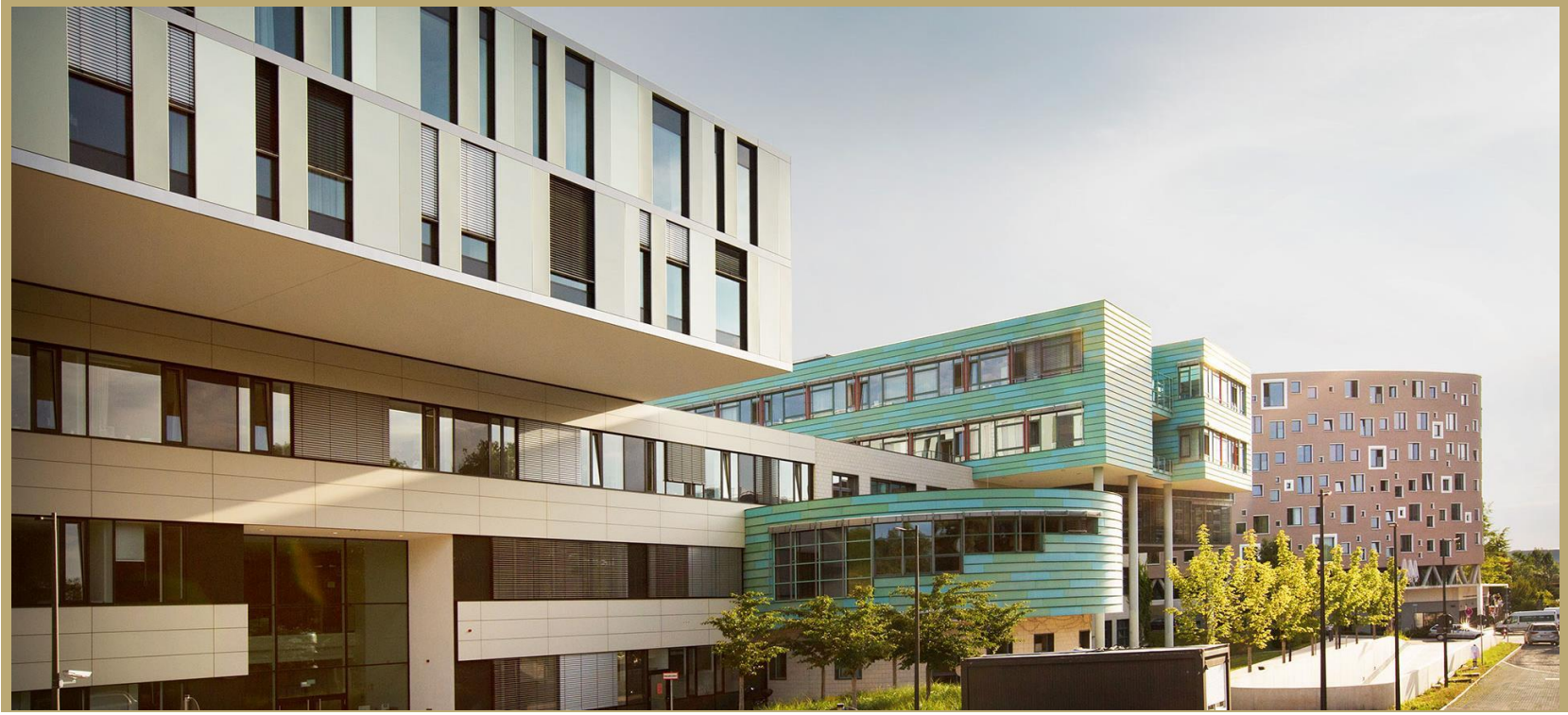
Follicular lymphoma, how many diseases?



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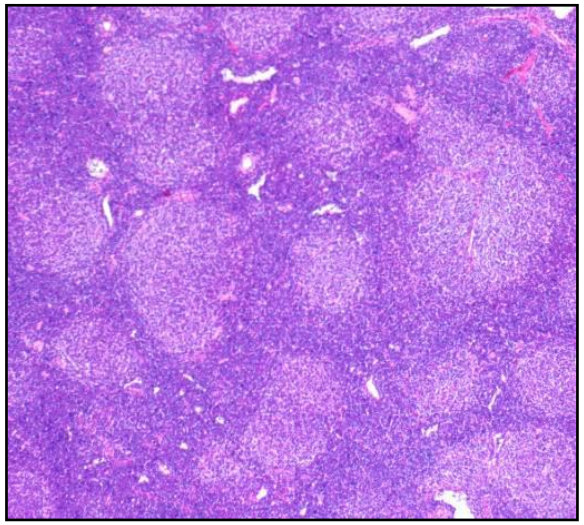
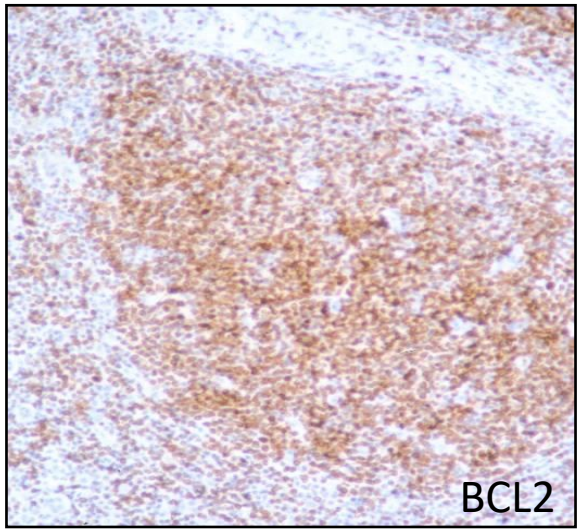
Tübingen

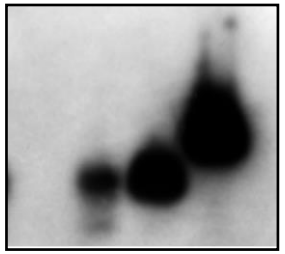
Follicular lymphoma





Morphology: Follicular proliferation of centrocytes and centroblasts associated with FDC

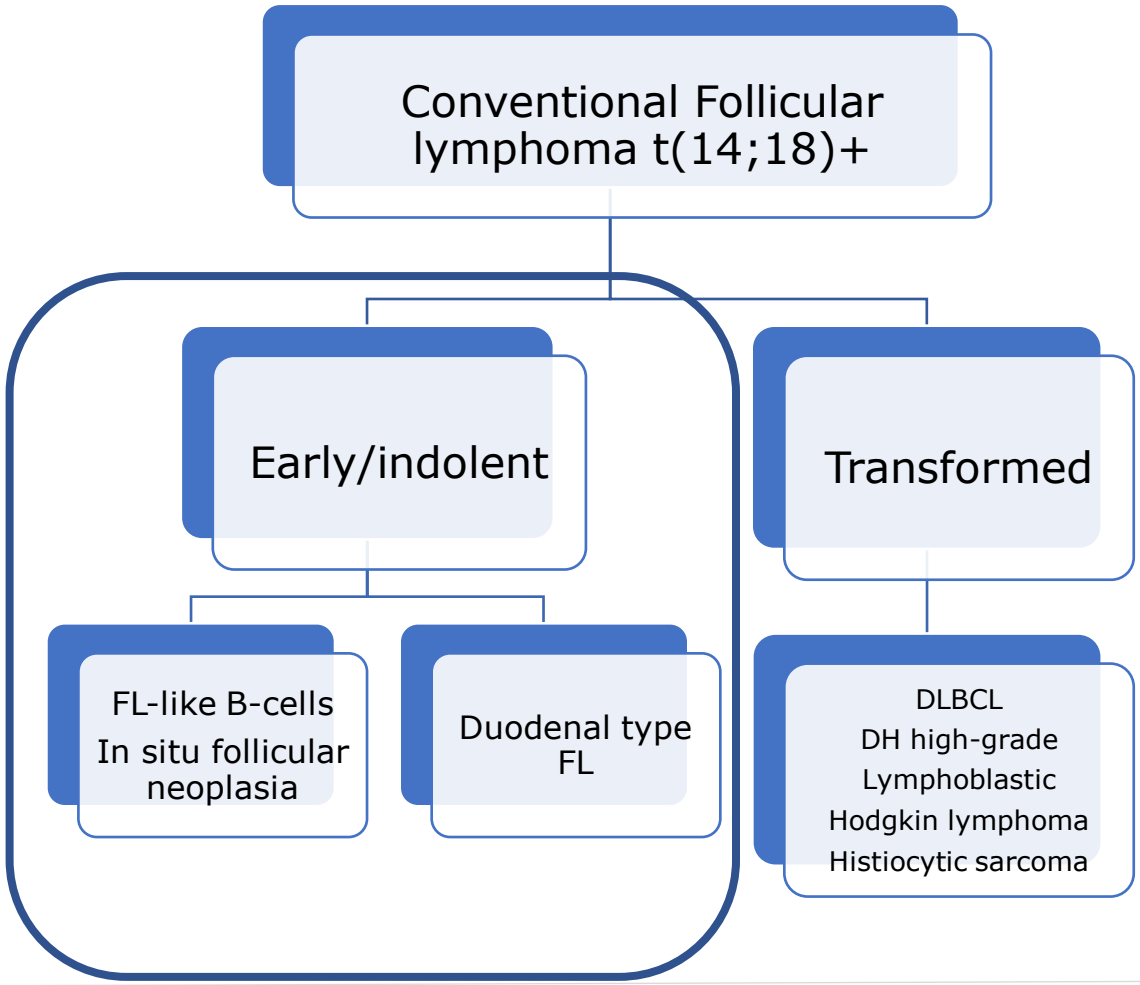
Immunophenotype: CD20+, CD19+, CD79a+
IgM, IgG, IgA, CD10+, BCL-2+, BCL-6+,
LMO2+, HGAL+, MEF2B+, EZH2+, GCET1+

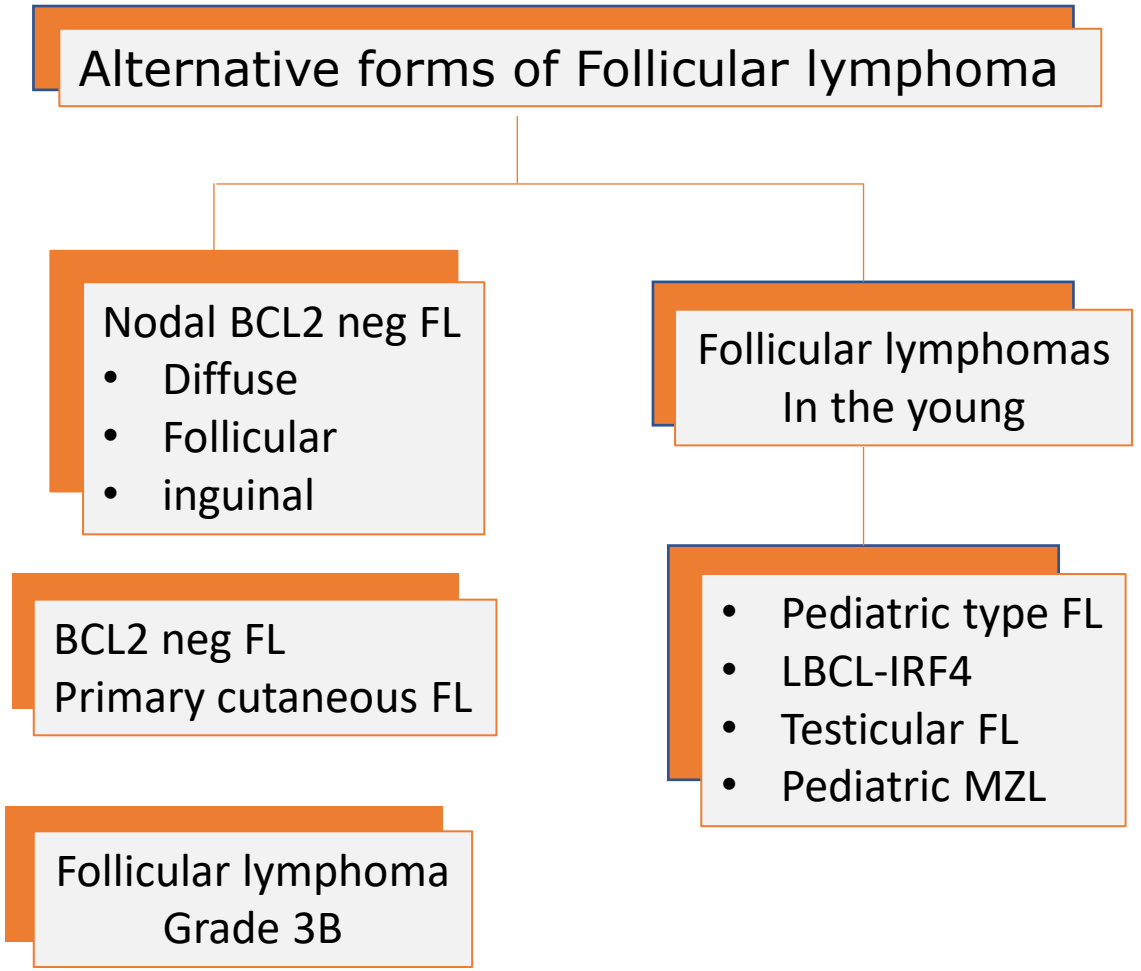


Genetics: JH/BCL-2 rearrangement
t(14;18); somatic mutations in VH

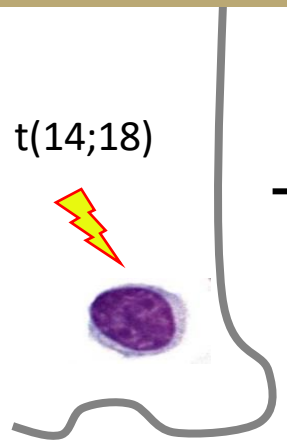
Clinical: Adults, indolent course but generally incurable. Most patients present with advanced stage disease, III/IVA

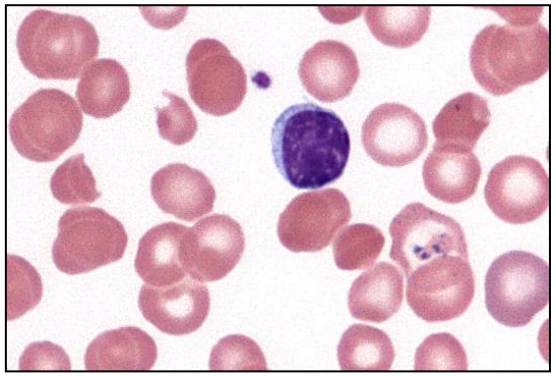
Evolving Spectrum of Follicular lymphoma





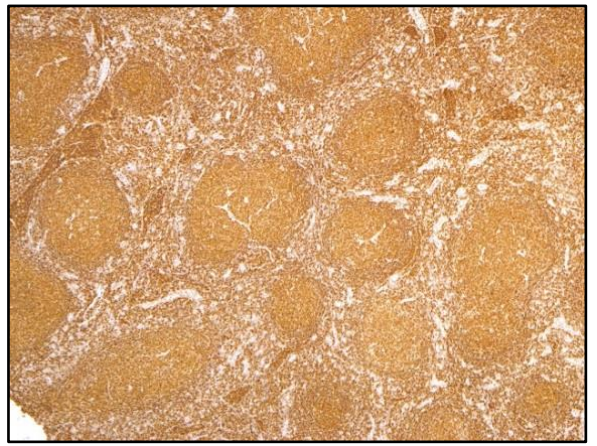
Follicular lymphoma pathogenesis

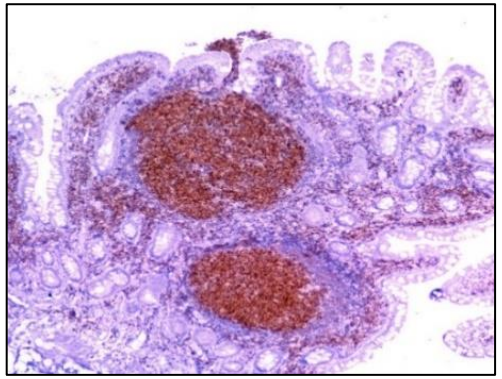


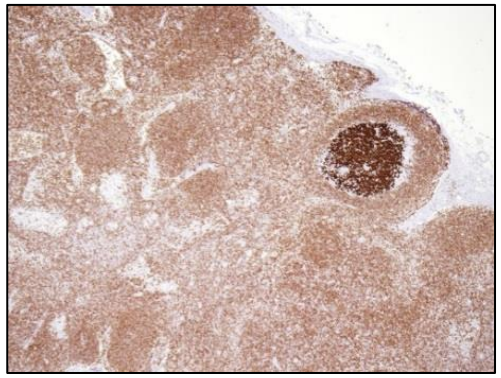


FL-like B-cell in healthy individuals
- t(14;18)+
- SHM
- CSR
- Intense trafficking

<0.01%







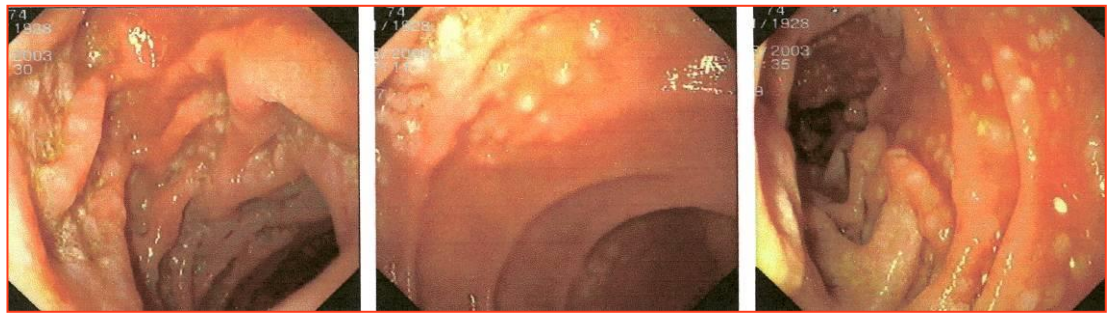
~2-3%

Duodenal -type follicular lymphoma
- Intestinal localized disease
- t(14;18)+
- Low level CNAs
- *CREBBP, TNFRSF14, EZH2* mutations
- Low frequency *KMT2D* mutations

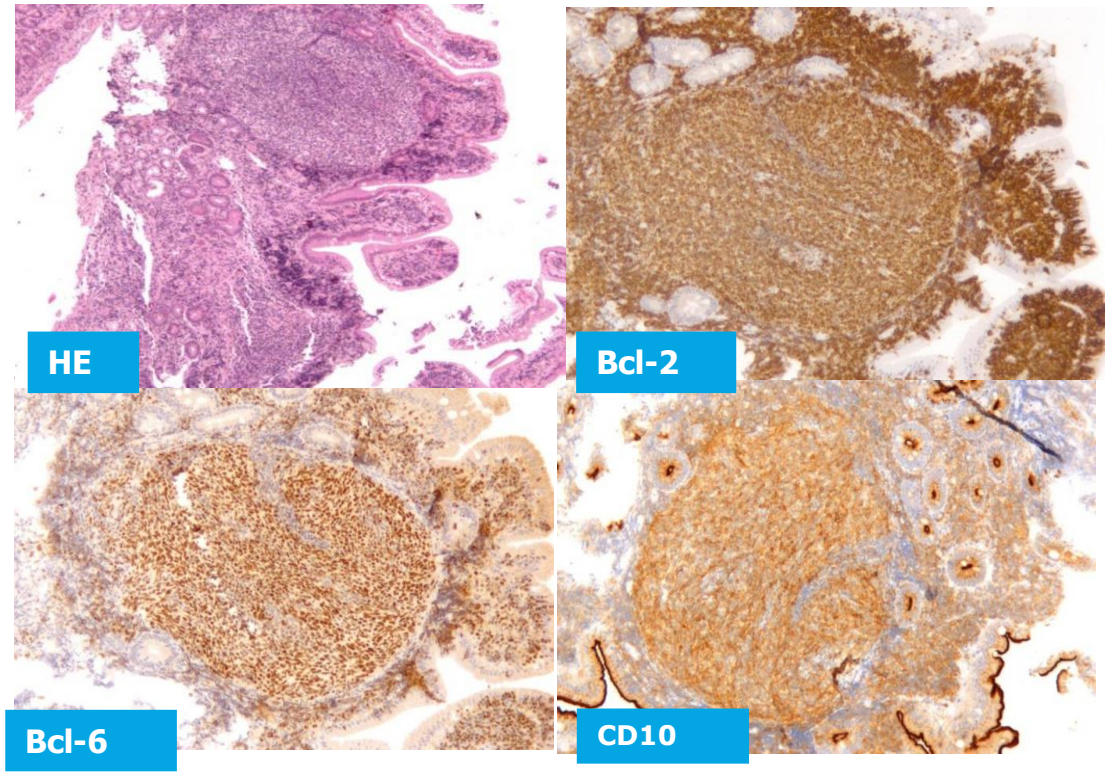
In-situ follicular neoplasia
- Nodal localized disease
- t(14;18)+
- Low level CNAs
- *CREBBP, TNFRSF14, EZH2* mutations
- Low frequency *KMT2D* mutations

Conventional folllicular lymphoma
- Systemic disease
- t(14;18)+
- High level CNAs
- *CREBBP, TNSF14, EZH2, BCL2* mutations
- Frequent mutations in *KMT2D*

Duodenal-type follicular lymphoma

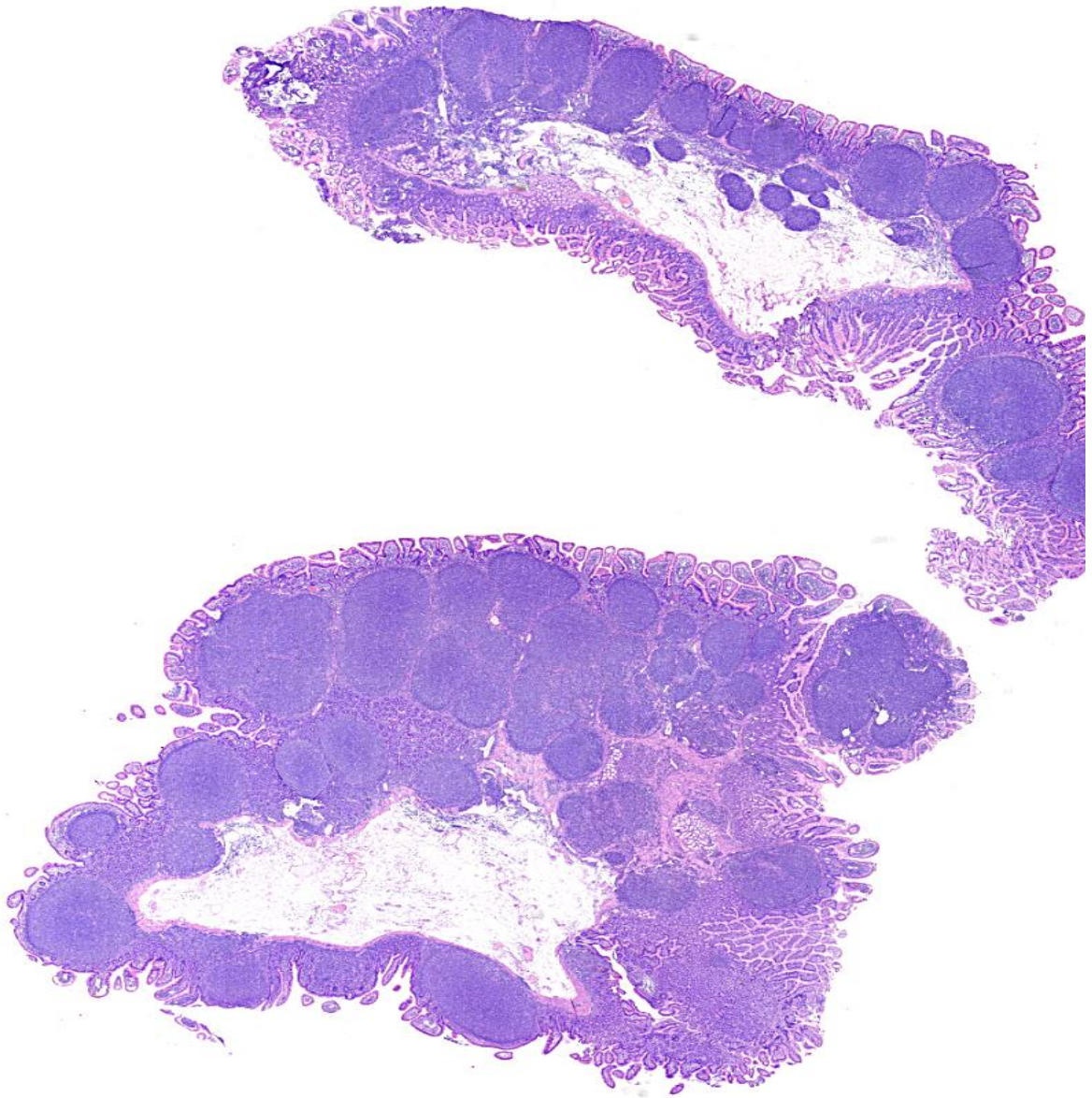


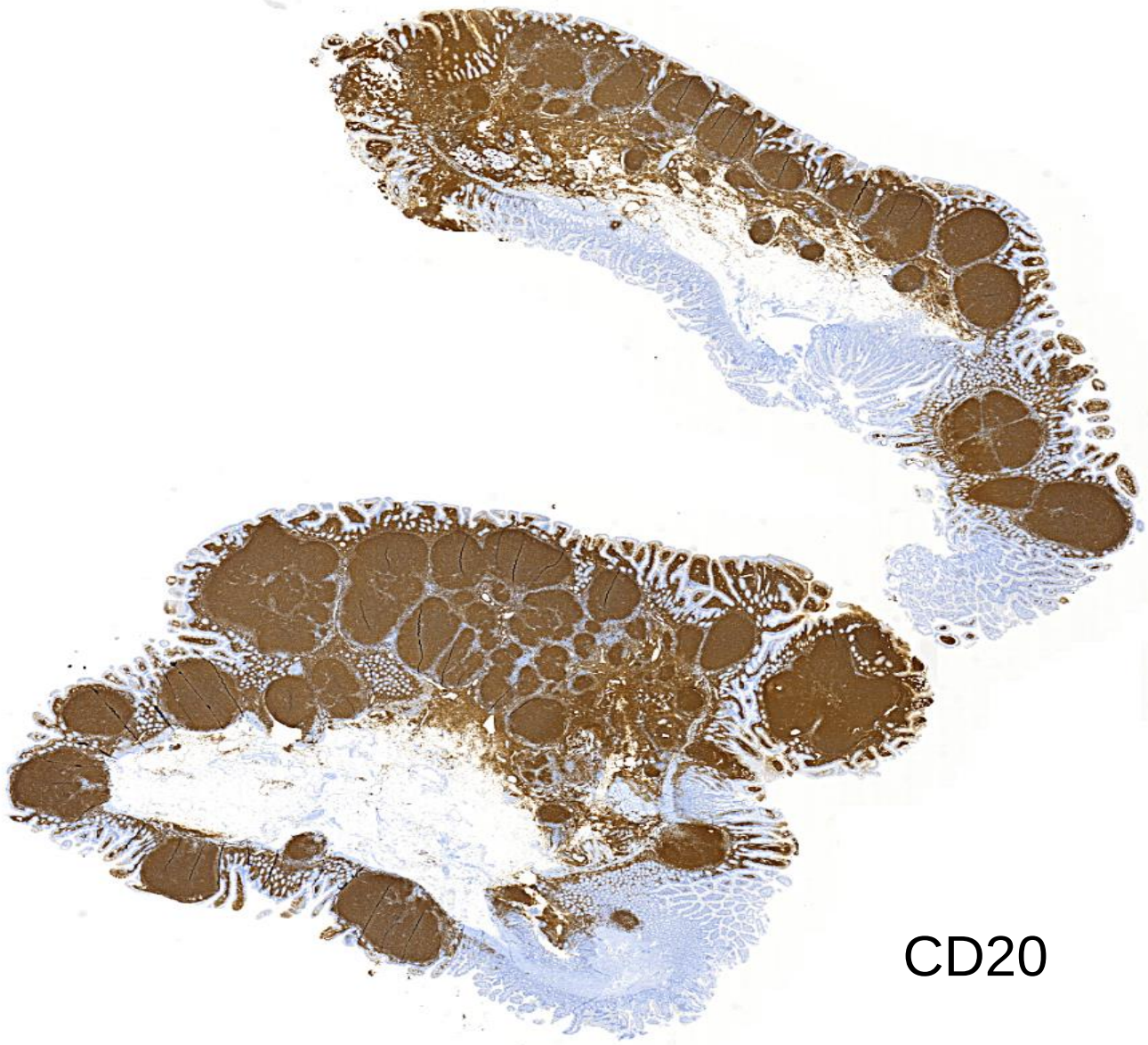
- Duodenal type FL is often diagnosed accidentally
- Is confined to mucosa/submucosa (stage IE citologically grade 1/2)
- Rarely patients develop nodal disease
- No large cell transformation
- Features similar to in situ follicular neoplasia
- Therapy: watch & wait or radiotherapy
- t(14;18) translocation is present



