Marginal Zone Lymphoma Biology and Rational Targets

Mini Symposium on MZL
23rd International Ultmann Chicago Lymphoma Symposium

Juan P. Alderuccio, MD

April 11th, 2026

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Designated Cancer Center

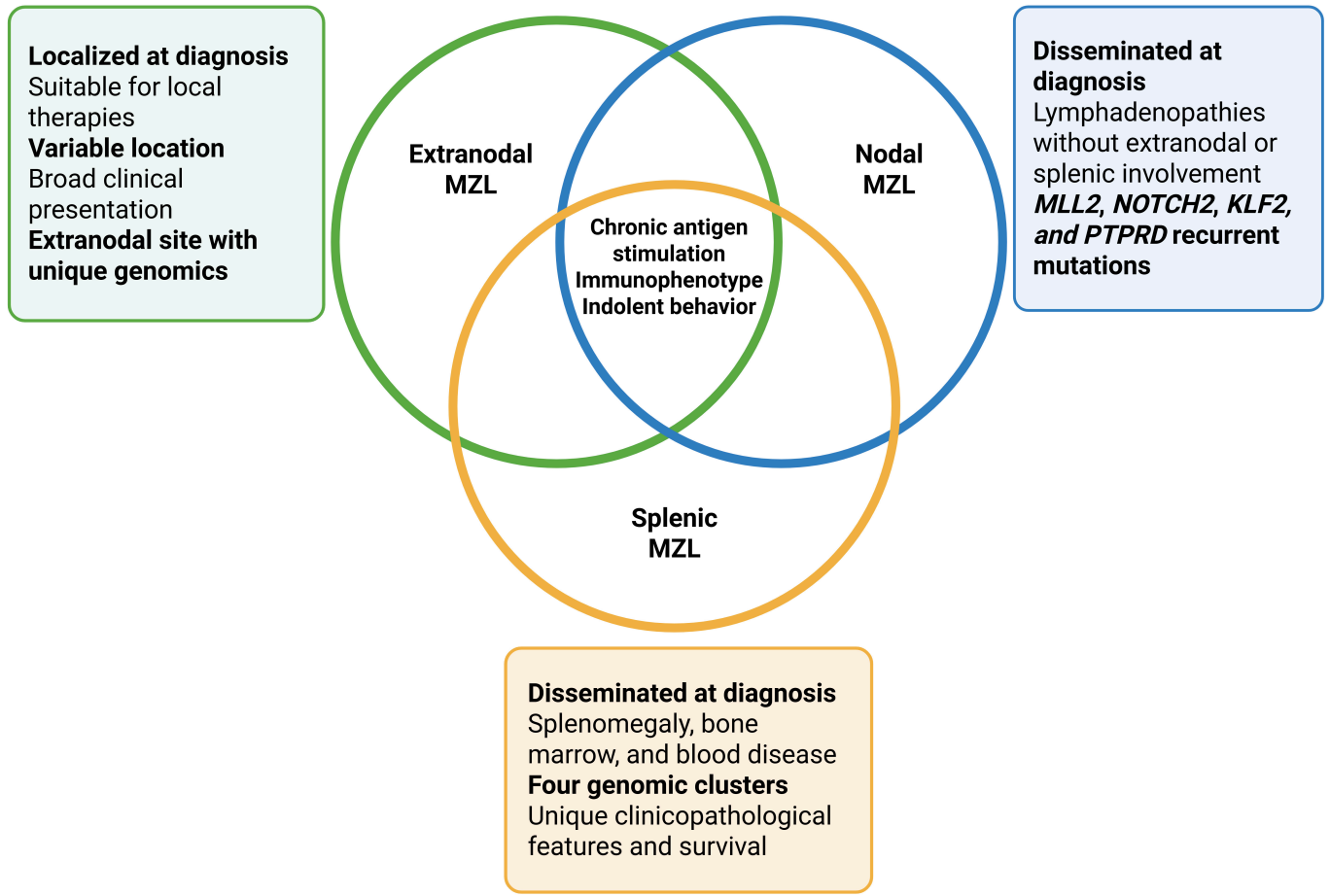
@SylvesterCancer

Disclosures

- **Consulting**: Novartis, ADC Therapeutics, Regeneron, Eli Lylli, AbbVie, Genmab, Natera, and Tanabe Pharma Corporation.
- **Research support**: ADC Therapeutics, Genmab, BeOne, Genentech, and Natera.

Marginal Zone Lymphoma

- MZL represents the second most common subgroup of indolent NHL.
- MZLs are characterized by a similar immunophenotype and indolent behavior with a median overall survival above 8 years
- MZL subtypes are associated with different clinical courses, treatment responses, and toxicity



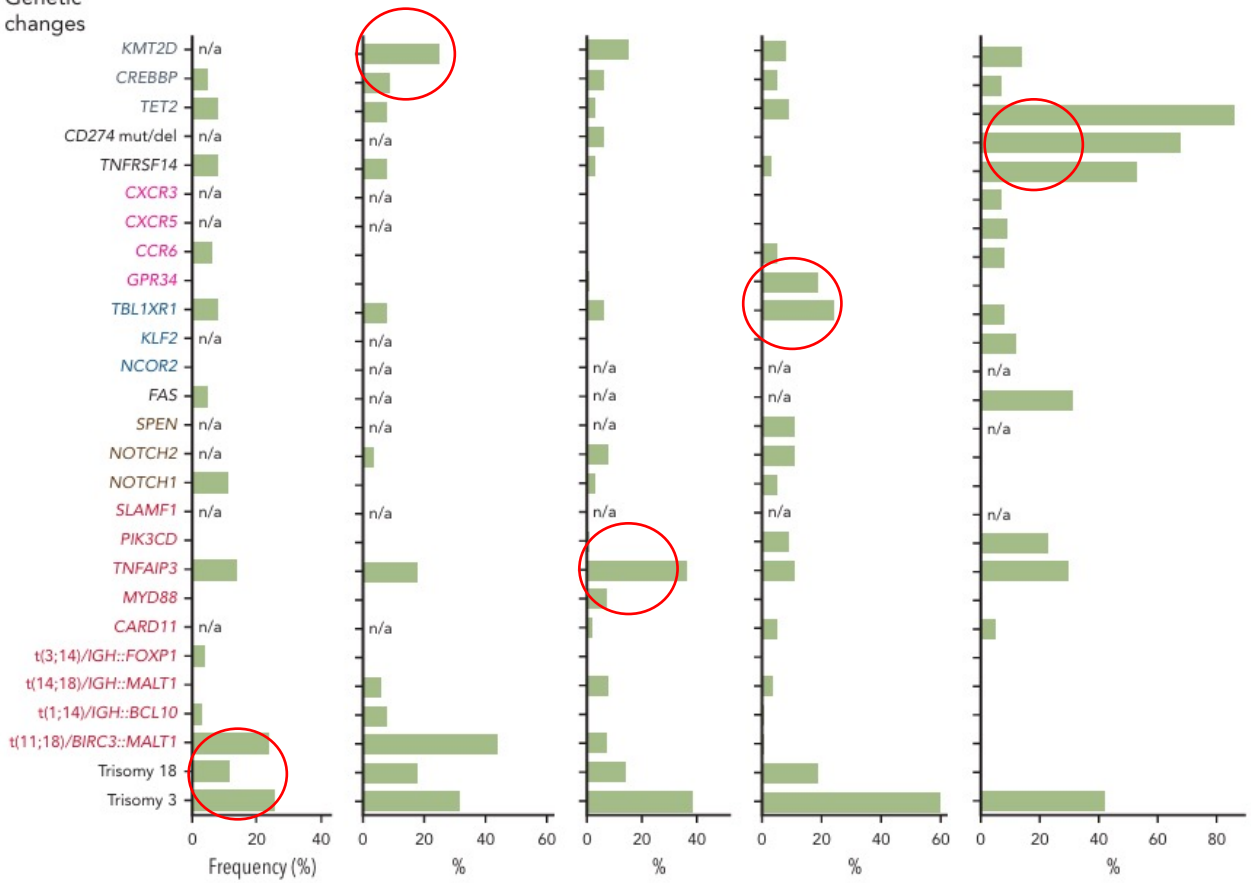
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Thieblemont C, et al. Blood 2026
Alderuccio JP & Noy A. Blood 2026

