**Official Title:** A Phase II Study Evaluating the Safety and Efficacy of Glofitamab in Combination with Rituximab (R) Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) in Circulating Tumor (ct)DNA High-Risk Patients with Untreated Diffuse Large B-Cell Lymphoma

**NCT Number:** NCT04980222

**Document Date:** Protocol Amendment Version 4: 17-Oct-2023

# PROTOCOL

| | |
|---|---|
| **PROTOCOL TITLE:** | **A PHASE II STUDY EVALUATING THE SAFETY AND EFFICACY OF GLOFITAMAB IN COMBINATION WITH RITUXIMAB (R) PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (CHOP) IN CIRCULATING TUMOR (ct)DNA HIGH-RISK PATIENTS WITH UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA** |
| **PROTOCOL NUMBER:** | GO43075 |
| **VERSION NUMBER:** | 4 |
| **TEST COMPOUNDS:** | Glofitamab (RO7082859),<br>Tocilizumab (RO4877533) |
| **STUDY PHASE:** | Phase II |
| **REGULATORY AGENCY IDENTIFIER NUMBERS:** | IND Number: 138178<br>EudraCT Number: 2021-001647-28<br>E*U CT Number*: *2023-504994-19-00*<br>CIV ID: To be determined<br>NCT Number: 04980222 |
| **SPONSOR NAME AND LEGAL REGISTERED ADDRESS:** | F. Hoffmann-La Roche Ltd<br>Grenzacherstrasse 124<br>4070 Basel, Switzerland |
| **APPROVAL:** | See electronic signature and date stamp on the final page of this document. |

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## PROTOCOL HISTORY

| Protocol | | Associated Country and/or Region-Specific Protocols | | |
|---|---|---|---|---|
| **Version** | **Date Final** | **Country and/or Region** | **Version** | **Date Final** |
| 4 | See electronic date stamp on final page of this document | United States | 3 | To be determined |
| 3 | 18 November 2022 | France | 2 | 23 February 2023 |
| | | United States | 2 | 18 November 2022 |
| 2 | 22 June 2021 | France | 1 | 26 January 2023 |
| | | United States | 1 | 12 November 2021 |
| 1 | 26 March 2021 | — | — | — |

## PROTOCOL AMENDMENT, VERSION 4:
## RATIONALE

Protocol GO40375 has been primarily amended to align with the latest Clinical Trials Regulation (CTR) requirements and with the Glofitamab program language. Changes to the protocol, along with a rationale for each change, are summarized below.

The following changes have been implemented to align with the Glofitamab program language:

- The schedule of activities has been updated to include severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing by antigen or PCR within 7 days prior to enrollment to determine study eligibility (Section 1.3 Table 1).
- HIV language has been updated to clarify the viral monitoring plan for this population given the potential risks associated with use of glofitamab (Section 1.3 Table 1 and Appendix A.6-1.1.6).
- The benefit-risk assessment related to COVID-19 section has been updated to include cytokine release syndrome (CRS) as a risk for glofitamab that occurs most commonly during step-up dosing, and the risk of COVID-19 vaccines potentiating CRS is unknown (Section 2.3).
- An exclusion criterion of a positive SARS-CoV-2 test within 7 days prior to enrollment (including rapid antigen test) has been added (Section 5.2).
- Additional language has been added in the Permitted Therapy section regarding recommendations on SARS-CoV-2 infection prophylaxis, vaccinations, and treatment (Section 6.8.1).
- Additional terms (i.e., acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia, and/or pulmonary toxicity) have been added to the Adverse Events of Special Interest section (Section 8.2.8).
- Additional language has been added to the Infections section to include recommendations for SARS-CoV-2 risk management, to provide guidance on study treatment interruption and resumption during and after a SARS-CoV-2 infection, and to emphasize that glofitamab should not be administered in the presence of an active infection (Appendix 6, Section A6-1.1.6).
- The footnote in the CRS management table and Schedule of Assessments for tocilizumab treatment of CRS has been updated to maintain tocilizumab exposures within established clinical boundaries for the safety and efficacy of tocilizumab (Appendix 6, A6-2.3.1 Table 1 and Appendix 7, Tables 1 and 2).
- Management guidelines for suspected tumor flare event in the mediastinum for patients with Grade ≤ 2 ejection fraction decrease at baseline was amended to remove prophylactic tracheostomy and to align with glofitamab program language (Appendix 6, A6-2.3.2 Table 3).

The following changes have been implemented to align with the latest CTR requirements:

- The synopsis has been further simplified to align with CTR and other guidelines

- Additional screening inclusion criteria regarding SARS-CoV-2 testing and vaccination status included for patients enrolled in France previously in GO43075 France v2 (Section 5.1.1)
- Additional SARS-CoV-2 viral prophylaxis measures included for patients enrolled in France previously in GO43075 France v2 (Section 6.1.5.2)
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 8.2.4)
- Appendix 17 has been revised to reflect a comprehensive list of investigational medicinal products and auxiliary medicinal products to align with CTR requirements.

In addition, the following changes have also been implemented:

- Survival follow-up has been extended to 24 months after end of treatment in order to adequately assess the secondary endpoint of progression free survival ([PFS]; Section 1.3, Table 1; Sections 4.7, 4.8)
- Definition of PFS has been clarified to include death due to any cause, to align with the definition in Section 9.4.3 (Section 3)
- CNS prophylaxis language has been updated to allow for administration of either intrathecal or high-dose methotrexate as part of the pre-planned therapy for a participant (Section 6.1.5.6)
- Clarification of reporting criteria to state that serious adverse events and adverse events of special interest will not be reported after the initiation of next anti-lymphoma therapy has been added (Appendix 3, Section A3-5.2)
- Appendix 6 has been updated to include that glofitamab is approved for treatment of patients with relapsed or refractory DLBCL after two or more lines of systemic therapy in certain regions
- Modifications has been made to the Cockcroft-Gault Formula to include weight instead of ideal body weight to align with clinical practice (Appendix 16)

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

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## PROTOCOL AMENDMENT ACCEPTANCE FORM

| | |
|---|---|
| **PROTOCOL TITLE:** | **A PHASE II STUDY EVALUATING THE SAFETY AND EFFICACY OF GLOFITAMAB IN COMBINATION WITH RITUXIMAB (R) PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (CHOP) IN CIRCULATING TUMOR (ct)DNA HIGH-RISK PATIENTS WITH UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA** |
| **PROTOCOL NUMBER:** | GO43075 |
| **VERSION NUMBER:** | 4 |
| **TEST COMPOUNDS:** | Glofitamab (RO7082859), Tocilizumab (RO4877533) |
| **SPONSOR NAME:** | F. Hoffmann-La Roche Ltd |

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

# 1. PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| PROTOCOL TITLE: | **A PHASE II STUDY EVALUATING THE SAFETY AND EFFICACY OF GLOFITAMAB IN COMBINATION WITH RITUXIMAB (R) PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (CHOP) IN CIRCULATING TUMOR (ct)DNA HIGH-RISK PATIENTS WITH UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA** |
| *REGULATORY AGENCY IDENTIFIERS:* | *IND Number: 138178*<br>*EudraCT Number: 2021-001647-28*<br>*EU CT Number: 2023-504994-19-00*<br>*CIV ID: To be determined*<br>*NCT Number: 04980222* |

**STUDY RATIONALE**

The purpose of this study is to assess the safety, efficacy, and pharmacokinetics of glofitamab in combination with *rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone* (R-CHOP) in *circulating –tumor DNA* (ctDNA) high-risk patients. ctDNA high-risk patients are those who fail to achieve ≥2 log-fold reduction in ctDNA levels between Day [redacted] of Cycle [redacted] Day [redacted] ([redacted]) and Day [redacted] of Cycle [redacted] ctDNA is a novel biomarker that offers the potential for an early, sensitive approach to identifying patients with *diffuse large B-cell lymphoma* (DLBCL) at a higher risk of front-line treatment failure.

In the front-line setting, a subset of patients with DLBCL have poor outcomes following treatment with R-CHOP immunochemotherapy. Despite this, R-CHOP remains the *standard-of-care* (SOC) treatment for DLBCL. Efforts to define baseline prognostic scores and develop biomarkers to improve on the *International Prognostic Index* (IPI) and to guide treatment decisions have so far proved unsuccessful.

In contrast to current baseline prognostic factors, ctDNA has the distinct advantage of permitting dynamic assessments early during a patient's treatment journey and in so doing, identify newly diagnosed individuals with suboptimal responses to immunochemotherapy who will likely progress in the absence of a change in treatment strategy and therefore may benefit from therapy intensification with glofitamab.

**OBJECTIVES AND ENDPOINTS**

This Phase II, open-label, multicenter study, will evaluate the safety, efficacy, and pharmacokinetics of glofitamab in combination with R-CHOP in individuals with ctDNA high-risk DLBCL in the first-line setting. Specific objectives and corresponding endpoints for the study are outlined in the following table.

In this protocol, "study treatment" refers to the combination of treatments assigned to participants as part of this study (i.e., R-CHOP, with or without glofitamab).

**Objectives and Corresponding Endpoints**

| Primary Objective | Corresponding Endpoint |
|---|---|
| • To evaluate the efficacy of glofitamab in combination with R-CHOP in ctDNA high-risk patients with previously untreated DLBCL | • EOT CR rate, as determined by the investigator according to the 2014 Lugano Response Criteria for Malignant Lymphoma (hereafter referred to as the 2014 Lugano Response Criteria) |
| **Secondary Objectives** | **Corresponding Endpoints** |
| • To evaluate the efficacy of glofitamab in combination with R-CHOP in ctDNA high-risk patients with previously untreated DLBCL | • ORR at the EOT, as determined by the investigator according to the 2014 Lugano Response Criteria<br>• PFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, according to the 2014 Lugano Response Criteria *or death due to any cause, whichever occurs first, as determined by the investigator*<br>• OS, defined as the time from the first study treatment to death from any cause |
| • To evaluate the safety of glofitamab in combination with R-CHOP in ctDNA high-risk participants with DLBCL | • Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0<br>For CRS, severity will be determined according to the ASTCT CRS Consensus Grading.<br>• Tolerability, as assessed by dose modifications, dose intensity, and study treatment discontinuation because of adverse events |
| • To characterize the serum PK profile of glofitamab in combination with R-CHOP | • Serum concentrations of glofitamab at specified timepoints<br>• Serum trough concentrations of glofitamab at specified timepoints<br>• Glofitamab PK parameters (e.g., $C_{max}$, AUC), as appropriate |
| • To evaluate potential effects of ADAs | • Relationship between ADA status and efficacy, safety, or PK endpoints |

ADA = anti-drug antibody; aLugano = automated response per 2014 Lugano Response Criteria; ASTCT = American Society for Transplantation and Cellular Therapy; AUC = area under the concentration-time curve; $C_{max}$ = maximum concentration; CR = complete response; CRS = cytokine-release syndrome; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating-tumor DNA; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EOT = end of treatment; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetic; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone;.

## OVERALL DESIGN *AND STUDY POPULATION*

This is a Phase II, multicenter study evaluating the safety and efficacy of glofitamab in combination with R-CHOP immunochemotherapy in high-risk individuals with untreated DLBCL, as assessed by ctDNA. Patients will be classified as being high risk of R-CHOP treatment failure if they demonstrate a < 2-log (100 ×-fold) decrease in ctDNA levels between baseline (prior to Day [redacted] of Cycle [redacted] and following [redacted] treatment cycle of R-CHOP (prior to Day [redacted] of Cycle [redacted]) using the experimental [redacted].

ctDNA high-risk patients will enroll in the study prior to Cycle [redacted] of Day [redacted] and commence step-up doses (2.5 mg, 10 mg, and 30 mg) of glofitamab, starting on Day 8 of Cycle 3.

For the purposes of this study, individuals who achieve at least a 2-log–fold reduction in ctDNA levels between baseline (prior to Day [redacted] of Cycle [redacted]) and following [redacted] treatment cycle of R-CHOP therapy (prior to Day [redacted] of Cycle [redacted] are considered to be at lower risk of R-CHOP treatment failure and will not be eligible for enrollment or rescreening.

For enrollment in Cycle [redacted] eligible patients will be treated with SOC doses of R-CHOP from Cycle [redacted] During Cycles [redacted] participants will be treated with R-CHOP in combination with glofitamab and will receive glofitamab monotherapy as consolidation during Cycles [redacted] PET/CT scans will be performed at the end of treatment (EOT), and an early interim PET/CT response assessment will be conducted following Cycle [redacted] results will be used to evaluate the correlation between imaging results and ctDNA levels.

*Several key aspects of the study design and study population are summarized below.*

| | | | |
|---|---|---|---|
| ***Phase:*** | *Phase II* | ***Population Type:*** | *Adult patients* |
| ***Control Method:*** | *None* | ***Population Diagnosis or Condition:*** | *Diffuse Large B-Cell Lymphoma* |
| ***Interventional Model:*** | *Single Group* | ***Population Age:*** | *≥18 years* |
| ***Test Products}:*** | *Glofitamab, Tocilizumab* | ***Site Distribution:*** | *multi-site and multi-region* |
| ***Active Comparator:*** | *None* | ***Study Treatment Assignment Method:*** | *None* |
| ***Number of Arms:*** | *1* | ***Number of Participants to Be Enrolled:*** | *Up to [redacted] patients screened in order to identify approximately [redacted] of ctDNA high-risk patients ([redacted]) a of the population in the first-line setting)* [a] |

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

## STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are glofitamab and tocilizumab. R-CHOP and any corticosteroid pretreatment are considered non-investigational medicinal products. CNS prophylaxis with intrathecal methotrexate, prophylaxis for neutropenia with granulocyte colony-stimulating factors (G-CSFs), and dexamethasone are also considered non-investigational medicinal products.

### GLOFITAMAB

Glofitamab will be administered on a step-up dosing schedule, starting on Day 8 of Cycle 3 (2.5 mg), Day 15 of Cycle 3 (10 mg), followed by 30 mg on Day 8 of Cycles 4–6 and Day 1 of Cycles 7–10, with each cycle being 21 days in length (i.e., every 3 weeks).

### TOCILIZUMAB

Tocilizumab will be administered as a rescue IMP when necessary to participants who experience a CRS event.

**RITUXIMAB**

Rituximab (375 mg/m$^2$) will be administered intravenously to participants every 21 days along with *cyclophosphamide, doxorubicin, vincristine, and prednisone* (CHOP). A locally approved standard-of-care biosimilar rituximab is permitted.

**CHOP CHEMOTHERAPY**

CHOP chemotherapy consists of IV cyclophosphamide, IV doxorubicin, vincristine administered by IV push, and oral prednisone or prednisolone. Standard CHOP will be administered for six 21-day cycles (including Cycles 1 and 2 during ctDNA screening) as follows:

- Cyclophosphamide: 750 mg/m$^2$ administered intravenously on Day 1
- Doxorubicin: 50 mg/m$^2$ administered intravenously or according to institutional guidelines on Day 1
- Vincristine: 1.4 mg/m$^2$ administered by IV push on Day 1 at a recommended cap of 2 mg
- Prednisone: 100 mg/day orally on Days 1–5 (prednisone on Day 1 may be administered intravenously, with the remaining doses on Days 2–5 to be administered orally)

At the discretion of the investigator, the dose of vincristine may be capped at 2 mg. For participants who are $\geq$70 years old, the dose of vincristine may be capped at 1.5 mg. Body surface area may be capped at 2 m$^2$ per institutional standards.

When rituximab and CHOP are scheduled to be administered on the same day, it is recommended that prednisone (100 mg) be given prior to the rituximab infusion.

**INTRATHECAL METHOTREXATE**

CNS prophylaxis with intrathecal methotrexate is recommended (but not mandated) in patients with a high-risk CNS IPI (defined as four or more of the following risk factors: age $>$60 years, Stage III or IV disease, more than two extranodal sites, the longest diameter greater than upper limit of normal, or kidney or adrenal gland involvement) and may be included as part of the planned protocol for a patient at the discretion of the treating investigator. If CNS prophylaxis is administered, the dose and schedule should be documented clearly and administered according to local guidelines.

**GRANULOCYTE COLONY-STIMULATING FACTOR**

In order to minimize the rate, severity, and duration of neutropenia-related complications, all participants should receive primary prophylaxis with G-CSF during Cycles 1–6.

Use of G-CSF is mandatory during Cycles 3–6 with either one of the following:

- Filagrastim: 5 μg/kg administered subcutaneously (rounded to 300 μg or 480 μg) once a day up to 48 hours after administration of R-CHOP (on Day 1 of Cycles 1–6) and continued for 7 days or until ANC is $>1.5\times10^9$/L on 2 consecutive days
- Pegfilgrastim: 6 mg administered subcutaneously up to 48 hours following administration of R-CHOP (on Day 1 of Cycles 1–6)

  Lenograstim is an acceptable alternative.

G-CSF may be given intravenously if preferred or when clinically indicated.

**DEXAMETHASONE**

Premedication with dexamethasone should be administered 1 hour prior to the administration of glofitamab; premedication with (500 or 1000 mg) oral acetaminophen or paracetamol and an antihistamine, such as (50 mg) diphenhydramine, should be administered approximately 30 minutes prior to the start of the infusion. *Premedication with dexamethasone will be optional during subsequent cycles based on investigator's assessment for participants who tolerate two 30-mg doses of glofitamab without experiencing CRS. However, if the participant experiences CRS, premedication with dexamethasone is required for subsequent glofitamab doses until no additional events of CRS are observed.*

**DURATION OF PARTICIPATION**

The total duration of study participation for each individual participant is expected to be approximately *34* months.

Treatment will continue until disease progression per 2014 Lugano Response Criteria.

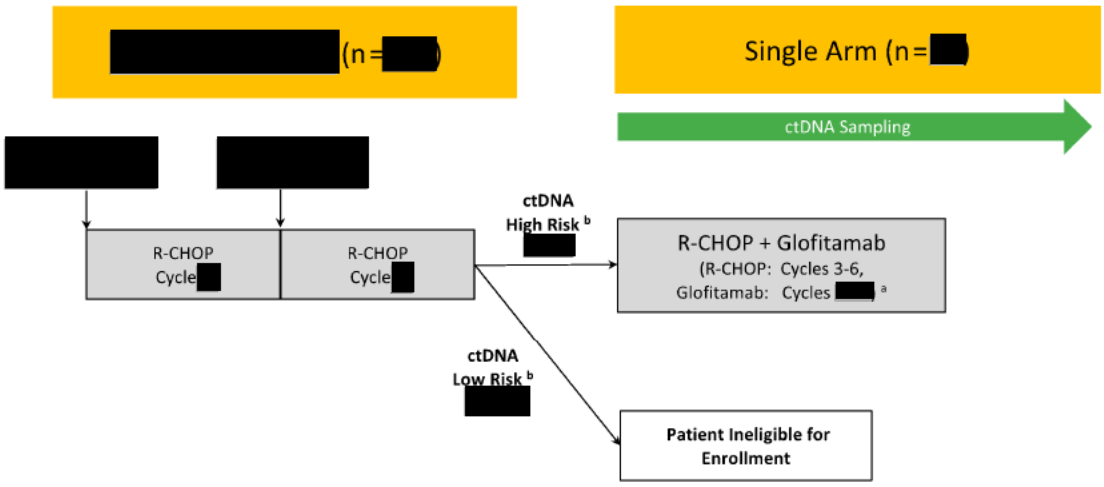
**INDEPENDENT DATA MONITORING COMMITTEE**

| | |
|---|---|
| ***Independent Committees:*** | *Not applicable* |
| ***Other Committees:*** | *Internal Monitoring Committee* |

## 1.2 STUDY SCHEMA

The study schema is presented in Figure 1, and the dosing schema is shown in Figure 2.

**Figure 1 Study Schema**

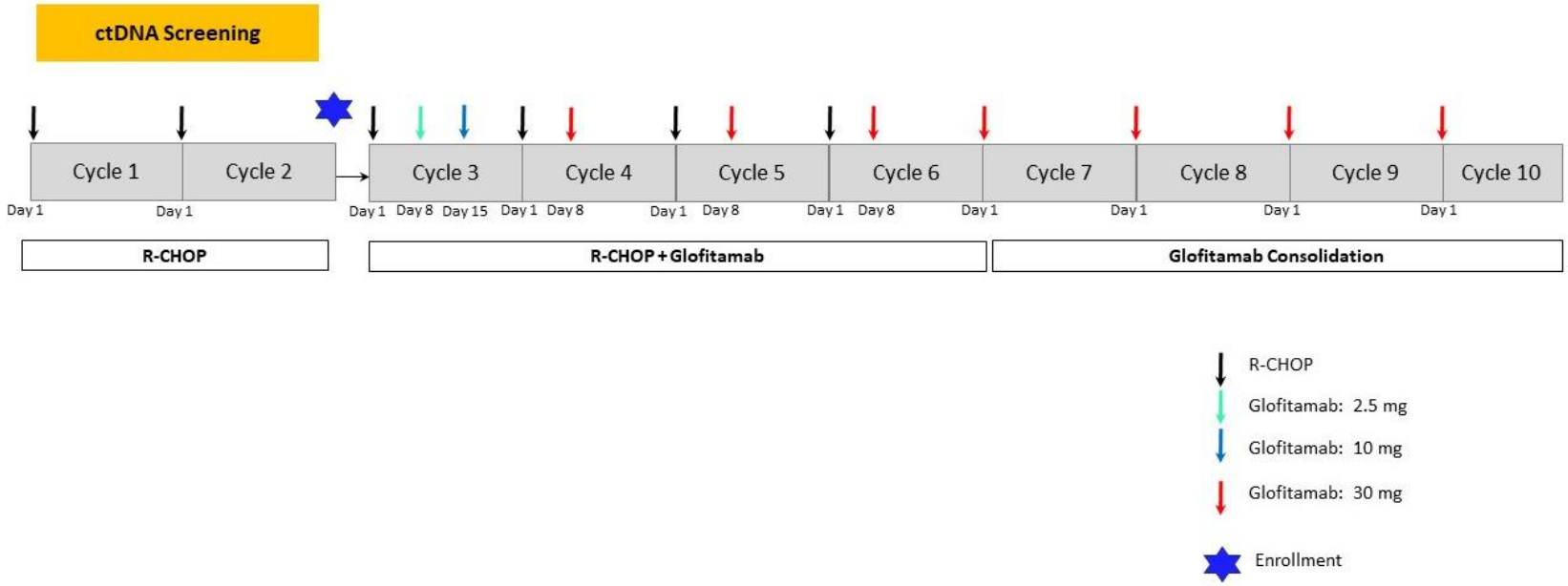



ctDNA = circulating tumor DNA; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone.

[a] Refer to schedule in Section 1.3, , for and details.

[b] ctDNA high-risk patients are those who do not achieve a ≥ 2-log (100×-fold) decrease in ctDNA levels between Day of Cycle and Day of Cycle Patients who demonstrate a ≥ 2-log fold decrease in ctDNA levels during the same timepoints are ctDNA low-risk patients and for the purposes of this study are screen failures and will be ineligible to proceed (see Table 2).

**Figure 2 Dosing Schema**




ctDNA = circulating tumor DNA; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone.

