A Phase II Study Evaluating the Efficacy of Mosunetuzumab in Combination with Polatuzumab Vedotin in Untreated Follicular Lymphoma

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Protocol Revision History

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Amendment #4 Version	**06 Dec 2024**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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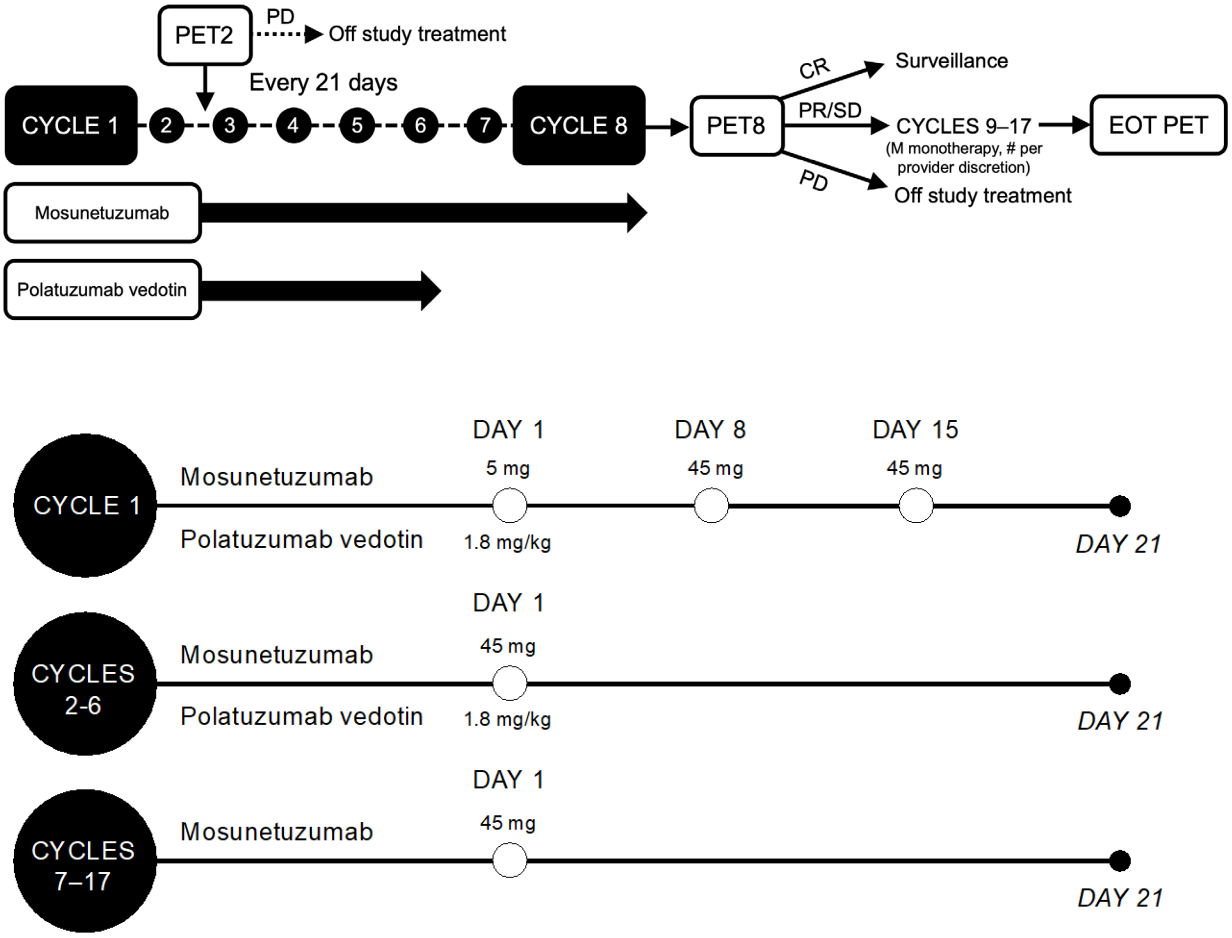
PROTOCOL SUMMARY

Title:	A Phase II Study Evaluating the Efficacy of Mosunetuzumab in Combination with Polatuzumab Vedotin in Untreated Follicular Lymphoma
Study Description:	Hypothesis: The combination of mosunetuzumab and polatuzumab vedotin will be safe and efficacious in patients with untreated follicular lymphoma who otherwise would receive standard of care multi-agent treatment including an anti-CD20 monoclonal antibody plus either alkylator-based chemotherapy or lenalidomide.
Objectives:	Primary Objective: 1. To evaluate the efficacy of the combination of mosunetuzumab and polatuzumab vedotin in patients with untreated follicular lymphoma. Secondary Objectives: 1. To evaluate additional metrics of efficacy of the combination of mosunetuzumab and polatuzumab vedotin in patients with untreated follicular lymphoma. 2. To assess the safety and tolerability of combining mosunetuzumab with polatuzumab vedotin in patients with untreated follicular lymphoma. 3. To assess the use of tocilizumab for management of cytokine release syndrome (CRS) in patients with untreated follicular lymphoma who receive mosunetuzumab and polatuzumab vedotin. Exploratory Objective: 1. To evaluate the dynamics of measurable residual disease (MRD) by plasma-derived circulating-tumor DNA (ctDNA) assessment in patients with untreated follicular lymphoma receiving mosunetuzumab and polatuzumab vedotin.
Endpoints:	Primary Endpoint: 1. Complete response (CR) as best response determined by PET-CT, per Deauville 5-point scale (Lugano 2014 criteria). Secondary Endpoints: 1. Partial response (PR), overall response (OR; CR + PR), stable disease (SD), and progressive disease (PD) as best response determined by PET-CT, per Deauville 5-point scale (Lugano 2014 criteria). 2. CR, PR, OR, SD, and PD rates by PET-CT after Cycle 8 of treatment (PET8), per Deauville 5-point scale (Lugano 2014 criteria).

	3. Interim CR, PR, OR, SD, and PD rates by PET-CT after Cycle 2 of treatment (PET2), per Deauville 5-point scale (Lugano 2014 criteria). 4. 24- and 48-month progression-free survival (PFS) and overall survival (OS) rates. 5. Time to and duration of first response (CR or PR). 6. Time to and duration of first CR. 7. Time to next treatment initiation. 8. Frequencies and grades of treatment-emergent adverse events (TEAE) including CRS. 9. Rate of treatment discontinuation due to TEAE. 10. Percentage of patients requiring any tocilizumab and number of total tocilizumab doses per patient for management of CRS. <u>Exploratory Endpoint:</u> 1. MRD by plasma-derived ctDNA assessment before, during, and after mosunetuzumab and polatuzumab vedotin administration.
Study Population:	Thirty-four patients will be enrolled to this study. Patients must have untreated follicular lymphoma grade 1–3A, stage II–IV by Ann Arbor criteria.
Phase:	II
Description of Sites / Facilities Enrolling:	This study will be active at the Siteman Cancer Center at Washington University School of Medicine.
Description of Study Intervention:	Mosunetuzumab is a novel CD3xCD20 bispecific antibody being studied in various subtypes of B cell lymphomas. In this study, patients will receive up to 17 cycles of mosunetuzumab (6 cycles in combination with polatuzumab vedotin and up to 11 additional cycles of single agent mosunetuzumab; patients who have achieved a CR after Cycle 8 will discontinue treatment at that point, while patients who achieve a PR or SD may continue to receive mosunetuzumab for an additional 9 cycles). Mosunetuzumab dosing will occur as follows: • Cycle 1 Day 1 – 5 mg SC • Cycle 1 Day 8 – 45 mg SC • Cycle 1 Day 15 – 45 mg SC • Day 1 of Cycles 2 through 17 – 45 mg SC Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate indicated for relapsed/refractory diffuse large B cell lymphoma in combination with bendamustine and a rituximab product. In this study, patients will receive up to 6 cycles of polatuzumab vedotin given intravenously at a dose of 1.8 mg/kg on Day 1 of Cycles 1 through 6.

Study Duration:	36 months (enrollment) + 12 months (treatment) + 60 months (follow-up) = 102 months
Participant Duration:	72 months maximum

SCHEMA


PET2
PD
Off study treatment
Every 21 days
CYCLE 1
2
3
4
5
6
7
CYCLE 8
PET8
CR
Surveillance
PR/SD
CYCLES 9–17
(M monotherapy, # per provider discretion)
EOT PET
PD
Off study treatment
Mosunetuzumab
Polatuzumab vedotin
CYCLE 1
DAY 1
DAY 8
DAY 15
Mosunetuzumab
5 mg
45 mg
45 mg
Polatuzumab vedotin
1.8 mg/kg
DAY 21
CYCLES 2-6
DAY 1
Mosunetuzumab
45 mg
Polatuzumab vedotin
1.8 mg/kg
DAY 21
CYCLES 7–17
DAY 1
Mosunetuzumab
45 mg
DAY 21

SCHEDULE OF ACTIVITIES

Screening procedures may take place up to 4 weeks prior to C1D1, unless otherwise noted. Cycles are 21 days long. If the PET-CT post-C2 shows PD, study treatment will be discontinued. If the PET-CT post-C8 shows CR or PD, study treatment will be discontinued; otherwise, treatment may continue for up to 17 cycles.

	Screening	**C1D1**	**C1D8[19]**	**C1D15[19]**	**D1 of C2–C6[19]**	**End of C2**	**D1 of C7–C17[19]**	**End of C8**	**EOT[21]**	**Follow-up[16]**
Informed consent	X									
Medical history	X									
Physical exam[22]	X	X	X	X	X		X[13]		X	X
ECOG PS	X	X			X		X[13]		X	
Vital signs	X	X	X	X	X		X		X	X
CBC w/ diff	X	X[7]	X	X	X		X		X	X
CMP	X	X[7]	X	X	X		X		X	X
LDH	X	X[7]	X	X	X		X		X	X
Uric acid[23]	X	X	X	X	X					
Phosphorous[23]	X	X	X	X	X					
Total IgG	X								X	
ECG	X									
Pregnancy test[1]	X[5]				X[5]		X[5]			
HBV/HCV serologies[2]	X									
HIV testing	X									
PET-CT scan	X[24]					X[11,12,14]		X[11,12,14]	X[14,15]	
CT scan										X[17]
FLIPI score[3]	X									
Mosunetuzumab[4]		X	X	X	X		X			
Polatuzumab vedotin[4]		X			X					
Archival tumor tissue	X[6]									
Research blood		X[8]	X[8]	X[8]	X[8,9]		X[8,9]		X	X[18]
AE assessment and concurrent medication review		Continuous from start of treatment through 30 days after last administration of study treatment, or until initiation of alternate treatment for lymphoma, whichever occurs earlier								
ICE scoring / ICANS grading[10]		X								
Progression / survival										X[20]

1. Women of childbearing potential only

2. Anti-HBc, anti-HBs, HBsAg, and anti-HCV
3. FLIPI score is sum of number of criteria met: [1] age ≥60 years; [2] >4 nodal sites involved; [3] elevated LDH; [4] hemoglobin <12 g/dL; [5] stage III or IV
4. Premedications as indicated in Section 5.2.
5. Negative serum pregnancy test within 7 days prior to C1D1; pregnancy tests starting C2D1 can be serum or urine per physician preference.
6. May be requested at any point during participation; repeat biopsy not required at baseline if archival tissue is unavailable/depleted; if archival tissue is unavailable/depleted, the patient can still be enrolled on the trial.
7. Must be drawn no more than 7 days prior to C1D1; if screening labs are within this window, labs need not be redrawn for C1D1.
8. Prior to treatment
9. Only C2D1, C3D1, C7D1, C9D1 (if PET-CT post-C8 does not show CR or PD, and study treatment is planned), and C13D1 (if PET-CT post-C8 does not show CR or PD, and study treatment is planned).
10. ICE scoring required on C1D1, and performed with ICANS grading after C1D1 per physician discretion.
11. To occur 3 weeks (-7/+7 days) after start of cycle and no more than 7 days prior to start of next cycle.
12. Patients with PD at PET-CT post-C2 or PET-CT post-C8 will discontinue study treatment at that time.
13. Beginning with C10, physical examination and performance status can be skipped on even cycles per physician discretion.
14. EOT if PET-CT post-C2 shows PD, or if PET-CT post-C8 shows CR or PD.
15. Only required if PET-CT post-C8 does not show CR or PD and patient goes on to receive study treatment beyond C8D1; should occur 4 weeks (-14/+14 days) after the final dose of study treatment.
16. Q3M (-1/+1 month) for 2 years, then Q6M (-1/+1 month) for 3 years (total of 5 years) post-EOT.
17. Preferred with contrast and including neck/chest/abdomen/pelvis; at 12, 24, and 36 months (-1/+1 month) post-EOT.
18. At 6, 12, and 24 months post-EOT, aligned with any surveillance imaging (if applicable) or follow-up.
19. Acceptable window for treatment day = -3/+3 days; labs may be drawn up to 3 days prior to treatment day.
20. After progression, patients will only be followed for survival via chart review.
21. EOT visit window = 4 weeks (-14/+14 days) after D1 of last cycle.
22. All patients will be required to undergo a baseline complete neurologic examination either during screening or prior to study treatment on C1D1. The examination is not required for eligibility or prior to registration. The examination should include an evaluation of mental status, cranial nerves, motor strength, sensation, and coordination. Patients should be routinely assessed for any signs or symptoms of neurologic toxicity as part of the on-treatment clinical examination.
23. Tumor lysis syndrome (TLS) risk and need for TLS prophylaxis will be determined per provider discretion. See Section 5.2 and Appendix D for additional information. Uric acid and phosphorous should be checked at screening, C1D1, C1D8, C1D15, and C2D1 if the patient is deemed high-risk for TLS by the treating physician, irrespective of TLS prophylaxis implementation.
24. Screening PET-CT may take place up to 8 weeks prior to C1D1.

1.0 INTRODUCTION

1.1 Study Rationale

Follicular lymphoma (FL) is typically characterized by a disease-course entailing multiple responses to therapy and subsequent relapses over many years. Mosunetuzumab is a bispecific CD3xCD20 antibody that has shown impressive single agent activity and safety in relapsed/refractory (rel/ref) FL, with complete remission rates >40% in many high-risk subgroups of patients in early clinical trials (Schuster et al. 2019, Assouline et al. 2020, Matasar et al. 2020, Budde et al. 2021). There is strong rationale for exploring frontline use of mosunetuzumab in the treatment of FL. First, mosunetuzumab would be predicted to be more active when administered in chemotherapy-naïve patients due to the deleterious effects of commonly used agents, such as bendamustine, on T cells. Second, this strategy would afford the opportunity to avoid the intrinsic detrimental consequences of aging on the T cell pool in older patients with relapsed FL. Additionally, based on its mechanism of action, mosunetuzumab would be expected to have fewer late effects than most first-line therapies for FL.

Polatuzumab vedotin is an antibody-drug conjugate that specifically targets the cytotoxic payload MMAE to B cells via an anti-CD79b monoclonal antibody component. One arm of the ROMULUS study explored the combination of polatuzumab vedotin and the anti-CD20 monoclonal antibody rituximab in the rel/ref FL setting, and a promising overall response rate of 70% (14/20) was reported (Morschhauser et al. 2019). In turn, polatuzumab vedotin may be a well-suited partner for mosunetuzumab given generally non-overlapping toxicities with no known evidence of abrogation of T cell function by polatuzumab vedotin.

We hypothesize that the combination of mosunetuzumab and polatuzumab vedotin will be safe and efficacious in patients with untreated FL who otherwise would receive standard of care multi-agent frontline treatment including an anti-CD20 monoclonal antibody (mAb) plus either alkylator-based chemotherapy or the immunomodulatory agent lenalidomide. The combination of mosunetuzumab and polatuzumab vedotin is currently being explored in the open-label, phase Ib/II GO40516 clinical trial investigating the safety, tolerability, pharmacokinetics, and efficacy of mosunetuzumab in combination with polatuzumab vedotin in patients with relapsed/refractory B cell non-Hodgkin lymphoma (B-NHL), including FL, transformed FL (t-FL), and diffuse large B cell lymphoma (DLBCL). In the preliminary dose-escalation cohort (Budde et al. 2021), cytokine release syndrome (CRS) was observed in only 2 of 22 patients (both grade 1), and no immune effector cell-associated neurotoxicity syndrome (ICANS) was observed. A complete response (CR) was achieved by all 3 of 3 patients with follicular lymphoma, and 12 of 22 patients overall achieved a CR. These preliminary data indicate that the combination of mosunetuzumab and polatuzumab vedotin has an acceptable safety profile and promising efficacy, which may make this approach an attractive therapeutic option for patients with untreated FL.

1.2 Background

1.2.1 Overview of Follicular Lymphoma

Follicular lymphoma (FL) is a common, indolent subtype of B-NHL characterized by heterogeneous presentations, as some patients require prompt intervention, whereas others tolerate watch-and-wait for years (Ardeshna et al. 2003, Solal-Céligny et al. 2012, Ardeshna et al. 2014, Armitage et al. 2016). Most patients' disease responds to modern induction treatments (Rummel et al. 2013, Flinn et al. 2014, Morschhauser et al. 2018), albeit with a range of short- and long-term toxicities. However, patients' subsequent clinical courses are highly variable. Many patients experience a disease-course entailing multiple responses to therapy with prolonged remissions and low-grade relapses over many years (Bachy et al. 2019, Batlevi et al. 2020), but others suffer progression of disease within 24 months of treatment initiation ('POD24') and have poor outcomes despite receiving subsequent therapy (Casulo et al. 2015, Jurinovic et al. 2016). Additionally, approximately 15% of patients with FL experience transformation to an aggressive histology, which contributes to nearly half of all deaths from FL (Wagner-Johnston et al. 2015, Freeman et al. 2019).

There is no predictive model to guide frontline treatment of FL. The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria were developed to exclude patients with high disease burden from a study comparing low-intensity treatment with watch-and-wait (Brice et al. 1997). Today, these criteria are often used to help identify patients likely to need chemotherapy (those with high disease burden; Ghielmini et al. 2005) in addition to an anti-CD20 antibody for frontline treatment. The Follicular Lymphoma International Prognostic Index (FLIPI; Solal-Céligny et al. 2004) is a widely used prognostic risk model and includes five adverse risk factors (age ≥60, advanced stage, hemoglobin <12 g/dL, >4 involved nodal areas, elevated lactate dehydrogenase). It is routinely applied in practice, but typically impacts neither decisions to pursue initial watch-and-wait versus treatment, nor which frontline treatment to recommend. While roughly 50% of patients requiring systemic treatment are high-risk by FLIPI, only 20% of them will experience treatment failure within two years after initiation. To better incorporate pathobiology, a clinicogenetic risk model ('m7-FLIPI') was developed to integrate the FLIPI, performance status, and mutation statuses of seven genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, *CARD11*; Pastore et al. 2015). Despite impressive performance metrics, the m7-FLIPI is not used routinely due to its output not influencing frontline treatment decisions.

Overall, despite our familiarity with many commonly mutated genes in FL, the mutational landscape of FL does not influence frontline clinical management. Further, we do not understand what distinguishes patients at high risk of early relapse or transformation, and there is growing interest in the internodal heterogeneity of FL. Given these issues in the field, the current approach to FL management focuses on disease control, as most patients live more than a decade

beyond their initial diagnosis. In turn, sequencing of therapies from the frontline setting through multiple relapses must account for how patient aging impacts therapeutic potential from mechanistic and tolerability perspectives, as well as potential late effects from prior lines of therapy.

1.2.2 Frontline Follicular Lymphoma Treatment Strategies

While approximately 10–15% of patients with FL present with stage I disease and can be considered for potentially curative radiation therapy (Lo et al. 2020), patients with stage II, III, or IV FL are treated with systemic therapy. The initiation, intensity, and duration of systemic therapy for FL are based on patients' goals and preferences, as the ability to delay subsequent lines of therapy by implementing more intensive frontline approaches comes at the expense of greater upfront toxicities. While the majority of patients with stage II, III, or IV FL are unlikely to be cured with conventional strategies, treatment should focus on symptom palliation, avoidance of complications from disease bulk and associated cytopenias, and improved quality of life.

In practice, one key factor influencing the choice of initial systemic treatment for FL is the histologic grade of the tumor as determined by the number of centroblasts per high power field (Barraclough et al. 2021). Grades 1, 2, or 3A FL are typically treated as one entity, whereas patients with grade 3B FL (in which solid sheets of centroblasts are present) are usually treated with regimens used for aggressive lymphomas (e.g., DLBCL). This is based on the similarities between FL grade 3B and DLBCL in terms of similar long-term outcomes, less frequent involvement of the bone marrow or peripheral blood, and more common larger masses at diagnosis.

For patients with stage II, III, or IV FL of grade 1, 2, or 3A who warrant treatment initiation, the choice of regimen depends on the presence of disease-related symptoms, organ dysfunction, and disease tempo. For patients with comorbid conditions that make them poor candidates for chemotherapy, a low tumor burden, and/or disease that progresses slowly over years, one common strategy is monotherapy with an anti-CD20 monoclonal antibody (mAb) such as rituximab (Ghielmini et al. 2005, Solal-Céligny et al. 2012, Ardeshna et al. 2014, Kahl et al. 2014). For all others, the standard of care is an anti-CD20 mAb plus alkylator-based chemotherapy (Marcus et al. 2005) or the immunomodulatory drug lenalidomide (Morschhauser et al. 2018). Today, many experts and guidelines favor the combination of bendamustine plus rituximab (BR) considering its decreased toxicity and similar efficacy compared to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Two large, randomized, phase III trials compared BR to alternative approaches including R-CHOP in patients with advanced stage FL (Rummel et al. 2013, Flinn et al. 2014), with BR resulting in similar complete and overall response rates, as well as overall survival. BR had the advantages of fewer infectious episodes, less neuropathy and stomatitis, and no alopecia. In the era of applying the Lugano 2014 criteria via PET-CT imaging, frontline BR is associated with an approximately 73% CR rate and 79% ORR

(Trotman et al. 2018).