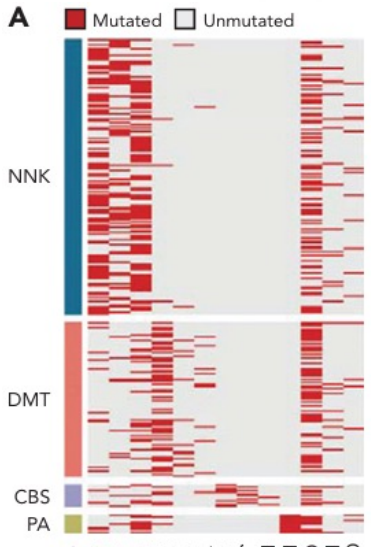
Extranodal MZL

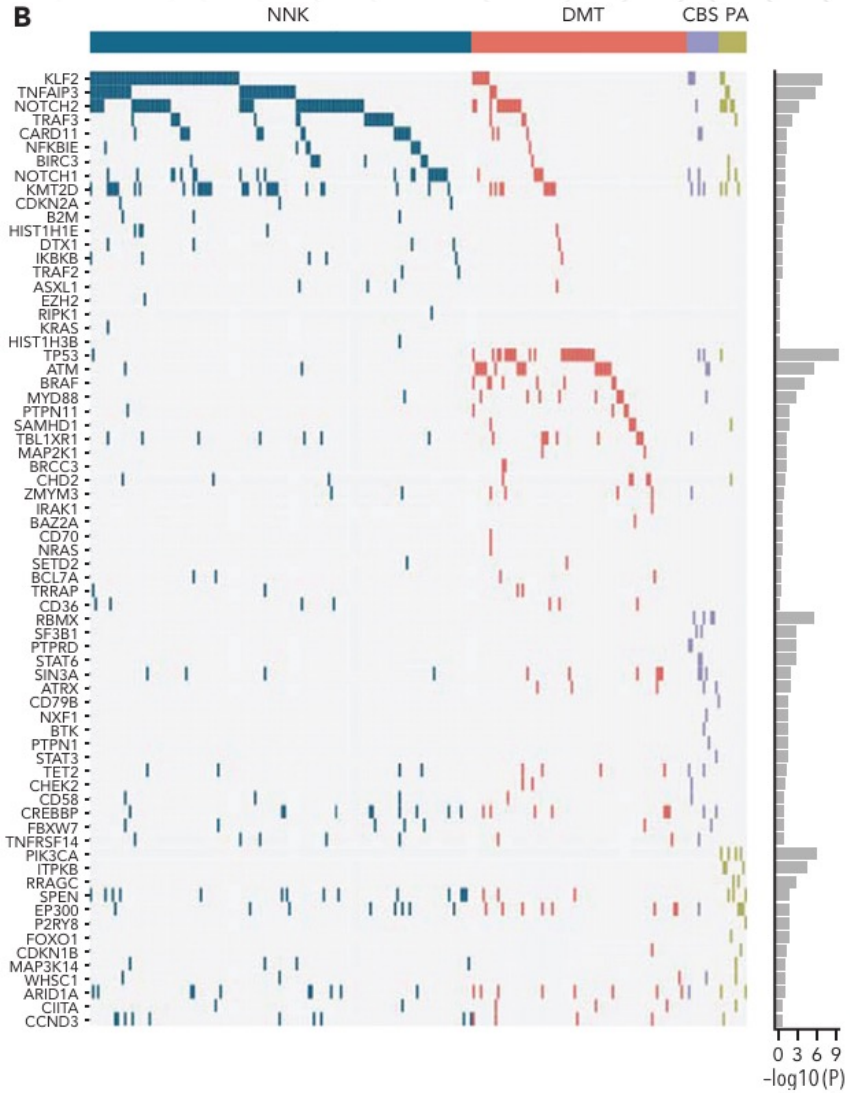
	Stomach	Lung	Ocular adnexa	Salivary gland	Thyroid
Aetiology	Helicobacter pylori	Achromobacter xylosoxidans?	Chlamydia Psittaci?	Sjögren syndrome	Hashimoto thyroiditis
IG gene usage	IGHV3-7 IGHV1-69 IGHV1-2 IGHV3-23	IGHV4-34	IGHV4–34 (18%) IGHV3-7 (9%) IGHV3-23 (14%) IGHV3-30 (12%)	IGHV1-69 (55%) IGHV3-7 (15%) IGHV4-59 IGHV3-30	IGHV3-23 (24%) IGHV4-61 (10%) IGHV4-34 (10%)

