Foundation for the Institute of Oncology Research

IOR
An institute affiliated to USI

Linfomi della Zona Marginale
Basi Biologiche

Davide Rossi, MD, PhD

Hematology
Institute of Oncology Research
Oncology Institute of Southern Switzerland
Bellinzona, Switzerland

Key aspects

Post-GC mature B-cells residing in the marginal zone

Subtypes defined by the anatomical site of origin (i.e., microenvironment)

- Extranodal (MALT): 70%
- Splenic: 20%
- Nodal: 10%

Median age ~60-65 years

Slight female predominance, especially in MALT lymphoma

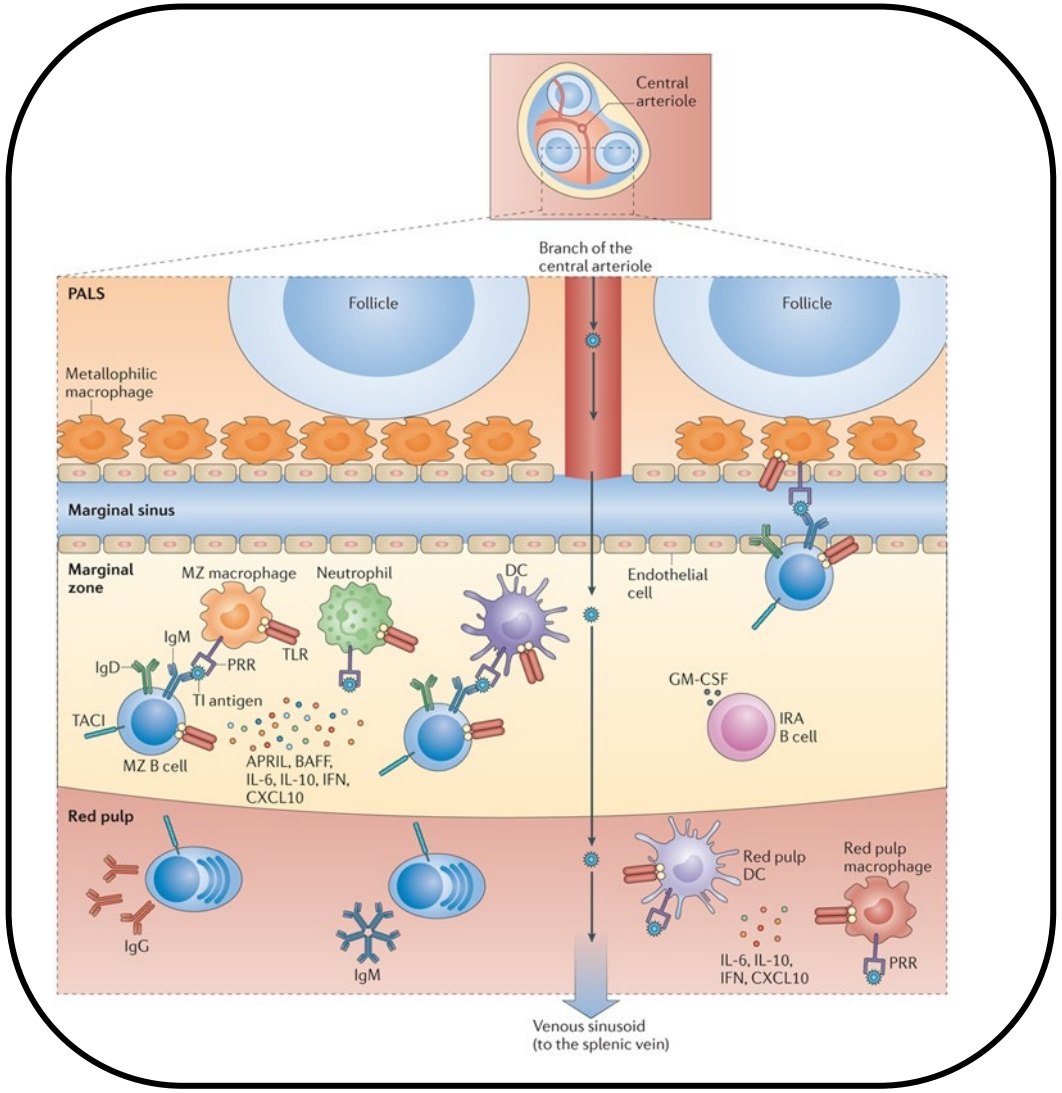
Risk factors

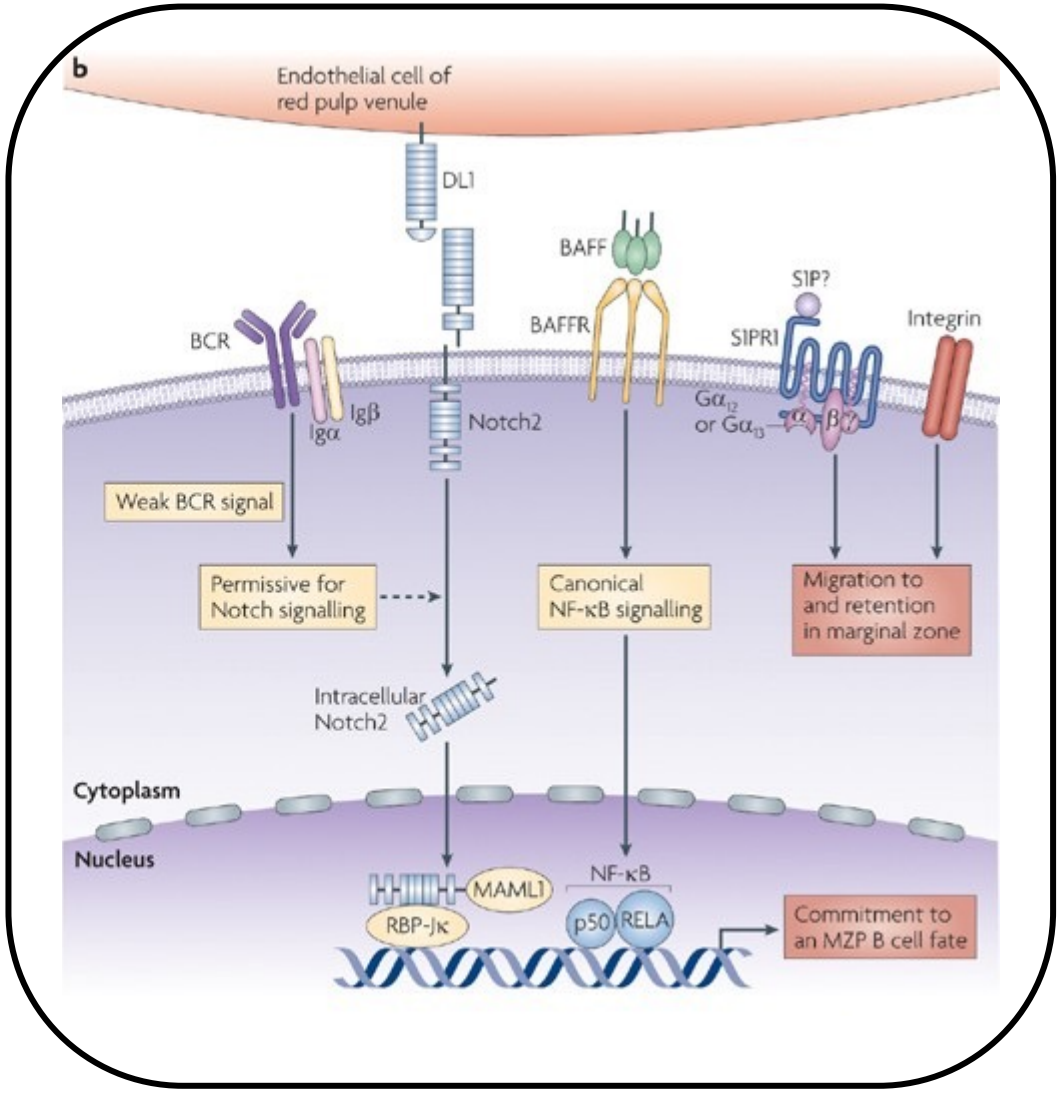
- Autoimmune diseases (Sjögren's syndrome, Hashimoto's thyroiditis)
- Chronic infections (*H. pylori*, *C. psittaci*, *B. burgdorferi*, C. *jejuni*, HCV)