An alternative frontline treatment approach for patients with advanced stage FL is the combination of an anti-CD20 mAb plus lenalidomide, an immunomodulatory agent that binds the cereblon E3 ubiquitin ligase complex. This triggers degradation of several key transcription factors and results in anti-tumor T and NK cell activation. Rituximab plus lenalidomide (given as the combination for 18 months followed by one additional year of rituximab) was compared to rituximab plus chemotherapy (given as the combination for six cycles followed by two years of maintenance rituximab) in the international phase III RELEVANCE study (Morschhauser et al. 2018). CR (by CT imaging) and 3-year PFS rates were similar in the two groups (48% vs. 53% for CR, and 77% vs. 78% for PFS, respectively). More neutropenia was noted in the rituximab plus chemotherapy group, compared to more cutaneous reactions in the rituximab plus lenalidomide group. While RELEVANCE was formally a negative study given its superiority design, the combination of an anti-CD20 mAb and lenalidomide is considered a reasonable frontline treatment option per the NCCN Guidelines (v5.2021).

Further, a variety of maintenance treatment approaches have been explored in FL, with the current preferred option being maintenance anti-CD20 mAb therapy after induction chemoimmunotherapy based on the PRIMA study (Bachy et al. 2019). Here, responding patients were randomized to observation or rituximab administered every 8 weeks for 2 years. The median PFS was 10.5 years in the rituximab maintenance arm compared with 4.1 years in the observation arm. However, no OS difference was seen, with 10-year OS estimates being approximately 80% in both study arms, and no change in the rate of aggressive transformation was seen. Unfortunately, rituximab maintenance was associated with a higher rate of grade 3+ adverse events driven largely by cytopenias and infections. How this risk-benefit tradeoff extrapolates to patients receiving bendamustine plus rituximab prior to maintenance anti-CD20 mAb therapy is not clear as no randomized study has specifically asked this question. A subset analysis of the GALLIUM study (Marcus et al. 2017; Hiddemann et al. 2018) that randomized patients to either obinutuzumab or rituximab during induction (with chemotherapy) and maintenance raised concerns of increased fatal adverse events among patients over age 70 years receiving anti-CD20 mAb maintenance after bendamustine-based induction. In total, there remains room for improvement in the frontline treatment of FL given the need to balance response rate, duration of treatment and responses, as well as short- and long-term toxicities.

1.2.3 Mosunetuzumab

Mosunetuzumab is a full-length, fully humanized IgG1 bispecific antibody targeting both CD3 (on the surface of T cells) and CD20 (on the surface of B cells) that is produced in Chinese hamster ovary (CHO) cells with use of the knobs-into holes technology (Atwell et al. 1997, Spiess et al. 2013). As a T cell-recruiting bispecific antibody targeting CD20-expressing B cells, mosunetuzumab is a

conditional agonist; targeted B cell killing is observed only upon simultaneous binding to CD20 on B cells and to CD3 on T cells (Sun et al. 2015). Engagement of both arms of mosunetuzumab results in the formation of an immunologic synapse between a target B cell and a cytotoxic T cell resulting in T cell activation in a target- and dose-dependent manner. Subsequent directed release of perforin and a cocktail of granzymes from T cells through the immunologic synapse results in B cell lysis. Preliminary results from early phase clinical trials (Budde et al. 2018, Schuster et al. 2019, Assouline et al. 2020, Matasar et al. 2020, Phillips et al. 2020, Bartlett et al. 2021, Budde et al. 2021) have motivated additional studies of mosunetuzumab in the frontline and second-line settings as a monotherapy and in combination with chemotherapy and/or other novel agents. Specifically, in the phase I/II GO29781 study, intravenous mosunetuzumab monotherapy has been explored at the recommended phase II dose (1/2/60/30 mg step-up dosing) in 90 patients with rel/ref FL who had received at least 2 prior lines of therapy (Budde et al. 2021, Budde et al. 2022). By independent review committee assessment, the overall response and CR rates were 80% and 60%, respectively, with 12-month event-free rates after first response of 62% in all responders and 76% in patients achieving CR. The most common AE was CRS (44% of patients), with only 2 of 90 patients experiencing grade 3–4 CRS, and AEs leading to mosunetuzumab discontinuation were uncommon (4%). Additional cohorts of patients with various rel/ref B-NHL subtypes received subcutaneous mosunetuzumab via step-up dosing, which identified the recommended phase 2 dose (RP2D) as 5/45/45 mg. No dose-limiting toxicities were observed, with the most common adverse events being injection site reactions, CRS, fatigue, headache, rash, neutropenia and pyrexia. CRS mostly occurred in cycle 1 and was low-grade in all patients (no grade 3+ CRS observed), which supports an outpatient treatment schedule. Across all histologies, the OR rate was 19/38 (50%), with eight of ten patients with rel/ref FL achieving objective responses (Bartlett et al. 2021).

1.2.4 Polatuzumab Vedotin

Polatuzumab vedotin is an antibody-drug conjugate (ADC) that contains a humanized IgG1 anti-CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent (MMAE) linked through a protease-cleavable linker (mc-vc-PAB). CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in most B cell-derived malignancies, including nearly all B cell lymphomas and CLL samples tested (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, making CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2009; Polson et al. 2007). MMAE, a potent analog of dolastatin 10, has a mode of action similar to vincristine, which is a component of standard chemotherapy used for treatment of lymphoma. Following internalization, the conjugate is cleaved by lysosomal enzymes to release MMAE, which binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth and induction of apoptosis (Bai et al. 1990; Francisco et al. 2003). This therapeutic approach takes advantage of the specific targeting capability and favorable PK properties of the antibody and the

cytotoxic activity of MMAE. Polatuzumab vedotin has demonstrated efficacy in nonclinical mouse xenograft models of human CD79b-positive B cell lymphomas, and it is approved for use in relapsed or refractory DLBCL based on improved complete response rates, PFS, and OS when polatuzumab vedotin was combined with BR compared to BR alone in rel/ref DLBCL (Sehn et al. 2019). Additionally, one arm of the ROMULUS study explored the combination of polatuzumab vedotin and the anti-CD20 monoclonal antibody rituximab in the rel/ref FL setting, and a promising overall response rate of 70% (14/20) was reported (Morschhauser et al. 2019). Based on the nonclinical and clinical data to date, polatuzumab vedotin has the potential to be an important therapeutic drug for the treatment of CD79b-positive B cell malignancies, either as monotherapy or in combination with other agents including chemotherapeutic agents as well as biological agents such as monoclonal or bispecific antibodies.

1.2.5 Correlative Studies Background

Understanding the mechanism of action of mosunetuzumab as well as identifying prognostic and predictive biomarkers for safety and clinical activity in patients with untreated FL receiving mosunetuzumab combined with polatuzumab vedotin forms the underlying rationale for their assessment in this study. The peripheral blood sampling schedule prior to, during, and after mosunetuzumab administration is designed to provide a detailed profile of the following:

- Expression of phenotypic markers of T cell function and potential markers of resistance to mosunetuzumab therapy.
- Dynamic quantitative changes in T, B, and natural killer (NK) cell counts.
- Monitoring for measurable residual disease (MRD) and establishing correlations with remission duration and survival.

In addition to peripheral blood sampling, archival tumor biopsies will be obtained where applicable for studies of genomic and immunologic correlates of response depth and duration, as well as toxicity.

1.3 Study Design

1.3.1 Overall Design

This is a single arm, open-label, phase II study treating patients with untreated follicular lymphoma with mosunetuzumab and polatuzumab vedotin. The hypothesis of this study is that the combination of mosunetuzumab and polatuzumab vedotin will be safe and efficacious in patients with untreated follicular lymphoma who otherwise would receive standard of care multi-agent treatment including an anti-CD20 monoclonal antibody and either alkylator-based chemotherapy or lenalidomide.

1.3.2 Justification for Dose and Schedule

A “step-up dosing” strategy for mosunetuzumab is clinically active and well-tolerated. It is in place to mitigate the potential for acute safety risks driven by systemic cytokine release following initial onset of target engagement (Bartlett et al. 2019). “Target doses” in each 21-day cycle are intended to maintain maximal efficacy and sustain durability of response while minimizing any potential safety risks in later cycles. Eight cycles of mosunetuzumab will be administered initially. Patients who achieve a CR after Cycle 8 stop treatment. Seventeen cycles are permitted for patients with a PR or SD at the end of Cycle 8 for potentially deepening responses. In clinical studies of patients with measurable disease receiving mosunetuzumab, those who do not achieve a CR with 8 cycles can receive up to 17 cycles to achieve high clinical response rates and durability while minimizing any acute or potential cumulative safety risks.

The rationale for subcutaneous (SC) dosing is to minimize cytokine-driven toxicities upon initial mosunetuzumab dosing. To further reduce the rate and severity of CRS events, and to improve patient convenience, mosunetuzumab SC step-up dosing regimens of 5/15/45 mg (F1) and 5/45/45 mg (F2) are being evaluated in Study GO29781 Group F. The C1D1 dose of 5 mg SC was selected as the projected C_{max} is similar to 1 mg IV, the recommended initial dose of the IV step-up dosing regimen. This starting dose of 5 mg was within the range evaluated in the Group D flat dosing schedule. The target dose was selected at 45 mg SC, as it is projected to provide a lower C_{max} (population pharmacokinetics [popPK] model predicted geometric mean ratio [GMR] = 0.37) but higher AUC ([GMR] = 1.49) at steady state than the 30 mg IV maintenance dose. Therefore, it is expected to be associated with sufficient exposure to drive anti-tumor activity with a potentially lower risk of CRS compared with mosunetuzumab IV 1/2/60/30 mg dosing. Two different doses (15 mg and 45 mg) were evaluated on C1D8 to further assess step-up dosing for CRS mitigation to reach the target dose of 45 mg. The 5/45/45 mg dosing regimen showed a comparable safety profile to the 5/15/45 mg dosing regimen but with a shortened window of CRS associated mostly with only the first two doses of mosunetuzumab during cycle 1. Further, the 5/45/45 mg dosing regimen also allows faster achievement of the target dose. Therefore, this dose is considered the preferred dose for mosunetuzumab SC monotherapy.

Polatuzumab vedotin is approved for use in the treatment of relapsed or refractory DLBCL in combination with bendamustine and rituximab (Sehn et al. 2020), being administered IV at 1.8 mg/kg once every 21 days for 6 cycles. It is being studied at this dosing strategy in other subtypes of B-NHL in combination with a variety of other agents.

1.4 Risk/Benefit Assessment

1.4.1 Known Potential Risks

The mechanism of action of mosunetuzumab is immune-cell activation against CD20 expressing cells; therefore, a spectrum of events involving infusion-related reactions (IRRs), target-mediated cytokine release, and/or hypersensitivity with or without emergent ADAs may occur. See the Mosunetuzumab Investigator's Brochure for a more detailed description of all anticipated risks for mosunetuzumab.

Disease-related factors that may be associated with an increased risk of severe CRS following chimeric antigen receptor (CAR) T cell therapy; and therefore, potentially other T cell engaging therapies, include, but are not limited to, lymphoma bone marrow involvement, extranodal disease, B cell lymphocytosis, and the presence of circulating peripheral malignant cells. Patients with the above disease-related factors may require additional monitoring (i.e., more frequent measurements of vital signs every 15 minutes) after mosunetuzumab administration (especially first dose), and management of treatment-emergent adverse events (including CRS) must adhere to guidance.

In study GO29781 of patients with relapsed/refractory NHL, clinical data supported a favorable efficacy and safety profile of 1/2/60/30 mg mosunetuzumab monotherapy administered intravenously (Cycle 1 Day 1: 1 mg, Cycle 1 Day 8: 2 mg, Cycle 1 Day 15: 60 mg, Cycle 2 Day 1: 60 mg, Day 1 of Cycle 3 and all subsequent cycles: 30 mg). An assessment of the GO29781 study with a clinical cutoff date of January 21, 2020 was conducted with 153 patients at the 1/2/60/30 mg dose. Of these patients, 44% had DLBCL and 31% had FL grade 1–3A. Other histologies included in this cohort were mantle cell lymphoma (13%) and transformed FL (10%). The median number of cycles received was 3 (1–13), and the median number of infusions was 5 (1–15). The vast majority of patients (95%) experienced an adverse event (AE) of any grade. Serious AEs and grade 3+ AEs were observed in 42% and 60% of patients, respectively. AEs leading to discontinuation occurred in 4% of patients. Most of the adverse events (37% any grade) were cytokine release syndrome (CRS). By Lee criteria, the CRS rates were 22%, 13%, 1%, and <1% for grades 1, 2, 3, and 4, respectively. By American Society for Transplantation and Cellular Therapy (ASTCT) criteria, the rate of CRS of any grade was 33%. The rates were 20%, 11%, 2%, and <1% for grades 1, 2, 3, and 4, respectively. Serious CRS-related AEs were observed in 19% of patients. The highest rate of CRS was observed from Cycle 1, Day 15 through Cycle 1 Day 21 (29% any grade). Reference for this is the internal SREP with clinical cutoff date (CCOD) of January 21, 2020.

Additional cohorts of patients with various subtypes of rel/ref B-NHL received mosunetuzumab by subcutaneous (SC) injection with step-up dosing (Bartlett et al. 2021). The RP2D was identified as 5/45/45 mg, which allows the target dose to be

reached quickly without additional CRS compared to 5/15/45 mg step-up dosing. The most common AEs of any grade observed in patients receiving single-agent SC mosunetuzumab were injection site reactions, fatigue, headache, rash, neutropenia, and pyrexia. CRS mostly occurred in cycle 1 and was low-grade in all 74 treated patients (no grade 3+ CRS observed), which supports an outpatient treatment schedule (Bartlett et al, 2021).

Concurrent administration of polatuzumab vedotin with mosunetuzumab is not expected to significantly influence the incidence and grade of CRS attributable to mosunetuzumab. The major risks for polatuzumab vedotin include IRR (approximately 15%), peripheral neuropathy (approximately 40%), cytopenias (approximately 40%), and infections (approximately 30%). See the Polatuzumab Vedotin Investigator's Brochure for a more detailed description of all anticipated risks for polatuzumab vedotin.

Potential overlapping toxicities between mosunetuzumab and polatuzumab vedotin include thrombocytopenia, neutropenia, infections, TLS, and hepatotoxicity.

1.4.2 Known Potential Benefits

Given the generally indolent nature of FL even when diagnosed at an advanced stage, treatment should focus on symptom palliation, avoidance of complications from disease bulk and associated cytopenias, and improved quality of life. Modern frontline treatment approaches typically entail a combination of an anti-CD20 mAb with alkylator-based chemotherapy, often followed by maintenance anti-CD20 mAb therapy for an additional two years. While these approaches offer promising response rates and remission durations, they come with substantial short- and long-term toxicities as well as treatment burdens. The less common alternative frontline strategy of an anti-CD20 mAb plus the immunomodulatory agent lenalidomide also comes with short- and long-term adverse effects. The combination of mosunetuzumab and polatuzumab vedotin studied herein incorporates two potent novel agents with potentially synergistic mechanisms of action, administered for a shorter overall duration than standard induction and maintenance strategies, and with few if any predicted late effects. The combination of mosunetuzumab and polatuzumab vedotin is being explored in the open-label, phase Ib/II GO40516 trial investigating the safety, tolerability, pharmacokinetics, and efficacy of mosunetuzumab in combination with polatuzumab vedotin in patients with relapsed/refractory B cell non-Hodgkin lymphoma (B-NHL), including follicular lymphoma (FL), transformed follicular lymphoma (t-FL), and diffuse large B cell lymphoma (DLBCL). In the preliminary dose-escalation cohort, cytokine release syndrome (CRS) was observed in only 2 of 22 patients (both grade 1), and no immune effector cell-associated neurotoxicity was observed. A complete response (CR) was achieved by all 3 patients with follicular lymphoma, and 12 of 22 patients overall achieved a complete response. These preliminary data indicate that the combination of mosunetuzumab and polatuzumab vedotin has an acceptable safety profile and promising efficacy, which may make this approach an attractive option

for the treatment of newly diagnosed follicular lymphoma.

1.4.3 Assessment of Potential Risks and Benefits

Patients with indolent lymphomas such as FL are managed with a strategy that focuses on disease control, as most patients live more than a decade beyond their initial diagnosis. In turn, sequencing of therapies from the frontline setting through multiple relapses must account for how patient aging impacts therapeutic potential from mechanistic and tolerability perspectives, as well as potential late effects from prior lines of therapy. The combination of mosunetuzumab and polatuzumab vedotin is an attractive strategy for study in the frontline treatment of FL as it offers the potential to spare patients the short- and long-term toxicities from exposure to classical cytotoxic chemotherapy agents and reduces their duration of exposure to B cell-depleting agents (e.g., standard of care induction plus maintenance anti-CD20 mAbs). These more intensive approaches can potentially be reserved for patients with FL whose disease relapses after combination mosunetuzumab and polatuzumab vedotin.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary		
1. To evaluate the efficacy of the combination of mosunetuzumab and polatuzumab vedotin in patients with untreated follicular lymphoma.	1. Complete response (CR) as best response determined by PET-CT, per Deauville 5-point scale (Lugano 2014 criteria).	Achieving CR in response to frontline FL treatment is a significant favorable prognostic factor associated with prolonged PFS and OS in a study of patients treated with chemoimmunotherapy (Trotman et al. 2018).
Secondary		
1. To evaluate additional metrics of efficacy of the combination of mosunetuzumab and polatuzumab vedotin in patients with untreated follicular lymphoma.	1. Partial response (PR), overall response (OR; CR + PR), stable disease (SD), and progressive disease (PD) as best response determined by PET-CT, per Deauville 5-point scale (Lugano 2014 criteria). 2. CR, PR, OR, SD, and PD rates by PET-CT after Cycle 8 of treatment (PET8), per Deauville 5-point scale (Lugano 2014 criteria).	Response rates, PFS, and OS are valuable metrics of therapeutic benefit in FL, as treatment should focus on avoidance of complications from disease bulk and associated cytopenias, optimizing treatment-free intervals, and preserving survival as possible.

	3. Interim CR, PR, OR, SD, and PD rates by PET-CT after Cycle 2 of treatment (PET2), per Deauville 5-point scale (Lugano 2014 criteria). 4. 24- and 48-month progression-free survival (PFS) and overall survival (OS) rates. 5. Time to and duration of first response (CR or PR). 6. Time to and duration of first CR. 7. Time to next treatment initiation.	
2. To assess the safety and tolerability of combining mosunetuzumab with polatuzumab vedotin in patients with untreated follicular lymphoma.	1. Frequencies and grades of treatment-emergent adverse events (TEAE) including CRS. 2. Rate of treatment discontinuation due to TEAE.	The combination of mosunetuzumab and polatuzumab vedotin aims to spare patients with FL exposure to classical cytotoxic chemotherapy and extended (>1 year) B cell-depleting therapy (via maintenance anti-CD20 mAb treatment). The TEAE profile and rate of treatment discontinuation due to TEAEs will reflect the tolerability of this novel frontline treatment strategy and whether further study in comparison to standard of care approaches is justified. Rate and grade of CRS will impact tolerability and feasibility of the study treatment strategy.
3. To assess the use of tocilizumab for management of cytokine release syndrome (CRS) in patients with untreated follicular lymphoma who receive mosunetuzumab and polatuzumab vedotin.	1. Percentage of patients requiring any tocilizumab and number of total tocilizumab doses per patient for management of CRS.	CRS is a TEAE uniquely associated with mosunetuzumab compared to standard of care FL treatments, and tocilizumab will be recommended for management of CRS.

Exploratory		
1. To evaluate the dynamics of measurable residual disease (MRD) by plasma-derived circulating-tumor DNA (ctDNA) assessment in patients with untreated follicular lymphoma receiving mosunetuzumab and polatuzumab vedotin.	1. MRD by plasma-derived ctDNA assessment before, during, and after mosunetuzumab and polatuzumab vedotin administration.	Emerging evidence suggests ctDNA is a prognostic marker for PFS in follicular lymphoma.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Diagnosis of follicular lymphoma grade 1–3A, stage II–IV by Ann Arbor criteria.

