

Marginal Zone Lymphomas

Prof. Emanuele Zucca, M.D.

Clinic of Hematology , Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland
International Extranodal Lymphoma Study Group, Institute of Oncology Research, Bellinzona, Switzerland
Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland



ROMA
HEMATOLOGY
CONFERENCE
the lymphomas

Rome

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Hotel nhow Roma

Conflict of Interest Disclosures

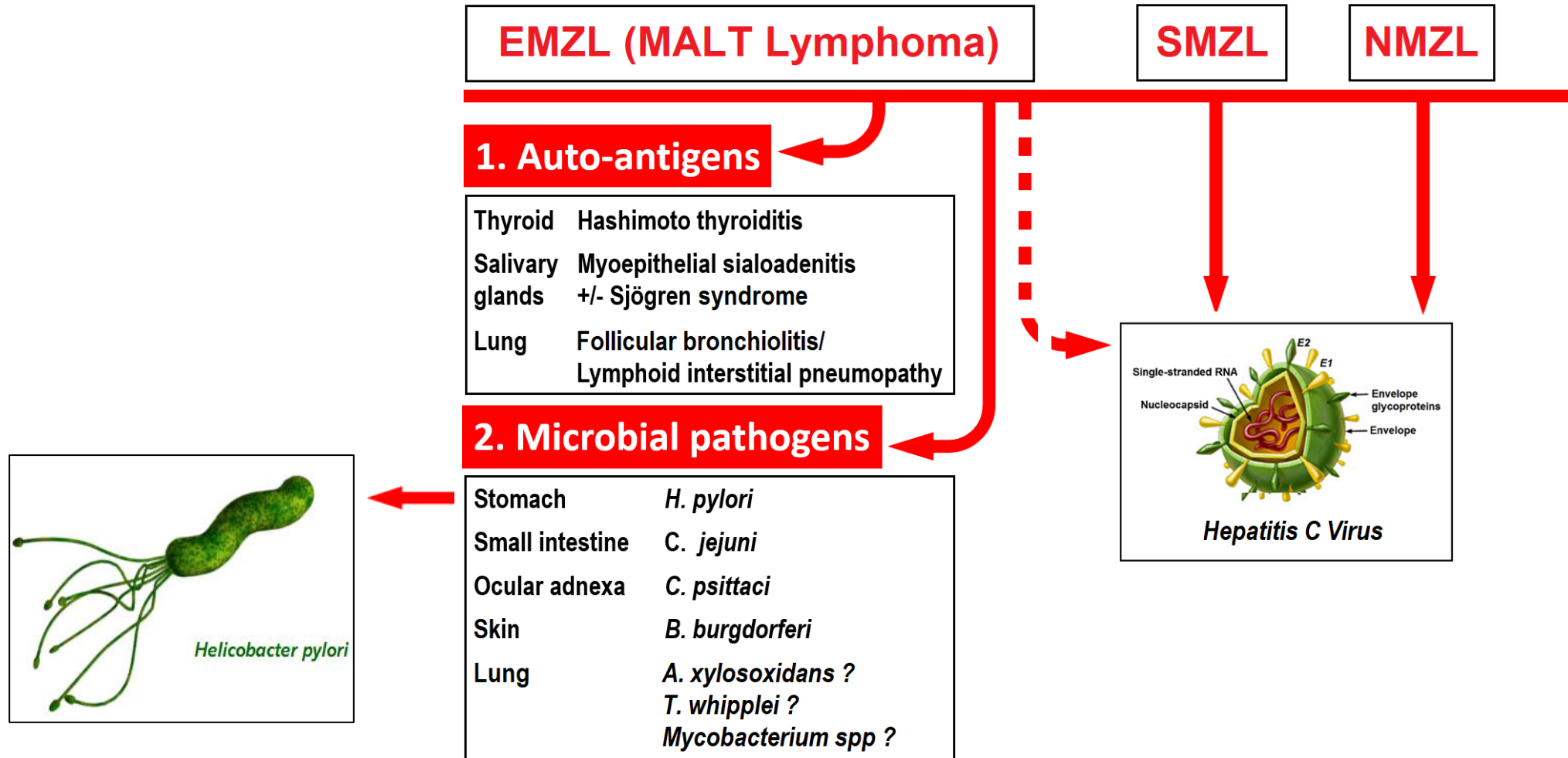
Company	Research support (Institutional)	Advisory board	Others
AstraZeneca	✓	✓	✓
Beigene/BeOne	✓	✓	✓
BMS/Celgene	✓	✓	
Kite Gilead			✓
Janssen	✓		✓
Regeneron			✓
MSD		✓	✓
Roche	✓	✓	
Sobi		✓	

MZL entities group across current classifying systems

Revised WHO-4 th 2016 <i>Swerdlow et al. Blood 2016</i>	ICC 2022 <i>Campo et al. Blood 2022</i>	WHO-5 th 2022 <i>Alaggio et al. Leukemia 2022</i>
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
Splenic MZL	Splenic MZL	Splenic MZL
Nodal MZL	Nodal MZL	Nodal MZL
Not considered as an entity	Primary cutaneous marginal zone lymphoproliferative disorder (new distinct entity)	Primary cutaneous MZL (new distinct entity)
Pediatric nodal MZL (provisional entity)	Pediatric nodal MZL (provisional entity)	Pediatric nodal MZL (distinct entity)

MZL link with chronic antigenic stimulation

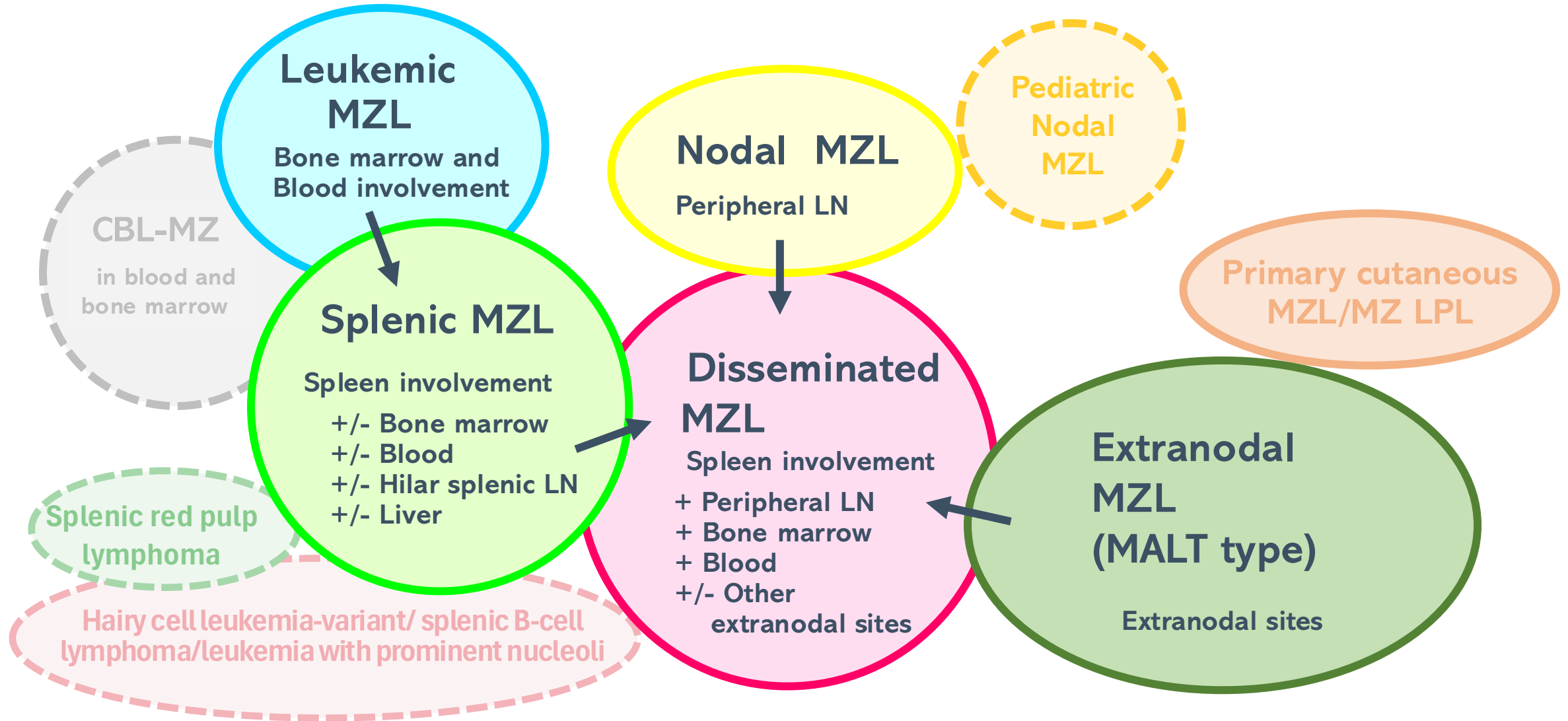
different causes at different sites



Causality criteria for bacteria associated with MZL

Melenotte Causality Criteria	Infectious Agents				
	<i>H. pylori</i>	<i>C. psittaci</i>	<i>B. burgdorferi</i>	<i>C. jejuni</i>	<i>A. xylosoxidans</i>
Epidemiological link	X	X	X		
Consistency	X	X	X	X	
Temporality	X		X		X
Anatomical Proximity	X	X	X		X
Bacteria detection within lymphoma microenvironment	X	X	X	X	X
In-vitro B cell transformation	X				
In-vivo transformation in animal models	X				
Lymphoma regression after bacteria eradication	X	X	X	X	

MZL a heterogeneous group of related clinical entities



Shared management problems across MZL

- General indolent course across all MZL subtypes
- Treatment remains largely empirical and differs by subtype
- Current frontline strategies provide prolonged disease control
- BTKi now a standard 2nd line option, but optimal sequencing is undefined
- Few therapies achieve durable disease control in R/R settings
- Unmet need for disease-specific clinical trials
- Lack of validated predictive biomarkers for treatment selection
- Unmet need to incorporate patient-centered outcomes into clinical trials

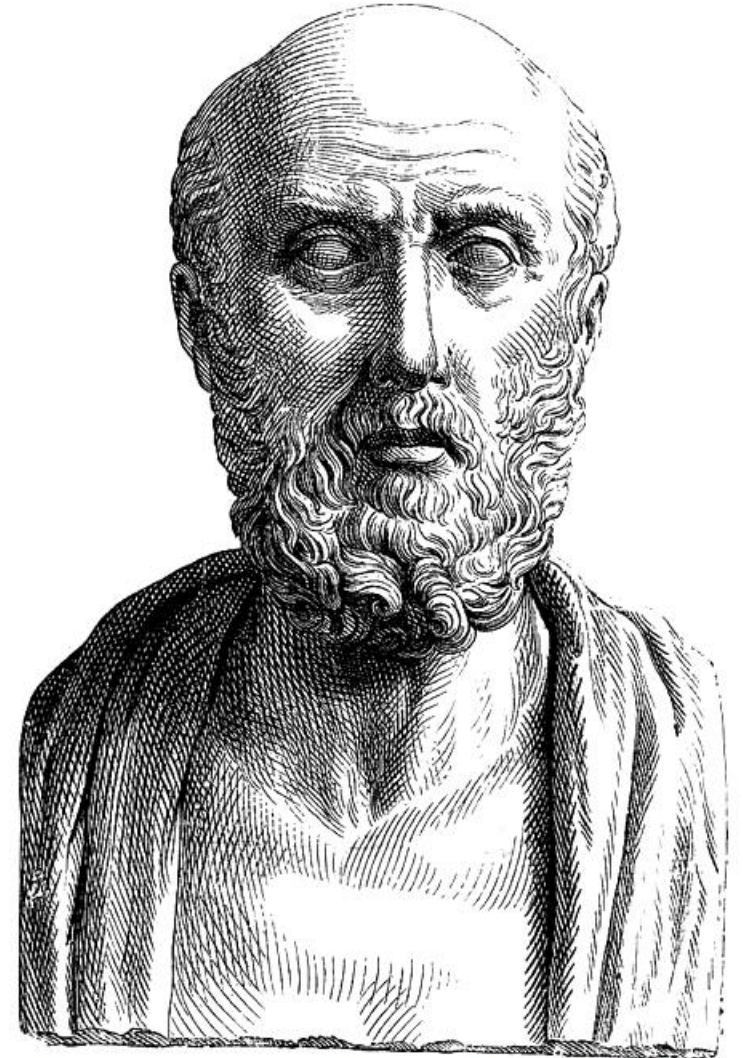
How to treat MZL?

- Who should be treated, when, and with what?
 - Better risk stratification to avoid overtreatment
 - Lack of validated predictive biomarkers

Primum Non Nocere

First do not harm

- Treatment may not always be necessary
- Cure is not usually the aim
- Most patients survive long-term despite relapse

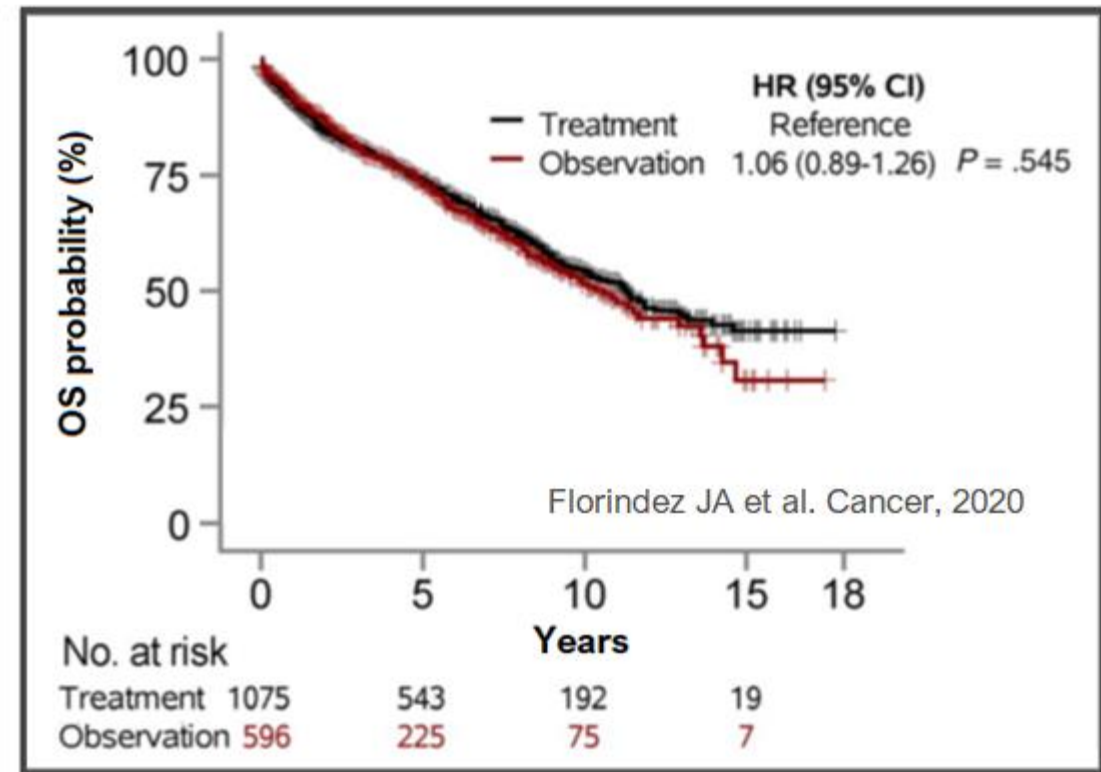


Hippocrates of Kos (460 – 370 BC)

Active surveillance is not detrimental

ESMO guidelines
Symptoms
Overt progression
Deep invasion
Bulky disease
Impending organ damage
Symptomatic or progressive splenomegaly
Patient preference
Autoimmune cytopenias

Zucca E et al. Ann Oncol, 2020



Asymptomatic patients with advanced-stage MZL, particularly splenic and nodal MZL, may be managed with observation until symptoms, cytopenias, organ compromise, or progression occur.
Median time to first treatment: 3-5 years

Zucca et al. (ESMO Guidelines), Ann Oncol 2020; Walewska et al. (British Society of Haematology Guideline), Br J Haematol 2023

MZL-Specific Prognostic Indices

Models	Components	Key Features
MALT-IPI (<i>Thieblemont, 2017</i>)	age, stage, LDH	the first validated EMZL-specific index
MALT-IPI-B (<i>Kim, 2021</i>)	age, stage, LDH, β 2-microglobulin	refined separation of intermediate-risk
Revised MALT-IPI (<i>Alderuccio, 2022</i>)	age, stage, LDH, multiple mucosal sites	better identification of high-risk
Korean MZL index (<i>Oh, 2007</i>)	nodal status, ECOG PS, stage	only for non-gastric EMZL
MDACC EMZL score (<i>Mazloom, 2010</i>)	B-symptoms, male sex, β 2-microglobulin,	heterogeneous treatment era, not independently validated
IIL SMZL model (<i>Arcaini, 2006</i>)	hemoglobin, albumin, LDH	predominantly pre-rituximab cohort
HPLL SMZL score (<i>Montalbán, 2012</i>) HPLL SMZL simplified score (<i>Montalbán, 2014</i>)	hemoglobin, platelets, LDH, extrahilar lymphadenopathy	heterogeneous treatment era, inconsistent assessment of extrahilar lymphadenopathy
MZL-IPI (<i>Arcaini 2024</i>)	LDH, hemoglobin, platelets, lymphocyte count, histologic subtype	unifying index applicable across all MZL subtypes

IPI and **FLIPI**, generally inferior compared to MZL-specific tools (*Heilgeist, 2013;Tracy, 2019*)
FLIPI24 may improve prognostic accuracy over MZL-IPI (*Vodicka, 2025*)

Who Should Receive Systemic Therapy and When?

