Official Title: A Phase III, Open-Label, Multicenter, Randomized, Study Evaluating the Safety and Efficacy of Polatuzumab Vedotin in Combination with Rituximab Plus Gemcitabine Plus Oxaliplatin (R-GEMOX) Versus R-GEMOX Alone in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma

NCT Number: NCT04182204

Document Date: Protocol Version 8: 06-May-2025

PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY EVALUATING THE SAFETY AND EFFICACY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH RITUXIMAB PLUS GEMCITABINE PLUS OXALIPLATIN (R-GEMOX) VERSUS R-GEMOX ALONE IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	MO40598
VERSION NUMBER:	8
EUDRACT NUMBER:	2018-003727-10
IND NUMBER:	109409
TEST PRODUCT:	Polatuzumab vedotin (RO5541077; anti-CD79b-VC-MMAE; DCDS4501S)
MEDICAL MONITOR:	[redacted] *Pharm.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic *signature and* date stamp *on final page of this document*

CONFIDENTIAL

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
8	See electronic date stamp on *the final* page *of this document*
7	24 March 2021
6	24 February 2021
5	12 June 2020
4	27 November 2019
3	5 September 2019
2	16 April 2019
1	24 January 2019

PROTOCOL AMENDMENT, VERSION 8: RATIONALE

Protocol MO40598 has been primarily amended to increase the sample size as a consequence of the change in the median overall survival (mOS) assumptions based on the availability of newer subsequent therapies in the relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) therapy landscape. Risks and management guidelines for polatuzumab vedotin have also been updated to align with the latest effective Polatuzumab Vedotin Investigator's Brochure (Version 13). Changes to the protocol, along with a rationale for each change, are summarized below:

- Determination of sample size (Section 6.1) has been updated due to a shift in the treatment landscape for R/R DLBCL, which has changed markedly since the authoring of this protocol in 2019. Assumptions of mOS have been updated based on the availability of newer treatments such as CAR T-cell therapy subsequent to POLARGO study treatment (Study MO40598). The new assumptions for mOS increased the number of events for the primary endpoint of overall survival from [redacted] to [redacted] events in order to maintain an [redacted] power with a two-sided alpha of [redacted]. As a result of the increase in number of events, the total sample size has been increased to approximately 250 patients. Sections 1.3, 3.1, 3.2, 4.1, 4.2, 6.1, and 9.5 have been updated accordingly.
- Language has been edited to clarify the assessments required during long-term follow-up and the methods for collection of information (Sections 3.1 and 4.6.1; Appendices 1 and 2).
- The definition of refractory has been clarified to include patients who did not respond to their last line of therapy (stable disease) in addition to those who experienced disease progression within 6 months of their last relapse (Sections 3.1, 3.3.2, and 4.1.1).
- Language has been added to clarify the end of study and length of study (Section 3.2).
- Inclusion criteria were clarified to include patients with newly transformed DLBCL from indolent lymphoma (no treatment received for the transformed lymphoma) if the patient has received an anthracycline containing chemotherapy regimen (such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for the indolent lymphoma (Section 4.1.1).
- To address the coronavirus disease 2019 (COVID-19) pandemic COVID-19 vaccines have been added as permitted therapy (Section 4.4.1.4).
- Risks for polatuzumab vedotin have been updated to align with the latest Polatuzumab Vedotin Investigator's Brochure (Version 13) (Section 5.1.1.1).
- Risks for rituximab, gemcitabine, and oxaliplatin have been removed from the protocol and references to the Rituximab Investigator's Brochure and Package Insert/Summary of Product Characteristics for gemcitabine and oxaliplatin have been added.

- Management guidelines for adverse events have been edited to clarify:
  - Recommendations for management of Grade 2 or 3 peripheral neuropathy (Sections 4.6.1 and 5.1.2.3) and Grade 2 non-hematologic toxicity (Section 5.1.2.3)
  - Study treatment can be delayed for a maximum of 14 days after the scheduled date of the next cycle (Section 5.1.2.2).
- Guidelines for recording special situations and adverse events associated with special situations in the Adverse Event electronic Case Report Form have been updated (Section 5.3.5.12).
- Additional minor changes were made to clarify and align different sections and documents:
  - Language was added to clarify how to count salvage and conditioning chemotherapies in prior lines of therapy (Sections 3.1, 3.3.2, and 4.1.1).
  - Language was edited to include abstinence/contraception time periods for all drugs (Section 4.1.1).
  - The time period to record concomitant medications was clarified (Section 4.5.2, Appendices 1 and 2).
  - Magnetic resonance imaging scans were added as an imaging modality for patients in whom contrast is contraindicated (Section 4.5.8).
  - The names of samples and study visits for pharmacokinetics were clarified (Appendix 4).
  - Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
  - Language regarding investigator reporting of pregnancies has been clarified (Section5.4.3.2).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during investigational medicinal product transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.3).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with the EU's Clinical Trials Regulation requirements (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports. The name of a Roche policy on data sharing has been corrected (Section 9.6).

- Appendix 15 has been added to designate all protocol-mandated therapies as an investigational medicinal product or a non-investigational medicinal product.

Additional minor changes have been made to repair typographical errors and to improve clarity and consistency. Substantive new information appears in Book Antigua italics (*Book Antigua italics*) in the amended protocol. This amendment represents cumulative changes to the original protocol.

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY EVALUATING THE SAFETY AND EFFICACY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH RITUXIMAB PLUS GEMCITABINE PLUS OXALIPLATIN (R-GEMOX) VERSUS R-GEMOX IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	MO40598
VERSION NUMBER:	8
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IND NUMBER:	109409
TEST PRODUCT:	Polatuzumab vedotin (RO5541077; anti-CD79b-VC-MMAE; DCDS4501S)
MEDICAL MONITOR:	[redacted], *Pharm.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY EVALUATING THE SAFETY AND EFFICACY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH RITUXIMAB PLUS GEMCITABINE PLUS OXALIPLATIN (R-GEMOX) VERSUS R-GEMOX IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	MO40598
VERSION NUMBER:	8
EUDRACT NUMBER:	2018-003727-10
IND NUMBER:	109409
TEST PRODUCT:	Polatuzumab vedotin (RO5541077; anti-CD79b-VC-MMAE; DCDS4501S)
PHASE:	Phase III
INDICATION:	Relapsed/refractory diffuse large B-cell lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Study MO40598 will evaluate the safety and efficacy of polatuzumab vedotin in combination with rituximab, gemcitabine, and oxaliplatin (Pola-R-GemOx) compared to rituximab, gemcitabine, and oxaliplatin alone (R-GemOx) in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL). Treatment will occur in two stages: 1) an initial safety run-in stage assessing Pola-R-GemOx; and 2) an RCT stage comparing Pola-R-GemOx versus R-GemOx.

Specific objectives and corresponding endpoints for each stage of the study are outlined in Synopsis Table 1 and Synopsis Table 2.

Synopsis Table 1. Objectives and Corresponding Endpoints: Safety Run-In (Stage 1)

Primary Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of Pola-R-GemOx as a combination therapy	• Incidence, nature and severity of physical findings and AEs, with a specific focus on PN, according to the NCI CTCAE v5.0
Secondary Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of Pola-R-GemOx as a combination therapy and to assess the immunogenicity of polatuzumab vedotin	• Incidence and assessment of PN, as measured by FACT/GOG-NTX-12 • Tolerability, as measured by dose interruptions, dose reductions and dose intensity • Prevalence of ADAs at baseline and incidence of ADAs during the study

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of Pola-R-GemOx	• CR, defined as the proportion of patients who achieve complete metabolic response based on PET-CT, according to Lugano 2014 response criteria, at the end of treatment as determined by the investigator • ORR, defined as the proportion of patients who achieve complete or partial metabolic responses, according to Lugano 2014 response criteria, at end of treatment as determined by the investigator • BOR, defined as the best response while on study, according to Lugano 2014 response criteria, as determined by the investigator • PFS, defined as the time from enrollment to the first occurrence of disease progression as determined by the investigator according to Lugano 2014 response criteria or death from any cause • OS, defined as time from *enrollment* to death from any cause • EFS_{eff}, defined as time from enrollment to the earliest occurrence of the below cases: - Disease progression or relapse - Death due to any cause • Initiation of any NALT
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To further evaluate the PK of polatuzumab vedotin	• PK of polatuzumab vedotin in combination with R-GemOx in patients with relapsed or refractory DLBCL

AE = adverse event; ADA = anti-drug antibody; BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EFS_{eff} = event-free survival; FACT/GOG-NTX-12 = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale; NALT = non-protocol–specified anti-lymphoma treatment; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; PK = pharmacokinetics; PN = peripheral neuropathy; Pola-R-GemOx = polatuzumab vedotin, rituximab, gemcitabine, and oxaliplatin; R-GemOx = rituximab plus gemcitabine plus oxaliplatin.

Synopsis Table 2. Objectives and Corresponding Endpoints: Randomized Controlled Trial (Stage 2)

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of Pola-R-GemOx compared with R-GemOx alone	• OS, defined as time from randomization to death from any cause
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Pola-R-GemOx compared with R-GemOx alone	Key secondary endpoints included in the hierarchical testing procedure: • PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to Lugano 2014 response criteria, or death from any cause • CR, defined as the proportion of patients who achieve complete metabolic response based on PET-CT, according to Lugano 2014 response criteria, at the end of treatment as determined by an IRC • ORR, defined as the proportion of patients who achieve complete or partial metabolic responses, *based on PET-CT* according to Lugano 2014 response criteria, at the end of treatment as determined by an IRC Secondary endpoints that will not be adjusted for testing multiplicity: • BOR, defined as the best response while on study, according to Lugano 2014 response criteria, as determined by the investigator • CR, defined as the proportion of patients who achieve complete metabolic response based on PET-CT, according to Lugano 2014 response criteria, at the end of treatment as determined by the investigator • ORR, defined as the proportion of patients who achieve complete or partial metabolic responses, according to Lugano 2014 response criteria, at the end of treatment as determined by the investigator • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to Lugano 2014 response criteria, or death from any cause, whichever occurs first • EFS_{eff}, defined as time from randomization to the earliest occurrence of the below cases: - Disease progression or relapse - Death due to any cause • Initiation of any NALT

Secondary PRO Objective	Corresponding Endpoint
• To evaluate impact of treatment and disease on aspects of health-related quality of life	• Time to deterioration in physical functioning and fatigue as measured by the EORTC QLQ-C30 • Time to progression in lymphoma symptoms as measured by the FACT-Lym subscale • Change from baseline in PN as measured by the FACT/GOG-NTX-12 subscale score
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of Pola-R-GemOx compared with R-GemOx and to assess the immunogenicity of polatuzumab vedotin	• Incidence, nature, and severity of AEs (including PN) according to NCI CTCAE v5.0 and physical findings • Tolerability, as assessed by dose interruptions, dose reductions and dose intensity • Prevalence of ADAs at baseline and incidence of ADAs during the study
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that: - Are prognostic of response to polatuzumab vedotin (i.e., predictive biomarkers) - Are associated with progression to a more severe disease (i.e., prognostic biomarkers) - Can provide evidence of polatuzumab vedotin activity, or can increase the knowledge and understanding of disease biology • To explore MRD as a prognostic marker in R/R DLBCL	• Associations between efficacy endpoints, including OS, PFS and CR rate, and exploratory biomarkers, which may include but are not limited to histological and molecular prognostic markers and profiles of circulating immune
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To further evaluate the PK of polatuzumab vedotin	• PK of polatuzumab vedotin in combination with R-GemOx in patients with relapsed or refractory DLBCL
Exploratory PRO Objectives	**Corresponding Endpoints**
• To evaluate impact of treatment and disease on aspects of health-related quality of life	• Descriptive summary statistics and the change from baseline for: - All scales for the EORTC QLQ-C30 - FACT-Lym subscale - FACT/GOG-NTX-12 - EQ-5D-5L

AE = adverse event; ADA = anti-drug antibody; BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS_{eff} = event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30; EQ-5D-5L = EuroQol 5-Dimension

Questionnaire, 5-Level Version; FACT/GOG-NTX-12 = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale; FACT-Lym Functional Assessment of Cancer Therapy-Lymphoma; IRC = Independent Review Committee; MRD = minimal residual disease; NALT = non-protocol–specified anti-lymphoma treatment; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; PK = pharmacokinetics; PN = peripheral neuropathy; Pola-R-GemOx = polatuzumab vedotin, rituximab, gemcitabine, and oxaliplatin; R/R = relapsed/refractory; R-GemOx = rituximab plus gemcitabine plus oxaliplatin

Study Design

Description of Study

Study MO40598 is a Phase III, multicenter, open-label RCT in patients with relapsed or refractory DLBCL. The study will consist of a Screening Period, a Treatment Period, and a Post-Treatment Period. The Post-Treatment Period will include an End of Treatment Visit occurring 28 days after the last dose of study treatment and a Follow-Up Period. Adverse events, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or until initiation of a non-protocol–specified anti-lymphoma treatment (NALT).

The overall design of the study is presented in Synopsis Figure 1.

Synopsis Figure 1 Study Schema

Pola = polatuzumab vedotin; R = randomize; R-GemOx = rituximab plus gemcitabine plus oxaliplatin; R/R DLBCL = relapsed or refractory diffuse large B-cell lymphoma.

Screening Period

To be eligible for Study MO40598, patients must have histologically-confirmed, relapsed or refractory DLBCL. Relapsed and refractory disease are defined as:

- Relapsed: Disease that has recurred following a response that lasted ≥ 6 months from completion of the last line of therapy
- Refractory: Disease that *did not respond to or that* progressed during therapy or progressed within 6 months (< 6 months) of *completion of* prior therapy

Patients may have undergone autologous hematopoietic stem cell transplantation (HSCT) prior to recruitment; *in such cases, salvage chemotherapy will be counted as one line of therapy and conditioning* chemotherapy followed by consolidative autologous Hematopoietic stem cell transplantation will be counted as *a separate* line of therapy. Patients may have undergone allogeneic HSCT prior to recruitment, so long as they are off of all immunosuppressive therapy and have no active graft versus host disease (GVHD); *in such cases, salvage chemotherapy will be counted as one line of therapy and conditioning* chemotherapy followed by allogeneic HSCT will be counted *a separate* line of therapy. Local therapies (e.g., radiotherapy) will not be considered as treatment lines.

Patients with peripheral neuropathy (PN) assessed to be greater than Grade 1 according to NCI CTCAE v5.0 will be excluded from enrollment. The grading of PN will be detailed in the protocol. Other inclusion and exclusion criteria are summarized in Section 4.1.1 and Section 4.1.2.

Treatment Period

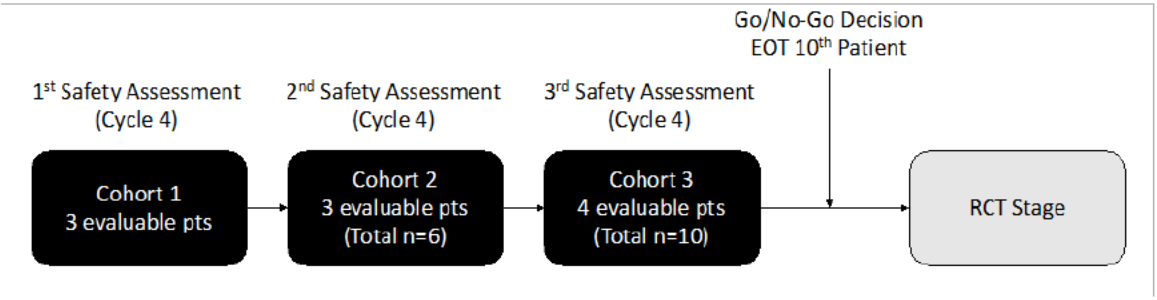
The Treatment Period will occur in two stages. Stage 1 will comprise a safety run-in, where approximately 10 patients will receive experimental study treatment with Pola-R-GemOx. The purpose of Stage 1 is to provide a preliminary safety assessment of the study treatment, prior to entering Stage 2 of the study. Stage 2 will comprise an RCT, where approximately 250 patients will be randomly assigned in a 1:1 ratio to receive either experimental study treatment with Pola-R-GemOx or control study treatment with R-GemOx. In both stages of the Treatment Period, patients will receive up to 8 cycles of Pola-R-GemOx or 8 cycles of R-GemOx, each administered on 21-day cycles. Dosing regimens are described in detail in Section 4.3.2. Dose delays/reductions will be permitted, as detailed in the protocol (Section 5.1.2).

Stage 1: Safety Run-In (Figure 2)

- At a limited number of sites (approximately 18 centers), approximately 13 patients will be treated with Pola-R-GemOx
- Accrual of these patients will be staggered across three cohorts until the number of evaluable patients required for each cohort (mentioned below) is reached. Evaluable patients are patients who complete at least 4 cycles of treatment or are discontinued because of Grade $\geq$ 3 PN:
  - Cohort 1: 3 evaluable patients
  - Cohort 2: 3 evaluable patients
  - Cohort 3: 4 evaluable patients

    Approximately 7 patients will be recruited in Cohort 3, with the aim of having at least 4 evaluable patients.
- Cohort 2 and Cohort 3 will not begin enrolling patients until all safety evaluations have been completed in Cohort 1 and Cohort 2, respectively, and recruitment of the next cohort has been approved (see below for how approval occurs). Patients who discontinue prior to Cycle 4 of treatment due to disease progression, death or any other reason that is not directly attributable to PN will be replaced until the required number of evaluable patients is reached.
- Once 3 evaluable patients from Cohort 1 complete 4 cycles or discontinue because of Grade $\geq$ 3 PN, the IMC, in collaboration with the Steering Committee (SC) (if necessary), will evaluate the total safety profile of Pola-R-GemOx, with a particular focus on PN. They will then approve or disapprove enrollment into the next cohort. This recommendation will be released to the Sponsor responsible. Cohort 2 will follow the same process.
- [redacted]
- In addition to the above, all patients from previous cohorts who proceeded beyond the fourth cycle of therapy will be re-evaluated by the IMC to assess the potential of cumulative neurotoxicity with Pola-R-GemOx, as well as the course of PN resolution.

Figure 2 Safety Run-In Schema (Stage 1)



EOT = end of treatment; evaluable = treated for at least 4 cycles of therapy or discontinued due to Grade ≥ 3 peripheral neuropathy; pts = patients; RCT = randomized controlled trial.

The Formal Go/No-Go Decision at the End of Stage 1

- When a minimum of 10 evaluable patients in the Treatment Period of Stage 1 have received the last dose of Pola-R-GemOx (i.e., completed Cycle 8 or discontinued between Cycle 5 and Cycle 8), the IMC will review the safety profile of the Stage 1 study population up to this point, focusing in particular on the frequency, course and reversibility of Grade ≥ 3 PN events.
  - [redacted]
- Based on the preceding information, the IMC will provide a recommendation, with the advice of the SC (if necessary), to the Sponsor responsible whether to continue to the RCT Stage.
- [redacted]

Stage 2: Randomized Controlled Trial

If Pola-R-GemOx combination therapy is deemed to be tolerable in the safety run-in, enrollment into the RCT stage will begin. Approximately 250 eligible patients will be randomized in a 1:1 ratio to receive either Pola-R-GemOx or R-GemOx. Randomization will be stratified by three factors: number of previous lines of systemic treatment (1 vs. ≥ 2), outcome of last systemic therapy (relapsed vs. refractory), and age (≤ 70 years vs. > 70 years).

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

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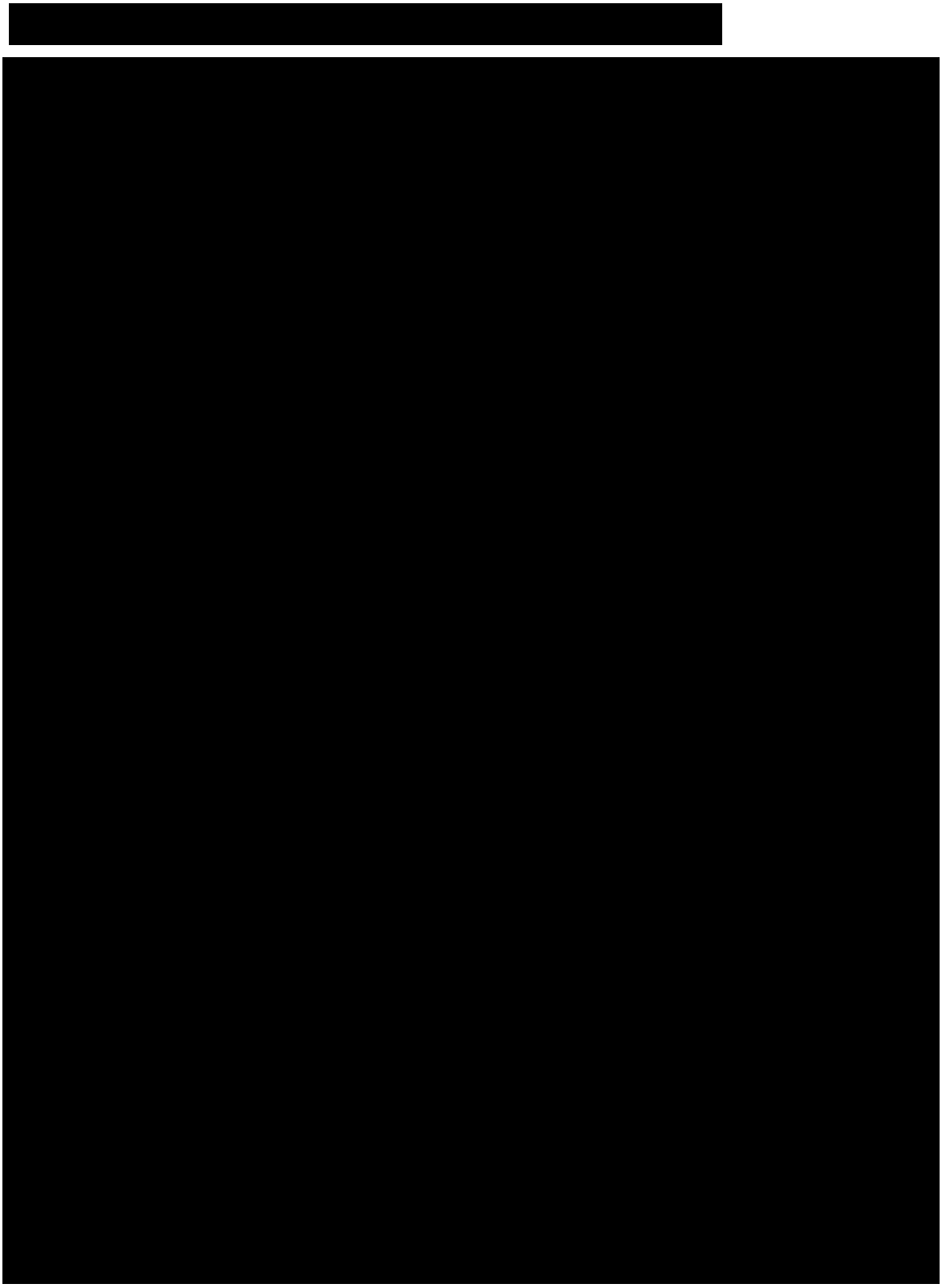


[redacted]

- [redacted]
- [redacted]

[redacted]

The objectives and endpoints of the two stages are provided in Section 2. Safety will be assessed by adverse events per NCI CTCAE v5.0, patient-reported FACT/GOG-NTX-12 score (Stage 1), clinical laboratory test results, ECG, and vital signs. Response assessments will be according to Lugano 2014 criteria, based on positron emission tomography–computed tomography (PET-CT) scans at screening and the end of treatment. All response assessments will be carried out by the investigator. In addition, the secondary outcomes of objective response rate (ORR) and CR rate in Stage 2 will be assessed by an Independent Review Committee, based on primary imaging data collected by the Sponsor.

Stage 1 and Stage 2 of the Treatment Period will also assess anti-drug antibodies (ADAs) and the sparse pharmacokinetic (PK) profile of polatuzumab vedotin in combination with R-GemOx. Stage 2 of the Treatment Period will also assess biomarkers (as per Synopsis Table 5) and additional patient-reported outcomes (EuroQol 5-Dimension Questionnaire, 5-Level Version [EQ-5D-5L], FACT/GOG-NTX-12, Functional Assessment of Cancer Therapy–Lymphoma [FACT-Lym], and EORTC QLQ-C30).