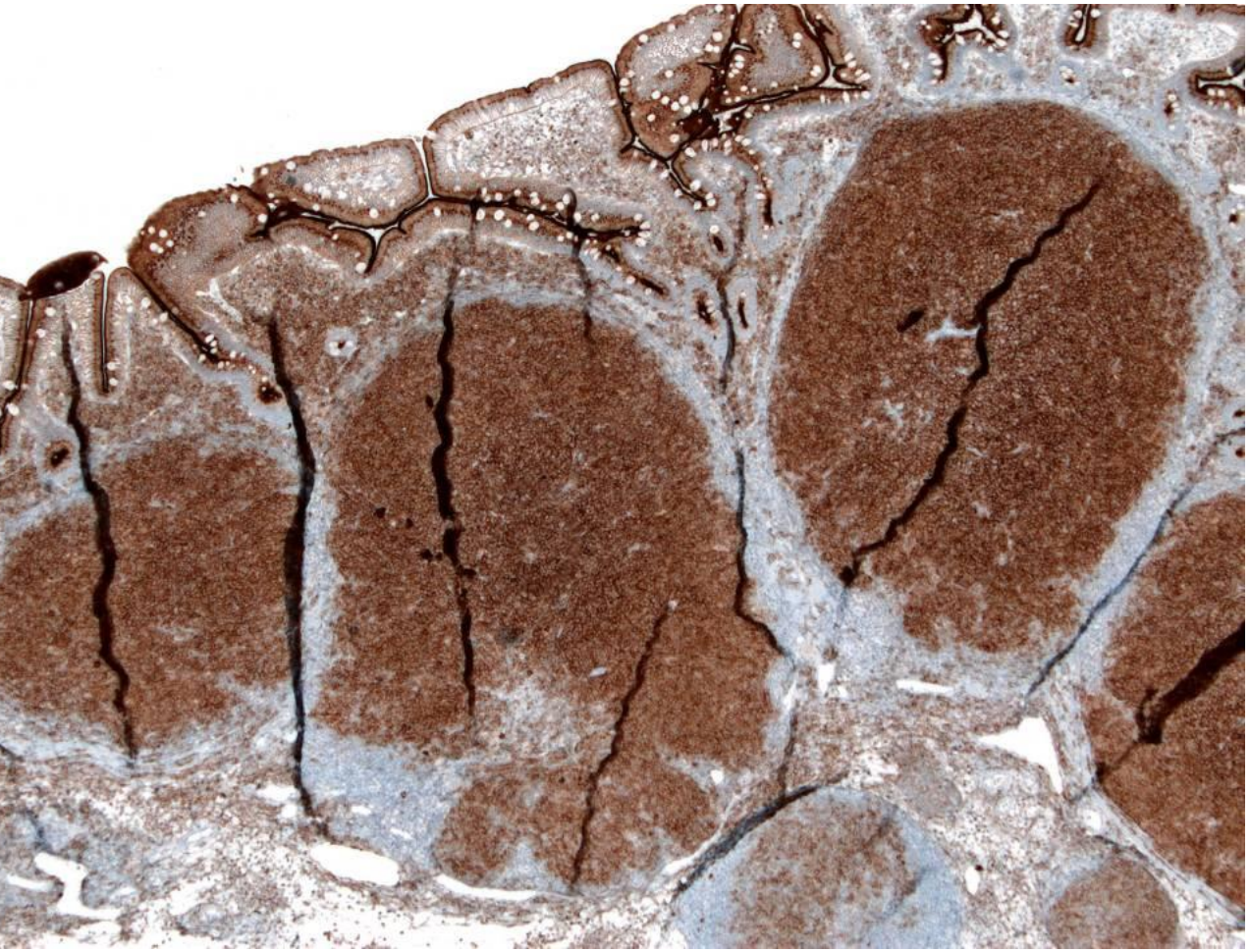
Schmatz AI et al., J Clin Oncol 2011, 29:1445

Morphological features

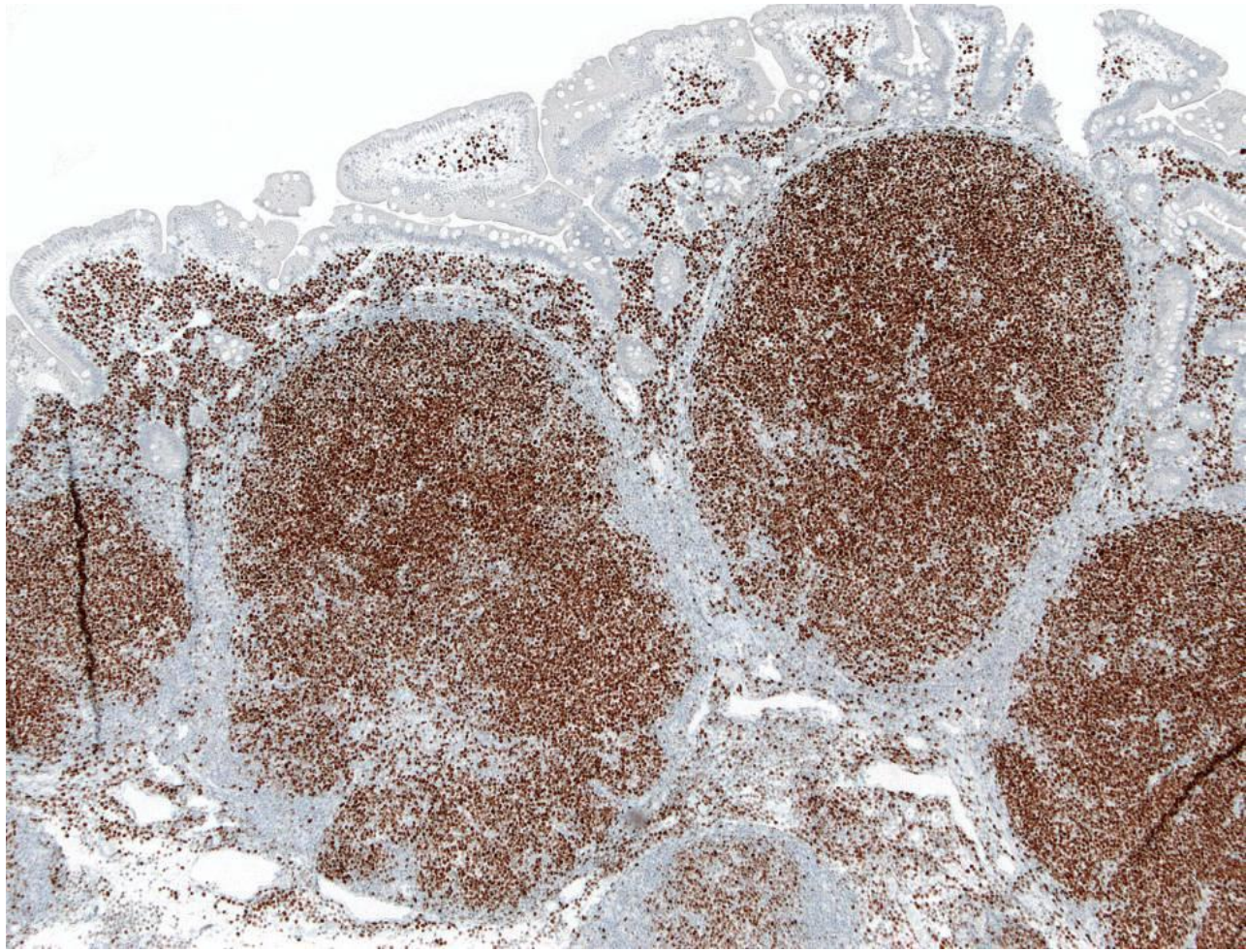




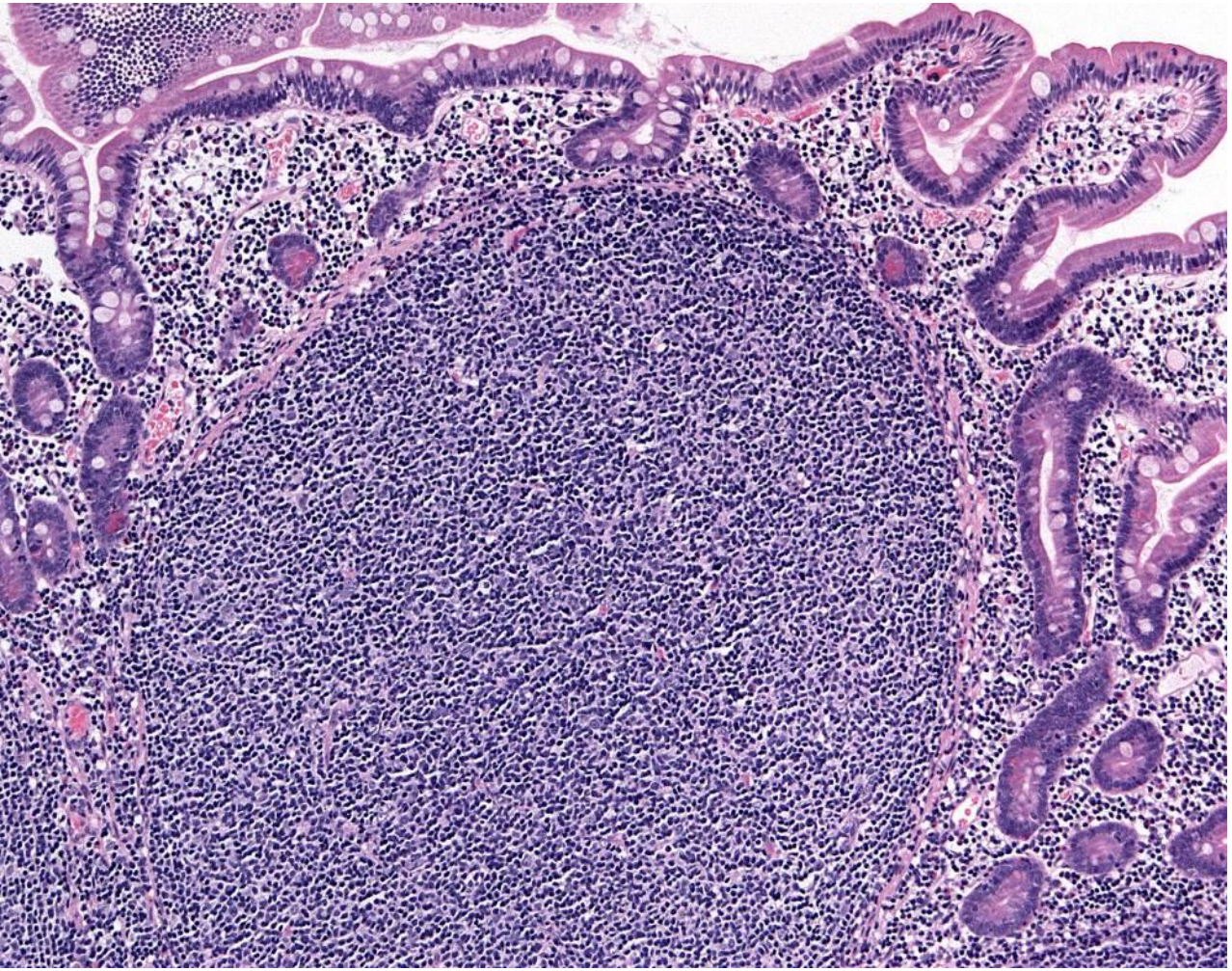
CD20

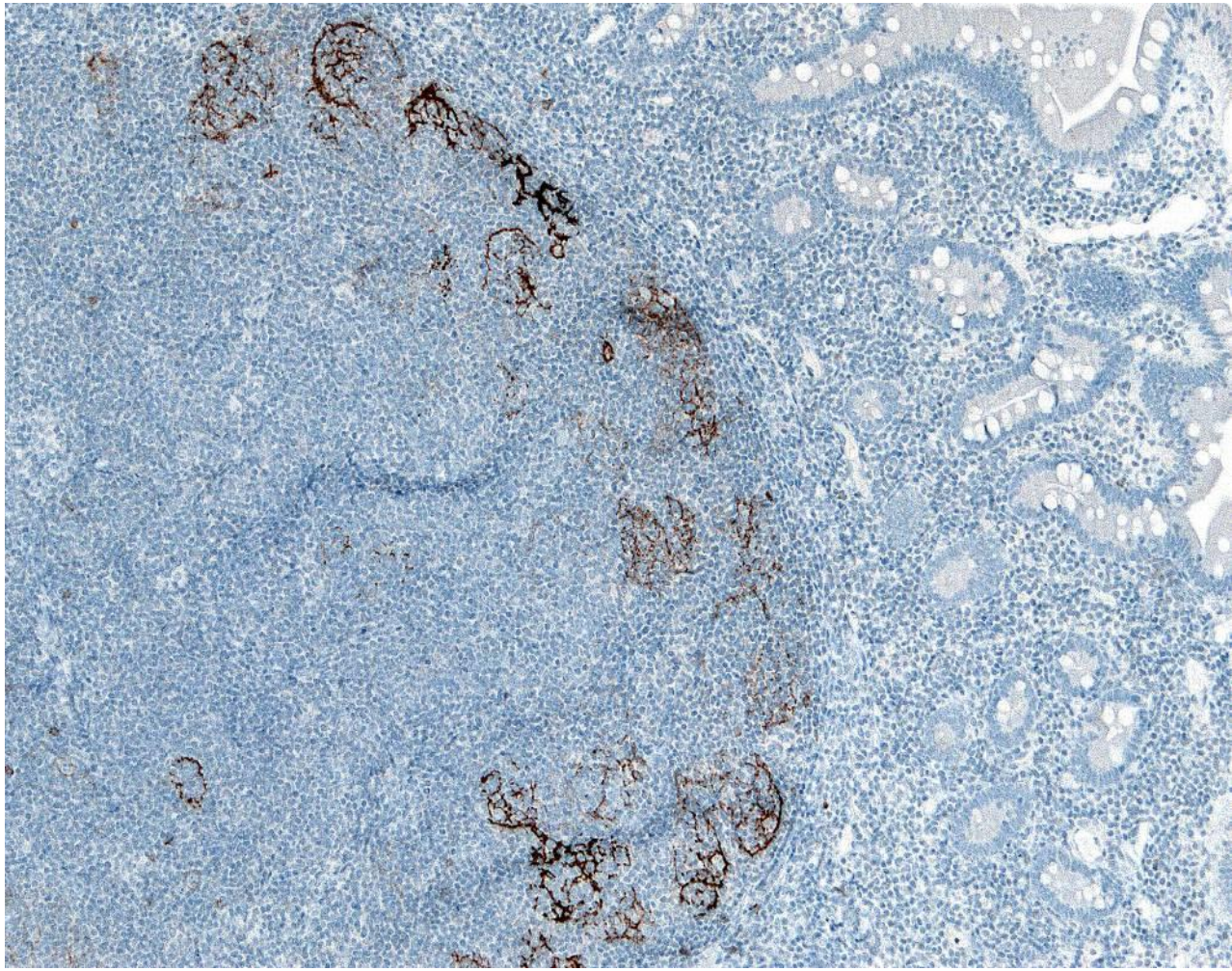


CD10



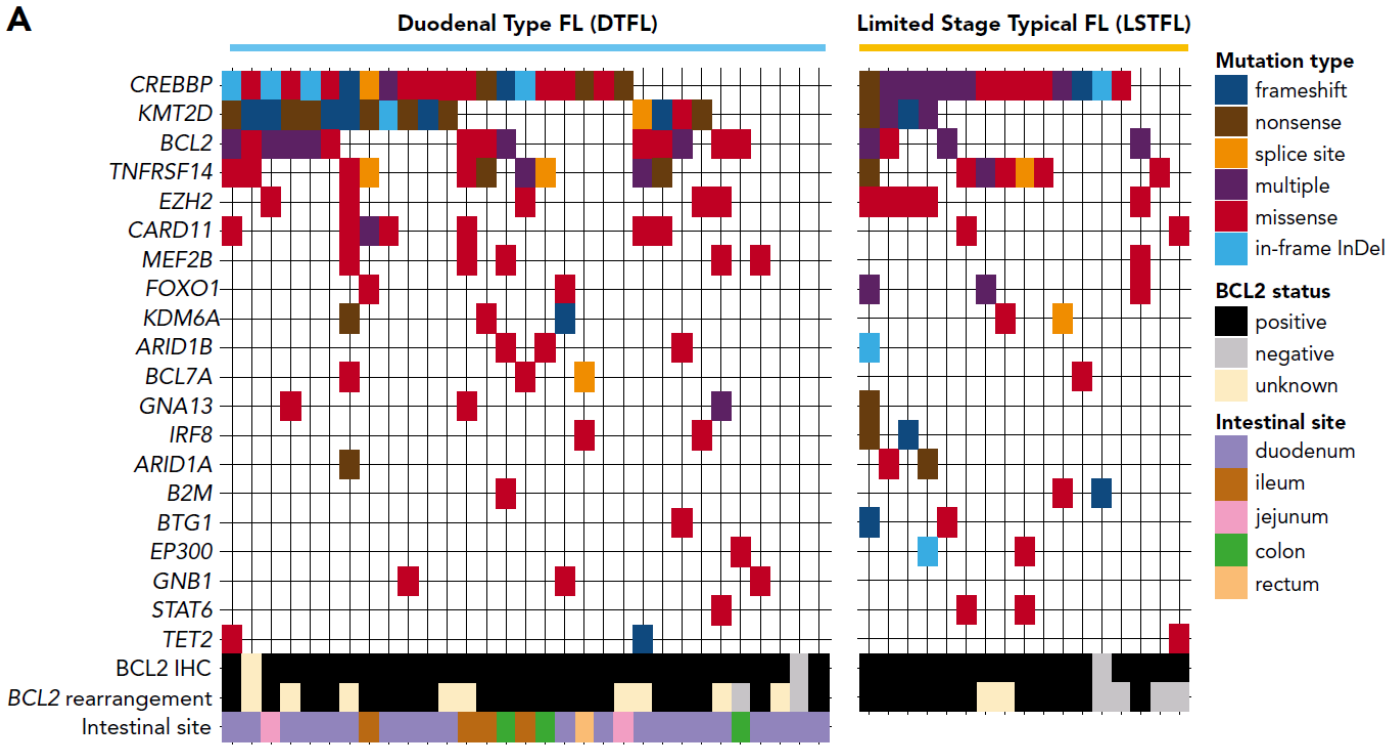
BCL6





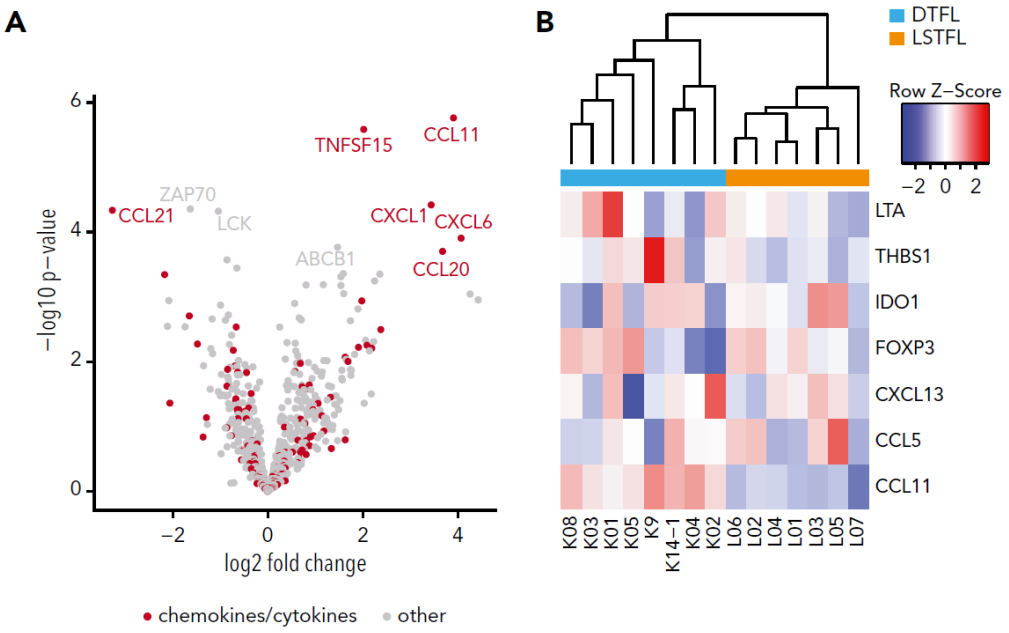
CD23

Duodenal-type follicular lymphoma



- Similar to ISFN the most frequent gene mutation is *CREBBP*
- The mutation frequencies were not different from nodal cFL
- Less multiple/biallelic *KMT2D* mutations

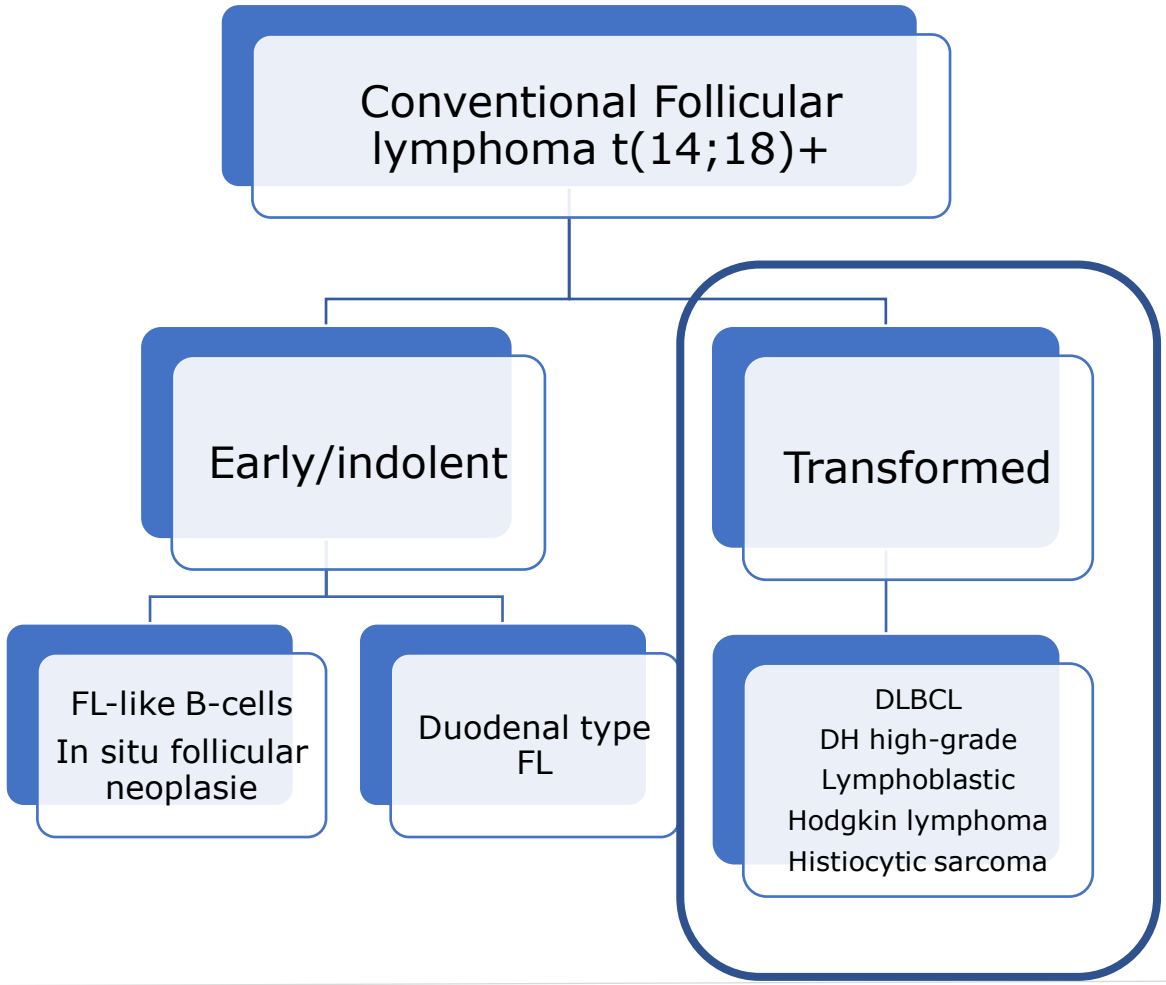
High CCL20 expression recruits proinflammatory Th17 cells

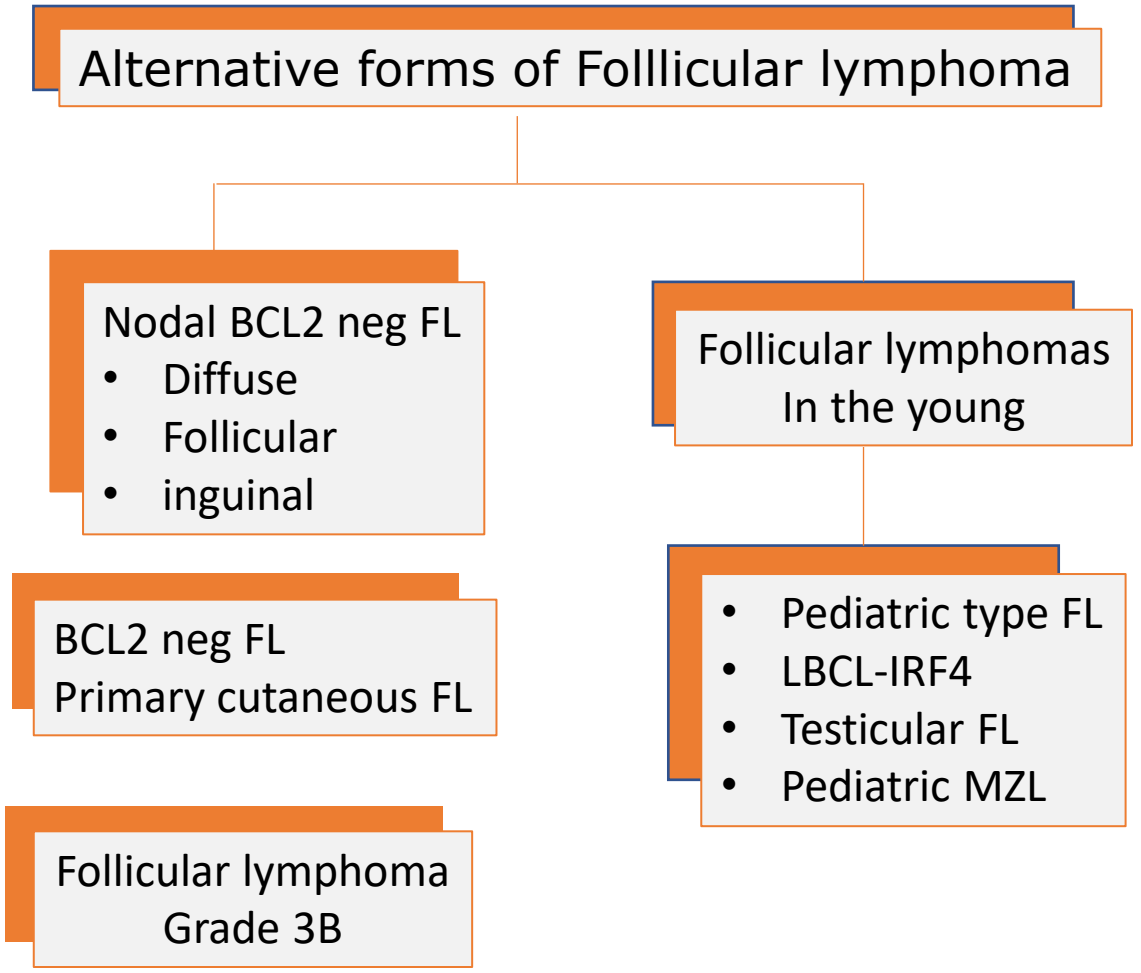


The immune microenvironment of DTFL is distinct from nodal FL and characterized by a chronic inflammation gene signature

blood® 18 OCTOBER 2018 | VOLUME 132, NUMBER 16

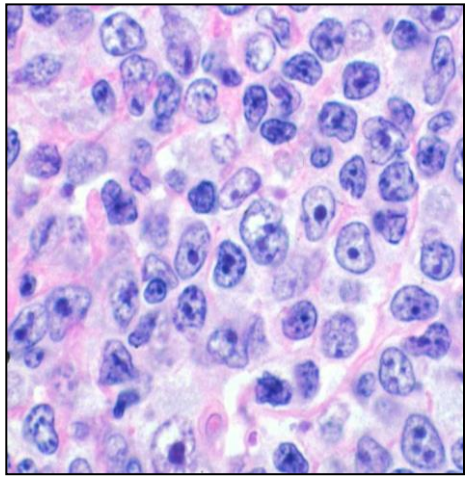
Evolving Spectrum of Follicular lymphoma