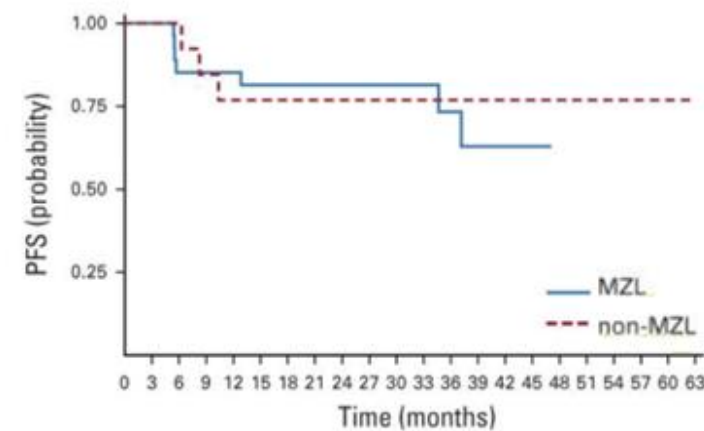
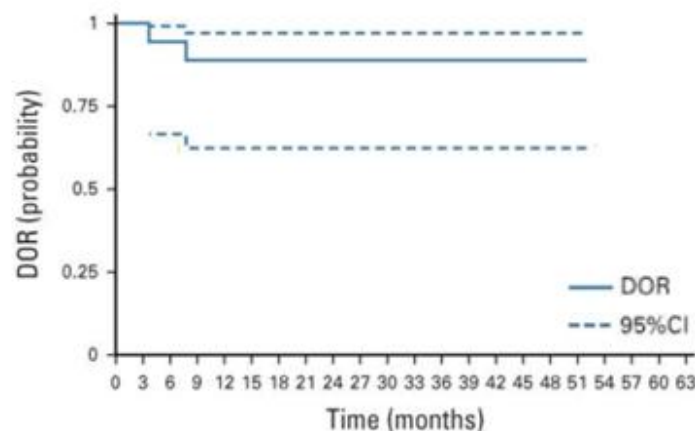
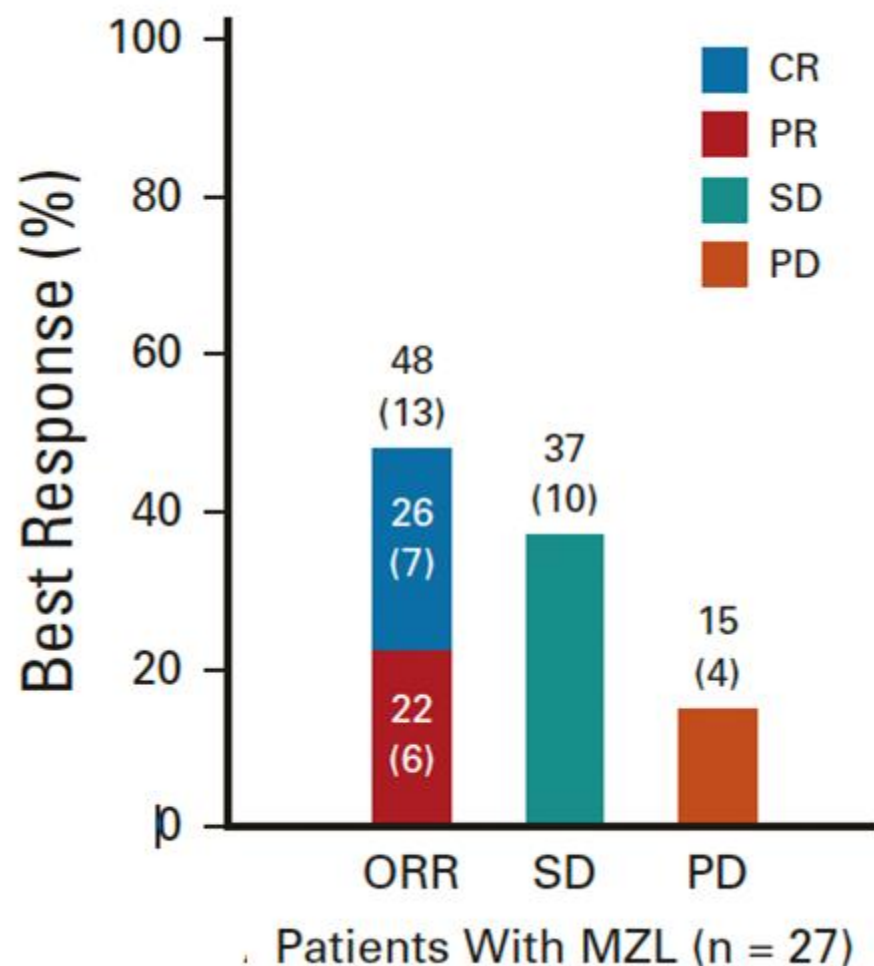
GELF criteria	NCCN guidelines	ESMO guidelines
≥ 3 lymph nodes of ≥ 3 cm Tumor mass of ≥ 7 cm Splenomegaly Cytopenia Leukemia Pleural effusion or ascites Organ compression B symptoms <i>Brice et al. J Clin Oncol 1997</i>	Candidate for a clinical trial Symptoms Gastrointestinal bleeding Threatened end-organ function Clinically significant or progressive cytopenia secondary to lymphoma Autoimmune cytopenia Clinically significant bulky disease Steady or rapid progression <i>NCCN Clinical Practice Guidelines in Oncology. Version 2. 2025</i>	Symptoms Overt progression Deep invasion Bulky disease Impending organ damage Symptomatic or progressive splenomegaly Patient preference Autoimmune cytopenias <i>Zucca et al. Ann Oncol 2020</i>

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

Treating the trigger: eradicate the infection

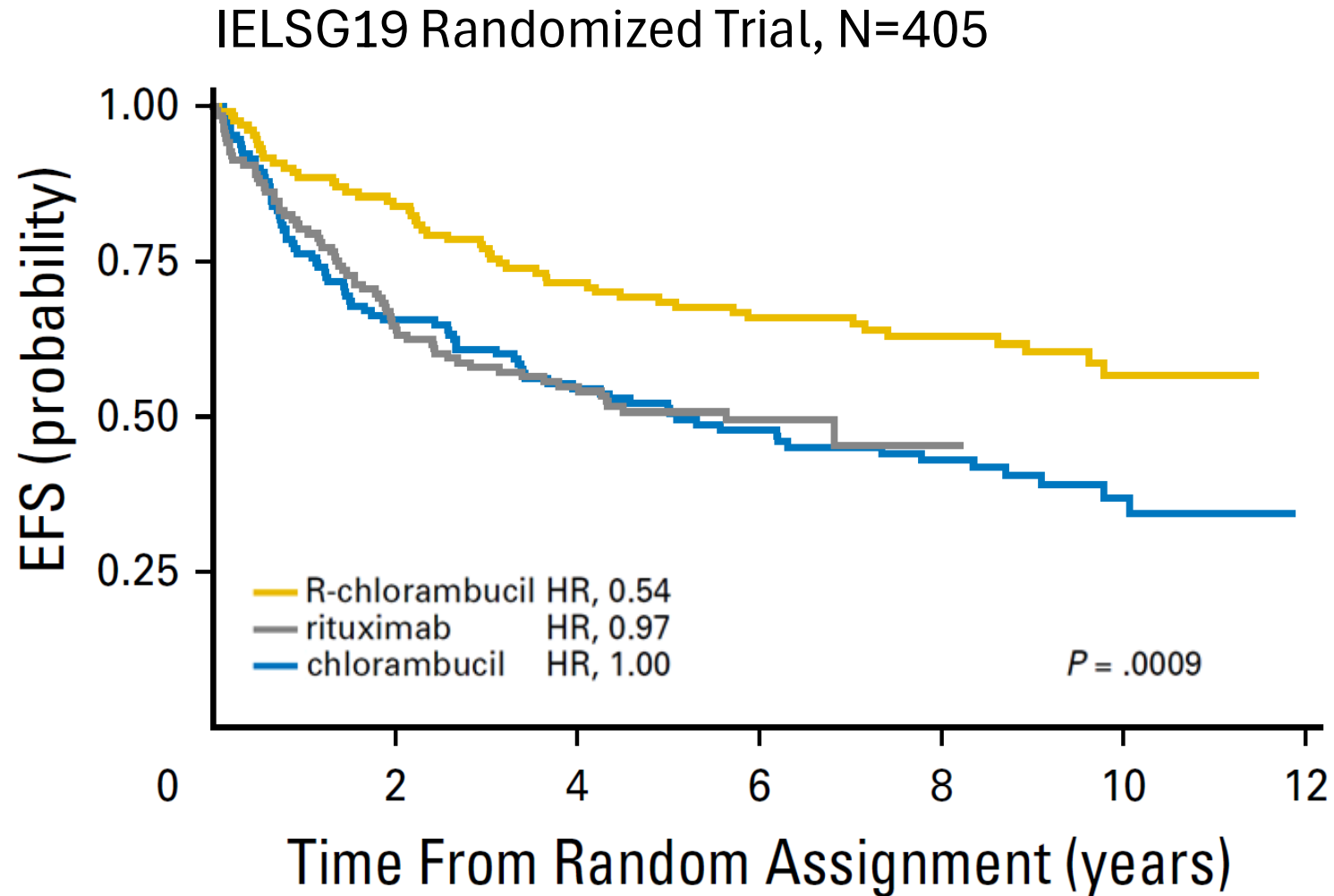
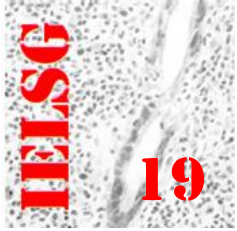
Anatomical primary lymphoma site	Bacterium spp.	Antibiotic regimen	Lymphoma remission rate	No. of patients	Type of study
Stomach <i>H. pylori</i> positive	<i>H. pylori</i>	Chm + PPI + Mtz or Amx	83%	88	Retrospective
		Triple Therapy ^a	78%	1408	Systematic review
		Chm + PPI + Mtz or Amx	83%	51	Retrospective,
		Chm + PPI + Mtz or Amx	84%	376	Retrospective
<i>H. pylori</i> negative	Unknown	Chm + PPI + Mtz or Amx	33%	14	Retrospective
		Triple Therapy ^a	29%	244	Systematic review
		Chm + PPI + Amx	32%	26	Retrospective
Non- <i>H. pylori</i> positive	<i>H. heilmannii</i>	PPI + Amx	100%	5	Retrospective
		Chm + PPI + Amx	100%	2	Retrospective
		Chm + PPI + Amx + vanoprazan	75%	16	Retrospective
Ocular adnexa	<i>C. psittaci</i>	Dxc	50% ^b	7	Retrospective
		Dcx ^c	45%	31	Metanalysis
		Dcx	37%	9	Prospective
Skin	<i>B. burgdorferi</i> spp.	Cph	50%	6	Case reports (1 with <i>B. afzelii</i>)
Small intestine	Unknown	Ttc	100%	7	Case series
	<i>C. jejuni</i>	Ttc alone or with Mtz or Amp	77%	76	Systematic review

BArT study of Direct-Acting Antivirals in HCV+ MZL

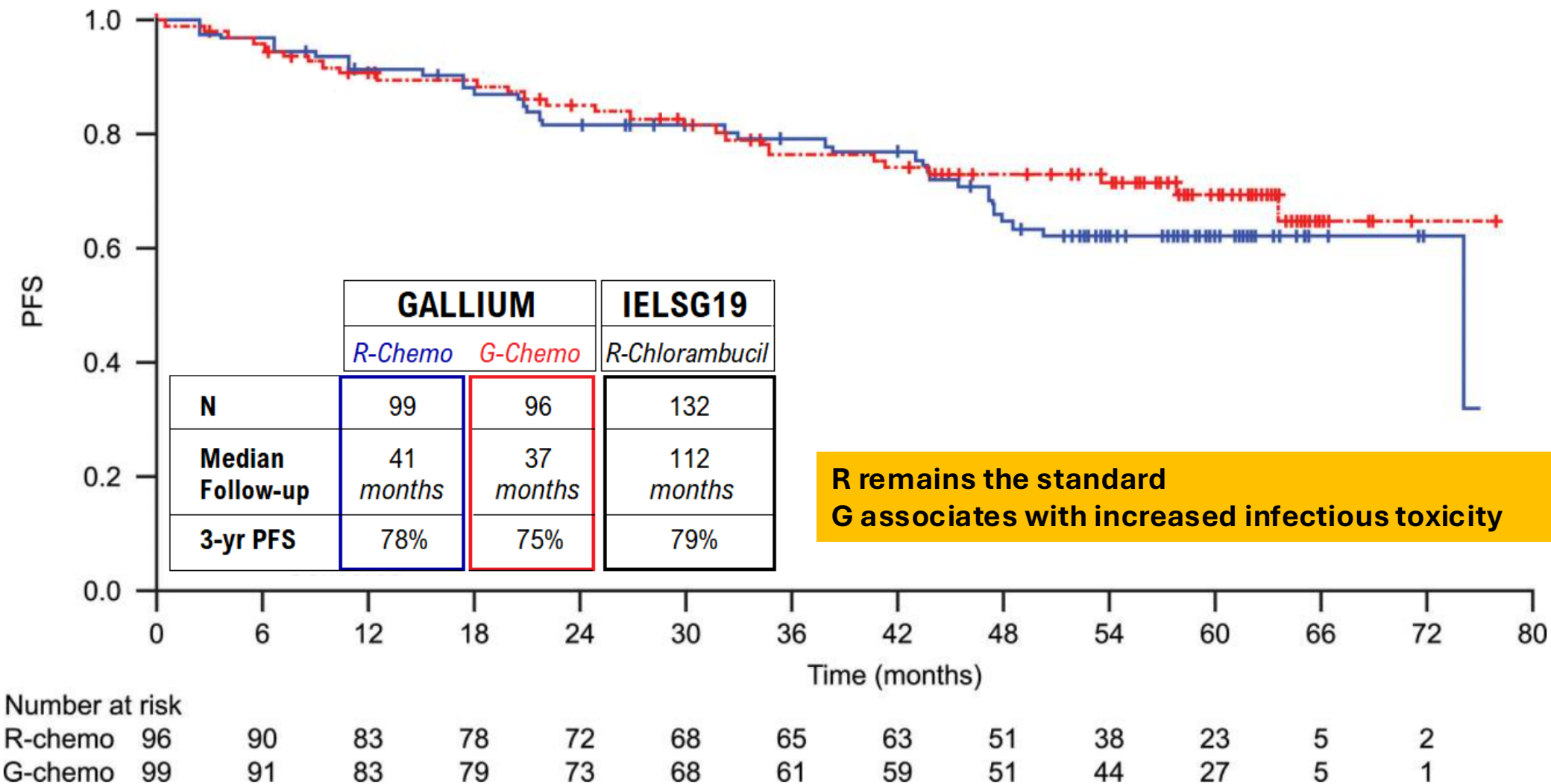


Histology	Response (%)				
	CR	PR	SD	PD	ORR
All indolent (N=40)	8 (20)	10 (25)	16 (40)	6 (15)	18 (45)
MZL (N=27)	7 (26)	6 (22)	10 (37)	4 (15)	13 (48)

