

3rd edition

Unmet challenges in high risk
hematological malignancies:
from benchside to clinical practice

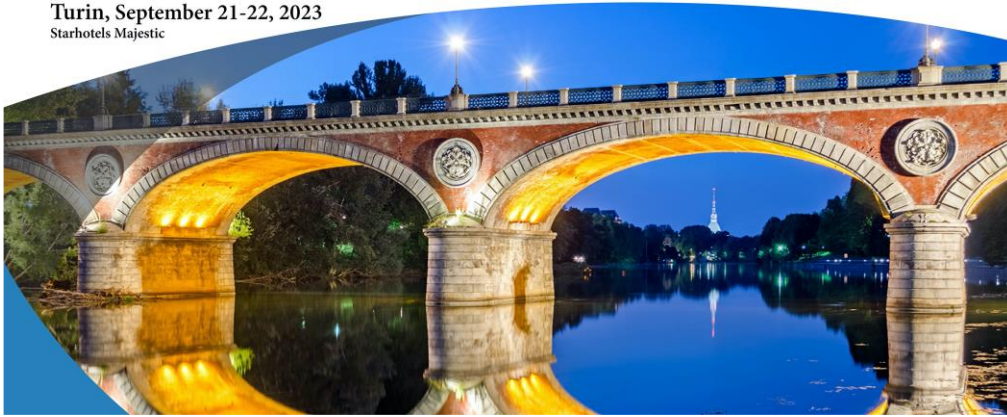
Turin, September 21-22, 2023

Starhotels Majestic

Scientific board:

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Umberto Vitolo (Candiolo-TO)



How I identify and treat high-risk marginal zone lymphoma

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Disclosures of Luca Arcaini

Consultant or advisory role	Advisory board: Roche, Janssen-Cilag, Verastem, Incyte, EUSA Pharma, Celgene/Bristol Myers Squibb, Kite/Gilead, ADC Therapeutics, Novartis
Speakers' Bureau	EUSA Pharma, Novartis
Research funding	Gilead Sciences

MZL: 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%**
-

Pathological classification

WHO 4 th ed		WHO 5 th 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	Splenic diffuse red pulp small B-cell lymphoma	Splenic B-cell lymphoma/leukemia, unclassifiable	Splenic diffuse red pulp small B-cell lymphoma
	Hairy cell leukemia-variant	Splenic B cell lymphoma/leukemia with prominent nucleoli (<i>encompassing HCL-v and some cases of B-cell PLL</i>)		Hairy cell leukemia-variant

Clinical presentation

EMZL

- Site-specific symptoms

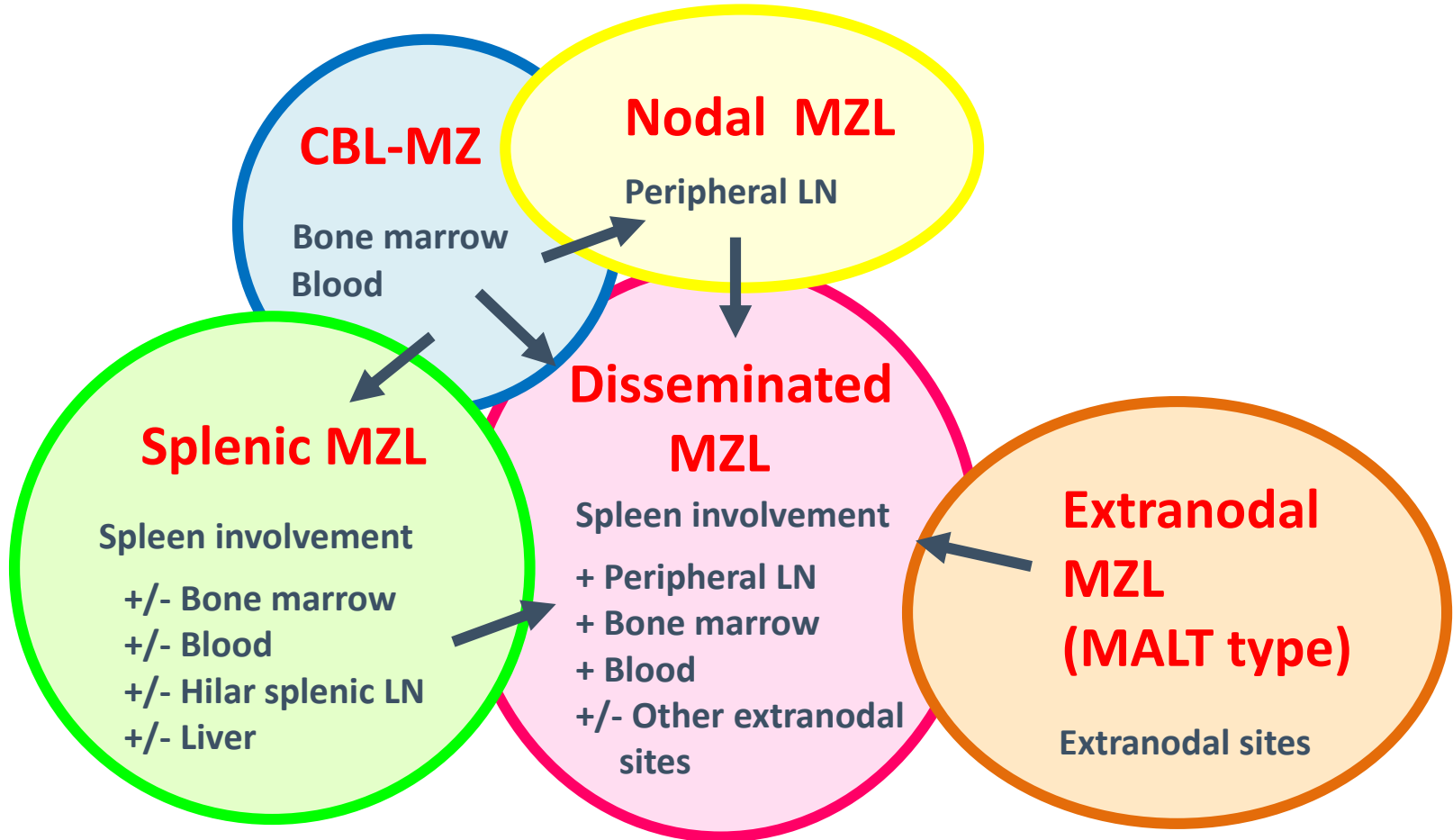
NMZL

- 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

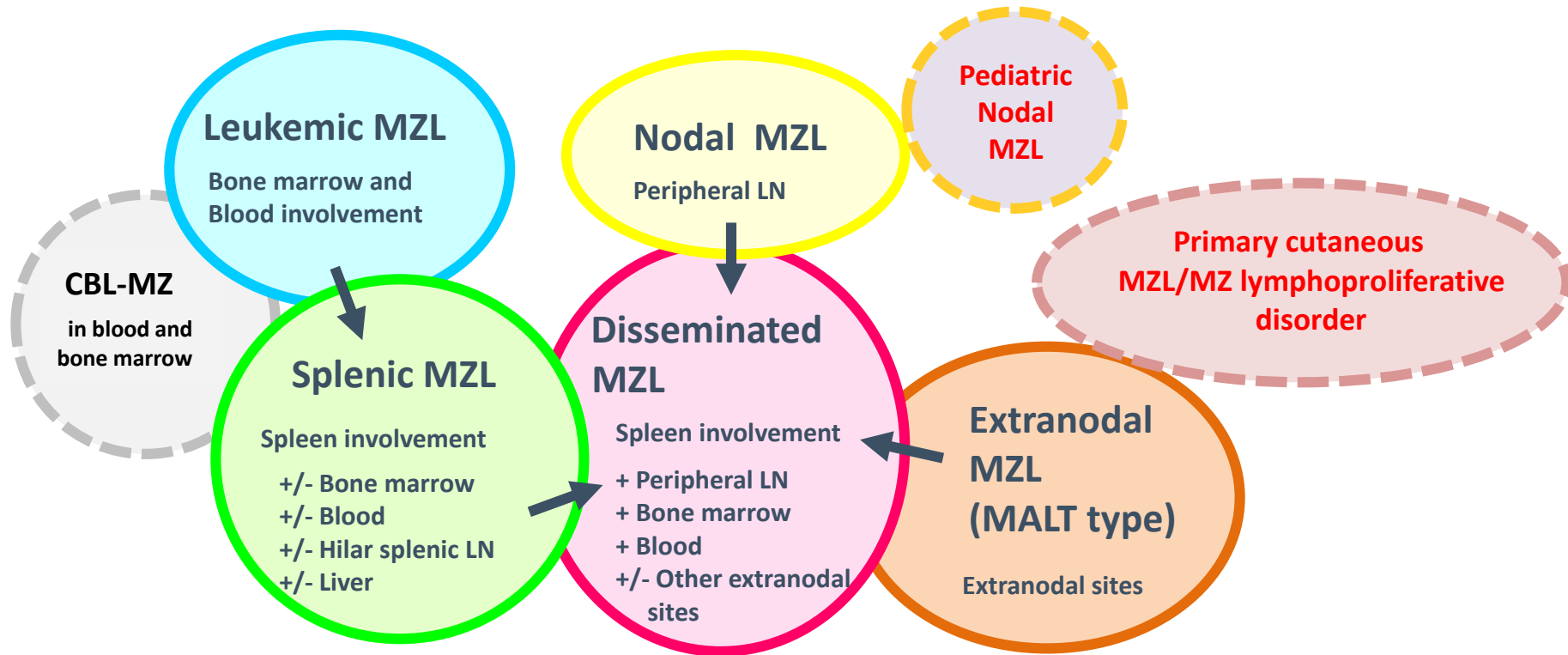
- Median age 67 years, usually no B symptoms, good PS
- Splenomegaly, leukemic picture
- Cytopenias to hypersplenism and BM infiltration
- Splenic hilar LNs in 25%
- AIHA, ITP and AID

MZL for clinicians: a continuum of related entities



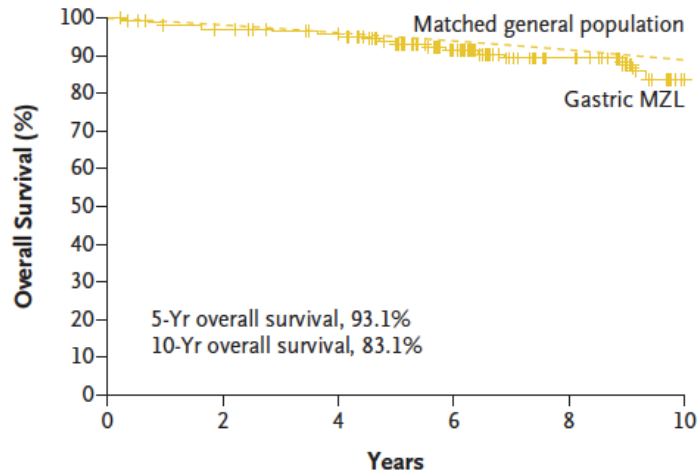
MZL a group of related clinical entities

differential diagnosis not always straightforward

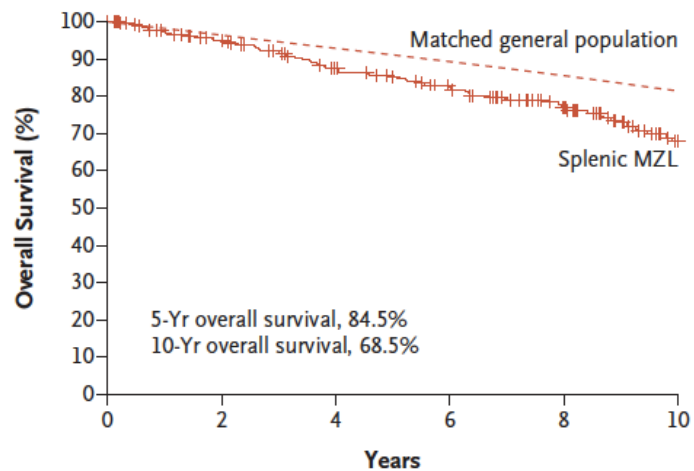


How I/we identify high-risk marginal zone lymphoma

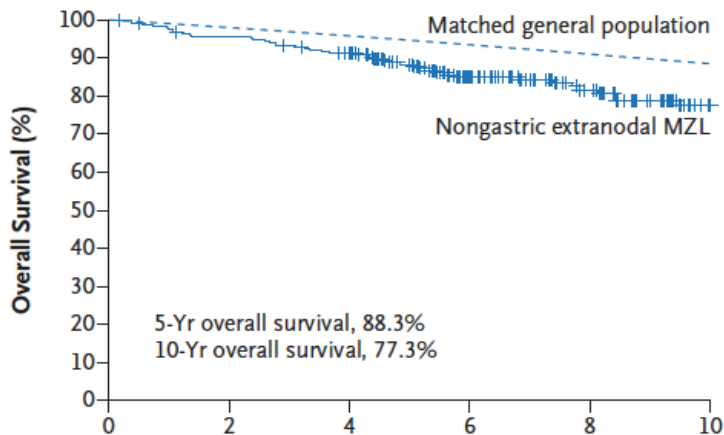
Gastric MZL



Splenic MZL



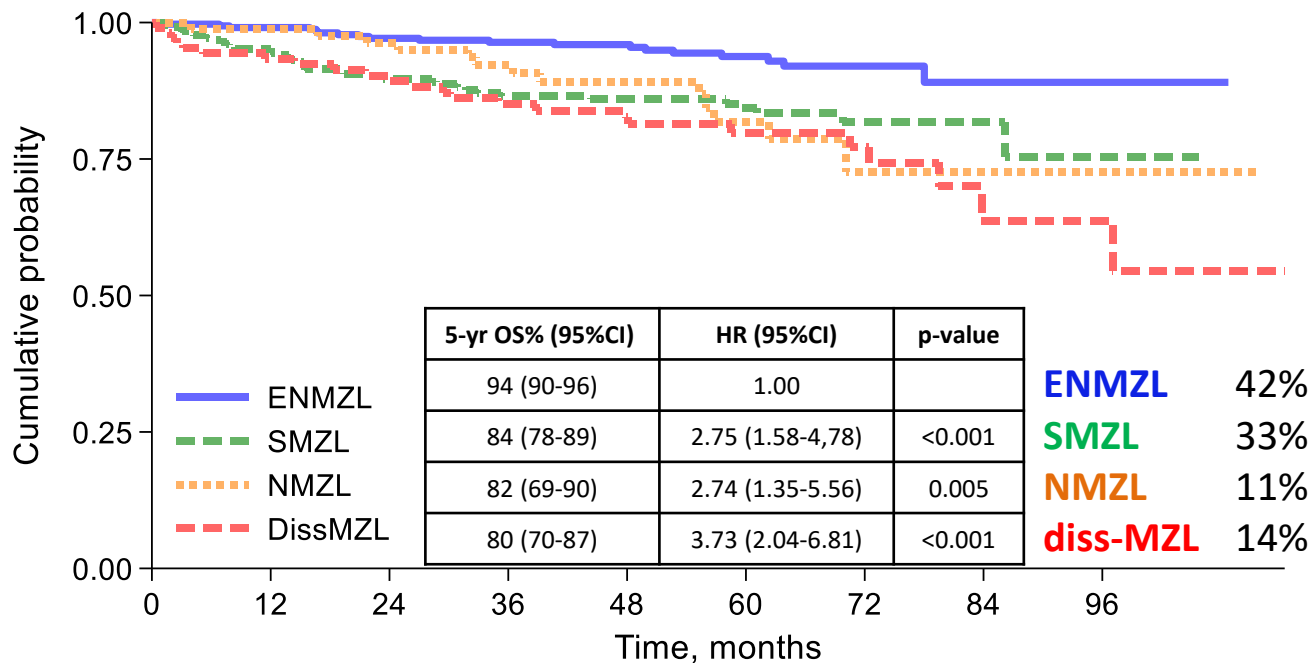
Nongastric Extranodal MZL



Overall survival

NF10: a prospective observational study

OS



at risk

EN	331	316	278	253	191	135	54	18	9
S	257	225	197	160	123	94	43	14	4
N	84	80	76	61	48	30	11	6	2
Dis	107	96	86	77	65	49	28	10	7

Prognostic assessment in MZL

SMZL

- IIL score
- HPLL score
- HPLLs score

Arcaini et al. Blood 2006

Montalban et al. BJH 2012

Montalban et al. Leukemia 2014

NMZL

- FLIPI?