2. One or more of the following criteria (adapted from GELF criteria):
   - Any nodal or extranodal tumor mass with diameter > 7 cm
   - Involvement of at least 3 nodal sites, each with diameter > 3 cm
   - Presence of any systemic or B symptoms
   - Splenic enlargement with inferior margin below the umbilical line
   - Compression syndrome (e.g., ureteral, orbital, gastrointestinal)
   - Pleural or peritoneal serous effusion (irrespective of cell content)
   - Cytopenia(s) attributable to lymphoma

3. At least 18 years of age.

4. ECOG performance status ≤ 2 (see Appendix A)

5. Adequate hematologic and organ function (unless due to underlying lymphoma per the investigator; see #6 below), defined as follows:
   - Absolute neutrophil count ≥ 1,000/mcL
   - Platelets ≥ 75,000/mcL
   - Hemoglobin ≥ 8 g/dL
   - Serum total bilirubin ≤ 1.5 x IULN (or ≤ 3 x IULN for patients with Gilbert syndrome)
   - AST(SGOT)/ALT(SGPT) ≤ 3 x IULN
   - Serum creatinine ≤ 1.0 x IULN or creatinine clearance ≥ 50 mL/min by Cockcroft-Gault

6. Patients with extensive bone marrow involvement by lymphoma and/or disease-related cytopenias (e.g., immune thrombocytopenia) may be enrolled if the following criteria are met:
   - Absolute neutrophil count ≥ 500/mcL
   - Platelet count ≥ 50,000/mcL without platelet transfusion within 14 days prior to the first dose of mosunetuzumab
   - Hemoglobin ≥ 7 g/dL without red blood cell transfusion within 7 days prior to the first dose of mosunetuzumab

7. The effects of mosunetuzumab on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (as defined in Section 5.7) prior to study entry, for the duration of study treatment, for 3 months following the final dose of mosunetuzumab, for 9 months after the final dose of polatuzumab vedotin, and for 3 months after the final dose of tocilizumab, as applicable. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study treatment, for 6 months after the final dose of polatuzumab vedotin, and for 2 months after the final dose of tocilizumab, as applicable.

8. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Prior history of aggressive B cell lymphoma such as diffuse large B cell lymphoma or high-grade B cell lymphoma.

2. Known history of treatment-emergent immune-related adverse events associated with prior immunotherapeutic agents.

3. Known history of macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH).

4. Current or past history of CNS lymphoma.

5. Any prior systemic therapy for follicular lymphoma.

6. Treatment with radiotherapy within 2 weeks prior to the first dose of mosunetuzumab (otherwise one measurable lesion outside of the radiation field must remain).

7. Treatment with any anti-CD20 monoclonal antibody within 4 weeks of Day 1 of Cycle 1.

8. Current or recent history (within the last 6 months) of CNS disease, such as stroke, epilepsy, CNS vasculitis, or serious progressive neurodegenerative disease, with clinically significant symptoms.

9. Treatment with systemic immunosuppressive medications, including but not limited to prednisone (> 20 mg), azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1.

   Note: The use of inhaled corticosteroids, mineralocorticoids for management of orthostatic hypotension, and single dose dexamethasone for nausea or B symptoms is permitted.

10. History of solid organ transplantation.

11. History of allogeneic stem cell transplantation.

12. Prior treatment with chimeric antigen receptor T cell therapy within 30 days before Day 1 of Cycle 1.

13. History of severe allergic or anaphylactic reaction to humanized, chimeric, or murine monoclonal antibodies (mAbs).

14. Known hypersensitivity to biopharmaceuticals produced in CHO cells or any component of the mosunetuzumab formulation, including mannitol.

15. History of erythema multiforme, Grade ≥ 3 rash, or blistering following prior treatment with immunomodulatory derivatives.

16. Known active bacterial, viral, fungal, or other infection, or any major episode of infection requiring treatment with IV antibiotics within 1 week of Day 1 of Cycle 1.

17. Known or suspected chronic active Epstein-Barr virus (EBV) infection.

18. Current Grade > 1 peripheral neuropathy by clinical examination or demyelinating form of Charcot-Marie-Tooth disease.

19. Active hepatitis B infection.
    a. Patients who are hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (HBcAb) positive, must be negative for hepatitis B virus (HBV) polymerase chain reaction (PCR) to be eligible for study participation

20. Active hepatitis C infection.
    a. Patients who are positive for hepatitis C virus (HCV) antibody must be negative for HCV by PCR to be eligible for study participation

21. Known history of human immunodeficiency virus (HIV) positive status.

22. History of progressive multifocal leukoencephalopathy (PML).

23. Administration of a live, attenuated vaccine within 4 weeks before first dose of study treatment or anticipation that such a live attenuated vaccine will be required during the study.
    a. Patients must not receive live, attenuated vaccines (e.g., FluMist®) while receiving study treatment or after the last dose until B cell recovery to the normal ranges.

24. Other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:
    a. Any of the following malignancies previously curatively treated: carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal, or squamous cell skin cancer
    b. Stage I melanoma, low grade, early stage localized prostate cancer, or any other previously treated malignancy that has been in remission without treatment for at least 2 years prior to enrollment

25. Active autoimmune disease requiring treatment.

26. History of autoimmune disease, including, but not limited to, myocarditis, pneumonitis, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    a. Patients with a remote history of, or well-controlled autoimmune disease, with a treatment free interval from immunosuppressive therapy for 12 months may be eligible to enroll if judged to be safe by the investigator.
    b. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone are eligible.
    c. Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    d. Patients with a history of disease-related immune thrombocytopenic purpura, or autoimmune hemolytic anemia may be eligible.

27. Evidence of any significant, uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including, but not limited to, significant cardiovascular disease (e.g., New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm).

28. Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1 Day 1 or anticipation of a major surgical procedure during the course of the study.

29. Pregnant or lactating or intending to become pregnant during the study.

a. Women of childbearing potential must have 1 negative serum pregnancy test result (minimum sensitivity, 25 mIU/mL) within 7 days of initiating Cycle 1 Day 1 of therapy.

30. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study, or which could affect compliance with the protocol or interpretation of results.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

The following steps must be taken before enrolling patients on this study:

1. Registration of consented patient in the Siteman Cancer Center OnCore database
2. Assignment of unique patient number (UPN)
3. Confirmation of patient eligibility

Patients must not start any protocol intervention or procedures prior to signing of informed consent.

4.1 Registration in OnCore Database

Patient registration to the Siteman Cancer Center OnCore database must occur within one business day of the patient signing consent.

4.2 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. The UPN must not include patient initials or other identifying information. All data will be recorded with this identification number on the appropriate CRFs.

4.3 Confirmation of Patient Eligibility and Enrollment

Patient eligibility will be confirmed using the information listed below:

1. Completed eligibility checklist, signed and dated by a member of the study team
2. Copy of appropriate source documentation confirming patient eligibility

4.4 OnCore Subject Status Definitions

Note: subject status should not be updated in OnCore until the subject is actively in that status; future dates are not allowed.

Subject Status	Definition
Consented	Patient has signed an IRB approved consent for the trial.
Eligible	Patient eligibility has been confirmed by Washington University PI or delegate.
Not Eligible	Patient did not meet eligibility criteria for the trial. Note that if a patient is determined to be eligible but never initiates study participation, they are not considered a screen fail.
On Study	Patient is confirmed eligible for the study and enrolled.
On Treatment	Patient is receiving study therapy. On Treatment date should be the date of the first study treatment.
Off Treatment	Patient has discontinued study therapy. Off Treatment date should be the last day any study treatment was administered.
On Follow Up	On Follow-up date should be the same date as Off Treatment date.
Off Study	Patient has fully discontinued all study procedures (including any follow-up procedures and/or review of medical record for outcomes data).

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.6 Strategies for Recruitment and Retention

All patients with newly diagnosed follicular lymphoma requiring treatment will be presented and discussed at the weekly Lymphoma Patient Review meeting, and they will be screened for relevant clinical trials.

5.0 TREATMENT PLAN

5.1 Pretreatment Laboratory Testing Requirements

Patients are required to meet the following laboratory testing requirements (unless due to underlying conditions as noted below) prior to receiving mosunetuzumab on Cycle 1 Day 1 (-7/+0 days):

- Absolute neutrophil count ≥ 1,000/mcL (or ≥ 500/mcL for patients with extensive bone marrow involvement by lymphoma and/or disease-related cytopenias)

- Platelets ≥ 75,000/mcL (or ≥ 50,000/mcL without platelet transfusion within 14 days prior to the first dose of mosunetuzumab for patients with extensive bone marrow involvement by lymphoma and/or disease-related cytopenias)
- Hemoglobin ≥ 8 g/dL (or ≥ 7 g/dL without red blood cell transfusion within 7 days prior to the first dose of mosunetuzumab for patients with extensive bone marrow involvement by lymphoma and/or disease-related cytopenias)
- Serum total bilirubin ≤ 1.5 x IULN (or ≤ 3 x IULN for patients with Gilbert syndrome)
- AST(SGOT)/ALT(SGPT) ≤ 3 x IULN
- Serum creatinine ≤ 1.0 x IULN or creatinine clearance ≥ 50 mL/min by Cockcroft-Gault

For Cycle 1 Day 8 and beyond, laboratory testing requirements will follow the guidance for mosunetuzumab dose interruptions based on TEAE as per Section 6.3.

5.2 Premedication Administration

Patients will receive 650 mg PO acetaminophen and 50 mg PO diphenhydramine at least 30 minutes prior to administration of polatuzumab vedotin for potential infusion-related reactions. Patients will also receive 250 mcg IV palonosetron prior to administration of polatuzumab vedotin for prevention of nausea.

Corticosteroid prophylaxis will be administered prior to mosunetuzumab weekly step-up dosing during Cycle 1. On C1D1, when both mosunetuzumab and polatuzumab vedotin are administered, corticosteroid prophylaxis will be given as 20 mg dexamethasone intravenously (preferred; or alternatively 80 mg methylprednisolone intravenously). When only mosunetuzumab is administered on C1D8 and C1D15, corticosteroid prophylaxis will be given as 20 mg dexamethasone orally (preferred; or alternatively 20 mg dexamethasone intravenously or 80 mg methylprednisolone intravenously). The administration of corticosteroid prophylaxis is optional for Cycle 2 and beyond unless the patient experiences CRS with the prior administration of mosunetuzumab, then prophylaxis with corticosteroids must be administered for subsequent doses until no additional CRS events are observed.

If not already premedicated for polatuzumab vedotin within 4 hours of each mosunetuzumab injection, all patients will receive 650 mg PO acetaminophen and 50 mg PO diphenhydramine at least 30 minutes prior to each mosunetuzumab injection.

Patients deemed by the investigator to be at high risk of TLS will receive allopurinol or a suitable alternative (such as rasburicase) at the discretion of the treating physician, along with adequate hydration (see Appendix D for additional details).

5.3 Study Intervention Description

Mosunetuzumab is a novel CD3xCD20 bispecific antibody being studied in various subtypes of B cell lymphomas.

Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate indicated in combination with bendamustine and a rituximab product for the treatment of patients with relapsed or refractory diffuse large B cell lymphoma.

5.4 Study Intervention Administration

Polatuzumab vedotin (if indicated per protocol) will be administered first, followed by mosunetuzumab at least 60 minutes after the completion of the polatuzumab vedotin infusion.

Polatuzumab vedotin will be administered intravenously at a dose of 1.8 mg/kg on Day 1 of Cycles 1 through 6. The initial dose of polatuzumab vedotin should be infused over 90 minutes. Patients should be monitored with vital signs taken every 30 minutes +/- 10 minutes prior to, during, and after the infusion for infusion-related reactions. Monitoring will continue for 90 minutes following completion of the initial dose. If the previous infusion was well-tolerated, subsequent doses of polatuzumab vedotin may be administered as 30-minute infusions and patients should be monitored with vital signs taken every 30 minutes +/- 10 minutes prior to, during, and after the infusion for at least 30 minutes after completion of the infusion. Baseline weight, defined as weight obtained within 28 days prior to C1D1, will be used for dosing calculation. If patient's body weight changes by more than 10% from baseline weight, the dose will be recalculated.

Mosunetuzumab will be administered subcutaneously (SC) over 30 seconds to 2 minutes in an outpatient setting (unless inpatient administration is preferred by the treating physician or is required based on grade and duration of prior CRS due to mosunetuzumab; see Appendix D) with immediate access to trained critical care personnel and facilities equipped to respond to and manage medical emergencies. The preferred injection site is the thigh; do not inject into areas where skin is red, bruised, tender, or hard, or areas where there are moles or scars. Patients will be observed for signs or symptoms of CRS (with vital signs taken every 30 minutes +/- 10 minutes) for at least 2 hours following all Cycle 1 injections. For patients with evidence of circulating peripheral malignant cells prior to initiation of study treatment, more frequent monitoring with vital signs every 15 minutes +/- 5 minutes after mosunetuzumab injection on Cycle 1 Day 1 should be considered. Subsequent injections starting with Cycle 2 Day 1 may be followed by 30-minute observation periods if the prior injection was tolerated with no CRS. Otherwise, 2-hour observation periods are required until an injection is tolerated with no CRS. Mosunetuzumab (flat dosing independent of body weight) will be administered in a step-up dosing schedule on a 21-day cycle:

- Cycle 1 Day 1 – 5 mg SC
- Cycle 1 Day 8 – 45 mg SC
- Cycle 1 Day 15 – 45 mg SC
- Day 1 of Cycles 2 through 17 – 45 mg SC

5.5 Definitions of Evaluability

Endpoint	Definition of Evaluability
Primary	
Complete response (CR) as best response determined by PET-CT, per Deauville 5-point scale (Lugano 2014 criteria).	All patients who receive any study treatment.
Secondary	
Partial response (PR), overall response (OR; CR + PR), stable disease (SD), and progressive disease (PD) as best response determined by PET-CT, per Deauville 5-point scale (Lugano 2014 criteria).	All patients who receive any study treatment.
CR, PR, OR, SD, and PD rates by PET-CT after Cycle 8 of treatment (PET8), per Deauville 5-point scale (Lugano 2014 criteria).	All patients who receive any study treatment and undergo PET8 response assessment.
Interim CR, PR, OR, SD, and PD rates by PET-CT after Cycle 2 of treatment (PET2), per Deauville 5-point scale (Lugano 2014 criteria).	All patients who receive any study treatment and undergo PET2 interim response assessment.
Progression-free survival (PFS)	All patients who receive any study treatment.
Overall survival (OS)	All patients who receive any study treatment.
Time to first response (CR or PR)	All patients who receive any study treatment and have a post-baseline response assessment showing CR or PR.
Duration of first response (CR or PR)	All patients who receive any study treatment and have a post-baseline response assessment showing CR or PR.
Time to first CR	All patients who receive any study treatment and have a post-baseline response assessment showing CR.
Duration of first CR	All patients who receive any study treatment and have a post-baseline response assessment showing CR.
TTNT	All patients who receive any study treatment.
Frequencies and grades of TEAEs including CRS	All patients who receive any study treatment.
Rate of treatment discontinuation due to TEAE	All patients who receive any study treatment.

Percentage of patients requiring any tocilizumab	All patients who receive any study treatment.
Number of total tocilizumab doses per patient for management of CRS	All patients who receive any study treatment.
Tertiary/Exploratory	
MRD by plasma-derived ctDNA assessment before, during, and after mosunetuzumab and polatuzumab vedotin administration	All patients who have ctDNA collections at baseline, EOT, and at least one on treatment collection.

Unless otherwise stated, all patients who receive any study treatment are evaluable for efficacy endpoints, regardless of disposition.

All patients who receive any study treatment are evaluable for the safety and tolerability endpoints. Patients are evaluated from first receiving study treatment until 30 days following the last administration of study treatment, study discontinuation/termination, or initiation of alternative lymphoma-directed therapy, whichever is earlier.

5.6 Concomitant Therapy and Supportive Care Guidelines

5.6.1 Permitted Therapy

Growth Factors

For neutropenia, granulocyte colony-stimulating factor (G-CSF) dosing should follow institutional standards. For patients who develop neutropenia, G-CSF is not routinely recommended for the treatment of uncomplicated neutropenia. However, G-CSF may be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes (Smith et al. 2015).

Prophylaxis for Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a known risk of anti-tumor therapy in hematologic malignancies including rarely FL. All patients should be well-hydrated prior to the first dose of study treatment. Initiation of tumor lysis prophylaxis prior to treatment initiation should be considered by the treating physician if the patient is deemed to be high-risk for TLS (see Appendix D; Coiffier et al. 2008).

Infection Prophylaxis

Anti-infective prophylaxis for viral, fungal, bacterial or Pneumocystis infections is permitted and should be instituted per institutional practice or investigator preference based on individual patient risk factors. Antibody-based prophylaxis for COVID-19 infection is permitted per institutional practice. All anti-infective prophylaxis used should be recorded appropriately in the eCRF.

Other Concomitant Medications

Anti-emetic therapy may be instituted for any patient if clinically indicated according to institutional practice. Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards.

SARS-CoV-2 Management

Prophylaxis

- Administration of anti-SARS-CoV-2 prophylaxis, if available, should be considered for all patients. The best timing of administration (i.e. before initiation of study treatment or during the study) should be in the investigator's judgement.

COVID-19 Vaccination

- COVID-19 vaccines (approved, non-live), including booster vaccines for novel variants, are strongly recommended for all patients. Information on SARS-CoV-2 vaccine administration should be collected even if it was given more than 7 days prior to initiation of study treatment.
- Factors to consider by investigators when making individualized decisions for patients receiving mosunetuzumab:
    - General condition of the patient and severity/seriousness of underlying disease
    - Potential risks associated with SARS-CoV-2 infection and potential benefits and risks from COVID-19 vaccination
    - Epidemiology of SARS-CoV-2 infection in the patient's location
- Providers should follow local practice guidelines for the timing of vaccination administration prior to initiating therapy to maximize potential therapeutic benefit.
- If COVID-19 vaccines are administered during study treatment, vaccination should be administered after completion of mosunetuzumab step-up dosing and at least one week after administration of the target mosunetuzumab dose. For subsequent treatment cycles after study treatment target dose has been administered, COVID-19 vaccines can be given at least one week before or after mosunetuzumab dosing.

Treatment for New-onset SARS-CoV-2 Infection During Study Treatment

- Appropriate therapy for new-onset SARS-CoV-2 infection during study treatment may include but is not limited to, antivirals and/or monoclonal antibodies in accordance with local institutional guidance (El Chaer et al. 2022).

5.6.2 Cautionary Therapy

CYP450 Enzymes

Given the expected pharmacology of mosunetuzumab, the transient release of cytokines may suppress CYP450 enzymes and cause drug-drug interactions. Preliminary clinical data indicate that mosunetuzumab induced a transient elevation

in plasma interleukin (IL)-6. However, physiologically based PK modeling and simulations based on IL-6 and CYP3A4 interaction indicated a low risk of the cytokine-mediated drug-drug interaction potential of mosunetuzumab on CYP450 enzyme expression or activity. Patients at the highest risk of a drug-drug interaction are those receiving concomitant medications that are CYP450 substrates and have a narrow therapeutic index (Appendix E). Such concomitant medications should be monitored for toxicity, and dose adjusted accordingly.

Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. Given the unknown safety profile of the investigational combination and unknown components of herbal therapies, the use of any herbal therapies is prohibited while receiving study treatment.

5.6.3 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Investigational or unlicensed/unapproved agents to treat lymphoma
- Administration of live vaccines
- Cytotoxic chemotherapy other than study treatments intended for treatment of lymphoma
- Radiotherapy for treatment of lymphoma
- Immunotherapy other than study treatments for treatment of lymphoma
- Immunosuppressive therapy (except medications indicated per protocol, including corticosteroids and tocilizumab, or short-course corticosteroids [≤0.5 mg/kg prednisone equivalent for ≤5 days] for management of AEs)
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate); adjuvant endocrine therapy for non-metastatic, hormone receptor-positive breast cancer is permitted.
- Biologic or targeted agents for treatment of lymphoma
- Herbal therapies
- Any therapies intended for the treatment of lymphoma, whether approved by local regulatory authorities or investigational

5.7 Women of Childbearing Potential

Women of childbearing potential are required to have a negative pregnancy test within 7 days prior to the first dose of mosunetuzumab. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal status (≥ 24 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Mullerian agenesis). Even in presence of infertility history, a reliable contraception, including 2 adequate methods of contraception, is indicated.

The effects of mosunetuzumab on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study treatment, for 3 months following the final dose of mosunetuzumab, for 9 months after the final dose of polatuzumab vedotin, and for 3 months after the final dose of tocilizumab, as applicable. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study treatment, for 6 months after the final dose of polatuzumab vedotin, and for 2 months after the final dose of tocilizumab, as applicable. Women must refrain from donating eggs during this same period, and men must refrain from donating sperm.

Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established and proper use of progestogen only hormonal contraceptives that inhibit ovulation, hormone releasing intrauterine devices, and copper intrauterine devices. Barrier methods must always be supplemented with the use of a spermicide.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

If a patient is suspected to be pregnant, mosunetuzumab should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient becomes pregnant during therapy or within 3 months after the last dose of mosunetuzumab, or if the female partner of a male study subject becomes pregnant while the study subject is receiving mosunetuzumab or within 2 months of the male study subject's last mosunetuzumab dose, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE. The investigator must be notified in order to facilitate outcome follow-up.

Additionally, if a female subject becomes pregnant while receiving polatuzumab or within 9 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving polatuzumab or within 6 months of the male study subject's last polatuzumab dose, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly,

any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

Women should discontinue breastfeeding during treatment with polatuzumab vedotin and for at least 3 months after the last dose of polatuzumab vedotin.

5.8 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for 17 cycles (12 months) or until one of the following criteria applies:

- CR on PET-CT scan after Cycle 8
- Treatment interruption > 21 days as a result of an adverse event (unless investigator believes the patient is continuing to derive clinical benefit from study treatment)
- Grade 4 CNS event
- Experiences 2 or more seizures
- Documented disease relapse or progression
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.9 Duration of Follow-up

Patients will be followed after EOT every 3 months (-1/+1 month) for 2 years and then every 6 months (-1/+1 month) until 5 years for progression and death from any cause.

5.10 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study team.

