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UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
FRED HUTCHINSON CANCER CENTER

Protocol Title: A pilot study of subcutaneous mosunetuzumab with or without polatuzumab vedotin and obinutuzumab for untreated indolent B-cell non-Hodgkin lymphoma

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CONTENTS

1.0 TRIAL SUMMARY

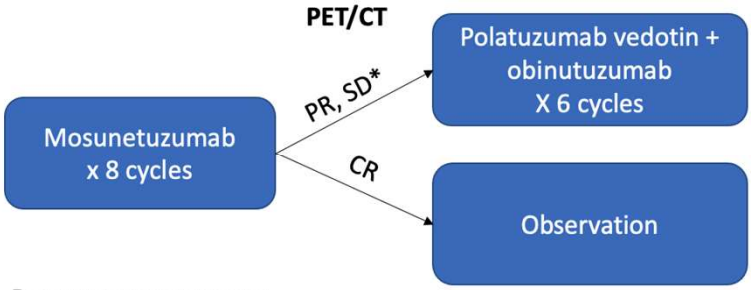
Abbreviated Title	Subcutaneous mosunetuzumab with or without polatuzumab vedotin and obinutuzumab for untreated indolent B-cell non-Hodgkin lymphoma
Trial Phase	Pilot Study
Clinical Indication	Indolent B-cell non-Hodgkin lymphoma (NHL) patients who have not received prior systemic therapy
Trial Type	Nonrandomized, prospective trial
Type of control	N/a
Route of administration	Subcutaneous, IV
Trial Blinding	n/a
Treatment Groups	n/a
Number of trial subjects	42
Estimated duration of trial	30 months (enrollment)
Duration of Participation	38 months

2.0 TRIAL DESIGN

Trial Design:
This is a nonrandomized, single-arm pilot study which will evaluate the activity of subcutaneous (SC) mosunetuzumab with or without polatuzumab vedotin and obinutuzumab in untreated indolent B-cell NHL.

Study duration: Subjects will be enrolled over 30 months. Last subject out (completing study follow-up) is projected to occur at around 38 months after study opening. Subsequently, patients may be followed for outcomes for up to 5 years after treatment completion using standard-of-care assessments per local institutional guidelines.

Trial Diagram



Response assessments
Post cycle 4: CT
Post cycle 8: PET/CT
Post cycle 11 (G+P only): CT
Post cycle 14: PET/CT

* Select subjects with PD may proceed through Part A to Part B provided they are deriving clinical benefit from the treatment (e.g. pseudoprogression)

Cycle length: 21 days

Abbreviations: CR: complete remission; CT: computed tomography; G: obinutuzumab; P: polatuzumab vedotin; PET/CT: Positron emission tomography/computed tomography

3.0 OBJECTIVES & HYPOTHESIS

Primary Objective:

Estimate the efficacy of this regimen as measured by the proportion of subjects who have achieved a complete response (CR) as the best response by the end of therapy.

Secondary Objective:
Estimate the end of treatment overall response rate (ORR).

Exploratory Objective:
Estimate the progression-free survival (PFS), and overall survival (OS) for this combination using the appropriate response criteria for the histology tested. Stratify ORR, CR, PFS, DOR (overall and by type of response), and OS by subjects receiving mosunetuzumab alone vs. mosunetuzumab followed by polatuzumab vedotin and obinutuzumab. Estimate the safety of this regimen as measured by the frequency of adverse events (AEs). Correlate clinical outcomes including but not limited to ctDNA analysis, genomics, cytokine levels.

4.0 BACKGROUND & RATIONALE

Background

While indolent B-cell non-Hodgkin lymphoma (iNHL) including follicular lymphoma (FL) is not curable with standard therapies, it is highly treatable with chemo-immunotherapy[1-3]. Retrospective studies have found that up to 80% of FL patients will have overall survival (OS) near age-matched controls, suggesting that many FL patients might have similar outcomes with less intensive therapy[4,5]. Lenalidomide + rituximab has previously been examined in the upfront setting for 24 months of treatment. While it is "chemo-free," notable adverse effects include fatigue, cytopenias, and is limited in patients with co-morbidities like chronic kidney disease. Mosunetuzumab, a CD3:CD20 bispecific antibody, and polatuzumab vedotin, an anti-CD79b antibody-drug conjugate, have shown significant activity across multiple B-cell NHL histologies[6-10]. The most recent data of mosunetuzumab monotherapy in relapsed/refractory indolent NHL demonstrated a CR rate of 41%[6]. In addition polatuzumab has been safely combined with obinutuzumab in relapsed/refractory follicular lymphoma with an overall response rate of 78%[11].

Obinutuzumab already has an FDA label for treatment-naïve[3] and relapsed/refractory[12] follicular lymphoma in combination with chemotherapy. Obinutuzumab has also been used to treat chronic lymphocytic leukemia/small lymphocytic lymphoma in different combinations in the upfront and relapsed refractory settings[13-15]. Obinutuzumab was found to be equivalent to rituximab in aggressive large B-cell lymphomas[15]. This makes obinutuzumab an effective partner monoclonal CD20 antibody for treatment of indolent B-cell NHL.

While chemo-immunotherapy is efficacious for untreated iNHL, short-term side effects like fatigue, alopecia, and infections are common, and long-term side effects like secondary malignancies can be seen[16]. Given the activity of mosunetuzumab and polatuzumab vedotin in the relapsed/refractory setting, it is reasonable to consider a cytoxic-chemotherapy-free approach for untreated indolent NHL and expect that CR rates will exceed those seen in the relapsed-setting.

We hypothesize that mosunetuzumab with or without polatuzumab vedotin plus obinutuzumab will produce high complete response rates in indolent non-Hodgkin lymphomas without the need for conventional cytoxic chemotherapy.

4.1 Mosunetuzumab: Pharmaceutical and Therapeutic Background

Mosunetuzumab is a full-length, fully humanized IgG1 bispecific antibody that targets CD3 and CD20[17]. This can redirect T-cells to engage and eliminate CD20+ B-cells. This can lead to T-cell activation, cytokine elevation, and increase in tumor-infiltrating lymphocytes[6,18].

4.2 Polatuzumab vedotin: Pharmaceutical and Therapeutic Background

Polatuzumab vedotin, an ADC that delivers the microtubule inhibitor MMAE in a targeted fashion to cells expressing CD79b, is being evaluated as a replacement strategy in B-cell NHL for the microtubule inhibitor, vincristine. CD79b is a cell surface antigen that is expressed ubiquitously on large B-cell lymphoma tumor cells, as well as other mature B cells[19,20]. The expression pattern of this surface antigen enables the application of polatuzumab vedotin in all mature B-cell lymphoma subtypes[20].

4.3 Rationale for Mosunetuzumab and Polatuzumab Vedotin with Obinutuzumab in Lymphoma

The most recent data of mosunetuzumab monotherapy in relapsed/refractory indolent NHL demonstrated an ORR and CR rate of 63% and 43% respectively[6]. These patients were examined with step-up dosing (i.e. 0.4/1.0/2.8 – 1.0/2.0/13.5mg , Cycle 1 Day 1/8/15). Grade 2 and 3 cytokine release syndrome was seen in 7.8% and 1.1% of patients, respectively[6].

The safety and clinical activity of the antibody-drug conjugate polatuzumab vedotin in relapsed/refractory NHL was examined in a phase 1b/2 study[10]. Single agent polatuzumab vedotin was associated with objective responses in 23/42 (54.8%) evaluable patients in the dose-expansion cohort (2.4 mg/kg), including 7/42 (16.7%) complete responses (CR). There was an acceptable safety profile at the maximum tolerated dose, with the most common grade 3-4 toxicities being neutropenia (40%), anemia (11%), and peripheral sensory neuropathy (9%). In addition polatuzumab has been safely combined with obinutuzumab in relapsed/refractory follicular lymphoma with an overall response rate of 78%[11]. The most common adverse events in > 20% of patients included fatigue (43%), diarrhea (34%), nausea (30%), constipation (21%), and headache (20%).

4.3.1 Rationale for Dose Selection/Regimen/Modification

Mosunetuzumab
Mosunetuzumab monotherapy has been examined in relapsed/refractory B-cell NHL[6] as well as untreated DLBCL in patients unfit for standard treatment[21].

Subcutaneous mosunetuzumab has been tested in a phase 1/1b with both flat dosing as well as step-up dosing [Matasar, 2020 #1294]. In the flat dosing cohort, patients were treated at 1.6 to 20 mg dose cohorts in a standard 3+3 design. A single DLT was observed at 1.6 mg (grade 4 neutropenia). Escalation otherwise proceeded without any other DLTs observed in other cohorts, and 26 patients treated at the final 20 mg dose. All CRS events across all cohorts were grade 1 (n=6, 26%) and grade 2 (n=2, 9%) and occurred during cycle 1. Efficacy in relapsed/refractory indolent NHL

patients were similar to results seen in the previously presented intravenous cohorts.

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 Cmax 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 Cmax (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 evaluate step-up dosing for CRS mitigation to reach the target dose of 45 mg. The 5/45/45 mg dosing regimen showed comparable safety profiles 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 target dose. Therefore, this dose is considered the preferred dose for mosunetuzumab SC monotherapy.

Polatuzumab vedotin combinations in B-cell NHL
Promising results led to the initiation of a phase 1b/2 clinical trial of polatuzumab vedotin in combination with R-CHP in DLBCL (R-CHOP with omission of vincristine)[9]. The MTD used in the combination regimen dose expansion cohort was 1.8 mg/kg. A recent update of this study found that the combination was well tolerated, with the most common grade 3-4 toxicities being neutropenia (30%), febrile neutropenia (18%), and thrombocytopenia (9%)[9]. Encouraging results in the dose expansion phase with high international prognostic index (IPI) patients led to the creation of a phase 3 randomized trial that has completed accrual comparing polatuzumab vedotin and R-CHP versus standard R-CHOP chemotherapy without known safety issues from a data safety monitoring committee (NCT03274492). The recommended dose of polatuzumab in this study was 1.8 mg/kg.

Polatuzumab vedotin has been safely combined with obinutuzumab in relapsed/refractory follicular lymphoma with an overall response rate of 78%[11]. The most common adverse events in > 20% of patients included fatigue (43%), diarrhea (34%), nausea (30%), constipation (21%), and headache (20%).

In addition, polatuzumab vedotin was recently FDA approved in combination with rituximab and bendamustine for patients with DLBCL who have received 2 prior lines of therapy. The recommend polatuzumab vedotin dose to be given every 3 weeks in this regimen is also 1.8 mg/kg.

4.3.2 Rationale for Endpoints:

The primary endpoint is estimating the efficacy of this regimen as measured by the proportion of subjects who have achieved a complete response (CR) as the best response by the end of therapy.

4.3.2.1 Secondary/Exploratory Endpoints:

Secondary endpoint is estimating the end of treatment overall response rate.

Exploratory endpoints include estimating the PFS and OS for this combination using the appropriate response criteria for the histology tested. These also include stratifying ORR, CR, PFS, DOR, and OS by subjects receiving mosunetuzumab alone vs. mosunetuzumab followed by polatuzumab vedotin and obinutuzumab. Additional endpoints include estimating the safety of this regimen as measured by the frequency of adverse events (AEs) and correlating clinical outcomes including but not limited to ctDNA analysis, genomics, cytokine levels.

