Official Title: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Polatuzumab Vedotin in Combination with Bendamustine and Rituximab Compared with Bendamustine and Rituximab Alone in Chinese Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

NCT Number: NCT04236141

Document Date: Protocol Version 2: 12 May 2020

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB COMPARED WITH BENDAMUSTINE AND RITUXIMAB ALONE IN CHINESE PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	YO41543
VERSION NUMBER:	2
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Polatuzumab vedotin, lyophilized (DCDS4501S, RO5541077)
MEDICAL MONITOR:	[redacted], M.D. Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
12-May-2020 15:28:16	[redacted]	[redacted]

PROTOCOL AMENDMENT, VERSION 2
RATIONALE

Protocol YO41543 has been amended to incorporate changes to diffuse large B-cell lymphoma (DLBCL) prognostic biomarkers as highlighted in a recent update of the WHO DLBCL Classification, including cell-of-origin subtypes (activated B cell and germinal center B cell subtypes) and patients with co-expression of BCL2 and MYC. Furthermore, the Sponsor is planning to investigate the efficacy of polatuzumab vedotin in patients with the expression of its target CD79b on DLBCL tumor cell surface. Efficacy analyses in these four biomarker populations are considered important for interpreting the efficacy of polatuzumab vedotin in this heterogeneous disease setting with different potential underlying molecular biology. Collectively, given the importance of these analyses, the Sponsor proposes to update these analyses from exploratory objective to biomarker objectives.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Sections 2.2, 2.3, and 2.4 have had mentions of exploratory objectives updated to reflect the current analysis plan.
- Sections 2.5 and 3.3.4 have been updated to reflect the incorporation of the updated WHO DLBCL classifications into biomarker objectives.
- Sections 4.1.1 and 4.1.3 have been updated to remove central pathology diagnosis to reflect sites' confirmed ability to diagnose DLBCL.
- Section 4.1.1 has been updated to remove requirement for a biopsy to be performed at screening if archival tissue is unavailable or inadequate.
- Sections 4.1.2, and 4.4.1.4 have been updated to clarify the instructions of monitoring for hepatitis B reactivation.
- Section 4.4.1.4 has been updated to reflect HBV assay sensitivity recommended by WHO.
- Section 4.5.3 has been updated to remove genitourinary component of the physical exam.
- Section 4.5.6 has been updated to remove bands from hematology test.
- Sections 4.5.6, 8.4, and 9.5 have been updated to remove reference to exploratory biomarkers.
- Section 6.1 has been updated to further clarify the rationale used in determining sample size.
- Sections 6.4.1 and 6.4.2 have been updated to further clarify statistical analysis methodology.
- Section 5.1 and 5.1.1 have been updated in accordance with the Polatuzumab Vedotin Investigator Brochure, Version 11. These include updated known and potential risks associated with polatuzumab vedotin.
- Appendix 1 has been updated to further clarify the need of dedicated CT scans.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB COMPARED WITH BENDAMUSTINE AND RITUXIMAB ALONE IN CHINESE PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	YO41543
VERSION NUMBER:	2
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Polatuzumab vedotin, lyophilized (DCDS4501S, RO5541077)
MEDICAL MONITOR:	[redacted], M.D. Ph.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 AMENDMENT SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB COMPARED WITH BENDAMUSTINE AND RITUXIMAB ALONE IN CHINESE PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	YO41543
VERSION NUMBER:	2
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Polatuzumab vedotin, lyophilized (DCDS4501S, RO5541077)
PHASE:	Phase III
INDICATION:	Diffuse large B-cell lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of polatuzumab vedotin plus bendamustine and rituximab (BR) compared with placebo plus BR in Chinese patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., polatuzumab vedotin/placebo, bendamustine, and rituximab).

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of polatuzumab vedotin plus BR compared with placebo plus BR in Chinese patients with R/R DLBCL on the basis of the following endpoint. This objective is to *investigate* whether the benefit (in terms of complete response [CR] rate at end of treatment assessment) of administrating polatuzumab vedotin plus BR in this study is consistent with the benefit observed in the global study, GO29365.

- CR at the end of treatment assessment (6–8 weeks after Cycle 6 Day 1 or final dose of study treatment) based on positron emission tomography–computed tomography (PET-CT), as determined by the Independent Review Committee (IRC) according to the Lugano Response Criteria for Malignant Lymphoma, hereafter referred to as the "Lugano Response Criteria" (Cheson et al. 2014)

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of polatuzumab vedotin plus BR compared with placebo plus BR in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- CR at the end of treatment assessment based on PET-CT, as determined by the investigator according to the Lugano Response Criteria

- Objective response (OR), defined as CR or partial response (PR), at the end of treatment assessment based on PET-CT, as determined by the investigator and IRC according to the Lugano Response Criteria
- CR at the end of treatment assessment based on computed tomography (CT) only, as determined by the investigator and IRC according to the Lugano Response Criteria
- OR, defined as CR or PR, at the end of treatment assessment based on CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- Best objective response, defined as CR or PR, while on study based on PET-CT or CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression, relapse, or death from any cause based on PET-CT or CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- Progression-free survival, defined as the period from date of randomization until the date of disease progression, relapse, or death from any cause based on PET-CT or CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- Event-free survival, defined as the time from date of randomization to any treatment failure including disease progression, relapse, initiation of new anti-lymphoma treatment, or death based on PET-CT or CT only, as determined by the investigator according to the Lugano Response Criteria
- Overall survival (OS), defined as the time from date of randomization until the date of death from any cause

Safety Objectives

The safety objective for this study is to evaluate the safety of polatuzumab vedotin plus BR compared with placebo plus BR in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence and nature of study drug discontinuation, dose reduction, and dose delay due to adverse events

Additionally, this study *will* evaluate the safety of polatuzumab vedotin plus BR compared with placebo plus BR from the patient's perspective to better understand treatment impact, tolerability, and reversibility on the basis of the following endpoint:

- Change from baseline in peripheral neuropathy as assessed through use of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-NTX)

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to characterize the PK for total antibody, antibody-conjugated monomethyl auristatin E (acMMAE), and unconjugated monomethyl auristatin E (MMAE) following polatuzumab vedotin administration, when combined with BR, in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- Serum concentration of total antibody at specified timepoints
- Plasma concentration of acMMAE at specified timepoints
- Plasma concentration of unconjugated MMAE at specified timepoints

Additionally, this study *will* evaluate potential relationships between polatuzumab vedotin exposure and the efficacy and safety of polatuzumab vedotin, when combined with BR, in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- Relationship between plasma concentration or PK parameters for polatuzumab vedotin and efficacy endpoints
- Relationship between plasma concentration or PK parameters for polatuzumab vedotin and safety endpoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to polatuzumab vedotin, when combined with BR, in Chinese patients with R/R DLBCL on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) for polatuzumab vedotin at baseline and incidence of ADAs during the study

Additionally, for this study *will* evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status for polatuzumab vedotin and efficacy, safety, or PK endpoints

Biomarker Objective

The biomarker objective for this study is to evaluate *the* response to polatuzumab vedotin*, when combined* with BR*, in Chinese* patients with *R/R DLBCL with* known prognostic factors, *such as* activated B cell *(*ABC*)-DLBCL or* germinal center B cell [GCB*]-DLBCL as analyzed through use of a centrally performed RNA-based assay, or co-expression of BCL2 and MYC (double-expressor, [DEL]) as analyzed through use of centrally performed immunohistochemistry (IHC) tests. In addition, the association between response and the expression of the target of polatuzumab vedotin, CD79b (as analyzed through use of a centrally performed IHC test) will be evaluated.*

- *CR at the end of treatment assessment based on PET-CT, as determined by the IRC according to the Lugano Response Criteria in populations of ABC-DLBCL, GCB-DLBCL, DEL, and expression of CD79b*
- *OR, defined as CR or PR, at the end of treatment assessment based on PET-CT, as determined by the IRC according to the Lugano Response Criteria in populations of ABC-DLBCL, GCB-DLBCL, DEL, and expression of CD79b*

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of polatuzumab vedotin in combination with BR compared with BR alone in Chinese patients with R/R DLBCL.

Approximately 42 Chinese patients will be randomized to one of the following treatment arms in a 2:1 ratio:

- Polatuzumab vedotin plus BR (experimental arm)
- Placebo plus BR (control arm)

Randomization will be conducted with the aid of an interactive web-based response system (IxRS) and will be stratified according to the following factors:

- DOR to most recent prior therapy: $\leq$ 12 months versus $>$ 12 months
- Number of prior therapies (1 vs. $\geq$ 2)

  For consistency with the pivotal study population (Study GO29365), patients with $\geq$ 2 prior lines of therapy will be capped within 70% of the whole population.

Refer to the protocol for the study design schema and the schedule of activities.

Study treatment will be administered by IV infusion every 21 days for up to 6 cycles, as described in the protocol. The first day of treatment will constitute Study Day 1. Refer to the protocol for details on study treatment dosage and administration.

All patients will be closely monitored for adverse events and serious adverse events throughout the study and for 90 days after the final dose of study treatment. Adverse events will be graded according to NCI CTCAE v5.0. Laboratory safety assessments will include regular monitoring of hematology and blood chemistry, and tests of immunological parameters.

Blood samples will be taken at various timepoints during the study to analyze the PK properties of polatuzumab vedotin (total antibody, acMMAE, and unconjugated MMAE), as well as the immunogenicity of polatuzumab vedotin, when given in combination with BR.

Response will be determined by an IRC and investigators using the Lugano Response Criteria (Cheson et al. 2014) at the following timepoints:

- Screening: within 35 days of Cycle 1 Day 1
- Interim response assessment: between Cycle 3 Day 15 and Cycle 4 Day 1
- End of treatment assessment: 6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment

For patients with disease progression occurring prior to the anticipated date of the end of treatment assessment, the visit date with the response assessment showing disease progression will be used in replacement of the end of treatment assessment.

Imaging at these timepoints must include PET scans in conjunction with diagnostic-quality CT scans with both oral and IV contrast. An independent review of the responses of all patients will also be conducted to confirm the primary CR endpoint.

Patients who complete the study treatment period will return to the clinic for a treatment completion visit 30 (± 5) days after the final dose of study treatment (Cycle 6 Day 1). Patients who discontinue study treatment prematurely will return to the clinic for a treatment discontinuation visit 30 (± 5) days after the final dose of study treatment.

Disease Progression and Follow Up

Following completion of treatment, patients who have not progressed will be followed clinically every 3 months (± 14 days) according to the schedule of activities. Tumor assessments should also be performed to confirm clinical suspicion of relapse or disease progression for documentation. Follow-up visit intervals should be determined from the end of treatment assessment.

CT (preferred) or PET-CT scans should be performed during follow-up:

- Every 6 months after the end of treatment assessment until disease progression, study withdrawal, end of study, or death, whichever comes first; or
- At any time that disease progression is suspected via clinical response assessment

For patients who have disease progression and have not started new anti-lymphoma therapy, follow-up should consist of recording of first new anti-lymphoma therapy, adverse events, and survival and continue to follow the above schedule. For patients who have disease progression and started a new anti-lymphoma therapy, contact will be made by telephone on at least an annual basis for survival. For patients who started a new anti-lymphoma therapy but do not have disease progression, assessments should be followed according to the schedule of activities, including response assessments and adverse events.

Patients who discontinue all components of study treatment prior to disease progression (e.g., for toxicity) will continue in the study and will be followed for progressive disease and OS (regardless of whether they subsequently receive a new anti-lymphoma therapy).

Study Treatment Regimen

Patients will receive a total of 6 cycles of polatuzumab vedotin or placebo in combination with BR. A cycle is typically 21 days.

For the purposes of ensuring consistent PK measurements, treatments will be administered sequentially in the order specified below.

Schedule for Cycle 1

Cycle 1 Day 1

- Rituximab 375 mg/m^2 IV infusion

Cycle 1 Day 2

- Polatuzumab vedotin/placebo IV infusion
- Bendamustine 90 mg/m^2 IV infusion

Cycle 1 Day 3

- Bendamustine 90 mg/m^2 IV infusion

Schedule for Cycles 2–6

As long as the observed individual patient safety profile of polatuzumab vedotin/placebo and BR allows all study treatment infusions to be given on the same day, then the study treatment infusions will be given sequentially on the same day for Cycles 2–6 and in the order specified below.

Cycles 2–6 Day 1

- Rituximab 375 mg/m^2 IV infusion
- Polatuzumab vedotin/placebo IV infusion
- Bendamustine 90 mg/m^2 IV infusion

Cycles 2–6 Day 2

- Bendamustine 90 mg/m^2 IV infusion

Independent Review Committee

An IRC composed of certified radiologists and a hematologist or oncologist with experience in malignant lymphoma will assess all patients for response on the basis of imaging results and biopsy results that are performed related to efficacy evaluation. Decisions will be guided by a Charter specific to the independent review.

Number of Patients

Approximately 42 patients with R/R DLBCL will be enrolled in this study.

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
- Able to comply with the study protocol and procedures, in the investigator's judgment
- Transplant ineligible patients with R/R DLBCL, classified as below:
  - Patients who are ineligible for second-line stem cell transplantation (SCT), with progressive disease or no response (stable disease [SD]) < 6 months from start of initial therapy (second-line refractory)
  - Patients who are ineligible for second-line SCT, with disease relapse after initial response ≥ 6 months from start of initial therapy (second-line relapsed)
  - Patients who are ineligible for third-line (or beyond) SCT, with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line or beyond refractory)
  - Patients who are ineligible for third-line (or beyond) SCT with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line or beyond relapsed)
- *Confirmed DLBCL diagnosis as:*
  - DLBCL, not otherwise specified (NOS) (including both GCB and ABC)
  - T-cell/histiocyte-rich large B-cell lymphoma
  - High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
  - High grade B-cell lymphoma, NOS
  - Primary mediastinal (thymic) large B-cell lymphoma
  - Epstein-Barr virus positive DLBCL, NOS
- For patients who have received prior bendamustine, a response duration > 1 year (for patients who have relapsed disease after a prior regimen)
- At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension as measured by CT or magnetic resonance imaging
- Availability of archival or freshly collected tumor tissue before study enrollment

  Formalin-fixed, paraffin-embedded tissue blocks are preferred.

  If a tissue block is not available, at least 11 unstained slides or freshly cut serial sections (3–5 µm in thickness), will be accepted.

Of note, receipt of tumor samples is not necessary prior to study enrollment.

- Life expectancy of at least 24 weeks
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Adequate hematologic function unless inadequate function is due to underlying disease, such as extensive bone marrow involvement or hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator. Adequate hematologic function is defined as follows:
  - Hemoglobin $\geq$ 9 g/dL
  - ANC $\geq 1.5 \times 10^9$/L
  - Platelet count $\geq 75 \times 10^9$/L
- 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 single highly effective or combined contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for $\geq$ 12 months after the final dose study treatment. 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 ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of highly effective 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. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $<$ 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

  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 who are not surgically sterile: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men must remain abstinent or to use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 6 months after the final dose of study treatment. 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 study treatment 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.
- Residence in the People's Republic of China

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 MAbs (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to bendamustine or rituximab
- History of sensitivity to mannitol (mannitol is an excipient in bendamustine)
    - Prior use of any MAb, radioimmunoconjugate, or antibody-drug conjugate within 5 half-lives or 4 weeks, whichever is longer, before Cycle 1 Day 1
- 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 $\leq$ 2 prior to Cycle 1 Day 1.

    Recent treatment with rituximab is allowed given the timing of the last dose was greater than 2 weeks prior to Cycle 1 Day 1.

    Should prior treatment fall under more than one exclusionary criterion (e.g., MAb and immunotherapy), the more conservative criterion must be met.
- Ongoing corticosteroid use $>$ 30 mg/day prednisone or equivalent, for purposes other than lymphoma symptom control

    Patients receiving corticosteroid treatment $\leq$ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy (Cycle 1 Day 1).

    Ongoing corticosteroid usage is permitted for the purpose of lymphoma symptom control. For further details refer to the protocol.
- Completion of autologous SCT within 100 days prior to Cycle 1 Day 1
- Prior allogeneic SCT
- Prior treatment with CAR T-cell therapy
- Eligibility for autologous SCT
- Grade 3b FL
- History of transformation of indolent disease to DLBCL
- Primary or secondary CNS lymphoma
- Current Grade $>$ 1 peripheral neuropathy
- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include, but are not limited to:

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

    A patient with any other malignancy that has been treated with surgery alone with curative intent and the malignancy has been in remission without treatment for $\geq$ 3 years prior to enrollment is eligible.

    Patients with low-grade, early-stage prostate cancer 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 requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Patients with suspected or latent tuberculosis

  Latent tuberculosis should be confirmed according to local testing requirements.
- 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 *monthly (or* on Day 1 of every cycle*) during the study* and for at least 12 months after the last cycle of study treatment. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.
- Positive test results for hepatitis C virus (HCV) antibody

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

  For patients with unknown HIV status, HIV testing will be performed at screening.
- Known infection human T-cell leukemia virus 1 virus
- Vaccination with a live vaccine within 28 days prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Pregnant or breastfeeding or intending to become pregnant during the study or within 12 months after the final dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
  - Serum creatinine clearance $<$ 40 mL/min (using Cockcroft-Gault formula)
  - AST or ALT $>$ 2.5 $\times$ upper limit of normal (ULN)
  - Total bilirubin $\geq$ 1.5 $\times$ ULN

    Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq$ 3 $\times$ ULN.
  - INR or PT $>$ 1.5 $\times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $>$ 1.5 $\times$ ULN in the absence of a lupus anticoagulant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

Criteria for Lymph Node Biopsy Tissue

Patients must meet following criteria for lymph node biopsy tissue:

- The specimen must contain adequate evaluable tumor cells ($\geq$ 20% for excisional biopsy and $\geq$ 50% if sample is a core biopsy) to enable relevant biomarker analysis.
- A tissue block (preferred) or 11 serial, freshly cut, unstained slides accompanied by an associated pathology report will be requested. Cytological or fine-needle aspiration samples are not acceptable. In countries that use a different fixative than formalin, available tissue block will be accepted and notation of the type of fixative should be included.

