I "LINFOMI INDOLENTI"

Milano, Best Western Hotel Madison
26-27 gennaio 2026

Linfomi della zona marginale

Il futuro..

Michele Merli

Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano

Disclosures of Michele Merli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Regeneron Inc			X				
Eli Lilly						X	
Abbvie							X
BeOne							X
Roche							X

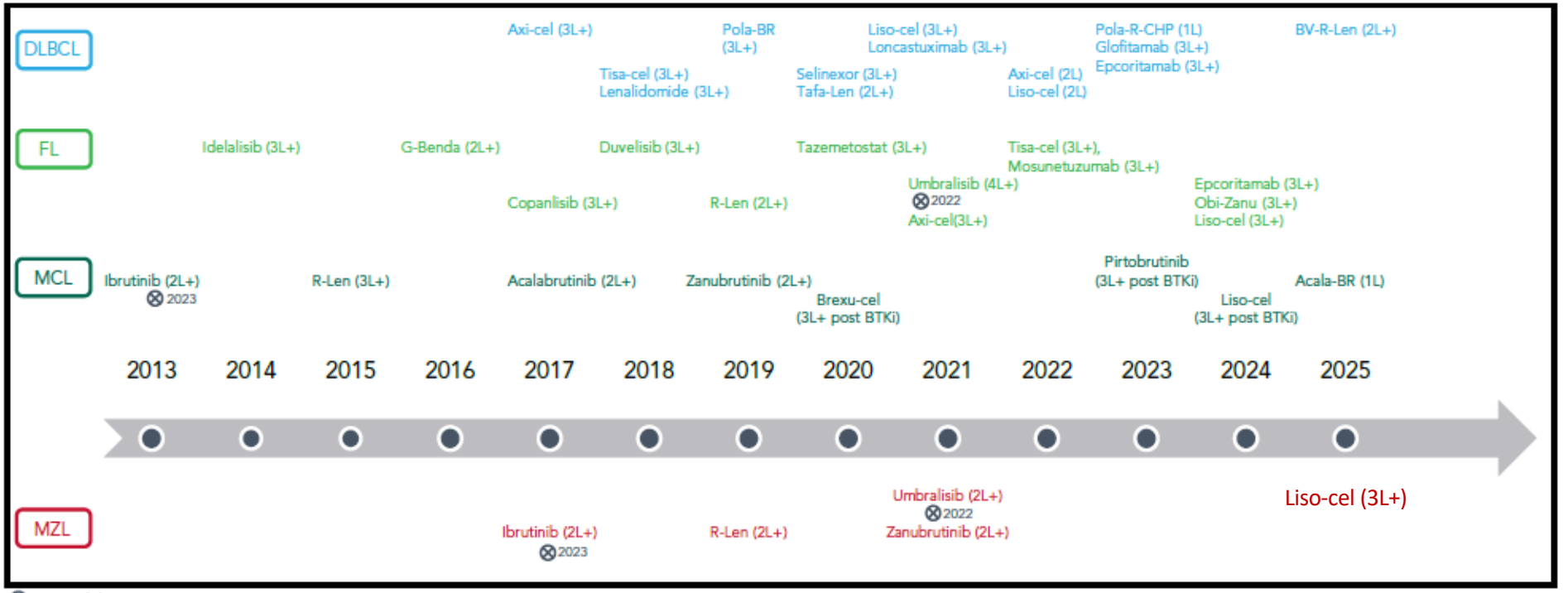
The future of treatment of MZL: initial considerations

- Increased difficulties in *drug development* in MZL due to:
  - diagnostic challenges (e.g. SMZL, no specific molecular or flow cytometry marker)
  - heterogeneity in biological and clinical features and trial populations
    - 3 subtypes (WHO 5^{h} Ed): EMZL, NMZL, SMZL; disseminated MZL recognized
  - heterogeneity in treatment eligibility criteria
  - heterogeneity in staging/restaging procedures (e.g. endoscopy, PET, Lugano criteria)
  - unclear standards of care that lead to inconsistent control arms
  - economic and regulatory disincentives in developing treatments for a rare and heterogeneous lymphoma subtype

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

Thieblemont C, Carras S, Bommier C, Blood 2026

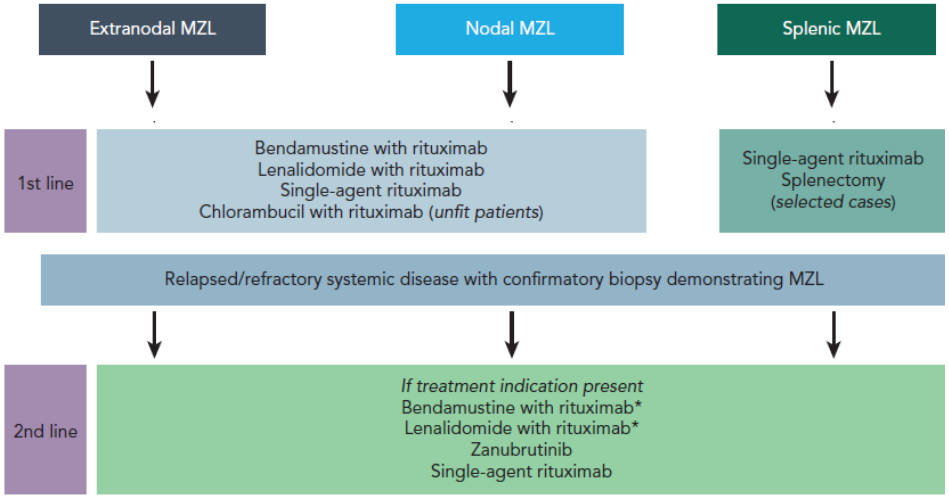
Novel agents approved for MZL



2022 : withdrawn in 2022

Modified from Thieblemont C, Carras S, Bommier C, Blood 2026

Unmet needs and trends for future better treatments in MZL

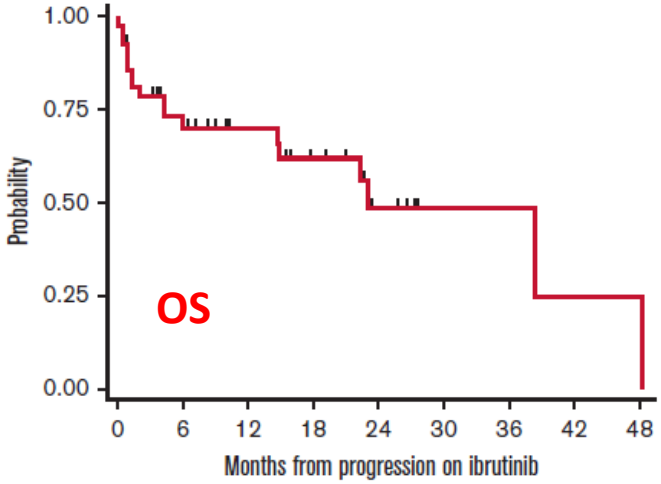


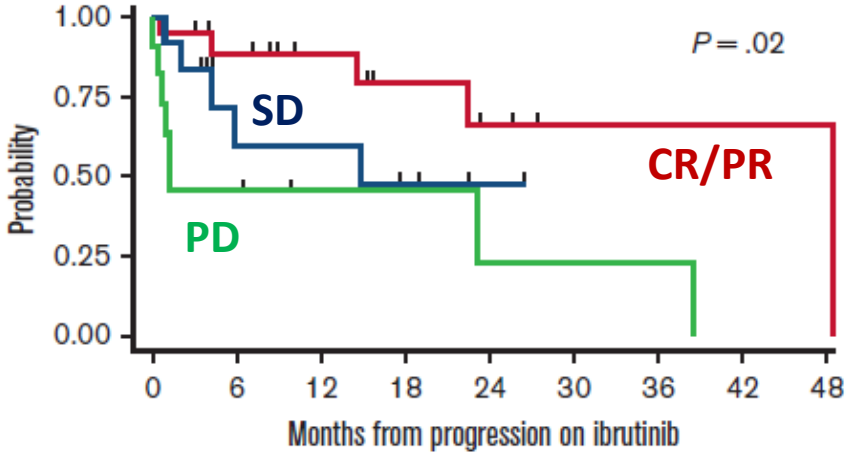
Alderuccio JP & Noy A, Blood 2026

- **1L therapy in localized disease:**
  - reduction of cumulative dosing of RT
    → risk-adapted ultra-low dose RT strategies
- **1L systemic therapy in advanced and symptomatic disease**
  - Chemo-free regimens (EMZL, NMZL)
  - Combination regimens
  - Elderly and frail patients
- **RR MZL:**
  - cBTKi-refractory disease (unmet need)
  - need for development of effective combination and time-limited regimens

Post-ibrutinib outcome in RR MZL

- Real-world multicenter retrospective study, 119 RR MZL pts treated with ibrutinib
- 47 relapses, 15 primary progressors (PP), 32 secondary progressors
- Only 25 received post-ibrutinib therapy (6 BR, 5 alkylator-based, 4 R2), **mPFS 18.2 m**
- **Median post-relapse OS: 23.1 m**, related to response to ibrutinib; very poor outcomes in PP

