**Official Title:** A Phase Ib/II, Open-Label, Multicenter, Randomized, Controlled Study Investigating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Mosunetuzumab (BTCT4465A) in Combination With Chop or Chppolatuzumab Vedotin in Patients With B-Cell Non-Hodgkin Lymphoma

**NCT Number:** NCT03677141

**Document Date:** Protocol Version 6: 27-May-2020

# PROTOCOL

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|---|---|
| **TITLE:** | **A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED, CONTROLLED STUDY INVESTIGATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF MOSUNETUZUMAB (BTCT4465A) IN COMBINATION WITH CHOP OR CHP-POLATUZUMAB VEDOTIN IN PATIENTS WITH B-CELL NON-HODGKIN LYMPHOMA** |
| **PROTOCOL NUMBER:** | GO40515 |
| **VERSION NUMBER:** | 6 |
| **EUDRACT NUMBER:** | 2018-001039-29 |
| **IND NUMBER:** | 120651 |
| **TEST PRODUCT:** | Mosunetuzumab (RO7030816; BTCT4465A), Polatuzumab vedotin (RO5541077; *DCDS4501S*), Rituximab (RO0452294), Tocilizumab (RO4877533) |
| **MEDICAL MONITOR:** | [redacted], *M.D., Ph.D.* |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **APPROVAL DATE:** | See electronic date stamp below |

## PROTOCOL AMENDMENT APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 27-May-2020 02:33:09 | Company Signatory | [redacted] |

## PROTOCOL HISTORY

| Protocol | |
|---|---|
| Version | Date Final |
| 5 | 21 August 2019 |
| 4 | 4 March 2019 |
| 3 | 27 October 2018 |
| 2 | 15 August 2018 |
| 1 | 23 April 2018 |

## PROTOCOL AMENDMENT, VERSION 6
## RATIONALE

Protocol GO40515 has been amended primarily to reduce the hospitalization requirement following mosunetuzumab administration, and to update the polatuzumab vedotin safety profile for consistency with the Investigator's Brochure. Changes to the protocol, along with a rationale for each change, are summarized below:

- The terminology for dosing has been updated from double step fractionated dosing to step-up dosing throughout the protocol.
- The efficacy and safety data for the mosunetuzumab background has been updated with data from the most recent clinical cut-off date (Sections 1.2.2.1 and 1.2.2.2).
- The background sections for mosunetuzumab and polatuzumab vedotin have been updated to refer to Investigator's Brochures and local prescribing information for additional detailed information (Section 1.2 and Section 1.3.).
- Based on the available safety data from GO40515 and from other mosunetuzumab studies, and following the recommendation of the IMC, the requirement for hospitalization has been reduced in Cycle 1 to 24 hours following the end of the infusion of the first dose of mosunetuzumab. (Sections 3.3.14, 4.3.2.1, 4.3.2.2, 4.3.3.2 Figure 3 and Figure 4, 5.1.1, and Appendices 1, 15 and 16).
- The eligibility requirement for creatinine and creatinine clearance has been clarified so that a patient with renal function that meets the required threshold at the time of enrollment may be eligible. The threshold for creatine clearance has been adjusted to 50 ml/min (Section 4.1.1).
- Patients with history of hemophagocytic lymphohistiocytosis (HLH) are now excluded from the study. It is hypothesized that these patients may be at an increased risk for severe cytokine release syndrome (CRS) based on overlapping mechanisms of excessive cytokine release (Section 4.1.2).
- The eligibility requirement for length of time from documented remission for patients with a history of malignancy that has been treated with curative intent has been reduced to ≥ 2 years from ≥ 5 years (Section 4.1.2).
- Tumor lysis syndrome (TLS) prophylaxis has been modified so that prophylaxis is based on patient risk for TLS and investigator's discretion. (Section 4.4.1.2, 5.1.2.2, 5.1.7.6, and Appendix 18)
- Based on current data in Study GO29781 that demonstrates the incidence of CRS is mainly observed in Cycles 1 and 2 of mosunetuzumab treatment, the corticosteroid premedication requirement has been changed to be optional for patients receiving single agent mosunetuzumab in Cycle 9 and beyond, if there was no CRS in the preceding dose cycle (Section 4.3.2.1).
- The regimen for polatuzumab vedotin has been revised so that polatuzumab vedotin and mosunetuzumab may be given on the same day in Cycles 1 and 2, for the Phase II portion of the study. (Section 3.3.2, Section 4.3.3.3, Figure 4, Appendix 1, Appendix 2)

- Baseline brain MRI was removed from the mandatory screening assessments as it has limited utility for diagnosing neurologic adverse events (AE) observed in mosunetuzumab-treated patients. In patients with CAR T-cell therapy and subsequent immune effector cell-associated neurotoxicity syndrome (ICANS), MRI seldom revealed structural abnormalities (Sections 4.5, 4.5.5.1, 5.1.2.2 and Appendices 1 and 15).
- Optional tumor biopsies have been revised to allow a biopsy after treatment initiation, preferably between C1D15 and C2D8 (Section 4.5.12, Appendix 1, Appendix 15, Appendix 16)
- Peripheral blood smear and flow cytometry have been added as screening assessments to detect malignant and/or atypical cells. The presence of malignant and/or atypical cells has been hypothesized to be a CRS risk factor (Section 4.5.6, Appendices 1 and 15).
- HLH diagnosis criteria and management guidelines for suspected and confirmed HLH have been updated (Sections 5.1.2.2, 5.1.7.5, and, Appendix 19)
- Management guidelines for patients with hepatitis B reactivation have been updated (Section 5.1.2.2)
- The risks associated with polatuzumab vedotin have been updated per the Investigator's Brochure with the following changes (Section 5.1.3):
    - Change from potential risk to known risk:
        - Myelosuppression as a consolidation of neutropenia (including febrile neutropenia), thrombocytopenia, and anemia.
        - Infections
        - Infusion-related events
        - Gastrointestinal toxicity (diarrhea, nausea, vomiting, constipation)
    - Addition of carcinogenicity as potential risk
- The neurology consultant has been removed from the internal monitoring committee (IMC) due to low incidence of severe neurologic adverse events associated with mosunetuzumab (Section 5.1.8).
- The instruction has been repeated that mosunetuzumab should not be held for uncomplicated neutropenia and uncomplicated thrombocytopenia during step-up dosing in the first cycle (Section 5.1.7 and Table 9)
- Text has been added about the risk of perforation and hemorrhage associated with tumor inflammation/flare in patients with lesions in the gastrointestinal tract (Section 5.1.2.2).
- The adverse events of special interest for mosunetuzumab have been updated to remove Grade 3 or greater neutropenia, because neutropenia is a known risk associated with mosunetuzumab (Section 5.2.3).

- The adverse events of special interest for polatuzumab vedotin have been reduced to Grade 2 or higher peripheral neuropathy (sensory and/or motor) and Grade 3 or higher infections (Section 5.2.3).
- The management of CRS has been updated to clarify that mosunetuzumab should be permanently discontinued if there is a Grade 4 CRS event or recurrence of Grade 3 CRS. Footnotes were added to provide further guidance for Grade 4 CRS or recurrent Grade 3 CRS cases in which further treatment with subsequent cycles may be considered if all specified requirements are satisfied (Table 10).
- For pregnancies in female partners of male patients, the time window for reporting a pregnancy after the last dose of polatuzumab vedotin was changed from 5 months to 6 months (Section 5.4.3.2)
- The time window for obtaining informed consent has been updated to 28 days (Appendices 1 and 15)
- The collection of information regarding B-symptoms has been changed to collection at screening only, because the information does not contribute to the study endpoints (Appendix 1, Appendix 15)
- Sample collection timepoints for blood for molecular analysis for MRD monitoring has been updated to Cycles 2, 4, and 6 only (Appendices 2 and 16)
- The Schedule for Tocilizumab Treatment of Severe or Life-Threatening Cytokine Release Syndrome has been updated to clarify that samples for cytokines and IL-6 pharmacodynamic markers are to be assessed by serum, instead of plasma, and to add additional assessment timepoints (Appendix 14).
- A typographical error in the product name for polatuzumab vedotin has been corrected throughout the protocol. The correct product name is DCDS4501S.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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## PROTOCOL AMENDMENT ACCEPTANCE FORM

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| **TITLE:** | **A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED, CONTROLLED STUDY INVESTIGATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF MOSUNETUZUMAB (BTCT4465A) IN COMBINATION WITH CHOP OR CHP-POLATUZUMAB VEDOTIN IN PATIENTS WITH B-CELL NON-HODGKIN LYMPHOMA** |
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| **MEDICAL MONITOR:** | [redacted], *M.D. PhD* |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**I agree to conduct the study in accordance with the current protocol.**

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

## PROTOCOL SYNOPSIS

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|---|---|
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| **PHASE:** | Ib/II |
| **INDICATION:** | B-Cell Non-Hodgkin Lymphoma |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**Objectives and Endpoints**

This Phase Ib/II, multicenter, randomized, open-label study will evaluate the safety, pharmacokinetics, and preliminary efficacy of mosunetuzumab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (M-CHOP) and, subsequently, in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) plus polatuzumab vedotin (CHP-pola) in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) (Phase Ib).

The Phase Ib portion of the study is designed to assess safety, tolerability, and the recommended Phase II dose (RP2D) of mosunetuzumab in combination with CHOP and in combination with CHP-pola. Following the Phase Ib portion, a Phase II safety cohort will evaluate M-CHOP in patients with previously untreated diffuse large B-cell lymphoma (DLBCL). If safety is deemed acceptable, M-CHP-pola will then be compared with rituximab in combination with CHP-pola (R-CHP-pola) in patients with previously untreated DLBCL (randomized Phase II).

The specific objectives and corresponding endpoints for the study are listed by phase below.

| Phase Ib | |
|---|---|
| **Safety Objectives (Primary Study Objective for Phase Ib)** | **Corresponding Endpoints** |
| M-CHOP:<br>• To evaluate the safety and tolerability of M-CHOP in patients with R/R B-cell NHL, including estimation of the MTD, determination of RP2D, and characterization of DLTs<br>M-CHP-pola:<br>• To evaluate the safety and tolerability of M-CHP-pola in patients with R/R B-cell NHL, including estimation of the MTD, determination of RP2D, and characterization of DLTs | • Occurrence and severity of adverse events including DLTs, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to the *ASTCT CRS Consensus Grading criteria* )<br>• Change from baseline in targeted vital signs<br>• Change from baseline in targeted clinical laboratory test results<br>• Number of cycles received and dose density and intensity (of planned 6 cycles of combination therapy) |
| **Pharmacokinetic Objectives** | **Corresponding Endpoints** |
| • To characterize the pharmacokinetics of mosunetuzumab when administered in combination with CHOP or CHP-pola<br>• To characterize the pharmacokinetics of polatuzumab vedotin when administered in combination with mosunetuzumab and CHP<br>• To characterize the relationship between serum pharmacokinetics, safety, biomarkers, and efficacy | • $C_{max}$<br>• $C_{min}$<br>• Total exposure (AUC), clearance, and volume of distribution at steady state, as estimated by population PK modeling, as appropriate and supported by data<br>• Relationship between serum pharmacokinetics and safety, biomarkers, or efficacy endpoints, as appropriate |
| **Efficacy Objectives** | **Corresponding Endpoints** |
| • To make a preliminary assessment of the anti-tumor activity of M-CHOP<br>• To make a preliminary assessment of anti-tumor activity of M-CHP-pola | *All radiographic assessments are according to the Lugano 2014 Response Criteria*<br>• CR rate at the time of primary response assessment based on PET-CT as determined by the investigator<br>• Best ORR, defined as CR or PR at any time on study based on PET-CT and/or CT scan as determined by the investigator<br>• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs first |
| **Immunogenicity Objectives** | **Corresponding Endpoints** |
| • To assess the immune response to mosunetuzumab<br>• To assess the immune response to polatuzumab vedotin<br>• Assess potential effect of mosunetuzumab ADA incidence on relevant clinical outcomes<br>• Assess potential effect of polatuzumab vedotin ADA incidence on relevant clinical endpoints | • Incidence of ADAs to mosunetuzumab<br>• Incidence of ADAs to polatuzumab vedotin<br>• Relationship between ADAs and pharmacokinetics, safety, efficacy, and biomarkers may be explored as appropriate |

| Exploratory Biomarker Objectives | Corresponding Endpoints |
|---|---|
| • To evaluate the relationship between M-CHOP and M-CHP-pola exposure and pharmacodynamic biomarkers, including but not limited to circulating cytokine levels and T-cell number and activation states<br>• To make a preliminary assessment of biologic markers that might act as predictors of susceptibility to developing adverse events following administration of M-CHOP and M-CHP-pola<br>• To make a preliminary assessment of biologic markers that might act as predictors of the anti-tumor activity of M-CHOP and M-CHP-pola<br>• To make a preliminary assessment of biologic markers that might act as predictors of the immunomodulatory activity of M-CHOP and M-CHP-pola | • Relationship between exploratory biomarkers (including cytokines, T cell and B cell counts, and T cell activation) and efficacy, safety, pharmacokinetics, immunogenicity, or other biomarker endpoints |
| **Phase II** | |
| **Primary Efficacy Objective** | **Corresponding Endpoint** |
| • To evaluate the efficacy of M-CHP-pola compared with R-CHP-pola in patients with previously untreated DLBCL | *All radiographic assessments are according to the Lugano 2014 Response Criteria*<br>• CR rate at the time of primary response assessment based on PET-CT, as determined by IRC |
| **Secondary Efficacy Objectives** | **Corresponding Endpoints** |
| • To evaluate the efficacy of M-CHP-pola compared with R-CHP-pola in patients with previously untreated DLBCL<br>• To evaluate the efficacy of M-CHOP in patients with previously untreated DLBCL | • CR rate at the time of primary response assessment based on CT only, as determined by the investigator<br>• ORR, defined as CR or PR at the time of primary assessment based on PET-CT, as determined by the investigator<br>• ORR, defined as CR or PR at the time of primary assessment based on CT only, as determined by the investigator<br>• Best ORR, defined as CR or PR at any time on study, based on PET-CT or CT only as determined by the investigator<br>• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs first<br>• PFS, defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs first<br>• PFS at 1 year, proportion of patients with disease progression or relapse as determined by the investigator, or death from any cause within 1 year of randomization<br>• EFS, defined as the time from randomization to the first occurrence of disease progression or relapse, as determined by the investigator, initiation of NALT, or death from any cause, whichever occurs first |

| | |
|---|---|
| | • Time to deterioration in physical functioning and fatigue *as measured by the EORTC QLQ-C30* and in *lymphoma symptoms as measured by* the FACT-Lym subscale |
| **Exploratory Efficacy Objectives** | **Corresponding Endpoints** |
| • To evaluate the clinical benefit of M-CHP-pola compared with R-CHP-pola in patients with previously untreated DLBCL<br>• To evaluate the clinical benefit of M-CHOP in patients with previously untreated DLBCL | • Proportion of patients achieving meaningful improvement in EORTC QLQ-C30 physical functioning and fatigue, and in *lymphoma symptoms in* the FACT-Lym subscale<br>• EORTC QLQ-C30 rate of treatment-related symptoms and FACT/GOG-NTX peripheral neuropathy rate<br>• All *remaining* scales of the EORTC QLQ-C30, the FACT-Lym subscale, and FACT/GOG-NTX peripheral neuropathy |
| **Safety Objectives** | **Corresponding Endpoints** |
| • To assess the safety and tolerability of M-CHP-pola compared with R-CHP-pola<br>• To assess the safety and tolerability of M-CHOP | • Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v5.0. For CRS, severity determined according to ASTCT CRS Consensus Grading criteria<br>• Change from baseline in targeted vital signs<br>• Change from baseline in targeted clinical laboratory test results and clinical assessments<br>• Number of cycles received and dose density and intensity (of planned 6 cycles of combination therapy) |
| **Pharmacokinetic Objectives** | **Corresponding Endpoints** |
| • To characterize the pharmacokinetics of mosunetuzumab when administered by IV infusion with CHOP and CHP-pola<br>• To characterize the pharmacokinetics of polatuzumab vedotin when administered by IV infusion with mosunetuzumab and CHP<br>• To assess the pharmacokinetics of rituximab in combination with CHP-pola compared with historical data (exploratory) | • $C_{max}$<br>• $C_{min}$<br>• Total exposure (AUC), clearance, and volume of distribution, as estimated by population PK modeling, as appropriate and supported by data |
| **Immunogenicity Objectives** | **Corresponding Endpoints** |
| *Secondary Immunogenicity Objectives* | |
| • To assess the immune response to mosunetuzumab<br>• To assess the immune response to polatuzumab vedotin<br>• Assess potential effect of mosunetuzumab ADA incidence to relevant clinical outcomes<br>• Assess potential effect of polatuzumab vedotin ADA incidence to relevant clinical endpoints | • Incidence of ADAs to mosunetuzumab<br>• Incidence of ADAs to polatuzumab vedotin<br>• Relationship between ADAs and pharmacokinetics, safety, efficacy, and biomarkers may be explored as appropriate |

| Exploratory Biomarker Objectives | Corresponding Endpoints |
|---|---|
| • To identify biomarkers that are predictive of response to M-CHOP and M-CHP-pola (predictive biomarkers), are associated with progression to a more severe disease state (prognostic biomarkers), are associated with acquired resistance to M-CHOP and M-CHP-pola, are associated with susceptibility to developing adverse events, can provide evidence of M-CHOP and M-CHP-pola activity, or can increase the knowledge and understanding of disease biology<br>• To make a preliminary assessment of response to M-CHOP and M-CHP-pola in different clinical and biologic prognostic DLBCL subgroups<br>• To make a preliminary assessment of MRD status following treatment with M-CHOP and M-CHP-pola | • Association between exploratory biomarkers, prognostic subtypes, including and molecular DLBCL prognostic subtypes such as cell of origin, and PET-CT CR, ORR, DOR, and PFS endpoints<br>• Relationship over time between ctDNA and radiographically-assessed tumor burden |
| **Exploratory Health Status Utility Objective** | **Corresponding Endpoint** |
| • To assess health status of patients | • Health status (EQ-5D-5L) |

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; AUC = area under the concentration-time curve; CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP-pola = CHP-polatuzumab vedotin; Cmax = maximum serum concentration; Cmin = minimum serum concentration; CR=complete response; CRS = cytokine release syndrome; CT = computed tomography; ctDNA = circulating-tumor DNA; DLBCL=diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; DOR = duration of response; EFS = event-free survival; EORTC QLQ-C30 = European Organisation of Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FACT/GOG-NTX=Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity; FACT-Lym=Functional Assessment of Cancer Therapy–Lymphoma subscale; IRC=Independent Review Committee; M-CHOP=mosunetuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; M-CHP-pola=mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; MRD=minimal residual disease; MTD=maximum tolerated dose; NALT=new anti-lymphoma therapy; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; NHL=non-Hodgkin lymphoma; ORR=objective response rate; PET=positron emission tomography; PET-CT=positron emission tomography–computed tomography; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; R-CHP=rituximab plus cyclophosphamide, doxorubicin, and prednisone; R-CHP-pola=rituximab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RP2D=recommended Phase II dose; R/R=relapsed or refractory.

## Study Design

### Description of Study

This study is divided into two phases: 1) a dose-finding Phase Ib portion, which will test the safety and tolerability of combinations of mosunetuzumab with chemotherapy and polatuzumab vedotin for the treatment of patients with previously treated B-cell NHL and 2) a randomized, open-label Phase II portion, which will compare the efficacy, safety, and tolerability of mosunetuzumab in combination with CHP-pola or CHOP versus R-CHP-pola in patients with

previously untreated DLBCL. The option to include the treatment arm of M-CHOP in the randomized Phase II portion of the study will be based on clinical data from a safety run-in group assessing the safety and tolerability of M-CHOP in patients with previously untreated DLBCL. The decision to include this third treatment arm will be made prior to initiating the randomized Phase II portion.

Phase Ib: Dose-Finding Phase in B-Cell Non-Hodgkin Lymphoma

*Group A: Dose-Finding Mosunetuzumab plus CHOP Group*

The goal of this Phase Ib portion is to establish the RP2D of mosunetuzumab in combination with CHOP (RP2D_A). The RP2D_A will be the starting mosunetuzumab dose used in Groups B and C. A 3+3 dose-finding design will be employed, using the dose-escalation/dose-de-escalation rules as defined in the protocol. The DLT assessment period will be C1D1 through C1D21 of M-CHOP treatment, and dose escalation/de-escalation will continue until the MTD or MAD is identified.

Patients with R/R B-cell NHL will receive 6 cycles of M-CHOP at 21-day intervals. The first cycle of mosunetuzumab will be administered as *step-up* doses on C1D1 (1 mg), C1D8 (2 mg), and C1D15 (13.5 mg) after CHOP administration in the first cohort, then will be determined according to dose escalation/de-escalation rules based on DLTs (see the protocol for the rationale for starting mosunetuzumab dose and the dose escalation/de-escalation rules). Full doses of mosunetuzumab (the C1D15 dose) will be administered on Day 1 of subsequent cycles.

The CHOP regimen consists of cyclophosphamide 750 mg/m$^2$ IV, doxorubicin 50 mg/m$^2$ IV, and vincristine 1.4 mg/m$^2$ (maximum dose of 2 mg) IV given on Day 1 and prednisone 100 mg/day orally (PO) given on Days 1–5 of every 21-day cycle for 6 cycles. On days that mosunetuzumab corticosteroid premedication (dexamethasone 20 mg IV or methylprednisolone 80 mg IV) overlaps with the prednisone 100 mg PO dose, the IV corticosteroid premedication should be omitted.

Patients with a PR or stable disease (SD) at the time of primary response assessment by PET-CT (6–8 weeks after C6D1 of study treatment or early treatment discontinuation) may continue mosunetuzumab treatment as a single agent for up to an additional 11 cycles in the absence of disease progression. For additional details on the M-CHOP regimen, refer to the protocol.

The Sponsor may open an expansion cohort of up to 20 patients to further assess safety, tolerability, PK, and preliminary evidence of anti-tumor activity at or below the MTD or MAD (see the protocol).

If the combination of *step-up dosing* M-CHOP is not tolerated because of DLTs occurring prior to the administration of the C1D15 mosunetuzumab dose, then alternative regimens may be assessed based on a review of the totality of the available data by the IMC. These may include, but are not limited to:

- Incorporating corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1. This modification will be prioritized, as it is consistent with recommendations for patients with DLBCL at risk for early treatment-related toxicities with R-CHOP treatment.
- Delaying the first dose of mosunetuzumab by 1 week in Cycle 1 with CHOP administration on C1D1 and maintaining mosunetuzumab *step-up dosing*, starting with 1 mg on C1D8, then 2 mg on C1D15, and the mosunetuzumab test dose on C2D1; this mosunetuzumab schedule modification will be assessed if pre-phase corticosteroid treatment does not sufficiently mitigate toxicities associated with *step-up dosing of* mosunetuzumab administration on C1D1 and C1D8. Delayed mosunetuzumab dosing may be assessed with pre-phase corticosteroid if this intervention provided some benefit in mitigating toxicities based on review of the safety data by the IMC, study investigators, and Sponsor study team.

All data and decisions regarding dosing and/or scheduling will be reviewed by the IMC. After the IMC has evaluated at least 3 patients with M-CHOP at the determined RP2D_A for at least one cycle, the Group C safety run-in evaluating M-CHOP in previously untreated DLBCL patients will be opened (refer to the protocol).

*Group B: Dose-Finding M-CHP-Pola Group*

The goal of this Phase Ib portion is to establish the mosunetuzumab RP2D in combination with CHP-pola (RP2D_B). The combination of mosunetuzumab and polatuzumab vedotin is being investigated in Study GO40516, a Phase Ib/II study in patients with R/R B-cell NHL. The mosunetuzumab dose selected for M-CHP-pola will not exceed the RP2D_A for M-CHOP or the RP2D for mosunetuzumab plus polatuzumab vedotin from Study GO40516.

Clinical data for mosunetuzumab plus polatuzumab vedotin, including treatment-emergent adverse events, Grade ≥3 adverse events, DLTs, MTD/MAD, and the RP2D from the Phase Ib portion of GO40516 will be reviewed by the GO40515 IMC and study team prior to initiating Group B enrollment with M-CHP-pola. If the same dose as the mosunetuzumab RP2D_A has been cleared in Study GO40516, that mosunetuzumab dose can be assessed in combination with CHP-pola in this study even if RP2D has not yet been declared for M-pola in Study GO40516 (refer to the protocol for additional details on Study GO40516).

A 3+3 dose-finding design will be employed, with potential dose de-escalation using the rules as defined in the protocol (the mosunetuzumab dose will not be escalated above the RP2D_A). The DLT assessment window will be from C1D1 through C1D21 of M-CHP-pola treatment, and dose finding will continue until the MTD or MAD is identified.

Patients with R/R B-cell NHL will receive 6 cycles of M-CHP-pola at 21-day intervals. The first cycle of mosunetuzumab will be administered as *step-up* doses on C1D2 (1 mg), C1D8 (2 mg), and C1D15 (mosunetuzumab [RP2D_A]) in the first cohort and option for dose de-escalation if not tolerated). Full doses of mosunetuzumab (C1D15 dose) will be administered on Day 2 of subsequent cycles, with the option of mosunetuzumab administration on Day 1 of each cycle starting in Cycle 3 if well tolerated.

The CHP-pola regimen consists of cyclophosphamide 750 mg/m$^2$ IV, doxorubicin 50 mg/m$^2$ IV, and polatuzumab vedotin 1.8 mg/kg IV given on Day 1 and prednisone 100 mg/day PO given on Days 1–5 of every 21-day cycle for 6 cycles. On days that mosunetuzumab corticosteroid premedication (dexamethasone 20 mg IV or methylprednisolone 80 mg IV) overlaps with the prednisone 100 mg PO dose, the IV corticosteroid premedication should be omitted.

Patients with a PR or SD at the time of primary response assessment by PET-CT (6–8 weeks after Cycle 6 of study treatment or early treatment discontinuation) may continue mosunetuzumab treatment as a single agent for up to an additional 11 cycles in the absence of disease progression. For additional details on the M-CHP-pola regimen, refer to the protocol.

The Sponsor may open an expansion cohort of up to 20 patients to further assess safety, tolerability, PK, and preliminary evidence of anti-tumor activity at or below the MTD or MAD.

If the combination of *step-up* M-CHP-pola is not tolerated due to DLTs occurring prior to the administration of the C1D15 mosunetuzumab dose, then alternative regimens may be assessed based on a review of the totality of the available data by the IMC. These may include, but are not limited to:

- Incorporating corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1. This modification will be prioritized, as it is consistent with recommendations for patients with DLBCL at risk for early treatment-related toxicities with R-CHOP treatment.
- Delaying of the first dose of mosunetuzumab by 1 week in Cycle 1 with CHP-pola administration on C1D1 and maintaining mosunetuzumab *step-up dosing*, starting with 1 mg on C1D8, then 2 mg on C1D15, and the mosunetuzumab test dose on C2D2; this mosunetuzumab schedule modification will be assessed if pre-phase corticosteroid treatment does not sufficiently mitigate toxicities associated with *step-up* mosunetuzumab administration on C1D1 and C1D8. Delayed mosunetuzumab dosing may be assessed with pre-phase corticosteroid if this intervention provided some benefit in mitigating toxicities based on review of the safety data by the IMC, study investigators, and Sponsor study team.

All data and decisions regarding dosing and/or scheduling will be reviewed by the IMC (refer to the protocol).

Phase II: Safety Cohort and Randomized Dose Expansion in DLBCL

*Group C: Safety Cohort of Mosunetuzumab plus* CHOP *in Previously Untreated DLBCL*

Prior to opening enrollment into the Group C safety cohort, the IMC will review the clinical data for all patients enrolled in Group A, including at least 3 patients treated at the mosunetuzumab RP2D_A plus CHOP who have received a minimum of 1 cycle of study treatment.

This safety cohort will be opened for patient enrollment prior to starting the randomized Phase II expansion cohorts to initially assess and confirm the safety of M-CHOP in patients with previously untreated DLBCL, where there exists the potential for a differential safety profile between first and subsequent lines of treatment. Mosunetuzumab at the RP2D_A plus CHOP will be tested in at least 10 and up to 40 patients with previously untreated DLBCL. The IMC will review safety data from the first 6 patients in order to confirm the recommended dose for the randomized Phase II portion of the study.

If the combination of mosunetuzumab RP2D_A plus CHOP is not tolerated in patients with previously untreated DLBCL, then alternative mosunetuzumab doses and/or regimens may be assessed based on a review of the totality of the available data by the IMC. If toxicities (Grade ≥3 and/or adverse events that would meet DLT criteria in dose-finding cohorts) are observed after the C1D15 mosunetuzumab dose, this may include testing lower C1D15 mosunetuzumab doses. If, on the other hand, such adverse events are observed after either the first (1 mg) or second (2 mg) mosunetuzumab dose, corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1, and/or delaying the first dose of mosunetuzumab by 1 week in Cycle 1 of CHOP (maintaining the *step-up dosing*, starting mosunetuzumab 1 mg on C1D8, then 2 mg on C1D15, and RP2D_A on C2D1) will be considered.

The iDMC will review safety data from the first 10 Group C patients who have received at least 2 cycles of study treatment at the IMC-recommended Phase II dose prior to making recommendations for opening enrollment into the Phase II randomized dose expansion.

*Phase II Randomized Dose Expansion*

Upon demonstrating the safety and tolerability of the combination of M-CHP-pola (dose and schedule as determined in Phase Ib) and of M-CHOP in patients with previously untreated DLBCL in the aforementioned safety cohort, and following the iDMC recommendation, patients with previously untreated DLBCL will be randomized to receive one of the following three regimens:

- Arm 1: M-CHP-pola (n=40)
- Arm 2: R-CHP-pola (n=20)
- Arm 3: M-CHOP (n=up to 30)

The opening of Arms 1, 2, and 3 are dependent on iDMC review based on acceptable safety of M-CHOP in patients with previously untreated DLBCL, and safety of M-CHP-pola in previously treated B-cell NHL. A randomization ratio of 2:1:2 will be used until a total of up to approximately 40 patients have received M-CHOP, including Group C and Arm 3. Thereafter, a ratio of 2:1 will be used to enroll patients into the M-CHP-pola or R-CHP-pola arm.

*In the Phase II portion of the study, patients in Arm 1 will receive 6 cycles of M-CHP-pola at 21-day intervals. The first cycle of mosunetuzumab will be administered as step-up doses on C1D1 (1 mg), C1D8 (2 mg), and C1D15 (mosunetuzumab [RP2D_B]) in the first cohort). Full doses of mosunetuzumab (C1D15 dose) will be administered on Day 1 of subsequent cycles*

**Number of Patients**

Approximately 40–60 patients will be enrolled in the Phase Ib dose-finding portion of the study. Up to an additional 70–100 patients will be enrolled in the safety run-in and Phase II portion of the study, for a total of approximately 110–160 patients enrolled in the study.

**Target Population**

Inclusion Criteria

*Inclusion Criteria for Phase Ib and Phase II Portions*

Patients must meet the following criteria for study entry in the Phase Ib and Phase II portions:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Able to comply with the study protocol and procedures, in the investigator's judgment
- At least one bi-dimensionally measurable nodal lesion, defined as > 1.5 cm in its longest dimension, or one bi-dimensionally measurable extranodal lesion, defined as > 1.0 cm in its longest diameter
- Confirmed availability of archival or freshly collected tumor tissue before study enrollment
- Life expectancy of at least 24 weeks
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Left ventricular ejection fraction (LVEF) defined by multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO) within the institutional limits of normal
- Adequate hematologic function (unless inadequate function is due to underlying disease, as established by extensive bone marrow involvement, or is due to hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) defined as follows:
  - Hemoglobin ≥ 9 g/dL
  - ANC ≥ $1.5 \times 10^9$/L
  - Platelet count ≥ $75 \times 10^9$/L
- *Serum creatinine ≤ULN; or estimated creatinine clearance ≥50 mL/min by Cockroft-Gault method or other institutional standard methods, e.g. based on nuclear medicine renal scan*
- For women of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 3 months after the final dose of mosunetuzumab, 12 months after the final dose of polatuzumab vedotin, 12 months after the final dose of rituximab, 12 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 3 months after the final dose of tocilizumab, as applicable. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of 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.
- 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 60 days after the final dose of mosunetuzumab, *6 months* after the final dose of polatuzumab vedotin, 3 months after the final dose of rituximab, 6 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 60 days after the final dose of tocilizumab, as applicable, to avoid exposing the embryo. 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 post-ovulation methods) and withdrawal are not acceptable methods of contraception.

*Inclusion Criteria for Phase Ib Portion*

Patients must also meet the following criteria for study entry in the Phase Ib portion (Groups A and B):

- Histologically confirmed B-cell NHL according to WHO 2016 classification (pathology report must provide WHO 2016 diagnosis) expected to express the CD20 antigen, except:
  - Plasma cell malignancies (e.g., lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, plasmacytoma, plasmablastic lymphoma)
  - Primary DLBCL of the CNS
  - Burkitt lymphoma
- R/R B-cell NHL after at least one prior systemic lymphoma therapy
- Treatment with at least one prior CD20-directed therapy (e.g., rituximab, obinutuzumab, ofatumumab, ibritumomab tiuxetan)
- Group B only: no prior treatment with polatuzumab vedotin

*Inclusion Criteria for Phase II Portion*

Patients must also meet the following criteria for study entry in the Phase II portion:

- Previously untreated, histologically confirmed DLBCL according to WHO 2016 classification

  Patients with a diagnosis of primary mediastinal DLBCL are not eligible.

  Patients with a diagnosis of high-grade B-cell lymphoma (HGBL) with rearrangements of MYC and BCL2 and/or BCL6 or HGBL, not otherwise specified (NOS), are allowed.
- IPI score of 2–5
- Ability and willingness to comply with the study protocol procedures, including PRO measures

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 12 months after the final dose of polatuzumab vedotin, 12 months after the final dose of rituximab, 12 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 3 months after the final dose of tocilizumab, as applicable.

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Prior treatment with mosunetuzumab
- Prior allogeneic stem-cell transplant
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to receive full dose of any of the individual components of R-CHP
- Contraindication to receive full dose of vincristine if planned study treatment includes vincristine (e.g., CHOP)
- Current Grade >1 peripheral neuropathy
- Patients with history of confirmed progressive multifocal leukoencephalopathy (PML)
- Known or suspected chronic active Epstein Barr virus (CAEBV) infection

- 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.

- Acute or chronic hepatitis C virus (HCV) infection

  Patients who are positive for HCV antibody must be negative for HCV by PCR.

- HIV seropositivity
- Administration of a live, attenuated vaccine within 4 weeks before first study treatment administration or anticipation that such a live, attenuated vaccine will be required during the study
- Prior solid organ transplantation
- *Known or suspected history of hemophagocytic lymphohistiocytosis*
- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with a history of disease-related immune thrombocytopenic purpura, autoimmune hemolytic anemia, *or other stable autoimmune diseases* may be eligible after review and approval by the Medical Monitor.

- Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) with the exception of pre-phase treatment with prednisone up to 100 mg daily for 7 days (or equivalent corticosteroid dose) prior to C1D1

  The use of inhaled corticosteroids is permitted.

  The use of mineralocorticoids for management of orthostatic hypotension is permitted.

  The use of physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.

- Current or past history of CNS lymphoma
- Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease

  Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits as judged by the investigator are allowed.

  Patients with a history of epilepsy who have had no seizures in the past 2 years while not receiving any anti-epileptic medications are allowed in the expansion cohorts only.

- Prior radiotherapy to the mediastinal/pericardial region
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.

  Patients with a malignancy that has been treated with curative intent will also be excluded unless the malignancy has been in documented remission without treatment for ≥ 2 *years* before enrollment.

- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, congestive heart failure, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks before C1D1
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Recent major surgery within 4 weeks before the start of C1D1, other than superficial lymph node biopsies for diagnosis
- Any of the following abnormal laboratory values within 14 days of initiation of study treatment:
  - AST or ALT > 2.5 × ULN
  - Total bilirubin ≥1.5 × ULN
  - INR >1.5 × ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT >1.5 × ULN in the absence of a lupus anticoagulant
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's or Medical Monitor's judgment, precludes the patient's safe participation in and completion of the study, or which could affect compliance with the protocol or interpretation of results

*Exclusion Criteria for Phase Ib Portion*

Patients who also meet any of the following criteria will be excluded from study entry in the Phase Ib portion:

- Prior treatment with > 250 mg/m$^2$ doxorubicin (or equivalent anthracycline dose)

  During the study, patients may not exceed a maximum cumulative lifetime dose of 550 mg/m$^2$ anthracyclines (i.e., doxorubicin), which includes treatment on this study.
- Prior treatment with chemotherapy, immunotherapy, and biologic therapy 4 weeks prior to C1D1

  A shorter interval may be acceptable for patients on oral targeted therapies upon discussion with the Medical Monitor.
- Prior treatment with radiotherapy within 2 weeks prior to C1D1

  If patients have received radiotherapy within 4 weeks prior to the initiation of study treatment, patients must have at least one measurable lesion outside of the radiation field.

  Patients who have only one measurable lesion that was previously irradiated but subsequently progressed are eligible.
- Adverse events from prior anti-cancer therapy resolved to ≤ Grade 1 (with the exception of alopecia and anorexia)

*Exclusion Criteria for Phase II Portion*

Patients who also meet any of the following criteria will be excluded from study entry in the Phase II portion:

- Patients with transformed lymphoma
- Prior therapy for B-cell NHL

**End of Study**

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur approximately 30 months after the last patient is enrolled to allow all patients to have up to 2.5 years of follow up.

**Length of Study**

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 60 months.

**Investigational Medicinal Products**

**Test Product (Investigational Drug)**

The investigational medicinal products (IMPs) for this study are mosunetuzumab, polatuzumab vedotin, rituximab, and tocilizumab.

Mosunetuzumab will be administered intravenously. In Cycle 1, patients will receive mosunetuzumab 1 mg on Day 1, 2 mg on Day 8, and the test dose on Day 15 (13.5 mg in the first Phase Ib cohort and then to be determined based on dose-escalation or de-escalation rules), with the Day 15 dose given on Day 1 of subsequent cycles of treatment. Patients with SD or PR at the end of the 6 cycles of treatment (i.e., primary response assessment) may continue mosunetuzumab as monotherapy at the Day 15 test dose for up to 11 additional cycles on Day 1 of each 21-day cycle.

Polatuzumab vedotin will be administered intravenously at a dose of 1.8 mg/kg on Day 1 of each 21-day cycle. The total dose of polatuzumab vedotin for each patient will depend on the patient's weight on Day 1 of each cycle (or within 72 hours prior to Day 1 of that cycle).

Rituximab will be administered intravenously at a dose of 375 mg/m$^2$ on Day 1 of each 21-day cycle.

Tocilizumab should be administered when necessary as described in the protocol for management of infusion-related reactions and cytokine release syndrome.

**Non-Investigational Medicinal Products**

Prednisone, cyclophosphamide, vincristine, and doxorubicin can be considered standard of care in the treatment of patients with B-cell NHL included in this study.

In patients with previously untreated DLBCL or patients considered to be at high risk for tumor lysis syndrome or acute toxicity with the first cycle of study treatment, a pre-phase treatment of prednisone at a dose of up to 100 mg PO every day for up to 7 days prior to C1D1 is permitted, at the discretion of the investigator. CHP and CHOP chemotherapy will be administered as described in the protocol.

**Statistical Methods**

**Primary Analysis**

PET-CT CR at the primary response assessment (6–8 weeks after C6D1 or last dose of study medication if study treatment is discontinued prior to Cycle 6) by IRC review will be used as the primary efficacy endpoint. Patients with missing or no response assessments will be classified as non-complete responders. The CR rate, defined as the percentage of patients with CR, will be estimated and the corresponding Clopper-Pearson exact 95% CI will be constructed for each treatment arm. The difference in CR rates between the combination of M-CHP-pola and R-CHP-pola arms will be estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution. An exploratory comparison of CR rates between the M-CHP-pola and R-CHP-pola arms will be conducted using the Cochran Mantel Haenszel Chi-square test adjusted for randomization stratification factors.

Response assessment is determined using the Lugano Response Criteria.

**Determination of Sample Size**

The sample size of the study is mainly driven by the Phase II portion, which focuses on the estimation of treatment effect using CR rate based on PET-CT. With 40 patients (M-CHP-pola in Arm 1, or M-CHOP in Group C and Arm 3 combined), the 95% CI exact Clopper-Pearson (Clopper and Pearson 1934) CIs for estimation of the true CR rate would have a margin of error not exceeding ±17%. With 40 patients and an observed CR rate of at least 60%, a true CR rate below 43% can be ruled out with 95% confidence. With 20 patients and an observed CR rate of at least 60%, a true CR rate below 36% can be ruled out with 95% confidence. In addition, with 40 patients in the M-CHP-pola arm (Arm 1) and 20 patients in the R-CHP-pola arm (Arm 2), observing a 75% (15 out of 20) CR rate in the R-CHP-pola arm and a 10% increase in CR rate of 85% (34 out of 40) in the M-CHP-pola arm, the 95% CI for the difference in CR rates is (–16%, 36%).

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ABC | activated B-cell–like |
| acMMAE | antibody-conjugated monomethyl auristatin E |
| ADA | anti-drug antibody |
| ADC | antibody-drug conjugate |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| AUC | area under the concentration–time curve |
| BiTE | bispecific T-cell engager |
| BR | bendamustine and rituximab |
| BSA | body surface area |
| C#D# | Cycle #, Day # (e.g., e.g., C1D1 is Cycle 1, Day 1) |
| CAEBV | chronic active Epstein Barr virus |
| CAR | chimeric antigen receptor |
| CCNAE | cognition or consciousness neurologic events |
| CHOP(-21) | cyclophosphamide, doxorubicin, vincristine, and prednisone (given in 21-day intervals) |
| CHP | cyclophosphamide, doxorubicin, and prednisone |
| CLL | chronic lymphocytic leukemia |
| $C_{max}$ | maximum serum concentration |
| $C_{min}$ | minimum serum concentration |
| CMV | cytomegalovirus |
| CR | complete response |
| CRS | cytokine release syndrome |
| CT | computed tomography (scan) |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating-tumor DNA |
| DEL | double-expressor lymphoma |
| DHL | double-hit lymphoma |
| DI-CCNAE | driving-impacting cognition or consciousness neurologic events |
| DILI | drug-induced liver injury |
| DLBCL | diffuse large B-cell lymphoma |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| EBV | Epstein-Barr virus |

| Abbreviation | Definition |
|---|---|
| EC | Ethics Committee |
| ECHO | echocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EFS | event-free survival |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire |
| EQ-5D-5L | EuroQol 5-Dimension, 5-Level Questionnaire |
| ESMO | European Society for Medical Oncology |
| FACT/GOG-NTX | Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity |
| FACT-Lym | Functional Assessment of Cancer Therapy–Lymphoma (subscale) |
| Fc | fragment crystallizable |
| FDA | Food and Drug Administration |
| FDG | fluorodeoxyglucose |
| FL | follicular lymphoma |
| GCB | germinal center B-cell–like |
| G-CSF | granulocyte colony-stimulating factor |
| GHS | global health status |
| GMR | geometric mean ratio |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HLH | hemophagocytic lymphohistiocytosis |
| HRQoL | health-related quality of life |
| ICH | International Council for Harmonisation |
| iDMC | Independent Data *Monitoring* Committee |
| IFN-γ | interferon-γ |
| IL-2 (-6, -10) | interleukin-2 (-6, -10) |
| IMC | Internal Monitoring Committee |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IPI | International Prognostic Index |

| Abbreviation | Definition |
|---|---|
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |
| IRR | infusion-related reaction |
| IxRS | interactive voice or web-based response system |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LVEF | left ventricular ejection fraction |
| M-CHOP | mosunetuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone |
| M-CHP-pola | mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin |
| MAD | maximum administered dose |
| MAS | macrophage activation syndrome |
| MCL | mantle cell lymphoma |
| MMAE | mono-methyl auristatin E |
| MRD | minimal residual disease |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| MUGA | multiple-gated acquisition (scan) |
| NALT | new anti-lymphoma therapy |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NCI CTCAE v5.0 | National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 |
| NGS | next-generation sequencing |
| NHL | non-Hodgkin lymphoma |
| NK | natural killer (cell) |
| NOS | not otherwise specified |
| ORR | objective response rate |
| OS | overall survival |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PD | pharmacodynamic |
| PET | positron emission tomography (scan) |
| PET-CT | positron emission tomography–computed tomography (scan) |
| PFS | progression-free survival |

| Abbreviation | Definition |
|---|---|
| PK | pharmacokinetic |
| PML | progressive multifocal leukoencephalopathy |
| PO | orally, by mouth |
| PR | partial response |
| PRO | patient-reported outcome |
| Q3W | every 3 weeks |
| QoL | quality of life |
| R | rituximab |
| RBR | Research Biosample Repository |
| R-CHOP (-21, -14) | rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (given in 21-day intervals, given in 14-day intervals) |
| R-CHP | rituximab plus cyclophosphamide, doxorubicin, and prednisone |
| R-CHP-pola | rituximab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin |
| RDI | relative dose intensity |
| RP2D | recommended Phase II dose |
| RP2D_A | RP2D of mosunetuzumab in combination with CHOP |
| RP2D_B | RP2D of mosunetuzumab in combination with CHP-polatuzumab vedotin |
| SD | stable disease |
| SOC | standard of care |
| TK | toxicokinetic |
| TLS | tumor lysis syndrome |
| TNF-α | tumor necrosis factor–α |
| ULN | upper limit of normal |
| WES | whole exome sequencing |
| WGS | whole genome sequencing |

# 1. BACKGROUND

## 1.1 BACKGROUND ON B-CELL MALIGNANCIES

Malignancies of B-cells include lymphomas and leukemias. Lymphomas of B-cell origin constitute a diverse set of neoplasms within the larger context of non-Hodgkin lymphoma (NHL). In the United States, B-cell lymphomas constitute approximately 80%–85% of all cases of NHL. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, accounting for approximately 30%–40% of all NHL diagnoses, followed by follicular lymphoma (FL; 20%–25% of all NHL diagnoses) and mantle cell lymphoma (MCL; 6%–10% of all NHL diagnoses). B-cell chronic lymphocytic leukemia (CLL) is the most common leukemia in adults, with approximately 20,000 new cases per year in the United States (American Cancer Society 2018).

The biologic heterogeneity of B-cell malignancies is reflected in the clinical course and outcome of individual diseases. Indolent diseases such as FL and CLL evolve slowly, with a median survival of 8–10 years. In contrast, more aggressive diseases such as DLBCL and MCL, if left untreated, have a median survival of 6 months.

Regardless of the biologic and clinical heterogeneity of B-cell lymphomas, patients with advanced stage B-cell malignancies are typically initially treated with intensive cytotoxic chemotherapy combined with monoclonal antibodies, such as the anti-CD20 monoclonal antibody rituximab (Rituxan®, MabThera®). Although durable responses can be achieved in some patients, the majority of patients will ultimately experience progressive or relapsed disease. Indolent B-cell malignancies including FL and CLL, as well as approximately half of all aggressive lymphomas, remain incurable despite advances in immunochemotherapy that have resulted in longer progression-free survival (PFS) (Coiffier et al. 2002; Feugier et al. 2005; Hiddemann et al. 2005; Vidal et al. 2012). Moreover, as NHL is frequently diagnosed in older patients, the ability to tolerate cytotoxic chemotherapy is a major barrier to treatment success. Consequently, there remains a need for novel treatments that can significantly extend disease-free survival and overall survival (OS), while providing at least acceptable, if not superior, safety and tolerability.

Recent developments have supported the effectiveness of therapies that utilize T cells in the treatment of B-cell malignancies. One approach involves the ex vivo manipulation of autologous or allogeneic T cells to express chimeric antigen receptors (CARs) that target lineage-specific surface molecules such as CD19. Anti-CD19 CAR-expressing T cells produced deep and durable responses in patients with relapsed or refractory (R/R) leukemias (Kochenderfer et al. 2012; Grupp et al. 2013). However, toxicities related to severe cytokine release syndrome (CRS), optimization of dose and schedule, and scalability of production to the broader cancer population constitute significant barriers to their clinical development. A second approach of T-cell–directed therapy involves the use of bispecific molecules that directly engage endogenous T cells with tumor cells. In hematologic malignancies, this approach has been demonstrated by the bispecific

T-cell engager molecule, blinatumomab (Bargou et al. 2008), a 55-kDa fusion protein derived from two single-chain peptides recognizing CD19 and CD3. The mechanism of action of blinatumomab is the redirected lysis of $CD19^+$ B cells by T cells. Evidence of potent clinical activity of blinatumomab in B-cell malignancies has been reported in patients with R/R NHL and leukemia (Bargou et al. 2008; Viardot et al. 2010, 2011). However, due to its size and structure, blinatumomab has a half-life of approximately 2 hours in humans, necessitating its administration by continuous infusion over a 4–8 week period (Nagorsen et al. 2012).

### 1.1.1 Background on Diffuse Large B-Cell Lymphomas

DLBCL, the most common histologic subtype of NHL, accounts for approximately 30% of NHL cases and is classified as an aggressive NHL (Armitage and Weisenburger 1998). Patients with DLBCL present with rapidly enlarging masses, often with local and systemic symptoms of fever, recurrent night sweats, and/or weight loss. Approximately 45%–60% of patients present with advanced-stage disease (Ann Arbor Stage III or IV). The incidence of DLBCL increases with age, with a median age of 64 years at presentation (Armitage and Weisenburger 1998). If left untreated, patients with DLBCL have a median survival of approximately 6 months.

DLBCL has distinct morphologic, immunophenotypic, and genetic features. Morphologically, the disease is characterized by complete or partial effacement of the nodal architecture by sheets of large atypical lymphoid cells. Immunophenotypically, the disease is characterized by the expression of pan B-cell antigens (CD19, CD20, CD22, CD79a, and CD79b) and surface and/or cytoplasmic immunoglobulin expression (Doggett et al. 1984; Dornan et al. 2009). Distinct genetic features have further subclassified DLBCL to reveal complex molecular patterns and distinct signaling mechanisms. Although there is no single somatic genetic change that defines the disease, the majority of cases have alterations in the immunoglobulin heavy gene (Klein et al. 1998). The most frequently dysregulated genes include *BCL6* (rearrangement in 35%–40%; mutation in 5' noncoding region in 70%), *BCL2* (translocation 15%, amplification 24%), and *MYC* (5%–15%) (Skinnider et al. 1999; Pasqualucci and Dalla-Favera 2015; Jamil and Mehta 2016). The negative prognostic impact of double hit (dual translocations in *BCL2* or *BCL6* and *MYC*, double-hit lymphoma [DHL]) and dual expressors (overexpression of *BCL2* and *MYC*, double-expressor lymphoma [DEL]) defines specific DLBCL subgroups with particularly poor outcomes using standard-of-care (SOC) therapies. Moreover, gene expression profiling has revealed more than two distinct molecular subsets of patients with DLBCL that further subtype the disease by cell of origin into germinal center B-cell–like (GCB; 55%–60%) and activated B-cell–like (ABC; 30%–35%) subgroups (10%–15% remain unclassified). Within cell-of-origin classification of DLBCL, the ABC subgroup has a poorer prognosis (Scott et al. 2015), and current strategies to improve outcome in ABC/non-GCB DLBCL include adding novel agents such as lenalidomide, ibrutinib, and

bortezomib to SOC therapy. Phase III studies that incorporate these agents are ongoing in patients with previously untreated DLBCL, and results have not yet been reported.

The International Prognostic Index (IPI) for aggressive NHL identifies five factors obtained at diagnosis used to stratify prognosis and OS. Patients with higher IPI scores, combined with biologically defined higher-risk patients (including the ABC subtype, DHL, and DEL DLBCL), represent the subset of patients with the poorest outcomes with current therapies. Several revisions to the IPI have been proposed including the revised-IPI (Sehn et al. 2007) and National Comprehensive Cancer Network (NCCN)-IPI (Zhou et al. 2014), which have helped to validate the IPI even after the addition of rituximab. While these newer classification systems have the potential to refine the prognostic ability of IPI, they have yet to be fully established in large prospective trials.

The SOC therapy for DLBCL involves multi-agent chemotherapy with complementary mechanisms of action combined with immunotherapy. Up to 8 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) given in 21-day intervals (R-CHOP-21) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like chemotherapy is considered to be the SOC therapy for patients with previously untreated DLBCL. Radiotherapy to limited stage, bulky, and extranodal diseases may also be considered in these patient populations (Tilly et al. 2015; Zelenetz et al. 2016). The basis for this recommendation originates from multiple randomized Phase III studies comparing CHOP to R-CHOP. One of these studies is the Groupe d'Étude des Lymphomes de l'Adulte LNH-98.5 study (BO16368), which demonstrated that the addition of rituximab (R) to CHOP given in 21-day intervals (CHOP-21), or R-CHOP-21, improved PFS and OS in patients 60–80 years of age (Coiffier et al. 2002). The most recent update of this study demonstrated that 10-year follow-up continued to demonstrate benefit of R-CHOP-21 compared with CHOP-21 in PFS (36.5% vs. 20%) and OS (43.5% vs. 28%) (Coiffier et al. 2010). In patients younger than 60 years of age, the MabThera International Trial compared the addition of R to CHOP or CHOP-like therapy (Pfreundschuh et al. 2006). More patients assigned to the R-containing regimens compared with chemotherapy alone achieved complete response (CR) or unconfirmed CR at the completion of therapy (86% vs. 68%); this difference was persistent, with 3-year PFS of 85% for R-containing regimens and 68% with chemotherapy alone. Among patients with low-risk disease, the 3-year event-free survival (EFS) is in the 90% range (Tilly et al. 2015). However, among patients with advanced-stage and/or poor molecular disease features, less than half of these patients are cured with the current SOC therapy. For example, patients with IPI 3–5 have a 5-year PFS ranging from 39% to 54% (Zhou et al. 2014).