Evidence of Clinical Synergism in Extranodal MZL

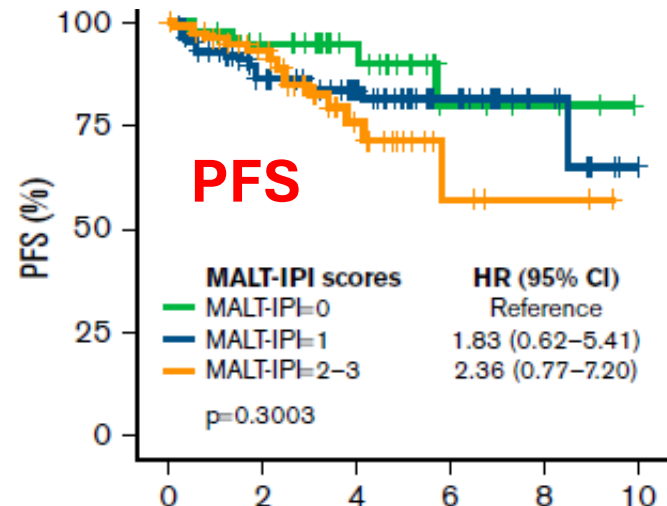
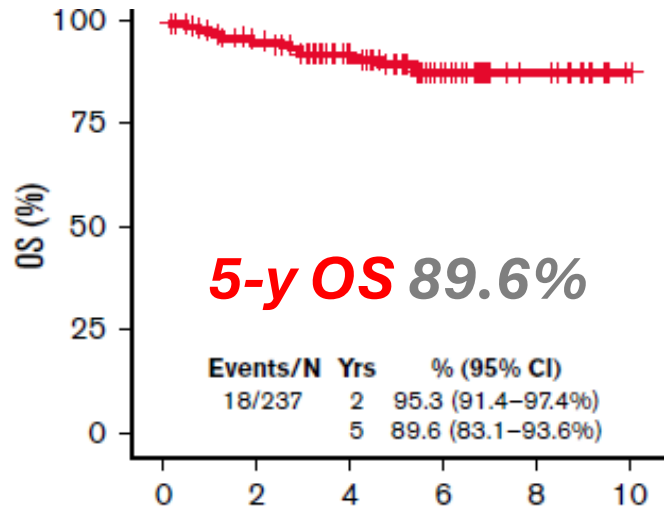
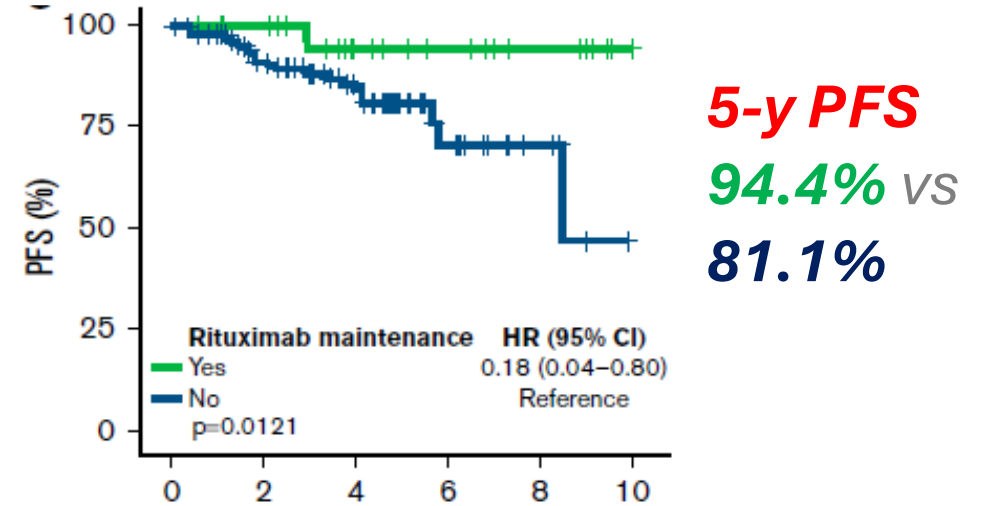
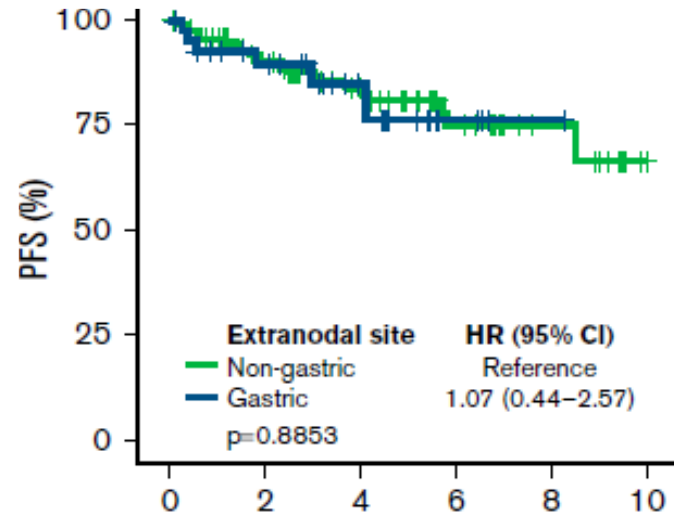
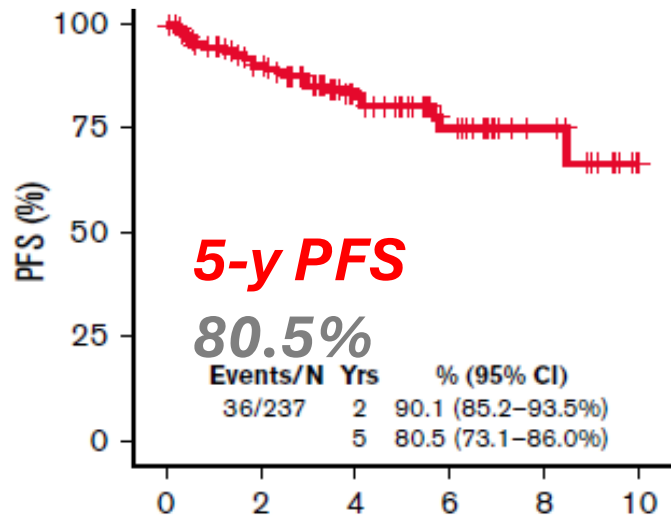


GALLIUM randomized study: PFS in patients with MZL



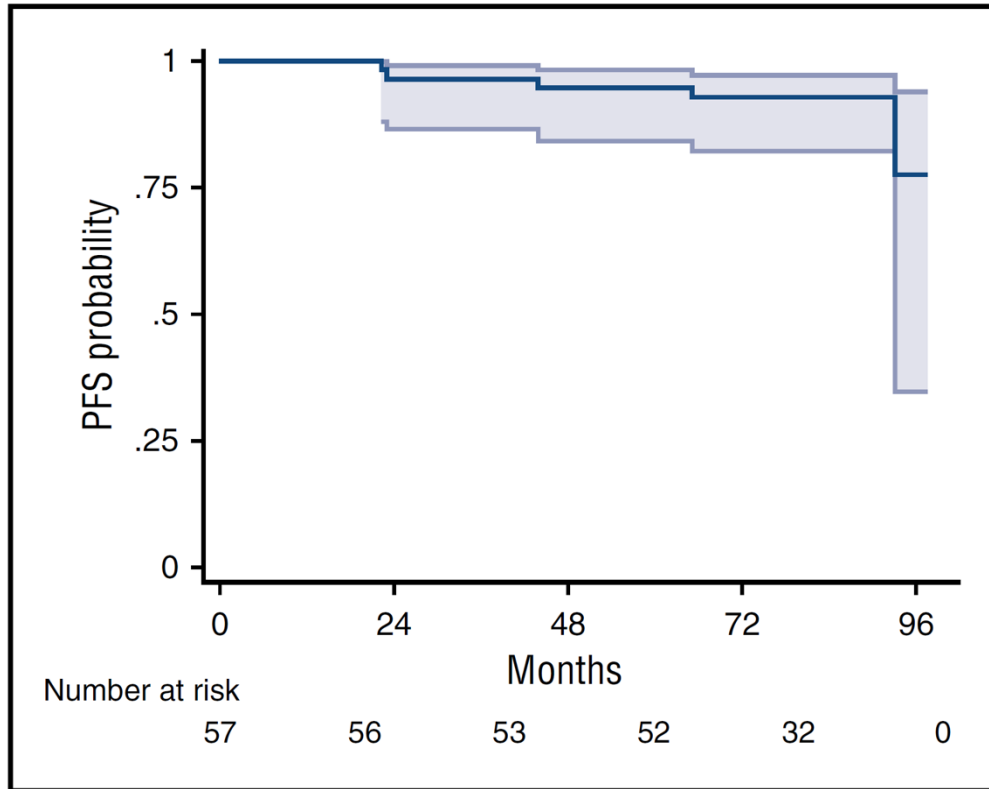
US-Italy retrospective study: BR in EMZL

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



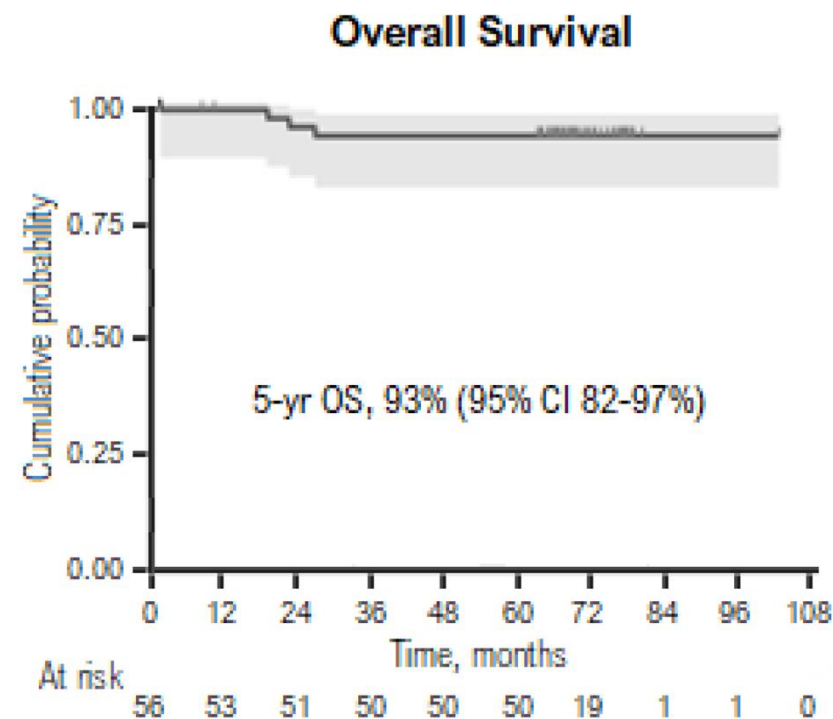
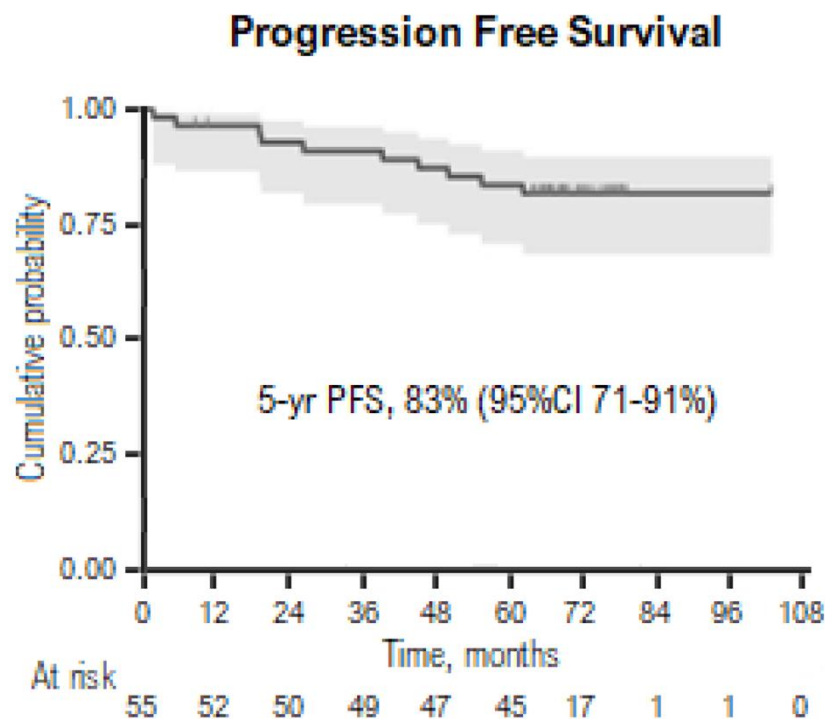
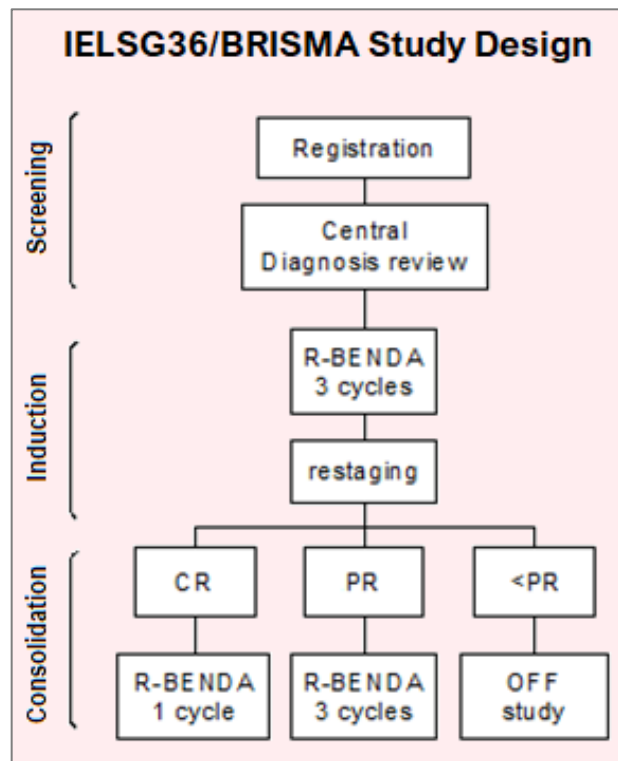
- ORR 93%, CR 81%
- **R maintenance: longer PFS, similar OS**
- Infections in 13% of pts (4% zoster)
- HT: 6% at 5y, 9.1% at 10y; SPM 3.4%

GELTAMO phase 2 study of frontline R-Bendamustine in EMZL



- Response-adapted design:
restaging after cycle 3:
 - 4 B-R cycles if CR
 - 6 B-R cycles if PR
- 75% CR after 3 cycles
- Only 25% (PR after 4 cycles) had 6x B-R
- 7-y PFS 92.8%, 7-y OS 96.5%

IELSG36-BRISMA phase II trial: long-term results



N= 56 (35% high risk HPLL)

ORR 91% (CR 73%)

G $\geq$ 3 toxicity, 68% (mainly hematological; G $\geq$ 3 neutropenia, 43%)

Splenectomy has been largely replaced by Rituximab

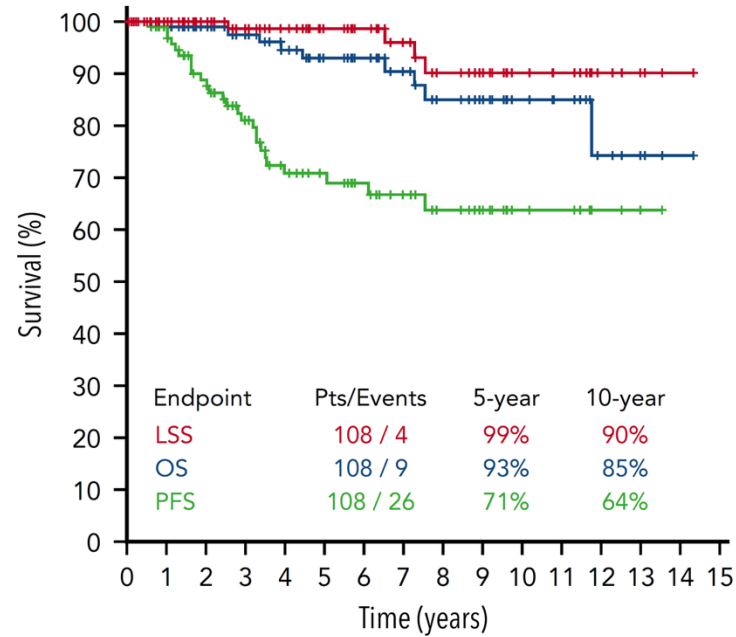
Series of SMZL patients treated with rituximab-based approach

Reference	Year	Study type	Scheme	Patient status	N	Response		OS
						ORR	Duration	
Rituximab monotherapy								
Bennett et al	2005	Retrospective	R mono	RR	11	91%	PFS 60% at 5 y	70% at 5 y
Tsimberidou et al	2006	Retrospective	R mono	First line	25	88%	FFS 86% at 3 y	95% at 3 y
Kalpadakis et al	2007	Retrospective	R mono	First line	16	100%	PFS 92% at 2.4 y	100% at 2.1 y
Else et al	2012	Retrospective	R mono	First line & RR	10	100%	DFS 89% at 3 y	NR
Kalpadakis et al	2013	Retrospective	R mono	First line	58	95%	PFS 73% at 5 y	92% at 5 y
Rituximab + chemotherapy								
Tsimberidou et al	2006	Retrospective	R-chemo	First line	6	83%	FFS 100% at 3 y	100% at 3 y
Cervetti et al	2010	Retrospective	R-2CDA	First line & RR	47	87%	PFS 80% at 5 y	86% at 5 y
Else et al	2012	Retrospective	R-chemo	First line & RR	33	100%	DFS 71% at 3 y	NR
Iannitto et al	2015	Prospective	R-COMP	First line	51	84%	PFS 54% at 6 y	72% at 6 y

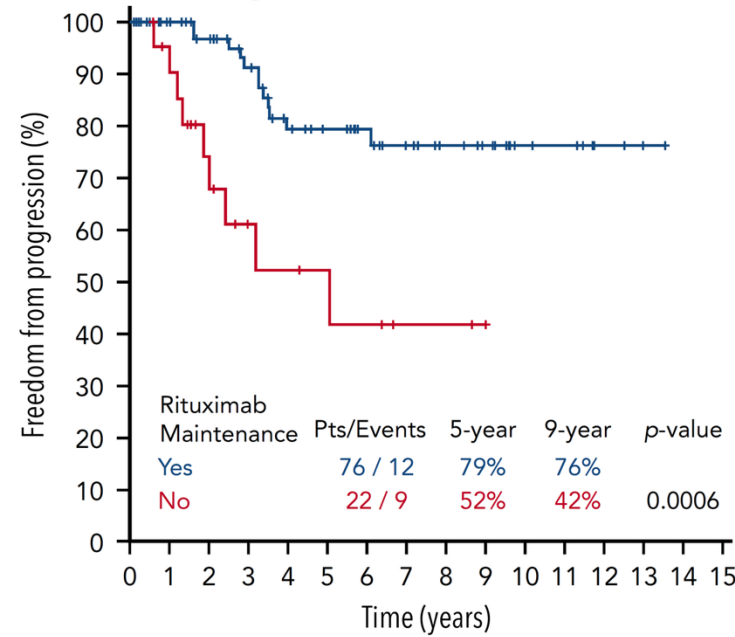
2CDA, 2-chlorodeoxyadenosine; chemo, chemotherapy; DFS, disease-free survival; R, rituximab; RR, relapsed/refractory.

