VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

A POST-GERMINAL CENTER B-CELL LYMPHOMA WITH «FOLLICULAR ARCHITECTURE»

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UNIVERSITÀ DEGLI STUDI DI BRESCIA

Sistema Socio Sanitario Regione Lombardia ASST Spedali Civili

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
None	None	None	None	None	None	None	None

CLINICAL DATA

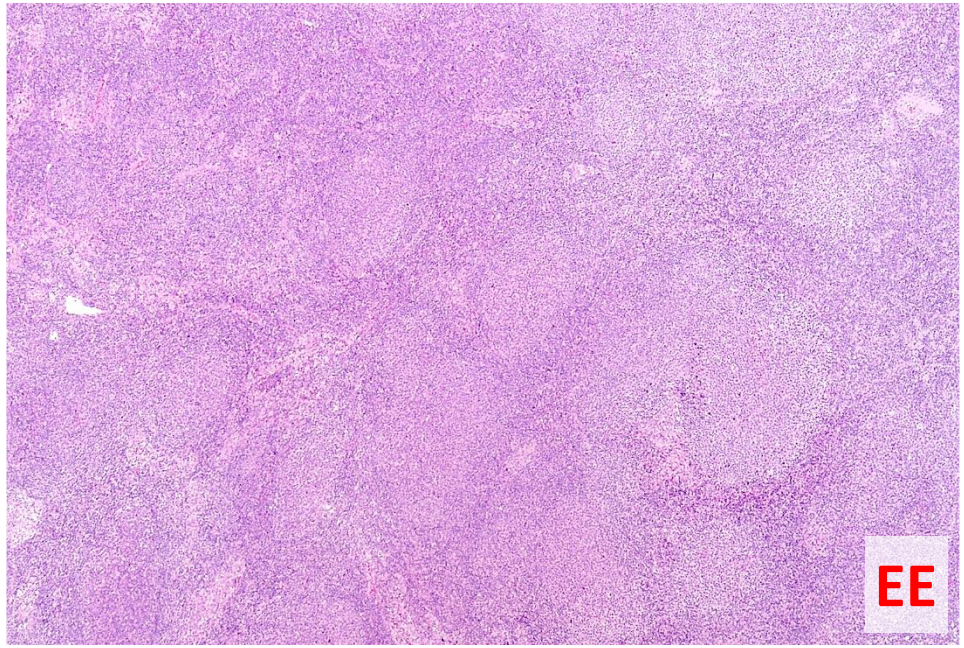
FONDAZIONE ITALIANA LINFOMI

FOLL-BIO:
From central pathology review

- **Female patient**
- 51-year-old
- Referred to the Azienda USL of Piacenza – Guglielmo da Saliceto Hospital 2017
