Official Title: **A PHASE IB/II STUDY EVALUATING THE SAFETY, TOLERABILITY AND ANTI-TUMOR ACTIVITY OF POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB OR OBINUTUZUMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA**

NCT Number: NCT01992653

Document Date: Protocol Version 9: 26-July-2017

PROTOCOL

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY, TOLERABILITY AND ANTI-TUMOR ACTIVITY OF POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB OR OBINUTUZUMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO29044
VERSION NUMBER:	9
EUDRACT NUMBER:	2013-003541-42
IND NUMBER:	109409
TEST PRODUCT:	Polatuzumab Vedotin (DCDS4501A)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 13 August 2013
DATES AMENDED:	Version 2: 21 February 2014 Version 3: 28 March 2014 Version 4 (France Only): 17 April 2014 Version 5: 18 July 2014 Version 6: 24 September 2015 Version 7 (France Only): 5 April 2016 Version 8: 23 September 2016 Version 9: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	26-Jul-2017 14:27:03

PROTOCOL AMENDMENT, VERSION 9:
RATIONALE

Protocol GO29044 has been amended to introduce second malignancies as an adverse event of special interest (AESI) for patients who have received obinutuzumab. The classification of second malignancies has been changed from a selected adverse event to AESI to more closely monitor this adverse event. Changes to the protocol, along with a rationale for each change, are summarized below:

- Second malignancies have been added as an AESI in Section 5.2.3. The duration of AE reporting for second malignancies has been changed to indefinitely in Section 5.3.1 and Section 5.7.
- The reporting of the term “sudden death” has been updated to also require the presumed cause of death (Section 5.4.7).
- Event reporting for hospitalization has been clarified (Section 5.4.10).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).
- A section on the publication of data and protection of trade secrets was added per internal standard operating procedures (Section 9.5).

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

PROTOCOL AMENDMENT, VERSION 9:
SUMMARY OF CHANGES

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

Adverse events of special interest for this study include the following:

[…]

- *Second malignancies*

SECTION 5.3.1: Adverse Event Reporting Period

Second malignancies will be reported indefinitely for patients who received obinutuzumab, regardless of relationship to study treatment (even if the study has been closed and even after initiation of new anti-lymphoma therapy; see Section 5.7).

SECTION 5.4.7: Deaths

~~The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ 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").*

SECTION 5.4.10: Hospitalization and Prolonged Hospitalization

~~The following~~ *An event that leads to* hospitalization ~~scenarios are~~ *under the following circumstances should* not ~~considered to~~ be *reported as an* adverse ~~*events*~~ *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, perform an efficacy measurement for the study)
- 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

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

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

SECTION 5.7: POST-STUDY ADVERSE EVENTS

The Sponsor should also be notified of events of second malignancies indefinitely for patients who received obinutuzumab.

SECTION 9.2: PROTOCOL DEVIATIONS

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.

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

This section has been added.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY, TOLERABILITY AND ANTI-TUMOR ACTIVITY OF POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB OR OBINUTUZUMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO29044
VERSION NUMBER:	9
EUDRACT NUMBER:	2013-003541-42
IND NUMBER:	109409
TEST PRODUCT:	Polatuzumab Vedotin (DCDS4501A)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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 to the CRO Monitor at your site.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY, TOLERABILITY AND ANTI-TUMOR ACTIVITY OF POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB OR OBINUTUZUMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO29044
VERSION NUMBER:	9
EUDRACT NUMBER:	2013-003541-42
IND NUMBER:	109409
TEST PRODUCT:	Polatuzumab Vedotin (DCDS4501A)
PHASE:	Ib/II
INDICATION:	B-Cell Non-Hodgkin's Lymphoma
SPONSOR:	Genentech, Inc.

OBJECTIVES

Primary Objectives

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of polatuzumab vedotin with rituximab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone (R-CHP) or obinutuzumab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone (G-CHP) administered to patients with B-cell non-Hodgkin's lymphoma (NHL)
- To determine the maximum tolerated dose (MTD) and schedule for polatuzumab vedotin given in combination with R-CHP or G-CHP to patients with B-cell NHL

Secondary Objectives

The secondary objectives of this study are the following:

- To characterize the pharmacokinetics of polatuzumab vedotin, cyclophosphamide, doxorubicin, and rituximab or obinutuzumab in patients when polatuzumab vedotin is given in combination with R-CHP or G-CHP
- To make a preliminary assessment of efficacy as measured by complete response (CR) rate determined by positron emission tomography (PET)-computed tomography (CT) scan of polatuzumab vedotin and R-CHP or G-CHP administered to patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in the expansion phase of the study
- To make a preliminary assessment of efficacy when polatuzumab vedotin and R-CHP or G-CHP are administered in combination to patients with previously untreated DLBCL, as measured by:
    - Objective response (OR) rate
    - CR rate as determined by CT scan
    - Duration of response (DOR)
    - Progression-free survival (PFS)

Event-free survival (EFS)

Overall survival (OS)

- To assess the immunogenicity of polatuzumab vedotin and obinutuzumab, as measured by the formation of anti-therapeutic antibodies (ATAs)
- To assess the potential relationships of such ATA (anti-polatuzumab vedotin or anti-obinutuzumab) formation with other outcome measures (e.g., pharmacokinetics, efficacy, safety)
- To evaluate peripheral neuropathy symptom severity and interference on daily functioning and to better understand treatment impact, tolerability, and reversibility, as measured by the Therapy-Induced Neuropathy Assessment Scale (TINAS)

Exploratory Objectives

The exploratory objectives of this study are the following:

- To assess the efficacy of therapy in different potential prognostic subgroups, including DLBCL genotypic subtypes (e.g., activated B cell–like, germinal-center B cell–like) and high Bcl-2 (Bcl-2–positive) expression
- To assess tumor expression of CD79b
- To assess prevalence and the correlation of lymphoma associated mutations with outcome
- To assess minimal residual disease as quantified by measurements of lymphoma-specific markers in peripheral blood
- To evaluate the prognostic significance of interim PET assessment
- Response, by Independent Review Committee (IRC), will be determined through use of the PET-CT scans based on a modified version of the Lugano Response Criteria for Malignant Lymphoma, hereinafter referred to as Modified Lugano 2014 criteria:

    To assess CR by PET at end of induction (EOI) by IRC

    To assess CR by CT at EOI by IRC

    To assess OR (defined as a CR or partial response [PR]) at EOI

    To assess best response of CR or PR during the study

    To evaluate patients who have positive PET scans at EOI: CR at 12 months

STUDY DESIGN

This is a Phase Ib/II, multicenter, open-label, dose-escalation study of polatuzumab vedotin administered by intravenous (IV) infusion in combination with standard doses of rituximab or obinutuzumab, cyclophosphamide, doxorubicin, and oral prednisone in patients with NHL whose disease is expected to express CD79b. Two parallel treatment arms will explore doses of polatuzumab vedotin in combination with R-CHP and G-CHP. The MTD or RP2D of polatuzumab vedotin in combination with R-CHP will be identified before it is combined with G-CHP. Once the MTD or RP2D is determined, polatuzumab vedotin will be dosed at MTD or RP2D -1 in combination with G-CHP to start the dose escalation of this combination. Study treatment will be given in every-21-day cycles, with the first day of treatment constituting Day 1 of the cycle. Patients will be treated for a total of six or eight cycles in accordance with local institutional practice.

Sites cannot enroll patients in rituximab-containing and obinutuzumab-containing phases simultaneously. Sites do not need to have prior experience with the rituximab-containing combination before enrolling patients with the obinutuzumab combination.

Patients will be evaluated for safety, tolerability, and pharmacokinetics of study treatment. Assessments for anti-tumor activity will be performed by the investigator using the Revised Response Criteria for Malignant Lymphoma at screening and at the following timepoints:

- Interim response assessment following four cycles of study treatment (i.e., at Cycle 4, between Days 15 and 21)
- Primary response assessment at the completion of study treatment

Patients with no evidence of OR (CR or PR) at the post–Cycle 4 tumor assessment may be discontinued from study treatment, at the discretion of the investigator.

Imaging at these timepoints must include 18F-fluorodeoxyglucose (FDG)-PET and a diagnostic-quality CT scan with both oral and IV contrast. A combined PET-CT scan is encouraged if feasible. An independent review of the responses of all patients will also be conducted to confirm the primary CR endpoint. Patients will also be evaluated every 3 months thereafter until disease progression, death, withdrawal of consent, or initiation of another anti-cancer therapy. Tumor assessments should also be performed to confirm clinical suspicion of relapse or disease progression for documentation.

Number of Patients

The study will enroll approximately 24–30 patients during the dose-escalation stage and approximately 60 patients in the expansion stage, at approximately 6–12 investigative sites in the United States and Europe.

Target Population

Inclusion Criteria

Dose-Escalation Portion of the Study

- Histologically confirmed B-cell NHL: Patients with newly diagnosed B-cell NHL or relapsed/refractory B-cell NHL are eligible.

  Note that patients in France with newly diagnosed B-cell NHL are not eligible.
- No more than one prior systemic treatment regimen for B-cell NHL (single agent anti-CD20 MAb therapy will not be counted as a prior treatment regimen)
- No prior treatment with anthracyclines

Expansion Portion of the Study

- Previously untreated patients with DLBCL
- International Prognostic Index score of 2–5

All Patients

- Age $\geq$ 18 years
- Signed informed consent form(s)
- At least one bi-dimensionally measurable lesion, defined as $>$ 1.5 cm in its longest dimension
- Ability and willingness to comply with the study protocol procedures
- Confirmed availability of archival or freshly collected tumor tissue before 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, as established by extensive bone marrow involvement or is due to hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) 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 contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 12 months for R-CHP arm or $\geq$ 18 months for the G-CHP arm after the last dose of study drug.

A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

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

- For women of childbearing potential, a negative serum pregnancy test result within 7 days prior to commencement of dosing. Women who are considered not to be of childbearing potential are not required to have a pregnancy test.
- For men, agreement to remain abstinent (refrain from heterosexual intercourse) 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 5 months after the last dose of study drug and agreement to refrain from donating sperm during this same period.

  Men with a pregnant partner must agree to remain abstinent or to use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo for the duration of the pregnancy.

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

  Male patients considering preservation of fertility should bank sperm before treatment with polatuzumab vedotin.

Exclusion Criteria

Exclusion Criteria for Dose-Escalation Portion of the Study

- Diagnosis of primary mediastinal DLBCL

Exclusion Criteria for Expansion Portion of the Study

- Patients with transformed lymphoma
- Prior therapy for NHL

All Patients

- Prior stem cell transplant
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to receive any of the individual components of R-CHP or G-CHP
- Current Grade > 1 peripheral neuropathy
- Ongoing corticosteroid use of > 30 mg/day of prednisone/prednisolone or equivalent. Patients receiving corticosteroid treatment with ≤ 30 mg/day of prednisone//prednisolone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration before Cycle 1 Day 1

  Note: If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day prednisone or equivalent can be given for a maximum of 7 days, but all tumor assessments must be completed prior to start of corticosteroid treatment.
- Primary CNS lymphoma
- Vaccination with live vaccines within 6 months before Cycle 1 Day 1

- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.

  Patients with a malignancy that has been treated with surgery alone with curative intent will also be excluded unless the malignancy has been in documented remission without treatment for ≥ 5 years before enrollment.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration, or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, congestive heart failure, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Left ventricular ejection fraction defined by multiple-gated acquisition (MUGA)/echocardiogram (ECHO) below the institutional lower limit of normal
- 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 before Cycle 1 Day 1
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody) or hepatitis C (hepatitis C virus [HCV] antibody)

  Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction to be eligible for study participation.
- Prior radiotherapy to the mediastinal/pericardial region
- Women who are pregnant, lactating, or who intend to become pregnant within a year after the last dose of study treatment in the rituximab cohort or within 18 months after the last dose of study treatment in the obinutuzumab cohort
- Recent major surgery within 6 weeks before the start of Cycle 1 Day 1, other than superficial lymph node biopsies for diagnosis.
- Any of the following abnormal laboratory values:

  Creatinine > 1.5 × upper limit of normal (ULN) or a measured creatinine clearance < 50 mL/min

  AST or ALT > 2.5 × ULN

  Total bilirubin ≥ 1.5 × ULN:

  INR > 1.5 × ULN in the absence of therapeutic anticoagulation

  PTT or aPTT > 1.5 × ULN in the absence of a lupus anticoagulant

End of Study

The end of the study is defined as the time point at which all patients enrolled into the study have either had at least 2 years of follow-up from the time of the Treatment Completion/Early Termination visit or have discontinued from the study. The Sponsor has the right to terminate the study at any time.

OUTCOME MEASURES

Safety Outcome Measures

The following safety outcome measures will be assessed:

- Incidence, nature, and severity of adverse events and serious adverse events

- Changes in vital signs, physical findings, ECGs, and clinical laboratory results during and following study treatment administration
- Incidence of anti-polatuzumab vedotin antibodies and anti-obinutuzumab antibodies

Pharmacokinetic/Pharmacodynamic Outcome Measures

The following pharmacokinetic (PK) parameters will be derived from the serum concentration–time profiles of total antibody (the sum of fully conjugated antibody, partially deconjugated antibody, and fully deconjugated antibody concentrations), plasma concentration–time profiles of conjugate (evaluated as antibody-conjugated mono-methyl auristatin E [acMMAE]) and unconjugated mono-methyl auristatin E (MMAE), following administration of polatuzumab vedotin, when appropriate as data allow.

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration observed (C_{max})
- Total clearance of drug (CL)
- Terminal half-life ($t_{1/2,terminal}$)
- Volume of distribution under steady-state conditions (V_{ss})

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and minimum concentration under steady-state conditions within a dosing interval (C_{min}), may also be calculated, when appropriate as data allow.

Limited sampling of serum concentrations of rituximab/obinutuzumab will be assessed and compared with historical data to evaluate potential PK interactions with polatuzumab vedotin. Plasma levels of cyclophosphamide and doxorubicin will be assessed and compared at the same timepoints of Cycle 1 (in the absence of polatuzumab vedotin) and Cycle 3 (in the presence of polatuzumab vedotin), and compared with historical data to evaluate potential PK interactions with polatuzumab vedotin.

Activity Outcome Measures

Response assessment will be determined using the modified version of the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007) and the modified version of the Lugano Response Criteria (Cheson et al. 2014).

The following activity outcome measures will be assessed:

- CR rate as defined as the percentage of patients with CR at the end of treatment, as assessed by the investigator, with and without FDG-PET.
- OR at the end of treatment, as assessed by the investigator, with and without FDG-PET. The overall response rate is defined as the percentage of patients with CR or PR at the end of treatment. All other cases are designated non-responders.
- DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse or death from any cause (PFS), as assessed by the investigator for the subgroup of patients with a best overall response of CR or PR. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.
- PFS, defined as the time from date of first dose of study drug to the first occurrence of progression or relapse, or death from any cause while in the study
- EFS is defined as the time from randomization to disease progression or relapse, as assessed by the investigator, death from any cause, or initiation of any new anti-lymphoma therapy (NALT). If the specified event (disease progression or relapse, death, initiation of an NALT does not occur, EFS will be censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS will be censored at the time of randomization.
- Relative dose intensity (DI) is defined as the ratio of the amount of a drug actually administered (actual DI) to the amount planned (planned DI) for a fixed time period

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

Immunogenicity Outcome Measures

ATA responses to polatuzumab vedotin and obinutuzumab will be characterized at predetermined timepoints.

Patient-Reported Outcome Measures

The patient-reported outcome (PRO) measures for this study are as follows:

- PRO of peripheral neuropathy symptom severity and symptom interference, as measured by the TINAS.

Biomarker Outcome Measures

- Gene expression profiles in tumor relating to:
  - DLBCL prognostic subgroups
  - Target (CD79b) biology
  - Expression of apoptotic regulators (including but not limited to Bcl-2)
  - Drug efflux transporters and other potential mediators of antibody-drug conjugate resistance
- Tumor immunohistochemistry of target (CD79b) expression and apoptotic regulators (including but not limited to Bcl-2)

INVESTIGATIONAL MEDICINAL PRODUCTS

Patients will receive treatment with one of two immunochemotherapy regimens in combination with polatuzumab vedotin:

R-CHP: rituximab plus CHP chemotherapy

G-CHP: obinutuzumab plus CHP chemotherapy

Patients will receive a total of six to eight cycles of polatuzumab vedotin in combination with R-CHP or G-CHP. A cycle is typically 21 days in duration.

See the protocol for details on dosage and administration of each product.

CONCOMITANT THERAPIES

Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days before screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form.

Patients who are receiving oral contraceptives, stable doses of hormone-replacement therapy, or other maintenance therapy should continue their use.

Other than prednisone/prednisolone that may be given as pre-phase treatment at the discretion of the treating investigator physician, corticosteroids may be used only for the treatment of conditions other than lymphoma (e.g., asthma).

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

See the protocol for guidelines on prophylaxis.

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; however, patients will be followed.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy other than cyclophosphamide, doxorubicin, and prednisolone or prednisone and intrathecal chemotherapy for CNS prophylaxis
- Immunotherapy or immunosuppressive therapy other than study treatments
- Radioimmunotherapy
- Hormone therapy other than contraceptives, hormone-replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts
- Any therapies (other than intrathecal CNS prophylaxis) intended for the treatment of lymphoma whether European Medicines Agencies or U.S. Food and Drug Administration approved or experimental
- Radiotherapy

Immunizations

Patients who participate in this study may not receive either primary or booster vaccination with live virus vaccines for at least 6 months before initiation of rituximab or 28 days prior to obinutuzumab or at any time during study treatment. Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases before study therapy.

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

STATISTICAL METHODS

Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, changes in ECGs, ECHO/MUGA scans, and changes in vital signs. All patients who receive any amount of any drug that was part of the combination study treatment will be included in the safety analysis.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after study treatment administration on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and toxicity grade per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. In addition, all serious adverse events, including deaths, will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to polatuzumab vedotin will be summarized.

Pharmacokinetic Analysis

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to polatuzumab vedotin will be summarized.

Individual and mean serum concentrations of total polatuzumab vedotin antibody (fully conjugated, partially deconjugated and fully deconjugated antibody) and rituximab and plasma concentrations of polatuzumab vedotin conjugate (evaluated as acMMAE), unconjugated MMAE, cyclophosphamide, and doxorubicin versus time data will be tabulated and plotted. The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2,terminal}$), as data allow. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range), as data allow. Non-compartmental, compartmental and/or population methods will be used, as data allow.

To assess PK drug interactions, PK parameters for each analyte of polatuzumab vedotin, rituximab, and obinutuzumab will be compared with historical single-agent data, as data allow. PK data of cyclophosphamide, and doxorubicin will be compared between Cycle 1 (in the absence of polatuzumab vedotin) and Cycle 3 (in the presence of polatuzumab vedotin), and compared to historical data, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted using PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, per the Sponsor's discretion and as data allow.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of polatuzumab vedotin, as data allow and at the Sponsor's discretion.

Activity Analyses

OR is defined as a CR or PR, as determined by investigator assessment with use of standard criteria. OR rate will be summarized. Patients with missing or no response assessments will be classified as non-responders. Among patients with an OR, DOR will be defined as the time from documentation of the first CR or PR to the time of disease progression, relapse, or death from any cause, as assessed by the investigator. If a patient does not experience death or disease progression before the end of the study, DOR will be censored on the day of the last tumor assessment. OS is defined as the period from the date of randomization until the date of death from any cause. For patients who have not died at the time of the analyses, OS will be censored on the last date when the patients are known to be alive.

PFS is defined as the time from the first day of study treatment (Day 1) to disease progression, relapse, or death from any cause, as assessed by the investigator. If a patient has not experienced progressive disease or death, PFS will be censored on the day of the last tumor assessment. If a post-baseline assessment is not available, PFS will be censored on Day 1.

The Kaplan-Meier approach will be used to estimate the distribution of DOR, PFS, and OS in all patients. Results will also be summarized separately among those patients in the dose-escalation part of the study and among those patients in the dose-expansion part of the study.

Patient-Reported Outcome Analyses

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

Missing Data

For PFS, patients who do not have documented disease progression or have died will be treated as censored observations on the date of the last tumor assessment. If no tumor assessments were performed after the baseline visit, PFS will be censored at the time of randomization.

For the response endpoints, patients with no response assessments (for any reason) will be considered non-responders.

Determination of Sample Size

The sample size required estimating the MTD is based on the dose-escalation rules. In addition, approximately 17 and 40 patients will be enrolled into expansion cohorts G-CHP and R-CHP respectively, in combination with the MTD of polatuzumab vedotin identified during dose escalation. With 40 patients, the 95% exact Clopper-Pearson CIs for the true CR rate would have a margin of error not exceeding 17%. The planned enrollment for this study is approximately 24–30 patients for dose-escalation cohorts and 60 patients for expansion cohorts for a total planned enrollment of 84–90 patients.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	activated B cell-like (subgroup)
acMMAE	antibody-conjugated mono-methyl auristatin E
ADC	antibody-drug conjugate
ADR	adverse drug reaction
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from Time 0 to infinity
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
CHP	cyclophosphamide, doxorubicin, and prednisolone or prednisone
CL	total clearance of drug
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma and serum concentration observed
C_{min}	minimum concentration under steady-state conditions within a dosing interval
CR	complete response
CRO	contract research organization
CT	computed tomography
DI	dose intensity
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EOI	end of induction
ePRO	electronic patient-reported outcome
FDA	U.S. Food and Drug Administration
FDG	^{18}F-fluorodeoxyglucose
FL	follicular lymphoma
GCB	germinal-center B cell–like (subgroup)
GCP	Good Clinical Practice

Abbreviation	Definition
G-CHP	Obinutuzumab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone
G-CSF	granulocyte colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
iNHL	indolent non-Hodgkin's lymphoma
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous
IXRS	Interactive Voice and Web Response System
LC/MS/MS	liquid chromatography tandem mass spectrometry
MAb	monoclonal antibody
MMAE	mono-methyl auristatin E
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NALT	new anti-lymphoma therapy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
OR	objective response
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	by mouth (orally)
PR	partial response

Abbreviation	Definition
PRO	patient-reported outcome
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
R-CHP	rituximab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone
RP2D	recommended Phase II dose
$t_{1/2,terminal}$	terminal half-life
TINAS	Therapy-Induced Neuropathy Assessment Scale
TLS	tumor lysis syndrome
ULN	upper limit of normal
V_{ss}	volume of distribution under steady-state conditions

1. BACKGROUND

1.1 NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignancy in adults. It is estimated that in 2010 there were 93,172 new cases of NHL in Europe and 65,540 new cases of NHL in the United States (American Cancer Society 2010; GLOBOCAN 2010). The majority of NHL is of B-cell origin with multiple histologic subtypes that confer different clinical outcomes. Generally, NHL can be divided into aggressive and indolent lymphomas. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL, accounting for approximately 30% of all cases of NHL (Armitage and Weisenburger 1998). Follicular lymphoma (FL) is the most common form of indolent NHL (iNHL) and accounts for approximately 20%–25% of all cases of newly diagnosed NHL. If left untreated, patients with aggressive lymphomas have a median survival of approximately 6 months, whereas patients with indolent lymphomas may live as long as 8–10 years.

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 CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone)-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; Pfreundschuh et al. 2006, 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 (R-CHOP) is considered to be the standard of care for patients with previously untreated DLBCL (Tilly et al. 2012; National Comprehensive Cancer Network® 2013), with approximately 60%–70% of patients being cured of their disease. In addition to newly diagnosed and relapsed/refractory DLBCL, R-CHOP is also used in other NHL indications, including relapsed FL and mantle-cell lymphoma (Hauptrock and Hess 2008).

Clinical factors at the time of initial diagnosis of NHL have been identified that influence the prognosis of patients with initial therapy. In DLBCL, an International Prognostic Index (IPI) for aggressive NHL (i.e., DLBCL) identified risk factors based on performance status and extent of disease that are prognostic of response to therapy and overall survival (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).

