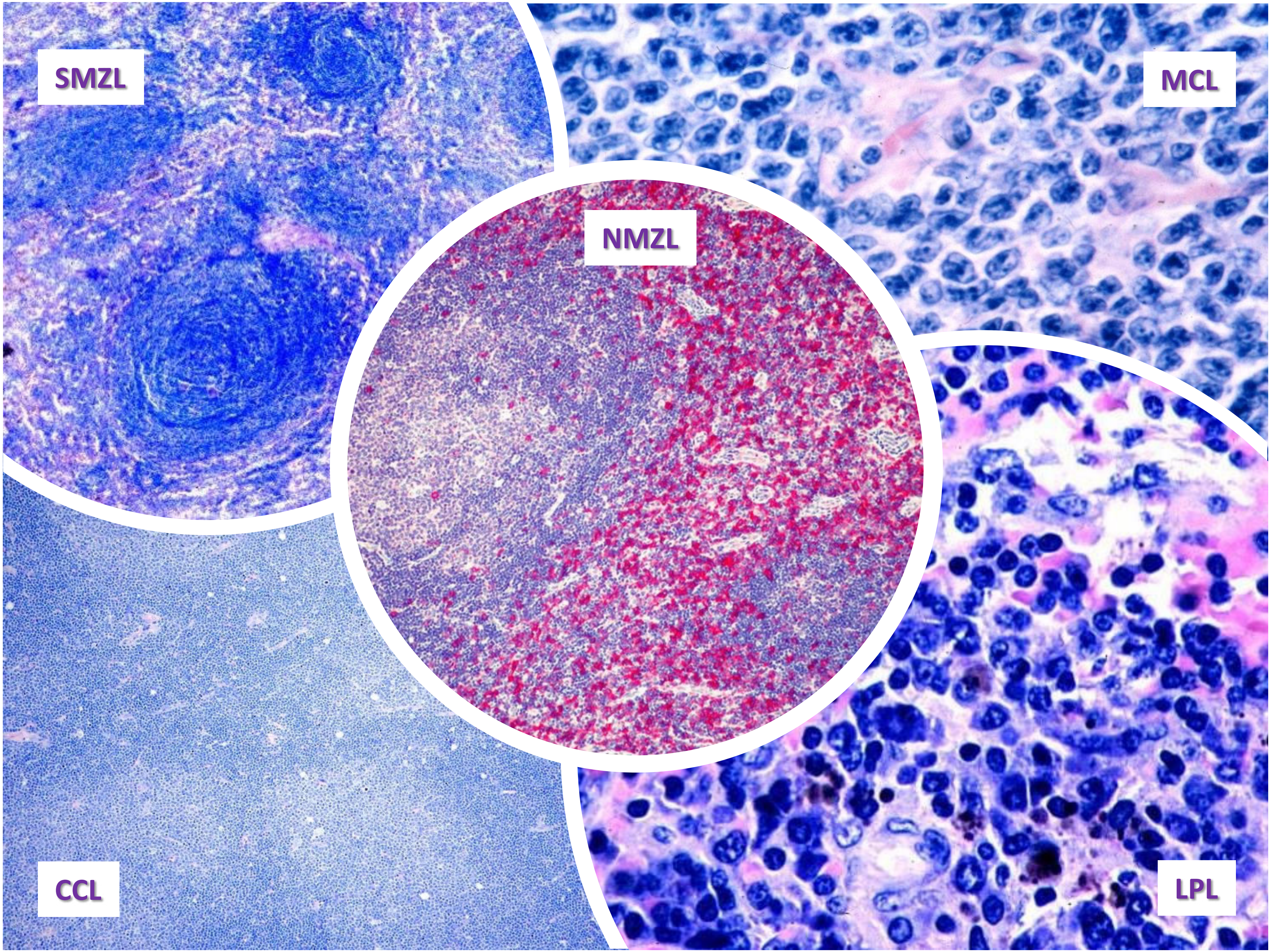
Stefano A. Pileri

CATANIA

14 settembre 2022
NH Catania Centro

Disclosures of Stefano A. Pileri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BeiGene						X	
Takeda						X	
Roche					X		
Diatech						X	


SMZL
MCL
NMZL
CCL
LPL

Tracking no: BLD-2022-015854-CR1

Title: Genomic profiling for clinical decision making in lymphoid neoplasms

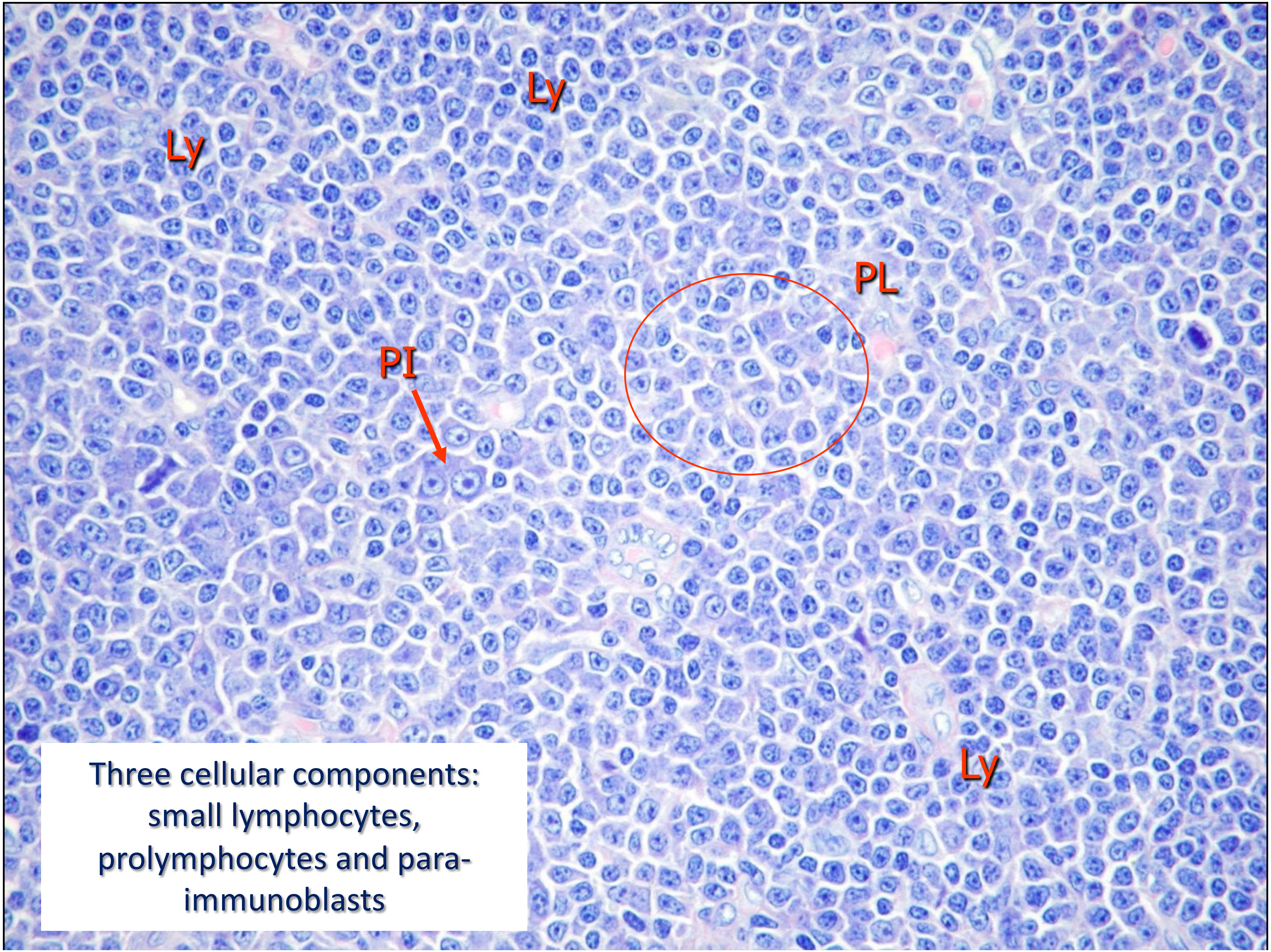
Running title: Genomic profiling of lymphomas

Authors: Laurence de Leval*[1], Ash A Alizadeh[2], P Leif Bergsagel[3], Elias Campo[4], Andrew Davies[5], Ahmet Dogan[6], Jude Fitzgibbon[7], Steven M Horwitz[8], Ari M Melnick[9], William G Morice[10], Ryan D Morin[11], Bertrand Nadel[12], Stefano A Pileri[13], Richard Rosenquist[14], Davide Rossi[15], Itziar Salaverria[16], Christian Steidl[17], Steven P Treon[18], Andrew D. Zelenetz[8,9], Ranjana H Advani[19], Carl E Allen[20], Stephen M Ansell[21], Wing C Chan[22], James R Cook[23], Lucy B Cook[24], Francesco d'Amore[25], Stefan Dirnhofer[26], Martin Dreyling[27], Kieron Dunleavy[28], Andrew L Feldman[10], Falko Fend[29], Philippe Gaulard[30], Paolo Ghia[31], John G Gribben[7], Olivier Hermine[32], Daniel J Hodson[33], Eric D Hsi[34], Giorgio Inghirami[35], Elaine S Jaffe[36], Kennosuke Karube[37], Keisuke Kataoka[38], Wolfram Klapper[39], Won Seog Kim[40], Rebecca L King[10], Young H Ko[41], Ann S LaCasce[18], Georg Lenz[42], José I Martin-Subero[43], Miguel A Piris[44], Stefania Pittaluga[36], Laura Pasqualucci[45], Leticia Quintanilla-Martinez[29], Scott J Rodig[46], Andreas Rosenwald[47], Gilles A Salles[8], Jesus San-Miguel[48], Kerry J Savage[17], Laurie H Sehn[17], Gianpietro Semenzato[49], Louis M Staudt[50], Steven H Swerdlow[51], Constantine S Tam[52], Judith Trotman[53], Julie M Vose[54], Oliver Weigert[27], Wyndham H Wilson[50], Jane N Winter[55], Catherine J Wu[18], Pier L Zinzani[56], Emanuele Zucca[15], Adam Bagg[57], David W Scott*[17]

Chronic lymphocytic leukaemia / small lymphocytic lymphoma

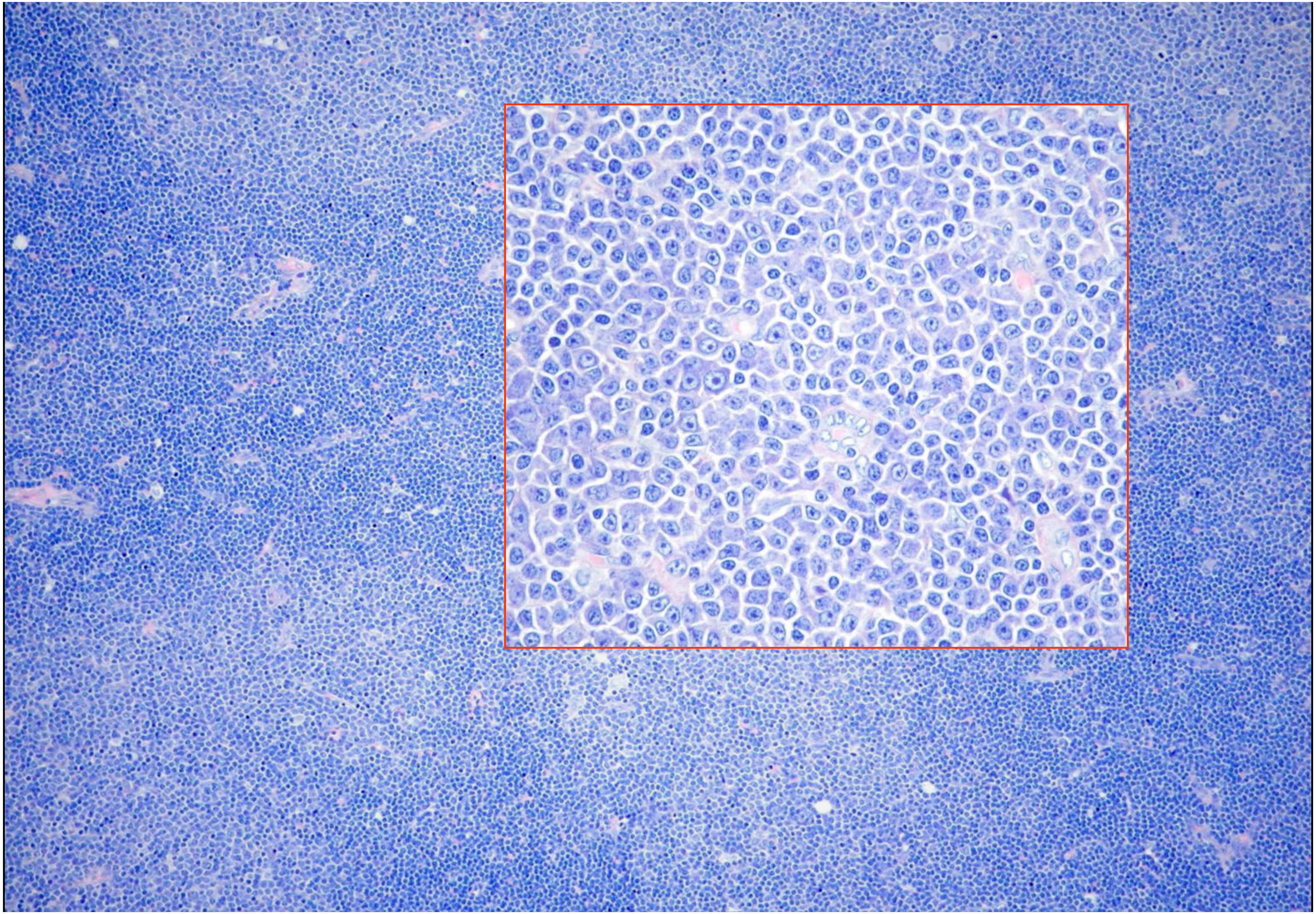
Definition

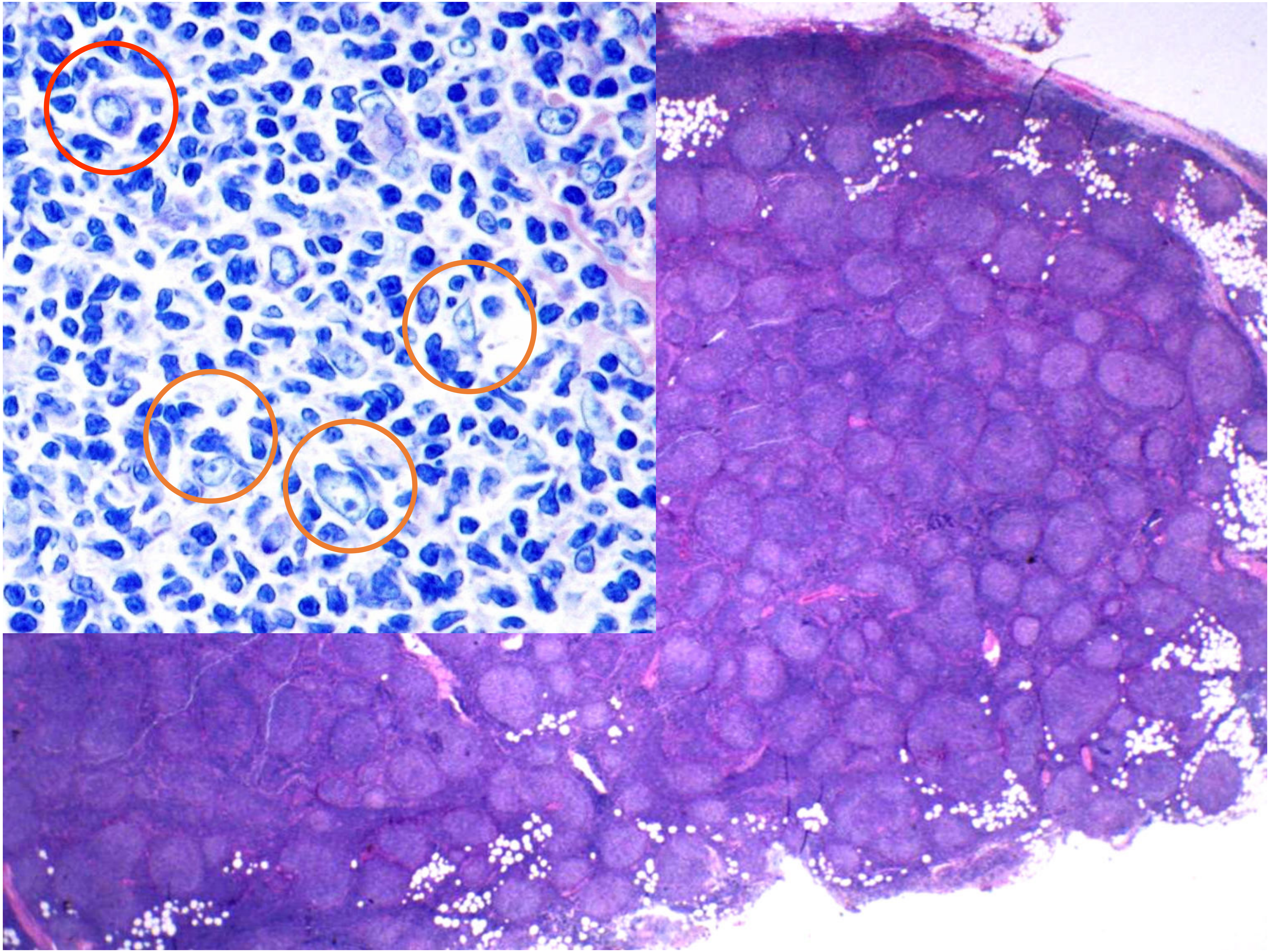
Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is a neoplasm composed of monomorphic small mature B cells that coexpress CD5 and CD23. There must be a monoclonal B-cell count $\geq 5 \times 10^9/L$, with the characteristic morphology and phenotype of CLL in the peripheral blood. Individuals with a clonal CLL-like cell count $< 5 \times 10^9/L$ and without lymphadenopathy, organomegaly, or other extramedullary disease are considered to have monoclonal B-cell lymphocytosis. Although CLL and SLL are the same disease, the term SLL is used for cases with a circulating CLL cell count $< 5 \times 10^9/L$ and documented nodal, splenic, or other extramedullary involvement {1523}.



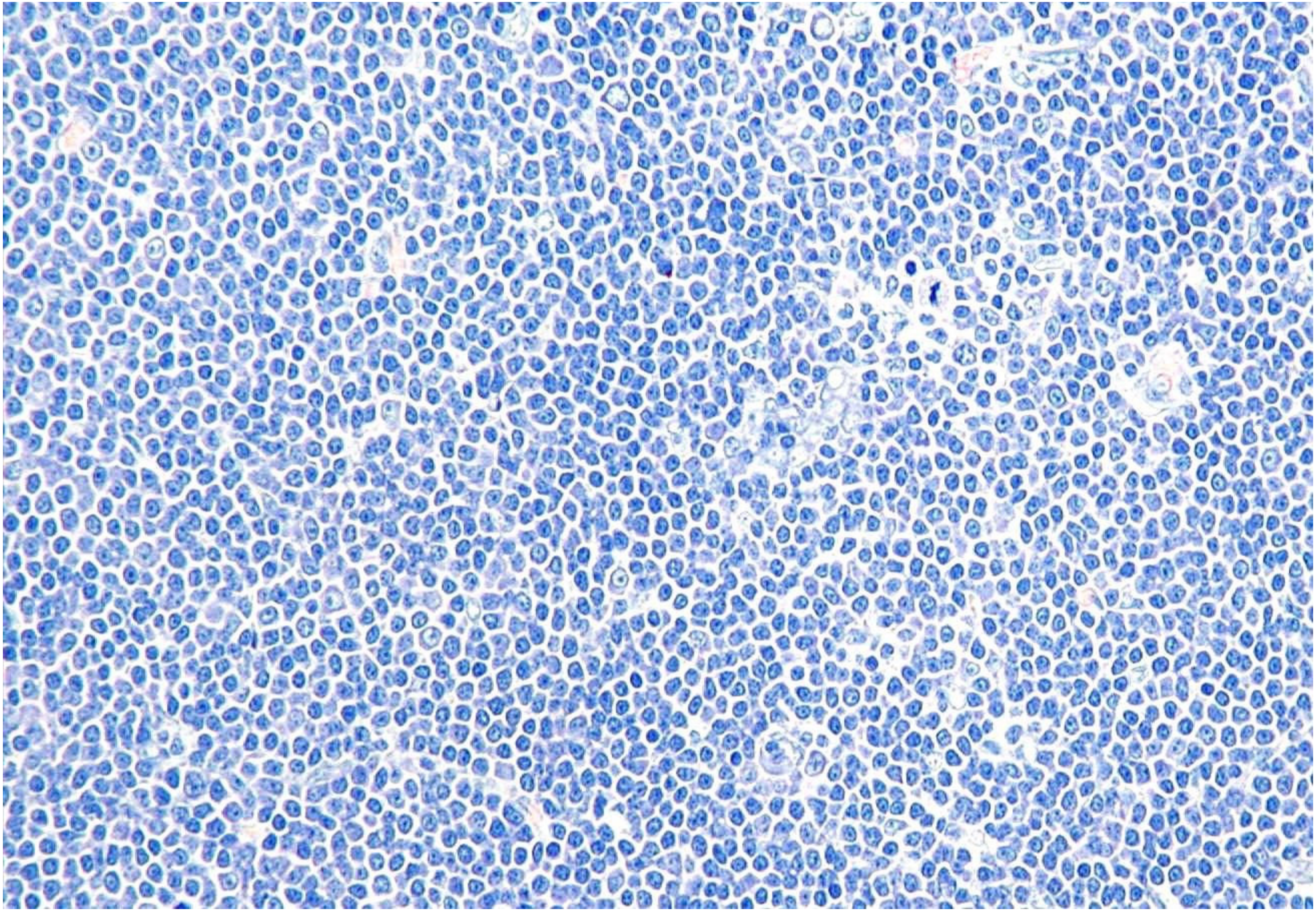
Three cellular components: small lymphocytes, prolymphocytes and para-immunoblasts

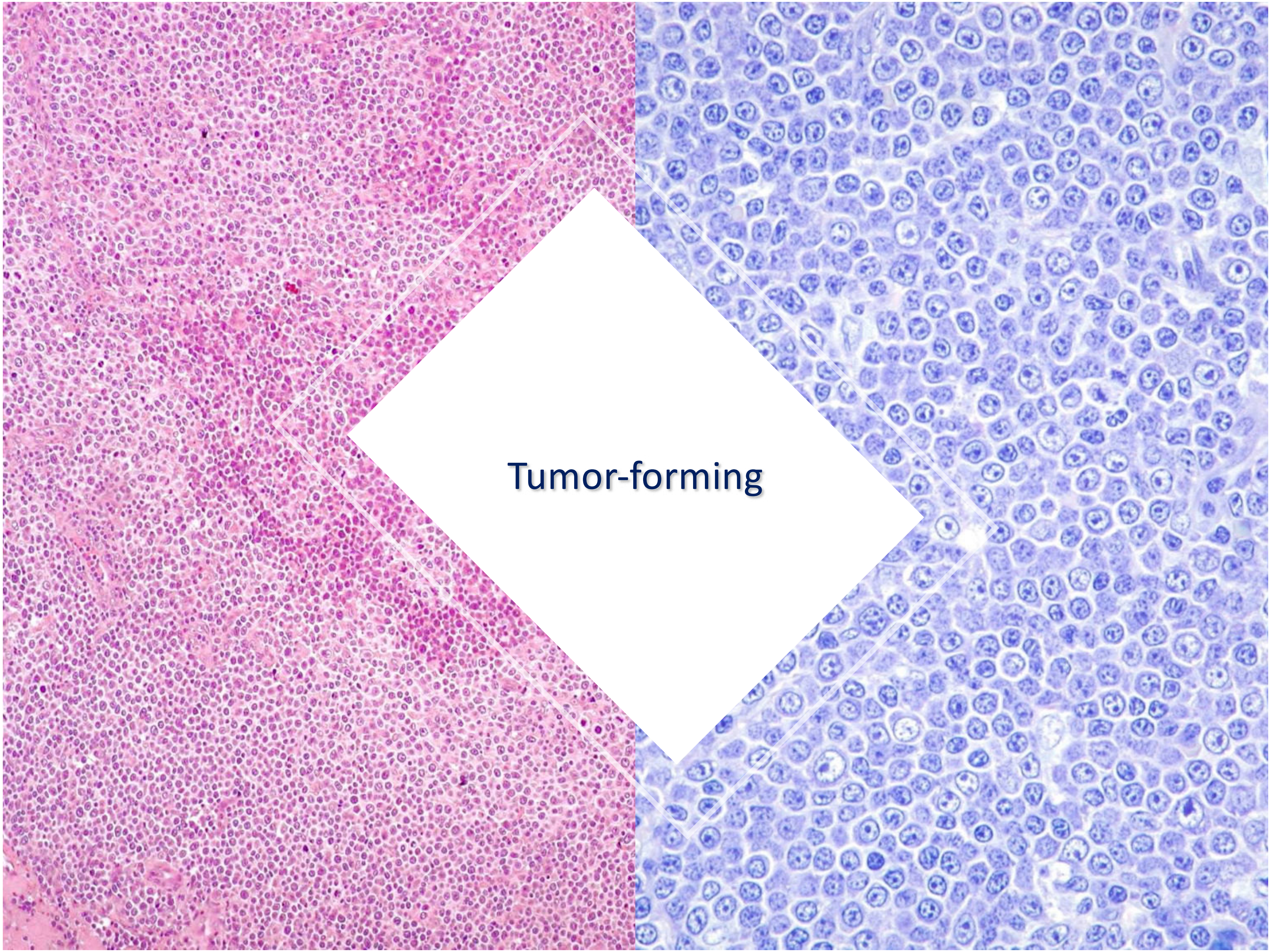
Pseudo-follicular pattern: 85% of cases (lymph node, bone-marrow, extranodal sites)

