La definizione del rischio

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Disclosures of Emilia Cappello

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

None

Marginal zone lymphoma (MZL)

MZLs: 7-8% of all non-Hodgking Lymphomas (NHLs)

Three distinct subtypes

According to **WHO-HAEM5** and **ICC:**

WHO-HAEM5 *(Alaggio R et al, Leukemia 2022)*	**ICC 2022** *(Campo E et al, Blood 2022)*
EMZL	**EMZL**
Primary cutaneous MZL	*Primary cutaneous lymphoproliferative disorder*
NMZL	**NMZL**
Paediatric NMZL	Paediatric NMZL
SMZL	**SMZL**
Splenic diffuse red pulp small B-cell lymphoma, Splenic B cell lymphoma/leukemia with prominent nucleoli	Splenic B cell lymphoma/leukemia, unclassificable

+ disseminated MZL: widespread disease without clear primary splenic, nodal or extranodal origin

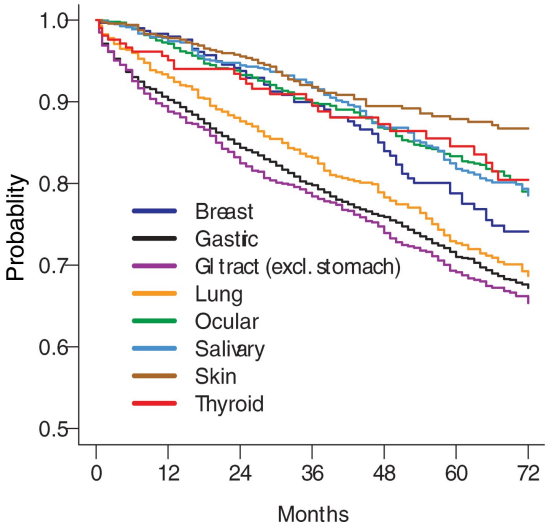
Some shared histopathological features, intra/inter-disease heterogeneity

Usually good outcome and prolonged survival

Survival outcomes – High risk MZLs

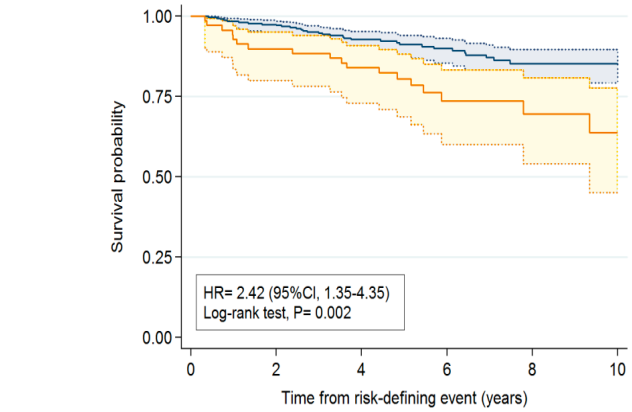
However, some patients experience different outcomes, with rapid progression and earlier mortality

OS by EMZL subtype



Olszewski AJ et al. Cancer 2013

OS by POD24 in EMZL

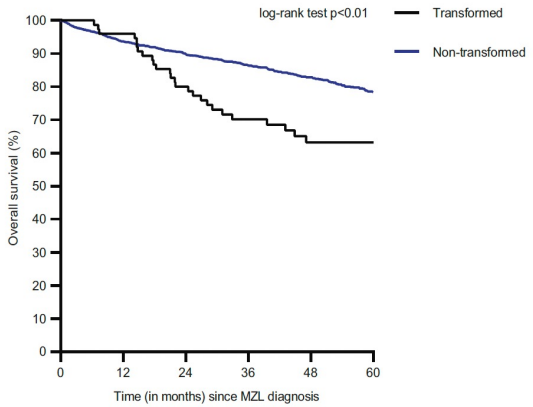


Number at risk

Early POD = No	315	298	211	142	64	1
Early POD = Yes	69	62	54	26	17	8

Conconi et al. Hematologica 2020

OS by HT in MZL



Number at risk

Non-transformed	1718	1607	1541	1167	823	483
Transformed	75	72	60	45	33	24

Bult et al. BCJ 2023

How to define and identify high-risk MZLs?

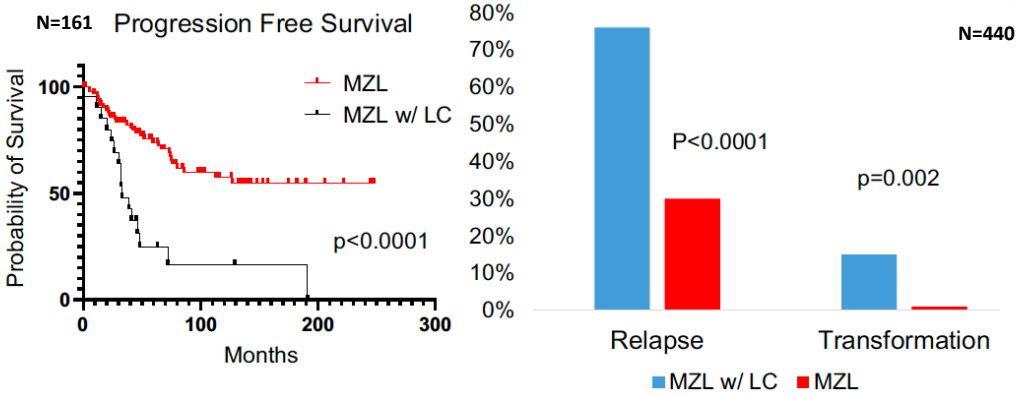
Risk stratification and high-risk features at diagnosis in MZL

High-risk histological features in MZL

*Large cells (LCs)

LCs group* MZL [20% pts] *vs* non-LCs[1]

- Higher rate of cases with Ki-67≥30%
- Advanced stages, ↑LDH
- **Shorter PFS** (33 mo vs NR)
- **Increased relapses** (76% vs 30%) **and HT** (15% vs 1%)

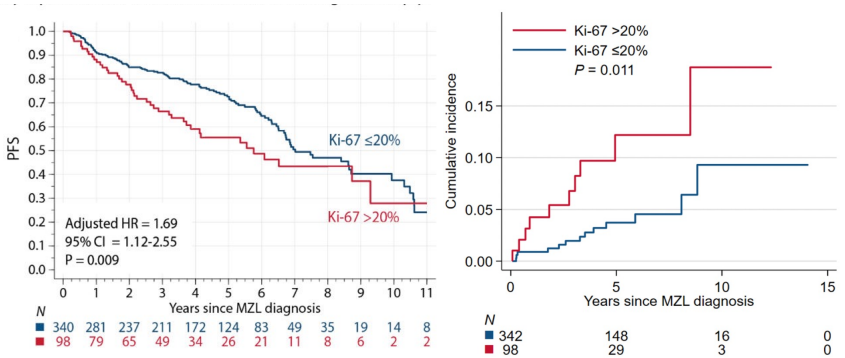


1. Stueber T et al., Hum Pathol. 2023

*Ki-67

Ki-67≥20% group [22% pts] *vs* <20%[2]

- **Worse PFS** (5.4 yrs vs 7 yrs) **and OS**
- **Higher CI of HT** (5-yrs CI of HT: 9.8% vs 3.9%) , ↑LDH
- LCs[#] presence associated with higher Ki-67
- Initial treatment did not impact PFS or OS in high Ki-67 or LC+



2. Grover, N.S et al. BCJ 2024

MZLs with higher Ki-67 and/or LC enrichment represent an higher risk subsets

Shorter FUP? Prioritize for experimental approaches? Re-biopsy at progression (HT?)