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/high IPI. Thus, there is still a need 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

1.2.1 Background on Nonclinical Data

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 (DCDS4501A) is an antibody-drug conjugate (ADC) that contains a humanized immunoglobulin-G1 (IgG1) anti–human CD79b MAb (MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-VC-PABC). MMAE has a mode of action similar to that of vincristine, which is a component of standard chemotherapy, R-CHOP, used for treatment of lymphoma. Following internalization, 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 to vincristine. Given that vincristine is commonly used in the treatment of NHL, it is hypothesized that the replacement of vincristine with polatuzumab vedotin in an anti-CD20 antibody + chemotherapy regimen will provide better efficacy and safety to patients with NHL.

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic, and toxicological studies were done to support the entry of polatuzumab vedotin into clinical trials. Because polatuzumab vedotin specifically recognizes CD79b on B cells of human but not on those of the cynomolgus monkey, rat, or mouse, a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to that of polatuzumab vedotin. Polatuzumab vedotin has demonstrated efficacy in nonclinical mouse xenograft models of human CD79b-positive NHL. Additionally, polatuzumab vedotin when combined with R-CHP (rituximab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone) demonstrated better anti-tumor activity compared with polatuzumab vedotin as single agent or compared with a current standard-of-care regimen (R-CHOP) in xenograft models of NHL. The pharmacokinetics and safety of polatuzumab vedotin and/or the surrogate ADC was characterized in repeat-dose toxicity studies in rats and cynomolgus monkeys. Polatuzumab vedotin and the surrogate ADC were well tolerated in both species at the tested doses. The predominant antigen-independent findings associated with polatuzumab vedotin or surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. The PK profiles of polatuzumab vedotin and the surrogate ADC suggested that the

pharmacokinetics of the ADC was driven mainly by the antibody component (similar serum concentration–time profile between ADC and total MAb).

Refer to the Investigator's Brochure for complete details of the biochemical composition and nonclinical studies of polatuzumab vedotin.

1.2.2 Polatuzumab Vedotin Clinical Data

On the basis of nonclinical data, polatuzumab vedotin is currently being evaluated in Phase I and Phase II studies in relapsed/refractory NHL. Complete and updated details of this data are provided in the Polatuzumab Vedotin Investigator's Brochure.

Study DCS4968g is a Phase I study to evaluate the safety and tolerability and anti-tumor activity of polatuzumab vedotin and to determine the maximum tolerated dose (MTD)/recommended Phase II dose (RP2D) as a single agent and in combination with rituximab in relapsed/refractory NHL. Study GO27834 is a randomized study to evaluate the safety and anti-tumor activity of polatuzumab vedotin in combination with rituximab in patients with relapsed/refractory DLBCL and FL. A second vc-MMAE ADC targeting CD22 (DCDT2980S) combined with rituximab is also being evaluated in this study. Patients are randomized to receive either polatuzumab vedotin or DCDT2980S in combination with rituximab.

1.2.2.1 Patient Enrollment

A total of 95 patients have been enrolled into the Phase I study (Study DCS4968g), of whom 32 patients with NHL (iNHL or DLBCL) were enrolled in single-agent dose escalation, 11 were enrolled in iNHL single-agent expansion cohort, 23 were enrolled in the DLBCL single-agent expansion cohort, and 9 patients were enrolled in the Phase Ib polatuzumab vedotin + rituximab combination treatment cohort. Enrollment into the study of patients with NHL has been completed.

Twenty patients with CLL were enrolled into single-agent dose-escalation cohorts of Study DCS4968g. Refer to the Polatuzumab Vedotin Investigator's Brochure for details regarding clinical data in patients with CLL.

As of 28 February 2013, preliminary safety data were available for all 95 patients enrolled in the dose-escalation and expansion cohorts.

1.2.2.2 Safety

Dose-Limiting Toxicities in NHL

In the Phase I Study DCS4968g, a dose-limiting toxicity (DLT) of Grade 4 neutropenia occurred in 1 patient out of 10 DLT-evaluable patients in the 2.4-mg/kg single-agent cohort and 1 patient out of 9 DLT-evaluable patients in the 2.4-mg/kg + rituximab cohort. Doses of polatuzumab vedotin > 2.4 mg/kg as monotherapy or in combination with rituximab were not assessed. Consequently, polatuzumab vedotin at 2.4 mg/kg was determined to be the RP2D as both monotherapy and in combination with rituximab.

Treatment Discontinuations for Adverse Events

In Study DCS4968g as of 28 February 2013 (the clinical data cutoff date), study treatment discontinuation because of adverse events not due to the disease under study was reported in 19 of 95 patients (20.0%), with study treatment–related adverse events leading to treatment discontinuation in 17 of 95 patients (17.9%). The treatment-related events included Grade 2 peripheral neuropathy (9 patients), Grade 3 peripheral neuropathy (3 patients), Grade 4 peripheral neuropathy (1 patient), Grade 3 diarrhea (1 patient), and Grade 2 hyperesthesia, Grade 2 asthenia, Grade 3 anemia, and Grade 4 thrombocytopenia (all four events occurring in 1 patient). Two adverse events resulting in treatment discontinuation were reported as not related to study treatment: Grade 3 worsening hyponatremia (1 patient) and Grade 4 invasive fungal infection (1 patient).

Adverse events that led to study treatment discontinuation and that were not due to the disease under study were reported in 5 patients with DLBCL: Grade 2 peripheral neuropathy (3 patients), Grade 3 peripheral neuropathy (1 patient), and Grade 3 diarrhea (1 patient). The only adverse event that led to treatment discontinuation and that was not due to the disease under study among the patients with CLL was Grade 4 invasive fungal infection (1 patient). All remaining events occurred in patients with iNHL, including a single event (Grade 2 peripheral neuropathy) reported among the 9 patients treated with the combination of polatuzumab vedotin + rituximab.

In Phase II Study GO27834, as of the clinical data cutoff (28 February 2013), treatment discontinuation due to adverse events had not been reported for any patient.

Adverse Events with Single-Agent Polatuzumab Vedotin

Adverse events regardless of relationship to study drug were reported in 66 of 66 patients (100%) with NHL (iNHL + DLBCL) who were treated with polatuzumab vedotin as a single agent. Treatment-emergent adverse events in > 20% of patients included neutropenia (44%), diarrhea (38%), pyrexia (32%), nausea (32%), neuropathy peripheral (30%), fatigue (23%), and cough (21%).

Grade ≥ 3 adverse events regardless of relationship to study drug were reported in 48 of 66 patients (72.7%) with NHL (iNHL or DLBCL). Neutropenia was the most common adverse event experienced by more than 35% of the 66 NHL patients. Thirty-one of 45 patients (68.8%) treated at the RP2D of 2.4 mg/kg experienced a Grade 3–5 adverse event. Grade 3-4 adverse event of neutropenia were experience by more than 10% of the patients. Three Grade 5 events were reported: 1 patient died of sepsis, 1 patient died of pulmonary vascular disorder, and 1 patient died of unknown cause. None of the deaths was assessed by the investigator to be related to study treatment.

Adverse Events with Polatuzumab Vedotin Combined with Rituximab

In the Phase Ib cohort of Study DCS4968g, adverse events regardless of relationship to study drug were reported in 9 of 9 patients (100%) who received polatuzumab vedotin

(2.4 mg/kg) plus rituximab (375 mg/m²). The most common adverse events that occurred in ≥2 patients were neutropenia, pyrexia, nausea, diarrhea, hyperuricemia, bone pain, fatigue, peripheral neuropathy, decreased appetite, chills, pain in extremity, pruritus, arthralgia, night sweats, hypokalemia, dysgeusia, increased blood creatinine, infusion-related reactions (IRRs), cough, constipation, thrombocytopenia, anemia, hyperglycemia, rash, alopecia, hypomagnesemia, upper abdominal pain, hyperhidrosis, myalgia, peripheral motor neuropathy, febrile neutropenia, hyperbilirubinemia, and tooth fracture.

Grade ≥3 adverse events regardless of relationship to study drug were reported in 7 of 9 patients (77.8%) receiving polatuzumab vedotin in combination with rituximab in the Phase Ib cohort of Study DCS4968g. Grade 3–4 neutropenia was reported in 5 patients, Grade 3–4 anemia in 2 patients, Grade 3–4 febrile neutropenia in 2 patients, and Grade 3–4 hyperglycemia in 2 patients. No Grade 5 adverse events were reported.

In the ongoing Phase II Study GO27834, adverse events regardless of relationship to study drug were reported in 15 of 15 patients (100%) who received polatuzumab vedotin (2.4 mg/kg) plus rituximab (375 mg/m²). The most common adverse events of all grades in ≥2 patients were fatigue, nausea, diarrhea, neutropenia, vomiting, dry mouth, asthenia, arthralgia, back pain, and headache.

In the Phase II study, Grade ≥3 adverse events regardless of relationship to study drug were reported in 4 of 15 patients (26.7%) receiving polatuzumab vedotin in combination with rituximab. Grade 3–4 neutropenia was reported in 2 patients, Grade 3 diarrhea in 1 patient, Grade 3 chest pain in 1 patient, Grade 3 decreased neutrophil count in 1 patient, and Grade 3 hypophosphatemia in 1 patient.

Serious Adverse Events

From ongoing Phase I Study DCS4968g, a total of 44 serious adverse events were reported among 22 patients in the single-agent NHL (iNHL + DLBCL) cohorts, 19 serious adverse events in 11 patients in the CLL cohort, and 15 serious adverse events in 4 patients treated with polatuzumab vedotin + rituximab. Among all patients, the most common serious adverse events (occurring in ≥2% of patients) were Grades 1–2 pyrexia (6 patients), Grade 3–4 febrile neutropenia (4 patients), Grade 4–5 lung infection (3 patients), Grade 3–4 diarrhea (3 patients), Grade 3–4 hyperglycemia (2 patients), Grade 3–4 hyponatremia (2 patients), Grade 2–3 mental status changes (2 patients), Grade 3–4 peripheral neuropathy (2 patients), Grade 3–4 neutropenia (2 patients), Grade 4–5 pneumonia (2 patients), and acute renal failure (Grade 1 in 1 patient and Grade 4 in 1 patient).

In the Phase II Study GO27834, a total of 2 serious adverse events were reported in 2 patients treated with polatuzumab vedotin + rituximab: Grade 2 pyrexia and Grade 2 chest tightness. Both serious adverse events were reported as not related to study drug treatment.

Refer to the Polatuzumab Vedotin Investigator's Brochure for complete and updated details related to safety.

Anti-Tumor Activity

In ongoing Phase I Study DCS4968g, preliminary anti-tumor activity data for best overall response were available for 88 of 95 patients (92.6%) as of the clinical data cutoff date. 86 of the 88 patients had relapsed/refractory iNHL, DLBCL, or CLL. Data regarding duration of response (DOR), progression-free survival (PFS), and OS were insufficiently mature for reporting. Most evidence of anti-tumor activity was observed at ADC doses $\geq$1.8 mg/kg. Among patients with relapsed/refractory iNHL, 13 of 22 (59%) patients treated with single-agent polatuzumab vedotin and 6 of 8 (75%) patients treated with polatuzumab vedotin + rituximab had an investigator-assessed objective response (OR). Among patients with relapsed/refractory DLBCL, 14 of 26 (54%) patients treated with single-agent polatuzumab vedotin and 1 of 1 patient treated with polatuzumab vedotin + rituximab had an investigator-assessed OR.

In the Phase II Study GO27834, anti-tumor activity data were not sufficiently mature to report as of the clinical data cutoff date, because most patients had not yet undergone on-treatment tumor assessments to evaluate response.

1.2.3 Pharmacokinetic and Pharmacodynamic Properties of Polatuzumab Vedotin

The PK properties of polatuzumab vedotin conjugate (evaluated as antibody-conjugated mono-methyl auristatin E [acMMAE]), total antibody, and unconjugated MMAE after the first dose of polatuzumab vedotin in patients with NHL, either as a single agent or in combination with rituximab, are summarized below. The PK properties after repeated doses of polatuzumab vedotin have not yet been characterized at the time of the current version of the protocol.

In patients with NHL, polatuzumab vedotin demonstrated a trend of linear pharmacokinetics for each measurement across the dose range from 0.1 to 2.4 mg/kg. At the RP2D of 2.4 mg/kg in patients with NHL, serum concentrations of total antibody and conjugate (evaluated as acMMAE) reached peak values at the end of infusion. The distribution of total antibody and acMMAE appears to be restricted to the serum compartment, with median volume of distribution under steady-state conditions (V_{ss}) values of 112 mL/kg and 73.3 mL/kg for total antibody and acMMAE, respectively. Median total clearance of drug (CL) of acMMAE was approximately similar to CL of total antibody. Median terminal half-life ($t_{1/2,terminal}$) values for total antibody and acMMAE were 5.85 and 6.22 days, respectively. The disposition of the MMAE component of the ADC (represented by acMMAE) appears to be dictated by its antibody component.

In single-agent dose escalation in patients with NHL, maximum plasma and serum concentration observed (C_{max}) and area under the concentration-time curve from Time 0 to infinity (AUC_{inf}) of unconjugated MMAE appear increased with dose across the dose

levels tested. At the RP2D of 2.4 mg/kg in patients with NHL, maximum concentrations of free MMAE occur 2–3 days after dosing. At all timepoints, MMAE concentrations were at least 100 times lower than acMMAE concentrations. The median $t_{1/2,terminal}$ value for unconjugated MMAE was 3.57 days, which is relatively long for a small molecule and more similar to the half-life of acMMAE, suggesting that the rate of elimination of MMAE may be limited by its release from the ADC. On the basis of its half-life, no accumulation of unconjugated MMAE is expected when polatuzumab vedotin is administered every 21 days.

The co-administration of rituximab did not affect the pharmacokinetics of polatuzumab vedotin in patients with NHL. Given the various mechanisms of action, an interaction with chemotherapy is not expected with polatuzumab vedotin.

Refer to the Polatuzumab Vedotin Investigator's Brochure for complete and updated details.

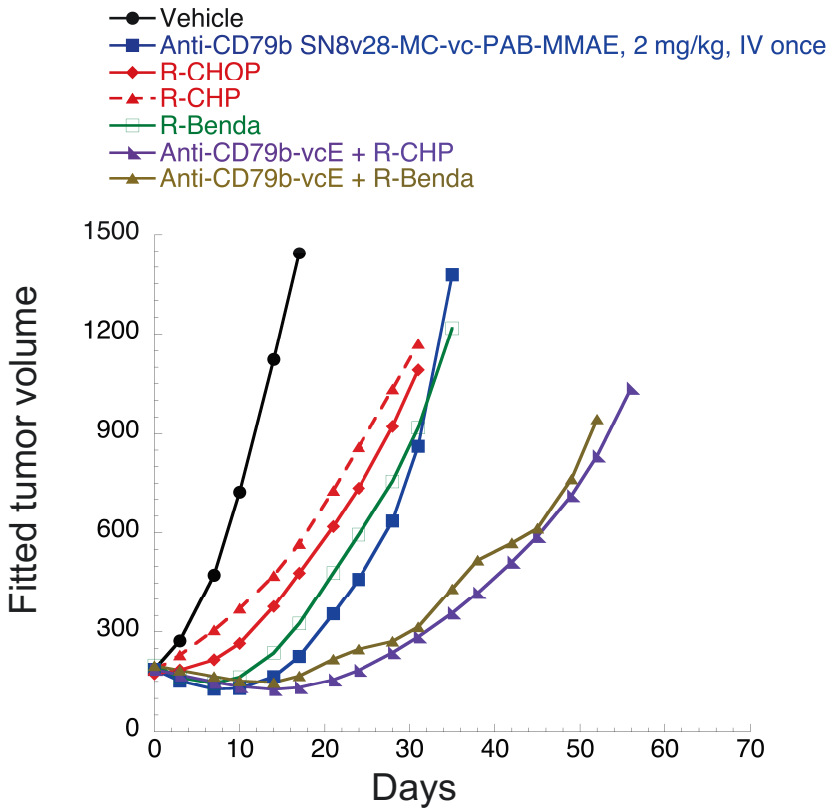
1.3 RATIONALE FOR DOING THIS STUDY

The addition of rituximab to standard CHOP chemotherapy has resulted in significantly improved outcomes and has demonstrated the importance of an anti-CD20 antibody combined with standard chemotherapy as an effective treatment for patients with newly diagnosed DLBCL. On the basis of the available clinical data (Coiffier et al. 2002; Habermann et al. 2006; Pfreundschuh et al. 2008), the 3-year PFS rate of patients with newly diagnosed DLBCL treated with R-CHOP had a range of 53%–76%, with a corresponding OS rate between 65% and 84%. Despite this progress, a significant number of patients are still not cured of the disease, especially those who present with one or more clinical risk factors at diagnosis as assessed by the IPI. Following progression on or relapse after first-line treatment, salvage regimens can induce a second remission, but less than half of patients experience prolonged PFS with second-line regimens without autologous stem-cell transplant. Even if patients are eligible for high-dose chemotherapy and autologous stem-cell transplant, less than half will be cured (Seyfarth et al. 2006). Therefore, obtaining the best outcome for patients with newly diagnosed disease is critically important for patients because this still offers the best chance for long-term survival.

Polatuzumab vedotin is an ADC designed for the targeted delivery of the potent microtubule inhibitor MMAE to lymphoma cells expressing CD79b. MMAE has a mechanism of action that is similar to that of vincristine. Phase I data to date suggest that polatuzumab vedotin has activity in relapsed/refractory DLBCL with a generally acceptable safety and tolerability profile. Because ADCs are believed to have a therapeutic index superior to that of systemically administered chemotherapy, polatuzumab vedotin has the potential to replace vincristine as part of the standard treatment regimen for DLBCL. Nonclinical data from murine xenograft models support the combination of R-CHP and polatuzumab vedotin and demonstrate significantly improved anti-lymphoma activity of the combination over R-CHP alone (see Figure 1;

Genentech data on file). Data from these xenograft models also suggest that it is reasonable to assume that vincristine ('O' in CHOP) can be replaced with polatuzumab vedotin as the additional contribution of vincristine (at least in this model) appears to be minimal.

Figure 1 Nonclinical Data in WSU-DLCL2



In addition to the potential of ADCs to replace systemic chemotherapy, development of next-generation anti-CD20 directed therapy may further enhance the efficacy of current standard immunochemotherapy regimens. Obinutuzumab ([G] also known as RO5072759, GA101, and Gazyva™/Gazyvaro™), a novel Type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and with previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining polatuzumab vedotin with obinutuzumab-containing regimens.

The combination of obinutuzumab with CHOP (G-CHOP) has been evaluated in several ongoing studies (see Table 1). Safety was acceptable, with no new or unexpected

adverse events observed. The most common adverse event was neutropenia. In patients with either previously untreated or relapsed/refractory FL response rates of > 95% were observed (Dyer et al. 2012; Radford et al. 2013). The overall response rate in patients with previously untreated DLBCL treated with G-CHOP was 83% (Zelenetz et al. 2013). Study BO21005 is an ongoing Phase III study that randomized patients with DLBCL to either receive R-CHOP vs G-CHOP.

Table 1 GA101 + CHOP for the Treatment of Lymphoma

Study	GAUDI Study BO21000 (Dyer et al. 2012)	GAUDI Study BO21000 (Radford et al. 2013)	GATHER Study GAO4915g (Zelenetz et al. 2013)	GOYA Study BO21005
N	40	28	80	1400
Patient population	1L FL	R/R FL	1L DLBCL	1L DLBCL
GA101 dose	1000 mg	1600/800 mg (n = 14)	1000 mg	1000 mg
Chemotherapy	CHOP	CHOP	CHOP	CHOP
Efficacy	ORR 95% CR 35% PR 60%	ORR 100% CR 64% PR 36%	ORR 83% CR 55% PR 28%	Detailed results not available
Neutropenia	45% (all grades) 43% (Grades 3/4)	57% (all grades) 50% (Grades 3/4)	7.5% (Grade 3) 22% (Grade 4)	Detailed results not available
Febrile neutropenia	10% (all Grades 3/4)	7% (all Grades 3/4)	6% (Grade 3) 7.5% (Grade 4)	Detailed results not available

1L = first line; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone or prednisone; CR = complete response; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; GA101 = Gazyva/Gazyvaro (obinutuzumab); ORR = overall response rate; PR = partial response; R/R = relapsed/refractory.

The goals of this Phase Ib/II study are to assess the safety, tolerability, and potential biologic and clinical activity of escalating doses of polatuzumab vedotin in combination with a standard regimen of an anti-CD20 antibody + chemotherapy without vincristine (R-CHP or obinutuzumab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone [G-CHP]) in patients with B-cell NHL. In the dose-finding portion of the study, the MTD of polatuzumab vedotin in combination with R-CHP or G-CHP will be determined. Following identification of the MTD, the dose-expansion portion of the study will further evaluate the safety and tolerability and clinical activity of R-CHP or G-CHP plus polatuzumab vedotin in patients with newly diagnosed DLBCL.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of polatuzumab vedotin with R-CHP or G-CHP administered to patients with B-cell NHL
- To determine the MTD and schedule for polatuzumab vedotin given in combination with R-CHP or G-CHP to patients with B-cell NHL

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are the following:

- To characterize the pharmacokinetics of polatuzumab vedotin, cyclophosphamide, doxorubicin, and rituximab or obinutuzumab in patients when polatuzumab vedotin is given in combination with R-CHP or G-CHP
- To make a preliminary assessment of efficacy as measured by CR rate determined by positron emission tomography (PET)-computed tomography (CT) scan (see Appendix 2 and Section 4.5.6) of polatuzumab vedotin and R-CHP or G-CHP administered to patients with previously untreated DLBCL in the expansion phase of the study
- To make a preliminary assessment of efficacy when polatuzumab vedotin and R-CHP or G-CHP are administered in combination to patients with previously untreated DLBCL (see Appendix 2 and Section 4.5.6), as measured by:

  OR rate

  CR rate as determined by CT scan

  DOR

  PFS

  Event-free survival (EFS)

  OS
- To assess the immunogenicity of polatuzumab vedotin and obinutuzumab, as measured by the formation of anti-therapeutic antibodies (ATAs)
- To assess the potential relationships of such ATA (anti-polatuzumab vedotin or anti-obinutuzumab) formation with other outcome measures (e.g., pharmacokinetics, efficacy, safety)
- To evaluate peripheral neuropathy symptom severity and interference on daily functioning and to better understand treatment impact, tolerability, and reversibility, as measured by the Therapy-Induced Neuropathy Assessment Scale (TINAS)

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are the following:

- To assess the efficacy of therapy in different potential prognostic subgroups, including DLBCL genotypic subtypes (e.g., activated B cell–like [ABC], germinal-center B cell–like [GCB]) and high Bcl-2 (Bcl-2–positive) expression
- To assess tumor expression of CD79b
- To assess prevalence and the correlation of lymphoma associated mutations with outcome
- To assess minimal residual disease (MRD) as quantified by measurements of lymphoma-specific markers in peripheral blood
- To evaluate the prognostic significance of interim PET assessment
- Response, by Independent Review Committee (IRC), will be determined through use of the PET-CT scans based on a modified version of the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 3), hereinafter referred to as Modified Lugano 2014 criteria:

    To assess CR by PET at end of induction (EOI) by IRC

    To assess CR by CT at EOI by IRC

    To assess OR (defined as a CR or partial response [PR]) at EOI

    To assess best response of CR or PR during the study

    To evaluate patients who have positive PET scans at EOI: CR at 12 months

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib/II, multicenter, open-label, dose-escalation study of polatuzumab vedotin administered by intravenous (IV) infusion in combination with standard doses of rituximab or obinutuzumab, cyclophosphamide, doxorubicin, and oral prednisone in patients with NHL whose disease is expected to express CD79b. Two parallel treatment arms will explore doses of polatuzumab vedotin in combination with R-CHP and G-CHP. The MTD or RP2D of polatuzumab vedotin in combination with R-CHP will be identified before it is combined with G-CHP. Once the MTD or RP2D is determined, polatuzumab vedotin will be dosed at MTD or RP2D -1 in combination with G-CHP to start the dose escalation of this combination. Study treatment will be given in every-21-day cycles, with the first day of treatment constituting Day 1 of the cycle (see Section 4.3 for specific treatment scheduling). Patients will be treated for a total of six or eight cycles in accordance with local institutional practice.

