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Genomic/molecular profiling of non-Hodgkin lymphomas (Marginal Zone Lymphoma)

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Disclosures

Honoraria from AbbVie, AstraZeneca, BeOne, BMS, Janssen, Lilly

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Key aspects

Mature B-cells neoplasm originating from MZB

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

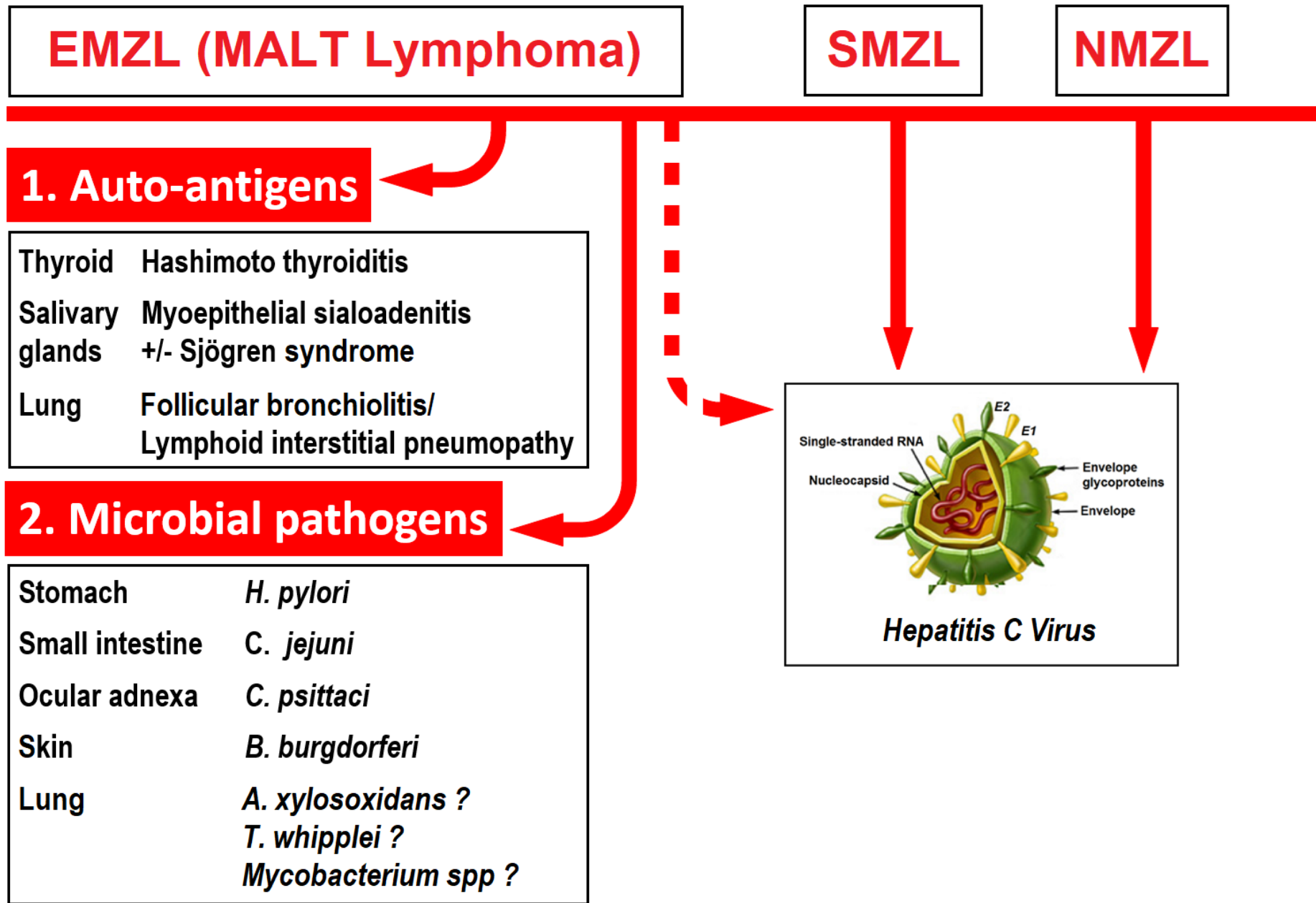
Risk factors

- Autoimmune diseases (Sjögren's syndrome: OR 30-38, Hashimoto's thyroiditis: OR 67-80)
- Chronic infections (*H. pylori* OR 2-6; HCV: OR 3.4)