Rituximab monotherapy in SMZL

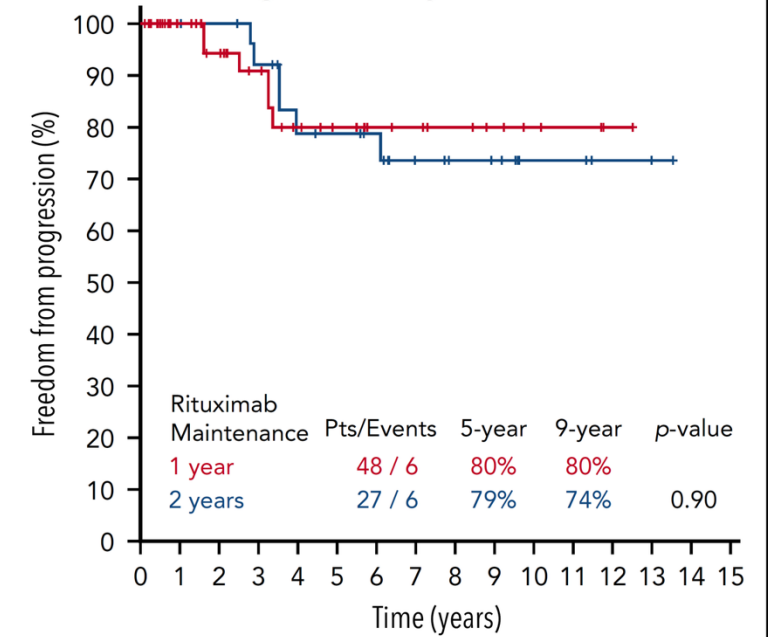
OS, LSS, and FFP in the entire cohort



FFP according to Maintenance



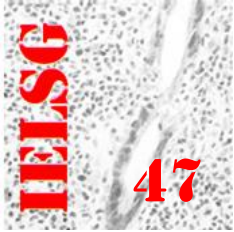
FFP according to 1 or 2 years maintenance



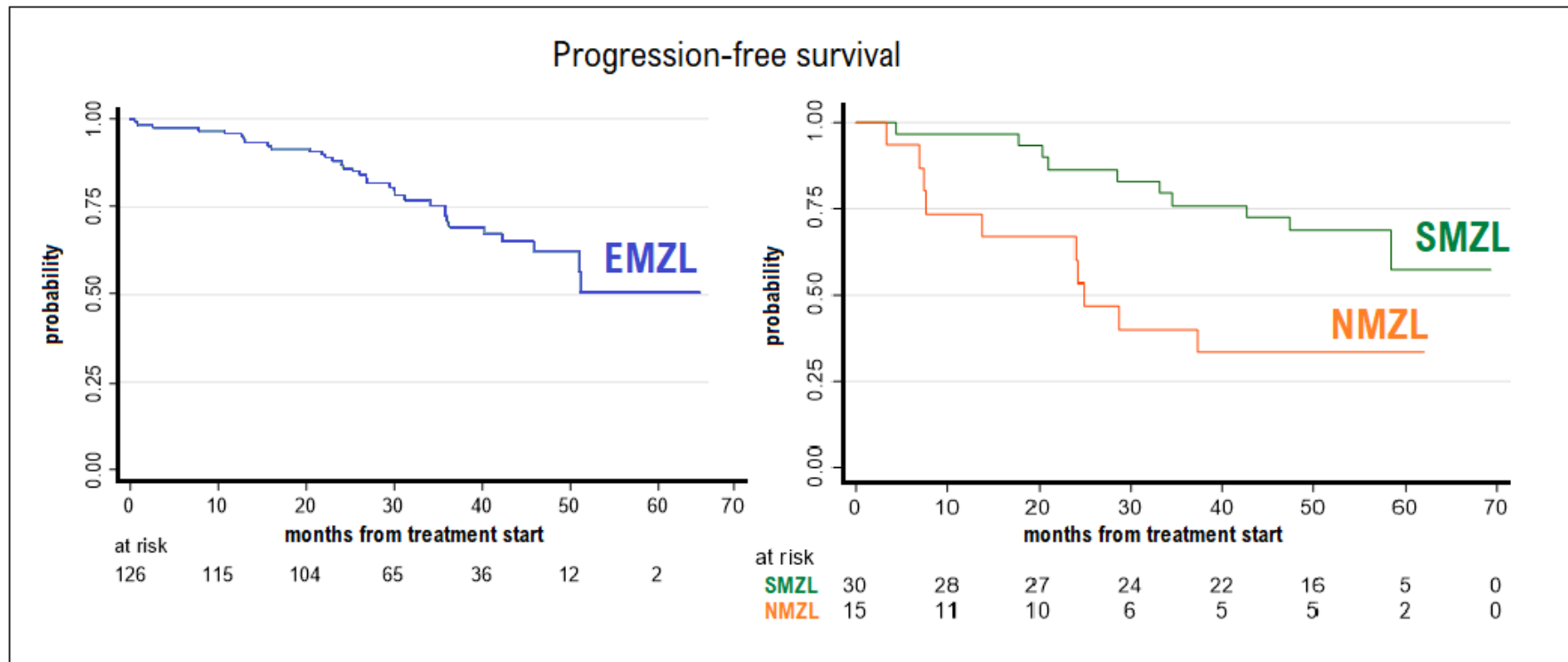
CR 47/106 (44%)
CRu 22/106 (21%)
PR 29/106 (27%)

prolonged responses and potential benefit from maintenance

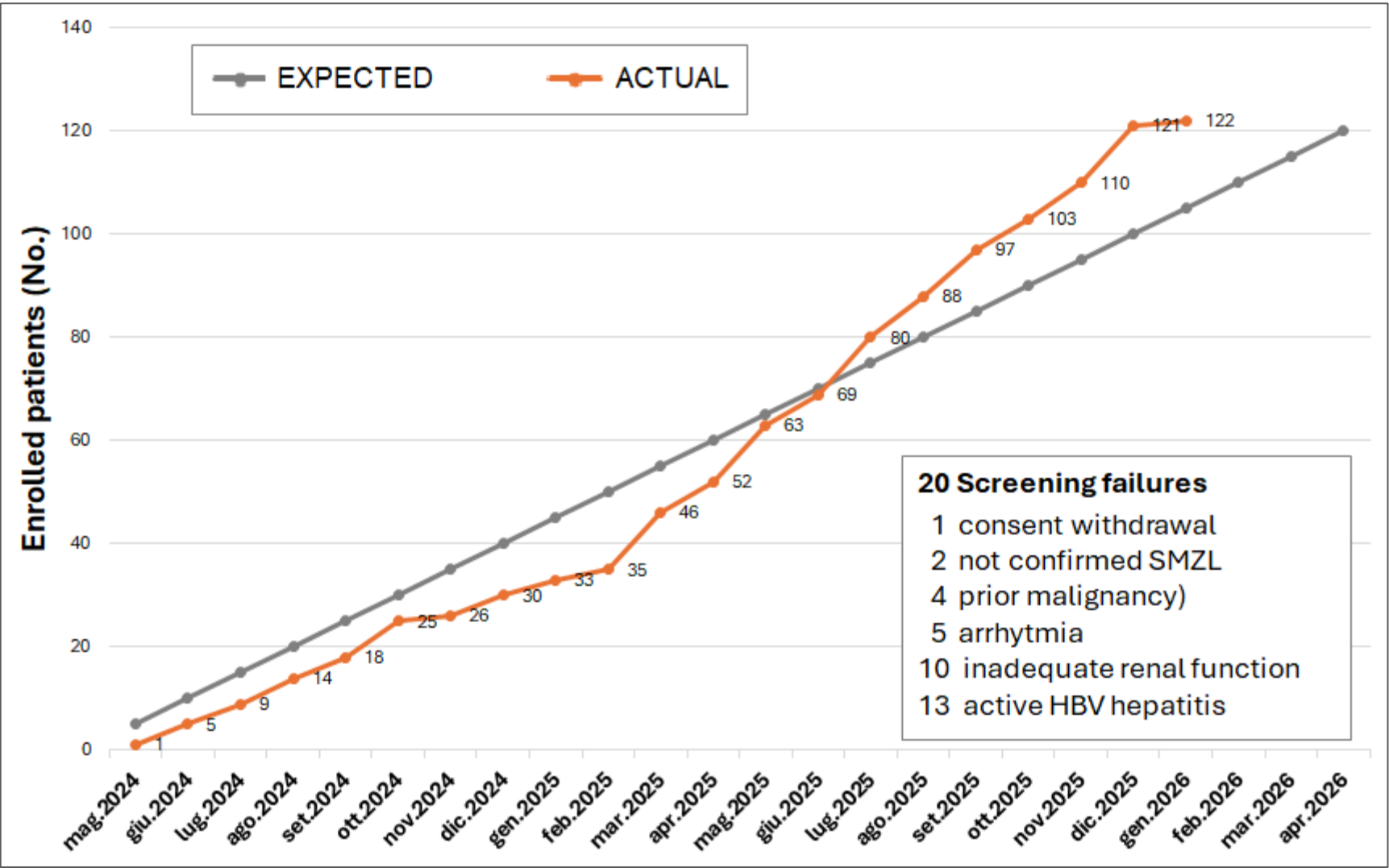
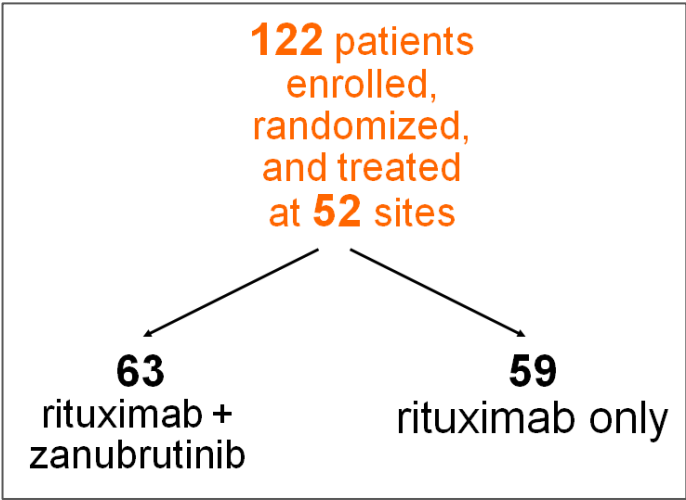
IELSG47/MALIBU study of R-ibrutinib in untreated MZL



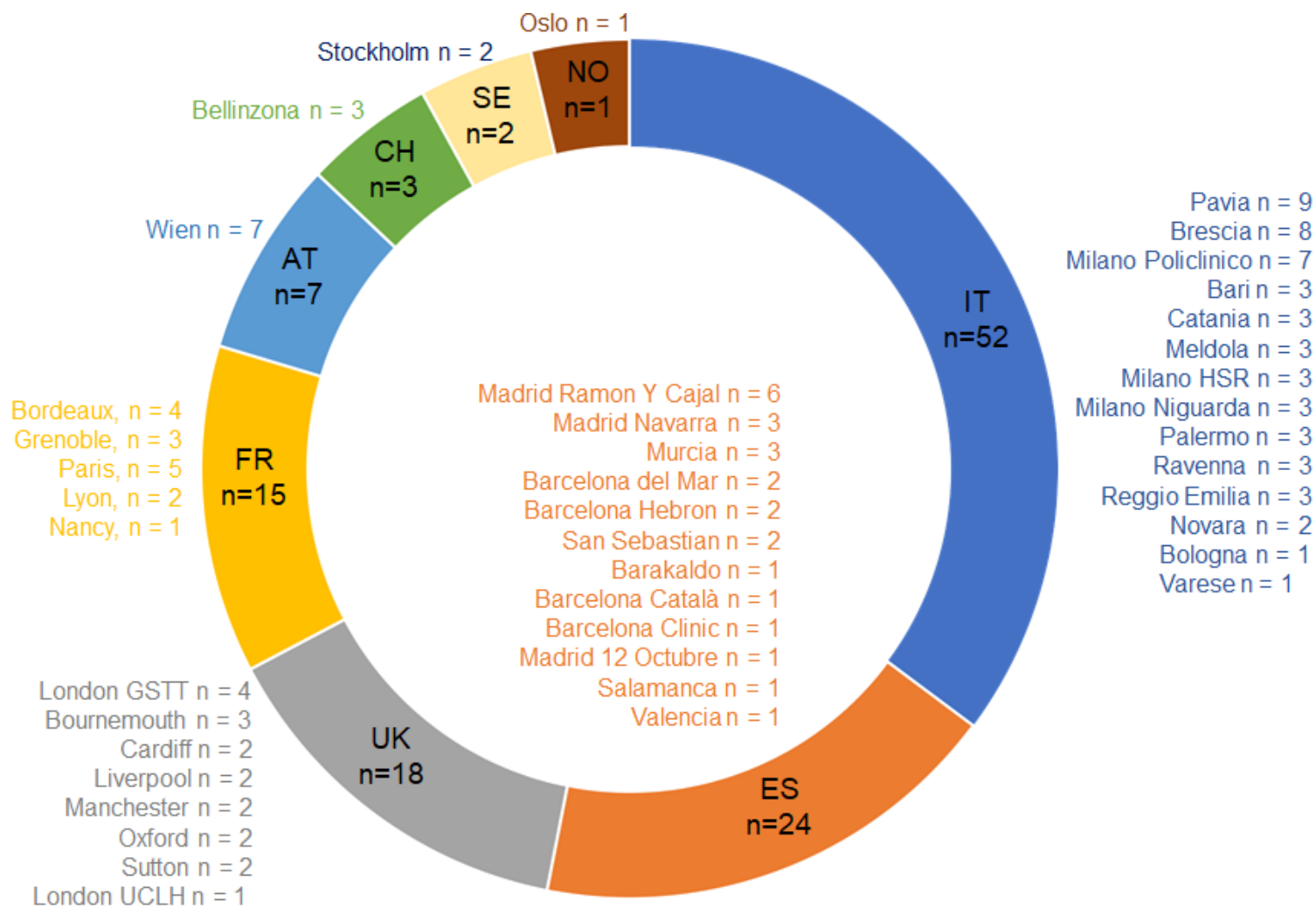
Subtype	Best ORR	Best CR	Median PFS
EMZL (n=130)	92%	62%	Not reached
SMZL (n=30)	97%	57%	Not reached
NMZL (n=15)	86%	53%	24.9 months



IELSG48/RITZ study: Frontline Rituximab vs R-Zanubrutinib in SMZL



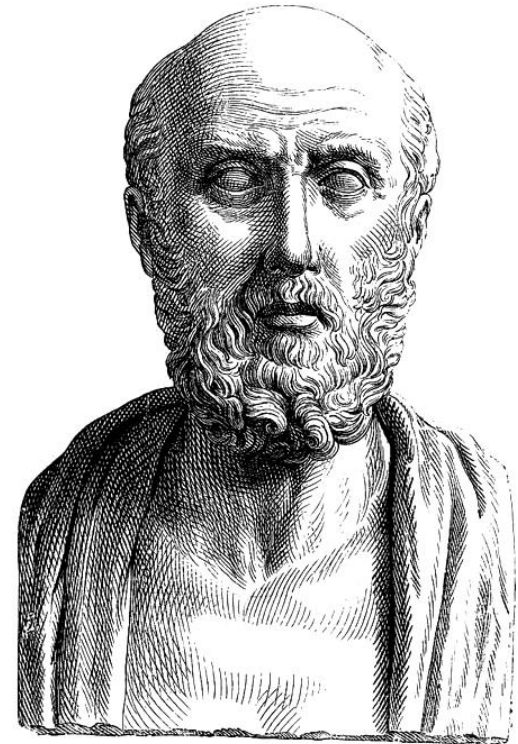
IELSG48/RITZ study international recruitment