Indolent course but may progress and transform

Differential diagnosis may be challenging (nodal and splenic MZL)

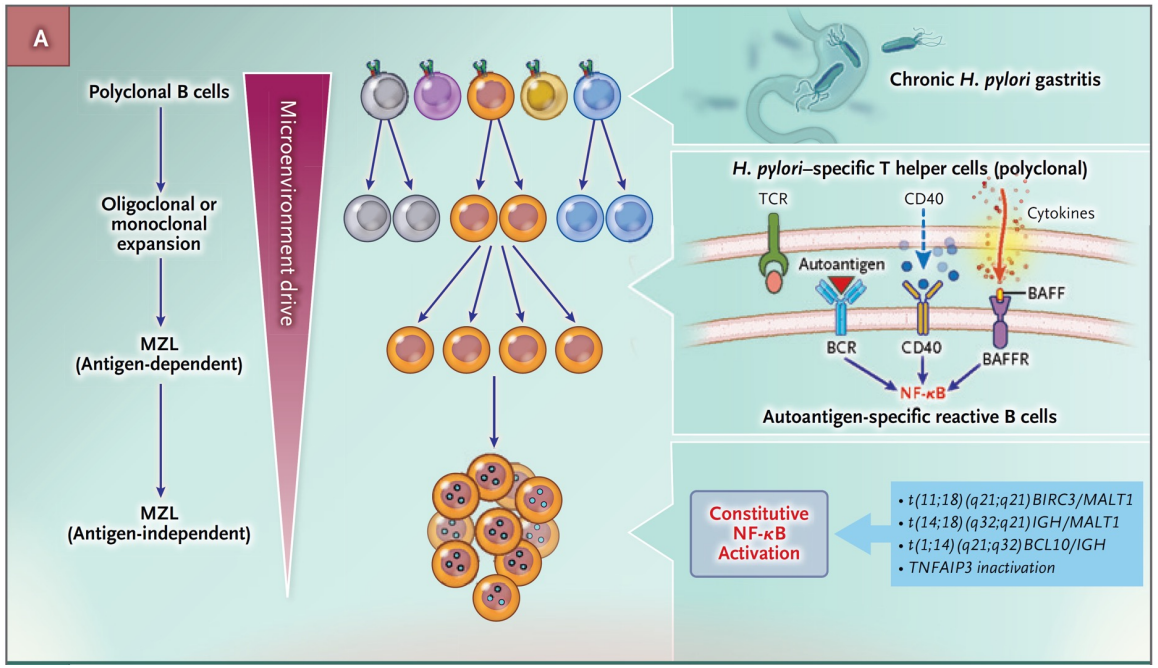
Cell of origin of MZL

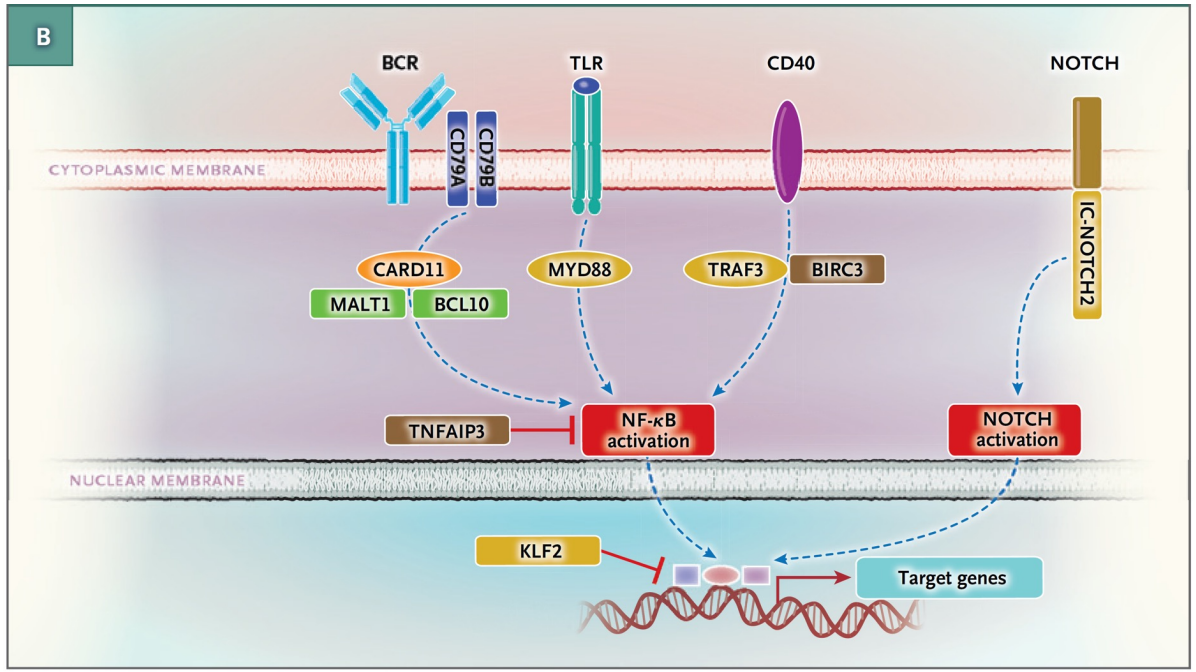




Cerutti A, Nat Rev Immunol 2013
Pillai S, Nat Rev Immunol 2019

Pathogenesis of MZL

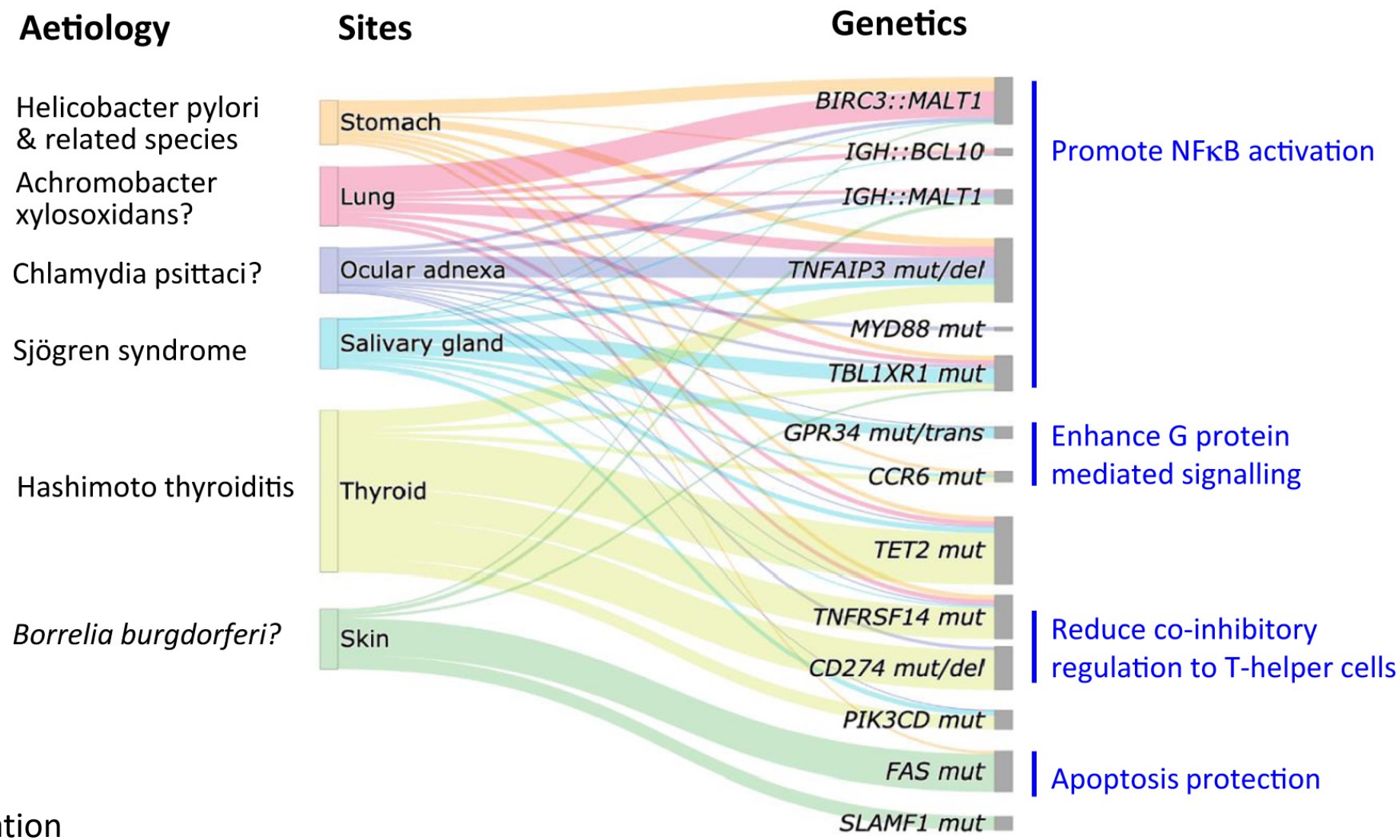




Rossi D, New Engl J Med. 2022

Site specific molecular heterogeneity of extranodal MZL