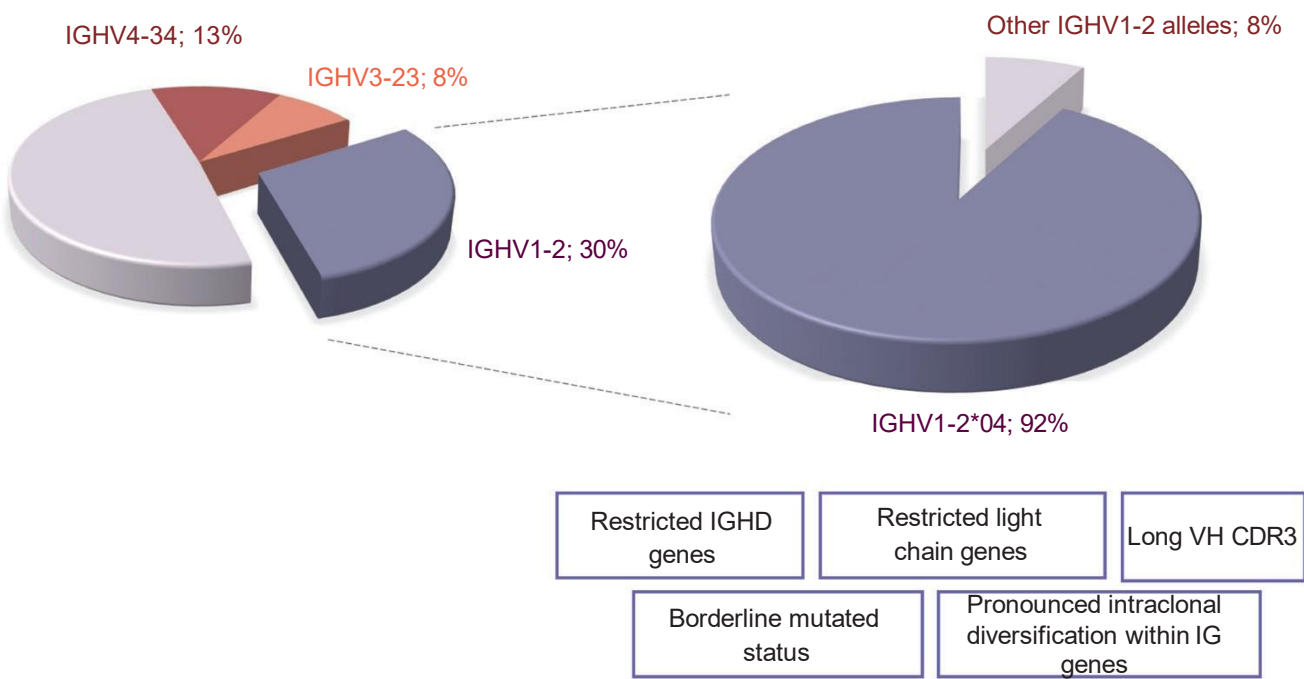
Indolent course but may progress and transform

The inflammatory ecosystem

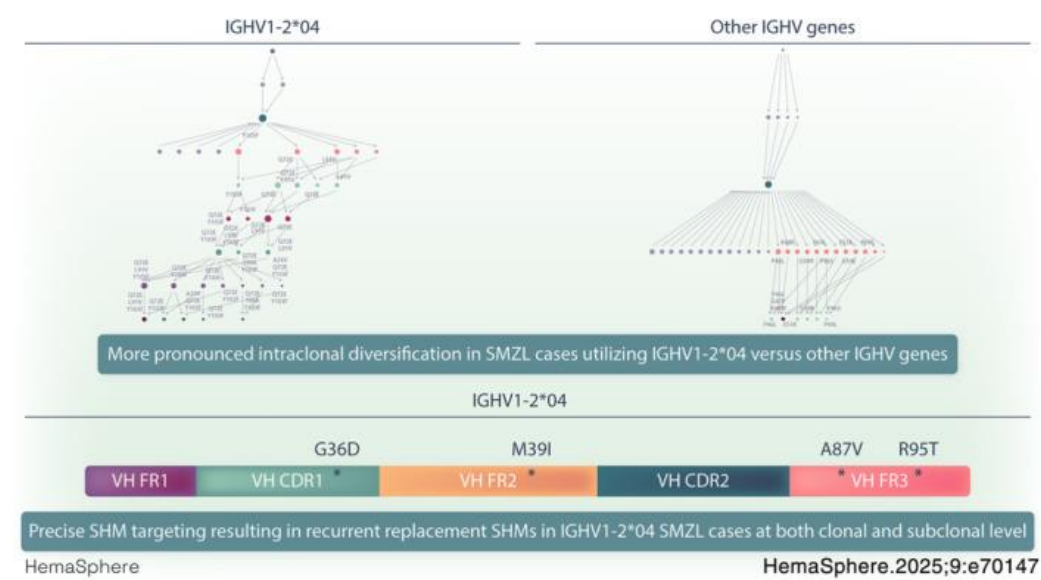
MZL link with chronic antigenic stimulation