6.0 TREATMENT MANAGEMENT GUIDELINES AND DOSE MODIFICATIONS

6.1 Mosunetuzumab and Polatuzumab Vedotin Treatment Management Guidelines

6.1.1 Known Risks Associated with Mosunetuzumab

Cytokine Release Syndrome (CRS)
The mechanism of action of mosunetuzumab is immune-cell activation against CD20 expressing cells; therefore, a spectrum of events involving infusion-related reactions (IRRs), target-mediated cytokine release, and/or hypersensitivity with or without emergent ADAs may occur. See the Mosunetuzumab Investigator's Brochure for additional details.

Disease-related factors that may be associated with an increased risk of severe CRS following chimeric antigen receptor (CAR) T cell therapy; and therefore, potentially other T cell engaging therapies, include, but are not limited to bone marrow involvement, extranodal disease, B cell lymphocytosis, and the presence of circulating peripheral malignant cells. Patients with the above disease-related factors will require additional monitoring (i.e., more frequent measurements of vital signs every 15 minutes) during mosunetuzumab dosing (especially first dose) should be undertaken.

To minimize the risk and sequelae of IRRs and CRS, corticosteroid premedication will be administered as described in Section 5.2.

Mild to moderate presentations of IRRs and/or CRS may include symptoms such as fever, headache, and myalgia, and may be treated symptomatically with analgesics, anti-pyretics, and anti-histamines as indicated.

Severe or life-threatening presentations of IRRs and/or CRS, such as hypotension, tachycardia, dyspnea, or chest discomfort, should be treated aggressively with supportive and resuscitative measures as indicated, including the use of tocilizumab and/or high-dose corticosteroids, IV fluids, and other supportive measures per local institutional practice. Severe CRS may be associated with other clinical sequelae such as disseminated intravascular coagulation and capillary leak syndrome, or may manifest as HLH. Standard of care for severe or life-threatening CRS resulting from immune-based mAb therapy has not been established; case reports and recommendations for CD19 CAR T cell have been published (Teachey et al. 2013; Lee et al. 2014; Maude et al. 2014; Neelapu et al. 2018; Lee et al. 2019; and FDA approval for 3 products describing risk management for CRS [Yescarta USPI; Kymriah USPI; Tecartus USPI]).

Management guidelines for IRRs and CRS following mosunetuzumab are summarized in Appendix D with the grading of CRS following ASTCT CRS Consensus Grading described in Appendix G. As noted in Appendix D, even moderate presentations of CRS in patients with extensive comorbidities should be

monitored closely with consideration given to intensive care unit (ICU) admission and tocilizumab administration.

Before patients receive any Cycle 1 dose of mosunetuzumab, a minimum of two doses of tocilizumab will be available on-site for each patient and will be ready for immediate administration (within 2 hours).

See Appendix H for anaphylaxis management.

Severe SARS-CoV-2 infection is associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ. If a trial subject develops severe CRS, the differential diagnosis should include SARS-CoV-2 and relevant testing performed at the discretion of the investigator.

Neutropenia

Neutropenia is a known class effect associated with other CD20-directed therapies such as rituximab and with the similar class agent blinatumomab. Reversible neutropenia has been observed following mosunetuzumab treatment. Some patients developing neutropenia have received growth factor support and/or temporary treatment holds. In nonclinical testing of mosunetuzumab in cynomolgus monkeys, hematology findings included transiently decreased WBC and platelet counts within the first day of exposure, followed by recovery or rebound recovery between Days 4 and 8. Minimal or no changes were present following subsequent doses. These findings are considered to be due to cytokine/chemokine-induced cell activation and redistribution. See the Mosunetuzumab Investigator's Brochure for additional details.

Patients will receive growth factor support per institutional standards. Patients who experience Grade 3 or 4 neutropenia should be closely monitored with more frequent assessments, as applicable. See Appendix D for the management of neutropenia.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a known risk of anti-tumor therapy in hematologic malignancies, including FL. TLS has been reported with blinatumomab, CAR T cell therapy, and other CD20-directed therapy (Porter et al. 2011). The inherent risk of TLS is dependent on the malignancy being treated and individual patient characteristics (Coiffier et al. 2008). There is the theoretical risk of TLS if treatment with mosunetuzumab results in the rapid destruction of a large number of tumor cells.

The general risk of TLS in FL is considered to be low. For patients with FL receiving mosunetuzumab, the risk of TLS is predicted to be higher for those with bulky disease, defined in the context of TLS as any lesion ≥ 10 cm on the screening PET-CT scan, and elevated pretreatment LDH levels, particularly in the presence

of dehydration or compromised renal function. Guidance on the diagnosis of and prophylaxis for the prevention of TLS is provided in Appendix D.

Infections

Owing to the anticipated mode of action resulting in profound B cell depletion, mosunetuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving other CD20-directed therapies as well as with blinatumomab (Blincyto USPI). Therefore, mosunetuzumab should not be administered in the presence of active severe infections. Investigators should exercise caution when considering the use of mosunetuzumab in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Signs and symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment. Particular attention should be given to patients who have had significant prior immunosuppressive treatment such as high-dose chemotherapy.

In the setting of a pandemic or epidemic, screening for active infections prior to and during study participation should be considered according to local/institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology, European Society for Medical Oncology).

Progressive multifocal leukoencephalopathy (PML) has been associated with treatment with CD20-directed therapies, including rituximab. The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations and consultation with a neurologist and diagnostic procedures including brain magnetic resonance imaging (MRI) and lumbar puncture, should be performed as clinically indicated.

Note that PML associated with rituximab generally occurred following long-term exposure (Carson et al. 2009); new onset of neurologic adverse events following initial doses of mosunetuzumab may be more likely owing to acute effects of mosunetuzumab.

Hepatitis B reactivation has been reported with other CD20-directed therapies. Patients with a history of chronic hepatitis B infection or positive test results for active or chronic HBV infection defined by HBsAg and/or positive total HBcAb and positive HBV PCR, or patients with HCV infection as assessed by PCR, will be excluded from this trial.

Human immunodeficiency virus has also been associated with development of secondary HLH. Patients with HIV and known or suspected chronic active Epstein-Barr virus (EBV) infection will be excluded from this trial due to the risk of secondary HLH.

COVID-19 Management While on Study

Investigators should strongly advise patients to implement behavioral modifications such as masking and social distancing in order to reduce the risk of contracting SARS-CoV-2 infections.

A positive PCR test for SARS-CoV-2 infection in an asymptomatic individual may be a sign of possible active infection that would require interruption of study therapy and clinical evaluation to assess the clinical course of the infection and administration of appropriate SARS-CoV-2 infection directed therapies.

If the participant develops SARS-CoV-2 infection during study treatment, study treatment should be interrupted and the infection should be managed as per local or institutional guidelines. The infection must be clinically resolved before resumption of study treatment. Investigators must rule out active infection and re-assess benefit-risk balance prior to resuming study treatment. Examples of ruling out an active infection include clinical evaluation of respiratory symptoms, radiological tests to confirm absence of pneumonia, and consideration of negative serial viral testing. Mosunetuzumab administration is not permitted during the presence of active infection.

Investigators should evaluate for and aggressively manage concomitant infections that may occur in the presence of SARS-CoV-2 infections.

Tumor Flare

Adverse events associated with tumor flare have been reported in Study GO29781. Consistent with the mechanism of action of mosunetuzumab, tumor flare is likely owing to the influx of T cells into tumor sites following mosunetuzumab administration. Reported tumor flare-associated adverse events generally have a short time to onset following mosunetuzumab administration. Based on safety data collected to date, tumor flare has manifested as new or worsening pleural effusions or localized swelling or pain at known lymphoma sites. In addition, depending on tumor size and anatomic location, tumor flare may potentially result in mass effects on vital structures, including airways, major blood vessels, gastrointestinal tract (risk of perforation and hemorrhage), and/or major organs. Patients with tumors at critical anatomic locations should be closely monitored for tumor flare. See Appendix D for the management of tumor flare.

Injection-Site Reactions

Localized injection-site reactions have been observed in study GO29781. The manifestations included erythema, pain, eczema, phlebitis, pruritus, and rash on injection site. Patients who experience localized injection-site reactions following SC administration of mosunetuzumab should be managed according to the guidelines detailed in Appendix D.

6.1.2 Potential Risks Associated with Mosunetuzumab

Hemophagocytic Lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome driven by pathologic activation of cytotoxic T-lymphocytes and macrophages ultimately leading to cytokine storm and organ damage if not treated appropriately. In adults, infections and malignancies are common triggers for HLH, and lymphomas represent the most common trigger for malignancy-associated HLH, with an incidence of 1–20% in lymphoma patients (Wang et al. 2017). HLH secondary to T cell engaging therapies, also described as Immune Effector Cell-associated HLH-like Syndrome (IEC-HS), is an emergent toxicity associated with life-threatening complications, where early detection and management is essential. HLH adverse events, including fatal cases, have been reported on mosunetuzumab clinical trial and compassionate use programs, observed in the context of disease progression and infections. The incidence of HLH on clinical trials and the compassionate use program is 0.7% (7 cases/1052 patients). HLH may resemble severe CRS with respect to clinical signs and symptoms, but may differ by presenting with a delayed onset, rapid increases in serum ferritin, and differences in cytokine profile. While symptoms may overlap with CRS, emergent treatment recommendations for HLH are distinct from those of CRS. For any case of suspected HLH, mosunetuzumab should be interrupted and treatment should be considered per current practice guidelines e.g. institutional guidelines or ASTCT expert consensus guidelines (Hines et al. 2023). Consensus guidelines recommend frontline treatment with anakinra (an interleukin-1 receptor antagonist), with or without corticosteroids. Expert consultation is recommended if HLH is suspected. See Appendix D, Table 9 for additional recommendations as well as Crombie et al. 2024.

For any suspected HLH, treatment with mosunetuzumab should be interrupted and management should be initiated per current practice guidelines, e.g. institutional guidelines or expert consensus guidelines (Hines et al. 2023, Crombie et al. 2024).

Neurologic Toxicity including ICANS

Neurologic toxicity including ICANS and HLH, including fatal cases, have been reported in patients receiving mosunetuzumab. All patients should be monitored and counselled for signs and symptoms of neurologic toxicity including ICANS and HLH following mosunetuzumab administration. Encephalopathy has been observed in in the setting of CRS and/or elevation in liver function tests (LFTs) following mosunetuzumab treatment (see the Mosunetuzumab Investigator's Brochure for details).

Neurologic toxicity has also been reported in patients treated with blinatumomab and CD19-directed CAR T cell therapy (Maude et al. 2014; Kochenderfer et al. 2015). Reported symptoms in patients treated with blinatumomab or CD19 CAR T cell therapy have included headache, confusion, aphasia, encephalopathy, tremor, seizure, and other neurologic events. The etiology of toxicity in these settings is uncertain and may not be responsive to cytokine-directed therapy such as tocilizumab but has generally improved with treatment discontinuation and

corticosteroids (Kochenderfer et al. 2015; Goebler et al. 2016; Viardot et al. 2016). In patients with B cell acute lymphoblastic leukemia treated with blinatumomab, neurologic toxicities were observed in approximately 50% of patients; Grade ≥ 3 neurologic toxicity was observed in approximately 15% of patients. The majority of neurologic adverse events resolved following interruption of blinatumomab, with some patients requiring treatment discontinuation (Blincyto USPI).

Neurologic adverse events will be monitored closely during the trial. All patients will be required to undergo Immune-Effector Cell-Associated Encephalopathy (ICE) assessment and ICANS grading (Appendix I) and a baseline complete neurologic examination prior to the first mosunetuzumab administration. The examination should include an evaluation of mental status, cranial nerves, motor strength, sensation, and coordination. Results of the neurologic examination should be documented in the patient's chart.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a clinical and neuropsychiatric syndrome that can occur following administration of T cell engaging therapies. Neurologic toxicity including ICANS have been reported in patients receiving mosunetuzumab. A recent cumulative analysis showed adverse events consistent with ICANS (Lee 2019), including severe and life-threatening events, in 1.9% among 1219 patients across mosunetuzumab clinical trials and compassionate use program.

Manifestations of ICANS reported in patients receiving mosunetuzumab included confusional state, delirium, disturbance in attention and cognitive disorder, disorientation, lethargy, memory impairment, and encephalopathy. The majority of cases of ICANS occurred during Cycle 1 of treatment. ICANS can occur in the setting of cytokine release syndrome (CRS), or independent of CRS. Mosunetuzumab treatment should be withheld or discontinued depending on the severity of ICANS, and treatment with corticosteroids, non-sedating anti-seizure medicinal products, supportive therapies and neurologic consultation may be required.

Patients should be routinely assessed for any signs or symptoms of neurologic toxicity as part of the on-treatment clinical examination. If new or worsening neurologic toxicity is suspected, see Appendix D (Table 5) for management guidelines, including guidelines for driving restrictions.

Thrombocytopenia

Reversible thrombocytopenia has been observed following mosunetuzumab treatment. Patients should be closely monitored for thrombocytopenia. Patients whose treatment is held due to thrombocytopenia should undergo regular laboratory testing and receive transfusion of blood products (e.g., platelet transfusion) according to institutional practice and discretion of the treating physician until the event resolves. Modifying the use of any concomitant therapies that may worsen thrombocytopenia-related events (e.g., platelet inhibitors and anti-coagulants)

should also be considered, especially during the first cycle of study treatment and higher platelet transfusion threshold is recommended.

Elevated Liver Enzymes and Hepatotoxicity
Transient Grade 3 AST elevation in the setting of Grade 2 CRS, Grade 3 hepatic encephalopathy, and Grade 4 elevated LFTs have been observed following mosunetuzumab treatment (refer to the Mosunetuzumab Investigator's Brochure for details). Patients who do not meet eligibility criteria for LFTs at screening will be excluded from this trial. The LFTs will be assessed regularly during study and should be managed according to guidelines in Appendix D.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Immunogenicity (Anti-Drug Antibodies)
As with any recombinant antibody, mosunetuzumab may elicit an immune response, and patients may develop antibodies against the molecule, which may have an effect on the benefit-risk profile of the agent. See the Mosunetuzumab Investigator's Brochure for additional details.

6.1.3 Known Risks Associated with Polatuzumab Vedotin

Myelosuppression: Consolidation of Neutropenia (including Febrile Neutropenia), Thrombocytopenia, and Anemia
Neutropenia, neutropenia-associated events, thrombocytopenia, and anemia, including serious and severe cases, have been reported in patients receiving polatuzumab vedotin. When polatuzumab vedotin was combined with the anti-CD20 monoclonal antibody rituximab in patients with a range of relapsed or refractory B-NHL subtypes, neutropenia of any Grade occurred in 31% of patients, was Grade ≥ 3 in 11% of cases, and neutropenia led to treatment discontinuation in 2.4% of patients. Febrile neutropenia occurred in 3.6% of patients. In the same cohort, thrombocytopenia of any Grade occurred in 6% of patients, was Grade ≥ 3 in 4.2% of cases, and did not lead to any treatment discontinuation. Finally, in the same cohort, anemia of any Grade occurred in 12.5% of patients, was Grade ≥ 3 in 5.4% of patients, and did not lead to any treatment discontinuation.

Peripheral Neuropathy (Sensory and/or Motor)
Patients receiving polatuzumab vedotin may develop peripheral neuropathy (sensory and/or motor). Patients receiving study treatment should be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, or

neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require a dose delay, change in dose, or discontinuation of treatment.

Study treatment dose and schedule modifications for peripheral neuropathy are described in Section 6.4. Supportive care measures may be implemented per investigator preference (e.g., gabapentin).

Infections
Patients receiving polatuzumab vedotin may be at a higher risk of developing infections. Serious infections, including opportunistic infections, such as pneumonia (including pneumocystis jirovecii and other fungal pneumonia), bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with polatuzumab vedotin. Several other risk factors in the patient population under study influencing patients' vulnerability to a higher risk of infections, particularly serious and opportunistic infection, include predisposition of the indication disease to infections, elderly population, and comorbidity.

Infusion-Related Reactions
IRRs have been reported in patients receiving polatuzumab vedotin. Commonly experienced events included nausea, vomiting, chills, fever, pruritus, hypotension, flushing, and other symptoms. In the majority of the patients, the events were Grade 1–2. Premedication for polatuzumab vedotin infusion administration are outlined in Section 5.2. Close monitoring throughout the infusion is required.

Gastrointestinal Toxicity (Diarrhea, Nausea, Vomiting, Constipation, and Anorexia)
Diarrhea, nausea, vomiting, constipation, and abdominal pain are reported frequently, with diarrhea and nausea being the most common (≥ 20%) treatment-emergent adverse events in Phase I and II clinical studies with polatuzumab vedotin. Diarrhea has been responsible for study drug modification and discontinuation. Most cases were low grade, with more serious cases being confounded by polypharmacy, comorbidities, or disease under study.

6.1.4 Potential Risks Associated with Polatuzumab Vedotin

Progressive Multifocal Leukoencephalopathy
One case of progressive multifocal leukoencephalopathy (PML) has been reported with polatuzumab vedotin treatment. Participants should be monitored closely for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. Polatuzumab vedotin and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumor Lysis Syndrome
There is a potential risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. While rarely seen with

polatuzumab vedotin, TLS is more likely to occur during cycle 1 of study treatment when patients have the highest tumor burden. It is also less common in patients with indolent B-NHL subtypes such as follicular lymphoma, compared to aggressive subtypes such as DLBCL that have higher baseline rates of tumor cell turnover. For patients experiencing TLS during the study, tumor lysis prophylaxis measures will be instituted for future cycles of study treatment based on the investigator's assessment of a patient's risk for recurrent TLS including their residual tumor burden.

Immunogenicity (Anti-Drug Antibodies)
As with any recombinant antibody, polatuzumab vedotin may elicit an immune response, and patients may develop antibodies against it. As patients will receive no more than six cycles of polatuzumab vedotin as part of study treatment, ADAs against polatuzumab vedotin will not be monitored in this study.

Reproductive Toxicity
Adverse effects on human reproduction and fertility are anticipated with the administration of polatuzumab vedotin, given the mechanism of action of MMAE. Standard exclusion criteria are used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

Fatigue and Asthenia
Fatigue or asthenia is a frequent treatment-emergent adverse event reported by participants with cancer while on many different therapies, and is considered a class effect of MMAE, other similar antibody-drug conjugates (ADCs), and with vincristine sulfate. Participants with cancer are more likely to experience fatigue/asthenia while not on any therapeutic regimen.

Renal Toxicity (Increased Serum Creatinine)
Preliminary safety observations in clinical trials with ADCs using the same linker and MMAE have suggested that some participants experience reduction of renal function during clinical trials. Most events occurred in the setting of dehydration or other inciting illnesses.

Joint Pain, Arthralgia, Skeletal Pain
Joint pain, arthralgia and skeletal pain are reported from the ongoing clinical trials of similar ADCs with the same linker and cytotoxic agent MMAE, and are considered an effect of MMAE as this is commonly reported with brentuximab vedotin (Adcetris USPI) other similar ADCs, and with vincristine sulfate.

Alopecia
Alopecia is reported from the ongoing clinical trials of similar ADCs with the same linker and cytotoxic agent MMAE, and is considered a class effect of MMAE as this is commonly reported with brentuximab vedotin (Adcetris USPI), other similar ADCs, and with vincristine sulfate. It is known to improve with cessation of treatment.

Cardiac Arrhythmias
While not observed in the non-clinical Good Laboratory Practice studies, several serious adverse events of cardiac toxicities have been experienced by participants receiving an ADC-vc-MMAE, which is in the same class as polatuzumab vedotin.

Ocular Toxicity
While not observed in non-clinical GLP studies, treatment-emergent adverse events of ocular toxicities have been experienced by participants receiving antibody drugs with the same drug conjugate (ADC-vc-MMAEs) as polatuzumab vedotin.

Dysgeusia
While not observed in the non-clinical GLP studies, treatment-emergent adverse events of dysgeusia or alteration of taste have been experienced by participants receiving ADC-vc-MMAEs which are in the same class as polatuzumab vedotin.

Drug-Drug Interaction (DDI)
Drug-drug interactions are a theoretical risk for polatuzumab vedotin. No clinically relevant DDIs have been identified in the ongoing studies. Participants who are receiving strong CYP3A inhibitors should be closely monitored for adverse reactions when given polatuzumab vedotin.

Hyperglycemia
Hyperglycemia has been observed in patients treated with polatuzumab vedotin as well as with other ADCs that use the same valine-citrulline-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications.

Hepatotoxicity
Hepatotoxicity has been observed in patients treated with polatuzumab vedotin in both the Phase I and Phase II trials. Although the relationship between hepatotoxicity and polatuzumab vedotin has not been definitively determined, transient, dose-related increases in hepatic enzymes were noted in nonclinical rat studies. No hepatotoxicity was noted following administration of the surrogate ADC in cynomolgus monkeys. Elevations of transaminases have been reported in patients receiving polatuzumab vedotin and have ranged in intensity from Grades 1–4. These have been reversible with and without dose modification/discontinuation.

Carcinogenicity
Polatuzumab vedotin may have carcinogenic potential given the mechanism of action of MMAE, the cytotoxic component of polatuzumab vedotin. Myelodysplastic syndrome and other second malignancies have been reported in Phase I and II clinical studies with polatuzumab vedotin. The majority of these patients had received multiple prior lines of anti-cancer therapy, and this was considered as a significant contributory factor.

Pulmonary Toxicity

Pulmonary toxicities have been reported from ongoing clinical trials of similar ADCs with the same linker and cytotoxic agent MMAE. As there is no identified antibody-antigen binding in the lung, this is considered to be possibly due to MMAE.