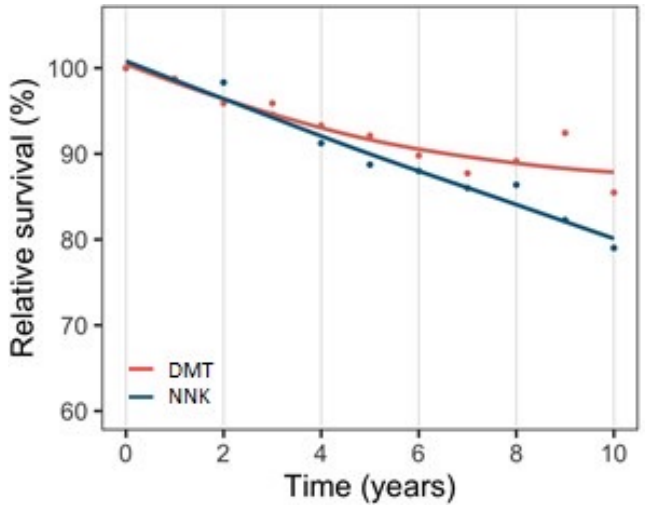
Extranodal marginal zone lymphoma



5th WHO Classification

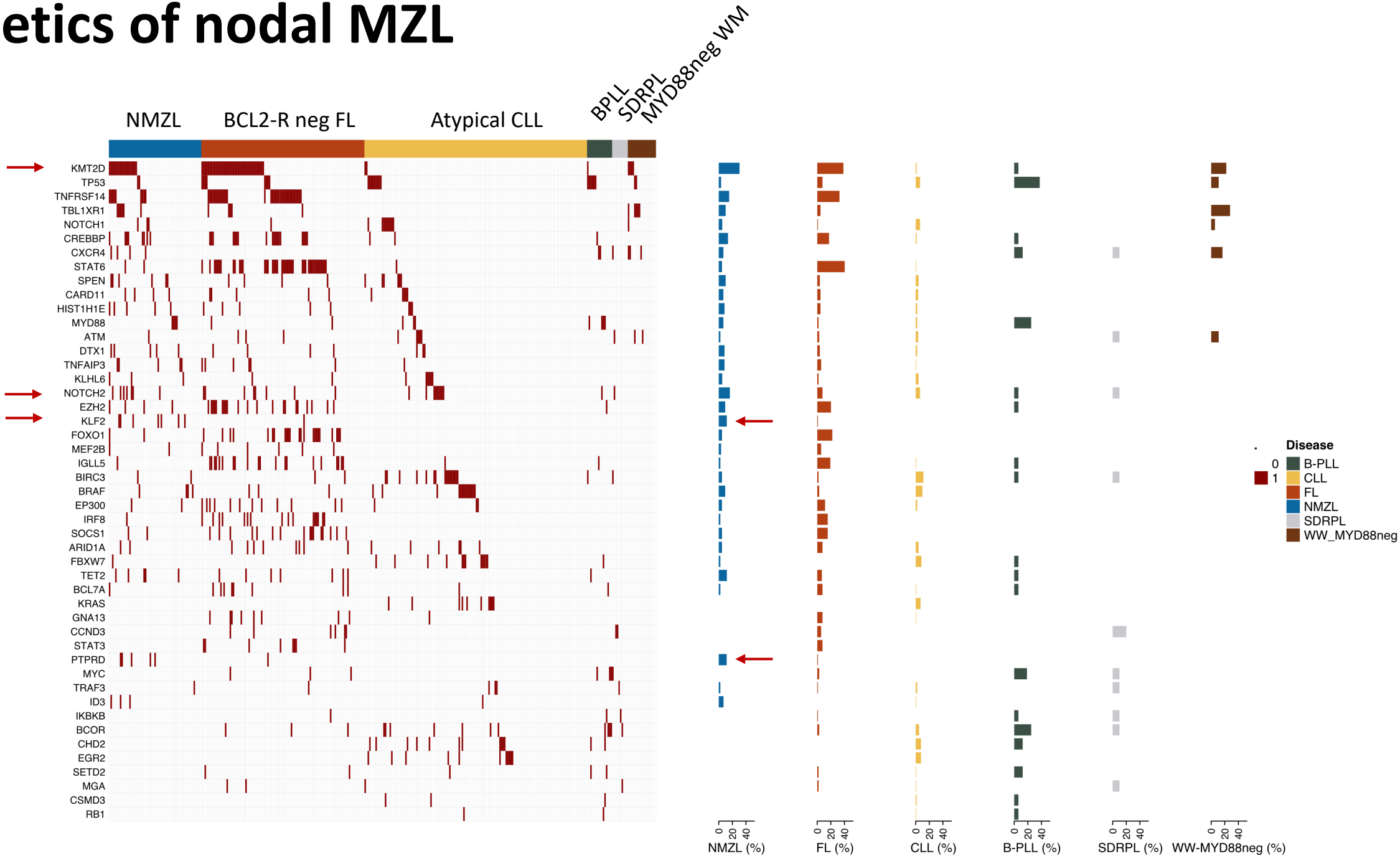
A Genetics of splenic MZL

- Lack of *MYD88* L265P among SMZL confirmed on spleen histology
- NNK
  - 58% of cases
  - NF-κB, NOTCH, and *KLF2* mutations
  - IGHV1-2*04 usage
  - Deletion 7q
- DMT
  - 32% of cases
  - DNA-damage response, MAPK, and TLR mutations