Evidence for antigen-driven lymphomagenesis



Zaragoza-Infante L, et al, AOL 2020



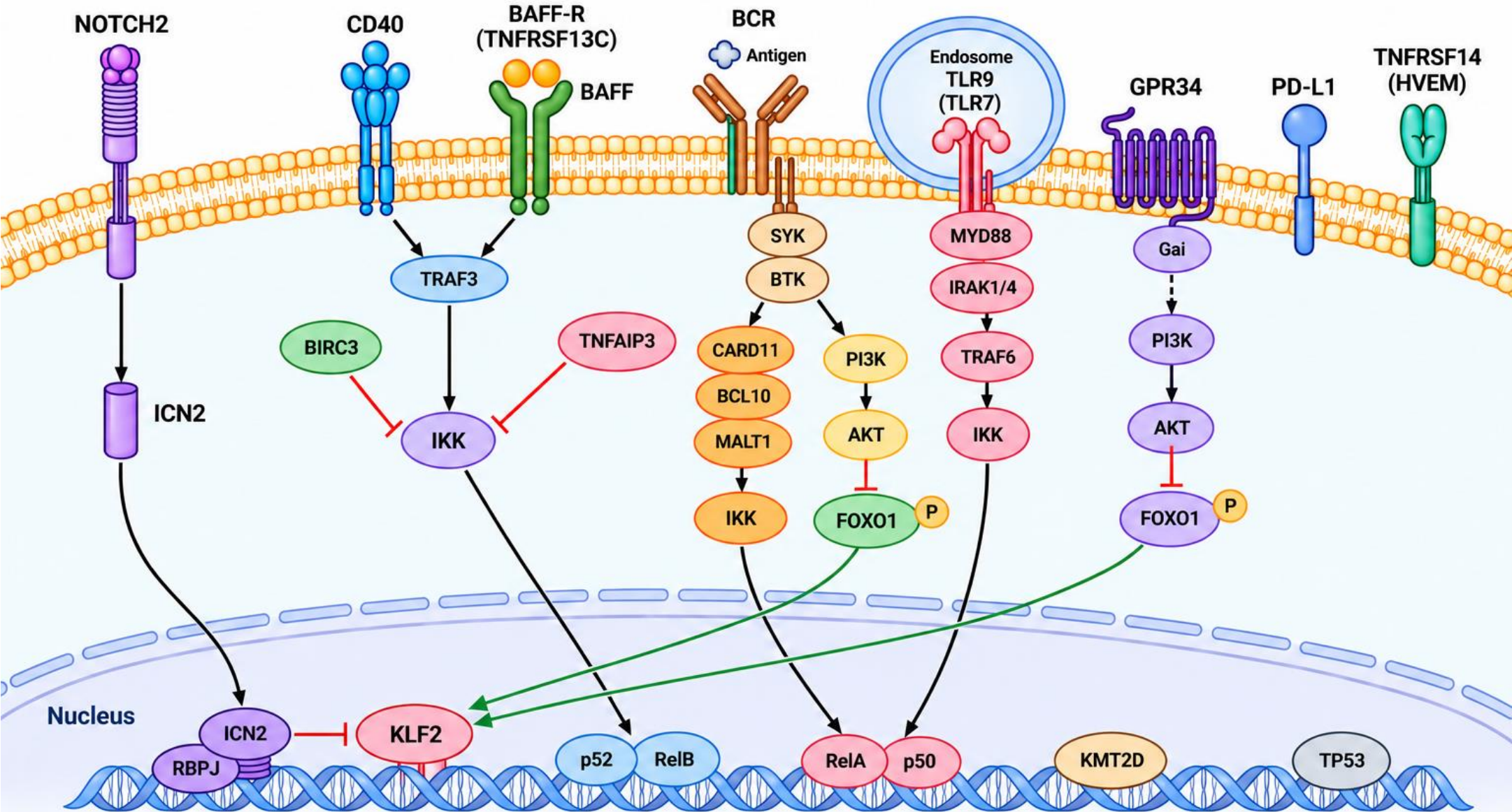
Zaragoza-Infante L,. Hemasphere. 2025

Restricted BCR configuration +
Poly/autoreactivity +
CDR3 sequence convergence +
Recurrent aa replacement +
Ongoing intraclonal diversification =

Chronic antigenic stimulation

B-cell pathway hijacking

MZB-cell signaling pathways hijacked during lymphomagenesis



Created with ChatGPT

Cerutti A, Nat Rev Immunol 2013; Pillai S, Nat Rev Immunol 2019; Rossi D, New Engl J Med. 2022; Du MQ. Blood. 2025; Bonfiglio F, Blood. 2022; Spina V, Blood. 2016; Pillonel V, Leukemia. 2018; Borgmann V, Blood Adv. 2026