If the archival tissue is unavailable or insufficient on the basis of the above criteria, the patient may still be eligible if the patient is willing to provide tissue from a pretreatment core or excisional/incisional biopsy of the tumor. Cytological or fine-needle aspiration samples are not acceptable. If a tissue block is provided, after necessary sections are cut, the remaining specimen will be returned to site upon request. Tissue collected on study will not be returned to sites.

Refer to the laboratory manual for additional details.

End of Study

The end of the study is defined as the timepoint at which approximately two-thirds of enrolled patients have experienced deaths, or all patients have discontinued from the study, whichever occurs first.

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

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 21 months.

Investigational Medicinal Products

Polatuzumab Vedotin and Placebo

Polatuzumab vedotin and placebo will be supplied by the Sponsor as a sterile, white to grayish-white, preservative-free lyophilisate in single-use vials. Polatuzumab vedotin or placebo should be prepared and administered in the same manner. For information on the formulation and handling of polatuzumab vedotin or placebo, see the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure.

Polatuzumab vedotin (1.8 mg/kg) or placebo will be administered by IV infusion on Day 2 of Cycle 1 and then Day 1 of Cycles 2–6.

Rituximab

Rituximab (MabThera®/Rituxan®) 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.

Rituximab (375 mg/m^2) will be administered by IV infusion on Day 1 of Cycles 1–6.

Bendamustine

Bendamustine hydrochloride will be supplied by the Sponsor. For information on the formulation, packaging, and handling of bendamustine hydrochloride, see the pharmacy manual.

Bendamustine (90 mg/m^2) will be administered by IV infusion over 30–60 minutes on 2 consecutive days of each cycle (Days 2 and 3 in Cycle 1 and then Days 1 and 2 in Cycles 2–6).

Statistical Methods

Primary Analysis

CR at end of treatment assessment (6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment) based on PET-CT, as determined by the IRC, will be used as the primary efficacy endpoint. The CR rate, defined as the percentage of patients with CR, will be estimated and the corresponding Clopper-Pearson exact 95% CI will be constructed for each treatment arm. The difference in CR rates between polatuzumab vedotin plus BR and placebo plus BR randomized arms will be estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution.

Determination of Sample Size

The primary endpoint of CR at the end of treatment assessment was used to determine the sample size of the study.

The primary objective of the study is to *investigate* whether the benefit (in terms of CR at the end of treatment assessment) of administrating polatuzumab vedotin plus BR in this study is consistent with the benefit observed in the global study GO29365. *CR rate at the end of treatment assessment* was increased from 17.5% in the BR arm to be 40% in the polatuzumab vedotin plus BR arm for study GO29365 (i.e., 22.5% *CR rate increase).*

In this study, 42 patients will be enrolled in a 2:1 randomization allocation to polatuzumab vedotin plus BR (experimental arm) or placebo plus BR arm (control arm). A total of 42 patients will provide an approximate 80% probability of observing at least 50% of the benefit in the CR rate at the end of treatment assessment observed in the global Study GO29365.

The expected enrollment duration is approximately 9 months and the primary analysis is expected to occur approximately 6 months of follow-up after the last patient is enrolled. The study will continue after primary analysis until about two-thirds of enrolled patients have experienced death or all patients have discontinued from study, whichever occurs earlier. Based on the observed median OS in Study GO29365 (4.7 months in the BR arm, 12.4 months in the polatuzumab vedotin plus BR arm), the final OS analysis is expected to occur approximately 10 months after the last patient is enrolled.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
aa-IPI	age-adjusted International Prognostic Index
ABC	activated B cell
acMMAE	antibody-conjugated monomethyl auristatin E
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AUC	area under the concentration–time curve
AUC_{inf}	area under the concentration–time curve from Time 0 to infinity
BOR	best objective response
BR	bendamustine and rituximab
BSA	body surface area
CAR	chimeric antigen receptor
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHP	cyclophosphamide, doxorubicin, and prednisone
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
C_{trough}	trough concentration
CMH	Cochran Mantel Haenszel
CR	complete response
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug–drug interaction
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
DEL	*double-expressor lymphoma*
EFS	event-free survival
FACT/GOG-NTX	Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity
FDA	(U.S.) Food and Drug Administration
FL	follicular lymphoma
GCB	germinal center B cell

Abbreviation	Definition
G-CSF	granulocyte colony-stimulating factor
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
HRQoL	health-related quality of life
HSV	herpes simplex virus
ICH	International Council for Harmonisation
IHC	*immunohistochemistry*
IMP	investigational medicinal product
iNHL	indolent non-Hodgkin lymphoma
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
MAb	monoclonal antibody
MMAE	monomethyl auristatin E
NALT	new anti-lymphoma treatment
NCA	non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
OR	objective response
OS	overall survival
PCR	polymerase chain reaction
PE	polyethylene
PET	positron emission tomography (scan)
PET-CT	positron emission tomography–computed tomography (scan)
PFS	progression-free survival

Abbreviation	Definition
P-gp	P-glycoprotein
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PopPK	population pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q3W	every 3 weeks
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CHP	rituximab plus cyclophosphamide, doxorubicin, and prednisone
R/R	relapsed or refractory
SCT	stem cell transplantation
SD	stable disease
$t_{1/2}$	terminal half-life
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
ULN	upper limit of normal
vc-MMAE	valine-citrulline-monomethyl auristatin E
VZV	*Varicella* zoster virus

1. BACKGROUND

1.1 BACKGROUND ON DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma (NHL), accounting for approximately 30% of all NHL cases (Armitage and Weisenburger 1998). DLBCL arises from mature B cells, the majority of which express a CD20 cell surface protein. Several genetic abnormalities have been identified in subsets of patients with DLBCL. The most frequently dysregulated genes include *BCL6* (35%–40%), *BCL2* (translocation 15%, amplification 24%), and *c-MYC* (15%).

Standard-of-care therapies for NHL involve multi-agent chemotherapy with non–cross-resistant mechanisms of action combined with immunotherapy. In DLBCL, the addition of the CD20-directed monoclonal antibody (MAb) rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone (CHOP)-based chemotherapy results in significantly improved survival, as demonstrated by three randomized prospective studies, comprising a total of approximately 2000 patients with newly diagnosed advanced DLBCL (Coiffier et al. 2002, 2007, 2010; Feugier et al. 2005; Habermann et al. 2006; Pfreundschuh et al. 2008). On the basis of the above studies, up to 8 cycles of rituximab combined with 6 or 8 cycles of CHOP or CHOP-like chemotherapy (rituximab plus CHOP [R-CHOP]) is considered to be the standard of care for patients with previously untreated DLBCL (Tilly et al. 2012; National Comprehensive Cancer Network [NCCN] 2014), with approximately 60% of patients being cured of their disease.

Although there is currently no way to prospectively identify individual patients 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 prognostic of overall survival (OS) (Shipp et al. 1993):

- Age ($\leq$60 vs. $>$60 years)
- Serum 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. Although patients with 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 (Shipp et al. 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).

For patients who are not cured by first-line therapy, high-dose chemotherapy followed by autologous stem cell transplantation (SCT) offers a second chance for cure in some of those patients. However, approximately half of patients will not respond to subsequent therapy because of refractory disease (Gisselbrecht et al. 2010), and a significant number are ineligible for this aggressive therapy because of age or comorbidities.

Patients who either relapse after or are ineligible for SCT because of refractory disease or frailty have poor outcomes. Responses to subsequent therapies range from 10% to 35% in most cases (Robertson et al. 2007; Coleman et al. 2008; Wiernik et al. 2008) with only occasional durable responses. The fact that most patients who are not cured by the standard frontline R-CHOP or comparable immunochemotherapy will die of lymphoma underscores the need for novel approaches in subsequent lines of therapy for this aggressive disease.

Despite improvements in clinical outcomes of patients with NHL due to advances in treatments such as rituximab, indolent B-cell malignancies remain incurable, as do approximately half of aggressive NHLs, especially those with intermediate or high IPI. A need exists for treatments that can significantly extend disease-free survival and OS in these patients, with at least acceptable, if not superior, safety and tolerability profiles.

1.2 BACKGROUND ON POLATUZUMAB VEDOTIN

CD79b is a cell surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B-cell derived malignancies, including nearly all NHL and chronic lymphocytic leukemia (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, 2009).

Polatuzumab vedotin is an antibody-drug conjugate (ADC) that contains a humanized IgG1 anti-human CD79b MAb (MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB). MMAE has a mode 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 at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released following cleavage of the linker by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth (Doronina et al. 2003). This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE and the increased potency of MMAE compared with 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.

1.2.1 Nonclinical Studies with Polatuzumab Vedotin

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

1.2.2 Clinical Studies with Polatuzumab Vedotin

Clinical data on polatuzumab vedotin in patients with NHL or CLL are available from *four* Phase I/Ib studies (DCS4968g, JO29138*, GO27834, and GO29044*) and *four* ongoing Phase Ib/II studies (GO29365, GO29833, GO29834, and BO29561) in patients with B-cell lymphoma:

- DCS4968g evaluated polatuzumab vedotin as a single agent and in combination with rituximab in patients with relapsed or refractory (R/R) B-cell lymphoma and CLL.
- JO29138 is evaluating polatuzumab vedotin as a single agent in Japanese patients with R/R B-cell lymphoma.
- GO27834 evaluated polatuzumab vedotin in combination with either obinutuzumab or rituximab in patients with R/R follicular lymphoma (FL) or DLBCL.
- GO29044 evaluated polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) or obinutuzumab plus cyclophosphamide, doxorubicin, and prednisone (CHP) in patients with newly diagnosed or R/R B-cell lymphoma.
- GO29365 is evaluating polatuzumab vedotin in combination with bendamustine plus rituximab or obinutuzumab in patients with R/R FL or DLBCL.
- GO29833 is evaluating polatuzumab vedotin in combination with venetoclax and either obinutuzumab or rituximab in patients with R/R FL or DLBCL, respectively.
- GO29834 is evaluating polatuzumab vedotin in combination with lenalidomide and either obinutuzumab or rituximab in patients with R/R FL or DLBCL, respectively.
- BO29561 is evaluating polatuzumab vedotin in combination with atezolizumab and either obinutuzumab or rituximab in patients with R/R FL or DLBCL, respectively.
- GO39942 (POLARIX) is evaluating polatuzumab vedotin in combination with R-CHP in patients with newly diagnosed DLBCL.

Single-agent safety and efficacy of polatuzumab vedotin was assessed in Study DCS4968g. Polatuzumab vedotin was assessed in patients with B-cell lymphoma at doses from 0.1 to 2.4 mg/kg every 3 weeks (Q3W). Among 86 patients with B-cell lymphoma or CLL treated with single-agent polatuzumab vedotin up to 2.4 mg/kg, the treatment-emergent events regardless of relationship to study drug reported in $>20\%$ of patients included neutropenia (38%), diarrhea (37%), pyrexia (31%), nausea (30%), peripheral sensory neuropathy (30%), fatigue (23%), and anemia (20%). Single-agent polatuzumab vedotin anti-tumor activity was observed at doses ≥ 1.8 mg/kg in patients with R/R indolent B-cell lymphoma and DLBCL. At a dose of 2.4 mg/kg, objective

responses were observed in 7 out of 16 patients (44%) with R/R indolent B-cell lymphoma and 14 out of 27 patients (52%) with R/R DLBCL. At a dose of 1.8 mg/kg, 2 partial responses (PRs) were observed in patients with R/R DLBCL (n=4). Based on the overall benefit–risk profile of polatuzumab vedotin, subsequent trials have mainly utilized a 1.8 mg/kg dose.

Clinical data from *previous* studies describing the safety and activity of polatuzumab vedotin combined with immunochemotherapy are summarized below.

Polatuzumab Vedotin, Bendamustine, and Rituximab in Relapsed or Refractory DLBCL

In the randomized Phase II study GO29365 (n=80), the addition of polatuzumab vedotin to bendamustine and rituximab (BR) has been shown to improve outcomes in transplant-ineligible patients with R/R DLBCL compared with BR alone (data from clinical cutoff date, 30 April 2018). Polatuzumab vedotin plus BR showed clinically meaningful efficacy with improvements in response rates that translated to prolongation of survival. The primary efficacy endpoint of CR rate at the primary response assessment based on positron emission tomography–computed tomography (PET-CT), as determined by an Independent Review Committee (IRC), was higher in the polatuzumab vedotin plus BR arm (40.0% [16 out of 40 patients]; 95% CI: 24.9% to 56.7%) compared with the BR arm (17.5% [7 out of 40 patients]; 95% CI: 7.3% to 32.8%). The difference in CR rates between arms was significant (Δ 22.5% in favor of polatuzumab vedotin plus BR; 95% CI: 2.6% to 40.2%; p=0.0261, Cochran Mantel Haenszel [CMH] χ^2). Duration of response (DOR), event-free survival (EFS), PFS, and OS were all higher with polatuzumab vedotin plus BR. The risk of death was reduced by 58% in patients treated with polatuzumab vedotin plus BR compared with BR (stratified hazard ration [HR]=0.42; 95% CI: 0.24 to 0.75; p=0.0023). Median OS was extended to 12.4 months (95% CI: 9.0 to not estimable) in the polatuzumab vedotin plus BR arm, from 4.7 months (95% CI: 3.7 to 8.3) in the BR arm. The treatment effect for survival was consistently observed across all subgroups of patients with R/R DLBCL tested. The safety profile of polatuzumab vedotin plus BR was acceptable and in line with that observed for BR.

Polatuzumab vedotin at 1.8 mg/kg in combination with bendamustine (90 mg/m^2) and rituximab (375 mg/m^2) was assessed in patients with R/R DLBCL or FL. Among 89 patients treated with the combination, the treatment-emergent events regardless of relationship to study drug reported in >20% of patients included neutropenia (43%), diarrhea (38%), nausea (38%), fatigue (36%), thrombocytopenia (29%), pyrexia (27%), anemia (26%), decreased appetite (25%), and constipation (20%).

The results of this study demonstrate that polatuzumab vedotin is an active agent in R/R DLBCL when given in combination with chemotherapy and a CD20-targeting MAb. This China-only study is bridging the R/R DLBCL randomized portion of Study GO29365.

Polatuzumab Vedotin in Previously Untreated DLBCL

The Phase Ib/II study GO29044 evaluated the recommended Phase II dose of polatuzumab vedotin at 1.8 mg/kg every 21 days with R-CHP in 45 patients with previously untreated DLBCL (Tilly et al. 2017). All 45 patients received at least one dose of study drug and 40 patients completed 6 or 8 cycles (23 and 17 patients, respectively). The safety profile (including hematologic toxicity, infections, and neurotoxicity) was comparable to that seen in the R-CHOP arm of the contemporary study BO21005/GOYA. The patients in Study GO29044 experienced similar rates of Grade 3 and 4 adverse events (57.8% vs. 60.3%), Grade 5 adverse events (2.2% vs. 4.3%), and serious adverse events (37.8% vs. 37.6%) when compared with the R-CHOP arm of BO21005/GOYA (Vitolo et al. 2016; Tilly et al. 2017).

Pharmacokinetic (PK) assessments did not demonstrate alterations to cyclophosphamide or doxorubicin PK when combined with polatuzumab vedotin, and dose intensity of R-CHP was also maintained with the incorporation of polatuzumab vedotin at 1.8 mg/kg.

Efficacy by positron emission tomography (PET), as measured by investigator-assessed response by modified Cheson 2007 criteria, was promising, with 78% achieving CR and 91% achieving OR at the end of treatment. In the context of the Phase II patient population having higher-risk features, such as 78% having IPI 3–5 (98% IPI 2–5) and a median age of 69 years, the treatment regimen of R-CHP plus polatuzumab vedotin 1.8 mg/kg, which is currently being further assessed in Study GO39942, has the potential to improve upon the current standard-of-care therapy (R-CHOP).

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

1.2.3 Pharmacokinetic and Immunogenicity Properties of Polatuzumab Vedotin

The PK characteristics of polatuzumab vedotin three key analytes (conjugate, total antibody, and unconjugated MMAE [Gorovits et al. 2013; Kaur et al. 2013]) after single-agent treatment in patients with NHL based on a non-compartmental analysis (NCA) in the Phase I study DCS4968g are summarized below. Results are based on a relatively intensive PK sampling schedule.

- The disposition of polatuzumab vedotin conjugate (evaluated as antibody-conjugated-MMAE [acMMAE]) appears driven by its antibody component. The PK properties of acMMAE and total antibody are largely similar and highly correlated, as characterized by a steady–state volume of distribution close to the physiological serum/plasma volume, low clearance, and relatively long terminal half-life ($t_{1/2}$).
- After the first dose of 1.8 mg/kg polatuzumab vedotin, the acMMAE mean (standard deviation) maximum plasma concentration (C_{max}) was 803 (233) ng/mL, the area under the concentration–time curve from Time 0 to infinity (AUC_{inf}) was 1860 (966) day • ng/mL, and the $t_{1/2}$ was 5.05 (1.60) days.