Approaches to improve SOC therapies have largely been unsuccessful, including attempts at maximizing dose density with R-CHOP given in 14-day intervals (R-CHOP-14) (Pfreundschuh et al. 2008; Cunningham et al. 2013; Delarue et al. 2013). Younger (age 18–59 years) non-GCB patients did have improved PFS and OS with rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone

followed by consolidation, though this regimen's toxicity may restrict its use in older patients (Récher et al. 2011). Recent large, randomized, Phase III studies in DLBCL including BO21005/GOYA (Vitolo et al. 2016), DA-EPOCH-R (Wilson et al. 2016), and REMARC (Thieblemont et al. 2016) did not demonstrate clinically meaningful benefit in previously untreated DLBCL for the experimental therapies being tested, reflecting a continued need to improve upon the SOC therapy.

An ongoing effort to improve on the SOC in previously untreated DLBCL involves the replacement of vincristine in R-CHOP with the antibody-drug conjugate (ADC) polatuzumab vedotin in Study GO39942/POLARIX (see Section 1.3 for additional details).

While R-CHOP-21 remains the SOC therapy in previously untreated DLBCL, one variable that is important to maintain is dose intensity. The European Society for Medical Oncology (ESMO) guidelines (Tilly et al. 2015) recommend that dose reductions due to hematological toxicity be avoided whenever possible (IDSA-USPS Evidence Level 1, A). The correlation of dose intensity to outcomes in DLBCL has been recognized in numerous studies. Kwak et al. (1990) incorporated a model of dose intensity and found that patients who received more than 75% of the planned doxorubicin dose over the first 12 weeks of therapy had improved survival compared with those patients who received 75% or less. Additional studies have recognized the importance of cyclophosphamide and doxorubicin and, in some cases, the entire CHOP regimen (Yamaguchi et al. 2011). Dose intensity studies have also estimated the effect of microtubule inhibitors (Utsu et al. 2016). This study found that patients who received >85% relative dose intensity (RDI) of cyclophosphamide, doxorubicin, and vincristine had significantly higher OS compared with patients who received >85% RDI of cyclophosphamide and doxorubicin but <85% RDI of vincristine, suggesting that vincristine dose delivery is also critical to better outcomes in DLBCL. This understanding that dose intensity is an important variable in previously untreated DLBCL outcomes underscores the need to provide optimal dosing of all components of treatment, including that of investigational agents.

For patients who are not cured by initial chemoimmunotherapy, high-dose chemotherapy followed by autologous stem-cell transplantation offers a second chance for cure. However, approximately half of these patients will not respond to subsequent therapy because of refractory disease (Gisselbrecht et al. 2010), and a significant number of patients are ineligible for this aggressive therapy because of age or comorbidities. Performance status is also a factor in novel approaches to R/R disease, such as autologous CD19 CAR T-cell therapy (Kochenderfer et al. 2015), as time required for cellular processing and treatment-related toxicities may restrict the population that can benefit from these newer therapeutics. Patients who either relapse after or are ineligible for stem-cell transplantation because of refractory disease or frailty have poor outcomes. Responses to subsequent therapies range from 10% to 35% in most cases (Seyfarth et al. 2006), with only occasional durable responses. The fact that most

patients who are not cured by the standard first-line R-CHOP or comparable chemoimmunotherapy will die of lymphoma underscores the need for novel approaches in upfront and subsequent lines of therapy for this aggressive disease.

## 1.2 BACKGROUND ON MOSUNETUZUMAB

Mosunetuzumab (RO7030816; BTCT4465A), is a full length, humanized anti-CD20/CD3 T-cell–dependent bispecific antibody of an IgG1 isotype that is produced using the knobs-into-holes technology (Atwell et al. 1997; Spiess et al. 2013). One Fab region of the antibody is directed against the extracellular domain of the CD3ε subunit of the T-cell receptor complex, and the other Fab region is directed against the extracellular domain of CD20 (Atwell et al. 1997; Spiess et al. 2013). Mosunetuzumab contains the N297G amino acid substitution in the fragment crystallizable (Fc) region according to Eu numbering (Edelman et al. 1969; Kabat et al. 1991). This substitution results in a non-glycosylated heavy chain that has minimal binding to Fcγ receptors and, consequently, prevents Fc effector functions. Mosunetuzumab is derived from Chinese hamster ovary cells.

As a T-cell–recruiting bispecific antibody targeting CD20-expressing B cells, mosunetuzumab is a conditional agonist; target B-cell killing is observed only upon simultaneous binding to CD20 on B cells and CD3 on T cells. Engagement of both arms of mosunetuzumab results in the formation of an immunologic synapse between a target B cell and a cytotoxic T cell resulting in T-cell activation in a target- and dose-dependent manner. T-cell activation is manifested by the expression of activation-related surface markers (e.g., CD69 and CD25), transient release of cytokines (e.g., interferon-γ [IFN-γ], tumor necrosis factor-α [TNF-α], interleukin [IL]-2, -6, and -10), and robust T-cell proliferation. Subsequent directed release of perforin and a cocktail of granzymes from T cells through the immunologic synapse result in B-cell lysis.

The near ubiquitous CD20 expression in DLBCL and validation of CD20 as a therapeutic target in its treatment (SOC R-CHOP-21) provide a rationale for the development of a T-cell–recruiting bispecific antibody targeting CD20, such as mosunetuzumab, for DLBCL (and other CD20-expressing B-cell NHLs). This study will investigate the combination of mosunetuzumab plus CHOP (M-CHOP) and mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone and polatuzumab vedotin (M-CHP-pola), with the goal of informing potential future development of mosunetuzumab that is likely to incorporate combinations with existing and/or novel agents. The combination of mosunetuzumab with rituximab plus CHOP is unlikely to be beneficial due to both antibodies targeting and competing for the same binding site, CD20, on B-cells with subsequent killing of CD20-expressing B cells.

### 1.2.1 Nonclinical Studies with Mosunetuzumab

Comprehensive pharmacologic, pharmacokinetic/toxicokinetic (PK/TK), pharmacodynamic (PD), and toxicology studies were conducted to support the entry of

mosunetuzumab into clinical trials and continued clinical development. In vitro studies with human peripheral blood mononuclear cells (PBMCs) and B-cell lymphoma cell lines and in vivo studies in cynomolgus monkeys support the mechanism of action of mosunetuzumab-induced T-cell activation, cytokine release, and proliferation in the presence of CD20-positive target B cells with subsequent killing of target cells. Single-dose and repeat-dose (up to 26-week) toxicity, PK/TK, and PD studies with mosunetuzumab following IV and/or SC administration in cynomolgus monkeys have been completed. The nonclinical PK behavior observed for mosunetuzumab is consistent with that expected for a humanized IgG1 monoclonal antibody with a component of target-mediated clearance. The acute toxicities associated with mosunetuzumab treatment are largely driven by stimulation of T cells, as evidenced by PD changes in cytokine levels and activated T-cell numbers. In repeat-dose toxicity studies in cynomolgus monkeys, the increase of cytokine levels, T-cell activation, and acute postdose observations were primarily limited to the first dose and were reduced or negligible following subsequent doses. Therefore, clinical strategies to control the extent of T-cell stimulation through alternative dose schedules or other prophylactic measures (such as pretreatment with corticosteroids) may be necessary to optimize the benefit–risk profile of mosunetuzumab when administered as a single agent and in combination with other anti-lymphoma agents where the combinatorial safety profile is currently not known.

Refer to the Mosunetuzumab Investigator's Brochure for details on nonclinical studies.

### 1.2.2 Clinical *Studies* with Mosunetuzumab

*In addition to Study GO40515, mosunetuzumab is being investigated in four ongoing open-label clinical studies: GO29781, GO40516, GO40554, and JO40295. Study GO29781 is a Phase I/Ib, dose-escalation trial evaluating mosunetuzumab as a single agent or combined with atezolizumab in patients with R/R B-cell NHL and CLL. Study GO40516 is a Phase Ib/II trial evaluating mosunetuzumab combined with polatuzumab vedotin in patients with B-cell NHL. Study GO40554 is a Phase I/II trial evaluating mosunetuzumab in patients with DLBCL who had a best response of partial response (PR) to first-line immunochemotherapy or patients with previously untreated DLBCL who were unable to tolerate full-dose, first-line immunochemotherapy. Study JO40295 is a Phase I dose-escalation trial evaluating mosunetuzumab in patients with R/R B-cell NHL.*

*Safety data are currently available from 500 patients treated with mosunetuzumab (data cutoff dates ranging from December 2019 to February 2020, as outlined in the Mosunetuzumab Investigator's Brochure). CRS and neutropenia are identified risks for mosunetuzumab. Infusion reactions, hemophagocytic lymphohistiocytosis (HLH), neurotoxicity, tumor lysis syndrome (TLS), infections, thrombocytopenia, elevated liver enzymes are potential risks that have been observed to date in clinical studies. Patients* experiencing CRS *have* exhibited a trend toward higher peak levels of IL-6 during the

first cycle. The IL-6 response and current safety profile of mosunetuzumab suggest that higher doses of mosunetuzumab may be more tolerable and potentially more efficacious when administered using the *step-up* dosing scheme.

*As of January 2020, efficacy data are available from 415 efficacy-evaluable patients in Study GO29781. Of these patients, 110 patients (27%) had a complete response (CR), 76 patients (18%) had a PR, 52 patients (13%) had stable disease and 160 patients (39%) had progressive disease as the best overall response.*

On the basis of available clinical PK data following Cycle 1 *flat* dosing and Cycle 1 *step-up* dosing in Study GO29781, mosunetuzumab serum drug concentrations *reached* maximum serum concentration ($C_{max}$) at the end of infusion (approximately 4 hours) and *declined* in a multi-phasic fashion. The apparent half-life estimates following *flat dosing ranged from 6 to 11 days. The* geometric mean apparent clearance *ranged* from 746–1602 mL/day following the 0.2 to 2.8 mg Cycle 1 *flat* dosing. Preliminary data indicate that the Cycle 1 area under the concentration–time curve (AUC) and $C_{max}$ of mosunetuzumab increased in an approximately dose-proportional manner over the dose range tested. Moderate PK variability was observed.

*As of 21 January 2020, 352 mosunetuzumab treated patients in study GO29781 were analyzed for anti-drug antibodies (ADAs) and 1 patient (0.3%) tested positive for ADAs against mosunetuzumab. This patient completed eight cycles of mosunetuzumab SC treatment, and was then treated with mosunetuzumab in combination with atezolizumab for an additional 13 cycles. The patient tested negative for antibodies to atezolizumab. The presence of ADAs to mosunetuzumab had no apparent impact on drug exposure and safety.*

Refer to the Mosunetuzumab Investigator's Brochure for additional details on clinical study results.

## 1.3 BACKGROUND ON POLATUZUMAB VEDOTIN

CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B-cell derived malignancies, including nearly all NHL and CLL (Dornan et al. 2009). Relating specifically to DLBCL, CD79b is expressed in essentially all tumor cells (Olejniczak et al. 2006; Pfeifer et al. 2015), enabling its use in all subtypes of DLBCL independent of dominant signaling pathways. Antibodies bound to CD79b are rapidly internalized, which makes CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007, 2009).

Polatuzumab vedotin (*DCDS4501S*) is an ADC that contains a humanized IgG1 anti-human CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent, monomethyl auristatin E (MMAE), linked through a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl.

MMAE has a mode of action that is similar to that of all vinca-alkaloids, including vincristine, which is a component of standard chemotherapy (e.g., R-CHOP used for treatment of lymphoma). Following binding at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released following cleavage of the linker by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth (Doronina et al. 2003). This therapeutic approach takes advantage of the specific targeting capability of the antibody, the cytotoxic activity of MMAE, and the increased potency of MMAE compared with vincristine. It is hypothesized that polatuzumab vedotin in combination with other novel agents will provide enhanced efficacy and safety to patients with NHL.

*Polatuzumab* vedotin has been approved in *some countries in* combination with bendamustine and a rituximab for the treatment of adult patients with R/R DLBCL. Refer to the local prescribing information for additional background information.

Refer to the Polatuzumab Vedotin Investigator's Brochure for details on nonclinical and clinical studies.

## 1.4 BACKGROUND ON RITUXIMAB

For general background on rituximab, please refer to the local prescribing information. For background on the combination of rituximab with a polatuzumab vedotin–containing regimen, please refer to the Polatuzumab Vedotin Investigator's Brochure.

## 1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Although durable responses can be achieved in some patients with B-cell malignancies, the majority of patients will ultimately experience progressive or relapsed disease (refer to Section 1.1). Treatments for R/R B-cell lymphomas include immunochemotherapies similar to those used in the first-line setting, including CHOP based chemotherapy with CD20 targeting monoclonal antibodies such as rituximab (NCCN 2018). There remains a critical need to develop novel treatments to improve outcomes for both patients with R/R B-cell NHL, as well as patients with previously untreated aggressive B-cell lymphomas, such as DLBCL. Patients with R/R B-cell NHL who are eligible to receive CHOP chemotherapy will be enrolled in the Phase Ib portion of this study. The Phase II portion will enroll patients with previously untreated DLBCL.

R-CHOP-21 remains the SOC therapy in previously untreated DLBCL; however, a substantial number of patients develop R/R disease after R-CHOP. The patient population that is least likely to be cured by SOC therapy may be identified using various methods including clinical prognostic scores, such as the IPI, or molecularly defined higher-risk groups, such as ABC, DEL, or DHL. Strategies that have so far been unable to demonstrate meaningful benefit over R-CHOP-21 include dose density with R-CHOP-14; dose intensity maximization with DA-EPOCH-R (dose-adjusted etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin + rituximab);

substitution strategies, such as the novel anti-CD20 monoclonal antibody obinutuzumab; additive agents in addition to R-CHOP, such as bevacizumab and lenalidomide; and maintenance strategies after R-CHOP with lenalidomide, everolimus, and enzastaurin.

Polatuzumab vedotin, an ADC that delivers the microtubule inhibitor MMAE in a targeted fashion to cells expressing CD79b, is being evaluated in previously untreated DLBCL as a replacement strategy for the microtubule inhibitor in R-CHOP, vincristine, in a randomized, double-blind, placebo-controlled study (GO39942/POLARIX). CD79b is a cell surface antigen that is expressed ubiquitously on DLBCL tumor cells, as well as on other mature B cells (Olejniczak et al. 2006; Pfeifer et al. 2015). The expression pattern of this surface antigen enables the application of polatuzumab vedotin in all DLBCL subtypes (Pfeifer et al. 2015). The use of a replacement strategy enables continuation of the dosing regimen of R-CHP every 21 days. Data from Study GO29044 suggest that replacement of vincristine with polatuzumab vedotin may provide greater clinical benefit in patients newly diagnosed with DLBCL (*refer to the Polatuzumab Vedotin Investigator Brochure).*

Mosunetuzumab, a CD20/CD3 T-cell dependent bispecific antibody, is currently being assessed in Study GO29781 as a single agent and in combination with atezolizumab. The replacement of rituximab with mosunetuzumab in combination with CHP-pola (or CHOP) has the potential to improve outcomes for patients with DLBCL through a novel mechanism of action whereby T cells are directly recruited to CD20-expressing lymphoma cells. Through this distinct and potent mechanism of action, mosunetuzumab has the potential of replacing rituximab as the CD20-directed therapy in this setting. Preliminary clinical data from the ongoing Study GO29781 in patients with R/R DLBCL and FL have demonstrated acceptable safety with durable CRs from single-agent mosunetuzumab treatment being observed in some patients (refer to the Mosunetuzumab Investigator's Brochure for additional details). An important question to be addressed in Study GO40515 is the safety and efficacy of incorporating mosunetuzumab in the treatment of patients with previously untreated DLBCL.

This is the first clinical evaluation of the combination of mosunetuzumab with CHOP or CHP-pola. The non-overlapping mechanisms of action of mosunetuzumab and CHOP or CHP plus polatuzumab vedotin, and available nonclinical and clinical data, provide a strong rationale for investigating the potential benefit of these combinations in patients with B-cell NHL. No nonclinical safety studies have been conducted with mosunetuzumab combined with polatuzumab vedotin and/or CHOP/CHP. Potential overlapping toxicities between mosunetuzumab and CHOP or CHP-pola based on clinical and nonclinical safety/toxicity profiles of these agents known to date include infusion-related reactions (IRRs), neutropenia and infections, thrombocytopenia, tumor lysis syndrome (TLS), peripheral neuropathy, and hepatotoxicity. These potential toxicities are considered to be monitorable, manageable, and reversible. In Study GO29781, most treatment-emergent adverse events, including CRS, occurred after the first dose of mosunetuzumab treatment with the highest frequency observed within the

first week of the first treatment cycle. Consequently, specific safety monitoring and mitigation measures, including mandatory hospitalization after the first administration of mosunetuzumab for 72 hours, have been incorporated into the safety plan (refer to Section 5 for details).

The study contains a Phase Ib and Phase II portion. The initial objective of the Phase Ib portion of Study GO40515 is to evaluate the optimal dose and schedule of mosunetuzumab as a replacement for rituximab in combination with CHOP in patients with R/R B-cell NHL, not limited to DLBCL, who are eligible to receive CHOP chemotherapy. In the next portion of the Phase Ib study, mosunetuzumab will be assessed in combination with CHP-pola in the same patient population.

All Phase Ib mosunetuzumab dosing decisions and RP2D determination for the combination with CHOP and with CHP-pola will be based on recommendations from an Internal Monitoring Committee (IMC; see Sections 3.3.9 and 5.1.8). In addition to the Phase Ib data generated in this study with M-CHOP, the IMC will also review clinical data and dosing decisions from Study GO40516, an open-label, randomized, multicenter, Phase Ib/II trial investigating the safety, tolerability, pharmacokinetics, and efficacy of mosunetuzumab alone or in combination with polatuzumab vedotin compared with immunochemotherapy in patients with R/R DLBCL or FL and all other sources, including the initial Phase I/IB Study GO29781. The primary objectives for the Phase Ib portion of Study GO40516 include the estimation of the MTD, determination of RP2D, and characterization of DLTs of mosunetuzumab when combined with polatuzumab vedotin. The IMC will review the available Phase Ib data from Study GO40516 and Study GO29781, in addition to the Phase Ib data from the M-CHOP combination in this study before making a recommendation on opening the M-CHP-pola combination (Group B; refer to Figure 1).

For the Phase II portion of the study, an initial safety cohort of at least 10 and up to approximately 40 patients with previously untreated DLBCL will receive M-CHOP to further assess safety and tolerability of this regimen in a first-line setting, where clinical outcomes may differ from the R/R setting based on differences in disease biology and immune functionality. Enrollment into this safety cohort will be staggered as in the Phase Ib dose-finding cohorts (refer to Section 3.1.2.2).

An Independent Data Monitoring Committee (iDMC), which is separate from the IMC, will assume reviewing responsibilities and review safety data after the first 10 patients in Phase II (Group C), and will meet approximately every 3 months during enrollment of the Phase II portion of the study to review safety data. The iDMC will review safety data from the Phase Ib portion of the study before enrollment is started in the Phase II randomized portion of the study. See Sections 3.3.10 and 5.1.9 for additional details.

After the safety data are available from the first 10 patients who have completed at least the first 2 cycles of study treatment at the IMC-confirmed RP2D, and upon

recommendation by the iDMC, patients with previously untreated DLBCL will be randomized to receive either R- CHP-pola (n=20), M-CHP-pola (n=40), or M-CHOP (up to n=30, to have a total of approximately 40 patients including the safety cohort). PET-CT CR rate as assessed by an IRC by the Lugano 2014 criteria (Cheson et al. 2014) will be the primary endpoint and safety, PFS, 1-year PFS, EFS, objective response rate (ORR), DOR, and specific patient-reported outcomes (PROs; European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire [EORTC QLQ-C30] and Functional Assessment of Cancer Therapy–Lymphoma [FACT-Lym]) will be key secondary endpoints (refer to Table 1) in order to make a robust comparison of differential safety, tolerability, and clinical activity. Eligible patients will have IPI between 2 and 5, which includes those with highest-risk disease (IPI 4–5) as well as high-intermediate risk disease (IPI 3). These populations continue to have poor outcomes in the R-CHOP treatment setting. IPI 2 is included because outcomes in this population are still substantially poorer than that seen in low-risk (IPI 0–1) patients, and patients with poor prognosis by molecularly defined methods (e.g., ABC, DHL, DEL) continue to have poorer outcomes with this IPI score (Johnson et al. 2009, 2012; Hu et al. 2013).

## 2. OBJECTIVES AND ENDPOINTS

This Phase Ib/II, multicenter, randomized, open-label study will evaluate the safety, pharmacokinetics, and preliminary efficacy of mosunetuzumab in combination with CHOP and, subsequently, in combination with CHP-pola in patients with R/R B-cell NHL (Phase Ib).

The Phase Ib portion of the study is designed to assess safety, tolerability, and the RP2D of mosunetuzumab in combination with CHOP and in combination with CHP-pola. Following the Phase Ib portion, a Phase II safety cohort will evaluate M-CHOP in patients with previously untreated DLBCL. If safety is deemed acceptable, M-CHP-pola will then be compared with R-CHP-pola in patients with previously untreated DLBCL (randomized Phase II; refer to Section 3.1.2.2 for additional details on how the regimen will be determined for the Phase II portion).

The specific objectives and endpoints are listed by phase in Table 1.

## Table 1 OBJECTIVES and Corresponding Endpoints

| Phase Ib | |
|---|---|
| **Safety Objectives (Primary Study Objective for Phase Ib)** | **Corresponding Endpoints** |
| M-CHOP:<br>• To evaluate the safety and tolerability of M-CHOP in patients with R/R B-cell NHL, including estimation of the MTD, determination of RP2D, and characterization of DLTs<br>M-CHP-pola:<br>• To evaluate the safety and tolerability of M-CHP-pola in patients with R/R B-cell NHL, including estimation of the MTD, determination of RP2D, and characterization of DLTs | • Occurrence and severity of adverse events including DLTs, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to the ASTCT CRS Consensus Grading criteria (Appendix 7)<br>• Change from baseline in targeted vital signs<br>• Change from baseline in targeted clinical laboratory test results<br>• Number of cycles received and dose density and intensity (of planned 6 cycles of combination therapy) |
| **Pharmacokinetic Objectives** | **Corresponding Endpoints** |
| • To characterize the pharmacokinetics of mosunetuzumab when administered in combination with CHOP or CHP-pola<br>• To characterize the pharmacokinetics of polatuzumab vedotin when administered in combination with mosunetuzumab and CHP<br>• To characterize the relationship between serum pharmacokinetics, safety, biomarkers, and efficacy | • $C_{max}$<br>• $C_{min}$<br>• Total exposure (AUC), clearance, and volume of distribution at steady state, as estimated by population PK modeling, as appropriate and supported by data<br>• Relationship between serum pharmacokinetics and safety, biomarkers, or efficacy endpoints, as appropriate |
| **Efficacy Objectives** | **Corresponding Endpoints** |
| • To make a preliminary assessment of the anti-tumor activity of M-CHOP<br>• To make a preliminary assessment of anti-tumor activity of M-CHP-pola | *All radiographic assessments are according to the Lugano 2014 Response Criteria* (Cheson et al. 2014; Appendix 3)<br>• CR rate at the time of primary response assessment based on PET-CT as determined by the investigator<br>• Best ORR, defined as CR or PR at any time on study based on PET-CT and/or CT scan as determined by the investigator<br>• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs first |

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Immunogenicity Objectives | Corresponding Endpoints |
|---|---|
| • To assess the immune response to mosunetuzumab<br>• To assess the immune response to polatuzumab vedotin<br>• Assess potential effect of mosunetuzumab ADA incidence on relevant clinical outcomes<br>• Assess potential effect of polatuzumab vedotin ADA incidence on relevant clinical endpoints | • Incidence of ADAs to mosunetuzumab<br>• Incidence of ADAs to polatuzumab vedotin<br>• Relationship between ADAs and pharmacokinetics, safety, efficacy, and biomarkers may be explored as appropriate |
| **Exploratory Biomarker Objectives** | **Corresponding Endpoints** |
| • To evaluate the relationship between M-CHOP and M-CHP-pola exposure and pharmacodynamic biomarkers, including but not limited to circulating cytokine levels and T-cell number and activation states<br>• To make a preliminary assessment of biologic markers that might act as predictors of susceptibility to developing adverse events following administration of M-CHOP and M-CHP-pola<br>• To make a preliminary assessment of biologic markers that might act as predictors of the anti-tumor activity of M-CHOP and M-CHP-pola<br>• To make a preliminary assessment of biologic markers that might act as predictors of the immunomodulatory activity of M-CHOP and M-CHP-pola | • Relationship between exploratory biomarkers (including cytokines, T cell and B cell counts, and T cell activation) and efficacy, safety, pharmacokinetics, immunogenicity, or other biomarker endpoints |
| **Phase II** | |
| **Primary Efficacy Objective** | **Corresponding Endpoint** |
| • To evaluate the efficacy of M-CHP-pola compared with R-CHP-pola in patients with previously untreated DLBCL | *All radiographic assessments are according to the Lugano 2014 Response Criteria* (Cheson et al. 2014; Appendix 3)<br>• CR rate at the time of primary response assessment based on PET-CT, as determined by IRC |

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Secondary Efficacy Objectives | Corresponding Endpoints |
|---|---|
| • To evaluate the efficacy of M-CHP-pola compared with R-CHP-pola in patients with previously untreated DLBCL<br>• To evaluate the efficacy of M-CHOP in patients with previously untreated DLBCL | • CR rate at the time of primary response assessment based on CT only, as determined by the investigator<br>• ORR, defined as CR or PR at the time of primary assessment based on PET-CT, as determined by the investigator<br>• ORR, defined as CR or PR at the time of primary assessment based on CT only, as determined by the investigator<br>• Best ORR, defined as CR or PR at any time on study, based on PET-CT or CT only as determined by the investigator<br>• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs first<br>• PFS, defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs first<br>• PFS at 1 year, proportion of patients with disease progression or relapse as determined by the investigator, or death from any cause within 1 year of randomization<br>• EFS, defined as the time from randomization to the first occurrence of disease progression or relapse, as determined by the investigator, initiation of NALT, or death from any cause, whichever occurs first<br>• Time to deterioration in physical functioning and fatigue *as measured by the EORTC QLQ-C30* and in *lymphoma symptoms as measured by* the FACT-Lym subscale |
| **Exploratory Efficacy Objectives** | **Corresponding Endpoints** |
| • To evaluate the clinical benefit of M-CHP-pola compared with R-CHP-pola in patients with previously untreated DLBCL<br>• To evaluate the clinical benefit of M-CHOP in patients with previously untreated DLBCL | • Proportion of patients achieving meaningful improvement in EORTC QLQ-C30 physical functioning and fatigue, and in *lymphoma symptoms in* the FACT-Lym subscale<br>• EORTC QLQ-C30 rate of treatment-related symptoms and FACT/GOG-NTX peripheral neuropathy rate<br>• All *remaining* scales of the EORTC QLQ-C30, the FACT-Lym subscale, and FACT/GOG-NTX peripheral neuropathy |

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Safety Objectives | Corresponding Endpoints |
|---|---|
| • To assess the safety and tolerability of M-CHP-pola compared with R-CHP-pola<br>• To assess the safety and tolerability of M-CHOP | • Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v5.0. For CRS, severity determined according to ASTCT CRS Consensus Grading criteria (Appendix 7)<br>• Change from baseline in targeted vital signs<br>• Change from baseline in targeted clinical laboratory test results and clinical assessments<br>• Number of cycles received and dose density and intensity (of planned 6 cycles of combination therapy) |
| **Pharmacokinetic Objectives** | **Corresponding Endpoints** |
| • To characterize the pharmacokinetics of mosunetuzumab when administered by IV infusion with CHOP and CHP-pola<br>• To characterize the pharmacokinetics of polatuzumab vedotin when administered by IV infusion with mosunetuzumab and CHP<br>• To assess the pharmacokinetics of rituximab in combination with CHP-pola compared with historical data (exploratory) | • $C_{max}$<br>• $C_{min}$<br>• Total exposure (AUC), clearance, and volume of distribution, as estimated by population PK modeling, as appropriate and supported by data |
| **Immunogenicity Objectives** | **Corresponding Endpoints** |
| *Secondary Immunogenicity Objectives* | |
| • To assess the immune response to mosunetuzumab<br>• To assess the immune response to polatuzumab vedotin<br>• Assess potential effect of mosunetuzumab ADA incidence to relevant clinical outcomes<br>• Assess potential effect of polatuzumab vedotin ADA incidence to relevant clinical endpoints | • Incidence of ADAs to mosunetuzumab<br>• Incidence of ADAs to polatuzumab vedotin<br>• Relationship between ADAs and pharmacokinetics, safety, efficacy, and biomarkers may be explored as appropriate |

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Exploratory Biomarker Objectives | Corresponding Endpoints |
|---|---|
| • To identify biomarkers that are predictive of response to M-CHOP and M-CHP-pola (predictive biomarkers), are associated with progression to a more severe disease state (prognostic biomarkers), are associated with acquired resistance to M-CHOP and M-CHP-pola, are associated with susceptibility to developing adverse events, can provide evidence of M-CHOP and M-CHP-pola activity, or can increase the knowledge and understanding of disease biology<br>• To make a preliminary assessment of response to M-CHOP and M-CHP-pola in different clinical and biologic prognostic DLBCL subgroups<br>• To make a preliminary assessment of MRD status following treatment with M-CHOP and M-CHP-pola | • Association between exploratory biomarkers, prognostic subtypes, including and molecular DLBCL prognostic subtypes such as cell of origin, and PET-CT CR, ORR, DOR, and PFS endpoints<br>• Relationship over time between ctDNA and radiographically-assessed tumor burden |
| **Exploratory Health Status Utility Objective** | **Corresponding Endpoint** |
| • To assess health status of patients | • Health status (EQ-5D-5L) |

ADA=anti-drug antibody; ASTCT=American Society for Transplantation and Cellular Therapy; AUC=area under the concentration-time curve; CHP=cyclophosphamide, doxorubicin, and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP-pola=CHP-polatuzumab vedotin; $C_{max}$=maximum serum concentration; $C_{min}$=minimum serum concentration; CR=complete response; CRS=cytokine release syndrome; CT=computed tomography; ctDNA=circulating-tumor DNA; DLBCL=diffuse large B-cell lymphoma; DLT=dose-limiting toxicity; DOR=duration of response; EFS=event-free survival; EORTC QLQ-C30=European Organisation of Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FACT/GOG-NTX=Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity; FACT-Lym=Functional Assessment of Cancer Therapy–Lymphoma subscale; IRC=Independent Review Committee; M-CHOP=mosunetuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; M-CHP-pola=mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; MRD=minimal residual disease; MTD=maximum tolerated dose; NALT=new anti-lymphoma therapy; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; NHL=non-Hodgkin lymphoma; ORR=objective response rate; PET=positron emission tomography; PET-CT=positron emission tomography–computed tomography; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; R-CHP=rituximab plus cyclophosphamide, doxorubicin, and prednisone; R-CHP-pola=rituximab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RP2D=recommended Phase II dose; R/R=relapsed or refractory.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

### 3.1.1 Overview of Study Design

This study is divided into two phases: 1) a dose-finding Phase Ib portion, which will test the safety and tolerability of combinations of mosunetuzumab with chemotherapy and polatuzumab vedotin for the treatment of patients with previously treated B-cell NHL and 2) a randomized, open-label Phase II portion, which will compare the efficacy, safety, and tolerability of mosunetuzumab in combination with CHP-pola or CHOP versus R-CHP-pola in patients with previously untreated DLBCL. The option to include the treatment arm of M-CHOP in the randomized Phase II portion of the study will be based on clinical data from a safety run-in group assessing the safety and tolerability of M-CHOP in patients with previously untreated DLBCL. The decision to include this third treatment arm will be made prior to initiating the randomized Phase II portion.

An overview of the study design is presented in Figure 1. The dosing schedules for M-CHOP, M-CHP-pola, and R-CHP-pola are described in Sections 4.3.3.2–4.3.3.4. Schedules of activities are provided in Appendix 1 and Appendix 2.

Approximately 40–60 patients will be enrolled in the Phase Ib dose-finding portion of the study. Up to an additional 70–100 patients will be enrolled in the safety run-in and Phase II portion of the study, for a total of approximately 110–160 patients enrolled in the study.

#### 3.1.1.1 Phase Ib: Dose-Finding Phase in B-Cell Non-Hodgkin Lymphoma

**Group A: Dose-Finding Mosunetuzumab plus CHOP Group**

The goal of this Phase Ib portion is to establish the RP2D of mosunetuzumab in combination with CHOP (RP2D_A). The RP2D_A will be the starting mosunetuzumab dose used in Groups B and C. A 3+3 dose-finding design will be employed, using the dose-escalation/dose-de-escalation rules as defined in Section 3.1.2.2. The DLT assessment period will be C1D1 through C1D21 of M-CHOP treatment, and dose escalation/de-escalation will continue until the MTD or MAD is identified.

Patients with R/R B-cell NHL will receive 6 cycles of M-CHOP at 21-day intervals. The first cycle of mosunetuzumab will be administered as *step-up* doses on C1D1 (1 mg), C1D8 (2 mg), and C1D15 (13.5 mg) after CHOP administration in the first cohort, then will be determined according to dose escalation/de-escalation rules based on DLTs (see Section 3.1.2.1; see Section 3.1.2.2 for the rationale for starting mosunetuzumab dose and the dose escalation/de-escalation rules). Full doses of mosunetuzumab (the C1D15 dose) will be administered on Day 1 of subsequent cycles.

The CHOP regimen consists of cyclophosphamide 750 mg/m$^2$ IV, doxorubicin 50 mg/m$^2$ IV, and vincristine 1.4 mg/m$^2$ (maximum dose of 2 mg) IV given on Day 1 and

prednisone 100 mg/day orally (PO) given on Days 1–5 of every 21-day cycle for 6 cycles. On days that mosunetuzumab corticosteroid premedication (dexamethasone 20 mg IV or methylprednisolone 80 mg IV) overlaps with the prednisone 100 mg PO dose, the IV corticosteroid premedication should be omitted.

Patients with a PR or SD at the time of primary response assessment by PET-CT (6–8 weeks after C6D1 of study treatment or early treatment discontinuation) may continue mosunetuzumab treatment as a single agent for up to an additional 11 cycles in the absence of disease progression. For additional details on the M-CHOP regimen, refer to Section 4.3.3.2.

The Sponsor may open an expansion cohort of up to 20 patients to further assess safety, tolerability, PK, and preliminary evidence of anti-tumor activity at or below the MTD or MAD (see Section 3.1.2.5).

If the combination of *step-up dosing* M-CHOP is not tolerated because of DLTs occurring prior to the administration of the C1D15 mosunetuzumab dose, then alternative regimens may be assessed based on a review of the totality of the available data by the IMC. These may include, but are not limited to:

- Incorporating corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1. This modification will be prioritized, as it is consistent with recommendations for patients with DLBCL at risk for early treatment-related toxicities with R-CHOP treatment (Pfreundschuh 2010; Tilly et al. 2015).
- Delaying the first dose of mosunetuzumab by 1 week in Cycle 1 with CHOP administration on C1D1 and maintaining mosunetuzumab *step-up dosing*, starting with 1 mg on C1D8, then 2 mg on C1D15, and the mosunetuzumab test dose on C2D1 (see Figure 2); this mosunetuzumab schedule modification will be assessed if pre-phase corticosteroid treatment does not sufficiently mitigate toxicities associated with *step-up dosing of* mosunetuzumab administration on C1D1 and C1D8. Delayed mosunetuzumab dosing may be assessed with pre-phase corticosteroid if this intervention provided some benefit in mitigating toxicities based on review of the safety data by the IMC, study investigators, and Sponsor study team.

All data and decisions regarding dosing and/or scheduling will be reviewed by the IMC (refer to Sections 3.3.9 and 5.1.8). After the IMC has evaluated at least 3 patients with M-CHOP at the determined RP2D_A for at least one cycle, the Group C safety run-in evaluating M-CHOP in previously untreated DLBCL patients will be opened (refer to Section 3.1.1.2).

### Group B: Dose-Finding M-CHP-Pola Group

The goal of this Phase Ib portion is to establish the mosunetuzumab RP2D in combination with CHP-pola (RP2D_B). The combination of mosunetuzumab and polatuzumab vedotin is being investigated in Study GO40516, a Phase Ib/II study in patients with R/R B-cell NHL (see Sections 1.2.2 and 1.5). The mosunetuzumab dose selected for M-CHP-pola will not exceed the RP2D_A for M-CHOP or the RP2D for mosunetuzumab plus polatuzumab vedotin from Study GO40516.

Clinical data for mosunetuzumab plus polatuzumab vedotin, including treatment-emergent adverse events, Grade ≥3 adverse events, DLTs, MTD/MAD, and the RP2D from the Phase Ib portion of GO40516 will be reviewed by the GO40515 IMC and study team prior to initiating Group B enrollment with M-CHP-pola. If the same dose as the mosunetuzumab RP2D_A has been cleared in Study GO40516, that mosunetuzumab dose can be assessed in combination with CHP-pola in this study even if RP2D has not yet been declared for M-pola in Study GO40516 (refer to Section 1.5 for additional details on Study GO40516).

A 3+3 dose-finding design will be employed, with potential dose de-escalation using the rules as defined in Section 3.1.2.2 (the mosunetuzumab dose will not be escalated above the RP2D_A). The DLT assessment window will be from C1D1 through C1D21 of M-CHP-pola treatment, and dose finding will continue until the MTD or MAD is identified.

Patients with R/R B-cell NHL will receive 6 cycles of M-CHP-pola at 21-day intervals. The first cycle of mosunetuzumab will be administered as *step-up* doses on C1D2 (1 mg), C1D8 (2 mg), and C1D15 (mosunetuzumab [RP2D_A]) in the first cohort and option for dose de-escalation if not tolerated). Full doses of mosunetuzumab (C1D15 dose) will be administered on Day 2 of subsequent cycles, with the option of mosunetuzumab administration on Day 1 of each cycle starting in Cycle 3 if well tolerated.

The CHP-pola regimen consists of cyclophosphamide 750 mg/m$^2$ IV, doxorubicin 50 mg/m$^2$ IV, and polatuzumab vedotin 1.8 mg/kg IV given on Day 1 and prednisone 100 mg/day PO given on Days 1–5 of every 21-day cycle for 6 cycles. On days that mosunetuzumab corticosteroid premedication (dexamethasone 20 mg IV or methylprednisolone 80 mg IV) overlaps with the prednisone 100 mg PO dose, the IV corticosteroid premedication should be omitted.

Patients with a PR or SD at the time of primary response assessment by PET-CT (6–8 weeks after Cycle 6 of study treatment or early treatment discontinuation) may continue mosunetuzumab treatment as a single agent for up to an additional 11 cycles in the absence of disease progression. For additional details on the M-CHP-pola regimen, refer to Section 4.3.3.3.

The Sponsor may open an expansion cohort of up to 20 patients to further assess safety, tolerability, PK, and preliminary evidence of anti-tumor activity at or below the MTD or MAD (see Section 3.1.2.5).

If the combination of *step-up* M-CHP-pola is not tolerated due to DLTs occurring prior to the administration of the C1D15 mosunetuzumab dose, then alternative regimens may be assessed based on a review of the totality of the available data by the IMC. These may include, but are not limited to:

- Incorporating corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1. This modification will be prioritized, as it is consistent with recommendations for patients with DLBCL at risk for early treatment-related toxicities with R-CHOP treatment (Pfreundschuh et al. 2010; Tilly et al. 2015).
- Delaying of the first dose of mosunetuzumab by 1 week in Cycle 1 with CHP-pola administration on C1D1 and maintaining mosunetuzumab *step-up dosing*, starting with 1 mg on C1D8, then 2 mg on C1D15, and the mosunetuzumab test dose on C2D2 (see Figure 2); this mosunetuzumab schedule modification will be assessed if pre-phase corticosteroid treatment does not sufficiently mitigate toxicities associated with *step-up dosing of* mosunetuzumab administration on C1D1 and C1D8. Delayed mosunetuzumab dosing may be assessed with pre-phase corticosteroid if this intervention provided some benefit in mitigating toxicities based on review of the safety data by the IMC, study investigators, and Sponsor study team.

All data and decisions regarding dosing and/or scheduling will be reviewed by the IMC (refer to Sections 3.3.9 and 5.1.8).

#### 3.1.1.2 Phase II: Safety Cohort and Randomized Dose Expansion in DLBCL

**Group C: Safety Cohort of Mosunetuzumab Plus CHOP in Previously Untreated DLBCL**

Prior to opening enrollment into the Group C safety cohort, the IMC will review the clinical data for all patients enrolled in Group A, including at least 3 patients treated at the mosunetuzumab RP2D_A plus CHOP who have received a minimum of 1 cycle of study treatment (refer to Section 3.1.2.6).

This safety cohort will be opened for patient enrollment prior to starting the randomized Phase II expansion cohorts to initially assess and confirm the safety of M-CHOP in patients with previously untreated DLBCL, where there exists the potential for a differential safety profile between first and subsequent lines of treatment. Mosunetuzumab at the RP2D_A plus CHOP will be tested in at least 10 and up to 40 patients with previously untreated DLBCL. The IMC will review safety data from the first 6 patients in order to confirm the recommended dose for the randomized Phase II portion of the study.

If the combination of mosunetuzumab RP2D_A plus CHOP is not tolerated in patients with previously untreated DLBCL, then alternative mosunetuzumab doses and/or

regimens may be assessed based on a review of the totality of the available data by the IMC. If toxicities (Grade ≥3 and/or adverse events that would meet DLT criteria in dose-finding cohorts) are observed after the C1D15 mosunetuzumab dose, this may include testing lower C1D15 mosunetuzumab doses. If, on the other hand, such adverse events are observed after either the first (1 mg) or second (2 mg) mosunetuzumab dose, corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1, and/or delaying the first dose of mosunetuzumab by 1 week in Cycle 1 of CHOP (maintaining the *step-up dosing*, starting mosunetuzumab 1 mg on C1D8, then 2 mg on C1D15, and RP2D_A on C2D1; see Figure 2) will be considered.

The iDMC will review safety data from the first 10 Group C patients who have received at least 2 cycles of study treatment at the IMC-confirmed RP2D prior to making recommendations for opening enrollment into the Phase II randomized dose expansion (see Section 3.1.5).

### Phase II Randomized Dose Expansion

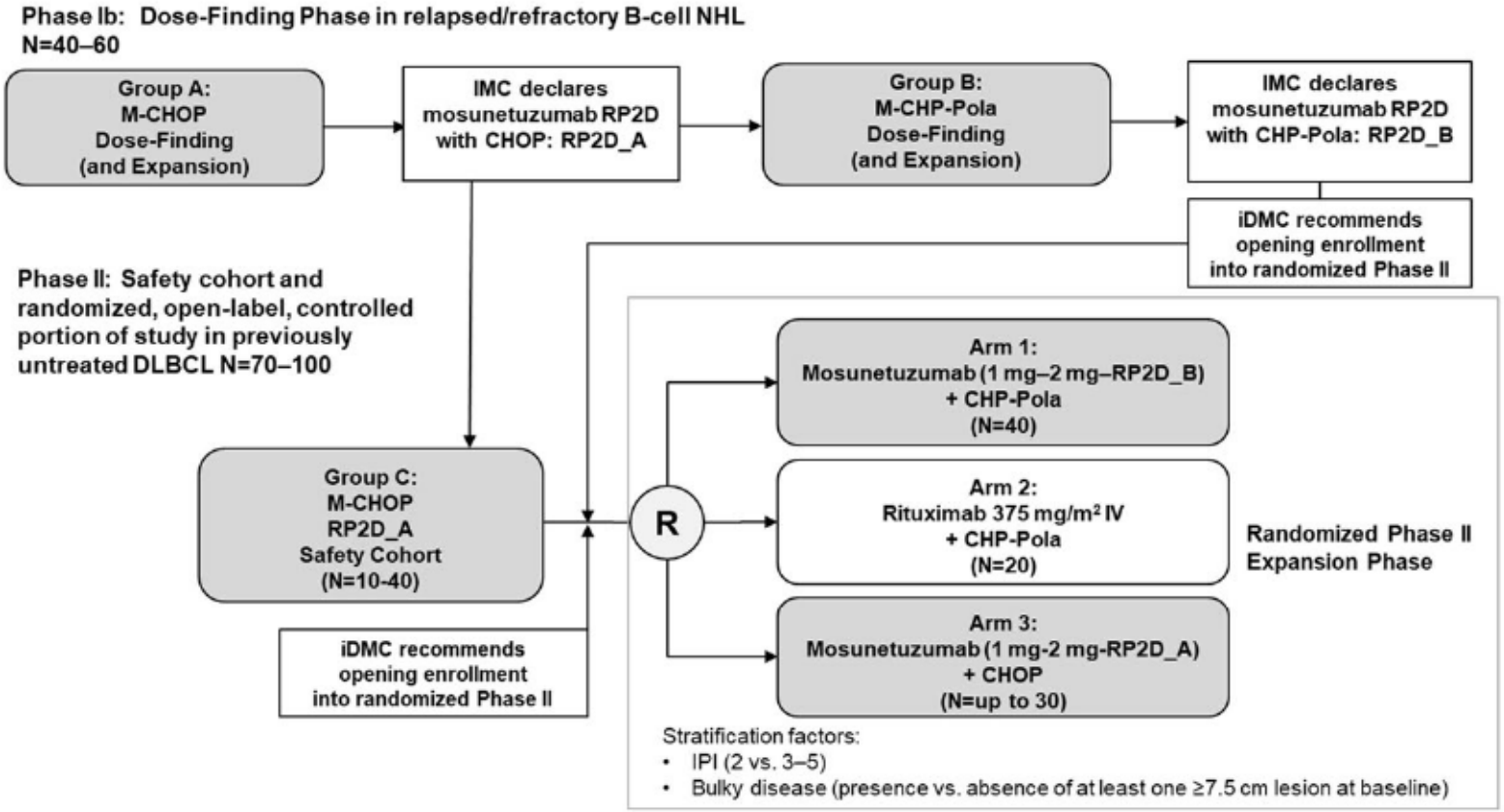
Upon demonstrating the safety and tolerability of the combination of M-CHP-pola (dose and schedule as determined in Phase Ib) and of M-CHOP in patients with previously untreated DLBCL in the aforementioned safety cohort, and following the iDMC recommendation, patients with previously untreated DLBCL will be randomized to receive one of the following three regimens:

- Arm 1: M-CHP-pola (n=40)
- Arm 2: R-CHP-pola (n=20)
- Arm 3: M-CHOP (n=up to 30)

The opening of Arms 1, 2, and 3 are dependent on iDMC review based on acceptable safety of M-CHOP in patients with previously untreated DLBCL, and safety of M-CHP-pola in previously treated B-cell NHL. A randomization ratio of 2:1:2 will be used until a total of up to approximately 40 patients have received M-CHOP, including Group C and Arm 3. Thereafter, a ratio of 2:1 will be used to enroll patients into the M-CHP-pola or R-CHP-pola arm.

*In the Phase II portion of the study, patients in Arm 1 will receive 6 cycles of M-CHP-pola at 21-day intervals. The first cycle of mosunetuzumab will be administered as step-up doses on C1D1 (1 mg), C1D8 (2 mg), and C1D15 (mosunetuzumab [RP2D_B]) in the first cohort). Full doses of mosunetuzumab (C1D15 dose) will be administered on Day 1 of subsequent cycles.*

## Figure 1 Study Schema




CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP = cyclophosphamide, doxorubicin, and prednisone; DLBCL = diffuse large B-cell lymphoma; IMC = Internal Monitoring Committee; IPI = International Prognostic Index; M-CHOP = mosunetuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; M-CHP-pola = mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; NHL = non-Hodgkin lymphoma; Pola = polatuzumab vedotin; R = randomization; RP2D = recommended Phase II dose; RP2D_A = recommended Phase II dose for M-CHOP; RP2D_B = recommended Phase II dose for M-CHP-pola; R/R = relapsed or refractory.
Note: After the dose-finding stage of M-CHOP and/or M-CHP-pola, up to 20 patients may be enrolled in an expansion cohort in patients with relapsed/refractory B-cell NHL.

### 3.1.2 Mosunetuzumab Dose-Finding Stage

#### 3.1.2.1 Definition of Dose-Limiting Toxicity

All adverse events, including DLTs, are to be reported according to instructions in Section 5.3 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) unless otherwise indicated. Although CRS will be graded according to the ASTCT CRS Consensus Grading criteria (Appendix 7), for dose-finding decisions, DLTs related to CRS will be defined based on individual signs and symptoms and laboratory data according to NCI CTCAE v5.0. If a patient experiences a DLT, he or she will be treated according to clinical practice and will be monitored for resolution of the toxicity (see Section 5.1.7 for management guidelines).

All adverse events should be considered to be related to study treatment unless such events are clearly attributed by the investigator to another clearly identifiable cause (e.g., documented tumor progression, concomitant medication, or pre-existing medical condition). Decreases in B cells, lymphopenia, and leukopenia due to lymphopenia will not be considered DLTs because they are expected PD outcomes of mosunetuzumab and polatuzumab vedotin treatment.

In the Phase Ib portion of the study (for either Group A or Group B), a DLT will be defined as any of the following adverse events occurring during the DLT assessment window (refer to Figure 2) in the absence of another clearly identifiable cause:

- Any adverse event regardless of grade that leads to a delay of more than 7 days to the start of the next cycle
- Any Grade ≥ 3 non-hematologic toxicity that is not attributable to disease progression or another clearly identifiable cause, with the following exceptions:

– Grade 3 diarrhea that responds to SOC therapy within 72 hours

– Grade 3 nausea or vomiting, in the absence of premedication, that responds to SOC therapy within 72 hours

– Grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant

– Grade 3 fatigue lasting ≤3 days

– For patients receiving the polatuzumab vedotin–containing regimen only (Group B): Reversible Grade 3 non-allergic infusion toxicities (including symptoms such as fever, chills/rigors, nausea, vomiting, pruritus, headache, rhinitis, rash, asthenia, and/or hypoxia in the absence of signs/symptoms of respiratory distress) occurring

during or within 24 hours after completing a polatuzumab vedotin infusion and resolving within 24 hours

Note: Grade ≥ 3 allergic toxicities such as wheezing, bronchospasm, shortness of breath, and/or stridor in the presence or absence of hypoxia, and/or urticaria are not excluded and should be considered DLTs. (Patients with infusion-related Grade ≥ 3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study drug on the first occurrence.)

– Grade 3 (NCI CTCAE v5.0) individual signs and symptoms of CRS after mosunetuzumab infusion that occurs in the context of Grade ≤2 CRS (as defined by ASTCT CRS Consensus Grading criteria [Lee et al. 2019]; see Appendix 7) and lasts <3 days

– Grade 3 elevation in ALT or AST, provided the following criteria are met:

Any Grade 3 AST or ALT elevation that lasts <3 days

ALT or AST level that is ≤8 × the upper limit of normal (ULN)

ALT or AST elevation that resolves to Grade < 2 (< 5 × ULN) within 7 days

Total and direct bilirubin and other laboratory parameters of liver synthetic function (e.g., prothrombin time) that are normal

No clinical signs or symptoms of hepatic injury

- Any case involving an increase in hepatic transaminase > 3 × baseline in combination with either an increase in direct bilirubin > 2 × ULN or clinical jaundice, without any findings of cholestasis or signs of hepatic dysfunction and in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential drug-induced liver injury (DILI) (according to Hy's Law) and will be considered a DLT unless the following criteria are met:

– Any AST or ALT>3 × ULN and total bilirubin>2 × ULN where no individual laboratory value exceeds Grade 3 and lasts<3 days will not be considered a DLT.

- Any Grade 3 or 4 hematological toxicity not attributable to another clearly identifiable cause with the exception of the following:

– Grade 3 or 4 lymphopenia, which is an expected outcome of therapy

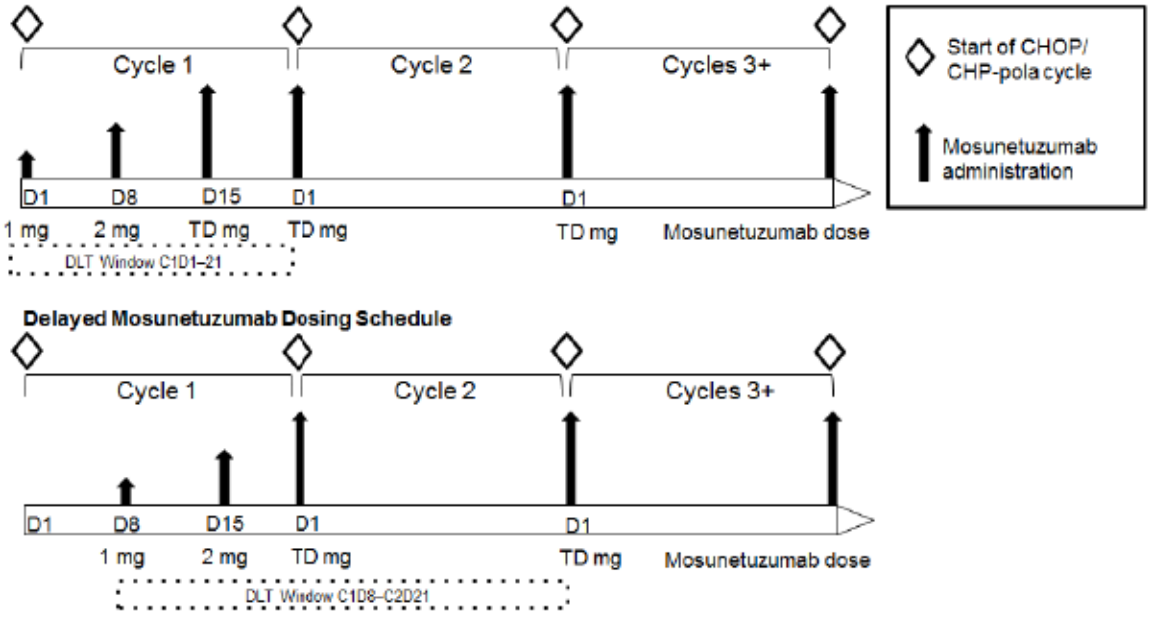
– Grade 3 or 4 neutropenia that is not accompanied by temperature elevation (oral or tympanic temperature of ≥ 100.4°F [38°C]) and improves to Grade ≤ 2 (or to ≥ 80% of the baseline value, whichever is lower) before C2D1(and also C3D1 if a patient is receiving mosunetuzumab on the delayed schedule starting on C1D8 with DLT assessment window from C1D8 until C2D21; note that neutropenia does not need to recover prior to *step-up* mosunetuzumab doses given within Cycle 1; refer to Figure 2)

– Grade 3 or 4 leukopenia

- Grade 3 or 4 thrombocytopenia that does not result in bleeding and improves to Grade ≤ 1 (or to ≥ 80% of the baseline value, whichever is lower) without platelet transfusion before C2D1 (and also C3D1 if a patient is receiving mosunetuzumab on the delayed schedule starting on C1D8 with DLT assessment window from C1D8 until C2D21; note that thrombocytopenia does not need to recover prior to *step-up* mosunetuzumab doses given within Cycle 1; refer to Figure 2)
- Grade 3 or 4 anemia that does not require an emergent transfusion

If a patient experiences a DLT as described above, the patient will be observed for resolution of the toxicity. If the DLT resolves to Grade ≤2 (or ≥80% of the baseline value) and it is determined to be in the patient's best interest to continue study treatment after discussion between the treating investigator and the Medical Monitor, the patient may continue to receive study treatment (refer to Section 3.1.2.4 for additional details on continuing study treatment beyond Cycle 1).

