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Strategies for initial treatment of MZL

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Preamble

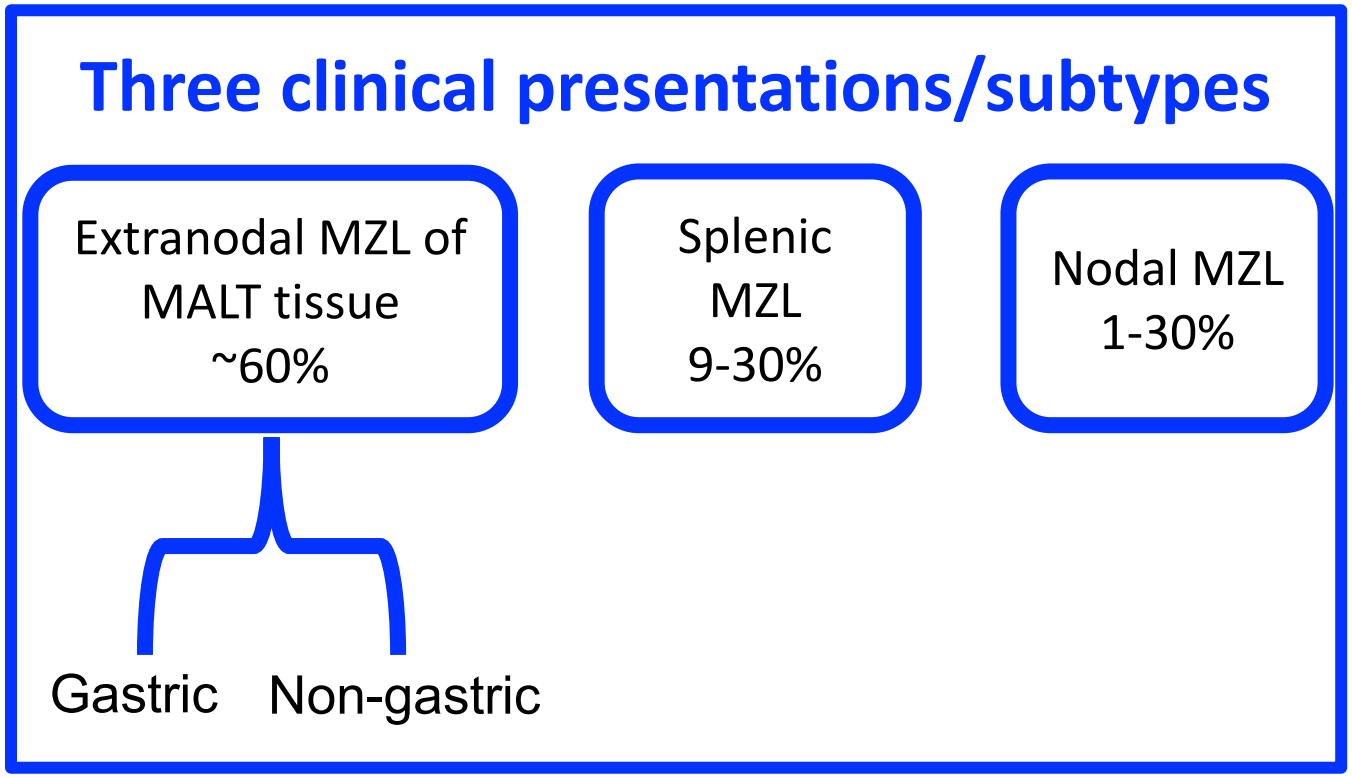
MARGINAL ZONE LYMPHOMA

The treatment of marginal zone lymphoma

Juan Pablo Alderuccio[1] and Ariela Noy[2]

- There is only one drug specifically FDA-approved for MZL
- Most data is derived from underpowered subset analyses in trials of indolent lymphomas
- Rarity and heterogeneity of MZL complicates clinical trial development
- Evaluating extranodal disease using Lugano criteria is challenging
- Management of relapsed/refractory disease is an area of unmet need

Marginal zone lymphoma: epidemiology and clinical subtypes



- 3rd most common mature B-NHL (~7500 new/year in US)
- Frequent stage IE presentation
- Indolent course
- ~90% 5-year survival

Overall incidence of MZL is increasing
SMZL is increasing
Gastric MZLs are decreasing
(Rossi and Zucca NEJM 2022)

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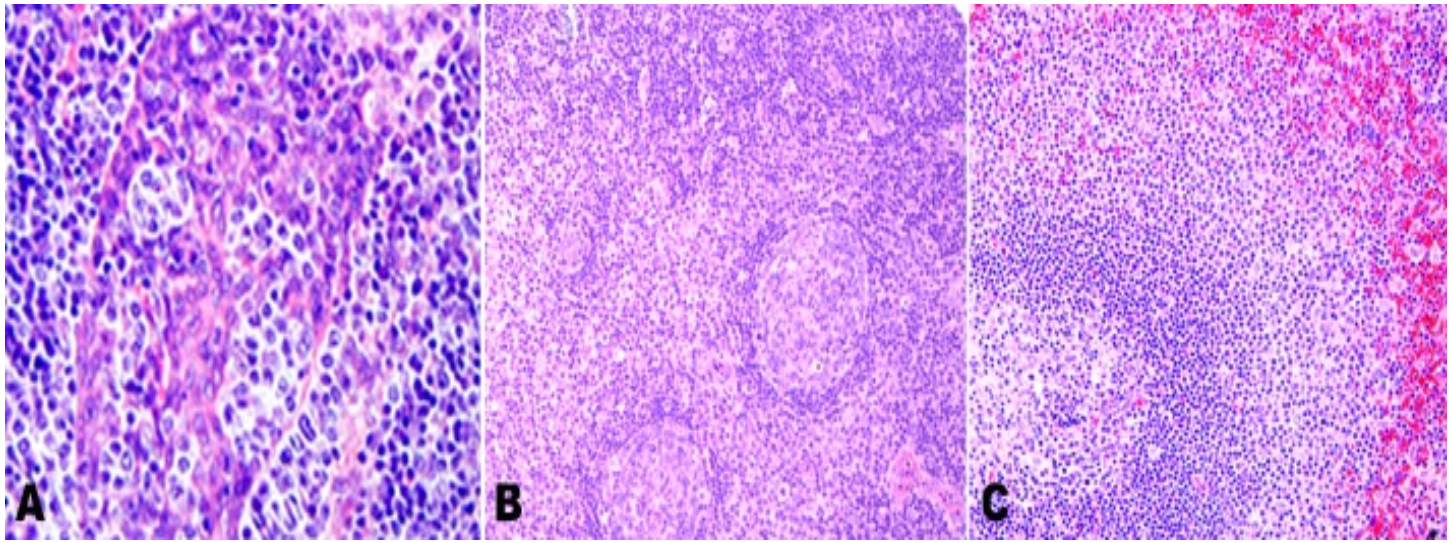
Cerhan and Haberman Ann Lymphoma 2021 Mar:5:1
Teras et al. CA Cancer J Clin (2016) 66: 443-459

Pathology and Immunophenotype



Lymphoepithelial lesion in EN MALT

Nodal MZL

Splenic MZL

Shared features:

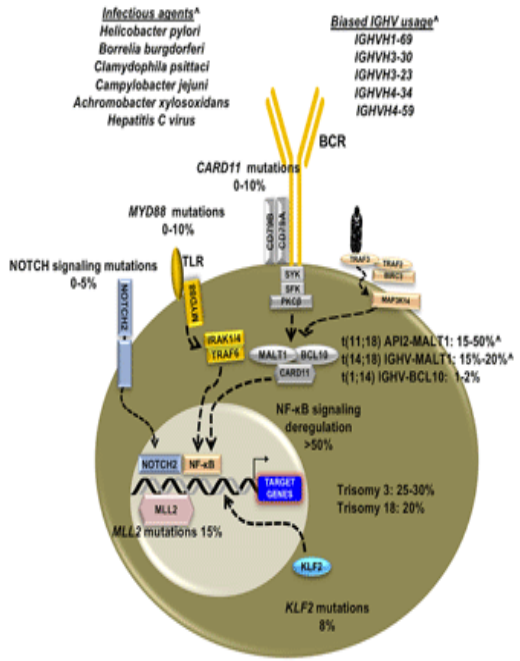
clonal expansion of centrocyte-like and monocytoid-like B-cells from marginal zone with interfollicular expansion, scattered immunoblasts*

Immunophenotype:

Positive: CD20+CD79a+CD19+

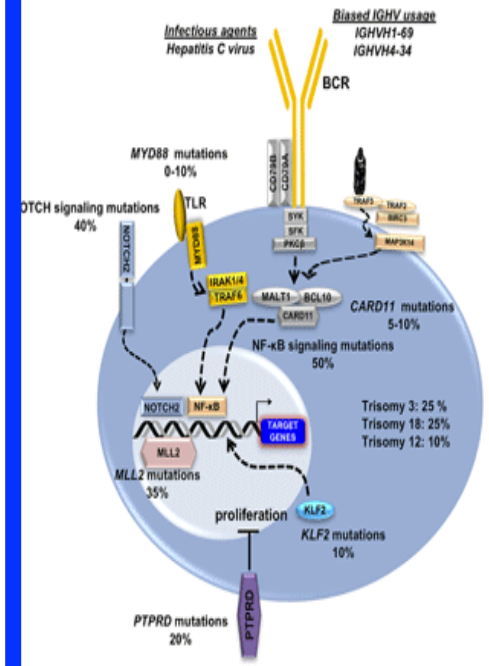
Negative: **CD5- CD10-** CD23- BCL6- cyclinD1- ***MYD88* mutation-**

Shared and distinct pathogenetic abnormalities



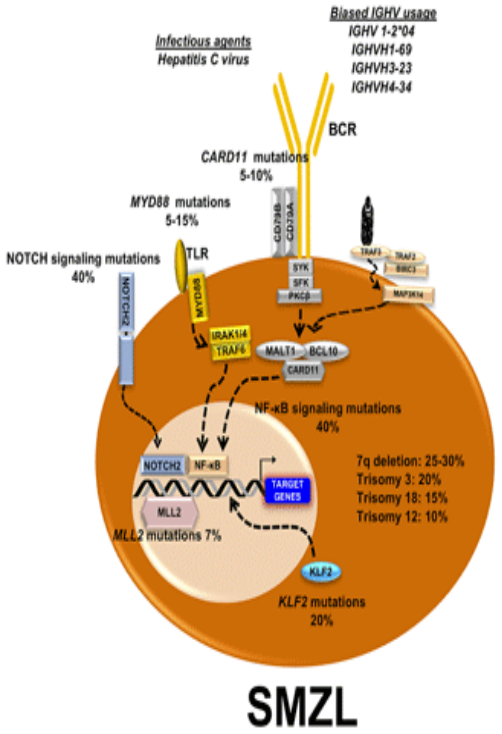
MALT lymphoma

Balanced translocations
Upregulation of BCL10, MALT1, BIRC3/MALT1



NMZL

20% PTPRD mutations
NOTCH mutations
Trisomies



SMZL

25-30% 7q deletion
NOTCH mutations
Trisomies
4 genetic clusters
(NNK, DMT, CBS, FA)

Unifying feature is deregulated NFkB signaling (with differing mechanisms)
--NFkB mutations in EN MZL
--methylation of KLF4 in SMZL

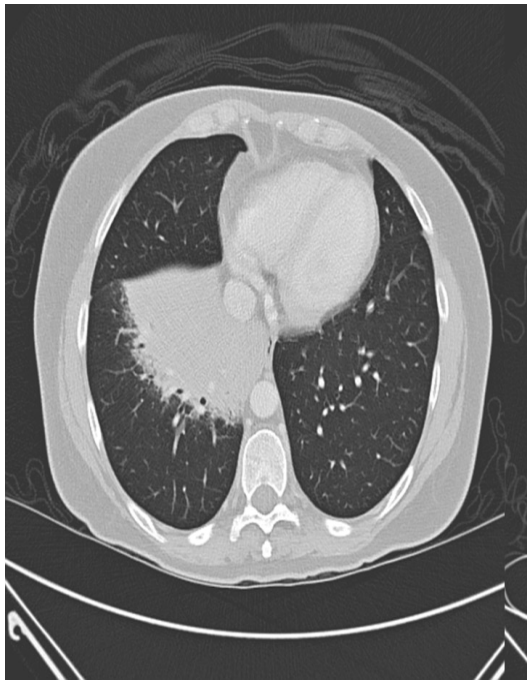
Rossi N Engl J Med. 2022 Feb 10;386(6):568-581
Bertoni F1000Res. 2018 Mar 28;7:406.

Clinical spectrum and other features

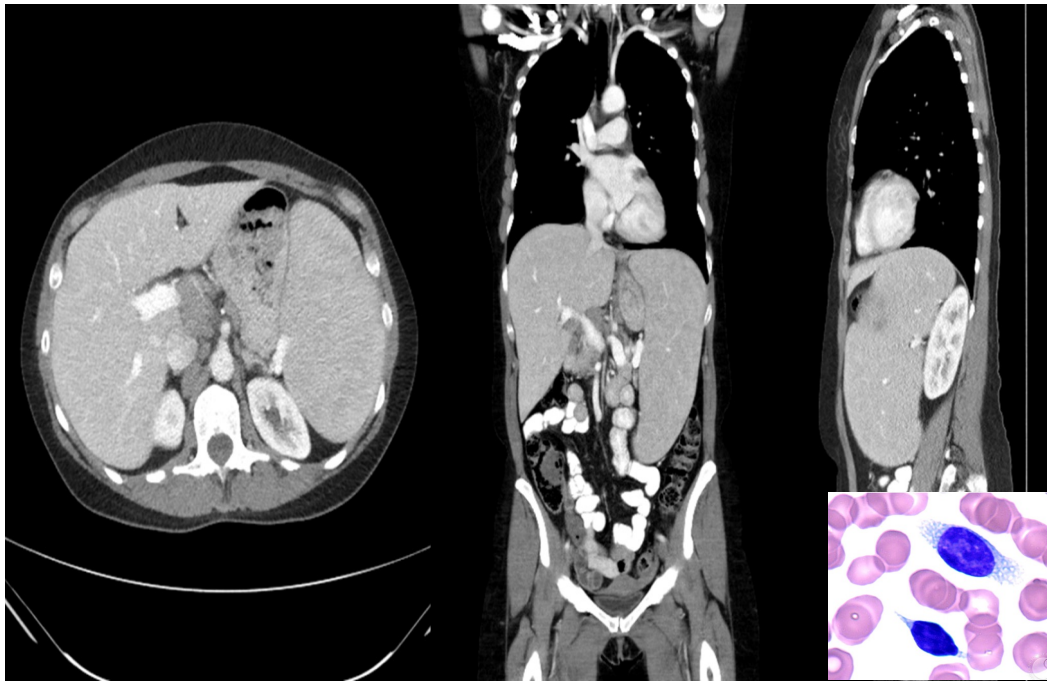
- **CBL-MZL**—premalignant clonal B-cell lymphocytosis of marginal zone origin
  - A systemic disorder with similarities to NMZL and SMZL
  - Precedes onset of MZL
- **Pediatric subtype of nodal MZL**
- **IPSID** (immunoproliferative small intestinal disease)
  - A form of MALT lymphoma
- **Relapsed/refractory MZL**
  - Plasmacytic differentiation
  - Frequent paraprotein production (~30% of SMZL will have Ig paraprotein)
  - paraneoplastic and autoimmune phenomena (20% of SMZL will have autoimmunity)
- **Transformation** of MZL to aggressive lymphoma
  - 5-10% incidence
  - Genomic classifiers suggest that DLBCL molecular subgroups C1 and BN2 might represent transformed MZL (associated with NOTCH and BCL6 translocations)

Rossi N Engl J Med. 2022 Feb 10;386(6):568-581

Clinical Presentation depends on the subtype

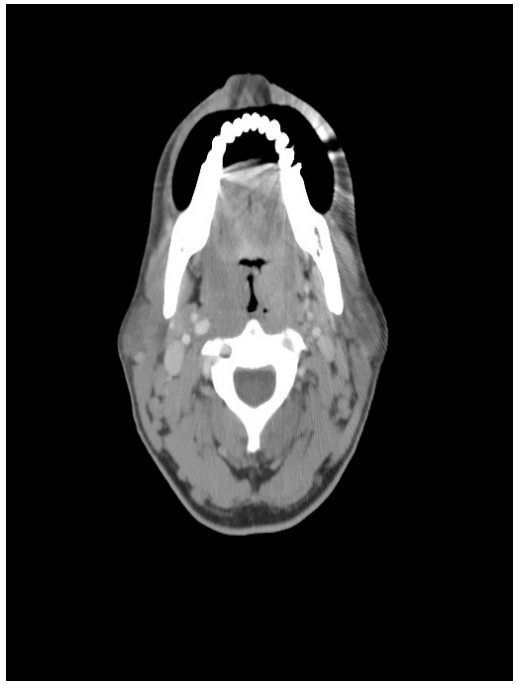


EN MZL



ASH image bank

SMZL



NMZL

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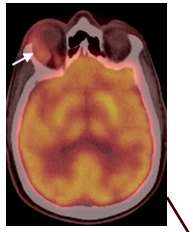
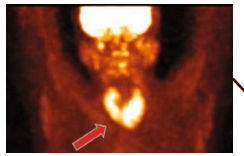
Clinical Presentations

