PROTOCOL

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY, TOLERABILITY AND ANTI-TUMOR ACTIVITY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH RITUXIMAB (R) OR OBINUTUZUMAB (G) PLUS BENDAMUSTINE (B) IN RELAPSED OR REFRACTORY FOLLICULAR OR DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	GO29365
VERSION NUMBER:	8
EUDRACT NUMBER:	2014-001361-28
IND NUMBER:	109409
NCT NUMBER:	*NCT02257567*
TEST PRODUCTS:	Polatuzumab vedotin, liquid (DCDS4501A) Polatuzumab vedotin, lyophilized (DCDS4501S)
MEDICAL MONITOR:	[redacted], *Pharm.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 23 May 2014

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
23-Mar-2020 16:56:09	Company Signatory	[redacted]

CONFIDENTIAL

DATES AMENDED:

Version 2: 27 April 2015
Version 3: 14 September 2015
Version 4: 11 July 2017
Version 5: 16 November 2017
Version 6: 31 May 2018
Version 7: 2 October 2018
Version 8: See electronic date stamp.

PROTOCOL AMENDMENT, VERSION 8:
RATIONALE

Protocol GO29365 has been amended to implement the following changes:

- Safety language for polatuzumab vedotin relating to the recategorization of identified risks has been updated to align with the informed consent form and the Investigator's Brochure (Section 5.1.1).
- Safety language for bendamustine relating to hepatitis B reactivation and skin reactions has been updated to align with the informed consent form and the United Kingdom Summary of Product Characteristics (Section 5.1.3).
- Medical Monitor and Emergency Medical Contact information has been updated (Section 5.4.1).
- Updated reporting requirements for cases of second malignancies to be reported indefinitely for all enrolled subjects (Sections 5.3.1, 5.4.2.2, and 5.6).
- Updated reporting requirements for cases of accidental overdose or medication error, which are no longer required to be reported within 24 hours after learning of the event (Section 5.3.5.12).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy *of the signed form to your local study monitor.*

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY, TOLERABILITY AND ANTI-TUMOR ACTIVITY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH RITUXIMAB (R) OR OBINUTUZUMAB (G) PLUS BENDAMUSTINE (B) IN RELAPSED OR REFRACTORY FOLLICULAR OR DIFFUSE LARGE B-CELL LYMPHOMA**
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PHASE:	Ib/II
INDICATION:	Follicular Lymphoma and Diffuse Large B-Cell Lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary Objectives (Main Study)

This section outlines the primary objectives for the main study cohorts (i.e., Phase Ib, Phase II expansion, and Phase II randomized cohorts in patients with relapsed or refractory [R/R] diffuse large B-cell lymphoma (DLBCL) and R/R follicular lymphoma [FL]), which use the initial liquid formulation of polatuzumab vedotin.

The primary objectives of the Phase Ib portion of the study are as follows:

- To assess the safety and tolerability of the combination of polatuzumab vedotin with bendamustine and rituximab (BR) or bendamustine and obinutuzumab (BG) when administered to patients with R/R FL or DLBCL
- To identify the Recommended Phase II Dose (RP2D) for polatuzumab vedotin given in combination with BR or with BG in patients with R/R FL or DLBCL

The primary objective of the Phase II portion of the study is as follows:

- To evaluate the efficacy of the combination of polatuzumab vedotin plus BR compared with BR alone in patients with R/R FL or DLBCL as measured by positron emission tomography (PET)-defined *complete response (*CR*)* rate using Modified Lugano Response Criteria (PET–computed tomography [CT] criteria) at the time of primary response assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) and as defined by the Independent Review Committee (IRC)

Secondary Objectives (Main Study)

This section outlines the secondary and exploratory objectives for the main study cohorts (i.e., Phase Ib, Phase II expansion, and Phase II randomized cohorts in R/R DLBCL and R/R FL), which use the initial liquid formulation of polatuzumab vedotin.

Safety Objectives

The safety objectives for this study are as follows:

- To assess the safety and tolerability of the combination of polatuzumab vedotin with BR or BG when administered to patients with R/R FL or DLBCL during the Phase II portion of the study
- To assess the immunogenicity of polatuzumab vedotin and obinutuzumab, as measured by the formation of anti-drug antibodies (ADAs)
- To assess the potential relationships of such ADAs (anti-polatuzumab vedotin and anti-obinutuzumab) formation with other outcome measures (e.g., pharmacokinetics, efficacy, safety)

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the pharmacokinetics of polatuzumab vedotin in combination with BR or BG in patients with R/R FL or DLBCL
- To assess potential PK interactions between polatuzumab vedotin and BR or BG
- To evaluate the PK exposure response (e.g., efficacy, safety) relationship

Secondary Efficacy Objectives (Main Study)

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of the combination of polatuzumab vedotin and BR compared with BR alone according to Modified Lugano 2014 response criteria as measured by:
  - CR at the time of Primary Response Assessment based on PET–CT, as determined by the investigator
  - Objective response (OR; CR or partial response [PR]) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
  - CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
  - OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
  - Best objective response (BOR; CR or PR) while on study either by PET-CT or CT only, as determined by the investigator
  - DLBCL cohorts only: BOR, DOR and PFS based on PET-CT or CT, as determined by IRC
- To evaluate the efficacy of the combination of polatuzumab vedotin plus BG according to Modified Lugano 2014 response criteria as measured by:
  - CR at the time of Primary Response Assessment based on PET-CT, as determined by the investigator and IRC
  - OR (CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
  - CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
  - OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
  - BOR (BOR, CR, or PR) while on study either by PET-CT or CT only as determined by the investigator
  - DLBCL cohorts only: BOR, DOR, and PFS while on study by either PET-CT or CT only, as determined by IRC

Patient-Reported Outcome Objective

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

- To make a preliminary assessment of biomarkers related to the drug targets and mechanism of action of polatuzumab vedotin and/or rituximab or obinutuzumab, and/or of biomarkers related to disease biology and/or assessments that inform the improvement of diagnostic tools, and that might predict disease response or resistance to treatment with polatuzumab vedotin in combination with BR or BG in R/R FL or DLBCL, including but not limited to, the following:
  - CD79b expression
  - DLBCL prognostic subtype (*activated B-cell type* [ABC]*/ germinal center B-cell type* [GCB])
  - Lymphoma-associated mutations and markers of tumor immunobiology
  - Regulators of apoptosis such as BCL-2
  - Minimal residual disease (MRD) as quantified by measurements of lymphoma-specific markers DNA extracted from peripheral blood. Lymphoma-specific markers from blood will be compared to those measured in DNA extracted from baseline tissue to identify the originating clone.
- To evaluate the prognostic significance of interim PET-CT assessment

The exploratory efficacy objectives for this study are to evaluate longer-term outcomes for patients using the Modified Lugano 2014 response criteria, as measured by the following:

- Duration of response (DOR) based on PET-CT or CT only, as determined by the investigator
- Progression-free survival (PFS) based on PET-CT or CT only, as determined by the investigator
- Event-free survival (EFS) based on PET-CT or CT only, as determined by the investigator
- Overall survival (OS)

Objectives for the New Formulation (*NF;* Lyophilized) Cohort

Arm G

Primary Objective

The primary objective for Arm G is to evaluate the pharmacokinetics and safety of polatuzumab vedotin (lyophilized) plus BR in patients with R/R DLBCL, as follows:

- Pharmacokinetics: To characterize the pharmacokinetics of polatuzumab vedotin (lyophilized) in combination with BR in patients with R/R DLBCL
- Safety: To assess the safety and tolerability of polatuzumab vedotin (lyophilized) in combination with BR

Secondary Objectives

Efficacy

The secondary objective for Arm G is to evaluate the efficacy of the combination of polatuzumab vedotin (lyophilized) plus BR as measured by and using Modified Lugano Response Criteria, as follows:

- CR at the time of Primary Response Assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study medication) based on PET-CT, as determined by investigator and IRC
- OR (CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC

- CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- BOR (CR or PR) while on study either by PET-CT or CT only, as determined by the investigator and IRC
- DOR based on PET-CT or CT only, as determined by the investigator and IRC
- PFS based on PET-CT or CT only, as determined by the investigator and IRC
- EFS based on PET-CT or CT only, as determined by the investigator
- OS

Safety

The safety objective for Arm G is to assess the immunogenicity of polatuzumab vedotin (lyophilized) as measured by the formation of ADAs.

Arm H

Primary Objective

The primary objective for Arm H of the study is to evaluate the efficacy of the combination of polatuzumab vedotin (lyophilized) plus BR in patients with R/R DLBCL, as measured by PET-CT–defined CR rate (using the Modified Lugano Response Criteria) at the time of Primary Response Assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) and as defined by the IRC.

Secondary Efficacy Objectives

The secondary efficacy objective for Arm H is to evaluate the efficacy of the combination of polatuzumab vedotin (lyophilized) plus BR, as measured by and using the Modified Lugano Response Criteria, as follows:

- CR at the time of Primary Response Assessment based on PET-CT, as determined by investigator
- OR (CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
- BOR (CR or PR) while on study either by PET-CT or CT only, as determined by the investigator and IRC
- DOR based on PET-CT or CT only, as determined by the investigator and IRC
- PFS based on PET-CT or CT only, as determined by the investigator and IRC
- EFS based on PET-CT or CT only, as determined by the investigator
- OS

Safety Objectives

The safety objectives for Arm H are as follows:

- To assess the safety and tolerability of polatuzumab vedotin (lyophilized) in combination with BR
- To assess the immunogenicity of polatuzumab vedotin (lyophilized), as measured by the formation of ADAs

Pharmacokinetic Objectives

The PK objective is to characterize the pharmacokinetics of polatuzumab vedotin (lyophilized) in combination with BR in patients with R/R DLBCL.

Exploratory Objectives

The exploratory objective for this arm of the study is to assess biomarkers related to the drug target and mechanism of action of polatuzumab vedotin and/or rituximab, and/or of biomarkers related to disease biology and/or assessments that inform the improvement of diagnostic tools,

and that might predict disease response with polatuzumab vedotin in combination with BR in R/R DLBCL, including, but not limited to, the following:

- CD79b expression
- DLBCL prognostic subtype (ABC/GCB)
- Regulators of apoptosis such as BCL-2 or c-MYC

Study Design

Description of Study

This design is a Phase Ib/II, multicenter, open-label study of polatuzumab vedotin administered by *intravenous (*IV*)* infusion in combination with standard doses of bendamustine (B) and rituximab (R) or obinutuzumab (G) in patients with relapsed or refractory FL or DLBCL. The study will consist of two stages: a Phase Ib safety run-in stage and a Phase II stage. The dose of polatuzumab vedotin in combination with BR or BG will be determined during the safety run–in stage of the study, separately for each lymphoma subtype (FL and DLBCL), and will be used in combination with BR or BG in the Phase II stage. The Phase II stage will be randomized for patients treated with R-containing regimens and be non-randomized for patients treated with the G-containing regimen. Throughout the study, there will be concurrent enrollment of patients having either FL or DLBCL.

The study will begin with a safety run-in stage followed by a randomization and expansion phase. During the safety run-in phase, 6 patients will be treated with polatuzumab vedotin in combination with the BR regimen. Once this cohort is safely cleared, 6 patients will be treated at the same dose level of polatuzumab vedotin in combination with the BG regimen. If the first 6 patients in the polatuzumab vedotin plus BR cohort safely clears after the first cycle, then the randomized Phase II stage comparing BR-containing regimens will commence and patients will be randomized to either polatuzumab vedotin plus BR or to BR alone (control arm). Randomization will occur separately for each of the two disease-specific cohorts of patients with either FL or DLBCL. If the first 6 patients in the polatuzumab vedotin plus BG cohort safely clear the first cycle, then the expansion stage for obinutuzumab-containing regimen will commence. Patients receiving polatuzumab vedotin plus BG will be enrolled into two expansion cohorts on the basis of histology of FL or DLBCL in order to expand the safety database and collect preliminary anti-lymphoma activity data.

The Phase II randomization portion of the study can commence once the safety run-in of the polatuzumab vedotin plus BR cohort has completed, which can occur before the BG safety run–in cohort is completed. The Phase II expansion portion of the study can commence once the safety run-in of the polatuzumab vedotin plus BG cohort has been completed.

Sites cannot enroll patients in rituximab-containing and obinutuzumab-containing phases simultaneously within the same histology.

The NF Cohort (Arm G and Arm H) is separate from the expansion and randomized phases of the main study.

In Arm G of the NF Cohort, patients with R/R DLBCL will be treated with polatuzumab vedotin (lyophilized) in combination with BR to gain clinical PK and safety experience with the new lyophilized formulation of polatuzumab vedotin. The NF Cohort is separate from the expansion and randomized phases. Initially, up to 30 patients were to be enrolled in order to ensure adequate number of PK-evaluable patients. Enrollment has been expanded to approximately 40 patients, which will include approximately 10 second-line (2L) patients (patients with one prior line of therapy) in order to evaluate the efficacy of polatuzumab vedotin (lyophilized) in combination with *BR* in the 2L setting. A PK-evaluable patient is defined as a patient from whom, at minimum, the PK samplings of all three analytes (i.e., total antibody, *antibody conjugated mono-methyl auristatin E [*acMMAE*]*, and unconjugated *mono-methyl auristatin E [*MMAE*]*) at Cycle 1 through Cycle 2, Day 1 are obtained.

In Arm H of the NF Cohort, patients with R/R DLBCL will be treated with polatuzumab vedotin (lyophilized) in combination with BR to further evaluate the clinical efficacy, to gain additional safety experience, and to expand evaluation in exploratory biomarker subsets. Approximately 60 patients in total will be enrolled in this arm. A minimum of approximately 30% of patients who have previously received only one prior line of therapy (i.e., 2L therapy) will be enrolled in

Arm H, and prioritization may be given to ensure such enrollment is achieved upon completion of enrollment in this arm.

Study treatment will be given in 28-day cycles for patients with FL and in 21-day cycles for patients with DLBCL. The first day of treatment will constitute Study Day 1. Patients will be treated up to a total of six cycles.

All patients will be evaluated for safety and efficacy according to the schedules of assessments.

All patients will be assessed for response to treatment by the investigator with the use of standard criteria according to the Modified Lugano Response Criteria at screening and at the following timepoints:

- Interim response assessment (between Cycle 3, Day 15 and Cycle 4, Day 1)
- Primary response assessment: 6–8 weeks after completion of study treatment (i.e., Day 1 of Cycle 6 or after last dose of study drug)

Imaging at these timepoints must include FDG-PET (^{18}F-fluorodeoxyglucose-positron emission tomography) 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 patients with either FL or DLBCL for the Phase Ib safety run-in stage at approximately 25 sites in the United States and Canada (up to 12 patients with the BR regimen and up to 12 patients with the BG regimen).

Approximately 80 sites globally will participate in the Phase II stage of the study, in which approximately 160 patients *with either R/R FL or R/R DLBCL* will receive a BR-containing regimen in the randomization portion and *approximately* 40 patients *with either R/R FL or R/R DLBCL* will receive a BG-containing regimen in the safety expansion portion.

Arm G of the Phase II NF Cohort will enroll approximately 40 patients with R/R DLBCL who will receive polatuzumab vedotin (lyophilized) with BR. Approximately 30–35 sites of the total sites in the study will participate in this portion of the study.

Arm H of the Phase II NF Cohort will enroll approximately 60 patients with R/R DLBCL who will receive polatuzumab vedotin (lyophilized) with BR. Approximately 45–50 sites will participate in this arm.

Target Population

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed *Informed Consent Form*
- Age ≥18 years
- Able to comply with the study protocol, in the investigator's judgment
- Histologically confirmed FL (Grade 1, 2, or 3a) or DLBCL
- Must have received at least one prior therapy for FL or DLBCL. Patients must have either relapsed or have become refractory to a prior regimen as defined below.

