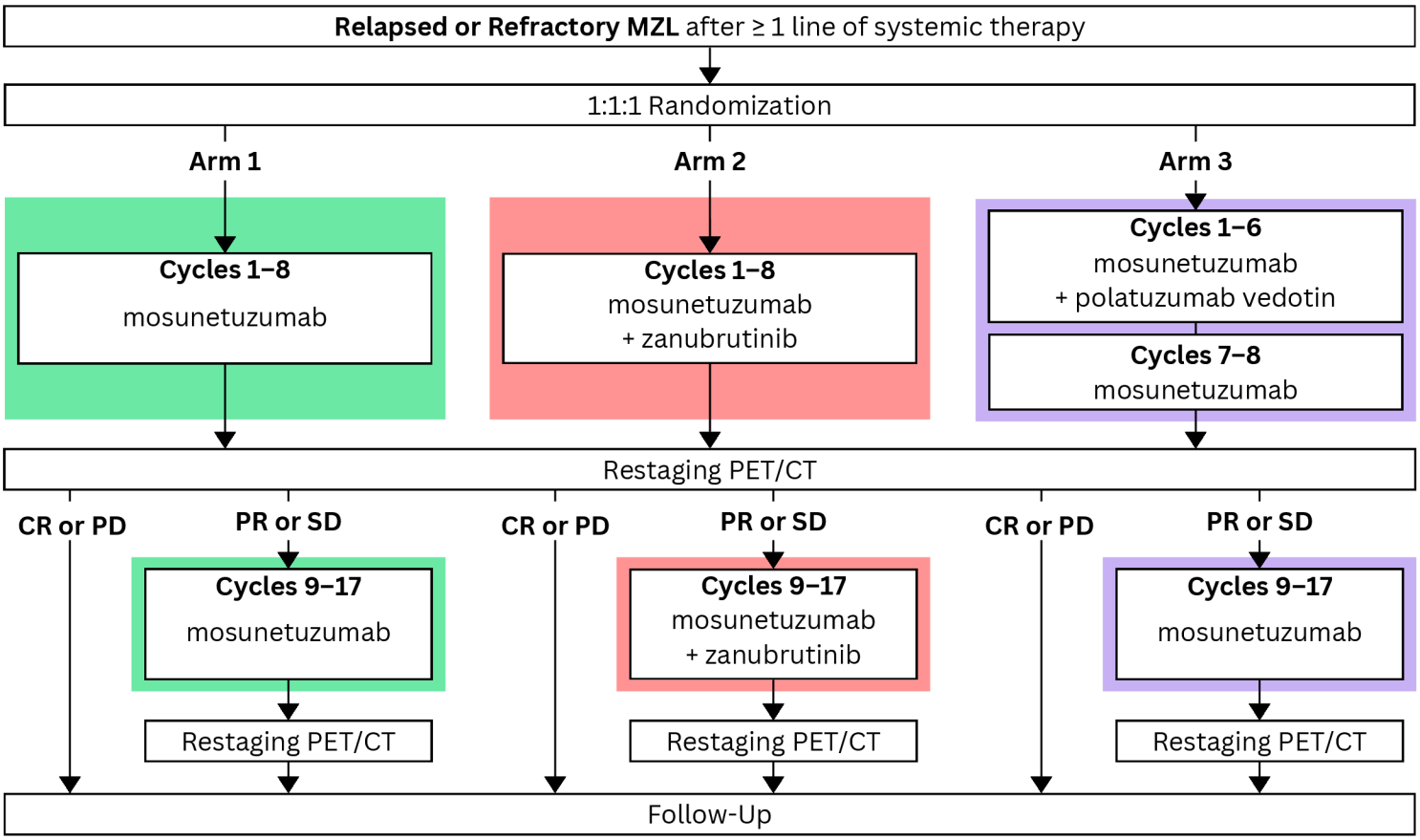
S2506 MOZART MZL: A Randomized Phase II Study Evaluating Mosunetuzumab Alone and in Combination with Either Zanubrutinib or Polatuzumab Vedotin for the Treatment of Participants with Relapsed/Refractory Marginal Zone Lymphoma

SCHEMA



TREATMENT OVERVIEW

ARM	AGENT	DOSE	ROUTE	CYCLES 1–8 [a]	CYCLES 9–17
Arms 1, 2 & 3	mosunetuzumab	45 mg [b]	SQ	Day 1 [c]	Day 1
Arm 2	zanubrutinib	320 mg	PO	Daily	Daily
Arm 3	polatuzumab vedotin	1.8 mg/kg	IV	Day 1 [d]	N/A

[a] One cycle = 21 days.
[b] Cycle 1 Day 1 mosunetuzumab dose is 5 mg.
[c] Cycle 1 Days 8 and 15 administer 45 mg of mosunetuzumab. Cycle 2 and beyond 45 mg administered on Day 1 only.
[d] Polatuzumab vedotin only given for Cycles 1–6.

KEY ELIGIBILITY

- ≥ 18 years old.
- Zubrod Performance Status 0–2.
- Histologically diagnosed CD20+ MZL. Splenic, nodal, and extranodal MZL subtypes allowed. Cutaneous-only MZL and gastrointestinal-only MZL (if only evaluable by endoscopic methods) not allowed.
- No prior exposure to polatuzumab vedotin.
- Must have relapsed/refractory MZL after ≥ 1 line of prior CD20-directed systemic therapy (monotherapy or in combination with chemotherapy or lenalidomide).
  - Prior antibiotic and radiation treatments for localized MZL disease allowed, but do not count as one line of systemic therapy.
- Must have measurable disease by PET-CT/CT defined by extranodal lesion ≥ 1 cm or nodal lesion ≥ 1.5 cm.
  - Splenic MZL must have spleen SUV (or any splenic mass) > liver SUV background and/or spleen size > 13 cm.
- Must meet criteria for further systemic therapy per the treating physician (Protocol Section 5.1.c.).

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A Randomized Phase II Study Evaluating Mosunetuzumab Alone and In Combination with Either Zanubrutinib or Polatuzumab Vedotin For The Treatment of Participants with Relapsed/Refractory Marginal Zone Lymphoma

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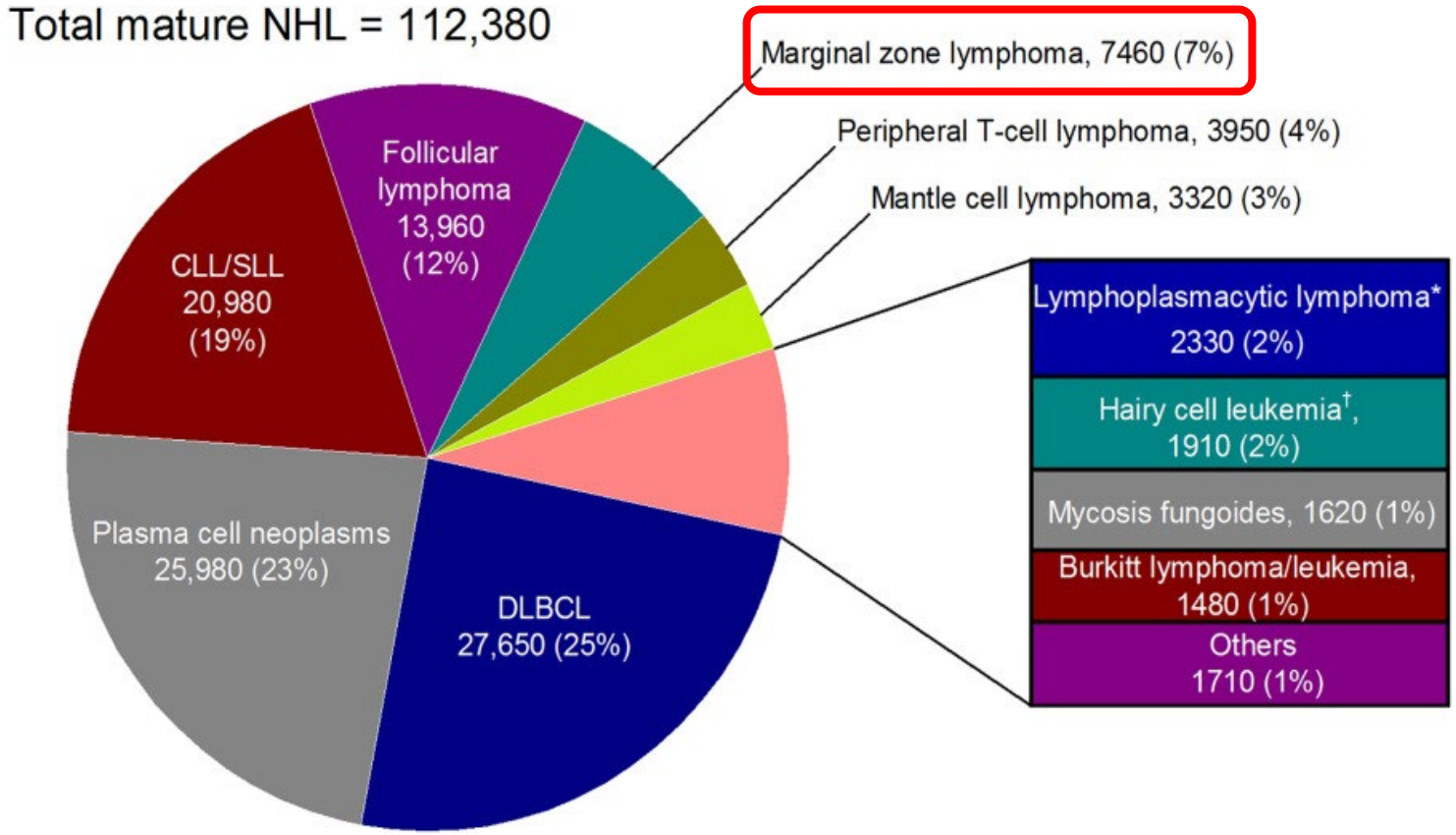
S2504/S2506 Kick Off Meeting, SWOG Spring 2026
May 1st, 2026