Synopsis Table 5 Biomarkers for Retrospective Exploratory Research (Stage 2)

Sample Type	Timing (All Mandatory)	Proposed Biomarkers
*DLBCL t*umor tissue *(fresh or archival)*	*Baseline*	• RNA-based gene expression profiling, including but not limited to cell-of-origin gene signature analysis • IHC and proteomic profiling, including BCL2 and MYC • Translocation profiles, including BCL2 and MYC • Mutation profiling by NGS, including but not limited to CD79b
Blood for MRD assays	Baseline, subsequent time points during treatment, and end of treatment (or discontinuation, whichever comes first)	• ctDNA level and clonal mutation profile • ctDNA as a peripheral measure of disease biology, prognosis, subsets, and treatment response
Blood for flow cytometry [a]	Baseline, subsequent time points during treatment, and end of treatment (or discontinuation, whichever comes first)	• Flow-cytometry–based profiling of circulating immune cells • To evaluate the prognostic value of patient immune fitness and investigate the effect of treatment regimen on circulating immune cells

ctDNA = circulating tumor DNA; IHC = immunohistochemistry; NGS = next-generation sequencing; MRD = minimal residual disease.

[a] The first 100 patients at selected sites will undergo flow cytometry.

Post-Treatment Period

Patients who complete study treatment per protocol (see Section 4.3.2) or discontinue from the study treatment early (e.g., if they terminated treatment early because of an adverse event) will enter the Post-Treatment Period, which will consist of an End of Treatment Visit occurring 28 (±7) days after the last dose of study treatment and then a *Long-term* Follow-Up Period. Assessments carried out at the End of Treatment Visit and during the *Long-term* Follow-Up Period are described in the Schedules of Activities in Appendix 1, Appendix 2*, Appendix 3, and Appendix 4.*

Patients in the Follow-Up Period will be assessed as follows *via clinic visits, telephone calls, and/or patient medical records approximately every 2 months until death, loss to follow-up, or study termination by the Sponsor:*

- Patients *who complete treatment or discontinue all study treatment prematurely due to reasons other than* disease progression will *continue standard long-term follow-up assessments including required ADA sampling and radiographic assessments until disease progression and will* be followed for NALT and survival.
- Patients who initiate NALT in the absence of progressive disease will continue to be followed for progression (*including radiographic assessments*), additional NALT, and survival.
- Patients with disease progression will be followed for NALT and survival.

Internal Monitoring Committee

An IMC will be established to monitor patient safety during the safety run-in and provide recommendations on whether the next cohorts or RCT should open. The IMC will include Sponsor representatives who are not associated with study conduct, at a minimum, representatives from Clinical Science, Safety Science and Biometrics. The IMC will review all necessary cumulative data at regular intervals during the study. The IMC will evaluate the total safety profile of Pola-R-GemOx, with a particular focus on PN. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities, will be detailed in an IMC Charter.

Independent Data Monitoring Committee

An iDMC will evaluate safety data periodically during the RCT (see Section 6.10). The analysis supporting iDMC review will be conducted by an independent Data Coordinating Center (iDCC) and provided to the iDMC. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

The guidelines for safety monitoring and predefined stopping rules for treatment-related deaths, PN events, and treatment delays that lead to treatment discontinuation will be provided in the iDMC charter.

Independent Review Committee

An Independent Review Committee (IRC) composed of board-certified radiologists and an oncologist with experience in malignant lymphoma will assess all patients for response (see Appendix 5) until end of treatment on the basis of imaging results and bone marrow biopsy results for all patients during the RCT. Decisions will be guided by a Charter specific to the independent review.

Number of Patients

Approximately 10 patients will be enrolled in the safety run-in phase, and approximately 2*50* patients will be enrolled in the randomized portion, for a total of approximately 2*60* patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically-confirmed diffuse large B-cell lymphoma, not otherwise specified or history of transformation of indolent disease to DLBCL
- Relapsed or refractory disease, defined as follows:
  - Relapsed: Disease that has recurred following a response that lasted ≥ 6 months from completion of the last line of therapy.
  - Refractory: Disease *that did not respond to or that* progressed during therapy or progressed within 6 months (< 6 months) of prior therapy.
- At least one (≥ 1) line of prior systemic therapy:
  - Patients may have undergone autologous HSCT prior to recruitment. *In such cases, salvage chemotherapy (e.g., rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP] and rituximab, ifosfamide, carboplatin, and etoposide phosphate [R-ICE]) will be counted as one line of therapy and conditioning* chemotherapy *(e.g., BEAM)* followed by consolidative autologous HSCT will be counted as *a separate* line of therapy.

  - Patients may have undergone allogeneic HSCT prior to recruitment, so long as they are off all immunosuppressive therapy and have no active GVHD. *In such cases, salvage chemotherapy (e.g., R-DHAP and R-ICE) will be counted as one line of therapy and conditioning* chemotherapy *(e.g., carmustine, etoposide, cytarabine, and melphalan [BEAM])* followed by allogeneic HSCT will be counted as *a separate* line of therapy.
  - *Patients may have undergone CAR T–cell therapy prior to recruitment. In such cases, cell collection, conditioning chemotherapy, and infusion will be counted as one line of therapy.*
  - Local therapies (e.g., radiotherapy) will not be considered as lines of treatment.
  - *For patients with history of transformation of indolent disease to DLBCL, it is preferred that patients have received at least one treatment for the transformed lymphoma. However, if there are cases where the patient has received an anthracycline-containing chemotherapy regimen (such as R-CHOP) for the indolent lymphoma only, then these patients can be considered as.*
- At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension as measured by computed tomography (CT) or magnetic resonance imaging (MRI)
- ECOG performance status of 0,1, or 2
  - Patients with an ECOG performance status of 3 can be considered in the RCT stage, but only if this status is DLBCL-related and if after a prephase of a 7-day steroid treatment during the screening phase (e.g., 1 mg/kg prednisone) an improvement in ECOG performance status to 2 or less is observed prior to enrolment.
- Adequate hematological function, as defined by:
  - Hemoglobin ≥ 8 g/dL
  - ANC $\geq 1.5 \times 10^9$/L or $\geq 0.5 \times 10^9$ if the neutropenia is attributable to underlying disease and before the administration of steroids
  - Platelet count $\geq 75 \times 10^9$/L or $\geq 50 \times 10^9$ if the thrombocytopenia is attributable to underlying disease
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 12 months after the final dose of polatuzumab vedotin, rituximab*, gemcitabine, or oxaliplatin*. Women must refrain from donating eggs during this same period.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile 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 requirements.
  - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below (the patient should receive advice on the possibility of opting for cryoconservation of sperm prior to start of study treatment due to the possibility of irreversible infertility following therapy with gemcitabine, oxaliplatin, or polatuzumab vedotin):
  - With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile 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 6 months after the final dose of *polatuzumab vedotin, rituximab,* oxaliplatin, and/or gemcitabine. Men must refrain from donating sperm during this same period.
  - With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of polatuzumab vedotin, rituximab, oxaliplatin, and*/or* gemcitabine to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to rituximab, gemcitabine, or oxaliplatin
- PN assessed to be Grade >1 according to NCI CTCAE v5.0 at enrollment
- Prior use of polatuzumab vedotin or a gemcitabine $+$ platinum-based agent combination
- Enrollment in any previous or ongoing polatuzumab vedotin trial
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1 Day 1
  - All acute, clinically-significant treatment-related toxicity from prior therapy, except for alopecia, must have resolved to Grade ≤ 2 prior to Cycle 1 Day 1.
- Planned autologous or allogeneic stem cell transplantation *or CAR T–cell therapy* at time of recruitment
  - Patients with only one prior therapy who are appropriate for stem cell transplantation are excluded from this trial. Reasons for transplant-ineligibility may include age, performance status, comorbidities, transplant failure or failed procedure, insufficient response to salvage therapy, patient refusal, or logistical reasons.
- Primary or secondary CNS lymphoma at the time of recruitment
- Richter's transformation or prior CLL
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
  - Creatinine $>1.5\times$ upper limit of normal (ULN) or a measured creatinine clearance <30 mL/min
  - AST or ALT >2.5 x ULN
  - Total bilirubin $\geq 1.5\times$ ULN. Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq 3\times$ ULN
  - INR or PT $>1.5\times$ ULN in the absence of therapeutic anticoagulation

  - PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant
- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include:
  - Patients with a history of curatively-treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the study are eligible.
  - A patient with any other malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for ≥ 2 years prior to enrollment is eligible.
  - Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection (as evaluated by the investigator) within 4 weeks prior to Cycle 1 Day 1
- Patients with suspected or latent tuberculosis
  - Latent tuberculosis needs to be confirmed by positive interferon-gamma release assay
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)
  - Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment.
- Positive test results for hepatitis C virus (HCV) antibody
  - Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Known history of HIV seropositive status
  - For patients with unknown HIV status, HIV testing will be performed at Screening if required by local regulations.
- Vaccination with a live vaccine within 4 weeks prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 months after the last dose of study drug
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

End of Study and Length of Study

The end of this study is defined as the date when the last patient, last visit, occurs which will be the timepoint at which all patients enrolled in the study have either had at least 2 years of follow-up from the time of the treatment-completion visit or have discontinued the study. The end of the study is expected to occur approximately 2.5 years after the last patient is enrolled.

After an initial safety-run in, the randomized stage for recruitment is expected to occur over approximately 19 months.

This is an event-driven trial. The clinical cut-off date for the *primary* OS analysis will be confirmed when the targeted number of mortality events [redacted] deaths) have occurred, which is expected approximately [redacted] months after the first patient is randomized (first patient in) in the RCT stage of the study.

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

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is Pola-R-GemOx. The control therapy is R-GemOx.

Polatuzumab Vedotin

Polatuzumab vedotin 1.8 mg/kg will be administered intravenously on Day 1 of each 21-day cycle for up to 8 cycles. Polatuzumab vedotin should be administered after rituximab on the same day or, in the event of a dose delay for rituximab, the following day (see below).

Patient weight obtained during screening (Day -28 to Day -1) should be used for dose determination for all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle is greater or less than 10% from the weight obtained during screening, the new weight should be used to calculate the dose. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. All subsequent doses should be modified accordingly. Dose adjustments for body weight changes $<10\%$ are also acceptable should this be local standard of care. Due to limited clinical experience in patients treated with 1.8 mg/kg polatuzumab vedotin at a total dose >240 mg, it is recommended not to exceed a dose of 240 mg per cycle.

The initial dose will be administered to patients who are well hydrated (as per local guidelines) over 90 ± 10 minutes. Premedication (e.g., 500–1000 mg of oral acetaminophen or paracetamol and *approximately* 50–100 mg diphenhydramine as per institutional standard practice) may be administered to an individual patient ≥ 30 minutes before starting administration of polatuzumab vedotin. Administration of corticosteroids is permitted at the discretion of the treating physician. If infusion-related reactions (IRRs) are observed with the first infusion in the absence of premedication, premedication must be administered before subsequent doses.

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

During administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 30 ± 5 minutes during the infusion, at the end of the infusion and every 30 ± 10 minutes for 90 minutes following completion of dosing at Cycle 1 and 30 ± 10 minutes following completion of dosing in subsequent cycles.

Please refer to the Pharmacy Manual for detailed instructions on administration of polatuzumab vedotin.

Rituximab

Rituximab (Mabthera/Rituxan®) 375 mg/m^2 will be administered intravenously on Day 1 of each 21-day cycle for up to 8 cycles. Rituximab should be administered before polatuzumab vedotin on the same day; in the event of a dose delay for rituximab, polatuzumab vedotin may be administered on the following day.

No dose modifications of rituximab are allowed.

During the administration of rituximab in Cycle 1, vital signs are to be obtained before infusion, then after the start of the infusion, approximately every 30 ± 5 minutes for 90 minutes, then every 30 ± 10 minutes until 1 hour after the end of the infusion. During administration of rituximab in subsequent cycles, vital signs are to be recorded before infusion, then after the start of infusion, and approximately every 30 ± 10 minutes until 1 hour after the end of infusion.

The patient's body surface area (BSA) calculated at screening should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by

$>$10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients (obesity defined as body mass index $\geq$30, as measured in kilograms divided by meters squared) may be implemented per institutional guidelines.

The rituximab administration should be completed at least 30 minutes before administration of other study treatments. The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). Administration of rituximab may be continued on the following day, if needed, for patients who experience an adverse event during the rituximab infusion. If a dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication and at the first infusion rate (see Synopsis Table 6).

All rituximab infusions should be administered to patients after premedication with oral acetaminophen (e.g., 500–1000 mg) and an antihistamine such as diphenhydramine hydrochloride (*e.g.,* 50–100 mg) $\geq$30 minutes before starting each infusion (unless contraindicated). An additional glucocorticoid (e.g., 100 mg IV prednisone or prednisolone or equivalent) is allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Rituximab infusions will be administered according to the instructions in Synopsis Table 6. If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as rapid infusion in accordance with local institutional guidelines.

During the treatment period, rituximab must be administered to patients in a setting where full emergency resuscitation facilities are immediately available. Patients should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 5.1.2.

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (such as the Braun Infusomat Space) should be used to control the infusion rate of rituximab. Administration sets with polyvinyl chloride (PVC), polyurethane (PUR), or polyethylene (PE) as a product contact surface and IV bags with polyolefine, polypropylene (PP), PVC, or PE as a product contact surface are compatible and can be used. Additional in-line filters should not be used because of potential adsorption. The in-line filter used for the administration of polatuzumab vedotin should not be used for the administration of rituximab.

After the end of the first infusion, the IV line or central venous catheter should remain in place for $\geq$2 hours in order to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

Synopsis Table 6 Administration of First and Subsequent Infusions of Rituximab

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

Gemcitabine

Gemcitabine 1000 mg/m^2 will be administered intravenously on Day 2 of each 21-day cycle for up to 8 cycles. Gemcitabine should be administered before oxaliplatin on the same day. In the event that rituximab dosing is split across two days, gemcitabine may be administered on Day 2 (i.e., the same day rituximab dosing is completed) or on the following day (see Section 4.3.2.2.

Dose modifications for gemcitabine are described in Section 5.1.2.1.

The method of administering gemcitabine is described in the local prescribing information.

Oxaliplatin

Oxaliplatin 100 mg/m^2 will be administered intravenously on Day 2 of each 21-day cycle for up to 8 cycles. Oxaliplatin should be administered after gemcitabine on the same day. In the event that rituximab dosing is split across two days, oxaliplatin may be administered on Day 2 (i.e., the same day rituximab dosing is completed) or on the following day (see Section 4.3.2.2).

Dose modifications for oxaliplatin are described in Section 5.1.2.1.

The method for administering oxaliplatin is described in local prescribing information.

Statistical Methods

Primary Analysis

The primary efficacy objective for the randomized part of this study is to evaluate the efficacy of Pola-R-GemOx compared with R-GemOx in patients with relapsed or refractory DLBCL on the basis of the following endpoint:

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

The primary efficacy analysis will be completed on the ITT population, with patients grouped according to their treatment assigned at randomization.

Data for patients without death will be censored at the date at which the patient was last known to be alive. Otherwise, data will be censored at the date of randomization.

Kaplan-Meier methodology will be used to estimate the OS for each treatment arm, and Kaplan-Meier curves will be produced. Overall survival will be compared between treatment arms by stratified logrank test. The hazard ratio (HR) for death will be estimated using a stratified Cox

proportional hazards model; the stratification factors will be the same as the randomization stratification factors by IxRS. The 95% confidence interval (CI) for the HR will be provided. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

The type I error (α) for this study is 0.05 (two-sided). Further details will be included in the SAP.

In case patients become eligible for HSCT and undergo a transplant (in their best interest), sensitivity analyses will be performed for OS and PFS to assess the impact this may have. For this, patient data will be censored at the time of transplant.

Determination of Sample Size

The primary objective of the randomized part of this study is to evaluate the efficacy of Pola-R-GemOx versus R-GemOx in patients with relapsed or refractory DLBCL as measured by OS. Assuming a median OS of [redacted] months in the R-GemOx arm and a randomization ratio of 1:1, [redacted] events are required to detect a between-group difference of [redacted] months in the median OS (HR = [redacted]) with [redacted] power and a 2-sided α of [redacted]. Based on the above statistical assumptions, and anticipating a recruitment period of approximately 19 months and a follow-up of 12 months after the last patient was randomized, a total of approximately 250 patients will be randomized, taking into account an estimated drop-out rate of [redacted].

In addition, approximately 10 patients will be enrolled in the safety run-in stage.

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
aa-IPI	age-adjusted International Prognostic Index
ABC	activated B–cell-like
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ASR	age-standardized risk
BCR	B-cell receptor
BEAM	carmustine, etoposide, cytarabine, and melphalan
BP	blood pressure
BR	bendamustine plus rituximab
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
COO	cell of origin
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CT	computed tomography
ctDNA	circulating tumor DNA
DAR	drug-to-antibody ratio
DLBCL	diffuse large B-cell lymphoma
DOR	duration of objective response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS_{eff}	event-free survival
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-Level Version
EWB	emotional well-being
FACT-G	Functional Assessment of Cancer Therapy–General Questionnaire
FACT/GOG-NTX-12	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale

Abbreviation	Definition
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
FDA	Food and Drug Administration
FPI	first patient in
FWB	functional well-being
GCB	germinal center B-cell–like
G-CSF	granulocyte colony-stimulating factor
GemOx	gemcitabine plus oxaliplatin
GVHD	graft versus host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBC	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
HSCT	*hematopoietic stem cell transplantation*
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IxRS	interactive voice or Web-based response system
LDH	lactate dehydrogenase
MAb	monoclonal antibody
MMAE	mono-methyl auristatin E
MRI	magnetic resonance imaging
NALT	non-protocol–specified anti-lymphoma treatment
NCCN	National Comprehensive Cancer Network
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
NHL	Non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PE	Polyethylene
PEF	peak expiratory flow

Abbreviation	Definition
PET	positron emission tomography
PFS	progression-free survival
P-gp	*P-glycoprotein*
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PN	*peripheral neuropathy*
Pola-R-GemOx	*polatuzumab vedontin plus rituximab, gemcitabine, and oxaliplatin*
PP	polypropylene
PRO	patient-reported outcome
PUR	polyurethane
PVC	polyvinyl chloride
PWB	physical well-being
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCT	randomized controlled trial
R-DHAP	rituximab, dexamethasone, cytarabine, and cisplatin
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide phosphate
R-GemOx	rituximab plus gemcitabine plus oxaliplatin
R/R	*relapsed or refractory*
SC	Steering Committee
SmPC	Summary of Product Characteristics from the European Medicines Agency
SoC	standard of care
SWB	social/family well-being
TOI	trial outcome index
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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

NHL comprises a heterogeneous group of lymphoproliferative disorders but most commonly presents as a defect in B-lymphocytes. Thus, the most common subtypes of NHL, all of B-cell origin, include diffuse large B-cell lymphoma (DLBCL; 32.5% of total NHL cases), chronic lymphocytic leukemia (CLL; 18.6%), follicular lymphoma (17.1%), marginal zone lymphoma (8.3%), and mantle cell lymphoma (4.1%) (Al-Hamadani et al. 2015). NHL can be divided into indolent and aggressive forms based on subtype.

Originating from mature B-cells, DLBCL is an aggressive NHL with a median survival of <1 year in untreated patients (Rovira et al. 2015). A majority of DLBCL cells express CD20, a membrane antigen that is important in cell cycle initiation and differentiation (Anderson et al. 1984). Several genetic abnormalities have been identified in patients with DLBCL, including defects in BCL6 (35%–40%), BCL2 (translocation 15%, amplification 24%), and cMYC (15%).

1.1.1 First-Line Treatment of Diffuse Large B-Cell Lymphoma

According to guidelines from the National Comprehensive Cancer Network (NCCN) (National Comprehensive Cancer Network 2018), first-line treatment of DLBCL in non-frail patients with adequate cardiovascular capacity should consist of the anti-CD20 monoclonal antibody rituximab in combination with a multi-agent chemotherapy. Typically, the multi-agent chemotherapy is comprised of individual agents with non-cross-resistant mechanisms of action, e.g., cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), or etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH). Efficacy outcomes for rituximab+CHOP (R-CHOP) or EPOCH+rituximab in this setting are summarized in Table 1.

Table 1 Efficacy of R-CHOP and EPOCH + Rituximab for First-Line Treatment of Diffuse Large B-Cell Lymphoma

	R-CHOP % (95% CI)	CHOP % (95% CI)	P-value
LNH-98.5 Study [a]			
CR/CRu	76	63	0.005
2-year EFS [b]	57 (50, 64)	38 (32, 45)	< 0.001
10-year PFS	36.5 (29.7, 43.3)	20.1 (14.6, 26.2)	< 0.0001
2-year OS	70 (63, 77)	57 (50, 64)	0.007
10-year OS	43.5 (36.4, 50.4)	27.6 (21.4, 34.3)	< 0.0001
	EPOCH + Rituximab % (95% CI)		
MabThera International Trial [c]			
CR/CRu	94	–	–
5-year PFS	79 (68, 87)	–	–
10-year EFS	47.8 (34.2, 61.4)	–	–
5-year OS	80 (69, 88)	–	–
10-year OS	63.6 (52.8, 74.4)	–	–

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CR = complete response; CRu = unconfirmed complete response; EFS = event-free survival; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; IPI = International Prognostic Index; PFS = progression-free survival; OS = overall survival; R-CHOP = rituximab, doxorubicin, vincristine, and prednisone.

[a] (Coiffier et al. 2002; Coiffier et al. 2010).

[b] An event was defined as disease progression or relapse, initiation of a new (unplanned) anticancer treatment (e.g., radiation therapy), or death from any cause without progression.

[c] (Wilson et al. 2008; Purroy et al. 2015). NB: Subjects treated median age 50 with majority low IPI).

1.1.2 Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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

Approximately half of patients with relapsed DLBCL fail to respond to second-line therapy because of refractory disease (Gisselbrecht et al. 2010), and a significant number are ineligible for aggressive therapy because of age or comorbidities. Furthermore, patients who either relapse after or are ineligible for stem cell transplantation because of refractory disease or frailty have poor outcomes. Thus, a significant clinical need exists for new therapeutic approaches in patients with R/R DLBCL.

1.1.3 Prognostic Risk Groups

Although there is currently no way to prospectively identify individual patients with NHL who will be cured, clinical factors are used to define prognostic risk groups associated with different outcomes. The International Prognostic Index (IPI) is a prognostic tool that identifies five significant clinical factors that are predictive of overall survival (OS) (International Non-Hodgkin's Lymphoma Prognostic Factors 1993) (Appendix 9):

- Age ($\leq$60 vs. $>$60 years)
- Serum lactate dehydrogenase (LDH, normal vs. elevated) level
- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2–4)
- Stage (I or II vs. III or IV)
- Extranodal-site involvement (0 or 1 vs. 2–4)

The IPI defines four distinct prognostic subgroups depending on the number of negative prognostic factors at diagnosis. Patients with DLBCL and low IPI (i.e., with no or only one negative prognostic finding) have overall excellent outcomes, with 3-year progression-free survival (PFS) of 80%–90% (Sehn et al. 2007; Advani et al. 2010); patients with higher risk have poorer outcomes, with a 3-year PFS range of 33%–70%.

Because age is an important consideration when determining the choice of treatment for DLBCL, the age-adjusted IPI (aa-IPI) was also developed and validated (International Non-Hodgkin's Lymphoma Prognostic Factors 1993). The aa-IPI is based on stage, serum LDH, and ECOG performance status and was prognostic of response to therapy and OS. Patients with a higher number of risk factors have lower rates of complete response (CR) to therapy, as well as lower rates of 5-year survival (Ziepert et al. 2010).

1.2 BACKGROUND ON POLATUZUMAB VEDOTIN

1.2.1 Polatuzumab Vedotin Mechanism of Action

CD79b is a cell surface antigen that is expressed solely on mature B cells, except for plasma cells. It is also expressed in a majority of B–cell-derived malignancies, including nearly all NHL and CLL samples tested (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, which makes CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007; Polson et al. 2009).

Polatuzumab vedotin (DCDS4501A [liquid formulation] and DCDS4501S [lyophilized formulation]) is an antibody-drug conjugate (ADC) that contains a humanized immunoglobulin G1 anti-human CD79b monoclonal antibody (MAb; MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl.

Mono-methyl auristatin E has a mechanism of action similar to that of vincristine, which is a component of standard chemotherapy (e.g., R-CHOP used for treatment of lymphoma). Following binding of polatuzumab vedotin at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released after cleavage of the linker by lysosomal enzymes. Mono-methyl auristatin E then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth (Doronina et al. 2003).

Thus, therapy with polatuzumab vedotin takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE, which has increased potency compared to vincristine. It is hypothesized that the addition of polatuzumab vedotin to a standard anti-CD20 antibody plus chemotherapy regimen will provide enhanced efficacy and safety to patients with NHL.

Refer to the Polatuzumab Vedotin Investigator's Brochure for further details on polatuzumab vedotin nonclinical studies.