Arcaini et al. BJH 2007

EMZL

- MALT-IPI
- MALT-IPI-B
- rMALT-IPI
- MALT-IPI-P

Thieblemont et al. Blood 2017

Kim et al. BJH 2020

Alderuccio et al. AJH 2022

Ren et al. BJH 2022

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

MALT-IPI (IELSG19)

Variables

Age > 70 y

Elevated LDH

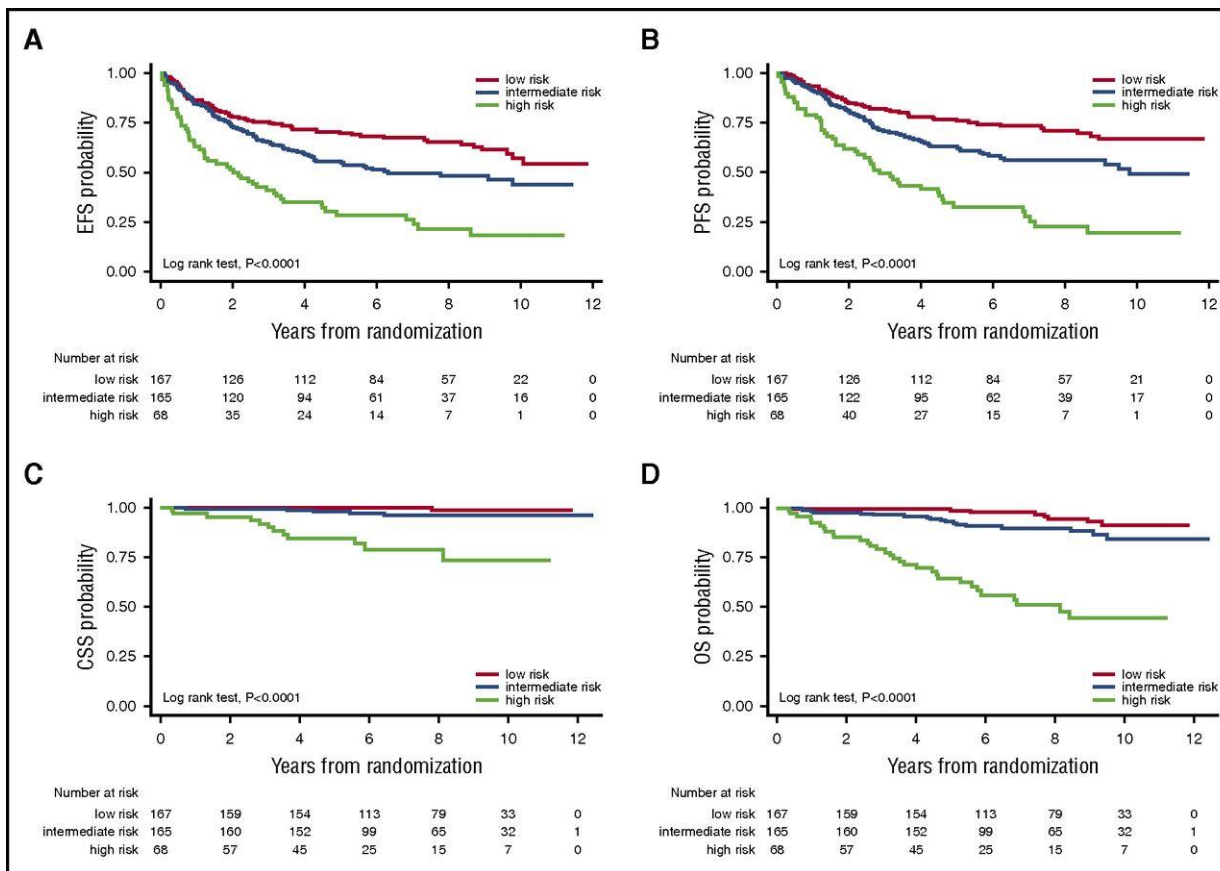
Ann Arbor III-IV

5-y EFS

0	70%
1	56%
2-3	29%

Thieblemont et al. Blood 2017

MALT-IPI



Variables

Age > 70 y

Elevated LDH

Ann Arbor III-IV

MALT-IPI vs revised MALT-IPI

MALT-IPI

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

5-y EFS

0	70%
1	56%
2-3	29%

Age 60 vs. 70 yrs¹
Multiple mucosal sites² (no BM, spleen
and bilateral involvement)

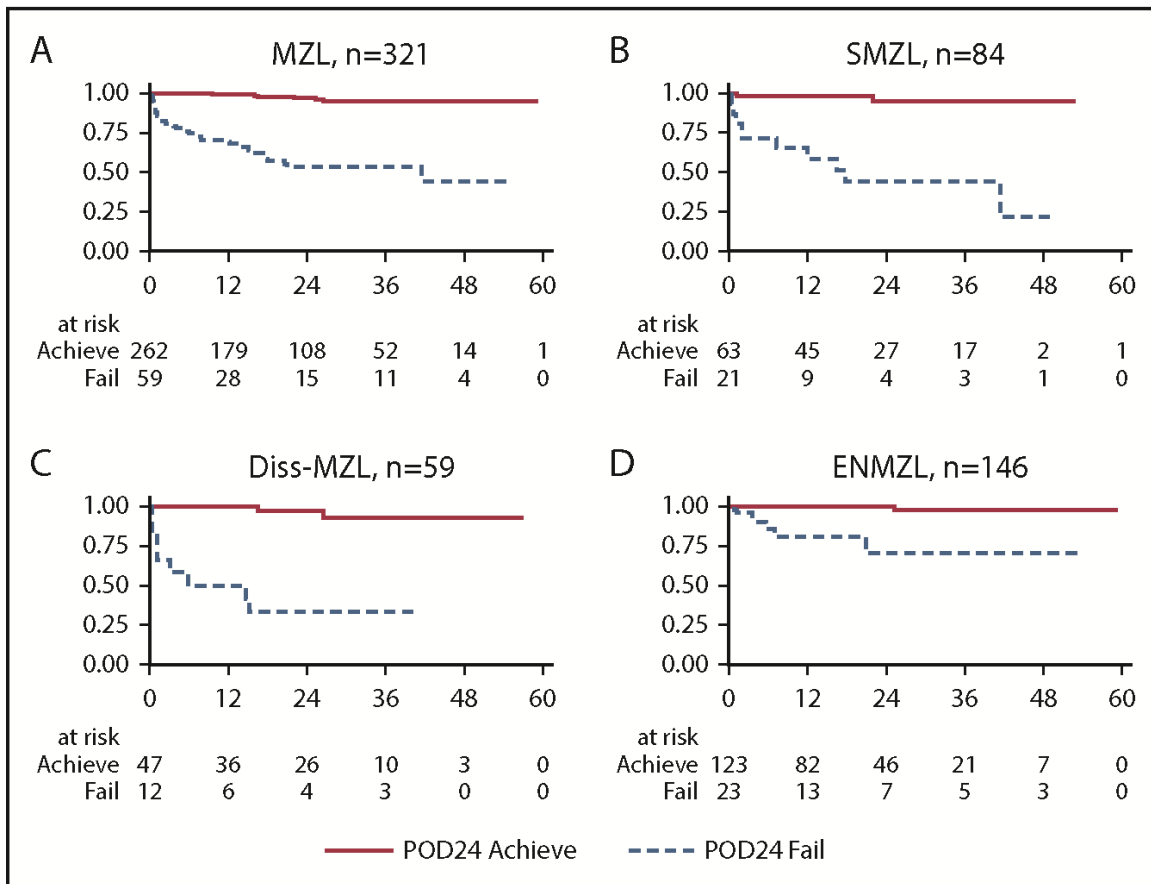
rMALT-IPI

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

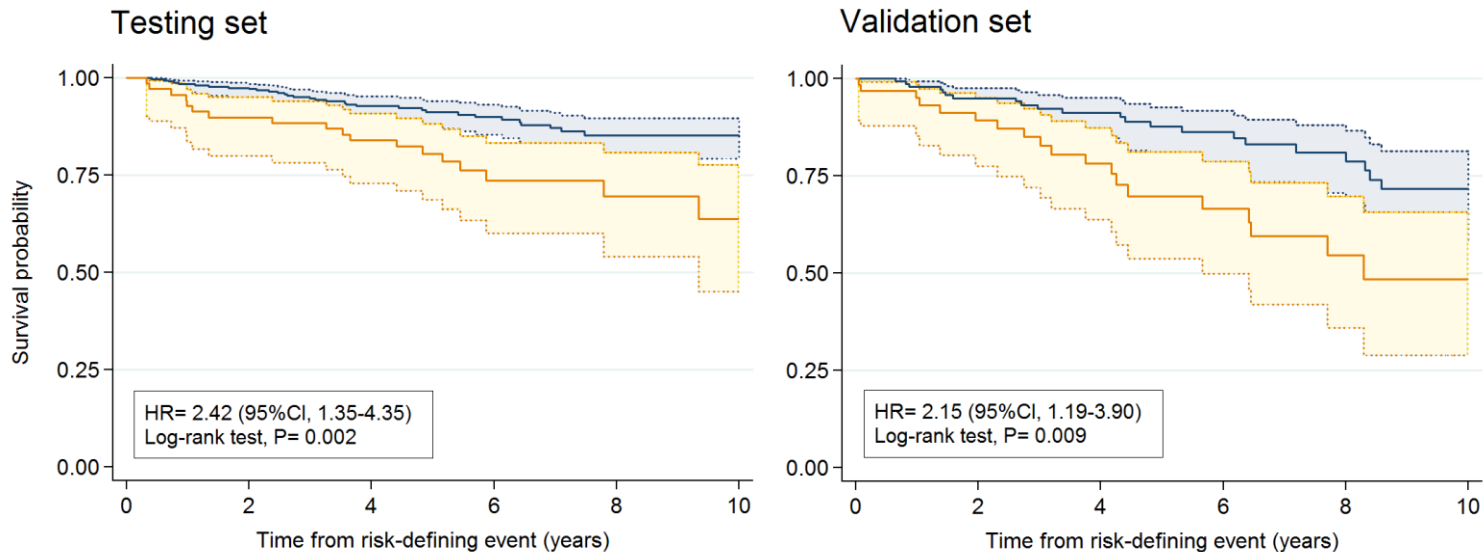
mPFS

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

POD24 in marginal zone lymphomas



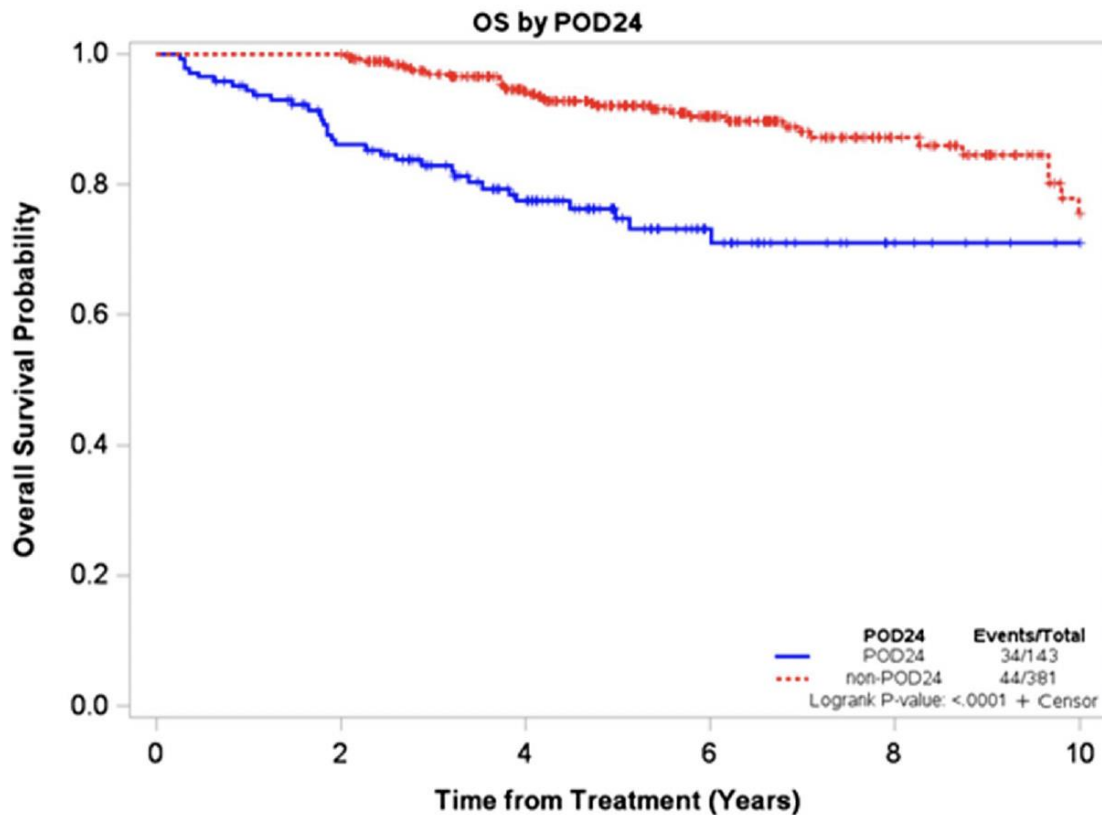
Impact of POD24 on MALT lymphoma survival



Number at risk

	0	2	4	6	8	10	0	2	4	6	8	10
— Early POD = No	315	298	211	142	64	1	160	121	84	55	36	25
— Early POD = Yes	69	62	54	26	17	8	64	44	31	20	9	6