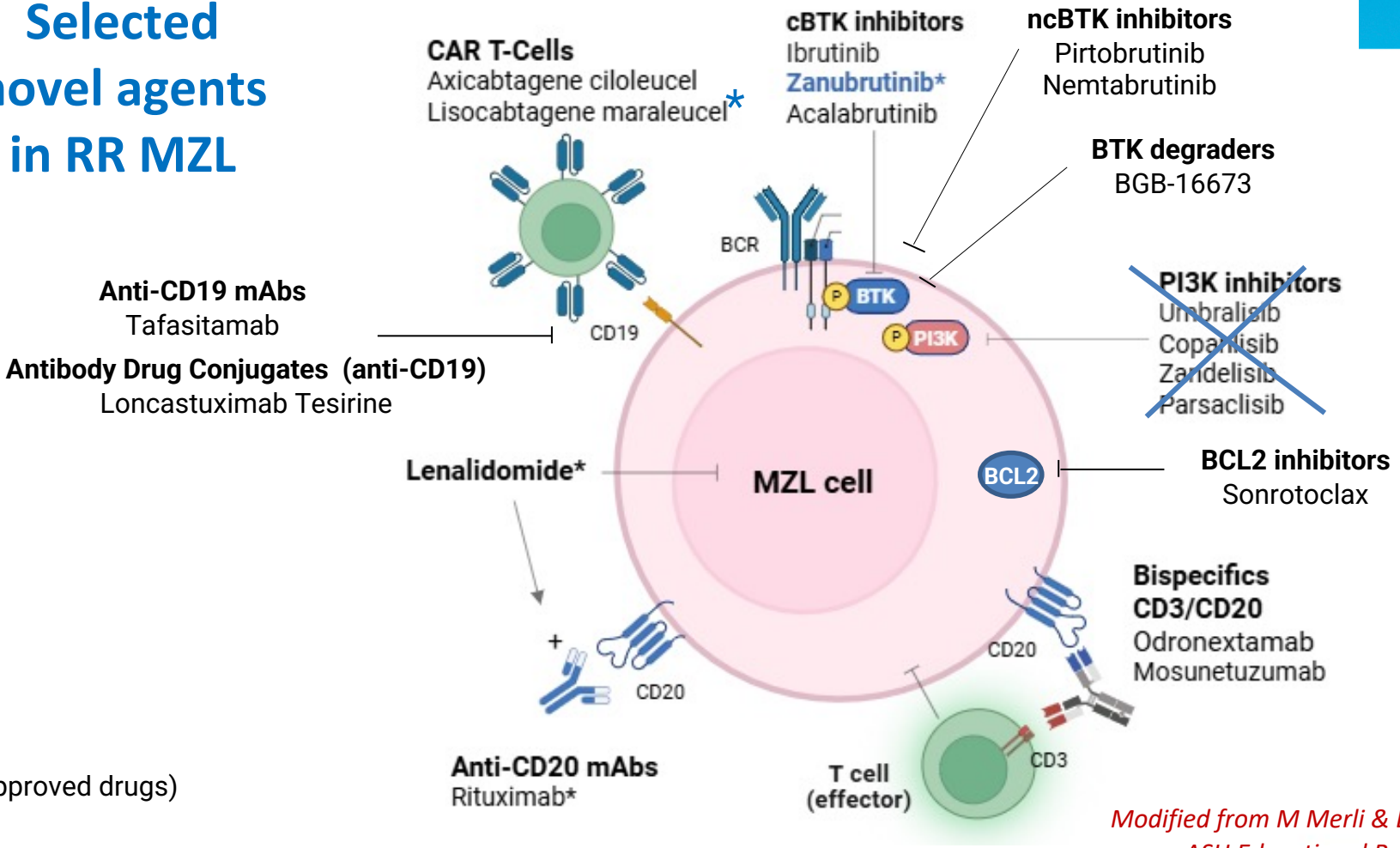




- **No data on outcomes post-zanubrutinib failure**
- **Unmet need**

Epperla N et al. Blood Adv 2023

Selected novel agents in RR MZL



(*approved drugs)

Modified from M Merli & L Arcaini
ASH Educational Book 2022

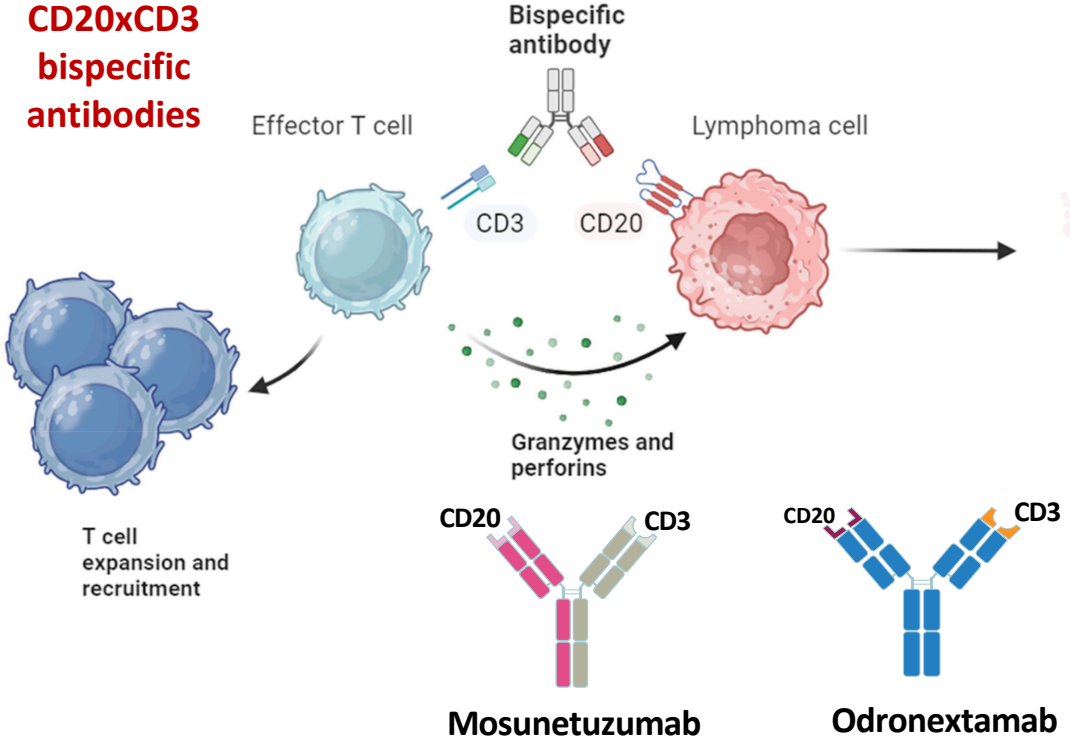
Novel drugs in RR MZL

Class	Target	Drug	Trial	N MZL pts	ORR %	mPFS (mo)
Covalent BTK inhibitors	BTK	Ibrutinib*	PCYC-1121	63	58	15.7
		Zanubrutinib†	MAGNOLIA	68	68	NR (71% 2y)
		Acalabrutinib	ACE-LY-003	43	53	27
Non-covalent BTK inhibitors		Pirtobrutinib	BRUIN 1/2	36	56	16.6
		Nemtabrutinib	BELLWAVE-003	23	52	NA
BTK degraders	BTK-E3 ligase	BGB-16673	CaDAnCe-101	36	56	NA
Apoptosis	BCL2	Sonrotoclax	BGB-11417-101	23	67	NA
IMIDS	Cereblon	R-Lenalidomide†	AUGMENT	63	65	20.2
		Chlaritromicin-Len	CLEO	43	50	40
BsAbs	CD20	Odronextamab	ELM2	35	77	NR (87.5% 1y)
ADC	CD19	Loncastuximab	NCT05296070	23	81	NR (91% 1y)
CAR T-Cells	CD19	Axi-cel	ZUMA-5	31	77	NR (53.9% 5y)
		Liso-cel†	TRANSCEND-FL	66	95	NR (85.7% 2y)

Noy A et al, Blood Adv 2020; Opat S et al, Blood Adv 2023; Strati P et al, BJH 2022; Patel K et al, Blood Adv 26; Tucci A et al, ASH25; Tam CS et al, ASH24; Tedeschi A et al, ASH23; Leonard J et al JCO 2019; Pirosa MC et al Haematologica 23; Kim T et al ASH24; Lossos I, ASH24; Neelapu S et al JCO25; Palomba et al ICML 25

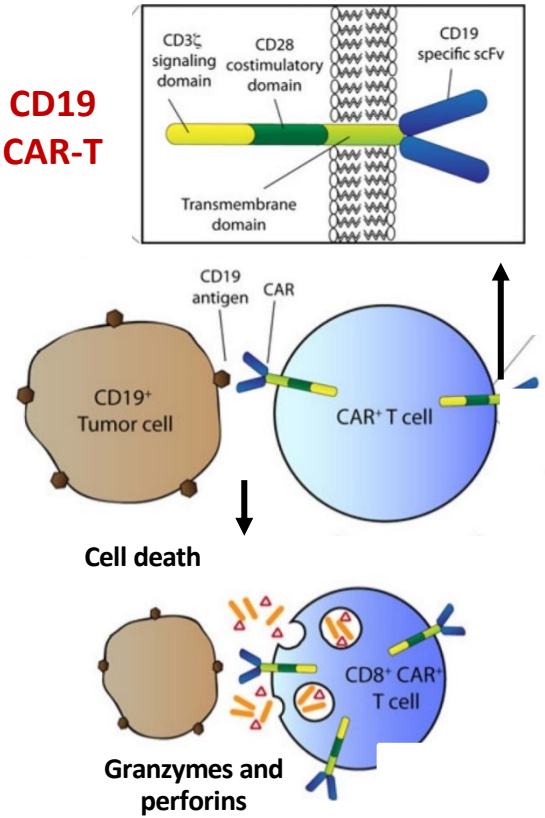
Engaging T-cells in MZL: bispecifics *vs* CAR T-Cells

CD20xCD3 bispecific antibodies



Adapted from **Cassanello G *et al***, *Oncoimmunlogy 2024*

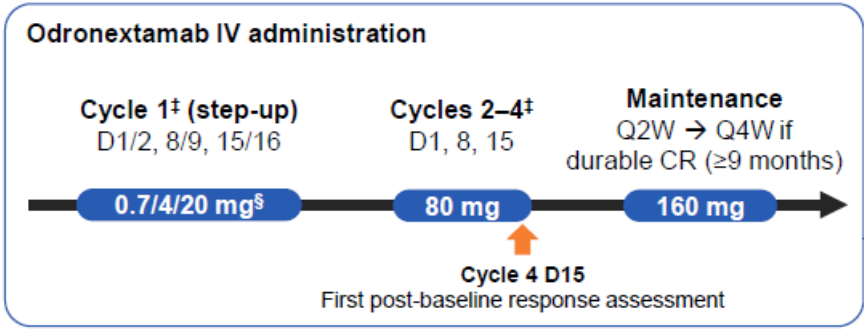
CD19 CAR-T



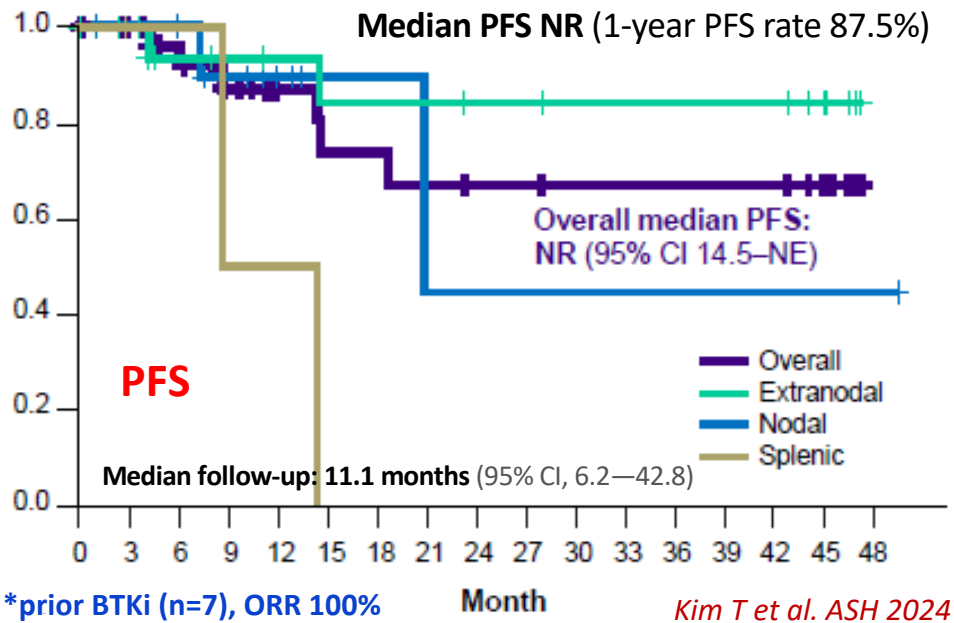
Adapted from **Davila M *et al***, *Int J Hematol 2013*

Odronextamab in +3L RR MZL: ELM-2 study

- Phase 2 study of Odronextamab in R/R MZL pts after ≥2 prior lines
- 42 MZL pts (21 EMZL, 15 NMZL, 5 SMZL, unknown 1), median 2 prior lines (2-8), prior BTK 28.6%
- Grade ≥3 CRS: 0% (35% grade 1; 22% grade 2), No ICANS; 24% grade ≥3 infections (no Grade 5)