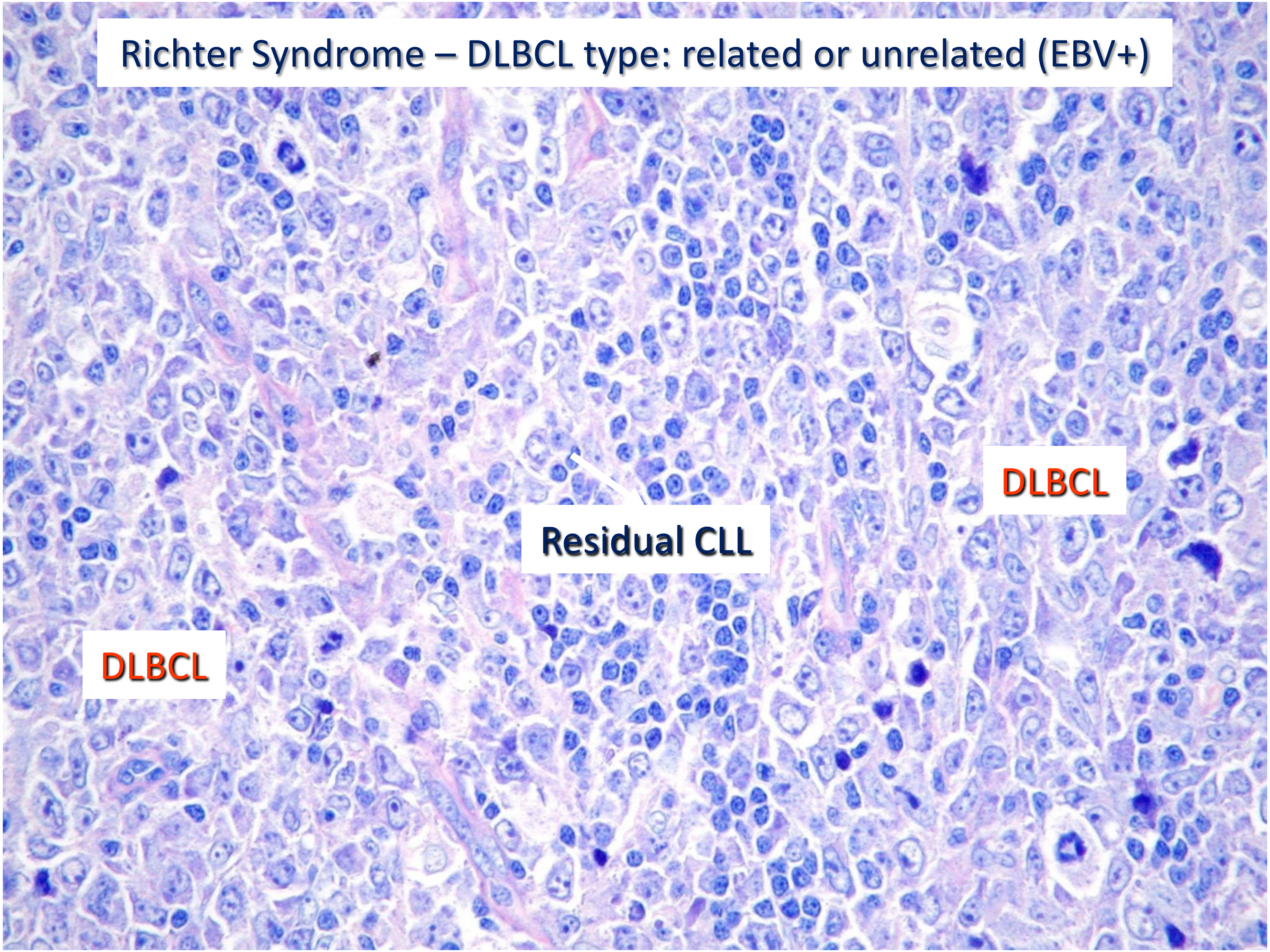




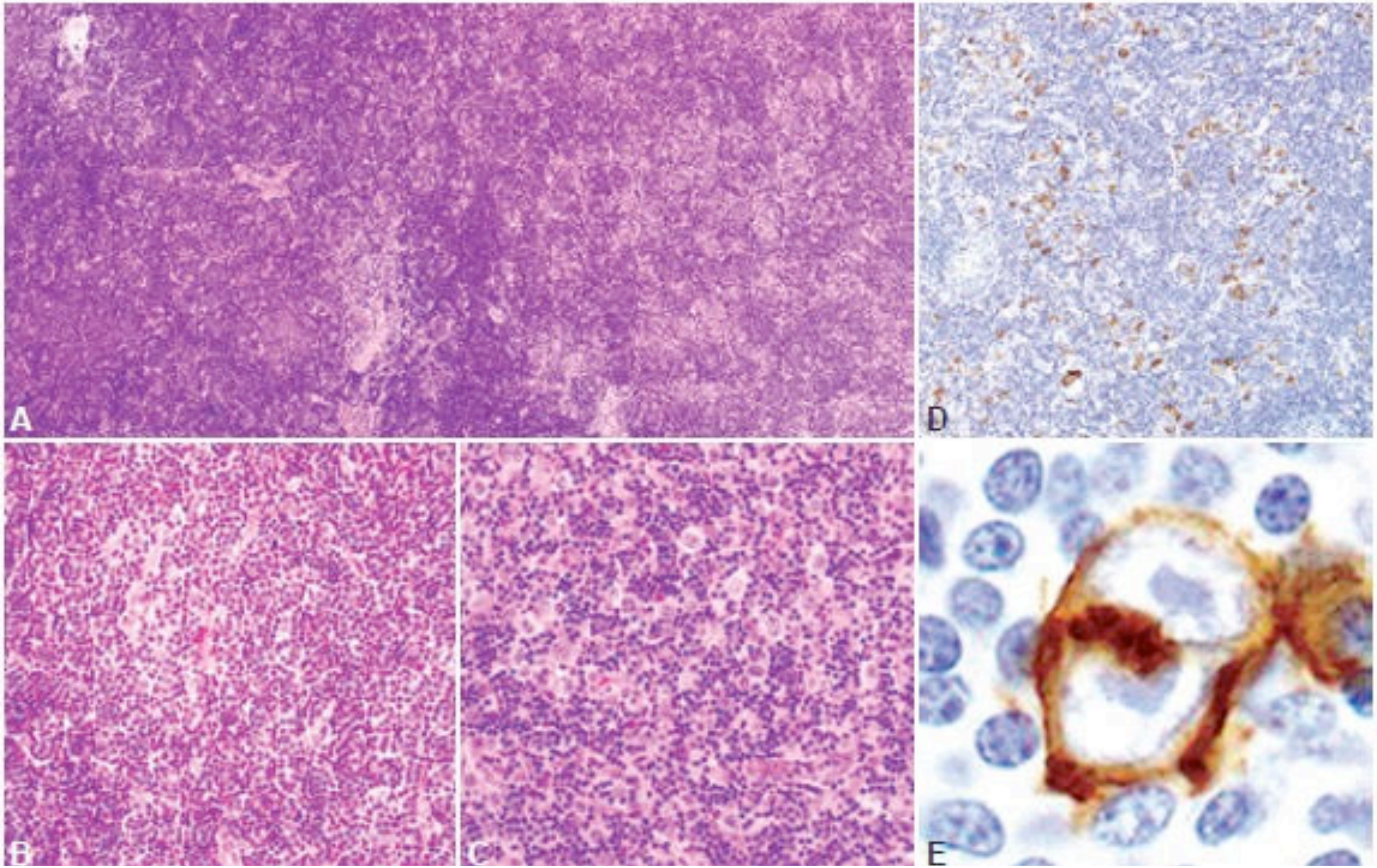
Diffuse growth pattern: 7% of cases; scanty prolymphocytes and paraimmunoblasts

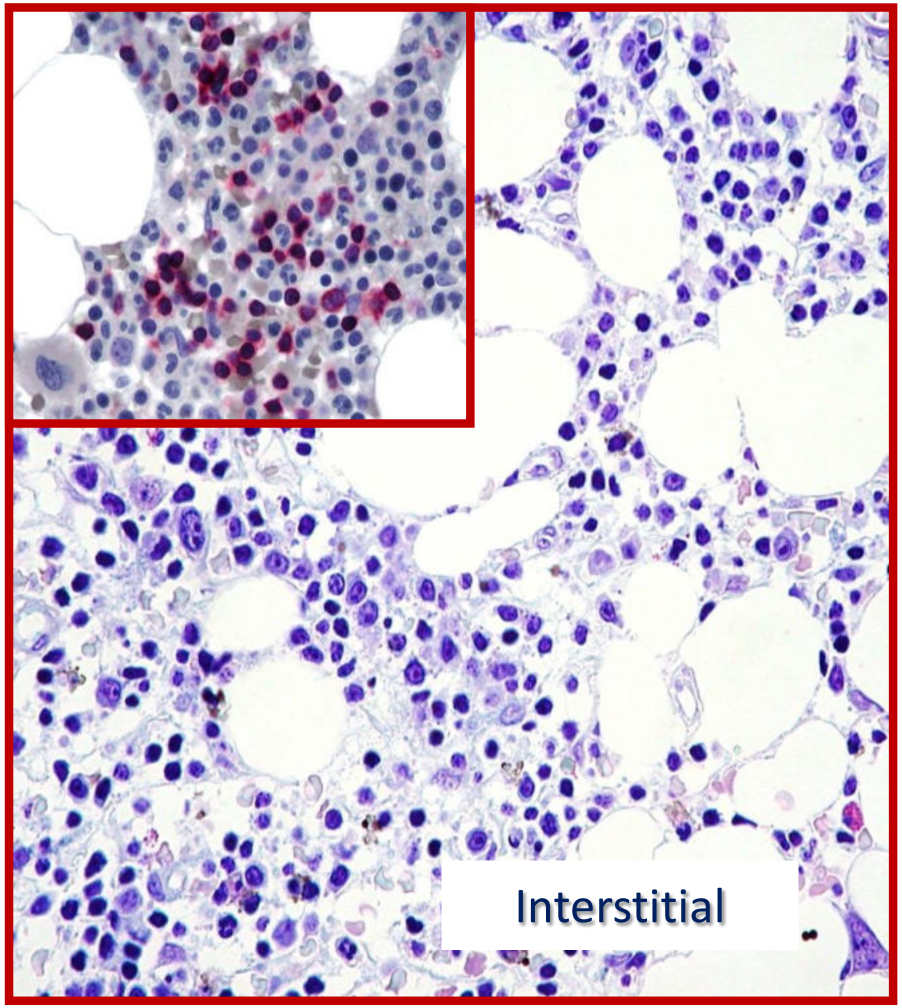


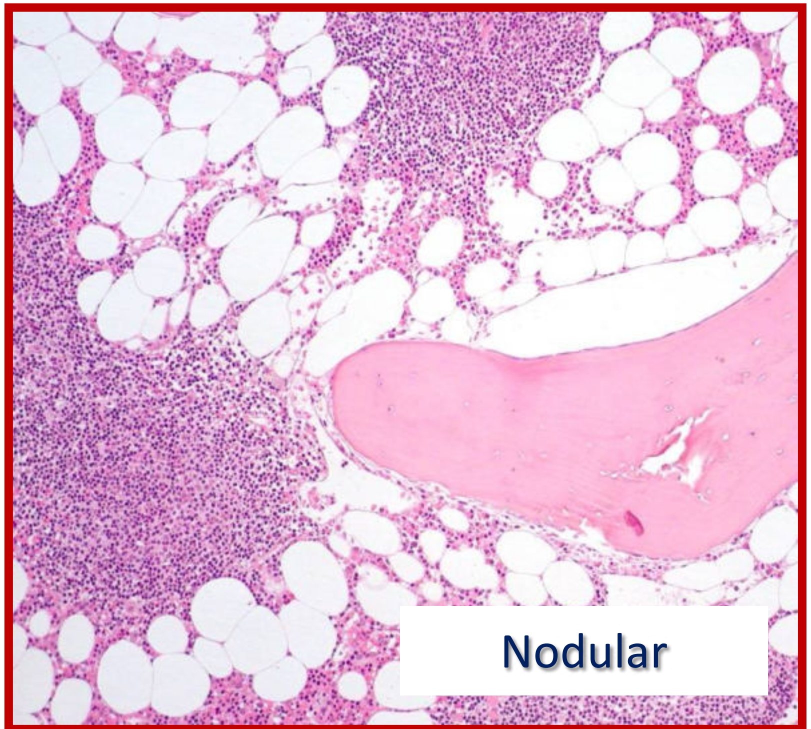

Tumor-forming

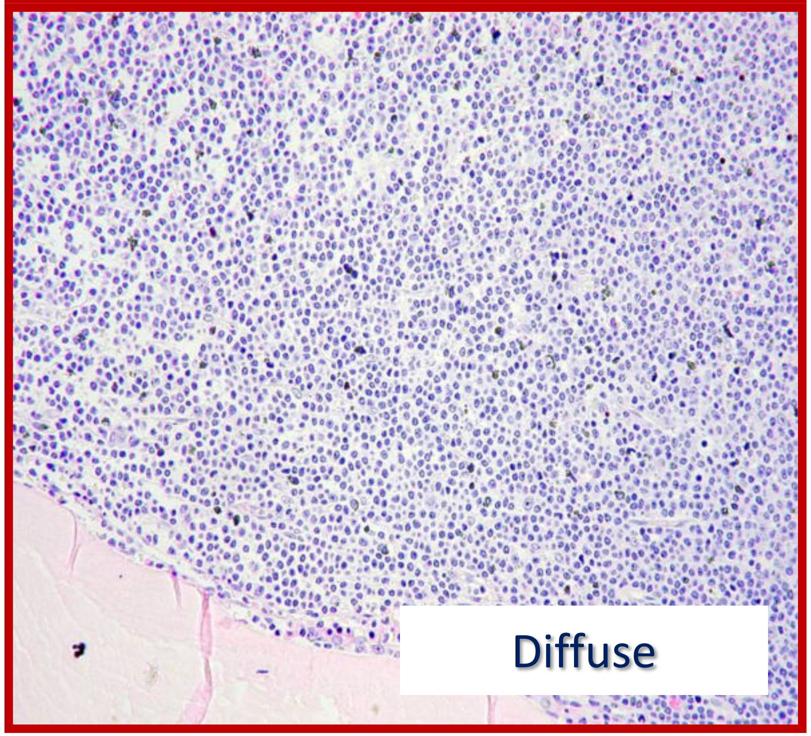

Richter Syndrome – DLBCL type: related or unrelated (EBV+)
DLBCL
Residual CLL
DLBCL

Richter Syndrome – Hodgkin type









Bone-marrow involvement

Pseudo-follicles (clear centres)
Useful for the diagnosis

Phenotype

CD20 + (weak but stronger in pseudo-follicles)

CD19, CD22, CD79a (homogeneously strong)

CD5 + (variable but stronger in pseudo-follicles)

CD23 + (variable but stronger in pseudo-follicles)

IgM/IgD+ (weak)

CD200 +

LEF1 +

ZAP70 (related to the IGVH mutational status: 85% concordance)

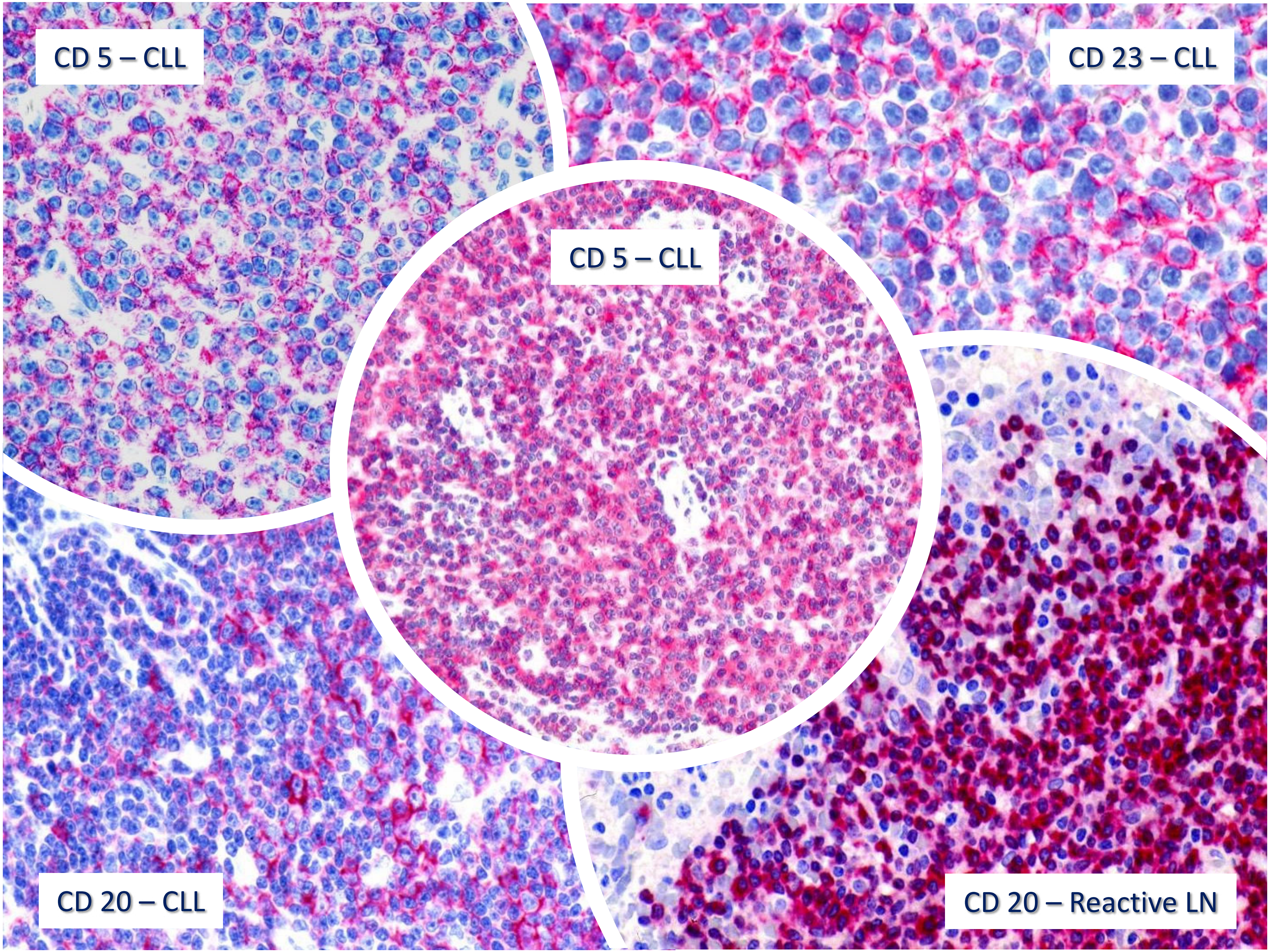
IRF4 (+ in pseudo-follicles)

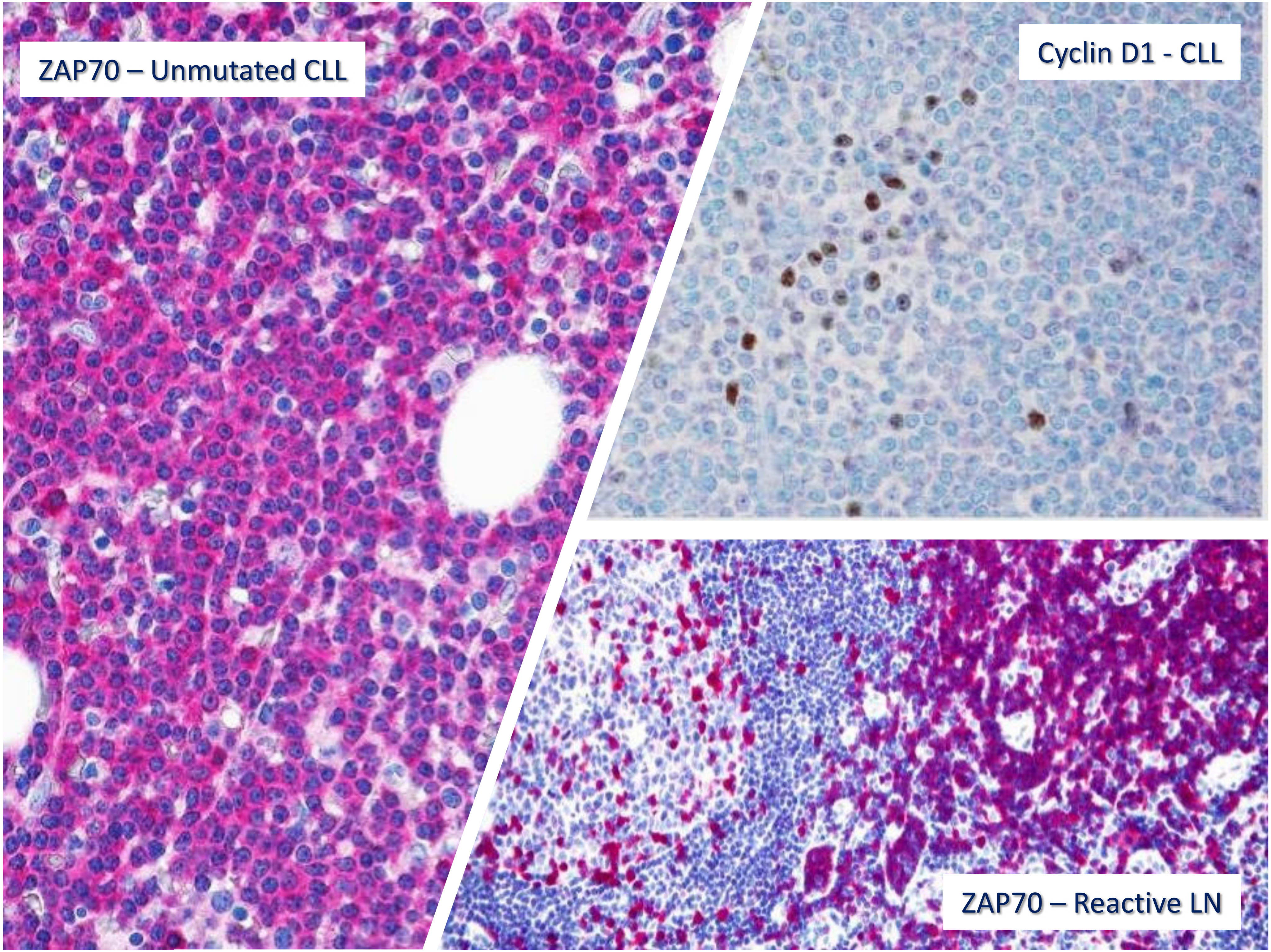
Cyclin D1 - (rare cases with weak, partial staining in the absence of t(11;14) and SOX11 positivity