1.2.2 Polatuzumab Vedotin Clinical Studies

Polatuzumab vedotin is currently being investigated in patients with B-cell hematological malignancies in nine clinical trials, including one completed study (DCS4968g) and eight ongoing studies (GO27834, GO29044, GO29365, JO29138, GO29833, GO29834, BO29561, and GO39942). These trials have evaluated or are evaluating polatuzumab vedotin as a single agent or in combination with rituximab and other anti-cancer agents.

Key objectives of the current study are to compare the safety and efficacy of polatuzumab vedotin in combination with R-GemOx versus R-GemOx alone in patients with relapsed or resistant DLBCL (see Section 1.3). Data from earlier polatuzumab vedotin studies most relevant to the current study are summarized below.

1.2.2.1 Efficacy

Data from Phase I Study DCS4968g, Phase II Study GO27834, and Phase Ib/II Study GO29044 showed that therapy with polatuzumab vedotin—alone or in combination with either rituximab or rituximab plus cyclophosphamide, doxorubicin, and prednisone—resulted in significant anticancer responses in patients with relapsed or refractory B-cell lymphomas (Table 2; Polatuzumab Vedotin Investigator's Brochure). This conclusion was confirmed and extended by recently published data from another Phase Ib/II study (GO29365), which directly assessed whether polatuzumab vedotin

could enhance the efficacy of a standard rituximab-containing regimen (Table 3). Notably, the latter study found that the addition of polatuzumab vedotin to bendamustine plus rituximab (BR) significantly extended survival time relative to BR alone (median overall survival [95% CI]: 12.4 [9.0–NE] months vs. 4.7 [3.7–8.3] months) in patients with relapsed or refractory DLBCL, consistent with expectation and, thus, validation of the clinical rationale for polatuzumab vedotin.

Table 2 Efficacy of Polatuzumab Vedotin (Alone or in Combination) in Patients with DLBCL in Studies DCS4968g, GO27834, and GO29044

	DCS4968g				GO27834	GO29044 [a]
Pola dose, mg/kg	< 1.8	1.8	2.4	2.4	2.4	1.0–1.8
Backbone	–	–	–	R	R	R-CHP
BOR, n (%)						
n	8	4	27	1	39	50
CR	0	0	4 (14.8)	0	8 (20.5)	38 (76.0)
PR	1 (12.5)	2 (50.0)	10 (37.0)	1 (100)	13 (33.3)	7 (14.0)
SD	0	1 (25.0)	4 (14.8)	0	5 (12.8)	0 (0.0)
PD	7 (87.5)	1 (25.0)	8 (29.6)	0	11 (28.2)	3 (6.0)
Missing	0	0	1 (3.7)	0	2 (5.1)	2 (4.0)
PFS						
n	–	4	27	–	39	–
Median (months)	–	4.6	5.0	–	5.6	–
95% CI	–	(1.4–13.9)	(2.3–6.8)	–	(4.3–12.8)	–

BOR = best overall response; BR = bendamustine, rituximab; CR = complete response; DLBCL = diffuse large B-cell lymphoma; PFS = progression-free survival; PD = progressive disease; pola = polatuzumab vedotin; PR = partial response; R = rituximab; R-CHP = rituximab, cyclophosphamide, doxorubicin, prednisone/prednisolone; SD = stable disease.

[a] Patients had newly diagnosed or relapsed/resistant disease.

Table 3 Overview of Efficacy of Polatuzumab Vedotin in Combination with Bendamustine/Rituximab in Patients with DLBCL (Study GO29365)

Study Phase	Randomized Phase	
Treatment	**BR Phase II**	**Pola + BR Phase II**
Sample Size	**n = 40**	**n = 40**
Primary Efficacy Endpoint		
CR at PRA by PET (IRC assessed)		
n (%)	7 (17.5%) [b]	16 (40.0%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(24.9, 56.7)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	22.5 (2.6, 40.2); p = 0.0261	
Secondary Efficacy Endpoints		
Response rates with PET		
OR (CR/PR) at PRA by PET (IRC assessed)		
n (%)	7 (17.5%) [b]	18 (45.0%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(29.3, 61.5)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	27.5 (7.2, 45.0); p = 0.0069	
CR at PRA by PET (INV assessed)		
n (%)	6 (15.0%) [b]	17 (42.5%)
95% CI for response rate (Clopper-Pearson)	(5.7, 29.8)	(27.0, 59.1)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	27.5 (7.7, 44.7); p = 0.0061	
OR (CR/PR) at PRA by PET (INV assessed)		
n (%)	7 (17.5%) [b]	19 (47.5%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(31.5, 63.9)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	30.0 (9.5, 47.4); p = 0.0036	
Response rates without PET (CT alone)		
CR at PRA by CT (IRC assessed)		
n (%)	1 (2.5%)	9 (22.5%)
95% CI for response rate (Clopper-Pearson)	(0.1, 13.2)	(10.8, 38.5)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	20.0 (5.5, 35.1); p = 0.0078	
OR (CR/PR) at PRA by CT (IRC assessed)		
n (%)	6 (15.0%) [b]	17 (42.5%)
95% CI for response rate (Clopper-Pearson)	(5.7, 29.8)	(27.0, 59.1)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	27.5 (7.7, 44.7); p = 0.0051	
CR at PRA by CT (INV assessed)		
n (%)	2 (5.0%)	8 (20.0%)
95% CI for response rate (Clopper-Pearson)	(0.6, 16.9)	(9.1, 35.7)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	15.0 (0.1, 30.2); p = 0.0454	
OR (CR/PR) at PRA by CT (INV assessed)		
n (%)	6 (15.0%) [b]	18 (45.0%)
95% CI for response rate (Clopper-Pearson)	(5.7, 29.8)	(29.3, 61.5)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	30.0 (9.9, 47.1); p = 0.0032	
BOR by PET-CT or CT (CR/PR) (INV assessed)		
n (%)	13 (32.5%)	28 (70.0%)
95% CI for response rate (Clopper-Pearson)	(18.6, 49.1)	(53.5, 83.4)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	37.5 (15.6, 54.7); p = 0.0006	

Table 3 Overview of Efficacy of Polatuzumab Vedotin in Combination with Bendamustine/Rituximab in Patients with DLBCL (Study GO29365), contd.

Study Phase	Randomized Phase	
Treatment	**BR**	**Pola + BR Phase II** **Phase II**
Sample Size	**n = 40**	**n = 40**
BOR (IRC assessed)		
n (%)	10 (25.0%)	25 (62.5%)
95% CI for response rate (Clopper-Pearson)	(12.69, 41.20)	(45.80, 77.27)
Δ (95% CI) (Wilson); p-value (CMH chi-square [a])	37.5 (15.82, 54.62); p = 0.0006	
DOR (IRC assessed)		
Patients with event, n (%)	8/10 (80.0%)	13/25 (52.0%)
median DOR (95% CI)	7.7 (4.0, 18.9)	12.6 (7.2, NE)
HR (95% CI); stratified p-value (log-rank)	0.47 (0.19, 1.14); p = 0.0889	
PFS (IRC assessed)		
Patients with event, n (%)	32 (80.0%)	25 (62.5%)
median PFS (95% CI)	3.7 (2.1, 4.5)	9.5 (6.2, 13.9)
HR (95% CI); stratified p-value (log-rank)	0.36 (0.21, 0.63); p = 0.0002	
Exploratory Efficacy Endpoints		
DOR (INV assessed)		
Patients with event, n (%)	11/13 (84.6%)	17/28 (60.7%)
median DOR (95% CI)	4.1 (2.6, 12.7)	10.3 (5.6, NE)
HR (95% CI); stratified p-value (log-rank)	0.44 (0.20, 0.95); p = 0.0321	
PFS (INV assessed)		
Patients with event, n (%)	35 (87.5%)	27 (67.5%)
median PFS (95% CI)	2.0 (1.5, 3.7)	7.6 (6.0, 17.0)
HR (95% CI); stratified p-value (log-rank)	0.34 (0.20, 0.57); p = 0.0001	
EFS (INV assessed)		
Patients with event, n (%)	38 (95.0%)	29 (72.5%)
median EFS (95% CI)	2.0 (1.5, 3.1)	6.4 (4.0, 11.1)
HR (95% CI); stratified p-value (log-rank)	0.30 (0.18, 0.50); p < 0.0001	
OS		
Patients with event, n (%)	28 (70.0%)	23 (57.5%)
median OS (95% CI)	4.7 (3.7, 8.3)	12.4 (9.0, NE)
HR (95% CI); stratified p-value (log-rank)	0.42 (0.24, 0.75); p = 0.0023	

BOR = best objective response; BR = bendamustine and rituximab; CMH = Cochran-Mantel-Haenszel; CR = complete response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS = event-free survival; INV = investigator; IRC = Independent Review Committee; NE = not estimable; OR = objective response; OS = overall survival; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; pola = polatuzumab vedontin; PR = partial response; PRA = primary response assessment (6−8 weeks after Cycle 6 Day 1 or last dose of study medication).

[a] Cochran-Mantel-Haenszel chi-square test adjusted for randomization stratification factors: DOR to prior therapy (≤ 12 months vs. > 12 months).

[b] Includes patients who achieved objective response (CR/PR) during the study.

1.2.2.2 Safety

Adverse events (AEs) associated with polatuzumab vedotin as a single agent and in combination with rituximab are summarized in Table 4 and Table 5, respectively.

Table 4 Adverse Events Occurring in ≥20% of Patients Treated with Single-Agent Polatuzumab Vedotin, by Pooled Dose Cohorts and Histology, in Study DCS4968g

Histology	B-cell lymphoma [a]			CLL	ALL
Dose cohort (mg/kg)	<1.8 n=17 [b]	1.8 n=6	2.4 n=45	≤1.8 n=18 [b]	n=86
Adverse event					
Neutropenia	5 (29%)	4 (67%)	20 (44%)	4 (22%)	33 (38%) [c]
Diarrhea	4 (24%))	3 (50%)	20 (44%)	5 (28%)	32 (37%)
Pyrexia	5 (29%)	2 (33%)	13 (29%)	7 (39%)	27 (31%)
Nausea	5 (29%)	3 (50%)	16 (36%)	2 (11%)	26 (30%)
Peripheral sensory neuropathy	5 (29%)	4 (67%)	17 (38%)	0	26 (30%) [d]
Fatigue	7 (41%)	3 (50%)	5 (11%)	5 (28%)	20 (23%)
Anemia	2 (12%)	1 (17%)	9 (20%)	5 (28%)	17 (20%)
Decreased appetite	5 (29%)	2 (33%)	4 (9%)	5 (28%)	16 (19%)
Headache	1 (6%)	1 (17%)	3 (7%)	5 (28%)	10 (12%)
Rash	0	1 (17%)	6 (13%)	4 (22%)	11 (13%)
Constipation	5 (29%)	2 (33%)	7 (16%)	2 (11%)	16 (19%)
Cough	6 (35%)	3 (50%)	5 (11%)	2 (11%)	16 (19%)

ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma.

Clinical cutoff: 25 February 2015.

[a] Aggregated histology of diffuse large B-cell lymphoma, indolent B-cell lymphoma and Mantle cell lymphoma.

[b] Aggregate of 0.1, 0.5 and 1.0 mg/kg dose cohorts for indolent B-cell lymphoma patients and 0.1, 0.25, 0.5 and 1.0 mg/kg dose cohorts for DLBCL patients, 0.25, 0.5, 1.0, and 1.8 mg/kg for CLL patients.

[c] Preferred terms: neutropenia (n = 33 [38%]) and febrile neutropenia (n = 2 [2%]).

[d] Preferred terms: peripheral sensory neuropathy (n = 26 [30%]), peripheral motor neuropathy (n = 5 [6%]), and neuropathy peripheral (n = 1 [1%]). Overall resolved, including all Peripheral Neuropathy Preferred terms = 35.8%.

Table 5 Adverse Events Occurring in ≥20% of B-Cell Lymphoma Patients Treated with Polatuzumab Vedotin Plus Rituximab in Study GO27834

Histology	FL		DLBCL	Combined
Treatment	Pola-R	Pola-R	Pola-R	Pola-R
Pola dose (mg/kg)	1.8 n=20	2.4 n=20	2.4 n=39	All n=79
Adverse Event				
Fatigue	13 (65%)	12 (60%)	23 (59%)	48 (61%)
Nausea	11 (55%)	11 (55%)	14 (36%)	36 (46%)
Peripheral neuropathy	6 (30%)	13 (65%)	14 (36%)	33 (42%) [a]
Diarrhea	6 (30%)	11 (55%)	15 (39%)	32 (41%)
Peripheral sensory neuropathy	11 (55%)	8 (40%)	9 (23%)	28 (35%) [b]
Neutropenia	8 (40%)	5 (25%)	10 (26%)	23 (29%)
Decreased appetite	4 (20%)	5 (25%)	12 (31%)	21 (27%)
Constipation	5 (25%)	5 (25%)	9 (23%)	19 (24%)
Cough	3 (15%)	3 (15%)	12 (31%)	18 (23%)
Arthralgia	5 (25%)	5 (25%)	6 (15%)	16 (20%)
Asthenia	0	7 (35%)	9 (23%)	16 (20%)
Pain in extremity	4 (20%)	5 (25%)	7 (18%)	16 (20%)
Pyrexia	6 (30%)	3 (15%)	7 (18%)	16 (20%)
Vomiting	3 (15%)	5 (25%)	8 (21%)	16 (20%)

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; Pola-R = polatuzumab vedotin combined with rituximab (375 mg/m^2 q3w).

Note: Patients were treated for 17 cycles, until PD or unacceptable toxicity.

Clinical cutoff: 21 April 2016.

[a] Overall 18 patients (55%) reported at least one event resolved.

[b] Overall 22 patients (79%) reported at least one event resolved.

Peripheral neuropathy (PN) was assessed in Study GO29365 in patients with R/R DLBCL who received polatuzumab vedotin in combination with bendamustine and rituximab. The overall incidence of PN in patients treated with pola-BR in Phase Ib/II combined was 40.0% (18/45 patients with 29 PN events) (see Table 6). The most frequently reported PN event by preferred term in patients treated with pola-BR was neuropathy peripheral (9 patients) followed by peripheral sensory neuropathy (6 patients). Six of the 18 patients with PN events had Grade 2 events (preferred terms: neuropathy peripheral (5 patients), peripheral sensory neuropathy, and muscular weakness (1 patient each). No Grade ≥3 or serious events of PN were reported in patients with R/R DLBCL treated with pola-BR. Ten of the 18 patients with R/R DLBCL

who had a PN event during treatment with pola-BR had a history of prior PN, and of these, 8 patients had ongoing Grade 1 PN at baseline.

One patient discontinued all study treatments due to loss of muscle mass, reported as the preferred term muscle atrophy (Grade 1), which was included under the conservative analysis of PN using the wide SMQ for PN. Polatuzumab vedotin dose was reduced in 2 patients, in both cases due to Grade 2 PN. In both cases, the event had resolved by the time of the clinical cutoff. Overall, the PN events had resolved in 10/18 patients without the need, in most cases, for delays or any change in dose of study treatment.

The median time to onset of PN in patients with R/R DLBCL treated with pola-BR was 1.8 months (0.0–4.9 months), and the median time to resolution was 1.2 months (0.0–22.4 months).

In the randomized Phase II, the incidence of all grade PN events was higher in the pola-BR arm compared to the BR arm (43.6% [17/39 patients with 26 events] vs. 7.7% [3/39 patients with 4 events]). The PN events reported in the BR arm were Grade 2 neuralgia, PN, muscular weakness, and decreased vibratory sense.

Based on these and other safety data, PN (both serious and non-serious) and neutropenia (both serious and non-serious) have been identified as potential risks of polatuzumab vedotin treatment.

Table 6 Summary of Peripheral Neuropathy in Patients with R/R DLBCL in the Safety Population of Study GO29365

Study Phase	Phase Ib	Phase II (randomized)		Phase Ib/II
Treatment	Pola + BR	BR	Pola + BR	Pola + BR (total)
Sample size	N = 6	N = 39	N = 39	N = 45
Total no. of PN events	3	4	26	29
Patients with at least one:				
any grade PN event	1 (16.7%)	3 (7.7%)	**17 (43.6%)**	18 (40.0%)
Grade ≥2 PN event	0	2 (5.1%)	**6 (15.4%)**	6 (15.4%)
Serious PN event	0	0	0	0
PN event leading to any study drug discontinuation	0	0	1 (2.6%)	1 (2.2%)
PN event leading to any study drug reduction	0	0	2 (5.1%) [a]	2 (4.4%) [a]
PN event leading to any study drug interruption	0	0	2 (5.1%) [a]	2 (4.4%) [a]

BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; PN = peripheral neuropathy; pola = polatuzumab; R/R = relapsed/refractory.

Note: Analyses of PN events were based on all preferred terms captured under the standardized MedDRA query "Peripheral Neuropathy [wide]" (20000034w).

Notes: PN event categories with ≥ 10% difference between pola + BR and BR arms in the randomized Phase II are shown in **bold** and underlined.

[a] Polatuzumab vedotin dose was reduced and bendamustine and rituximab dose was delayed in 2 patients.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The clinical development program for polatuzumab vedotin is based on the hypothesis that adding an anti-CD79b antibody to a standard regimen of anti-CD20 antibody (rituximab) plus chemotherapy will provide enhanced efficacy in patients with B-cell lymphomas. Prior clinical studies have supported this hypothesis (see Section 1.2.2 and the Polatuzumab Vedotin Investigator's Brochure). For instance, Study GO29365 directly compared polatuzumab vedotin plus BR to BR alone in patients with R/R DLBCL. Results showed that the addition of polatuzumab vedotin significantly improved objective response, PFS and, most notably, survival. Thus, early studies have validated the overall rationale for polatuzumab vedotin in the treatment of B-cell malignancies and encourage further studies on this potentially important therapeutic antibody.

Central to the development of polatuzumab vedotin as a clinical agent is assessment of its efficacy and safety profiles when used in combination with other rituximab-chemotherapy regimens. Consistent with its favorable NCCN recommendation (National Comprehensive Cancer Network 2018), gemcitabine plus oxaliplatin (GemOx) ± rituximab is one such second-line treatment for DLBCL and

one that is commonly used in the clinic. Efficacy outcomes for GemOx + rituximab (R-GemOx) in relapsed or refractory DLBCL are summarized in Table 7.

Table 7 Efficacy of GemOx ± Rituximab for Second-Line Treatment of B-Cell Lymphoma

	R-GemOx % (95% CI)	GemOx % (95% CI)
El Gnaoui et al. [a]		
2-year PFS	62 (44, 81)	
2-year EFS	43 (27, 60)	
2-year OS	66 (50, 82)	
Lopez et al. [b]		
ORR	43	
CR	34	
PR	9	
1-year PFS	29 (12, 46)	
1-year OS	41 (22, 60)	
Mounier et al. [c]		
5-year PFS	13 (5, 24)	
5-year OS	14 (6, 26)	
Corazzelli et al. [d]		
3.5-year FFS	28 (9, 47)	7 (0, 16)
3.5-year OS	37 (20, 55)	7 (0, 16)

aa-IPI = age-adjusted International Prognostic Index; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EFS = event-free survival; FFS = failure-free survival; GemOx = gemcitabine plus oxaliplatin; IPI = International Prognostic Index; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response. R-GemOx = rituximab, gemcitabine, and oxaliplatin.

[a] Includes patients with DLBCL, follicular cell lymphoma, and mantle cell lymphoma (El Gnaoui et al. 2007).

[b] Only includes patients with DLBCL; 69% of patients had an a*a*-IPI of 2 or 3; median follow-up = 13 (95% CI: 5 to 25) months (Lopez et al. 2008).

[c] Only includes patients with DLBCL; 71% of patients had IPI > 2 at baseline (Mounier et al. 2013).

[d] Includes patients with DLBCL, follicular cell lymphoma, and mantle cell lymphoma (Corazzelli et al. 2009).

As with other treatments in this setting, data from Table 7 demonstrates that R-GemOx provides encouraging efficacy in patients with relapsed or refractory DLBCL. Nonetheless, a high percentage of patients still fails to respond to the combination. It therefore becomes of significant interest to assess whether the addition of

polatuzumab vedotin to R-GemOx can provide additional efficacy in a safe and tolerable fashion in patients with relapsed or refractory DLBCL.

To address this issue, Study MO40598 will be a phase III, multicenter, open-label, randomized controlled trial comparing experimental therapy, polatuzumab vedontin plus R-GemOx (Pola-R-GemOx), versus control therapy, R-GemOx, in patients with relapsed or refractory DLBCL. A total of approximately 250 patients will be enrolled, allowing for the detection of a between-group difference of [redacted] months in the median OS (hazard ratio [HR] [redacted]), with [redacted] power and a two-sided α of [redacted] (see Section 6.1 for assumptions underlying sample size estimations). R-GemOx will be administered under standard clinical conditions as described in local prescribing information so that potentially positive results from this trial can be applied in the future to standard clinical practice.

Because this is the first study to assess the Pola-R-GemOx combination, particular attention will be paid to addressing potential safety concerns for enrolled patients. As described in Section 1.2.2, PN (both serious and non-serious) has been identified as a risk of polatuzumab vedotin treatment. This risk could be especially relevant in the current trial, as 30% to 40% of patients treated with oxaliplatin, one of the agents in the GemOx backbone, may also experience PN during and following treatment (Johnson et al. 2015). In addition to chronic neurotoxicities (Shahriari-Ahmadi et al. 2015), oxaliplatin may cause transient acute neuropathic pain, manifesting as cold-induced dysesthesia in the hands, face, and oral cavity (Staff et al. 2017). See Section 5.1.1.3 (Risks Associated with Gemcitabine and Oxaliplatin) for further information regarding oxaliplatin-associated PN.

Study MO40598 has a number of design features that address this potential PN risk. These include:

- Patients with baseline PN greater than Grade 1, as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0), will be excluded from enrollment.
- The study will have a safety run-in stage with a particular focus on PN as described in Section 3.1.
- Per current guidance (Polatuzumab Vedotin Investigator's Brochure), treatment with polatuzumab vedotin will be limited to 8 cycles of therapy to minimize risk for the potential development of PN.
- Polatuzumab vedotin will be administered at 1.8 mg/kg, which is the recommended dose (Polatuzumab Vedotin Investigator's Brochure).
- Appropriate guidance for managing Grade $>$ 2 PN events, which includes an initial dose delay and subsequent mandatory reduction, is provided in the protocol.

To further confirm the safety profile of Pola-R-GemOx, Study MO40598 has specific objectives to assess PN among the participants, based on the Functional Assessment of

Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity Subscale (FACT/GOG-NTX-12; see Section 3.3.6) (Calhoun et al. 2003; Huang et al. 2007).

Clinical studies on polatuzumab vedotin have also identified neutropenia (both serious and non-serious) as another potential risk of polatuzumab vedotin therapy. In an effort to manage this risk in Study MO40598, investigators will monitor absolute neutrophil counts throughout the Treatment Period (see Appendix 1 and Appendix 2). Any patient who develops new or worsening neutropenia will be managed as described in Section 4.4.1.5 and Section 5.1, which may include dose modification or discontinuation. Treatment for emergent neutropenia will be in accordance with local guidelines and protocol; prophylactic and therapeutic administration of granulocyte colony-stimulating factors will be required as per protocol and standard of care. Any signs of infection will be managed immediately, as appropriate.

Beyond the prior strategies for monitoring and managing adverse events of special interest (PN and neutropenia), several additional steps will be taken to ensure the safety of participants in Study MO40598. First, eligibility criteria have been chosen judiciously to select for an appropriate study population that is most likely able to tolerate study treatment. Second, administration of all study treatments will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. (Section 4.3). Third, adverse events will be closely monitored throughout the study (Section 5.1.1 and Section 5.1.2). Finally, the study will have an Internal Monitoring Committee (IMC) during the safety run-in stage and an independent Data Monitoring Committee (iDMC) during the randomized controlled trial (RCT) stage to assess safety signals on an ongoing basis.

With the above safety precautions in place, risks potentially associated with study treatment will be managed carefully in Study MO40598. Thus, given the strong clinical need for better therapies in the setting of relapsed or refractory DLBCL (see Section 1.1.2), it is deemed that comparing the benefits of Pola-R-GemOx combination therapy to current standard of care (R-GemOx) outweigh the risks in this study.

2. OBJECTIVES AND ENDPOINTS

Study MO40598 will evaluate the safety and efficacy of polatuzumab vedotin in combination with rituximab, gemcitabine, and oxaliplatin (Pola-R-GemOx) compared to rituximab, gemcitabine, and oxaliplatin alone (R-GemOx) in patients with relapsed or refractory DLBCL. Treatment will occur in two stages: 1) an initial safety run-in stage assessing Pola-R-GemOx; and 2) an RCT stage comparing Pola-R-GemOx versus R-GemOx.

Specific objectives and corresponding endpoints for each stage of the study are outlined in Table 8 and Table 9.

