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|---|---|
| Official Title: | A Phase Ib, Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Glofitamab or Mosunetuzumab in Combination With Gemcitabine Plus Oxaliplatin in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma and High-Grade Large B-Cell |
| NCT Number: | NCT04313608 |
| Document Date: | Protocol Version 2: 02-May-2020 |

# PROTOCOL

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|---|---|
| **TITLE:** | **A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF *GLOFITAMAB* OR MOSUNETUZUMAB IN COMBINATION WITH GEMCITABINE PLUS OXALIPLATIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND HIGH-GRADE LARGE B-CELL LYMPHOMA** |
| **PROTOCOL NUMBER:** | GO41943 |
| **VERSION NUMBER:** | *2* |
| **EUDRACT NUMBER:** | To be determined |
| **IND NUMBER:** | 138178 |
| **TEST PRODUCTS:** | *Glofitamab* (RO7082859), Mosunetuzumab (RO7030816), Obinutuzumab (RO5072759), Tocilizumab (RO4877533) |
| **MEDICAL MONITOR:** | [redacted], M.D. |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| ***DATE FINAL:*** | *23 December 2019* |
| **DATE *AMENDED*:** | See electronic date stamp below. |

## PROTOCOL AMENDMENT APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 02-May-2020 00:33:36 | Company Signatory | [redacted] |

## *PROTOCOL HISTORY*

| *Protocol* | |
|---|---|
| ***Version*** | ***Date Final*** |
| *1* | *23 December 2019* |

## PROTOCOL AMENDMENT, VERSION 1:
## RATIONALE

Protocol GO41943 has been amended to change the number of treatment cycles in order to allow increased total cycles of GemOx therapy consistent with published literature; to increase the duration of therapy of glofitamab therapy to 12 total cycles; to confirm the Sponsor's decision to open arm A (glofitamab-GemOx); and to confirm the recommended phase II dose (RP2D) of glofitamab monotherapy identified in the NP30179 study. Changes to the protocol, along with a rationale for each change, are summarized below:

- Throughout the protocol, text has been updated to use the international nonproprietary name glofitamab in place of the molecule designation RO7082859.
- Section 1.3 has been updated with clinical information included in the Glofitamab Investigator's Brochure, Version 5
- Section 3.1: has been updated with the information that the Sponsor has elected to open Arm A (Glofit-GemOx) on the basis of the totality of emerging PK, tolerability, and preliminary efficacy data. Additional changes include:
  - a change to the number of treatment cycles for Arm A. In the new treatment schedule, patients in the Glofit-GemOx arm will receive up to 8 cycles of Glofit-GemOx, followed by up to 4 cycles of glofitamab monotherapy, to complete up to 12 cycles of glofitamab. The Sponsor increased the duration of GemOx therapy based on published regimens of R-GemOx that utilize up to 8 cycles of therapy to maximize therapeutic intent. The Sponsor increased the number of cycles of glofitamab based on evidence of late responses in patients treated with glofitamab monotherapy (described in section 3.3.1). The revised Glofit-GemOx schedule has been made throughout the protocol, where applicable.
  - a change to the number of treatment cycles for Arm B. In the new treatment schedule, patients in the Mosun-GemOx arm will receive up to 8 cycles of Mosun-GemOx.
  - Section 3.1.2 has been revised to clarify that the IMC may recommend enrolling up to 20 patients in either study arm if in its view the tolerability of the combination requires further interrogation
- Section 3.3 has been updated to include additional rationale for the glofitamab dose and schedule and for pretreatment with obinutuzumab prior to the first dose of glofitamab.
- Section 4 has been revised with the following changes:
  - Section 4.1.1 has been revised to allow inclusion of patients with a platelet count $\geq 75 \times 10^9$/L without a transfusion in the week prior to starting study treatment.
  - Section 4.1.2 has been clarified to exclude patients who have failed only one prior line of therapy and who are candidates for stem cell transplantation, irrespective of whether they have relapsed or refractory disease.

- Section 4.1.2 has been revised to remove extraneous detail so as to communicate the exclusion criterion regarding live virus vaccine more clearly.
- Section 4.1.2 has been updated to exclude patients with prior allogeneic stem cell transplantation, given the unknown risk of triggering graft-versus-host disease or graft rejection in this population with this bispecific antibody.
- Section 4.1.2 has been revised to clarify criteria for prior treatment with immunosuppressive medications, including treatment with corticosteroids.
- Section 4.3.3.1; Section 4.3.5.2; Appendix 1 Table 1, have been updated with revised hospitalization requirements for patients in the Glofit-GemOx arm, based on emerging safety data with the step-up dosing regimen in study NP30179. Patients must be hospitalized for at least 24 hours after the infusion of glofitamab on Days 8 and 15 of Cycle 1. Patients with an event of CRS associated with the preceding dose of glofitamab should be hospitalized on Day 1 of Cycle 2.
- Section 4.3.5.2, Section 4.4., Section 5.1.3, Section 5.1.5 have been revised so that prophylaxis for tumor lysis syndrome should be considered for patients at risk of tumor lysis syndrome, instead of required for all patients.
- Section 4.4.1.1 has been revised to clarify that G-CSF should be started 1 to 2 days after Gem-Ox infusion in each cycle.
- Section 4.4.3 has been added with information that caution should be exercised in the administration of oxaliplatin in patients with a history of or a predisposition for prolongation of QT, in light of postmarketing reports of QT prolongation and torsades de pointes following oxaliplatin administration.
- Section 4.5.6, Appendix 1 Table 1 and Table 2, have been updated to adjust tumor and response evaluations for consistency with the revised treatment schedules in Arm A and Arm B.
- Section 4.5.7, Appendix 1 Table 1 and Table 2, have been revised to add guidance regarding peripheral blood smear and/or flow cytometry at screening and to add flow cytometry assessment of B lymphocytes (CD19+ B-cell counts). Malignant cells observed in peripheral blood and elevated B lymphocyte counts have been identified as potential risk factors for CRS in patients treated with glofitamab.
- Section 4.6.1 has been updated to remove hepatitis B reactivation and Grade 4 CRS from unacceptable toxicity that requires study treatment discontinuation, so as not to require discontinuation of treatment for potentially manageable toxicity. Updated guidance for management of hepatitis B reactivation (5.1.3) and Grade 4 CRS (Appendix 10), including study treatment discontinuation guidance, has been provided.

- Section 5 has been revised with the following changes:
  - Section 5.1.2 has been updated to add hemophagocytic lymphohistiocytosis as a potential risk associated with glofitamab to maintain consistency with the Investigator's Brochure.

- Section 5.1.3 has been updated with new management guidelines for hepatitis B reactivation.
- Section 5.1.7.1 has been revised to clarify and simplify the guidance for dose modifications and interruptions, with different guidance for hematologic and non-hematologic toxicity specified. Table 4 has been revised to allow for continuation of study therapy (as opposed to delaying therapy) for oxaliplatin-associated peripheral neuropathy, so as not to unnecessarily delay subsequent cycles of study treatment. Clarified guidance as to whether to dose-reduce or withhold oxaliplatin in the event of neuropathy is provided.
- Section 5.1.7.2 has been added to provide management and treatment discontinuation guidance for allergic/anaphylactic reactions.
- Section 5.2.3 has been updated to include tumor lysis syndrome as an adverse event of special interest for obinutuzumab.
- Section 5.3.5.1 has been updated to clarify instructions for recording adverse events of infusion-related reactions and cytokine-release syndrome.
- Section 5.5.5.11 has been updated to clarify that an event that leads to hospitalization should not be reported as an adverse event or serious adverse event if the hospitalization is for observation (e.g., prophylactic hospitalization prior to glofitamab or mosunetuzumab dosing, according to risk or prior occurrence of CRS) and the patient does not experience an adverse event.

- Appendix 1, Table 1 and Table 2, have been revised to require a complete neurologic examination only at the screening visit. The requirement for a complete neurologic examination at all treatment visits has been removed, unless clinically indicated. This change was made in light of emerging data suggesting that central nervous system toxicity associated with glofitamab seems less severe and less frequent than that reported with other similar class agent such as blinatumomab and CAR T-cell therapy, and that glofitamab CNS toxicity seems confined to events with short onset and duration and concomitant with CRS events (Glofitamab Investigator's Brochure).
- Appendix 2, Table 1 have been updated to include glofit PK and ADA sample collection at Cycle 12.
- Appendix 8 has been revised to reflect the current recommendations for the management of hemophagocytic lymphohistiocytosis.
- Appendix 10 has been updated with the following changes:
  - Including Table 2, reflects the current recommendations for the management of cytokine release syndrome, primarily to permit retreatment with glofitamab after grade 4 CRS under certain circumstances and with strict monitoring guidelines.
  - Moved the guidelines for the management of neutropenia and thrombocytopenia; to Section 5.1.7.1
  - Included management of suspected tumor inflammation or tumor flare for patients with lesions in the gastrointestinal tract.

- Including Table 8, reflects current management recommendations for patients with neurotoxicity associated with glofitamab, primarily to focus attention to signs and symptoms of neurologic toxicity associated with immune effector cells that may also reflect glofitamab-induced neurotoxicity.
- Patients with high tumor burden and considered by the investigator to be at risk for tumor lysis should receive tumor lysis prophylaxis. The requirement that all patients receive TLS prophylaxis has been removed given that the reported incidence of TLS in 127 patients treated with glofitamab monotherapy at doses ≥0.6 mg is <5% (Glofitamab Investigator's Brochure).
- Including Table 9, reflects current management recommendations for patients with liver function test abnormalities associated with glofitamab.

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

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| **TITLE:** | **A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF *GLOFITAMAB* OR MOSUNETUZUMAB IN COMBINATION WITH GEMCITABINE PLUS OXALIPLATIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND HIGH-GRADE LARGE B-CELL LYMPHOMA** |
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| **MEDICAL MONITOR:** | [redacted], M.D. |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

## PROTOCOL SYNOPSIS

| | |
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| **TITLE:** | **A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF *GLOFITAMAB* OR MOSUNETUZUMAB (RO7030816) IN COMBINATION WITH GEMCITABINE PLUS OXALIPLATIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND HIGH-GRADE B-CELL LYMPHOMA** |
| **PROTOCOL NUMBER:** | GO41943 |
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| **IND NUMBER:** | 138178 |
| **TEST PRODUCTS:** | *G*lofitamab, Mosunetuzumab (RO7030816), Obinutuzumab (RO5072759), Tocilizumab (RO4877533) |
| **PHASE:** | Phase Ib |
| **INDICATIONS:** | Relapsed or refractory B-cell lymphoma, including diffuse large B-cell lymphoma, not otherwise specified, high-grade B-cell lymphoma with *MYC*, *BCL2*, and/or *BCL6* rearrangements, and high-grade B-cell lymphoma, not otherwise specified |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**Objectives and Endpoints**

This study will evaluate the safety and preliminary efficacy of *glofitamab* in combination with gemcitabine and oxaliplatin (*Glofit*-GemOx) or mosunetuzumab in combination with gemcitabine and oxaliplatin (Mosun-GemOx) in patients with R/R DLBCL. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., *Glofit*-GemOx, administered following a single pretreatment 1000-mg dose of obinutuzumab or mosunetuzumab with gemcitabine plus oxaliplatin, or Mosun-GemOx).

**Safety Objectives**

Primary Safety Objective

The primary safety objective for this study is to evaluate the safety of the study treatment as a combination therapy on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5.0), with severity of cytokine-release syndrome (CRS) determined according to the American Society for Transplantation and Cell Therapy (ASTCT) Consensus Grading Criteria
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Secondary Safety Objective

The secondary safety objective is to evaluate the tolerability of study treatment as a combination therapy on the basis of the following endpoint:

- Tolerability, as measured by dose interruptions, dose reductions, dose intensity, and treatment discontinuation because of adverse events

**Efficacy Objective**

The efficacy objective for this study is to make a preliminary assessment of the efficacy of the study treatment on the basis of the following endpoints:

- Complete response (CR), defined as the proportion of patients whose best overall response is a CR based on positron emission tomography/computed tomography (PET/CT) during the study, as determined by the investigator according to the 2014 Lugano Response Criteria for malignant lymphoma (hereafter referred to as the 2014 Lugano Response Criteria)
- Objective response rate (ORR), defined as the proportion of patients whose best overall response is a partial response (PR) or a CR during the study, as determined by the investigator according to the 2014 Lugano Response Criteria

**Pharmacokinetic Objectives**

The pharmacokinetic (PK) objective for this study is to evaluate the pharmacokinetics of the CD20-CD3–bispecific antibody on the basis of the following endpoints:

- Minimum serum concentration
- Maximum serum concentration
- Area under the concentration–time curve for serum concentration–time profile estimated using a population-PK model, as the data allow

*Serum* samples for the analysis of obinutuzumab concentrations in Arm A will also be obtained and reported. These will be used to inform PK modeling.

The exploratory PK objective is to assess potential PK interactions between the CD20-CD3–bispecific antibody and gemcitabine plus oxaliplatin (GemOx) on the basis of the following endpoint:

- Serum concentration or PK parameters for CD20-CD3–bispecific antibody given in combination with GemOx compared with CD20-CD3–bispecific antibody given alone based on historical data

**Immunogenicity Objectives**

The immunogenicity objective for this study is to make a preliminary evaluation of the immune response to the CD20-CD3–bispecific antibody on the basis of the following endpoints:

- Prevalence of anti-drug antibodies (ADAs) against *glofitamab* at baseline and incidence of ADAs during the study
- Prevalence of ADAs against mosunetuzumab at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective is to evaluate potential effects of ADAs on the basis of the following endpoints:

- Relationship between *glofitamab* ADA status and safety, PK, or efficacy endpoints
- Relationship between mosunetuzumab ADA status and safety, PK, or efficacy endpoints

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to evaluate biomarkers that provide evidence of CD20-CD3–bispecific antibody activity on the basis of the following endpoints:

- PD biomarkers, such as T-cell activation and cytokine production

- *Tumor tissue will be obtained from all patients, if possible, in order to perform retrospective CD20 assessment and to further assess exploratory biomarkers that could provide information on the mechanism of action*
- The impact of GemOx combination therapy on these established mechanisms
- Exploratory biomarkers in blood and susceptibility to development of adverse events

## STUDY DESIGN

### Description of the Study

Study Design Overview

This is a Phase Ib, open-label, multicenter study designed to evaluate the safety and preliminary efficacy of a CD20-CD3–bispecific antibody in combination with gemcitabine and oxaliplatin in patients with R/R B-cell lymphoma, including patients with DLBCL, not otherwise specified (NOS); HGBCL with *MYC*, *BCL2*, and/or *BCL6* rearrangements; and HGBCL, NOS.

The study is structured to allow the enrollment of patients in one *or both* of the following two study arms:

- Arm A: *Glofit*-GemOx, administered following a single 1000-mg dose of *obinutuzumab*
- Arm B: Mosun-GemOx

Prior to the start of study enrollment, the Sponsor *elected to open Arm A* on the basis of the totality of emerging PK, tolerability, and preliminary efficacy data of both molecules administered as single agents and in combination with other therapies. The unselected arm will remain inactive and will be put on hold for enrollment. The Sponsor may also elect to open *Arm B* as a second study arm.

In Arm A, a total of 10 patients will be treated with *Glofit*-GemOx. Accrual of 10 patients will occur consecutively. Patients *in the Glofit-GemOx arm* will receive *a single IV dose of obinutuzumab pretreatment 7 days before the first dose of glofitamab, then up to 8* cycles of *glofitamab in combination with gemcitabine plus oxaliplatin, followed by up to 4* cycles *of glofitamab monotherapy, to complete up to a total of 12 cycles of glofitamab. It is expected that some patients will not be able to complete 8 cycles of GemOx therapy due to progressive disease or AEs.*

In Arm B, a total of 10 patients will be treated with Mosun-GemOx. Accrual of 10 patients will occur consecutively. Patients will receive *up to 8* cycles of Mosun-GemOx administered in 21-day cycles.

All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the final dose of study treatment. Adverse events will be graded according to the NCI CTCAE 5.0, with CRS graded according to the ASTCT 2019 CRS Consensus Grading Criteria.

Patients will be assessed for tumor response by PET/CT *and CT* after Cycles *4 and 8. Patients in Arm A will also be assessed for tumor response after Cycle 12. Tumor response will be assessed* using the 2014 Lugano Response Criteria.

Internal Monitoring Committee

Given that this is the first study of a *Glofit*–bispecific antibody in combination with gemcitabine and oxaliplatin, an internal monitoring committee (IMC) will be formed during the study to make recommendations on study conduct on the basis of trial safety data to ensure enhanced patient safety during study treatment. The IMC will consist of an IMC Medical Monitor Chair external to the study and Sponsor's representatives from Clinical Science and Safety Science who are external to the study team, and a Sponsor's representative from Biostatistics. The IMC will convene to review cumulative safety data, including the incidence and nature of serious adverse events, deaths, Grade ≥3 adverse events, and adverse events of special interest. The IMC will hold its first review after 3 patients have reached Day 7 of Cycle 2, and the committee will conduct its second review after 10 patients have reached at least Day 7 of Cycle 2 and at least 5 patients have completed two full cycles of treatment. *The IMC may recommend enrolling up to 20 patients in either study arm if in its view the tolerability of the combination requires further interrogation prior to investigation in subsequent studies.*

The IMC will operate according to a prespecified charter that will outline the IMC members, roles, responsibilities, and communication processes. The IMC will make recommendations on the basis of the data review to inform advancement to a Phase III study.

**Number of Patients**

Up to approximately 20 patients will be enrolled in the study, with approximately 10 patients in either Arm A or B at approximately six sites, *with potential enrollment up to 20 patients per arm*.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability and willingness to comply with the study protocol
- Life expectancy ≥ 12 weeks
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Histologically confirmed B-cell lymphoma, including one of the following diagnoses per the 2016 WHO classification of lymphoid neoplasms:
  - DLBCL, NOS
  - HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements
  - HGBCL, NOS
- R/R disease, defined as follows:
  - Relapse: disease that has recurred following a response that lasted ≥ 6 months after completion of last line of therapy
  - Refractory: disease that progressed during therapy or progressed within 6 months (< 6 months) of prior therapy
- At least one line of prior systemic therapy

  Patients are permitted to have undergone autologous hematopoietic stem cell transplant (HSCT) prior to enrollment; chemotherapy followed by consolidative autologous HSCT will be counted as one line of therapy.

  Local therapies (e.g., radiotherapy) will not be considered as a line of therapy.
- Confirmed availability of archival (or if unavailable, freshly collected) tumor tissue prior to enrollment

  If archival tissue is unavailable, tumor tissue must be obtained from a biopsy performed at screening. For patients who have inadequate or inaccessible tumor tissue for biopsy, the patient may still be eligible for the study after discussion with the Medical Monitor.
- At least one bi-dimensionally measurable nodal lesion or one bi-dimensionally measurable extranodal lesion, as measured on PET/CT scan
- Adequate hematologic function, defined as follows:
  - Hemoglobin ≥9.0 g/dL
  - ANC $\geq 1.0 \times 10^9$/L
  - Platelet count $\geq 75 \times 10^9$/L *(≥75,000/μL) without a transfusion in the week prior to starting study treatment*
- Adequate renal function, defined as measured or estimated creatinine clearance ≥40 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 18 months after the final dose of obinutuzumab, 6 months after the final dose of gemcitabine, 9 months after the final

dose of oxaliplatin, 3 months after the final dose of mosunetuzumab, 3 months after the final dose of tocilizumab, and 2 months after the final dose of *glofitamab*. Women must refrain from donating eggs during this same period.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile because of 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 requirements.

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

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

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 2 months after the final dose of *glofitamab*, 2 months after the final dose of mosunetuzumab, 2 months after the final dose of tocilizumab (if applicable), 3 months after the final dose of obinutuzumab, and 6 months after the final dose of oxaliplatin or gemcitabine to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

**Exclusion Criteria**

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

- *Patient has failed only one prior line* of *therapy* and candidate for stem cell transplantation
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to obinutuzumab, gemcitabine, oxaliplatin, or tocilizumab
- Prior treatment with a bispecific antibody targeting both CD20 and CD3, including *glofitamab* and mosunetuzumab
- Grade >1 peripheral neuropathy, as assessed according to the NCI CTCAE v5.0 at enrollment
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to first study treatment
- Treatment with monoclonal antibodies for the purposes of treating cancer within 4 weeks prior to the first study treatment
- Primary or secondary central nervous system (CNS) lymphoma at the time of recruitment or history of CNS lymphoma
- Current or history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease

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

- Any of the following abnormal laboratory values:
  - AST or ALT $>2.5\times$ the upper limit of normal (ULN)
  - Total bilirubin $\geq 1.5\times$ ULN
  - Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq 3\times$ ULN.
  - INR or PT $>1.5\times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $>1.5\times$ ULN in the absence of a lupus anticoagulant
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the following exceptions:

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the study are eligible.

  Patients with low-grade, early-stage prostate cancer (Gleason score $\leq 6$, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible.

  Patients with any other malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for $\geq 2$ years prior to enrollment are eligible.

  Patients receiving adjuvant endocrine therapy for non-metastatic, hormone receptor–positive breast cancer for $\geq 2$ years prior to enrollment are eligible.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection (as evaluated by the investigator) within 4 weeks prior to first study treatment
- Suspected or latent tuberculosis (as confirmed by positive IFN-$\gamma$ release assay)
- Positive test results for hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

  Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment and appropriate antiviral therapy.
- Positive test results for hepatitis C virus (HCV) antibody

  Patients who are positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Known HIV-seropositive status

  For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations.
- Known or suspected chronic active Epstein-Barr virus infection
- Known or suspected history of HLH
- History of progressive multifocal leukoencephalopathy
- Adverse events from prior anti-cancer therapy that have not resolved to Grade 1 or better (with the exception of alopecia and anorexia)
- Administration of a live, attenuated vaccine within 4 weeks prior to the first study treatment administration or anticipation that such a live, attenuated vaccine will be required during the study
- Prior solid organ transplantation

- *Prior allogeneic stem cell transplant*
- Active autoimmune disease requiring treatment

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

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

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

  Patients 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 may be eligible after discussion with the Medical Monitor.
- Prior *treatment with* systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-*tumor necrosis factor* agents within *4* weeks prior to first dose of study treatment
- *Corticosteroid therapy within 2 weeks prior to first dose of study treatment, with the following exceptions:*

  *Corticosteroid treatment ≤10 mg/day prednisone or equivalent within 2 weeks prior to the first dose of study treatment is permitted.*

  *Administration of* acute, low-dose *corticosteroids to treat cancer symptoms or side effects of treatment* (e.g., single dose of dexamethasone for nausea or B-symptoms) *is permitted..*

  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.
- Recent major surgery (within 4 weeks before the first study treatment) other than for diagnosis
- Clinically significant history of liver disease, including cirrhosis
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications
- Pregnancy or breastfeeding, or intention to become pregnant during the study or within 18 months after the final dose of study treatment in Arm A or within 12 months after the final dose of study treatment in Arm B

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

**End of Study**

The end of the study is defined as the date when the last patient, last visit occurs or the date when the last data point required for statistical analysis or protocol-defined safety monitoring is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately *13* months after the last patient is enrolled.

Owing to the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor. This will not constitute a premature termination of the study.

**Length of Study**

The total length of the study, from screening of the first patient to the end of study, is expected to be approximately 17 months.

**Investigational Medicinal Products**

The investigational medicinal products (IMPs) for this study are glofitamab, mosunetuzumab, obinutuzumab, and tocilizumab.

Gemcitabine and oxaliplatin are considered as standard of care in many countries for the treatment of patients with R/R DLBCL and are non-IMPs for this study. Premedication given prior to study treatment, including methylprednisolone, prednisone, prednisolone, diphenhydramine, and paracetamol, are non-IMPs for this study.

**Test Products (Investigational Drugs)**

Arm A: Glofitamab in Combination with Gemcitabine and Oxaliplatin (Glofit-GemOx)

*Obinutuzumab*

A single 1000-mg dose of obinutuzumab will be given on Day 1 of Cycle 1, 7 days prior to the first administration of glofitamab in order to reduce the potential risk of CRS induced by glofitamab -mediated systemic T cells.

Obinutuzumab will be administered using a standard bag infusion pump and must be administered in a clinic or hospital equipped for systemic (IV) cancer treatment.

*Glofitamab*

The first dose of glofitamab will be administered 7 days after the single 1000-mg dose of obinutuzumab on Day 1 of Cycle 1. Using a step-up dosing schedule, the first dose of 2.5 mg glofitamab will be administered on Day 8 of Cycle 1, followed by 10 mg on Day 15 of Cycle 1, and 30 mg on Day 1 of Cycles 2–12, with each cycle being 21 days in length (i.e., every 3 weeks).

In the event of a late or prolonged infusion for glofitamab during Cycles 2–8 because of late start in the day or slowed infusion rate owing to an infusion-related reaction (IRR), GemOx may be administered on the following day or as per local practice.

Patients will be hospitalized for at least 24 hours after the infusion of glofitamab on Days 8 and 15 of Cycle 1. Patients with an event of CRS associated with the preceding dose of glofitamab should be hospitalized on Day 1 of Cycle 2. The required hospitalization is an additional precautionary safety measure to ensure that patients are closely monitored during the first two cycles.

Arm B: Mosunetuzumab in Combination with Gemcitabine and Oxaliplatin (Mosun-GemOx)

*Mosunetuzumab*

Mosunetuzumab will be administered to patients using a step-up dosing schedule for Cycle 1, with 1 mg on Day 1 of Cycle 1, 2 mg on Day 8 of Cycle 1, and 60 mg on Day 15 of Cycle 1. The mosunetuzumab dose on Day 1 of Cycle 2 will be 60 mg, followed by 30 mg on Day 1 of Cycle 3 and then on Day 1 of subsequent cycles, up to 8 cycles. In the event of a late or prolonged infusion for mosunetuzumab during Cycles 2–6 because of late start in the day or slowed infusion rate owing to an IRR, GemOx may be administered on the following day or as per local practice.

Patients will be hospitalized for at least 48 hours postinfusion of mosunetuzumab on Day 1 of Cycle 1 as an additional precautionary safety measure to ensure that patients are closely monitored following the first dose of mosunetuzumab in combination with gemcitabine and oxaliplatin. Patients should be hospitalized on Day 1 of Cycle 2 for 24 hours following the dose of mosunetuzumab if the patient had Grade ≥2 event of CRS in Cycle 1.

**Non-Investigational Medicinal Products**

Arms A and B: Gemcitabine and Oxaliplatin (GemOx)

*Gemcitabine*

Gemcitabine will be administered intravenously to patients in both arms at 1000 mg/m$^2$ on Day 2 of Cycle 1. Starting at Cycle 2, gemcitabine may be given on Day 1 or Day 2 (per local practice) of each 21-day cycle for the subsequent cycles. Gemcitabine should be administered before oxaliplatin on the same day.

*Oxaliplatin*

Oxaliplatin will be administered intravenously to patients in both arms at 100 mg/m$^2$ on Day 2 of Cycle 1. Starting at Cycle 2, gemcitabine may be given on Day 1 or Day 2 (per local practice) of each 21-day cycle *for the subsequent cycles*. Oxaliplatin should be administered after gemcitabine on the same day.

*Tocilizumab*

Tocilizumab will be not administered to all patients but only to those patients experiencing severe CRS (rescue IMP). Tocilizumab will be supplied by the Sponsor. Refer to the local prescribing information for further instructions regarding recommended storage conditions and packaging configuration.

For patients requiring treatment of CRS, patients will receive tocilizumab by IV infusion. Patients who weigh ≥30 kg will receive 8 mg/kg tocilizumab and patients who weigh <30 kg will receive 12 mg/kg tocilizumab, not to exceed an 800 mg per dose. Treatment may be repeated every 8 hours as necessary (for a maximum of four doses).

**Statistical Methods**

All safety analyses will be based on the safety evaluable population grouped according to treatment arm. Safety will be determined by adverse events, laboratory tests, vital signs, ECGs, physical examinations, and ECOG Performance Status. The analysis methods for safety endpoints are listed in the table below. As appropriate, listings, summary tables, and graphs will be provided for safety and tolerability assessments.

**Safety Statistical Analysis Methods**

| Endpoint | Statistical Analysis Methods |
|---|---|
| Adverse events | The original terms recorded on the eCRF by the investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level. |
| Clinical laboratory tests | All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units) by individual listings with abnormal results flagged.<br>Summary tables of change from baseline over time will be displayed. Shifts in NCI CTCAE v5.0 grade events from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. |
| Vital signs | Vital signs data will be presented by individual listings with flagged values outside the normal ranges and abnormalities. In addition, tabular summaries will be used, as appropriate. |
| Tolerability | Dose interruptions, dose reductions, dose intensity, and treatment discontinuation because of adverse events will be listed and/or summarized, as appropriate. |

NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; SI = Système International d'Unités.

**Determination of Sample Size**

The study will enroll 10 patients in order to evaluate the safety and tolerability of the study treatment. A sample size of 10 was chosen to allow for a clinically meaningful assessment of safety. In addition, with a sample size of 10 patients, the true incidence rate of adverse events can be estimated to within 9.7%–34.5% assuming an observed incidence of 10% (i.e., within 95% Clopper-Pearson CI of 0.3% to 44.5%).

