Official Title: A Randomized, Open-Label, Multicenter Phase III Study Evaluating Efficacy and Safety of Mosunetuzumab in Combination with Polatuzumab Vedotin in Comparison with Rituximab in Combination with Gemcitabine Plus Oxaliplatin in Participants with Relapsed or Refractory Aggressive B-Cell Non-Hodgkin's Lymphoma

NCT Number: NCT05171647

Document Date: Protocol Amendment Version 5: 05-Oct-2024

PROTOCOL

PROTOCOL TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF MOSUNETUZUMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN IN COMPARISON WITH RITUXIMAB IN COMBINATION WITH GEMCITABINE PLUS OXALIPLATIN IN PARTICIPANTS WITH RELAPSED OR REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO43643
STUDY NAME:	SUNMO
VERSION NUMBER:	5
TEST COMPOUND(S):	Mosunetuzumab (RO7030816; BTCT4465A) Polatuzumab vedotin (RO5541077; DCDS4501S) Tocilizumab (RO4877533)
STUDY PHASE:	Phase III
EUDRACT NUMBER:	To be determined
IND NUMBER:	120651
NCT NUMBER:	NCT05171647
MEDICAL MONITOR:	[redacted] Ph.D.
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document

CONFIDENTIAL

PROTOCOL HISTORY

Protocol		Associated Country and/or Region-Specific Protocols		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
5	See electronic date stamp on the final page of this document.	—	—	—
4	20 February 2024	—	—	—
3	04 October 2023	US	2	23 May 2023
2	11 November 2022	US	1	17 January 2023
1	12 July 2021	—	—	—

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol GO43643, Version 5 has been primarily amended for the following reasons: to include the required language updates to the identified risks of hemophagocytic lymphohistiocytosis (HLH) and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS); to include updates from the recent protocol clarification letter (PCL) which provides clarification on post-treatment follow up visits after Month 30, and to include guidance for unscheduled additional survival follow-ups. Changes to the protocol, along with a rationale for each change are summarized below:

- The protocol has been updated to upgrade the potential risk of neurological adverse events to the identified risk of neurologic toxicity including ICANS. The potential risk of HLH has also been updated to an identified risk. This is following the Dear Investigator Letter issued on 28 June 2024. Related changes include the following:
  - Text in the protocol referring to ‘neurologic adverse events’ has been replaced with "neurologic toxicity including ICANS" (Section 2.3, 4.3.2, A6-2.3.5, and Appendix 22).
  - The description of risks associated with mosunetuzumab has been updated to include neurologic toxicity including ICANS and HLH as identified risks (Appendix 6).
  - The management guidelines have been updated to include neurologic toxicity including ICANS (Table A6-10) (Appendix 6).
  - The management guidelines have also been updated with criteria for diagnosing HLH (Table A6-6) and with guidelines for managing suspected or confirmed HLH (Table A6-7).
  - The assessment of severity of adverse events has been updated to include a reference to Appendix 21 for the ASTCT ICANS consensus grading for adults and ICE assessment. The assessment for severity for HLH events has been updated to include reference to a scale developed by the ASTCT working group (Table A6-8).
  - Additional guidance on the grading of ICANS and HLH have been updated. New cases of ICANS and HLH will continue to be graded using NCI CTCAE v5.0. In addition, ASTCT grade for ICANS and HLH should be provided in the Additional Case Details section on the Adverse Events eCRF page (refer to Appendix 21, and Table A6-8) (Sections 4.1.1.4 and A3-3.2).
- Patients who remain in post-treatment follow-up without disease progression or new anti-lymphoma therapy through the Month 30 visit, will then move into the long-term survival follow-up phase in which they will be followed for survival status and new anti-lymphoma therapy via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study). Guidelines for post-treatment follow-up visits after Month 30 have been updated in Section 1.3 (Tables 1 and 2, footnotes c and d) and Section 7.1.

- Guidance on unscheduled additional survival follow-ups have been included in Tables 1 and 2, footnote d.

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF MOSUNETUZUMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN IN COMPARISON WITH RITUXIMAB IN COMBINATION WITH GEMCITABINE PLUS OXALIPLATIN IN PARTICIPANTS WITH RELAPSED OR REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN'S LYMPHOMA**
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MEDICAL MONITOR:	[redacted] Ph.D.
SPONSOR NAME:	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 your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A RANDOMIZED, OPEN-LABEL, MULTICENTER PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF MOSUNETUZUMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN IN COMPARISON WITH RITUXIMAB IN COMBINATION WITH GEMCITABINE PLUS OXALIPLATIN IN PARTICIPANTS WITH RELAPSED OR REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN'S LYMPHOMA**

BRIEF TITLE: An Open-Label Study Evaluating the Efficacy and Safety of Mosunetuzumab in Combination with Polatuzumab Vedotin in Participants with Aggressive B-Cell Non-Hodgkin's Lymphoma

Study Rationale

The purpose of this study is to assess the efficacy and safety of mosunetuzumab in combination with polatuzumab vedotin (M + P) in participants with relapsed or refractory (R/R) diffuse-large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, transformed follicular lymphoma (trFL) and follicular lymphoma (FL) Grade 3B (FL3B) in comparison with a commonly used regimen in this participant population, rituximab, gemcitabine and oxaliplatin (R-GemOx). While there have been recent advances in treatments for patients with R/R DLBCL, including those with novel mechanisms of action, a high unmet medical need continues to exist particularly for those who are not eligible for autologous stem cell transplant (ASCT).

Objectives and Endpoints

This study will evaluate the efficacy and safety of M + P compared with R-GemOx in participants with R/R aggressive non-Hodgkin's lymphoma (aNHL), including DLBCL, high-grade B-cell lymphoma, trFL, and FL3B, who received at least one prior systemic therapy and are not candidates for ASCT.

Primary Objective	Corresponding Dual Primary Endpoints
● To evaluate the efficacy of M + P (Arm A) compared with R-GemOx (Arm B)	● ORR, defined as the proportion of participants in whom an objective response (CR or PR) was observed at any time during the study as determined by IRF ● PFS, defined as the time from randomization to the first occurrence of disease progression as determined by IRF, or death due to any cause, whichever occurs first

Secondary Objective	Corresponding Endpoints
● To evaluate the efficacy of M + P compared with R-GemOx	● ORR, defined as the proportion of participants in whom an objective response (CR or PR) was observed at any time during the study as determined by the investigator ● DOR, defined as the time from the first occurrence of a documented objective response to disease progression, or death from any cause, whichever occurs first as determined by the investigator and IRF ● OS, defined as the time from randomization to death from any cause ● PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator, or death due to any cause, whichever occurs first ● CRR, defined as the proportion of participants in whom CR was observed at any time during the study as determined by IRF and by the investigator ● DOCR, defined as the time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first. This will be determined by IRF and by the investigator. ● Time to deterioration in physical functioning and fatigue, as measured by the EORTC QLQ-C30 ● Time to deterioration in lymphoma symptoms, as measured by FACT-LymS
Safety Objective	**Corresponding Endpoint**
● To evaluate the safety and tolerability of M + P compared with R-GemOx	● Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0, including CRS, with severity determined according to the ASTCT CRS Consensus grading criteria ● Change from baseline in targeted vital signs ● Change from baseline in targeted clinical laboratory test results ● Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events ● Change from baseline in peripheral neuropathy, as measured by the FACT/GOG-Ntx

Exploratory Objectives	Corresponding Endpoint
• [redacted]	• [redacted]
Pharmacokinetic Objectives	**Corresponding Endpoint**
• [redacted]	• [redacted]
Health Status Utility Objective	**Corresponding Endpoint**
• [redacted]	• [redacted]
Immunogenicity Objectives	**Corresponding Endpoint**
• [redacted]	• [redacted]

Biomarker Objectives	Corresponding Endpoint
• [redacted] • [redacted] • [redacted] • [redacted]	• [redacted]

ADA = anti-drug antibody; [redacted] ASTCT = American Society for Transplantation and Cellular Therapy; CAR = chimeric antigen receptor; [redacted]; COO = cell-of-origin; CR = complete response; CRR = complete response rate; CRS = cytokine release syndrome; ctDNA = circulating tumor DNA; DH = double-hit lymphoma; DLBCL = diffuse-large B-cell lymphoma; DOCR = duration of complete response; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life–Core 30; FACT = Functional Assessment of Cancer Therapy; GOGNtx = Gynecologic Oncology Group–Neurotoxicity; [redacted] IRF = Independent Review Facility; LymS = lymphoma subscale; M = mosunetuzumab; [redacted] NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; P = polatuzumab vedotin; PFS = progression-free survival; PR = partial response; R-GemOx = rituximab, gemcitabine, oxaliplatin; R/R = relapsed or refractory; TBNK = T cell, B cell, natural killer cell; [redacted].

Overall Design

This is a Phase III, open-label, multicenter, randomized, controlled trial in participants with R/R DLBCL, high-grade B-cell lymphoma, trFL, or FL3B, who are not candidates for ASCT. Approximately 222 eligible participants will be randomized in 2:1 ratio to receive either M + P (Arm A) or R-GemOx (Arm B); this is the population from which the primary analysis will be performed. If China is included as a participating country, additional participants may be enrolled in an extended China enrollment cohort at China's sites, [redacted] to ensure a total of approximately [redacted] participants with R/R aNHL in a China subpopulation. The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at China's sites during that phase), and the China subpopulation will include all participants enrolled at China's sites (i.e., during both the global enrollment phase and the extended China enrollment phase).

Disclosure Statement

This is a Phase III intervention model with the primary purpose of evaluating efficacy and safety with two treatment arms that is open-label.

Number of Participants

Approximately 222 participants with R/R aNHL will be enrolled in this study. If China is included as a participating country, participants may be enrolled in an extended China enrollment cohort to ensure a total of approximately [redacted] participants in China.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Treatment

Polatuzumab Vedotin

Polatuzumab vedotin will be administered at 1.8 mg/kg IV for 6 cycles, which is the approved dose based on previous clinical studies. The total dose of polatuzumab vedotin for each participant will depend on the participant's weight on Cycle 1, Day 1 (or within 96 hours before Cycle 1, Day 1).

Mosunetuzumab

In this study, mosunetuzumab will be administered SC in a 21-day cycle with corticosteroid premedication, and a Cycle 1 step-up-dosing regimen that was established in the ongoing first-in-human Phase I/II Study GO29781 to mitigate the risk of acute toxicities (e.g., cytokine release syndrome and tumor lysis syndrome). With the Cycle 1 step-up-dosing regimen, mosunetuzumab is administered as [redacted]mg on Day 1, [redacted]mg on Day 8, and [redacted]mg on Day 15 ([redacted] mg). The target dose of [redacted]mg will be administered on Day 1 of subsequent cycles every 3 weeks. The [redacted]mg every 3 weeks (Q3W) dosing regimen is the recommended mosunetuzumab SC dosing regimen in monotherapy based on clinical data from Study GO29781.

Tocilizumab

Tocilizumab will be administered IV only to those participants who experience a CRS event for which tocilizumab is indicated.

Tocilizumab should be administered at a dose of 8 mg/kg IV (not exceeding 800 mg per infusion). The infusion should be administered IV over 60 minutes. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second dose may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time-period of 6 weeks of mosunetuzumab treatment, the total number of tocilizumab doses should not exceed 3 doses.

Rituximab

Rituximab will be administered at a dose of 375 mg/m^2 by IV infusion on Day 1 of each 14-day cycle (Cycles 1–8). The dose of rituximab should not be modified.

Gemcitabine

Gemcitabine will be administered at 1000 mg/m^2 IV on Day 1 of each 14-day cycle (Cycles 1–8). Gemcitabine should be administered before oxaliplatin on the same day. Gemcitabine should be administered in accordance with local institutional guidelines and prescribing information.

Oxaliplatin

Oxaliplatin will be administered at 100 mg/m^2 IV on Day 1 of each 14-day cycle (Cycles 1–8). Oxaliplatin should be administered after gemcitabine on the same day. Oxaliplatin should be administered in accordance with local institutional guidelines and prescribing information.

Duration of Participation

The total length of the study, from the screening of the first participant to the end of the study, is expected to be approximately 5 years.

Independent Data Monitoring Committee

An independent Data Monitoring Committee is being used.

1.2 STUDY SCHEMA

Figure 1 Study Schema

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities: Arm A

Arm A (M+P, 21-Day Cycle. Treatment Is Given Up To 8 Cycles)									
Days and Window	[redacted]								
Assessments and Procedures									
Informed consent [e]	x								
Demographic data	x								
General medical history and baseline conditions	x								
[redacted]									
ECOG PS	x	x			x	x	x	x	Q3M [c]
Concomitant medications [f]	x	x	x	x	x	x	x	x	
Adverse events [g]	x	x	x	x	x	x	x	x	
Vital signs [h, q, r]	x	x	x	x	x	x	x	x	Q3M [c]
Height, BSA, and weight [i]	x	x			x	x	x	x	
Complete physical examination [j]	x								
Targeted physical examination [k]		x	x	x	x	x	x	x	Q3M [c]
Single 12-lead ECG	x								
Radiographic evaluation [l]	x	x [l] at 8, 16, and 24 weeks (±1 week)							Q3M for the first two years on study, then at month 30 (±2 months) after Cycle 1 Day 1 [l, c]

Table 1 Schedule of Activities: Arm A (cont.)

Arm A (M + P, 21-Day Cycle. Treatment Is Given Up To 8 Cycles)									
Days and Window	[redacted]								
Assessments and Procedures									
Tumor biopsy [m, n]	x [m, n]				See footnote [m, n]			x [m, n]	
Blood sample for RBR (optional) [o]		x							
Participant-Reported Outcomes [p]		x			x	x (Cycles 3 and 5 only)	x (Cycle 7 only)	x	Q3M × 2 then Q6M [c]
Assessment of transplant eligibility status	x							x	
Survival and new anti-lymphoma therapy follow-up [d]									Q3M [d]
Study Drug Administration									
Polatuzumab vedotin [q]		x			x	x			
Mosunetuzumab [r]		x	x	x	x	x	x		

Table 1 Schedule of Activities: Arm A (cont.)

Arm A (M + P, 21-Day Cycle. Treatment Is Given Up To 8 Cycles)									
Days and Window	[redacted]								
Local Laboratory Tests [s]									
HBV, HCV, and HIV screening [t]	x								
HBV PCR (only for participants with occult or prior hepatitis B infection) [t]		Monthly testing							Q3M for 12 months
HIV viral load PCR (only for participants with a positive HIV serology test) [t]		Every 3 months (± 4 weeks)							Q6M for 12 months
Blood for EBV and CMV quantitative analysis by PCR [u]	x				x				
SARS-CoV-2 test [v]	x								
Hematology [w]	x	x	x	x	x	x	x	x	Q3M × 2 then Q6M [c]
Chemistry (serum) [x]	x	x	x	x	x	x	x	x	Q3M × 2 then Q6M [c]
C-reactive protein and serum ferritin	x	x	x	x	x	x	x	x	Q3M × 2 then Q6M [c]
Coagulation (aPTT, PT, INR)	x	x	x	x	x	x	x	x	Q3M × 2 then Q6M [c]
Pregnancy test [y]	x				x	x	x	x	
Total IgA, IgG, IgM [z]	x	Q3M, obtained at closest visit							
Central Laboratory Tests									
Blood biomarker sample		See Table 3							
Serum PK sample		See Table 3							
Serum ADA sample		See Table 3							

Table 1 Schedule of Activities: Arm A (cont.)

ADA = anti-drug antibody; [redacted] BSA = body surface area; [redacted]
CMV = cytomegalovirus; CR = complete response; CT = computed tomography (scan); ctDNA = circulating tumor DNA: D = Day; EBV = Epstein-Barr virus; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin-embedded; 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; [redacted] M = mosunetuzumab; [redacted] P = polatuzumab vedotin; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PD = progressive disease; PET = positron emission tomography (scan); PK = pharmacokinetic; PRO = participant-reported outcome; Q3M = every 3 months ± 1 month; Q6M = every 6 months; RBR = Research Biosample Repository; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Assessments are to be taken prior to study drug infusion/injection, unless otherwise specified. Pre-administration laboratory samples should be drawn 0–48 hours prior to study treatment infusion/injection.

For any dose delay resulting in a treatment-free interval of 6 weeks or longer, step-up dosing of mosunetuzumab is required with [redacted]mg administered on Day 1 of the first cycle after the dose delay (in combination with polatuzumab vedotin, if applicable), followed by the next planned dose on Day 8. The local assessments on the two dosing days should follow the Cycle 1, Day 1 and Cycle 1, Day 8 schedule, respectively.

In the event that a participant has a toxicity necessitating mosunetuzumab interruption for > 7 days prior to the Cycle 1, Day 8 dose, the participant is required to repeat the [redacted]mg mosunetuzumab (without polatuzumab vedotin) prior to resuming the planned treatment schedule (7 days after re-administration of the [redacted] mg dose). The local assessments on the two dosing days should follow the Cycle 1, Day 1 and Cycle 1, Day 8 schedule, respectively.

Please see Table 3 for additional instructions on central laboratory assessments.

[a] Screening and pretreatment tests and evaluations will be performed within 14 days preceding the first dose of study treatment. Fresh pretreatment biopsy, radiographic tumor assessment, quantitative PCR for detection of EBV and CMV, and bone marrow aspirate and biopsy (if applicable) may be performed up to 28 days preceding the first dose of study drug, providing no anti-tumor therapy was administered in this period. In addition, a serum pregnancy test should be performed within 7 days preceding the first dose of study treatment. Results of standard of care tests, radiographic tumor assessment 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. Archival tumor samples do not need to be within the 28 days screening window and are preferably obtained after the last anti-lymphoma treatment.

[b] Participants who complete the treatment period will return to the clinic for a treatment completion visit within 30 (± 7) days after the last dose of study drug. Participants who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit within 30 (± 7) days after the last dose of study drug. The visit at which response assessment shows PD may be used as the treatment discontinuation visit.

[c] Schedule corresponds to visit timepoints only for participants who complete or discontinue the study treatment but remain on the study without disease progression or new anti-lymphoma therapy. Perform assessments until disease progression, start of new anti-lymphoma therapy, withdrawal from study participation, *or until the Month 30 tumor assessment visit is completed,* whichever occurs first. Continue to follow participants on this schedule timed from the end of treatment/early termination visit (within 30 days after the last dose of mosunetuzumab administered; with the exception for tumor assessment, which is timed from Cycle 1, Day 1). Visits should occur within ± 1 month from the scheduled date. Other assessments/procedures can be performed at an earlier timepoint to align with the schedule of tumor assessment visit.

[d] When discontinued from treatment or post-treatment follow-up due to disease progression, start of new anti-lymphoma therapy, *or after completing the Month 30 tumor assessment visit,* participants should be followed for survival status and new anti-lymphoma therapy via telephone calls, participant medical records, and/or clinic visits approximately every 3 months *± 1 month* until death (unless the participant withdraws consent or the

Table 1 Schedule of Activities: Arm A (cont.)

Sponsor terminates the study). *All participants may be contacted periodically for additional survival and/or new anti-lymphoma therapy information unless the participant requests to be withdrawn from the study.* If the participant withdraws from the study, the site's staff may use a public information source (e.g., county records) to obtain information about survival status only.

[e] Informed consent must be documented before any study-specific screening procedure is performed.

[f] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 90 days after the last dose of study treatment or the initiation of next anti-lymphoma therapy, whichever is earlier. After this period, concomitant medications should be collected if they were used to manage serious adverse events that are believed to be related to prior study treatment.

[g] 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 next anti-lymphoma therapy, 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. 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 participant is lost to follow-up, or the participant 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.

[h] Includes systolic and diastolic blood pressure, respiratory rate, pulse oximetry, pulse rate, and body temperature while the participant 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.

[i] Height and BSA are required at screening only. After initiation of the study if there has been a $>$ 10% change in body weight since the last BSA assessment, BSA should be recalculated and documented in the eCRF.

[j] Complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. As part of the complete physical examination, the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly will be recorded the appropriate Tumor Assessment eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] 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 [e.g., clinical assessment for peripheral neuropathy in participants receiving polatuzumab vedotin]). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For pre-infusion timepoints, targeted physical examinations may be performed within 96 hours preceding study treatment administration unless otherwise specified.

[l] Assess response with use of image-based evaluation, using standard Lugano 2014 criteria. Positron emission tomography and diagnostic-quality CT scans are required at screening and at the interim response assessment at 8, 16 and 24 weeks ($\pm$ 1 weeks). Subsequent follow-up imaging studies should be performed every 3 months ($\pm$ 1 month) for the first two years on study, then at month 30 ($\pm$ 2 months) after Cycle 1 Day 1, until disease progression, start of new anti-lymphoma therapy, or study discontinuation, whichever is earlier. For participants who are in CR at 24 weeks, a CT scan with or without PET scan will be acceptable for subsequent scans. For participants who are not in CR at 24 weeks, continue imaging studies with PET and diagnostic-quality CT scans until CR or PD. A full tumor assessment, including radiographic assessment, must be performed any time disease progression or relapse is suspected. Scans should be performed according to the guidelines in the imaging manual provided to all sites.

[m] Submission of pretreatment biopsy tissue is mandatory. For China participants (if China participates in the study), collection of tissue samples should be in

Table 1 Schedule of Activities: Arm A (cont.)

accordance with local regulatory requirements. Tumor tissue biopsies during the study are optional.

[n] Pretreatment biopsy: Fresh pretreatment biopsy is preferred but archival tissue obtained preferably after the last anti-lymphoma treatment is acceptable if the conditions for fresh biopsy cannot be met. Biopsy tissues, whether fresh or archival, must be accompanied by the associated pathology report.

Optional during study biopsy: Obtain biopsy during the study between Cycle 1, Day 16 and Cycle 2, Day 8. A blood sample (ctDNA and PBMC) is required when a tumor biopsy is collected during the study for biomarker analysis (see Table 3 for biomarker sample collection).

Optional tumor biopsies: Additional tumor biopsies are optional and may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis).

Archival tissue samples must be accompanied by the associated pathology report. Tumor tissue samples should consist of representative tumor specimens in FFPE blocks (preferred) or at least 10 slides (preferably 15) containing unstained, freshly cut, serial sections.

[o] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for participants at participating sites who have provided written informed consent to participate. Obtain prior to study treatment.

[p] Questionnaires will be self-administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments (with the only exception of laboratory blood collection which needs to be performed prior to PRO questionnaire completion due to logistic reasons), and prior to administration of study treatment, unless otherwise specified.

[q] For polatuzumab vedotin infusions: During the administration of polatuzumab vedotin, vital signs should be assessed within 30 minutes before the start of the infusion, every 15 (± 5) minutes during the infusion, within 10 minutes after 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. For subsequent cycles, observation period can be 30 minutes. The time between the end of polatuzumab vedotin infusion and the mosunetuzumab injection should be at least 60 minutes for all cycles.

[r] For mosunetuzumab injections: Observation and vital signs with mosunetuzumab injection for Cycle 1, Day 1, 8, 15 and Cycle 2, Day 1 (or later cycle if CRS occurred during the previous cycle): check vital signs within 30 minutes pre-injection. Observe participants at least 30 minutes after injection. Check vital signs 30 (± 15) minutes after injection. Subsequent mosunetuzumab injections in the absence of CRS after last injection: check vital signs pre-injection. Observe participants at least 15 minutes. Check vital signs at least once during observation period. Participants with extended dose interruptions may need to repeat the step-up dosing when treatment is resumed. Please see Section A6–2.2 for details on the repeated step-up dosing.

[s] Details of protocol required safety laboratory assessments are listed in Table A2-1.

[t] HBsAg, HBsAb, HBcAb, HCV antibody, and HIV antibody serology are required. Participants with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable at the time of screening. These participants should be considered for prophylactic antivirals (e.g., entecavir) before and throughout the treatment, and must undergo monthly DNA testing while the patient is on treatment. During post treatment follow up, the HBV DNA testing will continue every 3 months (± 4 weeks) for 12 months after end of treatment visit. Participants who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
Participants who are positive for HIV may be eligible provided they are stable on antiretroviral therapy for at least 4 weeks, have a CD4 count ≥ 200/μL, have an undetectable viral load, and have not had a history of opportunistic infection attributable to AIDS within the last 12 months. Participants with a positive HIV result at screening should be monitored after receiving study treatment. HIV viral load will be performed every 3 months (± 4 weeks) until end of study treatment, and then every 6 months (± 4 weeks) during post treatment follow up for 12 months after end of treatment visit. If the HIV viral load is detected (positive), the participant should be treated per local institutional standards, and the Medical Monitor should be notified. Testing may be performed at the local institution. If local laboratory assessments are not available for testing, local laboratory collections may be waived only if samples are collected for central laboratory assessments of viral infections.

Table 1 Schedule of Activities: Arm A (cont.)

[u] Quantitative PCR for detection of active EBV and CMV should be performed at screening, Cycle 2, Day 1, and when clinically indicated on a peripheral blood sample per local laboratory requirements. 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.

[v] SARS-CoV-2 testing by antigen or PCR is required within 7 days prior to enrollment.

[w] Hematology includes CBC (including hemoglobin, hematocrit, RBC, WBC), platelet count, ANC, eosinophils, basophils, monocytes, absolute lymphocyte count, and other cells.

[x] Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate (or total carbon dioxide if considered standard of care for the region; may be measured using blood gas test per institutional practice), glucose, BUN or urea, creatinine, calcium, magnesium, phosphorous, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, GGT, LDH, and uric acid.

[y] All women of childbearing potential will have a serum pregnancy test at screening. Serum pregnancy should be performed within 7 days preceding the first dose of study treatment. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[z] Total IgA, IgG, IgM should be collected at least Q3M including during post-treatment follow-up period.

Table 2 Schedule of Activities: Arm B

	Arm B (R-GemOx, 14-Day Cycle)				
Arm B (Every 14 days) Days and window	[redacted]				
Assessments and Procedures					
Informed consent [e]	x				
Demographic data	x				
General medical history and baseline conditions	x				
[redacted]					
ECOG PS	x	x	x	x	Q3M [c]
Concomitant medications [f]	x	x	x	x	
Adverse events [g]	x	x	x	x	
Vital signs [h]	x	x	x	x	Q3M [c]
Height, BSA, and weight [i]	x	x	x	x	
Complete physical examination [j]	x				
Targeted physical examination [k]		x	x	x	Q3M [c]
Single 12-lead ECG	x				
Radiographic evaluation [l]	x	x [l] at 8 and 16 weeks (±1 week)			At 24 weeks and Q3M for the first two years on study, then at month 30 (±2 months) after Cycle 1 Day 1 [l, c]
Tumor biopsy [m]	x [m]	see footnote [m]		x [m]	
Blood sample for RBR (optional) [n]		x			

Table 2 Schedule of Activities: Arm B (cont.)

Arm B (R-GemOx, 14-Day Cycle)					
Arm B (Every 14 days) Days and window	[redacted]				
Participant-Reported Outcomes [o]		x	x (Cycles 2, 3, 5 ,7)	x	Q3M × 2 and then Q6M [c]
Assessment of transplant eligibility status	x			x	
Survival and new anti-lymphoma therapy follow-up					Q3M [d]
Study Drug Administration					
R-GemOx		x	x		
Local Laboratory Tests [p]					
HBV, HCV, and HIV screening [q]	x				
HBV PCR (only for participants with occult or prior hepatitis B infection) [q]		Monthly testing			Q3M for 12 months
HIV viral load PCR (only for participants with a positive HIV serology test) [q]		Every 3 months (± 4 weeks)			Q6M for 12 months
Blood for EBV and CMV quantitative analysis by PCR [r]	x		x (Cycle 2 only)		
SARS-CoV-2 test [s]	x				
Hematology [t]	x	x	x	x	Q3M × 2, then Q6M [c]
Chemistry (serum) [u]	x	x	x	x	Q3M × 2, then Q6M [c]
C-reactive protein and serum ferritin	x	x	x	x	Q3M × 2, then Q6M [c]

Table 2 Schedule of Activities: Arm B (cont.)

Coagulation (aPTT, PT, INR)	x	x	x	x	Q3M × 2, then Q6M [c]
Pregnancy test [v]	x		x	x	
Total IgA, IgG, IgM [w]	x	Q3M, obtained at closest visit			
Arm B (R-GemOx, 14-Day Cycle)					
		Cycle 1	**Cycles 2–8**		
Arm B (Every 14 days) Days and window	**Screening [a]**	**D1**	**D1 ± 2**	**Study Drug Completion or Early Discontinuation [b]**	**Post-Treatment Follow-Up [c] or Survival Follow-Up [d] after Study Drug Completion/ Discontinuation**
Central Laboratory Tests					
Blood biomarker sample		See Table 4			

[redacted] BSA = body surface area; [redacted] CMV = cytomegalovirus; CR = complete response; CT = computed tomography (scan); ctDNA = circulating tumor DNA; D = Day; EBV = Epstein-Barr virus; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin embedded; 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; [redacted] PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PD = progressive disease; PET = positron emission tomography (scan); PRO = participant-reported outcome; Q3M = every 3 months ± 1 month; Q6M = every 6 months ± 1 month; R-GemOx = Rituximab; Gemcitabine, Oxaliplatin; RBR = Research Biosample Repository; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Assessments are to be taken prior to study drug infusion/injection, unless otherwise specified. Pre-infusion laboratory samples should be drawn 0–48 hours prior to study treatment infusion/injection.

[a] Screening and pretreatment tests and evaluations will be performed within 14 days preceding the first dose of study treatment. Fresh pretreatment biopsy, radiographic tumor assessment, quantitative PCR for detection of active EBV and CMV, and bone marrow aspirate and biopsy (if applicable) may be performed up to 28 days preceding the first dose of study drug, providing no anti-tumor therapy was administered in this period. In addition, a serum pregnancy test should be performed within 7 days preceding the first dose of study treatment. Results of standard of care tests, radiographic tumor assessments 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. Archival tumor samples do not need to be within the 28 days screening window but are preferably obtained after the last anti-lymphoma treatment.

[b] Participants who complete the treatment period will return to the clinic for a treatment completion visit within 30 (±7) days after the last dose of study drug. Participants who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit within 30 (±7) days after the last dose of study drug. The visit at which response assessment shows PD may be used as the treatment discontinuation visit.

Table 2 Schedule of Activities: Arm B (cont.)

[c] Schedule corresponds to visit timepoints only for participants who complete or discontinue the study treatment but remain on the study without disease progression or new anti-lymphoma therapy. Perform assessments until disease progression, start of new anti-lymphoma therapy, withdrawal from study participation, *or until the Month 30 tumor assessment visit is completed,* whichever occurs first. Continue to follow participants on this schedule timed from the end of treatment/early termination visit (within 30 days after the last dose of mosunetuzumab administered; with the exception for tumor assessment, which is timed from Cycle 1, Day 1). Visits should occur within ±1 month from the scheduled date. Other assessments/procedures can be performed at an earlier timepoint to align with the schedule of tumor assessment visit.

[d] When discontinued from treatment or post-treatment follow-up due to disease progression*, start of* new anti-lymphoma therapy, *or after completing the Month 30 tumor assessment visit,* participants should be followed for survival follow-up and new anti-lymphoma therapy via telephone calls, participant medical records, and/or clinic visits approximately every 3 months *±1 month* until death (unless the participant withdraws consent or the Sponsor terminates the study). *All participants may be contacted periodically for additional survival and/or new anti-lymphoma therapy information unless the participant requests to be withdrawn from the study.* If the participant withdraws from the study, the site's staff may use a public information source (e.g., county records) to obtain information about survival status only.