Background

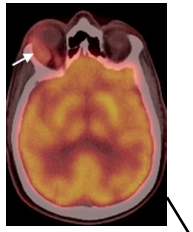
- Despite marginal zone lymphoma (MZL) being the **3rd most common** B-cell lymphoma, there are limited prospective randomized trials to assess the safety and efficacy for new treatments for relapsed/refractory (R/R) disease, and **never through the NCTN**.



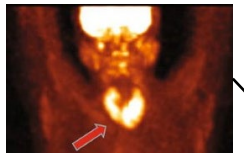
Teras et al. CA Cancer J Clin (2016) 66: 443-459

Disease Heterogeneity

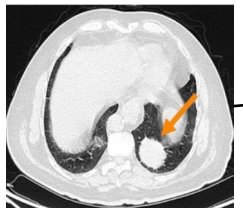
Ocular Extraocular



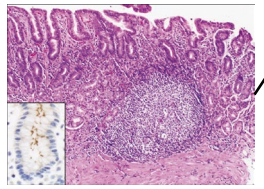
Endocrine



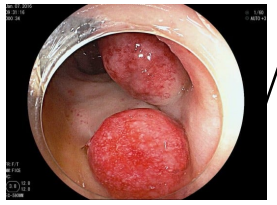
Lung



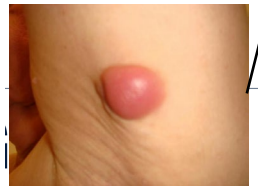
Stomach MALT



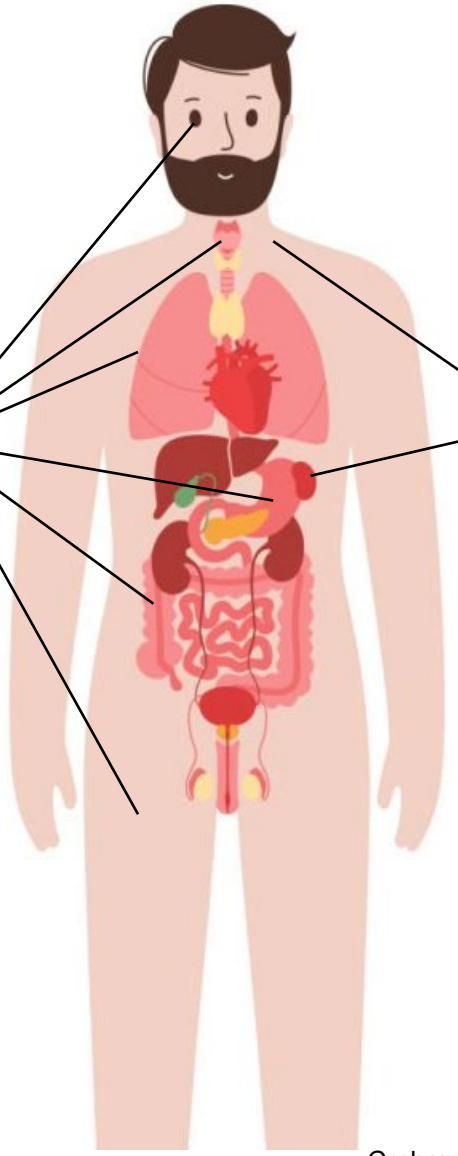
GI Tract



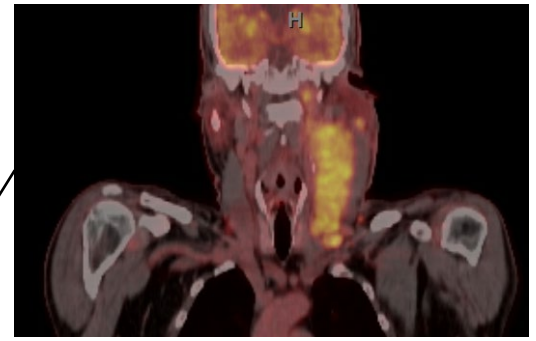
Skin

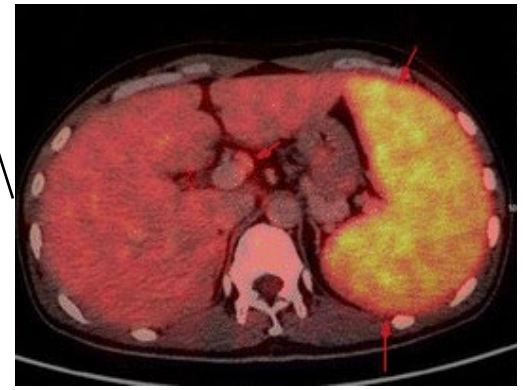


Extranodal (61%)



Nodal (30%) Splenic (9%)





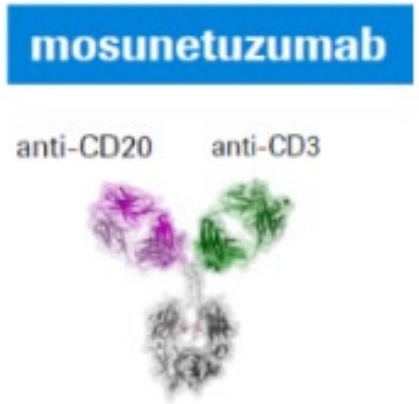
Cerhan JR and Habermann T. Ann Lymphoma (2021) 5:1.

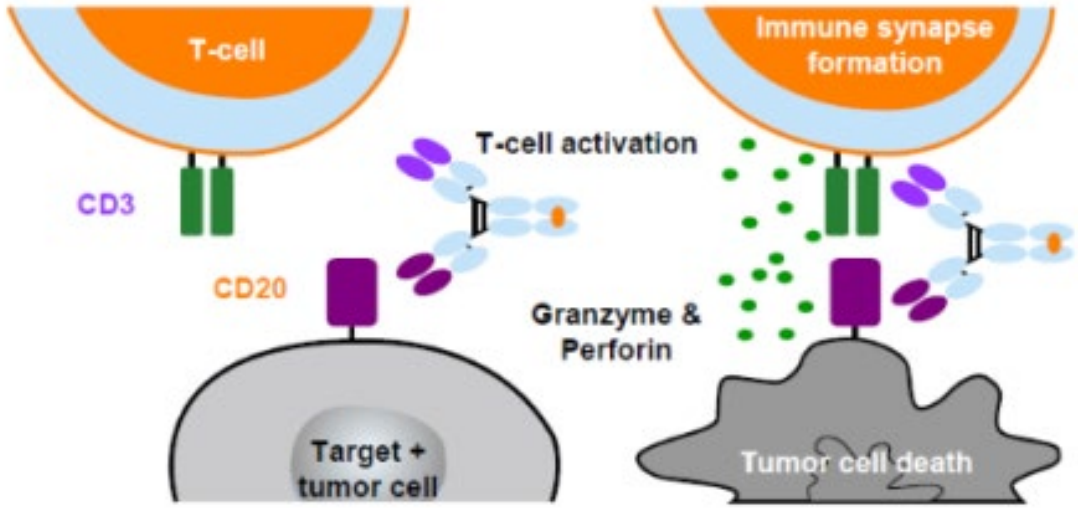
Background

- FDA approvals and inclusion of treatments into the NCCN Guidelines for R/R MZL have been based on as little as **24 patients** that were included as **subgroups** of an iNHL study or **single-arm** phase II studies investigating **indefinite** therapy durations.