Treatment of Relapsed/Refractory MZL

- Is treatment needed?
- What's the treatment goal?
- Cure is not necessarily the aim

Primum Non Nocere

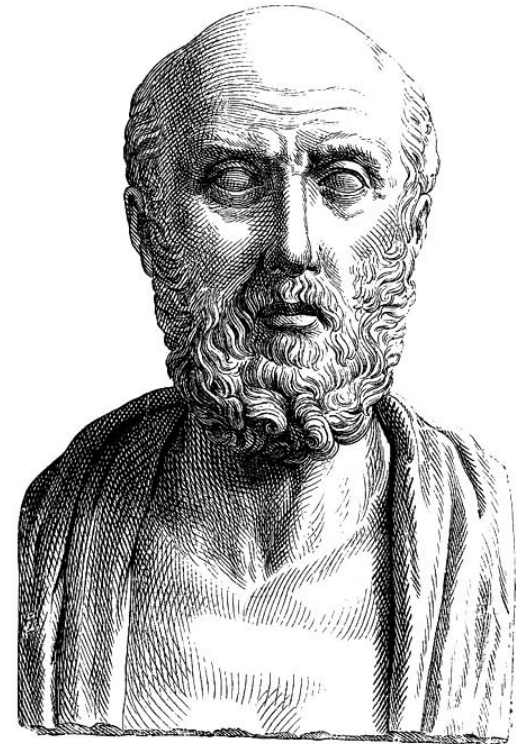


Hippocrates of Kos (460 –370 BC)

Risk assessment is crucial

- Most patients experience long survival despite multiple relapses
- Risk assessment is important to avoid over-treatment and under-treatment
- Repeat biopsy to exclude transformation (particularly if POD24)

Primum Non Nocere

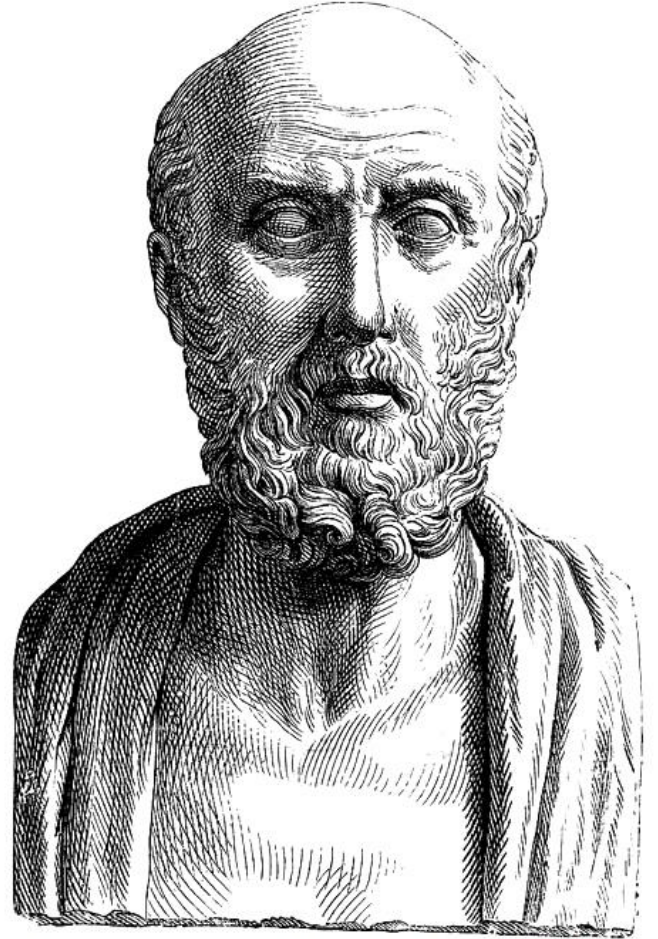


Hippocrates of Kos (460 –370 BC)

Management guidelines for R/R MZL

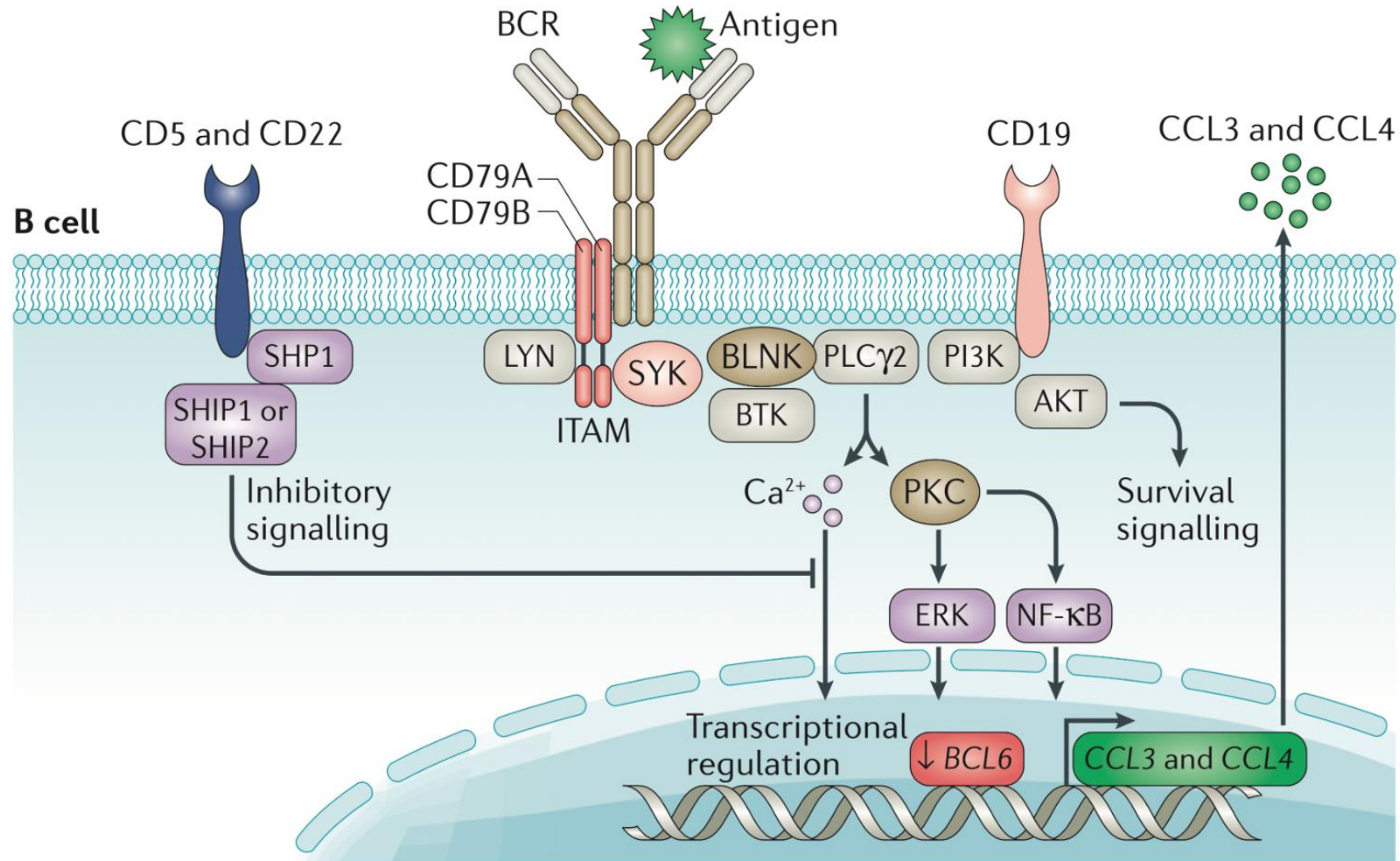
- Watch-and-wait in asymptomatic patients
- IS-RT for patients with localized relapses
- Repeat chemoimmunotherapy after long initial remissions
- BTK inhibitors could be a chemotherapy-free alternative
- Consider ASCT only for fit poor-risk patients (POD24)

How to treat patients in need of systemic therapy?



Hippocrates of Kos (460 – 370 BC)

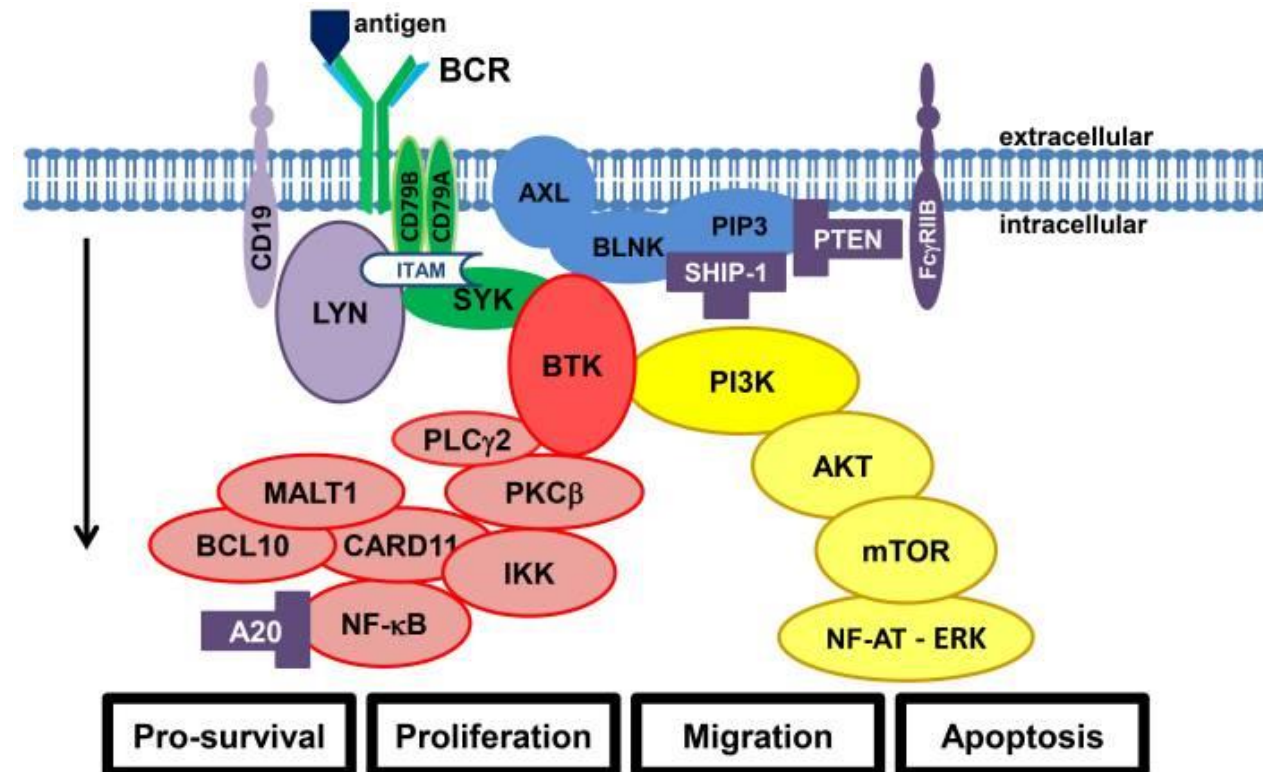
Several potential treatment targets in MZL



PI3K signalling in Marginal Zone Lymphoma

- BCR signaling critical to normal B cell development
- BCR signaling implicated in lymphomagenesis
- PI3K a downstream intermediary in the BCR pathway essential for BCR-dependent B cell survival
- Preclinical evidence suggests the PI3K-mTOR pathway is sufficient for driving the pathogenesis of MZL

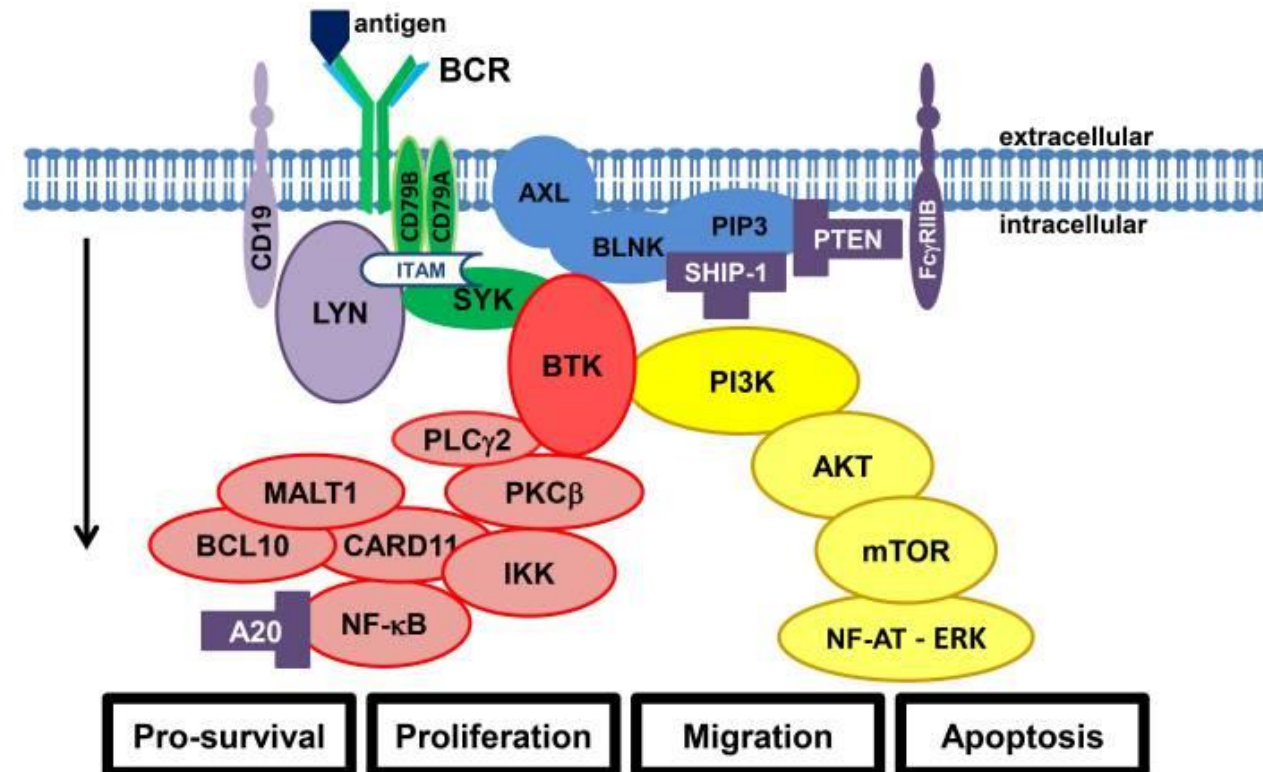
The B cell receptor (BCR) and its downstream pathways



PI3K signalling in Marginal Zone Lymphoma

- Durable ORR and/or PFS improvements in clinical trials
- FDA approved several PI3K δ inhibitors: idelalisib, copanlisib, duvelisib, umbralisib
- Subsequent revocation or voluntary withdrawal of indications due to safety concerns