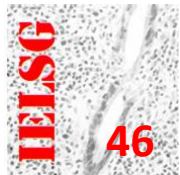
US multisite study



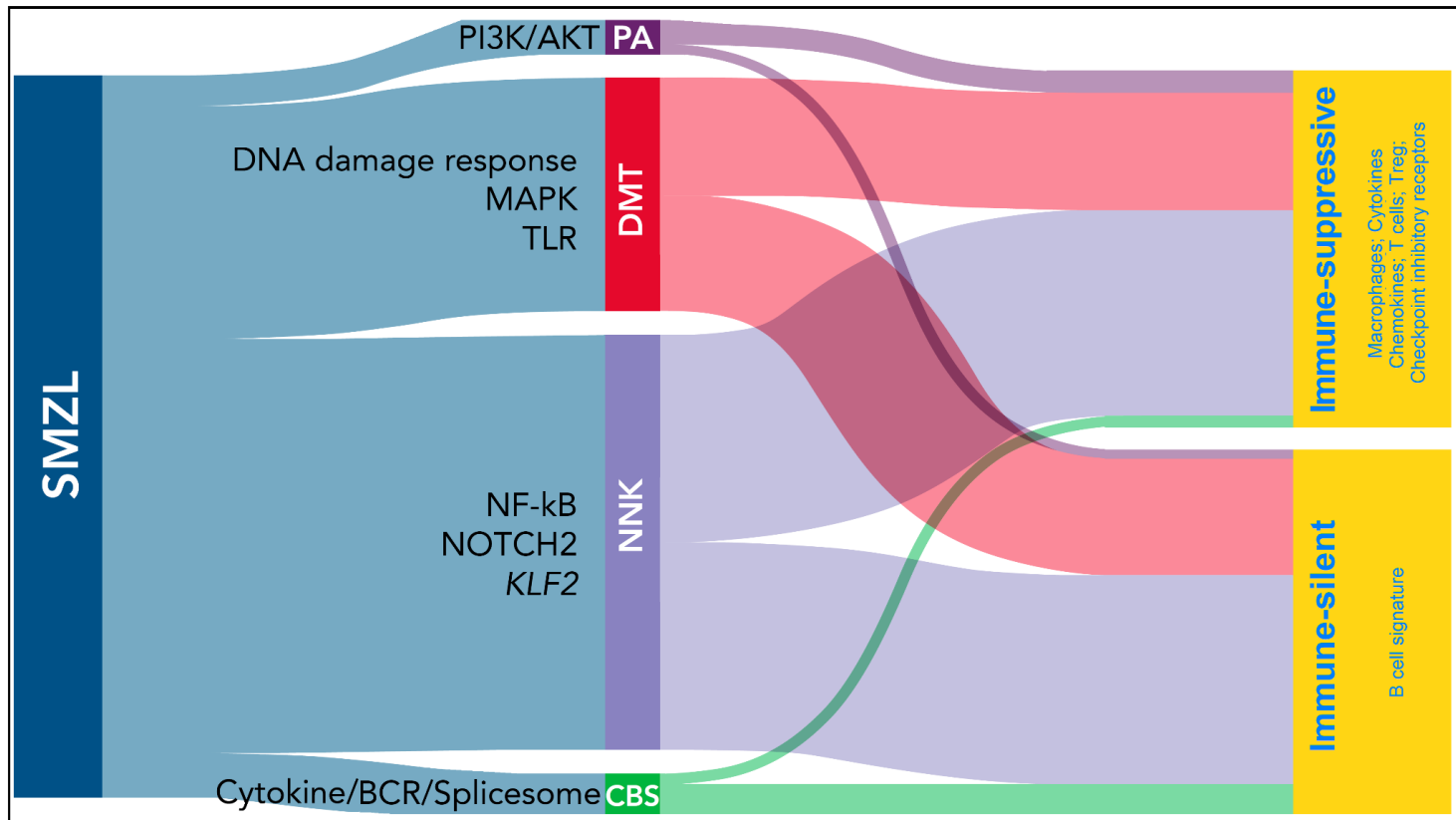
MC at dg and those who received first-line R → POD24 on logistic regression analysis

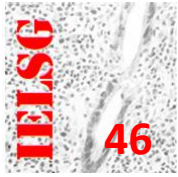
Pts with POD24 had a significantly higher risk for HT

	0	2	4	6	8	10
POD24	143	113	78	34	17	10
non-POD24	381	381	266	148	71	32
		Patients-at-Risk				



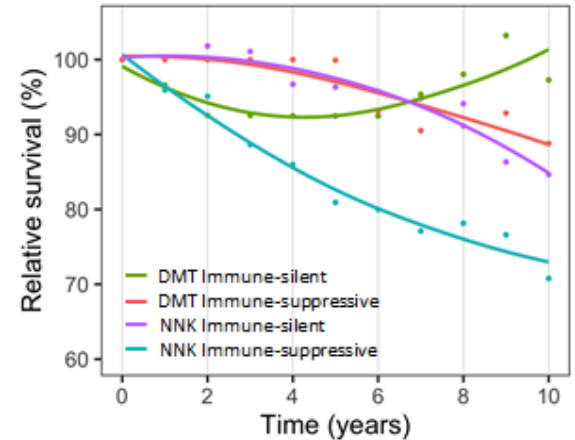
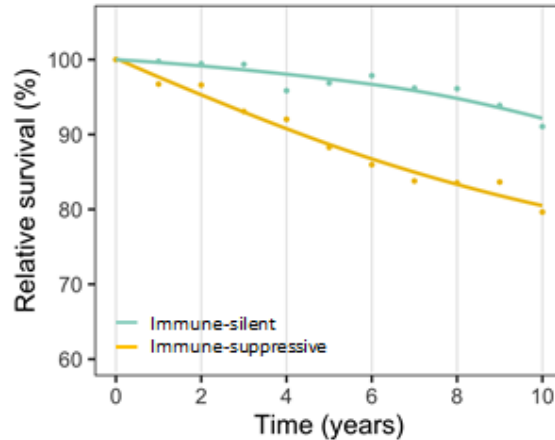
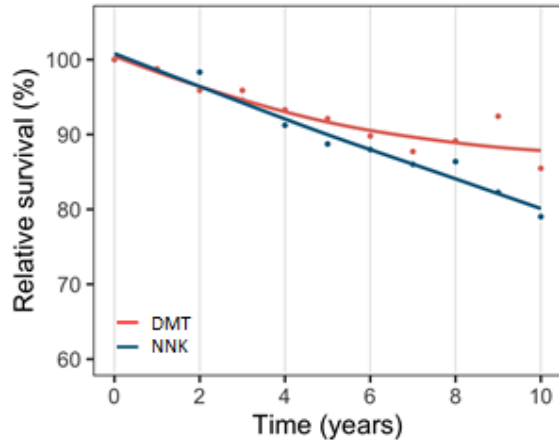
A new taxonomy for SMZL





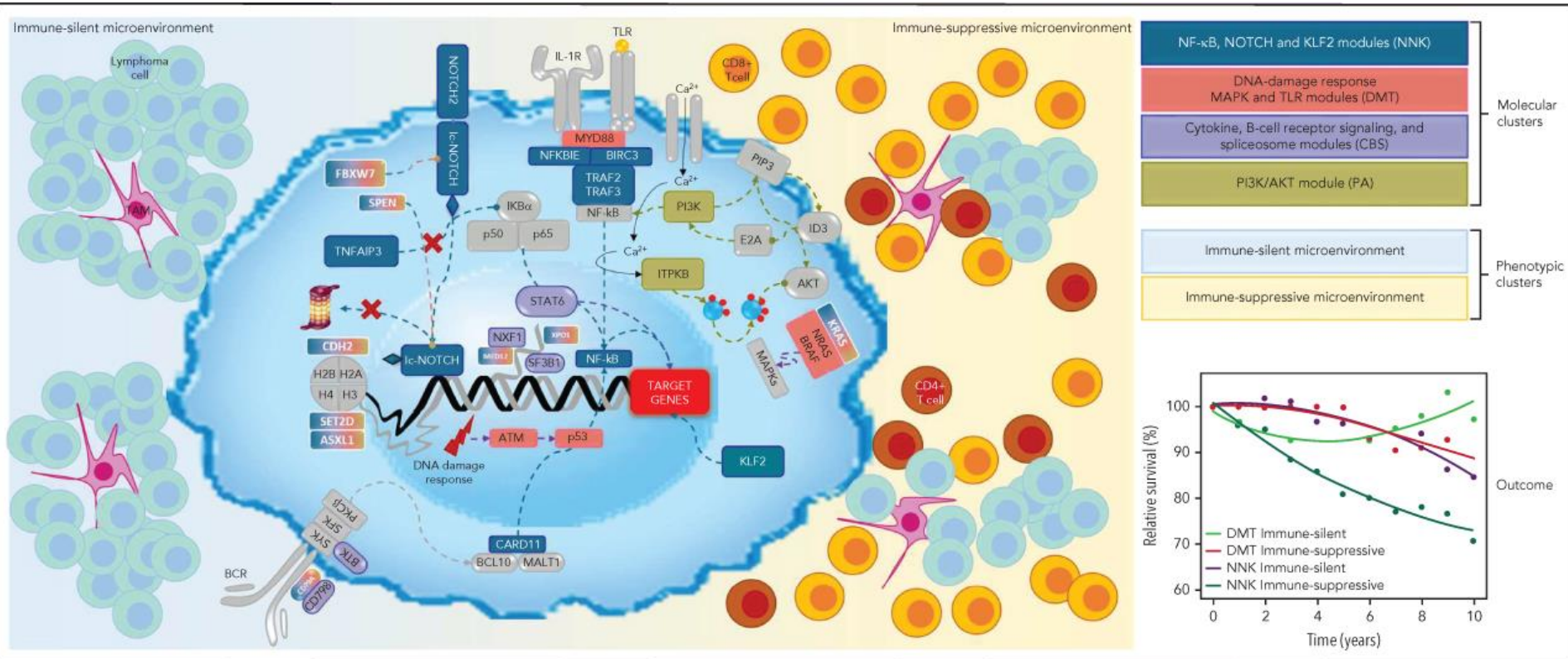
A new SMZL taxonomy

integrating molecular and clinical profiling



- 2 main genetic clusters:**
- **NNK** (~60%, mutations of NF- κ B, NOTCH and KLF2)
 - **DMT** (~30%, mutations affecting DNA damage response, MAPK and TLR)
- 2 microenvironment classes:**
- **Immune-suppressive** (50%)
 - **Immune-silent** (50%)

Molecular and phenotypic clusters



A prognostic score for entire spectrum of MZL ?

**Marginal Zone Lymphoma International Prognostic Index
(MZL-IPI): a prognostic score for the entire spectrum of
marginal zone lymphomas.
A FIL and SPORE-MER study**



The NF10 study by FIL

- Prospective observational study to investigate the prognosis of Indolent Non-Follicular B-Cell Lymphomas (INFL).
- Adult patients with biopsy-proven INFL
 - **SMZL** (bone marrow and/or splenic histology)
 - **ENMZL** (tissue biopsy)
 - **NMZL** (lymph node biopsy)
 - **Lymphocytic lymphoma** (lymph node biopsy)
 - **Lymphoplasmacytic lymphoma** (bone marrow histology or lymph node biopsy)
 - **CD5-negative leukemia** (bone marrow histology)
- No exclusion criteria
- Started in 2010;
- 47 active centers in Europe and South America
- 1340 patients eligible based on local pathology report



Study coordinators S. Luminari L. Arcaini

Study aims and design

Study aim: to identify and validate a prognostic model for patients with MZLs identified from the prospective NF10 study

Inclusion criteria

- Any MZL
- Adult age
- Start of systemic therapy (at diagnosis or after W&W)

Exclusion criteria

- Histology other than MZL
- Local treatment (RT)
- Antibiotics
- Observation without any systemic therapy

Main study endpoint: **Progression free survival (PFS)** calculated for all patients requiring systemic therapy from the date of treatment start to disease progression or death for any cause.

Definition of MZL subtypes in NF10

Histology of MZL required to entry in the dataset

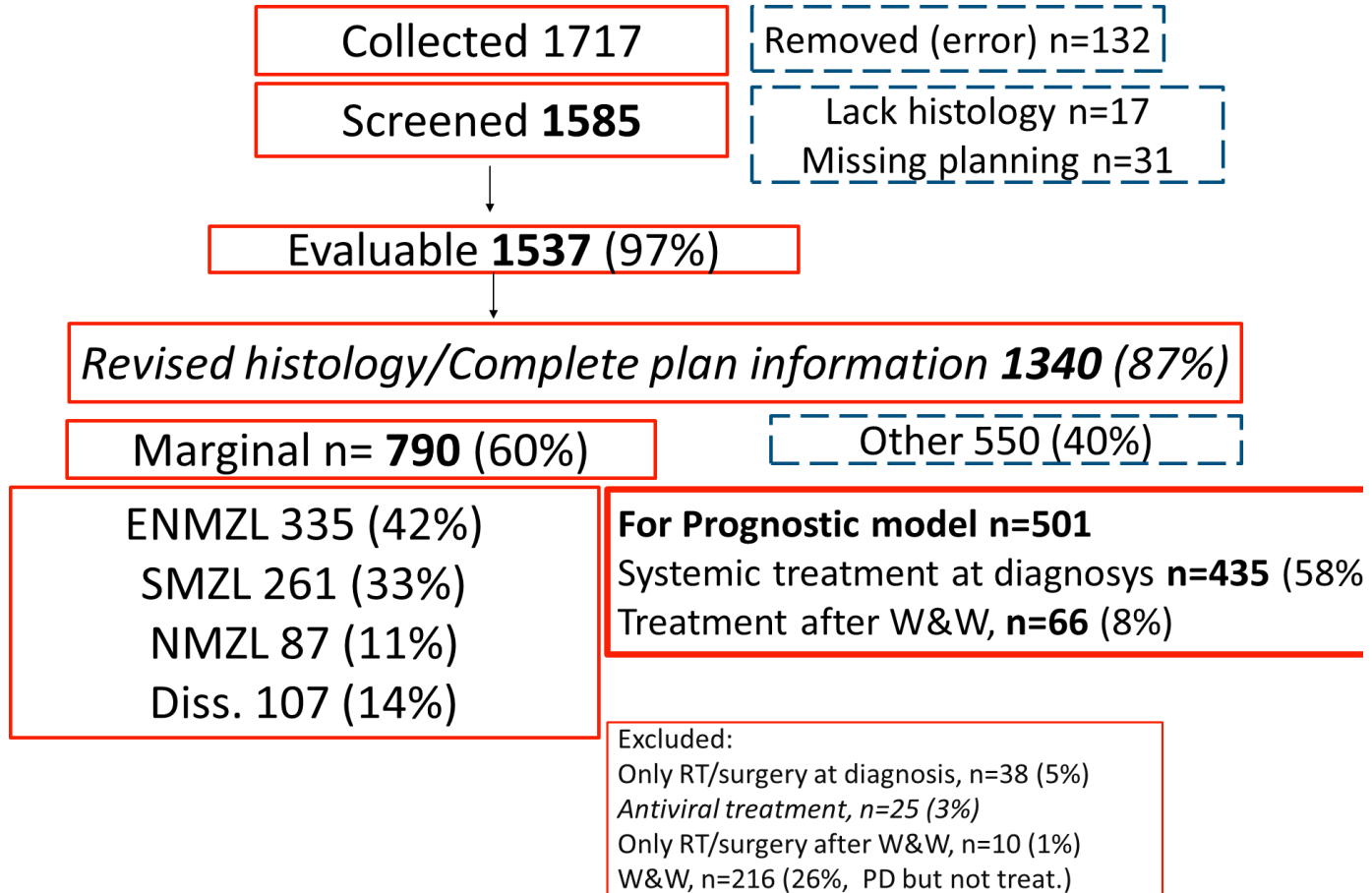
	Extranodal sites	Spleen*	LymphNodes***	Bone marrow	Peripheral blood**
ENMZL	Required (single or multiple sites)	NO	Only regional LN allowed	Allowed	NO
SMZL	NO	Required*	Only splenic hilar LN	Allowed	Allowed
NMZL	NO	NO	Required	Allowed	NO
dissMZL	Allowed	Allowed	Allowed	Allowed	Allowed

*Splenic involvement defined in case of splenic biopsy and/or nodular involvement and/or splenic enlargement (>13 cm in max diameter)

** clonal B-lymphocytes with features (cytology and/or FLOWcy) consistent with MZL. Cases with only PB involvement but without splenic or nodal or LN involvement were excluded.

