FONDAZIONE ITALIANA LINFOMI

I "LINFOMI INDOLENTI"

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Il caso del linfoma splenico della zona marginale

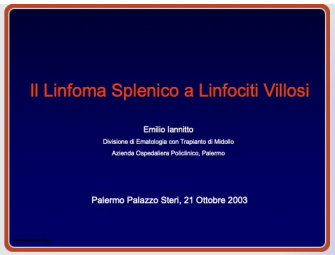
Luca Arcaini

DISCLOSURES

Consultant or advisory role	Roche, Janssen-Cilag, Verastem, Incyte, EUSA Pharma, Celgene/Bristol Myers Squibb, Kite/Gilead, ADC Therapeutics, Novartis
Speakers' Bureau	EUSA Pharma, Novartis, Kite, Beigene

Il caso del linfoma splenico

2003



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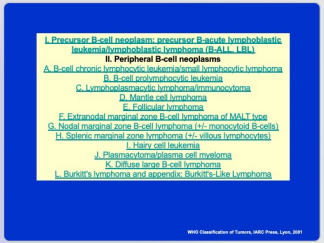

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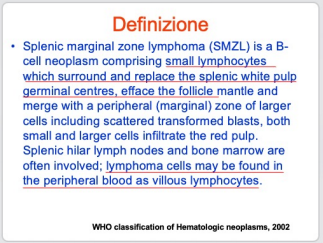

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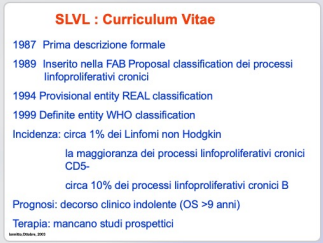

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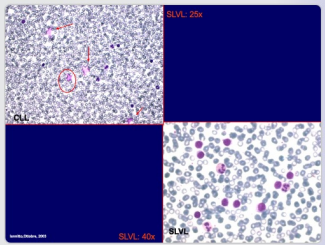

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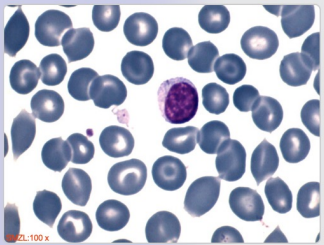

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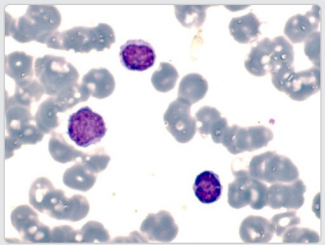

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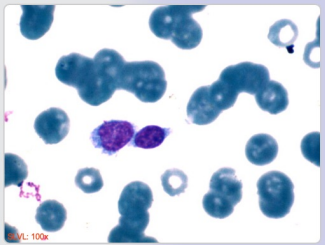

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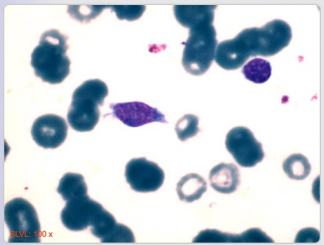

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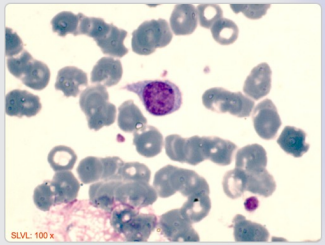
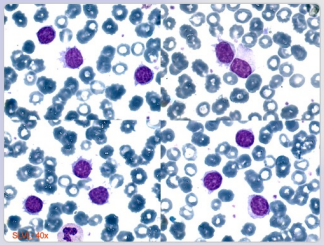
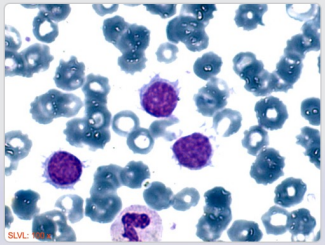
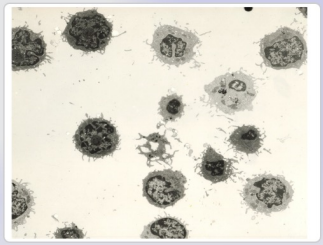
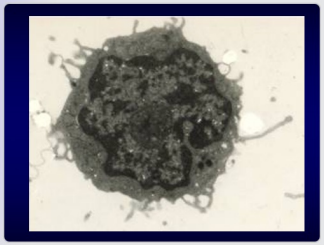










Il Linfoma Splenico a Linfociti Villosi

Emilio Iannitto
Divisione di Ematologia con Trapianto di Midollo
Azienda Ospedaliera Policlinico, Palermo

Palermo Palazzo Steri, 21 Ottobre 2003

1

I. Precursor B-cell neoplasm: precursor B-acute lymphoblastic leukemia/lymphoblastic lymphoma (B-ALL, LBL)

II. Peripheral B-cell neoplasms

A. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B. B-cell prolymphocytic leukemia
C. Lymphoplasmacytic lymphoma/immunocytoma
D. Mantle cell lymphoma
E. Follicular lymphoma
F. Extranodal marginal zone B-cell lymphoma of MALT type
G. Nodal marginal zone B-cell lymphoma (+/- monocytoid B-cells)
H. Splenic marginal zone lymphoma (+/- villous lymphocytes)
I. Hairy cell leukemia
J. Plasmacytoma/plasma cell myeloma
K. Diffuse large B-cell lymphoma
L. Burkitt's lymphoma and appendix: Burkitt's-Like Lymphoma

WHO Classification of Tumors, IARC Press, Lyon, 2001

2

Definizione

- Splenic marginal zone lymphoma (SMZL) is a B-cell neoplasm comprising small lymphocytes which surround and replace the splenic white pulp germinal centres, efface the follicle mantle and merge with a peripheral (marginal) zone of larger cells including scattered transformed blasts, both small and larger cells infiltrate the red pulp. Splenic hilar lymph nodes and bone marrow are often involved; lymphoma cells may be found in the peripheral blood as villous lymphocytes.

WHO classification of Hematologic neoplasms, 2002

SLVL : Curriculum Vitae

1987 Prima descrizione formale

1989 Inserito nella FAB Proposal classification dei processi linfoproliferativi cronici

1994 Provisional entity REAL classification

1999 Definite entity WHO classification

Incidenza: circa 1% dei Linfomi non Hodgkin

la maggioranza dei processi linfoproliferativi cronici CD5-

circa 10% dei processi linfoproliferativi cronici B

Prognosi: decorso clinico indolente (OS >9 anni)

Terapia: mancano studi prospettici

Diagnosis

They are not the same

At least 3 different marginal zone B-cell lymphoma entities

Revised WHO-4th	% of all lymphomas in SEER registries *
▪ Splenic MZL	**0.7%**
▪ Nodal MZL	**2.4%**
▪ Extranodal MZL of Mucosa-Associated Lymphoid-Tissue (MALT Lymphoma)	**5%**

* Olszewski and Castillo. Cancer 2013

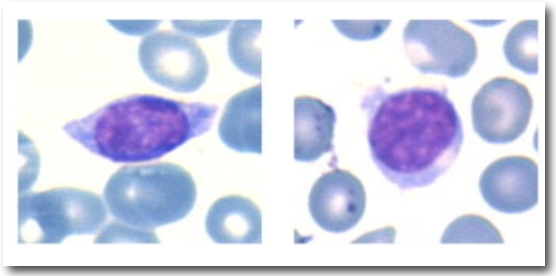
Pathological classification

WHO 4th ed		WHO 5th ed	ICC 2022	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (EMZL)	Extranodal site	**EMZL**	**EN-MZL**	
		Primary cutaneous MZL	**Primary cutaneous lymphoproliferative disorder**	
Nodal marginal zone lymphoma (NMZL)	Classic	**NMZL**	**NMZL**	Classic
	Paediatric NMZL	**Paediatric NMZL**		Paediatric NMZL
Splenic marginal zone lymphoma (SMZL)		**SMZL**	**SMZL**	
Splenic B-cell lymphoma/leukemia, unclassifiable	Splenic diffuse red pulp small B-cell lymphoma Hairy cell leukemia-variant	**Splenic diffuse red pulp small B-cell lymphoma** **Splenic B cell lymphoma/leukemia with prominent nucleoli** *(encompassing HCL-v and some cases of B-cell PLL)*	**Splenic B-cell lymphoma/leukemia, unclassifiable**	Splenic diffuse red pulp small B-cell lymphoma Hairy cell leukemia-variant

Swerdlow et al. Blood 2016 *Alaggio et al. Leukemia 2022* *Campo et al. Blood 2022*

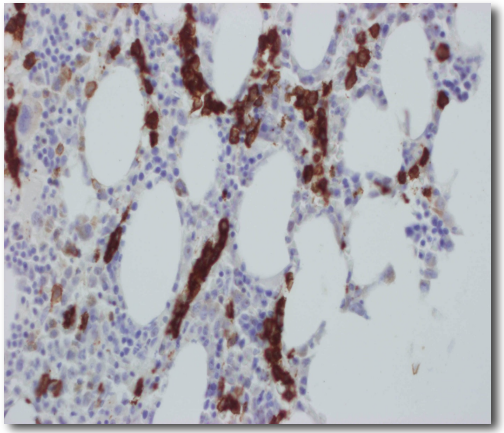
Is splenectomy necessary of SMZL diagnosis ?

- **Cytology**: villous lymphocytes



- **Flow cytometry**: IgM+/IgD+, SIg+ bright, CD79b+, CD20+, CD22+, FMC7+, CD103-, CD10-, CD23-/+ (30%), CD5-/+ (20%) – Matutes <3/5

- **Bone marrow histology**: intrasinusoidal infiltration showed by CD20 staining



Matutes et al. Leukemia 2008
Boveri et al. Ann Oncol 2016
Arcaini et al. Blood 2016

Minimal diagnostic criteria

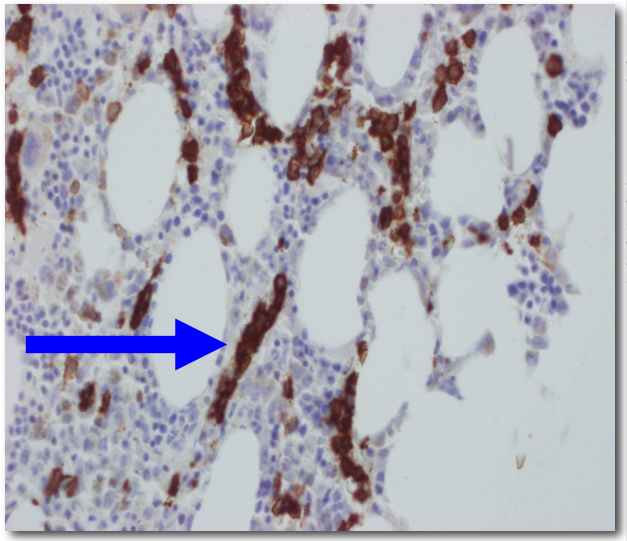
1- Splenic histology + CLL score ≤2

<u>in absence of spleen histology</u>

2- Typical morphology (PB and BM) + FC + CD20+ intrasinusal infiltrate

Matutes et al, Leukemia 2008

Bone marrow histology in SMZL



	SMZL
Positive BM biopsy	43 (90%)
FC positive	35
FC negative	5
Negative BM biopsy	5 (10%)
FC positive	2
FC negative	3
Median % of histological involvement (range)	40 (10–90)
Median % of FC involvement (range)	36 (7–81)
Histological patterns	
Nodular	38 (88%)
Intertrabecular only	12
Paratrabecular only	4
Inter- and paratrabecular	22
CD23+ dendritic cell meshwork[a]	18
Interstitial	1 (2%)
Massive	2 (5%)
Sinusoidal only	2 (5%)
Sinusoidal + other patterns	30 (70%)

Boveri et al, Annals of Oncology 2008

Transformed SMZL: an unmet clinical and biological need

Histological trasformation (HT) in MZLs is invariably associated with increased mortality and reduced survival (both OS and RS), irrespective of MZL subtype[1-3]

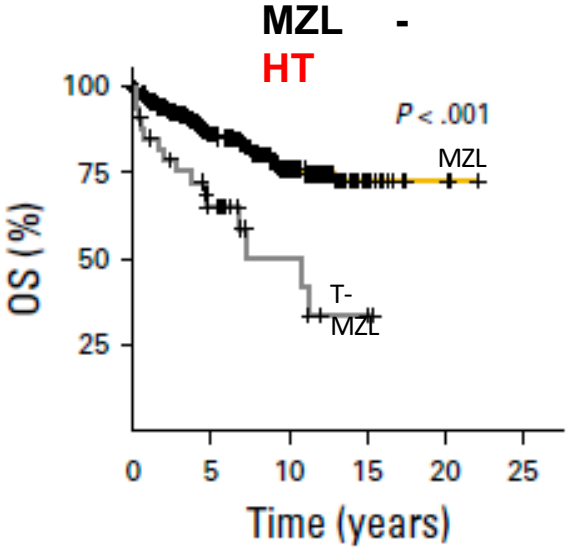


Fig. A - HT vs non-HT showed a significantly shorter OS: 5-year rate, 65% v 86%. ($p < 0.01$).

1. Alderuccio JP et al. JCO 2018

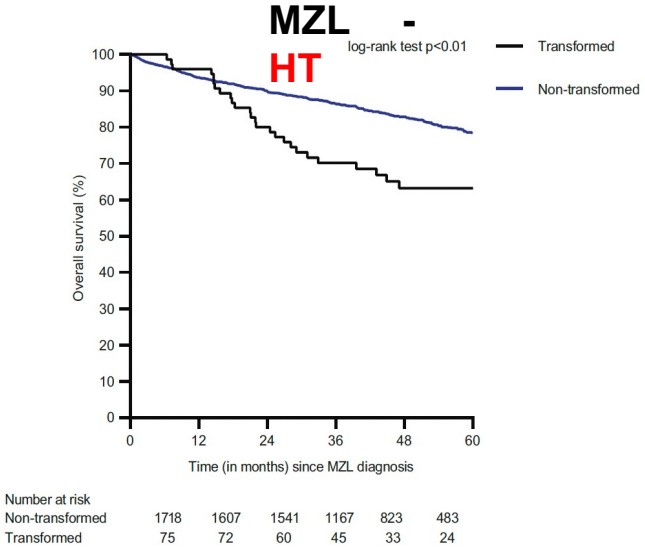


Fig. B - Estimated five-year OS: 63% and 78% for pts with or without tMZL ($p < 0.01$).

2. Bult J et al. Blood Cancer Journal 2023

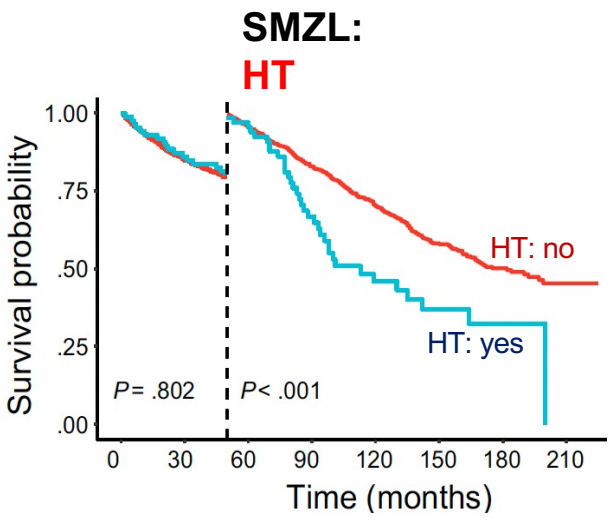


Fig. C - Estimated 10-year OS: 36.8% and 55.3% for pts with or without tSMZL ($p < 0.01$).

3. Du Y et al. Int J Can 2024

Transformed SMZL: incidence

Incidence of HT in MZL is variable among different series: 5 yr cumulative incidence: 2.5% to 15% and 10 yrs: 4.7% to 18%. Among MZLs, higher incidence was observed in patients with SMZL compared to patients with extranodal MZL and nodal MZL[2-3]

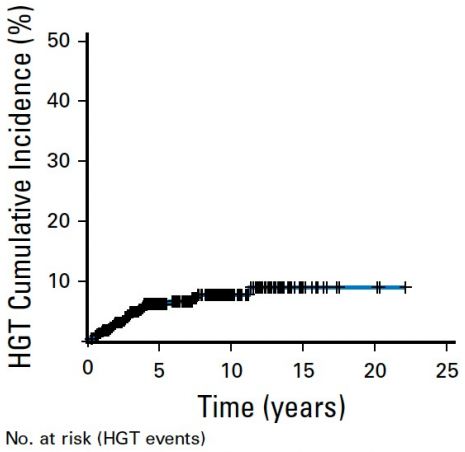


Fig. A - Kaplan-Meier curve for cumulative incidence of HT in 446 MZL patients (all subtypes).

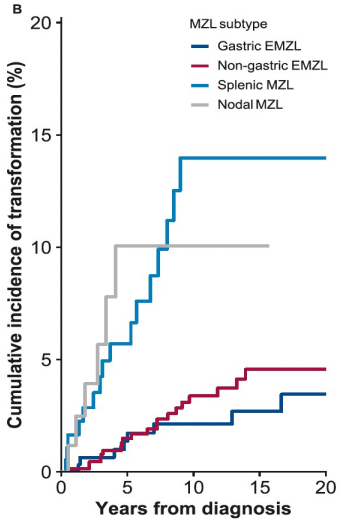


Fig. B - Cumulative incidence of transformation stratified by marginal zone lymphoma subtype.

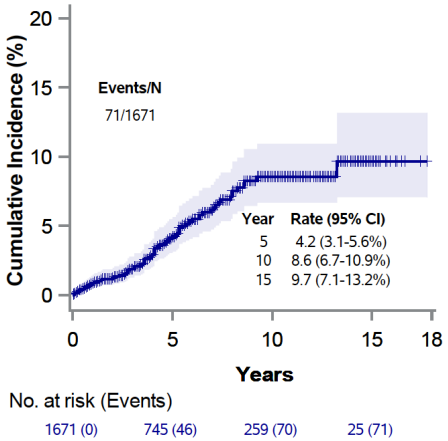


Fig. C - Cumulative incidence of diffuse large B-cell lymphoma (DLBCL) transformation in a **SMZL population.**

1. Alderuccio JP et al. JCO 2018

2. Kalashnikov et al. Blood Cancer Journal 2023

3. Du Y et al. Int J Can 2024

4. Florindez JA et al. Cancer 2020

Transformed SMZL: genomic landscape, what do we know so far?

tSMZL *vs* SMZL: higher genomic complexity, genomic evolution, hotspot mutations and CNAs

SMZL tissue at dx (n=27) + tSMZL tissue (n=32) → IGHV analysis rearrangement, Copy Number Alterations (CNV), Single Nucleotide Variants (SNV), Whole Genome Sequencing)

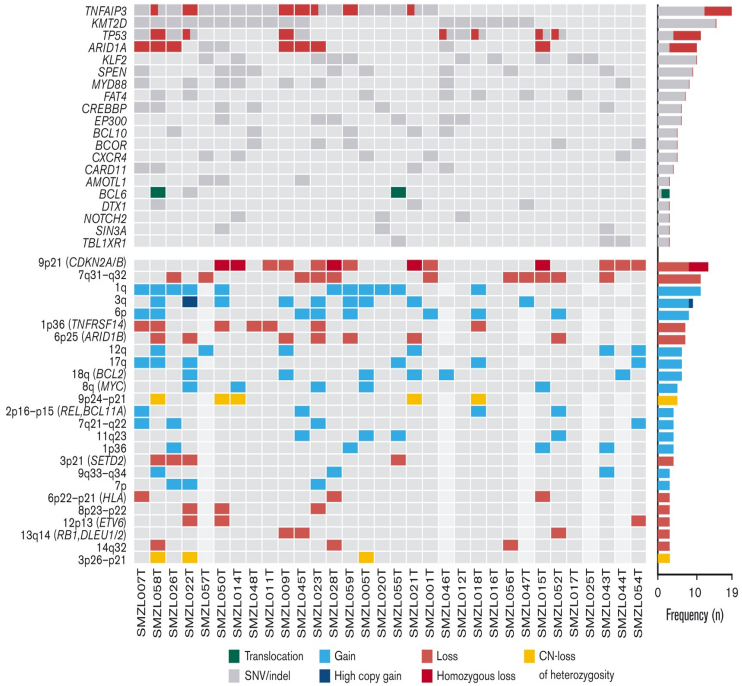
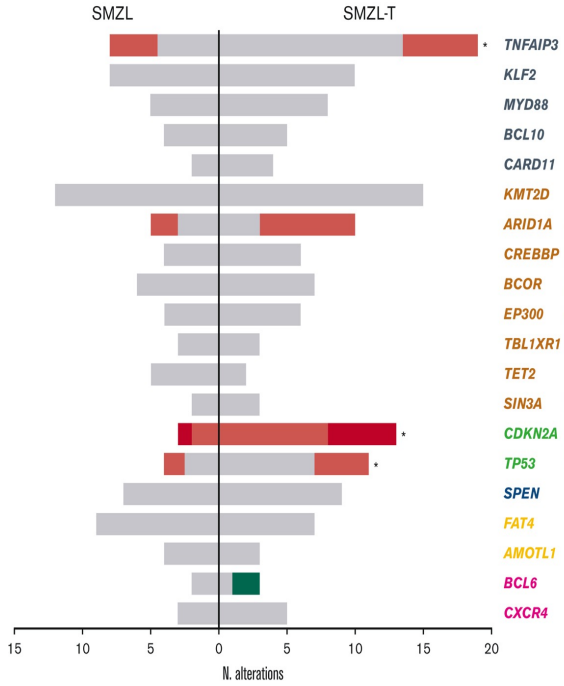
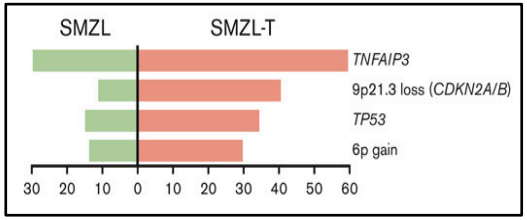


Fig. A Oncoprint displaying the recurrent alterations (n ≥ 3) found inSMZL-T cases.



