(High-risk) Marginal Zone Lymphoma

Davide Rossi, M.D., Ph.D.

Hematology
IOSI - Oncology Institute of Southern Switzerland
IOR - Institute of Oncology Research
USI – Universita' della Svizzera Italiana
Bellinzona - Switzerland

COI

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

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MZL in the ICC and WHO-HAEM5 classifications

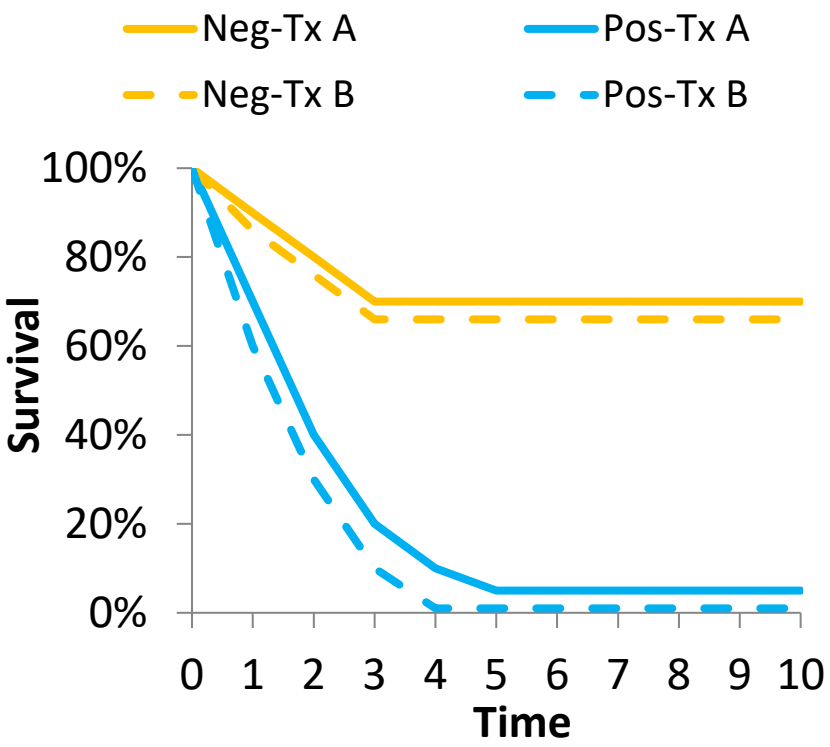
WHO-HAEM4	WHO-HAEM5	ICC
Splenic marginal zone lymphoma	Splenic marginal zone lymphoma	Splenic marginal zone lymphoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma	Nodal marginal zone lymphoma	Nodal marginal zone lymphoma
-	Primary cutaneous marginal zone lymphoma*	Primary cutaneous marginal zone lymphoproliferative disorder*

*Now recognized as a distinct entity to be segregated from other MALT lymphomas and designated as a lymphoproliferative disorder. Two subtypes are distinguished largely based on expression of either class-switched Ig or IgM.

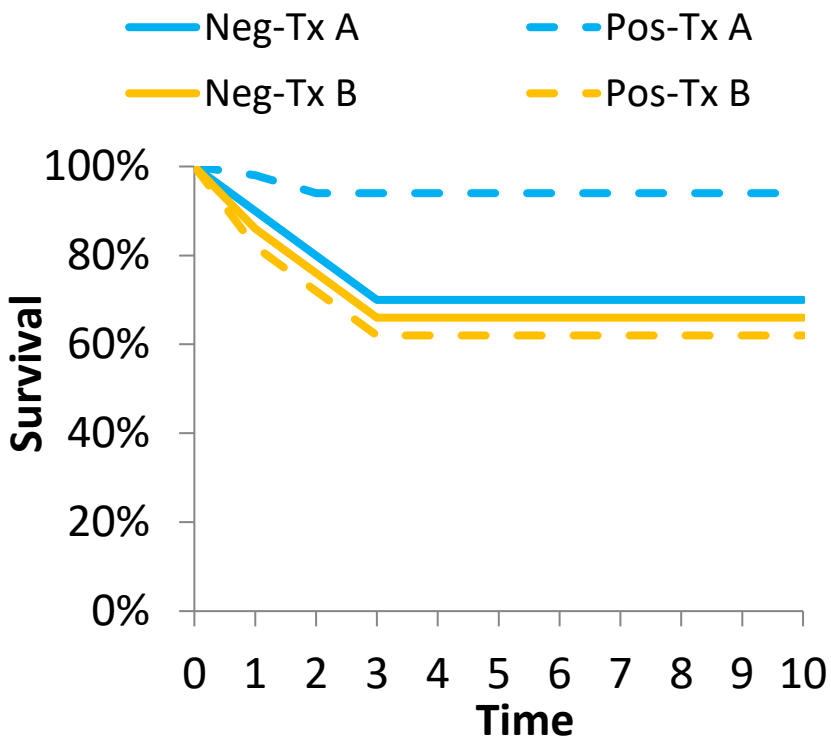
Campo E, Blood. 2022
Alaggio R, Leukemia. 2022

MZL lacks predictive biomarkers

Prognostic biomarker



Predictive biomarker



Most prognostic biomarkers of MZL comes from retrospective series

Ballman j Clin Oncol. 2015

Diagnosis

Diagnosis is challenging: wrong diagnosis affects outcome

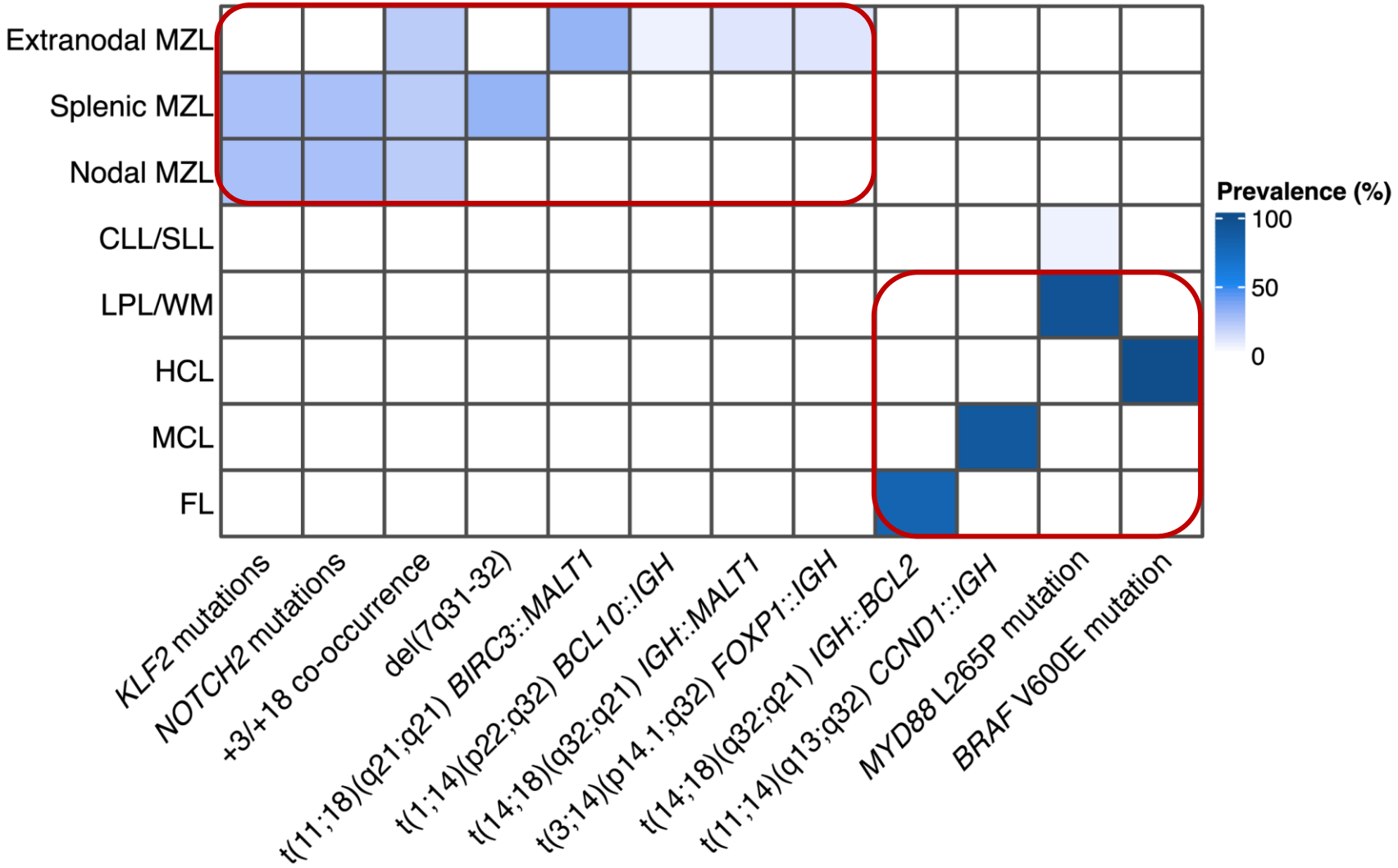
- Lack of phenotypic biomarkers with high PPV and NPV
- Diagnosis other than MZL in 20% of cases (LPL, MCL, CLL, FL)
- CD5 expression in 10% of MZL (20% in SMZL; 10% in NMZL, 5% in EMZL): DD with CLL and MCL
- Dissemination of occult EMZL in 20% of NMZL presenting in limited stage

