Società Italiana di Ematologia

FORMAZIONE SIE

I linfomi: un nome con almeno 40 sfaccettature!

25 giugno 2026

Bologna
Royal Hotel
Carlton

MARGINALE

Annarita Conconi

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Ospedale degli Infermi - Biella

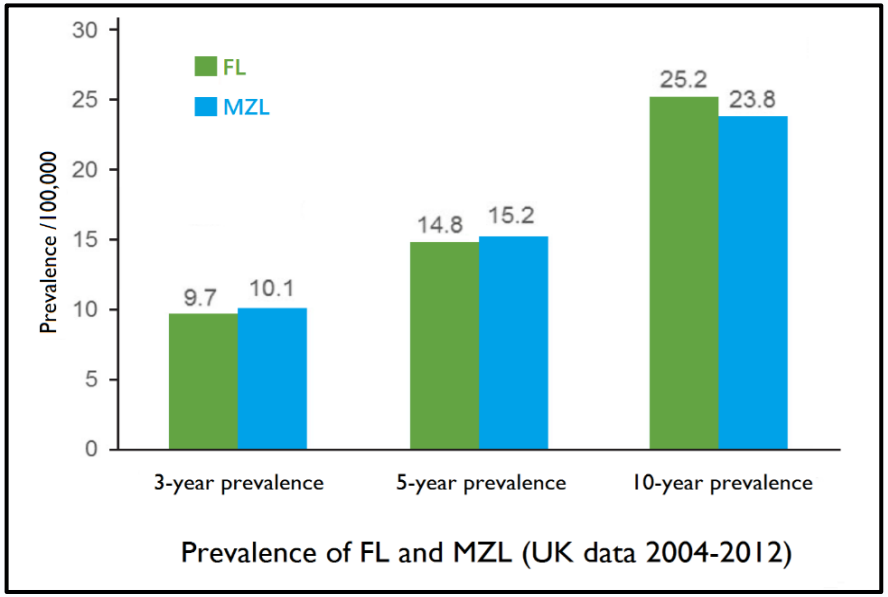
AZIENDA SANITARIA LOCALE DI BIELLA

Disclosures of Annarita Conconi

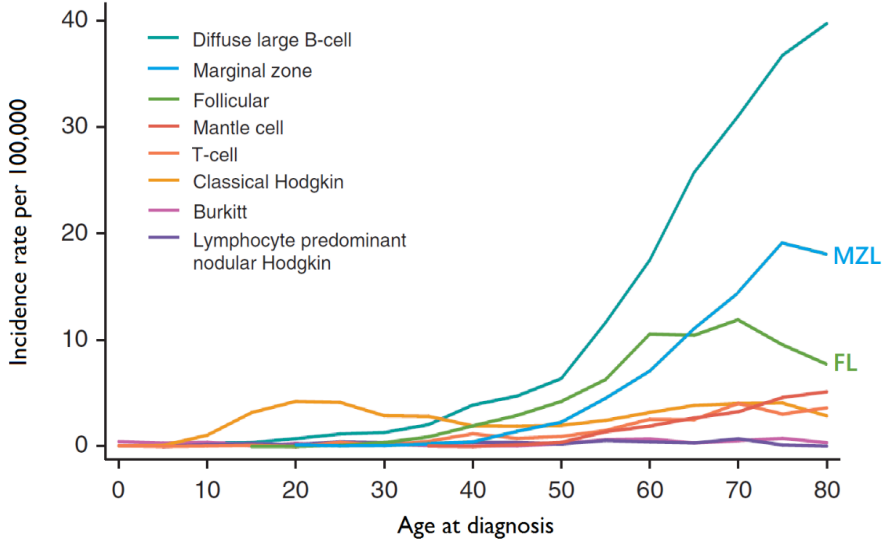
Company name	Research support	Employee	Consultant	Stockholder	Scientific lectures	Advisory board	Other
Roche					X	X	
Incyte						X	
Abbvie					X		
BMS					X		
Gilead						X	
Novartis					X	X	
Janssen					X		

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)

Marginal zone lymphoma: epidemiology



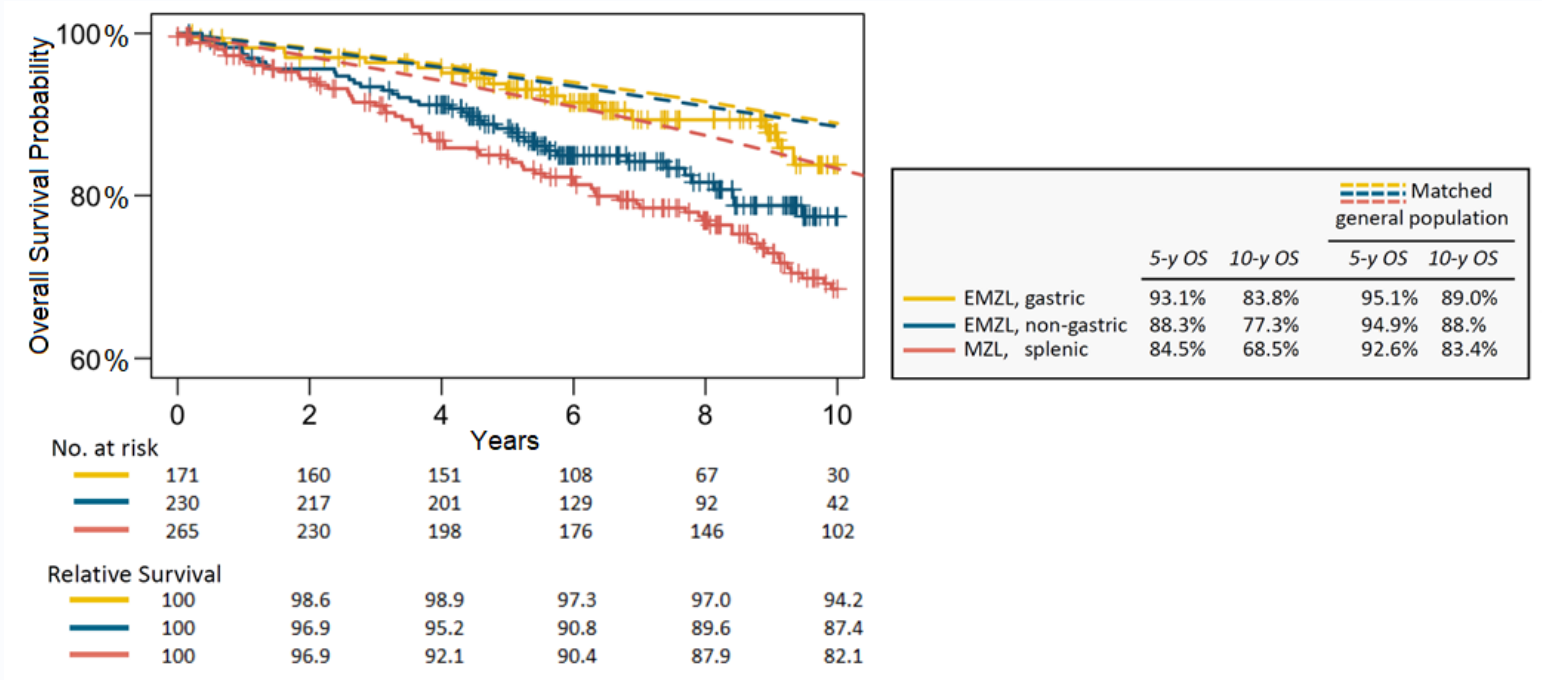
Prevalence of FL and MZL (UK data 2004-2012)



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

Cerhan JR et al. Ann Lymphoma 2021; Smith et al. BJC 2015

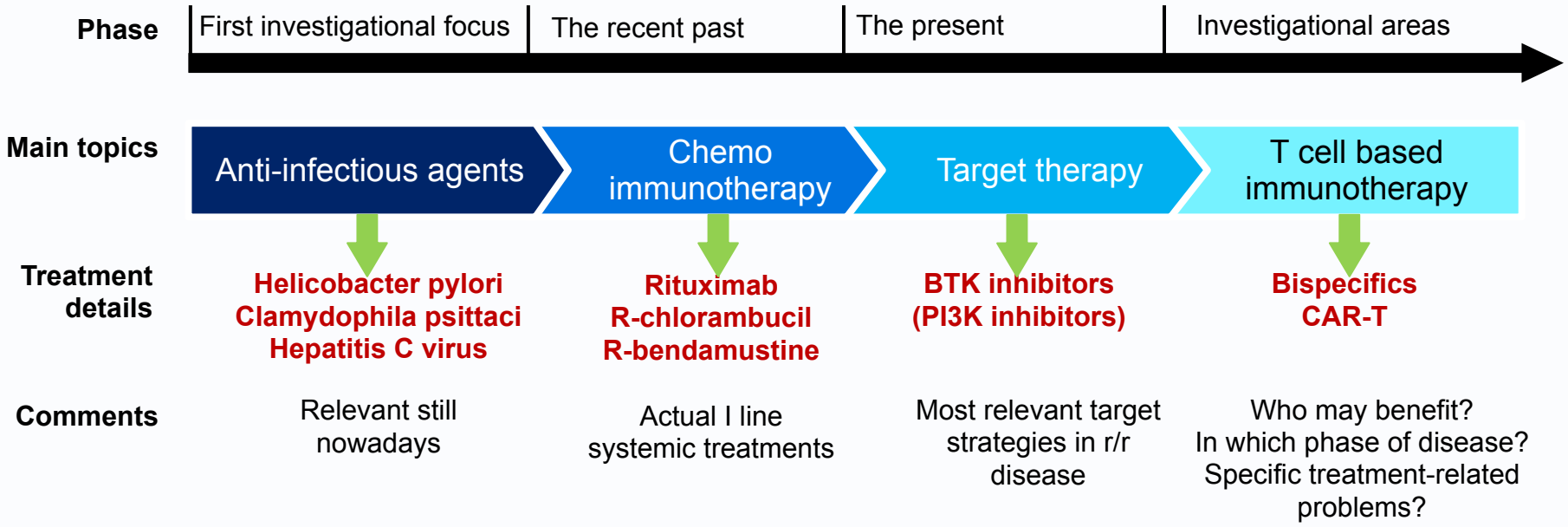
Overall and relative survival in the IELSG19 &IELSG46 studies



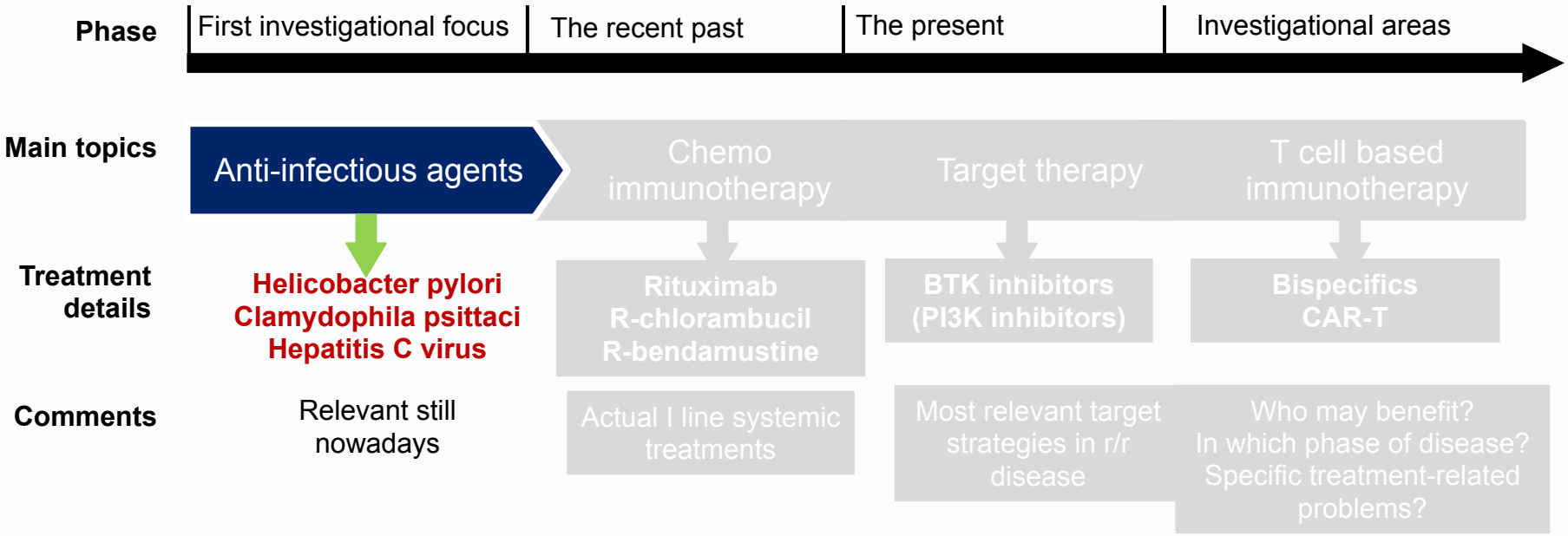
			Matched general population	
	5-y OS	*10-y OS*	*5-y OS*	*10-y OS*
EMZL, gastric	93.1%	83.8%	95.1%	89.0%
EMZL, non-gastric	88.3%	77.3%	94.9%	88.%
MZL, splenic	84.5%	68.5%	92.6%	83.4%