5.0 METHODOLOGY

Entry Criteria:

5.1 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Diagnosis of indolent B-cell non-Hodgkin lymphoma with no prior systemic therapy. Eligible histologies based on 2016 WHO classification[22] include:
    a. Follicular lymphoma (Grade 1-2 or 3a)
    b. Marginal zone lymphoma. Patients with MALT subtype of MZL may have relapsed or refractory disease after a course of antibiotic therapy.
2. Meet criteria for initiation of therapy that include one of the following
    a. Symptomatic disease (including but not limited to pain/discomfort, b-symptoms)
    b. Threatened end-organ function
    c. Progressive cytopenias (Leukopenia (WBC < 1,000/uL) OR Hemoglobin < 10 g/dL OR platelets < 100,000/uL)
    d. Steady progression

e. Bulky disease (one site at least 7 cm or at least four sites of 3 cm)
f. Hepatomegaly
g. Splenomegaly

3. Be willing and able to provide written informed consent for the trial.
4. Have had an informed discussion with the investigator as part of the consenting/screening process that included information on treatments for these conditions with known clinical benefit, and there is documented understanding that the patient is forgoing approved available therapies.
5. Be ≥ 18 years of age on day of signing informed consent.
6. Have measurable FDG-avid nodal disease, including at least 1 disease site measuring at least 1.5 cm in longest dimension on CT or FDG-PET, or FDG-avid extra nodal measurable site measuring at least 1.0 cm in longest dimension.
7. Have a performance status of 0-2 on the ECOG Performance Scale (PS)
8. Demonstrate adequate organ function as defined in Table 1 below:

Table 1: Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1,000/μL except in cases of marrow infiltration by lymphoma
Platelets	≥75,000 / mcL except in cases of marrow infiltration by lymphoma or hypersplenism
Hemoglobin	≥8 g/dL except in cases of marrow infiltration by lymphoma without red blood cell (RBC) transfusion within 14 days of first treatment
Renal	
Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≥ 40 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN (Patients with documented Gilbert disease may be enrolled if total bilirubin ≤ 3.0 x ULN) **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver involvement
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants, or subject is shown to have an antiphospholipid antibody on workup
[a]Creatinine clearance should be calculated per institutional standard.	

9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of ≤1% per year during the treatment period and for at least 3 months after the last dose mosunutuzimab or 6 months after the last dose of obinutuzumab. Women must refrain from donating eggs during this same period. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≤12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements. Examples of contraceptive methods with a failure rate of ≤1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. 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 post-ovulation methods) and withdrawal are not acceptable methods of contraception
10. For women of childbearing potential, a negative serum pregnancy test result during screening period. Women who are considered not to be of childbearing potential are not required to have a pregnancy test.
11. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below: With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 5 months after the last treatment. Men must refrain from donating sperm during this same period. 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 preventing drug exposure. Male patients considering preservation of fertility should bank sperm before study treatment.
12. Patients on agents that modulate CYP3A4 listed in appendix 14.4 should be aware that these agents are prohibited if they require treatment in Part B, and require discontinuation for at least 5 half-lives in order to proceed with Part B.

5.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Contraindication to any of the individual components of this regimen or history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, or known sensitivity or allergy to murine products
2. Prior systemic treatment for lymphoma with the exception of corticosteroids as outlined below. Prior radiotherapy is allowed provided that this site is not used as a measurable site to assess response.
3. Absolute lymphocyte count > 5000/μL.
4. 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
    - Patients with a remote history of, or well-controlled autoimmune disease, may be eligible to enroll after discussion with and confirmation by the principal investigator. Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
    - Patients with a history of disease-related immune thrombocytopenic purpura or autoimmune hemolytic anemia may be eligible for this study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        i. Rash must cover < 10% of body surface area. Disease is well controlled at baseline and requires only low-potency topical corticosteroids. No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months.
5. Prior solid organ transplantation
6. Current Grade >1 peripheral neuropathy by clinical examination or demyelinating form of Charcot-Marie-Tooth disease
7. Prior use of any monoclonal antibody within 3 months of the start of Cycle 1; any investigational therapy within 28 days prior to the start of Cycle 1; vaccination with live vaccines within 28 days prior the start of Cycle 1
8. Prior corticosteroid use for conditions related or unrelated to lymphoma are allowed provided that at least 14 days have lapsed since last dose and initiation of study therapy, except for patients who require corticosteroid pre-medication for IV contrast administration.
9. History of other malignancy that could affect compliance with the protocol or interpretation of results except with permission of the principal investigator. The following are eligible without a specific waiver:

- Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix at any time prior to the study are eligible.
- Patients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for ≥ 2 years prior to enrollment are eligible.
- Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible

10. Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm).
11. Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis
12. History or presence of an abnormal ECG that is clinically significant in the investigator's opinion.
13. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) which requires systemic treatment. Patients may proceed with screening during treatment for infection, but systemic treatment must be completed by cycle 1 day 1.
14. Positive test results for chronic hepatitis B infection (defined as positive hepatitis B surface antigen (HBsAg) serology):
    - Patients with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody and negative HBsAg) may be included if hepatitis B virus (HBV) DNA is undetectable at the time of screening. These patients must be willing to undergo monthly DNA testing and appropriate antiviral therapy as indicated by institutional standard
15. Positive test results for hepatitis C (hepatitis C virus (HCV) antibody serology testing)
    - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
16. History of uncontrolled HIV
    - Patients with known diagnosis of HIV must have undetectable viral load and be on anti-retroviral therapy
17. Patients with a history of progressive multifocal leukoencephalopathy
18. History of known central nervous system involvement
19. History of chronic active EBV
20. History of hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS).
21. Pregnancy or lactation or intending to become pregnant during study

5.3 Study Treatments

For the purposes of this protocol, Part A will refer to the subcutaneous (SC) mosunetuzumab monotherapy portion, while part B will refer to the polatuzumab vedotin and obinutuzumab combination portion.

Part A

The dosing of SC mosunetuzumab is listed in Table 2. Cycle length is 21 days. The rationale for this dosing is described in section 4.2.1. A step-up regimen will be employed to minimize the risk of CRS. Subjects will receive lower doses of the drug on cycle 1 day 1 and achieving the full dose on cycle 1 day 8. The full dose alone will be given on cycle 2 through 8 on day 1 only.

Table 2: SC mosunetuzumab dosing

	Cycle 1			Cycle 2-8
	Day 1	Day 8	Day 15	Day 1
Mosunetuzumab dose (SC)	5 mg	45 mg	45 mg	45 mg

Cycle length = 21 days

Subcutaneous mosunetuzumab will be prepared and administered according to appendix 14.15. Corticosteroids (dexamethasone 10 mg PO or equivalent) should be given pre-dose as well as 24 hours (+/- 4 hours) and 48 hours (+/- 4 hours) post dose during cycles 1 and 2. Oral acetaminophen (500-1000 mg) and/or diphenhydramine (25-50 mg) may also be administered per standard institutional practice prior to mosunetuzumab. Pre-medications from cycle 3 onward are optional provided that the patient did not have cytokine release syndrome during the previous cycle. Hydration and tumor lysis syndrome (TLS) prophylaxis is also at the discretion of the investigator. Corticosteroid administration in cycle 3 and beyond is up to the investigator. However, if a subject experiences CRS then corticosteroids should be administered for the subsequent doses until no CRS is observed.

For SC administration, mosunetuzumab will be administered by qualified staff over 30 seconds to 2 minutes. Refer to appendix 14.15 for more details including syringe size and preferred injection site. The recommended management of injection-site reactions is detailed in Appendix 14.14

Following each mosunetuzumab dose, patients will be observed at least 30 minutes for cycle 1 day 1 for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of CRS. If tolerated during C1D1, subsequent observation times can be reduced to 15 minutes.

Subjects who must permanently discontinue mosunetuzumab monotherapy due to toxicity should have a response assessment with positron emission tomography (PET)/CT as soon as is clinically feasible and be evaluated for consideration of treatment in Part B as outlined below. These subjects would then be realigned to cycle 9 day 1 provided at least 21 days ± 2 days have passed since the last mosunetuzumab injection

Subjects will undergo a computed tomography (CT) between cycle 4 day 1 and cycle 5 day 1. Those with at least stable disease (SD) or better by Lugano[23] criteria will proceed with treatment for cycles 5-8. Subjects with progressive disease (PD) at this timepoint may proceed with cycles 5-8 if the investigator assesses that the subject is deriving clinical benefit from the study medication (e.g. pseudoprogression). If there is no clinical benefit to this medication seen in patients with PD, subjects should receive additional therapy outside of the protocol.

Imaging with a PET/CT will be performed between cycle 8 day 1 and cycle 9 day 1. Subjects in a complete remission (CR) will not receive any further study therapy and will be observed in long term follow up. For this response assessment, a Deauville score will be assigned by the clinical radiology read. If the sub-investigator or principal investigator disagrees with the Deauville score assigned, another nuclear medicine physician will adjudicate the results.

All other subjects who do not achieve a CR may proceed with Part B of study treatment. Those with progressive disease (PD) may proceed with Part B only if they are deriving clinical benefit from the treatment (e.g., pseudoprogression, mixed response overall reduction in tumor) after discussion with the Principal Investigator.

Mosunetuzumab Dose Modifications/Toxicity Management

Administration of mosunetuzumab will be performed in a clinical setting with immediate access to a code team staff who are trained to monitor for and respond to medical emergencies. Additional management may take place after transfer to the University of Washington Medical Center, where there is access to neurology and nephrology consultation services in the event of cytokine release syndrome and tumor lysis syndrome, respectively.

The recommended management of CRS is listed in Appendix 14.5 and recommended management of hemophagocytic lymphohistiocytosis (HLH) is listed in Appendix 14.6. Details and recommended management of tumor lysis syndrome are listed in section 14.7 and 14.8.

Because TLS (Appendix 14.7 and 14.8) represents a pharmacodynamic effect of mosunetuzumab anti-tumor activity that may result in clinical benefit, patients who experience Grade 4 TLS may be considered for continued study treatment. In order to be considered for subsequent study treatment, all toxicities and laboratory abnormalities

related to TLS resolved within 2 weeks. The decision to continue study treatment should only be made after consultation with the study investigator and approval by the Principal Investigator. Any exceptions must have the approval of the principal investigator.

Patients who experience a treatment-related grade 3 non-hematologic adverse event or serious adverse event not mentioned above will be allowed to delay mosunetuzumab dosing for up to 2 weeks in order to recover from the toxicity. Additional delays must be discussed with the principal investigator prior to considerations of resuming study therapy.

In general, patients receiving mosunetuzumab who experience a Grade 4 non-hematological treatment-related adverse event should discontinue all study treatment and may not be re-treated. Subjects who discontinue mosunetuzumab due to toxicity may proceed to Part B at investigator discretion, but should have a repeat response assessment prior to initiating therapy in Part B.

For those non-hematologic 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 pre-existing medical condition), and thought to be attributable to mosunetuzumab, patients may continue to receive additional doses of mosunetuzumab, provided that the toxicity has resolved to Grade ≤1. Corticosteroids may be used as indicated for the management of non-CRS adverse events related to mosunetuzumab. One can consider resuming mosunetuzumab after resolution of the toxicity to Grade≤1 and steroid dosing of prednisone ≤10 mg PO daily or less

- For decreased lab values, the abnormality should have resolved to the lower limit of Grade ≤1, or return to ≥80% of the baseline value, whichever is lower.

- For neutropenia, the ANC should resolve to Grade ≤2 or return to ≥80% of the baseline value, whichever is lower.

- For increased lab values the abnormality should have resolved to the upper limit of Grade ≤1, or return to ≤120% of the baseline value, whichever is higher.

In the event that a patient has a toxicity in Cycle 1 necessitating mosunetuzumab interruption for >7 days, the Principal Investigator should be notified and the patient may be required to repeat mosunetuzumab at the highest dose previously tolerated prior to resuming the planned treatment schedule.