**Figure 2 Mosunetuzumab Dosing Schema**




C=cycle; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP=cyclophosphamide, doxorubicin, and prednisone; D=Day; DLT=dose-limiting toxicity; pola=polatuzumab vedotin; TD=test dose (initial TD=13.5 mg in Group A, Phase Ib).
Notes: Each cycle lasts 21 days. CHOP and CHP-pola are given starting Day 1 of each cycle of study treatment. Arrows represent mosunetuzumab administration, with longer arrows indicating higher mosunetuzumab dose. Mosunetuzumab is given on Day 2 of Cycles 1 and 2 when combined with CHP-pola *in Group B* and may be given on Day 1 in Cycles 3–6 if well tolerated.

#### 3.1.2.2 Starting Dose, Dose-Escalation/De-Escalation Rules and Determination of the Maximum Tolerated Dose

For safety monitoring and risk mitigation in the Phase Ib dose-finding cohorts and the Phase II safety cohort, treatment will be staggered such that the first patient treated at each dose level will receive his or her first infusion at least 72 hours prior to subsequent patients in that cohort. Subsequent patients in each cohort will be staggered such that their C1D1 treatments are administered ≥ 24 hours apart. Patients who receive study treatment and remain on study through the DLT assessment window will be considered DLT evaluable. Patients who discontinue from study treatment prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination and will be replaced by an additional patient at that same dose level. Patients who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs (excluding supportive care permitted or required per protocol) may be replaced at the discretion of the Medical Monitor.

For all dose-finding groups (i.e., Groups A and B), relevant demographic, adverse event, laboratory, dose administration, and PK (if available) data will be reviewed prior to dose-escalation/de-escalation decisions by the Sponsor's IMC, in consultation with the Medical Monitor, Safety Scientist, Statistician, Clinical Pharmacologist, Clinical Trial Leader, and Principal Investigators.

Cohorts may be expanded even in the absence of DLTs in order to evaluate non-DLT adverse events further or to collect additional safety or PK data. On the basis of a review of real-time safety data and available preliminary PK data, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

**Group A: Mosunetuzumab plus CHOP Dose Finding**

The starting dose level of *step-up* mosunetuzumab is 1 mg (C1D1), 2 mg (C1D8), and 13.5 mg (C1D15, mosunetuzumab test dose) in combination with CHOP in the first cohort (based on preliminary data from Study GO29781; for additional details, see Section 3.3.2). The DLT assessment window will be from C1D1 through C1D21 of M-CHOP treatment.

**Dose Escalation:** The *step-up* mosunetuzumab doses on C1D1 and C1D8 will remain constant in this dose-finding cohort. If the escalation rules outlined below are met, and based on IMC recommendation, the C1D15 test dose of mosunetuzumab may be increased by up to 100% (total cycle dose), or up to, but not exceeding, a dose corresponding to the maximum-assessed dose for mosunetuzumab using the *step-up dose* schedule as a single agent from Study GO29781. The mosunetuzumab dose may be rounded if the difference before and after the rounding is within 15% (e.g., 27 mg may be rounded to 30 mg).

Dose escalation of the mosunetuzumab C1D15 test dose will occur in accordance with the following rules:

- A minimum of 3 patients will initially be enrolled in each cohort.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next highest dose level may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next highest dose level may proceed.
- If 2 or more DLT-evaluable patients in a cohort experience a DLT, the MTD will have been exceeded and dose escalation will stop. An additional 3 patients will be evaluated for DLTs at the preceding dose level, unless 6 patients have already been evaluated at that level. However, if the dose level at which the MTD is exceeded is ≥25% higher than the preceding dose level, 6 patients may be evaluated at an intermediate dose level.
- If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., <33%) experience a DLT will be declared the MTD.
- If the MTD is not exceeded at any dose level, the highest dose administered in this study will be declared the MAD.
- As long as the MTD has not been exceeded, additional patients may be enrolled at a given dose level in a given cohort to explore factors influencing adverse events or to accumulate additional safety data.

**Dose De-Escalation:** The *step-up* mosunetuzumab doses on C1D1 and C1D8 will remain constant and the mosunetuzumab test dose may be reduced according to the following rules:

- In the event that the initial mosunetuzumab C1D15 test dose of 13.5 mg in combination with CHOP is above the MTD (i.e., ≥33% of DLT-evaluable patients experience a DLT), a reduced C1D15 dose level that is at least 25% lower may be evaluated in an additional cohort of 3 to 6 patients. If this dose level is again above the MTD, further C1D15 dose reductions of ≥25% of the preceding C1D15 dose may be assessed in subsequent cohorts of 3–6 patients. If a mosunetuzumab C1D15 dose of 2.8 mg is above the MTD, then dose de-escalation will be discontinued (note that 2.8 mg is the lowest Group B *step-up* mosunetuzumab C1D15 dose assessed in Study GO29781; *Refer to the Mosunetuzumab Investigator's Brochure).*
- The highest dose level where fewer than 2 out of 6 DLT-evaluable patients (i.e., <33%) experience DLTs will be declared the MTD.

**Modified Regimen to Be Tested if DLTs Occur Prior to Mosunetuzumab Test Dose:** If the MTD at any mosunetuzumab test dose level in combination with CHOP is exceeded as a result of at least one DLT occurring **prior to administration of the C1D15 test dose of mosunetuzumab** (i.e., after either the C1D1 1 mg or C1D8 2 mg mosunetuzumab dose) the following modified regimens may be evaluated:

- Incorporating corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1

  This modification will be prioritized, as it is consistent with recommendations for patients with DLBCL at risk for early treatment-related toxicities with R-CHOP treatment (Pfreundschuh et al. 2010; Tilly et al. 2015).

- Delaying of the first dose of mosunetuzumab by 1 week in Cycle 1 with CHOP administration on C1D1 and maintaining mosunetuzumab *step-up dosing*, starting with 1 mg on C1D8, then 2 mg on C1D15, and the mosunetuzumab test dose on C2D1 (see Figure 2)

- With this schedule, the DLT assessment window will extend from C1D8 until C2D21 (DLT window of 36 days). This mosunetuzumab schedule modification will be assessed if pre-phase corticosteroid treatment does not sufficiently mitigate toxicities associated with *step-up* mosunetuzumab administration on C1D1 and C1D8. Delayed mosunetuzumab dosing may be assessed with pre-phase corticosteroid if this intervention provided some benefit in mitigating toxicities based on review of the safety data by the IMC, study investigators, and Sponsor study team.

### Group B: M-CHP-Pola Dose Finding

This dose-finding cohort will be opened after a RP2D of M-CHOP has been declared (RP2D_A) (refer to Section 3.1.2.6). The mosunetuzumab *step-up* dose level established in combination with CHOP will be the initial dose level to be tested in combination with CHP-pola (i.e., mosunetuzumab 1 mg on C1D2, 2 mg on C1D8, and RP2D_A on C1D15). It should be noted that the first *step-up* dose of mosunetuzumab is given on C1D2 instead of C1D1 when combined with CHP-pola (see Sections 3.3.2 and 4.3.3 for additional details). The DLT assessment window will be from C1D1 through C1D21 of M-CHP-pola treatment.

If the M-CHOP dose finding establishes a delayed *step-up* dose schedule as the preferred regimen (i.e., mosunetuzumab 1 mg on C1D8, 2 mg on C1D15, and RP2D_A on C2D1), this schedule will also be implemented in the M-CHP-pola dose-finding cohorts. Similarly, if mitigation measures such as pre-phase treatment with prednisone 100 mg daily for 7 days immediately preceding C1D1 of study treatment is implemented in M-CHOP dose finding, this will also be applied in the M-CHP-pola dose-finding cohorts. If both delayed mosunetuzumab dosing and pre-phase corticosteroid treatment are implemented in the M-CHOP Group A, both will be applied in the M-CHP-pola combination in Group B as well. In addition, if Cohort C identifies the need for a delayed

*step-up* dose schedule or other risk mitigation measures, these will be implemented in Group B as well (see Section 3.1.1.2).

No dose escalation above the C1D15 mosunetuzumab RP2D_A is planned in combination with CHP-pola. The initial cohort assessing the mosunetuzumab RP2D_A will enroll 3–6 patients, and if <33% (i.e., <2 out of 6) DLT-evaluable patients experience DLTs, this dose will be declared the MAD and RP2D_B of mosunetuzumab in combination with CHP-pola.

**Dose De-Escalation:** The *step-up* mosunetuzumab doses on C1D1 and C1D8 will remain constant and the mosunetuzumab test dose may be reduced according to the following rules:

- In the event that the mosunetuzumab (C1D15) RP2D_A dose level in combination with CHP-pola is above the MTD (i.e., ≥33% of DLT-evaluable patients experience a DLT), a reduced C1D15 dose level that is at least 25% lower may be evaluated in an additional cohort of 3–6 patients. If this dose level is again above the MTD, further C1D15 dose reductions of ≥25% of the preceding C1D15 dose may be assessed in subsequent cohorts of 3–6 patients. If a mosunetuzumab C1D15 dose of 2.8 mg is above the MTD, then dose de-escalation will be discontinued (note that 2.8 mg is the lowest Group B *step-up* mosunetuzumab C1D15 dose assessed in Study GO29781; refer to the Mosunetuzamab Investigator's Brochure).
- The highest dose level where fewer than 2 out of 6 DLT-evaluable patients (i.e., <33%) experience DLTs will be declared the MTD.

**Modified Regimen to Be Tested if DLTs Occur Prior to Mosunetuzumab Test Dose:** If the MTD at any mosunetuzumab test dose level in combination with CHP-pola is exceeded because of at least one DLT occurring **prior to administration of the C1D15 test dose of mosunetuzumab** (i.e., after either the C1D2 1 mg or C1D8 2 mg mosunetuzumab dose), the following modified regimens may be evaluated:

- Including corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1

  This modification will be prioritized, as it is consistent with recommendations for patients with DLBCL at risk for early treatment-related toxicities with R-CHOP treatment (Pfreundschuh et al. 2010; Tilly et al. 2015).

- Delaying of the first dose of mosunetuzumab by 1 week in Cycle 1 with CHP-pola administration on C1D1 and maintaining mosunetuzumab *step-up dosing*, starting with 1 mg on C1D8, then 2 mg on C1D15, and the mosunetuzumab test dose on C2D1 (see Figure 2)

  With this schedule, the DLT assessment window will extend from C1D8 until C2D21 (DLT window of 36 days). This mosunetuzumab schedule modification will be assessed if pre-phase corticosteroid treatment does not sufficiently mitigate toxicities associated with *step-up dosing of* mosunetuzumab

administration on C1D2 and C1D8. Delayed mosunetuzumab dosing may be assessed with pre-phase corticosteroid if this intervention provided some benefit in mitigating toxicities based on review of the safety data by the IMC, study investigators, and Sponsor study team.

#### 3.1.2.3 Intrapatient Dose Escalation

No intrapatient dose escalation will be permitted in this study.

#### 3.1.2.4 Continuation of Mosunetuzumab with CHOP or CHP-Pola (Cycles 2–6)

Patients without a DLT during the DLT assessment window will be eligible to receive additional infusions of study treatment at the same dose level at which they were enrolled, provided that they meet the following criteria for acceptable toxicity and ongoing clinical benefit:

- **Acceptable toxicity:** All adverse events experienced with prior infusions that were not attributed to constitutional symptoms of the patient's cancer or intercurrent illness must have decreased to Grade 1 or baseline grade on or before the day of the next infusion. Exceptions on the basis of ongoing clinical benefit may be allowed after a careful assessment and discussion of benefit versus risk for the patient by the investigator as well as approval from the Medical Monitor. In addition, delay of therapy due to toxicities not attributed to study drug may not require discontinuation from the study but must be approved by the Medical Monitor. Dose modifications are described in Section 5.1.7.
- **Ongoing clinical benefit:** Patients must demonstrate improvement/stabilization in tumor burden according to the 2014 Lugano Response Criteria (Appendix 3), have no *clinical* signs or symptoms of progressive disease, or demonstrate clinical signs or symptoms of benefit, as judged by the investigator, independent of the radiographic assessment.

All tumors assessed at screening must be documented and re-assessed at each subsequent tumor evaluation (see Appendix 1 for tumor assessment schedule). For each patient, the same imaging modality should be used throughout the study (note that PET scans are not required for all imaging assessment timepoints; see Section 4.5.5.1 for details).

Women of childbearing potential will need to undergo a urine pregnancy test prior to each cycle of study treatment. If a urine pregnancy test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Patients who are pregnant must permanently discontinue study treatment.

Study treatment will be discontinued in patients who experience a DLT during the DLT assessment window if the toxicity does not return to baseline within 14 days of the next scheduled cycle of study treatment. Patients who experience a DLT during the DLT assessment window and whose toxicity returns to baseline within 14 days of the next

scheduled cycle of study treatment may be restarted at a dose level tolerated by the prior cohort following discussion with the Medical Monitor. A treatment delay beyond 14 days may be acceptable upon discussion with the Medical Monitor.

#### 3.1.2.5 Continuation of Mosunetuzumab as Single Agent (Cycles 7–17)

Patients who have either SD or a PR at the primary response assessment by PET-CT (6–8 weeks after C6D1 of study treatment) may continue treatment with mosunetuzumab for an additional 11 cycles as long as they meet the criteria for acceptable toxicity and ongoing clinical benefit outlined in Section 3.1.2.4. Patients who discontinue study treatment prior to Cycle 6 because of treatment-related toxicities are not eligible for additional mosunetuzumab treatment. Patients who receive mosunetuzumab continuation treatment more than 6 weeks after their last dose of mosunetuzumab will need to follow the *step-up dosing* schedule (i.e., mosunetuzumab 1 mg on C7D1, 2 mg on C7D8, and test dose on C7D15, followed by the test dose on Day 1 of subsequent cycles given every 21 days) and the schedule of clinical and laboratory assessments outlined in Appendix 1 and Appendix 2. Routine hospitalization with re-starting mosunetuzumab treatment after more than 6 weeks of treatment break is not required but allowed if the investigator considers this to be clinically indicated or if severe reactions occurred initially.

#### 3.1.2.6 Determination of Recommended Phase II Dose

The mosunetuzumab RP2Ds will be at or below the respective MTD (or MAD) for any combination regimen tested in the Phase Ib Groups A and B. A minimum of 3 patients for at least one cycle will be treated at a given mosunetuzumab dose level for the combination regimen in Group A and Group B before declaring RP2D_A and RP2D_B, respectively. The IMC will recommend RP2Ds based on the MTD/MAD determined in dose escalation and a review of the totality of the Phase Ib data that includes the safety profile of study treatment beyond the DLT assessment window. The IMC will review all treatment emergent adverse events, Grade ≥3 adverse events, serious adverse events, DLTs, and dose modifications due to adverse events. The IMC will make a recommendation for the RP2D of M-CHOP (RP2D_A) and M-CHP-pola (RP2D_B). Additional safety, tolerability, PK data, and preliminary efficacy data at the RP2D for either combination may be collected in Phase Ib expansion cohorts if recommended by the IMC.

### 3.1.3 Phase Ib Expansion

After the dose-finding stage of M-CHOP and/or M-CHP-pola, up to 20 patients may be enrolled in an expansion cohort for patients with previously treated B-cell NHL (i.e., the same patient population as the dose-escalation phase). Patients may be treated at or below the MTD or MAD to obtain additional safety, tolerability, and PK data, as well as preliminary anti-tumor activity at different mosunetuzumab dose levels.

If the frequency of Grade≥3 toxicities or other unacceptable toxicities at the initial expansion-stage dose level suggest that the MTD has been exceeded, enrollment at that

dose level of mosunetuzumab will be halted. Consideration will then be given to enrolling patients in an expansion cohort at a lower dose level or with an alternate regimen (see Section 3.1.2.2).

Patients in the dose-expansion cohort will be eligible to receive study treatment after Cycle 1 provided that they meet the same criteria for acceptable toxicity and ongoing clinical benefit as outlined for the dose-escalation cohorts in Section 3.1.2.4.

The decision to open an expansion cohort for either M-CHOP or M-CHP-pola will be made by the Sponsor, upon recommendation from the IMC and in consultation with the Principal Investigators based on a review of the data available at that time.

### 3.1.4 Phase II: Safety Group C

A minimum of 10 and a maximum of approximately 40 patients with previously untreated DLBCL will be enrolled in Group C prior to initiation of the randomized Phase II stage of this trial. Prior to opening enrollment into Group C, the IMC will review the clinical data for all patients enrolled in Group A, including at least 3 patients who have received a minimum of 1 cycle of M-CHOP (RP2D_A; refer to Section 3.1.1.2).

Patients will be treated with M-CHOP (RP2D_A) according to the schedule established in the Phase Ib stage of the trial. The IMC will review the first 6 patients having completed at least 2 cycles of M-CHOP to confirm the RP2D for the randomized Phase II expansion stage.

If, in the first 6 patients, the frequency of Grade 3 or higher toxicities or other unacceptable toxicities in the safety cohort suggest that the MTD for patients with previously untreated DLBCL has been exceeded, accrual at that dose level of mosunetuzumab will be halted; this decision will be made by the Sponsor, upon recommendation from the IMC in consultation with the Medical Monitor and Principal Investigators. Consideration will then be given to enrolling patients with one or more of the following modifications:

- If acute toxicity is generally observed prior to the mosunetuzumab C1D15 dose (i.e., after 1 mg infusion [given on C1D1 or C1D2] or 2 mg infusion on C1D8), the following adjustments to dose schedule and/or other mitigation strategies may be tested:

– Including corticosteroid pre-phase treatment (prednisone 100 mg daily) for 7 days prior to C1D1

  This modification will be prioritized, as it is consistent with recommendations for patients with DLBCL at risk for early treatment-related toxicities with R-CHOP treatment (Pfreundschuh et al. 2010; Tilly et al. 2015)

– Delaying of the first dose of mosunetuzumab by 1 week in Cycle 1 with CHOP administration on C1D1 and maintaining mosunetuzumab *step-up dosing*, starting

with 1 mg on C1D8, then 2 mg on C1D15, and the mosunetuzumab RP2D on C2D1 (see Figure 2)

This mosunetuzumab schedule modification will be assessed if pre-phase corticosteroid treatment does not sufficiently mitigate toxicities associated with *step-up dosing* mosunetuzumab administration on C1D1 or C1D2 and C1D8. Delayed mosunetuzumab dosing may be assessed with pre-phase corticosteroid if this intervention provided some benefit in mitigating toxicities based on review of the safety data by the IMC, study investigators, and Sponsor study team.

- If toxicity generally occurs after the C1D15 mosunetuzumab dose:
  - Reduction of mosunetuzumab to a dose level ≥ 25% lower than the initially tested RP2D

Patients in the safety cohort will be eligible to receive study treatment after Cycle 1 provided that they meet the same criteria for acceptable toxicity and ongoing clinical benefit as outlined for the dose-escalation cohorts in Section 3.1.2.4.

The iDMC will review safety data at least after the first 10 patients have completed at least 2 cycles of M-CHOP at the IMC-confirmed RP2D prior to making recommendations for the randomized Phase II expansion stage (refer to Section 3.1.5).

Enrollment may continue into Group C up to 40 patients until the randomized Phase II portion of the study is open to enrollment.

### 3.1.5 Phase II Randomized Dose Expansion

Once the first 10 patients in Group C have completed at least the first 2 cycles of study treatment at the IMC-confirmed RP2D to be evaluated in the randomized Phase II portion, the iDMC will assume responsibilities to review the safety data in Group C and will recommend whether the data support opening the randomized Phase II expansion to the Sponsor.

Phase II randomization will start only after the RP2D_B has been determined by the IMC, and the iDMC has recommended opening the randomized Phase II expansion.

The Phase II stage is a randomized, open-label, controlled portion of the study comparing the following treatment regimens in patients with previously untreated DLBCL (Figure 1):

- Arm 1: M-CHP-pola (n=40)
- Arm 2: R-CHP-pola (n=20)
- Arm 3: M-CHOP (n=up to 30)

A randomization ratio of 2:1:2 will be used until a total of up to 40 patients have received M-CHOP, including Group C safety cohort and Arm 3. Thereafter, a ratio of 2:1 will be used to enroll patients into the M-CHP-pola or R-CHP-pola arm.

The primary endpoint is PET-CT CR rate at the time of primary response assessment per the 2014 Lugano Response Criteria as assessed by an IRC. Refer to Table 1 for a complete list of Phase II objectives and endpoints.

Stratification factors are IPI (2 vs. 3–5) and presence or absence of bulky disease, defined as at least one ≥7.5 cm lesion at baseline.

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur approximately 30 months after the last patient is enrolled to allow all patients to have up to 2.5 years of follow up. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 60 months.

In addition, the Sponsor may decide to terminate the study at any time.

## 3.3 RATIONALE FOR STUDY DESIGN

The combination of the CD20-targeting monoclonal antibody rituximab in combination with CHOP is the current SOC for previously untreated DLBCL. An ongoing Phase III study (GO39942/POLARIX) is comparing R-CHOP with R-CHP-pola in this patient population. This Phase Ib/II study is designed to evaluate the potential of replacing rituximab in a regimen designed for the treatment of patients with DLBCL (and other B-cell NHLs).

### 3.3.1 Rationale for Polatuzumab Vedotin Dose and Schedule

*At the initiation of this study*, over 500 patients *had* been enrolled in eight trials administering polatuzumab vedotin to treat B-cell malignancies. At the dose of 1.8 mg/kg every 21 days, polatuzumab vedotin has been well tolerated as monotherapy and in combination with an anti-CD20 monoclonal antibody in patients with R/R B-cell NHL, with expected toxicities including cytopenias and peripheral neuropathy. In patients with previously untreated DLBCL, polatuzumab vedotin at 1.8 mg/kg in combination with R-CHP was administered to 45 patients, and polatuzumab vedotin at 1.8 mg/kg in combination with CHP and another anti-CD20 monoclonal antibody (obinutuzumab) was administered to 17 patients. The safety profile of R-CHP-pola is comparable to that observed when patients receive treatment with the SOC R-CHOP, with toxicity being primarily hematologic in nature (see the Polatuzumab Vedotin Investigator's Brochure for additional details). The combination of 6 cycles of R-CHP-pola is currently being investigated in a Phase III trial compared with 6 cycles of R-CHOP (rituximab given for a total of 8 cycles in both arms) as potential treatment for patients with previously untreated DLBCL (Study GO39942/POLARIX).

### 3.3.2 Rationale for Mosunetuzumab Dose and Schedule

**Mosunetuzumab**

In this study, mosunetuzumab will be administered intravenously on a 21-day cycle with premedications (corticosteroids, anti-pyretic, anti-histamines as described in Section 4.3.2.1) and on a Cycle 1 *step-up* dose schedule established in the ongoing first-in-human Phase I study, GO29781 (see Section 1.2.2 and Figure 2) to mitigate the risk of acute toxicities (e.g., CRS, TLS, CNS toxicity). With the Cycle 1 *step-up dosing* schedule, mosunetuzumab is given at a flat dose of 1 mg on Day 1 (or Day 2), 2 mg on Day 8, and the planned test dose on Day 15. The C1D15 dose will then be administered once per cycle in subsequent cycles.

The IL-6 response and current safety profile of mosunetuzumab in Study GO29781 suggest that higher doses of mosunetuzumab may be more tolerable and potentially more efficacious when administered using the *step-up* dosing scheme compared with *flat* dosing (refer to Section 1.2.2 and the Mosunetuzumab Investigator's Brochure for additional details). This provides a rationale for maintaining the same *step-up* dose schedule in combination with CHOP and CHP-pola. Therefore, the mosunetuzumab 1 mg C1D1 (or C1D2) dose level and the 2 mg C1D8 dose level will not be modified in the dose-finding portion of this study.

Dose escalation of the Day 15 test dose in the Phase I/Ib Study GO29781 is ongoing. As of 8 October 2018, both the 1.0 mg/2.0 mg/13.5 mg and the 1.0 mg/2.0 mg/20 mg dose levels using the Group B dosing schedule have cleared the DLT assessment period. No DLTs were observed in the 1.0 mg/2.0 mg/13.5 mg dose escalation cohort. Including the subsequent extension cohort, a total of 41 patients have received mosunetuzumab at 13.5 mg. Adverse events reported appeared to be consistent with those observed with mosunetuzumab at lower dose levels. The 1.0 mg/2.0 mg/20 mg dose level has also cleared the DLT assessment with 6 patients. There was one DLT of Grade 3 hypophosphatemia observed which was asymptomatic and resolved in 3 days with phosphate treatment. The maximum tolerated dose of mosunetuzumab has not yet been reached and dose escalation continues in Study GO29781.

Therefore, the mosunetuzumab starting dose for this study (in combination with CHOP) will be 1 mg (Day 1), 2 mg (Day 8), and 13.5 mg (Day 15), followed by 13.5 mg on Day 1 of all subsequent 21-day cycles of mosunetuzumab treatment. The rationale for the starting mosunetuzumab test dose level of 13.5 mg on Day 15 is based on the clinical data from Study GO29781 that supports the safety and tolerability of this dose as a single agent. Potential overlapping toxicities between mosunetuzumab in combination with CHOP or CHP-pola based on the safety/toxicity profiles of these agents known to date include IRRs/CRS, neutropenia and infections, thrombocytopenia, TLS, peripheral neuropathy, and hepatotoxicity. These potential toxicities are considered to be monitorable and manageable. In Study GO29781, most treatment-emergent adverse events, including CRS, occurred after the first dose of mosunetuzumab treatment with

the highest frequency observed within the first week of the first treatment cycle. Specific safety monitoring and mitigation measures, including mandatory hospitalization after the first administration of mosunetuzumab for *24 hours*, have been incorporated into the safety plan (*see* Section 5 for details).

### Mosunetuzumab in Combination with 6 Cycles of CHOP

The combination of 6 cycles of CHOP with the CD20-targeting antibody rituximab remains the SOC for the treatment of patients with previously untreated DLBCL. This regimen provides a rationale to test the T-cell engaging bispecific CD20/CD3–targeting antibody, mosunetuzumab, in combination with CHOP, replacing rituximab as a potentially superior CD20-targeting agent. In this combination, mosunetuzumab will be added to 6 cycles of CHOP given at standard doses and schedules (See Section 4.3.3.2 and Figure 3).

The starting dose of mosunetuzumab in the Phase Ib portion of this study is 1 mg (C1D1), 2 mg (C1D8), and 13.5 mg (C1D15), followed by 13.5 mg on Day 1 of subsequent cycles. On the basis of the dosing rules outlined in Section 3.1.2.2, the C1D15 dose may be escalated or de-escalated in this study to define the MTD/MAD and RP2D_A. Alternate dosing schedules and/or pretreatment with pre-phase corticosteroids prior to starting study treatment may be considered (see Section 3.1.2.2).

As described above, the rationale for starting with mosunetuzumab 1 mg (C1D1), 2 mg (C1D8), and 13.5 mg (C1D15) is that this dosing had acceptable safety and tolerability in Study GO29781. Furthermore, treatment-emergent adverse events most frequently occur early following the first infusions of mosunetuzumab (1 mg on Day 1, 2 mg on Day 8) rather than after the C1D15 mosunetuzumab dose and can generally be mitigated with management guidelines for treatment-emergent adverse events (see Section 5.1.7).

Patients will receive CHOP prior to receiving mosunetuzumab on Day 1 of each cycle, because administration of CHOP is generally well tolerated with SOC supportive medications (e.g., anti-emetics). On days that mosunetuzumab IV corticosteroid premedication overlaps with the prednisone 100 mg PO dose, the IV corticosteroid premedication should be omitted.

### Mosunetuzumab in Combination with 6 Cycles of CHP-Pola

While R-CHOP remains the SOC treatment for patients with previously untreated DLBCL, promising preliminary data with R-CHP-pola (Tilly et al. 2016, 2017) has led to a Phase III study comparing R-CHOP with R-CHP-pola in Study GO39942/POLARIX. This provides a rationale for testing mosunetuzumab in combination with CHP-pola, replacing the rituximab with the CD20/CD3–targeting bispecific antibody mosunetuzumab as a potentially superior CD20-targeting agent (see Section 4.3.3.3). In this combination, CHP-pola will be given on Day 1 of each cycle, followed by mosunetuzumab 1 mg on Day 2, 2 mg on Day 8, and the RP2D_A of mosunetuzumab

(RP2D_A=RP2D of mosunetuzumab in combination with CHOP) on Day 15 of the first cycle. Subsequently, the Day 15 dose of mosunetuzumab will be given on Day 2 of Cycle 2, and on Day 1 or 2 in Cycles 3 and beyond. Alternate dosing schedules and/or pretreatment with corticosteroids prior to starting study treatment may be considered (see Section 3.1.2.2).

*In the Phase 1 portion of the study, the* rationale for giving mosunetuzumab on Day 2 is to ensure patients have recovered from potential acute, treatment-emergent toxicities (e.g., infusion-related toxicities) due to polatuzumab vedotin before administering mosunetuzumab. If patients tolerate both polatuzumab vedotin and mosunetuzumab well in Cycles 1 and 2, both agents may be given on the same day in future subsequent cycles of treatment.

The rationale for starting with M-CHP-pola at the RP2D_A for M-CHOP is that the safety profile of CHOP and CHP-pola is generally comparable, with mainly hematologic toxicity (Tilly et al. 2016; Polatuzumab Vedotin Investigator's Brochure). Therefore, safety of the combination with mosunetuzumab may also be similar, and testing of the RP2D_A in combination with CHP-pola may enable determining the RP2D_B (mosunetuzumab RP2D in combination with CHP-pola) efficiently and minimize exposing patients to suboptimal doses of mosunetuzumab during dose escalation. Lower and/or alternate dosing schedules and/or pretreatment with corticosteroids prior to starting study treatment may be considered if the initial regimen does not have an acceptable safety profile (see Section 3.1.2.2).

*In the Phase II portion of the study, M-CHP-pola will be given on Day 1 of each cycle, with mosunetuzumab 1 mg on Day 1 of Cycle 1, 2 mg on Day 8, and the RP2D_B of mosunetuzumab (RP2D_B =RP2D of mosunetuzumab in combination with CHP-Pola) on Day 15 of the first cycle. Subsequently, the Day 15 dose of mosunetuzumab will be given on Day 1 of Cycle 2, and on Day 1 in Cycles 3 and beyond. The rationale for giving mosunetuzumab and CHP-Pola on the same day is based on data from the GO40516 study, and the GO40515 Group C M-CHOP cohort.*

Mosunetuzumab may be continued after completion of 6 cycles of combination therapy with CHOP or CHP-pola in patients who have either a PR or SD at the primary response assessment by PET-CT for up to an additional 11 cycles or in the absence of progressive disease and acceptable safety (see Section 3.1.2.4). The rationale for the option to continue dosing with mosunetuzumab is to evaluate whether mosunetuzumab treatment has the potential to provide additional clinical benefit in patients with active disease burden.

### 3.3.3 Rationale for Control Group

Comparing the efficacy and safety of M-CHP-pola with R-CHP-pola in the exploratory randomized Phase II portion of the study will enable a preliminary comparison of the relative impact of each CD20-targeting molecule with the CHP-pola backbone, thereby

informing future development in DLBCL. In order to minimize variability and cumulative toxicity between the treatment arms, polatuzumab vedotin plus CHP therapy will be limited to 6 cycles in this study (in both rituximab and mosunetuzumab arms).

### 3.3.4 Rationale for Patient Population and Analysis Groups

The goal of this study is to test the safety and tolerability and to determine the RP2D of mosunetuzumab in combination with CHP-pola and in combination with CHOP, with the ultimate goal of testing whether replacement of rituximab with mosunetuzumab as a potentially superior CD20-directed therapy can improve outcomes for patients with previously untreated DLBCL.

#### Phase Ib Patient Population

Patients with previously treated R/R B-cell NHL who have received at least one prior systemic therapy for their lymphoma including a CD20-targeting antibody (e.g., rituximab, obinutuzumab, ofatumumab) will be enrolled in the Phase Ib dose-finding cohorts. Because patients will be receiving chemotherapy with either CHOP or CHP-pola, they need to be considered appropriate candidates for CHOP-based therapy by investigators. Patients must have received no more than one prior cytotoxic chemotherapy–containing regimen and less than $\leq 250$ mg/m$^2$ prior treatment with doxorubicin (or equivalent anthracycline dose). The rationale for limiting the number of prior cytotoxic treatments and limiting prior anthracycline treatment is to reduce the risk of patients developing cumulative chemotherapy-related toxicities while on study treatment (e.g., left ventricular dysfunction, myelosuppression, peripheral neuropathy), which may limit both their ability to complete 6 cycles of mosunetuzumab-containing combination therapy and their potential to benefit from study treatment. Treatment with combinations of systemic chemotherapy with CD20-targeting antibodies is considered SOC in the initial treatment of many B-cell NHLs that are expected to express CD20 and may impact the safety profile of mosunetuzumab (e.g., depletion of both malignant and circulating non-malignant B-cells may potentially reduce the risk of acute treatment-emergent adverse events). The Phase I GO29781 study enrolled patients with B-cell NHL who generally had low baseline circulating B-cell levels related to prior lymphoma therapy (Genentech, data on file). Therefore, the initial assessment of mosunetuzumab in combination with CHOP and CHP-pola will be done in a similarly pretreated patient population using a mosunetuzumab dosing schedule established in the Phase I study.

To further assess tolerability of the regimen established in the Phase Ib portion, M-CHOP will be evaluated in a cohort of patients with previously untreated DLBCL in a safety run-in (Group C) prior to starting the randomized Phase II portion of the trial. Group C is designed to identify clinically significant differences in safety and tolerability of the study treatment in treatment-naive patients, where fundamental differences in disease and immune characteristics with the R/R setting would warrant changes in the study treatment regimen, as described in Section 3.1.2.2.

**Phase II Patient Population**

R-CHOP remains the SOC therapy in previously untreated DLBCL. Although about 60% of patients are cured with 6–8 cycles of R-CHOP chemotherapy, about 10%–15% have primary refractory disease and a further 20%–30% relapse (Chaganti et al. 2016).

Prognostic factors have been studied to define populations of greater unmet medical need and include both clinical factors and molecular characteristics. These clinical factors are most commonly defined through use of the IPI score. The target population of this study excludes patients with good prognostic factors (IPI 0–1) who already do well with standard therapy, while including patients who may not be adequately treated with SOC therapy (IPI 2–5).

### 3.3.5 Rationale for Open-Label Design

The safety profile of mosunetuzumab in patients with B-cell NHL remains to be fully characterized, and, to date, mosunetuzumab has not been combined with polatuzumab vedotin or chemotherapy. In this study, patients receiving the first dose of mosunetuzumab (with CHOP or CHP-pola) in Cycles 1 and 2 will be required to be hospitalized following the infusion to monitor patients closely for acute treatment-emergent toxicities and to provide early intervention if indicated. Patients receiving the control regimen of R-CHP-pola will not require routine hospitalization following treatment. Optimal medical management of patients on this study will be based on a close collaboration between the treating physician and Sponsor. Therefore, it is not practical for either the treating physician or the Sponsor's Medical Monitor to be blinded to treatment. The primary efficacy endpoint of the study (PET-CT CR rate) will be evaluated in a blinded fashion by the IRC (see Section 3.3.8).

### 3.3.6 Rationale for Stratification Factors

The stratification factors in this study are IPI score (IPI 2 vs. IPI 3–5) and presence or absence of bulky disease at baseline (defined as at least one ≥7.5-cm lesion).

IPI score is widely accepted as prognostic index for DLBCL, which predicts the risk of disease recurrence and overall treatment outcome in this patient population through five adverse prognostic risk factors: disease stage, age, performance status, serum lactate dehydrogenase (LDH) levels, and the presence or absence of multiple extranodal sites of lymphoma. Stratification during randomization will group patients with highest-risk disease (IPI 4–5) and high-intermediate risk disease (IPI 3), as these populations have been found across studies to have the poorest outcomes from R-CHOP (Sehn et al. 2007; Zhou et al. 2014). The IPI 3–5 group will be stratified against IPI 2, a population that typically has better prognosis, but, particularly when compared with low-risk patients (IPI 0–1), continue to have unmet medical need.

Bulky disease was found to be independently prognostic in the MinT study (Pfreundschuh et al. 2006) and was also found to be prognostic in the NCCN-IPI categorization (Zhou et al. 2014), although the scoring system in NCCN-IPI utilized

relative increases in LDH as a surrogate for bulk. Local practice may incorporate radiotherapy as consolidation to patients with bulky disease. In this study, bulky disease at diagnosis is defined as at least one lesion ≥7.5 cm and will be used as a stratification factor.

### 3.3.7 Rationale for Primary Efficacy Endpoint

PET-CT evaluation of fluorodeoxyglucose (FDG)-avid histologic types of B-cell NHL, such as DLBCL, is recommended per the 2014 Lugano classifications as a baseline staging assessment and an evaluation of response assessment in clinical trials (Cheson et al. 2014). The primary endpoint of PET-CT CR rate at the time of primary response assessment (6–8 weeks after Cycle 6 of study treatment or early treatment discontinuation) allows for a timely comparison of preliminary efficacy between M-CHP-pola and the control arm, R-CHP-pola (see Section 6.4.1 for statistical assumptions and plan for primary endpoint). Key secondary efficacy endpoints will be used to further characterize efficacy (CR assessed on CT, PFS, 1year PFS, EFS, ORR, DOR, $HRQoL$ as described in Table 1) and support conclusions based on the primary endpoint of PET-CT CR.

### 3.3.8 Rationale for Independent Review Committee for Response Assessment

An IRC for response assessment will assess all patients randomized to M-CHP-Pola or R-CHP-Pola in the Phase II portion of the study for primary response assessment by PET-CT through use of the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014), guided by a Charter specific to the independent review. The IRC functions to evaluate the primary endpoint, CR rate by PET-CT, in a standardized manner by board-certified radiologists, nuclear medicine specialists, and board-certified oncologists by blinded independent central review.

### 3.3.9 Rationale for Internal Monitoring Committee

Because this is the first trial to combine mosunetuzumab with CHOP and CHP-pola, an IMC will be utilized during the Phase Ib portion of the study to ensure enhanced patient safety while receiving study treatment. On the basis of trial safety data, the IMC will make recommendations on dose escalation and determination of the RP2D for M-CHOP and for M-CHP-Pola, and on opening enrollment into Phase II Group C (see Section 5.1.8 for details).

### 3.3.10 Rationale for Independent Data Monitoring Committee

An iDMC, external to the Sponsor, will be incorporated and assume reviewing responsibilities into the Phase II portion of the study to monitor patient safety. The iDMC will review safety data from Phase Ib and from patients enrolled in Phase II Group C, in order to make a recommendation whether to continue into the randomized Phase II portion of the study. During the Phase II portion of the study, the iDMC will monitor

patient safety, and provide recommendations to the Sponsor whether to continue, modify, or terminate the trial.

### 3.3.11 Rationale for the Treatment of Cytokine Release Syndrome Using Tocilizumab

CRS is a potentially life-threatening symptom complex, caused by the excessive release of cytokines by immune effector or target cells during an exaggerated and sustained immune response. CRS can be triggered by a variety of factors, including infection with virulent pathogens, or by medications that activate or enhance the immune response, resulting in a pronounced and sustained immune response.

Regardless of the inciting agent, severe or life-threatening CRS is a medical emergency. *If recognition or management is delayed*, it can result in significant disability or fatal outcome. Current clinical management focuses on treating the individual signs and symptoms, providing supportive care, and attempting to dampen down the inflammatory response using high-dose corticosteroids. However, this approach is not always successful, especially in the case of late intervention.

CRS is associated with elevations in a wide array of cytokines, including marked elevations in IFN-$\gamma$, IL-6, and TNF-$\alpha$ levels. Emerging evidence implicates IL-6 as a central mediator in CRS. IL-6 is a pro-inflammatory, multi-functional cytokine produced by a variety of cell types, which has been shown to be involved in a diverse array of physiological processes including T-cell activation. Regardless of the inciting agent, CRS is associated with high IL-6 levels (Panelli et al. 2004; Lee et al. 2014; Doessegger and Banholzer 2015), and IL-6 correlates with the severity of CRS with patients who experience severe or life-threatening CRS (CTC Grades 4 or 5) having much higher IL-6 levels compared with their counterparts who do not experience CRS or experience milder CRS reactions (CTC Grades 0–3) (Chen et al. 2016).

Tocilizumab (Actemra®/RoActemra®) is a recombinant, humanized, anti-human monoclonal antibody directed against soluble and membrane-bound IL-6R, which inhibits IL-6 mediated signaling. Blocking the inflammatory action of IL-6 using tocilizumab could therefore represent a novel approach for the treatment of CRS. Refer to the Tocilizumab Investigator's Brochure for additional nonclinical and clinical information regarding tocilizumab.

CRS is observed with T-cell recruiting therapies, including CAR-T cell therapy and bispecific molecules such as blinatumomab. There have been multiple reports in the literature of tocilizumab being used off-label to successfully treat severe or life-threatening CRS (Teachey et al. 2013; Lee et al. 2014, 2019; National Institutes of Health 2015), and tocilizumab is approved in the United States for the treatment of CAR T-cell–induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older.

Taken together, these findings indicate that patients treated with mosunetuzumab who develop CRS may benefit from tocilizumab therapy Table 10 and Appendix 7 describe recommendations regarding the management and grading of CRS.

### 3.3.12 Rationale for Granulocyte Colony-Stimulating Factor Prophylaxis

Transient neutropenia and less frequently febrile neutropenia are associated with myelosuppressive systemic therapies for B-cell lymphomas, including R-CHOP and R-CHP-pola (Coiffier et al. 2002, Polatuzumab Vedotin Investigator's Brochure). Neutropenia has also been reported in patients receiving mosunetuzumab in Study GO29781. The mechanism of mosunetuzumab related to neutropenia is unknown, and to date, it has been infrequently associated with febrile neutropenia (see the Mosunetuzumab Investigator's Brochure). To reduce the potential impact of neutropenia on treatment intensity with CHOP or CHP-pola that may negatively impact efficacy (Kwak et al. 1990; Yamaguchi et al. 2011; Utsu et al. 2016; Kanemasa et al. 2017), patients will be required to receive prophylactic granulocyte colony-stimulating factor (G-CSF) during the 6 cycles of CHOP or CHP-pola plus mosunetuzumab or rituximab in this study. The prophylactic use of G-CSF is consistent with the approach taken in Study GO39942/POLARIX comparing R-CHP-pola with R-CHOP in patients with previously untreated DLBCL.

Dosing of G-CSF should follow instructions in the package insert, American Society of Clinical Oncology guidelines (Smith et al. 2015), or each site's institutional standards. For patients who develop neutropenia despite prophylaxis, G-CSF is not routinely recommended for the treatment of uncomplicated neutropenia. However, G-CSF may be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes (Smith et al. 2015).

### 3.3.13 Rationale for Tumor Lysis Syndrome Prophylaxis

TLS is a known risk associated with effective B-cell NHL treatments, including chemoimmunotherapy (Coiffier et al. 2008). It is therefore also a potential risk with polatuzumab vedotin or mosunetuzumab treatment. TLS can occur if treatment results in the rapid destruction of a large number of tumor cells. To reduce this risk, patients will receive prophylaxis for TLS as described in Section 5.1.3.2.

### 3.3.14 Rationale for Hospitalization

Treatment-emergent toxicities, notably severe CRS and CNS toxicity, have been observed with mosunetuzumab as well as blinatumomab and CAR-T therapies (Kochenderfer et al. 2012; Grupp et al. 2013; Teachey et al. 2013). These toxicities generally occur upon first exposure to the therapeutic agent. While the mechanisms of action of these toxicities are not completely understood, it is believed that they are the result of immune cell activation resulting in inflammatory cytokine release. Temporally,

laboratory and clinical manifestations of cytokine release occur within several days of treatment and decrease in frequency and severity over time (Klinger et al. 2012; Davila et al. 2014).

On the basis of prior clinical experience with mosunetuzumab in Study GO29781 (see the Mosunetuzumab Investigator's Brochure for details), hospitalization will be required for all patients enrolled in the Phase Ib cohorts and the Phase II safety cohort. The hospitalization will be for *24 hours* following *the end of* the first mosunetuzumab dose in Cycle 1 (1 mg on Days 1 or 2). Patients are not required to be hospitalized following C1D8 or C1D15 mosunetuzumab dosing*, or for subsequent cycles*; however, investigators may choose to hospitalize a patient following any mosunetuzumab dose for close monitoring if indicated based on their clinical judgment.

Decisions to modify or discontinue the requirement for mandatory hospitalization in the study (including the randomized Phase II expansions) will be made based on the recommendation of the IMC and in consultation with study investigators.

### 3.3.15 Rationale for Pharmacokinetic and Anti-Drug Antibody Sampling Schedule

The PK sampling schedule that follows mosunetuzumab administration is designed to capture data at a sufficient number of timepoints to inform the concentration–time curve and to enable the characterization of the key PK parameters (including, but not limited to, $C_{max}$, $C_{min}$, and AUC) for mosunetuzumab in combination with CHOP or with CHP-pola. The PK sampling schedule for polatuzumab vedotin, evaluated as acMMAE and unconjugated MMAE, is designed to characterize key PK parameters of polatuzumab vedotin in combination with CHP and mosunetuzumab. Additionally, PK samples for polatuzumab vedotin total antibody will be collected based on a sparse sampling concurrent with ADA sampling for polatuzumab vedotin in order to inform the interpretation of any potential immune response towards polatuzumab vedotin. Predose serum rituximab or obinutuzumab PK samples are required in patients who have received prior treatment with rituximab or obinutuzumab in order to characterize any potential interactions between rituximab or obinutuzumab PK and the clinical effects of mosunetuzumab. Additionally, for patients in Arm B of the Phase II portion of the trial, sparse rituximab PK sampling will be used to assess rituximab PK compared with historical levels. These data will be used to understand the relationship of PK exposure to dose and support characterization of dose/exposure-response relationships in the combination setting.

Out of *352* evaluable postbaseline patients tested in Phase Ia study of mosunetuzumab (GO29781), *one patient (0.3%) tested positive for ADAs against mosunetuzumab. The presence of ADAs to mosunetuzumab had no apparent impact on drug exposure and safety* (refer to the Mosunetuzumab Investigator's Brochure). Because mosunetuzumab is a B cell–depleting agent and has demonstrated low immunogenicity rates in the Phase I study, the frequency of ADA sampling times for mosunetuzumab will be reduced in this

study compared with Study GO29781. Out of 258 evaluable postbaseline patients in the Phase Ib and II studies of polatuzumab vedotin (GO29365, GO27834, GO29044, and JO29138), only 3 patients (1.2%) tested positive for treatment-induced ADAs. Because polatuzumab vedotin is a B cell–depleting agent and has demonstrated low immunogenicity incidences in the Phase I and II study, the frequency of ADA sampling times will be reduced in this study compared with previous studies.

### 3.3.16 Rationale for Biomarker Assessments

Demonstrating PD activity of M-CHOP and M-CHP-pola, understanding the mechanism of action, and identifying prognostic and predictive biomarkers for safety and clinical activity form the underlying rationale for biomarker assessments in this study.

The peripheral blood sampling schedule following M-CHOP and M-CHP-pola is designed to provide evidence of biologic activity, and includes:

- Time course of cytokine release in relation to M-CHOP and M-CHP-pola PK and clinical safety during the DLT assessment period. Assessments of cytokine levels beyond the DLT assessment period will permit correlations with any chronic safety signals observed with continued M-CHOP or M-CHP-pola treatment.
- Expression of phenotypic markers of T-cell function and potential markers of resistance
- Dynamic quantitative changes in T-cell, B-cell, and natural killer (NK) cell counts

In addition, as tissue material is often limited, assessment of tumor-associated biomarkers in circulation is of high interest. Minimal residual disease (MRD) status, as determined by immunoglobulin high-throughput sequencing of circulating-tumor DNA (ctDNA) in peripheral blood, has been shown to reflect tumor burden in newly diagnosed and relapsed DLBCL (Kurtz et al. 2015). Furthermore, serial MRD assessment can predict early treatment failure and relapse from remission (Roschewski et al. 2014); thus, MRD has potential as a prognostic and predictive biomarker. In this study, MRD will be used to measure depth of treatment response and inform relationship with established clinical response assessments, such as PET-CT, monitor disease progression or recurrence, and track clonal tumor dynamics. Disease burden using peripheral blood samples ("MRD") will be measured at baseline and monitored at multiple timepoints on-treatment and at follow-up, including those coinciding with radiographic tumor assessments.

DLBCL is a highly heterogeneous disease for which several prognostic subgroups have been identified at the molecular level. As such, baseline tumor tissue will be obtained from all patients to enable exploratory analysis of tumor-associated biomarkers that may identify the most sensitive target population or inform optimization of the best therapeutic approach. In particular, recent studies have indicated that whole exome sequencing (WES) and/or whole genome sequencing (WGS) are necessary to classify biologically distinct subgroups of newly-diagnosed DLBCL with prognostic, and potentially predictive,

significance (Chapuy et al. 2018; Schmitz et al. 2018), supporting the need for WES/WGS in this study to better understand the efficacy of mosunetuzumab.

Tumor tissue and blood samples will be analyzed through use of next-generation sequencing (NGS) to identify gene signatures or mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

### 3.3.17 Rationale for Patient-Reported Outcomes

Health-related quality of life (HRQoL) is an important outcome in the care of patients with DLBCL and can be multifaceted. Depending on the specific diagnosis and treatment administered, patients may experience disease-related symptoms (e.g., B symptoms, fatigue), treatment-related symptoms (e.g., nausea, diarrhea), and subsequently may face limitations on daily functioning (e.g., physical activities, emotional functioning) (Jerkeman et al. 2001; Tholstrup et al. 2011). As the goal of measuring HRQoL is to quantify benefit of treatment from the patient perspective, the inclusion of PROs will assess the impact of treatment on concepts important to patients. These relevant disease- and treatment-related endpoints will be measured by the following PROs: the EORTC QLQ-C30, the FACT-Lym subscale, the Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx), and the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L). See Section 4.5.9 for more information.

## 4. MATERIALS AND METHODS

### 4.1 PATIENTS

Approximately 40–60 patients with B-cell NHL will be enrolled in the Phase Ib portion of this study. Up to an additional 70–100 patients with previously untreated DLBCL will be enrolled in the Phase II portion of the study, for a total of approximately 110–160 patients enrolled in the study.

### 4.1.1 Inclusion Criteria

Patients must meet the criteria for study entry as stated in following sections.

#### 4.1.1.1 Inclusion Criteria for Phase Ib and Phase II Portions

Patients must meet the following criteria for study entry in the Phase Ib and Phase II portions:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Able to comply with the study protocol and procedures, in the investigator's judgment

- At least one bi-dimensionally measurable nodal lesion, defined as > 1.5 cm in its longest dimension, or one bi-dimensionally measurable extranodal lesion, defined as > 1.0 cm in its longest diameter
- Confirmed availability of archival or freshly collected tumor tissue before study enrollment
- Life expectancy of at least 24 weeks
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Left ventricular ejection fraction (LVEF) defined by multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO) within the institutional limits of normal
- Adequate hematologic function (unless inadequate function is due to underlying disease, as established by extensive bone marrow involvement, or is due to hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) defined as follows:

– Hemoglobin ≥ 9 g/dL

– ANC ≥ 1.5 × $10^9$/L

– Platelet count ≥ 75 × $10^9$/L

- *Serum creatinine ≤ULN; or estimated creatinine clearance ≥50 mL/min by Cockroft-Gault method or other institutional standard methods, e.g. based on nuclear medicine renal scan*
- For women of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 3 months after the final dose of mosunetuzumab, 12 months after the final dose of polatuzumab vedotin, 12 months after the final dose of rituximab, 12 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 3 months after the final dose of tocilizumab, as applicable. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of 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.

- 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 60 days after the final dose of mosunetuzumab, *6 months* after the final dose of polatuzumab vedotin, 3 months after the final dose of rituximab, 6 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 60 days after the final dose of tocilizumab, as applicable, to avoid exposing the embryo. 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 post-ovulation methods) and withdrawal are not acceptable methods of contraception.

#### 4.1.1.2 Inclusion Criteria for Phase Ib Portion

Patients must also meet the following criteria for study entry in the Phase Ib portion (Groups A and B):

- Histologically confirmed B-cell NHL according to WHO 2016 classification (pathology report must provide WHO 2016 diagnosis) expected to express the CD20 antigen (Swerdlow et al. 2016), except:
  - Plasma cell malignancies (e.g., lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, plasmacytoma, plasmablastic lymphoma)
  - Primary DLBCL of the CNS
  - Burkitt lymphoma
- R/R B-cell NHL after at least one prior systemic lymphoma therapy
- Treatment with at least one prior CD20-directed therapy (e.g., rituximab, obinutuzumab, ofatumumab, ibritumomab tiuxetan)
- Group B only: no prior treatment with polatuzumab vedotin

#### 4.1.1.3 Inclusion Criteria for Phase II Portion

Patients must also meet the following criteria for study entry in the Phase II portion:

- Previously untreated, histologically confirmed DLBCL according to WHO 2016 classification

  Patients with a diagnosis of primary mediastinal DLBCL are not eligible.