Continuous safety monitoring will be performed to guide potential early stopping of enrollment in the event of unacceptable toxicity or futility in the treatment arm.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibody |
| ASCT | autologous stem cell transplant |
| ASR | age-standardized risk |
| ASTCT | American Society for Transplantation and Cell Therapy |
| AUC | area under the concentration–time curve |
| BR | bendamustine in combination with rituximab |
| CAR | chimeric antigen receptor |
| CCOD | clinical cutoff date |
| *Glofit*-GemOx | *glofitamab* in combination with gemcitabine and oxaliplatin |
| CDC | complement-dependent cytotoxicity |
| CHOP | cyclophosphamide, doxorubicin, vincristine, and prednisone |
| CLL | chronic lymphocytic leukemia |
| $C_{max}$ | maximum serum concentration |
| $C_{min}$ | minimum serum concentration |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CR | complete response |
| CRS | cytokine-release syndrome |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLBCL | diffuse large B-cell lymphoma |
| DLT | dose-limiting toxicity |
| EBV | Epstein-Barr virus |
| EC | Ethics Committee |
| $EC_{50}$ | 50% effective concentration |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| Fab | fragment antigen-binding |
| Fc | fragment crystallizable |
| FcγR | Fc-γ receptor |
| FDA | (U.S.) Food and Drug Administration |
| FFPE | formalin-fixed, paraffin-embedded |

| Abbreviation | Definition |
|---|---|
| FL | follicular lymphoma |
| G | obinutuzumab |
| G-CHOP | obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone |
| G-CSF | granulocyte colony-stimulating factor |
| GemOx | gemcitabine plus oxaliplatin |
| Gpt | obinutuzumab given as pre-treatment |
| Granzyme B | cytotoxic granule release |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HGBCL | high-grade B-cell lymphoma |
| HLH | hemophagocytic lymphohistiocytosis |
| HSCT | hematopoietic stem cell transplant |
| ICH | International Council for Harmonisation |
| IFN(-γ) | interferon(-γ) |
| IHC | immunohistochemistry |
| IL-2 (-6, -10, -12) | interleukin-2 (-6, -10, -12) |
| IL-6R | interleukin-6 receptor |
| IMC | independent Monitoring Committee |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IRB | Institutional Review Board |
| IRR | infusion-related reaction |
| IxRS | interactive voice or web-based response system |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| MAS | macrophage activation syndrome |
| Mosun-GemOx | mosunetuzumab in combination with gemcitabine and oxaliplatin |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NaCl | sodium chloride |
| NCI | National Cancer Institute |
| NCI CTCAE v5.0 | National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 |
| NHL | non-Hodgkin lymphoma |

| Abbreviation | Definition |
|---|---|
| NK | natural killer (cell) |
| NOS | not otherwise specified |
| ORR | objective response rate |
| OS | overall survival |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PK | pharmacokinetic |
| PML | progressive multifocal leukoencephalopathy |
| pola-BR | polatuzumab vedotin in combination with bendamustine and rituximab |
| PP | Polypropylene |
| PR | partial response |
| PVC | polyvinyl chloride |
| R | Rituximab |
| R-CHOP | rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone |
| R/R | relapsed or refractory |
| TCB | T cell–bispecific (antibody) |
| TCR | T cell-receptor |
| TK | Toxicokinetic |
| TLS | tumor lysis syndrome |
| $t_{max}$ | time to maximum concentration |
| TNF-α | tumor necrosis factor–α |
| ULN | upper limit of normal |
| U.S.P.I. | U.S. Package Insert |

# 1. BACKGROUND

## 1.1 BACKGROUND ON RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND HIGH-GRADE B-CELL LYMPHOMAS

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in the world and the thirteenth most common cancer overall (Bray et al. 2018). It is estimated that 509,590 new cases of NHL were diagnosed worldwide in 2018 (2.8% of the total new cancer cases) and 248,724 people died of the disease (2.6% of total cancer-related deaths). The age-standardized risks (ASRs) of newly diagnosed NHL across Northern, Southern, Eastern, and Western Europe ranged from 280.1 to 363.5 per 100,000 person-years for males and from 216.5 to 292.1 per 100,000 person-years for females. The ASRs of mortality from NHL across the same European regions were 118.4–171.0 and 76.2–92.0 per 100,000 person-years, respectively. In the United States, it is estimated that 74,680 people were diagnosed with NHL in 2018 (incidence, 19.4 per 100,000) and 19,910 patients died from the disease (National Cancer Institute [NCI] 2018).

NHL comprises a heterogeneous group of lymphoproliferative disorders but most commonly presents as a defect in B lymphocytes. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL of B-cell origin (32.5% of the total NHL cases) (Al-Hamadani et al. 2015).

Originating from mature B cells, DLBCL is an aggressive NHL with a median survival of <1 year in untreated patients (Rovira et al. 2015). Despite its aggressive disease course, approximately 50%–70% of patients may be cured with the current standard-of-care treatment that consists of rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy (Flowers et al. 2010). Nevertheless, R-CHOP is found to be inadequate in 30%–50% of patients because of either primary refractoriness or relapse after achieving a complete response (CR). Elderly patients remain a particularly difficult subset to treat given their reduced tolerance to cytotoxic chemotherapy.

A majority of DLBCL cells express CD20, a membrane antigen that is important in cell cycle initiation and differentiation (Anderson et al. 1984). CD20 is a clinically validated target in the treatment of B-cell malignancies. The use of rituximab, a monoclonal antibody targeting CD20, has resulted in significantly longer periods of progression-free survival (PFS) and overall survival (OS), especially when combined with chemotherapy.

Modern molecular characterization of aggressive B-cell malignancies has identified a high-risk subset of patients with DLBCL or patients with otherwise morphologically unclassifiable B-cell malignancies that harbor translocations in *MYC* and *BCL2* and/or *BCL6* that confer chemoresistance by synergistic activation of anti-apoptotic pathways (Sesques and Johnson 2017). Such double- and triple-hit lymphomas comprise

approximately 5%–10% of patients with DLBCL who have high-risk clinical features, such as increased extranodal involvement and lactate dehydrogenase (LDH) levels (Oki et al. 2014), and have inferior survival after R-CHOP–based therapy than would typically be expected in DLBCL (Johnson et al. 2009; Petrich et al. 2014). Recognizing inherent differences in biology and treatment responsiveness of such tumors, the 2016 revision of the World Health Organization's classification of lymphoid neoplasms designated all such double- or triple-hit aggressive B-cell malignancies (irrespective of whether they can be characterized morphologically as DLBCL) as high-grade B-cell lymphoma (HGBCL), with *MYC* and *BCL2* and/or *BCL6* rearrangements (Swerdlow et al. 2016).

An additional category of aggressive B-cell lymphomas shares morphologic features of both DLBCL and Burkitt lymphoma or of blastoid morphology without meeting the criteria for lymphoblastic lymphoma. These lymphomas, assuming they do not meet the criteria for double- or triple-hit lymphomas, are now characterized as HGBCL, not otherwise specified (NOS) (Swerdlow et al. 2016).

## 1.2 TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND HIGH-GRADE B-CELL LYMPHOMA

For patients who are not cured by first-line therapy, high-dose chemotherapy followed by autologous stem cell transplantation offers a second chance for long-term remission. For patients with relapsed or refractory (R/R) DLBCL who are not eligible for stem cell transplantation, owing to age, comorbidities, or other factors, there are different treatment options, including various chemo-immunotherapies (bendamustine in combination with rituximab [BR], rituximab in combination with gemcitabine and oxaliplatin, and gemcitabine, dexamethasone, and cisplatin). These chemo-immunotherapies tend to be used with the goal of palliation rather than long-term survival. Recently approved treatments in the R/R setting include chimeric antigen receptor (CAR) T-cell therapies and polatuzumab vedotin in combination with BR.

Approximately half of patients with relapsed DLBCL do not respond to second-line therapy because of refractory disease (Gisselbrecht et al. 2010), and a significant number of patients are ineligible for aggressive therapy because of age or comorbidities. Furthermore, patients who either relapse after or are ineligible for stem cell transplantation because of refractory disease or frailty have poor outcomes. Therefore, a significant clinical need exists for new therapeutic approaches for patients with R/R DLBCL.

Patients with R/R HGBCL typically fare worse than patients with DLBCL. For instance, a retrospective multicenter study of patients with DLBCL and HGBCL identified that patients with HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements in the relapse setting had a 4-year OS of 25% after autologous stem cell transplant (ASCT) compared

with an OS of 61% for patients with non–double hit disease (Herrera et al. 2018). Thus, novel therapies are urgently needed for patients with HGBCL as well.

## 1.3 BACKGROUND ON *GLOFITAMAB*

*Glofitamab* is a T cell–bispecific (TCB) antibody targeting CD20 expressed on B cells and CD3ε chain present on T cells. By simultaneously binding to human CD20-expressing tumor cells and to the CD3ε of the T cell–receptor (TCR) complex on T cells, it induces tumor cell lysis, in addition to T-cell activation, proliferation, and cytokine release.

Lysis of B cells mediated by *glofitamab* is CD20 specific and does not occur in the absence of CD20 expression or in the absence of simultaneous binding (cross-linking) of T cells to CD20-expressing cells. In addition to killing, T cells undergo activation because of CD3 cross-linking, as detected by an increase in T-cell activation markers (CD25 and CD69), cytokine release (interferon-γ [IFN-γ], tumor necrosis factor–α [TNF-α], interleukin [IL]-2, IL-6, and IL-10), cytotoxic granule release (Granzyme B), and T-cell proliferation.

*Glofitamab* is a human IgG1 with the fragment crystallizable (Fc) region bearing a novel, proprietary modification (P329G *LALA* mutation), which abrogates its binding in vitro to Fc-γ receptors (FcγR) and prevents FcγR-mediated co-activation of innate immune effector cells, including natural killer (NK) cells, monocytes/macrophages, and neutrophils without changes in functional binding to the neonatal Fc receptor, as well as complement-dependent cytotoxicity (CDC).

*Glofitamab* binds in a bivalent binding mode to human CD20, with 50% effective concentration ($EC_{50}$) values of binding ranging between 0.98 and 3.8 nM (on CD20-expressing human tumor cells) to 4.8 nM (on normal human B cells), as detected on flow cytometry. The anti-CD20 antibody used in *glofitamab* is the type II anti-CD20 binder used in obinutuzumab (Mössner et al. 2010). The antibody is cross-reactive to cynomolgus monkey CD20 with an $EC_{50}$ value of binding ranging between 1.3 and 3.3 nM (on normal cynomolgus monkey B cells).

Binding to T cells occurs through its second binding unit targeting CD3ε of the TCR complex. The anti-CD3 antibody used in *glofitamab* (CH2527 [VL_7-46(13) VH_23-3(12)]) cross-reacts with human CD3ε and cynomolgus monkey CD3ε chain but not with mouse CD3ε. *Glofitamab* has been generated by Roche by means of humanization of the parental SP34 antibody (Pessano et al. 1985; Salmerón et al. 1991; Conrad et al. 2007).

### 1.3.1 Nonclinical Studies with *Glofitamab*

Nonclinical studies conducted with *glofitamab* have demonstrated that it is a potent molecule with in vitro and in vivo activity. Consistent with its mechanism of action, *glofitamab* has been shown in vivo to eliminate B cells from the peripheral blood and

secondary lymphoid organs and to induce regression of aggressive lymphoma tumors (see Section 1.3).

See the *Glofitamab* Investigator's Brochure for more details about nonclinical studies.

### 1.3.2 Clinical Data with *Glofitamab*

*Glofitamab* is currently being investigated in *four* ongoing Phase I studies:

- Study NP30179 is a Phase I, open-label, multicenter, dose-escalation study of *glofitamab*, as a single agent and in combination with obinutuzumab, administered after a fixed, single *intravenous (*IV*)* dose of obinutuzumab given as pretreatment (Gpt). This early-in-human study consists of three parts: dose escalation (Parts I and II) and dose expansion (Part III) and is being conducted in patients with R/R NHL. The first patient was enrolled in the study in February 2017.
- Study NP40126 is a Phase Ib, two-part, multicenter, dose-finding study of *glofitamab* administered in combination with obinutuzumab (G), rituximab (R), and standard doses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (G/R-CHOP or R-CHOP) in patients with R/R NHL and untreated DLBCL. The first patient was enrolled in the study in March 2018.
- Study NP39488 is a Phase Ib, open-label, multicenter study of *glofitamab* in combination with atezolizumab and in combination with polatuzumab vedotin (plus a single pretreatment dose of Gpt) in adult patients with R/R NHL. This study has two parts: a dose-escalation part and an expansion part. The first patient was enrolled in the study in May 2018.
- *Study JO41190 is a multicenter, open-label, dose-escalation study to assess the safety, tolerability, and pharmacokinetics of glofitamab after a fixed, single IV dose of obinutuzumab given as pretreatment in patients with R/R NHL. The first patient was enrolled in the study in March 2020.*

#### 1.3.2.1 Safety Data with *Glofitamab*

A summary of the safety data from three *of the* ongoing *four* studies is presented below. The most common adverse event for *glofitamab* is cytokine-release syndrome (CRS), an identified risk for *glofitamab*. Other identified risks include neutropenia, pyrexia, and tumor inflammation or flare (see Section 5.1.1). For further information on *non*clinical and clinical studies to date, refer to the current version of the *Glofitamab* Investigator's Brochure.

**Study NP30179**

As of the clinical cutoff date (CCOD) of *18 December* 2019 for Study NP30179, *161* patients had been enrolled and received at least one dose of monotherapy with *glofitamab* at doses from 5 μg to 25 mg following with Gpt (1000 mg IV). Twenty-eight patients had been enrolled and received at least one dose of combination treatment with *glofitamab* (0.6, 4, 16, or 10 mg [Cycle 1] followed by 16 mg for subsequent cycles) and (1000 mg) after Gpt (1000 mg IV) (n=26) or had received only Gpt (n=2).

Safety data for patients receiving monotherapy are presented with a focus on the ≥0.6-mg doses of *glofitamab* (n=*127*). Safety data from 34 patients dosed at <0.6 mg have not been included, given that their inclusion may artificially lower the rates of the toxicities linked to a pharmacologically active dose of *glofitamab* (e.g., CRS in patients receiving 0.005–0.3 mg *glofitamab* occurred in 4 of 34 patients (11.8% [one Grade 1 adverse event (AE) and three Grade 2 events] versus *69* of *127* patients [*54.3*%] treated with doses ≥0.6 mg).

As of *18 December* 2019 in Study NP30179, a total of *1334* AEs (all grades) had been reported in *123* of *127* patients (*96.9%*) in the ≥0.6 mg *glofitamab monotherapy* dose groups. *Sixty-four* patients (*52.4*%) experienced Grade ≥3 *Common Terminology Criteria for Adverse Events (CTCAE) AEs.* Of these patients, *35* patients (*27.6*%) experienced Grade ≥3 AEs that were reported by the investigator as related to *glofitamab. Eighty-three* patients (*65.4*%) had serious adverse events *(SAEs),* of whom *66 (52.0*%) had *SAEs* related to *glofitamab* treatment. A total of *95* events of CRS have been reported in *69* patients (*54.3*%).

Of the 28 patients who have received combination treatment with *glofitamab* and obinutuzumab or received Gpt only in Study NP30179, a total of *27* patients *(96.4%)* have experienced *306 AEs. Twelve patients (42.9%) experienced Grade≥3 CTCAE AEs; of these patients, 8* patients (28.6%) experienced Grade≥3 AEs reported by the investigator as related to *glofitamab. Seventeen* patients (*60.7%) had SAEs of whom 15 (*53.6%) had *SAEs* related to *glofitamab. Thirty* events of CRS have been reported in *19* patients (*67.9*%).

*As of the CCOD in Study NP30179, in patients who received at least one dose of monotherapy treatment with glofitamab at doses ≥ 0.6 mg following obinutuzumab (1000 mg IV) or obinutuzumab alone, 2 AEs were reported which led to discontinuation of glofitamab treatment (One event of Grade 3 Cytomegalovirus chorioretinitis [1 mg glofitamab], and one event of Grade 5 hypovolemic shock [25 mg glofitamab]). As of the CCOD in Study NP30179, 1 AE was reported in a patient -who received glofitamab in combination with obinutuzumab, which led to discontinuation of glofitamab treatment in 1 patient (Grade 5 i*nfection [*obinutuzumab* +1 mg – 16 mg *glofitamab]).*

*As of the CCOD in Study NP30179, including patients receiving monotherapy at doses ≥0.6 mg and combination therapy (N=155*), a total of *19* deaths *(12.3%)* have been reported*, of which* 16 were *due* to disease progression (*10.3*%) and *3* were reported as Grade 5 *AEs (1.9%).*

- *Fifteen of these deaths, (*two Grade 5 *AEs [Preferred Terms: dyspnea due to disease progression and* hypovolemic shock *not related to glofitamab] and 13 deaths due to disease progression), were reported in patients who* had received *monotherapy treatment with glofitamab, or received obinutuzumab only, at doses ≥0.60 mg (N=127).*

- *In patients who have received combination* treatment *with glofitamab and obinutuzumab or received obinutuzumab only (N=28), 4 deaths were reported, of which one death was reported to be attributed to Grade 5 AE (Preferred Term: infection) and 3 deaths have been reported due to disease progression.*

*In addition, 5 deaths (14.7%) were reported in the 5–300 µg dose cohorts receiving monotherapy (N=34); 4 deaths (11.8%) were due to disease progression and 1* death *(2.9%) was attributed to septic shock (45 µg dose cohort, single agent glofitamab+obinutuzumab).*

To investigate the potential for improved tolerability of *glofitamab*, a step-up dosing schedule in Cycle 1 is being evaluated in Study NP30179.

### Study NP40126

As of the CCOD of *18 December* 2019, *14* patients *have* been enrolled *into Study NP40126. Five patients* received G-CHOP in Cycle 1 *followed by* treatment with *glofitamab* at *a dose of 70 µg in combination with R-CHOP from* Cycle 2 *onwards. Five* patients *received G-CHOP in Cycle 1 followed by treatment* with *glofitamab at a dose of* 1.8 mg *in combination with R-CHOP from Cycle 2 onwards. One patient received G-CHOP in Cycle 1 before withdrawing consent. Three further patients received R-CHOP in Cycle 1 prior to the clinical cut off.* As of the CCOD, a total of *177 AEs* had been reported in *13 of 14 patients (92.9%). Eleven* patients (*78.6*%) experienced *AEs* considered by the investigator to be related to *glofitamab. Eight* patients (*57.1*%) had *SAEs. Ten* patients (*71.4*%) experienced Grade≥3 *CTCAE AEs. Five* events of CRS *have* been reported in *4* patients (*28.6%*).

*In Study NP40126, no AEs leading to withdrawal of study treatment have been reported as of the CCOD.* One death was also reported, owing to disease progression.

### Study NP39488

As of the CCOD of *18 December* 2019, *40* patients *have* been enrolled *into Study NP39488, 38 of whom have* received treatment with *glofitamab* at doses of 0.07–6 mg following *obinutuzumab in combination with atezolizumab 1200 mg; 1 of whom has received treatment with glofitamab 2500 µg in combination with polatuzumab vedotin following Gpt; and 1 of whom received one dose of obinutuzumab without administration of glofitamab.* As of the CCOD, a total of *474 AEs* had been reported in all *40* patients (100%). Twenty-*eight* patients (*70.0*%) experienced *AEs* that were considered by the investigator to be related to *glofitamab*. Twenty-*three* patients (57.*5*%) had *SAEs*. Twenty-*eight* patients (*70.0*%) experienced Grade ≥3 *CTCAE AEs. Forty* events of CRS *have* been reported in *18 patients (45%).*

*As of the CCOD in Study NP39488, 3 AEs have been reported in patients which led to discontinuation of glofitamab treatment in 2 patients (Mycobacterium abscessus infection in one patient; myopathy also leading to discontinuation of atezolizumab and cytokine release syndrome in the other patient).*

A total of 15 deaths have been reported *in Study NP39488,* of which one was a Grade 5 *AE* (pneumonia in *one* patient in the 0.3-mg cohort *dose group), 13 were due to disease progression, and one death due to 'other' (the patient withdrew from the study and died due to euthanasia*).

*Safety data are not yet available from Study JO41190.*

#### 1.3.2.2 *Glofitamab* Efficacy

*At the time of the CCOD (18 December 2019), of the 127 patients enrolled in Study NP30179 to receive treatment with glofitamab as monotherapy at doses ≥0.6 mg, a total of 112 patients across all histologies had been evaluated for tumor response. Of these 112 patients at dose levels of ≥0.6 mg, 43 patients (38.4%) had complete responses (CR), 12 patients (10.7%) had partial responses (PR), 15 patients (13.4%) had stable disease, and 36 patients (32.1%) had progressive disease as assessed by the Investigator using positron emission tomography/computed tomography (PET/CT) Lugano analysis.*

*At the time of CCOD, all 28 patients enrolled to receive combination therapy with glofitamab at doses ≥0.6 mg with concurrent obinutuzumab at 1000 mg using an every 3 week (Q3W) dosing regimen had been evaluated for tumor response. Of these 28 patients, 14 patients (50.0%) had CR, 2 patients (7.1%) had PR, 3 patients (10.7%) had stable disease, and 7 patients (25.0%) had progressive disease as assessed by the Investigator using PET/CT Lugano analysis.*

*At the time of CCOD in Study NP39488, 38 patients were evaluable for the efficacy analysis. Across all doses and histologies, objective response rate (ORR) and CR rates by investigator assessment were 44.7% (17 of 38 patients) and 26.3% (10 of 38 patients), respectively (indolent NHL: 5 of 5 and 5 of 5 patients; aggressive NHL: 12 of 33 and 5 of 33 patients). At dosing cohorts >1800 µg (n=25), 15 responses were observed, including 9 CRs.*

Efficacy data are not yet available from Studies NP40126 and *JO41190*.

#### 1.3.2.3 *Glofitamab* Clinical Pharmacokinetics and Immunogenicity

The clinical pharmacology of *glofitamab* has been investigated in the ongoing Phase I single-agent Study NP30179. Clinical pharmacology and clinical pharmacokinetic (PK) data have not been reported yet from patients enrolled in the combination studies.

At the time of *CCOD (18 December 2019),* preliminary PK data were available from a total of *165* patients in the ongoing Study NP30179 who received *glofitamab* by IV infusion as a single agent following Gpt either on an every-2-week or every-3-week dosing schedule.

Following an initial 4-hour IV infusion, mean *glofitamab* concentrations increased rapidly with median time to maximum concentration ($t_{max}$) reached shortly after end of infusion,

approximately 4 hours across doses, and exhibited a biphasic disposition with an initial rapid distribution phase followed by a slower elimination phase. Single- and multiple-dose exposures of *glofitamab* increased in an approximately dose-proportional manner over the investigated dose range based on visual inspection of dose–exposure relationships from estimated PK parameters. No evidence for substantial accumulation was observed with multiple dosing for the investigated schedules comparing *glofitamab* PK parameters (area under the concentration–time curve [AUC] and maximum serum concentration [$C_{max}$]) across treatment cycles. *Glofitamab* PK parameters are associated with moderate between-patient variability (percent coefficient of variation approximately 20%–80% across doses).

As of the CCOD, *data from 171* patients *serum samples from Study NP30179 indicated that no patient was* positive for anti-drug antibodies (ADAs) *following administration of glofitamab*.

For further information, refer to the *Glofitamab* Investigator's Brochure.

## 1.4 BACKGROUND ON OBINUTUZUMAB GIVEN AS PRETREATMENT

Obinutuzumab is a humanized and glycoengineered type II anti-CD20 monoclonal antibody that recognizes the CD20 antigen present on normal and malignant B cells. It was developed for the treatment of hematologic malignancies, namely NHL and chronic lymphocytic leukemia (CLL). Showing a significant benefit over rituximab, obinutuzumab (Gazyva®/Gazyvaro®) has been approved in the European Union and by the U.S. Food and Drug Administration (FDA) for selected patients with CLL, untreated FL, and R/R FL.

Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high affinity binding to the CD20 antigen, high antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis, low CDC activity, and high direct cell death induction. Nonclinically, Gpt has been shown to debulk peripheral B cells and reduce systemic cytokine release (Bacac et al. 2018). The use of Gpt for mitigation of TLS and CRS is being evaluated in the ongoing Studies NP30179 and NP39488, with a single 1000-mg dose of obinutuzumab administered 7 days prior to the first dose of *glofitamab* (Dickinson et al. 2019).

## 1.5 BACKGROUND ON MOSUNETUZUMAB

Mosunetuzumab (RO7030816) is a full length, humanized anti-CD20/anti-CD3 T cell–dependent bispecific antibody of an IgG1 isotype that is produced using the knobs-into-holes technology (Atwell et al. 1997; Spiess et al. 2013). One Fab region of the antibody is directed against the extracellular domain of the CD3ε subunit of the TCR complex, and the other Fab region is directed against the extracellular domain of CD20 (Atwell et al. 1997; Spiess et al. 2013). Mosunetuzumab contains the N297G amino acid substitution in the Fc region according to E.U. numbering (Edelman et al. 1969; Kabat et

al. 1991). This substitution results in a non-glycosylated heavy chain that has minimal binding to FcγRs and, consequently, prevents Fc-effector functions. Mosunetuzumab is derived from Chinese hamster ovary cells.

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

The near ubiquitous CD20 expression in DLBCL and validation of CD20 as a therapeutic target in its treatment (standard-of-care R-CHOP-21) provide a rationale for the development of a T cell–recruiting bispecific antibody targeting CD20, such as mosunetuzumab, for DLBCL (and other CD20-expressing B-cell NHLs).

### 1.5.1 Nonclinical Studies with Mosunetuzumab

Comprehensive pharmacologic, PK/toxicokinetic (TK), pharmacodynamic (PD), and toxicology studies were conducted to support the entry of mosunetuzumab into clinical trials and continued clinical development. In vitro studies with human peripheral blood mononuclear cells (PBMCs) and B-cell lymphoma cell lines and in vivo studies in cynomolgus monkeys support the mechanism of action of mosunetuzumab-induced T-cell activation, cytokine release, and proliferation in the presence of CD20-positive target B cells with subsequent killing of target cells. Single-dose and repeat-dose (up to 26-week) toxicity, PK/TK, and PD studies with mosunetuzumab following IV and/or *subcutaneous (*SC*)* administration to cynomolgus monkeys have been completed. The nonclinical PK behavior observed for mosunetuzumab is consistent with that expected for a humanized IgG1 monoclonal antibody with a component of target-mediated clearance. The acute toxicities associated with mosunetuzumab treatment are largely driven by stimulation of T cells, as evidenced by PD changes in cytokine levels and number of activated T cells. In repeat-dose toxicity studies in cynomolgus monkeys, the increase of cytokine levels, T-cell activation, and acute postdose observations were primarily limited to the first dose and were reduced or negligible following subsequent doses.

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

### 1.5.2 Clinical Data with Mosunetuzumab

Evaluation of mosunetuzumab was initiated in Study GO29781, a Phase I/Ib, open-label, multicenter trial evaluating the safety and pharmacokinetics of escalating doses of

mosunetuzumab administered to patients with R/R B-cell NHL and CLL as a single agent and in combination with atezolizumab. In Study GO29781, mosunetuzumab has been studied according to the following dosing schedules in Groups A, B, D, and E (note that there is no Group C):

- Administered intravenously as a single agent in Cycle 1 using a flat dosing schedule (Group A)
- Administered intravenously as a single agent in Cycle 1 using a step-up dosing schedule, with escalation of dose levels on Days 1, 8, and 15 of Cycle 1, followed by administration of the highest dose level on Day 1 of subsequent cycles (Group B)
- Administered subcutaneously as a single agent in Cycle 1 using a flat dosing schedule (Group D)
- Administered intravenously as a single agent in Cycle 1 using a step-up dosing schedule with concurrent administration of atezolizumab starting in Cycle 2 (Group E)

In addition to the Phase I/Ib Study GO29781, mosunetuzumab is being investigated in the three following ongoing Phase Ib/II studies:

- Study GO40516 is a Phase Ib/II, open-label, multicenter study evaluating the safety, tolerability, pharmacokinetics, and efficacy of mosunetuzumab in combination with polatuzumab vedotin in patients with DLBCL and in patients with FL.
- Study GO40515 is a Phase Ib/II, open-label, multicenter study assessing the safety, tolerability, pharmacokinetics, and efficacy of mosunetuzumab in combination with CHOP or cyclophosphamide, doxorubicin, and prednisone in combination with polatuzumab vedotin in patients NHL, including patients with previously untreated DLBCL.
- Study GO40554 is a Phase Ib/II study evaluating mosunetuzumab as consolidation therapy in patients with DLBCL following immunochemotherapy in the front-line setting and as therapy in patients with previously untreated DLBCL who are unable to tolerate full-dose chemotherapy.

#### 1.5.2.1 Mosunetuzumab Safety

A summary of the safety data from ongoing studies is presented below. The most common AE for mosunetuzumab is CRS, an identified risk for mosunetuzumab. Neutropenia is also an identified risk (see Section 5.1.4). For further information on nonclinical and clinical studies to date, refer to the current version of the Mosunetuzumab Investigator's Brochure.

**Study GO29781**

In Study GO29781, dose escalation for Groups A and B is complete and dose escalation for Groups D and E is ongoing. In Group A, doses ranging from 0.05 to 2.8 mg have been tested in patients using the flat dosing schedule, and no further dose finding is ongoing in Group A. In Group B, dose levels of 2.8–60 mg have been tested in the step-up regimen of 1 mg on Day 1, 2 mg on Day 8, and a full dose on Day 15. The

60-mg dose cleared the dose-limiting toxicity (DLT) assessment period as of 6 May 2019. No further dose finding is ongoing in Group B. In general, AEs reported in the 27-, 45-, and 60-mg dose cohorts appeared to be consistent with those observed with mosunetuzumab at lower dose levels.

The maximum tolerated dose (MTD) for mosunetuzumab has not been reached in any of the dose-escalation groups described above. The maximum administered dose using the step-up dosing schedule is 60 mg mosunetuzumab. The current dosing schedule in expansion cohorts is mosunetuzumab administered on a step-up dosing schedule for Cycle 1, with 1 mg on Day 1 of Cycle 1, 2 mg on Day 8 of Cycle 1, and 60 mg on Day 15 of Cycle 1. The mosunetuzumab dose on Day 1 of Cycle 2 is 60 mg, followed by 30 mg on Day 1 of subsequent cycles.

As of 31 January 2019, a total of 205 patients had been treated with mosunetuzumab in Study GO29781. The most frequently observed AE considered by the investigator to be related to mosunetuzumab was CRS, occurring in 24.4% of safety-evaluable patients. All of the events were Grade 1 or 2 in severity according to the modified CRS grading system (Lee et al. 2014), except for one Grade 3 event observed in a patient treated in Group B. Serious adverse events were reported in 75 patients (36.6%), and in 23 patients (11.2%) of these patients, the SAEs were considered by the investigator as related to mosunetuzumab. Twenty-seven patients have experienced AEs with a fatal outcome: 23 patients experienced progression of malignant neoplasm (reported as an AE), 1 patient as the result of a large intestinal perforation, 1 patient with hemophagocytic lymphohistiocytosis (HLH), 1 patient with pneumonia, and 1 patient with *Candida* sepsis.

Neutropenia has been observed in Study GO29781 with mosunetuzumab treatment. As of 31 January 2019, 53 patients (25.9%) had experienced AEs of neutropenia. Of the 53 patients with reported AEs of neutropenia, febrile neutropenia, or decreased neutrophil count, 23 patients (11.2%) had a Grade 3 event and 27 patients (13.2%) had a Grade 4 event reported as the highest grade, including Grade 4 neutropenia events that qualified as DLTs. Neutropenia is a known risk associated with mosunetuzumab, as well as with gemcitabine and oxaliplatin. The observation of neutropenia with mosunetuzumab suggests that neutropenia may be a potentially overlapping toxicity when mosunetuzumab is combined with a chemotherapy-based regimen, such as gemcitabine and oxaliplatin, and will be assessed in this study (refer to Section 5 for details on mitigation strategies and safety monitoring).

### Study GO40516

Study GO40516 was designed to investigate the safety, tolerability, pharmacokinetics, and efficacy of mosunetuzumab in combination with polatuzumab vedotin in patients with B-cell NHL. As of the clinical cutoff date, 20 December 2018, for Study GO40516, 4 patients had been treated. The MTD had not been reached, and no DLT had been observed. One patient discontinued study treatment because of an SAE of Grade 3

pneumonitis and 1 patient had a Grade 5 AE with a fatal outcome attributed to malignant disease progression.