Lung injury not attributed to an infectious etiology, manifesting as pneumonitis, organizing pneumonia, or interstitial lung disease, has been rarely observed in patients receiving polatuzumab vedotin (<1%). Patients with a history of pneumonitis or other serious, uncontrolled pulmonary disease at baseline are excluded from this study. Pulmonary adverse events will be monitored closely during the trial through frequent vital signs assessment, complete physical examination, review of systems, and cross-sectional imaging.

6.2 Mosunetuzumab and Polatuzumab Vedotin Dose Modifications

The only permitted mosunetuzumab dose modifications are based on prior incidence and grade of CRS. For Grade 1 or 2 CRS, subsequent mosunetuzumab injections should include steroid premedication if not otherwise planned. For Grade 3 CRS after a 5 mg dose the next dose should be 5 mg, and after a 45 mg dose the next dose should be 20 mg. If the next dose is tolerated without Grade 3 or higher CRS, the subsequent dosing may be increased according to the planned dose levels. If Grade 3 or higher CRS recurs with subsequent doses, study treatment will be discontinued. Please refer to Table 1 in Appendix D for additional guidance.

The starting dose of polatuzumab vedotin is 1.8 mg/kg. One dose reduction to 1.4 mg/kg is permitted. If the patient necessitates further dose reductions at the 1.4 mg/kg dose, polatuzumab vedotin should be discontinued.

6.3 Mosunetuzumab and Polatuzumab Vedotin Treatment Interruption

Study treatment may be temporarily suspended in patients who experience toxicity considered by the investigator to be related to either study drug. If mosunetuzumab has been withheld for more than 28 days because of toxicity, the patient should be discontinued from study treatment. Resumption of treatment can be considered after discussion with the primary investigator. In addition, study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) after discussion with the primary investigator. The investigator will determine the acceptable length of treatment interruption. Instructions on restarting mosunetuzumab after a dose delay are described in Table 1.

In general, patients who experience a Grade 4 study treatment-related, non-hematological AE should discontinue all study treatment and may not be re-treated. Exceptions can be considered in cases of CRS and TLS. Because TLS represents a pharmacodynamic (PD) effect of study treatment that may result in clinical benefit, patients who experience Grade 4 TLS may be considered for continuation in the study. To be considered for

subsequent study treatment, all toxicities and laboratory abnormalities related to TLS should be resolved within 2 weeks. The decision to continue study treatment should only be made after consultation with the study investigator. Patients must be hospitalized for TLS prophylaxis and monitoring with the next study treatment dose.

Patients who experience a Grade 3 adverse event or a serious adverse event will be allowed to delay mosunetuzumab dosing for up to 2 weeks in order to recover from the toxicity. For those adverse events that are not considered by the investigator to be attributable to another clearly identifiable cause, (e.g., documented disease progression, concomitant medication, or preexisting medical condition), patients may continue to receive additional doses of mosunetuzumab, provided that the toxicity has resolved to Grade ≤ 1 within the time period stated above. For decreased laboratory values, the abnormality should have resolved to the lower limit of Grade ≤ 1, or return to ≥ 80% of the baseline value, whichever is lower

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed will be discontinued from study treatment and be followed for safety outcomes as described elsewhere in Section 5. Exceptions to this on the basis of ongoing clinical benefit may be allowed following investigator's assessment of risk versus benefit. Delay of therapy because of toxicities not attributed to mosunetuzumab or polatuzumab vedotin may not require discontinuation following investigator's assessment of risk versus benefit.

If a serious adverse event or adverse event of special interest (see Appendix B) occurs following step-up dosing (C1D1, C1D8, and/or C1D15), a treatment delay may occur up to 14 days and/or modification of the subsequent mosunetuzumab dose may occur at the discretion of the primary investigator following consultation with the treating investigator physician; refer to the instructions on restarting mosunetuzumab after a treatment delay described in Table 1. In the event that a patient has a non-hematologic toxicity prior to C1D15 dose that necessitates mosunetuzumab interruption for > 7 days, the patient will be required to repeat mosunetuzumab at the highest dose previously tolerated prior to resuming planned treatment schedule. Patients who discontinue study treatment for reasons other than progressive disease should continue to be followed according to the study calendar.

Table 1 Recommendations for Restarting Therapy After Dose Delay for Patients Treated with Mosunetuzumab SC Administered at 5/45/45mg Dosing Regimen

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)*, then resume the planned treatment schedule.
	Greater than 2 weeks	Repeat 5 mg (Cycle 1 Day 1)*, then administer 45 mg (Cycle 1 Day 8)* 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)*, then resume the planned treatment schedule.
	Greater than or equal to 6 weeks	Repeat 5 mg*, then administer 45 mg (Cycle 1 Day 15)* 7 days later and 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.
	Greater than or equal to 6 weeks	Repeat 5 mg (Cycle 2 Day 1)*, then administer 45 mg (Cycle 2 Day 8)* followed by 45 mg on Day 1 of subsequent cycles.
45 mg Cycle 2 onwards	3 weeks to less than 6 weeks	Administer 45 mg, then resume the planned treatment schedule.
	Greater than or equal to 6 weeks	Repeat 5 mg* on Day 1 during the next cycle, then administer 45 mg* on Day 8, followed by 45 mg on Day 1 of subsequent cycles.
*Administer premedication as per Cycle 1.		

6.4 Guidelines for Dose Delay, Modification, or Discontinuation of Mosunetuzumab and Polatuzumab Vedotin

In general, treatment delays, modifications, or discontinuation need only occur for AEs that are deemed related to either study medication. Also see Appendix D for recommended management of select AEs.

Mosunetuzumab dose delay may require the prior step-up dose to be repeated. See Section 6.3 for instructions.

Event(s) [a]	Dose Delay or Modification
Grade 3 or 4 neutropenia with or without infection or fever (first occurrence)	• Treatment during mosunetuzumab step-up dosing should not be held for uncomplicated neutropenia; otherwise, hold treatment until absolute neutrophil count recovers to ≥ 1000/mcL (or ≥ 500/mcL for patients with extensive bone marrow involvement by lymphoma and/or disease-related cytopenias at enrollment) • If event recovers in ≤ 21 days, dosing of mosunetuzumab +/- polatuzumab vedotin can be resumed at the same dose; if the event does not recover in 21 days, study treatment should be discontinued (see Section 5.8 and 6.3 for exceptions to this) • Growth factors (e.g., G-CSF) for neutropenia are permitted (in addition to primary prophylaxis) • Consider initiating prophylactic G-CSF with subsequent treatment if not already planned • Doses of mosunetuzumab and polatuzumab vedotin should not be modified for this reason
Recurrent Grade 3 or 4 neutropenia	• Hold treatment until absolute neutrophil count recovers to ≥ 1000/mcL (or ≥ 500/mcL for patients with extensive bone marrow involvement by lymphoma and/or disease-related cytopenias at enrollment) • If event recovers in ≤ 21 days, dosing of mosunetuzumab +/- polatuzumab vedotin can be resumed at the same dose; if the event does not recover in 21 days, study treatment should be discontinued (see Section 5.8 and 6.3 for exceptions to this) • Growth factors (e.g., G-CSF) for neutropenia are permitted (in addition to primary prophylaxis) • Consider initiating prophylactic G-CSF with subsequent treatment if not already planned • Doses of mosunetuzumab and polatuzumab vedotin should not be modified for this reason • Second recurrence: discontinue study treatment unless neutropenia is uncomplicated (without fever, or sign of infection) and occurs during Cycle 1 step-up dosing

Grade 3 or 4 thrombocytopenia (first occurrence)	• Treatment during mosunetuzumab step-up dosing should not be held for uncomplicated thrombocytopenia; otherwise, hold treatment until platelet count recovers to ≥ 75,000/mcL (or ≥ 50,000/mcL for patients with extensive bone marrow involvement by lymphoma and/or disease related cytopenias at enrollment) • If event recovers in ≤ 21 days, dosing of mosunetuzumab +/- polatuzumab vedotin can be resumed at the same dose; if the event does not recover in 21 days, study treatment should be discontinued (see Section 5.8 and 6.3 for exceptions to this) • Doses of mosunetuzumab and polatuzumab vedotin should not be modified for this reason
Recurrent Grade 3 or 4 thrombocytopenia	• Hold treatment until platelet count recovers to ≥ 75,000/mcL (or ≥ 50,000/mcL for patients with extensive bone marrow involvement by lymphoma and/or disease related cytopenias at enrollment) • If event recovers in ≤ 21 days, dosing of mosunetuzumab +/- polatuzumab vedotin can be resumed at the same dose; if the event does not recover in 21 days, study treatment should be discontinued (see Section 5.8 and 6.3 for exceptions to this) • Doses of mosunetuzumab and polatuzumab vedotin should not be modified for this reason • Second recurrence: discontinue study treatment unless thrombocytopenia is uncomplicated (without significant bleeding) and occurs during Cycle 1 step-up dosing
Grade 1 neuropathy (including peripheral sensory or motor neuropathy)	• No study treatment modification is recommended for Grade 1 sensory or motor peripheral neuropathy
Grade 2 or 3 neuropathy (including peripheral sensory or motor neuropathy)	• Delay study treatment if mosunetuzumab and polatuzumab vedotin are due for administration on the same day; otherwise, proceed with mosunetuzumab step-up dosing or monotherapy as indicated • If recovered to Grade ≤ 1 within ≤ 14 days: - If the dose of polatuzumab vedotin is 1.8 mg/kg, then reduce polatuzumab vedotin to 1.4 mg/kg (permanent dose reduction); mosunetuzumab may be administered at the recommended dose

	- If there was a prior dose reduction of polatuzumab vedotin to 1.4 mg/kg for Grade 2 or 3 peripheral neuropathy, polatuzumab vedotin must be permanently discontinued; mosunetuzumab may be administered at the recommended dose • If not recovered to Grade ≤ 1 until > 14 days, polatuzumab vedotin must be permanently discontinued; mosunetuzumab may be administered at the recommended dose
Grade 4 neuropathy (including peripheral sensory or motor neuropathy)	• Discontinue polatuzumab vedotin treatment permanently • Patients should be evaluated regarding the continuation of mosunetuzumab on the basis of their benefit-risk
Bilirubin between 1.5 and 3.0 mg/dL	• Dose reduction should be avoided if hyperbilirubinemia is not related to hepatic injury (i.e., hemolysis or Gilbert disease); in these cases, dose reduction considerations should be guided by direct bilirubin levels • Reduce polatuzumab vedotin to the next level (1.4 mg/kg; otherwise discontinue polatuzumab vedotin if a prior dose reduction has occurred) • With subsequent courses of treatment, if bilirubin has returned to ULN or lower, full doses may be given; evaluate for causality
Bilirubin > 3.0 mg/dL	• Dose delay should be avoided if hyperbilirubinemia is not related to hepatic injury (i.e., hemolysis or Gilbert disease); in these cases, dose delay considerations should be guided by direct bilirubin levels • Withhold mosunetuzumab and polatuzumab vedotin until improvement to Grade ≤ 1; evaluate for causality; reduce polatuzumab vedotin to the next level (1.4 mg/kg; otherwise discontinue polatuzumab vedotin if a prior dose reduction has occurred)
Grade 3 or 4 constipation or ileus	• Withhold polatuzumab vedotin until improvement to Grade ≤ 2; mosunetuzumab may be continued or delayed at the discretion of the investigator • Consider reducing polatuzumab vedotin to the next dose level after improvement to Grade ≤ 2 (1.4 mg/kg; otherwise discontinue polatuzumab vedotin if a prior dose reduction has occurred)
Grade 3 or 4 TLS	• Withhold all study treatment

	• Following complete resolution of TLS, study treatment may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy • See Section 6.3 and Appendix D for further guidance
Grade 3 IRR, second episode	• Discontinue mosunetuzumab or polatuzumab vedotin permanently • If IRR is attributed to polatuzumab vedotin, discontinue polatuzumab vedotin; mosunetuzumab may be continued • If IRR is attributed to mosunetuzumab, discontinue both mosunetuzumab and polatuzumab vedotin
Grade 3 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	• Assess toxicity for causality • Delay all study treatment until toxicity resolves to Grade ≤ 1 (as per Section 6.2) if toxicity is clinically significant and possibly related to the study drugs • Subsequent recurrence: based on the nature of the toxicity, decrease polatuzumab vedotin to a lower dose if toxicity is attributed to polatuzumab vedotin; there are no dose reductions for mosunetuzumab • Second recurrence: based on the nature of the toxicity and if the event is not clinically manageable and resolving in ≤ 14 days to at least Grade 2, discontinue study treatment permanently
Grade 4 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	• Discontinue all study treatment if toxicity is clinically significant and possibly related to the study drugs
Hepatitis B reactivation (as noted by new detectable HBV-DNA levels)	• HBV-DNA levels between WHO-recommended range of 29–100 IU/mL: re-test within 2 weeks; if still positive, hold all study treatment and treat patient with an appropriate nucleoside analogue; immediately refer patient to a gastroenterologist or hepatologist • HBV-DNA levels at WHO-recommended cutoff of > 100 IU/mL: hold all study treatment and treat the patient with an appropriate nucleoside analogue; immediately refer patient to a gastroenterologist or hepatologist

	• Rising HBV-DNA viral load (exceeding 100 IU/mL) while on an appropriate anti-viral therapy: discontinue all study treatment immediately

[a]All based on laboratory test results obtained within 72 hours before infusion/injection of Day 1 of that cycle.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines. All investigators treating patients on this study are responsible for ensuring that serious adverse events (as defined in Appendix B) are reported to the Sponsor-Investigator within an adequate timeframe for the event to be assessed by the Sponsor-Investigator for reporting to HRPO, QASMC, and/or FDA. **Note that for investigator-initiated studies, the term "Sponsor-Investigator" refers to the investigator holding the IND.**

Adverse events will be tracked from start of treatment through 30 days following the last administration of study treatment, or until initiation of alternate treatment for lymphoma, whichever occurs earlier. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Pre-existing medical conditions (baseline adverse events), defined as conditions identified during baseline assessment; these are not considered AEs and therefore should not be recorded on the toxicity CRF but shall instead be recorded on the medical history CRF; if a pre-existing condition worsens in severity, it should be reported in the toxicity CRF as an AE

Refer to the data submission schedule in Section 10 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to Genentech

The investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs, and Product Complaints with an AE where the patient has been exposed to the Product. Those events requiring expedited reporting as specified in Appendix B and C should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified in Appendix C:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am TO 5 pm PST)

Please see Appendix B for additional reporting requirements.

7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** The Siteman Cancer Center Protocol Development team (PD) facilitates reporting to FDA. Please see directions for preparing documentation and contacting PD below, and refer to the internal IND Safety Report SOP for additional guidance.

It is the responsibility of the WUSM Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix B for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix B) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse

event (refer to Appendix B) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Each report should be developed in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team (PD team, protocoldevelopment@wustl.edu) of each potentially reportable event within 1 business day after initial receipt of the information, and must send the completed FDA Form 3500A to PD no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the study. Relevant follow-up information must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.2 Sub-Investigator Reporting Requirements

All investigators treating patients on this study are responsible for ensuring that serious adverse events (as defined in Appendix B) are reported to the Sponsor-Investigator within 24 hours of learning of the event in order for the event to be assessed by the Sponsor-Investigator for reporting to HRPO, QASMC, and/or FDA.

7.3 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Mosunetuzumab

8.1.1 Mosunetuzumab Description

Mosunetuzumab is a full-length, humanized T cell recruiting bispecific antibody targeting CD20-expressing B cells. One fragment antigen-binding (Fab) region of the antibody is directed against the extracellular domain of the CD3e subunit of the T cell receptor (TCR) complex. The other Fab is directed against the extracellular domain of CD20. Heterodimerization of the two half-antibodies is driven by "knob" and "hole" modifications of the CH3 domain of the Fc region (Atwell et al. 1997; Spiess et al. 2013).

Chemical name: Recombinant humanized anti-CD20 and anti-CD3 monoclonal antibody
Chemical structure: H_2L_2 polypeptide structure consisting of two different light chains and two different heavy chains held together by disulfide bonds
Molecular weight: Approximately 146 kDa

8.1.2 Clinical Pharmacology

The mechanism of action of mosunetuzumab involves engaging T cells via CD3 with CD20-expressing cells, leading to T cell activation and T cell-mediated cytolysis of the CD20-expressing cells.

8.1.3 Pharmacokinetics and Drug Metabolism

The nonclinical PK behavior observed for mosunetuzumab is consistent with that expected for a humanized IgG1 monoclonal antibody with a component of target-mediated clearance. The proposed first-in-human (FIH) dose of mosunetuzumab was based on an estimate of the minimum anticipated biological effect level (MABEL) to minimize the potential for cytokine-mediated and/or infusion-related reactions (IRRs). No metabolism or excretion studies have been conducted to date.

8.1.4 Supplier

Mosunetuzumab will be provided by Genentech.

8.1.5 Dosage Form and Preparation

Mosunetuzumab is provided as a solution for injection. Mosunetuzumab will be administered by SC injection. Mosunetuzumab must be prepared for dosing under appropriate aseptic conditions as it does not contain preservatives. The dose solution should be used immediately to limit microbial growth in case of potential accidental contamination.

8.1.6 Storage and Stability

It must be refrigerated at 2-8ºC until use. If necessary, unopened mosunetuzumab vials may be stored at room temperature for up to 8 hours. Vials should not be frozen or shaken. Vials should be protected from light during storage.

8.1.7 Administration

Mosunetuzumab must be given subcutaneously over 30 seconds to 2 minutes. Refer to the pharmacy manual for more details including syringe size and preferred injection sites. Patients will be observed for signs or symptoms of CRS for at least 2 hours following all Cycle 1 injections. Subsequent injections starting with Cycle 2 Day 1 may be followed by 30-minute observation periods if the prior injection was tolerated with no CRS. Otherwise, 2-hour observation periods are required until an injection is tolerated with no CRS.

8.2 Polatuzumab Vedotin

8.2.1 Polatuzumab Vedotin Description

Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate (ADC) consisting of three components: (1) the humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for human CD79b; (2) the small molecule anti-mitotic agent MMAE; and (3) a protease-cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB) that covalently attaches MMAE to the polatuzumab antibody.

Molecular weight: Approximately 150 kDa

8.2.2 Clinical Pharmacology

Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate with activity against dividing B cells. The small molecule, MMAE, is an anti-mitotic agent covalently attached to the antibody via a cleavable linker. The monoclonal antibody binds to CD79b, a B cell specific surface protein, which is a component of the B cell receptor. Upon binding CD79b, polatuzumab vedotin is internalized, and the

linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

8.2.3 Pharmacokinetics and Drug Metabolism

The plasma exposure of acMMAE and unconjugated MMAE increased proportionally over a polatuzumab vedotin-piiq dose range from 0.1 to 2.4 mg/kg (0.06 to 1.33 times the approved recommended dosage). Cycle 3 acMMAE AUC were predicted to increase by approximately 30% over Cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. Unconjugated MMAE plasma exposures were <3% of acMMAE exposures, and the AUC and Cmax were predicted to decrease after repeated every-3-week dosing.

8.2.4 Supplier

Polatuzumab vedotin will be provided by Genentech.

8.2.5 Dosage Form and Preparation

Polatuzumab vedotin is provided as a 30 mg/vial or 140 mg/vial white to grayish-white lyophilized powder in a single-dose vial for reconstitution and further dilution.

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose, the total volume of reconstituted polatuzumab vedotin solution required, and the number of polatuzumab vedotin vials needed.
- Using a sterile syringe, slowly inject Sterile Water for Injection, USP, using the volume provided in the table below, into the polatuzumab vedotin vial, with the stream directed toward the inside wall of the vial to obtain a concentration of 20 mg/mL of polatuzumab vedotin-piiq.

Strength	Volume of Sterile Water for Injection, USP required for reconstitution
30 mg vial	1.8 mL
140 mg vial	7.2 mL

- Swirl the vial gently until completely dissolved. *Do not shake*.
- Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particulates. *Do not freeze or expose to direct sunlight.*
- If needed, store unused reconstituted polatuzumab vedotin solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours or at room

temperature (9°C to 25°C, 47°F to 77°F) up to a maximum of 8 hours prior to dilution. Discard vial when cumulative storage time prior to dilution exceeds 48 hours.

Dilution

- Dilute polatuzumab vedotin-piiq to a final concentration of 0.72–2.7 mg/mL in an intravenous infusion bag with a minimum volume of 50 mL containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.
- Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose.
- Withdraw the required volume of reconstituted solution from the polatuzumab vedotin vial using a sterile syringe and dilute into the intravenous infusion bag. Discard any unused portion left in the vial.
- Gently mix the intravenous bag by slowly inverting the bag. Do not shake.
- Inspect the intravenous bag for particulates and discard if present.
- If not used immediately, store the diluted polatuzumab vedotin solution as specified in the table below. Discard if storage time exceeds these limits. Do not freeze or expose to direct sunlight.

Diluent Used to Prepare Solution for Infusion	Diluted Polatuzumab Vedotin Solution Storage Conditions
0.9% Sodium Chloride Injection, USP	Up to 36 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
0.45% Sodium Chloride Injection, USP	Up to 18 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
5% Dextrose Injection, USP	Up to 36 hours at 2°C to 8°C (36°F to 46°F) or up to 6 hours at room temperature (9 to 25°C, 47 to 77°F)

8.2.6 Storage and Stability

Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not use beyond the expiration date shown on the carton. Do not freeze. Do not shake.

8.2.7 Administration

- Administer polatuzumab vedotin to well-hydrated participants as an intravenous infusion only.
- Polatuzumab vedotin must be administered using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein-binding in-line or add-on filter (0.2- or 0.22-micron pore size) and a catheter.
- Do not mix polatuzumab vedotin with or administer as an infusion with other drugs.