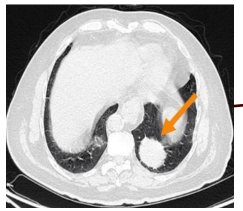
Ocular
Extraocular



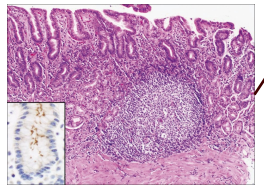
Endocrine



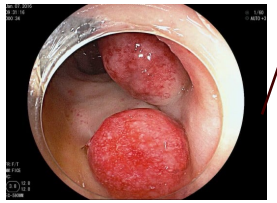
Lung



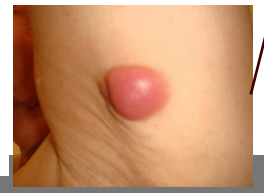
Stomach
MALT



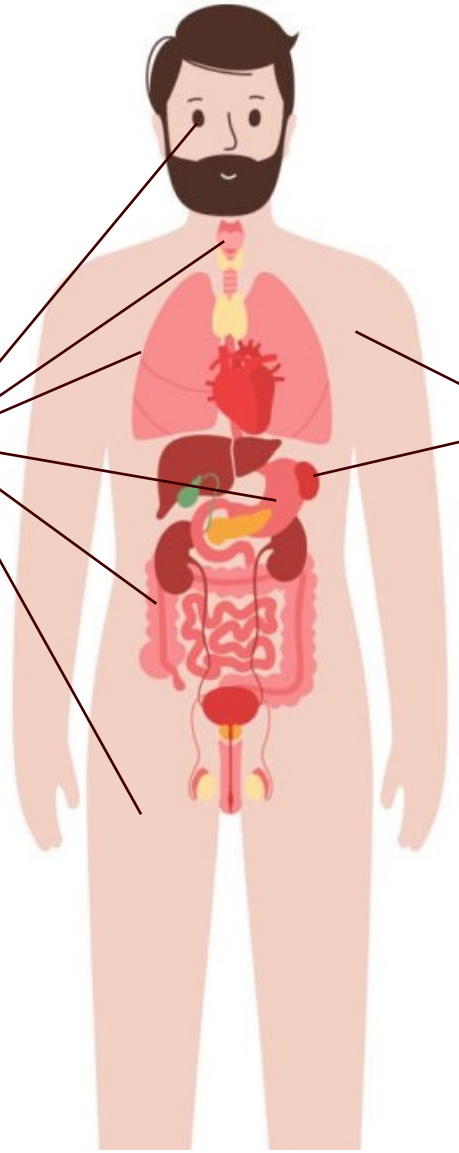
GI
Tract



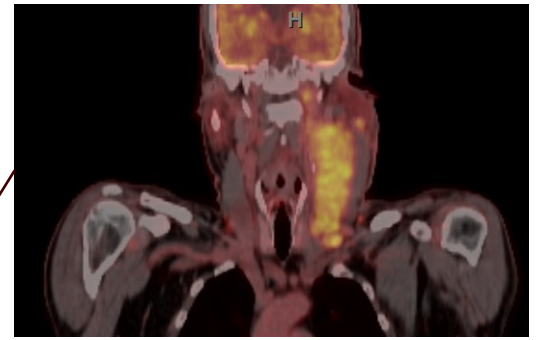
Skin

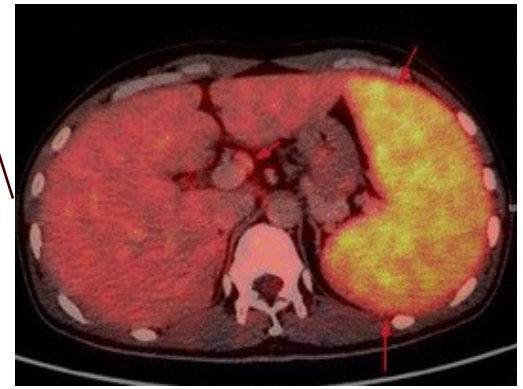


Extranodal (61%)



Nodal (30%)
Splenic (9%)





Slide courtesy of Dr. Boyu Hu

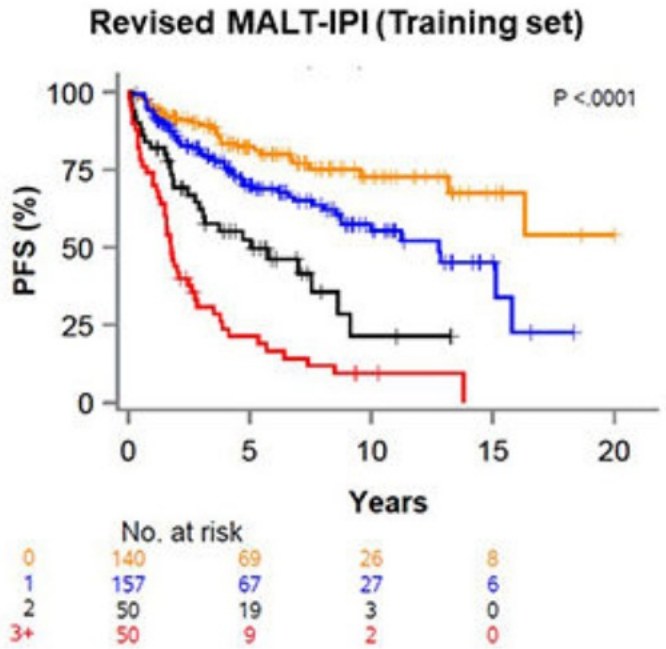
Cerhan JR and Habermann T. Ann Lymphoma (2021) 5:1.

HOW TO DETERMINE PROGNOSIS?
AND WHAT IS THE RISK FOR TRANSFORMATION?

Revised MALT IPI

Methods:

1. Developed in a large data set (n=397) by identifying candidate variables with highest prognostic association with PFS.
2. Validated in two independent cohorts, from the University of Iowa/Mayo Clinic (n=297) and from IELSG-19 study (n=400)



Prognostic factors

1. Age > 60 years
2. Elevated LDH
3. Stage III-IV

1 point

4. Multiple mucosal sites — 2 points

Risk groups

- Low risk (score 0)
- Low-medium risk (score 1, HR=1.85)
- Medium-high risk (score 2, HR=3.84)
- High risk (score ≥ 3, HR=8.48)

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Alderuccio Am J Hematol. 2022 Sep 19;97(12):1529–1537

Nodal MZL Clinical Presentation (MSKCC analysis, n=187 pts)

- Med age 62 years (IQR, 50-69)
- Clinical stage:
  41% limited stage
  59% advanced stage
- FLIPI (n = 139)
  0-1: 61 (44%)
  2: 35 (25%)
  ≥ 3: 43 (31%)

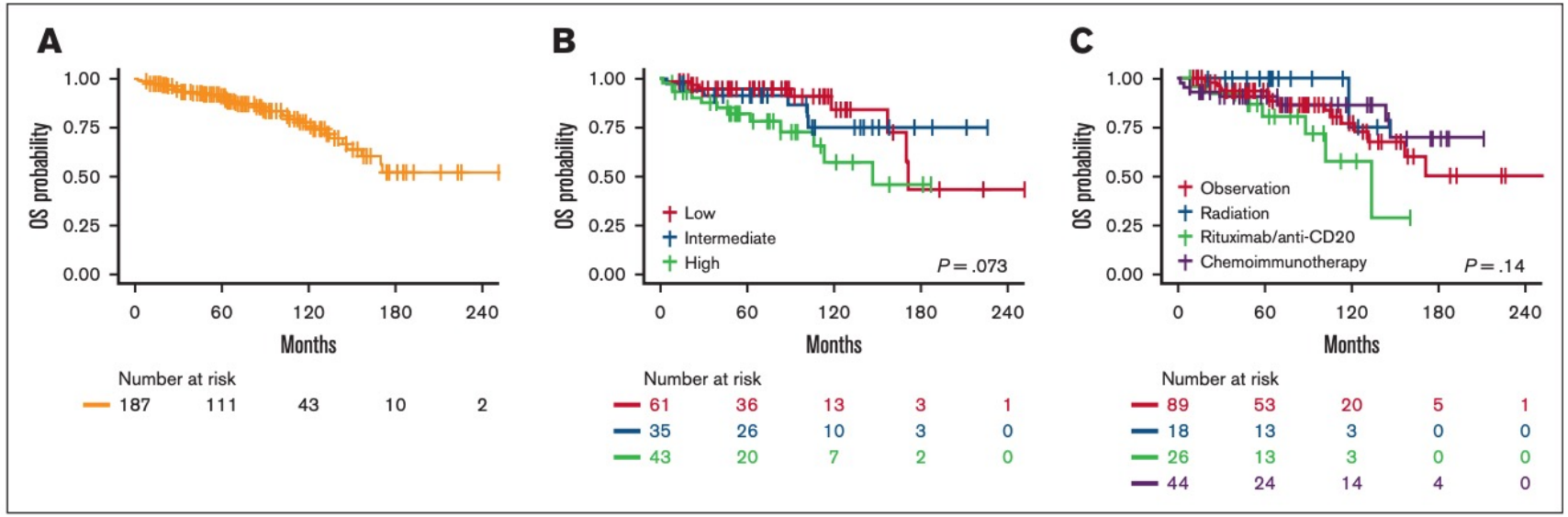

Figure 1. Overall Survival Estimates. Kaplan-Meier estimates for OS in the entire cohort (A), by baseline FLIPI risk group (B), and first management strategy (C).

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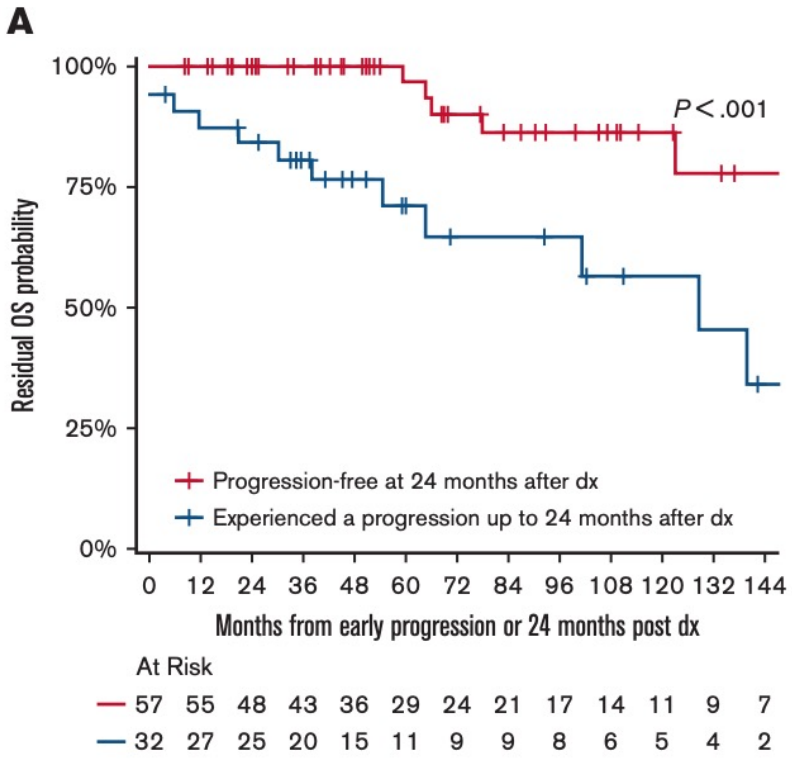
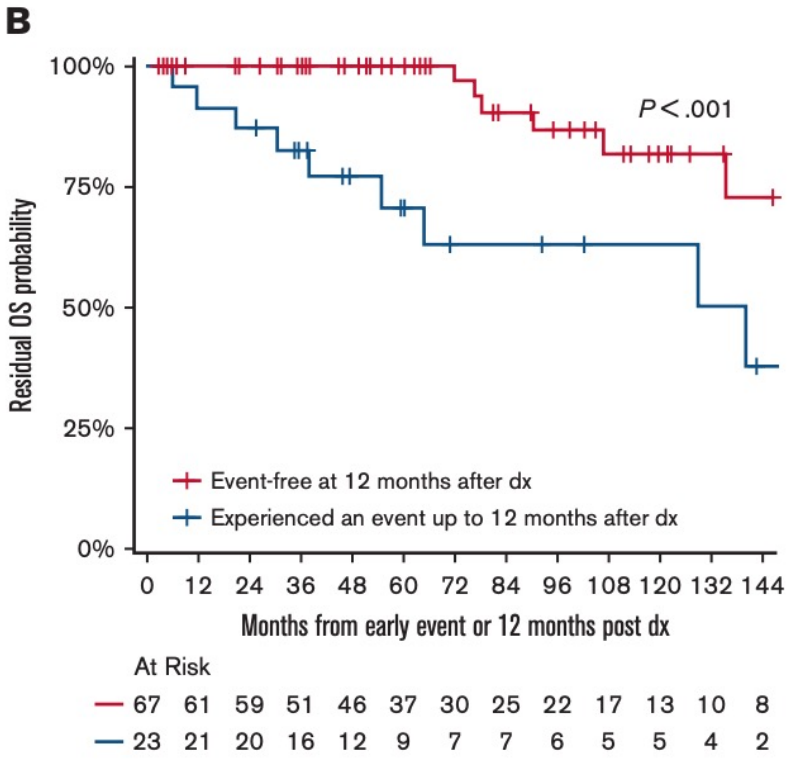
Stuver Blood Adv (2023) 7 (17): 4838–4847.

POD24 and EFS12 portend poor prognosis for overall survival



Outcome by POD24



Outcome by EFS12

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Stuver Blood Adv (2023) 7 (17): 4838–4847.

Consensus for MZL IPI systems needed

MALT-IPI

Revised MALT-IPI

SMZL IPI

FLIPI

IPI

- Patients from prospective NF10 study with TN MZL and receiving frontline systemic therapy were used to train a prognostic model
- Primary endpoint: PFS from start of treatment
- External validation in pooled analysis of two independent cohorts from the University of Iowa/Mayo Clinic Molecular Epidemiology Resource and University of Miami

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Arcaini eClinical Medicine Volume 72102592 June 2024

MZL-IPI: international prognostic analysis

A) MZL-IPI in training sample (n = 456)

Group	N (%) [#fail]	5-yr PFS% (95%CI)	HR (95%CI)	p
Low 0	123 (27) [19]	85 (76–90)	1.00	
Intermediate 1/2	258 (57) [79]	66 (60–72)	2.30 (1.39–3.80)	0.001
High 3/5	75 (16) [40]	37 (23–50)	5.41 (3.13–9.38)	<0.001
High vs Intermediate			2.35 (1.60–3.45)	<0.001

B) MZL-IPI in validation sample (n = 353)

Group	N (%) [#fail]	5-yr PFS% (95%CI)	HR (95%CI)	p
Low 0	94 (27) [46]	69 (58–77)	1.00	
Intermediate 1/2	192 (54) [101]	57 (49–64)	1.33 (0.94–1.89)	0.108
High 3/5	67 (19) [45]	45 (32–56)	2.08 (1.37–3.14)	<0.001
High vs Intermediate			1.56 (1.10–2.22)	0.013

PFS: progression-free survival. Any adverse factor was weighted = 1, and the sum of the worst prognostic category ranging from 0 to 5.