[e] Informed consent must be documented before any study-specific screening procedure is performed.

[f] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 90 days after the last dose of study treatment or the initiation of next anti-lymphoma therapy, whichever is earlier. After this period, concomitant medications should be collected if they were used to manage serious adverse events that are believed to be related to prior study treatment.

[g] 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 next anti-lymphoma therapy, 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. 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 participant is lost to follow-up, or the participant 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.

[h] Includes systolic and diastolic blood pressure, respiratory rate, pulse oximetry, pulse rate, and body temperature while the participant 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. During the administration of rituximab 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.

[i] Height and BSA are required at screening only. After initiation of the study if there has been a >10% change in body weight since the last BSA assessment, BSA should be recalculated and documented in the eCRF.

[j] Complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. As part of the complete physical examination, the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly will be recorded on the appropriate Tumor Assessment eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be

Table 2 Schedule of Activities: Arm B (cont.)

associated with tumor assessment [e.g., lymph nodes, liver, and spleen and those systems associated with symptoms], or potential drug-related toxicity [e.g., clinical assessment for peripheral neuropathy in participants receiving polatuzumab vedotin]). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For pre-infusion timepoints, targeted physical examinations may be performed within 96 hours preceding study treatment administration unless otherwise specified.

[l] Assess response with use of image based evaluation, using standard Lugano 2014 criteria. Positron emission tomography and diagnostic-quality CT scans are required at screening and at the interim response assessment at 8, 16 and 24 weeks (±1 weeks). Subsequent follow-up imaging studies should be performed every 3 months (±1 month) for the first two years on study, then at month 30 (±2 months) after Cycle 1 Day 1, until disease progression, start of new anti-lymphoma therapy, or study discontinuation, whichever is earlier. For participants who are in CR at 24 weeks, CT scan with or without PET scan will be acceptable for subsequent scans. For participants who are not in CR at 24 weeks, continue imaging studies with PET and diagnostic-quality CT scans until CR or PD. A full tumor assessment, including radiographic assessment, must be performed any time disease progression or relapse is suspected. Scans should be performed according to the guidelines in the imaging manual provided to all sites.

[m] Submission of pretreatment biopsy tissue is mandatory. Tumor tissue biopsies are optional during the study. For China participants (if China participates in the study), collection of tissue samples should be in accordance with local regulatory requirements.

Pretreatment biopsy: Fresh pretreatment biopsy is preferred but archival tissue obtained preferably after the last anti-cancer treatment is acceptable if the conditions for fresh biopsy cannot be met. Biopsy tissues, whether fresh or archival, must be accompanied by the associated pathology report.

Optional biopsy during the study: Obtain biopsy during the study between Cycle 1, Day 16 and Cycle 2, Day 8. A blood sample (ctDNA and PBMC) is required when a tumor biopsy is collected during the study for biomarker analysis (see Table 4 for biomarker sample collection).

Optional tumor biopsies: Additional tumor biopsies are optional and may be performed at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis).

Archival tissue samples must be accompanied by the associated pathology report. Tumor tissue samples should consist of representative tumor specimens in FFPE blocks (preferred) or at least 10 slides (preferably 15) containing unstained, freshly cut, serial sections.

[n] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for participants at participating sites who have provided written informed consent to participate. Obtain prior to study treatment.

[o] Questionnaires will be self-administered before the participant receives any information on disease status, prior to the performance of non-PRO assessment (with the only exception of laboratory blood collection which needs to be performed prior to PRO questionnaire completion due to logistic reasons), and prior to administration of study treatment, unless otherwise specified.

[p] Details of protocol required safety laboratory assessments are listed in Table A2-1.

[q] HBsAg, HBsAb, HBcAb, HCV antibody, and HIV antibody serology are required. Participants with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable at the time of screening. These participants should be considered for prophylactic antivirals (e.g., entecavir) before and throughout the treatment, and must undergo monthly DNA testing while the patient is on treatment. During post treatment follow up, the HBV DNA testing will continue every 3 months (±4 weeks) for 12 months after end of treatment visit. Participants who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation. Participants who are positive for HIV may be eligible provided they are stable on antiretroviral therapy for at least 4 weeks, have a CD4 count ≥ 200/μL, have an undetectable viral load, and have not had a history of opportunistic infection attributable to AIDS within the last 12 months. Participants with a positive HIV result at screening should be monitored after receiving study treatment. HIV viral load will be performed every 3 months (±4 weeks) until end of study treatment, and then every 6 months (±4 weeks) during post treatment follow up for 12 months after end of treatment visit. If the HIV viral load is detected (positive), the participant should be treated per local institutional standards, and the Medical

Table 2 Schedule of Activities: Arm B (cont.)

Monitor should be notified. Testing may be performed at the local institution. If local laboratory assessments are not available for testing, local laboratory collections may be waived only if samples are collected for central laboratory assessments of viral infections.

[r] Quantitative PCR for detection of active EBV and CMV should be performed at screening, Cycle 2, Day 1, and when clinically indicated on a peripheral blood sample per local laboratory requirements. 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.

[s] SARS-CoV-2 testing by antigen or PCR is required within 7 days prior to enrollment.

[t] Hematology includes CBC (including hemoglobin, hematocrit, RBC, WBC), platelet count, ANC, eosinophils, basophils, monocytes, absolute lymphocyte count, and other cells.

[u] Chemistry panel (serum) includes sodium, potassium, chloride, bicarbonate (or total carbon dioxide if considered the standard of care for the region, may be measured using blood gas test per institutional practice), glucose, BUN or urea, creatinine, calcium, magnesium, phosphorous, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, GGT, LDH, and uric acid.

[v] All women of childbearing potential will have a serum pregnancy test at screening. Serum pregnancy should be performed within 7 days preceding the first dose of study treatment. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[w] Total IgA, IgG, IgM should be collected at least Q3M including post-treatment follow-up period.

Table 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm A)

Visits	[redacted]										
Timepoints	**Pre** [a]	**Post Polatuzumab vedotin** [b]	**Pre** [a]	**Pre** [a]	**Pre** [a]	**Pre** [a]	**Pre** [a]	**Post Polatuzumab vedotin** [b]			
Rituximab and Obinutuzumab PK (serum) [f]	x										
Mosunetuzumab PK (serum)	x [g, h]		x [g]	x	x	x	x		x	x	
Polatuzumab vedotin for total Antibody PK (serum)	x [g]	x [g]			x		x	x	x	x	
Polatuzumab acMMAE and MMAE PK (plasma) [i]	x [g]	x [g]			x		x	x		x	
Mosunetuzumab ADA (serum)	x [g, h]				x		x		x	x	
Polatuzumab vedotin ADA (serum)	x [g]				x		x		x	x	
ctDNA (plasma) [j]	x [g, h]				x	x	x		x	x	x

Visits	[redacted]								[redacted]		
Timepoints	**Pre** [a]	**Post Polatuzumab vedotin** [b]	**Pre** [a]	**Pre** [a]	**Pre** [a]	**Pre** [a]	**Pre** [a]	**Post Polatuzumab vedotin** [b]			
PBMC [j] (whole blood)	x [g, h]				x	x	x	x	x	x	x
TBNK (whole blood)	x [g, h]				x	x	x		x	x	x
Cytokines (plasma)	x [g, h]	x [g, h]	x [g]	x	x						

acMMAE = antibody-conjugated monomethyl auristatin E; ADA = anti-drug antibody; ctDNA = circulating tumor DNA; MMAE = monomethyl auristatin E; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; TBNK = T-cell, B-cell and natural killer cell.

Note: For any dose delays resulting in a treatment free interval ≥ 6 weeks, repeat step-up dosing of mosunetuzumab is required, with [redacted]mg administered on Day 1 of the first cycle after the dose delay (in combination with polatuzumab vedotin, if applicable), followed by the next planned dose on Day 8.

In the event that a participant has a toxicity necessitating mosunetuzumab interruption for >7 days prior to the Cycle 1, Day 8 dose, the participant is required to repeat the [redacted]mg dose prior to resuming the planned treatment schedule (7 days after the administration of the [redacted]mg dose). The schedule of PK, ADA and biomarker samples after treatment resumption is described in the footnotes. Rituximab and/or obinutuzumab collections are not required for participants who need to repeat step- up dosing.

[a] ≤ 8 hours prior to the first study drug administration.

[b] 0–30 minutes after the end of infusion of polatuzumab vedotin.

[c] Anytime between Cycle 8, Day 15 and Cycle 8, Day 35.

[d] When discontinuation is decided.

[e] Every 3 months ± 1 month starting from 90 days after the treatment completion for the first 2 years on study and then at month 30 (± 2 months) after Cycle 1 Day 1, or until disease progression or treatment with a new anti-lymphoma therapy, whichever occurs first. Obtain samples at the closest corresponding scans or visits.

[f] The serum sample can be split into 2 samples for analysis of rituximab and obinutuzumab PK analysis.

Table 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm A) (cont.)

[g] For any dose delay resulting in a treatment-free interval of 6 weeks or longer, step-up dosing of mosunetuzumab is required with [redacted]mg administered on Day 1 of the first cycle after the dose delay (in combination with polatuzumab vedotin, if applicable), followed by the next planned dose on Day 8. The PK, ADA and biomarker sample collection on the two dosing days should follow the Cycle 1, Day 1 and Cycle 1, Day 8 schedule, respectively.

[h] In the event that a participant has a toxicity necessitating mosunetuzumab interruption for > 7 days prior to the Cycle 1, Day 8 dose, the participant is required to repeat the [redacted]mg mosunetuzumab (without polatuzumab vedotin) prior to resuming the planned treatment schedule (7 days after re-administration of the [redacted]mg dose). The PK, ADA and biomarker sample collection on the dosing day of the repeated [redacted]mg dose should follow the Cycle 1, Day 1 schedule.

[i] The plasma sample will be split into 2 samples for analyses of antibody-conjugated MMAE and unconjugated MMAE.

[j] ctDNA and PBMC samples will be collected at time points in the table and when an on-treatment biopsy is collected.

Table 4 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm B)

Visits	[redacted]						
Timepoints	**Pre [a]**	**Pre [a]**	**Pre [a]**	**Pre [a]**			
ctDNA [e] (plasma)	x	x	x	x	x	x	x
PBMC [e] (whole blood)	x	x	x	x	x	x	x
TBNK (whole blood)	x	x	x	x	x	x	x

ctDNA = circulating tumor DNA; PBMC = peripheral blood mononuclear cell; TBNK = T cell, B cell, natural killer cell.

Pharmacokinetic or immunogenicity evaluation is not required in participants in Arm B.

[a] ≤ 8 hours prior to the first study drug administration.

[b] Anytime between Cycle 8, Day 15 and Cycle 8, Day 35.

[c] When discontinuation is decided.

[d] Every 3 months (± 1 month) starting from 90 days after the treatment completion for the first 2 years on study, then at month 30 (± 2 months) after Cycle 1 Day 1, or until disease progression or treatment with a new anti-lymphoma lymphoma therapy, whichever occurs first. Obtain samples at the closest corresponding scans or visits.

[e] ctDNA and PBMC samples will be collected at timepoints in the table and when an on-treatment biopsy is collected.

Table 5 Schedule for Tocilizumab Treatment of Cytokine Release Syndrome

Assessment/Procedure [a]	Pre-TCZ Tx (within 24 hours)	TCZ IV Admin.	Post-TCZ Treatment [b, c]
TCZ administration (8 mg/kg [not exceeding 800 mg per infusion])		x	
Vital signs [d]	x [e]		Measure at least once daily or more as clinically indicated until resolution of CRS
Pressor documentation [f]	x [e]		
FiO_2	x [e]		
Pulse oximetry, resting	x [e]		
Local Laboratory Assessments			
Hematology	x		Measure at least once daily or more as clinically indicated until resolution of CRS
Liver function tests (AST, ALT, total bilirubin)	x		
Serum chemistry and creatinine [g]	x		
CRP, LDH, and serum ferritin	x		
Coagulation (aPTT, PT/INR, fibrinogen)	x		Measure at least once every 2 days or more as clinically indicated until resolution of CRS
Infection workup [h]	x		
Central Laboratory Assessments			
Serum cytokines [i]	x		15 (±5) minutes after completion of TCZ. Then 6 (±0.5) hours later, then 1, 2, 3 and 8 days later
Serum TCZ PK [i]	x		15 (±5) minutes after completion of TCZ. Then 6 (±0.5) hours later, then 1, 2, 3 and 8 days later. And approximately 8 weeks later.
Serum TCZ ADA	x		Approximately 8 weeks after

Table 5 Schedule for Tocilizumab Treatment of Cytokine Release Syndrome (cont.)

ADA = anti-drug antibodies; Admin. = administration; CRP = C-reactive protein; CRS = cytokine release syndrome; EBV = Epstein-Barr virus; eCRF = electronic Case Report Form; FIO_2 = fraction of inspired oxygen; LDH = lactate dehydrogenase; PK = pharmacokinetic; T/B/NK = T cell/B cell/natural killer cell; TCZ = tocilizumab; Tx = treatment.

Note: Record abnormalities or worsened clinically significant abnormalities on the Adverse Event eCRF.

[a] An assessment/procedure may be waived if a participant is hospitalized at a facility that does not have the capacity to perform the study assessment. Hospitalization should not be prolonged to perform study assessments in this schedule of assessments.

[b] If the TCZ dose is repeated, follow the same collection schedule to collect post-TCZ treatment samples after 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±48 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 participant 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, 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] Blood draws performed 15 minutes after the completion of TCZ infusion should not be drawn from the same line that was used to administer TCZ.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of mosunetuzumab in combination with polatuzumab vedotin (M + P) in participants with relapsed or refractory (R/R) diffuse-large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, transformed follicular lymphoma (FL) and FL Grade 3B (FL3B) in comparison with a commonly used regimen in this participant population, rituximab, gemcitabine and oxaliplatin (R-GemOx). While there have been recent advances in treatments for patients with R/R DLBCL, including those with novel mechanisms of action, a high unmet medical need continues to exist particularly for those who are not eligible for autologous stem cell transplant (ASCT).

2.2 BACKGROUND

Diffuse-large B-cell lymphoma is the most common aggressive form of non-Hodgkin's lymphoma (NHL; Armitage and Weisenburger 1998). Additionally, each year, around 3% of FLs transform into a higher-grade NHL, most commonly DLBCL (Lossos and Gascoyne 2011), leading to histologic transformation in one-third of patients in 10 years. These transformed follicular lymphoma (trFL), as well as the high-grade form of FL, namely FL3B, are treated with the same standard therapies as high-grade lymphomas.

While a majority of patients are cured with the combination of chemoimmunotherapy, the management of R/R disease can be challenging. For these patients, high-dose chemotherapy followed by ASCT offers an additional chance for a cure, but more than half of the patients who are considered for ASCT will experience R/R disease due to insufficient response to salvage therapy or relapsed disease after ASCT (Seyfarth et al. 2006; Gisselbrecht et al. 2010). Moreover, older and more frail patients are often ineligible for ASCT. Outcomes for patients who are not eligible for ASCT are poor (Thieblemont and Coiffier 2007) after available therapy such as R-GemOx (Mounier et al. 2013) or the combination of bendamustine and rituximab (BR; Ohmachi et al. 2013).

Mosunetuzumab (RO7030816; BTCT4465A), is a full length, humanized anti-cluster of differentiation (CD)20/CD3 bispecific IgG1 antibody (Atwell et al. 1997; Spiess et al. 2013) engineered for minimal binding to fragment crystallizable (Fc)-γ receptors. CD20 is a validated target in B-cell NHL, which provides a rationale for the development of a T−cell-recruiting bispecific antibody targeting CD20 for the treatment of these diseases. Mosunetuzumab has shown single-agent activity in indolent and aggressive NHL (aNHL), and has a manageable safety profile, which makes it an attractive agent to evaluate in combination with other agents. Mosunetuzumab (Lunsumio®) as a monotherapy has been approved by the European Commission (conditional marketing authorization) and by the FDA (accelerated approval) for the treatment of adult patients with R/R FL who have received at least two

prior systemic therapies. Clinical development is ongoing for additional indications including aNHL.

Polatuzumab vedotin (DCDS4501S) is an antibody-drug conjugate (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. 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 NHLs and chronic lymphocytic leukemias (CLLs; Dornan et al. 2009). Relating specifically to DLBCL, CD79b is expressed by essentially all tumor cells (Olejniczak et al. 2006; Pfeifer et al. 2015), enabling its use as a target in all subtypes of DLBCL, independent of dominant signaling pathways. Antibodies bound to CD79b are rapidly internalized, making CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007; 2009). Polatuzumab vedotin has shown single-agent activity in indolent and aggressive NHLs and has a manageable safety profile.

Polatuzumab vedotin in combination with BR is approved for the treatment of R/R DLBCL in many countries, including the European Union and the United States. Polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) has been approved by the European Commission for the treatment of adult patients with previously untreated DLBCL. On 19 April 2023, the FDA approved polatuzumab vedotin in combination with R-CHP for treatment of adult patients who have previously untreated DLBCL, not otherwise specified (NOS) or high-grade B-cell lymphoma and who have an International Prognostic Index (IPI) score of 2 or greater.

Detailed information on mosunetuzumab and polatuzumab vedotin is provided in the Mosunetuzumab and Polatuzumab Vedotin Investigator's Brochures.

2.3 BENEFIT-RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of M + P, to address a significant unmet medical need in patients with R/R DLBCL, high-grade B-cell lymphoma, trFL, and FL3B.

Mosunetuzumab administered as a single agent has shown an acceptable safety profile and promising activity in a Phase I/II clinical trial (Study GO29781) in participants with B-cell NHL. Identified risks of mosunetuzumab include cytokine release syndrome (CRS), neutropenia, infections, injection-site reactions, tumor lysis syndrome (TLS), tumor flare*, neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), hemophagocytic lymphohistiocytosis (HLH)*. Potential risks of mosunetuzumab include thrombocytopenia, elevated liver enzymes, and immunogenicity (ADAs).

Polatuzumab vedotin has shown an acceptable safety profile and clinical activity administered as either a single agent (Study DCS4968g), in combination with an anti-CD20 antibody (Study GO27834) or in combination with BR (Study GO29365; see Section 4.2.1) in B-cell NHL. Identified risks of polatuzumab vedotin include myelosuppression, peripheral neuropathy, infections, infusion-related reactions (IRRs) and gastrointestinal toxicity. Potential risks of polatuzumab vedotin are TLS, immunogenicity, reproductive toxicity, hyperglycemia, hepatoxicity and carcinogenicity. See the Polatuzumab Vedotin Investigator's Brochure for details of risks associated with polatuzumab vedotin.

A nonclinical mouse xenograft model of human B-cell lymphoma has shown that M + P showed synergistic anti-lymphoma activity. Supported by this data, the combination of mosunetuzumab (IV) and polatuzumab vedotin has been tested in participants with R/R B-cell NHL in a Phase Ib/II trial (Study GO40516), showing promising safety and efficacy (Budde et al. 2021).

See Appendix 6 for information on anticipated risks for mosunetuzumab and polatuzumab vedotin and risk mitigation measures, including guidelines for managing adverse events associated with mosunetuzumab and polatuzumab vedotin.

More detailed information about the known and expected benefits and risks of mosunetuzumab and polatuzumab vedotin may be found in the respective Investigator's Brochures.

Considering the poor prognosis of patients with R/R DLBCL, the efficacy data of M + P in this participant population with R/R DLBCL, the safety profile for mosunetuzumab and polatuzumab vedotin administered as monotherapy, and the risk mitigation measures for the study, the benefit–risk ratio is expected to be acceptable for M + P in the treatment setting of R/R DLBCL.

2.3.1 COVID-19 Benefit-Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, participants with comorbidities, including those with DLBCL, may be a more vulnerable participant population; however, it is unclear whether or how cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of COVID-19. Severe COVID-19 is associated with dysregulated immune response involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ. Participants with known active severe acute respiratory syndrome (SARS–CoV-2) infection will be excluded from the study (Section 5.2) and guidance on the risk of infection is provided in Appendix 6. Both mosunetuzumab and polatuzumab vedotin are B–cell-targeted therapies and mosunetuzumab has the identified risk of CRS. However, it is not known if there may be a potential for an increased risk of an enhanced inflammatory response in case of a SARS–CoV-2 infection while receiving mosunetuzumab.

CRS is a risk for mosunetuzumab that occurs most commonly during step-up dosing. Many COVID-19 vaccines are highly immunogenic and the associated risk of potentiating CRS is unknown.

Based on the mechanism of action and role of B-cells immune response, participants may have an increased risk of SARS−CoV-2 infection during CD20 targeted therapy.

Investigators should highlight to study participants the precautions that can prevent or mitigate SARS-CoV-2 infections (e.g., masking, social distancing, avoiding close contact with anyone infected with SARS-CoV-2, and informing their health care provider or general practitioner about close contacts and/or at first signs of infection).

To reduce the risk of COVID-19 during the study, administration of COVID-19 prophylaxis with the use of available agents in accordance with local institutional guidance (including but not limited to vaccines and monoclonal antibodies) is recommended before initiation of study treatment (El Chaer et al. 2022; see Section 6.8.1).

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of M + P compared with R-GemOx in participants with R/R aNHL, including DLBCL, high-grade B-cell lymphoma, trFL, and FL3B, who received at least one prior systemic therapy and are not candidates for ASCT. Specific objectives and corresponding endpoints for the study are outlined in Table 6.

In this protocol, "study treatment" refers to the combination of treatments assigned to participants as part of this study (i.e., M + P and R-GemOx).

Table 6 Objectives and Corresponding Endpoints

Primary Objective	
Efficacy Objective	**Corresponding Dual Primary Endpoint*s***
• To evaluate the efficacy of M + P (Arm A) compared with R-GemOx (Arm B)	• ORR, defined as the proportion of participants in whom an objective response (CR or PR) was observed at any time during the study as determined by IRF • PFS, defined as the time from randomization to the first occurrence of disease progression as determined by IRF, or death due to any cause, whichever occurs first
Secondary Objectives	
Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of M + P compared with R-GemOx	• ORR, defined as the proportion of participants in whom an objective response (CR or PR) was observed at any time during the study as determined by the investigator • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, or death from any cause, whichever occurs first as determined by the investigator and IRF • OS, defined as the time from randomization to death from any cause • PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator, or death due to any cause, whichever occurs first • CRR, defined as the proportion of participants in whom CR was observed at any time during the study as determined by IRF and by the investigator • DOCR, defined as the time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first. This will be determined by IRF and by investigator. • Time to deterioration in physical functioning and fatigue, as measured by the EORTC QLQ-C30 • Time to deterioration in lymphoma symptoms, as measured by FACT-LymS

Table 6 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of M + P compared with R-GemOx	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0, including CRS, with severity determined according to the ASTCT CRS Consensus grading criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events • Change from baseline in peripheral neuropathy, as measured by the FACT/GOG-Ntx
Exploratory Objectives	
Efficacy Objective	**Corresponding Endpoints**
• [redacted]	• [redacted]
Pharmacokinetic Objectives	**Corresponding Endpoints**
• [redacted]	• [redacted]
Health Status Utility Objective	**Corresponding Endpoint**
• [redacted]	• [redacted]

Table 6 Objectives and Corresponding Endpoints (cont.)

Immunogenicity Objective	Corresponding Endpoints
• [redacted]	• [redacted] • [redacted]
Biomarker Objectives	**Corresponding Endpoints**
• [redacted] • [redacted] • [redacted] • [redacted]	• [redacted]

ADA = anti-drug antibody; [redacted] ASTCT = American Society for Transplantation and Cellular Therapy; CAR = chimeric antigen receptor; [redacted]; COO = cell-of-origin; CR = complete response; CRR = complete response rate; CRS = cytokine release syndrome; ctDNA = circulating tumor DNA; DH = double-hit lymphoma; DLBCL = diffuse-large B-cell lymphoma; DOCR = duration of complete response; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life–Core 30; FACT = Functional Assessment of Cancer Therapy; GOGNtx = Gynecologic Oncology Group–Neurotoxicity; [redacted]; IRF = Independent Review Facility; LymS = lymphoma subscale; M = mosunetuzumab; [redacted] NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; P = polatuzumab vedotin; PFS = progression-free survival; PR = partial response; R-GemOx = rituximab, gemcitabine, oxaliplatin; R/R = relapsed or refractory; TBNK = T cell, B cell, natural killer cell; [redacted]

4. STUDY DESIGN

4.1 OVERALL DESIGN

4.1.1 Overview of Study Design

This is a Phase III, open-label, multicenter, randomized, controlled trial in participants with R/R DLBCL, high-grade B-cell lymphoma, trFL, or FL3B, who are not candidates for ASCT. Approximately 222 eligible participants will be randomized in a 2:1 ratio (see Section 4.2.3) to receive either M+P (Arm A) or R-GemOx (Arm B); this is the population from which the primary analysis will be performed. If China is included as a participating country, additional participants may be enrolled in an extended China enrollment cohort at China's sites, [redacted], to ensure a total of approximately [redacted] participants with R/R aNHL in a China subpopulation. The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at China's sites during that phase), and the China subpopulation will include all participants enrolled at China's sites (i.e., during both the global enrollment phase and the extended China enrollment cohort).

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 and Table 3 [Arm A]; Table 2 and Table 4 [Arm B]).

4.1.1.1 Randomization

Participants in this trial will be stratified at the time of randomization for the following 2 factors:

- Number of previous lines of systemic therapy for aggressive lymphoma (1 vs. ≥2)
- Outcome after last systemic therapy (relapsed vs. refractory)
  - Relapsed disease in this study is defined as disease that has recurred after having a documented history of response (CR or PR) ≥6 months in duration from completion of the last treatment.
  - Refractory disease is defined as disease that either did not respond to, or progressed within 6 months (<6 months) of last treatment.

4.1.1.2 Arm A Treatment (Mosunetuzumab+Polatuzumab Vedotin)

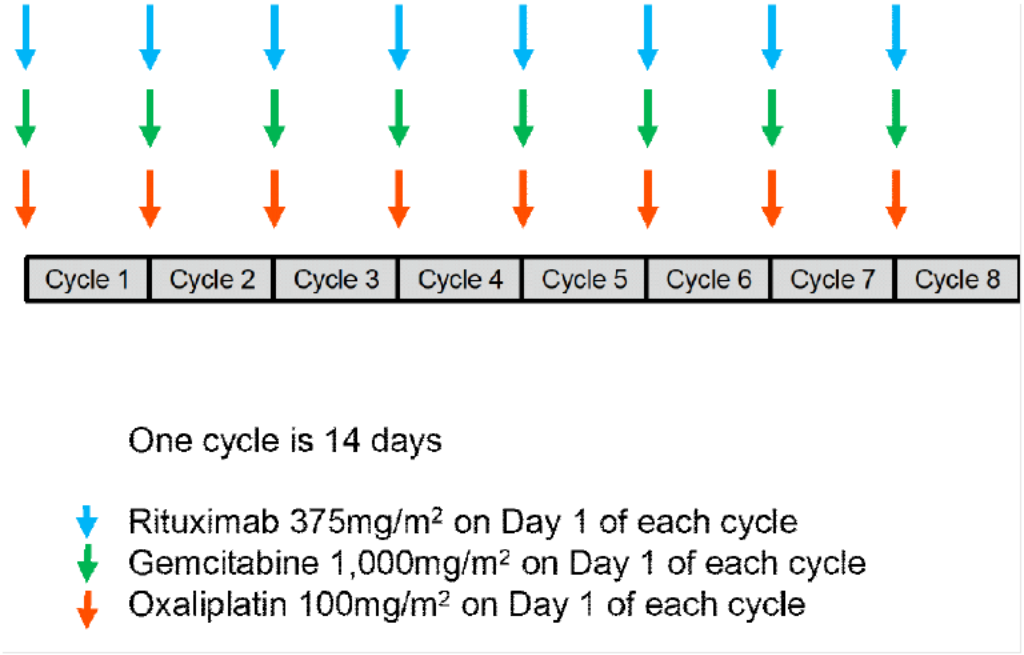
The Arm A treatment consists of mosunetuzumab administered subcutaneous (SC) and polatuzumab vedotin administered IV (see Figure 2). One cycle of treatment is 21 days. Mosunetuzumab will be administered [redacted] mg SC on Cycle 1, Day 1; [redacted] mg on Cycle 1, Day 8; Cycle 1, Day 15; and Day 1 of Cycles 2–8. Polatuzumab vedotin will be administered IV at 1.8 mg/kg on Day 1 of Cycles 1–6. Prophylactic (preemptive) or therapeutic use of granulocyte colony-stimulating factor (G-CSF) is permitted at the treating physician's discretion. Dosing will occur if a participant's clinical assessment and laboratory test values are acceptable, including peripheral neuropathy and other treatment related adverse events resolved to Grade ≤1, ANC ≥1000/mm^3 and platelet

count ≥75,000/mm^3 (see Section A6–2.2). Details of each drug administration are described in Section 6.1.

4.1.1.3 Arm B Treatment (Rituximab, Gemcitabine, Oxaliplatin)

The Arm B treatment consists of R-GemOx (see Figure 3). One cycle of treatment is 14 days. Rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2, and oxaliplatin 100 mg/m^2 will be administered IV on Day 1. Gemcitabine should be administered before administration of oxaliplatin. Prophylactic (preemptive) or therapeutic use of G-CSF is permitted at the treating physician's discretion. Dosing will occur if a participant's clinical assessment and laboratory test values are acceptable, including treatment-related adverse events resolved to Grade ≤1, ANC ≥1000/mm^3 and platelet count ≥75,000/mm^3 (see Section A6–2.2). If these required hematologic parameters are not met within 2 weeks after the last treatment, the treatment will be delayed. If such a delay occurs, it is acceptable to change the treatment cycle to every 21 days, instead of 14 days for the subsequent treatment. Treatment is administered for up to 8 cycles. Details of each drug administration is described in Section 6.1.

Figure 3 Arm B (Rituximab, Gemcitabine, Oxaliplatin) Dose and Schedule



Note: The cycle duration may be adjusted in case of delays.

4.1.1.4 Assessment During the Study

All participants will be monitored for adverse events, clinical laboratory test results and vital signs throughout the study and for at least 90 days after the final dose of study treatment or the initiation of next anti-lymphoma therapy, whichever is earlier (see Section 8.3.1). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, except for CRS severity, which will be determined per the American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading criteria (Lee et al. 2019; Appendix 11). *New events of ICANS and HLH that occur after approval of Protocol Version 5 will continue to be graded according to NCI CTCAE v5.0. In addition, ASTCT grading (Appendix 21 for ICANS and Table A6-8 for HLH) should be provided when describing the case within the additional case details of the Adverse Events eCRF (refer to the eCRF completion guidelines for additional details).* Response assessments will be performed according to the 2014 Lugano Response Criteria (Cheson et al. 2014; Appendix 10), as assessed on positron emission tomography (PET)/computed tomography scans. A schedule of activities is provided in Section 1.3. To characterize the pharmacokinetic (PK) profile and immune response in response to study treatment, blood samples will be taken at various timepoints before and after dosing (see Section 1.3, Table 3 and Table 4).