- Consult the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure for a complete list of compatible materials and specific dose preparation instructions.

9.0 CORRELATIVE STUDIES

The following archival tumor tissue and peripheral blood samples will be sent to one or several central laboratories, such as Foresight Diagnostics, or to the Investigator or a designee for analysis. Research may involve extraction of tumor-derived, peripheral blood mononuclear cell (PBMC) or PBMC subset-derived DNA and/or RNA. Research may involve analysis of mutations through genomic profiling using of next generation sequencing (NGS) of a comprehensive panel of genes. Exploratory biomarker research may include but will not be limited to: immunophenotyping of PBMC subsets by flow cytometry or mass cytometry, gene expression profiling of PBMC subsets by bulk or single-cell RNA sequencing, T cell receptor (TCR) repertoire sequencing, and mutation analysis of archival tumor tissue and cell-free circulating-tumor DNA including for the purpose of genomic analyses of tumor tissue and quantifying measurable residual disease (MRD). Research will aim to distinguish germline mutations from somatic mutations. NGS methods may include whole genome sequencing (WGS) or whole exome sequencing (WES).

Archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue will be delivered as either a block or 10 unstained slides. Archival tissue may be requested at any point during participation. Repeat biopsy is not required at baseline if archival tissue is unavailable/depleted. If archival tissue is unavailable/depleted, the patient can still be enrolled on the trial.

One sodium heparin peripheral blood tube (10 mL; green top), one serum tube (7 mL; red top), and three Streck cell-free DNA BCT tubes (10 mL each; tiger top; for ctDNA analysis) will be collected at the following time points:

- Prior to treatment on Cycle 1 Day 8 (-3/+0 days)
- Prior to treatment on Cycle 1 Day 15 (-3/+0 days)
- Prior to treatment on Cycle 2 Day 1 (-3/+0 days)
- Prior to treatment on Cycle 7 Day 1 (-3/+0 days)
- Prior to treatment on Cycle 13 Day 1 (-3/+0 days; if receiving C13D1 of mosunetuzumab based on PET-CT post-C8 showing PR or SD)
- 6 months post-EOT (-21/+21 days)
- 24 months post-EOT (-21/+21 days)

Six sodium heparin peripheral blood tubes (10 mL each; green top), one serum tube (7 mL; red top), and three Streck cell-free DNA BCT tubes (10 mL each; tiger top; for ctDNA analysis) will be collected at the following time points:

- Prior to treatment on Cycle 1 Day 1 (-7/+0 days)
- Prior to treatment on Cycle 3 Day 1 (-3/+0 days)
- Prior to treatment on Cycle 9 Day 1 (-3/+0 days; if receiving C9D1 of mosunetuzumab based on PET-CT post-C8 showing PR or SD)

- EOT (-3/+0 days)
- 12 months post-EOT (-21/+21 days)
- Time(s) of suspected progression/relapse

Additional archival tumor tissue and blood samples may also be requested/collected at the discretion of the treating physician to align with evaluation for refractory disease and/or suspected progression/relapse including dates of off-study imaging assessments, clinic visits, and/or tissue biopsies. Any change from the original sample collection day should be reviewed with the laboratory PI or PI's staff to facilitate timely sample processing:

Fehniger Laboratory
Attention: Tim Schappe / Michelle Becker-Hapak / David Russler-Germain
Washington University in St. Louis, Oncology/BMT
9900F BJCIH
425 South Euclid Avenue
St. Louis, MO 63110

Phone:
- (314) 362-1547 or (240) 888-1692

Fax:
- (314) 362-9333

Email:
- tfehnige@wustl.edu
- tschappe@wustl.edu
- mbecker-hapak@wustl.edu
- germaind@wustl.edu

Specimens will be transported at room temperature immediately to the Fehniger Lab, Monday through Friday, for receipt between 8 AM and 4 PM. Please notify the lab and/or Dr. Fehniger prior to submission. Sample collections that are outside those hours should be discussed with Drs. Fehniger or Russler-Germain at least 72 hours in advance. All samples are preferably drawn between 7 AM and 9 AM, for early morning delivery.

Some samples will be immediately processed for correlative assays, while others may be processed, cryopreserved, and stored in the Fehniger Lab (9th floor, BJCIH) in liquid nitrogen or -70°C freezers. No PHI will be included on sample vials, and samples may be stored for future research as new scientific findings arise in the field.

10.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
On-Study Form Medical History Form	Prior to starting treatment
Archival Tissue Correlative Form	At any point during participation
Treatment Form	Every cycle
Toxicity Form	Continuous
Research Blood Form	C1D1, C1D8, C1D15, C2D1, C3D1, C7D1, C9D1 (if applicable), C13D1 (if applicable), EOT, and 6-, 12-, and 24-months post-EOT, time(s) of suspected progression/relapse
CRS and ICANS Assessment Form	C1D1, time(s) of suspected CRS or ICANS
Tocilizumab Form	Time(s) of suspected CRS or ICANS
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 3 months for 2 years, then every 6 months for 3 years (total of 5 years) post-EOT
Subsequent Therapy Form	Every 3 months for 2 years, then every 6 months for 3 years (total of 5 years) post-EOT
Imaging and Tumor Measurement Forms	PET-CT scans at baseline, after cycle 2, after cycle 8, and at EOT (if applicable); CT scans at 12-, 24-, and 36-months post-EOT
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

10.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g., cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

11.0 MEASUREMENT OF EFFECT

Patients will be required to have undergone a baseline PET-CT prior to enrollment and will undergo restaging by PET-CT after Cycle 2 (PET2) and Cycle 8 (PET8). Patients with PD at PET2 or PET8 will discontinue study treatment. Patients who achieve a CR at PET8 will discontinue treatment at that point. Patients who achieve a PR or SD at PET8 may continue to receive mosunetuzumab for up to an additional 9 cycles at the discretion of their treating physician. If a

patient receives therapy beyond Cycle 8, an end-of-treatment PET-CT (EOT PET) will be obtained 2–6 weeks after completion of therapy. Post-treatment surveillance imaging will entail diagnostic quality CT scans of the neck, chest, abdomen, and pelvis (with IV contrast preferred) at 12-, 24-, and 36-months post-EOT. The modality and timing of additional surveillance imaging will be determined by the treating physician.

11.1 Lugano Response Criteria

There are 4 possible response categories (complete response, partial response, stable disease, and progressive disease) based on PET-CT defined in the table below. Corresponding response categories based on CT only are also provided. Patients who complete at least one cycle of therapy and have had their disease re-evaluated will be classified in one of the four response categories.

Response and Site	FDG PET-CT Response	CT Response
Complete	Complete metabolic response (CR)	Complete radiologic response (CR) (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow if there is indeterminate, unknown or positive bone marrow involvement at baseline. Confirmatory bone marrow biopsy is not required for patients without FDG avid disease and with no evidence of bone marrow involvement on baseline bone marrow biopsy. Bone marrow involvement is defined as normal by morphology; if indeterminate, IHC negative.	Normal by morphology; if indeterminate, IHC negative

Response and Site	FDG PET-CT Response	CT Response
Partial	Partial metabolic response (PR)	Partial remission (PR) (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 x 0 mm
		For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response (SD)	Stable disease (SD)
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease (PD)	Progressive disease (PD) requires at least 1 of the following PPD progression:

Response and Site	FDG PET-CT Response	CT Response
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥50% from PPD nadir and a An increase in LDi or SDi from nadir; 0.5 cm for lesions ≤ 2 cm, 1.0 cm for lesions > 2 cm
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node ≥ 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher

than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

12.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months and will provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules (see Section 13.2)
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

13.0 STATISTICAL CONSIDERATIONS

This is a single arm, open-label phase 2 study aimed at evaluating the efficacy of the combination of mosunetuzumab and polatuzumab vedotin in patients with follicular lymphoma who have not received prior systemic therapy. The primary endpoint is complete response (CR) as best response determined by PET-CT, per Deauville 5-point scale.

We will consider that the combination of mosunetuzumab and polatuzumab vedotin has poor efficacy if the CR rate is 45% or less. Observing an improved CR rate of 65% would be clinically meaningful and would warrant further investigation of this treatment strategy. The following optimal Simon two-stage design will be used to test the null hypothesis that the CR rate is $\leq 45\%$ versus the alternative hypothesis that the response rate is $\geq 65\%$. A Simon two-stage optimal design with power = 0.8 and significance level = 0.1 will require 34 evaluable patients. Sixteen patients will be treated in the first stage, and the trial will proceed to the second stage if nine or more patients experience CR in the first stage. If 19 or more patients achieve CR in total, then the study would be positive, and this treatment strategy would warrant further investigation in larger studies. If the true CR rate is 45%, the probability of stopping early is 74.4%.

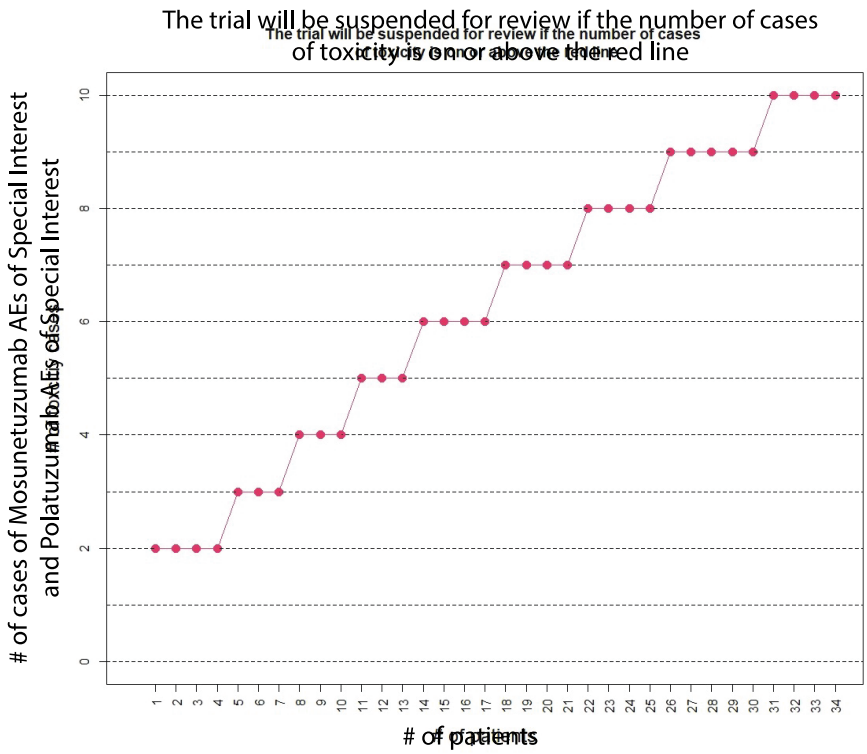
13.1 Endpoint Definitions

Progression-free survival (PFS) is defined as the time from study enrollment to the first occurrence of disease progression as determined by the investigator with use of the Lugano Response Criteria (Section 11.1) or death from any cause. Overall survival (OS) is defined as the time from study enrollment to death from any cause. Time to next treatment (TTNT) initiation is defined as the time from study enrollment to the first documented administration of a new anti-lymphoma treatment (including chemotherapy, radiotherapy, radioimmunotherapy, or immunotherapy) after completion of study treatment. Treatment-emergent adverse events (TEAE) are defined as adverse events that are possibly, probably, or definitely related to study treatment and occur on or after first dose of study treatment.

13.2 Toxicity monitoring

Patients will be monitored for adverse events (see Appendix B for additional details). The study will be suspended for review following the death of a patient during protocol-defined treatment, or within 30 days of the last dose of protocol-defined treatment or until initiation of new anti-cancer therapy (whichever is first). The study will not be suspended for review if a death was determined to be related to disease progression.

Mosunetuzumab Adverse Events of Special Interest and Polatuzumab Adverse Events of Special Interest, as defined in subsection H of Appendix B, will be used to determine the stopping rules with an expected rate of 16% and a maximum allowable rate of 35%. All accrued patients are included in the toxicity monitoring rule (N=34) because all may be evaluable for toxicity. A single continuous toxicity monitoring rule will be used for adverse events.



13.3 Final Data Analysis Plan

The primary objective is to evaluate the efficacy of the combination of mosunetuzumab and polatuzumab vedotin in patients with untreated follicular lymphoma. The secondary objectives are to assess the safety and tolerability of combining mosunetuzumab with polatuzumab vedotin in patients with untreated follicular lymphoma, and to assess the use of tocilizumab for management of cytokine release syndrome (CRS) in patients with untreated follicular lymphoma who receive mosunetuzumab and polatuzumab vedotin. Descriptive statistics will be used to summarize baseline patient characteristics (proportion and confidence interval, mean ± SD or minimum, Q1, median Q3, maximum and IQR). Treatment-emergent adverse events will be tabulated by patient, type, and severity. Complete response (CR), partial response (PR), overall response (OR; CR + PR), stable disease (SD), progressive disease (PD) rates, and rate of treatment discontinuation due to TEAE will be calculated with 95% exact binomial confidence intervals. Kaplan Meier estimates will be used to describe the median event time as well as 24- and 48-month progression-free survival (PFS) rate, overall survival (OS) rate, time to and duration of first response, time to and duration of first CR, and time to next treatment (TTNT) using 95% confidence intervals.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Definitions for Adverse Event Reporting and Genentech Specific Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting except for CRS (utilizes ASTCT grading; see Appendix G). A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.
d. Grade 4 and 5 events must be reported as serious adverse events.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Adverse Event Reporting Period

The study period during which AEs and SAEs (as described above where the patient has been exposed to Genentech product) must be reported begins at initiation of study treatment. It ends 30 days following the last administration of study treatment, study discontinuation/termination, or initiation of alternative lymphoma-directed therapy, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

F. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

G. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

H. Adverse Events of Special Interest

Definition: AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- 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 (or > 2 x baseline for patients with Gilbert's syndrome)
    - Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice (if not previously present for patients with Gilbert's syndrome)
- Suspected transmission of an infectious agent by the study drug, as defined below
    - 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.

The Mosunetuzumab Adverse Events of Special Interest Are:

- Grade ≥ 2 CRS
- Grade ≥ 2 neurologic adverse event
- Any suspected HLH
- Any grade pneumonitis, interstitial lung disease, acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia and/or other non-infectious pulmonary toxicity
- Tumor lysis syndrome (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 flare (e.g., manifestation of signs/symptoms associated with increased in size of known nodal or extranodal lesions by clinical or radiographic assessment, new onset or worsening of preexisting pleural effusions)

The Polatuzumab Adverse Events of Special Interest Are:

- Grade ≥ 2 peripheral neuropathy (sensory and/or motor)
- Grade ≥ 3 infections

I. Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse, or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient in order to be able to identify potential safety signals specific to a particular population

J. Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

K. Post-Study Adverse Events

During extended follow-up after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug), the investigator should report all deaths (regardless of cause) and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period (Quarterly) to ensure successful transmission of Single case reports.

L. Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by the investigator to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the

agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the investigator to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

M. Reporting to Regulatory Authorities, Ethics Committees, and Investigators

The investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

The investigator will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

The investigator will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

N. Aggregate Reports

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech.

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mailbox: ctvist_drugsafety@gene.com

O. Other Reports

The investigator will forward a copy of the Publication to Genentech upon completion of the Study.

P. Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

iis-heme-clinops-d@gene.com

And to Genentech Drug Safety CTV oversight mailbox at: ctvist_drugsafety@gene.com

Q. Queries

Queries related to the Study will be answered by the investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. The investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

R. Safety Crisis Management

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. The investigator agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

S. Compliance with Pharmacovigilance Agreement / Audit

The Parties shall follow their own procedures for adherence to AE reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda, and execution of the audit. The requesting Party will bear the cost of the audit.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Genentech**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Report no later than 15 calendar days after it is determined that the information qualifies for reporting
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	Report no later than 7 calendar days after initial receipt of the information
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Serious adverse drug reaction				Report within 15 calendar days of awareness date
Serious adverse events unrelated to study drugs (NOT SADRs)				Report within 30 calendar days of awareness date
Adverse event of special interest (AESI) related to study drugs				Report within 15 calendar days of awareness date
AESI unrelated to study drugs, or special situation report (pregnancy or other)				Report within 30 calendar days of awareness date
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Genentech**
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Report no later than 15 calendar days after it is determined that the information qualifies for reporting
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			If a product complaint, report within 15 calendar days of the awareness date
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Genentech**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Genentech**
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			
IND annual report				Copy to Genentech when submitted to the FDA. Email to ctvist_drugsafety@gene.com.

Serious Adverse Drug Reactions (SADRs):
Serious AE reports that are related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to Genentech within fifteen (15) calendar days of awareness date.

Other SAEs:
Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of awareness date.

Special Situation Reports
Pregnancy reports: While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Other Special Situation Reports, as defined above, shall be transmitted to Genentech within thirty (30) calendar days of awareness date.

AESIs

AESIs requiring expedited reporting (related or possibly related to Genentech product or where the causality is assessed as unknown or not provided) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others (non-related to Roche product) shall be sent within thirty (30) calendar days.

APPENDIX D: Recommended Management Guidelines for Specific Adverse Events Associated with Mosunetuzumab

This appendix provides guidelines for the management of patients who experience the following adverse events associated with mosunetuzumab:

- Cytokine Release Syndrome (CRS)
- Tumor Flare
- Neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS)
- Tumor Lysis Syndrome (TLS)
- Elevated Liver Enzymes
- Hemophagocytic Lymphohistiocytosis (HLH)
- Neutropenia
- Thrombocytopenia

CYTOKINE RELEASE SYNDROME

Cytokine release syndrome is an identified risk for mosunetuzumab.

Mild to moderate presentation of infusion-related reactions (IRRs) and/or CRS may include symptoms, such as fever, chills, vomiting, dizziness, hypertension, hypotension, dyspnea, restlessness, sweating, flushing, skin rash, tachycardia, tachypnea, headache, tumor pain, nausea, and/or myalgia, and may be treated symptomatically with analgesics, antipyretic medicines, and anti-histamines, as indicated. Such reactions typically occur during, shortly after an infusion, or within 24 hours after study drug infusion predominantly at the first infusion. The incidence and severity of CRS and IRRs typically decrease with subsequent infusions. Patients may also develop IgE-mediated hypersensitivity reactions to study treatment. Cytokine-release syndrome and IRRs may be indistinguishable from an anaphylactic reaction.

Severe or life-threatening presentations of IRRs and/or CRS, such as hypotension, tachycardia, dyspnea or chest discomfort, should be treated aggressively with supportive and resuscitative measures as indicated below, including the use of high-dose corticosteroids, IV fluids, and other supportive measures per institutional practice. Severe CRS may be associated with other clinical sequelae, such as disseminated intravascular coagulation, capillary leak syndrome, or macrophage activation syndrome. Standard of care for severe or life-threatening CRS resulting from immune-based therapy has not been established; case reports and recommendations have been published (Teachey et al. 2013; Lee et al. 2014; Maude et al. 2014; Thompson et al. 2019). Management guidelines for CRS following study treatment are summarized in Table 1 below.