## 1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

### Table 1 Schedule of Activities

| Assessment or Procedure (Window in Days) | Screening [a, b] | | | | Treatment [c] | | | | | | EOT and/or Tx Discon [redacted] Days after Final Dose of Study Tx) [d] | Survival Follow-Up (Q3M) [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle [redacted] | Cycle [redacted] | | Cycle [redacted] | | | Cycles [redacted] | | Cycles [redacted] | | |
| | Days –28 to –1 | Day [redacted] | Day [redacted] | Days [redacted] | Day [redacted] | Day [redacted] | Day [redacted] | Day [redacted] | Day [redacted] | Day [redacted] | | |
| Informed consent [b] | x | | | | | | | | | | | |
| Demographics (age, sex, and self-reported race/ethnicity) | x | | | | | | | | | | | |
| Medical history and baseline conditions | x | | | | | | | | | | | |
| Prognostic factors (Ann Arbor Staging and IPI) | x | | | | | | | | | | | |
| ECOG Performance Status | x | | | | x | | | x | | x | | |
| Concomitant medications [f] | x | | | x | x | x | x | x | x | x | x | |
| Adverse events [g] | x | x | x | x | x | x | x | x | x | x | x | |
| Height and BSA (at screening only), and weight [h] | x | | | | x | | | | | | | |
| Vital signs [i] | x | x | x | x | x | x | x | x | x | x | x | |

## Table 1 Schedule of Activities (cont.)

| Assessment or Procedure (Window in Days) | Screening [a, b] | | | | Treatment [c] | | | | | | EOT and/or Tx Discon [redacted] Days after Final Dose of Study Tx) [d] | Survival Follow-Up (Q3M) [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days –28 to –1 | Cycle [redacted] Day [redacted] | Cycle [redacted] Day [redacted] | Cycle [redacted] Days [redacted] | Cycle [redacted] Day [redacted] | Day [redacted] | Day [redacted] | Cycles [redacted] Day [redacted] | Day [redacted] | Cycles [redacted] Day [redacted] | | |
| Complete physical examination (including neurologic examination) [j] | x | | | | | | | | | | | |
| Targeted physical examination [k] | | | | x | x | x | x | x | x | x | x | |
| Single 12-Lead ECG [l] | x | | | | | x | | | x | x [l] | x | |
| Cardiac function: LVEF (MUGA scan or ECHO) | x | | | | | | | | | | x | |
| *SARS-CoV-2 test* [m] | *x* | *x* [n] | | | *x* [n] | | | *x* [n] | | *x* [n] | | |
| Tumor assessment [o] | x [p] | | | x [p] | | | | | | | x [o, p, q] | x [r] |
| Viral serology: HBV, HCV [s], and HIV [t, u] | x | | | | | | | | | | | |
| Bone marrow aspirate and biopsy [v] | x | | | | | | | | | | x | |
| Hematology [w] | x | x | x | x | x | x | x | x | x | x | x | |

## Table 1 Schedule of Activities (cont.)

| Assessment or Procedure (Window in Days) | Screening [a, b] | | | | Treatment [c] | | | | | | EOT and/or Tx Discon ([redacted] Days after Final Dose of Study Tx) [d] | Survival Follow-Up (Q3M) [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days –28 to –1 | Cycle [redacted] | Cycle [redacted] | | Cycle [redacted] | | | Cycles [redacted] | | Cycles [redacted] | | |
| | | Day [redacted] | Day [redacted] | Days [redacted] | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | | |
| Serum chemistry profile [x] | x | x | x | x | x | x | x | x | x | x | x | |
| Coagulation: aPTT, PT, INR, D-dimer, and fibrinogen [y] | x | | | | | | | | | | | |
| Pregnancy test [z] | x | x | | | x | | | x | | x | x [z] | |
| Quantitative immunoglobulins: IgA, IgG, and IgM | x | | | | | | | | | | x | |
| Serum PK and ADA samples | Please refer to [redacted] for the PK and ADA sample collection schedule. | | | | | | | | | | | |
| Blood samples for ctDNA analysis and [redacted] | Please refer to [redacted] for the [redacted] schedule. | | | | | | | | | | | |
| Tumor tissue sample [aa] | x | | | | | | | | | | | |
| Optional tumor biopsy and plasma sample [bb] | | | | | | | | | | | | x |
| TLS prophylaxis [cc] | | x | | | | | | | | | | |
| G-CSF [dd] | | x | x | | x | | | x | | | | |

## Table 1 Schedule of Activities (cont.)

| Assessment or Procedure (Window in Days) | Screening [a, b] | | | | Treatment [c] | | | | | | EOT and/or Tx Discon [redacted] Days after Final Dose of Study Tx) [d] | Survival Follow-Up (Q3M) [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days –28 to –1 | Cycle [redacted] | Cycle [redacted] | | Cycle [redacted] | | | Cycles [redacted] | | Cycles [redacted] | | |
| | | Day [redacted] | Day [redacted] | Days [redacted] | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | Day [redacted] (±[redacted]) | | |
| Glofitamab | | | | | | x [cc, ee] | x [ee] | | x [ee] | x | | |
| Rituximab | | x | x | | x | | | x | | | | |
| Cyclophosphamide | | x | x | | x | | | x | | | | |
| Doxorubicin | | x | x | | x | | | x | | | | |
| Vincristine | | x | x | | x | | | x | | | | |
| Prednisone [ff] | | x | x | | x | | | x | | | | |
| New anti-lymphoma therapy assessment | | | | | | | | | | | x | x |
| Survival follow-up | | | | | | | | | | | x | x |

$^{18F}$FDG = [$^{18F}$]fluoro-2-deoxy-D-glucose; ADA = anti-drug antibody; β-hCG = β-human chorionic gonadotropin; BSA = body surface area; CAR = chimeric antigen receptor; CRS = cytokine-release syndrome; CT = computed tomography (scan); ctDNA = circulating tumor DNA; Discon = discontinuation; DLBCL = diffuse large B-cell lymphoma; ECHO = echocardiogram; 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; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HLH = hemophagocytic lymphohistiocytosis; HSCT = hematopoietic stem-cell transplantation; Ig = immunoglobulin; IPI = International Prognostic Index; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; PCR = polymerase chain reaction; PET = positron emission tomography; PK = pharmacokinetic; PO = orally; Q3M = every 3 months; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; TLS = tumor lysis syndrome; Tx = treatment.

## Table 1 Schedule of Activities (cont.)

[a] Screening together with pretreatment tests and evaluations may be performed within [redacted] days prior to Day [redacted] Cycle [redacted] of R-CHOP. Radiographic tumor assessments obtained during screening are acceptable, provided that no anti-tumor therapy was administered during this period with the exception of low-dose corticosteroids. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window specified above may be used; such tests do not need to be repeated for screening.

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

[c] See Section 6.1 for details regarding the study treatment regimens and dosing.

[d] Participants who discontinue study treatment will be asked to return to the clinic for a treatment discontinuation visit [redacted] ± [redacted] days after their final dose of study treatment. Any study visit when the response assessment reveals disease progression may be used as the treatment discontinuation visit.

[e] Follow-up includes survival, new anti-lymphoma therapy (including HSCT or CAR T-cell therapy), and tumor assessments. Required long-term follow-up information, with the exception of tumor assessments, will be collected by means of telephone calls, patient medical records, and/or clinic visits every 90 days until death, loss to follow-up, or study termination by the Sponsor. If a participant withdraws from the study, the study team may use a public information source, when permissible, to obtain information about survival status. All participants will be periodically contacted for survival and new anti-cancer therapy information unless the participant requests to be withdrawn from the study. Please refer to Table 2 for [redacted], PK, and ADA sample collection during follow-up. An in-person visit is not required solely for the purpose of sample collection.

[f] Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by a participant 7 days prior to initiation of R-CHOP treatment in Cycle [redacted] until 6 months after the final dose of glofitamab study treatment (for ctDNA high-risk patients only). All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[g] After informed consent has been obtained but prior to initiation of study treatment in Cycle [redacted] only serious adverse events caused by a protocol-mandated intervention should be reported. Following initiation of study treatment in Cycle [redacted] all adverse events will be reported until 90 days after the final dose of study treatment or the initiation of new anti-lymphoma therapy, whichever occurs earlier. After this period, refer to Section 8.2.1 for reporting requirements.

[h] Height and BSA are required at screening only, unless there has been a $>10\%$ 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.

## Table 1 Schedule of Activities (cont.)

[i] Vital signs will include measurement of respiratory rate, pulse oximetry, pulse rate, and systolic/diastolic blood pressure (with the participant in a seated or semi-supine position), and temperature. For glofitamab infusions during Cycles [redacted] and [redacted]; vital signs should be monitored and recorded preinfusion, every 30 (±10) minutes during, at the end of the infusion, and 2 hours after infusion. For participants who tolerate glofitamab infusions during Cycles [redacted] and [redacted] in the absence of CRS, for subsequent cycles, vital signs should be assessed preinfusion, every 60 (±15) minutes during and 2 hours following the end of infusion. In cases when CRS occurs during Cycle [redacted] or [redacted], vital signs should be assessed preinfusion, every 30 (±10) minutes during, and at 30 (±10) minute intervals for 2 hours following the end of infusion. For participants who experience CRS but in subsequent cycles tolerate two consecutive glofitamab infusions without CRS, monitoring of vital signs may be adjusted to preinfusion, every 60 (±15) minutes during, and 2 hours after the end of infusion. The monitoring of vital signs should be more frequent in participants deemed to exhibit disease-related factors, which may confer an increased risk of severe CRS; for such patients, assessments should be performed at least every 15 minutes during the first infusion in Cycle [redacted] and up to at least 2 hours postinfusion. Refer to Appendix 7 for the schedule of activities for participants who receive tocilizumab for the treatment of CRS.

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

[k] Limited, symptom-directed physical examinations should be performed at specified post-baseline visits as clinically indicated.

[l] A single 12-lead ECG will be performed at screening and post-infusion on Day [redacted] of Cycle [redacted] through postinfusion on Day [redacted] of Cycle [redacted] and may be obtained at unscheduled timepoints as clinically indicated. The following should be recorded at baseline and at scheduled intervals on the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings). 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.

[m] *SARS-CoV-2 testing by antigen or PCR is required within 7 days prior to enrollment for all patients.*

[n] *For patients enrolled in France, SARS-CoV-2 PCR testing and negative result is required within 48 hours before study treatment administration at each treatment cycle.*

[o] Participants will undergo tumor assessments at screening, the interim response assessment (between Days [redacted] and [redacted] of Cycle [redacted] and at the EOT. At screening and EOT tumor assessments, $^{18F}$FDG-PET/CT and diagnostic CT scans are required. For the interim response assessment (between Days [redacted] and [redacted] of Cycle [redacted]), only an $^{18F}$FDG-PET/CT scan is required. Response will be evaluated according to the 2014 Lugano Response Criteria (see Appendix 11). During survival follow-up, response will continue to be evaluated every 6 months until the participant develops progressive disease, discontinues from the study, at any time disease progression is suspected, or until *24 months* from the EOT response assessment, whichever occurs first. Tumor assessments may be repeated at any time if progressive disease is suspected.

## Table 1 Schedule of Activities (cont.)

[p] CT and PET/CT scans are required at screening, between Days [redacted] and [redacted] of Cycle [redacted] and within 4 to 8 weeks after the final dose of study treatment (see Section 8.1 for details). Participants who discontinue treatment prematurely will be asked to return to the clinic for an early termination visit within 4 to 8 weeks after their final dose of study treatment or last datapoint determined. Response will be assessed using image-based evaluation according to 2014 Lugano Response Criteria (see Appendix 11). Scans should be performed according to the guidelines in the imaging manual provided to all sites.

[q] Participants who discontinue study treatment early for a reason other than disease progression should have a response assessment within 4 to 8 weeks from the final dose of study treatment, unless the most recent tumor assessment is ±28 days of the final dose of study treatment. Tumor assessments should continue to be performed at specified timepoints until disease progression or death or until *24 months* from the EOT response assessment, whichever occurs first.

[r] In the follow-up period, diagnostic CT scans, with or without FDG-PET, should be obtained until participants develop progressive disease, including participants who initiate a new anti-lymphoma therapy, as follows: at 6 months after the EOT response assessment, then every 6 months until disease progression, or death, or until *24 months* from the EOT response assessment, whichever occurs first. PET/CT scans should be obtained during the study and the follow-up period at any time clinical findings suggest disease progression, and response should be recorded on the eCRF.

[s] HBsAg, total HBcAb, HCV antibody, and HIV antibody serology are required. Participants with occult or previous hepatitis B infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable at the time of screening. Such participants must be willing to undergo HBV DNA testing on Day 1 of every cycle and every 3 months for at least 12 months after the final cycle of study treatment and appropriate antiviral therapy as indicated. Individuals who are positive for the HCV antibody must be negative for HCV by PCR to be eligible for study participation.

[t] *Participants who are positive for HIV may be eligible provided they are stable on antiretroviral therapy for at least 4 weeks, have a CD4 count ≥200/µL, have an undetectable viral load, and have not had a history of opportunistic infection attributable to AIDS within the last 12 months.*

[u] *Participants with positive HIV at screening should be monitored while receiving study treatment. HIV viral load will be performed every 3 months (± 4 weeks) in the first 6 months and subsequently every 6 months (± 4 weeks) until end of study treatment. If HIV viral load is detected (positive), the participant should be treated per local institutional standards, and the Medical Monitor should be notified. Testing may be performed at the local institution. If local laboratory assessments are not available for testing, local laboratory collections may be waived only if samples are collected for central laboratory assessments of viral infections.*

[v] A bone marrow aspirate and trephine biopsy are not mandatory at screening. However, if a bone marrow assessment is performed within 3 months prior to Day 1 of Cycle [redacted] for the purpose of diagnosis and staging of DLBCL, an authorized laboratory pathology report should be submitted (central receipt of bone marrow samples are not required). On the first occasion that a participant with bone marrow involvement at screening is assessed by CT rather than PET/CT scan, a repeat biopsy is necessary before a CR can be recorded. Otherwise, additional bone marrow biopsies are not mandatory and should be performed when clinically indicated (e.g., clinical suspicion of progressive disease in the bone marrow when there is discordance with radiographic imaging).

## Table 1 Schedule of Activities (cont.)

[w] Hematology includes CBC, WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (absolute counts of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[x] Serum chemistry panel includes bicarbonate, sodium, potassium, calcium, magnesium, phosphorus, chloride, glucose, BUN or urea, creatinine, creatinine clearance (calculated according to the Cockcroft-Gault formula; see Appendix 16), uric acid, total protein, albumin, phosphate, calcium, total and direct bilirubin, *alkaline phosphatase,* ALT, AST, GGT, and lactate dehydrogenase.

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

[z] All women of childbearing potential require a negative serum pregnancy test within 24 hours of starting R-CHOP treatment on Day [redacted] of Cycle [redacted] Pregnancy testing (urine or serum) will subsequently be performed within 24 hours prior to dosing on Day [redacted] of each cycle (Cycles [redacted], at the EOT, and at least monthly for 4 months following the EOT visit. If a urine pregnancy test is positive, it must be confirmed by a serum β-hCG level.

[aa] A baseline tissue sample is mandatory and availability of archival tumor biopsy tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides (freshly cut, serial sections) obtained at any point prior to any prephase steroids and Day [redacted], Cycle [redacted] dosing. All archival tissue must be submitted with an associated pathology report.

[bb] Additional tumor biopsies, particularly after progression are recommended but are optional and may be performed at any time at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis). When possible, tissue from such biopsies should be provided to the Sponsor for [redacted] Participants who elect to provide optional tumor biopsies are required to sign the Optional Tumor and Plasma Sample Informed Consent Form. A plasma sample for [redacted] will also be obtained at the time of optional tumor biopsy.

[cc] Participants with high tumor burden and/or considered to be at risk of TLS should be well hydrated and receive tumor lysis prophylaxis with 300 mg/day of allopurinol PO, starting within 48 to 72 hours prior to study treatment initiation until the end of Cycle [redacted] or at least 14 days. A suitable alternative treatment (e.g., rasburicase) can be administered in accordance with local guidelines (see Section 6.1.5.3 and Appendix 6).

[dd] To minimize the rate, severity, and duration of neutropenia-related complications, all participants should receive primary prophylaxis with G-CSF during Cycles [redacted]. Use of one of the following will be mandatory during Cycles [redacted]: 5 μg/kg SC filgrastim (rounded to 300 μg or 480 μg) up to 48 hours after administration of R-CHOP (on Day 1 of Cycles 1–6) and continued for 7 days or until ANC is $> 1.5 \times 10^9$/L on 2 consecutive days or 6 mg SC pegfilgrastim up to 48 hours following administration of R-CHOP (on Day 1 of Cycles 1–6). Lenograstim is an acceptable alternative. G-CSF may be given intravenously if preferred or when clinically indicated.

[ee] Participants who experienced Grade ≥ 2 CRS associated with the preceding dose of glofitamab should be admitted at least overnight for the next glofitamab dose. Investigators may choose to hospitalize a patient following any glofitamab dose for close monitoring if clinically indicated. Hospitalization should be considered for participants who lack support for close monitoring at home or who live a considerable distance away from the study center.

## Table 1 Schedule of Activities (cont.)

ff Prednisone 100 mg/day PO will be given on Days 1–5 for each cycle when CHOP is administered (also refer to Section 6.1.3).

**Table 2 Pharmacokinetic, Immunogenicity, and [redacted]**

| Visit | Timepoint(s) | R-CHOP, Sample Type(s) | | R-CHOP + Glofitamab, Sample Type(s) | | |
|---|---|---|---|---|---|---|
| | | [redacted] | Rituximab PK | [redacted] | Glofitamab PK | Glofitamab ADA |
| Cycle [redacted], Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | | | | |
| Cycle [redacted] Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | | | | |
| Cycle [redacted], Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | x | | | |
| Cycle [redacted] Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | x | | x | x |
| | EOT (at any time after the end of the infusion) | | | | x | |
| Cycle [redacted], Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | | | x | |
| Cycle [redacted] Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | x | | x | |
| Cycle [redacted] Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | | | x | x |

**Table 2 Pharmacokinetic, Immunogenicity, and [redacted] (cont.)**

| Visit | Timepoint(s) | R-CHOP, Sample Type(s) | | R-CHOP + Glofitamab, Sample Type(s) | | |
|---|---|---|---|---|---|---|
| | | [redacted] | Rituximab PK | [redacted] | Glofitamab PK | Glofitamab ADA |
| Cycle [redacted] Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | | | x | x |
| Cycle [redacted] Day [redacted] | Predose (≤4 hours prior to the first drug administration) | | | | x | x |
| Treatment completion/ discontinuation visit | Any time during the visit | | | | x | x |
| Follow-up [e] | *The first follow-up sample should be c*ollect*ed* at any time ≥90 days after the final infusion of glofitamab. | | | | x | x |

ADA = anti-drug antibody; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CT = computed tomography; EOT = end of treatment; [redacted]
PK = pharmacokinetic; R = rituximab.

[a] A plasma sample for [redacted] will be collected at the time of optional tumor biopsy and/or when CT scans are performed.

[b] Collect [redacted] in addition to [redacted] on Day [redacted] of Cycle [redacted] predose.

[c] This collection includes [redacted] isolated at site and [redacted] isolation at central laboratory.

[d] [redacted].

[e] Collect samples every 3 (± 1) months for 1 year and/or when CT scans are performed*, then every 6 months until the end of survival follow-up.* An in-person visit is not required solely for the purpose of collecting samples.

# 2. INTRODUCTION

## 2.1 BACKGROUND ON DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), affecting approximately 25,000 new patients in the United States and 1.5 million worldwide annually (Rodriguez-Abreu et al. 2007).

The disease exhibits striking biological and clinical heterogeneity. Although front-line treatment with rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) immunochemotherapy, given with or without radiotherapy, is curative in approximately 60% of cases, certain subsets of patients are refractory to (10%–15%) or relapse (20%–30%) following this standard-of-care (SOC) approach (Chaganti et al. 2016).

Five-year survival rates vary from 90% for low-risk patients with DLBCL to less than 40% to 50% for high-risk patients, defined according to the International Prognostic Index (IPI) (Mauer et al. 2014; Zhou et al. 2014). Therapy for patients with relapsed/refractory (R/R) DLBCL remains challenging and typically involves treatment with anti-CD20 antibodies and chemotherapy.

The IPI is widely used to risk stratify patients with DLBCL according to their age, biochemical parameters, performance status, and disease stage. No existing prognostic scoring systems are able to identify all high-risk patients with sufficient accuracy (International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993; Sehn et al. 2007; Zhou et al. 2014). Moreover, patients with DLBCL who respond suboptimally or who relapse after first-line SOC treatment are identified only after treatment completion when ultimately the salvageable potential is limited; hence, the need for optimizing effective drugs and rational treatment combinations in the front-line setting across all subgroups of patients.

### 2.1.1 Use of Interim Positron Emission Tomography/Computed Tomography in the DLBCL Treatment Pathway

$^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG)-PET/CT represents the gold-standard imaging technique in DLBCL. Its utility in identifying patients with DLBCL at high risk of suboptimal treatment responses or treatment failure to front-line immunochemotherapy has been demonstrated in Phase III clinical studies.

In the PETAL study (NCT00554164), patients with aggressive NHLs underwent interval PET assessment using the change in maximum standardized uptake method. PET-positive patients were randomly assigned to receive an additional six cycles of R-CHOP or six blocks of an intensive Burkitt's lymphoma protocol. Patients with CD20-positive, PET-negative NHL were randomly assigned or allocated to receive an additional four cycles of R-CHOP or the same treatment with an additional two doses of rituximab. The primary endpoint was event-free survival (EFS) (Dührsen et al. 2018).

Despite methodological challenges, PETAL demonstrated that although PET-based treatment intensification did not improve outcomes, interim PET was predictive of survival in patients with aggressive lymphomas treated with R-CHOP.

Recently the GAINED study (NCT01659099), a Phase III, open-label, randomized trial comparing obinutuzumab and rituximab chemo-immunotherapy (CHOP/ACVBP) in transplant-eligible patients with DLBCL, evaluated responses by PET during induction, 2 weeks after the second cycle (PET2) and 2 weeks following the completion of induction chemotherapy (PET4) in order to determine consolidation treatment (Le Gouill et al. 2020). PET2-negative/PET4-negative patients and PET2-positive/PET4-negative patients had similar PFS (89.9% vs. 83.9%, respectively) and OS (94.8% vs. 92.8%) outcomes. The 2-year PFS and OS in PET-positive patients were 62% and 83.1%. Results from this study suggest that interim PET assessment (PET2 plus PET4) may stratify patients into three risk groups: PET2 negative/PET4 negative, PET2 positive/PET4 negative, and PET4 positive. Identifying PET4-positive patients expediently at the PET2 stage may provide an opportunity for early interventions to improve the outcomes of patients destined for suboptimal or early treatment failures.

### 2.1.2 Circulating Tumor DNA as a Biomarker to Identify Patients with DLBCL Who Are Non-Responders to Treatment

Cell-free DNA (cfDNA) fragments are shed into the circulation following cell death in healthy people but detected at higher levels in patients with cancer. Novel methods such as next-generation sequencing (NGS), permit the targeted detection of ctDNA in blood samples from patients with DLBCL (Scherer et al. 2016). ctDNA is a novel biomarker that offers the exciting potential for a more sensitive, less-invasive yet dynamic approach to identifying patients with DLBCL who are at a higher risk of failing immunochemotherapy in the front line setting. Furthermore, in contrast to radiologic modalities, such as PET, ctDNA may detect a suboptimal treatment response with greater specificity and at an earlier timepoint.

In 2018, Kurtz et al. published an observational study measuring ctDNA after two and three cycles of treatment in 217 patients with DLBCL or primary mediastinal B-cell lymphoma using the cancer personalized profiling by deep sequencing (CAPP-Seq) method. Patients received rituximab-based chemotherapy regimens and were divided into two cohorts: Cohort 1 was subdivided into a “discovery set” ($n = 14$) and a “validation set 1” ($n = 130$), followed by an additional “validation set 2” ($n = 73$) in Cohort 2. The threshold for a molecular response (MR) was defined in the discovery set and subsequently tested in the validation sets. In the first validation set, the detection of an early MR (defined as $>$ 100-fold or 2-log decrease in ctDNA levels after one cycle of treatment) correlated with a significant improvement in 24-month EFS (83% relative to 50%; $p = 0.0015$). A major MR (MMR; defined as $>$ 2.5-log ctDNA decrease after two treatment cycles) correlated with a 24-month EFS (82% vs. 46%; $p < 0.001$).

Patients with an early MR who ultimately required salvage therapy (n = 36) had a superior 24-month EFS of 100% compared with 13%. Both early molecular response (EMR) and MMR were able to distinguish non-responders from responders, independent of PET/CT findings and treatment regimen. Notably, the presence of a ctDNA molecular response (EMR and MMR) identified improved OS and EFS in IPI high-risk (3–5) and low-risk (0–2) groups, highlighting the need for more sensitive prognostication in this disease setting.