Slide courtesy of Emanuele Zucca

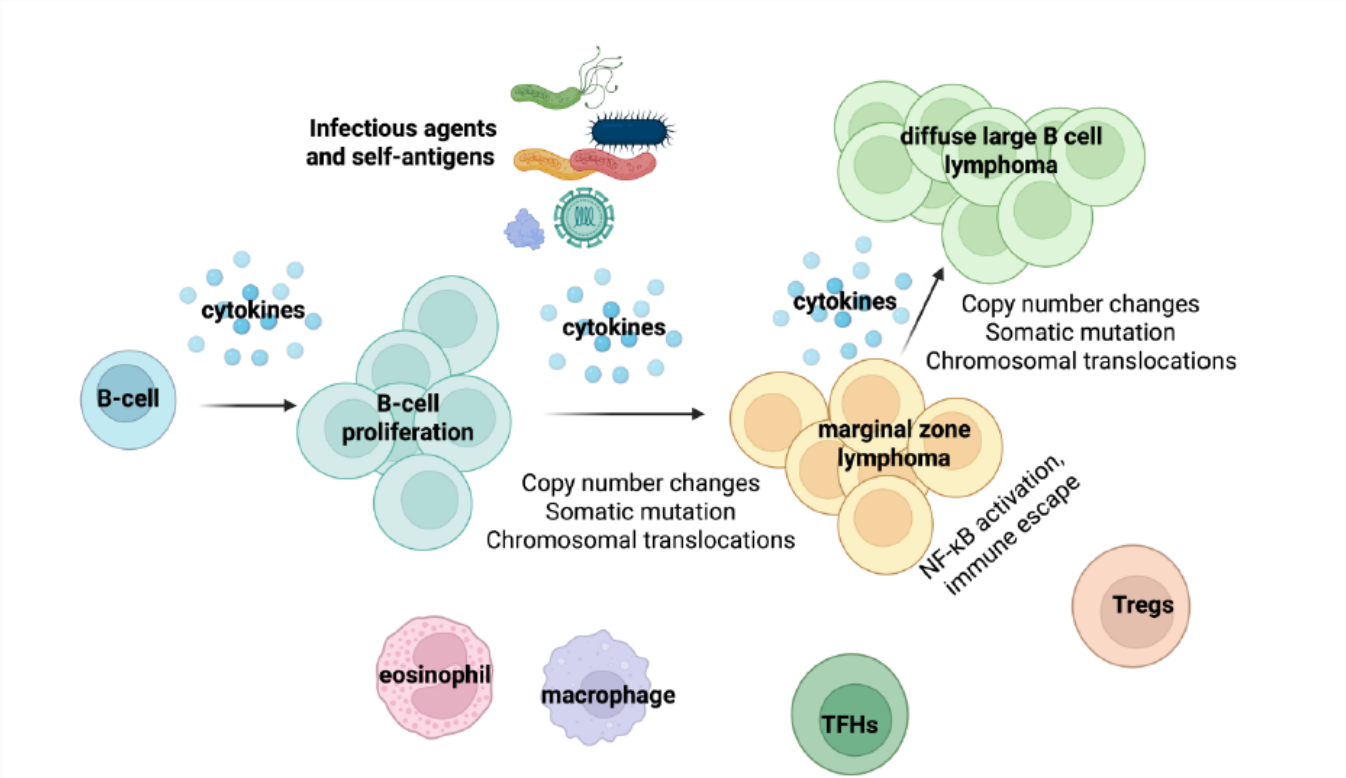
Treatment of marginal zone lymphomas: research areas over time



Treatment of marginal zone lymphomas: research areas over time



Marginal zone lymphoma: pathogenesis



Laurent C & Bertoni F. Blood 2025

Most gastric EMZL regress after *Helicobacter pylori* eradication

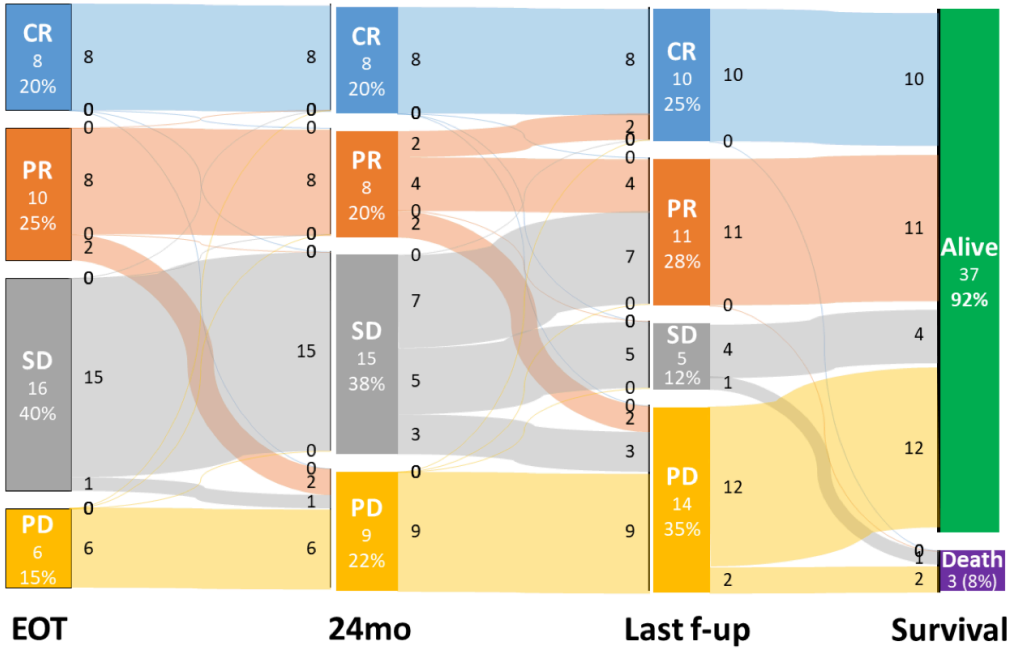
Reference	n	CR rate (%)	Time to CR (mos.)	Relapses (n)
Savio, 1996	12	84	2-4	0
Pinotti, 1997	45	67	3-18	2
Neubauer, 1997	50	80	1-9	5
Nobre Leitao, 1998	17	100	1-12	1
Steinbach, 1999	23	56	3-45	0
Montalban, 2001	19	95	2-19	0
Ruskone-Formestraux, 2001	24	79	2-18	2
Hancock, 2009	231	46	3-24	17
Zullo, 2010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

Predicting factors of response

- Endoscopic features
- t(11;18)

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

HCV eradication

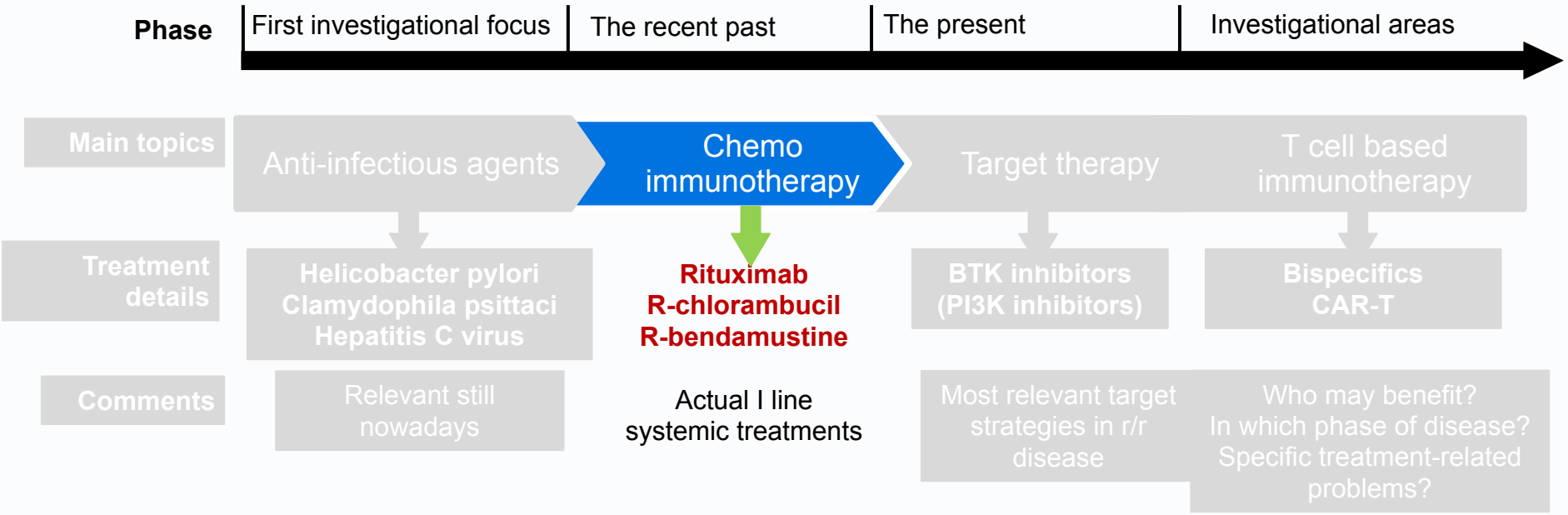


- 2/10 pts in PR at EOT (*2 MALT*) converted to CR during FU: →**best CR 25%** *(95% CI: 13-41)*
- 7/16 pts in SD at EOT (*3 SMZL, 2 NMZL, 1 MALT, 1 CD5-NOS*) converted to PR during FU: →**best ORR 63%** *(95% CI: 46-77)*

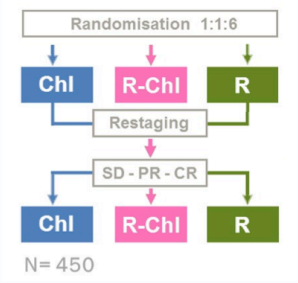
Histotype	N	Best ORR	Best CR
SMZL	6	50%	0%
MALT	14	79%	43%
NMZL	7	71%	43%
LPL	6	17%	0%
CD5- NOS	4	75%	25%
FL + SLL	3	66%	0%

Merli M et al. N Engl J Med 2026

Treatment of marginal zone lymphomas: research areas over time

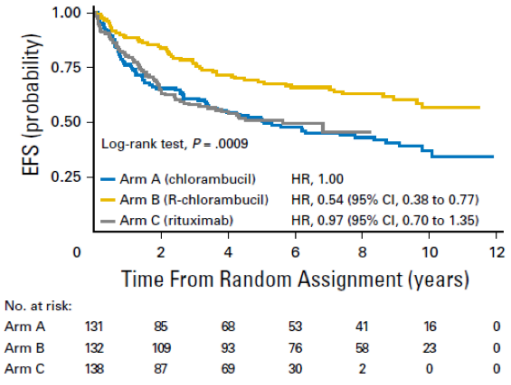


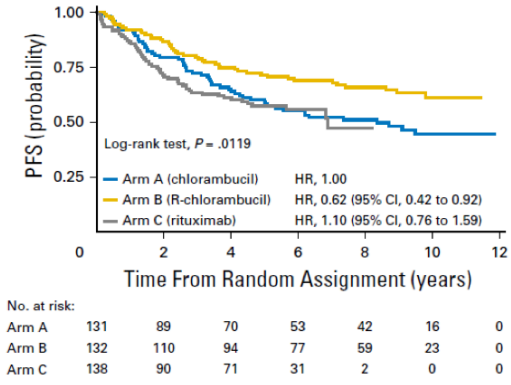
IELSG19 randomized trial: rituximab+chlorambucil in EMZL

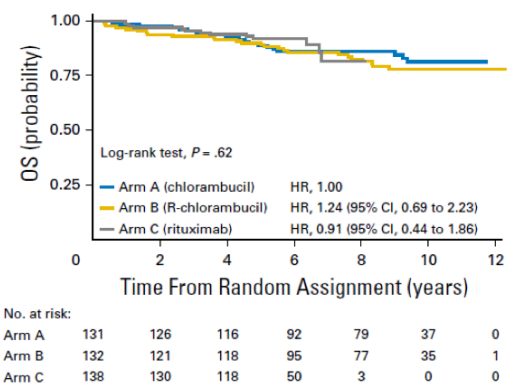


Response	All Patients (N = 401) No.	% (95% CI)	Arm A Chlorambucil (n = 131) No.	% (95% CI)	Arm B Chlorambucil Plus Rituximab (n = 132) No.	% (95% CI)	Arm C Rituximab (n = 138) No.	% (95% CI)
Complete remission*	264	65.8 (61.0 to 70.5)	83	63.4 (54.5 to 71.6)	104	78.8 (70.1 to 85.4)	77	55.8 (47.0 to 64.2)
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)

*$P < .001$.

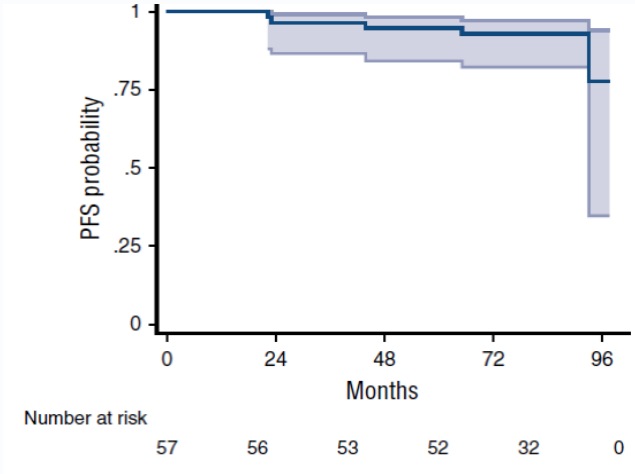


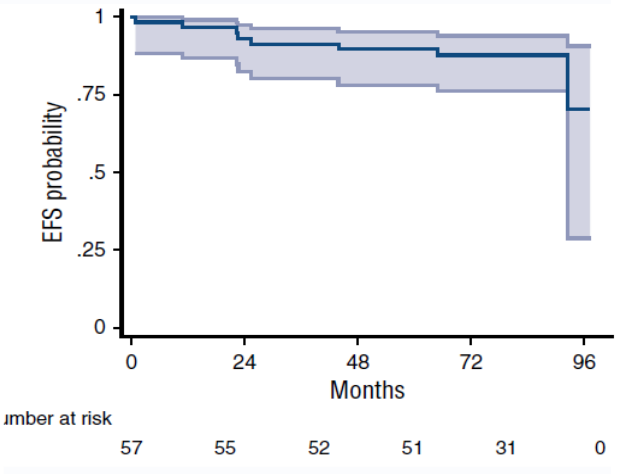


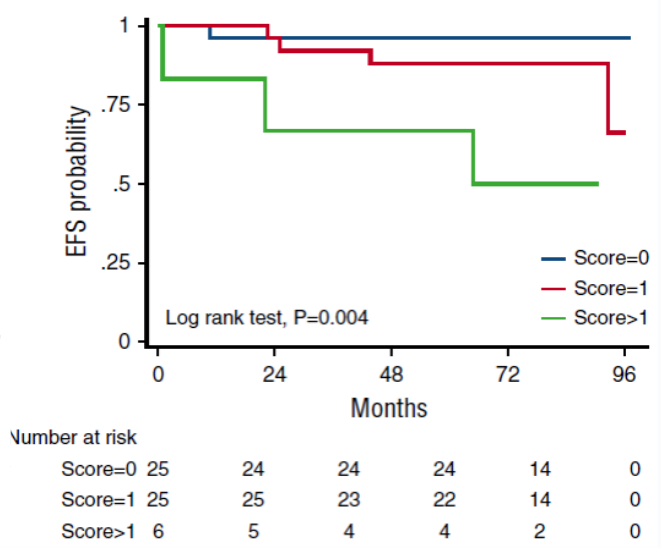


Zucca E, et al. J Clin Oncol 2017

GELTAMO phase-2 study:
R-Bendamustine as 1st-line response-adapted therapy in EMZL