**No standardized definition/quantification of LCs and no standardized cut-off for high risk Ki-67% in MZLs*

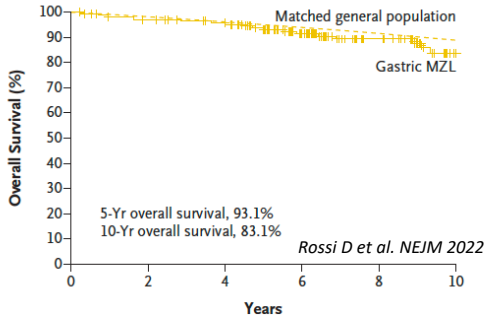
**At least 10 LCs per HPF by manual count of at least 10 random HPF*

#Arbitrarily evaluated groups with"any reported LC" or ">10% LC"

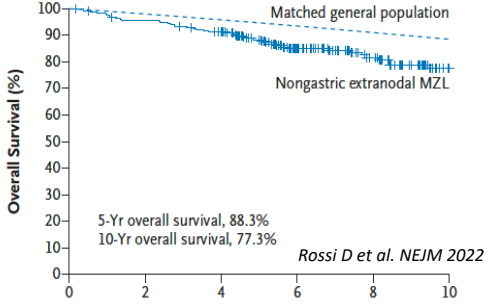
Stage disease at diagnosis, MMS - EMZL

Primary lymphoma location[1,2,3]

Gastric MZL

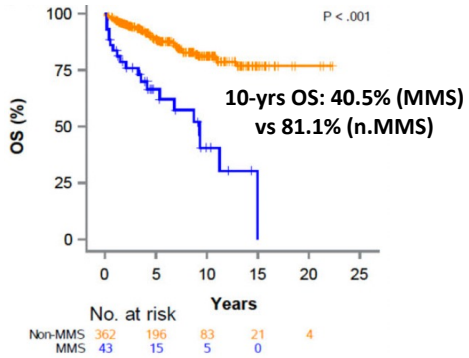


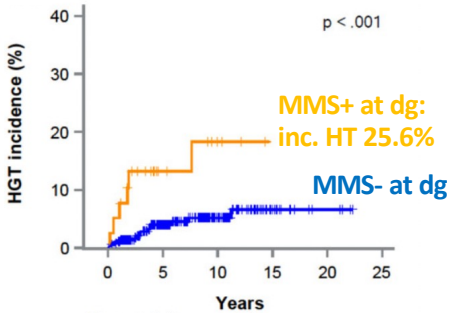
Nongastric Extranodal MZL



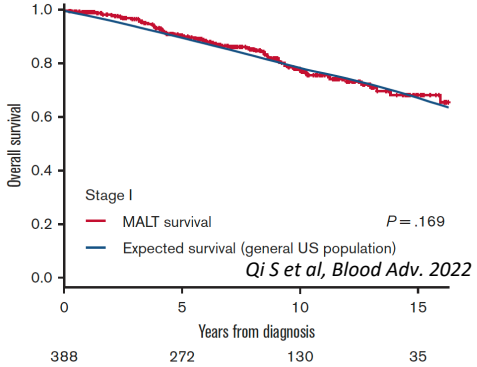
Multiple mucosal sites[4]

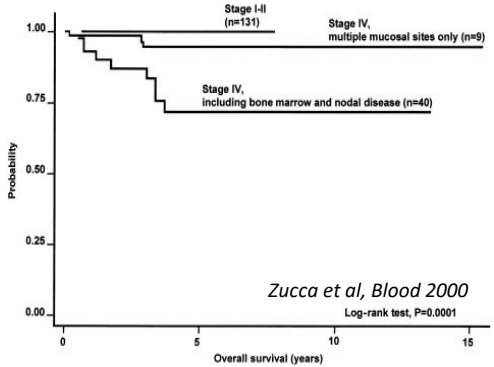
(11-37% EMZL pts)





Localized vs non-localized disease[5,4]





1. Zucca E. et al. JCO 2017, 2-3. Thieblemont C. et al. Blood 2000 and 2020

4. Alderuccio JP et al. Am J Hematol 2019

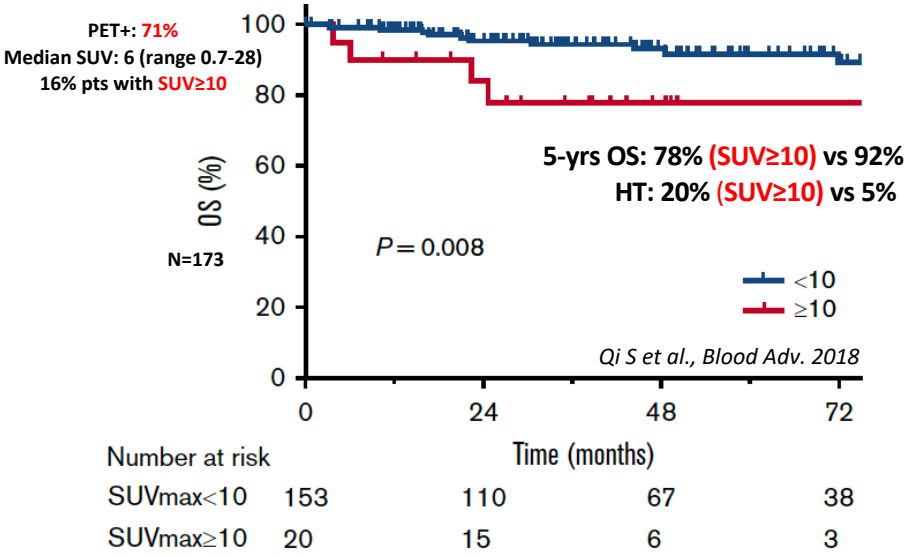
5. Zucca E. et al. Blood 2003. 6 Arcaini et al. Oncologist 2006

Staging in MZL: 18F-FDG PET

18F-FDG PET: not recommended by **Lugano classification** *(Cheson et al., JCO 2014)*

Variable detection rate → EMZL: 30-80%; **SMZL/NMZL:** 70-80% *(Ceriani et al., Ann Lymphoma 2020)*