  R/R FL

  Relapsed to prior regimen(s) after having a documented history of response (CR, CR unconfirmed [CRu], or PR) of ≥6 months in duration from completion of regimen(s)

  Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy

  R/R DLBCL

  Patients who are ineligible for second-line stem cell transplant (SCT), with progressive disease or no response (stable disease [SD]) <6 months from start of initial therapy (2L refractory)

Patients who are ineligible for second-line SCT, with disease relapse after initial response ≥6 months from start of initial therapy (2L relapsed)

Patients who are ineligible for third-line (or beyond) SCT, with progressive disease (PD) or no response (SD) <6 months from start of prior therapy (3L+refractory)

Patients who are ineligible for third-line (or beyond) SCT with disease relapse after initial response ≥6 months from start of prior therapy (3L+relapsed)

In addition to the above defined responses to prior regimens, the Phase II NF Cohort (Arm G and Arm H) includes the following diagnoses by 2016 World Health Organization (WHO) classification of lymphoid neoplasms:

- DLBCL, not otherwise specified (NOS) (including both GCB type and ABC type)
- T-cell/histiocyte-rich large B-cell lymphoma
- High-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements
- High grade B-cell lymphoma, NOS
- Primary mediastinal (thymic) large B-cell lymphoma
- Epstein-Barr virus positive DLBCL, NOS

- If the patient has received prior bendamustine, response duration must have been >1 year (for patients who have relapse disease after a prior regimen)
- At least one bi-dimensionally measurable lesion on imaging scan defined as >1.5 cm in its longest dimension
- Confirmed availability of archival or freshly collected tumor tissue prior to study enrollment

  The Phase II NF Cohort (Arm G and Arm H) will be required to submit tissue and pathology report for central pathology review.
- Life expectancy of at least 24 weeks
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Adequate hematologic function unless inadequate function is due to underlying disease, such as extensive bone marrow involvement or hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator. Adequate hematologic function is defined as follows:
  - Hemoglobin ≥9 g/dL
  - *Absolute neutrophil count* ≥1.5×10^9/L
  - Platelet count ≥75×10^9/L
- For women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea and age > 45 years) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent *(refrain from heterosexual intercourse)* or to use single highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for ≥ 12 months after the last dose of rituximab or for ≥18 months after the last dose of obinutuzumab, and agreement to refrain from donating eggs.

  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.

  Examples of highly effective contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

- 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 or to use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 6 months after the 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 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

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

- History of severe allergic or anaphylactic reactions to humanized or murine *monoclonal antibody (*MAbs*;* or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to bendamustine, rituximab, or obinutuzumab
- History of sensitivity to mannitol (mannitol is an excipient in bendamustine)
- Prior use of any *MAb,* radioimmunoconjugate, or antibody drug conjugate (ADC) within 5 half-lives or 4 weeks, whichever is longer, before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1, Day 1

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

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

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

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

    Ongoing corticosteroid usage is permitted for the purpose of lymphoma symptom control.
- Treatment with chimeric antigen receptor T-cell therapy within 100 days prior to Cycle 1, Day 1
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic *SCT*
- Eligibility for autologous SCT
- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Primary or secondary CNS lymphoma
- Current Grade >1 peripheral neuropathy

- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include, but are not limited to:

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

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

  Patients with low-grade, early-stage prostate cancer with no requirement for therapy at any time prior to study are eligible.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Patients with suspected or latent tuberculosis

  Latent tuberculosis should be confirmed according to local testing requirements.
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

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

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

  For patients with unknown HIV status, HIV testing will be performed at Screening if required by local regulations
- Known infection human T-cell leukemia virus 1 (HTLV-1) virus
- Vaccination with a live vaccine within 28 days prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1, Day 1) other than for diagnosis
- Women who are pregnant or lactating or who intend to become pregnant within a year of the last dose of study treatment in the rituximab cohorts or within 18 months of the last dose of study treatment in the obinutuzumab cohort
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:

  Creatinine >1.5×upper limit of normal (ULN) or a measured creatinine clearance <40 mL/min

  AST or ALT >2.5×ULN

  Total bilirubin ≥1.5×ULN. Patients with documented Gilbert disease may be enrolled if total bilirubin is ≤3×ULN

  International normalized ratio (INR) or *prothrombin time* (PT) >1.5×ULN in the absence of therapeutic anticoagulation

*Partial thromboplastin time (*PTT*)* or *activated partial thrombopastin time (*aPTT*)* >1.5×ULN in the absence of a lupus anticoagulant

- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

End of Study

The end of the study is defined as the timepoint at which all patients enrolled in the study have either had at least 2 years of follow-up from the time of the treatment-completion visit or have discontinued the study.

Length of Study

The length of study will be the time from screening of the first enrolled patient through 2 years after the treatment completion visit for the last enrolled patient. The length of study is expected to be 50 months.

Outcome Measures

Safety Outcome Measures

The determination of the polatuzumab vedotin RP2D in combination with BR or BG will be assessed using the following primary safety outcome measures for the Phase Ib portion of the study:

- 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
- Formation of ADAs

These safety outcome measures will also be assessed in the Phase II NF Cohort (Arm G and Arm H), in which patients with R/R DLBCL will be administered polatuzumab vedotin (lyophilized) plus BR.

Efficacy Outcome Measures

Response assessment will be determined according to Modified Lugano Response Criteria for Malignant Lymphoma.

- CR at primary response assessment (6–8 weeks after Cycle 6, Day 1, or last dose of study drug) based on PET–CT, as determined by the investigator and IRC
- OR (CR or PR) at primary response assessment based on PET–CT, as determined by the investigator and IRC
- CR at primary response assessment based on CT only, as determined by the investigator and IRC
- OR (CR or PR) at primary response assessment based on CT only, as determined by the investigator and IRC
- BOR (CR or PR) while on study based on PET–CT or CT only, as determined by the investigator
- NF cohort only: OS and EFS based on PET–CT or CT only, as determined by the investigator

In addition, for the DLBCL cohorts, IRC *and investigator*-assessed BOR, DOR and PFS will be performed.

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum and plasma concentrations of polatuzumab vedotin, bendamustine, rituximab, and obinutuzumab versus time

- PK parameters based on concentration–time data for polatuzumab vedotin, bendamustine, rituximab, and obinutuzumab when these drugs are given in combination

Serum and plasma concentrations of bendamustine and rituximab will not be assessed in the Phase II NF Cohort (Arm G and Arm H).

Patient-Reported Outcome Measure

The PRO measure for this study is as follows:

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

PRO measures will not be collected for the Phase II NF Cohort (Arm G and Arm H).

Exploratory Outcome Measures

The exploratory biomarker outcome measures for this study are as follows:

- Biomarkers related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab or obinutuzumab. These include, but are not limited to, the assessment of potentially prognostic subsets (i.e., cell of origin), CD79b expression levels, apoptotic regulators (e.g., BCL-2), markers of immune infiltration and/or regulation (e.g., CD8, PD-L1), and identification of other potential prognostic factors.
- Biomarkers will be assessed retrospectively using a tissue block (preferred) or 15 serial freshly cut, unstained slides plus punch biopsy of the tissue block from the time of initial diagnosis and, if possible, at the time of disease progression.
- For quantitative assessment of MRD levels of the lymphoma clone in circulation, blood will be collected at baseline, between Cycle 3, Day 15 and Cycle 4, Day 1, and at end of treatment corresponding to tumor assessments.

Biomarkers will not be collected or assessed in Arm G of the Phase II NF Cohort.

Analysis methods will include immunohistochemistry, RNA-based assessment of gene expression, next-generation sequencing of lymphoma DNA in tissue and in peripheral blood to determine the levels of the lymphoma clone. This analysis will enable a better understanding of the underlying biology of these tumors and how polatuzumab vedotin and rituximab or obinutuzumab alter their clinical course. Other exploratory analyses may be conducted should additional slides remain following the planned biomarker analyses.

The exploratory efficacy outcome measures for this study are as follows:

- 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, for the subgroup of patients with a BOR of CR or PR, based on PET–CT or CT only, as determined by the investigator assessment
- PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause, based on PET–CT or CT only, as determined by the investigator assessment
- EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression, relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET–CT or CT only, as determined by the investigator assessment.
- OS, defined as the time from the date of randomization or first treatment (for G-containing arms) to the date of death from any cause

<u>Investigational Medicinal Products</u>

Test Product: Polatuzumab Vedotin

Test Products: Rituximab, Bendamustine, Obinutuzumab

- Polatuzumab vedotin plus BR regimen

  Patients will receive rituximab 375 mg/m^2 intravenously on Day 1 of Cycle 1 and on Day 1 of each subsequent cycle for up to six cycles. Following rituximab infusion,

polatuzumab vedotin will be administered on Day 2 of Cycle 1, then on Day 1 of each subsequent cycle. Bendamustine 90 mg/m^2 will be administered intravenously on Days 2 and 3 of Cycle 1, then on Days 1 and 2 of each subsequent cycle.

- Polatuzumab vedotin plus BG regimen

  Patients will receive obinutuzumab 1000 mg intravenously on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent cycle for up to six cycles. Following obinutuzumab infusion, polatuzumab vedotin will be administered on Day 2 of Cycle 1, then on Day 1 of each subsequent cycle. Bendamustine 90 mg/m^2 will be administered intravenously on Days 2 and 3 of Cycle 1, then on Days 1 and 2 of each subsequent cycle.

Comparator (Phase II Randomized Portion of Study)

- BR regimen

  Patients will receive rituximab 375 mg/m^2 intravenously on Day 1 of Cycle 1 and on Day 1 of each subsequent cycle for up to six cycles. Following rituximab infusion, bendamustine 90 mg/m^2 will be administered intravenously on Days 2 and 3 of Cycle 1, then on Days 1 and 2 of each subsequent cycle.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Determination of Sample Size

The purpose of this study is to evaluate the safety, tolerability, and efficacy of polatuzumab vedotin in combination with BR or BG.

Phase Ib: Safety Run-In Stage

In this study, approximately 24 patients will be enrolled during the safety run-in portion of the study. This corresponds to treating a minimum 6 FL and 6 DLBCL patients with polatuzumab vedotin in combination with BR and 6 FL and 6 DLBCL patients with polatuzumab vedotin in combination with BG. A combination will be deemed safe for the purpose of moving to the Phase II part of the study as long as $<$2 safety events are observed in a given 6-patient cohort as this is consistent with requirements for identification of a candidate RP2D based upon a standard 3+3 design.

Phase II: Randomized and Expansion Stage

A total of 200 patients will be enrolled in Phase II (40 patients for each treatment arm and histology in the rituximab-containing regimens and 20 patients for each histology group in the obinutuzumab-containing regimen). In total, enrollment of approximately 224 patients is planned in order to evaluate the safety and efficacy of polatuzumab vedotin when combined with BR or BG. The expected enrollment duration is approximately 25 months and the total study duration is anticipated to be approximately 50 months.

The primary efficacy endpoint is CR rate as determined by PET-CT scan at the primary response assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) as assessed by IRC. The primary analysis will be estimation of treatment-specific PET-CT CR rates as well as the difference in PET-CT CR rates between patients randomized to treatment with polatuzumab vedotin in combination with BR and those randomized to treatment with BR alone for each histological subtype.

With 40 patients per arm, 95% exact Clopper-Pearson CIs for estimation of the true CR rate for would have a margin of error not exceeding $\pm$17%. The following tables show Clopper-Pearson exact 95% CIs corresponding to observed CR rates ranging from 60% to 80% based on sample sizes of 40 and 20, respectively. With 40 patients and an observed CR rate of at least 60%, a true CR rate below 43% can be ruled out with 95% confidence. With 20 patients and an observed CR rate of at least 60%, a true CR rate below 36% can be ruled out with 95% confidence. In addition, with 40 patients in each arm, assuming a 40% CR rate in the BR arm, and a 25% increase in CR rate when polatuzumab vedotin is added to BR, the 95% CI for the difference in CR rates is (3.8%, 46.2%).

Clopper-Pearson Exact 95% Confidence Intervals for Assumed Observed CR Rates based on Sample Size of 40 Patients

Polatuzumab vedotin+ BR CR rate	No. of Patients with CR (95% CI for rate)
80%	32 (64%, 91%)
75%	30 (59%, 87%)
70%	28 (53%, 83%)
65%	26 (48%, 79%)
60%	24 (43%, 75%)

BR=bendamustine+rituximab; CR=complete response.

Clopper-Pearson Exact 95% Confidence Intervals for Assumed Observed CR Rates based on Sample Size of 20 Patients

Polatuzumab vedotin+BG CR rate	No. of Patients with CR (95% CI for rate)
80%	16 (56%, 94%)
75%	15 (51%, 91%)
70%	14 (46%, 88%)
65%	13 (41%, 85%)
60%	12 (36%, 81%)

BG=bendamustine+obinutuzumab; CR=complete response.

With respect to assessment of safety based on a sample size of 20 in each of the BG arms, the chance of observing at least one adverse event with true incidence of ≥10% is at least 88%. With 40 patients in each of the BR arms, there is at least an 87% chance of observing at least one adverse event with true incidence of ≥5%.

Phase II: New Formulation Cohort

Arm G

For the NF Cohort (Arm G), the original sample size was approximately 20–30 patients. The objective of this cohort is to gain clinical PK experience with polatuzumab vedotin (lyophilized) in combination with BR in R/R DLBCL patients. The currently proposed PK sampling scheme is considered sufficient to characterize the pharmacokinetics of polatuzumab vedotin related analytes by using the population PK analysis approach. PK and safety outcomes will be descriptive. Safety will be analyzed as described for the other cohorts.

The sample size for Arm G was initally planned to be approximately 20–30 patients with the goal of obtaining 20 PK-evaluable patients. PK evaluable is defined as the patient having at minimum PK data of all three analytes collected from Cycle 1 until Cycle 2, Day 1 after dosing of polatuzumab vedotin. Since this evaluation is not a comparison of two randomized arms, it is not appropriate to prespecify the criteria of PK comparability. However, when compared to the available data for patients that received Phase I/II material, 20 patients would achieve >80% power to obtain a 90% confidence interval for the geometric mean ratio (GMR) that falls within the 80%–125% range, assuming that the true GMR equals 1.05 and the inter-individual variability of acMMAE area under the concentration time–curve (AUC) equals 20%.

In order to provide confirmatory support of the efficacy observed in the polatuzumab vedotin+BR arm in the randomized cohort, an additional 10 patients with one prior line of therapy will be enrolled into this NF cohort to achieve similar representation of patients by lines of therapy.

The total sample size of 40 (30+10) patients from Arm G would provide at least 87% power to detect PET CR of 40% under the hypotheses below, with one-sided $\alpha = 2.5\%$ for exact binomial one-sample test:

H0: PET CR rate $\leq$ 17.5%, H_1: PET CR rate >17.5%

Arm H

In order to further evaluate the clinical efficacy among patients with R/R DLBCL who are ineligible for transplant who received the new lyophilized formulation of polutuzumab vedotin in combination with BR, an additional arm (Arm H) has been added to the NF Cohort, which includes approximately an additional 60 patients with R/R DLBCL. Under the assumption of 40% PET-assessed CR rate at Primary Response Assessment, combining the 40 patients in Arm G of the NF Cohort with the 60 patients in Arm H (100 patients [40+60]) will provide a more precise 95% CI (Clopper-Pearson exact CI) of (30%, 50%) (see the table below). Furthermore, this 95% CI completely excludes the 95% CI [17.5% (11%, 26%)] of the CR rate observed in the randomized BR arm with an assumed number of 100 patients.

Estimated Polatuzumab Vedotin plus BR Complete Response Rate in R/R DLBCL

	n=40		n=60		n=100	
CR Rate	No. of Patients with CRs	95% CI of Rate	No. of Patients with CRs	95% CI of Rate	No. of Patients with CRs	95% CI of Rate
60%	24	(43%, 75%)	36	(47%, 72%)	60	(50%, 70%)
55%	22	(38%, 71%)	33	(42%, 68%)	55	(45%, 65%)
50%	20	(34%, 66%)	30	(37%, 63%)	50	(40%, 60%)
45%	18	(29%, 62%)	27	(32%, 58%)	45	(35%, 55%)
40%	16	(25%, 57%)	24	(28%, 53%)	40	(30%, 50%)
35%	14	(21%, 52%)	21	(23%, 48%)	35	(26%, 45%)
30%	12	(17%, 47%)	18	(19%, 43%)	30	(21%, 40%)

BR=bendamustine and rituximab; CI=confidence interval; CR=complete response; DLBCL=diffuse large B-cell lymphoma; R/R=relapsed or refractory.

Primary Efficacy Endpoint

CR at Primary Response Assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) as measured by PET-CT scan and as determined by an IRC will be used as the primary efficacy endpoint. This primary efficacy endpoint applies to the Phase II randomized cohorts treated with polatuzumab vedotin plus BR versus BR, as well as Arm H of the NF Cohort (individually and together with Arm G). The CR rate, defined as the percentage of patients with CR, will be estimated and the corresponding Clopper-Pearson exact 95% CI will be constructed for each treatment arm. The difference in CR rates between the combination of polatuzumab vedotin+BR and BR randomized arms will be estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution. An exploratory comparison of CR rates for the BR-containing regimens will be conducted using the Cochran Mantel Haenszel χ^2 test adjusted for randomization stratification factors.

Response assessment is determined using Modified Lugano Response Criteria.