Refer to the Mosunetuzumab Investigator's Brochure for full details of treatment-emergent adverse events.

#### 1.5.2.2 Mosunetuzumab Efficacy

In Study GO29781, investigator-assessed objective responses, including CRs, have been observed in patients with R/R NHL.

As of the CCOD of 31 January 2019, of the 186 patients in the primary efficacy-evaluable population across all treatment groups, 73 patients (39.2%) had investigator-assessed objective responses (a CR or a PR). Overall, 44 patients (23.7%) had CRs, 29 patients (15.6%) had PRs, 20 patients (10.8%) had stable disease, and 69 patients (37.1%) had progressive disease as best overall response assessed by the investigator per the International Working Group's criteria (Cheson et al. 2007). Objective responses were observed in patients with indolent and aggressive NHL histologies, including FL, DLBCL, transformed FL, mantle cell lymphoma, marginal zone lymphoma, and Richter transformation. As of the CCOD of 1 April 2019 for patients with aggressive NHL treated with the step-up dosing regimen across multiple dose levels, the ORR was 35.1% (34 of 98 patients) and the CR rate was 20.6% (20 of 98 patients) (Bartlett et al. 2019).

Refer to the Mosunetuzumab Investigator's Brochure for additional details on efficacy data.

#### 1.5.2.3 Mosunetuzumab Clinical Pharmacokinetics and Immunogenicity

On the basis of available clinical PK data following Cycle 1 flat dosing (Group A, n=33) and Cycle 1 step-up dosing (Group B, n=132) in Study GO29781, serum mosunetuzumab drug concentrations reached $C_{max}$ at the end of infusion (approximately 4 hours) and declined in a multiphasic fashion. The apparent half-life estimates following flat dosing range from 6 to 11 days. The shorter half-life estimates of mosunetuzumab compared with the typical half-life of 21 days for an IgG1 antibody, likely reflect a higher drug clearance, owing to the effect of target-mediated drug disposition at the tested dose levels. Preliminary PK results indicate that the geometric mean apparent clearance ranges from 746 to 1602 mL/day following the 0.2- to 2.8-mg flat dosing in Cycle 1. Preliminary data indicate that in Cycle 1, AUC and $C_{max}$ of mosunetuzumab increased in an approximately dose-proportional manner over the dose range tested. Moderate PK variability was observed.

Of the 53 evaluable postbaseline samples from patients tested in Study GO29781, none were confirmed positive for anti-mosunetuzumab antibodies.

Refer to the Mosunetuzumab Investigator's Brochure for additional details on clinical pharmacology and immunogenicity results.

## 1.6 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Up to 40% of patients with DLBCL who are treated in the first-line setting will progress within 3 to 4 years (Friedberg 2011), which includes approximately 10% of patients with refractory disease to first-line R-CHOP–like treatment. Patients with R/R DLBCL fit into one of two general categories: candidates or non-candidates for transplant.

High-dose therapy with ASCT is a potentially curative option but is only available for younger, fit patients who demonstrate chemosensitive disease (Tilly et al. 2015) and have access to a transplant center. Improvement of the response rates to salvage chemotherapy may increase the number of patients who can proceed to high-dose therapy with ASCT.

In addition, CAR T-cell therapies have recently produced high rates of durable responses for patients with R/R DLBCL (Schuster et al. 2019).

For patients who are not candidates for transplant and/or CAR T-cell therapy or for patients who have failed either of these treatment strategies, the goal of subsequent therapy is to induce a response and prolong survival, although currently not with curative intent. Unfortunately, there is no widely accepted standard of care in these settings. The treatment options for patients with R/R DLBCL who are not candidates for transplant (or who relapse after transplant) are summarized according to the National Comprehensive Cancer guidelines (see Table 1), and European Society for Medical Oncology practice guidelines (see Table 2).

### 1.6.1 Treatment of Patients with R/R DLBCL Who Are Not Candidates for Transplant (or Who Relapse after Transplant)

There are no universally established therapies for patients with R/R DLBCL who are not candidates for transplant or who relapse after transplant. The most commonly used regimens are gemcitabine and/or platinum-based therapies or BR (see Table 1 and Table 2).

**Table 1 Suggested Treatment Regimens for Second-Line and Subsequent Therapies for Non-Candidates for High-Dose Therapy per the NCCN Clinical Practice Guidelines**

| Suggested Treatment Regimens (In Alphabetical Order) |
|---|
| *Preferred regimens:* |
| GemOx (gemcitabine and oxaliplatin), with or without rituximab |
| *Polatuzumab vedotin with or without bendamustine, with or without rituximab (after two or more prior therapies)* |

**Table 1 Suggested Treatment Regimens for Second-Line and Subsequent Therapies for Non-Candidates for High-Dose Therapy per the NCCN Clinical Practice Guidelines (cont.)**

| Suggested Treatment Regimens (In Alphabetical Order) |
|---|
| *Other recommended regimens:* |
| CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) with or without rituximab |
| CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) with or without rituximab |
| DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) with or without rituximab |
| GDP (gemcitabine, dexamethasone, cisplatin/carboplatin), with or without rituximab |
| Gemcitabine and vinorelbine, with or without rituximab (category 3) |
| Rituximab |
| *Useful in certain circumstances:* |
| Bendamustine with or without rituximab (category 2B) |
| Brentuximab vedotin for CD30+ disease |
| Ibrutinib (non-GCB DLBCL) |
| Lenalidomide with or without rituximab (non-GCB DLBCL) |

CD=cluster of differentiation; DLBCL=diffuse large B-cell lymphoma; GCB=germinal center B-cell like; NCCN=National Comprehensive Cancer Network.

Source: NCCN Guidelines®, Version *1, 2020*.

**Table 2 Recommended Treatment Strategies in Diffuse Large B-Cell Lymphoma for Patients Who Are Not Candidates for Transplant per the ESMO Clinical Practice Guidelines**

| First Relapse/Progression | Two Relapses/Progressions |
|---|---|
| Platinum-based and/or gemcitabine-based regimens | Clinical trial with novel drugs |
| Clinical trials with novel drugs | Palliative care |

ESMO=European Society for Medical Oncology.

Source: Tilly et al. 2015.

Even with gemcitabine/platinum-based therapies, outcomes are poor for patients who are not candidates for transplant, especially if they relapse early (i.e., ≤12 months).

Rituximab combined with gemcitabine and oxaliplatin for patients in the first or second relapse who are not candidates for transplant showed a median PFS and OS of 3 and 6 months, respectively, in patients who relapsed within 1 year of their prior therapy (Mounier et al. 2013). Rituximab in combination with gemcitabine, dexamethasone, and cisplatin for the treatment of patients who did not ultimately proceed with transplant also showed poor outcomes with 2-year PFS and OS of 9% and 11%, respectively (Moccia et al. 2017). Similarly, in the CORAL study (rituximab in combination with dexamethasone, high-dose cytosine arabinoside and cisplatin or rituximab, ifosfamide, carboplatin, and etoposide phosphate), in patients who had received prior rituximab and

relapsed within 12 months and did not receive a transplant, the 3-year PFS was 14% (Gisselbrecht et al. 2010).

Of the therapies for patients who are not candidates for transplant, the combination of BR has been used and studied in prospective studies. The two largest studies were reported by Vacirca et al. (2014) and Ohmachi et al. (2013). The study conducted by Vacirca and colleagues included 95% of patients who had previously received rituximab therapy and the CR rate with BR given as second-line treatment and subsequent therapy was 15.3% (Vacirca et al. 2014), with a median PFS of 3.6 months. Improved responses were reported for the BR combination in Japanese patients with relapsed (but not refractory) DLBCL in the study published by Ohmachi and colleagues, with a CR of 37% and median PFS of 6.7 months. Of the 59 patients treated with BR, 97% had previously received rituximab (Ohmachi et al. 2013). The study excluded patients with refractory disease, limited the number of prior therapies to three with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, and used higher doses of dexamethasone (20 mg on Days 1–3 and 10 mg on Days 4 and 5) than typically used for BR. These factors may account for the higher response rates seen in the study. However, even in this study, the median PFS for patients who relapsed within 12 months was poor at 3.4 months (Ohmachi et al. 2013).

Polatuzumab vedotin, in combination with bendamustine and a rituximab product, was recently granted accelerated approval by the FDA for the treatment of adult patients with R/R DLBCL, NOS, after at least two prior therapies. In a study conducted by Sehn et al. (2017), patients with R/R DLBCL who were not candidates for transplant were randomized to receive either polatuzumab vedotin in combination with BR (pola-BR) or BR, with 40 patients in each arm. Patients in the pola-BR arm had a 40% CR rate on positron emission tomography (PET) imaging at the end of treatment, with a median PFS (assessed by an independent review committee) of 11.1 months and a median OS of 12.4 months. Patients in the BR arm had an 18% CR rate on PET imaging at the end of treatment, with a median PFS of 3.7 months and a median OS of 4.7 months (Sehn et al. 2017; Polivy® U.S. Package Insert).

It is difficult to compare directly the cohorts reported in these studies, although clearly the outcomes of patients who are not candidates for transplant are very poor. There are differences between the design of these studies based on eligibility criteria (i.e., limitations on prior lines of therapy, refractoriness) as well as historical context (e.g., how many patients had prior exposure to rituximab or what the first-line therapy was).

Although the data for CAR T-cell therapies after two or more lines of systemic therapy are promising (Neelapu et al. 2017; Schuster et al. 2019), ensuring the consistency, quality, and dose of autologous cell–based therapies remains non-trivial and potentially limits the broad adoption of this therapeutic mode beyond specialized centers. In addition, the cellular processing time may be prohibitive for a substantial proportion of

patients with rapidly progressive disease who may not have time to wait for leukapheresis scheduling or manufacturing time for CAR T-cell therapy.

The limited accessibility of CAR T-cell therapies to the broader patient population, coupled with the challenging toxicity profile, demonstrates that a high, unmet medical need continues to exist. Novel therapies are needed to further improve the treatment outcomes of patients with R/R DLBCL and to offer more patients a more effective treatment with improved survival.

The CD20-CD3 bispecific antibodies *glofitamab* and mosunetuzumab are engineered to redirect T cells to engage and eliminate malignant B cells by simultaneously binding to CD3ε on T cells and CD20 on lymphoma cells. With "off-the-shelf" accessibility and clinically manageable safety profile (especially with respect to the frequency and severity of CRS and neurotoxicity), *glofitamab* and mosunetuzumab both offer the potential for a significant improvement relative to current available regimens for the treatment of R/R DLBCL. Preliminary results from Phase I dose-escalation trials demonstrate encouraging clinical activity across multiple histologic subtypes of NHL, including strong and durable responses in patients with R/R aggressive NHL in the late-line setting.

### 1.6.2 Benefit–Risk Assessment

R/R DLBCL is difficult to treat and is usually life limiting. There are *few* treatment options available for patients with DLBCL who have relapsed or whose disease is refractory to commonly available treatments.

Single-agent treatment with *glofitamab* and with mosunetuzumab has demonstrated promising ORR and CR rates. Treatment with *glofitamab* or with mosunetuzumab will offer “off-the-shelf” accessibility without the need for bridging therapy and is likely to be more convenient and more readily available compared with CAR T-cell therapies. Similar to other T cell–engaging therapies, known toxicities with *glofitamab* and mosunetuzumab are CRS, tumor flare, and cytopenias. For mosunetuzumab, a step-up dosing regimen in the first cycle has been shown to mitigate CRS. For *glofitamab*, a similar step-up dosing treatment will be used to mitigate CRS toxicities in the first treatment cycle.

For patients with R/R DLBCL, chemo-immunotherapy is a current standard of care. Combining *glofitamab* or mosunetuzumab with gemcitabine plus oxaliplatin is anticipated to provide improved response rates compared with the combination of rituximab and gemcitabine plus oxaliplatin, while maintaining an acceptable safety profile. The strong efficacy demonstrated in the ongoing studies of *glofitamab* and of mosunetuzumab in addition to the efficacy anticipated from gemcitabine plus oxaliplatin will benefit patients with DLBCL in the second-line and subsequent settings, with a favorable benefit–risk profile. Moreover, gemcitabine and oxaliplatin do not interfere with T-cell function in the setting of immunotherapy, and a CD20-bispecific–GemOx combination has the potential to enhance the anti-tumor response because of complementary stimulatory effects on the immune system (refer to Section 3.3.5).

## 2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and preliminary efficacy of *glofitamab* in combination with gemcitabine and oxaliplatin (*Glofit*-GemOx) or mosunetuzumab in combination with gemcitabine and oxaliplatin (Mosun-GemOx) in patients with R/R DLBCL. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., *Glofit*-GemOx, administered following a single 1000-mg dose of *obinutuzumab*, or Mosun-GemOx).

### 2.1 SAFETY OBJECTIVES

The primary safety objective for this study is to evaluate the safety of the study treatment as a combination therapy on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5.0), with severity of CRS determined according to the American Society for Transplantation and Cell Therapy (ASTCT) Consensus Grading Criteria (see Appendix 4)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The secondary safety objective is to evaluate the tolerability of study treatment as a combination therapy on the basis of the following endpoint:

- Tolerability, as measured by dose interruptions, dose reductions, dose intensity, and treatment discontinuation because of AEs

### 2.2 EFFICACY OBJECTIVE

The efficacy objective for this study is to make a preliminary assessment of the efficacy of the study treatment on the basis of the following endpoints:

- CR, defined as the proportion of patients whose best overall response is a CR based on PET/computed tomography (CT) during the study, as determined by the investigator according to the 2014 Lugano Response Criteria for Malignant Lymphoma (hereafter referred to as the 2014 Lugano Response Criteria) (Cheson et al. 2014) (see Appendix 5)
- ORR, defined as the proportion of patients whose best overall response is a PR or a CR during the study, as determined by the investigator according to the 2014 Lugano Response Criteria

### 2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to evaluate the pharmacokinetics of the CD20-CD3–bispecific antibody on the basis of the following endpoints:

- Minimum serum concentration ($C_{min}$)

- $C_{max}$
- AUC for serum concentration–time profile estimated using a population-PK model, as the data allow

*Serum* samples for the analysis of obinutuzumab concentrations in Arm A will also be obtained and reported. These will be used to inform PK modeling.

The exploratory PK objective is to assess potential PK interactions between the CD20-CD3–bispecific antibody and gemcitabine plus oxaliplatin (GemOx) on the basis of the following endpoint:

- Serum concentration or PK parameters for CD20-CD3–bispecific antibody given in combination with GemOx compared with CD20-CD3–bispecific antibody given alone based on historical data

## 2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to make a preliminary evaluation of the immune response to the CD20-CD3–bispecific antibody on the basis of the following endpoints:

- Prevalence of ADAs against *glofitamab* at baseline and incidence of ADAs during the study
- Prevalence of ADAs against mosunetuzumab at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective is to evaluate potential effects of ADAs on the basis of the following endpoints:

- Relationship between *glofitamab* ADA status and safety, PK, or efficacy endpoints
- Relationship between mosunetuzumab ADA status and safety, PK, or efficacy endpoints

## 2.5 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to evaluate biomarkers that provide evidence of CD20-CD3–bispecific antibody activity on the basis of the following endpoints:

- PD biomarkers, such as T-cell activation and cytokine production
- *Tumor tissue will be obtained from all patients, if possible, in order to perform retrospective CD20 assessment and to further assess exploratory biomarkers that could provide information on the mechanism of action*
- The impact of GemOx combination therapy on these established mechanisms
- Exploratory biomarkers in blood and susceptibility to development of AEs

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

### 3.1.1 Study Design Overview

This is a Phase Ib, open-label, multicenter study designed to evaluate the safety and preliminary efficacy of a CD20-CD3–bispecific antibody in combination with gemcitabine and oxaliplatin in patients with R/R B-cell lymphoma, including patients with DLBCL, NOS; HGBCL with *MYC*, *BCL2*, and/or *BCL6* rearrangements; and HGBCL, NOS.

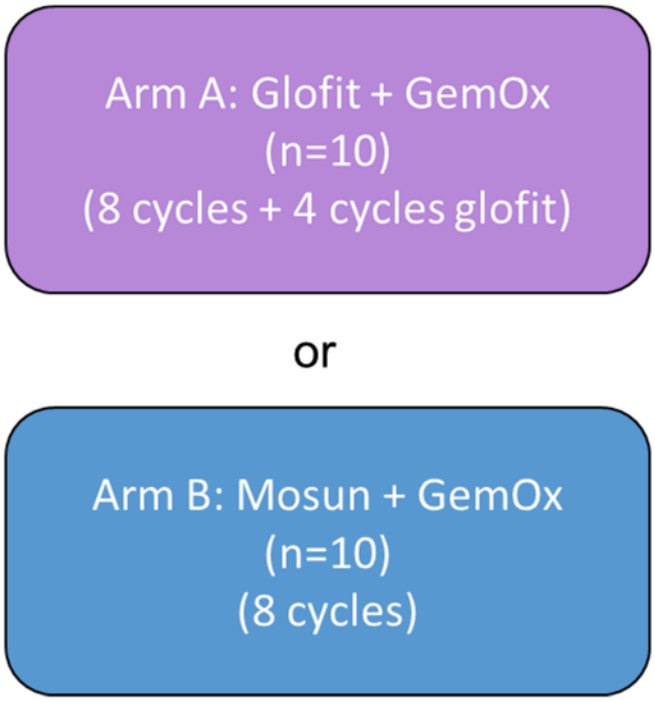
The study is structured to allow the enrollment of patients in one *or both* of the following two study arms:

- Arm A: *Glofit*-GemOx, administered following a single 1000-mg dose of *obinutuzumab*
- Arm B: Mosun-GemOx

Prior to the start of study enrollment, the Sponsor *elected to open Arm A* on the basis of the totality of emerging PK, tolerability, and preliminary efficacy data of both molecules administered as single agents and in combination with other therapies (described in *the protocol)*. The unselected arm will remain inactive and will be put on hold for enrollment. The Sponsor may also elect to open *Arm B* as a second study arm.

The overall design of the study is presented in Figure 1. The schedule of activities is provided in Appendix 1, and the PK, immunogenicity, and biomarker sample collection schedule is presented in Appendix 2.

**Figure 1 Study Schema**




GemOx=gemcitabine plus oxaliplatin; *Glofit=glofitamab; Mosun=*mosunetuzumab.

[a] *Glofitamab* will be administered following a single pretreatment dose of 1000 mg obinutuzumab on Day 1 of Cycle 1.

In Arm A, a total of 10 patients will be treated with *Glofit*-GemOx. Accrual of the 10 patients will occur consecutively. Patients *in the Glofit-GemOx arm* will receive *a single IV dose of obinutuzumab pretreatment 7 days before the first dose of glofitamab, then up to 8* cycles of *glofitamab in combination with gemcitabine plus oxaliplatin, followed by up to 4* cycles *of glofitamab monotherapy, to complete up to a total of 12 cycles of glofitamab. It is expected that some patients will not be able to complete 8 cycles of GemOx therapy due to progressive disease or AEs; refer to Section 4.6.2 for guidelines on early discontinuation due to toxicity.* The dosing regimen is described in detail in Section 4.3.2.

*The sponsor may elect to enroll up to 20 patients in either study arm based on internal monitoring committee (IMC) recommendations.*

In Arm B, a total of 10 patients will be treated with Mosun-GemOx. Accrual of 10 patients will occur consecutively. Patients will receive *up to 8* cycles of Mosun-GemOx administered in 21-day cycles. The dosing regimen is described in detail in Section 4.3.2.

All patients will be closely monitored for AEs throughout the study and for at least 90 days after the final dose of study treatment (see Section 5.6). Adverse events will be

graded according to the NCI CTCAE 5.0, with CRS graded according to the ASTCT 2019 CRS Consensus Grading (Lee et al. 2019; see Appendix 4).

Patients will be assessed for tumor response by PET/CT *and CT* after Cycles *4 and 8. Patients in Arm A will also be assessed for tumor response after Cycle 12. Tumor response will be assessed* using the 2014 Lugano Response Criteria (Cheson et al. 2014) (see Appendix 5).

For more details on tumor and response assessments, refer to Section 4.5.6.

### 3.1.2 Internal Monitoring Committee

Given that this is the first study of a *Glofit*–bispecific antibody in combination with gemcitabine and oxaliplatin, an IMC will be formed during the study to make recommendations on study conduct on the basis of trial safety data to ensure enhanced patient safety during study treatment. The IMC will consist of an IMC Medical Monitor Chair external to the study and Sponsor's representatives from Clinical Science and Safety Science who are external to the study team, and a Sponsor's representative from Biostatistics. The IMC will convene to review cumulative safety data, including the incidence and nature of serious adverse events, deaths, Grade ≥3 AEs, and adverse events of special interest. The IMC will hold its first review after 3 patients have reached Day 7 of Cycle 2, and the committee will conduct its second review after 10 patients have reached at least Day 7 of Cycle 2 and at least 5 patients have completed two full cycles of treatment. *The IMC may recommend enrolling up to 20 patients in either study arm if in its view the tolerability of the combination requires further interrogation prior to investigation in subsequent studies.*

The IMC will operate according to a prespecified charter that will outline the IMC members, roles, responsibilities, and communication processes. The IMC will make recommendations on the basis of the data review to inform advancement to a Phase III study.

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit occurs or the date when the last data point required for statistical analysis or protocol-defined safety monitoring is received from the last patient, whichever occurs later (see Section 6.5). The end of the study is expected to occur approximately *13* months after the last patient is enrolled.

Owing to the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor. This will not constitute a premature termination of the study.

The total length of the study, from screening of the first patient to the end of study, is expected to be approximately *17* months.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for *Glofitamab* Dose and Schedule

In this study, *glofitamab* will be administered to patients by IV infusion in 21-day cycles with step-up dosing in Cycle 1. The step-up dosing schedule is being assessed in an ongoing first-in-human Phase I study, NP30179, to mitigate the risk of acute toxicities (e.g., CRS, TLS, and CNS toxicity), as described in Section 1.3.2.1. *Pharmacokinetic modeling data from Study NP30179 indicates that average receptor occupancy during the first 24 hours of treatment with glofitamab is related to the risk and severity of CRS. The glofitamab 2.5-mg dose is anticipated to reduce the risk of CRS compared to what has been observed at higher first doses.* Following a single dose of 1000 mg obinutuzumab administered by IV infusion on Day 1 of Cycle 1, 7 days before initial dosing of *glofitamab*, the planned dosing of *glofitamab* is 2.5 mg on Day 8 of Cycle 1, 10 mg on Day 15 of Cycle 1, and 30 mg on Day 1 of Cycles 2–*12* (21-day cycles) administered by IV infusion. *The dose and schedule of glofitamab is based on emerging safety data from Study NP30179 investigating the step-up dosing regimen in glofitamab monotherapy.*

*Patients will receive up to 8 cycles of GemOx therapy (see Section 4.3.2), and up to 12 total cycles of glofitamab (8 cycles in combination with GemOx, 4 cycles as monotherapy). Complete responses have occurred in patients between Cycles 9–12 of glofitamab monotherapy on Study NP30179 (data on file).*

### 3.3.2 Rationale for Pretreatment with Obinutuzumab

*A single dose of obinutuzumab administered 7 days prior to the first dose of glofitamab is aimed at depleting peripheral B cells in order to attenuate the risk of CRS, which can result from rapid glofitamab-mediated T-cell activation via interaction with B-cell targets in the circulation (Klinger et al. 2012, Teachey et al. 2013, Teachey et al. 2016). The dose selected for the obinutuzumab pretreatment is the standard dose used in patients with R/R NHL in clinical trials (Salles et al. 2012, Salles et al. 2013, Sehn et al. 2015), and the ability of obinutuzumab to deplete peripheral B cells is supported by Phase I and II trial data of obinutuzumab treatment of patients with R/R DLBCL (Salles et al. 2012, Morschhauser et al. 2013).*

*Obinutuzumab has been shown across multiple ex vivo and in vivo nonclinical studies to more efficiently deplete B-cells compared with rituximab due to the ability of type II antibodies to induce direct cell death (Obinutuzumab Investigator's Brochure Version 14, Section 4.1.2.1; Herter et al. 2013). Obinutuzumab* has been shown nonclinically to debulk peripheral B cells and to reduce the occurrence of systemic cytokine release (Bacac et al. 2018). Clinical demonstration for the use of *pretreatment with obinutuzumab* as safety mitigation is being evaluated in the ongoing *S*tudy NP30179, during which a single 1000-mg dose of *obinutuzumab* is administered 7 days prior to the administration of *glofitamab* (Dickinson et al. 2019).

### 3.3.3 Rationale for Mosunetuzumab Dose and Schedule

In this study, mosunetuzumab will be administered in a 21-day cycle on a step-up dosing schedule in Cycle 1, with 1 mg on Day 1 of Cycle 1, 2 mg on Day 8 of Cycle 1, and 60 mg on Day 15 of Cycle 1. The mosunetuzumab dose on Day 1 of Cycle 2 will be 60 mg, followed by 30 mg on Day 1 of Cycles 3–6.

The step-up dosing schedule was established in the ongoing first-in-human Phase I Study GO29781 to mitigate the risk of acute toxicities (e.g., CRS, TLS, and CNS toxicity). Based on the overall safety, efficacy, and PK profile, the step-up dosing regimen has been established at 1 mg on Day 1, 2 mg on Day 8, and the Day 15 dose level has continued in dose escalation. In Study GO29781, the Day 15 dose levels of 27, 40.5, and 60 mg cleared the DLT assessment period as of 6 May 2019, and the maximum administered dose is 60 mg. Multiple expansion cohorts are being enrolled at this dose.

The step-up dosing regimen is supported by the observations that most treatment-emergent adverse events, including CRS, occurred after the first dose of mosunetuzumab, with the highest frequency observed within the first week of Cycle 1. Mosunetuzumab induced a transient elevation in plasma IL-6, with peak levels occurring in the majority of patients within 4 to 6 hours of the Day 1, Cycle 1 dose and returned to baseline by 24 hours. The kinetics, as well as the fold-change in IL-6 level relative to those at baseline, were associated with the incidence of AEs, most notably CRS. Patients experiencing CRS exhibited a trend toward higher peak levels of IL-6 during the first cycle. In patients who received a single-dose level of mosunetuzumab at all cycles, there was no clear dose dependence on the magnitude of the IL-6 increase. In the step-up dosing cohort, maximum levels of IL-6 were observed after the first dose, even when subsequently higher doses of mosunetuzumab were administered during step-up dosing and at subsequent cycles. The IL-6 response and current safety profile of mosunetuzumab suggest that higher doses of mosunetuzumab may be more tolerable and may be potentially more efficacious when administered using the step-up dosing scheme.

### 3.3.4 Rationale for Gemcitabine and Oxaliplatin Dose and Schedule

For this study, the schedule for chemotherapy dosing is 1000 mg/m$^2$ gemcitabine and 100 mg/m$^2$ oxaliplatin administered to patients on a 21-day schedule. The combination of gemcitabine and oxaliplatin, with or without rituximab, has been studied using a variety of schedules in the setting of R/R DLBCL and the first-line treatment setting of DLBCL. The schedule selected is *based on published regimens of R-GemOx that utilize up to 8 cycles of therapy (El Gnaoui et al., 2007; Mounier et al., 2013),* and is compatible with a 21-day schedule for the CD20-CD3–bispecific antibody.

### 3.3.5 Rationale for Combination of CD20-Bispecific Antibody with Gemcitabine and Oxaliplatin

GemOx and CD20-bispecific antibodies have each been shown to have efficacy in R/R DLBCL. Thus, it is anticipated that the combination of these agents will result in additive activity. However, there is additional rationale beyond this to support the combination in terms of complimentary effects on the tumor immune microenvironment.

While gemcitabine and oxaliplatin are cytotoxic chemotherapies, they have not been shown to inhibit anti-tumor cytotoxic T-lymphocyte function. Rather, the gemcitabine and oxaliplatin regimen can modulate the tumor immune microenvironment to enhance the immunogenicity of tumors, thus supporting combination with a T-cell directed therapy such as a CD20-bispecific antibody. This observation is supported by the following:

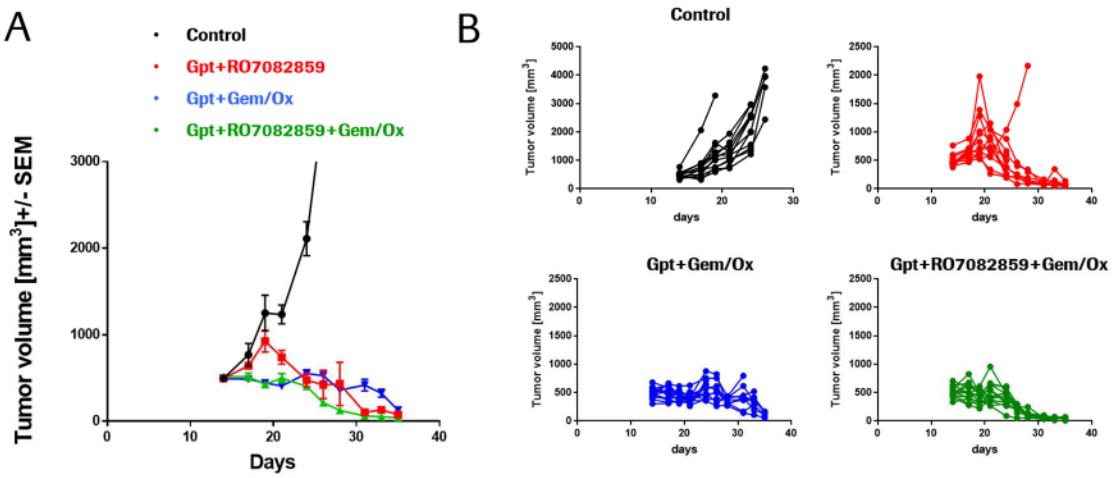
- Enhanced T cell–mediated cytolytic cell death and T-cell proliferation: Gemcitabine-induced upregulation of human leukocyte antigen class I results in and mediates increased tumor cell killing by cytotoxic T-lymphocytes. Oxaliplatin has no adverse effect on cytotoxic lymphocyte antigen function. Both gemcitabine and oxaliplatin have also been shown to lead to increased T-cell proliferation, mediated by augmented dendritic cell maturation and functionality (Liu et al. 2010).
- Enhanced antigen cross-presentation and priming of T cells for anti-tumor response: Gemcitabine has been shown to enhance tumor antigen cross-presentation without inducing CD8 tolerance. Gemcitabine-induced apoptosis of a hemagglutinin-transfected murine tumor model resulted in no loss of human antigen–specific CD8 cell functional tolerance. Furthermore, pretreatment with gemcitabine in this model induced enhanced responsiveness to a virus-generated anti-hemagglutinin signal in vivo, demonstrating evidence of T-cell priming and gemcitabine combinability with immunotherapeutic approaches (Nowak et al. 2003).
- Alteration of the tumor microenvironment to inhibit tumor suppressor cells: Gemcitabine has been shown in multiple studies to enhance immunotherapeutic effects of IFN or intrinsic anti-tumor activity of T cells by depleting myeloid-derived suppressor cells, which are known to inhibit CD8+ T-cell antigen reactivity (Vincent et al. 2010; Mundy-Bosse et al. 2011). Gemcitabine has also been shown to reprogram tumor-associated macrophages to promote immune-stimulating cytokine release, with decreased release of immunosuppressive cytokines (Di Caro et al. 2016). Oxaliplatin has been shown to enhance recognition of tumors by T cells and enhance antigen-specific T-cell proliferation by downregulating *STAT6*-induced expression of the T-cell inhibitor programmed death–ligand 2 (Lesterhuis et al. 2011).
- Combinability with immunotherapeutic approaches: Both gemcitabine and oxaliplatin have been combined with immunotherapeutic approaches in vivo and have shown additive effects, including in the following studies:
  - Gemcitabine and oxaliplatin in combination with cytotoxic T lymphocytes in murine lymphoma in vivo (Correale et al. 2008)

  - Oxaliplatin in combination with IL-12 in murine metastatic colon cancer in vivo (Gonzalez-Aparicio et al. 2011)
  - Gemcitabine in combination with CD40 agonists in pancreatic ductal adenocarcinoma in vivo and in a clinical case series (Beatty et al. 2011)
- Gemcitabine upregulation of CD20 in DLBCL: Gemcitabine has been shown to upregulate CD20 in DLBCL cell lines. This effect leads to increased cell surface rituximab binding concentrations as well as enhanced rituximab-mediated CDC (Hayashi et al. 2016). CD20 upregulation by gemcitabine could similarly lead to increased CD20-bispecific antibody binding capacity of the tumor.