  Patients with a diagnosis of high-grade B-cell lymphoma (HGBL) with rearrangements of MYC and BCL2 and/or BCL6 or HGBL, not otherwise specified (NOS), are allowed.

- IPI score of 2–5 (see Appendix 4)
- Ability and willingness to comply with the study protocol procedures, including PRO measures

### 4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 12 months after the final dose of polatuzumab vedotin, 12 months after the final dose of rituximab, 12 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 3 months after the final dose of tocilizumab, as applicable.

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Prior treatment with mosunetuzumab
- Prior allogeneic stem-cell transplant
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to receive full dose of any of the individual components of R-CHP
- Contraindication to receive full dose of vincristine if planned study treatment includes vincristine (e.g., CHOP)
- Current Grade >1 peripheral neuropathy
- Patients with history of confirmed progressive multifocal leukoencephalopathy (PML)
- Known or suspected chronic active Epstein Barr virus (CAEBV) infection
- 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.
- Acute or chronic hepatitis C virus (HCV) infection

  Patients who are positive for HCV antibody must be negative for HCV by PCR.
- HIV seropositivity
- Administration of a live, attenuated vaccine within 4 weeks before first study treatment administration or anticipation that such a live, attenuated vaccine will be required during the study
- Prior solid organ transplantation
- *Known or suspected history of hemophagocytic lymphohistiocytosis*
- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid

syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.

Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Patients with a history of disease-related immune thrombocytopenic purpura, autoimmune hemolytic anemia, or other stable autoimmune diseases may be eligible after review and approval by the Medical Monitor.

- Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) with the exception of pre-phase treatment with prednisone up to 100 mg daily for 7 days (or equivalent corticosteroid dose) prior to C1D1

  The use of inhaled corticosteroids is permitted.

  The use of mineralocorticoids for management of orthostatic hypotension is permitted.

  The use of physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.

- Current or past history of CNS lymphoma
- Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease

  Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits as judged by the investigator are allowed.

  Patients with a history of epilepsy who have had no seizures in the past 2 years while not receiving any anti-epileptic medications are allowed in the expansion cohorts only.

- Prior radiotherapy to the mediastinal/pericardial region
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.

  Patients with a malignancy that has been treated with curative intent will also be excluded unless the malignancy has been in documented remission without treatment for $\geq 2\ years$ before enrollment.

- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)

- Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, congestive heart failure, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks before C1D1
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Recent major surgery within 4 weeks before the start of C1D1, other than superficial lymph node biopsies for diagnosis
- Any of the following abnormal laboratory values within 14 days of initiation of study treatment:

– AST or ALT $>2.5\times$ ULN

– Total bilirubin $\geq 1.5\times$ ULN

– INR $>1.5\times$ ULN in the absence of therapeutic anticoagulation

– PTT or aPTT $>1.5\times$ ULN in the absence of a lupus anticoagulant

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

#### 4.1.2.1 Exclusion Criteria for Phase Ib Portion

Patients who also meet any of the following criteria will be excluded from study entry in the Phase Ib portion:

- Prior treatment with $>250$ mg/m$^2$ doxorubicin (or equivalent anthracycline dose)

  During the study, patients may not exceed a maximum cumulative lifetime dose of 550 mg/m$^2$ anthracyclines (i.e., doxorubicin), which includes treatment on this study.

- Prior treatment with chemotherapy, immunotherapy, and biologic therapy 4 weeks prior to C1D1

  A shorter interval may be acceptable for patients on oral targeted therapies upon discussion with the Medical Monitor.

- Prior treatment with radiotherapy within 2 weeks prior to C1D1

  If patients have received radiotherapy within 4 weeks prior to the initiation of study treatment, patients must have at least one measurable lesion outside of the radiation field.

  Patients who have only one measurable lesion that was previously irradiated but subsequently progressed are eligible.

- Adverse events from prior anti-cancer therapy resolved to ≤Grade 1 (with the exception of alopecia and anorexia)

#### 4.1.2.2 Exclusion Criteria for Phase II Portion

Patients who also meet any of the following criteria will be excluded from study entry in the Phase II portion:

- Patients with transformed lymphoma
- Prior therapy for B-cell NHL

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. Patients with R/R B-cell NHL (Phase Ib) and previously untreated DLBCL (Phase II) will be enrolled. Following the Phase Ib portion of this study and enrollment of the Phase II safety cohort, the randomized Phase II portion of the study will start. In this phase, patients will be randomized in a 2:1:2 ratio to receive M-CHP-pola, R-CHP-pola, or M-CHOP, respectively, until a total of up to 40 patients have received M-CHOP, including Group C safety cohort and Arm 3. Thereafter, a ratio of 2:1 will be used to randomize patients into the M-CHP-pola or R-CHP-pola arm.

Patients will be stratified by IPI score (2 vs. 3–5) and presence or absence of bulky disease, defined as at least one ≥7.5-cm lesion at baseline (see Section 3.3.6). After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the patient number will be assigned and the patient will be randomized to the treatment assignment via an interactive voice or web-based response system (IxRS). Randomization will be performed by the IxRS using stratified permuted blocks.

## 4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are mosunetuzumab, polatuzumab vedotin, rituximab, and tocilizumab.

Prednisone, cyclophosphamide, vincristine, and doxorubicin can be considered SOC in the treatment of patients with B-cell NHL included in this study.

### 4.3.1 Study Treatment Formulation, Packaging, and Handling

#### 4.3.1.1 Mosunetuzumab

Mosunetuzumab will be supplied by the Sponsor. For information on the formulation, packaging, and handling of mosunetuzumab, see the pharmacy manual and the Mosunetuzumab Investigator's Brochure.

#### 4.3.1.2 Polatuzumab Vedotin

Polatuzumab vedotin will be supplied by the Sponsor. For information on the formulation, packaging, and handling of polatuzumab vedotin, see the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure.

#### 4.3.1.3 Rituximab

Rituximab will be supplied by the Sponsor where required by local health authority regulations. For information on the formulation, packaging, and handling of rituximab, see the pharmacy manual and the local prescribing information.

#### 4.3.1.4 Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

Cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone will be supplied by the Sponsor where required by local health authority regulations. For information on the formulation, packaging, and handling of cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone, see the local prescribing information.

#### 4.3.1.5 Tocilizumab

Tocilizumab will be supplied by the Sponsor. For information on the formulation, packaging, and handling of tocilizumab, refer to the pharmacy manual and the Tocilizumab Investigator's Brochure.

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Sections 4.3.3.2–4.3.3.4.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.13.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.7.

#### 4.3.2.1 Mosunetuzumab

Mosunetuzumab will be administered intravenously according to the schedule outlined in Sections 4.3.3.2 and 4.3.3.3. Mosunetuzumab will be administered in a setting with immediate access to trained critical care personnel and facilities equipped to respond to and manage medical emergencies. Neurology consultation services should be readily available to address any neurologic adverse events that may arise as a result of

mosunetuzumab treatment (see Section 5.1.7.7 and Table 11), and nephrology consultation with acute dialysis capabilities should be readily available to address any renal toxicity that might accompany TLS (see Section 5.1.2.2).

Hospitalization requirements for patients receiving mosunetuzumab-containing study treatment are described in Sections 4.3.3.2 and 4.3.3.3.

Mosunetuzumab will be administered to well-hydrated patients. Corticosteroid premedication consisting of dexamethasone 20 mg IV or methylprednisolone 80 mg IV should be administered at least 1 hour prior to the administration of each mosunetuzumab dose. On days that the mosunetuzumab IV corticosteroid premedication (dexamethasone 20 mg IV or methylprednisolone 80 mg IV) overlaps with the prednisone 100 mg PO dose in the CHOP or CHP regimens, only the prednisone 100 mg dose should be administered, and the IV corticosteroid premedication should be omitted. In addition, premedication with oral acetaminophen or paracetamol (e.g., 500–1000 mg) and/or 50–100 mg diphenhydramine may be administered per standard institutional practice prior to administration of mosunetuzumab. *For patients who are receiving single agent mosunetuzumab following Cycle 6, steroid pre-medication is required in Cycles 7 and 8. Steroid premedication may be optional in subsequent doses (Cycle 9 and beyond), based on the investigator's assessment and if the patient did not have CRS in the preceding dose cycle. If a patient receives step-up dosing for a dose delay of more than 6 weeks from the previous dose, steroid pre-medication is required before each mosunetuzumab dose during the step-up dosing cycle.*

Initially, mosunetuzumab will be infused over 4 hours (±15 minutes). The infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. The recommended management of CRS/IRRs is detailed in Section 5.1.7.3, Section 5.1.7.4, and Table 10. Following each mosunetuzumab dose, patients will be observed at least 90 minutes for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of IRRs or CRS (note that patients will be monitored for *at least for 24 hours after the end of* the first dose of mosunetuzumab in Cycle 1). In the absence of infusion-related adverse events, the infusion time of mosunetuzumab in Cycles 2 and beyond may be reduced to 2 hours (± 15 minutes).

Guidelines for management of adverse events, including mosunetuzumab dosage and schedule modification and treatment interruption or discontinuation, are provided in Section 5.1.7.

#### 4.3.2.2 Polatuzumab Vedotin

The dose of polatuzumab vedotin for each patient will be 1.8 mg/kg IV and will be administered according to the schedule outlined in Sections 4.3.3.3 and 4.3.3.4. The total dose of polatuzumab vedotin for each patient will depend on the patient's weight on Day 1 of each cycle (or within 72 hours prior to Day 1 of that cycle). Patients may

receive the initial (Cycle 1) dose of polatuzumab vedotin unless the patient's body weight has changed by > 10% from baseline weight, in which case a new polatuzumab vedotin dose must be calculated. This new dose of polatuzumab vedotin may be given in subsequent cycles, unless the patient experiences another > 10% change in body weight, in which case a new polatuzumab vedotin dose must be calculated.

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

The initial dose will be administered over 90 (± 10) minutes to patients who are well hydrated. Premedication (e.g., 500–1000 mg of oral acetaminophen or paracetamol and 50–100 mg diphenhydramine as per institutional standard practice) may be administered to an individual patient before administration of polatuzumab vedotin. If IRRs are observed with the first infusion of polatuzumab vedotin in the absence of premedication, premedication must be administered before subsequent doses.

The polatuzumab vedotin infusion may be slowed or interrupted for patients who experience infusion-associated symptoms. Following the initial dose, patients will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If prior infusions have been well tolerated, subsequent doses of polatuzumab vedotin may be administered over 30 (± 10) minutes, followed by a 30-minute observation period after the infusion.

Other infusions, such as mosunetuzumab, should be started no sooner than 60 minutes after completion of polatuzumab vedotin infusion. In patients requiring a 90-minute observation time following polatuzumab vedotin administration, other infusions should be started after this observation period is completed.

For management of adverse events and guidance on dose modifications for polatuzumab vedotin, please refer to Section 5.1.7.

#### 4.3.2.3 Rituximab

Rituximab will be administered by IV infusion at a dose of 375 mg/m$^2$ and will be administered according to the schedule in Section 4.3.3.4. The dose of rituximab 375 mg/m$^2$ should not be modified.

Please consult the pharmacy manual and local prescribing information for a list of compatible materials and specific dose preparation instructions.

Rituximab will be administered after the prednisone dosing and before the cyclophosphamide, doxorubicin, and polatuzumab vedotin infusions. Once the rituximab infusion is completed, patients are to be observed for 30 minutes before the start of the other infusions. The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden or high peripheral lymphocyte count). For

patients who experience an adverse event during a rituximab infusion, administration of rituximab and cyclophosphamide, doxorubicin, and polatuzumab vedotin may be continued on the following day if required.

If a dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication (including prednisone) and at the first infusion rate. All rituximab infusions should be administered to patients after premedication with oral acetaminophen (e.g., 650–1000 mg) and an antihistamine such as diphenhydramine hydrochloride (50–100 mg) 30–60 minutes before starting each infusion (unless contraindicated). For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion. See Table 2 for a summary of recommendations regarding premedications for rituximab.

Rituximab infusions will be administered according to the instructions outlined in Table 2. If a patient tolerates the first cycle of study treatment without significant IRRs, rituximab may be administered as a rapid infusion (over 60–90 minutes) in accordance with local institutional guidelines and prescribing information.

During the treatment period, rituximab must be administered to patients in a setting where full emergency resuscitation facilities are immediately available. Patients should be under close supervision of the investigator at all times. For the management of adverse events please consult the local prescribing information. For management of IRRs and anaphylaxis, see also Section 5.1.7.3 and Table 9.

**Table 2 Premedication for Rituximab and Polatuzumab Vedotin**

| Timepoint | Patients Who Require Premedication | Premedication | Administration |
|---|---|---|---|
| Cycle 1, Day 1 | • All patients | • Corticosteroid [a] | Complete ≥ 1 hour prior to rituximab and/or polatuzumab vedotin. |
| | | • Antihistamine [b]<br>• Analgesic/ anti-pyretic [c] | Administer ≥ 30 minutes prior to rituximab infusion; may be administered to patients prior to administration of any polatuzumab vedotin. |
| Cycles 2 and beyond, Day 1 | • Patients with no IRR during the previous infusion | • Corticosteroid [a] | Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin. |
| | | • Antihistamine [b]<br>• Analgesic/ anti-pyretic [c] | Administer ≥ 30 minutes prior to infusion. These may be omitted at the investigator's discretion. |
| | • Patients with Grade 1 or 2 IRR during the previous infusion | • Corticosteroid [a] | Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin. |
| | | • Antihistamine [b]<br>• Analgesic/ anti-pyretic [c] | Administer ≥ 30 minutes prior to rituximab and/or polatuzumab vedotin. |
| | • Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion<br>• Patients with bulky disease | • Corticosteroid [a] | Complete ≥ 1 hour prior to rituximab and/or polatuzumab vedotin. |
| | | • Antihistamine [b]<br>• Analgesic/ anti-pyretic [c] | Administer ≥ 30 minutes prior to rituximab and/or polatuzumab vedotin. |

IRR = infusion-related reaction.

[a] Part of study treatment: 100 mg of prednisone. May be substituted with 100 mg of prednisolone or 80 mg of methylprednisolone. Hydrocortisone should not be used, as it has not been effective in reducing rates of IRRs.

[b] For example, 50–100 mg of diphenhydramine.

[c] For example, 650–1000 mg of acetaminophen/paracetamol.

**Table 3 Administration of First and Subsequent Infusions of Rituximab**

| First Infusion (Day 1) | Subsequent Infusions |
|---|---|
| • Begin infusion at an initial rate of 50 mg/hr.<br>• If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.<br>• If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred). | • If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/hr and follow instructions for the first infusion.<br>• If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hr), begin the infusion at a rate of 100 mg/hr.<br>• If no infusion reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.<br>• If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred). |

#### 4.3.2.4 CHP Chemotherapy Dosage and Administration

CHP chemotherapy consists of cyclophosphamide and doxorubicin administered by IV push and oral prednisone or prednisolone. For information on the order of administration, see Sections 4.3.3.2–4.3.3.4 and Figure 6.

- Cyclophosphamide 750 mg/m$^2$ IV on Day 1 over 1 hour or per local institutional practice
- Doxorubicin 50 mg/m$^2$ IV on Day 1 over 3–5 minutes or per local institutional practice
- Prednisone 100 mg/day PO on Days 1–5

  Note: Prednisone may be replaced with prednisolone (100 mg/day) at sites where prednisone is not available or is not the therapy of choice. On days when patients receive dexamethasone 20 mg IV or methylprednisolone 80 mg IV as mosunetuzumab premedication, the IV corticosteroid premedication should be omitted on that day.

Refer to the specific package inserts for preparation, administration, and storage guidelines. Body surface area (BSA) may be capped at 2 m$^2$ per institutional standards.

#### 4.3.2.5 CHOP Chemotherapy Dosage and Administration

Please refer to CHP Chemotherapy Dosage and Administration for cyclophosphamide, doxorubicin, and prednisone in Section 4.3.2.4.

The dose of vincristine for each patient will be 1.4 mg/m$^2$ (maximum 2 mg dose). Vincristine is typically administered as an IV infusion via minibag over approximately 10–30 minutes through a dedicated line and will be given on Day 1 of Cycles 1–6. Refer to the specific package inserts for preparation, administration, and storage guidelines. For dose modifications for vincristine, please refer to Sections 5.1.7.1 and 5.1.7.2 and Table 7 and Table 8.

#### 4.3.2.6 Tocilizumab

Tocilizumab should be administered when necessary as described in Section 5.1.7.4 and Table 10. Tocilizumab will be supplied by the Sponsor. Please refer to the pharmacy manual for administration instructions for tocilizumab. Note: if tocilizumab is administered, refer to Appendix 14 for the schedule of activities for tocilizumab treatment of CRS.

Any overdose or incorrect administration of tocilizumab should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

### 4.3.3 Pretreatment and Study Treatment Regimens

#### 4.3.3.1 Corticosteroid Pretreatment prior to Initiation of Study Treatment

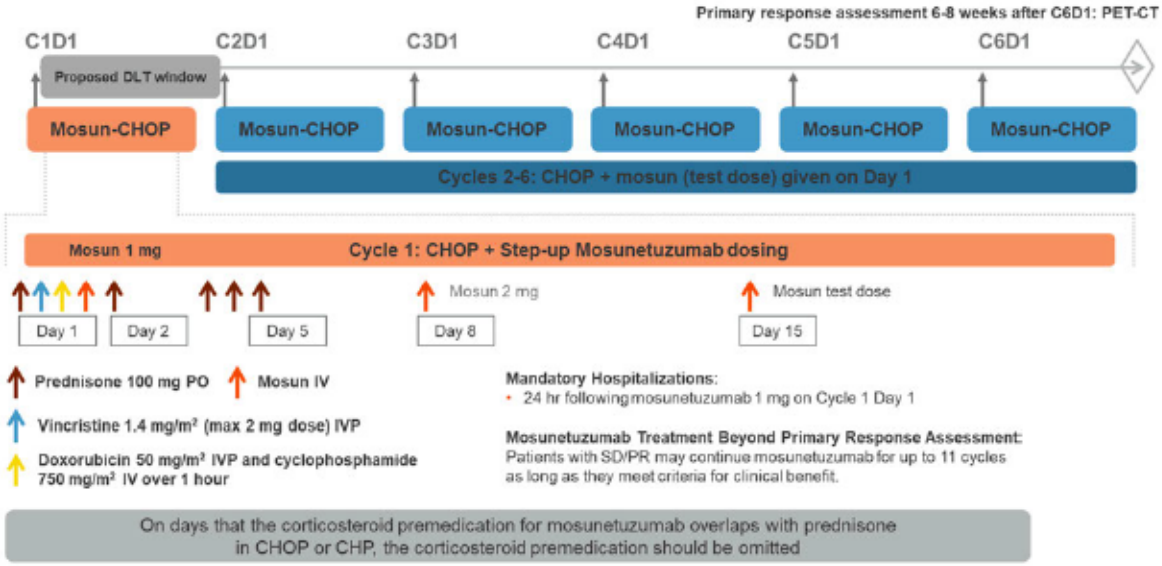
In patients with previously untreated DLBCL or patients considered to be at high risk for TLS or acute toxicity with the first cycle of study treatment, a pre-phase treatment of prednisone at a dose of up to 100 mg PO every day for up to 7 days prior to C1D1 is permitted, at the discretion of the investigator (Pfreundschuh 2010; Tilly et al. 2015). Vincristine is not permitted as part of the pre-phase treatment. The pre-phase treatment is not considered part of study treatment but will be recorded in the eCRF. The purpose of the pre-phase treatment is to prevent TLS in patients with extensive disease and to reduce toxicity associated with the first cycle of study treatment (e.g., CRS). Staging study assessments (i.e., CT/magnetic resonance imaging [MRI], PET-CT scan) must be performed prior to initiation of pre-phase treatment.

#### 4.3.3.2 Mosunetuzumab plus CHOP Regimen

The M-CHOP regimen is shown in Figure 3. Patients will receive 6 cycles, lasting 21 days each, of prednisone 100 mg daily for Days 1–5, vincristine 1.4 mg/m$^2$ (maximum 2 mg dose) on Day 1, doxorubicin 50 mg/m$^2$ on Day 1, cyclophosphamide 750 mg/m$^2$ on Day 1, and mosunetuzumab on Days 1, 8, and 15 in Cycle 1, and Day 1 of Cycles 2–6. In Cycle 1, patients will receive mosunetuzumab 1 mg on Day 1, 2 mg on Day 8, and the test dose on Day 15 (13.5 mg in the first Phase Ib cohort and then to be determined based on dose-escalation or de-escalation rules), with the Day 15 dose given on Day 1

of subsequent cycles of treatment. Patients with SD or PR at the end of the 6 cycles of treatment (i.e., primary response assessment) may continue mosunetuzumab as monotherapy at the Day 15 test dose for up to 11 additional cycles on Day 1 of each 21-day cycle.

**Figure 3 M-CHOP Regimen**




C=cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CT = computed tomography; D=day; DLT=dose-limiting toxicity; IVP = IV push; M-CHOP = mosunetuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; mosun = mosunetuzumab; PET = positron emission tomography; PO = orally; PR=partial response; SD=stable disease.

The dose of the CHOP agent should be calculated on the basis of a patient's body weight within 72 hours of C1D1. For changes >10% in body weight from baseline for all subsequent doses, the doses of all agents should be modified accordingly to the new weight/BSA. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments.

Patients receiving mosunetuzumab will receive corticosteroid premedication with the prednisone 100 mg that is part of CHOP, instead of the mosunetuzumab premedication of dexamethasone 20 mg IV or methylprednisolone 80 mg IV when mosunetuzumab and CHOP overlap. This oral corticosteroid dose, which is part of CHOP, will replace whenever the mosunetuzumab administration overlaps with that of the mosunetuzumab premedication IV corticosteroid premedication dosing.

Patients will be hospitalized for at least *24 hours* following *the end of* the first infusion of mosunetuzumab in Cycle 1 (C1D1). Other mosunetuzumab doses may be given as an outpatient with appropriate monitoring infrastructure if adverse events were acceptable with the first dose (see Section 5.2.1); however, investigators may choose to hospitalize patients for monitoring based on their clinical judgment. Patients who develop CRS or

neurotoxicity that requires medical intervention with the first dose are required to be hospitalized for subsequent doses of mosunetuzumab until they have tolerated an infusion without these acute toxicities.

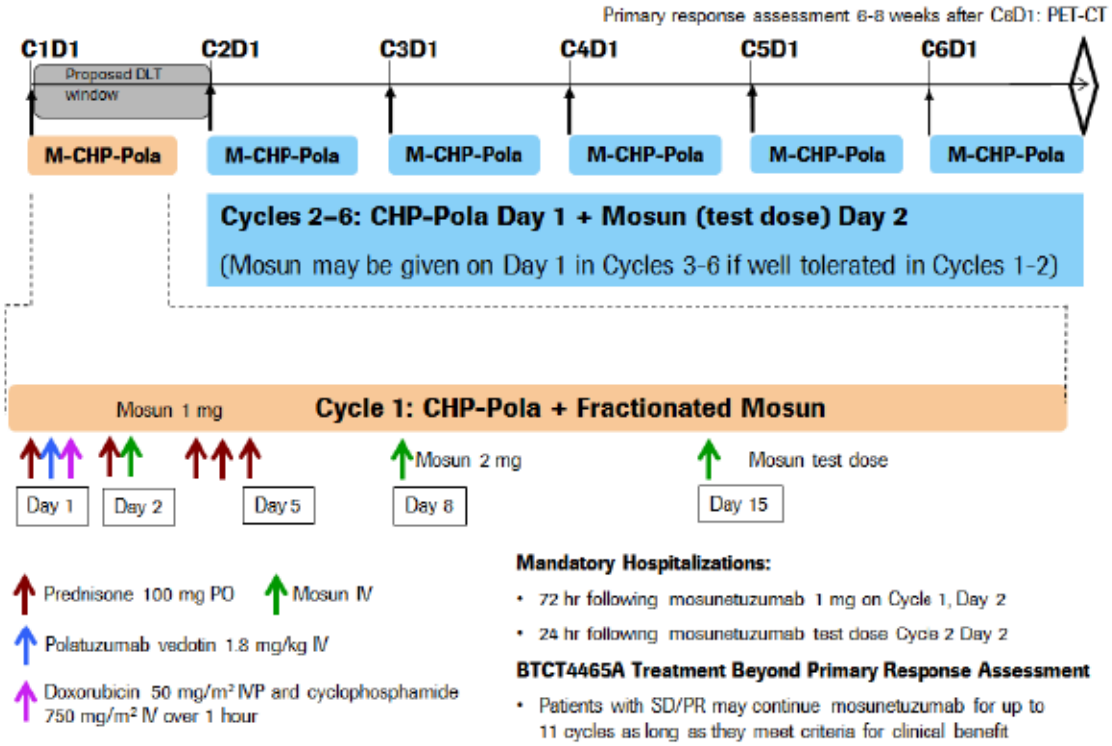
#### 4.3.3.3 Mosunetuzumab Plus CHP-Pola Regimen

The M-CHP-pola regimen is shown in Figure 4 *for Phase I Group B, and Figure 5 for Phase II Arm 1.*

*In Phase I Group B, patients* will receive 6 cycles, lasting 21 days each, of prednisone 100 mg daily for Days 1–5, polatuzumab vedotin 1.8 mg/kg, doxorubicin 50 mg/m$^2$ on Day 1, cyclophosphamide 750 mg/m$^2$ on Day 1, and mosunetuzumab on Days 2, 8, and 15 in Cycle 1, and Day 2 of Cycles 2–6 (with the option of giving mosunetuzumab on Day 1 in Cycles 3–6 if the infusion was well tolerated in Cycles 1 and 2). In Cycle 1, patients will receive mosunetuzumab 1 mg on Day 2, 2 mg on Day 8, and a test dose on Day 15, with the Day 15 test dose subsequently given on Day 2 (or Day 1 after Cycle 2) of subsequent cycles of treatment. Patients with SD or PR at the end of the 6 cycles of treatment may continue mosunetuzumab as monotherapy at the Day 15 dose for up to 11 additional cycles on Day 1 of each 21-day cycle.

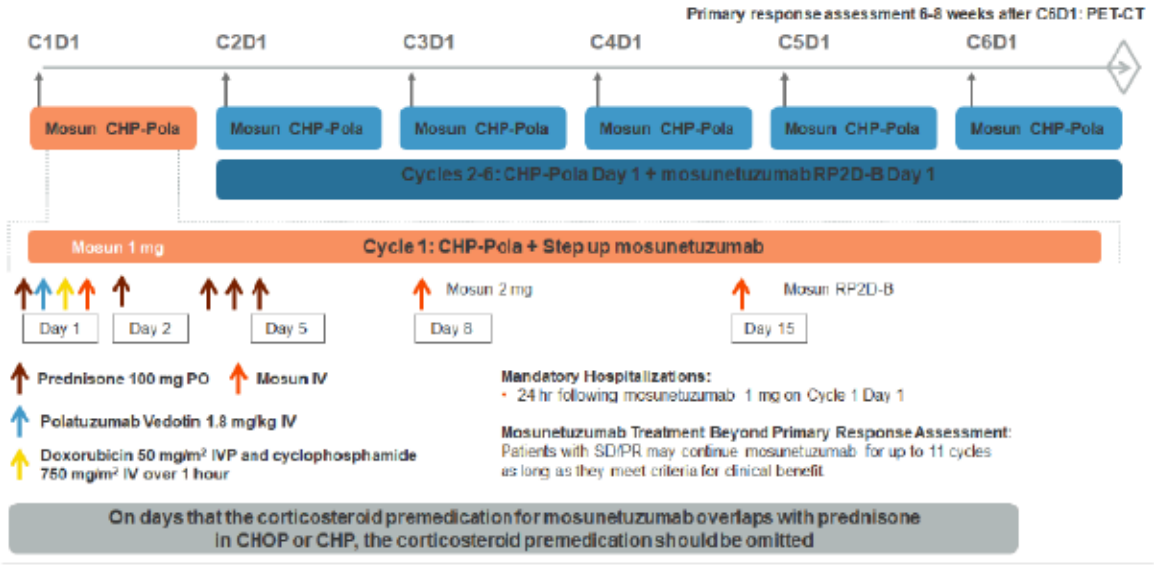
*In Phase II Arm 1, patients will receive 6 cycles, lasting 21 days each, of prednisone 100 mg daily for Days 1–5, polatuzumab vedotin 1.8 mg/kg, doxorubicin 50 mg/m$^2$ on Day 1, cyclophosphamide 750 mg/m$^2$ on Day 1, and mosunetuzumab on Days 1, 8, and 15 in Cycle 1, and Day 1 of Cycles 2–6. In Cycle 1, patients will receive mosunetuzumab 1 mg on Day 1, 2 mg on Day 8, and the RP2D B dose on Day 15, with the Day 15 dose subsequently given on Day 1 of subsequent cycles of treatment. Patients with SD or PR at the end of the 6 cycles of treatment may continue mosunetuzumab as monotherapy at the Day 15 dose for up to 11 additional cycles on Day 1 of each 21-day cycle.*

**Figure 4 M-CHP-Pola Regimen *Phase I, Group B***




C=cycle; CHP-Pola=cyclophosphamide, doxorubicin, and prednisone plus polatuzumab vedotin; CT=computed tomography; D=day; DLT=dose-limiting toxicity; IVP=IV push; M-CHP-pola = mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; mosun=mosunetuzumab; PET=positron emission tomography; PO=orally; PR=partial response; SD=stable disease.

**Figure 5: M-CHP-Pola Regimen Phase II, Arm 1**




*C=cycle; CHP-Pola =cyclophosphamide, doxorubicin, and prednisone plus polatuzumab vedotin; CT =computed tomography; D=day; IVP =IV push; M-CHP-pola = mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; mosun =mosunetuzumab; PET =positron emission tomography; PO =orally; PR=partial response; RP2D-B=recommended Phase II dose, Group B; SD=stable disease.*

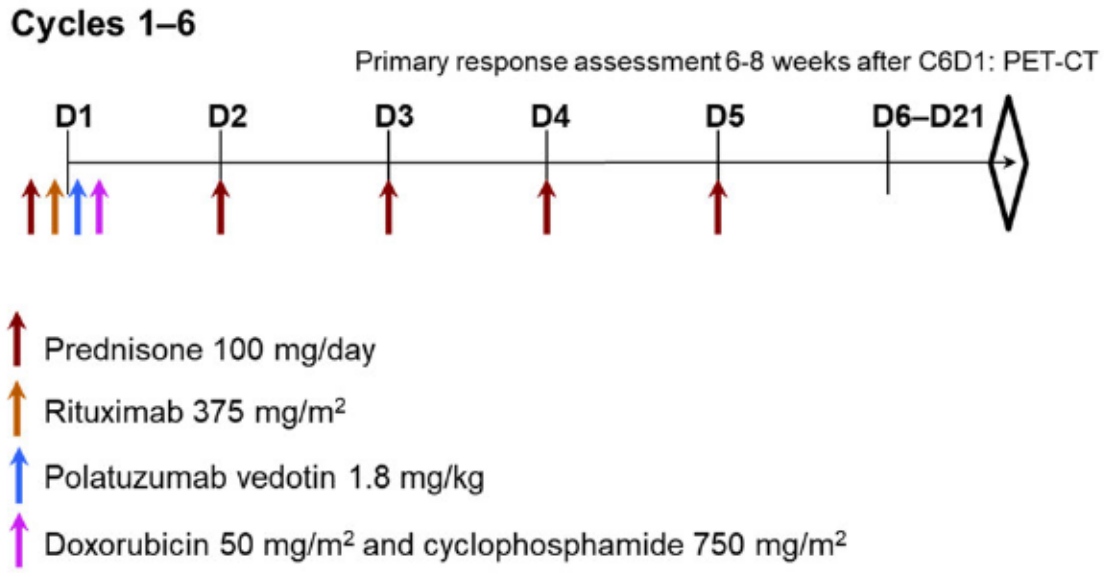
Patients receiving mosunetuzumab will receive premedication with dexamethasone 20 mg IV or methylprednisolone 80 mg IV. On days that mosunetuzumab IV corticosteroid premedication overlaps with the prednisone 100 mg oral dose, the IV corticosteroid premedication should be omitted.

Patients will be hospitalized for at least *24 hours* following *the end of* the first infusion of mosunetuzumab in Cycle 1. Other mosunetuzumab doses may be given as an outpatient with appropriate monitoring infrastructure if adverse events were acceptable with the first dose (see Section 5.1.1); however, investigators may choose to hospitalize patients for monitoring based on their clinical judgment. Patients who develop CRS or neurotoxicity that requires medical intervention with the first dose are required to be hospitalized for subsequent doses of mosunetuzumab until they have tolerated an infusion without these acute toxicities.

#### 4.3.3.4 R-CHP–Pola Regimen

Patients will receive 6 cycles, lasting 21 days each, of prednisone 100 mg daily for Days 1–5 of each cycle, rituximab 375 mg/m$^2$ on Day 1, polatuzumab vedotin 1.8 mg/kg on Day 1 (or Day 2 if rituximab infusion is prolonged due to infusion-related adverse events), doxorubicin 50 mg/m$^2$ on Day 1, and cyclophosphamide 750 mg/m$^2$ on Day 1 (see Figure 6).

**Figure 6 R-CHP-Pola Administration Schedule**




C=cycle; CT = computed tomography; D=day; PET = positron emission tomography.
Note: In patients whose rituximab infusion is prolonged due to infusion related adverse events on Day 1, polatuzumab vedotin may be given on Day 2 per the investigator's discretion.

### 4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (mosunetuzumab, polatuzumab vedotin, rituximab, and tocilizumab) will be provided by the Sponsor. Non-IMP medications (cyclophosphamide, doxorubicin, prednisone, and vincristine) may not be provided unless required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log or a Sponsor-approved equivalent.

### 4.3.5 Continued Access to IMPs: Mosunetuzumab, Polatuzumab Vedotin, Rituximab, and Tocilizumab

The Sponsor will offer continued access to Roche IMPs (mosunetuzumab, polatuzumab vedotin, rituximab, and tocilizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs (mosunetuzumab, polatuzumab vedotin, rituximab, and tocilizumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMPs (mosunetuzumab, polatuzumab vedotin, rituximab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for B-cell NHL and/or specifically DLBCL
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for B-cell NHL and/or specifically DLBCL
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

## 4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

### 4.4.1 Permitted Therapy

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

#### 4.4.1.1 Hematopoietic Growth Factors

Concomitant use of hematopoietic growth factors for anemia and thrombocytopenia, such as erythropoietin or thrombopoietin (oprelvekin, eltrombopag), should not be initiated or increased in dose from the start of the screening period until the completion of the DLT assessment period in the absence of a DLT. After the DLT assessment period has been completed or after a DLT has been documented, initiation or dose and schedule modifications of hematopoietic growth factors are allowed in accordance with instructions provided in the package inserts, institutional practice, and/or published guidelines.

For neutropenia, G-CSF is required as primary prophylaxis in Cycles 1–6 of study treatment. Dosing of G-CSF should follow each site's institutional standards or may be at the investigator's discretion. For patients who develop neutropenia despite prophylaxis, G-CSF is not routinely recommended for the treatment of uncomplicated neutropenia. However, G-CSF may be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes (Smith et al. 2015).

#### 4.4.1.2 Prophylaxis for Tumor Lysis Syndrome

TLS is a known PD effect of anti-tumor therapy in hematologic malignancies including NHL. All patients should be well hydrated prior to the first dose of study treatment. *Starting 2 days prior to the first dose of study treatment, it is desirable to maintain a fluid intake of approximately 2–3 L/day. In addition, all patients with high tumor burden and considered to be at risk for tumor lysis should be treated with 300 mg/day of allopurinol orally or a suitable alternative treatment (e.g., rasburicase), starting 48-72 hours prior to Day 1 of Cycle 1. Patients* should continue to receive repeated prophylaxis*, if deemed appropriate by the investigator,* and adequate hydration prior to each subsequent cycle of treatment.

#### 4.4.1.3 Infection Prophylaxis

Anti-infective prophylaxis for viral, fungal, bacterial, or *Pneumocystis* infections is permitted and should be instituted per institutional practice or investigator preference based on individual patient risk factors. Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the SOC may be treated prophylactically (*Taplitz et al. 2018; NCCN 2020*). All anti-infective prophylaxis used should be recorded appropriately in the eCRF.

#### 4.4.1.4 CNS Prophylaxis

CNS prophylaxis with intrathecal chemotherapy should only be given according to institutional practice and its use documented in the eCRF. CNS prophylaxis using high-dose IV methotrexate (e.g., 1 g/m$^2$ per cycle) is not permitted.

#### 4.4.1.5 Prophylaxis for Hemorrhagic Cystitis

Patients should be adequately hydrated before and after cyclophosphamide administration and should be instructed to void frequently. Mesna may be used as prophylaxis according to institutional practice.

#### 4.4.1.6 Pre-Planned Radiotherapy

Pre-planned radiotherapy (i.e., radiation that was planned before randomization to be given at the end of study treatment) may be administered to initial sites of bulky or extranodal disease according to institutional practice. If indicated, pre-planned radiotherapy should be administered within 8 weeks after the last study drug treatment and should start after the primary response assessment when PET-CT scans are completed. Any radiotherapy should be pre-planned by the center and documented prior to randomization (if applicable) and then entered in the eCRF once the patient is randomized. All unplanned radiotherapy administered to patients will be considered as a new anti-lymphoma treatment.

#### 4.4.1.7 Pre-Phase Corticosteroid Treatment

Pre-phase therapy with a maximum dose of prednisone 100 mg/day (or equivalent dose of alternative corticosteroid) for up to 7 days is permitted per investigator discretion and local institutional practice in patients with previously untreated DLBCL (see also Section 4.3.3.1).

#### 4.4.1.8 Other Concomitant Medications

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards.

Anti-emetic therapy may be instituted for any patient if clinically indicated according to institutional practice.

### 4.4.2 Cautionary Therapy

#### 4.4.2.1 Use of Calcium Channel Blockers

The use of any calcium channel entry blockers given concomitantly with an anthracycline drug may potentially increase the risk of cardiac toxicity associated with anthracycline administration. For patients on CHOP or CHP-pola, it is recommended that calcium channel blockers be avoided within 30 days of the administration of an anthracycline drug when possible and clinically appropriate.

#### 4.4.2.2 Medications Given with Precaution due to Effects Related to CYP450

**Mosunetuzumab:** Given the expected pharmacology of mosunetuzumab, the transient release of cytokines may suppress CYP450 enzymes and cause drug–drug interactions. Preliminary clinical data indicate that mosunetuzumab induced a transient elevation in plasma 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 (see Appendix 5). Such concomitant medications should be monitored for toxicity and dose adjusted accordingly.

**Polatuzumab vedotin**: 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 (Chen et al. 2015), strong CYP3A4 inhibitors may increase the exposure (e.g., AUC) of unconjugated MMAE by ~50% while acMMAE PK is not affected. Concomitant medications that are strong CYP3A4 inhibitors (see Appendix 6) 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 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 6. 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 Medical Monitor if questions arise regarding medications not listed in Appendix 6.

#### 4.4.2.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. A sample list of cautionary medications (including some herbal therapies) is included in Appendix 6. Herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator; herbal therapies intended as treatment of lymphoma are prohibited (see Section 4.4.3).

### 4.4.3 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Administration of live vaccines (see also Section 4.4.4.1)
- Cytotoxic chemotherapy other than study treatments intended for treatment of lymphoma

- Radiotherapy for treatment of lymphoma (except pre-planned radiotherapy as described in Section 4.4.1.6)
- Immunotherapy other than study treatments for treatment of lymphoma
- Immunosuppressive therapy (except medications indicated per protocol, including corticosteroids and tocilizumab)
- Hormone therapy for the treatment of cancer, whether approved by local regulatory authorities or investigational.

  Adjuvant endocrine therapy for non-metastatic, hormone receptor-positive breast cancer is permitted.
- Biologic or targeted agents for treatment of lymphoma
- Herbal therapies intended as treatment of lymphoma
- Any therapies intended for the treatment of lymphoma, whether approved by local regulatory authorities or investigational
- Pre-phase therapy with medications other than prednisone as described in Section 4.3.3.1 (e.g., vincristine)

Patients who require the use of any of these agents will be discontinued from study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 90 days following the patient's last dose of study treatment or until the patient receives another anti-cancer therapy, whichever occurs first. The above lists of medications are not necessarily comprehensive. The investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

### 4.4.4 Additional Restrictions

#### 4.4.4.1 Immunizations

Patients who participate in the study may not receive either primary or booster vaccination with live virus vaccines starting from at least 4 weeks before initiation of study treatment until B-cell recovery. Killed vaccines or toxoids should be given at least 4 weeks prior to the first dose of study treatment to allow development of sufficient immunity. The restriction applies to all treatment regimens in this study as they all contain either mosunetuzumab or rituximab that are expected to deplete normal B-cells in patients.

Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases before study therapy. Patients who require the use of vaccination with live virus vaccines will be discontinued from study treatment.

## 4.5 STUDY ASSESSMENTS

Screening and pretreatment tests and evaluations will be performed within 14 days preceding the first dose of study treatment (except radiographic tumor assessment

which may be performed up to 28 days preceding the first dose of study drug, providing no anti-tumor therapy was administered in this period. Results of SOC tests or examinations performed prior to obtaining informed consent and within the screening window specified above may be used; these tests do not need to be repeated for screening.

Refer to Appendix 1 and Appendix 2 for the schedules of assessments performed during the study.

### 4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including B symptoms (i.e., weight loss, night sweats, or fever), clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. B symptoms (i.e., weight loss, night sweats, or fever) will be assessed according to Appendix 1.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity data is collected in order to assess whether the enrolled population is reflective of the general population and to evaluate whether different treatment effects are observed among different populations.

### 4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. A complete neurologic examination, which includes an evaluation of mental status, cranial nerves, muscle strength, sensation, and coordination should be performed and documented in the patient chart. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), targeted symptom-directed physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be associated with tumor assessment [e.g., lymph nodes, liver, and spleen and those systems associated with symptoms], or potential drug-related toxicity; see Appendix 1). Neurologic examinations should include an assessment of mental status, cranial nerves, muscle strength, sensation, and coordination. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.4 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure, respiratory rate, pulse oximetry, pulse rate, and body temperature while the patient is in a sitting or semi-supine position. Every effort should be made to ensure that vital signs are obtained from patients in a consistent manner/position.

Vital signs for patients should be obtained according to the schedule of activities in Appendix 1. Additional vital sign monitoring should be performed if clinically indicated.

### 4.5.5 Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, diagnostic CT scans (or MRI scans), and PET-CT scans through use of the Lugano Response Criteria for Malignant Lymphoma (see Appendix 3). In the randomized Phase II expansions, the primary endpoint of PET-CT response at the time of primary response assessment (i.e., 6–8 weeks after Cycle 6 of study treatment or early treatment discontinuation) will also be as assessed by an IRC.

Bone marrow biopsies are not routinely required for response assessment but may be indicated in specific situations per the Lugano criteria (e.g., CT-only based response assessment or when residual uptake is seen on PET-CT; see Appendix 3).

#### 4.5.5.1 Radiographic Assessments

The same radiographic assessment modality should be used for all response evaluations, in order to ensure consistency across different timepoints. PET-CT scans in conjunction with diagnostic CT scans will be obtained in this study. PET-CT scans should include skull-base to mid-thigh. Full-body PET-CT scan should be performed when clinically appropriate. CT and PET-CT scans are required at screening and at the time of primary response assessment (6–8 weeks after the end of Cycle 6 study treatment) or the last study treatment for those who discontinue study drug prematurely. An interim assessment will be obtained after Cycle 4 (i.e., at Cycle 4, Days 15–21) and should include PET-CT and dedicated CT. If local practice prohibits obtaining both

assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time.

In the follow-up period, diagnostic CT scans without PET-CT scans will be obtained every 6 months until approximately 2 years following the primary response assessment or until patients develop progressive disease and/or the start of new lymphoma therapy. The 2-year radiographic follow-up period following the primary response assessment applies to all patients in this study. Therefore, patients receiving mosunetuzumab-containing study treatment with PR/SD at their primary response assessment who continue on single-agent mosunetuzumab treatment for up to 11 additional cycles after the initial 6 cycles of study treatment will be followed for 2 years after the primary response assessment.

All CT scans up to Year 2 of follow-up should include the neck (if involved at baseline), chest, abdomen, and pelvis. If disease in other areas is suspected, additional areas should be imaged. PET-CT scans may be obtained in the follow-up period per investigator discretion, and response should be recorded in the eCRF.

Imaging with CT is currently the preferred method for measuring target lesions selected for response assessment for NHL (Cheson et al. 2014), though MRI scans are acceptable in this study if CT scans are contraindicated; conventional CT and MRI scans should be performed with contiguous cuts of ≤8 mm in slice thickness. CT scans (with IV contrast) should include the chest, abdomen, and pelvis; CT scans of the neck should be included if clinically indicated. CT scans for response assessment may be limited to areas of prior involvement only if required by local regulatory authorities.

In patients for whom contrast is contraindicated (e.g., patients with contrast allergy or impaired renal clearance), CT or combined PET-CT scans without contrast, or MRI scans are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period. Details regarding imaging procedures in these cases will be provided in the Imaging Acquisition Manual.

At all times during the study, diagnosis of disease progression based on clinical examination must be confirmed on CT scan (or MRI scan if CT scan is contraindicated) as soon as feasible (maximum within 30 days) and prior to initiation of non–protocol specified anti-lymphoma therapy.

Radiographic assessments will be collected by an IRC for independent review, (e.g., as specified for patients enrolled in the untreated DLBCL expansion cohorts). However, clinical decisions during the study will be based on investigator-based tumor assessments.

### 4.5.6 Laboratory, Biomarker, and Other Biological Samples

The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manual.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: CBC (including hemoglobin, hematocrit, RBC, WBC), platelet count, ANC, absolute lymphocyte count, and other cells
- *Flow cytometry (preferred) and/or a peripheral blood smear is required at screening (if not done as part of standard-of-care tests) to detect malignant and/or atypical cells. If malignant cells are detected, the results must be discussed with the Medical Monitor.*
- Coagulation: aPTT, PT, INR, and fibrinogen

  Fibrinogen will be collected when monitoring systemic immune activation events (e.g., hemophagocytic lymphohistiocytosis [HLH], severe CRS).
- CSF assessment, as clinically indicated, for detection of CNS lymphoma
- Quantitative immunoglobulins: IgA, IgG, and IgM
- Serum chemistry: sodium, potassium, chloride, bicarbonate *or total carbon dioxide (if considered standard of care for the region),* glucose, BUN or urea, creatinine, calcium, magnesium, phosphorous, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, gamma-glutamyl transferase, LDH, and uric acid
- C-reactive protein
- Serum ferritin
- Viral serology and detection

– Hepatitis B (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody, and hepatitis B core antibody [HBcAb]; HBV DNA by PCR if acute or chronic HBV infection cannot be ruled out by serology results [www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf])

– HCV antibody; HCV RNA by PCR if the patient is HCV antibody positive

– Epstein-Barr virus (EBV) and cytomegalovirus (CMV) by quantitative PCR using peripheral blood samples

  Note that a paired peripheral blood sample should be collected for central laboratory assessments. If local laboratory assessments are not available for quantitative PCR detection of active EBV and CMV, local laboratory collections may be waived only if peripheral blood for viral infection test is collected for central laboratory assessments.

– HIV serology

- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test within 7 days before C1D1 of study treatment. Pregnancy testing (urine or serum) will

subsequently be performed on Day 1 of each cycle of therapy for all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. An additional serum pregnancy test will be performed at the treatment completion/early treatment termination visit

- Polatuzumab vedotin–specific local laboratory tests: Serum chemistry: amylase, lipase, and hemoglobin A1c

The following samples will be sent to a central laboratory and then to the Sponsor or a designee for analysis:

- Blood, plasma, *serum*, and PBMCs for exploratory research on biomarkers
- Serum samples for measurement of mosunetuzumab concentrations using a validated mosunetuzumab PK assay
- Serum samples for measurement of total antibody analyte concentrations for polatuzumab vedotin using a validated total antibody PK assay
- Lithium plasma for measurement of acMMAE and unconjugated MMAE concentrations for polatuzumab vedotin using validated unconjugated MMAE and acMMAE PK assays
- Serum samples for measurement of ADAs to mosunetuzumab using validated assays
- Serum samples for measurement of ADAs to polatuzumab vedotin using validated assays
- Serum samples for measurement of ADAs to tocilizumab using validated assays
- Serum samples for measurement of rituximab concentrations using a validated PK assay
- Serum samples for measurement of obinutuzumab concentrations using a validated PK assay
- Serum samples for measurement of tocilizumab concentration using validated tocilizumab PK assay in patients treated with tocilizumab
- Archival or newly collected baseline tumor tissue, obtained prior to study entry, for exploratory research on biomarkers

– The specimen must have an associated pathology report.

– The specimen must contain adequate evaluable tumor cells (≥20% for excisional biopsy and ≥50% for core biopsy).

– Formalin-fixed, paraffin-embedded tissue blocks are preferred over slides. For core biopsies, it is recommended that 3–5 cores are aligned and embedded into a single block. Tissue blocks that are not formalin fixed will be accepted in countries that use a fixative other than paraformaldehyde, but information on the type of fixative should be included. If a tissue block is not available, a minimum of 20 serial, freshly cut, unstained slides may be sent. Tumor tissue from fine-needle aspirates or bone metastases that have been decalcified is not acceptable.

- For samples that do not meet the minimum requirements for size or slide number, contact the Medical Monitor via site contact with tissue size, tumor content, and number of slides to determine eligibility.
- The sample should be shipped according to instructions provided in the laboratory manual.
- Slides from bone marrow biopsies taken prior to study entry, with the associated pathology report, should be provided when available. However, these additional samples cannot be used in place of the primary tumor tissue requirement. Bone marrow aspirates collected as part of required study assessments do not need to be sent to the central laboratory; however, the associated hematopathology report should be submitted when available.

Exploratory biomarker research may include, but will not be limited to, analysis of lymphocyte subpopulations, T-cell activation, T-cell receptor repertoire, cytokines associated with inflammation, circulating CD20 protein, ctDNA levels or MRD, and cell of origin. Research may involve extraction of DNA, ctDNA, or RNA, analysis of mutations, and genomic profiling through use of NGS. NGS methods may include WGS or WES, with the aim to analyze somatic mutations. At participating sites, blood may be used as a reference to distinguish germline mutations from somatic mutations (see Section 4.5.13).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.13), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum or plasma samples collected for PK and immunogenicity (ADA) analysis may be needed for additional PK or ADA assay development and validation and for additional immunogenicity characterization; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, *serum*, PBMC, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival blocks will be returned to the site upon request or no later than after the final Clinical Study Report has been completed. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 3 months after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if

samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

### 4.5.7 Electrocardiograms

Single ECG recordings will be obtained at screening and at treatment discontinuation (either early treatment termination or study treatment completion) and may be obtained at unscheduled timepoints as clinically indicated per investigator discretion (see Appendix 1). ECG monitoring during infusion of doxorubicin should be performed per local clinical practice.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The investigator's assessment of normal, abnormal and clinically significant, or abnormal and not clinically significant will be record on the eCRF. Clinically significant abnormalities on an ECG should be reported as adverse events. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively.

### 4.5.8 Echocardiogram or Multiple-Gated Acquisition Scan

For assessment of cardiac function (LVEF), an ECHO or MUGA scan should also be obtained at screening and early treatment termination/study treatment completion visit. An ECHO or MUGA scan may also be obtained as clinically indicated at any time during the study.

### 4.5.9 Patient-Reported Outcomes

PROs will be evaluated in patients enrolled in the randomized Phase II DLBCL expansion cohorts using four questionnaires in the following order: the EORTC

QLQ-C30, the FACT-Lym subscale, the FACT/GOG-NTX, and the EQ-5D-5L. These four questionnaires will be used to capture a patient's assessment of his or her overall HRQoL and health status.

The questionnaires, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments (except laboratory blood collections), and prior to the administration of study treatment, unless otherwise specified. Study site staff will ensure that PRO questionnaires are provided to patients for completion per the schedule of activities; before patients complete the visit, the site staff will confirm completion or alternatively document any reasons for not completing the questionnaires. In the event that the patient completes the PROs on a scheduled assessment but is not subsequently dosed, this will be recorded as an unplanned visit, and the PROs will be administered again at the subsequent rescheduled treatment visit.

#### 4.5.9.1 EORTC Quality of Life–Core 30 Questionnaire

The EORTC QLQ-C30 (Appendix 10) is a validated, reliable self-report measure (Aaronson et al. 1993). It consists of 30 questions that assess five domains of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status/quality of life (GHS/QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores are transformed to a 0–100 scale, with higher scores on the five domains and GHS/QoL reflective of better HRQoL, and higher scores on the symptom scales and single items reflective of poor HRQoL. The EORTC QLQ-C30 takes approximately 10 minutes to complete and has a recall period of the previous week.

#### 4.5.9.2 Functional Assessment of Cancer Therapy–Lymphoma Subscale

The 15-item FACT-Lym subscale (Appendix 11) was developed to assess HRQoL in patients with NHL. The FACT-Lym subscale enables assessment of the changes from baseline with respect to B symptoms and impact on HRQoL brought about by symptom worsening or alleviation and treatment toxicity. The subscale range is 0–60, with a higher score reflecting better HRQoL, and it has a recall period of the previous week. The validity and reliability of the FACT-Lym subscale for patients with NHL has been established (Hlubocky et al. 2013).

#### 4.5.9.3 Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity

The FACT/GOG-Ntx (Appendix 12) is a validated self-report scale for assessing platinum/paclitaxel-induced peripheral neuropathy (Huang et al. 2007). This scale is used to assess vincristine- and polatuzumab vedotin-induced neuropathy, as symptoms of chemotherapy-induced neuropathy caused by microtubule inhibitors do overlap with those seen in platinum/paclitaxel–containing regimens. The measure contains 11 items that assess sensory neuropathy (4 items), hearing neuropathy (2 items), motor neuropathy (3 items), and dysfunction associated with neuropathy (2 items), and it can be summed to create a total score. Items are rated on a 5-point response scale that ranges from "not at all" to "very much," with higher scores indicative of more extreme neuropathy. The FACT/GOG-NTX has a recall period of the previous week.