Table 3: **MZL-IPI from the final Cox PH model in progression free survival in training (A) and validate sample (B).**

Key prognostic factors:

- LDH > ULN
- Hgb < 12g/dL
- ALC < 1000
- Plts < 100K
- MZL subtype (SMZL v. ENMZL v. NMZL/dissMZL)

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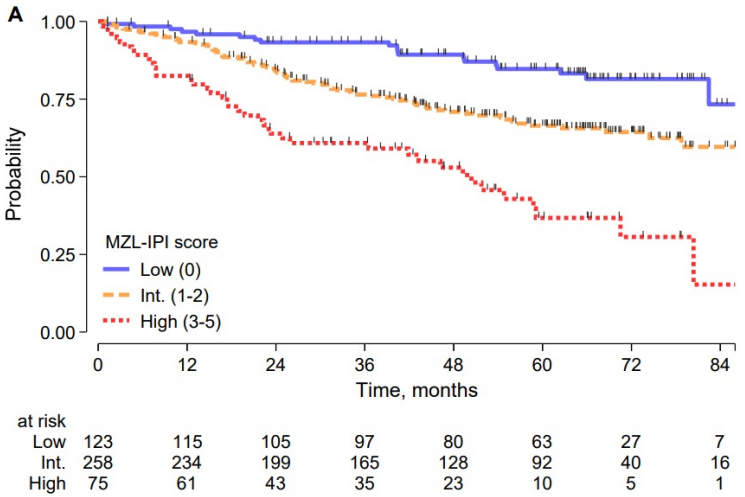
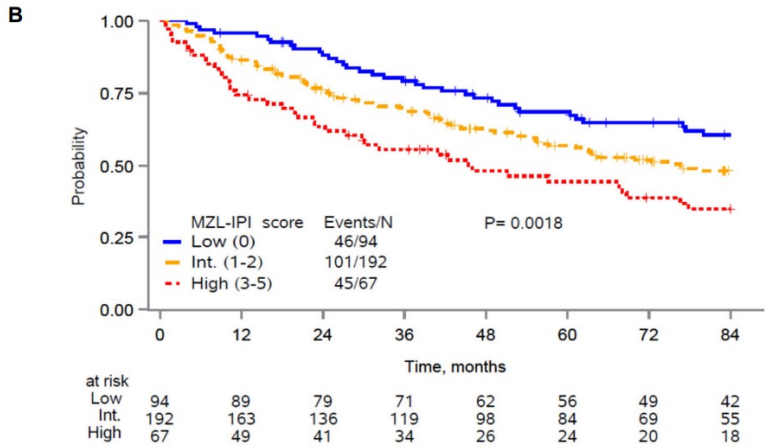
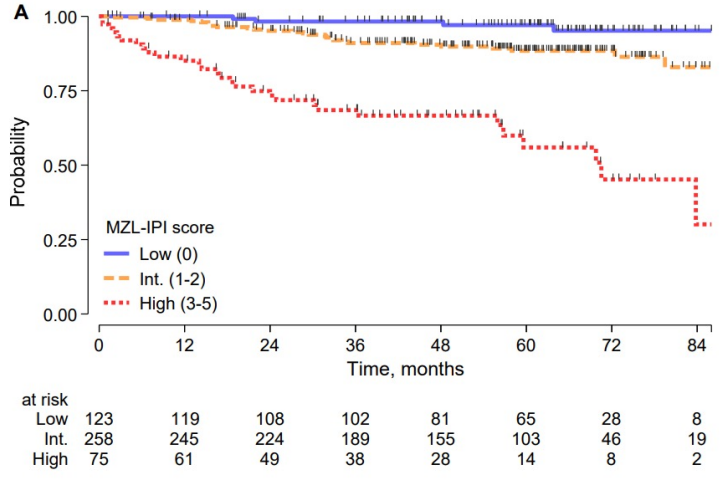
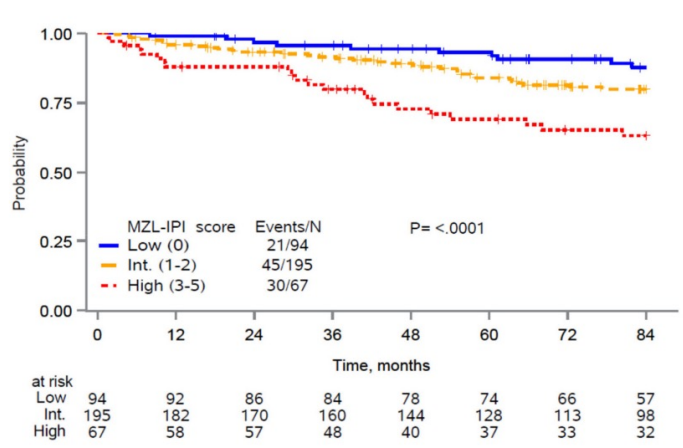
MZL-IPI and PFS/OS (international cohort)





PFS





OS

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Arcaini eClinical Medicine Volume 72102592 June 2024

Risk for histologic transformation (HT) in MZL: MER and clinical trial dataset

- **Method**: evaluation of patients enrolled in MER (n=529) and meta-analysis of 12 clinical trials (N=6161)
- HR for death after HT is 3.95
- Risk for HT varies by subtype in MER and clinical trial cohorts:
  EMZL (3% and 5%)
  SMZL (7% and 13%)
  NMZL (9% and 13%)

HT after MZL in the Molecular Epidemiology Cohort:

- 10-year overall survival after diagnosis was 66%
- Cumulative incidence of HT at 5 years was 2.7%
- 3.95-fold increased risk of death after HT
- Predictors of HT were ≥2 extranodal sites and MALT-IPI score ≥2
- After HT, OS was 79% at 5 years and 55% at 10 years

Meta-Analysis of 12 studies:

- Cumulative incidence of HT was 5% at 5 years and 8% at 10 years
- Cumulative incidence of HT at 5 years was highest in splenic MZL (7%) and nodal MZL (7%) and was much lower in Extranodal MZL (3%)

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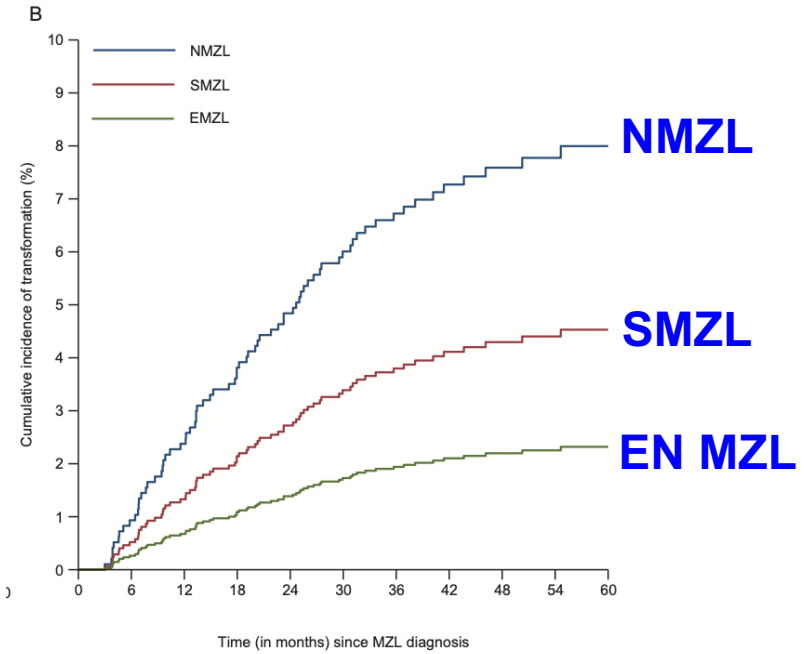
Bommier Blood Advances Volume 8, Issue 23, 10 December 2024, Pages 5939-594

Risk for histologic transformation (HT) in MZL: population-based analysis from Netherlands (n=1793)

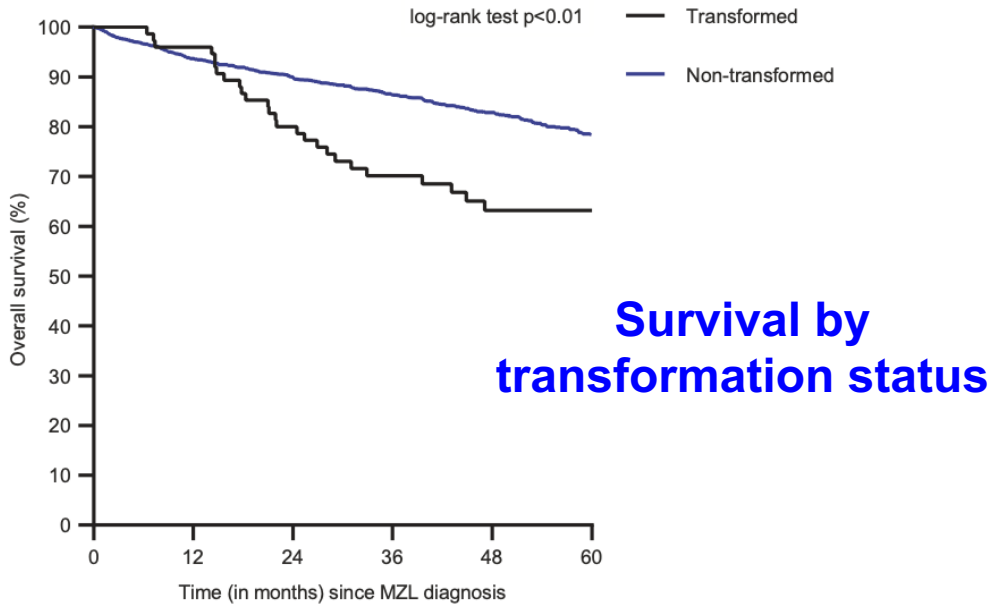


NMZL

SMZL

EN MZL

Risk for transformation by subtype



Survival by transformation status

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

Elevated LDH and nodal MZL subtype at MZL diagnosis associated with an increased risk of HT

Bult Blood Ca J 13, Article number: 130 (2023)

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SHOULD PET SCANS BE USED FOR STAGING?

Role of PET/CT staging in MZL

LUGANO 2014

"Therefore, the consensus was that PET-CT should be recommended for routine staging of FDG-avid, nodal lymphomas (essentially all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, mycosis fungoides, and **marginal zone NHLs**, unless there is a suspicion of aggressive transformation) as the gold standard"

****MZL is only mentioned ONCE in the entire manuscript****

ICML 2014

Role of PET-CT for staging

PET-CT should be used to select best site to biopsy in clinical practice and clinical trials but is not routinely recommended in lymphomas with low FDG avidity

Table 2. FDG Avidity According to WHO Classification

Histology	No. of Patients	FDG Avid (%)
Marginal zone lymphoma, nodal	14	100
MALT marginal zone lymphoma	227	54-81
Marginal zone lymphoma, splenic	13	53-67
Marginal zone lymphoma, unspecified	12	67

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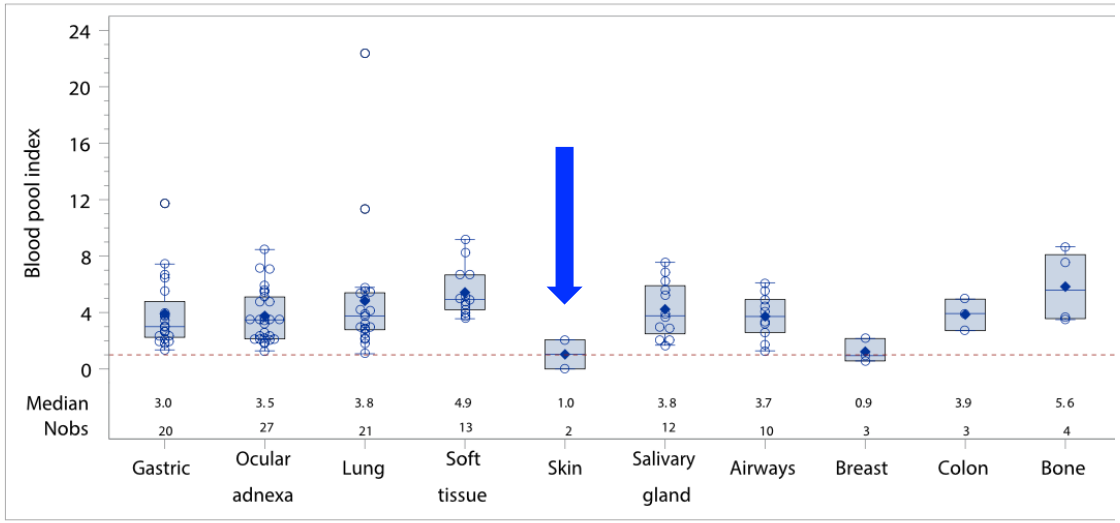
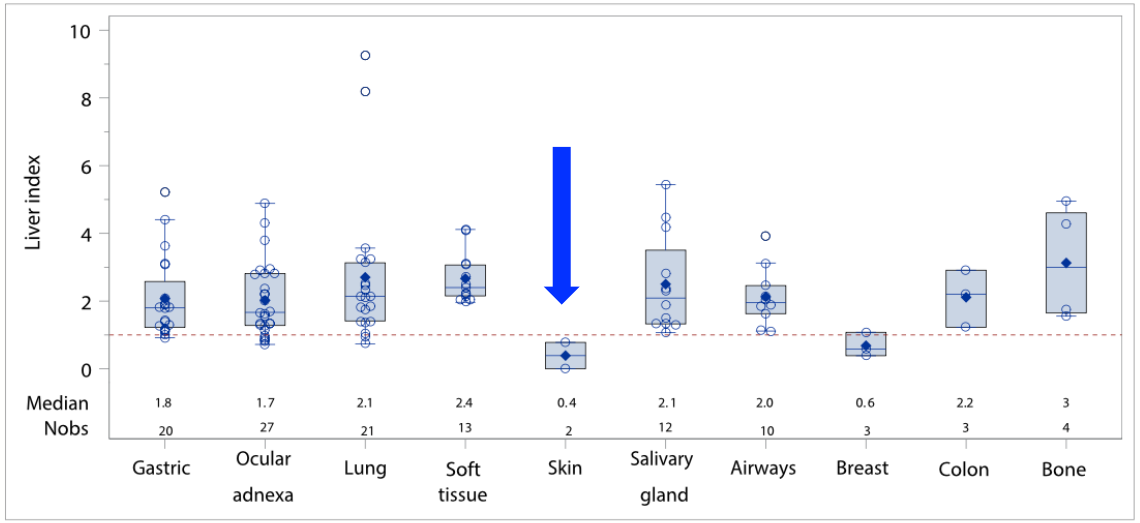
Cheson JCO 2014 Sep 20;32(27):3059-68; Barrington JCO 2014 Sep 20;32(27):3048-58

PET/CT is sensitive for EN MZL except for skin locations

D. Blood pool index (in sites with lymphoma size >=0.5 cm)



E. Liver index (in sites with lymphoma size >=0.5 cm)



Blood pool

Liver

"This study demonstrates that EMZL is commonly an FDG-avid disease, suggesting that PET/CT should be routinely used in the staging and response assessment workup of patients with EMZL"

Alderuccio Am J Hem 2025 Aug;100(8):1295-1304

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ICML Lugano conference 2025 update

"Given the variable FDG avidity in marginal zone lymphoma according to subtype, location, and volume of disease, it was suggested that PET/CT and ceCT and **could be used for staging**, and then response assessed only with PET/CT if avid at baseline."

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Cheson Hematol Oncol. 2025 Jul;43(4):e70103

TREATMENT

General Treatment Approach

- **Patients with localized disease**
  - Eradication of antigenic trigger
  - ISRT +/- rituximab
  - Rituximab +/- RT
- **Patients with systemic disease**
  - Treatment is based on GELF/NCCN/ESMO criteria
  - Observation of asymptomatic patients
  - Treatment options for symptomatic patients
    - Rituximab monotherapy +/- maintenance rituximab
    - Chemoimmunotherapy (i.e. BR)
    - Relapsed disease:
      - Lenalidomide-rituximab
      - Approved new agents and approaches include BTKi, CAR-T
      - Emerging agents include bispecific antibodies, antibody drug conjugates

ANTIMICROBIAL TREATMENT

EN MZL disease site and common genetic alterations/balanced translocations

SITE	ANTIGENIC ASSOCIATION	GENETIC ALTERATION
Stomach	H. Pylori	*MALT1, FOXP1, BCL10, MALT1, TNFAIP3 inact*
Intestinal	Campylobacter jejuni	*MALT1, BCL10*
Cutaneous	Borrelia Burgdorferi	*FOXP1, MALT1,*
Ocular adnexal	Chlamydia psittaci	*FOXP1, MALT1, TNFAIP3 inact*
Pulmonary	Achromonas xylosoxidans	*MALT1, BCL10, TNFAIP3 inact*
Salivary gland	Sjogren's disease	*MALT1, BCL10, TNFAIP3 inact*
Thyroid	Hashimoto's thyroiditis	*FOXP1, MALT1, TNFAIP3 inact*

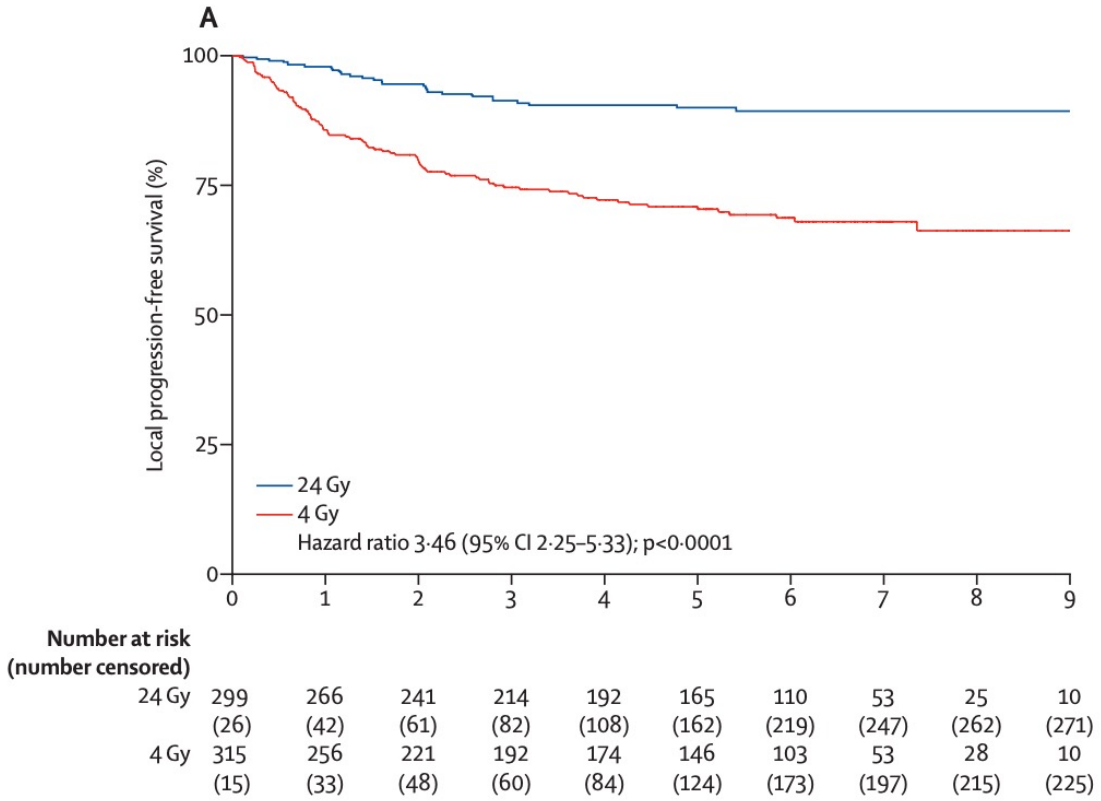
Key points:

- *t(11;18)* predicts for resistance to antimicrobial treatment in gastric EN MZL
- H. pylori eradication is standard of care for gastric EN MZL (and reasonable to try even if H. pylori testing is negative)
- Eradication of Hepatitis C is important in splenic MZL (but usually not definitive treatment)

Schrueder J Hematop. 2017 Sep 25;10(3-4):91-107

TREATMENT OF LIMITED STAGE DISEASE

Definitive radiotherapy in indolent B-NHL: 24Gy vs. 4Gy (FORT trial)



24Gy

4Gy

Method:

- 614 target sites in 548 patients were randomly assigned either 24 Gy in 12 fractions (n=299) or 4 Gy in two fractions (n=315)
  - **Only 84 pts with MZL**
  - **MZL and FL pts not separated**
- median follow-up 73.8 months
- Progression events: 27 in the 24 Gy group vs 90 in the 4 Gy group

NCCN and ESMO guidelines suggest 24Gy as the recommended treatment dose

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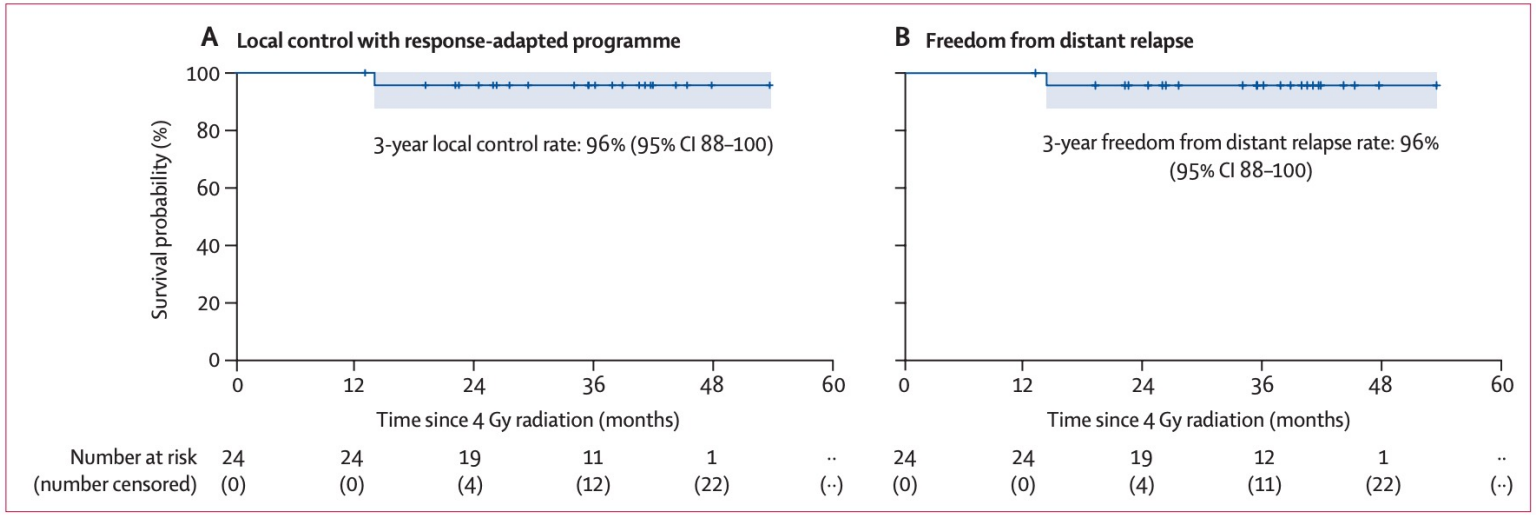
Hoskin Lancet Oncology Volume 22, Issue 3p332-340March 2021

Ultra low-dose radiotherapy for gastric EN MZL?

- N=24, single center analysis (MD Anderson Cancer Center)
- Mix of newly-diagnosed and relapsed HPE neg **gastric EN MZL**
- Patients treated with 4Gy
  →if CR, no more treatment (n=20)
  → if PR, re-eval at 6-9m
  → if persistent disease or PD, give 20Gy



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Gunther Lancet Haematology Volume 11, Issue 7e521-e529July 2024

Observation after full resection

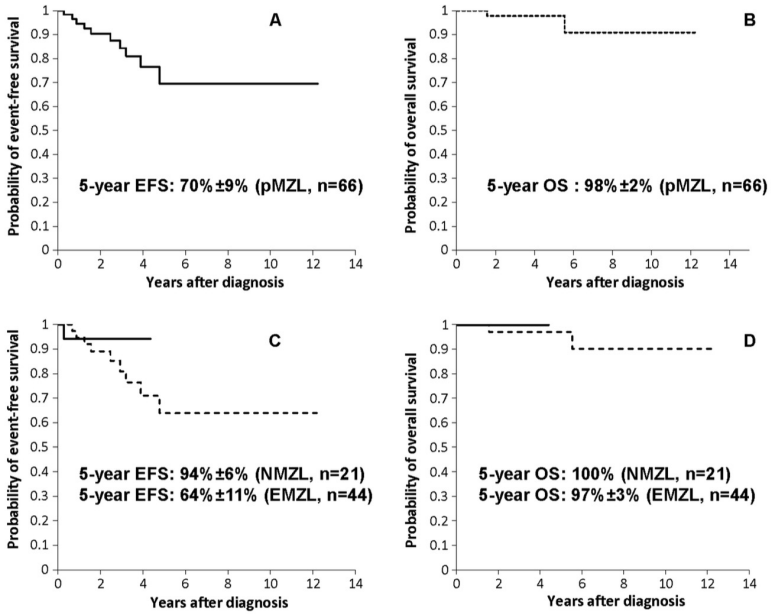
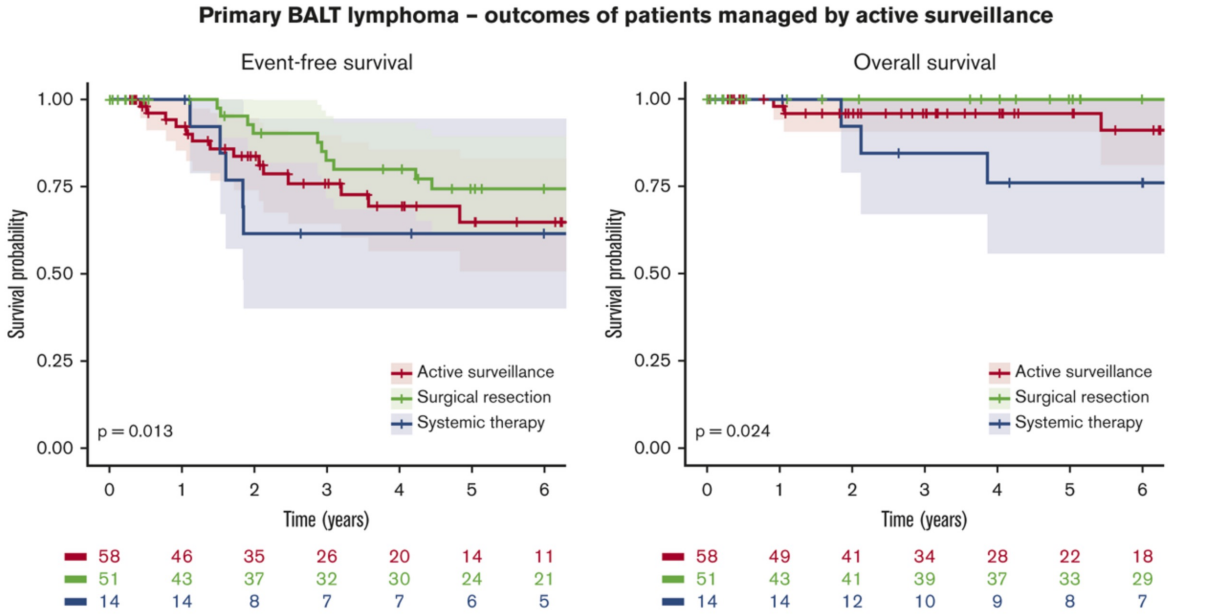


FIGURE 1 Five-year event-free survival and overall survival of the 66 patients with pediatric marginal zone lymphoma (pMZL; A and B) and of the 21 patients with nodal marginal zone lymphoma versus the 44 patients with extranodal marginal zone lymphoma (NMZL vs. EMZL; C and D)

Pediatric NMZL and EN MZL after full resection



With a median follow-up of 5 years, patients managed expectantly (n=58) had excellent outcomes, the majority requiring no treatment for the entire follow-up period (6-year EFS 65%), and few requiring more than a single line of therapy.

Pulmonary EN MZL after full resection

Ronceray Ped Blood Cancer 2018 Apr;65(4); Joffe Blood Adv (2021) 5 (2): 345–351

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INITIAL TREATMENT OF ADVANCED STAGE DISEASE

There are limited clinical trial data for patients with MZL

Study	Agent(s)	Study, n	Primary end point	Primary end point population	MZL, n (%)	MZL end point
Randomized phase 3 studies						
SELENE[102]	Ibrutinib + BR/R-CHOP vs placebo + BR/R-CHOP	403	PFS	FL and MZL	40 (14)	Subgroup
AUGMENT[29]	R2 vs placebo + R	358	PFS	FL and MZL	64 (18)	Subgroup
GALLIUM[95]	O + B/CHOP/CVP vs R + B/CHOP/CVP	1401	PFS	FL	196 (14)	Subgroup
GADOLIN[101]	BO vs B	396	PFS	FL, MZL, SLL, and LPL	47 (12)	Subgroup
BRIGHT[27]	BR vs R-CVP/R-CHOP	447	CR	FL, MZL, LPL, SLL, MCL, and unclassified	44 (10)	Subgroup
STiL[28]	BR vs R-CHOP	549	PFS	FL, MZL, LPL, SLL, MCL, and unclassified	115 (12)	Subgroup
IELSG-19[84]	R vs C vs CwR	454	EFS	EMZL	454 (100)	Primary
Single-arm phase 2 studies						
PCYC-1121[17]	Ibrutinib	63	ORR	MZL	100	Primary
MAGNOLIA[103]	Zanubrutinib	68	ORR	MZL	100	Primary
ACE-LY-003 (part 2)[104]	Acalabrutinib	43	ORR	MZL	100	Primary
ZUMA-5[131]	Axicabtagene ciloleucel	153	ORR	FL	24 (16)	Subgroup
BRISMA/IELSG-36[86]	BR	56	CR	SMZL	100	Primary
MALT 2008-01[85]	BR	60	EFS	EMZL	100	Primary
AGMT MALT-2[49]	R2	46	Objective/histologic response	EMZL	100	Primary

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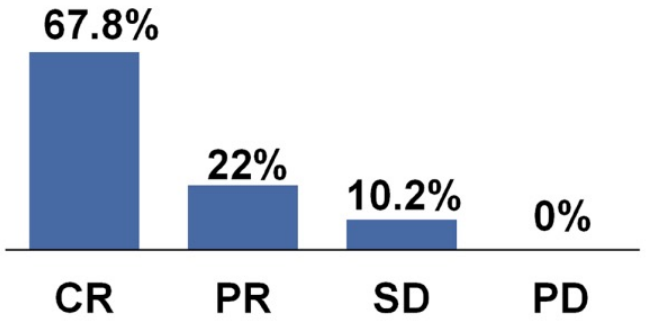
Alderuccio and Noy Blood 147 (2) 115

Rituximab monotherapy is active (but lower efficacy compared to FL)



4 doses of rituximab in EN MZL (n=59)

Table 3. Response to Treatment (n = 26)

	Patients	
	No.	%
Complete response	12*	46
Partial response	8	31
Stable disease	6	23

*Eleven of 12 complete responders were in stage I/II_1 at study entry.

4 doses of rituximab in gastric EN MZL (n=27)
46% CR rate

Response	No prior chemotherapy, n = 23	Prior chemotherapy, n = 11
ORR (%)	20 (87)†	5 (45)†
CR (%)	11 (48)	4 (36)
PR (%)	9 (39)	1 (9)
SD (%)	2 (9)	4 (36)
PD (%)	1 (4)	2 (18)

Decreased efficacy in relapsed disease

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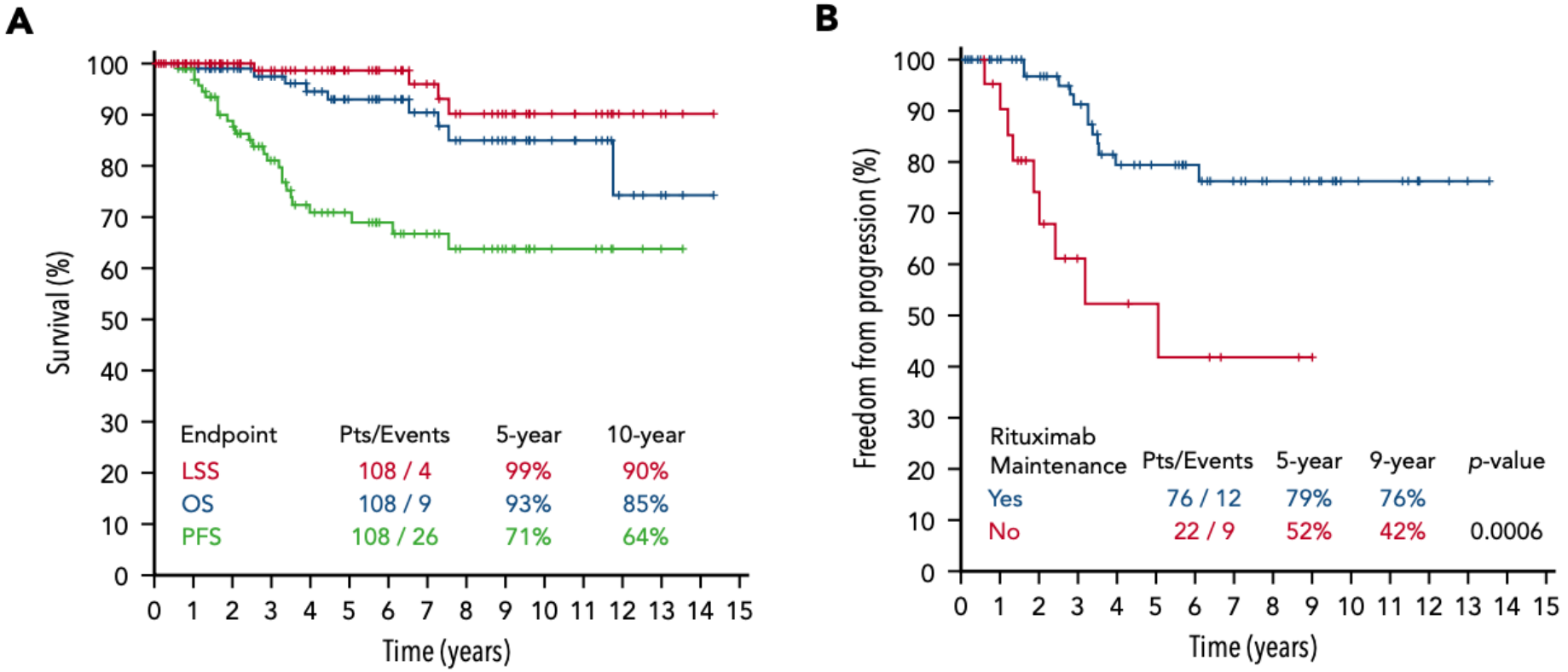
Conconi Blood (2003) 102 (8): 2741–2745; Kalpadakis Blood (2018) 132 (6): 666–670; Martinelli J Clin Oncol 2005 Mar 20;23(9):1979-83; Mazzoni Eur J Haematol 2025 Jan;114(1):70-78