Prognostic value of PET/CT in MALT

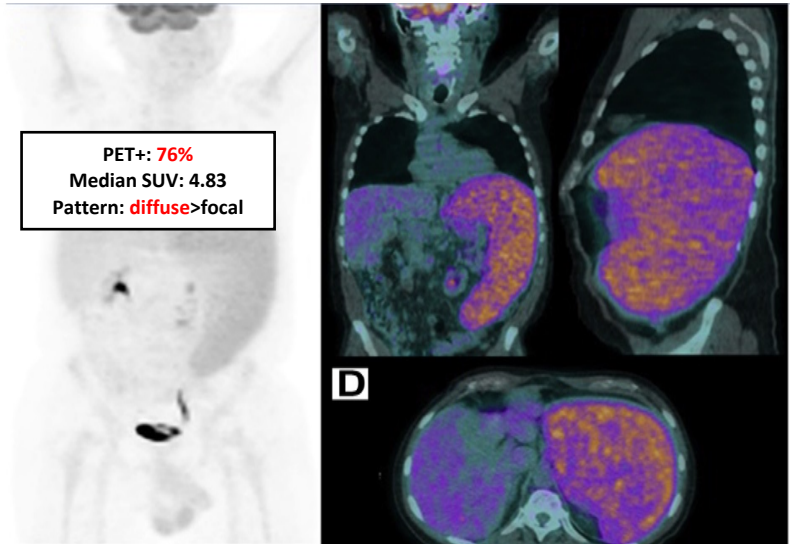


In EMZL SUV ≥10: inferior OS and higher rate of HT

Non significant correlation between SUV and Ki-67%

Qi S et al., Blood Adv. 2018

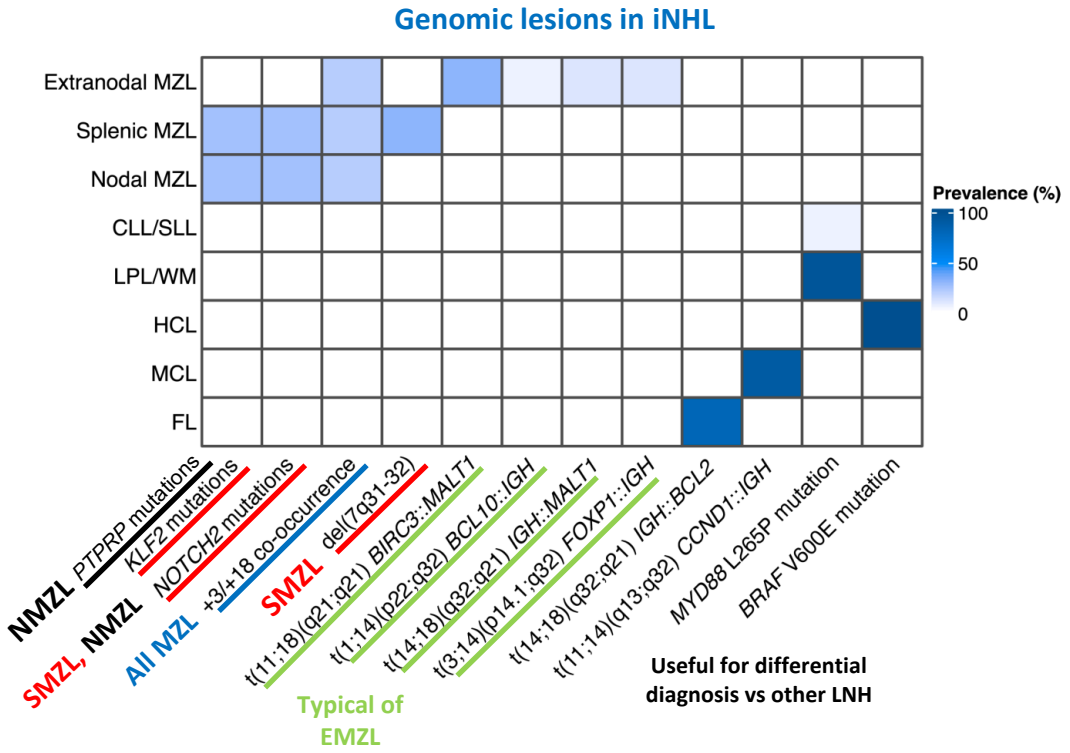
Prognostic value of PET/CT in SMZL



18F-FDG avidity significantly associated with Ki-67≥15%

Albano D et al, Abdom Radiol 2019

Genomic profiling of MZLs

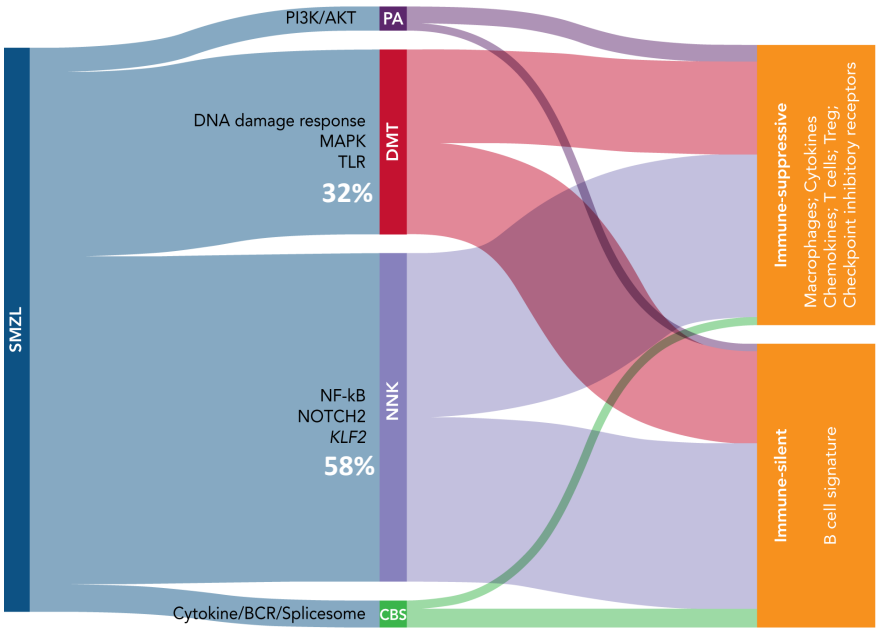


Currently: Biological prognostic factors → Inconsistent in clinical practice

de Leval et al. Blood 2022

Clarify SMZL biological heterogeneity: IELSG46 study

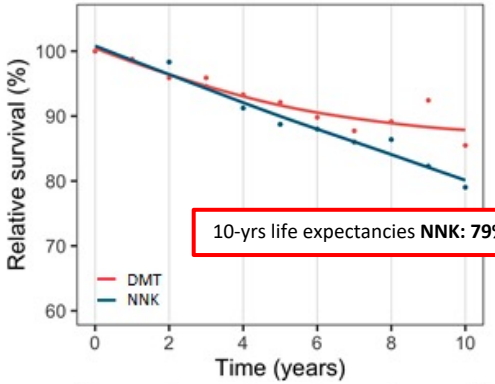
SMZL biological heterogeneity…



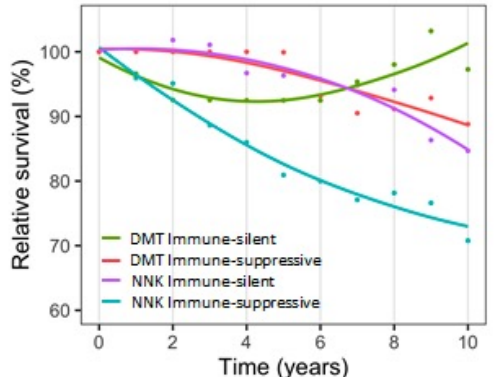
2 principal molecular clusters: **NNK and DMT**
2 micro-environment classes: **immuno-silent and immune-suppressive**