4.1.1.5 Continued Treatment of Non-Hodgkin Lymphoma in Arm A After Suspected Disease Progression

Experience with cancer immunotherapy for solid tumors has demonstrated that responding tumors may initially increase in size due to the influx of immune cells, a phenomenon known as “pseudoprogression” (Wolchok et al. 2009). Pseudoprogression has also been described in the context of lymphoma (Cheson et al. 2016; Salles et al. 2016), and similarly it is possible that mosunetuzumab and/or polatuzumab vedotin therapy may initially increase tumor size and metabolic activity by inducing the influx of T-cells into the tumor. Given this, a repeat tumor biopsy, if clinical disease progression is observed, is strongly encouraged. Additionally, if the study investigator believes that a participant with NHL receiving mosunetuzumab is deriving clinical benefit despite radiographic evidence of PD as defined by the Lugano 2014 criteria (Appendix 10), that participant in Arm A may continue study treatment provided the following criteria are met:

- There is an absence of symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease.
- There is no decline in Eastern Cooperative Oncology Group Performance Status (ECOG PS).
- There is an absence of tumor progression at critical anatomical sites including the central airway, the great vessels, and other organs or tissues where compromised function secondary to tumor progression would be expected to result acutely in severe and/or irreversible disability or death.

Participants must provide written consent to acknowledge discussion with the treating investigator of the benefit-risk balance of continuing study treatment in Arm A beyond radiographic progression. Participants continuing study treatment despite apparent radiographic progression will be strongly encouraged to undergo a repeat tumor biopsy to assess whether increases in tumor volume are due to immune cell infiltration or neoplastic proliferation, provided that such a biopsy can be performed safely on a non-target lesion. If true progression is suspected based on the investigator’s judgment, clinical factors, or biopsy findings that are consistent with neoplastic proliferation, or if radiographic disease progression is confirmed at a subsequent tumor assessment, the participant will be ineligible to receive further study treatment.

4.1.2 Independent Review Facility

An Independent Review Facility (IRF) will perform a centralized, independent review of images, and other clinical data as needed, prior to the efficacy analyses. Independent Review Facility membership and procedures will be detailed in an IRF charter. The IRF will be used to evaluate the study endpoints of progression-free survival (PFS), complete response rate (CRR), duration of response (DOR), duration of complete response (DOCR), and objective response rate (ORR) in a blinded manner.

4.1.3 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will evaluate safety and efficacy data periodically during the study. The analysis supporting iDMC review will be conducted by an independent Data Coordinating Center and provided to the iDMC. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

After each safety review, the iDMC may recommend continuing, modifying, stopping the study, or putting the study on hold pending further iDMC recommendation, as defined in the iDMC charter.

[redacted] If any of the following criteria are met, then accrual to the study will be paused and the iDMC will conduct a comprehensive review of safety data and may recommend continuing, modifying, or stopping the study.

The first iDMC review will occur after a minimum of [redacted] participants (approximately [redacted] participants in Arm A and approximately [redacted] participants in Arm B) receive [redacted] cycles of treatment. The safety monitoring parameters and the predefined stopping rules include:

- [redacted]
- [redacted]
- [redacted]

After the first iDMC review, reviews of safety data by iDMC will occur approximately every [redacted] months until the prespecified timepoint defined in the iDMC charter.

Two reviews of overall survival (OS) data by the iDMC will be performed for futility assessment. The first OS futility analysis by the iDMC will be conducted when there are approximately [redacted] OS events observed. The second OS futility analysis by the iDMC will be conducted at the time of the dual primary endpoint ORR analysis.

One futility analysis of progression-free survival (PFS) by IRF will be performed by the iDCC for iDMC review on the first [redacted] randomized participants at the time of the dual primary endpoint ORR analysis when the first [redacted] randomized participants have a minimum of [redacted] months of follow-up from the first response assessment.

The safety monitoring parameters and the predefined stopping rules include:

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs)/Ethics Committees (ECs).

4.2 RATIONALE FOR STUDY DESIGN

This study will enroll participants with a history of hematologic malignancy that is expected to express the CD20 antigen and CD79b antigen, specifically DLBCL, high-grade B-cell lymphoma, trFL, and FL3B. Local assessment to confirm CD20 expression is required during screening. Central confirmation of CD20 expression will not be required during eligibility screening prior to enrollment, but it will be evaluated retrospectively.

4.2.1 Rationale for Study Population

Up to 40% of patients with DLBCL who are treated in the first-line setting will experience disease progression within 3–4 years (Friedberg 2011), and more than half of the patients treated with second-line therapies do not achieve a complete remission (Gisselbrecht et al. 2010). Furthermore, since the introduction of the monoclonal anti-CD20 antibody rituximab, it has become more challenging to find effective therapies for the large proportion of patients with R/R DLBCL who have prior exposure to anti-CD20 antibody.

Each year around 3% of FLs transform into higher-grade NHL, most commonly DLBCL (Lossos and Gascoyne 2011), leading to almost a third of histologic transformation in 10 years. These patients with DLBCL transformed from a previous FL histology and have been treated with the same standard therapies as high-grade lymphomas. The study includes participants with this disease.

Follicular lymphoma Grade 3B is a distinct subgroup of FL that is more in common genetically, immunophenotypically, and clinically with DLBCL than with other indolent FLs, and the coexistence with DLBCL is frequent (Harris and Kluin 2011). The clinical course of patients with FL3B is similar to those with DLBCL, and FL3B is commonly treated as DLBCL (National Comprehensive Cancer Network [NCCN] 2020). Therefore, the study includes participants with FL3B in the primary analysis.

Several novel therapeutic agents have been approved for the management of R/R DLBCL in some countries.

Polatuzumab Vedotin, an ADC Targeting CD79b

In the randomized, Phase II part of Study GO29365 that evaluated participants with R/R DLBCL who were transplant-ineligible, polatuzumab vedotin in combination with BR

(n = 40) showed significant and clinically meaningful efficacy benefit over BR alone (n = 40) marked by a CRR at the end of the treatment (40.0% vs. 17.5%; p = 0.026), PFS (median 9.5 months vs. 3.7 months; $p < 0.001$) both assessed by IRF, and OS (median 12.4 months vs. 4.7 months; p = 0.002; Sehn et al. 2019).

Tafasitamab, a Humanized Anti-CD19 Monoclonal Antibody

Tafasitamab in combination with lenalidomide was evaluated in 81 participants with R/R DLBCL after receiving at least one line of therapy. The best response rate was 60%, including a best CRR of 43%, with a median DOR of 21.7 months (Salles et al. 2020). While the response rates and the duration of therapy were clinically significant, the study excluded or limited enrollment of a very high-risk population such as participants with primary refractory disease and double-hit lymphoma, and thus, provides a limited benefit in the area of the highest unmet medical need.

Selinexor®, an XPO1 Inhibitor

Selinexor was evaluated in 127 participants with R/R DLBCL (Kalakonda et al. 2020). Grade 3/4 thrombocytopenia was observed in 46% of participants. The ORR was 29%, including a CRR of 13%. While this is an oral dosing regimen with significant convenience, the untrivial myelosuppression and the low response rates may limit the actual use of this regimen in this setting.

Zynlonta® (loncastuximab tesirine), an ADC Targeting CD19

Loncastuximab tesirine was evaluated in 145 participants with R/R DLBCL after at least one line of therapy (Caimi et al. 2021). The best response rate was 48.3%, including a best CRR of 24.1%, with a median DOR of 10.3 months.

CD19 Chimeric Antigen Receptor (CAR) T cells

In addition, CD19-directed chimeric antigen receptor (CAR) T-cell therapies have become available in some countries (axicabtagene ciloleucel, tisagenlecleucel, and Breyanzi® [lisocabtagene maraleucel]). While these therapies have shown efficacy with durable CRs, their use may be limited for the general population with R/R DLBCL due to the toxicity profile which requires carefully selected participants and treatment in centers with specially trained staff. In addition, the waiting period associated with CAR T manufacture may be prohibitive in participants with rapidly progressing disease.

Despite the above-mentioned improvement in the therapeutic approaches in R/R DLBCL, the clinical outcome of patients with this condition, especially those who are not eligible for transplant, is still poor. Of note, tafasitamab, loncastuximab tesirine and CAR T products target the same antigen, CD19, raising the concern for potential cross resistance. Taken together, there remains a significant unmet medical need for patients with transplant-ineligible R/R DLBCL.

4.2.2 Rationale for Control Group

The type of control group in this study is an active treatment concurrent control. In participants with R/R DLBCL who are not candidates for ASCT, R-GemOx is a recommended regimen in the NCCN Guideline 2021. Given the established role as a commonly used therapy for patients with R/R DLBCL who are not candidates for ASCT, the R-GemOx regimen, as described by Mounier et al. (2013) serves as a reasonable option for the active treatment concurrent control. The study intends to show the difference in the PFS between participants treated with M+P and those treated with R-GemOx.

4.2.3 Rationale for Randomization Ratio

This study plans to enroll more participants into Arm A (M+P) than Arm B (R-GemOx) using the randomization ratio of 2:1. Unequal allocation of participants in randomized cancer clinical trials is used to ensure a larger population of participants is exposed to experimental treatment to assess adverse events known to be associated with the experimental agent. Because of the potentially serious nature of CRS with T−cell-engaging therapies such as mosunetuzumab, and because this trial represents the first randomized study utilizing mosunetuzumab in combination with polatuzumab vedotin, increasing exposure in the experimental arm would be beneficial to fully inform the safety profile of this combination therapy and management guidelines in the event that this fully powered trial meets its primary efficacy endpoint.

In Arm J of the clinical Study GO40516, mosunetuzumab given IV in combination with polatuzumab vedotin in participants with R/R DLBCL showed an ORR of 66% and CR rate of 49% based on 41 patients as of a clinical cutoff date [CCOD] of 15 March 2021. The Phase II study of R-GemOx (Mounier et al. 2013) showed an ORR of 55% and CR rate of 42% in 31 participants with R/R DLBCL who had been previously treated with rituximab; the median PFS and median OS was 4 months and 8 months, respectively. In the recent retrospective analysis of real-world data in participants with R/R DLBCL treated with R-GemOx, an end of treatment ORR of 38% and CR rate of 33% (Cazelles et al. 2021) was observed. The median PFS of R-GemOx in this population was 5 months and the median OS was 10 months. The difference in the response rates demonstrates the potentially meaningful benefit for participants to receive mosunetuzumab in combination with polatuzumab vedotin.

4.2.4 Rationale for Biomarker Assessments

Predictive and prognostic biomarkers, including biomarkers associated with disease biology, drug targets, the mechanism of action of the individual components or the synergistic activity of the combination may correlate with the outcome in participants with R/R DLBCL, high-grade B-cell lymphoma, trFL and FL3B treated in this study. Tumor biopsies will be obtained at baseline from participants with safely accessible tumors as detailed in Section 8.1.1 to assess tumor and tumor-immune microenvironment profiles using technologies such as immunohistochemistry (IHC),

gene expression or mutation profiling to evaluate associations with the drugs, prognostic subtypes or outcomes.

Additionally, exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

A loss of CD20 expression after mosunetuzumab treatment is a potential mechanism of resistance to anti-CD20 therapy, potentially similar to antigen-loss escape resistance mechanisms observed with other T-cell bispecific therapies (Topp et al. 2011). A repeat biopsy from a safely accessible tumor site should be considered at the time of disease progression after M+P treatment, which may be used to confirm CD20 expression and the status of lymphoma-infiltrating T cells.

In addition to the exploratory objectives listed above, specimens (if consent is given) stored in the Research Biosample Repository (RBR) will also be used for the following:

- To evaluate the association of biomarkers with efficacy and/or adverse events associated with M+P
- To increase the knowledge and understanding of disease biology and/or to develop biomarker or diagnostic assays and to establish the performance characteristics of these assays

Based on the continuous analysis of the data in this study and other cancer immunotherapy nonclinical and clinical studies, as well as new data from literature, the collection of samples or biomarker analyses with exploratory purposes may be stopped at any time.

4.2.5 Rationale for Pharmacokinetic and Anti-Drug Antibody Sampling Schedule

Sparse PK samples (see Table 3 and Table 4) will be collected in this Phase III study in order to estimate the population PK parameters of mosunetuzumab and polatuzumab vedotin and to compare these parameters with historical data. In addition, the effect of clinically relevant covariates (such as demographics) on the PK of mosunetuzumab will be examined, if possible, to understand their impacts. Lastly, exposure/safety and exposure/efficacy relationships will be assessed, as the data permit, to provide support for the clinical dose evaluated.

Since mosunetuzumab has demonstrated low immunogenicity rates in the Phase I/II Study GO29781, the frequency of ADA sampling times for mosunetuzumab will be reduced in this study compared with Study GO29781. Available information in the polatuzumab vedotin U.S. Food and Drug Administration (FDA) product label also have demonstrated low immunogenicity; thus, the frequency of ADA sampling times for polatuzumab vedotin will be kept at a minimum.

[redacted]

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

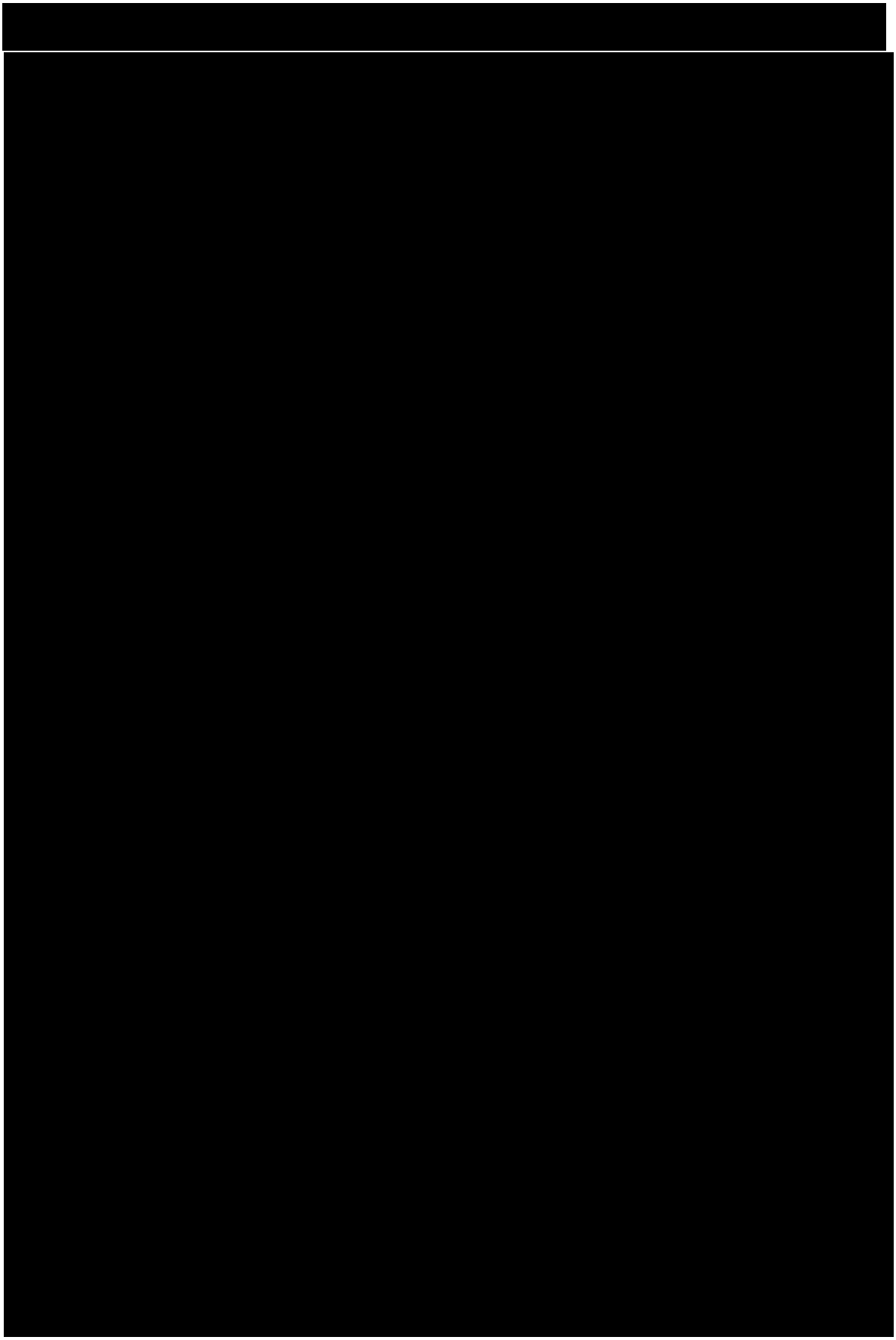
The dose and schedule of mosunetuzumab and polatuzumab vedotin for this study is based on experience from multiple studies, including Studies DCS4968g (polatuzumab vedotin), GO27834 (polatuzumab vedotin), GO29781 (mosunetuzumab), and GO40516 (combination of mosunetuzumab and polatuzumab vedotin).

4.3.1 Rationale for Polatuzumab Vedotin Dose and Schedule

Polatuzumab vedotin will be administered at 1.8 mg/kg IV for 6 cycles, which is the approved dose based on previous clinical studies. At the dose of 1.8 mg/kg every 21 days, polatuzumab vedotin was well-tolerated as monotherapy (Study DCS4968g) or in combination with an anti-CD20 monoclonal antibody (Study GO27834) in participants with R/R B-cell NHL, with expected toxicities including cytopenias and peripheral neuropathy. Study GO29365 then evaluated polatuzumab vedotin 1.8 mg/kg in combination with BR every 21 days for 6 cycles, which led to the approval of this combination in the US and internationally for R/R DLBCL.

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all required study visits of the study, including the last visit shown in the schedule of activities (see Section 1.3, Table 1 and Table 2).

The end of this study is defined as the date of the last visit of the last participant in the study (i.e., last participant in the global and extended China enrollment cohort combined if China is included), or the date at which the last data point required for statistical analysis (i.e., OS) or safety follow-up is received from the last participant (global enrollment and extended China enrollment cohort combined if China is included), whichever occurs later. The end of the study is expected to occur 2.5 years after the last participant is enrolled. The total length of the study, from the screening of the first participant to the end of the study, is expected to be approximately 5 years.

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

4.5 DURATION OF PARTICIPATION

For Arm A (M + P) and Arm B (R-GemOx), treatment will continue for a total of 8 treatment cycles. Treatment will be discontinued if there is disease progression or unacceptable toxicity. The average duration of study participation for each participant is expected to be approximately 2.5 years.

5. STUDY POPULATION

Approximately 222 participants with R/R aNHL will be enrolled in this study. If China is included as a participating country, additional participants may be enrolled in an extended China enrollment cohort to ensure a total of approximately [redacted] participants in China.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

- Participants who are capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the Informed Consent Form and in this protocol
- Participants who are age ≥ 18 years at the time of signing Informed Consent Form
- Participants who have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 (see Appendix 12)
- Participants who have a life expectancy of at least 12 weeks
- Participants who have CD20+ aggressive lymphoma as determined by the local hematopathology laboratory from the following diagnoses by 2016 World Health Organization classification of lymphoid neoplasms:
  - DLBCL, not otherwise specified (NOS)
  - High-grade B-cell lymphoma (NOS or double/triple hit)
  - trFL: The disease must be R/R to standard therapies for trFL
  - FL3B
- Participants who have received at least one prior systemic therapy for aNHL
- Participants who have either relapsed or have become refractory to a prior regimen must meet the following criteria:
  - Relapsed to prior regimen(s) after having a documented history of response (CR or PR) of ≥ 6 months in duration from completion of regimen(s)
  - Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy
- Participants must be ineligible for ASCT
- Participants who have measurable disease, defined as at least 1 bi-dimensionally measurable nodal lesion, defined as > 1.5 cm in its longest dimension, or at least 1 bi-dimensionally measurable extra nodal lesion, defined as > 1.0 cm in its longest dimension
- Participants who have a pathology report for the initial histopathology diagnosis and the most recent histopathology diagnosis prior to entering the study.
  A pathology report for the initial histopathology diagnosis (if available) and the most recent histopathology diagnosis prior to study entry, whether it is for fresh or archival tumor specimen, must be provided.
  - Participants with trFL must also have a pathology report completed at the time of disease transformation
- Participants whose representative tumor specimen and the corresponding pathology report are available for confirmation of diagnosis as well as for biomarker analysis.

- –
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- –
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- Participants who have adequate hepatic, hematologic, and renal functions defined by laboratory values below:
  - Hepatic function

    AST and ALT $\leq 2.5 \times$ upper limit of normal (ULN).

    Total bilirubin $\leq 1.5 \times$ ULN.

    Participants with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
  - Hematologic function

    Platelet count $\geq 75{,}000/mm^3$ without platelet transfusion within 14 days prior to first dose of study treatment.

    ANC $\geq 1000/mm^3$.

    Total hemoglobin ≥ 9 g/dL without red blood cell transfusion within 14 days prior to first dose of study treatment.
  - Participants with extensive marrow involvement of lymphoma and/or disease-related cytopenias (e.g., immune thrombocytopenia) may be enrolled if below is met

    Platelet count $\geq 50{,}000/mm^3$ without platelet transfusion within 14 days of study treatment.

    ANC $\geq 500/mm^3$.

    Any hemoglobin but without red blood cell transfusion within 7 days prior to first dose of study treatment.
  - Renal function

    Estimated creatinine clearance (CrCl) ≥ 30 mL/min by Cockroft-Gault method or other institutional standard methods (see Appendix 15).
  - Participants who have a negative HIV test at screening, with the following exception:

Individuals with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy for at least 4 weeks, have a CD4 count $\geq 200/\mu L$, have an undetectable viral load, and have not had a history of opportunistic infection attributable to AIDS within the last 12 months, and must be willing to undergo repeated HIV viral load testing.

- For women of childbearing potential: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception and agree 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, 9 months after the final dose of polatuzumab vedotin, 12 months after the final dose of rituximab, 6 months after the final dose of gemcitabine, 9 months after the final dose of oxaliplatin, 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 postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of polatuzumab vedotin, 3 months after the final dose of rituximab, 6 months after the final dose of oxaliplatin or gemcitabine, and 2 months 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 individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

- For participants enrolled in the extended China enrollment cohort at China's sites (if China participates in the study): must be current residents of [redacted] and be of Chinese ancestry

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

- Participants who are pregnant, breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 9 months after the final dose of polatuzumab vedotin, 12 months after the final dose of rituximab, 6 months after the final dose of gemcitabine, 9 months after the final dose of oxaliplatin, and 3 months after the final dose of tocilizumab, as applicable.
  - If breastfeeding stops prior to the first dose of study treatment, the participant can be eligible but breastfeeding should not resume for that child and for the time period as specified above.
- Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment
- Participants who have the inability to comply with protocol-mandated activity restrictions
- Participants who have received prior treatment with mosunetuzumab or other CD20-directed bispecific antibodies
- Participants who have received prior treatment with polatuzumab vedotin with the following exceptions:
  - Participants who have a documented response (PR or CR) to polatuzumab vedotin and an absence of PD within 12 months from the last dose of polatuzumab vedotin are allowed to enroll
  - Participants who received up to 2 doses of polatuzumab vedotin-containing regimen as bridging to CAR-T therapy, and either had a documented disease control (stable disease [SD], PR or CR), or were not assessed for response following treatment with polatuzumab vedotin are allowed to enroll
- Participants who have received prior treatment with R-GemOx or GemOx
- Participants who have a contraindication to any component of the study treatment
- Participants with current Grade >1 peripheral neuropathy
- Participants with Grade >1 persistent toxicity related to prior anti-lymphoma treatment (except for alopecia and anorexia, or other toxicities not considered a safety risk for the participant per investigator's judgment)

- Participants who have received anti-lymphoma treatments with monoclonal antibodies, radio-immunoconjugates or ADCs within 4 weeks before the first dose of study treatment
- Participants who have received treatment with any chemotherapeutic agent, or treatment with any other anti-lymphoma agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first dose of study treatment
- Participants who have received treatment with radiotherapy within 2 weeks prior to the first dose of study treatment

  Participants who have received radiotherapy within 4 weeks prior to the first study treatment administration must have at least one measurable lesion outside of the radiation field. Participants who have only one measurable lesion that was previously irradiated but subsequently progressed are eligible.
- Participants who have ASCT within 100 days prior to the first study treatment administration
- Participants who received prior treatment with CAR T therapy within 30 days before the first study treatment administration
- Participants who have had prior allogeneic stem cell transplantation
- Participants who have had solid organ transplantation
- Participants who have a known or suspected history of HLH
- Participants who have a history of confirmed progressive multifocal leukoencephalopathy
- Participants who have a history of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombination antibody-related fusion proteins)
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>90\%$), such as adequately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
  - Participants who have prostate cancer with no evidence of metastatic disease and are not on active therapy except for anti-androgen therapy are allowed
  - Participants who have a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed
  - Participants who have a malignancy that has been treated with curative intent and has been in remission without treatment for ≥ 2 years prior to the first study treatment administration will be allowed
- Participants who currently have or have had a history of CNS involvement of lymphoma
- Current or history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease

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

- Participants who have significant cardiovascular disease such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina
- Participants who have significant active pulmonary disease (e.g., bronchospasm and/or obstructive pulmonary disease)
- Participants with active symptoms of interstitial lung disease and/or pneumonitis, or those with a history of interstitial lung disease and/or pneumonitis within 6 months prior to the first dose of study treatment
- Participants who have a known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of the 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 2 weeks prior to the first study treatment administration
- Participants who have a known or suspected chronic active EBV infection
- Participants who have had a recent major surgery within 4 weeks prior to the first study treatment administration

  Protocol-mandated procedures (e.g., tumor biopsies and bone marrow biopsies) are permitted.
- Participants who have positive test results for chronic hepatitis B infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

  Participants 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 participants should be considered for prophylactic antivirals (e.g., entecavir) before and throughout the treatment, and must be willing to undergo repeated DNA testing.
- Participants who have acute or chronic hepatitis C virus (HCV) infection

  Participants who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation
- Participants who have been administered a live, attenuated vaccine within 4 weeks before the first dose of study treatment administration or anticipation that such a live, attenuated vaccine will be required during the study

  Participants must not receive live, attenuated vaccines (e.g., FluMist®) while receiving study treatment and after the last dose until B-cell recovery to the normal ranges. 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. See Section 6.8.1.1 for a guideline on COVID-19 vaccine administration.

Inactivated influenza vaccination should be given during local influenza season only.

- Participants who have positive SARS-CoV-2 test within 7 days prior to enrollment. Rapid antigen test result is acceptable
- Participants with a 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
  - Participants with a history of autoimmune disease with no ongoing symptoms, and with a treatment-free interval from immunosuppressive therapy for 12 months may be eligible to enroll if judged to be safe by the investigator
  - Participants with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible
  - Participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study
  - Participants with a history of disease-related immune thrombocytopenic purpura, or autoimmune hemolytic anemia may be eligible as long as relevant blood counts meet the criteria listed in the inclusion criteria
- Participants who have received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) with the exception of corticosteroid treatment $\leq$ 10 mg/day prednisone or equivalent within 2 weeks prior to first dose of study treatment
  - Participants who have received acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea or B-symptoms) may be enrolled in the study
  - 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
- Participants who received investigational therapy, whether or not intended for lymphoma treatment, within 7 days prior to initiation of study treatment
- Participants who have a clinically significant history of liver disease, including viral or other hepatitis, or cirrhosis
- Participants who have any serious medical condition or abnormality in clinical laboratory tests that, precludes the participant's safe participation in and in the

completion of the study, or which could affect compliance with the protocol or interpretation of results

Participants who do not meet the criteria for participation in this study (screen failure) may qualify for a re-screening opportunity. The investigator will record reasons for screen failure in the screening log.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1 and Appendix 4.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for 2 re-screening opportunities (for a total of 3 screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the Consent Form if they are re-screened within 28 days after previously signing the Consent Form.
The investigator will maintain a record of reasons for screen failure (see Section 8).

5.5 CRITERIA FOR TEMPORARILY DELAYING RANDOMIZATION OR ADMINISTRATION OF STUDY INTERVENTION

The following conditions may allow a participant to be randomized or administered study treatment once the conditions have resolved and the participant is otherwise eligible for participation in the study:

- Participant had active infection or required IV antibiotics within 2 weeks
- Participant has received systemic corticosteroid treatment $>$ 10 mg/day prednisone or equivalent within 2 weeks, with the exception listed in the exclusion criteria Section 5.2

6. STUDY TREATMENTS AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment or marketed product intended to be administered to a study participant according to the study protocol.

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

All other medicines described in the protocol and not specifically listed as IMPs should be considered non-investigational medicinal products (NIMPs).

6.1 STUDY TREATMENTS ADMINISTERED

The treatment regimens are summarized in Table 10 (Arm A) and Table 11 (Arm B) that provide a description of assigned study treatments for this study.

Table 10 Study Treatment Description (Arm A)

	Mosunetuzumab	**Polatuzumab vedotin**	**Tocilizumab**
Use	Experimental	Experimental	Other
Type of medicinal product	IMP	IMP	IMP
Drug form	Refer to the Pharmacy Manual and Investigator's Brochure		
Unit Dose Strength(s)			
Packaging			
Formulation(s)			
Dosage Level(s)	Cycle 1, Day 1: [redacted] mg Cycle 1, Day 8: [redacted] mg Cycle 1, Day 15: [redacted] mg Cycles 2–8, Day 1: [redacted] mg	1.8 mg/kg Q3W for 6 cycles	See Section 6.1.3
Labeling	Per local requirements		
Route of administration	SC	IV	IV
Source	Sponsor	Sponsor	Sponsor or Site [a]

IMP = investigational medicinal product; Q3W = every 3 weeks.

[a] Tocilizumab may be obtained locally by the study sites for emergency purposes if permitted by local regulations and will be formulated, prepared, and handled according to standard practice.

Table 11 Study Treatment Description (Arm B)

	Rituximab	Gemcitabine	Oxaliplatin
Use	Active comparator	Active comparator	Active comparator
Type of medicinal product	IMP	IMP	IMP
Drug form	Refer to the Local Institutional Guidelines and Prescribing Information		
Unit Dose Strength(s)			
Packaging			
Formulation(s)			
Dosage Level(s)	375 mg/m^2	1000 mg/m^2	100 mg/m^2
Route of administration	IV	IV	IV
Source	Sponsor	Sponsor	Sponsor

IMP = investigational medicinal product.

On days when two of the IMPs are given, the order of the administration in Arm A should be polatuzumab vedotin, followed by mosunetuzumab, and the interval between the end of polatuzumab vedotin infusion and the mosunetuzumab injection should be at least 60 minutes (see Section 6.1). In Arm B, gemcitabine should be administered before oxaliplatin. The administration of rituximab can be either before gemcitabine or after oxaliplatin (see Section 4.1.1.3).

Administration of study treatments will be performed in a monitored setting with immediate access to trained critical care personnel and facilities, and adequate equipment to respond to and manage potentially serious reactions and medical emergencies.

For management of IRRs associated with polatuzumab vedotin and CRS associated with mosunetuzumab, please see Appendix 6. For anaphylaxis precautions, see Appendix 7. For guidance on premedication, please see Sections 6.1.1 and 6.1.2.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in *Appendix 6*.

6.1.1 Polatuzumab Vedotin

The dose of polatuzumab vedotin will be 1.8 mg/kg. The total dose of polatuzumab vedotin for each participant will depend on the participant's weight on Cycle 1, Day 1 (or within 96 hours before Cycle 1, Day 1). If the participant's weight within 96 hours prior to Day 1 of a given treatment cycle increases or decreases > 10% from the weight obtained for Cycle 1, Day 1, the most recent weight should be used to calculate the dose. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. All subsequent doses should be modified accordingly.