- Multiple lymphadenopathies and leukocytosis.

↓

An excisional biopsy of a right laterocervical lymph node was performed. → On gross examination: irregular nodular mass with a maximum diameter of approximately 3 cm.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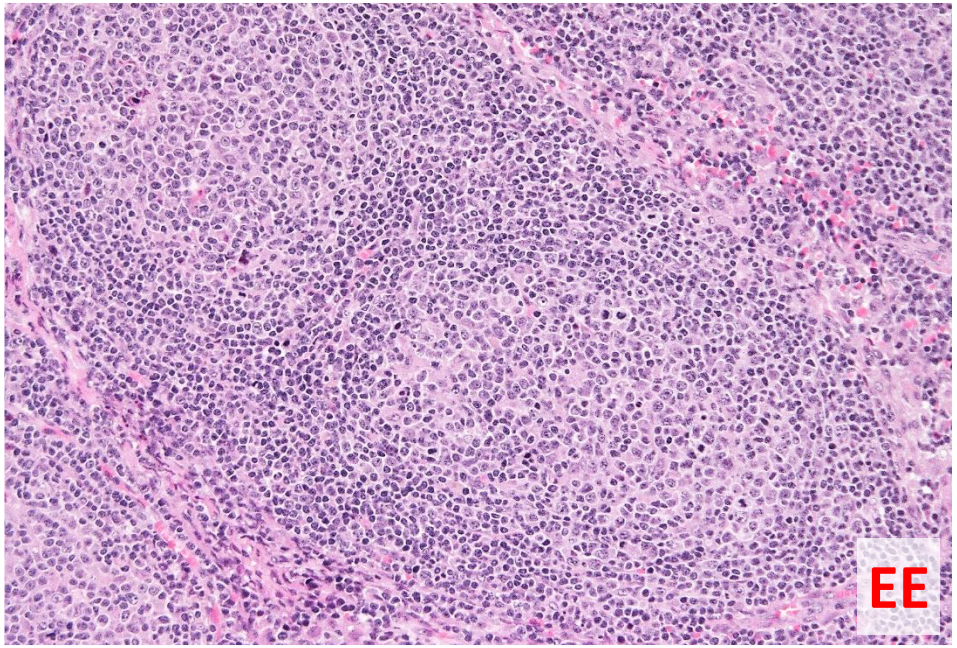
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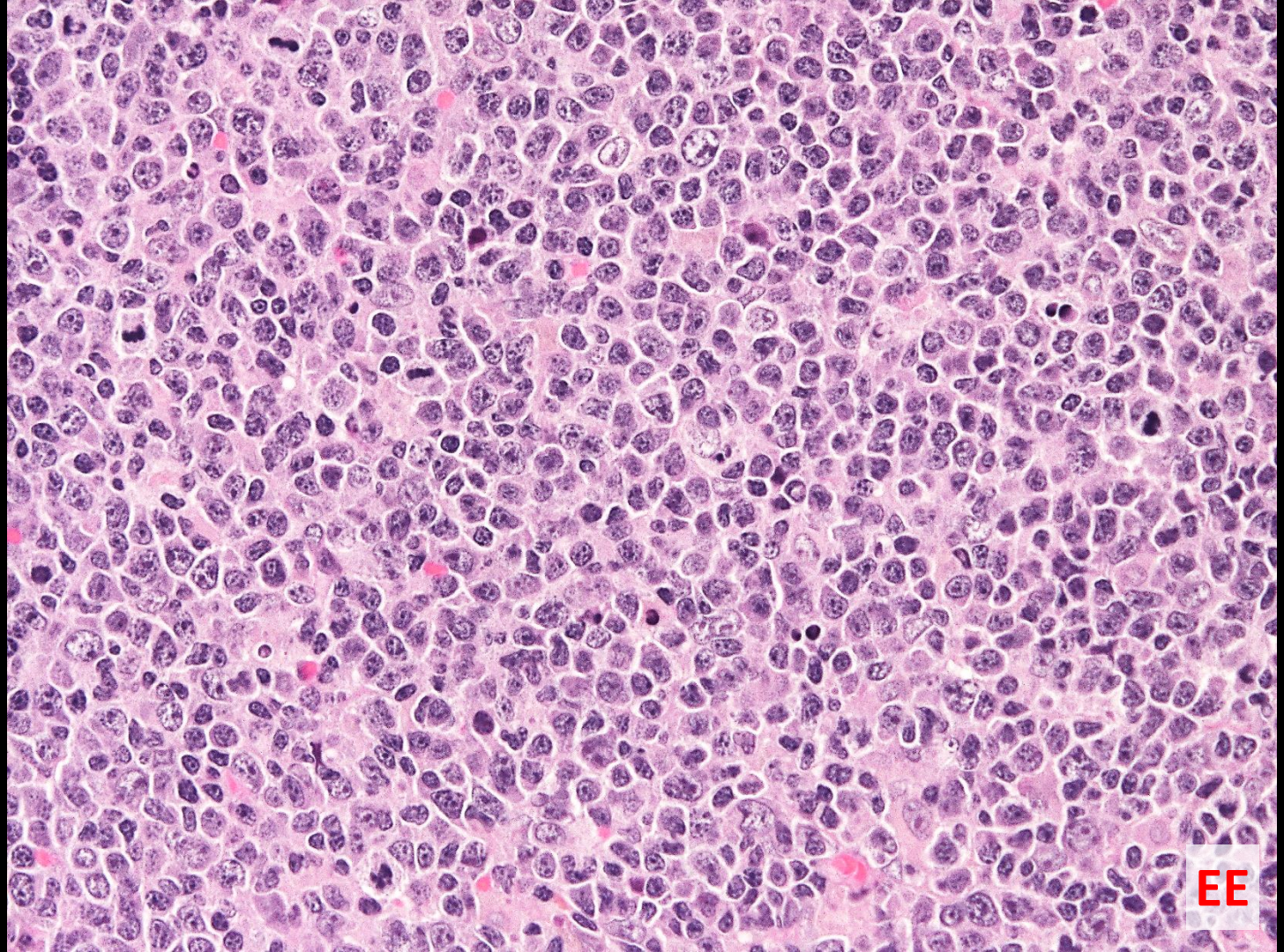
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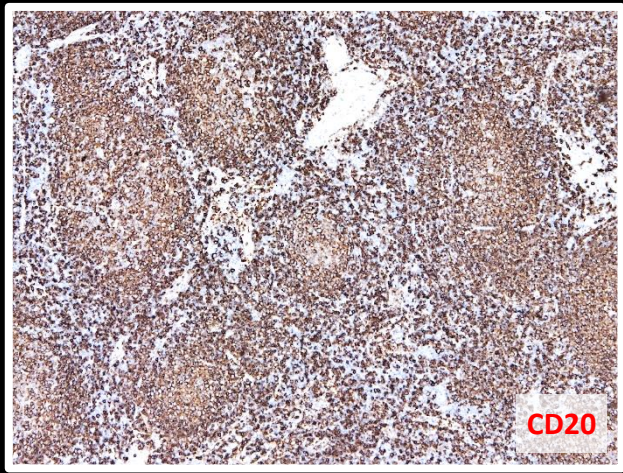
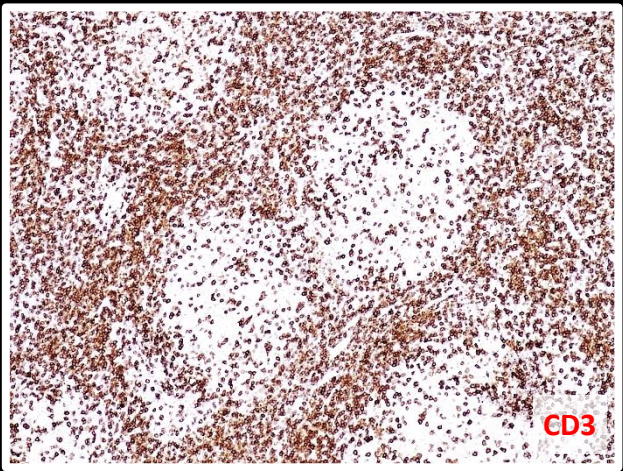