If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Patients who discontinue all study treatment for adverse events should continue to have disease assessments per institutional standard of care.

Additional guidance on the management of other risks that may be associated with mosunetuzumab is described in Appendix 14.9 (Neurologic AEs), Appendix 14.10 (Tumor Inflammation or flare), Appendix 14.11 (Neutropenia and thrombocytopenia), Appendix 14.12 (Infections) and Appendix 14.13 (Elevated Liver Enzymes).

Part B

For patients eligible for treatment in Part B, treatment will commence with cycle 9 day 1. This may be delayed for patients who require a washout of an agent listed in appendix 14.4. Cycle length is 21 days. Polatuzumab vedotin will be administered on day 1 of each cycle. Obinutuzumab 1000 mg will be administered (See table 5 and 6 for details on pre-medications and infusion related reaction management) on cycle 9 day 1, day 8, and day 15. From cycle 10 onwards obinutuzumab will only be administered on day 1 (1000 mg). Part B will be administered for 6 total cycles (through cycle 14). A response assessment by CT should be performed after cycle 11, and an end of treatment PET/CT should be performed after cycle 14. Obinutuzumab should be administered prior to polatuzumab vedotin on days that both drugs are administered.

Table 3: Part B dosing table

	Cycle 9			Cycle 10-14
	Day 1	Day 8	Day 15	Day 1
Obinutuzumab IV	1000 mg	1000 mg	1000 mg	1000 mg
Polatuzumab vedotin IV	1.8 mg/kg			1.8 mg/kg

Cycle length = 21 days

Dose Modification

These guidelines pertain to dose delays and modifications based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment. Table 4 shows the recommended steps of dose reduction for polatuzumab vedotin based on toxicities in Table 5 and Table 6. In general, obinutuzumab should be given at the fixed doses outlines above, but treatment may be interrupted due to toxicities as outlined in the sections below.

Table 4: Recommended steps of dose reduction for polatuzumab vedotin

Dose Level	Polatuzumab vedotin
Starting dose	1.8 mg/kg per cycle
First dose reduction	1.4 mg/kg per cycle
Second dose reduction	Permanently discontinue drug

Dose of polatuzumab vedotin should not be increased after a reduction unless there has been a change in attribution (no longer attributable to polatuzumab vedotin) of the adverse event that led to the initial reduction.

Treatment Interruptions and Schedule Modification

Refer to the obinutuzumab and polatuzumab vedotin US prescribing information for additional details.

Study treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug (see Table 4). Aside from the withholding of polatuzumab vedotin for neuropathy per Table 4 and Table 5, study drugs withheld for more than 14 days because of toxicity should be discontinued, unless resumption of treatment is approved following investigator discussion with the principal investigator. Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with principal investigator approval. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Specific guidelines around dosage modifications for Part B are detailed below.

Patients who are receiving study treatment and experience toxicities should undergo dose interruptions and reductions, per instructions in Table 5. All considerations of dose and schedule modifications should be discussed with the principal investigator.

Dose Discontinuation

Dosing delays exceeding 14 days in the initiation of the next planned cycle of treatment will require study treatment discontinuation unless principal investigator approval is obtained to continue on study treatment.

Patients should permanently discontinue polatuzumab vedotin if further dose reduction is indicated beyond 1.4 mg/kg. In this case, subjects may still continue to receive obinutuzumab monotherapy through cycle 14.

If an individual study drug (obinutuzumab or polatuzumab vedotin) is omitted during a cycle for any reason including toxicity while the other drug is administered, the omitted drug will not be made up at a later date.

Patients discontinuing individual agents should remain in the study and continue with all protocol-defined assessments and treatments.

Patients who discontinue all study treatment for adverse events should continue to have disease assessments per institutional standard of care.

GCSF may be administered at the discretion of the investigator for persistent neutropenia resulting in delay of treatment

Tumor Lysis Syndrome

As many patients will have partially treated lymphoma by Cycle 9 day 1, additional tumor lysis syndrome prophylaxis will be at the discretion of the investigator based on most recent imaging and laboratory values.

Table 5: Dose interruptions, reductions, and discontinuations of study agents

Event(s)	Dose delay or modification
Grade 3 or 4 neutropenia on day 1 of cycle 10-14 with or without infection or fever, first delay [a]	• Delay all study treatment for a maximum of 14 days. • When ANC recovers to ≥ 1000/µL, Polatuzumab vedotin dosing should remain t
Recurrent Grade 3 or 4 neutropenia on day 1 of cycle 11-14 with or without infection or fever	• Delay all study treatment for a maximum of 14 days. • If ANC recovers to ≥ 1000/µL within 7 days of day 1, Resume at same dose. If g required for neutrophil recovery, then next doses of polatuzumab vedotin dosing s GCSF use is at the discretion of the investigator, but recommended for subjects w interruption due to neutropenia.
Thrombocytopenia Grade 3-4	• Delay all study treatment for a maximum of 14 days • When platelet count recovers to ≥ 75,000/µl, treatment may resume. Polatuzuma reduction can be considered in patients with recurrent grade 3-4 thrombocytopenia • If primary cause is due to lymphoma, dose delay or reduction may not be needed
Bilirubin between 1.5 and 3.0 mg/dL	• Dose reduction to next lowest dose level should be avoided if hyperbilirubinemia hepatic injury (i.e., hemolysis or Gilbert's disease). In these cases, dose reduction be guided by direct bilirubin levels. In these cases, dose delay considerations shou bilirubin levels and polatuzumab vedotin should be held until direct bilirubin is Gr Obinutuzumab may continue as scheduled. • If the AE severity remains unchanged by the start of the next expected cycle date polatuzumab vedotin and administer obinutuzumab at the recommended dose. The polatuzumab vedotin and will not be made up at a later date. • Doses of polatuzumab vedotin should not be re-escalated for future cycles witho principal investigator. The withheld doses of polatuzumab vedotin and will not be date.
Bilirubin > 3.0 mg/dL	• Polatuzumab vedotin dose delay should be avoided if hyperbilirubinemia is not r injury (i.e., hemolysis or Gilbert's disease). In these cases, dose delay consideratio

	by direct bilirubin levels and polatuzumab vedotin should be held until direct bilir Obinutuzumab may continue as scheduled. • If the AE severity remains unchanged by the start of the next expected cycle date polatuzumab vedotin and administer obinutuzumab at the recommended dose. The polatuzumab vedotin and will not be made up at a later date. • Doses of polatuzumab vedotin should not be re-escalated for future cycles witho principal investigator. The withheld doses of polatuzumab vedotin and will not be date.
Grade 1 neuropathy	• No study treatment modification is recommended for Grade 1 sensory or motor p
Grade 2 sensory peripheral neuropathy	• Hold Polatuzumab vedotin until improvement to Grade ≤ 1. Continue obinutuzu • Resume at next lowest dose level when Grade ≤ 1. • If the AE severity remains unchanged by the start of the next expected cycle date polatuzumab vedotin and administer obinutuzumab at the recommended dose. The polatuzumab vedotin and will not be made up at a later date. • Doses of polatuzumab vedotin should not be re-escalated for future cycles witho principal investigator. The withheld doses of polatuzumab vedotin and will not be date.
Grade 3 sensory peripheral neuropathy, or Grade 2 or 3 motor peripheral neuropathy	• If the AE severity remains unchanged by the start of the next expected cycle date polatuzumab vedotin and administer obinutuzumab at the recommended dose. The polatuzumab vedotin and will not be made up at a later date. • When the AE improves to Grade ≤ 1 peripheral sensory neuropathy and/or Grad neuropathy, the polatuzumab vedotin can be restarted at a reduced dose.
Grade 4 neuropathy (including peripheral sensory or motor neuropathy)	• Discontinue polatuzumab vedotin treatment permanently. • Patients should be evaluated regarding the continuation of obinutuzumab monot their risk/benefit.
Grade 3 or 4 constipation or ileus	• Polatuzumab vedotin should be held until improvement to Grade ≤ 2. Obinutuzu continued, or delayed at the discretion of the investigator. • Consider reducing polatuzumab vedotin to the next dose level (Table 4) after im ≤2.

Grade 3 or 4 tumor lysis syndrome	• Treatment may continue for Grade 3 provided that there is no significant organ d necessitates pausing therapy. Treatment may be interrupted so that supportive care treatment resuming at the discretion of the investigator. Treatment should resume • Grade 4 should require treatment interruption until resolution of tumor lysis synd If treatment for a cycle is interrupted due to tumor lysis syndrome and cannot be s treatment can be omitted for the rest of the current cycle and resumed at the same cycle in conjunction with prophylactic therapy.
Grade 3 Infusion related reaction (IRR), second episode	• Discontinue obinutuzumab or polatuzumab vedotin permanently. • If IRR is attributed to obinutuzumab, continue polatuzumab vedotin • If IRR is attributed to polatuzumab vedotin, continue obinutuzumab
Anaphylaxis or Grade 4 IRR	• Discontinue obinutuzumab or polatuzumab vedotin permanently. • If anaphylaxis is attributed to obinutuzumab, continue polatuzumab vedotin • If anaphylaxis is attributed to polatuzumab vedotin, continue obinutuzumab
Grade 3 or 4 non-hematologic toxicity not otherwise specified (excluding nausea, vomiting, and diarrhea)	• Consider delaying all study treatment for a maximum of 14 days. • First occurrence: Based on the nature of the toxicity, decrease polatuzumab vedo • Second and subsequent recurrence: Based on the nature of the toxicity and if the manageable and resolving within 14 days of the date of the next scheduled cycle, discontinuation of suspect study treatment permanently.

[a] Based on laboratory results obtained within 72 hours before study treatment administration on Day 1 of each

Infusion-Related Reactions and Anaphylaxis
Medications including epinephrine for subcutaneous injections, corticosteroids, diphenhydramine hydrochloride for IV injection, and resuscitation equipment should be available for immediate use. Recommended management of infusion-related symptoms for Obinutuzumab is summarized in Table 6, but final decision for acute management is at the discretion of the investigator. Future administration of the study agent that caused the reaction should be dictated by the guidance in Table 6.

Table 6: Management of infusion related reactions

Infusion-related symptoms	**Guidance**
Grade 1-2	Slow or hold infusion. Give supportive treatment. Upon symptom resolution, may resume infusion-rate escalation at the investigator's discretion. Note: For Grade 2 wheezing or urticaria, patient must be premedicated for any subsequent doses
Grade 3	Discontinue infusion. Give supportive treatment. Upon symptom resolution, may resume infusion-rate escalation, at investigator discretion. Note: If the same adverse event recurs as Grade 3-4 despite adequate pre-medication, treatment for the attributable drug must be permanently discontinued. Note: For Grade 3 hypotension or fever, patient must be premedicated before re-treatment. If symptoms recur at same grade or higher, then patient must be permanently discontinued from study drug. Note: If patient has Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence, patient must be permanently discontinued from study drug.
Grade 4	Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue attributable study drug.