After reconstitution with sterile water for injection and dilution into IV bags that contain isotonic sodium chloride solution (0.9% NaCl), polatuzumab vedotin will be administered by IV infusion with use of a dedicated standard administration set with 0.2 μM or 0.22 μM in-line filters at a final polatuzumab vedotin concentration determined by the participant-specific dose. Compatibility of polatuzumab vedotin with IV bags, infusion lines, filters, and other infusion aids have been established with items made of specific materials of construction. 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 participants 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 participant before administration of polatuzumab vedotin. Administration of corticosteroids is permitted at the discretion of the treating physician. If IRRs are observed with the first infusion in the absence of premedication, premedication must be administered before subsequent doses.

The polatuzumab vedotin infusion may be slowed or interrupted for participants experiencing infusion-associated symptoms. Following the initial dose, participants 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. The time interval between the end of infusion of polatuzumab vedotin and the start of mosunetuzumab injection should always be at least 60 minutes.

6.1.2 Mosunetuzumab

Mosunetuzumab will be administered SC with a Cycle 1 step-up-dosing regimen. Flat dosing, [redacted], will be used for mosunetuzumab. In Cycle 1, participants will receive mosunetuzumab on Day 1 ([redacted] mg), Day 8 ([redacted] mg), and Day 15 ([redacted] mg). In Cycles 2–8, participants will receive mosunetuzumab on Day 1 ([redacted] mg).

Mosunetuzumab will be delivered by standard medical syringe with a final volume not to exceed 2.0 mL. Compatibility testing has shown that mosunetuzumab is stable in extension sets and polypropylene syringes.

Mosunetuzumab will be administered to well-hydrated participants. Corticosteroid premedication with 20 mg dexamethasone (preferred) or 80 mg methylprednisolone, either IV or oral, should be administered prior to the administration of each mosunetuzumab dose. The administration of corticosteroid premedication may be optional for Cycle 2 and beyond at the investigator's discretion. However, if the participant experiences CRS with prior administration of mosunetuzumab, premedication with steroids must be administered for subsequent doses until no additional CRS events

are observed. 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.

Mosunetuzumab will be administered by qualified staff over 30 seconds to 2 minutes. Refer to the pharmacy manual for more details, including syringe size and preferred injection site. During Cycles 1 and 2, and later cycles if CRS occurred after the last mosunetuzumab, participants will be observed for at least 30 minutes after mosunetuzumab for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of CRS. Vital signs should be recorded pre-injection (within 30 minutes) and then 30 (±15) minutes after mosunetuzumab administration. In Cycle 3 and beyond, in the absence of CRS after the last dose of mosunetuzumab, the observation time after the mosunetuzumab injection will be at least 15 minutes. Vital signs should be assessed prior to the mosunetuzumab injection (within 30 minutes prior to injection) and then at least once after the injection during the observation period.

Guidelines for mosunetuzumab dosage and schedule modification and treatment interruption or discontinuation are provided in Appendix 6, Table A6-3.

Although hospitalization is not mandated for participants in Arm A, the investigator should actively assess the need for hospitalization based on their individual conditions.

6.1.3 Tocilizumab

Tocilizumab will be administered IV only to those participants who experience a CRS event for which tocilizumab is indicated. Tocilizumab will be supplied by the Sponsor as an IMP. Due to the need to manage CRS urgently and potential accessibility limitations at the site, commercial tocilizumab can be obtained locally by the study site for emergency use purposes. It will be prepared, handled, and managed according to standard institutional practices.

All tocilizumab used in the study will be tracked and accounted for as required by International Council for Harmonisation (ICH) GCP. Tocilizumab supplied by the Sponsor will include a clinical study drug/IMP label. Commercial tocilizumab obtained locally by the study site will have the marketed product label. Refer to the local prescribing information for further instructions regarding recommended storage conditions and packaging configuration, as well as the Pharmacy Manual and the Tocilizumab Investigator's Brochure.

Note: If tocilizumab is administered, see Table 5 for the schedule of activities for tocilizumab treatment of CRS.

Tocilizumab should be administered at a dose of 8 mg/kg IV (not exceeding 800 mg per infusion). The infusion should be administered IV over 60 minutes. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second

dose may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time-period of 6 weeks of mosunetuzumab treatment, the total number of tocilizumab doses should not exceed 3 doses.

6.1.4 Rituximab

Rituximab will be administered at a dose of 375 mg/m^2 by IV infusion on Day 1 of each 14-day cycle (Cycles 1–8). The dose of rituximab should not be modified.

Rituximab must be administered in a clinic or hospital equipped for systemic cancer treatment. Full emergency resuscitation facilities should be immediately available. For the management of adverse events, including IRRs, please consult the local prescribing information. For management of anaphylaxis, also see Appendix 7. Once the rituximab infusion is complete, participants 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 participant is at increased risk for an IRR (high tumor burden or high peripheral lymphocyte count). For participants who experience an adverse event during a rituximab infusion, administration of R-GemOx may be continued on the following day, if required. Rituximab can be given either before gemcitabine or after oxaliplatin on the same day.

Table 12 Administration of Rituximab

First Infusion (Cycle 1, Day 1)	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hour • If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour • If an infusion-related 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 participant experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/hour and follow instructions for the first infusion • If the participant tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hour), begin the infusion at a rate of 100 mg/hour • If no infusion-related reaction occurs, increase the infusion rate in 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour • 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).

6.1.5 Gemcitabine

Gemcitabine will be administered at 1000 mg/m^2 IV on Day 1 of each 14-day cycle (Cycles 1–8). Gemcitabine should be administered before oxaliplatin on the same day. Gemcitabine should be administered in accordance with local institutional guidelines and prescribing information.

6.1.6 Oxaliplatin

Oxaliplatin will be administered at 100 mg/m^2 IV on Day 1 of each 14-day cycle (Cycles 1–8). Oxaliplatin should be administered after gemcitabine on the same day. Oxaliplatin should be administered in accordance with local institutional guidelines and prescribing information.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. Tocilizumab may be obtained locally by the study sites for emergency purposes, if permitted by local regulations, and will be prepared and handled according to standard practice. The study site is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor with use of the interactive voice or Web-based response system (IxRS) by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

Investigational medicinal products 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 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 accountability log.

Refer to the pharmacy manual and/or the applicable Investigator's Brochure or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

Participants will be randomly assigned to one of two treatment arms: Arm A or Arm B. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm (see Section 4.2.3). Randomization will be stratified by the number of prior treatment regimens for aggressive lymphoma (1 vs. ≥2) and the outcome after the last therapy (relapsed vs. refractory). See Section 4.1 for details.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the electronic Case Report Form (eCRF). The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Cases of accidental overdose, or medication error, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

The dose modification of mosunetuzumab, polatuzumab vedotin and oxaliplatin is permitted for management of drug-related- toxicities, as described in Appendix 6. The dose modification of rituximab, gemcitabine or tocilizumab is not permitted.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide Roche IMPs (mosunetuzumab, polatuzumab vedotin, rituximab, and tocilizumab) or any other study treatments to participants who have completed the study. The Sponsor may evaluate whether to continue providing mosunetuzumab, polatuzumab vedotin, rituximab, or tocilizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose of mosunetuzumab or polatuzumab vedotin. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor on the basis of clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Information on any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment until 90 days after the last dose of study treatment or start of new anti-lymphoma therapy, whichever is earlier, must be collected. The information on COVID-19 vaccine, prophylaxis, or COVID-19 directed therapy administration should be collected even if it was given more than 7 days prior to initiation of study treatment. After this period, concomitant medications should be collected if they were used to manage serious adverse events that are believed to be related to prior study treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists

(e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists). See Appendix 6.

Prophylactic use of hematopoietic growth factors or anti-infectives for viral, fungal, bacterial, or Pneumocystis infections are permitted and should be instituted per institutional practice or investigator preference based on individual participant risk factors. Participants in countries where prophylactic anti-viral medications for hepatitis B reactivation are the standard of care may be treated prophylactically (Taplitz et al. 2018; NCCN 2020).

Premedication with antihistamines, anti-pyretics, and/or analgesics may be administered at the discretion of the investigator.

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

In the event of new onset of SARS-CoV-2 infection during study treatment, appropriate therapy including, but not limited to, antivirals and/or monoclonal antibodies in accordance with local institutional guidance) is recommended (El Chaer et al. 2022).

6.8.1.1 COVID-19 Vaccines

COVID-19 vaccines (approved, non-live), including booster vaccines for novel variants, are strongly recommended for all participants. Information on SARS-CoV-2 vaccine administration should be collected even if it was given more than 7 days prior to initiation of study treatment.

Factors to consider by investigators when making individualized decisions for participants receiving mosunetuzumab:

- General condition of the patient and severity/seriousness of underlying disease
- Potential risks associated with SARS-CoV-2 infection and potential benefits and risks from COVID-19 vaccination
- Epidemiology of SARS-CoV-2 infection in the patient's location

Providers should follow local practice guidelines for the timing of vaccination administration prior to initiating therapy to maximize potential therapeutic benefit.

If COVID-19 vaccines are administered during study treatment, vaccination should be administered after completion of mosunetuzumab step-up dosing and at least one week after administration of the target mosunetuzumab dose. For subsequent treatment cycles after study treatment target dose has been administered, COVID-19 vaccines can be given at least one week before or after mosunetuzumab dosing.

6.8.2 Cautionary Therapy

6.8.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes and P-glycoprotein Inhibitors

Mosunetuzumab

Given the expected pharmacology of mosunetuzumab, the transient release of cytokines (most resolved within the first 24 hours of the Cycle 1, Day 1 dose) may suppress CYP450 enzymes and cause drug-drug interactions. Preliminary clinical data indicate that mosunetuzumab following IV dosing induced a transient elevation in plasma IL-6, with peak levels occurring in the majority of participants within 4–6 hours of the Cycle 1, Day 1 dose, and returned to baseline by 24 hours. Participants who may be of highest risk of a drug-drug interaction are those receiving concomitant medications that are CYP450 substrates and have a narrow therapeutic index (Appendix 20).
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 approximately 50%, while antibody-conjugated monomethyl auristatin E (acMMAE) PK is not affected. MMAE is also a P-glycoprotein (P-gp) substrate. Concomitant medications that are strong CYP3A4 and/or P-gp inhibitors (Appendix 20) should be considered cautionary as they may potentially lead to adverse reactions, which require close monitoring.

If a participant is taking any of the medications in the categories of strong CYP3A4 inhibitors and inducers and/or P-gp inhibitors, the investigator will assess and document the use of these medications known or suspected to fall in those categories.

A sample list of cautionary medications including CYP3A inhibitors/inducers and P-glycoprotein (P-gp) inhibitors can be found in Appendix 20. 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 20.

Tocilizumab

Cytochrome P450 enzymes in the liver are down-regulated by infection and inflammatory stimuli, including cytokines such as IL-6. Inhibition of IL-6 signaling in participants with rheumatoid arthritis who are treated with tocilizumab may restore CYP450 activities to higher levels than those participants not treated with tocilizumab, leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CY2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The effects of

tocilizumab on CYP2C8 or transporters are unknown. In vivo studies with omeprazole (metabolized by CYP2C19 and CYP3A4) and simvastatin (metabolized by CYP3A4) showed up to a 28% and 57% decrease in exposure 1 week following a single dose of tocilizumab, respectively.

The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index (see Appendix 20), where the dose is individually adjusted:

- Upon initiation or discontinuation of tocilizumab in participants being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed
- Prescribers should exercise caution when tocilizumab is coadministered with CYP3A4 substrate drugs where a decrease in effectiveness is undesirable (e.g., oral contraceptives, lovastatin, atorvastatin)
- The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy

6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. Herbal therapies intended for the treatment of lymphoma are prohibited.

6.8.3 Prohibited Therapy

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease progression is documented and the participant has discontinued study treatment

  Adjuvant endocrine therapy for non-metastatic, hormone receptor positive breast cancer and anti-androgen therapy for non-metastatic prostate cancer are permitted.
- Investigational therapy, whether intended for the treatment of lymphoma or not, is prohibited within 7 days prior to initiation of study treatment and during study treatment
- Systemic immunosuppressive therapy is prohibited (except medications indicated per protocol, including corticosteroids and tocilizumab)
- Live virus vaccines are prohibited for at least 4 weeks before initiation of or at any time during study treatment

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. See the schedule of activities (see Section 1.3, Table 1 and Table 2) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of an anti-lymphoma therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to Lugano 2014 criteria

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment completion or treatment discontinuation visit 30 (±7) days after the final dose of study drug.

Participants who discontinue study treatment for reasons other than documented disease progression or relapse, start of new anti-lymphoma therapy, or withdrawal from study participation should continue to be followed during post-treatment follow-up, as described in schedule of activities (see Section 1.3, Table 1 and Table 2). *Participants should continue post-treatment follow-up until disease progression, start of new anti-lymphoma therapy, withdrawal from study participation, or until the Month 30 tumor assessment visit is completed, whichever occurs first.*

During survival follow up, information on survival status and new anti-lymphoma therapy will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months *±1 month* until death (unless the participant withdraws consent or the Sponsor terminates the study). *All participants may be contacted periodically for additional survival and/or new anti-lymphoma therapy (NALT) information unless the participant requests to be withdrawn from the study.* If the

participant withdraws from the study, the site's staff may use a public information source (e.g., county records) to obtain information about survival status only.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.
The participant will be permanently discontinued both from the study treatment and from the study at this time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) 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.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

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 participants and for participants who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3, Table 1 and Table 2). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries and cancer history (including prior cancer therapies and procedures), will be recorded at baseline. Any medication and vaccines (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded at baseline. Demographic data, including age, sex, and self-reported race/ethnicity, will also 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.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately

upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening, every 8 weeks (±1 week) for the first 6 months following treatment initiation, and every 3 months (±1 month) for the first two years on study, then at month 30 (± 2 months) after Cycle 1 Day 1, regardless of dose delay, until disease progression, start of new anti-lymphoma therapy, or study discontinuation, whichever is earlier, per Lugano Criteria 2014 (Cheson et al. 2014; Appendix 10). At the investigator's discretion, tumor assessments may be repeated at any time if PD is suspected.

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined below.

8.1.1.1 Radiographic Assessments

Fluorodeoxyglucose (FDG) PET-CT scans, in conjunction with diagnostic-quality CT scans, are required at screening, the interim response assessment, and at the end-of-treatment (see Table 1 and Table 2 for details). After the end-of-treatment, radiographic assessments should be performed according to the schedule outlined in the schedule of activities (Section 1.3, Table 1 and Table 2). For participants who achieve metabolic CR at 24 weeks, a CT scan with or without PET scan will be acceptable for subsequent scans. For participants who do not achieve CR at 24 weeks, continue imaging studies with PET and diagnostic-quality CT scans until CR or PD. Diagnosis of disease progression based on clinical examination must be confirmed radiographically by imaging (e.g., CT scan, FDG PET-CT scan) or histopathologically by biopsy as soon as feasible (within 30 days) and prior to initiation of non–protocol-specified anti-lymphoma therapy.

All measurable and/or evaluable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator and the IRF on the basis of physical examinations, CT scans, FDG PET-CT scans.

Fluorodeoxyglucose PET-CT scans should extend from skull base to mid-thigh. Full-body FDG PET-CT scans should be performed when clinically appropriate.

Computed tomography scans with contrast (per institutional standard operating procedures) should include the chest, abdomen, and pelvis.

Computed tomography or magnetic resonance imaging (MRI) scans of other disease sites should be performed as clinically indicated. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan is permitted if it allows for consistent and precise measurement of target lesions during the study. Magnetic resonance imaging scans may be used instead of CT scans in participants for whom they are contraindicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Radiographic images will be submitted to an IRF for a quality and completeness check, for central review, and for temporary storage prior to transferring images to the Sponsor.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.1.2 Bone Marrow Examinations

Participants may use screening PET/CT scans to assess bone marrow involvement; bone marrow examinations are not required unless clinically indicated (Cheson et al. 2014).

8.1.1.3 Response Evaluation

Objective response will be determined by the investigator and the IRF at specified timepoints according to the Lugano Response Criteria (Cheson et al. 2014; see Appendix 10). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Endpoints (e.g., ORR, CRR, PFS, DOR, DOCR), will be calculated programmatically by the Sponsor on the basis of investigator and IRF assessments of response at each specified timepoint.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. As part of the complete physical examination, the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly will be recorded on the appropriate Tumor Assessment eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

A targeted, symptom-directed physical examination 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 [e.g., clinical assessment for peripheral neuropathy in participants receiving polatuzumab vedotin]). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinical assessments of peripheral neuropathy should be performed at screening, at Day 1 of each cycle, and at the treatment completion visit and recorded on the appropriate eCRF. These may be performed within 48 hours prior to the study visit date.

Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Vital signs will be measured in a seated position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse rate, blood oxygen saturation and respiratory rate.

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.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained during screening period (see Section 1.3, Table 1 and Table 2) with use of an ECG machine to calculate the heart rate and measures PR interval, QRS interval, QT interval, and QT interval corrected with use of Fridericia's formula (QTcF)/QT interval.

All ECG recordings must be performed with use of a standard high-quality, high-fidelity digital electrocardiograph machine. Lead placement should be as consistent as possible.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. The following should be recorded on the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

8.2.4 Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the schedule of activities (see Section 1.3, Table 1 and Table 2) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event Case Report Form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. 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.

Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study treatment or until start of a new line of anti-lymphoma therapy, whichever is earlier, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities (see Section 1.3, Table 1 and Table 2).

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3, Table 1 and Table 2 and will be conducted as outlined in Appendix 2.

[redacted]

[redacted]

[redacted]

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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. The paper Clinical Trial Adverse Event/Special Situations 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 e-mailing the form using the fax number or e-mail address provided to investigators. All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

After initiation of study drug, all adverse events will be reported from the start of treatment until 90 days after the final dose of study treatment or the initiation of next anti-lymphoma therapy, whichever is earlier, at the timepoints specified in the schedule of activities (see Section 1.3, Table 1 and Table 2).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discontinued from the study and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts.
All adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent.
Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authority (which includes the use of applicable systems, such as EudraVigilance), IRBs or ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Mosunetuzumab	Mosunetuzumab Investigator's Brochure
Polatuzumab vedotin	Polatuzumab vedotin Investigator's Brochure
Tocilizumab	Tocilizumab Investigator's Brochure
Rituximab	Rituximab Investigator's Brochure
Gemcitabine	Gemcitabine U.S. Prescribing Information
Oxaliplatin	Oxaliplatin U.S. Prescribing Information

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.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the associated study drug's Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant

during the study or within 9 months after the final dose of polatuzumab vedotin, 3 months after the final dose of mosunetuzumab or tocilizumab, 12 months after the final dose of rituximab, 9 months after the final dose of oxaliplatin, and 6 months after the final dose of gemcitabine.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 6 months after the final dose of polatuzumab vedotin, gemcitabine or oxaliplatin, 2 months after the final dose of tocilizumab, and 3 months after the final dose of rituximab.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. The Sponsor or a designee may follow up by telephone, fax, e-mail, 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.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

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 the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.8)
- Suspected transmission of an infectious agent by a study treatment, 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.8.1 Adverse Events of Special Interest Specific to Mosunetuzumab

- Grade ≥2 CRS
- Grade ≥2 neurologic adverse event
- Grade ≥2 injection-site reaction
- Any suspected HLH or macrophage activation syndrome
- Grade ≥3 TLS
- Grade ≥3 febrile neutropenia
- Grade ≥2 AST, ALT, or total bilirubin elevation
- Any Grade disseminated intravascular coagulation (minimum Grade 2 by definition)
- Grade ≥2 tumor flare (e.g., manifestation of signs/symptoms associated with an increase in size of known nodal or extranodal lesions by clinical or radiographic assessment, new onset or worsening of preexisting pleural effusions)
- Any grade pneumonitis, interstitial lung disease, acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia, and/or pulmonary toxicity

8.3.8.2 Adverse Events of Special Interest Specific to Polatuzumab Vedotin

- TLS any grade (minimum Grade 3 by definition)
- Second malignancies

8.3.9 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor:	[redacted] Ph.D. (Primary)
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted] MD, Ph.D. (Backup)
Mobile Telephone No.:	[redacted]
Roche Medical Responsible:	[redacted] Ph.D. (Secondary)
Mobile Telephone No.:	[redacted]

To ensure the safety of study participants, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Serum/plasma samples will be collected for measurement of serum/plasma concentrations of mosunetuzumab and polatuzumab vedotin as specified in the schedule of activities (see Section 1.3, Table 3 and Table 4). Predose serum rituximab and obinutuzumab PK samples are required to characterize any potential interactions between rituximab or obinutuzumab PK and the clinical effects of mosunetuzumab.

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of mosunetuzumab and polatuzumab vedotin. Samples collected for analyses of mosunetuzumab and polatuzumab vedotin concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Mosunetuzumab concentration data may be pooled with data from other studies using population PK model to derive PK parameters, as warranted by the data.
Potential correlations of relevant PK parameters with safety, efficacy, or biomarker outcomes may be explored. In addition, these data may be used to explore and characterize the potential PK interactions between mosunetuzumab and polatuzumab vedotin.

Genetic analyses will not be performed on serum samples unless consent for this was included in the Informed Consent Form. Participant confidentiality will be maintained. At visits during which serum samples for the determination of the PK of mosunetuzumab and polatuzumab vedotin will be taken, 1 sample of sufficient volume can be used.

Serum/plasma samples collected for PK analysis may be used for additional PK assay development and validation. Samples will be destroyed no later than 5 years after final Clinical Study Report has been completed.

8.5 PHARMACODYNAMICS

See Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

See Section 8.11.3 on the RBR for more information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood, peripheral blood mononuclear cells (PBMCs), and plasma samples for exploratory research on biomarkers
- Archival or newly collected tumor tissue sample obtained at baseline for determination of CD20 expression, for exploratory research on biomarkers, and for biomarker assay development

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.11.

Screening plasma, blood (if applicable) and tumor tissue samples, including those collected from individuals who do not enroll in the study (if permitted by the study participant and per institutional or country regulatory guidelines), may be used for future research and/or development of disease-related tests or tools.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 3 and Table 4). Biomarker samples will be sent to one or several central

laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11) biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the following exceptions:

- [redacted] However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than the date of final closure of the clinical database, whichever occurs first. For individuals who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants 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.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to mosunetuzumab and polatuzumab vedotin will be evaluated in serum samples collected from all participants according to the schedule of assessments (see Section 1.3, Table 3 and Table 4). Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to mosunetuzumab and polatuzumab vedotin and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to mosunetuzumab and polatuzumab vedotin and/or further characterize the immunogenicity of mosunetuzumab and polatuzumab vedotin.

The detection and characterization of antibodies to mosunetuzumab and polatuzumab vedotin will be performed through use of validated assay methods by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for mosunetuzumab and polatuzumab vedotin serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the

study treatment. Serum samples collected for immunogenicity analysis may be stored for a maximum of 5 years (or according to local regulations) after Clinical Study Report has been completed to enable further characterization of immunogenicity as well as development and validation of immunogenicity assay.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health utility data from the [redacted] will be evaluated in pharmacoeconomic models. Results from health economic data analyses will be reported separately from the Clinical Study Report.

8.10 CLINICAL OUTCOME ASSESSMENTS

Participant-reported outcome (PRO) instruments will be completed to assess the treatment benefit of M+P compared with R-GemOx. In addition, PRO instruments will enable the capture of each participant's direct experience with M+P.

Participant-reported outcomes data will be collected through use of the following instruments:

- The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30)
- Functional Assessment of Cancer Therapy–Lymphoma subscale (FACT-LymS)
- Functional Assessment of Cancer Therapy–Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx)
- [redacted]

8.10.1 Data Collection Methods for Clinical Outcome Assessments

Participant-reported outcomes instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3, Table 1 and Table 2). In the event participants are not able to come to the clinic for their scheduled assessment during post treatment follow up or long term survival follow up period., sites can call participants, and, using phone scripts, read questions verbatim to participants while capturing their responses on the paper questionnaire the participants would have completed upon coming to the clinic. Source documentation sufficient to pass an audit should be obtained, which includes information that the questionnaires were administered via phone. At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments (with the only exception of laboratory blood collection which needs to be performed prior to PRO questionnaire completion due to logistic reasons), and prior to the administration of study treatment, unless otherwise specified.

Participant-reported outcomes instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the

appropriate instruments to be administered in the correct order at each specified timepoint. The booklets will be labeled with the timepoint of administration.

During clinic visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 18 minutes at each specified visit
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions, but may read questions verbatim upon request
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments

Site staff should review all completed instruments and should ask the participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participants to complete the item or confirm that the item was intentionally left blank.

8.10.2 Description of Clinical Outcome Assessment Instruments

8.10.2.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 8). It consists of 30 questions that assess 5 aspects of participant functioning (physical, emotional, role, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), global health status and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week.
Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the global health status and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The EORTC QLQ-C30 takes approximately 10 minutes to complete.

[redacted]

[redacted]

8.10.2.3 FACT-Lym and LymS Subscale

The FACT-Lym is a validated, reliable self-report measure of health-related quality of life (HRQoL) aspects relevant to patients with lymphoma (Hlubocky et al. 2013). The full measure consists of the FACT-G physical, social/family, emotional, and functional well-being scales (27 items), as well as a lymphoma-specific symptoms scale (15 items). For this study, only the items that comprise the lymphoma-specific symptoms (LymS) scale (FACT-LymS) will be administered to participants (see Appendix 13). Each item is rated on a 5-point response scale that ranges from "not at all" to "very much," with higher scores indicative of better HRQoL.

8.10.2.4 FACT/GOG-Ntx

The FACT/GOG-Ntx is a validated self-report measure for assessing platinum/paclitaxel-induced peripheral neuropathy (Huang et al. 2007). This measure is used to assess 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 full measure consists of the FACT-G physical, social/family, emotional, and functional well-being scales (27 items), as well as a peripheral neuropathy symptoms scale (11 items). For this study, only the items that comprise the peripheral neuropathy scale will be administered to participants (see Appendix 14). The scale contains 4 subscales that assess sensory neuropathy (4 items), hearing neuropathy (2 items), motor neuropathy (3 items), and dysfunction associated with neuropathy (2 items), which can be summed to create a total score. Each item is rated on a 5-point response scale that ranges from "not at all" to "very much," with higher scores indicative of more extreme neuropathy.

8.11 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.11.1 Blood Samples for Whole-Genome Sequencing or Whole-Exome Sequencing (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, 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.

DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants.

The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.11.1) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing 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 participants are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may 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, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

See Section 8.7 for information on availability of data from biomarker analyses.

8.11.2 Optional Tumor Biopsies (Participants Providing Separate Consent)

Consenting participants will undergo optional tumor biopsies after study treatment initiation and may undergo additional biopsies during the study at any other time at the investigator's discretion (if deemed clinically feasible by the investigator).
Samples collected via resection, core--needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

The Informed Consent Form will contain a separate section that addresses optional biopsies. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of undergoing optional biopsies. Participants will be told that they are free to choose not to undergo optional biopsies and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to undergo optional

biopsies. Participants who choose not to undergo optional biopsies will not provide a separate signature. The investigator should document whether or not the participant has given consent to undergo optional biopsies and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for exploratory biomarker research as described in Section 8.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. See Section 8.7 for information on duration of sample storage and availability of data from biomarker analyses.

8.11.3 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.11.3.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. Research Biosample Repository samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- 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

8.11.3.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's 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 8.11.3) will not be applicable at that site.

8.11.3.3 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 M+P, diseases, or drug safety:

- Blood samples collected at baseline
- Tumor tissue samples collected at screening
- Tumor tissue samples collected at timepoints defined in Section 1.3 (Table 1 and Table 2)
- Tumor tissue samples from biopsies performed at the investigator's discretion during the study
- Leftover blood, serum, 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 variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing 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 participants are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may 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, see the laboratory manual.

Research Biosample Repository samples are to be stored until they are no longer needed or until they are exhausted. 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).

8.11.4 Confidentiality

Research Biosample Repository samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples 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 participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants 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 samples 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.

8.11.5 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 participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples 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 participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

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

8.11.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's decision through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by e-mailing the study number and participant number to the following e-mail address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.11.7 Monitoring and Oversight

Research Biosample Repository samples 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 samples 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 an individual's 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.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Analysis for ORR by IRF, one of the dual primary endpoints, will be conducted for the first [redacted] randomized participants (interim analysis population [IAP]) to test the following hypothesis (Section 9.2.2):

[redacted]

Analysis for PFS by IRF, one of the dual primary endpoints, will test the equality of PFS distribution in M+P versus R-GemOx in the intent-to-treat (ITT) population:

[redacted]

Details of the hierarchical testing for the dual primary endpoints and key secondary endpoint will be provided in Section 9.2.1 and in the Statistical Analysis Plan.

9.2 SAMPLE SIZE DETERMINATION

Assuming a median PFS of [redacted] months in the R-GemOx arm based on the largest multisite Phase II study of R-GemOx, other similar references and a real-world data analysis (Mounier et al. 2013; Cazelles et al. 2019; Schade et al. 2019), and a randomization ratio of 2:1 (see Section 4.2.3), [redacted] events are required to detect a between-group difference of [redacted] months in median PFS (hazard ratio = [redacted]) assuming an exponential distribution of PFS, with use of a log-rank test with [redacted]% power and a [redacted]-sided α of [redacted]. At the interim efficacy analysis for Study GO40516 (CCOD of 15 March 2021), a median PFS of [redacted] months (95% CI: 3.5, NE) was observed in 60 patients with R/R DLBCL receiving M+P. Although immature, these results are consistent with the assumed median PFS of [redacted] months for M+P.

Assuming a median OS of [redacted] months in the R-GemOx arm (Mounier et al. 2013; Cazelles et al. 2019; Schade et al. 2019), and considering an interim OS efficacy analysis at the time of the primary PFS analysis, a between-group difference of [redacted] months in median OS (hazard ratio = [redacted]) assuming an exponential distribution of OS would be detected with use of a log-rank test with [redacted]% power and a [redacted]-sided α of [redacted] (Section 9.2.4).

A total of approximately 222 participants will be randomized in this study.

The actual numbers of events for PFS and OS, and the analysis timings as described above have changed due to an extended enrollment timeline (See Sections 9.2.3 and 9.2.4 for updated projections). SUNMO completed enrollment except for the US and China, leading to extended follow up of patients enrolled outside the US and China. Initially the primary PFS analysis was powered at [redacted]%, and the final OS analysis was powered at [redacted]%. The extended enrollment timeline has increased the power for the primary analysis, as PFS events continue to accumulate beyond the target number of events throughout trial enrollment. Therefore, the study has adequate power to reclassify objective response rate as a dual primary endpoint along with PFS, and therefore, add an earlier interim analysis based on objective response rate to detect clinically meaningful improvement based on this intermediate efficacy endpoint (Sections 9.2.1 and 9.2.2).

9.2.1 Type I Error Control

The overall type I error rate for this study is strictly controlled at [redacted]% ([redacted]-sided) using the Fallback Method (see Section IV C in FDA Guidance on Multiple Endpoints in Clinical Trials 2017).

The ORR analysis will occur when the first [redacted] randomized participants have a minimum of [redacted] months of follow-up from the first response assessment. ORR will be tested at the [redacted]% [redacted]-sided α level.