CD20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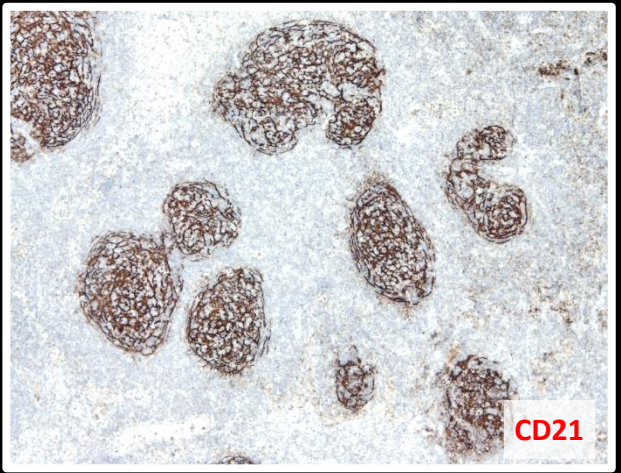
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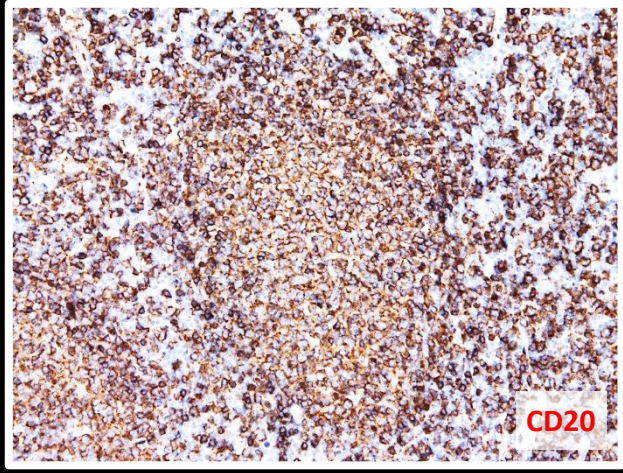
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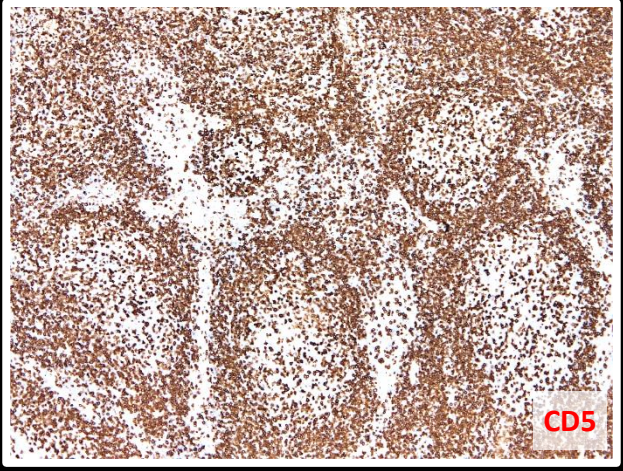
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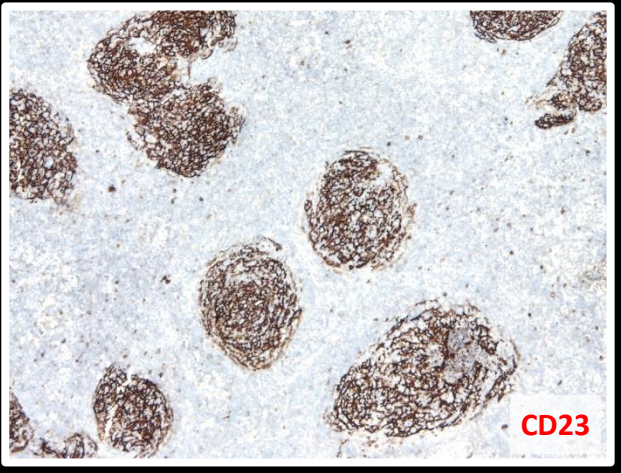
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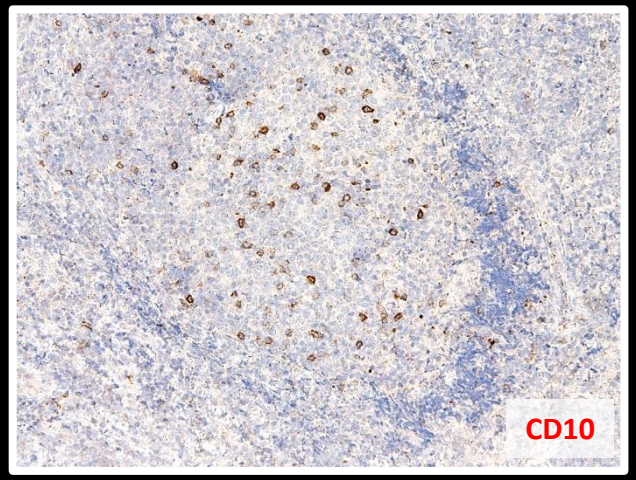
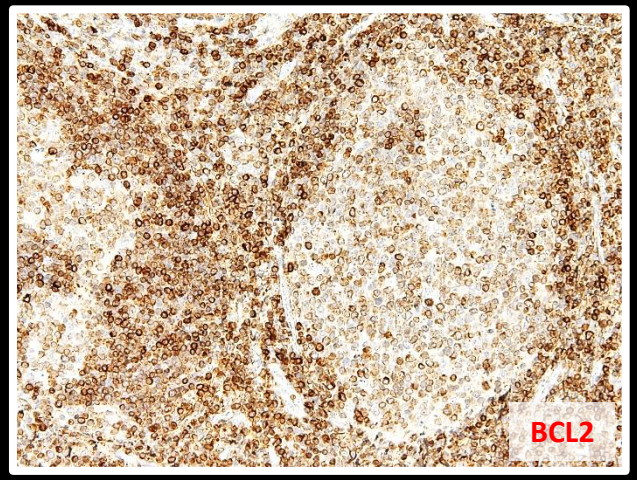
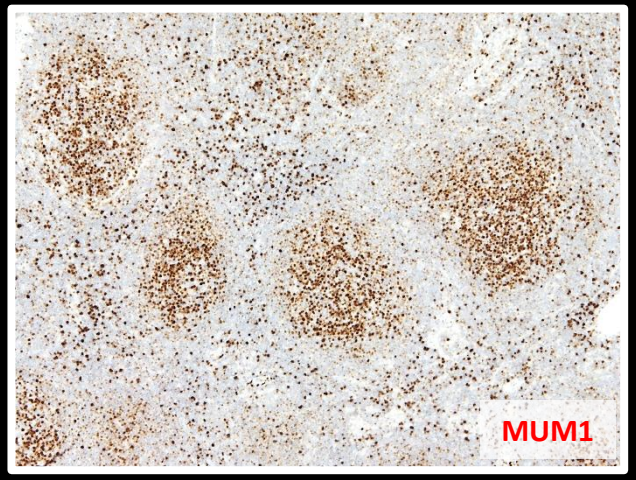
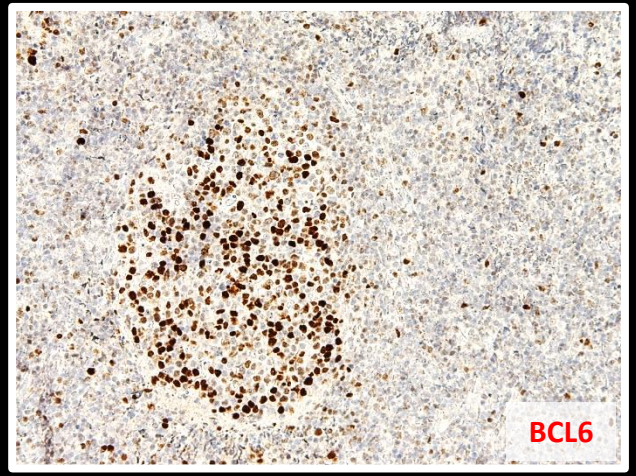
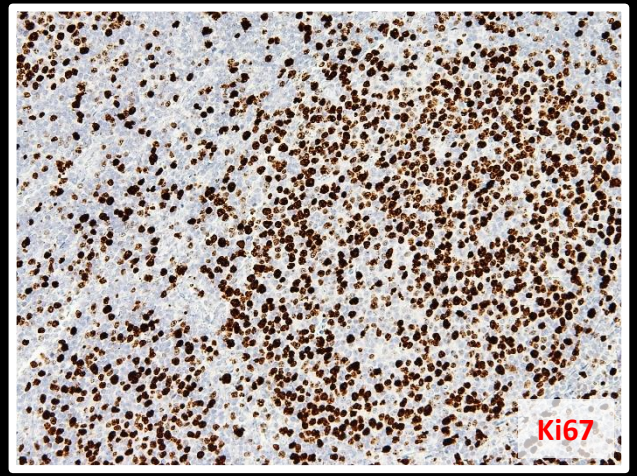
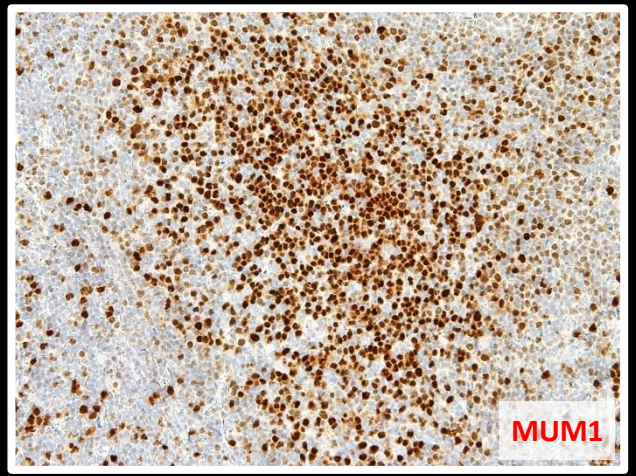