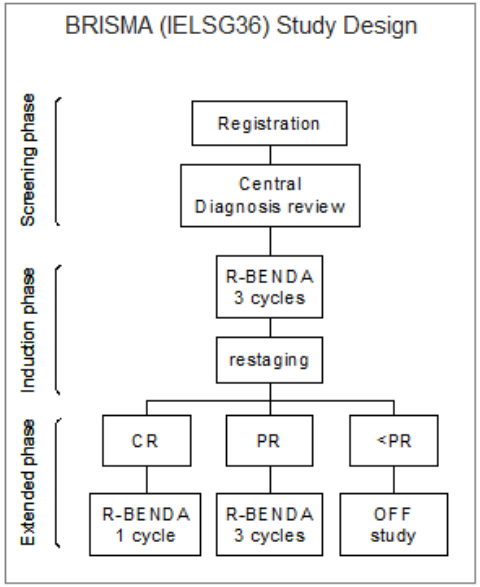


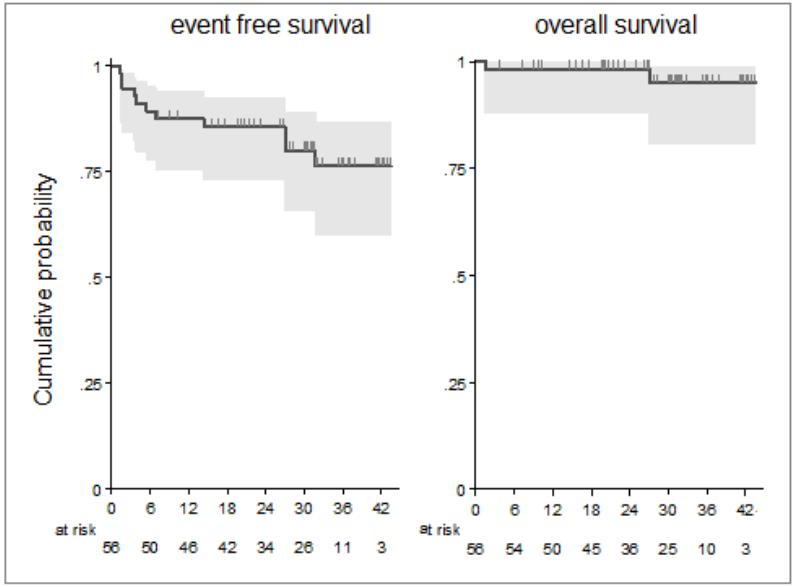




Salar A, et al. Blood 2017

IELSG36 (BRISMA) Phase II trial:
R-Bendamustine as 1st line therapy for SMZL





N evaluable, 56

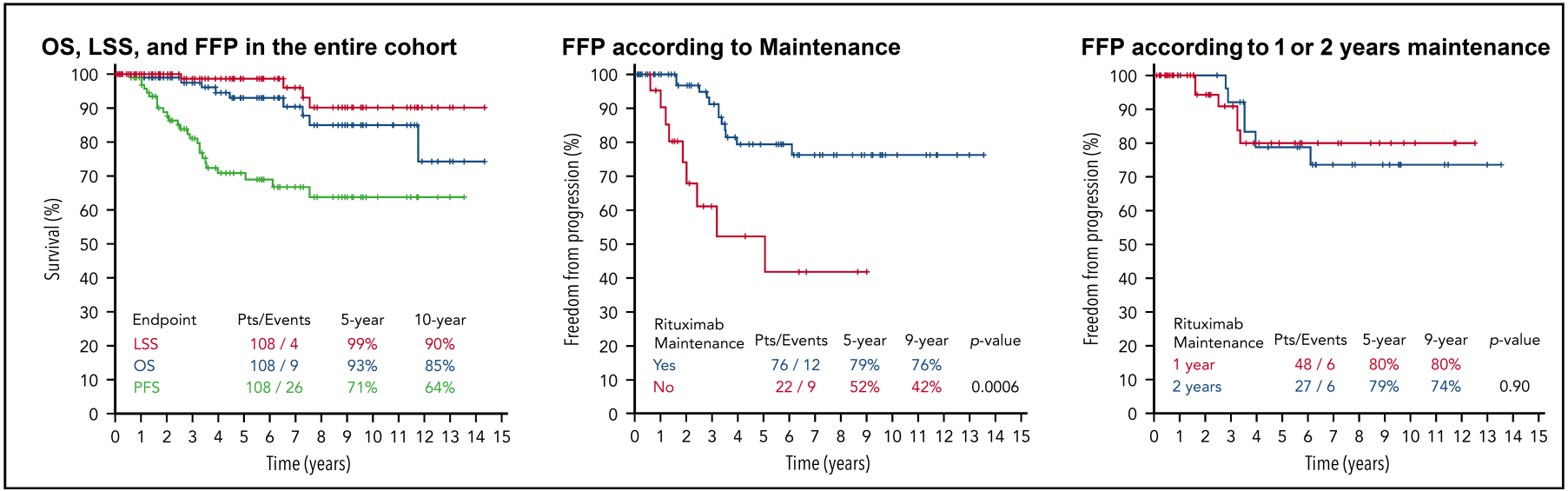
35% high risk HPLL

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

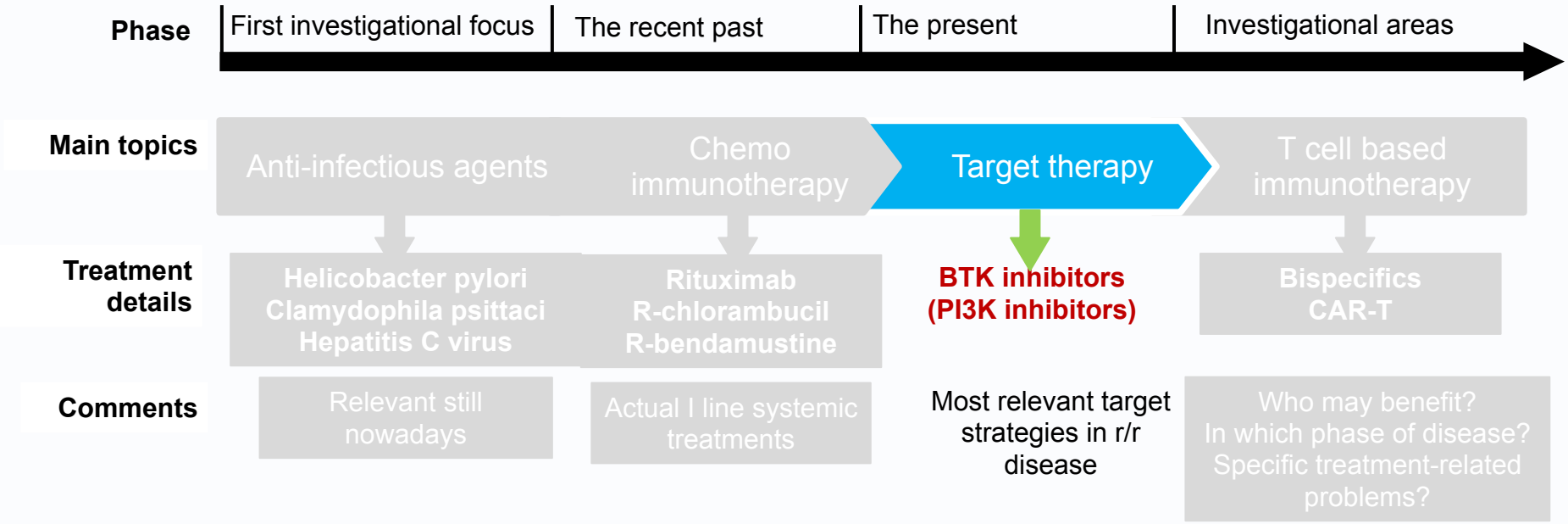
Rituximab monotherapy in SMZL: prolonged responses and potential benefit from maintenance



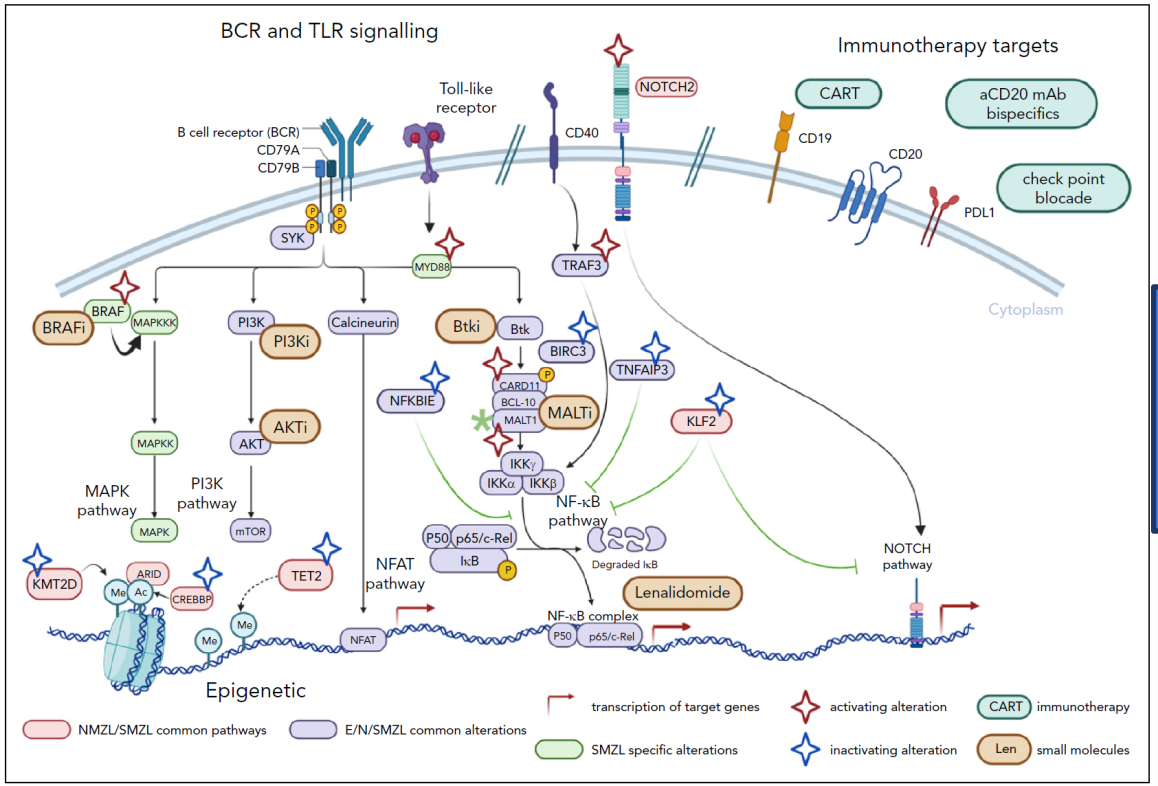
- ORR 92%
- CR 48%
- 3-y PFS 73%

Kalpadakis C, et al. Blood 2018

Treatment of marginal zone lymphomas: research areas over time



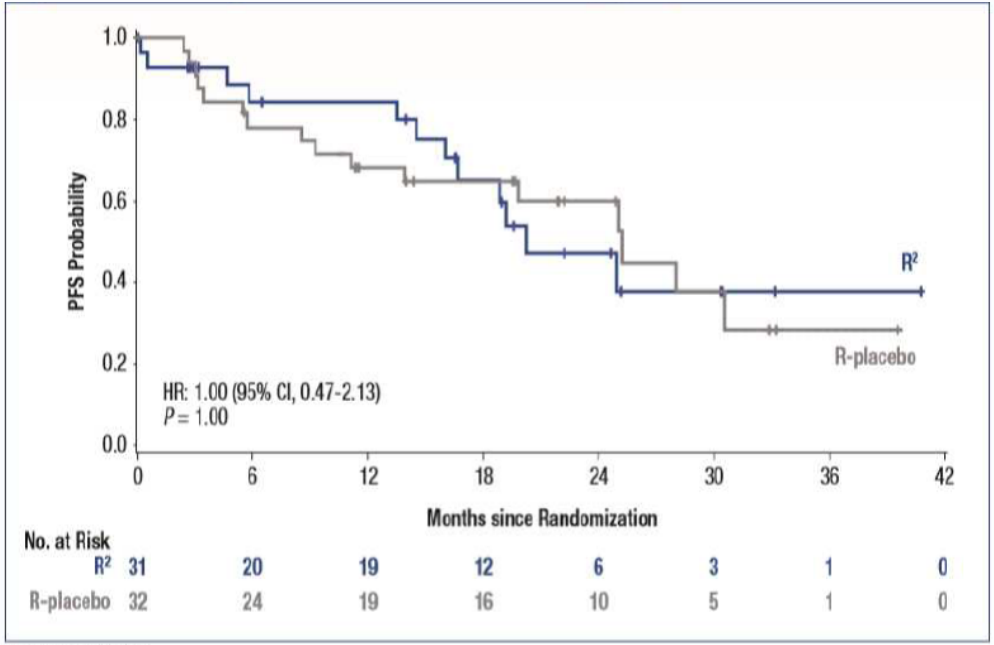
Targetable pathways in marginal zone lymphomas



Len
BTKi
PI3Ki)
BTKdeg

Thieblemont C et al. Blood 2026

Augment study: subset analysis of MZL

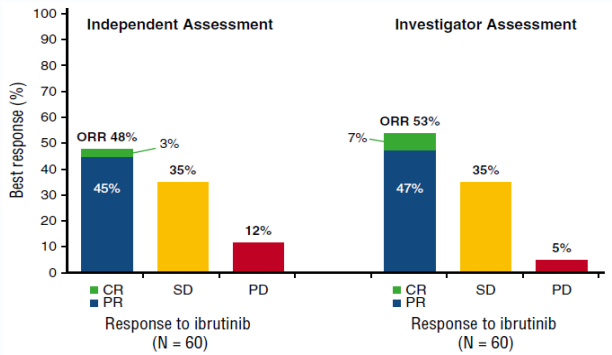


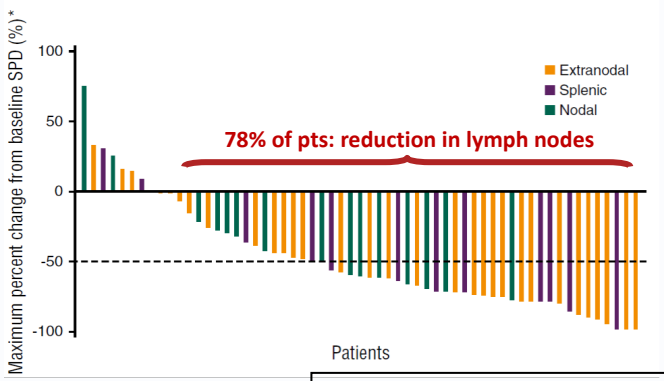
Median PFS for MZL patients : 20.2 mo R2 vs 25.2 mo R-placebo
(HR = 1.00; 95% CI, 0.47-2.13; P = 1.0)