Best ORR %	Overall (n=35)*	EMZL (n=19)	NMZL (n=12)	SMZL (n=3)
ORR	77.1	78.9	75	100
CR	77.1	78.9	75	100
SD	8.6	10.5	8.3	0
NE	14.3	10.5	16.7	0



*prior BTKi (n=7), ORR 100%

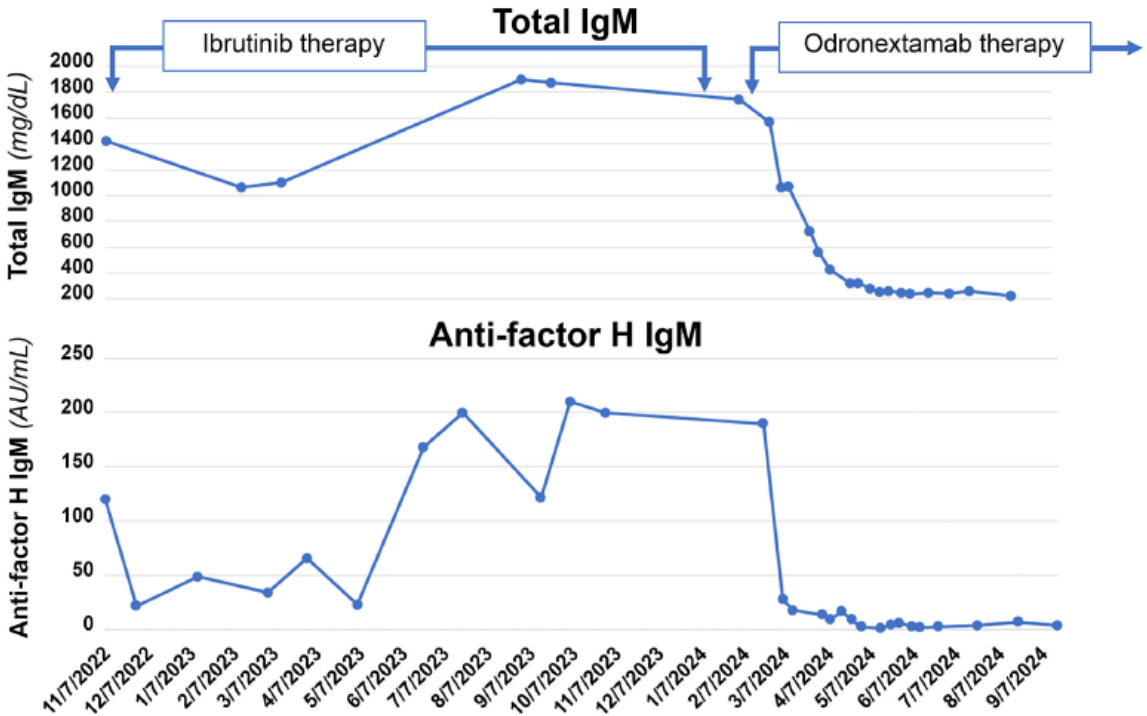
Kim T et al. ASH 2024

A case of MZL with anti-H IgM and aHUS treated with odronextamab

- **39y F, gastric EMZL**, t(11;18), HP+
- Tx: antibiotics, RTX x 4, BR
- At 53y: acute kidney failure, proteinuria, Coombs-negative hemolitic anemia → **aHUS**
- IgM spike, **Anti-H IgM**
- aHUS: eculizumab q4w
- MZL: ibrutinib (3rd line)→SD
- 4th line: *odronextamab* (ELM-2)

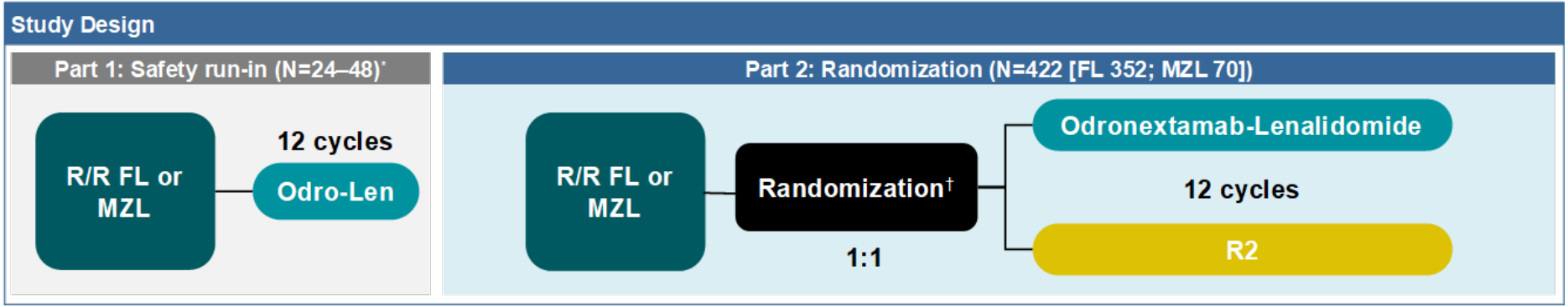
→ rapid IgM drop, anti-H cleared, eculizumab safely discontinued

- CR of MZL: ongoing at 36 months



Ardissino G, … Luminari S, Ferreri A, Merli M, Cugno M. Haematologica, 2025

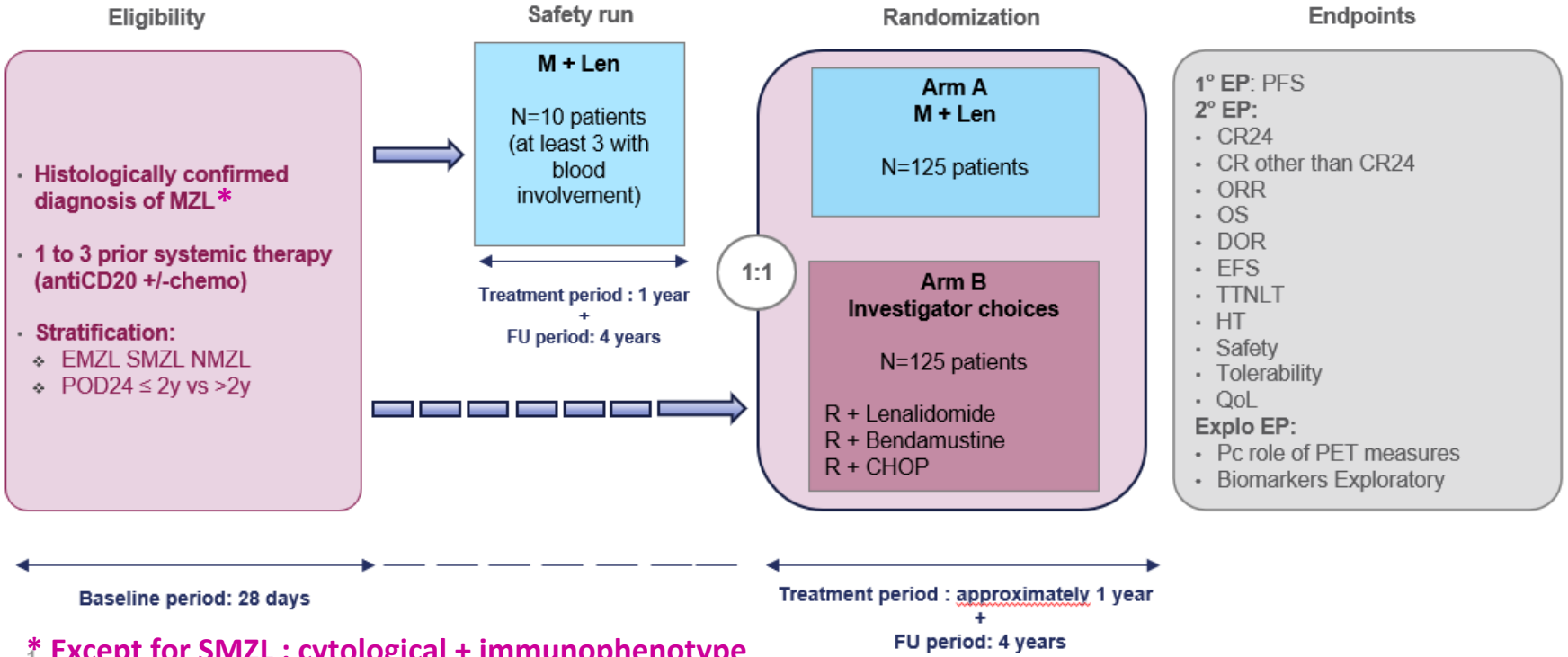
Phase 3 trial of odronextamab + lealidomide vs rituximab + lenalidomide in RR FL and MZL (OLYMPIA-5)



Vitolo U, Merli M et al, ASCO 2024

- Part 1 (safety run-in) terminated, Full dose 80 mg; Part 2 opened also in MZL cohort