- After the first dose of polatuzumab vedotin, the C_{max} and AUC_{inf} for acMMAE, total antibody, and unconjugated MMAE increased approximately dose-proportionally over the 0.1 to 2.4 mg/kg dose range.
- Mild increases of plasma acMMAE and serum total antibody pre-dose concentrations were observed with repeated Q3W dosing. The average Cycle 4 Day 1 pre-dose concentration was approximately 1.5-fold of the average concentration at Cycle 2 Day 1 pre-dose for acMMAE and 2.4-fold for total antibody.
- Unconjugated MMAE is a catabolite of polatuzumab vedotin and its pharmacokinetics appears to follow formation-rate limited kinetics, as indicated by relatively long $t_{1/2}$ (2.92 to 6.44 days across doses of 0.1–2.4 mg/kg). The time to maximum plasma concentration was 2.01–3.41 days across doses of 0.1–2.4 mg/kg. After the first dose of 1.8 mg/kg, the mean (standard deviation) C_{max} was 6.82 (4.73) ng/mL ($N = 6$).
- Plasma exposures of unconjugated MMAE were much lower compared with acMMAE ($< 1\%$ by C_{max}, and $< 3\%$ by AUC_{inf}, at 1.8 mg/kg).
- There was no apparent increase of plasma trough concentrations of unconjugated MMAE after repeated Q3W dosing.

The PK profiles and parameters were similar in the absence and presence of rituximab, suggesting that rituximab has little impact on polatuzumab vedotin pharmacokinetics in the patient population with R/R NHL. Given the various CYPs involved for metabolism of MMAE and bendamustine, the risks of PK interactions between them is low, as described below.

Drug-drug interaction (DDI) risk for polatuzumab vedotin given in combination with BR:

- There are no clinically meaningful drug interactions for polatuzumab vedotin given in combination with BR.

  Based on the population PK analysis, the rituximab combination was associated with mildly higher acMMAE Cycle 6 exposures (24% for area under the concentration–time curve [AUC], 5% for C_{max}) and moderately lower unconjugated MMAE Cycle 6 exposures (37% for AUC, 40% for C_{max}). This magnitude of higher acMMAE exposures is not expected to have a clinically relevant impact on safety based on the exposure-safety analysis. Bendamustine has no impact on acMMAE and unconjugated MMAE exposures.

  Polatuzumab vedotin does not affect the pharmacokinetics of rituximab and bendamustine. Both the observed data and the population PK simulated exposures were similar with or without polatuzumab vedotin combination ($< 10\%$ difference). The bendamustine PK parameters estimated by NCA are similar in patients who received polatuzumab vedotin plus BR versus BR alone ($< 20\%$ differences for each parameter).

- DDI potential for unconjugated MMAE with CYP3A substrate, inhibitor, or inducer as co-medications

  Based on a physiologically based pharmacokinetic model verified with clinical DDI data of brentuximab vedotin, an ADC with the same link-payload valine-citrulline-MMAE (vc-MMAE), co-administration of polatuzumab vedotin with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin) may result in changes of unconjugated MMAE exposure (48% higher AUC by ketoconazole, 49% lower AUC by rifampin); co-administration of polatuzumab vedotin does not appear to affect the exposure of midazolam, a CYP3A4 substrate. The 48% higher unconjugated MMAE exposures with a strong CYP3A inhibitor is not expected to have a clinically relevant impact on safety based on the exposure-safety analysis. Thus, no adjustment of starting dose is warranted when given in combination.

Key summary of ethnic sensitivity analysis in polatuzumab vedotin pharmacokinetics among the Asian population compared with the global population are presented below.

Overall, no clinically meaningful difference in the pharmacokinetics of polatuzumab vedotin has been observed for patients enrolled from Asia or patients of Asian race. Therefore, no adjustment of dose is warranted for Asian patients. Key PK findings relevant to the Asian population, assessed on the basis of both race and region, are as follows:

- In the pivotal study GO29365, the direct observed mean Cycle 4 acMMAE and total antibody C_{max} and trough concentration (C_{trough}), as well as unconjugated MMAE C_{trough}, were 9.9%−17.5% lower in patients enrolled from Asia (n = 10, South Korea being the only country) compared with patients enrolled outside of Asia (n = 124).
- Based on observed monotherapy PK data, when comparing the pharmacokinetics of polatuzumab vedotin among Japanese (Study JO29138) and global (Study DCS4968g) patients with NHL, no clinically relevant difference was observed. With the limited number of evaluable Japanese patients (n = 6), the dose-normalized C_{max} and AUC_{inf} were largely similar between the two studies. The dose-normalized C_{max} and AUC_{inf} for acMMAE, the key analyte of interest for exposure-safety/efficacy relationships, were comparable between Japanese and global patients. Some trends were observed toward higher total antibody exposure (~37%) and lower unconjugated MMAE exposure (~61%) in Japanese patients. However, on the basis of these results, no dose adjustment has been made for the ongoing registration-enabling Japanese Phase II Study JO40762, where a regimen of 1.8 mg/kg Q3W was selected.
- **Population pharmacokinetic (PopPK) evaluation on race:** Based on 460 NHL patients from Studies GO29365, DCS4968g, GO27834, and GO29044, race (Asian vs. non-Asian) was identified as a statistically significant covariate for central volume of acMMAE (V_1) in the popPK model, but the magnitude of impact on C_{max} was small (7.3% higher for Asian) based on the sensitivity analysis and thus not clinically meaningful. Asian (n = 18) and non-Asian (n = 422) patients showed nearly identical (< 1.2% difference) simulated Cycle 6 acMMAE C_{max} and AUC. For unconjugated

MMAE, exposure was numerically lower in Asian patients (18.6% for AUC and 16.9% for C_{max}) compared with non-Asian patients.

- **PopPK evaluation on region:** Region was not formally tested as a covariate in the popPK model, given that it is highly correlated with race. The simulated Cycle 6 exposures of patients enrolled from Asia ($n = 10$) and non-Asia regions ($n = 450$) suggested that acMMAE exposures in patients enrolled from Asia were nearly identical ($< 10\%$ difference) to the exposures of patients from non-Asia regions, while unconjugated MMAE exposures were numerically lower (25% for AUC and 23.2% for C_{max}) for patients enrolled from Asia.
- The prediction-corrected visual predictive check plots by popPK for acMMAE and unconjugated MMAE further confirmed there is no clinically meaningful difference by race and region.

In conclusion, observed PK data and popPK analyses suggest that there is no clinically meaningful difference in polatuzumab vedotin pharmacokinetics among the Asian population compared with the global population. Therefore, no adjustment of dose is warranted for Asian patients.

Key summary of anti-drug antibody (ADA) observations from clinical studies:

- As of September 2018, across all patients including Study GO29365 (excluding patients in Arm G) and six additional supportive studies, the postbaseline ADA incidence is 2.6% (14 out of 536 patients). The low observed incidence of ADAs is not unexpected given that the mechanism of action of polatuzumab vedotin is to target and kill B-cells and that most patients are co-medicated with rituximab.
- In Study GO29365 (excluding Arm G), the incidence of treatment-emergent (sum of treatment-induced and treatment-enhanced) ADA is 6.0% (8 of 134 patients).
- Based on the simulated exposures using individual empirical Bayes estimate parameters with partial covariate correction method, for the ADA-positive patients with NHL ($N = 12$ PK-evaluable patients with NHL), the acMMAE exposures are similar to the ADA-negative patients ($< 10\%$ difference). The unconjugated MMAE exposures are slightly higher in ADA-positive patients (10% for AUC, 24% for C_{max}), but the differences were not statistically significant (geometric mean ratios included 1). Thus, positive ADA response is not expected to have a clinically relevant impact on polatuzumab vedotin PK exposures.
- Due to the limited number of ADA-positive patients following administration of polatuzumab vedotin, no conclusions can be drawn concerning a potential effect of immunogenicity on safety or efficacy. However, no obvious correlation has been identified between ADA response and safety, and the emergence of ADAs to polatuzumab vedotin did not appear to impact efficacy of ongoing long-term responses in the few patients that were antibody positive.

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

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

DLBCL expresses the CD20 antigen, and anti-CD20 antibody therapy (rituximab) has been demonstrated to provide enhanced anti-tumor activity in combination with other agents targeting the disease leading to increased response rates, PFS and OS, which led to acceptance of rituximab as a standard component in initial therapy (Coiffier et al. 2002, 2007, 2010; Feugier et al. 2005; Hiddemann et al. 2005; Habermann et al. 2006; Herold et al. 2007; Marcus et al. 2008; Pfreundschuh et al. 2008; Salles et al. 2008).

Progress has been made in the treatment of DLBCL; however, a significant number of patients will not be cured of the disease. Instead, they will experience relapse or die of progression or treatment-related toxicity. There is a need for the continued development of safe and effective therapies for patients with disease that relapses or for those patients who develop refractory disease during or after first-line therapy.

Common regimens used to treat transplant-eligible patients with R/R DLBCL are also used to treat transplant-ineligible patients. Of note, not all of patients in these studies were pretreated with rituximab. It is known from an analysis of the CORAL study (Gisselbrecht 2010) that patients who were pretreated with rituximab and relapse have a much worse outcome than those patients who were rituximab naive. More commonly used chemotherapy regimens with or without rituximab for R/R DLBCL have overlapping toxicities (neurotoxicity and hematologic toxicity) with polatuzumab vedotin, making combination together unlikely. BR is active in R/R DLBCL but is associated with manageable hematologic toxicity. For these patients with DLBCL who are not candidates for high-dose therapy, BR is also a recommended second-line therapy (NCCN 2019).

Three studies have evaluated the combination of BR in R/R DLBCL (Ohmachi et al. 2013; Vacirca et al. 2014; Dang et al. 2018). In one of the Phase II trials, the OR rate was 63% (37% CR/unconfirmed CR) and median PFS was 6.7 months (Ohmachi et al. 2013); for the second Phase II trial, the OR rate was 46% and median PFS was 3.6 months (Vacirca et al. 2014). In the Phase III trial, in which 137 patients received BR, the OR rate was 48% (17% CR, 4% unconfirmed CR) and the median DOR was 7.2 months (6.5–10.8 months) (Dang et al. 2018).

Polatuzumab vedotin is an ADC designed for the targeted delivery of MMAE, a potent microtubule inhibitor to lymphoma cells expressing CD79b. MMAE has a mechanism of action that is similar to that of vincristine. Study GO29365 demonstrated a clinically meaningful benefit with the addition of the novel ADC, polatuzumab vedotin, to BR compared with BR alone. In the randomized comparison, the polatuzumab vedotin (1.8 mg/kg) plus BR combination showed significantly improved CR rates, PFS, and OS compared with BR alone. The risk of death was reduced by 58% in patients treated with polatuzumab vedotin plus BR compared with BR (stratified HR 0.42; $p = 0.0023$). Median OS was more than 2.5 times longer in patients receiving polatuzumab vedotin plus BR compared with BR alone (12.4 vs. 4.7 months).

The same trend has been observed within the Asian patient population. No previously reported Phase III randomized study has shown a survival benefit in this population of patients (Czuczman et al. 2017; Dang et al. 2018). Study GO29365 is the first randomized study to show survival benefit in transplant-ineligible patients with R/R DLBCL. In addition, currently available PK data from Asian patients treated with polatuzumab vedotin did not show clinical meaningful differences. The safety profile between Asia and the global population is consistent on the basis of data from Study GO29365. Considering there is no ethnic difference, the Sponsor believes the combination of polatuzumab vedotin plus BR can provide an available treatment option worldwide for patients with R/R DLBCL.

This China-only bridging study is designed to demonstrate comparable risk and benefit of polatuzumab vedotin plus BR in Chinese patients with R/R DLBCL and support the registration of the R/R DLBCL indication in China.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of polatuzumab vedotin plus BR compared with placebo plus BR in Chinese patients with R/R DLBCL. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., polatuzumab vedotin/placebo, bendamustine, and rituximab).

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of polatuzumab vedotin plus BR compared with placebo plus BR in Chinese patients with R/R DLBCL on the basis of the following endpoint. This objective is to *investigate* whether the benefit (in terms of CR rate at end of treatment assessment) of administrating polatuzumab vedotin plus BR in this study is consistent with the benefit observed in the global study, GO29365.

- CR at the end of treatment assessment (6–8 weeks after Cycle 6 Day 1 or final dose of study treatment) based on PET-CT, as determined by the IRC according to the Lugano Response Criteria for Malignant Lymphoma, hereafter referred to as the "Lugano Response Criteria" (Cheson et al. 2014; see Appendix 3)

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of polatuzumab vedotin plus BR compared with placebo plus BR in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- CR at the end of treatment assessment based on PET-CT, as determined by the investigator according to the Lugano Response Criteria

- OR, defined as CR or PR, at the end of treatment assessment based on PET-CT, as determined by the investigator and IRC according to the Lugano Response Criteria
- CR at the end of treatment assessment based on computed tomography (CT) only, as determined by the investigator and IRC according to the Lugano Response Criteria
- OR, defined as CR or PR, at the end of treatment assessment based on CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- Best objective response (BOR), defined as CR or PR, while on study based on PET-CT or CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression, relapse, or death from any cause based on PET-CT or CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- PFS, defined as the period from date of randomization until the date of disease progression, relapse, or death from any cause based on PET-CT or CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- EFS, defined as the time from date of randomization to any treatment failure including disease progression, relapse, initiation of new anti-lymphoma treatment (NALT), or death based on PET-CT or CT only, as determined by the investigator according to the Lugano Response Criteria
- OS, defined as the time from date of randomization until the date of death from any cause

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of polatuzumab vedotin plus BR compared with placebo plus BR in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence and nature of study drug discontinuation, dose reduction, and dose delay due to adverse events

Additionally, this study *will* evaluate the safety of polatuzumab vedotin plus BR compared with placebo plus BR from the patient's perspective to better understand treatment impact, tolerability, and reversibility on the basis of the following endpoint:

- Change from baseline in peripheral neuropathy as assessed through use of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-NTX)

2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the PK for total antibody, acMMAE, and unconjugated MMAE following polatuzumab vedotin administration, when combined with BR, in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- Serum concentration of total antibody at specified timepoints
- Plasma concentration of acMMAE at specified timepoints
- Plasma concentration of unconjugated MMAE at specified timepoints

Additionally, this study *will* evaluate potential relationships between polatuzumab vedotin exposure and the efficacy and safety of polatuzumab vedotin, when combined with BR, in Chinese patients with R/R DLBCL on the basis of the following endpoints:

- Relationship between plasma concentration or PK parameters for polatuzumab vedotin and efficacy endpoints
- Relationship between plasma concentration or PK parameters for polatuzumab vedotin and safety endpoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to polatuzumab vedotin, when combined with BR, in Chinese patients with R/R DLBCL on the basis of the following endpoint:

- Prevalence of ADAs for polatuzumab vedotin at baseline and incidence of ADAs during the study

Additionally, this study *will* evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status for polatuzumab vedotin and efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVE

The biomarker objective for this study is to evaluate *the* response to polatuzumab vedotin*, when combined* with BR*, in Chinese* patients *with R/R DLBCL* with known prognostic factors, *such as* activated B cell *(*ABC*)-DLBCL or* germinal center B cell [GCB*]-DLBCL, as analyzed through use of a centrally performed RNA-based assay, or co-expression of BCL2 and MYC (double-expressor [DEL]) as analyzed through use of centrally performed immunohistochemistry (IHC) tests. In addition, the association between response and the expression of the target of polatuzumab vedotin, CD79b (as analyzed through use of a centrally performed IHC test) will be evaluated.*

- *CR at the end of treatment assessment based on PET-CT, as determined by the IRC according to the Lugano Response Criteria in populations of ABC-DLBCL, GCB-DLBCL, DEL, and expression of CD79b*

- *OR, defined as CR or PR, at the end of treatment assessment based on PET-CT, as determined by the IRC according to the Lugano Response Criteria in populations of ABC-DLBCL, GCB-DLBCL, DEL, and expression of CD79b*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of polatuzumab vedotin in combination with BR compared with BR alone in Chinese patients with R/R DLBCL.

Approximately 42 Chinese patients will be randomized to one of the following treatment arms in a 2:1 ratio:

- Polatuzumab vedotin plus BR (experimental arm)
- Placebo plus BR (control arm)

Randomization will be conducted with the aid of an interactive web-based response system (IxRS) and will be stratified according to the following factors:

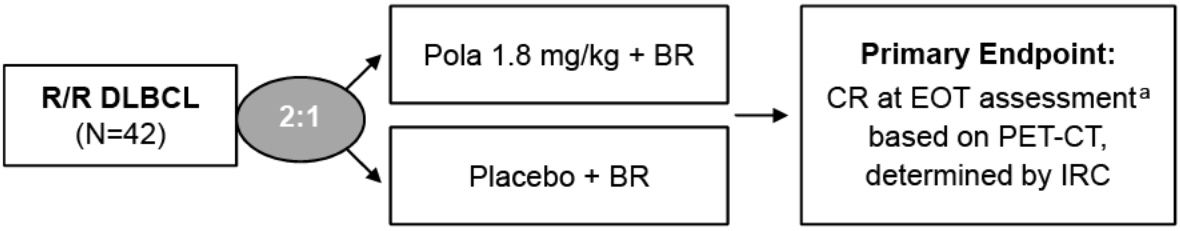
- DOR to most recent prior therapy: $\leq$ 12 months versus $>$ 12 months
- Number of prior therapies (1 vs. $\geq$2)

  For consistency with the pivotal study population (Study GO29365), patients with $\geq$2 prior lines of therapy will be capped within 70% of the whole population.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Study treatment will be administered by IV infusion every 21 days for up to 6 cycles, as described in Section 3.1.2 and Figure 2. The first day of treatment will constitute Study Day 1. Refer to Section 4.3.2 for details on study treatment dosage and administration.

Figure 1 Study Schema



Notes: The screening period is from Days –28 to –1. Study treatment will be administered every 21 days for 6 cycles, as described in Section 3.1.2.