Treatment	Reference	Study Phase	Total Patients	Number of MZL Patients	Significant Results
Obinutuzumab + bendamustine	Sehn et al. Lancet Oncol (2016)	R/R, III	396	46	24m PFS ~60%
R/R R^2	Leonard et al. JCO (2019)	R/R, III	358	63	mPFS 39.4m for R^2 vs. 14.1m for R-mono
Axicabtagene ciloleucel	Jacobson et al. Lancet Oncol (2022)	R/R, II	148	24	ORR 85%, CR 55% mPFS 12.0m
Ibrutinib	Noy et al. Blood (2017)	R/R, II	63	63	ORR 48%, CR 3% mPFS 14.2m, DOR 19.4m
Acalabrutinib	Strati et al. BJH (2022)	R/R, II	43	43	ORR 52.5%, CR 12.5% mPFS 27.4m
Zanubrutinib	Opat et al. Clin Cancer Res (2021)	R/R, II	68	68	ORR 68.2%, CR 25.8% 2-year PFS 70%

Mosunetuzumab





N=90 R/R FL

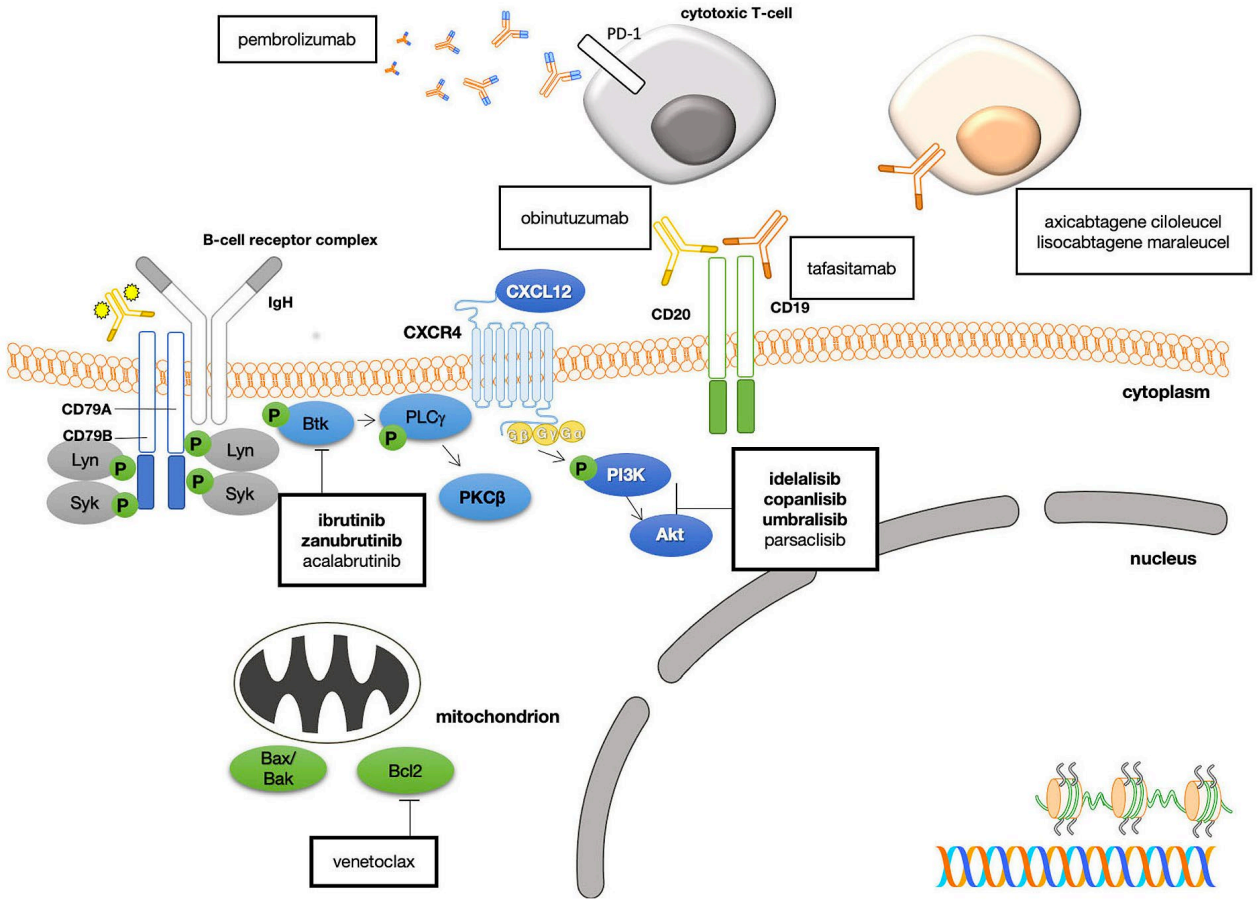
After 8 cycles → N=49 (54%) achieved a CR

N=16 treated beyond 8 cycles (18%) → N=5 (5%) additional patients achieved a CR

	Independent review committee assessment (n=90)	Investigator assessment (n=90)
Objective response rate*	72 (80·0% [70·3–87·7])	70 (77·8% [67·8–85·9])
Complete response rate*	54 (60·0% [49·1–70·2])	54 (60·0% [49·1–70·2])

Budde et al. Lancet Oncol (2022) 23 (8): 1055-1065.

Alternative Targets and Rational Combinations in MZL



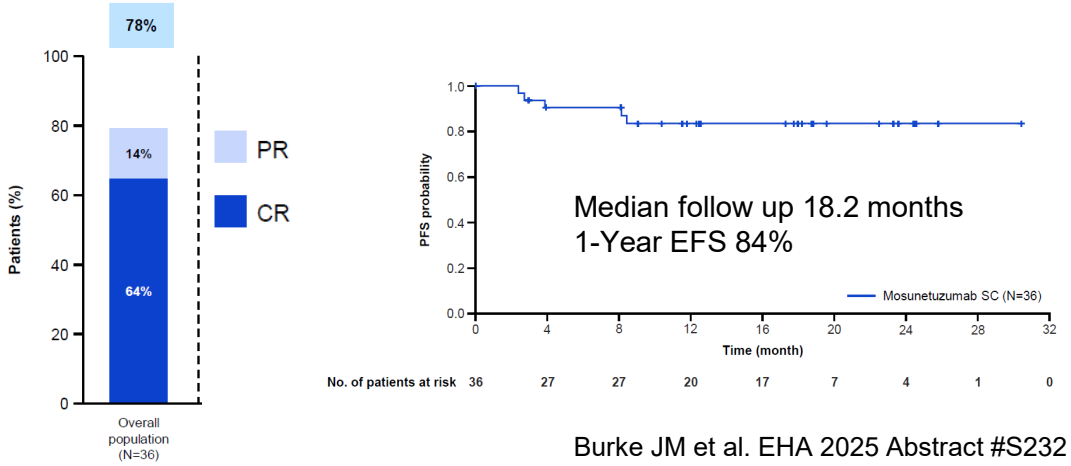
CD79b Expression in B-cell Neoplasms

CLL/SLL	LPL	FL	PBALL	MCL	MZL	DLBCL	HCL	Non-BCLL B cell leukemias	B-NHL-NOS
10/40	—	—	—	—	—	—	—	—	—
—	—	—	35/79	—	—	—	—	—	—
8/63	—	—	—	—	—	—	—	—	—
17/23	—	—	—	16/16	12/12	—	—	—	—
23/40	—	—	—	—	—	—	—	—	—
16/298	—	—	—	—	—	—	—	18/23	123/143
6/22	—	—	—	—	—	—	—	—	—
12/12	—	—	34/34	—	—	—	3/3	—	—
17/330	9/20	15/18	—	12/13	34/46	4/5	6/24	—	—
120/897 (13%)	9/20 (45%)	15/18 (83%)	79/113 (70%)	28/29 (96%)	46/58 (79%)	4/5 (80%)	9/27 (33%)	18/23 (78%)	123/143 (86%)

Cheah CY, Zucca E, Rossi D, Habermann TM. Haematologica (2022) 107 (1).
Chu, PG and Arber DA. AIMM (2001) 9 (2): 97-106

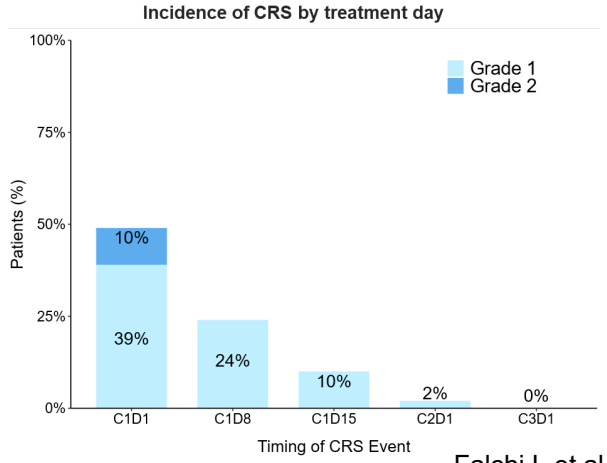
Mosunetuzumab and Combinations in B-cell Lymphomas

Mosunetuzumab in frontline MZL (MorningSun)



Burke JM et al. EHA 2025 Abstract #S232

Mosunetuzumab + Zanubrutinib (MITHIC-FL2)



Falchi L et al. ASH 2025 Abstract #463

Mosunetuzumab + Polatuzumab in DLBCL

AEs of Special Interest	N=120
CRS • Grade 3 • Grade 4	 3 (2.5%) 0
ICANS • Grades 3 and 4	 2 (1.6%)
Febrile Neutropenia	0

Budde LE et al. Nat Med (2024) 30: 229-239.