The B cell receptor (BCR) and its downstream pathways

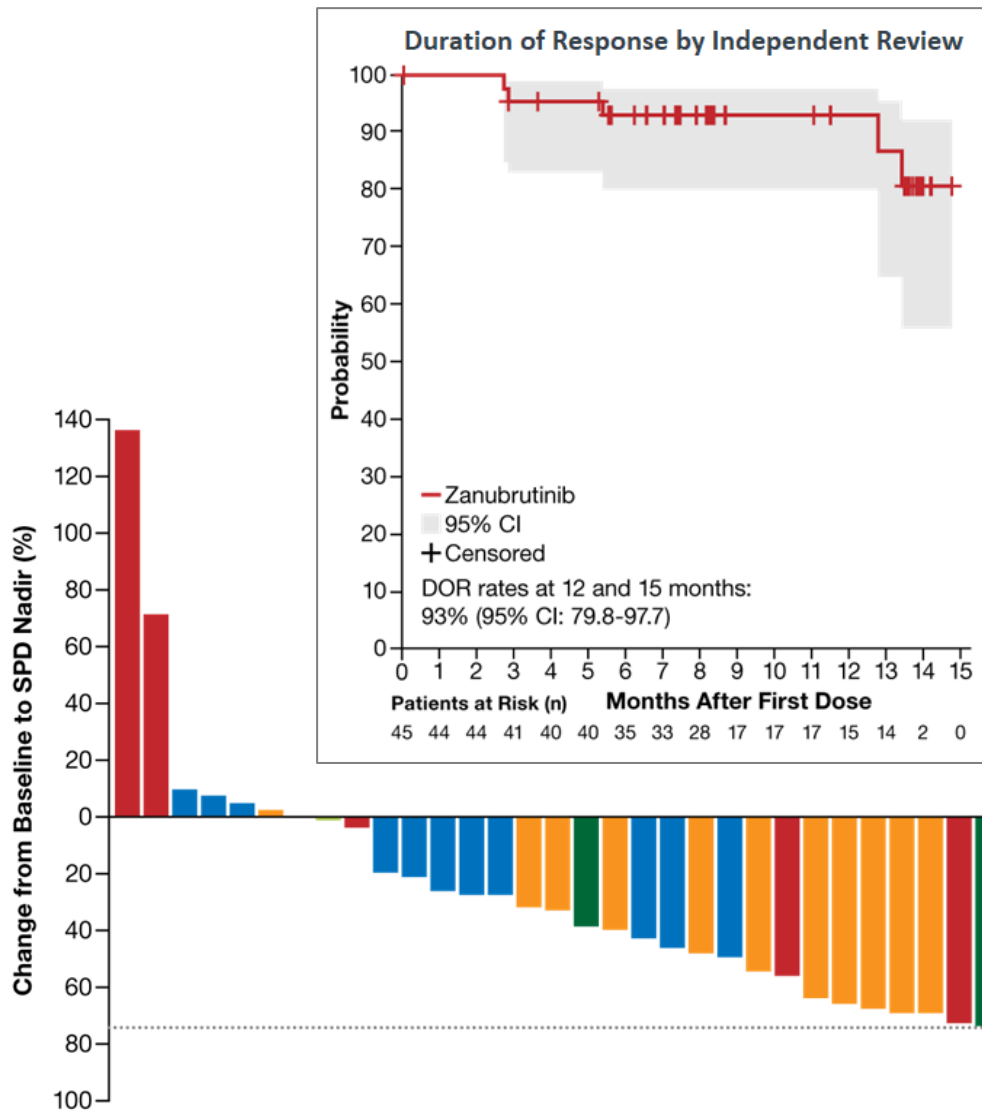


Efficacy of Covalent BTK Inhibitors in R/R MZL

Agent	Study	No. of patients	Median age (range)	Median lines of prior therapy (range)	ORR (95%CI)	CR	PFS	AE-related therapy halt	Median follow-up
Ibrutinib ¹	PCYC-1121 (NCT01980628)	63	66 yrs (30-92)	2 (1-9)	58% (45–71)	10%	median, 16 mos	19%	33 mos
Acalabrutinib ²	ACE-LY-003 (NCT02180711)	43	69 yrs (42–84)	1 (1–4)	53% (36–68)	13%	median, 27 mos	7%	13 mos
Zanubrutinib ³	MAGNOLIA (NCT03846427)	68	70 yrs (37-95)	2 (1-6)	68% (56–79)	26%	71% at 2 yrs	7%	27 mos
Orelabrutinib ⁴	ICP-CL-00104 (NCT03797456)	90	62 yrs (23-77)	1 (1-3)	59% (48–69)	11%	76% at 2 yrs	6%	24 mos

¹Noy A, et al. Blood Adv 2020 ²Strati P et al. Br. J Haematol 2022 ³Opat S et al. Blood Adv. 2023 ⁴Deng L et al. Am J Hematol. 2023

MAGNOLIA phase-2 trial of Zanubrutinib in R/R MZL



Zanubrutinib 160 mg twice a day

Most AE were grade 1 or 2

Most common AEs : diarrhea (22.1%), contusion (20.6%), constipation (14.7%)

Best response	EMZL (n=25)	NMZL (n=25)	SMZL (n=12)	Unknown (N=4)
ORR, n (%)	16 (64.0)	19 (76.0)	8 (66.7)	2 (50.0)
CR, n (%)	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)

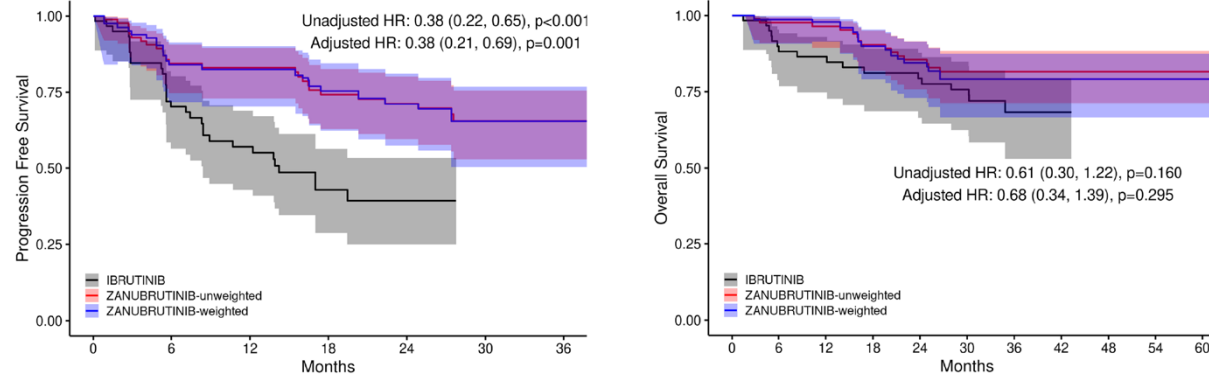
Waterfall plot

- Complete response
- Partial response
- Stable disease
- Non-progressive disease
- Progressive disease

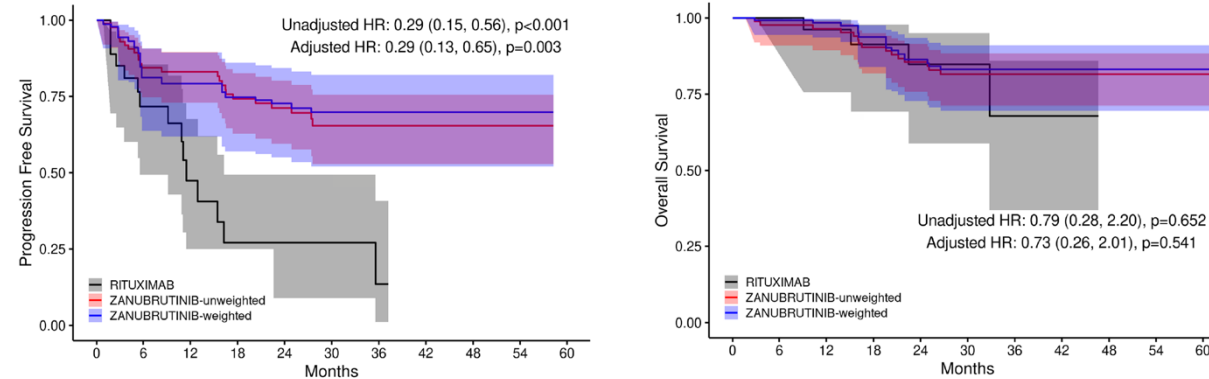
Matching-adjusted indirect comparison in R/R MZL

Zanubrutinib versus ibrutinib and rituximab

Zanubrutinib versus ibrutinib, Kaplan–Meier PFS and OS curves before and after matching adjustment



Zanubrutinib versus rituximab, Kaplan–Meier PFS and OS curves before and after matching adjustment

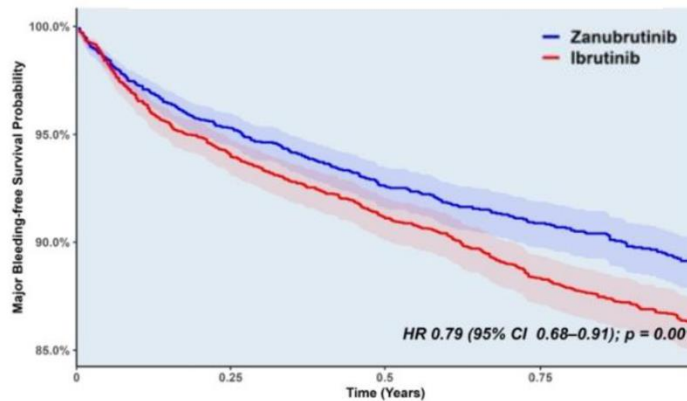


Logistic propensity score models used to estimate weights for the patient-level data from the phase II trials, MAGNOLIA and BGB-3111-AU-003, such that their characteristics matched the ibrutinib and rituximab aggregate-level data from PCYC-1121 and CHRONOS-3 studies, respectively.

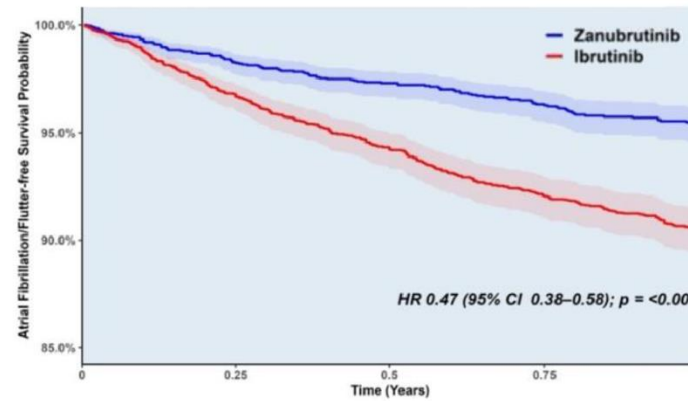
Comparative risk of adverse cardiovascular outcomes

Zanubrutinib vs Ibrutinib: Real-World Propensity-Matched analysis

Freedom from major bleeding



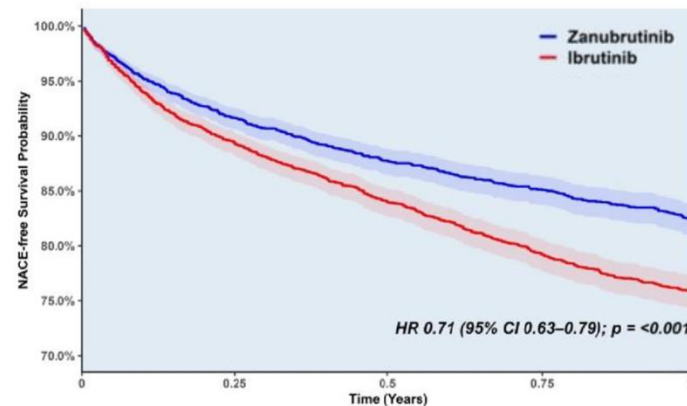
Freedom from atrial fibrillation/flutter



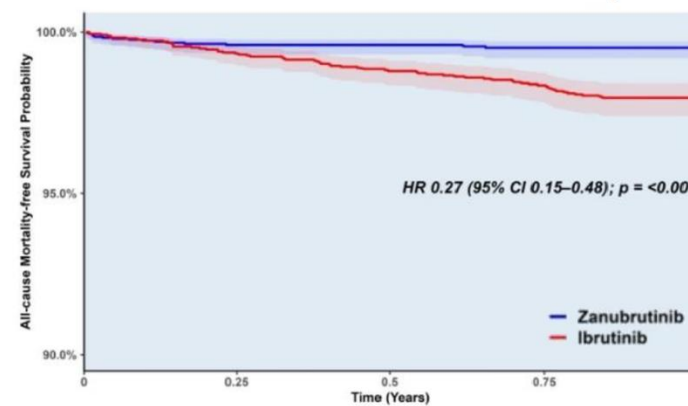
No significant difference in terms of

- intracranial hemorrhage
- ischemic stroke
- myocardial infarction
- ventricular arrhythmias
- heart failure,
- hypertension.

Freedom from net adverse clinical events

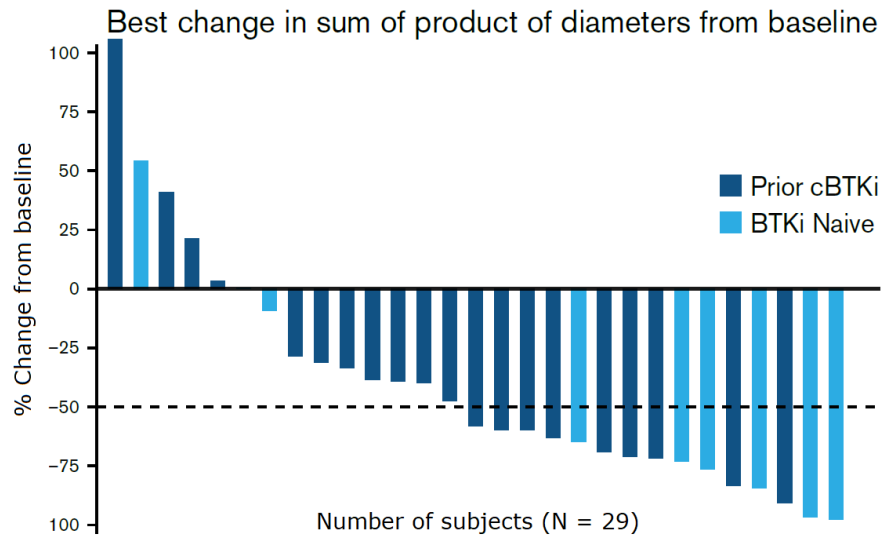


Freedom from all-cause mortality



Propensity matching performed across 41 covariates, including baseline demographic characteristics, relevant comorbidities, and medications. It yielded a total of 6,894 patients, 3,447 in the zanubrutinib cohort and 3,447 in the ibrutinib cohort.

Pirtobrutinib efficacy in heavily pretreated MZL



Safety

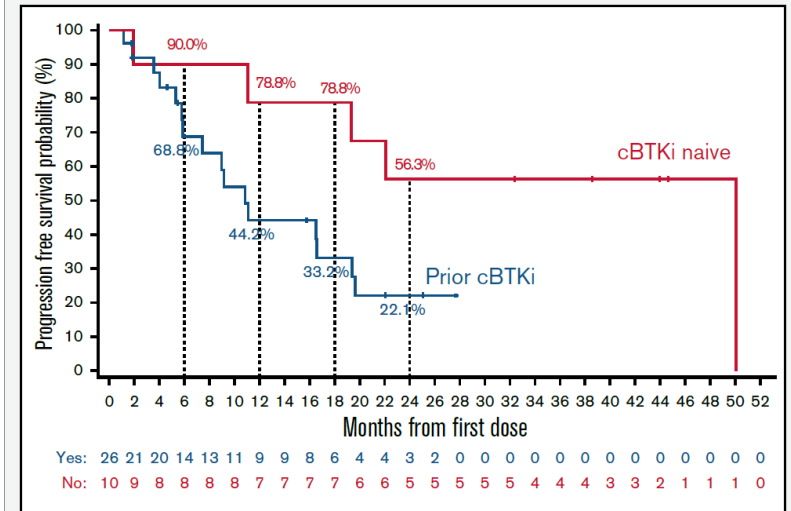
- Grade =3 TEAE: Neutropenia, 33%; Anemia, 17%; Infections, 14%; Thrombocytopenia, 11%
- AE leading to dose reduction, 11%
- AE leading to discontinuation, 11%

Best response

Response n (%)	All patients N = 36	Prior cBTKi n = 26	cBTKi naïve n = 10
ORR	20 (55.6)	(53.8)	6 (60)
PD	3 (8.3)	2 (7.7)	1 (10)
CR	3 (8.3)	1 (3.8)	2 (20)
PR	17 (47.2)	13 (50.0)	4 (40)
SD	13 (36.1)	10 (38.5)	3 (30)

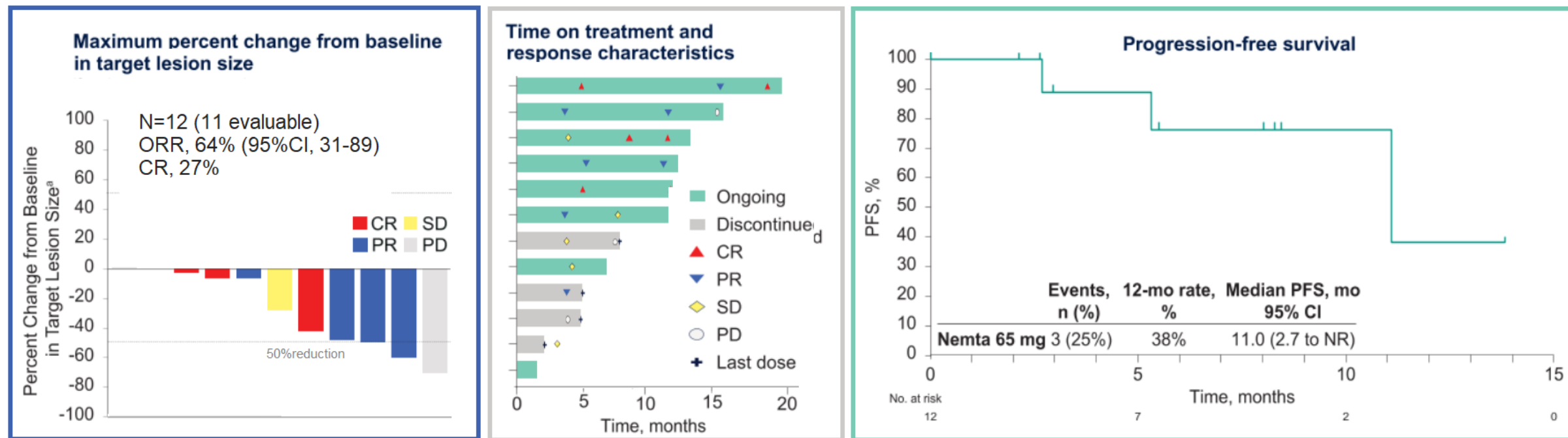
Progression-free survival

PFS	All MZL Patients	Prior cBTKi	cBTKi naïve
Median, months (95% CI)	16.59 (8.97, 22.08)	10.84 (5.88-19.38)	50.07 (1.94-NE)
Events/Total	21/36	16/26	5/10
Median Follow-up, months	27.73	25.07	43.96