Deaglio & Vaisitti, Blood 2022: Comment on Bonfiglio et al. Blood 2022

…and prognostic implications



10-yrs life expectancies **NNK: 79%,** DMT: 85.5%



Bonfiglio et al. Blood 2022

NNK -immunesuppressive excess mortality **(10-yrs RS: 70.8%)**

Prognostic scores - EMZL

MALT-IPI

Variables
Age > 70y
Elevated LDH
Ann Arbor III-IV

5-y EFS

0	70%
1	56%
2-3	29%

The **MALT-IPI** also distinguishes between different **PFS, OS**

Thieblemont et al. Blood 2017

rMALT-IPI

Variables
Age>60y
Elevated LDH
Ann Arbor III-IV
Multiple mucosal sites (2 Pts)

mPFS

0	NE
1	12.8y
2	5.8y
3-5	1.8 y

The **Revised MALT-IPI** can also detect patients at risk of **POD24** and **HT**

Alderuccio et al. AJH 2022

Courtesy of prof. LA

Prognostic scores - SMZL

SMZL IIL score

Variables
Hb < 12 g/dl
Elevated LDH
Albumin < 3.5 g/dl

Score
0 low risk
1 intermediate risk
2-3 high risk

5-y OS
0 83%
1 72%
2-3 56%

Arcaini et al. Blood 2006

SMZL HPLL score

Variables
Hb level
Plt count
LDH elevated
Extrahilar
Lymphadenopathy

5-y LSS
A 94%
B 78%
C 69%

Montalban et al. BJH 2012

SMZL HPLLs score

Variables
Hb < 9.5 g/dl
Plt < 80.000/mmc
Elevated LDH
Extrahilar lymphadenopathy

5-y LSS
A 95%
B 87%
C 68%

Montalban et al. Leukemia 2014

Courtesy of prof. LA

Prognostic scores - MZL-IPI

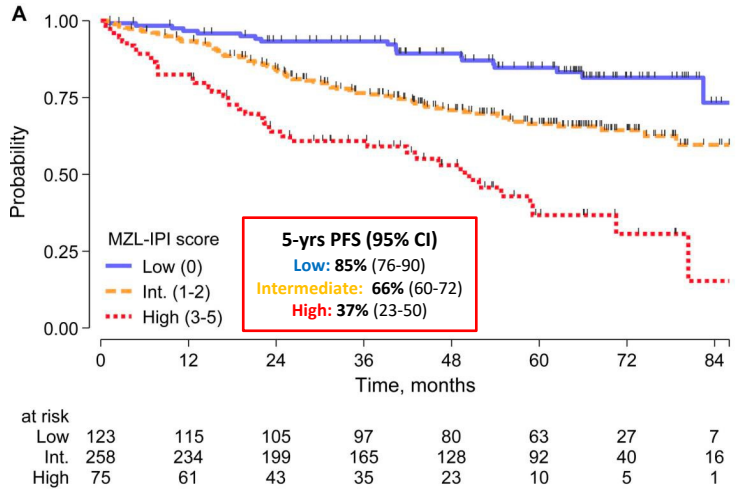
Newly diagnosed MZL (EMZL, SMZL, NMZL, dMZL) receiving **frontline systemic therapy at diagnosis or after observation**

Training cohort (n=501) from NF10 dataset (a FIL study), validation 2 external US cohorts

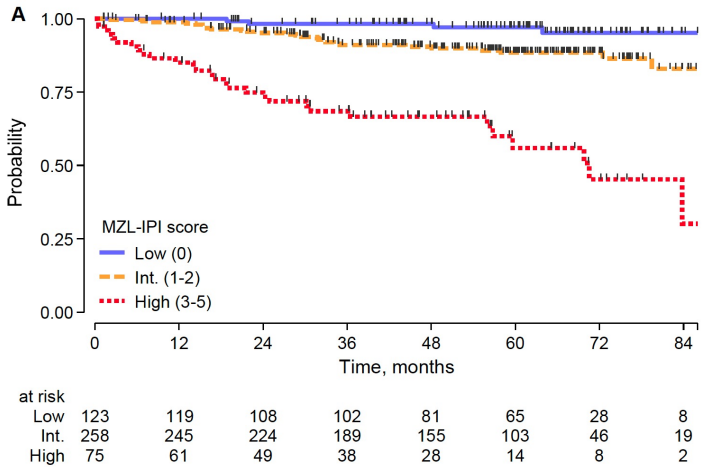
Primary endpoint: ***PFS***

5 variables: **LDH** (< or ≥ UNL), **Hb level** (< or ≥12g/dL), **PLT count** (< or ≥100×10^9/mmc), **ALC** (< or ≥1×10^9/mmc), **MZL subtype** (ENMZL and SMZL vs NMZL and dissMZL)

PFS according to MZL-IPI risk category



OS according to MZL-IPI risk category



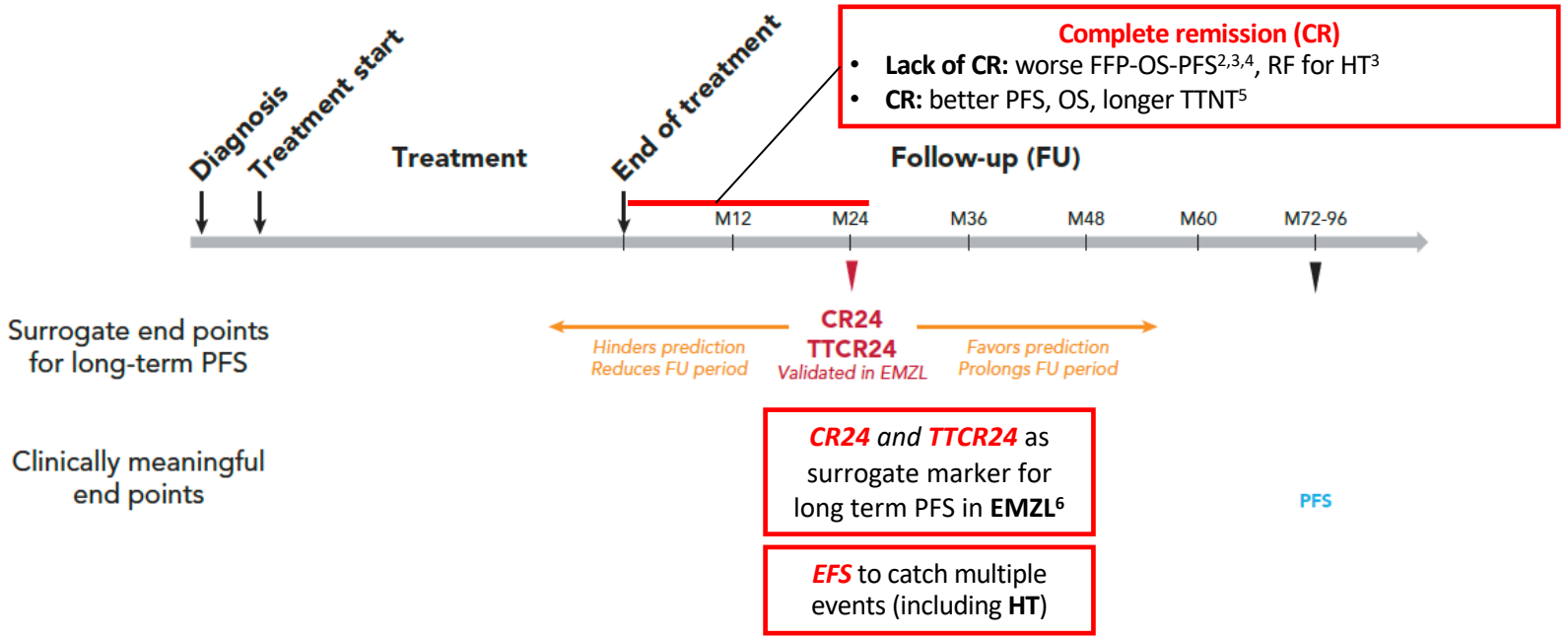
Currently, we do not perform treatment selection based on any prognostic model, overall, in MZL