We **hypothesize** that relapsed/refractory marginal zone lymphoma patients can be **safely** treated with combination zanubrutinib and mosunetuzumab or polatuzumab vedotin and mosunetuzumab with **increased complete response rates** as compared to mosunetuzumab monotherapy, allowing for more patients to be treated in a **time-limited** fashion.

Study Objectives

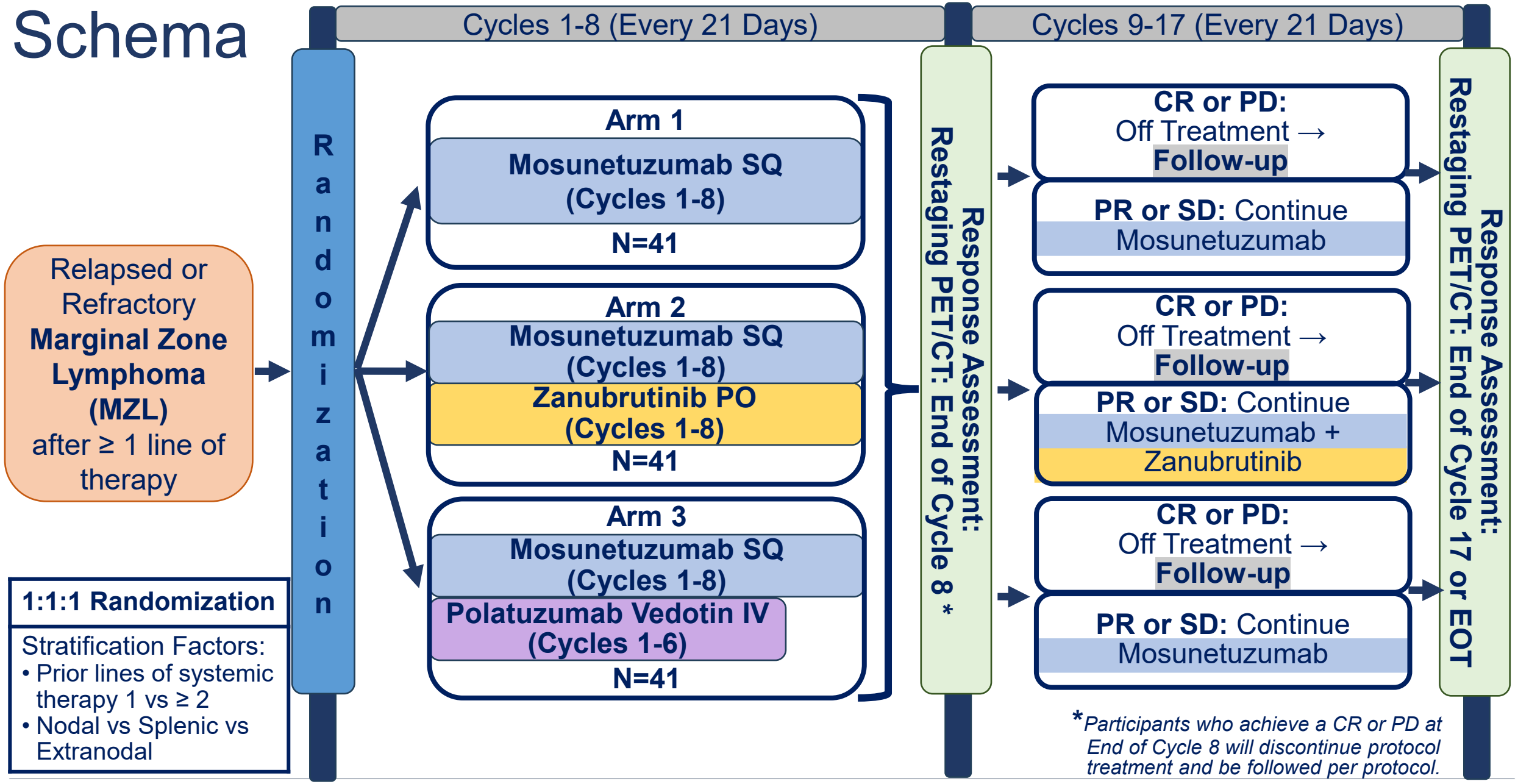
Primary Objectives

- To compare complete response (CR) rates in participants with relapsed/refractory marginal zone lymphoma randomized to mosunetuzumab SQ with or without zanubrutinib (Arm 2 versus Arm 1).
- To compare CR rates in participants with relapsed/refractory marginal zone lymphoma randomized to mosunetuzumab SQ with or without polatuzumab vedotin (Arm 3 versus Arm 1).

Secondary Objectives

- To compare progression-free survival (PFS) between:
  - Participants randomized to mosunetuzumab SQ with or without zanubrutinib (Arm 2 versus Arm 1), and,
  - Participants randomized to mosunetuzumab SQ with or without polatuzumab vedotin (Arm 3 versus Arm 1).
- To compare overall survival (OS) between:
  - Participants randomized to mosunetuzumab SQ with or without zanubrutinib (Arm 2 versus Arm 1), and,
  - Participants randomized to mosunetuzumab SQ with or without polatuzumab vedotin (Arm 3 versus Arm 1).
- To compare overall response rate (ORR) between:
  - Participants randomized to mosunetuzumab SQ with or without zanubrutinib (Arm 2 versus Arm 1), and,
  - Participants randomized to mosunetuzumab SQ with or without polatuzumab vedotin (Arm 3 versus Arm 1).
- To estimate duration of response (DoR) among responders within each treatment arm.
- To evaluate the frequency and severity of adverse events (AE) observed in each treatment arm.

Schema



SQ: subcutaneous; **CR**: complete response; **PD**: progressive disease; **PR**: partial response; **SD**: stable disease

Key Eligibility – Disease Criteria (1)

- Participants must have histologically diagnosed **CD20+ marginal zone lymphoma** (MZL) as per WHO criteria (See S2506 Protocol Section 4.0) including splenic, nodal, and extranodal subtypes, but **excluding** gastrointestinal-only MZL with disease assessments that can only be evaluated through endoscopic methods and cutaneous-only MZL.

  NOTE: A **repeat biopsy** to confirm MZL diagnosis is NOT required at time of relapse **unless**:
  - The participant has **received prior CD3/CD20 bispecific antibody**, then a repeat biopsy to document continued CD20+ MZL disease is required after the completion of the prior CD3/CD20 bispecific antibody therapy and prior to study registration.
  - The participant has **splenic MZL** in which a bone marrow biopsy pre-registration is required within 42 days prior to registration.

- Participants must have **measurable disease** by PET-CT (preferred), or CT as defined by extranodal lesion ≥ 1cm or nodal lesion ≥ 1.5cm.
  - Participants with splenic MZL are included in the study if spleen SUV (or any splenic masses) is > liver SUV background and/or spleen size is > 13cm.

Key Eligibility – Disease Criteria (2)

- Participants must have one or more of the following **criteria for further systemic therapy** as per the discretion of the treating physician:
  - Symptoms due to progressive or bulky nodal disease.
  - Progressive disease that is currently compromising or may compromise normal organ function if left untreated.
  - Presence of systemic B symptoms (i.e. fevers, weight loss, night sweats).
  - Presence of symptomatic extranodal disease.
  - Cytopenias due to bone marrow infiltration or hypersplenism.
  - An increase in the tempo of disease progression.
- **No** known or clinically suspected **transformation** to diffuse large B-cell lymphoma or high-grade B-cell lymphoma.
  - Participants with prior transformed disease but now in relapse with MZL only are allowed.