Deregulation of the cell cycle (CDKN2A/B, TP53, and TNFRSF14), DNA damage response (TP53, and ARID1A), and the NF-κB pathway (TNFAIP3)

Compared to indolent SMZL, transformation was associated with higher genomic complexity, *TNFAIP3* and *TP53* alterations, 9p21 (*CDKN2A/2B*) losses and 6p gain



Grau M et al. Blood Adv 2023

IELGS54 study

tSMZL: an unmet clinical need

Histological transformation in SMZL is invariably associated with **poor prognosis**

Little is known about tSMZL **underlying genomic abnormalities**, **pathway signatures**, and **microenvironment compositions**

The identification **SMZL molecular clusters** and immune-microenvironments classes in **IELSG46 study** demonstrated how genetic clusters are correlated with **different outcomes and clinical characteristics**

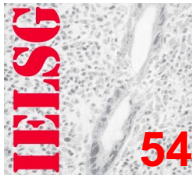
At the present, **no recommended or approved treatments** are intended **specifically** to tSMZL

Few studies have been dedicated **solely to tSMZL**

IELSG54 study

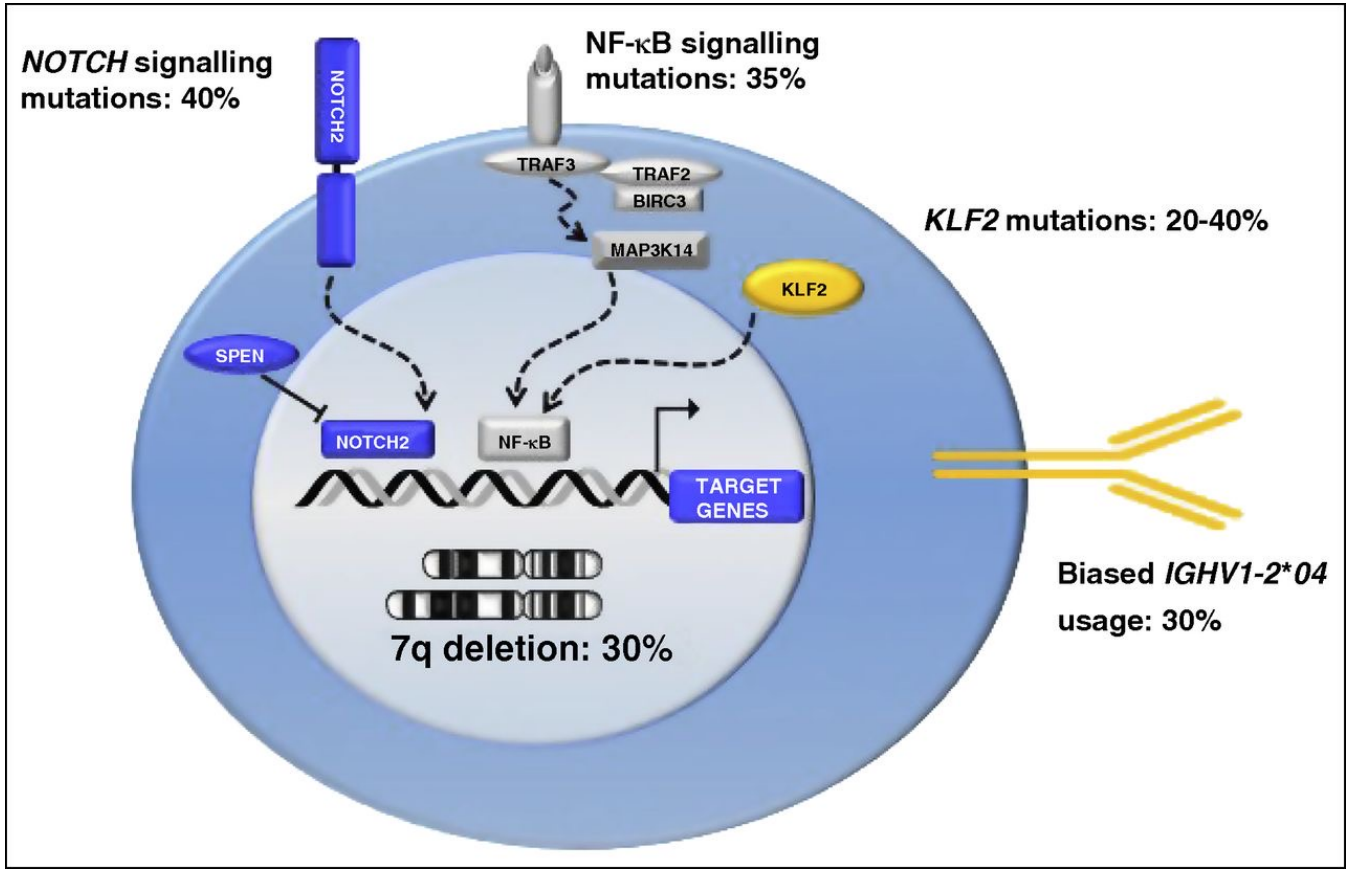
A retrospective, observational study whose principal aim is to describe the molecular and clinical profiling of tSMZL cases, and how these features contribute to the pathogenesis, affect outcome or may impact selection of therapies

UNIVERSITÀ DI PAVIA



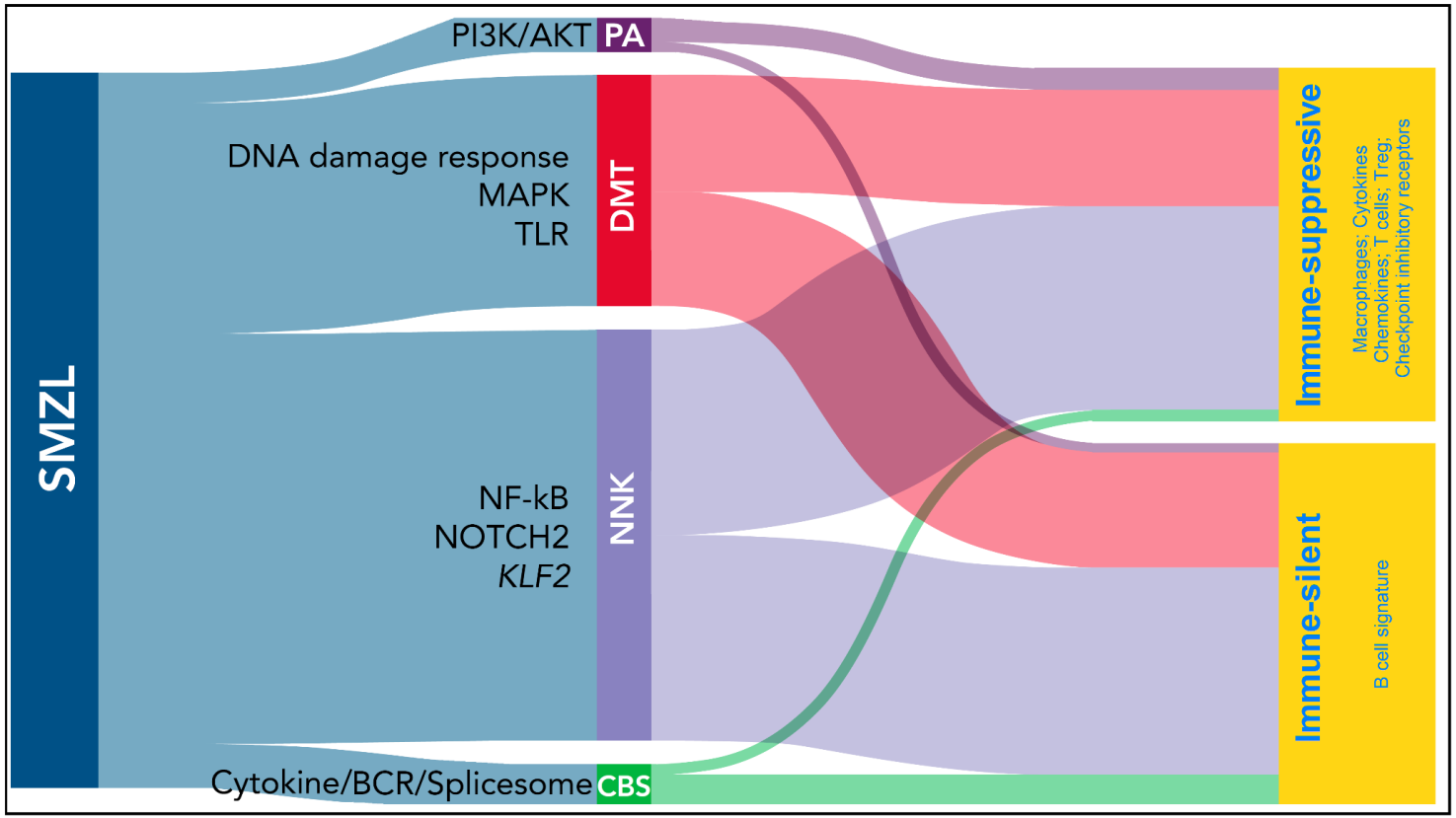
Pathogenesis

Key molecular alterations in SMZL



Arcaini et al. Blood 2016

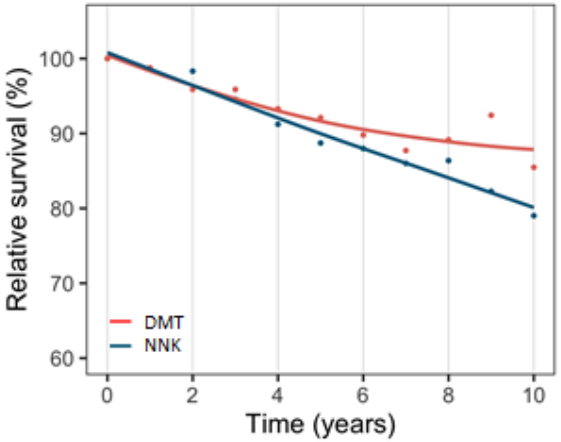
A new taxonomy for SMZL

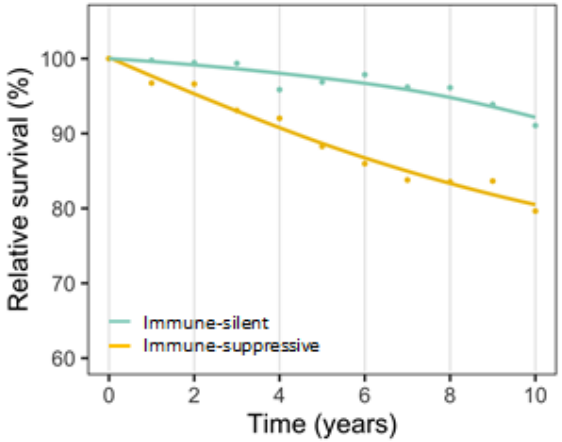


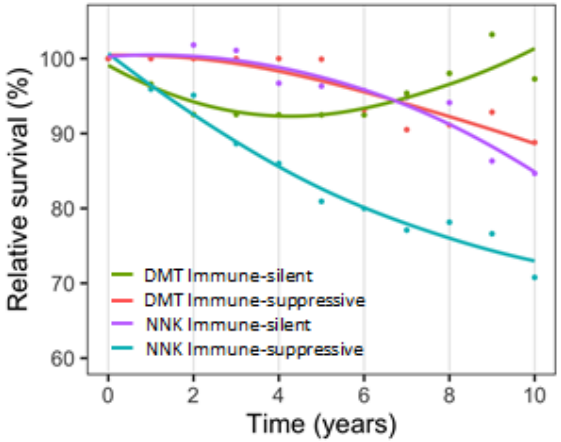
Deaglio & Vaisitti, Blood 2022: Comment on Bonfiglio et al. Blood 2022

A new SMZL taxonomy

integrating molecular and clinical profiling





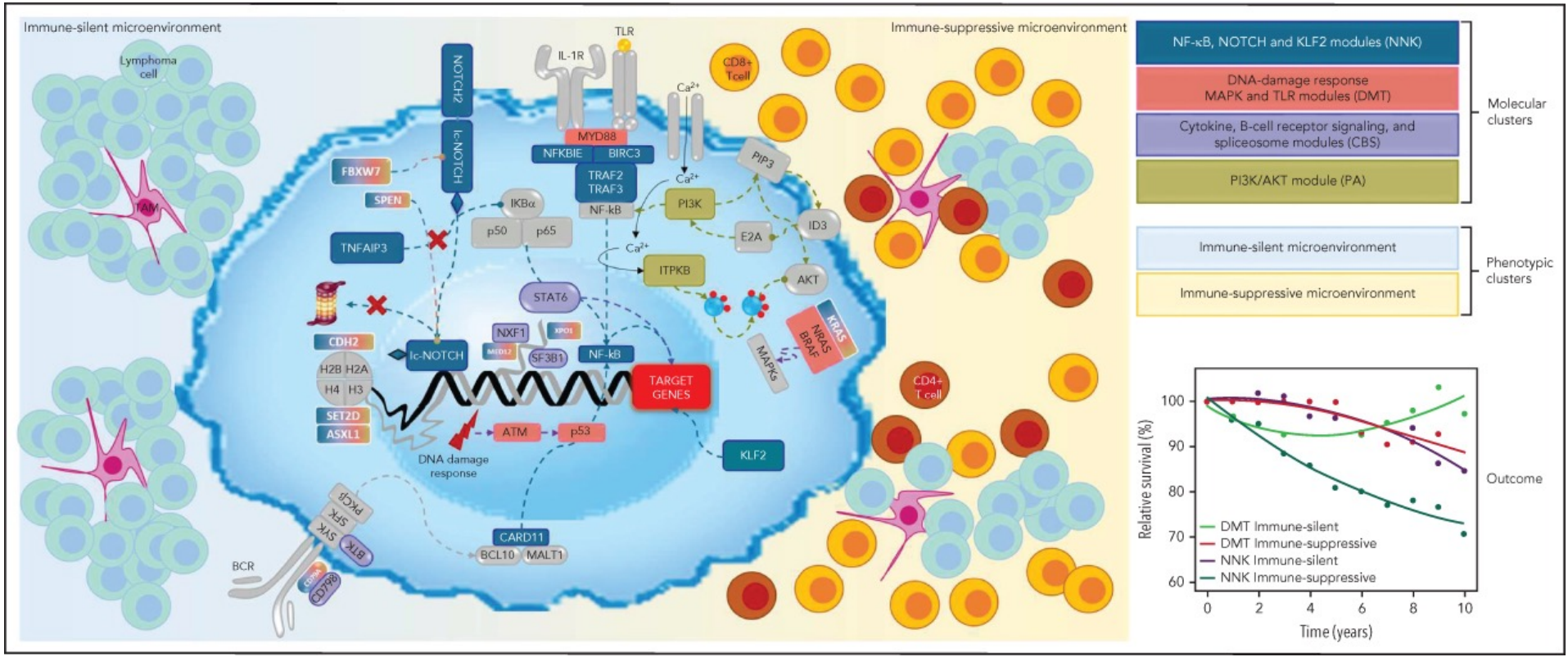


2 main genetic clusters: - **NNK** (~60%, mutations of NF-κB, NOTCH and KLF2)
- **DMT** (~30%, mutations affecting DNA damage response, MAPK and TLR)

2 microenvironment classes: - immune-suppressive (50%)
- immune-silent (50%)

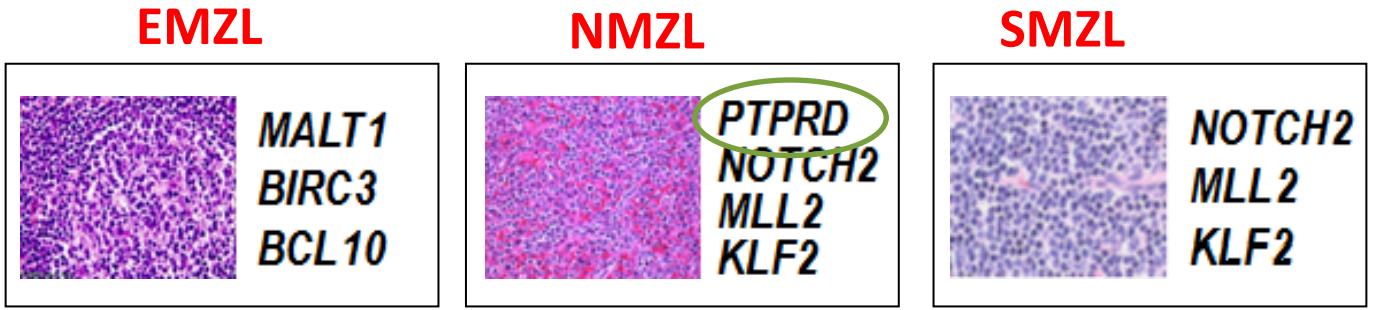
Bonfiglio et al. Blood 2022

Molecular and phenotypic clusters



Bonfiglio et al. Blood 2022

Are SMZL and NMZL different entities?



- The genetic signatures of NMZL and SMZL largely overlap
- NMZL lack 7q deletions (commonly found in SMZL)
- NMZL are enriched with MLL2 mutations (NMZL 34% *vs* SMZL 8%, P<.001)
- PTPRD mutations appear to be enriched in NMZL (being absent in SMZL and EMZL, and rare in other mature B-cell tumors)

Spina & Rossi. Best Pract Res Clin Haematol. 2017

Differential diagnosis

HCL: *lymphocytes with oval eccentric nuclei and reticular chromatin showing abundant pale cytoplasm with fine, evenly distributed projections.*

SMZL: *medium sized lymphocytes with round nuclei, dispersed chromatin and abundant pale cytoplasm showing thick polar villi.*

MCL: *medium sized lymphocytes with indented nuclei, condensed chromatin and indistinct nucleoli (left); larger blastoid cells with reticular chromatin and one or two nucleoli (right).*

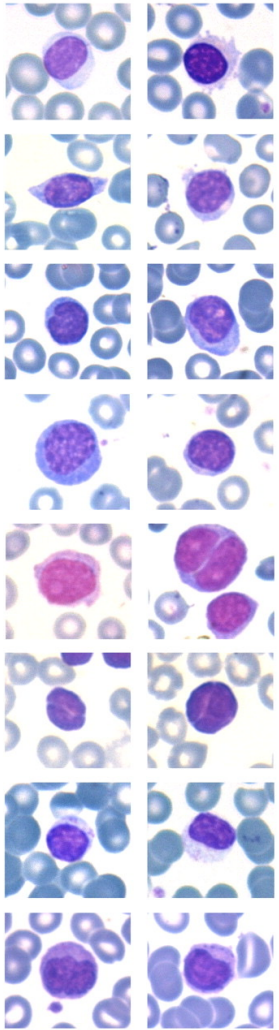
LPL: *large plasmacytoid lymphocytes with round nuclei, finely dispersed chromatin and rich basophilic cytoplasm (left); small round lymphocytes with denser chromatin and scanty cytoplasm (right).*

B-PLL: *medium to large cells with moderately condensed nuclear chromatin and prominent vescicular nucleoli, regular nuclear outline and weakly basophilic cytoplasm.*

FL: *small atypical lymphocytes with condensed chromatin, markedly irregular nuclear contours and deep nuclear grooves ("buttock cells").*

T-LGL: *medium sized cells with round nuclei and condensed or "ropey" chromatin, and ample cytoplasm with variable numbers of azurophilic granules.*

HSTL: *medium sized-to-large atypical lymphocytes with irregular nuclear contour, prominent nucleoli, and abundant cytoplasm that may contain scattered granules (right)*



Peripheral blood morphology

Iannitto & Tripodo, Blood 2011

Flow cytometry

	SMZL	CLL	MCL	HCL	HCL-v
sIg	Strong	Weak	Strong	Strong	Strong
CD5	+	+++	+++	−	−
CD23	+	+++	−	−	−
FMC7	+++	+	+++	+++	+++
CD11c	++	−	−	+++	+++
CD103	−	−	−	+++	++
CD123	−	−	−	+++	−
CD25	+	−	−	+++	−
CD27	++	+++	+++	−	++
CD200	−	+++	−	+++	−

SMZL: IgM+/IgD+, SIg +, CD20+, CD22+,CD24+, CD27+, FMC7+, CD79b+, CD103-, CD123-, CD10-, DBA44 + (75%), CD11c + (50%), CD23+ (30%), CD5 + (20%)

Arcaini et al. Blood 2016

Immunohistochemistry

	SMZL	LPL	SDRPL	HCL-v	HCL	EMZL/ NMZL	CLL	MCL	FL
CD20	+	+	+	+	+	+	−/+	+	+
CD79a	+	+	+	+	+	+	+	+	+
CD5	−/+	−/+	−/+	–	–	−/+	+	+	–
CD21	−/+	–	–	–	–	–	–	–	–
CD23	−/+	−/+	–	–	–	−/+	+	–	−/+
BCL1	–	–	–	−/+	+	–	–	+	–
DBA44	+/−	–	+	+	+	–	−/+	–	–
Annexin A1	–	–	–	–	+	–	–	–	–
CD103	–	–	–	+/−	+	–	–	–	–
CD123	–	–	–	–	+	–	–	–	–
IRTA1	–	–	–	–	–	+/−	–	–	–
IgM	+	+	+	+	+	+	+	+	+
IgD	+/−	–	−/+	+	+	−/+	+	+	+
CD10	–	–*	–	–	–	–	–	–*	+/−
BCL6	–	–	–	–	–	−/+	–	−/+	+
CD43	−/+	–	–	–	–	−/+	+	+	–
SOX11	–	–	–	–	–	–	–	+	–
LEF1	–	–	–	–	–	–	+	−/+	–