*** as per Cheson 2007 criteria

Patients' flow



Patient's characteristics and treatment details (n = 501)

Covariate	Status	Missing (n)	N	%
Age	>70		202	40
Sex	M	-	243	49
Stage	III-IV	8	398	81
Extranodal sites	>1	8	90	18
Nodal sites	>2	9	165	34
Symptoms	B	11	102	21
LDH	>UNL	18	154	32
ALC	<1 10 ⁹ /L	21	99	21
Hemoglobin	<12 g/dL	12	204	42
Platelets	<100 10 ⁹ /L	12	71	15
Treatment	At diagnosis	-	435	87
	From W&W		66	13
MZL subtype	ENMZL	-	197	39
	SMZL		166	33
	NMZL		60	12
	Diss.MZL		78	16

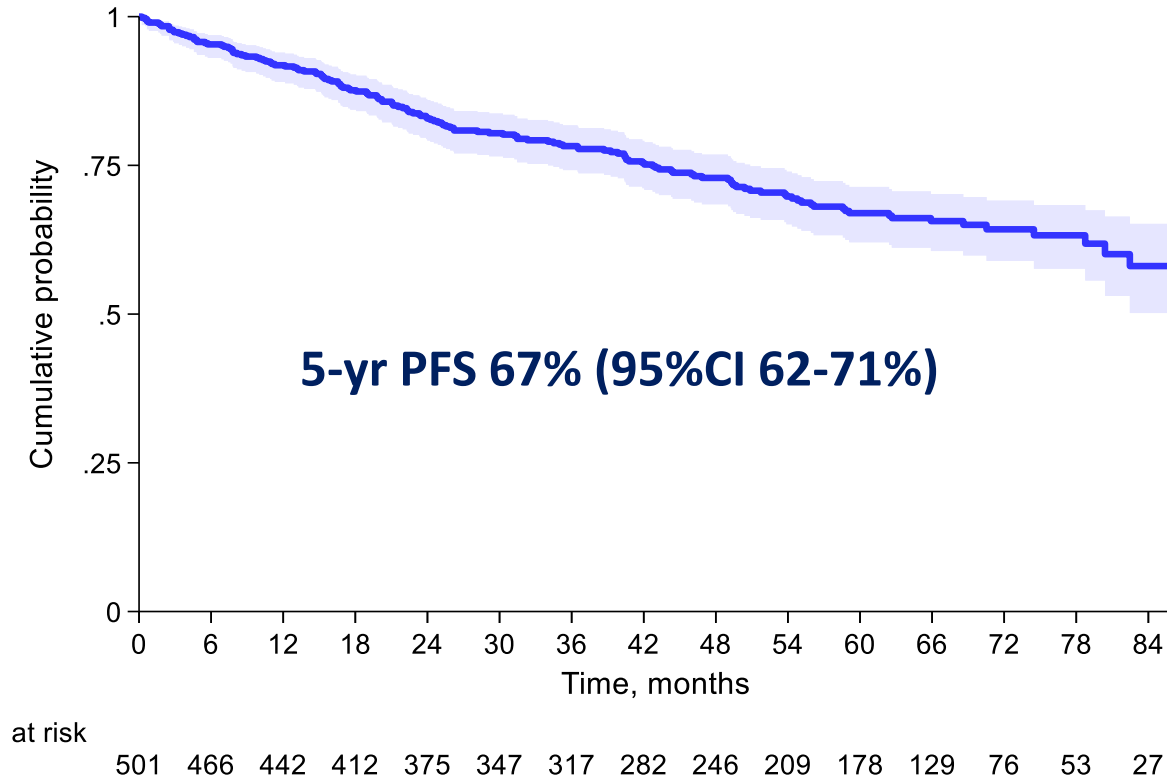
	At diagnosis	After W&W	Total
Treatment	n (%)	n (%)	n (%)
Mono-alkylating	29 (6.7)	4 (6.1)	33 (6.6)
Mono-rituximab	43 (9.9)	7 (10.6)	50 (10.0)
R-alkylating	118 (27.1)	3 (4.6)	121 (24.1)
R-CHOP like	59 (13.6)	10 (15.1)	69 (13.8)
R-bendamustine	179 (41.1)	29 (43.9)	208 (41.5)
R-fludarabine	4 (0.9)	5 (7.6)	9 (1.8)
Others	3 (0.7)	8 (12.1)	11 (2.2)
Total	435	66	501

Rituximab was used in: 91.2%
 Immunochemotherapy regimens were used in: 81.2%

Legend to table: LDH, Lactic Dehydrogenase; ALC, Absolute Lymphocyte counts; UNL, Upper Normal Limit; SMZL, Splenic Marginal Zone Lymphoma; ENMZL, Extranodal Marginal zone Lymphoma; NMZL, Nodal Marginal Zone Lymphoma; Diss, Disseminated; B2M beta2-microglobuline; LoDLIN, Longest diameter of largest lymphonode

Progression-free Survival from treatment start

N=501: Median follow up 61 mo (range 1-114) ; # events 150



Univariable analysis of PFS

Cases with complete details for 12 covariates (N=456, 138 events)

Covariate	Status	N (%) [#fail]	5yr-PFS % (95%CI)	Univariable	
Age	≤70	264 (58) [68]	73 (66-78)	1.00	
	>70	192 (42) [70]	58 (50-66)	1.71 (1.22-2.39)	0.002
Stage	I-II	92 (20) [16]	83 (72-89)	1.00	
	III-IV	364 (80) [122]	63 (57-68)	2.38 (1.41-4.01)	0.001
Nodal sites	0-2	304 (58) [80]	72 (66-77)	1.00	
	>2	152 (42) [58]	59 (49-67)	1.48 (1.06-2.08)	0.023
Symptoms	A	361 (79) [99]	70 (64-75)	1.00	
	B	95 (21) [39]	55 (43-65)	1.69 (1.17-2.45)	0.005
LDH	≤UNL	313 (69) [79]	73 (67-78)	1.00	
	>UNL	143 (31) [59]	53 (43-62)	2.00 (1.43-2.80)	<0.001
ALC	≥1 10 ⁹ /L	367 (80) [101]	71 (65-76)	1.00	
	<1 10 ⁹ /L	89 (20) [37]	51 (38-62)	1.76 (1.20-2.56)	0.003
Hemoglobin	≥12 g/dL	270 (59) [66]	74 (68-80)	1.00	
	<12 g/dL	186 (41) [72]	56 (47-63)	1.95 (1.39-2.72)	<0.001
Platelets	≥100 10 ⁹ /L	394 (86) [111]	70 (65-75)	1.00	
	<100 10 ⁹ /L	62 (14) [27]	45 (29-60)	2.29 (1.50-3.51)	<0.001
MZL subtype	SMZL/ENMZL	329 (72) [84]	71 (66-76)	1.00	
	NMZL/Diss.	127 (39) [54]	56 (46-65)	1.67 (1.19-2.36)	0.003

Covariates without correlation with PFS: **Sex, # Extranodal sites, W&W** vs immediate therapy

Legend to table: LDH, Lactic Dehydrogenase; ALC, Absolute Lymphocyte counts; UNL, Upper Normal Limit; SMZL, Splenic Marginal Zone Lymphoma; ENMZL, Extranodal Marginal zone Lymphoma; NMZL, Nodal Marginal Zone Lymphoma; Diss, Disseminated; B2m beta2-microglobuline; LoDLIN, Longest diameter of largest lymph node

Multivariable analysis of PFS

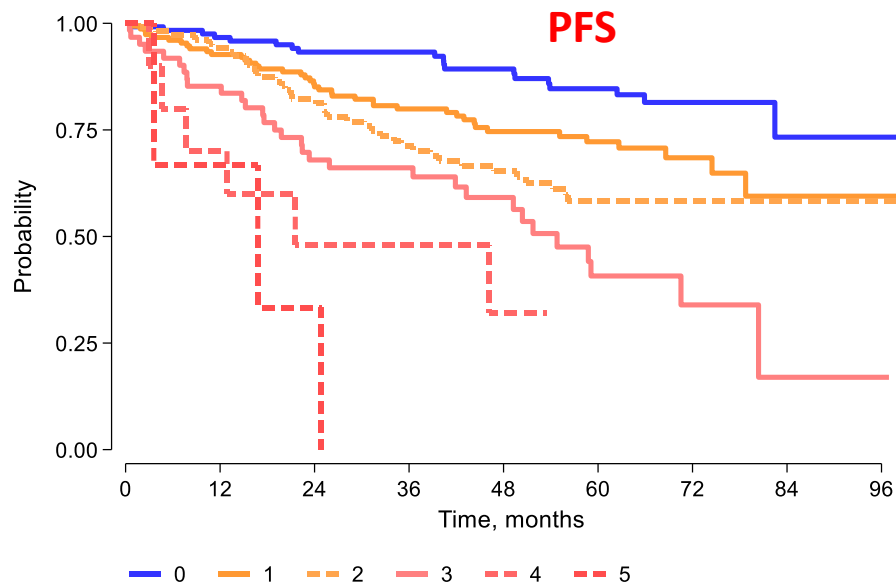
Cases with complete details for 12 covariates (N=456, 138 events)

Covariate	Status	Multivariable		Final model	
		HR (95%CI)	P	HR (95%CI)	P
Age	>70	1.40 (0.98-1.99)	0.061		
Stage	III-IV	1.78 (0.97-3.30)	0.064		
Extranodal sites	>1	0.77 (0.48-1.26)	0.305		
Nodal sites	>2	1.06 (0.72-1.55)	0.781		
Symptoms	B	1.38 (0.93-2.04)	0.110		
LDH	>UNL	1.54 (1.06-2.25)	0.025	1.60 (1.12-2.30)	0.011
ALC	<1 10 ⁹ /L	1.58 (1.07-2.35)	0.022	1.72 (1.17-2.53)	0.006
Hemoglobin	<12 g/dL	1.36 (0.92-2.01)	0.122	1.61 (1.13-2.30)	0.009
Platelets	<100 10 ⁹ /L	1.88 (1.17-3.04)	0.009	1.86 (1.18-2.92)	0.007
MZL subtype	ENMZL	1.00			
	SMZL	0.75 (0.43-1.33)	0.330	Ref. EN/S-MZL	
	NMZL/Diss.	1.46 (0.99-2.16)	0.059	1.66 (1.17-2.36)	0.004
	AIC	1543.4		1540.4	
				LR test (df 5)	0.171

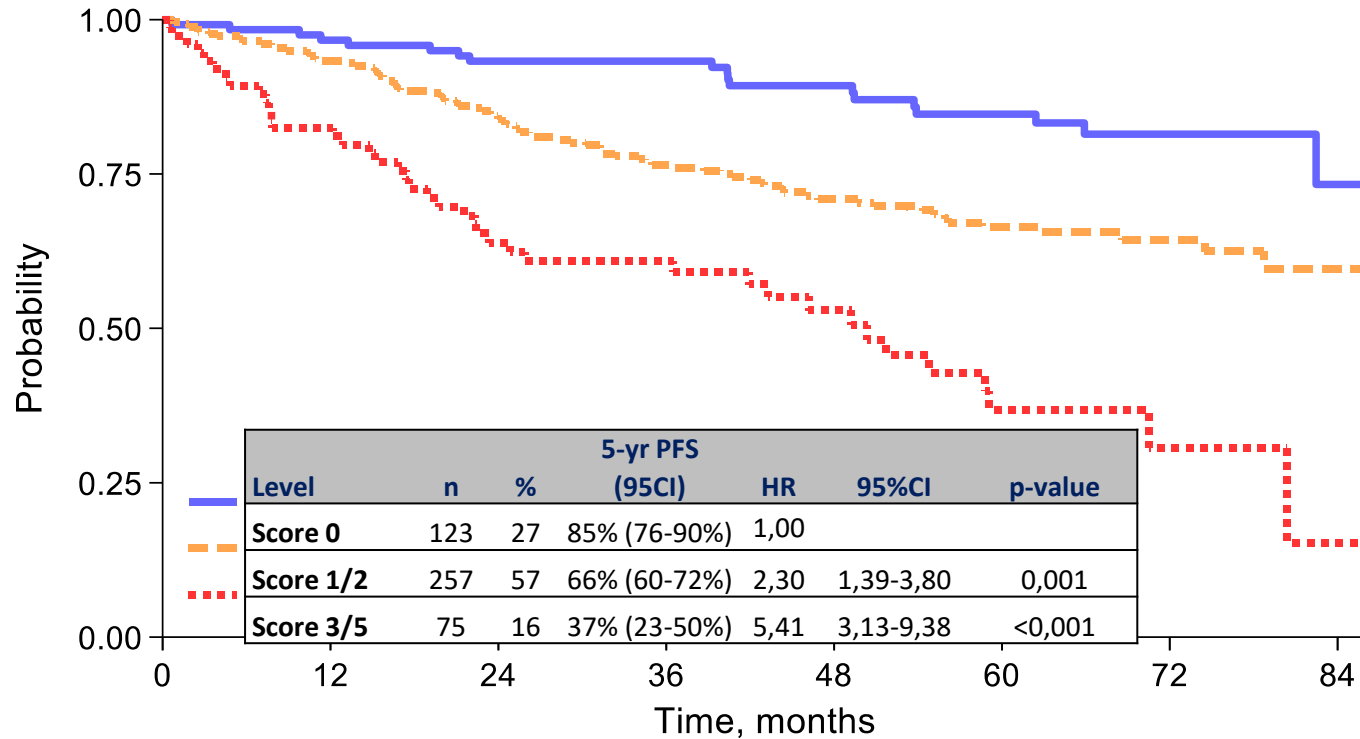
Legend to table: LDH, Lactic Dehydrogenase; ALC, Absolute Lymphocyte counts; UNL, Upper Normal Limit, NMZL, Nodal Marginal Zone Lymphoma; Diss, Disseminated

Building of the Marginal Zone Lymphoma International Prognostic Index (MZL-IPI)

Score level	N (%) [#fail]	5-yr PFS% (95%CI)
0	123 (27) [19]	85 (76-90)
1	151 (33) [41]	72 (63-79)
2	107 (23) [38]	58 (47-68)
3	61 (13) [31]	41 (26-55)
4	11 (2) [6]	NA
5	3 (1) [3]	NA
Total	456	-

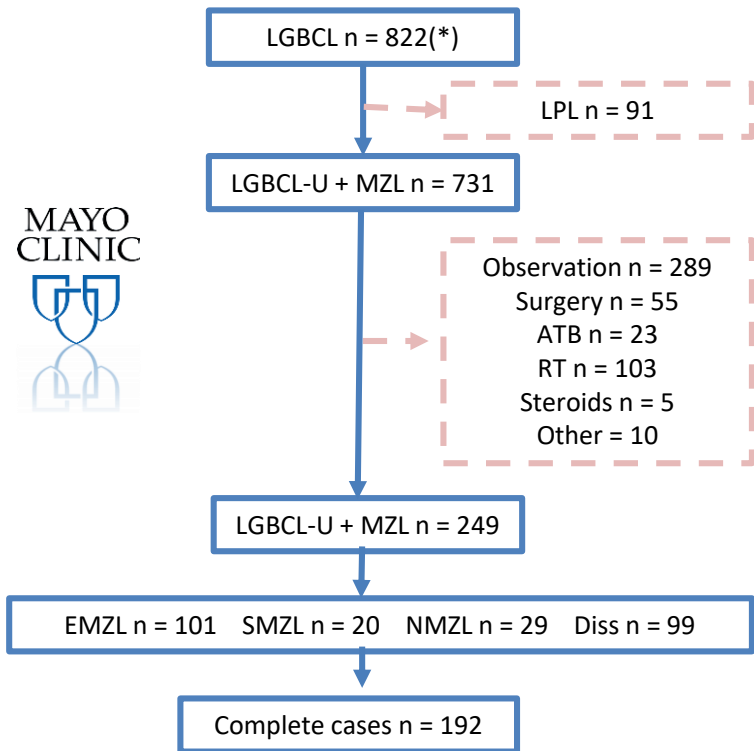


PFS according to MZL-IPI groups



Building of the independent validation set

A Spore/MER database of MZLs



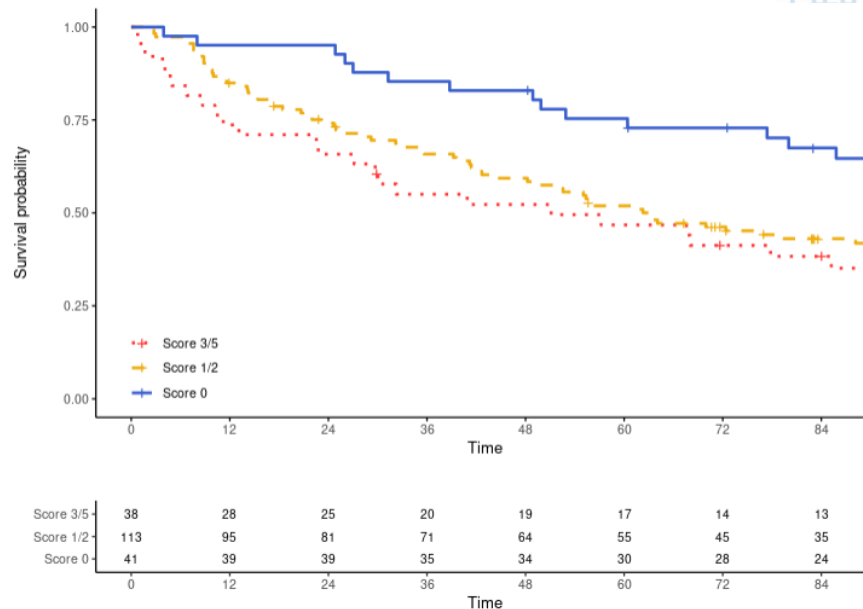
Covariate	Status	Missing (n)	N	%
Age	>70		73	29
Sex	M		120	48
Stage	III-IV	5	183	75
Extranodal sites	>1		75	30
Nodal sites	>4	2	13	13
Symptoms	B		39	16
LDH	>UNL	43	45	22
ALC	<1 10 ⁹ /L	31	57	26
Hemoglobin	<12 g/dL	33	95	44
Platelets	<100 10 ⁹ /L	17	23	10
MZL subtype	SMZL/ENMZL	-	121	49
	NMZL/Diss.		128	51
Treatment	AntiCD20		99	40
	ImmunoCT		114	46
	Other		36	14