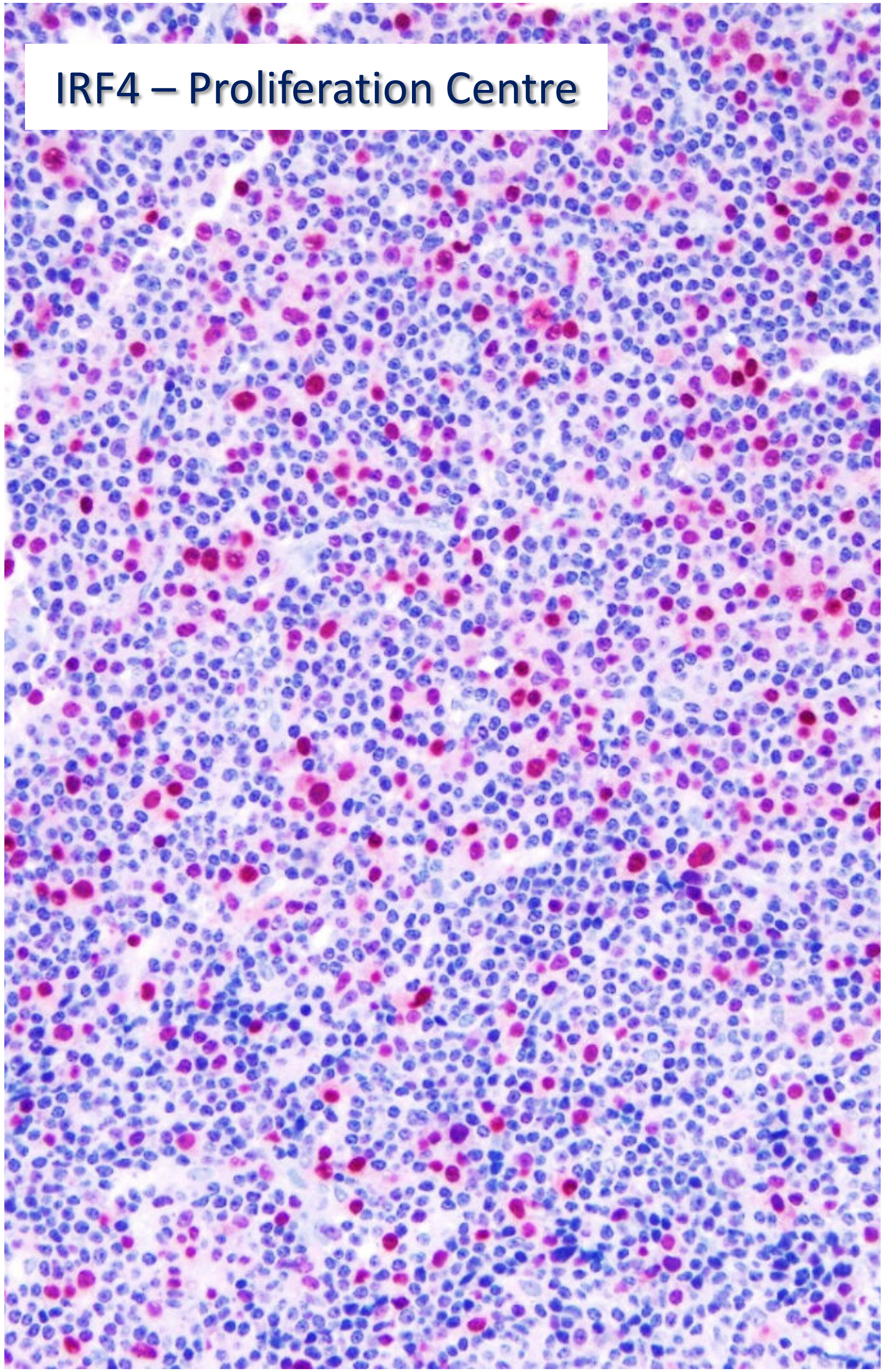
IRTA1, MNDA, T-bet -

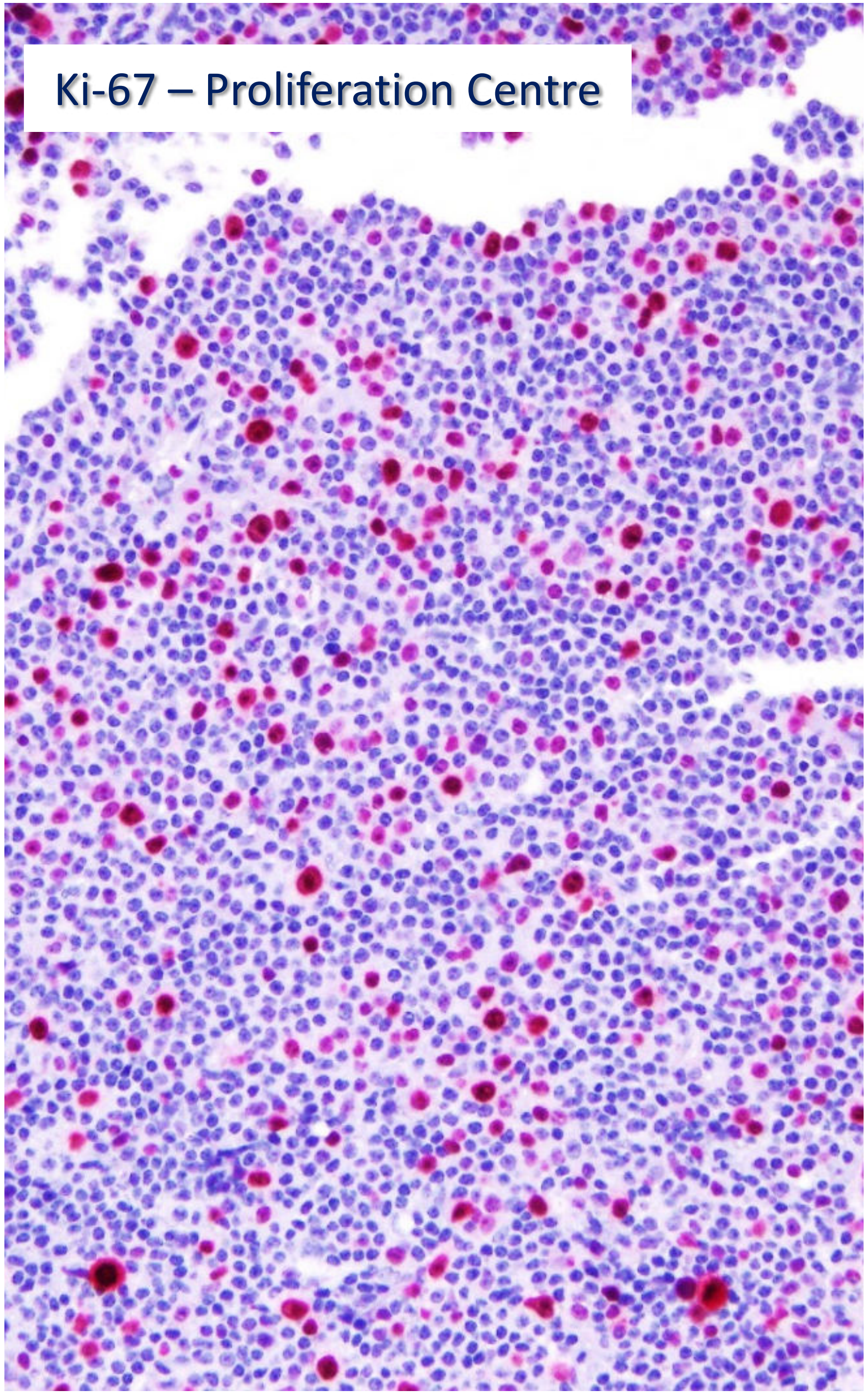
CD10, BCL6, LMO2 –

Ki-67 + (higher in pseudo-follicles)


CD 5 – CLL
CD 23 – CLL
CD 5 – CLL
CD 20 – CLL
CD 20 – Reactive LN

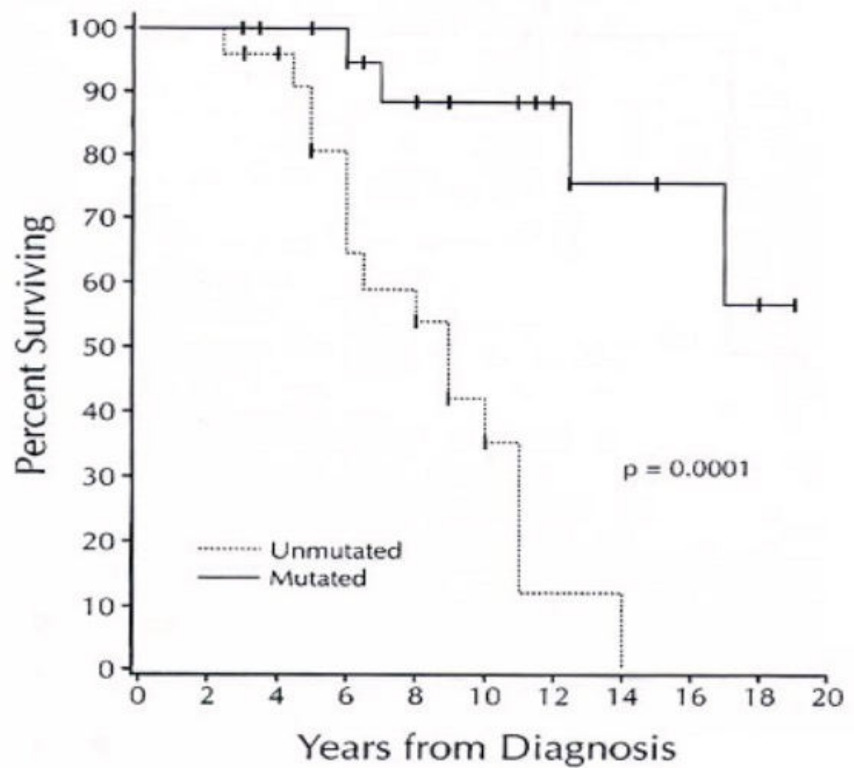

ZAP70 – Unmutated CLL
Cyclin D1 - CLL
ZAP70 – Reactive LN


IRF4 – Proliferation Centre

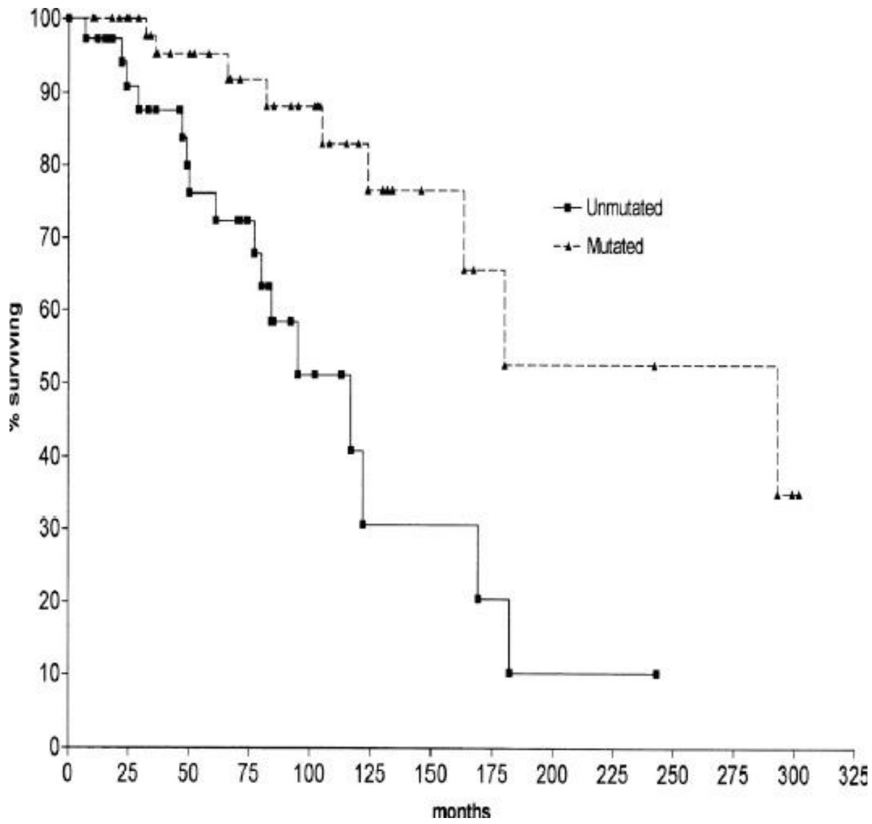

Ki-67 – Proliferation Centre

Molecular diagnostics

- BCR (IGHV) sequencing:
- Mutated (<98% identity with the germline configuration) (50 -70 %)
- Unmutated (>98% identity with the germline configuration) (30 -50%).
- Stereotyped subsets
- Cytogenetics/FISH
- Sequencing/NGS



Damle et al Blood 1999



Hamblin et al Blood 1999

KEY POINTS

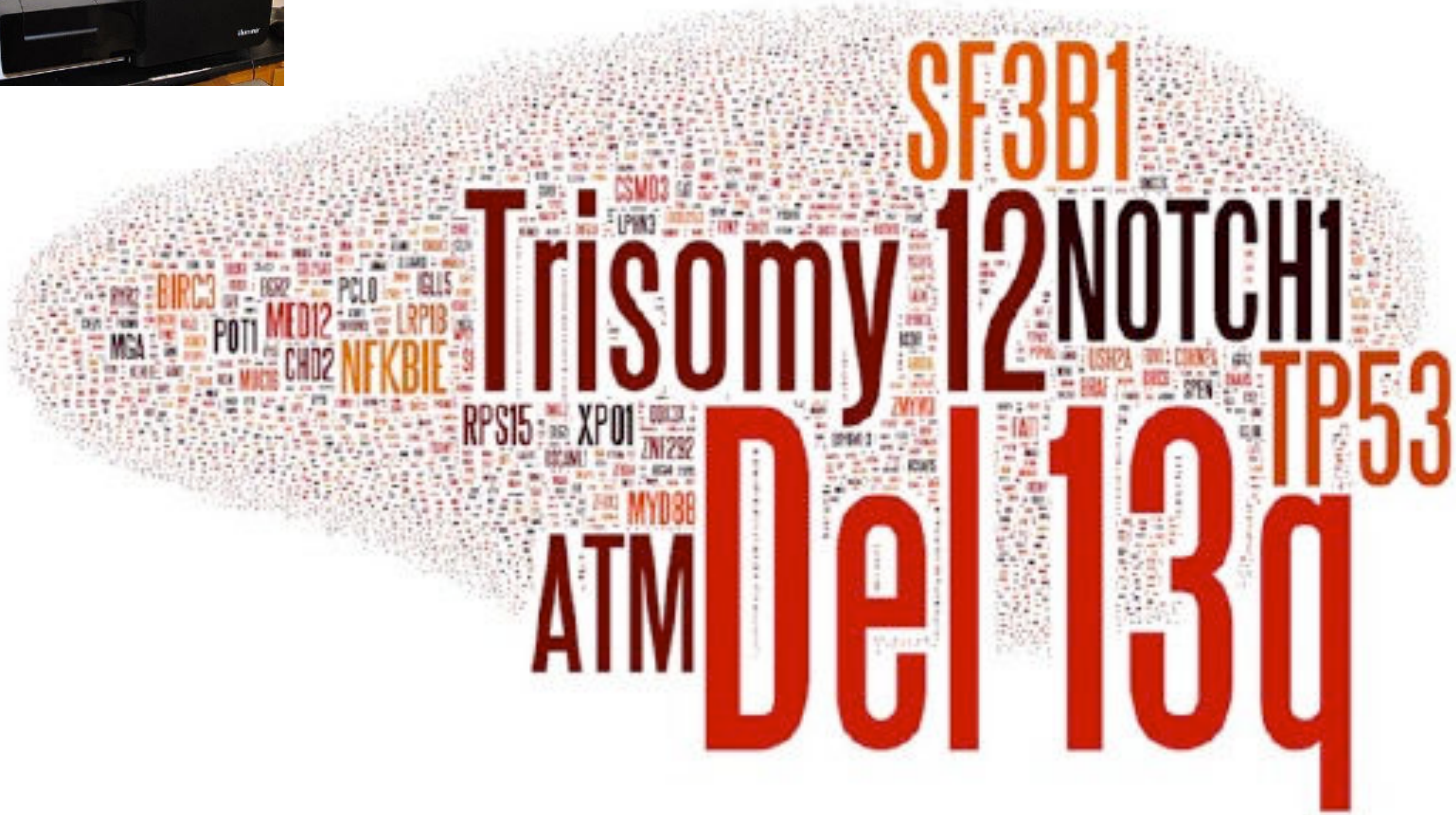
- In a series of 29 856 CLL patients, the incidence of BcR stereotypy peaked at 41%.
- Higher-order relations exist between stereotyped subsets, particularly for those from U-CLL, for which satellite subsets were identified.

Chronic lymphocytic leukemia (CLL) is characterized by the existence of subsets of patients with (quasi)identical, stereotyped B-cell receptor (BcR) immunoglobulins. Patients in certain major stereotyped subsets often display remarkably consistent clinicobiological profiles, suggesting that the study of BcR immunoglobulin stereotypy in CLL has important implications for understanding disease pathophysiology and refining clinical decision-making. Nevertheless, several issues remain open, especially pertaining to the actual frequency of BcR immunoglobulin stereotypy and major subsets, as well as the existence of higher-order connections between individual subsets. To address these issues, we investigated clonotypic IGHV-IGHD-IGHJ gene rearrangements in a series of 29 856 patients with CLL, by far the largest series worldwide. We report that the stereotyped fraction of CLL peaks at 41% of the entire cohort and that all 19 previously identified major subsets retained their relative size and ranking, while 10 new ones emerged; overall, major stereotyped subsets had a cumulative frequency of 13.5%. Higher-level relationships were evident between subsets, particularly for major stereotyped subsets with unmutated IGHV genes (U-CLL), for which close relations with other subsets, termed "satellites," were identified. Satellite subsets accounted for 3% of the entire cohort. These results confirm our previous notion that major subsets can be robustly identified and are consistent in relative size, hence representing distinct disease variants amenable to compartmentalized research with the potential of overcoming the pronounced heterogeneity of CLL. Furthermore, the existence of satellite subsets reveals a novel aspect of repertoire restriction with implications for refined molecular classification of CLL. **(*Blood.* 2021;137(10):1365-1376)**

Cytogentics/FISH

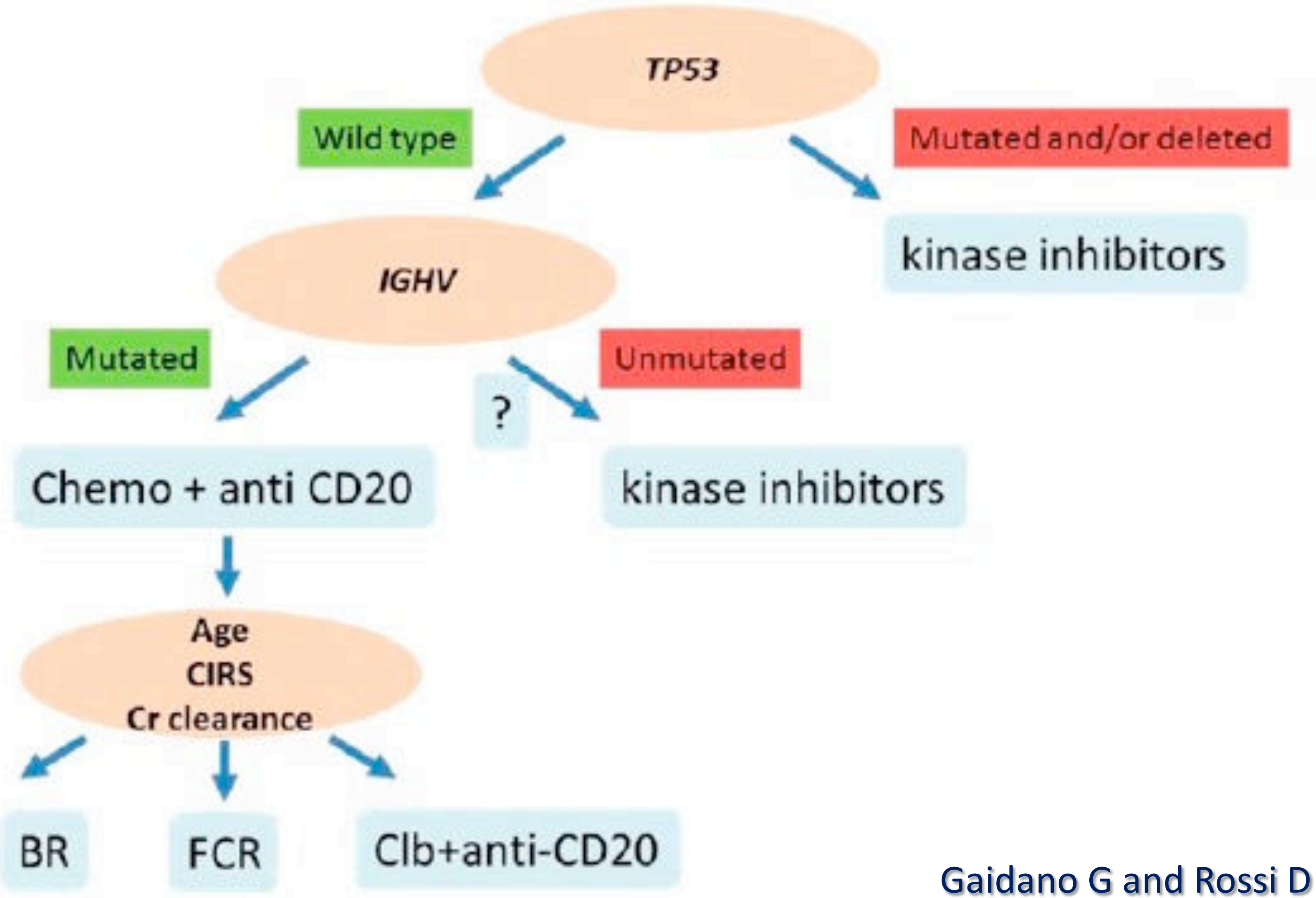
Aberration(s)	Frequency	
	Mutated IGHV n = 132 (44% of cases)	Unmutated IGHV n = 168 (56% of cases)
Clonal aberrations	80%	84%
13q deletion*	65%	48%
Isolated 13q deletion*	50%	26%
Trisomy 12	15%	19%
11q deletion*	4%	27%
17p deletion*	3%	10%
17p or 11q deletion*	7%	35%

*Significant difference between cases with and without IGHV mutation.