Leonard J et al. J Clin Oncol 2019
Thieblemont C, EHA 2019: abstract PS1262

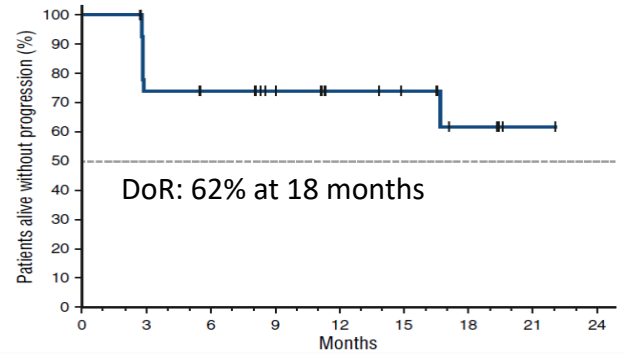
Ibrutinib in R/R marginal zone lymphomas: phase II trial

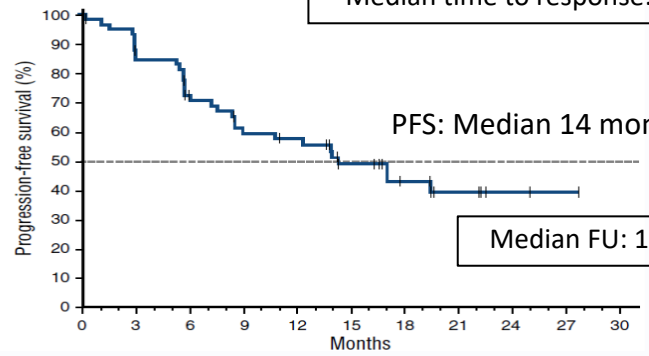
63 pts (32 EMZL, 14 SMZL, 17 NMZL), median 2 prior therapies





Median time to response: 4.5 months



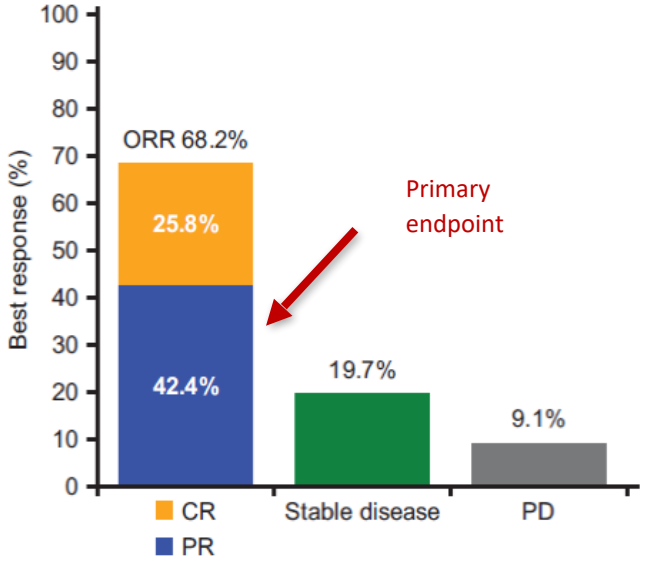


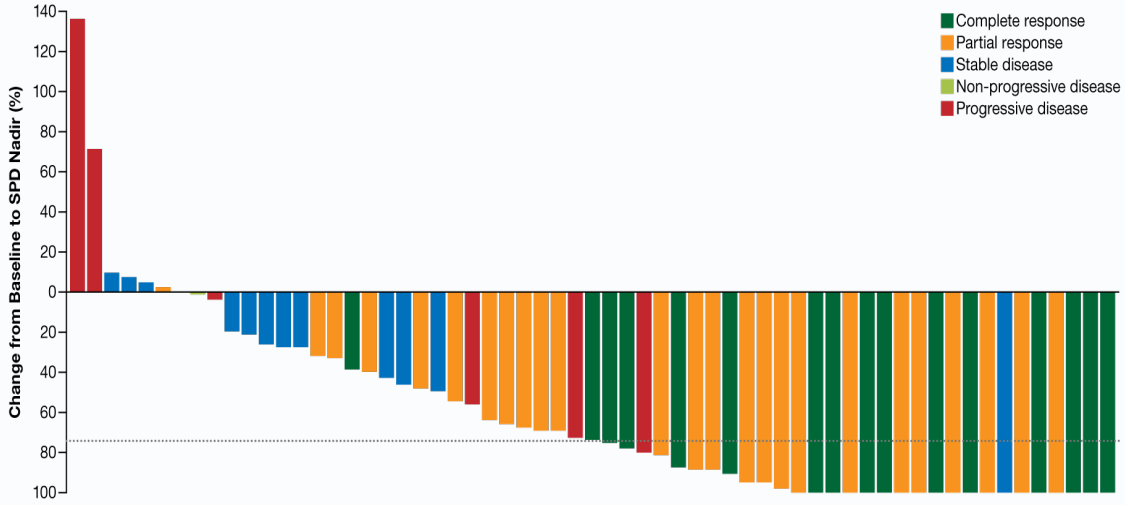
Median FU: 19.4 months

Noy A, et al. Blood 2017

Zanubrutinib in R/R MZL: Magnolia phase II trial

68 pts (26 EMZL, 12 SMZL, 26 NMZL, 4 unknown), median 2 (1-6) prior therapies



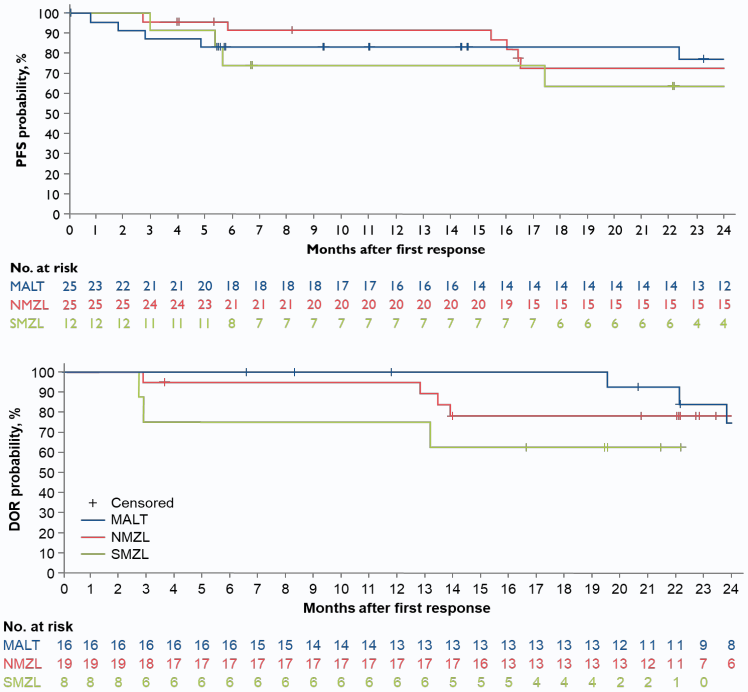


Best response	Extranodal (n=25)	Nodal (n=25)	Splenic (n=12)	Unknown (N=4)
ORR, n (%)	16 (64.0)	19 (76.0)	8 (66.7)	2 (50.0)
CR, n (%)	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)

Opat S, et al. Clin Cancer Res 2021

Zanubrutinib in R/R MZL: Magnolia phase II trial

Long-term results – median follow-up: 27.4 months



PFS rate at 24 months

Overall	**71%**
MALT	77%
NMZL	73%
SMZL	64%

DoR rate at 24 months

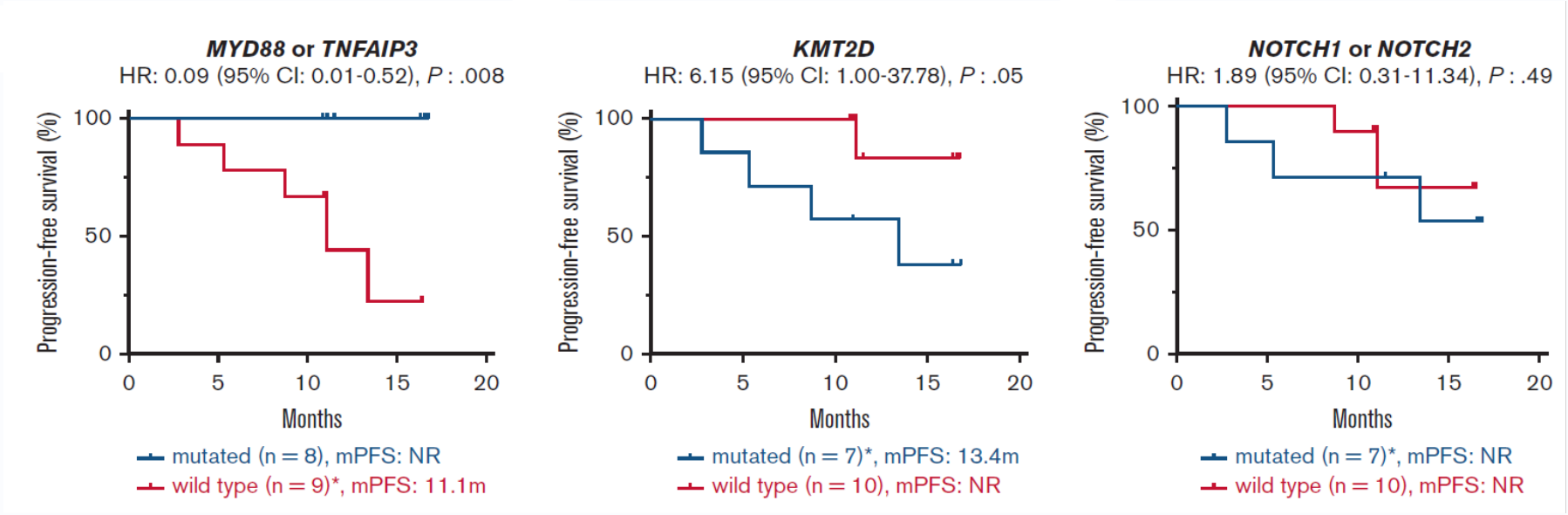
Overall	**73%**
MALT	75%
NMZL	78%
SMZL	NE

Opat S, et al. Blood Adv 2023

Opat S et al. Blood Adv 2023

Molecular associations of response to zanubrutinib in MZL

Australasian Leukaemia and Lymphoma Group – Magnolia sub-study



- NF-KB, NOTCH & BCR pathway genes in 89% of pts (baseline WES performed on 17 patients)
- MYD88, TNFAIP3, and KMT2D mutations correlate with PFS
- BTK and PLCG2 mutations confer acquired resistance of MZL to BTK inhibition

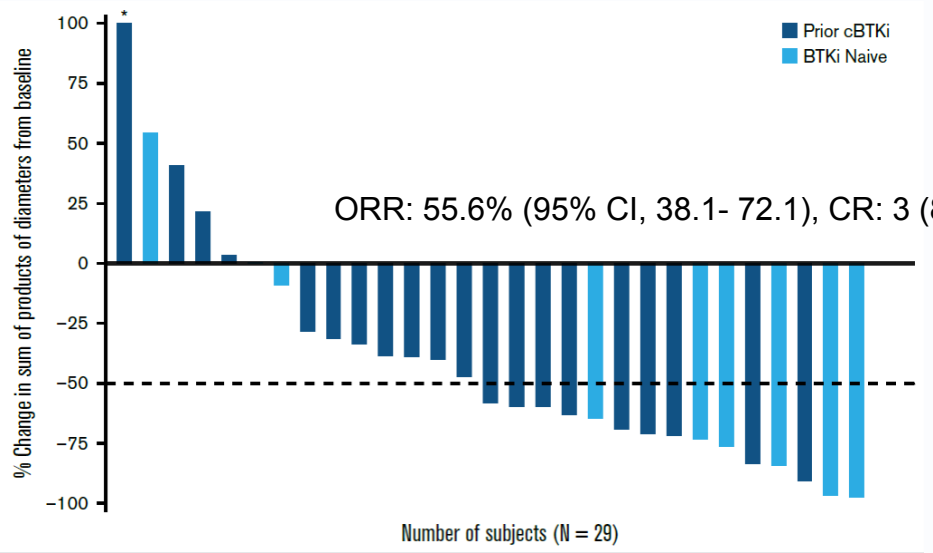
Tatarczuch M, et al . Blood Adv 2023

BTK inhibitor in R/R: 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

Pirtobrutinib in MZL: Results from Phase 1/2 BRUIN Study

36 pts, nodal (n=17), splenic (n=13), and extranodal (n=6) MZL
Median prior lines: 3 (2-10)
26 (72%) pts had prior cBTKi (discontinuation causes: 20 PD, 6 toxicity)

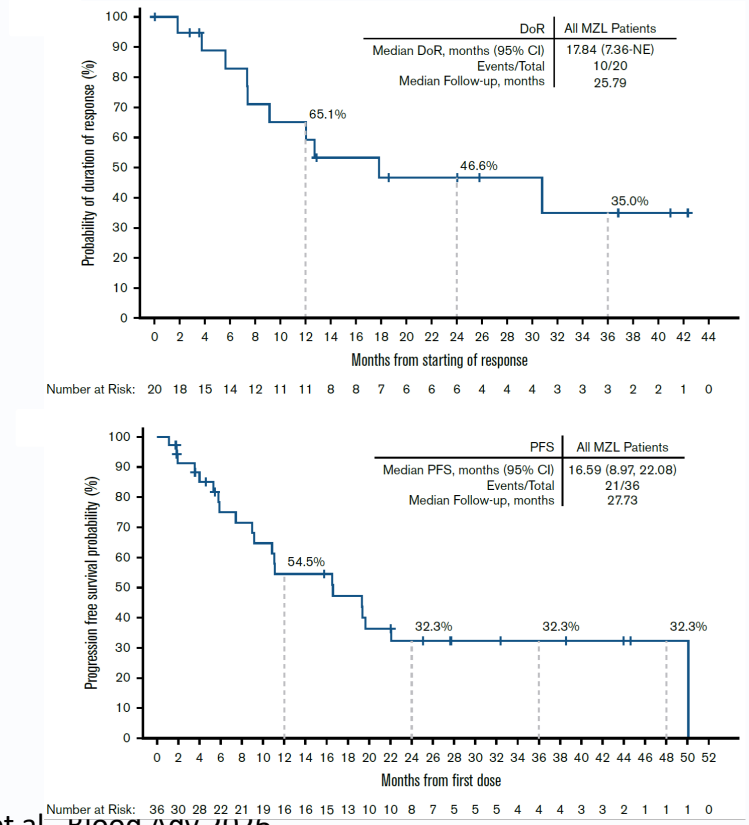


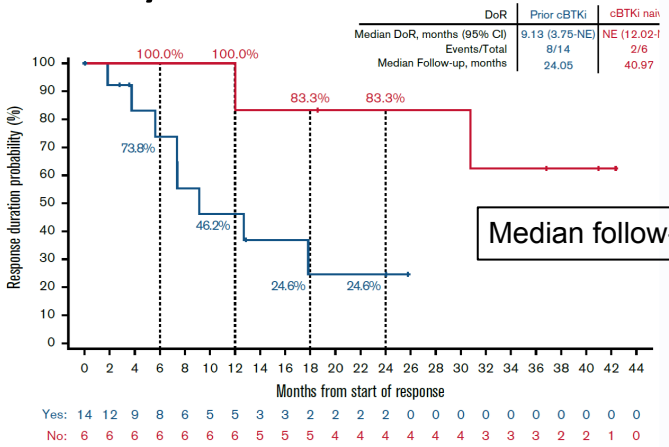
ORR: 55.6% (95% CI, 38.1- 72.1), CR: 3 (8.3%), PR: 17 (47.2%)