Table 7: Premedication for Obinutuzumab and Polatuzumab Vedotin

Timepoint	Patients who Require Premedication	Premedication	Administra
Cycle 9, Day 1	All patients	Corticosteroid[a]	Complete ≥ 1 hour prior to obinut
		Antihistamine drug[b] and analgesic/anti-pyretic[c]	Administer ≥ 30 minutes prior to may be re-administered administe administration of any polatuzuma
Cycle 9, Day 8, 15	Patients with no IRR during the previous infusion	Corticosteroid[a]	Complete ≥ 1 hour prior to obinut
		Antihistamine drug[b] and analgesic/anti-pyretic[c]	Administer ≥ 30 minutes prior to
	Patients with Grade 1 or 2 IRR during the previous infusion	Corticosteroid[a]	Complete ≥ 1 hour prior to obinut
		Antihistamine drug[b] and analgesic/anti-pyretic[c]	Administer ≥ 30 minutes prior to
	Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion OR Patients with bulky disease	Corticosteroid[a]	Complete ≥ 1 hour prior to obinut
		Antihistamine drug[b] and analgesic/anti-pyretic[c]	Administer ≥ 30 minutes prior to
Cycle 10 and beyond, Day 1	Patients with no IRR during the previous infusion	Corticosteroid[a]	Complete ≥ 1 hour prior to obinut .
		Antihistamine drug[b] and analgesic/anti-pyretic[c]	Administer ≥ 30 minutes prior to Antihistamine may be omitted *or* investigator's discretion.
	Patients with Grade 1 or 2 IRR during the previous infusion	Corticosteroid[a]	Complete ≥ 1 hour prior to obinut
		Antihistamine drug[b] and analgesic/anti-pyretic[c]	Administer ≥ 30 minutes prior to may be re-administered administe

			administration of any polatuzuma
	Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion OR Patients with bulky disease	Corticosteroid[a]	Complete ≥ 1 hour prior to obinu
		Antihistamine drug[b] and analgesic/anti-pyretic[c]	Administer ≥ 30 minutes prior to may be re-administered administe administration of any polatuzuma

[a] Methylprednisolone 80 mg or dexamethasone 20 mg or equivalent
[b] For example, diphenhydramine 25-50 mg IV/PO or equivalent
[c] For example, acetaminophen 650-1000 mg or equivalent

All obinutuzumab infusions should be administered to patients after premedication per above table. Additiona beyond what is outlined above (eg. Famotidine) may be administered at the discretion of the investigator.

Infection Prophylaxis

Anti-infective prophylaxis for viral, fungal, bacterial, or Pneumocystis infections should be instituted per institutional practice or investigator preference based on individual patient risk factors. Patients at risk for reactivation of Hepatitis B should receive prophylactic antiviral medications per institutional standard of care.

5.3.1 Timing of Dose Administration

Trial treatment should be generally be administered as outlined in section 5.2 starting on the day of each cycle as outlined in the Trial Flow Chart (Section 6.1). Missed doses of polatuzumab vedotin or obinutuzumab will not be made up.

The polatuzumab vedotin and obinutuzimab prescribing information contains specific instructions for polatuzumab vedotin reconstitution, preparation of the infusion fluid, and administration. The mosunetuzumab investigator brochure and appendix 14.15 will have the same information.

5.3.2 Trial Blinding/Masking

This is an open-label, single arm prospective trial; therefore, the investigator and subject will know the treatment administered.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator and the subject.

5.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Intrathecal methotrexate or cytarabine may be administered for central nervous system prophylaxis at the clinician’s discretion.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered are to be recorded after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Induction Phase of this trial:

- Chemotherapy not specified in this protocol
- Investigational agents other than mosunetuzumab, polatuzumab vedotin, and obinutuzumab
- Radiation therapy (may be administered more than 30 days after last dose of study therapy if planned for consolidation)
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- SARS-CoV-2 vaccines (mRNA, inactivated virus, and replication deficient viral vector vaccines) Concomitant administration of an approved non-live SARS-CoV-2 vaccine is permitted. Examples of permitted vaccines include mRNA, inactivated virus, and replication-deficient viral vector vaccines. The decision whether and when to administer a SARS-CoV-2 vaccine should be individualized by the investigator in consultation with the patient. Factors to consider when making the individualized decision for patients receiving mosunetuzumab include the following:
    - Risk of SARS-CoV-2 infection and potential benefit from the vaccine
    - General condition of the patient and potential complications associated with SARS-CoV-2 infection
    - Severity and seriousness of the underlying disease
    - Epidemiology of COVID-19 in the patient's location

Prior to starting study treatment, SARS-CoV-2 vaccines and other permitted vaccines should ideally be administered to patients before the start of immunosuppressive therapy, with the aim to complete the vaccination course at least one week prior to starting study treatment, unless a delay is clinically unacceptable.
If a SARS-CoV-2 vaccine is administered while the patient is already receiving study treatment, administration of the vaccine should be timed

to take place after completion of mosunetuzumab step-up dosing and at least one week after administration of the target dose.
The SARS-CoV-2 vaccine should be administered in the middle of a treatment cycle, for example one week before or after a dose of mosunetuzumab. Cytokine-release syndrome (CRS) is a risk for mosunetuzumab that occurs most commonly during step-up dosing. Many SARS-CoV-2 vaccines are highly immunogenic, and their risk of potentiating CRS is unknown.

In vitro data suggest that unconjugated MMAE is mainly metabolized by CYP3A4 and, to a lesser extent, by CYP2D6. Based on a validated physiological-based PK model simulation, strong CYP3A4 inhibitors may increase the exposure (e.g., area under the concentration–time curve) of unconjugated MMAE by ~50% while acMMAE PK is not affected.

If a patient is taking any of the medications in the categories of strong CYP3A4 inhibitors and inducers, the investigator will assess and document the use of these medications known or suspected to fall in those categories. A sample list of cautionary medications that fall into the categories within this section can be found in Appendix Section 14.4. The lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. Patients are prohibited from using strong CYP3A4 inhibitors in part B of the study, and as discussed in the inclusion/exclusion criteria, patients may need to wash out these medications before proceeding with part B of the study. In addition, the investigator should contact Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary. The Exclusion Criteria describes other medications which are prohibited in this trial.

Mosunetuzumab: Given the expected pharmacology of mosunetuzumab, the transient release of cytokines (most resolved within the first 24 hours of the C1D1 dose) may suppress CYP450 enzymes and cause drug-drug interactions. Preliminary clinical data indicate that mosunetuzumab induced a transient elevation in plasma IL-6, with peak levels occurring in the majority of patients within 4-6 hours of the C1D1 dose, and returning to baseline by 24 hours. Patients may be of highest risk of a drug-drug interaction are those receiving concomitant medications that are CYP450 substrates and have a narrow therapeutic index (Appendix 14.4). Such concomitant medications should be monitored for

toxicity, and dose adjusted accordingly.

A sample list of cautionary medications that fall into the categories within this section can be found in Appendix Section 14.4. The lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the principal investigator if questions arise regarding medications not listed above.

MMAE is a P-glycoprotein (P-gp) substrate but not a P-gp inhibitor. Concomitant medications that are P-gp inhibitors (Appendix Section 14.4) should be considered cautionary as they may potentially lead to adverse reactions, which require close monitoring. If a patient is taking any of the medications in the categories of P-gp inhibitors, the investigator will assess and document the use of these medications known or suspected to fall in those categories. A sample list of cautionary medications that fall into the categories within this section can be found in Appendix Section 14.4. The list of medications is not necessarily comprehensive.

5.5 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.5.1 Additional Events of Clinical Interest

An overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.6.2 Contraception

The study agents may have adverse effects on a fetus in utero. Furthermore, it is not known if the study agents have transient adverse effects on the composition of sperm.

Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 12 months after the last dose of study treatment. Women must refrain from donating eggs during this same period. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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 post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 5 months after the last dose of polatuzumab vedotin. Men must refrain from donating sperm during this same period.

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 preventing drug exposure. Male patients considering preservation of fertility should bank sperm before study treatment.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to Genentech. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.6.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study. The outcome of the pregnancy will be reported to Genentech without delay and within 2 business days of investigator knowledge if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Genentech. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Genentech and followed as described above and in Section 7.2.2.

5.6.4 Use in Nursing Women

It is unknown whether polatuzumab vedotin is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be discontinued from the trial at the discretion of the investigator. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Subjects who require cessation of study therapy but do not withdraw consent may remain in standard follow-up for up to 5 years.

A subject must be discontinued from study therapy for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression except as outlined in section 5.2
  Note: A subject may be granted an exception to continue on treatment with radiographic progression if clinically stable or clinically improved, at clinician discretion
- A required dose delay of more than 14 days except with permission of the principal investigator
- Adverse experiences deemed unacceptable by the investigator, including those described in Section 5.2 and Table 5
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test

- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

Subjects who discontinue for reasons other than progressive disease will complete end of treatment visit within 14 days of the decision to remove the subject from the study, but may be waived or performed at a later date at the discretion of the principal investigator. These subjects ideally will undergo end of treatment blood testing and response assessment as outlined in the schedule of events. Subjects should be seen 4-6 weeks after last dose of study medication for off study visit and AE assessment (may be combined with end of treatment visit). These subjects ideally will undergo end of treatment blood testing and response assessment as outlined in the schedule of events. However, all patients may have post-treatment follow-up for disease status up to 5 years at longest.

For those with unacceptable adverse experiences grade 3 or higher related to one of the study agents, follow-up on study until resolution to grade or stabilization of toxicities is required up to a maximum of 1 year from occurrence of the toxicity.

5.8 Subject Replacement Strategy

Subjects who fail to complete study therapy will not be replaced.

5.9 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Decision by principal investigator and ad hoc DSMC to terminate the study after a stopping rule has been met.
5. Plans to modify or discontinue the development of the study drug
   In the event of Genentech decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Part A Study Flow Chart

Treatment Cycle/Title	Screening Period	Part A					End of Treatment[9]
		Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 1 Day 15	Cycles 2-8 Day 1	
Scheduling Timing and Window	-42 to -1d			± 1 day	± 1 day	± 2 days	± 2 days
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Prior and Concomitant Medication Review	X	X		X	X	X	X
Trial Treatment Administration		X		X	X	X	
Post-study disease status							
Survival Status							
Review Adverse Events[2]	X	X		X	X	X	X
Physical Examination	X	X		X	X	X	X
Vital Signs and Weight	X	X		X	X	X	X
Height	X						
ECOG Performance Status	X	X		X	X	X	X
Pregnancy Test – Urine or Serum beta-HCG[1]	X						
PT/INR and aPTT	X						
CBC with Differential[8]	X	X		X	X	X[11]	X
Comprehensive Serum Chemistry Panel[8] and LDH	X	X	X[11]	X	X	X	X
Uric acid, Phosphate		X	X[11]				
HepB S Ag, Core Ab, Hep C and HIV screen	X						

Treatment Cycle/Title	Screening Period	Part A					End of Treatment[9]
		Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 1 Day 15	Cycles 2-8 Day 1	
Scheduling Timing and Window	-42 to -1d			± 1 day	± 1 day	± 2 days	± 2 days
Tumor Imaging[3]	X					X[3]	X[3]
Bone Marrow Biopsy and Aspirate[4]	X						X
Other Procedures (Optional)[5]	X						
Archival Tissue Collection, if Feasible[6]	X						
Correlative Studies Blood Collection[7]	X	X					X

Cycle length = 21 days.

