LINFOMI INDOLENTI NON FOLLICOLARI

Linfomi della zona marginale

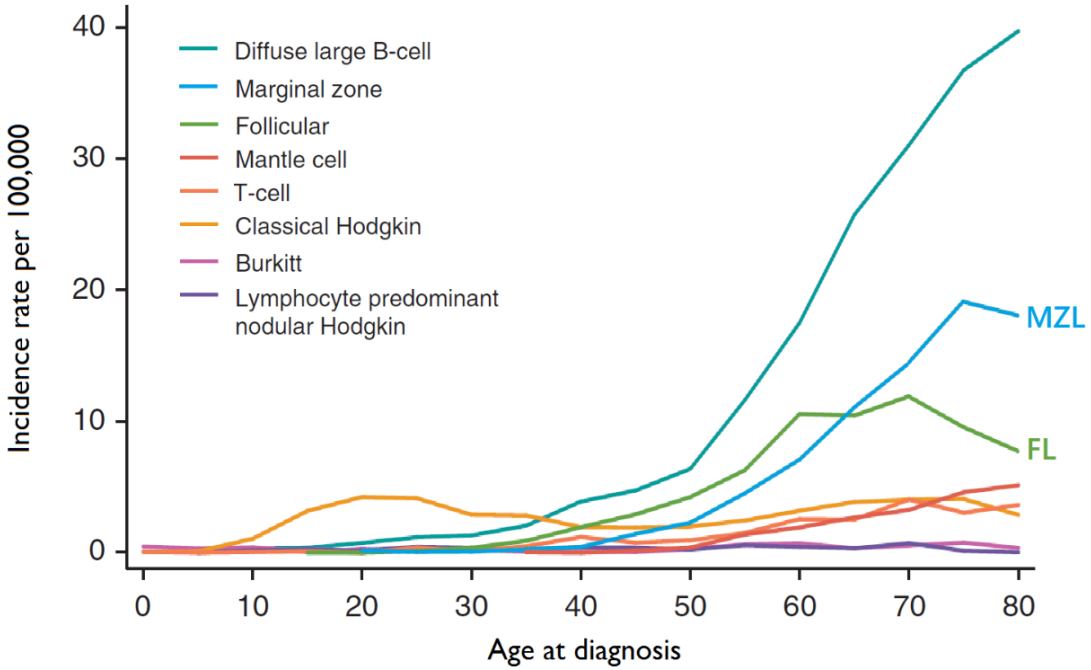
Gloria Margiotta Casaluci, Annarita Conconi

MZL entities across recent classifying proposals

Revised WHO-4th 2016	ICC 2022	WHO-5th 2022
Splenic MZL	Splenic MZL	Splenic MZL
Extranodal MZL of mucosa-associated lymphoid tissue, aka MALT lymphoma	Extranodal MZL of mucosa-associated lymphoid tissue, aka MALT lymphoma	Extranodal MZL of mucosa-associated lymphoid tissue, aka MALT lymphoma
Not considered as an entity	Primary cutaneous marginal zone lymphoproliferative disorder (new distinct entity)	Primary cutaneous MZL (new distinct entity)
Nodal MZL	Nodal MZL	Nodal MZL
Pediatric nodal MZL (provisional)	Pediatric nodal MZL (provisional)	Pediatric nodal MZL (distinct entity)

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

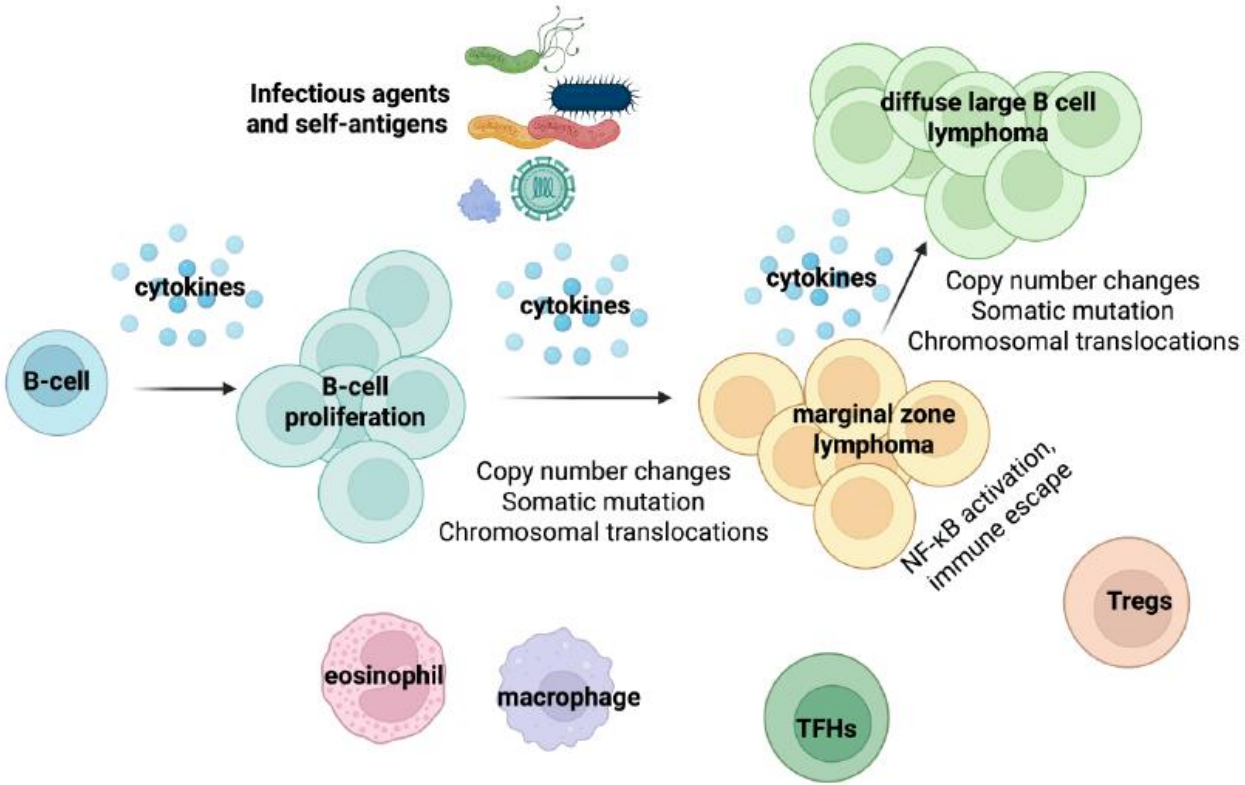
Marginal zone lymphoma: epidemiology



Age-Specific incidence by lymphoma subtype (UK data 2004-2012)

Smith et al. BJC 2015

MZL pathogenesis



Laurent C et al. Blood 2025

MZL - baseline investigations

- full blood count
- peripheral blood flow cytometric immunophenotyping (SMZL and NMZL)
- renal and liver function tests, LDH, beta-2-microglobulin, protein electrophoresis
- viral serology (HCV, HBV and HIV)
- computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis
- PET-CT scan recommended when localized treatment is planned or to guide biopsy if the histological transformation is suspected but current expert consensus supports its use for initial staging
- assessment for associated autoimmune phenomena
  - If suspected hemolysis: DAT, reticulocyte count, LDH and haptoglobin levels and (in selected cases) cold agglutinins screen
  - If suspected angioedema: measurement of C1 esterase inhibitor levels, assessment for anti–C1 esterase inhibitor antibodies, C3, C4 and C1q dosage
  - If suspected cryoglobulinaemia or in HCV-positive patients: cryoglobulin quantification and complement levels

EHA guidelines in preparation

MZL - baseline investigations

Selected patients		
Bone marrow aspirate (including flow cytometry), and trephine biopsy		*All patients with SMZL *Cases of associated cytopenias, and confirmation of early stage disease in non-gastric EMZL/MALT and NMZL
Site	**Test**	**Notes**
Gastro-intestinal sites		
Stomach	*EGD	Mandatory
	*Endoscopic US	Optional
	*Helicobacter pylori investigations	Mandatory
	*FISH or PCR for t(11;18)(q21;q21)	Optional
Small intestine (IPSID)	Campylobacter jejuni (PCR or ICH/ISH)	Optional (depending on regional epidemiology)
Colon	*Colonoscopy	Mandatory
	*EGD	Recommended