Rituximab has replaced splenectomy for initial treatment of SMZL



Rituximab monotherapy as a splenectomy-sparing approach

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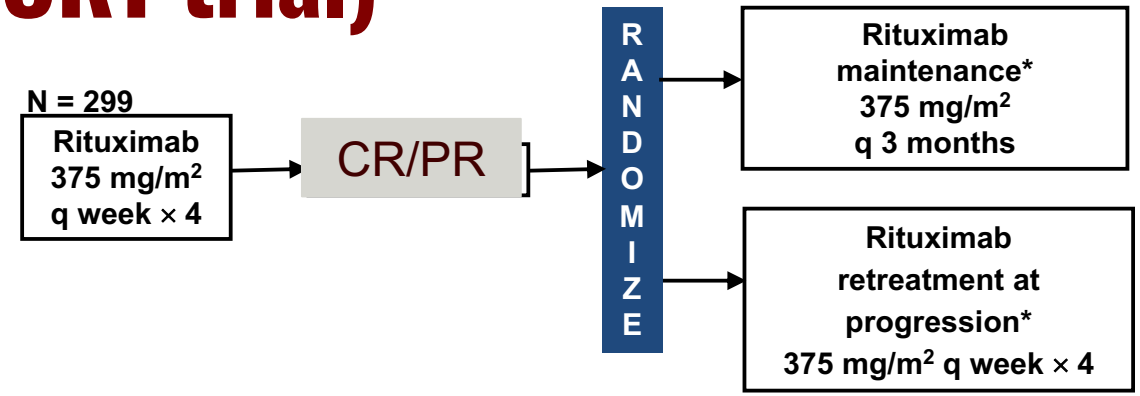
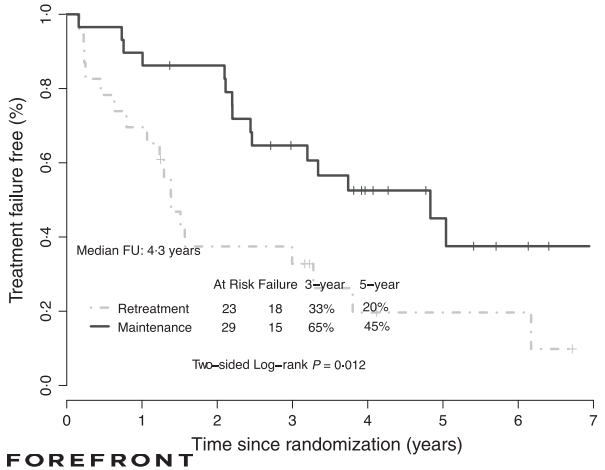
Conconi Blood (2003) 102 (8): 2741–2745; Kalpadakis Blood (2018) 132 (6): 666–670; Martinelli J Clin Oncol 2005 Mar 20;23(9):1979-83; Mazzoni Eur J Haematol 2025 Jan;114(1):70-78

Maintenance rituximab improves PFS, TTNT and duration of response (RESORT trial)

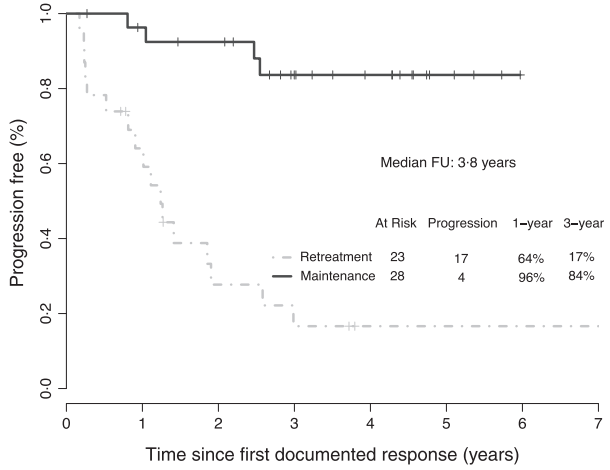
No diff in OS



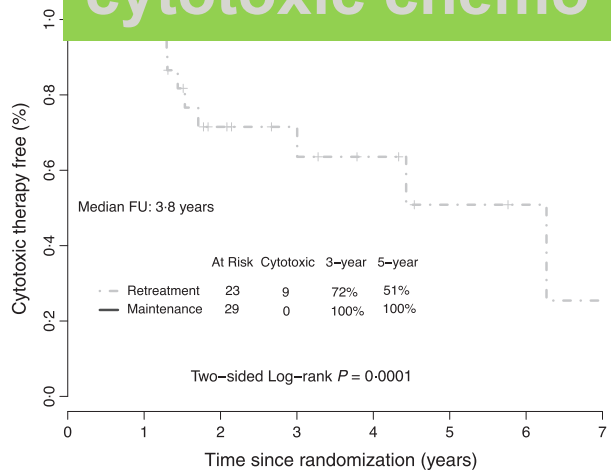
TTF



DR



Time to 1st cytotoxic chemo



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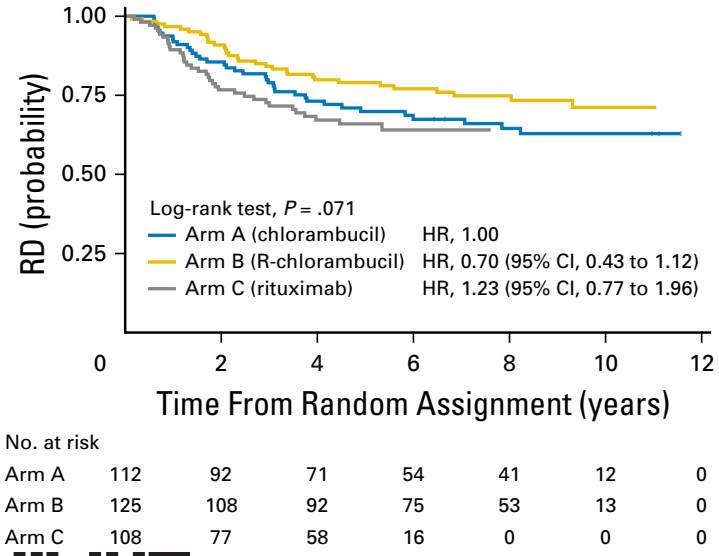
Williams Br J Haematol. 2016 Jun;173(6):867-75

Largest RP3 trial in MZL (IELSG-19): R-chl is superior to chl *AND* to rituximab monotherapy

MZL patients with no prior systemic therapy (n=454)

- Chl 6mg/m2 plus R weekly x 4, then monthly x 4(n=152)
- R weekly x 4, then monthly x 4 (n=151)
- Chl 6mg/m2 (n=151)

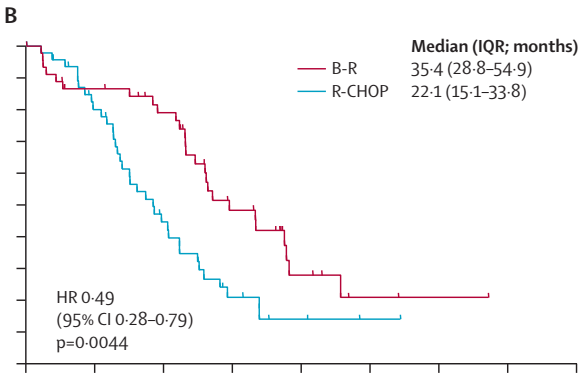


Response	Arm B Chlorambucil Plus Rituximab (n = 132) No.	% (95% CI)	Arm C Rituximab (n = 138) No.	% (95% CI)
Complete remission*	104	78.8 (70.1 to 85.4)	77	55.8 (47.0 to 64.2)
Partial remission	21	15.9 (10.1 to 23.3)	31	22.5 (15.8 to 30.3)
Stable disease	1	0.8 (0.02 to 4.1)	16	11.6 (6.8 to 18.1)
Progressive disease	4	3.0 (0.8 to 7.6)	12	8.7 (3.0 to 12.0)
Not assessed	2	1.5 (0.2 to 5.4)	2	1.5 (0.2 to 5.1)
Overall response rate *	125	94.7 (89.4 to 97.8)	108	78.3 (70.4 to 84.8)

Zucca J Clin Oncol. 2017 Jun 10;35(17):1905-1912

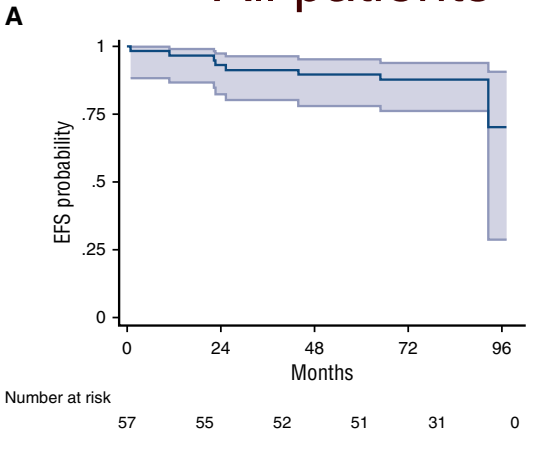
Bendamustine plus rituximab in TN MZL

PFS

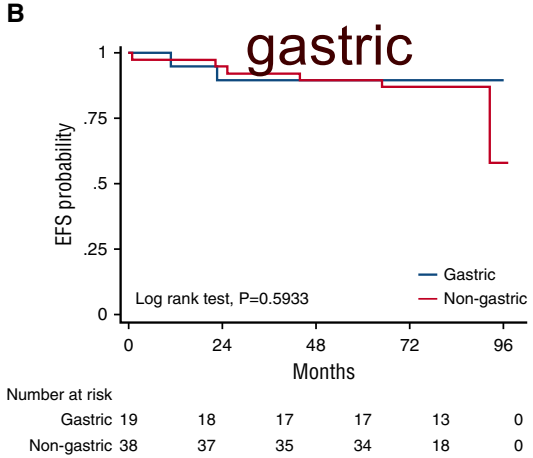


StIL Trial:
N=37 BR
N=30 R-CHOP
***difference is not statistically significant

All patients



Gastric vs. non-gastric



MALT 2008-01
N=57 evaluable
MZL

BR x 3

- **IF CR→ BR x 1 more**
- **IF PR→ BR x 3 more**

OS >96% at 7y

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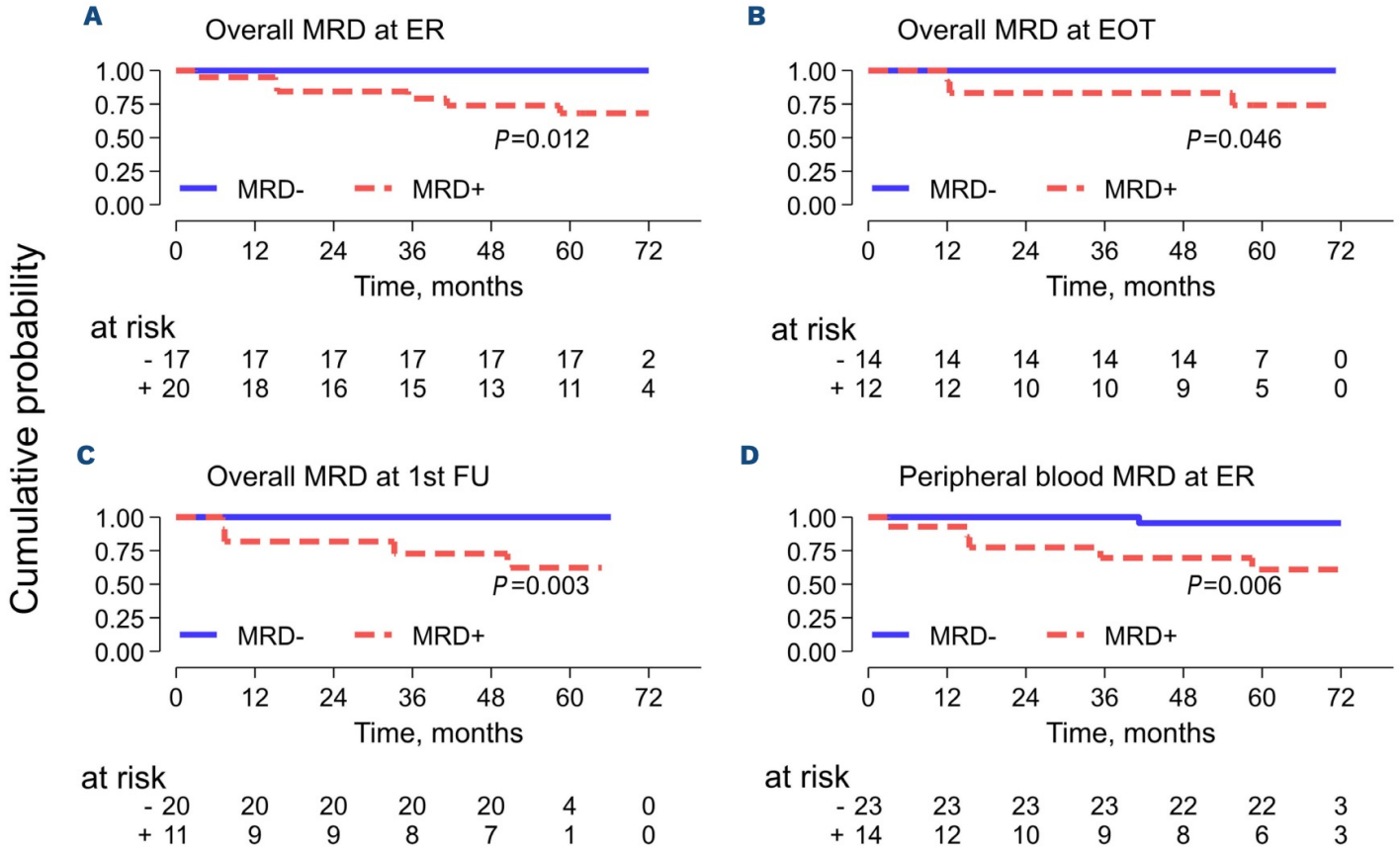
Rummel Lancet 2013; Salar Blood 2018

BRISMA-IELSG36 phase II study: MRD (via ddPCR) after BR is predictive of outcome



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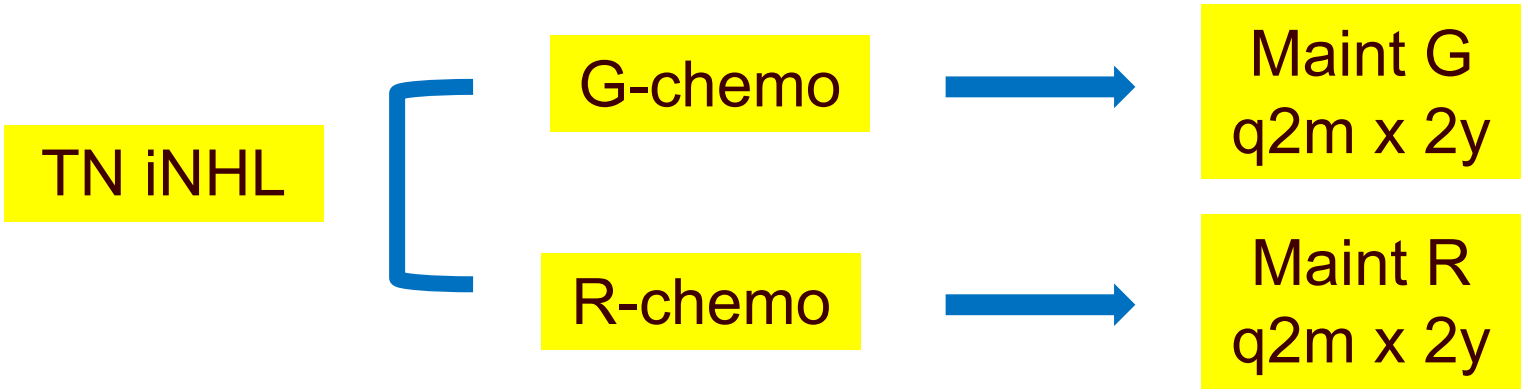
Obinutuzumab in MZL: GALLIUM subset analysis consistent with FL data



Parameter	G-chemo (n=99)	R-chemo (n=96)
Median observation time (range), months*	37.0 (0.6–54.4)	40.8 (0.2–52.8)
Number of PFS (INV) events (%)	21 (21.2)	26 (27.1)
HR for PFS (INV), G vs R (95% CL), p-value†	0.82 (0.45, 1.46), p=0.49	
HR for other time-to-event endpoints, G vs R (95% CL), p-value†		
PFS (IRC)‡	0.83 (0.46, 1.51), p=0.55	
Overall survival	0.90 (0.45, 1.81), p=0.78	
Time to new anti-lymphoma treatment	0.85 (0.48, 1.50), p=0.57	
Response at EOI by CT (INV)		
CR, n (%)	16 (16.2)	18 (18.8)
ORR, n (%)	82 (82.8)	78 (81.3)

Herold_et_al-2017-Hematological_Oncology.pdf

Selected ongoing clinical trials in 1L setting

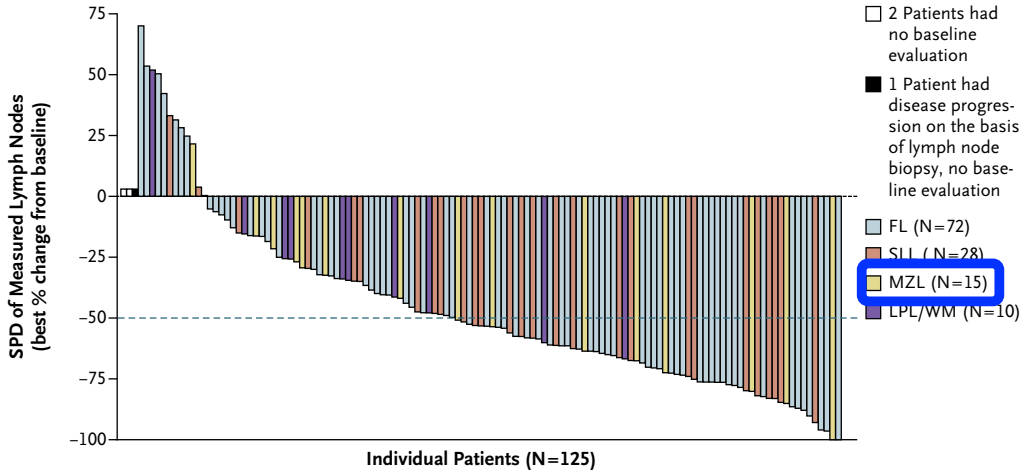
- Pirtobrutinib plus rituximab NCT06390956
- Epcoritamab monotherapy NCT06796998
- Rituximab plus venetoclax NCT06510309
- Mosunetuzumab monotherapy NCT06569680
- Tafa-Len-R in FL and MZL NCT06792825