Genetic changes



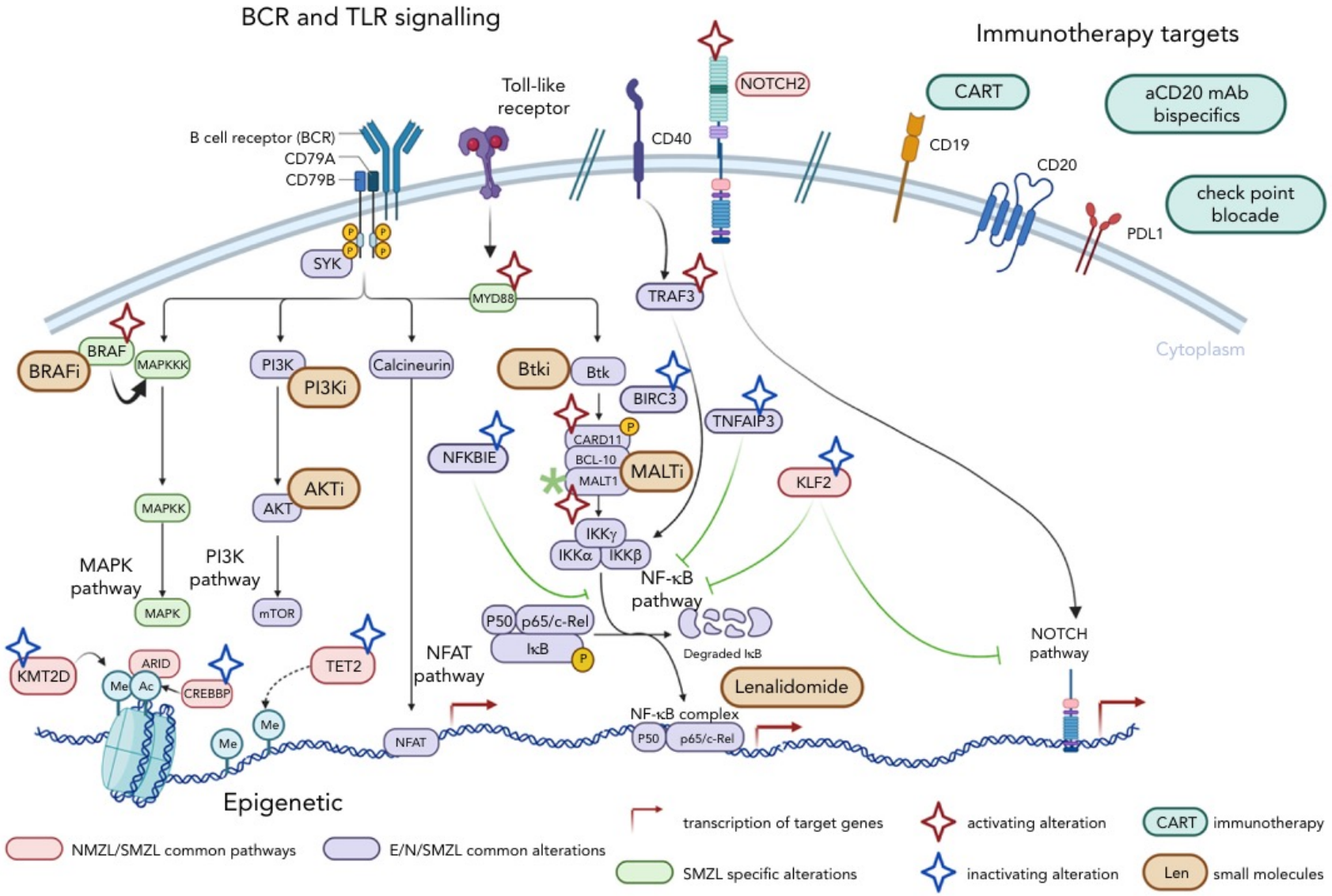
Splenic MZL





Qing-Du M. Blood 2025
Bonfiglio F, et al. Blood 2022

Targetable pathways in MZL

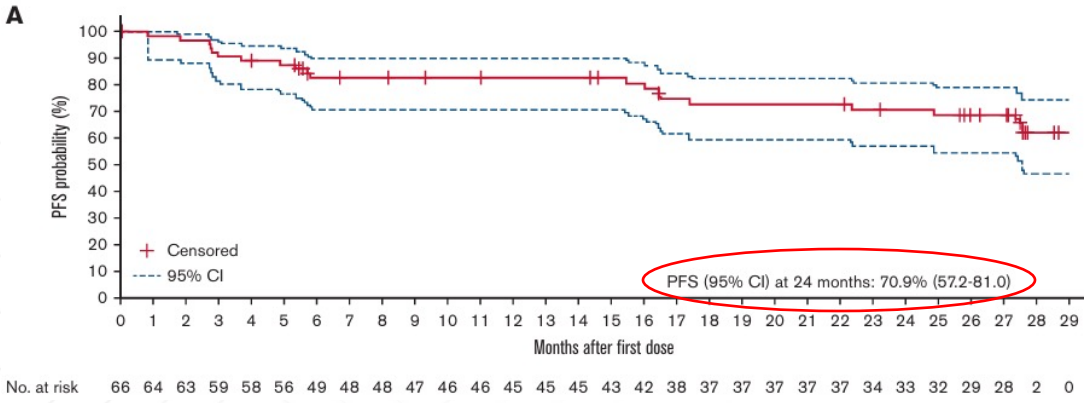


SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

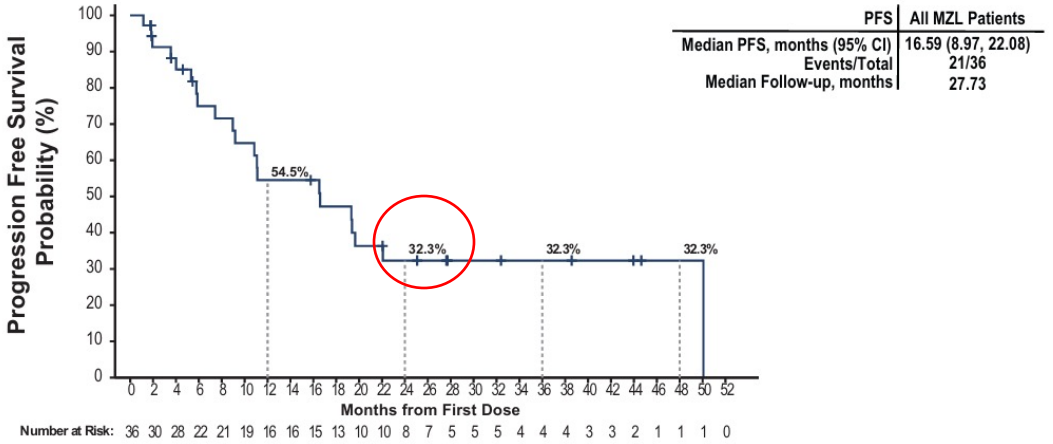
Thieblemont C, et al. Blood 2026

BTK inhibitors

Zanubrutinib



Pirtobrutinib



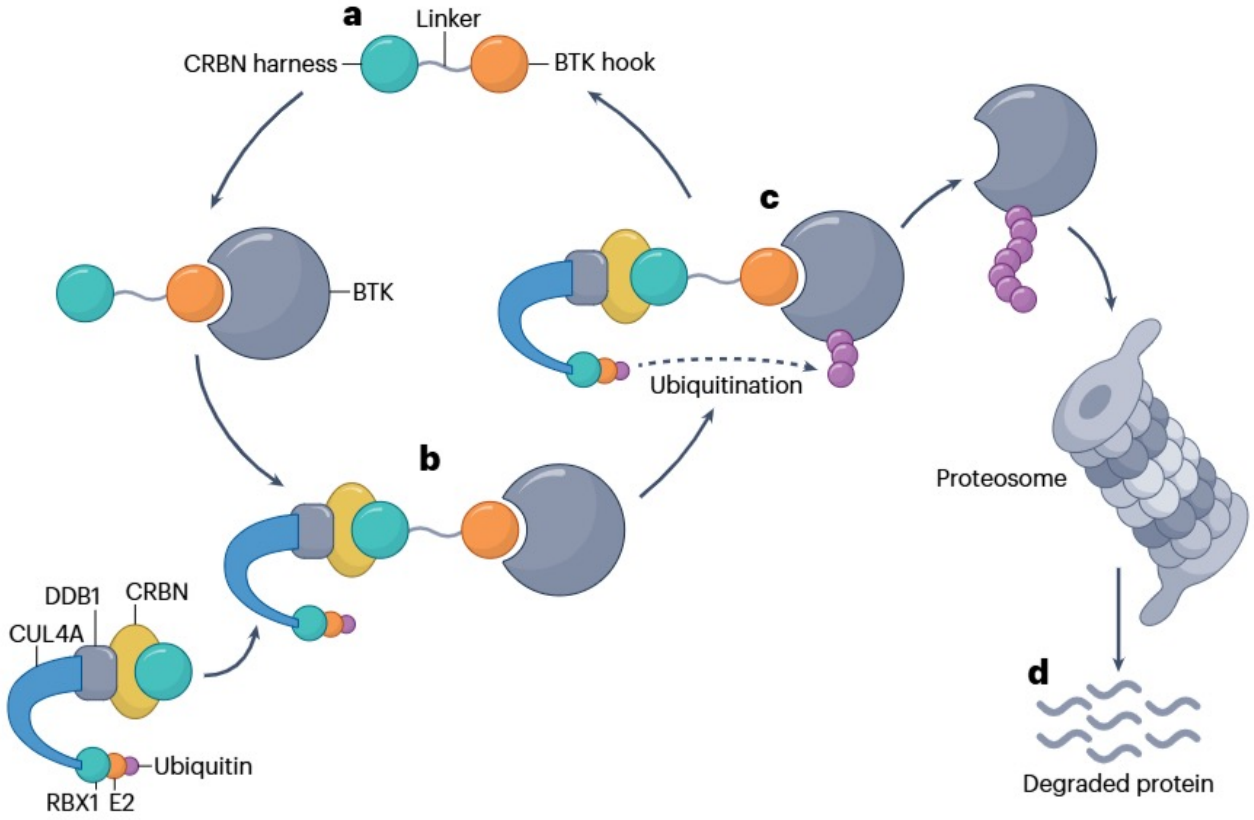
	Zanubrutinib	Pirtobrutinib
ORR	68.2%	55.6%
• **CR**	25.8%	8.3%
• **PR**	42.4%	47.2%
2-year PFS	70.9%	32.3%
2-year OS	85.9%	77%

72.2% with prior BTKi exposure

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Opat S, et al. Blood Adv 2023
Patel K, et al. Blood Adv 2026

BTK degraders



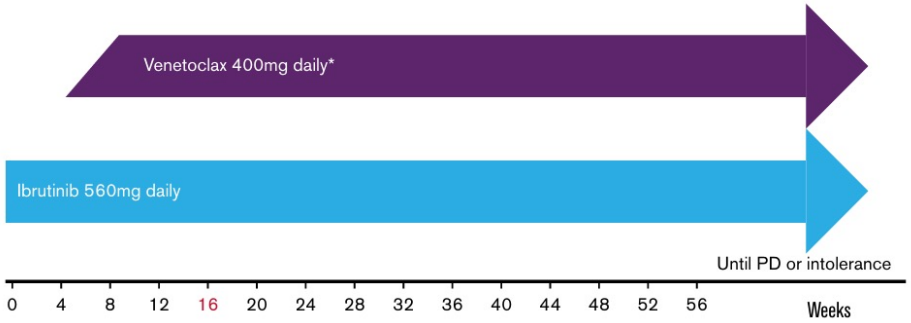
BGB-16673 (n= 36)	
Efficacy	
ORR	54.8%
CR	16.1%
Adverse Events	
Major hemorrhage	8.3%
Grade 1 A-fib	2.8%
Grade 3 febrile neutropenia	2.8%
TEAEs-related discontinuation	13.9%

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

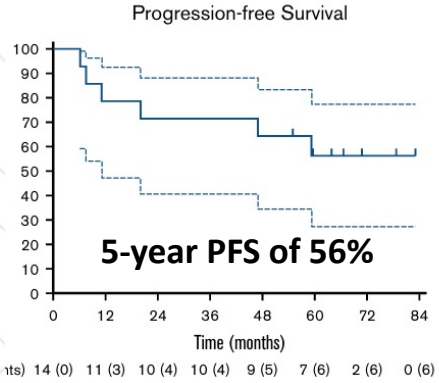
Stanchina MD, et al. Nat Rev Clin Oncol 2024
Guieze R, et al ASH 2025

BCL2 inhibitors

Venetoclax



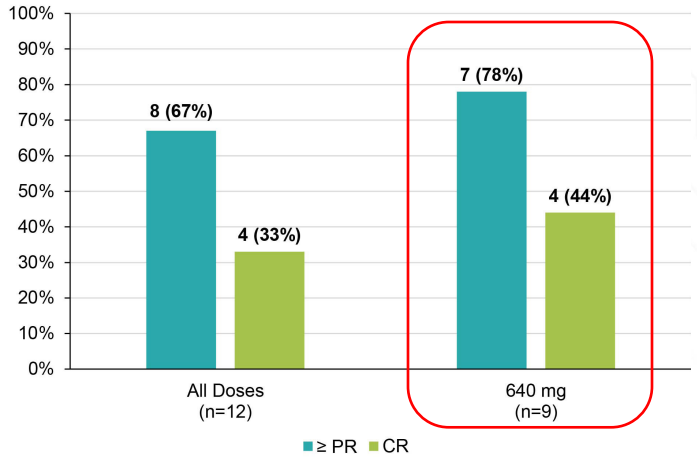
Week 16 efficacy assessment (n= 15)	
ORR	79%
• **CR**	43%
• **PR**	36%



Grade ≥3 TEAEs
- Neutropenia 40%
- Hypertension 20%
- Pneumonia 20%
- Febrile neutropenia 20%

Sonrotoclax

- **N= 13**
- **Median number of prior therapies 1 (range 1-3)**
- **Four patients previously treated with BTKi**
- **RP2D: 640mg**



Grade ≥3 TEAEs:
- Neutropenia (15%)
- Febrile neutropenia (15%)
- TLS (15%)

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Handunnetti S, et al. Blood Adv 2026
Tedeschi A, et al. ASH 2023