Cases that are not straightforward must be discussed with the pathologist:

- DD with MCL: Cyclin D1, SOX11
- DD with *IGH::BCL2* neg FL: CD10, BCL6, CD23
- DD with CLL: CD23, LEF1, 13q14
- DD with LPL: *MYD88* L265P
- DD with dissemination of occult EMZL: MALT pattern, PET/CT, extensive staging

Campo E, Am J Surg Pathol. 1999; Hsu A, Leuk Lymphoma. 2022; Bonfiglio F, Blood. 2022

Genomic characteristics distinguishing MZL



de Leval L, Blood. 2022

IELSG52

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

Transformation

Histologic transformation

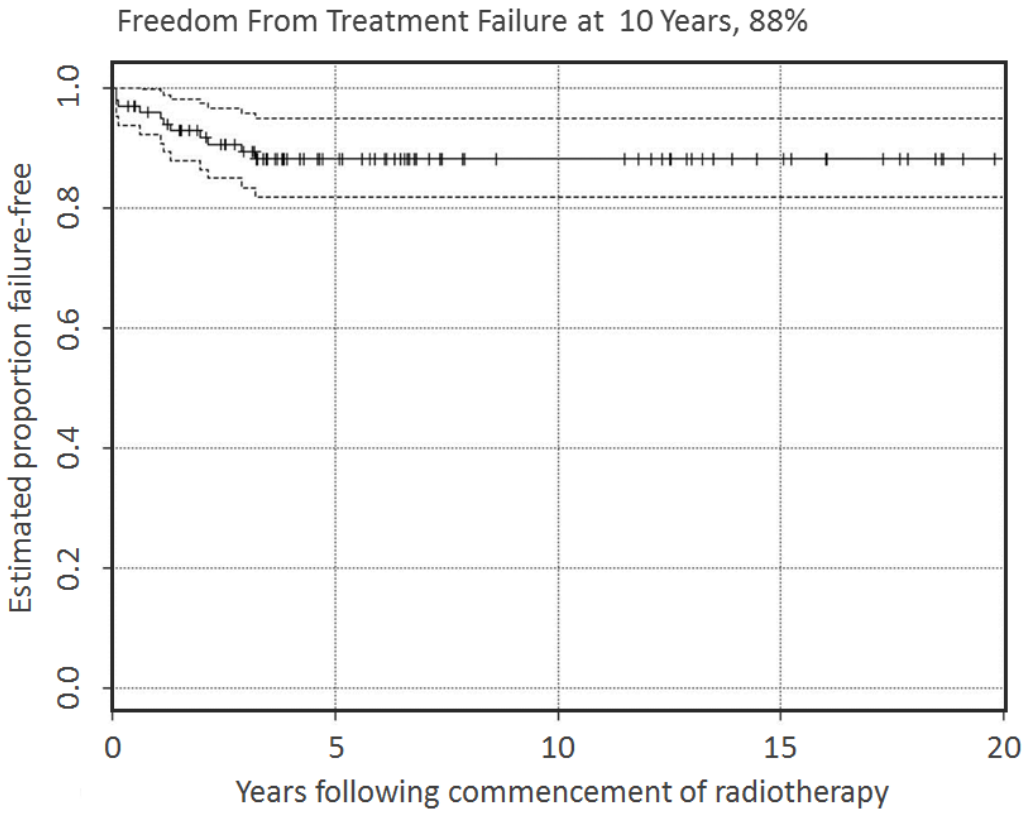
- 10-years cumulative incidence 8% (EMZL=3-5%, SMZL=7-13%, NMZL=9-13%)
- 5-years OS from transformation 55%
- Not well defined pathologic criteria (sheets of large cells): DD with MZL with increased scattered large cells

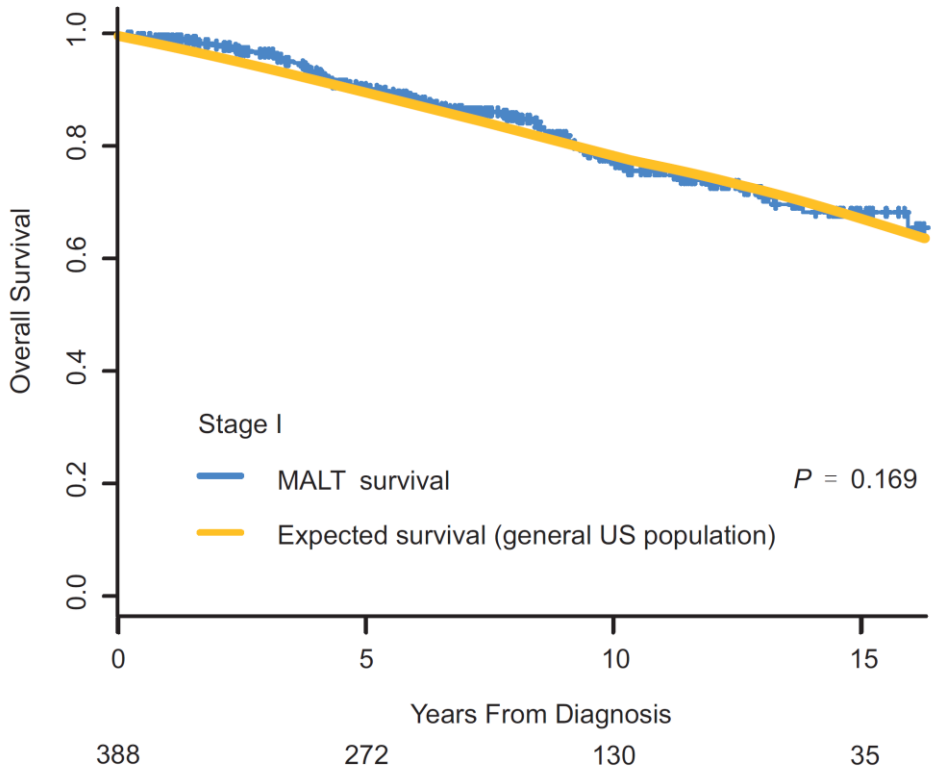
Specifically discuss cases with your pathologist; ask pathology revision
Guidelines recommend treatment like for LBCL
CAR T-cells

Bommier C, Blood Adv. 2024

Localized MZL (stage I and continuous stage II)

Excellent outcome of limited stage MZL





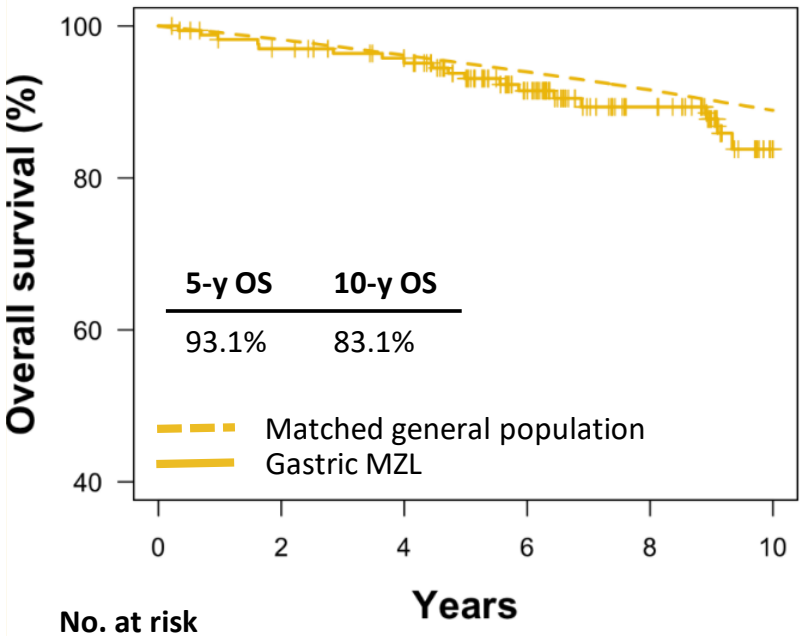
BIRC3::MALT1 fusion in HP+ gastric EMZL: lower rate of response to HP eradication
NCCN (but not ESMO) recommended

Wirth A, Ann Oncol. 2013; Alderuccio JP, Cancers, 2021; Qi S, Blood Adv. 2022

Disseminated MZL (non-contiguous stage II to IV)