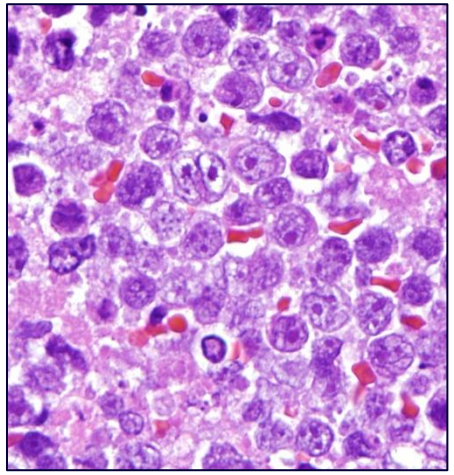


Transformed follicular lymphoma

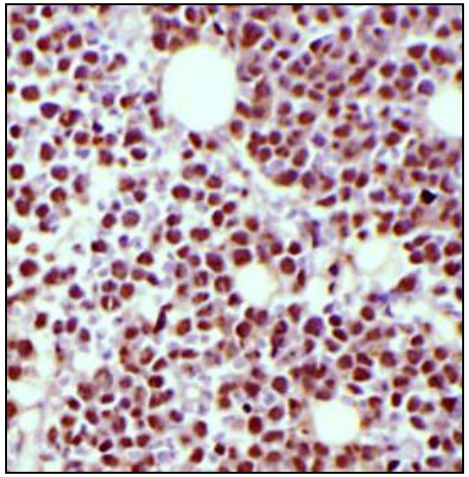
Cases show clonaly identity and retain the *BCL2* R



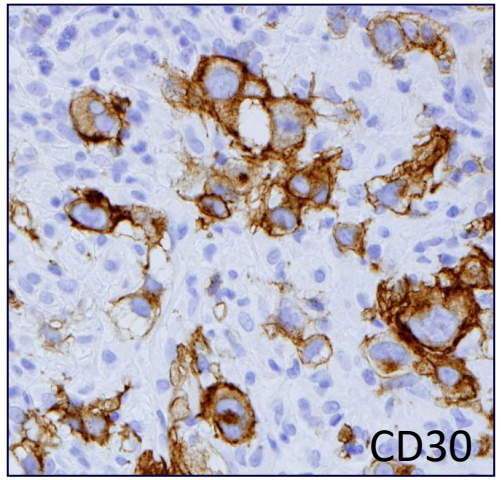
DLBCL
TP53



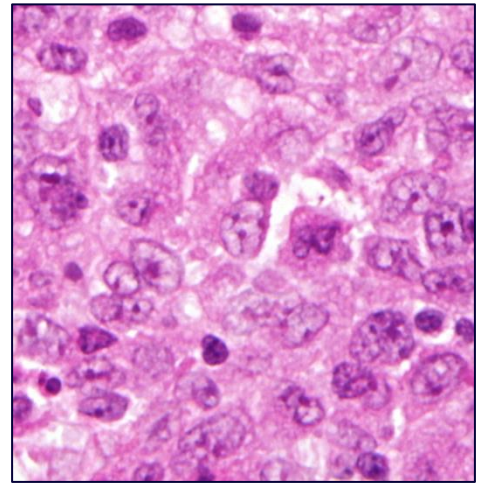
High-grade BCL
Double/triple hit
BCL2/MYC - R



B-ALL/LBL TdT+
MYC - R

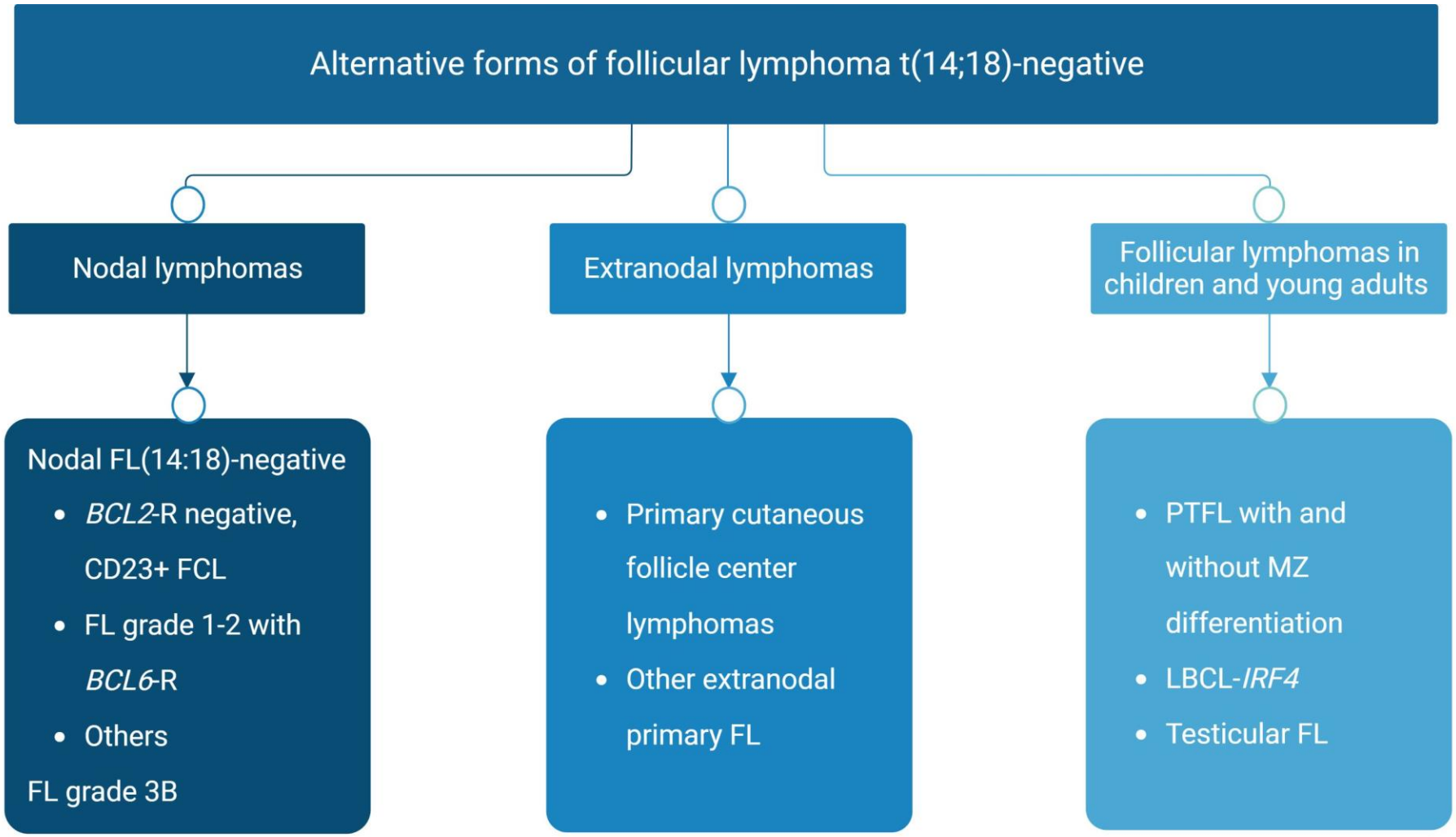


CHL



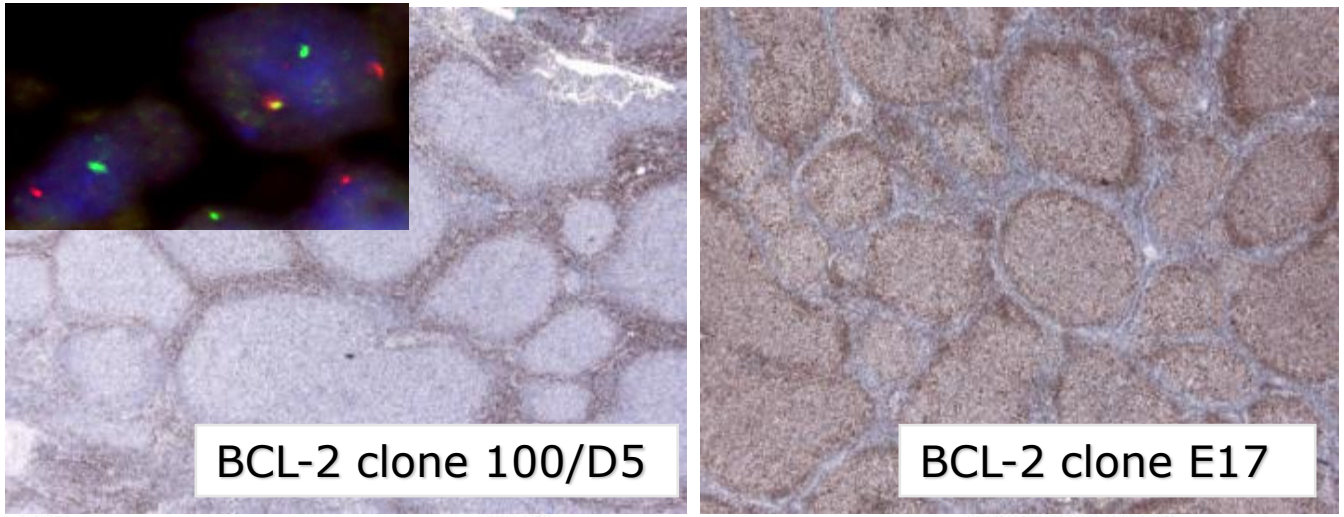
Histiocytic/
Dendritic sarcoma

Evolving Spectrum of Follicular lymphoma

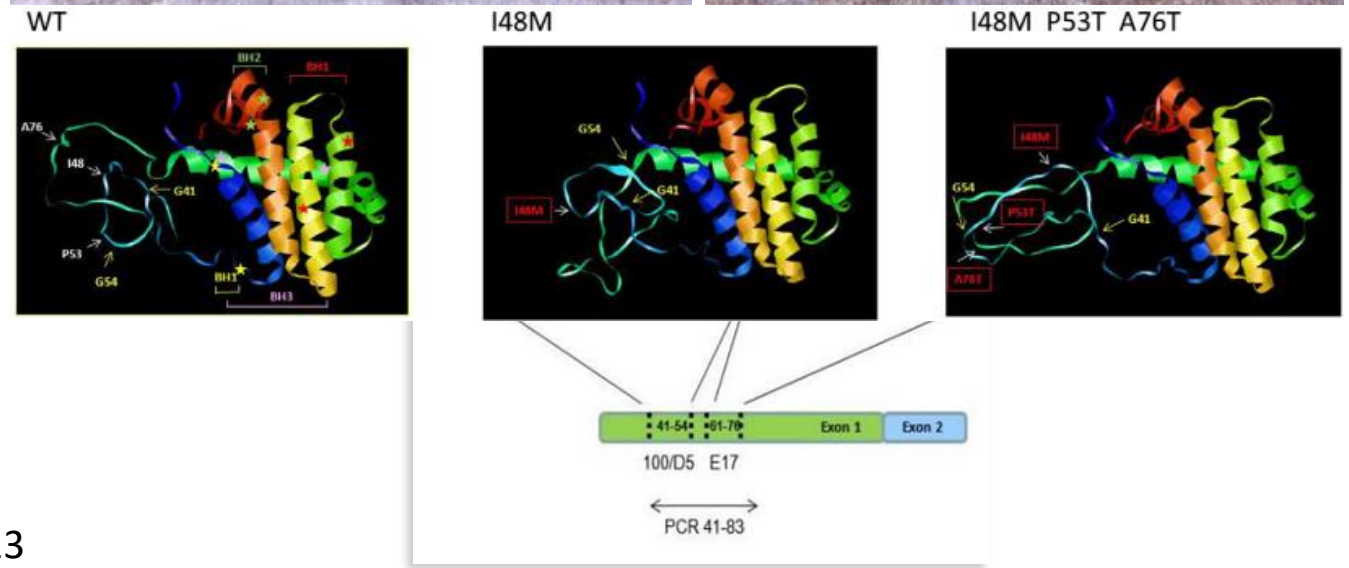


Nodal t(14;18)-neg follicular lymphoma

- In most studies, approx. 10% of follicular lymphoma Grade 1/2 are negative for BCL2 by immunohistochemistry
  - 50% with translocation t(14;18) by FISH

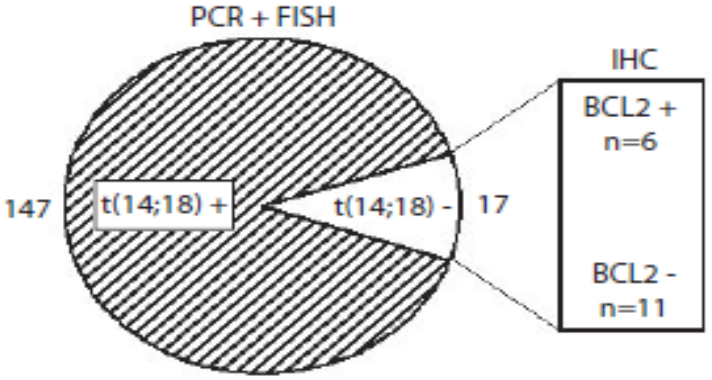


- Alternative BCL2 antibodies (E17, SP66) demonstrate BCL2 positivity in 11/12 t(14;18)+ cases



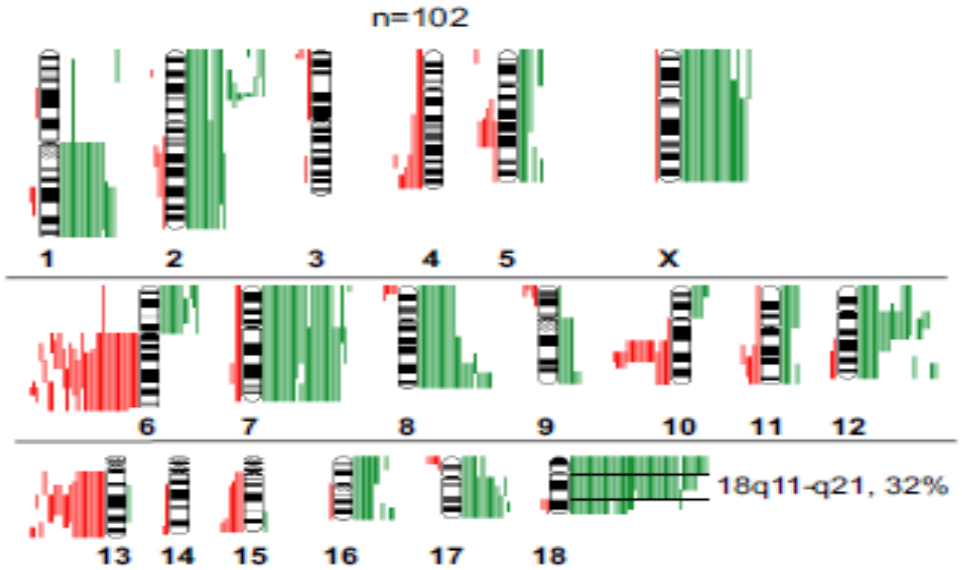
Adam et al, Hum Pathol 2013

Nodal t(14;18)-neg follicular lymphoma



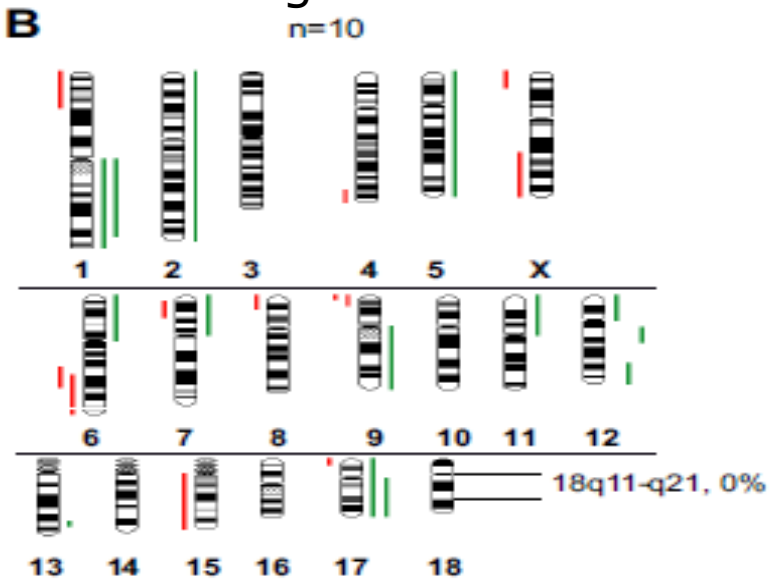
t(14;18) + FL

GC-signature



t(14;18) - FL

ABC-signature



Leich E et al. Blood. 2009 Jul 23;114(4):826-34

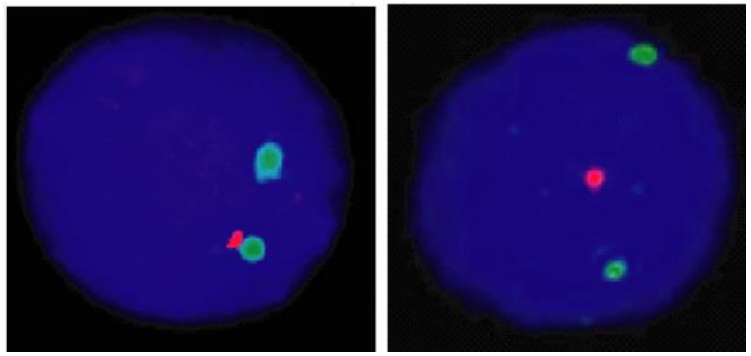
A distinctive subtype of t(14;18)-negative nodal follicular non-Hodgkin lymphoma characterized by a predominantly diffuse growth pattern and deletions in the chromosomal region 1p36

Tiemo Katzenberger,[1] Jörg Kalla,[1] Ellen Leich,[1] Heike Stocklein,[1,2] Elena Hartmann,[1] Sandra Barnickel,[1] Swen Wessendorf,[3] M. Michaela Ott,[4] Hans Konrad Müller-Hermelink,[1] *Andreas Rosenwald,[1] and *German Ott[1,2]

[1]Department of Pathology, University of Würzburg, Würzburg; [2]Department of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart; [3]Clinic for Internal Medicine III, University Hospital of Ulm, Ulm; and [4]Department of Pathology, Caritas-Krankenhaus, Bad Mergentheim, Germany

BLOOD, 29 JANUARY 2009 · VOLUME 113, NUMBER 5

- Analyzed 36 cases predominantly diffuse
- 28 of 29 analyzable cases lacked t(14;18)
- 27 of 29 showed deletion of 1p36
- All were grade I/II (12 grade I, 23 grade II)
- Frequent expression of CD23
- Large localized inguinal tumors



on isolated nuclei from paraffin-embedded tumor tissue are shown for when the BAC probe RP4-755G5 for the chromosomal region 1p36 (red signal) and the YAC probe 968g8 for the region 1p22 (green signal) are used. Loss of genetic material in 1p36 is evident, whereas 2 copies of the region 1p22 are retained (B).

Nodal t(14;18)-neg follicular lymphoma

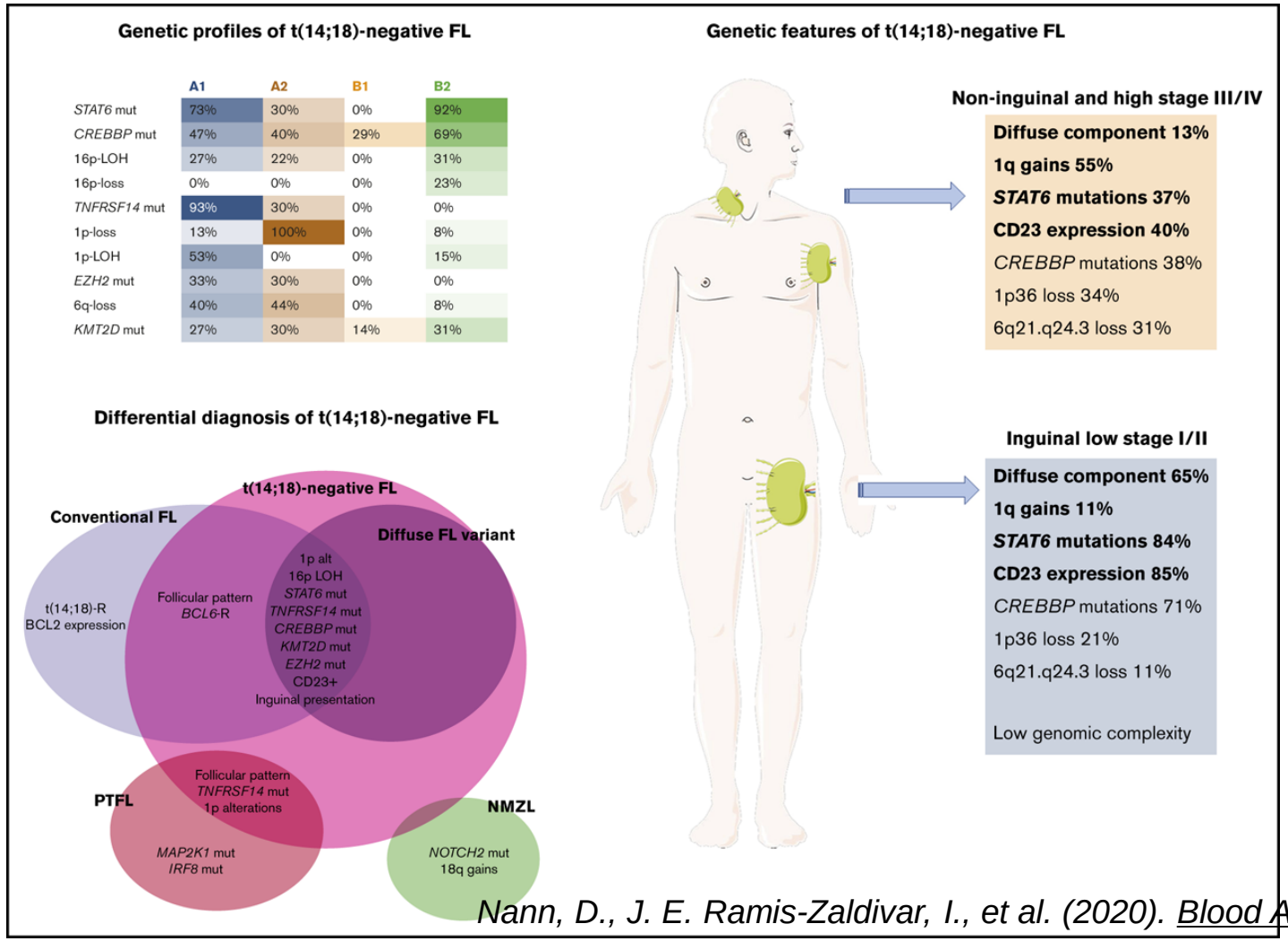
Study	# cases	diffuse	Inguinal	1p36	CD23	CD10	*STAT6* mutations	*CREBBP* mutations
Katzenberger 2009	28 cases	**100%**	83% 9% cervical 9% axillary	26 (93%)	77%	85%	ND	ND
Siddiqi 2016	9 cases	**100%**	5 (56%) Stage I/II	3 (33%)	**100%**	67%	8 (89%)	7 (78%)
Zamó 2018	6 cases	**100%**	NM	**100%**	NM	NM	5 (83%)	5 (83%)
Xian 2020	16 cases	**100%**	**100%**	4 (25%) CN-LOH (3;19%)	**100%**	100%	14 (88%) SOCS1 (6; 38%)	15 (94%) CN-LOH (63%)
Nann 2020	55 cases	D: 25% F/D: 15% F: 60%	20 (36%) Stage I/II	21%	85%	84%	84% SOCS1 (2; 10%)	71% CN-LOH (35%)

Diffuse pattern: less than 25% follicular pattern

NM: Not mentioned; ND:not done

BOLD: Inclusion criteria

Follicular lymphoma t(14;18)-neg is a genetically a heterogenous disease



Genetically, three main groups

1) Similar to conventional FL but with *STAT6* mut
2) Characterized by *STAT6/CREBBP* mutations
3) A group with few alterations (DDx nMZL)

- Predominantly inguinal but not exclusively
- Frequent *STAT6* mutations (70%)
- Frequent *CREBBP* mutations (62%) and *TNFRSF14* (45%)

- Frequent diffuse pattern but not exclusively
  - Fulfilling criteria of diffuse FL 40%
  - **Purely follicular 35%**
  - Follicular and diffuse 25%

Nann, D., J. E. Ramis-Zaldivar, I., et al. (2020). Blood Adv 4(22): 5652-5665.