Site specific molecular heterogeneity of MZL

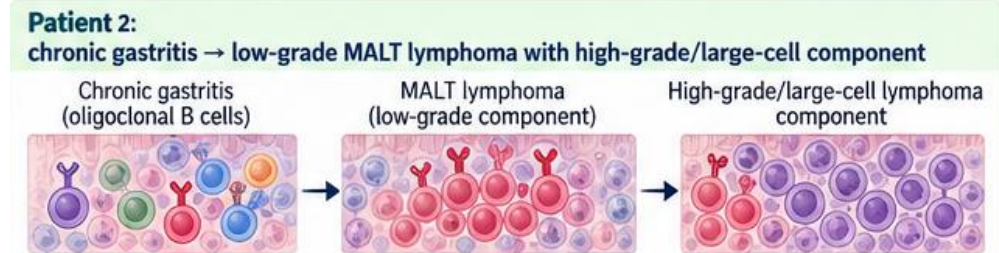
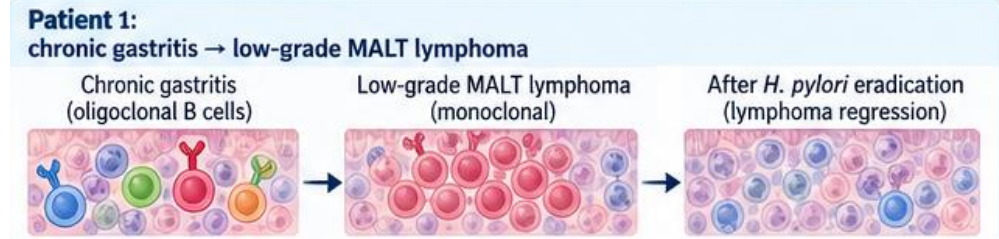
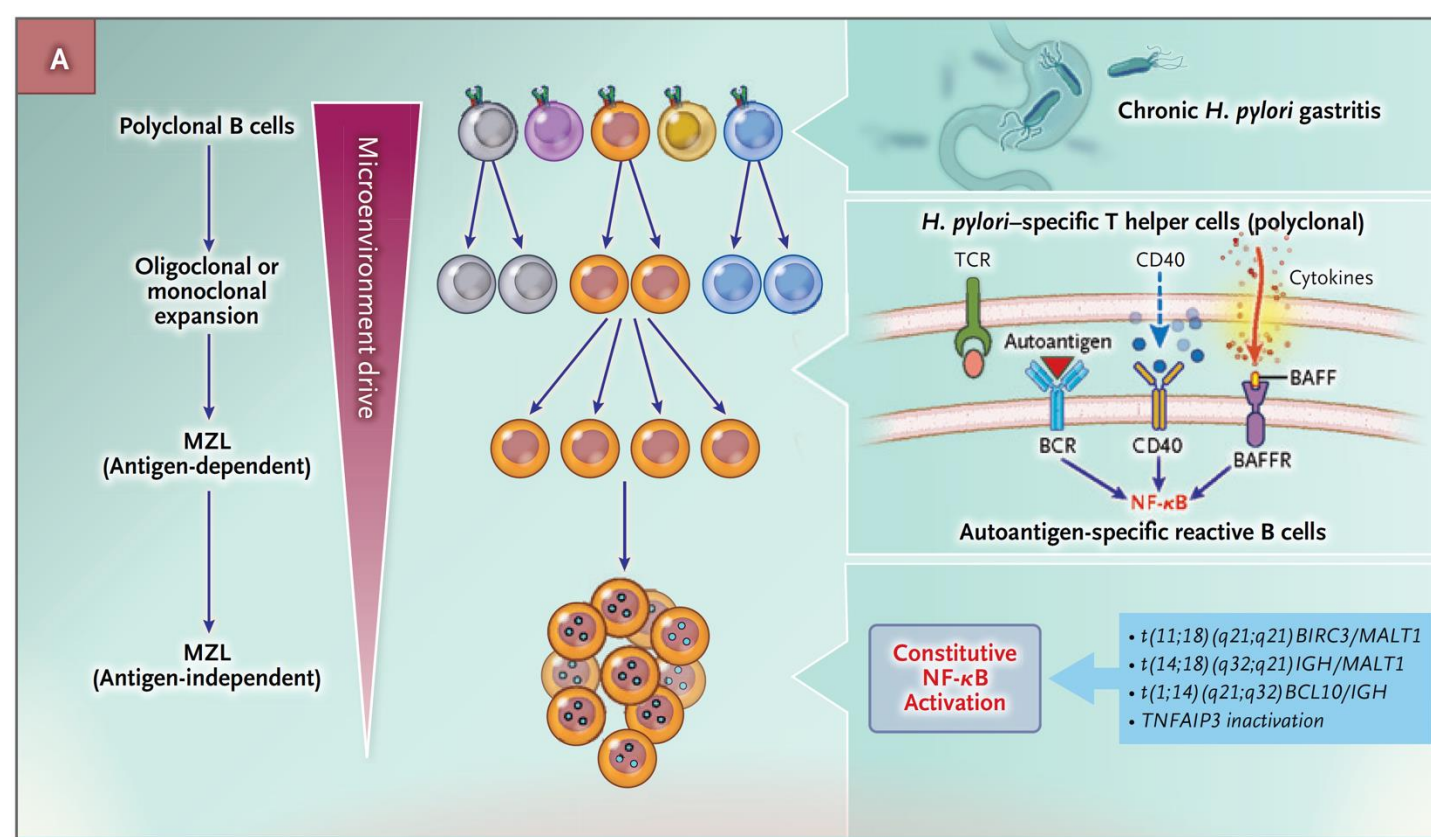


Cooperation among somatic genetic changes and TME

Site	Pathway	Genes
Gastric	BCR	MALT1, BCL10, TNFAIP3
Thyroid	Immune escape	CD274, TNFRSF14
Salivary gland	LysoPS-G protein	GPR34
Ocular adnexa	NF-kB	TNFAIP3
Splenic and nodal	Innate immunity	IGHV1-2*4, NOTCH2, KLF2, BIRC3

MZL precursors

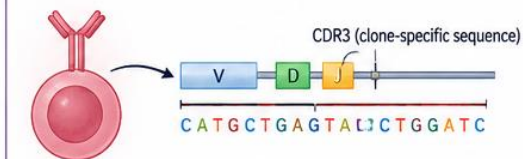
Marginal zone lymphomagenesis is as a multistep process occurring within ecosystems of antigen- or autoantigen-selected B cells



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Molecular detection of the lymphoma clone in earlier gastritis

Immunoglobulin heavy-chain (IGH)
CDR3 rearrangement as a clone-specific barcode



Each B-cell clone has a unique IGH rearrangement used for allele-specific PCR.