EHA guidelines in preparation

Selected patients		
Ocular adnexa	*CT scan or MRI of orbits	Mandatory
	*Ophtalmology examination	Mandatory
	*PCR for Chlamydia psittaci on tumour biopsy, peripheral blood mononuclear cells, conjunctival swab	Optional (regional epidemiology)
	*Autoimmune investigations for Sjögren syndrome (anti-SSA and antiSSB antibodies),	Recommended
Salivary glands	*CT scan or MRI or US	Mandatory
	*Autoimmune investigations for Sjögren syndrome (anti-SSA and antiSSB antibodies)	Recommended
Lung	*Bronchoscopy and bronchoalveolar lavage	Mandatory
	*EGD	Recommended
Breast	* bilateral MRI or CT scan	Mandatory
	*bilateral-ultrasound	Recommended
Thyroid	*Thyroid US or CT scan of the neck	Mandatory
	*Thyroid function tests	Mandatory
	*Autoimmune investigations for Hashimoto	Recommended
Skin	*PCR tumor biopsy for Borrelia Burgdorferi	Optional (regional epidemiology)

EHA guidelines in preparation

Primary gastric EMZL

STAGING OF EMZL OF THE STOMACH: COMPARISON OF DIFFERENT SYSTEMS

Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I	Confined to GI tract[a]			
	I_1 = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_2 = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II	Extending into abdomen			
	II_1 = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_2 = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

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		I_E	T3 N0 M0	Serosa
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EHA guidelines in preparation

MZL - Risk definition

EMZL	MALT-IPI [Thieblemont C. Blood 2017]			
	Risk factors	Score	Risk groups	Number of risk factors
	Age > 70	1	Low	0
	LDH > UNL	1	Intermediate	1
	Ann Arbor III-IV stage	1	High	≥ 2
	Revised MALT-IPI [Alderuccio JP. Am J Hematol 2022]			
	Risk factors	Score	Risk groups	Number of risk factors
	Age > 60	1	Low	0
	LDH > UNL	1	Low-medium	1
	Ann Arbor III-IV stage	1	Medium-high	2
	Presence of MMS	2	High	3+
SMZL	Splenic IPI [Arcaini L. Blood 2006]			
	Risk factors	Score	Risk groups	Number of risk factors
	LDH > UNL	1	Low	0
	Hb < 12 gr/dl	1	Intermediate	1
	Albumin < 3.5 gr/dl	1	High	2+
MZL	MZL-IPI [Arcaini L. EClinicalMedicine 2024]			
	Risk factors	Score	Risk groups	Number of risk factors
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	Hb < 12 gr/dl	1	Intermediate	1-2
	ALC < 1 x 109/L	1	High	3+
	PLT <100 × 109/L	1		

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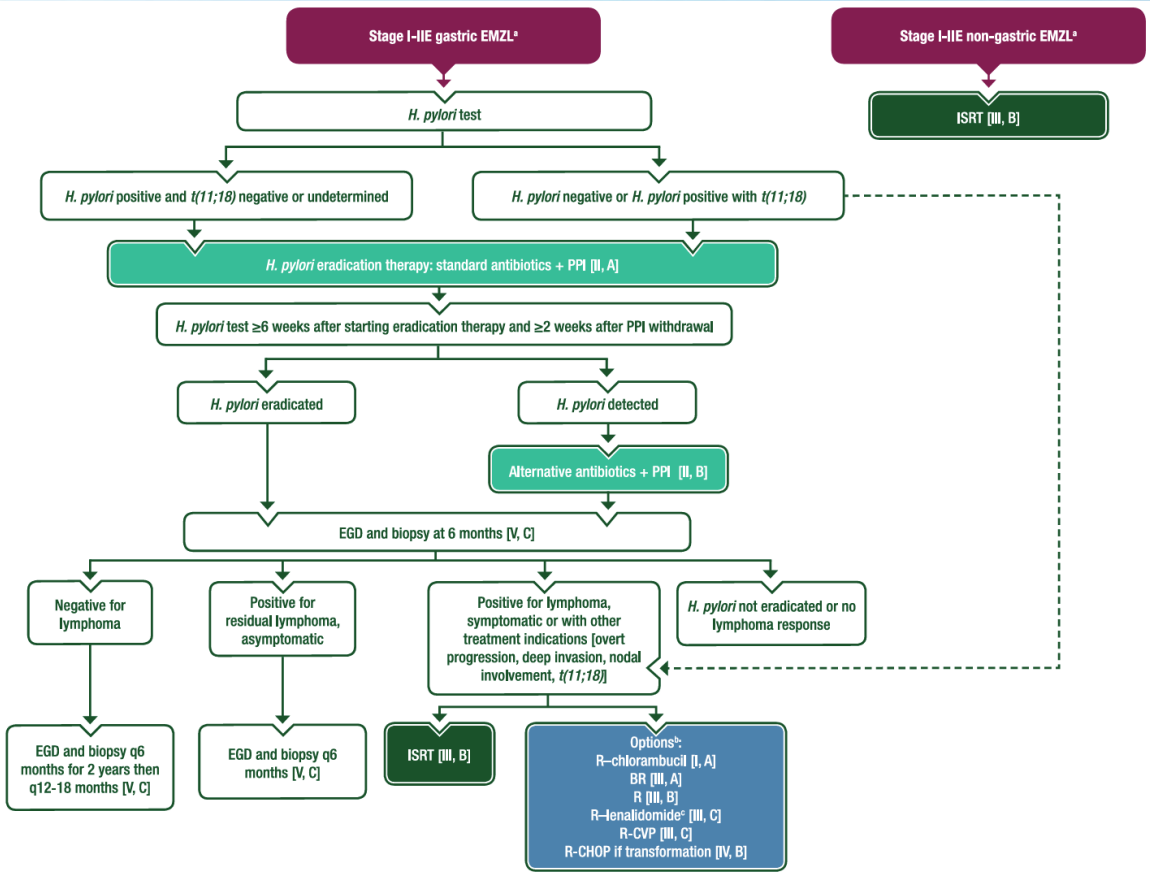
	ALC < 1 x 109/L	1	High	3+
	PLT <100 × 109/L	1		

EHA guidelines in preparation

Localized EMZL

First line therapy



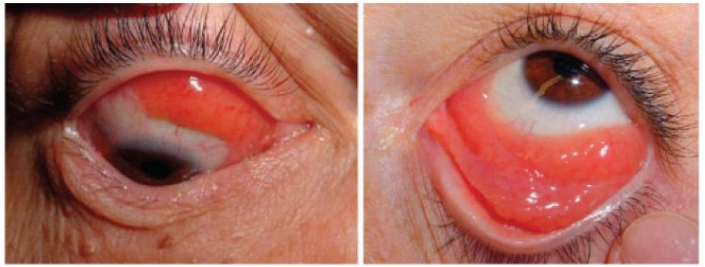
ESMO Clinical Practice Guidelines, 2

Most gastric MZL regress after H. pylori eradication

Reference	n	CR rate (%)	Time to CR (mos.)	Relapses (n)
Savio, 1996	12	84	2-4	0
Pinotti, 1997	45	67	3-18	2
Neubauer, 1997	50	80	1-9	5
Nobre Leitao, 1998	17	100	1-12	1
Steinbach, 1999	23	56	3-45	0
Montalban, 2001	19	95	2-19	0
Ruskone-Formestraux, 2001	24	79	2-18	2
Hancock, 2009	231	46	3-24	17
Zullo, 2010 (meta-analysis)	**1408**	**77.5**	**5 (median)**	**72/994**

mod. From Bertoni & Zucca, Lymphomas: Essentials for Clinicians 2015: 55-60

The case of localized ocular adnexa EMZL



Ferreri 2008

I line treatment in localized CP+ OA EMZL

doxycycline 100 mg x2/die, 4 weeks, 4 weeks rest – total 3 cycles (6 months)