CD10


BCL2


MUM1


BCL6


Ki67


MUM1

INITIAL DIAGNOSIS

At the referring laboratory, the diagnosis was:

follicular lymphoma, grade 3 according to WHO (2016)

«Notably lymphoma cells are CD10-negative and MUM1 positive»

CLINICAL FOLLOW UP AVAILABLE

- Complete remission following R-CHOP therapy
- 2 years of Rituximab maintenance
- 2024 (7 years from diagnosis): complete remission

INITIAL DIAGNOSIS

At the referring laboratory, the diagnosis was:

follicular lymphoma, grade 3 according to WHO (2016)

«Notably lymphoma cells are CD10-negative and MUM1 positive»

The patient was enrolled in the FIL *FOLL12* and *FOLLBIO* studies; therefore, the case was submitted for pathological review (Code: 0673FOLL12).

HISTOLOGICAL REVIEW

HISTOLOGICAL REVIEW

FIL FOLL12 and FOLLBIO studies
pathological review
(Code: 0673FOLL12)

For evaluation of the germinal center (GC) phenotype:

POSITIVE

NEGATIVE

HISTOLOGICAL REVIEW

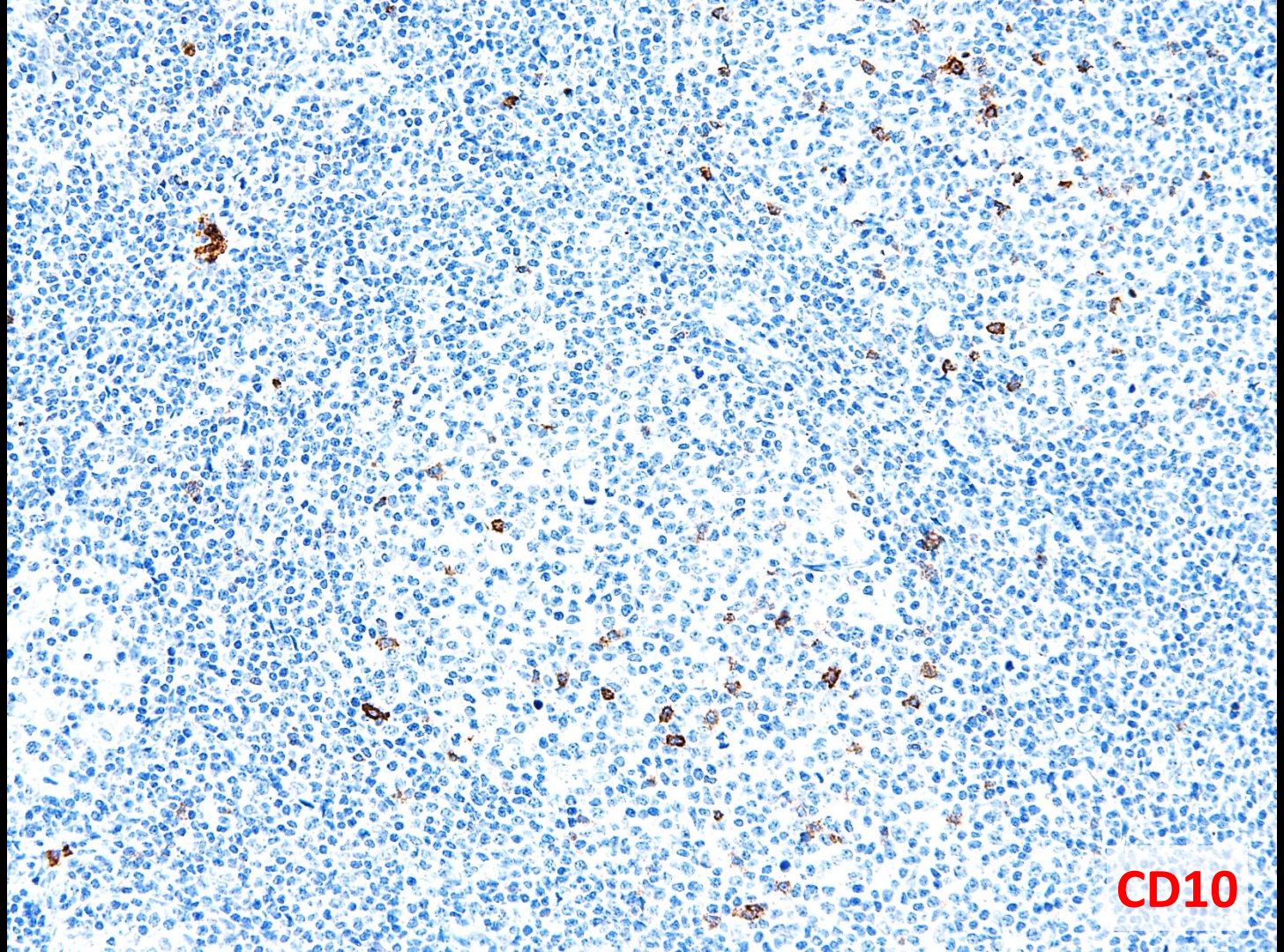
FIL FOLL12 and FOLLBIO studies
pathological review
(Code: 0673FOLL12)

For evaluation of the germinal center (GC) phenotype:

POSITIVE

NEGATIVE

- CD10


CD10

HISTOLOGICAL REVIEW

FIL FOLL12 and FOLLBIO studies
pathological review
(Code: 0673FOLL12)

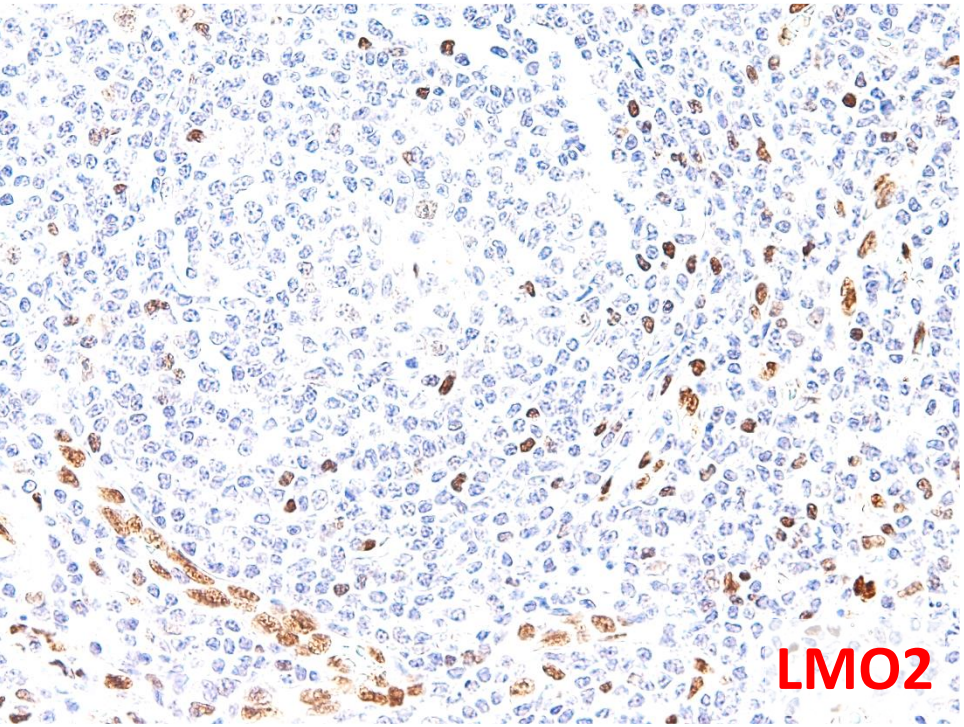
For evaluation of the germinal center (GC) phenotype:

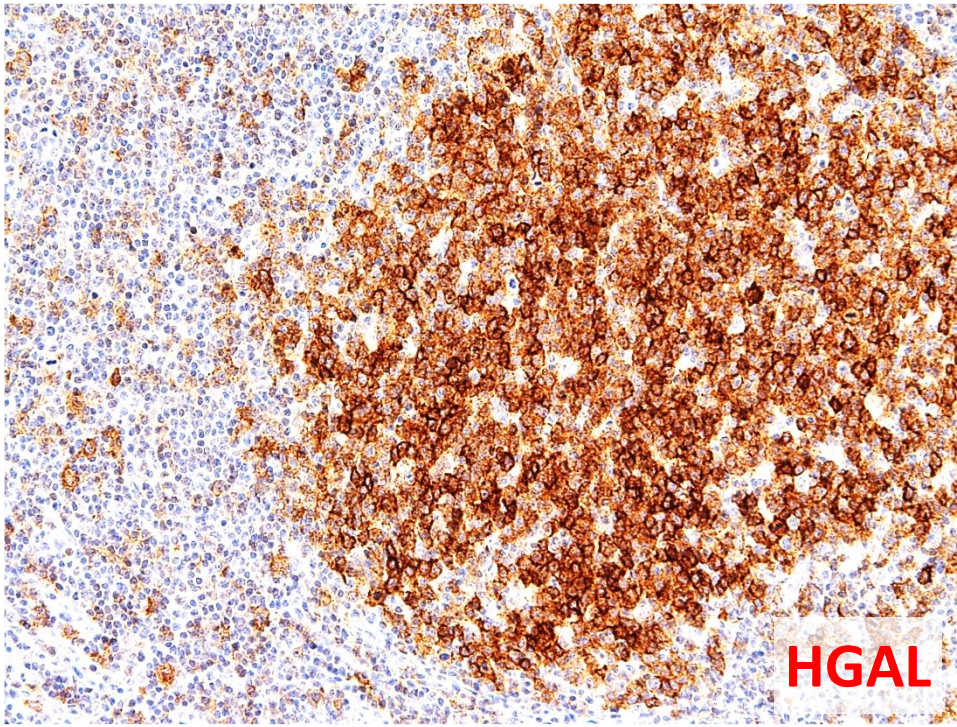
POSITIVE

- HGAL

NEGATIVE

- CD10
- LMO2


LMO2


HGAL

HISTOLOGICAL REVIEW

FIL FOLL12 and FOLLBIO studies
pathological review
(Code: 0673FOLL12)