BR = bendamustine and rituximab; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EOT=end of treatment; IRC = Independent Review Committee; PET-CT positron emission tomography–computed tomography (scan); Pola = polatuzumab vedotin; R/R = relapsed or refractory.

[a] The end of treatment assessment is 6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment.

All patients will be closely monitored for adverse events and serious adverse events throughout the study and for 90 days after the final dose of study treatment (see Section 5.3.1). Adverse events will be graded according to NCI CTCAE v5.0. Laboratory safety assessments will include regular monitoring of hematology and blood chemistry, and tests of immunological parameters.

Blood samples will be taken at various timepoints during the study to analyze the PK properties of polatuzumab vedotin (total antibody, acMMAE, and unconjugated MMAE), as well as the immunogenicity of polatuzumab vedotin, when given in combination with BR (see Appendix 2).

Response will be determined by an IRC and investigators using the Lugano Response Criteria (Cheson et al. 2014; Appendix 3) at the following timepoints:

- Screening: within 35 days of Cycle 1 Day 1
- Interim response assessment: between Cycle 3 Day 15 and Cycle 4 Day 1
- End of treatment assessment: 6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment

For patients with disease progression occurring prior to the anticipated date of the end of treatment assessment, the visit date with the response assessment showing disease progression will be used in replacement of the end of treatment assessment.

Imaging at these timepoints must include PET scans in conjunction with diagnostic-quality CT scans with both oral and IV contrast (see Section 4.5.5). An independent review of the responses of all patients will also be conducted to confirm the primary CR endpoint (see Section 3.1.3).

Patients who complete the study treatment period will return to the clinic for a treatment completion visit 30 (±5) days after the final dose of study treatment (Cycle 6 Day 1). Patients who discontinue study treatment prematurely will return to the clinic for a treatment discontinuation visit 30 (±5) days after the final dose of study treatment.

Disease Progression and Follow Up

Following completion of treatment, patients who have not progressed will be followed clinically every 3 months (±14 days) according to the schedule of activities (Appendix 1). Tumor assessments should also be performed to confirm clinical suspicion of relapse or disease progression for documentation. Follow-up visit intervals should be determined from the end of treatment assessment.

CT (preferred) or PET-CT scans should be performed during follow-up:

- Every 6 months after the end of treatment assessment until disease progression, study withdrawal, end of study, or death, whichever comes first; or
- At any time that disease progression is suspected via clinical response assessment

For patients who have disease progression and have not started new anti-lymphoma therapy, follow-up should consist of recording of first new anti-lymphoma therapy, adverse events, and survival and continue to follow the above schedule. For patients who have disease progression and started a new anti-lymphoma therapy, contact will be made by telephone on at least an annual basis for survival. For patients who started a new anti-lymphoma therapy but do not have disease progression, assessments should be followed according to the schedule of activities, including response assessments and adverse events.

Patients who discontinue all components of study treatment prior to disease progression (e.g., for toxicity) will continue in the study and will be followed for progressive disease and OS (regardless of whether they subsequently receive a new anti-lymphoma therapy).

3.1.2 Study Treatment Regimen

Patients will receive a total of 6 cycles of polatuzumab vedotin or placebo in combination with BR (see Figure 2). A cycle is typically 21 days.

For the purposes of ensuring consistent PK measurements, treatments will be administered sequentially in the order specified below.

Schedule for Cycle 1

Cycle 1 Day 1

- Rituximab 375 mg/m^2 IV infusion

Cycle 1 Day 2

- Polatuzumab vedotin/placebo IV infusion
- Bendamustine 90 mg/m^2 IV infusion

Cycle 1 Day 3

- Bendamustine 90 mg/m^2 IV infusion

Schedule for Cycles 2–6

As long as the observed individual patient safety profile of polatuzumab vedotin/placebo and BR allows all study treatment infusions to be given on the same day, then the study treatment infusions will be given sequentially on the same day for Cycles 2–6 and in the order specified below.

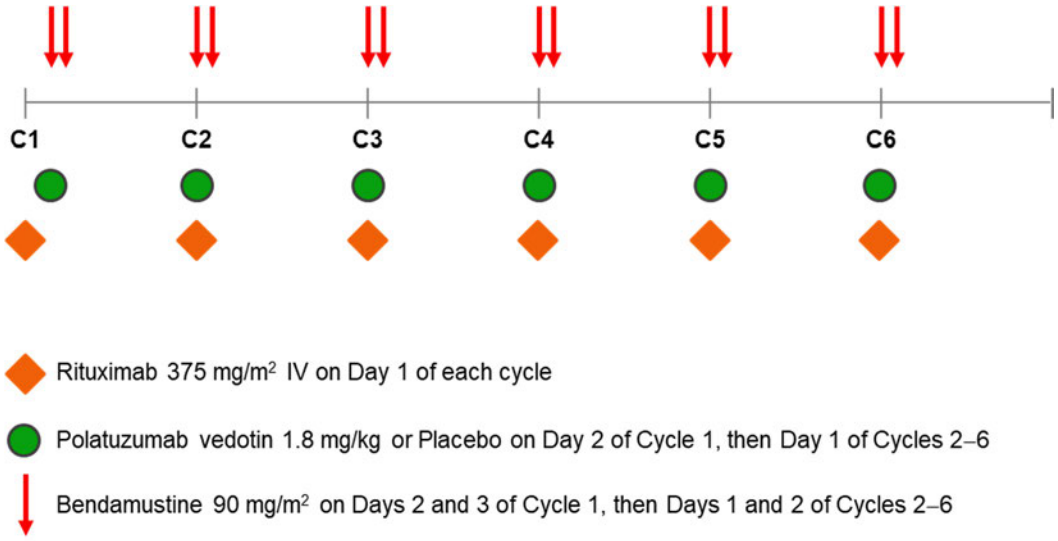
Cycles 2–6 Day 1

- Rituximab 375 mg/m^2 IV infusion
- Polatuzumab vedotin/placebo IV infusion
- Bendamustine 90 mg/m^2 IV infusion

Cycles 2–6 Day 2

- Bendamustine 90 mg/m^2 IV infusion

Figure 2 Polatuzumab Vedotin/Placebo plus BR Regimen



BR = bendamustine and rituximab; C = Cycle.

3.1.3 Independent Review Committee

An IRC composed of certified radiologists and a hematologist or oncologist with experience in malignant lymphoma will assess all patients for response (see Appendix 3) on the basis of imaging results and biopsy results that are performed related to efficacy evaluation. Decisions will be guided by a Charter specific to the independent review.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the timepoint at which approximately two-thirds of enrolled patients have experienced deaths, or all patients have discontinued from the study, whichever occurs first.

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

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 21 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Polatuzumab Vedotin Dose and Schedule

In Study GO29365, 6 cycles of treatment with polatuzumab vedotin 1.8mg/kg combined with rituximab (375mg/m^2) and bendamustine (90 mg/m^2) was well tolerated with a favorable risk and benefit profile. This data (n = 40) now expands to study Arms G and H with an additional 100 patients exposed at this dose level. There were no ethnic differences observed in Study GO29365, which have the same dose levels of study treatments that are considered appropriate for this China-only study.

3.3.2 Rationale for Patient Population

As previously stated, there continues to be a high unmet need worldwide for transplant-ineligible patients with R/R DLBCL. Current treatments available for this patient population have demonstrated a median PFS < 3 months (1.3–10 months) (Colosia et al. 2014); the median OS for non-eligible patients is only 6 months (Crump et al. 2017). For patients who relapse within 12 months, rituximab plus gemcitabine in combination with oxaliplatin (R + GemOx) demonstrated median PFS and OS of 3 months and 6 months, respectively. In a Phase II study of patients treated with BR in this patient population, the CR rate was only 15.3% with a median PFS of 3.6 months (Vacirca et al. 2014). Although chimeric antigen receptor (CAR) T-cell therapy is a revolutionary breakthrough in this area, patients may not be eligible for treatment, and treatment is not readily available. The 6-month response rate for treatment with CAR T-cell therapy is reported as 30%–54% (Neelapu et al. 2017; Schuster et al. 2017).

In Study GO29365, polatuzumab vedotin plus BR demonstrated a 40% CR rate versus the control arm (BR alone; 17.5% CR) in highly refractory patients (80% refractory to last prior therapy). The risk of death was reduced by 58% (stratified HR 0.42; p = 0.0023) and median OS was more than 2.5 times longer in patients treated with polatuzumab

vedotin plus BR compared with BR alone (12.4 vs. 4.7 months, respectively) (Sehn et al. 2018). Therefore, polatuzumab vedotin provides a new treatment choice for patients with R/R DLBCL.

Thus, there is an urgent clinical need for the study of new effective and tolerable therapies, such as polatuzumab vedotin plus BR, in transplant-ineligible patients with R/R DLBCL.

3.3.3 Rationale for Rituximab and Bendamustine Dose and Schedule

In Study GO29365, patients with R/R DLBCL receiving polatuzumab vedotin plus BR completed a median of 5 cycles with 46.7% completing all 6 treatment cycles and were treated for a median treatment duration of approximately 2.42 months for each individual component of study treatment. The majority of patients treated with polatuzumab vedotin plus BR received their planned doses of polatuzumab vedotin, bendamustine, and rituximab. Therefore, in this China-only bridging study of GO29365, the same dose level and schedule for bendamustine (90 mg/m^2 administered over 2 consecutive days on a 21-day cycle in patients with R/R DLBCL) will be used.

Three other studies have evaluated the combination of BR in patients with R/R DLBCL (Ohmachi et al. 2013; Vacirca et al. 2014; Dang et al. 2018). In these studies, rituximab was administered at a standard dose of 375 mg/m^2 on Day 1, followed by bendamustine 120 mg/m^2 over 2 consecutive days for up to 6 cycles. Cycles were administered on a 21-day (Ohmachi et al. 2013) or a 28-day cycle (Vacirca et al. 2014; Dang et al. 2018).

The most frequent Grade 3 or 4 adverse events observed in the Ohmachi and Vacirca studies were hematologic including neutropenia (Ohmachi: 31% Grade 3, 46% Grade 4; Vacirca: 29% Grade 3, 7% Grade 4) and febrile neutropenia (Ohmachi: 7% Grade 3, Vacirca: 7% Grade 4). Phase 3 data from the Dang study show that the most frequent adverse events occurring in patients receiving either BR or rituximab plus gemcitabine remain hematologic (thrombocytopenia: 87% any grade, 64% Grade $\geq$3; neutropenia: 35% any grade; 16% Grade $\geq$3).

In the Ohmachi study, 29% of patients (15 of 51 patients) who received Cycle 2 and 32% (14 of 44 patients) who received Cycle 3 required a dose reduction. Per study protocol, dose reductions of bendamustine from 120 mg/m^2 to 90 mg/m^2 were made for patients who developed Grade 4 hematologic toxicities, Grade $\geq$3 neutropenia lasting for 14 days or more, Grade $\geq$2 thrombocytopenia, or other Grade 3 or 4 non-hematologic toxicities. If toxicities recurred, then doses were further reduced to 60 mg/m^2. Because approximately one-third of patients required a dose reduction in Cycle 1, the pivotal study GO29365 has used a starting bendamustine dose of 90 mg/m^2 administered over 2 consecutive days on a 21-day cycle. Additionally, the International Consensus Panel recommended a bendamustine dose and schedule of 90 mg/m^2 Q3W when combined with rituximab for aggressive NHL (Cheson et al. 2010).

For transplant-ineligible patients with R/R DLBCL, there is no universal standard of care regimen used as no prior randomized trials have established the superiority of one regimen over another for this population (see Section 1.3). Guidelines such as those put forth by the NCCN include BR, which has shown activity in R/R DLBCL (Ohmachi et al. 2013; Vacirca et al. 2014; Hong et al. 2018).

In addition, cross-trial comparisons of survival outcomes between different regimens have significant limitations in terms of differences in enrolled or observed populations, such as numbers of refractory versus relapsed (or early relapsed) patients, numbers of prior lines of therapy (e.g., number of patients with one prior line vs. two or more, or if there was a maximum number of prior lines allowed in the trial), and when trials were conducted (some earlier trials occurred at a time when there were still a significant number patients who were not exposed to rituximab in first-line therapy). Thus, it remains difficult to draw definitive conclusions that regimens based on platinum or gemcitabine are truly superior to BR in the contemporary setting for the transplant-ineligible patient population with R/R DLBCL without a randomized trial. As BR has shown efficacy in two prospective single-arm trials and two randomized trials (Ohmachi et al. 2013; Vacirca et al. 2014; Dang 2018; Sehn et al. 2018), and is used in many centers to treat this population of patients, it is considered a relevant comparator.

As one of the first chemotherapy combinations explored in the clinical development plan, BR was selected to partner with polatuzumab vedotin to avoid potential overlapping of peripheral neuropathy that may be seen in platinum-based therapies. In order to assess the individual contribution of polatuzumab vedotin in the polatuzumab vedotin plus BR combination, BR was selected as the comparator.

3.3.4 Rationale for Biomarker Assessments

Biomarkers in the tumor that are associated with drug target, mechanism of action, and NHL biology may correlate with outcome and carry predictive or prognostic value. The activity of ADCs is dependent on a number of factors including the presence of the antibody target, internalization of the ADC, and sensitivity of the tumor cell to the payload drug; therefore, analysis of these factors may identify markers predictive of response. In addition, new therapeutic approaches in DLBCL appear to result in differential activity in DLBCL prognostic subgroups, including ABC versus GCB *and DLBCL with co-expression of BCL2 and MYC, all of which were recognized as prognostic markers by 2016 WHO DLBCL Classification (Swerdlow et al. 2016). Therefore,* it is of interest to understand the activity of a novel treatment*, such as polatuzumab vedotin plus BR,* in these DLBCL subtypes.

3.3.5 Rationale for Stratification Factors

For relapsed DLBCL, predictive factors have included initial remission duration of >1 year and the absence of bulky disease at the time of SCT (Sweetenham 2005).

In addition, in Study GO29365, prior treatment lines have shown a major impact on outcome. As a bridging study, this China-only study will use prior treatment lines ≥2 and remission duration of >1 year as stratification factors.

Given the marked heterogeneity in outcome based on these risk factors, patients will be stratified at randomization to take these factors into account.

3.3.6 Rationale for Clinical Outcome Assessments

3.3.6.1 PET-Defined Complete Response

PET scanning has been shown in multiple settings to be a more accurate tool for assessing activity of lymphoma than CT imaging. In aggressive lymphomas, such as DLBCL, PET-defined CR is a better predictor of PFS than response as defined by CT and now is the standard for fluorodeoxyglucose-avid lymphoma (Cheson 2015).

3.3.6.2 Patient-Reported Outcomes

In this study, peripheral neuropathy will be assessed using the FACT/GOG-NTX, as it is a treatment-related effect common to polatuzumab vedotin. The FACT/GOG-NTX evaluates treatment-induced neurologic symptoms (including sensory, hearing, motor, and dysfunction) and consists of 11 questions (see Appendix 5).

4. MATERIALS AND METHODS

Eligible patients must have R/R DLBCL and meet the following inclusion and exclusion criteria.

4.1 PATIENTS

Approximately 42 patients with R/R DLBCL will be enrolled in this study.

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
- Able to comply with the study protocol and procedures, in the investigator's judgment
- Transplant ineligible patients with R/R DLBCL, classified as below:
  - Patients who are ineligible for second-line SCT, with progressive disease or no response (stable disease [SD]) < 6 months from start of initial therapy (second-line refractory)
  - Patients who are ineligible for second-line SCT, with disease relapse after initial response ≥ 6 months from start of initial therapy (second-line relapsed)
  - Patients who are ineligible for third-line (or beyond) SCT, with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line or beyond refractory)

  - Patients who are ineligible for third-line (or beyond) SCT with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line or beyond relapsed)
- *Confirmed DLBCL diagnosis as:*
  - DLBCL, not otherwise specified (NOS) (including both GCB and ABC)
  - T-cell/histiocyte-rich large B-cell lymphoma
  - High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
  - High grade B-cell lymphoma, NOS
  - Primary mediastinal (thymic) large B-cell lymphoma
  - Epstein-Barr virus positive DLBCL, NOS
- For patients who have received prior bendamustine, a response duration > 1 year (for patients who have relapsed disease after a prior regimen)
- At least one bi-dimensionally measurable lesion, defined as > 1.5 cm in its longest dimension as measured by CT or magnetic resonance imaging (MRI)
- Availability of archival or freshly collected tumor tissue before study enrollment

  Formalin-fixed, paraffin-embedded tissue blocks are preferred.

  If a tissue block is not available, at least 11 unstained slides or freshly cut serial sections (3–5 μm in thickness), will be accepted.

  Of note, receipt of tumor samples is not necessary prior to study enrollment.
- Life expectancy of at least 24 weeks
- ECOG Performance Status of 0, 1, or 2
- Adequate hematologic function unless inadequate function is due to underlying disease, such as extensive bone marrow involvement or hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator. Adequate hematologic function is defined as follows:
  - Hemoglobin ≥ 9 g/dL
  - ANC ≥ 1.5×10^9/L
  - Platelet count ≥ 75×10^9/L
- 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 single highly effective or combined contraceptive methods with a failure rate of < 1% per year during the treatment period and for ≥ 12 months after the final dose study treatment. 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 regulations.

Examples of highly effective 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. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $<1\%$ per year. Barrier methods must always be supplemented with the use of a spermicide.

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 who are not surgically sterile: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men must remain abstinent or to use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 6 months after the final dose of study treatment. 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 study treatment 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.