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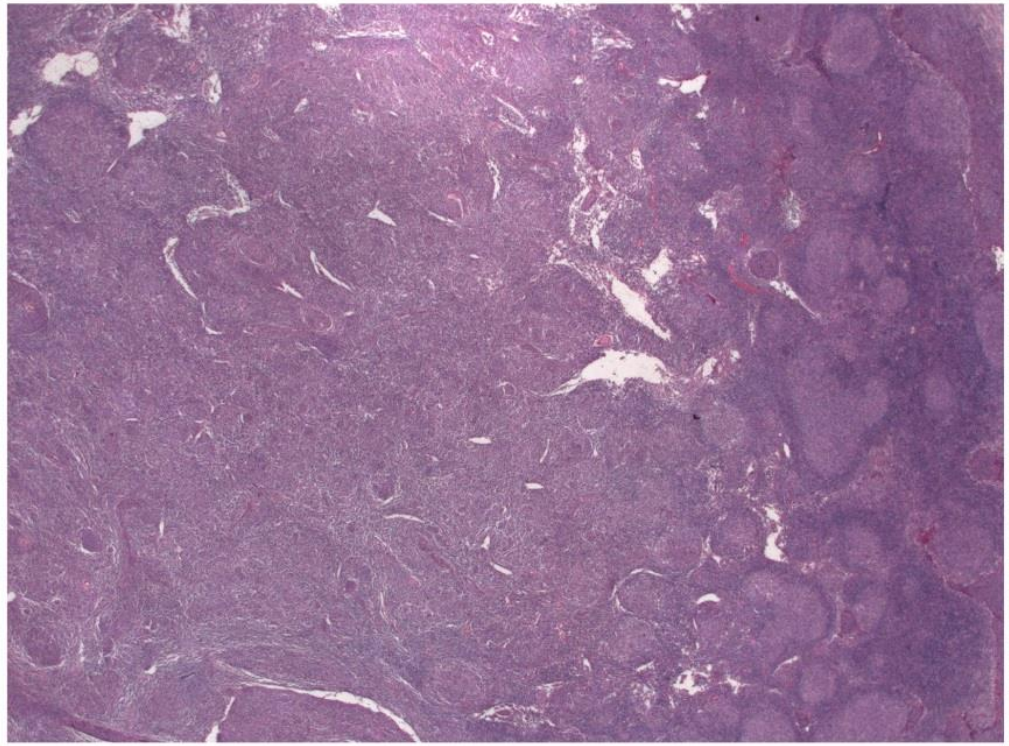
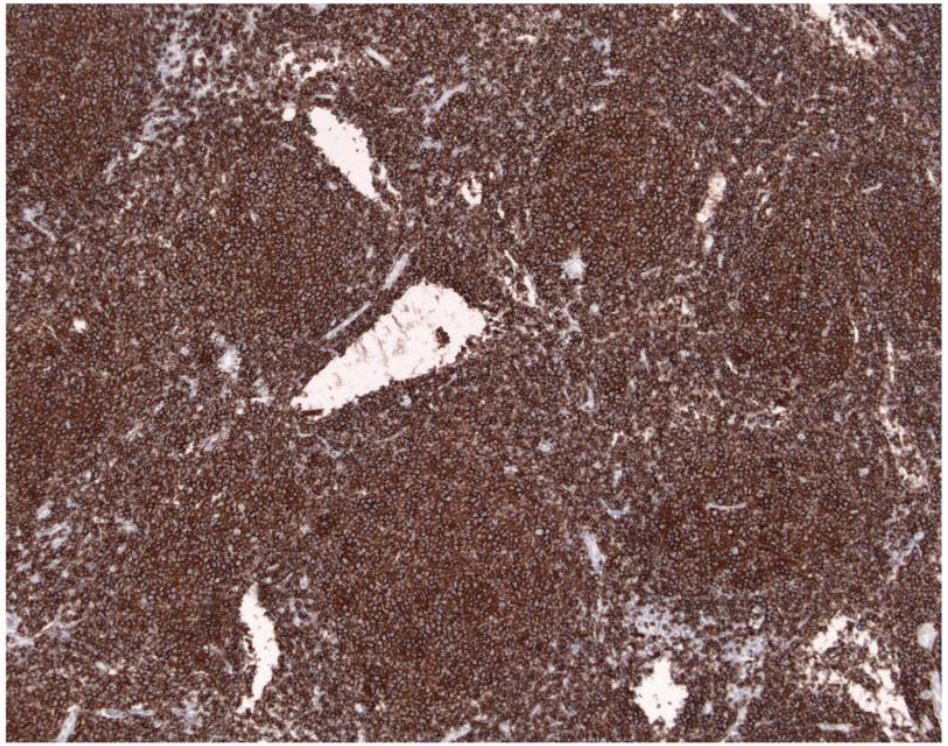
Eberhard Karls Universität Tübingen

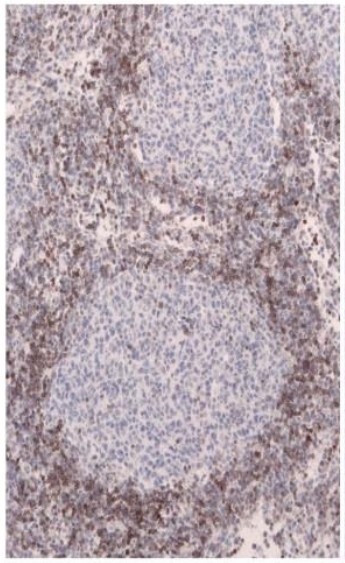




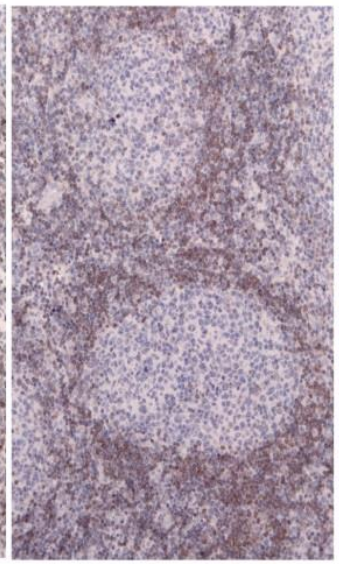
- FL11 –67 year-old
- Female
- Stage 1
- Inguinal LN
- Follicular/diffuse

Mutations :

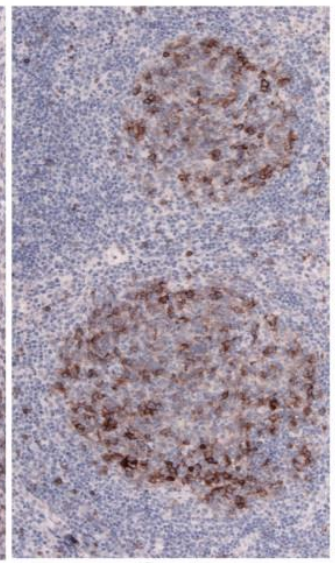
- *STAT6*
- *CREBBP*
- *TNFRSF14 (2)*
- *EZH2*
- *16p CNNLOH*



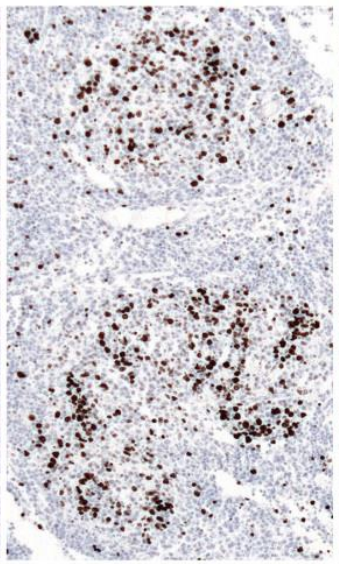
BCL2- Dako



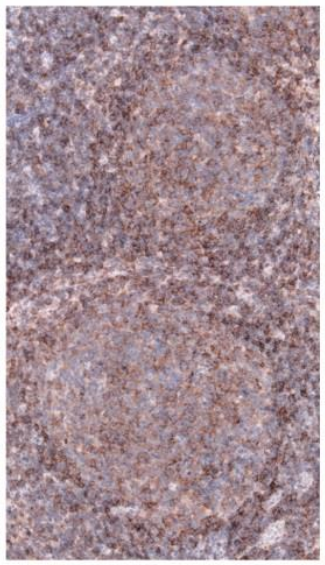
BCL2 E17

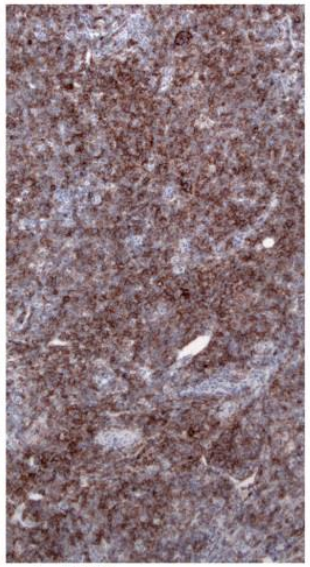


CD10



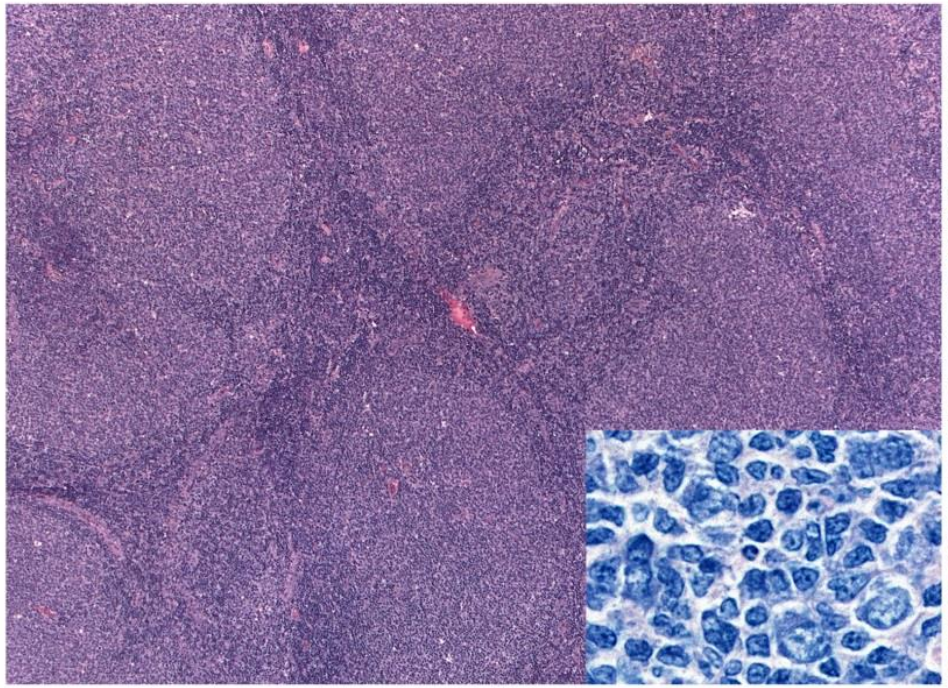
MIB1

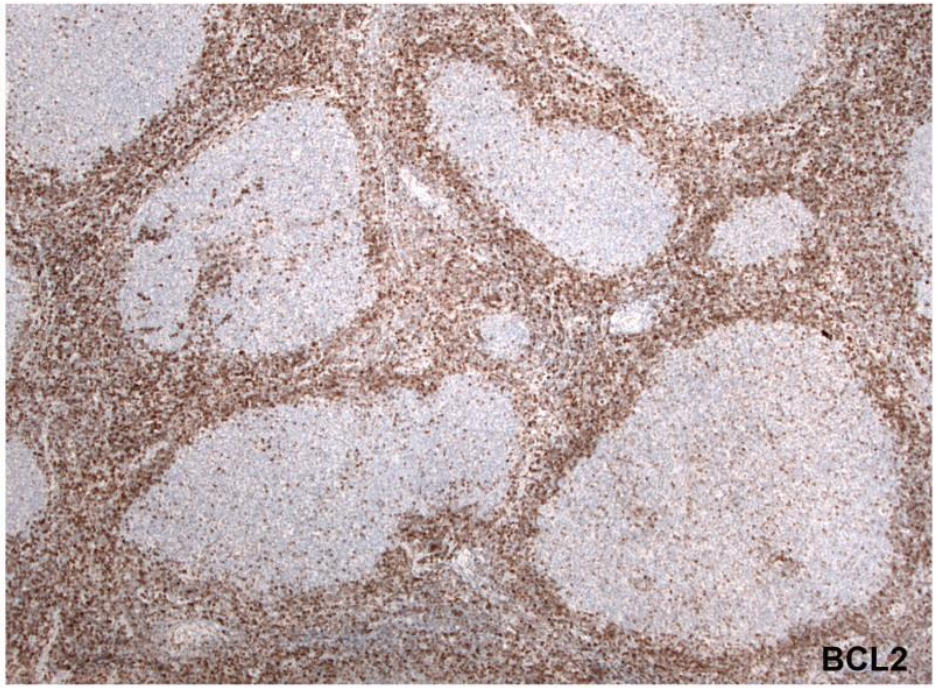


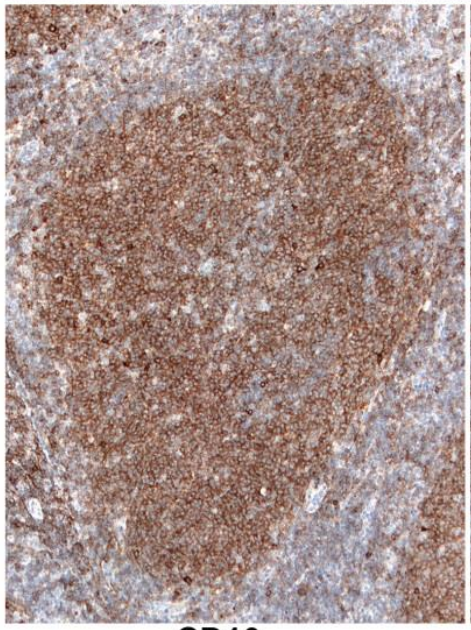


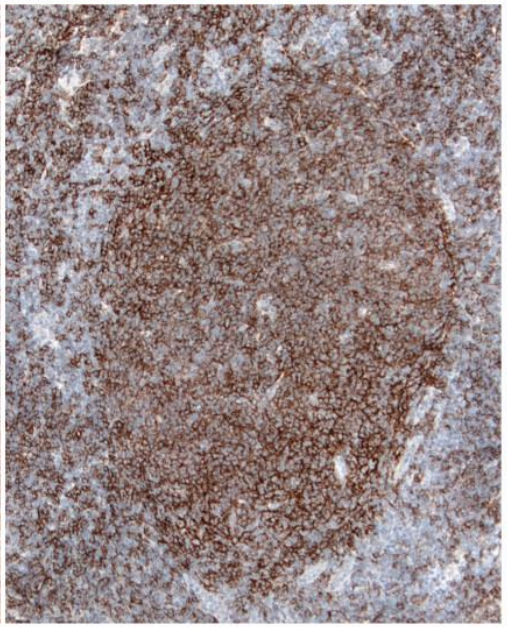
CD23 follicular and diffuse areas

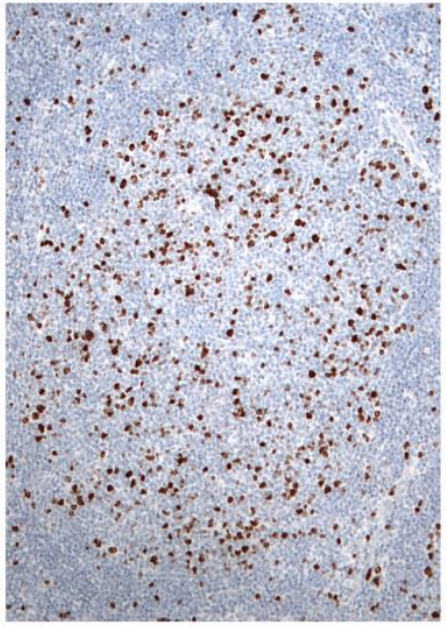
*CR

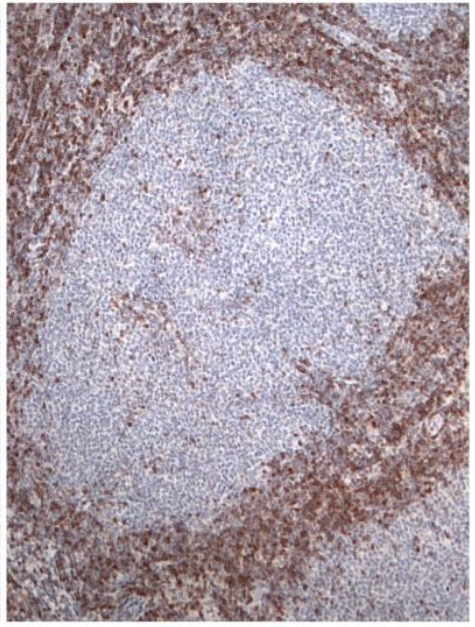












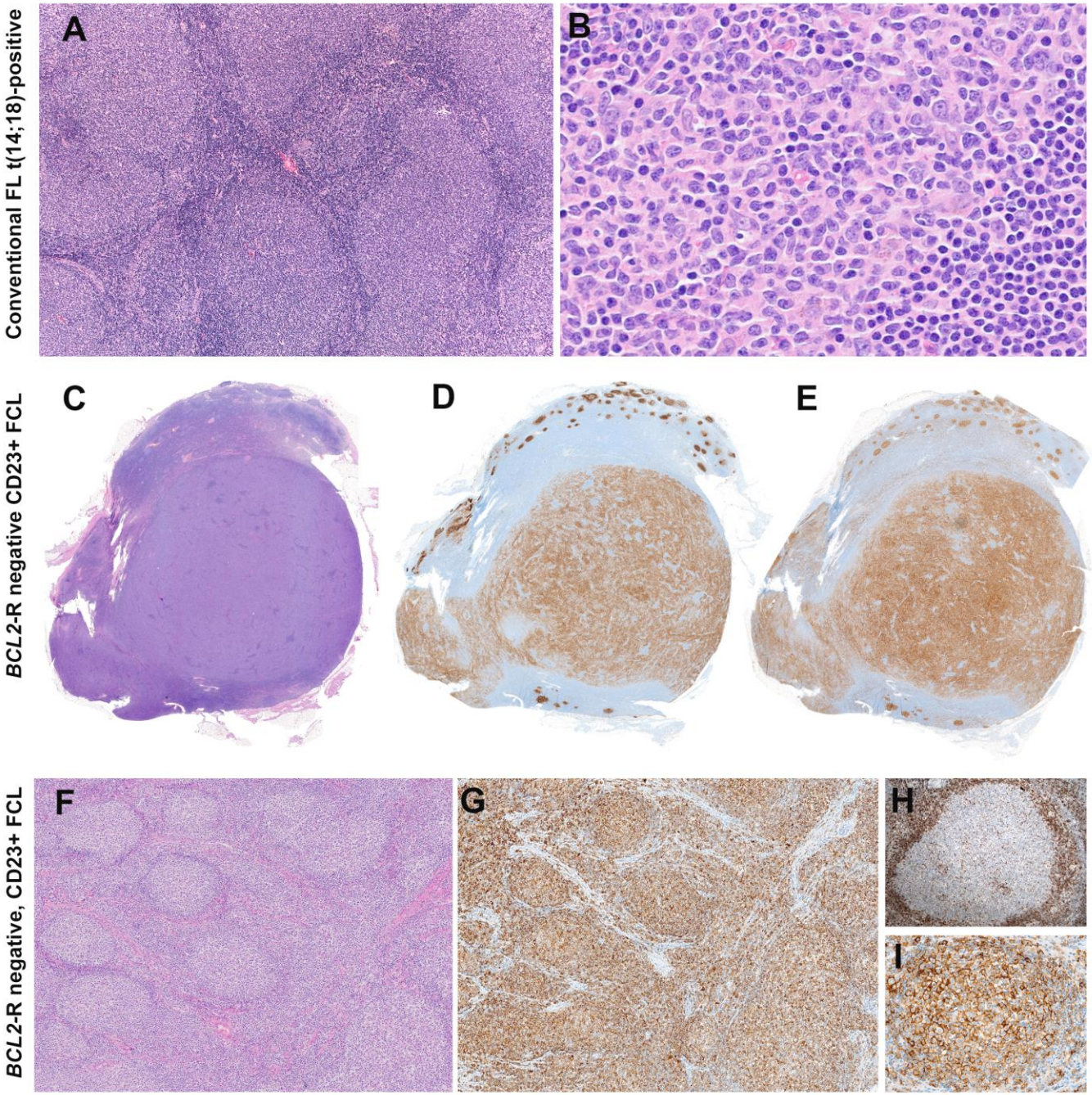
FL7 –72-year-old Female
Axillary LN
Stage IIIA
Follicular
Mutations:

- *STAT6*
- *CREBBP*
- *KMT2D*
- *16p deletion*

*6 years later (2015) recurred in the inguinal region. CR

Follicular lymphoma t(14;18)-neg

- *BCL2-R neg, CD23+ follicle center cell lymphoma*
- A provisional entity characterized by CD23 expression and *BCL2* R neg
- CD23 expression is a good surrogate marker of *STAT6* mutation
- More often in women 2:1
- Often early stage of the disease (I/II)
- Often in inguinal region but also axillary or neck
- Often diffuse but also follicular
- *STAT6* mutation associated with *CREBBP* and or *TNFRS14*

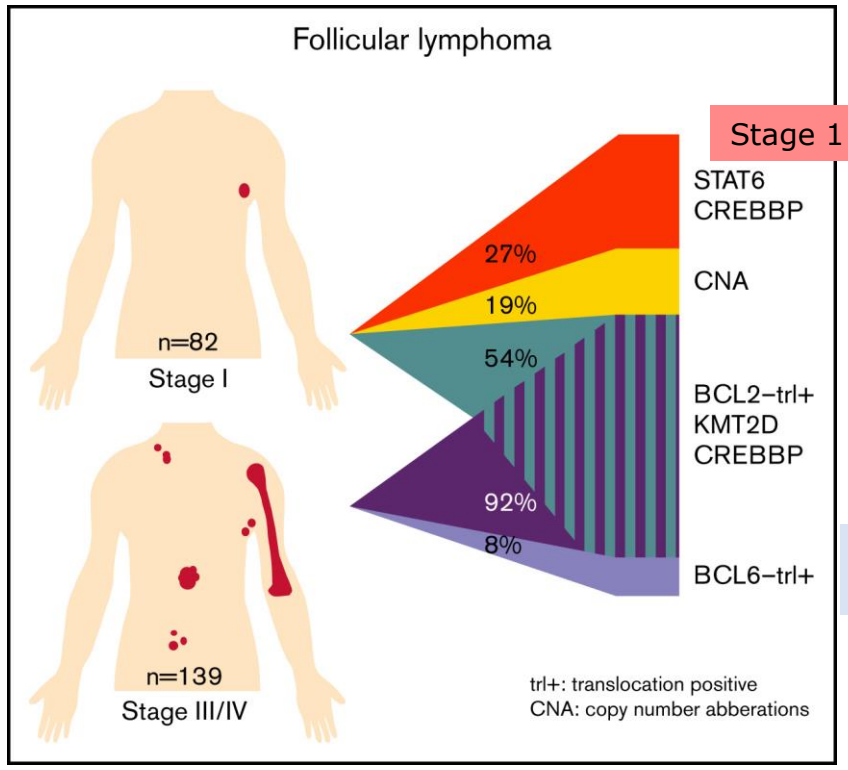


Campo E, Blood 2022

Salaverria, Weigert, Quintanilla-Martinez, Blood advances 2023 in review

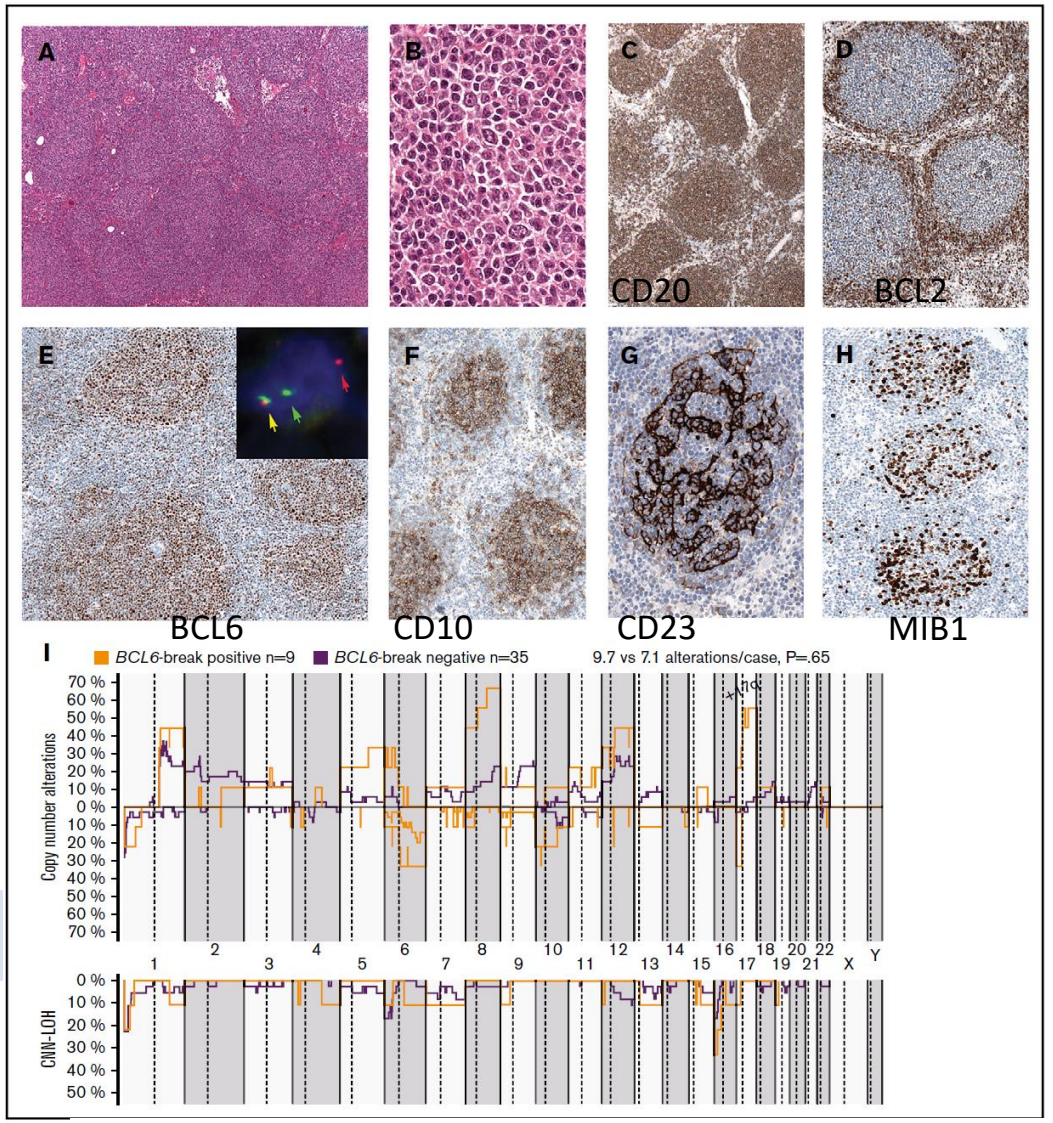
Are *BCL6*-R cases clearly distinct from *BCL2*-R FL?