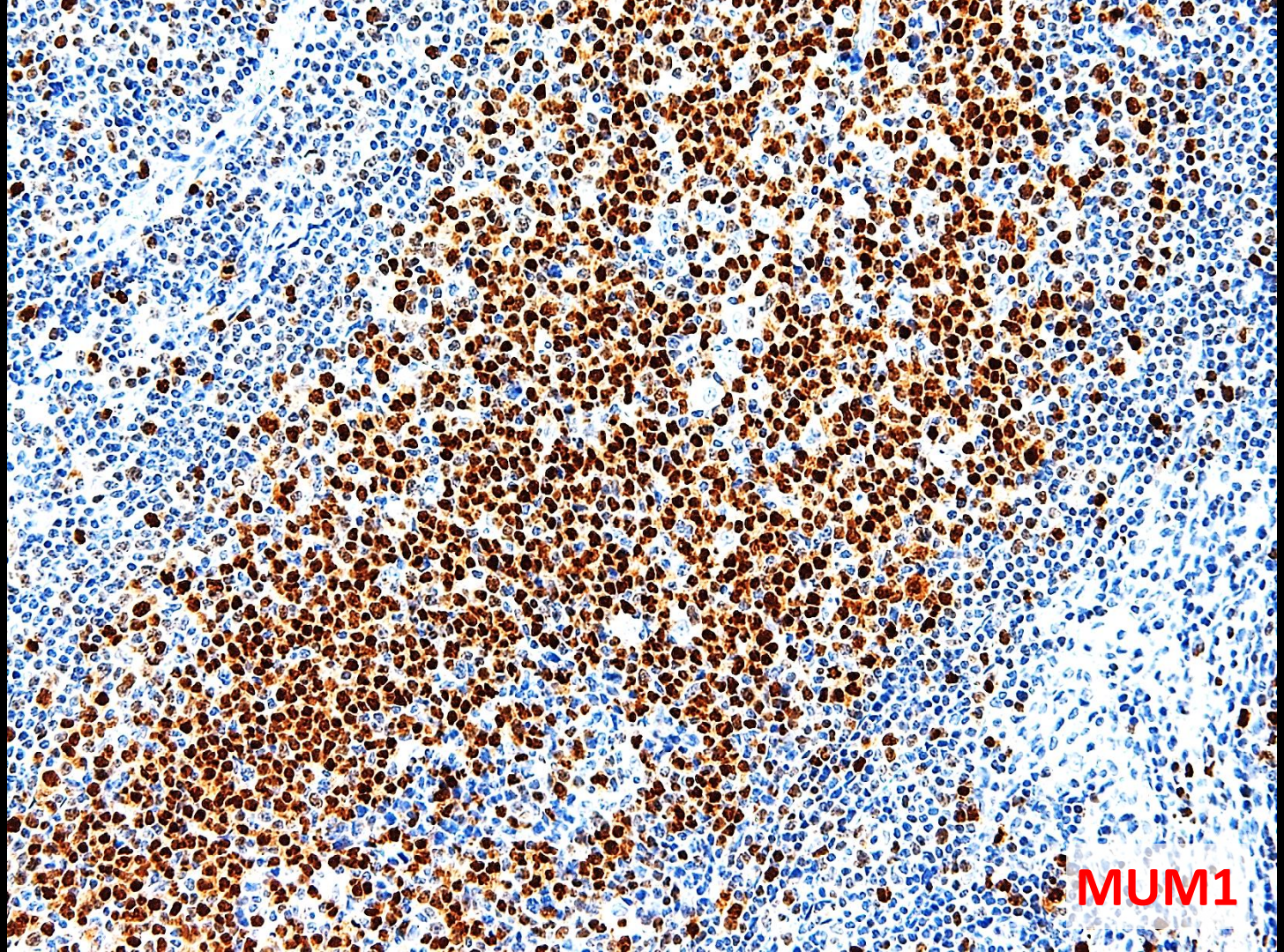
For evaluation of the germinal center (GC) phenotype:

POSITIVE

- HGAL
- BCL6
- MUM1

NEGATIVE

- CD10
- LMO2


MUM1

HISTOLOGICAL REVIEW

FIL FOLL12 and FOLLBIO studies
pathological review
(Code: 0673FOLL12)

For evaluation of the germinal center (GC) phenotype:

POSITIVE

- HGAL
- BCL6
- MUM1
- BCL2

NEGATIVE

- CD10
- LMO2

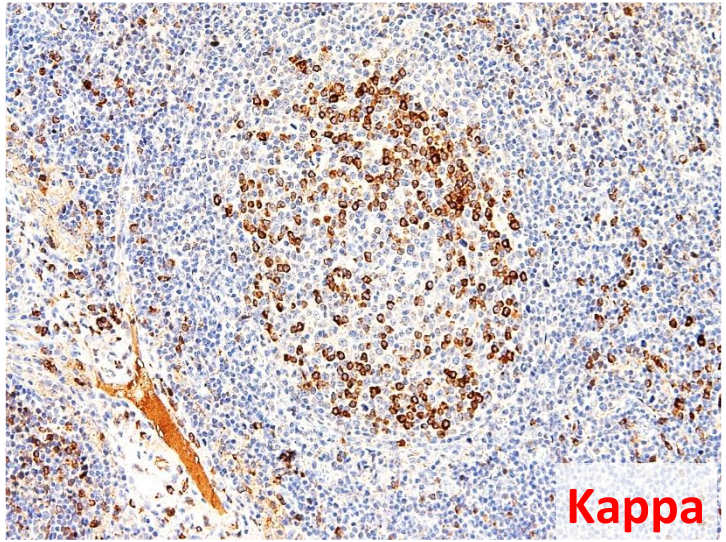
HISTOLOGICAL REVIEW

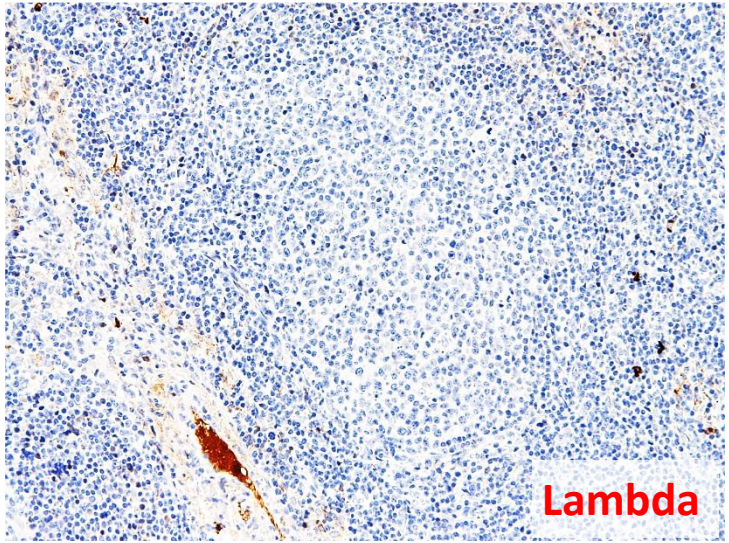
FIL FOLL12 and FOLLBIO studies
pathological review
(Code: 0673FOLL12)

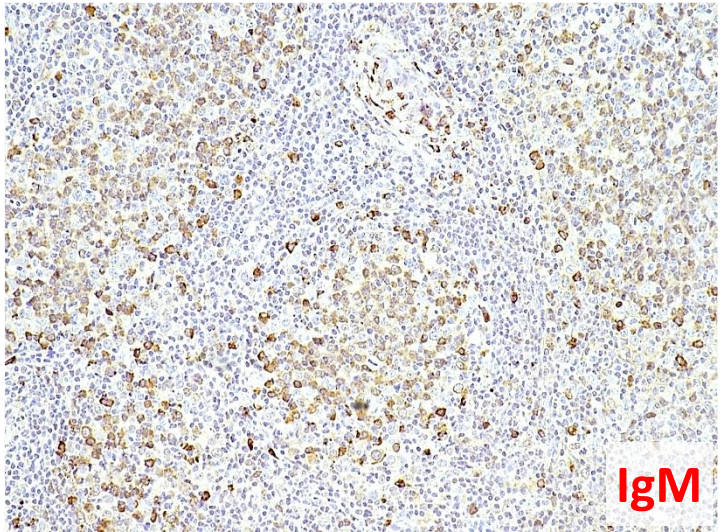
For evaluation of the germinal center (GC) phenotype:

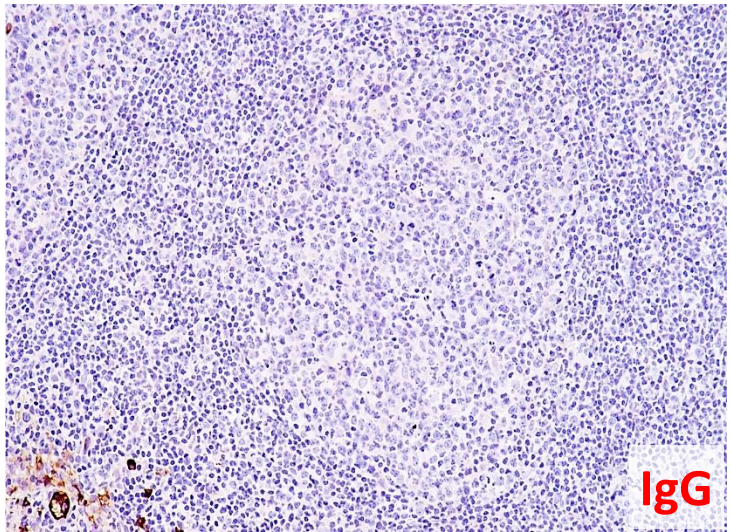
POSITIVE	NEGATIVE
• HGAL	• CD10
• BCL6	• LMO2
• MUM1	
• BCL2	

Monotypic kappa light chain


Kappa


Lambda


IgM


IgG

DIFFERENTIAL DIAGNOSIS:

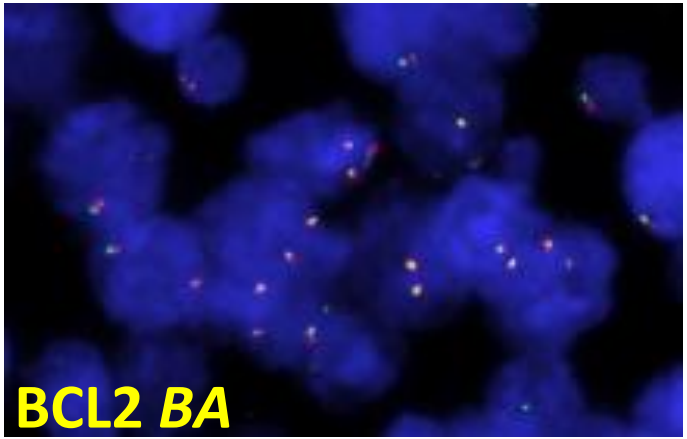
- Follicular lymphoma
- Large B-cell lymphoma with IRF4 rearrangement
- Marginal zone lymphoma
- Lymphoplasmacytic lymphoma

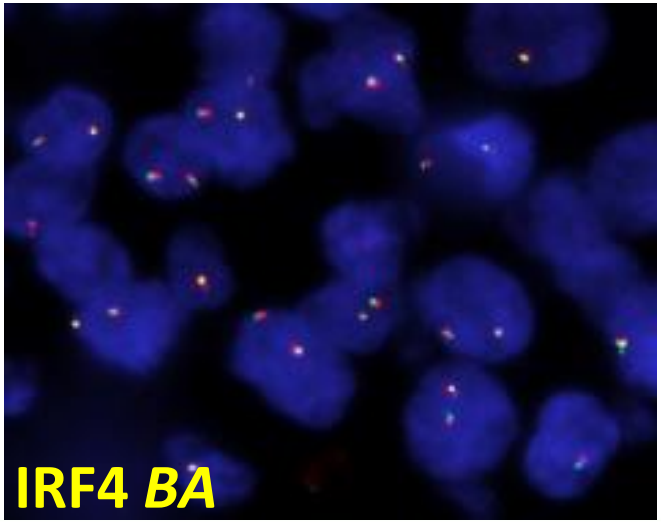
MOLECULAR STUDIES

FISH analysis:

BCL2 break apart probe: NEGATIVE FOR REARRANGEMENT

IRF4/DUSP22 break apart probe: NEGATIVE FOR REARRANGEMENT





MOLECULAR STUDIES

NGS analysis:

(targeted panel of 73 genes for B- and T-cell lymphomas):

- ***MYD88*** (NM_002468.4)
  c.728G>A, p.(Ser243Asn)
  VAF 40%
  S243N

- ***CD79B*** (NM_001039933.2)
  c.589T>G, p.(Tyr197Asp),
  VAF 11.6%
  Y197D

- ***CD79B*** (NM_001039933.2)
  c.590A>C, p.(Tyr197Ser),
  VAF 5.2%
  Y197S

- ***MYD88*** (NM_002468.4)

c.728G>A, p.(Ser243Asn) [VAF 40%]

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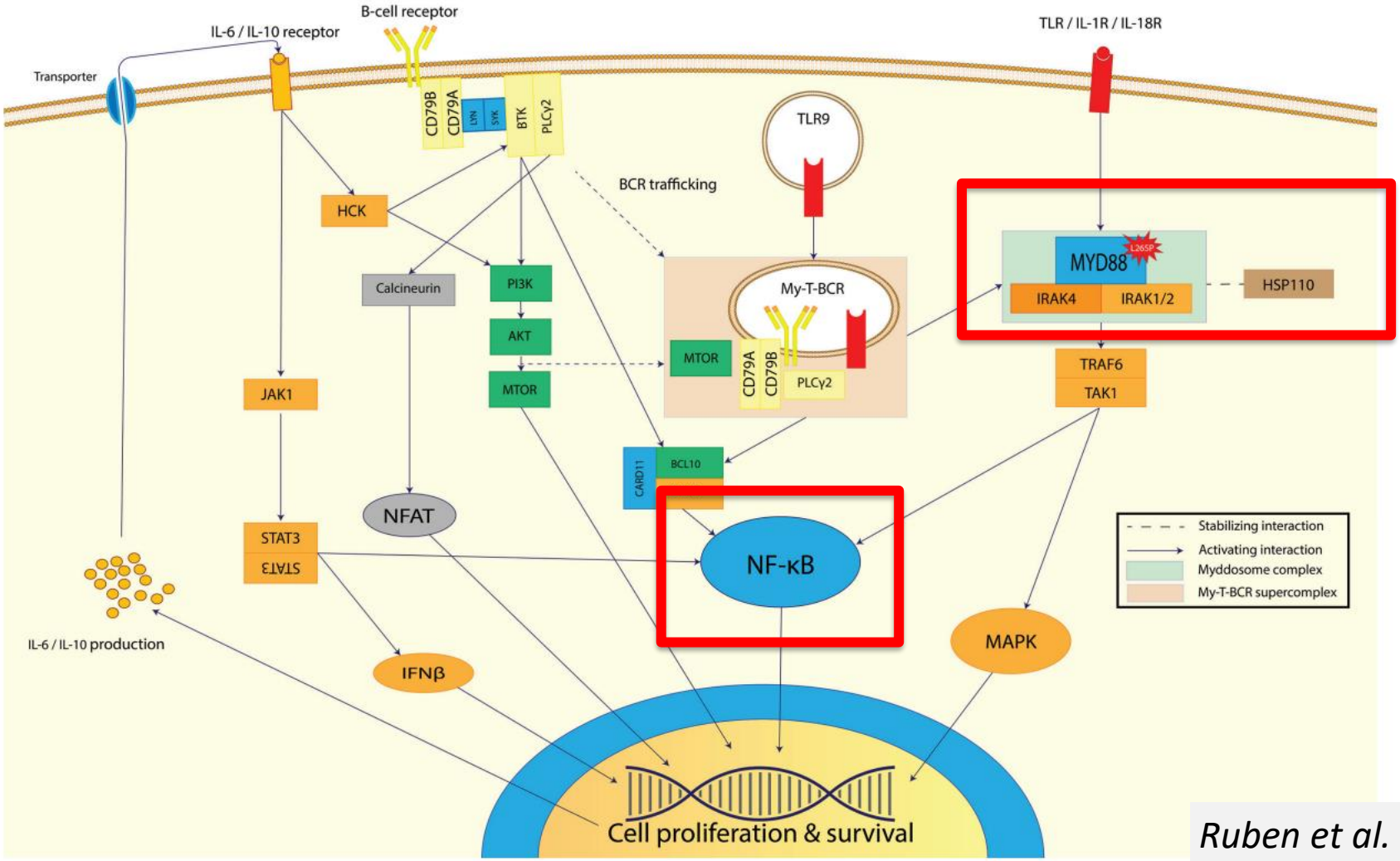
c.728G>A, p.(Ser243Asn) [VAF 40%]



Ruben et al. 2019

Br J Haematol. 2025 Jun;206(6):1604-1614. doi: 10.1111/bjh.20072. Epub 2025 Apr 20.