1. For women of child-bearing potential only. Should be repeated to ensure a value is also available within 72 hours of C1D1)
2. AE will be recorded from the time of a subject signing consent, up until off study visit.
3. See Section 7.1.2.5: Tumor Imaging: Baseline and post cycle 8 imaging is mandatory. This should consist of a FDG-PET and concurrent diagnostic CT scan of th if clinically indicated). Baseline imaging must be performed within 42 days of initiating study drug therapy. Post cycle 8 imaging should be performed any time betw cycle 9 day 1/end of treatment visit. An interim CT should be performed between Cycle 4 day 1 and cycle 5 day 1 (as close to cycle five day 1 as possible). Additior be performed at investigator discretion.
4. Screening bone marrow biopsy and aspirate may be completed up to 12 weeks prior to study enrollment, and at time of CR (as close to date of CR as possible). B waived at the discretion of the Principal Investigator.
5. See Section 7.1.4. Other procedures during screening are at the discretion of the treating investigator and may include standard-of-care assessments, central venou laboratory studies, or other measures.
6. The presence of archival tissue will be assessed during screening, and unstained slides may be collected. When available this tissue will be provided for central bi
7. Baseline correlative blood draw (eg. For ctDNA measurements) may be done at any time prior to the C1D1 dose. Additional correlative timepoints will be collect as well as around the time of any response assessment. Correlative blood draws should also be performed for the end of treatment or off study visit in patients who d assessment. Additional timepoints may be drawn at the time of other expected blood draws at the discretion of the investigator.
8. See Table 8 for details of these tests.
9: End of treatment visit should be scheduled at the time of the expected cycle 9 day 1, or within 14 days of removal from protocol. Subjects who are not in CR and proceed with Cycle 9 Day 1 of polatuzumab vedotin and obinutuzumab as outlined in section 5.2 and 6.2.
10. Study-mandated visits are not required, but the study team may query records to assess disease status or vital status for up to 5 years after completion of therap alternative therapy should have AEs recorded for up to 30 days after last dose of study therapy or first administration of alternate therapy, whichever comes first.
11. Monitoring for tumor lysis syndrome should be performed on cycle 1 day 2. Liver function testing is optional. Additional supportive care and monitoring can b as determined by baseline testing and risk factors.

6.2 **Part B Study Flow Chart**

Treatment Cycle/Title	Part B					C
	Cycle 9 Day 1	Cycle 9 Day 2	Cycle 9 Day 8	Cycle 9 Day 15	Cycles 10-14 Day 1	
Scheduling Timing and Window			± 1 day	± 1 day	± 2 days	
Prior and Concomitant Medication Review	X		X	X	X	
Trial Treatment Administration	X		X	X	X	
Post-study disease status						
Survival Status						
Review Adverse Events[1]	X		X	X	X	
Physical Examination	X		X	X	X	
Vital Signs and Weight	X		X	X	X	
Height						
ECOG Performance Status	X		X	X	X	
CBC with Differential[5]	X		X	X	X[11]	
Comprehensive Serum Chemistry Panel[5] and LDH	X	X[7]	X	X	X	
Uric acid, Phosphate	X	X[7]				
Tumor Imaging[2]					X[2]	
Bone Marrow Biopsy and Aspirate[3]						
Correlative Studies Blood Collection[4]	X					

Cycle length = 21 days

1. AE will be recorded from the time of a subject signing consent, up until off study visit.
2. A CT scan should be performed between cycle 11 day 1 and cycle 12 day 1 (as close to cycle 12 day 1 as possible). Post cycle 14 PET/CT (with concurrent diagn
time between cycle 14 day 1 and the off study visit (as close to the off study visit as possible) Baseline and post cycle 8 imaging is mandatory. This should consist o
diagnostic CT scan of the check, abdomen, and pelvis (neck if clinically indicated). Additional interim and surveillance scans can be performed at investigator discr
3. Screening bone marrow biopsy and aspirate may be completed up to 12 weeks prior to study enrollment, and at time of CR (if positive at enrollment or of not perf
to date of CR as possible). Bone marrow requirements may be waived at the discretion of the Principal Investigator.
4. Baseline correlative blood draw (eg. For ctDNA measurements) should be done at any time prior to the C9D1 dose, preferably at the time other C9D1 labs have b
timepoints will be collected with day 1 labs prior to cycle 10, 11, as well as around the time of any response assessment. Correlative blood draws should also be perf
study visit in patients who did not have a formal response assessment. Additional timepoints may be drawn at the time of other expected blood draws at the discretio
5. See Table 8 for details of these tests.
6. Study-mandated visits are not required, but the study team may query records to assess disease status or vital status for up to 5 years after completion of therap
alternative therapy should have AEs recorded for up to 30 days after last dose of study therapy or first administration of alternate therapy, whichever comes first. 7
lysis syndrome and proceed with Part B, additional lab monitoring and supportive care should be performed at the discretion of the investigator.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.1 and 6.2 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. Laboratory and imaging studies performed for standard of care purposes may be used to satisfy screening requirements, if they are performed within the appropriate timeframe noted in Section 6.1. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and/or Genentech for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative and Study-Related Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level. The informed consent will adhere to Institutional Review Board (IRB) requirements, and applicable laws and regulations.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Section 12.2). CRS grading will be per ASTCT consensus grading [Lee, 2019 #1260]. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with one of the study medications exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI). Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.1). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height is only required to be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 14.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.5 Tumor Imaging and Assessment of Disease

Tumor imaging consists of standard of care imaging at baseline during the screening period, including FDG-PET/CT with contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis.

For measurement of response, 2014 criteria as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" will be used (see Appendix 14.3).[23]

- **Baseline imaging** must be performed prior to initiating study drug therapy as outlined in the study calendar including PET/CT an diagnostic quality CT. Additional baseline imaging may be performed as indicated for standard of care and clinical purposes including MRI, or CT imaging of the neck.
- **Interim imaging** should be performed prior to Cycle 5, 9, and 12 as outlined in sections 6.1 and 6.2. Imaging prior to cycle 9 should be a PET/CT with concurrent diagnostic CT, while other interim imaging assessments can be a diagnostic CT alone unless additional imaging is clinically necessary.
- **Off study:** For patients only completing part A, the post cycle 8 scan will serve as the off study imaging. For patients participating in part B, end of treatment tumor imaging performed should be performed after cycle 14 day 1 and as close to the end of study visit (4-6 weeks, +/-7 days after cycle 14 day 1) as possible. Imaging should include PET/CT with diagnostic quality CT.

All CT scans should be performed with IV contrast unless contraindicated, and abdominal and pelvis scans should be performed with oral contrast.

All CT and FDG-PET/CT scans are to be interpreted locally; central review of radiology will not be performed. For response assessments with a PET/CT, the clinical read and images will be reviewed by the investigator, and if there are disagreements, a third person (radiologist) will adjudicate

7.1.2.6 Bone marrow aspirate and biopsy

A bone marrow aspirate and biopsy will be obtained up to 12 weeks before the first dose of study drug, and for confirmation of CR when indicated. FDG PET-CT may suffice for identification of bone marrow involvement[23] and bone marrow aspirate and biopsy requirements may

be waived by the principal investigator. These samples will be evaluated locally.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Assessment of available archival tumor tissue for correlative study analysis will be performed during the screening period. Any available pretreatment biopsy tissue may be used for correlative study analysis.

Peripheral blood correlative study samples may be collected as outlined in sections 6.1 and 6.2

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below and in section 6.1 and 6.2 (Study Flow Chart). All chemistry and hematology studies required to start a new cycle may be performed within 3 days of dosing prior to day 1 of that cycle.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry)

Laboratory tests for hematology, chemistry, and others are specified in Table 8 below. HBV Surface Antigen (Hep B S Ag), HBV Core Antibody (Hep B Core Ab), HIV screening, Hep C Ab screening will be performed during the screening period, and reviewed and managed at the study site as per clinical standard of care.

Table 8: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Urine pregnancy test †	Serum β-human chorionic gonadotropin (β-hCG)†
Hemoglobin	Alkaline phosphatase		
Platelet count	Alanine aminotransferase (ALT)		PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)		aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)		
	Carbon Dioxide, *(CO_2 or bicarbonate)*‡		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		HBV Surface Antigen, HBV Core Ab, HIV screen, Hep C Ab screening
	Potassium		
	Sodium		
	Total Bilirubin		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

Standard of care practices and procedures not specifically outlined in the protocol may be performed at the discretion of the investigator. Any additional imaging, additional laboratory studies for evaluation or management tumor lysis, and any medications for management of obinutuzumab/polatuzumab vedotin infusion reactions may be undertaken as guided by Section 5.2/Table 6 with additional supportive care as indicated by institutional standard of care.

7.1.5 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.6 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening Period

The screening period begins upon signing consent and includes evaluation of available tissue specimen for study-related, central review, any ancillary/staging/laboratory testing and standard-of-care evaluations (including "Other Procedures" as in Section 7.1.4) prior to Cycle 1 Day 1 of study therapy. The screening period may last up to 42 days.

7.1.6.2 Treatment Period

Subjects may be treated in Part A with mosunetuzumab for up to 8 cycles, and for those who do not achieve a CR, in Part B with polatuzumab vedotin and obinutuzumab for up to 6 cycles. Details of pre-medications and schedule of treatments, pre-medications, and assessments have been outlined in sections 5.2 and 6.0.

7.1.6.3 End of Treatment/Off Study Visit

At the completion of Part A, subjects will undergo a response assessment and clinic visit at the time of a possible cycle 9 day 1. For subjects with a CR, the visit that day will be called an end of treatment visit with labs/assessments outlined in section 6.1. An additional off-study visit 4-6 weeks after last dose of study drug will be required as well.

For subjects who do not achieve a CR in Part A and are eligible to proceed to Part B, Cycle 9 Day 1 will occur instead of an end of treatment visit. An off study visit alone will occur in lieu of an end of treatment visit 4-6 weeks after the last dose of study therapy. This visit will include review of tumor imaging (FDG PET-CT) as well as medical history, physical exam, and laboratory evaluations required for determination of remission status. Patients who come

off study early due to suspected progression or toxicity should have a clinic visit and tumor imaging as soon as it can be safely performed. Subjects who discontinue mosunetuzumab due to toxicity may undergo a response assessment, and if not in a CR, may proceed with part B. Remission status is to be determined according to 2014 Criteria ("The Lugano Classification")[23] as in Appendix 14.3.

For patients with equivocal post-induction imaging or clinical findings, in whom remission status cannot be clearly ascertained, further workup as per clinical standard of care including tumor biopsy or repeat imaging should be undertaken to confirm remission status (PR or CR) prior to proceeding onto the Follow-Up Period

7.1.6.4 Follow up

After the off study visit, subjects should be followed by their oncologist per institutional standard of care. Study-mandated visits are not required, but the study team may query records to assess disease status or vital status for up to 5 years after completion of therapy. Patients who come off study due to receive alternative therapy should have AEs recorded for up to 30 days after last dose of study treatment or first administration of alternate therapy, whichever comes first.

7.2 Assessment of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

7.2.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with B-cell non-hodgkin lymphomas that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which AEs and SAEs as described within where the patient has been exposed to Genentech product must be reported. Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination or initiation of alternate anti-lymphoma therapy, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other

means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the polatuzumab vedotin (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the study drugs (polatuzumab vedotin/ obinutuzumab/ mosunetuzumab), and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the polatuzumab vedotin; and/or the AE abates or resolves upon discontinuation of the polatuzumab vedotin, or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than the study drugs (polatuzumab vedotin/obinutuzumab/mosunetuzumab) (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to polatuzumab vedotin administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I)
or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE. CRS specific adverse events should be graded per ASTCT consensus guidelines[24].

Table 9: 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

f. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 days after the last dose of mosunetuzumab or polatuzumab (within 18 months after the last dose of obinutuzumab), or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 90 days after the last dose of mosunetuzumab/polatuzumab (or within 180 days after the last dose of obinutuzumab), 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.

g. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior study drug exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject (including pregnancy occurring in the partner of a male study subject) who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period.

h. 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.

i. AEs of Special Interest (AESIs)

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.