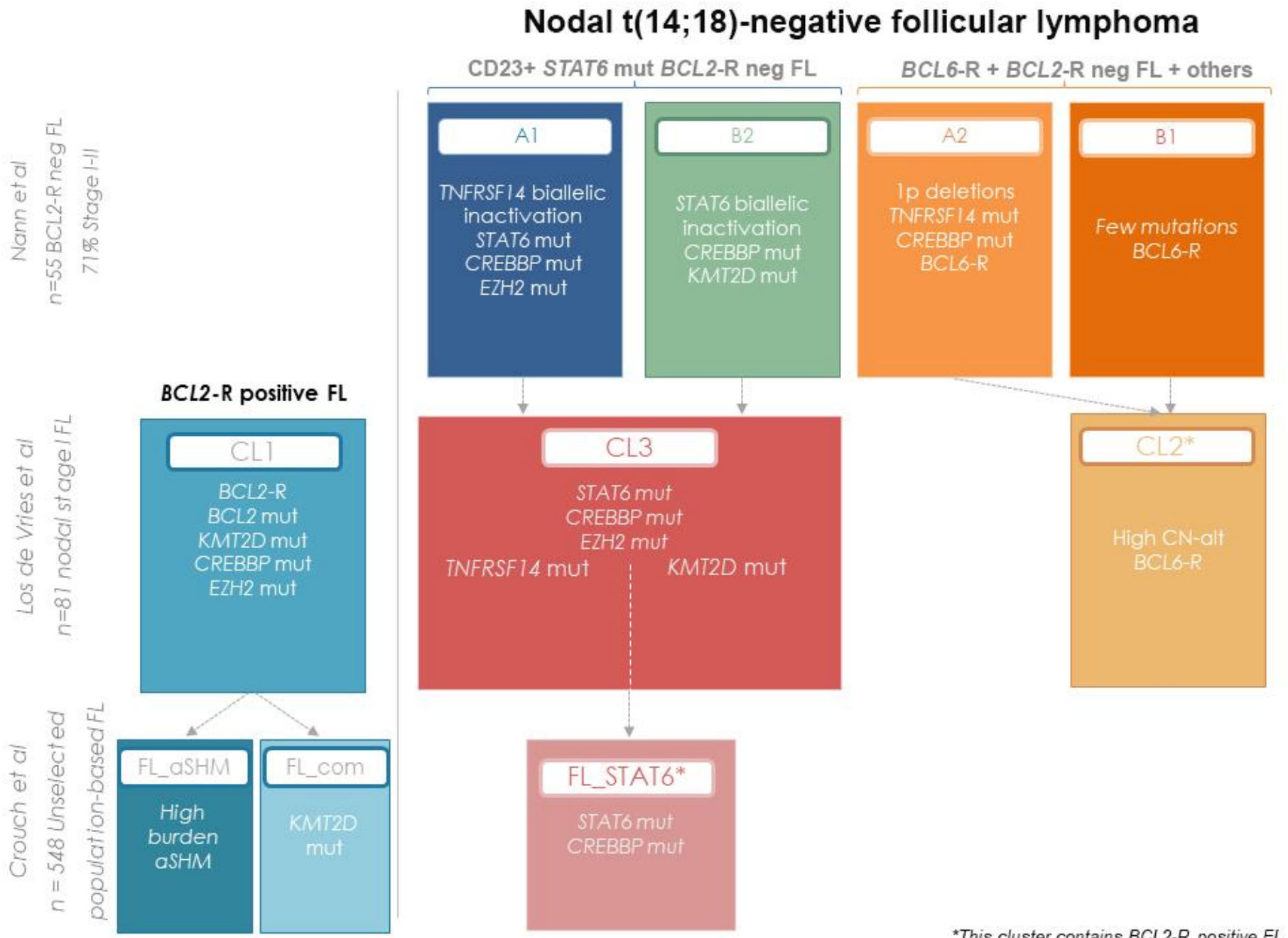
- The studies on *BCL6*-R FL are heterogeneous and difficult to compare with each other but considering the available data it seems that these cases are closer to FL t(14;18) positive than to FL t(14;18) negative.
  - All cases show follicular growth pattern
  - Clinical presentation stage III/IV



Stage 1:*BCL2*-R neg 41%

Stage III-IV: *BCL2*-R positive 92%
BCL6-R positive 8%,



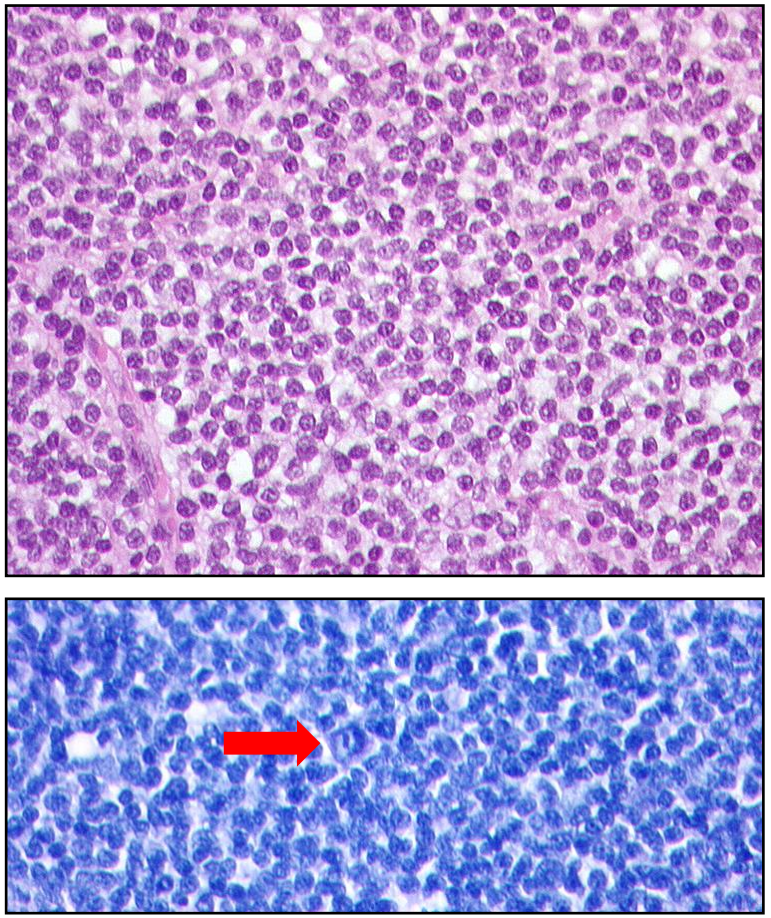


Salaverria, Weigert, Quintanilla-Martinez, Blood advances 2023 in review

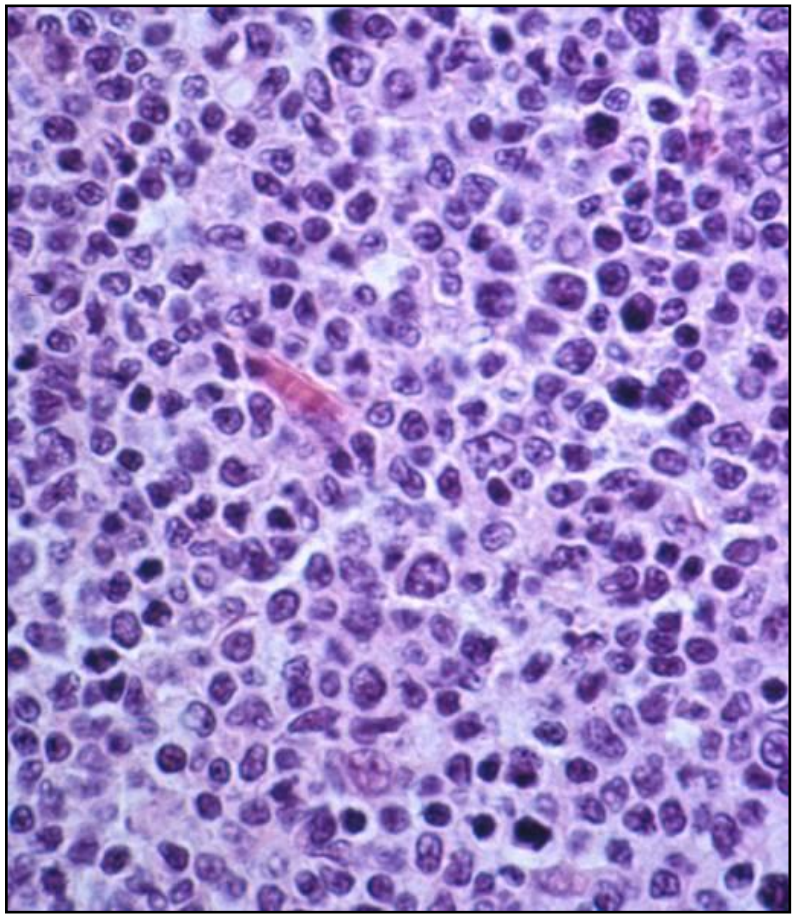
Follicular lymphoma. Cytologic grading

Historical basis of grading - empirical
counting centroblasts in 10 neoplastic follicles with 40x
grade 1 = 0-5 blasts per HPF;
grade 2= 6-15 blasts per HPF;
grade 3 = >15 blasts per HPF

WHO 5th edition does not require grading



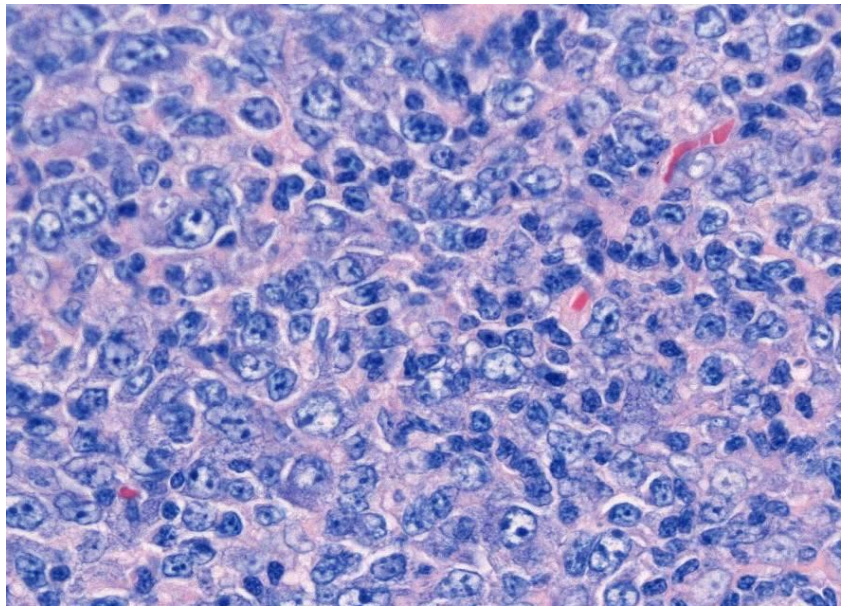
Grade 1



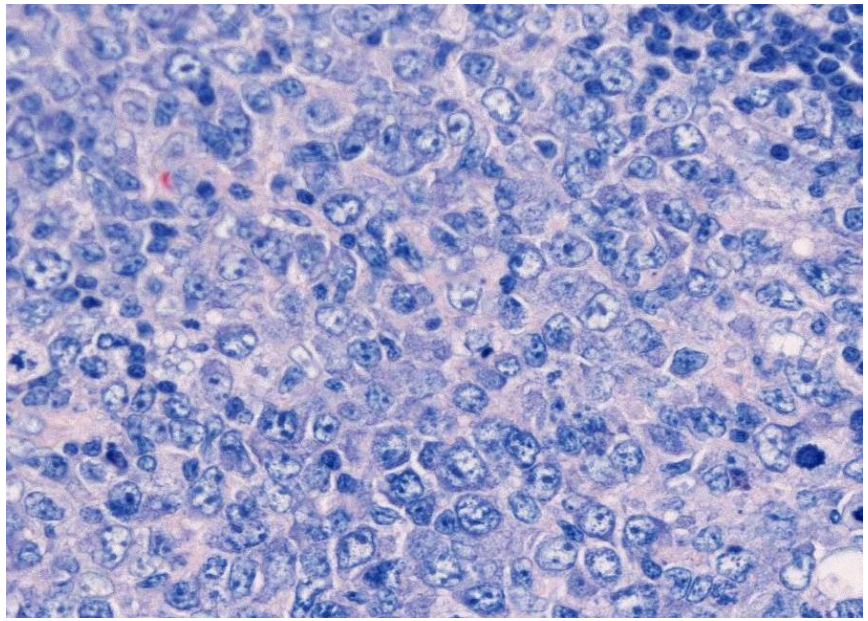
Grade 2

Follicular lymphoma. Cytologic grading

Grade 3A



- >15 centroblasts/HPF with cc
- Diffuse areas uncommon
- BM commonly involved
- CD10+,BCL6+,BCL2+,MUM1-
- t(14;18) common



Grade 3B

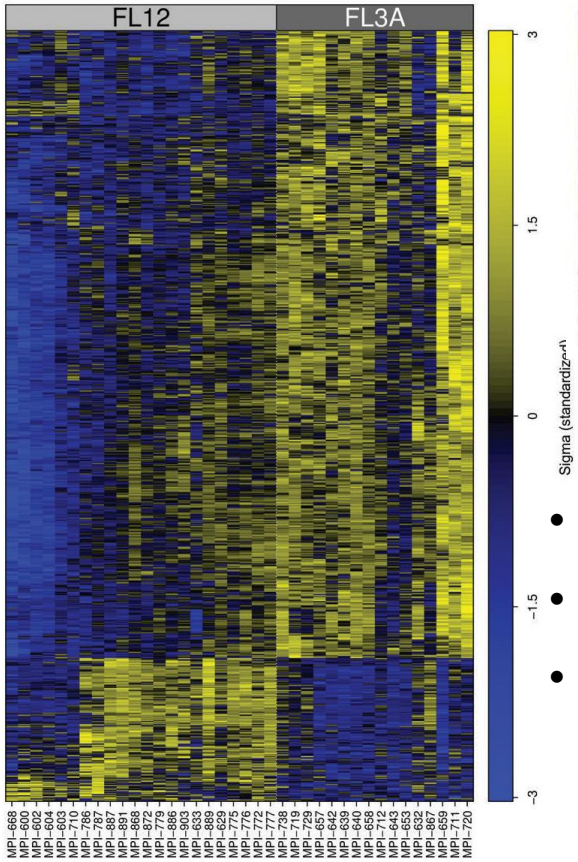
- Almost exclusively centroblasts
- Diffuse areas common - DLBCL
- BM infrequently involved
- CD10-, BCL6+,BCL2-/+,MUM1+/-
- t(14;18) uncommon, subset with IRF4/MUM1 translocation

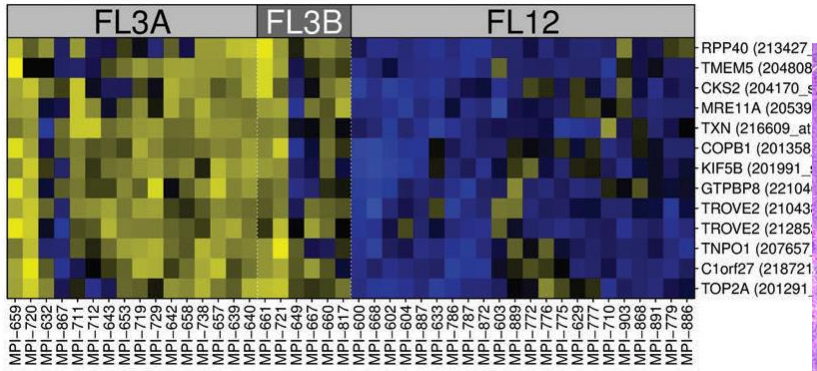
Pure FL 3B extremely rare – should it remains as FL or regarded as DLBCL?

Follicular lymphoma Grade 3B

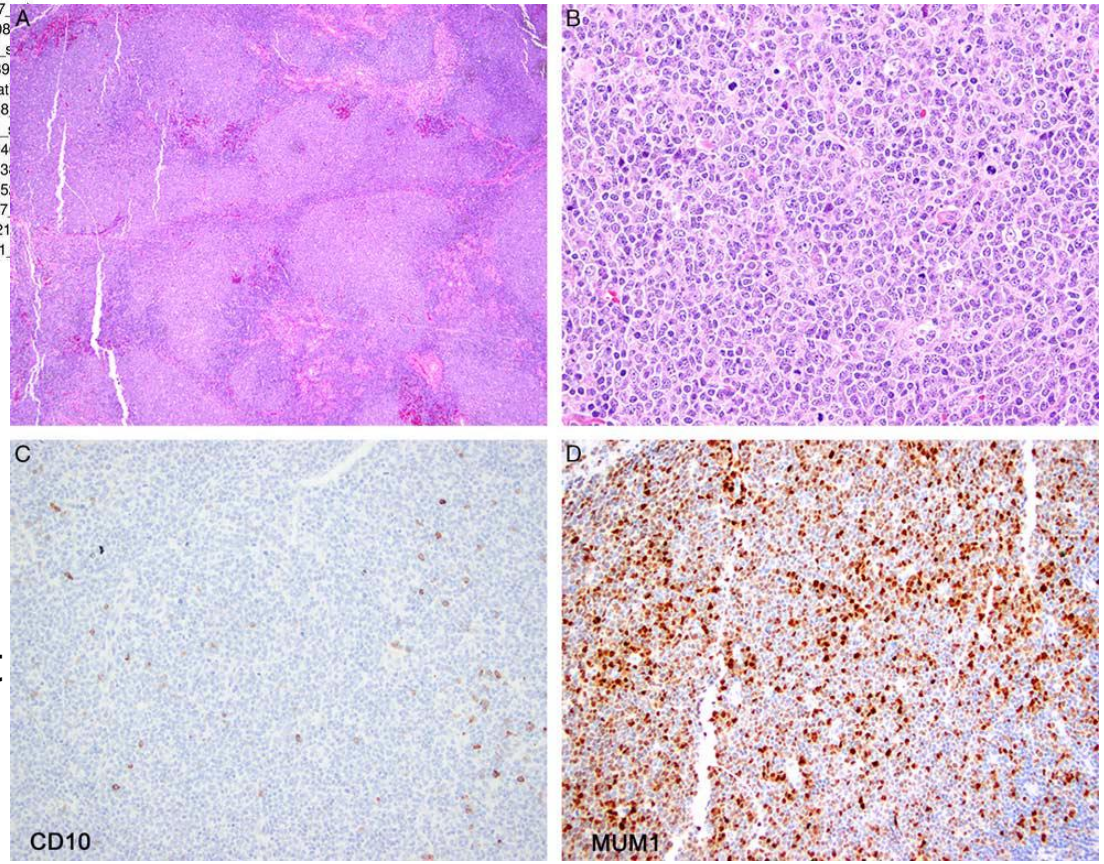
Study	#cases	CD10 (%)	BCL6 (%)	MUM1 (%)	BCL2 (%)	*BCL2*-R	*BCL6*-R	*MYC*-R	GEP
Bosga-Bouwe 2003, 2006	21	43	100	ND	67	33	33	14	ND
Katzenberger 2004	5	60	60	ND	60	0	0	20	ND
Guo 2005	14	57	79	ND	71	43	36	ND	ND
Karube 2007	22	0	54	100	50	5	30 62% Amp	ND	ND
Piccaluga 2008	4	ND	ND	ND	ND	ND	ND	ND	FL3B distinct but closer to FL3A than to DLBCL
Horn 2011	23	43	ND	42	45	9	17	22	ND
Horn 2018	6	ND	100	67	50	50	17	17	FL3B is closer to FL3A Different from FL1/2 and DLBCL
	95 cases	0-60%	54-100%	42-100%	45-70%	9-50%	0-36%	17-22%	

Follicular lymphoma Grade 3B





- Frequent lack of *BCL2*/IGH
- Frequent CD10- MUM1+
- GEP closer to FL3A and different from FL1/2 and DLBCL

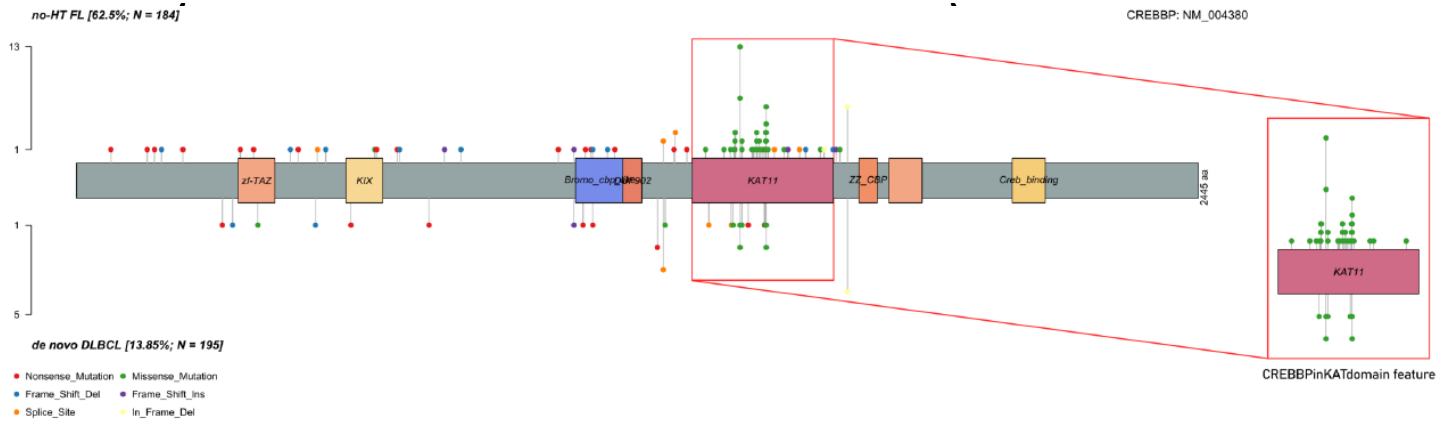


Horn H et al, Haematologica 2018

Chapman JR, et al AJSP 2020

Follicular lymphoma. Genetic subdivision

- WGS from 423 patients
  - Constrained FL (cFL)was enriched in *CREBBP* mutations affecting the KAT domain, *RRAGC, ATP6AP1* and *ATP6V1B2* mutations and was less likely to undergo transformation
  - DLBCL-like FL (dFL) was enriched in aSHM and higher risk to transformation



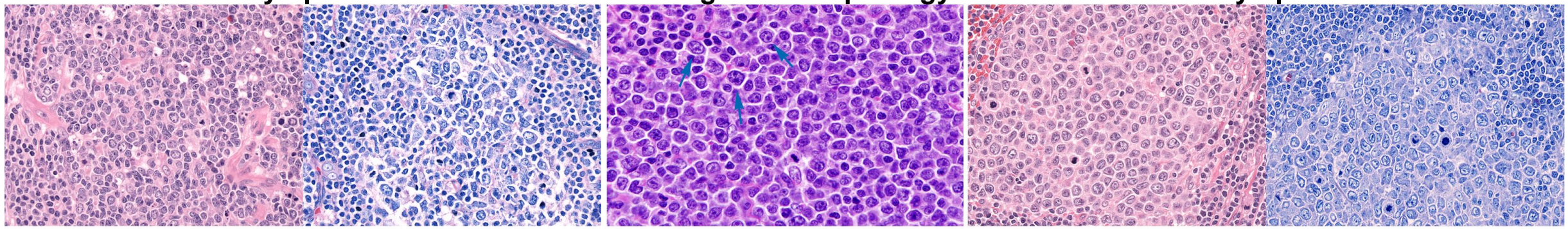
Grade 1-2: no HT 90%
pre-HT 10%
Grade 3A no-HT 60%
pre-HT 40%

Dreval K, Blood 2023 Apr 21. Online ahead of print

Follicular lymphoma 3B (FLBL 5th WHO)

Recommendations of the International Consensus classification (ICC)

Follicular lymphoma 3A | **Ambiguous morphology** | **Follicular lymphoma 3B**



Diffuse areas uncommon
BM frequently involved
CD10+/BCL6+/BCL2+
IRF4/MUM1-
***BCL2*-R common**

Positive

***BCL2*-R/CD10**

Negative

Diffuse areas common
BM infrequently involved
CD10-/BCL6+/BCL2-/+
IRF4/MUM1+/-
***BCL6*-R and *MYC*-R common**
***BCL2*-R uncommon**

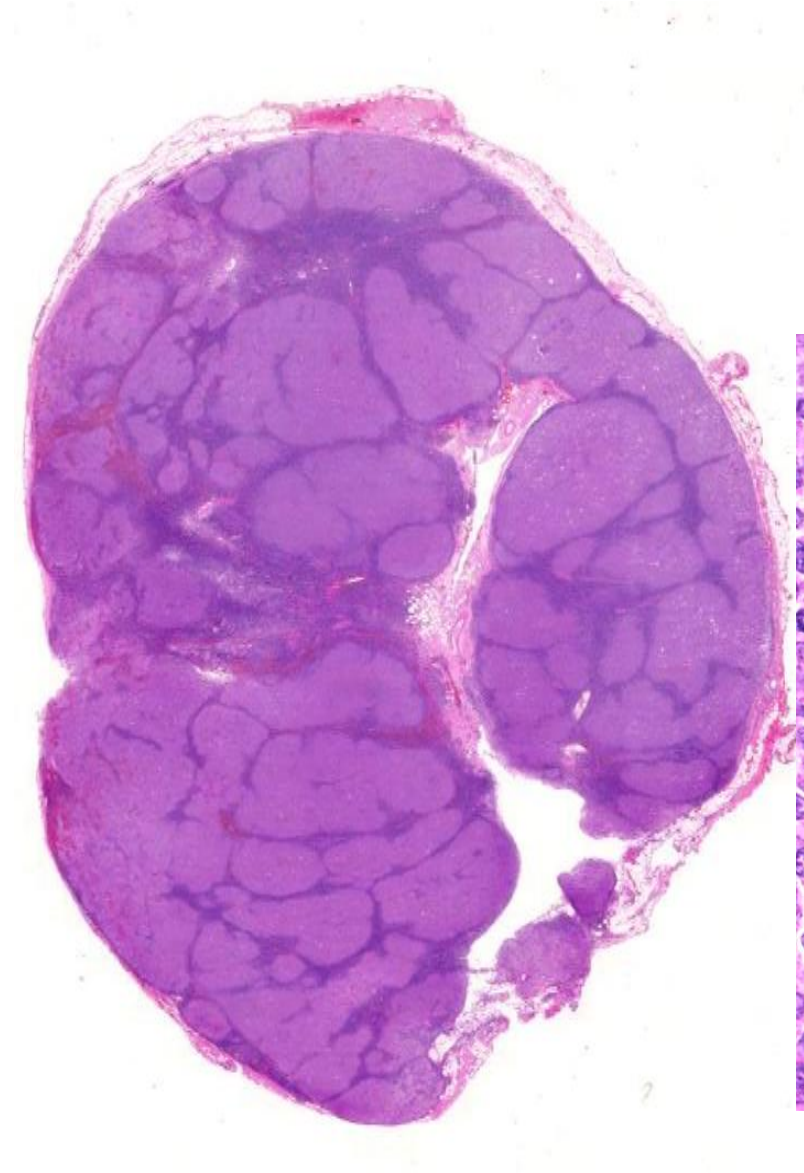
Blastoid morphology
Large centrocytic cells

IRF4/MUM1+

***IRF4*-FISH recommended**

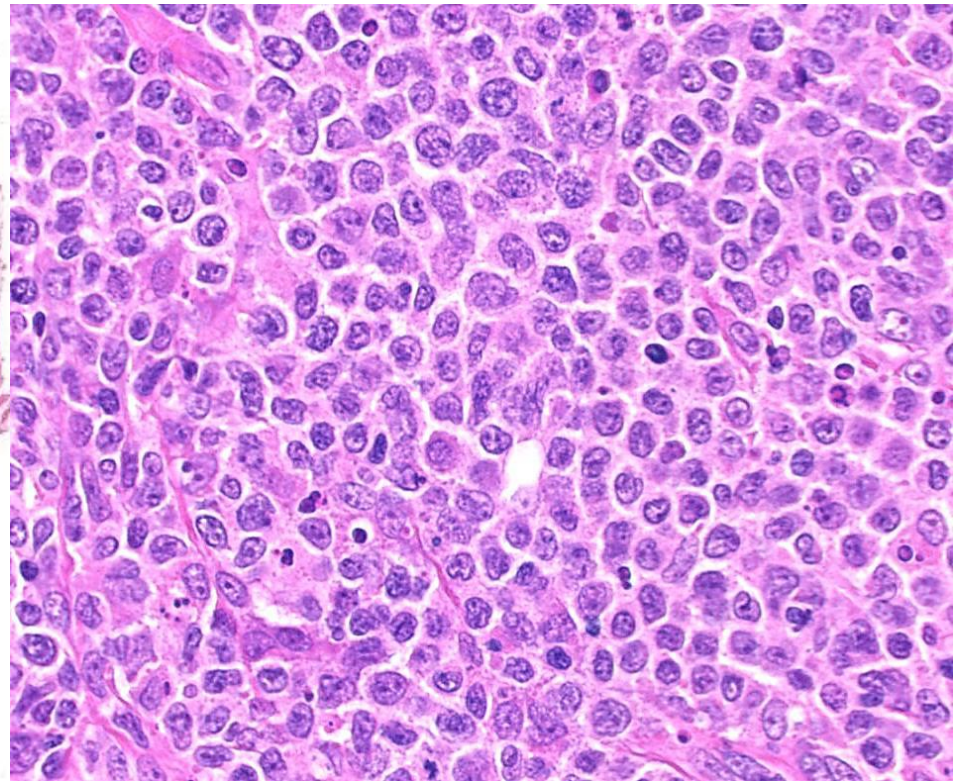
Campo E, Blood 2022

Follicular lymphoma 3B (FLBL 5th WHO)