#### 4.5.9.4 EuroQol 5-Dimension, 5-Level Questionnaire

The EQ-5D-5L (Appendix 13) is a generic, preference-based health utility measure that assesses health status and is used to inform pharmacoeconomic evaluations. The EQ5D-5L consists of two parts. The first part, a health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that allow for the creation of a single summary score. Overall scores typically range from 0 to 1, with low scores representing a higher level of dysfunction. The second part is a 0 to 100-point visual analog scale that assesses current health status, where higher scores are reflective of better health. The measure has a recall period of the current day.

### 4.5.10 Tissue Samples for Whole Genome or Whole Exome Sequencing (Patients at All Sites)

WGS or WES may be performed on DNA extracted from tissue collected for biomarker analysis (as described in Section 4.5.6) to identify somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety.

Genomics is increasingly informing overall understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, refer to the laboratory manual.

Samples undergoing WGS or WES will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Patient medical information associated with samples undergoing WGS or WES is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the WGS or WES analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

### 4.5.11 Blood Samples for Whole Genome or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, DNA may be extracted from blood collected for biomarker analysis (as described in Section 4.5.6) to enable WGS or WES, to serve as a reference for distinguishing somatic mutations from germline mutations. The samples may be sent to one or more laboratories for analysis.

Analysis of blood samples through WGS or WES is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for these analyses, this section of the protocol (Section 4.5.11) will not be applicable at that site.

For sampling procedures, storage conditions, and shipment instructions, refer to the laboratory manual.

Refer to Section 4.5.10 for additional rationale for WGS and WES and information on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

### 4.5.12 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at the time of progression *and after treatment initiation* unless no adequate tumor site is safely accessible. Tumor tissue can be obtained either from an excisional biopsy or from core-needle biopsy (recommended minimum 18-gauge diameter, 3–5 cores aligned and embedded into a single block) and should contain sufficient sample to generate a paraffin block or at least 20 unstained slides. Cytological or fine-needle aspiration samples are not acceptable. Additional tumor biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis). Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analyses. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.6. Refer to Section 4.5.6 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data.

### 4.5.13 Optional Samples for Research Biosample Repository

#### 4.5.13.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

#### 4.5.13.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

#### 4.5.13.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to mosunetuzumab, polatuzumab vedotin, or diseases:

- Optional blood sample for RBR, collected at baseline
- Leftover blood, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), NGS, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored no later than 15 years after the final Clinical Study Report has been completed. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

#### 4.5.13.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

#### 4.5.13.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

#### 4.5.13.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO40515 does not, by itself, constitute withdrawal of specimens from the RBR.

Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GO40515.

If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

#### 4.5.13.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

## 4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Use of an anti-cancer therapy other than those allowed per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to the Lugano Response Criteria for Malignant Lymphoma (Appendix 3)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment early will not be replaced except for patients in dose escalation or the safety run-in who discontinue prior to completion of the DLT assessment window for reasons other than a DLT (see Section 3.1.2.1).

Patients without disease progression who have discontinued all study treatment will be followed for approximately 2 years following the primary response assessment with clinic visits every 3 months and imaging every 6 months. Patients who develop disease progression will be followed until 90 days after the last dose of study treatment or

initiation of new anti-cancer therapy for safety monitoring, whichever is earlier. Patients with disease progression based on clinical evaluation should be imaged within 30 days for radiographic confirmation and prior to initiation of new anti-cancer therapy. See Appendix 1 for a detailed schedule of activities after study treatment discontinuation (unless the patient withdraws consent or the Sponsor terminates the study).

After treatment discontinuation, information on the new anti-cancer therapy will be collected via telephone calls and patient medical records every 3 months and/or clinic visits every 3 months for the first 6 months, then every 6 months thereafter, until approximately 2 years following the primary response assessment (unless death, loss to follow-up, the patient withdraws consent, or the Sponsor terminates the study, whichever occurs first). The date of when the first subsequent anti-cancer therapy was initiated will be collected.

### 4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced, except for patients in dose escalation or the safety run-in.

### 4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

### 4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PLAN

This is the first combination study in which mosunetuzumab will be administered to humans with CHOP or with CHP-pola. Mosunetuzumab is not approved in any territory. Currently, polatuzumab vedotin is approved in some countries in combination with bendamustine and rituximab for the treatment of *adult patients with* R/R DLBCL. Because the combination of mosunetuzumab plus polatuzumab vedotin is not yet approved, the safety plan for this study is primarily based on clinical experience with each investigational agent, as outlined in their respective Investigator's Brochures.

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (Sections 4.1.1 and 4.1.2) and close monitoring, as described below. As described in Section 3.1.2.2, enrollment of patients for DLT evaluation purposes will be staggered such that the first 2 patients in each dose-escalation cohort will have respective C1D1 treatments administered ≥72 hours apart. Subsequent patients in each cohort will be staggered such that their C1D1 treatments are administered ≥24 hours apart.

All patients will be monitored closely for toxicity. Patients will be assessed clinically for toxicity prior to each dose using the NCI CTCAE v5.0 grading scale unless otherwise stated. CRS severity will be graded according to the ASTCT CRS Consensus Grading criteria (see Appendix 7). All adverse events and serious adverse events will be recorded during the trial and for up to 90 days after the last dose of study treatment or until the initiation of another systemic anti-cancer therapy, whichever occurs first. To mitigate potential unknown risks, dosing beyond Cycle 1 will be limited to patients who do not demonstrate unacceptable toxicity or compelling evidence of disease progression (see Section 3.1.2.4). See Section 5.3 for details regarding safety reporting for this study.

Specific anticipated or potential toxicities associated with administration of mosunetuzumab, polatuzumab vedotin, rituximab, and CHP/CHOP, as well as the

measures taken to avoid or minimize such toxicities in this trial, are described in the following sections.

### 5.1.1 Mosunetuzumab Administration and Hospitalization

Administration of mosunetuzumab will be performed in a clinical setting with immediate access to a critical care unit and staff who are trained to monitor for and respond to medical emergencies. Neurology consultation services should be readily available to address any neurologic adverse events that may arise as a result of mosunetuzumab treatment (see Section 5.1.2.2, Neurologic Toxicity), and nephrology consultation with acute dialysis capabilities should be readily available to address any renal toxicity that might accompany TLS (see Section 5.1.2.2, Tumor Lysis Syndrome).

All patients enrolled in **Group A and Group B dose escalation** and Group C safety run-in will require inpatient monitoring, including hospitalization *for at least* 24 *hours* after the completion of mosunetuzumab administration on C1D1 (M-CHOP) and for at least *24 hours* after the completion of mosunetuzumab on C1D2 (M-CHP-pola) (see Sections 4.3.3.2 and 4.3.3.3 for details on study drug regimen). Patients may be hospitalized for monitoring on C1D8 or C1D15 for 24 hours at the discretion of the investigator in consultation with the Medical Monitor. Hospitalization requirements during subsequent cycles for any particular patient will be determined on the basis of the clinical course during the first *cycle*; patients with Grade 3 IRR, CRS, or TLS during Cycle 1 may also be hospitalized for observation during subsequent cycles at the discretion of the investigator with consultation of the Medical Monitor.

Decisions to modify or discontinue the requirement for hospitalization in expansion cohorts will be made based on the recommendation of the IMC (see Sections 3.3.9 and 5.1.8) and in consultation with study investigators.

### 5.1.2 Risks Associated with Mosunetuzumab

On the basis of clinical data to date with mosunetuzumab, the following known and suspected risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.7. Refer to the Mosunetuzumab Investigator's Brochure for complete and updated details.

#### 5.1.2.1 Known Risks Associated with Mosunetuzumab

**Cytokine Release Syndrome**

The mechanism of action of mosunetuzumab is immune-cell activation against CD20-expressing cells; therefore, a spectrum of events involving IRRs, target-mediated cytokine release, and/or hypersensitivity with or without emergent ADAs may occur. Other CD20-directed therapies and immunomodulatory therapies have been associated with IRRs, CRS, and/or hypersensitivity (Blincyto USPI; Gazyva USPI; Rituxan USPI). CRS has been reported in Study GO29781 and is an identified risk of mosunetuzumab. Refer to the current Mosunetuzumab Investigator's Brochure for details.

*To date, CRS events observed with mosunetuzumab have been mostly mild* to moderate *in severity and* include symptoms such as fever, headache, and myalgia, and *respond to symptomatic treatment* with analgesics, anti-pyretics, and antihistamines as indicated.

Severe or life-threatening presentations of IRRs and/or CRS, such as hypotension, tachycardia, dyspnea, or chest discomfort, should be treated aggressively with supportive and resuscitative measures as indicated, including the use of tocilizumab and/or high dose corticosteroids, IV fluids, and other supportive measures per local institutional practice. Severe CRS may be associated with other clinical sequelae such as disseminated intravascular coagulation, and capillary leak syndrome, or may manifest as HLH (see Section 5.1.2.2). Standard of care for severe or life threatening CRS resulting from immune-based monoclonal antibody therapy has not been established; case reports and recommendations for CD19 CAR-T have been published (Teachey et al. 2013; Lee et al. 2014, 2019; Maude et al. 2014; Neelapu et al. 2018; also see Section 5.1.2.2 and U.S. Food and Drug Administration [FDA] approval for two products describing risk management for CRS [Yescarta® USPI; Kymriah™ USPI]).

*Disease-related factors that may be associated with an increased risk of severe CRS following chimeric antigen receptor (CAR)-T-cell therapy, and therefore, potentially other T-cell engaging therapies, include (but are not limited to) lymphoma bone marrow involvement, extranodal disease, B cell lymphocytosis, and the presence of circulating peripheral malignant cells. Patients with the above disease-related factors must be discussed with the Medical Monitor; additional monitoring (i.e., more frequent measurements of vital signs) during mosunetuzumab dosing, especially with the first dose, should be undertaken (Section 4.5.4), and management of treatment-emergent AEs, including CRS, should adhere to guidance in Section 5.1.7.*

To minimize the risk and sequelae of IRRs and CRS, mosunetuzumab will be administered over a minimum of 4 hours in Cycle 1 in a clinical setting as described in Section 5.1.1. *Corticosteroid premedication must be administered as described in Section 4.3.3.1.*

Management guidelines for CRS following mosunetuzumab are summarized in Table 10, with the grading of CRS following the ASTCT CRS Consensus Grading criteria described in Appendix 7. *Given the mechanism of action of mosunetuzumab, IRRs and CRS may be indistinguishable from each other; therefore, their evaluation and treatment are identical (see Section 5.1.7.4, Table 10).*

Management of Grade ≥3 CRS should be immediately discussed between the treating investigator and the Medical Monitor. As noted in Table 10, even moderate presentations of CRS in patients with extensive comorbidities should be monitored closely with consideration given to ICU admission and tocilizumab administration.

Refer to Section 5.3.5.1 for adverse event reporting procedures related to IRRs and CRS. If tocilizumab is administered, refer to Appendix 14 for the schedule of activities for tocilizumab treatment of CRS. Refer to Appendix 8 for anaphylaxis management.

**Neutropenia**

Neutropenia is a known class effect associated with other CD20 directed therapies such as obinutuzumab and rituximab and with the similar class agent blinatumomab. Reversible neutropenia has been observed following mosunetuzumab- treatment in Study GO29781. Some patients developing neutropenia have received growth factor support and/or temporary treatment holds. Refer to the Mosunetuzumab Investigator's Brochure for details.

Patients who experience Grade 3–4 neutropenia should be closely monitored with more frequent assessments as applicable; see Section 4.4.1.1 for use of growth factor support.

#### 5.1.2.2 Potential Risks Associated with Mosunetuzumab

**Hemophagocytic Lymphohistiocytosis**

CRS with features of adult-onset secondary HLH[1] has been reported with blinatumomab as well as with CAR adoptive T-cell therapy (Blincyto USPI; Teachey et al. 2013; Lee et al. 2014). A fatal case of secondary HLH has been reported in Study GO29781 (refer to the current BTCT4465A [Mosunetuzumab] Investigator's Brochure for details).

While severe CRS and secondary HLH have overlapping presentation and symptoms, *secondary* HLH may be precipitated by other conditions including infections, autoimmune disease, and malignancies (Ramos-Casals 2014). The prevalence of these conditions in the study patient population makes the distinction between severe CRS and secondary HLH and identification of inciting factors challenging. On the one hand, in one series, B-cell malignancies were the most common malignancy associated with secondary HLH (Rivière et al. 2014). On the other hand, active infection with EBV is one of the most common infectious causes of secondary HLH (Hashemi-Sadraei et al. 2015; Schram and Berliner 2015), and reactivation of latent EBV may occur in patients with CLL (Rath et al. 2008), which in turn may lead to HLH (Lim et al. 2014). It remains unknown whether mosunetuzumab treatment may further increase the risk of developing HLH in patients who have additional risk factors.

In the setting of T-cell engaging therapies including mosunetuzumab, CRS is much more likely compared with secondary HLH; considering the overlapping presentation of symptoms, management of these patients should be primarily focused on treatment of CRS (see Table 10). In atypical cases such as late-onset CRS (past Cycle 1 completion

[1] For the purposes of the GO40515 protocol and study-related documents, *macrophage activation syndrome (MAS)* and HLH are considered to be synonymous terms.

of step-up dosing with mosunetuzumab) or CRS that is refractory to treatment, work up for HLH should be initiated.

All cases of suspected HLH should be discussed with the Medical Monitor immediately. While there is no currently universally accepted set of criteria for diagnosing secondary or reactive HLH in the adult population, proposed criteria have been published (*Henter et al. 2007,* Fardet et al. 2014; Hejblum et al. 2014*; McClain et al 2019*; see Section 5.1.7.5).

*The supportive management of HLH is generally similar to that of CRS (see Section 5.1.2.1). Specific diagnostic, monitoring and management guidelines for HLH are described in Appendix 19.*

Patients with HIV and known or suspected CAEBV will be excluded from this study (see Infections section below and also Section 4.1.2).

### Neurologic Toxicity

Encephalopathy has been observed in in the setting of CRS and/or elevation in liver function tests (LFTs) following mosunetuzumab treatment (refer to the Mosunetuzumab Investigator's Brochure for details).

Neurologic toxicity has also been reported in patients treated with blinatumomab and CD19 CAR T-cell therapy (Blincyto USPI; Maude et al. 2014; Kochenderfer et al. 2015). Reported symptoms in patients treated with blinatumomab or CD19 CAR T-cell therapy have included headache, confusion, aphasia, encephalopathy, tremor, seizure, and other neurologic events. The etiology of toxicity in these settings is uncertain and may not be responsive to cytokine-directed therapy such as tocilizumab, but has generally improved with treatment discontinuations and corticosteroids (Blincyto USPI; Viardot et al. 2010; Kochenderfer et al. 2015). In patients with B-cell acute lymphoblastic leukemia treated with blinatumomab, neurologic toxicities were observed in approximately 50% of patients; Grade ≥3 neurologic toxicity was observed in approximately 15% of patients. The majority of neurologic adverse events resolved following interruption of blinatumomab, with some patients requiring treatment discontinuation (Blincyto USPI).

Neurologic 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 neurologic disease may be excluded from this trial (see Section 4.1.2).

Patients should be routinely assessed for any signs or symptoms of neurologic toxicity as part of the on-treatment clinical examination (see Section 4.5.3). 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 should be performed if clinically indicated (Table 11).

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

- Patients with risk factors at baseline:

  For patients with the combination of aggressive NHL (including DLBCL, transformed FL, FL Grade 3b, primary mediastinal B-cell lymphoma, MCL, transformed marginal zone lymphoma) and abnormal (above institutional ULN) C-reactive protein at screening, the investigator should advise patients to refrain from driving or engaging in hazardous occupations or activities during Cycles 1–2 (approximately 6 weeks).

- Patients who develop specific adverse events while on mosunetuzumab:

  For patients who develop a neurologic adverse event that may affect driving (see Appendix 17 ) 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 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.

### Tumor Lysis Syndrome

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

The risk of TLS with mosunetuzumab in patients with NHL is predicted to be highest for those with bulky disease (defined in the context of TLS as any lesion ≥ 10 cm on the screening CT scan) and elevated pretreatment LDH levels, particularly in the presence of dehydration or compromised renal function. While *patients with* DLBCL, transformed lymphomas, and MCLs may be at higher risk of TLS as compared with follicular, marginal, and small cell- lymphomas (Cairo et al. 2010), any risk stratification based on tumor type must be considered along with the effectiveness of therapy (Howard et al.

2011). As mosunetuzumab has the potential for potent B-cell killing (Section 1.2), patients will receive prophylaxis for TLS *based on their risk (Section 5.1.7.6)*.

Prior to each mosunetuzumab treatment given during Cycles 1 and 2, the patient's serum chemistry and hematology laboratory samples should be obtained and reviewed and prophylactic measures initiated according to the guidelines described below. Access to nephrologist and acute dialysis services must be available in the event of clinically significant TLS *(see Appendix 18)*. Telemetry should also be considered. Similar monitoring and precautions will apply to the treatment arms in the Phase II portion of the study.

Specific prophylaxis recommendations for the prevention of TLS are described in Section 5.1.7.6.

### 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 (see Section 5.1.2.2, Neurologic Toxicity), as PML associated with rituximab generally occurred following long-term exposure (Carson et al. 2009).

Hepatitis B reactivation has been reported with CD20-directed therapies. Patients with positive test results for active HBV infection defined by HBsAg or positive total HBcAb *with* positive HBV PCR, or patients with HCV infection as assessed by PCR, will be excluded from this trial (Section 4.1.2). *Patients with occult or prior HBV infection (defined as negative HBsAg and positive HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment and*

*appropriate antiviral therapy. Patients who experience hepatitis B reactivation should start antiviral therapy (if not already initiated). Patients with rising viral load on appropriate antiviral therapy should consider study treatment discontinuation if in the investigator's opinion the benefit/risk profile of continued treatment is unfavorable.*

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 CHOP and CHP-pola. 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 (see Section 4.1.2).

### Thrombocytopenia

Thrombocytopenia is associated with other CD20-directed therapies as well as blinatumomab (Blincyto USPI). Reversible thrombocytopenia has been observed following mosunetuzumab treatment in Study GO29781. Refer to the Mosunetuzumab Investigator's Brochure for details.

Patients should be closely monitored for thrombocytopenia; regular laboratory tests should be performed until the event resolves. Transfusion of blood products (e.g., platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies, which could possibly worsen thrombocytopenia-related events such as platelet inhibitors and anticoagulants, should also be taken into consideration.

### Elevated Liver Enzymes and Hepatotoxicity

Transient Grade 3 AST elevation in the setting of Grade 2 CRS as well as Grade 3 hepatic encephalopathy/Grade 4 elevation in LFTs have been observed following mosunetuzumab treatment (refer to the Mosunetuzumab Investigator's Brochure for details).

Elevated liver enzymes have been reported with blinatumomab (Blincyto USPI), usually, but not exclusively, in the setting of CRS. Grade ≥3 liver enzyme elevations occurred in approximately 6% of patients outside the setting of CRS. Nearly all liver enzyme elevations resolved either with blinatumomab treatment interruption or while treatment continued. Some patients with resolved liver enzyme elevations were successfully rechallenged, suggesting a first-dose effect rather than direct toxicity (Blincyto Drug Approval Package).

Patients who do not meet eligibility criteria for LFTs at screening will be excluded from this trial (see Section 4.1.2). LFTs will be assessed regularly during study and should be managed according to guidelines in Table 12. Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug.

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

### Immunogenicity (Anti-Drug Antibodies)

As with any recombinant antibody, mosunetuzumab may elicit an immune response, and patients may develop antibodies against the molecule. Patients will be closely monitored for any potential immune response to mosunetuzumab in the first-line treatment setting, which may have an impact on the benefit–risk profile of the agent. Therefore, a risk-based strategy (Rosenberg and Worobec 2004a, 2004b, 2005; Koren et al. 2008) will be utilized to detect and characterize ADA responses to mosunetuzumab. Out of *352* evaluable post-baseline patients tested in Phase Ia study of mosunetuzumab (GO29781), *1 patient (0.3%) tested positive for ADAs against mosunetuzumab and the presence of ADAs to mosunetuzumab had no apparent impact on drug exposure and safety (refer to the Mosunetuzumab Investigator's Brochure)*. Because mosunetuzumab is a B cell–depleting agent and has demonstrated low immunogenicity rates in the Phase I study, the frequency of ADA sampling times for mosunetuzumab will be reduced in this study compared with Study GO29781.

### *Tumor* Inflammation/Flare

Adverse events associated with tumor inflammation/flare have been reported in Study GO29781. Consistent with the mechanism of action of mosunetuzumab, tumor flare is likely due to the influx of T-cells into tumor sites following mosunetuzumab administration. Reported tumor flare associated adverse events generally have a short time to onset following mosunetuzumab administration. Based on safety data collected to date, tumor flare has manifested as new or worsening pleural effusions. In addition, depending on tumor size and anatomic location, tumor flare may potentially result in mass effects on vital structures including airways, major blood vessels, *gastrointestinal tract (risk of perforation and hemorrhage) and/or major organs. If such manifestations are temporally associated with early mosunetuzumab dosing, the treating physician/study investigator should consider those events to be tumor flare and report as "tumor flare" or "tumor inflammation"*. Patients with tumors at critically anatomic locations should be closely monitored for tumor flare, and the treating physician/study investigator should contact the Medical Monitor to discuss risk assessment and mitigation strategies prior to mosunetuzumab treatment. Refer to the Mosunetuzumab's Investigator Brochure for complete and updated safety information.

## 5.1.3 Risks Associated with Polatuzumab Vedotin

On the basis of clinical data to date, the following known and suspected risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.7. Refer to the Polatuzumab Vedotin Investigator's Brochure for complete and updated details.

#### 5.1.3.1 Known Risks Associated with Polatuzumab Vedotin

*Myelosuppression*

*Myelosuppression is an identified risk that is a consolidation of three adverse drug reactions:* neutropenia (including febrile neutropenia*), thrombocytopenia, and anemia.*

Neutropenia, neutropenia-associated events, *thrombocytopenia, and anemia, including serious and severe cases, have been reported in patients receiving polatuzumab vedotin.* Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Treatment may be delayed or modified for hematologic toxicities as described in Table 8.

Prophylaxis with G-CSF is required for patients during Cycles 1–6 when polatuzumab vedotin is given in combination either with M-CHP or with R-CHP (see Section 4.4.1.1).

*Transfusion support for anemia and thrombocytopenia is permitted at the discretion of the investigator.*

**Peripheral Neuropathy (Sensory and/or Motor)**

Patients receiving polatuzumab vedotin may develop peripheral neuropathy (sensory and/or motor*) and* should be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, *myalgia,* weakness, gait disturbance, or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require a dose delay, change in dose, or discontinuation of treatment. Study treatment dose and schedule modifications for peripheral neuropathy are described in Table 8. Supportive care measures may be implemented per investigator preference (e.g., gabapentin). *The incidence of peripheral neuropathy increases as the number of treatment cycles received approaches eight or beyond, suggesting a cumulative nature of PN toxicity.*

**Infections**

*Patients receiving polatuzumab vedotin may be at a higher risk of developing infections. Serious infections, including opportunistic infections, such as pneumonia (including pneumocystis jirovecii and other fungal pneumonia), bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with polatuzumab vedotin. Several other risk factors in the patient population under study influencing* patients' vulnerability to a higher risk of infections, particularly serious and opportunistic *infection,* include predisposition of the indication disease to infections, elderly population, *and* comorbidity. In addition, neutropenia is a known risk for polatuzumab vedotin. Granulocytopenia is a major predisposing factor to infections in patients with B-cell lymphoma. The reported incidence of infection in chemotherapy courses for B-cell lymphoma associated with <500 granulocytes/µL was higher than those with ≥500 granulocytes/µL. Neutropenia events should be monitored closely and

any signs of infection should be treated as appropriate (Taplitz et al. 2018). *Anti-infective prophylaxis should be considered and is described in Section 4.4.1.3.*

### Infusion-Related Events

*Infusion related reactions have been reported in patients receiving polatuzumab vedotin. Commonly experienced events include nausea, vomiting, chills, fever, pruritus, hypotension, flushing, and other symptoms. In the majority of the patients, the events were Grade 1-2. Refer to the local prescribing information for additional information.*

### Gastrointestinal Toxicity (Diarrhea, Nausea, Vomiting, Constipation, Anorexia)

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

## 5.1.3.2 Potential Risks Associated with Polatuzumab Vedotin

### Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. TLS prophylaxis for treatment arms that include mosunetuzumab will follow the prophylaxis measures as described in Section 5.1.7.6.

For patients receiving R-CHP-pola in the Phase II portion of the study (Figure 1), TLS prophylaxis measures should be instituted per the investigator's risk assessment. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L or bulky lymphadenopathy) and who are considered to be at risk for TLS by the investigator will receive TLS prophylaxis (e.g., allopurinol ≥300 mg/day PO or a suitable alternative treatment such as rasburicase starting 48–72 hours before study treatment) and must be well hydrated before the initiation of study treatment at C1D1. These patients should continue to receive repeated prophylaxis and adequate hydration, as deemed appropriate by the investigator.

For patients with evidence of TLS, all study treatment should be suspended and the patient should be treated as clinically indicated. Following the complete resolution of TLS complications, treatment may be resumed at the full dose at the next scheduled infusion in conjunction with prophylactic therapy.

### Immunogenicity (Anti-Drug Antibodies)

As with any recombinant antibody, polatuzumab vedotin may elicit an immune response, and patients may develop antibodies against the molecule. Out of *481* evaluable postbaseline patients in the Phase Ib and II studies of polatuzumab vedotin (GO29365,

GO27834, GO29044, and JO29138), only *10 patients (2.1%)* tested positive for ADAs that were treatment-induced for polatuzumab vedotin. No conclusions could be drawn concerning the potential impact of ADAs on PK, efficacy, or safety due to a very low number of patients ADA-positive for polatuzumab vedotin.

Patients will be closely monitored for any potential immune response to polatuzumab vedotin in the first-line setting, which may have an impact on the benefit–risk profile of the agent. Therefore, a risk-based strategy (Rosenberg and Worobec 2004a, 2004b, 2005; Koren et al. 2008) will be utilized to detect and characterize ADA responses to polatuzumab vedotin. Because polatuzumab vedotin is a B cell–depleting agent and has demonstrated low immunogenicity rates in the Phase I and II study, the frequency of ADA sampling times will be reduced in this study compared with previous studies.

### Reproductive Toxicity

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

### Hyperglycemia

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

### Hepatotoxicity

Hepatotoxicity has been observed in patients treated with polatuzumab vedotin in both the Phase I and II trials. Although the relationship between hepatotoxicity and polatuzumab vedotin has not been definitively determined, transient, dose-related increases in hepatic enzymes were noted in nonclinical rat studies. No hepatotoxicity was noted following administration of the surrogate ADC in cynomolgus monkeys.

Elevations of transaminases have been reported in patients receiving polatuzumab vedotin and have ranged in intensity from Grades 1 to 4. These have been reversible with and without dose modification/discontinuation. For additional information, please refer to the current Polatuzumab Vedotin Investigator's Brochure.

### *Carcinogenicity*

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

For polatuzumab vedotin dose delay, modification, and discontinuation instructions, see Table 8.

### 5.1.4 Risks Associated with Rituximab

See the local prescribing information for rituximab for full information.

### 5.1.5 Risks Associated with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

Please see the local prescribing information for cyclophosphamide, doxorubicin, vincristine, and prednisone for full information.

For CHOP and CHP dose delay, modification, and discontinuation instructions, see Section 5.1.7.

### 5.1.6 Risk of Overlapping Toxicities with Mosunetuzumab plus CHOP and Mosunetuzumab plus CHP-Pola

Potential overlapping toxicities between mosunetuzumab in combination with CHOP or with CHP-pola based on the safety/toxicity profiles of these agents known to date include IRRs, neutropenia and infections, thrombocytopenia, TLS, peripheral neuropathy, and hepatotoxicity. As such, when these toxicities occur, attribution to a particular agent may be difficult.

As this is the first study combining mosunetuzumab with CHOP and with CHP-pola, the actual risk of these toxicities is unknown. In general, given the established safety profile and relatively short half-life of chemotherapy as compared with mosunetuzumab, treatment holds for potential overlapping toxicity are first recommended for CHOP/CHP components over mosunetuzumab. Treatment hold, dose modification, or discontinuation decisions should follow the recommendations in Table 8, as well as Sections 5.1.7.7 (neurologic toxicity), 5.1.7.8 (elevated liver enzymes and hepatotoxicity), and Section 5.1.7.9 (neutropenia and thrombocytopenia).

### 5.1.7 Management of Patients Who Experience Adverse Events

#### 5.1.7.1 Dose Delays and Dose Modifications

Cyclophosphamide and doxorubicin doses may be reduced as outlined in Table 5 and Table 6, respectively, per the guidelines in Table 8.

Polatuzumab vedotin doses may be reduced as outlined in Table 4 per the guidelines outlined in Table 8. The dose of polatuzumab vedotin and chemotherapy (cyclophosphamide or doxorubicin) may be reduced stepwise to a maximum of two levels for management of drug-related toxicities. Doxorubicin and cyclophosphamide doses may be reduced in parallel or separately (i.e., one or both agents may be reduced in 25%–50% increments per investigator preference and local institutional practice). If further dose reduction is indicated after two dose reductions, the patient must discontinue the specific study drug but may continue treatment with the remaining study

drugs at the investigator's discretion. Cyclophosphamide and doxorubicin doses may be re-escalated (even to the full dose)

For patients receiving vincristine, the dose of vincristine may be reduced stepwise to a maximum of two levels for management of drug-related toxicities, as outlined in Table 7 and per guidelines in Table 8. If further dose reduction is indicated after two dose reductions, the patient must discontinue vincristine but may continue treatment with the remaining study drugs at the investigator's discretion.

Guidance for treatment interruptions for adverse events is provided in Table 8 *and Section 5.1.7. Mosunetuzumab should not be held in Cycle 1 for uncomplicated neutropenia without associated fever or for thrombocytopenia without associated bleeding*. If administration of CHP-pola or CHOP is delayed, the administration of mosunetuzumab or rituximab should be delayed for the same time frame (i.e. all study drugs should be delayed for the same time frame so that they are all given together beginning on Day 1 of the same cycle).

*In the event that a patient has a toxicity in Cycle 1 necessitating mosunetuzumab interruption for >7 days, the Medical Monitor 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.*

Dose reductions of mosunetuzumab are allowed, but only following dose holds as described in Table 8, Table 10, Table 11, and Table 12. Dose reductions of mosunetuzumab are limited to Cycles 2 and beyond, and must first be discussed with the Medical Monitor. The dose of mosunetuzumab may be reduced to a lower dose level that has previously been cleared during dose escalation (Section 3.1.2.2). In the event that a lower dose (C1D15 test dose) of mosunetuzumab has not been tested, a dose reduction of 25% is recommended.

**Table 4 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 | 1.0 mg/kg per cycle |
| Third dose reduction | Discontinue drug. |

**Table 5 Recommended Steps of Dose Reduction for Cyclophosphamide**

| Dose Level | Cyclophosphamide |
|---|---|
| Starting dose | 100% of starting dose per cycle |
| First dose reduction [a] | 75% of starting dose per cycle |
| Maximum dose reduction [a] | 50% of starting dose per cycle or discontinue drug |
| Subsequent dose reduction | Discontinue drug. |

[a] Steps of dose reduction listed are suggested dose changes. Investigators may opt for alternative levels of dose reduction as clinically indicated.

**Table 6 Recommended Steps of Dose Reduction for Doxorubicin**

| Dose Level | Doxorubicin |
|---|---|
| Starting dose | 100% of starting dose per cycle |
| First dose reduction [a] | 75% of starting dose per cycle |
| Maximum dose reduction [a] | 50% of starting dose per cycle or discontinue drug |
| Subsequent dose reduction | Discontinue drug. |

[a] Steps of dose reduction listed are suggested dose changes. Investigators may opt for alternative levels of dose reduction as clinically indicated.

**Table 7 Recommended Steps of Dose Reduction for Vincristine**

| Dose Level | Vincristine |
|---|---|
| Starting dose | 100% of starting dose per cycle |
| First dose reduction | 75% of starting dose per cycle |
| Second dose reduction | 50% of starting dose per cycle |
| Third dose reduction | Discontinue drug |

#### 5.1.7.2 Treatment Interruption

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.

Study treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug (see Table 8). *Mosunetuzumab should not be held in Cycle 1 for uncomplicated neutropenia without associated fever or for thrombocytopenia without associated bleeding.* With the exception of withholding

vincristine or polatuzumab vedotin for neuropathy per Table 8, study drugs withheld for >14 days because of toxicity should be discontinued, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Study treatment may continue in the event one or more of the study drugs are discontinued as long as the investigator, in consultation with the Medical Monitor, believes that the patient is continuing to derive clinical benefit from remaining study treatments.

Study treatment may also be temporarily suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption. Specific guidelines around dosage modifications for Cycles 2–6 are detailed below. Patients who are receiving study treatment and experience toxicities should undergo dose interruptions and reductions per instructions in Table 8. All considerations of dose and schedule modifications should be discussed with the Medical Monitor.

In general, patients who experience a *serious* Grade 4 non-hematological adverse event should discontinue all study treatment and *should* not be re-treated. An exception to this relates to TLS. Because TLS represents a PD effect of study treatment that may result in clinical benefit, patients who experience Grade 4 TLS may be considered for continuation on study *treatment*. In order to be considered for subsequent study treatment, all toxicities and laboratory abnormalities related to TLS should be resolved within 2 weeks. Patients must be hospitalized for TLS prophylaxis and monitoring with the next study treatment dose (see Section 5.1.2.2, Tumor Lysis Syndrome). *The decision to continue study treatment should only be made after consultation with the Medical Monitor.*

**Table 8 Dose Interruptions, Reductions, and Discontinuations of Mosunetuzumab, Polatuzumab Vedotin, Rituximab, and CHP or CHOP**

| Event(s) | Dose Delay or Modification |
|---|---|
| Grade 3 or 4 neutropenia with or without infection or fever, first delay | • Delay all study treatment for a maximum of 14 days.<br>• *Do not delay mosunetuzumab for uncomplicated neutropenia without associated fever in Cycle 1.*<br>• Growth factors (e.g., G-CSF) for neutropenia are permitted (in addition to primary prophylaxis per Section 4.4.1.1).<br>• If ANC recovers to ≥1000/μL≤7 days after the scheduled date for the next cycle, administer the full dose of all study treatments.<br>• If ANC recovers to ≥1000/μL≥8 days after the scheduled date for the next cycle, consider reducing the dose of cyclophosphamide and/or doxorubicin to a lower dose level (see Table 5 and Table 6).<br>• Consider holding mosunetuzumab for persistent Grade 4 neutropenia and discuss with Medical Monitor (see Section 5.1.2.2, Neutropenia and Thrombocytopenia).<br>• The dose of mosunetuzumab, polatuzumab vedotin, vincristine, rituximab, and prednisone should not be modified for this reason. |
| Recurrent Grade 3 or 4 neutropenia with or without infection or fever | • Delay all study treatment for a maximum of 14 days.<br>• Growth factors (e.g., G-CSF) for neutropenia are permitted (in addition to primary prophylaxis per Section 4.4.1.1).<br>• If ANC recovers to ≥1000/μL≤7 days after the scheduled date for the next cycle, administer the current dose of cyclophosphamide and/or doxorubicin.<br>• If ANC recovers to ≥1000/μL≥8 days after the scheduled date for the next cycle, consider reducing the doses of cyclophosphamide and doxorubicin to the next dose level (see Table 5 and Table 6).<br>• Consider holding mosunetuzumab for persistent Grade 4 neutropenia and discuss with Medical Monitor (see Section 5.1.2.2, Neutropenia and Thrombocytopenia).<br>• If Grade 3 or 4 neutropenia persists despite growth factor support and following cyclophosphamide and doxorubicin dose reductions, in the absence of fever, the patient may continue study treatment at the investigator's discretion with consultation of the Medical Monitor.<br>• The dose of mosunetuzumab, polatuzumab vedotin, vincristine, rituximab, and prednisone should not be modified for this reason. |

**Table 8 Dose Interruptions, Reductions, and Discontinuations of Mosunetuzumab, Polatuzumab Vedotin, Rituximab, and CHP or CHOP (cont.)**

| Event(s) | Dose Delay or Modification |
|---|---|
| Grade 3 or 4 thrombocytopenia, first episode | • Delay all study treatment for a maximum of 14 days.<br>• *Do not delay mosunetuzumab for thrombocytopenia without associated bleeding in Cycle 1*<br>• If platelet count recovers to $\geq 75 \times 10^9$/L $\leq$ Day 7 after the scheduled date of the next cycle, administer full dose of all study drugs.<br>• If platelet count recovers to $\geq 75 \times 10^9$/L $\geqslant$ Day 8 after the scheduled date of the next cycle, consider reducing the dose of cyclophosphamide and/or doxorubicin to a lower dose level (see Table 5 and Table 6). Full dose/current dose of all other study drugs may be given.<br>• If the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of cyclophosphamide and/or doxorubicin.<br>• Consider holding mosunetuzumab for persistent Grade 4 thrombocytopenia and discuss with Medical Monitor (see Section 5.1.2.2, Neutropenia and Thrombocytopenia). |
| Recurrent Grade 3 or 4 thrombocytopenia | • If patient develops recurrent Grade 3–4 thrombocytopenia following cyclophosphamide and/or doxorubicin dose reductions, consider reducing the dose of cyclophosphamide and doxorubicin to the next dose level (see Table 5 and Table 6).<br>• Consider holding mosunetuzumab for persistent Grade 4 thrombocytopenia and discuss with Medical Monitor (see Section 5.1.2.2, Neutropenia and Thrombocytopenia). |
| Hemorrhagic cystitis | • Patients should be adequately hydrated before and after cyclophosphamide administration and should be instructed to void frequently.<br>• If gross hematuria develops, cyclophosphamide should be withheld until resolution of cystitis.<br>• A dose reduction of 50% for cyclophosphamide may be considered at the next cycle.<br>• Re-escalation of cyclophosphamide to the initial full dose is recommended if symptoms do not recur. |
| Grade 2–4 heart failure or Grade 3 or 4 LVSD | • Discontinue all study treatment permanently. |

**Table 8 Dose Interruptions, Reductions, and Discontinuations of Mosunetuzumab, Polatuzumab Vedotin, Rituximab, and CHP or CHOP (cont.)**

| Event(s) | Dose Delay or Modification |
|---|---|
| Bilirubin between 1.5 and 3.0 mg/dL | • Dose reduction should be avoided if hyperbilirubinemia is not related to hepatic injury (i.e., hemolysis or Gilbert syndrome). In these cases, dose reduction considerations should be guided by direct bilirubin levels.<br>• Reduce doxorubicin and vincristine dose by at least 25% of baseline and polatuzumab vedotin should be reduced to the next level (see Table 4).<br>• Consider holding mosunetuzumab and discuss with Medical Monitor (see Section 5.1.2.2, Elevated Liver Enzymes and Hepatotoxicity).<br>• With subsequent courses of treatment, if bilirubin has returned to ≤1 mg/dL, full doses may be given. Evaluate for causality. |
| Bilirubin >3.0 mg/dL | • Dose delay should be avoided if hyperbilirubinemia is not related to hepatic injury (i.e., hemolysis or Gilbert syndrome). In these cases, dose delay considerations should be guided by direct bilirubin levels.<br>• Withhold doxorubicin, vincristine, and polatuzumab vedotin until improvement to Grade ≤1. Evaluate for causality. Dosing of cyclophosphamide and prednisone may continue.<br>• Consider holding mosunetuzumab until improvement to Grade ≤1 and consider discontinuation; discuss with Medical Monitor (see Section 5.1.2.2, Elevated Liver Enzymes and Hepatotoxicity). |
| Grade 1 neuropathy | • No study treatment modification is recommended for Grade 1 sensory or motor peripheral neuropathy. |
| Grade 2 sensory peripheral neuropathy | • If the AE severity remains unchanged at the time of the next scheduled cycle, administer rituximab *or mosunetuzumab* and CHP at the recommended doses.<br>• Polatuzumab vedotin should be reduced one dose level per Table 4<br>• Vincristine should be reduced one dose level per Table 7.<br>• Should the AE remain Grade 2 in future cycles, further dose reductions should occur per Table 4 (polatuzumab vedotin) and Table 7 (vincristine). If the AE improves to Grade 1 by the start of the next cycle, administer vincristine or polatuzumab vedotin at the most recent dose.<br>• Dose of vincristine or polatuzumab vedotin should not be re-escalated for future cycles without discussion with the Medical Monitor. |

**Table 8 Dose Interruptions, Reductions, and Discontinuations of Mosunetuzumab, Polatuzumab Vedotin, Rituximab, and CHP or CHOP (cont.)**

| Event(s) | Dose Delay or Modification |
|---|---|
| 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 cycle, hold vincristine and polatuzumab vedotin and administer CHP components *and rituximab if applicable* at the recommended doses. The withheld doses of vincristine or polatuzumab vedotin will not be made up at a later date.<br>• Consider holding mosunetuzumab and discuss with the Medical Monitor (see also Section 5.1.2.2, Neurologic Toxicity).<br>• When the AE improves to Grade ≤2 peripheral sensory neuropathy and/or Grade ≤1 peripheral motor neuropathy, polatuzumab vedotin or vincristine can be restarted at a reduced dose *at the next cycle* per Table 4 and Table 7, respectively. |
| Grade 4 neuropathy (including peripheral sensory or motor neuropathy) | • Discontinue polatuzumab vedotin *and vincristine* treatment permanently.<br>• Patients should be evaluated regarding the continuation of CHP *and rituximab* on the basis of their benefit–risk.<br>• Consider discontinuation of mosunetuzumab and discuss with the Medical Monitor (See also Section 5.1.2.2, Neurologic Toxicity). |
| Grade 3 or 4 constipation or ileus | • Polatuzumab vedotin and vincristine should be held until improvement to Grade ≤2. All other study drugs may be continued or delayed at the discretion of the investigator.<br>• Consider reducing polatuzumab vedotin and vincristine to the next dose level per Table 4 and Table 7, respectively, after improvement to Grade ≤2. |
| Grade 3 or 4 tumor lysis syndrome | • Following complete resolution of tumor lysis syndrome, study treatment may be re-administered at the full/current dose during the next scheduled infusion in conjunction with prophylactic therapy.<br>• For mosunetuzumab specific tumor lysis syndrome guidance, see Section 5.1.2.2, Tumor Lysis Syndrome. |

**Table 8 Dose Interruptions, Reductions, and Discontinuations of Mosunetuzumab, Polatuzumab Vedotin, Rituximab, and CHP or CHOP (cont.)**

| Event(s) | Dose Delay or Modification |
|---|---|
| Grade 3 IRR, second episode | • Discontinue, polatuzumab vedotin, or rituximab permanently; continue CHP or CHOP.<br>• If IRR is attributed to polatuzumab vedotin, continue mosunetuzumab and rituximab.<br>• If IRR is attributed to rituximab, continue polatuzumab vedotin.<br>• If IRR is attributed to mosunetuzumab, continue polatuzumab vedotin, and follow Table 10. |
| Anaphylaxis or Grade 4 IRR | • Discontinue polatuzumab vedotin, rituximab, or mosunetuzumab permanently; continue CHP or CHOP.<br>• If anaphylaxis is attributed to polatuzumab vedotin, continue mosunetuzumab.<br>• If anaphylaxis is attributed to rituximab, continue polatuzumab vedotin.<br>• If anaphylaxis is attributed to mosunetuzumab, continue polatuzumab vedotin, and follow Table 10. |
| 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.<br>• Subsequent recurrence: Based on the nature of the toxicity, decrease one or more study drugs (polatuzumab vedotin, vincristine, cyclophosphamide, or doxorubicin) to a lower dose as described in Table 4–Table 7. Prednisone dose may be modified based on investigator preference. There are no dose reductions allowed for mosunetuzumab.<br>• Second and subsequent recurrence: Based on the nature of the toxicity and if the event is not clinically manageable and resolving within 14 days of the date of the next scheduled cycle, consider discontinuation of suspect study treatment permanently. |

AE=adverse event; CHP=cyclophosphamide, doxorubicin, and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; G-CSF=granulocyte colony-stimulating factor; IRR=infusion-related reaction; LVSD=left ventricular systolic dysfunction.

Note: All decisions regarding dose delays, modifications, and discontinuations should be done in consultation with and with the approval of the Medical Monitor.

#### 5.1.7.3 Infusion-Related Reactions and Anaphylaxis

Medications, including epinephrine for SC injections, corticosteroids, and diphenhydramine hydrochloride for IV injection, and resuscitation equipment should be available for immediate use. Guidelines for management of infusion-related symptoms for polatuzumab vedotin and rituximab are provided in Table 9 and for mosunetuzumab in Table 10. Also refer to Table 8 for dose modifications of study treatment regimen.

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, study treatment should be discontinued and no additional drug should be administered for that cycle. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment. See Appendix 8 for recommended management of anaphylaxis.

**Table 9 Management of Infusion-Related Symptoms for Polatuzumab Vedotin and Rituximab**

| Infusion-Related Symptoms | Guidance |
|---|---|
| Grade 1–2 | • Slow or hold infusion.<br>• Give supportive treatment. [a]<br>• Upon symptom resolution, may resume infusion-rate escalation at the investigator's discretion.<br>• Note: For Grade 2 wheezing or urticaria, patient must be premedicated for any subsequent doses. If symptoms recur, stop the infusion immediately and permanently discontinue study drug. |
| Grade 3 | • Discontinue infusion.<br>• Give supportive treatment. [a]<br>• Upon symptom resolution, may resume infusion-rate escalation, at investigator's discretion. [b]<br>• Note: If the same adverse event recurs with same severity, treatment must be permanently discontinued.<br>• Note: For Grade 3 hypotension or fever, patient must be pre-medicated before re-treatment. If symptoms recur, then study drug must be permanently discontinued.<br>• Note: If patient has Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence, permanently discontinue study drug. |
| Grade 4 | • Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue study drug. |

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

Refer to the NCI-CTCAE v5.0 for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text following this table.

[a] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the previous 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. Patients with hypotension who require vasopressor support must be permanently discontinued from study drug.

[b] Infusion-rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes.

#### 5.1.7.4 Cytokine Release Syndrome

Guidelines for CRS apply for patients receiving mosunetuzumab. Given the mechanism of action of mosunetuzumab, IRRs during or after infusion of mosunetuzumab may be clinically indistinguishable from each other, and their recommended treatment is the same. CRS resolution is defined as the patient no longer requiring vasopressor support or oxygen supplementation.

**Table 10 Management of Cytokine Release Syndrome for Patients Receiving Mosunetuzumab**

| *CRS Grade*[a] | *Action with Current Mosunetuzumab Infusion* | *Supportive Care* | *Anti-IL6/Corticosteroid Therapy* | *Action for Next Mosunetuzumab Dose* |
|---|---|---|---|---|
| *Grade 1*<br>*Fever ≥ 38°C* | • *Slow infusion to ≤ 50% or interrupt infusion until symptoms resolve; re-start at same rate.*<br>• *If symptoms recur with rechallenge, interrupt study treatment, do not resume, and manage per Grade 2.* | • *Symptomatic management of constitutional symptoms and organ toxicities.*<br>• *Consider empiric broad-spectrum antibiotics.*<br>• *Consider G-CSF if neutropenic.*<br>• *Maintenance IV fluids for hydration.*<br>• *Consider hospitalization until symptoms completely resolve.* | • *For prolonged CRS (> 2 days) in patients 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 premedications for next dose per Section 4.3.2.1.*<br>• *Consider 50% (or lower) rate of infusion for next step-up dose in Cycle 1 or 50% rate of infusion if next dose is same dose level (beyond Cycle 1).*<br>• *Consider hospitalization for next dose.* |
| *Grade 2*<br>*Fever ≥ 38°C with hypotension not requiring vasopressors*<br>*and/or*<br>*hypoxia requiring lowflow- oxygen* [b] *by nasal cannula or blow-by* | • *Hold further study treatment until symptoms resolved; consider re-starting infusion at 50% rate.*<br>• *If symptoms recur with rechallenge at decreased infusion rate, interrupt study treatment, do not resume, and manage per Grade 3.* | • *Symptomatic management of constitutional symptoms and organ toxicities.*<br>• *Consider ICU admission for hemodynamic monitoring.*<br>• *For hypotension: IV fluid bolus as needed; for persistent refractory hypotension (e.g., after two fluid boluses and anti-IL6 therapy), start vasopressors and manage per Grade 3.*<br>• *Rule out other inflammatory conditions which can mimic severe CRS (e.g., infections/ sepsis).* | • *Consider tocilizumab.* [c]<br>• *For persistent refractory hypotension after 1–2 doses of anti-IL6 therapy, consider dexamethasone 10 mg IV every 6 hours (or equivalent).* | • *May receive the next dose of mosunetuzumab if symptoms resolve to Grade ≤ 1 for 3 consecutive days with approval of Medical Monitor.*<br>• *Consider enhanced premedications for next dose.*<br>• *Consider 50% (or lower) rate of infusion for next step-up dose in Cycle 1 or 50% rate of infusion if next dose is same dose level (beyond Cycle 1).*<br>• *Consider hospitalization for next dose.* |

**Table 10 Management of Cytokine Release Syndrome for Patients Receiving Mosunetuzumab (cont.)**

| CRS Grade [a] | Action with Current Mosunetuzumab Infusion | Supportive Care | Anti-IL6/Corticosteroid Therapy | Action for Next Mosunetuzumab Dose |
|---|---|---|---|---|
| **Grade 2** *(cont.)*<br>Fever ≥ 38ºC<br>with hypotension not requiring vasopressors<br>and/or<br>hypoxia requiring low-flow oxygen b by nasal cannula or blow-by | | • Consider *empiric broad-spectrum antibiotics.*<br>• *If no improvement within 24 hours, initiate work up and assess* for *signs and symptoms of MAS/HLH as described in Section 5.1.7.4.* | • *Manage per Grade 3 if no improvement within 24 hours after starting* tocilizumab. | |

**Table 10 Management of Cytokine Release Syndrome for Patients Receiving Mosunetuzumab (cont.)**

| CRS Grade [a] | Action with Current Mosunetuzumab Infusion | Supportive Care | Anti-IL6/Corticosteroid Therapy | Action for Next Mosunetuzumab Dose |
|---|---|---|---|---|
| **Grade 3**<br>Fever ≥ 38ºC with hypotension requiring a vasopressor (with or without vasopressin)<br>and/or<br>hypoxia requiring high flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask | • Stop infusion, do not resume. | • Symptomatic management of organ toxicities, admit to ICU for hemodynamic monitoring.<br>• For hypotension: IV fluid bolus and vasopressors as needed.<br>• Rule out other inflammatory conditions which can mimic severe CRS (e.g., infections/ sepsis).<br>• Consider empiric broad-spectrum antibiotics.<br>• If no improvement within 24 hours, initiate work up and assess for signs and symptoms of MAS/HLH as described in Section 5.1.7.4. | • Administer tocilizumab [c]<br>• Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, manage as per Grade 4. [d]<br>• Manage per Grade 4 if no improvement within 18–24 hours after second dose of tocilizumab. | • May receive the next dose of mosunetuzumab if CRS event was responsive to treatment (i.e., clinical improvement within 8–12 hours following tocilizumab/corticosteroids administration) and symptoms resolve to Grade ≤ 1 for 3 consecutive days with approval of Medical Monitor *e*:<br>- Enhanced premedications for next dose<br>- Decrease to 50% (or lower) rate of infusion for next step-up dose in Cycle 1, or 50% rate of infusion if next dose is same dose level (beyond Cycle 1)<br>- Hospitalization for next dose<br>- *The next dose should be reduced to the next lower dose level that has been previously cleared during dose escalation.g Subsequent doses may not be re-escalated with signs/symptoms of Grade 3 or higher CRS at the reduced dose.*<br>- *If the reduced dose is tolerated with no signs/symptoms of Grade 3 or higher CRS, the patient may return to the next higher dose that has been previously cleared during dose escalation.*<br>• If Grade 3 CRS recurs with subsequent doses, *permanently discontinue mosunetuzumab.*[h] |

**Table 10 Management of Cytokine Release Syndrome for Patients Receiving Mosunetuzumab (cont.)**

| CRS Grade [a] | Action with Current Mosunetuzumab Infusion | Supportive Care | Anti-IL6/Corticosteroid Therapy | Action for Next Mosunetuzumab Dose |
|---|---|---|---|---|
| Grade 3<br>Fever ≥ 38ºC with hypotension requiring *a vasopressor (with or without* vasopressin)<br>and/or<br>hypoxia requiring *high flow* oxygen by *nasal cannula, face mask, non-rebreather mask, or Venturi mask* | • Stop infusion, do not resume. | • *Symptomatic management of organ toxicities, admit to* ICU *for* hemodynamic monitoring.<br>• *For hypotension:* IV *fluid bolus* and vasopressors as needed.<br>• Rule out other inflammatory conditions which can mimic severe CRS (e.g., *infections/* sepsis).<br>• Consider empiric broad-spectrum antibiotics.<br>• If no improvement within 24 hours, initiate work up and assess for signs and symptoms of MAS/HLH as described in Section 5.1.7.4. | • Administer tocilizumab [c]<br>• Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, *manage as per Grade 4.* [d]<br>• *Manage per Grade 4 if no improvement within 18–24 hours after second dose of tocilizumab.* | • *May receive the next dose* of mosunetuzumab *if CRS event was responsive to* treatment *(i.e., clinical improvement within 8–12 hours* following *tocilizumab/corticosteroids administration) and symptoms resolve to Grade ≤1 for 3 consecutive days* with *approval of* Medical Monitor *[g]:*<br>- *Enhanced premedications for next dose*<br>- *Decrease to 50% (or lower) rate of infusion for next step-up dose in Cycle 1, or 50% rate of infusion if next dose is same dose level (beyond Cycle 1)*<br>- *Hospitalization for next dose*<br>- *The next dose should be reduced to the next lower dose level that has been previously cleared during dose escalation. [g] Subsequent doses may not be re-escalated with signs/symptoms of Grade 3 or higher CRS at the reduced dose.*<br>- *If the reduced dose is tolerated with no signs/symptoms of Grade 3 or higher CRS, the patient may return to the next higher dose that has been previously cleared during dose escalation.*<br>• *If Grade 3* CRS recurs *with subsequent doses*, permanently discontinue *mosunetuzumab.* [h] |

**Table 10 Management of Cytokine Release Syndrome for Patients Receiving Mosunetuzumab (cont.)**

| *CRS Grade* [a] | *Action with Current Mosunetuzumab Infusion* | *Supportive Care* | *Anti-IL6/Corticosteroid Therapy* | *Action for Next Mosunetuzumab Dose* |
|---|---|---|---|---|
| *Grade 4*<br>*Fever ≥38°C*<br>*with hypotension requiring multiple vasopressors (excluding vasopressin)*<br>*and/or*<br>*hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)* | • *Stop infusion, do not resume.* | • *ICU admission and hemodynamic monitoring.*<br>• *Mechanical ventilation as needed.*<br>• *IV fluids and vasopressors as needed.*<br>• *Symptomatic management of organ toxicities.*<br>• *Rule out other inflammatory conditions which can mimic severe CRS (e.g., Infections/ sepsis)*<br>• *Consider empiric broad-spectrum antibiotics.*<br>• *If no improvement within 24 hours, initiate work up and assess for signs and symptoms of MAS/HLH as described in Section 5.1.7.4.* | • *Administer tocilizumab.* [c]<br>• *For patients refractory to tocilizumab, consider siltuximab, anakinra, and emapalumab, based on discretion of the investigator; management should be discussed with the Medical Monitor.* [d]<br>• *Dexamethasone 10 mg IV every 6 hours (or equivalent).*<br>• *If refractory, consider methylprednisolone 1000 mg/day IV.* [e, f] | • *Permanently discontinue mosunetuzumab* [h] |

*ASTCT =American Society for Transplantation and Cellular Therapy; BiPAP =bilevel positive airway pressure; CPAP =continuous positive airway pressure; CRS =cytokine release syndrome; G-CSF =granulocyte colony stimulating factor; HLH =hemophagocytic lymphohistiocytosis; MAS =macrophage activation syndrome.*

*a CRS grading per ASTCT (Lee et al. 2019). Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.*

*b Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery. Highflow-nasal cannula is defined as oxygen delivered at >6 L/minute.*

**Table 10 Management of Cytokine Release Syndrome for Patients Receiving Mosunetuzumab (cont.)**

c Tocilizumab should be administered at a dose of 8 mg/kg IV (8 mg/kg for participants at a weight of ≥30 kg only; 12 mg/kg for participants at a weight of <30 kg; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (up to a maximum of 4 doses). Refer to Appendix 14 for Schedule of Activities for tocilizumab treatment of CRS.

d Riegler et al. 2019.

e Antifungal prophylaxis should be strongly considered in patients receiving steroids for treatment of CRS.