RELAPSED/REFRACTORY DISEASE

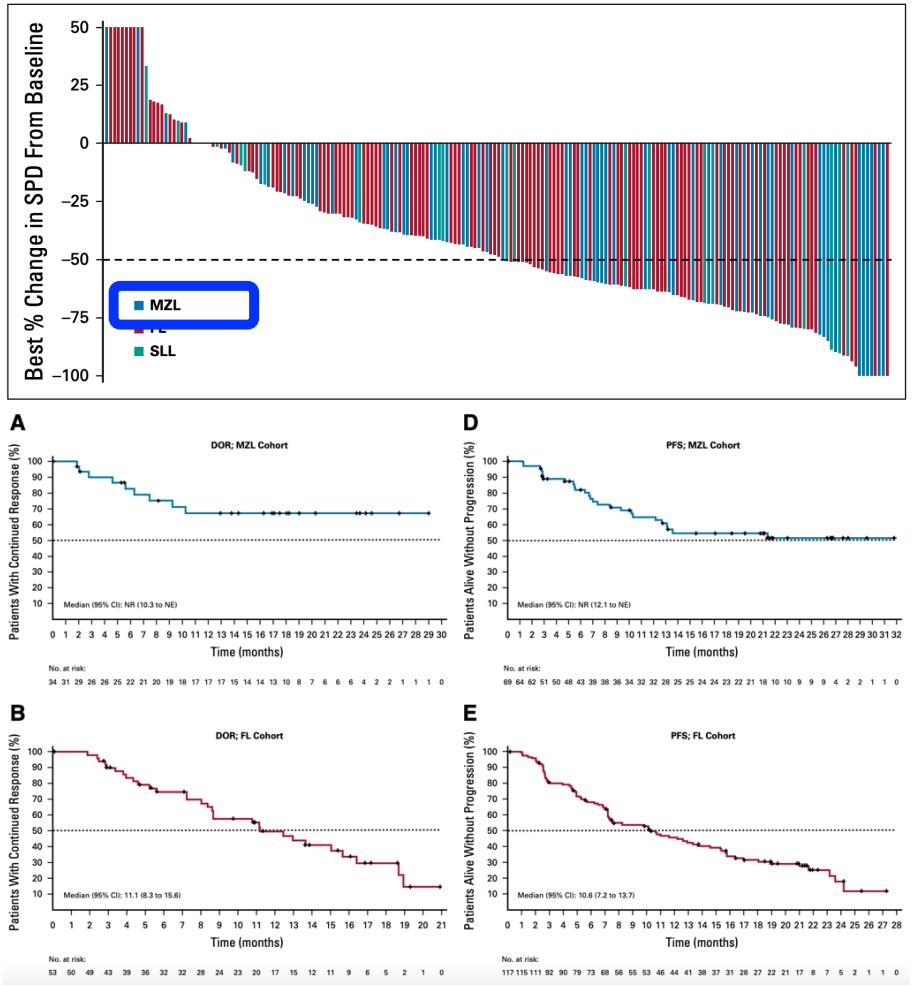
Treatment approach for relapsed/refractory MZL

- Retreatment with rituximab
- Bendamustine plus Obinutuzumab
- Lenalidomide-rituximab
- BTKi
- CAR-T
- Emerging agents: bispecific antibodies

PI3Ki: idelalisib in ref MZL (n=15) and umbralisib in rel/ref MZL (n=69)



ORR 49%; CR 16%
Possible better PFS and OS than FL



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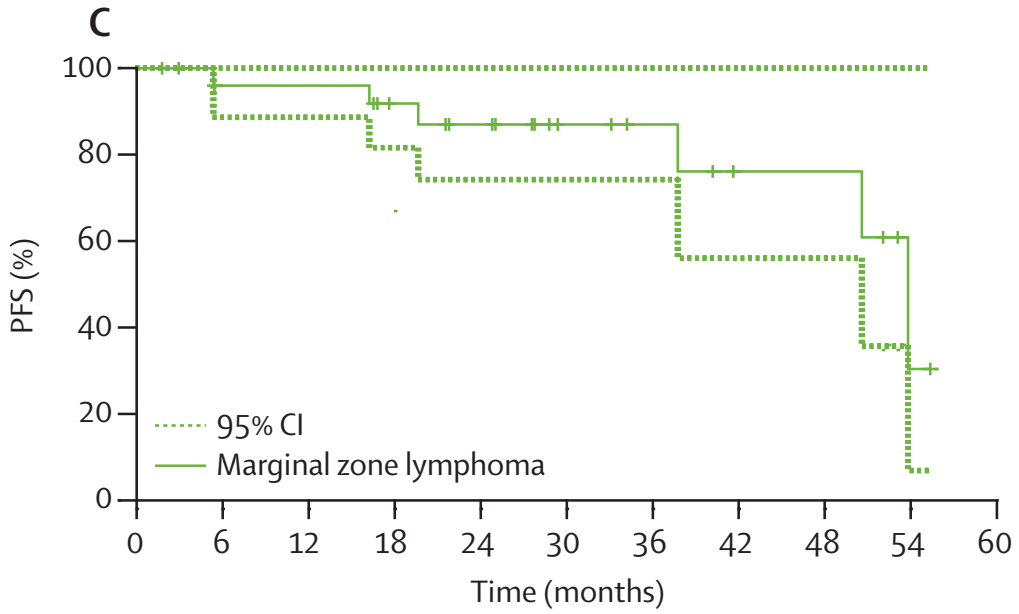
Gopal N Engl J Med. 2014 Mar 13;370(11):1008-18; Fowlder J Clin Oncol 2021 May 20;39(15):1609-1618

Lenalidomide plus rituximab: phase 2 trial



	Follicular lymphoma (n=50)	Marginal zone lymphoma (n=30)	Small lymphocytic lymphoma (n=30)
Age (years; median, range)	56 (35–84	59 (36–77)	59 (34–76)
Sex, female	22 (44%)	18 (60%)	12 (40%)
Stage			
III	23 (46%)	9 (30%)	0
IV	27 (54%)	21 (70%)	30 (100%)
High tumour burden (as per GELF)	27 (54%)	13 (43%)	14 (47%)

MARGINAL ZONE LYMPHOMA COHORT:

ORR 89%

CR 67%

Med PFS 53.8 months

3-year PFS 87%

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Fowler Lancet 2014

Lenalidomide plus rituximab: Multicenter Phase 2 (n=46)

Len 20mg/d plus rituximab x 6 cycles

- If CR, no more treatment
- If PR, 2 more cycles

- Med age 64y
- Primary location of EN MZL:
  - 30% stomach
  - 28% ocular adnexa
  - 11% lung
- Minimal prior rituximab
- Stage
  - 61% localized disease
  - 39% disseminated disease

RESULTS:

- Med f/u 27 m with 91% PFS
- ORR 80%, CR 54%
- Mean number of cycles = 6

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Kiewswetter Blood 2017

AUGMENT TRIAL: R2 vs R mono shows no added benefit for MZL patients

TABLE A4. Efficacy in Patients With Marginal Zone Lymphoma

Variable	Lenalidomide + Rituximab (n = 31)	Placebo + Rituximab (n = 32)	HR (95% CI)*	*P**
Best response, as assessed by IRC				
ORR, No. (% [95% CI])	20 (65 [45 to 81])	14 (44 [26 to 62])		.1313
CR, No. (% [95% CI])	9 (29 [14 to 48])	4 (13 [4 to 29])		.1289
PR, No. (%)	11 (35)	10 (31)		
SD, No. (%)	6 (19)	11 (34)		
PD/death, No. (%)	0	4 (13)		
Not done/missing/no evidence of disease at baseline, No. (%)	5 (16)	3 (9)		
Median PFS, as assessed by IRC, months (95% CI)	20.2 (16.0 to NR)	25.2 (11.1 to NR)	1.00 (0.47 to 2.13)	.9984
Median PFS, as assessed by investigator, months (95% CI)	19.2 (13.9 to 30.4)	22.1 (8.7 to NR)	1.04 (0.54 to 2.01)	.8918
Median EFS as assessed by IRC, months (95% CI)	20.2 (14.5 to NR)	25.1 (9.2 to NR)	1.18 (0.60 to 2.29)	.6324
Median DOR, as assessed by IRC, months (95% CI)	17.4 (13.2 to NR)	NR (8.4 to NR)	1.81 (0.56 to 5.84)	.3111
Median TTNLT, months (95% CI)	25.8 (17.7 to NR)	NR (21.6 to NR)	1.58 (0.68 to 3.67)	.3057
OS probability at 2 years, % (95% CI)	82 (61 to 92)	94 (77 to 98)	2.89 (0.56 to 14.92)	
Deaths, No. (%)	5 (16)	2 (6)		

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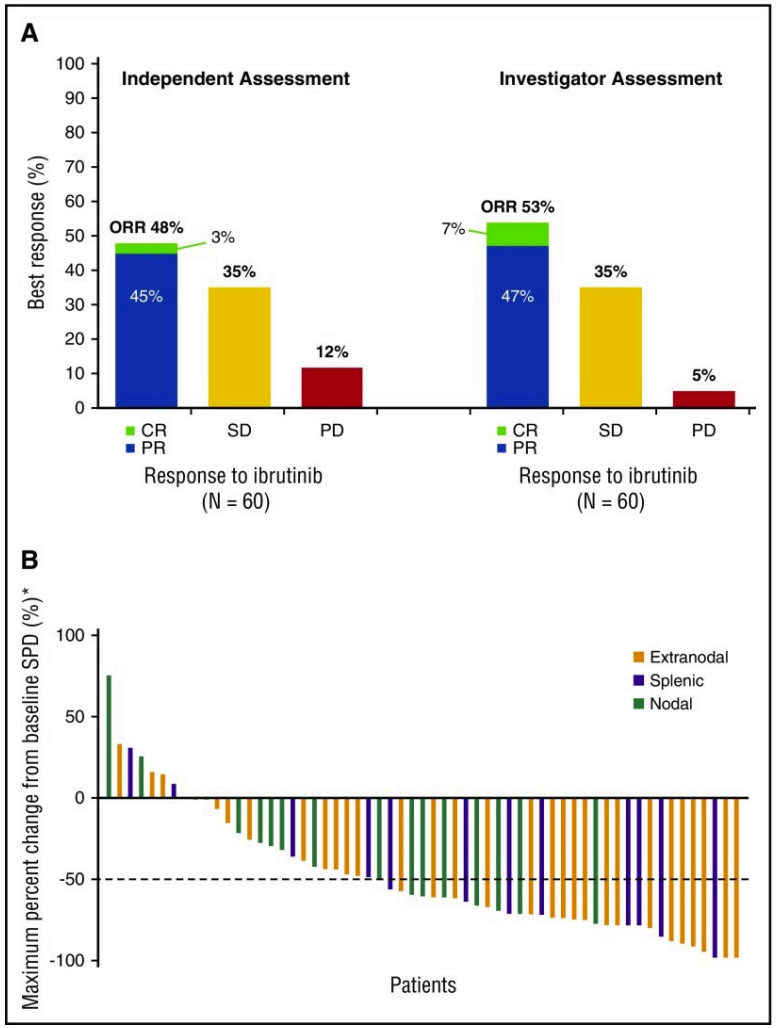
Leonard J Clin Oncol. 2019 May 10;37(14):1188-1199

Ibrutinib in rel/ref MZL

	N=63
Med Age	66 y (30-92)
PS ≥1	30 (48%)
EN MZL	32 (51%)
SMZL	14 (22%)
NMZL	17 (27%)
> 2 prior Rx	40 (64%)
Ref to last systemic Tx	14 (22%)



Primary endpoint: ORR

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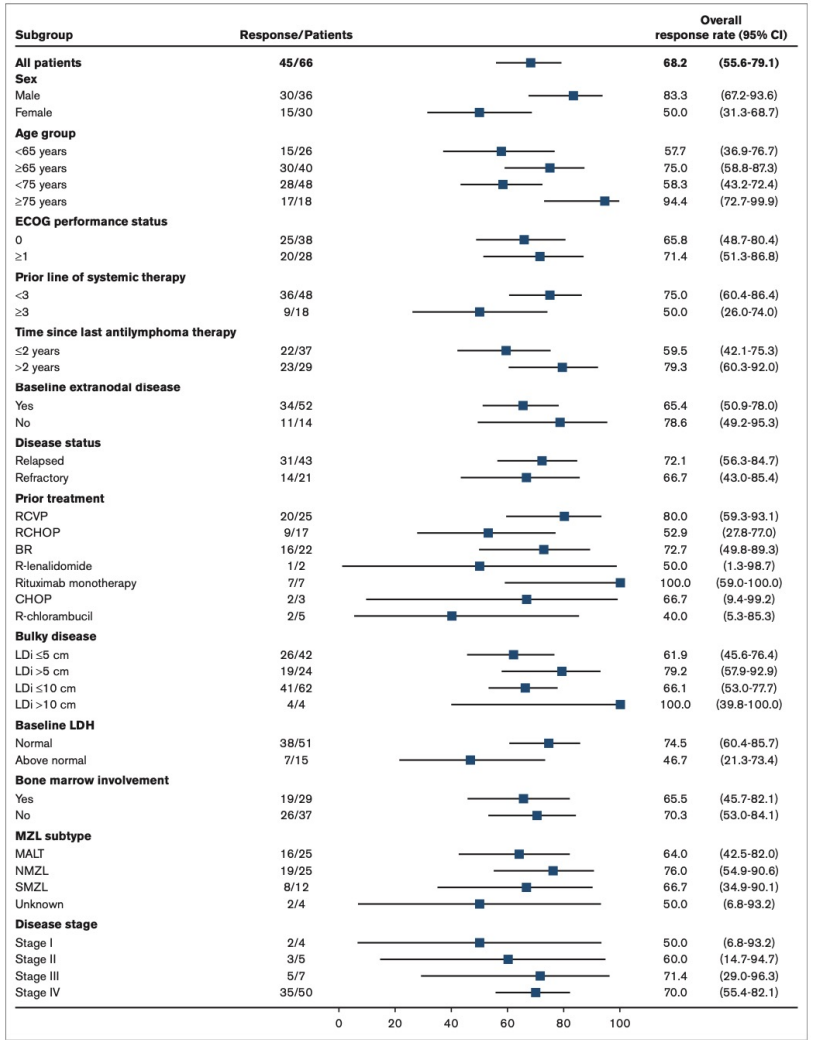
Noy Blood. 2017 Apr 20;129(16):2224-2232.

Zanubrutinib in RR MZL: MAGNOLIA Study (n=68) single arm trial

- Key patient characteristics:
  - Med age 70y, 27% over age 75y
  - 77% EN disease
  - 10% had non-FDG avid disease
  - MZL subtypes: EN MZL 38%, NMZL 38%, SMZL
  - Med 2L prior lines of therapy
- Results: med f/u 27.4 months,
  - **ORR 68.2; CR 26%**
  - 24-month DOR 72.9%
  - 24-month PFS 70.9%
  - 24-month OS 85.9%



Subgroup	Response/Patients	Overall response rate (95% CI)
All patients	**45/66**	**68.2 (55.6-79.1)**
Sex		
Male	30/36	83.3 (67.2-93.6)
Female	15/30	50.0 (31.3-68.7)
Age group		
<65 years	15/26	57.7 (36.9-76.7)
≥65 years	30/40	75.0 (58.8-87.3)
<75 years	28/48	58.3 (43.2-72.4)
≥75 years	17/18	94.4 (72.7-99.9)
ECOG performance status		
0	25/38	65.8 (48.7-80.4)
≥1	20/28	71.4 (51.3-86.8)
Prior line of systemic therapy		
<3	36/48	75.0 (60.4-86.4)
≥3	9/18	50.0 (26.0-74.0)
Time since last antilymphoma therapy		
≤2 years	22/37	59.5 (42.1-75.3)
>2 years	23/29	79.3 (60.3-92.0)
Baseline extranodal disease		
Yes	34/52	65.4 (50.9-78.0)
No	11/14	78.6 (49.2-95.3)
Disease status		
Relapsed	31/43	72.1 (56.3-84.7)
Refractory	14/21	66.7 (43.0-85.4)
Prior treatment		
RCVP	20/25	80.0 (59.3-93.1)
RCHOP	9/17	52.9 (27.8-77.0)
BR	16/22	72.7 (49.8-89.3)
R-lenalidomide	1/2	50.0 (1.3-98.7)
Rituximab monotherapy	7/7	100.0 (59.0-100.0)
CHOP	2/3	66.7 (9.4-99.2)
R-chlorambucil	2/5	40.0 (5.3-85.3)
Bulky disease		
LDi ≤5 cm	26/42	61.9 (45.6-76.4)
LDi >5 cm	19/24	79.2 (57.9-92.9)
LDi ≤10 cm	41/62	66.1 (53.0-77.7)
LDi >10 cm	4/4	100.0 (39.8-100.0)
Baseline LDH		
Normal	38/51	74.5 (60.4-85.7)
Above normal	7/15	46.7 (21.3-73.4)
Bone marrow involvement		
Yes	19/29	65.5 (45.7-82.1)
No	26/37	70.3 (53.0-84.1)
MZL subtype		
MALT	16/25	64.0 (42.5-82.0)
NMZL	19/25	76.0 (54.9-90.6)
SMZL	8/12	66.7 (34.9-90.1)
Unknown	2/4	50.0 (6.8-93.2)
Disease stage		
Stage I	2/4	50.0 (6.8-93.2)
Stage II	3/5	60.0 (14.7-94.7)
Stage III	5/7	71.4 (29.0-96.3)
Stage IV	35/50	70.0 (55.4-82.1)