<u>Adverse events of special interest for this study include the following:</u>

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN

- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), 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 polatuzumab vedotin Adverse Events of Special Interest are:

- Neuropathy of Grade 2 or Higher
- Grade 3 or higher infections
- Infusion Associated Reactions
- Hypersensitivity
- Progressive Multifocal Leukoencephalopathy (PML)
- Tumor Lysis Syndrome of any grade (Irrespective of causality)
- Second malignancies

The mosunetuzumab Adverse Events of Special Interest are:

- Grade ≥2 CRS
- Grade ≥ 2 neurologic adverse event
- Any suspected MAS/HLH
- TLS (minimum Grade 3 by definition)
- Febrile neutropenia (minimum Grade 3 by definition)
- Any grade disseminated intravascular coagulation (minimum Grade 2 by definition)
- Grade ≥2 AST, ALT, or total bilirubin elevation
- Grade ≥ 2 tumor inflammation/tumor flare, e.g. manifestation of signs/symptoms associated with increase in size of known nodal or extranodal lesions by clinical or radiographic assessment, new onset or worsening of pre-existing pleural effusions

The obinutuzumab Adverse Events of Special Interest are:

- All TLS (irrespective of seriousness, causality or severity)
- Second Malignancies

j. 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

k. 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.

l. Exchange of single case reports

The investigator will be responsible for collecting all protocol-defined Adverse Events (AEs) and Special Situation Reports (including pregnancy reports) originating from the Study for the Product.

Investigators must report all Adverse Events/Serious Adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (occurring in the partner of a male study subject) , other Special Situation Reports and Product Complaints with an AE where the patient has been exposed to the product, adequately to Genentech within the timelines described below. The completed MedWatch or Genentech approved reporting forms should be faxed immediately upon completion to Genentech Drug Safety at:

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)

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request
Investigators must report all the above mentioned single case reports to Genentech on a MedWatch or Genentech approved SAE form within one (1) business day of the awareness date.

The investigator will forward quarterly listings of non-serious AEs originating from the Study to Genentech/Roche

Reporting to Regulatory Authorities, Ethics Committees and Investigators

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 will be responsible for the distribution of safety information to its own investigators, where relevant.

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 expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Post Marketing Safety Reporting

Recently, the FDA announced an upcoming update to the PMSR (Post Marketing Safety Reporting) regulation which requires the MAH (Marketing Authorization Holder) to report product complaints to the FDA.

A product complaint is 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.

For all Investigator Initiated Studies (interventional and non-interventional):
Product Complaints with an AE should be reported via email/fax to:
usds_aereporting-d@gene.com OR 650-238-6067

Product Complaints without an AE (adverse event) should be reported via email to:
· For Interventional Investigator Initiated Studies:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

All complaints must be filed within 1 business day for pre-approved products and 15 calendar days for approved products. Complaints can be reported using a Medwatch, CIOMS or any Genentech-approved reporting form (same as SAEs, AESI etc.).

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 mail box: ctvist_drugsafety@gene.com.

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. 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:

polatuzumab-gsur@gene.com
And to Genentech Drug Safety CTV oversight mail box at:
ctvist_drugsafety@gene.com.

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.

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.

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.

Genentech
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SAFETY REPORTING FAX COVER SHEET
Genentech Supported Research
AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

8.0 STATISTICAL ANALYSIS PLAN: STUDY DESIGN AND STATISTICAL ANALYSIS PLAN

Mosunetuzumab has been extensively studied as monotherapy in the relapsed refractory setting[6]. However, we will have the following safety suspension parameters.

First, any on-treatment death will prompt a suspension of accrual and convention of an ad-hoc safety committee may recommend changes to the protocol and its analysis based on updated information, closure of the protocol, or continued accrual with no modifications.

In addition, we would expect that grade 4 non-hematologic toxicity will be uncommon (< 10%) and is uncommon is standard chemoimmunotherapy. We will suspend accrual until an ad hoc safety committee can be convened to review the event and make recommendations regarding protocol modification or closure if the following criteria are met: If the lower limit of a 95% confidence interval does not include the possibility of this rate being < 10%. Operationally, this would mean if ≥5/15, ≥7/30 or ≥9/42 patients have a grade 4 non-hematologic treatment-related toxicity (excluding CRS as this is evaluated separately).

Grade 2+ CRS is uncommon as well in the relapsed/refractory[6] as well as untreated setting[21] and would expect this rate to be < 15%. We will suspend accrual until an ad hoc safety committee can be convened to review the event and make recommendations regarding protocol modification or closure if the following criteria are met: If the lower limit of a 95% confidence interval does not include the possibility of this rate being < 15%. Operationally, this would mean if ≥6/15 ≥9/30 or 11/42 patients have a grade 2 or higher CRS event.

In addition, this protocol will be monitored by the institutional data safety monitoring committee at regular intervals.

As mosunetuzumab has been extensively studied as monotherapy in the relapsed refractory setting, and obinutuzumab and polatuzumab in combination were not associated with any significant safety concerns (for example, anti-CD20 antibodies can safely be combined with polatuzumab and combination chemotherapy for an equivalent length of time[7]), no specific safety stopping rules will be established. However, this protocol will be monitored by the institutional data safety monitoring committee at regular intervals.

Objectives include gaining a preliminary assessment of the potential efficacy of this regimen. This will be defined as the percentage of patients that achieve a complete remission (CR) following study treatment as the primary end point, best ORR as a secondary end point. Exploratory endpoints include with PFS and OS. A simple binary proportion will be used to estimate CR and ORR, and the Kaplan-Meier method will be used to estimate PFS and OS.

Combination chemotherapy with a CD20 monoclonal antibody is highly efficacious in the treatment of indolent lymphomas, but short and long term toxicities can be seen[1-3]. Since these studies did not all use PET-based assessments, it can be challenging to determine a reasonable

benchmark. However, recent retrospective studies would suggest the CR rate to upfront treatment is around 80%[25]. Given potential for less toxicity with the proposed treatment, an observed CR rate that is at least as high as this benchmark would be considered promising, pending examination of other endpoints plus toxicity data. Therefore we would consider this study to be successful and merit further investigation if the observed best response as CR rate that is at least 80% among the patients treated. We propose to treat a total of 42 patients, this number not based on considerations of statistical power to reject a null hypothesis, rather on considerations of feasibility and ability to accrue. We anticipate enrolling roughly 42 patients over a 30-month period, but if the protocol is open for 36 months before 42 patients have been enrolled, consideration will be given to closing the study. If we enroll 42 patients, 34 or more complete responses would meet this benchmark. Shown in the table below is the probability of 34 or more responses among 42 patients for a variety of assumed-true CR rates. A subject will be defined as efficacy evaluable if they have had at least one response assessment. Subjects who come off study treatment for any reason prior to a response assessment will not be considered response evaluable and will not be replaced. If fewer than 42 subjects are evaluable for response after completion of the study, we will recalculate the below tables with a goal of achieving a CR as best response in at least 80% of patients.

Assumed-true CR rate	Probability of 34 or more responses among 42 patients
.65	.02
.70	.08
.75	.24
.80	.53
.85	.83
.90	.98

Shown in the table below are the lower one-sided 80% and 90% confidence limits for a variety of observed response rates among 42 patients.

Observed response proportion	Point estimate	Lower one-sided 80%, 90% confidence limit
27/42	64%	57%, 53%
31/42	74%	66%, 63%
36/42	86%	79%, 76%
38/42	90%	85%, 82%

We also propose interim efficacy evaluations with suspension rules. Primary progressive disease with rituximab monotherapy[26] and rituximab + chemotherapy[1] is rare, with most cases likely due to occult transformation. If 2 out of the first 20 (or fewer) subjects have primary progressive disease (an observed rate of 10% or higher), the study will be suspended to enrollment pending the recommendations of an ad-hoc safety committee. The lower one-sided 80% confidence limit for 2/20 is 4%, and therefore with such an occurrence (or among fewer than 20 patients) we'd be reasonably confident that the true rate is greater than 4%. Since progressive disease in this population has been rare, this rule is relatively strict. Patients who

have suspected or biopsy-proven transformed disease will not count as an event for the purposes of this analysis. Since pseudo-progression can be seen with immunotherapy drugs like mosunetuzumab, subjects with overall reduced tumor burden that meet criteria for progression due to discordant response among tumor sites will also not count as an event for the purposes of this analysis.

We also acknowledge that chemo-immunotherapy is associated with high overall response rates of around 90%[1], and we propose an interim analysis with a suspension rule for lack of sufficient efficacy. If 14 or fewer of the first 20 subjects do not achieve an objective response of PR or CR as best response by the end of study treatment (an observed rate of 70% or less), the study will be suspended to enrollment pending the recommendations of an ad-hoc safety committee. The upper one-sided 80% confidence limit for 14/20 is 79%, and therefore with such an occurrence we'd be reasonably confident that the true response rate is less than 80%, the loose benchmark that we are using to define success for this trial.

In both cases, the ad-hoc safety committee may recommend changes to the protocol and its analysis based on updated information, closure of the protocol, or continued accrual with no modifications.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF INVESTIGATIONAL PRODUCT

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Investigational product will be provided by Genentech as summarized in below.

Table 10: Product Descriptions

Product Name	**Dosage Form**
Polatuzumab vedotin	Solution for Injection
Mosunetuzumab	Solution for Injection
Obinutuzumab	Solution for Injection

9.2 Packaging and Labeling Information

Investigational product will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Investigational product must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Investigational product may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the investigational product received from Genentech or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 DATA AND SAFETY MONITORING PLAN

Ongoing trial oversight is carried out by the Principal Investigator and study staff.. These individuals will communicate on a regular basis to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

Institutional support of trial monitoring will be in accordance with the FHCRC/UW Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates monitoring for data accuracy and compliance by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by a the Consortium Data Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

The IRB has the authority to suspend or terminate the study should it be deemed necessary.

11.0 RECORDS

Research staff under the supervision of the investigators will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

12.0 REGULATORY RESPONSIBILITIES OF SPONSOR-INVESTIGATOR

The Sponsor-Investigator will ensure that the study is conducted in accordance with all applicable institutional, state, and federal regulatory requirements, including, but not limited to: compliance with requirements for IRB and other regulatory approvals, monitoring responsibilities, reporting obligations, and compliance with standards for written informed consent from all patients entering the study. In addition, the IND sponsor will ensure oversight of the study via data and safety monitoring as described above.

13.0 REFERENCES

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14.0 APPENDICES

14.1 ECOG Performance Status

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.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

14.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

14.3 Response Criteria: "The Lugano Classification" [38]

Response and Site	**PET-CT–Based Response**	CT-Based Response
Complete	**Complete metabolic response**	Complete radiologic response (all of the following)
	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
Lymph nodes and extralymphatic sites	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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

Response and Site	**PET-CT–Based Response**	CT-Based Response
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (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 × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 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**	**Stable disease**
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

Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm 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 (eg, liver, spleen, kidneys, 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.