Gaidano G and Rossi D

Chronic lymphocytic leukemia/small lymphocytic lymphoma	IGHV mutation status[a] – IGHV sequencing		Prognostic and predictive. IGHV gene mutational status remains stable through the disease course and only needs to be performed once.	Determining BcR stereotypy and IGLV3-21[R110] mutation status for risk stratification; tracking of resistance mutations (*BTK*, *PLCG2* and *BCL2* – see supplemental table 3); WGS for mutations, CNAs, SVs and complex karyotype determination; MRD testing using HTS to guide therapy decisions.
	del(11q), +12, del(13q), del(17p)[a] - FISH		Prognostic and del(17p) is predictive. FISH testing should be performed prior to each new course of therapy.	
	TP53 mutations[a] - HTS		Prognostic and predictive. *TP53* sequencing should be performed prior to each new course of therapy unless already demonstrated.	
	Detection of complex karyotype (≥5 abnormalities) – cytogenetics[a] or SNP arrays		Prognostic	



Gaidano G and Rossi D

Lymphoplasmacytic lymphoma

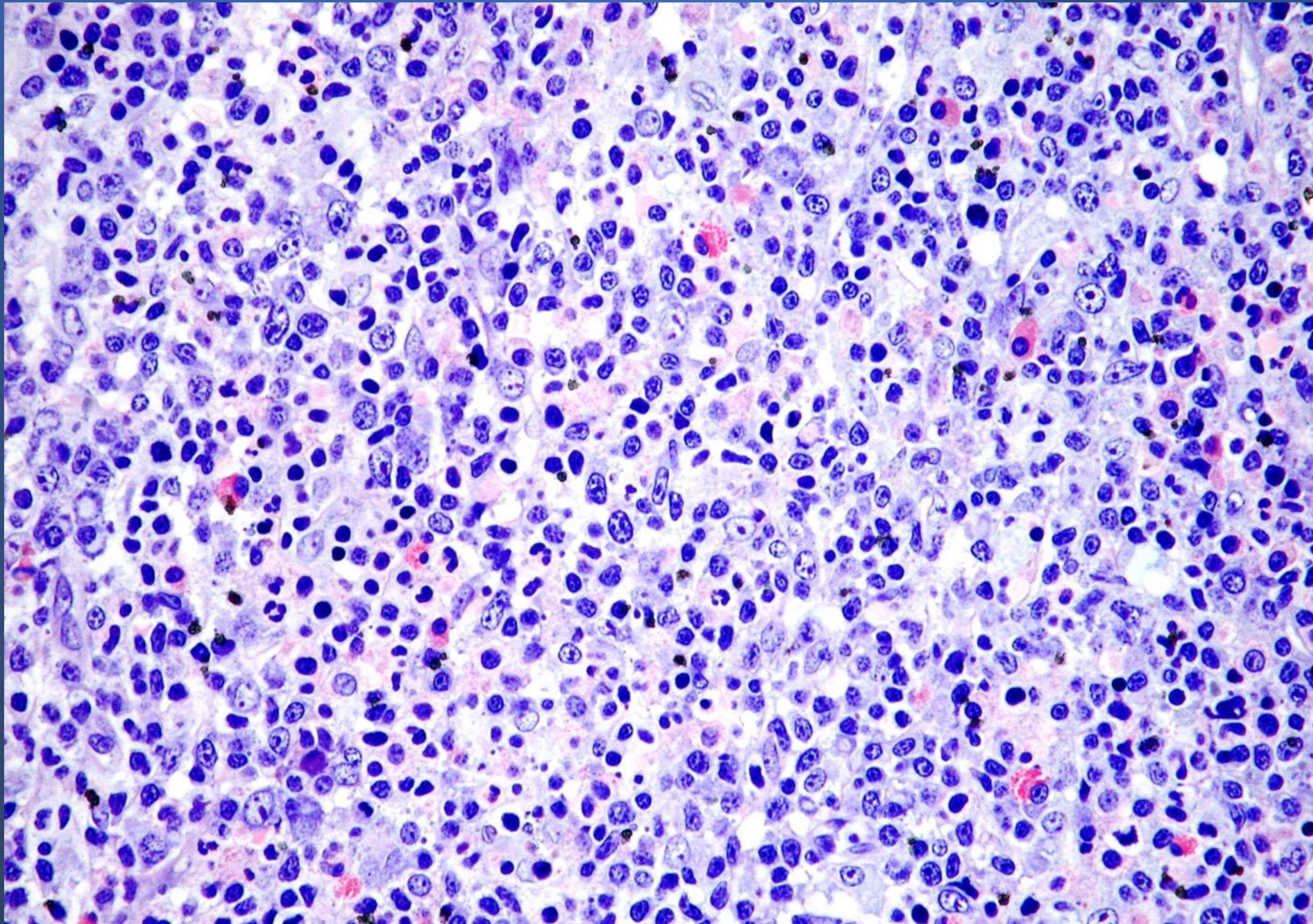
Small lymphocytes + plasmacytoid elements + plasma cells

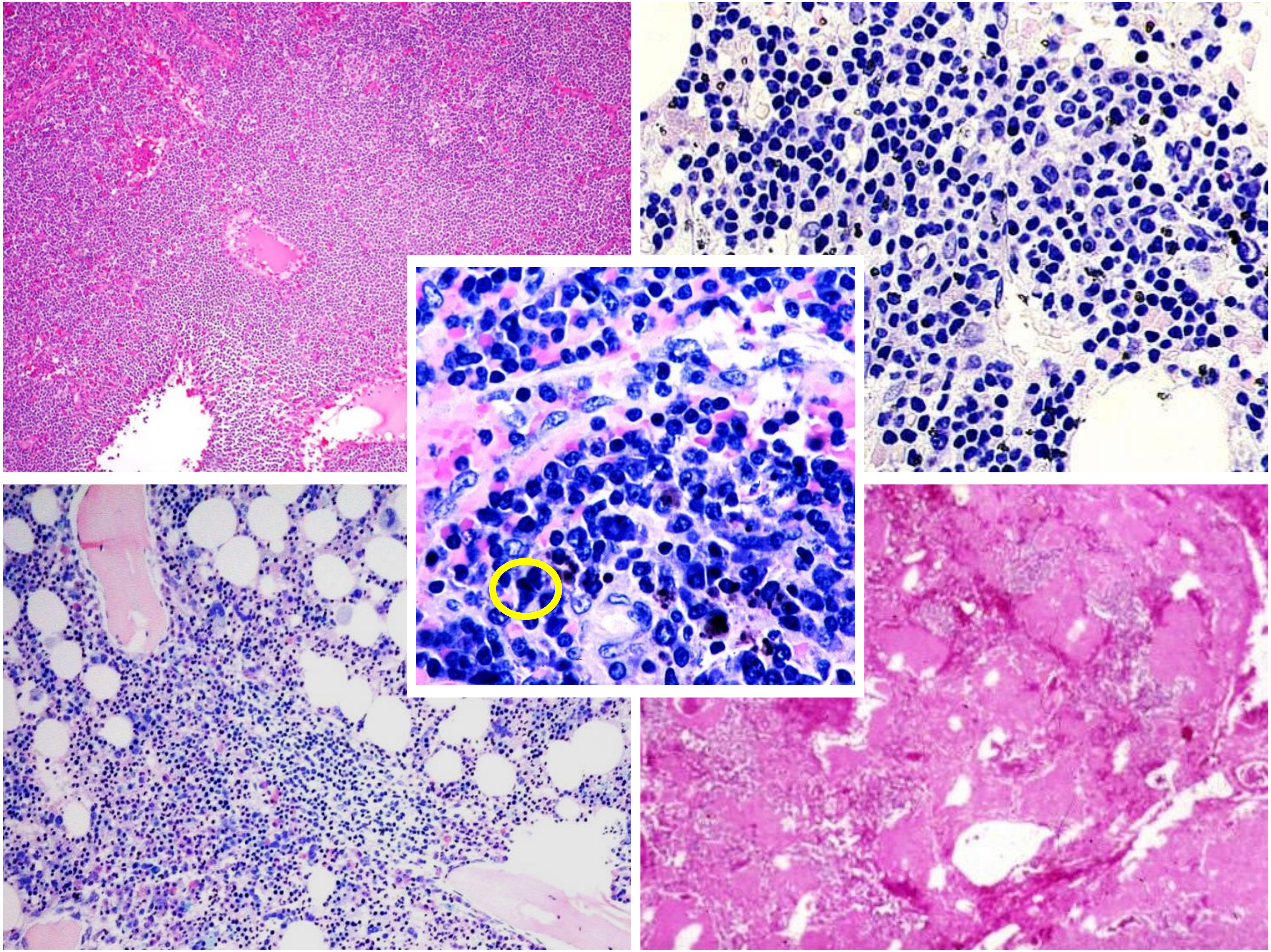
Exclusion diagnosis as other lymphomas can show plasmacellular differentiation

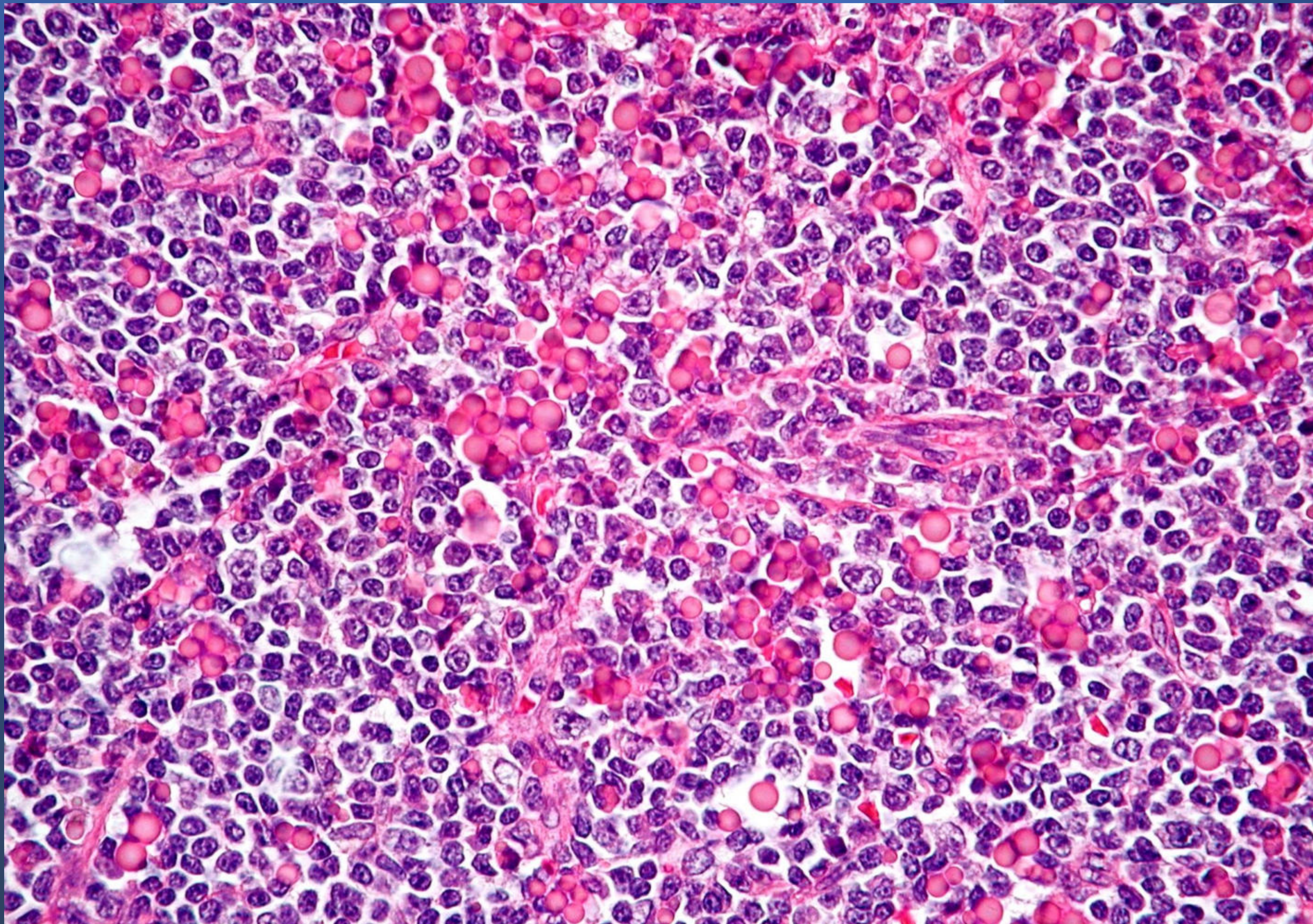
MYD88 L265P mutation characteristic but not exclusive

IgM paraprotein not necessarily required

WM found in a substantial subset, but not synonymous of LPL







Phenotype

CD19, CD20, CD22, CD79a, CD79b +

CD5 -

CD23 -/+

IgM+ (CYTOPLASMIC!)

IgD-

CD38+

IRF4 +/-

CD45 +/-

CD138 -

CD200 -

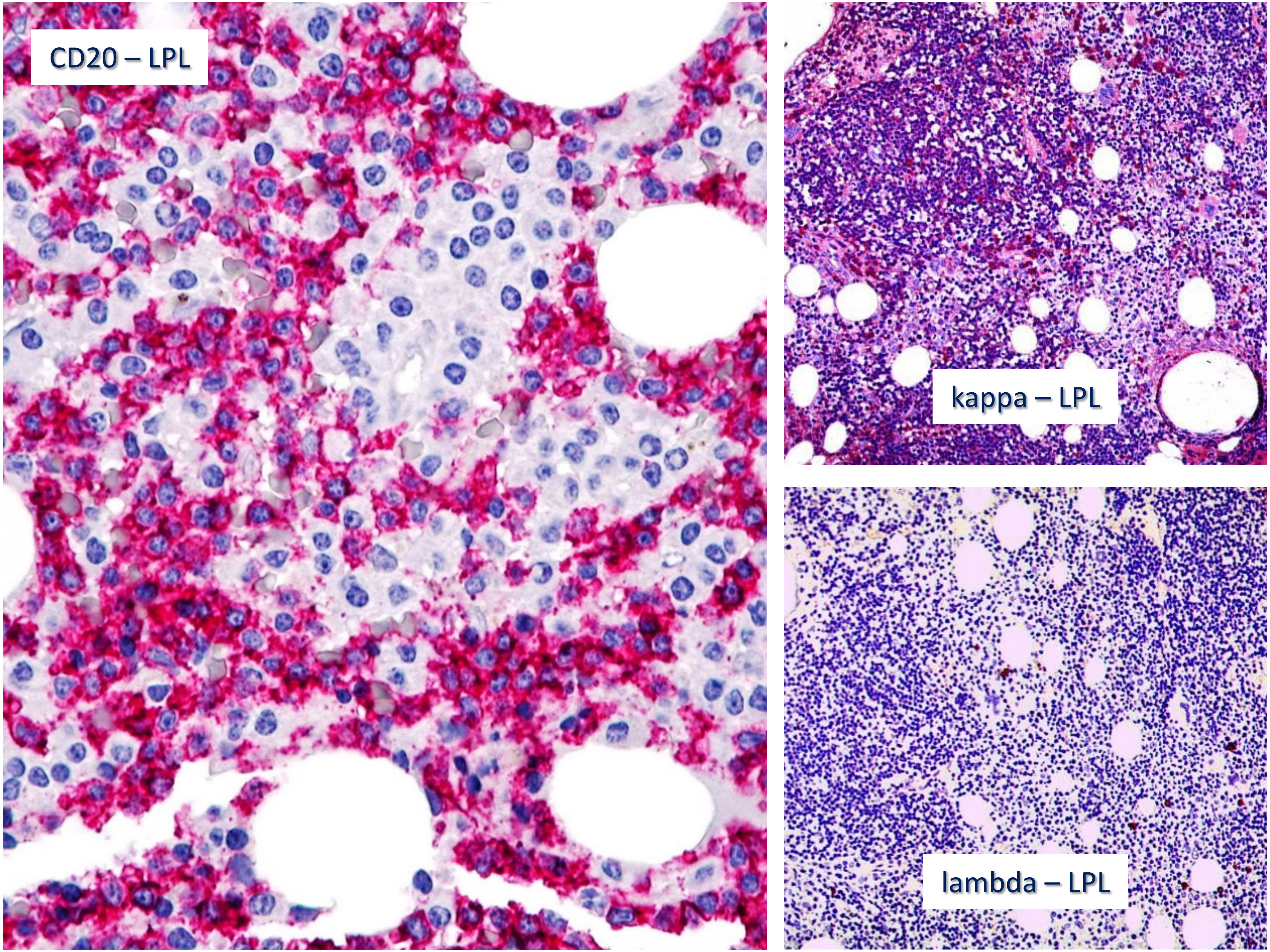
LEF1 -

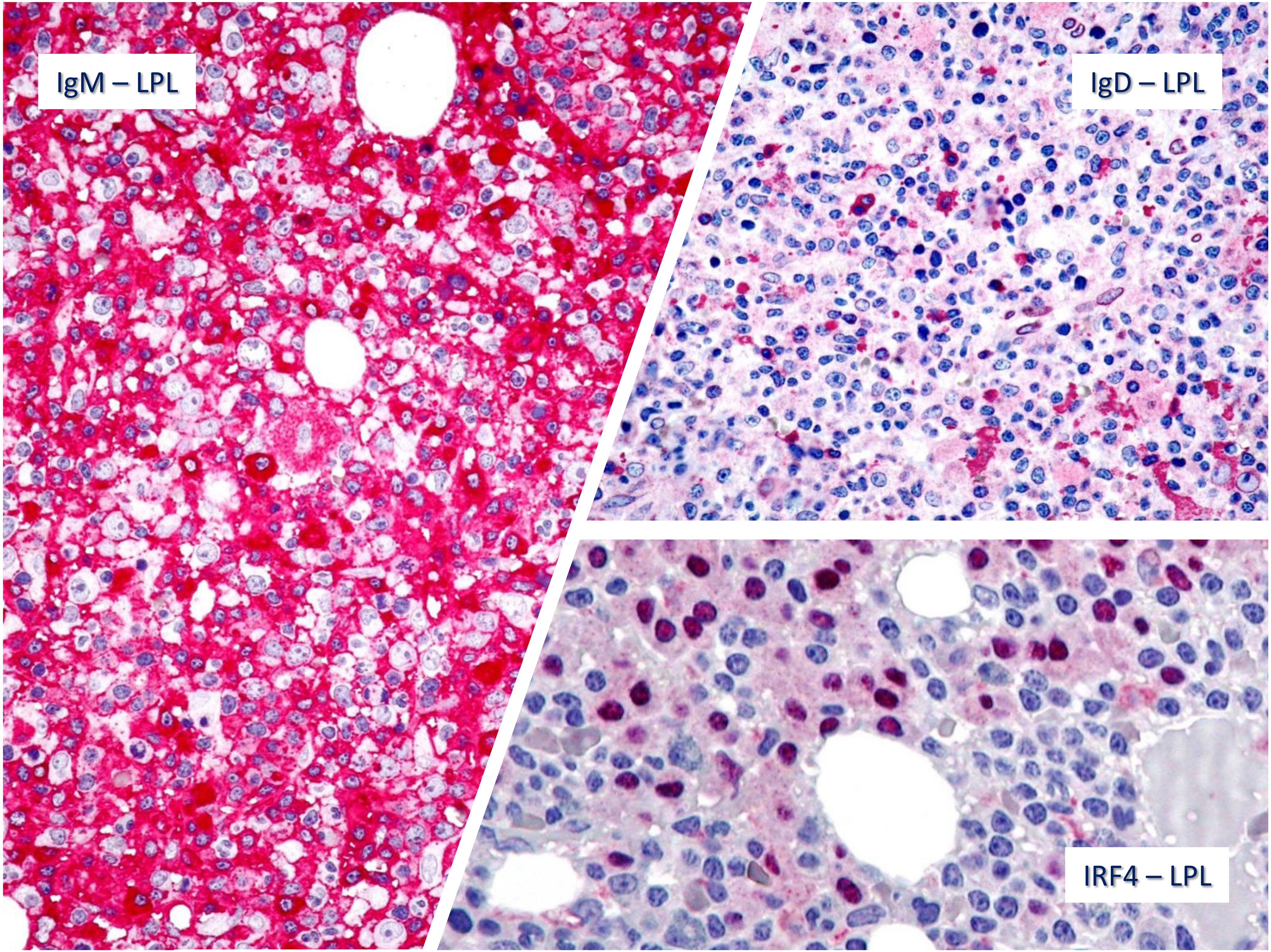
Cyclin D1 -

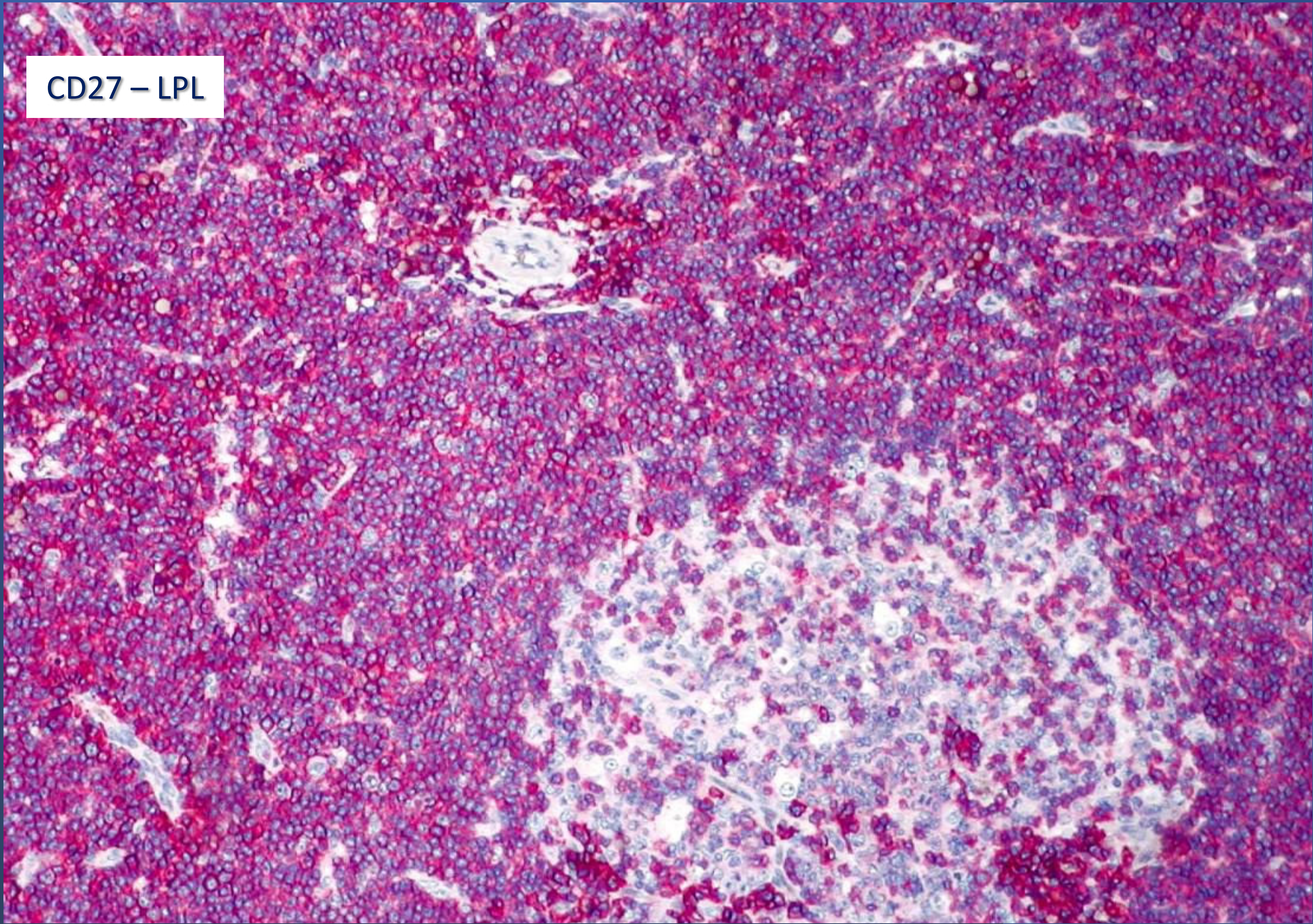
IRTA1, MNDA, T-bet -

CD10, BCL6, LMO2 –

Ki-67: low


CD20 – LPL
kappa – LPL
lambda – LPL


IgM – LPL
IgD – LPL
IRF4 – LPL


CD27 – LPL

haematologica
Journal of The Ferrata Storti Foundation

Inflammation in Waldenström macroglobulinemia is associated with 6q deletion and need for treatment initiation

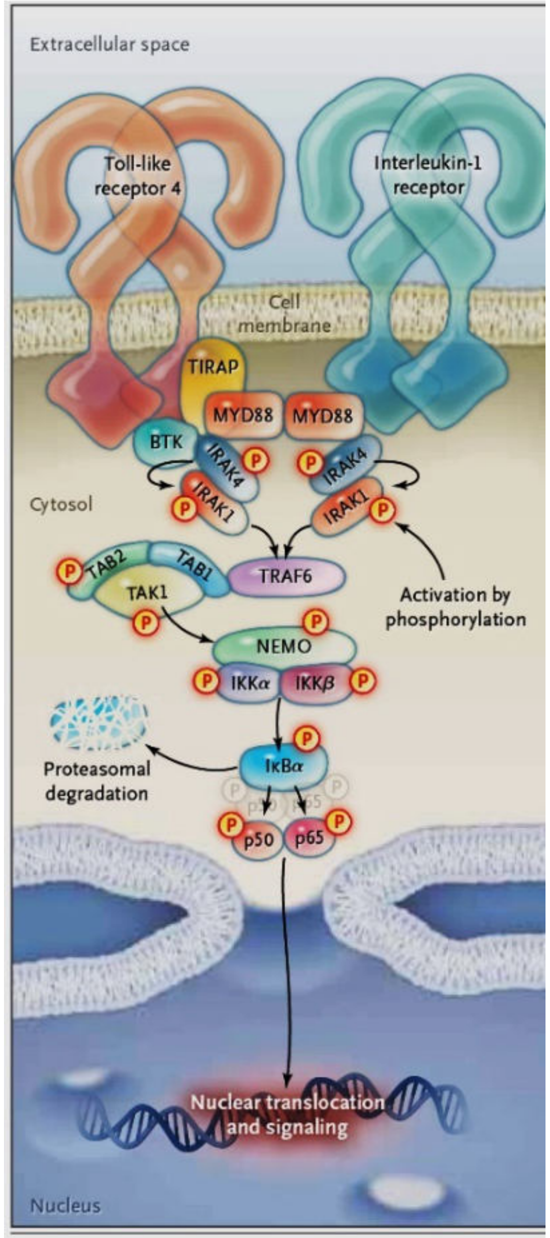
by Nathalie Forgeard, Marine Baron, Jonathan Caron, Clémentine Boccon-Gibod, Daphné Krzisch, Nayara Guedes, Véronique Morel, Nathalie Jacque, Maya Ouzegdouh, Sylvain Choquet, Clotilde Bravetti, Florence Nguyen-Khac, Elise Chapiro, Véronique Leblond, and Damien Roos-Weil

The NEW ENGLAND JOURNAL *of* MEDICINE

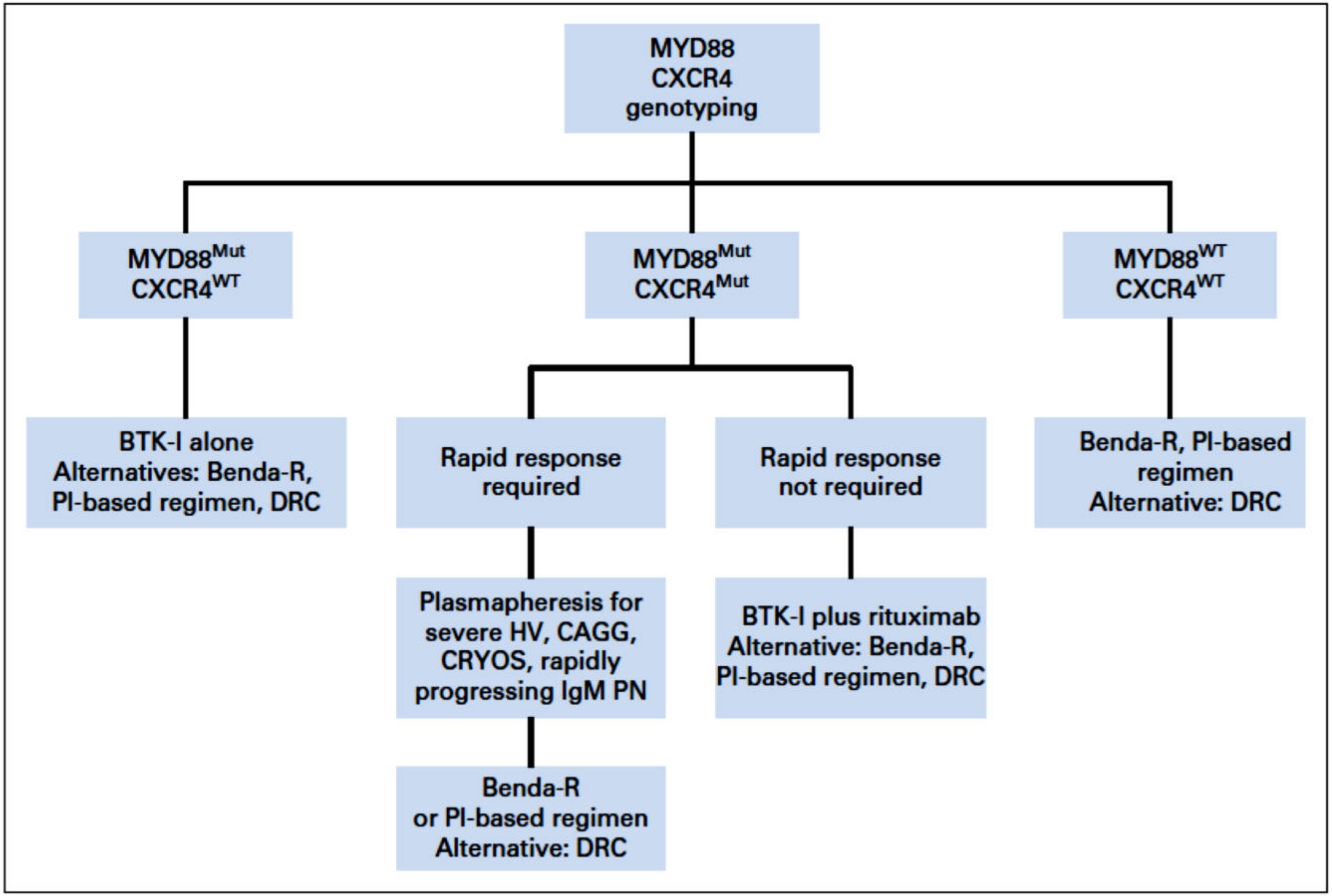
ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.