While assessing the optimal timepoint of ctDNA measurement, the authors were able to demonstrate that rapid reductions in ctDNA levels during Cycle 1 (Days 6–16) of treatment could discriminate responders (patients with a complete response [CR], as determined by PET/CT) from non-responders (Kurtz et al. 2018). A 2-log fold decrease in ctDNA levels at the start of Cycle [redacted] was able to significantly distinguish response groups. Taken together, these findings support the use of early dynamic ctDNA levels to identify patients with DLBCL who are at high risk of suboptimal responses and treatment failure and therefore may benefit from early intervention and use of novel therapies.

### 2.1.3 Background on AVENIO Oncology Assay for Non-Hodgkin Lymphoma Test

The AVENIO Oncology Assay for Non-Hodgkin's Lymphoma (AOA-NHL) Test uses targeted NGS and sequences genomic DNA isolated from peripheral mononuclear cells or plasma-depleted whole blood (PDWB) and plasma cell-free DNA (cfDNA) to detect ctDNA qualitatively as an indicator for minimal residual disease (MRD). The AOA-NHL Test can be used to determine ctDNA status in patients with DLBCL.

The AOA-NHL Test is an NGS tumor profiling and monitoring assay used to identify somatic DNA mutations in individuals with DLBCL by sequencing cfDNA isolated from patient plasma samples at different timepoints during a patient's treatment. cfDNA is composed of fragments of DNA that are shed into the bloodstream as a result of cell death in both normal and tumor tissue. The presence of somatic variants (those not inherited by the individual) is assumed to be present in DNA derived from the tumor, DNA referred to as ctDNA.

The AOA-NHL Test is a laboratory developed assay validated at Roche Molecular Systems (San Jose, California, USA). The AOA-NHL Test provides a streamlined end-to-end NGS solution from DNA extraction to bioinformatics data analysis and reporting. The test is based on the iDES-enhanced CAPP-Seq (integrated digital error suppression-enhanced cancer personalized profiling by deep sequencing) technology described in detail in Newman et al. (2014, 2016). Multiple studies have demonstrated the ability of deep sequencing of ctDNA to detect somatic variants at very low allelic fractions (Schwarzenbach et al. 2011; Narayan et al. 2012; Diehn et al. 2017). This makes the ctDNA assay suitable to monitor disease burden in patients undergoing treatment (Chin et al. 2019).

The test is designed to report the presence of tumor-derived DNA variants in a 466-gene panel spanning approximately 314 kilobase that is associated with the presence of disease and to assess the changes in levels of such variants in the peripheral blood from a patient throughout treatment. The AOA-NHL Test uses a proprietary bioinformatics pipeline to identify tumor-specific variants (TSVs) by subtracting sample variants that are present in matching normal PDWB samples from those variants detected in plasma samples. The pipeline also monitors the same TSVs from plasma samples collected at subsequent timepoints. A mean allele fraction for all detected TSVs is calculated to estimate the level of ctDNA per milliliter of plasma. The detection of these or a subset of these TSVs in a plasma sample indicates the presence of ctDNA in a patient's blood. The statistical significance of TSVs is expressed as a p-value that is calculated using Monte-Carlo statistics (Newman et al. 2016) to account for background variance.

The use of the AOA-NHL Test is experimental for identifying ctDNA high-risk patients with untreated DLBCL who may be eligible to participate in Study GO43075. The test will be limited to central analysis at Roche Molecular Systems in San Jose, CA, which is certified under the Clinical Laboratory Improvement Act (CLIA) of 1988 as qualified to perform high complexity clinical testing.

## 2.2 GLOFITAMAB BACKGROUND

Glofitamab is a human IgG1-bispecific antibody targeting CD20 expressed on the surface of B cells and CD3ε chain expressed on the surface of T cells. By means of binding to CD20 on tumor cells, glofitamab induces tumor cell lysis while achieving T-cell activation, proliferation, and cytokine release by simultaneously binding to CD3ε on the T cell–receptor complex. Unique to its structure, glofitamab contains two CD20 and a single CD3 binding domain (2:1 design), greatly enhancing the avidity for CD20 compared with a 1:1 format. This novel antibody demonstrates a managable safety profile and is currently undergoing rigorous investigation for use as both a single agent as well as a combination partner with other therapies in NHL.

## 2.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The purpose of this study is to assess the safety, efficacy, and pharmacokinetics of glofitamab in combination with R-CHOP in ctDNA high-risk patients. ctDNA high-risk patients are those who fail to achieve ≥2 log-fold reduction in ctDNA levels between Day [redacted] of Cycle [redacted] Day [redacted] ([redacted]) and Day [redacted] of Cycle [redacted]

ctDNA is a novel biomarker that offers the potential for an early, sensitive approach to identifying patients with DLBCL at a higher risk of front-line treatment failure.

Glofitamab has demonstrated an acceptable safety profile given as a monotherapy (Study NP30179) and in combination with R-CHOP (Study NP40126). See Appendix 6 for information on anticipated risks for glofitamab and risk mitigation measures.

Additionally, more detailed information about the known and expected benefits in the context of potential risks and adverse events associated with glofitamab treatment is provided in the Glofitamab Investigator's Brochure.

The selected dose and schedule of glofitamab are supported by emerging safety data from Study NP30179 investigating the step-up dosing regimen for glofitamab monotherapy. Glofitamab step-up dosing is intended to reduce the risk of cytokine-release syndrome (CRS), a primarily first dose effect with frequency and severity associated with higher initial glofitamab doses. As of the latest clinical cutoff date (18 December 2020) in Part 1 of Study NP40126, the 2.5-, 10-, and 30-mg dosing schedule in combination with R/G-CHOP has shown a promising benefit–risk profile in the R/R NHL setting (n = 26). Together, the data may support the ongoing use of the 2.5-, 10-, and 30-mg dosing schedule in Part 2 of Study NP40126 in the front-line DLBCL setting study as a safety run-in with 6–24 patients (see Glofitamab Investigator's Brochure for more details).

The function of glofitamab is not fully inhibited in the presence of saturating levels of either obinutuzumab or rituximab. Thus, the addition of glofitamab to R-CHOP may provide greater efficacy than R-CHOP alone. Currently available nonclinical data (see the Glofitamab Investigator's Brochure) also support a strong rationale to expect an improved benefit–risk profile with the combination of glofitamab and R-CHOP.

The safety data available from Part 1 of Study NP40126 include 26 patients in the R/R NHL setting who received obinutuzumab (G)/R-CHOP in combination with 2.5, 10, and 30 mg glofitamab. Potential overlapping risks for the combination regimen of glofitamab in combination with R-CHOP include TLS, infusion-related reactions (IRRs) and CRS, cytopenias, and infections (see Glofitamab Investigator's Brochure).

Altogether, this underscores the promising single-agent and G/R-CHOP combination activity of glofitamab. The aforementioned studies demonstrate a tolerable safety profile, and emerging data have revealed that CRS is the main dose-limiting toxicity, albeit signs and symptoms are confined to Cycle 1 in the vast majority of patients (for details, refer to the Glofitamab Investigator's Brochure).

Dedicated clinical management guidelines that mitigate many of these risks are outlined in this protocol (see Appendix 6) and in the local prescribing information.

### COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer are deemed clinically more vulnerable. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in retrospective analyses. It is unclear how cancer treatments, including chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of COVID-19 disease. Both

glofitamab administration and severe COVID-19 disease are associated with CRS (CRS involving the inflammatory cytokines interleukin [IL]-6, IL-10, IL-2, and interferon-γ [IFN-γ]). Administration of glofitamab may enhance the inflammatory response observed during SARS CoV-2 infection. In summary, clinical trials with glofitamab are ongoing and will continue during this pandemic. However, the risk of developing COVID-19 disease and subsequent sequelae in patients receiving glofitamab is currently unknown.

With reference to SARS-CoV-2 vaccines, an assessment was conducted to determine whether there is an impact of the SARS-CoV-2 vaccines on the benefit-risk assessment of this study protocol. There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 vaccination. Given that the mechanism of action of CD20–targeted therapies leads to B cell depletion, it is expected that the efficacy of SARS-CoV-2 vaccines may be diminished. See Section 6.8.1 for additional guidance on SARS-CoV-2 vaccine administration and timing.

*Cytokine release syndrome (CRS) is a risk for glofitamab that occurs most commonly during step-up dosing. Many COVID-19 vaccines are highly immunogenic and the associated risk of potentiating CRS is unknown.*

## 3. OBJECTIVES AND ENDPOINTS

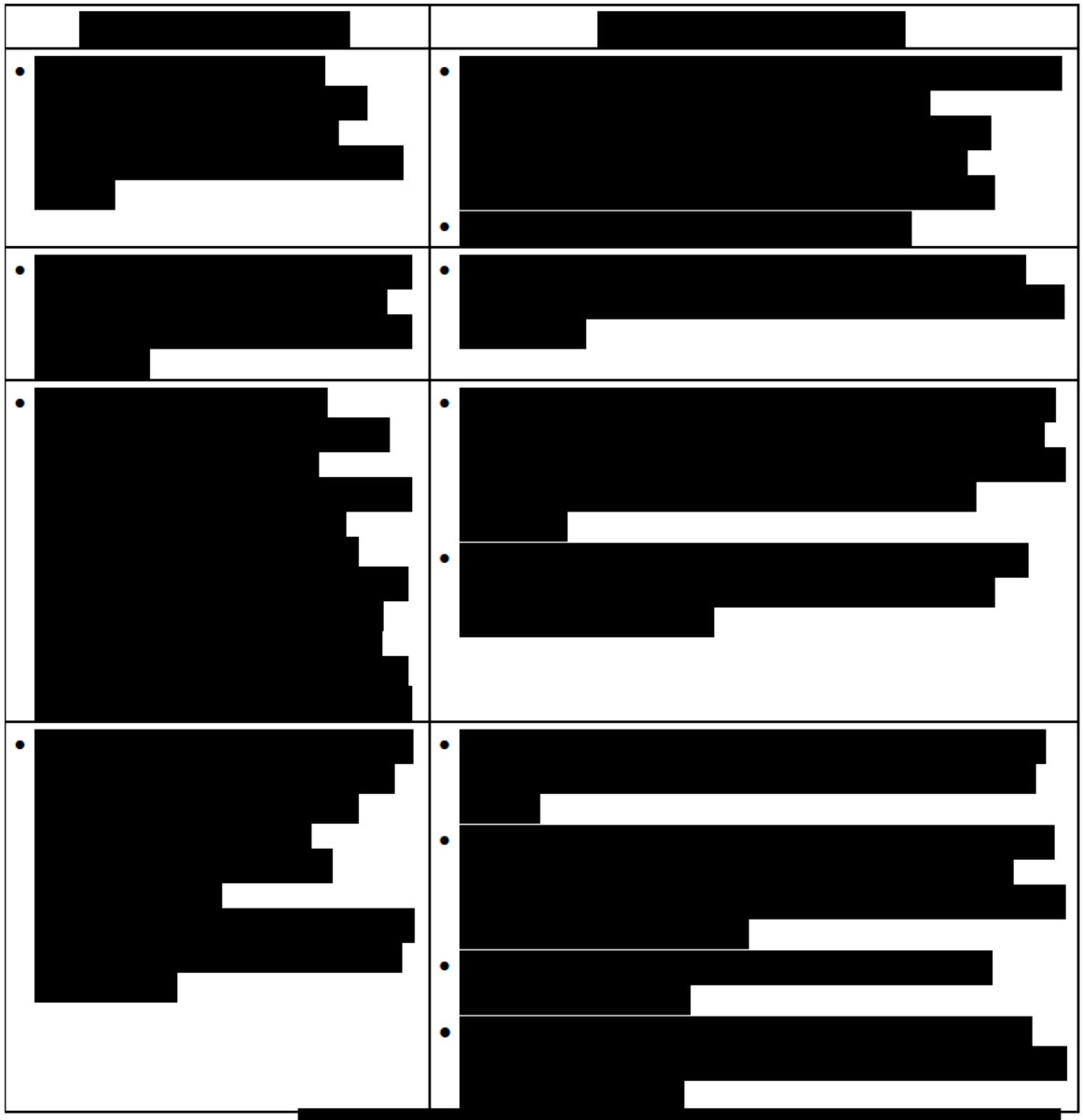
This Phase II, open-label, multicenter study, will evaluate the safety, efficacy, and pharmacokinetics of glofitamab in combination with R-CHOP in individuals with ctDNA high-risk DLBCL in the first-line setting. Specific objectives and corresponding endpoints for the study are outlined in Table 3.

In this protocol, “study treatment” refers to the combination of treatments assigned to participants as part of this study (i.e., R-CHOP, with or without glofitamab).

## Table 3 Objectives and Corresponding Endpoints

| Primary Objective | Corresponding Endpoint |
|---|---|
| • To evaluate the efficacy of glofitamab in combination with R-CHOP in ctDNA high-risk patients with previously untreated DLBCL | • EOT CR rate, as determined by the investigator according to the Lugano Response Criteria for Malignant Lymphoma (hereafter referred to as the 2014 Lugano Response Criteria) |
| **Secondary Objectives** | **Corresponding Endpoints** |
| • To evaluate the efficacy of glofitamab in combination with R-CHOP in ctDNA high-risk patients with previously untreated DLBCL | • ORR at the EOT, as determined by the investigator according to the 2014 Lugano Response Criteria<br>• PFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, according to the 2014 Lugano Response Criteria *or death due to any cause, whichever occurs first, as determined by the investigator*<br>• OS, defined as the time from the first study treatment to death from any cause |
| • To evaluate the safety of glofitamab in combination with R-CHOP in ctDNA high-risk participants with DLBCL | • Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0<br>– For CRS, severity will be determined according to the ASTCT CRS Consensus Grading.<br>• Tolerability, as assessed by dose modifications, dose intensity, and study treatment discontinuation because of adverse events |
| • To characterize the serum PK profile of glofitamab in combination with R-CHOP | • Serum concentrations of glofitamab at specified timepoints<br>• Serum trough concentrations of glofitamab at specified timepoints<br>• Glofitamab PK parameters (e.g., $C_{max}$, AUC), as appropriate |
| • To evaluate potential effects of ADAs | • Relationship between ADA status and efficacy, safety, or PK endpoints |

**Table 3 Objectives and Corresponding Endpoints (cont.)**



ADA = anti-drug antibody; [redacted]
ASTCT = American Society for Transplantation and Cellular Therapy; [redacted] AUC = area under the concentration-time curve; $C_{max}$ = maximum concentration; CR = complete response; CRS = cytokine-release syndrome; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating-tumor DNA; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EOT = end of treatment; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetic; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; [redacted]

# 4. STUDY DESIGN

## 4.1 OVERALL DESIGN

### 4.1.1 Overview of Study Design

This is a Phase II, multicenter study evaluating the safety and efficacy of glofitamab in combination with R-CHOP immunochemotherapy in high-risk individuals with untreated DLBCL, as assessed by ctDNA. Patients will be classified as being high risk of R-CHOP treatment failure if they demonstrate a <2-log (100×-fold) decrease in ctDNA levels between baseline (prior to Day [redacted] of Cycle [redacted] and following [redacted] treatment cycle of R-CHOP (prior to Day [redacted] of Cycle [redacted] please refer to Section 2.1.2) using the experimental AOA-NHL Test.

ctDNA high-risk patients will enroll in the study prior to Cycle [redacted] Day [redacted] and commence step-up doses (2.5 mg, 10 mg, and 30 mg) of glofitamab, starting on Day 8 of Cycle 3 (for the dosing schema, see Figure 2).

For the purposes of this study, individuals who achieve at least a 2-log–fold reduction in ctDNA levels between baseline (prior to Day [redacted] of Cycle [redacted]) and following [redacted] treatment cycle of R-CHOP therapy (prior to Day [redacted] of Cycle [redacted]) are considered to be at lower risk of R-CHOP treatment failure and will not be eligible for enrollment or rescreening. It is anticipated that up to [redacted] patients will be screened in order to identify approximately [redacted] of ctDNA high-risk patients ([redacted] of the population in the first-line setting) across approximately [redacted] nvestigative sites globally.

For enrollment in Cycle 3, eligible patients will be treated with SOC doses of R-CHOP from Cycle 1. During Cycles 3–6, participants will be treated with R-CHOP in combination with glofitamab and will receive glofitamab monotherapy as consolidation during Cycles 7–10 (see Figure 2). PET/CT scans will be performed at the end of treatment (EOT), and an early interim PET/CT response assessment will be conducted following Cycle [redacted]; results will be used to evaluate the correlation between imaging results and ctDNA levels.

To reduce the risk of CRS, glofitamab administration will utilize a step-up dosing schedule, consisting of 2.5 mg and 10 mg on Days 8 and 15 of Cycle 3, respectively. The total dose administered in Cycle 3 will not exceed the dose previously cleared for safety in Study NP40126 (for details, see Section 4.3 and the Glofitamab Investigator's Brochure). For subsequent cycles, 30 mg glofitamab will be given on Day 8 of Cycles 5 and 6 and on Day 1 of Cycles 7–10.

All participants will be closely monitored for adverse events throughout the study and for at least 90 days after the final dose of study treatment (see Section 8.2.1). Adverse events will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0), with CRS graded according

to the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 CRS Consensus Grading (Lee et al. 2019) (see Appendix 10).

An Internal Monitoring Committee (IMC) will be established to monitor patient safety during the study and make recommendations regarding study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment (see Section 4.6).

Participants will be assessed for radiologic tumor response by PET/CT and CT scans at the end of Cycle [redacted] (ctDNA screening), following the completion of treatment, and during the study follow-up period (see Section 1.3, Table 1 and Section 8.1.1 for details). Tumor response will be assessed by the investigator using the 2014 Lugano Response Criteria for Malignant Lymphoma (hereafter referred to as the 2014 Lugano Response Criteria) (Cheson et al. 2014) (see Appendix 11).

The study schema is illustrated in Section 1.2 (see Figure 1). The schedule of activities and the pharmacokinetic (PK), immunogenicity, and [redacted] schedule are provided in Section 1.3 (see Table 1 and [redacted], respectively).

## 4.2 RATIONALE FOR STUDY DESIGN

### 4.2.1 Rationale for Study Population

In the front-line setting, a subset of patients with DLBCL have poor outcomes following treatment with R-CHOP immunochemotherapy. Despite this, R-CHOP remains the SOC treatment for DLBCL. Efforts to define baseline prognostic scores and develop biomarkers to improve on the IPI and to guide treatment decisions have so far proved unsuccessful (Sehn et al. 2007).

In contrast to current baseline prognostic factors, ctDNA has the distinct advantage of permitting dynamic assessments early during a patient's treatment journey and in so doing, identify newly diagnosed individuals with suboptimal responses to immunochemotherapy who will likely progress in the absence of a change in treatment strategy and therefore may benefit from therapy intensification with glofitamab.

### 4.2.2 Rationale for Biomarker Assessments

DLBCL exhibits a striking heterogeneity in gene expression profiles and clinical outcomes, but its genetic causes remain to be fully elucidated.

Recently, two published studies have utilized [redacted]) to define new genetic subtypes of disease on the basis of the presence of recurrent genetic aberrations. Mutations were mapped to activated B cell–like (ABC) and germinal center B cell–like (GCB) subtypes of DLBCL, as originally identified by gene expression profiling. Schmitz and colleagues performed whole exome and transcriptome sequencing as well as array-based DNA copy number analyses and targeted amplicon resequencing on 574 mostly pretreatment DLBCL biopsy samples. The authors

identified four distinct genetic subtypes of disease with different recurring mutations correlating with clinical outcomes: *MCD*, *BN2*, *N1*, and *EZB* subtypes (Schmitz et al. 2018).

In parallel, Chapuy and colleagues classified 304 primary, previously untreated DLBCLs on the basis of low-frequency genetic alterations, recurrent mutations, somatic copy number alterations, and structural variants to define five different DLBCL subsets with differing high-frequency recurrent mutations (Chapuy et al. 2018).

[redacted] samples will be collected for [redacted] extraction to enable [redacted] or [redacted] to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with acquired resistance to glofitamab, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety.

In addition, because [redacted] material is often limited, assessment of tumor-associated biomarkers in the circulation is of high interest. Baseline ctDNA levels, as determined by next generation high-throughput sequencing of ctDNA in plasma, has been shown to reflect tumor burden in newly diagnosed patients with DLBCL (Kurtz et al. 2018). Furthermore, serial ctDNA assessments can be predictive of early treatment failure in patients with DLBCL in the first-line setting treated with rituximab in combination with chemotherapy regimens (Kurtz et al. 2018). Thus, ctDNA has potential as a prognostic and predictive biomarker. In this study, [redacted] samples obtained [redacted] to the start of study treatment will be obtained from all participants and tested for ctDNA levels by a central laboratory during the screening period. An additional sample will be obtained prior to Cycle [redacted], and the study will enroll [redacted] high-risk individuals, classified as patients who experience a $\leq$2-log ($<$100$\times$-fold) ctDNA decrease between baseline ([redacted]) and Day [redacted] of Cycle [redacted] (on-treatment) assessments. ctDNA will be also used to measure the depth and duration of treatment response, to inform relationships with established clinical response assessments such as PET/CT, and to track clonal tumor dynamics.

[redacted]

[redacted]

## 4.5 RATIONALE FOR TOCILIZUMAB AS TREATMENT FOR CYTOKINE-RELEASE SYNDROME

CRS is the result of excessive release of cytokines by immune effector or target cells during an exaggerated and sustained immune response. CRS can be triggered by a variety of factors, including infection with virulent pathogens or by medications that

activate or enhance the immune response, resulting in a pronounced and sustained immune response.

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

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

Tocilizumab is a recombinant, humanized, anti-human monoclonal antibody directed against the soluble and membrane-bound IL-6 receptor, which inhibits IL-6–mediated signaling. Blocking the inflammatory action of IL-6 with tocilizumab could therefore represent a novel approach for the treatment of CRS. Refer to the Tocilizumab Investigator's Brochure for additional preclinical and clinical information regarding tocilizumab.

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

Taken together, these findings indicate that participants treated with glofitamab who develop CRS may benefit from tocilizumab therapy.

## 4.6 INTERNAL MONITORING COMMITTEE

An IMC will be formed during the study to make recommendations on study conduct based on trial safety data to ensure enhanced patient safety while receiving study treatment. The IMC will consist of an IMC Medical Monitor Chair external to the study team and Sponsor representatives from Clinical Science, Safety Science, and

Biostatistics external to the study team. The IMC will convene to review cumulative safety data, including but not limited to the incidence and nature of serious adverse events, deaths, Grade ≥3 adverse events, dose reductions or dose delays in glofitamab, R-CHOP, and adverse events of special interest.

The IMC will operate according to a prespecified charter that will outline the IMC members, roles, responsibilities, and communication processes. The IMC may make recommendations regarding study conduct, including but not limited to the following: performing additional safety analyses, [redacted], amending the study protocol, holding enrollment pending further safety evaluations, holding/discontinuing study treatment, or terminating the study. The IMC will convene according to the schedule outlined in the IMC charter and may also be convened ad hoc and at the request of the Medical Monitor.

## 4.7 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure or visit shown in the schedule of activities, including survival follow-up visits conducted by telephone or on-site visits (see Section 1.3).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last datapoint required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur when all participants enrolled in the study have either had at least $24\ months$ of follow-up from the time of study treatment discontinuation or have discontinued from the study.

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

## 4.8 DURATION OF PARTICIPATION

The total duration of study participation for each individual participant is expected to be approximately $34$ months.

# 5. STUDY POPULATION

Approximately [redacted] participants with ctDNA high-risk untreated DLBCL will be enrolled in this study.