14.4 **Table 11:** List of CYP3A4 inhibitors/inducers and P-gp inhibitors

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP3A	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* 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,* cyclosporine,* darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine,
P-gp	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil		
* These are anti-cancer drugs; contact principal investigator before use			

	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: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

Table 12: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive Substrates	Substrates With Narrow Therapeutic Range
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6	Bupropion, efavirenz	
CYP2C8	Repaglinide	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole	S-mephenytoin S-mephenytoin
CYP3A	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, cisapride, cyclosporine, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

14.5 **Table 13:** Management of Cytokine Release Syndrome (CRS)

CRS Grade [a]	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Mosunetuzum
Grade 1 fever ≥ 38ºC	• Symptomatic management of constitutional symptoms and organ toxicities; if symptoms do not resolve, manage per Grade 2 • 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 and corticosteroids as per Grade 2	• Administer premedicat • Consider hospitalizatio it is a higher dose [e]
Grade 2 fever ≥ 38ºC [b] with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen [c] by nasal cannula or blow-by	• 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	• Consider tocilizumab [d] • 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 c mosunetuzumab as pla resolve to Grade ≤ 1 fo • Consider enhanced pre dose • Consider hospitalizatio it is a higher dose [e]

CRS Grade [a]	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Mosunetuzum
	• Rule out other inflammatory conditions, which can mimic severe CRS (e.g., infections/sepsis) • Consider empiric broad spectrum antibiotics • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH		
Grade 3 fever ≥ 38ºC [b] with hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi-mask	• Symptomatic management of organ toxicities, admit participant 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) • Consider empiric broad spectrum antibiotics	• Administer tocilizumab [d] • Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, manage as per Grade 4 [c] Manage per Grade 4, if no improvement within 18–24 hours after second dose of tocilizumab	• May receive the next c mosunetuzumab if CR responsive to treatmen improvement within 8- tocilizumab/corticoste and symptoms resolve 3 consecutive days • Enhanced premedicati • Hospitalize participant • If the event occurred a dose should be again 5

CRS Grade [a]	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Mosunetuzum
	• If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH	•	• If the event occurred a dose should be 20 mg • If the next dose is tole Grade ≥ 3 CRS, the pa to the originally planne • If Grade 3 CRS recurs doses, consider perma
Grade 4 fever ≥ 38° [b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (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) • Consider empiric broad spectrum antibiotics	• Administer tocilizumab [d] • For participant's refractory to tocilizumab, consider siltuximab, anakinra, dasatinib, and emapalumab, based on discretion of the investigator; management should be discussed with the Principal Investigator[f] • Administer 10 mg IV dexamethasone every 6 hours (or equivalent) • If refractory, consider 1000 mg/day IV methylprednisolone [g, h]	• Permanently discontin

CRS Grade [a]	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Mosunetuzum
	• If no improvement within 24 hours, initiate work-up and assess for signs and symptoms HLH		

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; C-PAP = continuous positive airw
CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive ca
IL = interleukin; IRR = infusion-related reaction.

[a] Cytokine release syndrome will be assessed according to the ASTCT Consensus Grading Criteria (Lee et al. 2019). Fever is defined as tempera attributable to any other cause. In participants who have CRS and then receive an anti-pyretic or anti-cytokine therapy such as tocilizumab or s longer required to grade subsequent CRS severity. Cytokine release syndrome grade is determined by the more severe event: hypotension or h to any other cause.

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

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

[d] Tocilizumab should be administered by IV infusion at a dose of 8 mg/kg (8 mg/kg for participants weighing ≥ 30 kg only and 12 mg/kg for part < 30 kg; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (for up to a maximum of 4 doses).

[e] Although hospitalization is not mandated, administration of mosunetuzumab should be performed in a clinical setting with immediate access to staff who are trained to monitor for and respond to medical emergencies and the investigator should actively assess the need for hospitalization individual conditions.

[f] Riegler et al. 2019.

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

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

[i] Resumption of mosunetuzumab may be considered in participants who are deriving benefit and have fully recovered from the adverse event. P re-challenged if all the criteria below are met:

- Individual risk-benefit assessment by Principal Investigator/treating physician favors continued treatment;
- The participant has recovered from previous toxicities and has sufficient organ function/reserve to receive subsequent doses;
- The participant has been adequately consented for risks associated with continued treatment and decides to receive subsequent doses;
- Subsequent doses are well-planned with precautionary measures, including dose reduction, hospitalizations, and enhanced premedications.

14.6 Management of Hemophagocytic Lymphohistiocytosis

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

The supportive management of hemophagocytic lymphohistiocytosis (HLH) is generally similar to that of cytokine-release syndrome. Specific diagnostic, monitoring and management guidelines for HLH are described below.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (<9 g/dL)
  - Platelet count <100x10^9/L (<100,000/µL)
- ANC <1.0X10^9/L (<1000/µL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (<150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell (NK) activity
- Ferritin >500 mg/L (>500 ng/mL)
- Soluble interleukin-2 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

In all cases of suspected HLH, the Principal Investigator should be immediately notified. Patients should be hospitalized with the following diagnostic and monitoring measures initiated:

- Frequent (e.g., every 4 hours) vital signs and physical examination including evaluation for splenomegaly
- Serial (at least daily) monitoring of serum chemistry, CBCs, liver function tests, ferritin, PT/PTT, fibrinogen, D-dimer, and triglycerides
- Consideration of bone marrow and/or lymph node biopsy to assess for hemophagocytosis and active infection, including assessment of Epstein-Barr virus (EBV) protein localization in T, B, and NK cells
- Complete infectious disease work-up, including the following:
  - Blood cultures (bacterial and fungal)
  - Urine cultures and urinalysis
  - Radiographic assessments (e.g., chest X-ray or computed tomography scan)
  - Assessment for active viral infections, including but not limited to EBV and cytomegalovirus
- If available, assessment for soluble IL-2 receptor and assessment of NK-cell function
- DNA for exploratory genetic testing of mutations potentially associated with HLH (e.g., PRF1, MUNC13-4, and STXBP2) should be considered (Zhang et al. 2011)

Patients with suspected HLH should be treated according to the guidelines the following table.

Table 14: Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected HLH	• Withhold study treatment and contact Principal Investigator. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider treatment for HLH with appropriate therapy
Confirmed HLH	• Permanently discontinue study treatment and contact the Principal Investigator. • Refer patient to a hematologist • Institute appropriate supportive care, including intensive care monitoring, if indicated per the institutional guidelines • Treat with appropriate HLH therapy according to institutional standards or published references (Schram and Berliner 2015)

14.7 **Table 15:** 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 >1.5c

		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

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, Version 5.0.
[a] In laboratory TLS, two 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 +0.8x (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).

14.8 **Management Guidelines for 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 should be obtained and results reviewed and prophylactic measures considered 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 have a creatinine clearance ³40 mL/min to participate in this trial.

All patients should be considered for prophylaxis for TLS prior to mosunetuzumab administration during Cycles 1 and 2. Prophylaxis guidelines include the following:

- Hydration, 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 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.

- Administration of an agent to reduce uric acid:

  Allopurinol (e.g., 300 mg/day orally beginning 72 hours prior to dose and continuing for 3-

7 days afterward) should be administered at the discretion of the investigator.

For patients with elevated uric acid levels prior to mosunetuzumab treatment or 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 be administered, unless contraindicated (Elitek® [rasburicase] U.S. Package Insert).

Treatment with allopurinol/rasburicase should continue as specified above, or if laboratory evidence of TLS is observed until normalization of serum uric acid or other laboratory parameters.

If the above measures are contraindicated or are otherwise inappropriate in the view of the investigator, the Principal Investigator should be contacted for further guidance.

- Laboratory monitoring during tumor lysis prophylaxis beyond protocol specified laboratory testing should follow institutional practice and the investigator's judgment.
- Note that uric acid measurement in the presence of rasburicase administration requires special handling (Elitek U.S. Package Insert).
- Telemetry should be considered for patients at high risk for TLS.
- Patients at high risk for TLS should continue to receive prophylaxis with allopurinol or rasburicase and adequate hydration with each subsequent dose of mosunetuzumab until the patient is no longer considered to be at 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; such cases should be discussed with the Principal Investigator.

14.9 **Table 16:** Management Guidelines for Neurologic AEs for Patients Receiving Mosunetuzumab

Event	Grade	Management

Seizure	Grade 1–2	• Withhold further study treatment; provide supportive care. • Consider treatment with corticosteroids. • Consider consultation with a neurologist; consider brain MRI, lumbar puncture, EEG. • Study treatment may be resumed with PI approval if no recurrent seizure for at least 3 days and with confirmation of baseline neurologic examination. a
	Grade 3–4	• Permanently discontinue study treatment; provide supportive care. • Consider treatment with corticosteroids. • Obtain neurology consultation.
Neurologic events not otherwise specified	Grade 1	• Notify PI. • Consider withholding study treatment during evaluation.
	Grade 2	• Notify PI. • Withhold mosunetuzumab and evaluate etiology. Consider imaging as appropriate. • Consider treatment with corticosteroids. • Consider neurology consultation. • Study treatment may be resumed when symptoms have returned to baseline ≥ 3 consecutive days without the need for medical management and with confirmation of baseline neurologic examination. a
	Grade 3	• Notify PI. • Withhold mosunetuzumab and evaluate etiology. Consider imaging as appropriate. • Consider treatment with corticosteroids. • Obtain neurology consultation. • Consider discontinuation mosunetuzumab if symptoms persist > 7 days. a • Mosunetuzumab may be resumed when symptoms have returned to baseline ≥ 3 consecutive days without the need for medical management and with baseline neurologic examination. • Permanently discontinue study treatment for recurrent Grade 3 event.

	Grade 4	• Notify PI. • Permanently discontinue mosunetuzumab. • Obtain neurology consultation.

MRI = magnetic resonance imaging.

[a] The overall benefit–risk of continued treatment with mosunetuzumab should be assessed by the study investigator in consultation with and approval of the Principal Investigator.

Neurologic toxicity will be monitored closely during the trial. All patients will be required to undergo 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. Patients with a history of central nervous system involvement will 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 drug-related neurotoxicity. Corticosteroids should be considered to treat suspected neurologic toxicity. Imaging studies (e.g., diffusion-weighted MRI) should be performed if clinically indicated (see Table above).

The investigator should instruct patients to refrain from driving or engaging in hazardous occupations or activities as follows:

- Patients who develop specific adverse events while on mosunetuzumab:

  For patients who develop a neurologic adverse event that may affect driving and for patients who develop CRS, HLH, or Grade 3-4 LFT elevation, the investigator should advise patients to refrain from driving or engaging in hazardous occupations or activities until the event is resolved.

  Patients who develop tremor, dizziness, insomnia, or a Grade ≥3 neurologic adverse event should be assessed by neurologic examination to determine if the adverse event may impair the ability of the patient 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.

14.10 Management Guidelines for Tumor Inflammation and 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 and tumor inflammation 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:

Consult the Principal Investigator prior to initiating treatment and 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 impact 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 inflammation/flare events in high-risk patients with lymphoma lesions in the oropharynx:

In case of a suspected tumor inflammation or flare event (including, but not limited to, dyspnea, increased labored breathing, hoarseness, wheezing, hypoxia), follow management guidelines summarized in Table 17. 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 17: Management of Suspected Tumor Inflammation or 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 inflammation or 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 inflammation or 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 inflammation or 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 after discussion with Principal Investigator.

ENT=ears, nose, and throat (specialist); NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

[a] Grade of triggering event dependent on presenting signs and symptoms of tumor inflammation

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

Before first administration of study treatment: Consult with the Principal Investigator prior to initiating 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 inflammation or 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 . After first administration, monitor ejection fraction weekly, or with shorter intervals if clinically required. In case of clinically significant improvement in two 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 18: Management of Suspected Tumor Inflammation or 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 three consecutive clinically significant worsening ejection fractions.

Table 18: Management of Suspected Tumor Inflammation or Flare Event in the Mediastinum (cont.)

Triggering Event [a]	Initial Management Recommendation	Action to Be Taken with Mosunetuzumab
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 three consecutive clinically significant worsening results.

NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation

[b] Preventative and interventional measures should be considered and discussed with the Principal Investigator, appropriate specialists, and the patient prior to mosunetuzumab dosing. When tumor inflammation 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 inflammation or flare event, follow the recommendations in Table 19. 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 19: Management of Suspected Tumor Inflammation and Flare Event Outside the Mediastinum and Oropharynx, Applicable Whenever Pain Management is Required for Tumor Inflammation Events

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 after discussion with Principal Investigator.

NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; NSAID=nonsteroidal anti-inflammatory drug.