Arcaini et al. eClinicalMedicine 2024

Treatment outcomes and high-risk features

Difficulties to find predictive and prognostic markers in clinical trials

New surrogated and/or dedicated endpoints: complete remission (CR)[1]



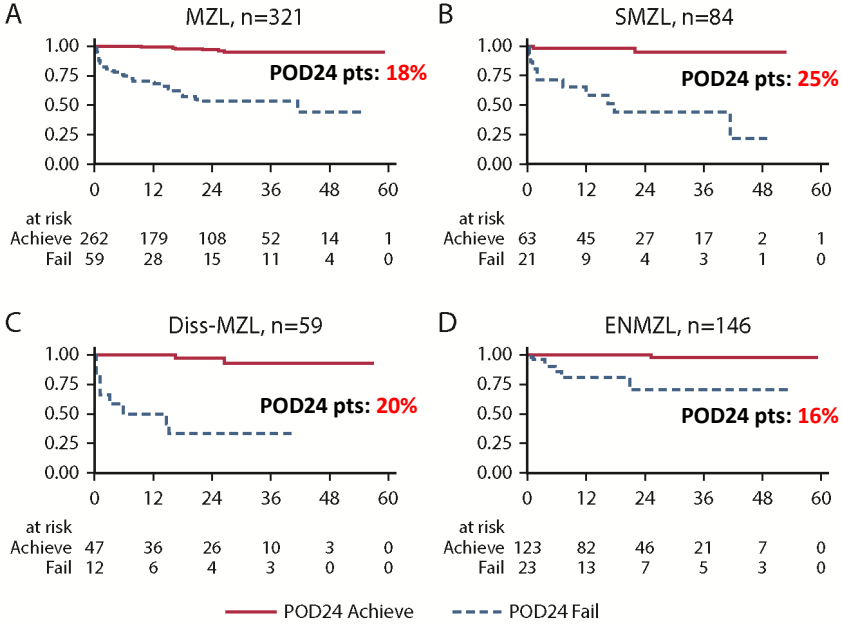
1. Thieblemont C. et al. Blood 2026 2. Thieblemont C. et al. Blood 2000 3. Alderuccio JP et al, JCO 2018 4. Alderuccio JP et al, Am J Hematol 2019 5. Wang H et al. Front. Immunol. 2024 6. Bommier C. et al, Blood 2024

Response assesment and its prognostic implications: POD24

Prognostic impact on OS by early pod (POD24) status in MZLs

NF10 dataset – POD24 and OS

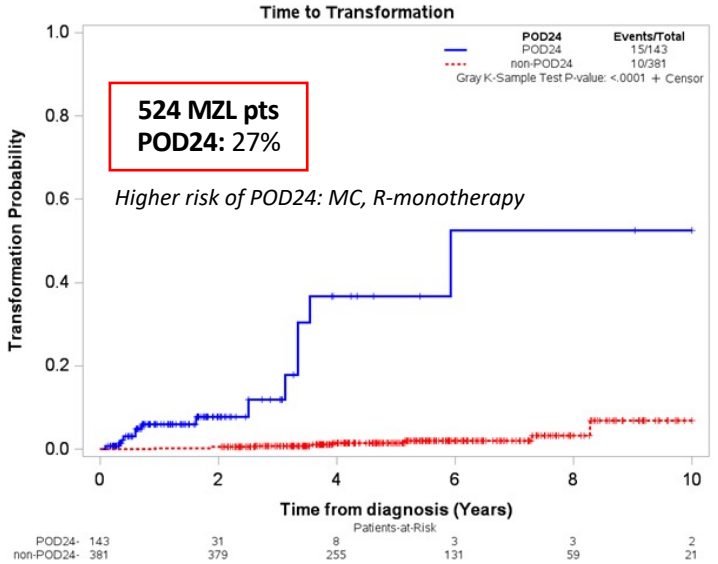
Luminari S. et al, Blood 2019



3-yrs OS: 53% vs 95% (POD24 *vs* non-POD24)

POD24 pts had a significantly higher risk for HT

Epperla et al. J Hematol Oncol 2023



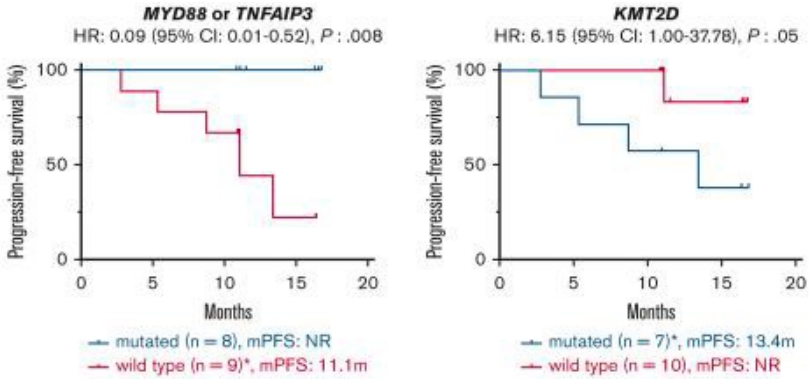
CI of HT at 3 and 5-yrs: 12% *vs* 1% and **37%** *vs* 2% (p<0.0001)

5-yrs OS: 75% vs 92% (POD24 *vs* non-POD24)

In patients with MZLS who received front-line systemic treatment, POD24 is associated with poorer survival and HT

Predictive biomarkers

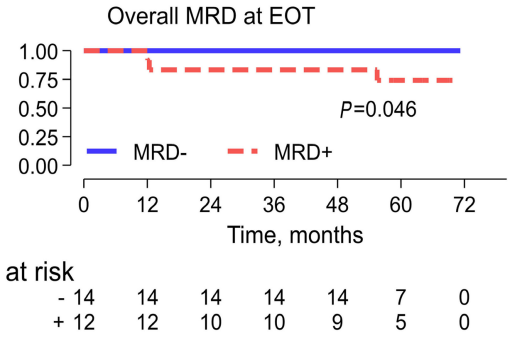
Biomarkers and therapy outcomes (Zanubrutinib)



MRD

BRISMA (IELSG36)