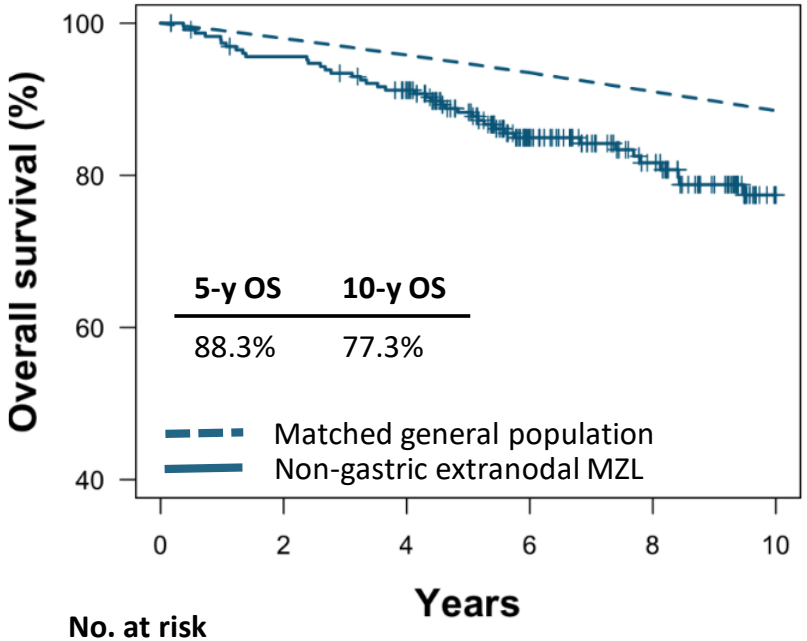
Disseminated MZL affect patient's life expectancy

Limited stage Gastric EMZL



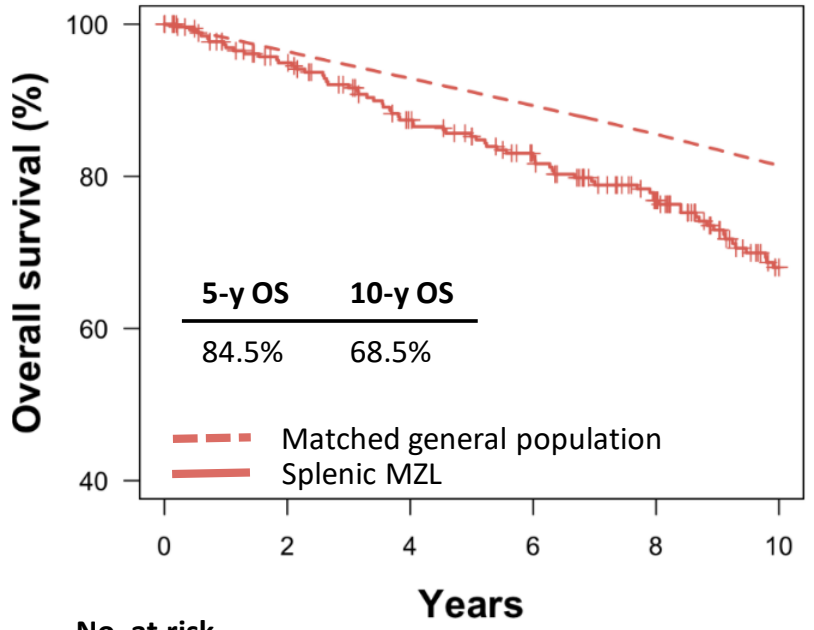
No. at risk						
	171	160	151	108	67	30
Relative Survival						
	100%	98.6%	98.9%	97.3%	97%	94%

Disseminated EMZL



No. at risk						
	230	217	201	129	92	42
Relative Survival						
	100%	96.9%	95.1%	90.8%	89.6%	87.4%

SMZL



No. at risk						
	265	230	198	176	146	102
Relative Survival						
	100%	96.9%	92.1%	90.4%	87.9%	82.1%

Rossi D, New Engl J Med. 2022

Histology

MZL with aggressive histologic presentation

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

Guidelines recommend chemoimmunotherapy rather than rituximab

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

Imaging

MZL with increased ^{18}FDG uptake

- ^{18}FDG uptake in 71% of cases (median SUVmax=6)
- SUVmax ≥10 in 16%
- Independent of Ki-67 ≥30%
- 5-years OS in SUVmax ≥10: 78% (vs 92%)
- 5-years transformation in SUVmax ≥10: 20% (vs 5%)

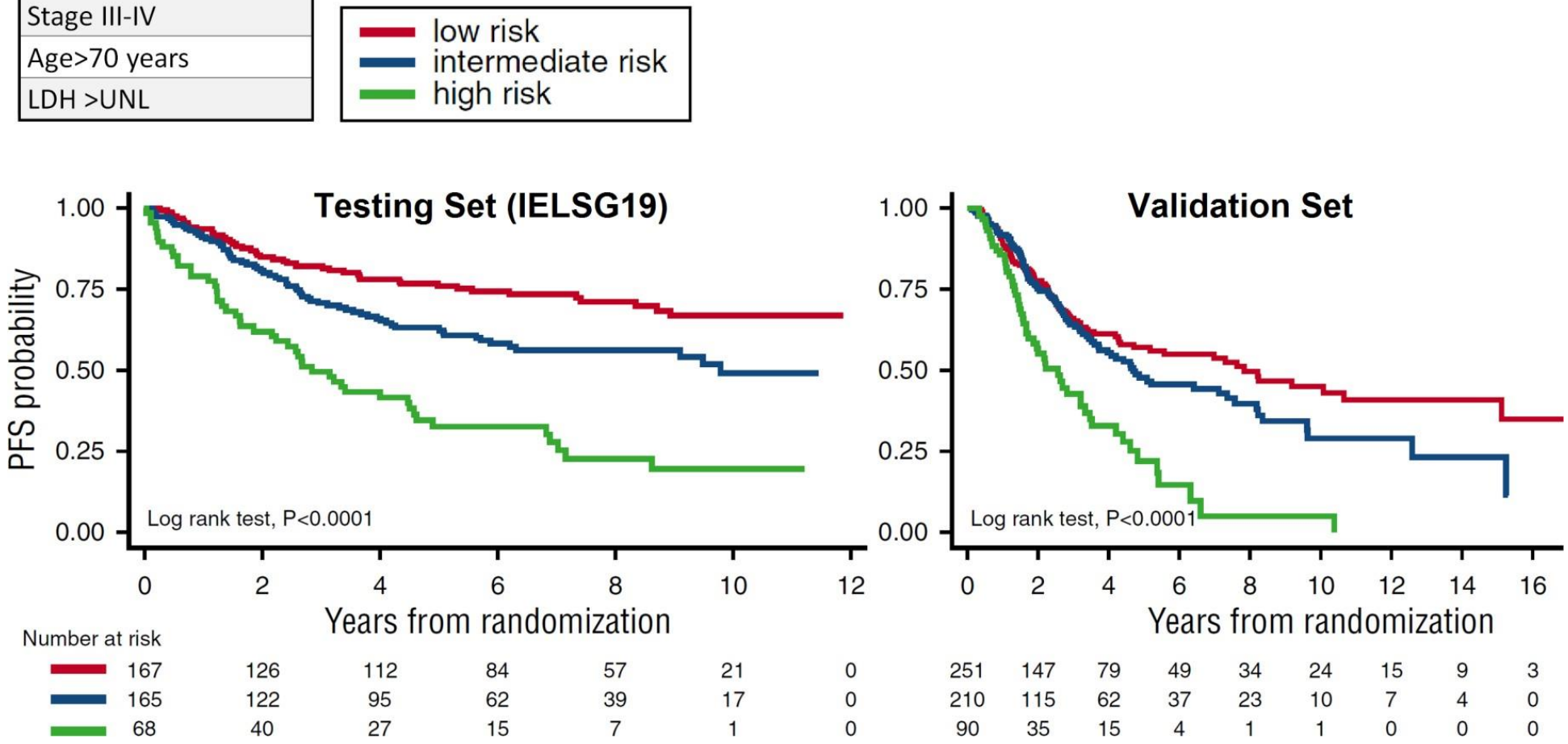
Guidelines recommend chemoimmunotherapy rather than rituximab