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

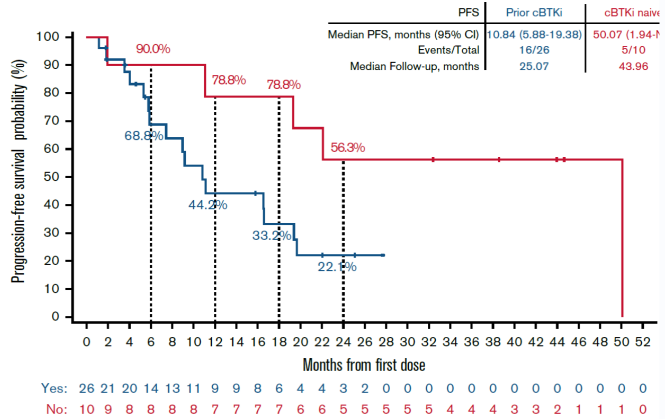
Patel K, et al. Blood Adv 2026

MZL: Results from Phase 1/2 BRUIN Study



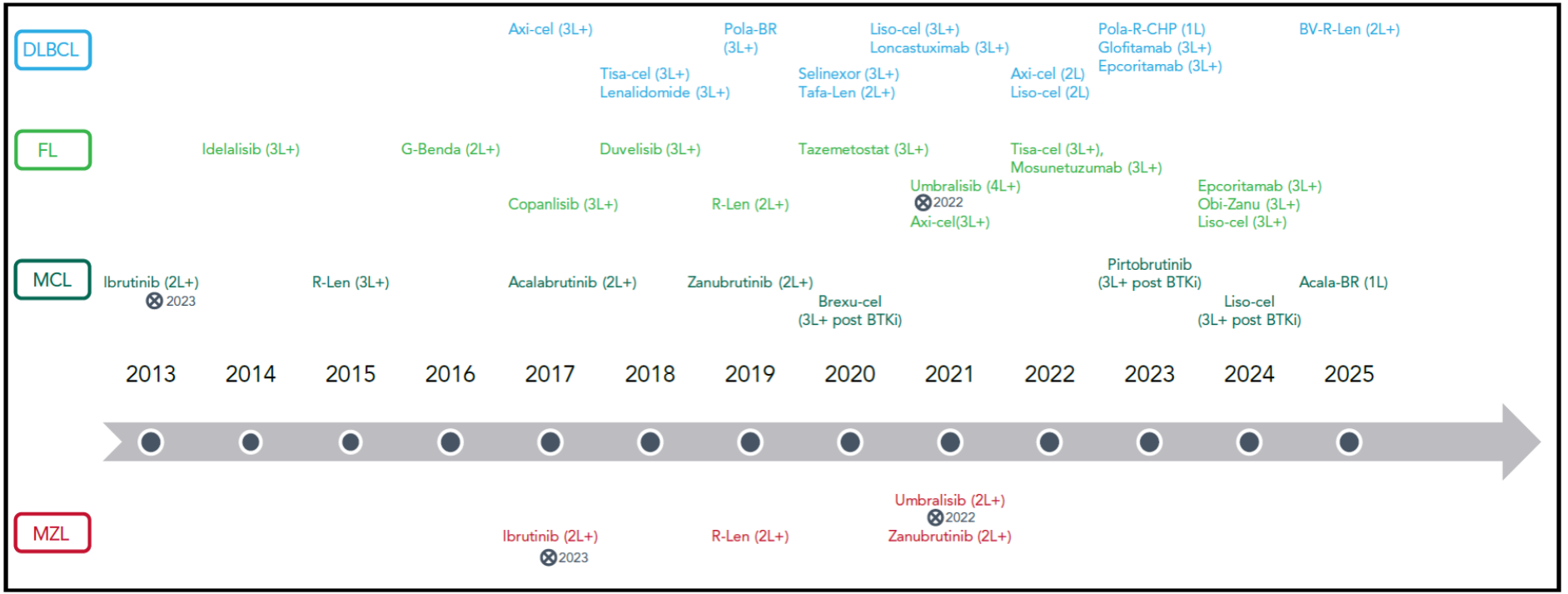


Median follow-up: 27.7 months



Patel K et al . Blood Adv 2026

Timeline of FDA approvals in B-cell non-Hodgkin lymphomas



2022 : withdrawn in 2022

Thieblemont C et al. Blood 2026

The barriers to drug development in marginal zone lymphomas

- heterogeneity in diagnostic criteria and trial populations
- unclear standards of care that lead to inconsistent control arms
- inadequacy of traditional end points
- underuse of innovative response tools
- the economic and regulatory disincentives in developing therapies for a rare and heterogeneous lymphoma

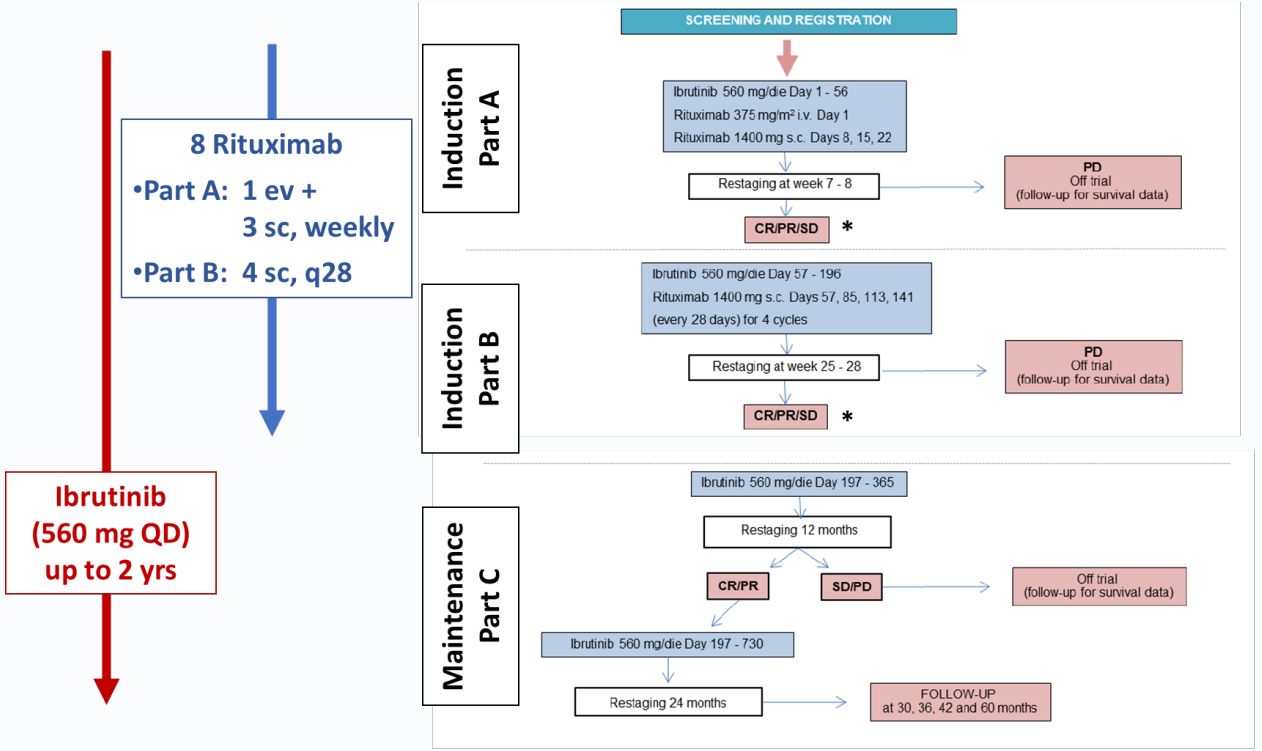
Thieblemont C et al. Blood 2026

Ibrutinib+rituximab in TN MZL: IELSG47/Malibu study

Phase II study

Stratification
EMZL, SMZL, NMZL

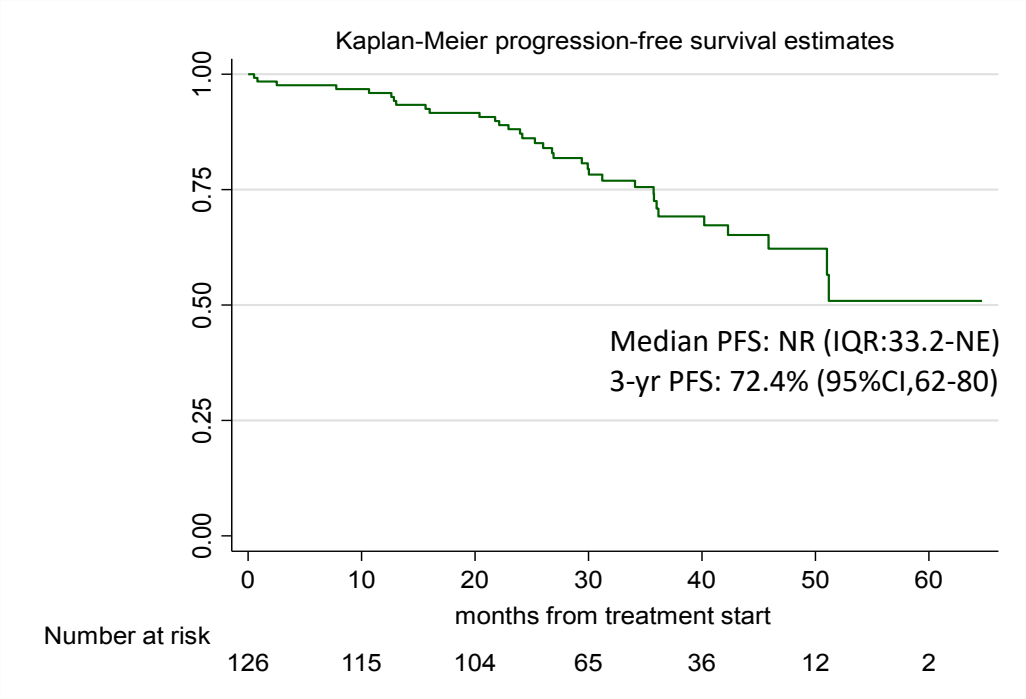
- **EMZL, n=130**
- **SMZL, n=30**
- **NMZL, n=15**



*patients in SD will continue study treatment at discretion of the investigator, if of clinical benefit

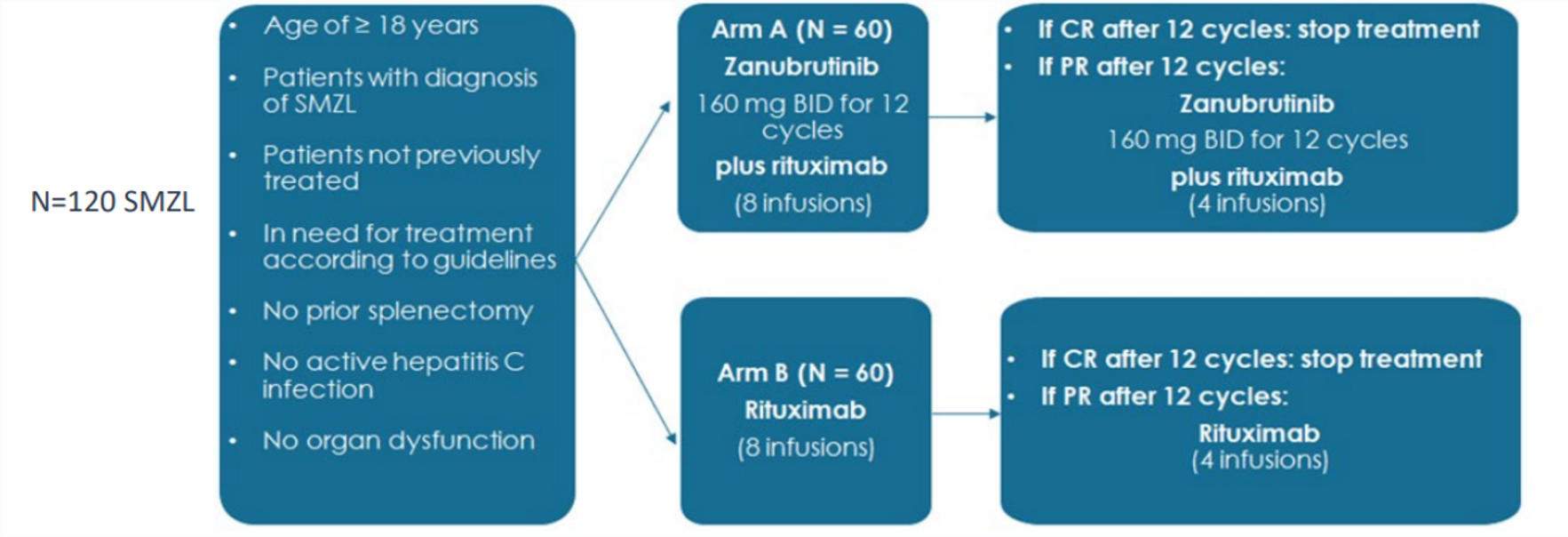
MALIBU study, EMZL: progression-free survival