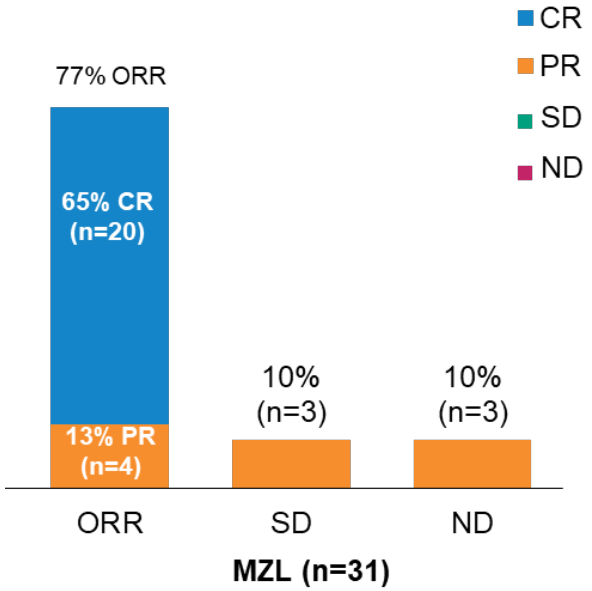
Marsun trial: study design/overview

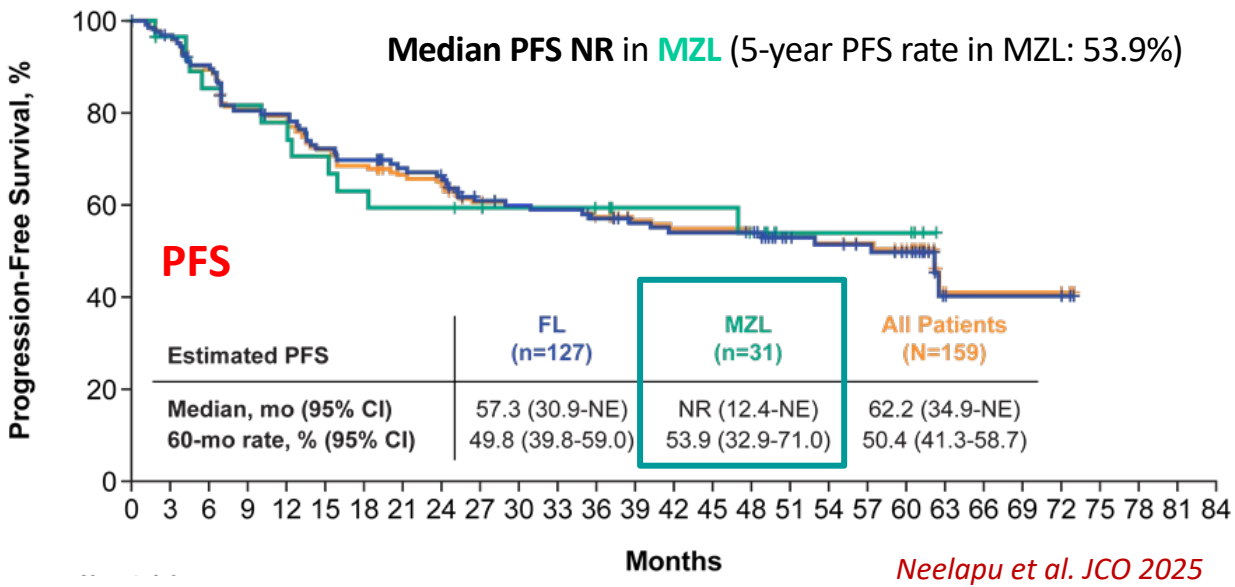


* Except for SMZL : cytological + immunophenotype

CAR T-Cells in +3L RR MZL: Axi-cel *(ZUMA-5, 5 year follow-up)*

- Phase 2 study of Axi-cel, R/R FL and MZL pts after ≥2 prior lines
- 124 pts FL, **31 MZL** (POD24 50%), median 3 prior lines (2-8)
- Grade ≥3 CRS in MZL: 2 pts (9%), Grade ≥3 ICANS in MZL: 9 pts (36%), no Gr 5



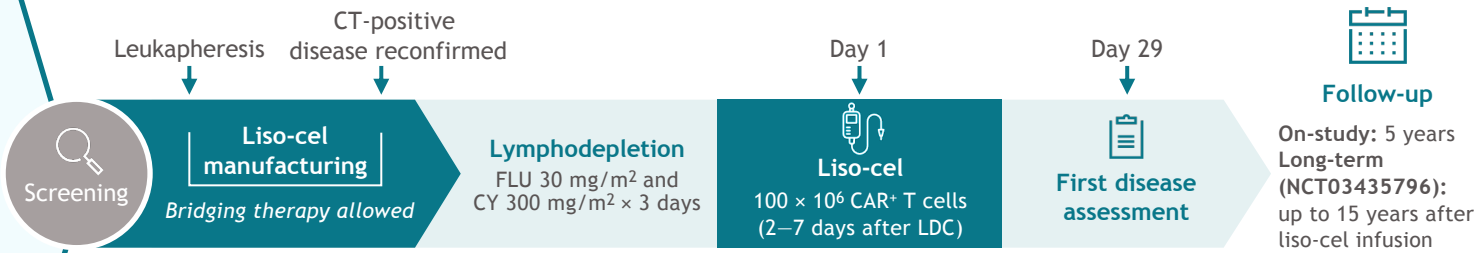


Neelapu et al. JCO 2025

TRANSCEND FL study design (Liso-cel): MZL cohort (3L+)

Key MZL eligibility criteria

- Age ≥ 18 years
- **MZL histologically confirmed** ≤ 6 months before screening as assessed by local pathology
- **R/R MZL (measurable disease) after ≥2 prior lines of systemic therapy**, including ≥ 1 line of combination systemic therapy, therapy with an anti-CD20 antibody and an alkylating agent, or had relapsed disease after HSCT
- ECOG PS ≤ 1
- Adequate bone marrow, kidney, liver, and cardiac function



Primary endpoint

- ORR (BOR of CR or PR) per IRC **by CT** using Lugano 2014 criteria[1] in the efficacy-evaluable set

Secondary endpoints

- CR rate, DOR, DOR if BOR is CR, and PFS per IRC by CT using Lugano 2014 criteria[1] in the efficacy-evaluable set; OS; safety; and cellular kinetics

Exploratory endpoints

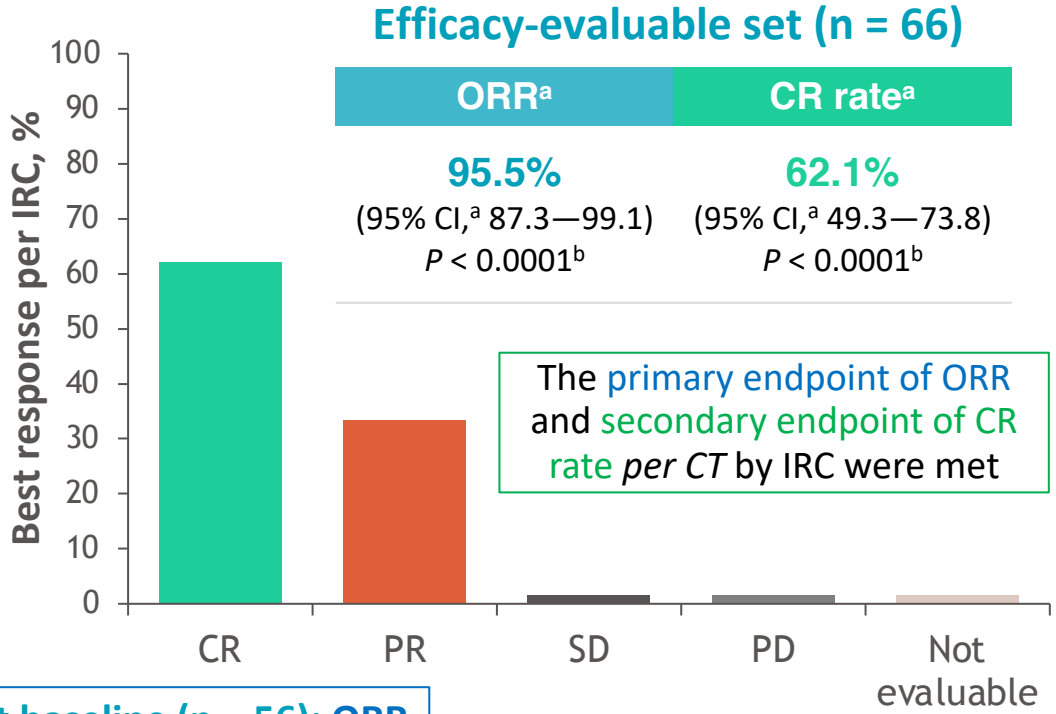
- B-cell aplasia

- Study endpoints of ORR and CR rate were tested hierarchically in the following order at 1-sided $\alpha = 0.025$ significance: ORR (H0: ORR ≤ 50%) and then CR rate (H_0: CR rate ≤ 5%)

Palomba L et al. ICML 2025

Liso-cel in MZL: ORR and CR rate per CT assessed by IRC

	Liso-cel—treated set (n = 67)
Median (range) age, y	62 (37—81)
< 65 y	37 (55)
≥ 65 y to < 75 y	20 (30)
≥ 75 y	10 (15)
MZL subtype, n (%)	
Nodal	32 (48)
Splenic	18 (27)
Extranodal	17 (25)
POD24, n (%)	24 (36)
Median (range) prior lines of systemic therapy[c]	3 (2—12)
Received prior BTKi, n (%)	26 (39)

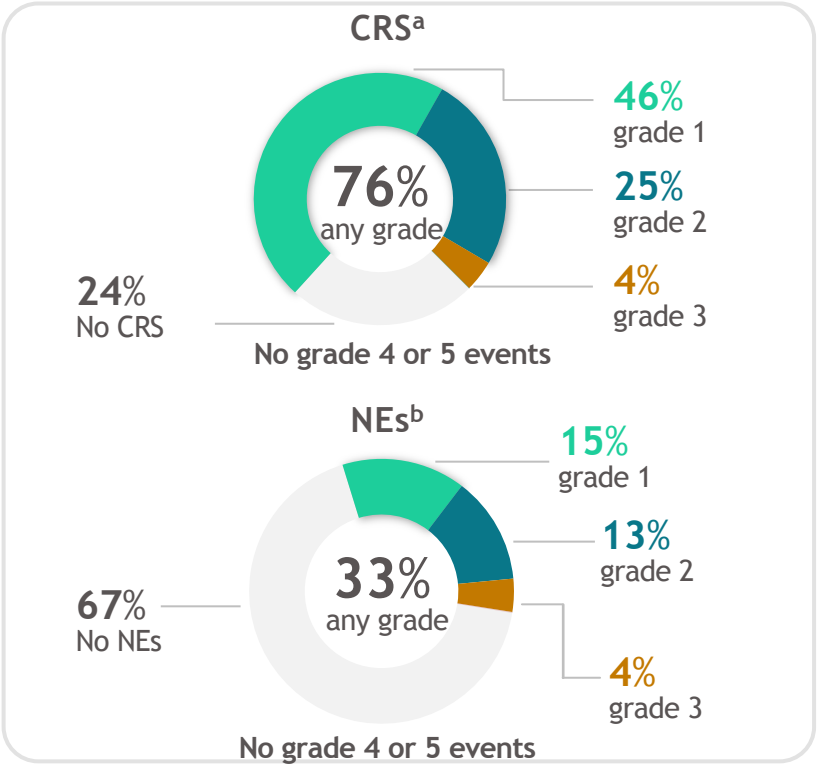


Among patients with PET-positive disease at baseline (n = 56): ORR was 98.2% and CR rate was 91.1%

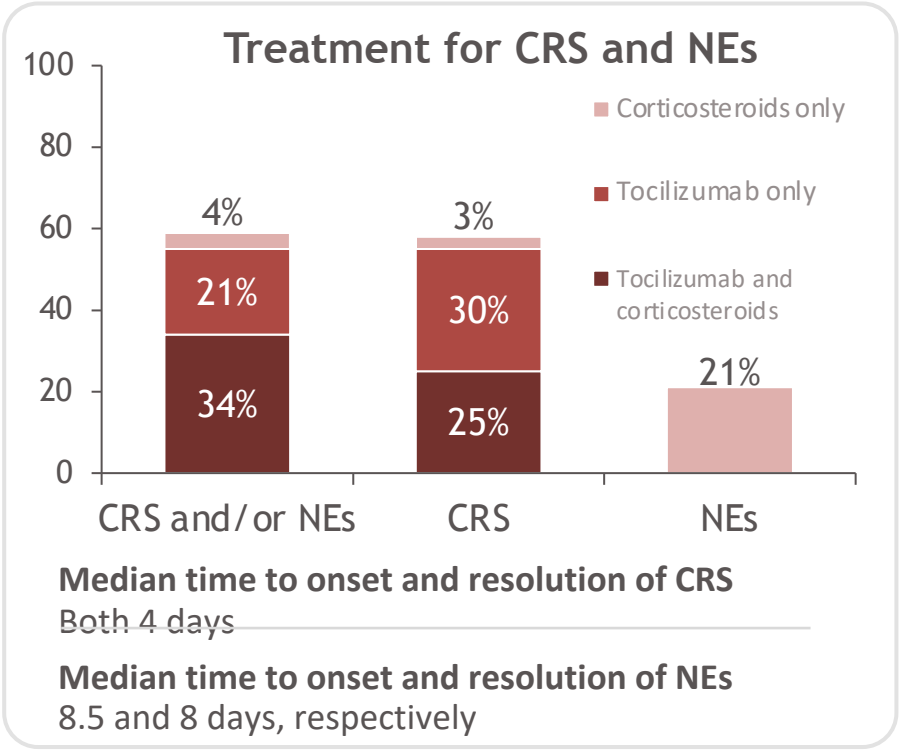
Palomba L et al. ICML 2025

Cytokine release syndrome and neurological events

CRS and NEs in liso-cel—treated set (n=67)