Sites cannot enroll patients in rituximab-containing and obinutuzumab-containing phases simultaneously. Sites do not need to have prior experience with the rituximab-containing combination before enrolling patients with the obinutuzumab combination.

Patients will be evaluated for safety, tolerability, and pharmacokinetics of study treatment. Assessments for anti-tumor activity will be performed by the investigator using the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007) at screening and at the following timepoints:

- Interim response assessment following four cycles of study treatment (i.e., at Cycle 4, between Days 15 and 21)
- Primary response assessment at the completion of study treatment

Patients with no evidence of OR (CR or PR) at the post-Cycle 4 tumor assessment may be discontinued from study treatment, at the discretion of the investigator.

Imaging at these timepoints must include ^{18}F-fluorodeoxyglucose (FDG)-PET and a diagnostic-quality CT scan with both oral and IV contrast. A combined PET-CT scan is encouraged if feasible. An independent review of the responses of all patients will also be conducted to confirm the primary CR endpoint (see Section 3.1.4). Patients will also be evaluated every 3 months thereafter until disease progression, death, withdrawal of consent, or initiation of another anti-cancer therapy. Tumor assessments should also be performed to confirm clinical suspicion of relapse or disease progression for documentation.

The study will enroll approximately 24–30 patients during the dose-escalation stage and approximately 60 patients in the expansion stage, at approximately 6–12 investigative sites in the United States and Europe. The study schema is illustrated in Figure 2.

3.1.1 Dose Escalation, Dose-Limiting Toxicity, and Determination of the Maximum Tolerated Dose

The dose-escalation stage of the study will assess the safety, tolerability, and pharmacokinetics of polatuzumab vedotin administered in combination with R-CHP or G-CHP. Patients must have histologically documented B-cell NHL with no restriction on the histologic subtype. Patients with newly diagnosed or relapsed/refractory NHL may be enrolled (note that patients in France with newly diagnosed B-cell NHL are not eligible for enrollment in the dose-escalation portion of the study). Patients with relapsed/refractory disease should have received only one prior treatment regimen and must be eligible for an anthracycline-containing therapy (i.e., must not have received prior CHOP therapy, or variants of CHOP). Prior vinca-alkaloid therapy is allowed if any resulting neuropathy does not exceed Grade 1 at enrollment.

The starting dose level for polatuzumab vedotin will be 1.0 mg/kg. The selection of the starting dose level is based on the absence of DLTs observed at this dose level when administered as a single agent in the Phase I study. R-CHP or G-CHP will be given at standard doses, with modifications for toxicity (see Section 5.1.7). In those instances where individual toxicities are attributed to polatuzumab vedotin, R-CHP or G-CHP dosing may be maintained, per the guidelines in Section 5.1.7.

Patients will be monitored for DLTs from Cycle 1 Day 1 to Cycle 2 Day 1 (minimum of 21 days). Any patient who does not complete the full DLT observation period for any reason other than DLT will be considered non-evaluable for dose-escalation decisions and/or MTD assessment and will be replaced by an additional patient at that same dose level.

All dose-escalation cohorts will consist of at least 3 patients. If a DLT is observed in 1 patient at a given dose level during the DLT observation period before dose escalation, additional patients will be enrolled at that dose level for a total of at least 6 patients.

At each dose level during escalation, the first patient treated at each dose level will receive the first infusion of polatuzumab vedotin at least 1 day before any subsequent patients in that cohort being treated in order to assess for any severe and unexpected acute drug or infusion-related toxicities.

Decisions regarding dose escalations will be made by the Sponsor Medical Monitor in consultation with the Safety Science Leader, and Biostatistician. All relevant safety data including but not limited to adverse event and laboratory data will be reviewed. Decisions will be made on the basis of this review and in consultation with the participating investigators on whether dose escalation should proceed and if so, to what dose level.

3.1.1.1 Definition of Dose-Limiting Toxicity

All adverse events, including DLTs, are to be reported according to instructions in Section 5.3 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 unless otherwise indicated. If a patient experiences a DLT, he or she will be treated according to clinical practice and will be monitored for resolution of the toxicity (see Section 5.6 for description of adverse event follow-up). All adverse events should be considered to be related to study treatment unless such events are clearly attributed by the investigator to another clearly identifiable cause (e.g., documented tumor progression). Decreases in B cells, lymphopenia, and leukopenia due to lymphopenia will not be considered DLTs because they are expected pharmacodynamic outcomes of rituximab and polatuzumab vedotin treatment. Granulocyte colony-stimulating factor (G-CSF) may be provided to patients for the management of neutropenia.

For dose-escalation purposes, a DLT will be defined as any of the following adverse events occurring during the DLT period that are attributed to study treatment and not attributable to another clearly identifiable cause:

- Any adverse event regardless of grade that leads to a delay of at least 7 days to the start of the next cycle

- Grade ≥ 3 non-hematologic toxicity that is not attributable to disease progression or another clearly identifiable cause, excluding the following:

  Grade 3 diarrhea that responds to standard-of-care therapy within 72 hours

  Grade 3 nausea or vomiting, in the absence of premedication, that responds to standard-of-care therapy within 72 hours

  Grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant

  Reversible Grade 3 non-allergic infusion toxicities (including symptoms such as fever, chills/rigors, nausea, vomiting, pruritus, headache, rhinitis, rash, asthenia, and/or hypoxia in the absence of signs/symptoms of respiratory distress) occurring during or within 24 hours after completing an infusion and resolving within 24 hours

  Grade ≥ 3 allergic toxicities such as wheezing, bronchospasm, shortness of breath, and/or stridor in the presence or absence of hypoxia, and/or urticaria are not excluded and should be considered DLTs. (Patients with infusion-related Grade ≥ 3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study drug on the first occurrence.)

  Grade 3 elevation in ALT or AST, provided the following criteria are met:

    ALT or AST level is no greater than $8 \times$ the upper limit of normal (ULN)

    ALT or AST elevation resolves to Grade < 2 ($< 5 \times$ ULN) within 7 days

    Total and direct bilirubin and other laboratory parameters of liver synthetic function (e.g., prothrombin time) are normal

    There are no clinical signs or symptoms of hepatic injury

    Any case involving an increase in hepatic transaminase $> 3 \times$ baseline AND an increase in direct bilirubin $> 2 \times$ ULN, WITHOUT any findings of cholestasis or jaundice or signs of hepatic dysfunction AND in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential drug-induced liver injury (DILI) (according to Hy's Law) and will be considered a DLT.

- All Grade 3 or 4 hematological toxicity considered by the investigator to be related to polatuzumab vedotin and not attributable to another clearly identifiable cause with the exception of the following:

  Lymphopenia, which is an expected outcome of therapy

  Grade 4 neutropenia (in the absence of G-CSF) that is not accompanied by temperature elevation (oral or tympanic temperature of ≥ 100.4°F [38°C]) and improves to Grade 3 within 1 week and further improves to Grade ≤ 2 (or to $\geq 80\%$ of the baseline value, whichever is lower) within another week

  Grade 3 neutropenia (in the absence of G-CSF) that is not accompanied by temperature elevation (oral or tympanic temperature of ≥ 100.4°F (38°C) and

improves to Grade <2 (or to $>80\%$ of the baseline value, whichever is lower) within 1 week

Grade 3 or 4 leukopenia

Grade 4 thrombocytopenia that does not result in bleeding and improves to Grade 3 within 1 week and further improves to Grade ≤ 2 (or to $\geq 80\%$ of the baseline value, whichever is lower) within another week without platelet transfusion

Grade 3 thrombocytopenia that does not result in bleeding and improves to Grade <2 (or to $\geq 80\%$ of the baseline value, whichever is lower) within 1 week without platelet transfusion

Grade 3 or 4 anemia that does not require an emergent transfusion

If a patient experiences a DLT as described above, the patient will be observed for resolution of the toxicity. If the DLT resolves to Grade ≤ 2 (or $\geq 80\%$ of the baseline value) and it is determined to be in the patient's best interest to continue study treatment (after discussion between the treating investigator and the Medical Monitor), the patient may continue to receive polatuzumab vedotin. The dose of polatuzumab vedotin may be reduced to the dose level tested in the previous cohort, with minimum dose level of 1.0 mg/kg. For details regarding dose reductions and interruptions, refer to Section 5.1.6.

3.1.1.2 Dose Escalation after Dose-Limiting Toxicity and Determination of the Maximum Tolerated Dose

The following dose-escalation rules will apply:

- At least 3 patients will be enrolled at each dose level of polatuzumab vedotin. If a DLT is observed in 1 patient at a given dose level during the DLT observation period, additional patients will be enrolled at that dose level for a total of at least 6 patients. All patients will be evaluated for DLTs before any dose-escalation decision.
- The dose of polatuzumab vedotin will be increased by no more than 50% for subsequent cohorts. For example, in the absence of establishing the MTD at the 1.0-mg/kg dose level, the next dose level will not exceed 1.5 mg/kg.
- Due to additional information regarding the risk/benefit profile of polatuzumab vedotin at the 2.4-mg/kg dose, the Sponsor is no longer pursuing the 2.4-mg/kg dose of polatuzumab vedotin at this time. The maximum polatuzumab vedotin dose was 2.4 m/kg as determined in the Phase I study (Study DCS4968g) and had been the RP2D.
- If DLTs are observed in $>33\%$ of the patients enrolled in a given cohort, further enrollment at that dose level and dose escalation will be halted, and that dose will be declared as exceeding the MTD. Dose levels intermediate between the two highest dose levels may be evaluated after consultation with the study investigators.

The highest dose level resulting in DLTs in less than one-third of a minimum of 6 patients will be declared the MTD. Additional patients may be enrolled at a given dose

level in the absence of DLTs to acquire additional safety data to inform the appropriate dose level for the expansion stage of the study.

G-CSF may be provided to patients for the management of neutropenia.

3.1.2 Phase II: Expansion Stage

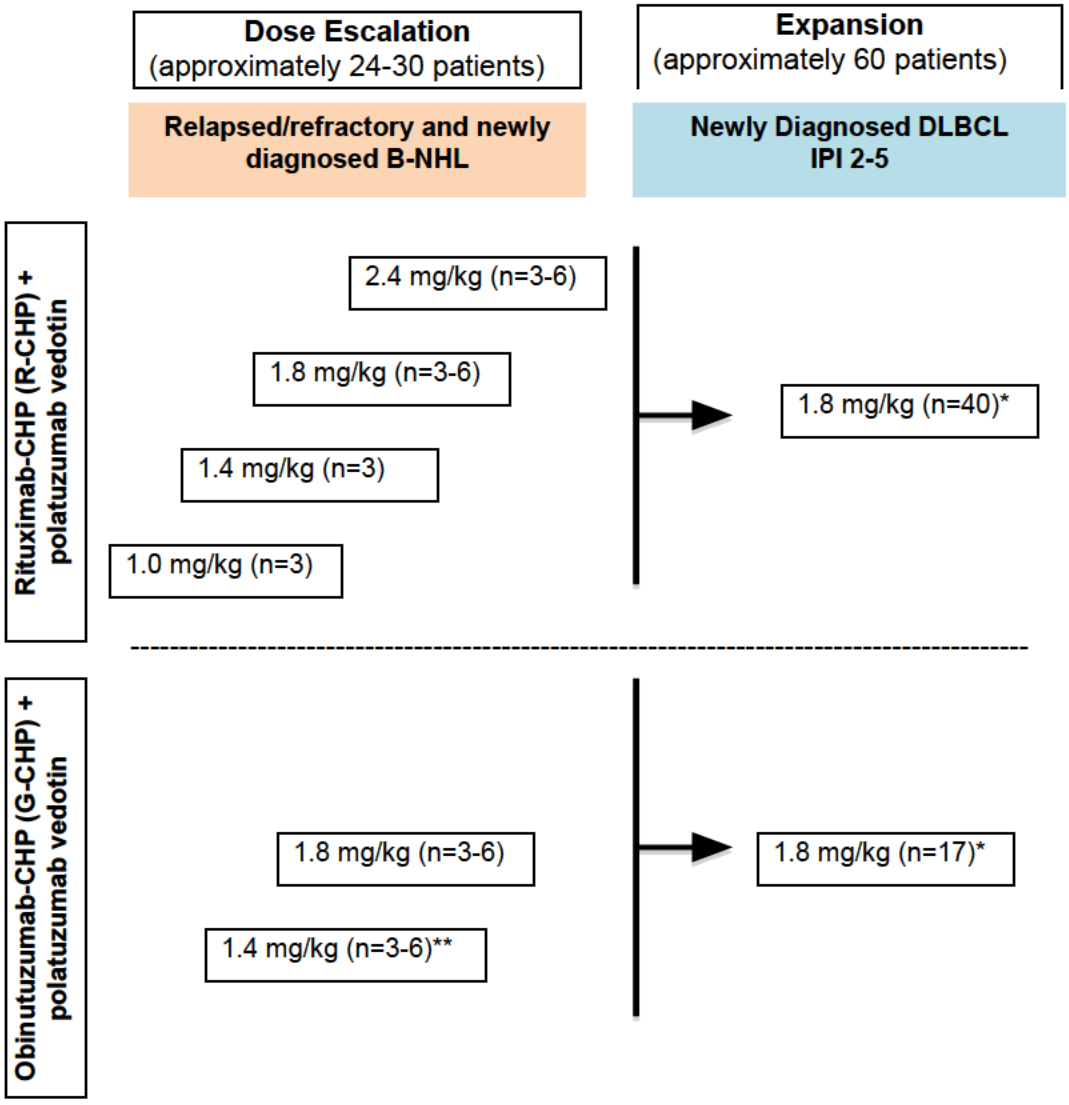
The expansion stage will include approximately 60 patients aged ≥18 years old at the time of study registration who have previously untreated DLBCL and with high-intermediate to high risk as defined by IPI score of 2–5 (see Appendix 8). Forty patients will receive R-CHP in combination with polatuzumab vedotin at a dose less than or equal to the MTD identified during escalation and an additional 17 patients will receive G-CHP in combination with polatuzumab vedotin at a dose less than or equal to the MTD identified during escalation. The purpose of the expansion stage is to evaluate the safety and preliminary efficacy of the selected dose and schedule for the combination therapy, determined from the dose-escalation portion of the study.

In the event that the observed toxicities during the expansion stage are different from what was predicted on the basis of the escalation portion of the study, additional expansion cohorts of approximately 40 patients may be enrolled to evaluate lower doses of polatuzumab vedotin. Additional patients may be enrolled in the expansion cohort in order to obtain additional safety, tolerability, and PK data, as well as data in specific biologic risk groups.

Patients in both the dose-escalation and expansion cohorts will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendix 1.

Tumor assessments, including CT and PET scans will be performed at screening, following Cycle 4 of treatment (i.e., at Cycle 4 Days 15-21), and at the Treatment Completion/Early Termination visit (obtained at 6-8 weeks after study treatment completion). CT scans (PET scans not required) will be performed every 6 months thereafter until approximately 2 years after the Treatment Completion/Early Termination visit or until progression or the start of an alternate lymphoma treatment regimen. Tumor assessments should also be performed to confirm clinical suspicion of relapse/progression, for documentation of disease progression or relapse, following the completion of study treatment.

Figure 2 Overview of Study Design



NOTE: For all patients, a total of six (or eight) cycles will be administered, in which polatuzumab vedotin will be administered in combination with R-CHP (rituximab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone) or G-CHP (obinutuzumab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone).

* The RP2D for polatuzumab vedotin in the R-CHP and G-CHP arms was identified as 1.8 mg/kg.

** The total number of cohorts will be determined on the basis of the observed safety/tolerability.

3.1.3 Internal Monitoring Committee

This study will employ an Internal Monitoring Committee (IMC) to monitor patient safety during the study and provide a recommendation on the dose to be taken forward into the dose expansion portion of the study after completion of the dose-escalation. The IMC will include the Roche/Genentech Medical Monitor, at least one other medical doctor or clinical scientist who is not directly involved in the study, and representatives from Clinical Drug Safety, Biostatistics, and Statistical Programming and Analysis. In addition

to the ongoing assessment of the incidence and nature of DLTs, adverse events (particularly Grades ≥ 3), serious adverse events, deaths, and laboratory abnormalities by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make one of the following recommendations: the trial continues as planned, a study arm stops, the protocol is amended, additional analyses need to be performed, or enrollment will be held pending further safety evaluations. Decisions will be made in consideration of the totality of the available data. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency, and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

3.1.4 Independent Review Committee

An IRC composed of board-certified radiologists and an oncologist with experience in malignant lymphoma will assess all patients for response (see Appendix 2 and Appendix 3) on the basis of imaging results, bone marrow biopsy results, and relevant clinical data during the Phase II portion of the study. Decisions will be guided by a Charter specific to the independent review.

3.2 END OF STUDY

The end of the study is defined as the time point at which all patients enrolled into the study have either had at least 2 years of follow-up from the time of the Treatment Completion/Early Termination visit or have discontinued from the study. The Sponsor has the right to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

Because R-CHOP is the standard of care for first-line treatment of patients with DLBCL (and other types of B-cell NHL) and the preliminary efficacy and safety profile of polatuzumab vedotin demonstrates promising efficacy and a tolerable safety profile, this study was designed to assess the combinability of polatuzumab vedotin with R-CHP in patients with newly diagnosed DLBCL and other types of B cell NHL. Because the mechanism of action of polatuzumab vedotin involves the targeted delivery of MMAE, a potent microtubule inhibitor that has the same binding site as the vinca alkaloids (vincristine), it is hypothesized that replacement of vincristine with a targeted microtubule inhibitor will result in an improved efficacy profile (given the increased potency of MMAE vs. vincristine). The dose-finding part of the study is open to all patients with B-cell lymphoma for whom R-CHOP or G-CHOP is considered a reasonable treatment option and who fulfill inclusion and exclusion criteria. Once a dose has been identified for Stage 2, the study will restrict enrollment to a group of patients with high medical need (newly diagnosed DLBCL patients who are aged ≥ 18 years and who have an IPI of 2–5) to further assess safety and efficacy of the combination. Patients with these characteristics have been shown to have poorer response and survival outcomes to

front-line therapy (Shipp et al. 1993; Ziepert et al. 2010). Administration of polatuzumab vedotin combined with R-CHP or G-CHP in these patients would increase the possibility of observing increased clinical benefit over patients with similar clinical characteristics historically treated with R-CHOP or G-CHOP.

The dose escalation of polatuzumab vedotin combined with R-CHP will begin at a dose level of 1.0 mg/kg, because this was the highest dose level at which no DLTs or clinically significant adverse events were observed during the Phase I study. The MTD of polatuzumab vedotin in combination with R-CHP will be identified before it is combined with G-CHP. Once the MTD is determined, polatuzumab vedotin will be dosed at MTD-1 in combination with G-CHP to start the dose escalation of this combination. Rules for dose escalation and final dose selection are outlined in Section 3.1.1.2.

3.3.1 Rationale for Obinutuzumab Dosing and Schedule

The combination of obinutuzumab with CHOP is being evaluated in several ongoing studies (see Table 1), including a Phase Ib trial in patients with previously untreated and relapsed/refractory FL (Study BO21000), a Phase II (Study GAO4915g, single arm G-CHOP) and a Phase III (Study BO21005, randomized R-CHOP vs G-CHOP) trials both in patients with previously untreated DLBCL.

The recommended dose and schedule for obinutuzumab in this regimen is 1000 mg on Days 1, 8, and 15 of Cycle 1 and Day 1 of each subsequent cycle (Cycles 2–6 or 8).

3.3.2 Rationale for Exploratory Biomarker Research Samples

Biomarkers associated with drug target, mechanism of action, and DLBCL biology may correlate with outcome in several ways. First, the activity of ADCs is dependent on a number of factors including but not necessarily limited to the presence of the antibody target, internalization of the ADC, and sensitivity of the tumor cell to the payload drug. Second, therapeutic approaches in DLBCL may result in differential activity in DLBCL prognostic subpopulations based on gene profile expression—that is, ABC versus GCB. Finally, resistance to cytotoxic treatment may be a result of high expression of anti-apoptotic regulators such as Bcl-2.

To assess target expression, DLBCL prognostic subpopulation, and levels of apoptotic regulators, archival or fresh tumor samples whose availability are required for study enrollment will be retrospectively analyzed for expression of CD79b; members of the Bcl-2 family; mutations associated with DLBCL biology including but not limited to CD79b, Myd88, CARD11 and A20; and genotypic classification of the DLBCL subpopulation—for example, ABC versus GCB. Results from these assays will be used to assess correlation with outcome.

Tumor-associated biomarkers may also be detected in blood. Since tumor tissue is often limited and difficult to acquire, assessment of blood-borne markers that are representative of the current disease state is of high interest.

3.3.3 Rationale for Pharmacokinetic Sampling

The PK sampling schedule following polatuzumab vedotin administration at Cycle 1 based on a 21-day cycle is designed to describe a detailed profile of the distribution and elimination of polatuzumab vedotin. The limited PK sampling schedule following polatuzumab vedotin at later cycles are obtained to assess pharmacokinetics after repeated dosing, given the likely changing effect of peripheral B-cell counts, tumor burden, and target antigen expression on target-mediated CL over multiple doses of polatuzumab vedotin.

Polatuzumab vedotin related analyte (total antibody, conjugate [evaluated as acMMAE] or unconjugated MMAE) concentration results will also contribute to future population PK analysis to investigate the effects of physiologic and disease-related covariates on polatuzumab vedotin disposition, if data allow, per Sponsor's decision.

Limited sampling for rituximab serum concentration measurements from this study will be obtained and compared with PK data from historical rituximab clinical studies. Pharmacokinetic data from these assessments will be used to inform potential future trials of this combination.

Limited PK sampling will be obtained for plasma concentrations of cyclophosphamide and doxorubicin. A comparison of the plasma concentration of cyclophosphamide, and doxorubicin between Cycle 1 (in the absence of polatuzumab vedotin) and Cycle 3 (in the presence of polatuzumab vedotin), and comparison with historical data will assess potential PK interactions when they are given in combination with polatuzumab vedotin.

3.3.4 Rationale for Patient-Reported Outcomes

Peripheral sensory neuropathy is an adverse drug reaction (ADR) of polatuzumab vedotin. Peripheral neuropathy in several forms, including sensory and/or motor neuropathy, is experienced by a majority of patients treated with polatuzumab vedotin. It is known that a discrepancy exists between healthcare provider interpretation and reporting of these events and a patient's self-assessment of their experience with peripheral neuropathy. This discrepancy is due, in part, to the lack of an adequate patient-reported measure of symptomatic burden of peripheral neuropathy on daily functioning. The primary objective of the patient-reported outcome (PRO) assessment in the Phase Ib/II study is to comprehensively assess and quantify the symptomatic burden and personal tolerability of this adverse event. The objective is to provide a better understanding of the clinical profile of polatuzumab vedotin from a patient perspective using a novel validated measure known as TINAS (Thomas et al. 2012).