Secondary Efficacy Endpoints

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

- CR at Primary Response Assessment based on PET-CT, as determined by the investigator
- CR at Primary Response Assessment based on PET-CT, as determined by IRC (for Phase II expansion (polatuzumab vedotin plus BG cohorts) and NF Cohort (Arm G) only)
- OR (CR or PR) at Primary Response Assessment based on PET-CT, as determined by the investigator and IRC
- CR at Primary Response Assessment based on CT only, as determined by the investigator and IRC
- OR (CR or PR) at Primary Response Assessment based on CT only, as determined by the investigator and IRC
- BOR (CR or PR) while on study based on PET-CT or CT only, as determined by the investigator
- DLBCL cohorts only: BOR, DOR and PFS based on PET-CT or CT only, as determined by IRC and investigator
- NF cohort only: OS and EFS based on PET-CT or CT only, as determined by the investigator

Exploratory Efficacy Endpoints

Among patients with a best overall response of CR or PR, DOR will be defined as the time from the initial CR or PR to the time of disease progression, relapsed or death from any cause, whichever occurs first. If a patient does not experience death or disease progression before the end of the study, DOR will be censored on the date of the last tumor assessment. DOR will be summarized descriptively with use of the Kaplan-Meier method. If analytically possible, median DOR will be estimated, along with the corresponding 95% CI using the method of Brookmeyer and Crowley (1982). No formal comparisons of DOR across treatment arms will be conducted.

PFS is defined as the period from the date of randomization or first treatment for non-randomized arms until the date of disease progression, relapse, or death from any cause, whichever occurs first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of last tumor assessment. If no tumor assessments were performed after the Screening Visit, PFS will be censored at the date of randomization/first treatment. The distribution of times for PFS will be summarized descriptively using the Kaplan-Meier method to estimate median (if analytically possible), 1-year, and 2-year PFS and 95% CIs using Greenwood's formula.

EFS is defined as the time from date of randomization or first treatment for non-randomized arms to any treatment failure including disease progression, relapse, initiation of *new anti–lymphoma treatment (*NALT*)*, or death, whichever occurs first. If the specified event (disease progression/relapse, death, start of an NALT) does not occur, patients will be censored at the date of last tumor assessment. For patients who do not have post-baseline tumor assessments or documentation of NALT, EFS will be censored at the time of randomization/first treatment.

OS is defined as the time from date of randomization or first treatment for non-randomized arms until the date of death from any cause. Patients who have not died will be censored at the last date known to be alive.

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

Duration of follow-up will be estimated by reverse Kaplan-Meier method.

Safety Analyses

Safety will be assessed through summaries of adverse events, summaries of changes from screening assessments in laboratory test results, ECGs, and changes in vital signs.

All collected adverse event data will be summarized by phase of the study, treatment arm, and histological subtype. All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and *National Cancer Institute*

*Common Terminology Criteria for Adverse Events (*NCI CTCAE*)* Version 4.03 toxicity grade. All serious adverse events will be listed separately and summarized.

Deaths reported during the study treatment period and those reported during follow-up after treatment discontinuation will be listed.

Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, pulse oximetry, and blood pressure) data will be displayed by time, with NCI CTCAE v4.03 Grade 3 and 4 values identified where appropriate.

Pharmacokinetic Analyses

Individual and mean serum and plasma concentrations of polatuzumab vedotin, bendamustine, rituximab, and obinutuzumab versus time data will be tabulated and plotted. Summary statistics of concentration data will be computed for each scheduled sampling time for each analyte. PK parameters, such as area under the concentration–time curve, maximum concentrations, systemic clearance, and steady-state volume of distribution may be estimated (as appropriate for the data collected). Estimates for these parameters will be tabulated and summarized (mean and standard deviation). PK parameters will be determined using the appropriate technique based on available data. Non-compartmental analysis and/or population PK analysis method may be applied for PK parameter estimation. Potential drug interactions may be assessed by comparison of PK in the current study with historical data. Potential correlations between PK variability and demographic and pathophysiological covariates may be explored by population PK analysis. Potential correlations between PK variability and pharmacodynamic, efficacy, and safety outcome may be explored by exploratory graphical analysis and PK-pharmacodynamic modeling. The assessment of PK parameters and related analysis will be performed per Sponsor's discretion, based on the appropriateness of the PK data collected, the trial outcome, and the future development path for polatuzumab vedotin.

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.

Patients enrolled in the NF Cohort (Arm G and Arm H), receiving polatuzumab vedotin (lyophilized) plus BR, will be exempt from completing the TINAS.

Exploratory Analyses

Exploratory analyses of biomarkers related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab or obinutuzumab will be conducted. Analyses will assess prognostic and/or predictive value of candidate biomarkers separately for each histological subtype and both investigator and IRC assessed outcomes. Specifically, the association between candidate biomarkers and PET-CT CR rate and OR rate and potentially other measures of efficacy and safety, independent of treatment, will be explored to assess potential prognostic value. In addition, the potential effect modification of treatment effect on PET-CT CR rate and OR rate and potentially other measures of efficacy and safety, by biomarker status, will be explored to assess potential predictive value.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
B	bendamustine
BG	bendamustine and obinutuzumab
BOR	best objective response
BR	bendamustine and rituximab
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	clearance
CLL	chronic lymphocytic leukemia
CR	complete response
Cru	complete response unconfirmed
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EORTC	European Organization for Research on the Treatment of Cancer
ESMO	European Society for Medical Oncology
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
FDA	(U.S.) Food and Drug Administration
FDG	^{18}F-flurodeoxyglucose
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G	GA101 or obinutuzumab
G-CSF	granulocyte colony-stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires

Abbreviation	Definition
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	*hepatitis B virus*
HIPAA	Health Insurance Portability and Accountability Act
HTLV-1	human T-cell leukemia virus 1
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
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 or Web-based response system
LMWH	low molecular-weight heparin
LPLV	last patient, last visit
Mab	monoclonal antibody
MC-VC-PABC	maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl
MMAE	mono-methyl auristatin E
MRD	minimal residual disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NALT	new anti-lymphoma treatment
NF	New Formulation
NHL	non-Hodgkin lymphoma
OR	objective response
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission topography
PFS	progression-free survival
PK	pharmacokinetic

Abbreviation	Definition
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
R	rituximab
RCR	Roche Clinical Repository
RP2D	Recommended Phase II Dose
R/R	relapsed or refractory
SCT	stem cell transplant
SD	stable disease
TEN	toxic epidermal necrolysis
TINAS	Therapy-induced neuropathy assessment score
TLS	tumor lysis syndrome
TMA	tissue microarray
TNS	Total Neuropathy Score
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON NON-HODGKIN'S LYMPHOMA

Non-Hodgkin 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 in the United States (American Cancer Society 2010; GLOBOCAN 2010). NHL is most often of B-cell origin and characterized by the expression of a membrane antigen, CD20, which is important in cell cycle initiation and differentiation (Anderson et al. 1984). NHL can be divided into indolent and aggressive lymphomas.

1.1.1 Follicular Lymphoma

Indolent NHLs are a heterogeneous group of malignant lymphomas and account for approximately one-third of all NHLs. Follicular lymphoma (FL) is the most common subtype of indolent NHL in the Western hemisphere and is associated with follicle-center B cells that typically contain the translocation t(14:18) which leads to overexpression of the intracellular anti-apoptotic protein BCL-2. The clinical course of FL is characterized by remission and relapse (Gallagher et al. 1986). The disease initially responds to radiation and to immunochemotherapy with conventional agents, but patients eventually experience multiple relapses distinguished by increasing refractoriness and decreasing duration of response in subsequent lines of therapy. Patients with advanced-stage disease are usually not cured with conventional treatment and often ultimately die from recurrent disease or treatment-related toxicity.

Currently, two prognostic tools are used for patients with FL: Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI2. The FLIPI is a risk score developed in order to better categorize expected outcomes of patients with FL on the basis of baseline clinical characteristics, including number of involved nodal sites, serum LDH level, age, stage, and hemoglobin level (Solal-Celigny et al. 2004). Although patients with low FLIPI risk tend to show long treatment-free intervals and survival times, higher-risk patients tend to progress quickly, with overall survival (OS) as short as 5 years. The FLIPI2 evaluates five parameters: age, bone marrow involvement, hemoglobin level, greatest diameter of the largest involved lymph node $>$6 cm, and serum beta-2 microglobulin levels (Federico et al. 2009).

No standard treatment exists for the management of advanced FL, and data from the National LymphoCare registry demonstrate that practice varies widely among physicians (Friedberg et al. 2009). For patients with FL requiring treatment, immunochemotherapy with rituximab (MabThera®, Rituxan®), a monoclonal antibody (MAb) directed against CD20, plus chemotherapy has demonstrated improvements in response rates, progression-free survival (PFS), and OS compared with chemotherapy alone in four studies (Hiddemann et al. 2005; Herold et al. 2007; Marcus et al. 2008; Salles et al. 2008). Rituximab in combination with chemotherapy (e.g., CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CVP [cyclophosphamide,

vincristine, and prednisone], or purine analogue-based schemes such as those with fludarabine or bendamustine) for newly diagnosed patients with advanced Stage III and IV disease requiring treatment is strongly supported by both the 2009 European Society for Medical Oncology Guidelines Working Group recommendations (level of evidence [I], and grade of recommendation [B]) and the 2010 National Comprehensive Cancer Network (NCCN) guidelines (Category 1 recommendation based on high-level evidence, with a uniform NCCN consensus) (Dreyling 2009; Zelenetz et al. 2010).

Despite these improvements, therapy for FL is not curative. It is important to introduce new agents that may improve the degree and duration of treatment response for these patients.

1.1.2 Diffuse Large B-Cell Lymphoma

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

Standard-of-care therapies for NHL involve multi-agent chemotherapy with non-cross–resistant mechanisms of action combined with immunotherapy. In DLBCL, the addition of the CD20-directed MAb rituximab to CHOP-based chemotherapy results in significantly improved survival, as demonstrated by three randomized prospective studies, comprising a total of approximately 2000 patients with newly diagnosed advanced DLBCL (Coiffier et al. 2002, 2007, 2010; Feugier et al. 2005, Habermann et al. 2006, Pfreundschuh et al. 2008). On the basis of the above studies, up to eight cycles of rituximab combined with six or eight 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; NCCN 2014), with approximately 60% of patients being cured of their disease.

Although there is currently no way to prospectively identify individual patients who will be cured, clinical factors are used to define prognostic risk groups associated with different outcomes. The International Prognostic Index (IPI) is a prognostic tool that identifies five significant clinical factors that are prognostic of overall survival (Shipp et al. 1993):

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

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

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

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

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

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

1.2 BACKGROUND ON THE MOLECULES

1.2.1 Polatuzumab Vedotin

1.2.1.1 Polatuzumab Vedotin Background and 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; Polson et al. 2009).

Polatuzumab vedotin (DCDS4501A [liquid formulation] and DCDS4501S [lyophilized formulation]) is an antibody drug conjugate (ADC) that contains a humanized immunoglobulin G1 (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 (e.g., R-CHOP used for treatment of lymphoma). Following binding at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released following cleavage of the linker by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth (Doronina et al. 2003). This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE and the increased potency of MMAE compared with vincristine. It is hypothesized that the addition of polatuzumab vedotin to a standard anti-CD20 antibody plus chemotherapy regimen will provide enhanced efficacy and safety to patients with NHL.

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic, and toxicological studies were conducted to support the entry of polatuzumab vedotin into clinical trials. Because polatuzumab vedotin specifically recognizes CD79b on B cells of humans–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 rituximab plus chemotherapy (rituximab in combination with cyclophosphamide, doxorubicin, and prednisone [CHP] or bendamustine) demonstrated better anti-tumor activity compared with polatuzumab vedotin as single agent or compared with a current standard of care regimen (R-CHOP or rituximab plus bendamustine [BR]) in xenograft models of NHL. The pharmacokinetics and safety of polatuzumab vedotin and the surrogate ADC were 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.

1.2.1.2 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 (R/R) NHL.

The original formulation of polatuzumab vedotin is a liquid formulation and was used in the main study (i.e., Phase Ib, Phase II expansion, and Phase II randomized cohorts) in patients with either R/R FL or R/R DLBCL. The liquid formulation is not stable after dilution into saline-containing IV bags, thus requiring a syringe pump for delivery. Therefore, a lyophilized formulation of polatuzumab vedotin has been developed to improve product stability upon dilution into saline-containing IV bags. An initial 170 mg/vial lyophilized configuration was developed and manufactured for a potentially higher dose configuration, which is no longer planned, and is currently in use in other clinical trials only for dosing up to 1.8 mg/kg. A 140 mg/vial drug product was subsequently developed to support a target dose of 1.8 mg/kg. The 170 mg/vial and the 140 mg/vial drug product differ in only the fill volume and yield the same product concentration and composition when reconstituted as prescribed. The lyophilized formulation of polatuzumab vedotin, referred to as "polatuzumab vedotin (lyophilized)" in this protocol, will be used in combination with BR in the Phase II New Formulation (NF) Cohort enrolling patients with R/R DLBCL. This additional cohort will hereafter be referred to as the NF Cohort.

Complete and updated details of these data are provided in the Polatuzumab Vedotin Investigator's Brochure.

As of February 2013, clinical experience with polatuzumab vedotin has been available from two studies:

- **Study DCS4968g:** 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)/RP2D as a single agent and in combination with rituximab in R/R NHL
- **Study GO27834:** A randomized Phase II study to evaluate the safety and anti-tumor activity of polatuzumab vedotin in combination with rituximab in patients with R/R DLBCL and FL. A second vc-MMAE ADC targeting CD22 (pinatuzumab vedotin) combined with rituximab is also being evaluated in this study. Patients are randomized to receive either polatuzumab vedotin or pinatuzumab vedotin in combination with rituximab

The clinical data cutoff dates for information about the ongoing Phase I study DCS4968g was 28 February 2013 and for the ongoing Phase II study GO27834, 22 February 2013.

Study DCS4968g (Phase I): Polatuzumab Vedotin Monotherapy and Polatuzumab Vedotin in Combination with Rituximab

A total of 95 patients have been enrolled into the Phase I study (Study DCS4968g), of whom 32 patients with NHL (indolent NHL [iNHL] or DLBCL) were enrolled in single-agent dose escalation, 11 patients were enrolled in an iNHL single-agent

expansion cohort, 23 patients were enrolled in the DLBCL single-agent expansion cohort, and 9 patients were enrolled in the Phase Ib polatuzumab vedotin plus rituximab combination treatment cohort. Enrollment of patients with NHL into the study has been completed.

The remaining 20 patients—all with CLL—were enrolled into single-agent dose escalation cohorts. For details regarding the clinical data in patients with CLL, refer to the Polatuzumab Vedotin Investigator's Brochure.

Safety

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

Dose-Limiting Toxicities in NHL

A dose-limiting toxicity (DLT) of Grade 4 neutropenia occurred in 1 of 10 DLT-evaluable patients in the 2.4-mg/kg single-agent cohort and in 1 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. Due to additional information about 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.

Treatment Discontinuations due to Adverse Events

As of 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%) and study treatment related adverse event 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 (each occurring in 1 patient). Two adverse events resulting in treatment discontinuation were reported as not related to study treatment and not due to the disease under study: Grade 3 worsening hyponatremia (1 patient) and Grade 4 invasive fungal infection (1 patient).

Adverse events resulting in study treatment discontinuation that were considered not related to the disease under study were reported in 6 patients with DLBCL: Grade 2 peripheral neuropathy (4 patients), Grade 3 peripheral neuropathy (1 patient), and Grade 3 diarrhea (1 patient). The only adverse event resulting in treatment discontinuation that was considered not related to the disease under study among the patients with CLL was Grade 4 invasive fungal infection (1 patient). All other events were reported in patients with iNHL, including five events of Grade 2 peripheral

neuropathy (4 patients), two events of Grade 3 peripheral neuropathy (2 patients), one event of Grade 3 neutropenia (1 patient), and one Grade 2 mucosal inflammation (1 patient). One patient with iNHL experienced five events that led to study treatment discontinuation (Grade 2 hyperesthesia, Grade 2 asthenia, Grade 3 anemia, Grade 3 thrombocytopenia, and Grade 4 thrombocytopenia).

Adverse Events with Single-Agent Polatuzumab Vedotin

Adverse events, regardless of relationship to study drug, were reported in all 66 patients (100%) with NHL (iNHL + DLBCL) who were treated with single-agent polatuzumab vedotin. Treatment-emergent adverse events reported in > 20% of patients included neutropenia (44%), diarrhea (38%), pyrexia (32%), nausea (32%), peripheral neuropathy (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 patients with NHL. 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 events of neutropenia were experienced by > 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 from an unknown cause. None of the deaths was assessed by the investigator as 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 reported 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.

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 plus DLBCL) cohorts,

19 serious adverse events were reported in 11 patients in the CLL cohort, and 15 serious adverse events were reported in 4 patients treated with polatuzumab vedotin plus rituximab. Among all patients, the most common serious adverse events (occurring in ≥2% of patients) were: Grade 1 or 2 pyrexia (6 patients), Grade 3 or 4 febrile neutropenia (4 patients), Grade 4 or 5 lung infection (3 patients), Grade 3 or 4 diarrhea (3 patients), Grade 3 or 4 hyperglycemia (2 patients), Grade 3 or 4 hyponatremia (2 patients), Grade 2 or 3 mental status changes (2 patients), Grade 3 or 4 peripheral neuropathy (2 patients), Grade 3 or 4 neutropenia (2 patients), Grade 4 or 5 pneumonia (2 patients), and acute renal failure (Grade 1 in 1 patient and Grade 4 in 1 patient).