Liso-cel—treated set (n=67)



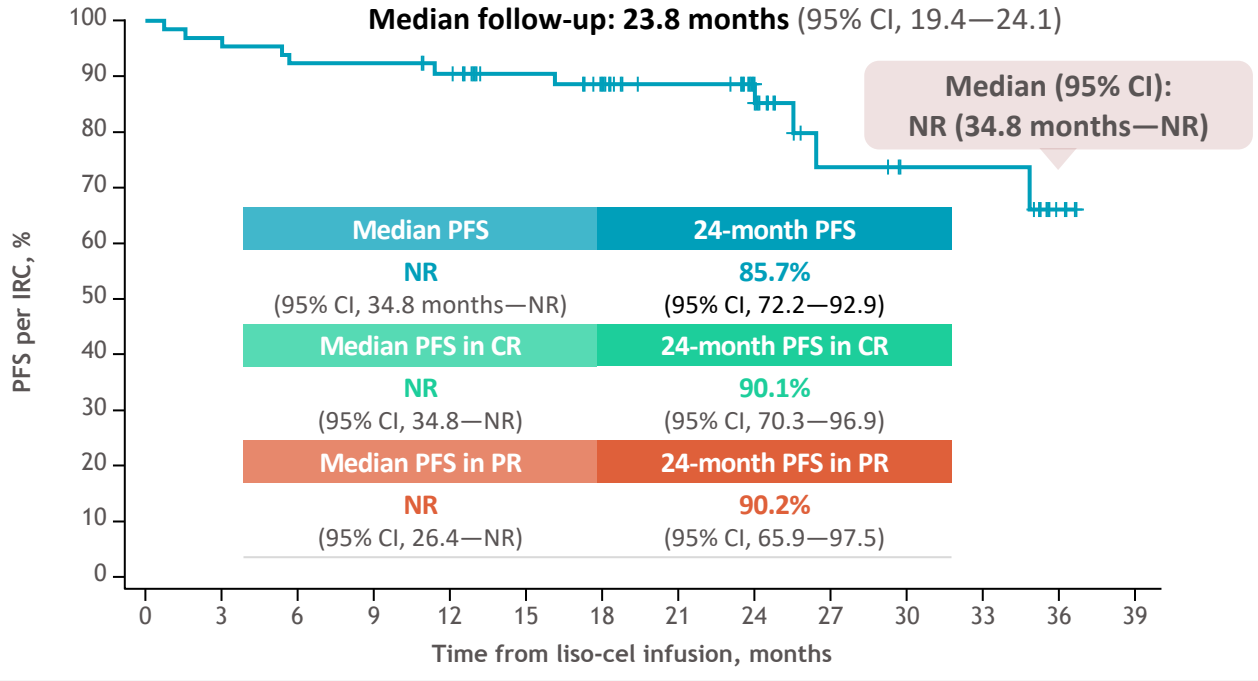
Median time to onset and resolution of CRS
Both 4 days

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

[a]Graded according to the Lee 2014 criteria;
[b]Defined as investigator-identified neurological AEs related to liso-cel and graded per the NCI CTCAE, version 5.0. NE, neurological event.

Palomba L et al. ICML 2025

Progression-free survival per CT assessed by IRC



Eleven patients had events and 55 patients were censored.

24-mo PFS	85.7%
24-mo DOR	88.6%
24-mo OS	90.4%

Approved by FDA on Dec 4, 2025

*"for adults with relapsed or refractory MZL who have received **at least two prior lines** of systemic therapy"*

Palomba L et al. ICML 2025

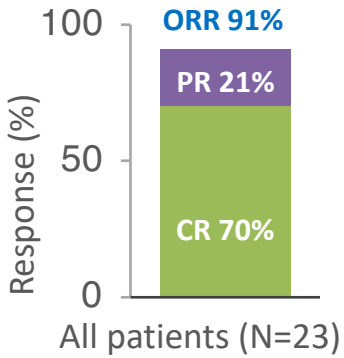
Loncastuximab tesirine (ADC) monotherapy in R/R MZL

Open-label multi-institutional investigator-initiated study evaluating safety and efficacy of the **anti-CD19 ADC Loncastuximab tesirine (6 cycles)** in R/R marginal zone lymphoma (NCT05296070)

23 patients enrolled

- Median age 65 yrs (45–82)
- ECOG PS 0–1: 100%
- stage III/IV: 83%
- POD24: 48%
- Relapsed: 61%
- Refractory: 39%
- Median prior LoT: 2 (1–4)

Response rates



Additional efficacy findings

93% of CRs currently maintained

64% of POD24 patients achieved CR

1 patient received prior CAR-T and achieved CR

67% 18-mo DoCR

92% 12-mo PFS

Lonca was generally well tolerated

%	Any Grade	Grade 3–4
Maculopapular rash	65	4
Increased AST	65	0
Increased ALT	61	9
Increased ALP	48	13
Neutropenia	43	17
Local oedema	43	0
Photosensitivity	30	4
Anaemia	30	4

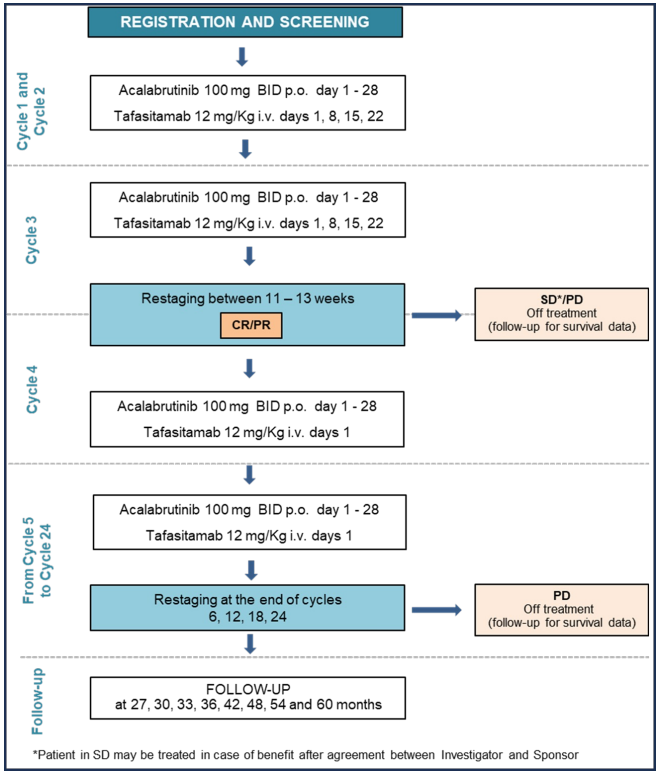
- 1 patient discontinued treatment
- 3 patients required Lonca dose reductions
- No treatment-related deaths occurred

Lonca demonstrates clinically meaningful activity in R/R MZL patients with a robust CR rate and the safety profile is consistent with known adverse events

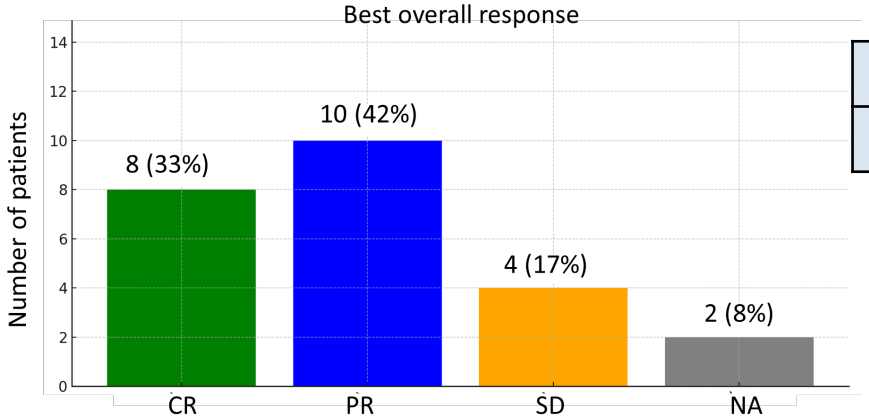
Lossos et al. ASH 2024; Poster #3032

IELSG-49: tafasitamab + acalabrutinib in RR MZL

- Single-arm, phase II clinical trial with a safety run-in phase for pts with R/R MZL needing Tx



- 24 pts (11 EMZL, 10 SMZL, 5 NMZL), median 2 prior lines (1-4)
- Hem toxicity, gr 3: thrombocytopenia 12.5%, neutropenia 8.5%
- Extra-hem. toxicity, gr 3: 1 event (chronic kidney disease)