Lymphoplasmacytic lymphoma	*MYD88* L265 mutation –AS-PCR testing on bone marrow[a] (or other highly sensitive HTS-based method – consider AS-PCR as a reflex test if negative)	Diagnostic. Aids in the differential with small B-cell lymphomas - see scenario 2A in Table 3		HTS methods for sensitive mutation detection
	CXCR4 mutations[b] – highly sensitive HTS-based method		Predictive of primary resistance to ibrutinib therapy.[160]	

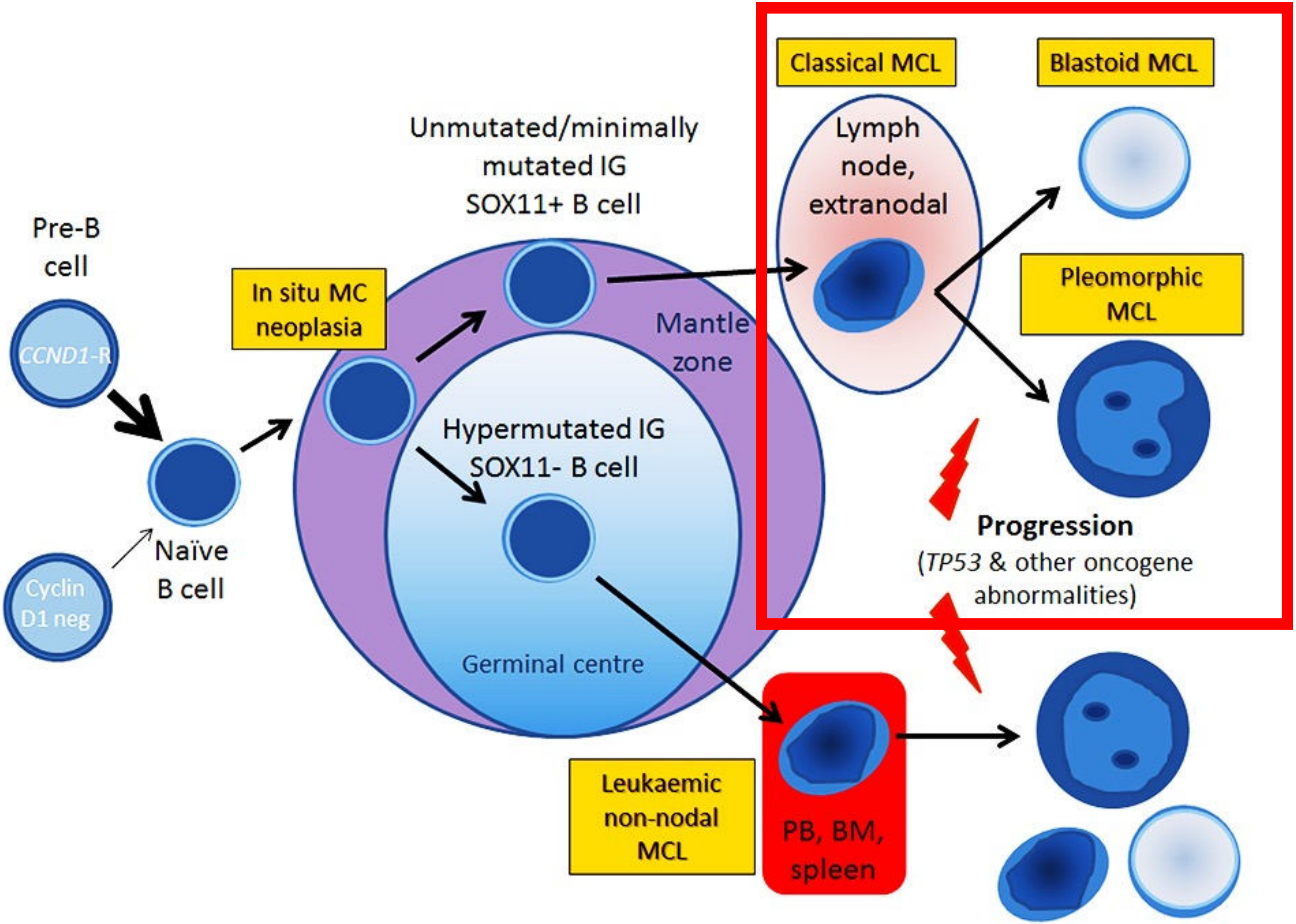


Treon et al. JCO, 2020

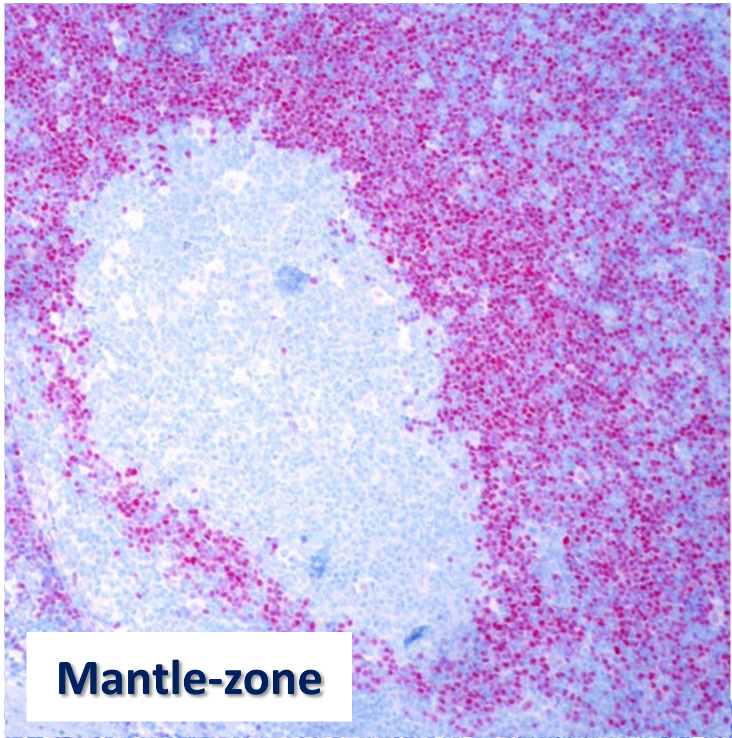
Mantle cell lymphoma

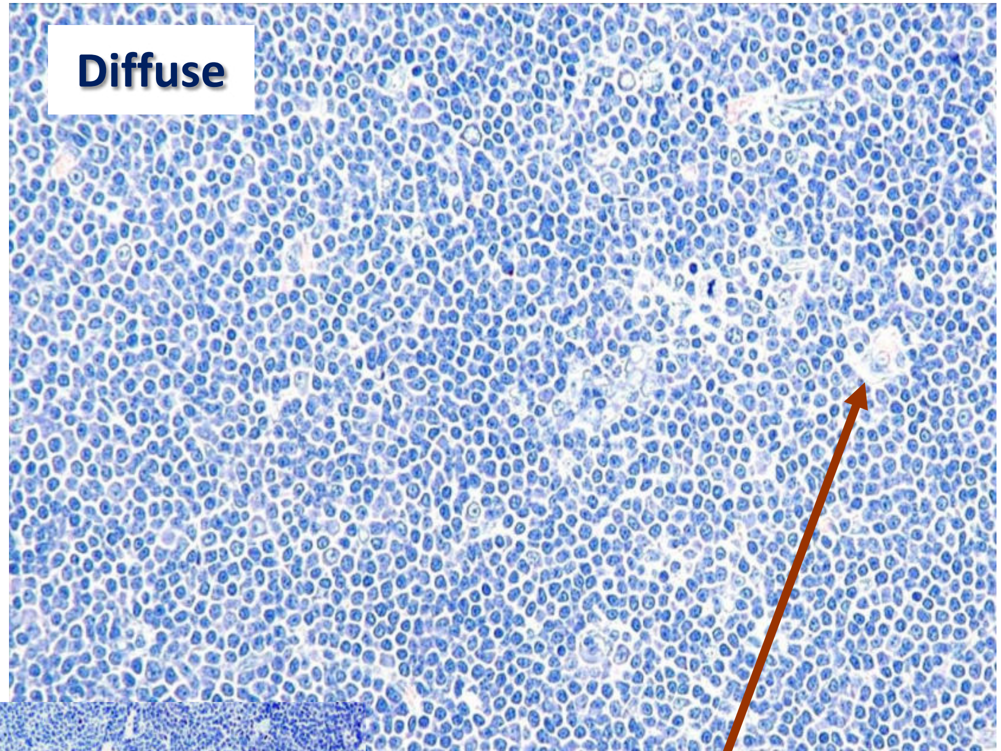
Definition

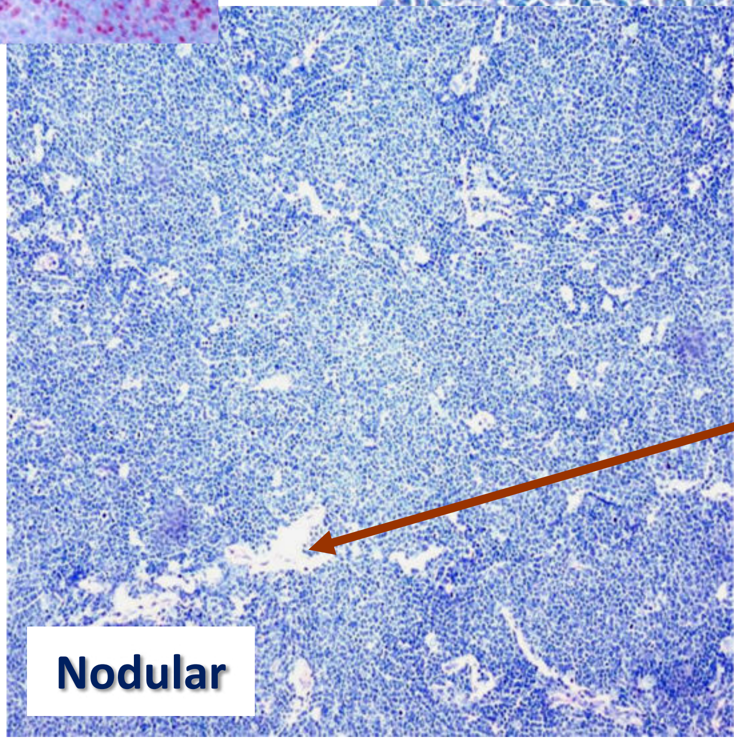
Mantle cell lymphoma is a mature B-cell neoplasm usually composed of monomorphic small to medium-sized lymphoid cells with irregular nuclear contours; in > 95% of cases, there is a *CCND1* translocation {245,543,2219,2269,3849, 4018}. Neoplastic transformed cells (centroblasts), paraimmunoblasts, and proliferation centres are absent. Mantle cell lymphoma has traditionally been considered a very aggressive and incurable lymphoma, but more indolent variants, including leukaemic non-nodal mantle cell lymphoma and in situ mantle cell neoplasia, are now also well recognized.


Classical MCL
Blastoid MCL
Unmutated/minimally mutated IG SOX11+ B cell
Lymph node, extranodal
Pre-B cell
CCND1-R
In situ MC neoplasia
Mantle zone
Pleomorphic MCL
Hypermutated IG SOX11- B cell
Naïve B cell
Cyclin D1 neg
Progression
(TP53 & other oncogene abnormalities)
Germinal centre
Leukaemic non-nodal MCL
PB, BM, spleen

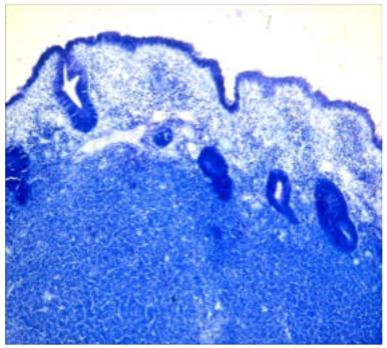
MCL Growth Patterns

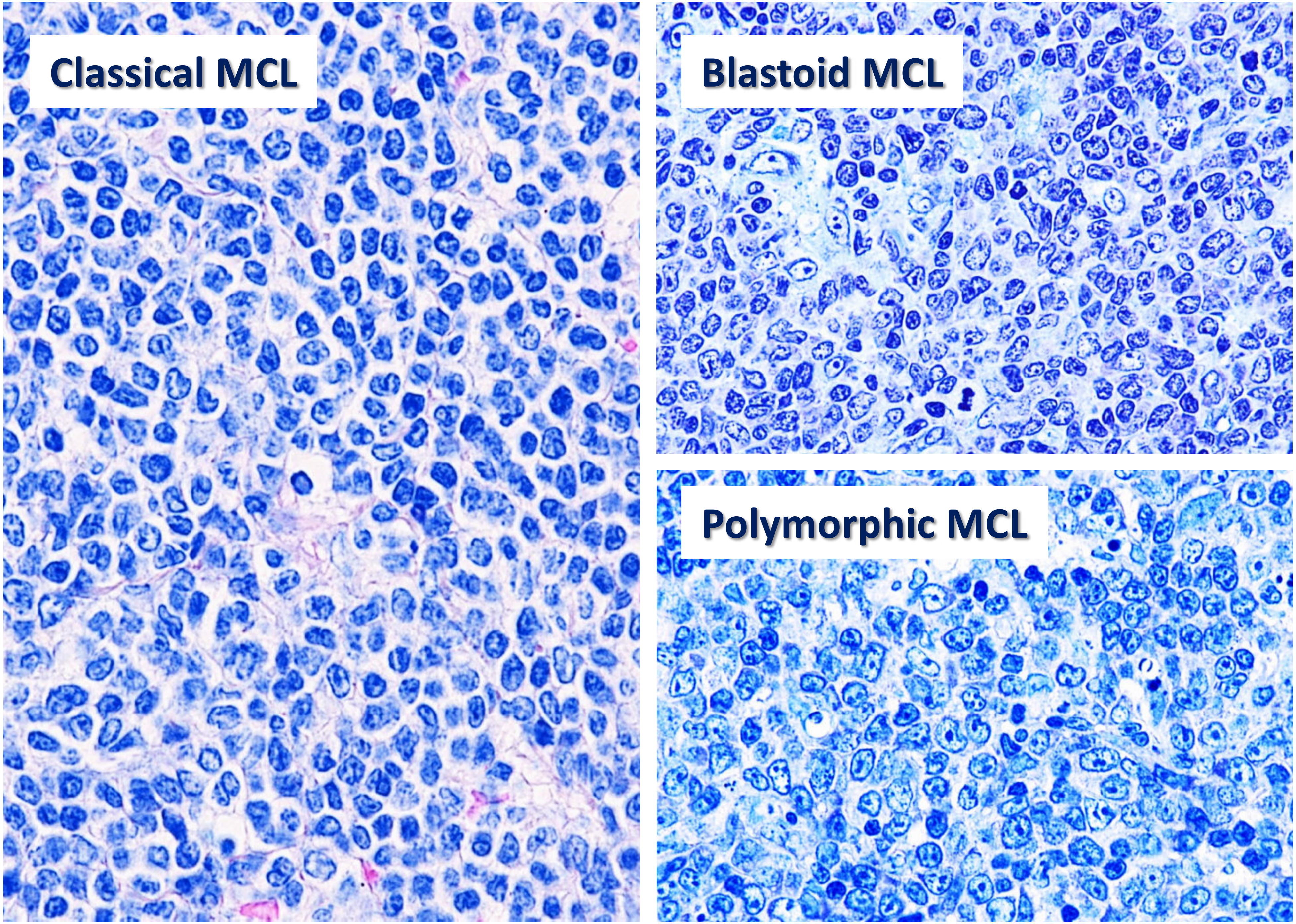






Epithelioid histiocytes




Classical MCL
Blastoid MCL
Polymorphic MCL

Phenotype

CD19, CD20, CD22, CD79a, CD79b +

CD5+

IgM+

IgD+

Cyclin D1+ (>95%)

SOX11+ (- in leukemic non nodal)

BCL2+

CD23 -

IRF4 -

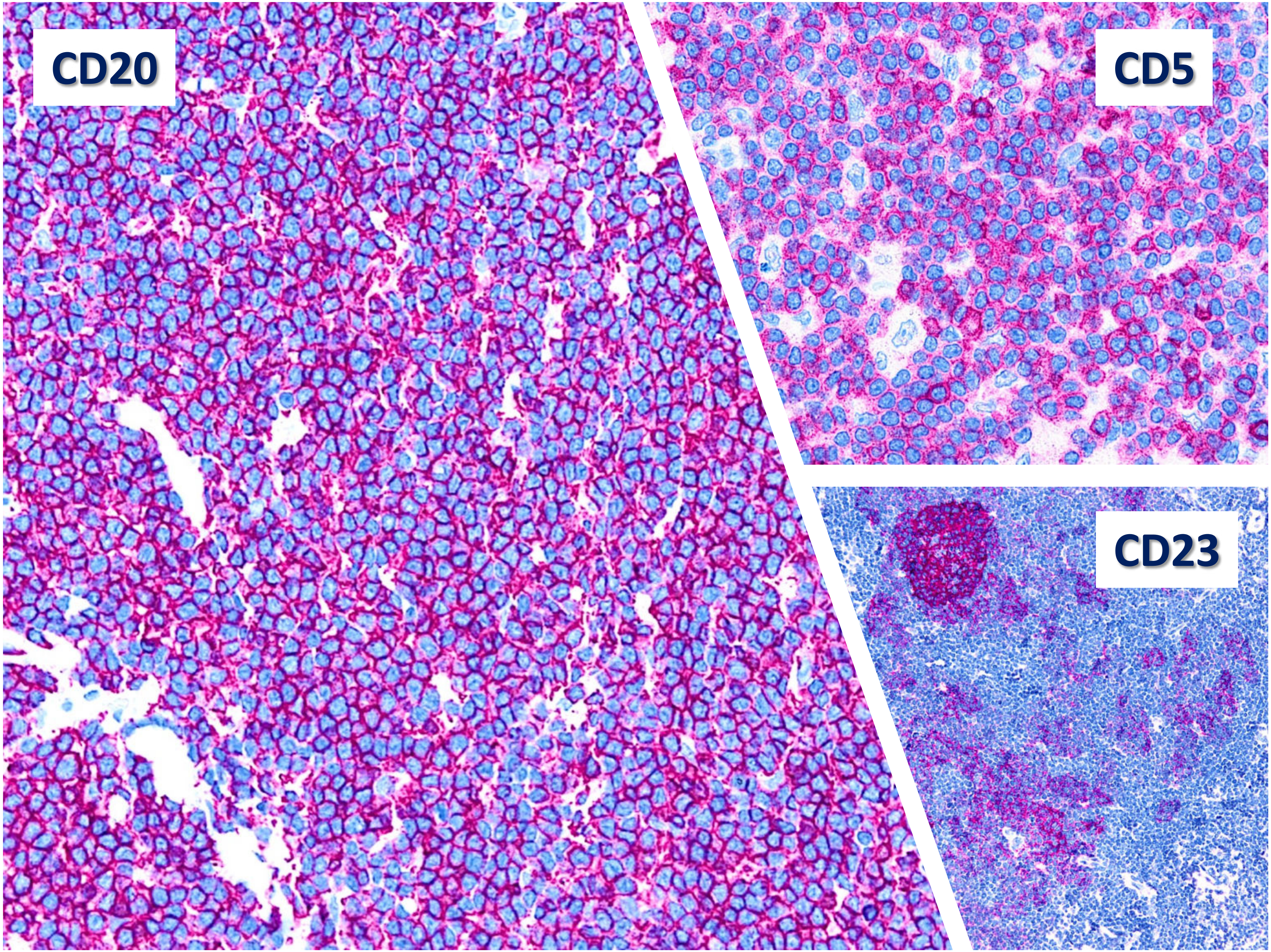
CD200 – (at times + in leukemic non nodal)

LEF1 – (at times + in blastoid/pleomorphic)

IRTA1, MNDA, T-bet -

CD10, BCL6, LMO2 –

Ki-67: variable


CD20
CD5
CD23

LYMPHOMA

Insights into the mechanisms underlying aberrant *SOX11* oncogene expression in mantle cell lymphoma

Roser Vilarrasa-Blasi [1,2✉], Núria Verdaguer-Dot[1], Laura Belver[3,4], Paula Soler-Vila[5], Renée Beekman[1], Vicente Chapaprieta [1], Marta Kulis[1], Ana C. Queirós[1], Maribel Parra [4], María José Calasanz [6,7], Xabier Agirre [6,7], Felipe Prosper [6,7,8], Sílvia Beà[1,2,7], Dolors Colomer [1,2,7], Marc A. Marti-Renom[5,9], Adolfo Ferrando [3], Elías Campo [1,2,7] and José Ignacio Martin-Subero [1,2,7,9✉]