Table 1: Recommendations for Management of Cytokine Release Syndrome for Patients Receiving Subcutaneous Mosunetuzumab (2023 Guidance)

CRS Grade [a]	Supportive Care	Anti-IL-6 / Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 1 fever ≥ 38ºC	• Provide symptomatic management of constitutional symptoms and organ toxicities • Consider empiric broad-spectrum antibiotics • Consider G-CSF if participant is neutropenic • Maintenance IV fluids for hydration • Consider hospitalization until symptoms completely resolve	• For prolonged CRS (> 2 days) in participants with significant symptoms and/or comorbidities (per investigator discretion [e.g., impaired cardiovascular function, reduced pulmonary reserve]), consider tocilizumab[c] and corticosteroids as per Grade 2	• May receive the next dose of mosunetuzumab if symptoms resolve for 3 consecutive days • Administer premedications for next dose • The participant should be monitored more frequently

Grade 2 fever ≥ 38ºC [b] with hypotension <u>not requiring</u> vasopressors and/or hypoxia requiring <u>low-flow oxygen</u> [cd] by nasal cannula or blow-by	• Provide symptomatic management of constitutional symptoms and organ toxicities • Consider ICU admission for hemodynamic monitoring • For hypotension: IV fluid bolus as needed; for persistent refractory hypotension (e.g., after 2 fluid boluses and anti-IL-6 therapy), start vasopressors and manage per Grade 3 • Rule out other inflammatory conditions, which can mimic severe CRS (e.g., infections/sepsis), undertake SARS-CoV-2 diagnostic PCR • Consider empiric broad-spectrum antibiotics • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH	• Consider tocilizumab [c] • For persistent refractory hypotension after 1 or 2 doses of anti-IL-6 therapy, consider 10 mg IV dexamethasone every 6 hours (or equivalent) • Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab	• May receive the next dose of mosunetuzumab as planned if symptoms resolve to Grade 1 or better for 3 consecutive days • Premedications should be maximized as appropriate • Consider hospitalization of the participant for the next dose

CRS Grade [a]	Supportive Care	Anti-IL-6 / Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 3 fever ≥ 38ºC [b] with hypotension requiring a vasopressor (with or without vasopressin) and/orhypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, nonrebreather mask, or Venturi-mask	• Symptomatic management of organ toxicities, admit patient to ICU for hemodynamic monitoring • For hypotension: IV fluid bolus and vasopressors as needed • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis), undertake SARS-CoV-2 diagnostic PCR • Consider empiric broad-spectrum antibiotics • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH	• Administer tocilizumab [c] • Dexamethasone 10 mg IV every 6 hours (or equivalent) • If CRS is refractory to tocilizumab and dexamethasone, manage as per Grade 4 with alternative immunosuppressants and 1000 mg/day methylprednisolone	• May receive the next dose of mosunetuzumab if CRS event was responsive to treatment (i.e., clinical improvement within 8–12 hours following tocilizumab/corticosteroids administration) and symptoms resolve to Grade 1 or better for 3 consecutive days • Premedications (e.g., antipyretic, antihistamine, and steroids) should be maximized as appropriate • Hospitalize patient for next dose • If the event occurs after the Cycle 1 Day 1 dose, consider repeating the same dose • If the event occurs after the Cycle 1 Day 8 dose or subsequent doses, the next dose should be reduced • If the next dose is tolerated without Grade ≥ 3 CRS, the participant may return to the originally planned dose [i] • If Grade 3 CRS recurs with subsequent doses, consider permanent discontinuation of mosunetuzumab

CRS Grade [a]	Supportive Care	Anti-IL-6 / Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 4 **fever ≥ 38ºC [b]** **with hypotension <u>requiring multiple vasopressors</u> (excluding vasopressin)** **and/or hypoxia requiring oxygen by <u>positive pressure</u> (e.g., C-PAP, Bi-PAP, intubation, and mechanical ventilation)**	• ICU admission and hemodynamic monitoring • Mechanical ventilation as needed • IV fluids and vasopressors as needed • Symptomatic management of organ toxicities • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis), undertake SARS-CoV-2 diagnostic PCR • Consider empiric broad-spectrum antibiotics • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms HLH	• Administer tocilizumab [c] • For participants refractory to tocilizumab, consider siltuximab, anakinra, dasatinib, and emapalumab, based on discretion of the investigator[ef] • Administer 10 mg IV dexamethasone every 6 hours (or equivalent) • If refractory, consider 1000 mg/day IV methylprednisolone [f, g]	• Permanently discontinue mosunetuzumab[h]

AE = adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; C-PAP = continuous positive airway pressure; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IL-6 = interleukin 6; IRR = infusion-related reaction; IV=intravenous; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

[a] Cytokine release syndrome will be assessed according to the ASTCT Consensus Grading Criteria (Lee et al. 2019). Fever is defined as temperature ≥ 38ºC not attributable to any other cause. In participants who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

[b] As participants may have received corticosteroid premedication, a fever response may be blunted. Therefore, adverse events attributed to mosunetuzumab consistent with a diagnosis of IRR or CRS, and associated with fever, hypotension or hypoxia not attributable to any other cause, should be recorded as CRS. Cytokine release syndrome events that manifest with hypotension and/or hypoxia, but with no fever, should be graded depending on management required for hypotension and/or hypoxia. These types of events correspond to minimum ASTCT Grade 2. Other adverse events occurring within 24 hours after mosunetuzumab administration should be reported as individual adverse events (e.g., headache or chills).

[c] Tocilizumab should be administered at a dose of 8 mg/kg IV (not exceeding 800 mg per infusion). If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second dose may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time-period of 6 weeks of mosunetuzumab treatment, the total number of tocilizumab doses should not exceed 3 doses.

[d] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low-flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

[e] Riegler et al. 2019.

[f] Anti-fungal prophylaxis should be strongly considered in participants receiving steroids for treatment of CRS.

[g] For example, 1000 mg/day IV methylprednisolone for 3 days, followed by a rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 13 hours for 2 days, and 60 mg every 12 hours for 2 days.

[h] Resumption of mosunetuzumab may be considered in participants who are deriving benefit and have fully recovered from the adverse event. Participants can be re-challenged with mosunetuzumab only after approval has been documented by the investigator (or an appropriate delegate). Further treatment will not be considered unless all the criteria below are met:

- Individual risk–benefit assessment by Principal Investigator/treating physician favors continued treatment
- The patient has recovered from previous toxicities and has sufficient organ function/reserve to receive subsequent doses
- The patient has been adequately consented for risks associated with continued treatment and decides to receive subsequent doses
- The above risk–benefit assessment and evaluation of participants are discussed with the Sponsor
- Subsequent doses are well planned with precautionary measures, including dose reduction, mandatory hospitalizations, and enhanced premedications

[i] Phase 3 study protocols included dose reductions to 20 mg after grade 3 CRS after the C1D8 dose (or subsequent doses). Appropriate dose reduction should be individualized based on the discretion of the investigator.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625–38.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

TUMOR FLARE

The mechanism of action of mosunetuzumab may result in a volumetric increase of lymphoma lesions leading to local compression and organ dysfunction. All patients should be carefully monitored for tumor flare events. Depending on the site of lesions, the following guidance should be followed.

For patients with lesions in the oropharyngeal region and prior to the first administration of mosunetuzumab:

- Evaluate anatomy of the region and consult an ears, nose, and throat specialist and acute care service in case tumor enlargement of a bulky oropharyngeal lesion may affect upper airways function. Individual assessment of benefits and risks should be discussed with the patient. In some situations, the patient should be considered for prophylactic tracheostomy prior to the first administration.
- Management of suspected tumor flare events in high-risk patients with lymphoma lesions in the oropharynx:

In case of a suspected tumor flare event (including, but not limited to, dyspnea, increased labored breathing, hoarseness, wheezing, hypoxia), follow management guidelines summarized in Table 2. Tracheostomy should be maintained until at least Cycle 2 dose is administered, if the benefit–risk assessment is deemed favorable (i.e., if patient is receiving benefit from study treatment).

Table 2 Management of Suspected Flare Event in the Oropharynx for High-Risk Patients with Bulky Lesions

Triggering Event [a]	Initial Management Recommendation (Action to Be Taken)	Action to Be Taken with Mosunetuzumab
Administer supportive measures (e.g., oxygen support, intubation, tracheostomy as indicated). Monitor patients closely as planned before study treatment administration. Ensure patient access to an intensive care unit is available.		
Grade 1 tumor flare	• Consult ENT specialist, if not already done so. If patient has not prophylactically tracheostomized, consider tracheostomy at event onset.	• Continue treatment
Grade 2 tumor flare	• Perform tracheostomy at event onset • If no resolution to Grade 1 or better within 48 hours, administer 1 mg/kg/day IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade 1 or better	• Hold until resolution to Grade 1 or better. If in place, keep tracheostomy until next cycle dosing, even after resolution to Grade 1 or better.
Grade 3 and 4 tumor flare	• Perform tracheostomy at event onset • Administer 2 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until resolution to Grade 1 or baseline value	• Hold until resolution to Grade 1 or better • Consider permanent discontinuation

ENT = ears, nose, and throat (specialist); NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Grade of triggering event dependent on presenting signs and symptoms of tumor flare; for events not specifically listed in NCI CTCAE v5.0, see Section 6.

For patients with mediastinal lymphoma around the heart and big vessels:

- Before first administration of study treatment: Obtain cardiology consultation and evaluate cardiac ejection fraction at baseline. Map bulky lesions whose enlargement may create acute impairment of organ function and plan emergency measures if deemed necessary (e.g., access to urgent echocardiography and other imaging, pericardiocentesis, if required). An analogous intervention of tracheostomy for upper airway obstruction may not be readily available for patients who may experience compression of critical structures in the mediastinum owing to surrounding mass effect; as such, the individual benefit–risk assessment should be discussed with the patient.

At first administration of mosunetuzumab: In case of a suspected tumor flare event (this may include, but is not be limited to, chest pain, dyspnea, hypoxia, cyanosis, syncope, cough, palpitations) follow management guidelines summarized in Table 3. After first administration, monitor ejection fraction weekly, or with shorter intervals if clinically required. In case of clinically significant improvement in 2 consecutive ejection fraction measurements, stop or reduce frequency of monitoring. Weekly monitoring can also be stopped based on investigator assessment after at least one monitoring after first administration in patients with Grade 2 ejection fraction at baseline.

Table 3 Management of Suspected Flare Event in the Mediastinum

Triggering Event [a]	Initial Management Recommendation	Action to Be Taken with Mosunetuzumab
Patients with Grade ≤ 2 ejection fraction decrease at baseline: Monitor patient closely as planned before study treatment administration. Ensure patient access to an intensive care unit is available.		
Grade 2	• Monitor patient closely	• Grade 2 events, hold until resolution to Grade < 2
Grade 3	• Administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade 2 or baseline value (consider escalating next day to 2 mg/kg/day if no improvement, or escalate to 2 mg/kg directly if event occurs during prophylactic treatment with steroids) • Ensure patient access to an intensive care unit is available	• Hold until resolution to Grade < 2. For Grade ≥ 3 toxicity lasting > 5 days, permanently discontinue study treatment.
Grade 4	• Administer 2 mg/kg/day of IV methylprednisolone or equivalent until Grade 2 • Ensure patient access to an intensive care unit is available	• Permanently discontinue study treatment
Patients with Grade ≥ 3 ejection fraction decrease at baseline: Monitor patients closely as planned before study treatment administration. Ensure patient access to an intensive care unit is available.		
Grade 3	• Undertake interventions [b] in case of worsening ejection fraction. Administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until baseline (consider escalating next day to 2 mg/kg/day if no improvement, or escalate to 2 mg/kg directly if event occurs during prophylactic treatment with steroids).	• Hold until resolution to baseline. Permanently discontinue study if weekly ejection fraction monitoring shows 3 consecutive clinically significant worsening ejection fractions.
Grade 4	• Undertake interventions [b] in case of worsening ejection fraction. Administer 2 mg/kg/day of IV methylprednisolone or equivalent until baseline.	• Hold until resolution to baseline. Permanently discontinue study treatment if weekly monitoring shows 3 consecutive clinically significant worsening results.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Grade of triggering event depends on presenting signs and symptoms; for events not specifically listed in NCI CTCAE, v5.0, see Section 6.

[b] Preventative and interventional measures should be considered, appropriate specialists, and the patient prior to mosunetuzumab dosing. When events manifest as pericardial effusions or tamponade, pericardiocentesis, or pericardial window may be considered. In case of external compression of the heart and great vessels, ″rescue″ interventions may not be available. Individual assessment of benefits and risks must be discussed with the patient.

For all other patients with suspected tumor flare event, follow the recommendations in Table 4. The management guidelines refer mostly to pain and may be followed whenever pain or other symptoms occur, owing to compression of neural structures by lymphoma.

Table 4 Management of Suspected Tumor Flare Event Outside the Mediastinum and Oropharynx, Applicable Whenever Pain Management is Required

Triggering Event [a]	Initial Management Recommendations	Action to Be Taken with Mosunetuzumab
Grade 1	• Manage pain with paracetamol and/or NSAID	• Continue treatment
Grade 2	• Manage pain with weak opioids such as tramadol, dihydrocodeine and codeine, which can be given in combination with non-opioid analgesics • Monitor patient closely • If no resolution to Grade 1 or better within 48 hours, administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade 1 or better	• Hold until resolution to Grade 1 or better
Grade 3	• Manage pain with strong opioids such as oxycodone, hydromorphone, buprenorphine or similar at high dose if required • Consider imaging patient and perform differential diagnosis for disease progression • Administer 2 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until resolution to Grade 1 or baseline value • Ensure patient access to an intensive care unit is available	• Hold until resolution to Grade 1 or better
Grade 4	• Follow all recommendations for Grade 3 event	• Hold until resolution to Grade 1 or better. Consider permanent discontinuation

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug.

[a] Grade of triggering event depends on presenting signs and symptoms; for events not specifically listed in NCI CTCAE, v5.0, see Section 6.

NEUROLOGIC ADVERSE EVENTS

Neurologic adverse events will be monitored closely during the trial. All patients will be required to undergo a baseline complete neurologic examination prior to study treatment; the examination should include an evaluation of mental status, cranial nerves, motor strength, sensation, and coordination. Results of the neurologic examination should be documented in the patient's chart. Patients with a history of neurologic disease may be excluded from this study.

Patients should be routinely assessed for any signs or symptoms of neurologic toxicity as part of the on-treatment clinical examination. If new or worsening neurologic toxicity is suspected, the patient should be referred to a neurologist for further evaluation of potential study treatment–related neurotoxicity. Corticosteroids should be considered to treat suspected neurologic toxicity. Imaging studies should be performed if clinically indicated. Recommended management guidelines for neurotoxicity are presented in Table 5 for mosunetuzumab.

The investigator should instruct patients to refrain from driving or engaging in hazardous occupations or activities if patients develop specific adverse events during mosunetuzumab treatment.

For patients who develop a neurologic adverse event that may affect driving and for patients who develop CRS, HLH, or Grade 3 or 4 LFT elevation, the investigator should advise patients to refrain from driving or engaging in hazardous occupations or activities until the event is resolved. Neurologic adverse events with the potential to impact cognition or consciousness that may affect driving (driving-impacting cognition or consciousness neurologic events [CCNAE]) include, but are not limited to, amnesia, aphasia, confusional state, delirium, depressed level of consciousness, disturbance in attention, encephalopathy, hallucination, hepatic encephalopathy, insomnia, memory impairment, seizure, visual hallucination, and vertigo.

Patients who develop tremor, dizziness, insomnia, or a Grade ≥ 3 neurologic adverse event should be assessed by neurologic examination to determine whether the adverse event may impair a patient's ability to drive or engage in hazardous occupations or activities. For patients assessed to be at increased risk, the investigator should advise the patient to refrain from driving or engaging in hazardous occupations or activities until the event is resolved.

Management of neurologic toxicity associated with mosunetuzumab is presented in Table 5.

Table 5 Management of Neurotoxicity including ICANS (Mosunetuzumab)

Event [a,b]	Actions
General guidance	• Consider hospitalizing the participant for monitoring as clinically needed. If clinically indicated, transfer participant to ICU and initiate measures for protection of airway. • Assess patients for ICE using the ICE score. • Consider imaging of the brain (MRI preferred), lumbar puncture, fundoscopy, and/or EEG, taking into account risks for procedures. • Rule out other causes (e.g., infection, cerebral hemorrhage, electrolyte imbalance, concomitant medications, other medical conditions). • Avoid medication that would cause further CNS depression. • See **Section 6.2** (Dose Modification Section) for guidance on restarting mosunetuzumab after dose delay. • Guidance for neurologic toxicity including ICANS concurrently with CRS: – Administer medications as outlined below: o Compare the corticosteroid regimen in the guidelines for ICANS below with the regimen in the guidelines for CRS (see **Table 1 in this Appendix** [CRS management guidelines table]) and administer the most aggressive regimen. Dexamethasone is the preferred corticosteroid. Administer tocilizumab as per guidelines for CRS (see **Table 1 in this Appendix** [CRS management guidelines table]).
Grade 1	• Continue mosunetuzumab and monitor neurologic toxicity symptoms. • If Grade 1 ICANS[b] consider a single dose of dexamethasone 10 mg, if not taking other corticosteroids.
Grade 2	• Withhold mosunetuzumab until neurologic toxicity symptoms improve to Grade 1 or baseline[c,d] • Provide supportive therapy and consider neurologic consultation and evaluation. • If Grade 2 ICANS[b] treat with dexamethasone 10 mg intravenously every 12 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper.
Grade 3	• Withhold mosunetuzumab until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 7 days[d,e] • For Grade 3 neurologic events lasting more than 7 days, consider permanently discontinuing mosunetuzumab. • Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation. • If Grade 3 ICANS[b] treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed.
Grade 4	• Permanently discontinue mosunetuzumab. • Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation. • If Grade 4 ICANS[b] treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed.

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICU = intensive care unit; MRI = magnetic resonance imaging; NCI = National Cancer Institute.

a Neurologic toxicity grading per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

b American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria.

c Consider the type of neurologic toxicity before deciding to withhold mosunetuzumab.

d See *Section 6.2 (Dose modifications)* for guidance on restarting mosunetuzumab after dose delay.

e Evaluate benefit/risk before restarting mosunetuzumab.

Note: this guidance does not apply to peripheral neuropathy

Reference

Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

TUMOR LYSIS SYNDROME

Treatment for laboratory and/or clinical presentations of tumor lysis syndrome (TLS) will follow institutional practice. Prior to each treatment given during Cycles 1 and 2, the patient's serum chemistry and hematologic laboratory samples (including uric acid and phosphorous for patients deemed by the investigator to be at high risk of TLS) should be obtained and the results reviewed. If appropriate, TLS prophylactic measures should be initiated according to the guidelines described below. Access to nephrology consultation with acute dialysis services must be available in the event of clinically significant TLS.

As mosunetuzumab has the potential for B cell killing, the potential risk of TLS in all patients must be considered, along with the need for prophylaxis for TLS prior to the initiation of mosunetuzumab. Owing to the potential risk of TLS following administration of study treatment, patients must meet the serum creatinine or creatinine clearance parameters as defined in Section 3.1 in order to participate in this trial.

All patients will be adequately hydrated prior to mosunetuzumab administration during Cycles 1 and 2, consisting of a fluid intake of approximately 2–3 L/day starting 24–48 hours prior to the first dose of mosunetuzumab. If a patient is hospitalized for the administration of study treatment, IV hydration at a rate of 150–200 mL/hour should begin at the conclusion of mosunetuzumab administration and continue for at least 24 hours thereafter. If a patient receives study treatment in the outpatient setting, fluid intake should be maintained at 2–3 L/day for at least 24 hours after mosunetuzumab administration. Modification of fluid rate should be considered for individuals with specific medical needs.

Laboratory monitoring during tumor lysis prophylaxis should follow institutional practice and the investigator's judgment. Treating physicians should consider administration of a uric acid reducing agent for all patients deemed to be at high risk for TLS (e.g., allopurinol 300 mg/day orally beginning 72 hours prior to dose and continuing for 3–7 days afterward). For patients with elevated uric acid levels prior to mosunetuzumab treatment and considered to be at high risk for TLS, rasburicase (e.g., 0.2 mg/kg IV over 30 minutes prior to first dose mosunetuzumab and daily for up to 5 days thereafter) should also be considered. Treatment with allopurinol and/or rasburicase should continue as specified above, or until normalization of serum uric acid or other laboratory parameters if laboratory evidence of TLS is observed. Note that uric acid measurement in the presence of rasburicase administration requires special handling.

Patients deemed by the investigator to be at high risk for TLS should continue to receive prophylaxis with allopurinol or rasburicase, if previously initiated, and adequate hydration with each subsequent dose of mosunetuzumab until the patient is no longer considered to be at high risk for TLS. Patients who develop either clinical or laboratory TLS during Cycle 1 should be considered for hospitalization during subsequent cycles for optimum hydration and monitoring. If the Howard criteria for TLS (see Table 6 below; Howard et al. 2011) are fulfilled at any time during the study (and not explained by alternative etiologies) or if there is a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g., increased serum creatinine or cardiac dysrhythmia), study treatment should be withheld and patients should be hospitalized, if appropriate, and adequately treated until normalization of laboratory abnormalities before treatment is restarted. Telemetry should be considered during the inpatient management of patients at high risk for TLS.

Table 6 Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Laboratory TLS [a]	Criteria for Classification of Clinical TLS [a]
Hyperuricemia	• Uric acid ≥ 8.0 mg/dL (475.8 μmol/L) in adults or above ULN range for age in children	–
Hyperphosphatemia	• Phosphorous > 4.5 mg/dL (1.5 mmol/L) in adults or > 6.5 mg/dL (2.1 mmol/L) in children	–
Hyperkalemia	• Potassium > 6.0 mmol/L	• Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	• Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 4.5 mg/dL (< 1.12 mml/L) [b]	• Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury [c]	• Not applicable	• Increase of 0.3 mg/dL (26.5 μmol/L) in serum creatinine level (or a single value > 1.5 × age-appropriate ULN range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of < 0.5 mL/kg/hr for 6 hours

Source: Howard et al. 2011.
TLS = tumor lysis syndrome; ULN = upper limit of normal.
Note: TLS should be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0.
[a] In laboratory TLS, 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.
[b] The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4–albumin in grams per deciliter).
[c] Acute kidney injury is defined as an increase of 0.3 mg/dL (26.5 μmol/L) in creatinine level or a period of oliguria lasting 6 or more hours. By definition, if acute kidney injury is present, the patient has clinical TLS (Levin et al. 2007).

ELEVATED LIVER ENZYMES

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug. For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Liver function tests will be assessed regularly during study and should be managed according to guidelines in Table 7 for mosunetuzumab.

Table 7 Management of Liver Function Test Abnormalities (Mosunetuzumab)

Abnormality	Action to Be Taken
Grade 1 AST or ALT elevation or AST/ALT $\geq 3 \times$ baseline value	• Continue mosunetuzumab • Monitor LFTs (including AST, ALT, bilirubin) weekly
Grade 2 AST or ALT elevation	**All events:** • Withhold mosunetuzumab • Monitor LFTs at least weekly and as clinically indicated until values resolve to normal or baseline value • Resume mosunetuzumab when resolved to Grade 1 or baseline value • Consider hepatology consultation • If event does not resolve to Grade ≤ 1 or baseline within 12 weeks permanently discontinue study treatment **In addition, if the event is immune related [a]:** • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent • If event resolves to Grade ≤ 1, taper corticosteroids per institutional practice
Grade 3 AST or ALT elevation	**All events:** • Withhold mosunetuzumab • Monitor LFTs every 24–48 hours until decreasing and then follow weekly • Obtain hepatology consultation; consider liver biopsy to assess hepatic injury [a] • Resume mosunetuzumab when resolved to Grade 1 or baseline value • If event does not resolve to Grade ≤ 1 or baseline within 12 weeks permanently discontinue study treatment • If event lasts > 5 days, permanently discontinue study treatment [b] **In addition, if the event is immune related [a]:** • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent • If no improvement within 48 hours after initiating corticosteroids, consider additional immunosuppressive agent(s) • If event resolves to Grade ≤ 1, taper corticosteroids per institutional practice

Abnormality	Action to Be Taken
Grade 4 AST or ALT elevation	**If the event is immune related [a]:** • Follow management guidelines as described for Grade 3 events **If the event is NOT immune related** • Permanently discontinue study treatment

ALT=alanine transaminase; AST=aspartate transaminase; LFT=liver function test; ULN=upper limit of normal.