Anti-Tumor Activity

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. Eighty-six of 88 patients (97.7%) had R/R iNHL, DLBCL, or CLL. Most evidence of anti-tumor activity was observed at ADC doses ≥1.8 mg/kg. Among patients with R/R iNHL, 13 of 22 patients (59%) treated with single-agent polatuzumab vedotin and 6 of 8 patients (75%) treated with polatuzumab vedotin plus rituximab had an investigator-assessed objective response (OR). Among patients with R/R DLBCL, 14 of 26 patients (54%) treated with single-agent polatuzumab vedotin and 1 of 1 patient treated with polatuzumab vedotin plus rituximab had investigator-assessed OR. Data regarding duration of response (DOR), PFS, and OS were insufficiently mature for reporting.

Study GO27834 (Phase II): Polatuzumab Vedotin in Combination with Rituximab

Safety

As of the clinical data cutoff (22 February 2013), preliminary clinical safety data were available for all 15 patients enrolled and randomized to the polatuzumab vedotin plus rituximab treatment arm. Treatment discontinuation due to adverse events had not been reported for any patient.

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 (all grades) reported in ≥2 patients were fatigue, nausea, diarrhea, neutropenia, vomiting, dry mouth, asthenia, arthralgia, back pain, and headache.

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 or 4 neutropenia was reported in 2 patients, Grade 3 diarrhea was reported in 1 patient, Grade 3 chest pain was reported in 1 patient, Grade 3 decreased neutrophil count was reported in 1 patient, and Grade 3 hypophosphatemia was reported in 1 patient.

A total of two serious adverse events were reported in 2 patients treated with polatuzumab vedotin plus rituximab: Grade 2 pyrexia and Grade 2 chest tightness. Both serious adverse events were reported as not related to study drug treatment.

Anti-Tumor Activity

In this ongoing study, 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.

1.2.1.3 Pharmacokinetic and Pharmacodynamic Properties of Polatuzumab Vedotin

The PK properties of polatuzumab vedotin conjugate (evaluated as antibody-conjugated MMAE [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 are under investigation, but data are not yet available.

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. On the basis of the results from DCS4968g, 2.4 mg/kg in patients with NHL, serum concentrations of total antibody and 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 mean steady-state volume of distribution (V_{ss}) values of approximately 70–87 mL/kg and approximately 93–109 mL/kg for acMMAE and total antibody, respectively. Mean clearance (CL) of acMMAE (approximately 15–21 mL/day/kg) was similar to CL of total antibody (approximately 11–19 mL/day/kg), suggesting that acMMAE CL was largely dominated by its antibody component. Mean terminal half-life for acMMAE was approximately 5.1–6.4 days and total antibody, approximately 8.1 days.

Unconjugated MMAE reached maximal concentrations at 2.01–3.42 days after the first dose, suggesting a delayed formation due to catabolism of the conjugate. There was a trend of increased C_{max} and area under the concentration–time curve $(AUC)_{inf}$ values with conjugate dose increase. At each dose level, C_{max} and AUC_{inf} values for unconjugated MMAE were substantially lower compared with its parent analyte acMMAE, suggesting that the total MMAE level in the systemic circulation after conjugate administration was mainly composed of conjugated MMAE. The $t_{½}$ values ranged from 2.93–5.81 days, which are relatively long for a small molecule and similar to the $t_{½}$ value for conjugate, suggesting that the kinetics of unconjugated MMAE could be dominated by its formation from the conjugate. On the basis of the $t_{½}$ values, a small amount of accumulation was expected upon every 3-week dosing.

The PK profiles and parameters were similar in the absence and presence of rituximab, suggesting that rituximab has little impact on polatuzumab vedotin PK in the R/R NHL

patient population. Given the various CYPs involved for metabolism of MMAE and bendamustine, the risks of PK interactions between them is low.

See the Polatuzumab Vedotin Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

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

Bendamustine with and without rituximab has demonstrated efficacy in patients with R/R iNHL (Rummel et al. 2005; Friedberg et al. 2008; Robinson et al. 2008; Kahl et al. 2010). Other available established therapies in this setting are either associated with high toxicity (e.g., fludarabine-based therapies, hematopoietic stem cell transplant) or have more limited effectiveness (e.g., R-CVP, rituximab monotherapy). In a Phase II trial examining the efficacy of BR in patients with R/R FL, the OR rate was 92% and median PFS was 23 months (Robinson et al. 2008). In addition, BR is recommended as a second-line therapy for patients with FL who either received alternative therapy in first line or who previously received bendamustine-based therapy and had a DOR of $\geq$ 1 year.

Commonly used regimens used to treat transplant eligible patients with R/R DLBCL are also used to treat transplant-ineligible patients (see Table 1). Of note, not all of patients in these studies were pretreated with rituximab. It is known from an analysis of the CORAL study (Gisselbrecht 2010) that patients who were pretreated with rituximab and relapse have a much worse outcome than those who were rituximab naive. More commonly used chemotherapy regimens with or without rituximab for R/R DLBCL have overlapping toxicities (neurotoxicity and hematologic toxicity) with polatuzumab vedotin, making combination together unlikely. BR is active in R/R DLBCL but is associated with manageable hematologic toxicity. For these patients with DLBCL who are not candidates for high-dose therapy, BR is also a recommended second-line therapy (NCCN Guidelines 2014).

Table 1 Treatment Regimens for Relapsed/Refractory DLBCL

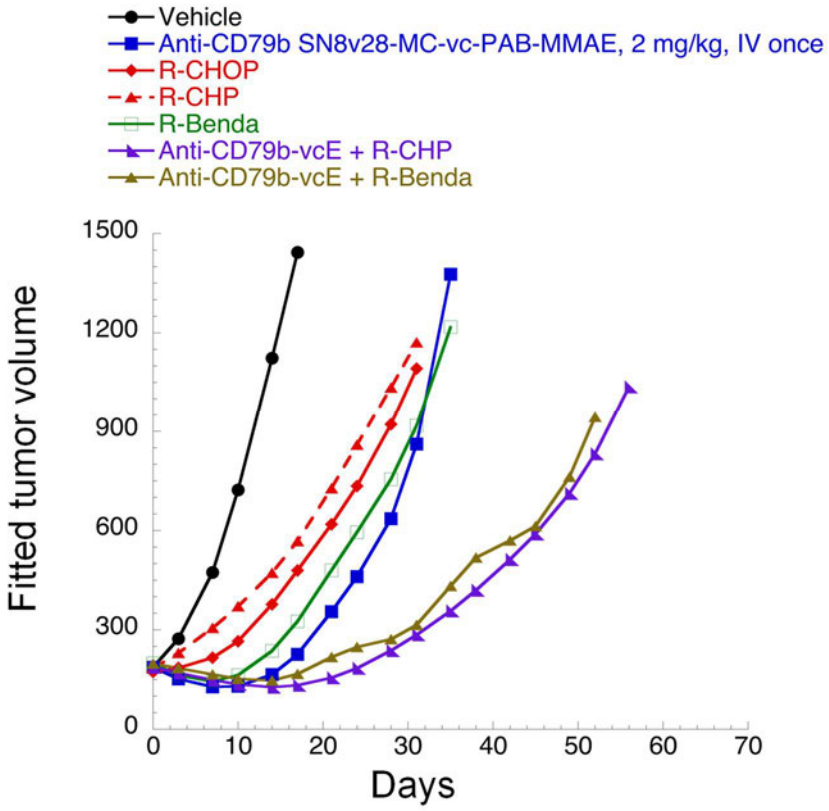
	R-ICE x 3 cycles (Gisselbrecht 2010)	R-DHAP x 3 cycles (Gisselbrecht 2010)	GDP x 2 cycles (Crump 2004)	R-GDP x 2 cycles (Crump 2013)	R-ESHAP X 1-6 cycles (Martin 2008)	R-GemOx x 4-8 cycles (Mounier 2013)	BR x 6 cycles (Ohmachi 2013)	BR x 6 cycles (Vacirca 2014)
N	202	194	52	619 (71% DLBCL)	163	49	59	59
ORR	64%	63%	49%	45%	73%	61%	63%	46%
CR/CRu	24%	28%	16%	—	35%	44%	37%	15%
PFS	31% at 3 y	42% at 3 y	—	—	38% at 5 y	13% at 5 y	mPFS 6.7 m	mPFS 3.6 m
OS	47% at 3 y	51% at 3 y	—	39% at 4 y	50% at 5 y	14% at 5 y	—	—
Transfusion	35% (PLT)	57% (PLT)	18% (PLT) 24% (PRBC)	18% (PLT)	30% (PLT) 47% (PRBC)	23% (PLT)	12% (PLT or PRBC)	NR
Heme toxicity and Infection (G3, G4)	Infection with neutropenia 17% Infection w/o neutropenia 6%	Infection with neutropenia 16% Infection w/o neutropenia 8%	Neutropenia (33%, 39%) FN 14% TCP (24%, 4%)	FN 9%	FN 34%	Neutropenia (73% G ≥ 3) FN (4% cycles) TCP (44% G3)	Neutropenia (31%, 46%) FN (7% G3) TCP (15%, 7%) Infection (12% G3)	Neutropenia (29%, 7%) Fever (29%) FN (7% G4) TCP (17%, 5%)
Neuro-toxicity	NR	NR	G ≥2 sensory: 10% G ≥2 motor: 4%	NR	G ≥2: 2 pts	G2: 37% G3: 8%	NR	NR

BR = bendamustine and rituximab; CR = complete response; CRu = CR unconfirmed; DLBCL = diffuse large B-cell lymphoma; FN = febrile neutropenia; G = Grade; GDP = gemcitabine, dexamethasone, cisplatin; m = months; R-DHAP = rituximab, dexamethasone, high dose cytarabine, cisplatin; R-ESHAP = rituximab, etoposide, methlyprednisolone, cytarabine, cisplatin; R-GDP = rituximab and GDP; R-GemOx = rituximab, gemcitabine, oxaliplatin; R-ICE = rituximab, ifosphamide, carboplatin, etoposide; N = number; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PLT = platelet; PRBC = packed red blood cell; pts = patients; TCP = thrombocytopenia; w/o = without; y = years.

Two studies have evaluated the combination of bendamustine and rituximab in R/R DLBCL (Ohmachi et al. 2013; Vacirca et al. 2014). In one of the Phase II trials, the OR rate was 63% (37% CR/CRu) and median PFS was 6.7 months (Ohmachi et al. 2013); for the second Phase II trial, the OR rate was 46% and median PFS was 3.6 months (Vacirca et al. 2014).

Polatuzumab vedotin is an ADC designed for the targeted delivery of MMAE, a potent microtubule inhibitor to lymphoma cells expressing CD79b. MMAE has a mechanism of action that is similar to that of vincristine. To date, Phase I data suggest that polatuzumab vedotin in combination with rituximab has activity in R/R FL and DLBCL with a generally acceptable safety and tolerability profile. Nonclinical data from murine xenograft models support the combination of bendamustine, rituximab, and polatuzumab vedotin and demonstrate significantly improved anti-lymphoma activity of the combination over BR alone (see Figure 1; Genentech data on file).

Figure 1 Preclinical Data in WSU-DLCL2



IV = intravenous; MMAE = mono-methyl auristatin; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP rituximab plus cyclophosphamide, doxorubicin, and prednisone.

Obinutuzumab (G*;* also known as RO5072759, GA101, and GazyvaTM), 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 being compared with rituximab in two large Phase III studies in patients with previously untreated DLBCL (Study BO21005) and with previously untreated iNHL, including FL (Study BO21223). Under the assumption that these studies will demonstrate greater clinical benefit with obinutuzumab compared with 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 bendamustine is being evaluated in several ongoing studies, including two Phase Ib trials in patients with previously untreated follicular lymphoma (BO21000) and previously untreated CLL (GAO4779g), and two Phase III trials in patients with previously untreated iNHL (BO21223) and rituximab-refractory iNHL (GAO4753g). Of the 41 patients with previously untreated follicular lymphoma in BO21000, 29% experienced Grade 3 or 4 neutropenia and 10% had Grade 3 or 4 infection (Dyer et al. 2012). In the GAO4779g study, 11 of 20 (55%) patients with CLL experienced a Grade 3 or 4 neutropenia (including 2 patients with Grade 3 or 4 febrile neutropenia) and 1 patient had a Grade 3 skin infection (Brown et al. 2013).

Clinical trials with BR and BG have demonstrated efficacy but have been associated with neutropenia. 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 plus chemotherapy (rituximab plus bendamustine [BR] or obinutuzumab plus bendamustine [BG]) in patients with R/R FL or DLBCL. The RP2D of polatuzumab vedotin in combination with BR or BG will be determined in the safety run-in portion of the study. Following identification of the RP2D, the expansion portion of the study will further evaluate the safety and tolerability and clinical activity of polatuzumab vedotin plus BR compared with BR and polatuzumab vedotin plus BG in patients with R/R FL or DLBCL.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES (MAIN STUDY)

This section outlines the primary objectives for the main study cohorts (i.e., Phase Ib, Phase II expansion, and Phase II randomized cohorts in patients with R/R DLBCL and R/R FL), which use the initial liquid formulation of polatuzumab vedotin.

Refer to Section 2.3 for the primary objectives of Arm G and Arm H of the NF Cohort (i.e., the Phase II NF Cohort in patients with R/R DLBCL), which uses the new lyophilized formulation of polatuzumab vedotin plus BR.

The primary objectives of the Phase Ib portion of the study are as follows:

- To assess the safety and tolerability of the combination of polatuzumab vedotin with BR or BG when administered to patients with R/R FL or DLBCL
- To identify the RP2D for polatuzumab vedotin given in combination with BR or with BG in patients with R/R FL or DLBCL

The primary objective of the Phase II portion of the study is as follows:

- To evaluate the efficacy of the combination of polatuzumab vedotin plus BR compared with BR alone in patients with R/R FL or DLBCL as measured by PET-defined CR rate using Modified Lugano Response Criteria (PET-CT criteria) (see Appendix 4) at the time of primary response assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) and as defined by the Independent Review Committee (IRC)

2.2 SECONDARY OBJECTIVES (MAIN STUDY)

This section outlines the secondary and exploratory objectives for the main study cohorts (i.e., Phase Ib, Phase II expansion, and Phase II randomized cohorts in R/R DLBCL and R/R FL), which use the initial liquid formulation of polatuzumab vedotin.

Refer to Section 2.3 for secondary objectives of Arm G and Arm H of the NF Cohort (i.e., the Phase II NF R/R DLBCL Cohort), which use the new lyophilized formulation of polatuzumab vedotin plus BR.

2.2.1 Safety Objectives

The safety objectives for this study are as follows:

- To assess the safety and tolerability of the combination of polatuzumab vedotin with BR or BG when administered to patients with R/R FL or DLBCL during the Phase II portion of the study
- To assess the immunogenicity of polatuzumab vedotin and obinutuzumab, as measured by the formation of anti-drug antibodies (ADAs)
- To assess the potential relationships of such ADAs (anti-polatuzumab vedotin and anti-obinutuzumab) formation with other outcome measures (e.g., PK, efficacy, safety)

2.2.2 Pharmacokinetic Objectives

The PK objectives for this study are as follows:

- To characterize the pharmacokinetics of polatuzumab vedotin in combination with BR or BG in patients with R/R FL or DLBCL
- To assess potential PK interactions between polatuzumab vedotin and BR or BG
- To evaluate the PK exposure response (e.g., efficacy, safety) relationship

2.2.3 Secondary Efficacy Objectives *(Main Study)*

The secondary efficacy objectives for this study are:

To evaluate the efficacy of the combination of polatuzumab vedotin and BR compared with BR alone according to Modified Lugano 2014 response criteria as measured by:

- CR at the time of Primary Response Assessment based on PET-CT, as determined by the investigator
- Objective response (OR; CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
- CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- Best objective response (BOR; CR or PR) while on study either by PET-CT or CT only, as determined by the investigator
- DLBCL cohorts only: BOR, DOR and PFS based on PET-CT or CT, as determined by IRC

To evaluate the efficacy of the combination of polatuzumab vedotin plus BG according to Modified Lugano 2014 response criteria as measured by:

- CR at the time of Primary Response Assessment based on PET-CT, as determined by the investigator and IRC
- OR *(*CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
- CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- Best objective response (BOR, CR, or PR) while on study either by PET-CT or CT only, as determined by the investigator
- DLBCL cohorts only: BOR, DOR, and PFS while on study by either PET-CT or CT only, as determined by IRC

2.2.4 Patient-Reported Outcome Objective

The patient-reported outcome (PRO) objective for this study is 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).