Opat Blood Adv 2023 Nov 28;7(22):6801-6811

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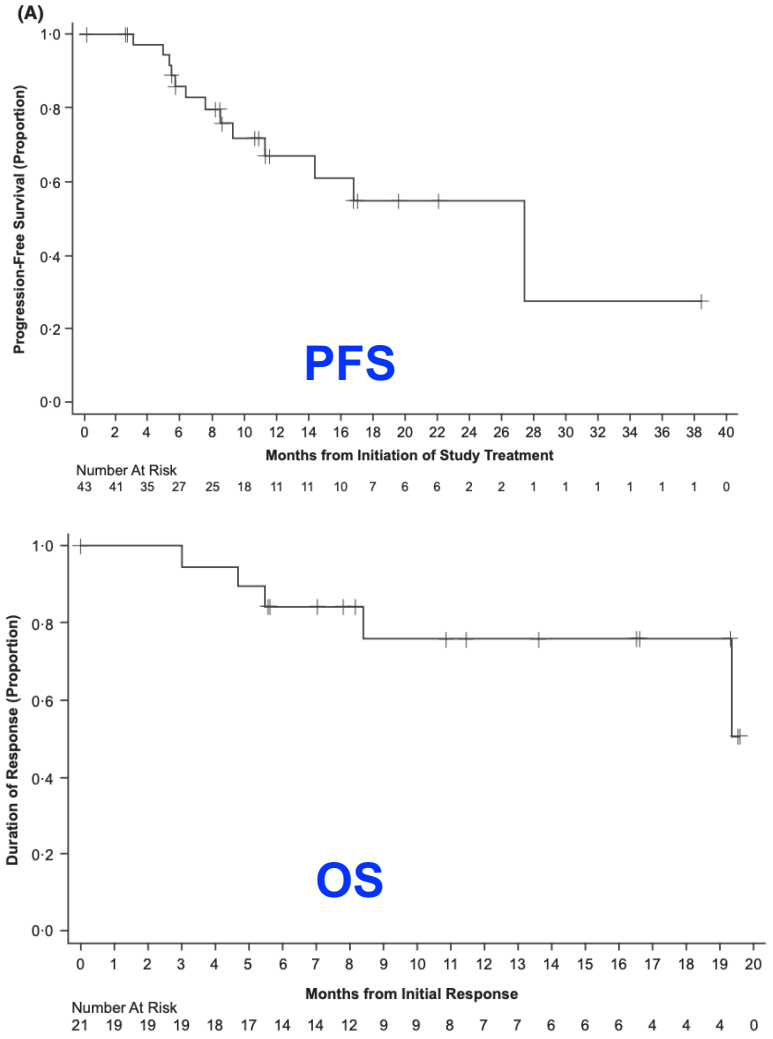
Acalabrutinib monotherapy (n=43)

- Patient Characteristics

MZL subtype, *n* (%)	
Extranodal	19 (44.2)
Gastric MALT	2 (4.7)
Non-gastric MALT	17 (39.5)
Nodal	13 (30.2)
Splenic	11 (25.6)

  - Med age 69; 46% ≥ 70y
  - Med 1 PLOT



ORR 53%
CR 5%

Strati Br J Haematol 2022 Oct;199(1):76-85

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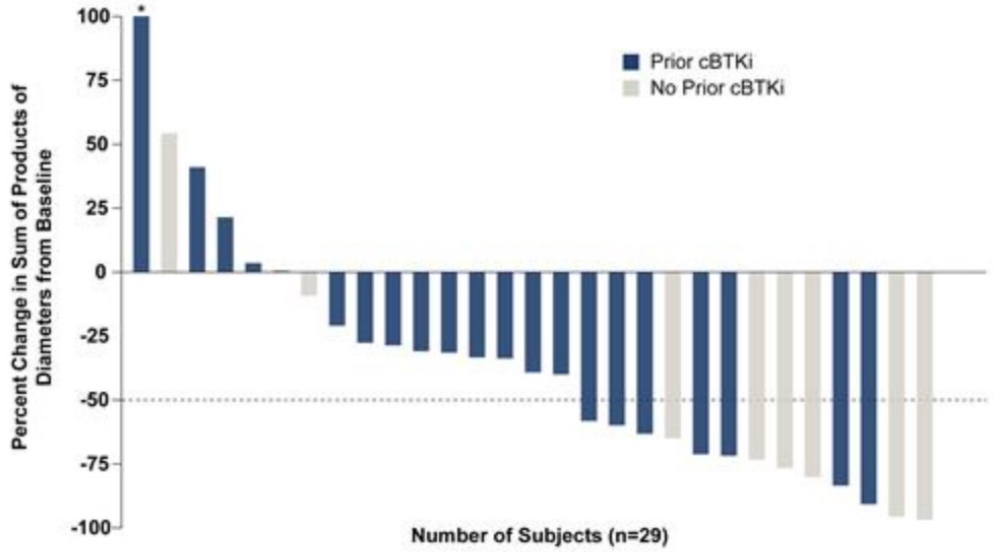
Pirtobrutinib in RR MZL: Phase 1/2 BRUIN

N=36
Med age 68y
Med PLOT 3
MZL subtype:
- 47% nodal
- 36% splenic
- 17% EN

26 pts (72%) with prior cBTKi,
- 20 (77%) pts discontinued for PD
- 6 (23%) discontinued for toxicity

Figure: Pirtobrutinib Efficacy in Marginal Zone Lymphoma patients



*Indicates patients with >100% increase in SPD, corresponding change from baseline is 181.6%

ORR 50%

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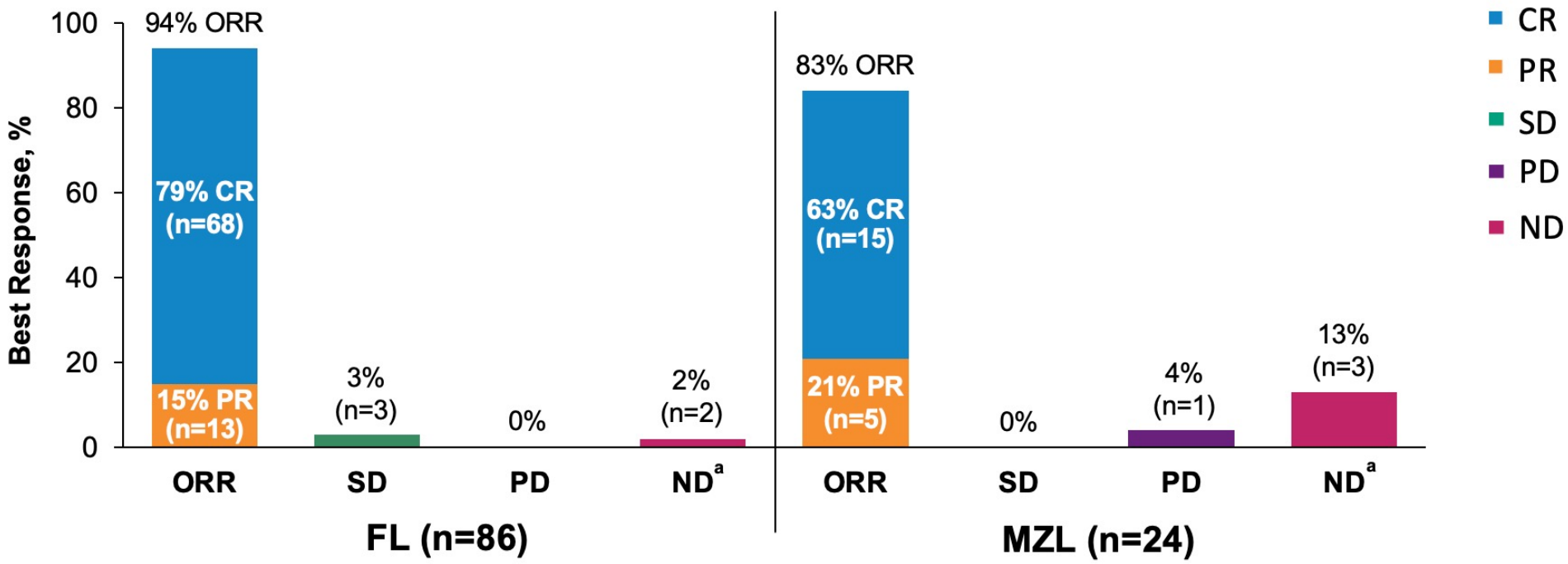
Patel Blood (2023) 142 (Supplement 1): 1660.

ZUMA-5: Axi-cel in MZL



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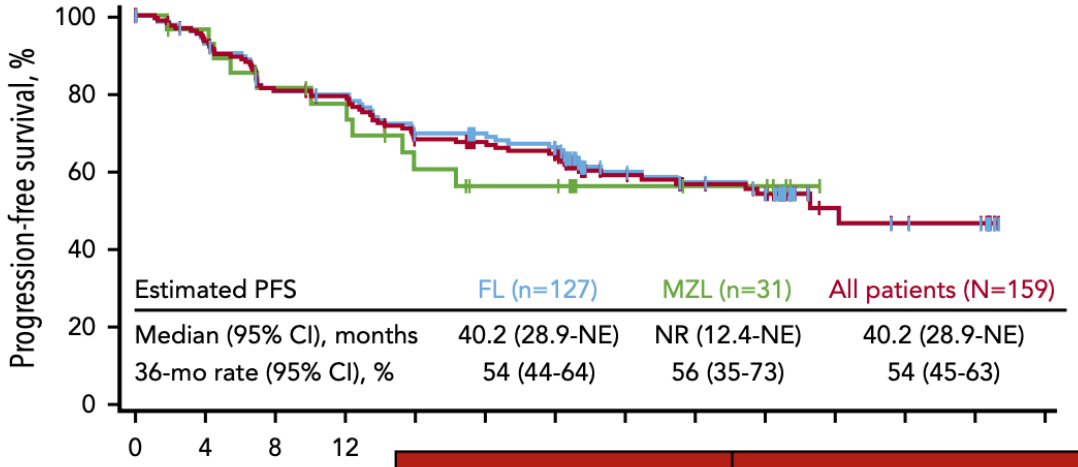
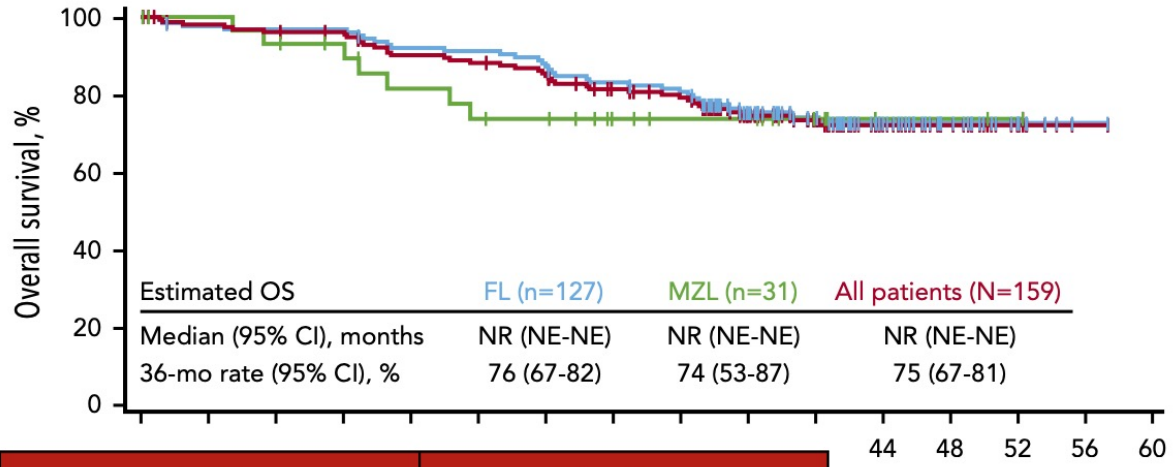
Neelapu ASH 2021

Axi-cel in MZL (n=31, f/u 32m)

A



B



n (%)	FL (n = 124)		MZL (n = 28)		All patients (N = 152)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	20 (16)	10 (8)	10 (36)	7 (25)	30 (20)	17 (11)
Serious AEs	11 (9)	10 (8)	4 (14)	3 (11)	15 (10)	13 (9)
Cytopenias	3 (2)	2 (2)	5 (18)	5 (18)	8 (5)	7 (5)
CRS	0	0	3 (11)	0	3 (2)	0
Neurologic events	0	0	1 (4)	1 (4)	1 (1)	1 (1)
Infections	14 (11)	6 (5)	7 (25)	2 (7)	21 (14)	8 (5)

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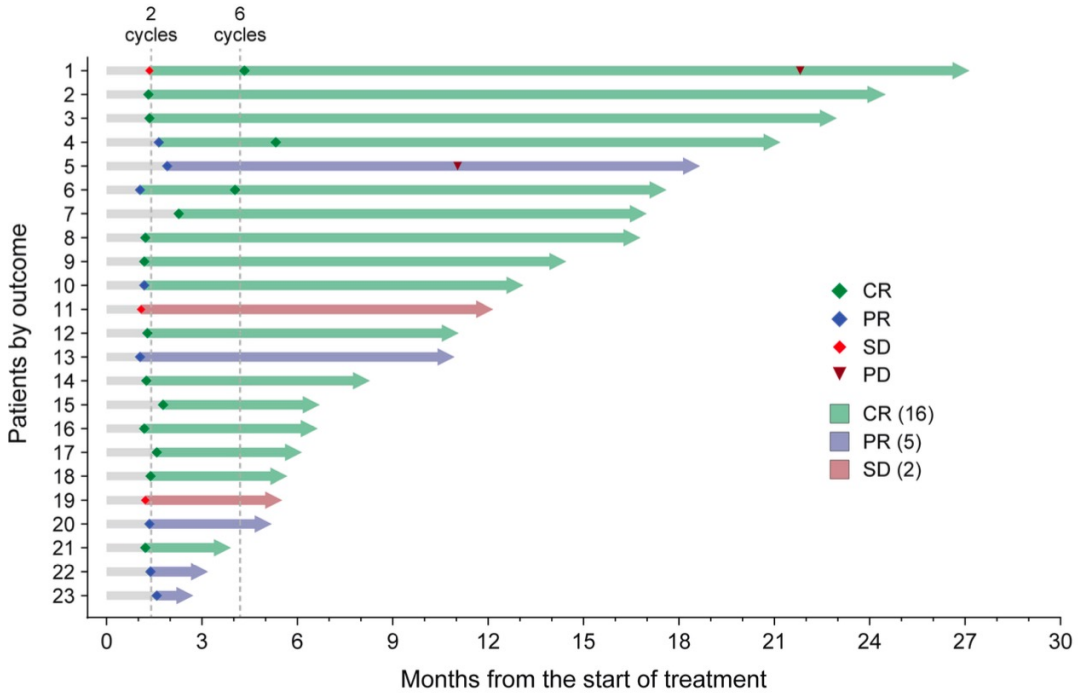
Neelapu Blood (2024) 143 (6): 496–506.