Table 8 Objectives and Corresponding Endpoints: Safety Run-In (Stage 1)

Primary Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of Pola-R-GemOx as a combination therapy	• Incidence, nature and severity of physical findings and AEs, with a specific focus on PN, according to the NCI CTCAE v5.0
Secondary Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of Pola-R-GemOx as a combination therapy and to assess the immunogenicity of polatuzumab vedotin	• Incidence and assessment of PN, as measured by FACT/GOG-NTX-12 • Tolerability, as measured by dose interruptions, dose reductions and dose intensity • Prevalence of ADAs at baseline and incidence of ADAs during the study
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Pola-R-GemOx	• CR, defined as the proportion of patients who achieve complete metabolic response based on PET-CT, according to Lugano 2014 response criteria (Appendix 5), at the end of treatment as determined by the investigator • ORR, defined as the proportion of patients who achieve complete or partial metabolic responses, according to Lugano 2014 response criteria (Appendix 5), at end of treatment as determined by the investigator • BOR, defined as the best response while on study, according to Lugano 2014 response criteria (Appendix 5), as determined by the investigator • PFS, defined as the time from enrollment to the first occurrence of disease progression as determined by the investigator according to Lugano 2014 response criteria (Appendix 5) or death from any cause • OS, defined as time from *enrollment* to death from any cause • EFS_{eff}, defined as time from enrollment to the earliest occurrence of the below cases: - Disease progression or relapse - Death due to any cause • Initiation of any NALT

Table 8 Objectives and Corresponding Endpoints: Safety Run-In (Stage 1), contd.

Exploratory Pharmacokinetic Objective	Corresponding Endpoints
• To further evaluate the PK of polatuzumab vedotin	• PK of polatuzumab vedotin in combination with R-GemOx in patients with relapsed or refractory DLBCL

AE = adverse event; ADA = anti-drug antibody; BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EFS_{eff} = event-free survival; FACT/GOG-NTX-12 = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale; NALT = non-protocol–specified anti-lymphoma treatment; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; PK = pharmacokinetics; PN = peripheral neuropathy; Pola-R-GemOx = polatuzumab vedotin, rituximab, gemcitabine, and oxaliplatin; R-GemOx = rituximab plus gemcitabine plus oxaliplatin.

Table 9 Objectives and Corresponding Endpoints: Randomized Controlled Trial (Stage 2)

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of Pola-R-GemOx compared with R-GemOx alone	• OS, defined as time from randomization to death from any cause
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Pola-R-GemOx compared with R-GemOx alone	Key secondary endpoints included in the hierarchical testing procedure: • PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to Lugano 2014 response criteria (Appendix 5), or death from any cause • CR, defined as the proportion of patients who achieve complete metabolic response based on PET-CT, according to Lugano 2014 response criteria (Appendix 5), at the end of treatment as determined by an IRC • ORR, defined as the proportion of patients who achieve complete or partial metabolic responses, *based on PET-CT* according to Lugano 2014 response criteria (Appendix 5), at the end of treatment as determined by an IRC

Table 9 Objectives and Corresponding Endpoints: Randomized Controlled Trial (Stage 2), contd.

Secondary Efficacy Objective	Corresponding Endpoints
	Secondary endpoints that will not be adjusted for testing multiplicity: • BOR, defined as the best response while on study, according to Lugano 2014 response criteria (Appendix 5), as determined by the investigator • CR, defined as the proportion of patients who achieve complete metabolic response based on PET-CT, according to Lugano 2014 response criteria (Appendix 5), at the end of treatment as determined by the investigator • ORR, defined as the proportion of patients who achieve complete or partial metabolic responses, according to Lugano 2014 response criteria (Appendix 5), at the end of treatment as determined by the investigator • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to Lugano 2014 response criteria, or death from any cause, whichever occurs first • EFS_{eff}, defined as time from randomization to the earliest occurrence of the below cases: - Disease progression or relapse - Death due to any cause - Initiation of any NALT
Secondary PRO Objective	**Corresponding Endpoint**
• To evaluate impact of treatment and disease on aspects of health-related quality of life	• Time to deterioration in physical functioning and fatigue as measured by the EORTC QLQ-C30 • Time to progression in lymphoma symptoms as measured by the FACT-Lym subscale • Change from baseline in PN as measured by the FACT/GOG-NTX-12 subscale score
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of Pola-R-GemOx compared with R-GemOx and to assess the immunogenicity of polatuzumab vedotin	• Incidence, nature, and severity of AEs (including PN) according to NCI CTCAE v5.0 and physical findings • Tolerability, as assessed by dose interruptions, dose reductions and dose intensity • Prevalence of ADAs at baseline and incidence of ADAs during the study

Table 9 Objectives and Corresponding Endpoints: Randomized Controlled Trial (Stage 2), contd.

Exploratory Biomarker Objectives	Corresponding Endpoints
• To identify biomarkers that: - Are prognostic of response to polatuzumab vedotin (i.e., predictive biomarkers) - Are associated with progression to a more severe disease (i.e., prognostic biomarkers) - Can provide evidence of polatuzumab vedotin activity, or can increase the knowledge and understanding of disease biology • To explore MRD as a prognostic marker in R/R DLBCL	• Associations between efficacy endpoints, including OS, PFS and CR rate, and exploratory biomarkers, which may include but are not limited to histological and molecular prognostic markers and profiles of circulating immune cells (see Table 12 for a description of proposed exploratory biomarkers)
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To further evaluate the PK of polatuzumab vedotin	• PK of polatuzumab vedotin in combination with R-GemOx in patients with relapsed or refractory DLBCL
Exploratory PRO Objectives	**Corresponding Endpoints**
• To evaluate impact of treatment and disease on aspects of health-related quality of life	• Descriptive summary statistics and the change from baseline for: - All scales for the EORTC QLQ-C30 - FACT-Lym subscale - FACT/GOG-NTX-12 - EQ-5D-5L

AE = adverse event; ADA = anti-drug antibody; BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS_{eff} = event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-Level Version; FACT/GOG-NTX-12 = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale; FACT-Lym Functional Assessment of Cancer Therapy-Lymphoma; IRC = Independent Review Committee; MRD = minimal residual disease; NALT = non-protocol–specified anti-lymphoma treatment; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; PK = pharmacokinetics; PN = peripheral neuropathy; Pola-R-GemOx = polatuzumab vedotin, rituximab, gemcitabine, and oxaliplatin; R/R = relapsed/refractory; R-GemOx = rituximab plus gemcitabine plus oxaliplatin.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study MO40598 is a Phase III, multicenter, open-label RCT in patients with relapsed or refractory DLBCL. The study will consist of a Screening Period, a Treatment Period, and

a Post-Treatment Period. The Post-Treatment Period will include an End of Treatment Visit occurring 28 days after the last dose of study treatment and a Follow-Up Period. Adverse events, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or until initiation of a non-protocol–specified anti-lymphoma treatment (NALT).

The overall design of the study is presented in Figure 1.

Figure 1 Study Schema

Pola = polatuzumab vedotin; R = randomize; R-GemOx = rituximab plus gemcitabine plus oxaliplatin; R/R DLBCL = relapsed or refractory diffuse large B-cell lymphoma.

Screening Period

To be eligible for Study MO40598, patients must have histologically-confirmed, relapsed or refractory DLBCL. Relapsed and refractory disease are defined as:

- Relapsed: Disease that has recurred following a response that lasted ≥ 6 months from completion of the last line of therapy
- Refractory: Disease that *did not respond to or that* progressed during therapy or progressed within 6 months (<6 months) of *completion of* prior therapy

Patients may have undergone autologous hematopoietic stem cell transplantation (HSCT) prior to recruitment; *in such cases, salvage chemotherapy will be counted as one line of therapy and conditioning* chemotherapy followed by consolidative autologous Hematopoietic stem cell transplantation will be counted as *a separate* line of therapy. Patients may have undergone allogeneic HSCT prior to recruitment, so long as they are off of all immunosuppressive therapy and have no active graft versus host disease (GVHD); *in such cases, salvage chemotherapy will be counted as one line of therapy and conditioning* chemotherapy followed by allogeneic HSCT will be counted *a separate* line of therapy. Local therapies (e.g., radiotherapy) will not be considered as treatment lines.

Patients with PN assessed to be greater than Grade 1 according to NCI CTCAE v5.0 will be excluded from enrollment. The grading of PN will be detailed in the protocol. Other inclusion and exclusion criteria are summarized in Section 4.1.1 and Section 4.1.2.

Treatment Period

The Treatment Period will occur in two stages. Stage 1 will comprise a safety run-in, where approximately 10 patients will receive experimental study treatment with Pola-R-GemOx. The purpose of Stage 1 is to provide a preliminary safety assessment of the study treatment, prior to entering Stage 2 of the study. Stage 2 will comprise an RCT, where approximately 250 patients will be randomly assigned in a 1:1 ratio to receive either experimental study treatment with Pola-R-GemOx or control study treatment with R-GemOx. In both stages of the Treatment Period, patients will receive up to 8 cycles of Pola-R-GemOx or 8 cycles of R-GemOx, each administered on 21-day cycles. Dosing regimens are described in detail in Section 4.3.2.
Dose delays/reductions will be permitted, as detailed in the protocol (Section 5.1.2).

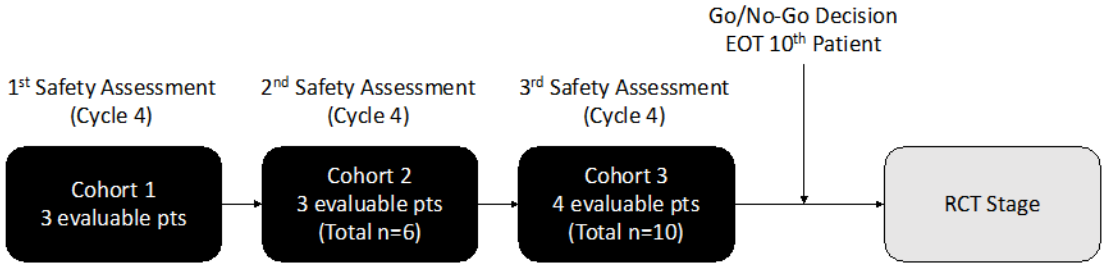
Stage 1: Safety Run-In (Figure 2)

- At a limited number of sites (approximately 18 centers), approximately 13 patients will be treated with Pola-R-GemOx
- Accrual of these patients will be staggered across three cohorts until the number of evaluable patients required for each cohort (mentioned below) is reached. Evaluable patients are patients who complete at least 4 cycles of treatment or are discontinued because of Grade $\geq$ 3 PN:
  - Cohort 1: 3 evaluable patients
  - Cohort 2: 3 evaluable patients
  - Cohort 3: 4 evaluable patients

    Approximately 7 patients will be recruited in Cohort 3, with the aim of having at least 4 evaluable patients.
- Cohort 2 and Cohort 3 will not begin enrolling patients until all safety evaluations have been completed in Cohort 1 and Cohort 2, respectively, and recruitment of the next cohort has been approved (see below for how approval occurs). Patients who discontinue prior to Cycle 4 of treatment due to disease progression, death or any other reason that is not directly attributable to PN will be replaced until the required number of evaluable patients is reached.
- Once 3 evaluable patients from Cohort 1 complete 4 cycles or discontinue because of Grade $\geq$ 3 PN, the IMC, in collaboration with the Steering Committee (SC) (if necessary), will evaluate the total safety profile of Pola-R-GemOx, with a particular focus on PN. They will then approve or disapprove enrollment into the next cohort. This recommendation will be released to the Sponsor responsible. Cohort 2 will follow the same process.
- [redacted]

- [redacted]
- In addition to the above, all patients from previous cohorts who proceeded beyond the fourth cycle of therapy will be re-evaluated by the IMC to assess the potential of cumulative neurotoxicity with Pola-R-GemOx, as well as the course of PN resolution.

Figure 2 Safety Run-In Schema (Stage 1)



EOT = end of treatment; evaluable = treated for at least 4 cycles of therapy or discontinued due to Grade ≥ 3 peripheral neuropathy; pts = patients; RCT = randomized controlled trial.

The Formal Go/No-Go Decision at the End of Stage 1

- When a minimum of 10 evaluable patients in the Treatment Period of Stage 1 have received the last dose of Pola-R-GemOx (i.e., completed Cycle 8 or discontinued between Cycle 5 and Cycle 8), the IMC will review the safety profile of the Stage 1 study population up to this point, focusing in particular on the frequency, course and reversibility of Grade ≥ 3 PN events.
  - [redacted]
- Based on the preceding information, the IMC will provide a recommendation, with the advice of the SC (if necessary), to the Sponsor responsible whether to continue to the RCT Stage.
- [redacted]

Stage 2: Randomized Controlled Trial

If Pola-R-GemOx combination therapy is deemed to be tolerable in the safety run-in, enrollment into the RCT stage will begin. Approximately 250 eligible patients will be randomized in a 1:1 ratio to receive either Pola-R-GemOx or R-GemOx. Randomization will be stratified by three factors: number of previous lines of systemic treatment

(1 vs. ≥2), outcome of last systemic therapy (relapsed vs. refractory), and age (≤70 years vs. >70 years).

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

The objectives and endpoints of the two stages are provided in Section 2. Safety will be assessed by adverse events per NCI CTCAE v5.0, patient-reported FACT/GOG-NTX-12 score (Stage 1), clinical laboratory test results, ECG, and vital signs. Response assessments will be according to Lugano 2014 criteria (Appendix 5), based on positron emission tomography–computed tomography (PET-CT) scans at screening and the end of treatment. All response assessments will be carried out by the investigator. In addition, the secondary outcomes of objective response rate (ORR) and CR rate in Stage 2 will be assessed by an Independent Review Committee, based on primary imaging data collected by the Sponsor.

Stage 1 and Stage 2 of the Treatment Period will also assess anti-drug antibodies (ADAs) and the sparse pharmacokinetic (PK) profile of polatuzumab vedotin in combination with R-GemOx. Stage 2 of the Treatment Period will also assess biomarkers (as per Table 12) and additional patient-reported outcomes (EuroQol 5-Dimension Questionnaire, 5-Level Version [EQ-5D-5L], FACT/GOG-NTX-12, Functional Assessment of Cancer Therapy–Lymphoma [FACT-Lym], and EORTC QLQ-C30).

Table 12 Biomarkers for Retrospective Exploratory Research (Stage 2)

Sample Type	Timing (All Mandatory)	Proposed Biomarkers
*DLBCL t*umor tissue *(fresh or archival)*	*Baseline*	• RNA-based gene expression profiling, including but not limited to cell-of-origin gene signature analysis • IHC and proteomic profiling, including BCL2 and MYC • Translocation profiles, including BCL2 and MYC • Mutation profiling by NGS, including but not limited to CD79b
Blood for MRD assays	Baseline, subsequent time points during treatment, and end of treatment (or discontinuation, whichever comes first)	• ctDNA level and clonal mutation profile • ctDNA as a peripheral measure of disease biology, prognosis, subsets, and treatment response
Blood for flow cytometry [a]	Baseline, subsequent time points during treatment, and end of treatment (or discontinuation, whichever comes first)	• Flow-cytometry–based profiling of circulating immune cells • To evaluate the prognostic value of patient immune fitness and investigate the effect of treatment regimen on circulating immune cells

ctDNA = circulating tumor DNA; IHC = immunohistochemistry; NGS = next-generation sequencing; MRD = minimal residual disease.

[a] The first 100 patients at selected sites will undergo flow cytometry.

Post-Treatment Period

Patients who complete study treatment per protocol (see Section 4.3.2) or discontinue from the study treatment early (e.g., if they terminated treatment early because of an adverse event) will enter the Post-Treatment Period, which will consist of an End of Treatment Visit occurring 28 (±7) days after the last dose of study treatment and then a *Long-term* Follow-Up Period. Assessments carried out at the End of Treatment Visit and during the *Long-term* Follow-Up Period are described in the Schedules of Activities in Appendix 1, Appendix 2, *Appendix 3 , and Appendix 4*.

Patients in the Follow-Up Period will be assessed as follows *via clinic visits, telephone calls, and/or patient medical records approximately every 2 months until death, loss to follow-up, or study termination by the Sponsor*:

- Patients *who complete treatment or discontinue all study treatment prematurely due to reasons other than* disease progression will *continue standard long-term*

follow-up assessments including required ADA sampling and radiographic assessments until disease progression and will be followed for NALT and survival.

- Patients who initiate NALT in the absence of progressive disease will continue to be followed for progression *(including radiographic assessments),* additional NALT, and survival.
- Patients with disease progression will be followed for NALT and survival.

3.1.1 Internal Monitoring Committee

An IMC will be established to monitor patient safety during the safety run-in and provide recommendations on whether the next cohorts or RCT should open. The IMC will include Sponsor representatives who are not associated with study conduct, at a minimum, representatives from Clinical Science, Safety Science and Biometrics. The IMC will review all necessary cumulative data at regular intervals during the study. The IMC will evaluate the total safety profile of Pola-R-GemOx, with a particular focus on PN. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities, will be detailed in an IMC Charter.

3.1.2 Independent Data Monitoring Committee

An iDMC will evaluate safety data periodically during the RCT (see Section 6.10). The analysis supporting iDMC review will be conducted by an independent Data Coordinating Center (iDCC) and provided to the iDMC. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

The guidelines for safety monitoring and predefined stopping rules for treatment-related deaths, PN events, and treatment delays that lead to treatment discontinuation will be provided in the iDMC charter.

3.1.3 Independent Review Committee

An Independent Review Committee (IRC) composed of board-certified radiologists and an oncologist with experience in malignant lymphoma will assess all patients for response (see Appendix 5) until end of treatment on the basis of imaging results and bone marrow biopsy results for all patients during the RCT. Decisions will be guided by a Charter specific to the independent review.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit, occurs which will be the timepoint at which all patients enrolled in the study have either had at least 2 years of follow-up from the time of the treatment-completion visit or have discontinued the study. The end of the study is expected to occur approximately 2.5 years after the last patient is enrolled.

After an initial safety-run in, the randomized stage for recruitment is expected to occur over approximately 19 months.

This is an event-driven trial. The clinical cut-off date for the *primary* OS analysis will be confirmed when the targeted number of mortality events ([redacted] deaths) have occurred, which is expected approximately [redacted] months after the first patient is randomized (first patient in) in the RCT stage of the study.

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Please see Section 1.3 (Study Rationale and Benefit Risk Assessment).

3.3.2 Rationale for Stratification Factors

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

- Number of previous lines of systemic therapy for DLBCL (1 vs. ≥2)
  - *Conditioning* chemotherapy followed by consolidative autologous HSCT will be counted as one line of therapy. *Conditioning* chemotherapy followed by allogeneic HSCT will be counted as one line of therapy. Local therapies (e.g., radiotherapy) will not be considered as lines of treatment.
- Outcome of last systemic therapy (relapsed vs. refractory)
  - Relapsed disease in this study is defined as disease that has recurred ≥6 months after completion of the last line of treatment.
  - Refractory disease is defined as disease that *did not respond to or that* progressed during therapy or progressed within 6 months (<6 months) of prior therapy.
- Age (≤70 years vs. >70 years)

The preceding stratification will produce treatment groups that are roughly equivalent in terms of disease progression and disease status, thereby ensuring comparability between the experimental (Pola-R-GemOx) and control (R-GemOx) arms.

3.3.3 Rationale for Polatuzumab Vedotin Dose and Schedule

The dose and schedule of polatuzumab vedotin in this study have been chosen based on experience from the Phase I Study DCS4968g, as well as other studies across the development program. In DCS4968g, administration of single-agent polatuzumab vedotin in patients with relapsed/refractory indolent NHL or DLBCL at doses ranging from 0.1 to 2.4 mg/kg resulted in approximately linear dose-proportional pharmacokinetics for antibody-conjugate, total antibody, and unconjugated MMAE. Furthermore, co-administration of rituximab had no effect on the PK of

polatuzumab vedotin, and vice versa. General safety profiles of polatuzumab vedotin alone and in combination with rituximab across this range of doses are summarized in Section 1.3 and described below in relation to dose and schedule choice.

From prior studies, PN and neutropenia have been identified as risks associated with polatuzumab vedotin therapy (Section 1.3, Section 5.1.1.1, and the Polatuzumab Vedotin Investigator's Brochure). These are also important risks for R-GemOx therapy (Section 3.1), necessitating caution in choice of dose and schedule of experimental study treatment in the current trial. Consequently, to optimize the safety of study participants, a dose and schedule of polatuzumab vedotin have been chosen that provide the lowest exposure to therapeutic antibody while still providing nearly maximal clinical effect. Specifically, polatuzumab vedotin will be administered at 1.8 mg/kg per dose for up to eight 21-day treatment cycles (corresponding to 6 months of total treatment). This dosing regimen is currently recommended by internal Roche guidance for all polatuzumab vedotin clinical trials as the optimal balance between safety and efficacy. Due to limited clinical experience in patients treated with 1.8 mg/kg polatuzumab vedotin at a total dose $>$240 mg, it is recommended not to exceed a dose of 240 mg per cycle.

Because this is the first study to evaluate Pola-R-GemOx therapy, Study MO40598 will also have a safety run-in period to assess PN risk, thereby validating initial safety, as well as continued assessments of PN and neutropenia throughout the Treatment Period (Section 1.3). The study also has dose reduction criteria designed to manage adverse events (Section 5.1.2).

3.3.4 Rationale for Rituximab Plus Gemcitabine Plus Oxaliplatin as the Control Therapy and for its Dose and Schedule

The clinical development program for polatuzumab vedotin is based on the hypothesis that adding an anti-CD79b antibody to a standard regimen of anti-CD20 antibody plus chemotherapy will provide enhanced efficacy in patients with B-cell lymphomas. Prior clinical studies are consistent with this hypothesis (see Section 1.3 and the Polatuzumab Vedotin Investigator's Brochure), although the number of rituximab-containing backbone therapies evaluated to date in combination with polatuzumab vedotin is relatively limited.

As R-GemOx is commonly used in the clinic for relapsed/refractory DLBCL and is recommended by the NCCN in this setting (National Comprehensive Cancer Network 2018), it is of significant interest to assess whether adding polatuzumab vedotin to R-GemOx provides the expected efficacy enhancement. Thus, the current prospective, randomized comparative trial will compare patients treated with experimental therapy (i.e., Pola-R-GemOx) versus those treated with control therapy (i.e., R-GemOx). In order that potentially positive results from this trial can be applied directly to clinical practice in the future, R-GemOx will be administered under standard clinical conditions, (i.e., as described in local prescribing information).

Control patients will receive R-GemOx at the currently recommended dosage and schedule for up to 8 cycles. An identical regimen consisting of 8 cycles of R-GemOx has been shown in published clinical studies to be effective and well tolerated in the setting of relapsed or refractory DLBCL, with Grade 3–4 infectious episodes observed in 22% of cycles (Mounier et al. 2013). Given that 8 cycles are also considered to be optimal for polatuzumab vedotin therapy based on current clinical studies (Section 3.3 and Polatuzumab Vedotin Investigators Brochure), it was deemed that 8 cycles of therapy in both treatment arms (R-GemOx and Pola-R-GemOx) would be used in this study.

3.3.5 Rationale for Biomarker Assessments

Diffuse large B-cell lymphoma is a heterogeneous disease and, consequently, a number of distinct proteomic and molecular profiles have been identified in patients who exhibit different prognoses and responses to standard-of-care (SoC) treatments (Lenz et al. 2008; Johnson et al. 2009; Johnson et al. 2012; Scott et al. 2015; Chapuy et al. 2018; Schmitz et al. 2018). The most established DLBCL biomarker subsets to date are molecularly-defined profiles consistent with developmental stage or cell of origin (COO) of the B-cell–originating tumor (i.e., the activated B-cell–like [ABC] profile) the germinal center B-cell–like (GCB) or unclassified profile, the BCL2/MYC double-expressor profile (characterized by elevated expression of both MYC and BCL2), and the BCL2/MYC double-hit profile (translocation in both BCL2 and MYC). In the recent revision of the WHO classification, a new molecular subgroup was defined, the high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (Swerdlow et al. 2016). In addition to their distinct molecular profiles, these DLBCL signatures have varied prognostic outcomes in front-line DLBCL patients when treated with the SoC therapy R-CHOP; for COO, the ABC subgroup characteristically has an inferior prognosis relative to GCB with R-CHOP treatment in front-line DLBCL (Alizadeh et al. 2000; Lenz et al. 2008; Nowakowski et al. 2016). For BCL2/MYC, the double-expressor and the double-hit patients also have reported inferior prognosis (Johnson et al. 2009; Johnson et al. 2012). More recently, molecular subtypes have been identified that transcend the categories aforementioned, with distinct genotypic, epigenetic and clinical characteristics. Examples include the four genetic subtypes described by Schmitz et al., and the five DLBCL subsets as described by Chapuy et al. It is likely that further work in this realm may redefine new treatment combinations in the future treatment regimens. The clinical implications of these DLBCL subsets have almost exclusively been studied in first-line DLBCL and are likely to be important in the development of new treatment regimens. However, the prognostic implication of these subsets in the relapsed or refractory setting is less clear, except that there are certain higher-risk subsets that tend to have higher rates of treatment failure with R-CHOP (Thieblemont et al. 2011; Camicia et al. 2015; Nowakowski et al. 2016).