2.2.5 Exploratory Objectives

The exploratory objectives for this study are as follows:

- To make a preliminary assessment of biomarkers related to the drug targets and mechanism of action of polatuzumab vedotin and/or rituximab or obinutuzumab, and/or of biomarkers related to disease biology and/or assessments that inform the improvement of diagnostic tools, and that might predict disease response or resistance to treatment with polatuzumab vedotin in combination with BR or BG in R/R FL or DLBCL including but not limited, to the following:
  - CD79b expression
  - DLBCL prognostic subtype (ABC/GCB)
  - Lymphoma-associated mutations and markers of tumor immunobiology
  - Regulators of apoptosis such as BCL-2
  - Minimal residual disease (MRD) as quantified by measurements of lymphoma-specific markers DNA extracted from peripheral blood. Lymphoma-specific markers from blood will be compared to those measured in DNA extracted from baseline tissue to identify the originating clone.
- To evaluate the prognostic significance of interim PET-CT assessment

The exploratory efficacy objectives for this study are to evaluate longer-term outcomes for patients using the Modified Lugano 2014 response criteria, as measured by the following:

- Duration of response (DOR) based on PET-CT or CT only, as determined by the investigator
- Progression-free survival (PFS) based on PET-CT or CT only, as determined by the investigator
- Event-free survival (EFS) based on PET-CT or CT only, as determined by the investigator
- Overall survival (OS)

2.3 OBJECTIVES FOR THE NEW FORMULATION (LYOPHILIZED) COHORT

2.3.1 Arm G

2.3.1.1 Primary Objective

The primary objective for Arm G is to evaluate the pharmacokinetics and safety of polatuzumab vedotin (lyophilized) plus BR in patients with R/R DLBCL, as follows:

- Pharmacokinetics: To characterize the pharmacokinetics of polatuzumab vedotin (lyophilized) in combination with BR in patients with R/R DLBCL
- Safety: To assess the safety and tolerability of polatuzumab vedotin (lyophilized) in combination with BR

2.3.1.2 Secondary Objectives

2.3.1.2.1 Efficacy

The secondary objective for Arm G is to evaluate the efficacy of the combination of polatuzumab vedotin (lyophilized) plus BR as measured by and using Modified Lugano Response Criteria, as follows:

- CR at the time of Primary Response Assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study medication) based on PET-CT, as determined by investigator and IRC
- OR (CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
- CR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- OR at the time of Primary Response Assessment based on CT only, as determined by the investigator and IRC
- BOR (CR or PR) while on study either by PET-CT or CT only, as determined by the investigator and IRC
- DOR based on PET-CT or CT only, as determined by the investigator and IRC
- PFS based on PET-CT or CT only, as determined by the investigator and IRC
- EFS based on PET-CT or CT only, as determined by the investigator
- OS

2.3.1.2.2 Safety

The safety objective for Arm G is to assess the immunogenicity of polatuzumab vedotin (lyophilized), as measured by the formation of ADAs.

2.3.2 Arm H

2.3.2.1 Primary Objective

The primary objective for Arm H of the study is to evaluate the efficacy of the combination of polatuzumab vedotin (lyophilized) plus BR in patients with R/R DLBCL, as measured by PET-CT–defined CR rate (using the Modified Lugano Response Criteria) (see Appendix 4) at the time of Primary Response Assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) and as defined by the Independent Review Committee (IRC).

2.3.2.2 Secondary Objectives

2.3.2.2.1 Efficacy Objectives

The secondary efficacy objective for Arm H is to evaluate the efficacy of the combination of polatuzumab vedotin (lyophilized) plus BR, as measured by and using the Modified Lugano Response Criteria, as follows:

- CR at the time of Primary Response Assessment based on PET-CT, as determined by investigator

- OR (CR or PR) at the time of Primary Response Assessment, based on PET-CT, as determined by the investigator and IRC
- BOR (CR or PR) while on study either by PET-CT or CT only, as determined by the investigator and IRC
- DOR based on PET-CT or CT only, as determined by the investigator and IRC
- PFS based on PET-CT or CT only, as determined by the investigator and IRC
- EFS based on PET-CT or CT only, as determined by the investigator
- OS

2.3.2.2.2 Safety Objectives

The safety objectives for Arm H are as follows:

- To assess the safety and tolerability of polatuzumab vedotin (lyophilized) in combination with BR
- To assess the immunogenicity of polatuzumab vedotin (lyophilized), as measured by the formation of ADAs

2.3.2.2.3 Pharmacokinetic Objectives

The PK objective is to characterize the pharmacokinetics of polatuzumab vedotin (lyophilized) in combination with BR in patients with R/R DLBCL.

2.3.2.3 Exploratory Objectives

The exploratory objective for this arm of the study is to assess biomarkers related to the drug target and mechanism of action of polatuzumab vedotin and/or rituximab, and/or of biomarkers related to disease biology and/or assessments that inform the improvement of diagnostic tools, and that might predict disease response with polatuzumab vedotin in combination with BR in R/R DLBCL, including, but not limited to, the following:

- CD79b expression
- DLBCL prognostic subtype (ABC/GCB)
- Regulators of apoptosis such as BCL-2 or c-MYC

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This design is a Phase Ib/II, multicenter, open-label study of polatuzumab vedotin administered by IV infusion in combination with standard doses of bendamustine (B) and rituximab (R) or obinutuzumab (G) in patients with relapsed or refractory FL or DLBCL. The study will consist of two stages: a Phase Ib safety run-in stage and a Phase II stage. The dose of polatuzumab vedotin in combination with BR or BG will be determined during the safety run-in stage of the study, separately for each lymphoma subtype (FL and DLBCL), and will be used in combination with BR or BG in the Phase II stage. The Phase II stage will be randomized for patients treated with R-containing regimens and be

non-randomized for patients treated with the G-containing regimen. Throughout the study, there will be concurrent enrollment of patients having either FL or DLBCL.

The study will begin with a safety run-in stage followed by a randomization and expansion phase. During the safety run-in phase, 6 patients will be treated with polatuzumab vedotin in combination with the BR regimen. Once this cohort is safely cleared, 6 patients will be treated at the same dose level of polatuzumab vedotin in combination with the BG regimen. If the first 6 patients in the polatuzumab vedotin plus BR cohort safely clears after the first cycle, then the randomized Phase II stage comparing BR-containing regimens will commence and patients will be randomized to either polatuzumab vedotin plus BR or to BR alone (control arm). Randomization will occur separately for each of the two disease-specific cohorts of patients with either FL or DLBCL. If the first 6 patients in the polatuzumab vedotin plus BG cohort safely clear the first cycle, then the expansion stage for obinutuzumab-containing regimen will commence. Patients receiving polatuzumab vedotin plus BG will be enrolled into two expansion cohorts on the basis of histology of FL or DLBCL in order to expand the safety database and collect preliminary anti-lymphoma activity data.

The Phase II randomization portion of the study can commence once the safety run-in of the polatuzumab vedotin plus BR cohort has completed, which can occur before the BG safety run-in cohort is completed. The Phase II expansion portion of the study can commence once the safety run-in of the polatuzumab vedotin plus BG cohort has been completed.

Sites cannot enroll patients in rituximab-containing and obinutuzumab–containing phases simultaneously within the same histology.

The NF Cohort (Arm G and Arm H) is separate from the expansion and randomized phases of the main study.

In Arm G of the NF Cohort, patients with R/R DLBCL will be treated with polatuzumab vedotin (lyophilized) in combination with BR to gain clinical PK and safety experience with the new lyophilized formulation of polatuzumab vedotin. Initially, up to 30 patients were to be enrolled in order to ensure adequate number of PK-evaluable patients. Enrollment has been expanded to approximately 40 patients, which will include approximately 10 second-line (2L) patients (patients with one prior line of therapy) in order to evaluate the efficacy of polatuzumab vedotin (lyophilized) in combination with BR in the 2L setting. A PK–evaluable patient is defined as a patient from whom, at minimum, the PK samplings of all three analytes (i.e., total antibody, acMMAE, and unconjugated MMAE) at Cycle 1 through Cycle 2, Day 1 are obtained.

In Arm H of the NF Cohort, patients with R/R DLBCL will be treated with polatuzumab vedotin (lyophilized) in combination with BR to further evaluate the clinical efficacy, to gain additional safety experience, and to expand evaluation in exploratory biomarker

subsets. Approximately 60 patients in total will be enrolled in this arm. A minimum of approximately 30% of patients who have previously received only one prior line of therapy (i.e., 2L therapy) will be enrolled in Arm H, and prioritization may be given to ensure such enrollment is achieved upon completion of enrollment in this arm.

Study treatment will be given in 28-day cycles for patients with FL and in 21-day cycles for patients with DLBCL. The first day of treatment will constitute Study Day 1. Patients will be treated up to a total of six cycles.

All patients will be evaluated for safety and efficacy according to the schedules of assessments (Appendix 1).

All patients will be assessed for response to treatment by the investigator with the use of standard criteria according to the Modified Lugano Response Criteria (Cheson et al. 2014; see Appendix 4) at screening and at the following timepoints:

- Interim response assessment (between Cycle 3, Day 15 and Cycle 4, Day 1)
- Primary response assessment: 6–8 weeks after completion of study treatment (i.e., Day 1 of Cycle 6 or after last dose of study drug)

Imaging at these timepoints must include FDG-PET (^{18}F fluorodeoxyglucose-positron emission tomography) 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 patients with either FL or DLBCL for the Phase Ib safety run-in stage at approximately 25 sites in the United States and Canada (up to 12 patients with the BR regimen and up to 12 patients with the BG regimen).

The Phase II stage of the study will enroll approximately 160 patients with either R/R FL or R/R DLBCL who will receive a BR-containing regimen (randomization portion) and approximately 40 patients with either R/R FL or R/R DLBCL who will receive a BG-containing regimen (safety expansion portion). Approximately 80 sites globally will participate in this portion of the study.

Arm G of the Phase II NF Cohort will enroll approximately 40 patients with R/R DLBCL who will receive polatuzumab vedotin (lyophilized) with BR. Approximately 30–35 sites of the total sites in the study will participate in this portion of the study.

Arm H of the Phase II NF Cohort will enroll approximately 60 patients with R/R DLBCL who will receive polatuzumab vedotin (lyophilized) with BR. Approximately 45–50 sites will participate in this arm. For an overview of the study design, see *Figure 2*.

Figure 2 Overview of Study Design

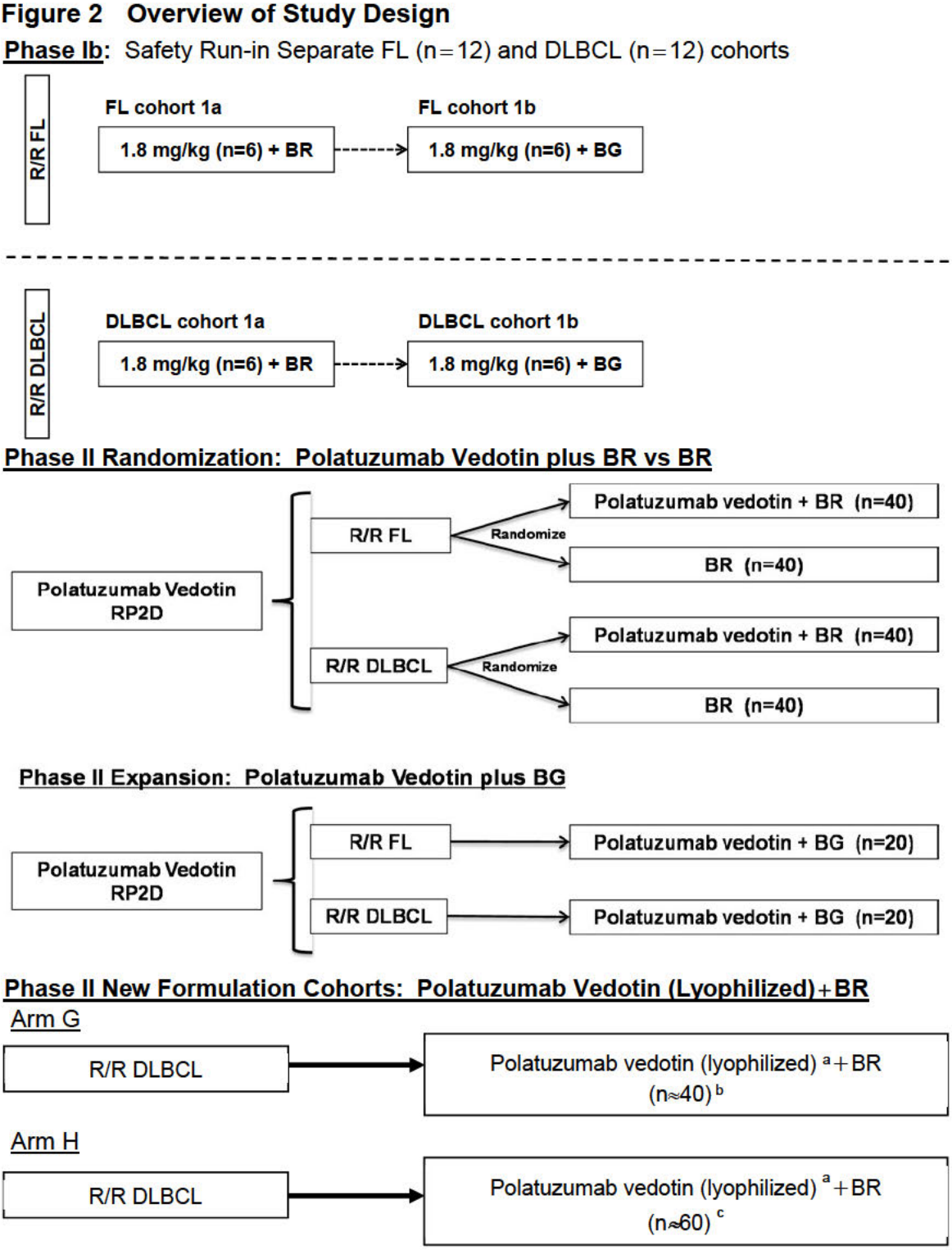


Figure 2 Overview of Study Design (cont.)

2L = second line; BR = bendamustine and rituximab; BG = bendamustine and obinutuzumab; D = Day; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; RP2D = recommended Phase II dose; R/R = relapsed or refractory.

Notes: Rituximab (375 mg/m^2) D1 of each cycle, or obinutuzumab (1000 mg) D1, D8, and D15 in Cycle 1, then D1 of each subsequent cycle plus bendamustine (90 mg/m^2) D2 and D3 in Cycle 1, then D1 and D2 in each subsequent cycle.

FL: Treatment administered every 28 days x 6 cycles.

DLBCL: Treatment administered every 21 days x 6 cycles.

[a] Polatuzumab vedotin (lyophilized) dose 1.8 mg/kg.

[b] Initially, approximately 20-30 patients were planned to be enrolled to ensure adequate number of PK-evaluable patients. A PK-evaluable patient is defined as a patient from whom at minimum the PK samplings of all three analytes (i.e., total antibody, acMMAE, and unconjugated MMAE) at Cycle 1 through Cycle 2, Day 1 are obtained. Approximately 10 additional patients with one prior line of therapy (i.e., 2L) will also be enrolled in this arm in order to evaluate the efficacy of polatuzumab vedotin (lyophilized) in combination with BR in this particular patient subpopulation, bringing the total arm size to approximately 40 patients.

[c] A minimum of approximately 30% of patients who previously received one prior line of therapy (i.e., 2L) will be enrolled in this arm to ensure a sufficient number of efficacy-evaluable patients for this particular subpopulation. Prioritization may be given to ensure such enrollment is achieved upon completion of enrollment in this arm.

3.1.1 Phase Ib: Safety Run-In Stage

The safety run-in stage of the study will assess the safety, tolerability, and pharmacokinetics of polatuzumab vedotin administered in combination with BR or BG. Prior vinca alkaloid therapy is allowed if any resulting neuropathy does not exceed Grade 1 at enrollment.

3.1.1.1 Cohort Dosing Regimen

Patients will be enrolled in separate FL and DLBCL cohorts in Phase Ib safety run-in as shown in Table 2. The dose level for polatuzumab vedotin will be 1.8 mg/kg. Cohort 1a refers to the cohort receiving rituximab. Cohort 1b refers to the cohort receiving obinutuzumab. The selection of the dose level was made on the basis of the absence of DLTs observed at this dose level when administered as a single agent in the Phase I study DCS4968g. Polatuzumab vedotin will be administered in combination with either BR or BG. Sites cannot enroll patients in rituximab-containing and obinutuzumab-containing phases simultaneously within the same histology.