I line treatment in localized CP- or doxy resistant OA EMZL

ISRT: 4 Gy in 2 fractions or 24 Gy in 12 fractions

Ocular adnexa EMZL

IELSG27

Cp+ su biopsia 39/44 (89%) → swab 97%, PMBC 69%

ORR 65% (poche CR), 2y PFS 60%→ migliori ORR e PFS nei pazienti che eradicano *Cp*

Eradicazione Cp 48%

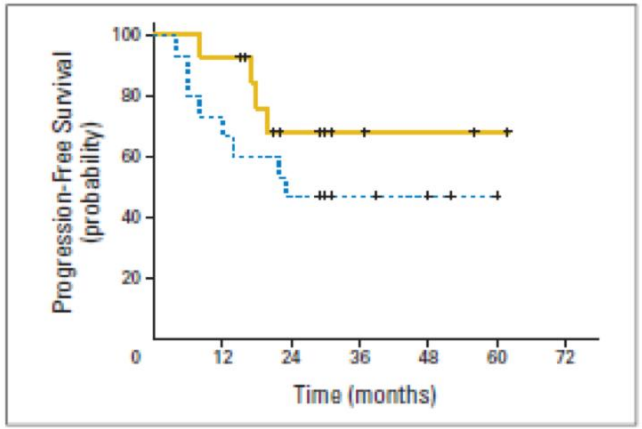


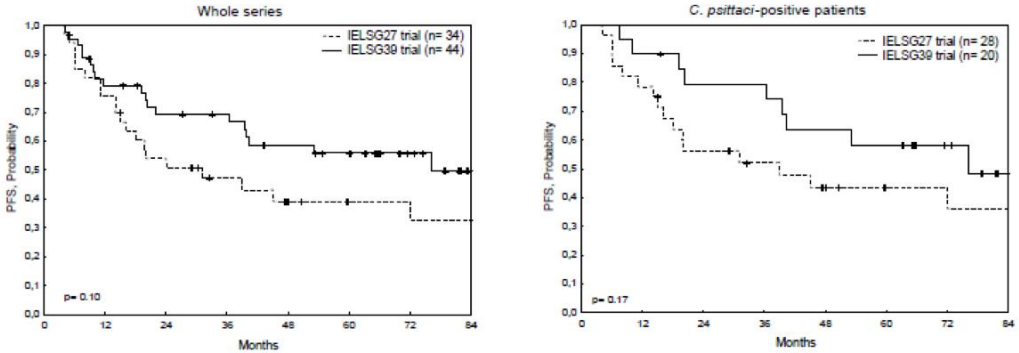
Fig 3. Progression-free survival (PFS) curves of patients registered in part A and divided according to *Chlamydophila psittaci* (Cpl eradication. Successful *Cp* eradication (solid line) was associated with better PFS.

IELSG39

Doxiciclina 100 mg bid per 4 settimane seguite da 4 settimane di stop per 3 cicli

Cp+ 64% 21/33 (11 pt con analisi in corso)

ORR 64% (metà CR), 2y PFS 75%→2y PFS *Cp*+ 90%

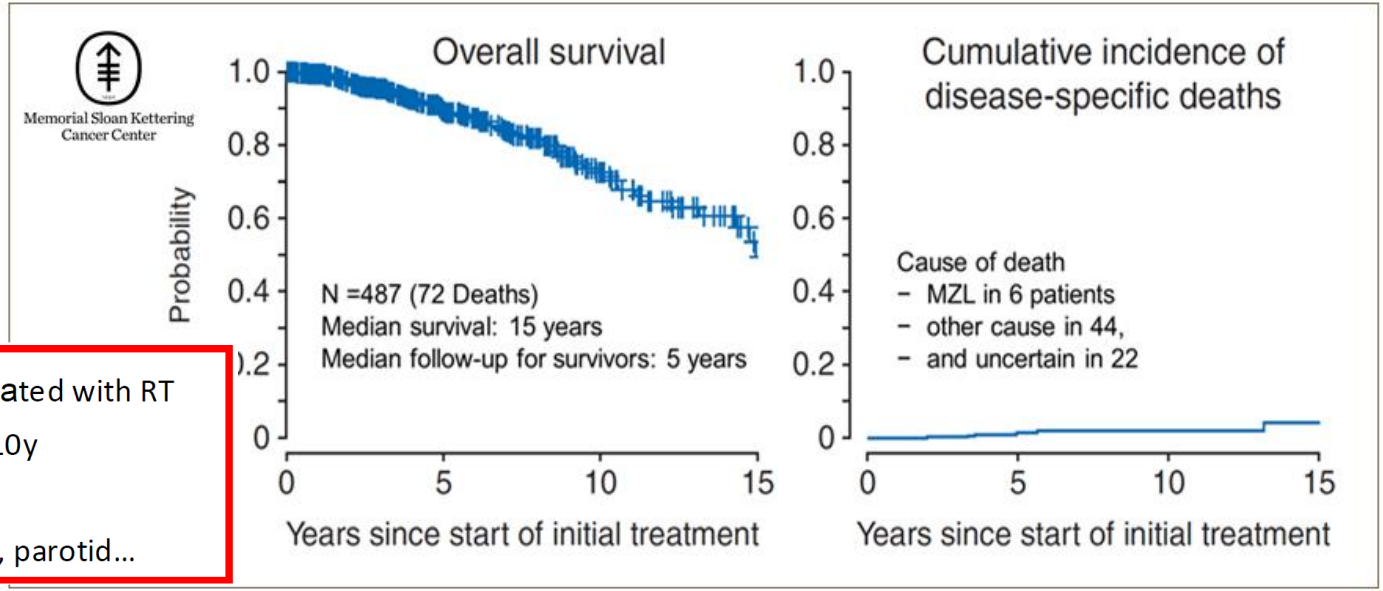


The six-month doxycycline treatment was associated with a trend towards better PFS in comparison with the shorter regimen used in the IELSG27 trial (median follow-up 75 months; range 5-155), both when whole populations (left figure) and Cp-positive subgroups (right figure) were analysed

RT in Early-Stage MALT Lymphoma

- 490 pts with I-IIE MZL treated with RT
- Local Relapse rate 4,6% at 10y
- PFS 57% at 10y
- Stomach, orbit, skin, breast, parotid…

RT dose
30 Gy. 65%
<30 Gy, 17%
>30 Gy, 15%
Unknown, 3%

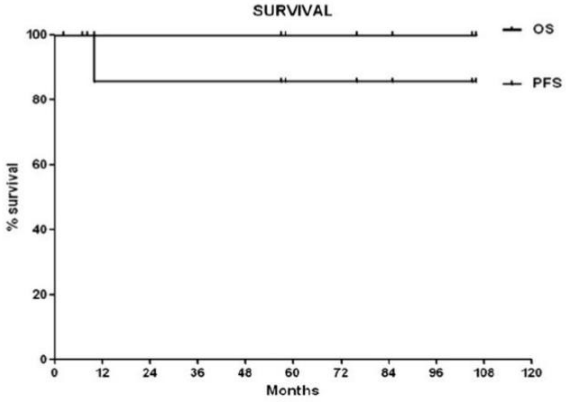


Teckie S, et al. Int J Radiation Oncol Biol Phys 2015
Teckie S, et al. Ann Oncol 2017

Low dose RT provides excellent outcomes in MZL (with NO toxicity…!)