Key Eligibility – Prior/Concurrent Therapy Criteria (1)

- Participants must have relapsed/refractory MZL after at least **one line of prior CD20-directed systemic therapy** (either as monotherapy or in combination with chemotherapy or lenalidomide).
    - **Prior antibiotic and radiation treatments** for localized MZL disease are allowed and **do not count** as one line of systemic therapy.
- Participants who have been treated with **prior BTKi or CD3/CD20 targeting bispecific antibodies** for their MZL must have completed treatment 180 days prior to registration and must have received a best response of either a partial or complete response.
- Participants being treated with **strong and moderate CYP3A4** inducers must be off these therapies within 14 days or 5 half-lives of the drug prior to registration, whichever is shorter.
- Participants must **not** have been treated with **prior polatuzumab vedotin** for any condition.

Key Eligibility – Clinical Laboratory Criteria (1)

- ≥ 18 years old at the time of registration
- Zubrod Performance Status of 0-2
- Within 28 days prior to registration, participants must have:
  - A complete medical history and physical exam.
  - Adequate organ and marrow function, defined as:

Absolute neutrophil count	≥ 1.0 x 10^3/uL
	Note: Participants with documented MZL bone marrow involvement or a known/ documented Fy(A-/B-) immunophenotype by completed Duffy antigen phenotyping (i.e., "Duffy-Null") must have ANC ≥ 0.5 x 10^3/uL. Growth factor use is allowed.
Platelets	≥ 75 x 10^3/uL
	Note: Participants with documented MZL bone marrow or splenic involvement must have platelets ≥ 50 x 10^3/uL.
Total bilirubin	< 1.5 x institutional upper limit of normal (IULN).
	Note: Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x IULN.
AST/ALT	≤ 3 × IULN

  - Calculated creatinine clearance ≥ 30 mL/min using the following Cockcroft-Gault Formula.
    A **Creatinine Clearance Calculator** can be found under **Tools** on the SWOG **ORP (CRA) Workbench**.
  - An international normalized ratio (INR) < 2 x ULN.

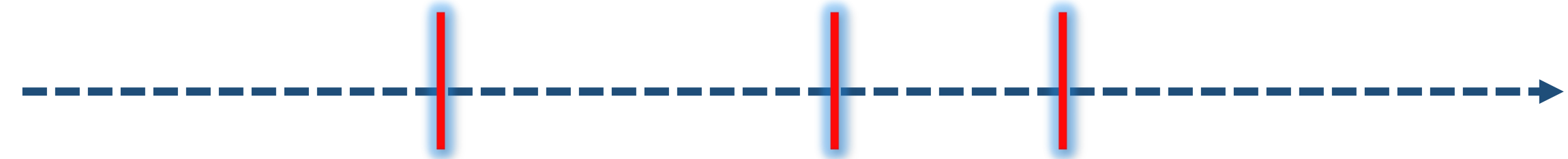
Statistical Considerations

Null Hypothesis CRR=50%[1]	Target CRR	Power	α	Patients Per Arm	Eligible Patients	Total Patients (Accounting for 10% ineligible)
Three Arm	**75%**	82%	One-sided 0.075	41	**123**	138

Response as assessed by the 2014 Lugano Criteria[2]

Planned Interim Analyses

Anticipated Accrual Length: 30 Months



Safety:
10 Patients Randomized to Each Arm

Futility:
50% of Patients Evaluated for Response

Accrual Feasbility:
18 Months Post Study Activation

Accrual/Month:
5-6 patients

1 Budde et al. Lancet Oncol (2022) 23 (8): 1055-1065.
2 Cheson et al. JCO (2014) 32 (27): 3059-3068.

Planned Interim Analyses Details

Safety

- **When**: 10 patients randomized to each arm (30 total).
- **During**: Weekly calls to discuss observed AEs and clinical management strategies.
- **Trigger**: Relative increase of SAEs ≥33% in the combination Arms (i.e. 2 and 3) as compared to mosunetuzumab monotherapy (i.e. Arm 1).

Futility

- **When**: 50% of patients Are evaluable for response (21 patients per arm).
- **Trigger**: CR rate in either combination arms (i.e. Arms 2 and 3) is less than the CR of mosunetuzumab monotherapy (Arm 1) **OR** CR <25% (<5 complete responders) in Arm 1.

Accrual Feasibility

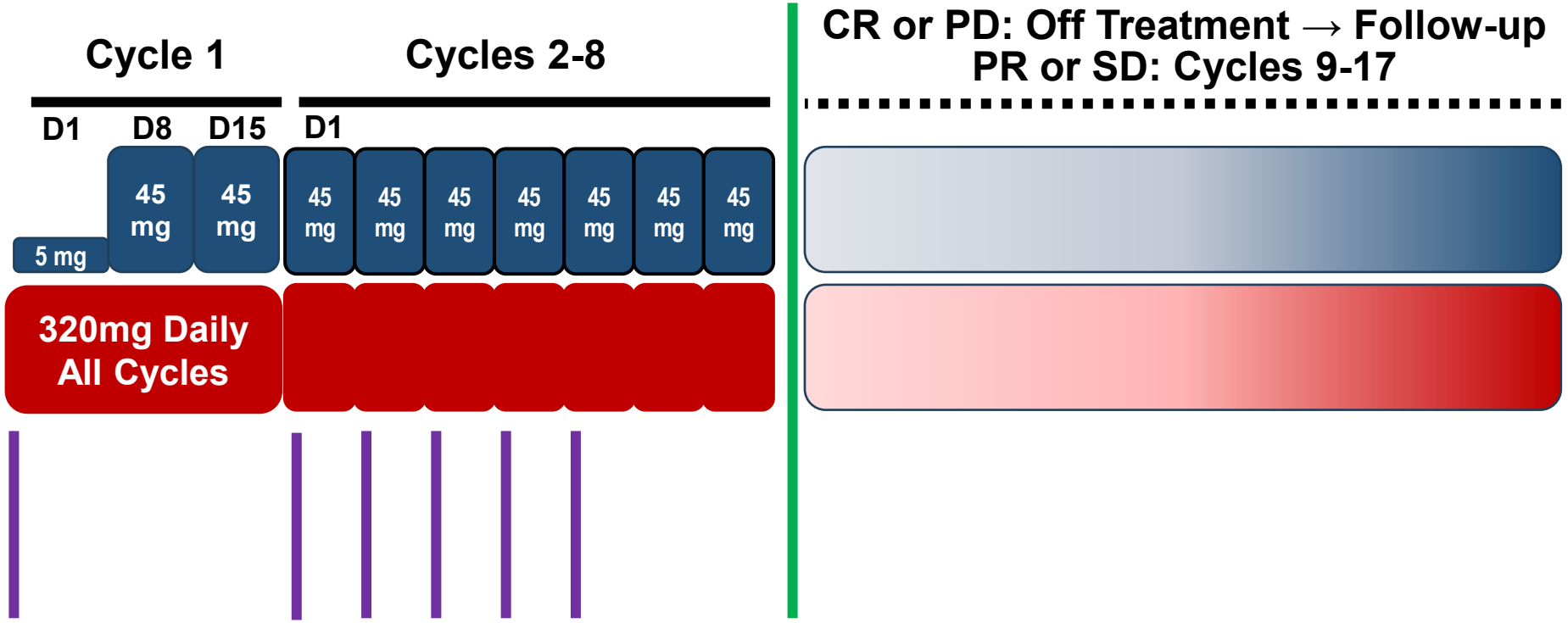
- **When**: Months 7-18 after study activation (12-month period).
- **Trigger**: <3 participants enrolled per month.

Action: S2506 study team, SWOG Executive Officers, SWOG Lymphoma Committee Chair(s), DSMC and CTEP to determine if termination of ≥ 1 treatment arms is appropriate. If mosunetuzumab monotherapy (Arm 1) at the interim futility analysis has a CR <25%, study will be considered for closure.