Development and characterization of the novel MYD88 mutated, 6q deleted BCWM.2 cell line for Waldenström macroglobulinaemia

Liu et al.

Oncotarget. 2016 Dec 17;8(5):7989–7998. doi: 10.18632/oncotarget.14008

Cani et al.

Next generation sequencing of vitreoretinal lymphomas from small-volume intraocular liquid biopsies: new routes to targeted therapies

Hematol Oncol. 2022 Dec;40(5):885-893. doi: 10.1002/hon.3073. Epub 2022 Sep 10.

Xie et al.

Clinical significance of MYD88 non-L265P mutations in diffuse large B-cell lymphoma

- ***CD79B*** (NM_001039933.2)
  c.589T>G, p.(Tyr197Asp),
  VAF 11.6%

- ***CD79B*** (NM_001039933.2)
  c.590A>C, p.(Tyr197Ser),
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- ***CD79B*** (NM_001039933.2)
  c.589T>G, p.(Tyr197Asp),
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  c.590A>C, p.(Tyr197Ser),
  VAF 5.2%
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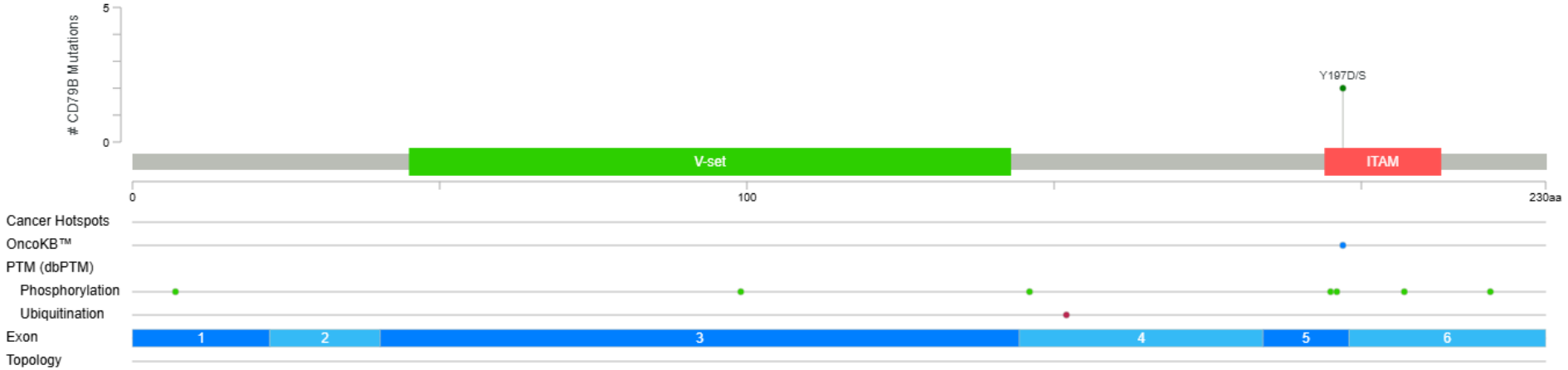
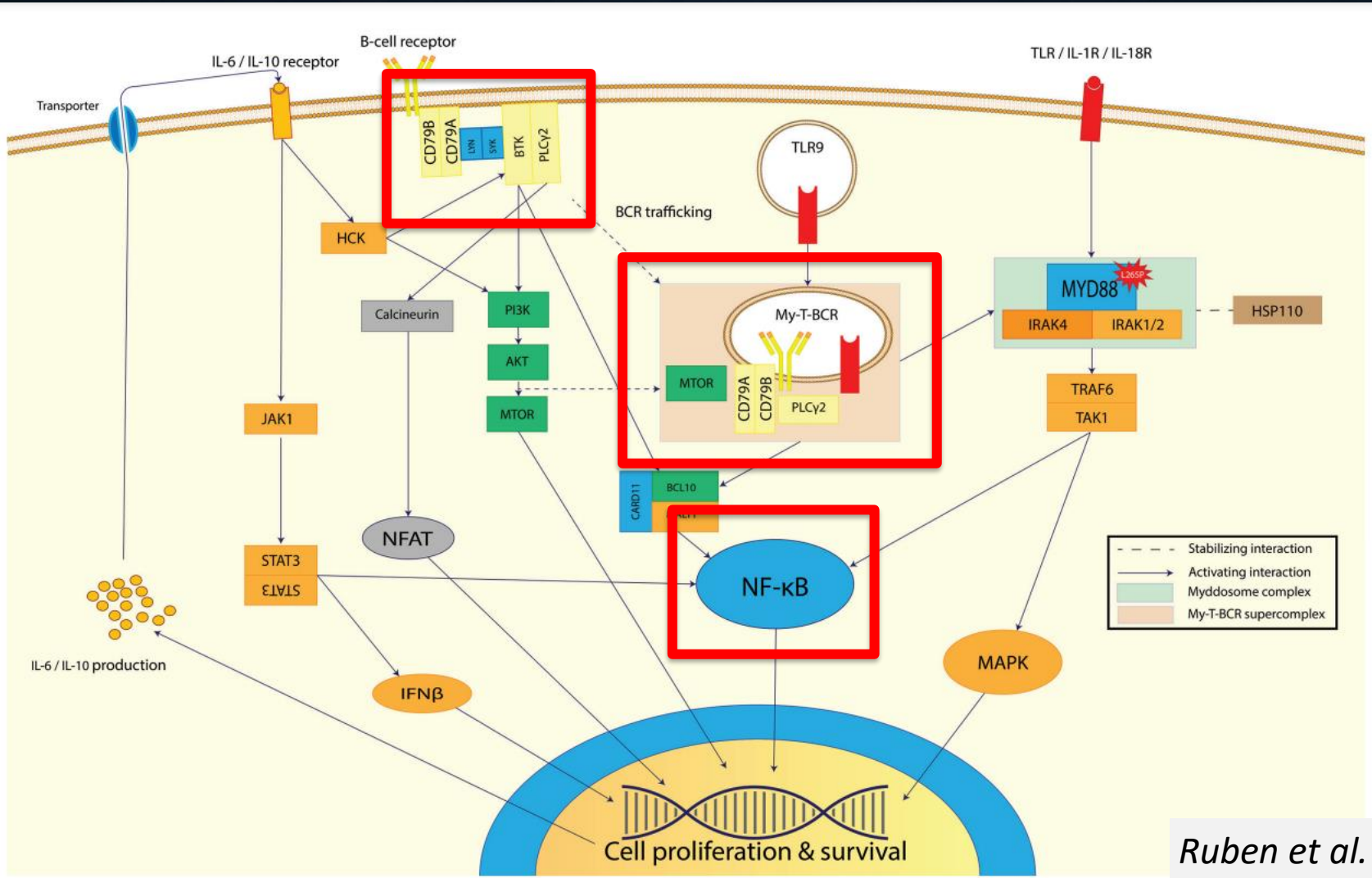