3.4 OUTCOME MEASURES

3.4.1 Safety Outcome Measures

- Incidence, nature, and severity of adverse events and serious adverse events

- Changes in vital signs, physical findings, ECGs, and clinical laboratory results during and following study treatment administration
- Incidence of anti-polatuzumab vedotin antibodies and anti-obinutuzumab antibodies

3.4.2 Pharmacokinetic and Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of fully conjugated antibody, partially deconjugated antibody, and fully deconjugated antibody concentrations), plasma concentration-time profiles of conjugate (evaluated as acMMAE) and unconjugated MMAE, following administration of polatuzumab vedotin, when appropriate as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- C_{max}
- CL
- $t_{1/2,terminal}$
- V_{ss}

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and minimum concentration under steady-state conditions within a dosing interval (C_{min}), may also be calculated, when appropriate as data allow.

Limited sampling of serum concentrations of rituximab/obinutuzumab will be assessed and compared with historical data to evaluate potential PK interactions with polatuzumab vedotin. Plasma levels of cyclophosphamide and doxorubicin will be assessed and compared at the same timepoints of Cycle 1 (in the absence of polatuzumab vedotin) and Cycle 3 (in the presence of polatuzumab vedotin), and compared with historical data to evaluate potential PK interactions with polatuzumab vedotin.

3.4.3 Activity and Dose Exposure Outcome Measures

Response assessment will be determined using the modified version of the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix 2) and the modified version of the Lugano Response Criteria (Cheson et al. 2014; see Appendix 3).

The following activity outcome measures will be assessed:

- CR rate as defined as the percentage of patients with CR at the end of treatment, as assessed by the investigator, with and without FDG-PET.
- OR at the end of treatment, as assessed by the investigator, with and without FDG-PET. The overall response rate is defined as the percentage of patients with CR or PR at the end of treatment. All other cases are designated non-responders.
- DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse or death from any cause (PFS), as

assessed by the investigator for the subgroup of patients with a best overall response of CR or PR. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.

- PFS, defined as the time from date of first dose of study drug to the first occurrence of progression or relapse, or death from any cause while in the study
- EFS is defined as the time from randomization to disease progression or relapse, as assessed by the investigator, death from any cause, or initiation of any new anti-lymphoma therapy (NALT). If the specified event (disease progression or relapse, death, initiation of a NALT does not occur, EFS will be censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS will be censored at the time of randomization.
- Relative dose intensity (DI) is defined as the ratio of the amount of a drug actually administered (actual DI) to the amount planned (planned DI) for a fixed time period
- OS, defined as the time from the date of randomization to the date of death from any cause.

3.4.4 Immunogenicity Outcome Measures

ATA responses to polatuzumab vedotin and obinutuzumab will be characterized at predetermined timepoints (see Appendix 4 and Appendix 5).

3.4.5 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- PRO of peripheral neuropathy symptom severity and symptom interference, as measured by the TINAS (Thomas et al. 2012; see Appendix 10)

3.4.6 Biomarker Outcome Measures

- Gene expression profiles in tumor relating to:
  - DLBCL prognostic subgroups
  - Target (CD79b) biology
  - Expression of apoptotic regulators (including but not limited to Bcl-2)
  - Drug efflux transporters and other potential mediators of ADC resistance
- Tumor immunohistochemistry of target (CD79b) expression and apoptotic regulators (including but not limited to Bcl-2)

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

Eligible patients who are in conformance with the following inclusion and exclusion criteria may enroll in this study.

4.1.2 Inclusion Criteria

Dose-Escalation Portion of the Study

- Histologically confirmed B-cell NHL: Patients with newly diagnosed B-cell NHL or relapsed/refractory B-cell NHL are eligible.

  Note that patients in France with newly diagnosed B-cell NHL are not eligible.

- No more than one prior systemic treatment regimen for B-cell NHL (single agent anti-CD20 MAb therapy will not be counted as a prior treatment regimen)
- No prior treatment with anthracyclines

Expansion Portion of the Study

- Previously untreated patients with DLBCL
- IPI score of 2–5 (see Appendix 8).

All Patients

- Age ≥ 18 years
- Signed informed consent form(s)
- At least one bi-dimensionally measurable lesion, defined as > 1.5 cm in its longest dimension
- Ability and willingness to comply with the study protocol procedures
- Confirmed availability of archival or freshly collected tumor tissue before study enrollment
- Life expectancy of at least 24 weeks
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Adequate hematologic function (unless inadequate function is due to underlying disease, as established by extensive bone marrow involvement or is due to hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) defined as follows:

  Hemoglobin ≥ 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 contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 12 months for R-CHP arm or ≥ 18 months for the G-CHP arm after the last dose of study drug.

  A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

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

- For women of childbearing potential, a negative serum pregnancy test result within 7 days prior to commencement of dosing. Women who are considered not to be of childbearing potential are not required to have a pregnancy test.
- For men, agreement to remain abstinent (refrain from heterosexual intercourse) 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 5 months after the last dose of study drug and agreement to refrain from donating sperm during this same period.

  Men with a pregnant partner must agree to remain abstinent or to use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo for the duration of the pregnancy.

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

  Male patients considering preservation of fertility should bank sperm before treatment with polatuzumab vedotin.

4.1.3 Exclusion Criteria

Exclusion Criteria for Dose-Escalation Portion of the Study

- Diagnosis of primary mediastinal DLBCL

Exclusion Criteria for Expansion Portion of the Study

- Patients with transformed lymphoma
- Prior therapy for NHL

All Patients

- Prior stem cell transplant
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to receive any of the individual components of R-CHP or G-CHP
- Current Grade $>$ 1 peripheral neuropathy
- Ongoing corticosteroid use of $>$ 30 mg/day of prednisone/prednisolone or equivalent. Patients receiving corticosteroid treatment with $\leq$ 30 mg/day of prednisone/prednisolone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration before Cycle 1 Day 1

  Note: If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day prednisone or

equivalent can be given for a maximum of 7 days, but all tumor assessments must be completed prior to start of corticosteroid treatment.

- Primary CNS lymphoma
- Vaccination with live vaccines within 6 months before Cycle 1 Day 1
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.

  Patients with a malignancy that has been treated with surgery alone with curative intent will also be excluded unless the malignancy has been in documented remission without treatment for $\geq$5 years before enrollment.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration, or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, congestive heart failure, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Left ventricular ejection fraction defined by multiple-gated acquisition (MUGA)/echocardiogram (ECHO) below the institutional lower limit of normal
- 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 before Cycle 1 Day 1
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Presence of positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [HBcAb]) or hepatitis C (hepatitis C virus [HCV] antibody)

  Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation.
- Prior radiotherapy to the mediastinal/pericardial region
- Women who are pregnant, lactating, or who intend to become pregnant within a year after the last dose of study treatment in the rituximab cohort or within 18 months after the last dose of study treatment in the obinutuzumab cohort
- Recent major surgery within 6 weeks before the start of Cycle 1 Day 1, other than superficial lymph node biopsies for diagnosis

- Any of the following abnormal laboratory values:

  Creatinine $> 1.5 \times$ ULN or a measured creatinine clearance < 50 mL/min

  AST or ALT $> 2.5 \times$ ULN

  Total bilirubin $\geq 1.5 \times$ ULN:

  INR $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation

  PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the Sponsor will provide the dose group assignment and the patient number will be assigned via the Interactive Voice and Web Response System (IXRS).

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Polatuzumab Vedotin

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

4.3.1.2 Rituximab

Rituximab (MabThera®/Rituxan®) will be supplied by the Sponsor where required by local health authority regulations. For information on the formulation, packaging and handling of rituximab, see the pharmacy manual, the local prescribing information (Rituxan® U.S. Package Insert; MabThera® SmPC 2016) and investigator's brochure for rituximab (MabThera®/Rituxan®).

4.3.1.3 Obinituzumab

Obinutuzumab (Gazyva™/Gazyvaro™), will be supplied by the Sponsor. For information on the formulation, packaging and handling of obinutuzumab, see the pharmacy manual, local prescribing information, and investigator's brochure for obinutuzumab (Gazyva™/Gazyvaro™).

4.3.1.4 Cyclophosphamide, Doxorubicin, and Prednisone

Cyclophosphamide, doxorubicin, and prednisolone or prednisone (CHP) will be supplied by the Sponsor where required by local health authority regulations. For information on the formulation, packaging and handling of CHP, see the local prescribing information for CHP.

4.3.2 Dosage, Administration, and Compliance

Patients will receive treatment with one of two immunochemotherapy regimens in combination with polatuzumab vedotin:

- R-CHP: rituximab plus CHP chemotherapy
- G-CHP: obinutuzumab plus CHP chemotherapy

Patients will receive a total of six to eight cycles of polatuzumab vedotin in combination with R-CHP or G–CHP. A cycle is typically 21 days in duration.

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

Pre-Phase Treatment: Day–7 to Day–1 (1 day prior to Cycle 1 Day 1)

- Prednisone/prednisolone 100 mg by mouth (orally; PO) every day

Administration of an approximately 7-day course of pre-phase treatment may be given at the discretion of the treating investigator physician. The purpose of pre-phase treatment is to prevent tumor lysis syndrome (TLS) in patients with extensive disease and to reduce toxicity of the first cycle of study treatment, e.g., cytokine release syndrome.

Cycles 1–2

Cycles 1–2 Day 1

- First treatment administered: prednisone/prednisolone 100 mg PO
- Second treatment administered: rituximab 375 mg/m^2 IV or obinutuzumab 1000 mg IV
- Third and fourth treatment administered: cyclophosphamide 750 mg/m2 IV and doxorubicin 50 mg/m^2 IV. The order of administration will be based on institutional practice. The order of administration of cyclophosphamide and doxorubicin used in Cycle 1 should be maintained for Cycles 2–6 (or 2–8). A PK analysis will be conducted to evaluate potential drug interactions. Because this is an important objective of this study, the length of infusions for cyclophosphamide and doxorubicin should be approximately the same for all cycles, as allowed by the observed safety profile of the infusions.

Cycles 1–2 Day 2

- First treatment administered: prednisone/prednisolone 100 mg PO
- Second treatment administered: polatuzumab vedotin administered IV. Refer to Section 3.1 for information regarding planned doses of polatuzumab vedotin to be tested.

Cycle 1 Only Day 8 and Day 15 (G-CHP only)

- Obinutuzumab 1000 mg IV

Cycles 3–6 (or 8)

As long as the observed individual patient safety profile of R-CHP or G-CHP and polatuzumab vedotin allows all study treatment infusions to be given on the same day, then the R-CHP or G-CHP and polatuzumab vedotin infusions will be given on a single day for Cycles 3–6 (or 8).

Cycles 3–6 (or 8) Day 1

- First treatment administered: prednisone/prednisolone 100 mg PO
- Second treatment administered: rituximab 375 mg/m^2 IV or obinutuzumab 1000 mg IV
- Third and fourth treatments administered: cyclophosphamide 750 mg/m^2 IV and doxorubicin 50 mg/m^2 IV. The order of administration of cyclophosphamide and doxorubicin used in Cycle 1 should be maintained for Cycles 2–6 (or 2–8). Because PK analysis to evaluate potential drug interactions is an important objective of this study, the length of infusions for cyclophosphamide and doxorubicin should be approximately the same for all cycles, as allowed by the observed safety profile of the infusions.
- Fifth treatment administered: polatuzumab vedotin administered IV. Refer to Section 3.1 for information regarding planned doses of polatuzumab vedotin to be tested.

The doses of the rituximab, polatuzumab vedotin, cyclophosphamide, and doxorubicin should be calculated on the basis of a patient's body weight at the screening assessment (Day–14 to Day–1). For changes $>$10% in body weight from screening, all subsequent doses should be modified accordingly. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments.

4.3.2.1 Polatuzumab Vedotin

The total dose of polatuzumab vedotin for each patient will depend on dose level assignment and the patient's weight on Day 1 of Cycle 1 (or within 96 hours before Cycle 1 Day 1). The total dose of polatuzumab vedotin should be adjusted for subsequent doses only if the patient's weight has changed by $>$10% from baseline.

Polatuzumab vedotin will be administered to patients by IV infusion with use of syringes and syringe pumps. Compatibility testing has shown that polatuzumab vedotin is stable in extension sets and polypropylene syringes. Extension sets and syringes used to deliver polatuzumab vedotin must be comprised of specific materials, please refer to the study team for a list of approved materials. Polatuzumab vedotin will be administered to patients by IV via syringe pump with IV infusion set containing a 0.22 µm in-line filter with a final volume of polatuzumab vedotin determined by the dose and patient weight.

The initial dose will be administered to well-hydrated patients over 90 ($\pm$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. If IRRs are observed with the first infusion in the absence of premedication, premedication must be administered before subsequent doses. Note that the prednisone/prednisolone component of R-CHP infusion will be administered before polatuzumab vedotin infusion for all treatment cycles.

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

For additional instructions on study drug preparation and administration, refer to the Investigator's Brochure.

4.3.2.2 Rituximab

Six to eight cycles of rituximab at 375 mg/m^2 will be administered IV to patients every 21 days (or over 28 days for those patients who experienced toxicity that necessitates an extended cycle duration). No dose modifications of rituximab are allowed.

Rituximab Preparation

All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood. Prepare the rituximab solution as follows:

- Refrigerate (2°C–8°C) all materials and solutions before use. Do not freeze or store at room temperature.
- Use sterile, non-pyrogenic disposable containers, syringes, needles, stopcocks, and transfer tubing, etc.
- Transfer of rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large-gauge needle.
- Transfer the appropriate amount of rituximab from the graduated syringe into a partially filled IV pack containing sterile pyrogen-free 0.9% NaCl solution (saline solution). Discard any unused portion left in the vial.
- Mix by inverting the bag gently. Do not use a vacuum apparatus to transfer the product from syringe to the plastic bag. Handle gently and avoid foaming, because this may lead to the denaturing of the product proteins.

It is recommended that rituximab be given at a dilution of 2 mg/mL for ease in calculating the dose.

Rituximab Administration

Rituximab will be administered after the prednisone/prednisolone dosing and before the cyclophosphamide, doxorubicin, and polatuzumab vedotin infusions. Once the rituximab

infusion is completed, patients are to be observed for 30 minutes before the start of CHP administration. For patients who experience an adverse event during a rituximab infusion, administration of rituximab and CHP chemotherapy may be continued on the following day if required. Empiric dose adjustment for obese patients (defined as a body mass index of ≥ 30, as measured in kilograms per meter squared) may be implemented per institutional guidelines. There will be no dose modification for changes in weight unless a patient's weight increases or decreases by $> 10\%$ from baseline weight.

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). Also, in patients who experience an adverse event during the rituximab infusion, administration of rituximab may be continued on the following day if needed. 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 2).

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). An additional glucocorticoid (e.g., 100 mg IV prednisone or prednisolone or equivalent) is allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Note: Do not use the evacuated glass containers that require vented administration sets, because this causes foaming as air bubbles pass through the solution.
The administration of rituximab will be accomplished by slow IV infusion. Do not infuse concomitantly with another IV solution or IV medications.

Rituximab infusions will be administered according to the instructions outlined in Table 2. Please note: A rapid infusion is not allowed.

Table 2 Administration of First and Subsequent Infusions of Rituximab

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

Note: A fast infusion is not allowed.

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 5.1.7.2.

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

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.

4.3.2.3 Obinutuzumab

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with polatuzumab vedotin and CHP, as outlined in Section 4.3.2.1.

Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2-6 or 2-8 (see Table 3). No dose modifications of obinutuzumab are allowed.

All obinutuzumab infusions should be administered after premedication with oral acetaminophen and an antihistamine (see Section 4.4.1.4). The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs if deemed appropriate by the investigator and should be administered prior to the obinutuzumab infusion. Premedication with prednisone/prednisolone is mandatory in patients who had an IRR and should continue until IRRs no longer occur during antibody infusion. For the management of IRRs and anaphylaxis, see Section 5.1.7.2.

If it is the strong preference of the investigator or of the site (e.g., for logistical reasons) or if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count), the administration of obinutuzumab infusion can be split over 2 days. In prior studies of obinutuzumab, 100 mg was administered on the first day, with the balance (900 mg) administered on the second day.

Table 3 Administration of First and Subsequent Infusions of Obinutuzumab

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/hour 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 reaction has resolved, 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, use full premedication including 100 mg prednisone/prednisolone (until no further infusion-related reaction occurs), 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/hour 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 reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).

In all parts of the study, obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available and patients should be under the close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 5.1.7.2.

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Administration sets with PVC, PUR, or PE as a product contact surface and IV bags with polyolefin, PP, PVC, or PE as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption.

After the end of the first infusion, the IV line or central venous catheter should remain in place for greater than or equal to 2 hours in order to be able 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, access (either through an IV line or central venous catheter) should remain in place for at least 1 hour from the end of the infusion, and if no adverse events occur after 1 hour, the IV access may be removed.

4.3.2.4 CHP Chemotherapy Dosage and Administration

CHP chemotherapy consists of cyclophosphamide and doxorubicin administered by IV push and oral prednisone or prednisolone. For information on the order of administration, please see Section 4.3.1.

- Cyclophosphamide 750 mg/m^2 administered IV on Day 1
- Doxorubicin 50 mg/m^2 administered IV on Day 1
- Prednisone 100 mg/day PO on Days 1–5

  Note: Prednisone may be replaced with prednisolone (100 mg/day) at sites where prednisone is not available or is not the therapy of choice.

Refer to the specific package inserts for preparation, administration, and storage guidelines. Body surface area (BSA) may be capped at 2 m^2 per institutional standards.

The rituximab or obinutuzumab administration should be completed at least 30 minutes before administration of other study treatments.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (polatuzumab vedotin, rituximab, obinutuzumab, CHP) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or 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.

4.3.4 Post-Trial Access to Polatuzumab Vedotin

The Sponsor (Genentech) is a member of the Roche group and is subject to Roche's global policies. The Sponsor will offer post-trial access to the study drug polatuzumab vedotin free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to IMP, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for DLBCL.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for DLBCL.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to IMP is available at the following Web site:

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

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days before screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Patients who are receiving oral contraceptives, stable doses of hormone-replacement therapy, or other maintenance therapy should continue their use.

Other than prednisone/prednisolone that may be given as pre-phase treatment at the discretion of the treating investigator physician (see Section 4.3.1), corticosteroids may be used only for the treatment of conditions other than lymphoma (e.g., asthma).

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

4.4.1.1 CNS Prophylaxis

CNS prophylaxis with intrathecal chemotherapy should only be given according to institutional practice and its use documented in the eCRF.

4.4.1.2 Prophylaxis for Hemorrhagic Cystitis

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

4.4.1.3 Treatment and Prophylaxis of Neutropenia

The use of G-CSF is allowed for treatment of neutropenia. G-CSF is strongly encouraged, especially in the obinutuzumab-containing cohorts as primary prophylaxis in each cycle of therapy (see Appendix 6) per the ASCO guidelines (Smith et al. 2006) or following each site's institutional standards.

4.4.1.4 Premedication before Rituximab and Obinutuzumab

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

- Acetaminophen/paracetamol (650–1000 mg) PO at least 30–60 minutes before the start of all infusions
- Antihistamine, such as diphenhydramine (25–50 mg), approximately 30–60 minutes before the start of each infusion (unless contraindicated)

On Cycle 1 Day 1, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given within 12 hours as pre-medication, but at least 60 minutes prior to the obinutuzumab infusion. After the first obinutuzumab infusion, additional glucocorticoids are 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.

4.4.1.5 Infection Prophylaxis

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial or Pneumocystis infections is permitted and should be instituted per institutional practice. Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the standard of care may be treated prophylactically.

4.4.2 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; however, patients will be followed as described in Section 4.5.13.4.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy other than CHP and intrathecal chemotherapy for CNS prophylaxis
- Immunotherapy or immunosuppressive therapy other than study treatments
- Radioimmunotherapy
- Hormone therapy other than contraceptives, hormone-replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts
- Any therapies (other than intrathecal CNS prophylaxis) intended for the treatment of lymphoma whether European Medicines Agencies or U.S. Food and Drug Administration (FDA) approved or experimental
- Radiotherapy

4.4.2.1 Immunizations

Patients who participate in this study may not receive either primary or booster vaccination with live virus vaccines for at least 6 months before initiation of rituximab or 28 days prior to obinutuzumab or at any time during study treatment. Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases before study therapy.

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

4.5 STUDY ASSESSMENTS

See Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

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

Tests that are performed as standard of care before obtaining informed consent may be used for screening and baseline assessments, provided that they have been performed within the allowable timeframe as described in the schedule of assessments.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. 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 and Demographic Characteristics

Medical history includes all clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, 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 the evaluation of the head, eyes, ears, nose, and throat and 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 also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. These will be recorded into the appropriate 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 clinical 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.

Formal assessments of peripheral neuropathy, including the use of the Total Neuropathy Score (TNS), should also be performed at Day 1 of each cycle.

4.5.4 Clinical Total Neuropathy Score Assessment

Patients may undergo a Clinical Total Neuropathy Assessment (Cavaletti et al. 2006, 2007) as shown in the schedule of assessments (see Appendix 1). The neuropathy assessments include subjective sensory symptoms, motor symptoms, autonomic symptoms and objective pinprick sensitivity and vibration sensitivity) to determine their total neuropathy score (see Appendix 9).

4.5.5 Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation as measured by pulse oximetry, and body temperature while the patient is in a seated or supine position. 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 rituximab or obinutuzumab administration visits, vital signs are to be obtained before infusion of rituximab or obinutuzumab, then after the start of the infusion approximately every 15 (± 5) minutes for 90 minutes, then every 30 (± 10) minutes until 1 hour after the end of the infusion.

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.

Additional monitoring of vital signs should be performed if clinically indicated.

4.5.6 Tumor and Response Evaluation

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, CT, PET, and/or magnetic resonance imaging (MRI) scans, and bone marrow examinations, through use of the Revised Response Criteria for Malignant Lymphoma (Juweid and Cheson 2006; Cheson et al. 2007; Juweid et al. 2007; see Appendix 2).

The response criteria for NHL have been updated in Appendix 3. The Modified Lugano Response Criteria (Cheson et al. 2014) will be used to evaluate CR by PET scan at the Primary Response Assessment by IRC as stated in the exploratory objective sections. The Modified Lugano Response Criteria will also be used to evaluate OR by PET as assessed by IRC.

Radiographic Assessments

CT and MRI are currently the best available and most reproducible methods for measuring target lesions selected for response assessment; conventional CT and MRI

should be performed with contiguous cuts of ≤10 mm in slice thickness. CT scans (with IV and oral contrast) should include the chest, abdomen, and pelvis; CT scans of the neck should be included if clinically indicated. CT scans for response assessment may be limited to areas of prior involvement only if required by local regulatory authorities.

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

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

FDG-PET (hereafter referred as "PET") scans in conjunction with CT scans will be obtained in this study. CT and PET scans are required at screening, following Cycle 4 of study treatment (i.e., at Cycle 4 Days 15–21), and at the Treatment Completion/Early Termination visit. End-of-treatment PET scan should be obtained 6–8 weeks after the last dose of study treatment. However, for patients with suspicion of progressive disease at the end of treatment, it is permissible to obtain the PET scan at 4 weeks after the last dose of study treatment. CT scans without PET scans will be obtained every 6 months thereafter until approximately 2 years following the Treatment Completion/Early Termination visit. Modified Revised Response Criteria for Malignant Lymphoma (see Appendix 2) will be used to assess overall response to study treatment. Patients who are assessed to have stable disease or progressive disease at the post–Cycle 4 tumor assessment may be discontinued from study treatment.

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 and should include biopsy for morphology. Repeat bone marrow examinations are required only in two circumstances:

- If involved with tumor at screening, a repeat bone marrow examination is required to confirm a radiological assessment of CR
- As evidence of relapse (if bone marrow assessment was negative at baseline) and there is no radiographic evidence of progression

4.5.7 Laboratory, Biomarker, and Other Biological Assessments

Local Laboratory Assessments

The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manuals.