Low-Dose Radiation Treatment in Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma: A Plausible Approach? A Single-Institution Experience in 10 Patients

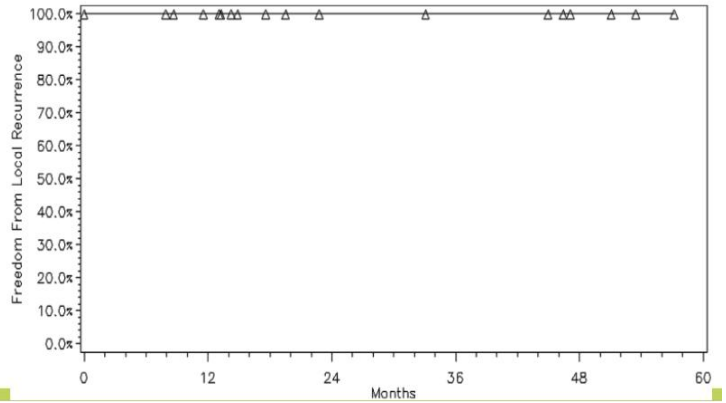
Theodore Girinsky, M.D.,* Amaury Paumier, M.D.,* Christophe Ferme, M.D.,† Colette Hanna, M.D.,† Vincent Ribrag, M.D.,† François Leroy-Ladurie,‡ and Mithra Ghalibafian, M.D.*



Clinical Investigation: Lymphoma

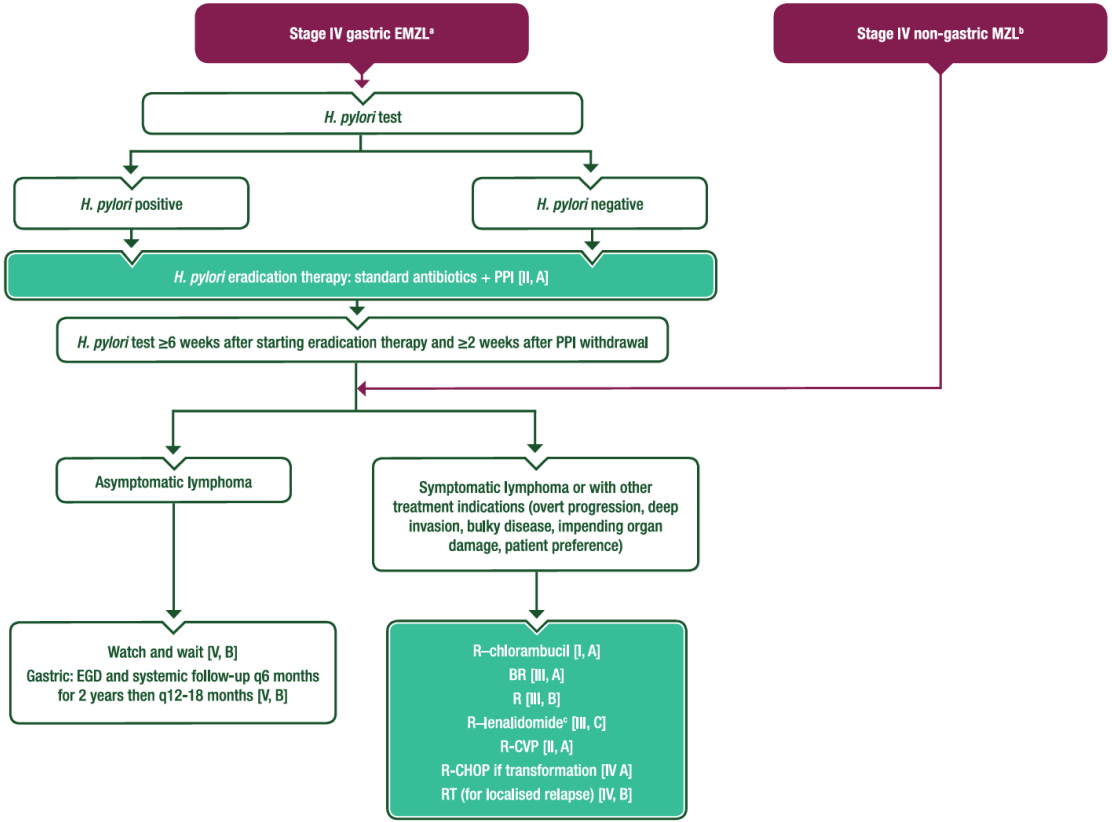
Low-Dose Radiation Therapy (2 Gy × 2) in the Treatment of Orbital Lymphoma

Carolina E. Fasola, MD, MPH,* Jennifer C. Jones, MD, PhD,† Derek D. Huang, MD,‡ Quynh-Thu Le, MD,* Richard T. Hoppe, MD,* and Sarah S. Donaldson, MD*



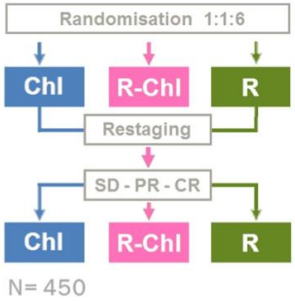
ADVANCED STAGE EMZL

First line treatment



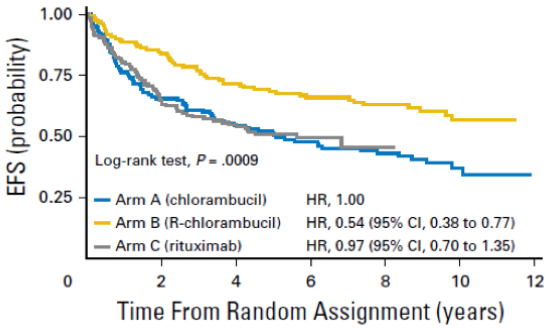
ESMO Clinical Practice Guidelines, 2025

Rituximab + chlorambucil
IELSG19 phase III randomized study (EZML)

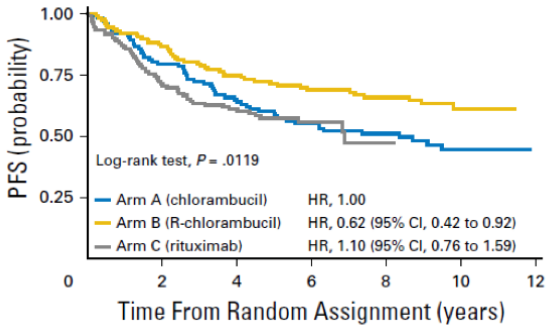


Response	All Patients (N = 401) No.	% (95% CI)	Arm A Chlorambucil (n = 131) No.	% (95% CI)	Arm B Chlorambucil Plus Rituximab (n = 132) No.	% (95% CI)	Arm C Rituximab (n = 138) No.	% (95% CI)
Complete remission*	264	65.8 (61.0 to 70.5)	83	63.4 (54.5 to 71.6)	104	78.8 (70.1 to 85.4)	77	55.8 (47.0 to 64.2)
Partial remission	81	20.2 (16.4 to 24.5)	29	22.1 (15.3 to 30.2)	21	15.9 (10.1 to 23.3)	31	22.5 (15.8 to 30.3)
Stable disease	28	7.0 (4.7 to 9.9)	11	8.4 (4.3 to 14.5)	1	0.8 (0.02 to 4.1)	16	11.6 (6.8 to 18.1)
Progressive disease	23	5.7 (3.7 to 8.5)	7	5.3 (2.2 to 10.7)	4	3.0 (0.8 to 7.6)	12	8.7 (3.0 to 12.0)
Not assessed	5	1.3 (0.4 to 2.9)	1	0.8 (0.02 to 4.2)	2	1.5 (0.2 to 5.4)	2	1.5 (0.2 to 5.1)
Overall response rate *	345	86.0 (82.2 to 89.3)	112	85.5 (78.3 to 91.0)	125	94.7 (89.4 to 97.8)	108	78.3 (70.4 to 84.8)

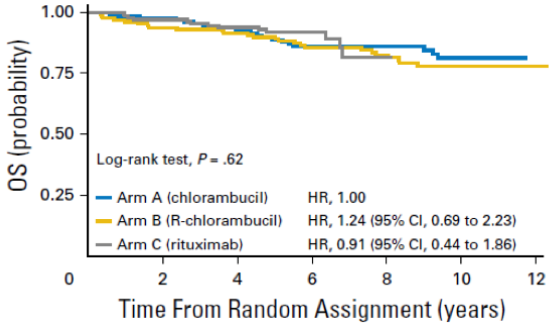
*$P < .001$.