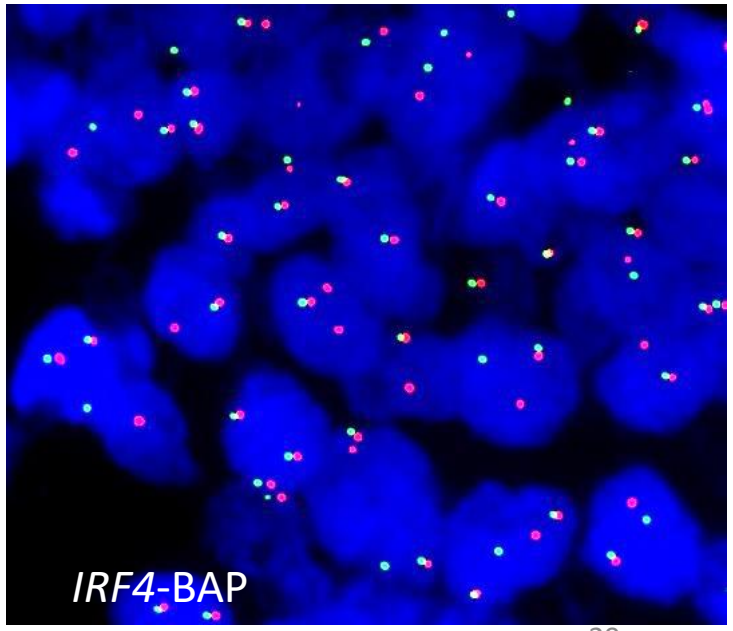


EAHP22-LYWS-1370

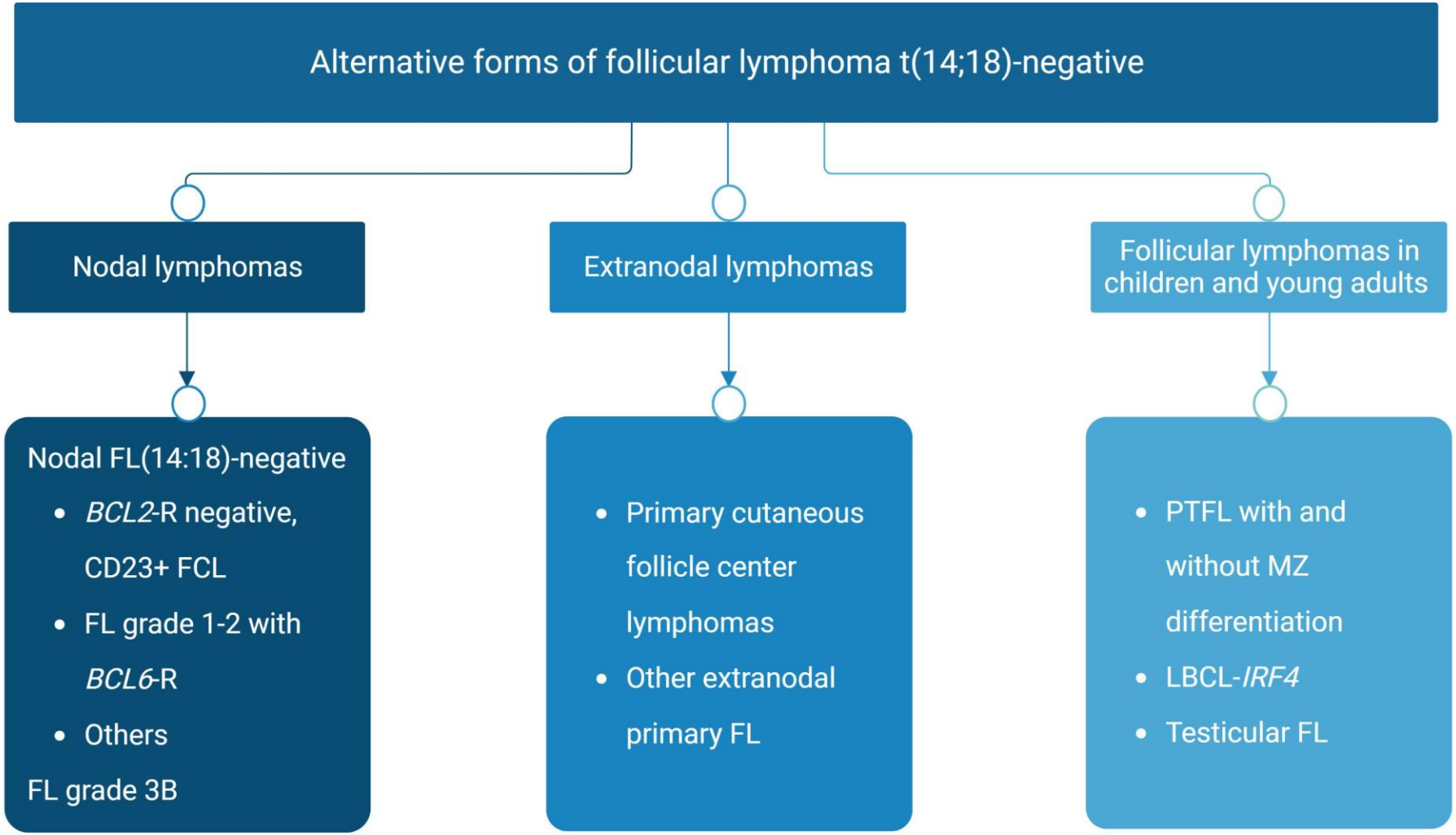
Bettina Bisig, Laussane



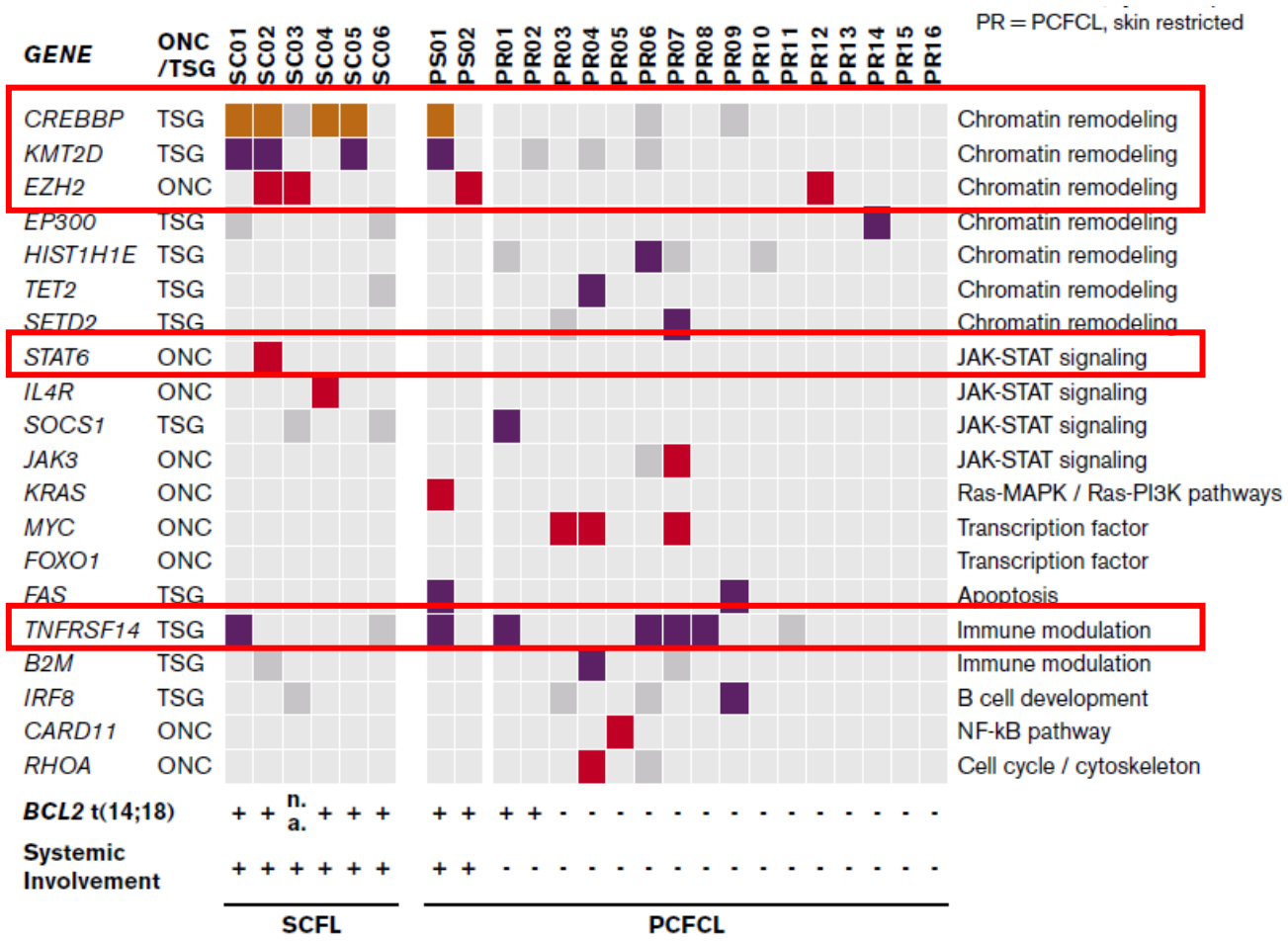
- 69 year-old man who presented in 2012 with isolated submandibular lymphadenopathy
- PET-TC showed multiple lymphadenopathy Stage IIA
- Treated 6x R-CHOP, CR for 10 years

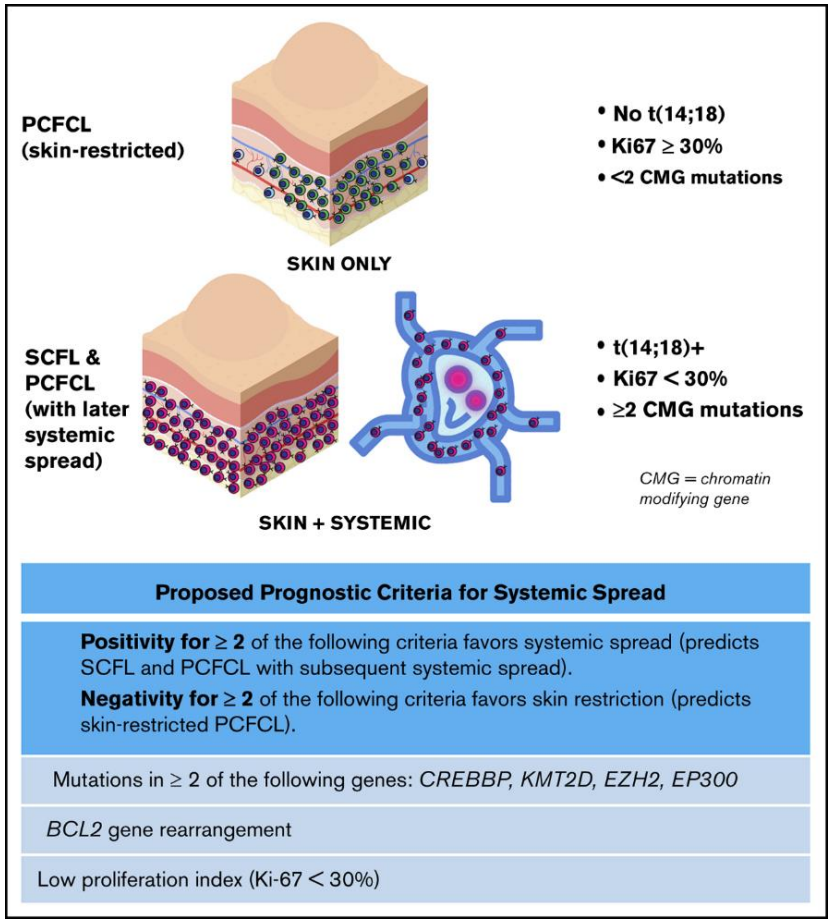


Evolving Spectrum of Follicular lymphoma



Primary cutaneous Follicle center lymphoma



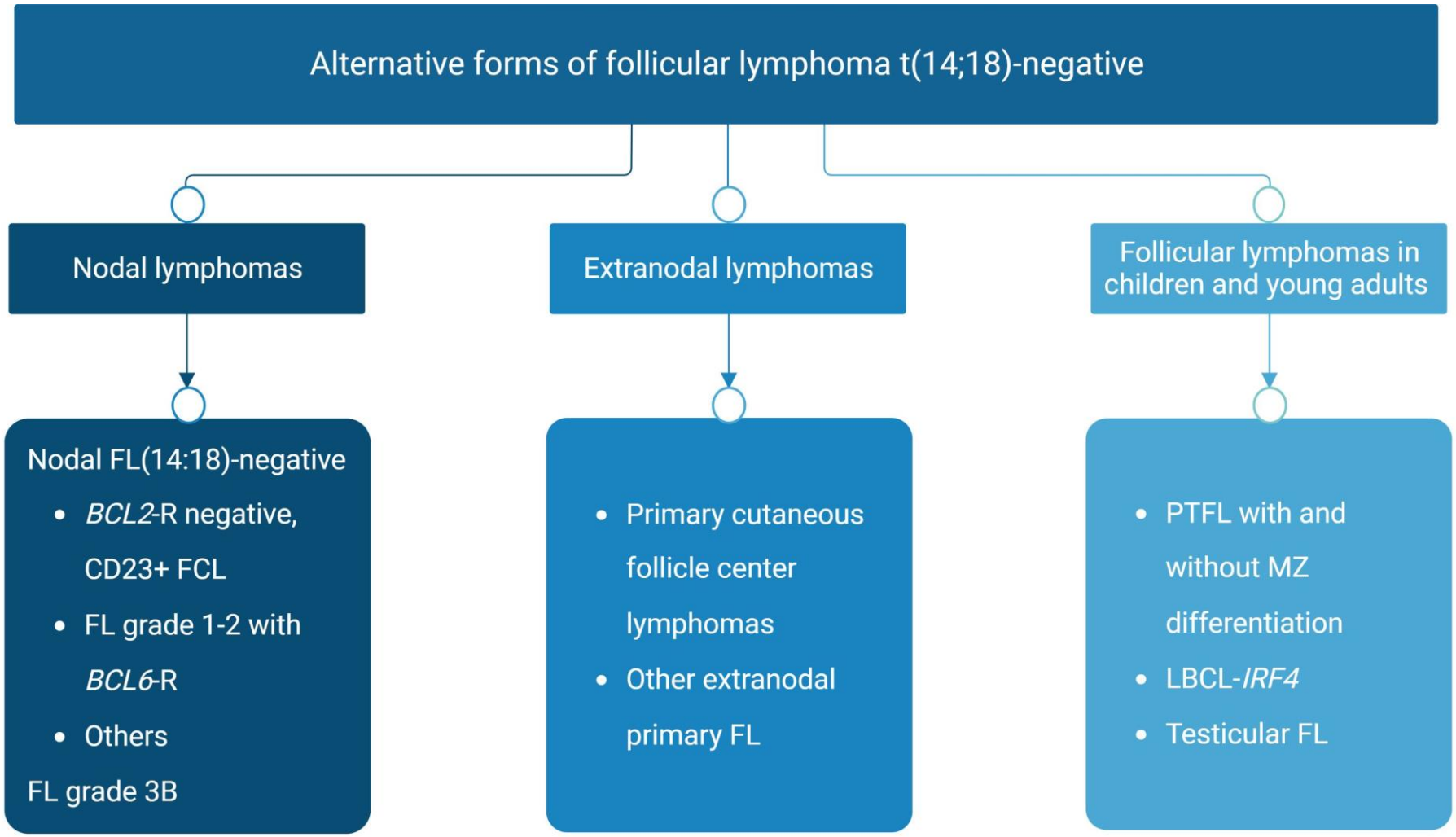


Xiaolong Alan Zhou, et alGenomic landscape of cutaneous follicular lymphomas reveals 2 subgroups with clinically predictive molecular features, Blood Adv, 2021,

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

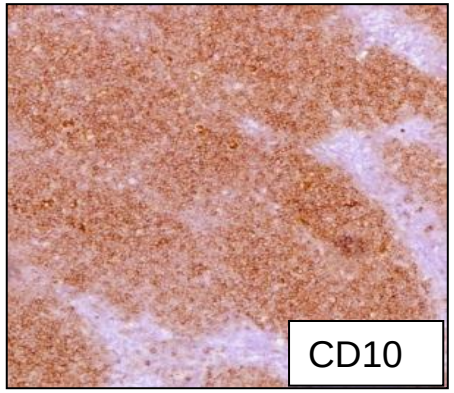
Barasch et al, Human Pathology (2020) 106, 93–105

Evolving Spectrum of Follicular lymphoma



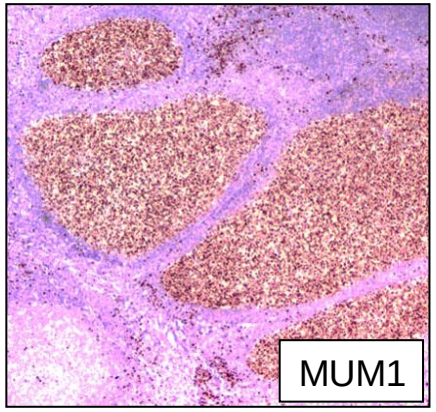
Follicular lymphoma in young patients (<30 years)

Pediatric type FL



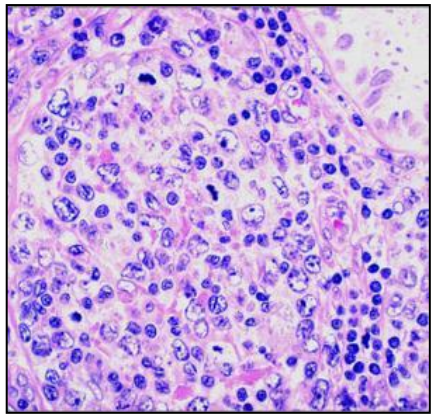
Clinically:
Nodal
Head an neck
Stage 1
M:F 20:1
Immunophenotype
CD10+,BCL6+
BCL2-, MUM1+
Genetically
TNFRS14 mutations
1p36 CN-LOH
MAP2K1 mutations

LBCL-*IRF4*



Clinically:
Tonsil/Waldeyer ring
M:F 1:1
May be diffuse
Immunophenotype
CD10+/-BCL6+/MUM1+
BCL2+/-
Genetically
IRF4 rearrangement
IRF4 mutations
NF-KB gene mutations
MYD88, CARD11

Testicular FL

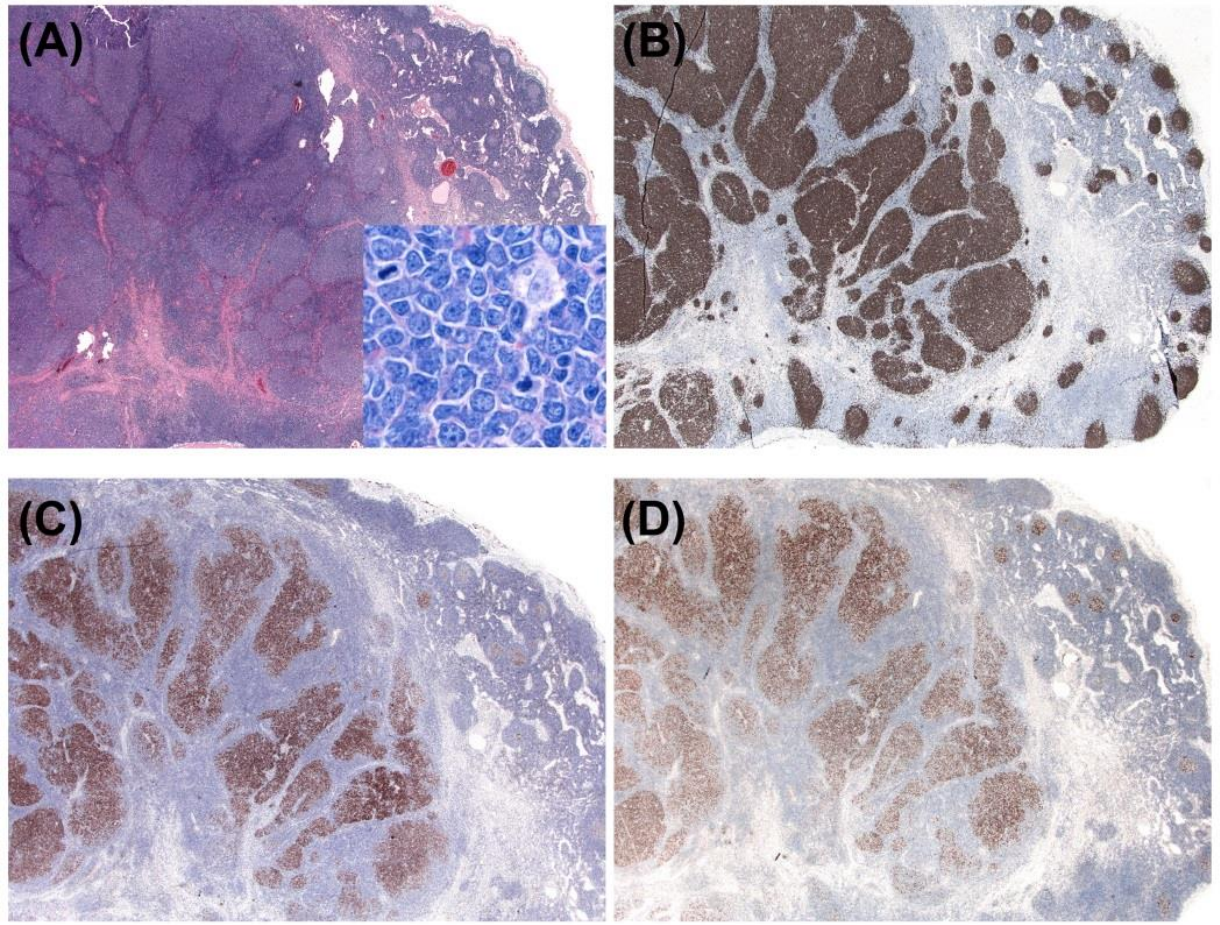


Clinically:
Testicular
Stage 1
Good prognosis
chemotherapy no required
Immunophenotype
CD10+,BCL6+
BCL2-, MUM1-
Genetically
Occasional *BCL6* breaks

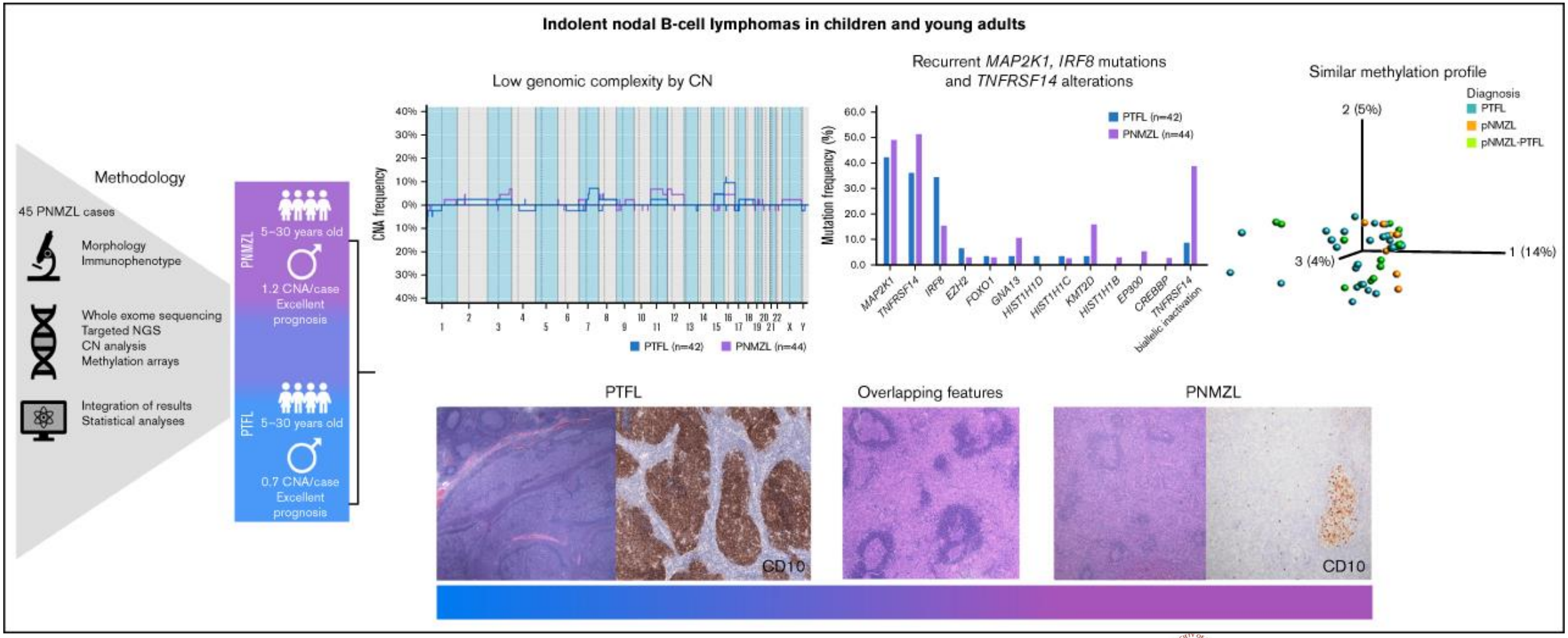
- Lack of *BCL2*/IGH
- High-grade cytology
- Localized disease (Stage 1)
- Chemotherapy is not required beyond surgical excision
- Excellent prognosis

Pediatric-type follicular lymphoma

- Clinically:
  - Predominantly in male patients
  - Predilection head/neck LN
  - Early stage disease
  - Good prognosis (watch & wait)
- Morphologically:
  - grade 3
  - Large, expansile serpiginous GC follicles
  - Lack of BCL2 expression
- Genetically:
  - no t(14;18)
  - Clonal analysis requiered!
    - IGH monoclonal



A unifying hypothesis for PNMZL and PTFL: morphological variants with a common molecular profile.



Salmeron-Villalobos, Egan, Borgmann et al, Blood Adv 2022

American Society of Hematology
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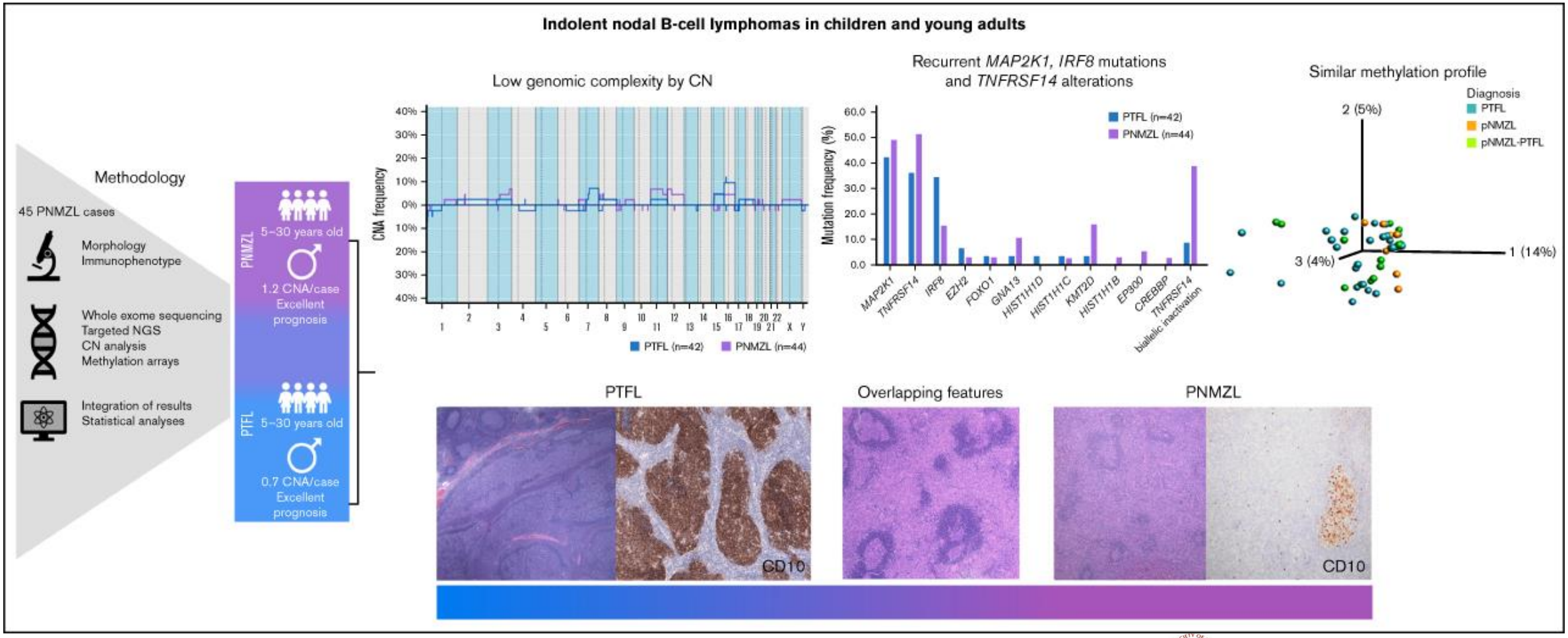
Universitätsklinikum Tübingen

PTFL with and without marginal zone differentiation



Salmeron-Villalobos, Egan, Borgmann et al, Blood Adv 2022

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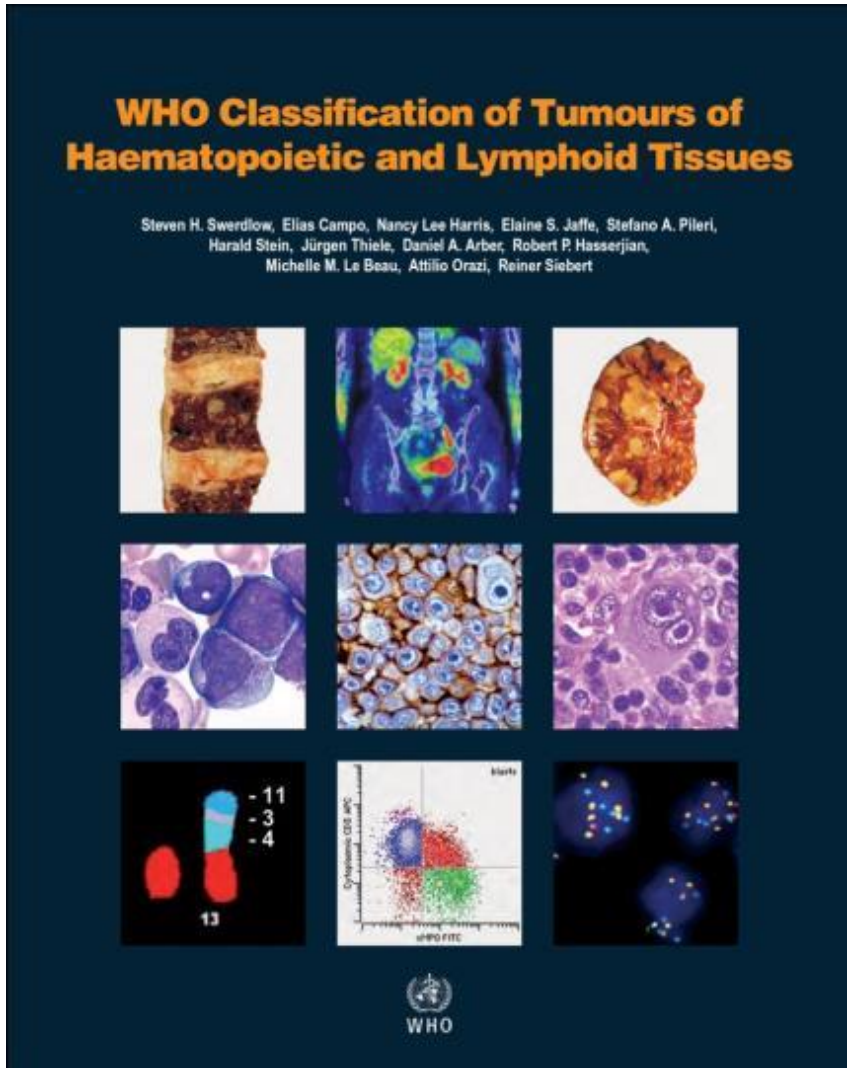
Large B-cell lymphoma with *IRF4*-rearrangement



Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement** ←
Primary cutaneous follicle center lymphoma

Provisional entities are listed in italics.
*Changes from the 2008 classification.