Mosunetuzumab

MorningSun Study: 1L MZL

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

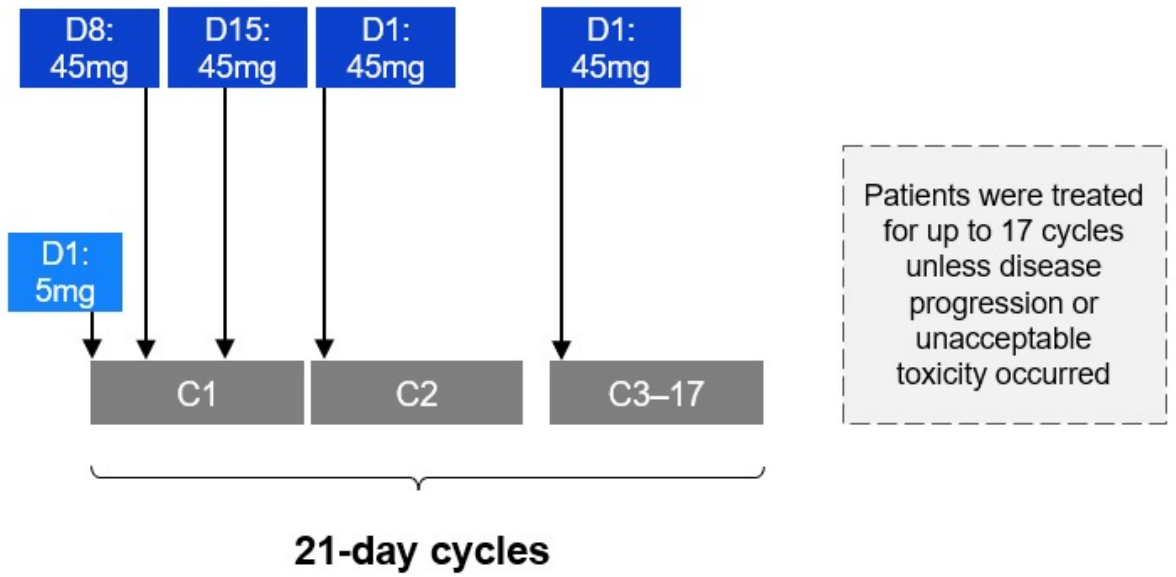
CRS mitigation

- 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

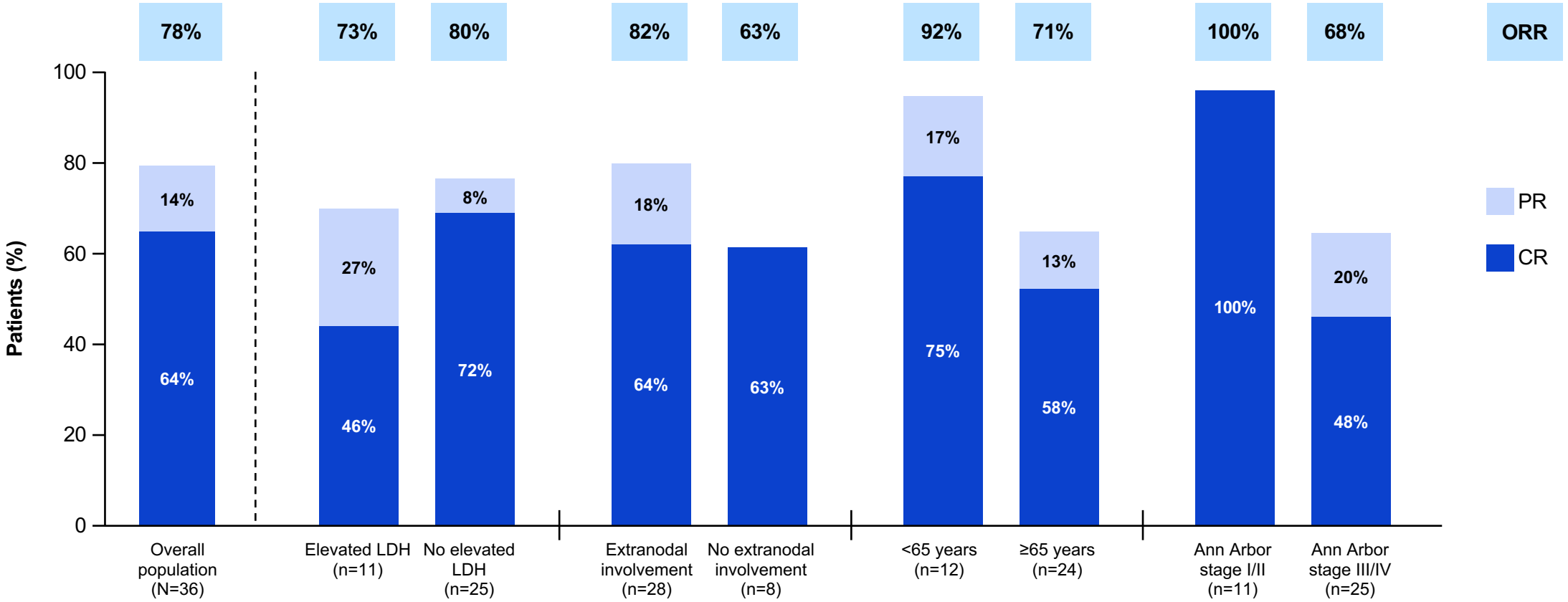


*Dexamethasone (20mg) or methylprednisolone (80mg); premedication with oral acetaminophen or paracetamol and/or diphenhydramine could also be administered prior to administration of mosunetuzumab.
C, cycle; CRS, cytokine release syndrome; D, day; DOCR, duration of complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; INV, investigator; MALT, mucosa-associated lymphoid tissue; ORR, objective response rate; PFS, progression-free survival.

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Burke J, et al. SOHO 2025

Efficacy: Best response rates

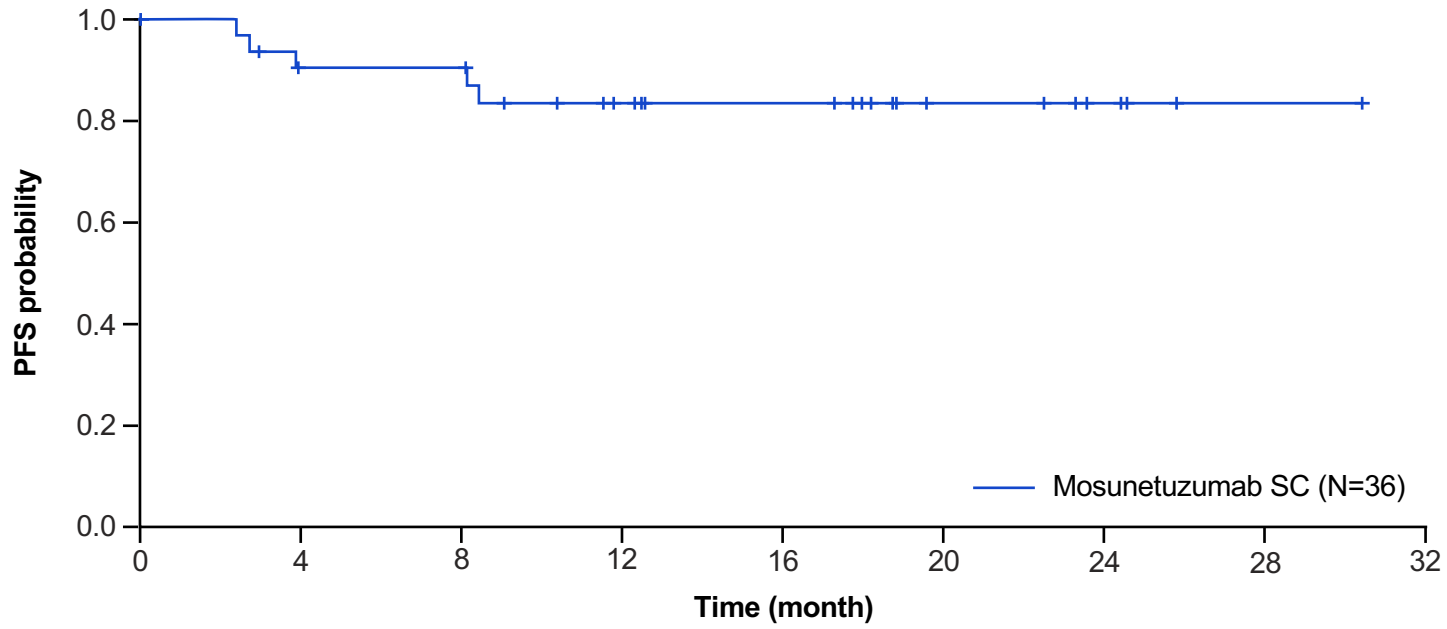


CR rates across high-risk subgroups were consistent with the overall population

CCOD: February 10, 2025.
CR, complete response; PR, partial response.

Burke J, et al. SOHO 2025

Efficacy results: PFS



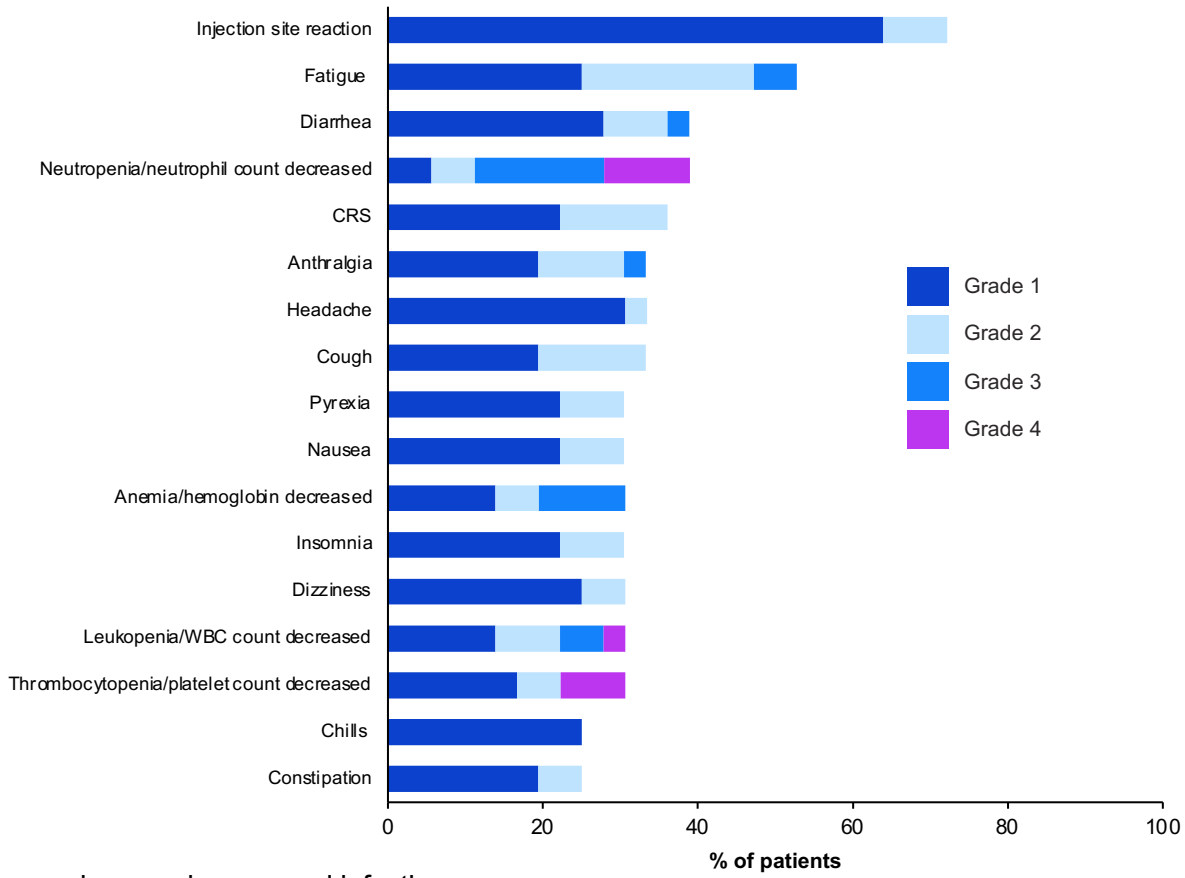
	N=36
Median PFS, months (95% CI)	NR (NE–NE)
6-month event-free rate, % (95% CI)	90.5 (73.4–96.8)
12-month event-free rate, % (95% CI)	83.6 (64.8–92.8)

CCOD: February 10, 2025.
NR, not reached.