Ruben et al. 2019

Sample name	Gene name	Transcript	Primary Tissue	Tissue Subtype 1	Primary Histology	Histology Subtype 1	Pubmed ID	Zygosity	Somatic Status	Sample Type
2081158	CD79B	ENST00000392795.7	Haematopoietic and lymphoid	NS	Lymphoid neoplasm	Diffuse large B cell lymphoma	24444466	Unknown	Previously Reported	Tumour Sample
2081159	CD79B	ENST00000392795.7	Haematopoietic and lymphoid	NS	Lymphoid neoplasm	Diffuse large B cell lymphoma	24444466	Unknown	Previously Reported	Tumour Sample
2129657	CD79B	ENST00000392795.7	Haematopoietic and lymphoid	NS	Lymphoid neoplasm	Diffuse large B cell lymphoma	20054396	Heterozygous	Confirmed Somatic	Tumour Sample
2218477	CD79B	ENST00000392795.7	Haematopoietic and lymphoid	NS	Lymphoid neoplasm			Unknown	Previously Reported	Tumour Sample
2395155				al ous m	Lymphoid neoplasm	Primary central nervous system lymphoma	25347427	Unknown	Previously Reported	Tumour Sample
2395158				al ous m	Lymphoid neoplasm	Primary central nervous system lymphoma	25347427	Unknown	Previously Reported	Tumour Sample
2395161	CD79B	ENST00000392795.7	Haematopoietic and lymphoid	Central nervous system	Lymphoid neoplasm	Primary	25347427	Unknown	Previously Reported	Tumour Sample
2669256	CD79B	ENST00000392795.7	Haematopoietic and lymphoid	Breast	Lymphoid neoplasm	Diffuse large B cell lymphoma	28803429	Unknown	Previously Reported	Tumour Sample
2757961	CD79B	ENST00000392795.7	Haematopoietic and lymphoid	NS	Lymphoid neoplasm	Diffuse large B cell	28153771	Unknown	Confirmed Somatic	Tumour Sample

DLBCL

PCNSL

- ***CD79B*** (NM_001039933.2) c.590A>C, p.(Tyr197Ser), **Y197S**

c.590A>C, p.(Tyr197Ser) Y197S

FINAL DIAGNOSIS

- Histological evidence of monotypic B-cell lymphoma with "**terminal differentiation**"

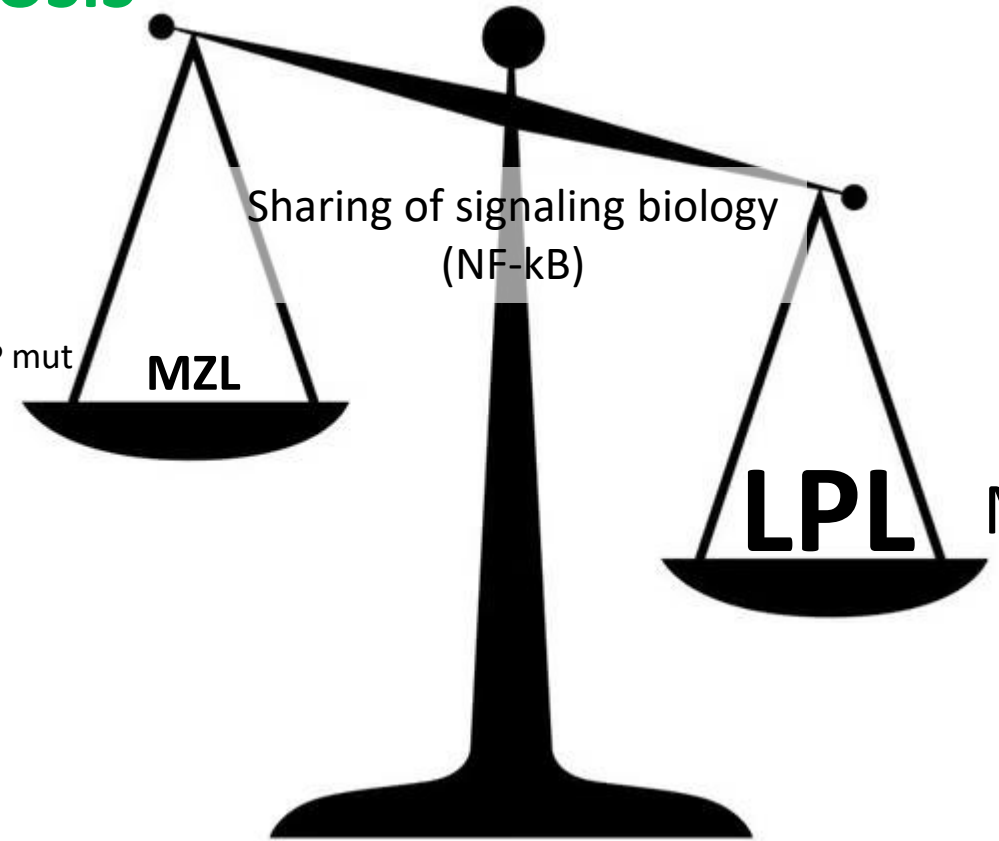
- Mutations **typically associated with post–germinal** center biology (i.e. on *MYD88* and *CD79B*)

- **Unconfirmed diagnosis of follicular lymphoma**

- **Lymphoma with plasmacytic differentiation**

FINAL DIAGNOSIS

- NOTCH2/KLF2/TNFAIP mut
- trisomy 3 / del7q
- MYD88/CD79B WT



MYD88/CD79B

Thanks

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Dr.ssa Emma Albertini
Dr.ssa Piera Balzarini
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Dr.ssa Francesca Filippini

Hematopathology Research Lab

Prof. William Vermi
Dr.ssa Daniela Medicina
Dr.ssa Anna Galvagni
Tecnici di Laboratorio

Molecular Pathology Lab

GIUSTIFICAZIONI BIOLOGICHE AL LPL

Le mutazioni nell'ITAM (Y196) determinano un'attivazione cronica del BCR e un conseguente aumento del NF-κB,

MYD88 S243N, pur non essendo la canonica L265P, minio TIR ed è stata riportata in neoplasie B mature come nte del pathway NF-κB."

La mutazione Gain of function (NF-kB cronico) (come con L256P) e quindi biologicamente coerente con un Linfoma Linfoplasmacitico

ao Y et al. The genomic landscape
haracterized by highly recurring
s, and small somatic deletions
. Blood 2014; 123: 1637–1646.

The 2014 study by Hunter et al. reports validated somatic **CD79B mutations in 2 out of 30 (7%) Waldenström macroglobulinemia patient samples,** specifically identifying missense mutations that often affect the **ITAM domain**. The study highlights these findings, **noting their presence within the context of MYD88-mutated cases** and their role as recurring somatic events, as stated in the text: "Other genes with validated somatic mutations in this series of patient samples included: ARID1A (5 of 30; 17%), CD79B (2 of 30; 7%), TP53 (2 of 30; 7%), MYBBP1A (2 of 30; 7%)...".

Figeac M, Herbaux C, Marot G et al.
in Waldenström macroglobulinemia.

The study by Poulain et al. (2016) highlights that **CD79B/A mutations (BCR pathway) are mutually exclusive to CXCR4 mutations** within Waldenström Macroglobulinemia, suggesting distinct genomic subgroups. The researchers found that CXCR4 mutations do not occur in the same clones as CD79B/A mutations, using this distinction to characterize clonal evolution

Chillón MC, García-Mateo A,
Waldenstrom macroglobulinemia by
uteen genes in a series of 61

Nello studio di Jimenez et al. (Blood 2015), il **CD79B risulta mutato nell'8% dei pazienti** analizzati tramite NGS, evidenziando il ruolo del gene nel profilo genetico della Macroglobulinemia di Waldenström.