Median FU:35.7 months



Conconi A et al. ICML 2025

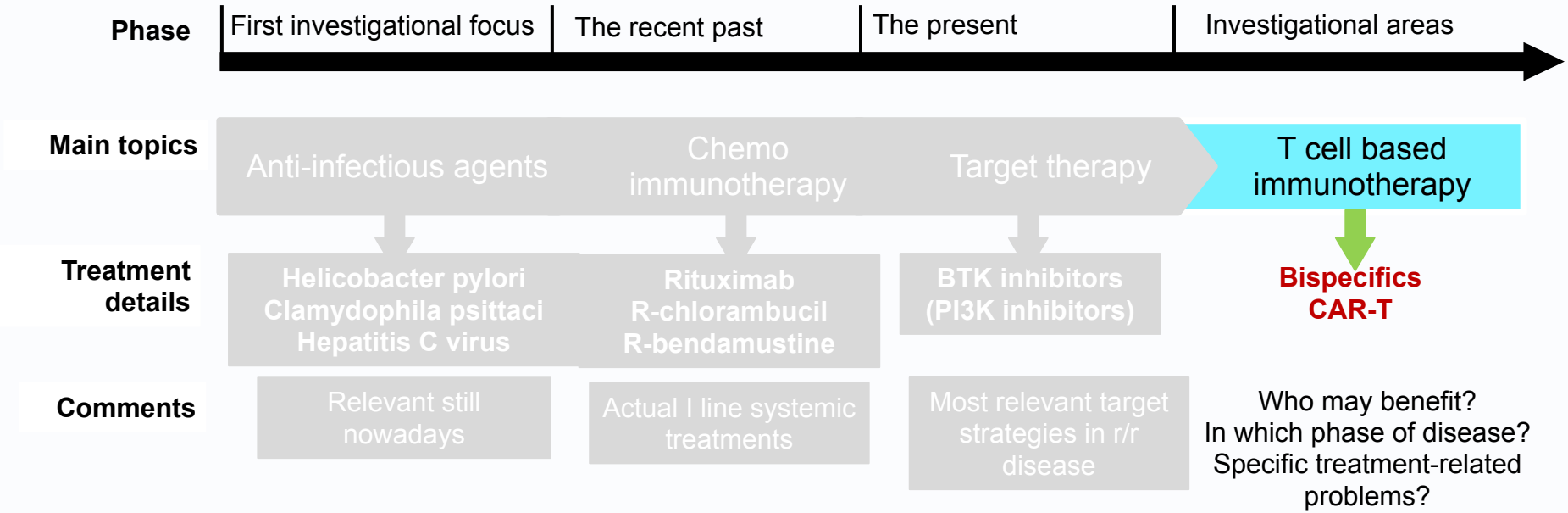
RITZ trial: Phase 3 randomized study comparing rituximab plus zanubrutinib to rituximab monotherapy in previously untreated, symptomatic SMZL



IELSG and 6 European Study Groups: SCI (former SAKK), FIL, LYSA, GELTAMO, NLG, NRCI

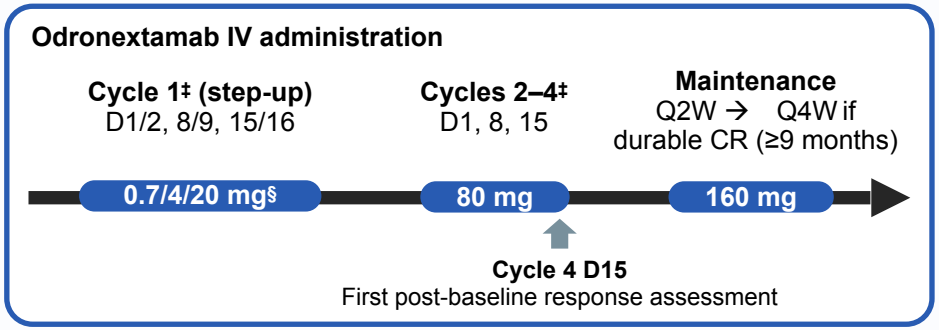
Slide courtesy of Luca Arcaini

Treatment of marginal zone lymphomas: research areas over time



Odronextamab in R/R MZL: phase II ELM-2 trial

42 pts (21 EMZL, 15 NMZL, 5 SMZL, 1 unk),
median 2 (1-8) prior therapies
refractory to last therapy 64.3%
prior BTK 28.6%



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

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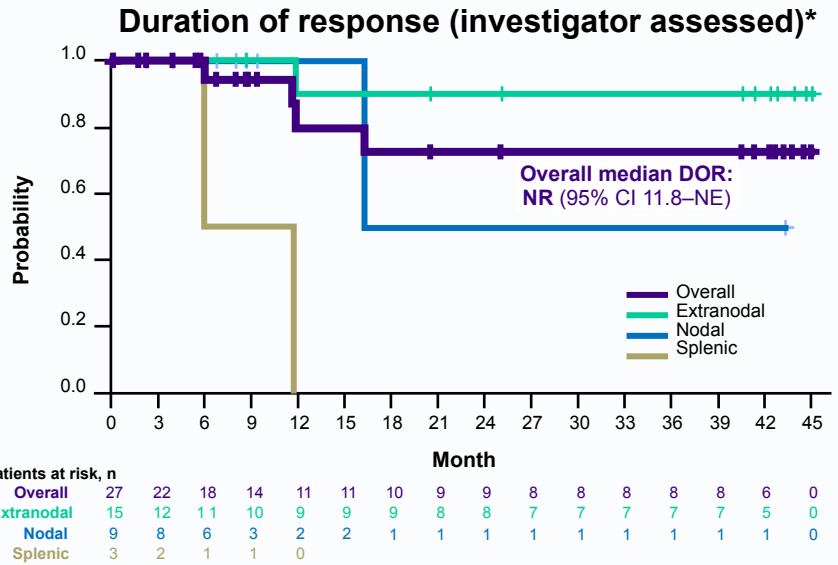
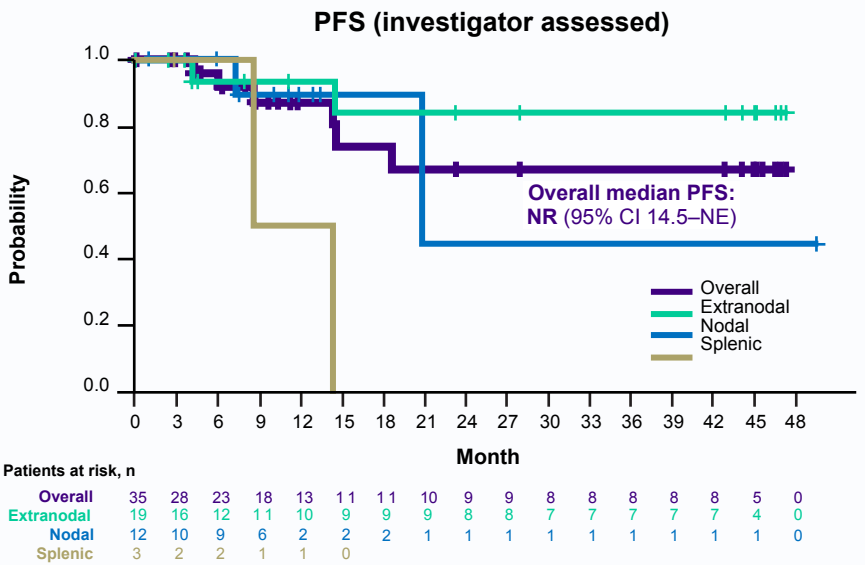
Odronextamab in R/R MZL: phase II ELM-2 trial





12-month PFS rate (95% CI):

	Overall	Extranodal	Nodal	Splenic
12-mo DOR (95% CI)	80.2 (49.6–93.3)	90.0 (47.3–98.5)	100 (100–100)	0.0 (NE–NE)

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)

Median follow-up for efficacy population: 11.1 months (95% CI 6.2–42.8)

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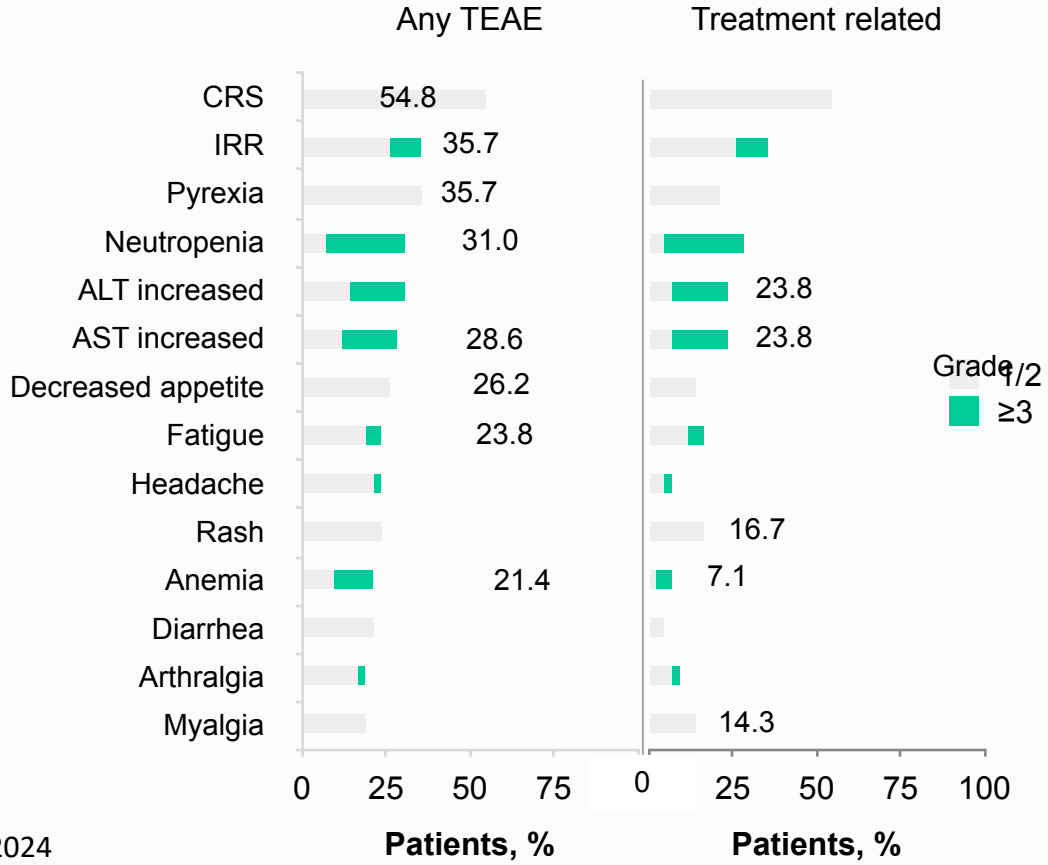
Odronextamab in R/R MZL: phase II ELM-2 trial



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Società Italiana di Ematologia

Odronextamab in R/R MZL: phase II ELM-2 trial

	0.7/4/20 mg			
	Overall (n=23)	Extranodal (n=10)	Nodal (n=9)	Splenic (n=4)
CRS (any grade), n (%)	13 (56.5)	5 (50.0)	5 (55.6)	3 (75.0)
Grade 1	8 (34.8)	5 (50.0)	2 (22.2)	1 (25.0)
Grade 2	5 (21.7)	0	3 (33.3)	2 (50.0)
Grade 3	0	0	0	0
Grade ≥4	0	0	0	0
Median time to onset CRS (range), hours	4.0 (−6.0–64.0)	4.0 (−6.0–18.7)	3.6 (0.0–64.0)	3.0* (3.0–3.0)
Median CRS duration (range), hours	6.2 (1.0–29.0)	5.5 (1.4–29.0)	6.0 (1.0–16.8)	6.7* (6.7–6.7)
Systemic steroid for CRS management, n (%)	8 (34.8)	2 (20.0)	3 (33.3)	3 (75.0)
Tocilizumab for CRS management, n (%)	7 (30.4)	2 (20.0)	3 (33.3)	2 (50.0)

- Safety profile was generally consistent across MZL subtypes, with CRS, IRR, and pyrexia among the most frequent TEAEs
- Treatment-related TEAEs leading to discontinuation: CRS (n=1)
- Overall safety consistent with that in 3L+ R/R FL in ELM-2