No. at risk:							
Arm A	131	85	68	53	41	16	0
Arm B	132	109	93	76	58	23	0
Arm C	138	87	69	30	2	0	0



No. at risk:							
Arm A	131	89	70	53	42	16	0
Arm B	132	110	94	77	59	23	0
Arm C	138	90	71	31	2	0	0

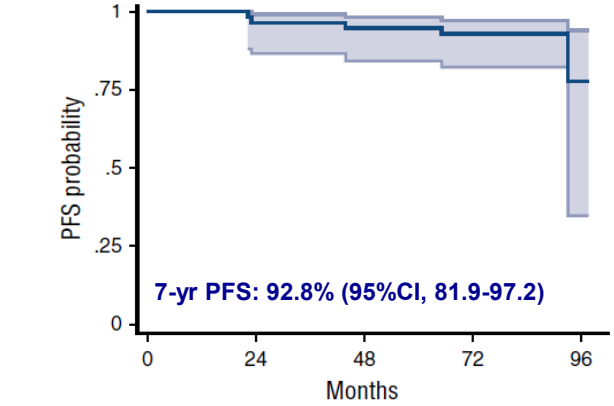


No. at risk:							
Arm A	131	126	116	92	79	37	0
Arm B	132	121	118	95	77	35	1
Arm C	138	130	118	50	3	0	0

Zucca E et al., JCO 2017

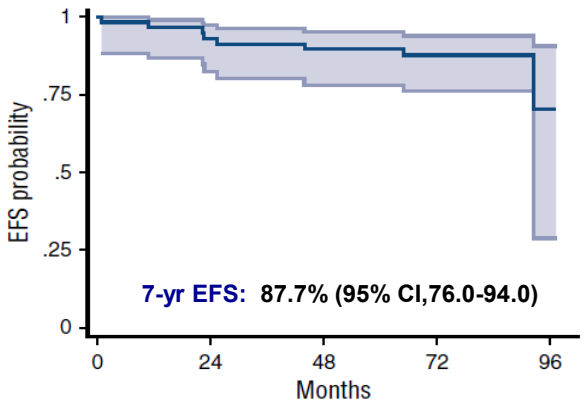
MALT-2008-01 GELTAMO phase-2 study

R-Bendamustine as 1st-line response-adapted therapy



Number at risk

0	24	48	72	96
57	56	53	52	32	0



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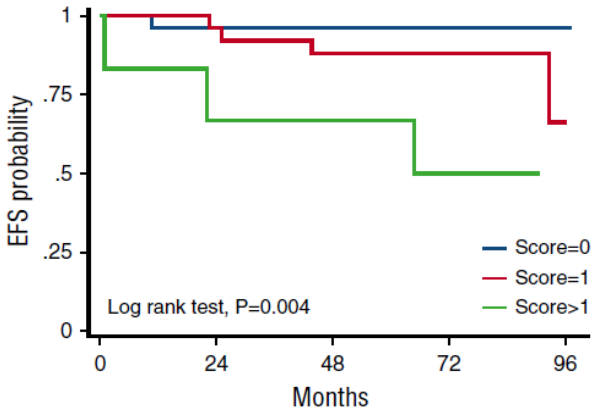
57	55	52	51	31	0



Number at risk

	0	24	48	72	96
Score=0	25	24	24	24	14	0
Score=1	25	25	23	22	14	0
Score>1	6	5	4	4	2	0

Salar A, et al. Blood 2017

NODAL MARGINAL ZONE LYMHPOMA

For patients with asymptomatic NMZL, a watchand-wait strategy is recommended.

Treatment of NMZL should broadly follow the principles applied for FL.

FIRST-LINE THERAPY

- **Localized stages:**

→ *Involved-site radiotherapy (ISRT) 24 Gy*

→ *A dose of 4 Gy may be considered in the palliative setting*

ESMO Clinical Practice Guidelines, 2025

Alderuccio JP, Noy A. Blood, 2026

NODAL MARGINAL ZONE LYMHPOMA

Table 1. Treatment indication in patients with advanced-stage MZL

GELF criteria[82]	NCCN guidelines[46]	ESMO guidelines[45]
≥3 lymph nodes of ≥3 cm Tumor mass of ≥7 cm Splenomegaly Cytopenia Leukemia Pleural effusion or ascites Organ compression B symptoms	Candidate for a clinical trial Symptoms Gastrointestinal bleeding Threatened end-organ function Clinically significant or progressive cytopenia secondary to lymphoma Autoimmune cytopenia Clinically significant bulky disease Steady or rapid progression	Symptoms Overt progression Deep invasion Bulky disease Impending organ damage Symptomatic or progressive splenomegaly Patient preference Autoimmune cytopenias

ESMO, European Society For Medical Oncology; GELF, Groupe d'Etude des Lymphomes Folliculaires.