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

## 5.1 INCLUSION CRITERIA

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

### 5.1.1 Screening Inclusion Criteria

Participants must meet the following criteria for study screening entry:

- Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the Informed Consent Form and in this protocol
- Age ≥18 years at the time of signing Informed Consent Form
- Previously untreated patients with CD20-positive DLBCL, including one of the following diagnoses made according to the 2016 WHO classification of lymphoid neoplasms (Swerdlow et al. 2016):
  - DLBCL, not otherwise specified, including GCB and ABC/non-GCB types as well as double-expressor lymphoma (coexpression of *MYC* and *BCL2*)
  - High-grade B-cell lymphoma (HGBCL) with *MYC* and *BCL2* and/or *BCL6* translocations

    The number of participants with HGBCL will be capped at 15% of the screening population.
  - Patients with de novo transformed follicular lymphoma
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2 (see Appendix 14)
- IPI 1–5 (see Appendix 13)
  - Patients with an IPI of 0 with bulky disease (>6 cm) are eligible.
- Life expectancy of ≥6 months
- Availability of archival collected tumor tissue at baseline
  - The original pathology report must be available for review by the site monitor. Baseline tissue sample is mandatory and availability of archival biopsied tumor tissue samples should be confirmed at screening.
- Adequate biomarker blood samples prior to initiation of R-CHOP on Day 1 of Cycle 1 and on Day 1 of Cycle 2 submitted for screening for determination of ctDNA status
- At least one bi-dimensionally FDG-avid measurable lymphoma lesion on PET/CT scan, defined as >1.5 cm in its longest dimension on CT scan
- Left ventricular ejection fraction (LVEF) ≥50%, as determined on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram (ECHO)
- Negative HIV test at screening, with the following exception:
  - Patients with a positive HIV test at screening are eligible provided that, prior to enrollment, they are stable on anti-retroviral therapy for at least 4 weeks, have a CD4 count ≥ 200/µL, *and* have an undetectable viral load, and have not had a history of opportunistic infection *attributable to AIDS* within the *last* 12 months.

- Adequate hematopoietic function (unless evidence of extensive bone marrow involvement or hypersplenism secondary to underlying lymphoma for which blood product transfusions are permitted), defined as follows:
  - Hemoglobin $\geq 9$ g/dL without transfusion of packed RBCs 7 days prior to the first study treatment
  - ANC $\geq 1.0 \times 10^9$/L
  - Platelet count $\geq 75 \times 10^9$/L
- *For patients enrolled in France:*
  - *SARS-CoV-2 PCR testing within 48 hours before study treatment administration at each treatment cycle*
  - *Vaccination status in line with French National guidelines/recommendations (COSV, ANRS MIE)*
- For women of childbearing potential: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:
  - Women must remain abstinent or use methods of contraception, including at least one method with a failure rate of $< 1\%$ per year, during the treatment period and for 12 months after the final dose of R-CHOP, 3 months after the final dose of tocilizumab, or 2 months after the final dose of glofitamab, whichever is longer.
  - Women must refrain from donating eggs during this same period.
  - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq 12$ continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
  - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - A barrier method may be used as the second contraceptive method. Hormonal contraceptive methods must be supplemented by a barrier method.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agree 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 6 months after the final dose of R-CHOP, 3 months after the final dose of tocilizumab (if applicable), or 2 months after the final dose of glofitamab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

### 5.1.2 Additional Inclusion Criterion for ctDNA High-Risk Participants

Following [redacted] cycles of R-CHOP, participants will be eligible to proceed with study enrollment only if the following inclusion criterion (in addition to the screening inclusion criteria listed in Section 5.1.1) is met:

- Plasma sample evaluated to be ctDNA high risk using the experimental AOA-NHL Test, defined as < 2-log fold reduction in ctDNA levels between Day [redacted] of Cycle [redacted] and Day [redacted] of Cycle [redacted] by central laboratory assessment

## 5.2 EXCLUSION CRITERIA

Participants who meet any of the following criteria will be excluded from study screening and subsequent enrollment:

- Inability to comply with the [redacted] and restrictions
- Current diagnosis of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma (gray-zone lymphoma), primary mediastinal (thymic) large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, Burkitt lymphoma, CNS lymphoma (primary or secondary involvement), primary effusion DLBCL, and primary cutaneous DLBCL
- Contraindication to any of the individual components of R-CHOP, including prior receipt of anthracyclines
- History of severe allergic or anaphylactic reactions to murine monoclonal antibodies, or known sensitivity or allergy to murine products
- Prior treatment for indolent lymphoma
- Prior use of any monoclonal antibody within 4 weeks or five half-lives, whichever is shorter, and/or any investigational therapy within 28 days for the purposes of treating cancer preceding the start of Cycle 1

- Prior solid organ or allogeneic stem cell transplant
- Vaccination of live vaccines within 28 days prior to the start of Cycle 1 (currently available SARS-CoV-2 vaccines, including mRNA and viral vector vaccines, are not live; for further details, see Section 6.8.1)
- *Positive SARS-CoV-2 test within 7 days prior to enrollment. Rapid antigen test result is also acceptable*
- Prior therapy for DLBCL and HGBCL with the exception of palliative, short-term treatment with corticosteroids
  - Patients who require lymphoma symptom control during screening may receive steroids in the following manner:

    Up to 1 mg/kg prednisone or equivalent to a maximum of 100 mg/day for 7 days may be used for lymphoma symptom control during screening after a diagnostic biopsy has been collected. For doses $>1$ mg/kg, the Medical Monitor is available for consultation.

    Patients receiving corticosteroid treatment with $\leq 30$ mg/day of prednisone or equivalent for reasons other than lymphoma symptom control (e.g., rheumatoid arthritis) must be documented to be on a stable dose for at least 4 weeks' duration prior to the start of Cycle 1.

    The use of mineralocorticoids and corticosteroids for the management of orthostatic hypotension and adrenal insufficiency respectively, are permitted.
- Receipt of 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 R-CHOP
- Blood transfusion within 7 days prior to screening unless there is evidence of lymphomatous bone marrow or splenic involvement in which case transfusion of blood products support is permitted
- Any of the following abnormal laboratory values:
  - Serum creatinine clearance $<40$ mL/min (calculated according to the Cockcroft-Gault formula; see Appendix 16)
  - INR $>1.5\times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $>1.5\times$ ULN in the absence of a therapeutic anticoagulant or lupus anticoagulant
  - AST or ALT $>2.5\times$ ULN (unless due to disease involvement)
  - Total bilirubin $>1.5\times$ ULN (Patients with documented Gilbert disease may be enrolled if the total bilirubin is $\leq 3\times$ ULN).
- Recent major surgery (within 6 weeks prior to the start of Day 1 of Cycle 1) other than for diagnosis
- Significant or extensive history of cardiovascular disease such as New York Heart Association Class III or IV cardiac disease or Objective Assessment Class C or D,

myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina.

- History of other cancers within 2 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
  - Patients with a malignancy treated with curative surgery alone are not eligible, unless the cancer has been in documented remission without treatment for $\geq$2 years prior to enrollment.
  - Patients with current low-grade, early-stage prostate cancer (Gleason score $\leq$6, Stage 1 or 2) with no requirement for therapy at any time prior to the study are eligible.
- Any active infection within 7 days prior to Day 1, Cycle 1 or at the time of enrollment, that would impact patient safety
  - In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society of Medical Oncology [ESMO]).
- Positive test result for hepatitis B surface antigen (HbsAg) at screening
  - Patients with occult or prior hepatitis B virus (HBV) infection (defined as negative HBsAg and positive total hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.
- Positive test result for hepatitis C virus (HCV) antibody at screening
  - Patients who are positive for other HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Suspected or latent tuberculosis
- History of progressive multifocal leukoencephalopathy
- Confirmed or suspected chronic active Epstein-Barr viral infection
- Known or suspected history of HLH
- Clinically significant history of liver disease, including viral or other hepatitis or cirrhosis
- Substance abuse, including non-prescription drug and alcohol dependence, within 12 months prior to screening
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study, including severe mental illness requiring hospitalization and antipsychotic medication
- 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 with the following possible exceptions:

  - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone
  - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for study.
  - Patients with a history of disease-related immune thrombocytopenic purpura, autoimmune hemolytic anemia, or other stable autoimmune diseases
  - Participants with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

    Rash must cover < 10% of body surface area.

    Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

    No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

- Malabsorption syndromes or other conditions that would interfere with enteral absorption
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 months after the final dose of R-CHOP, 3 months after the final dose of tocilizumab (if applicable), or 2 months after the final dose of glofitamab

## 5.3 LIFESTYLE CONSIDERATIONS

### 5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

### 5.3.2 Caffeine, Alcohol, and Tobacco

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

### 5.3.3 Activity

This study has no activity restrictions.

### 5.3.4 Contraception Requirements

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

## 5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be re-screened. The investigator will maintain a record of reasons for screen failure (see Section 8).

# 6. STUDY TREATMENT AND CONCOMITANT THERAPY

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

The investigational medicinal products (IMPs) for this study are glofitamab and tocilizumab. R-CHOP and any corticosteroid pretreatment are considered non-investigational medicinal products. CNS prophylaxis with intrathecal methotrexate, prophylaxis for neutropenia with granulocyte colony-stimulating factors (G-CSFs), and dexamethasone are also considered non-investigational medicinal products. *Appendix 17 identifies all IMPs and auxiliary medicinal products for this study.*

## 6.1 STUDY TREATMENTS ADMINISTERED

A description of assigned study treatments for this study is provided in Table 4.

## Table 4 Study Treatment Description

| | Glofitamab | Tocilizumab | Rituximab | CHOP | Dexamethasone | Allopurinol | Rasburicase | G-CSF | Methotrexate |
|---|---|---|---|---|---|---|---|---|---|
| Use | Experimental | Other | NIMP | NIMP | Premedication | Rescue medication | Rescue medication | Other | Other |
| Type of medicinal product | IMP | IMP | *AxMP* | *AxMP* | *AxMP* | *uAxMP* | *AxMP* | *AxMP* | *AxMP* |
| Drug form<br>Unit dose strength(s)<br>Formulation(s)<br>Packaging | Refer to the pharmacy manual and respective Investigator's Brochure. | | | Refer to the local prescribing information. | Refer to the local prescribing information. | Refer to the local prescribing information. | Refer to local prescribing information. | Refer to the local prescribing information. | Refer to the local prescribing information. |
| Dosage level(s) | Day 8, Cycle 3: 2.5 mg<br>Day 15, Cycle 3: 10 mg<br>Day 8, Cycles 4–6: 30 mg<br>Day 1, Cycles 7–10 : 30 mg | 8 mg/kg | 375 mg/m$^2$ | | 20 mg | 300 mg/day | | Filagrastim: 5 μg/kg<br>Pegfilgrastim: 6 mg | |

CHO = Chinese hamster ovary; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone; G-CSF = granulocyte colony-stimulating factor; IMP = investigational medicinal product; *AxMP = auxiliary medicinal product; uAxMP = unauthorized auxiliary medicinal product.*

**Table 4 Study Treatment Description (cont.)**

| | Glofitamab | Tocilizumab | Rituximab | CHOP | Dexamethasone | Allopurinol | Rasburicase | G-CSF | Methotrexate |
|---|---|---|---|---|---|---|---|---|---|
| Route of administration | IV infusion | IV infusion | IV infusion | [redacted] | IV | Oral | IV | SC | Intrathecal |
| Source | Sponsor | Sponsor or site; tocilizumab may be obtained locally by the study sites for emergency purposes if permitted by local regulations and will be formulated, prepared, and handled according to standard practice. | Site | Site | Site | Site | Site | Site | Site |

CHO = Chinese hamster ovary; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone; G-CSF = granulocyte colony-stimulating factor; IMP =investigational medicinal product; *AxMP = auxiliary medicinal product; uAxMP = unauthorized auxiliary medicinal product.*

The treatment regimens are summarized in Section 4.1.

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

### 6.1.1 Glofitamab

Glofitamab will be administered by IV infusion to participants intravenously according to the schedule outlined in Section 1.3, Table 1, and Section 4.1.1. 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 adverse events that may arise as a result of glofitamab treatment (Appendix 10), and nephrology consultation with acute dialysis capabilities should be readily available to address any renal toxicity that might accompany TLS (see Appendix 6). Participants should be under close observation by the investigator at all times.

Glofitamab will be administered to participants on a step-up dosing schedule, starting on Day 8 of Cycle 3 (2.5 mg), Day 15 of Cycle 3 (10 mg), followed by 30 mg on Day 8 of Cycles 4–6 and Day 1 of Cycles 7–10, with each cycle being 21 days in length (i.e., every 3 weeks). See Figure 2 for the dosing schema. An [redacted] (e.g., on Day [redacted] of Cycle [redacted]) or [redacted] (e.g., [redacted] mg on Day [redacted] of Cycle [redacted] and [redacted] mg on Day [redacted] of Cycle [redacted]) may also be introduced in the event these alternative schedules are explored in Study NP40126.

Premedication with 20 mg IV dexamethasone should be administered 1 hour prior to the administration of glofitamab; premedication with (500 or 1000 mg) oral acetaminophen or paracetamol and an antihistamine, such as (50 mg) diphenhydramine, should be administered approximately 30 minutes prior to the start of the infusion (see Table 5).

**Table 5 Premedications to be Administered Prior to Glofitamab Infusions**

| Timepoint | Participants Requiring Premedication | Premedication | Administration |
|---|---|---|---|
| Glofitamab [a, b] Cycle 3, Day 8 and onward; all doses | All participants | IV dexamethasone [a, d] | At least 60 minutes prior to the first dose of study treatment |
| | | Oral or IV analgesic/ antipyretic medication | At least 30 minutes prior to glofitamab infusion |
| | | Oral or IV antihistamine [c] | At least 30 minutes prior to glofitamab infusion |

CRS = cytokine-release syndrome; PO = orally.

[a] Optional at subsequent cycles based on investigator's assessment for participants who have tolerated two 30-mg doses of glofitamab without experiencing CRS.

[b] All glofitamab doses should be administered to well-hydrated participants. Closely monitor participants during the entire infusion.

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

[d] Administer 20 mg IV dexamethasone prior to glofitamab. If dexamethasone is not available or if the participant has an intolerance to dexamethasone, alternate corticosteroid (80 mg IV methylprednisolone, 100 mg prednisone PO, or 100 mg prednisolone by IV infusion) may be used for glofitamab premedication, after consultation with the Medical Monitor.

Notes: For glofitamab infusions during Cycles [redacted] and [redacted]; vital signs should be monitored and recorded preinfusion, every 30 (± 10) minutes during, at the end of the infusion, and 2 hours after infusion. For participants who tolerate glofitamab infusions during Cycles [redacted] and [redacted] in the absence of CRS, for subsequent cycles, vital signs should be assessed preinfusion, every 60 (± 15) minutes during the infusion, and 2 hours following the end of infusion. In cases when CRS occurs during Cycle [redacted] or [redacted], vital signs should be assessed preinfusion, every 30 (± 10) minutes during the infusion, and at 30-minute intervals (± 10 minutes) for 2 hours following the end of the infusion. For participants who experience CRS but in subsequent cycles tolerate two consecutive glofitamab infusions without CRS, monitoring of vital signs may be adjusted and include pre-infusion, every 60 (± 15) minutes during the infusion, and 2 hours after the end of infusion. The monitoring of vital signs should be more frequent in participants deemed to exhibit disease-related factors, which may confer an increased risk of severe CRS. For such patients, assessments should be performed at least every 15 minutes during the first infusion in Cycle 3 and up to at least 2 hours postinfusion.

See Appendix 8 for anaphylaxis precautions.

Guidelines for medical management of IRRs are provided in Appendix 6.

Glofitamab should be administered to well-hydrated participants. Participants at risk of TLS should receive TLS prophylaxis (for details, see Section 6.1.5.3).

[redacted]



Premedication with dexamethasone will be optional during subsequent cycles based on investigator's assessment for participants who tolerate two 30-mg doses of glofitamab without experiencing CRS. However, if the participant experiences CRS, premedication with dexamethasone is required for subsequent glofitamab doses until no additional events of CRS are observed. Please see Section 4.4 for hospitalization requirements. Participants with a Grade ≥2 event of CRS associated with the preceding dose of glofitamab should be hospitalized at least overnight for the next glofitamab dose. Investigators may choose to hospitalize a participant following any glofitamab dose for close monitoring if indicated based on his or her clinical judgment. Hospitalization should be considered for participants who lack support for close monitoring at home or who live a considerable distance from the study center.

In case of infusion-associated adverse events in a participant, the signs and symptoms should be fully resolved before the participant is discharged.

The recommended management of CRS is detailed in Appendix 6. The schedule activities for participants who receive tocilizumab for treatment of CRS is presented in Appendix 7.

Please refer to the pharmacy manual and the Glofitamab Investigator's Brochure for more details.

### 6.1.2 Rituximab

Rituximab will be administered intravenously to participants every 21 days, along with CHOP as detailed in Section 1.3, Table 1. Rituximab preparation and administration will be performed according to local prescribing information. No subcutaneous administration of rituximab is allowed in the study. A locally approved SOC biosimilar rituximab is permitted.

Rituximab must be administered to participants in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and

participants should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, refer to the local prescribing information and institutional guidelines.

| Treatment | Participants Requiring Premedication | Premedication | Administration |
|---|---|---|---|
| Rituximab [a, b] | All participants | IV corticosteroid [c] | At least 60 minutes prior to infusion |
| | | Oral or IV analgesic or antipyretic medication | At least 30 minutes prior to infusion |
| | | Oral or IV antihistamine [d] | |
| | Participants at risk of TLS (e.g., bulky disease or renal impairment [creatinine clearance $<$70mL/min or LDH $\geq 2 \times$ ULN, with or without bulky disease)] | Allopurinol or suitable alternative, such as rasburicase, along with adequate hydration [e] | |

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; LDH = lactate dehydrogenase; TLS = tumor lysis syndrome; ULN = upper limit of normal.

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

[b] All study doses will be administered to well-hydrated patients.

[c] 80 mg IV methylprednisone or equivalent dose of IV prednisone (100 mg), comprising the prednisone component of the CHOP treatment. Hydrocortisone should not be used as it has not been effective in reducing the rate of infusion reactions.

[d] For example, 50–100 mg diphenhydramine (unless contraindicated).

[e] TLS prophylaxis is also required during Cycle [redacted] of CHOP administration (see Section 6.1.5.3).

### 6.1.3 CHOP Chemotherapy

CHOP chemotherapy consists of IV cyclophosphamide, IV doxorubicin, vincristine administered by IV push, and oral prednisone or prednisolone. Standard CHOP will be administered for six 21-day cycles (including Cycles [redacted] and [redacted] during [redacted]) as follows:

- Cyclophosphamide: 750 mg/m$^2$ administered intravenously on Day 1
- Doxorubicin: 50 mg/m$^2$ administered intravenously or according to institutional guidelines on Day 1
- Vincristine: 1.4 mg/m$^2$ administered by IV push on Day 1 at a recommended cap of 2 mg

- Prednisone: 100 mg/day orally (PO) on Days 1–5 (prednisone on Day 1 may be administered intravenously, with the remaining doses on Days 2–5 to be administered PO)
  - Note: The dose of prednisone follows the National Comprehensive Cancer Network® (NCCN's) recommendations (2020), which are based on Czuczman et al. (1999) and Hiddemann et al. (2005). Prednisone may be replaced with prednisolone (1:1 conversion; 100 mg) in countries where prednisone is not available or is not the therapy of choice; it may be replaced with 80 mg methylprednisolone in countries or at sites that do not have access to prednisone.

CHOP will be administered according to the standard preparation and infusion procedures at each investigational site and after the rituximab infusion. Refer to the specific package inserts for preparation, administration, and storage guidelines.
At the discretion of the investigator, the dose of vincristine may be capped at 2 mg.
For participants who are ≥70 years old, the dose of vincristine may be capped at 1.5 mg.
Body surface area (BSA) may be capped at 2 $m^2$ per institutional standards.

When rituximab and CHOP are scheduled to be administered on the same day, it is recommended that prednisone (100 mg) be given prior to the rituximab infusion. *CHOP may be administered prior to rituximab if permitted per local guidelines.* If the Day [redacted] Cycle [redacted] dose of rituximab is split, then both infusions must happen with appropriate premedication and following infusion guidelines outlined in pharmacy manual(s) or Summary of Product Characteristics. If CHOP is started later than Day [redacted] of the cycle, then planned Day [redacted] of the next cycle should be calculated from the day when CHOP was initiated to maintain the regular chemotherapy interval of 21 days.

Guidelines for dosage modification and treatment interruption or discontinuation of all study drugs are provided in Appendix 6. See the local prescribing information for additional details on administration of rituximab and CHOP. Likewise, see the Investigator's Brochures and pharmacy manuals for more details on glofitamab.

### 6.1.4 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. Tocilizumab will be administered as a rescue IMP when necessary to participants who experience a CRS event (see Appendix 7). Tocilizumab will be supplied by the Sponsor as an IMP. Due to the need to manage CRS urgently and potential accessibility limitations at the site, commercial tocilizumab can be obtained locally by the study site for emergency use purposes. It will be prepared, handled, and managed according to standard institutional practices. Prior to infusing glofitiamab, the healthcare facility must have on-site access to tocilizumab and ensure that tocilizumab is available for the participant, if needed.

Note: If tocilizumab is administered, see Appendix 7 for the schedule of activities for participants treated with tocilizumab for CRS.

### 6.1.5 Prophylaxis

#### 6.1.5.1 Prophylaxis for Neutropenia: Administration of Granulocyte Colony-Stimulating Factor

In order to minimize the rate, severity, and duration of neutropenia-related complications, all participants should receive primary prophylaxis with G-CSF during Cycles [redacted]

Use of G-CSF is mandatory during Cycles [redacted] with either one of the following:

- Filagrastim: 5 μg/kg administered subcutaneously (rounded to 300 μg or 480 μg) once a day up to 48 hours after administration of R-CHOP (on Day [redacted] of Cycles [redacted]) and continued for 7 days or until ANC is $> 1.5 \times 10^9$/L on 2 consecutive days
- Pegfilgrastim: 6 mg administered subcutaneously up to 48 hours following administration of R-CHOP (on Day [redacted] of Cycles [redacted])
  - Lenograstim is an acceptable alternative.

G-CSF may be given intravenously if preferred or when clinically indicated.

#### 6.1.5.2 Prophylaxis for Viral Infections

Anti-infective prophylaxis for viral (including COVID-19), fungal, bacterial, or Pneumocystis infections is permitted and should be instituted per institutional practice or national guidelines/recommendations. It is strongly recommended that all participants receive primary prophylaxis with oral acyclovir, starting at Cycle [redacted] The preferred agent is a dose of acyclovir (400 mg twice a day for the duration of chemotherapy). Valcyclovir (500 mg twice a day) is a suitable alternative. The duration and schedule may be adjusted according to institutional guidelines. IV immunoglobulin therapy is permitted as prophylaxis against viral infections according to institutional practice or national guidelines/recommendations.

*For participants enrolled in France: Prophylactic administration of anti-SARS-CoV-2 antibodies (e.g., Evusheld) per French National guidelines/recommendations must be utilized for enrolled participants. Investigators must implement prompt, best-available therapy in any study participants who develop COVID-19 infection as per French National Guidelines/Recommendations (COSV, ANRS MIE).*

#### 6.1.5.3 Prophylaxis for Participants at High Risk for Tumor Lysis Syndrome

Participants with high tumor burden who are considered by the investigator to be at risk for tumor lysis should also receive tumor lysis prophylaxis prior to the initiation of treatment. High-risk factors for TLS include bulky disease, renal impairment (creatinine clearance $< 70$ mL/min), or lactate dehydrogenase $\geq 2 \times$ ULN, with or without bulky disease. In addition, all participants with high tumor burden should be treated with hydration and 300 mg/day allopurinol PO or a suitable alternative treatment

(e.g., rasburicase) starting within 48 to 72 hours prior to Day [redacted] of Cycle [redacted] of treatment until the end of Cycle [redacted] or at least 14 days.

#### 6.1.5.4 Prophylaxis for Hemorrhagic Cystitis

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

#### 6.1.5.5 Preplanned Radiotherapy

Preplanned radiotherapy (i.e., radiation that was scheduled before randomization to be given at the end of study treatment) may be administered to initial sites of bulky or extranodal disease according to institutional practice. If indicated, preplanned radiotherapy should be initiated within 8 weeks of the final dose of study treatment and should commence once all "end of treatment assessments," including PET/CT scans used for disease response assessment, are completed. Any radiotherapy should be preplanned by the investigator and documented prior to enrollment then entered in the eCRF once the patient is enrolled. Conversely, any unplanned radiotherapy administered to patients will be considered as a new anti-lymphoma treatment.