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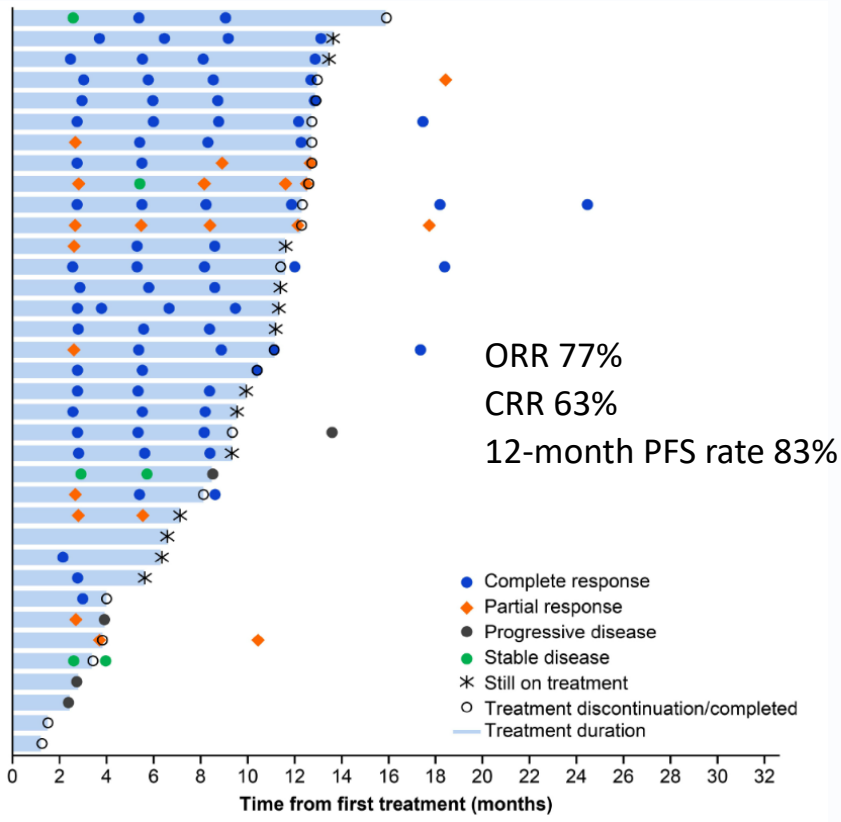
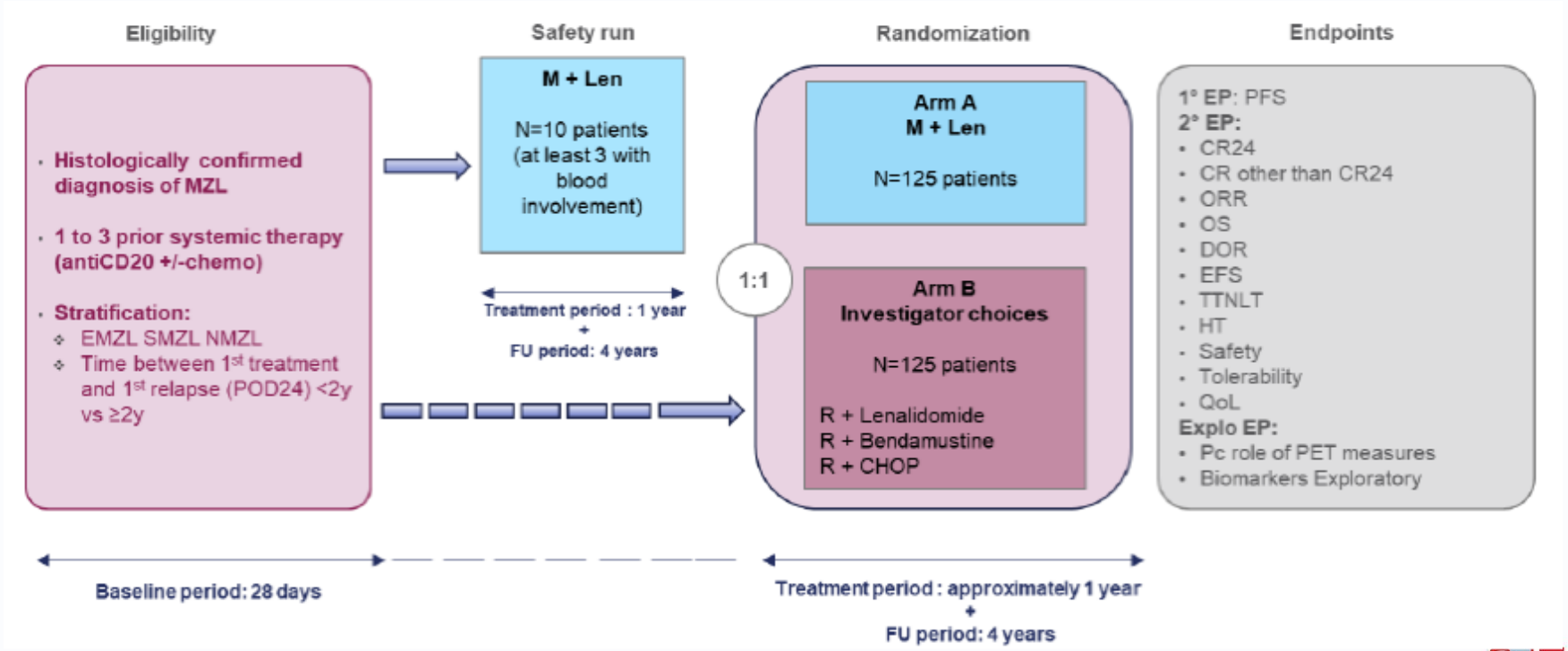
MorningSun study: mosunetuzumab sc in TN NHL - cohort of MZL

36 patients with previously untreated MZL
(mix of extranodal, splenic and nodal; 77% with EMZL)

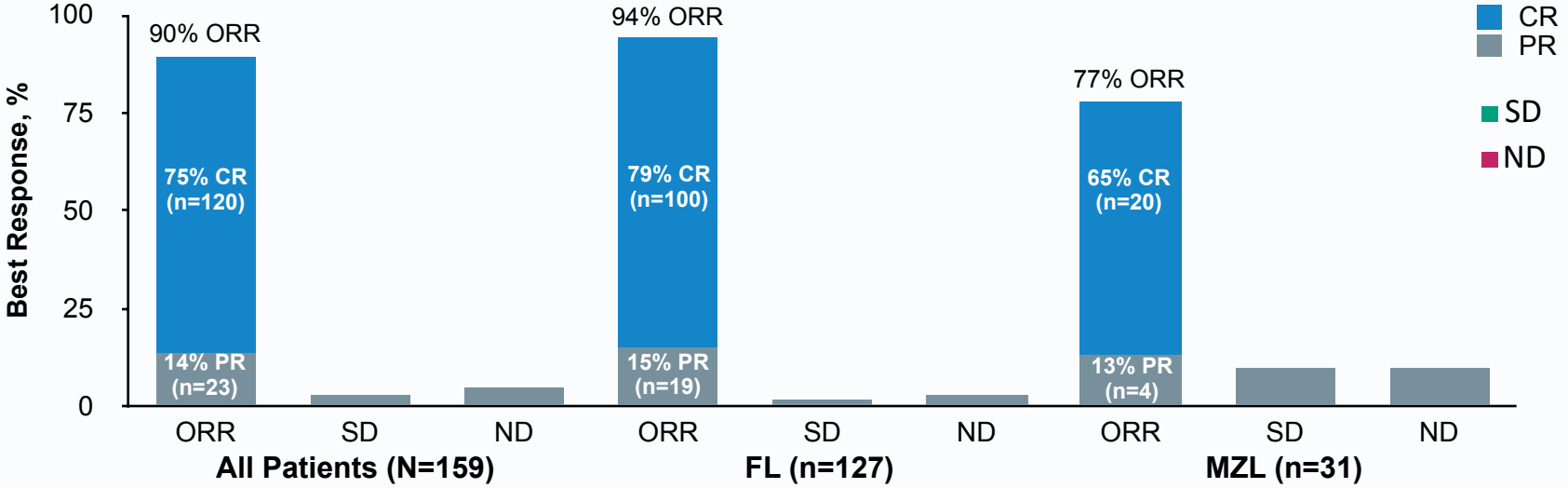


Burke J et al. EHA 2025

Marsun trial - Phase III Randomized Study Investigating Mosunetuzumab-Lenalidomide *vs* investigator choices in R/R MZL



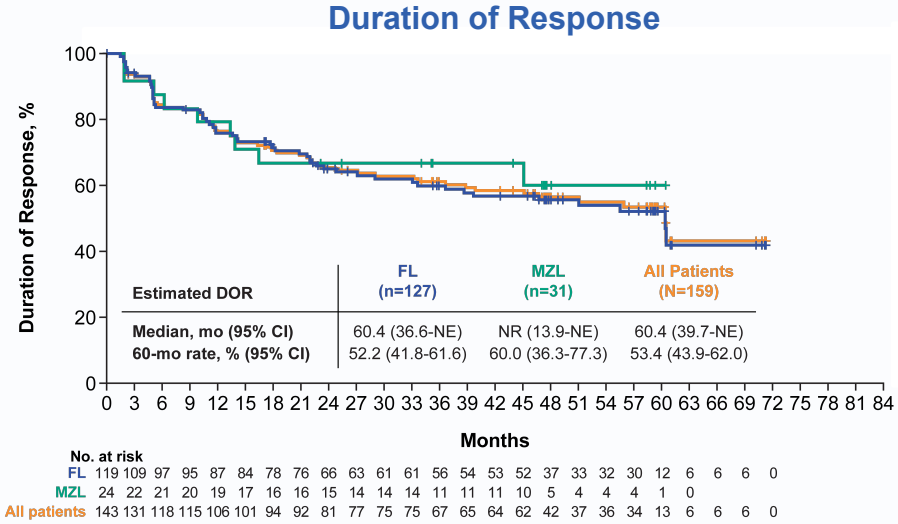
ZUMA-5, axi-cel in r/r iNHL: 5-year analysis

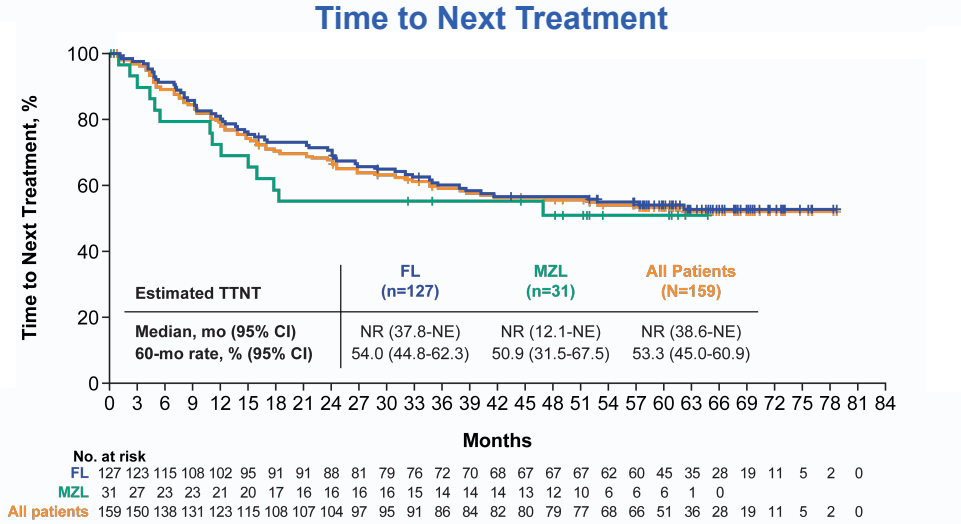


- Median follow-up from leukapheresis in enrolled patients with iNHL (N=159) was 64.6 months (range, 32.3-81.4)
  - In FL (n=127), median follow-up was 65.7 months (range, 56.7-81.4)
  - In MZL (n=31), median follow-up was 55.8 months (range, 32.3-76.4)
- Response remained consistent with prior analyses

Neelapu S et al. ASH 2024

ZUMA-5, axi-cel in r/r iNHL: 5-year analysis





At cutoff, 55% of patients (n=87) were alive without requiring any new anticancer therapy

Median DOR was 60.4 months, with an estimated 60-month DOR rate of 53.4%

- Ongoing response rate was 44% (FL: 43%, MZL: 48%)
- Among patients who achieved a CR, 58% remained in CR at data cutoff; median DOR was 60.5 months (95% CI, 60.4-NE)

Median TTNT remained not reached

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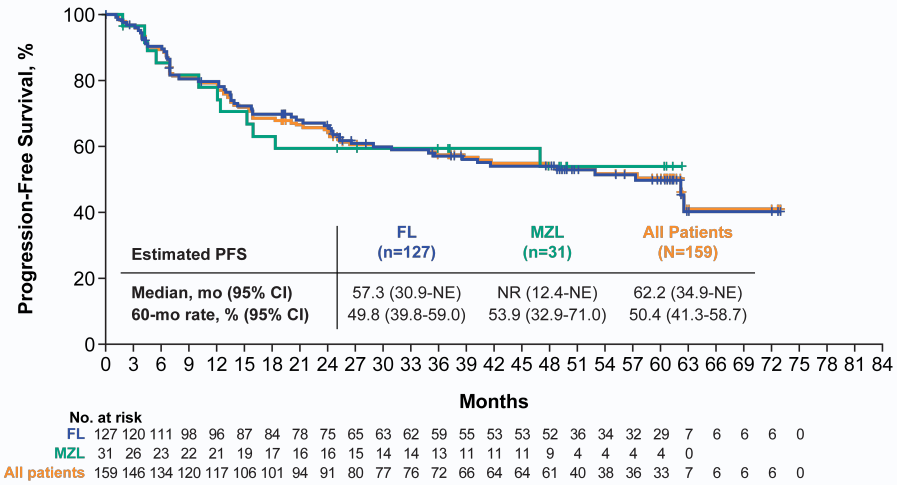
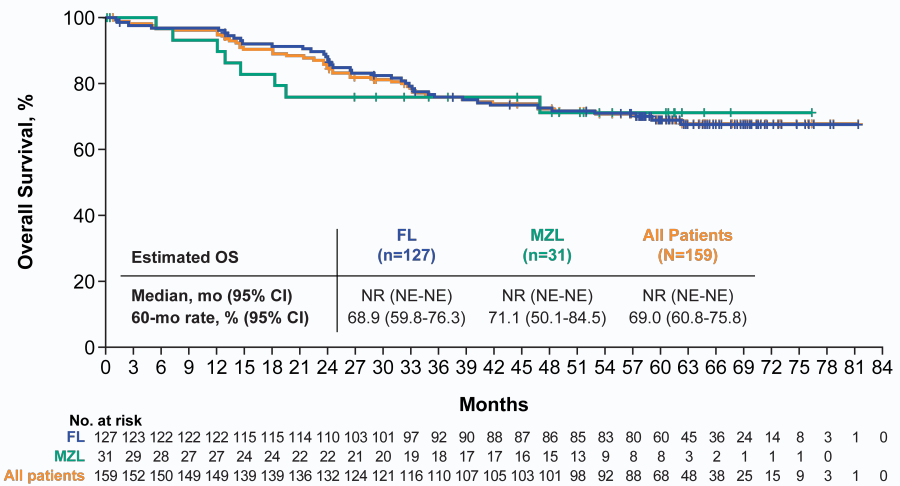
ZUMA-5, axi-cel in r/r iNHL: 5-year analysis

Progression-Free Survival



Overall Survival



Median PFS was 62.2 months; the 60-month PFS rate was 50.4%

Median OS remained not reached

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ZUMA-5, axi-cel in r/r iNHL: 5-year analysis

Following the 4-year analysis:

- 3 new events not related to axi-cel were reported, including Grade 3 prostate cancer, Grade 1 bladder cancer, and Grade 4 myelodysplastic syndrome
- 1 patient died due to pneumonia (not related to axi-cel)
  - No patients died of disease progression following the previous analysis

n, (%)	All Patients N=152	Years Post–Axi-Cel Infusion					
		0-1	1-2	2-3	3-4	4-5	>5
Patients who died	46 (30)	10 (7)	15 (10)	11 (7)	6 (4)	3 (2)	1 (1)
Relapse mortalities							
Progressive disease	14 (9)	5 (3)	5 (3)	2 (1)	1 (1)	1 (1)	0
Non-PD after PD	9 (6)	1 (1)	3 (2)	4 (3)	1 (1)	0	0
Non-relapse mortalities							
Secondary malignancy[a]	6 (4)	1 (1)	2 (1)	1 (1)	2 (1)	0	0
Cardiac-related	3 (2)	0	1 (1)	0	1 (1)	0	1 (1)
Infection-related[b]	11 (7)	2 (1)	2 (1)	4 (3)	1 (1)	2 (1)	0
Other[c]	3 (2)	1 (1)	2 (1)	0	0	0	0