Given the evidence above, the immunomodulatory effects of gemcitabine and oxaliplatin could address potential barriers to response to CD20-bispecific antibodies, thus leading to the potential for increased efficacy compared with either agent given as monotherapy.

*Additionally, combination studies of glofitamab with gemcitabine and oxaliplatin have been performed in two different CD20-expressing human cell line DLBCL xenograft models (OCI-Ly18 and WSU-DLCL2) in humanized NSG mice. The combination of glofitamab with gemcitabine and oxaliplatin improved the anti-tumor activity compared to monotherapy groups in both tumor models (Figure 2). (Glofitamab Investigator's Brochure).*

***Figure 2 Combination Treatment of Glofitamab with Gemcitabine and Oxaliplatin in OCI-Ly18 Tumor Model***




*RO7082859=glofitamab; Gpt=obinutuzumab pre-treatment; i.p=intraperitoneal; s.c=subcutaneous*

*OCI-Ly18 tumor cells were injected s.c. into hematopoietic stem-cell humanized NSG mice (HSC-NSG). Mice were randomized when average tumor volume reached ~400mm3. GAZYVA pre-treatment (Gpt) consisted of a single administration of the antibody i.v. at 30mg/kg. RO7082859 monotherapy was administered 3 days after upon Gpt, given i.v. at 0.5 mg/kg (for the first cycle) and at 1 mg/kg (from the second cycle onwards) on a once weekly schedule. Oxaliplatin (5mg/kg) and gemcitabine (50mg/kg) were given i.p. once weekly, starting 1 day upon Gpt. The combination of RO7082859 and Oxaliplatin/Gemcitabine was staggered during the first cycle (with Oxaliplatin (5 mg/kg)/Gemcitabine (50 mg/kg) administered i.p. 1 day post Gpt, followed by RO7082859 i.v. (0.5 mg/kg) 2 days after); the agents were given concomitantly from the second cycle onwards (Oxaliplatin (5 mg/kg)/Gemcitabine (50 mg/kg) i.p. and RO7082859 (1 mg/kg) i.v. once weekly). Control animals received phosphate buffer saline. A, shows the average tumor volume +/- SEM over time in all treatment groups. B, shows individual tumor growth kinetics of each mouse in the treatment groups.*

### 3.3.6 Rationale for Patient Population

Up to 40% of patients with DLBCL who are treated in the first-line setting will progress within 3 to 4 years (Friedberg 2011), which includes approximately 10% of patients with refractory DLBCL to first-line R-CHOP treatment. Patients with R/R DLBCL fit into one of two general categories: those who are candidates for transplant and those who are not candidates for transplant.

For patients who are not candidates for transplant and/or CAR T-cell therapy or patients who have not responded to either of these treatment strategies, the goal of second- and third-line therapy is to induce a response and prolong survival, although currently not with curative intent. Unfortunately, there is no widely accepted standard-of-care treatment in these settings.

Patients with R/R DLBCL is a patient population with a high, unmet medical need and with limited and challenging options for available therapy.

### 3.3.7 Rationale for Biomarker Assessments

The underlying rationale for the biomarker assessments in this study is to understand the mechanisms of action of CD20-CD3–bispecific antibody in combination with GemOx and preliminary assessment of biological markers that might be predictive of susceptibility to developing adverse events. *Glofitamab* and mosunetuzumab were designed to target tumors that express CD20 and to concurrently engage immune cells that lead to their activation and proliferation, which culminates in tumor lysis. Nonclinical studies have confirmed the expected mechanism of action by mediating tumor killing, induction of T-cell activation markers, cytokine release (IFN-γ, TNF-α, Granzyme B, IL-2, -6, and -10), and proliferation of T cells. Furthermore, the mechanism of action of *glofitamab* and mosunetuzumab is contingent on simultaneous binding (cross-linking) of CD3-positivie T cells to CD20-expressing tumor cells.

Therefore, samples for exploratory and PD analyses will be collected in the study in order to assess immune cell alterations in the peripheral blood. The peripheral blood sampling schedule following *glofitamab* or mosunetuzumab administration is designed for descriptive analysis of the following:

- Time course of cytokine release in relation to *glofitamab* or mosunetuzumab pharmacokinetics
- Expression of phenotypic markers of T-cell function including, but not limited to, markers of T-cell activation and proliferation as well as expression of programmed death–1 and other inhibitory molecules on T cells
- Dynamic quantitative changes in T-cell, B-cell, and NK-cell counts

In addition to peripheral blood sampling, diagnostic archival tumor tissue will be obtained from all patients, or if unavailable, freshly collected tissue, in order to perform retrospective CD20 assessment and to further assess exploratory biomarkers that may provide information on the mechanism of action.

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 be used to inform decisions on patient management.

# 4. MATERIALS AND METHODS

## 4.1 PATIENTS

Up to approximately 20 patients will be enrolled in the study, with approximately 10 patients in either Arm A or B*, with potential enrollment up to 20 patients per arm.*

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability and willingness to comply with the study protocol
- Life expectancy ≥12 weeks
- ECOG Performance Status of 0, 1, or 2 (see Appendix 6)
- Histologically confirmed B-cell lymphoma, including one of the following diagnoses per the 2016 WHO classification of lymphoid neoplasms:
  - DLBCL, NOS
  - HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements
  - HGCBL, NOS
- R/R disease, defined as follows:
  - Relapse: disease that has recurred following a response that lasted ≥6 months after completion of last line of therapy
  - Refractory: disease that progressed during therapy or progressed within 6 months (<6 months) of prior therapy
- At least one line of prior systemic therapy

  Patients are permitted to have undergone autologous hematopoietic stem cell transplant (HSCT) prior to enrollment; chemotherapy followed by consolidative autologous HSCT will be counted as one line of therapy.

  Local therapies (e.g., radiotherapy) will not be considered as a line of therapy.
- Confirmed availability of archival (or if unavailable, freshly collected) tumor tissue prior to enrollment

  If archival tissue is unavailable, tumor tissue must be obtained from a biopsy performed at screening. For patients who have inadequate or inaccessible tumor tissue for biopsy, the patient may still be eligible for the study after discussion with the Medical Monitor.
- At least one bi-dimensionally measurable nodal lesion or one bi-dimensionally measurable extranodal lesion, as measured on PET/CT scan

- Adequate hematologic function, defined as follows:
  - Hemoglobin ≥9.0 g/dL
  - ANC ≥$1.0 \times 10^9$/L
  - Platelet count ≥$75 \times 10^9$/L *(≥75,000/μL) without a transfusion in the week prior to starting study treatment*
- Adequate renal function, defined as measured or estimated creatinine clearance ≥40 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 18 months after the final dose of obinutuzumab, 6 months after the final dose of gemcitabine, *9* months after the final dose of oxaliplatin, 3 months after the final dose of mosunetuzumab, 3 months after the final dose of tocilizumab (if applicable; see Section 4.3.5.3 ), and 2 months after the final dose of *glofitamab*. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile because of 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 requirements.

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 2 months after the final dose of *glofitamab*, 2 months after the

final dose of mosunetuzumab, 2 months after the final dose of tocilizumab (if applicable), 3 months after the final dose of obinutuzumab, and 6 months after the final dose of oxaliplatin or gemcitabine to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

### 4.1.2 Exclusion Criteria

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

- *Patient has failed only one prior line* of *therapy* and *is a* candidate for stem cell transplantation
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to obinutuzumab, gemcitabine, oxaliplatin, or tocilizumab
- Prior treatment with a bispecific antibody targeting both CD20 and CD3, including *glofitamab* and mosunetuzumab
- Grade >1 peripheral neuropathy, as assessed according to the NCI CTCAE v5.0 at enrollment
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to first study treatment
- Treatment with monoclonal antibodies for the purposes of treating cancer within 4 weeks prior to the first study treatment
- Primary or secondary CNS lymphoma at the time of recruitment or history of CNS lymphoma
- Current or history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease

  Patients with a history of stroke who have not experienced a stroke or transient ischemic attack within the past 2 years and have no residual neurologic deficits, as judged by the investigator, are allowed.
- Any of the following abnormal laboratory values:
  - AST or ALT >2.5× the upper limit of normal (ULN)
  - Total bilirubin ≥1.5× ULN

    Patients with documented Gilbert disease may be enrolled if total bilirubin is ≤3× ULN.
  - INR or PT >1.5× ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT >1.5× ULN in the absence of a lupus anticoagulant

- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the following exceptions:

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the study are eligible.

  Patients with low-grade, early-stage prostate cancer (Gleason score ≤6, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible.

  Patients with any other malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for ≥2 years prior to enrollment are eligible.

  Patients receiving adjuvant endocrine therapy for non-metastatic, hormone receptor–positive breast cancer for ≥2 years prior to enrollment are eligible.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection (as evaluated by the investigator) within 4 weeks prior to first study treatment
- Suspected or latent tuberculosis (as confirmed by positive IFN-γ release assay)
- Positive test results for hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

  Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment and appropriate antiviral therapy.
- Positive test results for hepatitis C virus (HCV) antibody

  Patients who are positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Known history of HIV-seropositive status

  For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations.
- Known or suspected chronic active Epstein-Barr virus (EBV) infection
- Known or suspected history of HLH
- History of progressive multifocal leukoencephalopathy (PML)

- Adverse events from prior anti-cancer therapy that have not resolved to Grade 1 or better (with the exception of alopecia and anorexia)
- Administration of a live, attenuated vaccine within 4 weeks prior to the first study treatment administration or anticipation that such a live, attenuated vaccine will be required during the study
- Prior solid organ transplantation
- *Prior allogeneic stem cell transplant*
- Active autoimmune disease requiring treatment

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

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

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

  Patients 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 may be eligible after discussion with the Medical Monitor.
- Prior *treatment with* systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-*tumor necrosis factor* agents), within 4 weeks prior to first dose of study treatment
- *Corticosteroid therapy within 2 weeks prior to first dose of study treatment, with the following exceptions:*
  - *Corticosteroid treatment ≤10 mg/day prednisone or equivalent within 2 weeks prior to the first dose of study treatment is permitted.*
  - *Administration of* acute, low-dose *corticosteroids to treat cancer symptoms or side effects of treatment* (e.g., single dose of dexamethasone for nausea or B-symptoms) *is permitted.*

  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.
- Recent major surgery (within 4 weeks before the first study treatment) other than for diagnosis
- Clinically significant history of liver disease, including cirrhosis

- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications
- Pregnancy or breastfeeding, or intention to become pregnant during the study or within 18 months after the final dose of study treatment in Arm A or within 12 months after the final dose of study treatment in Arm B

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

## 4.2 METHOD OF TREATMENT ASSIGNMENT

This is a Phase Ib, non-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 patient, the study site will obtain a patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

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

The investigational medicinal products (IMPs) for this study are *glofitamab*, mosunetuzumab, obinutuzumab, and tocilizumab.

Gemcitabine and oxaliplatin are considered as standard of care in many countries for the treatment of patients with R/R DLBCL and are non-IMPs for this study. Premedication given prior to study treatment, including methylprednisolone, prednisone, prednisolone, diphenhydramine, and paracetamol, are non-IMPs for this study.

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

#### 4.3.1.1 Formulation and Packaging

***Glofitamab***

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

**Mosunetuzumab**

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

**Obinutuzumab**

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

### Gemcitabine and Oxaliplatin

Gemcitabine and oxaliplatin will be supplied by the Sponsor where required by local health authority regulations. For information on the formulation, packaging, and handling of gemcitabine and oxaliplatin, see the local prescribing information.

### Tocilizumab

Tocilizumab will be supplied by the Sponsor. Use of commercial tocilizumab may be permitted under certain circumstances and if approved by the national and/or local health authorities as applicable. A record of this approval should be kept on site and a copy provided to the Sponsor. For information on the formulation, packaging, and handling of tocilizumab, refer to the pharmacy manual and the Tocilizumab Investigator's Brochure.

## 4.3.2 Study Treatment Dosage, Administration, and Compliance

The study treatment regimens are summarized in Section 4.3.3.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.7.1.

## 4.3.3 Study Treatment Dosage

### 4.3.3.1 Arm A: *Glofitamab* in Combination with Gemcitabine and Oxaliplatin (*Glofit*-GemOx)

### Obinutuzumab

A single 1000-mg dose of *obinutuzumab* will be given on Day 1 of Cycle 1, 7 days prior to the first administration of *glofitamab* in order to reduce the potential risk of CRS induced by *glofitamab*-mediated systemic T cells.

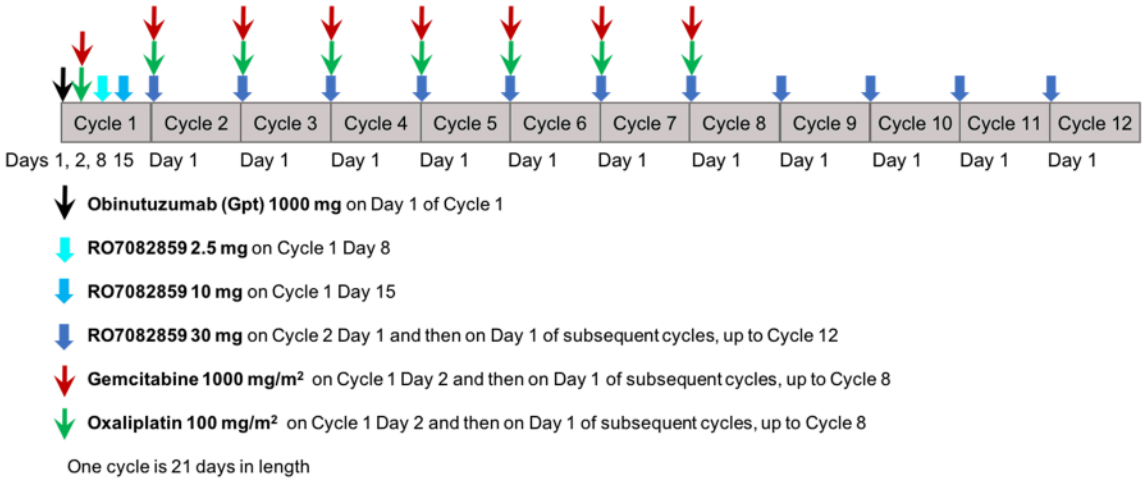
Obinutuzumab will be administered using a standard bag infusion pump and must be administered in a clinic or hospital equipped for systemic (IV) cancer treatment. See *Figure 3* for dosing regimen.

### *Glofitamab*

The first dose of *glofitamab* will be administered 7 days after the single 1000-mg dose of *obinutuzumab* on Day 1 of Cycle 1. Using a step-up dosing schedule, the first dose of 2.5 mg *glofitamab* will be administered on Day 8 of Cycle 1, followed by 10 mg on Day 15 of Cycle 1, and 30 mg on Day 1 of Cycles 2–*12*, with each cycle being 21 days in length (i.e., every 3 weeks).

In the event of a late or prolonged infusion for *glofitamab* during Cycles 2–*8* because of late start in the day or slowed infusion rate owing to an infusion-related reaction (IRR), GemOx may be administered on the following day or as per local practice. See *Figure 3* for the dosing regimen.

**Figure 3 Regimen for Patients in Arm A: *Glofitamab* in Combination with Gemcitabine and Oxaliplatin (*Glofit*--GemOx)**




GemOx=gemcitabine and oxaliplatin.
Note: For Cycles 1–~~6~~*8*, gemcitabine should be administered before oxaliplatin. For Cycles 2–*8*, *glofitamab* should be given before gemcitabine and oxaliplatin.

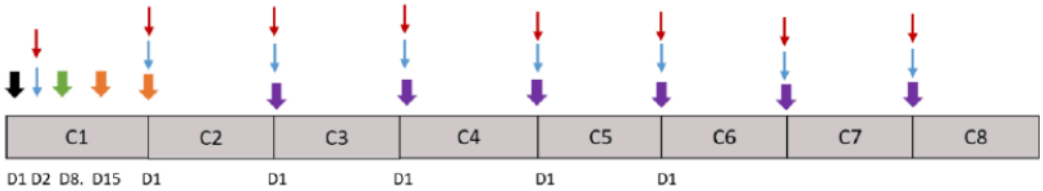
Patients will be hospitalized *for* at least *24 hours after the infusion* of *glofitamab* on Days 8 and 15 of Cycle 1. *Patients with an event of CRS associated with the preceding dose of glofitamab should be hospitalized* on Day 1 of Cycle 2. *The required hospitalization is* an additional precautionary safety measure to ensure that patients are closely monitored during the first two cycles.

#### 4.3.3.2 Arm B: Mosunetuzumab in Combination with Gemcitabine and Oxaliplatin (Mosun-GemOx)

**Mosunetuzumab**

Mosunetuzumab will be administered to patients using a step-up dose schedule for Cycle 1, with 1 mg on Day 1 of Cycle 1, 2 mg on Day 8 of Cycle 1, and 60 mg on Day 15 of Cycle 1. The mosunetuzumab dose on Day 1 of Cycle 2 will be 60 mg, followed by 30 mg on Day 1 of Cycle 3 *and then on Day 1 of subsequent cycles, up to 8 cycles*. See Figure 4 for the dosing regimen. In the event of a late or prolonged infusion for mosunetuzumab during Cycles 2–6 because of late start in the day or slowed infusion rate owing to an IRR, GemOx may be administered on the following day or as per local practice. For information on the formulation, packaging, and handling of mosunetuzumab, see the pharmacy manual and the Mosunetuzumab Investigator's Brochure.

**Figure 4 Regimen for Patients in Arm B: Mosunetuzumab Plus Gemcitabine Plus Oxaliplatin (Mosun-GemOx)**




| | |
|---|---|
| Mosunetuzumab | 1 mg IV on Cycle 1 Day 1 |
| Mosunetuzumab | 2 mg IV on Cycle 1 Day 8 |
| Mosunetuzumab | 60 mg IV on Cycle 1 Day 15 and on Cycle 2 Day 1 |
| Mosunetuzumab | 30 mg IV on Cycle 3 Day 1 and then on Day 1 of subsequent cycles, up to Cycle 8 |
| Gemcitabine | 1000 mg/m$^2$ on Cycle 1 Day 2 and then on Day 1 of each subsequent cycle, up to cycle 8 |
| Oxaliplatin | 100 mg/m$^2$ on Cycle 1 Day 2 and then on Day 1 of each subsequent cycle, up to Cycle 8 |

One cycle is 21 days in length

GemOx=gemcitabine and oxaliplatin; mosun=mosunetuzumab.
Notes: For Cycle 1, gemcitabine should be administered before oxaliplatin. For Cycles 2–8, mosunetuzumab should be given before gemcitabine, followed by oxaliplatin.

Patients will be hospitalized for at least 48 hours postinfusion of mosunetuzumab on Day 1 of Cycle 1 as an additional precautionary safety measure to ensure that patients are closely monitored following the first dose of mosunetuzumab in combination with gemcitabine and oxaliplatin. Patients should be hospitalized on Day 1 of Cycle 2 for 24 hours following the dose of mosunetuzumab if the patient had Grade ≥2 event of CRS in Cycle 1.

#### 4.3.3.3 Arms A and B: Gemcitabine and Oxaliplatin (GemOx)

**Gemcitabine**

Gemcitabine will be administered intravenously to patients in both arms at 1000 mg/m$^2$ on Day 2 of Cycle 1. Starting at Cycle 2, gemcitabine may be given on Day 1 or 2 (per local practice) of each 21-day cycle *for the subsequent cycles*. Gemcitabine should be administered before oxaliplatin on the same day.

**Oxaliplatin**

Oxaliplatin will be administered intravenously to patients in both arms at 100 mg/m$^2$ on Day 2 of Cycle 1. Starting at Cycle 2, gemcitabine may be given on Day 1 or 2 (per local practice) of each 21-day cycle *for the subsequent cycles*. Oxaliplatin should be administered after gemcitabine on the same day.

### 4.3.4 Tocilizumab

Tocilizumab is a recombinant, humanized, anti-human monoclonal antibody directed against soluble and membrane-bound IL-6 receptor, which inhibits IL-6–mediated signaling. Blocking the inflammatory action of IL-6 using tocilizumab could therefore be beneficial for the treatment of CRS. Refer to the Tocilizumab Investigator's Brochure for additional nonclinical and clinical information regarding tocilizumab. Tocilizumab will be not administered to all patients but only to those patients experiencing severe CRS (rescue IMP). Tocilizumab will be supplied by the Sponsor. Refer to the local prescribing information for further instructions regarding recommended storage conditions and packaging configuration.

For patients requiring treatment of CRS, patients will receive tocilizumab by IV infusion. Patients who weigh ≥30 kg will receive 8 mg/kg tocilizumab and patients who weigh <30 kg will receive 12 mg/kg tocilizumab, not to exceed an 800 mg per dose. Treatment may be repeated every 8 hours as necessary (for a maximum of four doses).

### 4.3.5 Administration

#### 4.3.5.1 Obinutuzumab Given as Pretreatment for Patients in Arm A (*Glofit*-GemOx)

*Obinutuzumab pretreatment* will be administered by IV infusion as an absolute (flat) dose of 1000 mg on Day 1 of Cycle 1 for patients in Arm A. The obinutuzumab infusion may be split over 2 days if a patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count) or experiences an AE during an infusion.

Premedication with corticosteroids (80 mg IV methylprednisolone or equivalent dose of *dexamethasone [20 mg IV],* prednisone [100 mg] or prednisolone [100 mg]) should be administered 1 hour prior to the administration of obinutuzumab; premedication with oral acetaminophen or paracetamol (500–1000 mg) and an antihistamine, such as diphenhydramine (50 mg), should be administered approximately 30 minutes prior to the start of the infusion.

Obinutuzumab should be administered to well-hydrated patients. Patients at high risk of TLS should receive TLS prophylaxis (see Section 4.4.1.2 ). Procedures for management of IRRs to obinutuzumab are presented in Section 5.1.3 and Appendix 10.

Refer to the Obinutuzumab Investigator's Brochure, pharmacy manual, and local prescribing information for preparation and administration.

#### 4.3.5.2 *Glofitamab*

*Glofitamab* will be administered intravenously according to the schedule outlined in Section 4.3.3.1 and Appendix 1. *Glofitamab* will be administered in a setting with immediate access to trained critical care personnel and facilities equipped to respond to and manage medical emergencies. Neurology consultation services should be readily available to address any neurologic AEs that may arise as a result of *glofitamab*

treatment (see Appendix 10), and nephrology consultation with acute dialysis capabilities should be readily available to address any renal toxicity that might accompany TLS (see Appendix 10).

Patients should be under close observation by the investigator at all times.

Premedication with corticosteroids (80 mg IV methylprednisolone or equivalent dose of *dexamethasone [20 mg IV],* prednisone [100 mg] or prednisolone [100 mg]) should be administered 1 hour prior to the administration of *glofitamab*; premedication with oral acetaminophen or paracetamol (500–1000 mg) and an antihistamine, such as diphenhydramine (50 mg), should be administered approximately 30 minutes prior to the start of the infusion.

*Glofitamab* should be administered to well-hydrated patients. *Patients at risk of TLS* should receive TLS prophylaxis (for details, refer to Section 4.4.1.2).

Initially, *glofitamab* will be administered over 4 hours (±15 minutes) on Days 8 and 15 of Cycle 1 and on Day 1 of Cycle 2. Following each *glofitamab* dose in Cycles 1–2, patients will be observed at least 90 minutes for fever, chills, rigors, hypotension, hypoxia, nausea, or other signs and symptoms of CRS. At Cycle 3 and beyond, if the patient has not had CRS with prior cycles, and has tolerated the preceding glofitamab infusion with no signs or symptoms of CRS, the window of observation may be shortened based on the discretion of the investigator. For patients who develop CRS with onset of associated signs/symptoms during *glofitamab* infusion, the infusion must be discontinued immediately with no further restarts of the infusion for this administration, unless limited to Grade 1 CRS. For patients who may be at an increased risk of CRS (see Section 5.1.1.1), patients who experienced CRS with their previous dose of *glofitamab* or who are in the investigator's judgment at increased risk of recurrent CRS with subsequent doses, the time of infusion may be extended to up to 8 hours. In the absence of infusion-related adverse events or CRS, the infusion time of *glofitamab* in Cycles 3 and beyond may be reduced to 2 hours (±15 minutes), at the discretion of the investigator (refer to Section 5.1.1.1). Alternately, patients who are, in the investigator's judgment, at an increased risk of recurrent CRS with subsequent doses, may have the time of infusion extended to up to 8 hours. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.7.1.

Patients will be hospitalized for at least *24 hours* postinfusion of *glofitamab* on Days 8 and 15 of Cycle 1. *Patients with an event of CRS associated with the preceding dose of glofitamab should be hospitalized* on Day 1 of Cycle 2. *The required hospitalization is* an additional precautionary safety measure to ensure that patients are closely monitored during the first two cycles. In case of infusion-associated AEs in patients, the signs and symptoms should be fully resolved before the patient is discharged. Additionally, hospitalization at subsequent cycles may be considered as described in Section 4.3.5.2.

The IMC may make modifications to hospitalization requirement based on emerging safety data as described in Section 3.1.2.

The schedule of tocilizumab assessments for patients who experience severe or life-threatening CRS is presented in Appendix 3. The recommended management of CRS is detailed in Appendix 10.

See the pharmacy manual and the *Glofitamab* Investigator's Brochure for more details.

**Table 3 Premedications before Gpt and *Glofitamab* Infusions**

| Timepoint | Patients Requiring Premedication | Premedication | Administration |
|---|---|---|---|
| Gpt [a] Cycle 1, Day 1 | All patients | IV glucocorticoids [b] | At least 60 minutes prior to obinutuzumab infusion |
| | | Oral or IV analgesic or anti-pyretic medicine | At least 30 minutes prior to obinutuzumab infusion |
| | | Oral or IV antihistamine [c] | |
| | Patients at risk of TLS (e.g., because of bulky disease or renal impairment creatinine clearance <70 mL/min) | Allopurinol or suitable alternative, such as rasburicase, along with adequate hydration | |
| *Glofitamab* [a, d] Cycle 1, Day 8 and onward; all doses | All patients | IV glucocorticoids [b] | At least 60 minutes prior to *glofitamab* infusion |
| | | Oral or IV analgesic/ anti-pyretic medication | At least 30 minutes prior to *glofitamab* infusion |
| | | Oral or IV antihistamine [c] | |
| | Patients at risk of TLS (e.g., because of bulky disease or renal impairment (creatinine clearance <70 mL/min) | Allopurinol or suitable alternative, such as rasburicase, along with adequate hydration | |

Gpt=obinutuzumab pretreatment; TLS=tumor lysis syndrome.

[a] Closely monitor patients during the entire infusion. Infusion reactions within 24 hours of receiving obinutuzumab have occurred.

[b] Administer methylprednisolone *80 mg IV* or equivalent dose of *dexamethasone [20 mg* IV*]*, prednisone~~;~~ *[100 mg] or prednisolone [100 mg];* hydrocortisone should not be used as it has not been effective in reducing the *incidence* of infusion reactions.

[c] For example, 50 mg diphenhydramine (unless contraindicated).

[d] All *glofitamab* doses will be administered to well-hydrated patients.

### 4.3.5.3 Mosunetuzumab

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

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

Patients will be hospitalized for at least 48 hours postinfusion of mosunetuzumab on Day 1 of Cycle 1. Patients should be hospitalized on Day 1 of Cycle 2 for 24 hours following the dose of mosunetuzumab if the patient had Grade ≥2 event of CRS in Cycle 1. In case of infusion-associated AEs in patients, the signs and symptoms should be fully resolved before the patient is discharged. Additionally, hospitalization at subsequent cycles may be considered as described in Section 4.3.3.2. The IMC may determine modifications to hospitalization requirement based on emerging safety data as described in Section 3.1.2.

Mosunetuzumab will be administered to well-hydrated patients. Corticosteroid premedication must be given prior to each mosunetuzumab dose. Either 20 mg IV dexamethasone or 80 mg IV methylprednisolone should be administered at least 1 hour prior to the administration of mosunetuzumab. 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.

Initially, mosunetuzumab will be infused over 4 hours (±15 minutes). The infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. The definitions of laboratory and clinical TLS are presented in Appendix 9, and the recommended management of CRS is detailed in Appendix 11.

Following each mosunetuzumab dose, patients will be observed at least 90 minutes for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of IRRs or CRS. In the absence of infusion-related adverse events or CRS, the infusion time of mosunetuzumab in Cycles 2 and beyond may be reduced to 2 hours (±15 minutes).

Guidelines for management of adverse events associated with mosunetuzumab are presented in Appendix 11. Mosunetuzumab guidelines for dosage modification and treatment interruption and discontinuation are provided in Section 5.1.7.1.

### 4.3.6 GemOx

Gemcitabine and oxaliplatin will be administered as described in Section 4.3.3.3.

### 4.3.7 Tocilizumab

Tocilizumab should be administered when necessary as described in Section 4.3.5.2. Tocilizumab will be supplied by the Sponsor. Refer to the pharmacy manual for administration instructions for tocilizumab. Note: If tocilizumab is administered, refer to Appendix 3 for the schedule of activities for tocilizumab treatment of severe or life-threatening CRS.