Samples for hematology, serum chemistry, pregnancy, and hepatitis B and C serology and quantitative immunoglobulin assessments will be analyzed at the study site's local laboratory. 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, platelet count, white blood cell count, and ANC
- Chemistry: glucose, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, calcium, phosphorous, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, amylase, lipase, uric acid and hemoglobin $A1_c$. At screening, all samples for laboratory tests will be obtained in a fasting state for all patients.
- Pregnancy test

  All women of childbearing potential who are sexually active (including those who have had a tubal ligation) will have a serum pregnancy test within 7 days before Cycle 1 Day 1 of study treatment. Women of childbearing potential who are not sexually active will have a serum pregnancy test within 28 days before Cycle 1 Day 1 of study treatment. An additional serum pregnancy test will be performed at the Treatment Completion/Early Termination visit.
- Coagulation: aPTT or PTT, PT, and INR
- Viral serology and detection

  Hepatitis B (HBsAg and HBcAb)

  HCV antibody; HCV RNA by PCR if the patient is HCV-antibody positive
- Quantitative immunoglobulins: IgG, IgA, and IgM

Central Laboratory Assessments

Samples for the following laboratory test will be sent to one or several central laboratories for analysis:

- PK sample assessments (see Appendix 2)
- Immunogenicity assessment (see Appendix 2)

  Serum samples for anti-polatuzumab vedotin antibody

  Serum samples for anti-obinutuzumab antibody
- Flow cytometry (CD19+, CD3+, T cells)
- Analysis of biomarker testing, gene expression, genetic mutations, and epigenetic assessment of blood and tissue samples will be performed at Genentech or other central laboratories.
- A peripheral blood sample for MRD analysis is required for all patients at C1D1, between Cycle 3 Day 15 and Cycle 4 Day 1 and at Treatment Completion Visit.

- Samples collected for PK and immunogenicity analyses may be used for assay development, validation and additional characterization, and additional safety and immunogenicity assessments, as appropriate.
- Biological samples, if not used up, will be destroyed within 5 years after the final clinical study report has been completed, unless the patient gives specific consent for the leftover samples to be stored for optional exploratory research (see Section 4.5.12).

4.5.8 Electrocardiogram and Echocardiogram or MUGA

A 12-lead ECG is required at screening and study treatment termination and as clinically indicated. ECGs for each patient should be obtained using the same machine wherever possible. Representative ECGs at each timepoint should be reviewed by the investigator or a qualified designee.

For assessment of cardiac function (left ventricular ejection fraction), an ECHO or MUGA scan is required for all patients at screening and Early Termination visit or Study Completion visit. An ECG, ECHO, or MUGA scan may also be done as clinically indicated by an adverse event, including cardiac or cardiovascular adverse events; consultation regarding the adverse event should occur with the Medical Monitor. During infusion of doxorubicin, ECG monitoring should be performed per clinical practice.

4.5.9 Patient-Reported Outcomes (PRO)

The TINAS is an 11-item questionnaire scored on a 0 to 10 scale, with 0 being the symptom is not present to 10 being the symptom is as bad as the patient can imagine. The questionnaire will be analyzed for the individual neuropathy symptoms experienced by a patient as well as the calculation of an overall neuropathy severity score. Additionally, a single item that asks patients to rate when numbness and tingling was at the worst will be used to predict the onset of peripheral neuropathy. The measure takes less than 5 minutes to complete. See Appendix 10 for a full description of the TINAS.

The TINAS scale will be completed weekly, preferably on the same day each week over the course of study treatment. Additionally, to collect information about the reversibility of peripheral neuropathy, following completion of treatment the TINAS will be completed once a week for the first 2 months, then once a month for 10 months.

The PRO instrument, translated as required into the local language, will be completed by the patient on his or her own electronic devices (i.e., mobile phone, tablet, or home computer) after the software is distributed by the investigator staff. If the patient does not own their own device, one will be provided by the electronic PRO (ePRO) vendor. All measures are to be completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be completed prior to the completion of other study assessments and the administration of study treatment.

Patients will use an ePRO device to capture PRO data. The device will be the patient's own (i.e., mobile phone, tablet, or home computer) with specialized software installed to allow for the secure access and transmission of the questionnaire. The ePRO software and instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted automatically via Web or wireless to a centralized database at the ePRO vendor. The data can be accessed securely by appropriate study personnel securely via the Internet.

Adverse event reports will not be derived from PRO data by the Sponsor. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported as outlined in Section 5.4.12.

4.5.10 Pharmacokinetic Assessment

Pharmacokinetics of polatuzumab vedotin will be characterized by measuring total antibody (fully conjugated, partially deconjugated and fully deconjugated antibody), conjugate (evaluated as acMMAE), and unconjugated MMAE concentrations through use of validated methods (see Section 4.7). Plasma samples may also be analyzed for other potential MMAE-containing catabolites, per the Sponsor's discretion. Pharmacokinetics of rituximab will be characterized by measuring rituximab concentrations with use of a validated method (see Section 4.7). Pharmacokinetics of obinutuzumab will be characterized by measuring obinutuzumab concentrations with use of a validated method (see Section 4.7). Pharmacokinetics of cyclophosphamide and doxorubicin will be assessed at the same time points of Cycle 1 (in the absence of polatuzumab vedotin) and Cycle 3 (in the presence of polatuzumab vedotin) to evaluate for any potential PK interactions with polatuzumab vedotin. These assessments will allow for further characterization of the pharmacokinetics of polatuzumab vedotin, the assessment of the drug interaction potential when they are given in combination with rituximab, cyclophosphamide, and doxorubicin, and the investigation of potential correlations between PK parameters and safety and/or activity, if data allow and per the Sponsor's discretion.

4.5.11 Immunogenicity Assessments

The immunogenicity evaluation will utilize a risk-based strategy and tiered approach (Rosenberg and Worobec 2004a, 2004b, 2005; Koren et al. 2008) designed to detect and characterize all ATA responses to polatuzumab vedotin. Patient samples will be first screened to detect all antibody responses to polatuzumab vedotin. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with polatuzumab vedotin) to assess the specificity of the positive response. Confirmed positive samples will be further characterized by competitive binding with the MAb component of polatuzumab vedotin to characterize whether the ATA responses are primarily to the MAb or the linker-drug regions of the ADC. The relative levels of ATA in confirmed positive samples will be determined in a titering assay. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

ATA responses to obinutuzumab will be detected and confirmed using a similar tiered approach. Patient samples will be first screened to detect all antibody responses to obinutuzumab. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with obinutuzumab) to assess the specificity of the positive response. The relative levels of ATA in confirmed positive samples will be determined in a titering assay.

4.5.12 Samples for Roche Clinical Repository

Genentech is a member of the Roche group and participates in the collection and/or submission of biological samples to the Roche Clinical Repository (RCR). Collection and submission of biological samples to the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted the necessary approval for RCR sampling, this section of the protocol will not be applicable at that site.

Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers:

- Residual tumor sample from lymph node biopsy may be submitted at the screening visit for DNA, RNA, or protein extraction
- Residual samples of peripheral blood and bone marrow aspirates from MRD analysis

The following samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers:

- Whole blood samples for DNA, RNA, or protein extraction will be drawn at the screening visit and at the end of treatment

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is “double-coded” by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A “linking key” between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche’s Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens 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.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO29044 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO29044.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately validated laboratory information

management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.13 Timing of Study Assessments

4.5.13.1 Screening and Pretreatment Assessments

All screening evaluations must be completed and reviewed by the investigator to confirm that patients meet all eligibility criteria and are approved for enrollment before the first study treatment infusion. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within the time frame specified in Appendix 1 relative to Cycle 1 Day 1. Results of standard-of-care tests or examinations performed before obtaining informed consent and within the timelines specified by Appendix 1 may be used; such tests do not need to be repeated for screening.

An Eligibility Screening Form documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator.

Refer to the Study Flowchart provided in Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.13.2 Assessments during Treatment

Adverse events, serious adverse events, and concomitant medication information should be recorded throughout the study.

Study visits for Cycle 1 through the Treatment Completion/Early Termination Visit should occur within ± 2 days from the scheduled date unless otherwise noted. That is, the Treatment Completion/Early Termination Visit and all subsequent follow-up visits should occur within ± 1 week of the scheduled date unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed before study drug infusion unless otherwise noted.

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle. Results must be reviewed and the review documented before study drug administration.

If a visit is scheduled on a holiday that precludes protocol-specified procedure, the procedure should be performed on the nearest following date. Subsequent protocol-specified procedures should remain synchronized with Day 1 of the most recent cycle.

Refer to the Study Flowchart provided in Appendix 1 for the schedule of treatment period assessments.

4.5.13.3 Study Treatment Completion Visit

Patients who complete the study treatment or discontinue from study treatment early will return 30 days after the last dose of study treatment for the study Treatment Completion visit or Early Termination visit.

For patients who have progressive disease during the treatment period, the visit at which a response assessment shows disease progression may be used as the Treatment Completion/Early Termination visit. Assessment of disease progression based on clinical examination must be confirmed by radiographic assessment as soon as practicable.

Refer to the Study Flowchart in Appendix 1 for assessments to be performed at the Treatment Completion/Early Termination visit.

4.5.13.4 Follow-Up Assessments

After completion of study treatment (Section 4.5.13.3), all patients will continue to be followed according to the schedule outlined in Appendix 1.

If response assessment shows PD during the follow-up period, assessments at subsequent visits will be limited (see Appendix 1). Diagnosis of disease progression based on clinical examination must be confirmed by CT scan as soon as possible (maximum, within 4 weeks) and prior to any NALT.

After a patient has PD during follow-up and starts a NALT, contact will be made with patients by telephone on an annual basis for survival.

Patients who discontinue study treatment early because of adverse event, and start a NALT in the absence of PD should be followed according to Appendix 1 unless they withdraw consent.

Ongoing adverse events related to study treatment will be followed until the event has resolved to baseline (pretreatment) grade or better, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or

when it has been determined that the study treatment or participation is not the cause of the adverse event. Such follow-up will require an assessment (per verbal report, at minimum) of any adverse events and serious adverse events for 90 days after the last dose of study drug or until the patient receives another anti-cancer therapy, whichever occurs first.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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 withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance (i.e., consistent failure to show up for scheduled visits, consistent missed treatment, etc.)

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

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

- Pregnancy
- Documented disease progression/relapse or in the absence of OR (PR or CR) at the tumor assessment following Cycle 4 of treatment (i.e., at Cycle 4 Days 15–21).
- Unacceptable toxicity (as described in Section 3.1.1)
- Patient/investigator decision. In these cases, patients should continue to be followed for both resolution of toxicity and disease progression as described in Section 4.5.13.4 and Appendix 1.

The reasons for early discontinuation of treatment must be documented on the appropriate eCRF.

In the event that a patient discontinues from study treatment early for reasons other than documented disease progression/relapse, he or she will proceed into the follow-up period until progression.

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

4.6.3 Study and Site 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.
- Data recording is inaccurate or incomplete

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

The Sponsor has the right to close or replace a site at any time. Reasons for closing or replacing 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 GCP
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

4.7 ASSAY METHODS

4.7.1 Total Polatuzumab Vedotin Antibody ELISA

Total polatuzumab vedotin antibody (fully conjugated, partially deconjugated and fully deconjugated antibody) will be measured in serum samples with use of validated ELISAs.

4.7.2 Conjugated (Evaluated as Antibody-Conjugated MMAE) Affinity Capture Enzyme-Release LC/MS/MS

acMMAE (a measure of MMAE conjugated to polatuzumab vedotin) will be measured in plasma samples with use of a validated affinity-capture enzyme-release liquid chromatography tandem mass spectrometry (LC/MS/MS) assay.

4.7.3 Unconjugated MMAE LC/MS/MS

Unconjugated MMAE will be measured in plasma samples using a validated LC/MS/MS method.

4.7.4 Rituximab ELISA

Rituximab will be measured in serum samples using a validated ELISA.

4.7.5 Obinutuzumab ELISA

Obinutuzumab will be measured in serum samples using a validated ELISA.

4.7.6 Cyclophosphamide LC/MS/MS

Cyclophosphamide will be measured in plasma samples with use of a validated LC/MS/MS method.

4.7.7 Doxorubicin LC/MS/MS

Doxorubicin will be measured in plasma samples with use of a validated LC/MS/MS method.

4.7.8 Polatuzumab Vedotin Anti-Therapeutic Antibody

ATAs against polatuzumab vedotin in serum samples will be measured using validated bridging antibody ELISA and characterized by competitive binding assays.

4.7.9 Obinutuzumab Anti-Therapeutic Antibody

ATAs against obinutuzumab in serum samples will be measured using a validated bridging antibody ELISA.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Polatuzumab vedotin is not approved and is currently in clinical development; the entire safety profile is not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed 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 last dose of study treatment.
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs and ECHOs or MUGA scans
- Assessment of physical findings on clinical physical examinations

Patients who have an ongoing study drug-related adverse event will be followed until the event has resolved to baseline grade or better, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, when it has

been determined that the study treatment or participation is not the cause of the adverse event, or when the study is terminated (see Section 4.5.13.4 for details of follow-up).

5.1.1 Risks Associated with Polatuzumab Vedotin

The clinical safety profile of polatuzumab vedotin based on clinical data obtained in the ongoing Phase I and Phase II studies is summarized in Section 1.2.1. 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 4.3. Refer also to the Investigator's Brochure for complete and updated details.

5.1.1.1 Known Risks: Neutropenia and Peripheral Neuropathy

Based on clinical experience with polatuzumab vedotin in patients treated in the current Phase I and Phase II studies, neutropenia including febrile neutropenia and peripheral neuropathy are identified risks of polatuzumab vedotin.

Neutropenia including Febrile Neutropenia

Neutropenia and neutropenia-associated events were reversible but in some cases resulted in protocol-mandated dose reductions and/or delays. 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. Treatment may be delayed or modified for hematologic toxicities as described in Table 5. The use of G-CSF for neutropenia is described in Section 4.4.1.3.

Peripheral Neuropathy (Sensory and/or Motor)

Patients receiving polatuzumab vedotin may develop peripheral neuropathy (sensory and/or motor). 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, 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.

Study treatment dose and schedule modifications for peripheral neuropathy are described in Table 5.

5.1.2 Potential Risks

5.1.2.1 Effects on the Relative Dose Intensity of R-CHP or G-CHP

Depending upon the toxicity profile observed with the addition of polatuzumab vedotin to R-CHP or G-CHP there may be a reduction in the relative DI of R-CHP or G-CHP that is administered.

5.1.2.2 Potential Risks Associated with Polatuzumab Vedotin

Infections

There are several factors in the patient population under study that influence their vulnerability to a higher risk of infections, particularly serious and opportunistic infections, including a single report of PML (see Polatuzumab vedotin IB version 7). The risk factors include pre-disposition of the indication disease to infections, elderly population, comorbidity, impaired capacity of bone marrow recovery with multiple lines of prior anti-cancer therapies.

In addition, neutropenia is an ADR for polatuzumab vedotin. Reports in the literature state that granulocytopenia, is a major predisposing factor to infections in patients with B-cell lymphoma. The reported incidence of infection in chemotherapy courses for B-cell lymphoma associated with <500 granulocytes /μL was higher than those with ≥ 500 granulocytes /μL. Neutropenia events should be monitored closely and any signs of infection should be treated as appropriate.

Infections of all grades have been reported in phase I and II clinical trials for polatuzumab vedotin. Fatal outcome has been reported in 5 patients, all in the Phase I study.

Infusion-Related Events

Some monoclonal antibodies may be associated with the development of allergic or anaphylactic reactions, to either the active protein or excipients. True allergic/anaphylactic reactions are rare after the first dose of a product, because they require prior sensitization. Patients with true allergic/anaphylactic reactions should not receive further doses of the product.

Monoclonal antibodies may also be associated with reactions that are clinically indistinguishable from true allergic/anaphylactic reactions but that are mediated through direct release of cytokines or other pro-inflammatory mediators. Such reactions are often termed “infusion-related reactions.” IRRs typically occur with the first infusion of a MAb product and are generally less frequent and/or less severe with subsequent infusions. They can often be managed by slowing the infusion rate and/or pretreatment with various medications.

Allergic/anaphylactic reactions and IRRs typically begin during or within several hours after completing the infusion. The onset of symptoms may be rapid, and some reactions may be life threatening.

Because of the potential for infusion reactions with protein drugs, administration of polatuzumab vedotin will be performed in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies. All patients will be monitored for infusion reactions during the infusion and immediately afterward (for additional instructions on the monitoring and management of infusion reactions, see

Section 4.3.2.2). Precautions for suspected anaphylactic reaction during study drug infusions are provided in Appendix 7. The initial dose of polatuzumab vedotin may be administered with premedication with acetaminophen, antihistamines, or corticosteroids per institutional standard practice at the discretion of the Investigator. Premedication should be instituted for subsequent doses if IRRs are observed in patients who receive their first dose of polatuzumab vedotin without premedications (see Section 4.3.2.2). Significant issues with polatuzumab vedotin IRRs have not been observed.

Similar considerations regarding infusion reactions are applicable for rituximab and obinutuzumab. Refer to Section 5.1.4 and Section 5.1.5.1 for additional information.

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 this 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 tumor lysis by the investigator will receive tumor lysis prophylaxis (e.g., allopurinol ≥ 300 mg/day PO or a suitable alternative treatment [according to institutional practice] starting before study treatment, refer to Section 5.1.7.1) and must be well hydrated before the initiation of study treatment at Cycle 1 Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion, as deemed appropriate by the investigator.

Bone Marrow Toxicity

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. Treatment may be delayed or modified for hematologic toxicities as described in Table 5.

Transfusion support for anemia and thrombocytopenia is also permitted at the discretion of the treating physician.

Immunogenicity (anti-therapeutic antibodies)

As with any recombinant antibody, polatuzumab vedotin may elicit an immune response and patients may develop antibodies against polatuzumab vedotin. Patients will be closely monitored for any potential immune response to polatuzumab vedotin. Appropriate screening, confirmatory, and characterization assays will be employed to assess ATAs before, during, and after the treatment with polatuzumab vedotin. Given the historically low immunogenicity rate of rituximab in NHL patients, ATAs 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 with reproductive 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.

GI Toxicity (diarrhea, nausea, vomiting, constipation, anorexia)

Diarrhea, constipation, anorexia, nausea and vomiting are reported frequently with diarrhea and nausea being the most common (≥ 30 %) treatment-emergent AEs in Phase I and II clinical studies using polatuzumab vedotin. With the exception of one event (Grade 4 diarrhea), all events were of Grade 1–3 severity. Diarrhea has been responsible for study drug modification and discontinuation. Most cases were low grade with more serious cases being confounded by poly pharmacy and comorbidity and disease under study

Hepatotoxicity

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

Elevations of transaminases have been reported in several patients receiving polatuzumab vedotin and have ranged in intensity from Grade 1–4. These have been reversible with and without dose modification/discontinuation. One event each of hepatomegaly/hepatic steatosis, cholecystitis acute, or hepatocellular injury has also been reported. For additional information please refer to the current version of the IB.

Pulmonary toxicity (Interstitial lung diseases)

Pulmonary toxicities have been reported from the ongoing clinical trials of similar ADCs with the same linker and cytotoxic agent MMAE. As there is no identified antibody antigen binding in the lung, this is considered to be possibly due to MMAE.

No events of pulmonary toxicities (interstitial lung disease) were reported in the Phase I study and three patients reported events of pulmonary toxicity(Pneumonitis, Pulmonary fibrosis and ILD) in Study GO27834 (Grade1–2). None of them were considered related to study drug by the investigator.

Joint pain/arthralgia/skeletal pain

Musculoskeletal pain, back pain and/or arthralgia have been reported as Grade 1–3 treatment-emergent adverse events in clinical studies using polatuzumab vedotin.

Cardiac Arrythmia

Serious and non-serious cardiac arrhythmia events have been observed in clinical trials using polatuzumab vedotin. The highest grade event reported was Grade 4. No clinically significant QTc prolongations were reported. For additional information, please refer to the latest IB.

Renal Toxicity

Preliminary safety observations in clinical trials with ADCs using the same linker and MMAE have suggested that some patients experience reduction of renal function during clinical trials.

Three patients experienced acute renal failure events. In all three, the events occurred in patients who received combination treatment of 2.4 mg/kg polatuzumab vedotin and rituximab. For additional information, please refer to the latest IB.

Ocular Toxicity

Treatment-emergent non-serious low grade severity ocular AEs were reported in Phase I/II clinical trials using polatuzumab vedotin. The broad spectrum of the reported terms of individual AEs did not suggest a pattern of a specific ophthalmologic toxicity. There was no evidence of permanent disabilities or treatment discontinuations reported. Most events were reversible as far as information was available.

Alopecia

Alopecia (Grades 1–2) has been reported as treatment-emergent adverse events in patients receiving polatuzumab vedotin as single-agent or in combination in clinical studies.

Dysgeusia

Treatment-emergent AEs of dysgeusia or alteration of taste have been experienced by patients receiving ADC-vc-MMAEs which are in the same class as polatuzumab vedotin.

Non-serious Grade 1–2 AEs of dysgeusia or taste alteration were reported in Phase I/II clinical studies using polatuzumab vedotin.

Genotoxicity/carcinogenicity (myelodysplastic syndrome)

MMAE, the cytotoxic component of polatuzumab vedotin, is a microtubule inhibitor targeting rapidly dividing cells and is expected to be carcinogenic. Patients who received chemotherapy with vincristine sulfate in combination with anticancer drugs known to be carcinogenic have developed second malignancies, although the contributing role of vincristine sulfate has not been determined.

Two cases of Grade 4 myelodysplastic syndrome have been reported in patients with r/r FL in Phase I and II clinical trials using polatuzumab vedotin. Both SAEs led to study treatment discontinuation.

5.1.3 Risks Associated with Cyclophosphamide, Doxorubicin, and Prednisone

The toxicity profile of CHP in the absence of vincristine is not well characterized; the side effects noted in this section are largely taken from the risks associated with the CHOP regimen.

The administration of CHP can be associated with nausea, vomiting, hair loss, leukopenia, anemia, thrombocytopenia, headache, elevated liver function tests, and dizziness. All patients who receive CHP are at risk for developing infections.

Cyclophosphamide has been associated with hemorrhagic cystitis.

Doxorubicin has been associated with myocardial toxicity, manifested as congestive heart failure, which may occur either during therapy or months to years after termination of drug use.

Prednisone may cause fluid retention, depression, and glucose intolerance and, upon withdrawal, has been associated with adrenal insufficiency.

For CHP dose delay, modification, and discontinuation instructions, see Table 5.

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

5.1.4 Risks Associated with Rituximab Therapy

Please see the prescribing information and IB for rituximab for full information.

a. Infusion-Related Reactions

Patients treated with rituximab in combination with chemotherapy 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, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Because of the potential for severe infusion reactions with rituximab, rituximab administration will occur in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. Medications and supportive care measures-including but not limited to epinephrine, antihistamines, glucocorticoids, IV

fluids, vasopressors, oxygen, bronchodilators, and acetaminophen/paracetamol-should be available for immediate use and instituted as medically indicated for use in the event of a reaction during administration.

Patients should receive premedication with acetaminophen/paracetamol, antihistamines, or corticosteroids, in accordance with standard clinical practice, before rituximab infusions.

The rituximab infusion should be interrupted for severe reactions on the basis of clinical judgment. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hour to 50 mg/hour.) when symptoms have completely resolved. Patients requiring close monitoring during all rituximab infusions include those with preexisting cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and those with high numbers of circulating malignant cells ($\geq$25,000/μL) with or without evidence of high tumor burden.

Additional details of anaphylaxis management are provided in Appendix 7.

b. Tumor Lysis Syndrome

Patients may be at risk for TLS. With rituximab treatment, acute renal failure, hyperkalemia, hypocalcemia, 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 interrupted and the patient treated through a correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, as clinically indicated. Following complete resolution of TLS complications, rituximab has been tolerated when re administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Patients deemed to be at high risk for TLS complications may at the investigator's discretion receive their initial dose of rituximab over 2 consecutive days (see Section 4.3.2.2).

c. Hepatitis B Exposure

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

Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and HBcAb positive) are at a lower risk for reactivation. In a study of 51 hepatitis B carriers with DLBCL who received rituximab, 12% of patients developed evidence of reactivation (Niitsu et al. 2010).