Albano D, Clin Lymphoma Myeloma Leuk. 2020
Qi S, Blood Adv. 2018

Clinical scores

MALT IPI a validated prognostic index

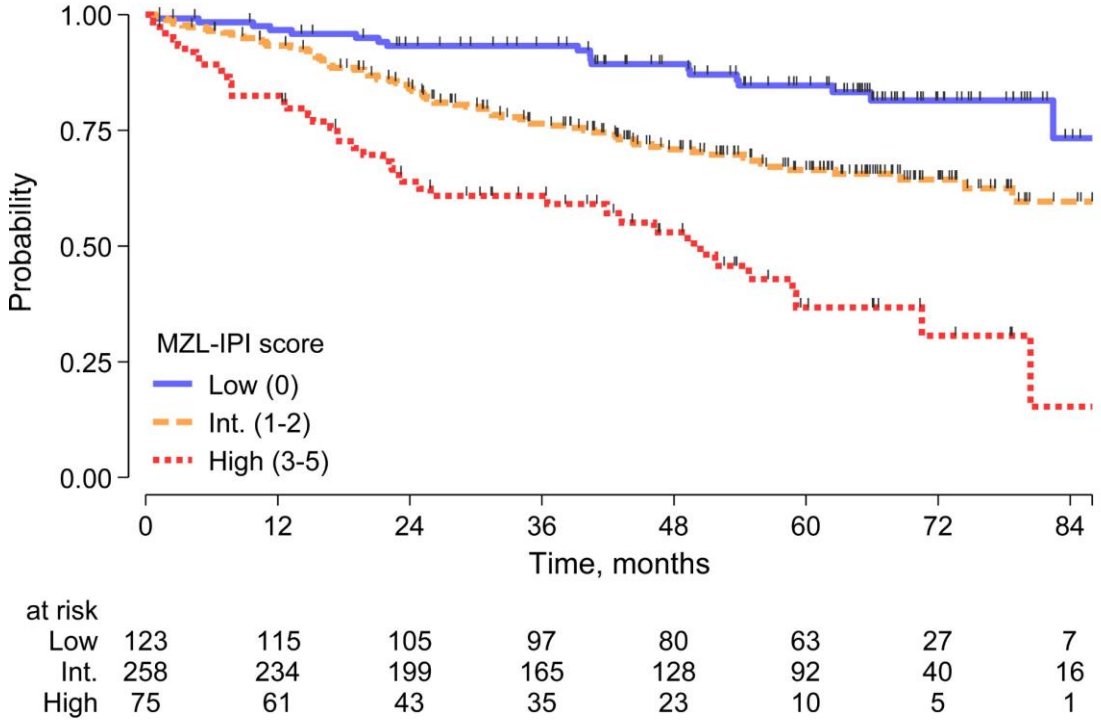
MALT-IPI Risk Factors
Stage III-IV
Age>70 years
LDH >UNL



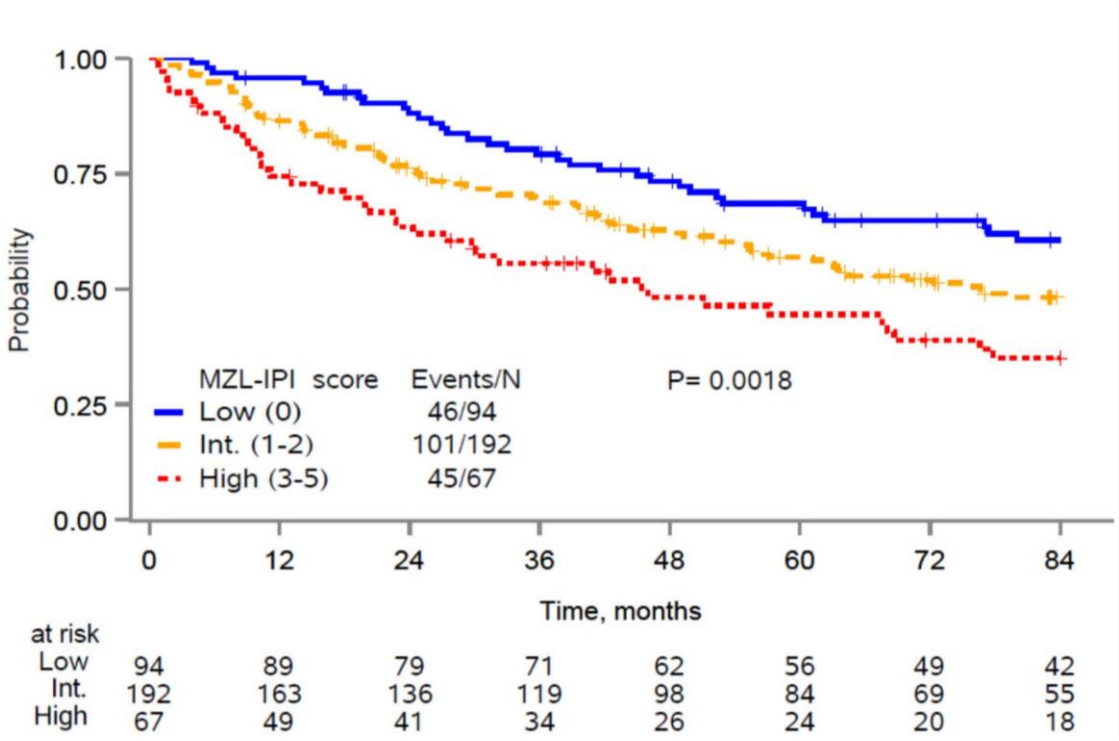
Thieblemont C, Blood. 2017

MZL-IPI a validated prognostic index

- LDH (< or ≥ upper normal limit, UNL)
- Hb level (< or ≥12 g/dL)
- Platelet count (< or ≥100 × 10^9/mmc),
- Absolute lymphocyte count (< or ≥1 × 10^9/mmc)
- MZL subtype (ENMZL and SMZL vs NMZL and dissMZL)



Training set



Validation set

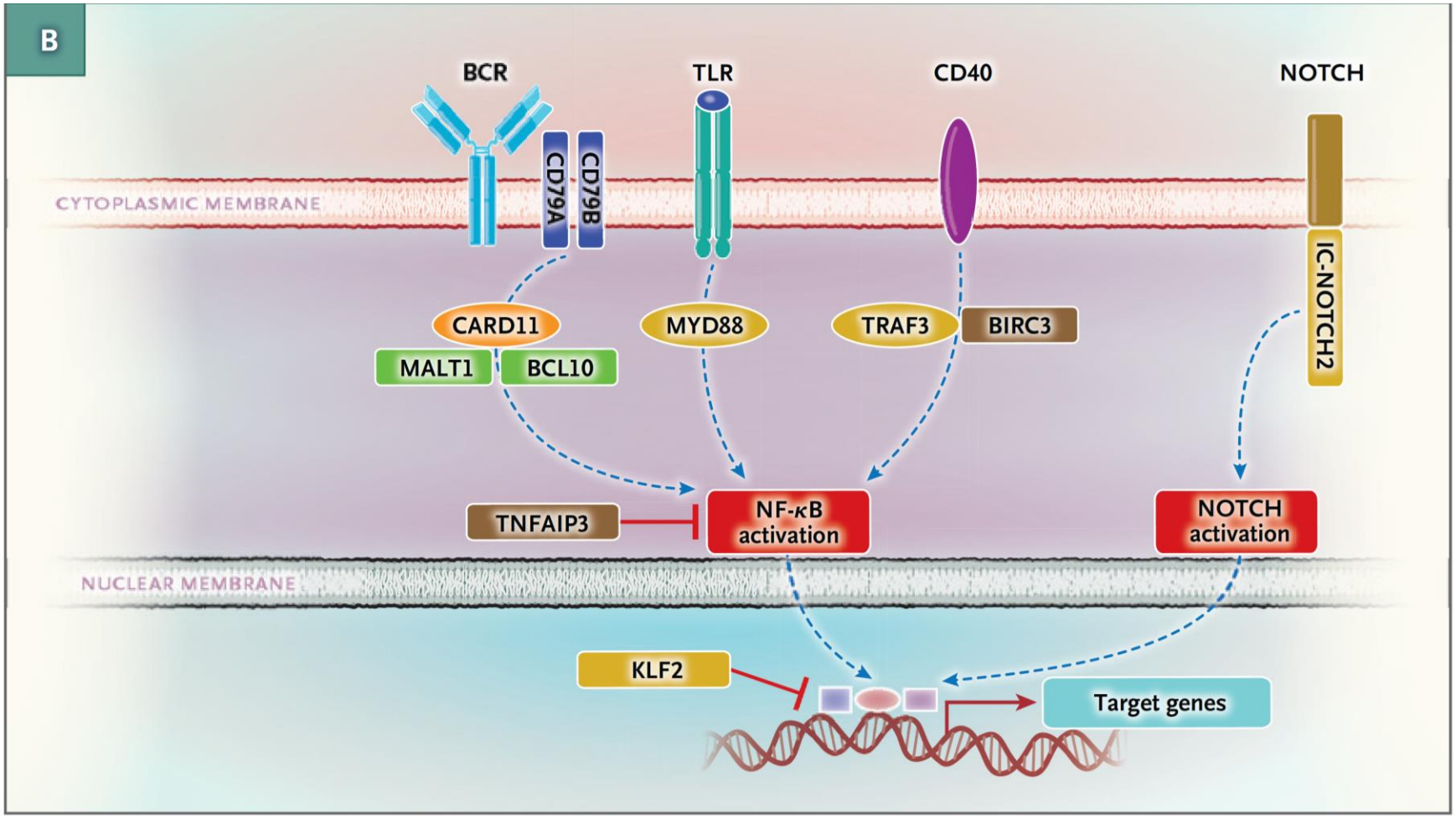
Consistently scored prognostic variables in MZL

	Older age	Advanced stage	High LDH	Extensive LN	Anemia	Thrombocytopenia	Lymphopenia
IPI	+	+	+	-	-	-	-
FLIPI	+	+	+	+	+	-	-
HPLL	+	+	+	+	+	+	-
MALT-IPI	+	+	+	-	-	-	-
MZL-IPI	+	+	+	+	+	+	+