MZL-IPI validation on the SPORE/MER dataset

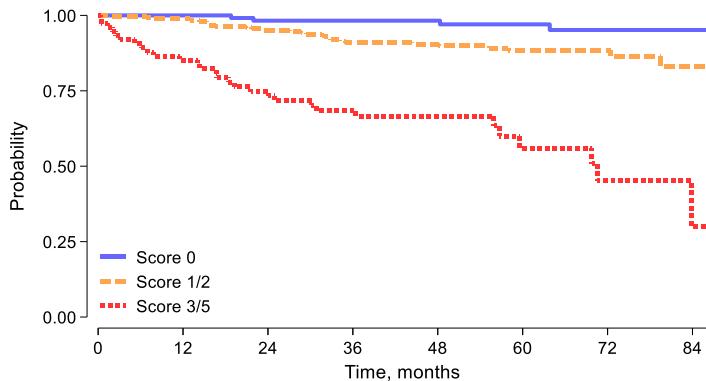


5-yr PFS 57% (95%CI 51% - 64%)

	Total	%	5-yr PFS% (95%CI)	HR (95% CI)	p
Low (0 RF)	41	21.3	75 (63-90)	1.00	
Int. (1-2 RF)	113	58.8	52 (43-62)	1.57 (0.97-2.54)	0.068
High (3-5 RF)	38	19.8	47 (33-66)	2.04 (1.15-3.62)	0.014



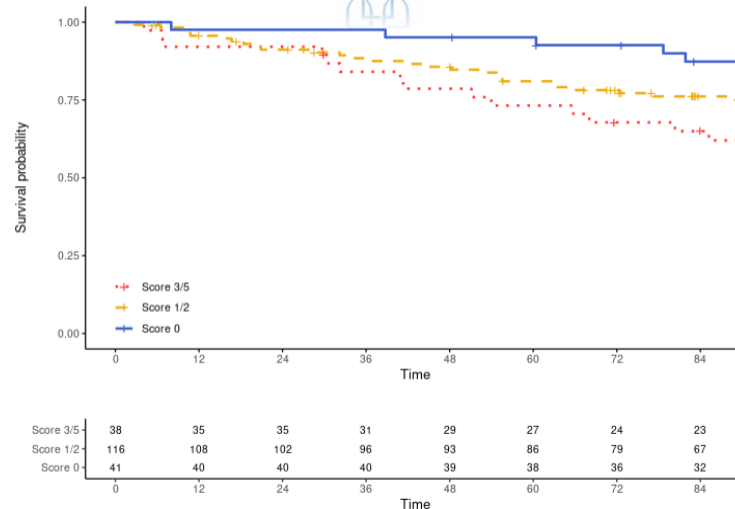
Prognostic role of MZL-IPI for Overall survival



at risk

Low	123	119	108	102	81	65	28	8
Int.	258	245	224	189	155	103	46	19
High	75	61	49	38	28	14	8	2

Score group	5-yr OS (95%CI)	HR (95%CI)	p
Low 0	97 (91-99)	1.00	
Intermediate 1-2	88 (83-92)	3.46 (1.21-9.89)	0.020
High 3/5	56 (40-69)	17.2 (6.04-49.0)	<0.001
High vs Interm.		4.97 (2.94-8.42)	<0.001

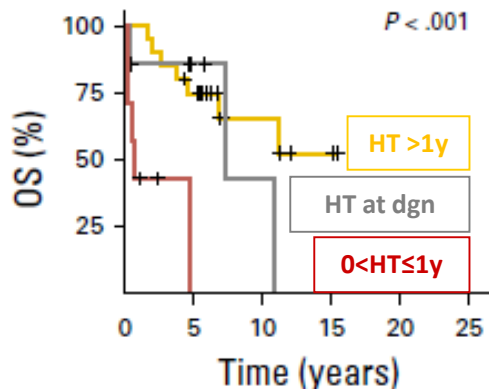
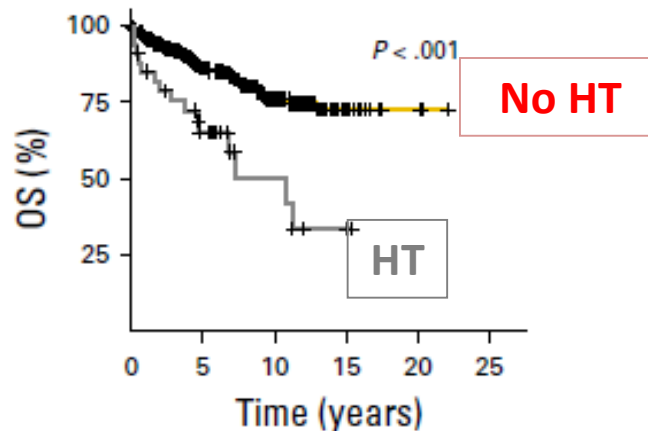
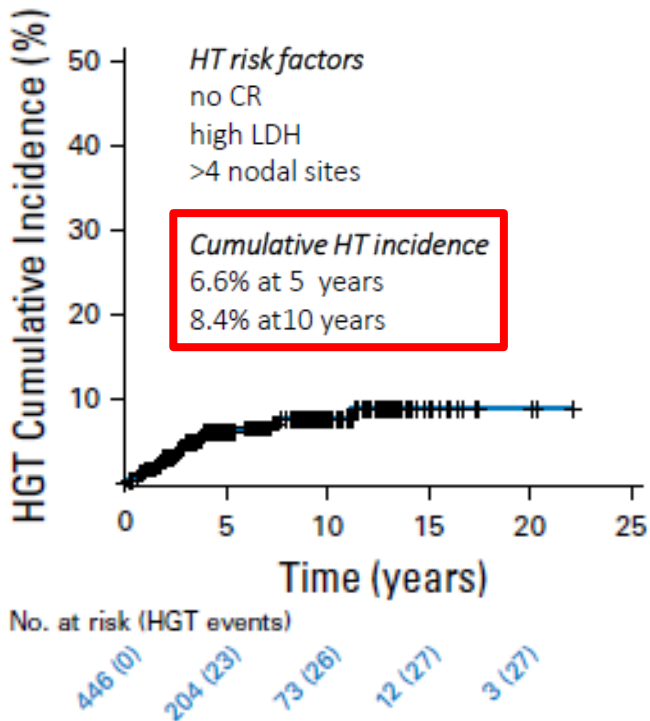


Score 3/5	38	35	35	31	29	27	24	23
Score 1/2	116	108	102	96	93	86	79	67
Score 0	41	40	40	40	39	38	36	32
	0	12	24	36	48	60	72	84

Score group	5-yr OS (95%CI)	HR (95%CI)	p
Low 0	95 (89-100)	1.00	
Intermediate 1-2	81 (74-89)	1.52 (0.77-3.01)	0.059
High 3/5	73 (60-89)	2.72 (1.29-5.74)	0.008
High vs Interm.		1.76 (1.007-3.085)	0.47

Histologic transformation of MZL

- 446 pts: 389 MALT, 29 NMZL, 35 SMZL



How we can treat (high-risk) marginal zone lymphoma

SMZL

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

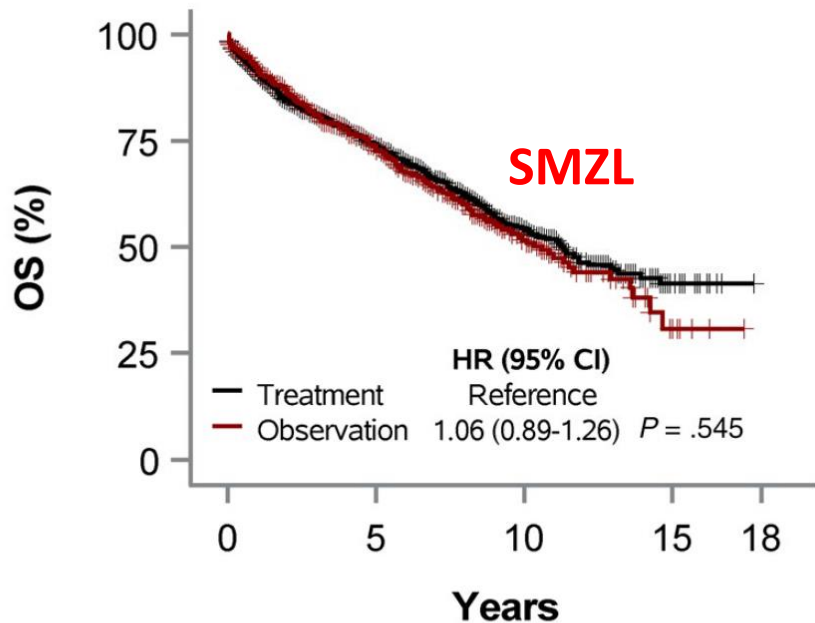
NMZL

- 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)

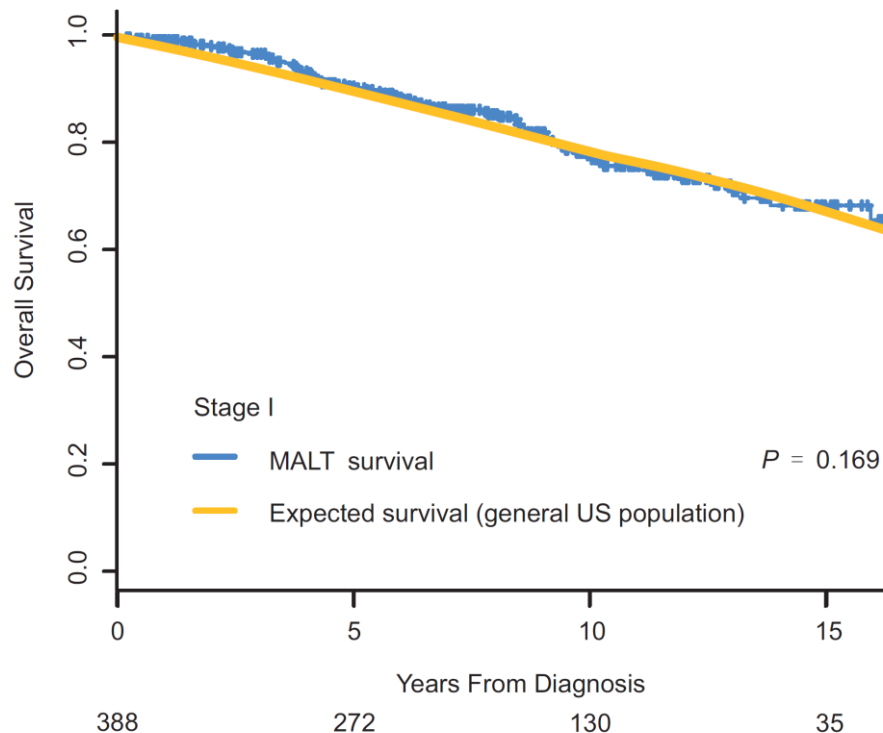
Active surveillance



No. at risk					
Treatment	1075	543	192	19	
Observation	596	225	75	7	

Florindez et al. Cancer 2020

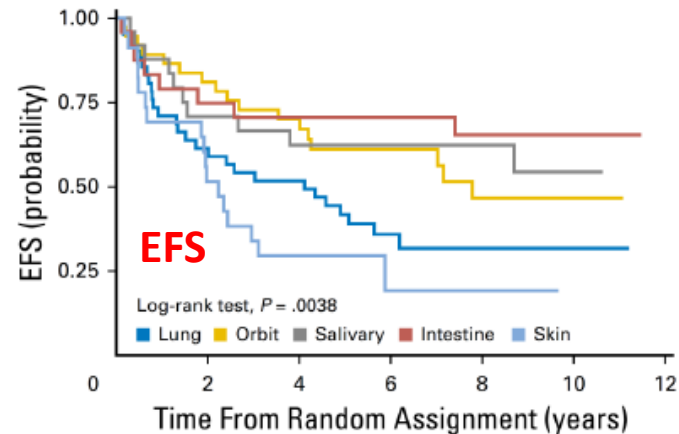
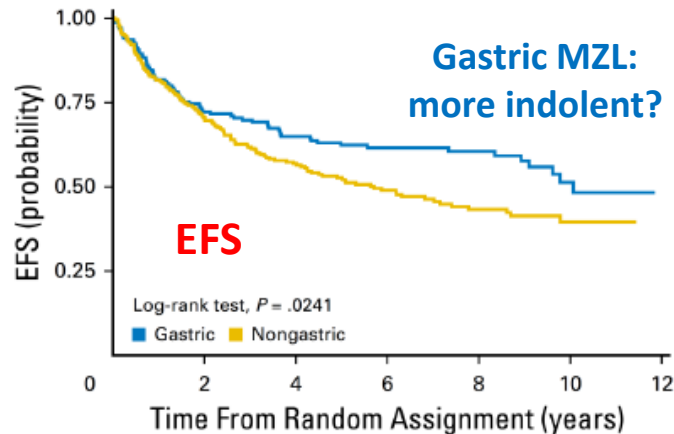
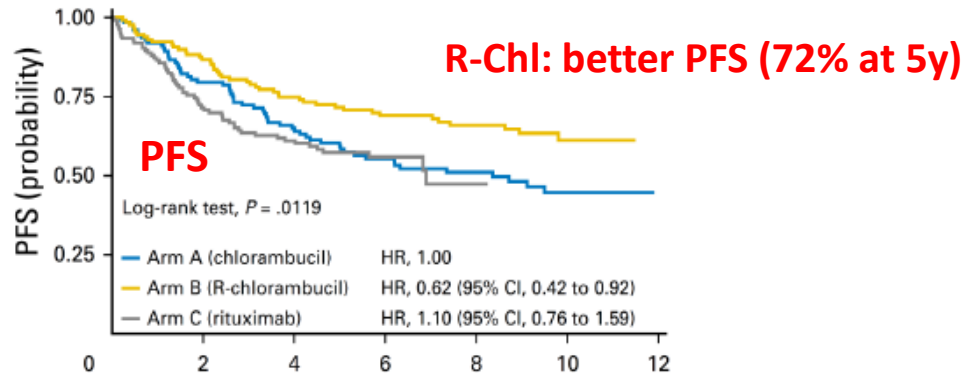
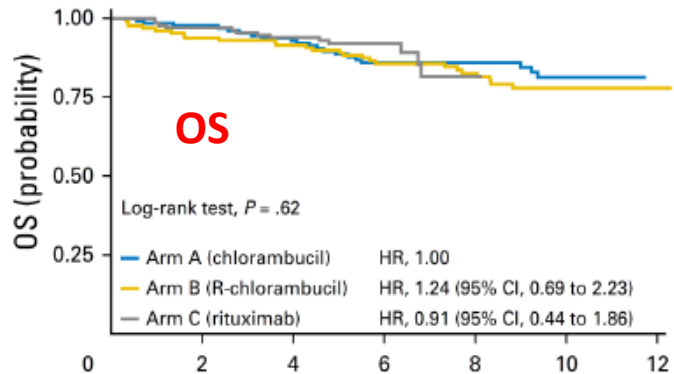
Outcome with local therapy