### 4.3.8 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor (*glofitamab*, mosunetuzumab, obinutuzumab, and tocilizumab). Non-IMPs (e.g., gemcitabine and oxaliplatin) will not be provided unless required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The IMPs should only be returned to the Sponsor if the site is unable to destroy IMPs per its standard operating procedure.

The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

### 4.3.9 Continued Access to *Glofitamab*, Mosunetuzumab, Obinutuzumab, and Tocilizumab

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

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

## 4.4 CONCOMITANT THERAPY

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

### 4.4.1 *Required Therapy*

#### 4.4.1.1 *Prophylaxis for Neutropenia*

*All patients will receive granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis during cycles of GemOx treatment. G-CSF should be started 1 to 2 days*

*after GemOx infusion in each cycle. Dosing of G-CSF should otherwise follow each site's institutional standards.*

#### 4.4.1.2 Prophylaxis for Tumor Lysis Syndrome

*Patients with high tumor burden and/or considered by the investigator to be at risk for tumor lysis should receive tumor lysis prophylaxis prior to the initiation of treatment (Coiffier et al. 2008) (see Appendix 10). All patients should be well hydrated. Starting 2 days prior to the first dose of study treatment, it is desirable to maintain a fluid intake of approximately 2-3 L/day. In addition, all patients with high tumor burden and considered to be at risk for tumor lysis should be treated with 300 mg/day of allopurinol orally or a suitable alternative treatment (e.g., rasburicase), starting 48-72 hours prior to Day 1 of Cycle 1. Patients should continue to receive repeated prophylaxis, if deemed appropriate by the investigator, and adequate hydration prior to each subsequent cycle of treatment.*

### 4.4.2 Permitted Therapy

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

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of <1% per year (see Section 4.1.1)
- Hormone-replacement therapy
- Treatment of CRS according to Appendix 3
- Treatment of HLH according to published recommendations and/or institutional practice (see Appendix 8)

#### 4.4.2.1 Infection Prophylaxis

Anti-infective prophylaxis for viral, fungal, bacterial, or *Pneumocystis* infections is permitted and should be instituted per institutional practice or investigator preference based on individual patient risk factors. Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the standard of care may be treated prophylactically (*Taplitz et al. 2018; National Comprehensive Cancer Network 2020*).

#### 4.4.2.2 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 not intended for the treatment of cancer may be used during the study at the discretion of the investigator; herbal therapies intended as treatment of lymphoma are prohibited (see Section 4.4.3).

### 4.4.3 *Cautionary Therapy*

*Caution should be exercised in the administration of oxaliplatin in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia (refer to oxaliplatin prescribing information).*

### 4.4.4 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Investigational, unlicensed, or unapproved agents
- Administration of live vaccines (see also Section 4.1.2)
- Cytotoxic chemotherapy other than study treatments intended for treatment of lymphoma
- Radiotherapy for treatment of lymphoma
- Immunotherapy other than study treatments for treatment of lymphoma
- Immunosuppressive therapy (except medications indicated per protocol, including corticosteroids and tocilizumab)
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)

  Adjuvant endocrine therapy for non-metastatic hormone receptor–positive breast cancer is permitted.
- Biologic or targeted agents for treatment of lymphoma
- Herbal therapies intended as treatment of lymphoma
- Any therapies intended for the treatment of lymphoma, whether approved by local regulatory authorities or investigational

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

## 4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. The PK, immunogenicity, and biomarker sampling collection schedule is presented in Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

### 4.5.1 Informed Consent Forms and Screening Log

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

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

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

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

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

### 4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

### 4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse oximetry, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated or semi-supine position, and temperature.

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.

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

### 4.5.5 ECOG Performance Status

Performance status will be measured using the ECOG Performance Status Scale at the timepoints specified in the schedule of activities in Appendix 1 and recorded on the eCRF (see Appendix 6).

### 4.5.6 Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, diagnostic CT scans (or magnetic resonance imaging [MRI] scans), and PET/CT scans, with results determined according to the 2014 Lugano Response Criteria (see Appendix 5).

Bone marrow biopsies are not routinely required for response assessment but may be indicated in specific situations per the 2014 Lugano Response Criteria (e.g., CT only–based response assessment or when residual uptake is seen on PET/CT scan).

#### Radiographic Assessments

The same radiographic assessment modality should be used for all response evaluations in order to ensure consistency across different timepoints. PET/CT scans in conjunction with diagnostic CT scans will be obtained in this study. PET/CT scans should include the base of the skull to mid-thigh. A full-body PET/CT scan should be performed when clinically appropriate.

*In the Glofit-GemOx arm,* CT and PET/CT scans are required at screening and at the time of primary response assessment (6–8 weeks after the end of Cycle *12 study treatment) or the last study treatment for patients who discontinue study treatment prematurely. Interim assessments will be obtained after Cycle 4 (i.e., Days 15–21 of Cycle 4) and after Cycle 8 (i.e., Days 15-21 of Cycle 8) and should include a PET/CT scan and a dedicated CT scan. If local practice prohibits obtaining both assessments after Cycle 4 or Cycle 8, a PET/CT scan alone (preferred) or CT scan alone may be obtained at these times.*

*In the Mosun-GemOx arm, CT and PET/CT scans are required at screening and at the time of primary response assessment (*6*–8 weeks after the end of Cycle 8* study treatment) or the last study treatment for patients who discontinue study treatment prematurely. An interim assessment will be obtained after Cycle *4* (i.e., Days 15–21 of Cycle *4*) and should include a PET/CT scan and a dedicated CT scan. If local practice prohibits obtaining both assessments after Cycle *4*, a PET/CT scan alone (preferred) or CT scan alone may be obtained at this time.

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

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

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

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

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

- Hematology: WBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells); and peripheral blood smear

  *A peripheral blood smear and/or flow cytometry is required at screening (if not done as part of standard-of-care tests) to detect malignant and/or atypical cells. If malignant cells are detected, the results must be discussed with the Medical Monitor.*

- *Flow cytometry assessment of B lymphocytes (CD19+ B-cell counts)*
- Coagulation: aPTT, PT, INR, and fibrinogen

  Fibrinogen will be collected when monitoring hyperinflammatory events (e.g., HLH and severe CRS).

- Quantitative immunoglobulins: IgA, IgG, and IgM

- Serum chemistry panel: sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, calcium, magnesium, phosphate, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, LDH, and urate
- C-reactive protein
- Serum ferritin
- Viral serology and detection
  - HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

    If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
  - HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

    If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
  - EBV and cytomegalovirus on quantitative PCR using peripheral blood samples
  - HIV serology
- Pregnancy test
- All women of childbearing potential will have a serum pregnancy test within 7 days prior to initiation of study treatment (Day 1 of Cycle 1).

  Pregnancy testing (urine or serum) will subsequently be performed on Day 1 of each cycle of therapy *(or within 24 hours before the dose on Day 1)* for all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. An additional serum pregnancy test will be performed at the treatment completion or early treatment termination visit

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum mosunetuzumab samples for PK analysis
- Serum *glofitamab* samples for PK analysis
- Serum mosunetuzumab samples for immunogenicity analysis
- Serum *glofitamab* samples for immunogenicity analysis
- Serum rituximab and obinutuzumab samples for PK analysis

  Rituximab and/or obinutuzumab PK sample is required only for patients in Arm B who have received prior treatments with rituximab and/or obinutuzumab.
- Blood samples for PBMC cell isolation
- Plasma samples for cytokines, including, but not limited to, IL-6 and IFN-γ
- Blood and plasma samples for exploratory assessments of candidate biomarkers that may provide evidence of *glofitamab* or mosunetuzumab activity

- Archival tumor tissue samples: Formalin-fixed, paraffin-embedded (FFPE) archival tumor tissue is requested from all patients at screening to assess CD20 expression, retrospectively, and to investigate baseline immune status

  Archival tumor tissue samples obtained at any time between the final dose of the last prior cancer regimen and the Day 1 of Cycle 1 are preferred.

  If a recent archival tissue is not available, a fresh biopsy should be obtained at screening if possible. This biopsy should be from safely accessible tumor sites (i.e., without unacceptable risk of a major procedural complication[s] per investigator assessment). Patients must have at least one measurable lesion that will not be biopsied in order to preserve the ability to radiographically assess tumor response. In cases where no archival tissue exists and where a fresh biopsy cannot be obtained with unacceptable risk, please contact the Medical Monitor.

  A representative FFPE tumor tissue in a paraffin block (preferred) or at least *15* slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. (Note: To protect tissue against oxidation and to allow immunohistochemistry [IHC] analysis in large batches, a FFPE tissue block is preferred over cut sections.)

Exploratory biomarker research may include, but will not be limited to, analysis of lymphocytes, T-cell activation, TCR repertoire, and cytokines associated with inflammation. Assays for exploratory analysis may include, but are not limited to, flow cytometry, IHC, and immunofluorescence. Additional exploratory biomarkers may be assessed based on evolving clinical and nonclinical data.

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

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- All unused central laboratory samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

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

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

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

### 4.5.8 Electrocardiograms

Single 12-lead ECG recordings will be obtained at screening and at treatment discontinuation (either early treatment discontinuation or study treatment completion) and may be obtained at unscheduled timepoints as clinically indicated per investigator discretion (see Appendix 1).

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

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

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

### 4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment

- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to the 2014 Lugano Response Criteria for Malignant Lymphoma (see Appendix 5)
- Unacceptable toxicity

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients will return to the clinic for a treatment completion or early discontinuation visit 6–8 weeks after the final dose of study treatment. The end of treatment response assessment can be done during this visit if it is 6–8 weeks after the final dose of study treatment (see Appendix 1 for additional details).

Patients who discontinue study treatment prematurely should return to the clinic for a treatment discontinuation visit (early discontinuation) within 4–8 weeks after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

Patients who discontinue from study treatment will be followed for 90 days from the final study treatment, until the start of a new anti-lymphoma therapy, or until death, whichever occurs first.

Following the study treatment discontinuation visit, patients will be followed for adverse events via telephone calls, patient medical records, and/or clinic visits until approximately 90 days following the final study treatment (unless death occurs, the patient is lost to follow-up, the patient withdraws consent, or the Sponsor terminates the study, whichever is earliest).

### 4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

### 4.6.3 Study Discontinuation

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

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

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

### 4.6.4 Site Discontinuation

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

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

## 5. ASSESSMENT OF SAFETY

### 5.1 SAFETY PLAN

*Glofitamab* (RO7082859) and mosunetuzumab (RO7030816) are not approved, and clinical development is ongoing. This is the first combination study in which *glofitamab* or mosunetuzumab will be combined with gemcitabine and oxaliplatin. The safety plan for patients in this study is based on clinical experience with *glofitamab* and mosunetuzumab in ongoing studies. The anticipated important safety risks for *glofitamab* and mosunetuzumab are outlined in the following sections. Refer to the *Glofitamab* Investigator's Brochure and the Mosunetuzumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients 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 treatment interruption or discontinuation, are provided in the following sections.

### 5.1.1 Risks Associated with *Glofitamab*

#### 5.1.1.1 *Identified* Risks Associated with *Glofitamab*

On the basis of clinical data to date with *glofitamab*, the following *identified* risks are described below. *Refer to the Glofitamab Investigator Brochure for a description of all anticipated risks for glofitamab.* Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.7 and Appendix 11.

**Cytokine-Release Syndrome**

Based on clinical data from Study NP30179, CRS is the most frequent *glofitamab*-related adverse event occurring in patients treated with *glofitamab* and is the main DLT. In the majority of patients, the CRS event occurred in Cycle 1, whereas for a few patients, the event recurred at subsequent cycles but normally with less severity (see the *Glofitamab* Investigator's Brochure for the most updated safety data).

Disease-related factors that may be associated with an increased risk of severe CRS following CAR T-cell therapy and potentially with other T cell–engaging therapies include (but are not limited to) lymphoma bone marrow involvement, extranodal disease, Richter transformation, B-cell lymphocytosis, and the presence of malignant circulating peripheral cells, assessed by peripheral blood smear (see Section 4.5.7). Refer to Appendix 10 and the *Glofitamab* Investigator's Brochure for further details on CRS. The schedule of tocilizumab assessments for patients who experience severe or life-threatening CRS is presented in Appendix 3. The recommended management of CRS is detailed in Appendix 10.

**Neutropenia *and Febrile Neutropenia***

In patients treated with *glofitamab*, neutropenia was commonly observed.

Neutropenia is the most likely overlapping toxicity between obinutuzumab and *glofitamab*, and with gemcitabine and oxaliplatin. Patients will receive growth factor support starting in the interval between GemOx dosing and before receiving the first infusion of *glofitamab*. All patients will receive G-CSF as primary prophylaxis in Cycles 1–*8* of study treatment. Refer to Appendix 10 for the management of hematologic abnormalities.

Refer to the *Glofitamab* Investigator's Brochure for further details on neutropenia *and febrile neutropenia*.

**Tumor Inflammation and Tumor Flare**

Adverse events associated with tumor inflammation have been reported with T cell–engaging therapies and are consistent with the mechanism of action leading to

influx of T cells into tumor sites. Events involving tumor inflammation or flare have been reported in Study NP30179. These events tend to occur with a short time to onset following *glofitamab* administration and present with varying degrees of severity. In addition, depending on tumor size and anatomic location, events associated with tumor inflammation or 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 inflammation, further medical and/or surgical management may be necessary.

Patients with tumors involving critical anatomic locations should be closely monitored for tumor inflammation, and prospective preventive or interventional measures may need to be considered or planned prior to dosing. Specific management guidelines are summarized in Appendix 10.

### Pyrexia

When the onset of pyrexia occurs with an interval longer than 24 hours from the last administration of glofitamab, pyrexia should be managed with appropriate antipyretic treatment. It is important to perform differential diagnosis for infections and disease progression (B-symptoms). Hospitalization may be appropriate for such cases and becomes compelling in the event of febrile neutropenia.

## 5.1.2 *Potential* Risks Associated with *Glofitamab*

On the basis of clinical data to date with *glofitamab*, the following *potential* risks associated with *glofitamab* treatment are described below. Guidelines for the management of these risks through dose and schedule modifications are described in Section 5.1.7.

### Central Nervous System Toxicity

Neurologic toxicity has been reported frequently with blinatumomab and CAR T-cell therapy (Blincyto® U.S. Package Insert; Maude et al. 2014; Kochenderfer et al. 2015). Reported symptoms include headache, confusion, aphasia, encephalopathy, tremor, seizure, and other neurologic events. These events have generally improved with treatment discontinuations and corticosteroids (Viardot et al. 2010; Kochenderfer et al. 2015). The mechanism of CNS toxicity remains unknown and has been hypothesized to include trafficking of activated T cells into the brain and cerebrospinal fluid (CSF) with subsequent local cytokine release (Nagorsen and Baeuerle 2011).

For the purposes of this study, all patients must be without CNS disease at baseline and agree to CNS monitoring by means of neurologic examination during treatment with *glofitamab*. To minimize the risk of CRS and neurologic events, all patients will receive prophylactic corticosteroids for obinutuzumab and for each *glofitamab* infusion. In case of neurologic events or signs, additional dexamethasone or methylprednisolone will be administered (see Appendix 10).

### *Hemophagocytic Lymphohistiocytosis*

*HLH, alternatively described as macrophage activation syndrome, has been reported with CAR T-cell therapy (Teachey et al. 2013, Lee et al. 2014). HLH should be included in the differential diagnosis for patients who develop a sepsis-like syndrome or severe CRS, and workup should include serum ferritin, which is typically dramatically elevated in HLH, as well as CBC, liver function tests (LFT), serum triglycerides, and coagulation profile. A bone marrow evaluation should also be considered. Guidelines for the management of HLH are provided in* Appendix 8.

### 5.1.3 Potential Overlapping Risks Associated with Obinutuzumab and *Glofitamab*

Based on the mode of action, class effects, nonclinical studies with each molecule and clinical studies with obinutuzumab, IRRs, immunogenicity, CRS, TLS, infections and PML, thrombocytopenia, neutropenia, and elevated liver enzymes are identified as potential overlapping toxicities (i.e., such events may occur with either study drug) in patients treated with obinutuzumab and/or *lofitamab*.

There is a risk of development of IRR from treatment with obinutuzumab; obinutuzumab IRRs can effectively be managed with appropriate measures, as outlined in Appendix 10, and should be reported as IRR. *Signs and symptoms of IRRs during or after glofitamab infusion* may be clinically indistinguishable from manifestations of CRS*; see Section 5.3.5.1 for guidance on reporting IRR* and CRS.

#### Immunogenicity

The risk of immunogenicity to *glofitamab* and to obinutuzumab is greatly reduced by the B cell–targeting nature of each therapeutic antibody, given that both healthy (ADA producing) and malignant CD20-positive cells will be lysed. All patients in this study will be monitored at regular intervals for the development of ADAs against *glofitamab*. Additional samples may be drawn at the time of treatment discontinuation or during the safety follow-up visit and may be drawn in patients who experience an IRR and who have clinical signs of hypersensitivity reaction, in particular immune–complex reactions. In any case, for each collected ADA sample, a corresponding PK sample will be collected at the same timepoint for the determination of *glofitamab* concentration.

#### Tumor Lysis Syndrome

TLS has been reported with blinatumomab, CAR T-cell therapy, and with CD20-directed therapies (Porter et al. 2011). The inherent risk of TLS is dependent on the malignancy being treated and individual patient characteristics (Coiffier et al. 2008). There is the theoretical risk of TLS if treatment with *glofitamab* results in the rapid destruction of a large number of tumor cells.

The risk of TLS with obinutuzumab and with *glofitamab* in patients with NHL is predicted to be highest for those patients with bulky disease (defined as any lesion ≥10 cm on the screening CT scan) and elevated pretreatment LDH levels, particularly in the presence of dehydration or compromised renal function. Given that *glofitamab* has the potential

for potent B-cell killing (see Section 1.3), patients *at risk for TLS should* receive prophylaxis for TLS. Specific prophylaxis recommendations for the prevention of TLS are described in Appendix 10.

### Infections, Progressive Multifocal Leukoencephalopathy, and Hepatitis B Reactivation

Owing to its anticipated mode of action resulting in profound B-cell depletion, both *glofitamab* and obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving other CD20-directed therapies (for more details, refer to the Obinutuzumab Investigator's Brochure). Therefore, *glofitamab* and obinutuzumab should not be administered to patients with active severe infections. Investigators should exercise caution when considering the use of *glofitamab* in patients with history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Particular attention should be given to patients who have had significant prior immunosuppressive treatment, such as high-dose chemotherapy.

PML has been associated with treatment with CD20-directed therapies, including obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to preexisting neurologic manifestations. The symptoms of PML are non-specific and can vary, depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual-field defects are common. Some signs/symptoms regarded as "cortical" (e.g., aphasia or visual–spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (CSF testing for John Cunningham viral DNA). The patient should be referred to a neurologist for the evaluation and treatment of PML. New-onset neurologic adverse events following initial doses of *glofitamab* may be possible, owing to acute effects of *glofitamab*.

Hepatitis B reactivation has been reported with CD20-directed therapies. Patients with a history of chronic hepatitis B infection or positive test results for active or chronic HBV infection defined by HBsAg and/or positive total HBcAb and positive HBV PCR, or patients with HCV infection as assessed by PCR, will be excluded from this study (Section 4.1.2). *Patients who experience hepatitis B reactivation should start antiviral therapy (if not already initiated). Patients with rising viral load on appropriate antiviral therapy should consider study treatment discontinuation if in the investigator's opinion the* benefit-risk *profile of continued treatment is unfavorable.*

### Thrombocytopenia

Thrombocytopenia is associated with CD20-directed therapies. In patients treated with *glofitamab*, thrombocytopenia was rarely considered to be associated with *glofitamab*. See the *Glofitamab* Investigator's Brochure for further details on thrombocytopenia.

Patients should be closely monitored for thrombocytopenia, and regular laboratory tests should be performed until the event resolves. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the investigator. Modifying the use of any concomitant therapies that may worsen thrombocytopenia-related events (such as platelet inhibitors and anticoagulants) should also be considered, especially during the first cycle of study treatment.

### Elevated Liver Enzymes

Elevated liver enzymes have been reported with blinatumomab (Blincyto U.S. Package Insert), usually but, not exclusively, in the setting of CRS. Elevated liver enzymes have also occurred in patients who received obinutuzumab in clinical trials and in patients who had normal baseline hepatic enzyme levels (AST, ALT, and ALP). The events occurred most frequently within 24–48 hours of the first infusion. In some patients, elevations in liver enzymes were observed concurrently with infusion reactions or TLS (refer to the *Glofitamab* and Obinutuzumab Investigator's Brochures).

Currently, there is no evidence of elevated liver enzymes in patients treated with *glofitamab*, with the exception of transient enzyme elevations in the context of CRS events. See the *Glofitamab* Investigator's Brochure for further details on nonclinical assessments of *glofitamab*. Patients with elevated LFTs at screening will be excluded from this study (see Section 4.1.2).

## 5.1.4 Risks Associated with Mosunetuzumab

### 5.1.4.1 Known Risks Associated with Mosunetuzumab

On the basis of clinical data to date with mosunetuzumab, the following known risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.7 and Appendix 11.

### Cytokine-Release Syndrome

The mechanism of action of mosunetuzumab is immune-cell activation against CD20-expressing cells; therefore, a spectrum of events involving IRRs, target-mediated cytokine release, and/or hypersensitivity with or without emergent ADAs may occur. CRS has been reported in mosunetuzumab studies and is an identified risk of mosunetuzumab. Based on clinical data from Study GO29781, CRS is the most frequent mosunetuzumab-related AE. All CRS events were Grade 1 or 2, with the exception of one Grade 3 event, determined according to the modified CRS grading system (Lee et al. 2014). The median time to first CRS onset is 2 days (range: 1–24 days) and median duration of event is 2 days (range: 1–20 days). All events were reversible and manageable with supportive care measures.

Management guidelines for CRS following mosunetuzumab are summarized in Appendix 11, with the grading of CRS according to the ASTCT CRS Consensus Grading presented in Appendix 4. The schedule of assessments for patients with severe or life-threatening CRS is provided in Appendix 3.

**Neutropenia** ***and Febrile Neutropenia***

Neutropenia is a known class effect associated with other CD20-directed therapies, such as obinutuzumab and rituximab, and with the similar class agent blinatumomab. Reversible neutropenia has been observed following mosunetuzumab treatment. Some patients developing neutropenia have received growth factor support and/or temporary treatment holds. *Febrile neutropenia has also been observed following mosunetuzumab treatment.*

All patients will receive G-CSF as primary prophylaxis during Cycles 1–*8* of study treatment. Patients who experience Grade 3 or 4 neutropenia should be closely monitored with more frequent assessments as applicable. Refer to Section 4.3.8 and Appendix 11 for the management of hematologic abnormalities.

### 5.1.5 Suspected Risks Associated with Mosunetuzumab

**Hemophagocytic Lymphohistiocytosis**

CRS with features of adult-onset secondary or reactive HLH has been reported with blinatumomab as well as adoptive CAR T-cell therapy (Blincyto U.S. Package Insert; Teachey et al. 2013; Lee et al. 2014). A fatal case of secondary HLH in a patient with evidence of chronic active EBV infection (positive for EBV, as assessed by EBV-encoded small RNA in situ hybridization) has been reported in Study GO29781 (refer to Section 1.5.2.1 and the current Mosunetuzumab Investigator's Brochure for details).

While severe CRS and HLH have overlapping presentation and symptoms, HLH may be precipitated by other conditions, including infections, autoimmune disease, and malignancies (Ramos-Casals et al. 2014). The prevalence of these conditions in the study patient population makes the distinction between severe CRS and HLH and identification of inciting factors challenging. For example, in one series, B-cell malignancies were the most common malignancy associated with reactive HLH (Rivière et al. 2014). Furthermore, active infection with EBV is one of the most common infectious causes of HLH (Hashemi-Sadraei et al. 2015; Schram and Berliner 2015), while reactivation of latent EBV may occur in patients with CLL (Rath et al. 2008), which in turn may lead to HLH (Lim et al. 2016). It remains unknown whether mosunetuzumab treatment may further increase the risk of developing HLH in patients who have additional risk factors. In the setting of T cell–engaging therapies, including mosunetuzumab, CRS is much more likely compared with secondary HLH. Considering the overlapping presentation of symptoms, management of such patients should be primarily focused on treatment of CRS (see Appendix 11). Treatment options in cases where tocilizumab, with or without high-dose corticosteroids, fail to induce the desired response will be based on published guidelines (La Rosée 2015, 2019; Schram and Berliner 2015) and considered between the Sponsor and investigator on a case-by-case basis, given that there is no standard of care in these clinical situations. In atypical cases, such as late-onset CRS (after completion of step-up dosing with mosunetuzumab)

or CRS that is refractory to treatment, workup for HLH should be initiated and all cases of suspected HLH should be discussed with the Medical Monitor immediately.

Although there is no currently universally accepted set of criteria for diagnosing secondary or reactive HLH in the adult population, proposed criteria have been published (Henter et al. 2007; Fardet et al. 2014; Hejblum et al. 2014; McClain and Eckstein 2019).

The supportive management of HLH is generally similar to that of CRS. Specific diagnostic, monitoring, and management guidelines for HLH are described in Appendix 8.

The schedule of tocilizumab assessments for patients who experience severe or life-threatening CRS is presented in Appendix 3. The recommended management of CRS is detailed in Appendix 11.

### Central Nervous System Toxicity

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

Neurologic toxicity has also been reported in patients treated with blinatumomab and CD19 CAR T-cell therapy (Maude et al. 2014; Kochenderfer et al. 2015). Reported symptoms in patients treated with blinatumomab or CD19 CAR T-cell therapy have included headache, confusion, aphasia, encephalopathy, tremor, seizure, and other neurologic events. The etiology of toxicity in these settings is uncertain and may not be responsive to cytokine-directed therapy such as tocilizumab but has generally improved with treatment discontinuation and corticosteroids (Viardot et al. 2010; Kochenderfer et al. 2015).

Neurologic toxicity will be monitored closely during this study. All patients will be required to undergo a baseline complete neurologic examination prior to the first mosunetuzumab administration; the examination should include an evaluation of mental status, cranial nerves, motor strength, sensation, and coordination. Results of the neurologic examination should be documented in the patient's chart. Patients with a history of neurologic disease may be excluded from this trial (see Section 4.1.2).

Patients should be routinely assessed for any signs or symptoms of neurologic toxicity as part of the on-treatment clinical examination (see Section 4.5.3). If new or worsening neurologic toxicity is suspected, refer to Appendix 11 for management guidelines, including guidelines for driving restrictions.

Patients with the combination of aggressive NHL and abnormal (above institutional ULN) C-reactive protein at screening should be advised to refrain from driving or engaging in hazardous occupations or activities during Cycles 1 and 2 (approximately 6 weeks).

### Tumor Lysis Syndrome

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

The risk of TLS with mosunetuzumab in patients with NHL is predicted to be highest for those with bulky disease (defined in the context of TLS as any lesion ≥10 cm on the screening CT scan) and elevated pretreatment LDH levels, particularly in the presence of dehydration or compromised renal function. Mosunetuzumab has the potential for potent B-cell killing; hence, patients *at risk for TLS should* receive prophylaxis for TLS.

Specific prophylaxis recommendations for the prevention of TLS are described in Appendix 11.

### Infections

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

PML has been associated with treatment with CD20-directed therapies, including rituximab and obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations, and consultation with a neurologist and diagnostic procedures, including brain MRI and lumbar puncture, should be performed as clinically indicated. Note, however, that new onset of neurologic adverse events following initial doses of mosunetuzumab may be more likely owing to acute effects of mosunetuzumab (see Section 1.5.2.1), given that PML associated with rituximab generally occurred following long-term exposure (Carson et al. 2009).

Hepatitis B reactivation has been reported with other CD20-directed therapies. Patients with a history of chronic hepatitis B infection or positive test results for active or chronic HBV infection, defined by HBsAg and/or positive total HBcAb and positive HBV PCR, or patients with HCV infection as assessed by PCR will be excluded from this trial (refer to Section 4.1.2).

Patients with HIV infection will be excluded from participation in the study because signs and symptoms of HIV may confound assessment of the safety profile of mosunetuzumab in combination with gemcitabine and oxaliplatin. HIV has also been associated with development of secondary HLH. Patients with HIV and known or suspected chronic active EBV infection will be excluded from this trial owing to the risk of secondary HLH (see Section 4.1.2).

### Thrombocytopenia

Reversible thrombocytopenia has been observed following mosunetuzumab treatment. Patients should be closely monitored for thrombocytopenia; regular laboratory tests should be performed until the event resolves. Transfusion of blood products (e.g., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

### Elevated Liver Enzymes

Transient Grade 3 AST elevations in the setting of Grade 2 CRS, Grade 3 hepatic encephalopathy, and Grade 4 elevated LFTs have been observed following mosunetuzumab treatment. Patients who do not meet eligibility criteria for LFTs at screening will be excluded from this trial (see Section 4.1.2). LFTs will be assessed regularly during study and should be managed according to guidelines in Appendix 11.

For patients receiving mosunetuzumab who develop isolated elevated bilirubin, consideration for withholding or discontinuing mosunetuzumab should be made and discussed with the Medical Monitor.

### Immunogenicity

As with any recombinant antibody, mosunetuzumab may elicit an immune response, and patients may develop antibodies against the molecule. Patients will be closely monitored for any potential immune response to mosunetuzumab, which may have an effect on the benefit–risk profile of the agent. 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. Of the 53 evaluable patients with postbaseline ADA samples tested in the Phase I study (GO29781) of mosunetuzumab, none of the patients were confirmed positive for anti-mosunetuzumab antibodies.

### Tumor Inflammation and Tumor Flare

Adverse events associated with tumor inflammation and tumor flare have been reported in Study GO29781. Consistent with the mechanism of action of mosunetuzumab, tumor flare is likely owing to the influx of T cells into tumor sites following mosunetuzumab administration. Reported tumor flare–associated adverse events generally have a short time to onset following mosunetuzumab administration. Based on safety data collected to date, tumor flare has manifested as new or worsening pleural effusions. In addition, depending on tumor size and anatomic location, tumor flare may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major

organs. Patients with tumors at critically anatomic locations should be closely monitored for tumor flare, and the treating physician or study investigator should contact the Medical Monitor to discuss benefit–risk assessment and mitigation strategies prior to mosunetuzumab treatment. Refer to Appendix 11 for the management of tumor flare.

### 5.1.6 Risks Associated with Gemcitabine and Oxaliplatin

See the local prescribing information for risks associated with gemcitabine and oxaliplatin use.