FIRST-LINE THERAPY

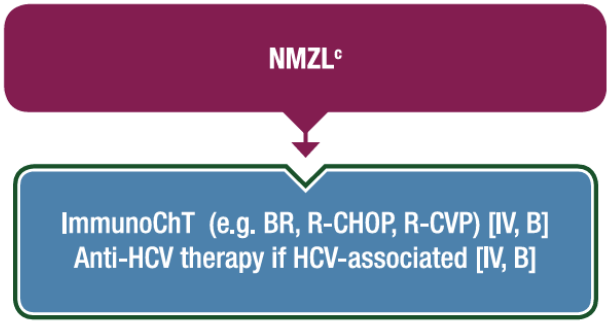
- **Advanced stages:**

→ *R-bendamustine*

→ *R-CVP*

→ *R-chlorambucil in unfit/frail patients*

→ *Single-agent rituximab in frail patients*



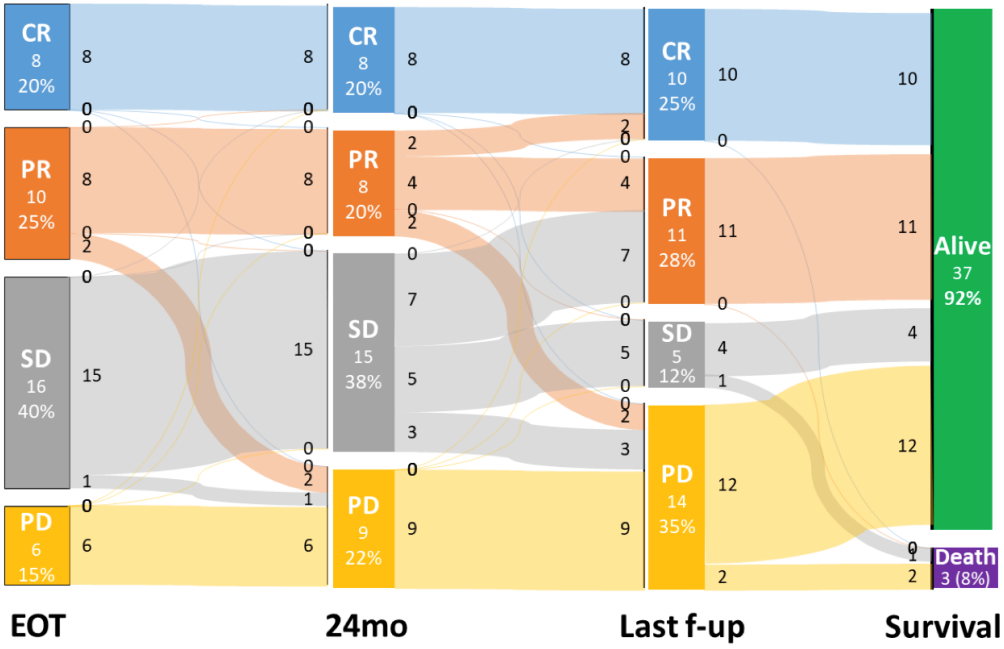
ESMO Clinical Practice Guidelines, 2025

Alderuccio JP, Noy A. Blood, 2026

HCV-positive MARGINAL ZONE LYMPHOMA

HCV positive patients: HCV eradication with DAA therapy

FIL-BArT study: 40 pts indolent LNH



- 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)*

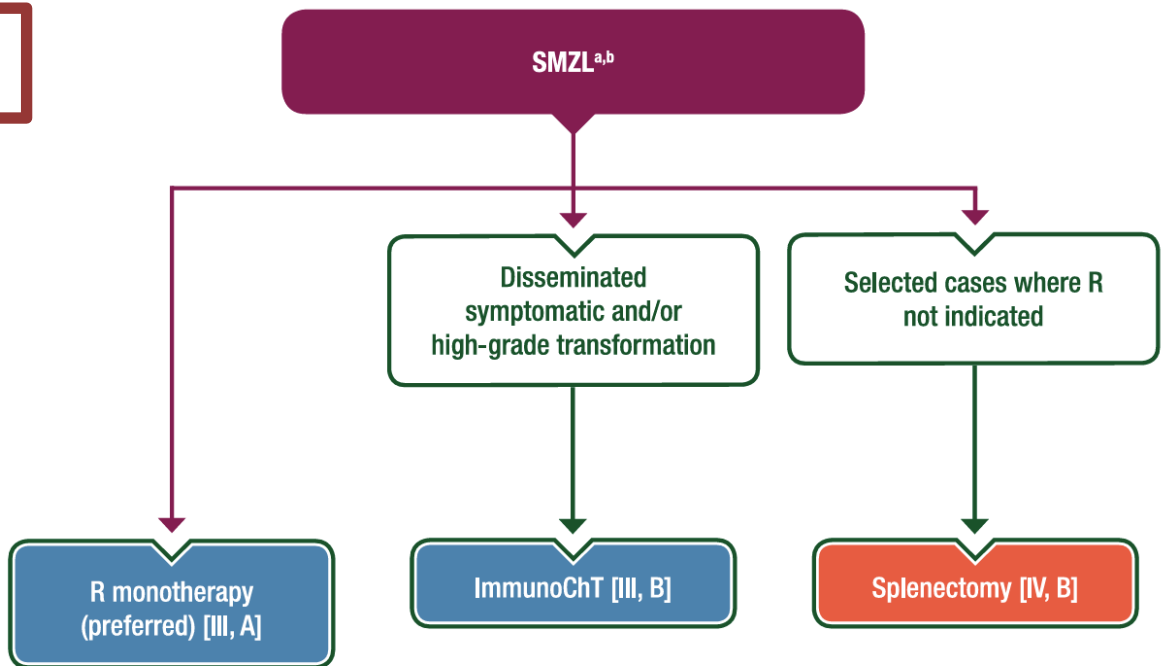
Histotype	N	Best ORR	Best CR
SMZL	6	50%	0%
MALT	14	79%	43%
NMZL	7	71%	43%
LPL	6	17%	0%
CD5- NOS	4	75%	25%
FL + SLL	3	66%	0%

Merli et al. NEJM 2026

SPLENIC MARGINAL ZONE LYMPHOMA

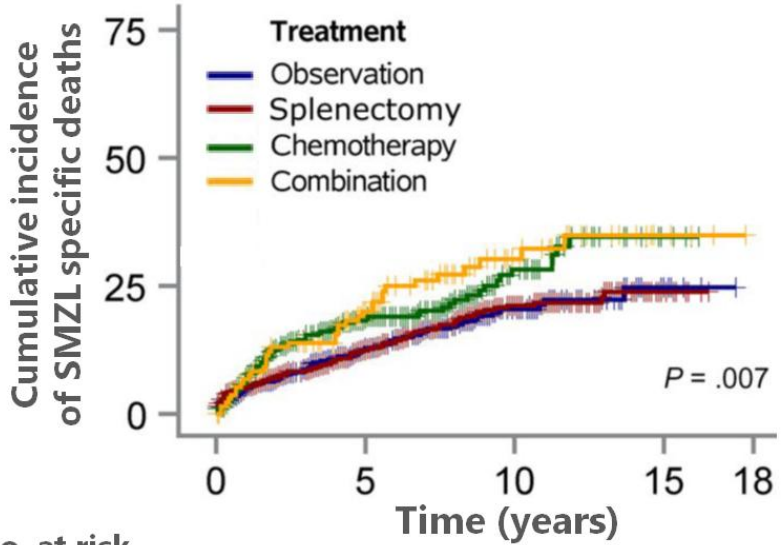
HCV-negative or HCV-positive without response to antiviral therapy