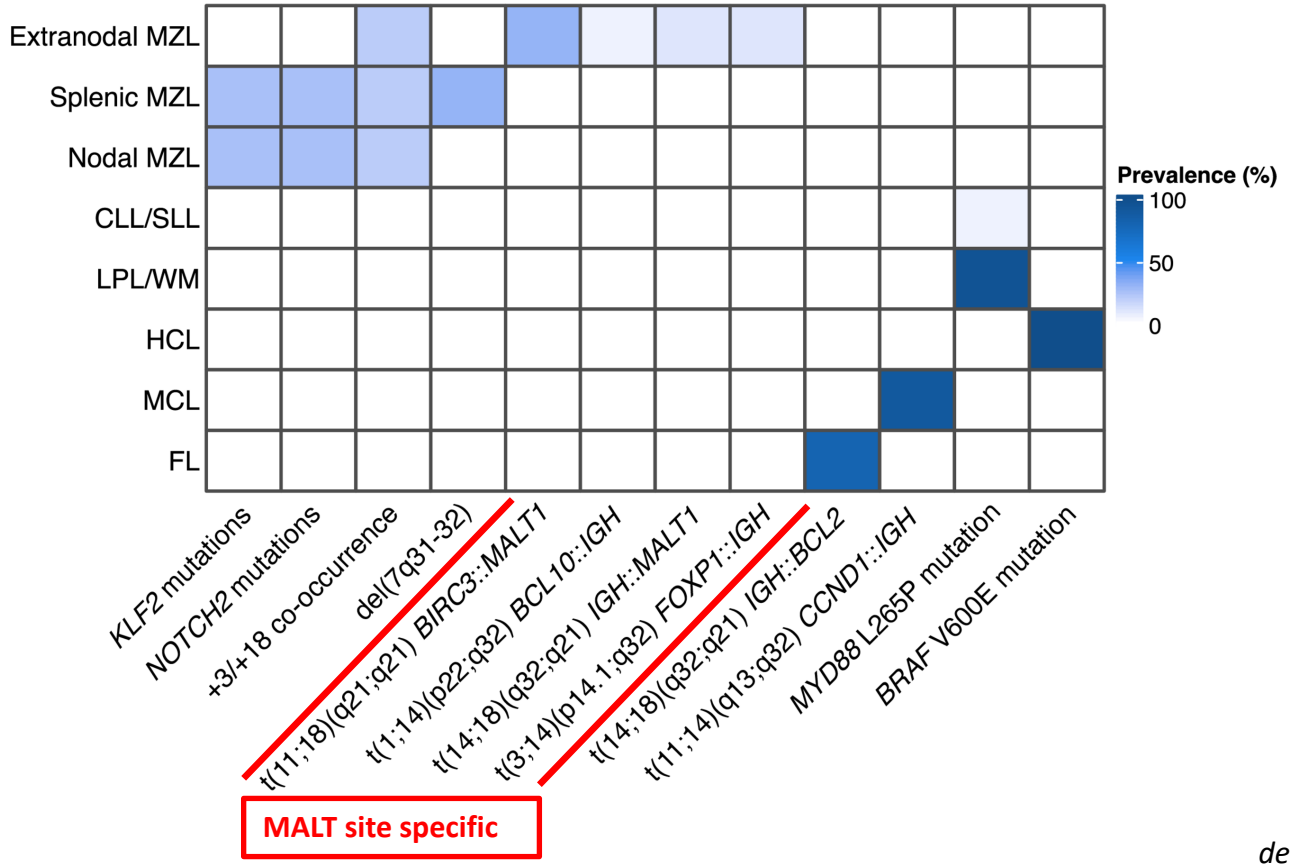
–, <25% of cases; –/+, 25%-50% of cases; +/–, 50%-75% of cases; +, >75% of cases.

FL, follicular lymphoma; NMZL, nodal marginal zone lymphoma; SDRPL, splenic diffuse red pulp lymphoma.

*Sporadic cases reported.

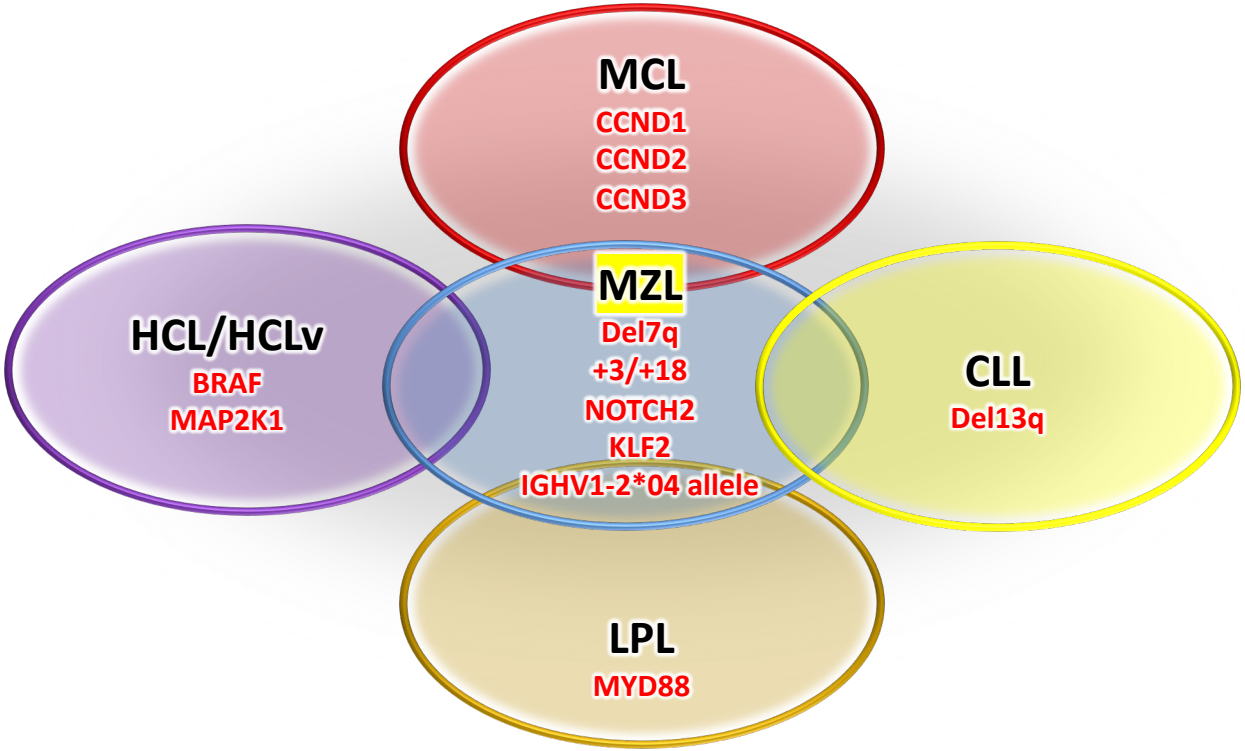
Arcaini et al. Blood 2016

Genomic profiling for differential diagnosis



de Leval et al. Blood 2022

MZL and mimicking diseases



Courtesy of Davide Rossi (modified)

Splenic B-cell lymphomas:
HCL, SDRPL, Splenic B-cell lymphoma/leukemia with prominent nucleoli (SBLPN, former HCLv)

WHO 5th ed.: **SBLPN** comprises B-PLL + HCLv + unrecognized leukemic MCL and progressed CLL

ICC: B-PLL distinct entity, HCL-v provisional entity

HISTOLOGY

- **SMZL** expansion of white pulp nodules
- **SDRPL** diffuse infiltration of the red pulp
- **HCL** diffuse splenic involvement often accompanied by reticulin fibrosis
- **SBLPN** diffuse splenic infiltration with medium- to large-sized cells and prominent nucleoli

Splenic B-cell lymphomas

BOM

SMZL nodular infiltration, often accompanied by a mixed interstitial/intrasinusoidal pattern
SDRPL predominantly intrasinusoidal pattern
HCL diffuse infiltration of HCL
SBLPN nonnodular infiltration observed in SBLPN

FC

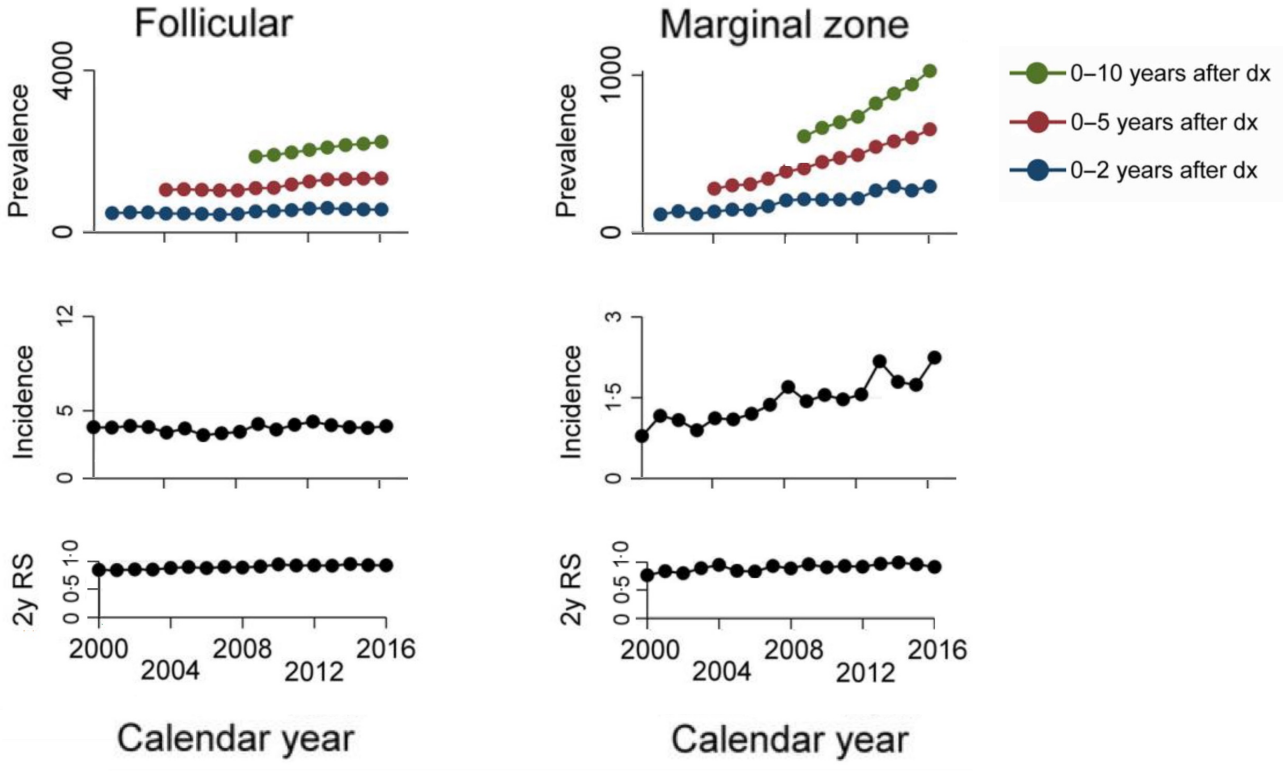
SMZL CD11c+, CD72/DBA44 variably but CD25-, CD103-, CD123-, and CD200-
SBLPN/HCLv CD25-, CD123-, CD11c+, CD103+
SDRPL lacks CD11c expression and is CD180+ (CD200:CD180 mean fluorescence intensity ratio of <0.5)

Biology

SBLPN MAP2K1 mut in 40% but are rare in SMZL and SDRPL and absent in HCL
SDRPL CCND3 and BCOR mutations occur in ~ 25% and are infrequent in SMZL and HCL

Epidemiology

Prevalence, incidence and relative survival of FL and MZL during the 21st century in Sweden



Eckberg et al. BJC 2020

Relative frequencies of MZL subtypes

Cohort	Country	Year of diagnosis	EMZL	SMZL	NMZL	*Reference*
ILSG Project	International	1988-1990	74%	8%	18%	*NHL Classification Proiect, Blood 1997*
SEER Registries	USA	2001-2005	62%	9%	29%	*Khalil, Br J Haem 2014*
SEER Registries	USA	2006-2009	57%	9%	34%	*Khalil, Br J Haem 2014*
NF10 Study	Italy	2010-2018	47%	40%	12%	*Luminari, Blood 2019*
RELINF Registry	Spain	2014-2018	44%	30%	26%	*Bastos-Oreiro, Ann Hematol 2020*
SEER Registries	USA	2001-2017*	61%	9%	30%	*Cerhan, Ann Lymphoma 2021*

*
- MZL age-standardized incidence rate, 1.96 per 100,000 person-years (7% of NHL)
- Incidence Increased +1% per year (+ 1.1% EMZL, +1.4% SMZL, and +0.5% NMZL)

Clinical presentation

Clinical presentation

EMZL

- Site-specific symptoms

NMZL

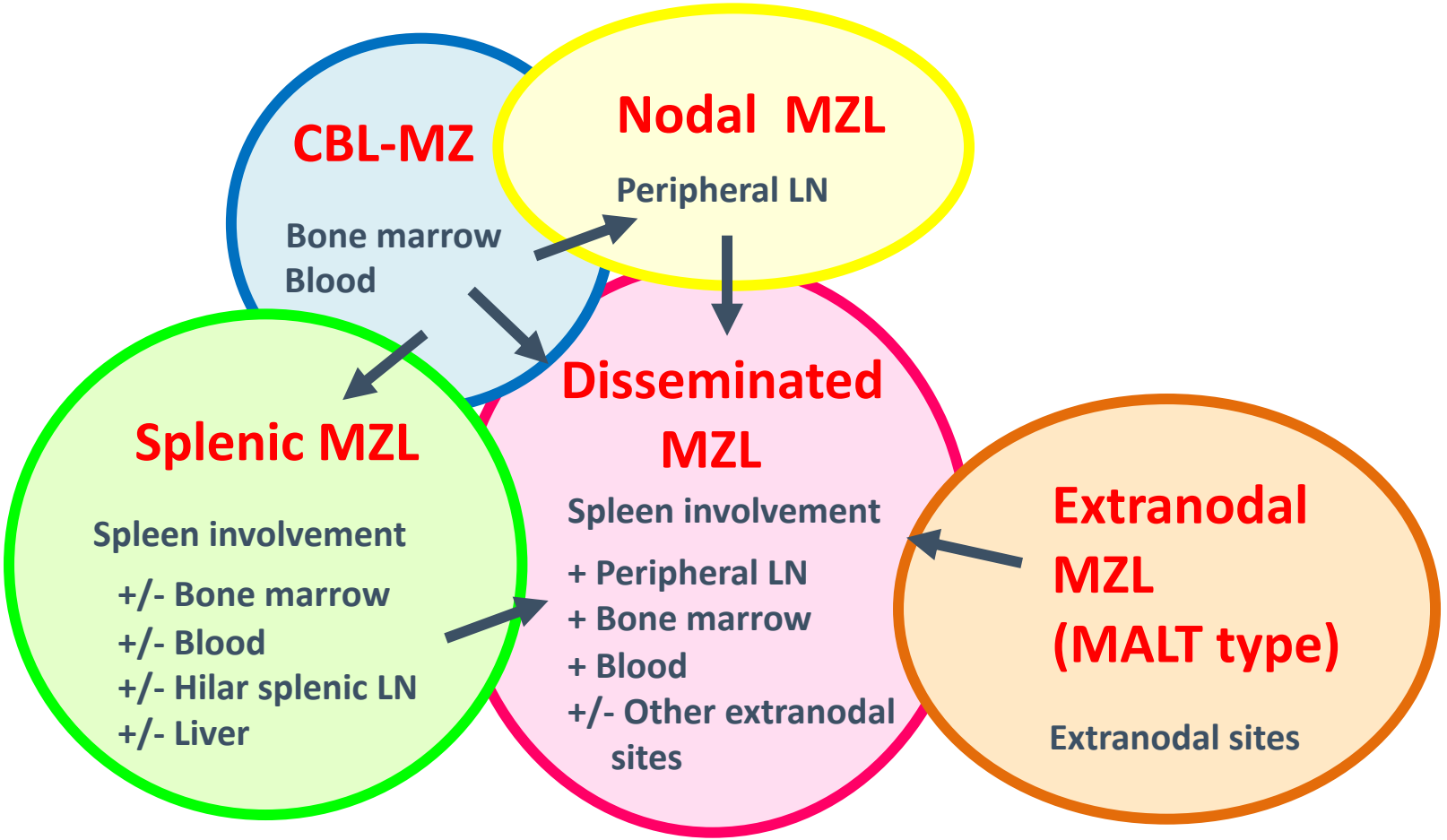
- Required ***exclusion*** of SMZL and MALT MZL
- Median age 50-64 yrs, usually no B symptoms, good PS
- Disseminated LN (50% stage III-IV), non-bulky in 2/3, BM+ 30%, 10% IgM+

SMZL

- Median age 67 years, usually no B symptoms, good PS
- Splenomegaly, leukemic picture
- Cytopenias to hypersplenism and BM infiltration
- Splenic hilar LNs in 25%
- AIHA, ITP and AID

Arcaini et al. Blood 2016
Thieblemont et al. Blood 2016
Rossi et al. NEJM 2022

MZL for clinicians: a continuum of related entities



Treatment

SMZL

- Symptomatic splenomegaly
- Anemia
- Thrombocytopenia
- Immune disorders
- Nodal disease ?
- Elevated LDH ?
- B symptoms ?

NMZL

- GELF criteria ?

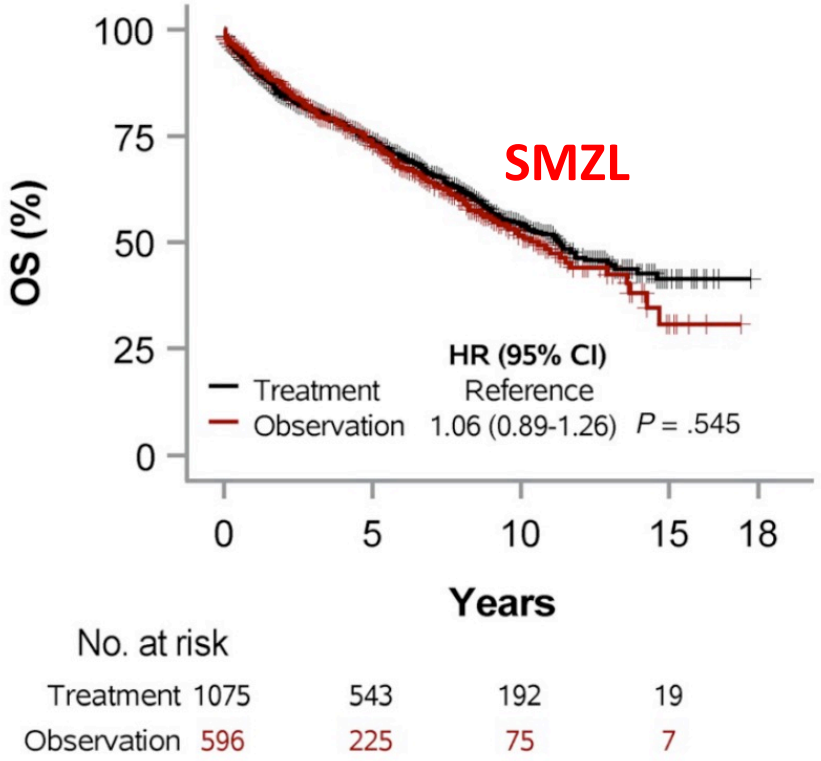
EMZL

- **Symptomatic disease (lymphoma-related symptoms):**
  - ❑ Disseminated, high tumor burden or bulky disease
  - ❑ Organ function damage
  - ❑ Contraindication or failure of local or anti-infective therapy
  - ❑ Rapidly progressive disease
- Patients with advanced stage asymptomatic disease should be actively observed (WW)

Zucca et al. Ann Oncol 2020

Zelenetz et al. J NCCN 2021

Active surveillance



Florindez et al. Cancer 2020

Splenic and Nodal Marginal Zone Lymphomas Are Indolent Disorders at High Hepatitis C Virus Seroprevalence with Distinct Presenting Features but Similar Morphologic and Phenotypic Profiles

Arcaini et al Cancer 2004

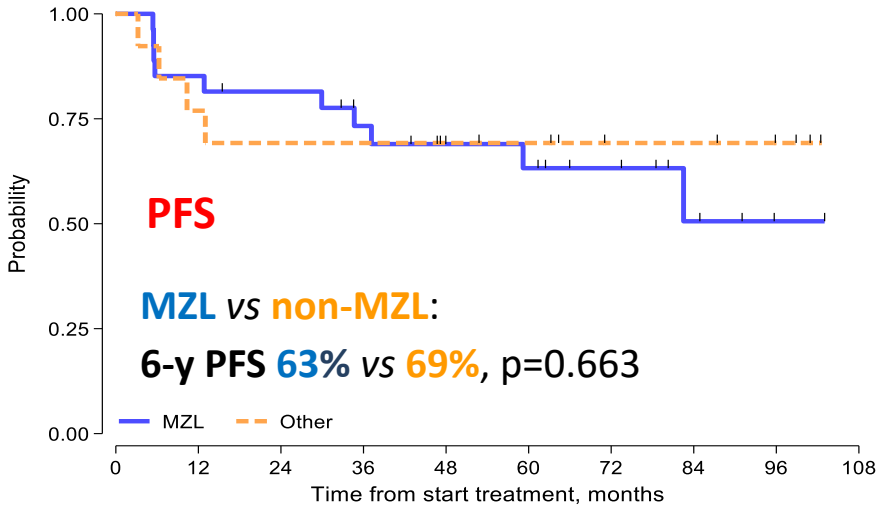
Brief report

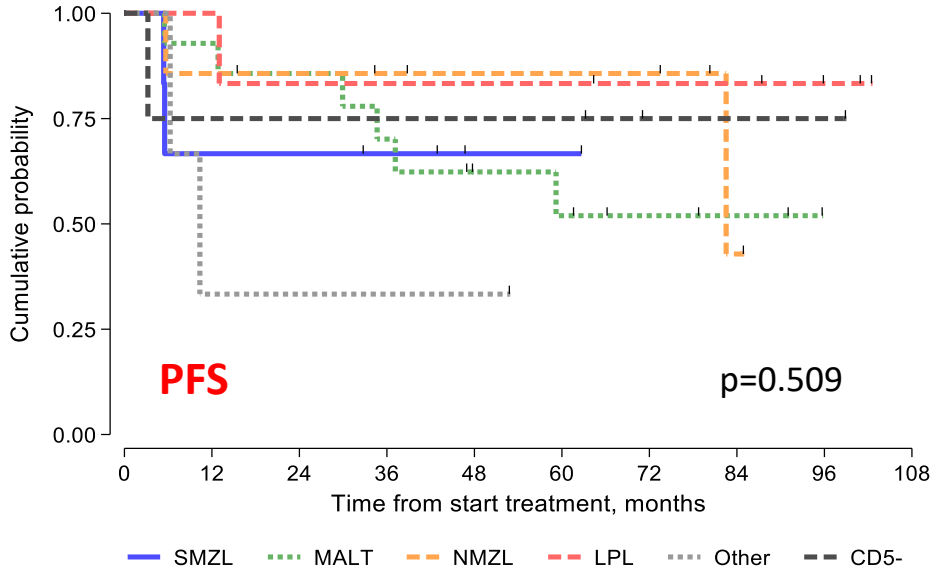
Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity?