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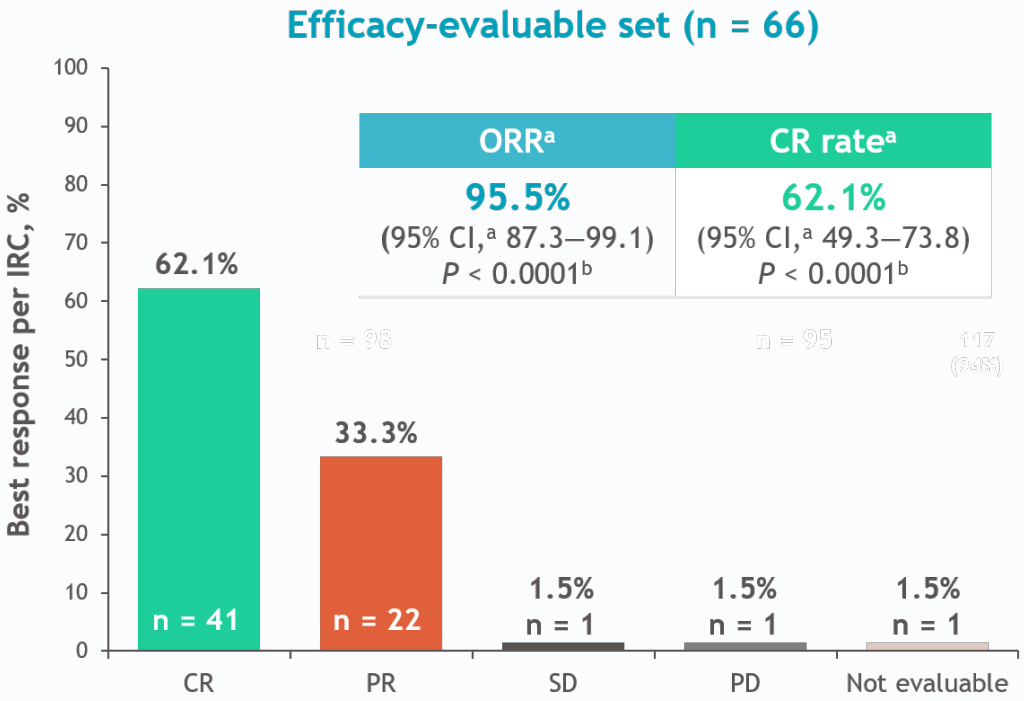
Trascend FL, liso-cel in r/r MZL

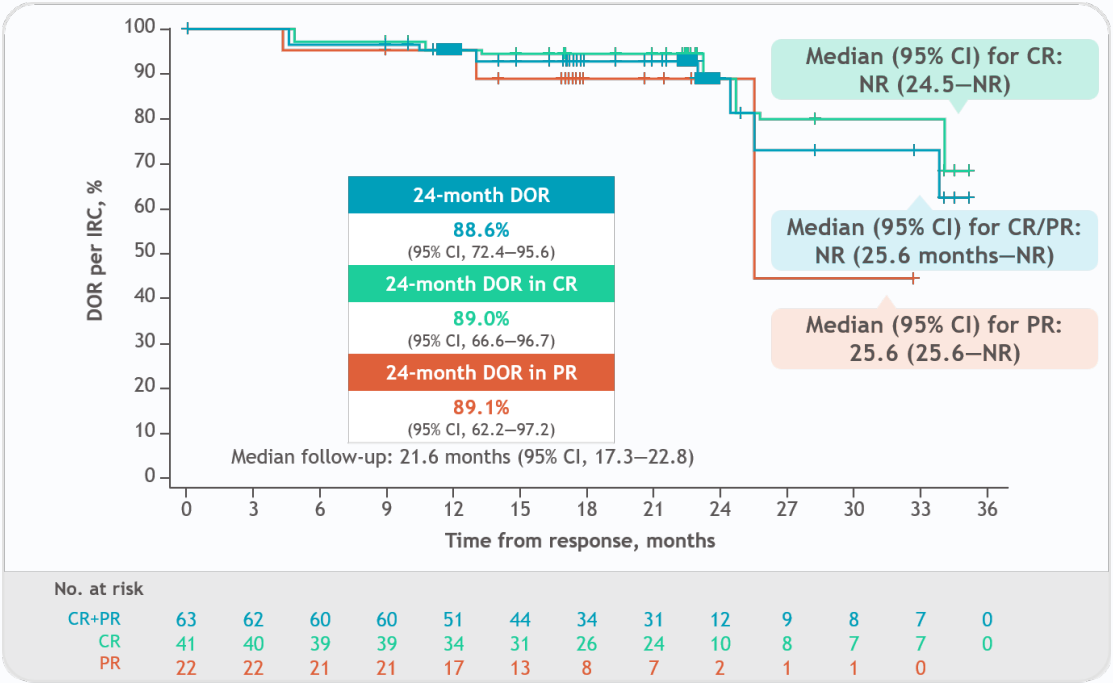
MZL subtype, n (%)	
Nodal	32 (48)
Splenic	18 (27)
Extranodal	17 (25)
Median (range) prior lines	3 (2—12)



- The primary endpoint of ORR and secondary endpoint of CR rate per CT assessed by IRC were met
- **Among patients with PET-positive disease at baseline (n = 56), ORR was 98.2%[c] and CR rate was 91.1%[c]**

Palomba ML et al. Lancet 2026

Trascend FL, liso-cel in r/r MZL, duration of response



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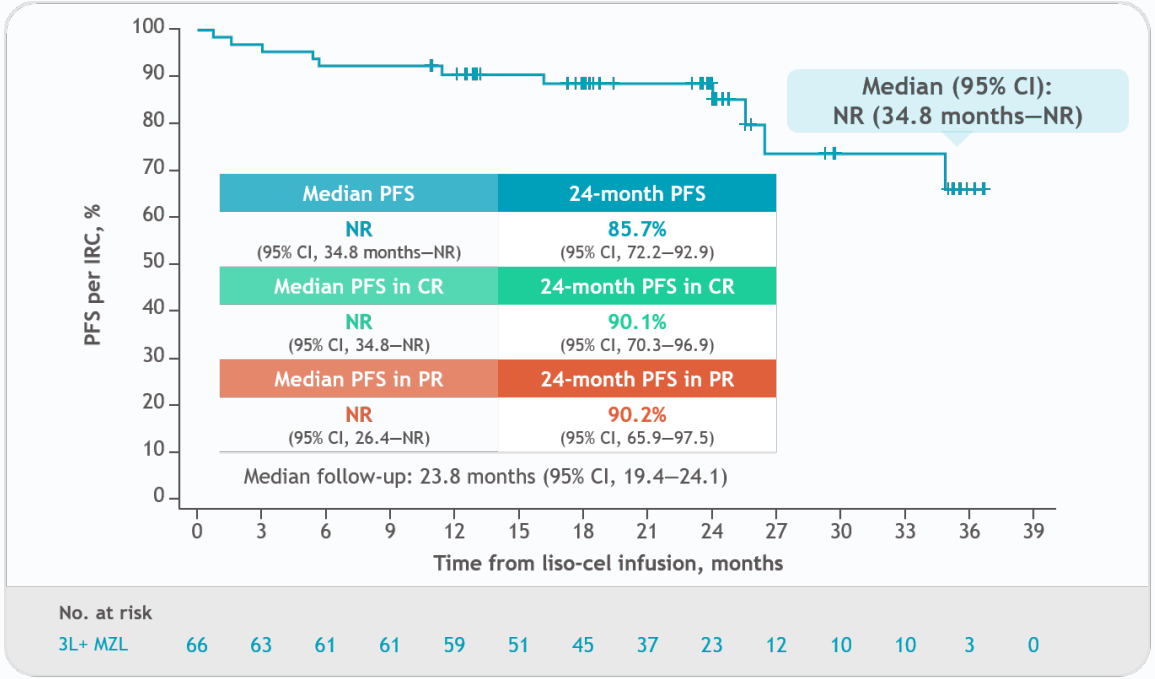
Trascend FL, liso-cel in r/r MZL, progression-free survival



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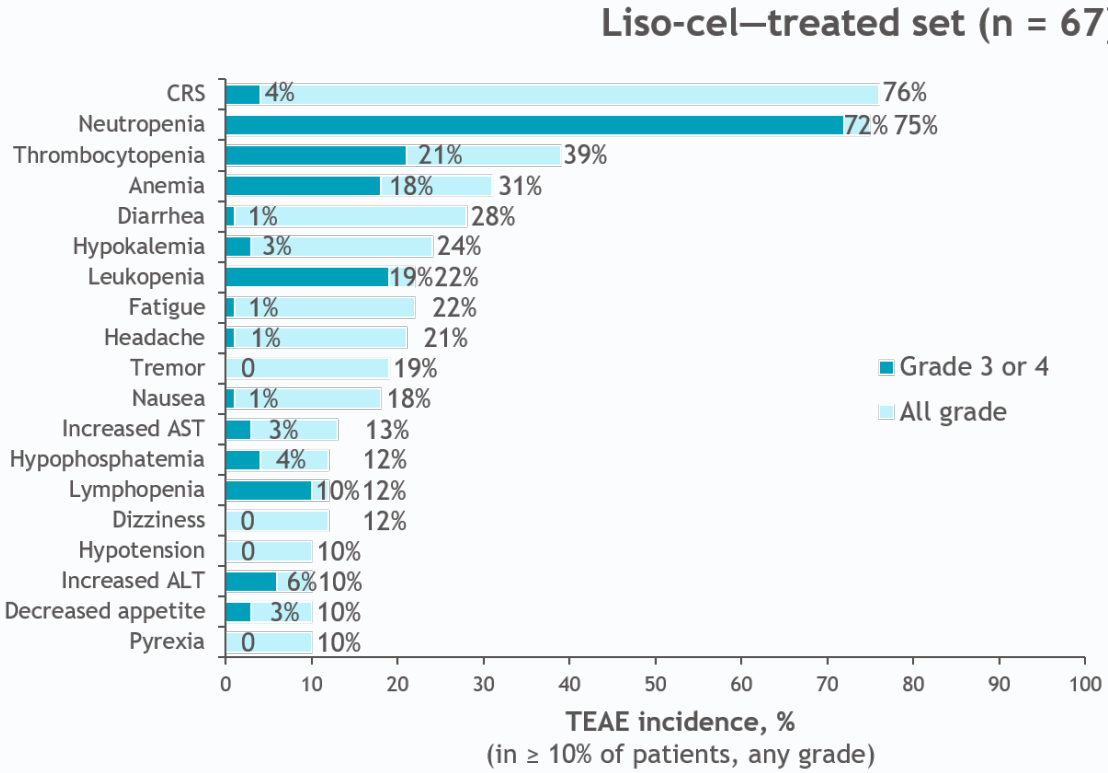
Trascend FL, liso-cel in r/r MZL. Most common TEAEs (≥ 10%)



Two grade 5 TEAEs occurred

- T-cell lymphoma on Day 32. Liso-cel transgene testing and integration site analysis suggested that the T-cell lymphoma was not derived from CAR T cells

- Neutropenic sepsis on Day 47

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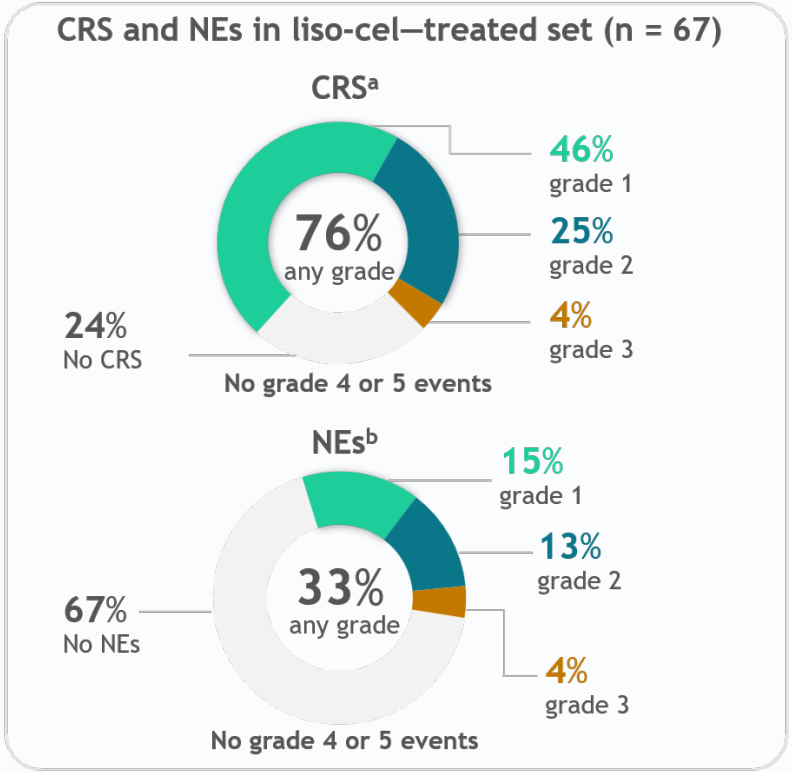
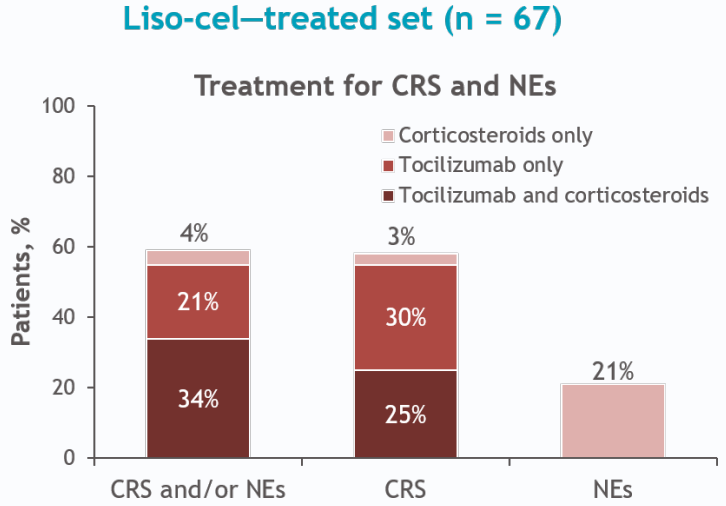
Trascend FL, liso-cel in r/r MZL. CRS and neurological events





Median time to onset and resolution of CRS
Both 4 days

Median time to onset and resolution of NEs
8.5 and 8 days, respectively

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Take home messages

- Antigen-driven process
- Targeted therapies under evaluation in combination programs and TN patients
- New perspectives in immunotherapy (BiAb, CAR-T)
- Need for identification of prognostic and predictive factors for patients/treatment selection
- Longer follow-up to define long term outcomes and identify long term toxicities