Overview of Treatments

Cycle Length: 21 Days

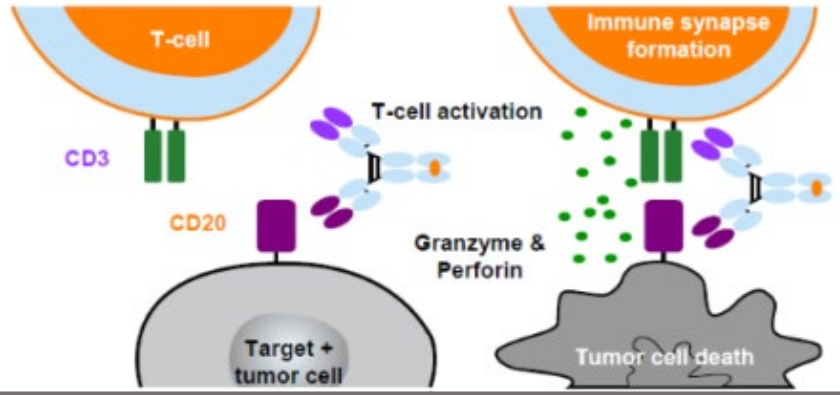
Arm 1 **Mosunetuzumab** SQ (alone)	
Arm 2 **Mosunetuzumab** SQ + **Zanubrutinib** PO	
Arm 3 [a] **Mosunetuzumab** SQ + **Polatuzumab Vedotin** IV 1.8 mg/kg	



Notes:
a. Polatuzumab vedotin is administered Day 1 of Cycles 1 through 6 only
b. Participants who achieve a CR after the first 8 treatment cycles will discontinue their assigned treatments and be moved to follow up. Participants who achieve a PR or SD after the first 8 treatment cycles will continue to mosunetuzumab (Arms 1 and 3) or mosunetuzumab + zanubrutinib (Arm 2) for an additional 9 treatment cycles (i.e., Cycles 9-17).

Mosunetuzumab – All Arms

- Mechanism of Action:
  Mosunetuzumab engages T-cells via CD3 with CD20+-expressing cells, leading to T-cell activation and T-cell mediated cytolysis of the CD20+-expressing cells.
- Pre-Medications:



Premedication Type [a]	Analgesic/Antipyretic	Antihistamine	Glucocorticoid
Drug Name	**Acetaminophen or paracetamol**	**Diphenhydramine or other H1 antihistamines**	**Dexamethasone [b]**
Dose	500 -100 mg	50 -100 mg	20 mg
Route of Administration	PO or IV	PO or IV	See footnotes [b]
Dosing Instructions	~30 minutes prior to mosunetuzumab SQ administration	~30 minutes prior to mosunetuzumab SQ administration	~1 hour prior to mosunetuzumab SQ administration

[a] **CRS or ICANS prophylaxis with tocilizumab or siltuximab is not allowed**.

[b] For participants receiving mosunetuzumab SQ, corticosteroid prophylaxis consisting of 20 mg dexamethasone (preferred) or 80 mg methylprednisolone should be administered orally or intravenously prior to mosunetuzumab SQ administration in all days of Cycle 1. The administration of corticosteroid premedication may be optional for Cycle 2 and beyond at the investigator's discretion. However, if the participant experiences Cytokine Release Syndrome (CRS) with prior administration of mosunetuzumab SQ, premedication with steroids must be administered for subsequent doses until no additional CRS events are observed.

Zanubrutinib – Arm 2

Mechanism of Action:

Zanubrutinib is a small molecule that inhibits Burton's tyrosine kinase (BTK) by forming a covalent bond with a cysteine residue in the BTK active site. The BTK signaling pathway normally activates pathways for B-cell proliferation. Nonclinical studies showed zanubrutinib inhibits malignant B-cell proliferation and decreased tumor growth.

Dose administration per protocol	**May be given 320mg daily or 160mg BID**

DDI dosing adjustments as per USPI:

Zanubrutinib Dose Modifications for Participants Requiring CYP3A Inhibitors or Inducers	
Co-administered Drug	**Recommended zanubrutinib dose**
Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions
Moderate or strong CYP3A inducer	Avoid concomitant use

Polatuzumab Vedotin – Arm 3

Mechanism of Action:

Polatuzumab vedotin is a monoclonal CD79b-directed antibody-drug conjugated to monomethyl auristatin E (MMAE) via a cleavable linker. CD79b is a B-cell specific surface signaling protein. Upon binding to CD79b, polatuzumab vedotin is rapidly internalized into the cell. Lysosomal proteases cleave the linker, enabling intracellular delivery of MMAE. MMAE is a cytotoxic anti-mitotic agent that binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

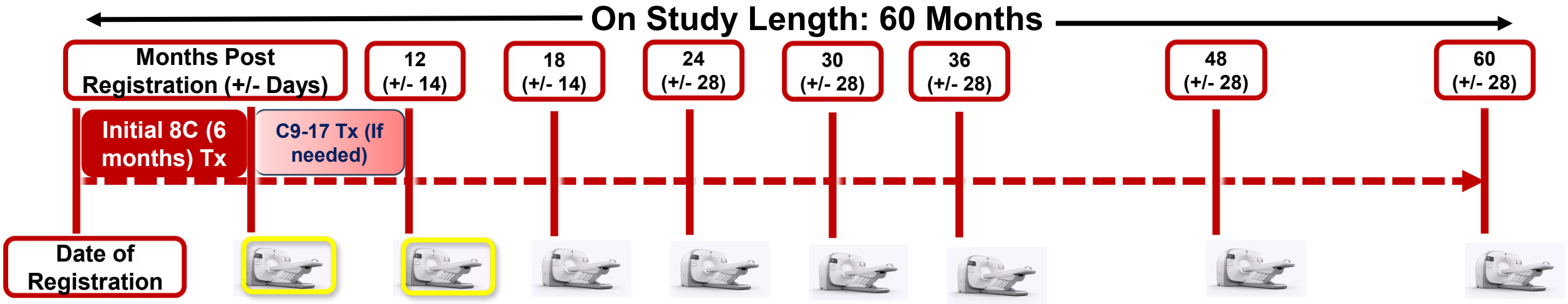
Table 7.3c: Timing of Medication and Treatment Administration for Arm 3	
Pre-medications prior to Polatuzumab vedotin (Cycles 1-6)	If giving, ≥ 30min prior to administration of polatuzumab vedotin
Polatuzumab vedotin - Administered in Cycles 1-6 only	• Infuse over 90 (±30) minutes during Cycle 1. • If Cycle 1 is well tolerated, all subsequent cycles can be infused over 30 (±30) minutes.
Rest Interval	≥ 60 minutes
Pre-medications prior to mosunetuzumab SQ and after the above rest interval	• Dexamethasone 20mg ~60 min prior to mosunetuzumab SQ for Cycles 1 and 2. • If acetaminophen and/or diphenhydramine were not previously given prior to polatuzumab vedotin, or ≥4 hours have elapsed from prior pre-medication administration, may administer both ~30 min prior to mosunetuzumab SQ.
Mosunetuzumab SQ	Administer over 30 seconds to 1 minute
Observation post-mosunetuzumab SQ	30 minutes for all doses given during Cycle 1, and then 15 minutes for all remaining cycles

Anticipated Adverse Events

Mosunetuzumab	Zanubrutinib	Polatuzumab Vedotin
• Cytokine release syndrome (CRS) • Neurologic and Headache • Hemophagocytic lymphohistiocytosis • Injection-site reaction • Neutropenia and febrile neutropenia • Thrombocytopenia • Infections • Tumor flare • Elevated Liver Enzymes and Hepatotoxicity • Tumor Lysis Syndrome • Hyperuricemia and Hypophosphatemia • Fatigue • Fever	• Cytopenias • Bleeding/Bruising • Atrial Fibrillation/Flutter • Elevated Liver Enzymes and Hepatotoxicity • Other GI • Infections (bacterial, viral, fungal, respiratory tract, pneumonia) • Fatigue • Musculoskeletal Pain • Rash	• Cytopenias • Infusion-Related Reactions • Peripheral Neuropathy • Constipation, Decreased Appetite, Diarrhea, Nausea, Vomiting • Hepatotoxicity • Fatigue • Mucositis • Infection, Pneumonia, Fever

Disease Assessment

- **End of Cycle 8**: PET CT to be performed at Cycle 8 Day 21 (-7 to +5 days)
- **End of Cycle 17 or End of Treatment (or if participant discontinued protocol treatment earlier)**: PET CT to be performed 3-12 weeks from date participant last received study treatment.
- End of Cycle 17 = 12-month post registration follow up.



Participants who achieved a CR or PD after the initial 8 cycles of therapy, or who were removed from protocol treatment for any reason prior to completing the initial 8 cycles, will have an additional follow up with CT of the neck, chest, abdomen, and pelvis with IV contrast at 1 year (12 months) (+/- 14 days) after their date of registration.