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

g *If Grade 3 CRS occurs in the step-up dosing cohorts following mosunetuzumab administration at Cycle 1 Day 1 or Cycle 1 Day 8, the next mosunetuzumab dose should be discussed with the Medical Monitor and a dose reduction should be considered. Exceptions may be considered to repeat the same step-up dose based on individual risk-benefit assessment.*

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

- *Individual risk-benefit assessment by principal investigator/treating physician favors continued treatment;*
- *The patient has recovered from previous toxicities and has sufficient organ function/reserve to receive subsequent doses;*
- *The patient has been adequately consented for risks associated with continued treatment and decides to receive subsequent doses;*
- *The above risk-benefit assessment and evaluation of patient's are discussed with the Sponsor;*
- *Subsequent doses are well planned with precautionary measures, including dose reduction, slow infusion rate at 50% or lower, mandatory hospitalizations, and enhanced premedications.*

#### 5.1.7.5 Hemophagocytic Lymphohistiocytosis

The supportive management of HLH is generally similar to that of CRS (see Section 5.1.7.4. Specific diagnostic, monitoring, and management guidelines for HLH are described *in Appendix 19*.

#### 5.1.7.6 Tumor Lysis Syndrome

Treatment for laboratory and/or clinical presentations of 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 reviewed and prophylactic measures initiated according to Section 4.4.1.2. Access to nephrology consultation with acute dialysis services must be available in the event of clinically significant TLS.*

*Patients with high tumor burden and considered by the investigator to be at risk for tumor lysis should receive tumor lysis prophylaxis prior to the initiation of treatment. All patients should be well hydrated. Starting 1–2 days prior to the first dose of study treatment, it is desirable to maintain a fluid intake of approximately 2-3 L/day. In addition, all patients with high tumor burden and considered to be at risk for tumor lysis should be treated with 300 mg/day of allopurinol orally or a suitable alternative treatment (e.g., rasburicase), starting 48–72 hours prior to Cycle 1 Day 1 of treatment and hydration. Patients should continue to receive repeated prophylaxis if deemed appropriate by the investigator and adequate hydration prior to each subsequent cycle of treatment.*

*If the Howard criteria for TLS (see Appendix 18) (Howard et al. 2011) are fulfilled at any time during the study (two or more electrolyte laboratory abnormalities present simultaneously) or if there is a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g., increased serum creatinine or cardiac dysrhythmia), study treatment should be withheld and patients should be hospitalized and adequately treated until normalization of laboratory abnormalities before treatment is restarted.*

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 Medical Monitor.

### 5.1.7.7 Neurologic Toxicity

Guidelines for neurologic toxicity apply for patients receiving mosunetuzumab. For patients developing peripheral neuropathy, refer to Table 8. For patients receiving both polatuzumab vedotin or vincristine and mosunetuzumab who develop Grade ≥ 3 peripheral sensory neuropathy and/or Grade ≥ 2 peripheral motor neuropathy, consideration for holding or discontinuing mosunetuzumab in addition to action taken with polatuzumab vedotin or vincristine should be made and discussed with the Medical Monitor.

**Table 11 Management Guidelines for Neurologic Disorders for Patients Receiving Mosunetuzumab**

| Event | Grade | Management |
|---|---|---|
| Seizure | Grade 1–2 | • Withhold further study treatment; provide supportive care.<br>• Consider treatment with corticosteroids.<br>• Consider consultation with a neurologist; consider brain MRI, lumbar puncture, EEG.<br>• Study treatment may be resumed with Medical Monitor approval if no recurrent seizure for at least 3 days and with confirmation of baseline neurologic examination. [a]<br>Consider dose reduction of mosunetuzumab when resuming. |
| | Grade 3–4 | • Permanently discontinue study treatment; provide supportive care.<br>• Consider treatment with corticosteroids.<br>• Obtain neurology consultation. |
| Neurologic events not otherwise specified [b] | Grade 1 | • Notify Medical Monitor.<br>• Consider withholding study treatment during evaluation. |
| | Grade 2 | • Notify Medical Monitor.<br>• Withhold mosunetuzumab and evaluate etiology. Consider imaging as appropriate.<br>• Consider treatment with corticosteroids.<br>• Consider neurology consultation.<br>• 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] |

**Table 11 Management Guidelines for Neurologic Disorders for Patients Receiving Mosunetuzumab (cont)**

| | | |
|---|---|---|
| Neurologic events not otherwise specified [b] (cont) | Grade 3 | • Notify Medical Monitor.<br>• Withhold mosunetuzumab and evaluate etiology. Consider imaging as appropriate.<br>• Consider treatment with corticosteroids.<br>• Obtain neurology consultation.<br>• Consider discontinuation mosunetuzumab if symptoms persist > 7 days. [a]<br>• Mosunetuzumab may be resumed when symptoms have returned to baseline ≥ 3 consecutive days without the need for medical management and with baseline neurologic examination.<br>• Permanently discontinue study treatment for recurrent Grade 3 event. |
| | Grade 4 | • Notify Medical Monitor.<br>• Permanently discontinue mosunetuzumab.<br>• 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 Medical Monitor.

[b] Refer to Table 8 for recommendations on managing study treatment if patients develop peripheral neuropathy. Table 11 does not apply to peripheral neuropathy.

#### 5.1.7.8 Elevated Liver Enzymes and Hepatotoxicity

Guidelines for hepatotoxicity in Table 12 apply for patients receiving mosunetuzumab.

For patients with isolated elevated bilirubin, refer to Table 8.

For patients receiving both polatuzumab vedotin and mosunetuzumab who develop isolated elevated bilirubin, consideration for withholding or discontinuing mosunetuzumab in addition to action taken with polatuzumab vedotin should be made and discussed with the Medical Monitor. Similarly, for patients developing elevated liver enzymes with or without elevated bilirubin, considerations for withholding or discontinuing polatuzumab vedotin should be made and discussed with the Medical Monitor.

Transient Grade 3 AST and ALT elevations have been observed with mosunetuzumab in the setting of CRS and have resolved with supportive treatment. HLH (Section 5.1.2.2) may present as acute liver failure (Lin et al. 2016; Jagtap et al. 2017). In instances where no alternative etiology (e.g. viral, neoplastic) is identified, an immune-mediated cause should be considered and evaluated.

**Table 12 Management Guidelines for Liver Function Test Abnormalities and Hepatotoxicity for Patients Receiving Mosunetuzumab**

| LFT Abnormality | Management |
|---|---|
| Grade 1 AST or ALT elevation<br>- OR -<br>AST/ALT ≥3×baseline value | • Continue mosunetuzumab<br>• Monitor LFTs (including AST, ALT, and bilirubin) weekly.<br>• For AST/ALT ≥3×baseline value but < Grade 1, notify Medical Monitor prior to subsequent study treatment. |
| Grade 2 AST or ALT elevation | **All events:**<br>• Withhold mosunetuzumab<br>• Monitor LFTs at least weekly and as clinically indicated until values resolve to normal or baseline.<br>• Resume mosunetuzumab when resolved to Grade ≤1 or baseline.<br>• Consider hepatology consultation.<br>**Events >5 days' duration:**<br>• Obtain hepatology consultation; evaluate etiology. |
| Grade 3 AST or ALT elevation | **All events:**<br>• Withhold mosunetuzumab.<br>• Monitor LFTs every 24–48 hours until decreasing, and then follow weekly.<br>• Obtain hepatology consultation; consider liver biopsy to assess hepatic injury. [a]<br>• Resume mosunetuzumab when resolved to Grade ≤ 1 or baseline.<br>**Events >5 days' duration**<br>• Resume mosunetuzumab when resolved to Grade ≤ 1 or baseline, following approval of Medical Monitor. [a] |
| Grade 4 AST or ALT elevation | • Permanently discontinue mosunetuzumab. [b]<br>• Follow management guidelines as described for Grade 3 events. |

CRS=cytokine release syndrome; LFT=liver function test; *HLH = hemophagocytic lymphohistiocytosis*

[a] Immune-related event should be considered when concurrent clinical and laboratory manifestations of CRS (Section 5.1.2.1) or *HLH* (Section 5.1.2.2) are present, or in instances where no alternative etiology (e.g. viral, neoplastic) can account for observed LFT abnormalities.

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

#### 5.1.7.9 Neutropenia and Thrombocytopenia in Patients Receiving Mosunetuzumab

Treatment holds and discontinuations for polatuzumab vedotin and chemotherapy for neutropenia and thrombocytopenia are described in Table 8. For patients receiving both polatuzumab vedotin or chemotherapy and mosunetuzumab who develop persistent Grade 4 neutropenia or thrombocytopenia, consideration for holding or discontinuing mosunetuzumab in addition to action taken with polatuzumab vedotin and chemotherapy should be made and discussed with the Medical Monitor. Mosunetuzumab step doses should not be held for uncomplicated neutropenia without associated fever or for thrombocytopenia without associated bleeding in Cycle 1. Any modification of mosunetuzumab dose schedule should be discussed with the Medical Monitor.

### 5.1.8 Internal Monitoring Committee

Because this is the first trial to combine mosunetuzumab with CHOP and CHP-pola, an IMC will be utilized during the Phase Ib portion of the study to make recommendations regarding study conduct on the basis of trial safety data to ensure enhanced patient safety while receiving study treatment.

The IMC will be established to monitor patient safety during the Phase Ib portion of the study and to make decisions regarding dose escalations and the RP2D for M-CHOP and M-CHP-Pola based on the plan described in Section 3.1.2. The IMC will also make recommendations about whether to continue mandatory hospitalizations with specific study treatment regimens. The IMC will also make a recommendation about whether to continue into the Phase II safety cohort. If the combination of mosunetuzumab RP2D_A plus CHOP is not tolerated in the first 6 patients with previously untreated DLBCL, then the IMC may make recommendations on assessing alternative mosunetuzumab doses or regimens.

The IMC will consist of the following members:

- The IMC Chair, who will be a Sponsor Medical Monitor not directly involved with the study
- Representatives from Clinical Science, Safety Science, and Biostatistics, who are all external to the Study Management Team

Representatives from other functional areas may serve as ad-hoc members of the IMC at the discretion of the IMC Chair or designee.

In addition to the ongoing assessment of the incidence and nature of toxicity, adverse events (particularly Grades ≥3), serious adverse events, deaths, and laboratory abnormalities by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the Phase Ib portion of the study. At the time of each review, the IMC may make one or more of the following recommendations regarding study conduct, including but not limited to, the following: performing additional safety analyses, amending the study protocol, holding patient

enrollment pending further safety evaluations, enrolling additional patients at a specific dose level and schedule to obtain additional safety data, holding/discontinuing study treatment, making decisions to modify or discontinue the requirement for hospitalization with study treatment, or terminating the study. Decisions will be made in consideration of the totality of the available data. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

### 5.1.9 Independent Data Monitoring Committee

An iDMC, external to the Sponsor, will be incorporated into the Phase II portion of the study to monitor patient safety. The iDMC will follow a charter that outlines their roles and responsibilities. The iDMC will review safety data from the Phase Ib portion of the study and from at least the first 10 patients enrolled in Phase II Group C at the IMC-confirmed RP2D, in order to make a recommendation whether to continue into the randomized Phase II portion of the study. During the Phase II portion of the study, the iDMC will meet approximately every 3 months to review safety data, and to provide recommendations to the Sponsor whether to continue, modify, or terminate the trial.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

### 5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### 5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential DILI that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- DLTs (see Section 5.2.4)
- Adverse events of special interest specific for mosunetuzumab:

– 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; refer to Section 5.1.2.2 and the Mosunetuzumab Investigator's Brochure for additional details

- Adverse events of special interest specific for polatuzumab vedotin:

– Grade *2 or higher* peripheral *neuropathy (sensory and/or motor)*

– *Grade 3 or higher infections*

### 5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT assessment window, adverse events identified as DLTs, as defined in Section 3.1.2.1, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### 5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study drug or the initiation of another anti-cancer agent, whichever is earlier.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

### 5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

### 5.3.3 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 unless otherwise specified (Appendix 7). Table 13 will

be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 13 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 (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 14):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

**Table 14 Causal Attribution Guidance**

| Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment? | |
|---|---|
| YES | There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge. |
| NO | An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug). |

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

### 5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### 5.3.5.1 Infusion-Related Reactions/Hypersensitivity Reactions and Cytokine Release Syndrome Attributed to Mosunetuzumab

Given the mechanism of action of mosunetuzumab, IRRs and CRS may be indistinguishable from one another (Section 5.1.2). Therefore, all adverse events consistent with a diagnosis of infusion-related event or CRS that are attributed to mosunetuzumab will be recorded singularly as CRS. Adverse events of CRS are graded using the ASTCT CRS Consensus Grading criteria (Appendix 7).

The one exception to this reporting guidance is if a clinical presentation suggests an immediate, acute hypersensitivity (e.g., generalized hives, mucosal edema, with or without wheezing and hypotension), a diagnosis of "allergic reaction" or "hypersensitivity reaction" or "anaphylaxis" should be used.

For adverse events with a diagnosis of "cytokine release syndrome" or "infusion-related reaction", associated signs, symptoms, and laboratory abnormalities should be recorded on the dedicated eCRF for CRS events. Each CRS or IRR event should be recorded separately on the Adverse Event eCRF. The associated signs and symptoms, including those relating to blood pressure and hypoxia, should be graded according to NCI-CTCAE v5.0 and recorded on the dedicated eCRF for CRS/IRR events. All other

laboratory abnormalities (e.g., LFTs, cytopenias) and end-organ adverse events (e.g., neurologic toxicities) should be reported separately in the adverse events eCRF. Ambiguous terms such as "systemic reaction" should be avoided.

In addition to documentations on the Adverse Event eCRF, non-serious Grade ≥ 2 CRS events should be reported as an adverse event of special interest (see Section 5.2.3).

#### 5.3.5.2 Infusion-Related Reactions Attributed to Polatuzumab Vedotin and Rituximab

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to the polatuzumab vedotin and rituximab infusion should be captured as a diagnosis of "infusion-related reaction," "hypersensitivity reaction," or "anaphylactic reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF.

#### 5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs and CRS (see Sections 5.3.5.1 and 5.3.5.2), a diagnosis (if known) should be recorded on the Adverse Event eCRF 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, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### 5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

#### 5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

#### 5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range

(e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

#### 5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

#### 5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.6)

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

#### 5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of underlying malignancy.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of underlying malignancy, "malignant neoplasm progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

#### 5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

#### 5.3.5.11 Lack of Efficacy or Worsening of NHL

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Lugano 2014 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is

any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

#### 5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Optional hospitalization for monitoring as described by the protocol (Section 5.1.1).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

#### 5.3.5.13 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. In addition, all special situations associated with mosunetuzumab, polatuzumab

vedotin, rituximab, or tocilizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

#### 5.3.5.14 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take

place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information for All Sites**

Medical Monitor: [redacted], *M.D., Ph.D.*
(Primary)

Telephone No.: [redacted]

Roche Medical Responsible: [redacted], Pharm.D. (Secondary)

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

### 5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

#### 5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >90 days after the last dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 12 months after the final dose of polatuzumab vedotin, 12 months after the final dose of rituximab, 12 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 3 months after the final dose of tocilizumab, as applicable. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until

conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 60 days after the last dose of mosunetuzumab, *6 months* after the last dose of polatuzumab vedotin, and 3 months after the last dose of rituximab, 6 months after the final dose of cyclophosphamide, doxorubicin, prednisone, or vincristine, and 60 days after the final dose of tocilizumab, as applicable. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### 5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

#### 5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug or the initiation of another anti-cancer agent, whichever is earlier), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

## 5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Mosunetuzumab Investigator's Brochure
- Polatuzumab Vedotin Investigator's Brochure
- Rituximab Investigator's Brochure
- Tocilizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Please refer to Section 3.1.1 for an overview of the study design, which includes a Phase Ib and a Phase II portion.

The safety data from each phase will be summarized separately by treatment arm and mosunetuzumab dose level and/or schedule. Safety analyses will include all treated patients according to the actual treatment received, including patients who received any amount of medication for both phases.

Efficacy analyses for the randomized Phase II portion will be conducted in accordance with the intent-to-treat principle, with patients allocated to the treatment arm to which they were randomized. Efficacy analyses for M-CHOP in the Phase II portion will include patients enrolled in the safety run-in for Group C and patients randomized to Arm 3. Efficacy analyses for the Phase Ib portion will be done separately by cohort and histologic type of B-cell NHL (as applicable in the Phase Ib portion of the study).

## 6.1 DETERMINATION OF SAMPLE SIZE

The sample size of the study is mainly driven by the Phase II portion, which focuses on the estimation of treatment effect using CR rate based on PET-CT. With 40 patients (M-CHP-pola in Arm 1, or M-CHOP in Group C and Arm 3 combined), the 95% CI exact Clopper-Pearson (Clopper and Pearson 1934) CIs for estimation of the true CR rate

would have a margin of error not exceeding ±17%. Table 15 and Table 16 show Clopper-Pearson exact 95% CIs corresponding to observed CR rates ranging from 60% to 80% based on sample sizes of 40 and 20, respectively. With 40 patients and an observed CR rate of at least 60%, a true CR rate below 43% can be ruled out with 95% confidence. With 20 patients and an observed CR rate of at least 60%, a true CR rate below 36% can be ruled out with 95% confidence. In addition, with 40 patients in the M-CHP-pola arm (Arm 1) and 20 patients in the R-CHP-pola arm (Arm 2), observing a 75% (15 out of 20) CR rate in the R-CHP-pola arm and a 10% increase in CR rate of 85% (34 out of 40) in the M-CHP-pola arm, the 95% CI for the difference in CR rates is (−16%, 36%).

**Table 15 Clopper-Pearson Exact 95% Confidence Intervals for Assumed Observed Complete Response Rates Based on Sample Size of 40 Patients**

| Observed CR Rate | Number of Patients with CR (95% CI for rate) |
|---|---|
| 80% | 32 (64%, 91%) |
| 75% | 30 (59%, 87%) |
| 70% | 28 (53%, 83%) |
| 65% | 26 (48%, 79%) |
| 60% | 24 (43%, 75%) |

CR = complete response.

**Table 16 Clopper-Pearson Exact 95% Confidence Intervals for Assumed Observed Complete Response Rates Based on Sample Size of 20 Patients**

| Observed CR Rate | Number of Patients with CR (95% CI for rate) |
|---|---|
| 80% | 16 (56%, 94%) |
| 75% | 15 (51%, 91%) |
| 70% | 14 (46%, 88%) |
| 65% | 13 (41%, 85%) |
| 60% | 12 (36%, 81%) |

CR = complete response.

With respect to assessment of safety based on a sample size of 20 in the R-CHP-pola arm (Arm 2), the chance of observing at least one adverse event with true incidence of ≥10% is at least 88%. With 40 patients (M-CHP-pola in Arm 1, or M-CHOP in Group C and Arm 3 combined), there is at least an 87% chance of observing at least one adverse event with true incidence of ≥5%.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized separately by treatment arm. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated by treatment arm. Major protocol violations, including violations of inclusion/exclusion criteria, will be summarized by treatment arm.

Study drug administration data will be listed by dose level and any dose modifications will be flagged. The number of doses, treatment cycles, and average dose received for each study drug for the schedule/treatment arm will be summarized using means, standard deviations, medians, and ranges by treatment arms.

## 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, and race will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. All summaries will be presented overall and by treatment arm and dose level for both phases of the study.

## 6.4 EFFICACY ANALYSES

The primary efficacy analyses will compare M-CHP-pola (Arm 1) versus R-CHP-pola (Arm 2) in the randomized Phase II portion, with patients grouped according to the treatment arm assigned at randomization. The secondary efficacy analyses will include patients enrolled in the safety run-in group (Group C) of M-CHOP and patients randomized to the M-CHOP arm (Arm 3) of the Phase II portion.

The efficacy analyses in the Phase Ib dose-finding portion of the study are exploratory. Descriptive summary statistics will be provided for all efficacy endpoints.

### 6.4.1 Primary Efficacy Endpoint

PET-CT CR at the primary response assessment (6–8 weeks after C6D1 or last dose of study medication if study treatment is discontinued prior to Cycle 6) by IRC review will be used as the primary efficacy endpoint. Patients with missing or no response assessments will be classified as non-complete responders. The CR rate, defined as the percentage of patients with CR, will be estimated and the corresponding Clopper-Pearson exact 95% CI will be constructed for each treatment arm. The difference in CR rates between the combination of M-CHP-pola and R-CHP-pola arms will be estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution. An exploratory comparison of CR rates between the M-CHP-pola and R-CHP-pola arms will be conducted using the Cochran Mantel Haenszel Chi-square test adjusted for randomization stratification factors (Agresti 2002).

Response assessment is determined using the Lugano Response Criteria (Cheson et al. 2014) specified in Appendix 3.

### 6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints of response rate are described below. Patients with missing or no postbaseline tumor assessment will be considered non-responders. Analyses of these endpoints will be identical to those described above for the primary efficacy endpoint of CR rate at primary response assessment measured by PET-CT scan as determined by IRC.

- CR rate at the time of primary response assessment based on CT only, as determined by the investigator
- ORR, defined as the percentage of patients with CR or PR at the time of primary response assessment based on PET-CT, as determined by the investigator
- ORR, defined as the percentage of patients with CR or PR at the time of primary response assessment based on CT only, as determined by the investigator
- Best ORR, defined as the percentage of patients with CR or PR at any time on study, based on PET-CT or CT only, as determined by the investigator

Among patients with a best overall response of CR or PR, DOR will be defined as the time from the first occurrence of a documented objective response to disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs first. If a patient does not experience death or disease progression before the end of the study, DOR will be censored on the date of the last tumor assessment. DOR will be summarized descriptively with use of the Kaplan-Meier method (Kaplan and Meier 1958). If analytically possible, median DOR will be estimated, along with the corresponding 95% CI using the method of Brookmeyer and Crowley (1982). No formal comparisons of DOR across treatment arms will be conducted because of the non-randomized nature of this analysis population. DOR will also be summarized for the subgroups of patients whose best objective response is PR and patients whose best objective response is CR.

PFS is defined as the time from randomization, or first treatment for non-randomized arms, to the first occurrence of disease progression, relapse, or death from any cause. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of last tumor assessment. For patients who do not have a postbaseline evaluable tumor assessment, PFS will be censored at the date of randomization, or first study treatment for non-randomized arms, plus 1 day. PFS will be assessed per investigator, using the Lugano 2014 Response Criteria (Cheson et al. 2014). PFS will be compared in an exploratory manner between the treatment arms of M-CHP-pola versus R-CHP-pola in the Phase II portion using the stratified log-rank test. The hazard ratio will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. The stratification factors to be used will be the same as the randomization stratification factors. Results from an unstratified

analysis will also be provided. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the distribution of PFS, and median (if analytically possible), 6-month and 1-year PFS for each treatment arm. The Brookmeyer-Crowley method (Brookmeyer and Crowley 1982) will be used to construct the 95% CI for the median PFS. The Greenwood's formula will be used to provide standard errors and the corresponding 95% CIs for 1-year PFS.

EFS, defined as the time from randomization, or first study treatment for non-randomized arms, to the first occurrence of any treatment failure including disease progression, relapse as determined by the investigator, initiation of new anti-lymphoma therapy (NALT), or death. For patients who do not experience the specified event (disease progression/relapse, death, start of an NALT), EFS will be censored at the date of last evaluable tumor assessment. For patients who do not have a postbaseline evaluable tumor assessment or documentation of NALT, EFS will be censored at the date of randomization, or first study treatment for non-randomized arms, plus 1 day. EFS will be assessed using the Lugano 2014 Response Criteria (Cheson et al. 2014). Analyses of EFS will be identical to those outlined previously for PFS.

Secondary PRO endpoints for the expansion phase include time-to-deterioration in the EORTC QLQ-C30 physical functioning and fatigue and in the FACT-Lym subscale *lymphoma symptoms*. Time-to-deterioration will be compared in an exploratory manner between the treatment arms of M-CHP-pola versus R-CHP-pola using a stratified log-rank test. For EORTC QLQ-C30 physical functioning and fatigue, deterioration is defined as a ≥ 10-point worsening from baseline (Osoba et al. 1998). For the FACT-Lym subscale, deterioration is defined as ≥ 3-point worsening from baseline (Carter et al 2008; Hlubocky et al. 2013). Analyses will be conducted with the intent-to-treat population. The hazard ratio for deterioration will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. Kaplan-Meier methodology will be used to estimate the median time to deterioration for each treatment arm, and Kaplan-Meier curves will be produced. Patients without occurrence of deterioration at the clinical cutoff date will be censored at the last available assessment. Supplemental item-level analyses will be conducted with the individual B-symptom items of the FACT-Lym subscale using a raw 1-point worsening.

### 6.4.3 Exploratory Efficacy Endpoints

Exploratory endpoints for the expansion phase include:

- Responder analyses examining the proportion of individuals meeting or exceeding meaningful change thresholds for EORTC QLQ-C30 physical functioning and fatigue and FACT-Lym subscale *lymphoma symptoms* will be conducted and compared between treatment groups. A raw 1-point change will be used for the B-symptom items of the FACT-Lym subscale.

- Appropriate longitudinal models will be used to compare scores of EORTC QLQ-C30 treatment-related symptoms and FACT/GOG-NTX peripheral neuropathy over time, between the treatment arms of M-CHP-pola and R-CHP-pola.
- Descriptive summary statistics and change from baseline will be calculated at each assessment for all scales of the EORTC QLQ-C30, FACT-Lym subscale, FACT/GOG-NTX, and EQ-5D-5L.

All primary and secondary efficacy endpoints will also be explored in the subgroups by stratification factors and subgroups by cell of origin (e.g., ABC, GCB).

## 6.5 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug, with patients grouped according to treatment received. Safety will be assessed through summaries of adverse events, summaries of changes from screening assessments in laboratory test results, ECGs, and changes in vital signs. All collected adverse event data will be summarized by phase of the study, treatment arm, and histological subtype for the Phase Ib portion. All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 toxicity grade (or, for CRS events, per ASTCT consensus grading criteria). All serious adverse events will be listed separately and summarized. Deaths reported during the study treatment period and those reported during follow-up after treatment discontinuation will be listed. DLTs and adverse events leading to treatment discontinuation will also be separately listed. Selected laboratory data will be listed, with values outside of normal ranges identified. Drug exposure will be summarized, including number of cycles received, cumulative dose, and dose intensity. An IMC will be set up to evaluate the cumulative safety data on a periodic basis (see Section 5.1.8 for details).

## 6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum concentration of mosunetuzumab versus time data will be tabulated and plotted by dose level. The $C_{max}$ and $C_{min}$, of mosunetuzumab will be summarized. For patients with dense PK sampling scheme, additional PK parameters will be calculated including AUC, drug clearance, and volume of distribution at steady state, as appropriate for data collected. Estimates for these parameters will be tabulated and summarized.

Serum or plasma trough and maximum concentrations for polatuzumab vedotin analytes (i.e., acMMAE, unconjugated MMAE, and total antibody) and rituximab, where applicable, will be summarized, as appropriate and as data allow. Predose obinutuzumab and rituximab concentrations will be summarized, where applicable. Compartmental, non-compartmental, and/or population methods may be considered. Additional PK analyses will be conducted as appropriate.

## 6.7 IMMUNOGENICITY ANALYSES

Validated screening, confirmatory *and titering* assays will be employed to assess ADAs before, during, and after treatment with mosunetuzumab and polatuzumab vedotin, *respectively* (see Appendix 2). Given the historically low immunogenicity rate of rituximab in patients with NHL, ADAs against this agent will not be monitored in this study.

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients are considered to have treatment-induced ADA responses if they are ADA negative or missing data at baseline and then develop an ADA response following study drug administration. Patients are considered to have treatment-enhanced ADA responses if they are ADA positive at baseline and the titer of one or more post baseline samples is at least 4-fold greater (i.e., at least 0.60 titer unit) than the titer of the baseline sample. Patients are considered to be negative for ADAs if they are ADA negative at all timepoints or if they are ADA positive at baseline but do not have any post baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may also be assessed as appropriate and reported in a descriptive manner via subgroup analyses.

## 6.8 BIOMARKER ANALYSES

Exploratory analyses of biomarkers related to tumor and disease biology as well as the mechanisms of action of M-CHP-pola and M-CHOP will be conducted. The association between candidate biomarkers and PET-CT CR rate and other measures of efficacy and safety, with treatment and independent of treatment, will be explored to assess potential predictive and prognostic value, respectively. The effects of baseline prognostic characteristics, including DLBCL subtypes (i.e., COO or genetically determined subtypes), on efficacy, will be evaluated using univariate and/or multivariate statistical methods such as Cox regression and logistic regression.

Exploratory PD analyses will include assessments of biomarkers in both blood and tumor tissue when available. Some, but not all, of the exploratory biomarkers that will be assessed are listed in Table 17.

**Table 17 Biomarkers for Pharmacodynamic Activity and Retrospective Exploratory Research**

| Sample Type | Timing | Proposed Biomarkers |
|---|---|---|
| Whole blood or PBMC isolated from whole blood | Baseline, on-treatment, and follow-up | • Lymphocyte numbers and T-cell activation status |
| DNA isolated from PBMC | Baseline, on-treatment, and follow-up | • TCR repertoire<br>• Genomic profile [a] |
| Plasma | Baseline, on-treatment, and follow-up | • Inflammatory cytokines and other circulating proteins |
| *Serum* | *Following tocilizumab administration* | • *IL-6, soluble IL-6R, sgp130* |
| ctDNA isolated from plasma | Baseline, on-treatment, end of treatment, and follow-up | • ctDNA as a peripheral measure of disease biology, prognosis, subsets and treatment response<br>• MRD |
| Tumor tissue | Baseline (archival or freshly collected prior to study) | • Tumor- and immune-related proteins |
| | Time of progression (optional) | |
| RNA/DNA extracted from tumor tissue | Baseline (archival or freshly collected prior to study) | • RNA-based gene expression profile, including but not limited to cell of origin gene signature<br>• Tumor genomic profile<br>• MRD index clone<br>• TCR repertoire |
| | Time of progression (optional) | |

; ctDNA=circulating tumor DNA; MRD=minimal residual disease; NGS=next-generation sequencing; PBMC = peripheral blood mononuclear cells; TCR=T-cell receptor.

[a] For patients at participating sites; see Section 4.5.11.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

## 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

## 7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

### 7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

### 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

## 8. ETHICAL CONSIDERATIONS

### 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or

European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

## 8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will

be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on germline mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

### 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

## 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

### 9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

### 9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

## 9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

## 9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 40 sites globally will participate to enroll approximately 110–160 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety during the Phase Ib portion of the study, and an iDMC during the Phase II portion of the study. Tumor response will be evaluated by an IRC during the Phase II portion of the study.

## 9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

## 9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

## 10. REFERENCES


Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Agresti A. Categorical data analysis. 2nd edition. New York:Wiley, 2002.

American Cancer Society.: Key statistics for chronic lymphocytic leukemia [resource on the Internet]. 2018 [cited 30 March 2018]. Available from: http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-key-statistics.

Armitage JO, Weisenburger DD. New approach to classifying non–Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non–Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780–95.

Atwell S, Ridgway JB, Wells JA, et al. Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library. J Mol Biol 1997;270:26–35.

Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T-cell-engaging antibody. Science 2008;321:974–7.

Blincyto® (blinatumomab) FDA Drug Approval Package, Amgen Inc. 2014 [updated November 2017; cited 12 May 2017]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

Blincyto® U.S. Package Insert, Amgen Inc. 2014 [updated March 2018; cited 27 February 2018]. Available from: http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/blincyto/blincyto_pi_hcp_english.ashx.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics1982;38:29–41.

Cairo MS, Coiffier B, Reiter A, et al. on behalf of the TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol 2010;149:578–86.

Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4834–40.

Carter GC, Liepa AM, Zimmermann AH, et al. Validation of the Functional Assessment of Cancer Therapy–Lymphoma (FACT-LYM) in patients with relapsed/refractory mantle cell lymphoma. Blood 2008;112:2376.

Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol 2016;174:43–56.

Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med 2018;24:679–90.

Chen F, Teachey DT, Pequignot E, et al. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. J Immunol Methods 2016;434:1–8.

Chen Y, Samineni D, Mukadam S, et al. Physiologically based pharmacokinetic modeling as a tool to predict drug interactions for antibody-drug conjugates. Clin Pharmacokinet 2015;54:81–93.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:1–9.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13.

Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767–78.

Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med 2002;346:235–42.

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040–5.

Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381:1817–26.

Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6:224ra25.

Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. Lancet Oncol 2013;14:525–33.

Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. Clin Transl Immunology 2015;4:e39.

Doggett RS, Wood GS, Horning S, et al. The immunologic characterization of 95 nodal and extranodal diffuse large cell lymphomas in 89 patients. Am J Pathol 1984;115:245–52.

Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti-CD79b antibody–drug conjugate, anti–CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood 2009;114:2721–9.

Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol 2003;21:778–84.

Edelman GM, Cunningham BA, Gall WE, et al. The covalent structure of an entire gammaG immunoglobulin molecule. Proc Natl Acad Sci U S A 1969;63:78–85.

Elitek® (rasburicase) U.S. Package Insert, sanofi-aventis U.S. LLC. 2002 [updated September 2017; cited 12 May 2017]. Available from: http://products.sanofi.us/elitek/elitek.html.

Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 2014;66:2613–20.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117–26.

Gazyva® (obinutuzumab) U.S. Package Insert, Genentech Inc. 2013 [updated November 2017; cited 27 February 2018]. Available from: http://www.gene.com/download/pdf/gazyva_prescribing.pdf.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184–90.

Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. New Engl J Med 2013;368:1509–18.

Hashemi-Sadraei N, Vejpongsa P, Baljevic M, et al. Epstein-Barr virus-related hemophagocytic lymphohistiocytosis: hematologic emergency in the critical care setting. Case Rep Hematol 2015;2015:491567.

Hejblum G, Lambotte O, Galicier L, et al. A web-based delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS One 2014;9:e94024.

*Henter JI, Horne AC, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Ped Blood Cancer 2007;48:124–31.*

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725–32.

Hlubocky FJ, Webster K, Cashy J, et al. The development and validation of a measure of health-related quality of life for non-Hodgkin's lymphoma: the Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym). Lymphoma 2013;2013:1–9.

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New Engl J Med 2011;364:1844–54.

Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. Blood 2013;121:4021–31.

Huang HQ, Brady MF, Cella D, et al. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer 2007;17:387–93.

Jagtap N, Sharma M, Rajesh G, et al. Hemophagocytic lymphohistiocytosis masquerading as acute liver failure: a single center experience. J Clin Exp Hepatol 2017;7:184–9.

Jamil MO, Mehta A. Diffuse large B-cell lymphoma: prognostic markers and their impact on therapy. Expert Rev Hematol 2016;9:471–7.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Jerkeman M, Kaasa S, Hjermstad M, et al. Health-related quality of life and its potential prognostic implications in patients with aggressive lymphoma: a Nordic Lymphoma Group Trial. Med Oncol 2001;18:85–94.

Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009;114:2273–9.

Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3452–9.

Kabat EA, Wu TT, Perry HM, et al. Sequences of proteins of immunological interest. 5th ed. NIH Publication No 91–3242. Bethesda, Maryland: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health,1991.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

Kanemasa Y, Shimoyama T, Sasaki Y, et al. The impacts of initial and relative dose intensity of R-CHOP on outcomes of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2017;58:736–9.

Klein U, Goossens T, Fischer M, et al. Somatic hypermutation in normal and transformed human B cells. Immunol Rev 1998;162:261–80.

Klinger M, Brandl C, Zugmaier G, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. Blood 2012;119:6226–33.

Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells. Blood 2012;119:2709–20.

Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol 2015;33:540–9.

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods 2008;333:1–9.

Kurtz DM, Green MR, Bratman SV, et al. Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing. Blood 2015;125:3679–87.

Kwak LW, Halpern J, Olshen RA, et al. Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. J Clin Oncol 1990;8:963–77.

Kymriah™ (tisagenlecleucel) U.S. Package Insert, Novartis Pharmaceuticals Corporation. 2017 [updated August 2017; cited 4 April 2018]. Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf.

La Rosee P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Program 2015;2015:190–6.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188–95.

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

Lim MY, Fedoriw Y, Ramanayake H, et al. Epstein-Barr virus reactivation and hemophagocytic lymphohistiocytosis in a patient with chronic lymphocytic leukemia. Leuk Lymphoma 2014;55:2938–41.

Lin S, Li Y, Long J, et al. Acute liver failure caused by hemophagocytic lymphohistiocytosis in adults: a case report and review of the literature. Medicine (Baltimore) 2016;95:e5431.

MabThera® (rituximab) Summary of Product Characteristics, Roche. 2009 [updated February 2018; cited 17 April 2018]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000165/human_med_000897.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124.

Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. New Engl J Med 2014;371:1507–17.

*McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis [resource on the Internet]. UptoDate 2019 [cited: 16 October 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis*

Nagorsen D, Kufer P, Baeuerle PA, et al. Blinatumomab: a historical perspective. Pharmacol Ther 2012;136:334–42.

National Institutes of Health (NIH). Recombinant DNA Advisory Committee (RAC). Cytokine release syndrome after T cell immunotherapy [videocast on the Internet]. 10 June 2015 [cited 30 January 2017]. Available from: https://videocast.nih.gov/summary.asp?Live=16420&bhcp=1.

National Comprehensive Cancer Network *(NCCN). Prevention* and treatment of cancer-related infections *(Version 1.2020).* [cited *May 2020*]. Available from: https://www.nccn.org/professionals/physician_gls/*pdf/infections.pdf.*

[NCCN] National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®): B-Cell lymphomas, version 2 [resource on the Internet]. 2018 [cited 5 April 2018]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx#site.

Neelapu SS, Locke FL, Bartlett NL, et al. Kte-C19 (anti-CD19 CAR T cells) induces complete remissions in patients with refractory diffuse large B-cell lymphoma (DLBCL): results from the pivotal phase 2 Zuma-1. Blood 2016;128:LBA-6.

Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47–62.

Olejniczak SH, Stewart CC, Donohue K, et al. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry. Immunol Invest 2006;35:93–114.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-realted quality-of-life scores. J Clin Oncol 1998;16:139–44.

Panelli MC, White R, Foster M, et al. Forecasting the cytokine storm following systemic interleukin (IL)-2 administration. J Transl Med 2004;2:17.

Pasqualucci L, Dalla-Favera R. The genetic landscape of diffuse large B-cell lymphoma. Semin Hematol 2015;52:67–76.

Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011;12:460–8.

Pfeifer M, Zheng B, Erdmann T, et al. Anti-CD22 and anti-CD79B antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes. Leukemia 2015;29:1578–86.

Pfreundschuh M. How I treat elderly patients with diffuse large B-cell lymphoma. Blood 2010;116:5103–10.

Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105–16.

Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379–91.

Polson AG, Calemine Fenaux J, Chan P, et al. Antibody drug conjugates for the treatment of non-Hodgkin's lymphoma: target and linker drug selection. Cancer Res 2009;69:2358–64.

Polson AG, Yu SF, Elkins K, et al. Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma. Blood 2007;110:616–23.

Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor–modified T cells in chronic lymphoid leukemia N Engl J Med 2011:365:725–33.

Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet 2014;383:1503–16.

Rath J, Geisler C, Christiansen CB, et al. Epstein-Barr virus reactivation is a potentially severe complication in chronic lymphocytic leukemia patients with poor prognostic biological markers and fludarabine refractory disease. Haematologica 2008;93:1424–6.

Récher C, Coiffier B, Haioun C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. Lancet 2011;378:1858–67.

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

Rituxan® (rituximab) U.S. Package Insert, Genentech Inc. 1997 [updated April 2018; cited 27 February 2018]. Available from: http://www.gene.com/download/pdf/rituxan_prescribing.pdf.

Rivière S, Galicier L, Coppo P, et al. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med 2014;127:1118–25.

Roschewski M, Dunleavy K, Pittaluga S, et al. Monitoring of circulating tumor DNA as minimal residual disease in diffuse large B-cell lymphoma. Blood 2014;124:139.

Rosenberg AS, Worobec AS. A risk-based approach to immunogenicity concerns of therapeutic protein products: Part I: considering consequences of the immune response to a protein. Biopharm International 2004a;17:22–26.

Rosenberg AS, Worobec AS. A risk-based approach to immunogenicity concerns of therapeutic protein products: Part II: considering host-specific and product-specific factors impacting immunogenicity. Biopharm International 2004b;17:34–42.

Rosenberg AS, Worobec AS. A risk-based approach to immunogenicity concerns of therapeutic protein products: Part III: effects of manufacturing changes in immunogenicity and the utility of animal immunogenicity studies. Biopharm International 2005;18:32–36.

Salles GA, Duell J, González-Barca E, et al. Single-arm phase I study of MOR208 combined with lenalidomide in patients with relapsed or refracotry diffuse large B-cell lymphoma: L-MIND. Blood 2017;130:4123.

Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. N Engl J Med 2018;378:1396–1407.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Scott DW, Mottok A, Ennishi D, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. J Clin Oncol 2015;33:2848–56.

Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007;109:1857–61.

Sehn LH, Herrera AF, Matasar MJ, et al. Addition of Polatuzumab Vedotin to Bendamustine and Rituximab (BR) Improves Outcomes in Transplant-Ineligible Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) Versus BR Alone: Results from a Randomized Phase 2 Study. Blood 2017;130:2821.

Seyfarth B, Josting A, Dreyling M, et al. Relapse in common lymphoma subtypes: salvage treatment options for follicular lymphoma, diffuse large cell lymphoma and Hodgkin disease. Br J Haematol 2006;133:3–18.

Skinnider BF, Horsman DE, Dupuis B, et al. Bcl-6 and Bcl-2 protein expression in diffuse large B-cell lymphoma and follicular lymphoma: correlation with 3q27 and 18q21 chromosomal abnormalities. Hum Pathol 1999;30:803–8.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33:3199–212.

Spiess C, Merchant M, Huang A, et al. Bispecific antibodies with natural architecture produced by co-culture of bacteria expressing two distinct half-antibodies. Nat Biotechnol 2013:31:753–8.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–90.

Taplitz RA, Kennedy EB, Bow EJ, et al. *Antimicrobial prophylaxis for adult patients with cancer-related immunosuppresion: ASCO and IDSA clinical practice guideline update. J Clin Oncol 2018; 36(30):3043–3054.*

Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood 2013;121:5154–7.

Thieblemont C, Tilly H, Gomez da Silva M, et al. First analysis of an international double-blind randomized phase III study of lenalidomide maintenance in elderly patients with DLBCL treated with R-CHOP in first line, the Remarc study from Lysa. Blood 2016;128:471.

Tholstrup D, Brown Pde N, Jurlander J, et al. Quality of life in patients with diffuse large B-cell lymphoma treated with dose-dense chemotherapy is only affected temporarily. Leuk Lymphoma 2011;52:400–8.

Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl 5):v116–25.

Tilly H, Morschhauser F, Bartlett NL, et al. Polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for patients with previously untreated diffuse large B-cell lymphoma (DLBCL): updated results of a phase Ib/II study. Blood 2016;128:1853.

Tilly H, Sharman J, Bartlett N, et al. Pola-R-CHP: polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, prednisone for patients with previously untreated diffuse large B-cell lymphoma. Hematol Oncol 2017;35:90–1.

Utsu Y, Takaishi K, Inagaki S, et al. Influence of dose reduction of vincristine in R-CHOP on outcomes of diffuse large B cell lymphoma. Ann Hematol 2016;95:41–7.

*Vallurupalli M and Berliner N. Emapalumab for the treatment of relapsed/refractory hemophagocytic lymphohistiocytosis. Blood 2019;134(21):1783-1786*

Viardot A, Goebeler M, Noppeney R, et al. Blinatumomab monotherapy shows efficacy in patients with relapsed diffuse large B-cell lymphoma. Blood 2011;118:1637.

Viardot A, Goebeler M, Scheele J, et al. Treatment of patients with non-Hodgkin lymphoma (NHL) with CD19/CD3 bispecific antibody blinatumomab (MT103):

double-step dose increase to continuous infusion of 60 μ/m²/d is tolerable and highly effective. Blood 2010;116:2880.

Vidal L, Gafter-Gvili A, Gurion R, et al. Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia. Cochrane Database Syst Rev 2012; CD009045.

Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final results from an open-label, randomized phase 3 study (GOYA). Blood 2016;128:470.

Wilson WH, Ho J, Pitcher BN, et al. Phase III randomized study of R-CHOP versus DA-EPOCH-R and molecular analysis of untreated diffuse large B-cell lymphoma: CALGB/Alliance 50303. Blood 2016;128:469.

Yamaguchi H, Hirakawa T, Inokuchi K, et al. Importance of relative dose intensity in chemotherapy for diffuse large B-cell lymphoma. J Clin Exp Hematop 2011;51:1–5.

Yescarta® (axicabtagene ciloleucel) U.S. Package Insert, Kite Pharma, Inc. 2017 [cited 4 April 2018]. Available from: https://www.yescarta.com/wp-content/uploads/yescarta-pi.pdf.

Zelenetz AD, Gordon LI, Wierda WG, et al. Diffuse large B-cell lymphoma version 1.2016. J Natl Compr Canc Netw 2016;14:196–231.

Zhang K, Jordan MB, Marsh RA, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. Blood 2011;118:5794–8.

Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837–42.

# Appendix 1
# Schedule of Activities

The tables below are applicable to all patients in the Phase Ib (dose finding) and Phase II (expansion) portions of the study. For all pharmacokinetic, immunogenicity, and biomarker samples, see Appendix 2. For assessments related to treatment with tocilizumab (if applicable), see Appendix 14.

## Screening, Cycles 1–4, Interim Response, and Cycles 5–6

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Informed consent [e] | x | | | | | | | | | | | |
| Demographic data | x | | | | | | | | | | | |
| General medical history and baseline conditions | x | | | | | | | | | | | |
| IPI (Phase II only) | x | | | | | | | | | | | |
| ECOG Performance Status | x | x | | | | x | | | | x | | x |
| B symptoms [f] | x | | | | | | | | | | | |
| Concomitant medications [g] | x | x | x | x | x | x | x | x | x | x | | x |
| Adverse events [h] | x | x | x | x | x | x | x | x | x | x | | x |
| Vital signs [i] | x | x | x | x | x | x | x | x | x | x | | x |
| Height, BSA, and weight [j] | x | x | | | | x | | | | x | | x |
| Complete physical [k] | x | | | | | | | | | | | |

## Appendix 1
## Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Complete neurologic examination [l] | x | | x | | | | x | | | x | | x |
| Peripheral neuropathy examination [m] | x | x | | x | x | x | | x | x | x | | x |
| Targeted physical examination [n] | | x | | x | x | x | | x | x | x | | x |
| Single 12-lead ECG [o] | x | | | | | | | | | | | |
| PET-CT [p] | x | | | | | | | | | | x | |
| EORTC QLQ-C30, FACT-Lym subscale, FACT/GOG-Ntx, and EQ-5D-5L (expansion cohorts only) [q] | | x | | | | x | | | | x [r] | | x [r] |
| ECHO or MUGA scan | x | | | | | | | | | | | |
| ***Local* Laboratory Samples** | | | | | | | | | | | | |
| HBV, HCV, and HIV screening [s] | x | | | | | | | | | | | |
| Peripheral blood for EBV and CMV titer by PCR [t] | x | | | | | x | | | | | | |

## Appendix 1
## Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| *Flow cytometry and/or peripheral blood smear* [u] | *x* | | | | | | | | | | | |
| Hematology [v] | x | x | | x | x | x | | x | x | x | | x |
| Chemistry (serum) [w] | x | x | | x | x | x | | x | x | x | | x |
| C-reactive protein and serum ferritin | x | x | | x | x | x | | x | x | x | | x |
| Coagulation (aPTT, PT, INR) [x] | x | x | | x | x | x | | x | x | | | |
| Polatuzumab vedotin specific laboratory tests [y] | x | x | | | | x | | | | x | | x |
| Pregnancy test [z] | x | | | | | x | | | | x | | x |
| Total IgA, IgG, IgM | x | | | | | | | | | | | |
| **Study Drug Administration** [aa] | | | | | | | | | | | | |
| *Phase Ib Group A* | | | | | | | | | | | | |
| Mosunetuzumab | | x [bb] | | x [bb] | x | x | | | | x | | x |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |

## Appendix 1
## Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Vincristine | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase Ib Group B* | | | | | | | | | | | | |
| Polatuzumab vedotin [ee] | | x | | | | x | | | | x | | x |
| Mosunetuzumab | | | x [bb] | x [bb] | x | | x | | | x [ff] | | x [ff] |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase II Group C* | | | | | | | | | | | | |
| Mosunetuzumab | | x [bb] | | x [bb] | x | x | | | | x | | x [ff] |
| Cyclophosphamide | | x | | | | x | | | | x | | x |

## Appendix 1
## Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Vincristine | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase II Arm 1* | | | | | | | | | | | | |
| Polatuzumab vedotin [ee] | | x | | | | x | | | | x | | x |
| Mosunetuzumab | | x [bb] | | x [bb] | x | x | | | | x [ff] | | x [ff] |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase II Arm 2* | | | | | | | | | | | | |
| Rituximab | | x | | | | x | | | | x | | x |

## Appendix 1
## Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Polatuzumab vedotin [ee] | | x | | | | x | | | | x | | x |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase II Arm 3* | | | | | | | | | | | | |
| Mosunetuzumab | | x [bb] | | x [bb] | x | x | | | | x | | x |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Vincristine | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |

## Appendix 1
## Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| *Central Laboratory* **Samples** | | | | | | | | | | | | |
| *Peripheral blood for viral infection test by quantitative PCR ss* | *x* | | | | | *x* | | | | | | |
| Serum samples for PK and ADA | | See Appendix 2. | | | | | | | | | | |
| Tumor tissue samples | | See Appendix 2. | | | | | | | | | | |
| Blood samples for biomarkers | | See Appendix 2. | | | | | | | | | | |

# Appendix 1
# Schedule of Activities (cont.)

## Cycles 7–17 and Beyond through Study Drug Completion/Early Discontinuation

| | | Cycle 7 [c, ii, jj] | | | | Cycle 8 [c, ii] | Cycles 9–17 [c, kk, ll] | SDC/ED [mm] | Follow-Up (Q3M) [nn] |
|---|---|---|---|---|---|---|---|---|---|
| | PRA [hh] | D1 | D2 | D8 | D15 | D1 | D1 | | |
| ECOG Performance Status | | x | | | | x | x | x | x |
| B symptoms [f] | | | | | | | | | |
| Concomitant medications [g] | x | x | x | x | x | x | x | x | x |
| Adverse events [h] | x | x | x | x | x | x | x | x | x |
| Vital signs [i] | x | x | x | x | x | x | x | x | x |
| Height (screening only), BSA, and weight [j] | x | x | | | | x | x | x | x |
| Targeted physical examination [n] | x | x | | x | x | x | x | x | x |
| Complete neurologic examination [l] | x | | | | | x | x | x | x |
| Peripheral neuropathy examination [m] | x | x | | x | x | x | x | x | x |
| Single 12-lead ECG [o] | | | | | | | | x | |
| PET-CT [p] | x | | | | | | | | |
| PET-CT or CT only [p] | | | | | | | x [p] | x | x [p] |
| EORTC QLQ-C30, FACT-Lym subscale, FACT/GOG-Ntx, and EQ-5D-5L (expansion cohorts only) [q] | | | | | | x | Every 3 months | x | x |
| ECHO or MUGA | | | | | | | | x | |

## Appendix 1
## Schedule of Activities (cont.)

| | | Cycle 7 [c, ii, jj] | | | | Cycle 8 [c, ii] | Cycles 9–17 [c, kk, ll] | SDC/ED [mm] | Follow-Up (Q3M) [nn] |
|---|---|---|---|---|---|---|---|---|---|
| | PRA [hh] | D1 | D2 | D8 | D15 | D1 | D1 | | |
| New anti-cancer therapy follow-up [oo] | | | | | | | | x | x |
| ***Local* Laboratory Samples** | | | | | | | | | |
| Hematology [v] | x | x | | x | x | x | x | x | x |
| Chemistry (serum) [w] | x | x | | x | x | x | x | x | x |
| C-reactive protein and serum ferritin | x | x | | x | x | x | x | x | x |
| Coagulation (aPTT, PT, INF) [x] | | x | | x | x | x | | | |
| Pregnancy test [z] | | x | | | | x | x | x | End of follow-up |
| Total IgA, IgG, IgM [pp] | | | | | | x | x [pp] | x | Every 6 months (collected at closest corresponding visit) [pp] |
| *Phase Ib Group A* | | | | | | | | | |
| Mosunetuzumab | | x [bb, kk] | | x [bb, kk] | x [bb, kk] | x [kk] | x [kk] | | |

## Appendix 1
## Schedule of Activities (cont.)

| | PRA [hh] | Cycle 7 [c, ii, jj] | | | | Cycle 8 [c, ii] | Cycles 9–17 [c, kk, ll] | SDC/ED [mm] | Follow-Up (Q3M) [nn] |
|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D1 | | |
| *Phase Ib Group B* | | | | | | | | | |
| *Mosunetuzumab* | | x [bb, kk] | | x [bb, kk] | x [bb, kk] | x [kk] | | | |
| *Phase II Group C* | | | | | | | | | |
| Mosunetuzumab | | x [bb, kk] | | x [bb, kk] | x [bb, kk] | x [kk] | | | |
| *Phase II Arm 1* | | | | | | | | | |
| Mosunetuzumab | | x [bb, kk] | | x [bb, kk] | x [bb, kk] | x [kk] | x [kk] | | |
| *Phase II Arm 3* | | | | | | | | | |
| Mosunetuzumab | | x [bb, kk] | | x [bb, kk] | x [bb, kk] | x [kk] | x [kk] | | |
| *Central Laboratory Samples* | | | | | | | | | |
| *Peripheral blood for viral infection test by quantitative PCR [ii, ss]* | | | | | | | | | |
| Serum samples for PK and ADA | See Appendix 2. | | | | | | | | |
| Tumor tissue samples for biomarkers | See Appendix 2. | | | | | | | | |
| Blood, plasma, and PBMC samples for biomarkers | See Appendix 2. | | | | | | | | |

# Appendix 1
# Schedule of Activities (cont.)

ADA=anti-drug antibody; BSA=body surface area; C=cycle; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP=cyclophosphamide, doxorubicin, and prednisone; CMV=cytomegalovirus; CRS=cytokine release syndrome; CT=computed tomography (scan); D=day; DLT=dose-limiting toxicity; EBV=Epstein-Barr virus; ECHO = echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire; EQ-5D-5L= EuroQol 5-Dimension, 5-Level (questionnaire); FACT/GOG-Ntx=Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity; FACT-Lym=Functional Assessment of Cancer Therapy–Lymphoma (subscale); GGT=gamma-glutamyl transferase; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HLH=hemophagocytic lymphohistiocytosis; IMC=Internal Monitoring Committee; IPI=International Prognostic Index; IRR=infusion-related reaction; LDH=lactate dehydrogenase; MAS=macrophage activation syndrome, MUGA = multiple-gated acquisition (scan); PCR = polymerase chain reaction; PET=positron emission tomography (scan); PK=pharmacokinetic; PO=orally; PRA=primary response assessment; PRO=patient-reported outcome; Q3M=every 3 months; RBR=Research Biosample Repository; SDC/ED=study drug completion/early discontinuation; TLS=tumor lysis syndrome.