Leukemia (2022) 36:583–587; https://doi.org/10.1038/s41375-021-01389-w

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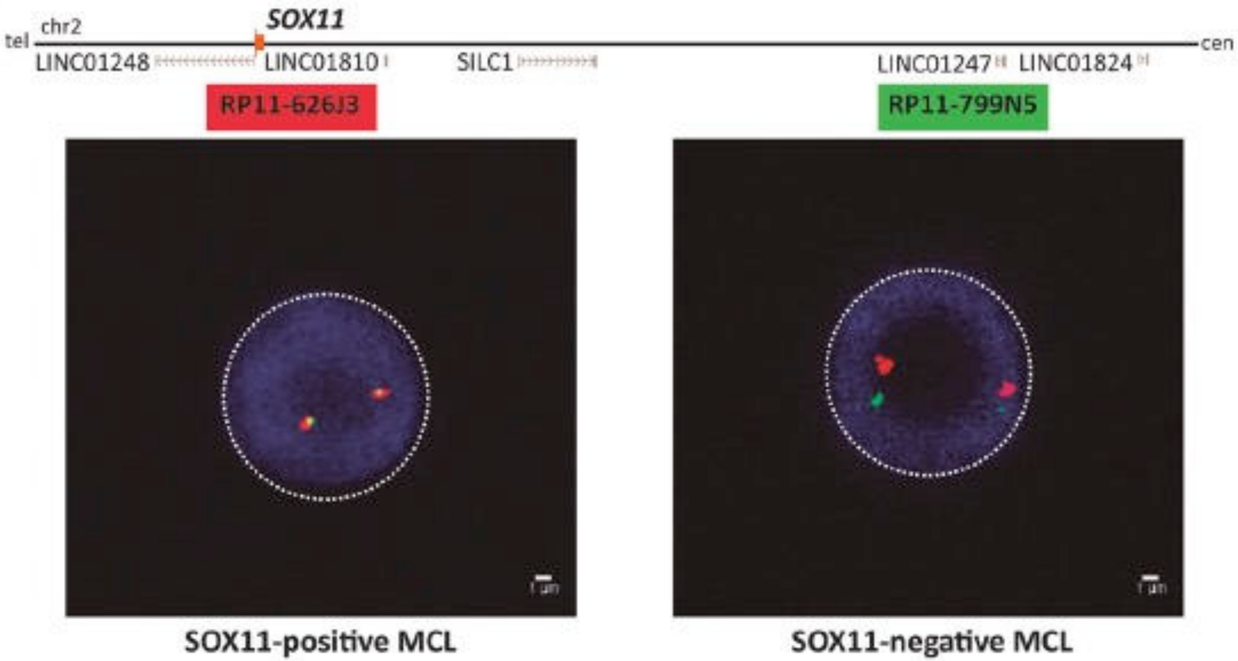
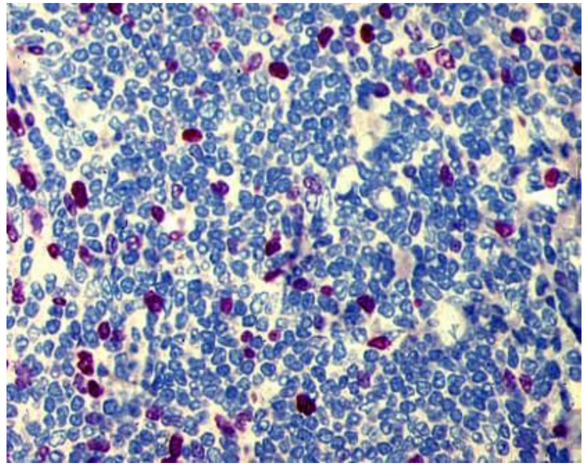


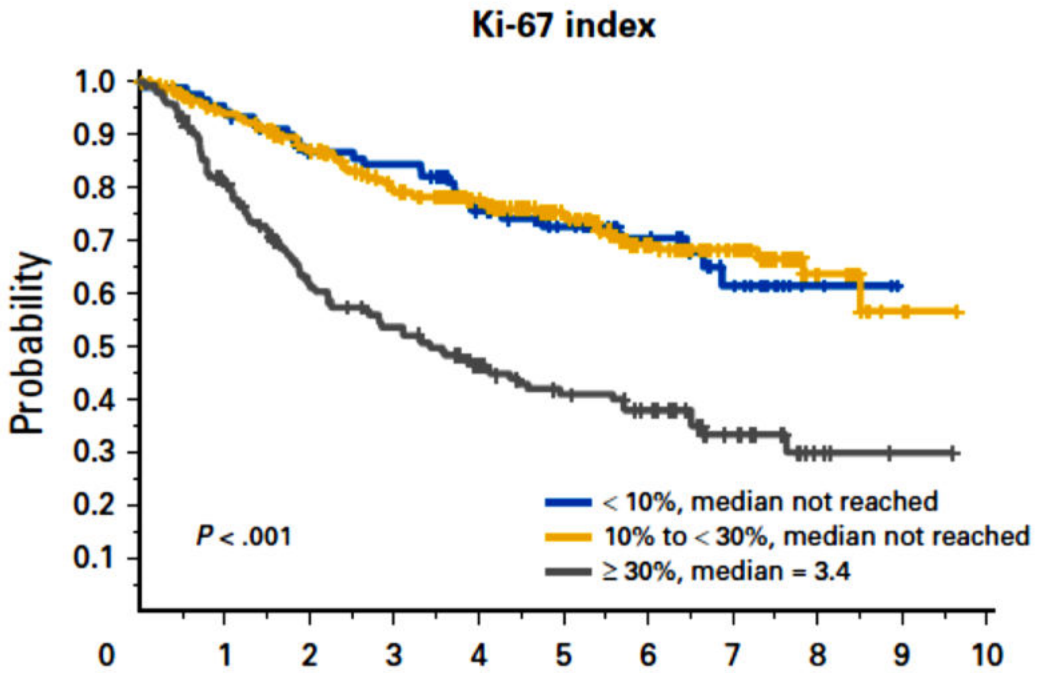
VOLUME 34 · NUMBER 12 · APRIL 20, 2016

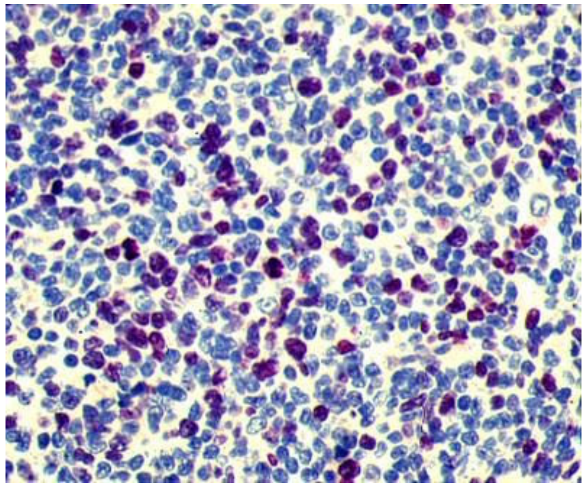
JOURNAL OF CLINICAL ONCOLOGY   ORIGINAL REPORT

Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network

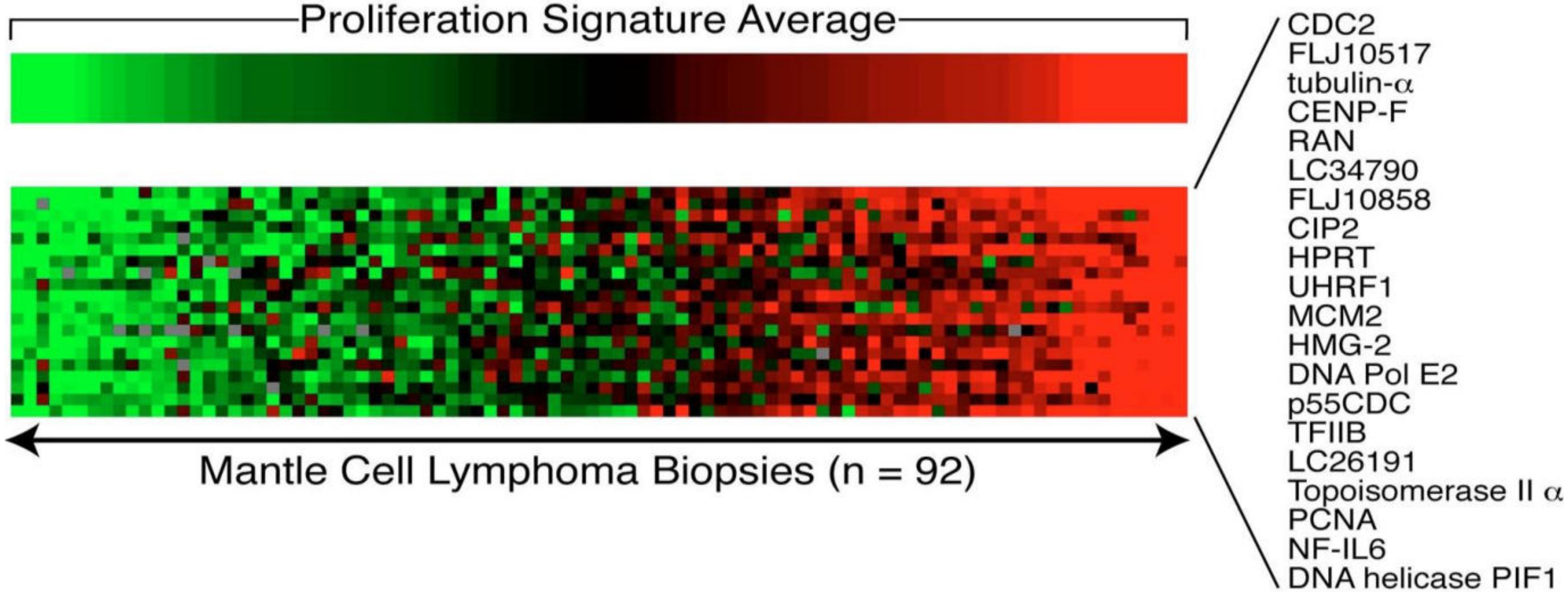
Eva Hoster, Andreas Rosenwald, Françoise Berger, Heinz-Wolfram Bernd, Sylvia Hartmann, Christoph Loddenkemper, Thomas F.E. Barth, Nicole Brousse, Stefano Pileri, Grzegorz Rymkiewicz, Roman Kodet, Stephan Stilgenbauer, Roswitha Forstpointner, Catherine Thieblemont, Michael Hallek, Bertrand Coiffier, Ursula Vehling-Kaiser, Réda Bouabdallah, Lothar Kanz, Michael Pfreundschuh, Christian Schmidt, Vincent Ribrag, Wolfgang Hiddemann, Michael Unterhalt, Johanna C. Kluin-Nelemans, Olivier Hermine, Martin H. Dreyling, and Wolfram Klapper

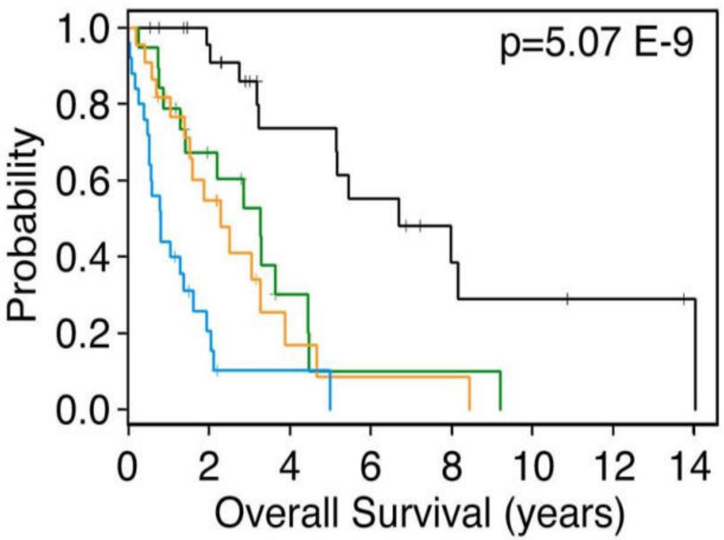




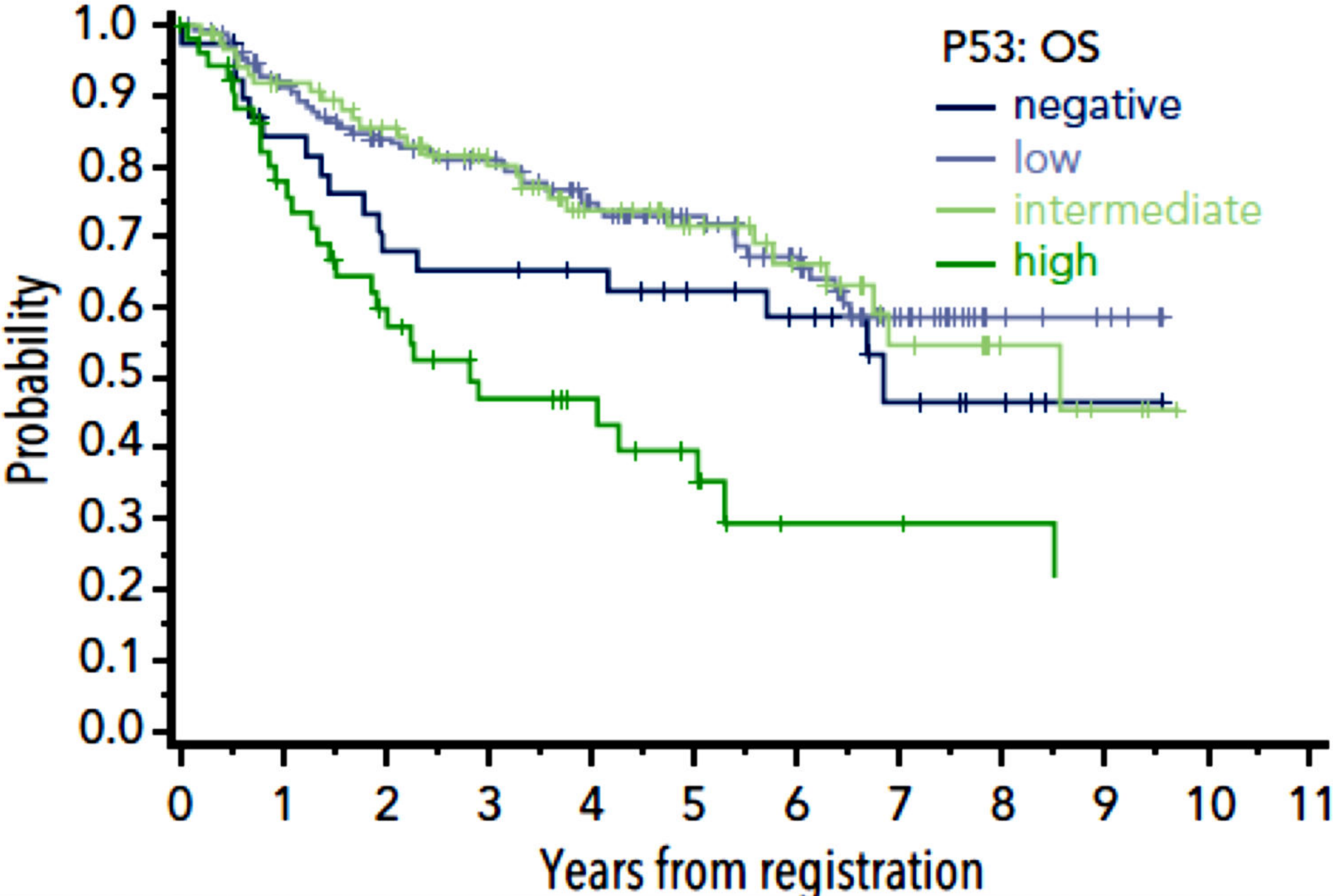


Variable Expression of Proliferation Signature Genes in Mantle Cell Lymphoma





Rosenwald A et LLMPP, Cancer Cell 2003; 3(2):185-97.


P53: OS
negative
low
intermediate
high
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
8
9
10
11
Years from registration

Virchows Arch. 2020 August ; 477(2): 259–267. doi:10.1007/s00428-020-02750-7.

Reproducibility of histologic prognostic parameters for mantle cell lymphoma: cytology, Ki67, p53 and SOX11

Giorgio A. Croci[1,2], Eva Hoster[3,4], Sílvia Beà[5,6], Guillem Clot[5,6], Anna Enjuanes[5,6], David W. Scott[7], José Cabeçadas[8], Luis Veloza[9], Elias Campo[5,6,9], Erik Clasen-Linde[10], Rashmi S. Goswami[11], Lars Helgeland[12], Stefano Pileri[13], Grzegorz Rymkiewicz[14], Sarah Reinke[1], Martin Dreyling[4], Wolfram Klapper[1]

LYMPHOID NEOPLASIA

Coding and noncoding drivers of mantle cell lymphoma identified through exome and genome sequencing

Prasath Pararajalingam,[1,*] Krysta M. Coyle,[1,*] Sarah E. Arthur,[1] Nicole Thomas,[1] Miguel Alcaide,[1] Barbara Meissner,[2,3] Merrill Boyle,[2,3] Quratulain Qureshi,[1] Bruno M. Grande,[1] Christopher Rushton,[1] Graham W. Slack,[2,3] Andrew J. Mungall,[4] Constantine S. Tam,[5,6] Rishu Agarwal,[5] Sarah-Jane Dawson,[5,6] Georg Lenz,[7] Sriram Balasubramanian,[8] Randy D. Gascoyne,[2,3] Christian Steidl,[2,3] Joseph Connors,[2,3] Diego Villa,[2,3] Timothy E. Audas,[1] Marco A. Marra,[2,3] Nathalie A. Johnson,[9] David W. Scott,[2,3] and Ryan D. Morin[1,4]

[1]Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada; [2]BC Cancer Centre for Lymphoid Cancer and [3]BC Cancer Research Centre, Vancouver, BC, Canada; [4]Michael Smith Genome Sciences Centre, Vancouver, BC, Canada; [5]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [6]University of Melbourne, Melbourne, VIC, Australia; [7]Department of Medicine A, Hematology, Oncology, and Pneumology, University Hospital Münster, Münster, Germany; [8]Janssen Research and Development, San Diego, CA; and [9]Department of Medicine, Jewish General Hospital, Montreal, QC, Canada

KEY POINTS

- RNA-binding proteins with roles in regulating alternative splicing, *DAZAP1, EWSR1, HNRNPH1*, are frequently mutated in MCL.
- Most somatic *HNRNPH1* mutations are intronic and disrupt regulation of HNRNPH1 through alternative splicing.

Mantle cell lymphoma (MCL) is an uncommon B-cell non-Hodgkin lymphoma (NHL) that is incurable with standard therapies. The genetic drivers of this cancer have not been firmly established, and the features that contribute to differences in clinical course remain limited. To extend our understanding of the biological pathways involved in this malignancy, we performed a large-scale genomic analysis of MCL using data from 51 exomes and 34 genomes alongside previously published exome cohorts. To confirm our findings, we resequenced the genes identified in the exome cohort in 191 MCL tumors, each having clinical follow-up data. We confirmed the prognostic association of *TP53* and *NOTCH1* mutations. Our sequencing revealed novel recurrent noncoding mutations surrounding a single exon of the *HNRNPH1*gene. In RNA-seq data from 103 of these cases, MCL tumors with these mutations had a distinct imbalance of *HNRNPH1* isoforms. This altered splicing of HNRNPH1 was associated with inferior outcomes in MCL and showed a significant increase in protein expression by immunohistochemistry. We describe a functional role for these recurrent noncoding mutations in disrupting an autoregulatory feedback mechanism, thereby deregulating HNRNPH1 protein expression. Taken together, these data strongly imply a role for aberrant regulation of messenger RNA processing in MCL pathobiology. **(*Blood*. 2020;136(5):572-584)**

Mantle cell lymphoma	*CCND1* rearrangement[b] - FISH	Consider if CCND1 IHC is negative		MRD testing using HTS to guide treatment decisions. WTS or targeted gene expression panel for proliferation and signatures of non-nodal versus conventional MCL.
	CCND2 and *CCND3* rearrangement[b] – FISH	Consider in *CCND1*-R negative tumors		
	TP53 mutation[a] – HTS*		Prognostic and guide management.[111]	

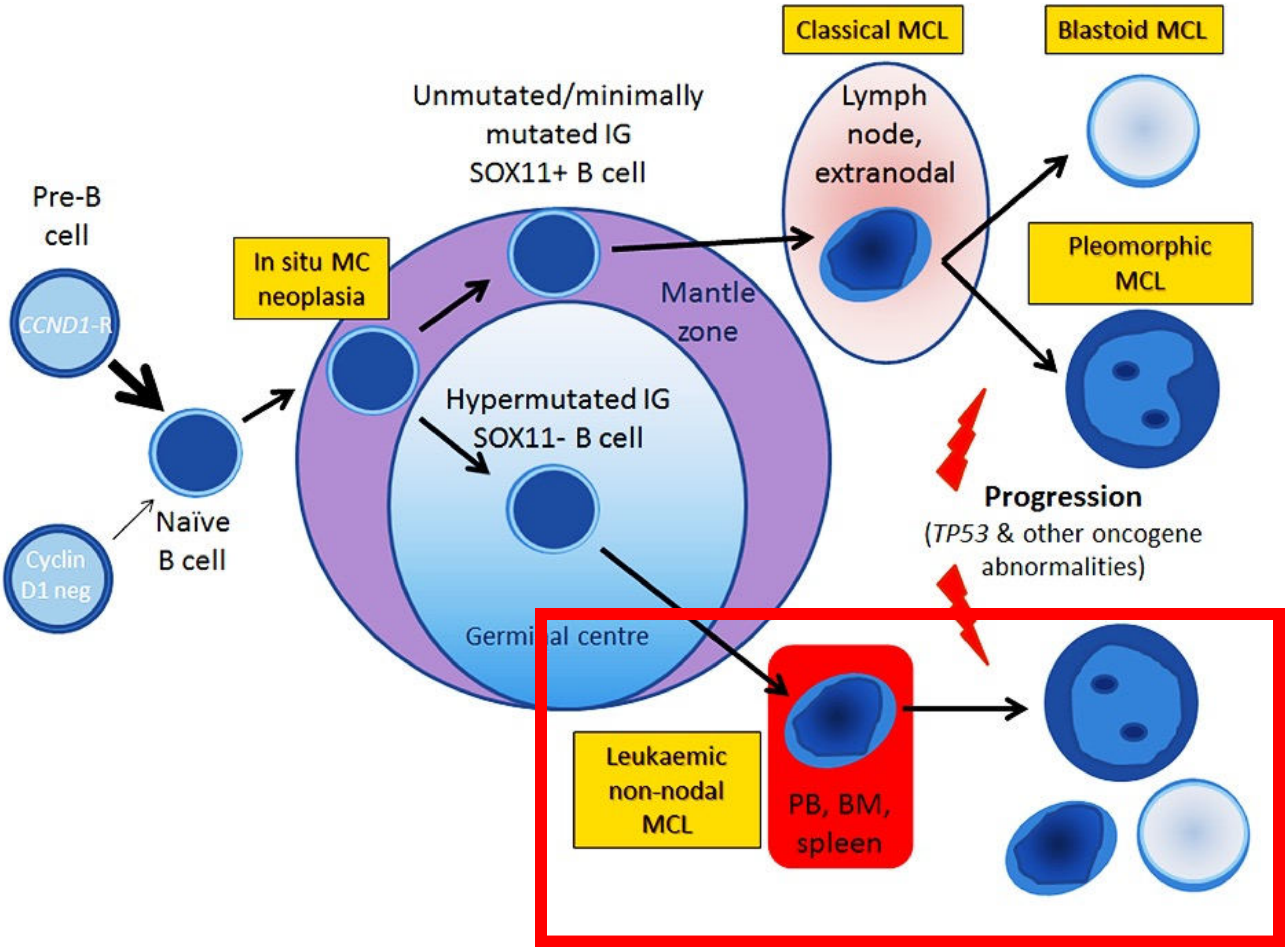
3148 blood® 26 MAY 2022 | VOLUME 139, NUMBER 21

Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study

Yuqin Song,[1] Keshu Zhou,[2] Dehui Zou,[3] Jianfeng Zhou,[4] Jianda Hu,[5] Haiyan Yang,[6] Huilai Zhang,[7] Jie Ji,[8] Wei Xu,[9] Jie Jin,[10] Fangfang Lv,[11] Ru Feng,[12] Sujun Gao,[13] Haiyi Guo,[14] Lei Zhou,[15] Jane Huang,[16] William Novotny,[16] Pil Kim,[16] Yiling Yu,[14] Binghao Wu,[14] and Jun Zhu[1]

KEY POINTS

- **Zanubrutinib demonstrated deep and durable responses and a favorable safety profile in R/R MCL at median 35.3 months follow-up.**
- **Zanubrutinib provided a high response rate (84% [78% CR]) and extended PFS (median 33.0 months) in patients with R/R MCL.**


Classical MCL
Blastoid MCL
Unmutated/minimally
mutated IG
SOX11+ B cell
Lymph
node,
extranodal
Pre-B
cell
In situ MC
neoplasia
Pleomorphic
MCL
Mantle
zone
CCND1-R
Hypermutated IG
SOX11- B cell
Progression
(TP53 & other oncogene
abnormalities)
Naïve
B cell
Cyclin
D1 neg
Germinal centre
Leukaemic
non-nodal
MCL
PB, BM,
spleen

Molecular and Cellular Pathobiology

Cancer Research

Genomic and Gene Expression Profiling Defines Indolent Forms of Mantle Cell Lymphoma