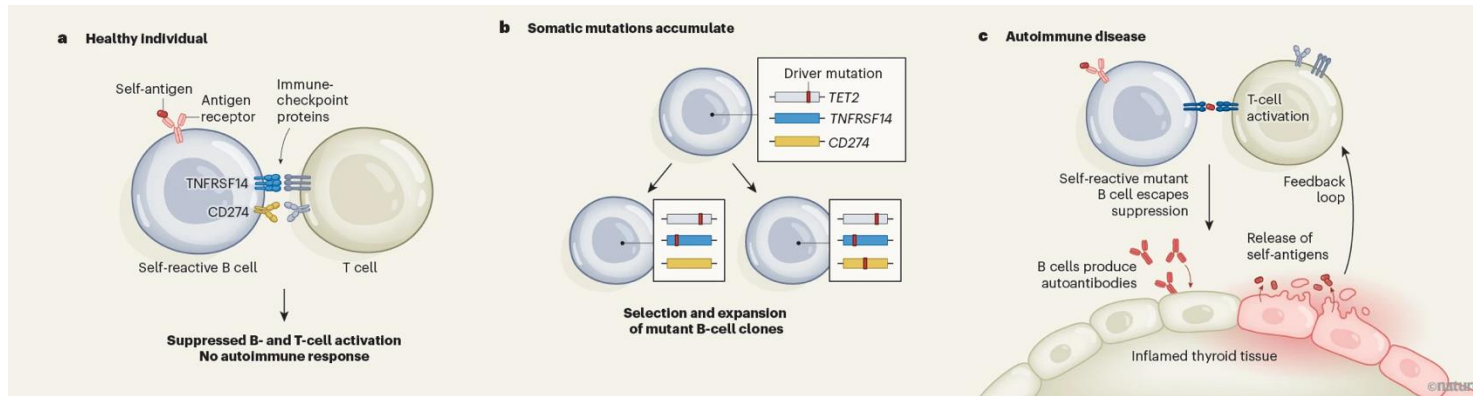
Patient-specific allele-specific PCR

Patient 1		Patient 2	
Gastritis (earlier)	MALT (lymphoma)	Gastritis (earlier)	MALT (lymphoma)

The lymphoma-specific IGH rearrangement is detectable by allele-specific PCR in earlier gastritis biopsies from the same patients.