Patients with serologic findings consistent with chronic HBV (HBsAg positivity and/or total HBcAb) or HCV infection (HCV RNA) are ineligible for this study.

Patients who demonstrate evidence of reactivation of hepatitis will discontinue study treatment.

d. Progressive Multifocal Leukoencephalopathy

Rare cases of progressive multifocal leukoencephalopathy (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 extremely rare but 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 stem-cell transplant. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

Physicians should consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes but is not limited to consultation with a neurologist, brain MRI, and lumbar puncture. Physicians should discontinue rituximab (and polatuzumab vedotin) and consider discontinuation or reduction of any immunosuppressive therapy in patients who develop PML.

e. Cardiac Toxicity

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life threatening. Treatment with CHP chemotherapy is a known risk factor for cardiotoxicity, and to mitigate this risk, patients will be required to undergo assessments of left ventricular ejection fraction at baseline and at the Treatment Completion Visit/Early Termination Visit.

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 after subsequent infusions of rituximab. Patients with preexisting cardiac conditions, including arrhythmias and angina have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and the immediate post-infusion period.

f. Infection

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

New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, *Varicella* zoster virus, West Nile virus, and hepatitis B and C.

g. 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. The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure. Stevens-Johnson syndrome and toxic epidermal necrolysis are considered mandatory as SAEs regardless of their clinical grade.

h. 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 post-marketing reports of rituximab, the mean time to documented gastrointestinal perforation was 6 days (range, 1–77) in patients with NHL.

5.1.5 Risks Associated with Obinutuzumab

No evidence available at the time of the approval of this protocol indicates that special warnings or precautions are appropriate other than those noted in the Obinutuzumab Investigator's Brochure and as described in the following sections.

5.1.5.1 Infusion-Related Reactions and Hypersensitivity Reactions (Including Anaphylaxis)

The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, fatigue, and other symptoms.

Respiratory infusion-related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE, v3.0, Grade 1 and 2 events), and $<10\%$ of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished. The events resolved with the slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

5.1.5.2 Tumor Lysis Syndrome

TLS has been reported with obinutuzumab administration. To date, no patient has required hemodialysis for renal failure. Patients with a high tumor burden, including

patients with a lymphocyte count $\geq 25 \times 10^9$/L, particularly patients with B-cell CLL and mantle cell lymphoma, are at increased risk for TLS and severe IRRs.

5.1.5.3 Neutropenia

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of G-CSF has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF is strongly recommended, especially in the obinutuzumab-containing cohort, according to the ASCO, EORTC, and European Society for Medical Oncology (ESMO) guidelines (see Appendix 6).

5.1.5.4 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of hemorrhage in patients treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants), may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

5.1.5.5 Infection

On the basis of its anticipated mode of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

Reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, Varicella zoster virus, herpes simplex virus, John Cunningham [JC] virus, and HCV) that were new, reactivated, or exacerbated have been reported with the B cell–depleting antibody rituximab mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic SCT. The risk of such infections with obinutuzumab is unknown. Particular attention should be given to patients who have previously received significant immunosuppressive treatment, such as high-dose chemotherapy and SCT.

JC viral infection (including fatal) that resulted in (PML with destructive infection of oligodendrocytes of the CNS white matter) have been reported in patients treated with anti-CD20 therapies, including rituximab and obinutuzumab.

The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as cortical (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes but is not limited to consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA).

Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the diagnosis and management of PML.

5.1.5.6 Worsening of Cardiac Conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with obinutuzumab. These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

5.1.5.7 Gastro-Intestinal (GI) Perforation

GI perforation has been reported in patients treated with obinutuzumab including fatal events. Patients with GI involvement should be monitored for signs of GI perforation.

5.1.6 Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 5. Additional guidelines are provided in the subsections below.

5.1.6.1 Dose Delays and Dose Modifications

Patients should be assessed clinically for toxicity before each dose using NCI CTCAE v4.0 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. Dosing of polatuzumab vedotin beyond Cycle 1 (i.e., at Cycle 2 and beyond) may be delayed, depending on the rapidity for reversal of toxicity as discussed in Table 5. Dose delays

beyond 2 weeks will require Medical Monitor approval. 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.

Specific guidelines around dosage modifications for Cycles 2–6 (or 8) are detailed below. Patients who are receiving study treatment and experience toxicities should undergo dose interruptions and reductions, per instructions in Table 5. All considerations of dose and schedule modifications should be discussed with and approved by the Medical Monitor. Any patient in whom similar toxicity recurs at the reduced dose should be discontinued from further polatuzumab vedotin treatment.

5.1.6.2 Dose Modifications

No dose modifications of rituximab (375 mg/m^2) or obinutuzumab (1000 mg) are allowed.

CHP and polatuzumab vedotin doses may be reduced (per the guidelines outlined in Table 5 with the approval of the Medical Monitor. Doses of polatuzumab vedotin will not be reduced to $<$1.0 mg/kg.

5.1.6.3 Schedule Modification

A patient's dosing may be changed to a 28-day cycle if it is felt 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—for example, cytopenia without requiring repeated treatment delays. Modifications to the dosing schedule in this fashion must be made in consultation with and with the approval of the Medical Monitor.

5.1.7 Management of Toxicities R-CHP or G-CHP and Polatuzumab Vedotin

5.1.7.1 Tumor Lysis Syndrome

Patients with high tumor burden and who are considered by the investigator to be at risk for tumor lysis should also receive tumor lysis prophylaxis before the initiation of treatment. Patients should be well hydrated. Starting 1 or 2 days before 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 who are considered to be at risk for tumor lysis should be treated with 300 mg/day of allopurinol PO or a suitable alternative treatment starting 48–72 hours before Cycle 1 Day 1 of treatment and hydration. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion, if deemed appropriate by the investigator.

For patients with evidence of TLS, all study treatment should be interrupted and the patient should be treated as clinically indicated. Following the complete resolution of TLS complications, treatment with R-CHP or G-CHP and polatuzumab vedotin may be resumed at the full dose at the next scheduled infusion in conjunction with prophylactic therapy.

5.1.7.2 Infusion-Related Reactions and Anaphylaxis

Medications including epinephrine for subcutaneous injections, 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 4 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, study treatment 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 Section 5.1.7.2 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 (≥ 500 mg) and/or H1- and H2-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, β2-agonists, epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice. See Section 5.1.7.2 for recommended management of anaphylaxis. Guidelines for the management of IRRs and anaphylaxis are detailed in Table 4. Dose reductions are detailed in Table 5 and Table 6.

Table 4 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 patient permanently discontinued from study drug.
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 patient must be permanently discontinued from study drug. Note: If patient has Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence, patient must be permanently discontinued from study drug.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue study drug.

Note: Refer to the NCI-CTCAE v4.0 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.

5.1.7.3 Neutropenia

Because neutropenia is a known risk of polatuzumab vedotin (see Section 5.1.1.1), the use of growth factor support (G-CSF) as prophylactic and therapeutic indications should be implemented (see Appendix 6) in order to allow continued dosing of polatuzumab vedotin.

Dose and schedule modifications for neutropenia are detailed in Table 5 and Table 6. 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. Dose delays and dose modifications due to adverse events not specified in Table 5 should proceed on the basis of the principle of maintaining the DI of R-CHP or G-CHP. 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 with the approval of the Medical Monitor.

No dose modifications of rituximab are allowed. Cyclophosphamide, doxorubicin, and polatuzumab vedotin doses may be re-escalated (even to the full dose) with the approval of the Medical Monitor.

If administration of chemotherapy is delayed, the administration of rituximab or obinutuzumab and CHP should be delayed for the same time frame; for example, if CHP therapy is delayed, administration of rituximab or obinutuzumab should also be delayed so that they are given together beginning on Day 1 of the same cycle.

5.1.7.4 Dose Delays and Dose Modifications

Guidelines for dose delay and modification of R-CHP or G-CHP and polatuzumab vedotin are shown in Table 5 and Table 6. 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. Dose delays and dose modifications due to adverse events not specified in Table 5 should proceed on the basis of the principle of maintaining the DI of R-CHP or G-CHP. 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 with the approval of the Medical Monitor.

No dose modifications of rituximab are allowed. Cyclophosphamide, doxorubicin, and polatuzumab vedotin doses may be re-escalated (even to the full dose) with the approval of the Medical Monitor.

If administration of chemotherapy is delayed, the administration of rituximab or obinutuzumab and CHP should be delayed for the same time frame; for example, if CHP therapy is delayed, administration of rituximab or obinutuzumab should also be delayed so that they are given together beginning on Day 1 of the same cycle.

Table 5 Dose Interruptions, Reductions, and Discontinuations of Polatuzumab Vedotin and R-CHP or G-CHP

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia with or without infection or fever, first delay [a]	• Delay all study treatment. • Administer growth factors, e.g., G-CSF for neutropenia as indicated and for all subsequent cycles • If ANC recovers to >1000/uL ≤ 7 days after the scheduled date for the next cycle, administer full dose of polatuzumab vedotin and R-CHP or G-CHP • If ANC recovers to >1000/uL ≥ 8 days after the scheduled date for the next cycle, reduce the dose of polatuzumab vedotin to the previously tested (lower) dose level. The minimum dose level of polatuzumab vedotin is 1.0 mg/kg. • 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 polatuzumab vedotin. For guidelines for dose delay for obinutuzumab on Cycle 1 Day 8 and Cycle 1 day 15, see Table 6.
Recurrent Grade 3 neutropenia	• Delay all study treatment. • If ANC recovers to >1000/uL ≤ 7 days after the scheduled date for the next cycle, administer full dose of polatuzumab vedotin and R-CHP or G-CHP. • If ANC recovers to >1000/uL ≥ 8 days after the scheduled date for the next cycle, then: If no prior dose reduction of polatuzumab vedotin: reduce the dose of polatuzumab vedotin to the previously tested (lower) dose level. Minimum dose level of polatuzumab vedotin allowed is 1.0 mg/kg. If there was a prior dose reduction of polatuzumab vedotin: the polatuzumab vedotin dose reduction should be maintained, and the doses of cyclophosphamide and doxorubicin should be reduced to 50% of the original dose. • If Grade 3 neutropenia persists despite growth factor support and following polatuzumab vedotin, cyclophosphamide, and doxorubicin dose reductions, in the absence of fever, patient may continue study treatment. • If patient develops Grade 3 febrile neutropenia or infection despite growth factor support and following polatuzumab vedotin, cyclophosphamide, and doxorubicin dose reductions, discontinue all study treatment permanently.

Event(s)	Dose Delay or Modification
Recurrent Grade 4 neutropenia	• Delay all study treatment. • If ANC recovers to $>1000/\mu L \leq 7$ days after the scheduled date for the next cycle, administer full dose of polatuzumab vedotin and R-CHP or G-CHP. • If ANC recovers to $>1000/uL \geq 8$ days after the scheduled date for the next cycle, then: If no prior dose reduction of polatuzumab vedotin: reduce the dose of polatuzumab vedotin to the previously tested (lower) dose level. Minimum dose level of polatuzumab vedotin is 1.0 mg/kg. If there was a prior dose reduction of polatuzumab vedotin: the polatuzumab vedotin dose reduction should be maintained, and the doses of cyclophosphamide and doxorubicin should be reduced to 50% of the original dose. • If patient develops Grade 4 neutropenia despite growth factor support and following polatuzumab vedotin, cyclophosphamide, and doxorubicin dose reductions, discontinue all study treatment permanently.
Severe thrombocytopenia (platelets $<$ 10,000/μL) and/or symptomatic bleeding in patients not receiving concomitant anticoagulants or platelet inhibitors	• Hold obinutuzumab in case of severe thrombocytopenia (platelets $<$ 10,000/μL) or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip any doses of obinutuzumab for sake of maintaining the chemo schedule.
Thrombocytopenia (platelets $<$ 20,000/μL and/or symptomatic bleeding in patients receiving concomitant anticoagulants or platelet inhibitors [b,c])	• Hold obinutuzumab in case of platelets $<$ 20.000/μL or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip any doses of obinutuzumab for sake of maintaining the chemo schedule. • For patients who are on LMWH, when thrombocytopenia with platelets $<$ 20,000/μL develops, reduce the dose of LMWH used.[b] • For patients who are on platelet inhibitors, when thrombocytopenia with platelets $<$ 20,000/μL develops, consideration should be given to temporarily pause their use.[b] • For guidelines for dose delay for obinutuzumab on Cycle 1 Day 8 and Cycle 1 Day 15, see Table 6.

Event(s)	Dose Delay or Modification
Grade 3 or 4 thrombocytopenia, first episode	• Delay all study treatment. • If platelet count recovers to $>75\times109$/L by Day 7 of the scheduled date of the next cycle, administer full dose of polatuzumab vedotin and R-CHP or G-CHP. • If platelet count recovers to $>75\times109$/L on or after Day 8 of the scheduled date of the next cycle, reduce the dose of cyclophosphamide and doxorubicin to 50% of the original dose. Full-dose polatuzumab vedotin may be given. • If the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of cyclophosphamide and doxorubicin.
Recurrent Grade 3 or 4 thrombocytopenia	• If patient develops Grade 3-4 thrombocytopenia following cyclophosphamide and doxorubicin dose reductions, discontinue all study treatment permanently.
Hemorrhagic cystitis	• Patients should be adequately hydrated before and after cyclophosphamide administration and should be instructed to void frequently. If gross hematuria develops, cyclophosphamide should be withheld until resolution of cystitis. A dose reduction of 50% for cyclophosphamide may be considered at the next cycle. Re-escalation of cyclophosphamide to the initial full dose is recommended if symptoms do not recur.
Grade 2-4 heart failure or Grade 3 or 4 LVSD	• Discontinue all study treatment permanently.
Bilirubin >3.0 mg/dL	• Delay all study treatment until resolution to Grade ≤ 1. Evaluate for causality.
Bilirubin between 1.5 and 3.0 mg/dL	• Reduce doxorubicin dose by at least 25% of baseline. With subsequent courses of treatment if bilirubin has returned to ≤ 1 mg/dL, full doses may be given. Evaluate for causality.
Grade 4 neurotoxicity (including peripheral neuropathy)	• Discontinue polatuzumab vedotin treatment permanently. • Patients should be evaluated regarding the continuation of R-CHP or G-CHP on the basis of their risk/benefit.

Event(s)	Dose Delay or Modification
Grade 2 or 3 neurotoxicity (including peripheral neuropathy)	• Delay all study treatment. • If recovered to Grade ≤ 1 within 14 days: If no prior dose reduction of polatuzumab vedotin for any reason: Reduce polatuzumab vedotin to the previously tested (lower) dose level (permanent dose reduction). Minimum dose level of polatuzumab vedotin is 1.0 mg/kg. R-CHP or G-CHP may be administered at their full doses. If there was a prior dose reduction of polatuzumab vedotin: Polatuzumab vedotin must be permanently discontinued. R-CHP or G-CHP administration at full doses should continue. • If not recovered to Grade ≤ 1 until 14 days or more after the scheduled date for the next cycle, polatuzumab vedotin treatment must be permanently discontinued. R-CHP or G-CHP may be administered at their full doses.
Grade 3 or 4 tumor lysis syndrome	• Following complete resolution of tumor lysis syndrome, study treatment may be re-administered at the full dose during next scheduled infusion in conjunction with prophylactic therapy.
Anaphylaxis or Grade 4 IRR	• Discontinue rituximab or obinutuzumab or polatuzumab vedotin permanently. • If anaphylaxis is attributed to rituximab or obinutuzumab, continue polatuzumab vedotin and CHP. • If anaphylaxis is attributed to polatuzumab vedotin, continue rituximab or obinutuzumab and CHP.
Grade 3 IRR, second episode	• Discontinue rituximab or polatuzumab vedotin permanently. • If IRR is attributed to rituximab or obinutuzumab, continue polatuzumab vedotin and CHP. • If IRR is attributed to polatuzumab vedotin, continue rituximab or obinutuzumab and CHP.
Grade 3 or 4 non-hematologic toxicity not otherwise specified	• Delay all study treatment for a maximum of 2 weeks. • Subsequent episodes: Decrease polatuzumab vedotin to the previously tested (lower) dose level. Once polatuzumab vedotin has been dose reduced to 1.0 mg/kg, then for subsequent episodes the polatuzumab vedotin dose reduction (to 1.0 mg/kg) should be maintained and the dose of cyclophosphamide should be reduced to 375 mg/m^2 and doxorubicin to 25 mg/m^2. • Final episode: discontinue all study treatment permanently.
Grade 2 non-hematologic toxicity not otherwise specified	• Delay all study treatment for a maximum of 2 weeks. • If improvement to Grade ≤ 1 or baseline, administer study treatment without modification.

Event(s)	Dose Delay or Modification
Hepatitis B reactivation (as evidenced by new detectable HBV DNA)	• HBV DNA between WHO-recommended range of 10 and 100 IU/mL: retest within 2 weeks. If still positive, patient should be treated with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or hepatologist. • HBV DNA WHO-recommended cutoff of > 100 IU/mL: the patient should be treated with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or hepatologist. • Increasing HBV DNA viral load while on an appropriate anti-viral therapy: discontinue all study treatment immediately.

CHP = cyclophosphamide, doxorubicin, and prednisone or prednisolone; G-CSF = granulocyte colony–stimulating factor; HBV = hepatitis B virus; IRR = infusion-related reaction; LVSD = left ventricular systolic dysfunction; R = rituximab; WHO = World Health Organisation.

Note: All decisions regarding dose delays, modifications and discontinuations should be done in consultation with and the approval of the Medical Monitor.

[a] Based on laboratory results obtained within 72 hours before study treatment administration on Cycle 1 Day 1.

[b] If the clinical condition of patient requires the use of concomitant anticoagulants, the patients are at increased risk of bleeding when thrombocytopenia with platelets < 20,000/μL develops. When possible, replace prior therapy with vitamin K antagonists with LMWH before Cycle 1 Day 1.

[c] Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.

Table 6 Guidelines for Dose Delay for Obinutuzumab on Cycle 1 Day 8 and Cycle 1 Day 15

Event(s)	Dose Delay or Modification
Febrile neutropenia or neutropenia with infection	• Hold obinutuzumab dose until fever or infection resolves. • If Cycle 1 Day 8 is delayed long enough that the patient is approaching Day 15, then skip Day 8 and administer Day 15 as previously scheduled (if infection or fever has resolved). • If Cycle 1 Day 15 is delayed long enough that the patient is approaching Cycle 2, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab + CHP and polatuzumab vedotin as scheduled (if infection or fever has resolved). • Note: Obinutuzumab should not be held for neutropenia without infection or fever.
Thrombocytopenia with platelet count < 20,000/μL and/or symptomatic bleeding	• Hold obinutuzumab dose if platelet count < 20,000/μL and/or symptomatic bleeding. • If Cycle 1 Day 8 is delayed long enough that the patient is approaching Day 15, then skip Day 8 and administer Day 15 as previously scheduled (if symptomatic bleeding has resolved). • If Cycle 1 Day 15 is delayed long enough that the patient is approaching Cycle 2, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab +-CHP and polatuzumab vedotin as scheduled (if symptomatic bleeding has resolved).

5.1.7.5 Dose Discontinuation

Dosing delay exceeding 14 days in the initiation of the next planned cycle of R-CHP or G-CHP and polatuzumab vedotin will require study treatment discontinuation unless Medical Monitor approval is obtained to continue on study treatment.

Patients discontinuing rituximab or obinutuzumab should continue with CHP and polatuzumab vedotin and remain in the study and continue with all protocol-defined assessments.

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 Section 4.5.

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; measurement of protocol-specified laboratory assessments; measurement of protocol-specified vital signs; and 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 guidelines for GCP, 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), except as described in Section 5.4.9
- 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:

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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 5.4.10)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 should 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 5.5.2 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 5.5.2 for reporting instructions). Adverse events of special interest for this study include the following:

- 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 5.4.6)
- 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 regulatory seriousness criteria or causality)
- *Second malignancies*

Real-time safety monitoring will be employed for DLT assessment and dose-escalation decisions.

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

Adverse events that meet the definition of a DLT during the DLT observation period (see Section 3.1) will be recorded on the Adverse Event eCRF and reported immediately to the Medical Monitor as described in Section 5.4. If a DLT also meets the definition of a severe adverse event, the event will also qualify for expedited reporting to the Sponsor (see Section 5.2.2 and Section 5.5.2 for reporting instructions).

During the DLT assessment window, adverse events identified as DLTs, as defined in Section 3.1.1.1, 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 5.5.2 for reporting instructions).

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 Section 5.4, Section 5.5, and Section 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 5.5.2 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 last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.7).

Second malignancies will be reported indefinitely for patients who received obinutuzumab, regardless of relationship to study treatment (even if the study has been closed and even after initiation of new anti-lymphoma therapy; see Section 5.7).

5.3.2 Eliciting Adverse Events

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 v4.0 will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 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 (v4.0), 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 5.5.2 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 5.5.2 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 or not 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 8):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially 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 8 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.

5.4 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.

5.4.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction (e.g., record dyspnea and hypotension as separate events rather than as a diagnosis of IRR).

Other Adverse Events

For adverse events other than IRRs, 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.

5.4.2 Adverse Events Occurring 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 recorded 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.

5.4.3 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, unless the severity increases. 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 a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.5.2 for reporting instructions). The initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

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.

5.4.4 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:

- 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
- Clinically significant in the investigator's judgment

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (e.g., cholestasis) needs to 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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.4.3).

5.4.5 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:

- 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 (including a diagnostic evaluation not mandated in this protocol) or a change in concomitant therapy
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.4.3).

5.4.6 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 5.6) 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 a adverse event of special interest (see Section 5.5.2).

5.4.7 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 lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.6.2).

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").*

During survival follow-up, deaths attributed to progression of lymphoma should be recorded only on the Survival eCRF.

5.4.8 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").

5.4.9 Lack of Efficacy or Worsening of Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the Revised Response Criteria for Malignant Lymphoma (see Appendix 2). 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.

5.4.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 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, perform an efficacy measurement for the study)
- 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

5.4.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2).

No safety data related to overdosing of polatuzumab vedotin are available.

5.4.12 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. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.5 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
- Adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis

- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.5.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information for sites in the United States:

Medical Monitor: [redacted], M.D.
Telephone No.: [redacted]

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.

5.5.2 Reporting Requirements for All Serious Adverse Events, Adverse Events of Special Interest, and Dose-Limiting Toxicities

5.5.2.1 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. A paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet should be completed and faxed or scanned and emailed to sponsor or its designee using the fax number or email address provided to investigators immediately (i.e., no more than 24 hours after learning of the event).

Sites in the United States:

Fax No.: [redacted]

Sites in France:

Fax No. [redacted]

Relevant follow-up information should be submitted to Genentech's Drug Safety Department or its designee as soon as it becomes available and/or upon request.

5.5.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 90 days after the last dose of study drug. DLTs will be reported during the DLT assessment window. 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 Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/ Adverse Event of Special Interest Reporting Form and fax cover sheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see fax numbers provided in Section 5.5.2.1). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post study adverse events are provided in Section 5.7.

5.5.3 Reporting Requirements for Pregnancies

5.5.3.1 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 90 days after the last dose of study drug. A 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.

5.5.3.2 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 5 months after the last dose of study drug. A 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. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will 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.

5.5.3.3 Abortions

Any 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).

5.5.3.4 Congenital Anomalies/Birth Defects and Abortions

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 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 5.5.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.6 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.6.1 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. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions in Section 5.5.3.1.

5.6.2 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, electronic mail, and/or a

monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, or autopsy report) in order to perform an independent medical assessment of the reported case.