Saadoun et al Blood 2004

BArT study: PFS by histotype

Median follow-up: 75 months *(95% CI: 63-87)*





Univariate analysis for PFS

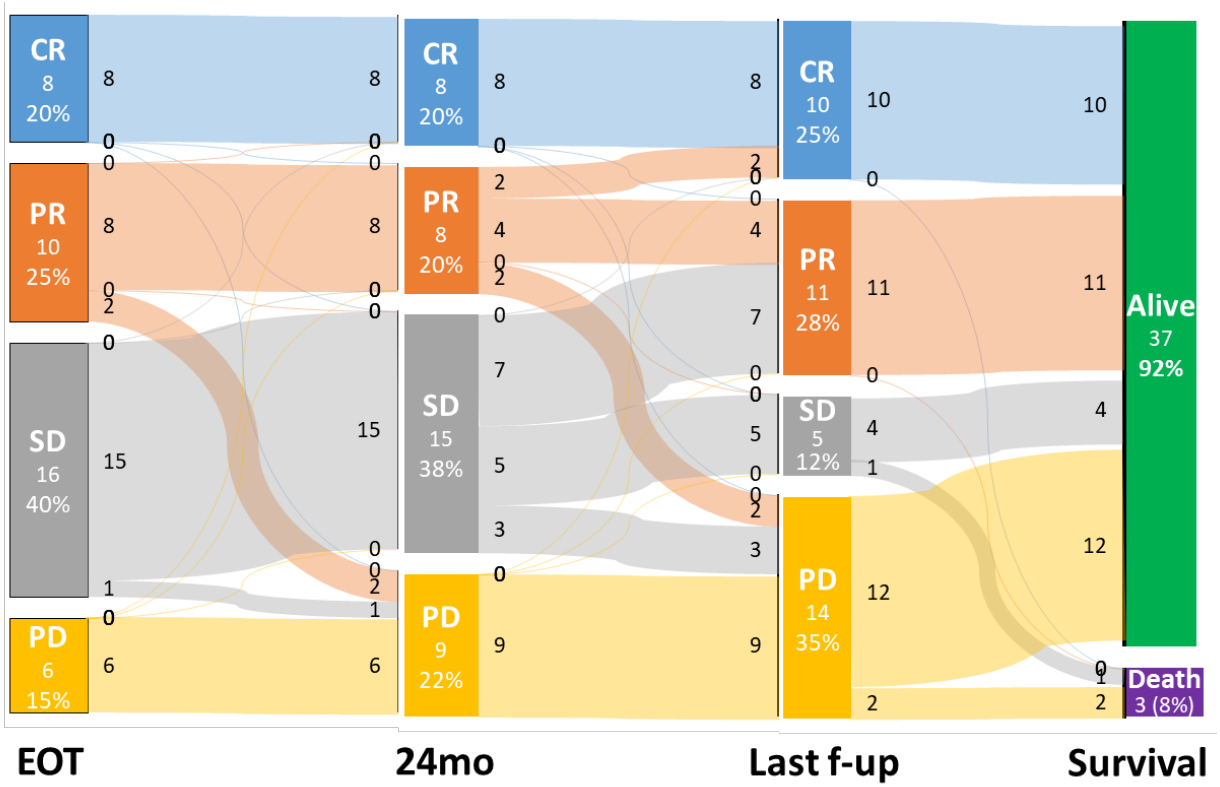
- (Log)WBC: HR 4.48 *(95%CI 1.41-14.2),* p=0.011
- Sex Male: HR 3.14 *(95%CI 1.05-9.40),* p=0.041

6y PFS:

- **SMZL:** 67%
- **MALT:** 52%
- **NMZL:** 86%
- **LPL:** 83%
- **Other (SLL + FL):** 33%
- **CD5-:** 75%

Merli et al. NEJM 2026

Improvement of responses and best responses

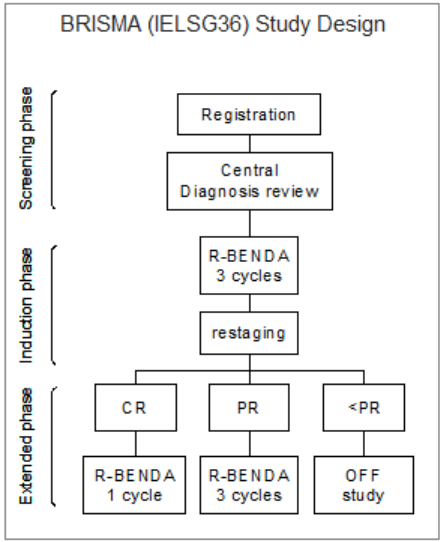


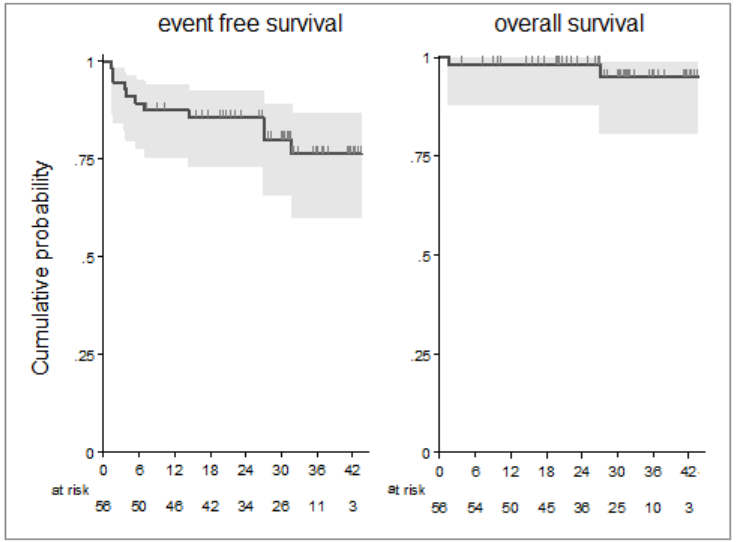
- 2/10 pts in PR at EOT (*2 MALT*) converted to CR during FU:
  →**best CR 25%** *(95% CI: 13-41)*
- 7/16 pts in SD at EOT (*3 SMZL, 2 NMZL, 1 MALT, 1 CD5-NOS*) converted to PR during FU:
  →**best ORR 63%** *(95% CI: 46-77)*

Histotype	N	Best ORR	Best CR
SMZL	6	50%	0%
MALT	14	79%	43%
NMZL	7	71%	43%
LPL	6	17%	0%
CD5- NOS	4	75%	25%
FL + SLL	3	66%	0%

Merli et al. NEJM 2026

IELSG36 (BRISMA) Phase II trial of Bendamustine and Rituximab as 1st line therapy for SMZL





N evaluable, 56

35% high risk HPLL

ORR, 91%
CR, 73%

SAE: 25%
G≥3 toxicity, 68%
(mainly haematological;
severe neutropenia, 43%)

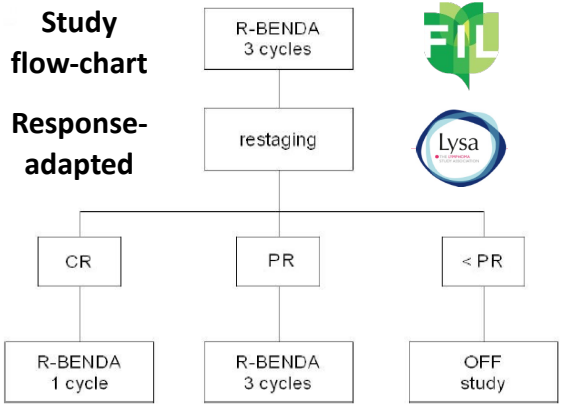
Iannitto et al. Br J Haematol 2018

BR as first-line therapy in SMZL: long-term f-up of BRISMA study

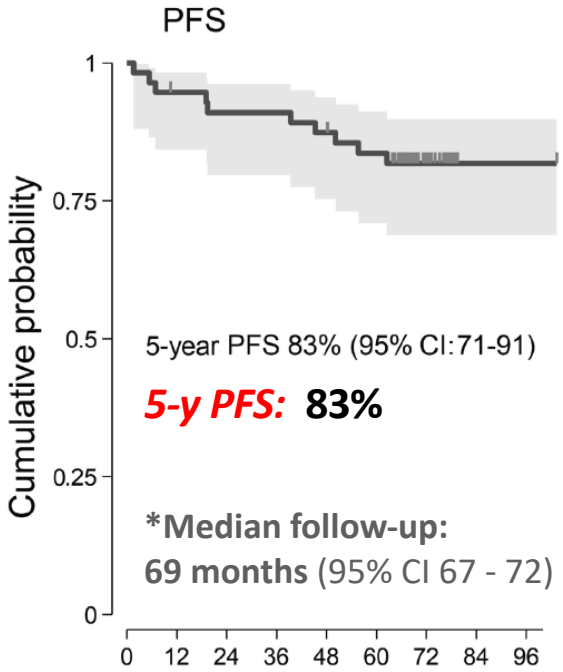
- **56 pts, SMZL**, symptomatic, diagnosis prospectively confirmed

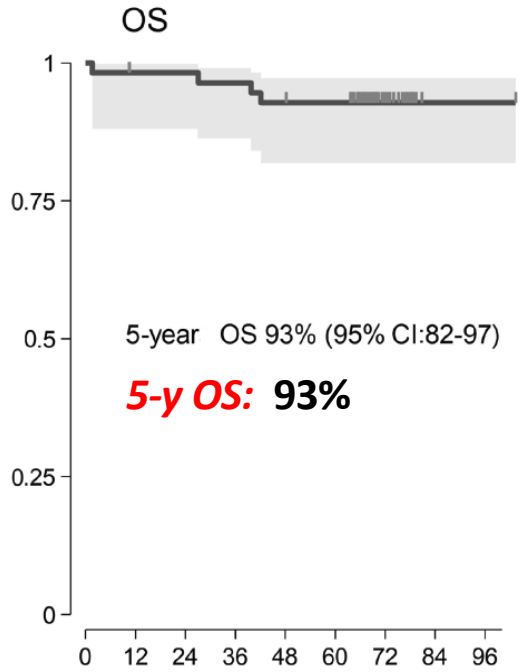
Study flow-chart

Response-adapted



- **ORR 91%, CR 73%**
- Grade ≥3 toxicity 68%
  - Grade ≥3 neutropenia 43%
  - Grade ≥3 infections 5.4% (FN 3.6%)
- 5y CI of SPM: 11%



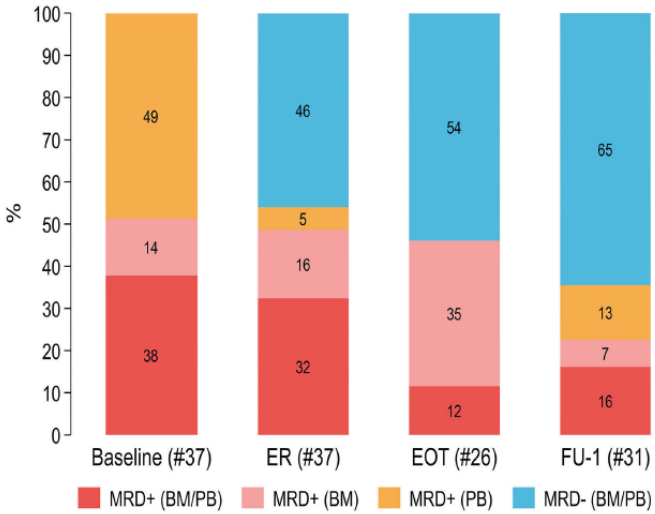


Iannitto E et al, Haematologica 2024

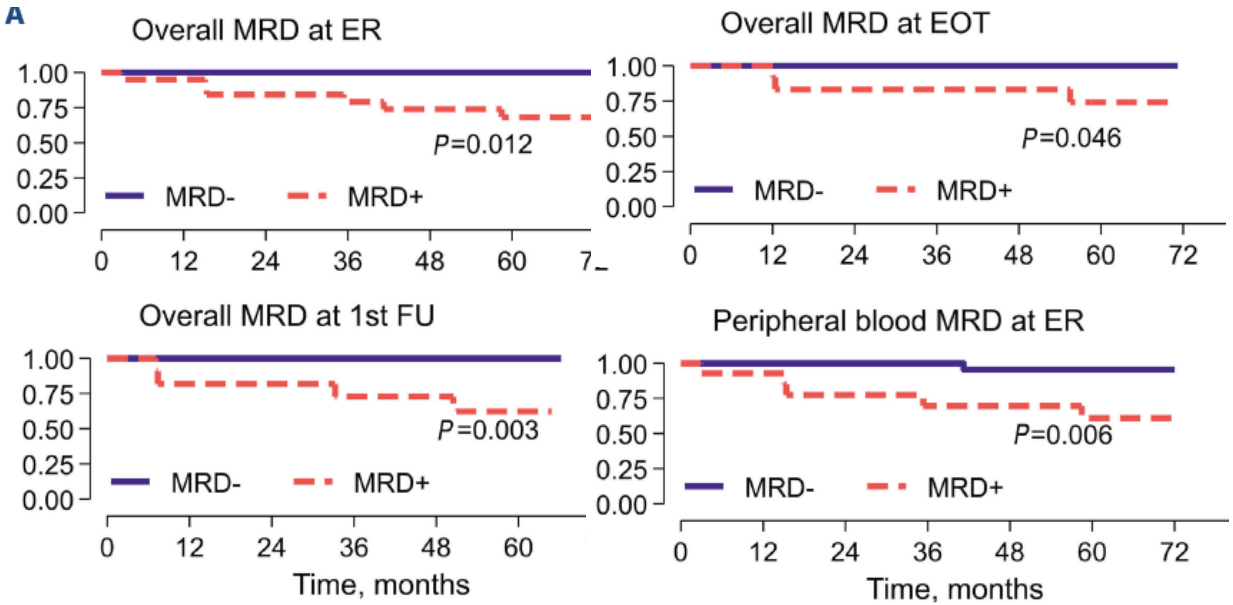
BRISMA: first MRD evaluation in SMZL

- **42/53 pts (79%): MRD marker (IgH)** with **ddPCR** → **good feasibility**

undetectable MRD	
Interim	46%
EOT	54%
1 year	65%



- **MRD status predict PFS at any timepoint**



***Median follow-up: 69 months** (95% CI 67-72)

Iannitto E et al, Haematologica 2024

Splenectomy in SMZL

- Traditionally first-line tp, restoration of cytopenias and fast resolution of spleen-related symptoms
- **5y PFS 50-60%, 5y OS 70-80%**
  - ***Pros***: definitive histological diagnosis; no further therapy in 50% of cases
  - ***Cons***: acute or late tox; not curative; DVT, bleeding, infections (5% overall toxic deaths)
- **Population-based studies**: improved outcome in Swedish study, no difference in SEER US study

Reference	N pts	ORR %	PFS % (y)	OS % (y)	Toxic deaths
Lenglet et al.	80	97	61 (5)	84 (5)	4
Xing et al.	42	NA	39 (10)	61 (10)	0
Pata et al.	43	90	35 (5)	75 (5)	NA
Kalpadakis et al.	27	85	58 (5)	77 (5)	1
Sima et al.	97	89	62	82	NA

Sima et al. BJH 2021
Florindez et al. Cancer 2020
Lenglet et al. Leuk & Lymph 2014
Xing et al. BJH2015
Pata et al. Leuk & Lymph 2016
Kalpadakis et al. Oncologist 2013

Surgical outcomes and postoperative complications after open splenectomy

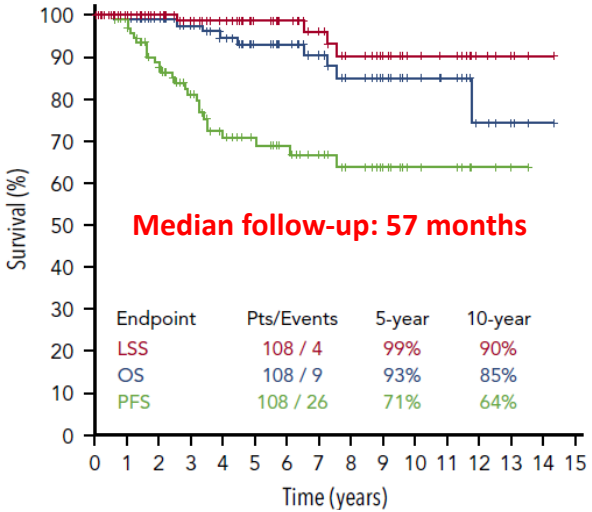
Medical complications:	10 (24.4%)*	Surgical complications:	10 (24.4%)*
Cardiac	2 (4.9%)	Intestinal obstruction	0
Pulmonary	8 (19.5%)	Acute pancreatitis	1 (2.4%)
Liver dysfunction	1 (2.4%)	Pancreatic fistula	1 (2.4%)
Renal dysfunction	0	Wound infection	1 (2.4%)
Deep venous thrombosis	1 (2.4%)	Portal vein thrombosis	1 (2.4%)
		Major bleeding	9 (21.9%)
		Patients requiring reoperation (any cause)	0

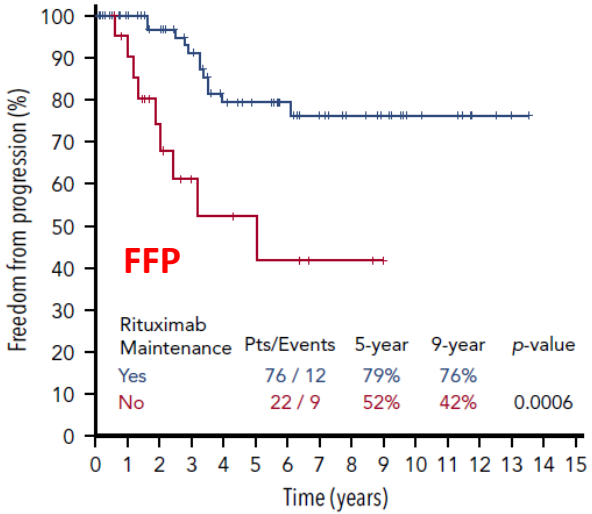
*More than one complication may be reported in the same patient.