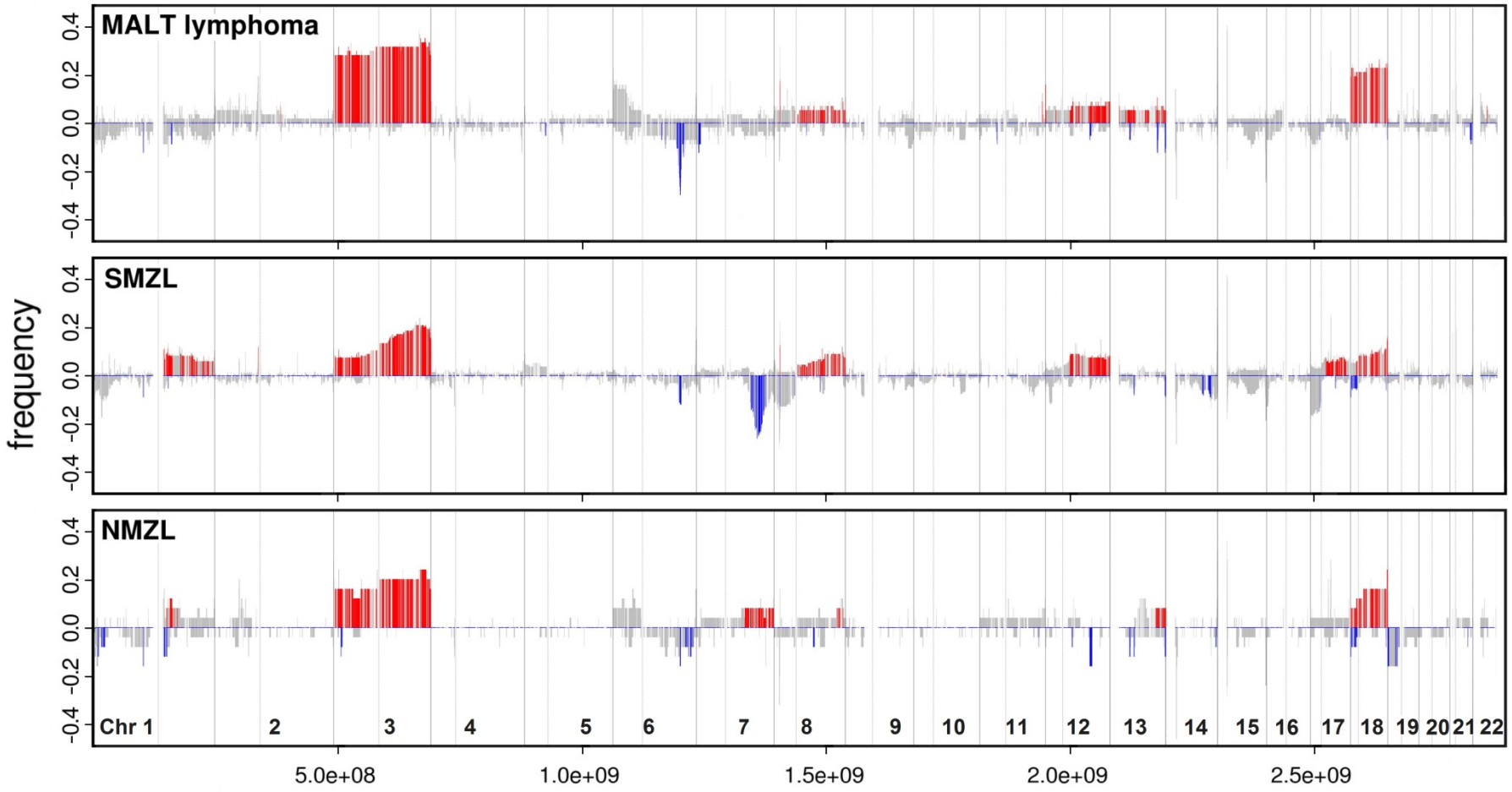


Bonfiglio F, Blood. 2022

Genetics of nodal MZL



Cytogenetics of MZL



Rinaldi A, et al. Blood 2011

Implications for diagnosis

Small B-cell lymphomas without defining features

- **Marginal zone lymphomas**
- Follicular lymphoma **without *IGH::BCL2***
- **Atypical** chronic lymphocytic leukemia
- Lymphoplasmacytic lymphoma **lacking *MYD88* L265P**
- Mantle cell lymphoma **lacking *IGH::CCND1***
- Splenic B-cell lymphoma/leukemia unclassifiable
- (B-cell prolymphocytic leukemia)

Small B-cell neoplasms with unexpected phenotypes

MZL phenotype CD5-/CD23-/BCL6-/CD10- (MZL? LPL?)

Unexpected phenotypes

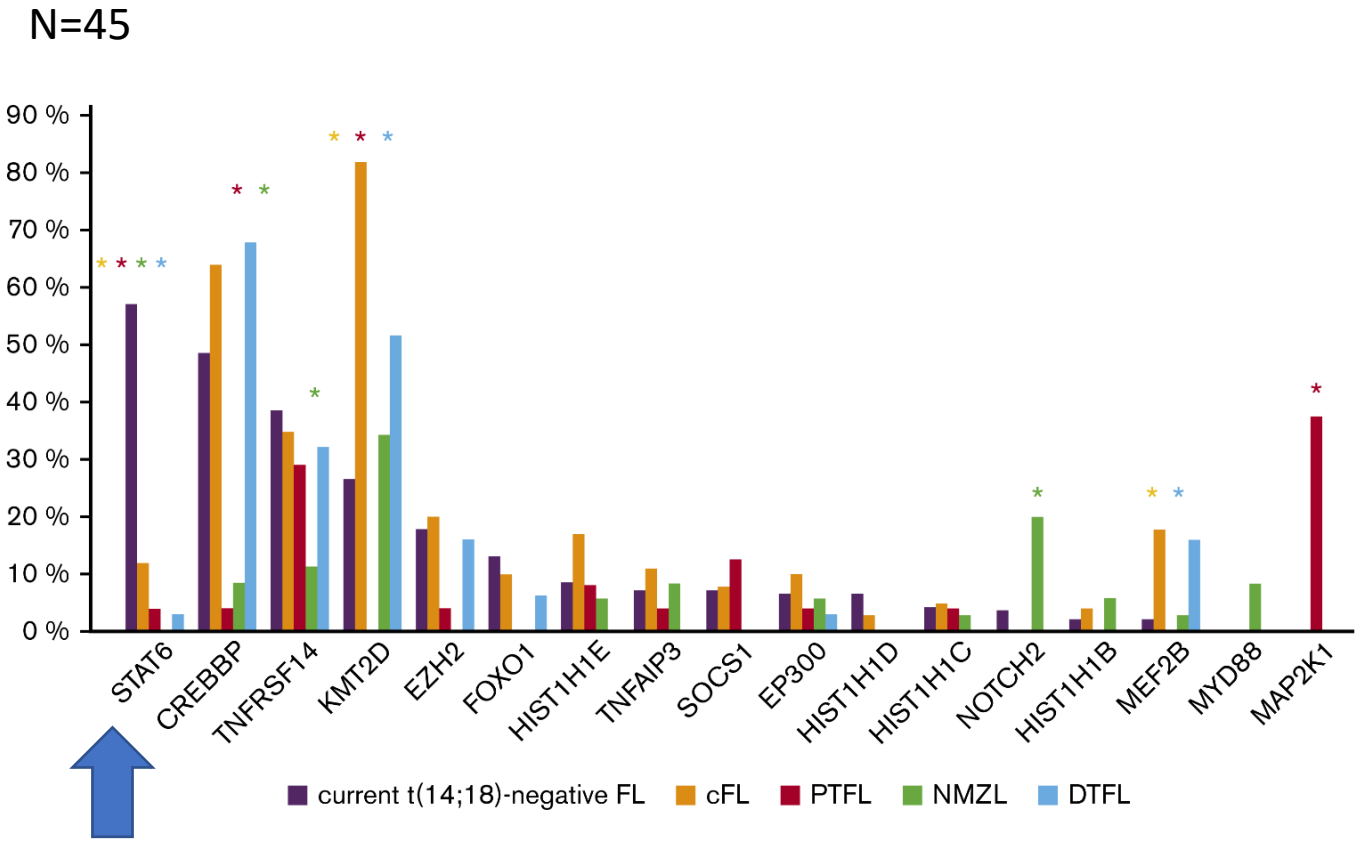
- CD5-/CD23+ (MZL? FL?)
- CD5+/CD23-/cyclin D1- (MZL? MCL?)
- CD5+/CD23+, but bright CD20+/sIg+, CD79b+, FMC7+ (MZL? CLL?)