### 5.1.7 Management of *Patients who Experience* Specific Adverse Events

For the management of AEs related to *glofitamab*, refer to Appendix 10. For the management of adverse events related to mosunetuzumab, refer to Appendix 11. For cases in which management guidelines are not covered in this protocol or in the Obinutuzumab or Tocilizumab Investigator's Brochure, patients should be managed as deemed appropriate by the investigator according to best medical judgment and local medical guidelines.

Clinical judgment may be applied and benefit–risk consideration may suggest deviating from these guidelines. In this specific case, decisions on study treatments will be taken by the investigator upon consultation with the Medical Monitor.

#### 5.1.7.1 Dose Modifications and Interruptions

Patients should be assessed clinically for toxicity before each dose of study treatment. Dose modifications should be based on physical examination findings, observed toxicities, and laboratory results. Dosing will occur only if a patient's clinical assessments and laboratory test values are acceptable. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule. All considerations of dose and schedule modifications should be discussed with the Medical Monitor.

*No dose modifications of glofitamab, obinutuzumab, rituximab, or gemcitabine are permitted. Oxaliplatin may be reduced per the guidelines in this section and Table 4.* Study treatment may be suspended for reasons other than toxicity (e.g., *assessment of pseudoprogression or delayed response) with Medical Monitor approval.*

*In case a cycle of therapy is delayed for more than 21 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 patient. For patients receiving glofitamab, if dose delay results in a treatment-free interval of 6 weeks or longer, obinutuzumab pretreatment should be re-initiated 7 days prior to resuming glofitamab treatment, and step-up dosing of glofitamab is required for the first cycle after the dose delay.*

### *Neutropenia and Thrombocytopenia*

During Cycle 1, no dose or schedule modifications for *glofitamab* or mosunetuzumab will be made for hematologic toxicity, which is an expected side effect of oxaliplatin and gemcitabine.

Subsequent cycles of therapy may commence when ANC reaches $\geq 1.0 \times 10^9/\mu L$, platelet count reaches $\geq 75{,}000/\mu L$, and related non-hematologic toxicities have resolved to Grade 1 or better.

*For treatment delays* more than *14 days due to decreased neutrophil* or *platelet counts, discontinue study treatment as described below:*

- *Discontinue GemOx*
  - Patients *are permitted to continue treatment with single agent glofitamab* or mosunetuzumab *when ANC reaches $\geq 1.0 \times 10^9/\mu L$, and platelet count reaches $\geq 75{,}000/\mu L$, to complete the planned total cycles of therapy. If a patient has a subsequent delay of >14 days due to decreased neutrophil or platelet counts, discontinue GemOx.*

### *Non-Hematologic Toxicities*

*Patients* who experience a *serious* Grade 4 related non-hematologic *AE* should discontinue study treatment. Exceptions may be warranted after discussion with *the* Medical Monitor taking into consideration benefit-risk ratio for a given individual patient and ad-hoc and patient-specific risk mitigations. *ubsequent cycles of therapy may commence when the non-hematologic toxicity recovers to* Grade *1 or better, and when hematologic parameters defined above are met.*

Study treatment may be temporarily suspended in patients who experience toxicity considered by the investigator to *necessitate interruption of* study *treatment. A delay of study treatment for up to 21 days will be acceptable to allow for recovery from non-hematologic toxicities.* If *study treatment* has been withheld for more than 21 days because of toxicity, the patient should be discontinued from treatment unless resumption of treatment is approved following investigator discussion with the Medical Monitor.

*In the event that a patient has a non-hematologic toxicity during the step-up dosing in Cycle 1 necessitating glofitamab or mosunetuzumab interruption for >7 days, the patient will be required to repeat glofitamab or mosunetuzumab at the highest dose previously tolerated prior to resuming the planned treatment schedule.*

*For patients receiving glofitamab, if dose delay results in a treatment-free interval of 6 weeks or longer, obinutuzumab pretreatment should be re-initiated 7 days prior to resuming treatment, and step-up dosing of glofitamab is required for the first cycle after the dose delay.*

*For patients receiving mosunetuzumab, if dose delay results in a treatment-free interval of 6 weeks or longer, step-up dosing of mosunetuzumab is required for the first cycle after the dose delay.*

See the local prescribing information for gemcitabine and oxaliplatin for full information.

Management of specific AEs associated oxaliplatin should be conducted according to Table 4.

**Table 4 Oxaliplatin Management of Neuropathy**

| Event | Management Guidelines |
|---|---|
| Acute pharyngolaryngeal dysesthesia (subjective sensation of dysphagia or dyspnea without stridor or wheezing) | • Avoid ice during infusion.<br>• Limit exposure to cold temperature or cold objects.<br>• 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 to 75 mg/m² and continue other study treatments. If the patient has Grade 2 neurosensory event at the time that subsequent doses are due, continue other study treatment and withhold oxaliplatin until recovered to Grade 1.* |
| Grade 3 peripheral sensory neuropathy, paresthesia, or gait disturbance | • *If the patient has any Grade 3 neurosensory event that recovers* to *at least* Grade 1<br>  • *by the time of the next scheduled* oxaliplatin dose, *reduce oxaliplatin to* 75 mg/m² *and continue other study treatments.*<br>  • *For persistent Grade 3 neurosensory events that do* not *recover* to *at least* Grade 1 *by* the *time of the 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. Consult the Medical Monitor to determine whether to continue other study treatment. |

### 5.1.7.2 *Allergic/Anaphylactic Reactions*

*Because of the potential for hypersensitivity, administration of study treatment will be performed in a hospital or clinic, where full resuscitation facilities with emergency equipment and staff trained to monitor medical situations and respond to medical emergencies are present on site. In the event of a suspected anaphylactic reaction during study treatment infusion, follow the procedures outlined in* (see Appendix 7) *. Patients with true allergic/anaphylactic reactions should not receive further doses of study treatment.*

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

### 5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### 5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Adverse events of special interest specific for either *glofitamab* or mosunetuzumab include the following:

- Grade ≥2 CRS
- Grade ≥2 neurologic adverse event
- Any suspected HLH

- TLS (minimum Grade 3 by definition)
- Febrile neutropenia (minimum Grade 3 by definition)
- Grade ≥2 AST, ALT, or total bilirubin elevation
- Any grade disseminated intravascular coagulation (minimum Grade 2 by definition)
- Grade ≥2 tumor inflammation or 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)

Adverse events of special interest for obinutuzumab include the following:

- Secondary malignancies
- *TLS (minimum Grade 3 by definition)*

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### 5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 90 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

### 5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE. CRS should be graded according to the ASTCT CRS Consensus Grading (Lee et al. 2019) (see Appendix 4).

**Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

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

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

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

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no"

accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

**Table 6 Causal Attribution Guidance**

| Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment? | |
|---|---|
| YES | There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge. |
| NO | An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug). |

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

### 5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### 5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

Adverse events that occur during or within 24 hours after study *treatment* administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., “infusion-related reaction” or “cytokine-release syndrome”) on the

Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated eCRF.

*Adverse events that occur during obinutuzumab administration or within 24 hours after end of obinutuzumab infusion and are judged to be related to obinutuzumab infusion should be captured as a diagnosis (e.g., "infusion-related reaction", on the Adverse Event eCRF.*

Given the mechanism of action of CD20- and CD3-bispecific antibodies, IRRs and CRS may be indistinguishable from one another. *Adverse events attributed to glofitamab or mosunetuzumab* consistent with a diagnosis of IRR or CRS, *and associated* with *fever not attributable* to *any other cause,* should be *recorded as Cytokine Release Syndrome* (Lee et al. 2019).

For adverse events with a diagnosis of IRR or CRS, associated signs, symptoms, and laboratory abnormalities should be recorded on the dedicated eCRF for CRS events. The event of CRS should be graded according to ASTCT CRS Consensus Grading (see Appendix 4). Individual signs and symptoms of CRS should be graded according to NCI CTCAE v5.0. If a patient experiences hypoxia or hypotension, this should be detailed in the eCRF, as well as the management of these symptoms, for example, pressor and oxygen use. If a patient experiences both a local and systemic reaction to the same administration of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the CRS eCRF. Organ toxicities that may occur concurrently with CRS (e.g., neurologic signs and symptoms, or liver associated enzyme abnormalities) should be reported separately on the Adverse Event eCRF.

An 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 “anaphylaxis” should be used.

Ambiguous terms such as "systemic reaction" should be avoided.

In addition to documentations on the Adverse Event eCRF, non-serious Grade ≥2 CRS events should be reported as a non-serious adverse event of special interest (see Section 5.2.3).

#### 5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs (see Section 5.3.5.1), 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.

#### 5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

#### 5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

#### 5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5×ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3×ULN) in combination with either an elevated total bilirubin (>2×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×ULN in combination with total bilirubin >2×ULN
- Treatment-emergent ALT or AST >3×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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

#### 5.3.5.8 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of DLBCL 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 drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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 5.6.

#### 5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

#### 5.3.5.10 Lack of Efficacy or Worsening of Diffuse Large B-Cell 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 the 2014 Lugano Response Criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

#### 5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- *Hospitalization for observation if patients are considered to be at risk for an AE* (e.g., prophylactic hospitalization prior to *glofitamab* or mosunetuzumab dosing, according to risk or prior occurrence of CRS)
    - *If the patient experiences an AE during such hospitalization, the event should be reported as an AE or a SAE.*

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

#### 5.3.5.12 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, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For *glofitamab*, mosunetuzumab, obinutuzumab, 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 *glofitamab*, mosunetuzumab, obinutuzumab, and 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 two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.3.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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 becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information**

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

### 5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

#### 5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the

EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >90 days after the final dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 18 months after the final dose of obinutuzumab, 6 months after the final dose of gemcitabine, 9 months after the final dose of oxaliplatin, 3 months after the final dose of mosunetuzumab, 3 months after the final dose of tocilizumab (if applicable; see Section 4.3.4), and 2 months after the final dose of *glofitamab*. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 2 months after the final dose of *glofitamab*, 2 months after the final dose of mosunetuzumab, 2 months after the last dose of tocilizumab (if applicable), *or* 3 months after the final dose of obinutuzumab, whichever is longer. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the

risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### 5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryo–fetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryo–fetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

#### 5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge

summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the final dose of study drug), 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 drug, 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 emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

## 5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

| Drug | Document |
|---|---|
| *Glofitamab* | *Glofitamab* Investigator's Brochure |
| Mosunetuzumab | Mosunetuzumab Investigator's Brochure |
| Obinutuzumab | Obinutuzumab Investigator's Brochure |
| Tocilizumab | Tocilizumab Investigator's Brochure |

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

No formal statistical model and no formal hypothesis testing is planned for this study.

## 6.1 DETERMINATION OF SAMPLE SIZE

The study will enroll 10 patients in order to evaluate the safety and tolerability of the study treatment. A sample size of 10 was chosen to allow for a clinically meaningful assessment of safety. In addition, with a sample size of 10 patients, the true incidence rate of adverse events can be estimated within 9.7% to 34.5% assuming an observed incidence of 10% (i.e., within 95% Clopper-Pearson CI of 0.3% to 44.5%) (see Table 7).

**Table 7 Clopper-Pearson 95% Confidence Intervals for the Observed Incidence of Adverse Events**

| Number of Adverse Events/ Observed Incidence of Adverse Events | 95% Clopper-Pearson Confidence Interval |
|---|---|
| 1 (10%) | 0.3% to 44.5% |
| 2 (20%) | 2.5% to 55.6% |
| 3 (30%) | 6.7% to 65.2% |
| 4 (40%) | 12.2% to 73.8% |
| 5 (50%) | 18.7% to 81.3% |

Note: The total number of patients is 10.

Continuous safety monitoring will be performed to guide potential early stopping of enrollment in the event of unacceptable toxicity or futility in the treatment arm.

## 6.2 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 8.

**Table 8 Analysis Populations**

| Analysis Population | Description |
|---|---|
| Safety evaluable | All patients who receive at least one dose of any study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis. |
| Pharmacokinetic | All patients who receive at least one dose of *glofitamab* or mosunetuzumab and who have data from at least one postdose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol or if their data are unavailable or incomplete, which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions about exclusions from the analysis will be made prior to database closure. |
| Immunogenicity | Patients who have at least one predose and one postdose ADA assessment will be included and analyzed according to the treatment they actually receive. |

ADA = anti-drug antibody; PK = pharmacokinetic.

## 6.3 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be captured. The study is an open-label study; therefore, no blinded treatment will be administered.

## 6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, and race will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

## 6.5 SAFETY ANALYSES

All safety analyses will be based on the safety evaluable population grouped according to treatment arm. Safety will be determined by adverse events, laboratory tests, vital signs, ECGs, physical examinations, and ECOG Performance Status. The analysis methods for safety endpoints are listed in Table 9. As appropriate, listings, summary tables, and graphs will be provided for safety and tolerability assessments.

**Table 9 Safety Statistical Analysis Methods**

| Endpoint | Statistical Analysis Methods |
|---|---|
| Adverse events | The original terms recorded on the eCRF by the investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level. |
| Clinical laboratory tests | All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units) by individual listings with abnormal results flagged.<br>Summary tables of change from baseline over time will be displayed. Shifts in NCI CTCAE v5.0 grade events from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. |
| Vital signs | Vital signs data will be presented by individual listings with flagged values outside the normal ranges and abnormalities. In addition, tabular summaries will be used, as appropriate. |
| Tolerability | Dose interruptions, dose reductions, dose intensity, and treatment discontinuation because of adverse events will be listed and/or summarized, as appropriate. |

NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; SI=Système International d'Unités.

## 6.6 EFFICACY ANALYSES

In this study, safety is the primary endpoint, and all efficacy endpoints are secondary.

Tumor response data will be reported using descriptive statistics. ORR and CRR will be summarized using frequencies and proportions.

## 6.7 PHARMACOKINETIC ANALYSES

All patients with a serum sample for PK analysis will be included to enable estimation of key parameters (i.e., AUC, $t_{max}$, $C_{max}$, and $C_{min}$).

Individual and mean plasma CD20-CD3–bispecific antibody concentration versus time data will be tabulated and plotted. The plasma pharmacokinetics of CD20-CD3–bispecific antibody will be summarized by estimating the $C_{max}$, $C_{min}$, and AUC, if appropriate. These parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, and minimum and maximum).

Additional PK analyses may be conducted as appropriate. In addition these data may be analyzed using population PK modeling and may be pooled with clinical data from other studies. These analyses will be reported separately from the Clinical Study Report.

Obinutuzumab serum concentrations will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, and minimum and maximum).

For Arm B, baseline serum concentrations of rituximab will be summarized (mean, standard deviation, coefficient of variation, median, and minimum and maximum).

### 6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized. When determining the postbaseline incidence, patients will be considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.6-titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

The baseline prevalence and postbaseline incidence will be descriptive only and no formal statistical test will be performed.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

### 6.9 BIOMARKER ANALYSES

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.

## 7. DATA COLLECTION AND MANAGEMENT

### 7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

## 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

## 7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly on the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

## 7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

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

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

## 8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of

the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

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

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

# 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

## 9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

## 9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

## 9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

## 9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

## 9.5 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.

Up to approximately 20 patients with R/R DLBCL will be enrolled in the study, with approximately 10 patients in either Arm A or B at approximately six sites. Treatment assignment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker, and PK tests), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will monitor and evaluate patient safety throughout the study (see Section 3.1.2).

## 9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

## 9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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# Appendix 1
# Schedule of Activities

**Table 1** *Schedule of Activities Arm A: Glofitamab in Combination with Gemcitabine Plus Oxaliplatin (Glofit-GemOx Arm)*

| | Screen[a] | Cycle 1 | | | | Cycle 2[b] | | Cycle 3[b] | Cycle 4[b] | | Cycles 5-7[b] | Cycle 8[b] | | Cycles 9-12[b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day(s) (window) | D -14 to -1 | D1 | D2 | D8 (±1) | D15 (±1) | D1 (±1) | D8 (±1) | D1 (±2) | D1 (±2) | Int Resp D15- 21 | D1 (±2) | D1 (±2) | Int Resp D15- 21 | D1 (±2) | Tx Completion or Early Discon[c,d,e,f] | Study Completion or Discon (90 days from final dose of sudy drug)[g] |
| Informed consent | X[h] | | | | | | | | | | | | | | | |
| Demographics (age, sex, and self-reported race/ethnicity) | X | | | | | | | | | | | | | | | |
| Medical history and baseline conditions | X | | | | | | | | | | | | | | | |
| ECOG Performance Status | X | X | | | | X | | X | X | | X | X | | X | X | X |
| Concomitant medications [i] | X | X | X | X | X | X | X | X | X | | X | X | | X | X | X |
| Adverse events [j] | X | X | X | X | X | X | X | X | X | | X | X | | X | X | X |
| Vital signs [k] | X | X | X | X | X | X | X | X | X | | X | X | | X | X | |
| Height and BSA (at screening only), weight [l] | X | X | | | | X | | X | X | | X | X | | X | X | |
| Complete physical examination [m] | X | | | | | | | | | | | | | | | |

*Table 1 Schedule of Activities Arm A: Glofitamab in Combination with Gemcitabine Plus Oxaliplatin (Glofit-GemOx Arm) (cont.)*

| Day(s) (window) | Screen[a] | Cycle 1 | | | | Cycle 2[b] | | Cycle 3[b] | Cycle 4[b] | | Cycles 5-7[b] | Cycle 8[b] | | Cycles 9-12[b] | Tx Completion or Early Discon[c,d,e,f] | Study Completion or Discon (90 days from final dose of sudy drug)[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Complete neurologic examination[n] | X | | | | | | | | | | | | | | | |
| Targeted physical examination[o] | | X | X | X | X | X | X | X | X | | X | X | | X | X | |
| Single 12-lead ECG[p] | X | | | | | | | | | | | | | | X | |
| Tumor assessment[q] | X | | | | | | | | | X | | | X | | X[c, q] | X[q] |
| Viral serology (HBV, HCV, and HIV)[r] | X | | | | | | | | | | | | | | | |
| Peripheral blood for viral infection test[s] | X | | | | | X | | | | | | | | | | |
| Hematology[t] | X | X | | X[u] | X | X | X | X | X | | X | X | | X | X | |
| Peripheral blood smear[v] | X[v] | | | | | | | | | | | | | | | |
| Serum chemistry profile[w] | X | X | | X | X | X | X | X | X | | X | X | | X | X | |
| B-Cell (CD19+) count[x] | | X | | X | | | | | | | | | | | | |
| CRP and serum ferritin | X | X | | X | X | X | X | X | | | X | | | X | | |

*Table 1 Schedule of Activities Arm A: Glofitamab in Combination with Gemcitabine Plus Oxaliplatin (Glofit-GemOx Arm) (cont.)*

| Day(s) (window) | Screen[a] | Cycle 1 | | | | Cycle 2[b] | | Cycle 3[b] | Cycle 4[b] | | Cycles 5-7[b] | Cycle 8[b] | | Cycles 9-12[b] | Tx Completion or Early Discon[c,d,e,f] | Study Completion or Discon (90 days from final dose of sudy drug)[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Coagulation: aPTT, PT, INR, and fibrinogen[y] | X | X | | X | X | X | | | | | | | | | | |
| Pregnancy test[z] | X | X[z] | | | | X | | X | X | | X | X | | X | | |
| Quantitative immunoglobulins: IgA, IgG, and IgM | X | | | | | | | | | | | | | | X | |
| Tumor tissue sample[aa] | X | | | | | | | | | | | | | | | |
| Serum samples for PK/ADA | See Appendix 2 for PK and ADA sampling schedule | | | | | | | | | | | | | | | |
| Blood samples for biomarkers | See Appendix 2 for the biomarker sampling schedule | | | | | | | | | | | | | | | |
| Study Treatment Administration[bb] | | | | | | | | | | | | | | | | |
| TLS prophylaxis[cc] | | X | | X | | X | | | | | | | | | | |
| Obinutuzumab | | X | | | | | | | | | | | | | | |
| Glofitamab | | | | X[u, dd] | X[dd] | X[dd] | | X | X | | X | X | | X | | |
| Gemcitabine | | | X | | | X | | X | X | | X | X | | | | |
| Oxaliplatin | | | X | | | X | | X | X | | X | X | | | | |

**Appendix 1: Schedule of Activities (cont.)**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| G-CSF [ee] | | | X [ee] | | | X [ee] | | X [ee] | X [ee] | | X [ee] | X [ee] | | | | |

*ADA=anti-drug antibody; BSA=body surface area; CMV=cytomegalovirus; CRP=C-reactive protein; CRS=cytokine-release syndrome; CT=computed tomography (scan); Discon=discontinuation; EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EOT=end of treatment; FFPE=formalin-fixed, paraffin-embedded; G-CSF=granulocyte colony-stimulating factor; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HLH=hemophagocytic lymphohistiocytosis; Ig=immunoglobulin; int resp=interim response; PCR=polymerase chain reaction; PET=positron emission tomography (scan); PK=pharmacokinetic(s); TLS=tumor lysis syndrome; Tx=treatment.*

*Notes: Assessments are to be performed prior to study treatment infusion, unless otherwise specified. Pre-infusion laboratory samples should be drawn 0-24 hours prior to study treatment infusion.*

[a] *Screening and pretreatment tests and evaluations will be performed within 14 days preceding the first dose of study treatment (except for the radiographic tumor assessment, which may be performed up to 28 days preceding the first dose of study treatment, provided that no anti-tumor therapy was administered during this period). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window specified above may be used; these tests do not need to be repeated for screening.*

[b] *For Cycle 2, study treatment infusion should occur on Day 1 of the cycle but may be given ±1 day from the scheduled date (with a minimum of 6 days after Day 15 of Cycle 1 dosing). For Cycles 3 and beyond, study treatment infusions should occur on Day 1 of each 21-day cycle but may be given ±2 days from scheduled date (with a minimum of 19 days between doses) for logistical or scheduling reasons. Other study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted.*

[c] *The end-of-treatment response assessment should occur 6 to 8 weeks after the final dose of study treatment.*

[d] *Patients who complete the treatment period will return to the clinic for a treatment completion visit 6–8 weeks after the final dose of study treatment. The end-of-treatment response assessment may be performed during this visit if it is 6–8 weeks after the final dose of study treatment.*

[e] *Patients who discontinue study drug prematurely for any reason other than disease progression should return to the clinic for a treatment discontinuation visit at 6 weeks (±2 weeks) after the last dose of study drug. The end-of-treatment response assessment can be done during this visit.*

[f] *Patients who discontinue study treatment prematurely because of disease progression should return to the clinic for a treatment discontinuation visit 28 days (±14 days) after their final dose of study drug. The study visit at which response assessment shows disease progression may be used as the early treatment discontinuation visit.*

[g] *Following the treatment discontinuation visit, patients will be followed for safety outcomes and survival by means of telephone calls, patient medical records, and/or clinic visits until 90 days following the final study dose (unless death, loss to follow-up, the patient withdraws consent or the Sponsor terminates the study, whichever is earliest).*

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

[i] *Concomitant medication consists of any medication used by a patient in addition to study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.j 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 final dose of study treatment or the initiation of another anti-cancer agent, whichever is earlier. Serious adverse events will be reported until 90 days after the final dose of study drug. After this period, refer to Section 5.6 for reporting requirements..*

[k] *Vital signs will include measurements of respiratory rate, pulse oximetry, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated or semi-supine position, and temperature. Cycles 1 and 2 glofitamab infusions: Check vital signs preinfusion, every 30 minutes (±10) during the infusion, at the end of the infusion, and 2 hours after infusion. For patients who tolerated Cycles 1 and 2 glofitamab infusions without the development of CRS, in subsequent cycles, vital signs should be assessed preinfusion, every 60 minutes (±15) during the infusion and for 2 hours after the end of infusion. For patients who experienced CRS in Cycle 1, vital signs should be assessed preinfusion, every 30 minutes (±10) during the infusion, and for 2 hours after the end of infusion. The monitoring of vital signs should be more frequent in patients with disease factors that may confer an increased risk of severe CRS, at least every 15 minutes during the first infusion in Cycle 1 for up to at least 2 hours postinfusion. Consult Appendix 3 for patients who receive tocilizumab.*

[l] *Height and BSA are required at screening only, unless there has been >10% change in body weight since the last BSA assessment, in which case, BSA should be recalculated and documented on the eCRF. Weight will be recorded at every indicated visit.*

[m] *Complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.*

[n] *A complete neurologic examination, which includes an evaluation of mental status, cranial nerves, muscle strength, sensation, and coordination should be performed and documented in the patient chart.*

[o] *Targeted, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated.*

[p] *Single 12-lead ECG recordings will be obtained at screening and at treatment discontinuation (either early treatment discontinuation or study treatment completion) and may be obtained at unscheduled timepoints as clinically indicated per investigator discretion. All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at the same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during the ECG recording.*

[q] *CT and PET/CT scans are required at screening, between Days 15-21 of Cycle 4, between days 15 and 21 of Cycle 8, and 6-8 weeks after the final dose of study treatment. See Section 4.5.6 for details. Assess response using image-based evaluation according to 2014 Lugano Response Criteria (see Appendix 5). Scans should be performed according to the guidelines in the imaging manual provided to all sites.*

[r] *HBsAg, total HBcAb, HCV antibody, and HIV antibody serology are required. Patients 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. Patients must be willing to undergo monthly HBV DNA testing and appropriate antiviral therapy as indicated. Patients who are positive for the HCV antibody must be negative for HCV by PCR to be eligible for study participation.*

[s] *Quantitative PCR detection of viral infection should include EBV and CMV at screening, predose on Day 1 of Cycle 2, and at other timepoints as clinically indicated for local laboratory assessment in addition to local laboratory assessments.*

[t] *Hematology includes WBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).*

[u] *After obinutuzumab pre-treatment, the platelet count must be ≥75,000/μL before administering the glofitamab 2.5-mg step-up dose.*

[v] *A peripheral blood smear is required at screening if not performed as part of standard-of-care tests. If malignant cells are detected, discuss with the Medical Monitor.*

[w] *Serum chemistry panel: sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, calcium, magnesium, phosphate, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, LDH, and urate.*

[x] *Flow cytometry assessment of B lymphocytes (CD19+ B-cell counts) will be conducted by the local laboratory. Flow cytometry assessment of B lymphocytes should be checked pre-infusion of obinutuzumab on Day 1 of Cycle 1 and Day 8 (up to 24 hours prior) of Cycle 1.*

[y] *Fibrinogen will also be collected when monitoring for specific adverse events (e.g., HLH or severe CRS), or at the discretion of the investigator.*

[z] *All women of childbearing potential will have a serum pregnancy test within 7 days prior to initiation of study treatment (Day 1 of Cycle 1). The pregnancy test for Day 1 of Cycle 1 does not need to be repeated if it was done within 7 days prior to initiation of study treatment. Pregnancy testing (urine or serum) will subsequently be performed within 24 hours prior to dosing on Day 1 of each cycle of therapy for all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.*

[aa] *Availability of most recent archival tumor tissue prior to study treatment (or if unavailable, freshly biopsied tumor tissue) should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides. Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue samples must have an associated pathology report. (Note: To protect tissue against oxidation and to allow immunohistochemistry [IHC] analysis in large batches, a FFPE tissue block is preferred over cut sections.)*

[bb] *See Section 4.3 for study treatment regimens and dosing.*

[cc] *Patients with high tumor burden and/or considered by the investigator to be at risk for tumor lysis should receive tumor lysis prophylaxis prior to the initiation of treatment. All patients should be well-hydrated (see Section 4.4.1.2 and Appendix 10).*

[dd] *Patients will be hospitalized for at least 24 hours after the infusion of glofitamab on Days 8 and 15 of Cycle 1. Patients with an event of CRS associated with the preceding dose of glofitamab should be hospitalized on Day 1 of Cycle 2. The required hospitalization is an additional precautionary safety measure to ensure that patients are closely monitored during the first two cycles.*

[88] *All patients will receive G-CSF as primary prophylaxis during cycles of GemOx treatment. G-CSF should be started 1 to 2 days after GemOx infusion in each cycle. Dosing of G-CSF should otherwise follow each site's institutional standards (see Section 4.4.1.1).*

*Table 2 Schedule of Activities Arm B: Mosunetuzumab in Combination with Gemcitabine Plus Oxaliplatin (Mosun-GemOx Arm)*

| | Screen[a] | Cycle 1 | | | | Cycle 2[b] | Cycle 3[b] | Cycle 4[b] | | Cycles 5-7[b] | Cycle 8[b] | Tx Completion or Early Discon[c,d,e,f] | Long-Term Follow-Up (90 days after final dose)[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day(s) (window) | D-14 to -1 | D1 | D2 | D8 (±1) | D15 (±1) | D1 (±1) | D1 (±2) | D1 (±2) | Int Resp D15- 21 | D1 (±2) | D1 (±2) | | |
| Informed consent[h] | X[f] | | | | | | | | | | | | |
| Demographics (age, sex, and self-reported race/ethnicity) | X | | | | | | | | | | | | |
| Medical history and baseline conditions | X | | | | | | | | | | | | |
| ECOG Performance Status | X | X | | | | X | X | X | | X | X | X | X |
| Concomitant medications[i] | X | X | X | X | X | X | X | X | | X | X | X | |
| Adverse events[j] | X | X | X | X | X | X | X | X | | X | X | X | |
| Vital signs[k] | X | X | X | X | X | X | X | X | | X | X | X | |
| Height and BSA (at screening only), weight[l] | X | X | | | | X | X | | | X | | X | |
| Complete physical examination[m] | X | | | | | | | | | | | | |
| G-CSF[cc] | | | X | | | X | X | X | | X | X | | |

*Table 2 Schedule of Activities Arm B: Mosunetuzumab in Combination with Gemcitabine Plus Oxaliplatin (Mosun-GemOx Arm) (cont.)*

| | Screen[a] | Cycle 1 | | | | Cycle 2[b] | Cycle 3[b] | Cycle 4[b] | | Cycles 5-7[b] | Cycle 8[b] | Tx Completion or Early Discon[c,d,e,f] | Long-Term Follow-Up (90 days after final dose)[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Complete neurologic examination[n] | X | | | | | | | | | | | | |
| Targeted physical examination[o] | | X | X | X | X | X | X | X | | X | X | X | |
| Single 12-lead ECG[p] | X | | | | | | | | | | | X | |
| Tumor assessment[q] | X | | | | | | | | X | | | X[c, q] | X[q] |
| Viral serology (HBV, HCV, and HIV)[r] | X | | | | | | | | | | | | |
| Peripheral blood for viral infection test[s] | X | | | | | X | | | | | | | |
| Hematology[t] | X | X | | X | X | X | X | X | | X | X | X | |
| Peripheral blood smear[u] | X | | | | | | | | | | | | |
| B-Cell (CD19+) Count[v] | X | X | | | | | | | | | | | |
| CRP and serum ferritin | X | X | | X | X | X | X | X | | X | X | | |
| Serum chemistry profile[w] | X | X | | X | X | X | X | X | | X | X | X | |
| Coagulation: aPTT, PT, INR, and fibrinogen[x] | X | X | | X | X | X | | | | | | | |
| Pregnancy test[y] | X | X | | | | X | X | X | | X | X | | |
| G-CSF[cc] | | | X | | | X | X | X | | X | X | | |