Both the International Consensus Classification and the 5th edition of the WHO recognize „Large B-cell lymphoma with *IRF4* rearrangement“ as a distinct entity

Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with *IRF4* rearrangement ←
High-grade B-cell lymphoma with 11q aberrations
Lymphomatoid granulomatosis
EBV-positive diffuse large B-cell lymphoma
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma

R. Alaggio et al.

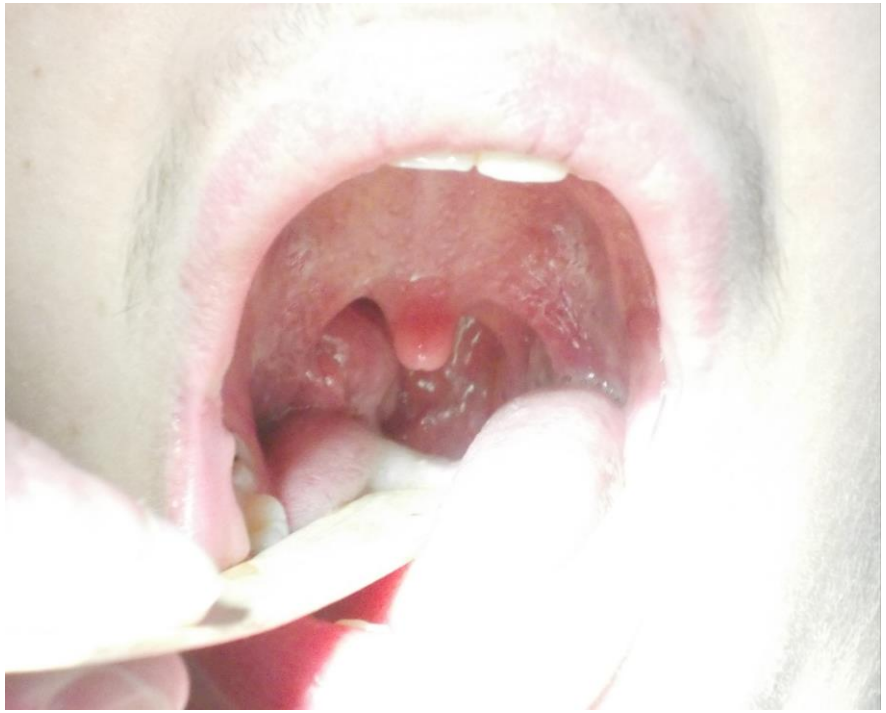
Leukemia (2022) 36:1720 – 1748

Large B-cell lymphoma with *IRF4* rearrangement

Translocations activating *IRF4* identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults

*Itziar Salaverria,[1] *Claudia Philipp,[2] *Ilske Oschlies,[3] *Christian W. Kohler,[4] *Markus Kreuz,[5] Monika Szczepanowski,[3] Birgit Burkhardt,[6] Heiko Trautmann,[7] Stefan Gesk,[1] Miroslaw Andrusiewicz,[1,8] Hilmar Berger,[5] Miriam Fey,[1] Lana Harder,[1] Dirk Hasenclever,[5] Michael Hummel,[9] Markus Loeffler,[5] Friederike Mahn,[1] Idoia Martin-Guerrero,[1] Shoji Pellissery,[1] Christiane Pott,[7] Michael Pfreundschuh,[10] Alfred Reiter,[6] Julia Richter,[1] Maciej Rosolowski,[5] Carsten Schwaenen,[11] Harald Stein,[9] Lorenz Trümper,[12] Swen Wessendorf,[11] Rainer Spang,[4] Ralf Küppers,[2] Wolfram Klapper,[3] and Reiner Siebert,[1] for the Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe, the German High-Grade Lymphoma Study Group, and the Berlin-Frankfurt-Münster-NHL trial group

- 20/427 lymphomas (17 in children and young adults)
  - 9 female and 11 male
  - Median age of 12 years (4-79 years)
  - 80% involved the head and neck region including the Waldeyer´s ring
  - 84% limited disease stage, favorable outcome
  - Often CD10- (40%), BCL6+, MUM1+ (GCB-type)
  - 13/20 cases were exclusively DLBCL
  - 7/20 FL grade 3 and FL/DLBCL

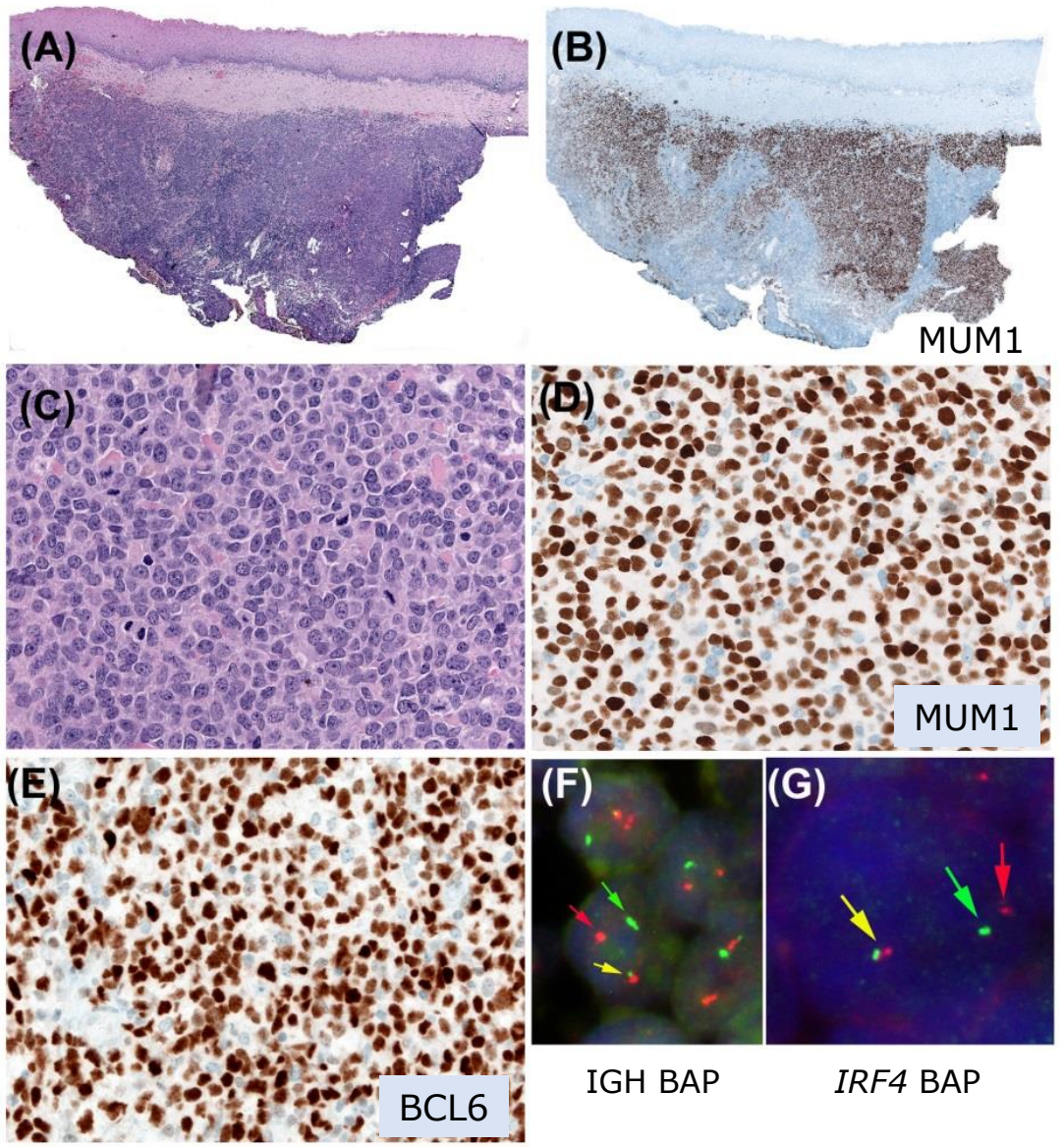


SALAVERRIA et al BLOOD, 7 JULY 2011 • VOLUME 118, NUMBER 1

Woessmann and Quintanilla-Martinez L, Hematological Oncology 2019;37:53

Large B-cell lymphoma with *IRF4* rearrangement

- MUM1 and BCL6 expression 100%
  - 90% demonstrable *IRF4* breaks
- BCL2 expression 63%
  - in the absence of the t(14;18)
- CD10- in approx 40%
- M:F; 1:1
- Median age 9 years (3-18)
- Follicular or Diffuse. Diffuse areas are frequently observed
- Potential for more aggressive clinical course

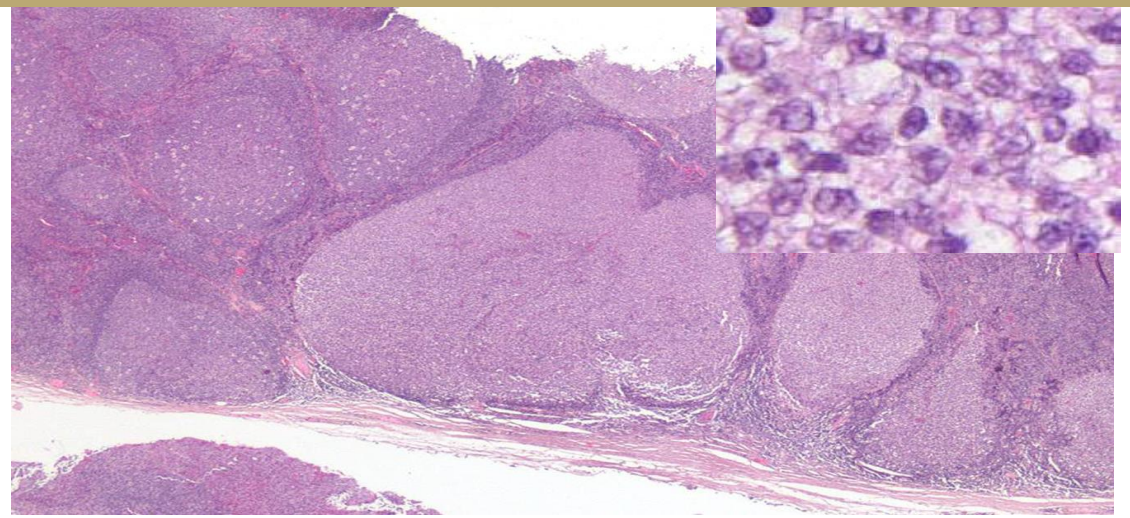


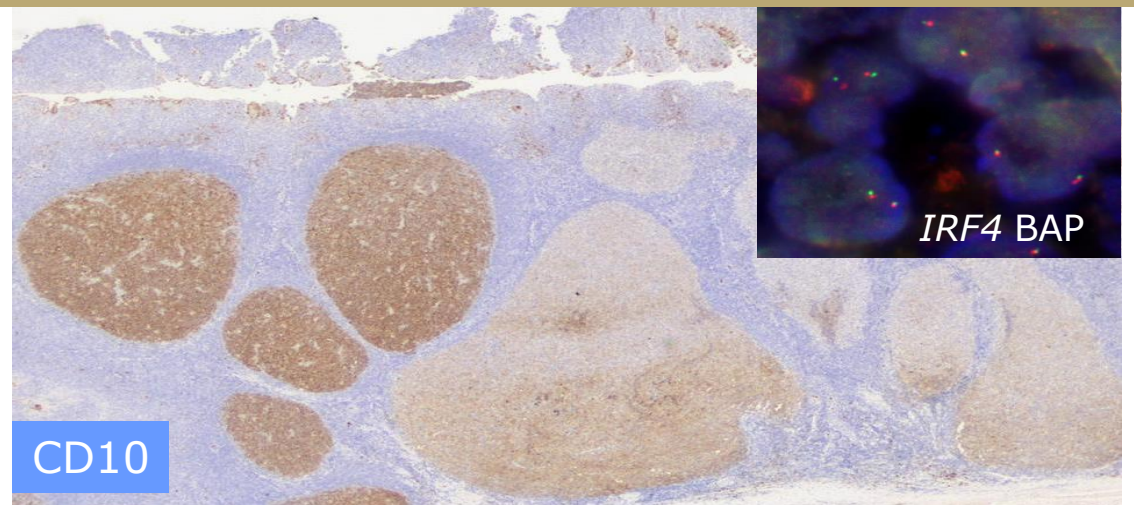
Liu Q et al, Am J Surg Pathol 2013; 37:333
Woessmann and Quintanilla-Martinez L, Hematological Oncology 2019;37:53

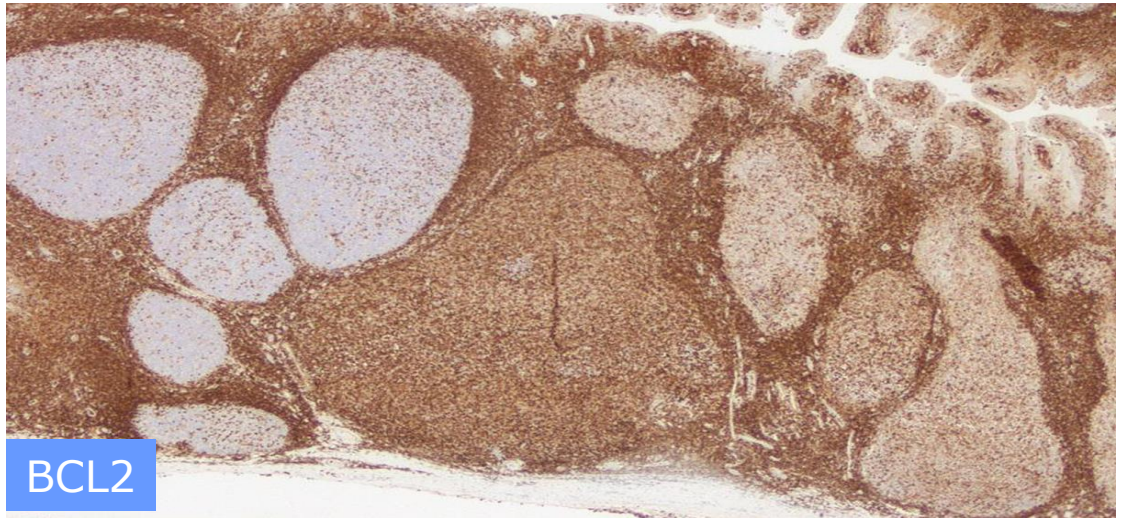
Comprehensive Cancer Center Tübingen - Stuttgart

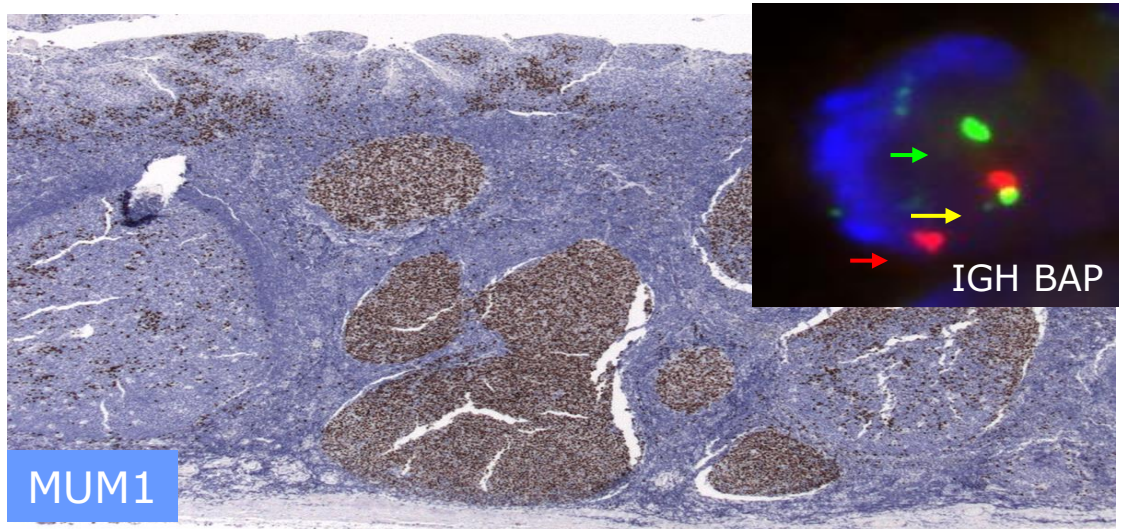
Eberhard Karls Universität Tübingen

Large B-cell lymphoma with *IRF4* rearrangement









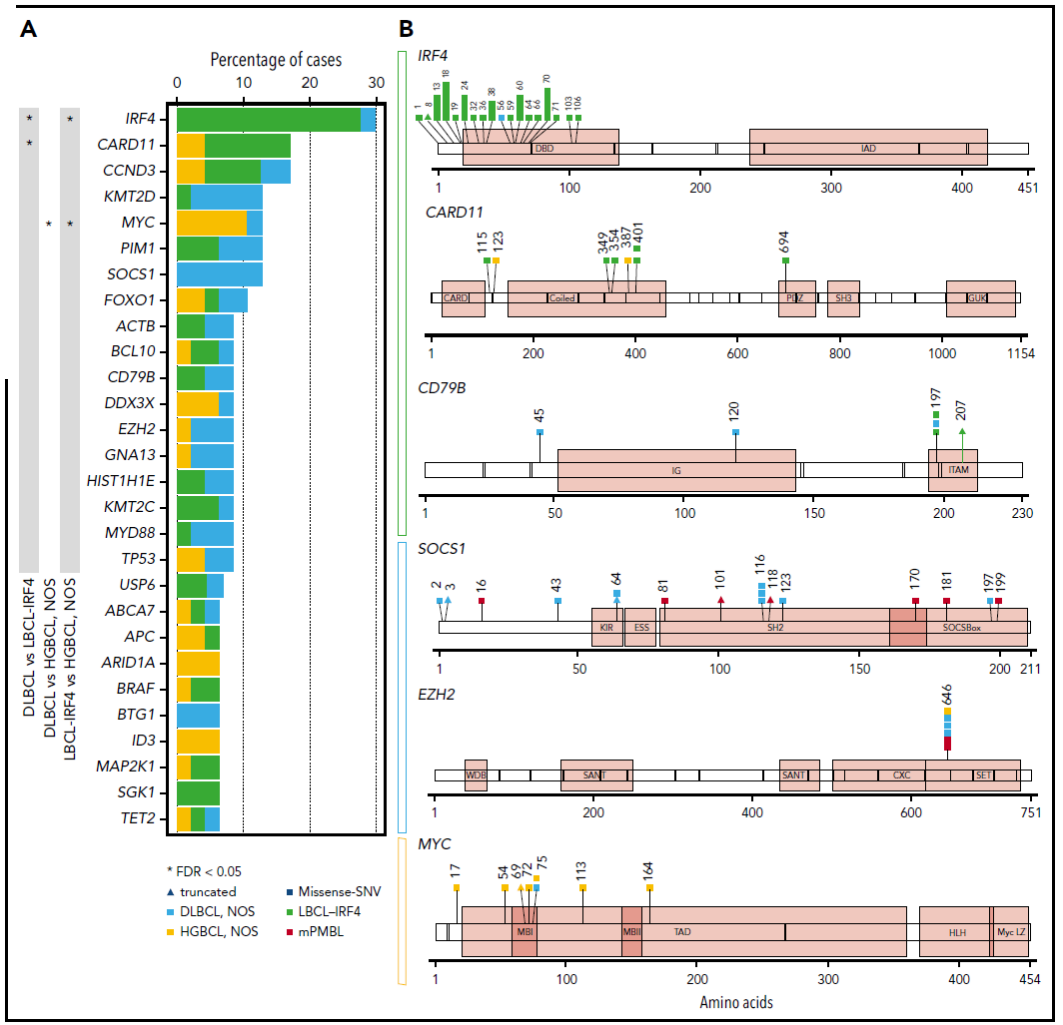
Quintanilla-Martinez, Virch Arch 2016

Large B-cell lymphoma with *IRF4* rearrangement

Distinct molecular profile of *IRF4*-rearranged large B-cell lymphoma

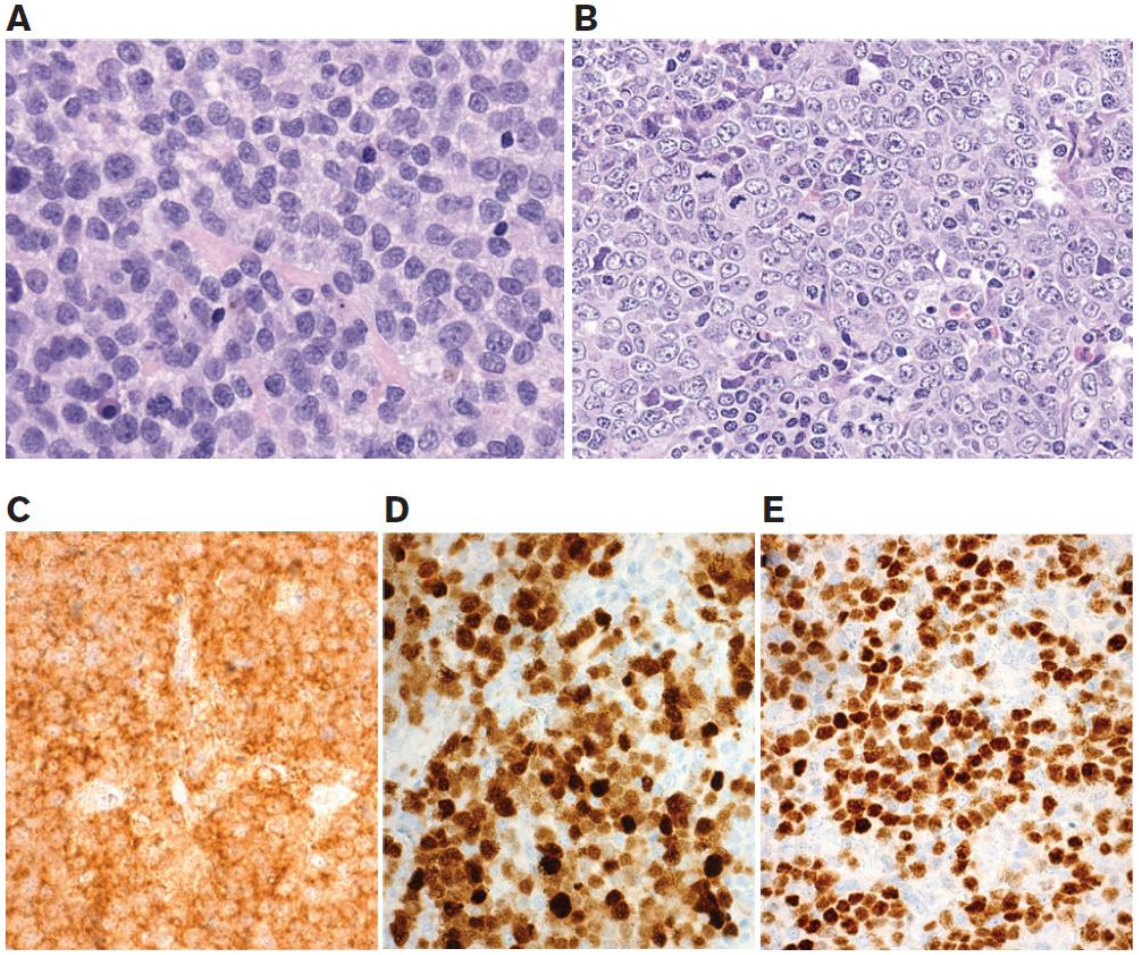
Joan Enric Ramis-Zaldivar,[1,2,*] Blanca Gonzalez-Farré,[1-3,*] Olga Balagué,[3] Verónica Celis,[4] Ferran Nadeu,[1,2] Julia Salmerón-Villalobos,[1] Mara Andrés,[5] Idoia Martin-Guerrero,[6,7] Marta Garrido-Pontnou,[8] Ayman Gaafar,[9] Mariona Suñol,[10] Carmen Bárcena,[11] Federico Garcia-Bragado,[12] Maitane Andión,[13] Daniel Azorín,[14] Itziar Astigarraga,[7] Maria Sagaseta de Ilurdoz,[15] Constantino Sábado,[16] Soledad Gallego,[16] Jaime Verdú-Amorós,[17] Rafael Fernandez-Delgado,[17] Vanesa Perez,[18] Gustavo Tapia,[19] Anna Mozos,[20] Montserrat Torrent,[21] Palma Solano-Páez,[22] Alfredo Rivas-Delgado,[3] Ivan Dlouhy,[3] Guillem Clot,[1,2] Anna Enjuanes,[1,2] Armando López-Guillermo,[3] Pallavi Galera,[23] Matthew J. Oberley,[24] Alanna Maguire,[25] Colleen Ramsower,[25] Lisa M. Rimsza,[26] Leticia Quintanilla-Martinez,[27] Elaine S. Jaffe,[23] Elías Campo,[1-3] and Itziar Salaverria[1,2]