The first PFS by IRF analysis will be performed by the iDCC for iDMC review to assess futility, at the time of the dual primary endpoint ORR analysis, on the first [redacted] randomized participants. The PFS futility boundary is set at PFS HR greater than [redacted] for mosunetuzumab and polatuzumab in comparison with R-GemOx. The second PFS analysis will be tested once at the planned primary PFS analysis [redacted] months after the last patient in (LPI), which is expected approximately [redacted] months after first patient in (FPI). If the ORR analysis is positive, the PFS analysis will use a [redacted]% [redacted]-sided α level. If the ORR analysis is negative, the PFS analysis will use a [redacted]% [redacted]-sided α level.

Depending on the number of events, there will be [redacted] analyses for the key secondary endpoint of OS based on hierarchical testing order to ensure the final OS analysis was powered at [redacted]% (Figure 7). The first and second OS analyses will be performed by the independent data coordinating center (iDCC) for iDMC review to

assess futility. The first OS analysis will be performed when approximately [redacted] OS events are observed. The second OS analysis will be performed at the time of the dual primary endpoint ORR analysis. For the first and second OS analyses, OS effect is considered detrimental if OS HR is greater than [redacted] for mosunetuzumab and polatuzumab vedotin compared to R-GemOx.

The third OS analysis will be conducted at the time of the primary PFS analysis to assess safety and efficacy. OS effect is considered detrimental if the observed OS HR is greater than [redacted]. OS will be formally tested for efficacy only if PFS is positive. Depending on the number of events, if the power for the third OS analysis is at least [redacted]% at the same α level as PFS (either at $\alpha=$[redacted]), the third OS analysis is considered final. If the power for the third OS analysis is less than [redacted]%, a group sequential test will be used, and a fourth OS analysis may be needed. The fourth OS analysis will be conducted when there are sufficient OS events to achieve a power of [redacted]%. The α levels for OS analyses depend on the spending function boundaries and actual number of OS events.

An overview of the type I error rate control strategy is shown in Figure 7. This figure is based on the projected number of events and analysis timings.

[redacted]

9.2.2 Dual Primary Endpoint: Objective Response Rate in Interim Analysis Population (IAP)

The ORR analysis will be conducted after the first [redacted] randomized participants (i.e. IAP) have a minimum of [redacted] months of follow-up from the first response assessment by IRF.

Assuming the ORR is [redacted]% in R-GemOx versus [redacted]% in M + P, this analysis has approximately [redacted]% power to detect a difference in ORR at [redacted]% [redacted]-sided α level. The following hypothesis will be tested at the [redacted]% [redacted]-sided α level for the first [redacted] R/R LBCL participants:

[redacted]

It is projected that an observed ΔORR of [redacted]% or better will result in a statistically significant difference between treatment arms. That is, a ΔORR of [redacted]% will be the minimal detectable difference for the analysis.

9.2.3 Dual Primary Endpoint: Progression-Free Survival in ITT

The first PFS by IRF analysis will be performed by the iDCC for iDMC review to assess futility, at the time of the dual primary endpoint ORR analysis, on the first [redacted] randomized participants. The PFS futility boundary is set at PFS HR greater than [redacted] for mosunetuzumab and polatuzumab in comparison with R-GemOx.

The primary PFS analysis will be conducted [redacted] months after LPI on the ITT population when approximately [redacted] events are observed. This analysis will have [redacted]% power at [redacted]% [redacted] sided α level if ORR analysis in IAP (Section 9.2.2) is positive or [redacted]% power at [redacted]% [redacted]-sided α level if ORR analysis is negative to detect a hazard ratio of [redacted] in M + P in comparison with R-GemOx (Figure 7).

The following assumptions are made for PFS:

- PFS curve follows an exponential distribution.
- Median PFS of [redacted] months in R-GemOX arm and [redacted] months in M +P arm (corresponding to a target HR of [redacted]).
- The drop out rate is [redacted]% over a [redacted]-month period.

An observed HR of [redacted] or better for PFS will result in a statistically significant difference between treatment arms if ORR is positive. An observed HR of [redacted] will be the minimal detectable difference for the analysis. Alternatively, an observed HR of [redacted] or better for PFS will result in a statistically significant difference between treatment arms if ORR is negative.

The timing of the primary PFS analysis is no longer event-driven because of the extended enrollment timeline. An event driven primary PFS analysis would likely result in sufficient events prior to LPI on study. Instead, the primary PFS analysis is conducted [redacted] months after LPI (i.e., [redacted] months from FPI) to allow all patients to complete treatment.

9.2.4 Key Secondary Endpoint: Overall Survival in ITT

Depending on the number of events, there will be three or four analyses for the key secondary endpoint of OS based on hierarchical testing order to ensure the final OS analysis is powered at [redacted]% (Figure 7). The first and second OS analyses will be performed by the independent data coordinating center (iDCC) for iDMC review to assess futility. The first OS analysis will be performed when approximately [redacted] OS events are observed. The second OS analysis will be performed at the time of the dual primary endpoint ORR analysis. For the first and second OS analyses, OS effect is considered detrimental if OS HR is greater than [redacted] for mosunetuzumab and polatuzumab vedotin compared to R-GemOx.

The third OS analysis will be conducted at the time of the primary PFS analysis to assess safety and efficacy. OS effect is considered detrimental if the observed OS HR is greater than [redacted]. OS will be formally tested for efficacy only if PFS is positive.

If ORR analysis in IAP (Section 9.2.2) is positive and PFS is positive, the third OS analysis will be conducted at the time of the primary PFS analysis when approximately [redacted] OS events are observed. This may be the only one OS analysis needed for efficacy, as power is approximately [redacted]%, at [redacted]-sided α of [redacted]%, to detect a hazard ratio of [redacted] in M + P in comparison with R-GemOx.

If ORR is negative and PFS is positive, a third OS analysis will be conducted at the time of the PFS analysis when approximately [redacted] OS events are observed, with [redacted]% power and a [redacted]-sided local α of [redacted]%. If the third OS analysis is negative, a fourth OS analysis will be conducted approximately [redacted] months after LPI when approximately [redacted] events are observed, with [redacted]% power and a [redacted]-sided local α of [redacted]%, to detect a hazard ratio of [redacted] in M + P in comparison with R-GemOx.

In general, depending on the number of events, if the power for the third OS analysis is at least [redacted]% at the same α level as PFS (either at α = [redacted]), the third OS analysis is considered final. If the power for the third OS analysis is less than [redacted]%, a group sequential test will be used, and a fourth OS analysis may be needed. The fourth OS analysis will be conducted when there are sufficient OS events to achieve a power of [redacted]%. The actual α levels for OS analyses depend on the spending function boundaries and actual number of OS events.

The following assumptions are made for OS:

- OS curve follows an exponential distribution
- Median OS of [redacted] months in the R-GemOx arm and [redacted] months in the M+P arm (corresponding to a target HR of [redacted])
- The drop-out rate is [redacted]% over a [redacted]-month period

An observed HR of [redacted] or better for OS will result in a statistically significant difference between the treatment arms if ORR is positive and PFS is positive. Alternatively, an observed HR of [redacted] at interim OS analysis and [redacted] at final OS analysis will result in a statistically significant difference between treatment arms if ORR is negative and PFS is positive.

Table 13 Analysis Timing and Stopping Boundaries for Overall Survival

[redacted]

9.3 ANALYSIS SETS

The following populations are defined:

Participant Analysis Set	Description
Enrolled	All participants who sign the Informed Consent Form
IAP	The first [redacted] randomized participants
ITT	All randomized participants
Evaluable	
Safety-evaluable	All participants randomly assigned to study treatment and who take at least 1 dose of study treatment, with participants grouped according to the treatment regimen actually received
PK-evaluable	The PK population for analysis will include all participants who have at least received 1 dose of mosunetuzumab and have at least 1 evaluable PK sample postdose for at least 1 analyte
Immunogenicity-evaluable	All participants who have at least 1 predose or 1 post-dose ADA assessment
PRO-evaluable	All randomized participants who have a baseline and at least 1 post-baseline assessment. The PRO-evaluable population will be used for descriptive analyses of visit summary and change from baseline analyses. All randomized participants (ITT) will be used for completion analyses and time to deterioration analyses.

ADA = anti-drug antibody; IAP = interim analysis population; ITT = intent-to-treat; PK = pharmacokinetic; PRO = participant-reported outcomes.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1 General Considerations

The analysis population for the primary and secondary efficacy analyses will consist of all randomized participants, with participants grouped according to the treatment assigned at randomization. The safety analysis population will consist of all randomized participants who received at least 1 dose of study treatment, with participants grouped according to the treatment received.

Hypothesis tests will be [redacted]-sided, unless otherwise indicated. The overall type I error (α) for this study will be controlled at [redacted]

9.4.2 Dual Primary Endpoints

9.4.2.1 ORR by IRF

The dual primary endpoint of ORR is defined as the proportion of participants in whom an objective response (CR or PR) was observed at any time during the study as determined by the IRF, according to Lugano 2014 Response Criteria.

The ORR analysis will be conducted after the first [redacted] randomized participants (i.e., IAP) have a minimum of [redacted] months of follow-up from the first response assessment by the IRF.

ORR by IRF will be evaluated once more at the time of primary PFS analysis. However, at the time of primary PFS analysis, ORR will be a supportive secondary endpoint that will not be included in the overall Type I error control strategy.

Assuming the ORR is [redacted]% in R-GemOx versus [redacted]% in M+P, this analysis has approximately [redacted]% power to detect a difference in ORR at [redacted]% [redacted]-sided α level. The following hypothesis will be tested at the [redacted]% [redacted]-sided α level for the first [redacted] R/R LBCL participants:

[redacted]

It is projected that an observed ΔORR of [redacted]% or better will result in a statistically significant difference between treatment arms. That is, a ΔORR of [redacted]% will be the minimal detectable difference (MDD) for the analysis.

ORR will be compared between treatment arms using the Cochran-Mantel-Haenszel test stratified by the IxRS-recorded stratification factors. Responses after initiation of NALT will not be included in the analysis of ORR.

9.4.2.1.1 Target of Estimation for the Dual Primary Efficacy Endpoint of ORR by IRF

To provide clarity on the target of estimation, the 5 attributes in the estimand framework are defined below:

Population:

- At the time of dual primary ORR analysis, the first [redacted] randomized participants (IAP population), analyzed by randomized treatment group.
- At the time of dual primary PFS analysis, all randomized participants (ITT population), analyzed by randomized treatment group.

Variable: ORR by IRF

Treatment: Participants will be randomized into either Arm A (M + P) or Arm B (R-GemOx). During the conduct of the study participants may also receive concomitant medications as detailed in Section 6.8 of the Protocol.

Intercurrent event and handling strategies:

- [redacted]

Population-level summary for the variable: Difference in proportion for ORR.

9.4.2.2 PFS by IRF

The dual primary endpoint of PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by the IRF with use of the Lugano 2014 Response criteria, or death from any cause, whichever occurs first. For participants who have neither progressed nor died as of the CCOD for analysis, PFS will be censored on the date of last disease assessment when the participant is known to be progression-free. For participants who do not have any evaluable post-baseline tumor assessments, PFS will be censored on the date of randomization. Additional censoring rules for participants who initiated new anti-lymphoma therapy or participants with two or more consecutive missed assessments are detailed in Section 9.4.2.2.1.

The primary endpoint of the study will test the equality of PFS distribution in M+P compared with R-GemOx:

[redacted]

Treatment comparisons will be made with use of a stratified log-rank test with a [redacted]-sided [redacted] level if ORR analysis in IAP (Section 9.2.2) is positive or [redacted] level if ORR analysis is negative. The randomization stratification factors to be used in the efficacy analyses are the number of previous lines of systemic therapy for DLBCL [redacted] and the outcome after the last systemic therapy (relapsed vs. refractory).

The Kaplan-Meier method will be used to estimate the median PFS, if reached, and PFS distribution for each treatment arm. The Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982) will be used to construct the [redacted]% CI for the median PFS for each treatment arm. Stratified Cox proportional-hazards models will be used to estimate the hazard ratio and its [redacted]% CI.

Further details will be provided in the Statistical Analysis Plan.

9.4.2.2.1 Target of Estimation for the Dual Primary Efficacy Endpoint of PFS by IRF

To provide clarity on the target of estimation, the 5 attributes in the estimand framework are defined below:

Population: Defined as all randomized participants, analyzed by randomized treatment group. Inclusion and exclusion criteria have been described in detail in Sections 5.1 and 5.2.

Variable: Progression-free survival, defined as time from randomization to the first occurrence of disease progression, as determined by the IRF with use of the Lugano 2014 Response criteria, or death from any cause, whichever occurs first. Participants who have neither progressed nor died at the CCOD for analysis and participants who are lost to follow-up will be censored on the date of the last evaluable tumor assessment. Participants who did not undergo a post-baseline tumor assessment and did not have a death event will be censored at the time of randomization.

Treatment: Participants will be randomized into either Arm A (M+P) or Arm B (R-GemOx). During the conduct of the study participants may also receive concomitant medications as detailed in Section 6.8.

Intercurrent events and handling strategies:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Population-level summary for the variable: Stratified hazard ratio.

9.4.3 Secondary Endpoints

To control the overall type I error rate at a [redacted]-sided [redacted] level of significance, a hierarchical testing procedure will be used to adjust for multiple statistical testing of the

primary and key secondary efficacy endpoints (Section 9.2.1 and Figure 7). The following key secondary endpoint will be formally tested:

- OS, defined as the time from randomization to death from any cause

The hierarchical ordering of selected secondary endpoints, and method for multiple testing adjustment are described in Section 9.2.1 and in the Statistical Analysis Plan.

The remaining secondary endpoints will be tested without adjusting for multiplicity.

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator, or death due to any cause, whichever occurs first
- CRR, defined as the proportion of participants in whom a CR was observed at any time during the study as determined by the IRF and by the investigator
- ORR, defined as the proportion of participants in whom an objective response (CR or PR) was observed at any time during the study as determined by the investigator
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression, or death from any cause, whichever occurs first, as determined by the IRF and by the investigator
- DOCR, defined as the time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first, as determined by the IRF and by the investigator
- Time to deterioration in physical functioning and fatigue, as measured by the EORTC QLQ-C30
- Time to deterioration in lymphoma symptoms, as measured by FACT-LymS

For the secondary endpoint of OS, for participants who have not died at the CCOD for the analysis, OS will be censored on the last date when the participants are known to be alive. Participants who do not have information after randomization will be censored at the date of randomization. The methodologies detailed for the PFS analysis (see Section 9.4.2) will be used for the OS analysis.

For the secondary efficacy endpoints of CRR and ORR, an estimate of CRR or ORR and its [redacted]% CI will be calculated with use of the Clopper-Pearson method for each treatment arm. The CIs for the difference in CRRs and ORRs between the two treatment arms will be determined with use of the Hauck-Andersen method. CRR and ORR will be compared between treatment arms using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. Responses after initiation of new anti-lymphoma therapy will not be included in the analysis of CRR and ORR.

For the secondary efficacy endpoints of DOR and DOCR, participants who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed and no death event occurred after the date of the first occurrence of a response (or complete response

for DOCR), DOR and DOCR will be censored at the date of the first occurrence of a response. The methodologies detailed for the PFS analysis (Section 9.4.2) will be used for the DOR and DOCR analysis, except that the analysis will not be stratified. DOR and DOCR analysis will be based on a non-randomized subset of participants (specifically, participants who achieved an objective response or a complete response); therefore, comparisons between treatment arms will be made for descriptive purposes.

Time to deterioration analyses will be performed on the EORTC QLQ-C30 and FACT-LymS. For the EORTC QLQ-C30 physical functioning and fatigue scores, time to deterioration in physical functioning and/or fatigue is defined as the time from randomization to the first documentation of a 10-point or more decrease and increase, respectively, from baseline. For the FACT-LymS, time to deterioration in lymphoma-specific symptoms is defined as the time from randomization to the first documentation of a 3-point or more decrease, from baseline. The hazard ratio for deterioration will be estimated using a stratified Cox proportional hazards model. The [redacted]% CI for the hazard ratio will be provided. Participants who do not have an observed deterioration at the time of clinical data cut-off date will be censored at the last non-missing assessment date. Participants without a post-baseline assessment will be censored at randomization.

Secondary Safety Endpoints:

- Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0, including CRS, with severity determined according to the ASTCT CRS grading criteria (Lee et al. 2019; Appendix 11)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events
- Change from baseline in peripheral neuropathy, as measured by the FACT/GOG-Ntx (Appendix 14)

All verbatim adverse event terms occurring on or after first study treatment will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 *(except CRS events, which will be graded according to the ASTCT CRS grading criteria [Lee et al. 2019; Appendix 11])*.

9.4.4 Exploratory Endpoints

Exploratory endpoints are defined in Section 3 (see Table 6). Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

9.4.5 Other Safety Analyses

Incidence of ADA response (presence of serum anti-mosunetuzumab or anti-polatuzumab vedotin) and the potential correlation with PK, pharmacodynamics, and safety parameters may be assessed.

9.4.6 Other Analyses

9.4.6.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.4.6.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, and race/ethnicity) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.4.6.3 Pharmacokinetic Analyses

The PK population for analysis will include all participants who have received at least 1 dose of mosunetuzumab and polatuzumab vedotin and have at least 1 evaluable PK sample post-dose for at least 1 analyte.

Individual and mean concentrations of mosunetuzumab (serum) and polatuzumab total antibody (serum), acMMAE (plasma) and unconjugated MMAE (plasma) versus time data will be tabulated and plotted. The pharmacokinetics of the above analytes will be summarized as the data will allow for by estimating selected PK parameters.
The population PK analysis will investigate the effects of certain covariates on the pharmacokinetics of mosunetuzumab, as data will allow for and at the Sponsor's discretion.

Exposure-response (safety and efficacy) analysis may be conducted using plasma/serum concentrations or relevant PK parameters and available drug effect (e.g., response rate and PFS) and toxicity data, per the Sponsor's discretion and as the data will allow for.

To assess for potential PK drug-drug interactions, PK parameters for mosunetuzumab and each analyte of polatuzumab vedotin will be compared with historical data, as the data will allow for.

9.4.6.4 Immunogenicity Analyses

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, [redacted]

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported with use of standard language/terminology.

9.4.6.5 Clinical Outcome Assessment Analyses

Participant-reported outcomes endpoints include time to deterioration in the EORTC QLQ-C30 physical functioning and fatigue scores and the FACT-LymS; a comparison of the FACT/GOG-NTx peripheral neuropathy score between the two treatment arms will be assessed. Time to deterioration will be compared between treatment arms with use of a stratified log-rank test. For EORTC QLQ-C30 physical functioning and fatigue scores, clinically meaningful deterioration is defined as a ≥ 10-point decrease and increase, respectively, from baseline (Osoba et al. 1998; Cocks et al. 2012). For the FACT-LymS, clinically meaningful deterioration is defined as ≥ 3-point decrease from baseline (Carter et al. 2008; Hlubocky et al. 2013). The hazard ratio for deterioration will be estimated with use of a stratified Cox proportional hazards model. The [redacted]% CI for the hazard ratio will be provided. Kaplan-Meier methodology will be used to estimate 1-year and 2-year rates, as well as the median time to deterioration (if reached) for each treatment arm, and Kaplan-Meier curves will be produced. Participants who do not have an observed deterioration at the time of the CCOD will be censored at the last non-missing assessment date. Participants without a post-baseline assessment will be censored at randomization. Supplemental item-level analyses will be conducted with the individual B-symptom items of the FACT-LymS using a raw 1-point worsening.

A mixed effects model for repeated measures will be used for comparing the EORTC QLQ-C30 treatment-related symptom score and the FACT/GOG-Ntx peripheral neuropathy score between treatment arms.

[redacted].

[redacted]

9.4.6.7 Health Status Utility Analyses

Health utility data from the [redacted] will be evaluated in pharmacoeconomic models. Results from health economic data analyses will be reported separately from the Clinical Study Report.

9.5 INTERIM ANALYSIS

[redacted]

[redacted]

9.6 ASIAN SUBPOPULATION ANALYSES

The Asian subpopulation analysis will be conducted only for China to meet local regulatory requirements, if China is included as a participating country. The objective of this subgroup analysis is to assess the treatment effect of M + P compared with R-GemOx in the Asia subpopulation, and to investigate the consistency in treatment effect between this Asian subpopulation and the global population for the purpose of registration in China.

The Asian subpopulation will include all participants enrolled at China's sites (i.e., during both the global enrollment phase and the extended China enrollment cohort) and the participants enrolled from other Asian countries/regions (e.g., [redacted], etc. during the global enrollment phase). Results from these analyses will be summarized in a separate Clinical Study Report.

The analysis of PFS in the Asian subpopulation will be performed when at least half of the Asian participants have had PFS events and no earlier than the primary analysis for the global population.

9.7 INDEPENDENT DATA MONITORING COMMITTEE

See Section 4.1.3 for information on the iDMC for this study.

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.

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 Bio 1997;270:26–35.

Blincyto® (blinatumomab kit) U.S. Prescribing Information, Amgen, Inc.

Breyanzi® (lisocabtagene maraleucel kit) U.S. Prescribing Information, Juno Therapeutics, Inc.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics1982;38:29–41.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Budde LE, Assouline S, Sehn LH, et al. Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: phase I dose-escalation study. J Clin Oncol 2022;40:481-91.

Budde EL, Olszewski AJ, Assouline S, et al. Mosunetuzumab plus polatuzumab vedotin has promising efficacy and a favorable safety profile in patients with relapsed/refractory aggressive B-cell non-hodgkin lymphoma: Updated results from a phase Ib/II study. Presented at American Society of Hematology, Atlanta, GA. 11–13 December 2021; Abstract # 533.

Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2021;22:790–800.

Carter GC, Liepa AM, Zimmermann AH, et al. Validation of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-LYM) in patients with relapsed/refractory mantel cell lymphoma. Blood 2008;112:2376.

Cazelles C, Belhadj K, Vellemans H, et al. Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed (R/R) DLBCL. A real life study in patients ineligible for autologous transplantation. Blood. 2019;134(Supplement 1):4115.

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;32:3059–68.

Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 2012;48:1713–21.

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's lymphoma. Blood 2009;114:2721–9.

El Chaer F, Auletta JJ, Chemaly RF. How I treat and prevent COVID-19 in patients with hematologic malignancies and recipients of cellular therapies. Blood 2022;140:673–84.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241–52.

Extermann M. Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 2000;35:181–200.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer: EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program 2011;2011:498–505.

Gazyva® (obinutuzumab injection, solution, concentrate) U.S. Prescribing Information, Genentech, Inc.

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.

Harris NL, Kluin P. Follicular lymphoma grade 3B: is it a real disease? Haematologica 2011;96:1244–6.

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.

Hines MR, Knight TE, McNerney KO, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transplant Cell Ther. 2023 Jul;29(7):438.e1-438.e16. doi: 10.1016/j.jtct.2023.03.006. Epub 2023 Mar 9. PMID: 36906275; PMCID: PMC10330221.

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.

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.

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.

Kalakonda N, Maerevoet Marie, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol 2020;7:e511–22.

Kymriah® (tisagenlecleucel injection suspension) U.S. Prescribing Information, Novartis Pharmaceuticals Corporation.

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.

Li X, Shao M, Zeng X, et al. Signaling pathways in the regulation of cytokine release syndrome in human diseases and intervention therapy. Signal Transduc Target Ther 2021;6:367.

Lossos IS, Gascoyne RD. Transformation of follicular lymphoma. Best Pract Res Clin Haematol 2011;24:147–63.

Miyoshi H, Arakawa F, Sato K, et al. Comparison of CD20 expression in B-cell lymphoma between newly diagnosed, untreated cases and those after rituximab treatment. Cancer Sci 2012;103:1567–73.

Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A Phase II Lymphoma Study Association trial. Haematologica 2013;98:1726–31.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. B-Cell Lymphoma and Prevention and Treatment of Cancer-Related Infections [resource on the Internet]. 2020. Available from: https://www.nccn.org/guidelines/category_1#site.

Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013;31:2103–9.

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.

Ong DM, Ashby M, Grigg A, et al. Comprehensive geriatric assessment is useful in an elderly Australian population with diffuse large B-cell lymphoma receiving rituximab-chemotherapy combinations. Br J Haematol. 2019 Oct;187(1):73–81.

Osoba D, Rodrigues G, Myles J, et al. Intrepreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44.

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.

PolivyTM (polatuzumab vedotin-piiq) United States Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761121s000lbl.pdf. Accessed 27 April 2020.

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.

Rituxan® (rituximab injection, solution) E.U. Summary of Product Characteristics.

Rituxan® (rituximab injection, solution) U.S.Prescribing Information, Genentech, Inc.

Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse-large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol 2020;21:978–88.

Schade JR, Kim C, Drill E, et al. Retrospective analysis of gemcitabine and oxaliplatin (GemOx)-based treatment in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. Blood. 2019;134(Supplement 1):2904.

Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse-large B-cell lymphoma. J Clin Oncol 2020;38:155–65.

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.

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.

Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol 2018;36:1443–53.

Tecartus® (brexucabtagene autoleucel suspension) U.S. Prescribing Information, Kite Pharma, Inc.

Thieblemont C, Coiffier B. Lymphoma in older patients. J Clin Oncol 2007;25:1916–23.

Topp MS, Kufer P, Gökbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acutate lymphoblastic leukemia patienst results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011;29:2493–8.

Tucci A, Ferrari S, Bottelli C, et al. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer 2009;115(19):4547–53.

Tucci A, Martelli M, Rigacci L, et al. Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma. Italian Foundation (FIL). Leuk Lymphoma 2015;56:921–6.

Xpovio® (selinexor tablet) U.S. Prescribing Information, Karyopharm Therapeutics Inc.

Yescarta® (axicabtagene ciloleucel suspension) U.S. Prescribing Information, Kite Pharma, Inc.

Zynlonta® (loncastuximab tesirine injection, powder, lyophilized, for solution) U.S. Prescribing Information, ADC Therapeutics America, Inc.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

TABLE OF CONTENTS

A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) or Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- 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
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 Code of Federal Regulations (CFR; U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014 (EEA sites only), and all other applicable local regulations

A1–2 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 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant's legally authorized representative.

Participants who are re-screened are required to sign a new Informed Consent Form.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also

be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 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 75 sites globally will participate to enroll approximately 222 participants. Enrollment will occur through an interactive voice or Web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8.2.4 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An independent Data Monitoring Committee will be employed to monitor and evaluate participant safety throughout the study. An Independent Review Facility (IRF) will collect, store, and review imaging data.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on genomic variants, 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/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants 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.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results.
In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant 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.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Investigators must document their review of each laboratory safety report.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
• Chemistry panel (serum): sodium, potassium, chloride, bicarbonate (or total carbon dioxide if considered standard of care for the region; may be measured using blood gas test per institutional practice), glucose, BUN or urea, creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, GGT, LDH, and uric acid
• C-reactive protein, serum ferritin
• Coagulation: INR, aPTT, PT, and fibrinogen [a]
• HIV serology and viral load: HIV-1/2 antibody and HIV PCR testing [b]
• HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA [c] for individuals with negative HBsAg and a positive HBcAb test
• HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test
• EBV and CMV by quantitative PCR with use of peripheral blood samples
• Quantitative immunoglobulins: IgA, IgG, and IgM
• Pregnancy test • All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Table A2-1 Protocol-Required Safety Laboratory Assessments (cont.)

CMV =cytomegalovirus; EBV = Epstein-Barr virus; 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; LDH = lactate dehydrogenase; PCR = polymerase chain reaction.

[a] Fibrinogen is only tested after tocilizumab is administered following Table 5.

[b] Participants with a positive HIV result at screening should be monitored after receiving study treatment. The HIV viral load will be performed every 3 months (± 4 weeks) until end of study treatment, and then every 6 months (± 4 weeks) during post treatment follow up for 12 months after end of treatment visit. If the HIV viral load is detected (positive), the participant should be treated per local institutional standards, and the Medical Monitor should be notified. Testing may be performed at the local institution. If local laboratory assessments are not available for testing, local laboratory collections may be waived only if samples are collected for central laboratory assessments of viral infections.

[c] Participants with occult or prior hepatitis B infection should undergo monthly DNA testing while the patient is on treatment. During post treatment follow up, the HBV test will continue every 3 months (± 4 weeks) for 12 months after end of treatment visit.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

TABLE OF CONTENTS

A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can; therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition

- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section A3–3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale; for CRS, severity will be determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus grading criteria. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

New events of ICANS and HLH that occur after approval of Protocol Version 5 will continue to be graded according to NCI CTCAE v5.0. In addition, ASTCT grading (Appendix 21 for ICANS and Table A6-8 for HLH) should be provided when describing the case within the additional case details of the Adverse Events eCRF (refer to the eCRF completion guidelines for additional details).

Table A3-1 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]

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE (cont.)

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

Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Examples of instrumental activities of daily living include 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 participants 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 A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of

causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

For participants receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information. New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes 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

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, e-mail, 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.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or the initiation of next anti-lymphoma therapy, whichever is earlier. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware 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 Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail 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 more than 90 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the final dose of study treatment or the initiation of next anti-lymphoma therapy, whichever is earlier), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event 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 e-mailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or e-mail address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF.
Avoid colloquialisms and abbreviations. Only 1 adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 CYTOKINE RELEASE SYNDROME/INJECTION-RELATED REACTIONS ATTRIBUTED TO MONSUNETUZUMAB

Systemic injection-related reactions with symptoms (e.g., fever, headache, myalgia, chills, and fatigue) and CRS may be indistinguishable from one another, given the mechanism of action of mosunetuzumab. Therefore, all adverse events consistent with a diagnosis of systemic reaction or CRS attributed to mosunetuzumab will be recorded singularly as CRS. Adverse events of CRS are graded using the ASTCT CRS Consensus Grading (Appendix 11). 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" related to mosunetuzumab SC, associated signs, symptoms, and laboratory abnormalities should be recorded on the dedicated eCRF for CRS events. Each CRS event should be recorded separately on the Adverse Event eCRF. The associated signs, symptoms, and

laboratory abnormalities should be graded according to NCI CTCAE v5.0 and also recorded separately on the dedicated eCRF for CRS events.

Localized injection-site reactions following SC mosunetuzumab administration should be captured as a diagnosis of "injection site reactions." Associated signs and symptoms will be recorded separately on the dedicated Injection Reaction eCRF. Please see Section A6–1.1.1 for details.

If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF.

In addition to documentations on the Adverse Event eCRF, non-serious Grade ≥2 CRS events and Grade ≥2 injection-site reactions should be reported as a non-serious adverse event of special interest.

A3–7.2 INFUSION-RELATED REACTIONS

Adverse events that occur during or within 24 hours after the infusion of polatuzumab vedotin, rituximab, gemcitabine or oxaliplatin and are judged to be related to study treatment infusion should be captured as a diagnosis of infusion-related 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 eCRF.

A3–7.3 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For adverse events other than cytokine release syndrome/infusion-related/injection reactions (see Section A3–7.1), 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.

A3–7.4 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 3 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.

A3–7.5 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant 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. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 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.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.6 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease 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., dose 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

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., ALP and bilirubin 5 × upper limit of normal [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 A3–7.5 for details on recording persistent adverse events).

A3–7.7 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease 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., dose 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 (e.g., 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 A3–7.5 for details on recording persistent adverse events).