EoT MRD+: inferior PFS



Iannitto E et al, Haematologica 2024

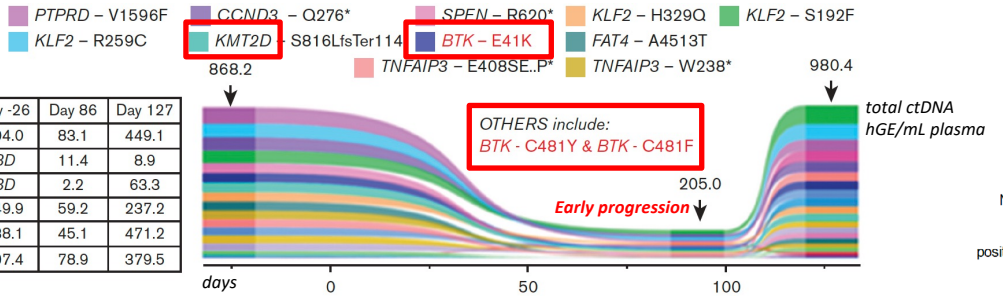
Circulating tumor DNA (ctDNA)

Detection of ctDNA mutations and evolution during zanubrutinib therapy in a SMZL case

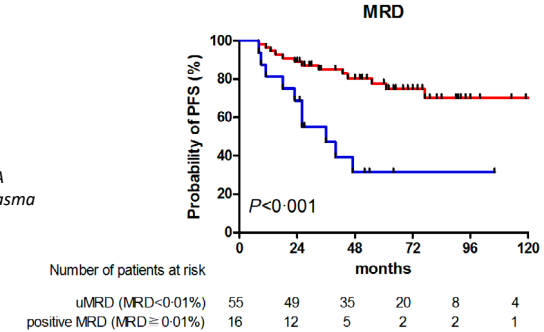
MZ03 (SPLENIC)

Progressive Disease

hGE/mL plasma	Day -26	Day 86	Day 127
BTK – E41K	504.0	83.1	449.1
BTK – C481Y	*BD*	11.4	8.9
BTK – C481F	*BD*	2.2	63.3
TNFAIP3 – W238*	449.9	59.2	237.2
TNFAIP3 – E408SE..P*	438.1	45.1	471.2
KMT2D – S816LfsTer114	497.4	78.9	379.5



Tatarczuch et al. Blood Adv 2023



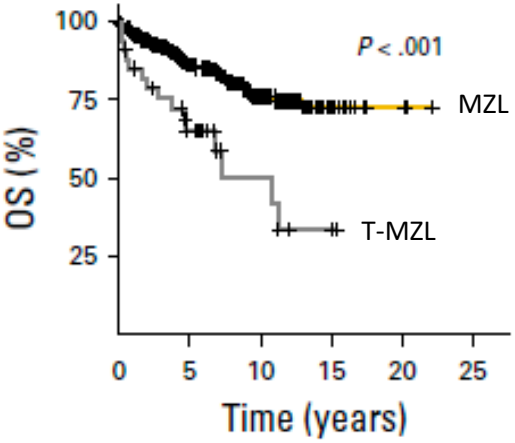
Lyu R et al, BJH 2018

Histological transformation in MZL (tMZL)

Histological transformation: tMZL

tMZL definition *(as per: **2022 EA4HP/SH lymphoma workshop**[1])*

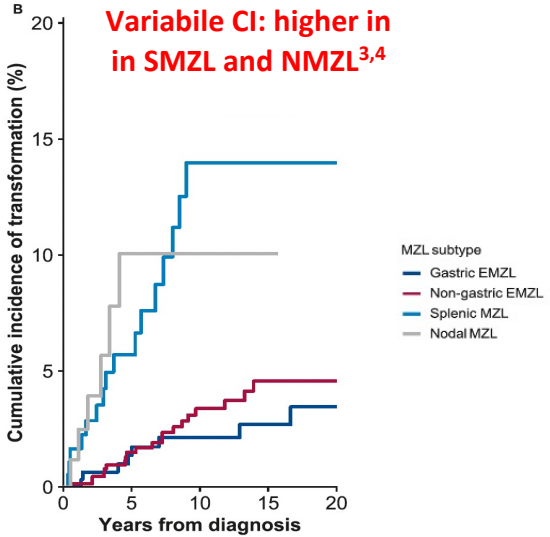
Reduced OS[2]



MZL with HT vs non-HT shorter OS
5-yrs rate, 65% vs 86% (p < 0.01)[2]

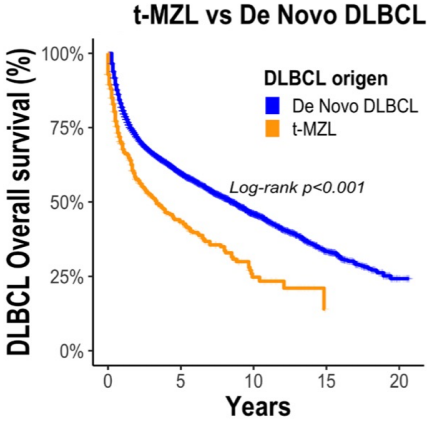
CI of HT in a MZL cohort (n=446):
6.6% at 5 yrs and 8.4% at 10 yrs.[4]

Variabile CI: higher in in SMZL and NMZL[3,4]



>5-y cumulative incidence **2% (EMZL)**[4]
>5-y cumulative incidence **4% (NMZL)**[4]
>5-y cumulative incidence **6% (SMZL)**[4]

Worse prognosis vs de novo DLBCL?[5]



mOS t-MZL: **3.33 yrs** (95% CI, 2.5-4.5) vs 8.58 yrs (95% CI, 8.0-9.1) for **de-novo DLBCL** [p<0.001]

Diagnosis of transformation of MZL to diffuse large B-cell lymphoma carries important clinical consequences with respect to treatment and prognosis

1. Zamò et al. Virchows Archiv 2023 2. Alderuccio JP et al. JCO 2018 3. Kalashnikov et al. Blood Cancer Journal 2023 4. Bommier C et al. Blood Adv 2024 5. Florindez et al. Blood Adv 2024

Clinical risk factors for HT in MZL at diagnosis

Clinical characteristics

All MZL:

- More than four nodal sites involved[1]
- Advanced Ann Arbor stage (III-IV)[2]

SMZL:

- Peripheral lymph node involvement at diagnosis[3]

EMZL

- Multimucosal sites[6]

Lab test

All MZL:

- Elevated lactate dehydrogenase (LDH)[1,7]
- Concomitant monoclonal paraprotein[4]

Previous treatment outcome

All MZL:

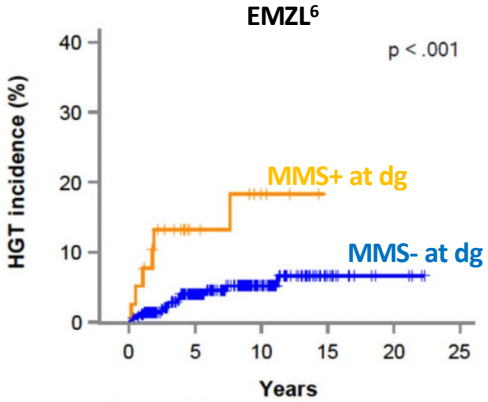
- Failure to achieve complete remission after initial treatment[1]
- POD24[4]

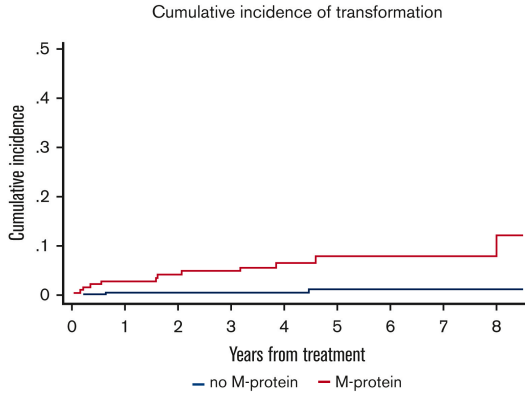
SMZL:

- Initial treatment strategy does not affect the incidence of HT[5]

Metabolic assesment

EMZL: SUV >/=10[8]



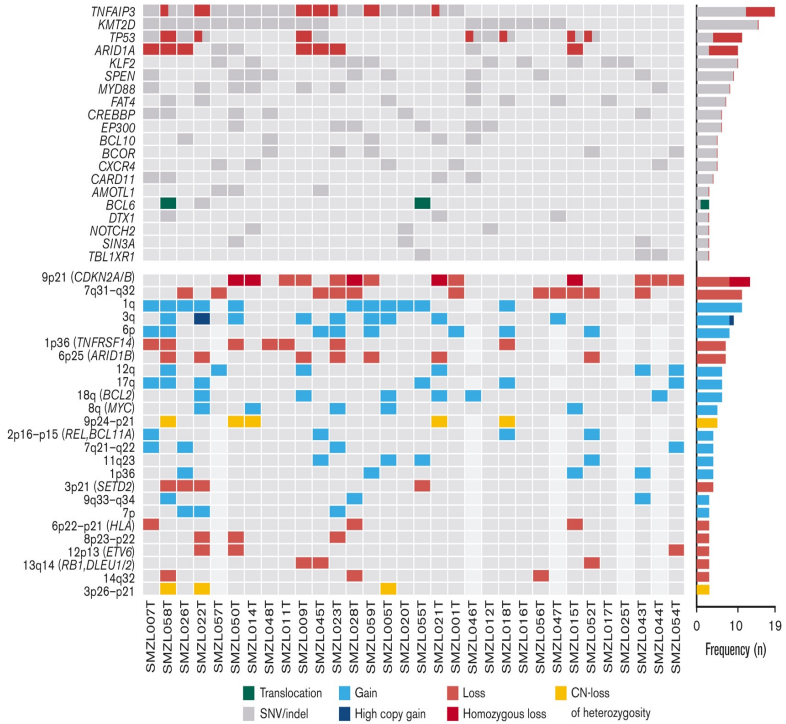


4. Epperla N et al. Blood Adv 2023

1. Alderuccio JP et al. JCO 2018 2. Maeshima AM et al. BHJ 2016 3. Dungarwalla M et al. BHJ 2008 4. Epperla N et al. Blood Adv 2023 5. Camacho et al. Am J Surg Pathol 2001 6. Alderuccio et al. AJH 2019 7. Bult et al. BCJ 2023 8. Qi S et al., Blood Adv. 2018

Biological risk factors for HT in SMZL

tSMZL



T-SMZL[5]: higher genomic complexity, *TNFAIP3* and *TP53* alterations, 9p21 (CDKN2A/2B) losses and 6p gain

Biological RFs for HT in SMZL

- Complex karyotype[1]
- 7q31-32 deletion[2,3]
- **High degree M** profile[3]
- ***IGHV1-02*04*** usage[3]
- ***NOTCH2*** mutations[3]
- ***TNFAIP3/A20*** mutations[4,5]
- ***TP53*** mutations[2,5]

Future directions:

IELSG54 study

Retrospective, observational study whose principal aim is to describe the molecular and clinical profiling of tSMZL cases

1. Bastidas-Mora G Maeshim al. BHJ 2022 2. Parry M et al. Clin Can Res 2015 3. Arribas AJ et al. Blood 2015 4. Clipson A et al. Leukemia 2015 5. Grau et al. Blood Adv 2023

Conclusions

- MZLs represent a heterogeneous group of indolent B-cell lymphomas with generally good prognosis
- A proportion of patients develops high-risk disease (HR-MZLs) with poorer survival
- Risk stratification in MZL requires an integrated approach (combining histological, clinical, radiological, molecular data and treatment response)
- Robust prognostic and predictive biomarkers are still lacking and don't currently influence treatment choice: **HR-MZL is an unmet need**
- Multicenter (clinical-biological-radiological) studies are needed to validate newer prognostic biomarkers and tools to improve HR MZL patients' outcomes

Grazie per l’attenzione!

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Divisione di Ematologia

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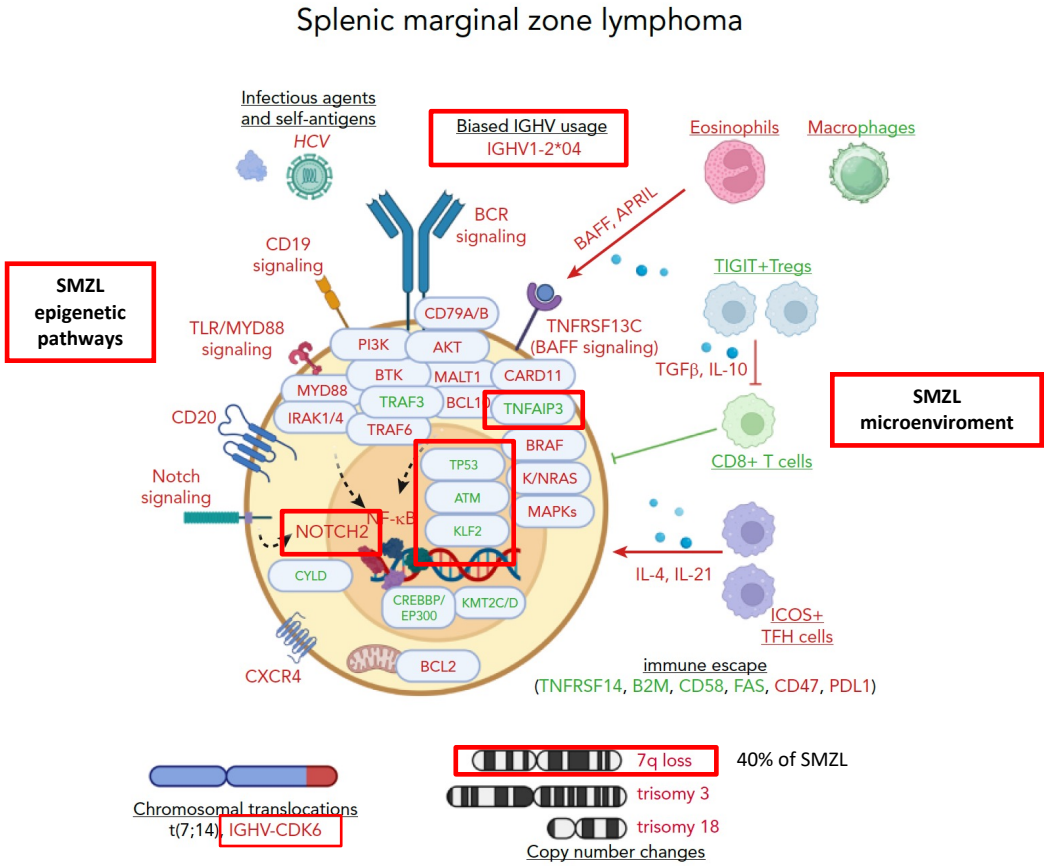
Dr. Sara Rattotti
Dr. Manuel Gotti
Dr. Roberta Sciarra
Dr. Chiara Cavalloni
Dr. Angelica Parisotto
Dr. Alessandro Mazzacane
Dr. Gianmarco Favrin
Dr. Martha Cecilia Berliner
Dr. Sofia Pedrali
Dr. Silvia Zibellini
Dr. Chiara Varraso
Dr. Cristina Picone
Dr. Virginia Valeria Ferretti