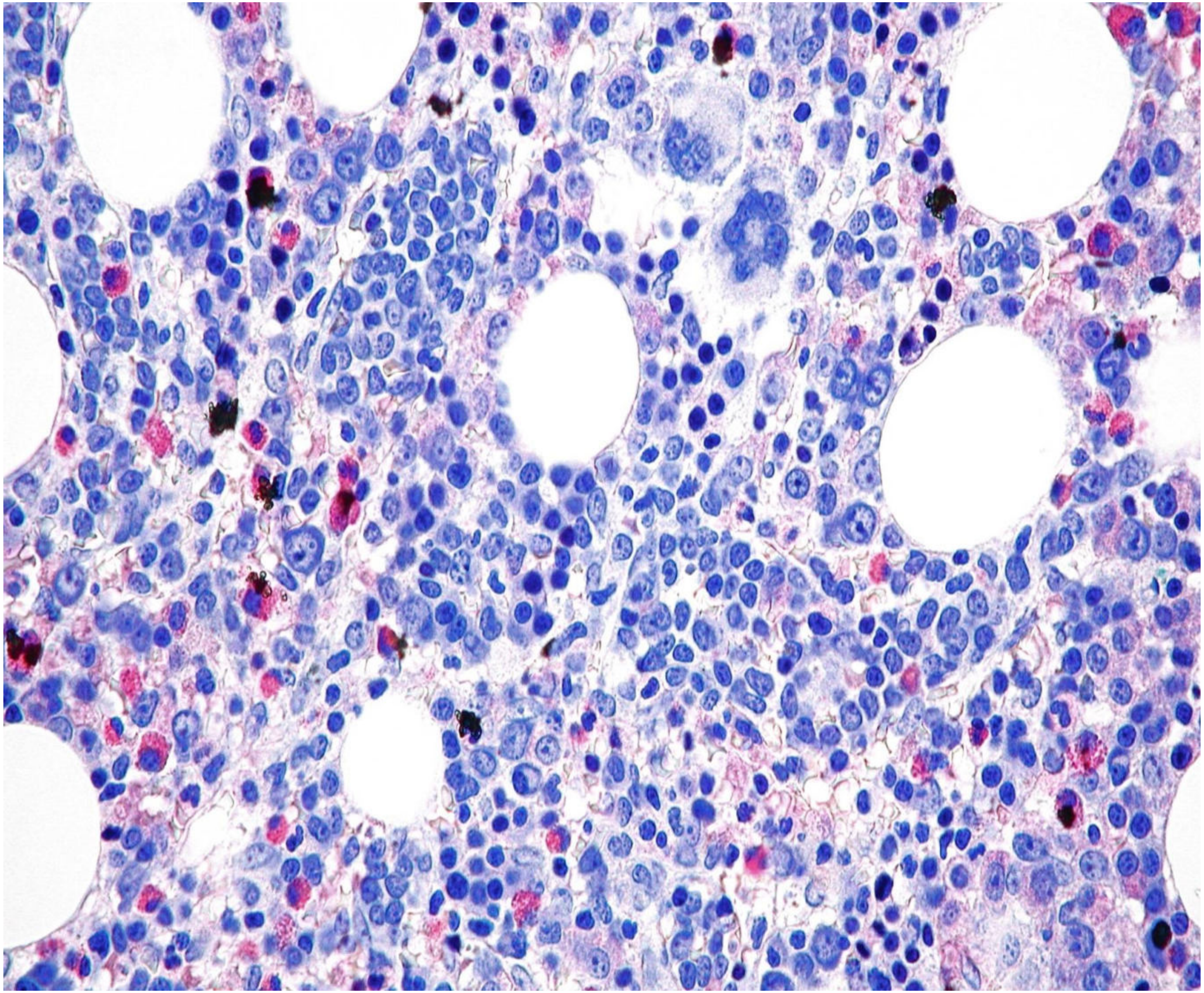
Verònica Fernàndez[1], Olga Salamero[2], Blanca Espinet[3], Francesc Solé[3], Cristina Royo[1], Alba Navarro[1], Francisca Camacho[4], Sílvia Beà[1], Elena Hartmann[5], Virginia Amador[1], Luis Hernández[1], Claudio Agostinelli[6], Rachel L. Sargent[7], Maria Rozman[1], Marta Aymerich[1], Dolors Colomer[1], Neus Villamor[1], Steven H. Swerdlow[7], Stefano A. Pileri[6], Francesc Bosch[2], Miguel A. Piris[4], Emili Montserrat[2], German Ott[8], Andreas Rosenwald[5], Armando López-Guillermo[2], Pedro Jares[1], Sergi Serrano[3], and Elías Campo[1]

Molecular and Cellular Pathobiology

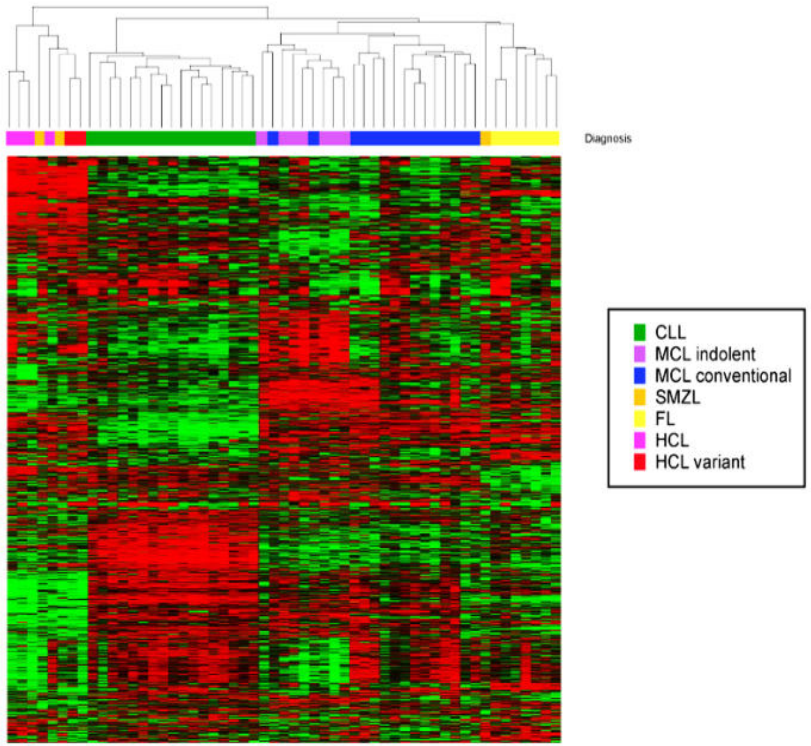
Cancer Research

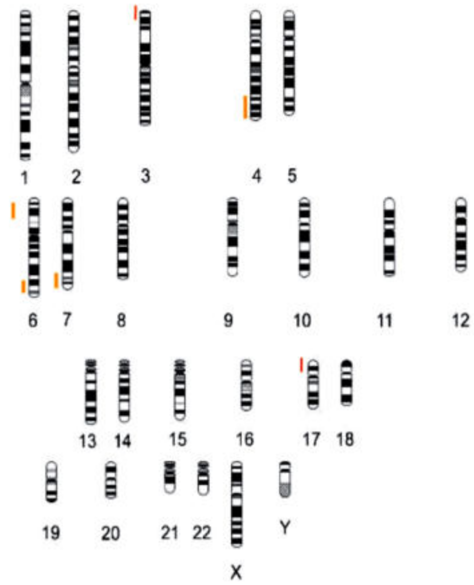
Molecular Subsets of Mantle Cell Lymphoma Defined by the *IGHV* Mutational Status and SOX11 Expression Have Distinct Biologic and Clinical Features

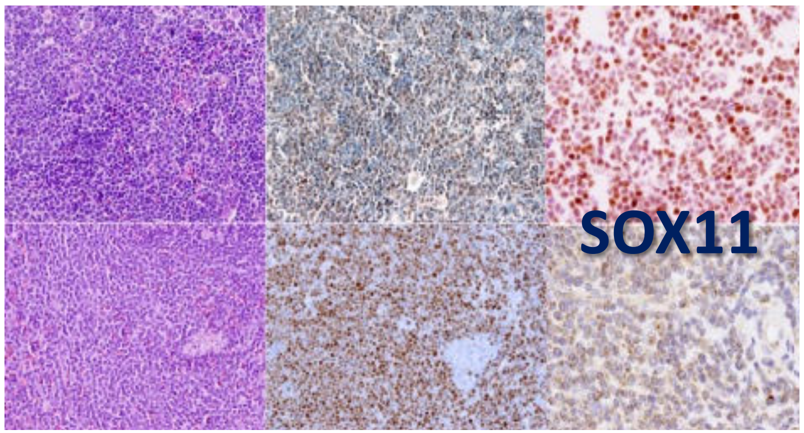
Alba Navarro[1], Guillem Clot[1], Cristina Royo[1], Pedro Jares[1], Anastasia Hadzidimitriou[4], Andreas Agathangelidis[4,5], Vasilis Bikos[4], Nikos Darzentas[4], Theodora Papadaki[7], Itziar Salaverria[1,8], Magda Pinyol[1], Xavier Puig[2], Jara Palomero[1], Maria Carmela Vegliante[1], Virgina Amador[1], Alejandra Martinez-Trillos[1], Lenka Stefancikova[12], Adrian Wiestner[13], Wyndham Wilson[13], Christiane Pott[9], Maria Jose Calasanz[3], Nicola Trim[14], Wendy Erber[15], Birgitta Sander[16], German Ott[10], Andreas Rosenwald[11], Dolors Colomer[1], Eva Giné[1], Reiner Siebert[8], Armando Lopez-Guillermo[1], Kostas Stamatopoulos[4,6], Sílvia Beà[1], and Elías Campo[1]

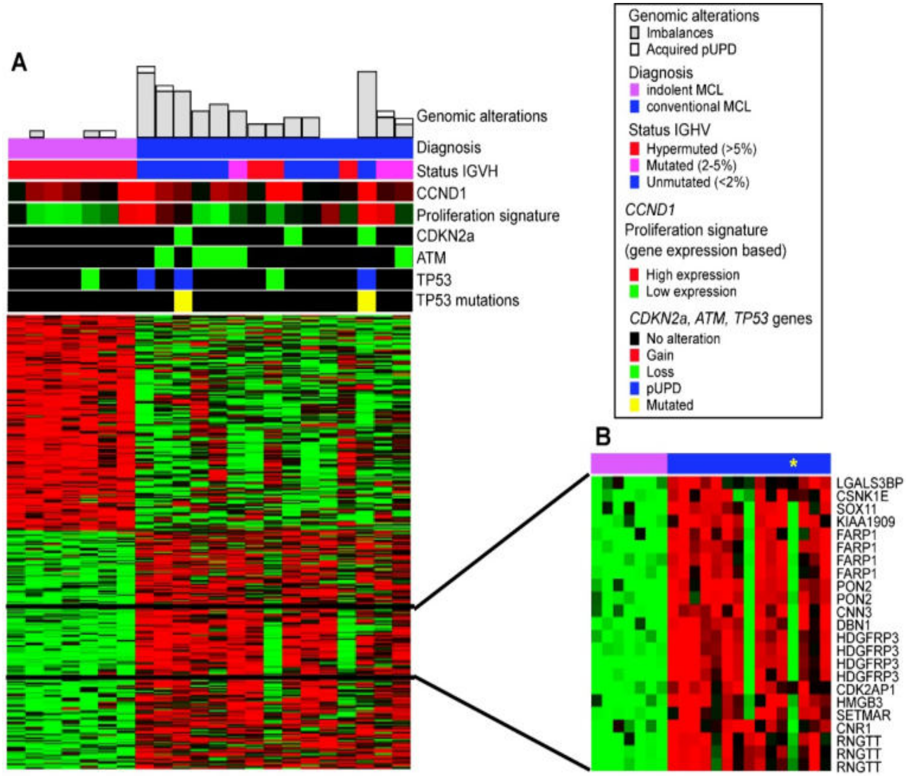


	cMCL (n=15)	iMCL (n=12)	P value
B symptoms (%)	33	0	0.03
Non-ambulatory performance status ECOG≥2 (%)	70	0	0.01
Nodal presentation (lymph nodes >1 cm) (%)*	**93**	**17**	**<0.001**
High serum LDH* (%)	46	0	0.03
Intermediate or high-risk MIPI	46	0	0.016
Morphology			0.007
Small cell (%)	13	67	
Classical	74	33	
Blastoid	13	-	
***IGHV* gene hypermutations (>5%)**	**20**	**70**	**< 0.04**
Genomic Profile			**<0.001**
1.imbalance	**13**	**100**	
≥ 2 imbalances	**87**	**0**	
Chemotherapy at any time (%)	100	17	
Dead patients (%)	**47**	**0**	**<0.001**
5-year overall survival (%)	49	100	0.03

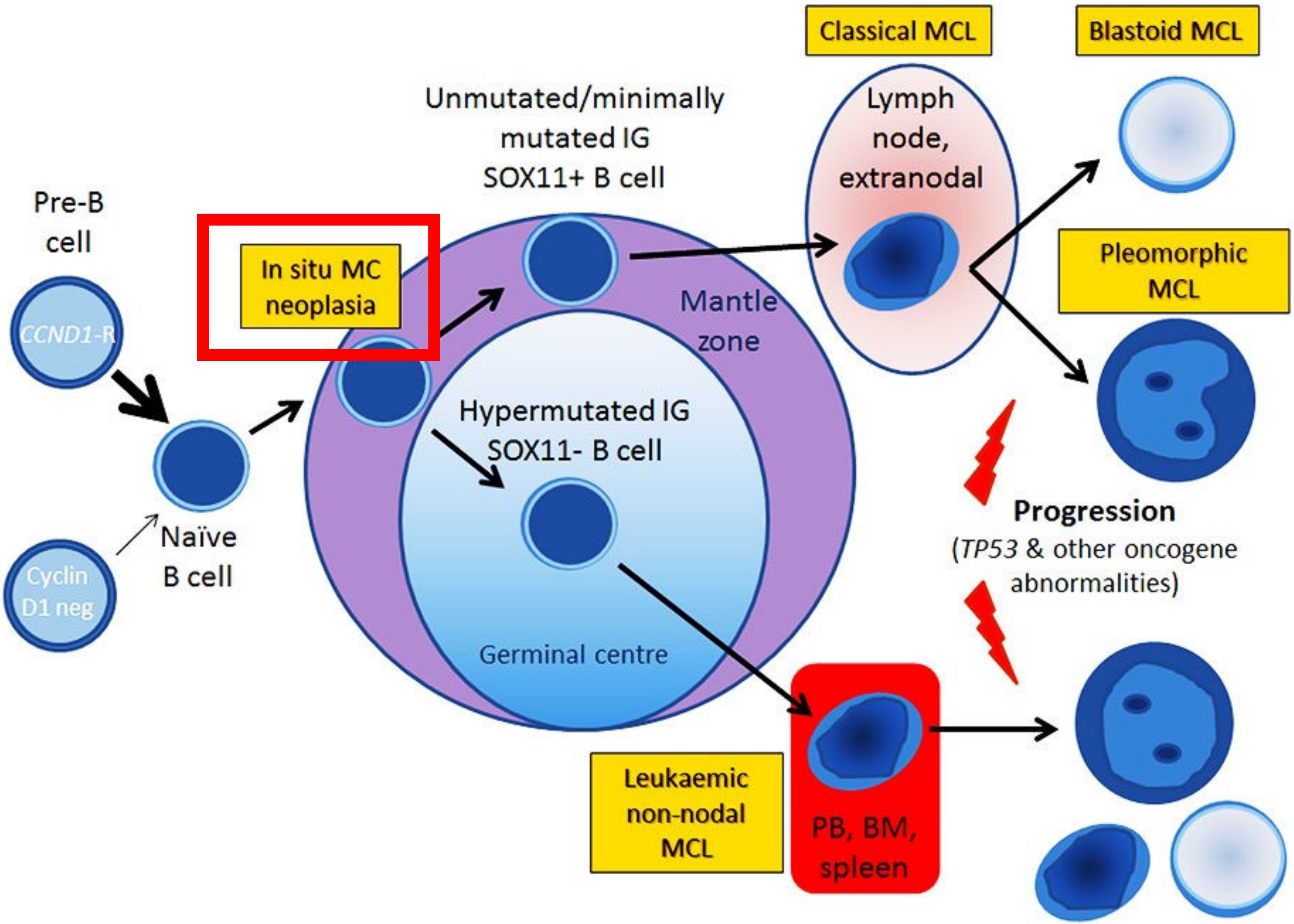




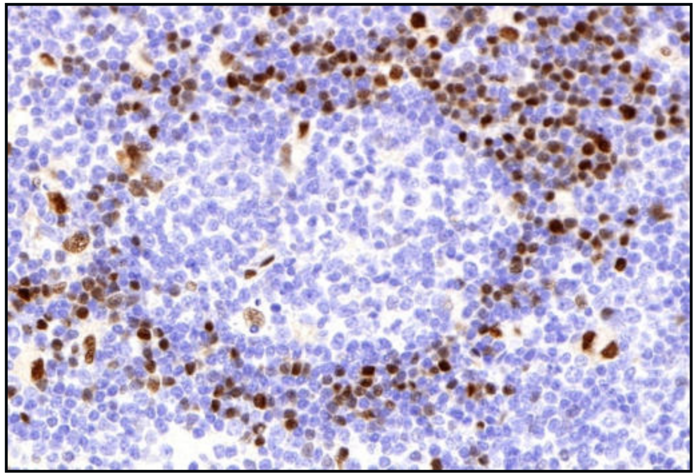




LNMCL shows a specific gene signature and SOX11 negativity



Classical MCL
Blastoid MCL
Unmutated/minimally mutated IG SOX11+ B cell
Lymph node, extranodal
Pre-B cell
In situ MC neoplasia
Pleomorphic MCL
CCND1-R
Mantle zone
Hypermutated IG SOX11- B cell
Progression
(TP53 & other oncogene abnormalities)
Naïve B cell
Cyclin D1 neg
Germinal centre
Leukaemic non-nodal MCL
PB, BM, spleen



LN with Cyclin D1+
In Situ Pattern

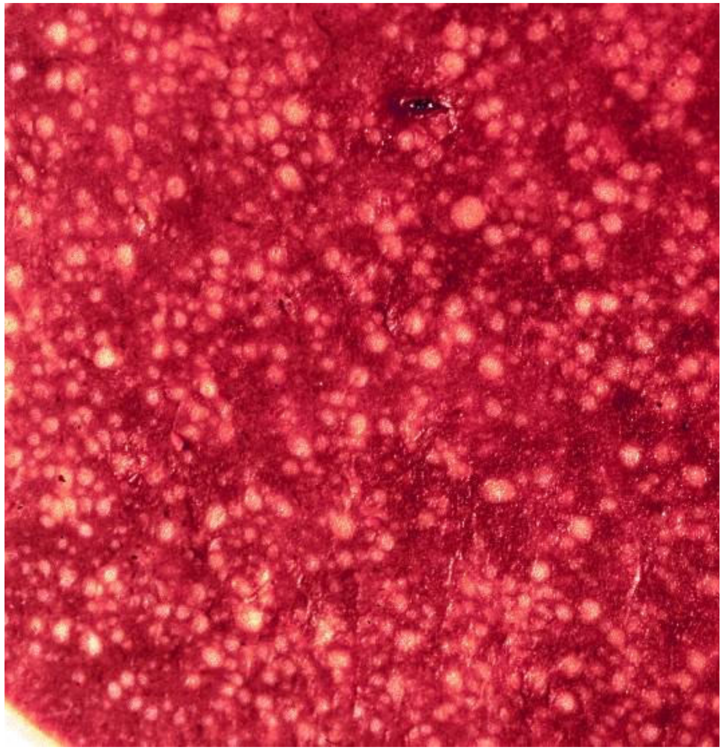
SOX11 negative
May be CD5 negative
Rare event: <1% of LNs
Low risk of Progression (<10%)

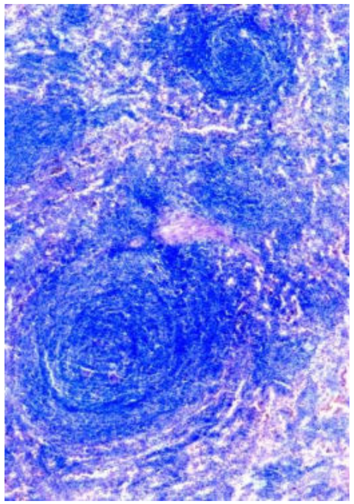
SOX11 positive
More often CD5 positive
Higher risk of progression
Similar pattern can be seen at relapse or at distant sites

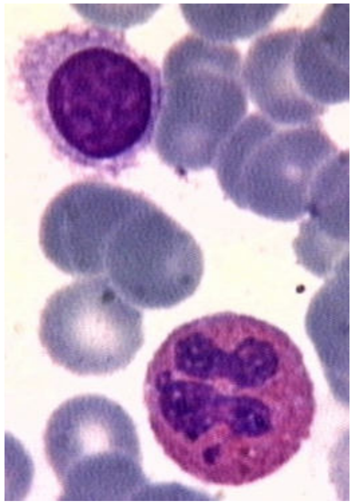
Splenic marginal zone lymphoma

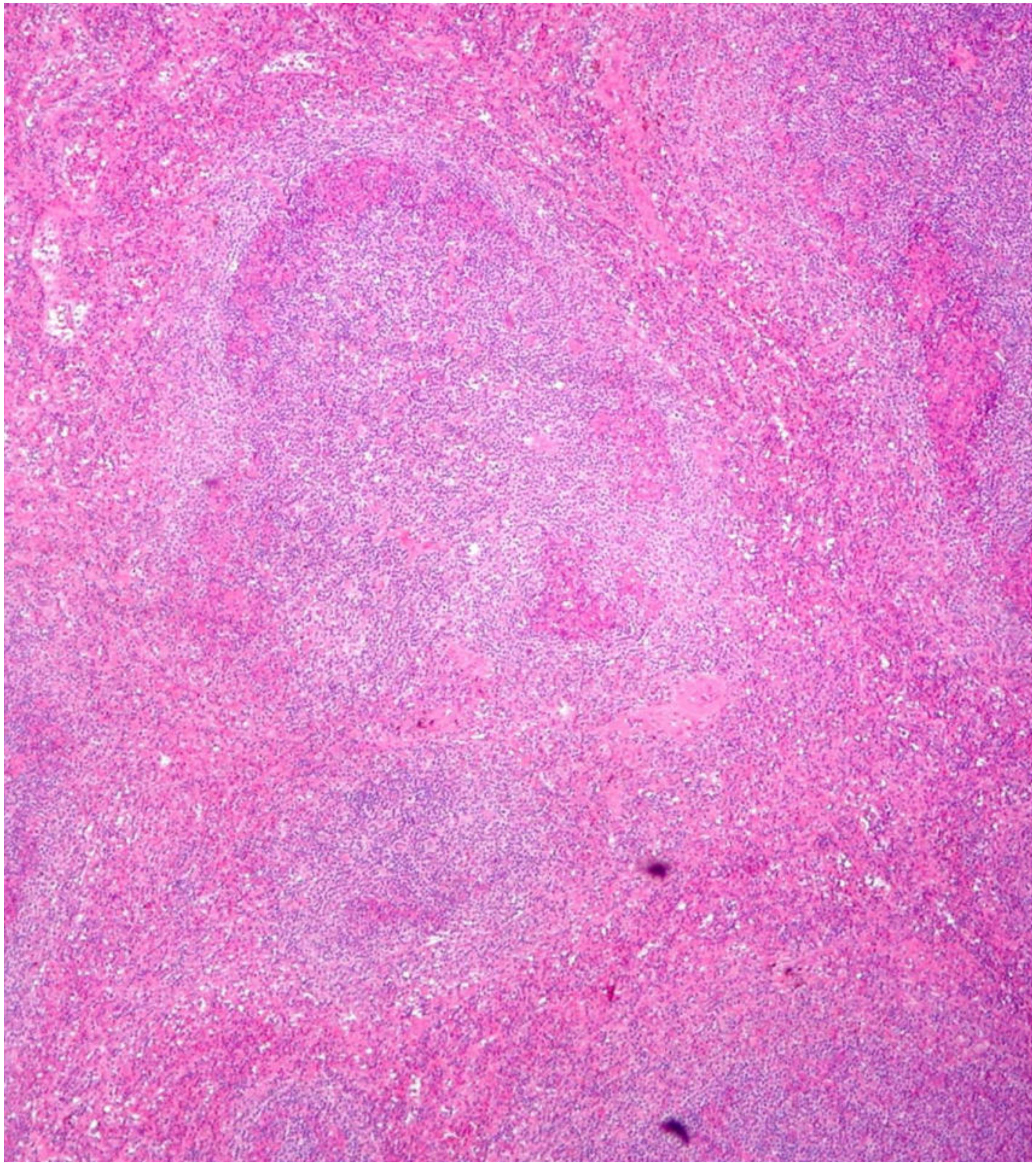
Definition

Splenic marginal zone lymphoma (SMZL) is a B-cell neoplasm composed of small lymphocytes that surround and replace the splenic white pulp germinal centres, efface the follicle mantle, and merge with a peripheral (marginal) zone of larger cells, including scattered transformed blasts; both small and larger cells infiltrate the red pulp. Splenic hilar lymph nodes and bone marrow are often involved; lymphoma cells are frequently found in the peripheral blood as villous lymphocytes.