: CT of the neck, chest, abdomen and pelvis with IV contrast

Dose Modifications/Interruptions – General Considerations

- **The maximum dose delay for any reason is 42 days.**
  - Dose interruptions of any treatment and discontinuations of Zanubrutinib or Polatuzumab vedotin are allowed to manage toxicity.
  - Missed doses of any of the treatments will not be made up.
- **The administration of Mosunetuzumab SQ is the priority (especially in Arms 2 and 3).**
  - Delays in mosunetuzumab SQ administration in Arms 2 and 3 should also delay Zanubrutinib or Polatuzumab vedotin treatment so the combinations can be administered together.
- **If Polatuzumab vedotin or Zanubrutinib must be permanently discontinued, the participant may continue to receive Mosunetuzumab SQ monotherapy**, provided that none of the criteria requiring discontinuation of Mosunetuzumab SQ have been met (See S2506 Protocol Section 7.6).
  - If Mosunetuzumab SQ must be permanently discontinued, the participant must be removed from protocol therapy.

Specimen Submission – Required with Participant Consent for Banking

Specimen Type / Amount	Timepoint	Kit Provided?	Important Notes
Archival Diagnostic Biopsy Tissue [a] • **FFPE block (preferred)** OR • 1 high-quality, 4-5 micron, H&E slide and 25 unstained, 4-5 micron, positively-charged slides, unbaked	• **Baseline** (Submit within 30 days after registration.) • **Time of Progression**	No	• The corresponding partially redacted **Diagnostic Pathology Report must be submitted.**
Whole Blood 20 mL peripheral blood in **TWO 10 ml Streck cfDNA Tubes**	• **Cycle 1, Day 1** (prior to treatment) • **Cycle 3, Day 1** (prior to treatment) • **Time of Progression**	Yes; **Order collection kits** via: https://kits.bpc-apps.nchri.org	• Ship same day as collected (or by next business day). • Store/ship ambient. • **Do not refrigerate or freeze.**

a. For participants who required a biopsy at study entry (i.e., participants with splenic MZL or participants who received prior treatment with CD3/CD20 bispecific antibody or a bone marrow biopsy for SMZL participants), representative biopsy tissue with the presence of MZL from the pre-registration biopsy may be submitted in lieu of archival diagnostic FFPE tissue

Patient Reported Outcomes

- Patient-reported symptomatic adverse events (AEs) are understudied in MZL, particularly with the therapeutic agents planned in this phase II randomized trial.
- PRO-CTCAE will be utilized to assess comparative tolerability of the study arms, by comparing the incidence and severity of symptomatic AEs between each treatment arm.
  - No protocol-directed action for PRO-CTCAE responses.
- Offered in English and Spanish and collected at the following 3 timepoints:

Required Studies	Prior to Reg [A]	Cycle 1 [B]			Cycles 2-7 [B] (± 3)	Cycle 8 [B] (± 3)	Cycles 9-17 [B, G, H] (± 3)	EOT [I, J]	Progression	Follow Up (Prior to Progression) [L]
		D1 (+ 1)	D8 (± 1)	D15 (± 1)						
Participant who consented to participate in the Patient-Reported Outcomes study:										
PRO-CTCAE		X			X (C2D1)	X (C8D1)				

- Anyone involved in the collection of patient-reported outcomes data in SWOG trials should review the Patient Reported Outcome Questionnaires training program available via CTSU CLASS (login required).

Drug Supply and Ordering – All Arms

Supply:

- **Mosunetuzumab and Polatuzumab vedotin** are supplied by Genentech and distributed by McKesson.
- **Zanubrutinib** is supplied by BeOne and distributed by McKesson.

Order Timing:

- Drug must be ordered after participant registration to S2506; No starter supplies are available.
- **Allow up to 5 business days after submission of the drug order request for study drug to arrive.**

Ordering Process:

- **3 separate Drug Order Forms:** Submit to: CRS.Orders@McKesson.com; Order Forms accessible from the S2506 protocol abstract page on the CTSU website under Documents tab>>Protocol Related Documents tab>>Pharmacy filter.
- Follow instructions on the form for order submission.

Criteria for Removal from Treatment

- Completion of protocol treatment.
- Progression of disease or symptomatic deterioration (as defined in S2506 Protocol Section 10.3).
- **Permanent discontinuation of Mosunetuzumab SQ.**
- Unacceptable toxicity.
- **Treatment delay for any reason > 42 days**.
- Pregnancy.
- **Achievement of complete response (CR) or progressive disease (PD) at restaging (End of Cycle 8).**
- The participant may withdraw from the protocol treatment at any time for any reason.

Conclusions

- MZL, especially R/R patients, is an understudied disease with S2506 MOZART MZL being the **first NCTN study** developed solely for MZL.

- All three treatment arms are chemotherapy-free and have the ability to establish a new **safe, efficacious and time-limited** treatment strategy for the disease.

- Very little (if any) currently competing studies in this space.

Acknowledgements

SWOG Study Chairs	Statisticians	NCTN Champions	SWOG Lymphoma Committee
Boyu Hu, MD, Chair Sonali Smith, MD, Co-Chair Joo Song, MD, TM Chair Ajay Major, MD, MBA, PRO Chair	Gabby Lopez, MS Hongli Li, MS Michael LeBlanc, PhD	Joanna Rhode, MD (ECOG/ACRIN) Narendranath Epperla, MD (ALLIANCE)	Bei Hu, MD Jonathan Friedberg, MD, MMSc Tricia Hernandez, Patient Advocate

SWOG Network Operations Center (NOC) and Statistics and Data Management Center (SDMC)		
SWOG Protocol Department	**SWOG Budget & Contracts**	**SDMC Data Operations**
Erin Rogers, Protocol Project Manager Laura Gildner, Clinical Trials Program Manager Crystal Miwa, Protocol Department Manager Dana Sparks, Director of Operations and Protocols	Chris Gilbert, Clinical Trial Budget Analyst Shane Barnes, Contract Attorney	Alex Rangel, Data Coordinator

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Larry Lyons Mei Wu Patricia Hill	Priya Hegde Kelly Terrill	Department of Health and Human Services (NIH/NCI) Cancer Treatment Research Grant Award: R50CA305062-01

Contact Information

Eligibility, RAVE, Data Submission:	SWOG Statistics and Data Management Center E-mail: lymphomaquestion@crab.org or Phone: 206/652-2267
Regulatory, Protocol, Informed Consent:	SWOG Network Operations Center E-mail: protocols@swog.org or Phone: 210/614-8808
Medical Queries (treatment or toxicity related questions):	Email: S2506@swog.org
QOL/PRO questions:	Contact Dr. Ajay Major at S2506@swog.org
Specimen collection kit questions	Email: bpcbank@nationwidechildrens.org
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	Email: technicalquestion@crab.org
Requests for Investigators Brochures:	Refer to S2506 Protocol Section15.0
Drug ordering, accountability, and temperature excursion questions:	Email: protocols@swog.org
Access to iMedidata Rave or Delegation of Task Log (DTL), Oncology Patient Enrollment Network (OPEN) questions	See Protocol Sections 14.3 or 13.5 or contact the CTSU Help Desk at: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Serious Adverse Event Reporting questions:	See Protocol Section 8.7 or Email: adr@swog.org

Thank you

Scan the QR code or follow the link below
to download the
S2506 Healthcare Provider Handout

https://www.swog.org/S2506HealthcareProviderHandout

Back Up Slides

Treatment Administration: Arm 1 Mosunetuzumab

AGENT	DOSE	ROUTE	Cycle 1 Schedule [a]			Cycles 2-17 [a, b]
			Day 1	Day 8	Day 15	Day 1
Mosunetuzumab SQ	5 mg	SubQ	X [c]			
Mosunetuzumab SQ	45 mg	SubQ		X [c]	X [c]	X [d]

[a] One cycle = 21 days

[b] Participants who achieve a CR or PD after the first 8 treatment cycles will discontinue treatment with mosunetuzumab SQ and participant will be moved to follow up. Participants who do not achieve a CR or PD (i.e. PR, SD) after the first 8 treatment cycles will continue to receive mosunetuzumab SQ for an additional 9 treatment cycles (i.e., Cycles 9-17). See S2506 Protocol Section 7.4.

[c] A dosing window of +1 day is permitted for Cycle 1 Day 1 treatments along with a +/- 1 day treatment window for Cycle 1 Day 8 and Cycle 1 Day 15.

[d] Protocol treatment should be administered on Day 1 (+/- 3 days) for Cycles 2-17.