- Residence in the People's Republic of China

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 MAbs (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products

- Contraindication to bendamustine or rituximab
- History of sensitivity to mannitol (mannitol is an excipient in bendamustine)
- Prior use of any MAb, radioimmunoconjugate, or ADC within 5 half-lives or 4 weeks, whichever is longer, before Cycle 1 Day 1
- 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 $\leq$ 2 prior to Cycle 1 Day 1.

    Recent treatment with rituximab is allowed given the timing of the last dose was greater than 2 weeks prior to Cycle 1 Day 1.

    Should prior treatment fall under more than one exclusionary criterion (e.g., MAb and immunotherapy), the more conservative criterion must be met.
- Ongoing corticosteroid use $>$ 30 mg/day prednisone or equivalent, for purposes other than lymphoma symptom control

    Patients receiving corticosteroid treatment $\leq$ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy (Cycle 1 Day 1).

    Ongoing corticosteroid usage is permitted for the purpose of lymphoma symptom control. For further details refer to Section 4.4.1.
- Completion of autologous SCT within 100 days prior to Cycle 1 Day 1
- Prior allogeneic SCT
- Prior treatment with CAR T-cell therapy
- Eligibility for autologous SCT
- Grade 3b FL
- History of transformation of indolent disease to DLBCL
- Primary or secondary CNS lymphoma
- Current Grade $>$1 peripheral neuropathy
- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include, but are not limited to:

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

    A patient with any other malignancy that has been treated with surgery alone with curative intent and the malignancy has been in remission without treatment for $\geq$ 3 years prior to enrollment is eligible.

    Patients with low-grade, early-stage prostate cancer 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 requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Patients with suspected or latent tuberculosis

  Latent tuberculosis should be confirmed according to local testing requirements.
- 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 *monthly (or* on Day 1 of every cycle*) during the study* and for at least 12 months after the last cycle of study treatment. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.
- Positive test results for hepatitis C virus (HCV) antibody

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

  For patients with unknown HIV status, HIV testing will be performed at screening.
- Known infection human T-cell leukemia virus 1 virus
- Vaccination with a live vaccine within 28 days prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Pregnant or breastfeeding or intending to become pregnant during the study or within 12 months after the final dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
  - Serum creatinine clearance $<$40 mL/min (using Cockcroft-Gault formula)
  - AST or ALT $>$ 2.5 $\times$ upper limit of normal (ULN)
  - Total bilirubin $\geq$ 1.5 $\times$ ULN

Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq 3 \times$ ULN.

  - INR or PT $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

4.1.3 Criteria for Lymph Node Biopsy Tissue

Patients must meet following criteria for lymph node biopsy tissue:

- The specimen must contain adequate evaluable tumor cells ($\geq$ 20% for excisional biopsy and $\geq$ 50% if sample is a core biopsy) to enable relevant biomarker analysis.
- A tissue block (preferred) or 11 serial, freshly cut, unstained slides accompanied by an associated pathology report will be requested. Cytological or fine-needle aspiration samples are not acceptable. In countries that use a different fixative than formalin, available tissue block will be accepted and notation of the type of fixative should be included.

If the archival tissue is unavailable or insufficient on the basis of the above criteria, the patient may still be eligible if the patient is willing to provide tissue from a pretreatment core or excisional/incisional biopsy of the tumor. Cytological or fine-needle aspiration samples are not acceptable. If a tissue block is provided, after necessary sections are cut, the remaining specimen will be returned to site upon request. Tissue collected on study will not be returned to sites.

Refer to the laboratory manual for additional details.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

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

Patients will be randomly assigned to one of two treatment arms: experimental arm (polatuzumab vedotin plus BR) or control arm (placebo plus BR). Randomization will occur in a 2:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- DOR to most recent prior therapy ($\leq$ 12 months vs. $>$ 12 months)

- Number of prior therapies (1 vs. ≥2)

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the clinical supply chain managers, sample handling staff, operational assay group personnel, and IxRS service provider.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

To optimize timelines for delivery of PK-related analyses, unblinded PK and ADA data may be released to selected clinical pharmacology personnel before the clinical cutoff date, prior to study unblinding.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and

personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Polatuzumab Vedotin and Placebo

Polatuzumab vedotin and placebo will be supplied by the Sponsor as a sterile, white to grayish-white, preservative-free lyophilisate in single-use vials. Polatuzumab vedotin or placebo should be prepared and administered in the same manner. For information on the formulation and handling of polatuzumab vedotin or placebo, see the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure.

4.3.1.2 Rituximab

Rituximab (MabThera®/Rituxan®) 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 Bendamustine

Bendamustine hydrochloride will be supplied by the Sponsor. For information on the formulation, packaging, and handling of bendamustine hydrochloride, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen is summarized in Section 3.1.2.

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

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

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4.

The 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 $>$ 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. *Sites may calculate the dose based on real-time weight.*

4.3.2.1 Polatuzumab Vedotin and Placebo

Polatuzumab vedotin (1.8 mg/kg) or placebo will be administered by IV infusion on Day 2 of Cycle 1 and then Day 1 of Cycles 2–6. Refer to Section 3.1.2 and Figure 2 for details on the study treatment regimen.

Given the double-blinded nature of this study, site staff will be unaware of the treatment assignment of each patient. The dosage, preparation, administration, and compliance for both polatuzumab vedotin and the placebo for polatuzumab vedotin will be identical.

After reconstitution with Sterile Water for Injection and dilution into IV bags that contain isotonic sodium chloride solution (0.9% NaCl), polatuzumab vedotin/placebo will be administered by IV infusion using a dedicated standard administration set with 0.2-μm or 0.22-μm in-line filters at a final polatuzumab vedotin/placebo concentration determined by the patient-specific dose. Compatibility of polatuzumab vedotin/placebo with IV bags, infusion lines, filters, and other infusion aids has been established with items made of specific materials of construction. Please consult the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure for a list of compatible materials and specific dose preparation instructions.

The initial dose will be administered to patients who are well hydrated over 90 (±10) minutes. Premedication (e.g., 500–1000 mg of oral acetaminophen or paracetamol and 50–100 mg diphenhydramine as per institutional standard practice) may be administered to an individual patient before administration of polatuzumab vedotin/placebo (which may have already been administered as a premedication for rituximab). If infusion-related reactions (IRRs) are observed with the first infusion of polatuzumab vedotin in the absence of premedication, premedication must be administered before subsequent doses per Table 2.

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

4.3.2.2 Rituximab

Rituximab (375 mg/m^2) will be administered by IV infusion on Day 1 of Cycles 1–6. Refer to Section 3.1.2 and Figure 2 for details on the study treatment regimen. No dose modifications of rituximab are allowed.

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 1).

All rituximab infusions should be administered to patients after premedication with oral acetaminophen (e.g., 650–1000 mg) and an antihistamine, such as diphenhydramine hydrochloride (50–100 mg), 30–60 minutes before starting each infusion (unless contraindicated). A 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 1. If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as rapid infusion (over 90 minutes) 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 5.1.4.3.

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (such as the B. Braun Infusomat® Space) should be used to control the infusion rate of rituximab. Administration sets with polyvinyl chloride (PVC), polyurethane, or polyethylene (PE) as a product contact surface and IV bags with polyolefine, polypropylene, 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 1 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 the patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as rapid infusion (over 90 minutes) in accordance with local institutional guidelines. • 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 Bendamustine

Bendamustine (90 mg/m^2) will be administered by IV infusion over 30–60 minutes on 2 consecutive days of each cycle (Days 2 and 3 in Cycle 1 and then Days 1 and 2 in Cycles 2–6). Refer to Section 3.1.2 and Figure 2 for details on the study treatment regimen.

BSA will be calculated at screening and should be used to calculate the dose of bendamustine 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 kg/m^2) may be implemented per institutional guidelines.

Administration of bendamustine should follow any rituximab and polatuzumab vedotin administration, if applicable. The administration rate of bendamustine may be implemented per institutional guidelines.

Premedication with antiemetics may be administered as per institutional guidelines (see Section 4.4). Granulocyte colony-stimulating factor (G-CSF) will be required as primary prophylaxis during each cycle of therapy. The decision not to administer G-CSF as primary prophylaxis should be made in consultation with and following the approval of the Medical Monitor.

Dose modification and dose delays will be implemented for hematologic toxicities.

4.3.3 Premedication

Patients should receive premedication as outlined in Table 2.

Table 2 Premedication for Rituximab and Blinded Polatuzumab Vedotin/Placebo

Timepoint	Patients Who Require Premedication	Premedication	Administration
Cycle 1 Day 1	All patients	Corticosteroid [a]	Complete ≥ 1 hour prior to rituximab infusion.
		Antihistamine drug [b] Analgesic/antipyretic [c]	Administer ≥ 30 minutes prior to rituximab infusion.
Cycle 1, Day 2	All patients	Corticosteroid [a]	Permitted at the discretion of the treating physician.
		Antihistamine drug [b] Analgesic/antipyretic [c]	Administer ≥ 30 minutes prior to polatuzumab vedotin/placebo infusion.
Cycles 2 and beyond, Day 1	Patients with no IRR during the previous infusion	Corticosteroid [a]	Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin/placebo infusion. May be omitted at the investigator's discretion.
		Antihistamine drug [b] Analgesic/antipyretic [c]	Administer ≥ 30 minutes prior to infusion. May be omitted or adapted at the investigator's discretion.
	Patients with Grade 1 or 2 IRR during the previous infusion	Corticosteroid [a]	Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin/placebo infusion.
		Antihistamine drug [b] Analgesic/antipyretic [c]	Administer ≥ 30 minutes prior to rituximab and/or polatuzumab vedotin/placebo infusion.
	Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion Patients with bulky disease	Corticosteroid (mandatory)	Complete ≥ 1 hour prior to rituximab and/or polatuzumab vedotin/placebo infusion.
		Antihistamine drug [b] Analgesic/antipyretic [c]	Administer ≥ 30 minutes prior to rituximab and/or polatuzumab vedotin/placebo infusion.

IRR = infusion-related reaction.

[a] A 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. Hydrocortisone should not be used, as it has not been effective in reducing rates of IRRs.

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

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

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (polatuzumab vedotin/placebo, rituximab, and bendamustine) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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.

4.3.5 Continued Access to Polatuzumab Vedotin and Rituximab

Currently, the Sponsor does not have any plans to provide Roche IMPs (polatuzumab vedotin and rituximab) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing polatuzumab vedotin and 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 drug to the treatment completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Oral contraceptives will be allowed.
- 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), if clinically indicated.
- Antiemetic therapy may be instituted for any patient if clinically indicated. Bendamustine has a moderate risk of emesis (Cheson et al. 2010). It is recommended that bendamustine infusions be administered following premedication with a serotonin (e.g., 5HT3) antagonist (i.e., dolasetron, ondansetron, etc.) or according to institutional practice.

- Systemic steroid therapy will not be allowed either during or within 7 days before the first dose of study treatment with the exception of the following:
  - Inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease
  - Premedication before rituximab, polatuzumab vedotin or bendamustine
  - Topical steroids
  - Stable replacement corticosteroid therapy for an inherited or acquired deficiency
  - Ongoing corticosteroid use for lymphoma symptom control
  - Corticosteroid treatment $\leq$30 mg/day of prednisone or equivalent on a stable dose prior to study enrollment and initiation of therapy (see Section 4.1.2)

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Vitamin D substitution is encouraged for patients with vitamin D deficiency (Bittenbring et al. 2014). Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.1.1 Treatment and Prophylaxis of Neutropenia

The administration of G-CSF is required as a primary prophylaxis in each cycle of therapy. 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. The decision not to administer G-CSF as primary prophylaxis should be made in consultation with and following the approval of the Medical Monitor.

4.4.1.2 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 syndrome (TLS) 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 (i.e., rasburicase), starting 48–72 hours prior to Cycle 1 Day 1 of treatment and hydration. Patients should continue to receive repeated prophylaxis with allopurinol if deemed appropriate by the investigator and adequate hydration prior to each subsequent cycle of treatment.

4.4.1.3 Prophylaxis for Infections

Given the risk of infections associated with bendamustine and the potential added risk with polatuzumab vedotin, antiviral (coverage for herpes simplex virus [HSV] and *Varicella* zoster virus [VZV]), and anti-pneumocystis prophylaxis are required beginning at the initiation of study treatment and continuing for at least 6 months after the completion of study treatment. If clinically indicated, anti-infective prophylaxis for other infectious agents is permitted.

4.4.1.4 Monitoring and Treatment for Hepatitis B Reactivation

Patients who are both HBsAg negative and HBcAb positive may be included in this study. These patients should have HBV DNA levels obtained monthly *(or on Day 1 of every cycle)* during the study and for at least 12 months after the last cycle of therapy 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 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 *within the WHO-recommended range of 29*–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 antiviral medication, study treatment will be permanently discontinued (see Section 5.1.4 and Table 4).

Prophylactic antiviral medications for hepatitis B reactivation will follow the institution's standard of care.

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes and P-Glycoprotein

In vitro data suggest that unconjugated MMAE is mainly metabolized by CYP3A4 and, to a lesser extent, by CYP2D6. Based on a validated physiological-based PK model simulation and a clinical DDI study of brentuximab vedotin, which contains identical maleimidocaproyl-valine-citrulline-MMAE (mc-vc-MMAE) linker/payload as polatuzumab vedotin (Han et al 2013), ketoconazole as a strong CYP3A4 inhibitor increases the exposure (e.g., AUC) of unconjugated MMAE by approximately 34%, while rifampin as a strong CYP3A4 inducer increases the exposure (e.g., AUC) of unconjugated MMAE by

approximately 46%. Concomitant medications that are strong CYP3A4 inhibitors (see Appendix 6) should be considered cautionary as they may potentially increase exposure to unconjugated MMAE leading to adverse reactions, which require close monitoring.

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

A sample list of cautionary medications that fall into the categories within this section can be found in Appendix 6. The lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed in Appendix 6.

MMAE is a P-glycoprotein (P-gp) substrate but not a P-gp inhibitor. Concomitant medications that are P-gp inhibitors (see Appendix 6) should be considered cautionary as they may potentially increase exposure to unconjugated MMAE leading 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. A sample list of cautionary medications that fall into the categories within this section can be found in Appendix 6. The list of medications is not necessarily comprehensive.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies should not be used because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown. A sample list of cautionary medications (including some herbal therapies) is included in Appendix 6. 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 therapies is prohibited during the study:

- Cytotoxic therapies (other than intrathecal CNS prophylaxis and study treatment) intended for the treatment of lymphoma whether Center for Drug Evaluation of China approved or experimental.
- Immunotherapy or immunosuppressive therapy other than study treatments used for the intention of treating lymphoma (e.g., for an adverse event)

- Any unplanned radiotherapy
- Hormone therapy other than contraceptives, hormone-replacement therapy, or megestrol acetate
- Biologic agents used for the intention of treating lymphoma other than clinically indicated hematopoietic growth factors
- Pre-phase therapy, other than the use of prednisone (see Table 2 in Section 4.3.3)

4.4.3.1 Immunizations

Patients who participate in this study may not receive either primary or booster vaccination with live virus vaccines at any time during study treatment. Investigators should review the vaccination status of potential study patients being considered for this study and follow the national guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases before study therapy.

Per the Rituximab Investigator's Brochure, the safety of immunization with live viral vaccines following MabThera/Rituxan therapy has not been studied, and vaccination with live virus vaccines is not recommended. Refer to the Rituximab Investigator's Brochure for additional safety information.

4.5 STUDY ASSESSMENTS

Screening and pretreatment tests and evaluations will be performed within 28 days before first dose, unless otherwise specified. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before first dose may be used; such tests do not need to be repeated for screening. Bone marrow biopsies collected within 90 days prior to Day 1 of study treatment are acceptable. Samples obtained more than 90 days prior to Day 1 require prior approval by the Medical Monitor before the patient can be randomized.

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

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

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to

record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history 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, reproductive status, smoking history, alcohol and drugs abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/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, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. 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.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. 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]). 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, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

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.

During the administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 15 (± 5) minutes during the infusion, at the end of the infusion and every 30 (± 10) minutes for 90 minutes following completion of dosing at Cycle 1 and 30 (± 10) minutes following completion of dosing in subsequent cycles.

During rituximab administration visits, vital signs are to be measured prior to the start of the infusion of rituximab as well as at the end of the rituximab infusion. Additional vital sign measurements that are obtained as per the institution's standard of care are to be recorded on the eCRF.

4.5.5 Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the IRC and the investigator on the basis of physical examinations, CT scans, PET-CT scans, and bone marrow examinations using the Lugano Response Criteria (Cheson et al. 2014).

Radiographic Assessments

PET-CT scans should include skull-base to mid-thigh. Full-body PET-CT scan should be performed when clinically appropriate.

CT scans with oral and IV contrast should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. CT scans for response assessment may be limited to areas of prior involvement only if required by local regulatory authorities. 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 are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period. Details regarding imaging procedures in these cases will be provided in the Imaging Manual.

PET scans, in conjunction with diagnostic-quality CT scans, are required at the following visits:

- Screening: within 35 days of Cycle 1 Day 1
- Interim response assessment: between Cycle 3 Day 15 and Cycle 4 Day 1
- End of treatment assessment: 6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment

CT (preferred) or PET-CT scans should be performed during follow-up:

- Every 6 months after end of treatment assessment until disease progression, study withdrawal, end of study, or death, whichever comes first; or
- At any time that disease progression is suspected via clinical response assessment

The Lugano Response Criteria (see Appendix 3) will be used to assess overall response to study treatment.

The same radiographic assessment modality should be used for all response evaluations to ensure consistency across different timepoints.

At all times during the study, diagnosis of disease progression based on clinical examination must be confirmed by imaging (e.g., CT, PET-CT) as soon as feasible (maximum, within 30 days) and prior to initiation of non–protocol specified anti-lymphoma therapy.