*Table 2 Schedule of Activities Arm B: Mosunetuzumab in Combination with Gemcitabine Plus Oxaliplatin (Mosun-GemOx Arm) (cont.)*

| | Screen[a] | Cycle 1 | | | | Cycle 2[b] | Cycle 3[b] | Cycle 4[b] | | Cycles 5-7[b] | Cycle 8[b] | Tx Completion or Early Discon[c,d,e,f] | Long-Term Follow-Up (90 days after final dose)[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Quantitative immunoglobulins: IgA, IgG, and IgM | X | | | | | | | | | | | X | |
| Tumor tissue sample | X[z] | | | | | | | | | | | | |
| Serum PK/ADA | See Appendix 2 for the PK and ADA sampling schedule | | | | | | | | | | | | |
| Blood samples for biomarkers | See Appendix 2 for the biomarker sampling schedule | | | | | | | | | | | | |
| Study Treatment Administration[aa] | | | | | | | | | | | | | |
| TLS prophylaxis[bb] | | X | | | | X | | | | | | | |
| Mosunetuzumab | | X | | X | X | X | X | X | | X | X | | |
| Gemcitabine | | | X | | | X | X | X | | X | X | | |
| Oxaliplatin | | | X | | | X | X | X | | X | X | | |
| G-CSF[cc] | | | X | | | X | X | X | | X | X | | |

*ADA=anti-drug antibody; BSA=body surface area; CMV=cytomegalovirus; CRP=C-reactive protein; CRS=cytokine-release syndrome; CT=computed tomography (scan); Discon=discontinuation; EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; FFPE=formalin-fixed, paraffin-embedded; G-CSF=granulocyte colony-stimulating factor; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HLH=hemophagocytic lymphohistiocytosis; Ig=immunoglobulin; interim resp=interim response; PCR=polymerase chain reaction; PET=positron emission tomography (scan); PK=pharmacokinetic(s); TLS=tumor lysis syndrome; Tx=treatment*

*Notes: Assessments are to be performed prior to study treatment infusion, unless otherwise specified. Pre-infusion laboratory samples should be drawn 0-24 hours prior to study treatment infusion.*

[a] *Screening and pretreatment tests and evaluations will be performed within 14 days preceding the first dose of study treatment (except for the radiographic tumor assessment, which may be performed up to 28 days preceding the first dose of study treatment, provided that no anti-tumor therapy was administered during this period). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window specified above may be used; these tests do not need to be repeated for screening.*

[b] *For Cycle 2, study treatment infusion should occur on Day 1 of the cycle but may be given ±1 day from the scheduled date (with a minimum of 20 days after the Day 1 of Cycle 1 dosing). For Cycles 3 and beyond, study treatment infusions should occur on Day 1 of each 21-day cycle but may be given ±2 days from scheduled date (with a minimum of 19 days between doses) for logistical or scheduling reasons. Other study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted.*

[c] *The end-of-treatment response assessment should occur 6 to 8 weeks after the final dose of study treatment.*

[d] *Patients who complete the treatment period will return to the clinic for a treatment completion visit 6–8 weeks after the final dose of study treatment. The end-of-treatment response assessment may be performed during this visit if it is 6–8 weeks after the final dose of study treatment.*

[e] *Patients who discontinue study drug prematurely for any reason other than disease progression should return to the clinic for a treatment discontinuation visit at 6 weeks (±2 weeks) after the last dose of study drug. The end-of-treatment response assessment can be done during this visit.*

[f] *Patients who discontinue study treatment prematurely because of disease progression should return to the clinic for a treatment discontinuation visit 28 days (±14) after their final dose of study drug. The study visit at which response assessment shows disease progression may be used as the early treatment discontinuation visit.*

[g] *Following the treatment discontinuation visit, patients will be followed for safety outcomes and survival by means of telephone calls, patient medical records, and/or clinic visits until 90 days following the final study dose (unless death, loss to follow-up, the patient withdraws consent or the Sponsor terminates the study, whichever is earliest).*

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

[i] *Concomitant medication consists of any medication used by a patient in addition to study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.*

[j] *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 final dose of study treatment or the initiation of another anti-cancer agent, whichever is earlier. Serious adverse events will be reported until 90 days after the final dose of study drug. After this period, refer to Section 5.6 for reporting requirements*

[k] *Vital signs will include measurements of respiratory rate, pulse oximetry, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated or semi-supine position, and temperature. Cycles 1 and 2 mosunetuzumab infusions: Check vital signs preinfusion, every 30 minutes (±10) during the mosunetuzumab infusion, at the end of the infusion, and 2 hours after infusion. For patients who tolerated Cycles 1 and 2 mosunetuzumab infusions without the development of an infusion-related reaction, in subsequent cycles, vital signs should be assessed preinfusion, every 60 minutes (±15) during the infusion and for 2 hours after the end of infusion. For patients who experienced an infusion-related reaction in Cycle 1, vital signs should be assessed preinfusion, every 30 minutes (±10) during the infusion, and for 2 hours after the end of infusion.*

[l] *Height and BSA are required at screening only, unless there has been >10% change in body weight since the last BSA assessment, in which case, BSA should be recalculated and documented on the eCRF. Weight will be recorded at every indicated visit.*

[m] *Complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.*

[n] *A complete neurologic examination, which includes an evaluation of mental status, cranial nerves, muscle strength, sensation, and coordination should be performed and documented in the patient chart.*

[o] *Targeted, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated.*

[p] *Single 12-lead ECG recordings will be obtained at screening and at treatment discontinuation (either early treatment discontinuation or study treatment completion) and may be obtained at unscheduled timepoints as clinically indicated per investigator discretion. All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at the same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during the ECG recording.*

[q] *CT and PET/CT scans are required at screening, Days 15-21 of Cycle 4, between Days 15 and 21 of Cycle 8 (for patients who complete treatment) or 6-8 weeks after the final dose of study treatment (for patients who discontinue treatment early). See Section 4.5.6 for details. Assess response using image-based evaluation according to 2014 Lugano Response Criteria (see Appendix 5 ). Scans should be performed according to the guidelines in the imaging manual provided to all sites.*

[r] *HBsAg, total HBcAb, HCV antibody, and HIV antibody serology are required. Patients 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. Patients must be willing to undergo monthly HBV DNA testing and appropriate antiviral therapy as indicated. Patients who are positive for the HCV antibody must be negative for HCV by PCR to be eligible for study participation.*

[s] *Quantitative PCR detection of viral infection should include EBV and CMV at screening, predose on Day 1 of Cycle 2, and at other timepoints as clinically indicated for local laboratory assessment in addition to local laboratory assessments.*

[t] *Hematology includes WBC count, hemoglobin, hematocrit, platelet count, and differential count (absolute counts of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).*

[u] *A peripheral blood smear is required at screening if not performed as part of standard-of-care tests.*

[v] *Flow cytometry assessment of B lymphocytes (CD19+ B-cell counts) will be conducted by the local laboratory.*

[w] *Serum chemistry panel: sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, calcium, magnesium, phosphate, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, LDH, and urate.*

[x] *Fibrinogen will also be collected when monitoring for specific adverse events (e.g., HLH or severe CRS) or at the discretion of the investigator.*

[y] *All women of childbearing potential will have a serum pregnancy test within 7 days prior to initiation of study treatment (Day 1 of Cycle 1). The pregnancy test for Day 1 of Cycle 1 does not need to be repeated if it was done within 7 days prior to initiation of study treatment. Pregnancy testing (urine or serum) will subsequently be performed within 24 hours prior to dosing on Day 1 of each cycle of therapy for all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.*

[z] *Availability of most recent archival tumor tissue prior to study treatment (or if unavailable, freshly biopsied tumor tissue) should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides. Where possible, tissue from these biopsies should be provided to the Sponsor for exploratory analysis. All tissue samples must have an associated pathology report. (Note: To protect tissue against oxidation and to allow immunohistochemistry [IHC] analysis in large batches, a FFPE tissue block is preferred over cut sections.)*

[aa] *See Section 4.3 for study treatment regimens and dosing.*

[bb] *Patients with high tumor burden and/or considered by the investigator to be at risk for tumor lysis should receive tumor lysis prophylaxis prior to the initiation of treatment. All patients should be well-hydrated (see Section 4.4.1.2 and Appendix 10).*

[cc] *All patients will receive G-CSF as primary prophylaxis during cycles of GemOx treatment. G-CSF should be started 1 to 2 days after GemOx infusion in each cycle. Dosing of G-CSF should otherwise follow each site's institutional standards (see Section 4.4.1.1).*

# Appendix 2
# Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

## Table 1 Pharmacokinetic and Immunogenicity Sampling Schedule: Patients in the *Glofit*-GemOx Arm Only (Arm A)

| Visit | Timepoint(s) | PK and ADA Sample Type(s) |
|---|---|---|
| Cycle 1, Day 1 | Predose of obinutuzumab [a] | • Obinutuzumab PK (serum)<br>• *Glofitamab* ADA (serum) |
| | End of obinutuzumab infusion [b] | • Obinutuzumab PK (serum) |
| Cycle 1, Day 8 | Predose *glofitamab* [a] | • Obinutuzumab PK (serum)<br>• *Glofitamab* PK (serum) |
| | End of *glofitamab* infusion [b] and 12, 24, and 48 hours postinfusion (or up to departure from hospitalization period) | • *Glofitamab* PK (serum) |
| Cycle 2, Day 1 | Predose *glofitamab* [a] | • Obinutuzumab PK (serum)<br>• *Glofitamab* PK (serum)<br>• *Glofitamab* ADA (serum) |
| | End of *glofitamab* infusion [b] and 6, 20, and 44 hours postinfusion (or the period up until departure from hospital) | • *Glofitamab* PK (serum) |
| Cycle 3, Day 1 | Predose *glofitamab* [a] | • Obinutuzumab PK (serum)<br>• *Glofitamab* PK (serum)<br>• *Glofitamab* ADA (serum) |
| | End of *glofitamab* infusion [b] | • *Glofitamab* PK (serum) |
| Cycles 4 and 5, Day 1 | Predose *glofitamab* [a] | • *Glofitamab* PK (serum)<br>• *Glofitamab* ADA (serum) |
| | End of *glofitamab* infusion [b] | • *Glofitamab* PK (serum) |
| Cycle 6, Day 1 | Predose *glofitamab* [a] | • Obinutuzumab PK (serum)<br>• *Glofitamab* PK (serum)<br>• *Glofitamab* ADA (serum) |
| | End of *glofitamab* infusion [b] | • *Glofitamab* PK (serum) |
| *Cycle 12 Day 1* | *Predose glofitamab*[a] | • *Glofitamab PK (serum)*<br>• *Glofitamab ADA (serum)* |
| | *End of glofitamab infusion*[b] | • *Glofitamab PK (serum)* |

## Table 1 Pharmacokinetic and Immunogenicity Sampling Schedule: Patients in the *Glofit*-GemOx Arm Only (Arm A) (cont.)

| Visit | Timepoint(s) | PK and ADA Sample Type(s) |
|---|---|---|
| Treatment completion [c, d] | At visit | • Obinutuzumab PK (serum)<br>• *Glofitamab* PK (serum)<br>• *Glofitamab* ADA (serum) |

ADA=anti-drug antibody; CR=complete response; GemOx=gemcitabine and oxaliplatin; IRR=infusion-related reaction; PK=pharmacokinetic; PR=partial response.

[a] Draw PK samples preinfusion ≤8 hours prior to the Day 1, Cycle 1 infusion: Draw preinfusion PK samples 0–4 hours prior to infusion for all remaining predose PK samples.

[b] Draw end-of-infusion PK samples within 0–30 minutes postinfusion

[c] Patients who complete the treatment period *or discontinue treatment early* will return to the clinic for a treatment completion visit at 6 weeks (±2) after the final dose of study drug. The end-of -treatment response assessment can be done during this visit if it is 6–8 weeks after the final dose of study treatment.

[d] Unscheduled PK samples will also be taken if there is a dose interruption, dose reduction, Grade≥3 IRR, and at the time of disease response (first timepoint of a CR or PR).

## Table 2 Pharmacokinetic and Immunogenicity Sampling Schedule: Patients in the Mosun-GemOx Arm Only (Arm B)

| Visit | Timepoint(s) | Sample Type(s) |
|---|---|---|
| Cycle 1, Day 1 | Predose of mosun [a] | • Mosun PK (serum)<br>• Mosun ADA (serum)<br>• Rituximab PK (serum) [b]<br>• Obinutuzumab PK (serum) [b] |
| | EOI of mosun (within 30 minutes after the EOI) | • Mosun PK (serum) |
| | 2 hours postinfusion of mosun | • Mosun PK (serum) |
| Cycle 1, Day 2 | Predose of GemOx[a] | • Mosun PK (serum) |
| Cycle 1, Days 8 and 15 | Predose of mosun [a] | • Mosun PK (serum) |
| | EOI (within 30 minutes) of mosun | • Mosun PK (serum) |
| Cycle 1, Days 9 and 16 | 24 hours after start of mosun infusion | • Mosun PK (serum) |
| Cycles 2– 6, Day 1 | Predose of mosun [a] | • Mosun PK (serum)<br>• Mosun ADA (serum)<br>• Rituximab PK (serum; Cycle 2 only) [b]<br>• Obinutuzumab PK (serum; Cycle 2 only) [b] |
| | EOI (within 30 minutes) of mosun | • Mosun PK (serum) |
| Treatment completion [c, d] | At visit | • Mosun PK (serum)<br>• Mosun ADA (serum) |

ADA=anti-drug antibody; CR=complete response; EOI=end of infusion; GemOx=gemcitabine and oxaliplatin; IRR=infusion-related reaction; mosun=mosunetuzumab; PK=pharmacokinetic; PR=partial response.

[a] Draw preinfusion samples within 4 hours prior to infusion.

[b] Predose serum rituximab and/or obinutuzumab PK sample for Cycles 1 and 2 is required only for patients who have received prior treatments with rituximab and/or obinutuzumab.

[c] Patients who complete the treatment period *or discontinue treatment early* will return to the clinic for a treatment completion visit at 6 weeks (±2) after the final dose of study drug. The end-of -treatment response assessment can be done during this visit if it has been 6–8 weeks after the final dose of study drug.

[d] Unscheduled PK samples will also be taken if there is a dose interruption, dose reduction, Grade≥3 IRR, and at the time of disease response (first timepoint of a CR or PR).

## Table 3 Biomarker Sampling Schedule: Patients in the *Glofit*-GemOx Arm Only (Arm A)

| Visit | Timepoint(s) | Sample Type(s) |
|---|---|---|
| Cycle 1, Day 1 | Predose of obinutuzumab [a] | • Plasma biomarkers<br>• PBMC collection |
| | 2 hours postinfusion of obinutuzumab | • Plasma biomarkers |
| Cycle 1, Day 2 | Predose of GemOx [a] | • Plasma biomarkers |
| | 2 hours postinfusion of GemOx | • Plasma biomarkers |
| Cycle 1, Day 8 | Predose of *glofitamab* [a] | • Plasma biomarkers<br>• PBMC collection |
| | 2 hours postinfusion of *glofitamab* | • Plasma biomarkers |
| Cycle 1, Day 9 | 24 hours postinfusion of *glofitamab* | • Plasma biomarkers |
| Cycle 1, Day 15 | Predose of *glofitamab* [a] | • Plasma biomarkers |
| | 2 hours postinfusion of *glofitamab* | • Plasma biomarkers |
| Cycle 1, Day 16 | 24 hours postinfusion of *glofitamab* | • Plasma biomarkers |
| Cycle 2, Day 1 | Predose of *glofitamab* [a] | • Plasma biomarkers<br>• PBMC collection |
| | Predose of GemOx [b] | • Plasma biomarkers |
| | End of GemOx infusion | • Plasma biomarkers |
| Cycle 2, Day 2 | 24 hours postinfusion of *glofitamab* | • Plasma biomarkers |
| Cycle 3, Day 1 | Predose of *glofitamab* [a] | • Plasma biomarkers |
| | Predose of GemOx [b] | • Plasma biomarkers |
| | End of GemOx infusion | • Plasma biomarkers |
| Cycle 3, Day 2 | 24 hours postinfusion of *glofitamab* | • Plasma biomarkers |
| Cycle 4, Day 1 | Predose of *glofitamab* [a] | • Plasma biomarkers<br>• PBMC collection |
| Cycle 5, Day 1 | Predose of *glofitamab* [a] | • Plasma biomarkers |
| Cycle 6, Day 1 | Predose of *glofitamab* [a] | • Plasma biomarkers<br>• PBMC collection |

GemOx=gemcitabine and oxaliplatin; PBMC=peripheral blood mononuclear cell.

[a] Draw preinfusion samples –4 hours prior to infusion.

[b] *Draw preinfusion samples 30 minutes prior to infusion.*

## Table 4 Biomarker Sampling Schedule: Patients in the Mosun-GemOx Arm Only (Arm B)

| Visit | Timepoint(s) | Sample Type(s) |
|---|---|---|
| Cycle 1, Day 1 | Predose of mosun [a] | • Plasma biomarkers<br>• PBMC collection |
| | 2 hours postinfusion of mosun | • Plasma biomarkers |
| Cycle 1, Day 2 | Predose of GemOx [a] | • Plasma biomarkers |
| | 2 hours postinfusion of GemOx | • Plasma biomarkers |
| Cycle 1, Day 8 | Predose of mosun [a] | • Plasma biomarkers |
| | 2 hours postinfusion of mosun | • Plasma biomarkers |
| Cycle 1, Day 9 | 24 hours after start of mosun infusion | • Plasma biomarkers |
| Cycle 1, Day 15 | Predose of mosun [a] | • Plasma biomarkers |
| | 2 hours postinfusion of mosun | • Plasma biomarkers |
| Cycle 1, Day 16 | 24 hours after start of mosun infusion | • Plasma biomarkers |
| Cycle 2, Day 1 | Predose of mosun [a] | • Plasma biomarkers<br>• PBMC collection |
| | Predose of GemOx [b] | • Plasma biomarkers |
| | End of GemOx infusion | • Plasma biomarkers |
| Cycle 2, Day 2 | 24 hours after start of mosun infusion | • Plasma biomarkers |
| Cycle 3, Day 1 | Predose of mosun [a] | • Plasma biomarkers |
| | Predose of GemOx [b] | • Plasma biomarkers |
| | End of GemOx infusion | • Plasma biomarkers |
| Cycle 3, Day 2 | 24 hours after start of mosun infusion | • Plasma biomarkers |
| Cycle 4, Day 1 | Predose of mosun [a] | • Plasma biomarkers<br>• PBMC collection |
| Cycle 5, Day 1 | Predose of mosun [a] | • Plasma biomarkers |
| Cycle 6, Day 1 | Predose of mosun [a] | • Plasma biomarkers<br>• PBMC collection |

GemOx=gemcitabine and oxaliplatin; mosun=mosunetuzumab; PBMC=peripheral blood mononuclear cell.

[a] Draw preinfusion samples within 4 hours prior to infusion.

[b] Draw preinfusion samples approximately 30 minutes prior to infusion.

# Appendix 3
# Schedule of Assessments for Tocilizumab Treatment of Severe or Life-Threatening Cytokine-Release Syndrome

| Assessment/Procedure [a] | Pre-TCZ Tx (within 24 hours) | TCZ Admin | Post-TCZ Treatment [b, c] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 6 hours | 1 day | 2 days | 3 days | 8 days | 8 weeks |
| TCZ administration (8 mg/kg for patients weighing ≥30 kg and 12 mg/kg for patients weighing <30 kg; doses exceeding 800 mg per infusion are not recommended) | | x | | | | | | |
| Vital signs [d] | x [e] | | Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization. [e] | | | | | |
| Pressor documentation [f] | x [e] | | Record at least every 6 hours until pressors are discontinued. [e] | | | | | |
| $FiO_2$ | x [e] | | Record at least every 6 hours until the patient is on room air. [e] | | | | | |
| Pulse oximetry (while patient is resting) | x [e] | | Measure at least every 6 hours until resolution to baseline and then every 12 hours until the end of hospitalization. [e] | | | | | |
| Local laboratory assessments | | | | | | | | |
| Hematology | x | | x | x | x | x | x | |
| Liver function tests (AST, ALT, and total bilirubin) | x | | x | x | x | x | x | |
| Serum chemistry and creatinine [g] | x | | x | x | x | x | x | |
| CRP, LDH, and serum ferritin | x | | x | x | x | x | x | |
| Coagulation (aPTT, PT/INR, and fibrinogen) | x | | x | x | x | x | x | |
| Infection workup [h] | x | | | | | | | |
| Central laboratory assessments | | | | | | | | |

| Assessment/Procedure [a] | Pre-TCZ Tx (within 24 hours) | TCZ Admin | Post-TCZ Treatment [b, c] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 6 hours | 1 day | 2 days | 3 days | 8 days | 8 weeks |
| Central laboratory assessments | | | | | | | | |
| *Serum* cytokines | x | *x* | x | x | x | x | x | |
| *Serum* IL-6 PD markers [i] | x | x [j] | x | x | x | x | x | |

ADA=anti-drug antibody; admin=administration; CRP=C-reactive protein; EBV=Epstein-Barr virus; eCRF=electronic Case Report Form; $FiO_2$=fraction of inspired oxygen; IL-6=interleukin-6; IL-6R=interleukin-6 receptor; LDH=lactate dehydrogenase; NK=natural killer; PBMC=peripheral blood mononuclear cell; PD=pharmacodynamic; TCZ=tocilizumab; Tx=treatment.

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

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

[b] If the tocilizumab dose is repeated, follow schedule following the second tocilizumab dose.

[c] For post-tocilizumab treatment timepoints: 6 hours (±30 minutes), 1 day (24 hours [±4]), 2 days (48 hours [±4]), 3 days (72 hours [±4]), and 8 days (192 hours [±48]) , and 8 weeks (56 days [±48 hours]) after completion of tocilizumab infusion.

[d] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated or supine position, and temperature.

[e] The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

[f] Document vasopressor type and dose on the Concomitant Medication eCRF.

[g] Includes sodium, potassium, chloride, bicarbonate, glucose, and BUN.

[h] Includes assessment for bacterial, fungal, and viral infections: cultures, serology tests, 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-, and NK-cell markers.

[i] Includes IL-6, soluble IL-6R, and sgp130.

[j] Blood draws for serum plasma IL-6 PD markers will be performed within 15 minutes after the end of tocilizumab infusion and will be drawn from the arm that was not used to administer tocilizumab.

# Appendix 4
# American Society for Transplantation and Cellular Therapy Cytokine-Release Syndrome Consensus Grading

| CRS Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 [d] |
|---|---|---|---|---|---|
| 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, facemask, non-rebreather mask, or Venturi mask | Requiring positive pressure (e.g., C-PAP, BiPAP, intubation, and mechanical ventilation) | |
| | | | | | Death |

BiPAP=bilevel positive airway pressure; C-PAP=continuous positive airway pressure; CRS=cytokine-release syndrome; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

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

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

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

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

[d] Grade 5 CRS is defined as death due to CRS.

# Appendix 5
# 2014 Lugano Response Criteria for Malignant Lymphoma

## TARGET AND NON-TARGET LESIONS

Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be $>$15 mm in the longest diameter (LDi). Measurable extranodal disease may be included in the six representative, measured lesions. At baseline, measurable extranodal lesions should be greater than 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as 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.

| 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 extra-lymphatic sites | Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] | Target nodes/nodal masses must regress to ≥1.5 cm in LDi |
| | It is recognized that in Waldeyer ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake. | No extralymphatic sites of disease |
| 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 |

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET/CT-Based Response | CT-Based Response |
| Partial response | Partial metabolic response | Partial remission (all of the following) |
| Lymph nodes and extra-lymphatic 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 5×5 mm as the default value |
| | At end of treatment, these findings indicate residual disease | When no longer visible, 0×0 mm<br>For a node >5×5 mm but smaller than normal, use actual measurement for calculation |
| Non-measured lesion | Not applicable | Absent or 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 |

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET/CT-Based Response | CT-Based Response |
| No response or stable disease | No metabolic response | Stable disease |
| Target nodes/nodal masses, extranodal lesions | Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment | <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met |
| Non-measured lesion | Not applicable | No increase consistent with progression |
| Organ enlargement | Not applicable | No increase consistent with progression |
| New lesions | None | None |
| Bone marrow | No change from baseline | Not applicable |

| 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 one of the following: |
| Individual target nodes/nodal masses | Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or | PPD progression |
| Extranodal lesions | New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment | An individual node/lesion must be abnormal with:<br>LDi >1.5 cm and<br>Increase by ≥50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≥2 cm<br>1.0 cm for lesions >2 cm<br>In the setting of splenomegaly (>13 cm), the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline.<br>New or recurrent splenomegaly<br>New or clear progression of preexisting non-measured lesions |
| New lesions | New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered | Regrowth of previously resolved lesions<br>A new node >1.5 cm in any axis<br>A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma<br>Assessable disease of any size unequivocally attributable to lymphoma |
| Bone marrow | New or recurrent FDG-avid foci | New or recurrent involvement |

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

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in study involving PET in which de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, 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., gastrointestinal 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.

## REFERENCES

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:1–9.

# Appendix 6
# Eastern Cooperative Oncology Group 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 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 infusion:

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

## PROCEDURES

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

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

# Appendix 8
# Management of Hemophagocytic Lymphohistiocytosis

## HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

The supportive management of hemophagocytic lymphohistiocytosis (HLH) is generally similar to that of cytokine-release syndrome (see Appendix 10 and Appendix 11). Specific diagnostic, monitoring and management guidelines for HLH are described below.

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

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (<9 g/dL)
  - Platelet count $<100\times10^9$/L (<100,000/μL)
- ANC $<1.0\times10^9$/L (<1000/μL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (<150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell (NK) activity
- Ferritin >500 mg/L (>500 ng/mL)
- Soluble interleukin-2 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

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

- Frequent (e.g., every 4 hours) vital signs and physical examination including evaluation for splenomegaly
- Serial (at least daily) monitoring of serum chemistry, CBCs, liver function tests, ferritin, PT/PTT, fibrinogen, D-dimer, and triglycerides
- Consideration of bone marrow and/or lymph node biopsy to assess for hemophagocytosis and active infection, including assessment of Epstein-Barr virus (EBV) protein localization in T, B, and NK cells
- Complete infectious disease work-up, including the following:
  - Blood cultures (bacterial and fungal)
  - Urine cultures and urinalysis

  - Radiographic assessments (e.g., chest X-ray or computed tomography scan)
  - Assessment for active viral infections, including but not limited to EBV and cytomegalovirus
- If available, assessment for soluble IL-2 receptor and assessment of NK-cell function
- DNA for exploratory genetic testing of mutations potentially associated with HLH (e.g., *PRF1*, *MUNC13-4*, and *STXBP2*) should be considered (Zhang et al. 2011)

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

**Table 1 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis**

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

HLH=hemophagocytic lymphohistiocytosis.

## REFERENCES

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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 9
# Definitions of Laboratory and Clinical Tumor Lysis Syndrome

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

TLS=tumor lysis syndrome; ULN=upper limit of normal.

Note: TLS should be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

[a] In laboratory TLS, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

[b] The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter +0.8×(4–albumin in grams per deciliter).

[c] Acute kidney injury is defined as an increase of 0.3 mg/dL (26.5 μmol/L) in creatinine level or a period of oliguria lasting 6 or more hours. By definition, if acute kidney injury is present, the patient has clinical TLS (Levin et al. 2007).

Source: Howard et al. 2011.

## REFERENCES

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364:1844–54.

Levin A, Warnock DG, Mehta RL, et al., on behalf of the Acute Kidney Injury Network Working Group. Am J Kidney Dis 2007;50:1–4. doi: 10.1053/j.aikd.2007.05.008.

# Appendix 10
# Management of Specific Adverse Events Associated with *Glofitamab*

This appendix provides guidelines for the management of patients who experience adverse events associated with *glofitamab* in the following sections:

- *Cytokine-Release Syndrome and Infusion-Related Reactions*
- *Tumor Inflammation and Tumor Flare*
- *Central Nervous System Toxicity*
- *Tumor Lysis Syndrome*
- *Elevated Liver Enzymes*

## CYTOKINE-RELEASE SYNDROME AND INFUSION-RELATED REACTION

Cytokine-release syndrome (CRS) is an identified risk for *glofitamab. Infusion-related reaction is an identified risk for obinutuzumab.* Premedication measures to reduce infusion-related reactions (IRRs) to obinutuzumab and CRS to *glofitamab* are described in Section 4.3.5.

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

*Reactions related to obinutuzumab should be recorded as IRRs.*

*Given the mechanism of action of glofitamab, IRRs and CRS may be indistinguishable from one another. Adverse events attributed to glofitamab consistent with a diagnosis of IRR or CRS, and associated with fever not attributable to any other cause, should be recorded as CRS (Lee et al. 2019).*

*It is anticipated that with the mechanism of action of T cell–bispecific treatment (i.e., glofitamab), clinical signs of symptoms of IRR and CRS will be dependent on a systemic increase of cytokines and therefore the most appropriate term for reporting is "cytokine-release syndrome."*

*Patients who experience symptoms of IRRs during obinutuzumab infusion should be managed according to the guidelines in Table 1.*

*Patients who experience symptoms of CRS during or after glofitamab infusion should be managed according to the guidelines in Table 2.*

## Table 1 Management Guidelines for Obinutuzumab-Associated Infusion-Related Reaction

| Adverse Event | Management |
|---|---|
| Grade 1 or 2 IRR (mild and moderate) | • Reduce infusion rate and treat symptoms.<br>• Upon resolution of symptoms, continue infusion.<br>• If patient does not experience any IRR symptoms, escalation of infusion rate may resume at 50-mg/hr increments every 30 minutes without exceeding 400 mg/hr. |
| Grade 3 IRR (severe) | • Temporarily interrupt infusion and treat symptoms.<br>• Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred).<br>• If patient does not experience any further IRR symptoms, escalation of infusion rate may resume at 50-mg/hr increments of every 30 minutes without exceeding 400 mg/hr. |
| Grade 4 IRR (life threatening) | • Stop infusion and permanently discontinue therapy. |

IRR=infusion-related reaction.