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation.

14.11 Management Guidelines for Neutropenia and Thrombocytopenia

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. Guidelines for neutropenia management are outlined in Table 20.

Table 20: Management Guidelines for Neutropenia

Event	Initial Management Recommendation Action to Be Taken with Study Treatment
Grade 3 or 4 neutropenia In Cycle 1	Granulocyte Colony Stimulating factors (e.g., G-CSF) for neutropenia are permitted. Mosunetuzumab step doses should not be held for uncomplicated neutropenia. The dose of mosunetuzumab should not be modified for this reason.
Grade 3 or 4 neutropenia in Cycles 2–8	Delay all study treatment until ANC recovery following guidelines below: Granulocyte Colony Stimulating factors (e.g., G-CSF) for neutropenia are permitted. If ANC recovers to ≥ 1000/μcL within ≤ 14 days after the scheduled date for the next cycle, administer the full dose of all study treatments. If ANC recovers to ≥ 1000/μcL within > 14 to ≤ 21 days after the scheduled date for the next cycle, follow lenalidomide dose modification Section 5.1.6.1. The patient may continue study treatment with mosunetuzumab at the investigator's discretion with consultation of the Principal Investigator. Consider holding mosunetuzumab for persistent Grade 4 neutropenia (> 21 days after the scheduled dose of the next cycle) and discuss with Principal Investigator The dose of mosunetuzumab should not be modified for this reason

G-CSF = granulocyte-colony stimulating factor.

Patients who experience febrile neutropenia should be managed according to local guidelines or as per institutional practice.

THROMBOCYTOPENIA

All patients should be monitored at each cycle for thrombocytopenia, and patients experiencing thrombocytopenia should undergo blood cell monitoring until resolution of the event to Grade 1 (platelet count ≥ 75,000/μcL). Guidelines for thrombocytopenia management are outlined in Table 21.

Table 21: Management Guidelines for Thrombocytopenia

Event	Initial Management Recommendation and Action to Be Taken with Study Treatment
Grade 2, 3, or 4 thrombocytopenia (platelet count <75,000/μcL) in Cycle 1	Mosunetuzumab step doses should not be held for uncomplicated thrombocytopenia. The dose of mosunetuzumab should not be modified for this reason.
Grade 2, 3, or 4 thrombocytopenia (platelet count <75,000/μcL) in Cycles 2–8	Delay all study treatment until platelet recovery following guidelines below: If platelet count recovers to ≥75,000/μcL within ≤ 14 days after the scheduled date for the next cycle, administer the full dose of all study treatments. If platelet count recovers to ≥75,000/μcL within >14–21 days after the scheduled date for the next cycle, discuss with Principal Investigator. The patient may continue study treatment with mosunetuzumab at the investigator's discretion with consultation of the Principal Investigator. Consider holding mosunetuzumab for persistent Grade 2 or higher thrombocytopenia (> 21 days after the scheduled dose of the next cycle) and discuss with Principal Investigator. The dose of mosunetuzumab should not be modified for this reason.

14.12 **Management Guidelines for Infections**

Due to its 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 blinatumomab (Blincyto USPI; Gazyva USPI; Rituxan 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 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. PML has been associated with treatment with CD20-directed therapies including rituximab and obinutuzumab. 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 MRI and lumbar puncture should be performed as clinically indicated. Note, however, that new onset neurologic adverse events following initial doses of mosunetuzumab may be more likely due to acute effects of mosunetuzumab as PML associated with rituximab generally occurred following long-term exposure.

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. Patients with HIV infection will be excluded from participation in the study, because signs and symptoms of HIV may confound assessment of the safety profile of mosunetuzumab in combination with polatuzumab vedotin. HIV has also been associated with development of secondary HLH. Patients with HIV and known or suspected chronic active EBV infection will be excluded from this trial due to the risk of secondary HLH.

14.13 **Management Guidelines for 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.

LFTs will be assessed regularly during study and should be managed according to guidelines in Table 22 for mosunetuzumab.

Table 22: Management of Liver Function Test Abnormalities (Mosunetuzumab)

Abnormality	Action to Be Taken
Grade 1 AST or ALT elevation or AST/ALT ≥3× baseline value	• Continue mosunetuzumab • Monitor LFTs (including AST, ALT, and bilirubin) weekly. • For AST/ALT ≥3× baseline value but Grade 1, notify Principal Investigator prior to subsequent study treatment.
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. **Events >5 days' duration:** • Obtain hepatology consultation; evaluate etiology.
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. **Events >5 days' duration** • Resume mosunetuzumab when resolved to Grade 1 or baseline value, following approval of Principal Investigator. [a]
Grade 4 AST or ALT elevation	• Permanently discontinue mosunetuzumab. [b] • Follow management guidelines as described for Grade 3 event.

ALT=alanine transaminase; AST=aspartate transaminase; CRS=cytokine-release syndrome; HLH=hemophagocytic lymphohistiocytosis; LFT=liver function test.

[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 Principal Investigator.

14.15 **Injection Site Reaction Management**

Table 23: 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. • Consult dermatology. • 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 mosunetuzumab SC. • Consider continuing study treatment with mosunetuzumab IV after discussion with Principal Investigator.

14.16 Mosunetuzmab pharmacy preparation

PHARMACY INFORMATION

How mosunetuzumab is supplied: Mosunetuzumab for SC injection is provided as solution for injection Ro703-0816/F03-01 and Ro703-0816/F05-02 by Genentech, Inc.

Mosunetuzumab drug product in Formulation F03 is provided as a sterile, colorless to brownish yellow liquid solution and contains no preservatives. Each single dose, 2-mL vial contains 45 mg (net quantity) of mosunetuzumab, formulated with 45 mg/mL mosunetuzumab in a solution containing histidine, acetic acid, sucrose, polysorbate 20, and L- methionine, at pH 5.8.

Mosunetuzumab drug product in Formulation F05 is provided as a sterile, colorless to brownish liquid solution and contains no preservatives. Each single dose, 2-mL vial contains 5 mg (net quantity) of mosunetuzumab, formulated with 10 mg/mL mosunetuzumab in a solution containing histidine, acetic acid, sucrose, polysorbate 20, and L- methionine, at pH 5.8.

Storage: Mosunetuzumab (F03, F05) must be refrigerated at 2°C-8°C (36°F-46°F) until use.

Mosunetuzumab should not be used beyond the expiration date provided by the manufacturer. Vials should not be frozen or shaken and should be protected from light during storage.

Stability: If necessary, unopened mosunetuzumab vials may be stored at ambient temperature (8°C-25C [46°F-77°F]) for up to 8 hours.

Route of administration: Subcutaneous. Intravenous formulations of mosunetuzumab are not used in this study.

Preparation of mosunetuzumab for SC. injection

Equipment
For preparation of the dose solution, polypropylene/polycarbonate, disposable sterile syringes with latex-free rubber components are recommended. Use an appropriately sized stainless steel needle (e.g. 21G 1” or 18G) for withdrawal, pooling, or transfer of the drug product.

Equipment needed:

- Stainless steel needles of 27G (or similar suitable gauge) are to be used for administration of dose solution.
- Perform pooling, transfer and administration of the study drug with polypropylene or polycarbonate disposable syringes with latex-free rubber components.

- Use polyethylene stoppers or polypropylene tip caps/syringe caps for sealing filled syringes to prevent evaporation if storage in syringe is required.
- Empty sterile glass vials may be used for pooling of drug product if required per site best practice.
- The smallest size syringe that can accurately deliver the injection volume should be used.
- When administered subcutaneously, mosunetuzumab will be delivered by medical syringe with a final mosunetuzumab volume not to exceed 2.0 mL.

Preparation

Dose preparation must occur under aseptic conditions, as the mosunetuzumab contains no preservatives.

- Visually inspect drug product solution for particulate matter and discoloration prior to dose solution preparation. Do not use the vial if the solution is cloudy, is discolored, or contains particulate matter.

- Each vial, Drug Product, or diluent, should be used for one dilution/one injection only. Partially used vials should NOT be re-used, they should be discarded immediately.

- The Drug Product, or diluent should be allowed to acclimate to room temperature for approximately 30 minutes prior to preparation for administration.

Perform manipulations of the study drug and diluent with standard disposable syringes and stainless steel needles. Always use the smallest syringe that will hold the required volume to manipulate solutions. For preparation of the dose solution, polypropylene/polycarbonate, disposable sterile syringes with latex-free rubber components are recommended. Stainless steel needles of 18 Gauge (G) are recommended for withdrawal of the investigational product.

<u>Preparing the syringe for injection (F05 - 5 mg/0.5 mL or F03 - 45 mg/1 mL):</u>

1. See Table 24 below for drug volumes for 5 mg/0.5 mL and Table 25 for 45 mg/1 mL.
2. Remove the plastic flip-off seal from drug product vial(s), and swab the top of the vial with an alcohol swab.
3. Place a transfer needle (19G x 1½" or 19G x 1.1" or 18G x1½" or 18G) onto a Luer lock syringe (smallest size that can accurately deliver the dose) using aseptic technique.
4. Push the needle into the center of the vial stopper.
5. Withdraw study drug from the inverted vial.
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the needle. If pooling is required for the dose level, pool drug product per site best practices.
7. The transfer needle should be discarded after withdrawal of the vial contents and must not be used for the subcutaneous injection.
8. Attach a 27-gauge x ½-inch sterile injection needle (or similar needle suitable for subcutaneous injection) firmly onto the syringe by screwing it tightly onto the Luer lock. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.

9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.
10. Hold the syringe at eye level, and carefully push the plunger rod until the plunger tip is aligned with the line that marks the appropriate dose volume on the syringe.
11. Visually inspect drug product solution for particulate matter and discoloration after dose solution preparation. Do not use the syringe if the solution is cloudy, is discolored, or contains particulate matter.

Table 24: Study Drug (mosunetuzumab, F05, 5 mg/ 0.5mL) for Subcutaneous Injection

Dose level (mg)	Volume of study drug (mL)	Number of vials required	Administered volume (mL)
5.0	0.5	1	0.5
20.0	2.0	4	2.0
Above 20.0	Please use a 45 mg/1 mL vial volume		

Table 25: Study Drug (mosunetuzumab, F03, 45 mg/ 1mL) for Subcutaneous Injection

Dose level (mg)	Volume of study drug (mL)	Number of vials required	Administered volume (mL)
45.0	1.0	1	1.0

Do not shake or freeze syringes containing dose solution. Protect from direct sunlight (exposure to indoor ambient light is acceptable).

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.

If not used immediately, the dose solution in vial or syringe may be stored refrigerated at 2-8°C (36-46°F) for up to 24 hours prior to administration. The dose solution in vial or syringe may be temporarily held at 9-25°C (47-77°F) up to a maximum of 4 hours. The dose solution should be discarded if the cumulative storage time of the dose solution prior to administration exceeds 24 hours.

If the prepared dose solution is stored at 2-8°C (36-46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration.

The filled syringe without injection needle attached should be capped or stoppered (to prevent evaporation) and protected from direct sunlight if storage is required before administration.

Filled syringes with the injection needle already attached (either before or after adjusted to final volume) must be used immediately as the solution may dry and clog the injection needle.

14.17 **Management of Neurologic toxicity including ICANS**

Grade[a, b]	Actions
Grade 1	- Continue Mosunetuzumab and monitor neurologic toxicity symptoms. - If Grade 1 ICANS,[b] consider a single dose of dexamethasone 10mg, 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.

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 Delayed or Missed Doses for guidance on restarting Mosunetuzumab after dose delay.

e - Evaluate benefit/risk before restarting Mosunetuzumab.