A3–7.8 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ ULN) 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 $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN 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 A3–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.9 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of aggressive NHL should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5).

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").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.10 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").

A3–7.11 LACK OF EFFICACY OR WORSENING OF LYMPHOMA

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of lymphoma on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of lymphoma"). 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 Criteria (Cheson et al. 2014; Appendix 10). 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.

A3–7.12 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., in-patient 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 A3–2), 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 for study treatment administration and monitoring up to 24 hours
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant 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 that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.13 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. 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 or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For mosunetuzumab,

polatuzumab vedotin, rituximab, and tocilizumab, 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.

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.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

A3–7.14 PARTICIPANT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from participant-reported outcomes (PRO) data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile participant reports of treatment-related symptoms via PRO data with investigator reports of adverse events. Sites are not expected to review the PRO data for adverse events.

Appendix 4
Contraceptive and Barrier Guidance

TABLE OF CONTENTS

A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 9 months after the final dose of polatuzumab vedotin, 3 months after the final dose of tocilizumab, 12 months after the final dose of rituximab, 6 months after the final dose of gemcitabine, 9 months after your dose of oxaliplatin. 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 the investigator becomes aware of the pregnancy), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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 or 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 6 months after the final dose of polatuzumab vedotin, and 2 months after the final dose of tocilizumab, 6 months after the final dose of oxaliplatin or gemcitabine, and 3 months after the final dose of rituximab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form 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 e-mailing the form using the fax number or e-mail 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 participant

exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the 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 with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant 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.

A4–3 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 the investigator becomes aware of the event; see Section A3–5).

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 the investigator becomes aware of the event; see Section A3–5). 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.

A4–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment 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 the investigator becomes aware of the event; see Section A3–5).

Appendix 5
Genetics: Use and Analysis of DNA

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to mosunetuzumab and polatuzumab vedotin and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to mosunetuzumab and polatuzumab vedotin and aNHL. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

DNA samples will be analyzed for molecular subsets of diffuse-large B-cell lymphoma. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to mosunetuzumab and polatuzumab vedotin or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on mosunetuzumab and polatuzumab vedotin or cancer continues but no longer than 5 years or other period as per local requirements.

Appendix 6
Safety Plan: Management of Identified and Potential Risks

TABLE OF CONTENTS

On 3 June 2022 and 22 December 2022, mosunetuzumab (Lunsumio) as a monotherapy has been approved by the European commission (via conditional approval) and the FDA (via accelerated approval) for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies. Clinical development is ongoing for additional indications, including aggressive non-Hodgkin's lymphoma (aNHL). On 24 May 2022, the European Commission granted the full marketing authorization for the use of polatuzumab vedotin in combination with R-CHP for the treatment of adult patients with first-line diffuse large B-cell lymphoma (DLBCL). On 19 April 2023, the FDA approved polatuzumab vedotin in combination with R-CHP for treatment of adult patients who have previously untreated DLBCL, NOS or high-grade B-cell lymphoma and who have an IPI score of 2 or greater. Polatuzumab vedotin has also been approved in combination with bendamustine and rituximab in some countries for the treatment of relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Rituximab, gemcitabine, and oxaliplatin are approved and used for the treatment of cancer, including lymphoma. The rituximab, gemcitabine, and oxaliplatin treatment regimen (R-GemOx) is commonly used in clinical practice for the treatment of relapsed or refractory aNHL and is listed in national and international guidelines (National Comprehensive Cancer Network/European Society for Medical Oncology). Refer to local prescribing information for further details of approved use of approved study drugs. The safety plan for participants in this study is based on clinical experience with study drugs in completed and ongoing studies. The anticipated important safety risks for study drugs are outlined below. Please refer to the Mosunetuzumab and Polatuzumab Vedotin Investigator's Brochure, or local prescribing information for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants.
Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dose modification and treatment interruption or discontinuation, are provided below.

A6–1 RISKS ASSOCIATED WITH THE STUDY DRUGS

A6–1.1 RISKS ASSOCIATED WITH MOSUNETUZUMAB

A6–1.1.1 Known Risks Associated with Mosunetuzumab

On the basis of clinical data to date with mosunetuzumab, the identified risks are described below. Refer to the Mosunetuzumab Investigator's Brochure for a description of all anticipated risks for mosunetuzumab.

A6–1.1.1.1 Cytokine Release Syndrome

CRS is a known risk associated with mosunetuzumab. The mechanism of action of mosunetuzumab is immune cell activation against CD20-expressing cells; therefore, a spectrum of events involving injection-related reactions, target-mediated cytokine release, and/or hypersensitivity with or without emergent anti-drug antibodies (ADAs), may occur. Other CD20-directed therapies and immunomodulatory therapies have been associated with IRRs, CRS, and/or hypersensitivity (Rituxan® U.S. Prescribing Information [USPI]; Gazyva® USPI; Blincyto® USPI).

CRS following mosunetuzumab administration has been reported in clinical trials of mosunetuzumab 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 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 institutional practice. Severe CRS may be associated with other clinical sequelae such as disseminated intravascular coagulation, capillary leak syndrome, or may manifest as HLH. The 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 chimeric antigen receptor (CAR) T-cell therapy have been published (Teachey et al. 2013; Lee et al. 2014, Maude et al. 2014; Neelapu et al. 2018; also see U.S. Food and Drug Administration (FDA) approval for 3 products describing risk management for CRS [Yescarta USPI®; Kymriah® USPI; Tecartus® USPI]).

Disease-related factors may be associated with an increased risk of severe CRS following CAR T-cell therapy. Therefore, similar features may be associated with increased CRS risk with T−cell-engaging therapies. These include, but are not limited to, lymphoma bone marrow involvement, extranodal disease, B-cell lymphocytosis, and the presence of circulating peripheral malignant cells. Additional monitoring (i.e., more frequent measurements of vital signs) during mosunetuzumab dosing (especially first dose) should be undertaken and management of treatment-emergent adverse events (including CRS) must adhere to guidance in Section A6–2.3.1.

To minimize the risk and sequelae of CRS, corticosteroid premedication should be administered as described in Section 6.1.2.

See Appendix 3 for adverse event reporting procedures related to CRS. See Table A6-5 for CRS grading scale. See Appendix 7 for anaphylaxis management. Management guidelines for CRS are described in Section A6–2.3.1.

A6–1.1.1.2 Neutropenia

Neutropenia is a known risk associated with mosunetuzumab and is a class effect associated with other CD20-directed therapies as well as blinatumomab (Blincyto USPI). Reversible neutropenia has been observed following mosunetuzumab treatment in Study GO29781. Some participants developing neutropenia have received growth factor support and/or temporary treatment holds. See the Mosunetuzumab Investigator's Brochure for details. The use of growth factor should be considered in participants who experience Grade 3–4 neutropenia, and such participants should be closely monitored with more frequent assessments as applicable. See Table A6-3 and Section A6–2.2.

A6–1.1.1.3 Infections

Infections are a known risk associated with mosunetuzumab. Infections have been observed in Study GO29781.

Mosunetuzumab should not be administered in the presence of active severe infections. Investigators should exercise caution when considering the use of mosunetuzumab in participants with history of recurring or chronic infections or with underlying conditions that may predispose participants to infections. See Section 4.1.1.2 and Section A6–2.2.

Investigators should strongly advise participants to implement behavioral modifications such as masking and social distancing in order to reduce the risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

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

If the participant develops SARS-CoV-2 infection during study treatment, study treatment should be interrupted and the infection should be managed as per local or institutional guidelines (see Section 6.8.1). The infection must be clinically resolved before resumption of study treatment. Investigators must rule out active infection and re-assess benefit-risk balance prior to resuming study treatment. Examples of ruling out an active infection include clinical evaluation of respiratory symptoms, radiological tests to confirm absence of pneumonia, and consideration of negative serial viral testing. Mosunetuzumab administration is not permitted during the presence of active infection.

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

Participants who are HIV positive may be eligible to enroll in the study if specific criteria are met (see Section 5.1). Signs and symptoms of HIV may confound assessment of the safety profile of mosunetuzumab in combination with polatuzumab vedotin. HIV has also been associated with development of secondary HLH. *Participants* with positive HIV should be monitored per local institutional standards while receiving study treatment.

A6–1.1.1.4 Tumor Flare

Adverse events associated with tumor flare have been reported with T-cell-engaging therapies and are consistent with the mechanism of action of mosunetuzumab, leading to the influx of T cells into tumor sites. Events involving tumor flare have been reported with mosunetuzumab. These events tend to occur with a short time to onset following mosunetuzumab administration and present with varying degrees of severity. In addition, depending on tumor size and anatomic location, events associated with tumor flare may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major organs. Depending on the nature of the tumor flare, further medical and/or surgical management may be necessary. If such manifestations are associated with mosunetuzumab, the investigator should consider those events to be tumor flare and report as “tumor flare”.

The recognition of tumor flare may be supported by clinical presentation and temporal association. Tumor flare events tend to have an early onset (Cycles 1 and 2), are transient, and affect organ systems in proximity to tumor involvement. When medically feasible and clinically indicated, a biopsy of the involved site should be obtained to confirm the diagnosis of tumor flare (characterized by immune cell infiltrates) and to exclude other causes, including infection and disease progression. If the clinical presentation involves a new or worsening of pleural or pericardial effusion or ascites, a sample of the fluid may be collected and analyzed.

Participants with tumors involving critical anatomic locations should be closely monitored for tumor flare, and prospective preventive or interventional measures may need to be considered or planned prior to dosing. See the Mosunetuzumab Investigator’s Brochure for the most updated information on tumor flare.

A6–1.1.1.5 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a known risk associated with mosunetuzumab and is a known pharmacodynamic effect of anti-tumor therapy in hematologic malignancies, including non-Hodgkin’s lymphoma (NHL). Tumor lysis syndrome 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 participant characteristics (Coiffier et al. 2008). There is the theoretical risk of TLS if treatment with mosunetuzumab results in the rapid destruction of tumor cells.

The risk of TLS with mosunetuzumab in participants 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 computed tomography [CT] scan) and elevated pretreatment LDH levels, particularly in the presence of dehydration or compromised renal function. While DLBCL, transformed lymphomas, and mantle cell lymphomas 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).

Management guidelines for TLS, including prophylactic measures, are described in Section A6–2.3.4.

A6–1.1.1.6 Injection-Site Reactions

As CD4+ and CD8+ T cells (Mueller et al. 2014) as well as B cells (Egbuniwe et al. 2015) reside in the skin, localized reactions following mosunetuzumab SC administration may occur. The injection-site reactions are an identified risk of mosunetuzumab. Injection-site reactions have been observed in Study GO29781. As of 2 June 2021, injection-site reactions have been reported in 32 participants (47.7%) of 67 participants receiving SC administration of mosunetuzumab. Thirty-one events (46.2%) were Grade 1 and 3 events (4.5%) were Grade 2. No serious injection-site reactions were reported.

See Appendix 3 for adverse event reporting procedures related to injection-site reactions. Management guidelines for injection-site reactions are described in Section A6–2.3.3.

A6–1.1.1.7 Neurologic Toxicity Including ICANS

The symptoms and the presentation of ICANS are varied. The earliest manifestations of ICANS are tremor, dysphagia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy. Subtle manifestations can progress to more severe and potentially life-threatening presentations, including seizures, raised intracranial pressure with cerebral edema, and coma (Lee et al. 2019, Borrega et al. 2019). ICANS has been reported with T cell-redirecting therapies such as bispecific antibodies and CAR T-cell therapies (Maude et al. 2014; Kochenderfer et al. 2015; Blincyto® U.S. Prescribing Information [USPI]; Columvi™ USPI; Lunsumio™ USPI; Tecvayli® USPI).

Neurologic toxicity including ICANS has been reported in patients receiving mosunetuzumab, including severe and life-threatening events. ICANS may occur concurrently with or independently from CRS.

Manifestations of ICANS reported in patients receiving mosunetuzumab included confusional state, delirium, disturbance in attention and cognitive disorder, disorientation, lethargy, memory impairment, and encephalopathy. The majority of cases of ICANS occurred during Cycle 1 of mosunetuzumab treatment.

Management guidelines for neurologic toxicity including ICANS are described in Section A6–2.3.5.

A6–1.1.1.8 Hemophagocytic Lymphohistiocytosis

HLH, a rare condition characterized by inappropriate immune activation, is an identified risk with mosunetuzumab.

HLH is a pathological and biochemical hyperinflammatory syndrome that may present with fever, hepatosplenomegaly, organ failure, and neurologic toxicities and is associated with progression or new onset of hyperferritinemia, cytopenias, coagulopathy with hypofibrinogenemia, and/or elevation of liver enzymes (Hines et al. 2023). HLH may be precipitated by other conditions, such as infections, autoimmune disease, and malignancies (Ramos-Casals et al. 2014; Setiadi et al. 2022), and has been reported with T cell–redirecting therapies such as bispecific antibodies and CAR T-cell therapies (Teachey et al. 2013; Sandler et al. 2020; Kennedy et al. 2021; Abecma® U.S. Prescribing Information [USPI]; Blincyto® USPI; Carvykti® USPI). In the context of CAR T-cell and other immune effector cell therapies, this phenomenon has been described as immune effector cell–associated hemophagocytic lymphohistiocytosis–like syndrome (Hines et al. 2023).

Proposed criteria for diagnosing secondary or reactive HLH in the adult population have been published (Henter et al. 2007; Hejblum et al. 2014; Fardet et al. 2014; McClain and Eckstein 2014; Hines et al. 2023). For management guidelines, see A6–2.3.2.

A6–1.1.2 Potential Risks Associated with Mosunetuzumab

The clinical risks associated with mosunetuzumab are not fully known at this time. This section summarizes the potential risks of treatment with mosunetuzumab. The risks described below are based on available clinical and nonclinical data, the anticipated mechanism of action and clinical experience from molecules of the same class.

A6–1.1.2.1 Thrombocytopenia

Thrombocytopenia is a potential risk associated with mosunetuzumab and 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.

In nonclinical testing of mosunetuzumab in cynomolgus monkeys, hematology findings included transiently decreased WBC, lymphocyte, monocyte, eosinophil, basophil, and platelet counts within the first day of mosunetuzumab exposure, followed by recovery or rebound recovery between Days 4–8. See the Mosunetuzumab Investigator's Brochure for further details on nonclinical assessments on mosunetuzumab.

Participants 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. See Section 4.1.1.2 and Section A6–2.2.

A6–1.1.2.2 Elevated Liver Enzymes

Elevated liver enzymes are a potential risk associated with mosunetuzumab. 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.

In nonclinical testing with mosunetuzumab in cynomolgus monkeys, dose-dependent increases in serum total bilirubin along with C-reactive protein, fibrinogen, PT, and aPTT were observed, consistent with mosunetuzumab-induced cytokine release and an acute-phase protein response, with minimal activation of the coagulation system. Possible drug-related microscopic findings in the liver included single-cell hepatocyte degeneration/necrosis and immune cell infiltration in the portal area. All findings showed evidence of reversibility. See the Mosunetuzumab Investigator's Brochure for further details on nonclinical assessments on mosunetuzumab.

Participants with elevated LFTs at screening will be excluded from this trial (see Section 5.2).

Management guidelines for elevated liver enzymes are described in Section A6–2.3.6.

A6–1.1.2.3 Immunogenicity (Anti-Drug Antibodies)

As with any recombinant antibody, mosunetuzumab may elicit an immune response, and participants may develop antibodies against the molecule. Participants will be closely

monitored for any potential immune response to mosunetuzumab, 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.

A6–1.2 RISKS ASSOCIATED WITH POLATUZUMAB VEDOTIN

A6–1.2.1 Known Risks Associated with Polatuzumab Vedotin

Based on clinical experience with polatuzumab vedotin in patients treated in the current Phase I and Phase II studies, the identified risks are described below. Refer to the Polatuzumab Vedotin Investigator's Brochure for a description of all anticipated risks for polatuzumab vedotin.

A6–1.2.1.1 Myelosuppression: Consolidation of Neutropenia (Including Febrile Neutropenia), Thrombocytopenia, and Anemia

Neutropenia, neutropenia-associated events, thrombocytopenia, and anemia, including serious and severe cases, have been reported in participants receiving polatuzumab vedotin. Adequate hematologic function should be confirmed before initiation of study treatment. Participants 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 A6-3.
The prophylactic (preemptive) or therapeutic use of G-CSF is permitted at the treating physician's discretion. Transfusion support for anemia and thrombocytopenia is permitted at the discretion of the investigator.

A6–1.2.1.2 Peripheral Neuropathy (Sensory and/or Motor)

Peripheral neuropathy (sensory and/or motor) is a known risk associated with polatuzumab vedotin. Participants receiving study treatment should be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, or neuropathic pain. Participants 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 A6-3. Supportive care measures may be implemented per investigator preference (e.g., gabapentin).

A6–1.2.1.3 Infections

Infection is a known risk associated with polatuzumab vedotin. Participants 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 participants

treated with polatuzumab vedotin. Several other risk factors in the participant population under study influencing participants' 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 participants 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 (Flowers et al. 2013; National Comprehensive Cancer Network 2017). Anti-infective prophylaxis should be considered and is described in Section 6.8.1.

A6–1.2.1.4 Infusion-Related Reactions

Infusion-related reactions have been reported in participants receiving polatuzumab vedotin. Commonly experienced events included nausea, vomiting, chills, fever, pruritus, hypotension, flushing, and other symptoms. In the majority of the participants, the events were Grade 1–2.

Premedication for polatuzumab vedotin infusion administration are outlined in Section 6.1.1. Close monitoring throughout the infusion is required, IRRs should be managed as outlined in Table A6-3, and reporting of infusion-related reactions are outlined in Section A3–7.2.

A6–1.2.1.5 Gastrointestinal Toxicity (Diarrhea, Nausea, Vomiting, Constipation)

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

A6–1.2.2 Potential Risks Associated with Polatuzumab Vedotin

A6–1.2.2.1 Progressive Multifocal Leukoencephalopathy

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

A6–1.2.2.2 Immunogenicity (Anti-Drug Antibodies)

As with any recombinant antibody, polatuzumab vedotin may elicit an immune response, and participants may develop antibodies against it. Participants will be closely monitored for any potential immune response to polatuzumab vedotin. Appropriate screening, confirmatory, and characterization assays will be employed to assess ADAs before, during, and after the treatment with polatuzumab vedotin.

A6–1.2.2.3 Hepatotoxicity (Hyperbilirubinemia, Transaminase (ALT and/or AST Elevations)

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

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

For polatuzumab vedotin dose delay, modification, and discontinuation instructions, see Table A6-1.

A6–1.2.2.4 Reproductive Toxicity

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

A6–1.2.2.5 Fatigue and Asthenia

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

A6–1.2.2.6 Hyperglycemia

Hyperglycemia has been observed in participants 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.

A6–1.2.2.7 Renal Toxicity (Increased Serum Creatinine)

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

A6–1.2.2.8 Pulmonary Toxicity (Interstitial Lung Disease)

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

A6–1.2.2.9 Joint Pain, Arthralgia, Skeletal Pain

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

A6–1.2.2.10 Alopecia

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

A6–1.2.2.11 Cardiac Arrhythmias

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

A6–1.2.2.12 Ocular Toxicity

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

A6–1.2.2.13 Dysgeusia

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

A6–1.2.2.14 Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of tumor cells. If any evidence of TLS occurs during the study, tumor lysis prophylaxis measures will be instituted.

Management guidelines for TLS, including prophylactic measures, are described in Section A6–2.3.4.

A6–1.2.2.15 Genotoxicity/Carcinogenicity (Myelodysplastic Syndrome)

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

A6–1.2.2.16 Drug-Drug Interaction (DDI)

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

A6–1.3 RISKS OF OVERLAPPING TOXICITIES WITH MOSUNETUZUMAB AND POLATUZUMAB VEDOTIN

Potential overlapping toxicities between mosunetuzumab and polatuzumab vedotin include thrombocytopenia, neutropenia and infections, TLS, and hepatotoxicity. As such, when these toxicities occur, attribution to a particular agent may be difficult. Treatment hold or discontinuation decisions should in general, apply to both agents in response to these toxicities. See Section A6–2 for details.

A6–1.4 RISKS ASSOCIATED WITH RITUXIMAB

Please see the current Rituximab Investigator's Brochure for full information.

A6–1.5 RISKS ASSOCIATED WITH GEMCITABINE AND OXALIPLATIN

Please see the Prescribing Information/Summary of Product Characteristics for Gemcitabine and Oxaliplatin for full information on risks.

A6–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A6–2.1 DOSE MODIFICATIONS

Dose modifications of tocilizumab, rituximab or gemcitabine are not allowed.
Dose modifications are allowed for mosunetuzumab, polatuzumab vedotin and oxaliplatin for specific non-hematologic adverse events, as detailed in Section A6–2.3. The doses of the drugs must not be escalated after a dose reduction except for CRS events as indicated in Table A6-5. The doses of study drugs must not be modified for hematologic toxicities.

Table A6-1 Dose Levels and Doses for Study Drugs

Dose Level	Mosunetuzumab	Polatuzumab Vedotin	Oxaliplatin
Standard dose	See Table A6-5 for Dose Adjustment after Grade 3 CRS	1.8 mg/kg	100 mg/m^2
Dose level −1		1.4 mg/kg	75 mg/m^2
Dose level −2		Discontinue drug	Discontinue drug

CRS = cytokine-release syndrome.

A6–2.2 TREATMENT INTERRUPTION

For both Arm A and Arm B treatment, subsequent cycles of therapy may commence when ANC reaches ≥ 1000/μL, platelet count reaches ≥ 75,000/μL, and related non-hematologic toxicities have resolved to Grade ≤ 1, otherwise delay the treatment. For participants with extensive bone marrow involvement of lymphoma, and/or disease-related cytopenias at study entry, subsequent cycles of therapy may commence when ANC reaches ≥ 500/μL, platelet count reaches ≥ 50,000/μL, and related non-hematologic toxicities have resolved to Grade ≤ 1.

For participants receiving mosunetuzumab, if dose delay results in a treatment-free interval of 6 weeks or longer, step-up dosing of mosunetuzumab is required with [redacted] mg mosunetuzumab (in combination with polatuzumab vedotin, if applicable) administered on Day 1 of the first cycle after the dose delay, followed by the next planned dose on Day 8 (Table A6-2). Corticosteroid prophylaxis should be administered on both days to mitigate CRS risks.

In general, if one study drug is delayed, the administration of the other study drugs 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 D1 of the same cycle). Exceptions may occur to maintain the schedule of mosunetuzumab step-up.

In the event that a participant has a toxicity necessitating mosunetuzumab interruption for > 7 days prior to the Cycle 1 Day 8 dose (i.e. time since the [redacted] mg dose is greater than 2 weeks), the participant is required to repeat the [redacted] mg mosunetuzumab dose (without polatuzumab vedotin) prior to resuming the planned treatment schedule 7 days after the administration of the [redacted] mg dose; Table A6-2). Corticosteroid prophylaxis should be administered on both days to mitigate CRS risks.

After the [redacted] mg step-up dose is administered, local and central study assessment should be repeated as specified in Table 1 and Table 3.

For treatment interruptions after Cycle 1, Day 8 or Cycle 1, Day 15, treatment should be continued without repeating step-up dosing, unless the treatment-free interval is 6 weeks or longer (see above).

For Arm B, if these required hematologic parameters are not met within 2 weeks after the last treatment, and a similar delay is expected to occur for subsequent treatment, it is acceptable to change the treatment cycle to every 21 days, instead of 14 days.
For treatment delays more than 14 days due to decreased neutrophil or platelet counts, discontinue study treatment. In case a cycle of therapy is delayed for more than 14 days for reasons other than toxicity, re-initiation of treatment may be allowed if the investigator and Sponsor consider this in the best interest of the participant.

If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing a 14 or 21-day schedule as applicable.

Table A6-2 Recommendations for Restarting Therapy Following Dose Delay for Patients in Arm A (Mosunetuzumab SC [redacted] mg)

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)
[redacted]		

Table A6-3 Guidelines for Dose Delay, Modification or Discontinuation of Mosunetuzumab, Polatuzumab Vedotin and Rituximab

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia with or without infection or fever [a] First occurrence	• Delay study treatment for a maximum of 14 days. • Growth factors (e.g., G-CSF) for neutropenia are permitted (in addition to primary prophylaxis per Section A6–1.1.1.2). • Dose of mosunetuzumab, polatuzumab vedotin, and rituximab should not be modified for this reason. • For participants receiving mosunetuzumab, see Section A6–1.1. Consider holding mosunetuzumab for persistent Grade 4 neutropenia.
Recurrent Grade 3 or 4 neutropenia	• Delay study treatment for a maximum of 14 days. • Growth factors (e.g., G-CSF) for neutropenia are permitted (in addition to primary prophylaxis per Section A6–1.1.1.2). • Dose of mosunetuzumab, polatuzumab vedotin, and rituximab should not be modified for this reason. • For participants receiving mosunetuzumab, see Section A6–1.1. Consider holding mosunetuzumab for persistent Grade 4 neutropenia. • If Grade 3–4 neutropenia persists despite growth factor support, in the absence of fever, participant may continue study treatment at the investigator's discretion.
Grade 3 or 4 thrombocytopenia First occurrence	• Delay study treatment for a maximum of 14 days. • If platelet count recovers to ≥ 75,000/μL ≤ Day 7 of the scheduled date of the next cycle, administer full dose of study treatment. • Dose of mosunetuzumab polatuzumab vedotin, and rituximab should not be modified for this reason. • For participants receiving mosunetuzumab, see Section A6–1.1. Consider holding mosunetuzumab for persistent Grade 4 thrombocytopenia.

Table A6–3 Guidelines for Dose Delay, Modification or Discontinuation of Mosunetuzumab, Polatuzumab Vedotin and Rituximab (cont.)

Event(s)	Dose Delay or Modification
Recurrent Grade 3 or 4 thrombocytopenia	• Delay all study treatment for a maximum of 14 days. • If platelet count recovers to ≥ 75,000/μL ≤ Day 7 after the scheduled date of the next cycle, administer full dose of all study drugs. • Dose of mosunetuzumab, polatuzumab vedotin, and rituximab should not be modified for this reason. • For participants receiving mosunetuzumab, see Section A6–1.1. Consider holding mosunetuzumab for persistent Grade 4 thrombocytopenia.
Grade 1 peripheral neuropathy	• No study treatment modification is recommended for Grade 1 sensory or motor peripheral neuropathy.
Grade 2 or 3 peripheral neuropathy (including peripheral sensory or motor neuropathy)	• Delay all study treatment. • If recovered to Grade ≤ 1 within ≤ 14 days of the scheduled date of the next cycle: – If the dose of polatuzumab vedotin is 1.8 mg/kg, then reduce polatuzumab vedotin to 1.4 mg/kg (permanent dose reduction). Mosunetuzumab may be administered at the recommended dose. – If there was a prior dose reduction of polatuzumab vedotin to 1.4 mg/kg for Grade 2 or 3 peripheral neuropathy, polatuzumab vedotin must be permanently discontinued. Mosunetuzumab may be administered at the recommended dose. • If not recovered to Grade ≤ 1 until > 14 days or after the scheduled date for the next cycle, polatuzumab vedotin must be permanently discontinued. Mosunetuzumab may be administered at the recommended dose.
Grade 4 peripheral neuropathy (including peripheral sensory or motor neuropathy)	• Discontinue polatuzumab vedotin treatment permanently. • Participants should be evaluated regarding the continuation of mosunetuzumab on the basis of their benefit-risk.

Table A6–3 Guidelines for Dose Delay, Modification or Discontinuation of Mosunetuzumab, Polatuzumab Vedotin and Rituximab (cont.)

Event(s)	Dose Delay or Modification
Bilirubin > 3.0 mg/dL	• Delay all treatment until resolution to ≤ 1.5 mg/dL within ≤ 14 days. Evaluate for causality. • Dose delay should be avoided if hyperbilirubinemia is not related to hepatic injury (i.e., hemolysis or Gilbert disease). In these cases, dose delay considerations should be guided by direct bilirubin levels. • Consider withholding mosunetuzumab (see Section A6–2.3.6, Elevated Liver Enzymes and Hepatotoxicity).
Grade 3 or 4 constipation or ileus	• Withhold polatuzumab vedotin until improvement to Grade ≤ 2. Mosunetuzumab may be continued or delayed at the discretion of the investigator. • Consider reducing polatuzumab vedotin to the next dose level (see Table A6-1) after improvement to Grade ≤ 2.
Grade 3 or 4 TLS	• Withhold all study treatment. The participant's next dose may be delayed for up to 14 days. • Following complete resolution TLS, study treatment may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy. • For mosunetuzumab-specific TLS guidance, see Section A6–2.3.4, Tumor Lysis Syndrome.
Grade 3 IRR, second episode	• Discontinue polatuzumab vedotin or rituximab permanently. – If IRR is attributed to polatuzumab vedotin, discontinue polatuzumab vedotin and continue mosunetuzumab and follow Table A6-4 – If IRR is attributed to rituximab, discontinue rituximab and continue with GemOx and follow Table A6-4.

Table A6–3 Guidelines for Dose Delay, Modification or Discontinuation of Mosunetuzumab, Polatuzumab Vedotin and Rituximab (cont.)

Event(s)	Dose Delay or Modification
Grade 3 or 4 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	• Consider delaying all study treatment for a maximum of 14 days. • Subsequent recurrence: Based on the nature of the toxicity, decrease polatuzumab vedotin to a lower dose as described in Table A6-1). There are no dose reductions for mosunetuzumab. • 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.
Hepatitis B reactivation (as noted by new detectable HBV-DNA levels)	• HBV-DNA levels between WHO-recommended range of 29–100 IU/mL: Re-test within 2 weeks. If still positive, hold all study treatment and treat participant with an appropriate nucleoside analogue. Immediately refer participant to a gastroenterologist or hepatologist. • HBV-DNA levels at WHO-recommended cutoff of > 100 IU/mL: Hold all study treatment and treat the participant with an appropriate nucleoside analogue. Immediately refer participant to a gastroenterologist or hepatologist. • Rising HBV-DNA viral load (exceeding 100 IU/mL) while on an appropriate anti-viral therapy: Discontinue all study treatment immediately.

G-CSF = granulocyte colony-stimulating factor; GemOx = gemcitabine, oxaliplatin; HBV = hepatitis B virus; IRR = infusion-related reaction; TLS = tumor lysis syndrome; WHO = World Health Organization.

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

A6–2.3 MANAGEMENT GUIDELINES

Table A6-4 Management of Infusion-Related Reactions from Polatuzumab Vedotin (Arm A) or Rituximab (Arm B)

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

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: Participants should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the previous 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids (e.g., prednisolone 100 mg IV or equivalent), and/or bronchodilators. Participants 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/hour every 30 minutes.

A6–2.3.1 Management of Cytokine Release Syndrome (Arm A)

Management guidelines for CRS following mosunetuzumab treatment are summarized with the grading of CRS following the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria (Lee et al. 2019; Appendix 11) and described in Table A6-5.