Safety profile: Overview

n (%)	N=36
Any grade AE	36 (100)
Grade 3/4 AEs	23 (63.9)
Most common Grade 3/4 AEs (≥10%)	
Neutropenia/neutrophil count decreased	10 (27.8)
Anemia	4 (11.1)
Grade 5 AEs	0
Select AEs of interest	
ICANS	0
Serious AEs*	14 (38.9)
AE leading to mosunetuzumab discontinuation†	6 (16.7)

Most common AEs (≥25% incidence)

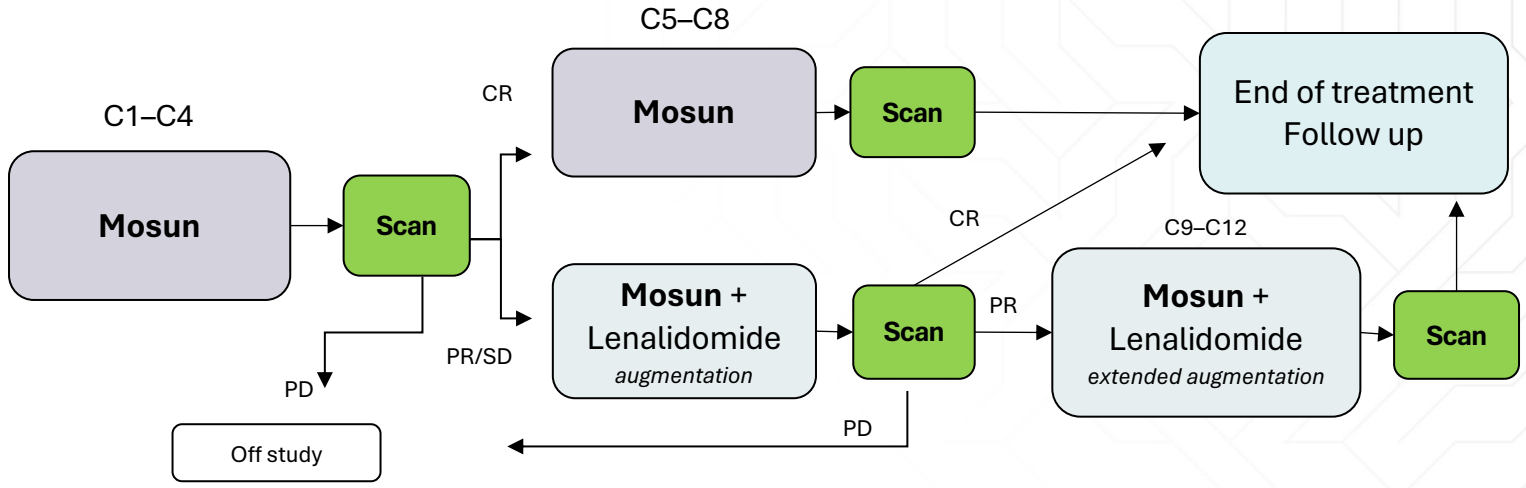


CCOD: February 10, 2025.

*Anemia, hemolytic anemia, necrotic lymphadenopathy, COVID-19, COVID-19 pneumonia, sepsis, norovirus, wound infection, femur fracture, platelet count decreased, colon adenocarcinoma, confusional state, pleural effusion, respiratory failure (n=1 [2.8%] each); CRS (n=3 [8.3%]); some patients may have experienced more than one AE. †Hemolytic anemia, sinusitis, femur fracture, platelet count decreased, respiratory failure, maculopapular rash (n=1 each). COVID-19, coronavirus disease 2019; ICANS, immune cell-associated neurotoxicity syndrome; WBC, white blood cell.

Mosunetuzumab with response-driven lenalidomide augmentation

- 52 patients from 3 centers
- **Key eligibility criteria:**
  - Age ≥18 years; performance status: ECOG 0-2
  - CD20+ FL (G1-3A) or MZL (any subtype)
    - **FL**: GELF criteria
    - **MZL**: need to treat per investigator
  - No prior systemic therapy for lymphoma
  - No autoimmune disease, no CNS lymphoma
  - No immunosuppressive therapy, EBV or CMV viremia
  - No other concurrent malignancy, HIV,
  - No severe COPD, other severe comorbidities
  - ANC ≥ 1 x10^9/L, Hgb ≥ 9 g/dL, platelets ≥75 x10^9/L
- **Primary endpoint:** **CR at end of therapy**
    - Lugano or International SMZL criteria;
    - gastric MALT lymphoma: confirmed with endoscopy
  - Toxicity rates
  - PFS; POD24, OS, DOR/CR
  - Exploratory biomarkers



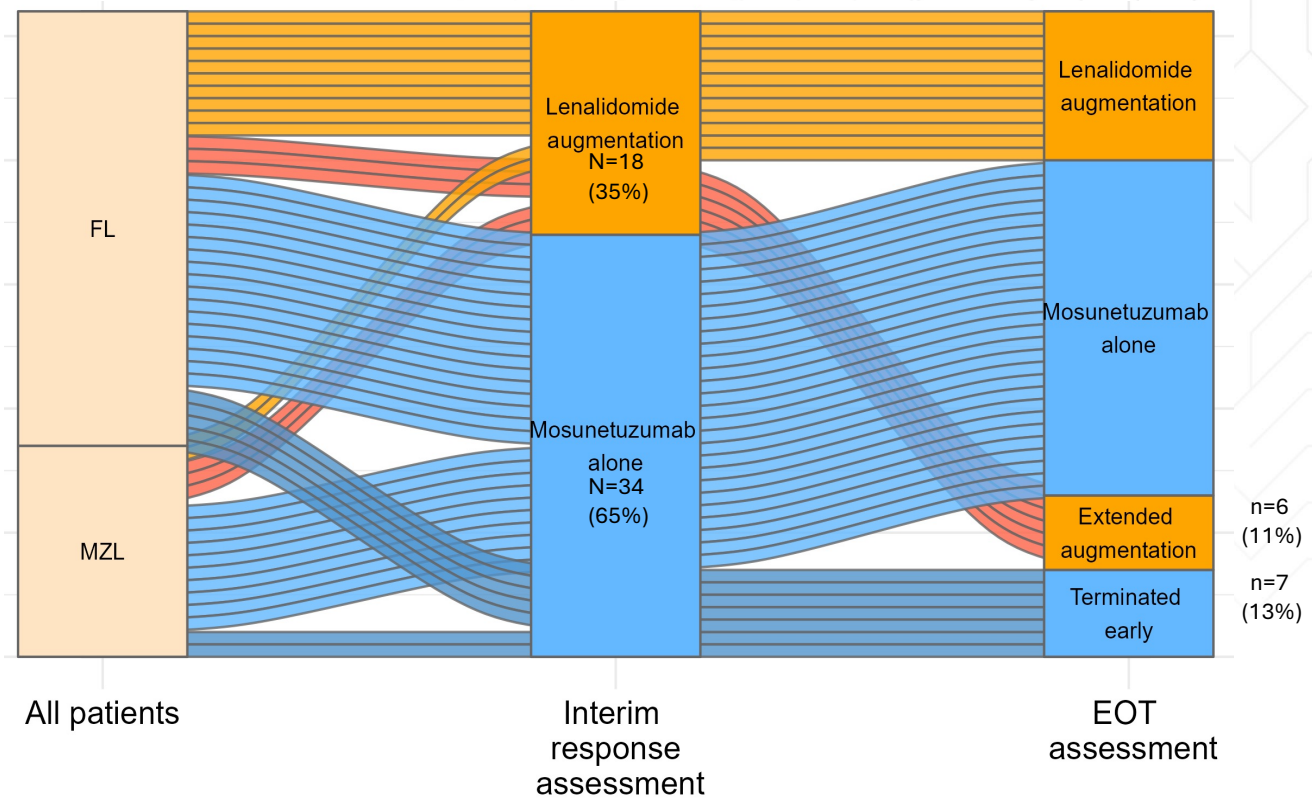
- **Mosunetuzumab:**
  - Subcutaneous
  - Cycle 1 step-up dosing:
    - Day 1: 5 mg, D8/15: 45 mg
  - Cycle 2-8 (or 12): Day1, 45 mg
  - Dexamethasone premedication in C1, C2
- **Lenalidomide:**
  - Response-adapted after C4
  - 10 mg daily continuous dosing
  - Optional extension through C12

- **Primary hypothesis**: 80% power, one-sided a 0.047, n=52 (two-stage design)
  - CR at EOT >53% using RELEVANCE CT criteria
  - PET CT criteria for EOT response reporting

Olszewski A, et al. ASH 2025

Results: patient characteristics

	N = 52
Age (median, range)	65 (30-89)
Sex	Male 50%, Female 50%
Histology:	
• **FL**	35 (67%)
• G1/2	• 25 (50%)
• G3A	• 4 (8%)
• Unspecified	• 5 (10%)
• **MZL**	17 (33%)
• MALT MZL	• 8 (15%)
• NMZL	• 6 (12%)
• SMZL	• 3 (6%)
Race/ethnicity	
• White non-Hispanic	42 (81%)
• Hispanic (any race)	5 (10%)
• Black	3 (6%)
• Asian	2 (3%)
ECOG Performance status:	
0	26 (50%)
1	24 (46%)
2	2 (4%)