Phenotype

CD19, CD20, CD22, CD79a, CD79b +

IgM+

IgD+

MNDA+

DBA44+/-

IRF4 -/+

BCL2+ (weak)

Annexin A-

CD5- (exceptions)

CD23-

Cyclin D1 –

SOX11-

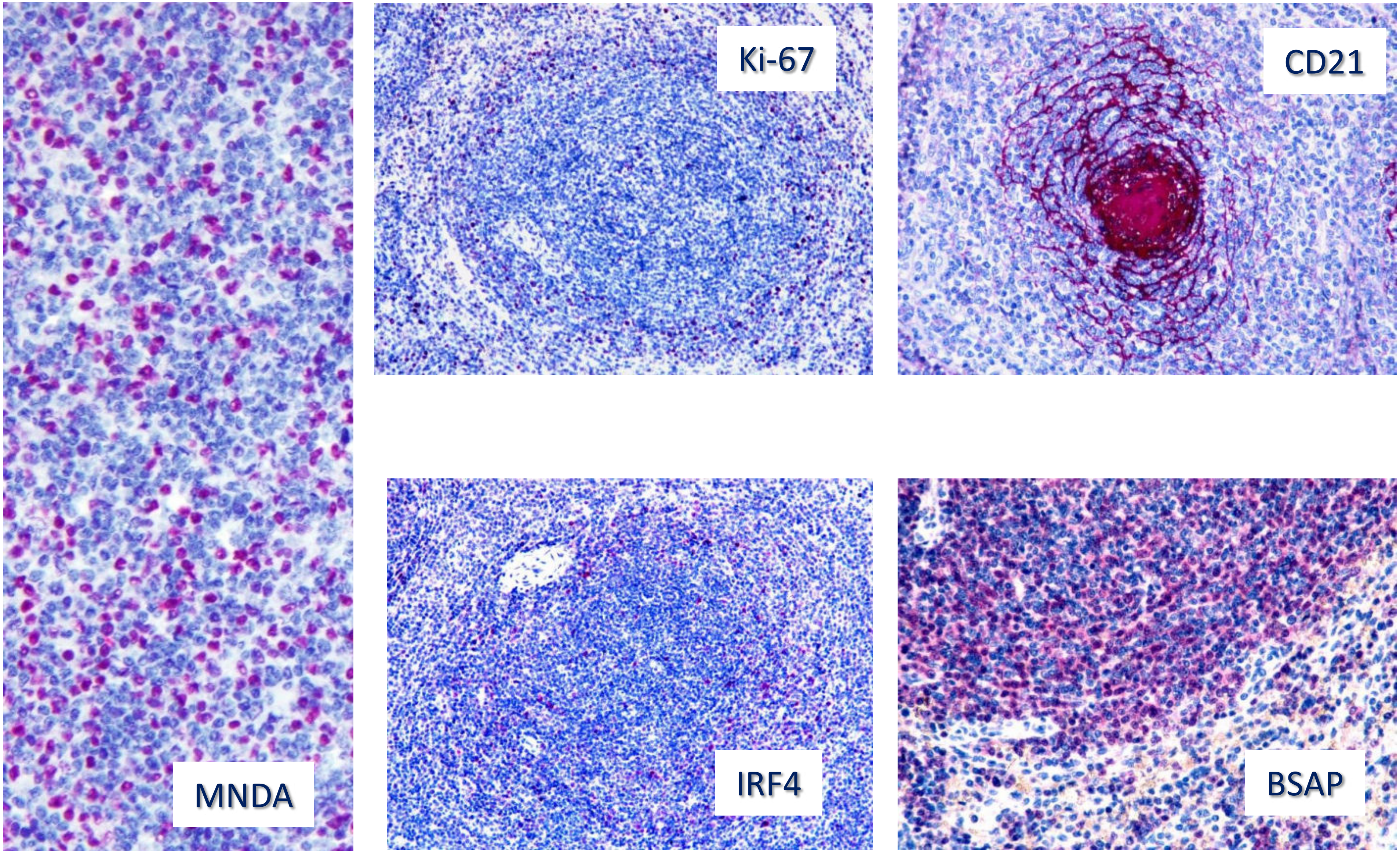
CD200 –

LEF1 –

IRTA1, T-bet -

CD10, BCL6, LMO2 –

Ki-67: variable

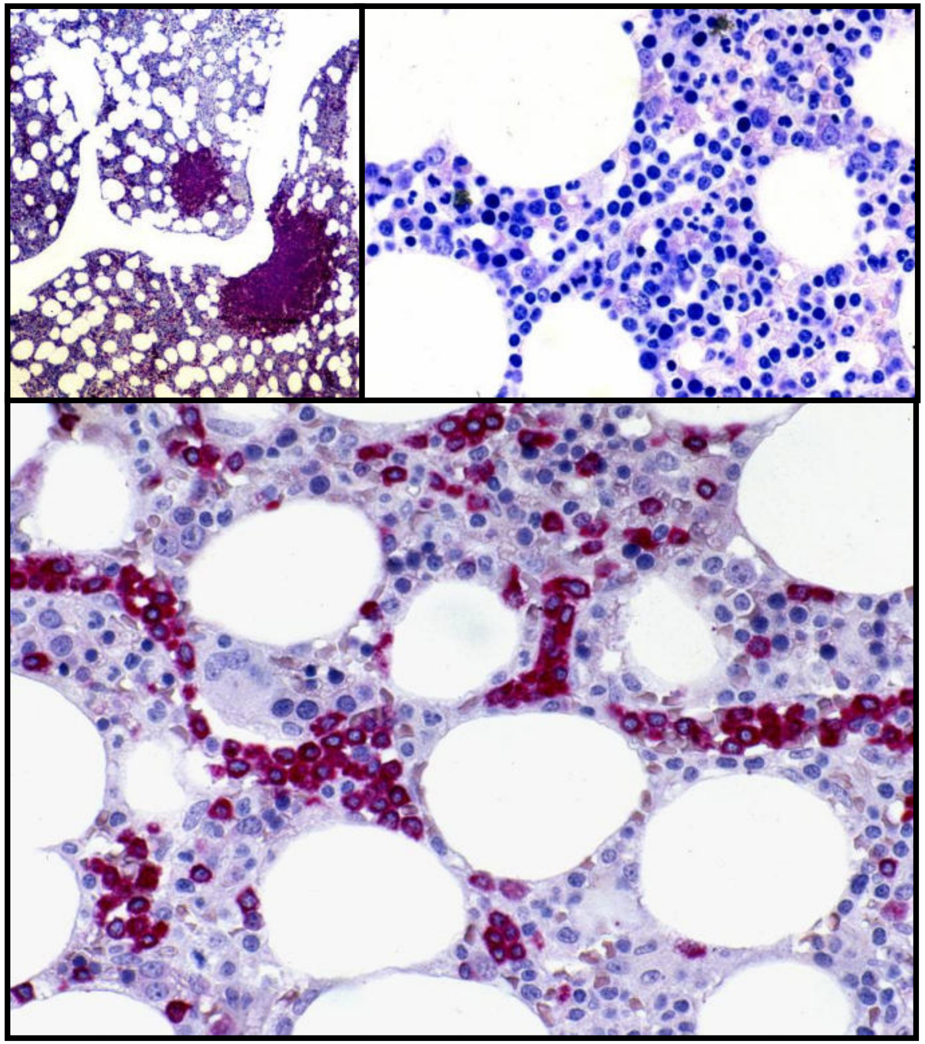

MNDA
Ki-67
CD21
IRF4
BSAP

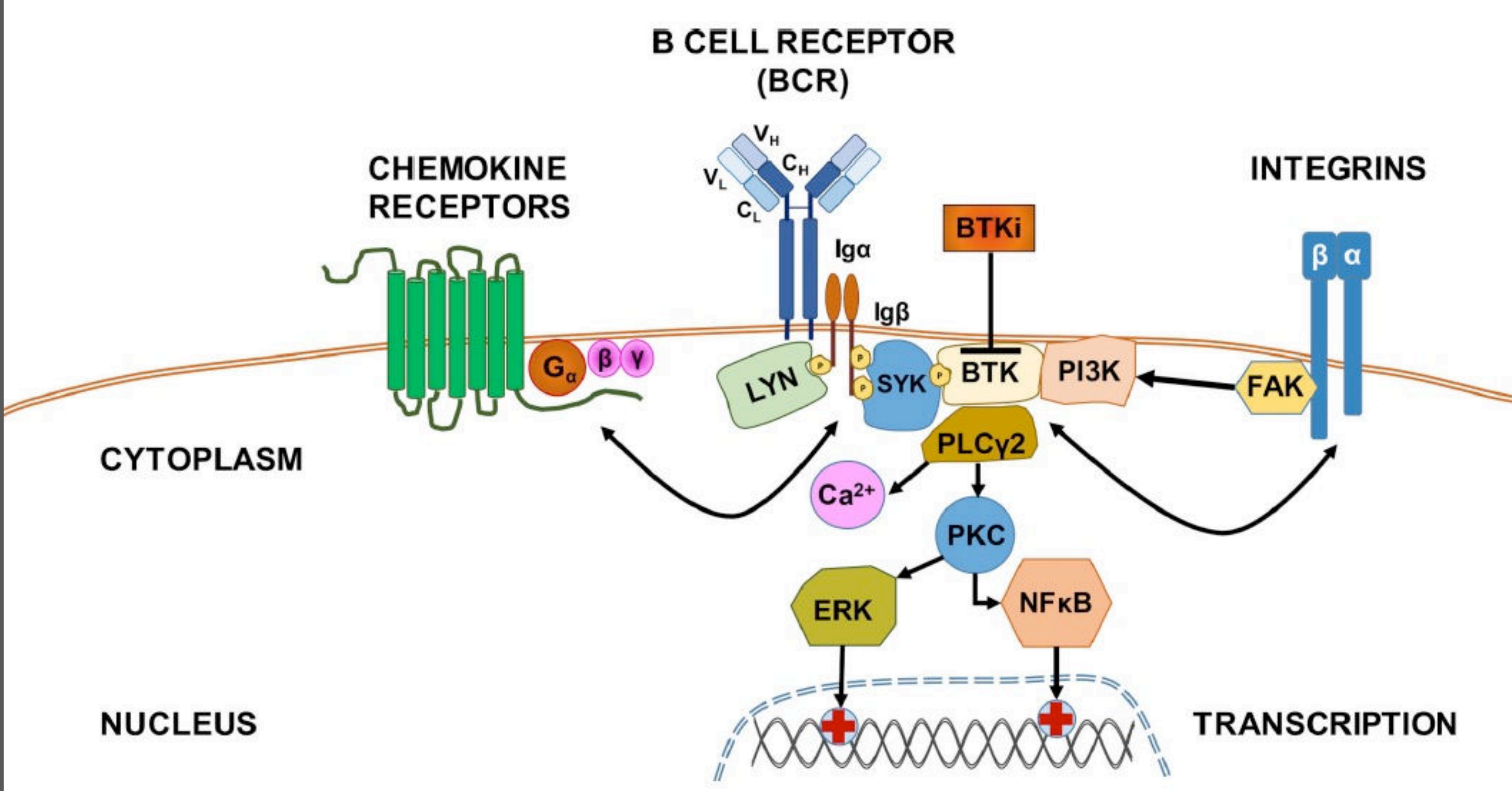
BM involvement

nodular,

Interstitial.

Intra-sinusoidal

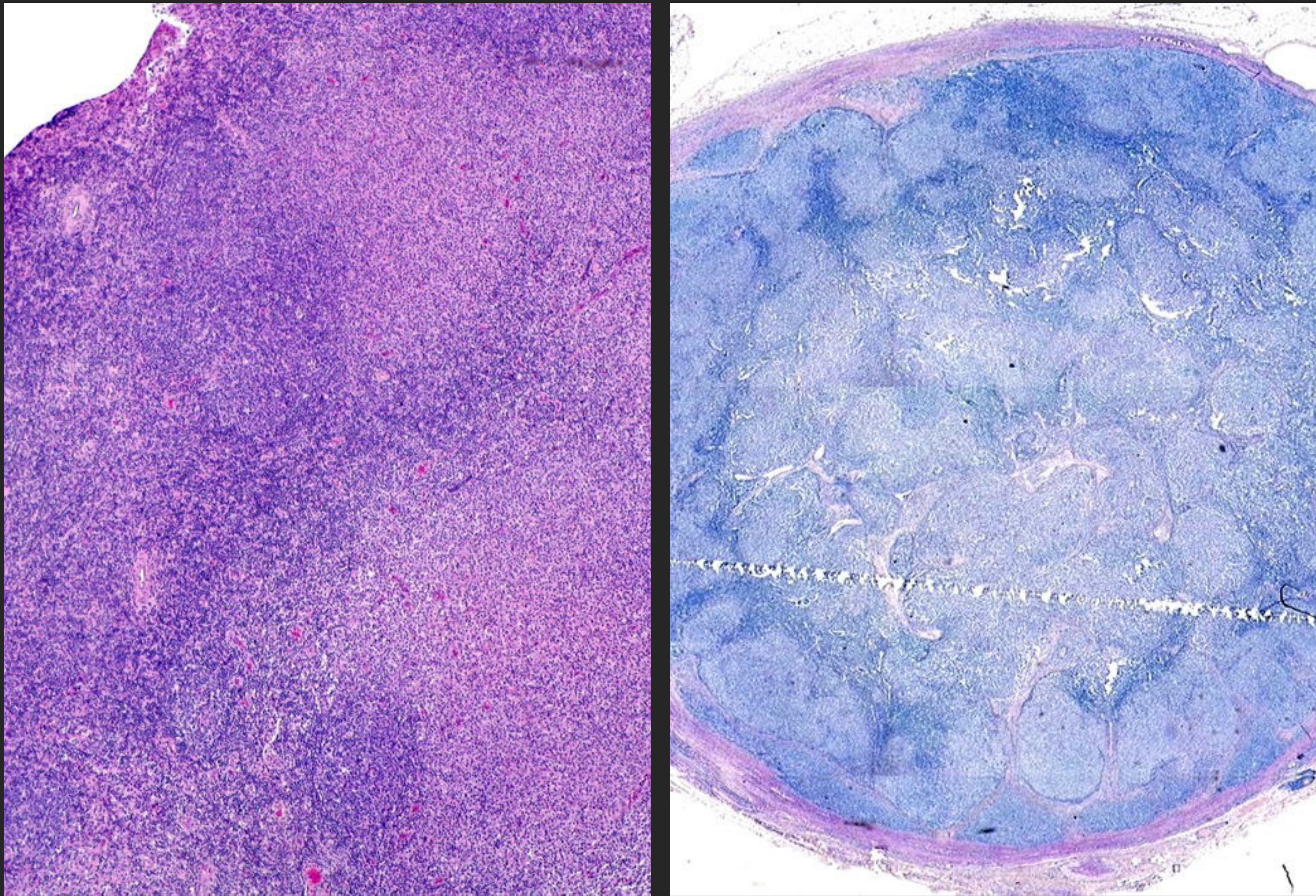


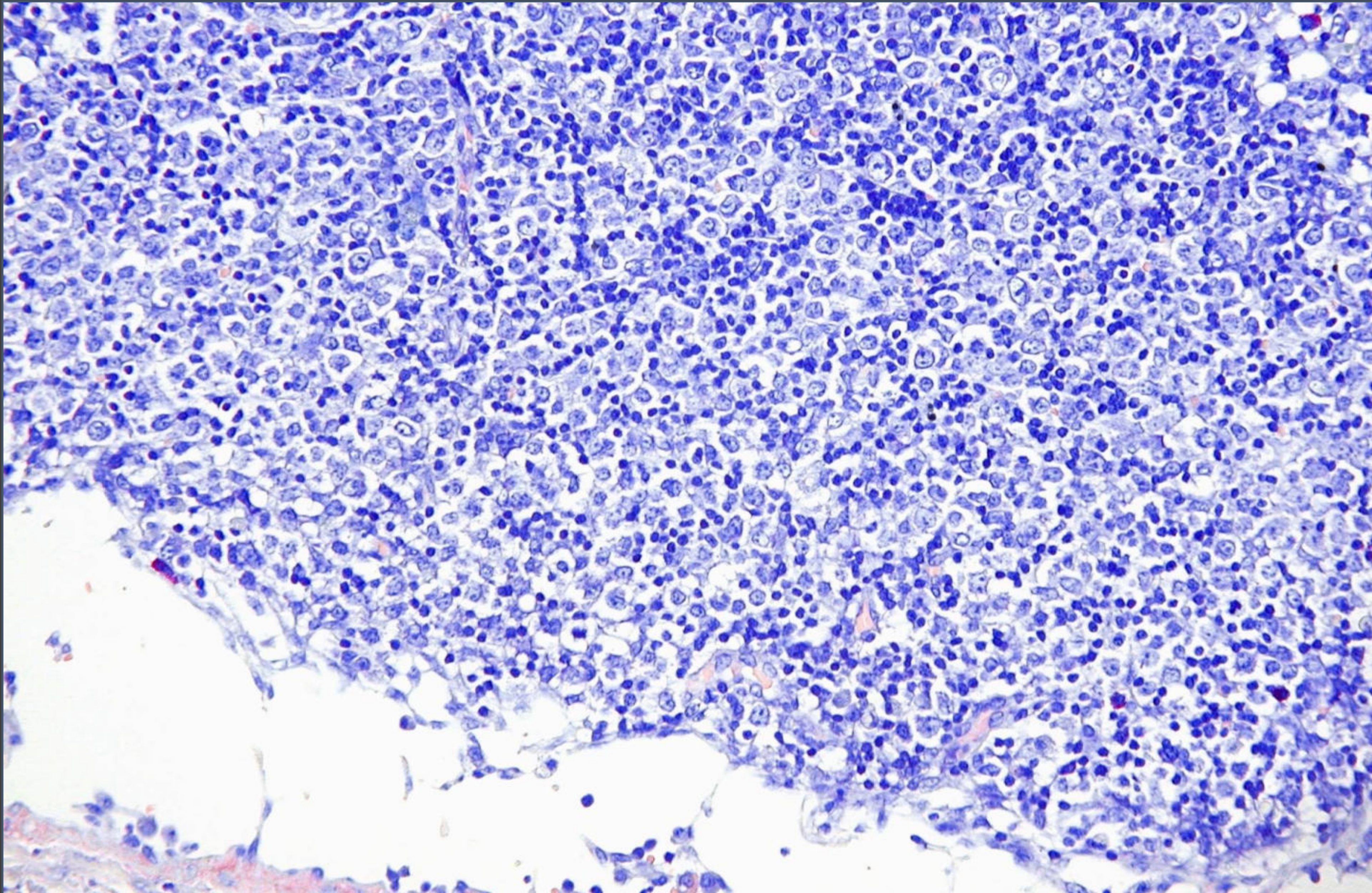

B CELL RECEPTOR
(BCR)
CHEMOKINE
RECEPTORS
INTEGRINS
V_H
C_H
V_L
C_L
Igα
Igβ
BTKi
β
α
G_α
β
γ
LYN
SYK
BTK
PI3K
FAK
CYTOPLASM
PLCγ2
Ca2+
PKC
ERK
NFκB
NUCLEUS
TRANSCRIPTION

Nodal marginal zone lymphoma

Definition

Nodal marginal zone lymphoma (NMZL) is a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by marginal zone lymphoma (MZL) of the extranodal or splenic types, but without evidence of extranodal or splenic disease.





Phenotype

CD19, CD20, CD22, CD79a, CD79b +

IgM/G+

IgD-/+

IRTA1+, T-bet+ (monocytoid); MNDA+ (splenic-type)

IRF4-/+ (plasma cell differentiation)

BCL2+ (weak)

CD5- (rarely +)

CD23-

Cyclin D1 –

SOX11-

CD200 –

LEF1 –

CD10, BCL6 (colonization), LMO2 –

Ki-67: variable

Splenic marginal zone lymphoma	del(7q)[b], +3, +18[88] – cytogenetics and FISH *KLF2, NOTCH2* mutations[88] - HTS	Detection is useful in certain circumstances to support the diagnosis		
Nodal marginal zone lymphoma	+3, +18[88] – cytogenetics and FISH *KLF2, NOTCH2, PTPRP*[88] mutations - HTS	Detection is useful in certain circumstances to support the diagnosis		

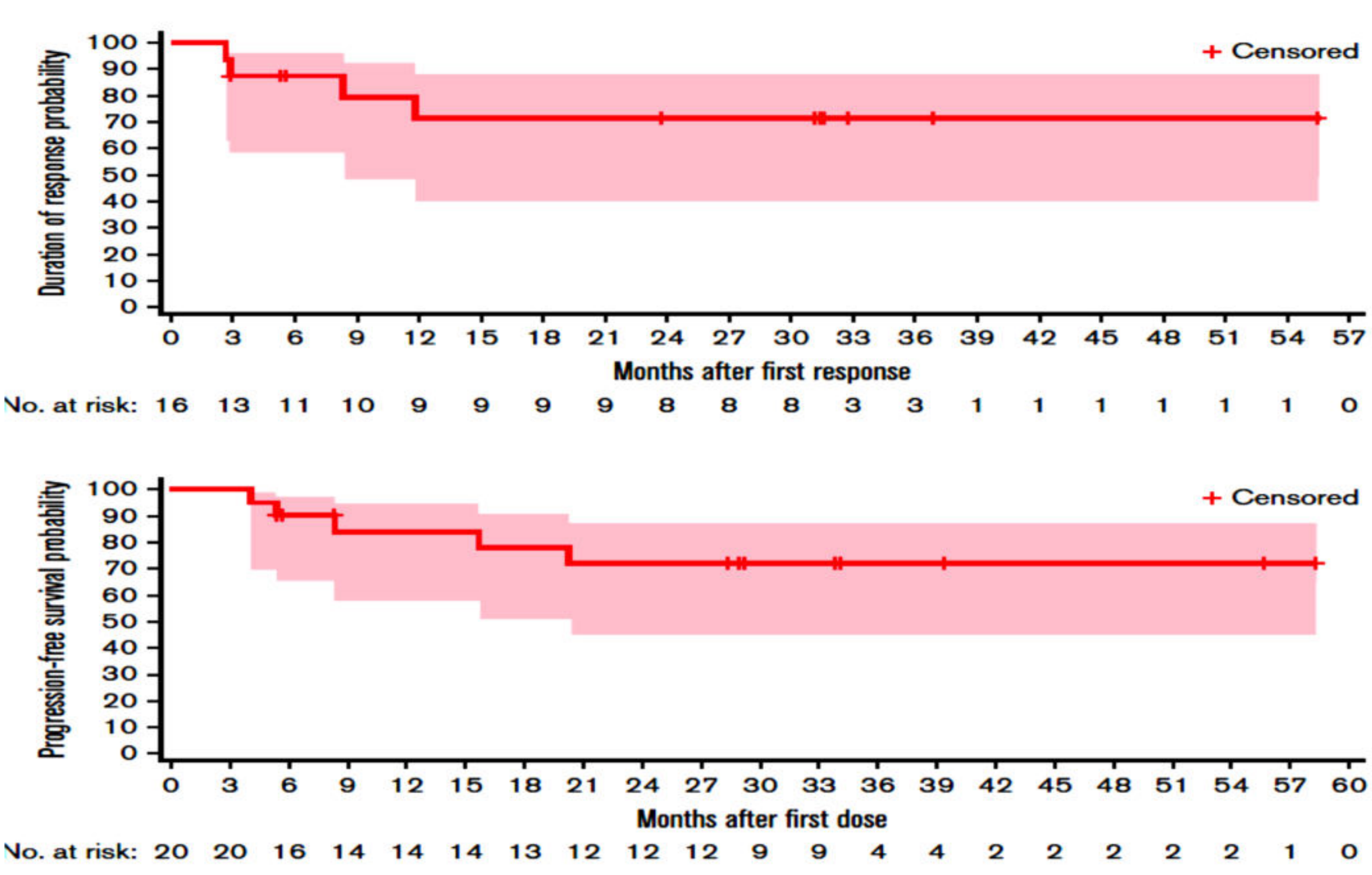
REGULAR ARTICLE

blood advances

Check for updates

Zanubrutinib monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma

Tycel Phillips,[1] Henry Chan,[2] Constantine S. Tam,[3,4] Alessandra Tedeschi,[5] Patrick Johnston,[6] Sung Yong Oh,[7] Stephen Opat,[8,9] Hyeon-Seok Eom,[10] Heather Allewelt,[11] Jennifer C. Stern,[12] Ziwen Tan,[11] William Novotny,[11] Jane Huang,[13] and Judith Trotman[14,15]



V. Tabanelli, S. Fiori, A. Calleri, F. Melle, G. Motta, S. Mazzara, M.R. Sapienza, M. Del Corvo, P. Antoniotti, M. Giuffrida, G. Procida, V. Rossi, E Derenzini