#### 6.1.5.6 Central Nervous System Prophylaxis

CNS prophylaxis with intrathecal *or systemic* methotrexate *may be given according to institutional practice as part of the pre-planned protocol for a participant. CNS prophylaxis with systemic methotrexate may be given only after completion of the treatment discontinuation/completion response assessment at the discretion of the treating investigator.*

### 6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor where required by local regulations. The study site (i.e., investigator or other authorized personnel) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

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

monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

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

## 6.3 TREATMENT ASSIGNMENT

This is a 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 participant, the study site will obtain the participant's identification number and treatment assignment through the IxRS.

## 6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the eCRF. The dose of study treatment and study participant identification number will be confirmed at the time of dosing by a member of the study site staff other than the person administering study treatment.

## 6.5 DOSE MODIFICATION

The dose of glofitamab can be reduced for management of drug-related toxicities as described in Appendix 6.

Guidelines for dose delays and/or modifications of rituximab and/or CHOP should be followed using the local prescribing information.

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

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

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

## 6.7 TREATMENT OF OVERDOSE

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

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities.
3. Optional: Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).

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

## 6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to the end of therapy visit must be recorded on the Concomitant Medications eCRF(s} along with the following information:

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

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

### 6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local

standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or $H_2$-receptor antagonists (e.g., famotidine, cimetidine) or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and $\beta_2$-adrenergic agonists).

Use of the following concomitant therapies is permitted as described below:

- Participants who use oral contraceptives (with a failure rate of $< 1\%$ per year; see Section 5.1), hormone-replacement therapy, or other maintenance therapy should continue their use.
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) to non-target sites as outlined below:
  - Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measureable disease).
  - Study drug treatment may be continued during palliative radiotherapy.
- Pain medications administered per standard clinical practice
- Inactive influenza vaccination
- Bisphosphonates for prevention of skeletal-related events
- Intrathecal methotrexate for CNS prophylaxis (see Section 6.1.5.6 for additional details)
- Anti-infective prophylaxis for viral (see Section 6.1.5.2), fungal, bacterial, or *Pneumocystis* infection should be initiated per institutional practice or investigator preference on the basis of an individual patient's risk factors.
  - Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the SOC may be treated prophylactically (Flowers et al. 2013; Reddy et al. 2015; NCCN 2020). All use of anti-infective prophylaxis should be recorded appropriately on the eCRF.
- TLS prophylaxis and therapy according to published recommendations and/or institutional practice (see Section 6.1.5.3)
- Anti-emetic prophylaxis and antidiarrheal prophylaxis per institutional guidelines
  - The use of anti-emetic medications must be documented on the eCRF.
- Prophylactic and therapeutic use of G-CSF (filgrastim or pegfilgrastim) in accordance with institutional practice and/or published guidelines (Smith et al. 2015) (see Section 6.1.5.1)

- Treatment of severe CRS or HLH according to published recommendations as described in Appendix 6 and/or institutional practice is permitted.
  - Participants who experience glofitamab infusion-related symptoms may be treated symptomatically.
    - Participants who experience glofitamab-associated CRS may be treated symptomatically. Given the expected pharmacology of glofitamab, the release of cytokines in the immediate period after the first infusion of each compound may lead to secondary alteration of cytochrome P450 (CYP450) enzymes, with risk of subsequent drug–drug interactions. Based upon nonclinical models, this risk is the highest during the first 24 hours after infusion. Systemic cytokine release is considered a "first-pass effect" that may be related, in part, to levels of circulating CD20-positive target cells, and targets will decline with R-CHOP and continued glofitamab dosing. Participants at highest risk for drug–drug interactions are those receiving concomitant medications that are CYP450 substrates. As such, medications fitting this description should be monitored closely and the dose adjusted as necessary (see Appendix 6). The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator may consult with the Medical Monitor if he or she has any questions.
- *Prophylactic anti–SARS-CoV-2 therapy*

  *Administration of anti–SARS-CoV-2 prophylaxis, if available, should be considered for all patients. The best timing of administration (i.e., before initiation of study treatment or during the study) should be in the investigator's judgment.*
- *Vaccinations (such as COVID-19)*

  *COVID-19 vaccines (approved, non-live), including booster vaccines for novel variants, are strongly recommended for all patients. Information on SARS-CoV-2 vaccine administration should be collected even if it was given more than 7 days prior to initiation of study treatment.* The decision to administer a SARS-CoV-2 vaccine should be individualized by the investigator in consultation with the patient.

  Factors to consider when making the individualized decision for patients receiving glofitamab include the following:

  – *Potential risks associated with* SARS-CoV-2 infection and potential benefit*s and risks* from *COVID-19 vaccination*

  – General condition of the patient *and severity/seriousness of underlying disease*

  – Epidemiology of *SARS-CoV-2 infection* in the patient's location

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

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

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

### 6.8.2 Cautionary Therapy

#### 6.8.2.1 Medications Given with Precaution Due to Effects Related to Cytochrome P450 Enzymes

The use of any calcium channel entry blockers given concomitantly with an anthracycline drug may potentially increase the risk of cardiac toxicity associated with anthracycline administration. It is recommended that calcium-channel blockers be avoided within 30 days of the administration of an anthracycline drug when possible and as clinically appropriate.

**Tocilizumab**

CYP450 enzymes in the liver are downregulated by infection and inflammatory stimuli, including cytokines such as IL-6. Inhibition of IL-6 signaling in patients with rheumatoid arthritis who are treated with tocilizumab may restore CYP450 activities to higher levels than those patients not treated with tocilizumab, leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CY2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The effects of tocilizumab on CYP2C8 or transporters are unknown. In vivo studies with omeprazole (metabolized by CYP2C19 and CYP3A4) and simvastatin (metabolized by CYP3A4) showed up to a 28% and 57% decrease in exposure 1 week following a single dose of tocilizumab, respectively.

The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index (see Appendix 15), when the dose is individually adjusted:

- Upon initiation or discontinuation of tocilizumab in participants being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed.
- Prescribers should exercise caution when tocilizumab is co-administered with CYP3A4 substrate drugs for which a decrease in effectiveness is undesirable (e.g., oral contraceptives, lovastatin, atorvastatin).

- The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

#### 6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 6.8.2.1) may be used during the study at the discretion of the investigator; herbal therapies intended for the treatment of lymphoma are prohibited.

### 6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) within 28 days prior to initiation of study treatment and during study treatment
- Concomitant therapy intended for the treatment of cancer (including but not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) for various time periods prior to starting study treatment, depending on the agent, and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances after consultation with the Medical Monitor (see Section 6.8.1 for details)
- The administration of live, attenuated influenza vaccine (e.g., FluMist®) during treatment and within 28 days following the final dose of *study treatment*
- Biologic agents other than hematopoietic growth factors and anti-COVID-19 therapy, which are allowed if clinically indicated as described in Section 6.8.1 and used in accordance with instructions provided in the package inserts
  - For participants who develop SARS-CoV-2 severe infections, therapy including administration of convalescent plasma as treatment for COVID-19 may be permitted after consultation with the Medical Monitor.
- Steroid therapy with antineoplastic intent, with exceptions, including inhaled steroids for asthma, topical steroids, or replacement or stress corticosteroids during the study at any time
  - Other indications to be discussed in advance with the Medical Monitor.

Participants who require the use of any of these agents will be discontinued from treatment with glofitamab. Participants who are discontinued from study treatment will be followed for safety outcomes for 3 months following the participant's final dose of glofitamab or until the participant receives another anti-cancer therapy, whichever comes first, and thereafter for survival.

The above list of medications is not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication, as well as the internet references provided below when determining whether a certain medication is

potentially contraindicated during treatment with glofitamab. In addition, the investigator may consult with the Medical Monitor if questions arise regarding medications not listed above.

#### 6.8.3.1 Immunizations

Participants who participate in the study may not receive either primary or booster vaccination with live virus vaccines for at least 4 weeks prior to the initiation of or at any time during study treatment or after the final dose of study treatment until the range of B-cell counts recover to normal range. Participants who require the use of vaccination with live virus vaccines will be discontinued from study treatment.

## 7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

### 7.1 DISCONTINUATION OF STUDY TREATMENT

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

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Confirmed disease progression per investigator assessment according to 2014 Lugano Response Criteria (see Appendix 11) or symptomatic deterioration attributed to disease progression
- Unacceptable toxicity

Participants who discontinue study treatment prematurely (prior to their planned Cycle [redacted] will be asked to return to the clinic for a study completion or early termination visit and follow-up assessments (see Section 8). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

In the event that a participant discontinues from study treatment early for reasons other than progressive disease, he or she will proceed to the follow-up period per the schedule of activities until progression (see Section 1.3, Table 1).

See the schedule of activities in Section 1.3, Table 1, for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

## 7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

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

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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3, Table 1). See the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

## 7.3 PARTICIPANTS LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to

return to the clinic and determine if there are ways to support participant participation.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (when possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

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

## 8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status will be recorded at baseline. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded.

Demographics, including age, sex, and self-reported race/ethnicity, will also be recorded. Prognostic factors according to Ann Arbor staging and IPI (see Appendix 12 and Appendix 13, respectively) will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

## 8.1 EFFICACY ASSESSMENTS

### 8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening, the interim response assessment (between Days [redacted] and [redacted] of Cycle [redacted]), and at the EOT using $^{18F}$FDG-PET/CT and diagnostic CT scans (see Section 1.3, Table 1). Response will be evaluated according to the 2014 Lugano Response Criteria (see Appendix 11). During survival follow-up, response will continue to be evaluated every 6 months until the participant develops progressive disease, discontinues from the study, at any time disease progression is suspected, or until $24\ months$ from the EOT response assessment, whichever occurs first. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Clinical response assessment should include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly by physical examination.

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

#### 8.1.1.1 Radiographic Assessments

FDG-PET/CT scans, in conjunction with diagnostic-quality CT scans, are required at screening and the EOT (see Section 1.3, Table 1). Only FDG-PET/CT scans are required at the interim response assessment (Days [redacted]–[redacted] of Cycle [redacted]). At all times during the study, diagnosis of disease progression based on clinical examination must be confirmed by imaging (e.g., CT scan, FDG-PET/CT scan) as soon as feasible (within 30 days) and prior to initiation of non–protocol-specified anti-cancer therapy.

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).

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

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

CT scans with contrast (per institutional standard operating procedures) should include the chest, abdomen, and pelvis. CT or MRI scans of other disease sites should be performed as clinically indicated. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan is permitted if it allows for consistent and precise measurement of target lesions during the study. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Diagnostic contrast-enhanced CT scans obtained as part of a PET/CT scan may be used in lieu of dedicated CT scans.

Details regarding imaging procedures will be provided in an imaging manual.

Radiographic images may be submitted to an independent review facility for a quality and completeness check, for potential central review, and for temporary storage prior to transferring images to the Sponsor.

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

#### 8.1.1.2 Response Evaluation

Objective response will be determined by the investigator at specified timepoints according to the 2014 Lugano Response Criteria (Cheson et al. 2014) (see Appendix 11). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Efficacy endpoints (e.g., CR at the EOT, EOT ORR, and PFS) will be calculated programmatically by the Sponsor on the basis of investigator assessments of response at each specified timepoint.

### 8.1.2 Bone Marrow Assessments

A bone marrow aspirate and trephine biopsy are not mandatory at screening; however, if a bone marrow assessment is performed within 3 months prior to Day [redacted] of Cycle [redacted] for the purpose of diagnosis and staging of DLBCL, an authorized laboratory pathology report should be supplied (central receipt of bone marrow samples are not required). On the first occasion that a patient with bone marrow involvement at screening is assessed by CT rather than PET/CT scan, a repeat biopsy is necessary before a CR

can be recorded. Otherwise, additional bone marrow biopsies are not mandatory and should be performed when clinically indicated (e.g., clinical suspicion of progressive disease in the bone marrow when there is discordance with radiographic imaging; please see Appendix 11).

### 8.1.3 Physical Examinations

A complete physical examination will include, at a minimum, assessment of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary exams may be performed if clinically indicated. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. As part of the complete physical examination, the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly will be recorded on the appropriate Tumor Assessment eCRF.

A targeted, symptom-directed, physical examinations will include, at a minimum, assessments of the skin, respiratory, cardiovascular systems, and abdomen (liver and spleen) and should be performed at specified postbaseline visits and as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. As part of tumor assessment, targeted physical examination should also include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, splenomegaly, or other findings of concern for lymphoma, which will be recorded on the appropriate Tumor Assessment eCRF.

### 8.1.4 Vital Signs

Vital signs will be assessed with a completely automated device while the participant is in a in a seated or semi-supine position after 5 minutes rest and will include temperature, pulse rate, pulse oximetry, respiratory rate, and systolic and diastolic blood pressure. Manual techniques will be used only if an automated device is unavailable.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or unresolved clinically significant abnormalities on the Adverse Event eCRF.

### 8.1.5 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3, Table 1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (per Fridericia's formula [QTcF]/QT) intervals.

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

as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

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

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor is available for consultation.
SOC treatment may be instituted at the investigator's discretion. If a PK sample is not scheduled for that timepoint, a PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Appendix 6. The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

### 8.1.6 Cardiac Assessment: ECHO or MUGA Scan

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

### 8.1.7 Clinical Safety Laboratory Assessments

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

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

participant's condition. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
  - Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days of the final dose of study treatment (or initiation of another systemic anticancer therapy, whichever comes first) should be repeated until the values return to normal or baseline or are are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified. This is not required if a participant has discontinued study treatment and started a new treatment regimen.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities.

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

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

### 8.1.8 Unscheduled Visits

Unscheduled visits may be performed if clinically indicated. Participants will undergo the specified assessments, and additional assessments may be performed if clinically indicated, as determined by the investigator.

### 8.1.9 Pregnancy Testing

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

## 8.2 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

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

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

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

### 8.2.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug in Cycle [redacted], only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. All other medical occurrences that begin before the start of study treatment in Cycle [redacted] but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 90 days after the final dose of rituximab, tocilizumab, or glofitamab at the timepoints specified in the schedule of activities (see Section 1.3, Table 1).

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

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

### 8.2.2 Method of Detecting Adverse Events and Serious Adverse Events

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

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

### 8.2.3 Follow-Up of Adverse Events and Serious Adverse Events

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

### 8.2.4 Regulatory Reporting Requirements for Serious Adverse Events

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements *for expedited* safety reporting to regulatory authorit*ies (which includes the use of applicable systems, such as EudraVigilance)*, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

| Drug | Document |
|---|---|
| Glofitamab | Glofitamab 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.

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

### 8.2.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 12 months after receiving R-CHOP, 3 months after the final dose of tocilizumab (if applicable), or 2 months after the final dose of glofitamab.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within at least 6 months after the final dose of R-CHOP, 3 months after the final dose of tocilizumab (if applicable), or 2 months after the final dose of glofitamab.

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

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

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

### 8.2.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

### 8.2.7 Anticipated Events Not Qualifying for Expedited Reporting

Certain adverse events are anticipated to occur in the study population at some frequency independent of study treatment exposure and will be excluded from expedited reporting. These anticipated events include but are not limited to the following:

- Deaths attributed solely to disease progression are exempt from serious adverse event reporting.

### 8.2.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.7)
- Suspected transmission of an infectious agent by a study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

Adverse events of special interest specific for glofitamab include the following:

- Grade ≥2 cytokine release syndrome
- Grade ≥2 neurologic adverse event
- Suspected hemophagocytic lymphohistiocytosis
- Tumor lysis syndrome (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 flare (e.g., manifestation of signs/symptoms associated with an increase in size of known nodal or extranodal lesions by clinical or radiographic assessment)
- Any grade *pneumonitis,* interstitial lung disease*, acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia, and/or pulmonary toxicity*
- Colitis of any grade (excluding infectious etiology)

### 8.2.9 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week. Details will be provided separately.

## 8.3 PHARMACOKINETICS

Samples will be collected for measurement of serum concentrations of glofitamab and rituximab, as well as ADAs as specified in the schedule of activities (see Section 1.3, Table 2).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

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

Samples will be used to evaluate the pharmacokinetics of glofitamab and rituximab. Samples collected for analyses of serum glofitamab or rituximab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the Informed Consent Form. Participant confidentiality will be maintained. At visits when serum samples for the determination of glofitamab concentrations will be obtained, one sample of sufficient volume can be used.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

## 8.4 PHARMACODYNAMICS

See Section 8.6 for information on pharmacodynamic biomarkers.

## 8.5 GENETICS

See Section 8.6 and Appendix 5 for information on genetic biomarkers.

## 8.6 BIOMARKER ASSESSMENTS

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

- [redacted] and [redacted] samples for determination of [redacted] status for determination of eligibility for enrollment
- [redacted], and [redacted] samples for [redacted] (including biomarker assay development)
- Archival tumor tissue sample obtained at baseline for [redacted] and biomarker assay development
  - A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology reportprior to study enrollment. If less than 15 slides are available, the individual may still be eligible.
  - Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular

context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

- Baseline tissue sample is mandatory and availability of archival biopsied tumor tissue samples should be confirmed at screening.

[redacted] may include but will not be limited to analysis of cytokines associated with response and/or inflammation, [redacted] or MRD assessment, and molecular profiling, including but not limited to cell of origin.

[redacted] may involve extraction of [redacted], or [redacted] and analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. DNA extracted from blood may be compared with [redacted] extracted from [redacted] to identify somatic variants by distinguishing germline variants from somatic variants. [redacted] methods may include [redacted] or [redacted] of [redacted] samples.

Screening [redacted], and [redacted] samples, including those obtained from individuals who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

[redacted] according to the schedule outlined in Section 1.3 (see Table 1 and [redacted]). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Biomarker samples (and their derivatives) will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the following exceptions:

- [redacted] samples (and their derivatives) that undergo [redacted] or [redacted] will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- [redacted], and [redacted] samples (and their derivatives) that undergo [redacted] analyses will be destroyed no later than 10 years after the final Clinical Study Report has been completed.
- For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than the date of final closure of the clinical database, whichever occurs first. For individuals who are not enrolled, remaining archival

tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

Given the complexity and [redacted], data derived from these analyses will generally not be provided to study investigators or patients unless required by law. Outcomes from ctDNA analyses conducted to inform potential eligibility for the study will be provided to study investigators. If allowed by local laws, the investigator may share the results with the participant. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

## 8.7 IMMUNOGENICITY ASSESSMENTS

Antibodies to glofitamab will be evaluated in serum samples collected from all participants according to the schedule of assessments. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to glofitamab and the titer of confirmed positive samples will be reported. Other analyses may be performed such as further characterization of the immunogenicity response to glofitamab.

The detection of antibodies to glofitamab will be performed through use of a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for glofitamab serum concentration to enable interpretation of the antibody data. ADAs may be further characterized. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to glofitamab.

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

Participants who elect to provide optional tumor samples will be required to sign a separate Optional Tumor and Plasma Sample Informed Consent Form for collection of samples.

### 8.8.1 Tumor Biopsies (Participants Providing Separate Consent)

Consenting participants may undergo additional on-treatment biopsies at the time of disease progression or at any time at the investigator's discretion (e.g., to confirm disease recurrence or progression or to confirm an alternate histologic diagnosis, if deemed clinically feasible by the investigator). Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional,

punch, or forceps biopsy are preferred. A plasma sample for [redacted] will also be collected at the time of optional tumor biopsy.

The Informed Consent Form will contain a separate section that addresses optional biopsies. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of undergoing optional biopsies. Participants will be told that they are free to choose not to undergo optional biopsies and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to undergo optional biopsies. Participants who choose not to undergo optional biopsies will not provide a separate signature. The investigator should document whether or not the participant has given consent to undergo optional biopsies and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for [redacted] as described in Section 8.6. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. See Section 8.6 for information on the duration of sample storage and availability of data from biomarker analyses.

# 9. STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

## 9.2 SAMPLE SIZE DETERMINATION

The purpose of this study is to assess the safety and efficacy of glofitamab in combination with R-CHOP in ctDNA high-risk participants with previously untreated DLBCL in the first-line setting.

Approximately [redacted] participants will be screened to enroll [redacted] evaluable participants to study treatment on the basis of a previously reported ctDNA high-risk rate of approximately [redacted] in patients with DLBCL in the first-line setting after one cycle of R-CHOP therapy (Kurtz et al. 2018).

The primary efficacy endpoint is the CR rate at the EOT per the 2014 Lugano Response Criteria, as assessed by the investigator.

With [redacted] patients, the exact Clopper-Pearson (Clopper and Pearson 1934) [redacted] CIs for estimation of the true CR rate at the EOT would have a margin of error not exceeding [redacted] Table 6 shows the Clopper-Pearson exact [redacted] CIs corresponding to observed CR rates ranging from [redacted] A best CR rate of 40% has been previously reported for patients with high-risk ctDNA DLBCL in the first-line setting receiving SOC R-CHOP therapy (Kurtz et al. 2018). With [redacted] participants and an observed CR rate of at least [redacted] a true CR rate below [redacted] or above [redacted] can be ruled out with [redacted] confidence.

**Table 6 Clopper-Pearson Exact [redacted] CIs for Assumed Observed Complete Response Rates Based on Sample Size of [redacted] Participants**

| Observed CR Rate | Number of Participants with a CR ([redacted] CI for the Rate) |
|---|---|
| [redacted] | |

CR = complete response.

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

## 9.3 ANALYSIS SETS

The following populations are defined:

| Participant Analysis Set | Description |
|---|---|
| Screened | All participants who sign the Informed Consent Form and have ctDNA samples collected on Day [redacted] of Cycle [redacted] and Day [redacted] of Cycle [redacted] |
| Enrolled | All screened participants who test positive, are assessed as being at ctDNA high risk, and consent to study treatment |
| Evaluable | All enrolled participants who receive at least one dose of study treatment after enrollment |
| Safety | All enrolled participants who receive at least one dose of study treatment after enrollment. Participants will be analyzed according to the treatment they actually receive. |

ctDNA = circulating tumor DNA.

## 9.4 STATISTICAL ANALYSES

This section is a summary of the planned statistical analyses of the most important endpoints, including the primary and secondary endpoints.

### 9.4.1 General Considerations

The final analysis will be based on patient data collected through study discontinuation. Baseline data are the last data obtained prior to initiation of any study treatment.

In general, data will be summarized as warranted and listings will be used in place of tables when samples sizes are small. Continuous variables will be summarized using means, standard deviations, median, and ranges; categorical variables will be summarized using counts and percentages.

### 9.4.2 Primary Endpoint

The primary efficacy endpoint is EOT CR rate, as measured by PET-CT scan and as determined by the investigator according to 2014 Lugano Response Criteria (see Appendix 11), as defined in Section 3 (see Table 3). The CR rate, defined as the percentage of participants with a CR at the EOT, will be estimated and the corresponding Clopper-Pearson exact [redacted] CI will be constructed for the study cohort.

### 9.4.3 Secondary Endpoints

The secondary efficacy endpoints are EOT ORR, PFS, and OS, as defined in Section 3 (see Table 3).

ORR is defined as a CR or a PR at the EOT, as measured by PET-CT scan and determined by the investigator (see Section 3, Table 3). Analysis of the ORR will be identical to that outlined above for the primary efficacy endpoint of CR rate at the EOT, as measured by PET/CT scan.

PFS is defined as the time from the first study treatment to the first occurrence of disease progression, relapse, or death from any cause, whichever occurs first. For participants who do not experience disease progression, relapse, or die, PFS will be censored at the date of last evaluable tumor assessment. For participants who do not have a postbaseline evaluable tumor assessment, PFS will be censored at the date of first study treatment plus 1 day. PFS will be assessed per investigator using the 2014 Lugano Response Criteria (Cheson et al. 2014). The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the distribution of PFS, median (if analytically possible) 6-month and 1-year PFS, with the 95% CI for the median PFS constructed using the Brookmeyer-Crowley method (Brookmeyer and Crowley 1982). Greenwood's formula will be used to provide standard errors and the corresponding 95% CIs for 6-month PFS and 1-year PFS.