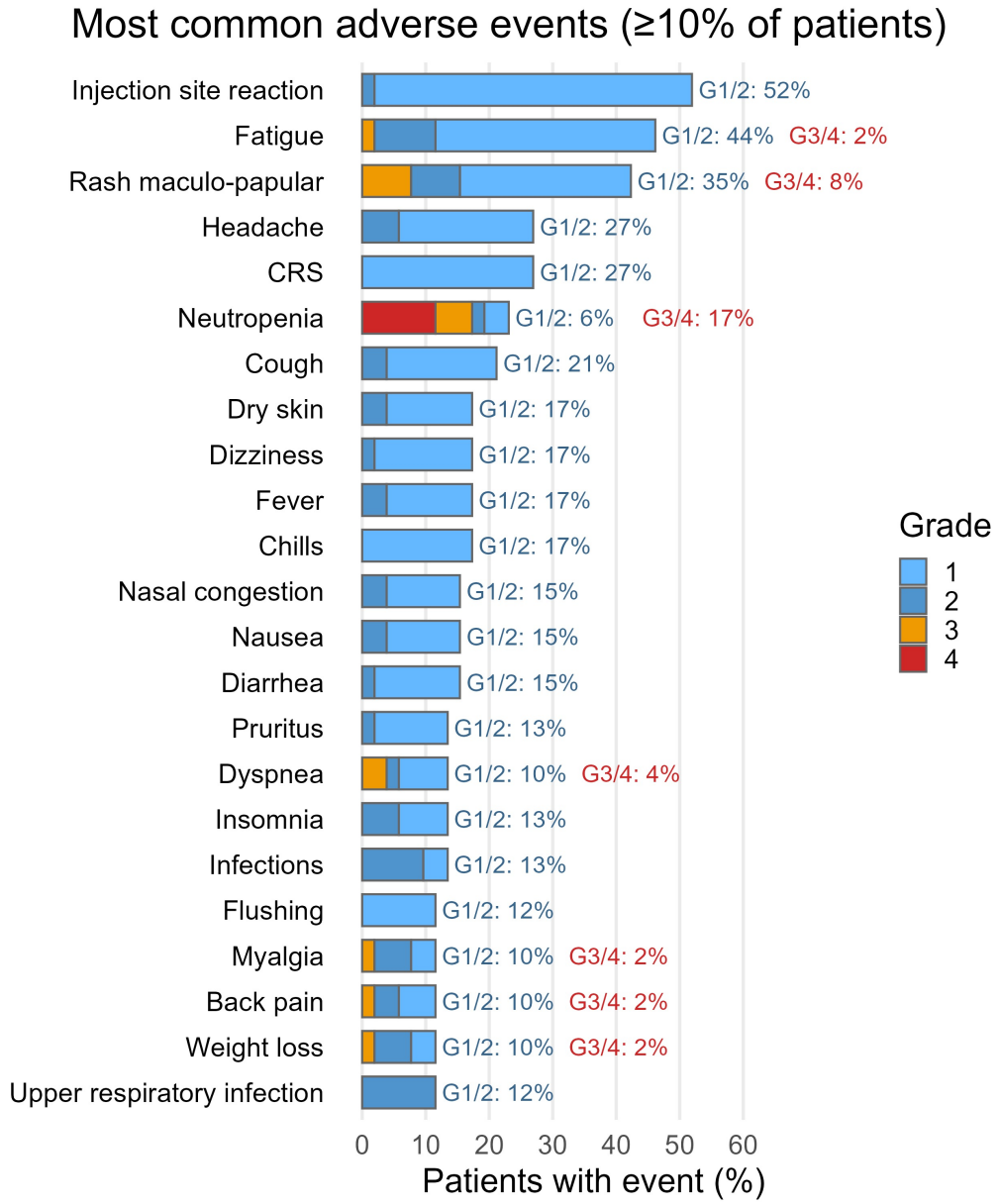


Flow of patients on study with response-adapted lenalidomide augmentation

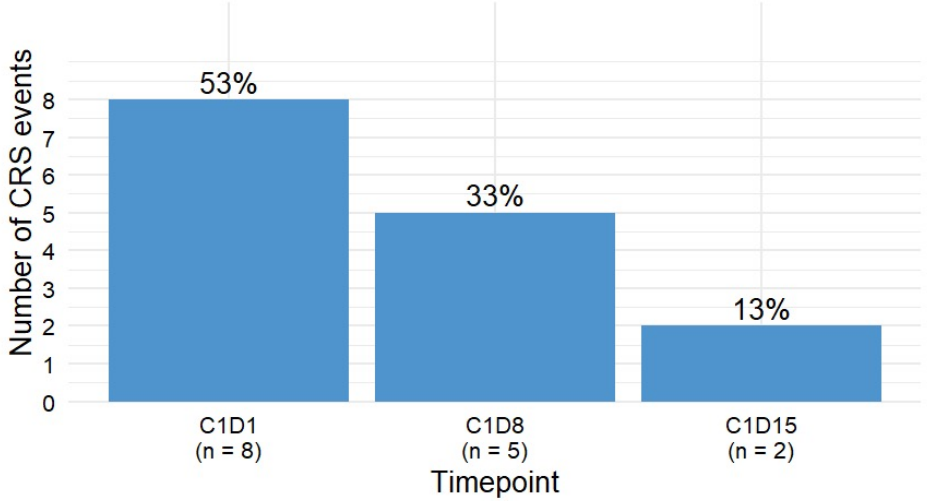
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Olszewski A, et al. ASH 2025

Safety



All CRS events occurred during Cycle 1 of study treatment



CRS was more common in SMZL and associated with a higher baseline absolute lymphocyte count

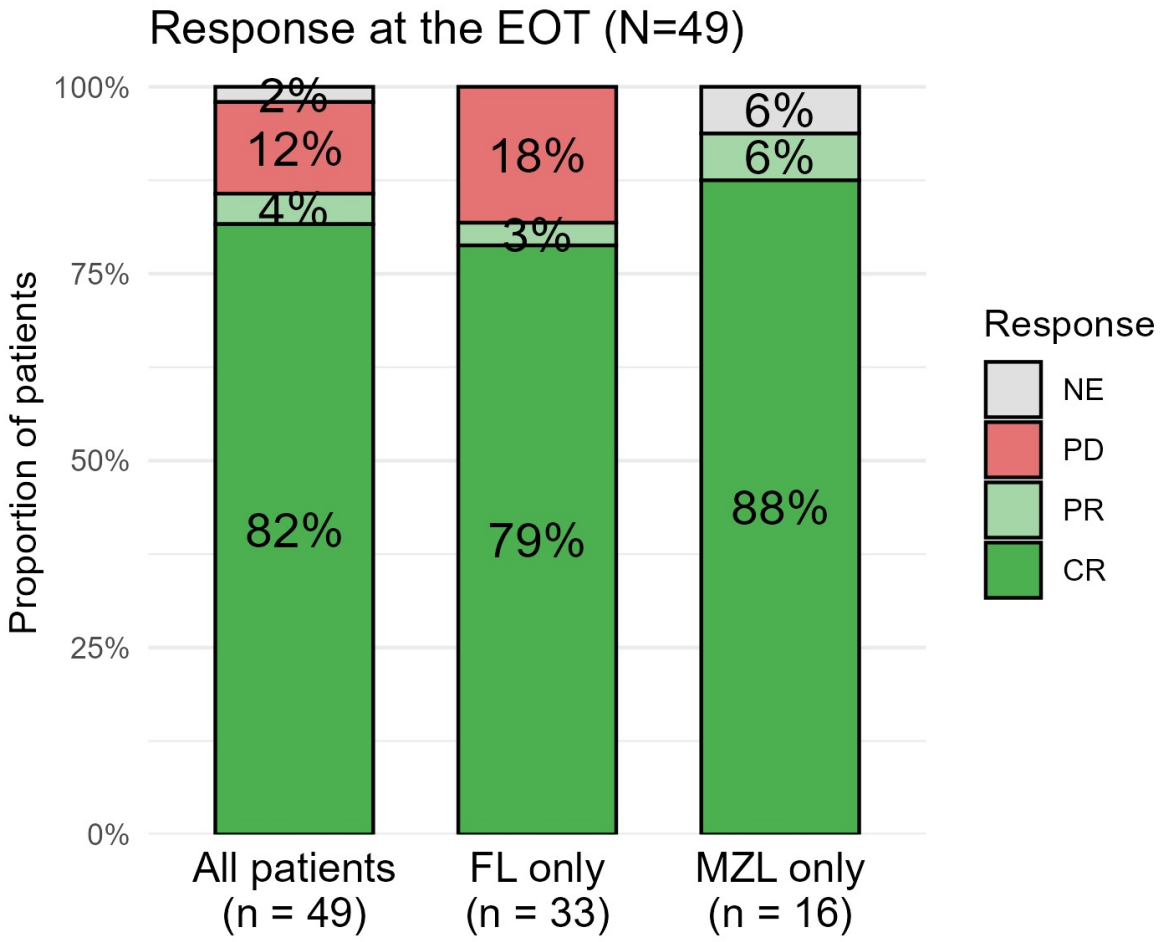
Notable infections:

- **n=1** COVID-19 pneumonia
- **n=2** *Pneumocystis jirovecii* pneumonia
- **n=3** *Herpes zoster* infections