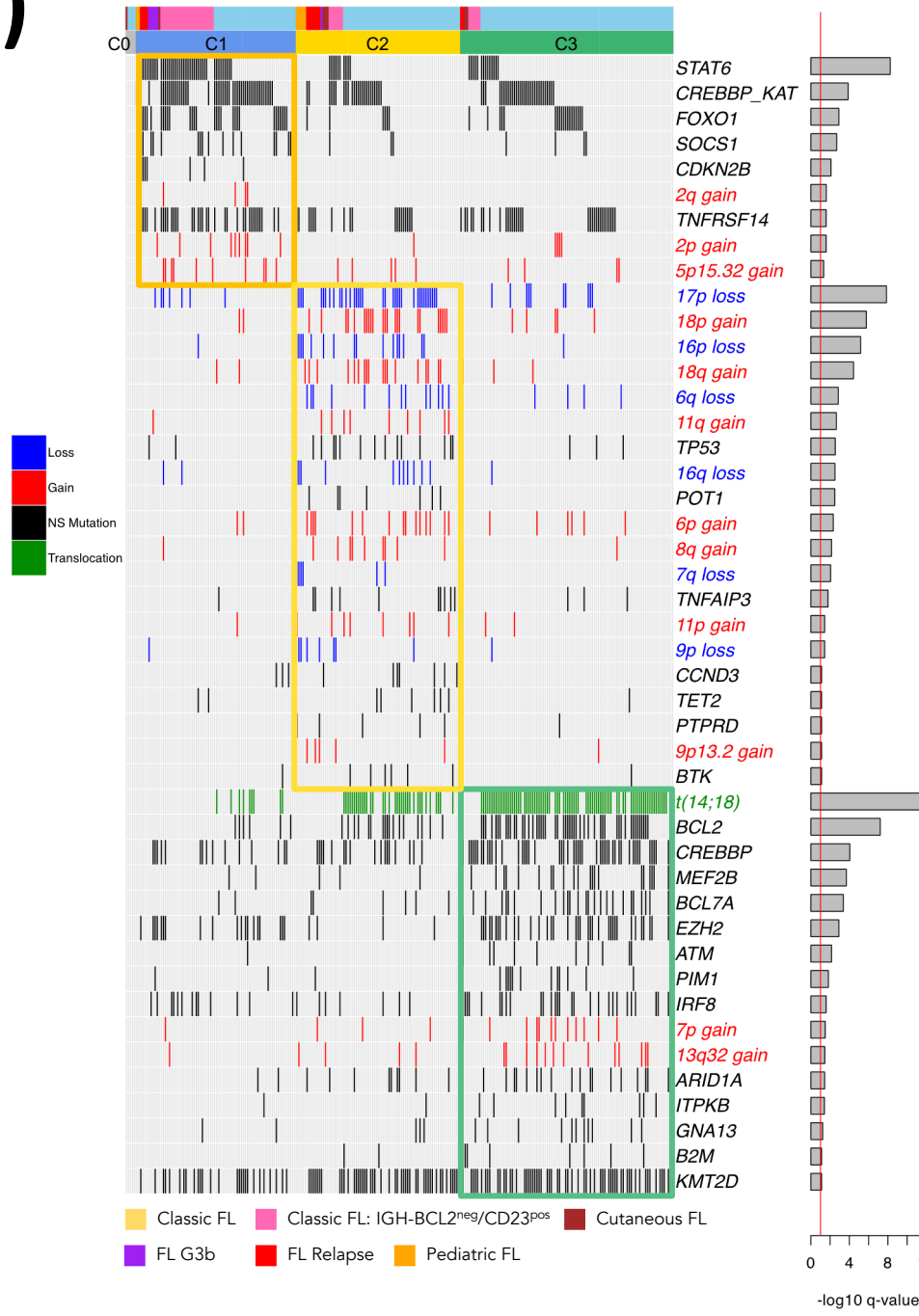
Dissemination of occult EMZL in 20% of NMZL presenting in limited stage

Wrong diagnosis in 20-30% of cases

Diagnosis is challenging: wrong diagnosis affects outcome

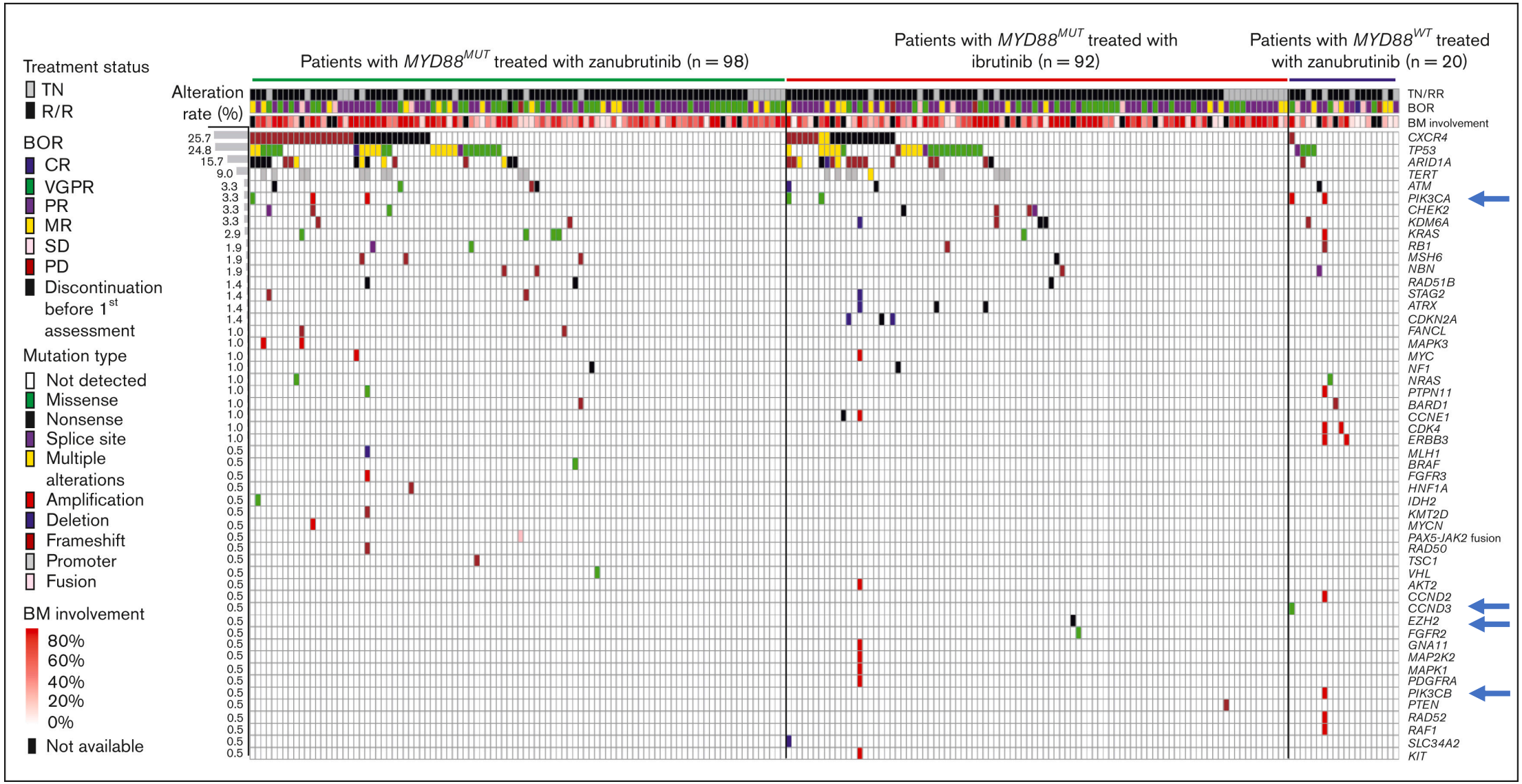
Follicular lymphoma (without *IGH::BCL2*)