Asymptomatic patient:
→ *Watch and wait*



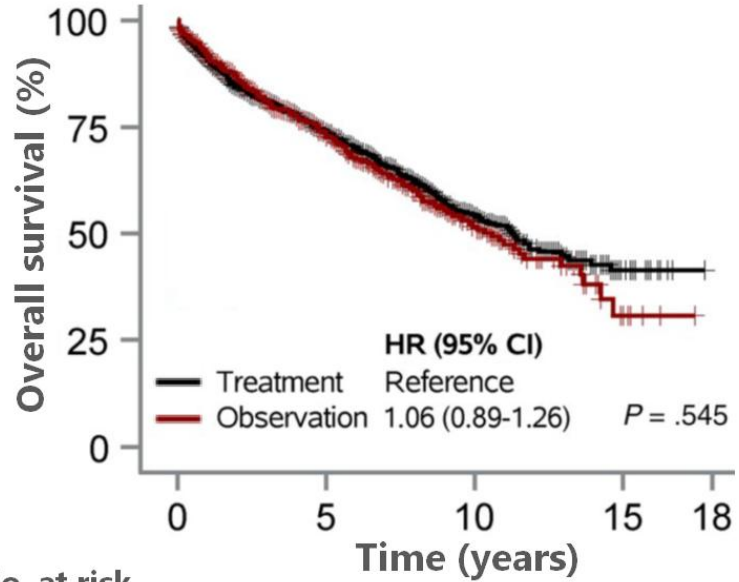
ESMO Clinical Practice Guidelines, 2025

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

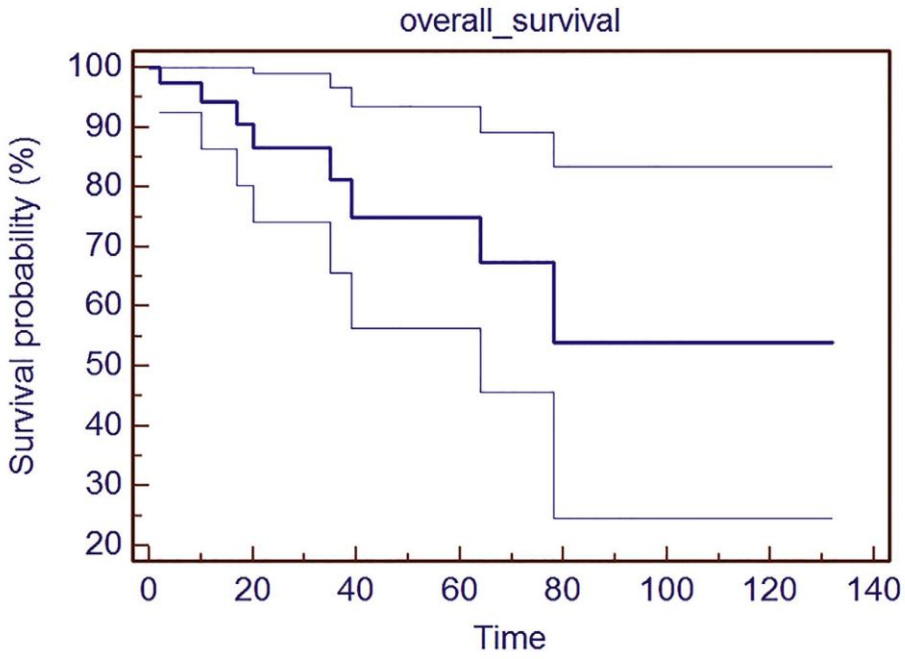


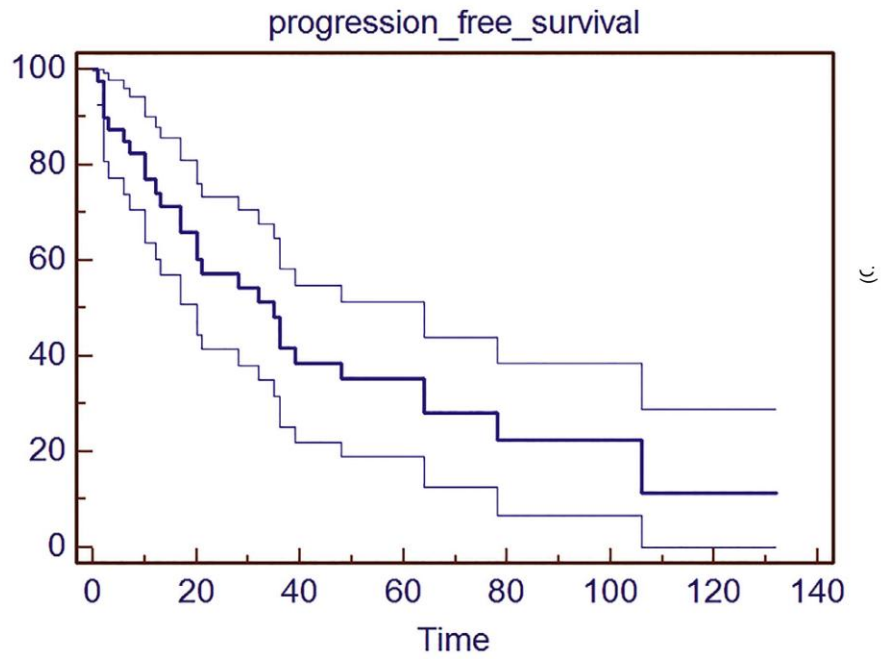
No. at risk

Treatment	1075	543	192	19
Observation	596	225	75	7

Florindez JA, Cancer 2020

Splenic MZL outcome after first-line splenectomy





Pata et al. *International Journal of Surgery* 2016

First-line splenectomy for splenic MZL

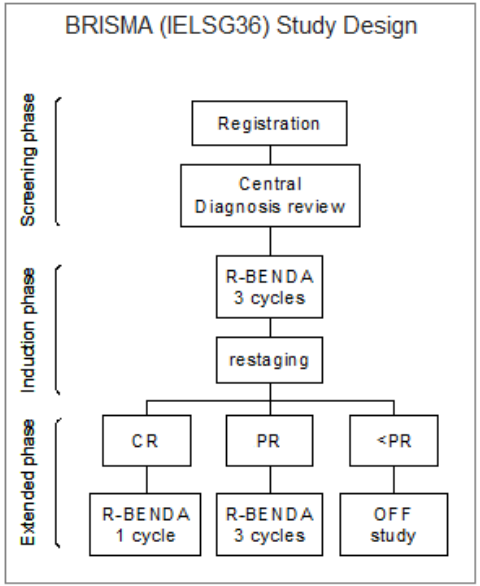
Surgical outcomes and postoperative complications after open splenectomy

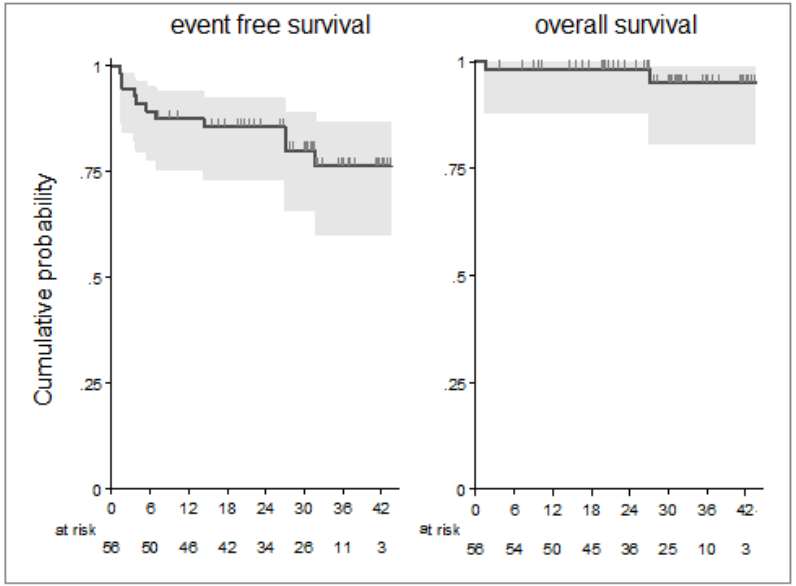
Medical complications:	10 (24.4%)*	Surgical complications:	10 (24.4%)*
Cardiac	2 (4.9%)	Intestinal obstruction	0
Pulmonary	8 (19.5%)	Acute pancreatitis	1 (2.4%)
Liver dysfunction	1 (2.4%)	Pancreatic fistula	1 (2.4%)
Renal dysfunction	0	Wound infection	1 (2.4%)
Deep venous thrombosis	1 (2.4%)	Portal vein 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

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





N evaluable, 56

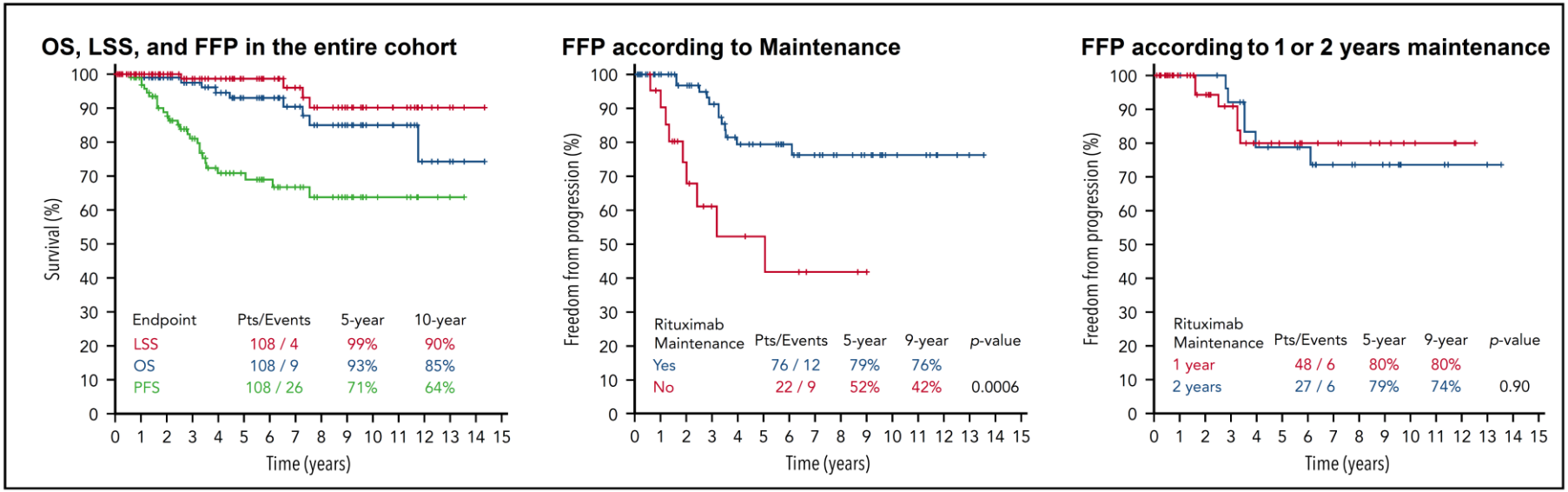
35% high risk HPLL

ORR, 91%
CR, 73%
3-yr PFS: 90% (95% CI: 77–96)
3-yr EFS: 80% (95% CI, 65–89)

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

Iannitto et al. Br J Haematol. 2018;183:755-765.