Polyclonal premalignant B cells in chronically inflamed tissue

Autoimmune thyroid conditions

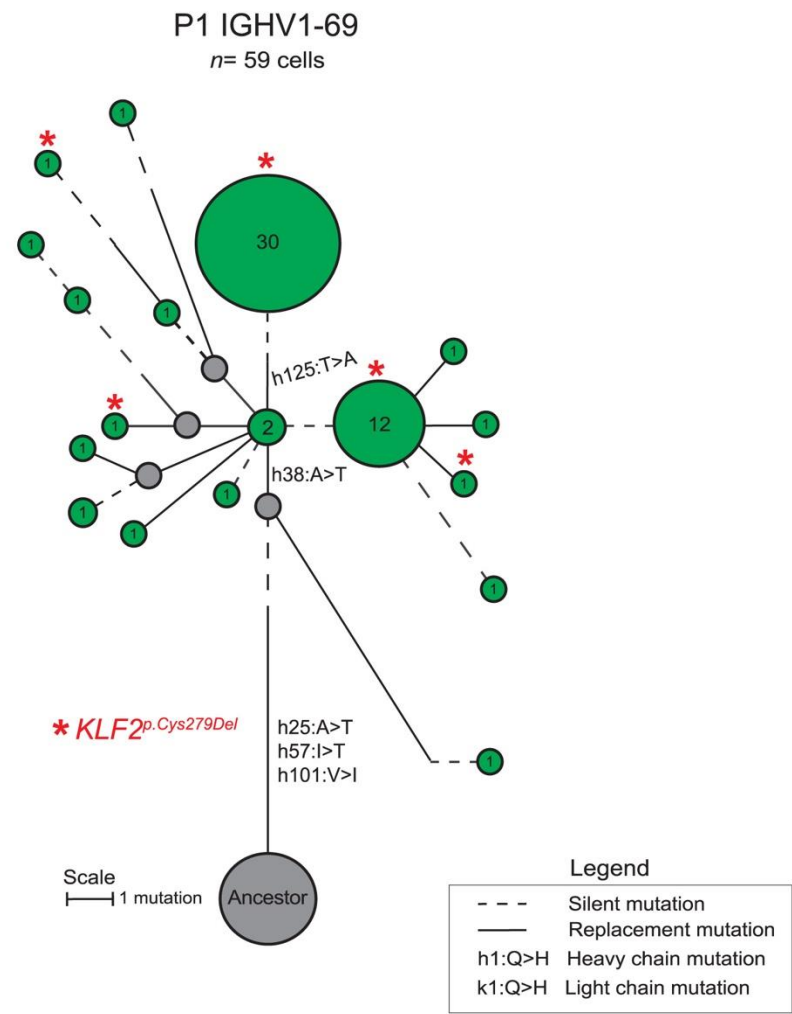


Nicola PA, Nature. 2026

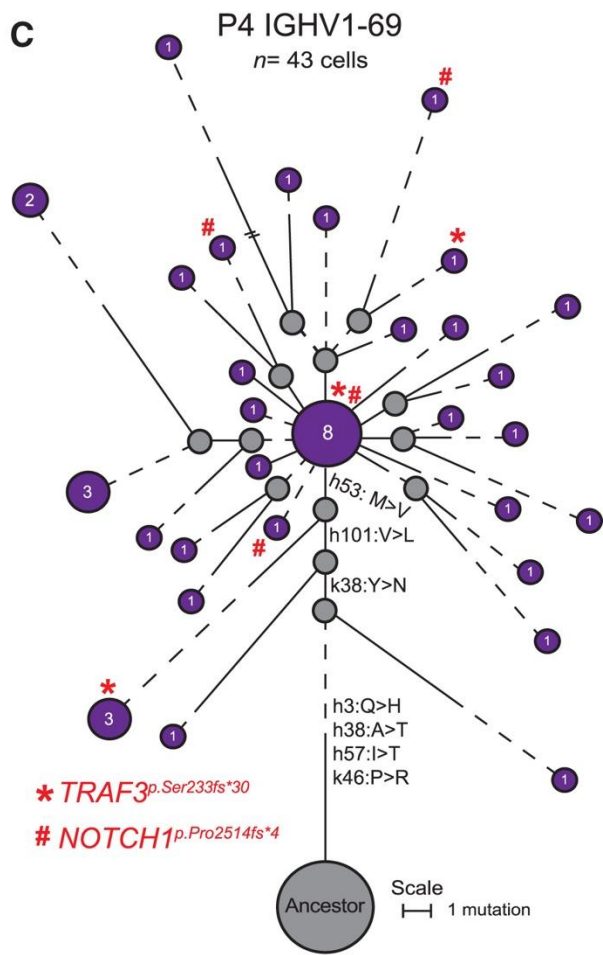
- Hundreds of independent B-cell clones acquire somatic driver mutations
- Each clone accounts for a small fraction of cells
- The myriad mutant clones in each donor amounted to a substantial fraction of B cells
- Driver mutations *TNFRSF14/HVEM* and *CD274/PD-L1* (recurrent in thyroid EMZL)
- Loss of *TNFRSF14* and *CD274* immune checkpoints in B cells enables self-reactive B cells to escape suppression and produce autoantibodies

Acquisition of lymphoma driver mutations in the autoimmune clones in HCV patients with cryoglobulinemia

B



C



- Chronic antigenic stimulation generates large mutated autoreactive precursor clones
- Lymphoma driver mutations arise prior to clonal tree branching

Diagnostic challenges

Small B-cell neoplasms without defining features

- **Marginal zone lymphomas**
- Follicular lymphoma **without** *IGH::BCL2*
- **Atypical** chronic lymphocytic leukemia
- Lymphoplasmacytic lymphoma **lacking** *MYD88 L265P*
- **Splenic** B cell lymphomas
 - B-cell prolymphocytic leukemia
 - Hairy cell leukemia variant
 - Splenic diffuse red pulp B cell lymphoma