B2-macroglobulin: not appropriately assessed

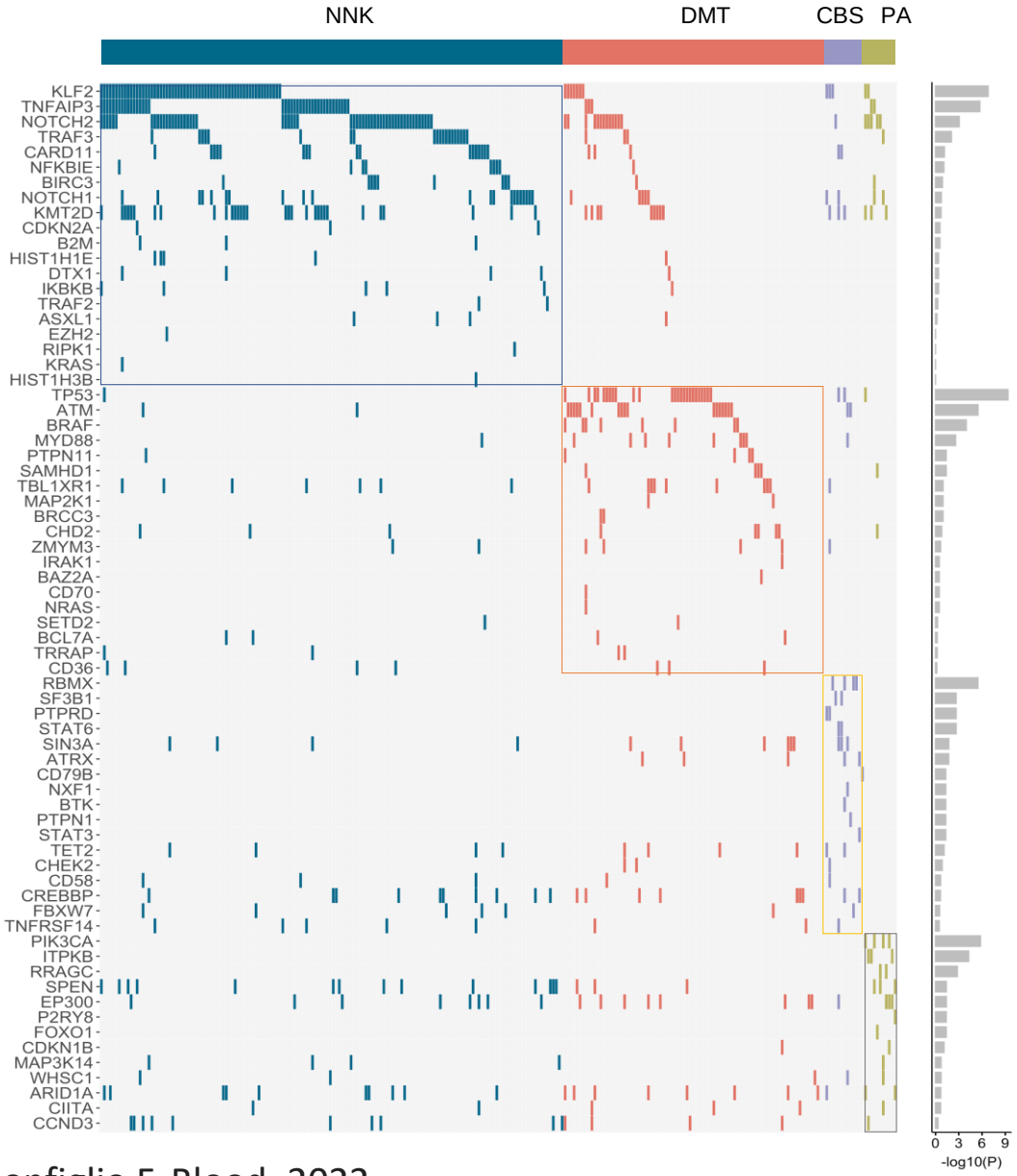
Molecular aspects

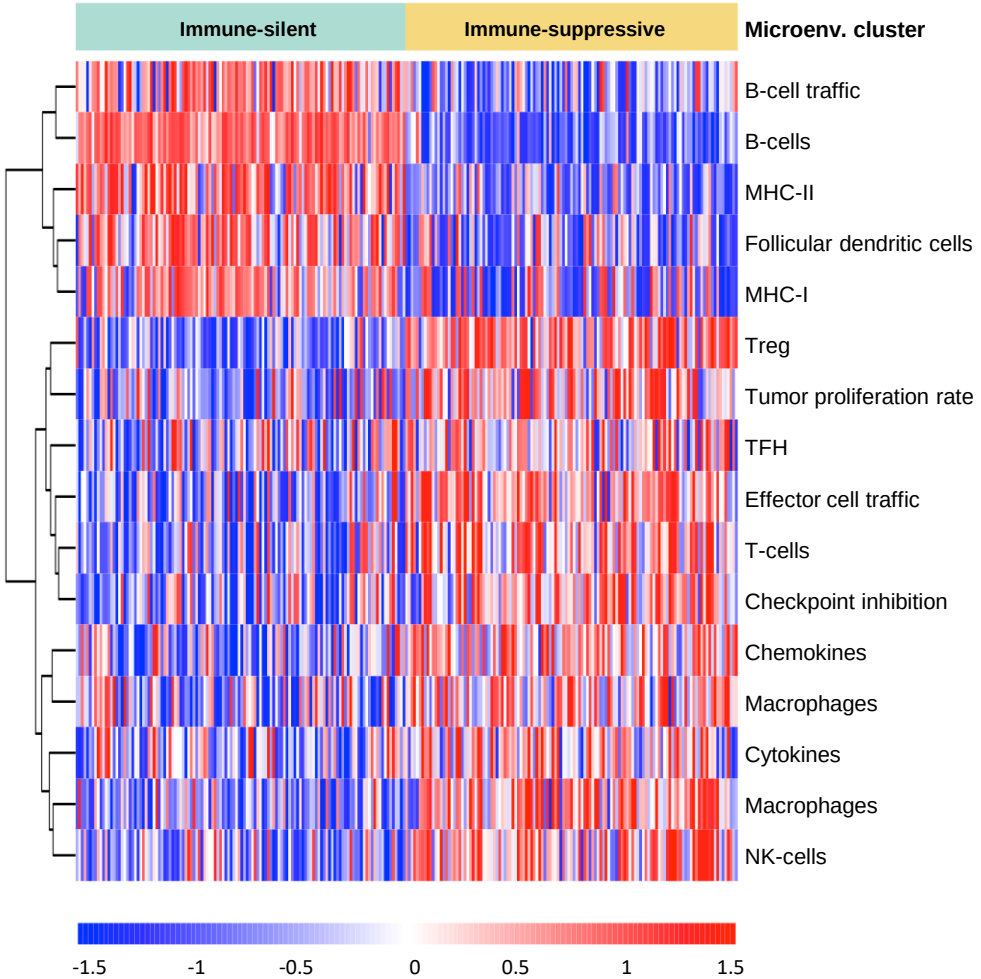
Molecular pathways of MZL

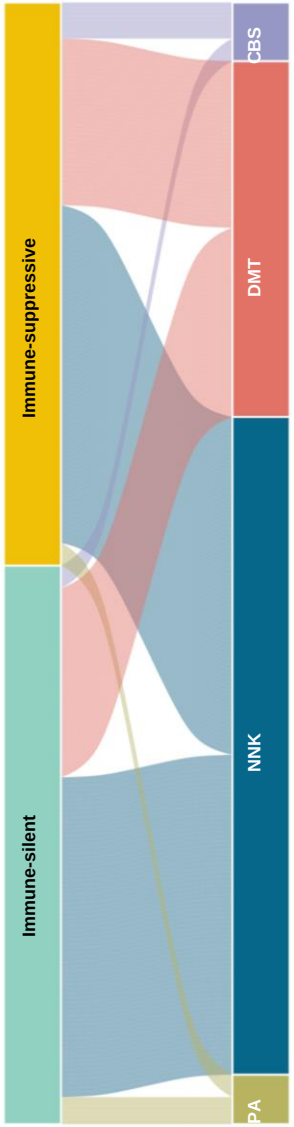


Rossi D, New Engl J Med. 2022

A genetic classifier for SMZL

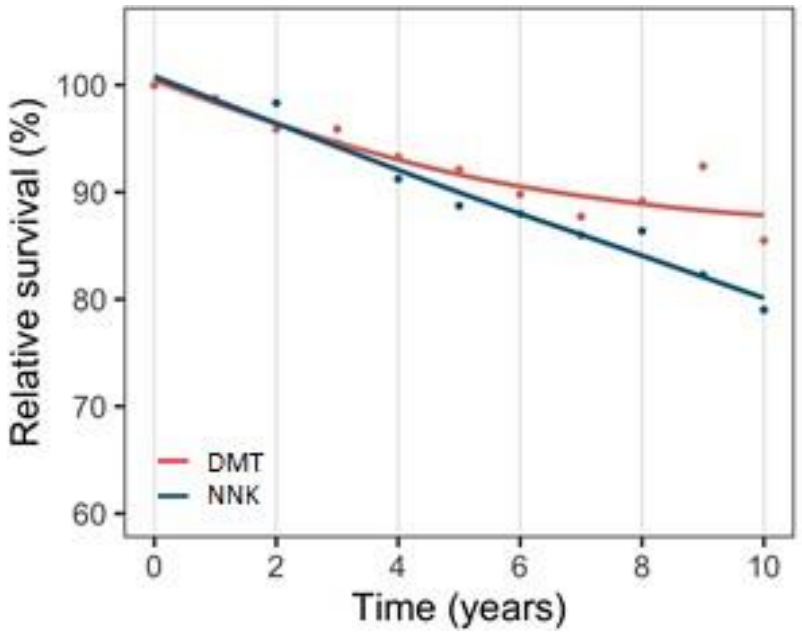


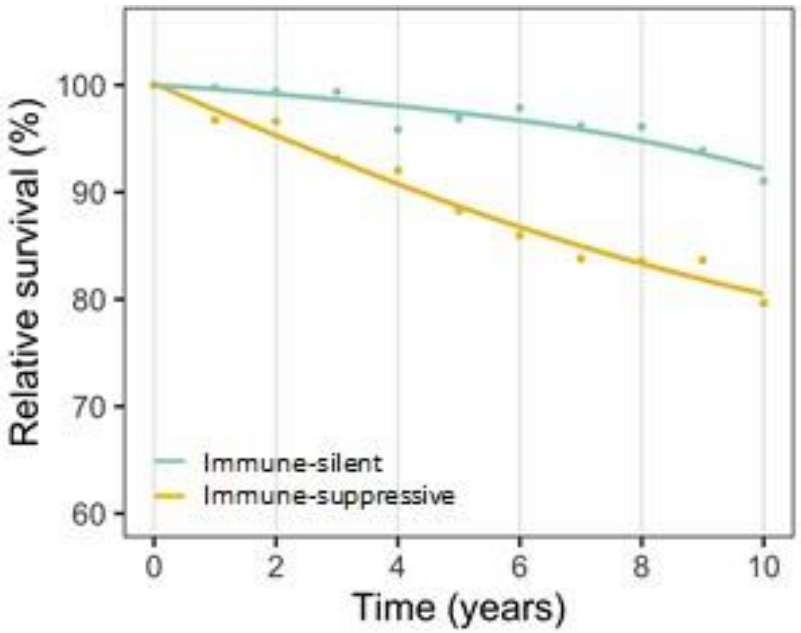


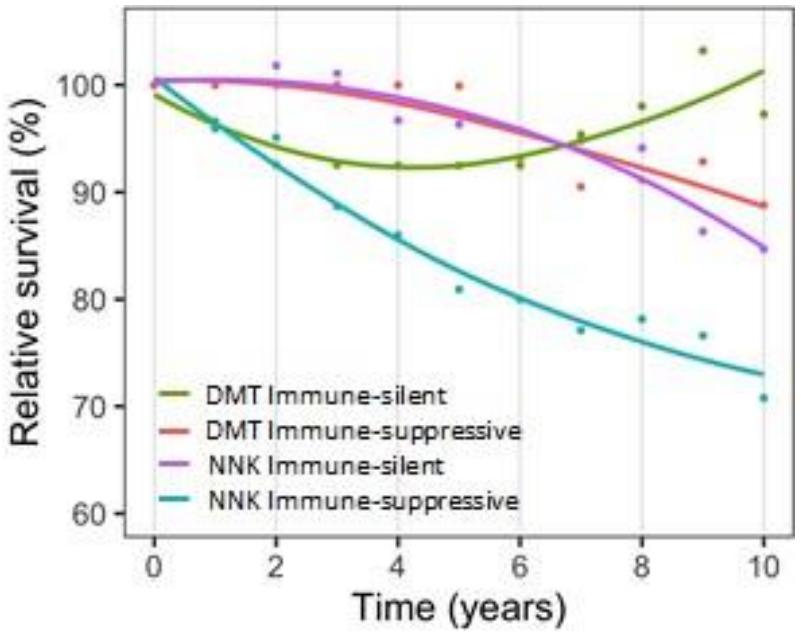


Bonfiglio F, Blood. 2022

Integrated molecular prognostics of SMZL







Bonfiglio F, Blood. 2022

Risk of symptomatic progression

Risk of symptomatic progression: modified GELF criteria

Massive nodal involvement: At least one nodal or extranodal mass >7 cm in diameter