OS is defined as the time from the first study treatment to death from any cause. Analysis of OS will be identical to that outlined above for PFS.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to

summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

Safety will be assessed through summaries of exposure to study treatment, occurrence and severity of adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. For CRS, severity will be determined according to the ASTCT CRS Consensus Grading (see Appendix 10). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and causes of death will be summarized.



[redacted]

[redacted]

[redacted]

[redacted]

### 9.4.5 Other Safety Analyses

The incidence of ADA response (i.e., presence of serum or anti-glofitamab antibodies) and the potential correlation with PK, pharmacodynamic, and safety parameters may be assessed.

### 9.4.6 Other Analyses

#### 9.4.6.1 Summaries of Conduct of Study

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

#### 9.4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics (including age, sex, self-reported race/ethnicity, IPI, and ECOG Performance Status) will be summarized across both screened and enrolled participants in the study.

#### 9.4.6.3 Pharmacokinetic Analyses

Individual and mean serum concentration data for glofitamab and rituximab will be tabulated and may be presented graphically, if considered appropriate and data allow. Peak and trough concentration serum rituximab data will be summarized and reported (geometric mean, standard deviation, median, and minimum and maximum).
Serum glofitamab data, including $C_{max}$, AUC, and other PK parameters, will be reported

and summarized (geometric mean, standard deviation, median, and minimum and maximum), if calculable.

In addition serum rituximab and glofitamab concentration data may be analyzed using population PK methodology and may be combined with data from other clinical studies. The output of population PK modeling will not be reported in the Clinical Study Report but will form a separate report.

Additional PK analyses may be conducted as appropriate.

#### 9.4.6.4 Immunogenicity Analyses

The number and proportion of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, participants are 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 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants 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 4-fold greater than the titer of the baseline sample (treatment unaffected).

## 9.5 INTERIM ANALYSES

### 9.5.1 Interim Safety Analyses

The IMC will review all cumulative safety data on a periodic basis according to the IMC charter or more frequently as indicated or requested by the Medical Monitor. The IMC may make recommendations regarding study conduct, including but not limited to the following: performing additional safety analyses, amending the study protocol, holding participant enrollment pending further safety evaluations, holding/discontinuing study treatment, making decisions to [redacted] with study treatment, or terminating the study. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRB/EC. Full details of the IMC process will be included in the IMC Charter.

### 9.5.2 Optional Interim Efficacy Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct an interim efficacy analysis. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

## 9.6 INDEPENDENT DATA MONITORING COMMITTEE

There is no independent Data Monitoring Committee for this study.

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# Appendix 1
# Regulatory, Ethical, and Study Oversight Considerations

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## A1–1. REGULATORY AND ETHICAL CONSIDERATIONS

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (European Economic Area sites only), and all other applicable local regulations

## A1–2. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 4.7).

## A1–3. INFORMED CONSENT PROCESS

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

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

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

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

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

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional [redacted] The investigator or authorized designee will explain to each participant the objectives of the [redacted]. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for [redacted] Participants who decline to participate in this optional research will not provide this separate signature.

## A1–4. DATA PROTECTION

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

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the

participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

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

## A1–5. ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately [redacted] sites globally will participate to enroll approximately [redacted] participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Radiographic images may be submitted to an independent review facility for a quality and completeness check, for potential central review, and for temporary storage prior to transferring images to the Sponsor.

## A1–6. DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on somatic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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

Outcomes from circulating tumor DNA analyses conducted to inform potential eligibility for the study will be provided to study investigators. If allowed by local laws, the investigator may share the results with the participant. The aggregate results of any

conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Given the complexity and [redacted], data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

## A1–7. DATA QUALITY ASSURANCE

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

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

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

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

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

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

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

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention

period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

## A1–8. SOURCE DOCUMENTS

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

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

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

## A1–9. STUDY AND SITE CLOSURE

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

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

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

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

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

inform the participants and should ensure appropriate participant therapy and/or follow-up.

## A1–10. PUBLICATION POLICY

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

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## A1–11. PROTOCOL DEVIATIONS

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

# Appendix 2
# Clinical Safety Laboratory Tests

The tests detailed in Table 1 will be performed by the local or central laboratory. If the local laboratory results are used to make either a study treatment decision or a response evaluation, the results must be entered on the electronic Case Report Form.

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

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

## Table 1 Protocol-Required Safety Laboratory Assessments

| Local Laboratory Tests |
|---|
| • Hematology: CBC, WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute differential counts for neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells<br>• Chemistry panel (serum): bicarbonate, sodium, potassium, calcium, magnesium, phosphorus, chloride, glucose, BUN or urea, creatinine, creatinine clearance (calculated according to the Cockcroft-Gault formula; see Appendix 16), uric acid, total protein, albumin, phosphate, calcium, total and direct bilirubin, *alkaline phosphatase,* ALT, AST, GGT, and lactate dehydrogenase<br>• Coagulation: D-dimer, INR, aPTT, PT, and fibrinogen<br>• *SARS-CoV-2 PCR or Antigen testing*<br>• HIV serology: HIV-1 antibody, HIV-1/2 antibody, and HIV-2 antibody<br>• HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test<br>Individuals with a positive quantitative HBV DNA at screening (must be < 500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests as outlined in the schedule of activities (see Section 1.3, Table 1).<br>• HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test<br>• Quantitative immunoglobulins: IgA, IgG, and IgM<br>• Pregnancy testing: All women of childbearing potential require a negative serum pregnancy test within 24 hours of starting R-CHOP treatment on Day [redacted] of Cycle [redacted]. Pregnancy testing (urine or serum) will subsequently be performed within 24 hours prior to dosing on Day [redacted] of each cycle (Cycles [redacted], at the EOT, and at least monthly for [redacted] months following the EOT visit. If a urine pregnancy test is positive, it must be confirmed by a serum β-human chorionic gonadotropin level. |
| **Central Laboratory Tests** |
| • PK samples<br>• ADA samples<br>• Biomarker samples |

ADA = antidrug-antibody; EOT = end of treatment; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; PK = pharmacokinetic; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone.

Investigators must document their review of each laboratory safety report.

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

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## A3–1. DEFINITION OF ADVERSE EVENT

Adverse Event Definition

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

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

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication
  - Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse events or serious adverse events if they fulfill the definition of an adverse event or serious adverse event. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event (see Section A3–7.10).

Events NOT Meeting the Definition of Adverse Event

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)
- The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen
- Lack of efficacy will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

## A3–2. DEFINITION OF SERIOUS ADVERSE EVENT

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

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

- Results in death
- Is life threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during

hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity
  - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

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

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

### A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

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

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

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

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

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

### A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE, v5.0) grading scale. *For CRS, severity will be determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus grading criteria.* The investigator will use the grading scale in Table 1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

## Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
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] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

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

## A3–3.3 ASSESSMENT OF CAUSALITY

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

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

The investigator will use clinical judgment to determine the relationship.

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

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

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

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

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

Causality will be assessed individually for each protocol-mandated therapy.

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

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

### A3–3.4.1 Investigator Follow-Up

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

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed Case Report Form.

The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information. New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant

follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.2.1), resolution of adverse events (with dates) should be documented on the Adverse Event electronic Case Report Form (eCRF) and in the participant's medical record to facilitate source data verification.

### A3–3.4.2 Sponsor Follow-Up

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

## A3–4. REPORTING OF SERIOUS ADVERSE EVENTS

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

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

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

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

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

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken offline, the site can report this information

on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

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

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

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

### A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

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

### A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment *or the initiation of next anti-lymphoma therapy, whichever is earlier*. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and 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 more than 30 days after the final dose of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or 90 days after the final dose of rituximab, tocilizumab, or glofitamab are provided in Section A3–6.

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

After the end of the adverse event reporting period (defined as 30 days after the final dose of CHOP, or 90 days after the last dose of rituximab, tocilizumab, or glofitamab *or the initiation of next anti-lymphoma therapy, whichever is earlier*), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or email address provided to investigators.

## A3–7. PROCEDURES FOR RECORDING ADVERSE EVENTS

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

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

### A3–7.1 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 Infusion-Related Reaction (IRR) or Cytokine Release Syndrome (CRS) eCRF.

Reactions related to rituximab should be recorded as IRRs. See Section A6–2.3.8 for management of IRRs.

Given the mechanism of action of glofitamab IRRs and CRS may be indistinguishable from one another. In addition, patients are receiving dexamethasone premedication with glofitamab, fever response may be blunted. Therefore, adverse events attributed to glofitamab consistent with a diagnosis of IRR or CRS, and associated with fever, hypotension, or hypoxia not attributable to any other cause, should be recorded as CRS (Lee et al. 2019). See Section A6–2.3.1 for management of CRS.

For adverse events with a diagnosis of IRR or CRS, associated signs, symptoms, and laboratory abnormalities should be recorded on the dedicated eCRF. Events of CRS should be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading (Lee et al. 2019) (see Appendix 10), including events without fever but with hypotension or hypoxia. 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 CRS eCRF, as well as the management of these symptoms, for example, pressor and oxygen use. 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. Adverse events attributable to glofitamab and consistent with a diagnosis of IRR or CRS, but not associated with fever, hypotension, or hypoxia, 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 documentation on the Adverse Event eCRF, non-serious Grade $\geq 2$ CRS events should be reported as a non-serious adverse event of special interest (see Section 8.2.6).

## A3–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

## A3–7.3 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.

## A3–7.4 PERSISTENT OF RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became

serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

## A3–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

## A3–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

## A3–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

## A3–7.8 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.2.1) 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 treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

## A3–7.9 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").

## A3–7.10 LACK OF EFFICACY OR WORSENING OF DIFFUSE LARGE B-CELL LYMPHOMA

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of diffuse large B-cell lymphoma on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of 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 2014 Lugano Response Criteria (Cheson et al. 2014). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

## A3–7.11 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 A3 2.), except as outlined below.

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

- Hospitalization for respite care
- Hospitalization for observation if participants are considered to be at risk for an adverse event (e.g., hospital stay extended for observation after a CRS event has fully resolved or prophylactic hospitalization prior to glofitamab dosing, according to risk or prior occurrence of CRS)
  - If the participant experiences an adverse event during such hospitalization, the event should be reported as an adverse event or a serious adverse event. Planned hospitalization required by the protocol (e.g., for study treatment administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition.
  - The participant has not experienced an adverse event.
  - Hospitalization due solely to progression of the underlying cancer

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

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours
- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

## A3–7.12 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 or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For glofitamab 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, rituximab, 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 glofitamab and tocilizumab 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 glofitamab and tocilizumab 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 glofitamab and tocilizumab 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.

## A3–7.13 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

## 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;32:3059–68.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188–95.

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

# Appendix 4
# Contraceptive and Barrier Guidance

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## A4–1. PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 12 months after the final dose of rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), 3 months after the final dose of tocilizumab (if applicable), or 2 months after the final dose of glofitamab, 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 the investigator becomes aware 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 electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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

## A4–2. PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 6 months after the final dose of R-CHOP, 3 months after the final dose of tocilizumab (if applicable), or 2 months after the final dose of glofitamab, whichever is longer. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and 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 the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

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

An investigator who is contacted by the male 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.

## A4–3. ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

## A4–4. ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

# Appendix 5
# Genetics: Use and Analysis of DNA

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

DNA samples will be used for research related to diffuse large B-cell lymphoma (DLBCL) and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to glofitamab and/or DLBCL. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.

DNA samples may be analyzed for identification of disease-specific somatic variations. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

DNA samples derived from blood will be analyzed for circulating tumor DNA using the AVENIO Oncology Assay for Non-Hodgkin's Lymphoma Test. Additional analysis may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

In all genetic analyses, germline [redacted] from [redacted] or blood will be used only as a control to identify somatic mutations and not for analysis of inherited genetic variants.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to glofitamab or study treatments of this class to understand the DLBCL or related conditions.

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

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

The samples will be retained while research on glofitamab in combination with R-CHOP continues or DLBCL continues but no longer than the period specified in Section 8.6 or other period as per local requirements.

See Section 8.6 for information on duration of sample storage and availability of data from biomarker analyses.

# Appendix 6
# Safety Plan: Management of Identified and Potential Risks

Glofitamab is approved *for treatment of patients with relapsed or refractory DLBCL after two or more lines of systemic therapy in certain regions*, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with glofitamab in completed and ongoing studies. The anticipated important safety risks for glofitamab are outlined below. Please refer to the Glofitamab Investigator's Brochure for a complete summary of safety information.

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

For cases in which management guidelines are not covered in this protocol or in the Rituximab Investigator's Brochure or in the prescribing information, participants should be managed as deemed appropriate by the investigator according to best medical judgment and local medical guidelines.

## A6–1. RISKS ASSOCIATED WITH STUDY TREATMENT

### A6–1.1 RISKS ASSOCIATED WITH GLOFITAMAB

On the basis of clinical data to date with glofitamab, identified risks are described below. Refer to the Glofitamab Investigator's Brochure for a description of all anticipated risks for glofitamab. Guidelines for the management of the risks by means of dose interruptions and other actions are described in the following sections of this appendix.

#### A6–1.1.1 Cytokine Release Syndrome

Based on clinical data from Study NP30179, cytokine release syndrome (CRS) is the most frequent glofitamab-related adverse event in patients treated with glofitamab and is the main dose-limiting toxicity. In the majority of patients, the CRS event occurred in Cycle [redacted] whereas for a few patients, the event recurred at subsequent cycles but usually 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 chimeric antigen receptor modified T-cell (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, as assessed by peripheral blood smear. See Table 1 of this appendix and to the Glofitamab Investigator's

Brochure for further details on CRS. The schedule of assessments for patients who receive tocilizumab for the treatment of CRS is presented in Appendix 7.
The recommended management of CRS is detailed in Table 1of this appendix.

Severe coronavirus disease 2019 (COVID-19) is associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ. If a participant develops severe CRS during the study, a differential diagnosis with testing to rule out COVID-19 infection should be considered.

### A6–1.1.2 Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including Grade 4 neutropenic events, have been commonly observed in patients treated with glofitamab. The frequency of febrile neutropenia or infections during neutropenic events appears low. However, events may increase when glofitamab is combined with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Neutropenic patients have a higher risk of developing infections. The recommended management of neutropenia and febrile neutropenia is presented in Section A6–2.3.6.

Fever in neutropenic patients should be considered a medical emergency, and febrile neutropenic patients (Grade 3 and higher) should receive initial doses of antibacterial therapy within an hour of triage. Febrile neutropenic episodes usually require admission to an inpatient facility, although carefully selected patients may be managed as outpatients after systematic assessment beginning with a validated risk index (e.g., Multinational Association for Supportive Care in Cancer [MASCC] score or Talcott's rules). Participants are classified as being at low risk when MASCC scores are ≥21 or they are in Talcott group 4, and when no other risk factors are present. Low-risk participants should either be monitored for at least 4 hours to determine suitability for outpatient management or be admitted to the hospital. Amoxicillin or clavulanate (or clindamycin if participant is allergic to penicillin) is recommended as empiric therapy in low-risk participants. Higher-risk participants should receive IV antibiotics in a hospital setting. The choice of antibiotics is determined per the institutional standard of care, but antibacterial therapy is expected to be initiated within an hour of triage.

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

### A6–1.1.3 Tumor Flare

Adverse events associated with tumor flare 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 flare have been reported in Study NP30179 with glofitamab monotherapy. These events tend to occur within a short time following

glofitamab administration and present with varying degrees of severity. In addition, depending on tumor size and anatomic location, events associated with tumor flare may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major organs. Depending on the nature of the tumor flare, additional medical and/or surgical management may be necessary. If such manifestations are associated with glofitamab, the investigator should consider those events to be tumor flare and report as "tumor flare."

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

Participants at high risk of tumor flare requiring prophylactic intubation for safe administration of glofitamab and who are at high risk of CRS may be eligible to enroll at the investigator's discretion following consultation with the Medical Monitor.

Participants with tumors involving critical anatomic locations should be closely monitored for tumor flare, and prospective preventative or interventional measures may need to be considered or planned prior to dosing. Specific management guidelines are presented in Section A6–2.3.2. See the most recent Glofitamab Investigator Brochure for *the* most updated information on tumor flare.

### A6–1.1.4 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 consider differential diagnoses such as infections and disease progression (B-symptoms). Hospitalization may be appropriate for such cases and becomes compelling in the event of febrile neutropenia.

### A6–1.1.5 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported with blinatumomab, CAR T-cell therapy, and with CD20-directed therapies (BLINCYTO®2020; GAZYVA® 2017; RITUXAN® 2020; 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 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 lactate dehydrogenase levels, particularly in the presence of dehydration or compromised renal function. Given that glofitamab has the potential for potent B-cell killing, patients at risk for TLS should receive prophylaxis for TLS. Specific prophylaxis recommendations for the prevention of TLS are described in Section 6.1.5.3.

### A6–1.1.6 Infections

Due to its anticipated mode of action resulting in profound B-cell depletion, both glofitamab and rituximab may be associated with an increased risk of infections. Infections have been reported in patients receiving other CD20-directed therapies (BLINCYTO® 2020, RITUXAN® 2020, GAZYVA® 2017). Therefore, study treatment should not be administered to patients with active infections unless the infection is considered minor by the investigator (e.g., localized tinea corporis) and do not have systemic symptoms such as fever. Serious and fatal cases of pneumonia have been observed in patients receiving glofitamab. Investigators should exercise caution when considering the use of glofitamab in participants with a history of recurring or chronic infections. Particular attention should be given to participants who have had significant prior immunosuppressive treatment, such as high-dose chemotherapy (see Section 5.2). In the setting of a pandemic or epidemic, screening for active infections prior to and during study participation should be considered according to local/institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology and European Society for Medical Oncology).

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

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

*If the patient develops SARS-CoV-2 infection during study treatment, study treatment should be interrupted and the infection should be managed as per local or institutional guidelines (See Section 6.8.1). The infection must be clinically resolved before resumption of study treatment. Investigators must rule out active infection and re–assess benefit-risk balance prior to resuming study treatment. Examples of ruling out an active infection include clinical evaluation of respiratory symptoms, radiological tests to confirm absence of pneumonia, and consideration of negative serial viral*

*testing. Glofitamab administration is not permitted during the presence of active infection.*

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

*Patients who are HIV positive may be eligible to enroll in the study if specific criteria are met (see Section 5.1.1). Signs and symptoms of HIV may confound assessment of the safety profile of glofitamab in combination with R-CHOP. HIV has also been associated with the development of secondary HLH. Patients with positive HIV should be monitored per local institutional standards while receiving study treatment.*

## A6–1.2 POTENTIAL RISKS ASSOCIATED WITH GLOFITAMAB

On the basis of clinical data to date with glofitamab, the potential risks associated with glofitamab treatment are described below. Guidelines for the management of these risks through dose interruptions and other actions are described in Sections A6–2.1 and A6–2.2.

### A6–1.2.1 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 with subsequent local cytokine release (Nagorsen and Baeuerle 2011).

For the purposes of this study, all participants 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 participants will receive prophylactic corticosteroids for each glofitamab infusion. In case of neurologic events or signs, additional dexamethasone will be administered (see Section A6–2.1).

### A6–1.2.2 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH), alternatively described as macrophage activation syndrome (MAS), 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, serum triglycerides, and coagulation profile. A bone marrow

evaluation should also be considered. Guidelines for the management of HLH are provided in Section A6–2.3.7.

### A6–1.2.3 Immunogenicity

The risk of immunogenicity to glofitamab and to rituximab is greatly reduced by the B cell–targeting nature of each therapeutic antibody, given that both healthy and antidrug antibody [ADA]-producing) and malignant $CD20^+$ cells will be lysed.
All participants 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 obtained from participants 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 pharmacokinetic (PK) sample will be collected at the same timepoint for the determination of glofitamab concentration.

### A6–1.2.4 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been associated with treatment with CD20-directed therapies, including rituximab. The diagnosis of PML should be considered in any patient presenting with new-onset 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 (cerebrospinal fluid 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.

### A6–1.2.5 Hepatitis B Reactivation

Hepatitis B reactivation has been reported with CD20-directed therapies. Individuals with positive test results for active hepatitis B virus (HBV) infection defined by hepatitis B surface antigen (HBsAg) or positive total hepatitis B core antibody (HBcAb) with positive HBV polymerase chain reaction (PCR), or individuals with hepatitis C virus (HCV) infection, as assessed by PCR, will be excluded from this study (see Section 5.2).
Participants with occult or prior HBV infection (defined as negative HBsAg and positive HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day [redacted] of every cycle and every 3 months for at least 12 months after the last cycle of study treatment and appropriate antiviral therapy (Hwang et al. 2020). Participants who experience hepatitis B reactivation should start

antiviral therapy (if not already initiated). Participants 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.

### A6–1.2.6 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.

Participants 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 exacerbate thrombocytopenia-related events (such as platelet inhibitors and anticoagulants) should also be considered, especially during the first cycle of study treatment.

### A6–1.2.7 Elevated Liver Enzymes

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. Individuals with elevated liver function tests at screening will be excluded from this study (see Section 5.1.2). Management of liver abnormalities is provided in Section A6–2.3.6.

### A6–1.2.8 Colitis

Observations from a nonclinical study showed changes in the gastrointestinal tract including erosion and single cell necrosis. The risk of changes in the gastrointestinal tract of glofitamab in humans is not known. Adverse events of colitis and enterocolitis related to glofitamab, have been reported in early phase clinical studies. Symptoms included diarrhea, weight loss, worsening pain, and abdominal distention.

Refer to the Glofitamab Investigator's Brochure for a detailed description of potential safety risks.

## A6-1.3 RISKS ASSOCIATED WITH RITUXIMAB

See the local prescribing information for rituximab for full information.

## A6-1.4 RISKS ASSOCIATED WITH CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (CHOP)

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

## A6-1.5 RISK OF OVERLAPPING TOXICITIES WITH GLOFITAMAB AND R-CHOP

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

### A6–1.5.1 Overlapping Risk with Hematologic Toxicity

Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy is associated with a significant bone marrow toxicity affecting all the linages with consequent anemia and cytopenia. Nadir is expected to occur between 8 and 14 days after the end of the cycle. Severe toxicity and its effects are expected to be more intense at the end of the first cycle. In the Phase III study BO21005, the incidence of Grade $\geq 3$ neutropenia was higher at the end of the first cycle in both study arms (30.6% and 42.5% of patients in the R-CHOP and G-CHOP arms, respectively) compared with the rate reported in the subsequent cycles (maximum, 17.9%; minimum, 3.6%).

In nonclinical testing of glofitamab in cynomolgus monkeys, hematologic findings included transiently decreased WBCs, lymphocyte, monocyte, and basophil counts within the first day of glofitamab exposure, followed by recovery or rebound recovery (following a single dose). Neutrophils were mildly decreased 4 days after the first dose of glofitamab and recovered to baseline and/or control values by Day 35 and/or Day 91, indicating recovery. Platelets were mildly decreased on the days after treatment with glofitamab, followed by a rebound increase after 1 week and return to baseline on Day 35.

Management recommendations for hematologic toxicity are presented in Section A6–2.3.6.

## A6–2. MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

## A6–2.1 DOSE AND SCHEDULE MODIFICATIONS OF GLOFITAMAB

Glofitamab dosing will occur only if a participant's clinical assessment 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 as applicable. All considerations for dose and schedule modifications should be discussed with the Medical Monitor. Subsequent cycles of R-CHOP 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 participants who develop CRS with onset of associated signs and symptoms during the glofitamab infusion, the infusion must be discontinued immediately with no further restarts of the infusion for this administration, unless symptoms are limited to Grade 1 and respond to symptomatic treatment (see Table 1). The dose and rate of infusion of glofitamab for the subsequent administration should be discussed with the Medical Monitor. For participants who may be at increased risk of CRS (i.e., participants who experienced CRS with their previous dose of glofitamab or who are at increased risk of recurrent CRS with subsequent doses), the next dose and time of infusion may be extended to up to 8 hours. Modifications to infusion time in these circumstances should be discussed with the Medical Monitor. See Section A6□2.3.6 for guidance on neutropenia and thrombocytopenia toxicity. Glofitamab should only be initiated when hemoglobin ≥9.0 g/dL.