Loncastuximab teserine in RR MZL (n=23)

Characteristic	Patients (N = 23)
Age, median (range)	65 (45-82)
Gender (M:F)	8:15
Race, n (%) Asian Black non-Hispanic White Hispanic White non-Hispanic	 2 (9) 1 (4) 9 (39) 11 (48)
MZL type, n (%) EMZL NMZL SMZL	 14 (61) 7 (30) 2 (9)
Stage, n (%) I III IV	 4 (17) 2 (9) 17 (74)

Characteristic	Patients (N = 23)
ECOG PS 0-1, n (%)	23 (100)
POD24, n (%)	11 (48)
Median previous lines of treatment (range)	2 (1-4)
Relapsed, n (%)	14 (61)
Refractory, n (%)	9 (39)
Previous treatments,[a] n (%) Rituximab XRT R-CHOP BR BTKi R^2 RICE	 8 (35) 7 (30) 7 (30) 6 (26) 4 (17) 3 (13) 2 (9)

UPDATE: presentation at ICML 2025



ORR 91%
CR 70%
1 patient post-CAR-T had CR

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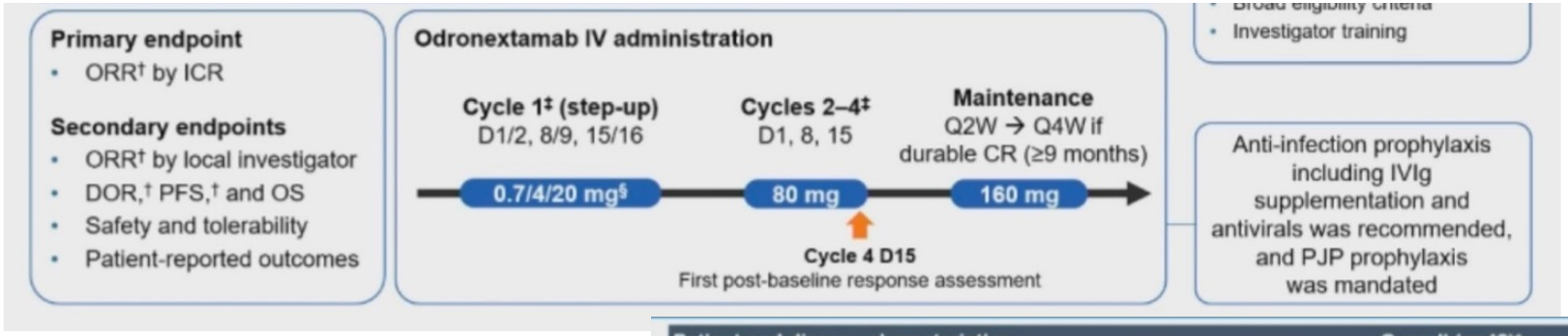
Lossos ASH 2024

Odronextamab in RR MZL (ELM-2 Study; n=42)



Patient and disease characteristics		Overall (n=42)*	Extranodal (n=21)	Nodal (n=15)	Splenic (n=5)
Median age (range), years		63.5 (34–82)	59.0 (34–82)	66.0 (38–80)	73.0 (52–80)
Age, %	*≥65 / ≥75*	47.6 / 23.8	33.3 / 19.0	66.7 / 26.7	60.0 / 40.0
Male, %		45.2	42.9	46.7	40.0
Ann Arbor stage III/IV, %		83.3	76.2	93.3	80.0
Bulky disease, %		9.5	14.3	0	20.0
Race, %	*White / Asian / Black or African American / Not reported*	47.6 / 38.1 / 4.8 / 9.5	33.3 / 57.1 / 4.8 / 4.8	60.0 / 26.7 / 6.7 / 6.7	80.0 / 0 / 0 / 20.0
ECOG PS, %	*0 / 1*	45.2 / 54.8	42.9 / 57.1	46.7 / 53.3	40.0 / 60.0
IPI score, %	*3 / 4–5*	19.0 / 9.5	23.8 / 0	13.3 / 20.0	20.0 / 20.0
Median number of prior lines of therapy (range)		2 (1–8)	2 (1–8)	2 (1–4)	2 (2–4)
Number of prior lines,† %	*≥2 / ≥3 / ≥4 / ≥5*	83.3 / 31.0 / 19.0 / 2.4	76.2 / 38.1 / 19.0 / 4.8	93.3 / 20.0 / 13.3 / 0	100 / 40.0 / 40.0 / 0
Primary refractory, %		33.3	38.1	33.3	20.0
Refractory to last line of therapy, %		64.3	57.1	80.0	60.0
Refractory to anti-CD20 antibody in any line, %		47.6	52.4	53.3	20.0
Double refractory to alkylator/anti-CD20 antibody in any line, %		33.3	42.9	33.3	0
Prior BTKi, %		28.6	19.0	33.3	60.0
Prior bendamustine, %		33.3	33.3	40.0	20.0
Prior ASCT, %		7.1	9.5	6.7	0
POD24, %		50.0	57.1	60.0	0

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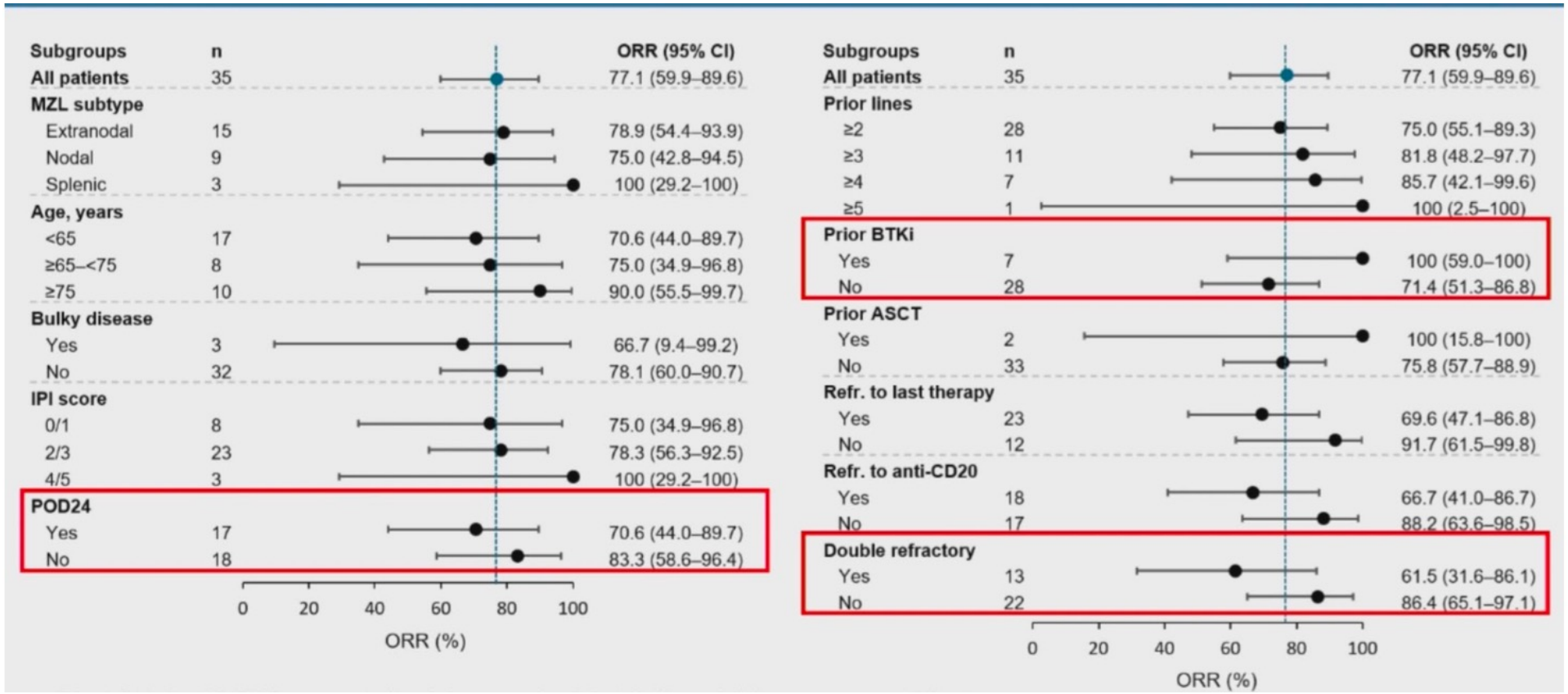
Odronextamab in RR MZL (n=42)



- 77% ORR and CR
- Med PFS/OS not reached with med f/u 11m)
- Similar safety profile to other lymphomas

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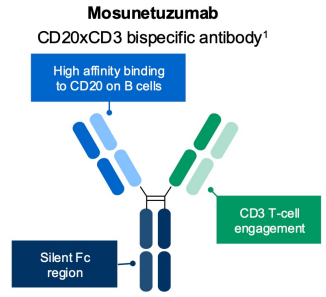
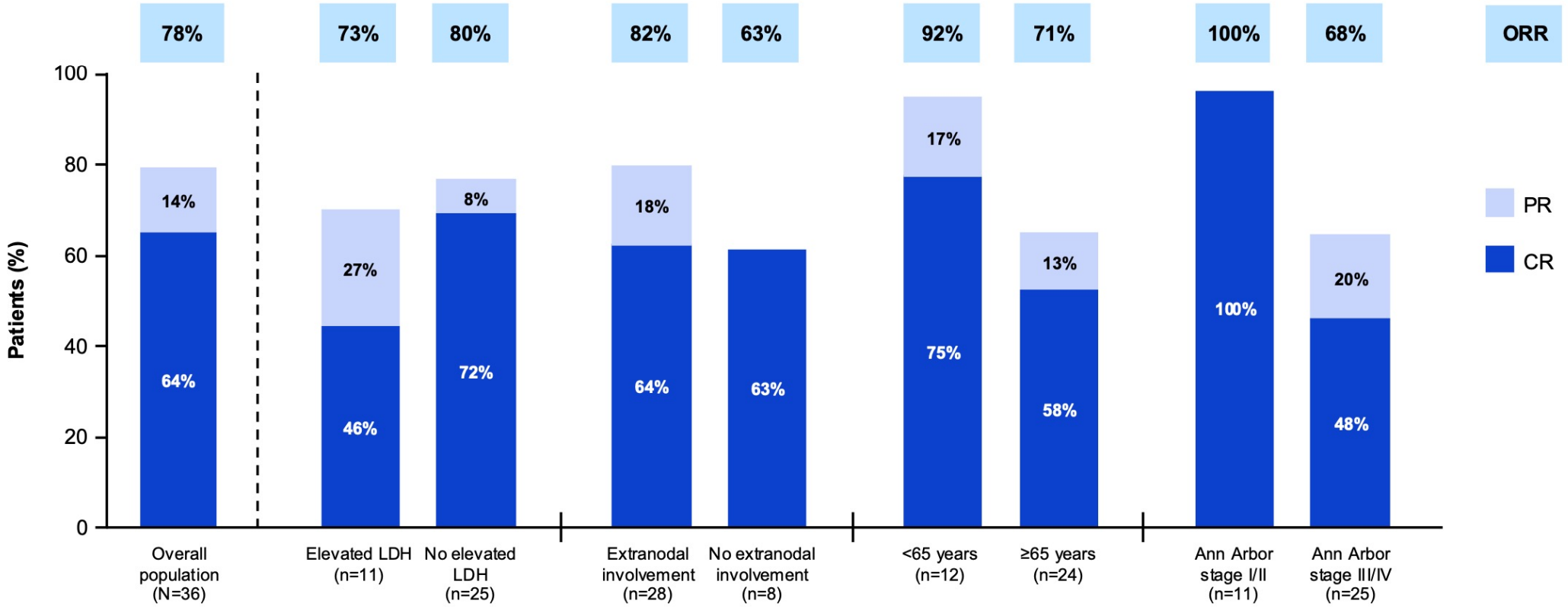
Emerging data with mosunetuzumab

Agent/regimen	No. pts with MZL	Key patient features	ORR/CR	comments
Mosunetuzumab (Olszewski 2024, BrUOG-401) plus len augmentation	15	Treatment-naïve population	86%/86%	
Mosunetuzumab (Lynch ASH 2023)	3	Treatment-naïve population	100%** (MZL not separately reported)	No G2+ CRS

MorningSun: Open-label Phase II trial of the efficacy and safety of subcutaneous mosunetuzumab▼ (Mosun SC) as frontline (1L) treatment in symptomatic patients with marginal zone lymphoma (MZL)





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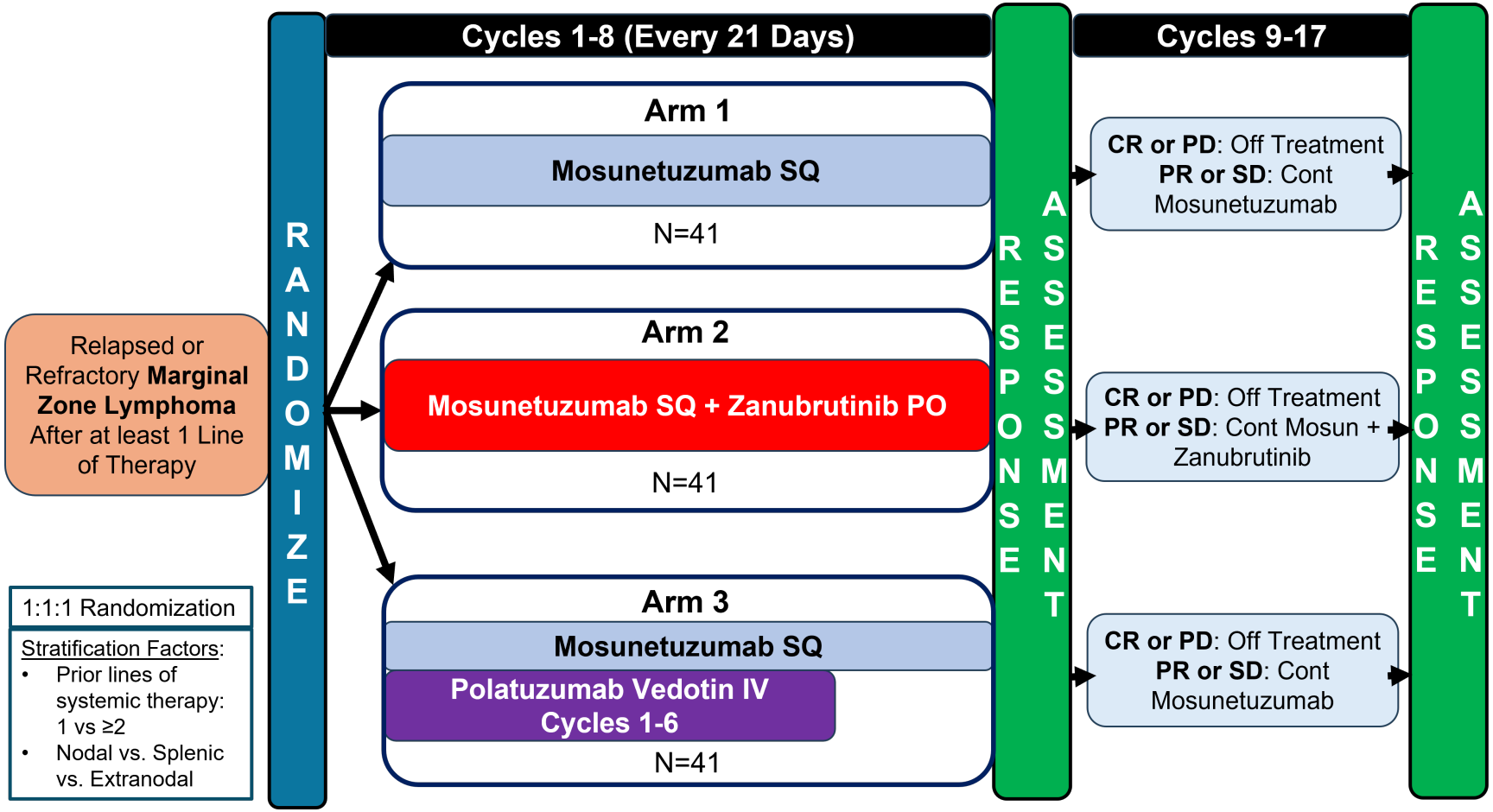
Burke EHA 2025

S2506 SCHEMA: coming soon!!!



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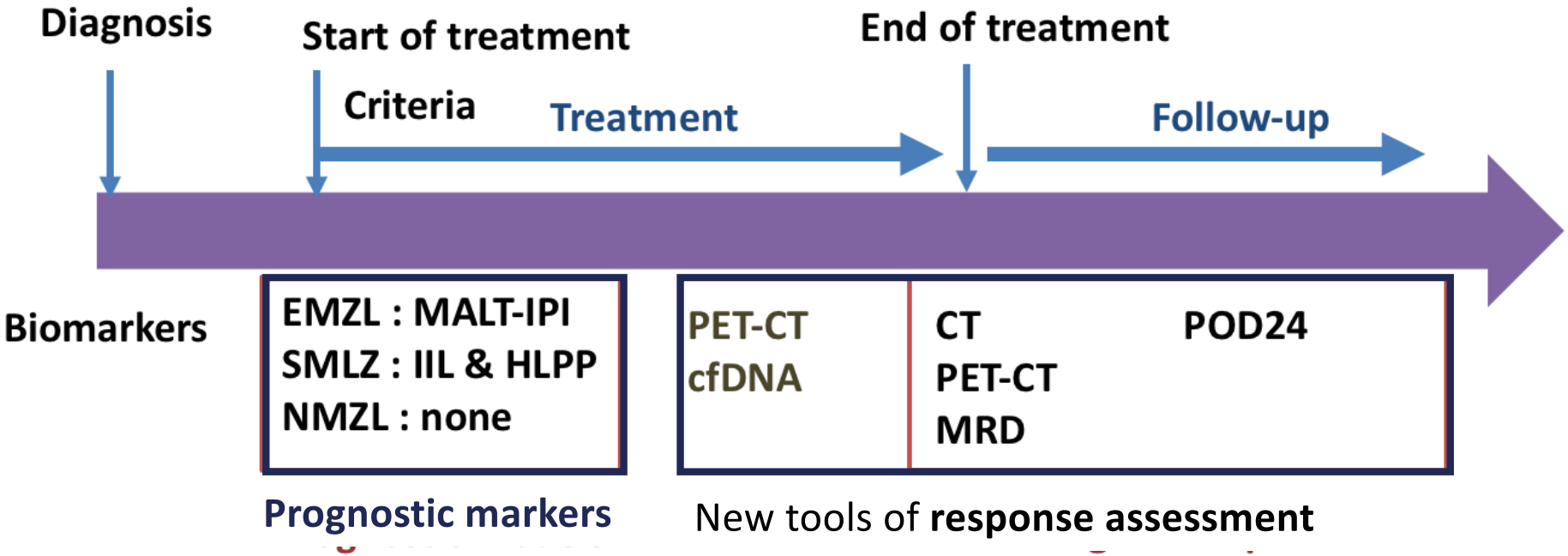
How do we move forward given heterogeneity, relative rarity, difficulty staging/response assessment, etc? Markers in MZL



***Slide from Catherine Thieblemont

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Biomarkers Definitions Working Group, Clin Pharmacol Ther 2001; Thieblemont, NY MZL workshop 2019

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Emerging immunotherapy advances for non-Hodgkin lymphomas