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

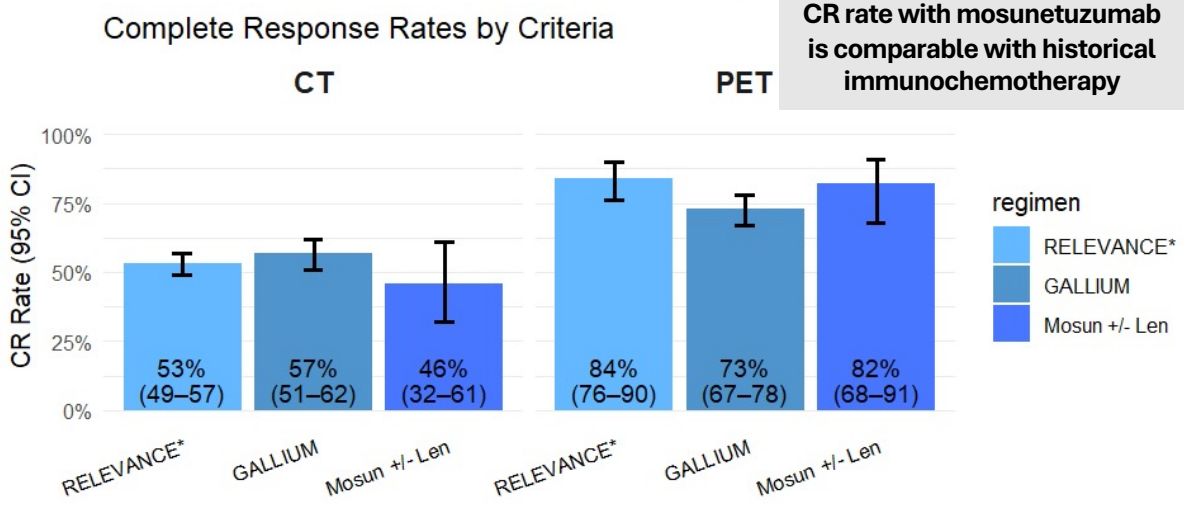
Olszewski A, et al. ASH 2025

Efficacy



n=3 patients still on therapy: 2 with CR, 1 with PR

	Response rate (95%CI)	CR rate (95%CI)
All patients	**86%** (73–94%)	**82%** (68–91%)
FL	82% (65–93%)	79% (61–91%)
MZL	94% (70–100%)	88% (62–98%)



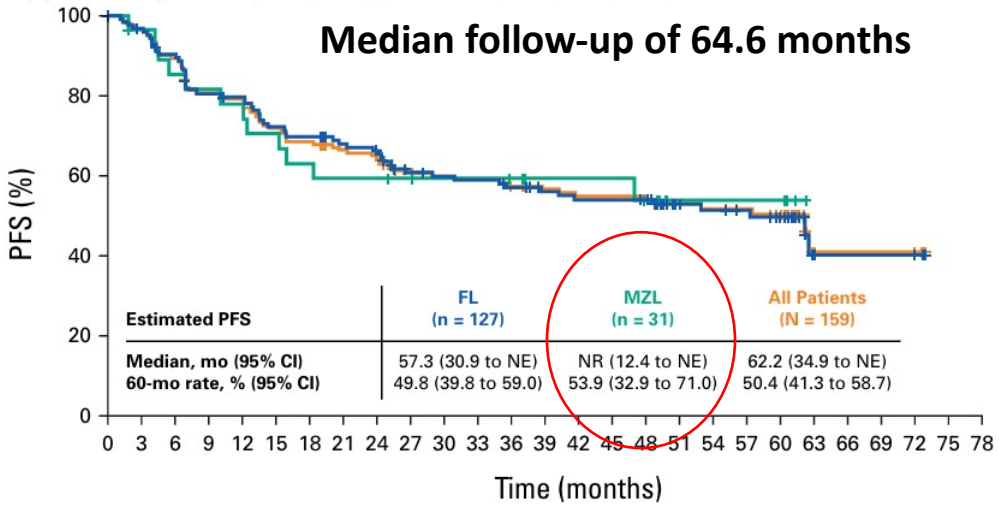
CR rate with mosunetuzumab is comparable with historical immunochemotherapy

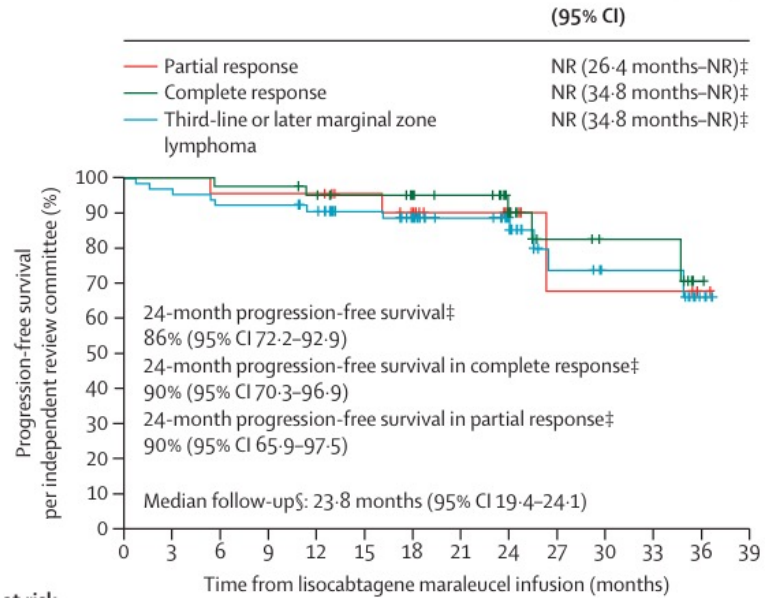
* only subset of RELEVANCE patients (n=141) had PET available

Olszewski A, et al. ASH 2025

CAR T-cell

	Axi-cel			Liso-cel
	FL (n= 127)	**MZL (n= 31)**	All pts (n= 159)	**MZL (n= 66)**
ORR	94%	**77%**	90%	**95%**
CR	79%	**65%**	75%	**62%**
PR	15%	**13%**	14%	**33%**





Neelapu S, et al. Blood 2024
Neelapu S, et al. J Clin Oncol 2025
Palomba L, et al. Lancet 2026

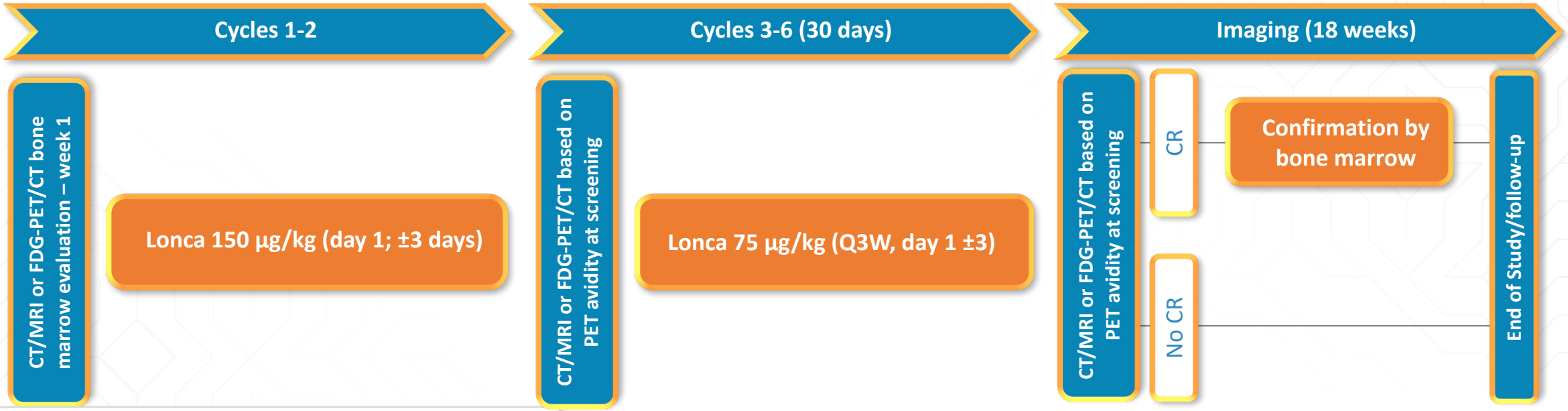
Adverse Events				
	Axi-cel*		Liso-cel	
AE	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
CRS	82%	7%	76%	4%
Neutropenia	36%	33%	75%	72%
Thrombocytopenia	20%	15%	39%	21%
Anemia	39%	25%	31%	18%
Neurotoxicity	59%	19%	33%	4%
Infections		18%		16%
HLH		-		4%
Secondary malignancies		tMDS/tAML: 7% (n= 11)		12% AML (n= 2), MDS, TCL (n= 1)

5-year nonrelapse mortality of 15%

**** Includes FL and MZL (n= 148)***

Jacobson C, et al. Lancet Oncol 2022
Neelapu S, et al. Blood 2024
Neelapu S, et al. J Clin Oncol 2025
Palomba L, et al. Lancet 2026

Loncastuximab tesirine



Select inclusion criteria

- Estimated enrollment: 50 participants
- R/R MZL previously treated with ≥ 1 line of systemic therapy
- Symptomatic
- Met predefined criteria for an MZL subtype
- POD24