Table 2 Safety Run-In Cohorts of Polatuzumab Vedotin with Starting Doses of Bendamustine and Rituximab or Obinutuzumab

Histology	Dose Cohort	Starting Doses		
		Polatuzumab vedotin	Bendamustine	Anti-CD20 Antibody
FL (every 28 day dosing)	1a (n=6)	1.8 mg/kg	90 mg/m^2	Rituximab 375 mg/m^2
	1b (n=6)	1.8 mg/kg	90 mg/m^2	Obinutuzumab 1000 mg
DLBCL (every 21 day dosing)	1a (n=6)	1.8 mg/kg	90 mg/m^2	Rituximab 375 mg/m^2
	1b (n=6)	1.8 mg/kg	90 mg/m^2	Obinutuzumab 1000 mg

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma.

Patients will be monitored for adverse events during the safety observation period from Cycle 1, Day 1 to Cycle 2, Day 1 for a minimum of 28 days for FL patients and 21 days for DLBCL patients. Any patient who does not complete the full safety-observation period for any reason other than adverse events will be considered non-evaluable for safety run-in analysis decisions and/or RP2D assessment and will be replaced by an additional patient in the same cohort.

For each cohort during the safety run-in, the first patient treated will receive the first infusion of polatuzumab vedotin at least 24 hours before any subsequent patient in that cohort is treated in order to allow sufficient time to assess the occurrence of any severe and unexpected acute drug or infusion-related toxicities.

During the safety run-in, a safety analysis will be performed after the first 3 patients receiving polatuzumab vedotin plus BR have completed the safety observation period. After the first 3 patients have safely cleared as determined by an internal safety review, an additional 3 patients will be added to the same cohort. The IMC will perform a safety analysis after 6 patients in each histology group have completed the safety observation period. Once the IMC provides a recommendation for the RP2D for the polatuzumab plus BR regimen, enrollment into the polatuzumab vedotin plus BG and the Phase II randomization portion will commence. After the first 3 patients have safely cleared as determined by an internal safety review, an additional 3 patients will be added to the same cohort. Decisions will be made by the Sponsor's Medical Monitor in consultation with the Safety Science Leader, Biostatistician, and participating investigators. The decision to continue enrollment in the current cohort or to open the next cohort will be based upon review of all relevant safety data including but not limited to adverse event and laboratory data.

3.1.1.2 Definition of Safety Criteria during Safety Run-In

During the safety run-in stage of the study, toxicity that will prevent further enrollment into Phase Ib and opening of Phase II will be defined as any of the following study treatment related adverse events occurring during the safety observation period as described below.

All adverse events are to be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, unless otherwise indicated. If a patient experiences an adverse event as defined below, he or she will be treated according to clinical practice and will be monitored for resolution of the toxicity. Decreases in B cells, lymphopenia, and leukopenia due to lymphopenia will not be considered an adverse event because they are expected pharmacodynamic outcomes of rituximab, obinutuzumab, or polatuzumab vedotin treatments.

The following criteria will be used in the safety analysis during the safety run-in stage:

- 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 attributed to disease progression or another clearly identified 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 an AE meeting safety run-in criteria. (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

    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 an adverse event meeting safety run-in criteria.

- All Grade 3 or 4 hematological toxicities 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 granulocyte colony-stimulating factor (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 ≥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 ≥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 ≥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 an adverse event as described above, the patient will be observed for resolution of the toxicity. If the adverse event resolves to Grade ≤2 (or to ≥80% of the baseline value) and if 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.

3.1.1.3 Decision Rules for Safety Run-In Stage

Safety data from the patients enrolled during the Safety Run-In Stage will be used to determine the dose of polatuzumab vedotin used during the Phase II randomization and expansion stage of the study.

The following rule will apply during the safety run-in:

- If any adverse events, as defined per Section 3.1.1.2 are observed in ≥33% of the patients enrolled in a given cohort, further enrollment of the cohort will be halted.

Additional patients may be enrolled into a given cohort in the absence of excess toxicity to acquire additional safety data. Additional patients may be enrolled at dose levels below 1.8 mg/kg of polatuzumab vedotin (i.e., 1.4 mg/kg) based upon review of all safety data by the Sponsor (including the IMC).

3.1.2 Phase II: Randomized and Expansion Stage and New Formulation Cohort

The study will include approximately 160 patients who will receive a BR-containing regimen in the randomized Phase II portion (see Figure 3) and 40 patients who will receive a BG-containing regimen in the safety expansion portion (non-randomized; see Figure 4). In addition, in the Phase II NF Cohort, approximately 100 patients will receive polatuzumab vedotin (lyophilized) with BR (~40 patients in Arm G and ~60 patients in Arm H).

Patients in the Phase II portion will receive polatuzumab vedotin at the RP2D determined during the Phase Ib portion of the study. Sites cannot enroll patients in rituximab-containing and obinutuzumab-containing phases simultaneously within the same histology.

3.1.2.1 Randomized Bendamustine plus Rituximab-Containing Regimen

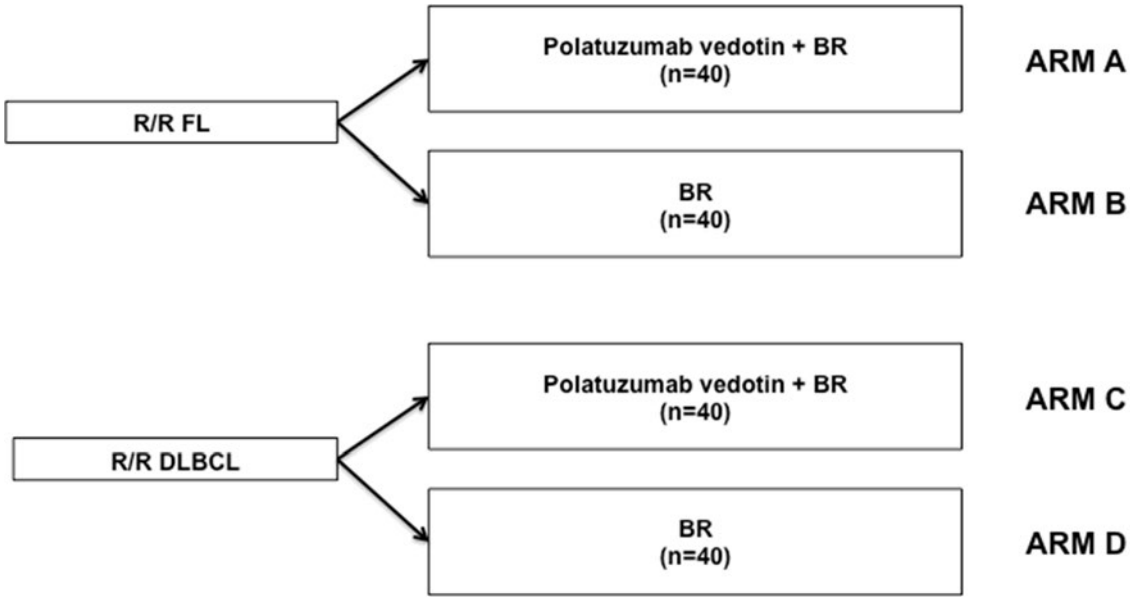
Approximately 80 patients with R/R FL will be randomized to receive polatuzumab vedotin plus BR (Arm A) or BR alone (Arm B). Approximately 80 patients with R/R DLBCL will be randomized to receive polatuzumab vedotin plus BR (Arm C) or BR alone (Arm D) (see Figure 3).

Patients will be randomized 1:1 within each histology group with the use of stratified permuted blocks such that all treatment arms will enroll the same number of patients (n=40 in each of the treatment arms). Randomization will be stratified according to the following factors:

- DOR to prior therapy: ≤12 months versus >12 months (DLBCL, FL)
- Disease burden: high versus low (FL only)

High-disease burden by modified GELF criteria (named for the cooperative group Groupe d'Etude des Lymphomes Folliculaires) (Brice et al. 1997), defined as presence of any one of the following: largest nodal or extranodal mass ≥7 cm, three or more nodal sites with diameter >3 cm, ascites or pleural effusion, risk of organ compression or compromise, symptomatic splenic enlargement, LDH, beta-2 microglobulin greater than ULN, or presence of systemic symptoms.

Figure 3 Phase II Randomized: Polatuzumab Vedotin Plus BR vs BR

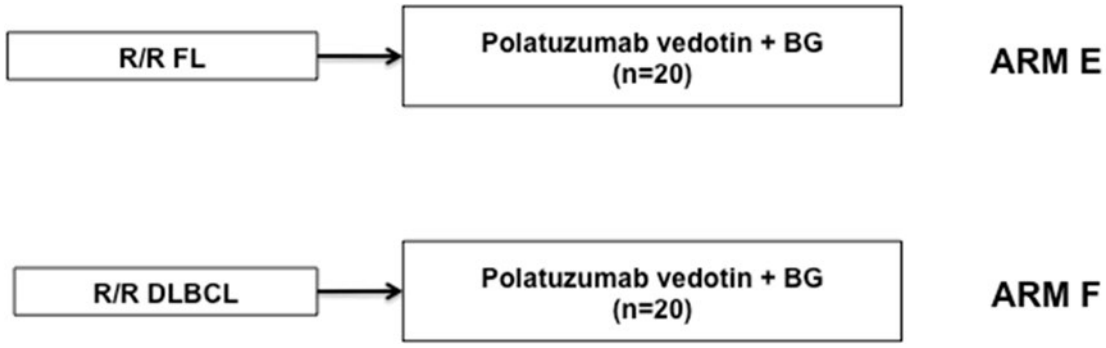


BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; R/R = relapsed or refractory.

3.1.2.2 Non-Randomized Bendamustine Plus Obinutuzumab Containing Regimen

Approximately 20 patients with R/R FL (Arm E) and 20 patients with R/R DLBCL (Arm F) will receive polatuzumab vedotin plus BG in the safety-expansion stage (see Figure 4).

Figure 4 Phase II Expansion: Bendamustine Plus Obinutuzumab Regimen



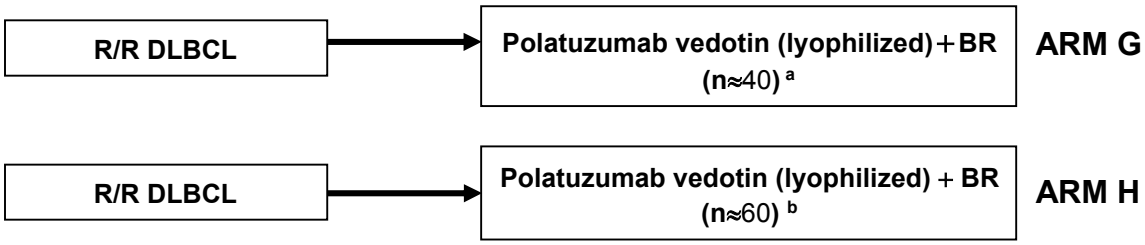
BG = bendamustine plus obinutuzumab; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; R/R = relapsed or refractory.

A schedule of assessments is provided in Appendix 1.

3.1.2.3 Phase II New Formulation Cohort: Polatuzumab Vedotin (Lyophilized) plus BR

Approximately 100 patients with R/R DLBCL will receive polatuzumab vedotin (lyophilized) plus BR in the NF Cohort with approximately 40 patients in Arm G and approximately 60 patients in Arm H (see Figure 5).

Figure 5 Phase II: Non-Randomized NF Cohort



2L=second line; BR = bendamustine plus rituximab; DLBCL = diffuse large B-cell lymphoma; NF = new formulation; PK = pharmacokinetic; R/R = relapsed or refractory.

[a] Intially, up to 30 patients were to be enrolled to ensure adequate number of PK-evaluable patients. Approximately 10 additional patients with one prior line of therapy (i.e. 2L) will also be enrolled in this arm in order to evaluate the efficacy of polatuzumab vedotin (lyophilized) in combination with BR in this particular patient subpopulation, bringing the total arm size to approximately 40 patients.

[b] A minimum of approximately 30% of patients with one prior line of therapy (i.e., 2L) will be enrolled in this arm to ensure a sufficient number of efficacy-evaluable patients for this particular subpopulation. Prioritization may be given to ensure such enrollment is achieved upon completion of enrollment in this arm.

3.1.3 Internal Monitoring Committee

An IMC will be established to monitor patient safety throughout the study and provide a recommendation on whether to continue into Phase II of the study after completion of the Phase Ib safety run-in stage. The IMC will include the Roche/Genentech Medical Monitor, at least one other medical doctor or Clinical Science representative 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 toxicity as defined in Section 3.1.1.3, 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, including the NF cohort. 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 Independent Review Committee (IRC) composed of board-certified radiologists and an oncologist with experience in malignant lymphoma will assess all patients for response (see Appendix 4) on the basis of imaging results and bone marrow biopsy results for all patients 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 timepoint at which all patients enrolled in the study have either had at least 2 years of follow-up from the time of the treatment–completion visit or have discontinued the study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Polatuzumab Vedotin Dose and Schedule

Polatuzumab vedotin dosing for this study was based on the experience from the ongoing Phase I Study DCS4968g with single-agent polatuzumab vedotin in relapsed and refractory patients with iNHL and DLBCL. Most evidence of anti-tumor activity was observed at doses ≥1.8 mg/kg.

Bendamustine in combination with anti-CD20 monoclonal antibodies has its own degree of myelosuppression; therefore, the dose of polatuzumab vedotin that is given with standard doses of bendamustine and rituximab or bendamustine and obinutuzumab may not reach the same MAD (maximum assessed dose) as that achieved with polatuzumab vedotin monotherapy. The number of cycles (six 21-day or 28-day cycles) of this regimen (polatuzumab vedotin plus BR or BG) that will be evaluated in this study is consistent with other anti-CD20 plus bendamustine regimens used to treat NHL and has been shown to be sufficient to provide durable responses.

The NF Cohort involving patients with R/R DLBCL will be treated with the 140 mg/vial lyophilized formulation of polatuzumab vedotin (Arm G and Arm H) in combination with BR. The initial formulation of polatuzumab vedotin is a liquid formulation and was used in the initial cohorts of this study (i.e., Phase Ib, Phase II expansion, and Phase II randomized) in patients with either R/R FL or R/R DLBCL. A 170 mg/vial lyophilized formulation of polatuzumab vedotin was developed to support an initial expected clinical dose of 2.4 mg/kg and is currently in use in other clinical trials. A 140 mg/vial lyophilized drug product was subsequently developed to support a target dose of 1.8 mg/kg. Both the 170 mg/vial and 140 mg/vial lyophilized drug products differ in only the fill volume. The 140 mg/vial lyophilized polatuzumab vedotin is planned for later clinical trials and proposed for commercialization and will be used in combination with BR in the Phase II NF Cohort (Arm G and Arm H) enrolling patients with R/R DLBCL.

3.3.2 Rationale for Rituximab and Bendamustine Dosing and Schedule

Bendamustine with and without rituximab has demonstrated efficacy in patients with R/R iNHL (Rummel et al. 2005; Friedberg et al. 2008; Robinson et al. 2008; Kahl et al. 2010). Other available established therapies in this setting are either associated with high toxicity (e.g., fludarabine-based therapies, hematopoietic stem cell transplant) or have more limited effectiveness (e.g., R-CVP, rituximab monotherapy).

Indolent NHL, Including Follicular Lymphoma

Two studies have investigated bendamustine in combination with rituximab in R/R indolent lymphomas (Robinson et al. 2008; Rummel et al. 2010). In both studies, rituximab was administered at a standard dose of 375 mg/m^2 on Day 1, followed by bendamustine 90 mg/m^2 on Days 1 and 2 of a 28-day cycle. The major Grade 3 or Grade 4 toxicity with this regimen was reversible neutropenia, observed in 36% of patients.

DLBCL

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

The most frequent Grade 3 or 4 adverse events observed in both studies were hematologic including neutropenia (Ohmachi: 31% Grade 3, 46% Grade 4; Vacirca: 29% Grade 3, 7% Grade 4) and febrile neutropenia (Ohmachi: 7% Grade 3, Vacirca: 7% Grade 4).

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

Rituximab plus Bendamustine as Control Group

BR is considered a relevant comparator arm because other available established therapies in both the R/R FL and DLBCL settings are either associated with high toxicity (e.g., fludarabine-based therapies, hematopoietic stem cell transplant) or have more

limited effectiveness (e.g., R-CVP, rituximab monotherapy). Furthermore, BR is recommended as a second-line therapy for patients with FL who either received alternative therapy in first line or who previously received bendamustine-based therapy and had a DOR of ≥1 year. In a Phase II trial examining the efficacy of BR in patients with R/R FL, the OR rate was 92% and median PFS was 23 months (Robinson et al. 2008). For patients with DLBCL who are not candidates for high-dose therapy, BR is also a recommended second-line therapy (NCCN Guidelines 2014).