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

Bone Marrow Assessments

Bone marrow examinations are required at screening (within 3 months of Cycle 1 Day 1) for staging purposes in all patients. In addition, the definition of CR requires clearing of previously infiltrated bone marrow in CT based response. Bone marrow examinations should include a biopsy for morphology and an aspirate for local hematology (optional if standard of care at the site).

Repeat bone marrow examinations are required only in two circumstances:

- To confirm a radiological assessment of CR if there was bone marrow involvement with tumor at screening
- If required for confirmation of relapse in the bone marrow

Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Local Laboratory Assessments

Samples for hematology, serum chemistry, pregnancy, hepatitis B and C serology, and quantitative immunoglobulin assessments will be analyzed at the study site's local laboratory. In the event the study site's local laboratory cannot adhere to protocol requirements for $HBV\ DNA$ tests, the option to submit samples for analysis to the central laboratory is available. Laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle.

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

- Hematology (hemoglobin, hematocrit, RBC count, WBC count, platelet count, and percent or absolute differential [neutrophils, lymphocytes, eosinophils, basophils, and monocytes])

- Serum chemistry: sodium, potassium, glucose, BUN or urea, creatinine, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, ALP, LDH, uric acid/urate, hemoglobin A_{1c} (HbA_{1c}), amylase, and lipase

  At screening, samples will be obtained in a fasting state for all patients. Subsequent laboratory tests can be non-fasting. HbA_{1c} will be measured only at screening and at Cycle 4 Day 1 and can be obtained in a non-fasting state. Only at screening, obtain β-2 microglobulin.

- Coagulation: INR or PT, and PTT or aPTT
- HIV serology: HIV antibody
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.

- HCV serology: HCV antibody

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

- Quantitative immunogloblulins: IgG, IgA, and IgM
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test within 7 days before Cycle 1 Day 1 of study treatment. In addition, a serum or urine pregnancy test must be performed prior to study treatment on 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.

- Bone marrow biopsy and aspirate

  Bone marrow biopsy and aspirate are required at screening in all patients and at the end of treatment assessment for all patients who have achieved a radiographic CR in whom bone marrow involvement was diagnosed by morphology at screening. Bone marrow biopsy is optional, but strongly recommended, for responders without documented bone marrow involvement at screening.

Central Laboratory Assessments

Plasma, serum, and tumor tissue samples for biomarker, ADA, and PK analyses will be sent to one or several Roche-designated central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Lymphocyte subsets

  Whole blood samples will be collected and analyzed by flow cytometry for B cells (CD19 positive), T-cell counts (positive for CD3, CD4, and CD8), and natural killer-cell counts (CD16 and $CD56^{+}$) at screening, end of treatment assessment visit, and every 6 months (from the treatment completion visit) until end of study or patient discontinuation.

- Plasma and serum samples for PK analysis (polatuzumab vedotin/placebo; see Appendix 2)
  - Serum concentration of total antibody
  - Plasma concentration of acMMAE
  - Plasma concentration of unconjugated MMAE
- Serum samples for immunogenicity analysis (polatuzumab vedotin/placebo; see Appendix 2)
- *Pretreatment tumor* tissue sample is required (archival tissue or fresh pretreatment biopsy is acceptable) *and to be submitted according to local regulations.* Tumor blocks are preferred. If a tumor block is not available, a minimum of 11 serial freshly cut, unstained slides are required.

Biomarker research in tumor tissue *will* include analysis of DLBCL prognostic subtype (ABC/GCB), and expression of *BCL2*, *MYC*, and *CD79b*.

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

Biological samples will be destroyed *after* the final Clinical Study Report has been completed:

- Plasma and/or serum samples collected for PK or immunogenicity analysis and characterization (including domain specificity) will be destroyed after the final *study results have* been *reported*.
- Tumor tissue samples collected for biomarker research will be destroyed after the final *study results have* been *reported*.
- Remaining archival tissue blocks will be returned to local pathology according to country-specific procedures.

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

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

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.7 Electrocardiograms

A resting 12-lead ECG is required at screening, on Cycle 3 Day 1, at the treatment completion visit, and as clinically indicated. ECGs for each patient should be obtained with the use of the same machine when possible. Interpretation of the ECG should be performed by a qualified investigator or sub-investigator.

4.5.8 Patient-Reported Outcome Assessment

Patient-reported outcome (PRO) data will be collected to document the treatment benefit and more fully characterize the safety profile of polatuzumab vedotin. PRO data will be obtained through use of the FACT/GOG-NTX scale (see Appendix 5).

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

The scale, translated into the local language as appropriate, should be completed in its entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, paper versions of the FACT/GOG-NTX scale will be self-administered or interviewer administered (as appropriate) 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. The data from the questionnaires will be entered into the EDC system by site staff.

Study site staff will ensure that the FACT/GOG-NTX scale is provided to the patients for completion per the schedule of activities (see Appendix 1), and before the patients complete the visit the site staff will confirm completion or alternatively document any reasons for not completing the scale.

The FACT/GOG-NTX will be administered on Day 1 of every cycle, at treatment completion/discontinuation, at the end of treatment assessment, and at specified planned post-treatment visits thereafter until the close of the study (every 3 months after the treatment completion visit).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to the Lugano Response Criteria (Appendix 3)
- Unacceptable toxicity (as described in Section 5.1 and Table 4)
- Patient/investigator decision

In these cases, patients should continue to be followed for both resolution of toxicity and disease progression as described in Sections 5.5 and 5.6, and in Appendix 1.

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

Patients will return to the clinic for treatment discontinuation visit 30 (±5) days after the final dose of study treatment and should obtain tumor response assessments. Assessments should continue to follow the schedule as outlined in Appendix 1.

In the case where a patient experiences disease progression, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

Polatuzumab Vedotin

A patient should permanently discontinue polatuzumab vedotin if any of the following occur:

- Grade 4 peripheral neuropathy

- Grade 3 peripheral neuropathy that leads to a treatment delay of 14 days or more and does not improve to Grade ≤ 1 within 14 days
- Recurrence of a Grade ≥ 2 peripheral neuropathy at the reduced dose

Rituximab

A patient should permanently discontinue rituximab if any of the following occur:

- Grade 4 infusion-related symptom or anaphylaxis

  The patient should be withdrawn from study treatment immediately and supportive treatment given.
- Recurrence of Grade 3 infusion-related symptoms at re-challenge, regardless of timing (e.g., within same session or at the next session)

Polatuzumab Vedotin/Placebo plus Bendamustine and Rituximab

A patient should permanently discontinue polatuzumab vedotin/placebo plus BR if any of the following occur:

- Grade 3 or 4 hematologic toxicity that does not resolve to Grade ≤ 2 and delays treatment by > 14 days despite administration of growth factors
- Grade ≥ 2 non-hematologic toxicity that does not resolve to Grade ≤ 1 or baseline value and delays treatment by > 14 days
- Hepatitis B reactivation despite initiation of the appropriate antiviral therapy
- Disease progression

4.6.2 Patient Discontinuation from the Study

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

Reasons for 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
- 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 prematurely withdraw from the study during the treatment period will complete the

end of treatment assessments (see Appendix 1). 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 only if permitted by local regulations.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Polatuzumab vedotin is not approved in China, and clinical development is ongoing. 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. Please refer to the Polatuzumab Vedotin Investigator's Brochure for a complete summary of safety information.

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

Safety will be evaluated through the monitoring of the following:

- Serious adverse events that are attributed to protocol-mandated interventions from the time of signing informed consent until the first dose of study treatment on Cycle 1 Day 1
- All adverse events, including serious and non-serious adverse events, from Cycle 1 Day 1 until 90 days after the final dose of study treatment

  After this period, the investigator should report all serious adverse events that are believed to be related to prior study drug treatment for an indefinite period of time (even after the study has been closed).
- All adverse events of special interest that the investigator considers related to study drug from Cycle 1 Day 1 until 12 months after the final dose of study treatment
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs and echocardiogram or multiple-gated acquisition scans if clinically indicated
- Assessment of physical findings on clinical physical examinations

5.1.1 Risks Associated with Polatuzumab Vedotin

On the basis of clinical data to date, the following known and suspected risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.4. Refer to the Polatuzumab Vedotin Investigator's Brochure for complete and updated details.

5.1.1.1 Known Risks Associated with Polatuzumab Vedotin

Based on clinical experience with polatuzumab vedotin in patients treated in the current Phase I and II studies, *the following* are identified risks of polatuzumab vedotin.

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

Neutropenia*,* neutropenia-associated events (including febrile neutropenia)*, thrombocytopenia, and anemia, including serious and severe cases,* have been *reported* in *patients receiving polatuzumab vedotin*. Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Study treatment for hematologic toxicities may be delayed or modified as described in Table 4. *Primary G-CSF prophylaxis is required for neutropenia.* The use of G-CSF for neutropenia is described in Section 4.4.1.1. *Transfusion support for anemia and thrombocytopenia is permitted at the discretion of the investigator.*

Peripheral Neuropathy (Sensory and/or Motor)

Patients receiving polatuzumab vedotin may develop peripheral neuropathy, including peripheral sensory and/or motor neuropathy. These events have generally been reversible to varying degrees as much as available, 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 peripheral neuropathy may require a dose delay, change in dose, or discontinuation of treatment and should be managed according to the protocol. Neuropathy will be monitored by the standard clinical evaluation per investigator's discretion and reported according to NCI CTCAE.

Study treatment dose and schedule modifications for peripheral neuropathy are described in Table 4.

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 populations under study influencing patients' vulnerability to a higher risk of infections, particularly serious and opportunistic *infection,* include predisposition of the indication disease to infections, elderly population, *and* comorbidity. In addition, neutropenia is a known risk for polatuzumab vedotin. 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 $\geq$ 500 granulocytes/μL. *Anti-infective prophylaxis should be considered and is described in Section 4.4.1.3.*

Infusion-Related Reactions

IRRs 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.

Premedication for polatuzumab vedotin infusion administration are outlined in Table 2. Close monitoring throughout the infusion is required, and IRRs should be managed as outlined in Table 3.

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.

5.1.1.2 Potential Risks Associated with Polatuzumab Vedotin

Below are potential risks of polatuzumab vedotin. See the Polatuzumab Vedotin Investigator's Brochure for full information.

Effects on the Relative-Dose Intensity of Bendamustine and Rituximab

Depending upon the toxicity profile observed with the addition of polatuzumab vedotin to BR, there may be a reduction in the relative-dose intensity of BR that is administered.

Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. If any evidence of TLS occurs during the study, tumor lysis prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L or bulky lymphadenopathy) and who are considered to be at risk for TLS by the investigator will receive tumor lysis prophylaxis (e.g., allopurinol $\geq$300 mg/day orally or a suitable alternative treatment such as rasburicase 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 and adequate hydration, 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.

Hyperglycemia

Hyperglycemia has been observed in patients treated with polatuzumab vedotin as well as 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 anti-hyperglycemic medications.

Hepatotoxicity

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

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

For blinded polatuzumab vedotin/placebo dose delay, modification, and discontinuation instructions, see Table 4.

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.

5.1.2 Risks Associated with Rituximab

Please see the current Rituximab Investigator's Brochure for full information.

For rituximab dose delay, modification, and discontinuation instructions, see Table 4.

5.1.2.1 Infusion-Related Reactions

Patients treated with rituximab are at risk for IRRs. Fatal infusion reactions within 24 hours of rituximab infusion can occur; approximately 80% of fatal reactions occurred with the first infusion. Severe reactions to rituximab typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

5.1.2.2 Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. With rituximab treatment, acute renal failure, hyperkalemia, hypocalcaemia, hyperuricemia, or hyperphosphatemia from

tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of TLS. For patients with evidence of TLS, rituximab should be discontinued and the patient treated as clinically indicated.

5.1.2.3 Hepatitis B Virus Reactivation

HBV reactivation with subsequent fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of rituximab treatment and approximately 1 month after the last dose.

Patients with chronic hepatitis B (HBsAg-positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg-negative and anti-HBcAb-positive) are at a lower risk for reactivation. Patients who demonstrate evidence of reactivation while receiving an appropriate antiviral therapy will be discontinued from study treatment.

5.1.2.4 Progressive Multifocal Leukoencephalopathy

Rare cases of PML have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson et al. 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is rare, but PML should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic SCT. Most cases of PML were diagnosed within 12 months of the patient's last infusion of rituximab.

5.1.2.5 Cardiac Toxicity

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life threatening. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and with subsequent infusions of rituximab. Patients with preexisting cardiac conditions, including angina and arrhythmias, and who have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and in the post-infusion period.

5.1.2.6 Infection

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy. New

or reactivated viral infections include cytomegalovirus, HSV, parvovirus B19, VZV, West Nile virus, HBV, and HCV.

5.1.2.7 Severe Mucocutaneous Reactions

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.

5.1.2.8 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In postmarketing reports of rituximab, the mean time to documented gastrointestinal perforation was 6 days (range: 1–77 days) in patients with NHL.

5.1.3 Risks Associated with Bendamustine

5.1.3.1 Myelosuppression

Patients treated with bendamustine are likely to experience myelosuppression. Blood counts will be monitored weekly during the first cycle and then frequently throughout subsequent cycles of treatment. Patients who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The use of G-CSF for the primary prophylaxis is required. The decision not to administer G-CSF as primary prophylaxis should be made in consultation with and following the approval of the Medical Monitor.

5.1.3.2 Infection

Infection, including pneumonia and sepsis, has been reported. Patients with myelosuppression after treatment with bendamustine are more susceptible to infections. The study physician will treat patients with clinical evidence of infection appropriately. See Section 5.1.4 for monitoring plans and Table 4 for instructions for dose delay and modification of bendamustine. Antiviral (coverage for HSV, VZV) and anti-pneumocystis prophylaxis are required *per Section 4.4.1.3*. Opportunistic infections have occurred with treatment of bendamustine. Evaluation for opportunistic infections is recommended in cases of unexplained and prolonged fever, unexplained transaminitis, or unexplained/ongoing symptoms such as diarrhea, nausea, and neurological changes.

5.1.3.3 Infusion-Related Reactions and Anaphylaxis

Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus, and rash. In rare instances, severe anaphylaxis and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Patients should be monitored clinically and discontinue drug for every reaction.

5.1.3.4 Tumor Lysis Syndrome

TLS has been reported in association with bendamustine treatment in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

5.1.3.5 Skin Reactions

A number of skin reactions have been reported with bendamustine treatment, including rash, toxic skin reactions, and bullous exanthema. In a study of bendamustine in combination with rituximab, one case of TEN occurred. TEN has been reported for rituximab. Cases of Stevens-Johnson syndrome and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. Patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine should be withheld.

5.1.3.6 Long-Term Stem-Cell Toxicity

Premalignant and malignant diseases, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma, have developed in patients treated with bendamustine.

5.1.3.7 Extravasation of Bendamustine

Erythema, marked swelling, and pain from bendamustine extravasation have resulted in hospitalization. Precautions should be taken to avoid extravasation, including monitoring of the IV infusion site for redness, swelling, pain, infections, and necrosis during and after administration of bendamustine.

5.1.3.8 Transfusion-Associated Graft versus Host Disease

Rare cases of transfusion-associated graft-versus-host disease have been reported following treatment of low-grade B-cell malignancies with purine analogues (i.e., fludarabine or cladribine). The situation with newer purine antagonists such as bendamustine is unclear. Transfusions, if required, should be performed according to national guidelines.

5.1.3.9 Drug Interactions

Certain medications may interact with bendamustine. Caution should be used or alternative treatments with medications that are not CYP1A2 inhibitors or inducers should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed. CYP1A2 inhibitors and inducers are not contraindicated. During treatment with bendamustine, patients will be provided with a card to keep with them that provides

notification to other health care providers that the patient is taking bendamustine as a participant in a clinical study.

5.1.4 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 4. Additional guidelines are provided in the subsections below.

5.1.4.1 Dose Delays and Dose Modifications

Patients should be assessed clinically for toxicity before each dose using NCI CTCAE v5.0 unless otherwise stated. These guidelines pertain to dose delays and modifications 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 and dose modifications due to adverse events not specified in this section should proceed on the principle of maintaining the dose intensity of bendamustine. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment in consultation with and the approval of the Medical Monitor.

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

Bendamustine and polatuzumab vedotin doses may be reduced (per the guidelines outlined in Table 4) with the approval of the Medical Monitor.

If administration of chemotherapy is delayed, the administration of rituximab and polatuzumab vedotin should be delayed for the same time frame (e.g., if bendamustine therapy is delayed, administration of rituximab and polatuzumab vedotin should also be delayed so that they are given together beginning on Day 1 of the same cycle).

5.1.4.2 Treatment Interruption and Schedule Modification

Study treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. Aside from the withholding of blinded polatuzumab vedotin for neuropathy per Table 4, study drugs withheld for $>$14 days because of toxicity should be discontinued, unless resumption of treatment is approved following investigator discussion with the Medical Monitor

Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Patients who have received Cycle 1 treatment may have the dosing schedule changed to a 28-day cycle if it is considered by the investigator that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia without requiring repeated treatment delays). Modifications of this type to the dosing schedule must be made in consultation with the Medical Monitor and have the approval of the Medical Monitor.

5.1.4.3 Non-Hematologic Toxicities

Infusion-Related Reactions and Anaphylaxis

Medications including epinephrine for SC injection, corticosteroids, diphenhydramine hydrochloride for IV injection, and resuscitation equipment should be available for immediate use. Management of infusion-related symptoms for rituximab is summarized in Table 3 according to the administration rates in Section 4.3.2.2. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, rituximab should be discontinued and no additional drug should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment. See Appendix 4 for recommended management of anaphylaxis.