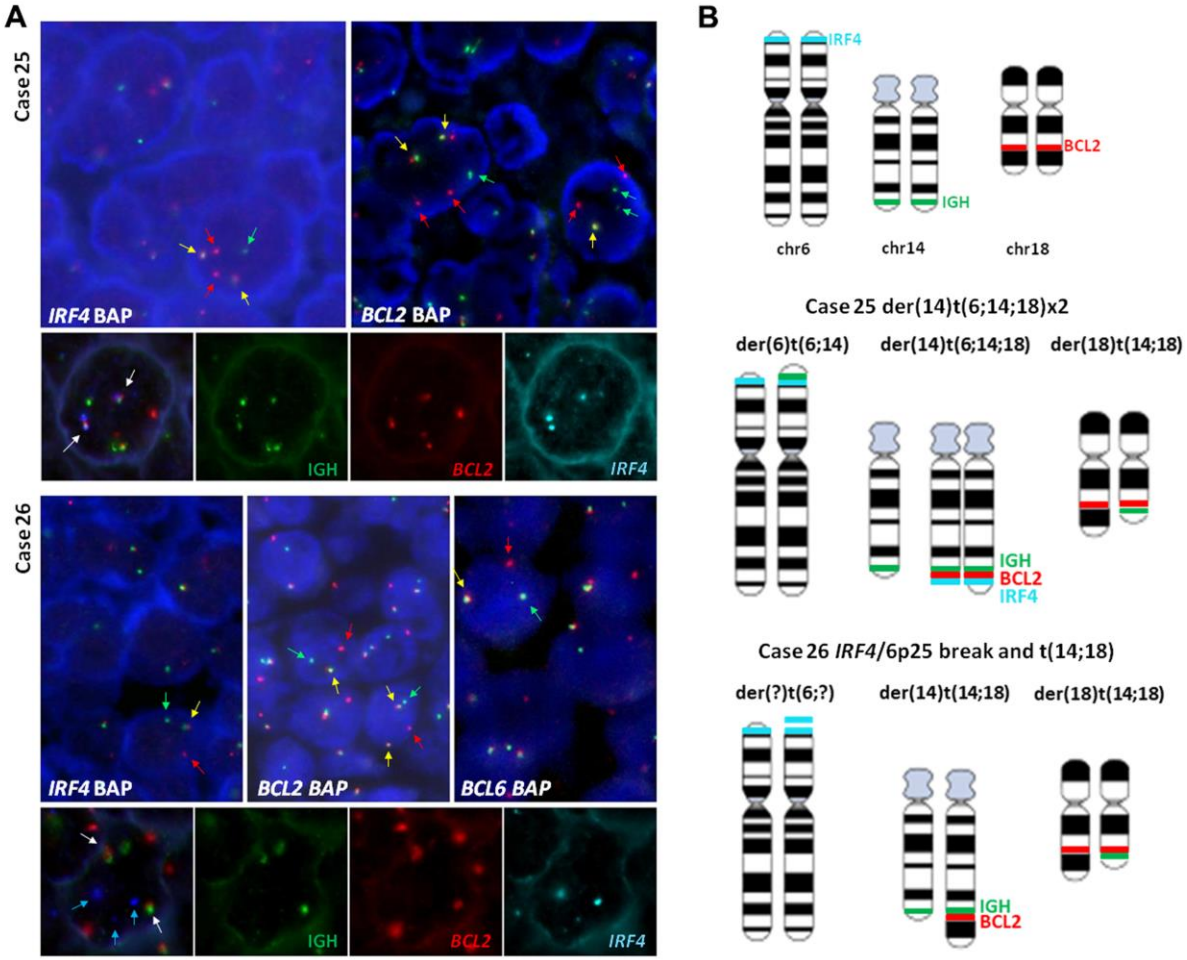
- The study included only children and young adults (<25 years)
- LBCL-*IRF4* reveals mostly GCB-GEP and a mutational profile distinct from other LBCL
- Frequent mutations in *IRF4* and NF-κB pathway (*CARD11, CD79B, MYD88*)
- Expression of CD10+, BCL6+, MUM1+



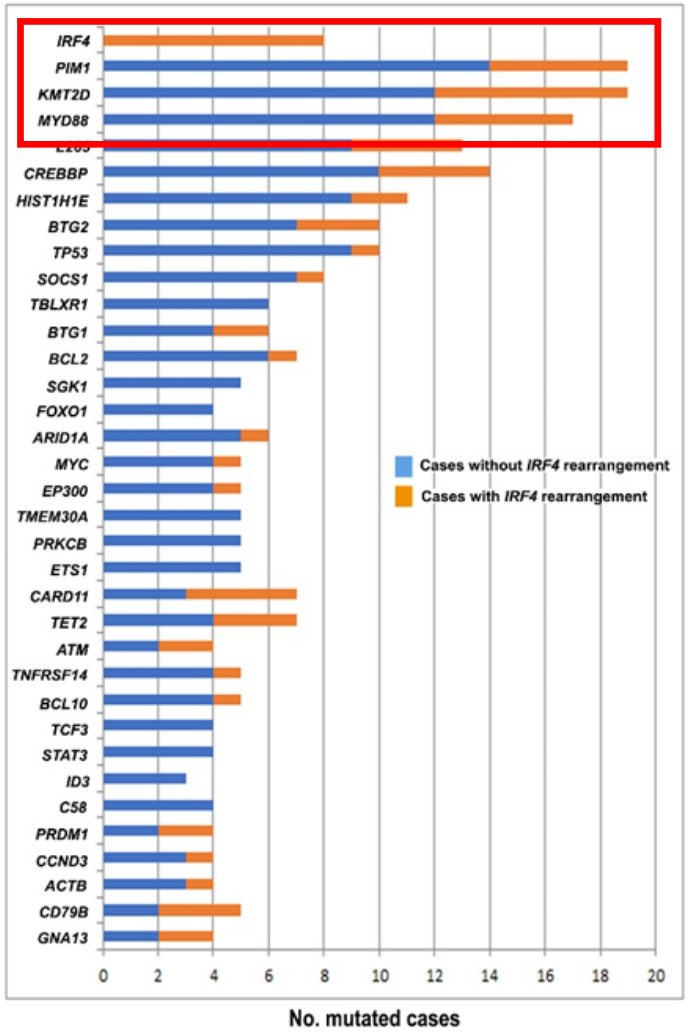
blood® 23 JANUARY 2020 | VOLUME 135, NUMBER 4

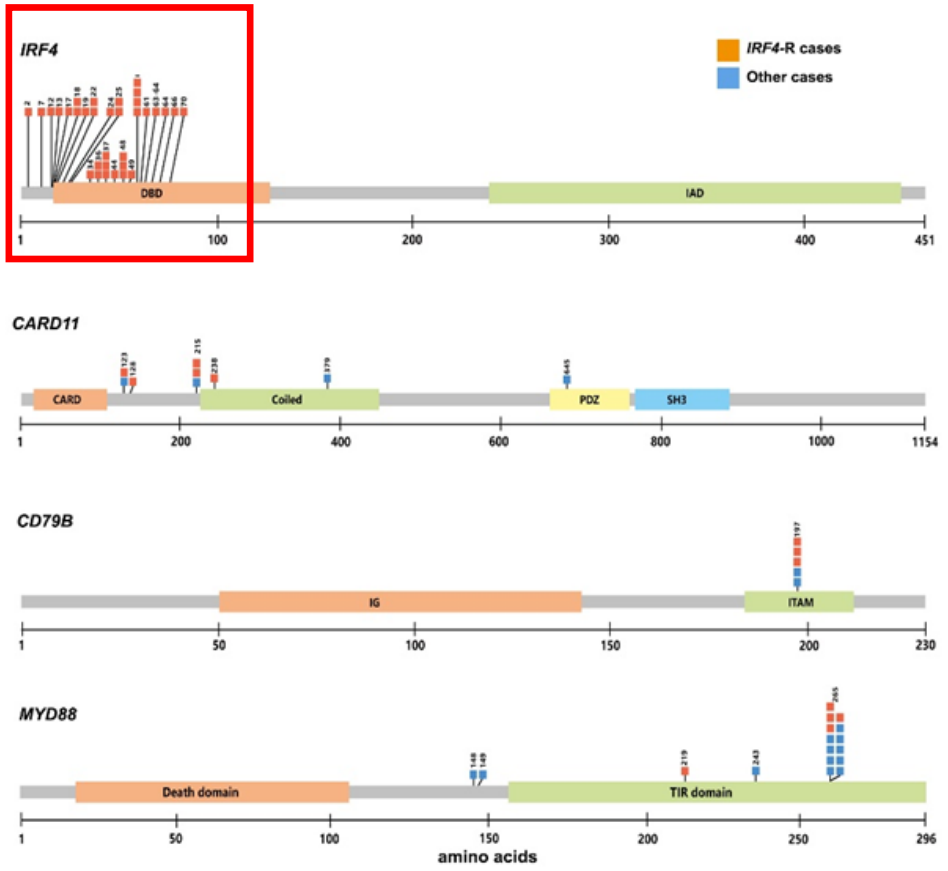
LBCL-*IRF4* in adults





Results- Mutations





- A total of 392 driver mutations in 55 analyzed cases (mean 10.62 mut/case)
- Most recurrently mutated genes: *KMT2D* and *PIM1*, followed by *MYD88* and *CREBBP*
- *IRF4* mutations were exclusively identified in cases with *IRF4* rearrangement (aSHM)

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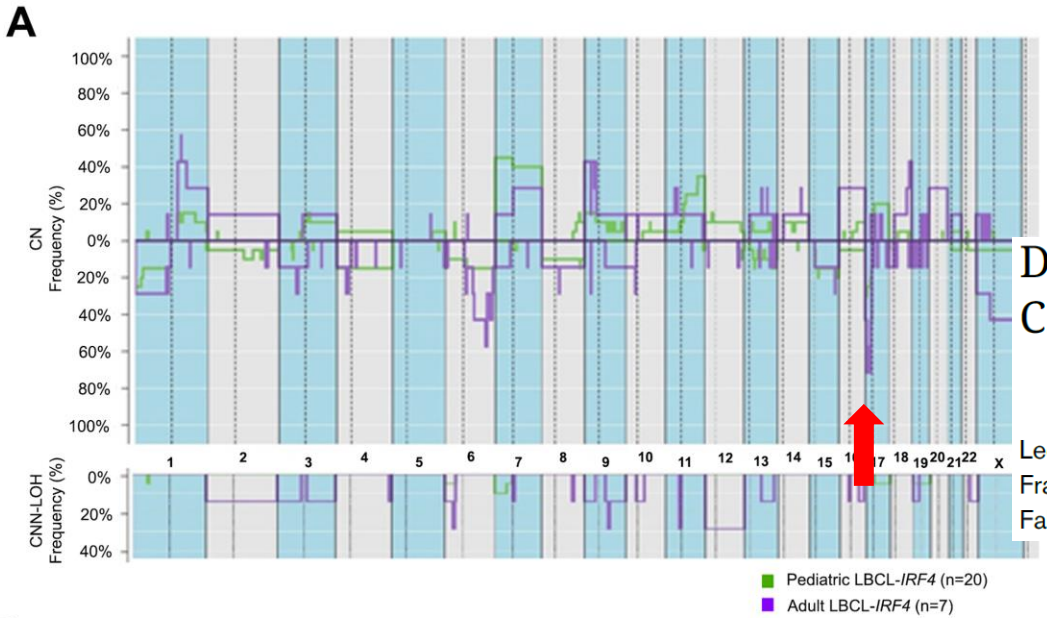
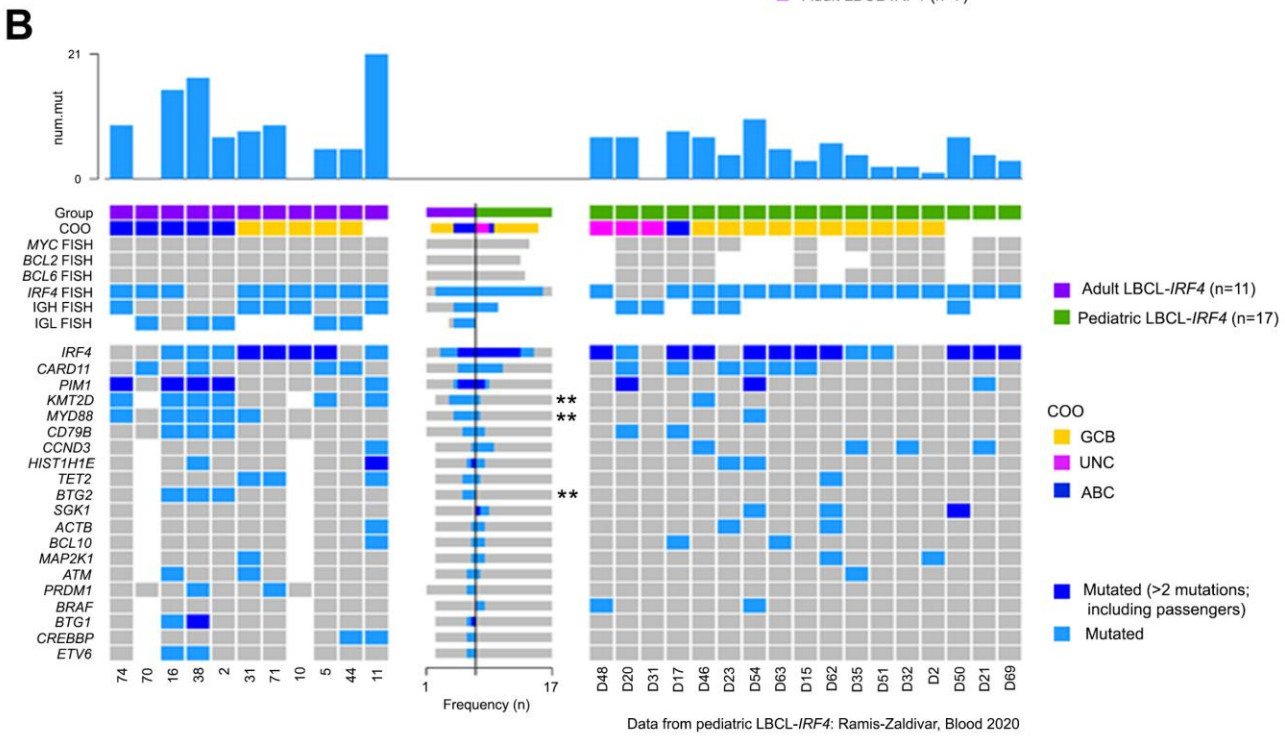
LBCL-*IRF4* in adults



Diffuse large B-cell lymphomas in adults with aberrant coexpression of CD10, BCL6, and MUM1 are enriched in *IRF4* rearrangements

Leonie Frauenfeld,[1,*] Natalia Castrejon-de-Anta,[2,*] Joan Enric Ramis-Zaldivar,[3,4] Sebastian Streich,[1] Julia Salmerón-Villalobos,[3,4] Franziska Otto,[1] Annika Katharina Mayer,[1] Julia Steinhilber,[1] Magda Pinyol,[2] Barbara Mankel,[1] Colleen Ramsower,[5,6] Irina Bonzheim,[1] Falko Fend,[1] Lisa M. Rimsza,[5,6] Itziar Salaverria,[3,4] Elias Campo,[2-4,†] Olga Balagué,[2-4,†] and Leticia Quintanilla-Martinez[1,7,†]

LARGE B-CELL LYMPHOMAS WITH *IRF4* REARRANGEMENT IN ADULTS blood advances 12 APRIL 2022 • VOLUME 6, NUMBER 7



Data from pediatric LBCL-*IRF4*: Ramis-Zaldivar, Blood 2020

- No differences in recurrent CN altered regions, but adult cases has higher genetic complexity (16.85 alt/case in adults vs 6.25 alt/case in pediatric cases; P=0.33)
- Higher mutational load in adult cases (10.7 vs 4.7 mutations/case) with higher frequency of *KMT2D, MYD88* and *BTG2* mutations (Fisher; P<0.05)

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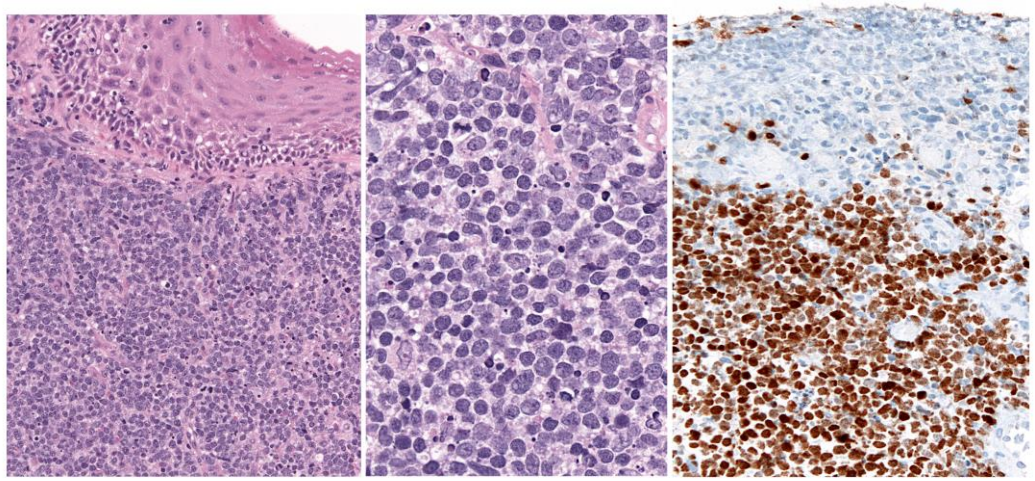
How to suspect the diagnosis of LBCL-*IRF4*-R

Children and young adults

Waldeyer´s ring



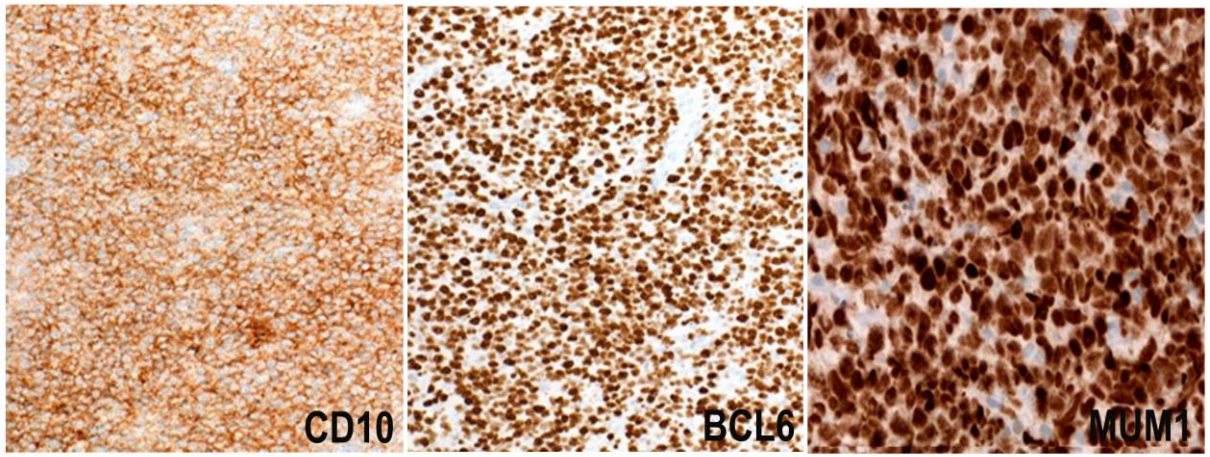
Localization
Tonsil and GI
Diffuse/follicular

Strong MUM1+
Aberrant CD5 expression

Do *IRF4* and IGH FISH analyses
Mutational analysis (optional)

Adults and elderly patients

Lymph node



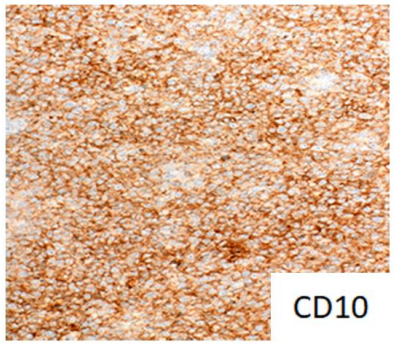
Diffuse/follicular
Follicular 3B

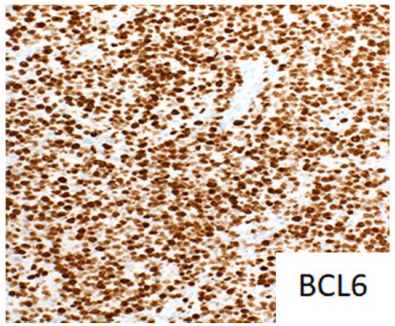
Triple positive
CD10+BCL6+MUM1+

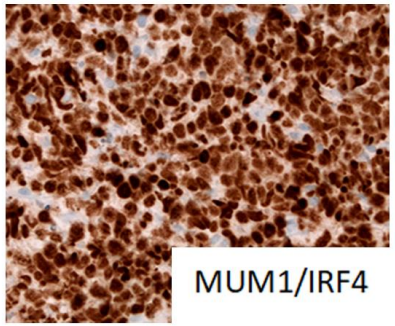
Strong MUM1+

Do *IRF4* and IGH FISH analyses
Mutational analysis (optional)
BCL2, BCL6 and *MYC*
- BCL2-R and MYC-R not accepted

Diffuse large B-cell lymphoma in adults with aberrant co-expression of CD10, BCL6 and MUM1/IRF4





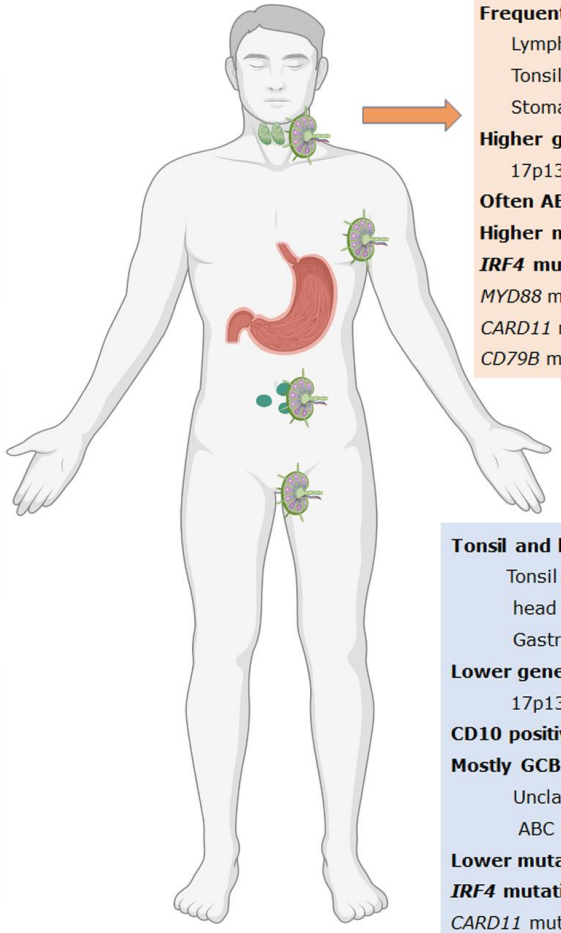


Group 1 (26%)
No translocations
Mostly ABC/MCD profile

Group 2 (22%)
IRF4 translocations only
Frequent *IRF4* mutations

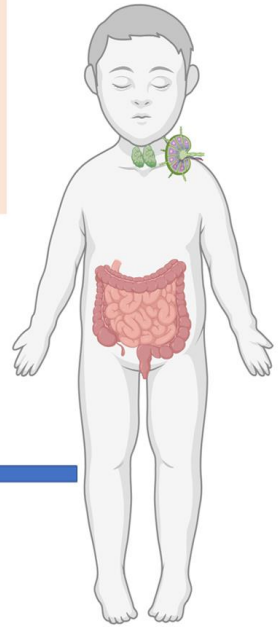
Group 3 (52%)
BCL2/BCL6/MYC/IRF4/IGH translocations
Mostly GCB/EZB profile

Adult DLBCL-*IRF4*



Frequent lymph node presentation
Lymph node 45%
Tonsil 27%
Stomach 18%
Higher genetic complexity 16.8 alt/case
17p13.2 loss 71%
Often ABC COO 50%
Higher mutational load 10.7/case
***IRF4* mutations 82%**
MYD88 mutations 45%
CARD11 mutations 36%
CD79B mutations 27%

Pediatric LBCL-*IRF4*

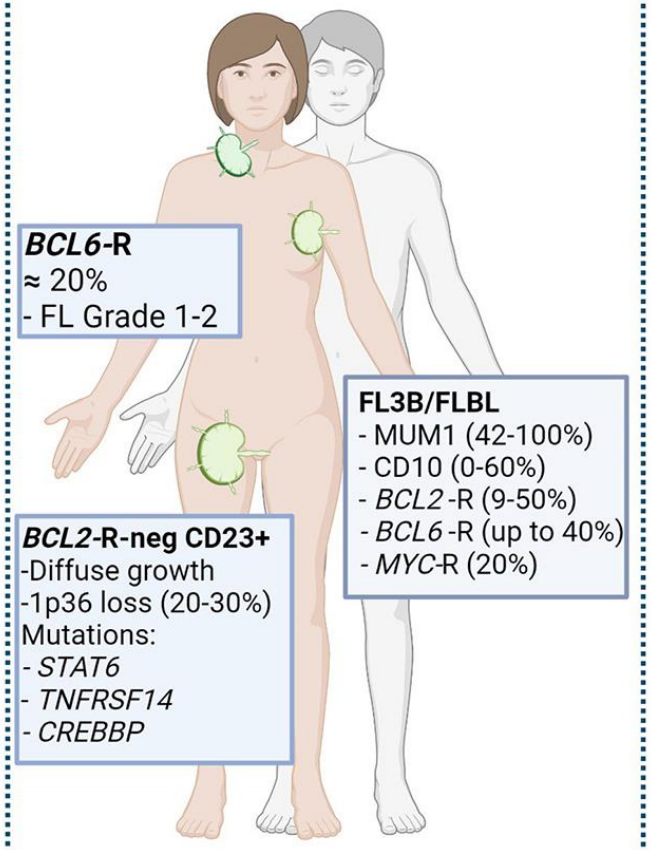


Tonsil and head and neck lymph nodes
Tonsil 40%
head and neck LN 40%
Gastrointestinal tract 10%
Lower genetic complexity 6.2 alt/case
17p13.2 loss 25%
CD10 positive 55%
Mostly GCB COO 72%
Unclassified 21%
ABC COO 7%
Lower mutational load 4.7/case
***IRF4* mutations 76%**
CARD11 mutations 35%
MAP2K1 mutations 12%

Frauenfeld et al blood advances 12 APRIL 2022 • VOLUME 6, NUMBER 7

Alternative forms of follicular lymphoma t(14;18)-negative

Nodal presentation

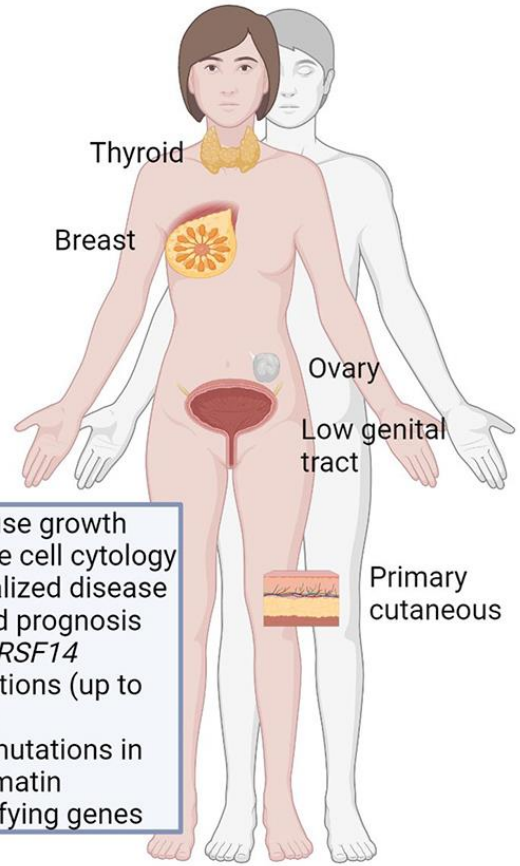


***BCL6*-R**
≈ 20%
- FL Grade 1-2

FL3B/FLBL
- MUM1 (42-100%)
- CD10 (0-60%)
- *BCL2* -R (9-50%)
- *BCL6* -R (up to 40%)
- *MYC*-R (20%)

***BCL2*-R-neg CD23+**
-Diffuse growth
-1p36 loss (20-30%)
Mutations:
- *STAT6*
- *TNFRSF14*
- *CREBBP*

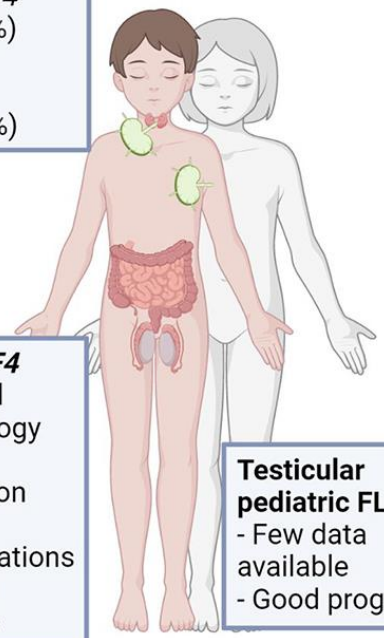
Extranodal presentation



-Diffuse growth
-Large cell cytology
-Localized disease
-Good prognosis
-TNFRSF14 mutations (up to 60%)
-No mutations in chromatin modifying genes

Follicular lymphomas in children and young adults

PTFL
-Localized disease
-Good prognosis
-TNFRSF14 (up to 54%)
-MAP2K1 (40-50%)
-IRF8 (30%)



LBCL- *IRF4*
-Large cell moprphology
-High proliferation
-IRF4-R
*-IRF4-m*utations
-Excellent prognosis

Testicular pediatric FL
- Few data available
- Good prognosis

Salaverria, Weigert, Quintanilla-Martinez, Blood advances 2023, in review

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kav wiener krankenanstalten verbund Unternehmen Gesundheit

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All Wales Lymphoma Panel -1998-

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