3.3.3 Rationale for Obinutuzumab and Bendamustine Dosing and Schedule

The combination of obinutuzumab with bendamustine is being evaluated in several ongoing studies, including two Phase Ib trials in patients with previously untreated follicular lymphoma (BO21000) and previously untreated CLL (GAO4779g), and two Phase III trials in patients with previously untreated iNHL (BO21223) and rituximab-refractory iNHL (GAO4753g). Of the 41 patients with previously untreated follicular lymphoma in BO21000, 29% experienced Grade 3 or 4 neutropenia and 10% had Grade 3 or 4 infection (Dyer et al. 2012). In the GAO4779g study, 11 of 20 (55%) patients with CLL experienced a Grade 3–4 neutropenia (including 2 patients with Grade 3 or 4 febrile neutropenia) and 1 patient had a Grade 3 skin infection (Brown et al. 2013).

In all of these studies, bendamustine is administered at the standard dose (90 mg/m^2) and on the schedule used in combination with other anti-CD20 MAbs in the front-line and R/R NHL setting. 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).

To maintain consistency with these ongoing trials, the same bendamustine and obinutuzumab dosing schedule will be administered. However, the study regimen will be administered using a 28-day cycle for patients with FL and using a 21-day cycle for patients with DLBCL as reported in the bendamustine and rituximab combination trials (Robinson et al. 2008; Rummel et al. 2010; Ohmachi et al. 2013; Vacirca et al. 2014).

3.3.4 Rationale for Stratification Factors

The clinical course of FL is extremely variable. Although a major determinant of prognosis in newly diagnosed FL is the FLIPI, in relapsed disease the most powerful predictor of outcome is the depth and duration of response to previous therapy. Patients with response duration of >1 year to prior therapy had markedly better duration of response to rituximab-based subsequent therapy at relapse (Coiffier et al. 2011).

In addition to previous response duration, the prognosis of patients with relapsed FL is affected by tumor burden. Although the method for measurement of disease burden varies, the two major approaches are the FLIPI and the GELF criteria. In relapsed FL, the GELF criteria appeared to be superior in predicting PFS (Coiffier et al. 2011).

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

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

3.3.5 Rationale for PET-Defined Complete Response

PET scanning has been shown in multiple settings to be a more accurate tool for assessing activity of lymphoma than CT imaging. In aggressive lymphomas, such as DLBCL, PET-defined CR is a better predictor of PFS than response as defined by CT. The correlation of PET-defined response and PFS has not been as extensively studied in indolent lymphomas. However, a recent evaluation of PET-defined response in patients with FL treated with standard induction therapy using rituximab plus chemotherapy demonstrated that although PFS was not different between patients achieving PR versus CR, as defined by CT scan, when response criteria incorporating PET were used, patients who achieved PET-negative CR had a significantly longer PFS than did patients achieved only a PR as defined by PET (Trotman et al. 2011). These findings indicate that response, as defined by PET, correlates with longer-term outcomes in patients with FL, similar to aggressive lymphomas.

3.3.6 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 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 the TINAS (Thomas et al. 2012).

3.3.7 Rationale for Collecting Lymph Node Biopsy Samples and Peripheral Blood for Biomarker Studies

Biomarkers in the tumor that are associated with drug target, mechanism of action, and NHL biology—including immune infiltrate—may correlate with outcome and carry predictive or prognostic value. The activity of ADCs is dependent on a number of factors including the presence of the antibody target, internalization of the ADC, and sensitivity of the tumor cell to the payload drug; therefore, analysis of these factors may identify markers predictive of response. In addition, new therapeutic approaches in DLBCL

appear to result in differential activity in DLBCL prognostic activated B cell (ABC) versus germinal center B cell (GCB); it is, therefore, of interest to understand the activity of a novel treatment in these DLBCL subtypes. Finally, resistance to cytotoxic treatment may be a result of high expression of anti-apoptotic regulators such as BCL-2. Novel immune therapy approaches for treatment of tumors aim to re-enable a host immune response against the tumor cells. Assessments of apoptotic regulators and immune-infiltrate and their correlation with response are warranted for potential future treatments in combination with BCL-2 inhibitors and immune therapy.

To understand resistance mechanisms to rituximab, bendamustine, or polatuzumab vedotin, collection of a lymph node tissue sample for biopsy is requested from patients who have progressive disease (PD) after a response. This biopsy will allow for the assessment of changes that may be involved in resistance to treatment and for developing novel treatment approaches.

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

3.4 OUTCOME MEASURES

3.4.1 Safety Outcome Measures

The determination of the polatuzumab vedotin RP2D in combination with BR or BG will be assessed using the following primary safety outcome measures for the Phase Ib portion of the study:

- 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
- Formation of ADAs

These safety outcome measures will also be assessed in the Phase II NF Cohort (Arm G and Arm H) in which patients with R/R DLBCL will be administered polatuzumab vedotin (lyophilized) plus BR.

3.4.2 Efficacy Outcome Measures

Response assessment will be determined according to Modified Lugano Response Criteria for Malignant Lymphoma (Lugano Classification; Cheson et al. 2014; see Appendix 4).

- CR at primary response assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) based on PET-CT, as determined by the investigator and IRC
- OR (CR or PR) at primary response assessment based on PET-CT, as determined by the investigator and IRC

- CR at primary response assessment based on CT only, as determined by the investigator and IRC
- OR (CR or PR) at primary response assessment based on CT only, as determined by the investigator and IRC
- BOR (CR or PR) while on study based on PET-CT or CT only, as determined by the investigator
- NF cohort only: OS and EFS based on PET-CT or CT only, as determined by the investigator

In addition, for the DLBCL cohorts, IRC and investigator-assessed BOR, DOR, and PFS will be performed.

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum and plasma concentrations of polatuzumab vedotin, bendamustine, rituximab, and obinutuzumab versus time
- PK parameters based on concentration–time data for polatuzumab vedotin, bendamustine, rituximab, and obinutuzumab when these drugs are given in combination

Serum and plasma concentrations of bendamustine and rituximab will not be assessed in the Phase II NF Cohort (Arm G and Arm H).

Refer to Appendix 2 for the schedule of PK assessments.

3.4.4 Patient-Reported Outcome Measure

The PRO outcome measure for this study is as follows:

- PROs of peripheral neuropathy symptom severity and symptom interference, as measured by the TINAS (Thomas et al. 2012; see Appendix 8)

PRO measures will not be collected for the Phase II NF Cohort (Arm G and Arm H).

3.4.5 Exploratory Outcome Measures

The exploratory biomarker outcome measures for this study are as follows:

- Biomarkers related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab or obinutuzumab. These include, but are not limited to, the assessment of potentially prognostic subsets (i.e., cell of origin), CD79b expression levels, apoptotic regulators (e.g., BCL-2), markers of immune infiltration and/or regulation (e.g., CD8, PD-L1), and identification of other potential prognostic factors.
- Biomarkers will be assessed retrospectively using a tissue block (preferred) or 15 serial freshly cut, unstained slides plus punch biopsy of the tissue block from the time of initial diagnosis and, if possible, at the time of disease progression.

- For quantitative assessment of MRD levels of the lymphoma clone in circulation, blood will be collected at baseline, Cycle 3, Day 15 and Cycle 4, Day 1, and at end of treatment corresponding to tumor assessments.

Biomarkers will not be collected or assessed in Arm G of the Phase II NF Cohort.

Analysis methods will include immunohistochemistry, RNA-based assessment of gene expression, next-generation sequencing of lymphoma DNA in tissue and in peripheral blood to determine the levels of the lymphoma clone. This analysis will enable a better understanding of the underlying biology of these tumors and how polatuzumab vedotin and rituximab or obinutuzumab alter their clinical course. Other exploratory analyses may be conducted should additional slides remain following the planned biomarker analyses.

The exploratory efficacy outcome measures for the main study are as follows:

- 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, for the subgroup of patients with a best overall response of CR or PR, based on PET-CT or CT only, as determined by the investigator assessment
- PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause, based on PET-CT or CT only, as determined by the investigator assessment
- EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression, relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET-CT or CT only, as determined by the investigator assessment
- OS, defined as the time from the date of randomization or first treatment (for G-containing arms) to the date of death from any cause

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form (ICF)
- Age 18 years
- Able to comply with the study protocol, in the investigator's judgment
- Histologically confirmed FL (Grade 1, 2, or 3a) or DLBCL

- Must have received at least one prior therapy for FL or DLBCL. Patients must have either relapsed or have become refractory to a prior regimen as defined below.

  R/R FL

  Relapsed to prior regimen(s) after having a documented history of response (CR, CR unconfirmed [CRu], or PR) of ≥6 months in duration from completion of regimen(s)

  Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy

  R/R DLBCL

  Patients who are ineligible for second-line stem cell transplant (SCT), with progressive disease or no response (stable disease [SD]) <6 months from start of initial therapy (2L refractory)

  Patients who are ineligible for second-line SCT, with disease relapse after initial response ≥6 months from start of initial therapy (2L relapsed)

  Patients who are ineligible for third-line (or beyond) SCT, with progressive disease or no response (SD) <6 months from start of prior therapy (3L+refractory)

  Patients who are ineligible for third-line (or beyond) SCT with disease relapse after initial response ≥6 months from start of prior therapy (3L+relapsed)

  In addition to the above defined responses to prior regimens, the Phase II NF Cohort (Arm G and Arm H) will include the following diagnoses by 2016 WHO classification of lymphoid neoplasms:

  - DLBCL, not otherwise specified (NOS) (including both germinal center B-cell type and activated B-cell type)
  - T-cell/histiocyte-rich large B-cell lymphoma
  - High-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements
  - High grade B-cell lymphoma, NOS
  - Primary mediastinal (thymic) large B-cell lymphoma
  - Epstein-Barr virus positive DLBCL, NOS
- If the patient has received prior bendamustine, response duration must have been >1 year (for patients who have relapsed disease after a prior regimen)
- At least one bi-dimensionally measurable lesion on imaging scan defined as >1.5 cm in its longest dimension
- Confirmed availability of archival or freshly collected tumor tissue prior to study enrollment

  The Phase II NF Cohort (Arm G and Arm H) will be required to submit tissue and pathology report for central pathology review.
- 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, such as extensive bone marrow involvement or hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator. Adequate hematologic function is defined as follows:
  - Hemoglobin ≥ 9 g/dL
  - ANC $\geq 1.5 \times 10^9$/L
  - Platelet count $\geq 75 \times 10^9$/L
- For women who are not postmenopausal (≥ 12 months of non–*therapy*-induced amenorrhea and age > 45 years) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent *(refrain from heterosexual intercourse)* or to use single highly effective or combined contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for ≥ 12 months after the last dose of rituximab or for ≥ 18 months after the last dose of obinutuzumab, and agreement to refrain from donating eggs.

  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.

  Examples of highly effective contraceptive methods with a failure rate of $< 1\%$ per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $<1\%$ per year. Barrier methods must always be supplemented with the use of a spermicide.
- 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 or to use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 6 months after the 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 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.

4.1.2 Exclusion Criteria

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

- History of severe allergic or anaphylactic reactions to humanized or murine MAbs (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to bendamustine, rituximab, or obinutuzumab
- History of sensitivity to mannitol (mannitol is an excipient in bendamustine)
- Prior use of any MAb, radioimmunoconjugate, or ADC within 5 half-lives or 4 weeks, whichever is longer, before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1, Day 1

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

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

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

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

  Ongoing corticosteroid usage is permitted for the purpose of lymphoma symptom control. For further details refer to Section 4.4.1.6.
- Treatment with chimeric antigen receptor T-cell therapy within 100 days prior to Cycle 1, Day 1
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic SCT
- Eligibility for autologous SCT
- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Primary or secondary CNS lymphoma
- Current Grade $>$1 peripheral neuropathy

- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include, but are not limited to:

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

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

  Patients with low-grade, early-stage prostate cancer with no requirement for therapy at any time prior to study are eligible.

- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with intravenous (IV) antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Patients with suspected or latent tuberculosis

  Latent tuberculosis should be confirmed according to local testing requirements.

- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

  Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.

- Positive test results for hepatitis C virus (HCV) antibody

  Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Known history of HIV seropositive status

  For patients with unknown HIV status, HIV testing will be performed at Screening if required by local regulations

- Known infection human T-cell leukemia virus 1 (HTLV-1) virus
- Vaccination with a live vaccine within 28 days prior to treatment

- Recent major surgery (within 6 weeks before the start of Cycle 1, Day 1) other than for diagnosis
- Women who are pregnant or lactating or who intend to become pregnant within a year of the last dose of study treatment in the rituximab cohorts or within 18 months of the last dose of study treatment in the obinutuzumab cohort
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
  - Creatinine $>1.5\times$ULN or a measured creatinine clearance <40 mL/min
  - AST or ALT $>2.5\times$ULN
  - Total bilirubin $\geq 1.5\times$ULN

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

4.1.3 Criteria for Lymph Node Biopsy Tissue

- Eligible patients must have available at the study site a representative formalin-fixed, paraffin-embedded tumor specimen that enabled the definitive diagnosis of FL or DLBCL.
- The specimen must contain adequate evaluable tumor cells ($\geq$20% for excisional biopsy and $\geq$50% if sample is a core biopsy) to enable relevant biomarker analysis.
- A tissue block (preferred) or 15 serial, freshly cut, unstained slides plus punch biopsy of the tissue block accompanied by an associated pathology report will be requested. Punch biopsy is required only with the slide submission. Cytological or fine-needle aspiration samples are not acceptable. In countries that use a different fixative than formalin, available tissue block will be accepted and notation of the type of fixative should be included.

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

Patients enrolled into Arm G of the Phase II NF Cohort will only need to submit tissue and pathology report for central pathology review to confirm diagnosis; no exploratory biomarkers studies will be conducted for this arm. Tissue requirements will be updated in the laboratory manual. Refer to the laboratory manual for more details.

Exploratory biomarker studies will be conducted for patients enrolled in Arm H of the Phase II NF Cohort. Tumor tissue samples will be required along with the corresponding pathology report for central pathology review to confirm diagnosis. Tissue requirements will be updated in the laboratory manual. Refer to the laboratory manual for more details.

A central pathology review of all DLBCL patients, including those in the main study, will be performed to confirm diagnosis. If needed, additional slides from previously collected samples may be requested for DLBCL patients in the main study. Refer to the laboratory manual for more details.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. Patients with either R/R FL or R/R DLBCL will be enrolled. Following the Phase Ib portion of this study, allocation to the bendamustine plus rituximab or the combination of polatuzumab vedotin with bendamustine plus rituximab arms will be randomized and stratified by duration of response to prior therapy (≤12 months vs. >12 months) and disease burden (high vs. low) (see Section 3.1.2.1). Randomization will be performed by an interactive voice or Web-based response system (IxRS) using stratified permuted blocks. Patients will be assigned in an equivalent ratio (1:1) to one of the two treatment arms for each histology group (FL and DLBCL).

After the recommended dose of polatuzumab vedotin in combination with bendamustine plus obinutuzumab is determined, the patients will then be enrolled into the dose expansion portion (20 patients in each histology group).

Enrollment tracking will be performed by the IxRS for all arms, including patients in the NF Cohort.

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 patient number will be assigned and the patient will be randomized to the treatment assignment via the 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. The lyophilized formulation of polatuzumab vedotin will be used in combination with BR in the NF Cohort (Arm G and

Arm H). Patients in all the other cohorts (Arms A–F) will receive the initial liquid formulation.

The original formulation of polatuzumab vedotin is a single-use liquid formulation provided in a 100 mg/10 mL drug product. It is not stable after dilution into saline-containing IV bags, thus requiring a syringe pump for delivery. Therefore, a lyophilized formulation of polatuzumab vedotin has been developed, as 170 mg/vial drug product and 140 mg/vial drug product, to improve product stability upon dilution into saline-containing IV bags. The 170 mg/vial drug product and the 140 mg/vial drug product yield the same product concentration and composition after reconstitution with the intended sterile water for injection reconstitution volumes of 8.8 mL and 7.2 mL, respectively. The 140 mg/vial drug product will be used in this study.

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. For information on the formulation, packaging, and handling of rituximab, see the pharmacy manual and investigator's brochure for rituximab (MabThera/Rituxan).

4.3.1.3 Bendamustine

Bendamustine hydrochloride will be supplied by the Sponsor. Bendamustine hydrochloride is marketed by Cephalon previously as the licensed product Treanda® and now as Bendeka® for the United States and is marketed in Germany by Mundipharma International Corporation Ltd under the name Levact®. For information on the formulation, packaging, and handling of bendamustine hydrochloride, refer to the pharmacy manual.

4.3.1.4 Obinutuzumab

Obinutuzumab (Gazyva® in the United States) will be supplied by the Sponsor. For information on the formulation, packaging, and handling of obinutuzumab, see the pharmacy manual, and investigator's brochure for obinutuzumab (Gazyva).

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Bendamustine plus Rituximab Regimen

Patients will receive a total of six cycles bendamustine and rituximab (BR) (see Figure 5). A cycle is typically 28 days for FL and 21 days for DLBCL.