[a] Immune-related event should be considered when concurrent clinical and laboratory manifestations of CRS or HLH are present, or in instances where no alternative etiology (e.g., viral, neoplastic) can account for observed LFT abnormalities.

[b] Resumption of mosunetuzumab may be considered in patients who are deriving benefit and who have fully recovered from the immune-related event. Patients may resume dosing with mosunetuzumab only after documented approval by the investigator.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

Guidelines for Hemophagocytic Lymphohistiocytosis

HLH and cytokine release syndrome (CRS) that occur subsequent to T cell−redirecting therapy have overlapping features, and HLH−like symptoms may be seen in individuals with severe CRS. Although HLH is distinct from CRS in this setting, overlapping clinical features may make it difficult to distinguish HLH from CRS. Temporally, HLH may have a delayed onset and can occur as CRS is resolving or after CRS has resolved. In addition, HLH can occur in the absence of CRS.

HLH should be diagnosed on the basis of criteria developed by an ASTCT working group (Hines et al. 2023), as outlined in Table 8 below (Criteria for diagnosing HLH). When reporting HLH events, severity will be graded according to a scale developed by the ASTCT working group (see Table 10 – ASTCT grading scale for HLH). Patients with suspected or confirmed HLH should be treated according to the guidelines in Table 9 (Management guidelines for HLH).

Table 8 Criteria for Diagnosing Hemophagocytic Lymphohistiocytosis

Diagnostic Strength	Clinical or Laboratory Manifestations [a]
Required manifestation	• Ferritin rapidly rising and/or ferritin $>2\times$ ULN or baseline
Most common manifestations	• Onset with resolving or resolved CRS, or worsening inflammatory response after initial improvement with CRS-directed therapy [b] • Hepatic transaminase $>5\times$ ULN if baseline was normal or $>5\times$ baseline if baseline was abnormal • Fibrinogen <1.5 g/L (150 mg/dL) or $<$ LLN • Hemophagocytosis in bone marrow or other tissue • Cytopenias: [c] new onset, worsening, or refractory
Other manifestations that may be present	• Lactate dehydrogenase $>$ LLN • Other coagulation abnormalities (e.g., elevated PT or PTT) • Direct bilirubin $>$ LLN • Splenomegaly: new onset • Fever: new onset [d] or persistent • Neurotoxicity • Pulmonary manifestations (e.g., hypoxia, pulmonary infiltrates, pulmonary edema) • Renal insufficiency: new onset • Fasting triglycerides >2.99 mmol/L (265 mg/dL)

CRS = cytokine release syndrome; HLH = hemophagocytic lymphohistiocytosis; LLN = lower limit of normal; ULN = upper limit of normal.

[a] A diagnosis can be made only when manifestations are not attributable to alternative etiologies, including CRS, infection, and/or disease progression.

[b] HLH can also occur in the absence of CRS.

[c] Generally, at least one lineage (platelets, neutrophils, hemoglobin) will qualify as Grade 4 cytopenia.

[d] As distinguished from CRS onset or recrudescence.

Table 9 Management Guidelines for Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected or confirmed HLH, any grade	• For suspected HLH, withhold mosunetuzumab and initiate workup for HLH. For confirmed HLH, permanently discontinue mosunetuzumab. If HLH is not confirmed and participant improves, treatment may be resumed at the investigator's discretion. • Consult with hematologist with experience in managing HLH. • Identify triggering etiology. Selection of therapy should be etiology-driven. • Initiate supportive care. Admit participant to ICU if clinically indicated. • Perform laboratory tests at least daily until participant is stable. Consider evaluating CBC with differential, creatinine, urea or BUN, PT, aPTT, fibrinogen, D-dimer, AST, ALT, ALP, total and direct bilirubin, albumin, LDH, ferritin, and CRP. • Assess for bacterial, viral, [a] and fungal infections in blood, urine, sputum, and (if indicated) in lung tissue (via bronchoscopy) or in cerebrospinal fluid, and manage infections as per institutional practice. • To support a diagnosis of HLH, consider testing for triglycerides, soluble CD25 (soluble IL-2 receptor), NK cell function, IFN-γ , CXCL9 ratio, CXCL10, IL-10, IL-18, and DNA sequencing panel for HLH susceptibility genes, as available. • Consider bone marrow aspiration with or without biopsy and (for new or increasing lymphadenopathy) lymph node biopsy to test for alternative etiologies. • Monitor cardiopulmonary, neurologic, and other organ function closely. Perform ECG and chest X-ray (or CT scan) if clinically indicated. • For HLH treatment, recommend administering an IL-1 blocking agent (e.g., anakinra) with or without IV corticosteroids (dexamethasone 10-40 mg daily [10 mg every 6 hours is most common] or equivalent if dexamethasone is unavailable). [b] If an IL-1 blocking agent is not readily available, refer to local or institutional guidelines for management of HLH. • If event remains refractory or worsens, add corticosteroids if not already started, consider increasing the dose of the IL-1 blocking agent or corticosteroid, or consider adding a JAK inhibitor (e.g., ruxolitinib). • For life-threatening events, consider adding an agent in another class, such as a kinase inhibitor, cytotoxic agent, or cytokine blocker (e.g., ruxolitinib, etoposide, or emapalumab). • Participants with cytopenias or coagulopathy should be treated as per institutional practice.

CMV = cytomegalovirus; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; EBV = Epstein Barr virus; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IFN = interferon; IL = interleukin; JAK = Janus kinase; LDH = lactate dehydrogenase; NK = natural killer; ULN = upper limit of normal.

Note: Refer to Hines et al. (2023) for additional information on management of participants with HLH.

[a] Test for viral reactivation or new viral infections (e.g., EBV, CMV).

[b] If corticosteroids have been initiated, they must be tapered as per institutional practice.

Table 10 ASTCT Grading Scale for Hemophagocytic Lymphohistiocytosis

Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
HLH [a]	Asymptomatic or mild symptoms; requires observation and/or clinical and diagnostic evaluation; intervention not indicated	Mild to moderate symptoms, with intervention indicated (e.g., immunosuppressive agents directed at HLH, transfusions for asymptomatic hypofibrinogenemia)	Severe or medically significant but not immediately life-threatening (e.g., coagulopathy with bleeding requiring transfusion support, or hospitalization required for new-onset acute kidney injury, hypotension, or respiratory distress)	Life-threatening consequences; urgent intervention indicated (e.g., life-threatening bleeding or hypotension, respiratory distress requiring intubation, dialysis indicated for acute kidney injury)	Death

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; HLH = hemophagocytic lymphohistiocytosis; NCI CTCAE v5.0 = National Cancer Institute's Common Terminology Criteria for Adverse Events, Version 5.0; ULN = upper limit of normal.

Note: The ASTCT grading scale (Hines et al. 2023) is based on the CTCAE v5.0 "immune system disorders, other" category.

[a] HLH is a pathological and biochemical hyperinflammatory syndrome that may present with fever, hepatosplenomegaly, organ failure, and neurologic toxicities and is associated with progression or new onset of hyperferritinemia, cytopenias, coagulopathy with hypofibrinogenemia, and/or elevation of liver enzymes. HLH and CRS that occur subsequent to T cell−redirecting therapy have overlapping features, and HLH-like symptoms may be seen in individuals with severe CRS. Although HLH is distinct from CRS in this setting, overlapping clinical features may make it difficult to distinguish HLH from CRS. Temporally, HLH may have a delayed onset and can occur as CRS is resolving or after CRS has resolved. In addition, HLH can occur in the absence of CRS.

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NEUTROPENIA

All patients should be monitored at each cycle for neutropenia, and patients experiencing neutropenia should undergo blood cell monitoring until resolution of the event to Grade 2 or lower. Guidelines for neutropenia management are outlined in Table 11. Participants who experience febrile neutropenia should be managed according to local guidelines or as per institutional practice.

Table 11 Management Guidelines for Neutropenia

Grade	Management
Grade 1 or 2	• Manage according to institutional practice
Grade 3 or 4 in Cycle 1	• Growth factors (e.g., G-CSF) for neutropenia are permitted • Mosunetuzumab step-up doses should not be held for uncomplicated neutropenia • The dose of mosunetuzumab should not be modified
Grade 3 or 4 in Cycles 2-17	• Delay all study treatment until ANC recovery following guidelines below: • Growth factors (e.g., G-CSF) for neutropenia are permitted • Consider holding mosunetuzumab for persistent Grade 4 neutropenia (> 21 days after the scheduled dose of the next cycle) • The dose of mosunetuzumab should not be modified

G-CSF = granulocyte colony-stimulating factor

THROMBOCYTOPENIA

All patients should be monitored at each cycle for thrombocytopenia. Patients experiencing thrombocytopenia should undergo blood cell monitoring until resolution of the event to Grade 1 (platelet count ≥75,000/μcL). Thrombocytopenia management guidelines are outlined in Table 12.

Table 12 Management Guidelines for Thrombocytopenia

Event	Occurrence	Actions to Be Taken
Grade 3, 4 thrombocytopenia	1,2,3	• Continue mosunetuzumab • Mosunetuzumab step-up doses should not be held for uncomplicated (without significant bleeding) thrombocytopenia in Cycle 1
	4	• Continue mosunetuzumab
	5	• Discontinue mosunetuzumab
Grade 3, 4 thrombocytopenia that results in significant bleeding	1	• Withhold mosunetuzumab until bleeding resolves
	2	• Withhold mosunetuzumab until bleeding resolves
	3	• Discontinue mosunetuzumab

INJECTION SITE REACTIONS

Participants who experience localized injection-site reactions following SC administration of mosunetuzumab should be managed according to the guidelines detailed in Table 13.

Table 13 Management Guidelines for Injection-Site Reactions

Grade	Management
Grade 1	• Consider treatment with topical steroids • Continue mosunetuzumab in subsequent cycles
Grade 2	• Notify principal investigator • Initiate treatment with topical steroids • If progressive after 24 hours, consider prednisone or equivalent 10-30 mg/day • Continue mosunetuzumab in subsequent cycles after improvement to Grade ≤1
Grade 3	• Notify principal investigator • Withhold mosunetuzumab • Initiate prednisone 1 mg/kg/day or equivalent • Obtain a dermatology consultation • Taper steroids after improvement to Grade ≤1 • Continue mosunetuzumab in subsequent cycles after improvement to Grade ≤1
Grade 4	• Notify principal investigator • Management as for Grade 3 • Permanently discontinue SC mosunetuzumab.

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APPENDIX E: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes [a]	Sensitive Substrates [b]	Substrates with Narrow Therapeutic Range [c]
CYP1A2	• Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	• Theophylline, tizanidine
CYP2B6 [d]	• Bupropion, efavirenz	–
CYP2C8	• Repaglinide [e]	• Paclitaxel
CYP2C9	• Celecoxib	• Warfarin, phenytoin
CYP2C19	• Lansoprazole, omeprazole, S-mephenytoin	• S-mephenytoin
CYP3A [f]	• Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	• Alfentanil, astemizole [g], cisapride [g], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [g]
CYP2D6	• Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	• Thioridazine

AUC = area under the concentration–time curve; OATP1B1 = organic anion transporting polypeptide 1B1; P-gp = P-glycoprotein.

[a] Note that this is not an exhaustive list. For an updated list, see the following ink: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

[b] Sensitive CYP substrates refer to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[c] Cytochrome P450 substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., torsades de pointes).

[d] The AUC of these substrates were not increased by 5–fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

[e] Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.

[f] Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

[g] Withdrawn from the U.S. market because of safety reasons.

APPENDIX F: Sample List of Cautionary Medications

(A) Inhibitors

CYP	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A	• Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,[a] indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole	• Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib, [a] cyclosporine, [a] darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,[a] isavuconazole, tofisopam, verapamil	• Chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

[a] These are the anti-cancer agents.

(B) Inducers

CYP	Strong Inducers	Moderate Inducers	Weak Inducers
CYP3A	• Avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	• Bosentan, efavirenz, etravirine, modafinil, nafcillin	• Armodafinil, rufinamide

Source: U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [resource on the Internet]. 2017 [cited 18 April 2018]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

APPENDIX G: ASTCT Cytokine Release Syndrome Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [a]	• Temperature ≥ 38ºC	• Temperature ≥ 38ºC	• Temperature ≥ 38ºC	• Temperature ≥ 38ºC
		with		
Hypotension	• None	• Not requiring vasopressors	• Requiring a vasopressor with or without vasopressin	• Requiring multiple vasopressors (excluding vasopressin)
		and/or [b]		
Hypoxia	• None	• Requiring low-flow nasal cannula [c] or blow-by	• Requiring high-flow nasal cannula [c], facemask, nonrebreather mask, or Venturi mask	• Requiring positive pressure (e.g., C-PAP, BiPAP, intubation, and mechanical ventilation)

Source: Lee et al. 2019.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; C-PAP = continuous positive airway pressure; CRS = cytokine-release syndrome; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Organ toxicities associated with CRS may be graded according to NCI CTCAE, v5.0, but they do not influence CRS grading.

By convention, Grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome.

[a] Fever is defined as ≥ 38°C not attributable to any other cause. In patients who have CRS and then receive anti-pyretic or anti-cytokine therapy such as tocilizumab or corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] Cytokine-release syndrome grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

APPENDIX H: Anaphylaxis Precautions

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
4. Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
5. Continue to observe the participant and document observations.
6. Draw serum/plasma samples for immunogenicity testing.
7. Ask participant to return for washout immunogenicity sample if appropriate.

APPENDIX I: ICE Scoring AND ICANS Grading (Lee et al. 2019)

Immune Effector Cell-Associated Encephalopathy (ICE) score
Orientation: orientation to year, month, city, hospital: 4 points
Naming: ability to name 3 objects (e.g., point to clock, pen, button): 3 points
Following commands: ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
Writing: ability to write a standard sentence (e.g., "Our national bird is the bald eagle"): 1 point
Attention: ability to count backwards from 100 by 10: 1 point

Neurotoxicity Domain	ICANS Grade 1	ICANS Grade 2	ICANS Grade 3	ICANS Grade 4
ICE score *	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness †	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between.
Motor findings ‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Elevated ICP / cerebral edema	N/A	N/A	Focal/local edema on neuroimaging §.	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.

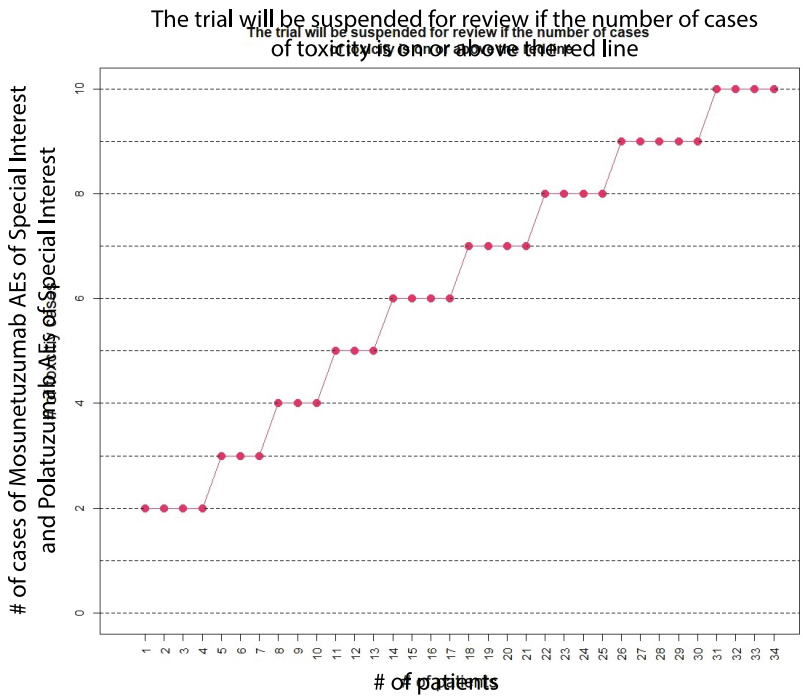
ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

APPENDIX J: Study-Specific DSM Tables

Protocol Objectives and Subject Evaluability	
Objective/Endpoint	**# of patients evaluable for this endpoint to date** (please refer to evaluability section of protocol (Section 5.5) for definitions)
Primary	
To evaluate the efficacy (CR as best response) of the combination of mosunetuzumab and polatuzumab vedotin in patients with untreated follicular lymphoma.	
Secondary	
To evaluate additional metrics of efficacy of the combination of mosunetuzumab and polatuzumab vedotin in patients with untreated follicular lymphoma.	CR Overall = PR Overall = OR (CR + PR) Overall = SD Overall = PD Overall = CR PET2 = PR PET2 = OR (CR + PR) PET2 = SD PET2 = PD PET2 = CR PET8 = PR PET8 = OR (CR + PR) PET8 = SD PET8 = PD PET8 = PFS 24 months = PFS 48 months = OS = Time to first response (CR or PR) = Duration of first response (CR or PR) = Time to 1st CR = Duration of 1st CR = TTNT =
To assess the safety and tolerability of combining mosunetuzumab with polatuzumab vedotin in patients with untreated follicular lymphoma.	TEAEs = Tx discontinuation due to TEAEs =
To assess the use of tocilizumab for management of cytokine release syndrome (CRS) in patients with untreated follicular lymphoma who receive mosunetuzumab and polatuzumab vedotin.	% of all patients requiring tocilizumab =

	# of total tocilizumab doses per patient for management of CRS =
Exploratory	
To evaluate the dynamics of measurable residual disease (MRD) by plasma-derived circulating-tumor DNA (ctDNA) assessment in patients with untreated follicular lymphoma receiving mosunetuzumab and polatuzumab vedotin.	

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? Yes
Description of interim futility analysis from the protocol An optimal Simon two-stage design is used to test the null hypothesis that the CR rate is ≤ 45% versus the alternative hypothesis that the response rate is ≥ 65%. Sixteen patients will be treated in the first stage, and the trial will proceed to the second stage if nine or more patients experience CR in the first stage.
Has interim futility analysis been conducted as of the date of this report?
If yes, please insert results of interim futility analysis
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? Yes
If yes, please insert text describing early stopping rules from the protocol The study will be suspended for review following the death of a patient during protocol-defined treatment or within 30 days of the last dose of protocol-defined treatment or until initiation of new anti-cancer therapy (whichever is first). The study will not be suspended for review if a death was determined to be related to disease progression. Mosunetuzumab AESI and polatuzumab AESI (defined below) will be used to determine the stopping rules with an expected rate of 16% and a maximum allowable rate of 35%. A single continuous toxicity monitoring rule will be used for AEs as shown in the graph below:



Mosunetuzumab AESI are as follows:

- Grade ≥ 2 CRS
- Grade ≥ 2 neurologic adverse event
- Any suspected HLH
- Any grade pneumonitis, interstitial lung disease, acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia and/or other non-infectious pulmonary toxicity
- Tumor lysis syndrome (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 flare (e.g., manifestation of signs/symptoms associated with increased in size of known nodal or extranodal lesions by clinical or radiographic assessment, new onset or worsening of preexisting pleural effusions)

Polatuzumab AESI are as follows:

- Grade ≥ 2 peripheral neuropathy (sensory and/or motor)
- Grade ≥ 3 infections

If yes, please provide data describing whether any patients have met the stopping rules:

Have any patients died?	If yes, provide UPN(s)	If yes, cause of death
Have any patients experienced a mosunetuzumab AESI?	If yes, provide UPN(s)	If yes, specific AESI

Have any patients experienced a polatuzumab AESI?	If yes, provide UPN(s)	If yes, specific AESI
Have any patients experienced a suspected transmission of an infectious agent by the study drug?	If yes, provide UPN(s)	
Have any patients experienced a drug-induced liver injury as defined by Hy's Law?	If yes, provide UPN(s)	

Response							
UPN	**On tx date**	**# cycles complete**	**First response**	**Duration of first response**	**Best response**	**Date of Progression**	**Patient replaced?**

Aggregated Response Data				
Response	**After C2**	**After C8**	**At EOT**	**Best Response (any assessment*)**
CR				
PR				
SD				
PD				
NE				

* includes unscheduled assessments

Treatment Discontinuation and Survival				
UPN	**Reason off tx**	**Off tx date**	**Vital status**	**If dead, cause**

Summary of Specimen Collections			
Type of specimen	**Time point**	**# of patients eligible for collection at this time point**	**% of patients who have reached this time point and had the specimen collected**
Archival FFPE tumor tissue	At any point during participation		
Peripheral blood	C1D1		
Peripheral blood	C1D8		
Peripheral blood	C1D15		
Peripheral blood	C2D1		
Peripheral blood	C3D1		
Peripheral blood	C7D1		
Peripheral blood	C9D1		
Peripheral blood	C13D1		
Peripheral blood	EOT		
Peripheral blood	6 months post-EOT		
Peripheral blood	12 months post-EOT		
Peripheral blood	24 months post-EOT		
Peripheral blood	Time of suspected progression/relapse		