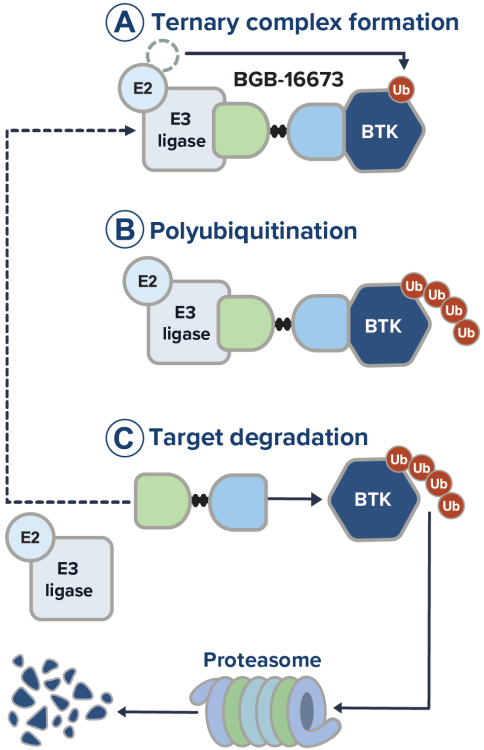
ORR	75%
CR	33%

Safe combination, high ORR and CR in RR MZL

Stathis A et al. ICML 2025

BTK degraders: BGB-16673

CaDAnCe-101 R/R NHL

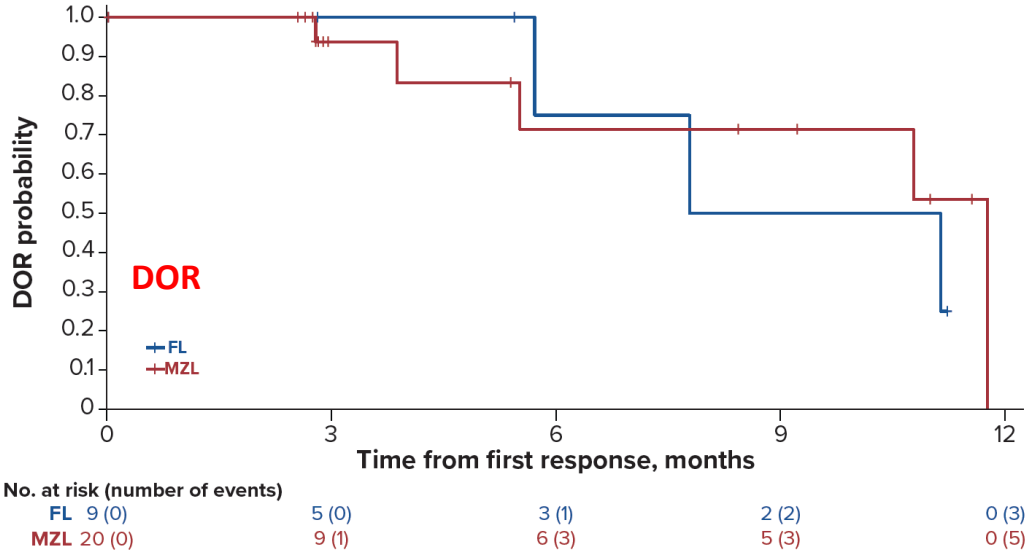


- Catalytic pharmacology not requiring sustained target binding
- Can interrupt formation of oncogenic protein complexes (scaffolding)
- Can penetrate the blood brain barrier
- Potential to overcome resistance mutations (eg, BTK C481S, C481F, C481Y, L528W, and V416L)
- **BGB-16673** treatment led to **substantial reductions in BTK protein levels in peripheral blood and tumor tissue** in **CaDAnCe-101**, the ongoing *first-in-human* study
- BGB-16673 is being investigated in a variety of B-cell malignancies including follicular lymphoma (FL) and marginal zone lymphoma (MZL)

Guièze R, et al. ASH 2025; #3584

BGB-16673 in RR MZL (CaDAnCe-101 NHL study)

Best response, n (%)	FL (n=24)	MZL (n=36)
CR	3 (2.5)	**6 (16.7)**
PR	6 (25)	**14 (38.9)**
SD	6 (25)	10 (27.8)
PD	8 (33.3)	4 (11.1)
Discontinued	0	2 (5.6)
NE	1 (4.2)	0
ORR	9 (37.5)	**20 (55.6)**
Time to first response, mo, median (range)	2.7 (2.6-2.8)	2.8 (2.6-2.9)



- Well tolerated, low rate of discontinuation
- Responses also seen in MZL pts previously treated with cBTK inhibitors (15/30)

- Follow-up after response still immature
- 21 MZL pts remained on treatment at the data cut-off
- PD was the most common reason for treatment discontinuation (n=10, 27.0%)

Guièze R, et al. ASH 2025; #3584

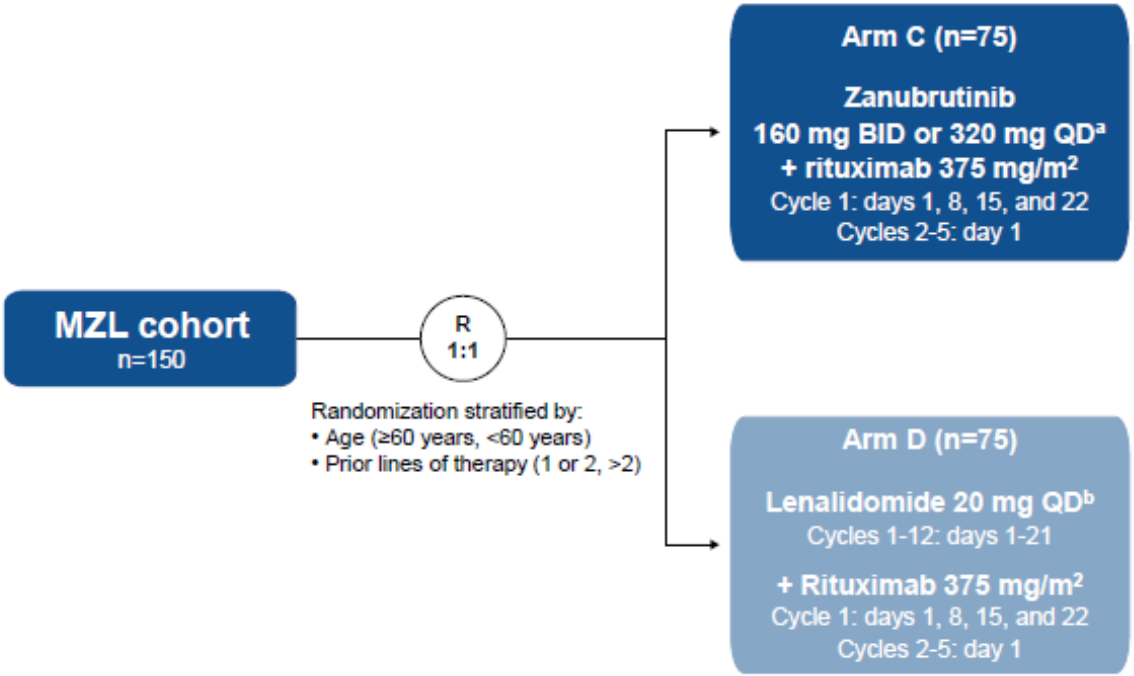
Ongoing studies in RR MZL

ClinicalTrials.gov N (Title)	Experimental regimen	Class	Subtype	Phase	N pts	Comparator	Geographic origin of sponsor
NCT0600611 (MARSUN)	**Mosunetuzumab + Lenalidomide**	BsAb (CD3xCD20) + IMID	All	3	260	R2, BR/R-CHOP	France (LYSA)
NCT0510086 (MAHOGANY)	**Rituximab + Zanubrutinib**	anti-CD20 +BTKi	All	3	150	R2	Pharmaceutical Company
NCT06569680 (OLYMPIA-5)	**Odronextamab + Lenalidomide**	BsAb (CD3xCD20) + IMID	All	3	70	R2	Pharmaceutical Company
NCT0656350	**Mosunetuzumab + Zanubrutinib**	BsAb (CD3xCD20) + BTKi	All	2	36	/	United States (MDACC)

+1 ph 2 study from China (Orelabrutinib + Len)

Modified from Thieblemont C, Carras S, Bommier C, Blood 2026

Phase 3 trial of zanubrutinib + rituximab *vs* rituximab + lenalidomide in RR FL and MZL (MAHOGANY)



Primary endpoint
- PFS per IRC using CT-based Lugano 2014 criteria[1]

Key secondary endpoint
- ORR per IRC using CT-based Lugano 2014 criteria[1]

Secondary endpoints
- OS
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using CT- and PET/CT-based Lugano 2014 criteria[1])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

First-line therapy

Mosunetuzumab sc in 1L (MorningSun study*, MZL cohort)

Key inclusion criteria

- Symptomatic MZL (splenic, nodal, and extranodal, including gastric/MALT)
- Previously untreated, with an indication to start systemic therapy
- ECOG performance status 0–2

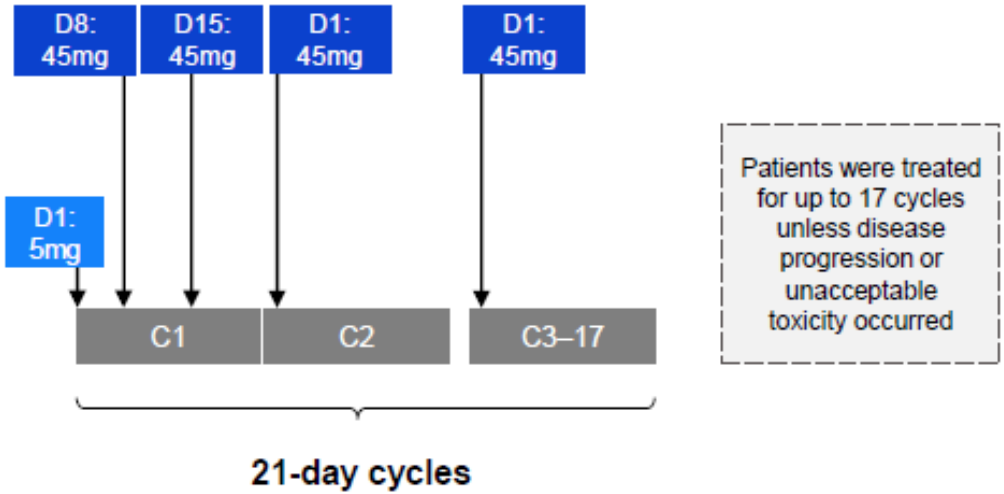
CRS mitigation

- Mosunetuzumab SC step-up dosing in C1
- Corticosteroid prophylaxis* was mandatory in C1–2 and optional thereafter
- Hospitalization was not mandatory

Endpoints

- Primary: INV-assessed ORR by Lugano criteria
- Key secondary: PFS, DOR, DOCR, time to response, safety

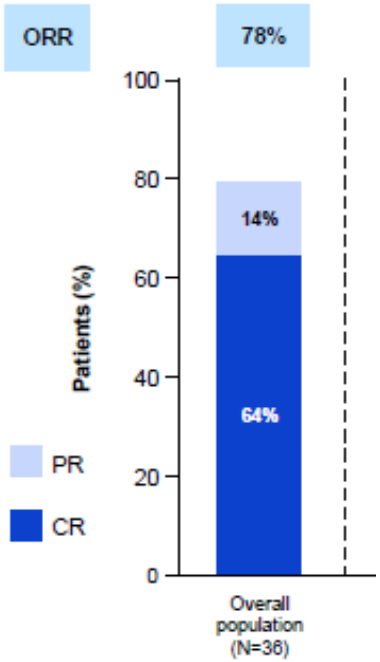
Mosunetuzumab SC administration

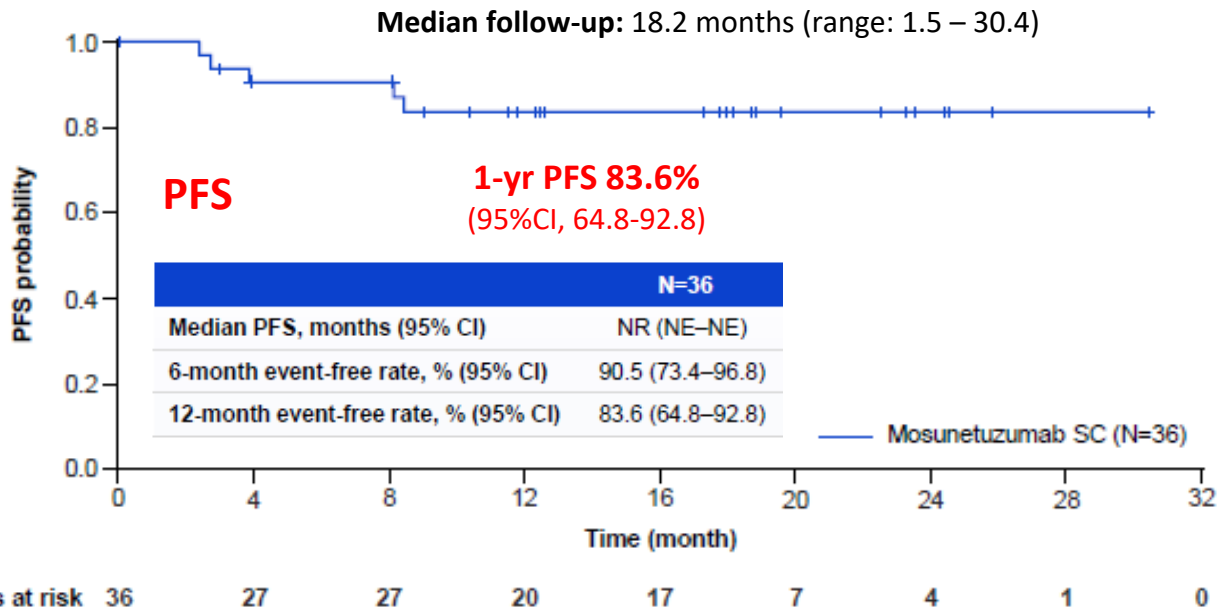


Dexamethasone (20mg) or methylprednisolone (80mg); premedication with oral acetaminophen or paracetamol and/or diphenhydramine could also be administered prior to administration of mosunetuzumab. **Ongoing Phase II basket study (NCT05207670)**