Premedication Type	Analgesic/Antipyretic	Antihistamine	Glucocorticoid
Premedication Name	Acetaminophen	Diphenhydramine	Dexamethasone
Dose	500-100mg	50-100mg	20mg
Route of Administration	PO or IV	PO or IV	See footnotes [a]
Dosing Instructions	~30 minutes prior to Mosunetuzumab SQ administration	~30 minutes prior to Mosunetuzumab SQ administration	~1 hour prior to Mosunetuzumab SQ administration

Treatment Administration:
Arm 2 Mosunetuzumab + Zanubrutinib

AGENT	DOSE	ROUTE	Cycle 1 Schedule [a]			Cycles 2-17 [a, b]
			Day 1	Day 8	Day 15	Day 1
Mosunetuzumab SQ	5 mg	SubQ	X [d]			
Mosunetuzumab SQ	45 mg	SubQ		X [d]	X [d]	X [e]
Zanubrutinib	320 mg	PO [f]	Daily; Days 1-21 [c]			

[a] One cycle = 21 days

[b] Participants who achieve a CR or PD after the first 8 treatment cycles will discontinue treatment with mosunetuzumab SQ and zanubrutinib and participant will be moved to follow up. Participants who do not achieve a CR or PD (i.e., PR, SD) after the first 8 treatment cycles will continue to receive mosunetuzumab SQ and zanubrutinib for an additional 9 treatment cycles (i.e., Cycles 9-17). See S2506 Protocol Section 7.4.

[c] Zanubrutinib is to be taken by mouth daily. At the discretion of the treating investigator, zanubrutinib may also be taken 160 mg by mouth twice daily with doses taken 8 hours apart. Doses should be taken at approximately the same time each day.

[d] A dosing window of +1 day is permitted for Cycle 1 Day 1 treatments along with a +/- 1 day treatment window for Cycle 1 Day 8 and Cycle 1 Day 15.

[e] Protocol treatment should be administered on Day 1 (+/- 3 days) for Cycles 2-17.

[f] Refer to S2506 Protocol Sections 7.5 and 18.5 for drug compliance documentation and Intake Calendar requirements.

Zanubrutinib Dose Modifications for Participants Requiring CYP3A Inhibitors or Inducers	
Co-administered Drug	Recommended zanubrutinib dose
Strong CYP3A inhibitor	80 mg once daily; Interrupt dose as recommended for adverse reactions
Moderate CYP3A inhibitor	80 mg twice daily; Modify dose as recommended for adverse reactions
Moderate or strong CYP3A inducer	Avoid concomitant use

Treatment Administration:
Arm 3 Mosunetuzumab + Polatuzumab Vedotin

AGENT	DOSE	ROUTE	Cycle 1 Schedule [a]			Cycles 2-17 [a, b]
			Day 1	Day 8	Day 15	Day 1
Polatuzumab vedotin	1.8 mg/kg	IV	X [d]			X [c]
Mosunetuzumab SQ	5 mg	SubQ	X [d]			
Mosunetuzumab SQ	45 mg	SubQ		X [d]	X [d]	X [e]

[a] One cycle = 21 days
[b] Participants who achieve a CR or PD after the first 8 treatment cycles will discontinue treatment with mosunetuzumab SQ and polatuzumab vedotin and participant will be moved to follow up. Participants who do not achieve a CR or PD (i.e., PR, SD) after the first 8 treatment cycles will continue to receive mosunetuzumab SQ for an additional 9 treatment cycles (i.e., Cycles 9-17). See S2506 Protocol Section 7.4.
[c] Polatuzumab vedotin will be administered during Cycles 1-6 only.
[d] A dosing window of +1 day is permitted for Cycle 1 Day 1 treatments along with a +/- 1 day treatment window for Cycle 1 Day 8 and Cycle 1 Day 15.
[e] Protocol treatment should be administered on Day 1 (+/- 3 days) for Cycles 2-17.

Table 7.3c: Timing of Medication and Treatment Administration for Arm 3	
Pre-meds prior to polatuzumab vedotin	If giving, ≥ 30min prior to administration of polatuzumab vedotin
Polatuzumab vedotin	Infuse over 90 (±30) minutes during Cycle 1, and if Cycle 1 was well tolerated, all subsequent cycles can be infused over 30 (±30) minutes.
Rest Interval	≥60 minutes
Pre-medications prior to mosunetuzumab SQ and after the above rest interval	• Dexamethasone 20 mg ~60 min prior to mosunetuzumab SQ for Cycles 1 and 2. • If acetaminophen and/or diphenhydramine were not previously given prior to polatuzumab vedotin, or ≥ 4 hours have elapsed from prior pre-medication administration, may administer both ~30 min prior to mosunetuzumab SQ.
Mosunetuzumab SQ	Administer over 30 seconds to 2 minutes
Observation post-mosunetuzumab SQ	30 minutes for all doses given during C1, and then 15 minutes for all remaining cycles

Bone Marrow Biopsies for Participants with splenic MZL

For participants with splenic MZL ONLY:

- **Bone Marrow Biopsy (BMBx) is REQUIRED** within 42 days prior to registration
- BMBx also needed at the same time that a PET CT is required for response assessment (after Cycle 8, after Cycle 17 or EOT, and at time of progression) IF: the bone marrow biopsy immediately prior demonstrated presence of MZL. (Refer to S2506 Protocol Section 9.0 [Study Calendar] - Footnote N).

Examples:

Example Participant with Splenic MZL	Presence of Lymphoma on Screening Bone Marrow Biopsy?	After Cycle 8		After Cycle 17 Bone Marrow Biopsy
		PET Response	Bone Marrow Biopsy Required?	
#1	No	CR	No, since screening BMBx was negative	N/A as patient achieved CR after Cycle 8 and discontinued treatment
#2	Yes	PR	Yes, and was **negative** for lymphoma	Not required since post Cycle 8 Bone Marrow Biopsy was negative

Complete remission in splenic MZL requires:

- **Negative PET CT** as per Lugano Criteria, **AND**
- **Negative Bone Marrow Biopsy (BMBx)**

AEs of Special Interest

Adverse Events of Special Interest for the S2506 study	• Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
	  • Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN.
	  • Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice.
	• Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), defined as: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Mosuntuzumab SQ	• Grade ≥ 2 CRS • Grade ≥ 2 injection-site reaction • Grade ≥ 2 neurologic adverse event • Any suspected HLH • Any grade pneumonitis, interstitial lung disease, acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia, and/or pulmonary toxicity TLS (minimum Grade 3 by definition) • Febrile neutropenia (minimum Grade 3 by definition) • Any grade disseminated intravascular coagulation (minimum Grade 2 by definition) • Grade ≥ 2 AST, ALT, or total bilirubin elevation • Grade ≥ 2 tumor inflammation/tumor flare, e.g., manifestation of signs/symptoms associated with increase in size of known nodal or extranodal lesions by clinical or radiographic assessment, new onset or worsening of pre-existing pleural effusions.
Polatuzumab Vedotin	• Tumor lysis syndrome of any grade (irrespective of causality) • Second malignancies

Dose Modifications and Dose Levels

Table 8.3: Dose Levels			
Dose Level (DL)	**Zanubrutinib**	**Polatuzumab Vedotin**	**Mosunetuzumab SQ**
Starting Dose	320 mg daily [a]	1.8 mg/kg per cycle	45mg after C1D1
First dose reduction (DL -1)	160 mg daily [a]	1.4 mg/kg per cycle	No dose modifications are allowed for SQ mosunetuzumab except for Grade 3 CRS [b]
Second dose reduction (DL -2)	80mg daily	Discontinue drug	
Third dose reduction (DL -3)	Discontinue drug		

[a] At the discretion of the treating investigator, zanubrutinib may also be administered 160 mg BID at the starting dose and 80 mg BID at DL-1.

[b] In participants experiencing Grade 3 CRS after at least the C1D8 dose, dose reduction of mosunetuzumab SQ to 5 mg for all subsequent doses may be appropriate.

Table 8.3b Recommendations for Restarting Therapy After Dose Delay for Participants Treated With Mosunetuzumab SQ		
Last Dose Administered	**Time Since the Last Dose Administered**	**Action for Next Dose(s)**
5 mg (Cycle 1 Day 1)	1 week to 2 weeks	Administer 45 mg (Cycle 1 Day 8) [a], then resume the planned treatment schedule
	Greater than 2 weeks	Repeat 5 mg (Cycle 1 Day 1) [a], then administer 45 mg (Cycle 1 Day 8) [a] 7 days later and resume the planned treatment schedule
45 mg (Cycle 1 Day 8)	1 week to less than 6 weeks	Administer 45 mg (Cycle 1 Day 15) [a], then resume the planned treatment schedule
45 mg (Cycle 1 Day 15)	1 week to less than 6 weeks	Administer 45 mg (Cycle 2 Day 1), then resume the planned treatment schedule
45 mg (Cycle 2+)	3 weeks to less than 6 weeks	Administer 45 mg, then resume the planned treatment schedule
		[a] Administer premedication as per Cycle 1. See S2506 Protocol Section 7.1.