CD79b is the molecular target of polatuzumab vedotin. In vivo, CD79b heterodimerizes with CD79a, thereby forming an essential component of the multi-protein B-cell receptor (BCR) complex, which is critical for functional BCR expression and B-cell signaling.

CD79b is consistently expressed in mature B-cells and in mature B-cell malignancies (Chu and Arber 2001; Olejniczak et al. 2006; Polson et al. 2009).

Exploratory biomarkers for this study may include, but are not limited to: the target of polatuzumab vedotin (CD79b), established prognostic biomarkers in DLBCL (cell-of-origin, BCL2/MYC double-expression and BCL2/MYC double-translocation), gene expression analysis, and tumor mutation profiling by next-generation sequencing (NGS). These biomarkers will be tested in Stage 2 of the study (RCT). Serial or longitudinal collection of plasma samples will be collected in Stage 2 of this study. Non-invasive, blood collection will enable the assessment of circulating tumor DNA (ctDNA), which is believed to come from apoptotic remains of tumor cells. The ctDNA can be quantified and also assessed for its genomic mutations. Beyond associating this information at baseline with clinical efficacy for prognostic and treatment effect evaluation, this information will also allow for monitoring of residual disease at the molecular level and for tracking clonal evolution.

3.3.6 Rationale for the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale (FACT/GOG-NTX-12)

Peripheral neuropathy has been identified as a potential risk of polatuzumab vedotin treatment (Section 3.1, Section 5.1.1.1, and Polatuzumab Vedotin Investigator's Brochure). Therefore, to ensure patient safety, PN will be monitored throughout the study using the NCI CTCAE v5.0 (see Appendix 1 and Appendix 2). However, while the sensory section of the NCI CTCAE v5.0 has good validity, it has been shown to be fairly insensitive in predicting chemotherapy-induced PN (Shimozuma et al. 2012). In light of this, several neuropathy-specific scales have been developed that capture aspects of chemotherapy-induced PN frequently missed by simple and more general toxicity scales, such as the NCI CTCAE v5.0 (Curcio 2016).

The FACT/GOG-NTX contains 11 items scored from 0–4, and scores are summed for a range of 11–44 (Curcio KR 2016). The FACT/GOG-NTX was initially developed with the input of expert clinicians and patients who reported symptoms of chemotherapy-induced PN within the past month (Calhoun et al. 2003). The questionnaire was validated with women diagnosed with gynecologic malignancies who received taxanes and platinum compounds, well-known neurotoxic drugs (Calhoun et al. 2003; Huang et al. 2007).

Kopec et al. (2006) modified the FACT/GOG-NTX by adding one item specific to oxaliplatin, which is of particular interest given that one of the members of the chemotherapy backbone in this study is oxaliplatin. This version has been renamed the FACT/GOG-NTX-12 (Appendix 10). The revised version was tested in patients with colon cancer. Reliability was good (Cronbach alpha = 0.85), and the questionnaire scores were correlated with the National Cancer Institute-Sanofi criteria. The FACT/GOG-NTX-12 was also shown to be sensitive to changes in chemotherapy-induced PN over time. Combined with its relative ease of administration, these features

make the FACT/GOG-NTX-12 ideally suited to clinical studies and will be used in this study to assess chemotherapy-induced PN.

3.3.7 Rationale for EQ-5D-5L, EORTC QLQ-C30 and FACT-Lym Patient-Reported Outcome Assessments

Patient-reported outcome (PRO) assessments provide a unique perspective on disease and treatment burden and complement the evaluation of clinical benefits associated with specific therapies. Patient-relevant outcomes are now integral components of treatment, regulatory and reimbursement decision-making, as well as important considerations in many of today's quality initiatives (Institute of Medicine [U.S.], Committee on Quality of Health Care in America 2001). Consequently, to supplement the growing database of information on the health-related quality of life (HRQoL) effects of polatuzumab vedotin therapy in combination with rituximab plus chemotherapy, patients in Stage 2 of Study MO40598 (randomized controlled trial) will complete the following PRO instruments, according to the Schedule of Activities in Appendix 2:

- The EuroQol 5-Dimension Questionnaire, 5-level version: The EQ-5D-5L is a widely used validated self-report health status questionnaire that is used to calculate a health status utility score for health economic analyses (EuroQol 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (Appendix 12). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status.
- European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire, Core 30: The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 13). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The EORTC QLQ C30 module takes approximately 10 minutes to complete.
- The Functional Assessment of Cancer Therapy–Lymphoma: The FACT-Lym is a validated HRQoL instrument used specifically in patients with lymphoma (Appendix 11). The FACT-Lym is composed of the 27-item Functional Assessment of Cancer Therapy–General Questionnaire (FACT-G), which measures health-related quality of life in patients undergoing any type of cancer therapy, plus the 15-item Lymphoma Subscale, which assesses how lymphoma-specific symptoms impact HRQoL (Cella et al. 1993; Cella et al. 2005). Each item of the FACT-Lym is answered using a 5-point Likert scale.

3.3.8 Rationale for the Independent Data Monitoring Committee

An iDMC will be incorporated to monitor patient safety during the RCT instead of the IMC. As a result, although this is an open-label study and the investigators and patients

are unblinded, the Sponsor and study team performing the primary analysis will not have access to aggregated statistical outputs by treatment arm indicating treatment. An unblinded iDMC will facilitate evaluation of the safety profile during the RCT. The iDMC will provide recommendations to the Sponsor whether to continue, modify or terminate the trial.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 10 patients will be enrolled in the safety run-in phase, and approximately 2*50* patients will be enrolled in the randomized portion, for a total of approximately 2*60* patients.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically-confirmed diffuse large B-cell lymphoma, not otherwise specified or history of transformation of indolent disease to DLBCL
- Relapsed or refractory disease, defined as follows:
  - Relapsed: Disease that has recurred following a response that lasted ≥6 months from completion of the last line of therapy.
  - Refractory: Disease *that did not respond to or that* progressed during therapy or progressed within 6 months (<6 months) of prior therapy.
- At least one (≥1) line of prior systemic therapy:
  - Patients may have undergone autologous HSCT prior to recruitment. *In such cases, salvage chemotherapy (e.g., rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP] and rituximab, ifosfamide, carboplatin, and etoposide phosphate [R-ICE]) will be counted as one line of therapy and conditioning* chemotherapy *(e.g., BEAM)* followed by consolidative autologous HSCT will be counted as *a separate* line of therapy.
  - Patients may have undergone allogeneic HSCT prior to recruitment, so long as they are off all immunosuppressive therapy and have no active GVHD. *In such cases, salvage chemotherapy (e.g., R-DHAP and R-ICE) will be counted as one line of therapy and conditioning* chemotherapy *(e.g., carmustine, etoposide, cytarabine, and melphalan [BEAM])* followed by allogeneic HSCT will be counted as *a separate* line of therapy.
  - *Patients may have undergone CAR T-cell therapy prior to recruitment. In such cases, cell collection, conditioning chemotherapy, and infusion will be counted as one line of therapy.*

  - Local therapies (e.g., radiotherapy) will not be considered as lines of treatment.
  - *For patients with history of transformation of indolent disease to DLBCL, it is preferred that patients have received at least one treatment for the transformed lymphoma. However, if there are cases where the patient has received an anthracycline-containing chemotherapy regimen (such as R-CHOP) for the indolent lymphoma only, then these patients can be considered as eligible.*
- At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension as measured by computed tomography (CT) or magnetic resonance imaging (MRI)
- ECOG performance status of 0,1, or 2
  - Patients with an ECOG performance status of 3 can be considered in the RCT stage, but only if this status is DLBCL-related and if after a prephase of a 7-day steroid treatment during the screening phase (e.g., 1 mg/kg prednisone) an improvement in ECOG performance status to 2 or less is observed prior to enrolment.
- Adequate hematological function, as defined by:
  - Hemoglobin ≥ 8 g/dL
  - ANC $\geq 1.5 \times 10^9$/L or $\geq 0.5 \times 10^9$ if the neutropenia is attributable to underlying disease and before the administration of steroids
  - Platelet count $\geq 75 \times 10^9$/L or $\geq 50 \times 10^9$ if the thrombocytopenia is attributable to underlying disease
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 12 months after the final dose of polatuzumab vedotin*,* rituximab*, gemcitabine, or oxaliplatin*. Women must refrain from donating eggs during this same period.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile 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 requirements.
  - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or

postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below (the patient should receive advice on the possibility of opting for cryoconservation of sperm prior to start of study treatment due to the possibility of irreversible infertility following therapy with gemcitabine, oxaliplatin, or polatuzumab vedotin):
  - With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile 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 6 months after the final dose of *polatuzumab vedotin, rituximab,* oxaliplatin, and/or gemcitabine. Men must refrain from donating sperm during this same period.
  - With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of polatuzumab vedotin, rituximab*,*oxaliplatin, and*/or* gemcitabine to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

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

- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to rituximab, gemcitabine, or oxaliplatin
- PN assessed to be Grade >1 according to NCI CTCAE v5.0 at enrollment
- Prior use of polatuzumab vedotin or a gemcitabine $+$ platinum-based agent combination
- Enrollment in any previous or ongoing polatuzumab vedotin trial
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1 Day 1

- All acute, clinically-significant treatment-related toxicity from prior therapy, except for alopecia, must have resolved to Grade ≤ 2 prior to Cycle 1 Day 1.

- Planned autologous or allogeneic stem cell transplantation *or CAR T-cell therapy* at time of recruitment
  - Patients with only one prior therapy who are appropriate for stem cell transplantation are excluded from this trial. Reasons for transplant-ineligibility may include age, performance status, comorbidities, transplant failure or failed procedure, insufficient response to salvage therapy, patient refusal, or logistical reasons.
- Primary or secondary CNS lymphoma at the time of recruitment
- Richter's transformation or prior CLL
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
  - Creatinine $> 1.5\times$ upper limit of normal (ULN) or a measured creatinine clearance < 30 mL/min
  - AST or ALT > 2.5 x ULN
  - Total bilirubin $\geq 1.5\times$ ULN. Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq 3\times$ ULN
  - INR or PT $> 1.5\times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $> 1.5\times$ ULN in the absence of a lupus anticoagulant
- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include:
  - Patients with a history of curatively-treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the study are eligible.
  - A patient with any other malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for ≥ 2 years prior to enrollment is eligible.
  - Patients with low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study are eligible.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection (as evaluated by the investigator) within 4 weeks prior to Cycle 1 Day 1

- Patients with suspected or latent tuberculosis
  - Latent tuberculosis needs to be confirmed by positive interferon-gamma release assay
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)
  - Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment.
- Positive test results for hepatitis C virus (HCV) antibody
  - Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Known history of HIV seropositive status
  - For patients with unknown HIV status, HIV testing will be performed at Screening if required by local regulations.
- Vaccination with a live vaccine within 4 weeks prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 months after the last dose of study drug
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

4.2 METHOD OF TREATMENT ASSIGNMENT

Study MO40598 is an open-label trial. *The Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification of any eligibility criteria and may share risk factor information pertinent to the patient but the decision of whether a patient meets the eligibility criteria to enroll to the protocol is the responsibility of the PI.* The study site will obtain the patient number and treatment assignment from an interactive voice or Web-based response system (IxRS).

The Treatment Period will occur in two stages:

Stage 1: Safety Run-In

- During the safety run-in (Figure 2), approximately 13 patients will be treated with Pola-R-GemOx.

- Accrual of these patients will be staggered across three cohorts:
  - Cohort 1: 3 evaluable patients
  - Cohort 2: 3 evaluable patients
  - Cohort 3: 4 evaluable patients

    Approximately 7 patients will be recruited in Cohort 3, with the aim of having at least 4 evaluable.
- Within each cohort, safety will be evaluated when the number of intended evaluable patients complete 4 cycles of treatment, with a focus on acute PN toxicities. Once all safety evaluations have been conducted within a cohort and further subject accrual is cleared, the next cohort will open to recruitment.
- Once at least 10 evaluable patients in the safety run-in have received the last dose of Pola-R-GemOx, the safety and tolerability of the Pola-R-GemOx regimen will be assessed by the IMC, and a decision will be made whether to continue into the RCT stage of the study. The SC will be available for consultation during this time.
- Only a limited number of sites (approximately 18 centers) will be open for accrual into the safety run-in.

Stage 2: Randomized Control Trial

- If Pola-R-GemOx combination therapy is deemed tolerable in Stage 1, newly enrolled patients will be randomized in a 1:1 ratio to receive either Pola-R-GemOx or R-GemOx.
- Randomization will be performed by IxRS using stratified permuted blocks. Stratification factors will include: 1) number of previous lines of therapy for DLBCL; 2) relapsed versus refractory status; and 3) age.
- Approximately 2*50* eligible patients are expected to enroll in this stage of the study.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is Pola-R-GemOx. The control therapy is R-GemOx.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Polatuzumab Vedotin

Polatuzumab vedotin will be supplied by the Sponsor as a lyophilized formulation (140 mg/vial). Prior to administration, the lyophilized powder will be reconstituted with sterile water for injection to a volume of 7.2 mL.

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

4.3.1.2 Rituximab

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

4.3.1.3 Gemcitabine

Gemcitabine will be supplied by the Sponsor. For information on the formulation, packaging, and handling of gemcitabine, see the pharmacy manual and the Gemcitabine Summary of Product Characteristics (SmPC).

4.3.1.4 Oxaliplatin

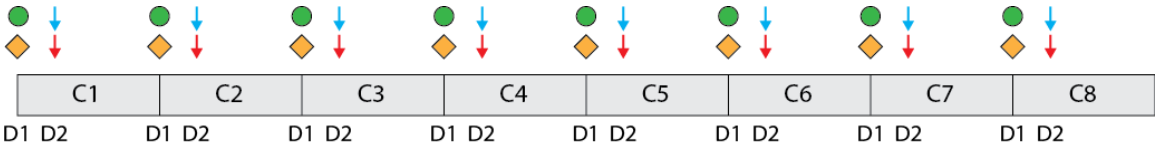
Oxaliplatin will be supplied by the Sponsor. For information on the formulation, packaging, and handling of oxaliplatin, see the pharmacy manual and the Oxaliplatin SmPC.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Therapeutic regimens in this study are summarized in Figure 3 and Figure 4 and described in more detail in the following sections. Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

Figure 3 Regimen in the Experimental Treatment Group: Polatuzumab Vedotin Plus Rituximab Plus Gemcitabine Plus Oxaliplatin



Rituximab	375 mg/m^2 IV on Day 1 of each cycle for up to 8 cycles [a]
Polatuzumab vedotin	1.8 mg/kg IV on Day 1 of each cycle for up to 8 cycles
Gemcitabine	1000 mg/m^2 IV on Day 2 of each cycle for up to 8 cycles [b]
Oxaliplatin	100 mg/m^2 IV on Day 2 of each cycle for up to 8 cycles

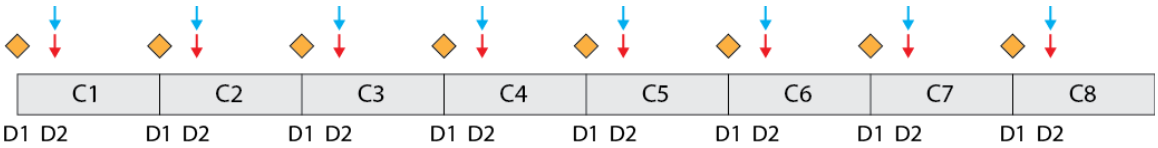
1 cycle = 21 days

C = cycle; D = day.

[a] Rituximab should be administered before polatuzumab vedotin.

[b] Gemcitabine should be administered before oxaliplatin.

Figure 4 Regimen in the Control Group: Rituximab Plus Gemcitabine Plus Oxaliplatin



Rituximab 375 mg/m^2 IV on Day 1 of each cycle for up to 8 cycles
Gemcitabine 1000 mg/m^2 IV on Day 2 of each cycle for up to 8 cycles [a]
Oxaliplatin 100 mg/m^2 IV on Day 2 of each cycle for up to 8 cycles

1 cycle = 21 days

C = cycle; D = day.

[a] Gemcitabine should be administered before oxaliplatin.

4.3.2.1 Polatuzumab Vedotin

Polatuzumab vedotin 1.8 mg/kg will be administered intravenously on Day 1 of each 21-day cycle for up to 8 cycles. Polatuzumab vedotin should be administered after rituximab on the same day or, in the event of a dose delay for rituximab, the following day (see below).

Patient weight obtained during screening (Day −28 to Day −1) should be used for dose determination for all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle is greater or less than 10% from the weight obtained during screening, the new weight should be used to calculate the dose. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. All subsequent doses should be modified accordingly. Dose adjustments for body weight changes $<10\%$ are also acceptable should this be local standard of care. Due to limited clinical experience in patients treated with 1.8 mg/kg polatuzumab vedotin at a total dose >240 mg, it is recommended not to exceed a dose of 240 mg per cycle.

The initial dose will be administered to patients who are well hydrated (as per local guidelines) over 90 ± 10 minutes. Premedication (e.g., 500–1000 mg of oral acetaminophen or paracetamol and *approximately* 50–100 mg diphenhydramine as per institutional standard practice) may be administered to an individual patient ≥30 minutes before starting administration of polatuzumab vedotin. Administration of corticosteroids is permitted at the discretion of the treating physician. If infusion-related reactions (IRRs) are observed with the first infusion in the absence of premedication, premedication must be administered before subsequent doses.

The polatuzumab vedotin infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be

observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion associated symptoms. If prior infusions have been well tolerated, subsequent doses of polatuzumab vedotin may be administered over 30 ± 10 minutes, followed by a 30-minute observation period after the infusion.

During administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 30 ± 5 minutes during the infusion, at the end of the infusion and every 30 ± 10 minutes for 90 minutes following completion of dosing at Cycle 1 and 30 ± 10 minutes following completion of dosing in subsequent cycles.

Please refer to the Pharmacy Manual for detailed instructions on administration of polatuzumab vedotin.

4.3.2.2 Rituximab

Rituximab (Mabthera/Rituxan®) 375 mg/m^2 will be administered intravenously on Day 1 of each 21-day cycle for up to 8 cycles. Rituximab should be administered before polatuzumab vedotin on the same day; in the event of a dose delay for rituximab, polatuzumab vedotin may be administered on the following day.

No dose modifications of rituximab are allowed.

During the administration of rituximab in Cycle 1, vital signs are to be obtained before infusion, then after the start of the infusion, approximately every 30 ± 5 minutes for 90 minutes, then every 30 ± 10 minutes until 1 hour after the end of the infusion. During administration of rituximab in subsequent cycles, vital signs are to be recorded before infusion, then after the start of infusion, and approximately every 30 ± 10 minutes until 1 hour after the end of infusion.

The patient's body surface area (BSA) calculated at screening should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by > 10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients (obesity defined as body mass index ≥ 30, as measured in kilograms divided by meters squared) may be implemented per institutional guidelines.

The rituximab administration should be completed at least 30 minutes before administration of other study treatments. The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). Administration of rituximab may be continued on the following day, if needed, for patients who experience an adverse event during the rituximab infusion. If a dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication and at the first infusion rate (see Table 13).

All rituximab infusions should be administered to patients after premedication with oral acetaminophen (e.g., 500–1000 mg) and an antihistamine such as diphenhydramine hydrochloride (*e.g.,* 50–100 mg) ≥30 minutes before starting each infusion (unless contraindicated). An additional glucocorticoid (e.g., 100 mg IV prednisone or prednisolone or equivalent) is allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Rituximab infusions will be administered according to the instructions in Table 13. If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as rapid infusion in accordance with local institutional guidelines.

During the treatment period, rituximab must be administered to patients in a setting where full emergency resuscitation facilities are immediately available. Patients should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 5.1.2.

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (such as the Braun Infusomat Space) should be used to control the infusion rate of rituximab. Administration sets with polyvinyl chloride (PVC), polyurethane (PUR), or polyethylene (PE) as a product contact surface and IV bags with polyolefine, polypropylene (PP), PVC, or PE as a product contact surface are compatible and can be used. Additional in-line filters should not be used because of potential adsorption. The in-line filter used for the administration of polatuzumab vedotin should not be used for the administration of rituximab.

After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥2 hours in order to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

Table 13 Administration of First and Subsequent Infusions of Rituximab

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

4.3.2.3 Gemcitabine

Gemcitabine 1000 mg/m^2 will be administered intravenously on Day 2 of each 21-day cycle for up to 8 cycles. Gemcitabine should be administered before oxaliplatin on the same day. In the event that rituximab dosing is split across two days, gemcitabine may be administered on Day 2 (i.e., the same day rituximab dosing is completed) or on the following day (see Section 4.3.2.2).

The method of administering gemcitabine is described in the local prescribing information.

4.3.2.4 Oxaliplatin

Oxaliplatin 100 mg/m^2 will be administered intravenously on Day 2 of each 21-day cycle for up to 8 cycles. Oxaliplatin should be administered after gemcitabine on the same day. In the event that rituximab dosing is split across two days, oxaliplatin may be administered on Day 2 (i.e., the same day rituximab dosing is completed) or on the following day (see Section 4.3.2.2).

The method for administering oxaliplatin is described in local prescribing information.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (polatuzumab vedotin, rituximab, gemcitabine, and oxaliplatin) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the

shipment condition and content. Any damaged shipments will be replaced. *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.*

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

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

4.3.4 Continued Access to Polatuzumab Vedotin, Rituximab, Oxaliplatin, and Gemcitabine

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

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy

- Other maintenance therapies

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Guidelines for specific supportive therapies are provided in the following subsections.

4.4.1.1 Premedication Before Polatuzumab Vedotin

Per protocol, polatuzumab vedotin infusions should immediately follow rituximab infusions. Consequently, as premedication is required before all rituximab infusions (see Section 4.4.1.2), additional premedication for polatuzumab vedotin is not required.

However, if there is a delay in dosing of polatuzumab vedotin, then polatuzumab vedotin should be administered following premedication. Premedication will consist of *approximately* 500–1000 mg of oral acetaminophen or paracetamol and *approximately* 50–100 mg diphenhydramine (as per institutional standard practice) administered ≥30 minutes before starting administration of polatuzumab vedotin. Administration of corticosteroids is permitted at the discretion of the treating physician.

4.4.1.2 Premedication Before Rituximab

All rituximab infusions should be administered to patients after premedication. The following premedication is required before rituximab therapy:

- Acetaminophen/paracetamol (e.g., 500–1000 mg) orally at ≥30 minutes before the start of all infusions
- Antihistamine, such as diphenhydramine (e.g., 50–100 mg), ≥30 minutes before the start of each infusion (unless contraindicated)

4.4.1.3 Premedication for Patients at High Risk for Tumor Lysis Syndrome

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

4.4.1.4 Prophylaxis for Infections

Anti-infective prophylaxis for pneumocystis and herpesvirus infections is mandatory and should be instituted per institutional practice or investigator preference based on individual patient risk factors. Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the standard of care, patients should be

treated prophylactically (Flowers et al. 2013; NCCN 2017). All anti-infective prophylaxis should be recorded appropriately in the eCRF.

With reference to coronavirus disease 2019 (COVID-19) vaccines, an assessment was conducted to determine whether there is any impact of the COVID-19 vaccines on the benefit-risk assessment of this study protocol. Given the mechanism of action of rituximab, it is expected that the efficacy of COVID-19 vaccines may be diminished in patients who are B-cell depleted. The investigator should use clinical judgement to decide on the most suitable timing of vaccination, and where possible, COVID-19 vaccines should be administered to patients before they start immunosuppressive therapy. The COVID-19 vaccines may also be administered at any time during the study provided they are non-live vaccines. If administered during the study, the COVID-19 vaccines are considered concomitant medications. The COVID-19 vaccines must be administered in accordance with the approved/authorized vaccine label (or equivalent) and official immunization instructions. Based on this assessment, no additional risk mitigation measures related to COVID-19 vaccination are proposed at this time. The recommendations listed above and the current safety monitoring and management guidelines and risk-mitigation measures provided in the study protocol are considered adequate.

4.4.1.5 Treatment and Prophylaxis of Neutropenia

The administration of granulocyte colony-stimulating factor (G-CSF) as a primary prophylaxis in each cycle of therapy is required and should be administered as per local/institutional guidelines. The dose and form of G-CSF will be at the discretion of the investigator. The use of additional G-CSF is allowed for the treatment of neutropenia per investigator discretion.