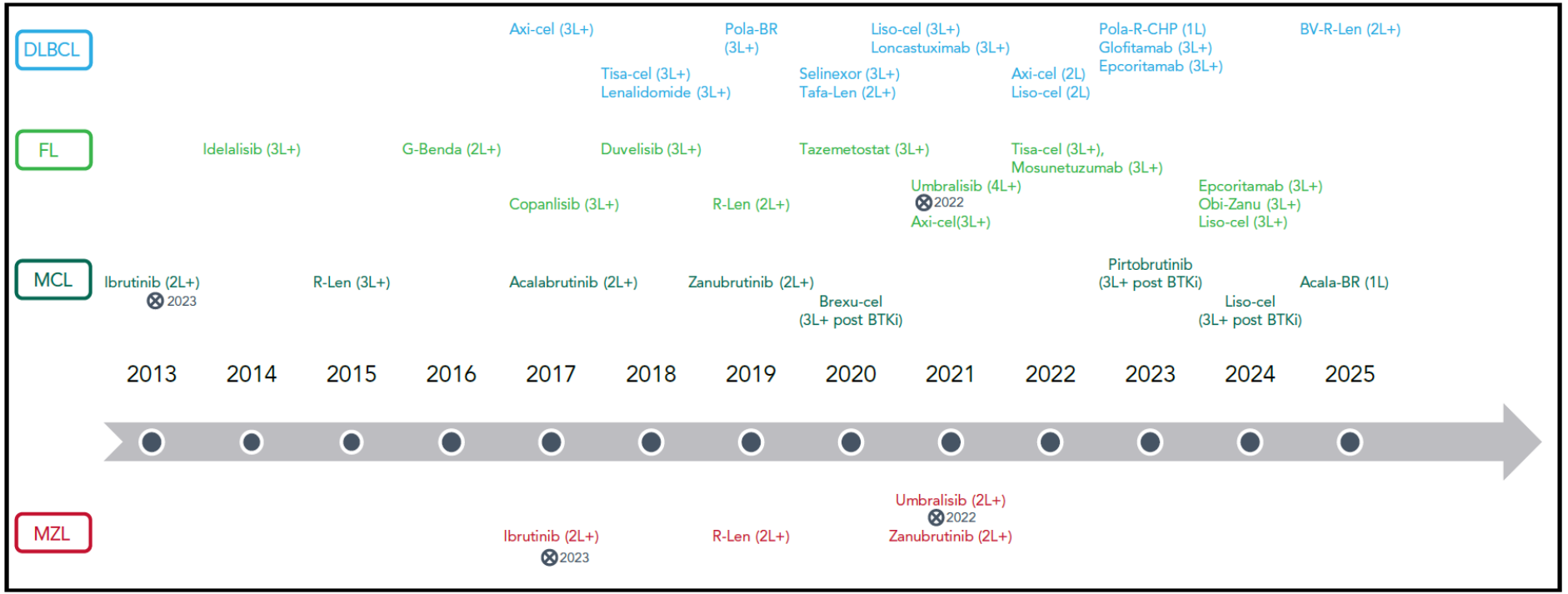
Rituximab monotherapy in SMZL: prolonged responses and potential benefit from maintenance



- ORR 92%
- CR 48%
- 3-y PFS 73%

Kalpadakis C, et al. Blood 2018 Epub

Novel agents approved for MZL



2022 : withdrawn in 2022

→ few dedicated clinical trials→ few drugs approved compared to other B-NHL subtypes

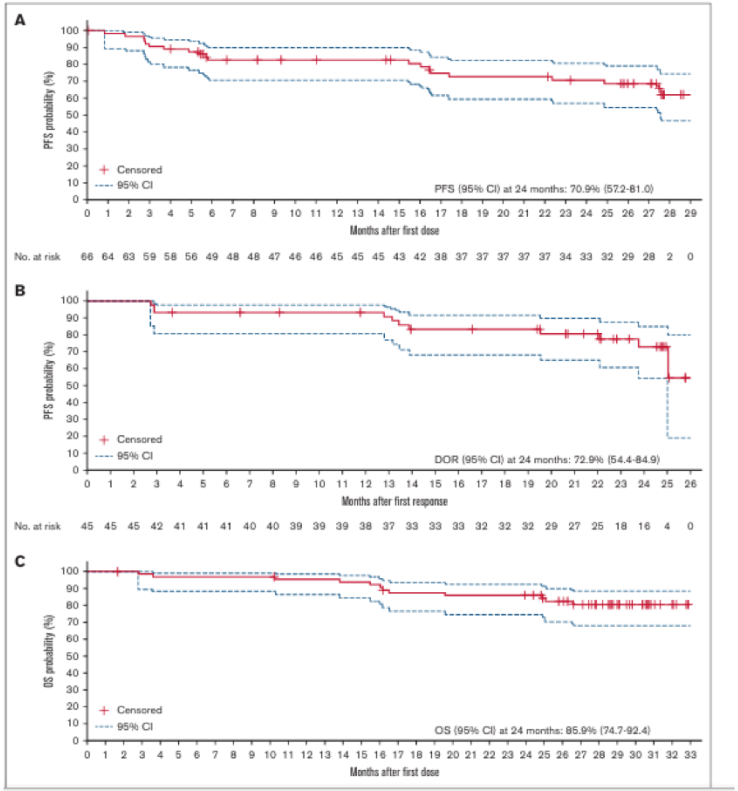
Thieblemont C, Carras S, Bommier C, Blood 2026

BTK inhibitor in R/R MZL: summary of phase II trials

Agent	Pts nr	Median age (years)	Median prior lines (range)	ORR	AEs-rel Stop (%)	PFS	Median FU (months)
ibrutinib	63	66 (30-92)	2 (1-9)	48% (95%CI, 35-62)	17	Median 14.2 mos	19.4
acalabrutinib	43	69 (42–84)	1 (1–4)	52.5% (95%CI, 36–68)	7	Median 27.4 mos	13.3
zanubrutinib	68	70 (37-95)	2 (1-6)	68% (95% CI, 56–79)	7.4	2-ys: 71%	27.4
orelabrutinib	90	62 (23-77)	1 (1-3)	58.9% (95% CI, 48–69)	6.3	2-ys: 75.8%	24.3

MAGNOLIA phase II trial: ZANUBRUTINIB

Median FU: 27.4 months



Zanubrutinib 320 mg orally
until progression/unacceptable toxicity

Table 1. Summary of IRC-assessed disease responses by MZL subtypes (efficacy analysis set)

	Extranodal (MALT) (n = 25)	Nodal (n = 25)	Splenic (n = 12)	Unknown* (n = 4)	Total† (N = 66)
ORR, % (95% CI)‡	64.0 (42.5-82.0)	76.0 (54.9-90.6)	66.7 (34.9-90.1)	50.0 (6.8-93.2)	68.2 (55.6-79.1)
Best overall response, n (%)					
CR	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	17 (25.8)
PR	6 (24.0)	14 (56.0)	7 (58.3)	1 (25.0)	28 (42.4)
Stable disease	4 (16.0)	5 (20.0)	3 (25.0)	1 (25.0)	13 (19.7)
Progressive disease	3 (12.0)	1 (4.0)	1 (8.3)	1 (25.0)	6 (9.1)
Nonprogressive disease§	1 (4.0)	0	0	0	1 (1.5)
Discontinued study before first assessment	1 (4.0)	0	0	0	1 (1.5)
Median time to response, mo (IQR)	2.8 (2.7-2.9)	2.8 (2.7-3.8)	3.6 (2.7-6.0)	2.7 (2.6-2.8)	2.8 (2.7-3.7)

Safety profile:

- Atrial fibrillation/flutter: 2.9%
- Hypertension: 4.4%
- Neutropenia G ≥3: 11.8%

Opat S et al., Blood Adv 2023

RELAPSED/REFRACTORY MZL

(EZML, NMZL, SMZL)

If treatment indication present:

ZANUBRUTINIB (after at least one line anti-CD20)

Chemo-immunotherapy

Rituximab single agent

Consider enrollments in clinical trials

ESMO Clinical Practice Guidelines, 2025

Grazie per l'attenzione!