Notes: Assessments are to be taken prior to study drug infusion, unless otherwise specified. Pre-infusion laboratory samples should be drawn 0–24 hours prior to study treatment infusion.

Mosunetuzumab will be administered for up to a total of 17 cycles if applicable; polatuzumab vedotin (if applicable) will be administered for up to 6 cycles; and rituximab will be administered for up to 6 cycles if applicable.

[a] Screening and pretreatment tests and evaluations will be performed within 14 days preceding the first dose of study treatment (except pretreatment biopsy and radiographic tumor assessment, which may be performed up to 28 days preceding the first dose of study drug, providing no anti-tumor therapy was administered in this period). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window specified above may be used; these tests do not need to be repeated for screening.

[b] Patients enrolled in Groups A, B, and C will be hospitalized for at least 24 hours after the completion of the first dose of mosunetuzumab *administration in Cycle 1*. Upon review of the data by the IMC, if mosunetuzumab is considered tolerable, the requirement for hospitalization may be reconsidered for Arms 1 and 3.

[c] For Cycle 2, study drug infusion should occur on Day 1 of the cycle but may be given ±1 day from the scheduled date (with a minimum of 6 days after the C1D15 dosing). In Cycle 3 and beyond, study drug infusions should occur on Day 1 of each 21-day cycle but may be given ±2 days from scheduled date (with a minimum of 19 days between doses) for logistic/scheduling reasons. Other study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted.

[d] The interim response assessment will occur between C4D15 and C4D21.

# Appendix 1
# Schedule of Activities (cont.)

[e] Informed consent must be documented before any study-specific screening procedure is performed. *Informed consent may be obtained 28 days preceding the first dose of study drug.*

[f] Unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[g] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the study completion/discontinuation visit.

[h] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study treatment or the initiation of another anti-cancer agent, whichever is earlier. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event (if believed to be related to prior study drug treatment) that occurs after the end of the adverse event reporting period (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[i] For all groups/arms: Includes systolic and diastolic blood pressure, respiratory rate, pulse oximetry, pulse rate, and body temperature while the patient is in a sitting or semi-supine position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
For hospitalized mosunetuzumab infusions: Vital signs with mosunetuzumab infusions: Check vital signs pre-infusion, every 30 (±10) minutes during the infusion, at the end of the infusion, and then every 60 (±10) minutes until 6 hours after the end of infusion. Thereafter, vital signs should be checked every 4 hours until hospital or clinic discharge.

All other Cycle 1 and Cycle 2 mosunetuzumab infusions: Check vital signs pre-infusion, every 30 (±10) minutes during the infusion, at the end of the infusion, and 2 hours after infusion. For patients who tolerated Cycles 1 and 2 mosunetuzumab infusions without the development of IRRs, in subsequent cycles, vital signs should be assessed pre-infusion, every 60 (±15) minutes during the infusion and for 2 hours after the end of infusion. For patients who experienced an IRR in Cycle 1, vital signs should be assessed pre-infusion, every 30 (±10) minutes during the infusion and for 2 hours after the end of infusion.

For polatuzumab vedotin infusions: Polatuzumab vedotin is to be administered after prednisone. During the administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes following completion of dosing at Cycle 1 and 30 (±10) minutes following completion of dosing in subsequent cycles (see Section 4.3.2.2).

For rituximab infusions: During the administration of rituximab or in Cycle 1, vital signs are to be obtained before infusion of rituximab, then after the start of the infusion, approximately every 15 (±5) minutes for 90 minutes, then every 30 (±10) minutes until 1 hour after the end of the infusion. During administration of rituximab in subsequent cycles, vital signs are to be recorded before infusion of rituximab, then after the start of infusion, and approximately every 30 (±10) minutes until 1 hour after the end of infusion (see Section 4.3.2.3).

[j] Height and BSA are required at screening only, unless there has been >10% change in body weight since the last BSA assessment, in which case BSA should be recalculated and documented in the eCRF. Weight will be recorded at every indicated visit.

[k] Complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] A complete neurologic examination, which includes an evaluation of mental status, cranial nerves, muscle strength, sensation, and coordination should be performed and documented in the patient chart. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[m] Peripheral neuropathy will be evaluated by history and physical examination at each scheduled visit and collected in a specific eCRF. This eCRF does not take the place of adverse event reporting for peripheral neuropathy.

[n] Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be associated with tumor assessment, or potential drug-related toxicity). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For pre-infusion timepoints, targeted physical examination may be performed within 96 hours preceding study treatment administration unless otherwise specified.

[o] See Section 4.5.7 for details. Single 12-lead ECG recordings will be obtained at screening and at end of treatment. ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. During infusion of doxorubicin, continuous ECG monitoring should be performed per local clinical practice.

[p] See Section 4.5.5 for details. Assess response using image-based evaluation using Lugano 2014 criteria (see Appendix 3). PET and diagnostic-quality CT scans are required at screening, at the interim response assessment, and at the primary response assessment visit. Perform CT scan with or without PET during follow-up every 6 months for 2 years after primary response assessment, or until disease progression or study discontinuation, whichever is earlier. CT scans with or without PET obtained during Cycles 9–17, if eligible for continued treatment may also serve as the scans required during the 2-year follow up after PRA. Additional scans are not required. A full tumor assessment including radiographic assessment must be performed any time disease progression or relapse is suspected. If disease progression or relapse is suspected before the primary response assessment, both PET and diagnostic-quality CT scans should be performed for tumor assessment. Scans should be performed according to the guidelines in the imaging manual provided to all sites.

[q] PROs will be evaluated in patients randomized in the Phase II (Arms 1, 2, and 3) portion of the study using the EORTC QLQ-C30, FACT-Lym subscale, FACT/GOG-Ntx, and EQ-5D-5L questionnaires. The questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments (except laboratory blood collections), and prior to the administration of study treatment, unless otherwise specified.

[r] C4D1 and C6D1 only.

[s] HBsAg, HBsAb, HBcAb, HCV antibody, and HIV antibody serology are required. 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. Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

## Appendix 1
## Schedule of Activities (cont.)

[t] Quantitative PCR for detection of active EBV and CMV should be performed at screening, C2D1, and when clinically indicated on a peripheral blood sample per local lab requirements. Paired samples should also be collected for central lab assessments at the same timepoints (see *footnote ss* for sample types required for central lab assessments). If local laboratory assessments are not available for quantitative PCR detection of active EBV and CMV, local laboratory collections may be waived only if sample is collected for central lab assessments of viral infections. If EBV or CMV levels are detected (positive), contact the Medical Monitor for additional recommendations, and repeat quantitative PCR monitoring weekly until DNA levels decrease, and then continue to monitor by quantitative PCR at every cycle until two consecutive negative (undetectable) results.

[u] *Flow cytometry (preferred) and/or a peripheral blood smear is required at screening (if not done as part of standard-of-care tests) to detect malignant and/or atypical cells. If malignant cells or atypical cells are detected, the results must be discussed with the Medical Monitor.*

[v] Hematology includes CBC (including hemoglobin, hematocrit, RBC, WBC), platelet count, ANC, absolute lymphocyte count, and other cells.

[w] Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate *or total carbon dioxide (if considered standard of care for the region),* glucose, BUN or urea, creatinine, calcium, magnesium, phosphorous, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, GGT, LDH, and uric acid.

[x] Fibrinogen will be collected when monitoring systemic immune activation events (e.g., MAS/HLH, severe CRS).

[y] In addition to the other listed laboratory tests, polatuzumab vedotin–specific laboratory tests include amylase, lipase, and hemoglobin A1c (see Section 4.5.6).

[z] All women of childbearing potential will have a serum pregnancy test at screening within 7 days before C1D1 of study treatment. Urine or serum pregnancy tests will be performed on Day 1 of each cycle of therapy for all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[aa] See Sections 4.3.3.2–4.3.3.4 for study treatment regimens and dosing. See Figure 3, Figure 4, and Figure 6 for order of administration of study treatments.

[bb] If the combination of the *step-up dosing of* mosunetuzumab plus other study treatments is not tolerated because of DLTs occurring prior to the administration of the C1D15 mosunetuzumab dose, then alternative regimens may be assessed (see Sections 3.1.1.1 and 3.1.1.2).

[cc] Prednisone 100 mg/day PO is given on Days 1–5 for each cycle when CHOP or CHP is administered. On days when mosunetuzumab IV corticosteroid premedication overlaps with the prednisone 100 mg dose, the IV corticosteroid premedication should be omitted.

# Appendix 1
# Schedule of Activities (cont.)

[dd] Days –7 to –1. Administration of an approximate 7 days of pre-phase treatment (consisting of prednisone/prednisolone 100 mg PO daily) between Days –7 to –1, may be given at the discretion of the treating study investigator in patients with previously untreated TLS or patients considered to be at high risk for TLS or acute toxicity with the first cycle of study treatment. This may be added for all patients based on review of safety data (see Section 4.3.3.1).

[ee] If CHP-pola is not tolerable, an alternative regimen of CHOP without polatuzumab vedotin will be substituted (see Sections 3.1.1.2 and 3.1.2.2).

[ff] If patients tolerate both the polatuzumab vedotin and mosunetuzumab infusions well in Cycles 1 and 2, they may be given on the same day for future subsequent cycles of treatment (see Section 3.3.2).

[ss] *For quantitative PCR detection of viral infection, which may include but is not limited to EBV and CMV. At screening; C2D1 pre-dose; at other timepoints when clinically indicated; paired peripheral blood samples should be sent for central laboratory assessments, in additional to local laboratory assessments (see footnote [t]).*

[hh] Primary response assessment will occur 6–8 weeks after C6D1 or last study treatment, whichever is earlier.

[ii] Patients who receive mosunetuzumab more than 6 weeks after their last dose of mosunetuzumab, will need to follow the *step-up dosing* schedule (i.e., mosunetuzumab 1 mg on C7D1, 2 mg C7D8, and test dose on C7D15, followed by the test dose on Day 1 of subsequent cycles given every 21 days) (see Appendix 2). Routine hospitalization with re-starting mosunetuzumab treatment after more than 6 weeks of treatment break is not required, but allowed if the investigator considers this to be clinically indicated.

[jj] Cycle 7 will occur approximately 6–8 weeks after Cycle 6 for eligible patients receiving mosunetuzumab (see Section 3.1.2.5).

[kk] Patients eligible for extended treatment with mosunetuzumab (see Sections 4.3.3.2 and 4.3.3.3) may receive up to a total of 17 cycles of mosunetuzumab.

[ll] Assessments are to be taken prior to each dose of study drug, unless otherwise specified. Pre-infusion laboratory samples should be drawn 0–24 hours prior to study treatment infusion.

[mm] Patients who complete the treatment period will return to the clinic for a study drug completion visit 4–8 weeks after the last dose of study drug. Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit (early discontinuation) within 4–8 weeks after the last dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[nn] The follow-up period of 2 years starts after primary response assessment, though patients may continue on single-agent treatment if applicable to their assigned group or arm. If a patient discontinues the study prior to the PRA, then the 2-year follow-up period will begin at the time of study drug discontinuation. Patients will return to the clinic every 3 months for the first 6 months, and then every 6 months for laboratory assessments.

## Appendix 1
## Schedule of Activities (cont.)

[oo] When completed/discontinued from treatment, patients should be followed for first new anti-cancer therapy via telephone calls and patient medical records every 3 months and/or clinic visits every 3 months for the first 6 months, then every 6 months thereafter, until approximately 2 years following the primary response assessment (unless death, loss to follow-up, the patient withdraws consent or the Sponsor terminates the study, whichever occurs first). The date of when the first subsequent anti-cancer therapy was initiated will be collected.

[pp] IgG, IgA, and IgM will be collected every 6 months from screening sample (e.g., at screening, approximately Cycle 8, Cycle 16, study drug completion/early discontinuation, and, if applicable, during follow-up).

# Appendix 2
# Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments

**Table 1: M-CHOP Treatment Groups (Phase Ib Group A, Phase II Group C, Phase II Arm 3)**

| Timepoint [a] | Scr. | Cycle 1 | | | | | | | | | | Cycles 2–6 | | | Cycles 7–17 [b] | | | | PRA/ ED [c] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D15 | | | D1 | | | D1 (also on C7D8 and C7D15, if *step -up* dosing regimen used) [d] | | | | | |
| | | Pre-Chemo [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | 24 hr [f] | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | Pre-Chemo [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | 24 hr [f] | | |
| Plasma for biomarkers [g] | | x | x | x | x | x | x | | x | x | | x [h] | | x [h] | x [i] | x [i] | x [i] | x [i] | | |
| Blood for TBNK | | x | | x | | | | | | | | x [j] | | x [j] | x [i] | | x [i] | | x [k] | |
| Blood for flow cytometry | | x | | x | | | | | | | | x [j] | | x [j] | x [i] | | x [i] | | | |
| PBMCs for biomarkers | | x | | | | | | | | | | x [j] | | | x [i] | | | | x | x [m] |
| Blood for molecular analysis *for MRD* [n] | | x | | | x | x | | | x | | | x [o] | | | x [p] | | | | x | x [q] |
| Blood for RBR (optional) [r] | | (x) | | | | | | | | | | | | | | | | | | |
| Fresh (or archival) tumor tissue sample [s] | x | (x) [s] | | | | | | | | | | | | | | | | | | |
| Serum for mosunetuzumab PK (dense) [t] | | x | x | x | x | x | x | x | x | x | x | x | x | x [j] | x [d, u] | x [d] | | | x | x [v] |
| Serum for mosunetuzumab PK (sparse) [t] | | x | x | | | x | x | | x | x | | x | x | | x [d, u] | x [d] | | | x | x [v] |
| Serum for mosunetuzumab ADAs [w] | | x | | | | | | | | | | x | | | x | | | | x | |
| Serum for obinutuzumab PK [x] | | x | | | | | | | | | | | | | | | | | | |
| Serum for rituximab PK [x] | | x | | | | | | | | | | | | | | | | | | |

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

ADA=anti-drug antibody; C=Cycle; chemo=chemotherapy; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP=cyclophosphamide, doxorubicin, and prednisone; CR=complete response; CT=computed tomography; D=Day; ED=early discontinuation; EOI=end of infusion; M-CHOP=mosunetuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; MOS=mosunetuzumab; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cells; PET=positron emission tomography; PK=pharmacokinetic; PR=partial response; PRA=primary response assessment; Pre=predose; PT=post-treatment; RBR=Research Biosample Repository; Scr.=screening; SD=stable disease; SDC=study drug completion; TBNK=T, B, and natural killer cells; WES=whole exome sequencing; WGS=whole genome sequencing; (x)=conditional/optional (refer to footnote).

[a] Timepoints listed are relative to the end of mosunetuzumab infusion for each cycle, unless otherwise noted.

[b] Samples to be collected only for SD/PR patients at end of Cycle 6 that opt to continue treatment with mosunetuzumab for 11 additional cycles.

[c] Perform within 6–8 weeks after the last infusion of mosunetuzumab, to coincide with PET-CT assessment. For patients who discontinue the study drug prematurely (early discontinuation), perform within 4–8 weeks after the last dose of study drug.

[d] In Cycle 7, if *step -up* dosing regimen is implemented, serum mosunetuzumab PK samples will be collected at predose (0–4 hours prior to the infusion of mosunetuzumab) on Days 1, 8 and 15 and within 30 minutes after completion of mosunetuzumab infusion on C7D1. Additional predose samples will be collected in Cycles 8 and 16 (see footnote [u]).

[e] Draw predose laboratory samples 0–4 hours prior to infusion of the first drug: chemotherapy on Day 1 of Cycles 1–6 and mosunetuzumab on Days 8 and 15 of Cycle 1 and Day 1 of Cycles 7–17.

[f] Perform EOI mosunetuzumab assessments within 30 minutes after completion of mosunetuzumab infusion. "2 hr post-MOS" corresponds to 2 hours (± 30 minutes) after completion of mosunetuzumab infusion; "24 hr" corresponds to 24 hours (± 4 hours) from beginning of mosunetuzumab infusion.

[g] For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration. Please refer to Appendix 14.

[h] Cycles 2, 3, and 5 only.

[i] Cycle 7, Day 1 only.

[j] Cycles 2 and 5 only.

[k] For CR patients at end of Cycle 6.

[l] Cycles 7 and 16, Day 1 only.

[m] Collect 6 months after SDC for patients that are CR after 6 cycles.

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[n] Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).

[o] Cycles 2, 4 and 6 only

[p] *Cycles 7, 11, and 16, Day 1 only.*

[q] Collect during follow-up visits as described in Appendix 1, footnote "*nn*": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.

[r] With consent to optional research, a blood sample will be requested at baseline for collection and storage at the RBR.

[s] Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. *Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion.* Tissue biopsy at the time of tumor progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis). Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.

[t] The dense PK sampling for mosunetuzumab applies to all patients in the dose-escalation cohorts in Group A and in the Group C safety cohort (if M-CHOP regimen is used). The sparse PK sampling for mosunetuzumab applies to all patients in the expansion cohorts in Group A and for patients in Arm 3 (M-CHOP regimen) of the Phase II dose-expansion cohorts.

[u] Cycles 7, 8, and 16 only.

[v] During the post-treatment follow-up at≥90 days after last mosunetuzumab administration.

[w] Predose serum ADA for mosunetuzumab will be collected in Cycles 1, 2, 6, 16, and ED or PRA.

[x] Predose serum rituximab or obinutuzumab PK is required for patients who have received prior treatment with rituximab or obinutuzumab only.

# Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 2: M-CHP-Pola Treatment Groups (Phase Ib Group B)**

| Timepoint [a] | Scr. | Cycle 1 | | | | | | | | | | | | Cycles 2–6 | | | | | Cycles 7–17 [b] | | | | PRA/ED [c] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | D2 | | | D3 | D8 | | | D15 | | | D1 | | D1/D2 [d] | | | D1 (also on C7D8 and C7D15, if *step-up* dosing regimen used) [e] | | | | | |
| | | Pre-Chemo [f] | EOI-Pola | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr (Post-MOS) [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Pola | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr (Post-MOS) [g] | | |
| Plasma for biomarkers [h] | | x | | x | x | x | x | x | x | | x | x | | x [i] | | x [i,j] | | x [i] | x [k] | x [k] | x [k] | x [k] | | |
| Blood for TBNK | | x | | x | | x | | | | | | | | x [l] | | x [j,l] | | x [l] | x [k] | | x [k] | | x [m] | |
| Blood for flow cytometry | | x | | x | | x | | | | | | | | x [l] | | x [l] | | x [l] | x [k] | | x [k] | | | |
| PBMCs for biomarkers | | x | | | | | | | | | | | | x [l] | | | | | x [n] | | | | x | x [o] |
| Blood for molecular analysis *for MRD* [p] | | x | | | | | x | x | | | x | | | x [q] | | | | | x [r] | | | | x | x [s] |
| Blood for RBR (optional) [t] | | (x) | | | | | | | | | | | | | | | | | | | | | | |
| Fresh (or archival) tumor tissue sample [u] | x | (x) [u] | | | | | | | | | | | | | | | | | | | | | | |
| Serum for mosunetuzumab PK (dense) [v] | | | | x | x | x | x | x | x | x | x | x | x | | | x | x | x [l] | x [e,w] | x [e] | | | x | x [x] |
| Serum for mosunetuzumab PK (sparse) [v] | | | | x | x | | | x | x | | x | x | | | | x | x | | x [e,w] | x [e] | | | x | x [x] |
| Serum for mosunetuzumab ADAs [y] | | | | x | | | | | | | | | | | | x | | | x | | | | x | |
| Serum for obinutuzumab PK [z] | | x | | | | | | | | | | | | | | | | | | | | | | |

# Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 2: M-CHP-Pola Treatment Groups (Phase Ib Group B)**

| Timepoint [a] | Scr. | Cycle 1 | | | | | | | | | | | | Cycles 2–6 | | | | | Cycles 7–17 [b] | | | | PRA/ED [c] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | D2 | | | D3 | D8 | | | D15 | | | D1 | | D1/D2 [d] | | | D1 (also on C7D8 and C7D15, if *step-up* dosing regimen used) [e] | | | | | |
| | | Pre-Chemo [f] | EOI-Pola | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr (Post-MOS) [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Pola | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr (Post-MOS) [g] | | |
| Serum for rituximab PK [z] | | x | | | | | | | | | | | | | | | | | | | | | | |
| Plasma polatuzumab vedotin PK for acMMAE and unconjugated MMAE (dense) [aa] | | x | x | x | | | x | x | | | x | | | x | x | | | | x [w] | | | | x | x |
| Plasma polatuzumab vedotin PK for acMMAE and unconjugated MMAE (sparse) [aa] | | x | x | x | | | | x | | | x | | | x | x | | | | x [w] | | | | x | x |
| Serum polatuzumab vedotin PK for total antibody [bb] | | x | | | | | | | | | | | | x | | | | | | | | | x | |
| Serum for polatuzumab vedotin ADAs [y] | | x | | | | | | | | | | | | x | | | | | | | | | x | |

acMMAE =antibody-conjugated monomethyl auristatin E; ADA =anti-drug antibody; C =Cycle; chemo =chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP =cyclophosphamide, doxorubicin, and prednisone; CR =complete response; CT =computed tomography; D =Day; ED =early discontinuation; EOI =end of infusion; IMC =Internal Monitoring Committee; MMAE =monomethyl auristatin E;

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

M-CHP-pola=mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; MOS=mosunetuzumab; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cells; PET=positron emission tomography; PK=pharmacokinetic; pola=polatuzumab vedotin; PR=partial response; PRA=primary response assessment; Pre=predose; PT=post-treatment; RBR=Research Biosample Repository; Scr.=screening; SD=stable disease; SDC=study drug completion; TBD=T-cell–dependent bispecific (antibody); TBNK=T, B, and natural killer cells; WES=whole exome sequencing; WGS=whole genome sequencing; (x)=conditional/optional (refer to footnote).

[a] Timepoints listed are relative to the end of polatuzumab or mosunetuzumab infusion for each cycle, unless otherwise noted.

[b] Samples to be collected only for SD/PR patients at end of Cycle 6 that opt to continue treatment with mosunetuzumab for 11 additional cycles.

[c] Perform within 6–8 weeks after the last infusion of mosunetuzumab to coincide with PET-CT assessment.

[d] In Cycle 2, mosunetuzumab will be administered on Day 2 when combined with CHP-Pola *in Phase I Group B*. In Cycles 3–6, mosunetuzumab will be administered on either Day 1 or Day 2, depending on each patient's ability to tolerate the mosunetuzumab plus polatuzumab vedotin combination during the first 2 cycles.

[e] In Cycle 7, if *step-up* dosing regimen is implemented, serum mosunetuzumab PK samples will be collected at predose (0–4 hours prior to the infusion of mosunetuzumab) on Days 1, 8 and 15 and within 30 minutes after completion of mosunetuzumab infusion on C7D1. Additional predose samples will be collected in Cycles 8 and 16 (see footnote [w]).

[f] Draw predose laboratory samples 0–4 hours prior to infusion of the first drug: chemotherapy on Day 1 of Cycles 1–6 and mosunetuzumab on Days 2, 8, and 15 of Cycle 1, Day 2 of Cycle 2, either Day 1 or 2 of Cycles 3–6, and Day 1 of Cycles 7–17.

[g] Perform EOI assessments within 30 minutes after completion of polatuzumab or mosunetuzumab infusion. "2 hr post-MOS" corresponds to 2 hours (±30 minutes) after completion of polatuzumab or mosunetuzumab infusion; "24 hr" corresponds to 24 hours (±4 hours) from beginning of mosunetuzumab infusion.

[h] For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration. Please refer to Appendix 14.

[i] Cycles 2, 3, and 5 only.

[j] For Cycles 3 and 5, collect only if mosunetuzumab is given on Day 2.

[k] *Cycle 7, Day 1* only.

[l] *Cycles 2 and 5 only.*

[m] For CR patients at end of Cycle 6.

[n] Cycles 7 and 16, Day 1 only.

[o] Collect 6 months after SDC for patients that have a CR after 6 cycles.

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[p] Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).

[q] *Cycles 2, 4 and 6 only*

[r] Cycles 7, 11, and 16, Day 1 only.

[s] Collect during follow-up visits as described in Appendix 1, footnote "*nn*": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.

[t] With consent to optional research, a blood sample will be requested at baseline for collection and storage at the RBR.

[u] Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. *Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion.* Tissue biopsy at the time of tumor progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis), *and between C1D15 and C2D8.* Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.

[v] The dense PK sampling for mosunetuzumab applies to all patients in the dose-escalation cohorts in Group B and in the Group C safety cohort (if M-CHP-pola is used). The sparse PK sampling for mosunetuzumab applies to all patients in the expansion cohorts in Group B.

[w] Cycles 7, 8, and 16 only for mosunetuzumab serum PK. Cycle 8 only for polatuzumab vedotin plasma PK.

[x] During the post-treatment follow-up at ≥90 days after last mosunetuzumab administration.

[y] Predose serum ADA for mosunetuzumab will be collected in Cycles 1, 2, 6, 16, and ED or PRA. Predose serum ADA for polatuzumab vedotin will be collected in Cycles 1, 2, 6, and ED or PRA.

[z] Predose serum rituximab or obinutuzumab PK is required for patients who have received prior treatment with rituximab or obinutuzumab only.

[aa] The plasma sample will be split into two samples for analyses of acMMAE and unconjugated MMAE concentrations. The dense plasma PK sampling scheme for polatuzumab vedotin applies to all patients in Group B (dose-escalation and expansion cohorts).

[bb] Serum polatuzumab vedotin PK for total antibody will be collected at predose (0–4 hours prior to the infusion of polatuzumab vedotin) in Cycles 1, 2, 6, and ED or PRA.

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*Table 3: M-CHP-Pola Treatment Group (Phase II Arm 1)*

| *Timepoint* [a] | *Scr.* | *Cycle 1* | | | | | | | | | | | | *Cycles 2–6* | | | | | *Cycles 7–17* [b] | | | | *PRA/ED* [c] | *PT Follow-Up* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *D1* | | | | | *D2* | *D8* | | | *D15* | | | *D1* | | | | | *D1 (also on C7D8 and C7D15, if step-up dosing regimen used)* [d] | | | | | |
| | | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | | |
| *Plasma for biomarkers* [g] | | x | | x | x | x | x | x | x | | x | x | | x [h] | | | | x [h] | x [i] | x [i] | x [i] | x [i] | | |
| *Blood for TBNK* | | x | | x | | x | | | | | | | | x [j] | | | | x [j] | x [i] | | x [i] | | x [k] | |
| *Blood for flow cytometry* | | x | | x | | x | | | | | | | | x [j] | | | | x [j] | x [i] | | x [i] | | | |
| *PBMCs for biomarkers* | | x | | | | | | | | | | | | x [j] | | | | | x [l] | | | | x | x [m] |
| *Blood for molecular analysis for MRD* [n] | | x | | | | | x | x | | | x | | | x [o] | | | | | x [p] | | | | x | x [q] |
| *Blood for RBR (optional)* [r] | | (x) | | | | | | | | | | | | | | | | | | | | | | |
| *Fresh (or archival) tumor tissue sample* [s] | x | (x) [s] | | | | | | | | | | | | | | | | | | | | | | |

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*Table 3: M-CHP-Pola Treatment Group (Phase II Arm 1)*

| *Timepoint* [a] | *Scr.* | *Cycle 1* | | | | | | | | | | | | *Cycles 2–6* | | | | | *Cycles 7–17* [b] | | | | *PRA/ED* [c] | *PT Follow-Up* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *D1* | | | | | *D2* | *D8* | | | *D15* | | | *D1* | | | | | *D1 (also on C7D8 and C7D15, if step-up dosing regimen used)* [d] | | | | | |
| | | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | | |
| *Serum for mosunetuzumab PK* | | | | x | x | | x | x | x | | x | x | | | | x | x | | x [d,t] | x [d] | | | x | x [u] |
| *Serum for mosunetuzumab ADAs* [v] | | | | x | | | | | | | | | | | | x | | | x | | | | x | |
| *Plasma polatuzumab vedotin PK for acMMAE and unconjugated MMAE* [w] | | x | x | x | | | x | x | | | x | | | x | x | | | | x [t] | | | | x | x [u] |
| *Serum polatuzumab vedotin PK for total antibody* [x] | | x | | | | | | | | | | | | x | | | | | | | | | x | |

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*Table 3: M-CHP-Pola Treatment Group (Phase II Arm 1)*

| Timepoint [a] | Scr. | Cycle 1 | | | | | | | | | | | Cycles 2–6 | | | | | Cycles 7–17 [b] | | | | PRA/ED [c] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | | | D2 | D8 | | | D15 | | | D1 | | | | | D1 (also on C7D8 and C7D15, if step-up dosing regimen used) [d] | | | | | |
| | | Pre-Chemo [e] | EOI-Pola | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | 24 hr (Post-MOS) [f] | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | Pre-Chemo [e] | EOI-Pola | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | Pre-MOS [e] | EOI-MOS [f] | 2 hr Post-MOS [f] | 24 hr (Post-MOS) [f] | | |
| *Serum for polatuzumab vedotin ADAs* [p] | | x | | | | | | | | | | | | x | | | | | | | | | | |

*acMMAE =antibody-conjugated monomethyl auristatin E; ADA =anti-drug antibody; C =Cycle; chemo =chemotherapy; CHOP =cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP =cyclophosphamide, doxorubicin, and prednisone; CR = complete response; CT =computed tomography; D =Day; ED =early discontinuation; EOI =end of infusion; IMC =Internal Monitoring Committee; MMAE =monomethyl auristatin E; M-CHP-pola =mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; MOS =mosunetuzumab; MRD =minimal residual disease; PBMC =peripheral blood mononuclear cells; PET = positron emission tomography; PK =pharmacokinetic; pola =polatuzumab vedotin; PR =partial response; PRA =primary response assessment; Pre =predose; PT =post-treatment; RBR =Research Biosample Repository; Scr. =screening; SD =stable disease; SDC =study drug completion;*
*TBD =T-cell–dependent bispecific (antibody); TBNK =T, B, and natural killer cells; WES =whole exome sequencing; WGS =whole genome sequencing; (x) =conditional/optional (refer to footnote).*

[a] *Timepoints listed are relative to the end of polatuzumab or mosunetuzumab infusion for each cycle, unless otherwise noted.*

[b] *Samples to be collected only for SD/PR patients at end of Cycle 6 that opt to continue treatment with mosunetuzumab for 11 additional cycles.*

[c] *Perform within 6–8 weeks after the last infusion of mosunetuzumab to coincide with PET-CT assessment.*

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[d] *In Cycle 7, if step-up dosing regimen is implemented, serum mosunetuzumab PK samples will be collected at predose (0–4 hours prior to the infusion of mosunetuzumab) on Days 1, 8 and 15 and within 30 minutes after completion of mosunetuzumab infusion on C7D1. Additional predose samples will be collected in Cycles 8 and 16 (see footnote w).*

[e] *Draw predose laboratory samples 0–4 hours prior to infusion of the first drug: chemotherapy on Day 1 of Cycles 1–6 and mosunetuzumab on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycles 2, –6, and Day 1 of Cycles 7–17.*

[f] *Perform EOI assessments within 30 minutes after completion of polatuzumab or mosunetuzumab infusion. "2 hr post-MOS" corresponds to 2 hours (± 30 minutes) after completion of polatuzumab or mosunetuzumab infusion; "24 hr" corresponds to 24 hours (± 4 hours) from beginning of mosunetuzumab infusion.*

[g] *For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration. Please refer to Appendix 14.*

[h] *Cycles 2, 3, and 5 only.*

[i] *Cycle 7, Day 1 only.*

[j] *Cycles 2 and 5 only.*

[k] *For CR patients at end of Cycle 6.*

[l] *Cycles 7 and 16, Day 1 only.*

[m] *Collect 6 months after SDC for patients that have a CR after 6 cycles.*

[n] *Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).*

[o] *Cycles 2, 4 and 6 only.*

[p] *Cycles 7, 11, and 16, Day 1 only.*

[q] *Collect during follow-up visits as described in Appendix 1, footnote "nn": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.*

[r] *With consent to optional research, a blood sample will be requested at baseline for collection and storage at the RBR.*

[s] *Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion. Tissue biopsy at the time of tumor*

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis), and between C1D15 and C2D8. Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.*

[t] *Cycles 7, 8, and 16 only for mosunetuzumab serum PK. Cycle 8 only for polatuzumab vedotin plasma PK.*

[u] *During the post-treatment follow-up at ≥ 90 days after last mosunetuzumab administration.*

[v] *Predose serum ADA for mosunetuzumab will be collected in Cycles 1, 2, 6, 16, and ED or PRA. Predose serum ADA for polatuzumab vedotin will be collected in Cycles 1, 2, 6, and ED or PRA.*

[w] *The plasma sample will be split into two samples for analyses of acMMAE and unconjugated MMAE concentrations.*

[x] *Serum polatuzumab vedotin PK for total antibody will be collected at predose (0–4 hours prior to the infusion of polatuzumab vedotin) in Cycles 1, 2, 6, and ED or PRA.*

# Appendix 2
# Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*Table 4*: **Control Treatment Group (R-CHP–Pola, Phase II Arm 2)**

| Timepoint [a] | Scr. | Cycle 1 | | | | | | | | | | Cycles 2–6 | | | PRA/ED [b] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D15 | | | D1 | | | | |
| | | Pre-Chemo [c] | EOI [d] | 2 hr Post-EOI [d] | 24 hr [d] | Pre [c] | EOI [d] | 2 hr Post-EOI [d] | Pre [c] | EOI [d] | 2 hr Post-EOI [d] | Pre-Chemo [c] | EOI [d] | 2 hr Post-EOI [d] | | |
| Plasma for biomarkers [e] | | x | x | x | x | x | | | x | | | x [f] | | x [f] | | |
| Blood for TBNK | | x | | x | | | | | | | | x [g] | | x [g] | x | |
| Blood for flow cytometry | | x | | x | | | | | | | | x [g] | | x [g] | | |
| PBMCs for biomarkers | | x | | | | | | | | | | x [g] | | | x | x [h] |
| Blood for molecular analysis *for MRD* [i] | | x | | | x | x | | | x | | | x [j] | | | x | x [k] |
| Blood for RBR (optional) [l] | | (x) | | | | | | | | | | | | | | |
| Fresh (or archival) tumor tissue sample [m] | x | (x) [m] | | | | | | | | | | | | | | |
| Serum for rituximab PK [n] | | x | x | | | | | | | | | x | x | | x | x |
| Plasma polatuzumab vedotin PK for MMAE [n, o] | | x | x | | | | | | | | | x | x | | x | x |
| Serum polatuzumab PK for total antibody [p] | | x | | | | | | | | | | x | | | x | |
| Serum for polatuzumab vedotin ADAs [p] | | x | | | | | | | | | | x | | | x | |

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

acMMAE = antibody-conjugated monomethyl auristatin E; ADA = anti-drug antibody; C = Cycle; chemo = chemotherapy; CT = computed tomography; D = Day; ED = early discontinuation; EOI = end of infusion; MMAE = monomethyl auristatin E; MRD = minimal residual disease; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; PRA = primary response assessment; Pre = predose; PT = post-treatment; RBR = Research Biosample Repository; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin, and prednisone; Scr. = screening; SDC = study drug completion; TBNK = T, B, and natural killer cells; WES = whole exome sequencing; WGS = whole genome sequencing; (x) = conditional/optional (refer to footnote).

[a] Timepoints listed are relative to the end of chemotherapy infusion for each cycle, unless otherwise noted.

[b] Perform within 6–8 weeks after the last infusion of mosunetuzumab to coincide with PET-CT assessment.

[c] Draw predose laboratory samples 0–4 hours prior to infusion of the first drug (chemotherapy) on Day 1.

[d] Perform EOI assessments within 30 minutes after completion of chemotherapy (for R-CHOP) or polatuzumab vedotin (for R-CHP-pola) infusion. "2 hr Post-EOI" corresponds to 2 hours (±30 minutes) post-EOI; "24 hr" corresponds to 24 hours (±4 hours) from beginning of chemotherapy infusion.

[e] For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration.

[f] Cycles 2, 3, and 5 only.

[g] Cycles 2 and 5 only.

[h] Collect 6 months after SDC.

[i] Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).

[j] *Cycles 2, 4 and 6 only*

[k] Collect during follow-up visits as described in Appendix 1, footnote "*nn*": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.

[l] With consent to optional research, a blood sample will be requested at screening for collection and storage at the RBR.

[m] Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. *Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion.* Tissue biopsy at the time of tumor progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression

## Appendix 2
## Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

or to confirm an alternate histologic diagnosis*) and between Cycle 1 Day 15 and Cycle 2 Day 8*. Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.

n Plasma polatuzumab PK and rituximab PK samples will be collected at the specified timepoints in Cycles 1, 2, 4, 6, ED or PRA, and >90 days after the last dose of the respective agent.

o The plasma sample will be split into two samples for analyses of acMMAE and unconjugated MMAE concentrations.

p Serum total polatuzumab vedotin PK and ADA samples will be collected at predose in Cycles 1, 2, 6 and ED or PRA.

# Appendix 3
# Lugano Response Criteria for Malignant Lymphoma
# (Cheson et al. 2014)

## Target and Non-Target Lesions

Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be greater than 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the six representative, measured lesions. At baseline, measurable extranodal lesions should be greater than 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease as non-target lesions (e.g. cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

## Split Lesions and Confluent Lesions

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and smallest diameter (SDi) are no longer needed to determine progression.

# Appendix 3
# Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| Complete | Complete metabolic response | Complete radiologic response (all of the following) |
| Lymph nodes and extralymphatic sites | Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b]<br>It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake. | Target nodes/nodal masses must regress to ≤1.5 cm in LDi<br>No extralymphatic sites of disease |
| Non-measured lesion | Not applicable | Absent |
| Organ enlargement | Not applicable | Regress to normal |
| New lesions | None | None |
| Bone marrow | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminate, IHC negative |

# Appendix 3
# Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| Partial | Partial metabolic response | Partial remission (all of the following) |
| Lymph nodes and extralymphatic sites | Score 4 or 5 [b] 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<br>For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation |
| Non-measured lesion | 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 |

# Appendix 3
# Lugano Response Criteria for Malignant Lymphoma
# (Cheson et al. 2014) (cont.)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| No response or stable disease | No metabolic response | Stable disease |
| Target nodes/nodal masses, extranodal lesions | Score 4 or 5 [b] 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 |
| Non-measured lesion | 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 |

# Appendix 3
# Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| 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 [b] 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:<br>LDi > 1.5 cm and<br>Increase by ≥ 50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≤2 cm<br>1.0 cm for lesions >2 cm<br>In the setting of splenomegaly (> 13 cm), the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline.<br>New or recurrent splenomegaly<br>New or clear progression of preexisting non-measured lesions |
| New lesions | New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered | Regrowth of previously resolved lesions<br>A new node > 1.5 cm in any axis<br>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<br>Assessable disease of any size unequivocally attributable to lymphoma |
| Bone marrow | New or recurrent FDG-avid foci | New or recurrent involvement |

# Appendix 3
# Lugano Response Criteria for Malignant Lymphoma
# (Cheson et al. 2014) (cont.)

5PS = 5-point scale; CCT = 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] 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 under treatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured 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 (e.g., 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 (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] 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.

# Appendix 4
# International Prognostic Index

| International Prognostic Index (IPI) | |
|---|---|
| **Risk Factors** | |
| Ann-Arbor Stage III or IV | |
| Age > 60 years | |
| Serum LDH > 1 × ULN | |
| ECOG Performance Status ≥ 2 | |
| Extranodal involvement ≥ 2 | |
| **IPI Risk Group** | **Number of IPI Risk Factors** |
| Low | 0 or 1 |
| Low-intermediate | 2 |
| High-intermediate | 3 |
| High | 4 or 5 |

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; ULN = upper limit of normal.

The results of FDG-PET should not be taken into account for calculation of IPI as this prognostic score was established without FDG-PET.

Adapted from: Shipp et al. 1993.

## REFERENCES

Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive Non-Hodgkin's Lymphoma. N Engl J Med 1993;329:987–94.

# Appendix 5
# Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

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

AUC = area under the concentration–time curve; CYP = cytochrome P450 enzymes.

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

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

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

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

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

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

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

# Appendix 6
# Sample List of Cautionary Medications

(A) 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, tacrolimus, ticagrelor |

* These are the anticancer agents; contact medical monitor before use.

(B) Inducers

| | Strong Inducers | Moderate Inducers | Weak Inducers |
|---|---|---|---|
| **CYP3A** | avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort | bosentan, efavirenz, etravirine, modafinil, nafcillin | armodafinil, rufinamide |

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

# Appendix 7
# ASTCT Cytokine Release Syndrome Consensus Grading

| CRS Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 | *Grade 5* |
|---|---|---|---|---|---|
| Fever [a] | Temperature ≥38ºC | Temperature ≥38ºC | Temperature ≥38ºC | Temperature ≥38ºC | |
| | | with | | | |
| Hypotension | None | Not requiring vasopressors | Requiring a vasopressor with or without vasopressin | Requiring multiple vasopressors (excluding vasopressin) | |
| | | and/or [b] | | | |
| Hypoxia | None | Requiring low-flow nasal cannula [c] or blow-by | Requiring high-flow nasal cannula, facemask, nonrebreather mask or Venturi mask | Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) | |
| | | | | | *Death* [d] |

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events.

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

[a] Fever is defined as a temperature ≥38ºC not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is determined by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event, hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5 ºC, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

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

[d] *Grade 5 CRS is defined as death due to CRS.*

# Appendix 8
# Recommended Anaphylaxis Management

**The following equipment is needed in the event of a suspected anaphylactic reaction during study drug administration:**

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry)
- Oxygen and masks for oxygen delivery
- Airway management devices per SOC
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H1 and H2 blockers)
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

**The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug administration:**

- Stop the study drug administration.
- Call for additional assistance.
- Maintain an adequate airway.
- Provide oxygen.
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

# Appendix 9
# ECOG Performance Status Scale

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

# Appendix 10
# European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

# Appendix 10
# European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 11
# Functional Assessment of Cancer Therapy-Lymphoma Lymphoma (FACT-Lym) Subscale

**FACT-Lym (Version 4)**

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| P2 | I have certain parts of my body where I experience pain | 0 | 1 | 2 | 3 | 4 |
| LEU1 | I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin) | 0 | 1 | 2 | 3 | 4 |
| BRM3 | I am bothered by fevers (episodes of high body temperature) | 0 | 1 | 2 | 3 | 4 |
| E13 | I have night sweats | 0 | 1 | 2 | 3 | 4 |
| LYM1 | I am bothered by itching | 0 | 1 | 2 | 3 | 4 |
| LYM2 | I have trouble sleeping at night | 0 | 1 | 2 | 3 | 4 |
| [illegible] | I get tired easily | 0 | 1 | 2 | 3 | 4 |
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| [illegible] | I have a loss of appetite | 0 | 1 | 2 | 3 | 4 |
| [illegible] | I have trouble concentrating | 0 | 1 | 2 | 3 | 4 |
| [illegible] | I worry about getting infections | 0 | 1 | 2 | 3 | 4 |
| LEU6 | I worry that I might get new symptoms of my illness | 0 | 1 | 2 | 3 | 4 |
| LEU7 | I feel isolated from others because of my illness or treatment | 0 | 1 | 2 | 3 | 4 |
| BRM9 | I have emotional ups and downs | 0 | 1 | 2 | 3 | 4 |
| LEU4 | Because of my illness, I have difficulty planning for the future | 0 | 1 | 2 | 3 | 4 |

# Appendix 12
# Functional Assessment of Cancer Treatment/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-Ntx)

**FACT/GOG-NTX (Version 4)**

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| NTX 1 | I have numbness or tingling in my hands | 0 | 1 | 2 | 3 | 4 |
| NTX 2 | I have numbness or tingling in my feet | 0 | 1 | 2 | 3 | 4 |
| NTX 3 | I feel discomfort in my hands | 0 | 1 | 2 | 3 | 4 |
| NTX 4 | I feel discomfort in my feet | 0 | 1 | 2 | 3 | 4 |
| NTX 5 | I have joint pain or muscle cramps | 0 | 1 | 2 | 3 | 4 |
| NTX 11 | I feel weak all over | 0 | 1 | 2 | 3 | 4 |
| NTX 6 | I have trouble hearing | 0 | 1 | 2 | 3 | 4 |
| NTX 7 | I get a ringing or buzzing in my ears | 0 | 1 | 2 | 3 | 4 |
| NTX 8 | I have trouble buttoning buttons | 0 | 1 | 2 | 3 | 4 |
| NTX 9 | I have trouble feeling the shape of small objects when they are in my hand | 0 | 1 | 2 | 3 | 4 |
| Ax6 | I have trouble walking | 0 | 1 | 2 | 3 | 4 |

# Appendix 13
# EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire


**Health Questionnaire**

**English version for the UK**

# Appendix 13
# EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire (cont.)

Under each heading, please tick the ONE box that best describes your health TODAY.

**MOBILITY**

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

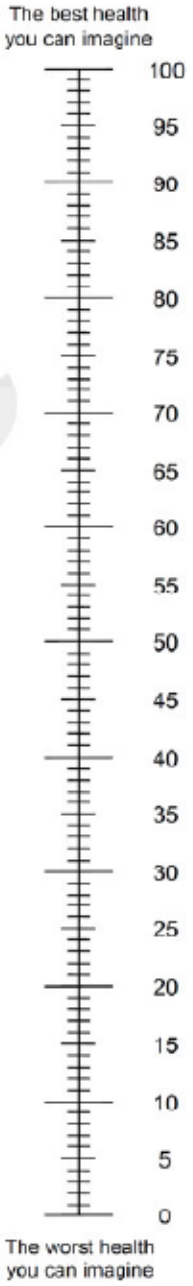
**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

# Appendix 13
# EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



## Appendix 14
## Schedule for Tocilizumab Treatment of Severe or Life-Threatening Cytokine Release Syndrome

| Assessment/Procedure [a] | Pre-TCZ Tx (within 24 hours) | TCZ Admin. | Post-TCZ Treatment [b, c] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 6 hours | 1 day | 2 days | 3 days | 8 days | *8 weeks* |
| TCZ administration (8 mg/kg for patients ≥30 kg; 12 mg/kg for patients <30 kg; doses exceeding 800 mg per infusion are not recommended) | | x | | | | | | |
| Vital signs [d] | x [e] | | Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization [e] | | | | | |
| Pressor documentation [f] | x [e] | | Record at least every 6 hours until pressors are discontinued [e] | | | | | |
| $FiO_2$ | x [e] | | Record at least every 6 hours until patient on room air [e] | | | | | |
| Pulse oximetry, resting | x [e] | | Measure at least every 6 hours until resolution to baseline, and then every 12 hours until end of hospitalization [e] | | | | | |
| **Local Laboratory Assessments** | | | | | | | | |
| Hematology | x | | x | x | x | x | x | |
| Liver function tests (AST, ALT, total bilirubin) | x | | x | x | x | x | x | |
| Serum chemistry and creatinine [g] | x | | x | x | x | x | x | |
| CRP, LDH, and serum ferritin | x | | x | x | x | x | x | |
| Coagulation (aPTT, PT/INR, fibrinogen) | x | | x | x | x | x | x | |
| Infection workup [h] | x | | | | | | | |
| **Central Laboratory Assessments** | | | | | | | | |
| *Serum* cytokines | x | *x* | x | x | x | x | x | |

## Appendix 14
## Schedule for Tocilizumab Treatment of Severe or Life-Threatening Cytokine Release Syndrome (cont.)

| Assessment/Procedure [a] | Pre-TCZ Tx (within 24 hours) | TCZ Admin. | Post-TCZ Treatment [b, c] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 6 hours | 1 day | 2 days | 3 days | 8 days | *8 weeks* |
| *Serum* IL-6 PD markers [i] | x | x [j] | x | x | x | x | x | |
| Serum TCZ pharmacokinetics | x | x [j, k] | x | x | x | x | x | |
| Serum TCZ ADA | x | | | | | | | x |

ADA = anti-drug antibodies; Admin. = administration; CRP = C-reactive protein; EBV = Epstein-Barr virus; eCRF = electronic Case Report Form; IL-6 = interleukin 6; LDH = lactate dehydrogenase; PD = pharmacodynamic; TCZ = tocilizumab; Tx = treatment.

Note: Record abnormalities or worsened clinically significant abnormalities on the Adverse Event eCRF.

a An assessment/procedure may be waived by the Medical Monitor if a patient is hospitalized at a facility that does not have the capacity to perform study the assessment. Hospitalization should not be prolonged to perform study assessments in this schedule of assessments.

b If TCZ dose is repeated, follow schedule following the second TCZ dose.

c For post-TCZ treatment timepoints: 6 hours (±30 minutes), 1 day (24 ±4 hours), 2 days (48 ±4 hours), 3 days (72 ±4 hours), 8 days (192 ±4 hours), *and 8 weeks (56 days ±48* hours) after completion of TCZ infusion.

d Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated or supine position, and temperature.

e The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

f Document vasopressor type and dose in the concomitant medication eCRF.

g Includes sodium, potassium, chloride, bicarbonate *or total carbon dioxide (if considered standard of care for the region),* glucose, and BUN.

h Includes assessment for bacterial, fungal, and viral infections: cultures, serologies and molecular diagnostic tests. Assessment of pretreatment and on-treatment EBV status should be conducted, including enumeration of EBV viral load in PBMC and plasma, and evaluation of EBV encoded ribonucleotides (EBER) or EBV nuclear antigen (EBNA) with T/B/NK cell markers.

i Includes IL-6, soluble IL-6R, sgp130.

## Appendix 14
## Schedule for Tocilizumab Treatment of Severe or Life-Threatening Cytokine Release Syndrome (cont.)

j Blood draws for serum TCZ PK and *serum* IL-6 PD markers will be performed within 15 minutes post-end of TCZ infusion and will be drawn from the arm that was not used to administer TCZ.

k For patients experiencing anaphylaxis or hypersensitivity to TCZ leading to TCZ infusion interruption/termination, obtain sample at time of event and at least 8 weeks thereafter (to allow for washout of TCZ).

# Appendix 15
# Alternate Schedule of Activities

The tables below are applicable to all patients in the Phase Ib (dose finding) and Phase II (expansion) portions of the study. For all pharmacokinetic, immunogenicity, and biomarker samples, see Appendix 16. For assessments related to treatment with tocilizumab (if applicable), see Appendix 14.