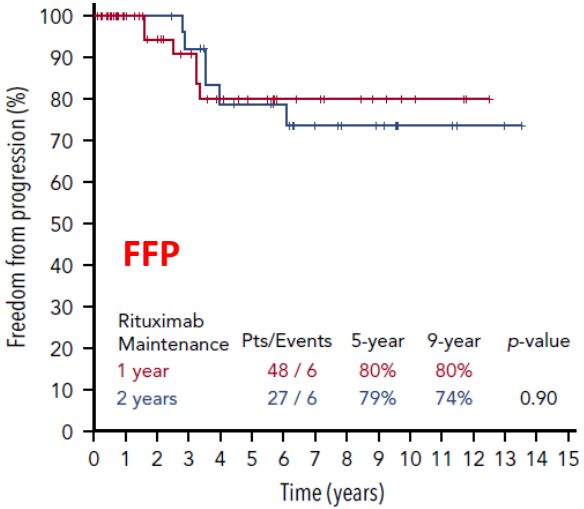
Pata et al. Leuk Lymphoma 2015

Rituximab monotherapy in SMZL

- **Retrospective study**, 3 centers, **108 pts**
- **R monotherapy x 6 weekly courses**
- If CR/CRu/PR → **R maintenance** (q2 mo) for **1 or 2 years**, *at physician discretion*
- After induction: CR 44%, CRu 21%, PR 27% (ORR 92%)
- 78 pts underwent R maint, 14/22 pts in PR → CR; 26 PD events, 9 deaths (4 for PD)

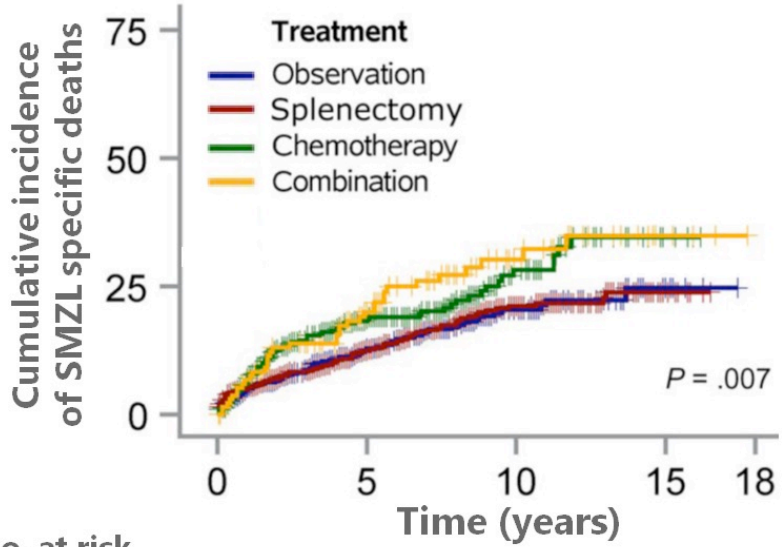






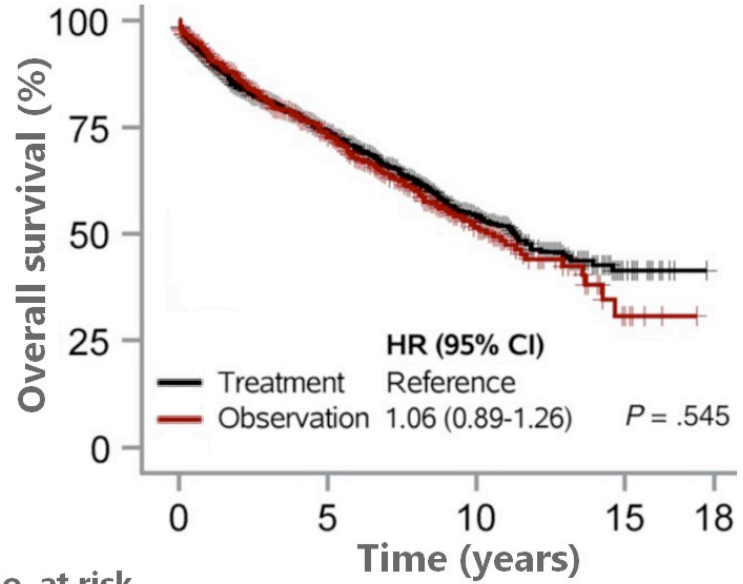
Kalpadakis et al. Blood 2018

Initial management of SMZL does not affect survival



No. at risk

Observation	596	225	75	7
Splenectomy	542	299	122	11
Chemotherapy	393	170	45	4
Combination	140	74	25	4



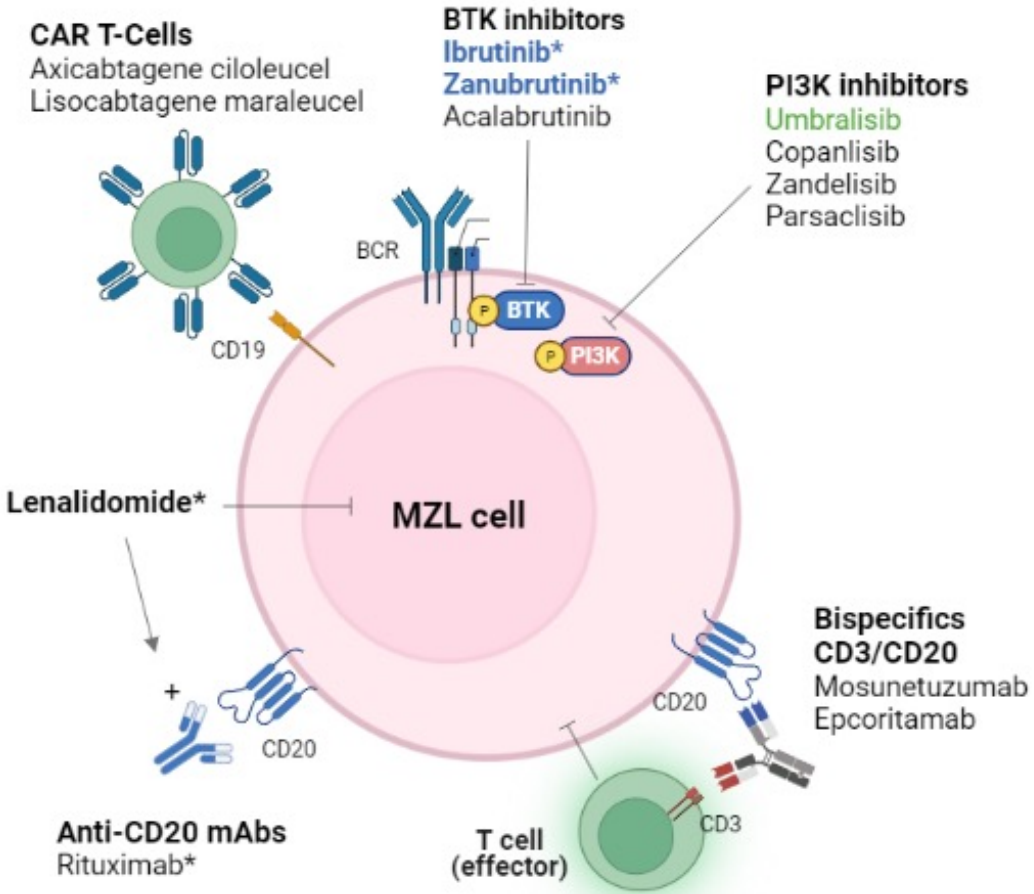
No. at risk

Treatment	1075	543	192	19
Observation	596	225	75	7

Florindez JA, Cancer 2020

Toward a chemo-free frontline therapy in (S)MZL?

Selected novel agents active in R/R MZL

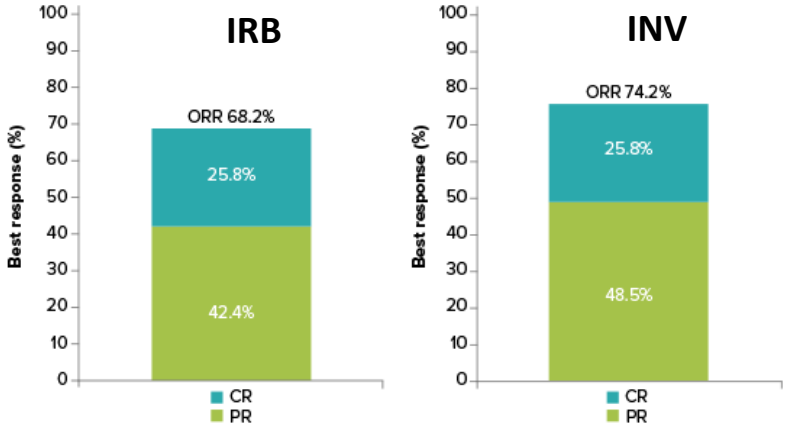


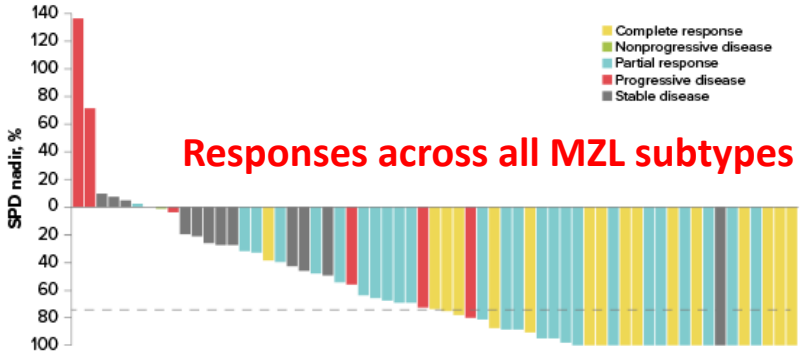
(*approved drugs)

Modified from ASH Educational Book 2022

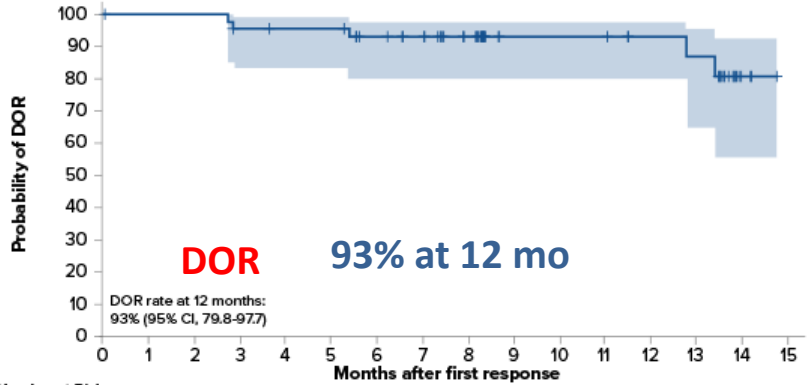
Zanubrutinib in RR MZL: *Magnolia study* (phase II)

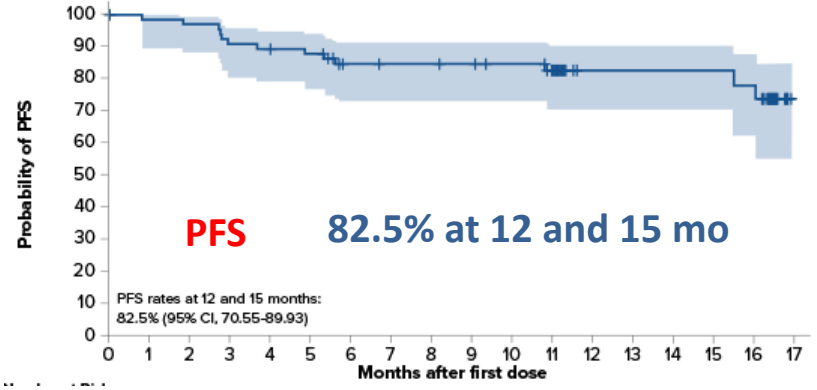
- **68 pts (26 Ex, 12 Sp, 26 No, 4 diss), ≥1 anti-CD20, median 2 tp;** Dose: **160 mg BID Median f-up: 15.7 mo**





Responses across all MZL subtypes





Opat et al. CCR 2021

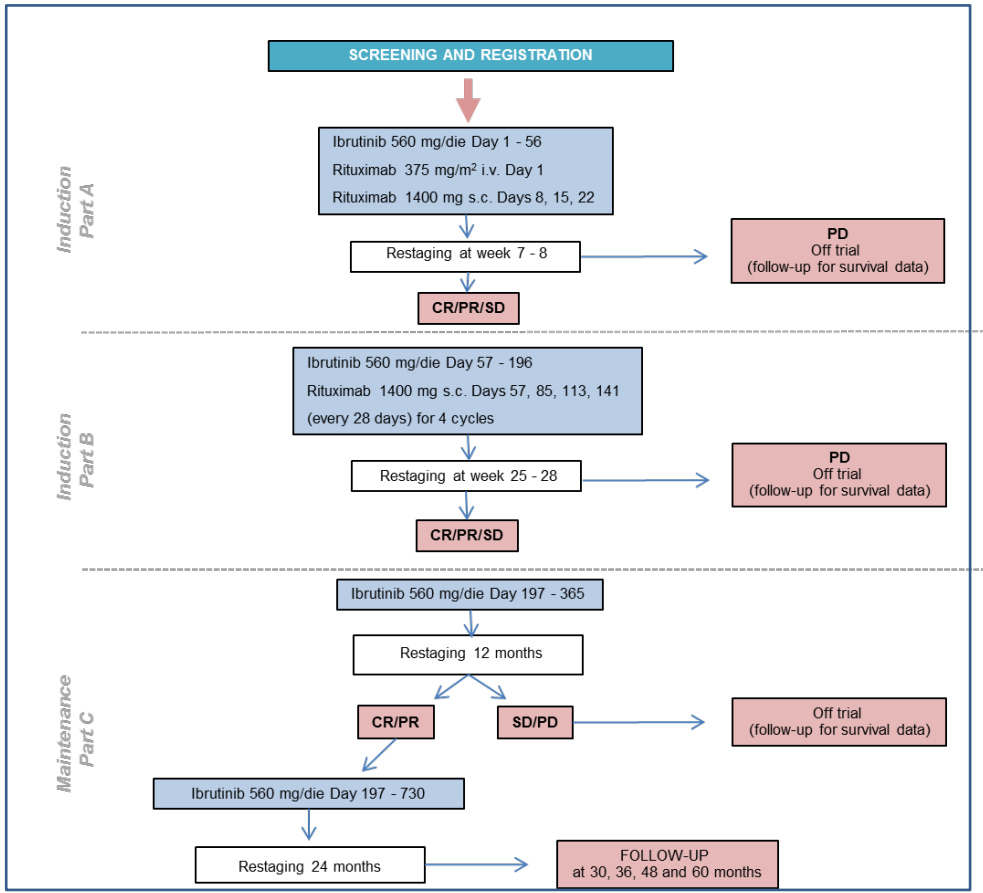
IELSG47 MALIBU

N=175
130 EMZL (from gastric and non-gastric sites); 30 SMZL and 15 NZML

Primary endpoints

CR rate at 12 months

5-year PFS (co-primary endpoint)



IELSG47 MALIBU: SMZL and NMZL

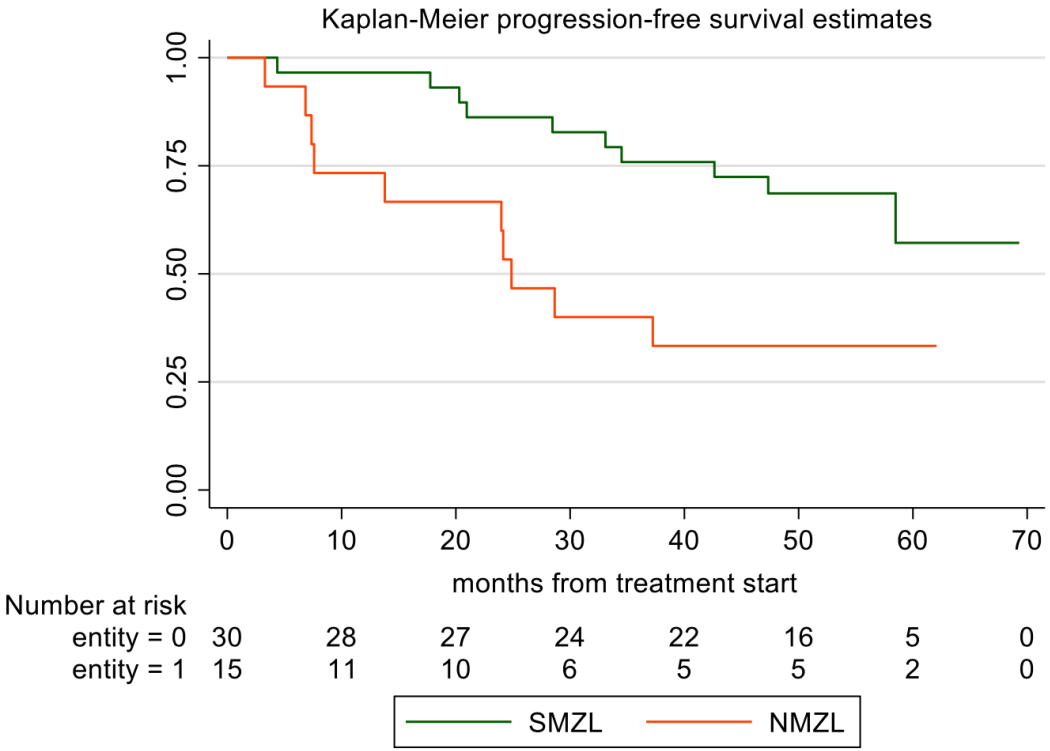
	SMZL (n=30)	NMZL (n = 15)	Total (n = 45)
Characteristic	n (%)	n (%)	n (%)
Age, median (range), years	67.5 (44-81)	68 (53-79)	68 (44-81)
Age ≥ 65 years	18 (60)	10 (67)	28 (62)
Age > 70 years	13 (43)	5 (33)	18 (40)
Male	12 (40)	5 (33)	17 (38)
ECOG PS 0	15 (50)	10 (67)	25 (56)
ECOG PS > 1	0	2 (13)	2 (4)
Stage III/IV	30 (100)	13 (87)	43 (96)
Bone marrow involvement	30 (100)	9 (60)	39 (87)
Hemoglobin, median (range), g/dL	10.5 (7.7-14.8)	12.9 (8.4-16.0)	10.8 (7.7-16)
- Anemia <10 gr/dl	11 (37)	3 (20)	14 (31)
- Anemia <12 gr/dl	25 (83)	5 (33)	30 (67)
Platelets median (range), 10^9/L	138 (89-430)	170 (79-274)	147 (79-430)
- Thrombocytopenia < 100 10^9/L	5 (17)	1 (7)	6 (13)

Dati confidenziali per cortesia della dott.ssa Conconi – non riprodurre

IELSG47 MALIBU: SMZL and NMZL

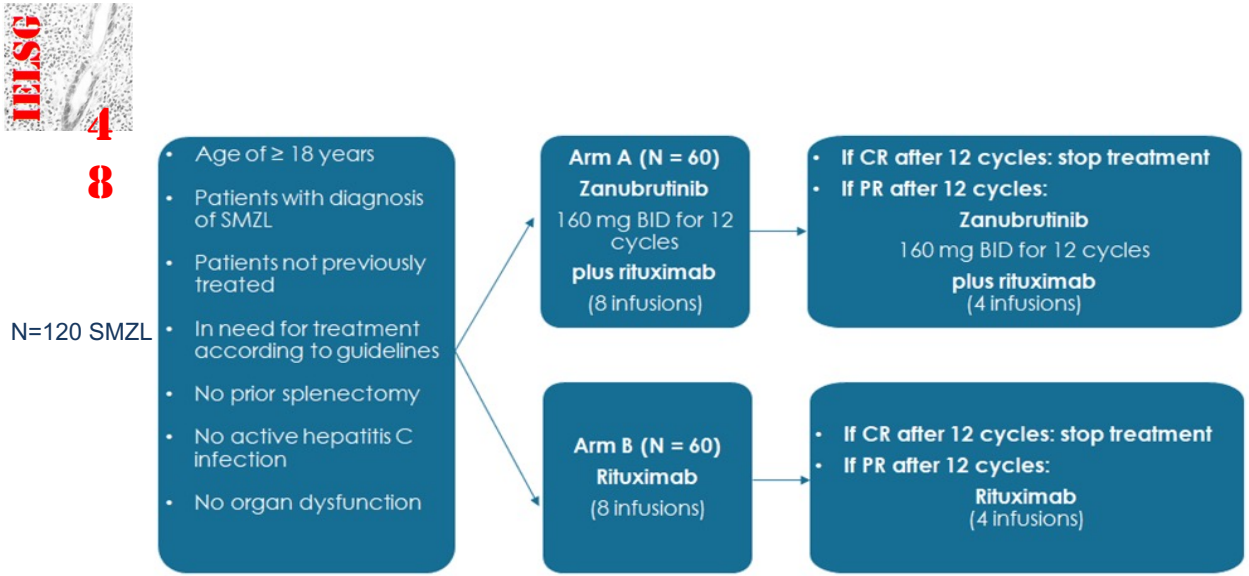
	SMZL		NMZL		Total	
Response	At 12 months n (%)	Best n (%)	At 12 months n (%)	Best n (%)	At 12 months n (%)	Best n (%)
Overall response	24 (96)	29 (97)	9 (90)	13 (86)	33 (94)	42 (93)
Complete response	11 (44)	17 (57)	8 (80)	8 (53)	19 (54)	25 (56)
Partial response	13 (52)	12 (40)	1 (10)	5 (33)	14 (40)	17 (38)
Stable disease	1 (4)	1 (3)	0	1 (7)	1 (3)	2 (4)
Progressive disease	0	0	1 (10)	1 (7)	1 (3)	1 (2)
Not assessed	5	0	5	0	10	0

IELSG47 MALIBU: SMZL and NMZL



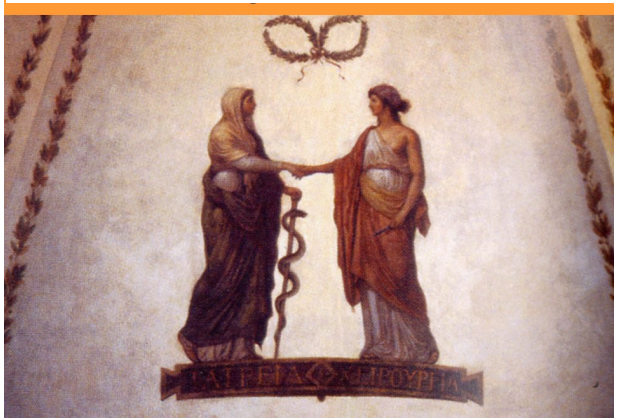
Dati confidenziali per cortesia della dott.ssa Conconi – non riprodurre

Randomized trial for untreated SMZL



SPONSOR INSTITUTES	IELSG 7 European Study Groups (SAKK, FIL, LYSA, GELTAMO, NLG, GLA, NRCI)
STUDY TITLE	Phase 3, interventional, multicentre, open label, randomized study comparing rituximab plus zanubrutinib to rituximab monotherapy in previously untreated, symptomatic splenic marginal zone lymphoma (RITZ)