Participants who experience a serious Grade 4 study treatment–related non-hematologic adverse event should discontinue study treatment. Exceptions may be warranted after discussion with the Medical Monitor, taking into consideration the benefit–risk ratio for a given individual participant and ad-hoc and participant-specific risk mitigations. Subsequent 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 participants 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 participant should be discontinued from treatment unless resumption of treatment is approved by the investigator following consultation with the Medical Monitor.

For patients who receive step-up dosing, if a treatment delay of glofitamab occurs for >7 days (14 days between glofitamab step-up dosing), the last tolerated step-up dose should be repeated.

If a dose delay results in a treatment-free interval of 6 weeks or longer, re-initiation of step-up dosing of glofitamab with dexamethasone premedication is required for the first cycle after the dose delay.

In the event that a patient experiences a recurrence of a toxicity of the same or higher grade following re-exposure to glofitamab, the investigator, *following consultation* with the Medical Monitor, will have the option to reduce the dose of glofitamab once to a lower dose level. This may done to allow participants who could potentially benefit from glofitamab to continue receiving study drug.

Patients who discontinue study treatment for reasons other than progressive disease should continue to be followed per the schedule of activities (see Section 1.3).

Resumption of glofitamab may be considered in patients who are deriving benefit and have fully recovered from the adverse event. Participants can be rechallenged with glofitamab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

If R-CHOP is delayed by 21 days or greater due to a hematologic toxicity related to glofitamab, the investigator, *following consultation* with the Medical Monitor, may discontinue glofitamab and continue therapy with R-CHOP alone.

### A6–2.2 DOSE MODIFICATIONS OF RITUXIMAB AND CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE

Guidelines for dose delays and/or modifications of rituximab and/or cyclophosphamide, doxorubicin, vincristine, and prednisone should be followed using the prescribing information.

### A6–2.3 MANAGEMENT GUIDELINES

The following sections provides guidelines for the management of patients who experience adverse events associated with study treatment:

- CRS
- Tumor flare
- Neurologic adverse events
- TLS
- Elevated liver enzymes
- Hematologic toxicity
- IRRs due to rituximab
- HLH

For the management of toxicities specific to R-CHOP, refer to the local prescribing information and institutional guidelines.

#### A6–2.3.1 Cytokine Release Syndrome

CRS is an identified risk for glofitamab. Premedication measures to reduce CRS to glofitamab are described in Section 6.1.5.3.

Mild to moderate presentation of 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 treatment infusion predominantly at the first infusion. The incidence and severity of CRS typically decrease with subsequent infusions. Participants may also develop IgE-mediated hypersensitivity reactions to study treatment.

It is anticipated that with the mechanism of action of T cell−bispecific treatment (i.e., glofitamab), clinical signs and 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.”

Participants who experience symptoms of CRS after glofitamab administration should be managed according to the guidelines in Table 1.

## Table 1 Management Guidelines for Cytokine Release Syndrome for Participants 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. [c]<br>• Monitor fluid balance; administer IV fluids if indicated.<br>• Consider hospitalization of participant until symptoms completely resolve. | • Administration of tocilizumab is recommended for Grade 1 CRS for participants with prolonged symptoms (≥2 days); for participants with significant symptoms of CRS besides fever such as pain, tachycardia, or rigors; for participants with comorbidities (e.g., impaired cardiovascular function, reduced pulmonary reserve) with increased risk of complications from more severe grades of CRS; or for participants with prior Grades 2 and CRS. IV corticosteroids [c] may also be administered in addition to tocilizumab at the investigator's discretion (see Section 6.1.4). [d] | • Continue treatment at the next planned dose.<br>• Premedicate participant with acetaminophen and an antihistamine for all subsequent infusions.<br>• Consider extending infusion time (slower infusion rate) for subsequent doses.<br>• Consider hospitalization of participant for next dose if prolonged CRS. |

## Table 1 Management Guidelines for Cytokine Release Syndrome for Participants 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 fever [b] ≥ 38ºC with:<br>– Hypotension not requiring vasopressors and/or [e]<br>– Hypoxia [f] 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), undertake SARS-CoV-2 diagnostic PCR. If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. | • Administer tocilizumab (see Section 6.1.4) [f]<br>• Administer IV corticosteroids (e.g., methylprednisolone or dexamethasone every 6 hours).<br>• Manage per Grade 3 event if no improvement within 8 to 12 hours after starting tocilizumab. | • Participant may receive the next dose of study treatment if symptoms resolve to Grade 1 or better for 3 consecutive days; the Medical Monitor is available for consultation; the dose of glofitamab for the subsequent administration must be discussed with the Medical Monitor.<br>• Premedicate participant with acetaminophen and an antihistamine for all subsequent infusions.<br>• Consider extending infusion time (slower infusion rate) for subsequent doses.<br>• Hospitalize participant for next dose. |

## Table 1 Management Guidelines for Cytokine Release Syndrome for Participants 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 fever [b] ≥ 38ºC with:<br>– Hypotension requiring a vasopressor (with or without vasopressin) and/or [e]<br>– Hypoxia [f] 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 participant 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), undertake SARS-CoV-2 diagnostic PCR. If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. | • Administer tocilizumab (see Section 6.1.4).<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 to 12 hours after the second dose of tocilizumab. | • Participant may receive the next dose of study treatment if symptoms resolve to Grade 1 or better for 3 consecutive days; the Medical Monitor is available for consultation; the dose of glofitamab for the subsequent administration must be discussed with the Medical Monitor.<br>• Premedicate participant with acetaminophen and an antihistamine for all subsequent infusions.<br>• Consider extending infusion time (slower infusion rate) for subsequent doses.<br>• Hospitalize participant 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 participant permanently discontinued from study treatment. |

## Table 1 Management Guidelines for Cytokine Release Syndrome for Participants 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>and/or [e]<br>– Hypoxia [f] 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>• Participant 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), undertake SARS-CoV-2 diagnostic PCR. If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. | • Administer tocilizumab (see Section 6.1.4).[d]<br>• Administer IV corticosteroids (e.g., 2 mg/kg/day IV methylprednisolone or 10 mg IV dexamethasone every 6 hours).<br>• For participants 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 study treatment 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 the Medical Monitor prior to giving glofitamab.<br>• Participants are required to be hospitalized for subsequent dosing until no further CRS event occurs.<br>• Premedicate participant with acetaminophen and an antihistamine for all subsequent infusions.<br>• Required use of 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 if the glofitamab infusion must be stopped immediately, the participant must be permanently discontinued from study treatment. |

## Table 1 Management Guidelines for Cytokine Release Syndrome for Participants Receiving Glofitamab (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 = growth colony-stimulating factor; HLH = hemophagocytic lymphohistiocytosis; IL = interleukin; IRR = infusion-related reaction; ICU = intensive care unit; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] CRS grading will be determined according to the ASTCT Consensus Grading (Lee et al. 2019) (see Appendix 10).

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. In participants 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. As participants are receiving dexamethasone premedication with glofitamab, fever response may be blunted. Therefore, adverse events attributed to glofitamab consistent with a diagnosis of CRS, and associated with fever, hypotension or hypoxia not attributable to any other cause, should be recorded as CRS.

[c] Participants 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.

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

[e] CRS grade is determined by the more severe event: hypotension or hypoxia, not attributable to any other cause.

[f] 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.

[g] Source: Riegler et al. 2019.

### A6–2.3.2 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 participants should be carefully monitored for tumor flare events. Depending on the site of lesions, the guidance below should be followed.

For participants 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 participant. In some situations, the participant should be considered for prophylactic tracheostomy prior to the first administration.
- Management of suspected tumor flare events in high-risk participants with lymphoma lesions in the oropharynx:
  - In case of a suspected tumor flare event (including but not limited to dyspnea, increased labored breathing, hoarseness, wheezing, hypoxia), follow management guidelines summarized in Table 2. Tracheostomy should be maintained until at least the Cycle 2 dose is administered, if the benefit–risk assessment is deemed favorable (i.e., if participant is receiving benefit from study treatment).

For participants 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 participants 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 participant.
- At first administration of glofitamab: In case of a suspected tumor flare event (this includes but is not be limited to chest pain, dyspnea, hypoxia, cyanosis, syncope, cough, palpitations) follow management guidelines summarized in Table 3. After first administration, monitor ejection fraction weekly, or with shorter intervals if clinically required. In case of clinically significant improvement in 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 participants with Grade 2 ejection fraction at baseline.

- For all other participants with suspected flare event, follow the recommendations in Table 4. The management guidelines refer mostly to pain and may be followed whenever pain or other symptoms occur, owing to compression of neural structures by lymphoma.
- For participants 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 and colonic perforation and hemorrhage. Individual assessment of the benefits and risks should be discussed with the participant.

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

| Triggering Event [a] | Initial Management Recommendation | Action to Be Taken with Glofitamab |
|---|---|---|
| Administer supportive measures (e.g., oxygen support, intubation, tracheostomy as indicated). Monitor participants closely as planned before study treatment administration. Ensure participant access to an intensive care unit is available. | | |
| Grade 1 tumor flare | • Consult ENT specialist, if not already done so. If participant has not prophylactically tracheostomized, consider tracheostomy at event onset. | • Continue treatment. |
| Grade 2 tumor 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 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 flare; for events not specifically listed in NCI CTCAE v5.0, see Section A3–2.

[b] Preventative and interventional measures should be considered and discussed with the Medical Monitor, appropriate specialists, and the participant prior to glofitamab dosing. When tumor flare 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 participant.

## Table 3 Management of Suspected Tumor Flare Event in the Mediastinum

| Triggering Event [a] | Initial Management Recommendation | Action to Be Taken with Glofitamab |
|---|---|---|
| Participants with Grade ≤2 ejection fraction decrease at baseline: Monitor participant closely as planned before study treatment administration. Ensure participant access to an intensive care unit is available. | | |
| Grade *2* tumor flare | • *Monitor patient closely.* | • *Grade 2 events, hold until resolution to Grade < 2.* |
| Grade *3* tumor flare | • *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 tumor flare | • *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 flare; for events not specifically listed in NCI CTCAE, see Section A3–2.

[b] Preventative and interventional measures should be considered and discussed with the Medical Monitor, appropriate specialists, and the participant prior to glofitamab dosing. When tumor flare 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 participant.

## Table 3 Management of Suspected Tumor Flare Event in the Mediastinum (cont.)

| Triggering Event [a] | Initial Management Recommendation | Action to Be Taken with Glofitamab |
|---|---|---|
| Participants with Grade ≥3 ejection fraction decrease at baseline: Monitor participants closely as planned before study treatment administration. Ensure participant 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 flare; for events not specifically listed in NCI CTCAE, see Section A3–2.

[b] Preventative and interventional measures should be considered and discussed with the Medical Monitor, appropriate specialists, and the participant prior to glofitamab dosing. When tumor flare 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 participant.

## Table 4 Management of Suspected Tumor Flare Event Outside the Mediastinum and Oropharynx, Applicable Whenever Pain Management Is Required for Tumor Flare 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 participant 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 participant 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 flare for events not specifically listed in NCI CTCAE, see Section A3–2.

### A6–2.3.3 Neurologic Adverse Events

All participants 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 participant's chart. Participants with a history of neurologic disease may be excluded from this trial.

Participants should be routinely assessed for any signs or symptoms of neurologic adverse events as part of the clinical examination during treatment. If new or worsening neurologic adverse events are suspected, such as expressive aphasia, confusional state, encephalopathies, seizures, cerebral edema (Lee et al. 2019), the participant should be referred to a neurologist for further evaluation of potential study treatment–related neurologic adverse events. Dexamethasone should be considered to treat suspected neurologic adverse events. Imaging should be performed if clinically indicated. Recommended management guidelines for neurologic adverse events (except peripheral neuropathy) associated with glofitamab are presented in Table 5.

**Table 5 Management of Neurologic Adverse Events Associated with Glofitamab**

| Event | Initial Management Recommendation | Action to Be Taken |
|---|---|---|
| Grade 1 | • Monitor for worsening toxicity. | • Continue treatment unless clinical situation warrants delay in therapy; consider consultation with Medical Monitor. |
| Grade 2 or 3 | • Consider referral to neurologist.<br>• Perform imaging and other diagnostic test to ascertain etiology.<br>• Consider treatment with 10 mg IV dexamethasone every 6 hours as needed. | • Withhold glofitamab and R-CHOP until recovery to Grade 1 or better.<br>• For Grade 3 event lasting > 7 days, consider discontinuation.<br>• Administer glofitamab and R-CHOP after consultation with Medical Monitor. |
| Grade 4 | • Follow Grade 3 recommendations.<br>• Refer participant to neurologist for appropriate management. | • Discontinue study treatment. Exceptions may be warranted after discussion with Medical Monitor and benefit–risk considerations. |

R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone.

Decisions on whether to continue or to hold glofitamab treatment for any Grade 1 neurologic adverse events will be at the discretion of the study investigator and with

discussion with the Medical Monitor. For Grade ≥2 neurologic adverse events, treatment with glofitamab should be held until the adverse event returns to Grade 1 or better for at least 3 days without any medication. For Grade 3 neurologic adverse events lasting for >7 days, the overall benefit–risk assessment of continued treatment with glofitamab should be assessed by the study investigator in consultation with the Medical Monitor. If Grade 3 neurologic adverse events recurs in any subsequent cycles, glofitamab should be permanently discontinued. Glofitamab should be permanently discontinued for Grade ≥3 seizures.

For peripheral neuropathy, dose interruption for vincristine should follow the guidance in Table 6.

## Table 6 Management of Peripheral Neuropathy Associated with Vincristine

| Event | Action to Be Taken |
|---|---|
| Grade 1 neuropathy (including peripheral sensory or motor neuropathy) | • No study treatment modification is recommended for Grade 1 sensory or motor peripheral neuropathy. |
| Grade 2 sensory peripheral neuropathy | • If the adverse event remains unchanged at the time of next scheduled cycle, administer glofitamab, rituximab, and CHOP at the recommended doses.<br>• Vincristine should be reduced at least 25% of baseline or current dose.<br>• In the event that the adverse event remains Grade 2 in subsequent cycles, further 25% dose reduction of vincristine should occur. If the adverse event improves to Grade 1 by the start of the next cycle, administer vincristine at the most recent dose.<br>• Dose of vincristine should not be re-escalated for subsequent cycles without discussion with the Medical Monitor.<br>• If further dose reduction is indicated after two dose reductions, the patient must discontinue vincristine but may continue treatment with the remaining study drugs at the investigator's discretion. |
| Grade 3 sensory peripheral neuropathy, or Grade 2 or 3 motor neuropathy | • If severity of the adverse event remains unchanged by the start of the next cycle, hold vincristine and administer CHP components and rituximab if applicable at the recommended doses.<br>• Glofitamab may be administered at the recommended dose.<br>• The withheld doses of vincristine will not be made up at a later date. When the adverse event improves to Grade $\leq$2 peripheral sensory neuropathy and/or Grade 1 or better peripheral motor neuropathy, vincristine can be restarted at a reduced dose (25% of baseline or current dose) at the next cycle.<br>• If further dose reduction is indicated after two dose reductions, the patient must discontinue vincristine but may continue treatment with the remaining study drugs at the investigator's discretion. |
| Grade 4 neuropathy (including peripheral sensory or motor neuropathy) | • Discontinue vincristine treatment permanently.<br>• Patients should be evaluated regarding the continuation of CHP and rituximab on the basis of the benefit–risk assessment.<br>• Patients should be evaluated regarding the continuation of glofitamab on the basis of the benefit–risk assessment. |

CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone.

### A6–2.3.4 Tumor Lysis Syndrome

Participants 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. Participants should be well hydrated. Starting 1–2 days prior to the first dose of R-CHOP in Cycle 1, it is desirable to maintain a fluid intake of approximately 2–3 L/day. In addition, all participants 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 [redacted], Cycle [redacted] of treatment and hydration. Participants should continue to receive repeated prophylaxis if deemed appropriate by the investigator and adequate hydration prior to each subsequent cycle of treatment.

Treatment for laboratory and/or clinical presentations of TLS will follow institutional practice. Prior to each treatment given during Cycles [redacted] and [redacted], the participant's serum chemistry and hematologic laboratory samples should be obtained and reviewed and prophylactic measures initiated as outlined in Section 6.1.5.3. Access to nephrology consultation with acute dialysis services must be available in the event of clinically significant TLS.

If the Howard criteria for TLS (see Appendix 10) (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 the participant should be hospitalized and adequately treated until normalization of laboratory abnormalities before treatment is restarted.

### A6–2.3.5 Elevated Liver Enzymes

For participants with elevated liver function tests (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 7 for glofitamab.

## Table 7 Management of Liver Function Test Abnormalities

| Abnormality | Action to Be Taken |
|---|---|
| AST/ALT $>10\times$ ULN, with total bilirubin $\leq 2\times$ ULN | • Hold study treatment.<br>• Consult hepatologist.<br>• Monitor LFTs per clinical discretion.<br>• Consider restarting study treatment after discussion with the Medical Monitor if AST/ALT $\leq 10\times$ ULN with bilirubin $<2\times$ ULN.<br>• Permanently discontinue glofitamab for life-threatening immune-related hepatic events. |
| AST/ALT $>3\times$ ULN, with total bilirubin $>2\times$ ULN | • Hold study treatment.<br>• Consult hepatologist.<br>• Monitor LFTs per clinical discretion.<br>• Consider restarting study treatment after discussion with the Medical Monitor if AST/ALT $\leq 3\times$ ULN with bilirubin $<2\times$ ULN.<br>• Permanently discontinue glofitamab for life-threatening immune-related hepatic events.<br>• Any case involving an increase in AST/ALT $>3\times$ ULN and an increase in direct bilirubin $>2\times$ 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. |

CRS = cytokine-release syndrome; DILI = drug-induced liver injury; LFT = liver function test; ULN = upper limit of normal.

### A6–2.3.6 Hematologic Toxicity

Neutropenia, febrile neutropenia, and thrombocytopenia are associated with other CD20-directed therapies, as well as blinatumomab. In order to mitigate the risk of severe cytopenia, glofitamab dosing will be initiated starting in Cycle [redacted] and onward. Participants having severe bone marrow dysfunction at baseline will be excluded from study as specified in Section 5.1. Granulocyte colony-stimulating factor (G-CSF) support will be mandated for this trial (see Section 6.1.5.1). G-CSF should be given within 48 hours of each CHOP administration until normal count recovery. If in subsequent cycles, a delay or modification in G-CSF support is judged to be needed, follow institutional guidelines and perform medical assessment. Actions to be taken for hematologic toxicity are presented in Table 8. If R-CHOP is delayed by 21 days or greater due to a hematologic toxicity related to glofitamab, the investigator, after

discussion with the Medical Monitor, may discontinue glofitamab and continue therapy with R-CHOP.

## Table 8 Recommendations for Managing Hematologic Toxicity

| Event | Action to Be Taken |
|---|---|
| Grade 1 neutropenia | • Monitor blood cell counts weekly.<br>• Continue treatment. |
| Grade 2 neutropenia | • Monitor blood cell counts weekly.<br>• Consider holding treatment in the presence of comorbidities or complications. |
| Grade 3 or 4 neutropenia, with or without infection or fever [a] | • Monitor blood cells at least twice a week until an increase of neutrophils is noticed.<br>• Administer growth factor support.<br>• Delay doses of all study treatment for this cycle.<br>• If R-CHOP has been administered, then dosing with glofitamab can also proceed despite Grade 3 or 4 neutropenia in the **absence** of fever and infection.<br>• If ANC recovers to ≥1000/μL prior to the scheduled date of study drug administration for the next cycle, administer full dose of study treatment.<br>• If ANC recovers to ≥1000/μL on or after the scheduled date study drug administration or the next cycle, then:<br>– Consider dose reduction of cyclophosphamide and doxorubicin per institutional guidelines.<br>– If Grade 3 neutropenia persists despite growth factor support and following cyclophosphamide and doxorubicin dose reductions, in the absence of fever, the participant may continue with study treatment. |

R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone.

[a] All on the basis of laboratory results obtained within the time frame listed in the schedule of activities (Section 1.3, Table 1) prior to infusion of Day 1 of that cycle.

## Table 8 Recommendations for Managing Hematologic Toxicity (cont.)

| Event | Action to Be Taken |
|---|---|
| Grade 1 or 2 thrombocytopenia | No dose reduction or delay |
| Grade 3 or 4 thrombocytopenia | • Delay doses of all study treatments.<br>• If platelet count recovers to > 50,000/mL prior to the scheduled study treatment administration date of the next cycle, administer full dose of study treatment.<br>• If platelet count recovers to > 50,000/mL on or after the scheduled date of study treatment administration of the next cycle, consider reducing the R-CHOP per institutional guidelines.<br>• If the participant had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of cyclophosphamide and doxorubicin. |

R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone.

[a] All on the basis of laboratory results obtained within the time frame listed in the schedule of activities (Section 1.3, Table 1) prior to infusion of Day 1 of that cycle.

For the management of hematologic toxicities, dose modifications summarized in Table 8 must be followed.

Note: A hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia and leukopenia are expected outcomes of the therapy and will be not managed.

### A6–2.3.7 Hemophagocytic Lymphohistiocytosis

The supportive management of hemophagocytic lymphohistiocytosis (HLH) is generally similar to that of cytokine release syndrome (see Section A6–2.3.1). Specific diagnostic, monitoring and management guidelines for HLH are described below.

Participants with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A participant 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 < $100 \times 10^9$/L (< 100,000/μL)

  - ANC $< 1.0 \times 10^9$/L ($< 1000/\mu L$)
- 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 (NK) cell activity
- Ferritin $> 500$ mg/L ($> 500$ ng/mL)
- Soluble interleukin-2 (IL-2) receptor (soluble CD25) elevated $\geq 2$ standard deviations above age-adjusted laboratory-specific norms

In all cases of suspected HLH, the Medical Monitor should be immediately notified. Participants should be hospitalized with the following diagnostic and monitoring measures initiated:

- Frequent (e.g., every 4 hours) vital signs
- Physical examination including evaluation for splenomegaly
- Serial (at least daily) monitoring of serum chemistry, CBCs, LFTs, ferritin, PT and 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 workup, including the following:
  - Blood cultures (bacterial and fungal)
  - Urine cultures and urinalysis
  - Radiographic assessments (e.g., chest X-ray or CT scan)
  - Assessment for active viral infections, including but not limited to EBV and 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).

Participants with suspected HLH should be treated according to the guidelines in Table 9. In the case of confirmed HLH, permanently discontinue study treatment.

## Table 9 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

| Event | Management |
|---|---|
| Suspected HLH | • Withhold study treatment and contact Medical Monitor.<br>• Consider participant 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 participant 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.

### A6–2.3.8 Infusion-Related Symptoms

IRR is a risk of rituximab. For management recommendations of IRRs, see Table 10.

**Table 10 Management of Infusion-Related Symptoms: Rituximab**

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

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

Note: Refer to the NCI-CTCAE v5.0 scale for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in Appendix 8, Anaphylactic Precautions.