## Screening, Cycles 1–4, Interim Response, and Cycles 5–6

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Informed consent [e] | x | | | | | | | | | | | |
| Demographic data | x | | | | | | | | | | | |
| General medical history and baseline conditions | x | | | | | | | | | | | |
| IPI (Phase II only) | x | | | | | | | | | | | |
| ECOG Performance Status | x | x | | | | x | | | | x | | x |
| B symptoms [f] | x | | | | | | | | | | | |
| Concomitant medications [g] | x | x | x | x | x | x | x | x | x | x | | x |
| Adverse events [h] | x | x | x | x | x | x | x | x | x | x | | x |
| Vital signs [i] | x | x | x | x | x | x | x | x | x | x | | x |
| Height, BSA, and weight [j] | x | x | | | | x | | | | x | | x |
| Complete physical [k] | x | | | | | | | | | | | |
| Complete neurologic examination [l] | x | | x | | | | x | | | x | | x |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | Screening [a] (−14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Peripheral neuropathy examination [m] | x | x | | x | x | x | | x | x | x | | x |
| Targeted physical examination [n] | | x | | x | x | x | | x | x | x | | x |
| Single 12-lead ECG [o] | x | | | | | | | | | | | |
| PET-CT [p] | x | | | | | | | | | | x | |
| EORTC QLQ-C30, FACT-Lym subscale, FACT/GOG-Ntx, and EQ-5D-5L (expansion cohorts only) [q] | | x | | | | x | | | | x [r] | | x [r] |
| ECHO or MUGA | x | | | | | | | | | | | |
| ***Local* Laboratory Samples** | | | | | | | | | | | | |
| HBV, HCV, and HIV screening [s] | x | | | | | | | | | | | |
| Peripheral blood for EBV and CMV titer by PCR [t] | x | | | | | x | | | | | | |
| *Flow cytometry and/or peripheral blood smear* [u] | x | | | | | x | | | | | | |
| Hematology [v] | x | x | | x | x | x | | x | x | x | | x |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | Screening [a] | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (–14 days) | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Chemistry (serum) [w] | x | x | | x | x | x | | x | x | x | | x |
| C-reactive protein and serum ferritin | x | x | | x | x | x | | x | x | x | | x |
| Coagulation (aPTT, PT, INR) [x] | x | x | | x | x | x | | x | x | | | |
| Polatuzumab vedotin specific laboratory tests [y] | x | x | | | | x | | | | x | | x |
| Pregnancy test [z] | x | | | | | x | | | | x | | x |
| Total IgA, IgG, IgM | x | | | | | | | | | | | |
| **Study Drug Administration [aa]** | | | | | | | | | | | | |
| *Phase Ib Group A* | | | | | | | | | | | | |
| Mosunetuzumab | | | | x [bb] | x [bb] | x [bb] | | | | x | | x |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Vincristine | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | Screening [a] | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (–14 days) | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| *Phase Ib Group B* | | | | | | | | | | | | |
| Polatuzumab vedotin [ee] | | x | | | | x | | | | x | | x |
| Mosunetuzumab | | | | x [bb] | x [bb] | | x [bb] | | | x [ff] | | x [ff] |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase II Group C* | | | | | | | | | | | | |
| Mosunetuzumab | | | | x [bb] | x [bb] | x [bb] | | | | x [ff] | | x [ff] |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Vincristine | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase II Arm 1* | | | | | | | | | | | | |
| Polatuzumab vedotin [ee] | | x | | | | x | | | | x | | x |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Mosunetuzumab | | | | x [bb] | x [bb] | | x [bb] | | | x [ff] | | x [ff] |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| *Phase II Arm 2* | | | | | | | | | | | | |
| Rituximab | | x | | | | x | | | | x | | x |
| Polatuzumab vedotin [ee] | | x | | | | x | | | | x | | x |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| Phase II Arm 3 | | | | | | | | | | | | |
| Mosunetuzumab | | | | x [bb] | x [bb] | x [bb] | | | | x [ff] | | x [ff] |
| Cyclophosphamide | | x | | | | x | | | | x | | x |
| Doxorubicin | | x | | | | x | | | | x | | x |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | Screening [a] (–14 days) | Cycle 1 [b] | | | | Cycle 2 [b, c] | | | | Cycles 3–4 [c] | Interim Response [d] | Cycles 5–6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D2 | D8 | D15 | D1 | | D1 |
| Vincristine | | x | | | | x | | | | x | | x |
| Prednisone (Days 1–5) [cc] | | x | x | | | x | x | | | x | | x |
| Pre-phase corticosteroid treatment [dd] | Days –7 to –1 | | | | | | | | | | | |
| ***Central Laboratory* Samples** | | | | | | | | | | | | |
| *Peripheral blood for viral infection test by quantitative PCR* [ee] | *x* | | | | | *x* | | | | | | |
| Serum samples for PK and ADA | | See Appendix 16. | | | | | | | | | | |
| Tumor tissue samples for biomarkers | | See Appendix 16. | | | | | | | | | | |
| Blood, plasma, and PBMC samples for biomarkers | | See Appendix 16. | | | | | | | | | | |

# Appendix 15
# Alternate Schedule of Activities (cont.)

## Cycles 7–17 and Beyond through Study Drug Completion/Early Discontinuation

| | PRA [hh] | Cycle 7 [c, ii, jj] | | | | Cycle 8 [c, ii] | Cycles 9–17 [c, kk, ll] | SDC/ED [mm] | Follow-Up (Q3M) [nn] |
|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D1 | | |
| ECOG Performance Status | | x | | | | x | x | x | x |
| B symptoms | | | | | | | | | |
| Concomitant medications [g] | x | x | | | | x | x | x | x |
| Adverse events [h] | x | x | | | | x | x | x | x |
| Vital signs [i] | x | x | | | | x | x | x | x |
| Height (screening only), BSA, and weight [j] | x | x | | | | x | x | x | x |
| Targeted physical examination [n] | x | x | | | | x | x | x | x |
| Complete neurologic examination [l] | x | x | | | | x | x | x | x |
| Peripheral neuropathy examination [m] | x | x | | | | x | x | x | x |
| Single 12-lead ECG [o] | | | | | | | | x | |
| PET-CT [p] | x | | | | | | | | |
| PET-CT or CT only [p] | | | | | | | x [p] | x | x [p] |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | PRA [hh] | Cycle 7 [c, ii, jj] | | | | Cycle 8 [c, ii] | Cycles 9–17 [c, kk, ll] | SDC/ED [mm] | Follow-Up (Q3M) [nn] |
|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D1 | | |
| EORTC QLQ-C30, FACT-Lym subscale, FACT/GOG-Ntx, and EQ-5D-5L (expansion cohorts only) [q] | | | | | | x | Every 3 months | x | x |
| ECHO or MUGA | | | | | | | | x | |
| New anti-cancer therapy follow-up [oo] | | | | | | | | x | x |
| ***Local* Laboratory Samples** | | | | | | | | | |
| Hematology [v] | x | x | | x | x | x | x | x | x |
| Chemistry (serum) [w] | x | x | | x | x | x | x | x | x |
| C-reactive protein and serum ferritin | x | x | | x | x | x | x | x | x |
| | | | | | | | | | |
| Pregnancy test [z] | | x | | | | x | x | x | End of follow-up |
| Total IgA, IgG, IgM [pp] | | | | | | x | x [pp] | x | Every 6 months (collected at closest corresponding visit) [pp] |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | PRA [hh] | Cycle 7 [c, ii, jj] | | | | Cycle 8 [c, ii] | Cycles 9–17 [c, kk, ll] | SDC/ED [mm] | Follow-Up (Q3M) [nn] |
|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D1 | | |
| **Study Drug Administration** | | | | | | | | | |
| *Phase Ib Group A* | | | | | | | | | |
| Mosunetuzumab | | x [kk] | | x [kk] | x [kk] | x [kk] | x [kk] | | |
| *Phase Ib Group B* | | | | | | | | | |
| Mosunetuzumab | | x [kk] | | x [kk] | x [kk] | x [kk] | x [kk] | | |
| *Phase II Group C* | | | | | | | | | |
| Mosunetuzumab | | x [kk] | | x [kk] | x [kk] | x [kk] | x [kk] | | |
| *Phase II Arm 1* | | | | | | | | | |
| Mosunetuzumab | | x [kk] | | x [kk] | x [kk] | x [kk] | x [kk] | | |
| *Phase II Arm 3* | | | | | | | | | |
| Mosunetuzumab | | x [kk] | | x [kk] | x [kk] | x [kk] | x [kk] | | |
| *Central Laboratory* **Samples** | | | | | | | | | |
| *Peripheral blood for viral infection test by quantitative PCR [t, ss]* | | | | | | | | | |

## Appendix 15
## Alternate Schedule of Activities (cont.)

| | PRA [hh] | Cycle 7 [c, ii, jj] | | | | Cycle 8 [c, ii] | Cycles 9–17 [c, kk, ll] | SDC/ED [mm] | Follow-Up (Q3M) [nn] |
|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D8 | D15 | D1 | D1 | | |
| Serum samples for PK and ADA | See Appendix 16. | | | | | | | | |
| Tumor tissue samples for biomarkers | See Appendix 16. | | | | | | | | |
| Blood, plasma, and PBMC samples for biomarkers | See Appendix 16. | | | | | | | | |

ADA =anti-drug antibody; BSA =body surface area; C =cycle; CHOP =cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP =cyclophosphamide, doxorubicin, and prednisone; CMV =cytomegalovirus; CRS =cytokine release syndrome; CT =computed tomography (scan); D =day; DLT =dose-limiting toxicity; EBV =Epstein-Barr virus; ECHO = echocardiogram; ECOG =Eastern Cooperative Oncology Group; eCRF =electronic Case Report Form; ED =early discontinuation; EORTC QLQ-C30 =European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire; EQ-5D-5L =EuroQol 5-Dimension, 5-Level (questionnaire); FACT/GOG-Ntx =Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity; FACT-Lym =Functional Assessment of Cancer Therapy–Lymphoma (subscale); GGT =gamma-glutamyl transferase; HBcAb =hepatitis B core antibody; HBsAb =hepatitis B surface antibody; HBsAg =hepatitis B surface antigen; HBV =hepatitis B virus; HCV =hepatitis C virus; HLH =hemophagocytic lymphohistiocytosis; IMC =Internal Monitoring Committee; IPI =International Prognostic Index; IRR =infusion-related reaction; LDH =lactate dehydrogenase; MAS =macrophage activation syndrome, MRI =magnetic resonance imaging; MUGA = multiple-gated acquisition (scan); PCR =polymerase chain reaction; PET =positron emission tomography (scan); PK =pharmacokinetic; PO =orally; PRA =primary response assessment; PRO =patient-reported outcome; Q3M =every 3 months; RBR =Research Biosample Repository; SDC =study drug completion.

Notes: Assessments are to be taken prior to study drug infusion, unless otherwise specified. Pre-infusion laboratory samples should be drawn 0–24 hours prior to study treatment infusion.

Mosunetuzumab will be administered for up to a total of 17 cycles if applicable; polatuzumab vedotin (if applicable) will be administered for up to 6 cycles; and rituximab will be administered for up to 6 cycles, if applicable.

[a] Screening and pretreatment tests and evaluations will be performed within 14 days preceding the first dose of study treatment (except pretreatment biopsy and radiographic tumor assessment which may be performed up to 28 days preceding the first dose of study drug, providing

no anti-tumor therapy was administered in this period). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window specified above may be used; these tests do not need to be repeated for screening.

[b] Patients enrolled in Groups A, B, and C dose escalation will be hospitalized for at least 24 hours after the completion of the first dose of mosunetuzumab *administration* in Cycle *1*. Upon review of the data by the IMC, if mosunetuzumab is considered tolerable, the requirement for hospitalization may be reconsidered for Arms 1 and *3*.

[c] For Cycle 2, study drug infusion should occur on Day 1 of the cycle but may be given ±1 day from the scheduled date (with a minimum of 6 days after the C1D15 dosing). In Cycles 3 and beyond, study drug infusions should occur on Day 1 of each 21-day cycle but may be given ±2 days from scheduled date (with a minimum of 19 days between doses) for logistic/scheduling reasons. Other study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted.

[d] The interim response assessment will occur between C4D15 and C4D21.

[e] Informed consent must be documented before any study-specific screening procedure is performed. *Informed consent may be obtained 28 days preceding the first dose of study drug.*

[f] Unexplained weight loss > 10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[g] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the study completion/discontinuation visit.

[h] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study treatment or the initiation of another anti-cancer agent, whichever is earlier. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event (if believed to be related to prior study drug treatment) that occurs after the end of the adverse event reporting period (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

## Appendix 15
## Alternate Schedule of Activities (cont.)

[i] For all groups/arms: Includes systolic and diastolic blood pressure, respiratory rate, pulse oximetry, pulse rate, and body temperature while the patient is in a sitting or semi-supine position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
For hospitalized mosunetuzumab infusions: Vital signs with mosunetuzumab infusions: Check vital signs pre-infusion, every 30 (±10) minutes during the infusion, at the end of the infusion, and then every 60 (±10) minutes until 6 hours after the end of infusion. Thereafter, vital signs should be checked every 4 hours until hospital or clinic discharge.
All other Cycle 1 and 2 mosunetuzumab infusions: Check vital signs pre-infusion, every 30 (±10) minutes during the infusion, at the end of the infusion, and 2 hours after infusion. For patients who tolerated Cycle 1 and 2 mosunetuzumab infusions without the development of IRRs, in subsequent cycles, vital signs should be assessed pre-infusion, every 60 (±15) minutes during the infusion and for 2 hours after the end of infusion. For patients who experienced an IRR in Cycle 1, vital signs should be assessed pre-infusion, every 30 (±10) minutes during the infusion and for 2 hours after the end of infusion.
For polatuzumab vedotin infusions: Polatuzumab vedotin is to be administered after prednisone. During the administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes following completion of dosing at Cycle 1 and 30 (±10) minutes following completion of dosing in subsequent cycles (see Section 4.3.2.2).
For rituximab infusions: During the administration of rituximab or in Cycle 1, vital signs are to be obtained before infusion of rituximab, then after the start of the infusion, approximately every 15 (±5) minutes for 90 minutes, and then every 30 (±10) minutes until 1 hour after the end of the infusion. During administration of rituximab in subsequent cycles, vital signs are to be recorded before infusion of rituximab, then after the start of infusion, and approximately every 30 (±10) minutes until 1 hour after the end of infusion. See Section 4.3.2.3.

[j] Height and BSA are required at screening only, unless there has been > 10% change in body weight since the last BSA assessment, in which case BSA should be recalculated and documented in the eCRF. Weight will be recorded at every indicated visit.

[k] Complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] A complete neurologic examination, which includes an evaluation of mental status, cranial nerves, muscle strength, sensation, and coordination, should be performed and documented in the patient chart. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

## Appendix 15
## Alternate Schedule of Activities (cont.)

[m] Peripheral neuropathy will be evaluated by history and physical examination at each scheduled visit and collected in a specific eCRF. This eCRF does not take the place of adverse event reporting for peripheral neuropathy.

[n] Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be associated with tumor assessment, or potential drug-related toxicity). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For pre-infusion timepoints, targeted physical examination may be performed within 96 hours preceding study treatment administration unless otherwise specified.

[o] See Section 4.5.7 for details. Single 12-lead ECG recordings will be obtained at screening and at end of treatment. ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. During infusion of doxorubicin, continuous ECG monitoring should be performed per local clinical practice.

[p] See Section 4.5.5 for details. Assess response using image based evaluation, using Lugano 2014 criteria (see Appendix 3). PET and diagnostic-quality CT scans are required at screening, at the interim response assessment, and at the primary response assessment visit. Perform CT scan with or without PET during follow up every 6 months for 2 years after primary response assessment, or until disease progression or study discontinuation, whichever is earlier. CT scans with or without PET obtained during Cycles 9–17 if eligible for continued treatment may also serve as the scans required during the 2-year follow up after PRA. Additional scans are not required. A full tumor assessment including radiographic assessment must be performed any time disease progression or relapse is suspected. If disease progression or relapse is suspected before the primary response assessment, both PET and diagnostic-quality CT scans should be performed for tumor assessment. Scans should be performed according to the guidelines in the imaging manual provided to all sites.

[q] PROs will be evaluated in patients randomized in the Phase II (Arms 1, 2, and 3) portion of the study using the EORTC QLQ-C30, FACT-Lym subscale, FACT/GOG-Ntx, and EQ-5D-5L questionnaires. The questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments (except laboratory blood collections), and prior to the administration of study treatment, unless otherwise specified.

[r] For C4D1 and C6D1 only.

[s] HBsAg, HBsAb, HBcAb, HCV antibody, and HIV antibody serology are required. Patients with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody and negative HBsAg) may be included if 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. Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

## Appendix 15
## Alternate Schedule of Activities (cont.)

[t] Quantitative PCR for detection of active EBV and CMV should be performed at screening, C2D1, and when clinically indicated on a peripheral blood sample per local laboratory requirements. Paired samples should also be collected for central laboratory assessments at the same timepoints (see footnote *ss for sample types required for central laboratory assessments*). If local laboratory assessments are not available for quantitative PCR detection of active EBV and CMV, local laboratory collections may be waived only if sample is collected for central laboratory assessments of viral infections. If EBV or CMV DNA levels are detected (positive), contact the Medical Monitor for additional recommendations, and repeat quantitative PCR monitoring weekly until DNA levels decrease, and then continue to monitor by quantitative PCR at every cycle until two consecutive negative (undetectable) results.

[u] *Flow cytometry (preferred) and/or a peripheral blood smear is required at screening (if not done as part of standard-of-care tests) to detect malignant and/or atypical cells. If malignant cells or atypical cells are detected, the results must be discussed with the Medical Monitor.*

[v] Hematology includes CBC (including hemoglobin, hematocrit, RBC, WBC), platelet count, ANC, absolute lymphocyte count, and other cells.

[w] Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate *(or total carbon dioxide (if considered standard of care for the region),* glucose, BUN or urea, creatinine, calcium, magnesium, phosphorous, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, GGT, LDH, and uric acid.

[x] Fibrinogen will be collected when monitoring systemic immune activation events (e.g., MAS/HLH, severe CRS).

[y] In addition to the other listed laboratory tests, polatuzumab vedotin–specific laboratory tests include amylase, lipase, and hemoglobin A1c (see Section 4.5.6).

[z] All women of childbearing potential will have a serum pregnancy test at screening within 7 days before C1D1 of study treatment. Urine or serum pregnancy tests will be performed on Day 1 of each cycle of therapy for all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[aa] See Sections 4.3.3.2–4.3.3.4 for study treatment regimens and dosing. See Figure 3, Figure 4, and Figure 6 for order of administration of study treatments.

[bb] If the combination of the *step-up dosing of* mosunetuzumab plus other study treatments is not tolerated because of DLTs occurring prior to the administration of the C1D15 mosunetuzumab dose, then alternative regimens may be assessed. The C1D1 mosunetuzumab dose would be omitted. The C1D8 mosunetuzumab dose would consist of 1 mg and the C1D15 dose would consist of 2 mg. The C2D1 or C2D2 mosunetuzumab administration would be the first full test dose. Mosunetuzumab is given on Day 2 of Cycle 2 when combined with CHP-pola. This DLT window would be 36 days in length. See Sections 3.1.1.1 and 3.1.1.2.

## Appendix 15
## Alternate Schedule of Activities (cont.)

[cc] Prednisone 100 mg/day PO is given on Days 1–5 for each cycle when CHOP or CHP is administered. On days when mosunetuzumab IV corticosteroid premedication overlaps with the prednisone 100 mg dose, the IV corticosteroid premedication should be omitted.

[dd] Days –7 to –1. Administration of an approximate 7 days of pre-phase treatment (consisting of prednisone/prednisolone 100 mg PO daily) between Days –7 to –1 may be given at the discretion of the treating study investigator in patients with previously untreated TLS or patients considered to be at high risk for TLS or acute toxicity with the first cycle of study treatment. This may be added for all patients based on review of the safety data (see Section 4.3.3.1).

[ee] If CHP-pola is not tolerable, an alternative regimen of CHOP without polatuzumab vedotin will be substituted. See Sections 3.1.1.2 and 3.1.2.2.

[ff] If patients tolerate both the polatuzumab vedotin and mosunetuzumab infusions well in Cycles 1 and 2, they may be given on the same day for future subsequent cycles of treatment. See Section 3.3.2.

[gg] *For quantitative PCR detection of viral infection, which may include, but is not limited to, EBV and CMV. At screening; C2D1 predose; at other timepoints when clinically indicated; paired peripheral blood samples should be sent for central laboratory assessments, in additional to local laboratory assessments (see footnote [t]).*

[hh] PRA will occur 6–8 weeks after C6D1 or last study treatment, whichever is earlier.

[ii] Patients who receive mosunetuzumab more than 6 weeks after their last dose of mosunetuzumab, will need to follow the *step-up dosing* schedule (i.e., mosunetuzumab 1 mg on C7D1, 2 mg C7D8, and test dose on C7D15, followed by the test dose on Day 1 of subsequent cycles given every 21 days) (see Appendix 2). Routine hospitalization with re-starting mosunetuzumab treatment after more than 6 weeks of treatment break is not required, but it is allowed if the investigator considers this to be clinically indicated.

[jj] Cycle 7 will occur approximately 6–8 weeks after Cycle 6 for eligible patients receiving mosunetuzumab. See Section 3.1.2.5.

[kk] Patients eligible for extended treatment with mosunetuzumab (see Sections 4.3.3.2 and 4.3.3.3) may receive up to a total of 17 cycles of mosunetuzumab.

[ll] Assessments are to be taken prior to each dose of study drug, unless otherwise specified. Pre-infusion laboratory samples should be drawn 0–24 hours prior to study treatment infusion.

[mm] Patients who complete the treatment period will return to the clinic for a SDC visit 4–8 weeks after the last dose of study drug. Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit (ED) within 4–8 weeks after the last dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[nn] The follow-up period of 2 years starts after PRA, though patients may continue on single agent mosunetuzumab if applicable to the assigned group or arm. If a patient discontinues the study prior to the PRA, then the 2-year follow-up period will begin at the time of study drug

discontinuation. Patients will return to the clinic every 3 months for the first 6 months and then every 6 months for laboratory assessments and targeted physical examinations.

[oo] When completed/discontinued from treatment, patients should be followed for first new anti-cancer therapy via telephone calls and patient medical records every 3 months and/or clinic visits every 3 months for the first 6 months, then every 6 months thereafter, until approximately 2 years following the primary response assessment (unless death, loss to follow-up, the patient withdraws consent or the Sponsor terminates the study, whichever occurs first). The date of when the first subsequent anti-cancer therapy was initiated will be collected.

[pp] IgG, IgA, and IgM will be collected every 6 months from screening sample (e.g., at screening, approximately Cycle 8, Cycle 16, study drug completion/early discontinuation, and, if applicable, during follow-up).

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments

**Table 1: M-CHOP Treatment Groups (Phase Ib Group A, Group C; Phase II Arm 3)**

| | | Cycle 1 | | | | | | | | | | | Cycles 2–6 | | | | | | Cycles 7–17 [b] | | | | PRA/ED [c] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D9 | D15 | | | D1 | | | D1/D2 [d] | | | D1 (Also on C7D8 and C7D15, if *step-up* dosing regimen used) [e] | | | | | |
| Timepoint [a] | Scr. | Pre-Chemo [f] | EOI-Chemo [g] | 2 hr Post-Chemo [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Chemo [g] | 2 hr Post-Chemo [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | | |
| Plasma for biomarkers [h] | | x | | | x | x | x | x | x | x | x | x | x [i] | | | x [i,j] | | x [i] | x [k] | x [k] | x [k] | x [k] | | |
| Blood for TBNK | | x | | | | x | | x | | | | | x [i] | | | x [j,i] | | x [i] | x [k] | | x [k] | | x [m] | |
| Blood for flow cytometry | | x | | | | x | | x | | | | | x [i] | | | x [j,i] | | x [i] | x [k] | | x [k] | | | |
| PBMCs for biomarkers | | x | | | | | | | | | | | x [i] | | | | | | x [n] | | | | x | x [o] |
| Blood for molecular analysis *for MRD* [p] | | x | | | x | x | | | | x | | | x [q] | | | | | | x [r] | | | | x | x [s] |
| Blood for RBR (optional) [t] | | (x) | | | | | | | | | | | | | | | | | | | | | | |
| Fresh (or archival) tumor tissue sample [u] | x | (x) [u] | | | | | | | | | | | | | | | | | | | | | | |
| Serum for mosunetuzumab PK (dense) [v] | | | | | | x | x | x | x | x | x | x | | | | x | x | x [i] | x [c, w] | x [c] | | | x | x [x] |

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 1: M-CHOP Treatment Groups (Phase Ib Group A, Group C; Phase II Arm 3)**

| | | Cycle 1 | | | | | | | | | | | Cycles 2–6 | | | | | | Cycles 7–17 [b] | | | | PRA/ ED [c] | PT Follow -Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D9 | D15 | | | D1 | | | D1/D2 [d] | | | D1 (Also on C7D8 and C7D15, if *step -up* dosing regimen used) [e] | | | | | |
| Timepoint [a] | Scr. | Pre-Chemo [f] | EOI-Chemo [g] | 2 hr Post-Chemo [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Chemo [g] | 2 hr Post-Chemo [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | | |
| Serum for mosunetuzumab PK (sparse) [v] | | | | | | x | x | | | x | x | | | | | x | x | | x [c, w] | x [c] | | | x | x [x] |
| Serum for mosunetuzumab ADAs [y] | | | | | | x | | | | | | | | | | x | | | x | | | | x | |
| Serum for obinutuzumab PK [z] | | x | | | | | | | | | | | | | | | | | | | | | | |
| Serum for rituximab PK [z] | | x | | | | | | | | | | | | | | | | | | | | | | |

ADA =anti-drug antibody; C =Cycle; chemo =chemotherapy; CHOP =cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP =cyclophosphamide, doxorubicin, and prednisone; CR =complete response; CT =computed tomography; D =Day; ED =early discontinuation; EOI =end of infusion; M-CHOP =mosunetuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; MOS =mosunetuzumab; MRD =minimal residual disease; PBMC =peripheral blood mononuclear cells; PET =positron emission tomography; PK =pharmacokinetic; PR =partial response; PRA =primary response assessment; Pre =predose; PT =post-treatment; RBR =Research Biosample Repository; Scr. =screening; SD =stable disease; SDC =study drug completion; TBNK =T, B, and natural killer cells; WES =whole exome sequencing; WGS =whole genome sequencing; (x) =conditional/optional (refer to footnote).

## Appendix 16
## Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[a] Timepoints listed are relative to the end of chemotherapy or mosunetuzumab infusion for each cycle.

[b] Samples to be collected only for patients with SD/PR at end of Cycle 6 that opt to continue treatment with mosunetuzumab for 11 additional cycles.

[c] Perform within 6–8 weeks after the last infusion of mosunetuzumab to coincide with PET-CT assessment. For patients who discontinue the study drug prematurely (early discontinuation), perform within 4–8 weeks after the last dose of study drug.

[d] When combined with CHP-pola, mosunetuzumab will be administered on C2D2. If a patient tolerates the treatment well in Cycles 1 and 2, starting in Cycle 3, patients may receive mosunetuzumab on Day 1 of Cycles 3–6.

[e] In Cycle 7, if step-*up* dosing regimen is implemented, serum mosunetuzumab PK samples will be collected at predose (0–4 hours prior to the infusion of mosunetuzumab) on Days 1, 8, and 15 and within 30 minutes after completion of mosunetuzumab infusion on C7D1. Additional predose samples will be collected in Cycles 8 and 16 (see footnote [v]).

[f] Draw predose laboratory samples 0–4 hours prior to infusion of the first drug: chemotherapy on Day 1 of Cycles 1–6 and mosunetuzumab on Days 8 and 15 of Cycle 1, Day 2 of Cycle 2, and Day 1 of Cycles 7–17.

[g] Perform EOI assessments within 30 minutes after completion of chemotherapy or mosunetuzumab infusion. "2 hr Post-MOS" corresponds to 2 hours (±30 minutes) post-EOI of mosunetuzumab; "24 hr" corresponds to 24 hours (± 4 hours) from beginning of chemotherapy or mosunetuzumab infusion.

[h] For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration. Please refer to Appendix 14.

[i] Cycles 2, 3, and 5 only.

[j] For Cycles 3 and 5, collect only if mosunetuzumab is given on Day 2.

[k] Cycle 7, Day 1 only.

[l] Cycles 2 and 5 only.

[m] For patients with CR at end of Cycle 6.

[n] Cycles 7 and 16, Day 1 only.

[o] Collect 6 months after SDC for patients with CR after 6 cycles.

[p] Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).

## Appendix 16
## Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[q] Cycles *2, 4 and 6 only*

[r] *Cycles* 7, 11, and 16, Day 1 only.

[s] Collect during follow-up visits as described in Appendix 15, footnote "*nn*": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.

[t] With consent to optional research, a blood sample will be requested at baseline for collection and storage at the RBR.

[u] Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. *Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion.* Tissue biopsy at the time of tumor progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis). Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.

[v] The dense PK sampling for mosunetuzumab applies to all patients in the dose-escalation cohorts in Group A and in the Group C safety cohort (M-CHOP regimen). The sparse PK sampling for mosunetuzumab applies to all patients in the expansion cohorts in Group A and for patients in Arm 3 (M-CHOP regimen) of the Phase II dose-expansion cohorts.

[w] Cycles 7, 8, and 16 only.

[x] During the post-treatment follow-up at ≥90 days after last mosunetuzumab administration.

[y] Predose serum ADA for mosunetuzumab will be collected in Cycles 1, 2, 6, 16, and ED or PRA.

[z] Predose serum rituximab or obinutuzumab PK is required for patients who have received prior treatment with rituximab or obinutuzumab only.

## Appendix 16
## Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 2: M-CHP-Pola Treatment Groups (Phase Ib Group B)**

| | | Cycle 1 | | | | | | | | | | | Cycles 2–6 | | | | | | Cycles 7–17 [b] | | | | PRA/ ED [c] | PT Follow -Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D9 | D15 | | | D1 | | | D1/D2 [d] | | | D1 (Also on C7D8 and C7D15, if -up dosing regimen used) [e] | | | | | |
| Timepoint [a] | Scr. | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | | |
| Plasma for biomarkers [h] | | x | | | x | x | x | x | x | x | x | x | x [i] | | | x [i, j] | | x [i] | x [k] | x [k] | x [k] | x [k] | | |
| Blood for TBNK | | x | | | | x | | x | | | | | x [l] | | | x [j, l] | | x [l] | x [k] | | x [k] | | x [m] | |
| Blood for flow cytometry | | x | | | | x | | x | | | | | x [l] | | | x [j, l] | | x [l] | x [k] | | x [k] | | | |
| PBMCs for biomarkers | | x | | | | | | | | | | | x [l] | | | | | | x [n] | | | | x | x [o] |
| Blood for molecular analysis *for MRD* [p] | | x | | | x | x | | | | x | | | x [q] | | | | | | x [r] | | | | x | x [s] |
| Blood for RBR (optional) [t] | | (x) | | | | | | | | | | | | | | | | | | | | | | |
| Fresh (or archival) tumor tissue sample [u] | x | (x) [u] | | | | | | | | | | | | | | | | | | | | | | |

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 2: M-CHP-Pola Treatment Groups (Phase Ib Group B)**

| | | Cycle 1 | | | | | | | | | | | Cycles 2–6 | | | | | | Cycles 7–17 [b] | | | | PRA/ED [c] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D9 | D15 | | | D1 | | | D1/D2 [d] | | | D1 (Also on C7D8 and C7D15, if -up dosing regimen used) [e] | | | | | |
| Timepoint [a] | Scr. | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | | |
| Serum for mosunetuzumab PK (dense) [v] | | | | | | x | x | x | x | x | x | x | | | | x | x | x [l] | x [e,w] | x [e] | | | x | x [x] |
| Serum for mosunetuzumab PK (sparse) [v] | | | | | | x | x | | | x | x | | | | | x | x | | x [e,w] | x [e] | | | x | x [x] |
| Serum for mosunetuzumab ADAs [y] | | | | | | x | | | | | | | | | | x | | | x | | | | x | |
| Serum for rituximab PK [z] | | x | | | | | | | | | | | | | | | | | | | | | | |
| Serum for obinutuzumab PK [z] | | x | | | | | | | | | | | | | | | | | | | | | | |

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 2: M-CHP-Pola Treatment Groups (Phase Ib Group B)**

| | | Cycle 1 | | | | | | | | | | | Cycles 2–6 | | | | | | Cycles 7–17 [b] | | | | PRA/ ED [c] | PT Follow -Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D9 | D15 | | | D1 | | | D1/D2 [d] | | | D1 (Also on C7D8 and C7D15, if -up dosing regimen used) [e] | | | | | |
| Timepoint [a] | Scr. | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | | |
| Plasma polatuzumab vedotin PK for acMMAE and unconjugated MMAE (dense) [aa] | | x | x | | x | x | | | | x | | | x | x | | | | | x [w] | | | | x | x |
| Plasma polatuzumab vedotin PK for acMMAE and unconjugated MMAE (sparse) [aa] | | x | x | | | x | | | | x | | | x | x | | | | | x [w] | | | | x | x |
| Serum polatuzumab vedotin PK for total antibody [bb] | | x | | | | | | | | | | | x | | | | | | | | | | x | |

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 2: M-CHP-Pola Treatment Groups (Phase Ib Group B)**

| | | Cycle 1 | | | | | | | | | | | Cycles 2–6 | | | | | | Cycles 7–17 [b] | | | | PRA/ ED [c] | PT Follow -Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D9 | D15 | | | D1 | | | D1/D2 [d] | | | D1 (Also on C7D8 and C7D15, if -up dosing regimen used) [e] | | | | | |
| Timepoint [a] | Scr. | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-Chemo [f] | EOI-Pola [g] | 2 hr Post-Pola [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | Pre-MOS [f] | EOI-MOS [g] | 2 hr Post-MOS [g] | 24 hr [g] | | |
| Serum for polatuzumab vedotin ADAs [y] | | x | | | | | | | | | | | x | | | | | | | | | | x | |

acMMAE = antibody-conjugated monomethyl auristatin E; ADA = anti-drug antibody; C = Cycle; chemo = chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP = cyclophosphamide, doxorubicin, and prednisone; CR = complete response; CT = computed tomography; D = Day; ED = early discontinuation; EOI = end of infusion; IMC = Internal Monitoring Committee; M-CHP-pola = mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; MMAE = monomethyl auristatin E; MOS = mosunetuzumab; MRD = minimal residual disease; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; Pola = polatuzumab vedotin; PR = partial response; PRA = primary response assessment; Pre = predose; PT = post-treatment; RBR = Research Biosample Repository; Scr. = screening; SD = stable disease; SDC = study drug completion; TBNK = T, B, and natural killer cells; WES = whole exome sequencing; WGS = whole genome sequencing; (x) = conditional/optional (refer to footnote).

## Appendix 16
## Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[a] Timepoints listed are relative to the end of polatuzumab vedotin or mosunetuzumab infusion for each cycle.

[b] Samples to be collected only for patients with SD/PR at end of Cycle 6 who opt to continue treatment with mosunetuzumab for 11 additional cycles.

[c] *Perform within 6–8 weeks after the last infusion of mosunetuzumab to coincide with PET-CT assessment.*

[d] In Cycle 2, mosunetuzumab will be administered on Day 2 when combined with CHP-pola *in Phase I Group B*. In Cycles 3–6, mosunetuzumab will be administered on either Day 1 or 2, depending on each patient's ability to tolerate the mosunetuzumab plus polatuzumab vedotin combination during the first 2 cycles.

[e] In Cycle 7, if step-*up* dosing regimen is implemented, serum mosunetuzumab PK samples will be collected at predose (0–4 hours prior to the infusion of mosunetuzumab) on Days 1, 8, and 15 and within 30 minutes after completion of mosunetuzumab infusion on C7D1. Additional predose samples will be collected in Cycles 8 and 16 (see footnote [w]).

[f] Draw predose laboratory samples 0–4 hours prior to infusion of the first drug: chemotherapy on Day 1 of Cycles 1–6 and mosunetuzumab on Days 8 and 15 of Cycle 1, Day 2 of Cycle 2, either Day 1 or 2 of Cycles 3–6, and Day 1 of Cycles 7–17.

[g] Perform EOI assessments within 30 minutes after completion of polatuzumab vedotin or mosunetuzumab infusion. "2 hr Post" corresponds to 2 hours (±30 minutes) post-EOI; "24 hr" corresponds to 24 hours (±4 hours) from beginning of polatuzumab vedotin or mosunetuzumab infusion.

[h] For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration. Please refer to Appendix 14.

[i] Cycles 2, 3, and 5 only.

[j] For Cycles 3 and 5, collect only if mosunetuzumab is given on Day 2.

[k] Cycle 7, Day 1 only.

[l] Cycles 2 and 5 only.

[m] For patients with CR at end of Cycle 6.

[n] Cycles 7 and 16, Day 1 only.

[o] Collect 6 months after SDC for patients with CR after 6 cycles.

[p] Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).

[q] *Cycles 2, 4, and 6 only.*

## Appendix 16
## Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[r] Cycles 7, 11, and 16, Day 1 only.

[s] Collect during follow-up visits as described in Appendix 15, footnote "*mm*": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.

[t] With consent to optional research, a blood sample will be requested at baseline for collection and storage at the RBR.

[u] Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. *Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion.* Tissue biopsy at the time of tumor progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis). Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.

[v] The dense PK sampling for mosunetuzumab applies to all patients in the dose-escalation cohorts in Group B and in the Group C safety cohort (if M-CHP-pola is used). The sparse PK sampling for mosunetuzumab applies to all patients in the expansion cohorts in Group B.

[w] Cycles 7, 8 and 16 only.

[x] During the post-treatment follow-up at ≥ 90 days after last mosunetuzumab administration.

[y] Predose serum ADA for mosunetuzumab will be collected in Cycles 1, 2, 6, 16, EOT, and ED or PRA. Predose serum ADA for polatuzumab vedotin will be collected in Cycles 1, 2, 6, and ED or PRA.

[z] Predose serum rituximab or obinutuzumab PK is required for patients who have received prior treatment with rituximab or obinutuzumab only.

[aa] The plasma sample will be split into two samples for analyses of antibody-conjugated MMAE and unconjugated MMAE concentrations. The dense plasma PK sampling scheme for polatuzumab vedotin applies to all patients in Group B (dose-escalation and expansion cohorts/

[bb] Serum polatuzumab vedotin PK for total antibody will be collected at predose (0–4 hours prior to the infusion of polatuzumab vedotin) in Cycles 1, 2, 6, and ED or PRA. Polatuzumab vedotin total antibody PK and ADA will not be collected if mosunetuzumab+CHOP is selected as a regimen.

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*Table 3: M-CHP-Pola Treatment Group (Phase II Arm 1)*

| *Timepoint* [a] | *Scr.* | *Cycle 1* | | | | | | | | | | | | *Cycles 2–6* | | | | | *Cycles 7–17* [b] | | | | *PRA/ED* [c] | *PT Follow-Up* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *D1* | | | | | *D2* | *D8* | | | *D15* | | | *D1* | | | | | *D1 (also on C7D8 and C7D15, if step-up dosing regimen used)* [d] | | | | | |
| | | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | | |
| *Plasma for biomarkers* [g] | | x | | x | x | x | x | x | x | | x | x | | x [h] | | | | x [h] | x [h] | x [h] | x [h] | x [i] | | |
| *Blood for TBNK* | | x | | x | | x | | | | | | | | x [l] | | | | x [l] | x [l] | | x [l] | | x [k] | |
| *Blood for flow cytometry* | | x | | x | | x | | | | | | | | x [j] | | | | x [j] | x [i] | | x [i] | | | |
| *PBMCs for biomarkers* | | x | | | | | | | | | | | | x [j] | | | | | x [l] | | | | x | x [m] |
| *Blood for molecular analysis for MRD* [n] | | x | | | | | x | x | | | x | | | x [o] | | | | | x [p] | | | | x | x [q] |
| *Blood for RBR (optional)* [r] | | (x) | | | | | | | | | | | | | | | | | | | | | | |
| *Fresh (or archival) tumor tissue sample* [s] | x | (x) [s] | | | | | | | | | | | | | | | | | | | | | | |
| *Serum for mosunetuzumab PK* | | | | x | x | | x | x | x | | x | x | | | | x | x | | x [d,t] | x [d] | | | x | x [u] |
| *Serum for mosunetuzumab ADAs* [v] | | | | x | | | | | | | | | | | | x | | | x | | | | x | |

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*Table 3: M-CHP-Pola Treatment Group (Phase II Arm 1)*

| *Timepoint* [a] | *Scr.* | *Cycle 1* | | | | | | | | | | | | *Cycles 2–6* | | | | | *Cycles 7–17* [b] | | | | *PRA/ED* [c] | *PT Follow-Up* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *D1* | | | | | *D2* | *D8* | | | *D15* | | | *D1* | | | | | *D1 (also on C7D8 and C7D15, if step-up dosing regimen used)* [d] | | | | | |
| | | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-Chemo* [e] | *EOI-Pola* | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *Pre-MOS* [e] | *EOI-MOS* [f] | *2 hr Post-MOS* [f] | *24 hr (Post-MOS)* [f] | | |
| *Plasma polatuzumab vedotin PK for acMMAE and unconjugated MMAE* [w] | | x | x | x | | | x | x | | | x | | | x | x | | | | x [t] | | | | x | x [u] |
| *Serum polatuzumab vedotin PK for total antibody* [x] | | x | | | | | | | | | | | | x | | | | | | | | | x | |
| *Serum for polatuzumab vedotin ADAs* [v] | | x | | | | | | | | | | | | x | | | | | | | | | x | |

*acMMAE=antibody-conjugated monomethyl auristatin E; ADA=anti-drug antibody; C□Cycle; chemo=chemotherapy; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP=cyclophosphamide, doxorubicin, and prednisone; CR=complete response; CT=computed tomography; D=Day; ED=early discontinuation; EOI=end of infusion; IMC=Internal Monitoring Committee; MMAE=monomethyl auristatin E; M-CHP-pola=mosunetuzumab plus cyclophosphamide, doxorubicin, prednisone, and polatuzumab vedotin; MOS=mosunetuzumab; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cells; PET=positron emission tomography; PK=pharmacokinetic; pola=polatuzumab vedotin; PR=partial response; PRA=primary response assessment; Pre=predose; PT=post-treatment;*

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

*RBR=Research Biosample Repository; Scr.=screening; SD=stable disease; SDC=study drug completion; TBD=T-cell–dependent bispecific (antibody); TBNK=T, B, and natural killer cells; WES=whole exome sequencing; WGS=whole genome sequencing; (x)=conditional/optional (refer to footnote).*

[a] *Timepoints listed are relative to the end of polatuzumab or mosunetuzumab infusion for each cycle, unless otherwise noted.*

[b] *Samples to be collected only for SD/PR patients at end of Cycle 6 that opt to continue treatment with mosunetuzumab for 11 additional cycles.*

[c] *Perform within 6–8 weeks after the last infusion of mosunetuzumab to coincide with PET-CT assessment.*

[d] *In Cycle 7, if step-up dosing regimen is implemented, serum mosunetuzumab PK samples will be collected at predose (0–4 hours prior to the infusion of mosunetuzumab) on Days 1, 8 and 15 and within 30 minutes after completion of mosunetuzumab infusion on C7D1. Additional predose samples will be collected in Cycles 8 and 16 (see footnote w).*

[e] *Draw predose laboratory samples 0–4 hours prior to infusion of the first drug: chemotherapy on Day 1 of Cycles 1–6 and mosunetuzumab on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycles 2, –6, and Day 1 of Cycles 7–17.*

[f] *Perform EOI assessments within 30 minutes after completion of polatuzumab or mosunetuzumab infusion. "2 hr post-MOS" corresponds to 2 hours (±30 minutes) after completion of polatuzumab or mosunetuzumab infusion; "24 hr" corresponds to 24 hours (±4 hours) from beginning of mosunetuzumab infusion.*

[g] *For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration. Please refer to Appendix 14.*

[h] *Cycles 2, 3, and 5 only.*

[i] *Cycle 7, Day 1 only.*

[j] *Cycles 2 and 5 only.*

[k] *For CR patients at end of Cycle 6.*

[l] *Cycles 7 and 16, Day 1 only.*

[m] *Collect 6 months after SDC for patients that have a CR after 6 cycles.*

[n] *Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).*

[o] *Cycles 2, 4 and 6 only*

## Appendix 16
## Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[p] *Cycles 7, 11, and 16, Day 1 only.*

[q] *Collect during follow-up visits as described in Appendix 1, footnote "nn": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.*

[r] *With consent to optional research, a blood sample will be requested at baseline for collection and storage at the RBR.*

[s] *Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion. Tissue biopsy at the time of tumor progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis), and between C1D15 and C2D8. Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.*

[t] *Cycles 7, 8, and 16 only for mosunetuzumab serum PK. Cycle 8 only for polatuzumab vedotin plasma PK.*

[u] *During the post-treatment follow-up at ≥ 90 days after last mosunetuzumab administration.*

[v] *Predose serum ADA for mosunetuzumab will be collected in Cycles 1, 2, 6, 16, and ED or PRA. Predose serum ADA for polatuzumab vedotin will be collected in Cycles 1, 2, 6, and ED or PRA.*

[w] *The plasma sample will be split into two samples for analyses of acMMAE and unconjugated MMAE concentrations.*

[x] *Serum polatuzumab vedotin PK for total antibody will be collected at predose (0–4 hours prior to the infusion of polatuzumab vedotin) in Cycles 1, 2, 6, and ED or PRA.*

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

**Table 4: Control Treatment Groups (R-CHP-Pola, Phase II Arm 2)**

| | | Cycle 1 | | | | | | | | | | Cycles 2–6 | | | PRA/ ED [b] | PT Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | | | D2 | D8 | | | D15 | | | D1 | | | | |
| Timepoint [a] | Scr. | Pre [c] (Chemo) | EOI [d] | 2 hr Post-EOI [d] | 24 hr [d] | Pre [c] | EOI [d] | 2 hr Post-EOI [d] | Pre [c] | EOI [d] | 2 hr Post-EOI [d] | Pre [c] (Chemo) | EOI [d] | 2 hr Post-EOI [d] | | |
| Plasma for biomarkers [e] | | x | x | x | x | x | | | x | | | x [f] | | x [g] | | |
| Blood for TBNK | | x | | x | | | | | | | | x [h] | | x [h] | x | |
| Blood for flow cytometry | | x | | x | | | | | | | | x [h] | | x [h] | | |
| PBMCs for biomarkers | | x | | | | | | | | | | x [h] | | | x | x [i] |
| Blood for molecular analysis *for MRD* [j] | | x | | | x | x | | | x | | | x [k] | | | x | x [l] |
| Blood for RBR (optional) [m] | | (x) | | | | | | | | | | | | | | |
| Fresh (or archival) tumor tissue sample [n] | x | (x) [n] | | | | | | | | | | | | | | |
| Serum for rituximab PK [o] | | x | x | | | | | | | | | x | x | | x | x |
| Plasma polatuzumab vedotin PK for MMAE [o, p] | | x | x | | | | | | | | | x | x | | x | x |
| Serum polatuzumab vedotin PK for total antibody [q] | | x | | | | | | | | | | x | | | x | |
| Serum for polatuzumab vedotin ADAs [q] | | x | | | | | | | | | | x | | | x | |

acMMAE=antibody-conjugated monomethyl auristatin E; ADA=anti-drug antibody; C=Cycle; chemo=chemotherapy; CT=computed tomography; D=Day; ED=early discontinuation; EOI=end of infusion; MMAE=monomethyl auristatin E; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cells; PE=positron emission tomography; PK=pharmacokinetic; PR=partial response; PRA=primary response assessment; Pre=predose; PT=post-treatment; RBR=Research Biosample Repository; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP=rituximab plus cyclophosphamide, doxorubicin, and prednisone; Scr.=screening; SDC=study drug completion; TBNK=T, B, and natural killer cells; WES=whole exome sequencing; WGS=whole genome sequencing; (x)=conditional/optional (refer to footnote).

# Appendix 16
# Alternate Schedule of Samples for Biomarker, Pharmacokinetic, and Anti-Drug Antibody Assessments (cont.)

[a] Timepoints listed are relative to the end of chemotherapy infusion for each cycle, unless otherwise noted.

[b] Perform within 6–8 weeks after the last infusion of mosunetuzumab, to coincide with PET-CT assessment.

[c] Draw predose laboratory samples 0–4 hours prior to infusion of the first drug (chemotherapy) on Day 1.

[d] Perform EOI assessments within 30 minutes after completion of chemotherapy (for R-CHOP) or polatuzumab vedotin (for R-CHP-pola) infusion; "2 hr Post-EOI" corresponds to 2 hours (±30 minutes) post-EOI; "24 hr" corresponds to 24 hours (±4 hours) from beginning of chemotherapy infusion.

[e] For patients receiving tocilizumab, additional samples should be collected pre- and post-tocilizumab (6, 24, 48, and 72 hours, and Day 8) administration.

[f] Cycles 2, 3, and 5 only.

[g] Cycle 2 only.

[h] Cycles 2 and 5 only.

[i] Collect 6 months after SDC.

[j] Samples for MRD monitoring should be drawn as scheduled for all patients, but MRD analysis may only be done in selected patients. Baseline samples from patients at participating sites will also be analyzed by WES/WGS (see Section 4.5.11).

[k] *Cycles 2, 4, and 6 only.*

[l] Collect during follow-up visits as described in Appendix 15, footnote "*nn*": starting from either PRA or discontinuation, collect every 3 months for 6 months and then every 6 months until 2 years have elapsed.

[m] With consent to optional research, a blood sample will be requested at screening for collection and storage at the RBR.

[n] Baseline tissue sample is mandatory and availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, obtained at any time before study entry. If available, slides from bone marrow biopsies performed prior to study entry should also be provided in addition to (but cannot be in place of) the primary tumor. *Optional tissue biopsy after treatment initiation is preferred between C1D15 and C2D8, but may be performed at any time per investigator's discretion.* Tissue biopsy at the time of tumor progression is optional. Additional biopsies may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis) *and between Cycle 1 Day 15 and Cycle 2 Day 8.* Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue must have an associated pathology report.

[o] Plasma polatuzumab vedotin PK and rituximab PK samples will be collected at the specified timepoints in Cycles 1, 2, 4, 6, ED or PRA, and>90 days after the last dose of the respective agent.

[p] The plasma sample will be split into two samples for analyses of acMMAE and unconjugated MMAE concentrations.

[q] Serum polatuzumab vedotin PK and ADA samples will be collected at predose in Cycles 1, 2, 6, and ED or PRA.

# Appendix 17
# Neurologic Adverse Events that May Affect Driving

Patients should be advised by the study investigator of potential neurologic toxicity, which may include seizures and alterations of consciousness.

Neurologic adverse events with the potential to impact cognition or consciousness that may affect driving (driving-impacting cognition or consciousness neurologic events [DI-CCNAE]) include, but are not limited to: amnesia, aphasia, confusional state, delirium, depressed level of consciousness, disturbance in attention, encephalopathy, hallucination, hepatic encephalopathy, insomnia, memory impairment, seizure, visual hallucination, and vertigo.

Neurologic adverse events with the potential to impact cognition or consciousness (cognition or consciousness neurologic events [CCNAE]) may include, but are not limited to: dizziness, insomnia, postural dizziness, and tremor. Patients with CCNAEs or Grade ≥3 neurologic adverse events should be assessed by neurologic examination to evaluate risk of impairment for driving or engaging in hazardous occupations or activities. When necessary, consult the Medical Monitor and obtain neurology consultation for evaluation of neurologic events that have the potential to impact cognition or consciousness.

# *Appendix 18*
# *Definitions of Laboratory and Clinical Tumor Lysis Syndrome.*

**Table 1. Definitions of Laboratory and Clinical Tumor Lysis Syndrome.***

| Metabolic Abnormality | Criteria for Classification of Laboratory Tumor Lysis Syndrome | Criteria for Classification of Clinical Tumor Lysis Syndrome |
|---|---|---|
| Hyperuricemia | Uric acid >8.0 mg/dl (475.8 μmol/liter) in adults or above the upper limit of the normal range for age in children | |
| Hyperphosphatemia | Phosphorus >4.5 mg/dl (1.5 mmol/liter) in adults or >6.5 mg/dl (2.1 mmol/liter) in children | |
| Hyperkalemia | Potassium >6.0 mmol/liter | Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia |
| Hypocalcemia | Corrected calcium <7.0 mg/dl (1.75 mmol/liter) or ionized calcium <4.5 mg/dl (1.12 mmol/liter)† | Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia |
| Acute kidney injury‡ | Not applicable | Increase in the serum creatinine level of 0.3 mg/dl (26.5 μmol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal 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 hr |

* In laboratory tumor lysis syndrome, 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 tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams per deciliter).

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury are from Levin et al.[11]

*Adapted from: Howard et al. 2011.*

*Note: Tumor lysis syndrome should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.*

# *Appendix 19*
# *Management of Hemophagocytic Lymphohistiocytosis*

## *HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS*

*The supportive management of hemophagocytic lymphohistiocytosis (HLH) is generally similar to that of cytokine-release syndrome (see Table 10) 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) (<100 g/L [10 g/dL] for infants <4 weeks old)*
- *Platelet count <100x10⁹/L (100,000/μL)*
- *ANC <1.0x10⁹/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 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 Medical Monitor 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 chemistries, complete blood counts, liver function tests (LFTs), 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 EBV protein localization in T/B/NK cells;*
- *Complete infectious disease work-up including:*
  - *Blood cultures (bacterial and fungal)*
  - *Urine cultures and urinalysis*

- *Radiographic assessments (e.g., chest X-ray or CT scan)*
- *Assessment for active viral infections, including but not limited to EBV and CMV*
- *If available, assessment for soluble CD25 and assessment of NK cell function*
- *DNA for exploratory genetic testing of mutations potentially associated with HLH, e.g., PRF1, MUNC13-4, STXBP2 should be considered (Zhang et al. 2011)*

*Patients with suspected HLH should be treated according to the guidelines in* Table 1. *In the case of confirmed HLH, permanently discontinue study treatment.*

**Table 1 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis**

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

HLH =hemophagocytic lymphohistiocytosis.