Burke J et al. EHA 2025

Mosunetuzumab sc in 1L: efficacy

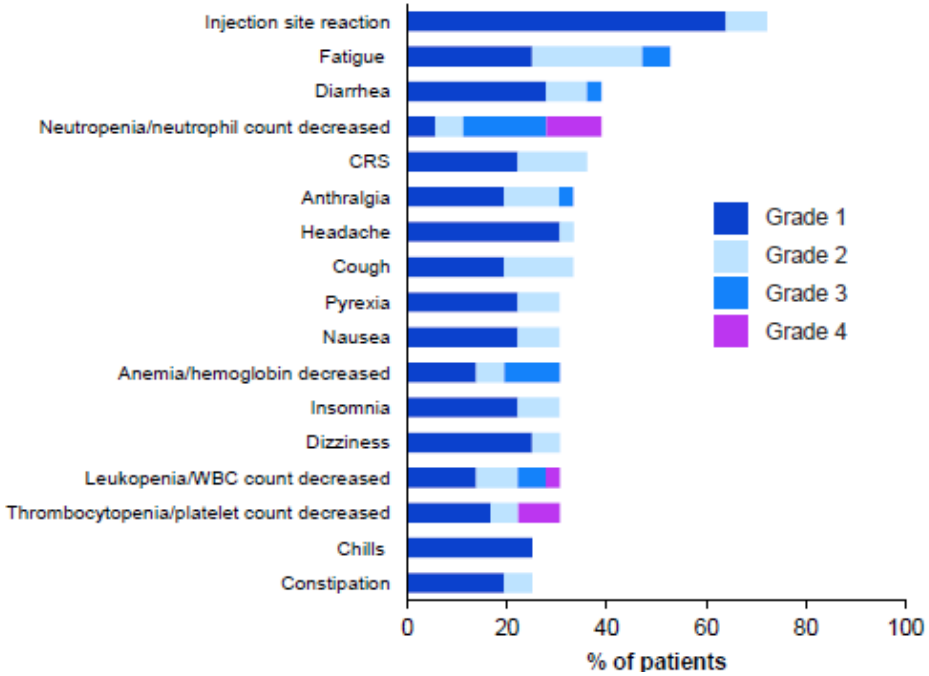


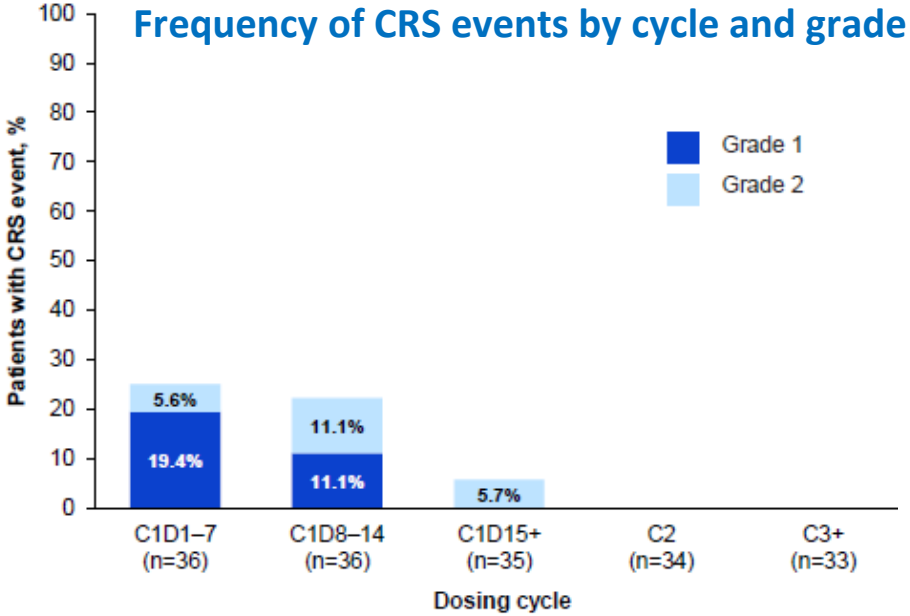


- Median time to response: 2.8 months (range: 2.4–5.4)
- At the time of analysis, 23 patients (63.9%) were still in CMR

Burke J et al. EHA 2025

Mosunetuzumab sc in 1L: safety

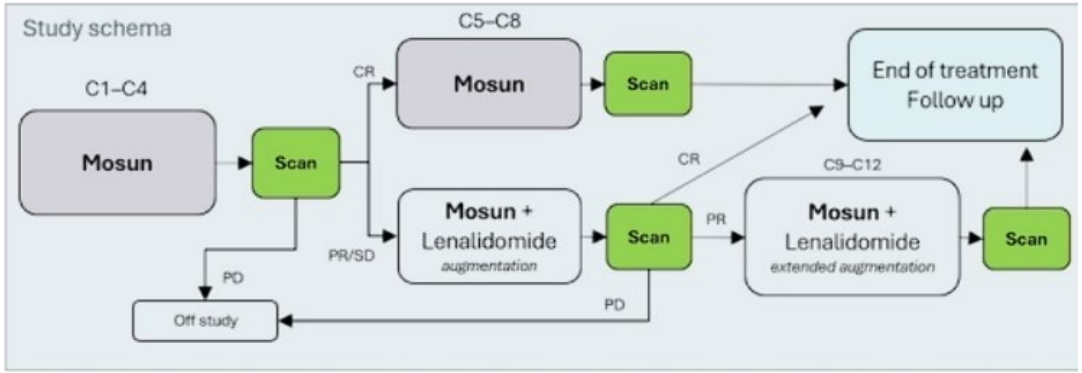




- CRS events were predominantly Grade 1; all occurred during Cycle 1 and all resolved
- Infections any grade: 83.3%; grade 3: 13.9%; predominantly resolved, no fatalities

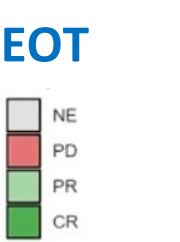
Burke J et al. EHA 2025

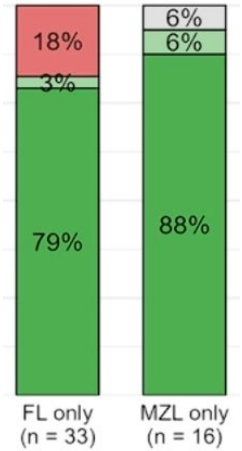
Mosunetuzumab + lenalidomide augmentation in 1L



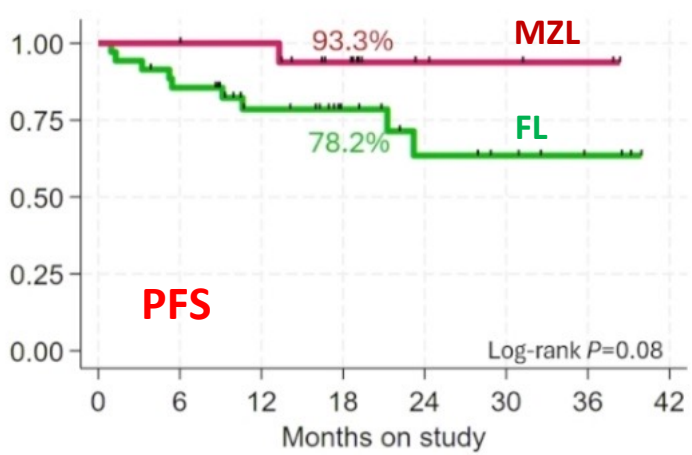
- **BrUOG Ph 2 study, 1L FL/MZL**
- **If <CR after C4: Len augmentation** (Len 10 mg continously)
- **17 MZL pts** (8 EMZL, 6 NMZL, 3 SMZL)
- MZL: 4 pts Len augmentation
- **Toxicity** (all pts):
  - **CRS 27%,** all G1 and in C1 (more common in SMZL [66%], associated with high ALC)
  - 2 PJP, 3 HZV (prophylaxis not mandated)

EOT





MZL	
ORR	94%
CR	88%



Olszewski A et al. ASH 2025

Ongoing studies in 1L MZL

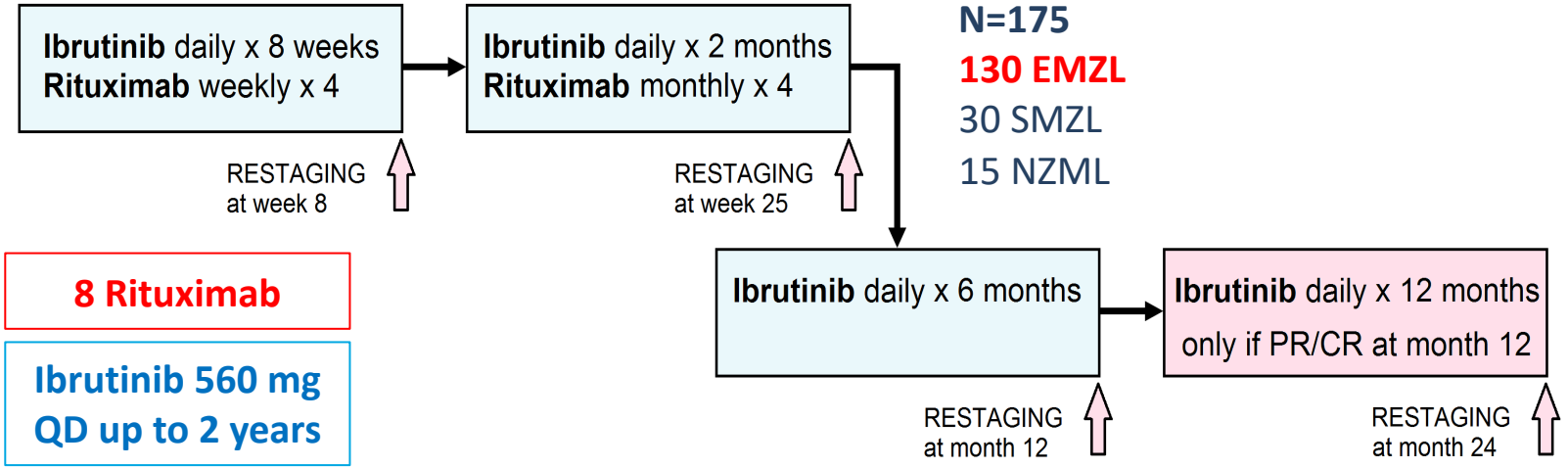
NCT N (Title)	Experimental regimen	Subtype	Phase	N pts	Comparator	Geographic origin
NCT06390956 (PIONER-MZL)	**Pirtobrutinib + Rituximab**	All	2	23	/	United States (Utah)
NCT0679699	**Epcoritamab**	All	2	25	/	United States (Miami)
NCT06569680	**Mosunetuzumab**	EMZL	2	35	/	United States (Miami)
NCT0679282	**Tafasitamab-R2**	All (+FL)	2	65	/	United States (Boston)
NCT05735834 (IELSG 48 - RITZ)	**Rituximab + Zanubrutinib**	SMZL	3	120	Rituximab	Europe (IELSG)
NCT06510309	**Rituximab + Venetoclax**	All	2	33	/	United States (Boston)
NCT05783596	**Glofitamab**	All (+FL)	2	47	/	United States (Boston)
NCT0635031	**Rituximab + Zanubrutinib**	All (+FL)	2	43	/	United States (MOFFITT)
NCT0644247	**Mosunetuzumab**	All	2	20	/	United States (Fred Hutch)
NCT04883437	**Obinutuzumab + Acalabrutinib**	All (+FL)	2	49	/	Uniited States (EMORY)