4.4.1.6 Monitoring and Treatment for Hepatitis B Reactivation

Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included in this study if HBV DNA is undetectable. These patients should have HBV DNA levels obtained on Day 1 of every cycle and for at least 12 months after the last cycle of study treatment by means of real-time PCR, with the use of an assay that has a sensitivity of at least 29 IU/mL.

If the HBV-DNA assay becomes positive and is above the WHO's cutoff of 100 IU/mL, study treatment will be held and the patient should be treated (for at least 1 year after the last dose of rituximab) with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume study treatment once HBV DNA levels decrease to undetectable levels.

If the HBV DNA assay becomes positive and is $\leq$100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, study treatment will be held, and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of rituximab) and immediately referred to a gastroenterologist or

hepatologist for management. Patients may resume study treatment once the HBV DNA levels decrease to undetectable levels.

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving anti-viral medication, study treatment will be permanently discontinued (see Section 5.1.2.3, Table 14).

Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the standard of care may be treated prophylactically.

4.4.1.7 Other Concomitant Medications

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin *or G-CSF*), if clinically indicated.

Anti-emetic therapy may be instituted for any patient if clinically indicated.

4.4.2 Cautionary Therapy

Caution should be exercised in the administration of oxaliplatin in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia. The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. Electrocardiogram recordings will be obtained at specified timepoints, as outlined in the Schedule of Activities (see Appendix 1 and Appendix 2), and as clinically indicated. In case of QT prolongation, oxaliplatin treatment should be discontinued, as per the SmPC.

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Mono-methyl auristatin E is a substrate of the CYP450 enzymes, specifically CYP3A. Published data suggest that MMAE is neither an inhibitor nor inducer of CYP3A. Patients who are receiving strong CYP3A inhibitors should be closely monitored for adverse reactions when given polatuzumab vedotin (Han et al. 2013).

Mono-methyl auristatin E is a P-glycoprotein (P-gp) substrate, but not a P-gp inhibitor. Concomitant medications that are P-gp inhibitors should be considered cautionary, as they may potentially lead to adverse reactions which require close monitoring. If a patient is taking any of the medications in the categories of P-gp inhibitors, the investigator will assess and document the use of these medications known or suspected to fall in those categories.

Other medications that are not prespecified study treatments may need to be used with caution in this study. The investigator should consult the prescribing information and contact the Medical Monitor if questions arise regarding the safe use of any concomitant medication.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Treatment with other concomitant anti-tumor agents not defined in this protocol as study treatment, radiotherapy, or other concurrent investigational agents of any type will result in withdrawal of patients from study treatment.

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

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 2 weeks prior to initiation of study treatment and during study treatment.
- Cytotoxic chemotherapy, other than gemcitabine, oxaliplatin, and intrathecal chemotherapy for CNS prophylaxis
- Immunotherapy or immunosuppressive therapy *for the purpose of treating lymphoma*, other than study treatments
- Radioimmunotherapy
- Hormone therapy, other than contraceptives, stable hormone-replacement therapy, or megestrol acetate
- Biologic agents for the treatment of lymphoma
  - Biological agents that are supportive therapies, such as hematopoietic growth factors, are allowed if clinically indicated and used in accordance with instructions provided in the package inserts.
- Any therapy (other than intrathecal CNS prophylaxis) intended for the treatment of lymphoma, whether it is approved by the European Medicines Agency or the U.S. Food and Drug Administration (FDA) or is experimental
- Radiotherapy
- Immunizations
  - Patients who participate in this study may not receive either primary or booster vaccinations with live virus vaccines for at least 28 days before initiation of rituximab, at any time during study treatment, or until B-cell recovery. Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases before study therapy.

Patients who require the use of any of these agents will be discontinued from study treatment.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study are provided in Appendix 1 and Appendix 2. All activities must be performed and documented for each patient.

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

4.5.1 Informed Consent Forms and Screening Log

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

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies, reason for transplant ineligibility, 2016 WHO classification, current Ann Arbor stage, and procedures), ECOG performance status, and reproductive status will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment *until 28 days after the last dose of study drug* will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity, since this is a global study and Non-Hodgkin's lymphoma, in epidemiological studies, has been shown to vary in incidence, histological subtypes, age of presentation and responses to treatment based on race and ethnicity.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems (monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

As part of tumor assessment, physical examinations should include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly (clinical response assessment). These will be recorded on the appropriate Tumor Assessment eCRF.

Limited, symptom-directed physical examinations should be performed at specified post baseline visits and as clinically indicated. Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment [lymph nodes, liver, and spleen]). Limited physical exam should also monitor for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated *or supine* position, and temperature. Weight, height, and BSA will also be recorded. Height and BSA are required at screening only, unless there has been $>$10% change in body weight since the last BSA assessment, in which case BSA should be recalculated and documented in the eCRF.

4.5.5 Assessment of the International Prognostic Index

The IPI is a clinician-assessed tool that is prognostic of OS in patients with NHL (International Non-Hodgkin's Lymphoma Prognostic Factors 1993) (Section 1.1.3). The instrument is based on measurements of five clinical factors, including age, serum LDH level, ECOG performance status, cancer stage, and extra-nodal site involvement.

The method for assessing IPI is described in Appendix 9.

4.5.6 Assessment of Eastern Cooperative Oncology Group Performance Status

The ECOG performance status is a clinician-assessed tool that describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.) (ECOG-ACRIN Cancer Research Group 2018).

The method for assessing ECOG performance status is described in Appendix 8.

4.5.7 Assessment of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale

The FACT/GOG-NTX-12 is a 12-item patient-reported outcome instrument that was designed to measure chemotherapy-induced PN (Kopec et al. 2006). Individual items on the subscale assess sensory neuropathy, motor neuropathy, hearing neuropathy, and dysfunction associated with neuropathy; in addition, there is one item specific to oxaliplatin. The FACT/GOG-NTX-12 takes approximately 5 minutes to complete.

The FACT/GOG-NTX-12 is provided in Appendix 10.

4.5.8 Tumor and Response Evaluations

Response will be assessed by the investigator and, for CR and ORR in Stage 2, by an Independent Review Committee on the basis of physical examinations and PET-CT scans using Lugano Response Criteria (Cheson et al. 2014) (Appendix 5). Scans will be carried out as follows (see also Appendix 1 and Appendix 2):

- Screening: PET-CT scan
- Mid-Treatment: PET-CT scan or CT scan
  - Completed between Cycle 4, Day 15 and Cycle 5, Day 1
- End of Treatment: PET-CT scan
- Long-Term Follow-up: CT scans *or PET-CT (if indicated)*
  - Completed every 6 months until progression or the end of the study, whichever comes first

All primary imaging data used for tumor assessments until end of treatment will be collected by the Sponsor to enable centralized, independent review of response endpoints by an IRC; IRC assessments of CR and ORR in Stage 2 are mandated in this study (see Section 2).

Positron emission tomography–computed tomography scans should include skull-base to mid-thigh. Full-body PET-CT scan should be performed when clinically appropriate. Image enhancement systems (such as GE Healthcare's Q.Clear or similar) must not be used.

Computed tomography scans with IV contrast should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. Computed tomography scans for response assessment may be limited to areas of prior involvement only if required by local regulatory authorities. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

In patients for whom contrast is contraindicated, (e.g., patients with contrast allergy or impaired renal clearance), CT or combined PET-CT scans without contrast*, or MRI*

scans are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period.

Positron emission tomography scans, in conjunction with diagnostic-quality CT scans, will be obtained in this study at the times indicated in the Schedule of Activities (Appendix 1 and Appendix 2). Computed tomography scans without PET scans will also be obtained at the times indicated in the Schedule of Activities (Appendix 1 and Appendix 2). Lugano Response Criteria (Appendix 5) will be used to assess overall response to study treatment.

The same CT/MRI assessment modality should be used for all response evaluations to ensure consistency across different timepoints (Note: PET-CT is mandatory at the screening and end-of-treatment assessments).

A full tumor assessment including radiographic assessment must be performed any time disease progression or relapse is suspected.

Patients with a response of PR or CR for whom subsequent therapy is indicated (e.g., CAR-T therapy or autologous stem cell transplantation) will continue on study and remain evaluable.

Bone marrow biopsies: As noted in guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology, focal uptake of FDG into bone marrow during PET-CT is more sensitive than bone marrow biopsy for assessing infiltration in DLBCL and is highly specific. Thus, bone marrow biopsies are not mandated in this study. However, bone marrow biopsies *prior to treatment* should be mandatory for transformed DLBCL patients to check for occult bone marrow involvement by follicular lymphoma, which may not show on PET-CT. Moreover, at the discretion of the investigator, bone marrow biopsies may be conducted in patients with negative bone signal on PET-CT if he or she feels the results could change prognosis and treatment.

If bone marrow biopsies are conducted, the results will be collected on the eCRF.

4.5.9 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Serum or plasma chemistry: sodium, potassium, chloride, bicarbonate (or CO_2), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and (if available) direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and LDH
- Coagulation: INR or PT, and PTT or aPTT

- Viral serology:
  - HIV

    For patients with unknown HIV status, HIV testing will be performed at Screening if required by local regulations.
  - Hepatitis B surface antibody, HBsAg, and total HBcAb
  - HBV-DNA by PCR if the patient is HBcAb positive
  - HCV antibody
  - HCV RNA by PCR if the patient is HCV antibody positive
- Pregnancy test
  - All women of childbearing potential will have a serum pregnancy test at screening. Monthly pregnancy testing should be performed for medicinal products (IMPs or protocol-mandated NIMPs) that are genotoxic or have demonstrated or suspected teratogenicity.

The following samples will be sent to the Sponsor or a designee for analysis:

- Stage 1 and Stage 2 in Pola-R-GemOx Patients:
  - PK blood samples

    Blood samples for PK analysis of polatuzumab vedotin: Serum polatuzumab vedotin total antibody (which includes all drug-to-antibody ratio [DAR] species, including DAR 0 and DAR $\geq$1), plasma polatuzumab vedotin conjugate (evaluated as antibody-conjugated MMAE), and plasma unconjugated MMAE concentrations will be quantified with the use of validated methods. At the discretion of the Sponsor, these samples may also be analyzed for other potential catabolites, if considered necessary.

    Depending on the ongoing assessment of study data, the frequency of polatuzumab vedotin PK sampling may be halted or reduced later in the study. Pharmacokinetic samples may be used for additional exploratory biomarker analyses.
  - ADA blood samples

    Serum samples for anti-polatuzumab vedotin antibody: A validated antibody-bridging ELISA will be used to screen for and confirm the presence of anti-polatuzumab vedotin antibodies in patient samples, as well as to characterize and determine the titer of confirmed ADA-positive samples.

    Depending on the ongoing assessment of study data, the frequency of polatuzumab vedotin ADA sampling may be halted or reduced later in the study.

- Stage 2 ONLY:
  - Exploratory biomarker research may include, but will not be limited to, analysis of protein expression, analysis of genes or gene signatures, analysis of circulating tumor DNA, analysis of circulating lymphocytes. Research may involve extraction of DNA, ctDNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. Next-generation sequencing methods may include whole genome sequencing (WGS) or whole exome sequencing (WES) of tissue. DNA extracted from blood may be used to identify somatic variants by distinguishing germline variants from somatic variants. Analysis will be focused on genome variations that are not inherited.
  - Mandatory, newly-collected $DLBCL$ tumor tissue sample at baseline (or archival sample if fresh sample not available) and blood and plasma samples for biomarker research (see Appendix 3)

    Analysis of biomarker testing on $DLBCL$ tumor tissue and plasma samples will be performed at central laboratories.

    Exploratory biomarker research may include but will not be limited to the biomarkers listed in Table 12 . Results from biomarker research will not be shared with investigators or study participants unless required by law, given the complexity and exploratory nature of these analyses.

    Biological samples, if not used up, will be destroyed within 5 years after the final clinical study report has been completed.

    For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination. Availability of archival or freshly biopsied $DLBCL$ tumor tissue samples should be confirmed at screening. If the patient has had anti-lymphoma treatment between the time of the prior biopsy and the time of study treatment initiation, a core-needle biopsy is recommended, if feasible and safe by investigator judgment. Formalin-fixed paraffin-embedded tissue blocks are preferred over slides. If a tissue block is not available, a minimum of $10–15\ slides\ (15\ preferred,$ or in accordance with local regulatory requirements) serial, freshly cut, unstained slides is acceptable.

    If archival tissue is unavailable or unacceptable according to above criteria, a pretreatment core needle, excisional, or incisional tumor biopsy is required if feasible and safe by investigator judgment. Cytological or fine-needle aspiration samples are not acceptable.

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

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions: screening $DLBCL$ tumor tissue, plasma and/or serum samples collected for PK, ADA, and biomarker analyses may be needed for assay development, validation, additional characterization (such as neutralizing antibody analysis) and additional safety and immunogenicity assessments, as appropriate; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

4.5.10 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the Schedule of Activities (see Appendix 1 and Appendix 2) and as clinically indicated.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Caution should be exercised in the administration of oxaliplatin in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia. The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. In case of QT prolongation, oxaliplatin treatment should be discontinued, as per the SmPC.

4.5.11 Clinical Outcome Assessment

Patient-reported outcome PRO instruments will be completed to assess the treatment benefit and more fully characterize the safety profile of polatuzumab vedotin. In addition, PRO instruments will enable the capture of each patient's direct experience with polatuzumab vedotin.

PRO data will be collected through use of the following instruments: FACT/GOG-NTX-12, EQ-5D-5L, EORTC QLQ-C30, and FACT/Lym. Details about these instruments are provided in Section 4.5.11.2.

The questionnaires, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient receives any information on disease status, prior to the

performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

4.5.11.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1) and at home every second month during the long term follow up. At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in preprinted booklets to enable the instrument to be administered at each specified timepoint.

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

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be approximately 30 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

During the follow up period, PRO questionnaires may be completed at home and returned to the clinic. Patients should be given the following instructions for completing PRO instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.

- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.11.2 Description of Clinical Outcome Assessments Instruments

The FACT/GOG-NTX-12 (Appendix 10) is a 12-item patient-reported outcome instrument that was designed to measure chemotherapy-induced PN (Kopec et al. 2006). Individual items on the subscale assess sensory neuropathy, motor neuropathy, hearing neuropathy, and dysfunction associated with neuropathy; in addition, there is one item specific to oxaliplatin. The FACT/GOG-NTX-12 takes approximately 5 minutes to complete.

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (Appendix12). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 5 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (Appendix 13). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The EORTC QLQ C30 module takes approximately 10 minutes to complete.

The FACT-Lym is a validated HRQoL instrument used specifically in patients with lymphoma. It is composed of the 27-item FACT-G, which measures health-related quality of life in patients undergoing any type of cancer therapy, plus the 15-item Lymphoma-Specific Subscale (FACT-Lym LYMS; range 0–60), which assesses the HRQoL impacts of more lymphoma-specific symptoms (Cella et al. 1993; Cella et al. 2005) (Appendix 11). Functional Assessment of Cancer Therapy–General Questionnaire items are divided into four primary HRQoL domains: physical well-being (PWB; seven items; range, 0–28), social/family wellbeing (SWB; seven items; range, 0–28), emotional well-being (EWB; six items; range, 0–24), and functional well-being (FWB; seven items; range, 0–28). The FACT-Lym LYMS consists of common lymphoma disease and/or treatment-related symptoms (e.g., pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue, and loss of appetite). Three summary scales: FACT-Lym trial outcome index (FACT-Lym TOI; range, 0–116; composed of the PWB, FWB, and FACT-Lym LYMS scales); FACT-G (range, 0–108; composed of the

PWB, FWB, SWB, and EWB), and the FACT-Lym total score (FACT-Lym TOT, range, 0–168; composed of all of the scales) can also be calculated. Higher scores are reflective of better HRQoL. Each item of the FACT-Lym is answered using a 5-point Likert scale ranging from 0 = "not at all" to 4 = "very much". The FACT-Lym takes approximate 5–10 minutes to complete.

Clinically meaningful minimally important differences (i.e., the smallest amount of change considered important to patients) at the individual subscale and FACT-Lym TOT level are prespecified and will be used to define the proportion of patients reporting meaningful changes on the FACT-Lym LYMS (≥3 points), FACT-Lym TOI (≥6 points), and FACT-Lym TOT (≥7 points) as a result of treatment (Carter et al. 2008).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Grade 4 IRR
  - The patient should be withdrawn from study treatment immediately and polatuzumab vedotin, rituximab, gemcitabine, and oxaliplatin treatment should be permanently discontinued.
- Recurrence of Grade 3 IRR at rechallenge
- Infusion-related Grade ≥3 wheezing, hypoxia, or generalized urticaria
- Grade ≥3 hematological toxicity that does not resolve to Grade ≤2 or baseline value within ≤14 days after last dose and that has a reasonable possibility of being related to the administration of any of the study drugs for both arms following the recommended dose reduction (Table 14)
- Multiple recurrences of Grade 4 neutropenia with infection despite G-CSF support, at clinician's discretion
- Grade 4 *PN*
- *Discontinue polatuzumab vedotin and oxaliplatin if patient develops Grade ≥2 PN that does not improve* to Grade ≤1 by Day 15 after the scheduled date for next cycle *(Table 1)*
- *Discontinue polatuzumab vedotin if patient previously had Grade 2 PN that resulted in dose reduction of polatuzumab vedotin or oxaliplatin and Grade ≥2 PN* recurs and improves to Grade ≤*1 within 14 days after scheduled date of next cycle (Table 1)*
- *Discontinue oxaliplatin if patient previously had a dose reduction of oxaliplatin and a discontinuation of polatuzumab vedotin and Grade ≥2 PN recurs (Table 1)*

- *Discontinue all study treatment if patient previously had Grade 3 PN and Grade ≥ 2 PN recurs (Table 1)*
- Disease progression
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. During Stage 2, patients who discontinue study treatment prematurely will not be replaced.

*All p*atients will return to the clinic for an End of Treatment/Discontinuation Visit 28 days after the last dose of study drug (see Appendix 1 and Appendix 2 for additional details). After treatment discontinuation, information on survival follow-up *and* new anti-cancer therapy will be collected *via* clinic visits*, telephone calls, and/or patient medical records* approximately every 2 months until the end of the study (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.2 Patient Discontinuation from Study

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

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
    - Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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

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

At least three documented attempts to contact a patient is required before considering a patient lost to follow up. Of these three attempts two should involve calls to the patient or

the patients' primary care provider at different times of the day and one should include written communication to the patients' home address.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with polatuzumab vedotin in completed and ongoing studies. The anticipated important safety risks for polatuzumab vedotin are outlined below in Section 5.1.1.1. Please refer to the Polatuzumab Vedotin Investigator's Brochure for a complete summary of safety information.

Please refer to the Rituximab Investigator's Brochure for a complete summary of safety information for rituximab. Please refer to the gemcitabine SmPC and the oxaliplatin SmPC for complete summaries of safety information for gemcitabine and oxaliplatin.

Finally, a potentially important safety risk (thrombocytopenia) for Pola-R-GemOx and R-GemOx combination therapy is outlined below in Section 5.1.1.4.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. A safety run-in will assess PN risk of Pola-R-GemOx combination therapy prior to randomization to the two study treatments. Patients will undergo safety

monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Study Treatment

5.1.1.1 Risks Associated with Polatuzumab Vedotin

The clinical safety profile of polatuzumab vedotin is based on clinical data obtained in ongoing and completed studies. On the basis of clinical data to date, the risks are described below. Guidelines for management of these risks through dose and schedule modifications are described in Table 14 of Section 5.1.2.3 (Management Guidelines). See the Polatuzumab Vedotin Investigator's Brochure for full information on the risks associated with polatuzumab vedotin.

Peripheral Neuropathy *(Sensory and/or Motor)*

Patients receiving polatuzumab vedotin may develop PN, including peripheral sensory and/or motor neuropathy. These events have generally been reversible to varying degrees, but it is not known if full reversibility can be expected or predicted. Patients in clinical trials with polatuzumab vedotin should be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain. Patients experiencing new or worsening PN may require a dose delay, dose reduction, or discontinuation of treatment and should be managed according to the protocol. Monitoring will include the use of the NCI CTCAE v5.0 and the FACT/GOG-NTX-12 (Appendix 10).

Study treatment dose and schedule modifications for PN are described in Section 5.1.2.

Myelosuppression: Consolidation of Neutropenia (Including Febrile Neutropenia), Thrombocytopenia, and Anemia

Neutropenia and neutropenia-associated events (e.g., febrile neutropenia, thrombocytopenia, and anemia, including serious and severe cases) have generally been reversible but in some cases have resulted in protocol-mandated dose reductions and/or delays. Adequate hematologic function, including RBCs and platelets, should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Study treatment for hematologic toxicities may be delayed or modified as described in Section 5.1.2. The use of G-CSF for neutropenia is described in Section 5.1.2.3 (Table 14). G-CSF primary prophylaxis is required for neutropenia. The decision not to administer G-CSF as primary prophylaxis should be *discussed* with the Medical Monitor. Transfusion support for anemia and thrombocytopenia is permitted at the discretion of the investigator.

Infections

Patients receiving polatuzumab vedotin may be at a higher risk of developing infections. Serious infections, including opportunistic infections, such as pneumonia (including pneumocystis jirovecii and other fungal pneumonia), bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with polatuzumab vedotin. Several other risk factors in the patient population under study influencing patients' vulnerability to a higher risk of infections, particularly serious and opportunistic infection, include predisposition of the indication disease to infections, elderly population, and comorbidity. The use of anti-infective prophylaxis is required for patients on study and is described in Section 4.4.1.4.

Reports in the literature indicate that granulocytopenia is a major predisposing factor to infections in patients with B-cell lymphoma (Bishop et al. 1981). The reported incidence of infection in chemotherapy courses for B-cell lymphoma associated with <500 granulocytes/μL was higher than those with ≥ 500 granulocytes/μL.

Infusion-Related Events

Infusion-related events have been reported in patients receiving polatuzumab vedotin. Commonly experienced events included nausea, vomiting, chills, fever, pruritus, hypotension, flushing, and other symptoms. In the majority of the patients, the events were Grade 1–2.

All patients will be monitored for infusion reactions during the infusions and immediately afterwards (for additional instructions on the monitoring and management of infusion reactions, see Section 5.1.2). Recommended management of suspected anaphylactic reactions during study drug infusions is provided in Appendix 7. For premedication guidance for polatuzumab vedotin infusion, see to Section 4.3.2.1.

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

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

Progressive Multifocal Leukoencephalopathy

One case of progressive multifocal leukoencephalopathy (PML) has been reported with polatuzumab vedotin treatment. Patients should be monitored closely for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. Polatuzumab vedotin and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumor Lysis Syndrome

Tumor lysis syndrome is a risk if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, tumor lysis prophylaxis measures will be taken. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 109$/L or bulky lymphadenopathy) and who are considered to be at risk for tumor lysis by the investigator will receive tumor lysis prophylaxis (e.g., allopurinol ≥ 300 mg/day orally or a suitable alternative treatment [according to institutional practice] starting 12–24 hours before study treatment) and must be well hydrated before the initiation of study treatment at Cycle 1 Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion, as deemed appropriate by the investigator.

Immunogenicity *(Anti-Drug Antibodies)*

As with any recombinant antibody, polatuzumab vedotin may elicit an immune response, and patients may develop antibodies against it. Patients will be closely monitored for any potential immune response to polatuzumab vedotin.

Appropriate screening, confirmatory, and characterization assays will be employed to assess ADAs before, during, and after the treatment with polatuzumab vedotin. Given the historically low immunogenicity rate of rituximab in patients with NHL, ADAs against rituximab will not be monitored in this study.

Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of polatuzumab vedotin given the mechanism of action of MMAE. Standard exclusion criteria are used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods. Given the possibility of irreversible infertility with polatuzumab vedotin, advice should be provided to patients regarding the option of cryopreservation of sperm prior to the start of study treatment.

Hyperglycemia

Hyperglycemia has been observed in patients treated with polatuzumab vedotin and with other ADCs that use the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of standard-of-care antihyperglycemic medications.

Hepatotoxicity

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

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

Carcinogenicity

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

5.1.1.2 Risks Associated with Rituximab

See the *current* Rituximab Investigator's Brochure for full information on the risks associated with rituximab.

For rituximab dose delay and discontinuation instructions, see Table 1.

5.1.1.3 Risks Associated with Gemcitabine *and Oxaliplatin*

See the *Package Insert/SmPC* for gemcitabine *and oxaliplatin* for full information.

For gemcitabine and oxaliplatin dose delay, modification, and discontinuation instructions, see Table 1.