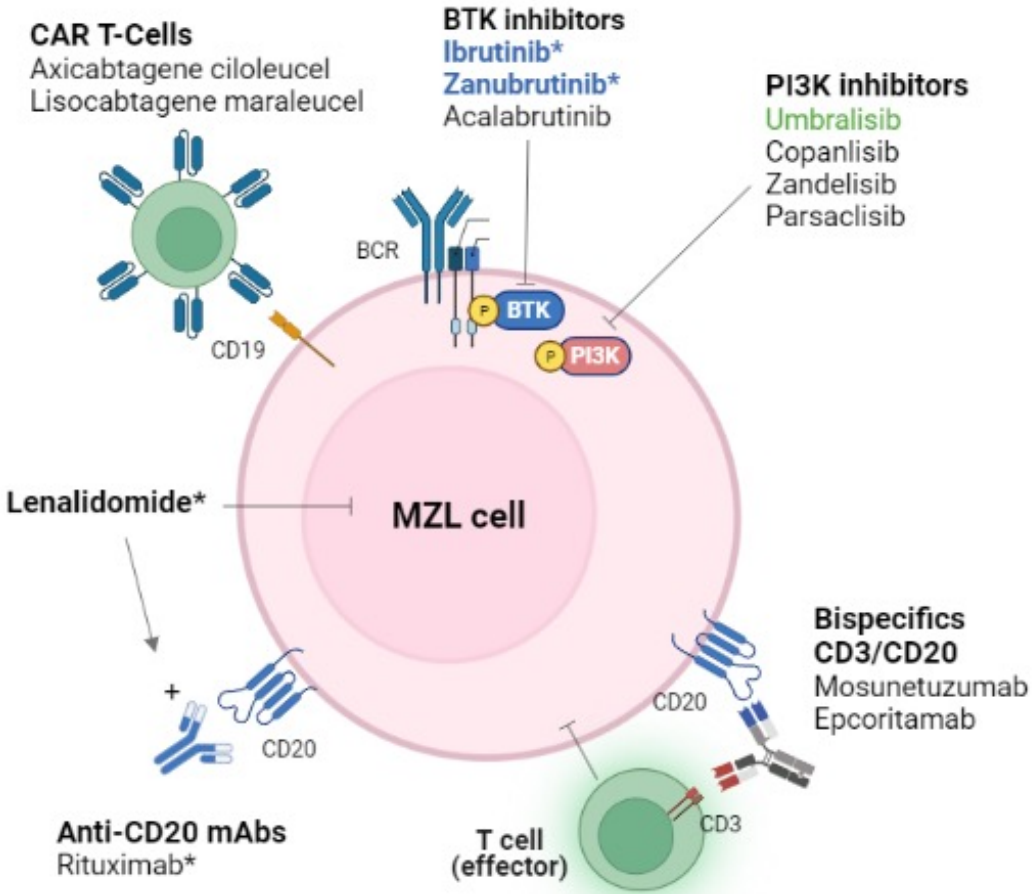
Rituximab is infused at the dose of 375 mg/m2 iv on days 1, 8, 15, and 22 of cycle 1 (28 days per cycle), then on day 1 of cycles 3, 6, 9, and 12 (28 days per cycle).
After cycle 12:
A. Patients in CR will stop treatment and enter the follow-up phase.
B. Patients in PR will go on with rituximab 375 mg/m2 IV on day 1 of cycles 15, 18, 21, and 24 (28 days per cycle).
C. Patients in SD or PD will discontinue treatment and will enter the follow-up phase.



Aula Scarpa, Teatro Anatomico, Università di Pavia (1758)

Toward a chemo-free frontline therapy in MZL?

Selected novel agents active in R/R MZL



(*approved drugs)

Modified from ASH Educational Book 2022

Novel drugs in RR MZL

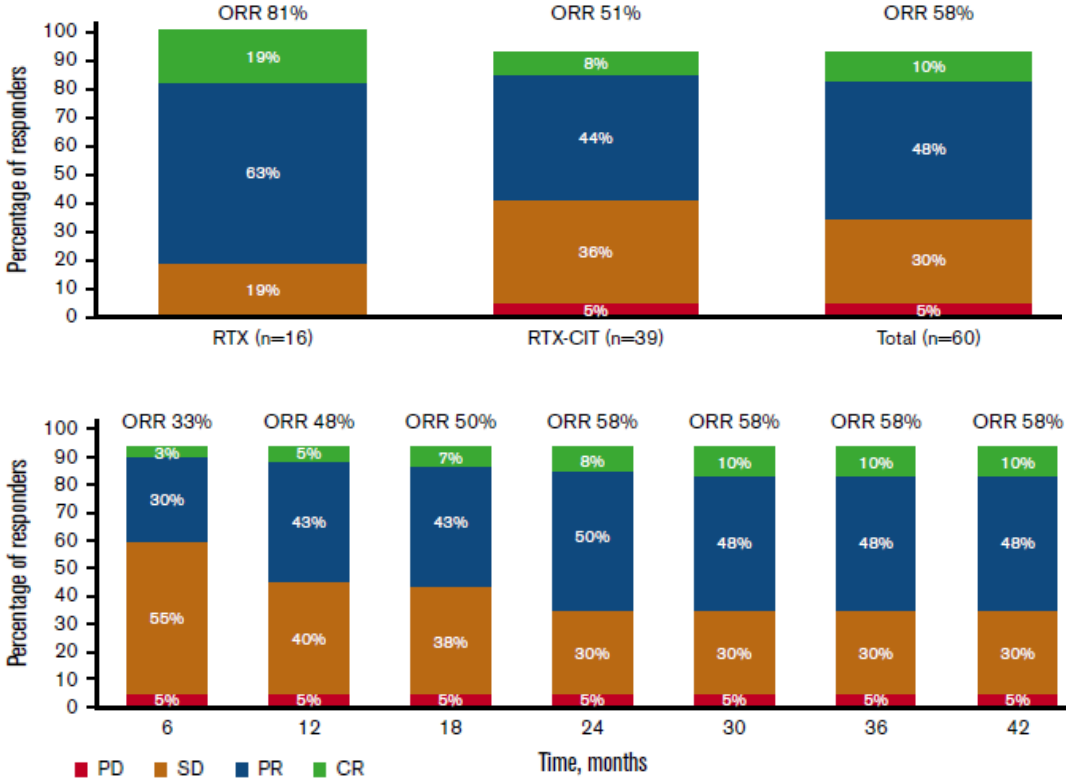
Signalling pathway	Target	Drug	N MZL pts	ORR %	mDOR (mo)
Pi3K/AKT/mTOR	PI3K δ	Idelalisib	15	47	18.4
		Umbralisib‡	69	49	NR
		Umbralisib+ublituximab	72	68	NR
		Zandelisib	4	100	NA
		Parsaclisib	100	58	12.2
	PI3K γ,δ	Duvelisib	18	39	15.5 (mPFS)
	PI3K α,δ	Copanlisib	23	78	17.4
		Copanlisib+rituximab	66	76	22.1 (mPFS)
B-Cell receptor	BTK	Ibrutinibł	63	48	27.6
		Zanubrutinibł	68	68	93% at 2 y
		Acalabrutinib	43	53	76% at 1 y
Apoptosis	BCL2	Venetoclax	3	66	2.3; 23.6
NF-κB	Cereblon	R-Lenalidomideł	31	65	17.4

NR: not reached; NA not available; ł approved by FDA after 1 prior line with anti-CD20 ‡approval withdrawn by FDA due to safety reasons

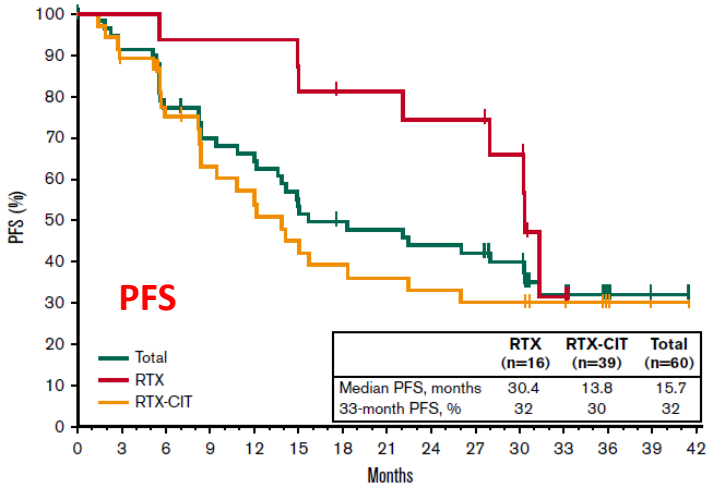
Wagner-Johnson et al, Leuk&Lymph 2021; Fowler et al JCO 2021; Chavez et al, ASH 2021; Pagel et al, Lancet Oncol 2022; Phillips et al, ASH 2021; Jacobsen et al, SOHO 2019; Panayiotidis et al, Blood Adv 2021; Matsar et al, Lancet Oncol 2021; Noy et al, Blood 2017, Blood Adv 2020; Opat et al, CCR 2021; Strati et al BJH 2022; Davids et al, JCO 2017; Leonard et al JCO 2019

Ibrutinib in RR MZL, final analysis of phase 2 study

- **33.1 months of follow-up: ORR 58%** (INV-based)

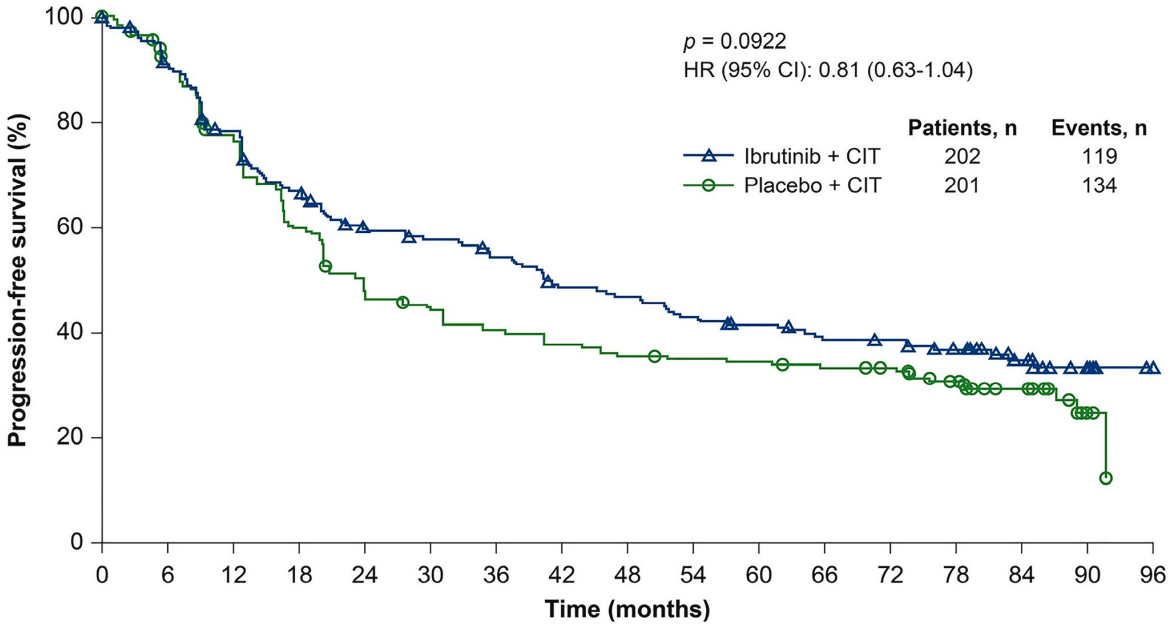


- **mDOR 27.6 mo**
- **mPFS 15.7 mo, mOS NR** (72% at 33 mo)
- No difference in ORR, PFS, OS subtypes
- mPFS better if only prior R (30.4 mo) vs prior R-CHT (13.8 mo)
- KMT2D and CARD11 mut -> shorter DOR



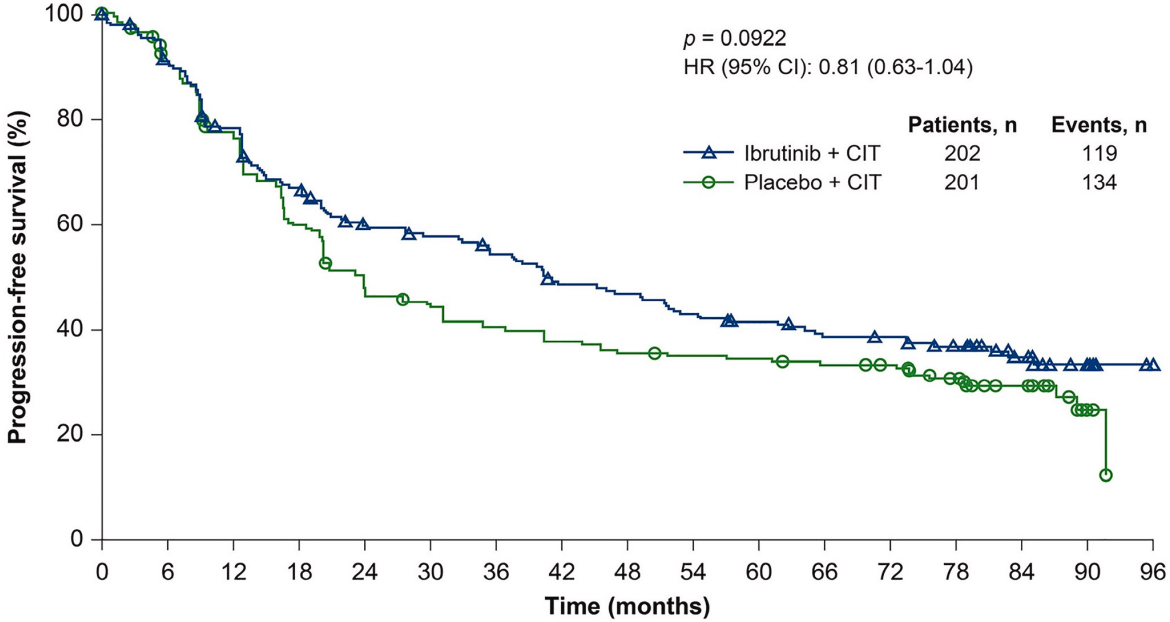
Noy et al. Blood Adv 2020

IBRUTINIB PLUS BR OR R-CHOP IN R/R FL OR MZL: THE PHASE 3 SELENE STUDY



Nastoupil et a. 17 ICML, 2023; LBA 2

Ibrutinib plus BR or R-CHOP in R/R FL or MZL: The phase 3 SELENE study

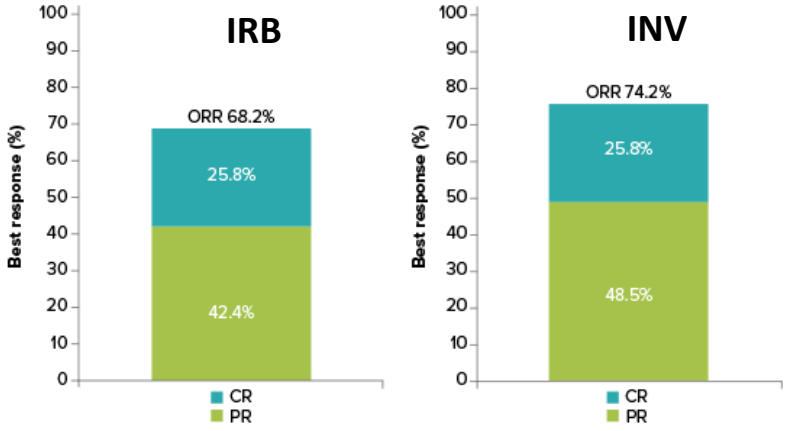


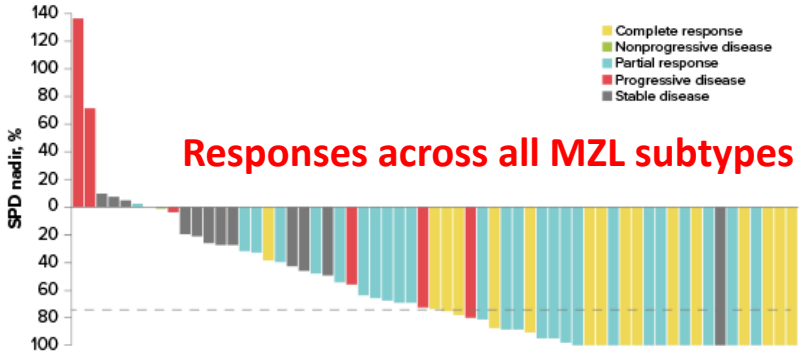
April 6, 2023 – AbbVie announced today the intent to voluntarily withdraw, in the U.S., accelerated ibrutinib approvals for patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy

Nastoupil LJ et a. 17 ICML, 2023; LBA 2

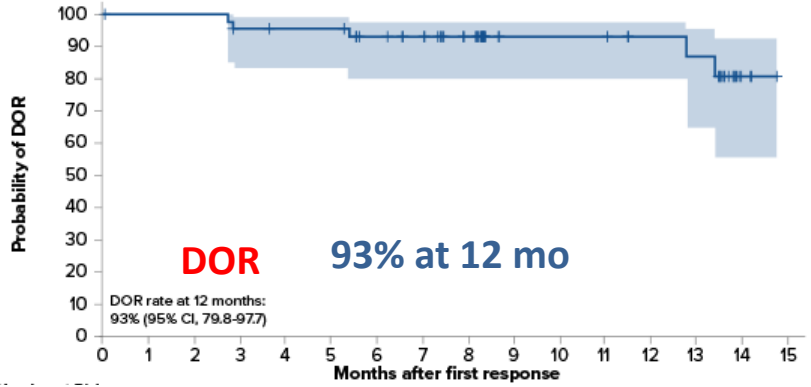
Zanubrutinib in RR MZL: *Magnolia study* (phase II)

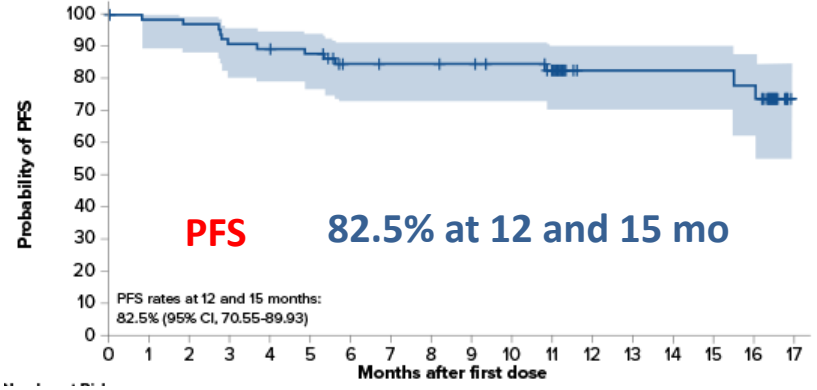
- **68 pts (26 Ex, 12 Sp, 26 No, 4 diss), ≥1 anti-CD20, median 2 tp;** Dose: **160 mg BID Median f-up: 15.7 mo**





Responses across all MZL subtypes



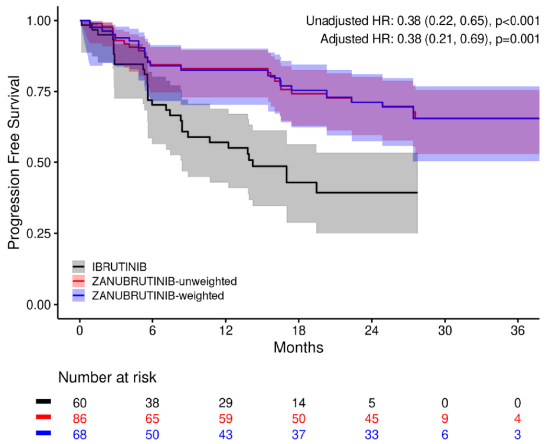


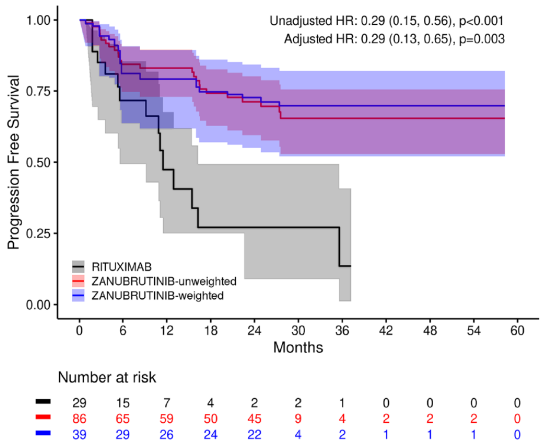
Opat et al. CCR 2021

Matching-adjusted indirect comparisons of zanubrutinib vs. ibrutinib and vs. rituximab) in r/r MZL: ORR and PFS

	Zanubrutinib sample size (*N*)	ORR OR (95% CI)	PFS HR (95% CI)
Zanubrutinib vs ibrutinib (*N* = 60)			
unadjusted model	86	**2.64 (1.32, 5.28)**	**0.38 (0.22, 0.65)**
adjusted model	68	**2.37 (1.13, 4.96)**	**0.38 (0.21, 0.69)**
Zanubrutinib vs rituximab (*N* = 29)			
unadjusted model	86	**3.51 (1.46, 8.44)**	**0.29 (0.15, 0.56)**
adjusted model	39	**5.09 (1.84,14.08)**	**0.29 (0.13, 0.65)**

Notes: All bolded values are statistically significant at the 0.05 significance level.
Abbreviations: CI: confidence interval; HR: hazard ratio; OR: odds ratio; ORR: overall response rate; PFS: progression-free survival.