Patients who experience rituximab-associated infusion-related temperature elevations of $>38.5°C$ or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol (500–1000 mg) and/or H_1- and H_2- histamine receptor antagonists (e.g., diphenhydramine hydrochloride) and ranitidine. Serious infusion-related events, manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress, should be managed with additional supportive therapies (e.g., supplemental oxygen, β_2-agonists, epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice. See Appendix 4 for recommended management of anaphylaxis.

Guidelines for the management of IRRs and anaphylaxis are detailed in Table 3.

Table 3 Management of Infusion-Related Symptoms

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

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

Refer to the NCI-CTCAE v5.0 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/hour every 30 minutes.

Table 4 Guidelines for Dose Delay or Modification of Polatuzumab Vedotin, Rituximab, or Bendamustine

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia on Day 1 of any cycle with or without infection or fever [a] First delay	• Delay all study treatment. Treatment cannot be delayed for more than 2 weeks. • Administer growth factors as appropriate (e.g., G-CSF for neutropenia as indicated and for all subsequent cycles). • If ANC recovers to > 1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of polatuzumab vedotin, bendamustine, and rituximab • If ANC recovers to > 1000/μL on or after Day 8 of the scheduled date for the next cycle, reduce the dose of bendamustine to 70 mg/m^2. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of bendamustine. Decisions must be made in consultation with and with approval of the Medical Monitor.
Recurrent Grade 3 or 4 neutropenia on Day 1 of any cycle	• Delay doses of all study treatment. Treatment cannot be delayed for more than 2 weeks. • If ANC recovers to > 1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of study treatment. • If ANC recovers to > 1000/μL on or after Day 8 of the scheduled date for the next cycle, then: – If the dose of bendamustine is 90 mg/m^2, then reduce bendamustine to the next lowest dose level of 70 mg/m^2 (1st dose reduction) and maintain polatuzumab vedotin dose of 1.8 mg/kg. If there was a prior dose reduction, then reduce bendamustine to the next lowest dose level of 50 mg/m^2 (2nd dose reduction) and maintain polatuzumab vedotin dose at 1.8 mg/kg. – No dose reductions of polatuzumab vedotin for neutropenia are allowed. – No more than two dose reductions of bendamustine are allowed. If patient develops persistent Grade 3 or 4 neutropenia despite growth factor support and after bendamustine dose reductions, permanently discontinue all study treatment.

Table 4 Guidelines for Dose Delay or Modification of Polatuzumab Vedotin, Rituximab, or Bendamustine (cont.)

Event(s)	Dose Delay or Modification
Grade 3 or 4 thrombocytopenia on Day 1 of any cycle, first episode	• Delay doses of all study treatment. • If platelet count recovers to $>$75,000/μL by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment. • If platelet count recovers to $>$75,000/μL on or after Day 8 of the scheduled date of the next cycle, reduce the dose of bendamustine to the next dose level (70 mg/m^2). • If the patient had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of bendamustine.
Recurrent Grade 3 or 4 thrombocytopenia	• Delay doses of all study treatment. • If platelet count recovers to $>$75,000/μL by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment • If platelet count recovers to $>$75,000/μL on or after Day 8 of the scheduled date of the next cycle, then: – If the dose of bendamustine is 90 mg/m^2, then reduce bendamustine to the next lower dose level of 70 mg/m^2 (1st dose reduction) and maintain polatuzumab vedotin dose of 1.8 mg/kg. If there was a prior dose reduction, then reduce bendamustine to the next lowest dose level of 50 mg/m^2 (2nd dose reduction) and maintain polatuzumab vedotin dose at 1.8 mg/kg. – No more than two dose reductions of bendamustine are allowed. – If patient develops Grade 4 thrombocytopenia following polatuzumab vedotin and bendamustine dose reductions, discontinue all study treatment permanently.
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay is required.

Table 4 Guidelines for Dose Delay or Modification of Polatuzumab Vedotin, Rituximab, or Bendamustine (cont.)

Event(s)	Dose Delay or Modification
Grade 2 or 3 peripheral neuropathy (including its signs and symptoms)	• Delay all study treatment. • If recovered to Grade ≤ 1 within ≤ 14 days of the scheduled date of the next cycle: – If the dose of polatuzumab vedotin is 1.8 mg/kg, then reduce polatuzumab vedotin to 1.4 mg/kg (permanent dose reduction). BR may be administered at their full doses. – If there was a prior dose reduction of polatuzumab vedotin to 1.4 mg/kg for Grade 2 or 3 neurotoxicity, all study treatment must be permanently discontinued. – If not recovered to Grade ≤1 until >14 days or after the scheduled date for the next cycle, all study treatment must be permanently discontinued.
Grade 4 peripheral neuropathy (including its signs and symptoms)	• Discontinue polatuzumab vedotin permanently and discontinue all other treatment.
Total bilirubin > 3.0 mg/dL	• Delay 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 drug should be discontinued.
Grade 3 or 4 TLS	• Hold all study treatment. The patient's next dose may be delayed for up to 14 days. • Following complete resolution TLS, study treatment may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy.
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 after discussion with the Medical Monitor.
Grade 2 non-hematologic toxicity	• Delay study treatment for a maximum of 14 days. • If improvement to Grade ≤1 or baseline, administer previous doses of study treatment.
Grade 1 non-hematologic toxicity	• No dose reduction or delay is required.

Table 4 Guidelines for Dose Delay or Modification of Polatuzumab Vedotin, Rituximab, or Bendamustine (cont.)

Event(s)	Dose Delay or Modification
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.

BR = bendamustine and rituximab; DILI = drug-induced liver injury; G-CSF = granulocyte colony-stimulating factor; HBV = hepatitis B virus; LMWH = low molecular-weight heparin; TLS = tumor lysis syndrome; ULN = upper limit of normal.

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

Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity because it is an expected outcome of therapy.

Dose Discontinuation

Dosing delay exceeding 14 days in the initiation of the next planned cycle of polatuzumab vedotin/placebo plus BR and will require study treatment discontinuation unless Medical Monitor approval is obtained to continue on study treatment.

If scheduled dosing coincides with a holiday that precludes dosing, commence dosing on the nearest following date, with subsequent dosing continuing on a 21- or 28-day schedule as applicable.

Patients who discontinue all study treatment for adverse events should remain in the study and continue to have disease assessments until progression and standard follow up per the schedule of activities (Appendix 1).

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- TLS of any grade (irrespective of causality)
- Second malignancies
- Grade 2 or higher peripheral neuropathy (sensory and/or motor)
- Grade 3 or higher Infections
- HBV reactivation

5.2.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Neutropenia, including febrile neutropenia (all grades)
- Peripheral neuropathy (sensory and/or motor, all grades)
- Infections (all grades)
- Hepatic toxicity (all grades)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

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

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 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

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 IRR).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ 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).

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 DLBCL

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the Lugano Response Criteria (Appendix 3). 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 are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For polatuzumab vedotin/placebo 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.

In addition, all special situations associated with polatuzumab vedotin/placebo 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.

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

5.3.5.13 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)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more

than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

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

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

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

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 12 months after the final 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 final 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Polatuzumab Vedotin Investigator's Brochure
- Rituximab Investigator’s Brochure
- Summary of Product Characteristics for bendamustine

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint of CR at the end of treatment assessment was used to determine the sample size of the study.

The primary objective of the study is to *investigate* whether the benefit (in terms of CR at the end of treatment assessment) of administrating polatuzumab vedotin plus BR in this study is consistent with the benefit observed in the global study GO29365. *CR rate at the end of treatment assessment* was increased from 17.5% in the BR arm to be 40% in the polatuzumab vedotin plus BR arm for study GO29365 (i.e., 22.5% *CR rate increase).*

In this study, 42 patients will be enrolled in a 2:1 randomization allocation to polatuzumab vedotin plus BR (experimental arm) or placebo plus BR arm (control arm). *A total of 42 patients* will *provide an approximate* 80% probability *of observing at least 50% of the benefit in the CR rate at the end of treatment assessment observed in the global Study GO29365.*

The expected enrollment duration is approximately 9 months and the primary analysis is expected to occur approximately 6 months of follow-up after the last patient is enrolled. The study will continue after primary analysis until about two-thirds of enrolled patients have experienced death or all patients have discontinued from study, whichever occurs earlier. Based on the observed median OS in Study GO29365 (4.7 months in the BR arm, 12.4 months in the polatuzumab vedotin plus BR arm), the final OS analysis is expected to occur approximately 10 months after the last patient is enrolled.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, and duration of malignancy) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

CR at end of treatment assessment (6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment) based on PET-CT, as determined by the IRC, will be used as the primary efficacy endpoint. The CR rate, defined as the percentage of patients with CR, will be estimated and the corresponding Clopper-Pearson exact 95% CI will be constructed for each treatment arm. The difference in CR rates between polatuzumab vedotin plus BR and placebo plus BR randomized arms will be estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution.

6.4.2 Secondary Efficacy Endpoints

Response rate is defined as the percentage of patients with CR, OR, or BOR as described below. For the endpoint of OR, patients without a postbaseline tumor assessment will be considered non-responders.

Analyses of these endpoints will be identical to those described above for the primary efficacy endpoint of CR rate measured by PET-CT scan.

- CR at the end of treatment assessment based on PET-CT, as determined by the investigator
- OR, defined as CR or PR, at the end of treatment assessment based on PET-CT, as determined by the investigator and IRC
- CR at the end of treatment assessment based on CT only, as determined by the investigator and IRC
- OR, defined as CR or PR, at the end of treatment assessment based on CT only, as determined by the investigator and IRC
- BOR, defined as CR or PR, while on study based on PET-CT or CT only, as determined by the investigator and IRC

Among patients with a BOR of CR or PR, DOR, as determined by the investigator and IRC, will be defined as the time from the initial CR or PR to the time of disease progression, relapse, or death from any cause, whichever occurs first. If a patient does not experience death or disease progression before the end of the study, DOR will be censored on the date of the last tumor assessment. *Kaplan-Meier methodology will be used to estimate median DOR for each treatment group and to construct DOR curves for visual descriptions of the difference between the experimental and control arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DOR for each treatment group (Brookmeyer and Crowley 1982). The unstratified Cox proportional hazard model will be used to estimate the DOR HR between the two treatment groups and its 95%CI.*

PFS, as determined by the investigator and IRC, is defined as the period from the date of randomization until the date of disease progression, relapse, or death from any cause, whichever occurs first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of last tumor assessment. If no tumor assessments were performed after the screening visit, PFS will be censored at the date of randomization.

EFS, as determined by the investigator, is defined as the time from date of randomization to any treatment failure including disease progression, relapse, initiation of NALT, or death, whichever occurs first. If the specified event (disease progression/relapse, death, start of an NALT) does not occur, patients will be censored at the date of last tumor assessment. For patients who do not have postbaseline tumor assessments or documentation of NALT, EFS will be censored at the time of randomization.

OS is defined as the time from date of randomization until the date of death from any cause. Patients who have not died will be censored at the last date known to be alive.

Analyses of PFS, EFS, and OS will be identical to those outlined previously for DOR.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

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

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

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

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

The FACT/GOG-NTX will be scored using a corresponding user manual. Summary statistics of the FACT/GOG-NTX total and individual items with their changes from baseline will be calculated at each assessment timepoint.

6.6 PHARMACOKINETIC ANALYSES

The PK population for analysis will include all patients who have at least one evaluable PK sample postdose for at least one analyte.

Individual and mean serum concentrations of total polatuzumab vedotin antibody (fully conjugated, partially deconjugated and fully deconjugated antibody), plasma concentrations of polatuzumab vedotin conjugate (evaluated as acMMAE), and unconjugated MMAE versus time data will be tabulated and plotted after appropriate grouping. The pharmacokinetics of the above analytes will be summarized after appropriate grouping, as the data will allow, by estimating selected PK parameters, such as AUC and C_{max}. The population PK analysis will investigate the effects of certain covariates on the pharmacokinetics of polatuzumab vedotin related analytes, as the data will allow and at the Sponsor's discretion. These covariates may include renal and hepatic impairment, as data will allow.

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

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

6.7 IMMUNOGENICITY ANALYSES

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

have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

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

6.8 BIOMARKER ANALYSES

PET-CT CR and OR rate will be analyzed in following subgroups: (1) patients with ABC-DLBCL as analyzed through use of a centrally performed RNA-based assay, (2) patients with GCB-DLBCL as analyzed through use of a centrally performed RNA-based assay, (3) patients with co-expression of BCL2 and MYC (double-expressor, DEL) as analyzed through use of centrally performed IHC tests, and (4) patients with expression of CD79b as analyzed through use of a centrally performed IHC test.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

Roche will retain study data for 25 years after the final 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 will comply with applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to

document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

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.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written Investigational New Drug 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.

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 10 sites in China will participate to enroll approximately 42 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 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Tumor response and progression will be evaluated by an IRC and the investigator.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

Advani RH, Chen H, Habermann TM, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the U.S. Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPI). Br J Haematol 2010;151:143–51.

Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780–95.

Bishop JF, Schimpff SC, Diggs, CH, et al, Infections during intensive chemotherapy for non-Hodgkin's lymphoma. Ann Intern Med 1981;95:549–55.

Bittenbring JT, Neumann F, Altmann B, et al. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. J Clin Oncol 2014;32:3242–8.

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

Calabrese LH, Molloy ES, Huang D, et al. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum 2007;56:2116–28.

Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4384–8.

Cheson BD. Staging and response assessment in lymphomas: the new Lugano classification. Chin Clin Oncol. 2015;4:5.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol 2014;32:3059–68.

Cheson BD, Wendtner C-M, Pieper A, et al. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an International Consensus Panel. Clin Lymphoma Myeloma Leuk 2010;10:21–7.

Coiffier B. Rituximab therapy in malignant lymphoma. Oncogene 2007;26:3603–13.

Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med 2002;346:235–42.

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040–5.

Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 2008;112:2228–32.

Colosia A, Njue A, Trask PC, et al. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review. Clin Lymphoma Myeloma Leuk 2014;14:343–55.e6.

Czuczman MS, Trněný M, Davies A, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. Clin Cancer Res 2017;23:4127–37.

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800–8.

Dang NH, Ogura M, Castaigne S, et al. Randomized, phase 3 trial of inotuzumab ozogamicin plus rituximab versus chemotherapy plus rituximab for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. Br J Haematol 2018;182:583–6.

Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti-CD79b antibody–drug conjugate, anti–CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood 2009;114:2721–9.

Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol 2003;21:778–84.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117–26.

Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a Phase II multicenter, single-agent study. J Clin Oncol 2008;26:204–10.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184–90.

Goldberg SL, Angora AL, Alter RS, et al. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002;99:1486–8.

Gorovits B, Alley SC, Bilic S, et al. Bioanalysis of antibody–drug conjugates: American Association of Pharmaceutical Scientists Antibody–Drug Conjugate Working Group position paper. Bioanalysis. 2013;5:997–1006.

Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121–7.

Han TH, Gopal AK, Ramchandren R, et al. CYP3A-mediated drug-drug interaction potential and excretion of brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive hematologic malignancies. J Clin Pharmacol 2013;53:866–77.

Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group hematology and oncology study. J Clin Oncol 2007;25:1986–92.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of German Low-Grade Lymphoma Study Group. Blood 2005;106:3725–32.

Hong JY, Yoon DH, Suh C, et al. Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a multicenter retrospective analysis. Ann Hematol 2018;97:1437–43.

Huang HQ, Brady MF, Cella D, et al. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer 2007;17:387–93.

Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. Cancer 2010;116:106–14.

Kaur S, Xu K, Saad OM, et al. Bioanalytical assay strategies for the development of antibody-drug conjugate biotherapeutics. Bioanalysis 2013;5:201–26.

Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579–6.

[NCCN] National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®): non-Hodgkin's lymphomas (Version 1) [resource on the Internet] 2014. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx

[NCCN] National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®): non-Hodgkin's lymphomas [resource on the Internet] 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531–44.

Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013;21:2103–9.

Pfreundschuh M, Schubert J, Ziepert M, et al. German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105–16.

Polson AG, Calemine Fenaux J, Chan P, et al. Antibody drug conjugates for the treatment of non-Hodgkin's lymphoma: target and linker drug selection. Cancer Res 2009;69:2358–64.Polson AG, Yu SF, Elkins K, et al. Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma. Blood 2007;110:616–23.Robertson MJ, Kahl BS, Vose JM, et al. Phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2007;25:1741–6.

Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473–9.

Rummel MJ, Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non Hodgkin's lymphoma. J Clin Oncol 2005;23:3383–9.

Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA GOELAMS FL2000 study. Blood 2008;112:4824–31.

Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med 2017;377:2545–54. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007;109:1857–61.

Sehn LH, Herrera AF, Matasar MJ, et al. Polatuzumab vedotin (Pola) plus bendamustine (B) with rituximab (R) or obinutuzumab (G) in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): updated results of a Phase (Ph) Ib/II study. Blood 2018;132:1683.

Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987–94.

Sweetenham JW. Diffuse large B-cell lymphoma: risk stratification and management of relapsed disease. Hematology Am Soc Hematol Educ Program 2005;252–9.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.

Tholstrup D, Brown PDN, Jurlander J, et al. Quality of life in patients with diffuse large B-cell lymphoma treated with dose-dense chemotherapy is only affected temporarily. Leuk Lymphoma 2011;52:400–8.

Tilly H, Sharman J, Bartlett N, et al. Pola-R-CHP: polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, prednisone for patients with previously untreated diffuse large B-cell lymphoma. Hematol Oncol 2017;35:90–1.

Tilly H, Vitolo U, Walewski J, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii78–82.

Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93:403–9.

Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final results from an open-label, randomized phase 3 study (GOYA). Blood 2016;128:470.

Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952–7.

Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:2373–80.

Appendix 1
Schedule of Activities

		Treatment												Treatment Completion/ Discont. [d]	EOT Assessment [e]	
		Cycle 1					Cycle 2		Cycle 3			Cycles 4–6		30 (±5) days after final dose	6–8 weeks after C6D1 or final dose	Follow-Up [f]
Day [a] (Window)	Screen (–28 days) [b]	D1 [c]	D2	D3	D8 (± 1)	D15 (± 1)	D1 (± 2)	D2	D1 (± 2)	D2	D15 (± 1)	D1 (± 2)	D2			
Informed consent [g]	x															
Demographic data	x															
General medical history and baseline conditions	x															
Concomitant medications [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [i]
ECOG PS	x													x	x	x
IPI	x															
Complete physical exam [j]	x															
Targeted physical examination [k]		x					x		x			x		x	x	x
Vital signs [l]	x	x	x	x			x		x			x		x	x	x
Height, weight, and BSA [m]	x	x					x		x			x				
12-lead ECG	x								x					x		

Appendix 1: Schedule of Activities (cont.)

Day [a] (Window)	Screen (–28 days) [b]	Treatment												Treatment Completion/ Discont. [d]	EOT Assessment [e]	Follow-Up [f]
		Cycle 1					Cycle 2		Cycle 3			Cycles 4–6		30 (±5) days after final dose	6–8 weeks after C6D1 or final dose	
		D1 [c]	D2	D3	D8 (± 1)	D15 (± 1)	D1 (± 2)	D2	D1 (± 2)	D2	D15 (± 1)	D1 (± 2)	D2			
FACT/GOG-NTX [n]		x					x		x			x		x		x (every 3 mo.)
Clinical response assessment [o]	x						x		x		x	x		x	x	x
CT scan and PET-CT scan [p]	x [q]										x				x	(x) [r]
Rituximab [s]		x					x		x			x				
Polatuzumab vedotin or placebo [t]			x				x		x			x				
Bendamustine [u]			x	x			x	x	x	x		x	x			
Hematology [v]	x	x			x	x	x		x			x		x	x	x
Serum chemistry [w]	x	x			x	x	x		x			x		x	x	x
Coagulation panel [x]	x															
Viral serology [y]	x															
Serum IgA, IgG, and IgM	x													x	x	x
Pregnancy test [z]	x						x		x			x		x		
Bone marrow biopsy and aspirate [aa]	x													(x)	(x)	(x)

Appendix 1: Schedule of Activities (cont.)

Day [a] (Window)	Screen (–28 days) [b]	Treatment												Treatment Completion/ Discont. [d]	EOT Assessment [e]	Follow-Up [f]
		Cycle 1					Cycle 2		Cycle 3			Cycles 4–6		30 (±5) days after final dose	6–8 weeks after C6D1 or final dose	
		D1 [c]	D2	D3	D8 (± 1)	D15 (± 1)	D1 (± 2)	D2	D1 (± 2)	D2	D15 (± 1)	D1 (± 2)	D2			
Tumor tissue sample for *prognostic* biomarker studies [bb]	x															
Lymphocyte subsets [cc]		x													x	x (every 6 mo.)
Anti-drug antibody (polatuzumab vedotin)	See Appendix 2															
PK assessment (polatuzumab vedotin)	See Appendix 2															
Survival follow-up/ status [dd]														x	x	x

BSA = body surface area; C = cycle; CR = complete response; CT = computed tomography (scan); D = day; Discont. = discontinuation; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = electronic Case Report Form; EOT = end of treatment; FACT/GOG-NTX = Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity; HbA_{1c} = hemoglobin A_{1c}; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IPI = International Prognostic Index; mo = month; PCR = polymerase chain reaction; PET-CT = positron emission tomography–computed tomography (scan); PK = pharmacokinetic; (x) = conditional/optional (refer to footnote).

[a] On treatment days, all assessments must be performed on the day of the specified visit unless a time window is specified in this schedule of assessments. On treatment days, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified.

[b] Screening and pretreatment tests and evaluations will be performed within 28 days before first dose, unless otherwise specified. Results of standard-

of-care tests or examinations performed before obtaining informed consent and within 28 days before first dose may be used; such tests do not need to be repeated for screening. Bone marrow biopsies collected within 90 days prior to Day 1 of study treatment are acceptable. Samples obtained more than 90 days prior to Day 1 require prior approval by the Medical Monitor before the patient can be randomized.

[c] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding Cycle1 Day 1 administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[d] Patients who complete the study treatment period will return to the clinic for a treatment completion visit 30 (± 5) days after the final dose of study treatment (Cycle 6 Day 1). Patients who discontinue study treatment prematurely will return to the clinic for a treatment discontinuation visit 30 (± 5) days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[e] All patients will be asked to return to the clinic for the end of treatment assessment. This visit is to take place between 6 and 8 weeks after Cycle 6 Day 1 or the final dose of study treatment. For patients with disease progression occurring prior to the anticipated date of the end of treatment assessment, the visit date with the response assessment showing progressive disease may be used in replacement of the end of treatment assessment.

[f] Following completion of treatment, patients who have not progressed will be followed clinically every 3 months (± 14 days). Follow-up visit intervals should be determined from treatment completion visit.

[g] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained no more than 28 days before initiation of study treatment.

[h] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF (see Section 4.4).

[i] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the final dose of study drug. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events or non-serious adverse events of special interest (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.

[j] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly (clinical response assessment), which will be recorded on the appropriate Tumor Assessment eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed (targeted) physical examinations should be performed.

[k] 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]). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Vital signs include respiratory rate, pulse rate, pulse oximetry, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. During the administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 15 (± 5) minutes during the infusion, at the end of the infusion, and every 30 (± 10) minutes for 90 minutes following completion of dosing at Cycle 1 and 30 (± 10) minutes following completion of dosing in subsequent cycles. During rituximab administration visits, vital signs are to be measured prior to the start of the infusion of rituximab as well as at the end of the rituximab infusion. Additional vital sign measurements that are obtained as per the institution's standard of care are to be recorded on the eCRF.

[m] Height is required at screening only. BSA is required at screening only unless there has been > 10% change in body weight since the last BSA assessment, in which case BSA should be recalculated and documented on the eCRF. It is recommended that the Mosteller BSA formula (Mosteller et al.1987) be used; however, BSA may be calculated using the investigator's preferred formula.

[n] The FACT/GOG-NTX (see Appendix 5) will be administered on Day 1 of every cycle, at treatment completion/discontinuation, and at specified planned post-treatment visits thereafter until the close of the study (every 3 months after the treatment completion visit). Paper versions of the FACT/GOG-NTX scale will be self-administered or interviewer administered (as appropriate) 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. The data from the questionnaires will be entered into the EDC system by site staff. See Section 4.5.8 for additional details.

[o] Clinical response assessment of tumor conducted via physical examination.

[p] *CT scans and* PET-CT scans are required at screening, the interim response assessment (between Cycle 3 Day 15 and Cycle 4 Day 1), and the end of treatment assessment (6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment). *Diagnostic contrast enhanced CT scans obtained as part of a PET-CT may be used in lieu of dedicated CT scans.* All other imaging may be CT only. The Lugano Response Criteria (see Appendix 3) will be used to assess overall response to study treatment.

[q] Screening PET-CT must be obtained within 35 days of Cycle 1 Day 1.

[r] CT (preferred) or PET-CT scans should be performed during follow-up every 6 months after end of treatment assessment until disease progression, study withdrawal, end of study, or death, whichever comes first; or at any time that progression is suspected via clinical response assessment.

[s] Rituximab (375 mg/m^2) will be administered by IV infusion on Day 1 of Cycles 1–6. No dose modifications of rituximab are allowed. Rituximab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine (see Section 4.3.2.2).

[t] Polatuzumab vedotin (1.8 mg/kg) or placebo will be administered by IV infusion on Day 2 of Cycle 1 then Day 1 of Cycles 2–6 (see Section 4.3.2.1).

[u] Bendamustine (90 mg/m^2) will be administered by IV infusion over 30–60 minutes on 2 consecutive days of each cycle (Days 2 and 3 in Cycle 1, then Days 1 and 2 in Cycles 2–6) (see Section 4.3.2.3).

[v] Hematology includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, and percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes). Results should be obtained within 3 days before study treatment administration.

[w] Serum chemistry includes sodium, potassium, glucose, BUN or urea, creatinine, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, ALP, LDH, uric acid/urate, HbA_{1c}, amylase, and lipase. At screening, samples will be obtained in a fasting state for all patients. HbA_{1c} will only be measured at screening and at Cycle 4 Day 1 and can be obtained in a non-fasting state. Only at screening, obtain β-2 microglobulin. Results should be obtained within 3 days before study treatment administration.

[x] INR or, PT, and PTT or aPTT. Results should be obtained within 3 days before study treatment administration.

[y] At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed at screening and monthly (*or* on Day 1 of each cycle) during the study treatment period, and for at least 12 months after the completion of study treatment to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[z] All women of childbearing potential will have a serum pregnancy test at screening within 7 days before Cycle 1 Day 1. In addition, a serum or urine pregnancy test must be performed prior to study treatment on Day 1 of each subsequent cycle (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.

[aa] Bone marrow biopsy and aspirate are mandatory in all patients at screening and should include biopsy for morphology. The bone marrow assessment must be performed within 3 months of the Cycle 1 Day 1. For patients with bone marrow involvement (presence of lymphoma) at screening, a repeat bone marrow biopsy and aspirate should be repeated at the end of treatment assessment in patients who achieve radiologic CR or if there is clinical suspicion of progressive disease in the bone marrow in the absence of progressive disease as demonstrated by radiographic imaging. Bone marrow assessments will be performed locally.

[bb] *Pretreatment tumor* tissue sample is required (archival tissue or fresh pre-treatment biopsy is acceptable) *and to be submitted according to local regulations.* Tumor blocks are preferred. If a tumor block is not available, a minimum of 11 serial freshly cut, unstained slides are required. Remaining archival tissue blocks will be returned to local pathology according to country-specific procedures.

[cc] *Whole* blood samples will be collected at screening, end of treatment assessment, and every 6 months (from the treatment completion visit) until the end of study or patient discontinuation.

[dd] *During* the follow-up period (i.e., after treatment completion): For patients who have disease progression and have not started new anti-lymphoma therapy, follow-up should consist of recording of first new anti-lymphoma therapy, adverse events, and survival and continue to follow the above schedule. *In the case where a patient experiences* disease progression*, information on survival follow-up* and new anti-*cancer* therapy will be *collected via* telephone *calls, patient medical records, and/or clinic visits approximately every 6 months until death (unless the patient withdraws consent or the Sponsor terminates the study).* For patients who started a new anti-lymphoma therapy but do not have disease progression,

assessments should be followed according to the schedule of activities, including response assessments and adverse events.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples (Polatuzumab Vedotin/Placebo)

Study Visit	Sample Timepoint [a]	Samples (polatuzumab vedotin/placebo) [b]
Cycle 1 Day 2	Pre-polatuzumab vedotin/placebo infusion	ADA (serum), PK (serum and plasma) [c]
	End of polatuzumab vedotin/placebo infusion	PK (serum and plasma) [c]
Cycle 1 Day 8	6 days (± 1 day) after Day 2 infusion	PK (serum and plasma) [c]
Cycle 1 Day 15	13 days (± 1 day) after Day 2 infusion	PK (serum and plasma) [c]
Cycle 2 Day 1	Pre-polatuzumab vedotin/placebo infusion	ADA (serum), PK (serum and plasma) [c]
	End of polatuzumab vedotin/placebo infusion	PK (serum and plasma) [c]
Cycle 3 Day 1	Pre-polatuzumab vedotin/placebo infusion	PK (serum and plasma) [c]
	End of polatuzumab vedotin/placebo infusion	PK (serum and plasma) [c]
Cycle 3 Day 8	7 days (± 1 day) after Day 1 infusion	PK (serum and plasma) [c]
Cycle 3 Day 15	14 days (± 1 day) after Day 1 infusion	PK (serum and plasma) [c]
Cycle 4 Day 1	Pre-polatuzumab vedotin/placebo dose	ADA (serum), PK (serum and plasma) [c]
	End of polatuzumab vedotin/placebo infusion	PK (serum and plasma) [c]
Treatment Completion/ Discontinuation	Approximately 30 days ± 5 after final infusion	ADA (serum), PK (serum and plasma) [c]
Post-treatment (Follow-up visit at Months 3, 6, and 12)	Random sample	ADA (serum) Concentration (serum only)

ADA = anti-drug antibody; BR = bendamustine and rituximab; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

[a] Pre-infusion samples should be drawn 0–4 hours before the start of *polatuzumab vedotin* infusion. End-of-infusion samples should be drawn 30 minutes (± 15 minutes) after the end of *polatuzumab vedotin* infusion, unless otherwise specified.

[b] Up to 11-mL whole-blood samples will be taken for polatuzumab vedotin/placebo PK (conjugate [evaluated as antibody-conjugated MMAE], polatuzumab vedotin/placebo total antibody, and unconjugated MMAE), polatuzumab vedotin/placebo ADA, and polatuzumab vedotin concentration sample at each specified timepoint with separate tubes for plasma or serum samples.

[c] Polatuzumab vedotin/placebo PK, including serum PK samples for total antibody and plasma PK samples for conjugate (evaluated as antibody-conjugated MMAE) and unconjugated MMAE. Per the sampling schedule above, approximately 12 PK sampling points will be pre-specified from each patient treated with polatuzumab vedotin/placebo plus BR up to Cycle 4 Day 1, and additional PK sampling points will be at treatment completion/termination visit and follow-up visits. All PK samples and ADA samples should be drawn from the arm opposite from the infusion arm. In patients with indwelling catheters, a PK sample may be drawn from the catheter after sample flushing.

Appendix 3
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

Response should be determined on the basis of radiographic and clinical evidence of disease. For the end of treatment assessment, an FDG-PET (18F fluorodeoxyglucose positron emission tomography)/CT (computed tomography) scan will be performed 6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment, as assessed by an Independent Review Committee and the investigator. Assessment of the PET-CT scan should follow the criteria presented below (Cheson et al. 2014).

Target and Non-Target Lesions

Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be greater than 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the six representative, measured lesions. At baseline, measurable extranodal lesions should be greater than 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-measured disease as non-target lesions (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

Split Lesions and Confluent Lesions

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and smallest diameter (SDi) are no longer needed to determine progression.

Appendix 3: Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

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 $\leq$1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Appendix 3: Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Response and Site	PET-CT–Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Appendix 3: Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Response and Site	PET-CT–Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Appendix 3: Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly (>13 cm), the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Appendix 3: Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

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 (scan); PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

Appendix 4
Recommended Anaphylaxis Management

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

REQUIRED EQUIPMENT AND MEDICATION

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

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 5
Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX)

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
H112	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

Appendix 6
Sample List of Cautionary Medications

(A) Inhibitors

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,[a] indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole	amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib, [a] cyclosporine, [a] darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, [a] isavuconazole, tofisopam, verapamil	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

[a] These are the anticancer agents; contact Medical Monitor before use.

(B) Inducers

	Strong Inducers	Moderate Inducers	Weak Inducers
CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, modafinil, nafcillin	armodafinil, rufinamide

(C) Examples of clinical inhibitors for P-gp transporters

Transporter	Gene	Inhibitor
P-gp [a]	ABCB1	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

[a] Most of P-gp inhibitors also inhibit CYP3A.

Source: U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [resource on the Internet]. 2017 [cited 29 March 2019]. Available from: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table3-3

Appendix 7
Commonly Used CYP1A2 Inhibitors and Inducers (Drugs, Foods, Over the Counter Medications, and Supplements)

On the basis of the U.S. Package Insert for bendamustine, no formal clinical assessments of pharmacokinetic drug drug interactions between bendamustine and other drugs have been conducted. Bendamustine's active metabolites, gamma hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites.

The medications listed below are not contraindicated; however, caution should be used or alternative treatments with medications that are not CYP1A2 inhibitors or inducers should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed for the patient's medical condition. This list is not exhaustive.

Appendix 7: Commonly Used CYP1A2 Inhibitors and Inducers (Drugs, Foods, Over the Counter Medications, and Supplements) (cont.)

CYP1A2 Inhibitors	
Amiodarone	Imipramine
Amitriptyline	Isoniazid
Amlodipine	Ketoconazole
Anastrozole	Lidocaine
Caffeine	Losartan
Cimetidine (Tagamet)	Erythromycin
Ciprofloxacin (Cipro)	Estrogens
Citalopram	Mexiletine
Clarithromycin	Mexiletine
Clotrimazole	Modafenil
Clozapine	Nifedipine
Diclofenac	Olanzapine
Diltiazem	Omeprazole
Echinacea	Ondansetron
Ethinyl Estradiol	Paroxetinee
Fluoroquinolones	Propafenone
Fluconazole	Propanolol
Fluvoxamine	Ranitidine
Gemfibrozil	Rofecoxib
Ginseng	Sertraline
CYP1A2 Inducers	
Barbiturates (e.g., Phenobarbital)	Rifampin (e.g., Rifadin)
Cruciferous vegetables (broccoli, cauliflower, arugula, brussel sprouts, cabbage, kale, chard, turnips, radishes, wasabi, bok choy, watercress, collard greens)	Smoking
Char-grilled meat	Triamterene (Dyrenium)
Carbamazepine (e.g., Tegretol)	Zolmitriptan (Zomig)
Primidone	

Adapted from ctep.cancer.gov/protocolDevelopment/docs/cyp1a2.doc.