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

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

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# Appendix 7
# Schedule of Activities for Tocilizumab Treatment of Cytokine Release Syndrome

## Table 1 Schedule of Activities for Tocilizumab Treatment of CRS: First Tocilizumab Dose

| Assessment or Procedure [a] | Pre-TCZ Tx (within 24 hr) | TCZ Admin | Post-TCZ Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 6 hr (±3 hr) | 24 hr (±4 hr) | 48 hr (±4 hr) | 72 hr (±4 hr) | 8 days/ 192 hr (±48 hr) | 8 weeks [b] |
| TCZ administration [c] | | 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 participant on room air [e] | | | | | |
| Pulse oximetry, resting | x [e] | | Measure at least every 6 hours until resolution to baseline, and then every 12 hours until end of hospitalization [e] | | | | | |
| Local laboratory assessments | | | | | | | | |
| Hematology | x | | x | x | x | x | x | |
| Liver function tests (AST, ALT, 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 | |

## Table 1 Schedule of Activities for Tocilizumab Treatment of CRS: First Tocilizumab Dose (Cont.)

| Assessment or Procedure [a] | Pre-TCZ Tx (within 24 hr) | TCZ Admin | Post-TCZ Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 6 hr (±3 hr) | 24 hr (±4 hr) | 48 hr (±4 hr) | 72 hr (±4 hr) | 8 days/ 192 hr (±48 hr) | 8 weeks [b] |
| Coagulation (aPTT, PT/INR, and fibrinogen) | x | | x | x | x | x | x | |
| Infection workup [h] | x | | | | | | | |
| Central laboratory assessments | | | | | | | | |
| Serum IL-6 pharmacodynamic markers [i] | x | x[j] | x | x | x | x | x | |
| Serum TCZ pharmacokinetics | x | x[j] | x | x | x | x | x | x |
| Serum TCZ ADA | x | | | | | | | x |

ADA = anti-drug antibody; Admin = administration; BUN = blood urea nitrogen; CRP = C-reactive protein; CRS = cytokine-release syndrome; EBV = Epstein-Barr virus; eCRF = electronic Case Report Form; IL-6 = interleukin-6; IL-6R = interleukin-6 receptor; LDH = lactate dehydrogenase; TCZ = tocilizumab; Tx = treatment.

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

[a] An assessment or a procedure may be waived by the Medical Monitor if a participant is hospitalized at a facility that does not have the capacity to perform the study assessment. Hospitalization should not be prolonged to perform study assessments in this schedule of activities. Note: This schedule of assessments applies to participants receiving their first dose of tocilizumab. For subsequent doses, see Table 2.

[b] Sample should be collected approximately 8 weeks (±14 days) after the final dose of TCZ.

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

[d] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated or supine position, and temperature.

[e] The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

[f] Document vasopressor name and dose on the Concomitant Medication eCRF.

## Table 1 Schedule of Activities for Tocilizumab Treatment of CRS: First Tocilizumab Dose (Cont.)

[g] Includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, and BUN or urea.

[h] Evaluate for bacterial, fungal, and viral infections using cultures, serologies, and molecular diagnostic tests as clinically indicated based on the individual participant's status and local practice for febrile oncology participants. At a minimum, blood cultures should be obtained.

[i] Includes IL-6, soluble IL-6R, and sgp130 (if assay available).

[j] Blood draws for serum TCZ pharmacokinetics and serum IL-6 pharmacodynamic markers should be performed within 15 minutes after the end of TCZ infusion and should be drawn from the arm that was not used to administer TCZ.

## Table 2 Schedule of Activities for Tocilizumab Treatment of CRS: Second Dose

| Assessment or Procedure [a] | Pre-TCZ Tx (within 24 hours) | TCZ Admin | Post-TCZ Treatment | | |
|---|---|---|---|---|---|
| | | | Within 15 minutes after the End of TCZ Infusion | 24 hr (±4 hr) | 8 weeks [b] |
| TCZ administration [c] | | 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 participant on room air. [e] | | |
| Pulse oximetry, resting | x [e] | | Measure at least every 6 hours until resolution to baseline, and then every 12 hours until end of hospitalization. [e] | | |
| Local laboratory assessments | | | | | |
| Hematology | x | | | | |
| Liver function tests (AST, ALT, and total bilirubin) | x | | | | |
| Serum chemistry and creatinine [g] | x | | | | |
| CRP, LDH, and serum ferritin | x | | | | |
| Coagulation (aPTT, PT/INR, and fibrinogen) | x | | | | |
| Infection workup [h] | x | | | | |

## Table 2 Schedule of Activities for Tocilizumab Treatment of CRS: Second Dose (cont.)

| Assessment or Procedure [a] | Pre-TCZ Tx (within 24 hours) | TCZ Admin | Post-TCZ Treatment | | |
|---|---|---|---|---|---|
| | | | Within 15 minutes after the End of TCZ Infusion | 24 hr (±4 hr) | 8 weeks [b] |
| TCZ administration [c] | | x | | | |
| Central laboratory assessments | | | | | |
| Serum IL-6 pharmacodynamic markers [i] | x | | x *j* | x | |
| Serum TCZ pharmacokinetics [b] | x | | x *j* | x | x |
| Serum TCZ ADA | | | | | x |

ADA = anti-drug antibody; CRP = C-reactive protein; CRS = cytokine-release syndrome; EBV = Epstein-Barr virus; eCRF = electronic Case Report Form; IL-6 = interleukin-6; IL-6R = interleukin-6 receptor; LDH = lactate dehydrogenase; PBMC = peripheral blood mononuclear cell; TCZ = tocilizumab; Tx = treatment.

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

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

[b] Sample should be collected approximately 8 weeks (±14 days) after the last dose of tocilizumab.

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

[d] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated or supine position, and temperature.

[e] The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

[f] Document vasopressor name and dose on the Concomitant Medications eCRF.

[g] Includes sodium, potassium, chloride, bicarbonate, glucose, and BUN or urea.

[h] Evaluate for bacterial, fungal, and viral infections using cultures, serologies, and molecular diagnostic tests as clinically indicated based on the individual participant's status and local practice for febrile oncology participants. At a minimum, blood cultures should be obtained.

## Table 2 Schedule of Activities for Tocilizumab Treatment of CRS: Second Dose (cont.)

[i] Includes IL-6, soluble IL-6R, and sgp130 (if assay available).

[j] Blood draws for serum tocilizumab pharmacokinetics and serum IL-6 pharmacodynamic markers should be performed within 15 minutes after the end of TCZ infusion and should be drawn from the arm that was not used to administer TCZ.

# Appendix 8
# Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

## REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, 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 administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
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 epinephrine first, followed by antihistamines, albuterol, or other medications, as required by participant status and directed by the physician in charge.
6. Continue to observe the participant and document observations.

# Appendix 9
# Definitions of Laboratory Abnormalities 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 mmol/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 |

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 afterwards. 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.

| Metabolic Abnormality | Criteria for Classification of Laboratory TLS [a] | Criteria for Classification of Clinical TLS [a] |
|---|---|---|
| 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 mmol/L) in serum creatinine level (or a single value $>$1.5 $\times$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 afterwards. 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 $+0.8\times$(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. Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis 2007;50:1-4.

# Appendix 10
# American Society for Transplantation and Cellular Therapy
# Cytokine-Release Syndrome Consensus Grading

| CRS Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 [a] |
|---|---|---|---|---|---|
| Fever [b] | 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 [c] | | |
| Hypoxia | None | Requiring low-flow nasal cannula [d] 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; IRR = infusion-related adverse event; 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] Grade 5 CRS is defined as death due to CRS.

[b] Fever is defined as a temperature ≥38°C not attributable to any other cause. In participants who have CRS then receive antipyretic or anti-cytokine 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. Because patients are receiving dexamethasone as premedication with glofitamab, fever response may be blunted. Therefore, adverse events attributed to glofitamab consistent with a diagnosis of IRR or CRS and associated with fever, hypotension or hypoxia not attributable to any other cause, should be recorded as CRS.

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

[d] 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.

# Appendix 11
# 2014 Lugano Response Criteria for Malignant Lymphoma

Response should be determined on the basis of radiographic and clinical evidence of disease. Assessment of the positron emission tomography/computed tomography (PET/CT) scan should follow the criteria presented below (Cheson et al. 2014). Contrast-enhanced CT is preferred for more precise measurements of nodal masses and differentiation between normal anatomy and disease nodal infiltration of mediastinum and abdominal cavity.

## TARGET AND NON-TARGET LESIONS

Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be greater than 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the six representative, measured lesions. At baseline, measurable extranodal lesions should be greater than 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-measured disease as non-target lesions (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

## SPLEEN INVOLVEMENT

Spleen may be of normal size or enlarged, homogeneous splenomegaly or diffuse infiltration with small lesions or large solid mass.

A single measurement that correlates well with volume is preferable and the cut off $>$ 13 cm in the vertical length for splenomegaly is recommended.

## LIVER INVOLVEMENT

Measurement of liver size is not reliable by CT. Liver involvement is similar to the spleen involvement as diffuse increased or focal uptake on PET, with or without focal lesions.

## BONE MARROW INVOLVEMENT

If applicable, bone marrow involvement uptake in PET is scored using the 5-point scale as nodal sites.

## 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 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]<br>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. | Target nodes/nodal masses must regress to $\leq$ 1.5 cm in LDi.<br>No extralymphatic sites of disease. |
| Non-measured lesion | Not applicable | Absent |
| Organ enlargement | Not applicable | Regress to normal |
| New lesions | None | None |
| Bone marrow | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminate, IHC negative |

| 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 | $\geq$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 $5 \times 5$ mm as the default value. |
| | At end of treatment, these findings indicate residual disease. | When no longer visible, assign $0 \times 0$ mm as the default value. |
| | | For a node $> 5 \times 5$ 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 new FDG-avid foci | 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 $\geq$ 50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions $\leq$ 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 participants 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 lesions 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 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 12
# Ann Arbor Staging

| Grade | Description |
|---|---|
| Stage I | Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) [a] |
| Stage II | Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE) |
| Stage III | Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES) |
| Stage IV [b] | Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement |

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic B-symptoms of significant unexplained fever (>38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

[a] The designation "E" generally refers to extranodal contiguous extension (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE, rather than Stage IV.

[b] Involvement of bone marrow at screening will always qualify for Ann Arbor Stage IV and should be recorded as extranodal involvement.

Adapted from: Carbone et al. 1971; Lister et al. 1989.

## REFERENCES


Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860–1.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. J Clin Oncol 1989;7:1630–6.

# Appendix 13
# International Prognostic Index

| Risk Factors | |
|---|---|
| Ann-Arbor Stage III or IV | |
| Age $>60$ years | |
| Serum LDH $>1\times$ ULN | |
| ECOG Performance Status $\geq 2$ | |
| Extranodal involvement $\geq 2$ | |
| **IPI Risk Group** | **Number of IPI Risk Factors** |
| Low | 0 or 1 |
| Low-intermediate | 2 |
| High-intermediate | 3 |
| High | 4 or 5 |

ECOG=Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of IPI given that this prognostic score was established without FDG-PET.

Adapted from: Shipp et al. 1993.

## REFERENCES

Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive Non-Hodgkin's Lymphoma. N Engl J Med 1993;329:987–94.

# Appendix 14
# Eastern Cooperative Oncology Group Performance Status Scale

| Grade | Description |
|---|---|
| 0 | Fully active, able to carry on all predisease 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 |

## REFERENCES

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.

# Appendix 15
# Examples of Sensitive In Vivo Cytochrome P450 Substrates and CYP Substrates with Narrow Therapeutic Range

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

AUC = area under the concentration–time curve.

[a] Note that this is not an exhaustive list.

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

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

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

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

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

[g] Withdrawn from the United States market because of safety reasons.

## CYP3A Inhibitors

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

[a] These are anti-cancer agents; please contact the Medical Monitor before use.

Source: U.S. Food and Drug Administration. Drug development and drug Interactions: table of substrates, inhibitors and inducers [resource on the internet]. 2017 [cited: 17 April 2018]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

## CYP3A Inducers

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

Source: U.S. Food and Drug Administration. Drug development and drug Interactions: table of substrates, inhibitors and inducers [resource on the internet]. 2017 [cited: 17 April 2018]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

# Appendix 16
# Cockcroft–Gault Equation

*Creatinine clearance (CrCl) will be calculated using the following formula:*

$$CrCl\ (men) = \frac{(140 - Age)}{72} \times \frac{weight\ (kg)}{serum\ creatinine\ (mg/dL)}$$

$$CrCl\ (women) = \frac{(140 - Age)}{72} \times \frac{weight\ (kg)}{serum\ creatinine\ (mg/dL)} \times [0.85\ if\ female]$$

*Adapted from Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine [editorial]. Nephron 1992;62:249*

# Appendix 17
# Investigational Medicinal Product and *Auxiliary* Medicinal Product Designations (for Use in the European Economic Area)

## Table 1 Investigational, *Authorised Auxiliary,* and *Unauthorised Auxiliary* Medicinal Product Designations for European Economic Area

| Product Name | IMP/NIMP Designation | Marketing Authorization Status in EEA | Used within Marketing Authorization |
|---|---|---|---|
| Glofitamab (RO7082859) | IMP (test product) | *Authorized* | *No* [a] |
| Tocilizumab (RO4877533) | IMP (other) [b] | Authorized | No [b] |
| Rituximab | *AxMP* (background therapy) [c] | Authorized | Yes |
| Cyclophosphamide | *AxMP* (background therapy ) [c] | Authorized | Yes |
| Doxorubicin | *AxMP* (background therapy) [c] | Authorized | Yes |
| Vincristine | *AxMP* (background therapy) [c] | Authorized | Yes |
| Prednisone | *AxMP (background therapy)* [c] | Authorized | Yes |

*AxMP =auxiliary medicinal product; ctDNA = circulating tumor DNA;* EEA=European Economic Area; DLBCL=diffuse large B-cell lymphoma; IMP=investigational medicinal product.

[a] *Glofitamab is not approved in ctDNA high-risk patients with untreated DLBCL.*

[b] Tozilizumab is not approved for treatment of cytokine release syndrome induced by bispecific antibodies.

[c] Rituximab, cyclophophamide, doxorubicin, vincristine, and prednisone, together known as "R-CHOP," are approved for the treatment of DLBCL, classified as *AxMPs* (background therapy), recognized as Standard of Care in patients with DLBCL, and approved for the treatment of small-cell lung cancer.

[d] This classification also covers premedication and/or prophylaxis treatments in the study.

## Table 1 Investigational and *Authorised Auxiliary* Medicinal Product Designations for European Economic Area (*cont.*)

| Product Name | IMP/NIMP Designation | Marketing Authorization Status in EEA | Used within Marketing Authorization |
|---|---|---|---|
| Allopurinol | *AxMP* (rescue medication) [d] | Authorized | *Yes* |
| Rasburicase | *AxMP* (rescue medication) [d] | Authorized | *Yes* |
| Dexamethasone | *AxMP* (rescue medication) [d] | Authorized | Yes |
| G-CSF | *AxMP* (rescue medication) [d] | Authorized | Yes |
| Methotrexate | *AxMP* (rescue medication) [d] | Authorized | Yes |
| Paracetamol | *AxMP* (rescue medication) [d] | Authorized | Yes |
| Diphenydramine | *AxMP* (rescue medication) [d] | Authorized | Yes |
| Methylprednisolone | *AxMP* (rescue medication) [d] | Authorized | Yes |
| Prednisolone | *AxMP* (rescue medication) [d] | Authorized | Yes |
| *Acyclovir* | *AxMP (rescue medication)* [d] | *Authorized* | *Yes* |
| *Valacyclovir* | *AxMP (rescue medication)* [d] | *Authorized* | *Yes* |

*AxMP =auxiliary medicinal product; ctDNA = circulating tumor DNA; EEA =European Economic Area; DLBCL =diffuse large B-cell lymphoma; IMP =investigational medicinal product;.*

[a] *Glofitamab is not approved in ctDNA high-risk patients with untreated DLBCL.*

[b] *Tozilizumab is not approved for treatment of cytokine release syndrome induced by bispecific antibodies.*

[c] *Rituximab, cyclophophamide, doxorubicin, vincristine, and prednisone, together known as "R-CHOP," are approved for the treatment of DLBCL, classified as AxMPs (background therapy), recognized as Standard of Care in patients with DLBCL, and approved for the treatment of small-cell lung cancer.*

[d] *This classification also covers premedication and/or prophylaxis treatments in the study.*

# Appendix 18
# Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

## PROTOCOL AMENDMENT, VERSION 3 (18 NOVEMBER 2022)

Protocol GO40375 has been amended to clarify [redacted] but now at the investigators discretion. Changes to the protocol, along with a rationale for each change, are summarized below:

- Text has been updated to clarify [redacted] but at the investigator's discretion in Cycles [redacted] and [redacted] based on the most recent CRS and safety data (Section 1.3, Table 1; Sections 4.1.1, 4.4; Appendix 1).
- It has been clarified that in survival follow-up, response assessments should continue through new anti-lymphoma therapy and until 1 year from the end of treatment response assessment (Section 1.3, Table 1; Section 8.1.1).
- Addition of a [redacted] sample at Cycle [redacted] Day [redacted] to allow for an additional genomic control sample (Section 1.3, Table 2).
- Clarification that BUN or urea may be collected (Section 1.3, Table 2; Appendix 2, Table 1).
- Additional clarification and alignment on adverse event reporting periods throughout course of study (Section 1.3, Table 1, Schedule of Activities; Section A-3.6).
- Update of the testing laboratory name from Ariosa Dignostics Clinical Laboratory to Roche Molecular Systems to reflect the updated company name (Section 2.1.3).
- Clarification that the use of the AOA-NHL Test for identifying ctDNA high-risk patients with untreated DLBCL is experimental (Sections 2.1.3, 4.1.1, 5.1.2).
- The exclusion criterion for patients with a positive HIV test has been removed, and an inclusion criterion for patients with a negative HIV test has been added to expand patient eligibility and support the inclusion of representative patient populations, including those disproportionately affected by HIV (Puronen CE et al. Immunotherapy in people with HIV and cancer. Front Immunol 2019;10:2060) (Sections 5.1 and 5.2).
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility and during study conduct have been clarified (Sections 5.1.1, 5.2, 6.1.1, 6.8, 8.1.5, 8.1.7, 8.2.9, 8.6, A6-1.1.3, A6-2.1, A6-2.3.1, A6-2.3.6).
- The inclusion criterion has been updated to specify that patients with de novo transformed follicular lymphoma are eligible without the requirement for a bone marrow biopsy (Section 5.1.1).
- The exclusion criterion has been updated to specify that patients with T-cell/histiocyte–rich large B-cell lymphoma are not eligible to enroll into the study (Section 5.2).

- The exclusion criterion has been updated to clarify that monoclonal antibody use within 4 weeks or five half-lives, whichever is shorter, and/or investigational therapy within 28 days for the purposes of treatment cancer prior to Cycle 1 would be exclusionary (Section 5.2).
- Clarification has been provided on which autoimmune diseases would be exclude a patient from participating in the study (Section 5.2).
- Addition of dexamethasone, allopurinol, and rasburicase as non-investigational medicinal products (NIMPs) (Section 6.1, Table 4).
- Clarification that anti-infective prophylaxis for COVID-19 is permitted (Section 6.1.5.2).
- Infection has been upgraded from a potential risk to an identified risk due to the occurrence of several serious and two fatal adverse events of pneumonia related to glofitamab in addition to a plausible mechanism of B-cell depletion that can lead to risk of infection (Sections 6.8.2.1, 8.1.7, A6-1.1.6).
- Amended prohibited therapies to include clarification on permitted biologic agents, including COVID-19 therapies (Section 6.8.3).
- Clarification that if less than 15 archival tumor slides are available, the patient is still eligible for the study (Section 8.6).
- Language has been clarified to indicate that any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants (Section A1-1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section A1-4).
- Clarification on glofitamab dose continuation/modification under certain graded neutropenic/thrombocytopenic events (Section A6, Table 8).
- General guidance on how to assess and report a tumor flare (TF) event has been added to the safety section to help the investigator identify a TF event following treatment with glofitamab (Section A6-1.1.3).
- Addition of Howard Criteria for tumor lysis syndrome as this was missing from the previous version of the protocol (Appendix 9).
- Addition of investigational medicinal product (IMP) and NIMP designations table to align with updated guidance on IMP/NIMP classification (Appendix 18).

## PROTOCOL AMENDMENT, VERSION 2: (22 JUNE 2021)

Protocol GO40375 has been amended to include the use of an Internal Monitoring Committee, to add an [redacted] to clarify

hematologic criteria to initiate the next cycle of therapy, and to update the identified and potential risks of glofitamab. Changes to the protocol, along with a rationale for each change, are summarized below:

- A complete physical examination has been added at the screening timepoint in the Schedule of Activities (Table 1).
- Additional [redacted], glofitamab PK, and glofitamab anti-drug antibody sampling timepoints have been updated at Cycle [redacted], Day [redacted] and Cycle [redacted] Day [redacted] (Table 2).
- Tumor lysis syndrome (TLS) and infection have been upgraded to identified risks from potential risks of glofitamab (Section 2.3, Appendix 6 A6-1.1).
- Added exclusion criteria for patients with significant or extensive cardiovascular disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina, to encourage investigators to consider objective evidence of cardiac disease, independent of symptoms, in their assessment of whether a patient should come on study (Section 5.2).
- Colitis has been added as a new potential risk of glofitamab based on preclinical observations and adverse event data from early phase clinical studies (Section 2.3, Appendix 6 A6-1.2).
- [redacted] and other quantitative indices in Section 3, Table 3 and Section 9.4.
- An Internal Monitoring Committee will be established to monitor patient safety during the course of the study as described in Sections 4.1.1, 4.4, 4.6, and 9.5.1.
- Clarification has been provided in Appendix 6-2.1 for the hematologic parameters that need to be met in order to commence subsequent cycles of therapy.
- In order to maintain treatment with the R-CHOP backbone and to maintain dose intensity, glofitamab may be discontinued if R-CHOP is delayed by 21 days or more (Appendix 6-2.1).

# Appendix 19
# Abbreviations

| Abbreviation or Term | Definition |
|---|---|
| ABC | activated B cell–like |
| ADA | anti-drug antibody |
| [redacted] | |
| AOA-NHL | AVENIO Oncology Assay for Non-Hodgkin's Lymphoma (Test) |
| ASCT | autologous stem cell transplantation |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| [redacted] | |
| AUC | area under the concentration–time curve |
| BSA | body surface area |
| cfDNA | cell-free DNA |
| CHOP | cyclophosphamide, doxorubicin, vincristine, and prednisone |
| CLIA | Clinical Laboratory Improvement Act |
| $C_{max}$ | maximum concentration |
| COVID-19 | coronavirus disease 2019 |
| CR | complete response |
| CRS | cytokine-release syndrome |
| CT | computed tomography |
| ctDNA | circulating tumor DNA |
| CYP | cytochrome P450 |
| DLBCL | diffuse large B-cell lymphoma |
| DOR | duration of response |
| $^{18}$F-FDG | $^{18}$F-fluorodeoxyglucose |
| EC | Ethics Committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EFS | event-free survival |
| EOT | end of treatment |
| EMR | early molecular response |
| FDA | (U.S.) Food and Drug Administration |
| $^{18F}$FDG | [$^{18}$F]fluoro-2-deoxy-D-glucose |
| FDG | fluorodeoxyglucose |

| Abbreviation or Term | Definition |
|---|---|
| FFPE | formalin-fixed, paraffin-embedded |
| G | obinutuzumab |
| GCB | germinal B-cell like |
| G-CSF | granulocyte colony-stimulating factor |
| GM-CSF | granulocyte-macrophage 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 |
| HGBCL | high-grade B-cell lymphoma |
| HLH | hemophagocytic lymphohistiocytosis |
| ICH | International Council for Harmonisation |
| iDES-enhanced CAPP-Seq | integrated digital error suppression-enhanced cancer personalized profiling by deep sequencing |
| IFN-γ | interferon-γ |
| IL-6 | interleukin-6 |
| IMC | internal 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 |
| LPLV | last participant, last visit |
| LVEF | left ventricular ejection fraction |
| MASCC | Multinational Association for Supportive Care in Cancer |
| MMR | major molecular response |
| MR | molecular response |
| MRD | minimal residual disease |
| MRI | magnetic resonance imaging |
| MUGA | multigated acquisition |
| NCCN® | National Comprehensive Cancer Network® |

| Abbreviation or Term | Definition |
|---|---|
| NCI CTCAE, v5.0 | National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 |
| NGS | next-generation sequencing |
| NHL | non-Hodgkin lymphoma |
| NIMP | non-investigational medicinal product |
| 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 |
| PO | orally (by mouth) |
| PR | partial response |
| QTcF | QT interval corrected through use of Fridericia's formula |
| R | rituximab |
| R-CHOP | rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone |
| R/R | refractory or relapsed |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SOC | standard of care |
| TLS | tumor lysis syndrome |
| [redacted] | |
| TSV | tumor-specific variant |
| ULN | upper limit of normal |
| [redacted] | |

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