Bulky disease: Three or more lymph nodes with diameters of 3 cm or more

Systemic symptoms: B symptoms (fever >38°C, night sweats, weight loss >10% in 6 months)

Splenomegaly: Symptomatic or massive splenomegaly

Bone marrow involvement: Cytopenia due to BM infiltration (Hb <10 g/dL, ANC <1,000/µL, Plt <100,000/µL)

Effusions: pleural effusion or ascites related to the lymphoma

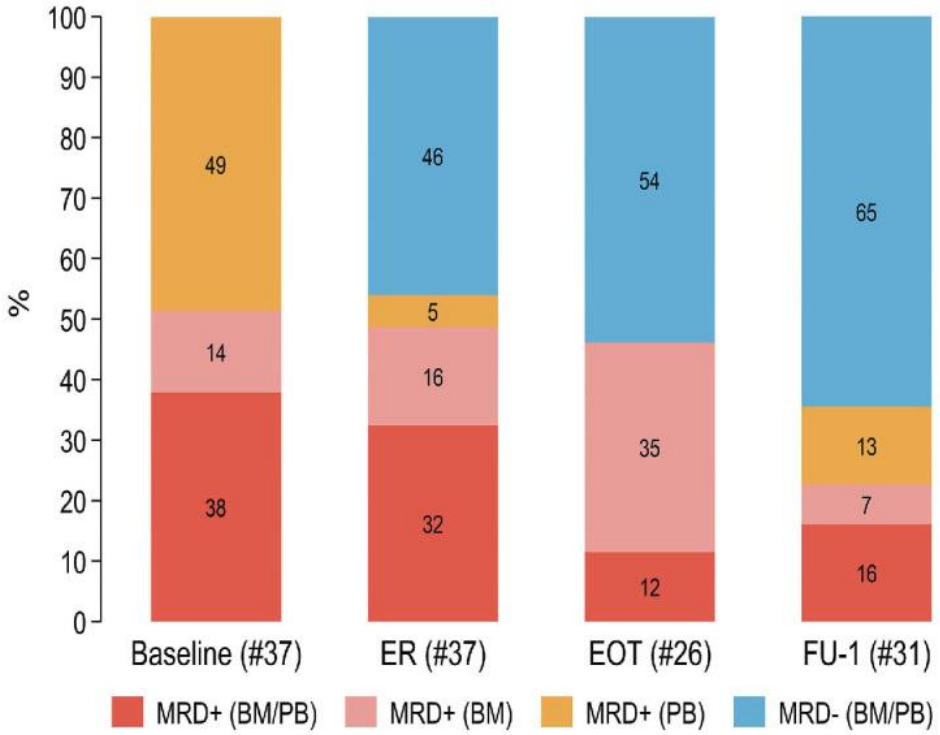
Compression syndrome: Organ compression by tumor mass, e.g., kidney obstruction or GI involvement

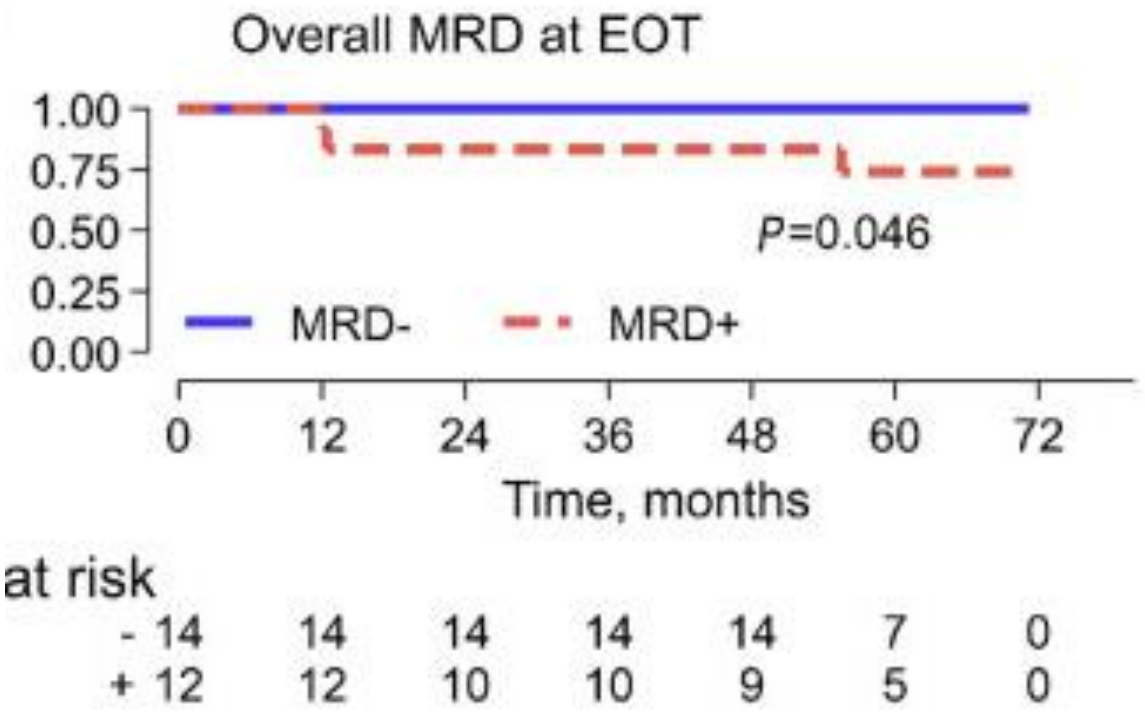
Low tumor volume in 30% of cases
Active surveillance is not detrimental in case of low tumor volume
Median time to first treatment: 3-5 years