5.1.1.4 Risks Associated with Pola-R-GemOx and R-GemOx Combination Therapy

Pola-R-GemOx and R-GemOx may have the potential to lead to severe thrombocytopenia due to the cumulative hematologic toxicities of component agents. Patients treated with concomitant anticoagulants may therefore be at a greater risk for bleeding.

Treating physicians should consider switching patients already on oral anticoagulation to LMWH prior to Cycle 1 Day 1, if possible. Decisions on treatment and dose of anticoagulants and anti-platelet agents in patients with severe thrombocytopenia (< 50 g/L) should be made on a case-by-case basis. More frequent monitoring of the complete blood count (CBC) or platelet transfusions may be required at the discretion of the treating physician.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

Patients should be assessed clinically for toxicity before each dose of study treatment (Pola-R-GemOx or R-GemOx) using NCI CTCAE v5.0, unless otherwise stated. Dose modifications should be based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment

administration. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable. Dose modifications due to adverse events not specified in this protocol should proceed on the principle of maintaining a dose intensity of 100%. The determination of all dose modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment. All decisions regarding dose delays, modifications, and discontinuations may be discussed with the Medical Monitor if desired.

Polatuzumab vedotin

Polatuzumab vedotin doses may be reduced per the guidelines in Table 14 .

Peripheral neuropathy is consistent with the mechanism of action of antibody-conjugated MMAE and was frequently reported across all polatuzumab vedotin regimens. Cumulative toxicity was observed as the incidence and severity of PN events increased when polatuzumab vedotin was dosed beyond 6 cycles or dosed higher than 1.8 mg/kg. When polatuzumab vedotin was administered up to 6 cycles in the regimen of pola + BR, PN events were almost entirely Grade 1–2 in severity, with most events reaching only Grade 1 in peak severity. Peripheral neuropathy events were effectively managed with dose delay/interruption and dose reductions of polatuzumab vedotin if necessary with few treatment discontinuations from refractory PN observed.

A guidance for the management of PN is described in Section 5.1.2.3 (Table 14).

Rituximab

No dose modifications of rituximab (375 mg/m^2) are allowed.

Gemcitabine

Gemcitabine may be reduced per the guidelines in Table 14.

Oxaliplatin

Oxaliplatin may be reduced per the guidelines in Table 14.

5.1.2.2 Dose Delays/Treatment Interruption

Patients should be assessed clinically for toxicity before each dose of study treatment (Pola-R-GemOx or R-GemOx) using NCI CTCAE v5.0, unless otherwise stated. Dose delays/treatment interruptions should be based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

Dose delays or treatment interruption will occur according to the guidance in Table 14 . *Toxicity that leads to a delay of >14 days in the initiation of the next planned treatment cycle should require study treatment discontinuation unless the investigator assesses an ongoing clinical benefit with continuing study treatment (may discuss with*

the Medical Monitor). Study treatment may continue with the remaining study drugs in the event that one or more study drugs are discontinued.

5.1.2.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 14 . Additional guidelines are provided in the subsections below. Note: Lymphopenia is not considered to be a hematologic toxicity, as it is an expected outcome of therapy.

Table 14 Guidelines for Management of Patients Who Experience Adverse Events

Event(s) [a]	Dose Delay or Modification
Grade 3 or 4 neutropenia	• Hold all study treatment until ANC recovers to > 1000/μL • Administer growth factors, if necessary, per the recommendations in Appendix 6 • If ANC recovers to > 1000/μL on or before Day 7, resume all study treatment without any additional dose reductions • If ANC recovers to > 1000/μL after Day 7: – Restart all study treatment, with dose reduction of gemcitabine to 750 mg/m^2 for current and subsequent cycles – If gemcitabine dose reduction has already occurred, then consider dose reduction of polatuzumab vedotin to 1.4 mg/kg for current and subsequent cycles – If both gemcitabine and polatuzumab vedotin have already been dose reduced, then discontinue all study treatment
Grade 3 or 4 thrombocytopenia	• Hold all study treatment until platelets recover to > 75,000/μL • If platelets recover to > 75,000/μL on or before Day 7, resume all study treatment without any additional dose reductions • If platelets recover to > 75,000/μL after Day 7: – Restart all study treatment, with dose reduction of gemcitabine to 750 mg/m^2 for current and subsequent cycles – If gemcitabine dose reduction has already occurred, then consider dose reduction of polatuzumab vedotin to 1.4 mg/kg for current and subsequent cycles • If both gemcitabine and polatuzumab vedotin have already been dose reduced, then discontinue all study treatment

Table 14 Guidelines for Management of Patients Who Experience Adverse Events, contd.

Event(s) [a]	Dose Delay or Modification
Grade 2 or 3 PN	• Delay all study treatment until improvement to Grade ≤ 1 • If recovered to Grade ≤ 1 within ≤ 14 days *after the scheduled date of the next cycle:* – Restart study treatment with polatuzumab vedotin at a permanently reduced dose of 1.4 mg/kg and oxaliplatin at a dose of 75 mg/m^2 – If a prior dose reduction to 1.4 mg/kg for polatuzumab vedotin or 75 mg/m^2 for oxaliplatin has occurred, discontinue polatuzumab vedotin alone if the patient previously had Grade 2 PN. • If not recovered to Grade ≤ 1 *by Day 15 after* the scheduled date for the next cycle, oxaliplatin and polatuzumab vedotin must be permanently discontinued • If the patient previously had Grade 3 PN, discontinue all study treatment. • *If oxaliplatin has been dose reduced and polatuzumab vedotin has been discontinued previously, discontinue oxaliplatin*
Grade 4 PN (including its signs and symptoms)	• Discontinue all study treatment
Pharyngolaryngeal dysesthesia	• Prolong oxaliplatin infusion to 6 hours
Total bilirubin > 3.0 mg/dL	• Delay all treatment until resolution to ≤1.5 mg/dL within ≤ 14 days. Evaluate for causality. • Any case involving an increase in hepatic transaminase > 3 × baseline AND an increase in direct bilirubin > 2 × ULN, WITHOUT any findings of cholestasis or jaundice or signs of hepatic dysfunction AND in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential DILI, and all study treatment should be discontinued
Grade 3 or 4 tumor lysis syndrome	• Hold all study treatment. The patient's next dose may be delayed for up to 14 days. • Following complete resolution of TLS, study treatment may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy.

Table 14 Guidelines for Management of Patients Who Experience Adverse Events, contd.

Event(s) [a]	Dose Delay or Modification
QT-interval prolongation	• If the QTcF interval increases by > 500 msec, or if it increases by > 60 msec from baseline, oxaliplatin should be discontinued.
Grade 3 or 4 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	• Delay study treatment for a maximum of 14 days • If improvement to Grade ≤ 1 or baseline, continue study therapy at full dose, or dose reduce at the discretion of the investigator per site's standard and may be discussed with the Medical Monitor
Grade 2 non-hematologic toxicity	• *Consider d*elay*ing* study treatment for a maximum of 14 days • If improvement to Grade ≤ 1 or baseline, *continue study therapy at full dose, or reduce dose at the discretion of the investigator per site's standard and may be discussed with the Medical Monitor*
Grade 1 non-hematologic toxicity	• No dose reduction or delay
Hepatitis B reactivation (as noted by new detectable HBV-DNA levels)	• HBV-DNA levels between WHO-recommended range of 29 and 100 IU/mL: Re-test within 2 weeks. If still positive, hold all study treatment and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. • HBV-DNA levels at WHO-recommended cutoff of > 100 IU/mL: hold all study treatment and treat the patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. • Rising HBV-DNA viral load (exceeding 100 IU/mL) while on an appropriate anti-viral therapy: discontinue all study treatment immediately.

DILI = drug-induced liver injury; HBV = hepatitis B virus; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PN = peripheral neuropathy; QTcF = QT interval corrected through use of Fridericia's formula TLS = tumor lysis syndrome; ULN = upper limit of normal.

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

Note: All decisions regarding dose delays, modifications, and discontinuations may be discussed with the Medical Monitor if desired.

[a] All based on laboratory test results obtained within 72 hours before infusion of Day 1 of that cycle.

Table 15 Management of Infusion-Related Symptoms: Rituximab and Polatuzumab Vedotin

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

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

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

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

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.3.5.13.

5.2.1 Adverse Events

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v5.0; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- PN Grade $\geq$ 3
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Tumor lysis syndrome of any grade (irrespective of causality)
- Progressive multifocal leukoencephalopathy
- Systemic hypersensitivity reactions/anaphylactic and anaphylactoid reactions, as defined by Sampson's criteria (see Appendix 14)

- Second malignancies

Real time safety monitoring will be employed throughout the trial.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.3.5.13–5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

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

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 16 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE v5.0.

Table 16 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE v5.0

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 17):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 17 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the

Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of DLBCL should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The IMC in Stage 1 or iDMC in Stage 2 will monitor the frequency of deaths from all causes.

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

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Diffuse Large B-Cell Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Lugano 2014 response criteria (see Appendix 5) (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.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

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

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

  The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations *and* adverse events associated with a special situation*s are to be reported* separately on the Adverse Event eCRF *as outlined in the sections below.*

Reporting Special Situations

In addition, all special situations associated with polatuzumab vedotin and rituximab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the *drug name and "accidental overdose" as the* event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the *name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the* event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the *drug name and "accidental overdose" as the event term*. Check the "Accidental overdose" and "Medication error" boxes. *Enter a description of the error in the additional case details.*
- *Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.*

Reporting Adverse Events Associated with Special Situations

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 learning of the event; see Section 5.4.2). For polatuzumab vedotin and rituximab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the *adverse event term*. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the *adverse event term*. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the *adverse event term*. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require *two entries on* the Adverse Event eCRF pages, one *entry* to report the accidental overdose *(special situation)* and one *entry* to report the *adverse event (*headache*)*. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Accidental overdoses or medication errors (see Section 5.3.5.12 for details on reporting requirements)

*For serious adverse events and adverse events of special interest, t*he investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board/Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

To ensure the safety of study *participants*, *access to the Medical Monitors is available 24 hours per day, 7 days per week. A*n Emergency Medical Call Center will *also be available 24 hours per day, 7 days per week. T*he *Emergency* Medical *Call Center will connect the investigator with an Emergency Medical Contact*, provide medical translation service if necessary, and track all calls. *Contact information, including t*oll-free numbers for the *Emergency Medical Call Center*, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial 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.

5.4.2.2 Events That Occur after Study Drug Initiation

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

In the event that the EDC system is unavailable, the paper Clinical Trial 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. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 1 year after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drug. 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 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 becomes available.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the last dose of study drug or the initiation of NALT), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

All patients with AEs of PN should be followed up after discontinuation of study treatment for possible deterioration (Coasting phenomenon) and thereafter until resolution or stabilization.

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

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

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

Drug	Document
Polatuzumab vedotin	Polatuzumab Vedotin Investigator's Brochure
Rituximab	Rituximab Investigator’s Brochure
Gemcitabine	Gemcitabine $U.K.$ Summary of Product Characteristics
Oxaliplatin	Oxaliplatin $U.K.$ Summary of Product Characteristics

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.

The sponsor will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase III, multicenter, open-label, randomized controlled trial designed to evaluate safety and efficacy of polatuzumab vedotin administered by IV infusion in combination with rituximab, gemcitabine, and oxaliplatin in patients with relapsed or refractory DLBCL.

The analysis populations are defined as follows:

- ITT population: all randomized patients, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received
- Safety run-in population: patients who received any amount of any study drug during safety run-in phase
- Safety population: patients who received any amount of any study drug during the randomized part
- PRO-evaluable population: PRO-evaluable population will include all randomized patients who have a baseline and at least 1 post-baseline assessment. All PRO analyses will be performed based on the treatment arm assigned at randomization.
- Pharmacokinetic-Evaluable Population: The PK population includes all patients who have received at least one dose of polatuzumab vedotin and have at least one post-dose polatuzumab vedotin concentration result.

For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization. For all safety analyses, patients will be grouped according to the treatment actually received.

Hypothesis tests will be two-sided, unless otherwise indicated. The type I error (α) for this study is 0.05 (two-sided).

Further details of the analyses will be provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective of the randomized part of this study is to evaluate the efficacy of Pola-R-GemOx versus R-GemOx in patients with relapsed or refractory DLBCL as

measured by OS. Assuming a median OS of [redacted] months in the R-GemOx arm and a randomization ratio of 1:1, [redacted] events are required to detect a between-group difference of [redacted] months in the median OS (HR=[redacted]) with [redacted] power and a 2-sided α of [redacted]. Based on the above statistical assumptions, and anticipating a recruitment period of approximately 19 months and a follow-up of 12 months after the last patient was randomized, a total of approximately 250 patients will be randomized, taking into account an estimated drop-out rate of [redacted].

In addition, approximately 10 patients will be enrolled in the safety run-in stage.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and discontinuation from the study will be summarized by treatment arm for all randomized patients. The reasons for study discontinuation will be tabulated.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics (in particular, stratification variables) will be summarized by treatment arm for all randomized patients. Continuous variables will be summarized with use of means, standard deviations, medians, ranges, and inter-quartile ranges. Categorical variables will be summarized by proportions.

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for the randomized part of this study is to evaluate the efficacy of Pola-R-GemOx compared with R-GemOx in patients with relapsed or refractory DLBCL on the basis of the following endpoint:

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

The primary efficacy analysis will be completed on the ITT population, with patients grouped according to their treatment assigned at randomization.

Data for patients without death will be censored at the date at which the patient was last known to be alive. Otherwise, data will be censored at the date of randomization.

Kaplan-Meier methodology will be used to estimate the OS for each treatment arm, and Kaplan-Meier curves will be produced. Overall survival will be compared between treatment arms by stratified logrank test. The hazard ratio (HR) for death will be estimated using a stratified Cox proportional hazards model; the stratification factors will be the same as the randomization stratification factors by IxRS. The 95% confidence

interval (CI) for the HR will be provided. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

The type I error (α) for this study is 0.05 (two-sided). Further details will be included in the SAP.

In case patients become eligible for HSCT and undergo a transplant (in their best interest), sensitivity analyses will be performed for OS and PFS to assess the impact this may have. For this, patient data will be censored at the time of transplant.

6.4.2 Secondary Efficacy Endpoints

The following sections detail the analysis planned for the secondary endpoints of the randomized part of the study. Similar analyses will be performed for the safety run-in phase, but will be restricted to descriptive statistics.

To control the overall type I error rate at a two-sided 0.05 level of significance, a hierarchical testing procedure will be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. Key secondary endpoints will be tested in the following order:

- PFS
- CRR at end of treatment (based on response including PET-CT data) as determined by an IRC
- ORR at end of treatment (based on response including PET-CT data) as determined by an IRC

A given hypothesis in the bulleted list above will only be rejected once all previous hypotheses have been rejected at a 2-sided 0.05 level of significance.

No multiplicity adjustment will be performed for the testing of other endpoints and should be interpreted with caution.

6.4.2.1 Complete Response Rate

Complete response rate is defined as the proportion of patients who had a complete metabolic response (based on response including PET-CT data) according to Lugano 2014 response criteria (Appendix 5) at the end of treatment, as determined by IRC. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

Complete response rate will be analyzed using the intent-to-treat population.

An estimate of CRR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method. The difference in CRR between treatment arms will be calculated, and its 95% CI will be calculated using the normal

approximation to the binomial distribution. CRR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint OS.

The same analysis will be repeated for the CRR using the response not including PET data, and therefore considering patients who had complete response instead of complete metabolic response, as determined by the investigator and IRC.

6.4.2.2 Objective Response Rate

An objective response is defined as either a complete or partial metabolic responses (based on response including PET-CT data) according to Lugano 2014 response criteria at end of treatment, as determined by IRC. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

Objective response rate is defined as the proportion of patients who had an objective response.

Objective response rate will be analyzed using the intent-to-treat population.

An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution. Objective response rate will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint OS.

The same analysis will be repeated for the ORR using the response not including PET data, objective response (based on response not including PET data) being then defined as either a complete or partial response (based on response not including PET data) at end of treatment, as determined by the investigator and IRC.

6.4.2.3 Best Overall Response

Best overall response (BOR) is defined as the best response while on study (based on response including PET-CT or CT data) according to Lugano 2014 response criteria (Appendix 5), as determined by investigator.

Best overall response will be analyzed using the ITT population.

An estimate of BOR rates will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method.

6.4.2.4 Progression-Free Survival

Progression-free survival will be defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator, or death due to any cause, whichever occurs first. Patients who die without a reported disease progression will be considered as an event on the date of death. Patients who have neither progressed nor died at the time of analysis (clinical-cut off) and patients who are lost to follow-up will be censored on the date of the last evaluable tumor assessment. Patients who did not undergo a post-baseline tumor assessment will be censored at the time of randomization. Kaplan-Meier estimates and the associated 95% CIs of the median, 25th and 75th percentile will be presented. The Kaplan-Meier curve will provide a visual description of the differences across treatment arms. Estimates of the treatment effect will be expressed as hazard ratios, using a stratified Cox proportional-hazards analysis including 95% confidence limits.

6.4.2.5 Duration of Response

Duration of response (DOR) will be assessed in patients who had an objective response, as determined by the investigator, using Lugano 2014 response criteria (Appendix 5). Duration of response is defined as the time interval from the date of the first occurrence of a complete or partial response (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response. Duration of response is based on a non-randomized subset of patients (specifically, patients who achieved an objective response), therefore, comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis, except that the analysis will not be stratified.

6.4.2.6 Event-Free Survival

Event free survival (EFS_{eff}) is defined as the time from randomization to first to the earliest occurrence of the below cases:

- Disease progression or relapse
- Death due to any cause
- Initiation of any NALT

Patients with no EFS_{eff} events will be censored at the time of the last evaluable tumor assessment. Patients who did not undergo a post-baseline tumor assessment will be censored at the time of randomization. The methodologies detailed for the PFS analysis will be used for the EFS_{eff} analysis.

6.4.2.7 Patient-Reported Outcomes

The PRO-evaluable population will be used for descriptive analyses of visit summary and change from baseline, responder analyses, and mixed-effects model repeated measures (MMRM) modeling, unless specified otherwise. ITT population will be used for completion analyses and time-to-deterioration analyses.

EORTC QLQ-C30

For EORTC QLQ-C30 questionnaire, summary statistics at each visit and change from baseline of linear-transformed scores will be reported for all the items and the subscales.

Time to deterioration is defined as the time from randomization to the first documentation of a 10-point decrease in EORTC QLQ-C30 physical functioning scale from baseline. For fatigue, time to deterioration is defined as the time from randomization to the first documentation of a 10-point increase from baseline. Patients who do not have an observed deterioration at the time of clinical data cut-off will be censored i) at the last non-missing assessment date if post-baseline assessment ii) on the date of randomization if no post-baseline assessment. The hazard ratio for time to deterioration will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. Kaplan-Meier methodology will be used to estimate the time to deterioration for each treatment arm, and Kaplan-Meier curves will be produced. Median and 95% CI will be estimated.

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers 2001). Missing data will be assessed and reported by time point. In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale will be considered as missing. Completion rates will be summarized by number and proportion of patients among those expected to complete the EORTC QLQ-C30 at each timepoint.

FACT-Lym Subscale

For each of the FACT-Lym questionnaire scales, descriptive statistics at each visit and changes from baseline will be reported by treatment arm.

Time to deterioration is defined as the time from randomization to the first documentation of a >3-point decrease from baseline (Carter et al. 2008; Hlubocky et al. 2013). Patients who do not have an observed deterioration at the time of clinical data cut-off will be censored i) at the last non-missing assessment date if post-baseline assessment ii) on the date of randomization if no post-baseline assessment. The hazard ratio for time to deterioration will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. Kaplan-Meier methodology will be used to estimate the time to deterioration for each treatment arm, and Kaplan-Meier curves will be produced. Median and 95% CI will be estimated. Supplemental item-level analyses

will be conducted with the individual B-symptom items of the FACT-Lym LymS using a raw 1-point worsening.

For missing items within the questionnaire, prorated scores will be calculated according to developer guidance (Webster et al. 2003). PRO completion rates will be summarized at each timepoint by treatment arm.

FACT/GOG-NTX-12

FACT/GOG-NTX scores will be reported throughout the trial, including during Stage 1 (Safety Run-In) and Stage 2 (RCT).

For each of the FACT/GOG-NTX-12 questionnaire scales, descriptive statistics at each visit and changes from baseline will be reported by treatment arm.

For missing items within the questionnaire, prorated scores will be calculated according to developer guidance (Calhoun et al. 2003). PRO completion rates will be summarized at each timepoint by treatment arm.

For neurotoxicity subscale, descriptive statistics at each visit and changes from baseline will also be reported on the safety run-in population.

EQ-5D-5L

The EQ-5D-5L Questionnaire is a health utility measure to assess patients' health status using 5 dimensions. All five dimensions can be combined in a five-digit number which then describes the patient's health state. This descriptive number is converted to a single summary index utility score by using published weights; in this study we use the UK crosswalk value set (as published by the EuroQol Research Foundation at http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d, Devlin et al 2017).

Additionally, in the second part of the questionnaire, the current health status is measured by the visual analog scale (VAS) with values ranging from 0 to 100.

For each of the EQ-5D-5L assessments over time, the number and percentage of patients in each of the five categories for each question will be evaluated. A summary of the EQ-5D-5L index utility score at each visit and the associated change from baseline will also be provided by treatment arm. Similar analysis will be performed for EuroQoL visual analog scale (EQ-VAS).

The index utility score and VAS will be analyzed by mixed linear models. In addition, the proportion of patients who report changes that exceed the clinically meaningful threshold on the EQ-5D-5L index and the EQ-VAS scores will be reported. A clinically meaningful improvement threshold is defined as a change of $+0.07$ points in the index utility score and $+7$ points in the VAS score.

Further analysis might be conducted separately.

6.5 SAFETY ANALYSES

The safety analysis will be completed on the safety analysis population. The safety analysis population will consist of all randomized patients who received at least one dose of study drug.

As described in Section 3.1, the safety run-in will evaluate the benefit-risk profile of polatuzumab vedotin plus R-GemOx, with a particular focus on PN, in a stage-gated recruitment process. The decision to continue to the randomized phase of the study will be determined on the basis of how many patients have Grade ≥3 PN after 4 cycles of therapy that does not resolve within 14 days (see Section 3.1). Safety will be assessed through summaries of adverse events and study treatment exposures and will be presented by treatment arm.

Verbatim descriptions of adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will be summarized separately: adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade ≥3 adverse events, adverse events leading to death, serious adverse events, and adverse events of special interest, see Section 5.2.3. In addition, exposure-adjusted analyses, as well as analysis of recurrent AEs, will be provided as appropriate.

All deaths and causes of death will be summarized.

Relevant laboratory values will be summarized by time, with NCI CTCAE v5.0 Grade 3 and Grade 4 values identified, where appropriate. Changes in NCI CTCAE v5.0 grade will be tabulated by treatment arm.

For Stage 1, PN, as measured by FACT/GOG-NTX-12 score, will be summarized. In addition, the rate of PN based on AE will be calculated, including all patients that have completed Cycle 2 or reported this type of event before.

Descriptive statistics will be presented for cumulative study medication doses, dose modifications/interruptions, and duration of exposure. Electrocardiograms will be analyzed descriptively. Changes in vital signs will be analyzed using descriptive statistics for continuous variables.

Further details of any additional analyses will be provided in the Statistical analysis plan (SAP).

6.6 PHARMACOKINETIC ANALYSES

This study incorporates sparse PK sampling of polatuzumab vedotin to enable population PK analysis and to potentially enable additional exploratory correlative analyses of PK with pharmacodynamic, safety and/or efficacy endpoints. These analyses will be performed at the Sponsor's discretion as appropriate and may involve pooling of data from other clinical studies. If performed, the results of these analyses may be reported separately from the Clinical Study Report.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients who received at least one dose of polatuzumab vedotin with at least one evaluable post-baseline ADA sample. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive and ADA-negative patients at baseline (baseline prevalence) and after baseline (postbaseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but are tested positive for ADAs following study drug exposure (treatment-induced ADA response); or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least [redacted] titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post baseline 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 [redacted] titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported using standard language/terminology. Further details of any additional analyses will be provided in the Statistical Analysis Plan (SAP).

6.8 BIOMARKER ANALYSES

Exploratory analyses of biomarkers related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab will be conducted. Analyses will assess prognostic and/or predictive value of candidate biomarkers. The association between candidate biomarkers and OS, PFS and PET-CT CR rate and potentially other measures of efficacy and safety, with treatment and independent of treatment, will be explored to assess potential predictive and prognostic value, respectively. The effects of baseline prognostic characteristics, including DLBCL subtypes (i.e., COO) and mutation profiles on efficacy, will be evaluated using univariate and/or multivariate statistical methods. Further details of any additional analyses will be provided in the Statistical Analysis Plan (SAP).