Nemtabrutinib (non-covalent BTKi) in R/R MZL

Preliminary Results from the Phase 2 Bellwave-003 Study (ASH 2024)



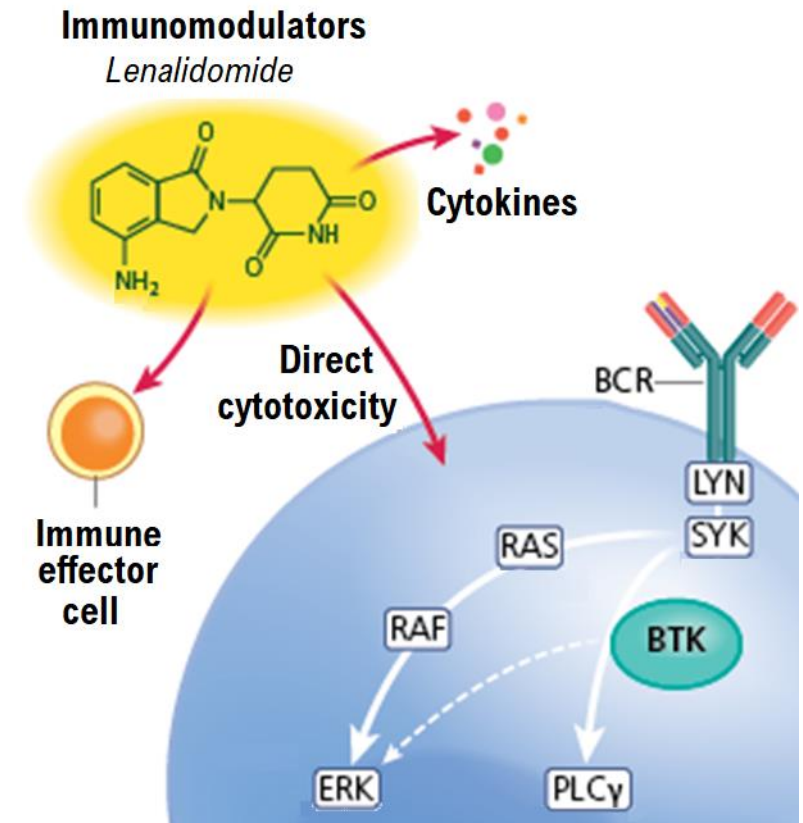
Pts with R/R MZL must have had prior chemoimmunotherapy and a covalent BTKi.

Eligible pts received nemtabrutinib at the RP2D of 65 mg once daily until unacceptable toxicity, progression, or withdrawal.

R plus Lenalidomide: why to combine them?

- NK cell-mediated synergism between IMiDs and rituximab in mouse models
- Lenalidomide boosts ADCC of rituximab-treated CD20+ cells
- Promising results of early phase 2 studies

Hernandez-Ilizaliturri et al. Clin Cancer Res 2005
Wu et al. Clin Cancer Res 2008
Fowler et al. Lancet Oncol 2014
Martin et al. Ann Oncol 2017



Rituximab-lenalidomide studies in MZL

Author	Design	Population	N	ORR (%)	CR (%)	Median PFS (mos)	2-yr OS (%)
Kiesewetter Blood 2017	Phase 2	De novo and R/R	46	80	54	NA	
Becnel BJH 2019	Phase 2	De novo	30	93	73	59	
Leonard JCO 2019	Phase 3 R ² vs R	R/R	31 vs 32	65 vs 44	29 vs 13	19 vs 22	82 vs 94
Cassanello Haematologica 2019	Retrospective	R/R	15	nr	40	22	nr

R2 efficacy in the MZL cohort of the AUGMENT trial

Variable	Lenalidomide + Rituximab (n = 31)	Placebo + Rituximab (n = 32)	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)	
Median PFS, as assessed by investigator, months (95% CI)	19.2 (13.9 to 30.4)	22.1 (8.7 to NR)	.8918
Median EFS as assessed by IRC, months (95% CI)	20.2 (14.5 to NR)	25.1 (9.2 to NR)	.6324
Median DOR, as assessed by IRC, months (95% CI)	17.4 (13.2 to NR)	NR (8.4 to NR)	.3111
Median TTNLT, months (95% CI)	25.8 (17.7 to NR)	NR (21.6 to NR)	.3057
OS probability at 2 years, % (95% CI)	82 (61 to 92)	94 (77 to 98)	
Deaths, No. (%)	5 (16)	2 (6)	

Still a role for Hematopoietic Stem Cell Transplant in MZL ?

EBMT retrospective study

ASCT (n=874)

AlloHSCT (n=169)

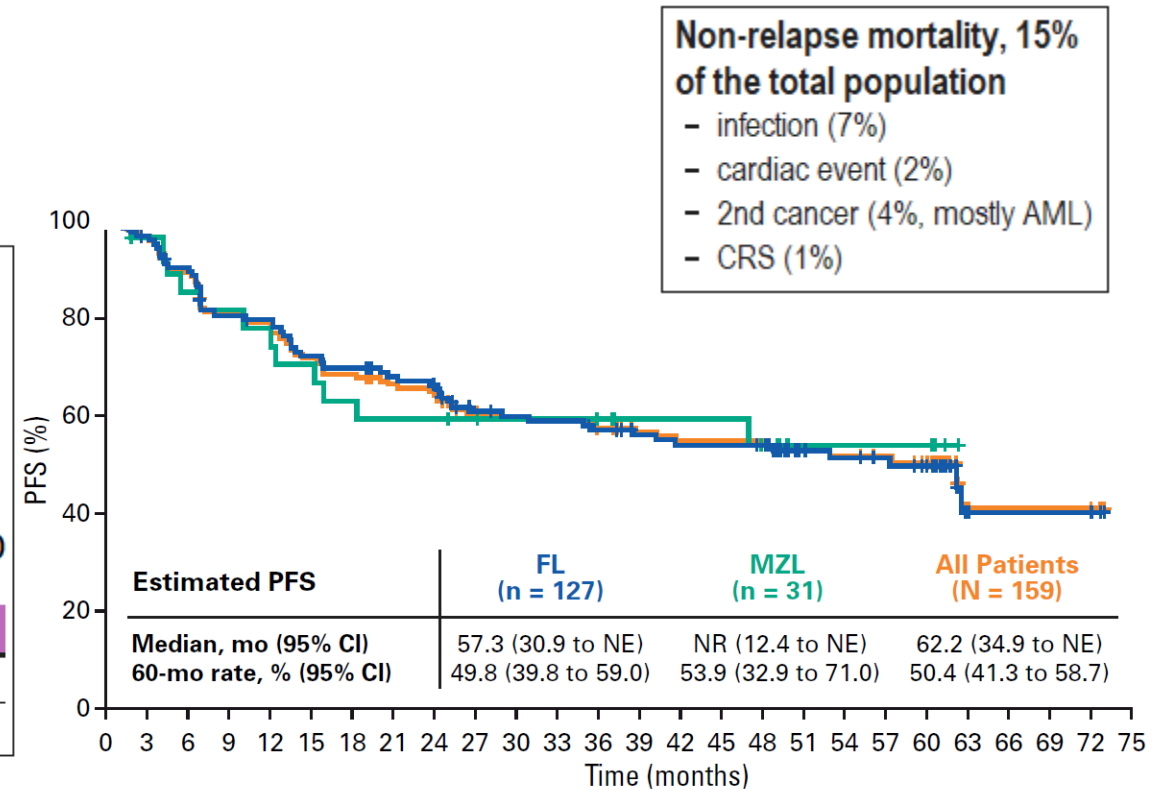
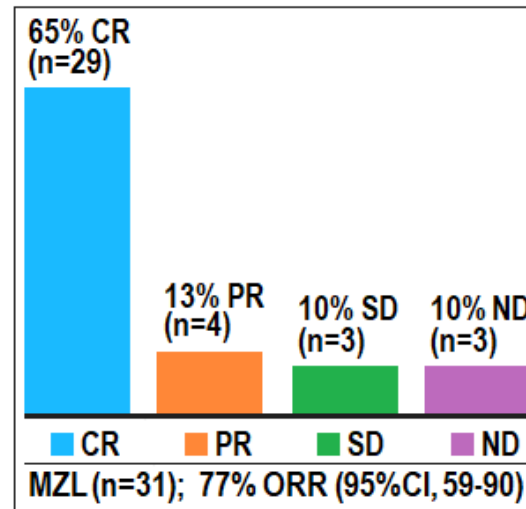
• Non-relapse mortality	8% (95%CI, 6-11) at 3 yr	32% (95%CI, 24-40) at 4 yr
• Overall relapse rate	38% at 3 yr	23% at 4 yr
• 10-yr PFS	28% (95%CI, 22-35)	39% (95%CI, 29-49)
• 10-yr OS	45% (95%CI, 37-54)	51% (95%CI, 42-60)

- Limited indication (refractory POD24)
- Poorer OS in refractory pts vs CR pre-ASCT: HR, 1.7 (95%CI, 1.1-2.5)
- Acute GvHD grade ≥ 3 , 17%
- Extensive chronic GvHD, 40% at 4yr post-allo

ZUMA-5: Axicabtagene Ciloleucel in Relapsed/Refractory MZL

Baseline Characteristics of MZL Patients (n = 31)

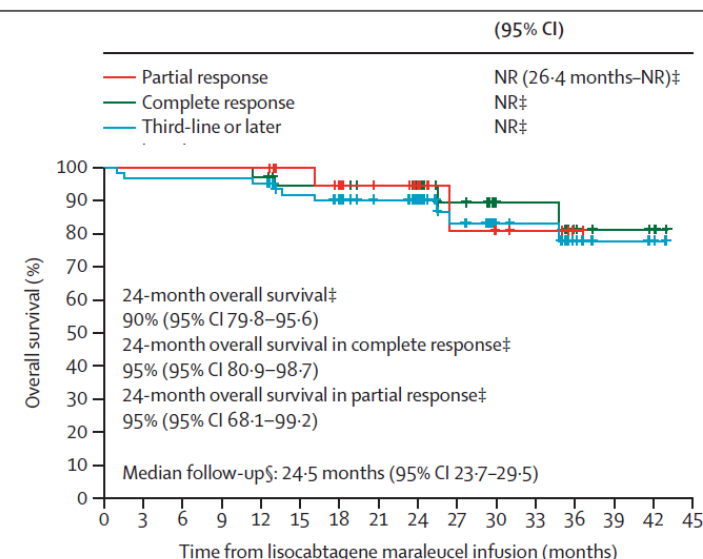
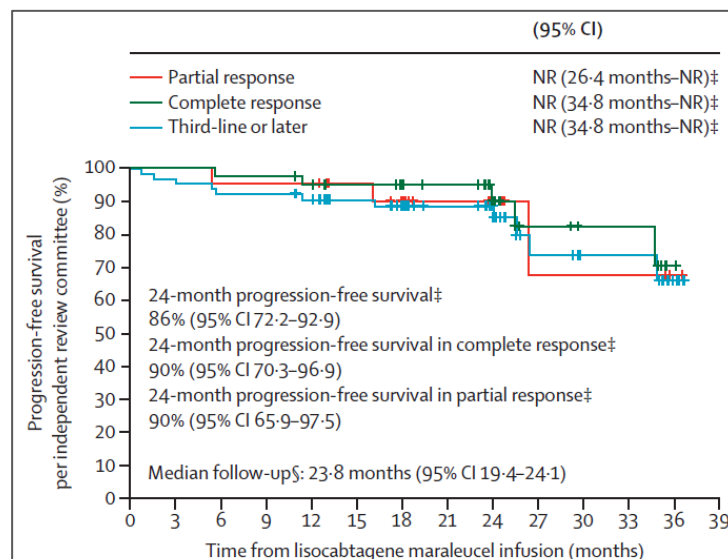
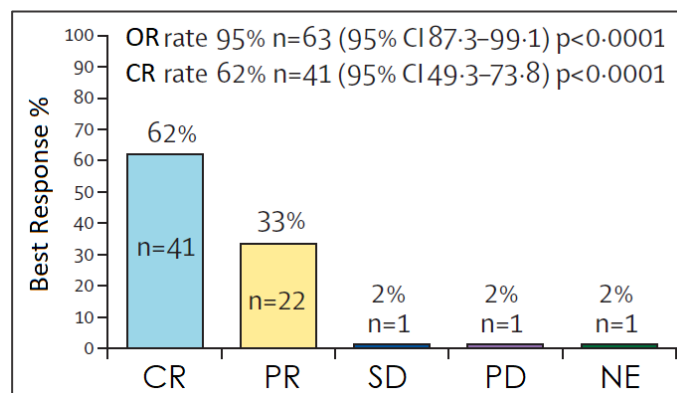
Characteristic	No. (%)
Age ≥65 years	14 (45)
Male sex	15 (48)
ECOG PS 1	16 (52)
Stage III-IV disease	29 (94)
High-risk FLIPI (≥3)	—
High tumor bulk (GELF criteria)	16 (52)
Prior lines of therapy ≥3	20 (65)
R/R subgroup	
Refractory to last prior therapy	25 (81)
POD24 from first anti-CD20 mAb	18 (60)
Lymphoma in bone marrow	14 (45)



Primary Analysis Results of TRASCEND FL: Lisocabtagene Maraleucel in Relapsed/Refractory MZL

Liso-cel-treated analysis set (n=67)	
Age ≥65 years	30 (45%)
Male Sex	39 (58%)
MZL subtype	
Nodal	32 (48%)
Splenic	18 (27%)
Extranodal-mucosa-associated lymphoid tissue	17 (25%)
ECOG performance status 0 at screening	37 (55%)
Ann Arbor Stage IV at screening	49 (73%)
mGELF criteria	41 (61%)
Bulky disease at screening	15 (22%)
High risk FLIPI at screening	41 (61%)
Refractory to last systemic therapy**	26 (39%)
Relapsed after last systemic therapy**	41 (61%)
Progression of disease ≤24 months from initiation of first-line chemoimmunotherapy	24 (36%)
Bone marrow involvement at screening	28 (42%)

Treatment-related AEs in all pts
G3 CRS, 4% (no G4–5 CRS).
G3 neurological AEs, 4% (no G4–5 events)
G≥3 infections in 16%

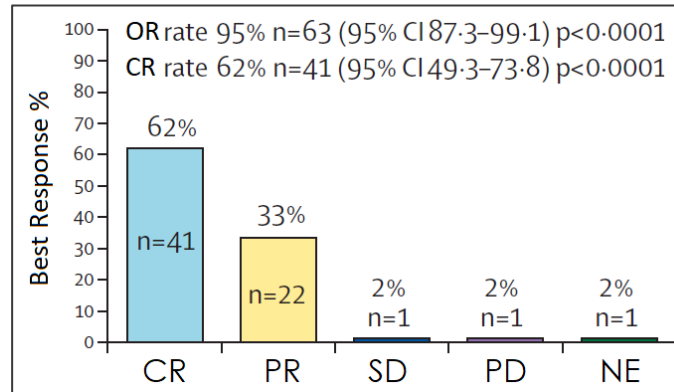


Limited indication (refractory POD24)