Nann D, et al, Blood Adv. 2020

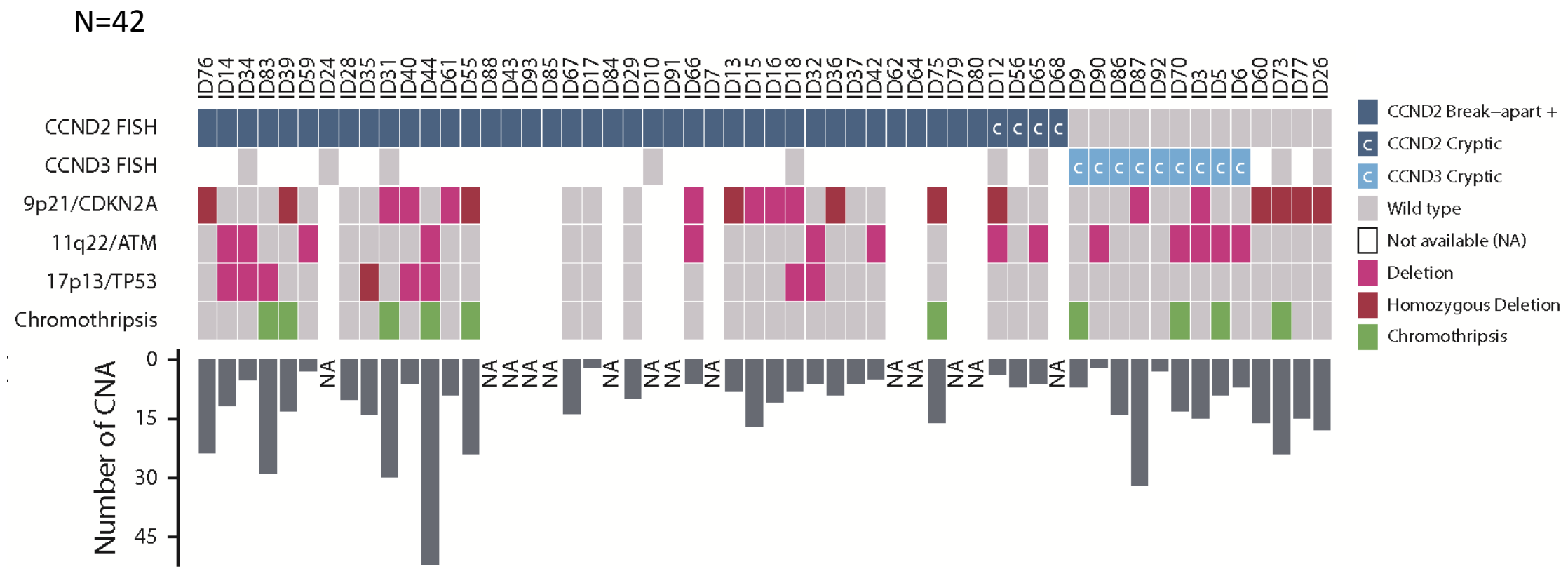
MYD88 wild type LPL



Does it really exist? No genetic biomarkers

Tam CS, et al, Blood Adv. 2024

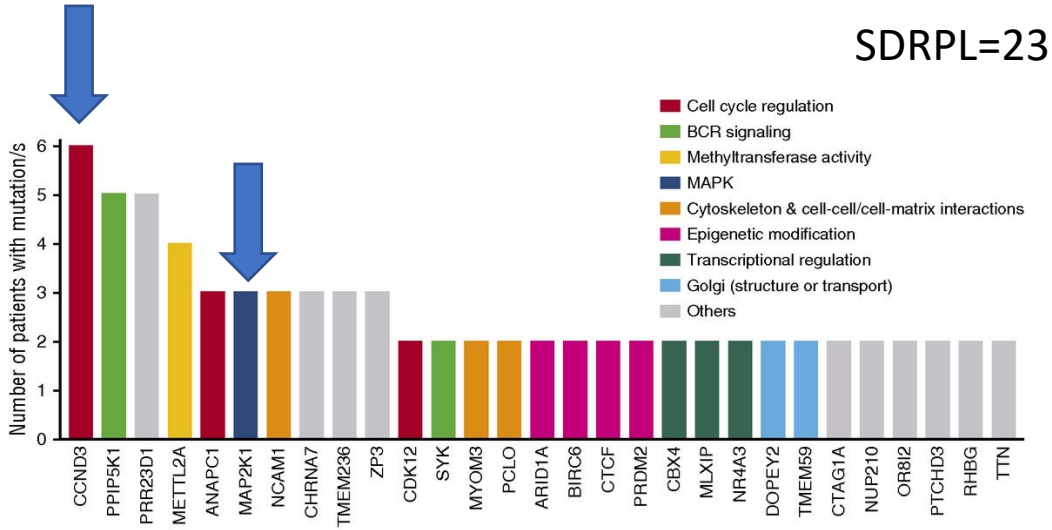
Genetics of Cyclin D1 negative MCL



CCND2 and CCND3 translocation are the best biomarkers

Martín-Garcia D, et al, Blood. 2018

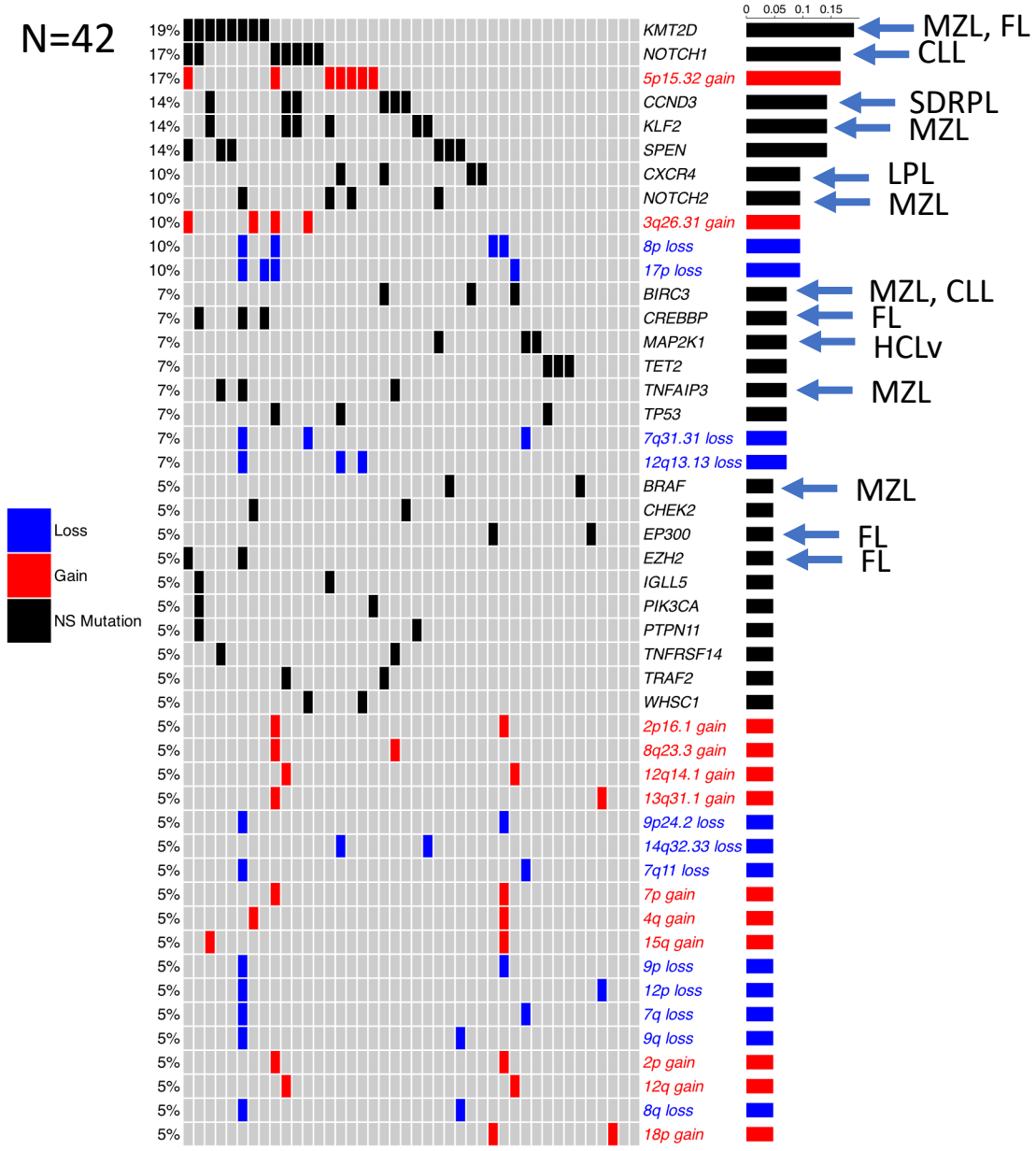
Splenic B-cell lymphomas unclassifiable



Curiel-Olmo S, et al. Blood. 2017

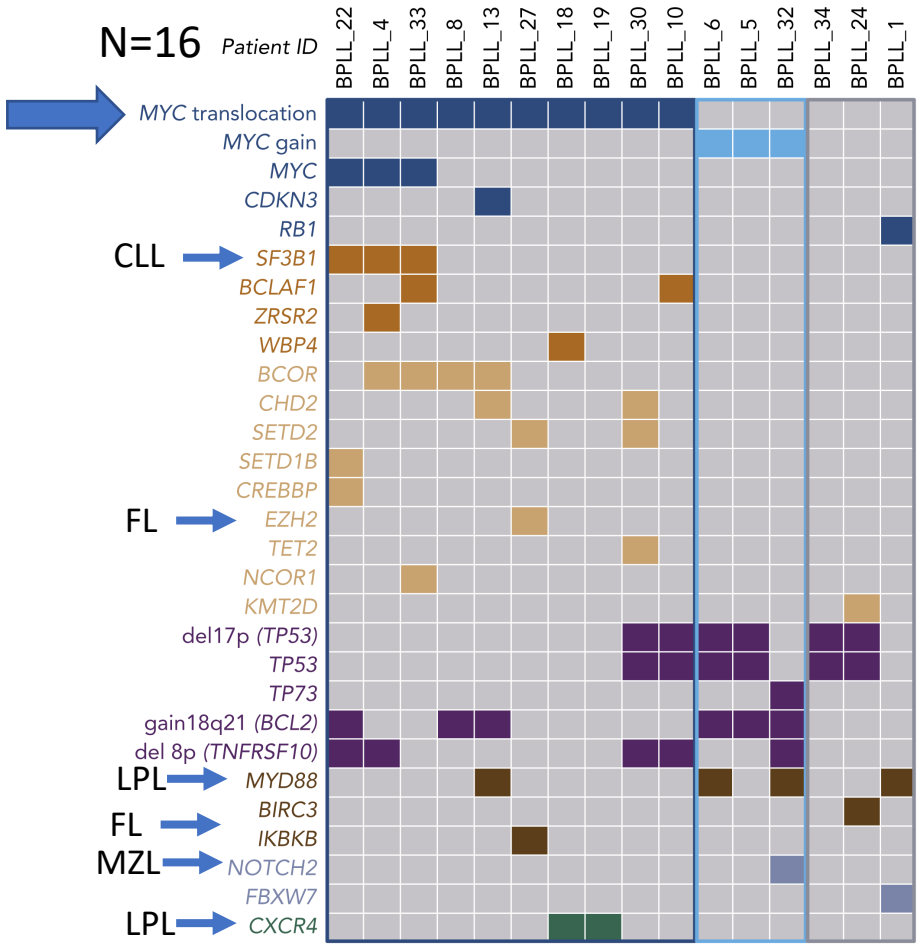
MAP2K1 mutations in 50% of HCLv (n=7)

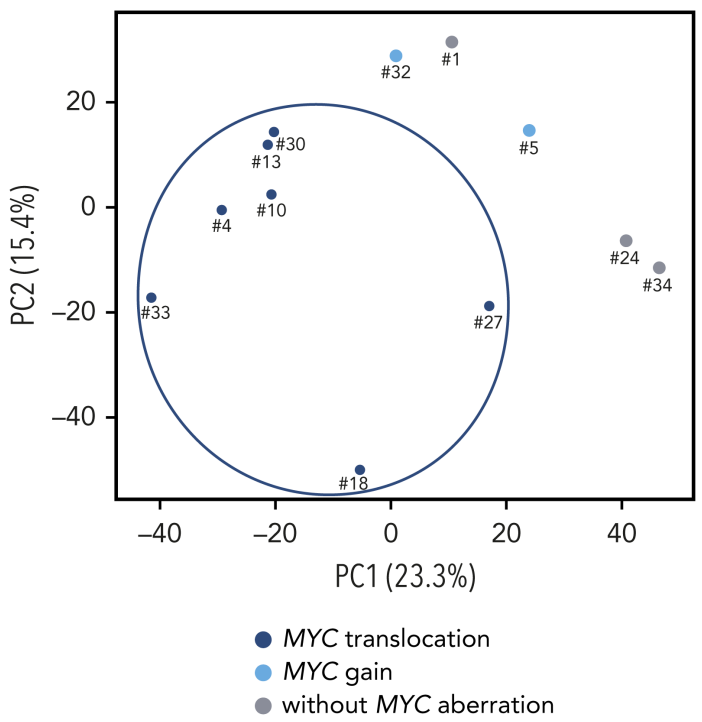
Waterfall JJ, et al. Nat Gent. 2014



Unpublished

Genetics of B-PLL





MYC translocation (mostly with IG) is a biomarker of B-PLL

Chapiro E, et al, Blood. 2019

Extended diagnostics

- Marginal zone lymphomas → **+3, +12, +18, -7, *KLF2* m, *NOTCH2* m**
- Dissemination of an occult MALT MZL → **extensive imaging**
- Follicular lymphoma without *IGH::BCL2* → **GCB IHC marker, *STAT6* m**
- Chronic lymphocytic leukemia → **+12, -13q, *SF3B1* m, *NOTCH1* m**
- Lymphoplasmacytic lymphoma → ***MYD88* L265P**
- Mantle cell lymphoma lacking *IGH::CCND1* → **IHC SOX11**
- Splenic B-cell lymphoma/leukemia unclassifiable → ***MAP2K1* m, *CCND3* m**

Clinico-pathologic variants

MZL non-CLL type/CBL-MZ

- Isolated lymphocytosis
- Matutes score <3
- No clinical evidence of MZL