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

Severe SARS−CoV-2 infection is associated with CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ. If a participant develops severe CRS, the differential diagnosis should include SARS−CoV-2 and relevant testing performed at the discretion of the investigator. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table A6-5 Guidelines for Management of Cytokine Release Syndrome after Mosunetuzumab in Arm A (M+P)

CRS Grade [a]	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 1 fever ≥ 38ºC	• Symptomatic management of constitutional symptoms and organ toxicities; if symptoms do not resolve, manage per Grade 2 • Consider empiric broad spectrum antibiotics • Consider G-CSF if participant is neutropenic • Maintenance IV fluids for hydration • Consider hospitalization until symptoms completely resolve	• For prolonged CRS (> 2 days) in participants with significant symptoms and/or comorbidities (per investigator discretion, e.g., impaired cardiovascular function, reduced pulmonary reserve), consider tocilizumab and corticosteroids as per Grade 2	• May receive the next dose of mosunetuzumab if symptoms resolve for 3 consecutive days • Administer premedications for next dose per Section 6.1.1 • The participant should be monitored more frequently

Table A6–5 Guidelines for Management of Cytokine Release Syndrome after Mosunetuzumab in Arm A (M+P) (cont.)

CRS Grade [a]	• Supportive Care	• Anti–IL-6 or Corticosteroid Therapy	• Action for Next Mosunetuzumab Dose
Grade 2 fever ≥ 38ºC [b] with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen [c] by nasal cannula or blow-by	• Symptomatic management of constitutional symptoms and organ toxicities • Consider ICU admission for hemodynamic monitoring • For hypotension: IV fluid bolus as needed; for persistent refractory hypotension (e.g., after 2 fluid boluses and anti–IL-6 therapy), start vasopressors and manage per Grade 3 • Rule out other inflammatory conditions, which can mimic severe CRS (e.g., infections/sepsis) • Consider empiric broad spectrum antibiotics • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH as described in Section A6–2.3	• Consider tocilizumab [d] • For persistent refractory hypotension after 1 or 2 doses of anti–IL-6 therapy, consider 10 mg IV dexamethasone every 6 hours (or equivalent) • Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab	• May receive the next dose of mosunetuzumab as planned if symptoms resolve to Grade ≤ 1 for 3 consecutive days • Consider enhanced premedications for next dose • Consider hospitalization for the next dose if it is a higher dose [e]

Table A6–5 Guidelines for Management of Cytokine Release Syndrome after Mosunetuzumab in Arm A (M+P) (cont.)

CRS Grade [a]	• Supportive Care	• Anti–IL-6 or Corticosteroid Therapy	• Action for Next Mosunetuzumab Dose
Grade 3 fever ≥ 38ºC [b] with hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non- rebreather mask, or Venturi-mask	• Symptomatic management of organ toxicities, admit participant to ICU for hemodynamic monitoring • For hypotension: IV fluid bolus and vasopressors as needed • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis) • Consider empiric broad spectrum antibiotics	• Administer tocilizumab [d] • Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, manage as per Grade 4 [c] Manage per Grade 4, if no improvement within 18–24 hours after second dose of tocilizumab	• May receive the next 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 • Enhanced premedications for next dose • Hospitalize participant for next dose • If the event occurred after [redacted] mg, the next dose should be again [redacted] mg

Table A6–5 Guidelines for Management of Cytokine Release Syndrome after Mosunetuzumab in Arm A (M+P) (cont.)

CRS Grade [a]	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
	• If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH (see Section A6–2.3)		• If the event occurred after [redacted] mg, the next dose should be [redacted] mg • If the next dose is tolerated without Grade ≥ 3 CRS, the participant may return to the originally planned dose • If Grade 3 CRS recurs with subsequent doses, consider permanent discontinuation
Grade 4 fever ≥ 38° [b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., C-PAP, Bi-PAP, intubation, and mechanical ventilation)	• ICU admission and hemodynamic monitoring • Mechanical ventilation as needed • IV fluids and vasopressors as needed • Symptomatic management of organ toxicities • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis) • Consider empiric broad spectrum antibiotics	• Administer tocilizumab [d] • For participant's refractory to tocilizumab, consider siltuximab, anakinra, dasatinib, and emapalumab, based on discretion of the investigator; management should be discussed with the Medical Monitor [f] • Administer 10 mg IV dexamethasone every 6 hours (or equivalent) • If refractory, consider 1000 mg/day IV methylprednisolone [g, h]	• Permanently discontinue mosunetuzumab [i]

Table A6–5 Guidelines for Management of Cytokine Release Syndrome after Mosunetuzumab in Arm A (M+P) (cont.)

CRS Grade [a]	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
	• If no improvement within 24 hours, initiate work-up and assess for signs and symptoms HLH (see Section A6–2.3)		

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

[a] Cytokine release syndrome will be assessed according to the ASTCT Consensus Grading Criteria (Lee et al. 2019; see Appendix 11). Fever is defined as temperature ≥ 38ºC not attributable to any other cause. In participants who have CRS and then receive an anti-pyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. Cytokine release syndrome grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

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

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

[d] See Table 5 for tocilizumab treatment for CRS. Tocilizumab should be administered at a dose of 8 mg/kg IV (not exceeding 800 mg per infusion). If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second dose may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time-period of 6 weeks of mosunetuzumab treatment, the total number of tocilizumab doses should not exceed 3 doses.

Table A6–5 Guidelines for Management of Cytokine Release Syndrome after Mosunetuzumab in Arm A (M+P) (cont.)

[e] Although hospitalization is not mandated for participants in Arm A, the investigator should actively assess the need for hospitalization based on their individual conditions.

[f] Riegler et al. 2019.

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

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

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

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

A6–2.3.2 Management of Hemophagocytic Lymphohistiocytosis (Arm A)

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

HLH should be diagnosed on the basis of criteria developed by an ASTCT working group (Hines et al. 2023), as outlined in Table A6-6*. When reporting new HLH events, severity will continue be graded according to NCI CTCAE v.5.0. In addition ASTCT grading (Table A6-8) should be used when describing event details within the Additional Case Details section on the Adverse Events eCRF page (refer to the eCRF guidelines for additional details). Patients with suspected or confirmed HLH should be treated according to the guidelines in* Table A6-7*.*

Table A6-6 Criteria for Diagnosing Hemophagocytic Lymphohistiocytosis

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

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

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

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

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

[d] *As distinguished from CRS onset or recrudescence.*

Table A6-7 Management Guidelines for Hemophagocytic Lymphohistiocytosis

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

Table A6-7 Management Guidelines for Hemophagocytic Lymphohistiocytosis (cont.)

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

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

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

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

Table A6-8 ASTCT Grading Scale for Hemophagocytic Lymphohistiocytosis

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

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

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

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

A6–2.3.3 Injection-Site Reactions After Mosunetuzumab SC (Arm A)

Participants who experience localized injection-site reactions following SC administration of mosunetuzumab should be managed according to the guidelines detailed in Table A6-9.

Table A6-9 Management Guidelines for Injection-Site Reactions

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

A6–2.3.4 Tumor Lysis Syndrome (Arm A and B)

Treatment for laboratory and or clinical presentations of TLS will follow institutional practice. Prophylaxis of TLS should follow local institutional practice; however, for participants in Arm A, the following measures must be implemented.

All participants in Arm A should receive adequate hydration prior to study drug administration during Cycles 1 and 2. In general, it is recommended that participants receive oral or IV hydration consisting of a fluid intake of approximately 2–3 L/day starting 24–48 hours prior to the study drug administration and at least 24 hours after study drug administration. Modification of the fluid rate should be considered for individuals with specific medical needs.

In addition, administration of an agent to reduce uric acid should be considered:

- Allopurinol (e.g., 300 mg/day orally beginning 72 hours prior to dose and continuing for 3–7 days afterward) for those participants judged to be of low or intermediate risk of developing TLS, per investigator's discretion
- For participants with elevated uric acid levels prior to study treatment or considered to be at high risk for TLS: Rasburicase (e.g., 0.2 mg/kg IV over 30 minutes prior to first dose mosunetuzumab and daily for up to 5 days thereafter) should be administered, unless contraindicated (Elitek® USPI)

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

A6–2.3.5 Neurologic *Toxicity Including ICANS* (Arm A)

All participants will be required to undergo a complete physical examination that includes a neurological system evaluation at screening (baseline) prior to study treatment and targeted physical examination as per the Schedule of Activities (see Section 1.3). Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. If there is a baseline Immune Effector Cell-Associated Encephalopathy (ICE) score, record it in the participant's chart.

Participants should be routinely assessed for any signs or symptoms of neurologic toxicity including ICANS as part of the on-treatment clinical examination (see Section 8.2). If new or worsening neurologic toxicity is suspected, see A6–2.3.5 *for management guidelines and Section 8.3 for adverse event reporting.*

The American Society for Transplantation and Cellular Therapy (ASTCT) ICANS Consensus Grading for Adults (Lee et al. 2019) and Immune Effector Cell-Associated Encephalopathy (ICE) scoring system are summarized in Appendix 21 and Table A6-10. Imaging studies should be performed if clinically indicated.

For participants developing peripheral neuropathy, see Table A6-3. For participants receiving both polatuzumab vedotin and mosunetuzumab who develop Grade ≥2 peripheral sensory neuropathy and/or peripheral motor neuropathy, consideration for holding or discontinuing mosunetuzumab in addition to action taken with polatuzumab vedotin should be made.

The investigator should instruct participants to refrain from driving or engaging in hazardous occupations or activities if the participants develop specific adverse events while on mosunetuzumab:

- For participants who develop a neurologic *toxicity, including ICANS,* that may affect driving (see *Appendix 22*) and for participants who develop CRS, HLH, or Grade 3–4 LFT elevation, the investigator should advise participants to refrain from driving or engaging in hazardous occupations or activities until the event is resolved.
- Participants who develop tremor, dizziness, insomnia, or a Grade ≥3 neurologic adverse event should be assessed by neurologic examination to determine if the adverse event may impair the ability of the participant to drive or engage in hazardous occupations or activities. For participants assessed to be at increased risk, the investigator should advise the participant to refrain from driving or engaging in hazardous occupations or activities until the event is resolved.

Table A6-10 Management Guidelines for Neurologic *Toxicity Including ICANS* for Participants Receiving Mosunetuzumab

Event [a, b]	*Action to Be Taken*
General Guidance	• *Consider hospitalizing the participant for monitoring as clinically needed. If clinically indicated, transfer participant to ICU and initiate measures for protection of airway.* • *Assess patients for ICE using the ICE score.* • *Consider imaging of the brain (MRI preferred), lumbar puncture, fundoscopy, and/or EEG, taking into account risks for procedures.* • *Rule out other causes (e.g., infection, cerebral hemorrhage, electrolyte imbalance, concomitant medications, other medical conditions).* • *Avoid medication that would cause further CNS depression.* • *See Section A6–2.2 for guidance on restarting mosunetuzumab after dose delay.* • *Consult the Medical Monitor* • *Guidance for neurologic toxicity including ICANS concurrently with CRS:* – *Administer medications as outlined below:* o *Compare the corticosteroid regimen in the guidelines for ICANS below with the regimen in the guidelines for CRS (see Table A6-5) and administer the most aggressive regimen. Dexamethasone is the preferred corticosteroid.* – *Administer tocilizumab as per guidelines for CRS (see Table A6-5).*
Grade 1	• *Continue mosunetuzumab and monitor neurologic toxicity symptoms.* • *If Grade 1 ICANS, [b] consider a single dose of dexamethasone 10 mg, if not taking other corticosteroids.*
Grade 2	• *Withhold mosunetuzumab until neurologic toxicity symptoms improve to Grade 1 or baseline. [c, d]* • *Provide supportive therapy and consider neurologic consultation and evaluation.* • *If Grade 2 ICANS, [b] treat with dexamethasone 10 mg intravenously every 12 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper.*

Table A6-10 Management Guidelines for Neurologic *Toxicity Including ICANS* for Participants Receiving Mosunetuzumab (cont.)

Grade 3	• *Withhold mosunetuzumab until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 7 days.* [d, e] • *For Grade 3 neurologic events lasting more than 7 days, consider permanently discontinuing mosunetuzumab.* • *Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation.* • *If Grade 3 ICANS,* [b] *treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids until improvement to Grade 1, then taper. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed.*
Grade 4	• *Permanently discontinue mosunetuzumab.* • *Provide supportive therapy, which may include intensive care, and consider neurology consultation and evaluation.* • *If Grade 4 ICANS,* [b] *treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids until improvement to Grade 1, then taper. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed.*

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

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

[b] *ASTCT consensus grading criteria.*

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

[d] *See Section A6–2.2 for guidance on restarting mosunetuzumab after dose delay.*

[e] *Evaluate benefit–risk before restarting mosunetuzumab.*

A6–2.3.6 Elevated Liver Enzymes and Hepatotoxicity (Arm A)

Guidelines for hepatotoxicity in Table A6-11 apply for participants receiving mosunetuzumab.

For participants with isolated elevated bilirubin, see Table A6-3.

For participants 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. Similarly, for participants developing elevated liver enzymes with or without elevated bilirubin, considerations for withholding or discontinuing polatuzumab vedotin should be made.

Transient Grade 3 AST and ALT elevations have been observed with mosunetuzumab in the setting of CRS and have resolved with supportive treatment. Hemophagocytic lymphohistiocytosis (see Section A6–1.1.2.1) 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 A6-11 Management Guidelines for Liver Function Test Abnormalities and Hepatic Events for Participants Receiving Mosunetuzumab

LFT Abnormality	Management
Grade 1 AST or ALT elevation	• Continue mosunetuzumab. • Notify Medical Monitor and monitor LFTs (including AST, ALT, and bilirubin) weekly
Grade 2 AST or ALT elevation	**All events:** • Withhold mosunetuzumab • Monitor LFTs at least weekly and as clinically indicated until values resolve to normal or baseline • Resume mosunetuzumab when resolved to Grade $\leq$ 1 or baseline • Consider hepatology consultation **Events > 5 days' duration:** • Obtain hepatology consultation; evaluate etiology

Table A6–11 Management Guidelines for Liver Function Test Abnormalities and Hepatic Events for Participants Receiving Mosunetuzumab (cont.)

LFT Abnormality	Management
Grade 3 AST or ALT elevation	**All events:** • Withhold mosunetuzumab • Monitor LFTs every 24–48 hours until decreasing, and then follow weekly • Obtain hepatology consultation; consider liver biopsy to assess hepatic injury [a] • Resume mosunetuzumab when resolved to Grade ≤ 1 or baseline **Events > 5 days' duration** • Resume mosunetuzumab when resolved to Grade ≤ 1 or baseline [a]
Grade 4 AST or ALT elevation	• Permanently discontinue mosunetuzumab [b] • 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 A6–1.1.1.1) HLH (Section A6–1.1.2.1) 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 participants who are deriving benefit and who have fully recovered from the immune-related event. Participants may resume dosing with mosunetuzumab only after discussion with the investigator and the Medical Monitor.

A6–2.4 MANAGEMENT OF ADVERSE EVENTS (ARM B)

The management guidelines for oxaliplatin-induced neuropathy in participants in Arm B is summarized in Table A6-12. The management of other non-hematologic adverse events in Arm B should follow institutional standard or guidelines. Of note, hematologic toxicities may lead to dose interruption as described in Section A6–2.2 but not dose modification.

Table A6-12 Guidelines for Management of Participants who Experience Oxaliplatin-Induced Neuropathy (Arm B)

Event	Management Guidelines
Acute pharyngolaryngeal dysesthesia (subjective sensation of dysphagia or dyspnea without stridor or wheezing)	• Avoid ice during infusion • Limit exposure to cold temperature or cold objects • Consider prolongation of infusion for up to 6 hours or per institutional guidelines
Grade 2 peripheral sensory neuropathy, paresthesia, or gait disturbance	• For persistent Grade 2 neurosensory events that do not recover to at least Grade 1 by the time of the next scheduled oxaliplatin dose, reduce oxaliplatin by one level and continue other study treatments • If the participant has Grade 2 neurosensory event at the time that subsequent doses are due, continue other study treatment and withhold oxaliplatin, and • If neurosensory event recovered to Grade ≤ 1 at the start of subsequent cycle, continue treatment with reduced oxaliplatin dose by one level • If neurosensory event does not recover to Grade ≤ 1 for another cycle, discontinue oxaliplatin
Grade 3 peripheral sensory neuropathy, paresthesia, or gait disturbance	• If the participant has Grade 3 neurosensory event any time during the study that recovers to at least Grade 1 by the time of the next scheduled oxaliplatin dose, reduce oxaliplatin by one level and continue study treatments • If the participant has Grade 3 neurosensory event any time during the study that does not recover to Grade ≤ 1 by the time of next scheduled oxaliplatin dose, or for recurrent Grade 3 events, permanently discontinue oxaliplatin
Grade 4 peripheral sensory neuropathy, paresthesia, or gait disturbance	• Permanently discontinue oxaliplatin

REFERENCES

Adcetris® (brentuximab vedotin) U.S. Prescribing Information, Seagen, Inc.

Blincyto® (blinatumomab kit) U.S. Prescribing Information, Amgen, Inc.

Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumor lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol 2010;149:578–86.

Coiffier B, Altman A, Pui C, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based erview. J Clin Oncol 2008;26:2767–78.

Egbuniwe IU, Karagiannis SN, Nestle FO, et al. Revisiting the role of B cells in skin immune surveillance. Trends Immunol 2015;36:102–11.

Elitek® (rasburicase kit) U.S. Prescribing Information, Sanofi-Aventis U.S., LLC.

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.

Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2013;31:794–810.

Gazyva® (obinutuzumab injection) U.S. Prescribing Information, Genentech, Inc.

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.

Hines MR, Knight TE, McNerney KO, et al. Immune effector cell−associated hemophagocytic lymphohistiocytosis-like syndrome. Transplant Cell Ther 2023;29:438.e1−e16.

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364:1844–54.

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.

Kennedy VE, Wong C, Huang CY, et al. Macrophage activation syndrome-like (MAS-L) manifestations following BCMA-directed CAR T cells in multiple myeloma. Blood Adv 2021;5:5344−8.

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.

Kymriah® (tisagenlecleucel injection suspension) U.S. Prescribing Information, Novartis Pharmaceuticals Corporation.

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.

Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507–17.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis [resource on the Internet]. Up-to-Date 2019 [cited: 16 October 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. B-Cell Lymphoma and Prevention and Treatment of Cancer-Related Infections [resource on the Internet]. 2017. Available from: https://www.nccn.org/guidelines/category_1#site

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.

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.

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 injection, solution) U.S. Prescribing Information, Genentech, Inc.

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.

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;17:22–6.

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;18:32–6.

Sandler RD, Tattersall RS, Schoemans H, et al. Diagnosis and management of secondary HLH/MAS following HSCT and CAR-T cell therapy in adults; a review of the literature and a survey of practice within EBMT centres on behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front Immunol 2020;11:524.

Scram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Setiadi A, Zoref-Lorenz A, Lee CY, et al. Malignancy-associated haemophagocytic lymphohistiocytosis. Lancet Haematol 2022;9:e217−27.

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 2016;128:1441.

Tecartus® (brexucabtagene autoleucel suspension) U.S. Prescribing Information, Kite Pharma, Inc.

Viardot A, Goebeler ME, Hess G, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. Blood 2016;127:1410–6.

Yescarta® (axicabtagene ciloleucel suspension) U.S. Prescribing Information, Kite Pharma, Inc.

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.

Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), SC, IV, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

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

3. Stop the study treatment administration, if possible.
4. Call for additional medical assistance.
5. Maintain an adequate airway.
6. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
7. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
8. Continue to observe the participant and document observations.

Appendix 8
European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30)

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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
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

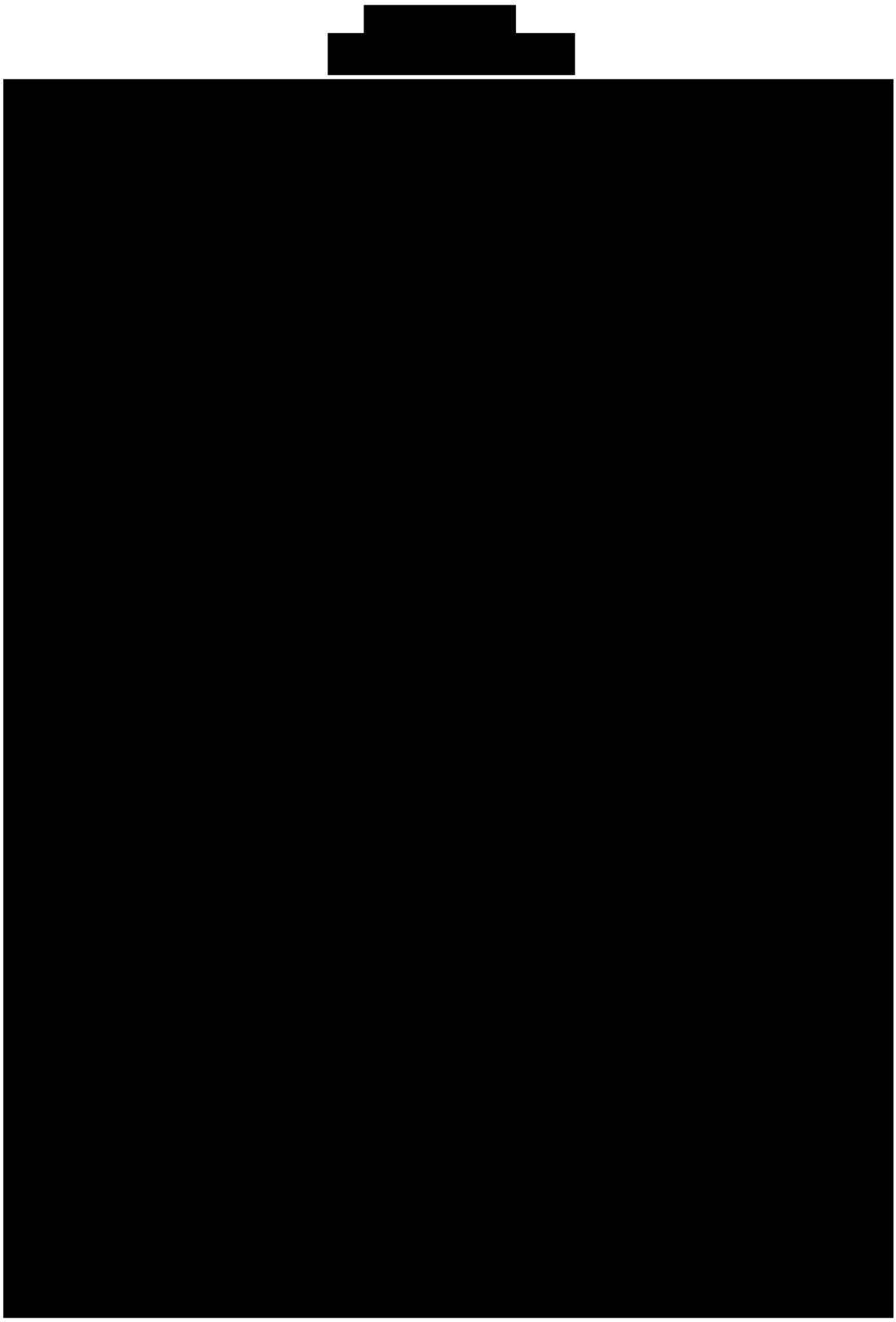
For the following questions please circle the number between 1 and 7 that best applies to you

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



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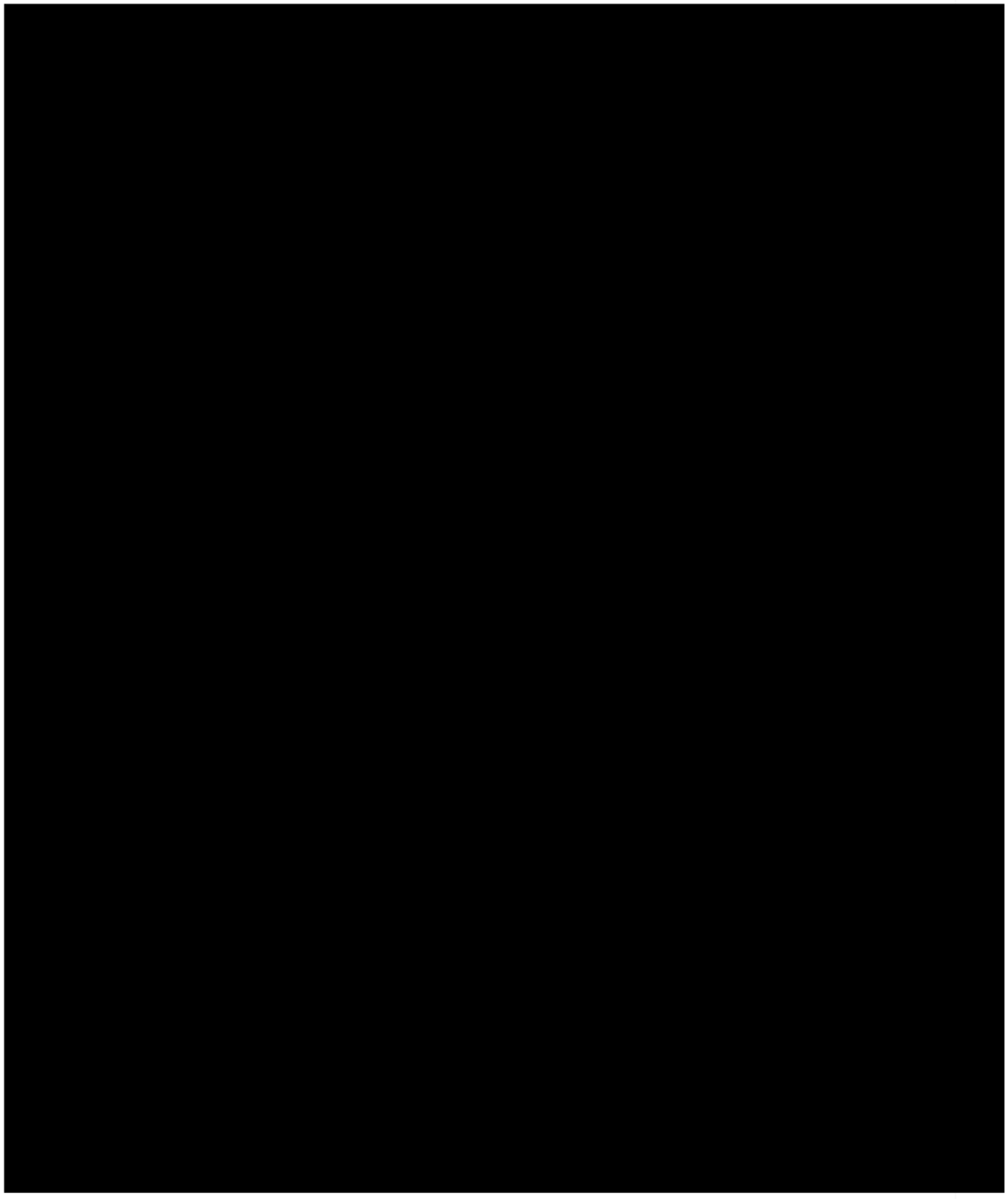

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Appendix 10
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

TARGET AND NON-TARGET LESIONS

Up to 6 of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters should be identified from different body regions representative of the participant'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 6 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 non-measured disease as non-target lesions (e.g., cutaneous, gastrointestinal, 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 10: Lugano Response Criteria for Malignant Lymphoma

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] 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 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
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 For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation

Appendix 10: Lugano Response Criteria for Malignant Lymphoma

Revised Criteria for Response Assessment		
Response and Site	**PET–CT-Based Response**	**CT-Based Response**
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
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 six 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 10: Lugano Response Criteria for Malignant Lymphoma

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 nadir[c] (baseline can be the nadir when there has not been prior regression of the involved lesions) and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly (> 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. New or recurrent splenomegaly 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 A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Appendix 10: Lugano Response Criteria for Malignant Lymphoma

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; 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 participants indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).
Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 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.

[c] Deviation from Lugano Criteria (Cheson 2014): Progressive Metabolic Disease (PMD) assessment to be compared to nadir, not baseline (unless the nadir is the baseline visit)

Appendix 11
American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Criteria for Cytokine Release Syndrome

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

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

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS.

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

REFERENCE

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

Appendix 12
Eastern Cooperative Oncology Group (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 13
Functional Assessment of Cancer Therapy–Lymphoma
Lymphoma Subscale

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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
B53	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
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
On1	I have a loss of appetite	0	1	2	3	4
HR	I have trouble concentrating	0	1	2	3	4
N3	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 14
Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity

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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
HI12	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
An6	I have trouble walking	0	1	2	3	4

Appendix 15
Calculation of Creatinine Clearance With Use of the Cockcroft–Gault Formula

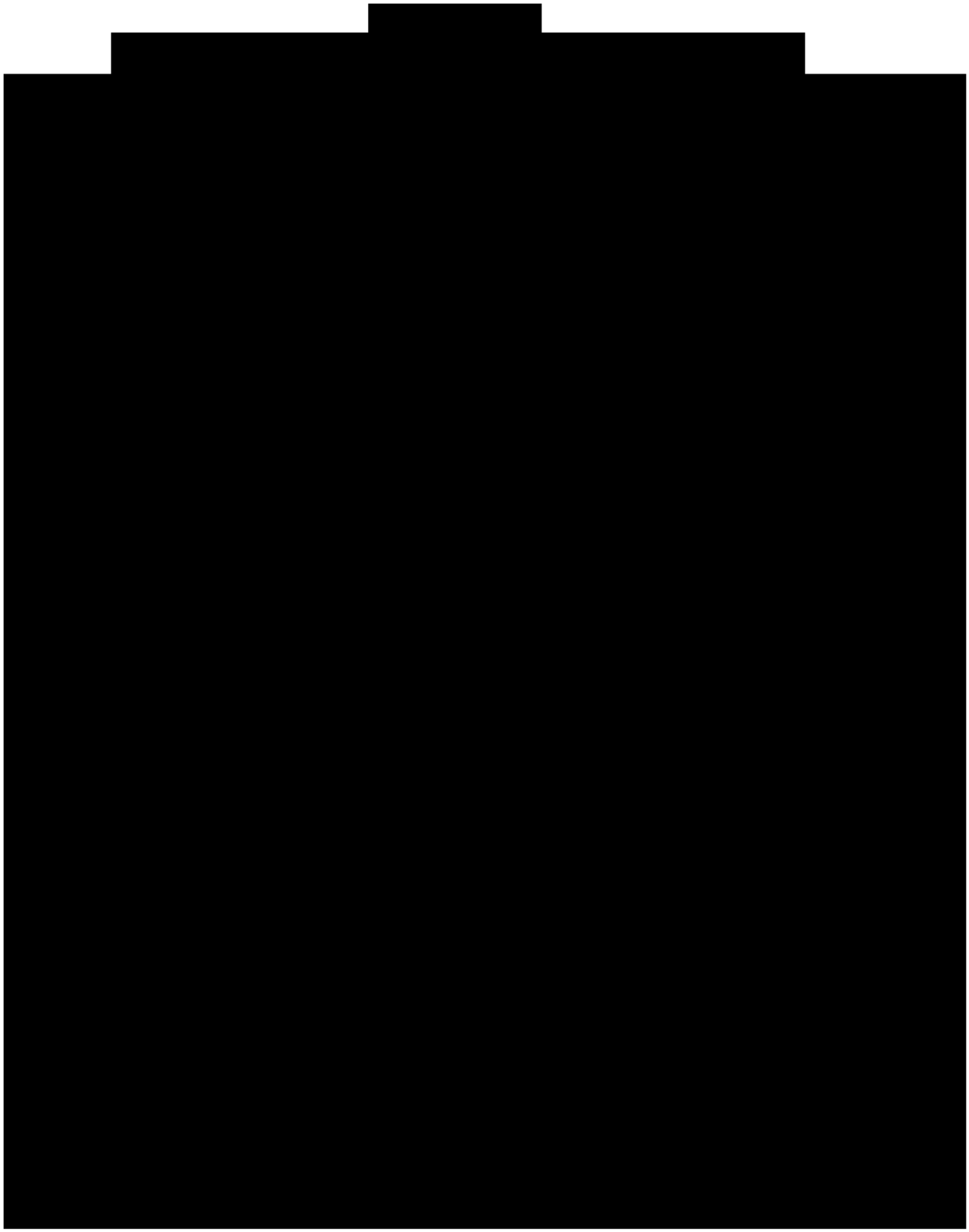
Creatinine clearance (CrCl) will be calculated with use of the following formula:

$$\text{CrCl (men)} = (140 - \text{Age}) \times \text{weight [in kilograms]} / \text{Serum Cr (mg/dL)} \times 72$$

$$\text{CrCl (women)} = 0.85 \times (140 - \text{Age}) \times \text{weight [in kilograms]} / \text{Serum Cr (mg/dL)} \times 72$$

REFERENCE

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine [editorial]. Nephron 1992;62:249.