## Table 2 Management Guidelines for Cytokine-Release Syndrome for Patients Receiving *Glofitamab*

| CRS Grade [a] | Action with Current *Glofitamab* Infusion (If Symptoms Occur during Infusion) | Supportive Care | Anti-IL-6 or Corticosteroid Therapy | Action for Next *Glofitamab* Dose |
|---|---|---|---|---|
| Grade 1 fever [b] ≥38ºC | • Discontinue infusion.<br>• Upon symptom resolution, restart infusion at a reduced rate.<br>• If symptoms recur, discontinue infusion for this dose. | • Provide supportive therapy. [e]<br>• Monitor fluid balance; administer IV fluids if indicated.<br>• Consider hospitalization of patient until symptoms completely resolve. | • If Grade 1 symptoms are prolonged (≥ 2 days) or for patients with significant symptoms or comorbidities at the investigator's discretion (e.g., impaired cardiovascular function, reduced pulmonary reserve), consider administration of IV corticosteroids [e] and tocilizumab *(see Appendix 3)*. [f] | • Continue treatment with *glofitamab* at the next planned dose.<br>• Pre-medicate patient with acetaminophen and an antihistamine for all subsequent infusions.<br>• Consider extending infusion time (slower infusion rate) for subsequent doses.<br>• Consider hospitalization of patient for next dose. |

## Table 2 Management Guidelines for Cytokine-Release Syndrome for Patients Receiving *Glofitamab* (cont.)

| CRS Grade [a] | Action with Current *Glofitamab* Infusion (If Symptoms Occur during Infusion) | Supportive Care | Anti-IL-6 or Corticosteroid Therapy | Action for Next *Glofitamab* Dose |
|---|---|---|---|---|
| Grade 2<br><br>fever [b] ≥38° C with:<br>– Hypotension not requiring vasopressors<br><br>and/or [c]<br>– Hypoxia [d] requiring low-flow oxygen by nasal cannula or blow-by | • Discontinue infusion.<br>• Upon symptom resolution do not resume *infusion*. | • Follow Grade 1 recommendations.<br>• Monitor cardiac and organ function closely (in an ICU if appropriate); manage constitutional symptoms and *maintain fluid balance*.<br>• For hypotension: Administer IV fluid bolus as needed; for persistent refractory hypotension after two fluid boluses and anti–IL-6 therapy, start vasopressors and manage as per Grade 3.<br>• For hypoxia: Treat with oxygen.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH. | • Administer tocilizumab *(see Appendix 3)*. [f]<br>• *Administer* IV corticosteroids (e.g., methylprednisolone*or* dexamethasone every 6 hours)<br>• Manage per Grade 3 event if no improvement within 8–12 hours after starting tocilizumab. | • Patient may receive the next dose of *glofitamab* if symptoms resolve to Grade 1 or better for 3 consecutive days with approval of Medical Monitor; the dose of *glofitamab* for the subsequent administration must be discussed with the Medical Monitor.<br>• Pre-medicate patient with acetaminophen and an antihistamine for all subsequent infusions.<br>• Consider extending infusion time (slower infusion rate) for subsequent doses.<br>• Consider hospitalization of patient for next dose. |

## Table 2 Management Guidelines for Cytokine-Release Syndrome for Patients Receiving *Glofitamab* (cont.)

| CRS Grade [a] | Action with Current *Glofitamab* Infusion (If Symptoms Occur during Infusion) | Supportive Care | Anti-IL-6 or Corticosteroid Therapy | Action for Next *Glofitamab* Dose |
|---|---|---|---|---|
| Grade 3<br>fever [b] ≥ 38ºC with:<br>– Hypotension requiring a vasopressors (with or without vasopressin)<br><br>and/or [c]<br>– Hypoxia [d] requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask | • Discontinue infusion.<br>• Upon symptom resolution do not resume infusion. | • Follow Grade 1 recommendations.<br>• Recommend cardiopulmonary and organ function monitoring of patient in an ICU; administer IV fluids as clinically indicated; closely monitor and maintain fluid balance.<br>• For hypotension: Administer IV fluid bolus as needed; vasopressor support for hypotension at high and repeated doses as required.<br>• For hypoxia: Treat with oxygen.<br>• Rule out other inflammatory conditions, which can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. | • Administer tocilizumab *(see Appendix 3)*. [f]<br>• Administer IV corticosteroids (e.g., 2 mg/kg/day methylprednisolone or 10 mg IV dexamethasone every 6 hours).<br>• Manage per Grade 4 event if no improvement within 8–12 hours after the second dose of tocilizumab. | • Patient may receive the next dose of *glofitamab* if symptoms resolve to Grade 1 or better for 3 consecutive days with approval of Medical Monitor; the dose of *glofitamab* for the subsequent administration must be discussed with the Medical Monitor.<br>• Pre-medicate patient with acetaminophen and an antihistamine for all subsequent infusions.<br>• Consider extending infusion time (slower infusion rate) for subsequent doses.<br>• Consider hospitalization of patient for next dose.<br>• If symptoms recur despite premedications, with the same or greater severity at subsequent cycles, the infusion must be stopped immediately and the patient permanently discontinued from study treatment. |

## Table 2 Management Guidelines for Cytokine-Release Syndrome for Patients Receiving *Glofitamab* (cont.)

| CRS Grade [a] | Action with Current *Glofitamab* Infusion (If Symptoms Occur during Infusion) | Supportive Care | Anti-IL-6 or Corticosteroid Therapy | Action for Next *Glofitamab* Dose |
|---|---|---|---|---|
| Grade 4<br>fever [b] ≥ 38ºC with:<br>– Hypotension requiring multiple vasopressors (excluding vasopressin)<br><br>and/or [c]<br>– Hypoxia [d] requiring oxygen by positive pressure ventilation (e.g., C-PAP, BiPAP, intubation, *or* mechanical ventilation) | • Discontinue infusion of *glofitamab*.<br>• Upon symptom resolution do not resume infusion. | • Follow Grade 3 recommendations.<br>• Patient requires ICU admission for hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed.<br>• Manage organ toxicities symptomatically.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. | • Administer tocilizumab *(see Appendix 3)*. [f]<br>• Administer IV corticosteroids (e.g., 2 mg/kg/day IV methylprednisolone or 10 mg IV dexamethasone every 6 hours).<br>• For patients who are refractory to tocilizumab therapy, consider other therapies (e.g., siltuximab, anakinra, or emapalumab at the discretion of the investigator; management should be discussed with the Medical Monitor. [g] | • *Permanently discontinue glofitamab unless symptoms resolve to Grade 1 or better for 7 consecutive days and evidence of clinical benefit is present in the opinion of the investigator (such as clinical evidence of tumor shrinkage after treatment). Subsequent dosage and administration must be discussed with and approved by the Medical Monitor prior to giving glofitamab.*<br>• *Patients are required to be hospitalized for subsequent dosing until no further CRS event occurs.*<br>• *Pre-medicate patient with acetaminophen and an antihistamine for all subsequent infusions.*<br>• *Must use extended infusion time (slower infusion rate) for subsequent glofitamab doses until no CRS event occurs.*<br>• *If CRS recurs at a Grade 3 severity or higher, the glofitamab infusion must be stopped immediately and the patient permanently discontinued from study treatment.* |

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=growth colony stimulating factor; HLH=hemophagocytic lymphohistiocytosis; IRR=infusion-related reaction; ICU=intensive care unit;.

[a] CRS grading will be determined according to the ASTCT consensus grading criteria (Lee et al. 2019) (refer to Appendix 4).

[b] Fever is defined as temperature ≥ 38°C, not attributable to any other cause. In patients who develop CRS, followed by antipyretic or anticytokine therapy (e.g., tocilizumab or steroids), fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia,

[c] CRS grade is determined by the more severe event: hypotension or hypoxia, not attributable to any other cause.

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

[e] Patients should be treated with acetaminophen and an antihistamine (e.g., diphenhydramine), if they have not been administered in the previous 4 hours. Corticosteroids (e.g., 100 mg IV prednisolone, 10 mg IV dexamethasone, or equivalent) should be administered for Grade ≥2 CRS. Treat fever and neutropenia as required; consider broad-spectrum antibiotics and/or G-CSF if indicated.

[f] Tocilizumab should be administered at a dose of 8 mg/kg IV (8 mg/kg for patients weighing ≥30 kg and 12 mg/kg for patients weighing <30 kg (doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (for up to a maximum of four doses) *(see Appendix 3)*.

[g] Reference: Riegler et al. 2019.

## TUMOR INFLAMMATION AND TUMOR FLARE

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

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

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

  In case of a suspected tumor inflammation or flare event (including, but not limited to, dyspnea, increased labored breathing, hoarseness, wheezing, hypoxia), follow management guidelines summarized in Table 5. Tracheostomy should be maintained until at least Cycle 2 dose is administered, if the benefit–risk assessment is deemed favorable (i.e., if patient is receiving benefit from study treatment).

## Table 5 Management of Suspected Tumor Inflammation or Flare Event in the Oropharynx for High-Risk Patients with Bulky Lesions

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

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

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE v5.0, refer to Section 5.3.3, Table 5.

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

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

- At first administration of *glofitamab*: In case of a suspected tumor inflammation or flare event (this may include, but is not be limited to, chest pain, dyspnea, hypoxia, cyanosis, syncope, cough, palpitations) follow management guidelines summarized in Table 6. After first administration, monitor ejection fraction weekly, or with shorter intervals if clinically required. In case of clinically significant improvement in two consecutive ejection fraction measurements, stop or reduce frequency of monitoring. Weekly monitoring can also be stopped based on investigator assessment after at least one monitoring after first administration in patients with Grade 2 ejection fraction at baseline.

## Table 6 Management of Suspected Tumor Inflammation or Flare Event in the Mediastinum

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

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

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE, refer to Section 5.3.3, Table 5.

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

## Table 6 Management of Suspected Tumor Inflammation or Flare Event in the Mediastinum (cont.)

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

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

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE, refer to Section 5.3.3, Table 5.

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

For all other patients with suspected tumor inflammation or flare event, follow the recommendations in Table 7. The management guidelines refer mostly to pain and may be followed whenever pain or other symptoms occur, owing to compression of neural structures by lymphoma.

## Table 7 Management of Suspected Tumor Inflammation and Flare Event Outside the Mediastinum and Oropharynx, Applicable Whenever Pain Management Is Required for Tumor Inflammation Events

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

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

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE, refer to Section 5.3.3, Table 5.

*For patients with lesions in the gastrointestinal tract and prior to the first administration of glofitamab, consult the Medical Monitor prior to initiating treatment and evaluate anatomy of the region and the risk of gastric/colonic perforation and hemorrhage in the event of tumour flare. Individual assessment of benefits and risks should be discussed with the patient.*

## CENTRAL NERVOUS SYSTEM TOXICITY

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

Patients should be routinely assessed for any signs or symptoms of neurologic toxicity as part of the on-treatment clinical examination. If new or worsening neurologic toxicity is suspected *such as expressive aphasia, confusional state, encephalopathies, seizures, cerebral edema (Lee et al. 2019)*, the patient should be referred to a neurologist for further evaluation of potential study treatment–related neurotoxicity. Corticosteroids should be considered to treat suspected neurologic toxicity. Imaging studies should be performed if clinically indicated. Recommended management guidelines for neurotoxicity are presented in Table 8 for *glofitamab*.

For peripheral neuropathy due to oxaliplatin, refer to *Section 5.1.4, Table 3*.

**Table 8 Management of Neurotoxicity *Associated with Glofitamab***

| Event | Initial Management Recommendation | Action to Be Taken with *Glofitamab* |
|---|---|---|
| Neurotoxicity Grade 1 | • Monitor for worsening toxicity. | • Continue treatment *unless clinical situation warrants delay in therapy; consider* consultation with Medical Monitor. |
| Neurotoxicity Grade 2 or 3 | • Consider referral to neurologist.<br>• Perform imaging and other diagnostic test to ascertain etiology.<br>• Consider treatment with 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until baseline. | • Withhold *glofitamab* until recovery to Grade 1 or better.<br>• For Grade 3 event lasting >7 days, consider discontinuation.<br>• Administer *glofitamab* after consultation with Medical Monitor. |
| Neurotoxicity Grade 4 | • Follow Grade 3 recommendations.<br>• Refer patient to neurologist for appropriate management. | • Discontinue study treatment. Exceptions may be warranted upon discussion with Medical Monitor and benefit–risk considerations. |

Decisions on whether to continue or to hold *glofitamab* treatment for any Grade 1 neurotoxicity will be at the discretion of the study investigator with the approval of the Medical Monitor. For Grade ≥2 neurologic toxicity, treatment with *glofitamab* should be held until the toxicity returns to Grade 1 or better for at least 3 days without any medication. If restarting *glofitamab* following toxicity resolution, dose reduction as described in Section 5.1.7.1 may be considered. For Grade 3 neurologic toxicity lasting >7 days, the overall benefit–risk assessment of continued treatment with *glofitamab* should be assessed by the study investigator in consultation with and approval of the Medical Monitor. If Grade 3 neurologic toxicity recurs in any subsequent cycles, *glofitamab* should be permanently discontinued. *Glofitamab* should be permanently discontinued for Grade ≥3 seizures.

## TUMOR LYSIS SYNDROME

Treatment for laboratory and/or clinical presentations of tumor lysis syndrome (TLS) will follow institutional practice. Prior to each treatment given during Cycles 1 and 2, the patient's serum chemistry and hematologic laboratory samples should be obtained and

reviewed and prophylactic measures initiated according to Section 4.4.1.2. Access to nephrology consultation with acute dialysis services must be available in the event of clinically significant TLS.

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

If the Howard criteria for TLS (see Appendix 9) (Howard et al. 2011) are fulfilled at any time during the study (two or more electrolyte laboratory abnormalities present simultaneously) or if there is a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g., increased serum creatinine or cardiac dysrhythmia), study treatment should be withheld and patients should be hospitalized and adequately treated until normalization of laboratory abnormalities before treatment is restarted.

## ELEVATED LIVER ENZYMES

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

LFTs will be assessed regularly during study and should be managed according to guidelines in Table 9 for *glofitamab*.

*Manage gemcitabine and oxaliplatin as per local prescribing information.*

## *Table* 9 Management of Liver Function Test Abnormalities

| Abnormality | Action to Be Taken |
|---|---|
| AST/ALT >10× ULN, with total bilirubin ≤2× ULN | • Hold *glofitamab*.<br>• Consult hepatologist.<br>• Monitor LFTs *per clinical discretion*.<br>• Consider restarting *glofitamab* after discussion with the Medical Monitor if AST/ALT ≤*10*·× ULN with bilirubin <2×ULN.<br><br>Permanently discontinue *glofitamab* for life-threatening immune-related hepatic events. |
| AST/ALT >3× ULN, with total bilirubin >2× ULN | • Hold *glofitamab*.<br>• Consult hepatologist.<br>• Monitor LFTs *per clinical discretion*.<br>• Consider restarting *glofitamab* after discussion with the Medical Monitor if AST/ALT ≤3× ULN with bilirubin <2× ULN.<br>• Permanently discontinue *glofitamab for life-threatening immune*-related hepatic events.<br><br>*Any case involving an increase in AST/ALT > 3 × ULN AND an increase in direct bilirubin > 2 × ULN (WITHOUT any findings of cholestasis) or jaundice or signs of hepatic dysfunction AND in the absence of other contributory factors (e.g., worsening of metastatic disease, concomitant CRS, concomitant exposure to known hepatotoxic agent, or a documented infectious etiology) is suggestive of potential DILI, and drug should be discontinued.* |

LFT=liver function test; ULN=upper limit of normal.

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# Appendix 11
# Management Guidelines for Specific Adverse Events Associated with Mosunetuzumab

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

## CYTOKINE-RELEASE SYNDROME

Cytokine-release syndrome (CRS) is an identified risk for mosunetuzumab.

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

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

If a patient experiences an isolated episode of fever within 24 hours after infusion of mosunetuzumab, not accompanied by other IRR-like symptoms as described above, the adverse event reporting term will be fever and not CRS. Table 1 presents management guidelines for CRS and IRRs for patients receiving mosunetuzumab.

## Table 1 Recommendations for Management of Infusion-Related Reactions and Cytokine-Release Syndrome for Patients Receiving Mosunetuzumab

| CRS Grade [a] | Action with Current Mosunetuzumab Infusion | Supportive Care | Anti–IL-6 or Corticosteroid Therapy | Action for Next Mosunetuzumab Dose |
|---|---|---|---|---|
| Grade 1<br>fever ≥ 38ºC | • Slow infusion to ≤ 50% or interrupt infusion until symptoms resolve; re-start at same rate.<br>• If symptoms recur with rechallenge, interrupt study treatment, do not resume, and manage per Grade 2. | • Symptomatic management of constitutional symptoms and organ toxicities.<br>• Consider empiric broad-spectrum antibiotics.<br>• Consider G-CSF if patient is neutropenic.<br>• Maintenance IV fluids for hydration.<br>• Consider hospitalization until symptoms completely resolve. | • For prolonged CRS (> 2 days) in patients with significant symptoms and/or comorbidities (per investigator discretion, e.g., impaired cardiovascular function, reduced pulmonary reserve), consider tocilizumab and corticosteroids as per Grade 2. | • Administer premedications for next dose per Section 4.3.5.3<br>• Consider 50% (or lower) rate of infusion for next step-up dose in Cycle 1 or 50% rate of infusion if next dose is same dose level (beyond Cycle 1).<br>• Consider hospitalization of patient for next dose. |
| Grade 2<br>fever ≥ 38ºC<br>with hypotension not requiring vasopressors<br>and/or<br>hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by | • Hold further study treatment until symptoms resolved; consider re-starting infusion at 50% rate.<br>• If symptoms recur with rechallenge at decreased infusion rate, interrupt study treatment, do not resume, and manage per Grade 3. | • Symptomatic management of constitutional symptoms and organ toxicities.<br>• Consider ICU admission for hemodynamic monitoring.<br>• For hypotension: IV fluid bolus as needed; for persistent refractory hypotension (e.g., after two fluid boluses and anti-IL-6 therapy), start vasopressors and manage per Grade 3.<br>• Rule out other inflammatory conditions, which can mimic severe CRS (e.g., infections/ sepsis). | • Consider tocilizumab. [c]<br>• For persistent refractory hypotension after one or two doses of anti–IL-6 therapy, consider 10 mg IV dexamethasone every 6 hours (or equivalent). | • May receive the next dose of mosunetuzumab if symptoms resolve to Grade 1 or better for 3 consecutive days with approval of Medical Monitor.<br>• Consider enhanced premedications for next dose.<br>• Consider 50% (or lower) rate of infusion for next step-up dose in Cycle 1 or 50% rate of infusion if next dose is same dose level (beyond Cycle 1).<br>• Consider hospitalization of patient for next dose. |

## Table 1 Recommendations for Management of Infusion-Related Reactions and Cytokine-Release Syndrome for Patients Receiving Mosunetuzumab (cont.)

| CRS Grade [a] | Action with Current Mosunetuzumab Infusion | Supportive Care | Anti–IL-6 or Corticosteroid Therapy | Action for Next Mosunetuzumab Dose |
|---|---|---|---|---|
| Grade 2 (cont.)<br>fever ≥ 38ºC<br>with hypotension not requiring vasopressors<br>and/or<br>hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by | | Consider empiric broad-spectrum antibiotics.<br>If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH as described in Appendix 8. | Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab. | |
| Grade 3<br>fever ≥38ºC<br>with hypotension requiring a vasopressor (with or without vasopressin)<br>and/or<br>hypoxia requiring high flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask | Stop infusion, do not resume. | Symptomatic management of organ toxicities, admit patient to ICU for hemodynamic monitoring.<br>For hypotension: IV fluid bolus and vasopressors as needed.<br>Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis).<br>Consider empiric broad-spectrum antibiotics.<br>If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH (see Appendix 8). | Administer tocilizumab [x]<br>Dexamethasone 10 mg IV every 6 hours (or equivalent).<br>If refractory, manage as per Grade 4. [c]<br>Manage per Grade 4 if no improvement within 18–24 hours after second dose of tocilizumab. | May receive the next dose of mosunetuzumab if CRS event was responsive to treatment (i.e., clinical improvement within 8–12 hours following tocilizumab/corticosteroids administration) and symptoms resolve to Grade ≤ 1 for 3 consecutive days with approval of Medical Monitor:<br>– Enhanced premedications for next dose<br>– Decrease to 50% (or lower) rate of infusion for next step-up dose in Cycle 1, or 50% rate of infusion if next dose is same dose level (beyond Cycle 1)<br>– Hospitalize patient for next dose.<br>– If Grade 3 CRS recurs with subsequent doses, consider permanent discontinuation. |

## Table 1 Recommendations for Management of Infusion-Related Reactions and Cytokine-Release Syndrome for Patients Receiving Mosunetuzumab (cont.)

| CRS Grade [a] | Action with Current Mosunetuzumab Infusion | Supportive Care | Anti–IL-6 or Corticosteroid Therapy | Action for Next Mosunetuzumab Dose |
|---|---|---|---|---|
| Grade 4<br>fever ≥ 38°<br>with hypotension requiring multiple vasopressors (excluding vasopressin)<br>and/or<br>hypoxia requiring oxygen by positive pressure (e.g., C-PAP, BiPAP, intubation, and mechanical ventilation) | • Stop infusion, do not resume. | • ICU admission and hemodynamic monitoring.<br>• Mechanical ventilation as needed.<br>• IV fluids and vasopressors as needed.<br>• Symptomatic management of organ toxicities.<br>• Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis)<br>• Consider empiric broad-spectrum antibiotics.<br>• If no improvement within 24 hours, initiate work up and assess for signs and symptoms HLH (see Appendix 8). | • Administer tocilizumab. [c]<br>• For patients refractory to tocilizumab, consider siltuximab, anakinra, and emapalumab, based on discretion of the investigator; management should be discussed with the Medical Monitor. [d]<br>• Administer 10 mg IV dexamethasone every 6 hours (or equivalent).<br>• If refractory, consider 1000 mg/day IV methylprednisolone. [e, f] | • Permanently discontinue mosunetuzumab. |

## Table 1 Recommendations for Management of Infusion-Related Reactions and Cytokine-Release Syndrome for Patients Receiving Mosunetuzumab (cont.)

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; C-PAP=continuous positive airway pressure; CRS=cytokine-release syndrome; G-CSF=granulocyte colony-stimulating factor; HLH=hemophagocytic lymphohistiocytosis; ICU=intensive care unit; IL-6=interleukin-6.

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

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

.[c] Tocilizumab should be administered by IV infusion at a dose of 8 mg/kg (8 mg/kg for patients weighing ≥ 30 kg only and 12 mg/kg for patients weighing < 30 kg; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (for up to a maximum of 4 doses). Refer Appendix 3 for schedule of activities for tocilizumab treatment of CRS.

[d] Riegler et al. 2019.

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

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

## TUMOR INFLAMMATION AND TUMOR FLARE

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

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

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

  In case of a suspected tumor inflammation or flare event (including, but not limited to, dyspnea, increased labored breathing, hoarseness, wheezing, hypoxia), follow management guidelines summarized in Table 4. Tracheostomy should be maintained until at least Cycle 2 dose is administered, if the benefit–risk assessment is deemed favorable (i.e., if patient is receiving benefit from study treatment).

## Table 4 Management of Suspected Tumor Inflammation or Flare Event in the Oropharynx for High-Risk Patients with Bulky Lesions

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

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

[a] Grade of triggering event dependent on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE v5.0, refer to Section 5.3.3, Table 5.

For patients with mediastinal lymphoma around the heart and big vessels (including primary mediastinal B-cell lymphoma):

- Before first administration of study treatment: Consult with the Medical Monitor prior to initiating treatment. Obtain cardiology consultation and evaluate cardiac ejection fraction at baseline. Map bulky lesions whose enlargement may create acute impairment of organ function and plan emergency measures if deemed necessary (e.g., access to urgent echocardiography and other imaging, pericardiocentesis, if required). An analogous intervention of tracheostomy for upper airway obstruction may not be readily available for patients who may experience compression of critical structures in the mediastinum owing to surrounding mass effect; as such, the individual benefit–risk assessment should be discussed with the patient.
- At first administration of mosunetuzumab: In case of a suspected tumor inflammation or flare event (this may include, but is not be limited to, chest pain, dyspnea, hypoxia, cyanosis, syncope, cough, palpitations) follow management guidelines summarized in Table 5. After first administration, monitor ejection

fraction weekly, or with shorter intervals if clinically required. In case of clinically significant improvement in two consecutive ejection fraction measurements, stop or reduce frequency of monitoring. Weekly monitoring can also be stopped based on investigator assessment after at least one monitoring after first administration in patients with Grade 2 ejection fraction at baseline.

## Table 5 Management of Suspected Tumor Inflammation or Flare Event in the Mediastinum

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

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

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE, refer to Section 5.3.3, Table 5.

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

## Table 5 Management of Suspected Tumor Inflammation or Flare Event in the Mediastinum (cont.)

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

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

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE, refer to Section 5.3.3, Table 5.

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

For all other patients with suspected tumor inflammation or flare event, follow the recommendations in Table 6. The management guidelines refer mostly to pain and may be followed whenever pain or other symptoms occur, owing to compression of neural structures by lymphoma.

## Table 6 Management of Suspected Tumor Inflammation and Flare Event Outside the Mediastinum and Oropharynx, Applicable Whenever Pain Management Is Required for Tumor Inflammation Events

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

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

[a] Grade of triggering event depends on presenting signs and symptoms of tumor inflammation; for events not specifically listed in NCI CTCAE, refer to Section 5.3.3, Table 5.

## CENTRAL NERVOUS SYSTEM TOXICITY

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

Patients should be routinely assessed for any signs or symptoms of neurologic toxicity as part of the on-treatment clinical examination. If new or worsening neurologic toxicity is suspected, the patient should be referred to a neurologist for further evaluation of potential study treatment–related neurotoxicity. Corticosteroids should be considered to treat suspected neurologic toxicity. Imaging studies should be performed if clinically indicated. Recommended management guidelines for neurotoxicity are presented in Table 7 for mosunetuzumab.

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

- Patients with risk factors at baseline:

  For patients with the combination of aggressive non-Hodgkin's lymphoma (NHL) (including diffuse large B-cell lymphoma, transformed follicular lymphoma (FL), FL, Grade 3b primary mediastinal B-cell lymphoma, mantle cell lymphoma, transformed marginal zone lymphoma) and abnormal (above institutional upper limit of normal), and C-reactive protein at screening, the investigator should advise patients to refrain from driving or engaging in hazardous occupations or activities during Cycles 1 and 2 (approximately 6 weeks).

- Patients who develop specific adverse events during mosunetuzumab treatment:

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

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

### Neurologic Adverse Events that May Affect Driving

Patients should be advised by the study investigator of potential neurologic toxicity, which may include seizures and alterations of consciousness.

Neurologic adverse events with the potential to impact cognition or consciousness that may affect driving (driving-impacting cognition or consciousness neurologic events [DI-CCNAE]) include, but are not limited to, amnesia, aphasia, confusional state, delirium, depressed level of consciousness, disturbance in attention, encephalopathy, hallucination, hepatic encephalopathy, insomnia, memory impairment, seizure, visual hallucination, and vertigo.

Neurologic adverse events with the potential to impact cognition or consciousness (cognition or consciousness neurologic events [CCNAE]) may include, but are not limited to, dizziness, insomnia, postural dizziness, and tremor. Patients with CCNAEs or Grade≥3 neurologic adverse events should be assessed by neurologic examination to evaluate risk of impairment for driving or engaging in hazardous occupations or activities. When necessary, consult the Medical Monitor and obtain neurology consultation for evaluation of neurologic events that have the potential to impact cognition or consciousness.

For peripheral neuropathy due to oxaliplatin, refer to Section 5.1.7.1, Table 4.

Management of neurotoxicity associated with mosunetuzumab is presented in Table 7.

## Table 7 Management of Neurotoxicity (Mosunetuzumab)

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

## Table 7 Management of Neurotoxicity (Mosunetuzumab) (cont.)

| Event | Management |
|---|---|
| Neurologic event, not otherwise specified, [b] Grade 4 | • Notify Medical Monitor.<br>• Permanently discontinue mosunetuzumab.<br>• Obtain neurology consultation. |

MRI=magnetic resonance imaging.

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

[b] Table 7 does not apply to peripheral neuropathy.

**TUMOR LYSIS SYNDROME**

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

As mosunetuzumab has the potential for B-cell killing, the potential risk of TLS in all patients must be considered, along with the need for prophylaxis for TLS prior to the initiation of mosunetuzumab. Owing to the potential risk of TLS following administration of study treatment, patients must have a creatinine clearance ≥40 mL/min to participate in this trial.

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

- Hydration, consisting of a fluid intake of approximately 2–3 L/day starting 24–48 hours prior to the first dose of mosunetuzumab

  If a patient is hospitalized for the administration of study treatment, IV hydration at a rate of 150–200 mL/hr should begin at the conclusion of mosunetuzumab administration and continue for at least 24 hours thereafter.

  If a patient receives study treatment in the outpatient setting, fluid intake should be maintained at 2–3 L/day for at least 24 hours after mosunetuzumab administration.

  Modification of fluid rate should be considered for individuals with specific medical needs.

- Mandatory administration of an agent to reduce uric acid:

  Allopurinol (e.g., 300 mg/day orally beginning 72 hours prior to dose and continuing for 3–7 days afterward) should be administered for those patients judged to be of low or intermediate risk of developing TLS.

  For patients with elevated uric acid levels prior to mosunetuzumab treatment or considered to be at high risk for TLS: rasburicase (e.g., 0.2 mg/kg IV over 30 minutes prior to first dose mosunetuzumab and daily for up to 5 days thereafter) should be administered, unless contraindicated (Elitek® [rasburicase] U.S. Package Insert).

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

  If treatment with allopurinol or rasburicase is contraindicated or is otherwise inappropriate in the view of the investigator, the Medical Monitor should be contacted for further guidance.
- Laboratory monitoring during tumor lysis prophylaxis should follow institutional practice and the investigator's judgment.
- Note that uric acid measurement in the presence of rasburicase administration requires special handling (Elitek U.S. Package Insert).
- Telemetry should be considered for patients at high risk for TLS

Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities prior to the administration of mosunetuzumab in Cycles 1 and beyond, otherwise the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing. Laboratory abnormalities suggestive of TLS should prompt immediate action by the treating clinicians, and TLS should be treated aggressively per institutional practice.

Patients at high risk for TLS should continue to receive prophylaxis with allopurinol or rasburicase and adequate hydration with each subsequent dose of mosunetuzumab until the patient is no longer considered to be at risk for TLS. Patients who develop either clinical or laboratory TLS during Cycle 1 should be considered for hospitalization during subsequent cycles for optimum hydration and monitoring; such cases should be discussed with the Medical Monitor.

If the Howard criteria for TLS (see Appendix 9) (Howard et al. 2011) are fulfilled at any time during the study (two or more electrolyte laboratory abnormalities present simultaneously) or if there is a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g., increased serum creatinine or cardiac dysrhythmia), study treatment should be withheld and patients should be hospitalized

and adequately treated until normalization of laboratory abnormalities before treatment is restarted.

## ELEVATED LIVER ENZYMES

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

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

LFTs will be assessed regularly during study and should be managed according to guidelines in Table 8 for mosunetuzumab.

## Table 8 Management of Liver Function Test Abnormalities (Mosunetuzumab)

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

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

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

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

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