Bommier C, Hematol Oncol. 2024; Florindez JA, Cancer. 2020

Minimal residual disease

Persistence of mMRD after BR in SMZL

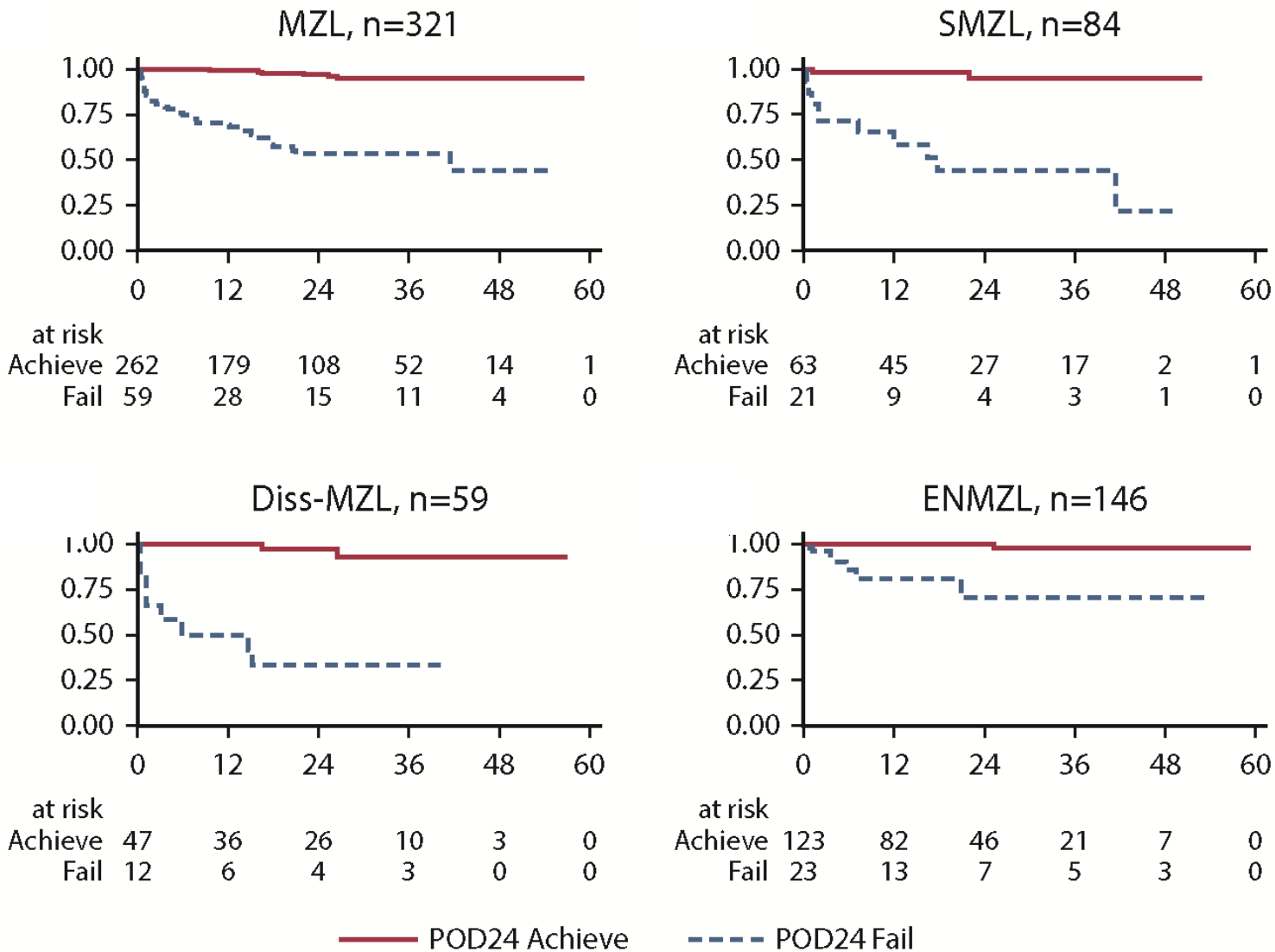




Iannitto E, Haematologica 2024

Early progression

POD24 as a prognosticator of survival in MZL

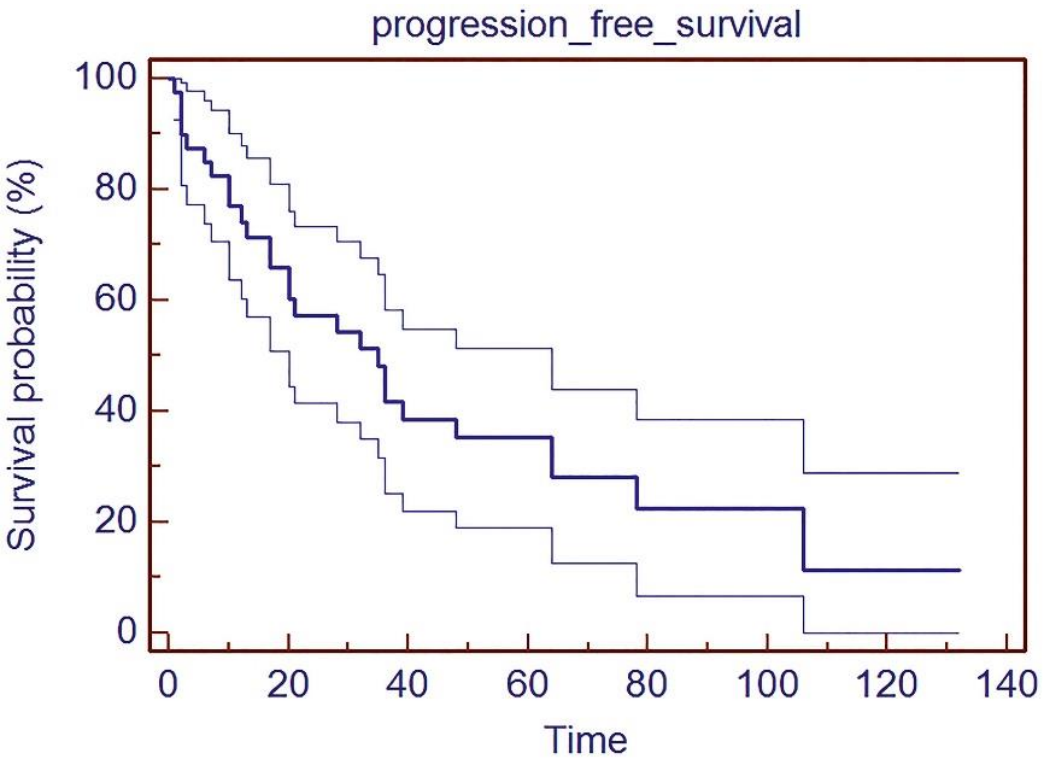


Luminari et al. Blood 2019

Treatment specific risk factors

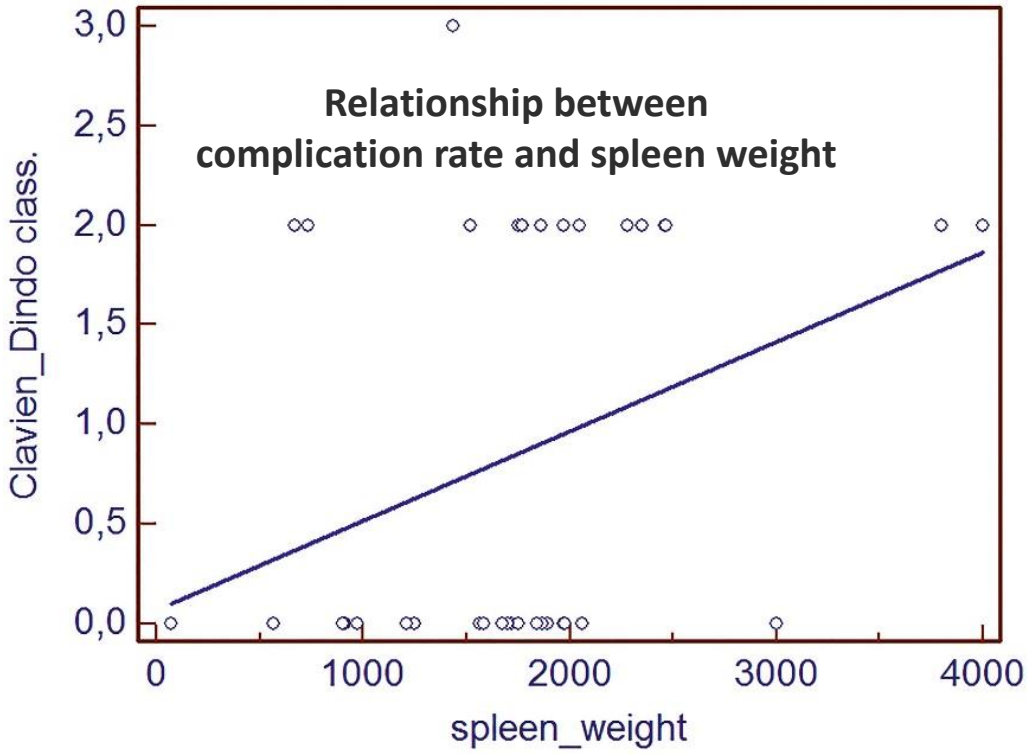
High-Risk for splenectomy in SMZL

Relief of volume-related symptoms: **100%**
Hematologic response: **80%**
TRM: **0%**