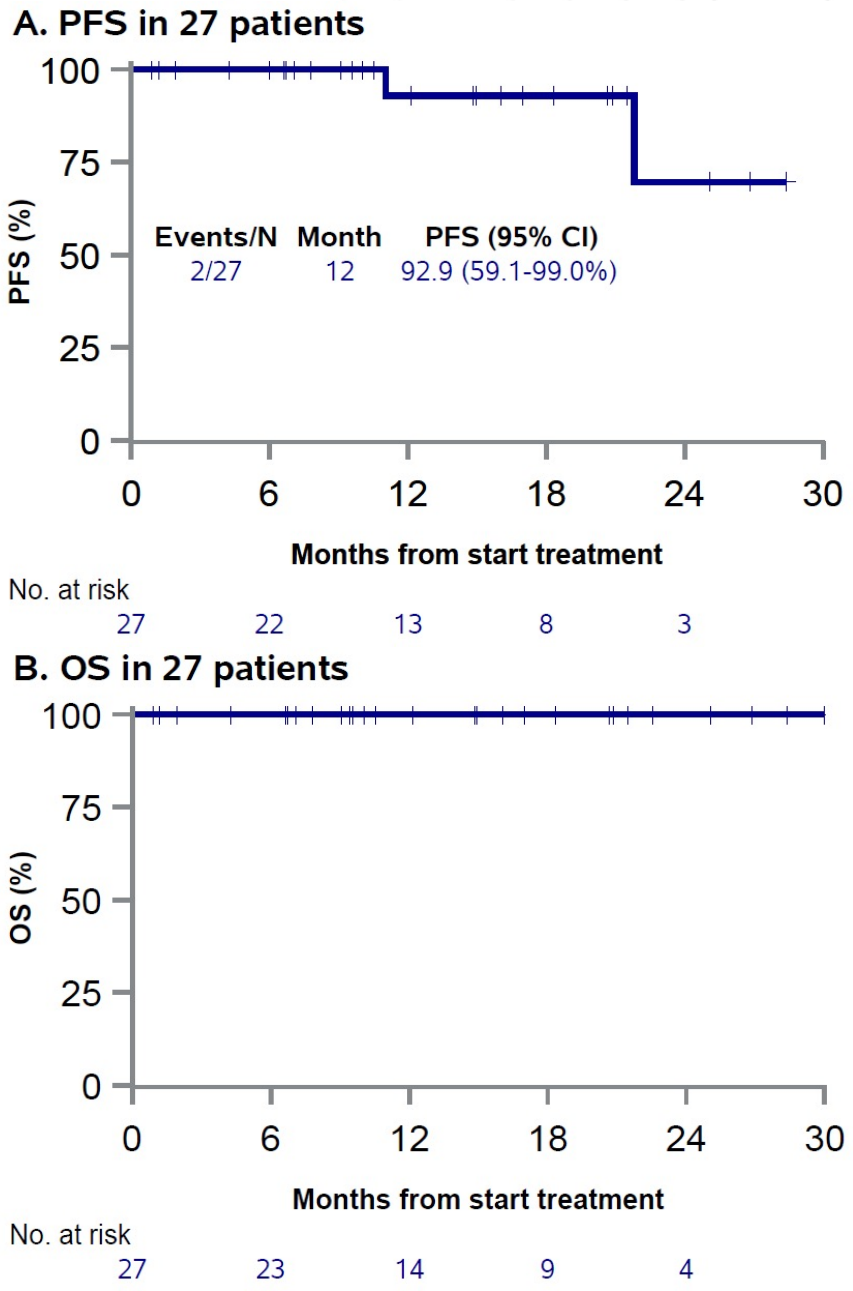
Study endpoints

- Primary endpoint: CR after 6 cycles based on Lugano 2014 criteria using PET-CT (if FDG avid at presentation) or MRI or CT (for nonavid disease)

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Lossos I, et al. ASH 2024.

Response and Safety (n= 26)		
	Response	
ORR	85%	
CR	69%	
	TEAEs	
	Any grade	**Grade ≥3**
Photosensitivity	68%	
Elevated LFTs	68%	22.7%
Infections	50%	13.6%
Pedal edema	4.5%	

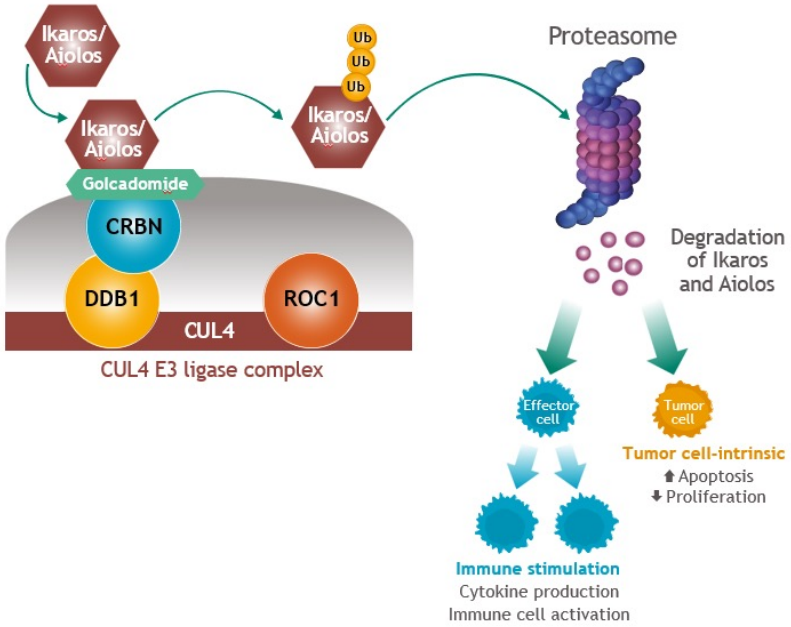


SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Lossos I, et al. ASH 2024.

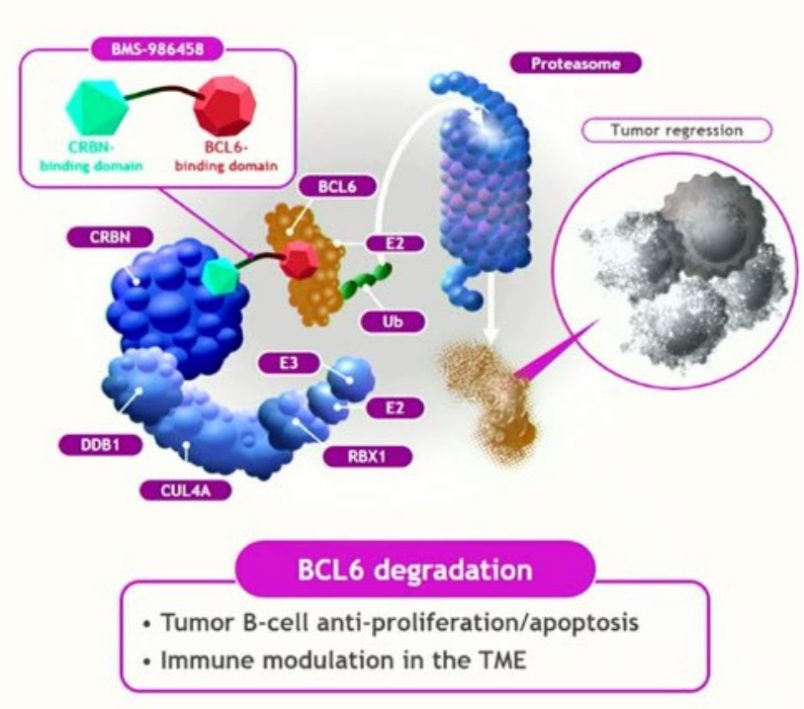
Novel agents in the pipeline

Golcadomide



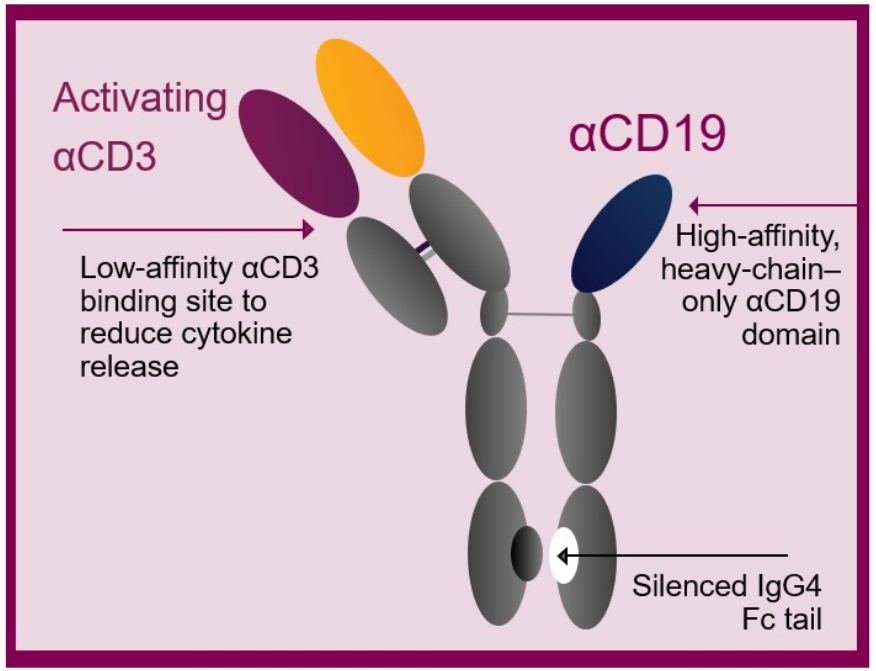
ORR: 83%
CR: 53%
Grade ≥3 neutropenia (48%)
Anemia (24%)
Thrombocytopenia (18%)

BMS-986458



ORR: 80%
CR: 40%
Arthralgia: 19.4%
Fatigue: 16%

Surovatamig



ORR and CR rate of 100%
Grade ≥3 neutropenia (20%)
CRS: 57%
Headache: 33%

Chavez JC, et al. ASH 2024
Morschhauser F, et al. ASH 2025
Hou JZ, et al. ASH 2025

Moving the needle in MZL

- **Recognition of MZL as a group of biologically and clinically heterogeneous entities**
  - Presentation, treatment response, and toxicity
- **Defined criteria for treatment initiation; not only relapsed/refractory status**
  - Opportunity to identify factors associated with shorter survival
- **Exclusion of primary cutaneous extranodal MZL**
- **Development of robust surrogate endpoints (e.g., CR24)**
  - IELSG-19: 5-yr EFS in the rituximab arm of 50%
- **Lack of robust data on HRQOL from recent studies**
  - Inclusion in the decision-making process
- **Time-limited treatment strategies**
  - Combination of antiCD3xCD20 bispecific antibodies with BTKi or golcadomide
- **ctDNA may help in the discovery of druggable pathways**

Thank you!

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Designated Cancer Center