- Morphologic heterogeneity
- Mixed patterns of BM infiltration
- Del(7q), *NOTCH*, NF-kB, KLF2, MYD88, CCND3, MAP2K1

Xochelli A, Blood 2014
Bruscaggin A, Br J Haematol. 2014
Kalpadakis C, Hematol Oncol. 2017
Defrancesco I, Hematol Oncol. 2020
Parker H, Blood Adv. 2018

SMZL with nodal dissemination

- Extra hilar lymph nodes: 20-30%
- Risk factor of the HPLL and MZL-IPI

Genetic lesion	Enrichment	P(Adj)
del7q31.33	1.13	0.9
KLF2	0.97	0.9
NOTCH2	1.20	0.9
amp12q24.13	1.38	0.9
del1p36.32	0.28	0.9
del11q12.3	0.55	0.9
KMT2D	1.65	0.9
TNFAIP3	1.37	0.9
amp22q12.1.	1.04	0.9
NOTCH1	0.52	0.9
CREBBP	0.44	0.9
CARD11	1.83	0.9
amp15q26.1.	0.48	0.9
SPEN	1.53	0.9
TP53	0.35	0.9
ARID1A	0.58	0.9
ATM	0.38	0.9
TBL1XR1	1.64	0.9
TRAF3	1.64	0.9
CCND3	0.82	0.9
EP300	1.51	0.9
TET2	0.26	0.9
MYD88	1.11	0.9
SIN3A	1.11	0.9

Arcaini L, EClinicalMedicine. 2024
Bonfiglio F, Blood. 2022
Iannitto E, Br J Haematol. 2018
Arcaini L, Blood. 2006
Montalbán C, Abraira V, Arcaini L, Domingo-Domenech E, Guisado-Vasco P, Iannitto E, Br J Haematol. 2012
Berger F, Blood. 2000

MZL with aggressive histologic presentation

- Increased number of scattered large cells
  - Definition: large cells >10 per HPF
  - Ki-67 expression $\geq$30%
- Prevalence: 20% (more common in NMZL)
- Presentation with advanced stage and increased LDH
- Shorter PFS, increased rate of relapse, increased rate of transformation