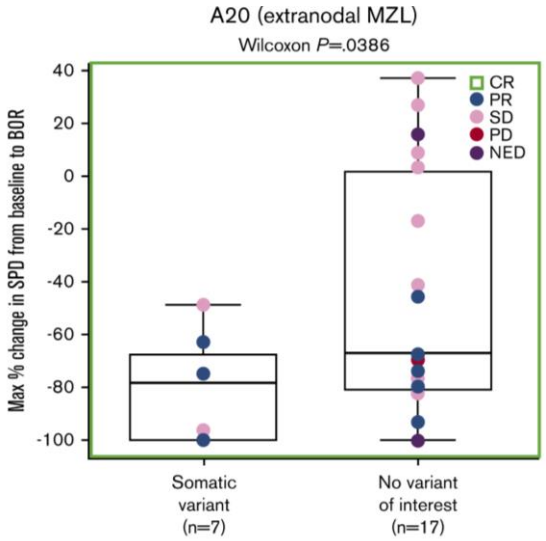
Perioperative complications

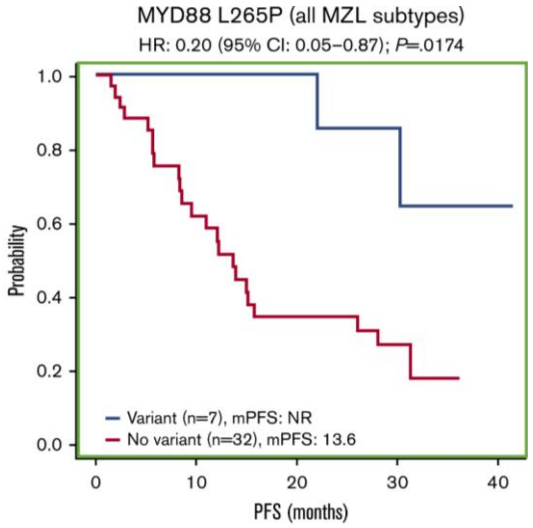
MEDICAL COMPLICATIONS	**23%**
Pulmonary	18%
SURGICAL COMPLICATIONS	**23%**
Major bleeding	20%
REOPERATION	**0%**
RBC TRANSFUSION	**30%**

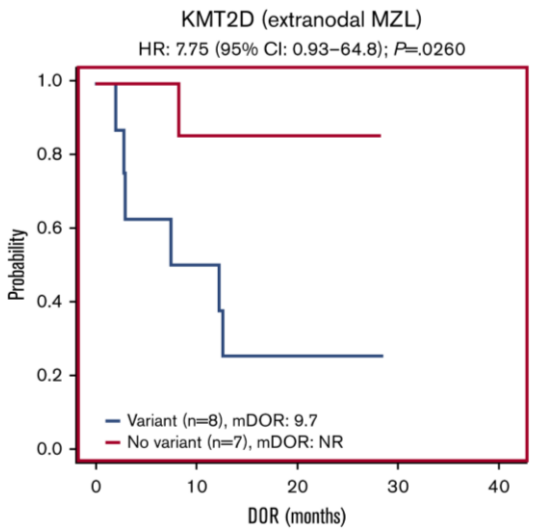


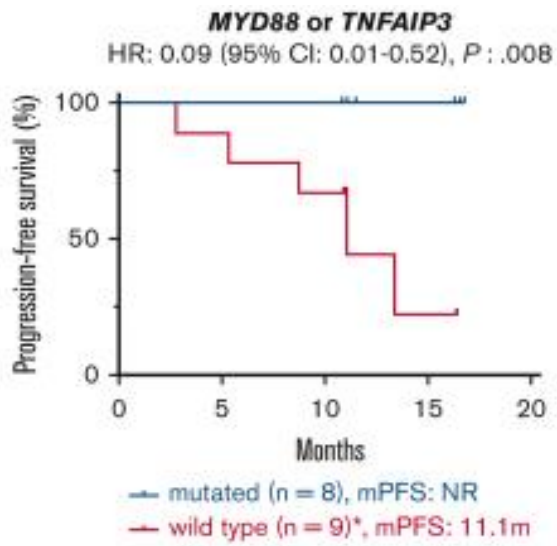
Pata G, Int J Surg. 2017

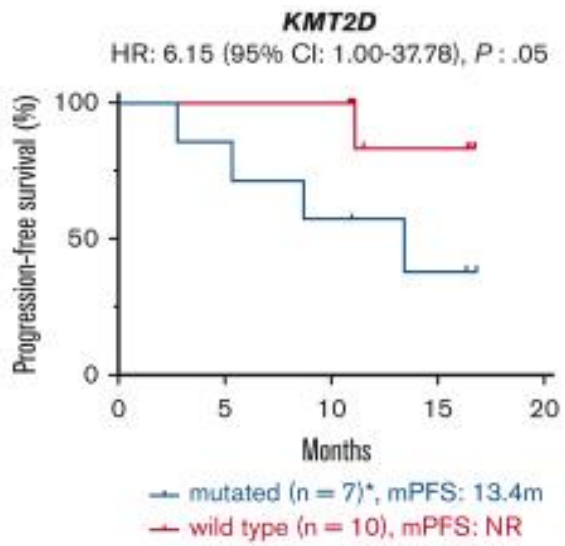
Molecular markers of sensitivity to BTKi











Noy A, Blood Adv 2020; Tatarczuch M, Blood Adv 2023

IELSG48

Phase 3, interventional, multicentre, open label, randomized study comparing rituximab plus zanubrutinib to rituximab monotherapy in previously untreated symptomatic splenic marginal zone lymphoma

Co-PI

Luca Arcaini, Davide Rossi

Steering committee

Francesco Bertoni, Christian Buske, Bjørn Østenstad, Ida Blok Sillesen, Antonio Salar, Catherine Thieblemont, Renata Walewska, Bjørn Wahlin, Emanuele Zucca

Summary

- Wrong diagnosis is the worst predictive/prognostic factor
- Lack of predictive biomarkers (because of the lack of Ph 3 trial)
- Level of evidence on prognostic biomarkers: mostly Grade III-IV
- MALT-IPI, MZL-IPI, POD24 are validated prognostic factors: Clinical utility?
- Biomarkers that are at the prime-time for treatment tailoring:
  - Transformation
  - Aggressive presentation in disseminated MZL (high number of large cells, Ki-67 $\geq$30%, High LDH, SUVmax $\geq$10)

Perspectives

Prognostic markers at baseline	
NGS	**48 (65%)**
TP53	43 (58%)
NOTCH2	30 (41%)
KLF2	19 (26%)
KMT2D	16 (22%)
TNFAIP3	15 (20%)
PTPRD	5 (7%)
Other	2 (3%)
PET-CT	**39 (53%)**
TMTV	25 (34%)
SUVmax	16 (22%)
Deauville score	14 (19%)
Any measurement	9 (12%)
Other	3 (4%)
cfDNA	**29 (39%)**
Cytogenetics	**21 (28%)**
del(17p)	11 (15%)
t(11;18)	11 (15%)
t(14;18)	8 (11%)
del(7q)	5 (7%)
t(1;14)	5 (7%)
+3	3 (4%)
+18	3 (4%)
6q23-	2 (3%)
Any abnormality	6 (8%)
Other	1 (1%)
Other	**6 (8%)**

Prognostic markers during follow-up	
PET-CT	**42 (57%)**
Deauville score	23 (31%)
TMTV	17 (23%)
ΔSUVmax	14 (19%)
SUVmax	13 (18%)
ΔTMTV	8 (11%)
Any measurement	9 (12%)
Other	3 (4%)
cfDNA	**41 (55%)**
ΔcfDNA baseline-EOT	24 (32%)
ΔcfDNA baseline-interim	20 (27%)
cfDNA levels	14 (19%)
Any measurement	7 (10%)
Other	1 (1%)
MRD	**27 (36%)**
Sample: Blood	21 (78%)
Sample: Bone marrow	6 (22%)
Technique: Flow cytometry	14 (52%)
Technique: PCR	13 (48%)
Other	**2 (3%)**

Bommier C, Hemasphere 2022