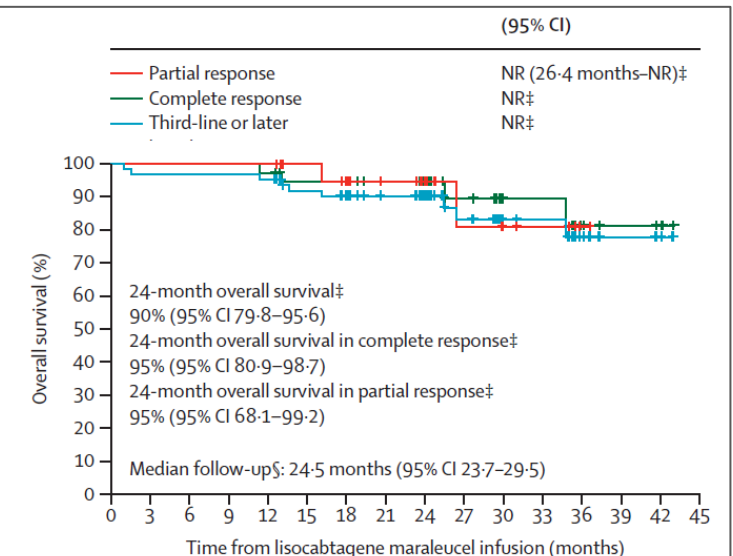
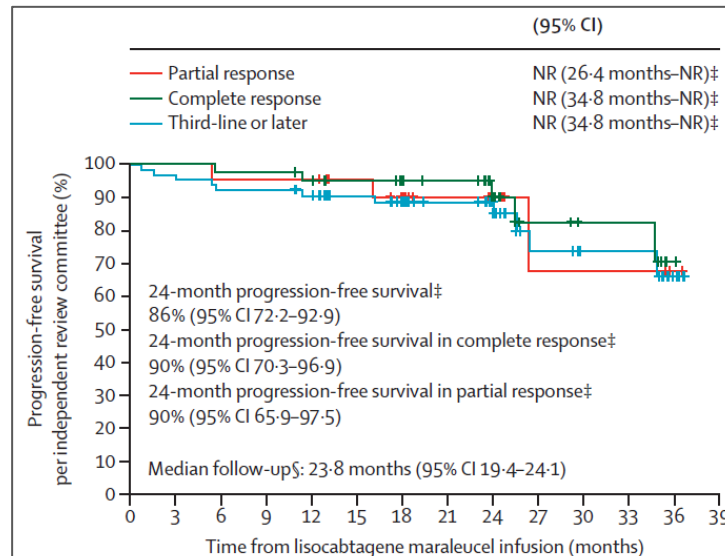
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On December 4, 2025, the FDA approved Liso-cel for adults with r/r MZL who have received ≥2 prior lines of systemic therapy



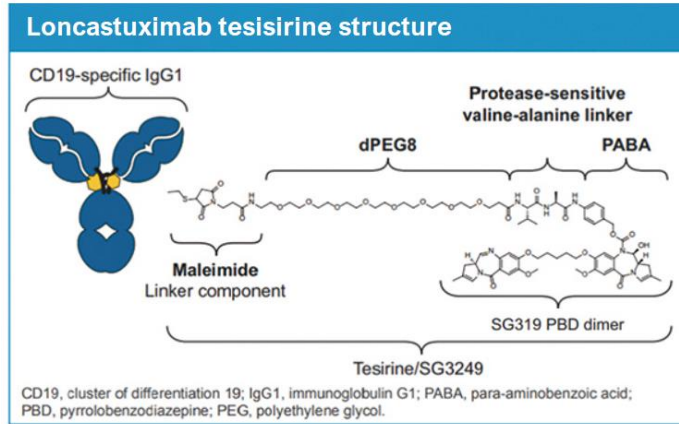
A glimpse into the next years



Novel chemo-free treatments under investigation

- BCL2 inhibitors
- BTK degraders
- New PI3K δ inhibitors
- ...

Limited Duration Loncastuximab Tesirine in r/r MZL

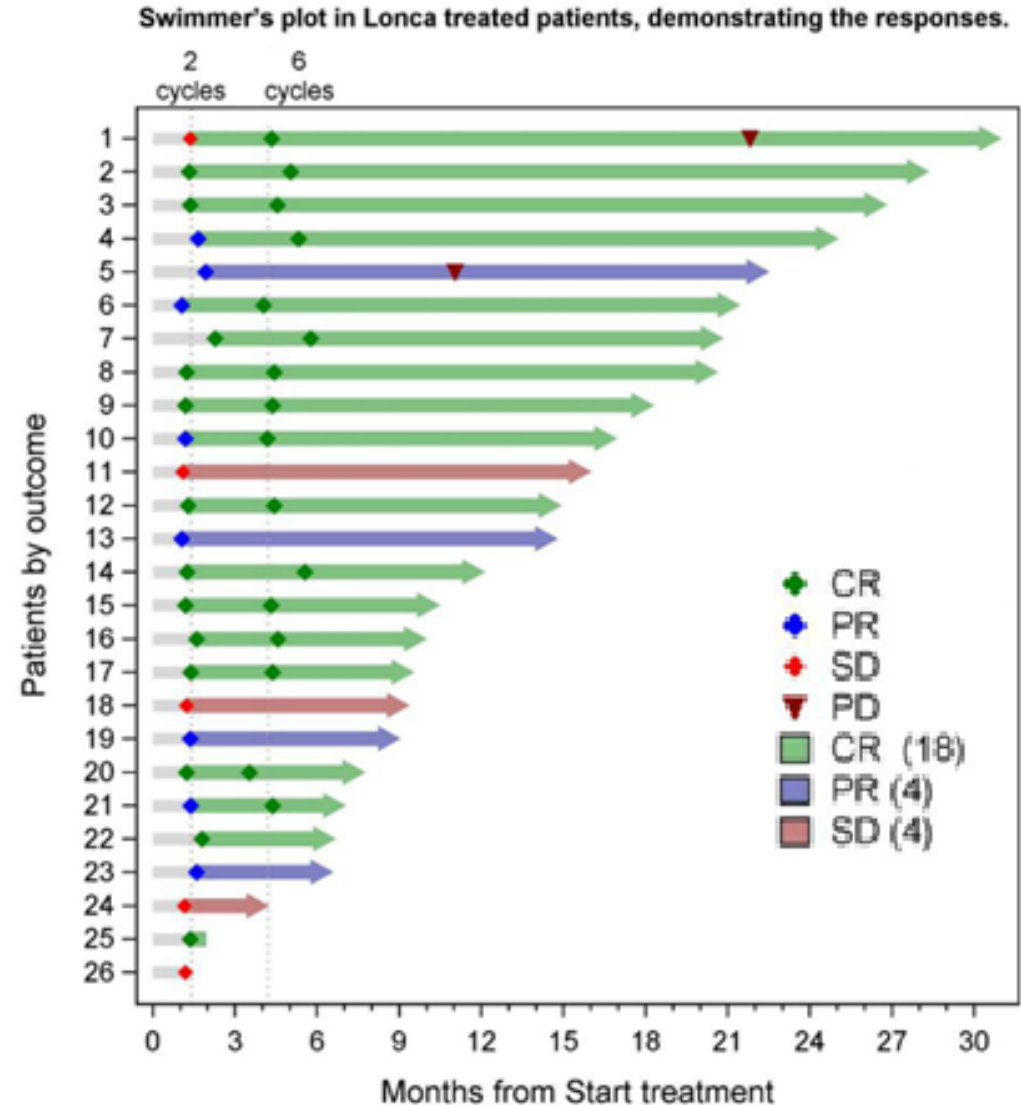


Loncastuximab 0.15 mg/kg i.v. for 2 cycles followed by 0.075 mg/kg for 4 cycles

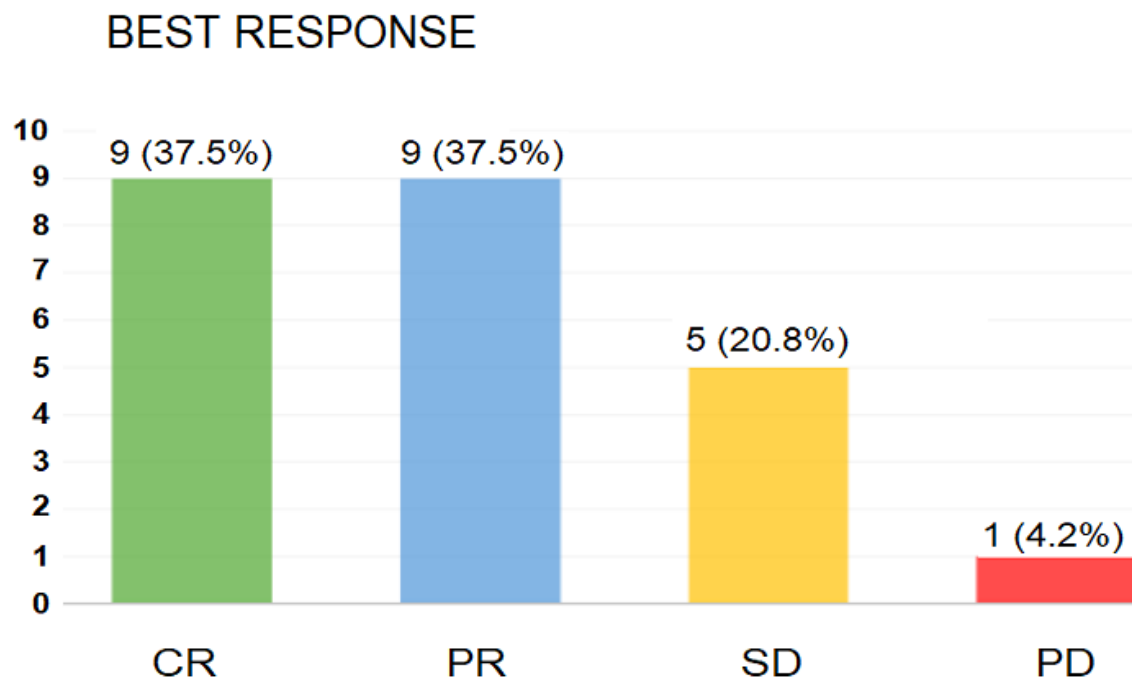
18 ICML update of the ongoing study

- N= 67;
- ORR 91%
- CR 69%; (61.5% in POD 24)
- CR at 18 months was 83.3%

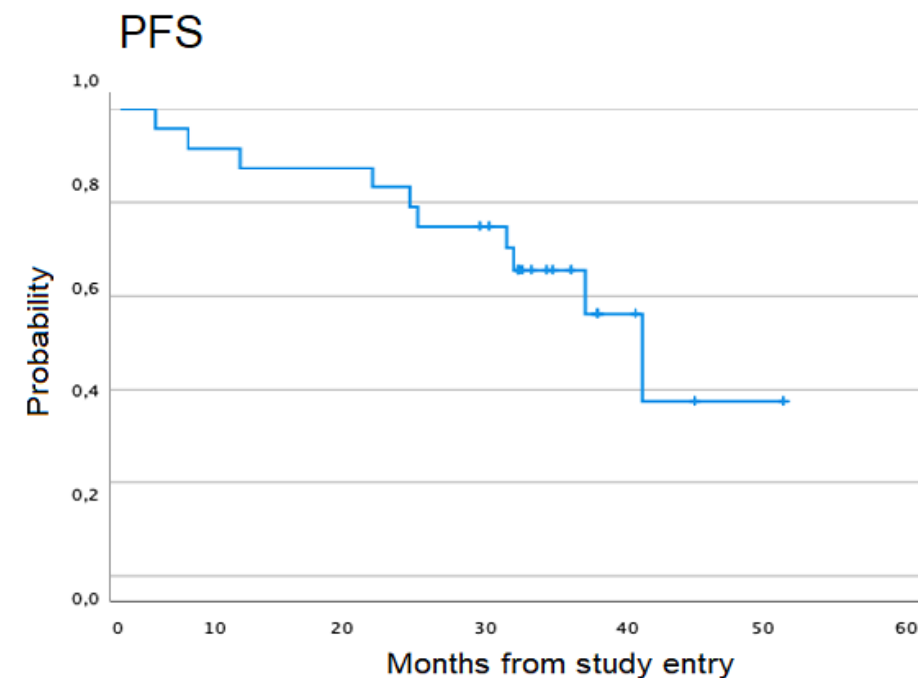
Lossos et al. ASH 2024 and ICML 2025



IELSG49 Phase 2 study of Acalabrutinib plus tafasitamab in R/R MZL



N= 24
ORR, 75% (95% CI, 53–90%)

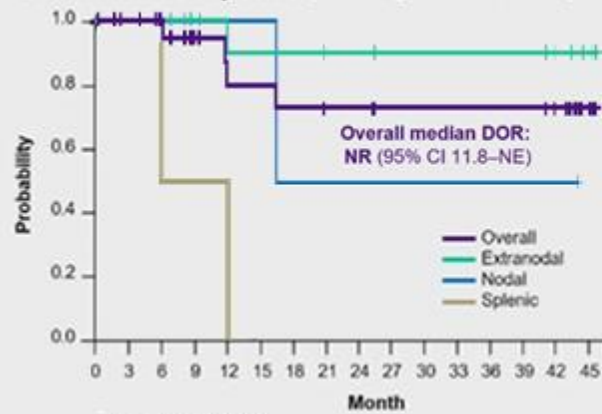


Median follow-up, 35 months
3-year PFS, 66% (95% CI, 42–81%)

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Odronextamab: R/R MZL cohort of the ELM-2 trial

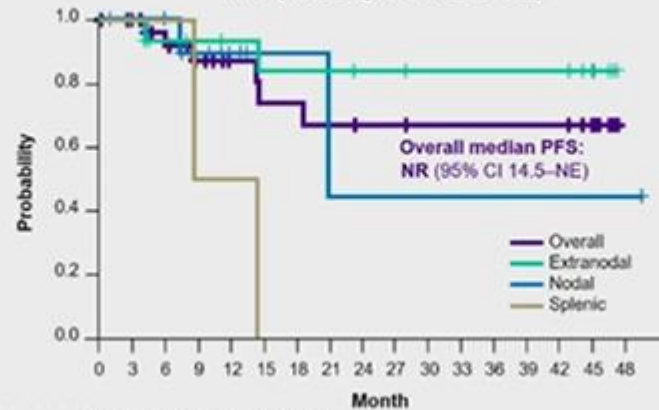
Duration of response (investigator assessed)



12-mo DOR (95% CI)

Overall	Extranodal	Nodal	Splenic
80.2 (49.6-93.3)	90.0 (47.3-98.5)	100 (100-100)	0.0 (NE-NE)

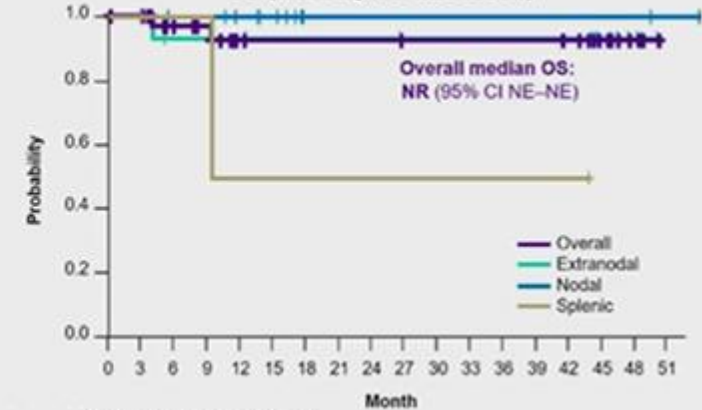
PFS (investigator assessed)



12-month PFS rate (95% CI)

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

OS (investigator assessed)



12-month OS rate (95% CI)

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

Best response %	Overall (n=35)	Extranodal (n=19)	Nodal (n=12)	Splenic (n=3)
ORR	77.1 (95% CI 59.9-89.6)	78.9 (95% CI 54.4-93.9)	75.0 (95% CI 42.8-94.5)	100 (95% CI 29.2-100)
CR	77.1 (95% CI 59.9-89.6)	78.9 (95% CI 54.4-93.9)	75.0 (95% CI 42.8-94.5)	100 (95% CI 29.2-100)



Odronextamab

human CD20xCD3 bispecific antibody

Take-home messages

- Distinct entities with subtype-specific and site-specific features
- Excellent prognosis for most, but not all, patients
- Aggressive therapy is unnecessary in most cases
- Treatment should be individualized based on patient characteristics
- Larger number of patients and longer follow-up is warranted to better understand the potential of novel therapies

Frontline therapy: unmet needs and key open questions

- What is the optimal subtype-specific strategy?
 - Limited comparative evidence across subtypes
 - Most studies pool subtypes, masking differential benefit
- Can immunochemotherapy be replaced?
 - Need for randomized trials of novel targeted combinations
- How should we measure benefit?
 - PFS requires lengthy studies
 - Surrogate endpoints (PET, ctDNA MRD, CR24/EFS24) need validation

Second-line therapy: unresolved questions

- Can novel immunotherapies change the paradigm? What is the optimal sequence? How durable are responses? Who benefits from which agent?
 - Lack of head-to-head trials
 - Evidence largely from single-arm studies
 - Need longer-term efficacy and safety data for BTKi and emerging immunotherapies
 - BsAb and ADCs toxicity, and positioning relative to BTKi remain uncertain
 - Molecularly guided selection remain insufficient
 - Need incorporation of patient-reported outcomes, QL, and treatment-free intervals
- How can trials become more informative?
 - histologic heterogeneity, inconsistent control arms, and underpowered MZL cohorts hinder drug development



2027 IELSG Annual Meeting

March 5-6, 2027



Auditorium Bellinzona
Viale Stefano Franscini 32
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