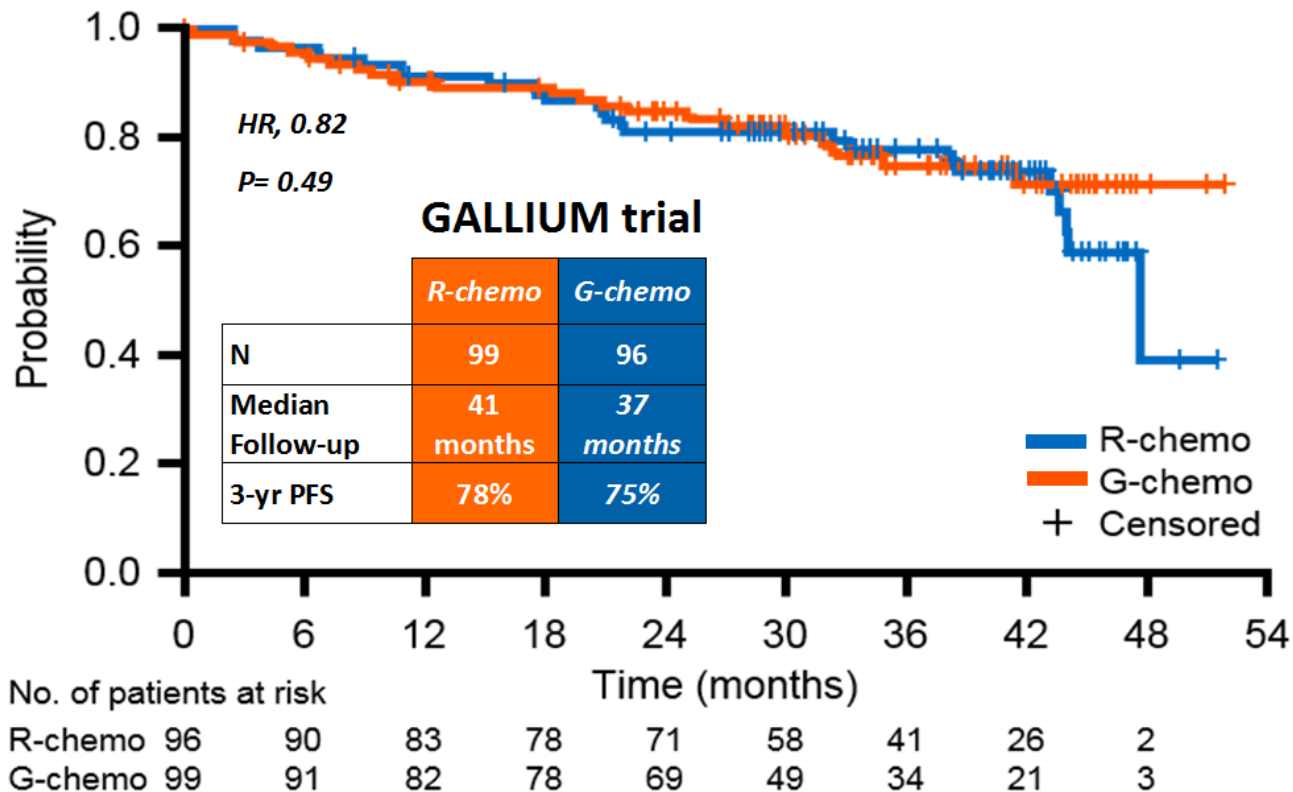
Qi et al. Blood Adv 2022

IELSG-19: randomized study in EMZL

- 401 pts: Chlorambucil (Arm A) vs R-Chlorambucil (B) vs Rituximab (C)



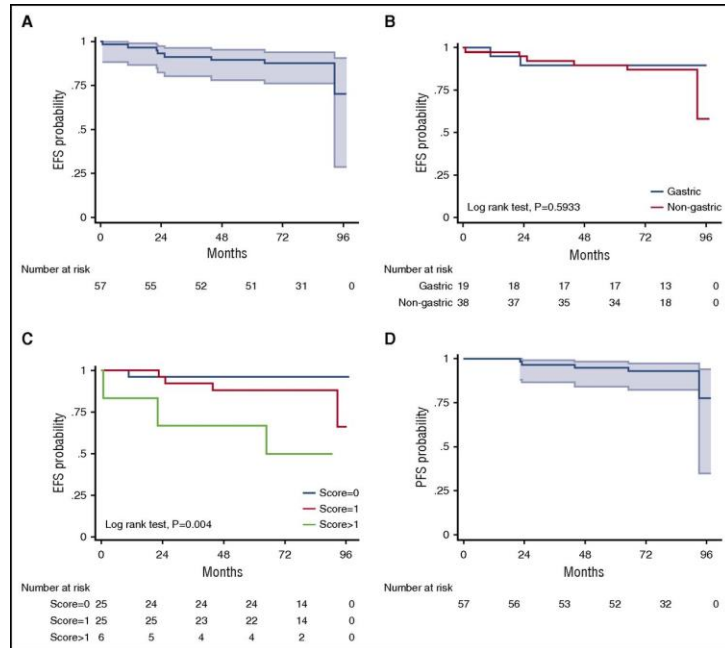
Immunochemotherapy with obinutuzumab or rituximab in patients with untreated MZL



BR as first-line therapy in EMZL



- GELTAMO phase 2 study, R-Bendamustine as 1st-line therapy
- Resp-adapted: restaging after cycle 3: 4 BR cycles if CR, 6 BR cycles if PR



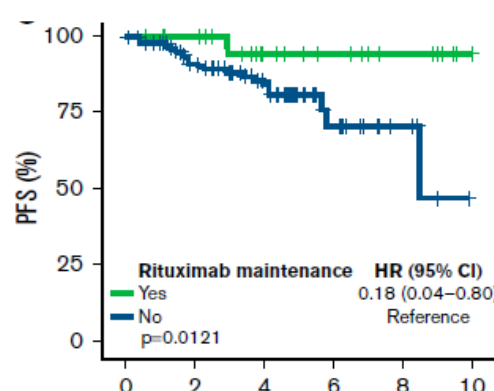
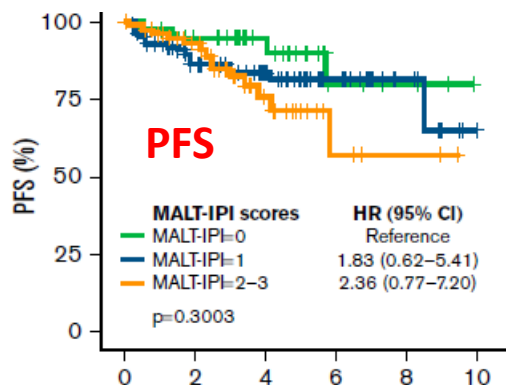
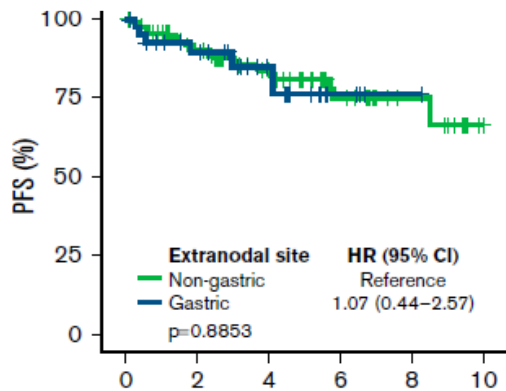
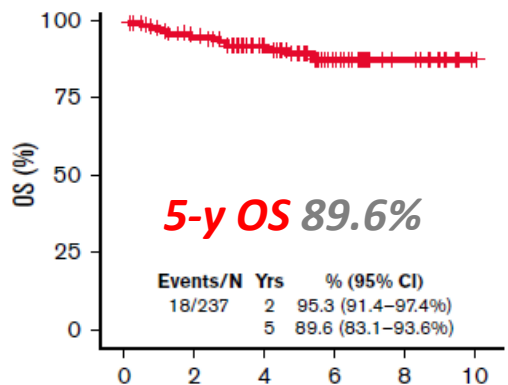
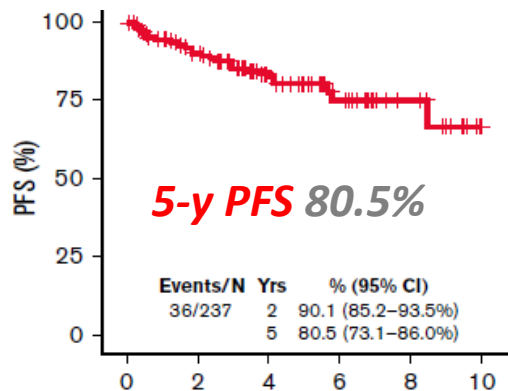
- 75% CR after 3 cycles → total **4 BR**
- Only 25% (PR after 4 cycles) received 6 BR
- **CR 98%**, PR 2%
- **7-y PFS 92.8%**, **7-y OS 96.5%**
- No EFS differences between gastric and non-gastric EZML

Outcome according to MALT-IPI (n = 57)

Number of risk factors	N (%)	EFS at 7 years, % (95% CI, %)	PFS at 7 years, % (95% CI, %)	OS at 7 years, % (95% CI, %)
0	25 (44.6)	96.0 (74.8-99.4)	100	96.0 (74.8-99.4)
1	25 (44.6)	88.0 (67.3-96.0)	91.8 (71.1-97.9)	96.0 (74.8-99.4)
>1	6 (10.7)	50.0 (11.1-80.4)	66.7 (19.5-90.4)	100
P (log rank)		.004	.049	.662

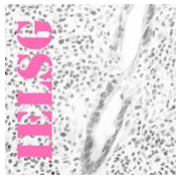
US-Italy retrospective study: BR in EMZL

- 237 pts, median age 63 y, stage III/IV 75%, MALT-IPI high risk 33%, Median 6 BR, 20% RM

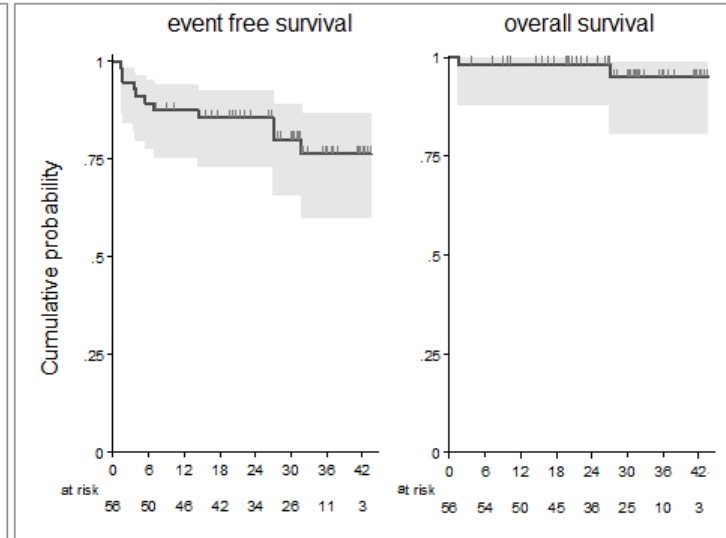
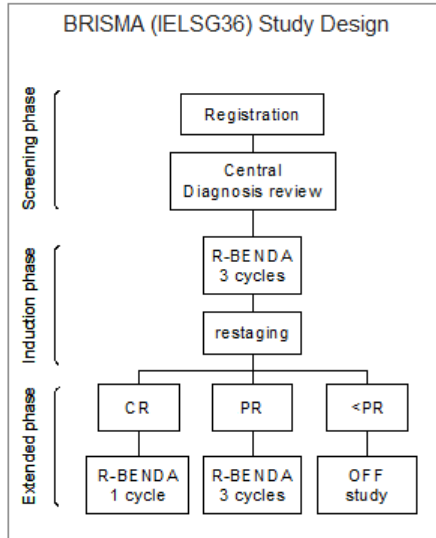


5-y PFS
94.4% VS
81.1%

- ORR 93%, CR 81%
- R maintenance: longer PFS, similar OS
- Infections in 13% of pts (4% zoster)
- HT: 6% at 5y, 9.1% at 10y; SPM 3.4%



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 \geq 3 toxicity, 68%
**(mainly haematological;
severe neutropenia, 43%)**



Novel drugs in RR MZL

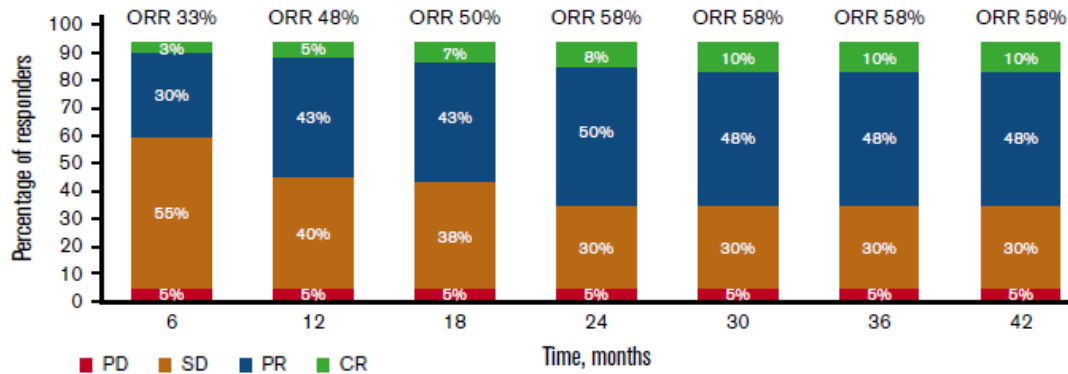
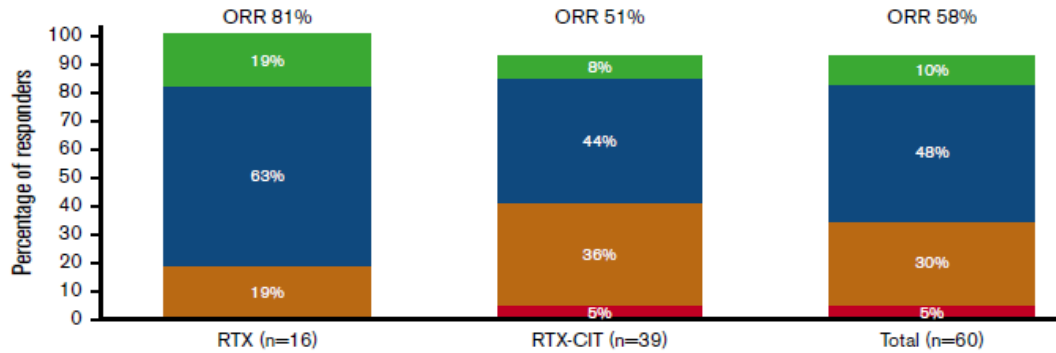
Signalling pathway	Target	Drug	N MZL pts	ORR %	mDOR (mo)
Pi3K/AKT/mTOR	PI3K δ	Idelalisib	15	47	18.4
		Umbralisib [†]	69	49	NR
		Umbralisib+ublituximab	72	68	NR
		Zandelisib	4	100	NA
		Parsaclisib	100	58	12.2
	PI3K γ,δ	Duvelisib	18	39	15.5 (mPFS)
	PI3K α,δ	Copanlisib	23	78	17.4
		Copanlisib+rituximab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