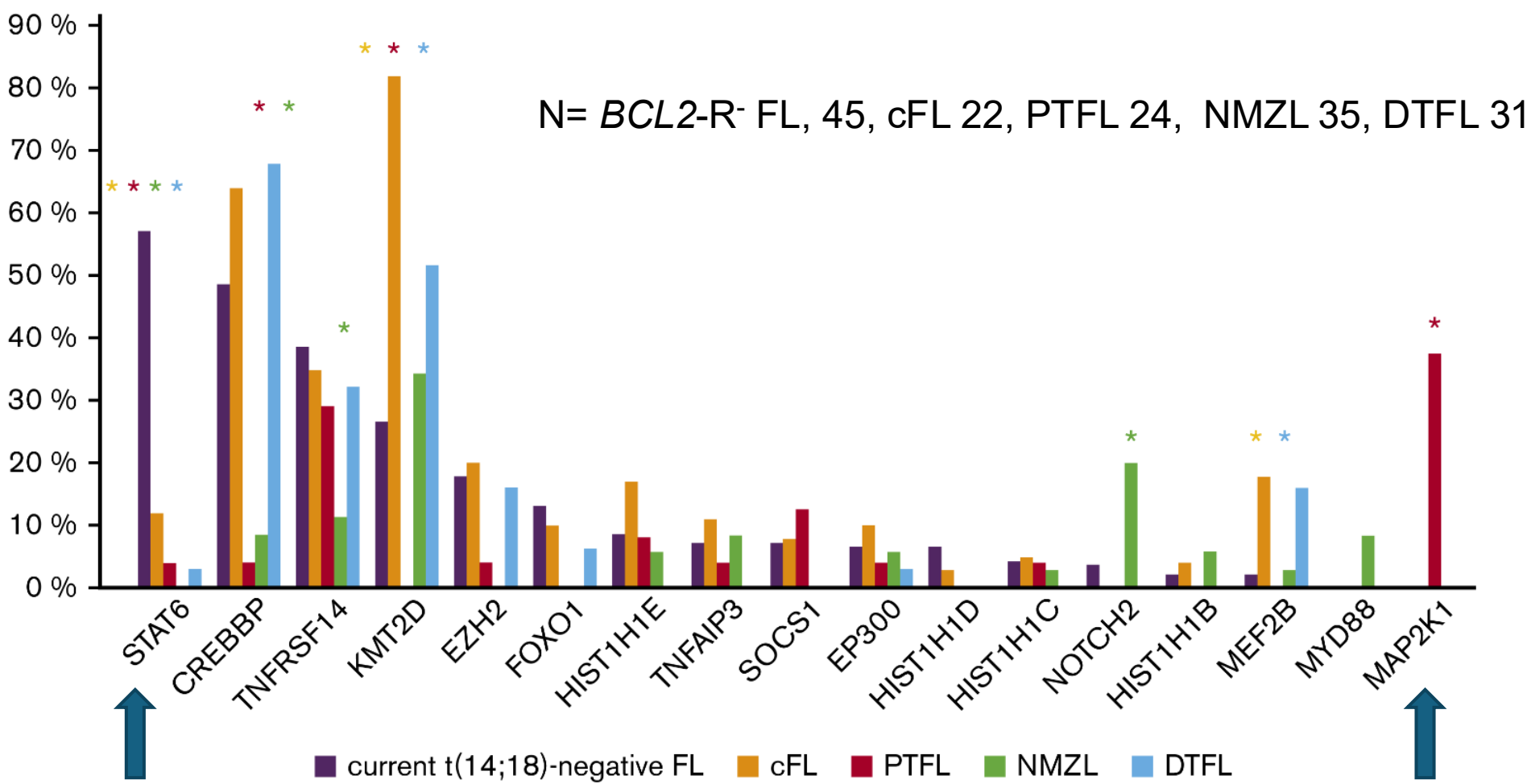
Small B-cell neoplasms with unexpected phenotypes

Unexpected phenotypes

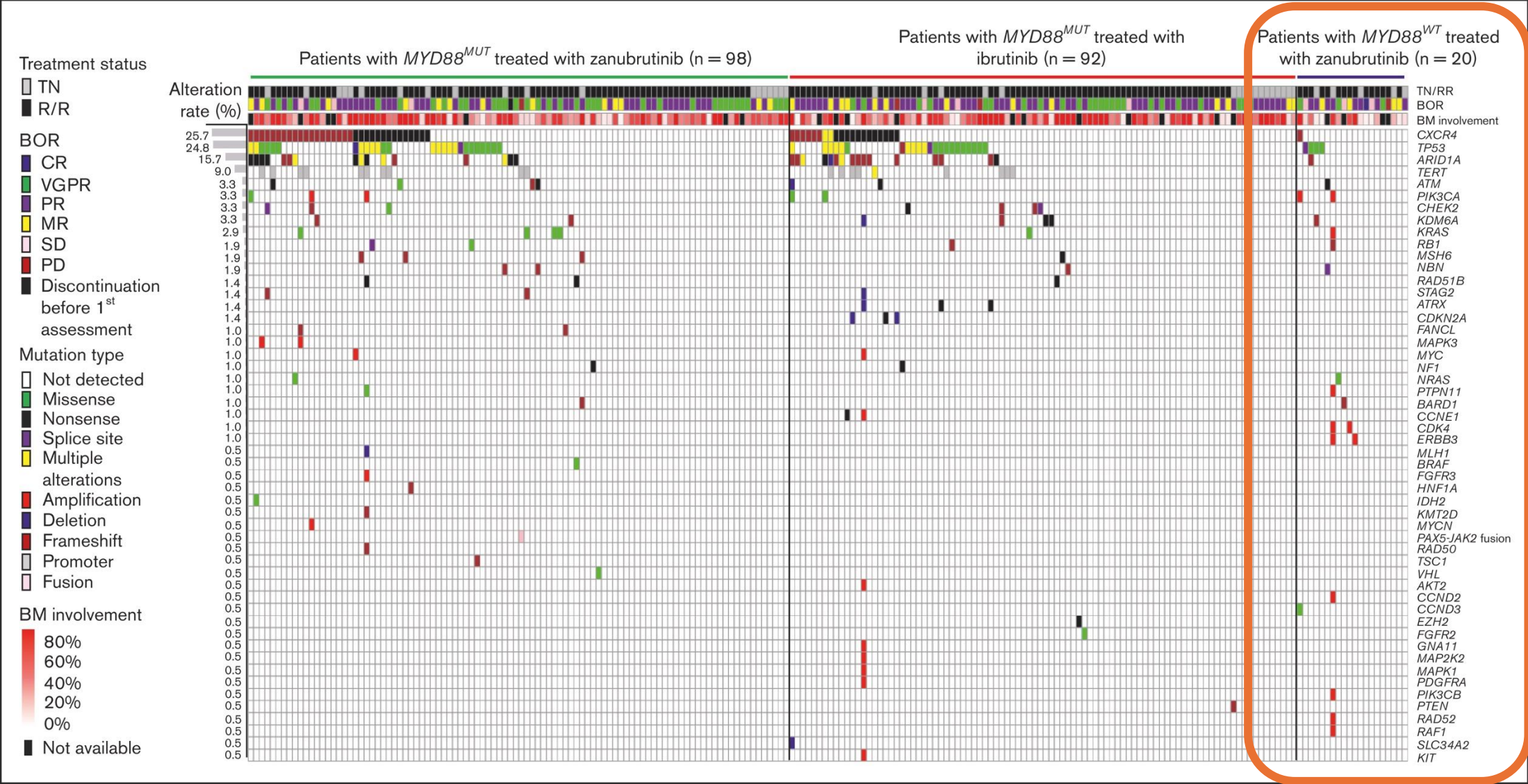
- CD5-/CD23-/**BCL6+**/CD10- (MZL? FL?)
- CD5-/**CD23+** (MZL? FL?)
- **CD5+/CD23+**, bright CD20+/sIg+, CD79b+, FMC7+ (MZL? CLL?)