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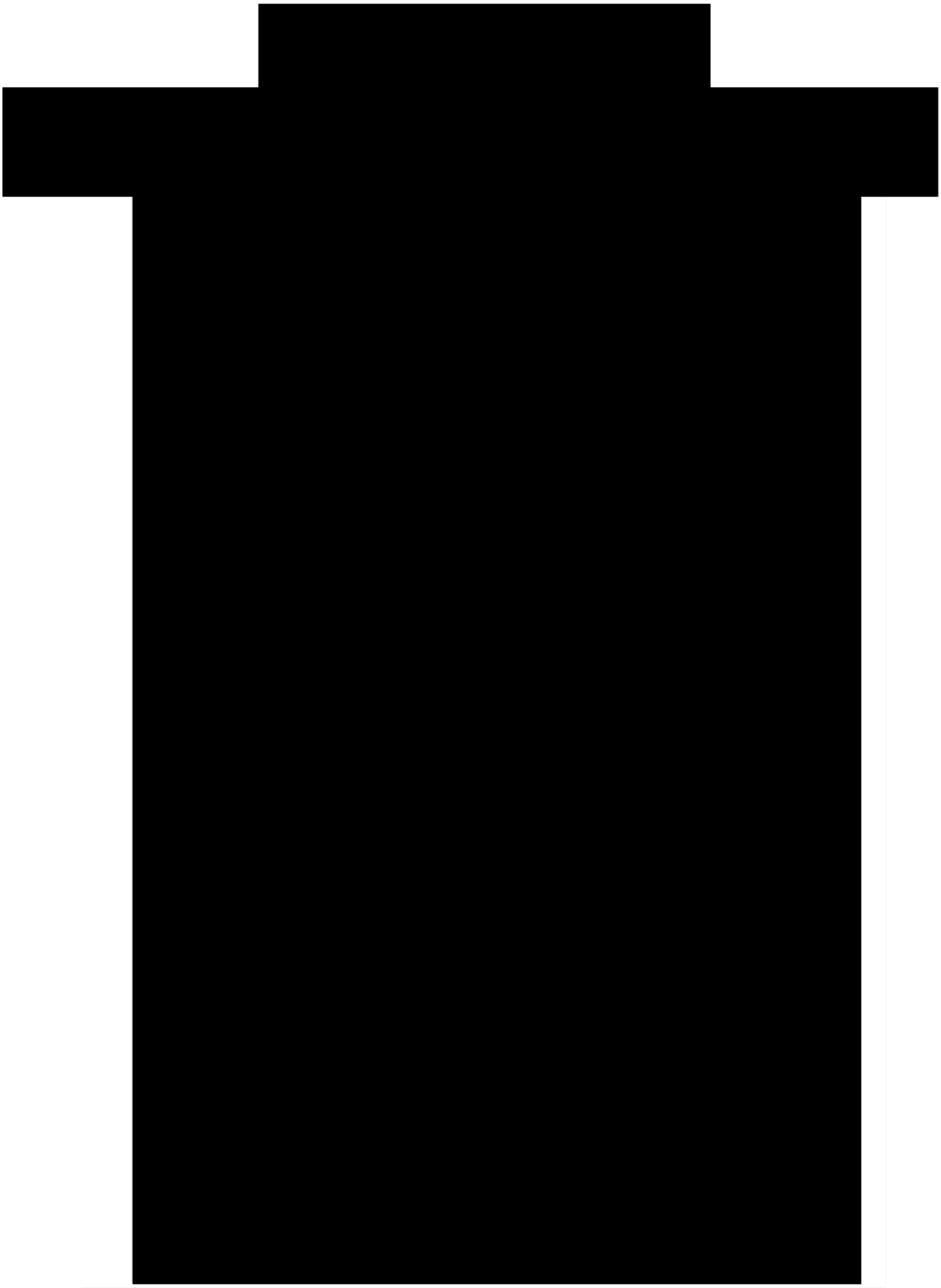
REFERENCES

Fondazione Italiana Linfomi. EPI Elderly Prognostic Index. [resource on the Internet] 2022. Available from: https://redcap.filinf.it/surveys/?s=89AFXML8AK.

Parmelee PA, Thuras PD, Katz IR, et al. Validation of the cumulative illness rating scale in a geriatric residential population. J Am Geriatr Soc 1995;43:130–7.

Merli F, Luminari S, Tucci A, et al. Simplified geriatric assessment in older patients with diffuse large B-cell lymphoma: The prospective elderly project of the Fondazione Italiana Linfomi. J Clin Oncol 2021;39:1214–22.

Merli F, Luminari S, Rossi G, et al. Outcome of frail elderly patients with diffuse large B-cell lymphoma prospectively identified by Comprehensive Geriatric Assessment: Results from a study of the Fondazione Italiana Linfomi. Leuk Lymphoma 2014;55:38–43.



[redacted]

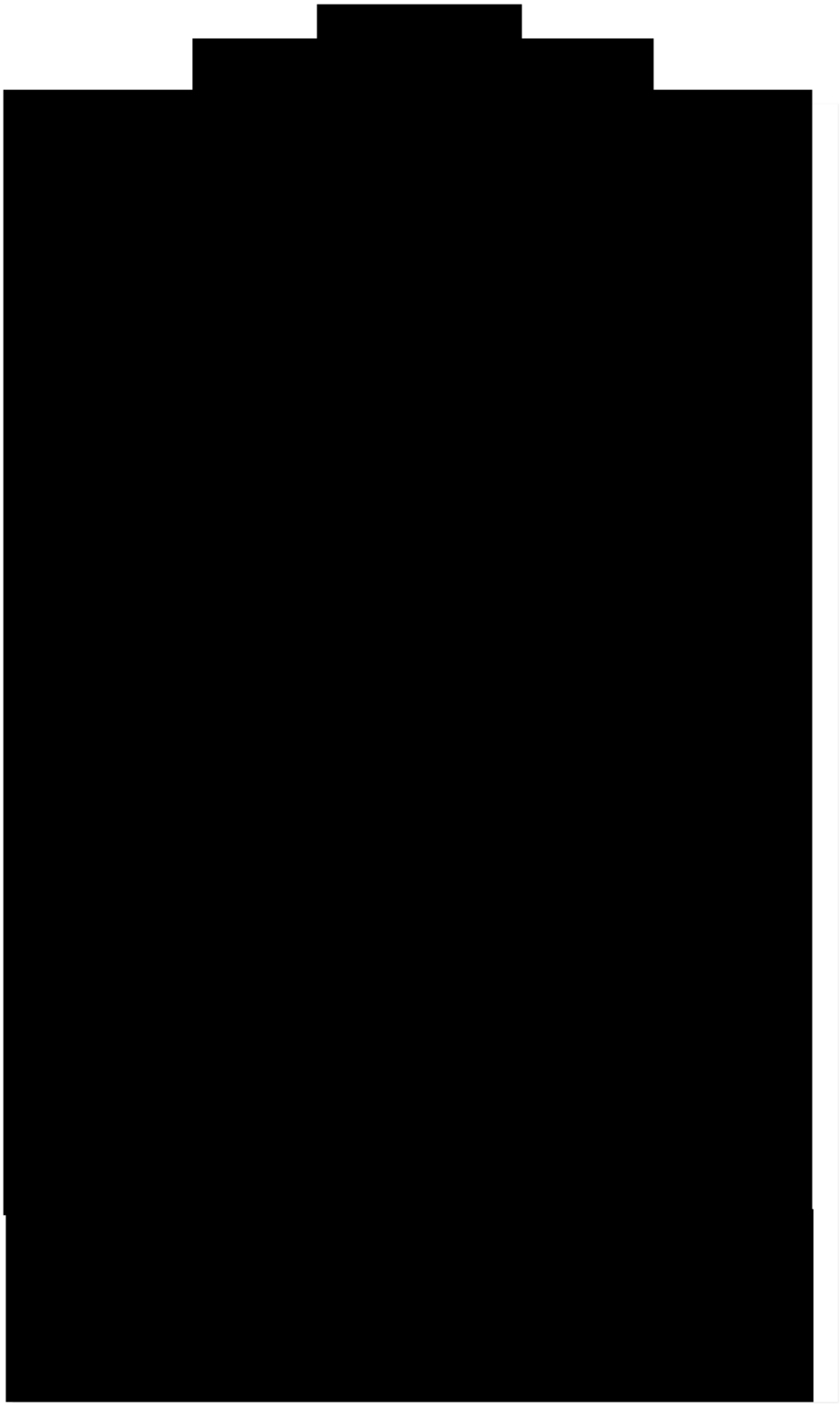
REFERENCE

Katz S, Downs TD, Cash HR, et al. Progress in the development of the index of ADL. Gerontologist 1970;10:20–30.

[redacted]

REFERENCE

Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86.



For additional instructions and download in your local language go to:
https://www.mnaelderly.com/mna_forms.html.

[redacted]

REFERENCES

Vellas B, Villars H, Abellan G, et al. Overview of the MNA--Its history and challenges. J Nutr Health Aging 2006;10:456–63.

Rubenstein LZ, Harker JO, Salvà A, et al. Screening for undernutrition in geriatric practice: Developing the short-form mini nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001;56:M366–72.

Appendix 20
Sample List of Cautionary Medications

(A) Inhibitors

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,[1] 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, [1] cyclosporine, [1] darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, [1] isavuconazole, tofisopam, verapamil	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

[1] These are the anti-cancer agents; contact Medical Monitor before use.

P-gp	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

(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

FDA = U.S. Food and Drug Administration.

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

Appendix 21
ASTCT ICANS Consensus Grading for Adults and ICE Assessment

ASTCT ICANS Consensus Grading for Adults

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

ASTCT = American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICP = intracranial pressure; min = minute; NA = not applicable; NCI = National Cancer Institute.

Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

[a] A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

[b] Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

[c] Tremors and myoclonus associated with immune effector cell therapies may be graded accordingly to NCI CTCAE, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to NCI CTCAE.

Immune Effector Cell-Associated Encephalopathy Assessment

If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess the following:

- Orientation (oriented to year, month, city, hospital = 4 points)
- Naming (name three objects; e.g., point to clock, pen, button = 3 points)
- Following commands (e.g., "show me two fingers" or "close your eyes and stick out your tongue" = 1 point)
- Writing (ability to write a standard sentence = 1 point), and
- Attention (count backwards from 100 by tens = 1 point)

If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points

Reference

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

Appendix 22
Neurologic Toxicity Including ICANS that May Affect Driving

Participants should be advised by the study investigator of potential neurologic toxicity, which may include seizures and alterations of consciousness.

Neurologic toxicity including ICANS 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 toxicity including ICANS 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. Participants with CCNAEs or Grade ≥3 *neurologic toxicity including ICANS* 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 23
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 4 (20 February 2024):

Protocol GO43643, Version 4 has been primarily amended to add objective response rate (ORR) as a dual primary endpoint and include additional futility analyses to incorporate [redacted] *Changes to the protocol, along with a rationale for each change, are summarized below:*

- *ORR assessed by Independent Review Facility (IRF) has been designated as a dual primary endpoint for the efficacy objective (Figure 1 and Table 6).*
  - *Section 9.1, Section 9.2.2, and Section 9.4.2 have been updated to include the definition, hypothesis testing, and the target of estimation for the dual primary endpoint of ORR by IRF.*
  - *Section 9.5.1 has been updated to clarify the planned analysis for ORR. The dual primary endpoint of ORR by IRF analysis will be conducted on the first* [redacted] *randomized participants. This analysis is considered the primary analysis for ORR and the interim analysis for the study.*
- *Table 1, Table 2, and Table A2-1 have been updated to extend the polymerase chain reaction (PCR) monitoring time period for patients with occult or prior hepatitis B infection and patients with positive human immunodeficiency virus (HIV) test at screening, which will include the first 12 months during post-treatment follow-up:*
  - *Participants with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody [HBcAb] and negative hepatitis B surface antigen [HBsAg]) may be included if hepatitis B virus (HBV) DNA is undetectable at the time of screening. These participants should be considered for prophylactic antivirals (e.g., entecavir) before and throughout the treatment, and must undergo monthly DNA testing while the patient is on treatment. During post treatment follow up, the HBV DNA testing will continue every 3 months (±4 weeks) for 12 months after end of treatment visit.*
  - *Participants who are positive for HIV may be eligible provided they are stable on antiretroviral therapy for at least 4 weeks, have a CD4 count ≥200/μL, have an undetectable viral load, and have not had a history of opportunistic infection attributable to acquired immunodeficiency syndrome (AIDS) within the last 12 months. Participants with a positive HIV result at screening should be monitored after receiving study treatment. HIV viral load will be performed every 3 months (±4 weeks) until end of study treatment, and then every 6 months (±4 weeks) during post treatment follow up for 12 months after end of treatment visit.*
  - *The relevant eligibility criteria (Section 5.1) has been clarify that participants with occult or prior hepatitis B infection or those who are positive for HIV*

must be willing to undergo repeated testing during the study as specified above.

- *Section 4.1.3 has been updated to clarify that the independent Data Monitoring Committee (iDMC) will evaluate both safety and efficacy data periodically during the study.*
- *Section 9.2.1 and Section 9.5.2 have been updated to include a futility analysis for progression-free survival (PFS) by IRF and a second overall survival (OS) futility analysis. The first PFS by IRF analysis will be performed by the iDCC for iDMC review to assess futility, at the time of the dual primary endpoint ORR analysis, on the first [redacted] randomized participants. The PFS futility boundary is set at PFS hazard ratio (HR) greater than [redacted] for mosunetuzumab and polatuzumab in comparison with rituximab, gemcitabine, oxaliplatin (R-GemOx). The first OS futility analysis will be performed when approximately [redacted] OS events are observed. The second OS futility analysis will be performed at the time of the dual primary endpoint ORR analysis. For the first and second OS analyses, OS effect is considered detrimental if OS HR is greater than [redacted] for mosunetuzumab and polatuzumab vedotin compared to R-GemOx.*

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.

PROTOCOL AMENDMENT, VERSION 3: (4 OCTOBER 2023)

Protocol GO43643, Version 3 has been primarily amended to add an interim analysis based on overall response rate (ORR) and to incorporate [redacted] Changes to the protocol, along with a rationale for each change, are summarized below:

- [redacted], language related to participants with positive HIV test has been updated to clarify the viral monitoring plan for this population, given the potential risks associated with the use of mosunetuzumab. Additionally, if local HIV laboratory assessments are not available for testing, local test may be waived if central laboratory assessment samples are collected (Tables 1 and 2 of Section 1.3, Table A2-1 of Appendix 2 and Appendix A.6–1.1.1.3).
- Language on participants with occult or prior hepatisis B infection in the Schedule of Activities has been updated to align with that in the the exclusion criteria (Tables 1 and 2 of Section 1.3 and Table A2-1 of Appendix 2).
- Additional timepoint for radiographic studies and biomarker sample collections have been added at month 30 (±2 months) after Cycle 1 Day 1 for both Arm A and Arm B (Tables 1, 2, 3, and 4 of Section 1.3). The average duration of study participation for each participant has been updated from 2 years to 2.5 years (Section 4.5).

- A timepoint for mosunetuzumab and polatuzumab vedotin pharmacokinetics (PK) and anti-drug antibody (ADA) sample collection has been removed during post treatment follow up at ≥90 days after the last dose of mosunetuzumab (Table 3 of Section 1.3).
- Guidance regarding tocilizumab dosing for cytokine release syndrome (CRS) has been updated to maintain tocilizumab exposures within established clinical boundaries for the safety and efficacy of tocilizumab (Table 5 of Section 1.3, Section 6.1.3., Table A6-5 of Appendix 6).
- Section 2.2 and Appendix 6 have been updated to include US FDA approval of mosunetuzumab as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies, and polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) in adult patients who have previously untreated diffuse-large B-cell lymphoma, not otherwise specified or high-grade B-cell lymphoma and who have an International Prognostic Index score of 2 or greater.
- The benefit–risk assessment section has been updated to include CRS as a risk for mosunetuzumab that occurs most commonly during step-up dosing, and to clarify that the risk of COVID-19 vaccines potentiating CRS is unknown (Section 2.3.1).
- Section 4.1.3 has been updated to add assessment of potential overall survival (OS) detriment to the stopping rules based on the independent Data Monitoring Committee (iDMC) review. The iDMC meeting frequency has been updated from approximately every [redacted] months to approximately every [redacted] months. The stopping rule parameter regarding Grade≥3 CRS has been updated from≥10% to≥ 5% for mosunetuzumab for the subsequent iDMC reviews after the first iDMC review.
- [redacted]
- The total length of study has been adjusted to be approximately 5 years based on the current enrollment (Section 4.4).
- The sample size and timing of the China extension cohort has been clarified such that additional participants may be enrolled from China in an extended China enrollment cohort to ensure a total of approximately [redacted] participants in China (Section 5).
- The inclusion criteria have been updated to reflect that all participants on study are transplant ineligible, and the creatinine clearance threshold has been lowered to≥ 30 mL/min (Section 5.1).
- The exclusion criteria have been updated to exclude participants with Grade> 1 persistent toxicity related to prior anti-lymphoma treatment (with certain exceptions), and to exclude participants with a history of interstitial lung disease and/or

pneumonitis within 6 months prior to the first dose of study treatment or those with active symptoms (Section 5.2).

- An exclusion criterion of a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test within 7 days prior to enrollment (including rapid antigen test) has been added (Section 5.2).
  - The schedule of activities has been updated to include SARS-CoV-2 testing by antigen or PCR within 7 days prior to enrollment to determine study eligibility (Tables 1 and 2 of Section 1.3).
- Section 6 has been updated to specify that all other medicines described in the protocol and not specifically listed as investigational medicinal products (IMPs) should be considered non-investigational medicinal products (NIMPs).
- Section 6.8 has been updated such that information on coronavirus disease 2019 vaccine administration should be collected even if it was given more than 7 days prior to initiation of study treatment.
- Additional language has been added in the Permitted Therapy section regarding recommendations on SARS-CoV-2 infection prophylaxis, vaccinations, and treatment (Section 6.8.1).
- The section on cautionary therapy has been updated to include P-glycoprotein inhibitors (Section 6.8.2.1).
- [redacted]
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 8.3.4).
- Additional terms (i.e., acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia, and/or pulmonary toxicity) have been added to the Adverse Events of Special Interest section (Section 8.3.8.1).
- Section 8.10.1 has been modified to allow remote administration of participant-reported outcome instruments in the event that participants were not able to come to the clinic for the scheduled assessment.
- An interim analysis for ORR has been incorporated (Study Schema Figure 1). The extended enrollment timeline for the study has increased the power for the primary analysis, as PFS events will continue to accumulate beyond the target number of events while the trial enrolls. Therefore, the study has adequate power to add an interim analysis for objective response rate, which will include the first [redacted] randomized subjects. The hypothesis testing, sample size, timing of analysis for the interim ORR analysis, as well as the Type I error control have been included (Sections 9.1, 9.2 and 9.5).

- Section 9.4.3 has been updated to include statistical analysis methods used for the secondary efficacy endpoints.
- Section 9.5.3 has been updated to include assessment for OS detriment.
- Language has been clarified to indicate that any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, except for administrative changes or changes necessary to eliminate an immediate hazard to study participants (Section A1-1 of Appendix 1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section A1-4 of Appendix 1).
- Additional language has been added to the Infections section to include recommendations for SARS-CoV-2 risk management, to provide guidance on study treatment interruption and resumption during and after a SARS-CoV-2 infection, and to emphasize that mosunetuzumab should not be administered in the presence of an active infection (Section A6-1.1.1.3 of Appendix 6).
- General guidance on assessment and reporting of tumor flare events has been updated to help the investigator identify tumor flare event following treatment with mosunetuzumab (Section A6−1.1.1.4 of Appendix 6).
- Additional language has been added to streamline dose delays and provide dosing flexibility due to logistics or holiday (Section A6-2.2 of Appendix 6).
- A new table (Table A6-2) has been added to provide additional clarity on how mosunetuzumab treatment should be re-initiated based on potential dose delay scenarios (Section A6-2.2 of Appendix 6).
- The CRS management table has been updated to provide additional guidance on action for the next mosunetuzuamb dose following Grade 1 CRS event (Table A6-5 of Appendix 6).
- Recommendation for dose reduction following Grade 1−2 seizure has been removed, based on cumulated clinical data and exposure-response analyses (Table A6-7 of Appendix 6).
- Based on feedback from experts in the lymphoma disease area, one clarification has been added to Appendix 10 (Lugano Response Criteria for Malignant Lymphoma) regarding the disease progression assessment based on PET-CT. For disease progression based on individual target nodes/nodal masses, the intensity of uptake should be compared from nadir instead of baseline to define progressive metabolic disease.
- [redacted]

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.

PROTOCOL AMENDMENT, VERSION 2: (11 NOVEMBER 2022)

Protocol GO43643 has been primarily amended to update the pharmacokinetic (PK) objectives and the corresponding endpoint; to add a simplified geriatric assessment (sGA) for participants 65 years and older; to clarify the study assessments during post-treatment follow-up and survival follow-up; to add instructions regarding continued treatment with mosunetuzumab in combination with polatuzumab vedotin after suspected disease progression; to add additional information for the mosunetuzumab subcutaneous (SC) dose and schedule rationale; to clarify exclusion criteria for current or past history of CNS disease and autoimmune disease; to update the corticosteroid prophylaxis schedule for mosunetuzumab SC injection; to add instructions on the need to repeat step-up dosing in Arm A after dose delays; to add a blood sample collection schedule after tocilizumab administration; to provide updated recommendations on coronavirus disease 2019 (COVID-19) management. Changes to the protocol, along with a rationale for each change, are summarized below:

- Figure 1 Study Schema has been updated to include high-grade B-cell lymphoma (not otherwise specified or double/triple hit) to be consistent with the protocol inclusion criteria
- Tables 1 and 2 have been amended to include a sGA, to include footnotes to clarify the post-treatment follow up schedule and survival follow-up schedule, to provide clarification that bicarbonate or total carbon dioxide may be measured with use of a blood gas test per institutional guidelines, to add guidance on vital signs collections schedule after rituximab infusion, to add clarification on the concomitant medication data collection schedule in footnote d, and to allow quantitative polymerase chain reaction (PCR) for detection of active Epstein-Barr virus (EBV) and cytomegalovirus (CMV) to be performed 28 days prior to start of study drug administration in footnote a. Blood for viral infection test by quantitative PCR, serum PK sample and serum anti-drug antibody (ADA) sample has been removed from central laboratory assessments in the schedule of activities for Arm B.
- Tables 1 and 3 have been amended to provide guidance on local assessments, PK, immunogenicity, and biomarker collection schedule if step-up dosing needs to be repeated after dose interruption
- Table 5 has been added to the protocol for to provide a sample collection schedule after tocilizumab administration for cytokine release syndrome (CRS)
- Table 6 PK objectives and endpoints have been amended to allow the Sponsor to conduct proper analysis as data permits

- Section 2.3.1 and Section 6.8.1 have been amended to provide guidance on COVID-19 prophylaxis. In addition, recommendations on COVID-19 testing during screening and guidance on treatment resumption after COVID-19 infection have been added in Section A6−1.1.1.3.
- Section 4.1.1 and Section 5 have been amended to include the language that if China participates in the study, additional participants may be enrolled in an extended China enrollment phase at China sites after completion of the global enrollment. The definition of the end of the study if China participates in the study is further clarified in Section 4.4. Additional guidance on sample collections according to local regulations if China participates in the study are specified in Section 5.1 and Section 8.7
- Section 4.1.1.1 has been amended to align the definition for refractory disease with that defined in Section 5.1
- Section 4.1.1.5 has been added to the protocol to provide guidance on continued treatment with mosunetuzumab in combination with polatuzumab vedotin after suspected disease progression
- Section 4.1.3 has been amended to clarify the participant number for Arm A and Arm B for the first independent Data Monitoring Committee (iDMC) review
- Section 4.2 has been amended to clarify that local assessment to confirm cluster of differentiation (CD) 20 expression is required during screening
- Section 4.2.6 has been added to the protocol to provide rationale for sGA
- Section 4.3.2 has been amended to provide additional information for mosunetuzumab SC dose selection and schedule
- Section 5.1 inclusion criteria have been amended to include participants with known HIV if they meet specific criteria
- Section 5.2 exclusion criteria have been amended to allow enrollment of breastfeeding women if breastfeeding stops, to provide additional clarification on enrollment of participants with history of specific CNS disease, to provide clarification that participants with certain autoimmune disease might be eligible to enroll if they meet protocol specified criteria, to allow participants who had previously received polatuzumab vedotin to enroll if certain criteria are met, and to specify tissue sample requirements for China sites if China participates in the study
- Section 6.1.2 has been amended to provide additional guidance on corticosteroid premedication to allow dexamethasone 20 mg or 80 mg methylprednisolone, either IV or orally, as prophylaxis for CRS for mosunetuzumab
- Section 6.8 has been amended to clarify the timeframe when concomitant medication information needs to be collected in the electronic Case Report Form
- Section 6.8.1.1 has been amended to replace all severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) with COVID-19 and to provide guidelines on the timing for COVID-19 vaccine administration before or during treatment

- Section 6.8.3 was amended to remove intrathecal chemotherapy for CNS prophylaxis as a permitted therapy due to the low probability of participants needing CNS prophylaxis in the study population as this study enrolls participants with aggressive non-Hodgkin's lymphoma in the relapsed/refractory setting and excludes participants with active and historical CNS disease
- Section 7.1 has been amended to clarify the assessments required during post-treatment follow up for participants who discontinue study treatment for reasons other than disease progression, start of new anti-lymphoma therapy or withdraw consent
- Section 8.1.1.1 has been amended to clarify the radiographic assessment requirements for participants who achieve metabolic complete response (CR) at 24 weeks vs. participants who do not achieve CR at 24 weeks. For participants who achieve metabolic CR at 24 weeks, a computed tomography (CT) scan with or without positron emission tomography (PET) scan will be acceptable for subsequent scans. For participants who do not achieve CR at 24 weeks, imaging studies with PET and diagnostic-quality CT scans should continue until CR or progressive disease (PD). Additionally, this section added language to allow magnetic resonance imaging (MRI) scans instead of CT scans in participants who are contraindicated.
- Section 8.2.6 (8.2.6.1, 8.2.6.2, 8.2.6.3 and 8.2.6.4), have been added to the protocol to provide background information on sGA, including Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Cumulative Illness Rating Scale-Geriatrics (CIRS-G), and Mini Nutritional Assessment-Short Form (MNA®-SF)
- [redacted]
- Section 8.4 has been amended to require predose serum rituximab and obinutuzumab PK samples to characterize any potential interactions between rituximab and/or obinutuzumab PK and the clinical effects of mosunetuzumab
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.11.6)
- Section 9.4.2.1 has been added to the protocol to provide clarity on the target of estimation and the 5 attributes in the estimand framework
- Section 9.4.6.6 has been added to the protocol to provide statistical analysis method on sGA prognostic impact on progression-free survival (PFS) and overall survival (OS)
- Section 9.6 has been added to provide guidance on Asian subpopulation analyses if China is included as a participating country
- Section A6-1.1.1.4 has been amended to provide guidance on how to assess a potential tumor flare event.

- Section A6-1.2.2.1 has been added to include progressive multifocal leukoencephalopathy (PML) as a potential risk associated with polatuzumab vedotin.
- Section A6-2.2 has been amended to provide additional guidance on the need to repeat step-up dosing schedule after treatment interruption in Arm A.
- Table A6-2 has been added to the protocol to provide guidelines for dose delay, modifications or discontinuation of mosunetuzumab, polatuzumab vedotin and rituximab
- Section A6-2.3.5 and Appendix 21 have been amended to include instructions for participants to refrain from driving or engaging in hazardous occupations or activities if the participants develop specific adverse events while on mosunetuzumab treatment.
- [redacted]

Appendix 24
Abbreviations

Abbreviation or Term	Definition
acMMAE	antibody-conjugated monomethyl auristatin E
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADL	activity of daily living
AIDS	acquired immunodeficiency syndrome
aNHL	aggressive non-Hodgkin's lymphoma
ASCT	autologous stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
BR	bendamustine and rituximab
CAR	chimeric antigen receptor
CCOD	clinical cutoff date
CD	cluster of differentiation
CGA	comprehensive geriatric assessment
CIRS-G	Cumulative Illness Rating Scale-Geriatric
COVID-19	coronavirus disease 2019
CR	complete response
CRR	complete response rate
CRS	cytokine release syndrome
CT	computed tomography (scan)
DLBCL	diffuse-large B-cell lymphoma
DOCR	duration of complete response
DOR	duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy–Gynecologic Oncology Group–Neurotoxicity
FACT-LymS	Functional Assessment of Cancer Therapy–Lymphoma Subscale
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin embedded
FIL	Fondazione Italiana Linfomi

Appendix 24: Abbreviations

Abbreviation or Term	Definition
FL	follicular lymphoma
FL3B	follicular lymphoma Grade 3B
G-CSF	granulocyte colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR	Hazard ratio
HRQoL	health-related quality of life
IADL	Instrumental Activities of Daily Living
ICANS	*immune effector cell-associated neurotoxicity syndrome*
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IL	interleukin
IMP	investigational medicinal product
IPI	International Prognostic Index
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
IxRS	interactive voice or Web-based response system
M + P	mosunetuzumab in combination with polatuzumab vedotin
MMAE	monomethyl auristatin E
MNA®-SF	Mini Nutritional Assessment-Short Form
MRI	magnetic resonance imaging
NALT	*new anti-lymphoma therapy*
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NOS	not otherwise specified
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell

Appendix 24: Abbreviations

Abbreviation or Term	Definition
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography (scan)
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PopPK	population pharmacokinetics
PRO	participant-reported outcome
Q3W	every 3 weeks
QLQ-Core30	Quality of Life-Core 30
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
R-CHP	rituximab plus cyclophosphamide, doxorubicin, and prednisone
R-GemOx	rituximab, gemcitabine, oxaliplatin
R/R	relapsed or refractory
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
sGA	simplified geriatric assessment
TLS	tumor lysis syndrome
trFL	transformed follicular lymphoma
ULN	upper limit of normal
USPI	United States Prescribing Information
WES	whole-exome sequencing
WGS	whole-genome sequencing

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