+11 studies from China with Orelabrutinib combinations

Modified from Thieblemont C, Carras S, Bommier C, Blood 2026

MALIBU Trial

Phase II Study of Ibrutinib and Rituximab in untreated MZL



Primary endpoints: 1-yr CR rate and 5-yr PFS
BIOBANKING: Liquid biopsy at staging and any restaging
PET scan: at staging and end of therapy (month 12)

Study opened in Q4 2019
Pts enrolment closed in March 2023

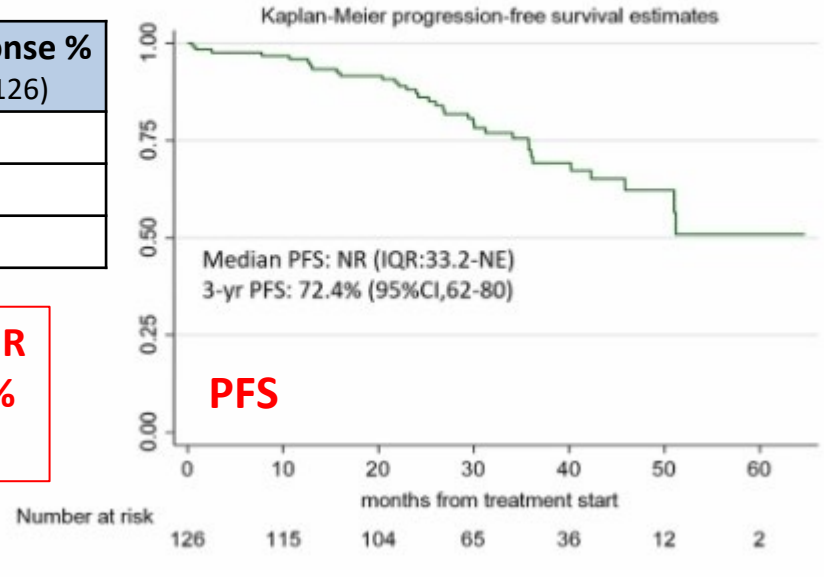
MALIBU Trial: Preliminary results

EMZL

Median F-up 35.7 months

	Best response % (N=107/126)
ORR	92.3
CR	62.1
PR	30.2

Median PFS: NR
3-yr PFS 72.4%
(95%CI, 62-80)



Conconi A et al. ICML 2025

SMZL, NZML

Median F-up 41 months

	SMZL (N=30)	NMZL (N=15)
Best ORR	96	90
Best CR	44	80
Best PR	52	10
Median PFS, mo (95% CI)	**47.2** (34.4-NE)	**24.8** (7.34-NE)

p=0.02

Thieblemont C et al. ICML 2025

RITZ study: first Ph3 randomized study in SMZL *(R-Zanubrutinib vs R)*

- Age of ≥ 18 years
- Patients with diagnosis of SMZL
- Patients not previously treated
- In need for treatment according to guidelines
- No prior splenectomy
- No active hepatitis C infection
- No organ dysfunction

Arm A (N = 60)
Zanubrutinib
160 mg BID for 12 cycles
plus rituximab
(8 infusions)

- **If CR after 12 cycles: stop treatment**
- **If PR after 12 cycles:**
  Zanubrutinib
  160 mg BID for 12 cycles
  plus rituximab
  (4 infusions)

Arm B (N = 60)
Rituximab
(8 infusions)

- **If CR after 12 cycles: stop treatment**
- **If PR after 12 cycles:**
  Rituximab
  (4 infusions)

Accrual completed (120 pts) in Dec 2025

Primary Endpoint

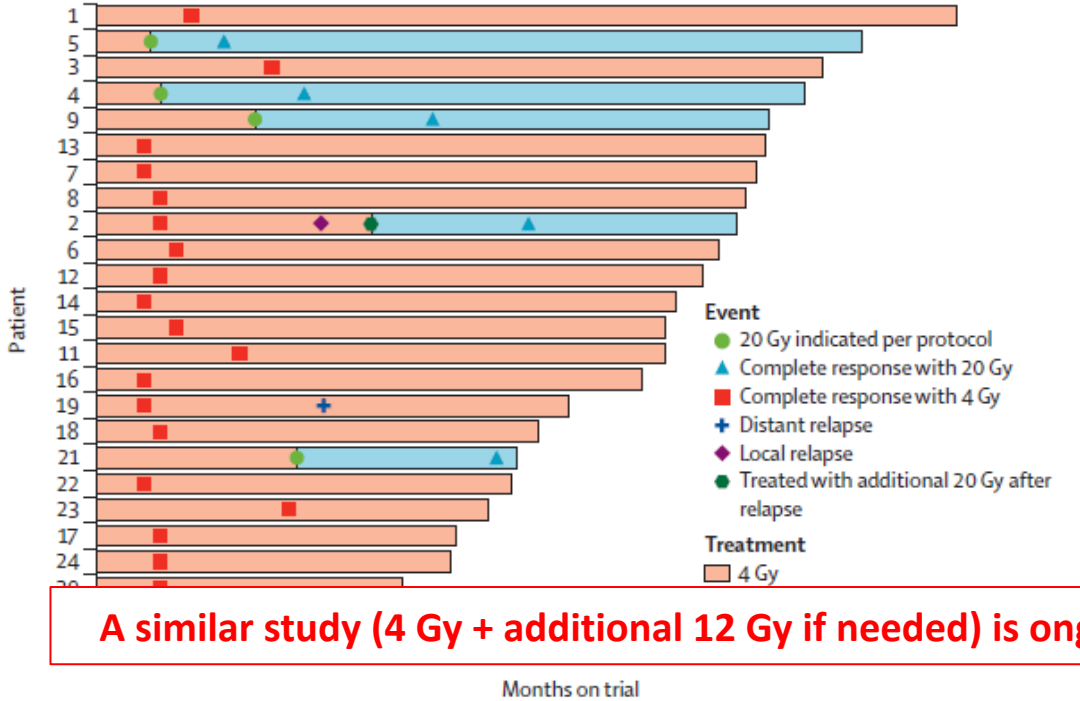
- **PFS at 3 years** according to Cheson 2007

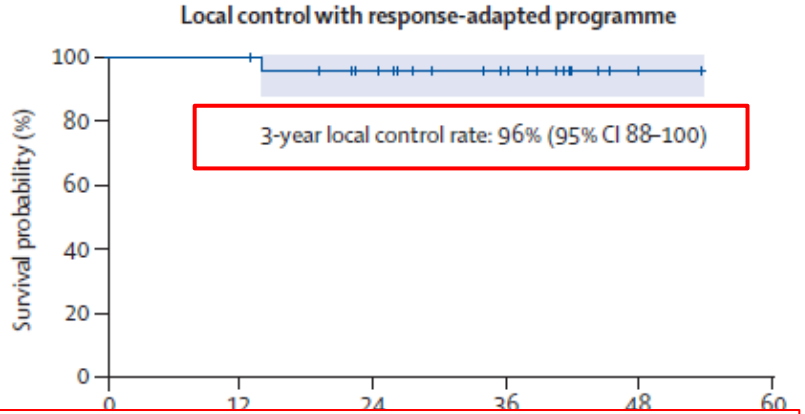
Secondary Endpoints

- CR at 6, 12, 18 and 24 mos
- Best ORR
- DoR, TTNT
- OS
- Safety
- QoL
- Correlatives: mutational profiling on circulating tumor DNA (ctDNA)

Response-adapted ultra-low dose RT (4 Gy) in gastric EMZL

- **Gastric HP-negative EMZL,** newly diagnosed or R/R (previous antibiotics or systemic Tx)
- **4 Gy (2 x 2):** restaging after 3-4 mo (endoscopy + imaging):
  - **CR**: observation
  - **PR**: restaging after 6-9 mo: if not CR→ 20 Gy
  - **PD**: 20 Gy





A similar study (4 Gy + additional 12 Gy if needed) is ongoing for all Stage 1-2 MZL (NCT05929612)

Gunther J et al. Lancet Haemat 2024

The future of treatment of MZL: conclusions

- RR MZL *cBTKi-refractory* is an unmet need: ncBTKi, BsAbs, Liso-cel, ADC, BTK degraders
- Liso-cel is the first CAR T-cell approved by FDA for 3L+ MZL (91% PET- CR, 2y PFS 85.7%)
- BsAbs (odronextamab) are highly efficacious in 3L+ MZL and are currently tested in 2L+ in association with Len (Olympia-5, MARSUN)
- Preliminary data of ADC (loncastuximab) and BTK degraders (BGB-11673) are encouraging
- Preliminary results of BaAbs (mosunetuzumab) ±Len in 1L are promising
- BTKi + anti-CD20 are promising in 1L, especially in SMZL (MALIBU, RITZ)
- Need to design large randomized trials in 1L advanced EMZL and NMZL (BsAbs +X)
- Risk-adapted strategies with ultra-low dose RT are promising in localized disease

Acknowledgments

Ematologia, Policlinico (Milano)

Alessandro Bosi
Cecilia Fidanza
Nicolò Rampi
Francesca Gaia Rossi
Maria Goldaniga
Francesco Passamonti

FONDAZIONE ITALIANA LINFOMI

Luca Arcaini *(Pavia)*
Stefano Luminari (*Reggio Emilia*)
Annarita Conconi *(Aviano)*
Marzia Varettoni *(Pavia)*
Candida Vitale *(Torino)*
Simone Ferrero *(Torino)*
Annamaria Frustaci *(Milano Niguarda)*
Andrès JM Ferreri *(Milano HSR)*
Elena Flospergher *(Milano HSR)*
Marco Brociner *(Varese)*
Guido Gini *(Ancona)*