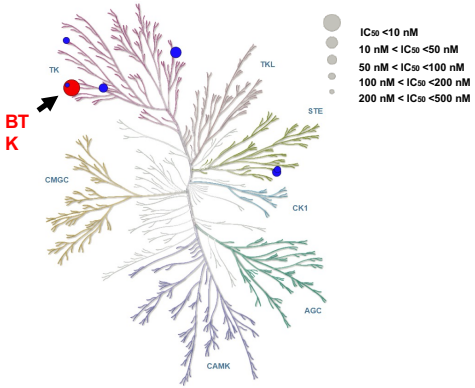




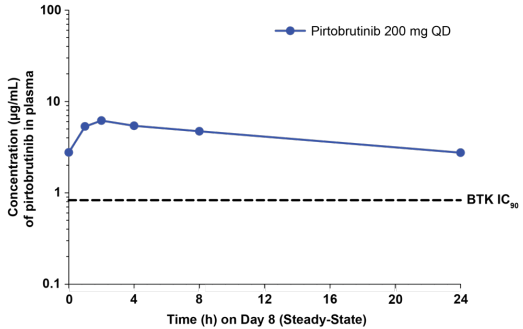
Thieblemont et al. Leuk Lymphoma 2025

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

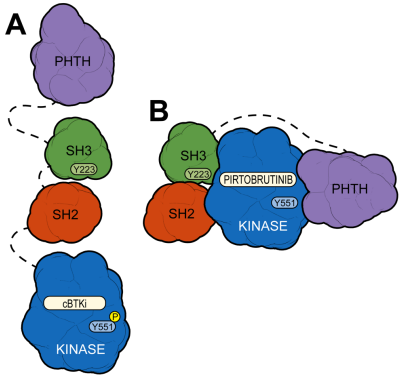
Highly selective for BTK[4-5]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



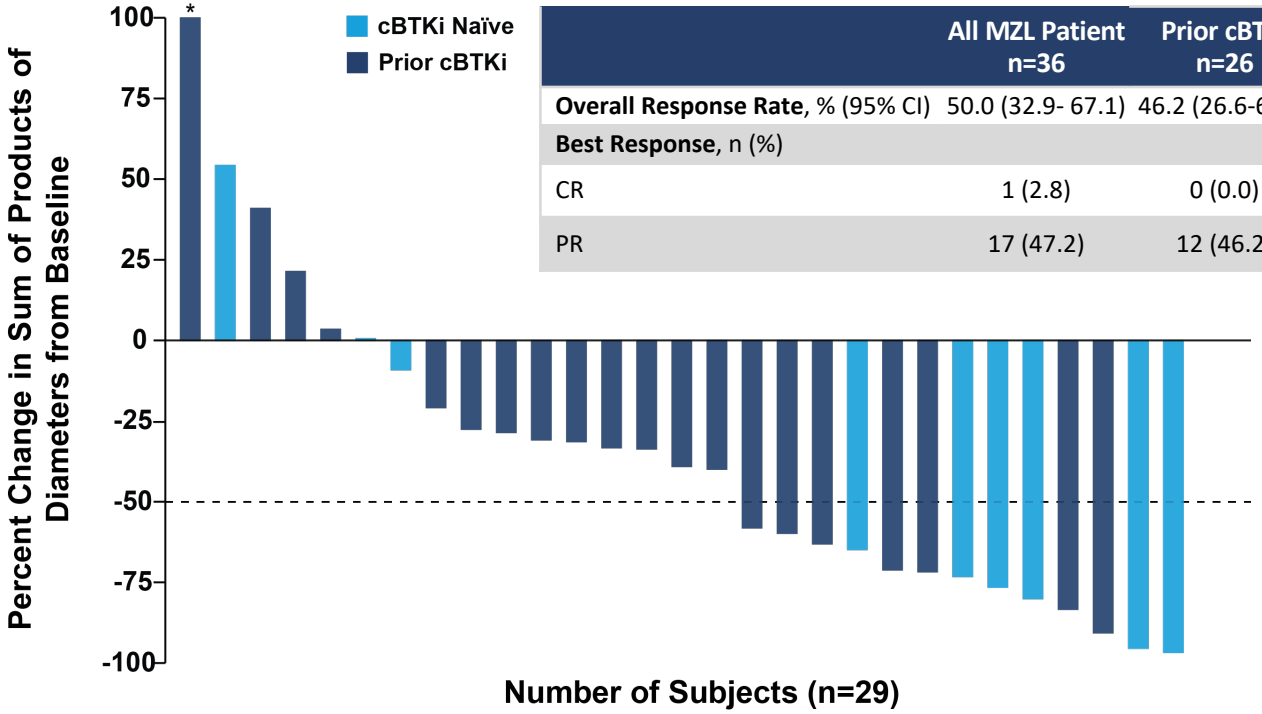
Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[6]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[6]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[6]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[6]

Patel et al. ASH 2023

Pirtobrutinib efficacy in RR MZL



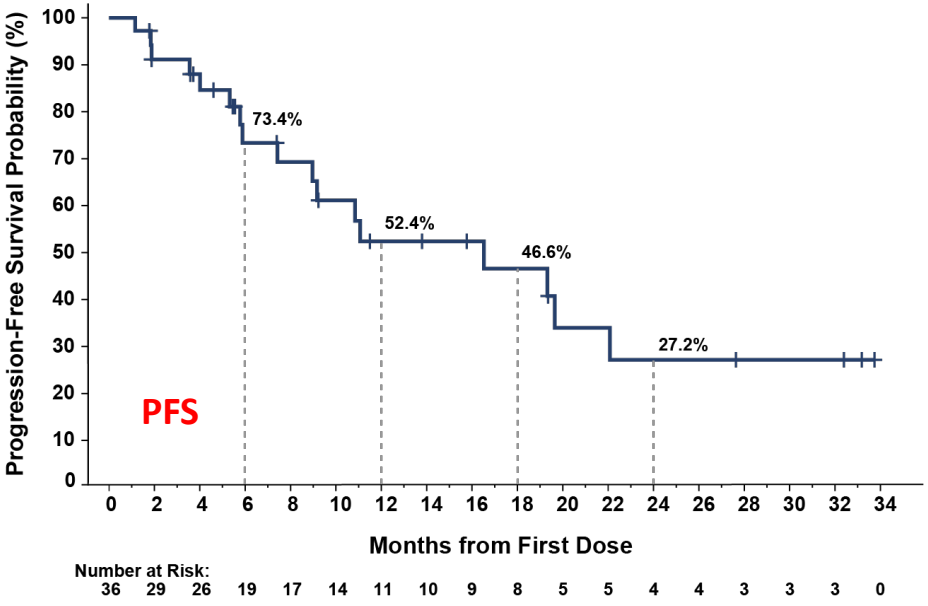
	All MZL Patient n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Overall Response Rate, % (95% CI)	50.0 (32.9- 67.1)	46.2 (26.6-66.6)	60.0 (26.2-87.8)
Best Response, n (%)			
CR	1 (2.8)	0 (0.0)	1 (10.0)
PR	17 (47.2)	12 (46.2)	5 (50.0)

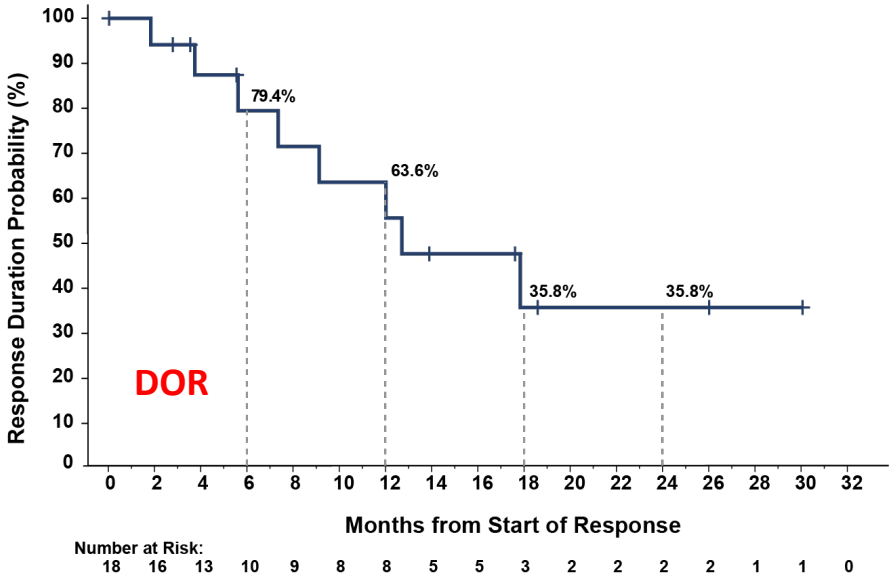
- Median time-to-response was 1.9 months (range, 1.6-19.3)

Pirtobrutinib in RR MZL: PFS and DOR

	All MZL Patients n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Median PFS, months (95% CI)	16.5 (7.4-22.1)	9.2 (5.8-NE)	NE (1.9-NE)
Median Follow-up, months	15.8	11.5	32.4
Events/Total (n/n)	17/36	13/26	4/10

	All MZL Patients n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Median DOR, months (95% CI)	12.7 (5.6-NE)	7.4 (3.8-12.7)	NE (12.0-NE)
Median Follow-up, months	17.6	NE	18.6
Events/Total (n/n)	8/18	7/12	1/6

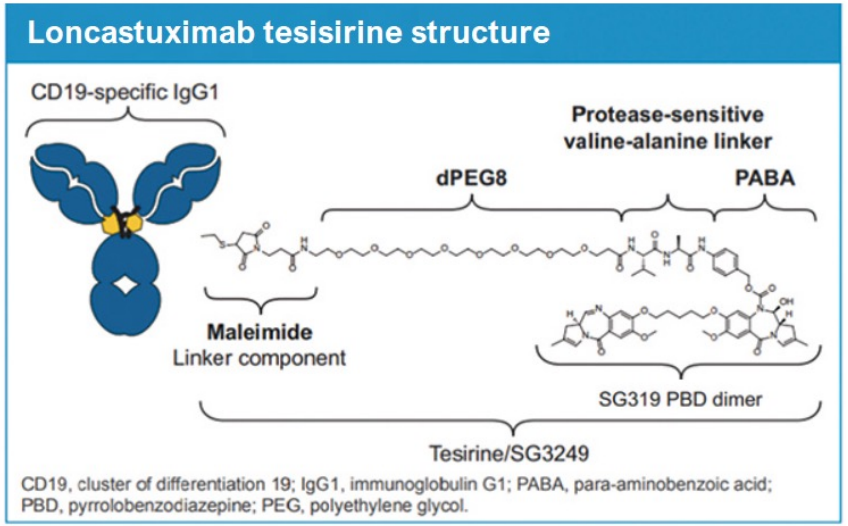





BRIGHT
FUTURE
AHEAD

Limited Duration Loncastuximab Tesirine in r/r MZL

- Loncastuximab 0.15 mg/kg i.v. for 2 cycles followed by 0.075 mg/kg for 4 cycles
- N=23, median age, 65 years
- **ORR, 91%** (21/23);
- **CR, 70%** (16/23)
- CR in 7 of 11 patients (64%) with POD24 and one patient relapsing after CAR-T
- Median CR duration, 11.5 months
- Manageable toxicity

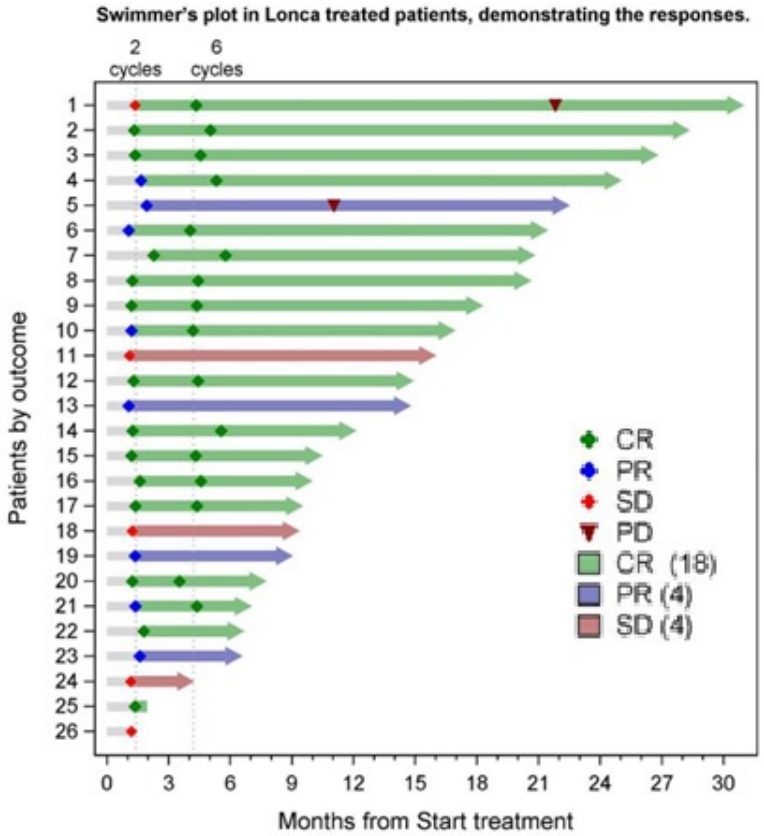


Lossos et al. ASH 2024

Limited Duration Loncastuximab Tesirine in r/r MZL

18 ICML update of the ongoing study

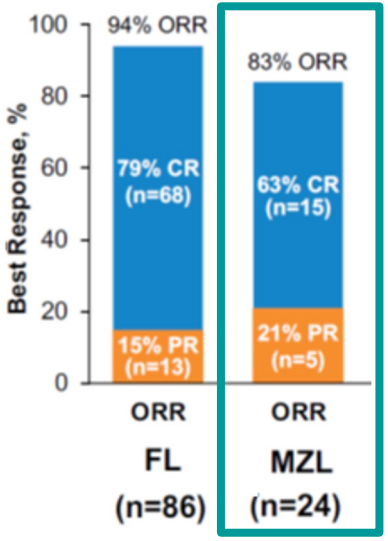
- N= 67;
- CR 69%; (61.5% in POD 24)
- CR at 18 months was 83.3%

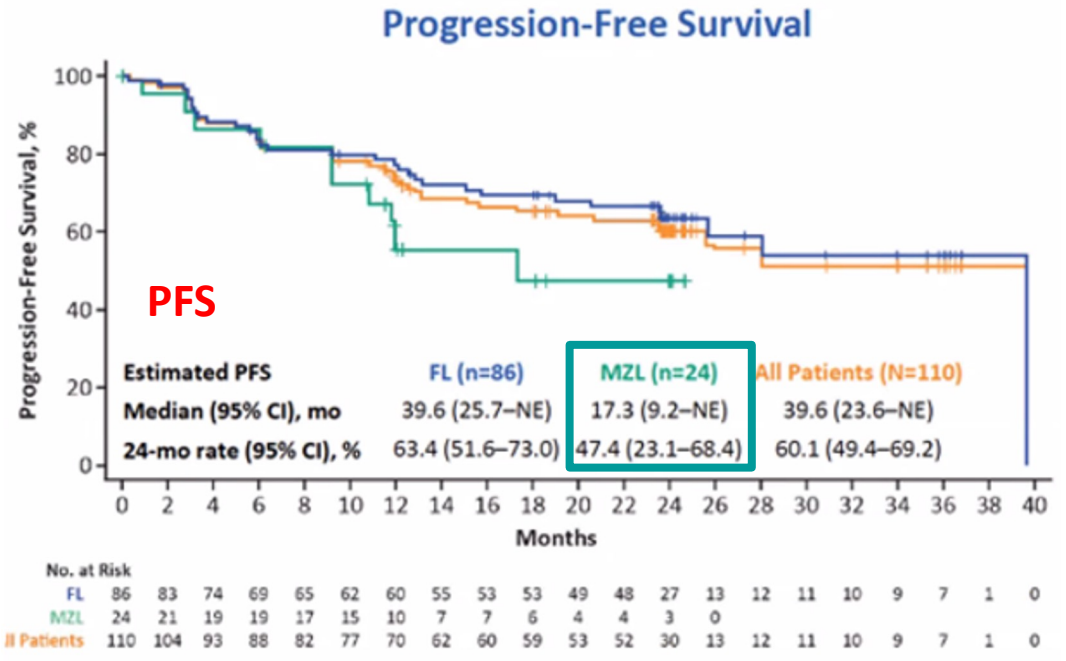


Lossos et al. ICML 2025

CAR T-Cells *(ZUMA-5)*

- Axicel,R/R FL and MZL pts after ≥2 prior lines
- 124 FL, **25 MZL** (POD24 50%)
- Median 3 prior lines (2-8)
- Grade ≥3 CRS: 2 pts (9%)
- Grade ≥3 ICANS: 9 pts (36%), no Gr 5



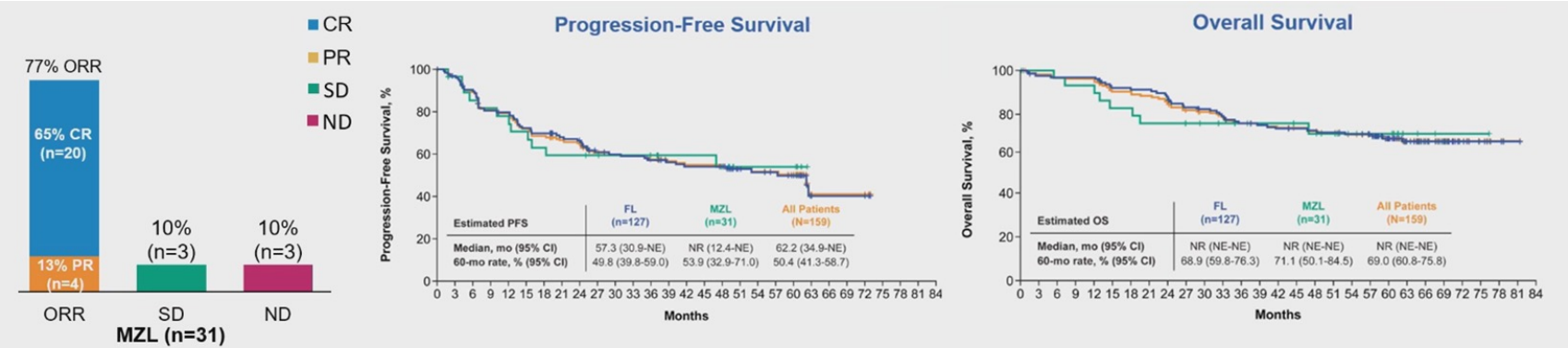


Median FU: MZL: 23,8 mo

Neelapu et al. ASH 2021 Abstract #93
Jacobson et al. Lancet Oncology 2022

Neelapu et al. #4660, Mon Poster III (3-y F-UP)
Wang et al. #1989, Sat Poster I

5-year follow-up of the ZUMA-5 trial



- After a median follow-up of >5 years in ZUMA-5, axi-cel continued to demonstrate durable responses and long-term survival
  - Over half of patients were alive at data cutoff without the need for a subsequent therapy
- Safety outcomes with axi-cel remained consistent with previous analyses, and no new safety signals were observed

ORR, 77% (CR, 65%) **5-yr PFS, 54%** **5-yr OS, 71%**

Neelapu SS et al. *Blood* 2024; 144 (Supplement 1): 864-6

Phase 2 Transcend Study
Lisocabtagene maraleucel in R/R MZL patients

- **77 leukapheresis**
  67 (87%) received liso-cel
  66 (86%) evaluable

- 48% nodal; 27% splenic and 25% MALT

- Median age 62, 36% POD24; 39% refractory

- Median prior lines of therapy: 3 (2-18)

- **ORR 95.5%; CR 62%**
- **At 24 months: DOR 89%; PFS 86%; OS 90%**

- *Toxicities:*
- G5: PTCL; neutropenic sepsis
- CRS 76% (4% G3 no G4-5)
- ICANS 33% 4% (4% G3 no G4-5)
- Prolonged cytopenia 42%; MAS-HLH 4%

Palomba et al. ICML 2025

Odronextamab in +3L R/R MZL: ELM-2 study

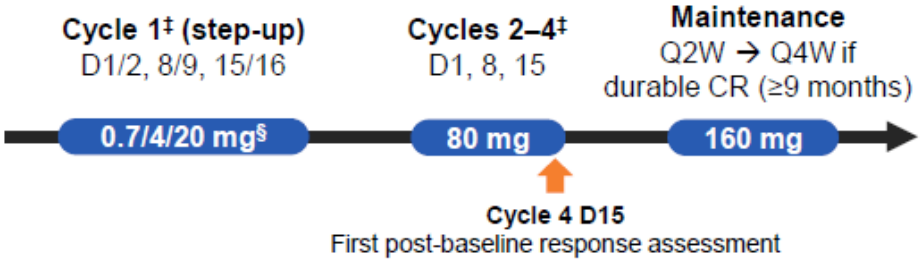
- Phase 2, open-label, multicohort, multicenter study of odronextamab monotherapy in patients with R/R B-NHL (NCT03888105)

Key eligibility criteria
- ≥18 years old
- MZL (extranodal, splenic, or nodal subtype)*
- ECOG PS 0 or 1
- Refractory to, or relapsed after, ≥2 prior lines of systemic therapy

Primary endpoint
- ORR† by ICR

Secondary endpoints
- ORR† by local investigator
- DOR,† PFS,† and OS
- Safety and tolerability
- Patient-reported outcomes