5.7 POST-STUDY ADVERSE EVENTS

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after the end of the adverse event reporting period if the event is believed to be related to prior study drug treatment. *The Sponsor should also be notified of events of second malignancies indefinitely for patients who received obinutuzumab.*

The investigator should report these events directly to the Sponsor or its designee by completing and faxing or emailing a paper Serious Adverse Event Reporting Form/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators using the fax numbers provided below.

Sites in the United States:

Fax: 650-225-4682

Sites in France:

Fax: [redacted]

5.8 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
- Obinutuzumab Investigator’s Brochure
- Local prescribing information for CHP medications

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 sample size required for estimating the MTD is based on the dose-escalation rules described in Section 3.1.1.2. In addition, approximately 17 and 40 patients will be enrolled into the expansion cohorts for G-CHP and R-CHP, respectively, in combination with the MTD of polatuzumab vedotin identified during dose escalation. With 40 patients the 95% exact Clopper-Pearson CIs for the true CR rate would have a margin of error not exceeding 17%. The planned enrollment for this study is approximately 24–30 patients for dose-escalation cohorts and 60 patients for expansion cohorts for a total planned enrollment of 84–90 patients.

6.2 SUMMARIES OF CONDUCT OF THE STUDY

The final analysis will be based on patient data collected through patient discontinuation or study discontinuation, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who received at least one dose of study treatment. All summaries will be presented according to the assigned dose level of polatuzumab vedotin.

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. All summaries will be presented overall and by treatment group.

Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of each study medication received. All summaries will be presented by treatment group and disease specific cohort.

6.3 SAFETY ANALYSES

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, changes in ECGs, ECHO/MUGA scans, and changes in vital signs. All patients who receive any amount of any drug that was part of the combination study treatment will be included in the safety analysis.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after study

treatment administration on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and toxicity grade per NCI CTCAE v4.0. In addition, all serious adverse events, including deaths, will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to polatuzumab vedotin will be summarized.

6.4 PHARMACOKINETIC ANALYSES

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to polatuzumab vedotin will be summarized.

Individual and mean serum concentrations of total polatuzumab vedotin antibody (fully conjugated, partially deconjugated and fully deconjugated antibody) and rituximab and plasma concentrations of polatuzumab vedotin conjugate (evaluated as acMMAE), unconjugated MMAE, cyclophosphamide, and doxorubicin versus time data will be tabulated and plotted. The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2,terminal}$), as data allow. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range), as data allow. Non-compartmental, compartmental and/or population methods will be used, as data allow.

To assess PK drug interactions, PK parameters for each analyte of polatuzumab vedotin, rituximab, and obinutuzumab will be compared with historical single-agent data, as data allow. PK data of cyclophosphamide, and doxorubicin will be compared between Cycle 1 (in the absence of polatuzumab vedotin) and Cycle 3 (in the presence of polatuzumab vedotin), and compared to historical data, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted using PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, per the Sponsor's discretion and as data allow.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of polatuzumab vedotin, as data allow and at the Sponsor's discretion.

6.5 ACTIVITY ANALYSES

OR is defined as a CR or PR, as determined by investigator assessment with use of standard criteria (Cheson et al. 2007). OR rate will be summarized. Patients with missing or no response assessments will be classified as non-responders. Among patients with an OR, DOR will be defined as the time from documentation of the first CR or PR to the time of disease progression, relapse, or death from any cause, as assessed by the investigator. If a patient does not experience death or disease progression before the end of the study, DOR will be censored on the day of the last tumor assessment. OS is defined as the period from the date of randomization until the date of death from

any cause. For patients who have not died at the time of the analyses, OS will be censored on the last date when the patients are known to be alive.

PFS is defined as the time from the first day of study treatment (Day 1) to disease progression, relapse, or death from any cause, as assessed by the investigator. If a patient has not experienced progressive disease or death, PFS will be censored on the day of the last tumor assessment. If a post-baseline assessment is not available, PFS will be censored on Day 1.

The Kaplan-Meier approach will be used to estimate the distribution of DOR, PFS, and OS in all patients. Results will also be summarized separately among those patients in the dose-escalation part of the study and among those patients in the dose-expansion part of the study.

6.6 PATIENT-REPORTED OUTCOME ANALYSES

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

6.7 HANDLING OF MISSING DATA

For PFS, patients who do not have documented disease progression or have died will be treated as censored observations on the date of the last tumor assessment. If no tumor assessments were performed after the baseline visit, PFS will be censored at the time of randomization.

For the response endpoints, patients with no response assessments (for any reason) will be considered non-responders.

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.

ePRO data will be collected through use of an electronic device. This device will be the patient's own electronic devices (i.e., mobile phone, tablet, or home computer) with specialized software installed to ensure the secure collection and transmission of the data. If the patient does not own their own device, one will be provided by the ePRO vendor. The software is designed for entry of data in a way that is attributable, secure, accurate, and in compliance with U.S. FDA regulations for electronic records (21 Code of Federal Regulations [CFR] Part 11). The ePRO device data are available for view access only via secure access to a Web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an electronic patient-reported outcome (ePRO) device to capture PRO data. This device will be the patient's own electronic devices (i.e., mobile phone, tablet, or home computer) with specialized software installed to ensure the secure collection and transmission of the data. If the patient does not own their own device, one will be provided by the ePRO vendor. The data will be transmitted via Web or wireless automatically to a centralized database at the ePRO vendor. The data can be reviewed by site staff via secure access to a Web server.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 where 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 the pharmacy, 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 7.6.

To facilitate source data verification, 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 regulatory authorities.

7.5 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 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for

the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records should 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.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's 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 Form 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.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. 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 before 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 Form 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 and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

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

8.4 CONFIDENTIALITY

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

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or 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 the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives and collaborators, and the IRB/EC for each study site, if appropriate.

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 (i.e., LPLV).

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

Genentech, Inc., a member of the Roche group, is the sponsor of this study. A contract research organization (CRO) may provide clinical monitoring, data management, and medical monitoring support. Genentech will conduct CRO oversight, approve patient eligibility, make decisions regarding dosing levels and schedules, provide primary medical monitoring, and conduct statistical programming and analysis.

EDC will be utilized for this study. An IXRS will be used to assign patient numbers. A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5.7; otherwise, local laboratories will be used. A central independent review facility will be used to collect radiographic and nuclear medicine scans, which may be analyzed at a later time.

9.5 *PUBLICATION 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, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.6 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

American Cancer Society. Cancer Facts & Figures 2010. Atlanta (GA): American Cancer Society 2010.

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.

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.

Cavaletti G, Frigeni B, Lanzani F, et al. The total neuropathy score as assessment tool for grading the course of chemotherapy-induced peripheral neurotoxicity: comparison with the National Cancer Institute-Common Toxicity Scale. J Peripher Nerv Syst 2007;12:210–5.

Cavaletti G, Jann S, Pace A, et al. Multi-center assessment of the total neuropathy score for chemotherapy-induced peripheral neurotoxicity. J Peripher Nerv Syst 2006;11:135–41.

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, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

Coiffier B, Lepage E, Briére 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.

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;21:778–4.

Dyer MJS, Grigg A, González M, et al. Obinutuzumab (GA101) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or bendamustine in patients with previously untreated follicular lymphoma (FL): results of the phase Ib GAUDI study (BO21000) [abstract]. Blood 2012;120:3686.

GLOBOCAN 2008 (IARC). Section of cancer information [resource on the Internet]. (11/8/2010). Available from: http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=990.

Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101–10.

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.

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.

Hauptrock B, Hess G. Rituximab in the treatment of non-Hodgkin's lymphoma. Biologics 2008;2:3121–7.

Juweid M, Cheson BD. Positron emission tomography (PET) in post-therapy assessment of cancer. N Engl J Med 2006;354:496–507.

Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007;25:571–8.

Koren E, Smith HW, Shores E, et al. Recommendations on risk based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods 2008;333:1–9.

MabThera® (rituximab) Summary of Product Characteristics (SmPC), Roche Pharma AG. 2016 Jun [cited 2016 Jul 19]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf.

National Comprehensive Cancer Network®. Clinical practice guidelines for advanced diffuse large B-cell lymphoma™ [resource on the Internet]. 2013. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Niitsu N, Hagiwara Y, Tanae K, et al. Prospective analysis of hepatitis B virus reactivation in patients with diffuse large B-cell lymphoma after rituximab combination chemotherapy. J Clin Oncol 2010;29:5097–100.

Pfreundschuh M, Schubert J, Ziepert M, et al. 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.

Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379–91.

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.

Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood 2013;122:1137−43.

Rituxan® U.S. Package Insert, Biogen Idec Inc. and Genentech, Inc.; South San Francisco, CA; February 2013.

Rosenberg AS, Worobec A. A risk-based approach to immunogenicity concerns of therapeutic protein products, part 1: considering consequences of the immune response to a protein. BioPharm International 2004a;17:22–6.

Rosenberg AS, Worobec A. A risk-based approach to immunogenicity concerns of therapeutic protein products, part 2: considering host-specific and product-specific factors impacting immunogenicity. BioPharm International 2004b;17:34–42.

Rosenberg AS, Worobec A. A risk-based approach to immunogenicity concerns of therapeutic protein products, part 3: effects of manufacturing changes in immunogenicity and the utility of animal immunogenicity studies. BioPharm International 2005;18:32–36.

Seyfarth B, Josting A, Dreyling M, et al. Relapse in common lymphoma subtypes: salvage treatment options for follicular lymphoma, diffuse large cell lymphoma and Hodgkin disease. Br J Haematol 2006;133:3–18.

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.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

Thomas SK, Mendoza TR, Vichaya EG, et al. Validation of the chemotherapy-induced neuropathy scale. J Clin Oncol 2012;30:9140.

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–vii82.

Zelenetz AD, Mobasher M, Costa LJ, et al. Safety and efficacy of obinutuzumab (GA101) plus CHOP chemotherapy in first-line advanced difuse large B-cell lymphoma: results from the phase 2 Gather study (GAO4915g) [abstract]. Blood 2013;122:1820.

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 Assessments

Assessment	Screening		Treatment Period																				TCV/ ETV [a]	P-T [b]
Days	– 28 to – 1	– 14 to – 1	C1 D1	C1 D2	C1 D8	C1 D15	C2 D1	C2 D2	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1 [c]	C7 D8 [c]	C8 D1 [c]	C8 D8 [c]			
Informed consent	x																							
Inclusion/exclusion criteria	x																							
Demographics and medical history [d]	x																							
Complete physical exam [e]	x																							
Targeted physical exam [f]			x		(x)	(x)	x			x		x		x		x		x		x			x	x
Height (at screening only), weight, BSA		x	x				x			x		x		x		x		x		x				
Vital signs [g]		x	x	x	x	x	x	x		x		x		x		x		x		x			x	x
ECOG PS	x		x				x			x		x		x		x		x		x			x	x
Hematology and serum chemistry [h]		x	x		x	x	x			x		x		x		x		x		x			x	x
Serum pregnancy test [i]		x																					x	
B-symptoms [j]		x																					x	x (q6m)
Coagulation (PT, aPTT, and INR)		x																					x	
Viral serology [k]	x																							
Serum IgA, IgG, and IgM		x																					x	
Bone marrow exam [l]	x													[l]									[l]	[l]x [k]
CT scan [m]	Please see footnote m.																							
PET scan [m]	Please see footnote m.																							
Tumor assessment	x													x									x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

Appendix 1
Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period																				
Days	– 28 to – 1	– 14 to – 1	C1 D1	C1 D2	C1 D8	C1 D15	C2 D1	C2 D2	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1 [c]	C7 D8 [c]	C8 D1 [c]	C8 D8 [c]	TCV/ ETV [a]	P-T [b]
Adverse event [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Echocardiogram or MUGA	x																					x	
12-lead ECG	x																					x	
Rituximab [o]			x				x			x		x		x		x		x		x			
Obinutuzumab [o]			x		x	x	x			x		x		x		x		x		x			
Doxorubicin [o]			x				x			x		x		x		x		x		x			
Cyclophosphamide [o]			x				x			x		x		x		x		x		x			
Prednisone (Days 1–5 of each cycle) [o]			x[n]	x[n]			x[n]	x[n]		x[n]		x[n]		x[n]		x[n]		x[n]		x[n]			
Polatuzumab vedotin [p]				x				x		x		x		x		x		x		x			
Pharmacokinetic samples	See Appendix 4 and Appendix 5																						
Archival (or fresh) tumor tissue sample [q]	x																						
Leukocyte immunophenotyping [r]			x				x															x	
MRD biomarker studies (whole blood) [s]			x									x										x	
Exploratory biomarker studies [t]			x																			x	
Pre-phase treatment [u]		x																					
Peripheral neuropathy assessments [v]			x				x			x		x		x		x		x		x		x	x
Patient-reported outcomes (TINAS) w			Weekly on the same day each week during study treatment period.																			Weekly for 2 months, then monthly for 10 months	

Appendix 1
Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period																				
Days	– 28 to – 1	– 14 to – 1	C1 D1	C1 D2	C1 D8	C1 D15	C2 D1	C2 D2	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1 [c]	C7 D8 [c]	C8 D1 [c]	C8 D8 [c]	TCV/ ETV [a]	P-T [b]
Optional residual tumor tissue			(x)									(x)										(x)	
Optional RCR blood sample [y]	(x)																					(x)	

BSA = body surface area; C = cycle; CHP = cyclophosphamide, doxorubicin, and prednisolone or prednisone; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ETV = Early Termination Visit; HCV = hepatitis C virus; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PS = Performance Status; P-T = post-treatment; PT = prothrombin time; PET = positron emission tomography; q6m = every 6 months; R = rituximab; RCR = Roche Clinical Repository; TINAS = Therapy-Induced Neuropathy Assessment Scale; TCV = Treatment Completion Visit; (x) = conditional/optional (refer to footnote).

Notes: The visit window during each cycle of study treatment is ± 2 days. The window for the treatment discontinuation/early termination and post-treatment study visits is ± 1 week (unless otherwise specified). Please refer to Appendix 4 and Appendix 5 for the schedule of PK assessments (Cycle 3, Day 2 PK sampling also required in the expansion portion of the study per Appendix 5).

[a] Patients should return for this study visit within 30 days after receiving their last dose of study drug, including all patients who withdraw/discontinue because of progression of disease or for any other reason, anytime during the study treatment period.

[b] Post treatment study visits will occur 3, 6, 9, 12 months after the last dose of study treatment and every 6 months thereafter until the close of the study (after at least 2 years of follow-up after the end of study treatment for all of the enrolled patients.

[c] These visits will be conducted only at those sites that choose eight cycles of R-CHP or G-CHP and polatuzumab vedotin.

[d] At screening, obtain demographic data and complete medical history. On Day 1, obtain medical history since the screening visit.

[e] Complete physical examination includes all systems described in the body of the protocol, including assessment of lymph nodes, hepatomegaly, and splenomegaly.

[f] The targeted physical examination should include only systems of most clinical relevance (i.e., cardiovascular, respiratory, those associated with clinical signs/symptoms, and lymph nodes, liver, and spleen). On Cycle 1 Day 8 and Cycle 1 Day 15, a physical examination can be performed at the discretion of the investigator if clinically indicated.

[g] Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature while patient is seated or supine. On polatuzumab vedotin infusion days, 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. On rituximab and obinutuzumab infusion days, obtain vital signs before the infusion of rituximab or obinutuzumab, then after the start of the infusion approximately every 15 (±5) minutes for 90 minutes, then approximately every 30 (±10) minutes until the 1 hour after the end of infusion.

[h] Hematology includes hemoglobin, platelet count, white blood cell count, and ANC. Results should be obtained within 3 days before the study treatment. Serum chemistry includes glucose, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, calcium, phosphorous, total bilirubin, direct bilirubin, total protein,

albumin, ALT, AST, LDH, alkaline phosphatase, uric acid, amylase and lipase. At screening, a fasting blood glucose should be obtained for all patients. $HbA1_c$ will be measured at Cycle 4 Day 1.

[i] All women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 28 days before Cycle 1 Day 1 of study treatment if not sexually active and within 7 days of Cycle 1 Day 1 if sexually active.

[j] B-symptoms include weight loss, night sweats, and fever.

[k] Hepatitis B (HBsAg and total HB core antibody), and hepatitis C antibody serology required. PCR testing will be required in those patients who are HCV antibody positive to determine eligibility. HTLV-1 screening also required in patients from endemic countries.

[l] A bone marrow biopsy and aspirate are mandatory at screening and should include biopsy for morphology. The bone marrow assessment must be performed within 4 months of the Cycle 1 Day 1 as long as it was for the purpose of diagnosis and staging of diffuse large B-cell lymphoma. For patients with bone marrow involvement at screening, a repeat biopsy at the end of therapy is mandatory only to confirm a complete response. [l]: Perform bone marrow biopsy to confirm complete response if bone marrow biopsy at screening shows presence of lymphoma or there is clinical suspicion of progressive disease in the bone marrow in the absence of progressive disease as demonstrated by radiographic imaging.

[m] CT and PET scans are required at screening, following Cycle 4 of study treatment (i.e., at Cycle 4 Days 15–21),and at the Treatment Completion/Early Termination visit (6–8 weeks after the last dose of study treatment). CT scans will be obtained every 6 months thereafter for an additional four radiographic assessments (last radiographic assessment will be performed approximately 2 years following the Treatment Completion/Early Termination visit). CT scan (with IV and oral contrast) of the chest, abdomen, pelvis (including inguinal/femoral regions), and neck, if clinically indicated. Any time the investigator suspects disease progression, a full tumor assessment including anatomic scans must be performed. MRIs may be used instead of CT scans with contrast in patients for whom CT scans with contrast are contraindicated. The results of PET scans that are performed as part of the routine clinical care at the institution should be recorded on the CRF.

[n] Patients will be evaluated for new adverse events at each study visit until 90 days after completing or discontinuing study treatment. Unresolved adverse events will be followed from Cycle 1 Day 1 until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent.

[o] Rituximab 375 mg/m^2 will be administered on Day 1 of each cycle. Obinutuzumab will be administered as 1000 mg on Day 1, 8, and 15 of Cycle 1, then Day 1 of each subsequent cycle. CHP consists of cyclophosphamide 750 mg/m^2 IV on Day 1 of each cycle, doxorubicin 50 mg/m^2 IV on Day 1 of each cycle, and prednisone (prednisolone) 100 mg orally on Days 1–5 of each cycle. When rituximab or obinutuzumab is administered on the same day as prednisone (prednisolone), it is recommended that prednisone (prednisolone) be given before the rituximab or obinutuzumab infusion. The order of administration of study treatment will be determined by local institutional practice. Empiric dose adjustment in obese patients (defined as a body mass index ≥ 30, as measured in kg/m^2) may be implemented per institutional guidelines. There will be no dose modification for changes in patients' weight unless the weight increases or decreases by > 10% from weight on Cycle 1 Day 1. Rituximab or obinutuzumab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride (unless contraindicated). Allopurinol should be administered for patients with high tumor burden, if pretreatment with allopurinol is deemed appropriate. Please see Section 4.3.1 for information regarding the order of administration of study treatments. **During infusion of doxorubicin, continuous ECG monitoring should be performed per clinical practice.**

[p] Polatuzumab vedotin will be administered on Day 2 of Cycles 1 and 2. If well tolerated, then all study treatments may be administered on the same day during subsequent cycles.

Appendix 1
Schedule of Assessments (cont.)

[q] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time before study entry.

[r] CD3+, CD19+, etc.

[s] Peripheral blood sample (10-mL per sample) for MRD analysis in all patients at Cycle 1 Day 1 (prior to dosing), between Cycle 3 Day 15 and Cycle 4 Day 1, and at the Treatment Completion Visit.

[t] 5-mL each of whole blood and plasma prior to treatment and treatment completion.

[u] Day -7 to -1. Administration of an approximate 7 day of pre-phase treatment (consisting of prednisone/prednisolone 100 mg PO daily) between Days -7 to -1 may be given at the discretion of the treating investigator physician.

[v] Patients may undergo a Clinical Total Neuropathy Assessment (to include subjective sensory symptoms, motor symptoms, autonomic symptoms; to include objective pinprick sensitivity, vibration sensitivity, strength testing and deep tendon reflex testing).

[w] The TINAS is the patient reported outcomes instrument. TINAS should be completed weekly, preferably on the same day each week during the course of study treatment. On study visit days, TINAS should be completed before all other assessments during the study visit. Following the study treatment period, the TINAS will be completed once a week for the first 2 months, then once per month for the next 10 months.

[x] With consent to optional research, residual tumor specimens are requested at screening and optional blood samples are requested at screening and at the end of multi-agent therapy visit or end of treatment/early termination visit for collection and storage at the RCR.

[y] With consent to optional research, a blood sample will be requested at screening and at the end of treatment/early termination visit for collection and storage at the Roche Clinical Repository.

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma

SELECTION OF TARGET LESIONS

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions at baseline

  All nodal lesions must measure:

  $>$ 1.5 cm in greatest transverse diameter (GTD) regardless of short axis measurement, or

  $>$ 1.0 cm in short axis regardless of the GTD measurement
- All extranodal lesions must measure $\geq$ 10 mm in the GTD and twice the reconstruction interval of the scan.
- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

Measurable extranodal disease should be assessed in a manner similar to that used for nodal disease. For these recommendations, the spleen is considered nodal disease.

SELECTION OF NON-TARGET LESIONS

Non-target lesions will be qualitatively assessed at each subsequent time point. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions. Examples of non-target lesions include:

- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly and hepatomegaly
- Measurable lesions beyond the maximum number of six
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites
- For this study, a significant increase in existing pleural effusions, ascites, or other fluid collections will be considered sufficient evidence of progression and will not require cytological proof of malignancy. Effusions, ascites or other fluid collections will be followed as non-target lesions.

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma (cont.)

Existing effusions/ascites: Effusions, ascites or other fluid collections will be followed as non-target lesions. At each time point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.

New effusions/ascites: Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions.

REPORTING CONVENTIONS

UNABLE TO EVALUATE (UE) LESION CATEGORY

This category is reserved for target and non-target lesions that are deemed unevaluable because 1) subsequent (post-baseline) examinations had not been performed, 2) lesions could not be evaluated because of poor radiographic technique or poorly defined margins, or 3) lesions identified at baseline were not at a subsequent time point.

Examples of UE lesions are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples the boundaries of the lesion can be difficult to distinguish. Every effort should be made to assign measurements to lesions that develop less distinct margins because they become much smaller. Another example is the instance when lesions identified at baseline were not imaged at a subsequent time point unless the lesions are not imaged because of complete resolution. Lesions that cannot be measured or evaluated will be classified for that time point as UE.

If a target lesion is classified as UE after baseline, the SPD/area (whichever applies) of the target lesions cannot accurately be determined for that time point a response of CR, PR, or SD cannot be assigned for that time point and the response assessment will be UE unless unequivocal progression is determined on the basis of non-target or new lesions, or the evaluable target lesions.

PD can be determined without evaluation of all sites of disease based on the GTD, area or SPD for target lesions, evaluation of unequivocal progression in non-target lesions or observation of a new lesion within the available radiographic or clinical assessments.

TOO SMALL TO MEASURE (TSTM) /BELOW MEASURABLE LIMIT (BML) LESION CATEGORY

Any target lesion findings identified on baseline images, which at a subsequent time point decreases in size to < 5 mm in any dimension, should be categorized as TSTM. The lesion, node or mass should be assigned measurements of 5 mm $\times$ 5 mm (for the

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma (cont.)