6.9 SUBGROUP ANALYSES

To assess the consistency of treatment benefit study results in subgroups defined by demographic and relevant baseline characteristics, OS, PFS, and response rate in these subgroups will be evaluated.

Consistency of treatment benefit will be assessed using stratified Cox Proportional hazards models, and hazard ratios with 95% confidence intervals will be estimated. Forest plots will be used to summarize the results.

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates, including quality checking to be performed on the data.

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

Patient-reported outcome data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff. Paper copies of each questionnaire are source documents (see Section 7.3) and will be maintained at the study site.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for

trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal

health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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.

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks.

Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 80–95 sites globally will participate to enroll approximately 2*50* patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety during the safety run-in (Stage 1). An iDMC will be employed during the randomized clinical trial part of the study (Stage 2). Further details will be given in the IMC and iDMC charters.

An IRC will assess tumor response during Stage 2, following a specific charter.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and*/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 made available upon request, provided the requirements of Roche's global

policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

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

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities: Safety Run-In (Stage 1)

	Screening [a]		Treatment					Unplanned Visit [b]	End of Treatment/ Discontinuation 28 (±7) Days After Last Dose of Study Treatment [c]	Long-Term Follow-Up Every 2 Months (±14 days) [d]
			C1	C1	C2–8	C2–8	Mid-Treatment Assessment			
Day (Window [days])	–28 to –1	–7 to –1	1 (±2)	2	1 (±2)	2 (±2)	C4D15 – C5D1			
Informed consent [e]	x									
Demographic data	x									
Medical history and baseline conditions [f]	x									
FACT/GOG-NTX-12			x		x				x	x
ECOG PS	x		x					x	x	
IPI	x									
HIV (if necessary), HBV and HCV serology [g]	x									
Coagulation [h]	x									
Vital signs [i]	x		x	x	x	x		x	x	
Weight	x		x		x				x	
Height	x									
Body surface area	x									
Complete physical examination [j]	x								x	
Limited physical examination [k]			x		x					x [l]
ECG	x			x [m]		x [m]			x	
Hematology [n]		x	x		x				x	x
Chemistry [o]		x	x		x				x	x

Appendix 1
Schedule of Activities: Safety Run-In (cont.)

	Screening [a]		Treatment					Unplanned Visit [b]	End of Treatment/ Discontinuation 28 (±7) Days After Last Dose of Study Treatment [c]	Long-Term Follow-Up Every 2 Months (±14 days) [d]
			C1	C1	C2–8	C2–8	Mid-Treatment Assessment			
Day (Window [days])	–28 to –1	–7 to –1	1 (±2)	2	1 (±2)	2 (±2)	C4D15 – C5D1			
Pregnancy test [p]		x	Day 1 of Every Cycle						x	x
Rituximab			x		x					
Polatuzumab vedotin			x		x					
Gemcitabine				x		x				
Oxaliplatin				x		x				
Radiographic assessment (PET-CT/CT) [q]	x [r]						x	x [s]	x	x [t]
Bone marrow biopsy [u]	x									
Anti-drug antibody samples	See Appendix 4									
Pharmacokinetic samples	See Appendix 4									
Concomitant medications [v]	x	x	x	x	x	x		x	x	
Adverse events [w]	x	x	x	x	x	x		x	x	
Survival follow-up										x

ADA = anti-drug antibody; C = cycle; CT = computed tomography; D = day; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic Case Report Form; FACT/GOG-NTX-12 = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibody; HBsAg = hepatatis B surface antigen; HCV = hepatitis C virus; IPI = International Prognostic Index; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NALT = non-protocol–specified anti-lymphoma treatment; PET = positron emission tomography.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 1
Schedule of Activities: Safety Run-In (cont.)

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 7 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Visit not specified by the protocol. Assessments should be performed as clinically indicated.

[c] Patients who discontinue study drug will return to the clinic for a*n end of* treatment visit 28 days after the last dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit, with additional follow-up (e.g., by telephone) at a time that corresponds to the time needed to eliminate the drug. If subsequent lymphoma treatment is planned, this visit can occur earlier than 28 days. Patients who complete a full course of therapy should return to the clinic 28 days after the *last dose* of *study drug* for assessments of vital signs, weight, hematology, chemistry, pregnancy, response, concomitant medications, and adverse events, as well as to receive a complete physical examination and an ECG reading.

[d] Required follow-up information will be collected *via* clinic visits*, telephone calls, and/or patient medical records approximately* every 2 months from the End of Treatment/Discontinuation Visit until death, loss to follow-up, or study termination by the Sponsor. Patients in the Follow-Up Period will be assessed as follows:

- Patients *who complete treatment or discontinue all study treatment prematurely due to reasons other than* disease progression will *continue standard long-term follow-up assessments including required ADA sampling and radiographic assessments until disease progression and will* be followed for NALT and survival.
- Patients who initiate NALT in the absence of progressive disease will continue to be followed for progression *(including radiographic assessments),* additional NALT*,* and survival.
- Patients with disease progression will be followed for NALT and survival.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies, reason for transplant ineligibility, 2016 WHO classification, current Ann Arbor stage, and procedures), ECOG performance status, and reproductive status.

[g] For patients with unknown HIV status, HIV testing will be performed at Screening if required by local regulations in accordance with national and/or institutional guidelines. HBV serology includes HBsAb, HBsAg, and total HBcAb and, if indicated due to anti-HBcAb antibody positivity, PCR testing for HBV DNA. Patients with occult or prior HBV infection may be included in this study if HBV DNA is undetectable, provided they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment by means of real-time PCR, with the use of an assay that has a sensitivity of at least 29 IU/mL. See Section 4.4.1.6. HCV serology includes anti-HCV antibody testing and, if indicated due to anti-HCV antibody positivity, PCR testing for HCV RNA. See Section 4.5.8.

[h] INR or PT, and PTT or aPTT. See Section 4.5.8.

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

[j] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems (monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain). Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Limited physical exam should also monitor for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Only on visits where CT is planned.

[m] Caution should be exercised in the administration of oxaliplatin in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia (see Section 4.4.2). The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin and as clinically indicated. Record clinically significant abnormalities on the Adverse Event eCRF.

[n] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes). *Laboratory assessments required by protocol should be performed within 72 hours before D1 of each cycle. If screening laboratory assessments are performed within 72 hours before C1D1, they are not required to be repeated at C1D1.*

[o] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate (or CO_2), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and *(if available)* direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and LDH. *Laboratory assessments required by protocol should be performed within 72 hours before D1 of each cycle. If screening laboratory assessments are performed within 72 hours before C1D1, they are not required to be repeated at C1D1.*

[p] All women who are not postmenopausal (≥ 12 months of non-therapy–induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days before Cycle 1 Day 1. In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed prior to Day 1 of each subsequent cycle of study treatment (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

[q] Radiographic assessment must occur by PET-CT scan at screening, PET-CT scan or CT scan at mid-treatment, PET-CT scan at end of treatment, and CT scan during long-term follow-up.

[r] Radiographic assessment >28 days prior to treatment is permissible, so long as the radiographic assessment is made prior to *C1D1* and after the last line of therapy. In the event of a contraindication to CT contrast agents, MRI assessments are permissible.

[s] A full tumor assessment including radiographic assessment must be performed any time disease progression or relapse is suspected.

Appendix 1
Schedule of Activities: Safety Run-In (cont.)

[t] CT scans every 6 months until progression or until the end of the study, whichever occurs first.

[u] Bone marrow biopsies are not mandated in this study (see Section 4.5.8). However, bone marrow biopsies *prior to treatment* should be mandatory for transformed DLBCL patients to check for occult bone marrow involvement by follicular lymphoma, which may not show on PET-CT. Moreover, at the discretion of the investigator, bone marrow biopsies may be conducted in patients with negative bone signal on PET-CT if he or she feels the results could change prognosis and treatment. If bone marrow biopsies are conducted, the results will be collected on the eCRF.

[v] Medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from *7* days prior to initiation of study drug until 28 days after the last dose of study drug.

[w] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days or the initiation of NALT after the last dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 2
Schedule of Activities: Randomized Controlled Trial (Stage 2)

Day (Window [days])	Screening [a]		Treatment					Unplanned Visit [b]	End of Treatment/ Discontinuation 28 (±7) Days After Last Dose of Study Treatment [c]	Long-Term Follow-Up Every 2 Months (±14 Days) [d]
			C1	C1	C2–8	C2–8	Mid-Treatment Assessment			
	–28 to –1	–7 to –1	1 (±2)	2	1 (±2)	2 (±2)	C4D15 – C5D1			
Informed consent [e]	x									
Demographic data	x									
Medical history and baseline conditions [f]	x									
FACT/GOG-NTX-12			x		x				x	x
Patient-reported outcomes (EQ-5D-5L, FACT-Lym and EORTC QLQ-C30) [g]			x		x				x	x
ECOG PS	x		x					x	x	
IPI	x									
HIV (if necessary), HBV and HCV serology [h]	x									
Coagulation [i]	x									
Vital signs [j]	x		x	x	x			x	x	
Weight	x		x		x				x	
Height	x									
Body surface area	x									
Complete physical examination [k]	x								x	
Limited physical examination [l]			x		x					x [m]

Appendix 2
Schedule of Activities: Randomized Controlled Trial (cont.)

Day (Window [days])	Screening [a]		Treatment					Unplanned Visit [b]	End of Treatment/ Discontinuation 28 (±7) Days After Last Dose of Study Treatment [c]	Long-Term Follow-Up Every 2 Months (±14 Days) [d]
			C1	C1	C2–8	C2–8	Mid-Treatment Assessment			
	−28 to −1	−7 to −1	1 (±2)	2	1 (±2)	2 (±2)	C4D15 – C5D1			
ECG	x			x [n]		x [n]			x	
Hematology [o]		x	x		x				x	x
Chemistry [p]		x	x		x				x	x
Pregnancy test [q]		x	Day 1 of Every Cycle						x	x
Rituximab			x		x					
Polatuzumab vedotin (Only if assigned to Pola-R-GemOx)			x		x					
Gemcitabine				x		x				
Oxaliplatin				x		x				
Radiographic assessment (PET-CT/CT) [r]	x [s]						x	x [t]	x	x [u]
Bone marrow biopsy [v]	x									
Biomarker *DLBCL* tumor tissue samples	See Appendix 3									
Biomarker blood and MRD samples	See Appendix 3									
Anti-drug antibody samples	See Appendix 4									
Pharmacokinetic samples	See Appendix 4									

Appendix 2
Schedule of Activities: Randomized Controlled Trial (cont.)

	Screening [a]		Treatment					Unplanned Visit [b]	End of Treatment/ Discontinuation 28 (±7) Days After Last Dose of Study Treatment [c]	Long-Term Follow-Up Every 2 Months (±14 Days) [d]
			C1	C1	C2–8	C2–8	Mid-Treatment Assessment			
Day (Window [days])	−28 to −1	−7 to −1	1 (±2)	2	1 (±2)	2 (±2)	C4D15 – C5D1			
Concomitant medications [w]	x	x	x	x	x	x		x	x	
Adverse events [x]	x	x	x	x	x	x		x	x	
Survival follow-up										x

ADA = anti-drug antibodies; C = cycle; CT = computed tomography; D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30; eCRF = electronic Case Report Form; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-Level Version; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; FACT/GOG-NTX-12 = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Scale; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IPI = International Prognostic Index; LDH = lactate dehydrogenase; MRD = minimal residue disease; MRI = magnetic resonance imaging; NALT = non-protocol–specified anti-lymphoma treatment; PET = positron emission tomography; Pola = polatuzumab vedotin; R-GemOx = rituximab plus gemcitabine plus oxaliplatin.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 7 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Visit not specified by the protocol. Assessments should be performed as clinically indicated.

[c] Patients who discontinue study drug will return to the clinic for an *end of* treatment visit 28 days after the last dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit, with additional follow-up (e.g., by telephone) at a time that corresponds to the time needed to eliminate the drug. If subsequent lymphoma treatment is planned, this visit can occur earlier than 28 days. Patients who complete a full course of therapy should return to the clinic 28 days after the *last dose* of *study drug* for assessments of vital signs, weight, hematology, chemistry, pregnancy, response, concomitant medications and adverse events, as well as to receive a complete physical examination and an ECG reading.

[d] Required follow-up information will be collected *via* clinic visits*, telephone calls, and/or patient medical records* every 2 months from the End of Treatment/Discontinuation Visit until death, loss to follow-up, or study termination by the Sponsor. Patients in the Follow-Up Period will be assessed as follows:

- Patients *who complete treatment or discontinue all study treatment prematurely due to reasons other than* disease progression will *continue standard long-term follow-up assessments including required ADA sampling and radiographic assessments until disease progression and will* be followed for NALT and survival.
- Patients who initiate NALT in the absence of progressive disease will continue to be followed for progression *(including radiographic assessments),* additional NALT*,* and survival.
- Patients with disease progression will be followed for NALT and survival.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies, reason for transplant ineligibility, 2016 WHO classification, current Ann Arbor stage, and procedures), ECOG performance status, and reproductive status.

[g] Questionnaires will be administered before the patient receives any information on disease status, prior to the performance of non-PRO/ClinRO assessments, and prior to the administration of study treatment. After cycle 3, these will be done every other cycle (i.e. Cycle 5 would be the next cycle).

[h] For patients with unknown HIV status, HIV testing will be performed at Screening if required by local regulations in accordance with national and/or institutional guidelines. HBV serology includes HBsAb, HBsAg, and total HBcAb and, if indicated due to anti-HBcAb antibody positivity, PCR testing for HBV DNA. Patients with occult or prior HBV infection may be included in this study if HBV DNA is undetectable, provided they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment by means of real-time PCR, with the use of an assay that has a sensitivity of at least 29 IU/mL. See Section 4.4.1.6. HCV serology includes anti-HCV antibody testing and, if indicated due to anti-HCV antibody positivity, PCR testing for HCV RNA. See Section 4.5.8.

[i] INR or PT, and PTT or aPTT. See Section 4.5.8.

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

[k] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems (monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain). Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Limited physical exam should also monitor for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[m] Only on visits where CT is planned.

[n] Caution should be exercised in the administration of oxaliplatin in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia (see Section 4.4.2). The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin and as clinically indicated. Record clinically significant abnormalities on the Adverse Event eCRF.

[o] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes). *Laboratory assessments required by protocol have to be performed within 72 hours before D1 of each cycle. If screening laboratory assessments are performed within 72 hours before C1D1, they are not required to be repeated at C1D1.*

[p] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate (or CO_2), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and *(if available)* direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and LDH. *Laboratory assessments required by protocol have to be performed within 72 hours before D1 of each cycle. If screening laboratory assessments are performed within 72 hours before C1D1, they are not required to be repeated at C1D1.*

[q] All women who are not postmenopausal ($\geq$12 months of non-therapy–induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days before Cycle 1 Day 1. In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed prior to Day 1 of each subsequent cycle of study treatment (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

[r] Radiographic assessment must occur by PET-CT scan at screening, PET-CT scan or CT scan at mid-treatment, PET-CT scan at end of treatment, and CT scan during long-term follow-up.

[s] Radiographic assessment >28 days prior to treatment is permissible, so long as the radiographic assessment is made prior to *C1D1* and after the last line of therapy. In the event of a contraindication to CT contrast agents, MRI assessments are permissible.

[t] A full tumor assessment including radiographic assessment must be performed any time disease progression or relapse is suspected.

[u] CT scans every 6 months until progression or until the end of the study, whichever occurs first.

[v] Bone marrow biopsies are not mandated in this study (see Section 4.5.8). However, bone marrow biopsies *prior to treatment* should be mandatory for transformed DLBCL patients to check for occult bone marrow involvement by follicular lymphoma, which may not show on PET-CT. Moreover, at the discretion of the investigator, bone marrow biopsies may be conducted in patients with negative bone signal on

PET-CT if he or she feels the results could change prognosis and treatment. If bone marrow biopsies are conducted, the results will be collected on the eCRF.

[w] Medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 28 days after the last dose of study drug.

[x] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days or the initiation of NALT after the last dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 3
Schedule of Biomarker Samples: Randomized Controlled Trial (Stage 2)

Biosample	**Screening**	**Treatment period**								**EOT / Discontinuation**
Days	–28 to 1	C1, D1	C2, D1	C3, D1	C4, D1	C5, D1	C6, D1	C7, D1	C8, D1	
Mandatory collection [a]										
Fresh (or archival) *DLBCL* tumor tissue sample [b]	x									
Blood for MRD assay (predose) [c]		x	x	x		x				x
Blood for flow cytometry (predose) [d]		x		x						x

C = cycle; D = day; EOT = end of treatment; MRD = minimal residual disease.

[a] Up to 20 ml of whole blood sample will be collected at each specified time point.

[b] Availability of archival or freshly biopsied *DLBCL* tumor tissue samples should be confirmed at screening. If the patient has had anti-lymphoma treatment between the time of the prior biopsy and the time of study treatment initiation, a core-needle biopsy is recommended, if feasible and safe by investigator judgment. Formalin-fixed paraffin-embedded tissue blocks are preferred over slides. If a tissue block is not available, a minimum of *10–15 slides (*15 *preferred,* or in accordance with local regulatory requirements) serial, freshly cut, unstained slides is acceptable, with an associated pathology report, obtained at any time before study entry. If archival tissue is unavailable or unacceptable according to above criteria, a pretreatment core needle, excisional, or incisional tumor biopsy is required if feasible and safe by investigator judgment. Cytological or fine-needle aspiration samples are not acceptable

c Peripheral whole-blood sample may be obtained up to 3 days before the study visit.

d Approximately the first 100 patients at participating sites will undergo flow cytometry assessments.

Appendix 4
Schedule for Serum and Plasma Pharmacokinetic Samples: Safety Run-In (Stage 1) and RCT (Stage 2)

Study Visit	Sample Time Points [a]	Samples
Cycle 1 Day 1	Pre-pola infusion	Pola acMMAE & *unconjugated* MMAE PK (plasma) [b] Pola ADA & total antibody *PK* (serum)
	End of Pola infusion	Pola acMMAE & *unconjugated* MMAE PK (plasma) [b]
Cycle 4 Day 1	Pre-pola infusion	Pola acMMAE & *unconjugated* MMAE PK (plasma) [b] Pola ADA & total antibody *PK* (serum)
	End of Pola infusion	Pola acMMAE & *unconjugated* MMAE PK (plasma) [b]
Treatment Completion / Early Termination	*End of Treatment visit*	Pola ADA & total antibody *PK* (serum)
Long-Term Follow-up (2 months) [c]	Anytime during visit	Pola ADA & total antibody *PK* (serum)

acMMAE = antibody-conjugated monomethyl auristatin E; ADA = anti-drug antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetics; pola = polatuzumab vedotin; RCT = randomized controlled trial.

Notes: Pre-infusion samples should be drawn 0−4 hours before the start of infusion. End−of−infusion samples should be drawn 30 minutes (±15 minutes) unless otherwise specified.

[a] Up to 11-mL whole-blood samples will be taken for polatuzumab vedotin ADA and PK (polatuzumab vedotin total antibody, acMMAE, and unconjugated MMAE) at each specified time point, with separate tubes for plasma or serum samples.

[b] Polatuzumab vedotin PK, including PK samples for acMMAE and unconjugated MMAE.

[c] ADA and total antibody sample collection at Month 2 of the Post-Treatment Follow-Up Period may be replaced instead with a collection at Month 4. It is not necessary to carry out ADA and total antibody sample collection at both Month 2 and Month 4 of the Post-Treatment Follow-Up Period.

Appendix 5
Lugano Response Assessment Criteria

Response should be determined on the basis of radiographic and clinical evidence of disease according to Lugano response assessment criteria, as summarized below.

Target and Non-Target Lesions

Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be greater than 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the six representative, measured lesions. At baseline, measurable extranodal lesions should be greater than 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease as non-target lesions (e.g. cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

Split Lesions and Confluent Lesions

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and smallest diameter (SDi) are no longer needed to determine progression.

Appendix 5
Lugano Response Assessment Criteria (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	$\geq 50\%$ decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm $\times$ 5 mm as the default value When no longer visible, 0×0 mm For a node > 5 mm $\times$ 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by $> 50\%$ in length beyond normal
New lesions	None	None

Appendix 5
Lugano Response Assessment Criteria (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic response	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression;

Appendix 5
Lugano Response Assessment Criteria (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by > 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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.

Appendix 5
Lugano Response Assessment Criteria (cont.)

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: any disease not selected as measured, dominant disease, and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2, uptake $\leq$ mediastinum; 3, uptake $>$ mediastinum but $\leq$ 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.

Reference: 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;32:3059–67.

Appendix 6
Recommendations for the Use of White Blood Cell Growth Factors

Primary Prophylactic G-CSF Administration (First and Subsequent Cycle Use)

Primary prophylaxis with growth-colony stimulating factor (G-CSF) is required.

Therapeutic Use of G-CSF

G-CSF administration should be considered for the following patients:

- Patients with febrile neutropenia who are at high risk for infection-associated complications; or
- Patients who have prognostic factors that are predictive of poor clinical outcome, e.g., prolonged ($>$10 days) and profound ($<$100/μL) neutropenia, age $>$65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of fever development

Reference: Smith et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

Appendix 7
Recommended Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry)
- Oxygen and masks for oxygen delivery
- Airway management devices per standard of care
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H1 and H2 blockers)
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion
- Call for additional assistance!
- Maintain an adequate airway
- Provide oxygen
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge
- Continue to observe the patient and document observations

Appendix 8
Eastern Cooperative Oncology Group Performance Status

GRADE	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.

Appendix 9
International Prognostic Index

How to Score

Prognostic Factor	Parameters	Score
Age	≤60 years	0
	>60 years	1
ECOG performance status	0 or 1	0
	2–4	1
Stage	1 or 2	0
	3 or 4	1
Serum LDH	≤1 × ULN	0
	>1 × ULN	1
Extranodal involvement [a]	≤1 site	0
	>1 site	1

ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ULN = upper limit of normal.

[a] Extranodal involvement per Cheson et al. 2014 can include sites that have focal uptake by PET-CT (e.g., spleen, liver, bone, thyroid, cutaneous, GI, bone, kidneys, pleural or pericardial effusions, and ascities).

Prognostic Risk Group Definitions

No. of Risk Factors [a]	Risk Group
0 or 1	Low
2	Low intermediate
3	High intermediate
4 or 5	High

No. of risk factors = total score based on the first table in this appendix.

Reference: International Non-Hodgkin's Lymphoma Prognostic Factors, P. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987–94.

Appendix 10
Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity 12-Item Questionnaire

FACT/GOG-NTX-12 (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HH2	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
Aa6	I have trouble walking	0	1	2	3	4
NTX 10	I have pain in my hands or feet when I am exposed to cold temperatures	0	1	2	3	4

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Appendix 11
Functional Assessment of Cancer Therapy–Lymphoma

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

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Appendix 12
EuroQol Group 5-Dimension 5-Level Questionnaire

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Health Questionnaire

English version for the UK

Sample

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Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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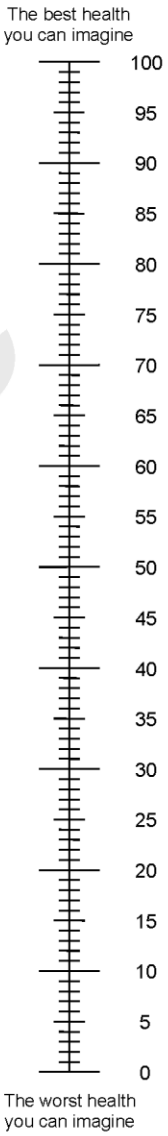
Sample

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample

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Appendix 13
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 13
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30 (cont.)

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Appendix 14
Sampson's Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   - Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline PEF

Source: Sampson, H. A., A. Munoz-Furlong, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

Appendix 15
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in EEA and U.K.*	*Used within Marketing Authorization*
Polatuzumab vedotin (RO5541077)	*IMP (test product)*	*Approved*	*No* [a]
Rituximab (RO452294)	*IMP* [b]	*Approved*	*No*
Gemcitabine	*Non-Roche IMP* [b]	*Not Approved* [c]	*Not Applicable* [d]
Oxaliplatin	*Non-Roche IMP* [b]	*Not Approved* [c]	*Not Applicable* [d]

EEA = European Economic Area; GemOx = gemcitabine plus oxaliplatin; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; LPI = local product information; U.K. = United Kingdom.

[a] *Polatuzumab vedotin is not approved in combination with R-GemOx.*

[b] *Rituximab, Gemcitabine, and Oxaliplatin are each considered to be an IMP test product as well as an IMP comparator.*

[c] *Gemcitabine and Oxaliplatin are not approved in all participating countries.*

[d] *Rituximab, Gemcitabine, and Oxaliplatin are used for an indication not included in the LPI for that product.*

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