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

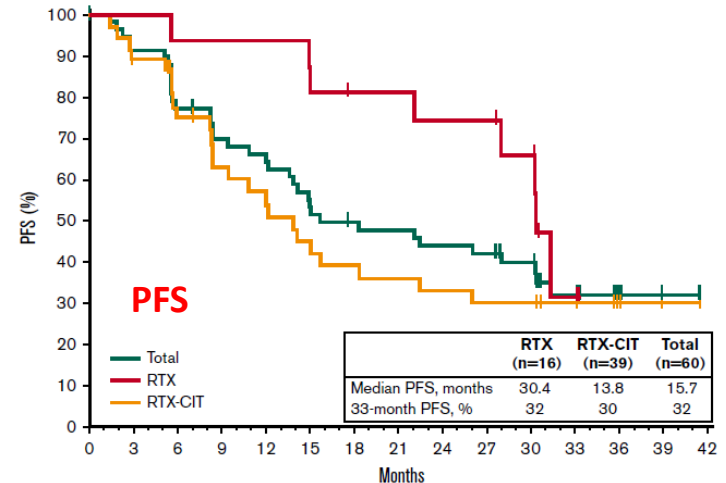
Wagner-Johnson et al, *Leuk&Lymph* 2021; Fowler et al *JCO* 2021; Chavez et al, *ASH* 2021; Pagel et al, *Lancet Oncol* 2022; Phillips et al, *ASH* 2021; Jacobsen et al, *SOHO* 2019; Panayiotidis et al, *Blood Adv* 2021; Matsar et al, *Lancet Oncol* 2021; Noy et al, *Blood* 2017, *Blood Adv* 2020; Opat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

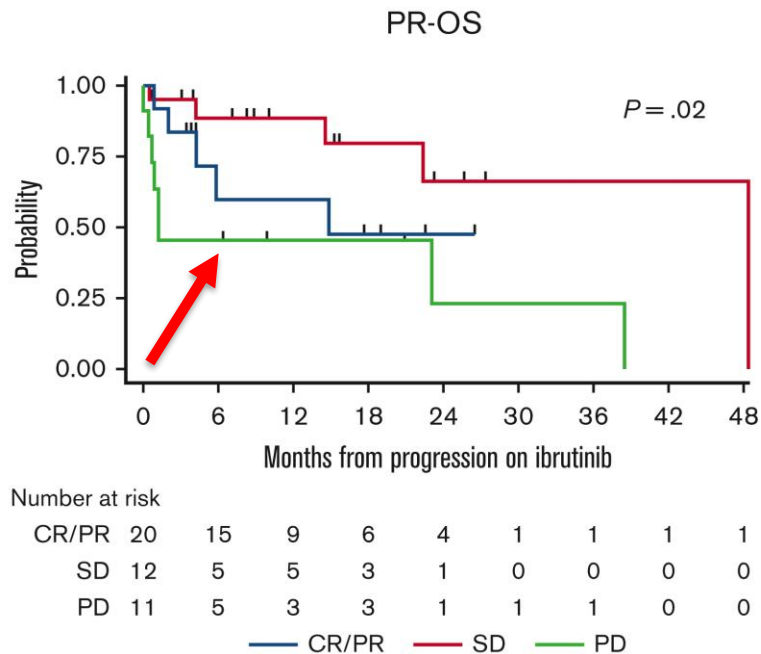
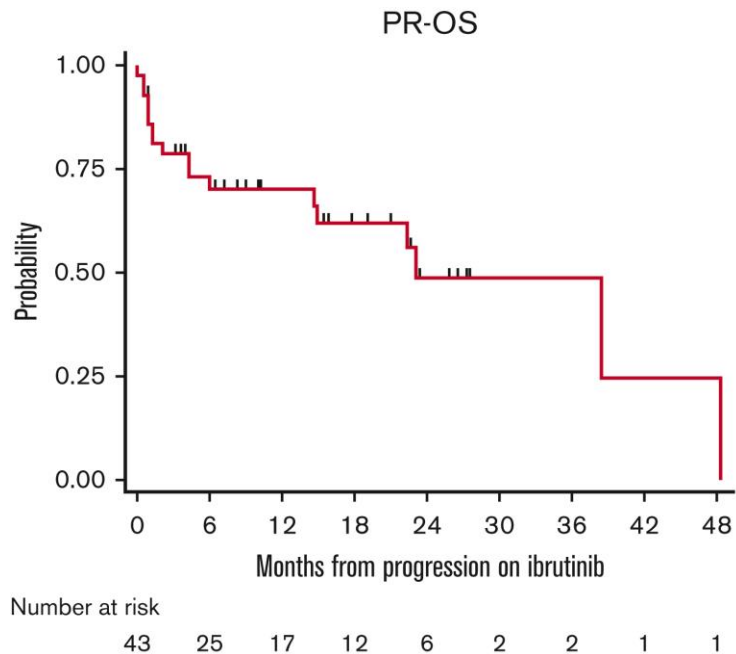
• **33.1 months of follow-up: ORR 58% (INV-based)**



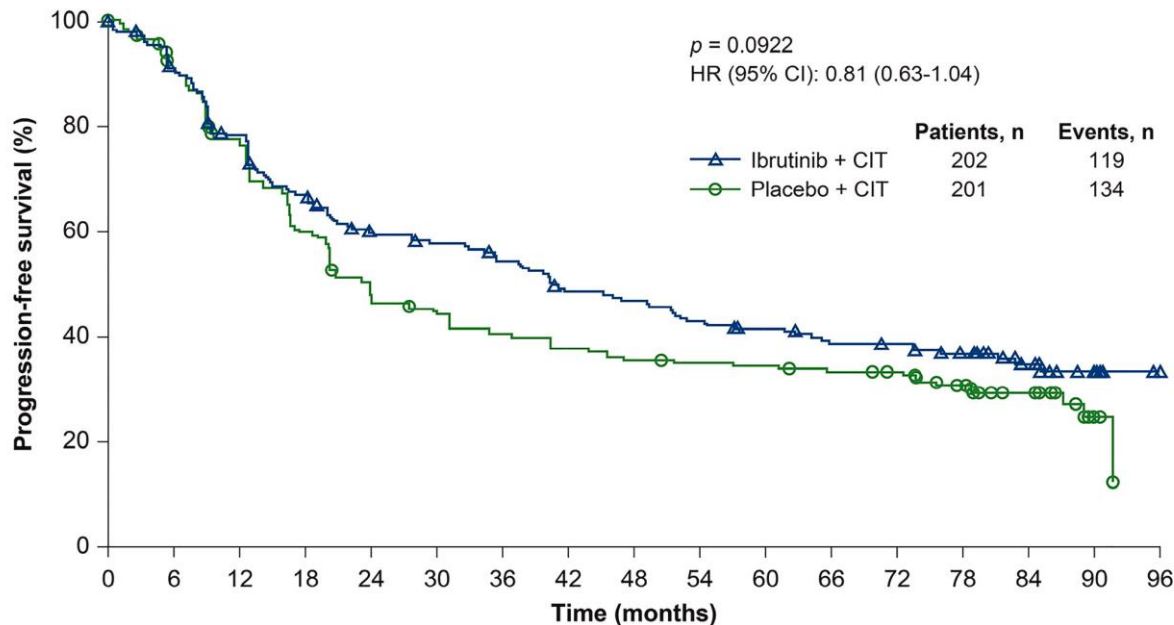
- mDOR 27.6 mo
- mPFS 15.7 mo, mOS NR (72% at 33 mo)
- No difference in ORR, PFS, OS subtypes
- mPFS better if only prior R (30.4 mo) vs prior R-CHT (13.8 mo)
- **TNFAIP3 (A20) and MYD88** better response
- **KMT2D and CARD11 mut** -> shorter DOR



Post-ibrutinib relapse outcomes



Ibrutinib + BR or R-CHOP in R/R FL or MZL: the phase 3 selene study



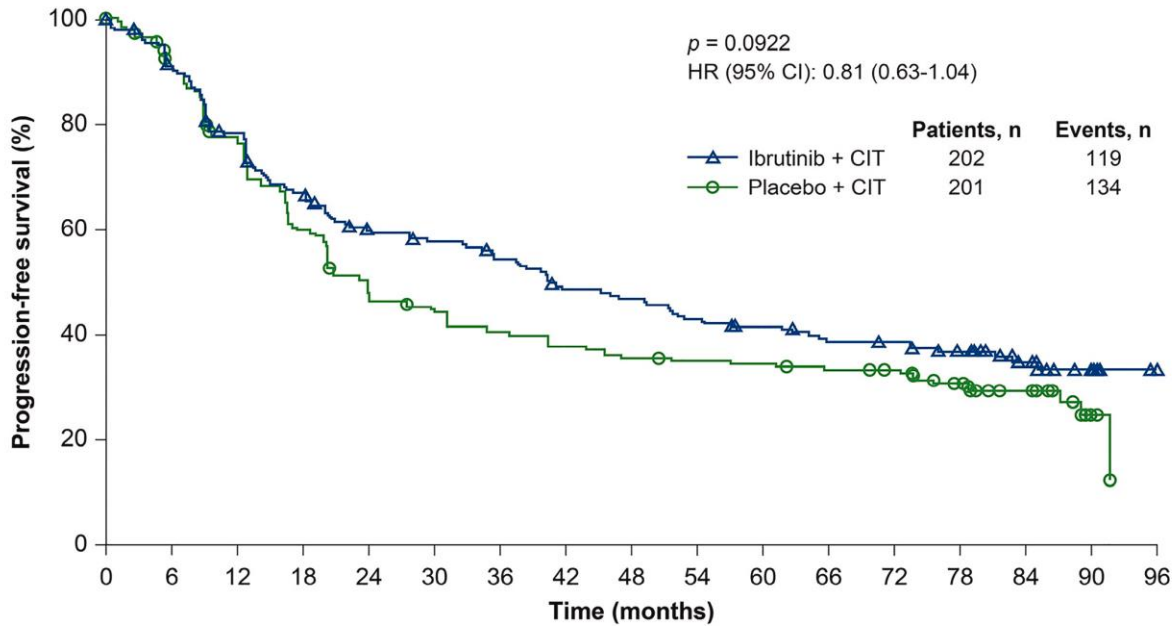
56 MZL

Median PFS NR in the i arm vs 91.6 mo in the placebo arm

Similar ORR and CR rates

Median DOR NR in the i arm vs 89.2 mo in the placebo arm

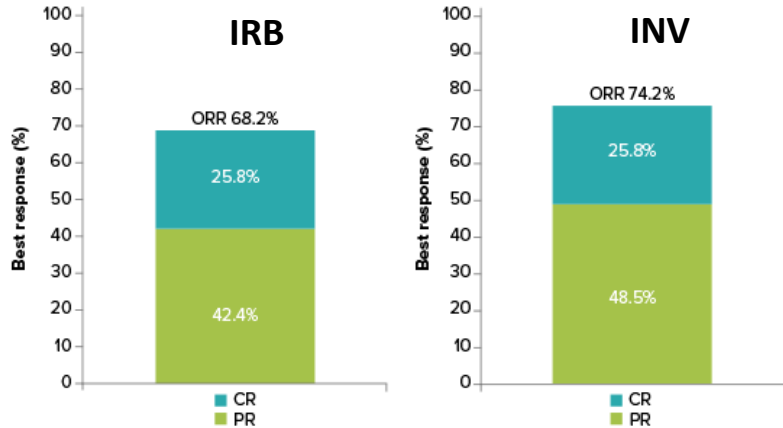
Ibrutinib plus BR or R-CHOP in R/R FL or MZL: The phase 3 SELENE study



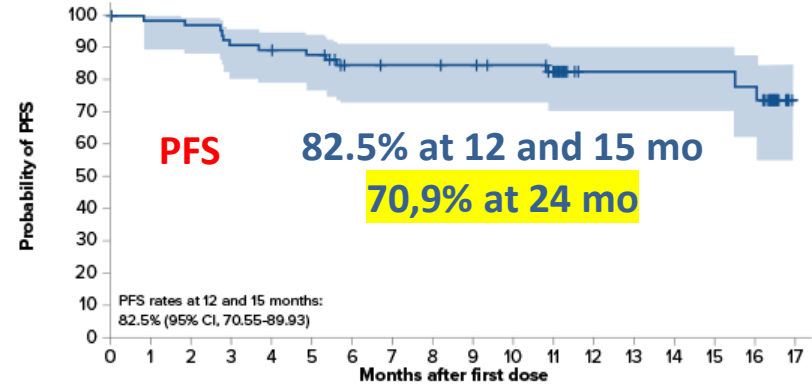
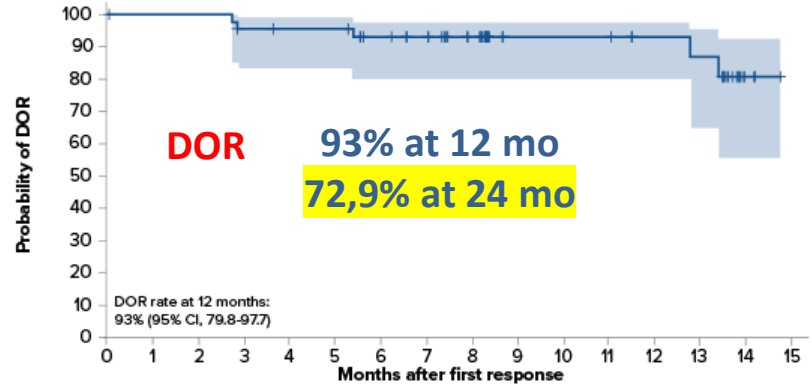
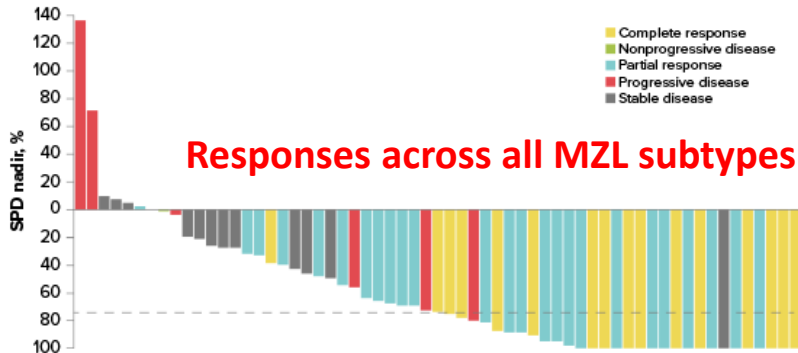
April 6, 2023 – AbbVie announced today the intent to voluntarily withdraw, in the U.S., accelerated ibrutinib approvals for patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy

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

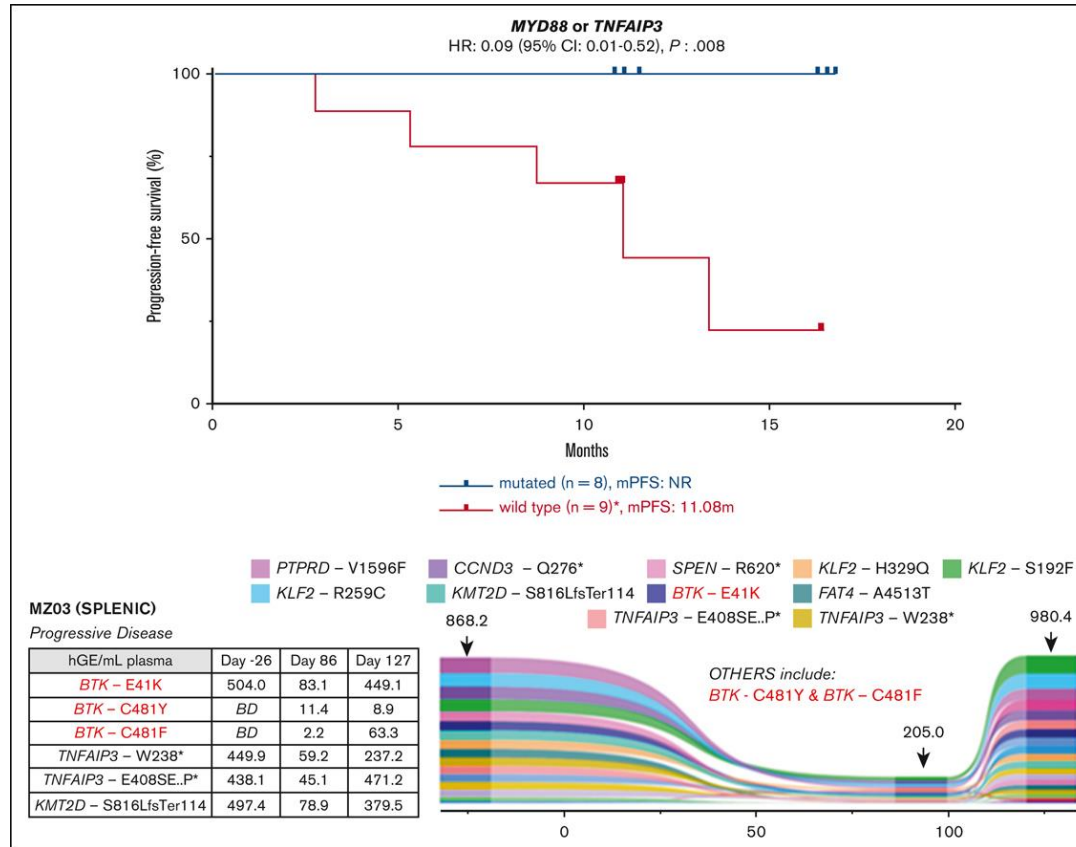
• 68 pts (26 Ex, 12 Sp, 26 No, 4 diss), ≥1 anti-CD20, median 2 tp; Dose: 160 mg BID Median f-up: 15.7 mo



Same after median f-up: 27.4 mo



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



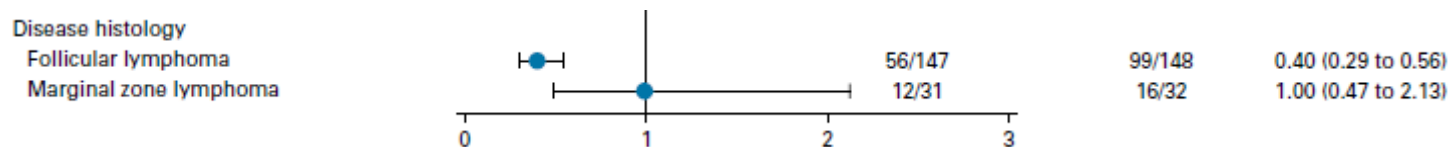
NOTCH not informative as in MCL and CLL

Rituximab-Lenalidomide (R²) in R/R MZL

AUGMENT study: Ph III, placebo-controlled, R² in R/R FL or MZL, RTX sensitive

- 358 pts (295 FL, **63 MZL** → 30 MALT, 18 NMZL, 15 SMZL)
- PFS advantage for the whole cohort (HR 0.46), but not in MZL (**mPFS 20.2 mo**)
- → small sample size and imbalance in baseline prognostic factors

Leonard et al. JCO 2019



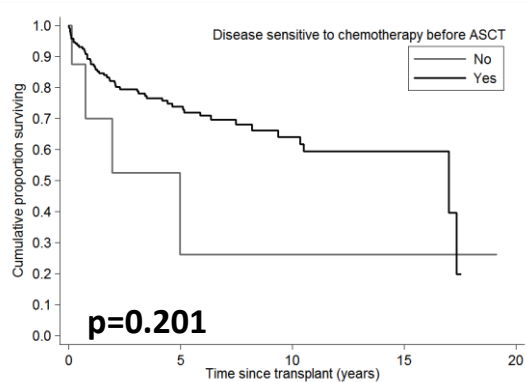
MAGNIFY study: Ph IIIb, placebo-controlled, R² induction in R/R FL or MZL → **maintenance R² vs R**

	Overall (FL + MZL) (n = 393)	All MZL (n = 74)	Nodal (n = 43)	Splenic (n = 16)	MALT (n = 15)
Median PFS, mo (95% CI)*	40.1 (37.6-NR)	41.2 (38.4-NR)	41.6 (26.5-NR)	38.4 (5.4-41.2)	NR (16.6-NR)
ORR, n (%)	270 (69)	50 (68)	29 (67)	8 (50)	13 (87)
CR + CRu, n (%)	158 (40)	29 (39)	18 (42)	4 (25)	7 (47)
Median DOR, mo (95% CI)	39.0 (36.8-NR)	38.6 (29.4-NR)	39.0 (22.4-NR)	35.8 (40.5-NR)	NR (NR-NR)

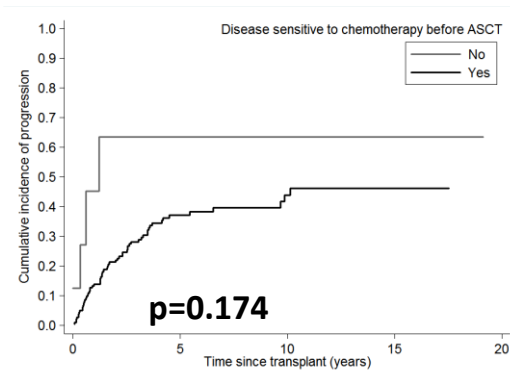
- 37% discontinued tp
 - 14% due to AEs
- Gr ≥3 AEs:
 - 41% neutrop. (FN 1%)
 - 13% thrombocytopenia

Coleman et al. ASH 2020

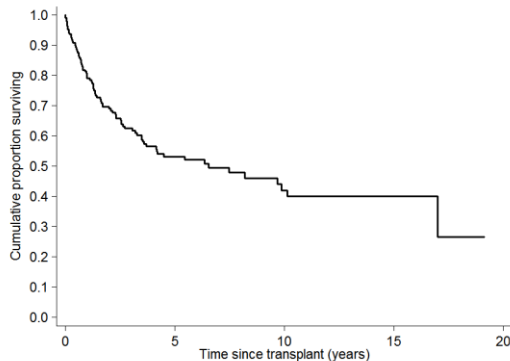
Autotransplant in MZL



5-yrs OS in CHT-sens MZL: 74%
5-yrs OS in CHT-res MZL: 26%



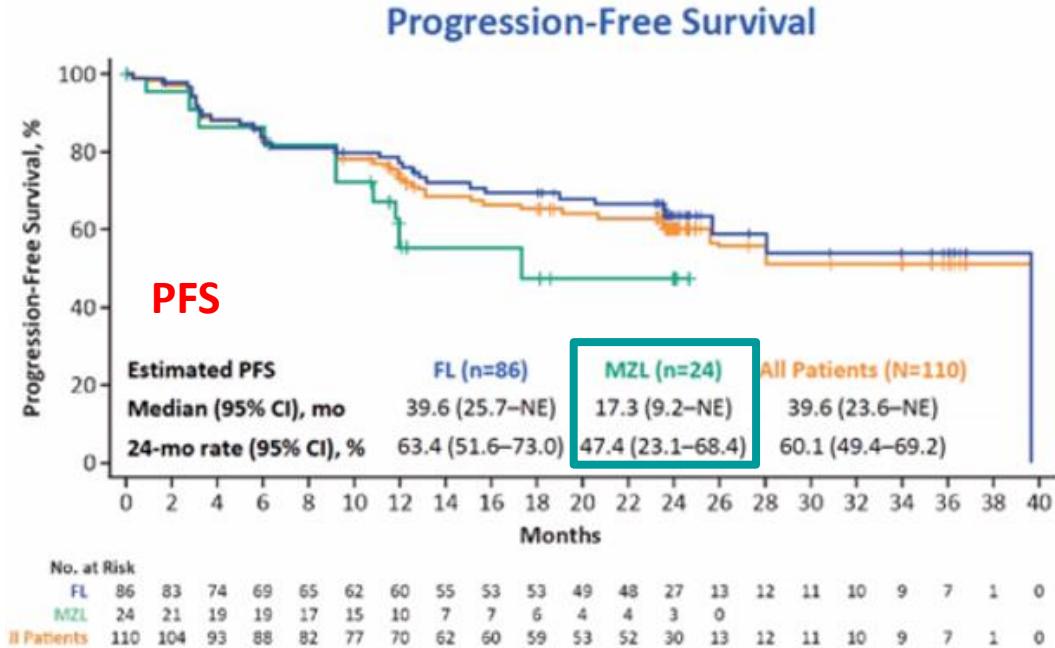
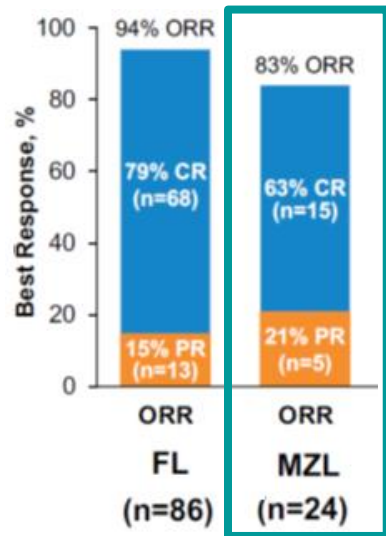
5-yrs IR in CHT-sens disease: 37%
5-yrs IR in CHT-res disease: 63%



Median EFS: 6.6 yrs
5-yrs EFS: 53%

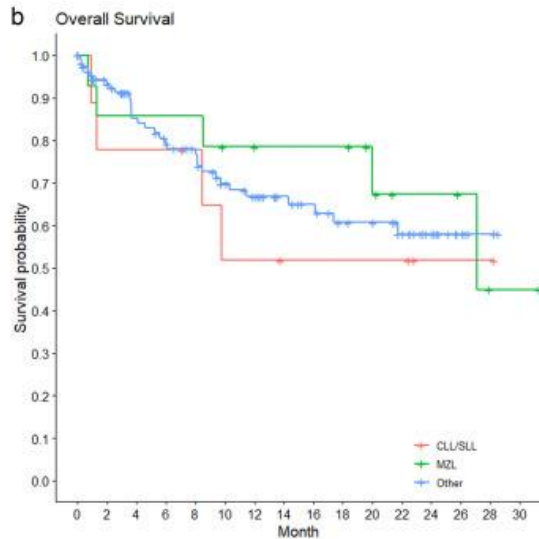
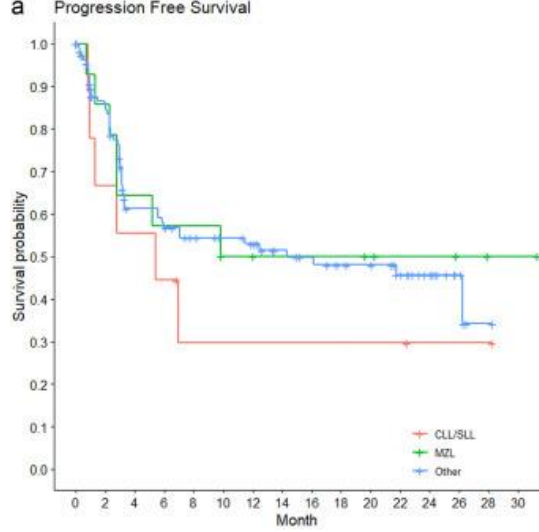
CAR T-Cells (ZUMA-5)

- 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

CAR T-Cells in tMZL



How I (can try to suggest how to) treat high-risk marginal zone lymphoma

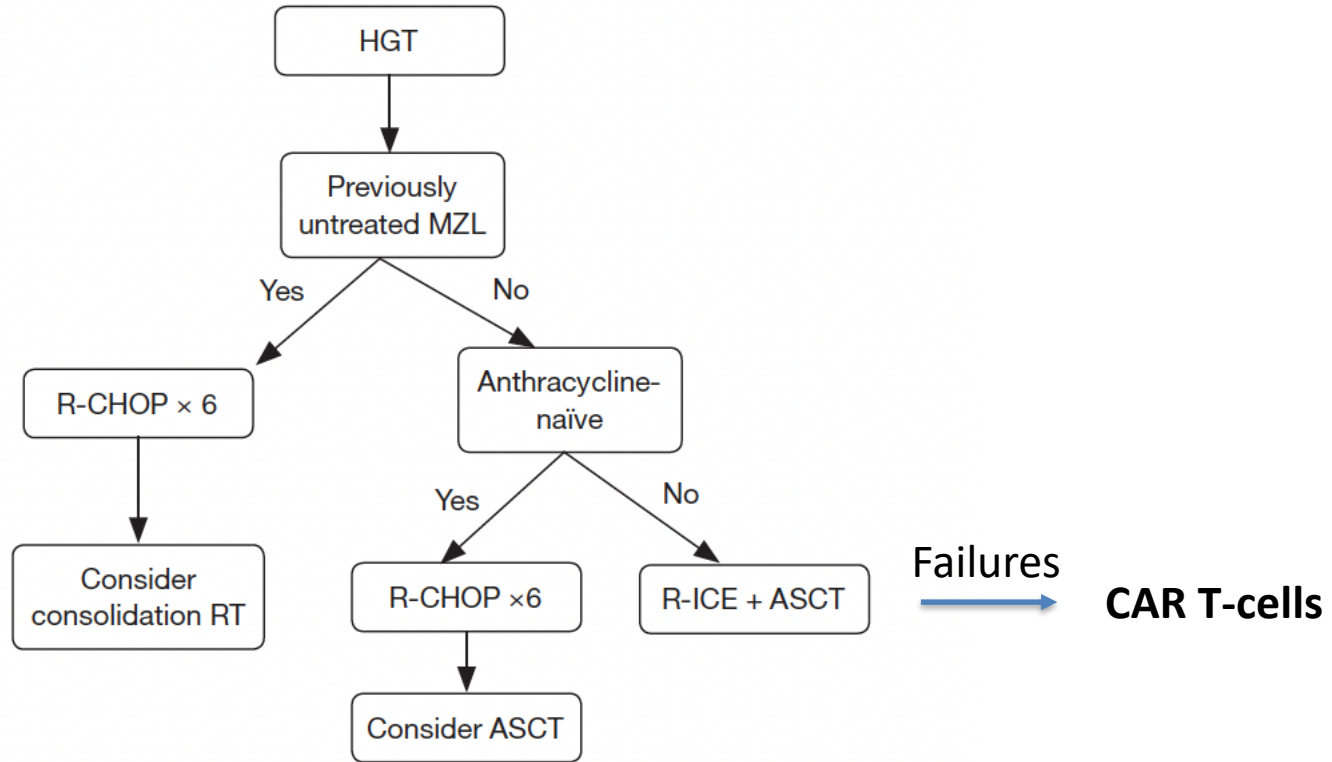
FIRST LINE IN NOT TRANSFORMED MZL

- **MALT MZL:** high MALT-IPI or HIGH rMALT-IPI R- Benda x 4
- **SMLZ:** high tumor burden and extrasplenic disease, young, no comorbidity R-BENDA (!
R-CHOP for transformation, search for it)
- **NMZL:** difficult to say
- **Disseminated MZL:** I-CHT (R-Benda ?)

RELAPSED/REFRACTORY NOT TRANSFORMED MZL after I-CHT

- BTKi
- BTKi failures → R2, bispecific abs, CAR-T not available → I-CHT if not a clinical trial available (for instance with a non covalent BTKi)

TRANSFORMED MZL



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Aula Scarpa, Anatomical Theatre, University of Pavia (1758)