Odronextamab IV administration



Measures taken to facilitate diverse, inclusive enrollment:
- Diverse trial sites
- Translated consents
- Extended screening windows
- Broad eligibility criteria
- Investigator training

Anti-infection prophylaxis including IVIg supplementation and antivirals was recommended, and PJP prophylaxis was mandated

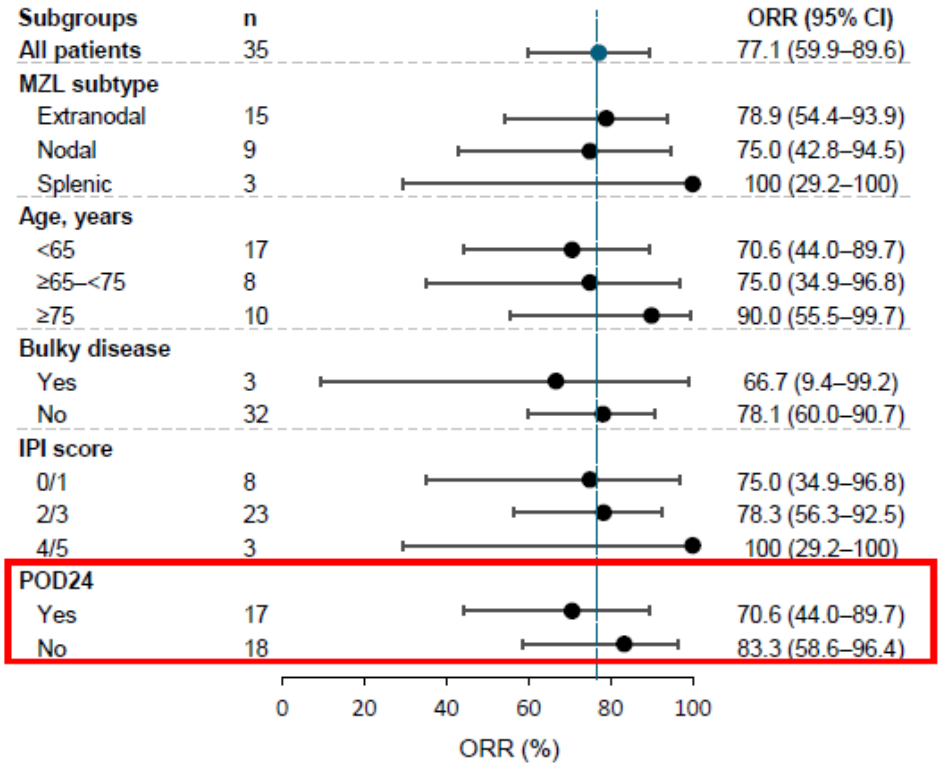
Kim et al. ASH 20204

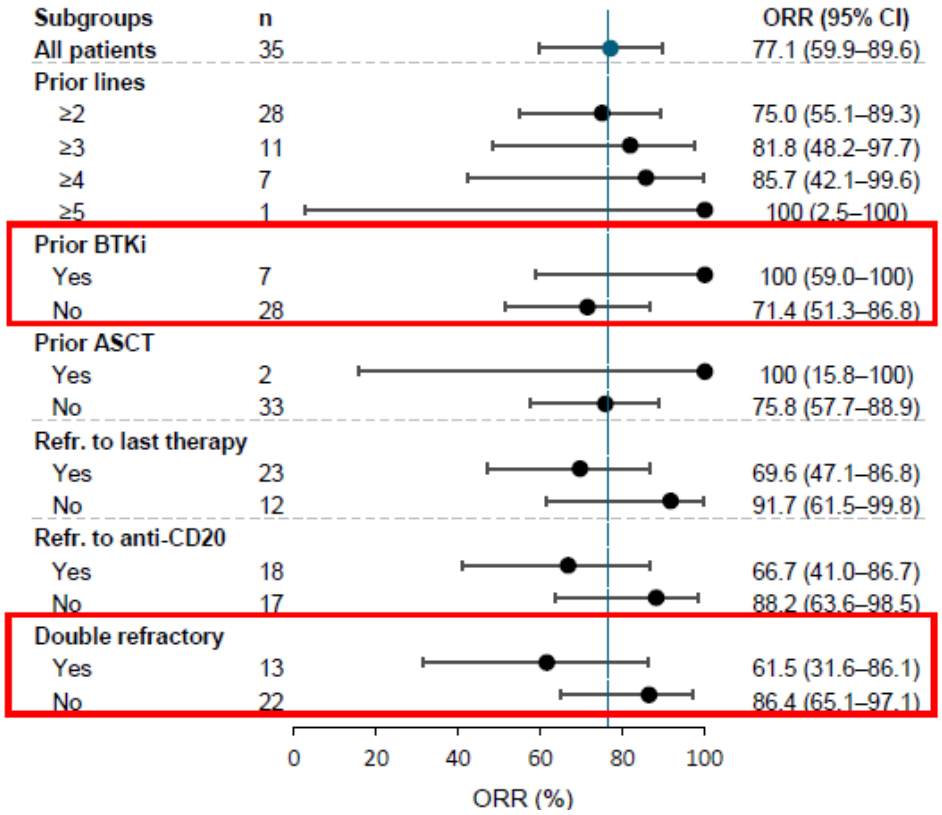
Odronextamab in +3L R/R MZL: efficacy

Best overall response, %*	Overall (n=35)	Extranodal (n=19)	Nodal (n=12)	Splenic (n=3)
Objective response rate (ORR)	77.1 (95% CI 59.9–89.6)	78.9 (95% CI 54.4–93.9)	75.0 (95% CI 42.8–94.5)	100 (95% CI 29.2–100)
Complete response	77.1 (95% CI 59.9–89.6)	78.9 (95% CI 54.4–93.9)	75.0 (95% CI 42.8–94.5)	100 (95% CI 29.2–100)
Partial response	0	0	0	0
Stable disease	8.6	10.5	8.3	0
Progressive disease	0	0	0	0
Not evaluable	14.3	10.5	16.7	0

All responders achieved CR

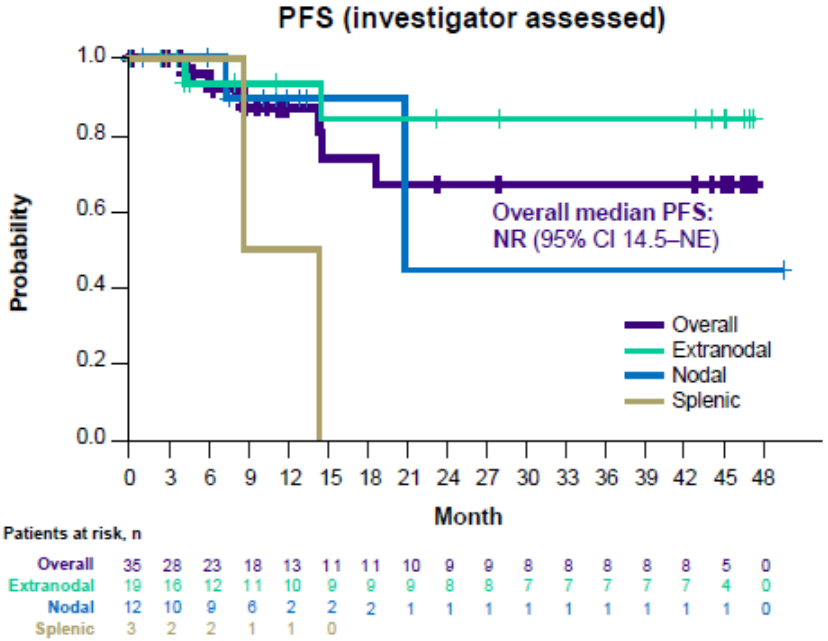
Odronextamab R/R MZL: efficacy across subgroups

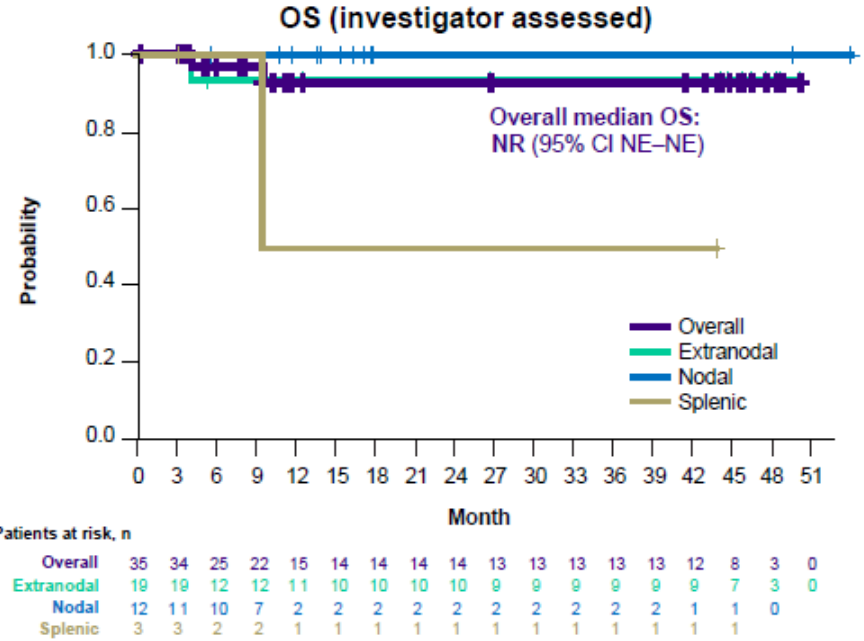




Efficacy was observed across high-risk subgroups

Odronextamab R/R MZL: PFS and OS





12-month PFS rate (95% CI):

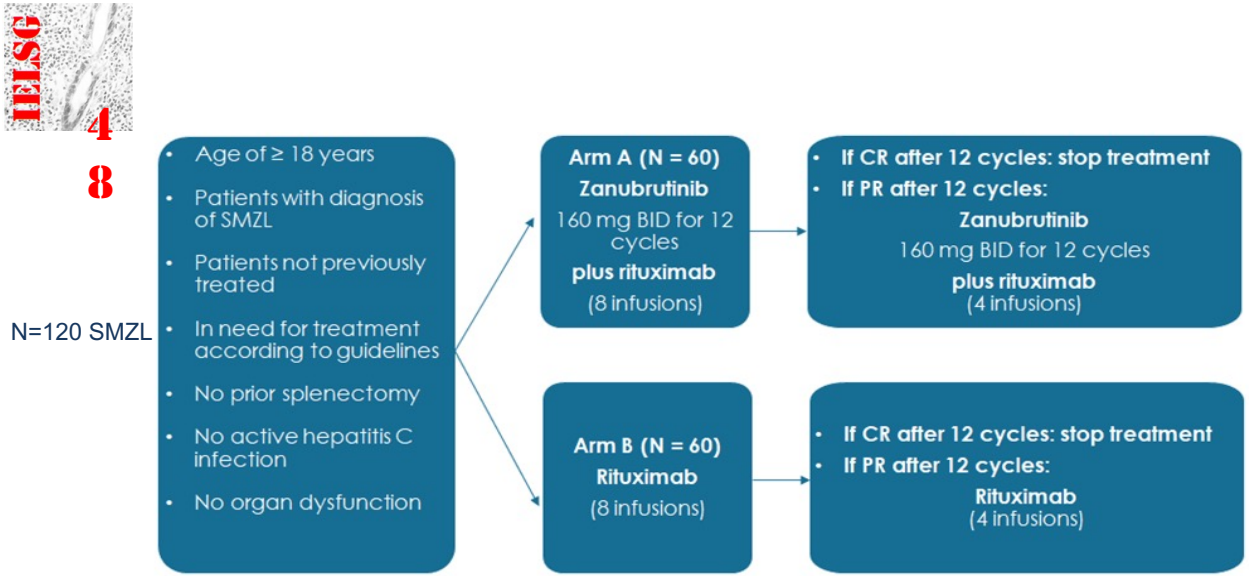
Overall	Extranodal	Nodal	Splenic
87.5 (65.9–95.8)	93.3 (61.3–99.0)	88.9 (43.3–98.4)	50.0 (0.6–91.0)

12-month OS rate (95% CI):

Overall	Extranodal	Nodal	Splenic
92.2 (71.8–98.0)	93.3 (61.3–99.0)	100 (100–100)	50.0 (0.6–91.0)

Neither median PFS nor median OS were reached

Randomized trial for untreated SMZL

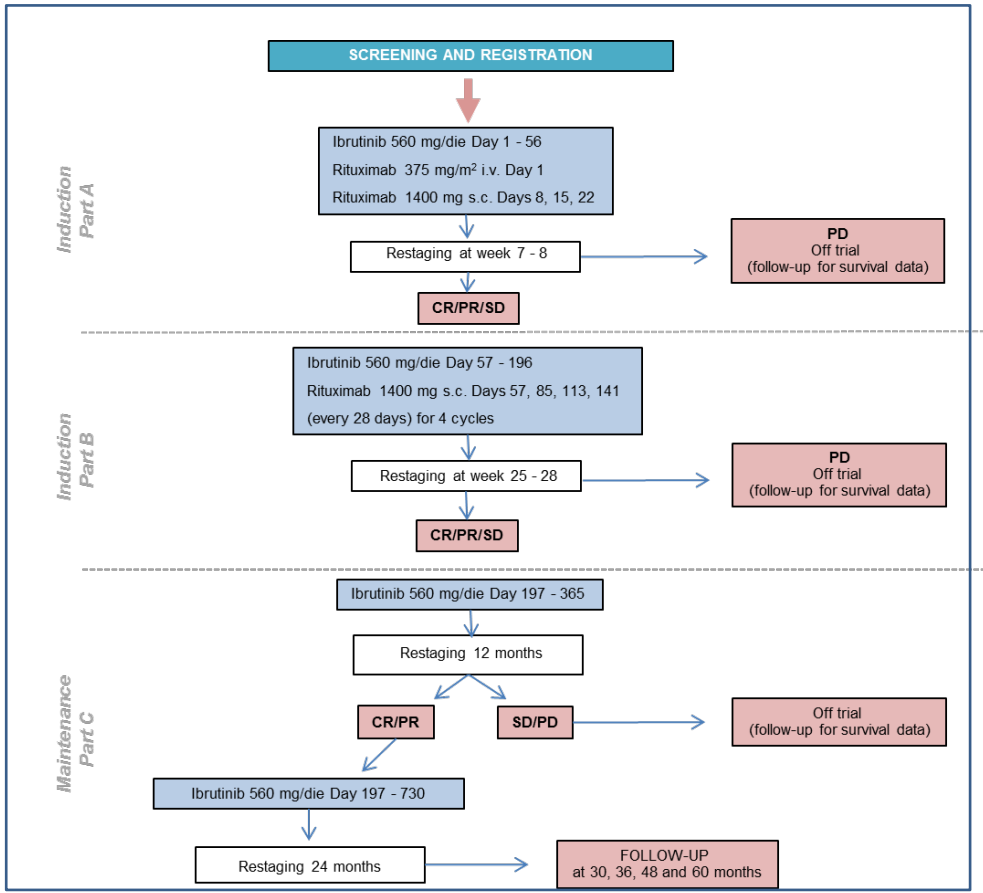


SPONSOR INSTITUTES	IELSG 7 European Study Groups (SAKK, FIL, LYSA, GELTAMO, NLG, GLA, NRCI)
STUDY TITLE	Phase 3, interventional, multicentre, open label, randomized study comparing rituximab plus zanubrutinib to rituximab monotherapy in previously untreated, symptomatic splenic marginal zone lymphoma (RITZ)

Rituximab is infused at the dose of 375 mg/m2 iv on days 1, 8, 15, and 22 of cycle 1 (28 days per cycle), then on day 1 of cycles 3, 6, 9, and 12 (28 days per cycle).
After cycle 12:
A. Patients in CR will stop treatment and enter the follow-up phase.
B. Patients in PR will go on with rituximab 375 mg/m2 IV on day 1 of cycles 15, 18, 21, and 24 (28 days per cycle).
C. Patients in SD or PD will discontinue treatment and will enter the follow-up phase.

IELSG47 MALIBU

N=175
130 EMZL (from gastric and non-gastric sites); 30 SMZL and 15 NZML

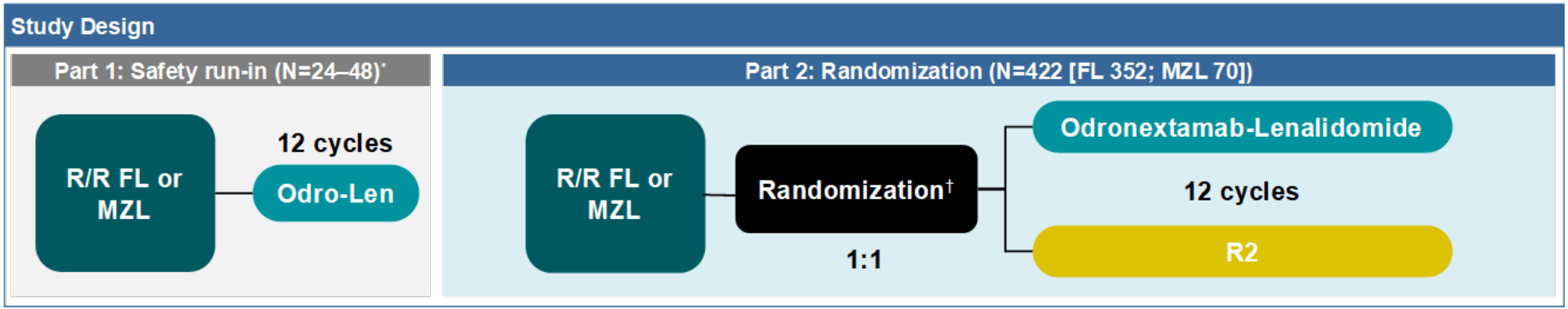


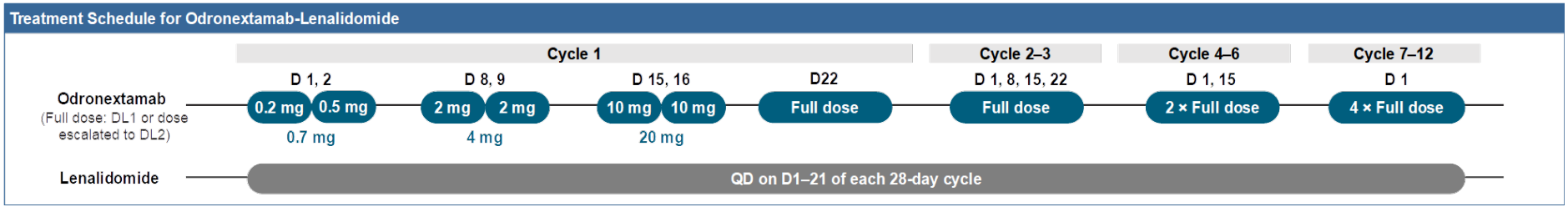
Primary endpoints

CR rate at 12 months

5-year PFS (co-primary endpoint)

Phase 3 trial of odronextamab plus lenalidomide versus rituximab plus lenalidomide in relapsed/refractory (R/R) follicular lymphoma (FL) and marginal zone lymphoma (MZL) (OLYMPIA-5)

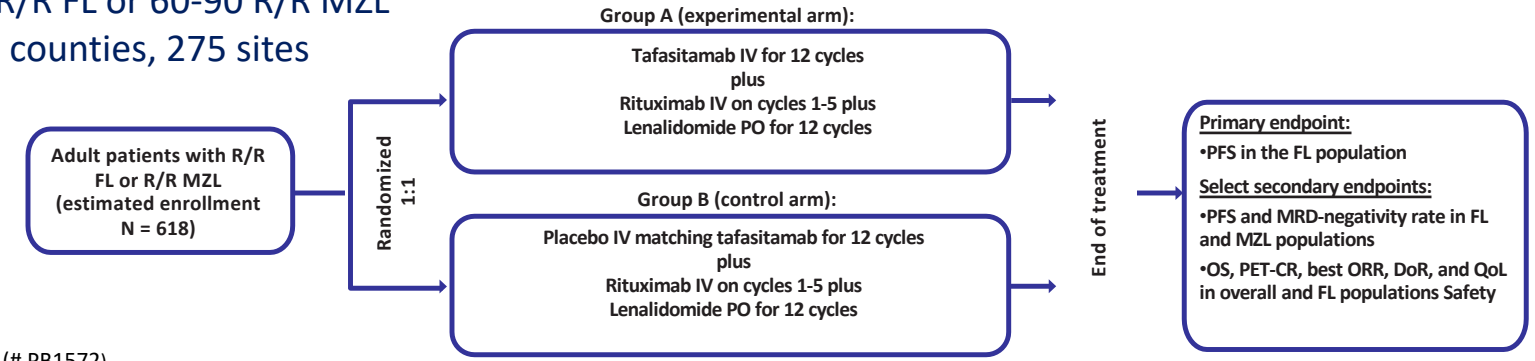




PHASE 3 STUDY OF TAFASITAMAB + LENALIDOMIDE AND RITUXIMAB VS PLACEBO + LENALIDOMIDE AND RITUXIMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA (FL) OR MARGINAL ZONE LYMPHOMA (MZL): INMIND

Key Points:

- **Trial in Progress (currently enrolling)**
- phase 3 double-blind
- 1:1 randomization
  Tafa-Len-Ritux vs placebo-Len-Ritux
- 528 R/R FL or 60-90 R/R MZL
  31 counties, 275 sites



Scholz C. EHA 2021 (# PB1572)

Randomized trials

A Study of Zanubrutinib Plus Anti-CD20 Versus Lenalidomide Plus Rituximab in Participants With Relapsed/Refractory Follicular or Marginal Zone Lymphoma (MAHOGANY)

Marsun trial: study design/overview