Back up slides

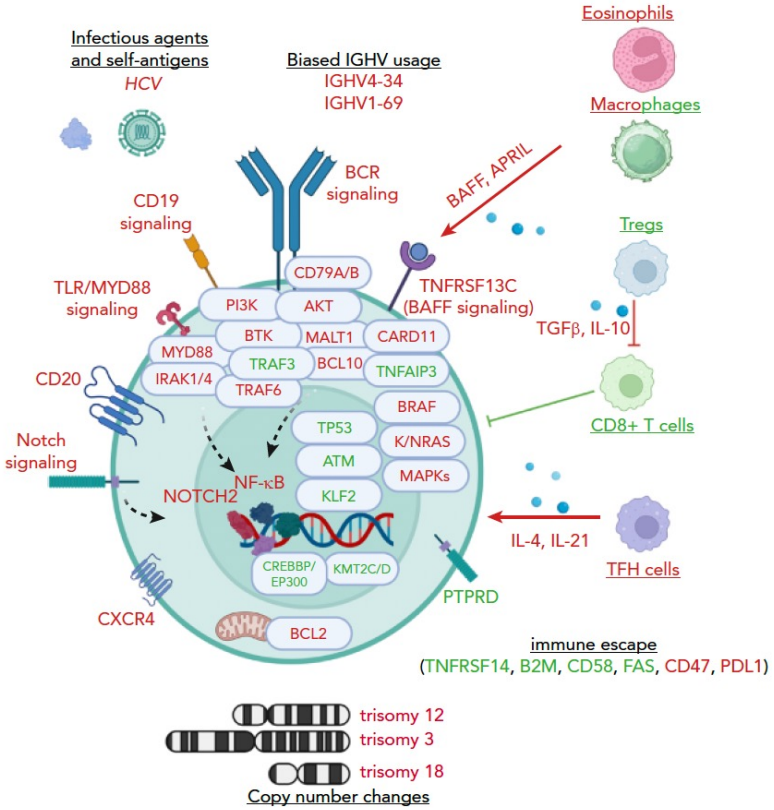
Recurrent biological abnormalities in *SMZL*



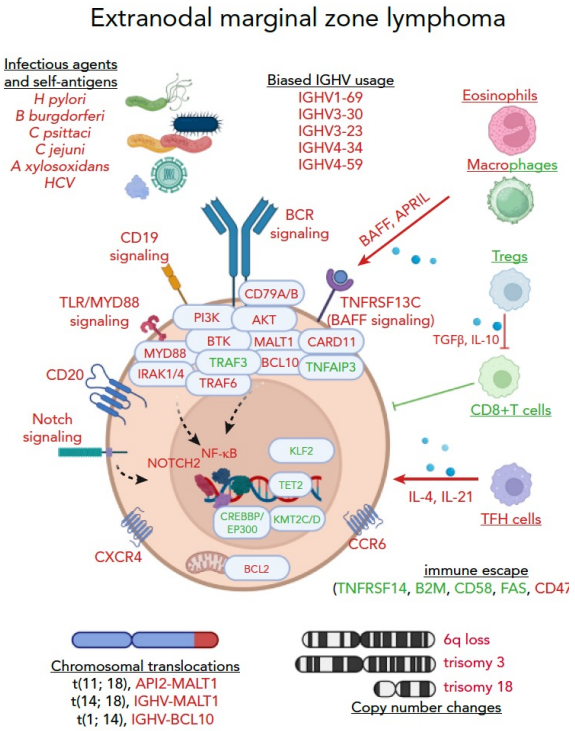
Clarify NMZL biological heterogeneity: IELSG52 study

IELSG52

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



Recurrent genetic abnormalities and *IGHV* use in EMZL



gEMZL t(11;18)/*BIRC3::MALT1*

- Low probability of response to antibiotics[1,2,3]
- More commonly Hp-neg[4]
- Avanced stages[4]

gEMZL Hp-neg

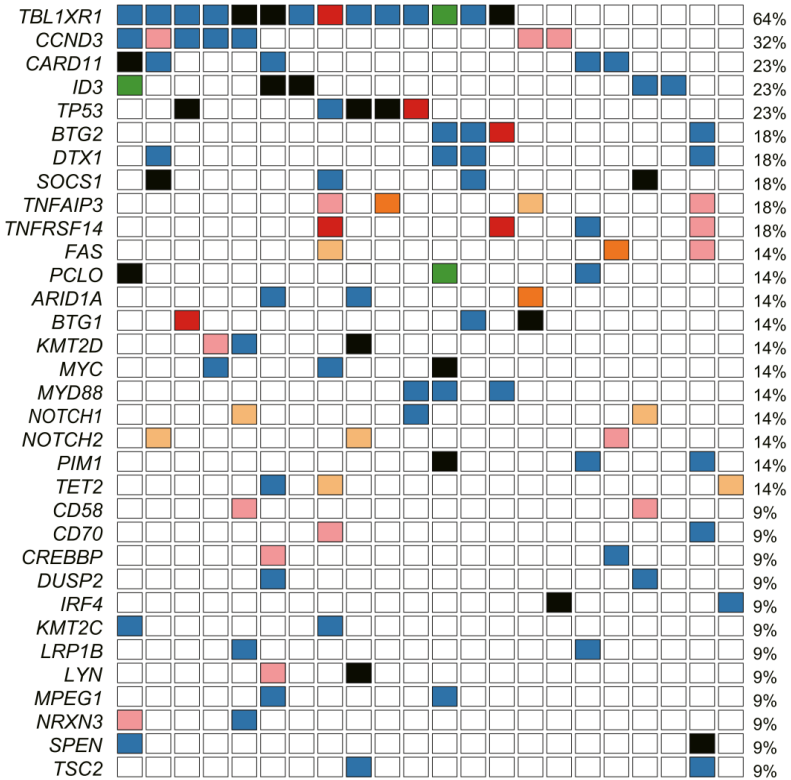
- **More genetic aberrations** (86% *NF-κB* pathway alterations), with no impact on PFS[4,5]

Du MQ. Blood 2025

1. Liu H et al, Gastroenterology 2012 2. Dong G et al, Int J Hematol 2008 3. Nakamura S et al. Gut 2012 4. Ye H et al. Blood 2003 5. Kiesewetter B et al. Cancers 2021

Biological risk factors for HT in MZL

Non-synonimous somatic mutations in tMZLs



T-MZL: elevated expression of MUM1, BCL6, Ki-67 and C-MYC. **Frequent mutations:** ***TBL1XR1*** (63.6%) ***CCND3*** (32%), ***TP53*** (23%), ***CARD11*** (23%), and ***ID3*** (23%). ***ID3*** and ***TBL1XR1*** more frequent in HT MZL than in de novo DLBCL

Li A et al. Cancer 2024