Wrong diagnosis in 20-30% of cases

Follicular lymphoma (without *IGH::BCL2*)



MYD88 wild type lymphoplasmacytic lymphoma



Does it really exist? No genetic biomarkers

Extended diagnostics

- **Marginal zone lymphomas** → *MALT1*-R, +3, +12, +18, -7, *KLF2* m, *NOTCH2* m
- Follicular lymphoma without *IGH::BCL2* → *STAT6* m
- Chronic lymphocytic leukemia → -13q, *SF3B1* m, *NOTCH1* m
- Lymphoplasmacytic lymphoma → *MYD88* L265P
- Splenic diffuse red pulp B-cell lymphoma → *MAP2K1* m, *CCND3* m
- Hairy cell leukemia variant → *MAP2K1* m, *CCND3* m
- B-cell prolymphocytic leukemia → *TP53* abn, *MYC*-R

Perspectives



IELSG46

Integrated molecular and clinical profiling to optimize outcome prediction in Splenic Marginal Zone Lymphoma

+400 SMZL

NGS and digital pathology review



IELSG52

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

+1000 NMZL

WES and digital pathology review

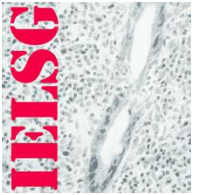
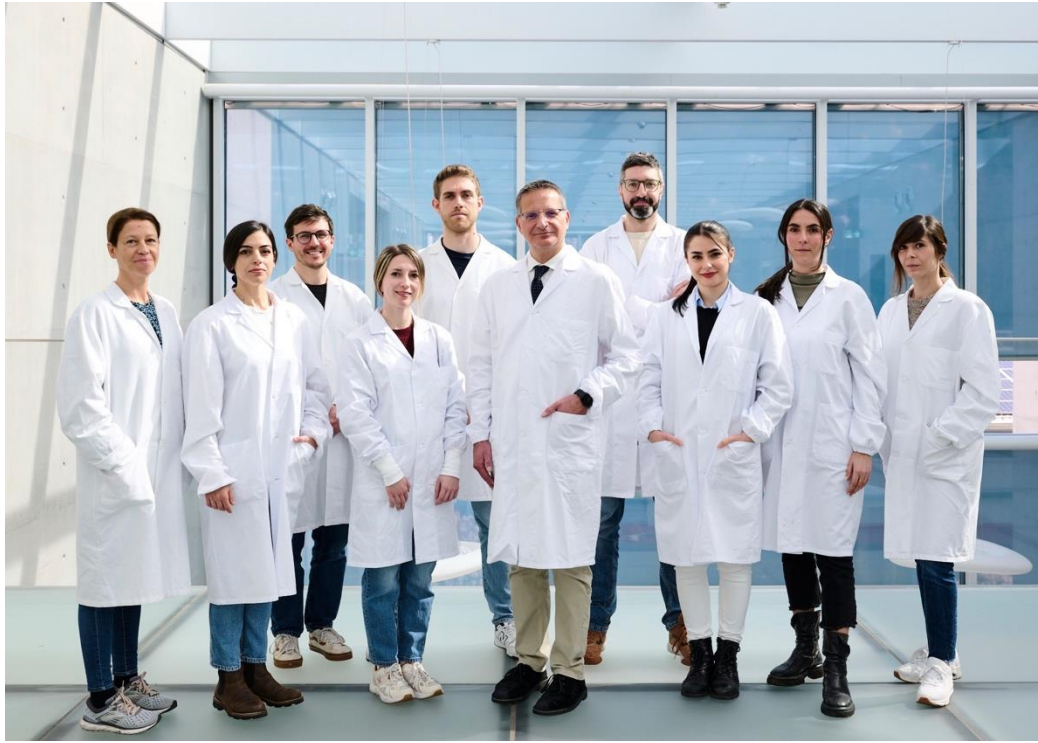


IELSG47-IELSG48-IELSG49

Determinants of response to Bruton's Tyrosine Kinase inhibitors in marginal zone lymphomas

+250 MZL

Baseline genetics and MRD using ctDNA



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