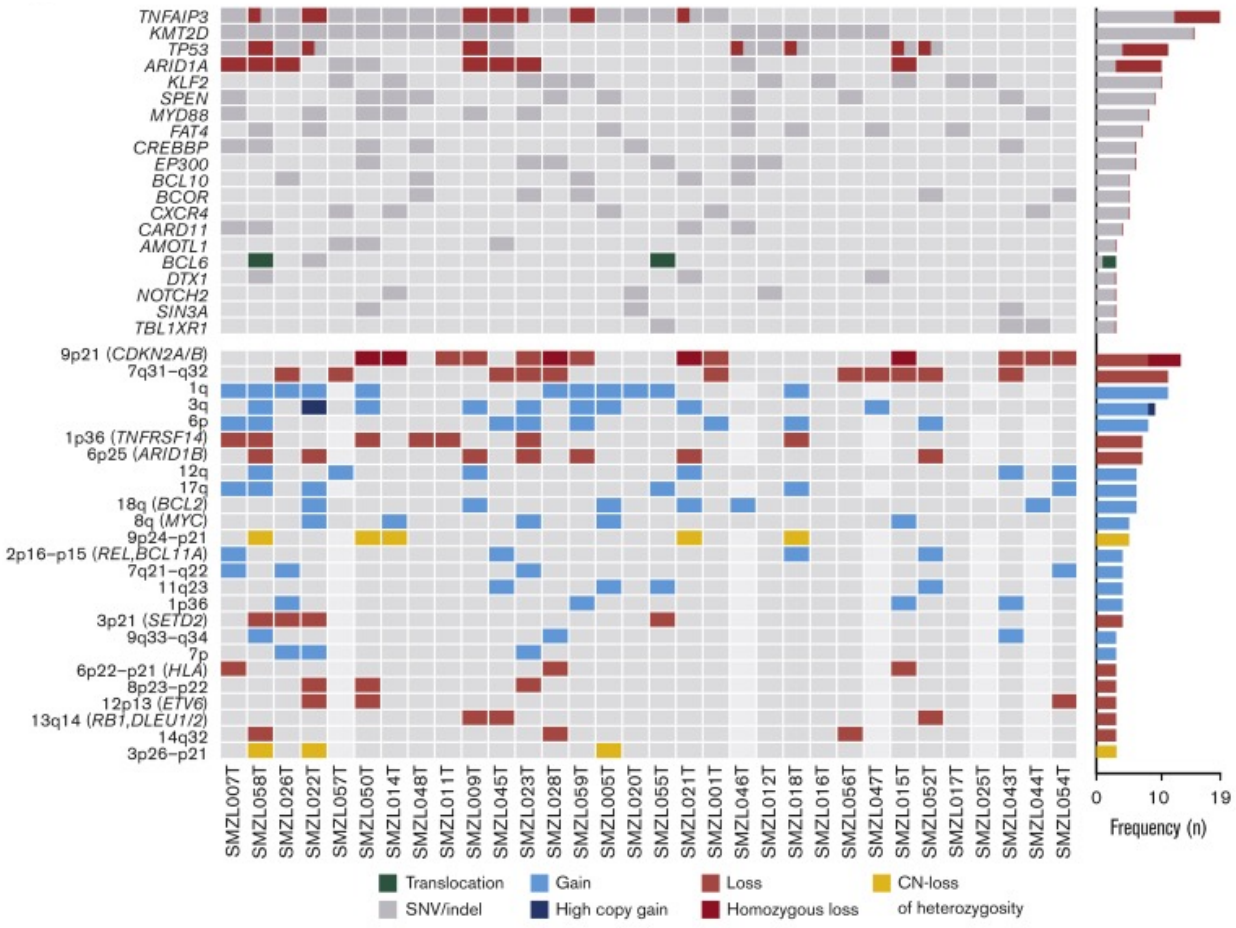
Stueber T, Hum Pathol. 2023
Pettit B, Haematologica. 2005

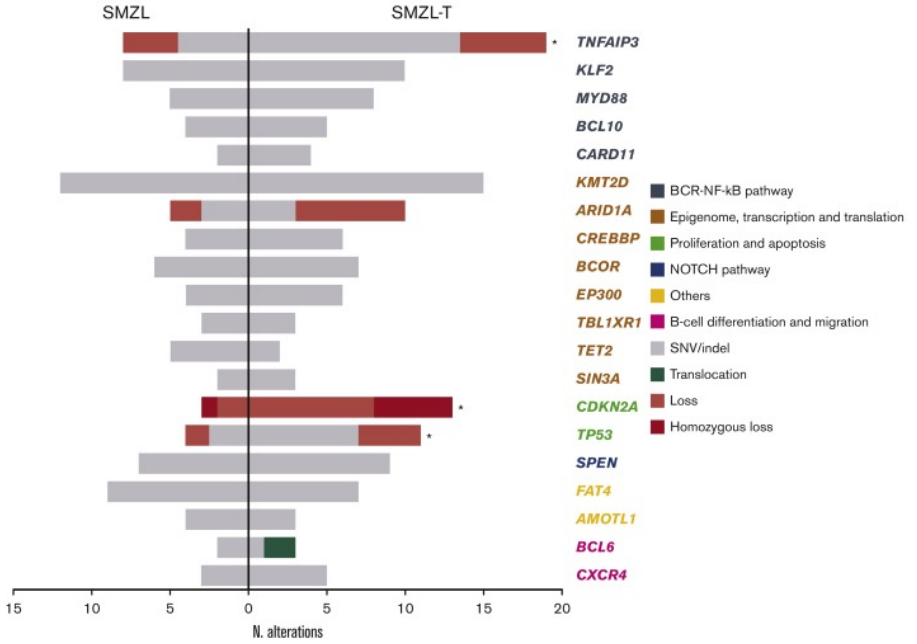
Histologic transformation

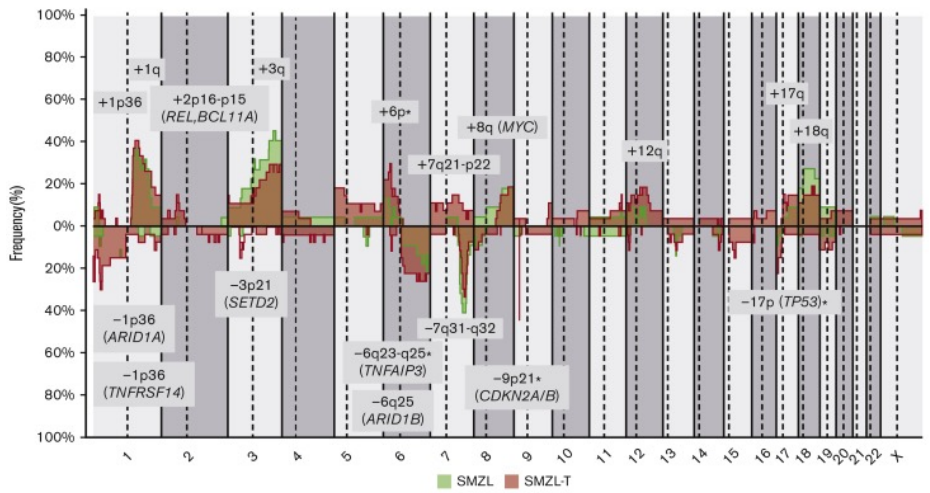
- 10-years cumulative incidence 8% (EMZL=3-5%, SMZL=7-13%, NMZL=9-13%)
- 5-years OS from transformation 55%
- Not well defined pathologic criteria (sheets of large cells): DD with MZL with increased scattered large cells

Bommier C, Blood Adv. 2024

Genetics of transformed SMZL







Grau M, Blood Adv. 2023

IELSG52

Integrated molecular and clinical profiling to improve disease characterization and outcome prediction in nodal marginal zone lymphoma

IELSG54

Integrated Molecular and Clinical Profiling of Transformed Splenic Marginal Zone Lymphoma