GTD and the short axis) on the Source Document for the purpose of calculating the area. If that lesion increases in size to ≥5 mm in any dimension afterward, its true size (GTD and short axis) should be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

Table 1 Timepoint Response

Target Lesions	Non-Target Lesions	New Lesions[1]	Time Point Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE	No	UE
PR	UE	No	UE
PR	CR	No	PR
PR	SD	No	PR
SD	UE	No	UE
SD	CR	No	SD
SD	SD	No	SD
PD	ANY	Yes/No	PD
ANY	PD	Yes/No	PD
ANY	ANY	Yes	PD
UE	Non-PD	No	UE
UE	UE	No	UE
CR	NA[3]	No	CR
PR	NA[3]	No	PR
SD	NA[3]	No	SD
NA[2]	SD	No	SD
NA[2]	CR	No	CR
NA[2]	UE	No	UE
NA[2]	NA[3]	No	UE

Modified version of Cheson et al. 2007.

[1] Identification of new lesions at a post-baseline time point will result in a response assessment of PD. If an identified new lesion subsequently becomes UE, the time point response will be recorded as PD unless the new lesion has proven to have resolved.

[2] No target lesions identified at baseline.

[3] No non-target lesions identified at baseline.

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma (cont.)

Response should be determined on the basis of radiographic and clinical evidence of disease using the modified Cheson et al. (2007) criteria below. For the end-of-treatment response assessment, an FDG-PET scan will be performed approximately 6–8 weeks after completion of after last dose of antibody immunochemotherapy. Assessment of PET should follow the criteria described by Juweid et al. (2007), which is presented in the table, Response Definitions for Clinical Trials.

COMPLETE REMISSION (CR)

To assess response using CT only, the designation of CR requires the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (>20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.
- A second response assessment should be made with incorporation of PET imaging results as follows:
- The designation of CR requires the following: All CR requirements as described above with use of a CT only–determined CR.
- Typically FDG-avid lymphoma: In patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: In patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma (cont.)

PARTIAL REMISSION (PR)

The first response should be based on CT criteria only:

A ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: 1) they should be clearly measurable in at least 2 perpendicular dimensions; 2) if possible, they should be from disparate regions of the body; 3) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

- No increase in the size of the other nodes, liver, or spleen
- Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria but who have persistent morphologic bone marrow involvement will be considered partial responders.
- No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis).

A second response assessment should be made with PET imaging.

- Typically FDG-avid lymphoma: For patients with no pretreatment PET scan or whose PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site.
- Variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

STABLE DISEASE (SD)

- A patient is considered to have stable disease when that patient fails to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see Relapsed Disease [after Complete Remission] or PD [after Partial Remission or Stable Disease]).

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma (cont.)

- Typically FDG-avid lymphoma: PET imaging should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

RELAPSED DISEASE (RD; AFTER CR) OR PROGRESSIVE DISEASE (PD; AFTER PR OR SD)

Lymph nodes should be considered abnormal if the long axis is >1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm, it should only be considered abnormal if its short axis is >1.0. Lymph nodes ≤ 1.0 cm $\times \leq 1.0$ cm will not be considered as abnormal for relapse or progressive disease.

- Appearance of any new lesion >1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of <1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or >1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node >1 cm in its short axis
- Lesions should be PET-positive if observed in a typical FDG-avid lymphoma or the lesion was PET-positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).
- Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.
- In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a study in patients with mucosa-associated lymphoid tissue lymphoma), response should be assessed as above but only using CT scans. However, residual masses should not be assigned unconfirmed CR status but should be considered PRs.

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma (cont.)

Table 2 Response Definitions for Clinical Trials (Revised International Working Group Criteria 2007)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive before therapy; mass of any size permitted if PET negative b) Variably FDG-avid or PET negative; regression to normal size on CT	No palpable, nodules; nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate on morphology and immunohistochemistry; bone marrow should be negative
PR	Regression of measurable disease and no new sites	A ≥ 50% decrease in SPD of up to six largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive before therapy; one or more PET positive at previously involved site b) Variably FDG-avid or PET negative; regression on CT	A ≥ 50% decrease in SPD of nodules (for single nodule in the greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive before therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive before therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive before therapy	50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR = complete response; CT = computed tomography; FDG = ^{18}F-fluorodeoxyglucose; PD = progressive disease; PET = positron-emission tomography; PR = partial response; SPD = sum of the product of the diameters.

Excerpted from: Juweid et al. 2007.

Appendix 2
Modified Revised Response Criteria for Malignant Lymphoma (cont.)

In this study, for purposes described in the exploratory objective, only positron emission tomography and computed tomography (PET and CT) based response criteria will be used. Additionally, if the bone marrow was involved by lymphoma before treatment, the designation of a CR requires normal bone marrow by morphology. If indeterminate by morphology, immunohistochemistry should be negative.

REFERENCES

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007;25:571–8.

Appendix 3
Modified Criteria for Response Assessment: The Lugano Classification

Response should be determined on the basis of radiographic and clinical evidence of disease. For the Primary Response Assessment, an FDG-PET (^{18}F-fluorodeoxyglucose-positron emission tomography) scan will be performed 6–8 weeks after Cycle 6 Day 1 as assessed by IRC and by investigator. Assessment of the PET scan should follow the criteria described by Cheson et al. (2014) presented below.

Selection of measured dominant (indicator) lesions:

- Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters

  A measurable node must have an LDi greater than 1.5 cm.

  A measurable extranodal lesion should have an LDi greater than 1.0 cm.
- 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, and lungs), GI involvement, cutaneous lesions, or those noted on palpation.
- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

Selection of non-measured (non-indicator) 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, and 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).

Appendix 3
Modified Criteria for Response Assessment: The Lugano Classification (cont.)

Modifications to the Lugano Criteria:

- If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (> 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.
- For PET/CT-based PR, criteria for both PET/CT and CT response must be met, defined in table Appendix 3.

Appendix 3
Modified Criteria for Response Assessment: The Lugano Classification (cont.)

Table 1 The Modified Lugano Classification

Response	Site	PET-CT–based Response	CT-based Response
Complete	Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS** It is recognizes that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Appendix 3
Modified Criteria for Response Assessment: The Lugano Classification (cont.)

Table 1 The Modified Lugano Classification (cont.)

Response	Site	PET-CT–based Response	CT-based Response
Partial	Lymph nodes and extralymphatic sites	Score of 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal

Appendix 3
Modified Criteria for Response Assessment: The Lugano Classification (cont.)

Table 1 The Modified Lugano Classification (cont.)

Response	Site	PET-CT–based Response	CT-based Response
Partial (cont).	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
None / Stable	Target nodes/nodal masses, extranodal lesions	Score 4 or 5** with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD for up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Nonmeasured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable

Appendix 3
Modified Criteria for Response Assessment: The Lugano Classification (cont.)

Table 1 The Modified Lugano Classification (cont.)

Response	Site	PET-CT–based Response	CT-based Response
Progressive	Individual target nodes/nodal lesions	Score 4 or 5** with an increase in intensity of uptake from baseline and/or	PPD progression: An individual node/lesion must be abnormal with at least one of the following: • 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 cms
	Nonmeasured lesions	None	New or clear progression of preexisting
	Organ enlargement		In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	New 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-acid foci	New or recurrent involvement

Appendix 3
Modified Criteria for Response Assessment: The Lugano Classification (cont.)

Table 1 The Modified Lugano Classification (cont.)

5-PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

*A 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 under treatment)

**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 3
Modified Criteria for Response Assessment: The Lugano Classification (cont.)

REFERENCES

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

Appendix 4
R-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Sampling Schedule

Ideally, all pharmacokinetic (PK) samples and anti-therapeutic antibody (ATA) samples will 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 ample flushing.

PHASE IB DOSE ESCALATION (R-CHP PLUS POLATUZUMAB VEDOTIN)

The PK sampling schedule below is applicable to patients who receive the rituximab-containing regimen in the dose escalation portion of the study. A total of 16 samples will be collected from each patient treated with R-CHP plus polatuzumab vedotin.

Appendix 4
R-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Sampling Schedule (cont.)

Table 1 PK Sampling Schedule (Phase 1b Dose-Escalation: R-CHP Plus Polatuzumab Vedotin)

Study Visit	Sample Time point(s) [a]	Samples
Cycle 1 Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (± 15 minutes) after the end of the polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 1 Day 8	6 days (± 1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 1 Day 15	13 days (± 1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 2 Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (± 15 minutes) after end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 3 Day 1	Pre-polatuzumab vedotin dose	Polatuzumab vedotin PK (serum and plasma) [b]
	30 minutes (± 15 minutes) post end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 3 Day 8	7 days (± 1 day) post- Day 1 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 4 Day 1	Pre-polatuzumab vedotin dose	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (± 15 minutes) post end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Post-treatment follow-up (Month 3)	Random sample	Polatuzumab vedotin ATA (serum), Polatuzumab vedotin PK (serum and plasma) [b]

ATA = anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

[a] Up to 5-mL whole-blood samples will be taken for polatuzumab vedotin PK (polatuzumab vedotin total antibody, unconjugated MMAE and conjugate [evaluated as antibody conjugated MMAE], and polatuzumab vedotin ATA at each specified time point, with separate tubes for plasma or serum samples.

[b] Polatuzumab vedotin PK, including serum PK samples for conjugate antibody and conjugate (evaluated as antibody conjugated MMAE) and unconjugated MMAE.

Appendix 4
R-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Sampling Schedule (cont.)

PHASE II DOSE EXPANSION (R-CHP PLUS POLATUZUMAB VEDOTIN)

The PK sampling schedule below is applicable to the first 20 patients who receive the rituximab-containing regimen in the dose expansion portion of the study. The remaining 20 patients will follow only the polatuzumab vedotin PK and ATA sampling schedule. Per the sampling schedule (see below), a total of 31 samples will be collected from the first 20 patients treated with R-CHP plus polatuzumab vedotin and a total of 17 samples (for only polatuzumab vedotin PK and ATA) will be collected for the remaining 20 patients.

Appendix 4
R-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Sampling Schedule (cont.)

Table 2 PK Sampling Schedule (Dose-Expansion)

Study Visit	Sample Time point(s) [a]	Samples
Cycle 1 Day 1	Pre-rituximab infusion	Rituximab PK (serum)
	30 minutes (± 15 minutes) post end of rituximab infusion	Rituximab PK (serum)
	End (± 2 minutes) of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	3 hours (± 5 minutes) post end of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	2 hours (± 5 minutes) post end of doxorubicin administration	Doxorubicin PK (plasma)
Cycle 1 Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (±15 minutes) after the end of the polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
	23 hours (±15 minutes) post end of cyclophosphamide infusion on Cycle 1 Day 1	Cyclophosphamide PK (plasma)
	24 hours (±15 minutes) post end of doxorubicin administration on Cycle 1 Day 1	Doxorubicin PK (plasma)
Cycle 1 Day 8	6 days (±1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 1 Day 15	13 days (±1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]

Appendix 4
R-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Sampling Schedule (cont.)

Table 2 PK Sampling Schedule (Dose-Expansion) (cont.)

Study Visit	Sample Time point(s) [a]	Samples
Cycle 2 Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (± 15 minutes) after end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 3, Day 1	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) b
	30 minutes (± 15 minutes) after end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
	End (± 2 minutes) of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	3 hours (± 5 minutes) post end of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	2 hours (± 5 minutes) post end of doxorubicin administration	Doxorubicin PK (plasma)
Cycle 3 Day 2	23 hours (± 15 minutes) post end of cyclophosphamide infusion on Cycle 3 Day 1	Cyclophosphamide PK (plasma)
	24 hours (± 15 minutes) post end of doxorubicin administration on Cycle 3 Day 1	Doxorubicin PK (plasma)
Cycle 4, Day 1	Pre-rituximab dose	Rituximab PK (serum)
	30 minutes (± 15 minutes) post end of rituximab infusion	Rituximab PK (serum)
	Pre-polatuzumab vedotin dose	Polatuzumab vedotin ATA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	30 minutes (± 15 minutes) post end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]

Appendix 4
R-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Sampling Schedule (cont.)

Table 2 PK Sampling Schedule (Dose-Expansion) (cont.)

Study Visit	Sample Time point(s) [a]	Samples
Treatment Completion/ Early Termination	Approximately 15–30 days after last infusion	Polatuzumab vedotin ATA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
Post-treatment follow-up (Month 3)	Random sample	Polatuzumab vedotin ATA (serum), Polatuzumab vedotin PK (serum and plasma) [b]

ATA = anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

[a] Up to 5-mL whole-blood samples will be taken for rituximab PK, polatuzumab vedotin PK (polatuzumab vedotin total antibody, free MMAE and antibody conjugated MMAE), polatuzumab vedotin ATA, polatuzumab vedotin concentration, cyclophosphamide and doxorubicin PK at each specified time point, with separate tubes.

[b] Polatuzumab vedotin PK, including serum PK samples for total antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix 5
G-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Schedule

PHASE IB DOSE ESCALATION (G-CHP PLUS POLATUZUMAB VEDOTIN)

The PK sampling schedule below is applicable to patients who receive the obinutuzumab-containing regimen in the dose escalation portion of the study. Per the sampling schedule (see below), 21 samples will be collected from each patient treated with G-CHP plus polatuzumab vedotin.

Appendix 5
G-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Schedule (cont.)

Table 1 Phase Ib Dose Escalation (G-CHP plus Polatuzumab Vedotin)

Study Visit	Sample Time point(s) [a]	Samples
Cycle 1 Day 1	Pre-obinutuzumab infusion	Obinutuzumab ATA (serum), Obinutuzumab PK (serum)
Cycle 1 Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (±15 minutes) after the end of the polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 1 Day 8	6 days (±1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 1 Day 15	13 days (±1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 2 Day 1	Pre-obinutuzumab infusion	Obinutuzumab ATA (serum), Obinutuzumab PK (serum)
Cycle 2 Day 2	Pre- polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (±15 minutes) after end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 4, Day 1	Pre-obinutuzumab infusion	Obinutuzumab ATA (serum), Obinutuzumab PK (serum)
	Pre-polatuzumab vedotin dose	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (±15 minutes) post end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]

Appendix 5
G-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Schedule (cont.)

Table 1 Phase Ib Dose Escalation (G-CHP plus Polatuzumab Vedotin) (cont.)

Study Visit	Sample Time point(s) [a]	Samples
Post-treatment follow-up (Month 3)	Random sample	Obinutuzumab ATA (serum), Obinutuzumab PK (serum), Polatuzumab vedotin ATA (serum), Polatuzumab vedotin PK (serum and plasma) [b]

ATA = anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

[a] Up to 5-mL whole-blood samples will be taken for polatuzumab vedotin PK (polatuzumab vedotin total antibody, unconjugated MMAE and conjugate [evaluated as antibody conjugated MMAE], polatuzumab vedotin ATA, obinutuzumab PK, and obinutuzumab ATA at each specified time point, with separate tubes for plasma or serum samples.

[b] Polatuzumab vedotin PK, including serum PK samples for conjugate antibody and conjugate (evaluated as antibody conjugated MMAE) and unconjugated MMAE.

Appendix 5
G-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Schedule (cont.)

PHASE II DOSE EXPANSION (G-CHP PLUS POLATUZUMAB VEDOTIN)

The PK sampling schedule below is applicable to the first 20 patients who receive the obinutuzumab-containing regimen in the dose expansion portion of the study. The remaining 20 patients will follow only the polatuzumab vedotin and obinutuzumab PK and ATA sampling schedule. Per the sampling schedule (see below), a total of 38 samples will be collected from the first 20 patients treated with G-CHP plus polatuzumab vedotin and a total of 28 samples (for only polatuzumab vedotin and obinutuzumab PK and ATA) will be collected from the remaining 20 patients.

Appendix 5
G-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Schedule (cont.)

Table 2 Phase II Dose Expansion (G-CHP plus Polatuzumab Vedotin)

Study Visit	Sample Timepoint(s) [a]	Samples
Cycle 1 Day 1	Pre-obinutuzumab infusion	Obinutuzumab ATA (serum), Obinutuzumab PK (serum)
	End of obinutuzumab infusion	Obinutuzumab PK (serum) [b]
	End (± 2 minutes) of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	3 hours (± 5 minutes) post end of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	2 hours (± 5 minutes) post end of doxorubicin administration	Doxorubicin PK (plasma)
Cycle 1 Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ATA (serum); Polatuzumab vedotin PK (serum and plasma) [b]
	30 minutes (±15 minutes) after the end of the polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
	23 hours (±15 minutes) post end of cyclophosphamide infusion on Cycle 1 Day 1	Cyclophosphamide PK (plasma)
	24 hours (±15 minutes) post end of doxorubicin administration on Cycle 1 Day 1	Doxorubicin PK (plasma)
Cycle 1 Day 8	6 days (±1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 1 Day 15	13 days (±1 day) after Day 2 infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 2 Day 1	Pre-obinutuzumab infusion	Obinutuzumab ATA (serum), Obinutuzumab PK (serum)
	End of obinutuzumab infusion	Obinutuzumab PK (serum) [b]
Cycle 2 Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b] Polatuzumab vedotin ATA (serum)
	30 minutes (±15 minutes) after end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]

Appendix 5
G-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Schedule (cont.)

Table 2 Phase II Dose Expansion (G-CHP plus Polatuzumab Vedotin) (cont.)

Study Visit	Sample Timepoint(s) [a]	Samples
Cycle 3, Day 1	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
	30 minutes (± 15 minutes) after end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
	End (± 2 minutes) of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	3 hours (± 5 minutes) post end of cyclophosphamide infusion	Cyclophosphamide PK (plasma)
	2 hours (± 5 minutes) post end of doxorubicin administration	Doxorubicin PK (plasma)
Cycle 3 Day 2	23 hours (± 15 minutes) post end of cyclophosphamide infusion on Cycle 3 Day 1	Cyclophosphamide PK (plasma)
	24 hours (± 15 minutes) post end of doxorubicin administration on Cycle 3 Day 1	Doxorubicin PK (plasma)
Cycle 4, Day 1	Pre-obinutuzumab infusion	Obinutuzumab ATA (serum), Obinutuzumab PK (serum)
	End of obinutuzumab infusion	Obinutuzumab PK (serum) [b]
	Pre-polatuzumab vedotin dose	Polatuzumab vedotin ATA (serum); Polatuzumab vedotin PK (serum and plasma) [b]
	30 minutes (± 15 minutes) post end of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]

Appendix 5
G-CHP Plus Polatuzumab Vedotin Pharmacokinetic and Anti-Therapeutic Antibody Schedule (cont.)

Table 2 Phase II Dose Expansion (G-CHP plus Polatuzumab Vedotin) (cont.)

Study Visit	Sample Timepoint(s) [a]	Samples
Treatment Completion/ Early Termination	Approximately 15–30 days after last infusion	Polatuzumab vedotin ATA (serum); Polatuzumab vedotin PK (serum and plasma) [b]
Post-treatment follow-up (Month 3)	Random sample	Obinutuzumab ATA (serum), Obinutuzumab PK (serum), Polatuzumab vedotin ATA (serum), Polatuzumab vedotin PK (serum and plasma)

ATA = anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

[a] Up to 5-mL whole-blood samples will be collected for rituximab PK, polatuzumab vedotin PK (polatuzumab vedotin total antibody, free MMAE and antibody conjugated MMAE), polatuzumab vedotin ATA, obinutuzumab PK, obinutuzumab ATA, and cyclophosphamide and doxorubicin PK at each specified time point, in separate tubes.

[b] Polatuzumab vedotin PK, including serum PK samples for total antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix 6
Recommendations for the Use of White Blood Cell Growth Factors

PRIMARY PROPHYLACTIC G-CSF ADMINISTRATION (FIRST AND SUBSEQUENT CYCLE USE)

Primary prophylaxis with G-CSF is recommended if **any** of the following clinical factors are present:

- Age $>$ 65 years
- Poor Performance Status
- Previous history of febrile neutropenia
- Open wounds or active infections
- More advanced cancer
- Extensive prior treatment, including large radiation therapy ports
- Cytopenias due to bone marrow involvement by tumor
- Other serious comorbidities

SECONDARY PROPHYLACTIC G-CSF ADMINISTRATION

Prophylactic G-CSF administration is recommended for patients who fulfill each of the following circumstances:

- Experienced a neutropenic complication from a prior cycle of study treatment
- Primary prophylactic G-CSF was not received; and
- The intent is to avoid dose reduction of the ADC, where the effect of the reduced dose on disease-free or treatment outcome is not known

THERAPEUTIC USE OF G-CSF

G-CSF administration should be considered for the following patients:

- Patients with febrile neutropenia who are at high risk for infection-associated complications; or
- Patients who have prognostic factors that are predictive of poor clinical outcome, e.g., prolonged ($>$ 10 days) and profound ($<$ 100/μL) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of fever development

REFERENCES

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

Appendix 7
Recommended Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (ECG, blood pressure, pulse oximetry
- Oxygen and masks for oxygen delivery
- Airway management devices per standard of care
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H1 and H2 blockers)
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Maintain an adequate airway
- Provide oxygen.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 8
International Prognostic Index for Non-Hodgkin's Lymphoma

Table 1 International Prognostic Index (IPI)

International Prognostic Index (IPI)	
Risk Factors	
Ann-Arbor Stage III or IV	
Age > 60 years	
Serum LDH > 1 × ULN	
ECOG Performance Status ≥ 2	
Extranodal involvement ≥ 2	
IPI Risk Group	Number of IPI Risk Factors
Low	0 or 1
Low-intermediate	2
High-intermediate	3
High	4 or 5

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; ULN = upper limit of normal.

The results of FDG-PET should not be taken into account for calculation of IPI as this prognostic score was established without FDG-PET.

Adapted from: Shipp et al. 1993.

REFERENCES

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

Appendix 9
Total Neuropathy Score Clinical Assessment

Table 1 Total Neuropathy Score – Nurse (TNSn)

TNSn	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms extend above knees or elbows
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/ assistance	Paralysis
Autonomic symptoms	None	1 yes	2 yes	3 yes	4 or 5 yes
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee

Sources: Cavaletti et al. 2006, 2007.

REFERENCES

Cavaletti G, Frigeni B, Lanzani F, et al. The total neuropathy score as assessment tool for grading the course of chemotherapy-induced peripheral neurotoxicity: comparison with the National Cancer Institute-Common Toxicity Scale. J Peripher Nerv Syst 2007;12:210–5.

Cavaletti G, Jann S, Pace A, et al. Multi-center assessment of the total neuropathy score for chemotherapy-induced peripheral neurotoxicity. J Peripher Nerv Syst 2006;11:135–41.

Appendix 10
Therapy-Induced Neuropathy Assessment Scale (TINAS)

	Not present 0	1	2	3	4	5	6	7	8	9	As bad as you can imagine 10
1. Hot or burning sensations in hands or feet at their worst?	○	○	○	○	○	○	○	○	○	○	○
2. Sensations of 'pins and needles' in arms or legs at their worst?	○	○	○	○	○	○	○	○	○	○	○
3. Numbness or tingling in your hands or feet at its worst?	○	○	○	○	○	○	○	○	○	○	○
4.Sensations of 'electric shock' at their worst?	○	○	○	○	○	○	○	○	○	○	○
5. Pain when touching cold things at its worst?	○	○	○	○	○	○	○	○	○	○	○
6. Cramps in your hands or feet at their worst?	○	○	○	○	○	○	○	○	○	○	○
7. Discomfort when touching things at its worst?	○	○	○	○	○	○	○	○	○	○	○
8. Discomfort when your skin comes into contact with something (e.g. blanket, clothing) at its worst?	○	○	○	○	○	○	○	○	○	○	○
9. Trouble grasping small objects (e.g. buttoning buttons, handling coins, holding a pen) at its worst?	○	○	○	○	○	○	○	○	○	○	○
10. Trouble walking due to loss of feeling in your legs or feet at its worst?	○	○	○	○	○	○	○	○	○	○	○
11. Difficulty with your balance due to loss of feeling in your legs or feet at its worst?	○	○	○	○	○	○	○	○	○	○	○

Source: Thomas et al. 2012.

REFERENCES

Thomas SK, Mendoza TR, Vichaya EG, et al. Validation of the chemotherapy-induced neuropathy scale. J Clin Oncol 2012;30(Suppl 15):9140.