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

Schedule for Cycle 1

Cycle 1, Day 1

- Rituximab 375 mg/m^2 IV infusion

Cycle 1, Day 2 and Day 3

- Bendamustine 90 mg/m^2 IV infusion

Schedule for Cycles 2–6

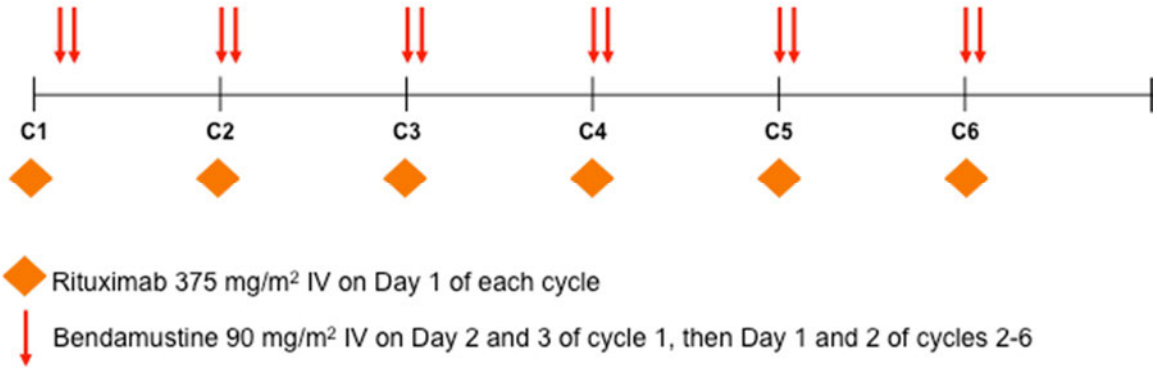
Cycles 2–6, Day 1

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

Cycles 2–6, Day 2

- Bendamustine 90 mg/m^2 IV infusion

Figure 6 Bendamustine plus Rituximab Regimen



C = Cycle; IV = intravenous.

4.3.2.2 Polatuzumab Vedotin plus BR Regimen

Patients will receive a total of six cycles of polatuzumab vedotin in combination with BR (see Figure 7). A cycle is typically 28 days for FL and 21 days for DLBCL. Patients in the NF Cohort (Arm G and Arm H) will follow the same schedule and dosing requirements as patients in the other Phase II cohorts (Arms A–F).

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

Schedule for Cycle 1

Cycle 1, Day 1

- Rituximab 375 mg/m^2 IV infusion

Cycle 1, Day 2

- Polatuzumab vedotin IV infusion

- Bendamustine 90 mg/m^2 IV infusion

Cycle 1, Day 3

- Bendamustine 90 mg/m^2 IV infusion

Schedule for Cycles 2–6

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

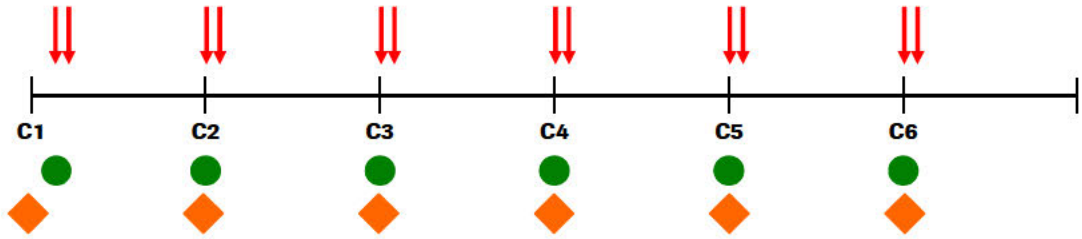
Cycles 2–6, Day 1

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

Cycles 2–6, Day 2

- Bendamustine 90 mg/m^2 IV infusion

Figure 7 Polatuzumab Vedotin plus BR Regimen



Rituximab 375 mg/m² IV on Day 1 of each cycle

Polatuzmab vedotin 1.8 mg/kg IV on Day 2 of Cycle 1, then Day 1 of each subsequent cycle

Bendamustine 90 mg/m² IV on Day 2 and 3 of cycle 1, then Day 1 and 2 of cycles 2-6

BR = bendamustine and rituximab; C = Cycle; D = Day; IV = intravenous.
Follicular lymphoma patients will continue to receive study treatment every 28 days for up to 6 cycles.
Diffuse large B-cell lymphoma patients will receive study treatment every 21 days for up to 6 cycles.

4.3.2.3 Polatuzumab Vedotin plus BG Regimen

Patients will receive a total of six cycles of polatuzumab vedotin in combination with BG (see Figure 8). A cycle is typically 28 days for FL and 21 days for DLBCL.

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

Schedule for Cycle 1

Cycle 1, Day 1

- Obinutuzumab 1000 mg IV infusion

Cycle 1, Day 2

- Polatuzumab vedotin 1.8 mg/kg IV infusion
- Bendamustine 90 mg/m^2 IV infusion

Cycle 1, Day 3

- Bendamustine 90 mg/m^2 IV infusion

Cycle 1, Day 8 and Day 15

- Obinutuzumab 1000 mg IV infusion

Schedule for Cycles 2–6

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

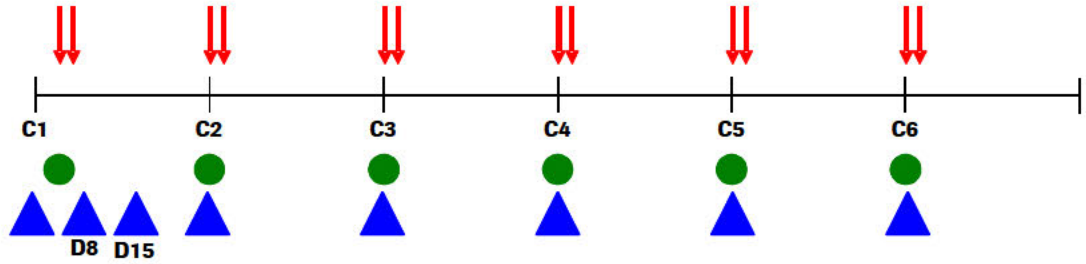
Cycles 2–6, Day 1

- Obinutuzumab 1000 mg IV infusion
- Polatuzumab vedotin 1.8 mg/kg IV infusion
- Bendamustine 90 mg/m^2 IV infusion

Cycles 2–6, Day 2

- Bendamustine 90 mg/m^2 IV infusion

Figure 8 Polatuzumab Vedotin plus BG Regimen



▲ Obinutuzumab 1000 mg IV on Day 1, 8, and 15 of Cycle 1, then Day 1 of each Cycle 2-6

● Polatuzmab vedotin 1.8 mg/kg IV on Day 2 of Cycle 1, and Day 1 of each subsequent cycle

↓ Bendamustine 90 mg/m² IV on Day 2 and 3 of Cycle 1, then Day 1 and 2 of Cycles 2-6

BG = bendamustine and obinutuzumab; C = Cycle; D = Day; IV = intravenous.
Follicular lymphoma patients will continue to receive study treatment every 28 days for up to 6 cycles.
Diffuse large B-cell lymphoma patients will receive study treatment every 21 days for up to 6 cycles.

4.3.2.4 Polatuzumab Vedotin

The patient weight obtained during screening (Day –28 to Day –1) should be used for dose determination for all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle >10% from the weight obtained during screening, the new weight should be used to calculate the dose. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. All subsequent doses should be modified accordingly.

Patients in the NF Cohort (Arm G and Arm H) will follow the same schedule and dosing requirements as patients in the other Phase II cohorts (Arms A–F). *Refer to* the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure for additional preparation instructions.

Polatuzumab vedotin (liquid formulation) will be administered to patients by IV infusion with use of syringes and syringe pumps with use of a 0.22-μm in-line filter on the infusion set following dilution in 0.9% NaCl, with a final polatuzumab vedotin concentration determined by dose and patient weight. 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 composed of specific materials; consult the study team for a list of approved materials.

Polatuzumab vedotin (lyophilized) is handled differently than the liquid formulation and does not require a syringe pump for IV administration. *R*efer to the pharmacy manual for instructions on preparation and administration.

The following administration instructions apply to the liquid and lyophilized formulations.

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

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

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

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

4.3.2.5 Rituximab

Rituximab 375 mg/m^2 will be administered by IV infusion with bendamustine alone or in combination with polatuzumab vedotin and bendamustine, as outlined in Section 4.3.2.1 and Section 4.3.2.2. Rituximab will be administered on Day 1 of Cycles 1–6. No dose modifications of rituximab are allowed.

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

The rituximab administration should be completed at least 30 minutes before administration of other study treatments. The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). Administration of rituximab may be continued on the following day, if needed, for patients who experience an adverse event during the rituximab infusion. If a

dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication and at the first infusion rate (see Table 3).

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.

Rituximab infusions will be administered according to the instructions in Table 3. If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as rapid infusion (e.g., over 60–90 minutes) in accordance with local institutional guidelines.

During the treatment period, rituximab must be administered to patients in a setting where full emergency resuscitation facilities are immediately available. Patients should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 5.1.5.5.

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

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

Table 3 Administration of First and Subsequent Infusions of Rituximab

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

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

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

4.3.2.6 Obinutuzumab

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with polatuzumab vedotin and bendamustine, as outlined in Section 4.3.2.3. Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–6 (see Table 4). No dose modifications of obinutuzumab are allowed.

All obinutuzumab infusions should be administered after premedication with oral acetaminophen and an antihistamine (see Section 4.4.1.2). 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 5.1.5.5.

The administration of obinutuzumab should be completed at least 30 minutes before administration of other study treatments. 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. If the dose of obinutuzumab is split over 2 days, patients may receive 100 mg on Day 1 and 900 mg on Day 2.

Table 4 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 $\geq$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 5.1.5.5.

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 ≥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.

For further details, refer to the label of Gazyva.

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

4.3.2.7 Bendamustine

All patients will receive bendamustine administered intravenously on 2 consecutive days of each 21-day or 28-day cycle for up to six cycles. The dose and schedule of bendamustine administered will depend on whether the patient has R/R FL or R/R DLBCL.

R/R Follicular NHL:

- Bendamustine at 90 mg/m^2 administered IV over 30–60 minutes on 2 consecutive days (Days 2 and 3 in Cycle 1, then Days 1 and 2 in Cycles 2–6) of each cycle, for up to six cycles. Each cycle is 28 days.

R/R DLBCL:

- Bendamustine at 90 mg/m^2 administered IV over 30–60 minutes on 2 consecutive days (Days 2 and 3 in Cycle 1, then Days 1 and 2 in Cycles 2–6) of each cycle, for up to six cycles. Each cycle is 21 days.

BSA will be calculated at screening and should be used to calculate the dose of bendamustine throughout the study unless the patient's weight increases or decreases by >10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients (obesity defined as body mass index ≥30 kg/m^2) may be implemented per institutional guidelines.

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

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

Dose modification and dose delays will be implemented for hematologic toxicities. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.5.2.

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

4.3.3 Investigational Medicinal Product Accountability

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

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

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

4.3.4 Post-Trial Access to Polatuzumab Vedotin

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., covered by the patient's insurance or otherwise does not 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 FL or DLBCL
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for FL or 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 Internet 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 prior to screening to the study treatment completion visit, which is 30 (±5) days after the last dose of study treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients may continue to use oral contraceptives, hormone-replacement therapy, or other maintenance therapies.

MMAE is a substrate of the cytochrome P450 (CYP450) enzymes, specifically CYP3A. Published data suggest that MMAE is neither an inhibitor nor inducer of CYP3A. Patients who are receiving strong CYP3A inhibitors should be closely monitored for adverse reactions when given polatuzumab vedotin (Han et al. 2013).

4.4.1.1 Treatment and Prophylaxis of Neutropenia

The administration of G-CSF is required as a primary prophylaxis in each cycle of therapy. The dose and form of G-CSF will be at the discretion of the investigator. The use of additional G-CSF is allowed for the treatment of neutropenia per investigator discretion. The decision not to administer G-CSF as primary prophylaxis should be made in consultation with and following the approval of the Medical Monitor.

4.4.1.2 Premedication 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) orally 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 glucocorticoids (e.g., 100 mg prednisone or prednisolone or equivalent) 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.

4.4.1.3 Premedication for Patients at High Risk for Tumor Lysis Syndrome

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

4.4.1.4 Prophylaxis for Infections

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

4.4.1.5 Monitoring and Treatment for Hepatitis B Reactivation

Patients who are both HBsAg negative and anti-HBc positive may be included in this study. These patients should have HBV DNA levels obtained monthly during the study and for at least 12 months after the last cycle of therapy by means of real time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

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

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

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

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving anti-viral medication, study treatment will be permanently discontinued (see Section 5.1.5, Table 7).

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

4.4.1.6 Other Concomitant Medications

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

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

Systemic steroid therapy will not be allowed either during or within 7 days before the first dose of study treatment with the exception of the following:

- Inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease (COPD)
- Premedication before rituximab, obinutuzumab, polatuzumab vedotin or bendamustine (see Section 4.4.1.2)
- Topical steroids
- Stable replacement corticosteroid therapy for an inherited or acquired deficiency
- Ongoing corticosteroid use for lymphoma symptom control
- Corticosteroid treatment $\leq$30 mg/day of prednisone or equivalent on a stable dose prior to study enrollment and initiation of therapy (see Section 4.1.2)

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.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy, other than bendamustine and intrathecal chemotherapy for CNS prophylaxis
- Immunotherapy or immunosuppressive therapy, other than study treatments
- Radioimmunotherapy

- Hormone therapy, other than contraceptives, stable 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 therapy (other than intrathecal CNS prophylaxis) intended for the treatment of lymphoma whether it is approved by the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA) or is experimental
- Radiotherapy

4.4.2.1 Immunizations

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

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

4.5 STUDY ASSESSMENTS

Unless otherwise stated, the baseline measurement for any given assessment will be defined as the last value obtained before the first dose of study drug. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.1 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. ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before 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 Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies, reason for transplant ineligibility, 2016 WHO classification, current Ann Arbor stage, and procedures), ECOG performance status,

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

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Prognostic Indices

FLIPI and FLIPI2 clinical factors obtained at diagnosis and at enrollment will be collected for patients with FL. IPI clinical factors at diagnosis and at enrollment will be collected for patients with DLBCL. See Appendix 10 for description of the FLIPI, FLIPI2, and IPI.

4.5.4 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment [lymph nodes, liver, and spleen]). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Total Neuropathy Score Clinical Assessment

All patients participating in the study should undergo a Clinical Total Neuropathy Assessment (Cavaletti et al. 2006; Cavaletti et al. 2007) as shown in the schedule of assessments (see Appendix 1). The neuropathy assessments include subjective sensory symptoms, motor symptoms, and autonomic symptoms and objective pinprick sensitivity, vibration sensitivity, strength testing, and deep tendon reflex testing to determine the total neuropathy score (see Appendix 7).

Patients enrolled in the NF Cohort (Arm G and Arm H), receiving polatuzumab vedotin (lyophilized) in combination with BR, will be exempt from the Clinical Total Neuropathy Assessment. Investigators will assess neuropathy per usual clinical practices and document neuropathy as an adverse event.

4.5.6 Vital Signs

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

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

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

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

4.5.7 Tumor and Response Evaluations

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

Radiographic Assessments

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

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

In patients for whom contrast is contraindicated (e.g., patients with contrast allergy or impaired renal clearance), CT or combined PET-CT scans without contrast are permitted so long as they permit consistent and precise measurement of target lesions during the

study treatment period. Details regarding imaging procedures in these cases will be provided in the Imaging Manual.

PET scans, in conjunction with diagnostic-quality CT scans, will be obtained in this study. PET and diagnostic-quality CT scans are required at screening, after Cycle 3 of study treatment (i.e., between Cycle 3, Day 15, and Cycle 4, Day 1), and at the primary response assessment visit. CT scans without PET scans will be obtained every 6 months until approximately 2 years after the treatment completion visit. The Modified Lugano Response Criteria (see Appendix 4) will be used to assess overall response to study treatment.

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

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 for staging purposes in all patients. In addition, the definition of CR requires clearing of previously infiltrated bone marrow. Bone marrow examinations should include a biopsy for morphology and an aspirate for local hematology (optional if standard of care at the site).

Repeat bone marrow examinations are required in two circumstances.

If there was bone marrow infiltration at screening, then a subsequent bone marrow biopsy (trephine) at the primary response assessment visit is required for clinical response evaluation for all patients who may have achieved a CR. In patients with a PR and continued bone marrow involvement, a subsequent bone marrow examination may be required to confirm a CR at a later timepoint.

An optional biopsy should be done at the time of relapse or transformation if bone marrow involvement is suspected. A tissue sample should be collected at that time. A formalin-fixed, paraffin-embedded tissue block over 15–20 unstained sections on coated slides is preferred.

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

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Local Laboratory Assessments

Samples for hematology, serum chemistry, pregnancy, hepatitis B and C serology, and quantitative immunoglobulin assessments will be analyzed at the study site's local laboratory. In the event the study site's local laboratory cannot adhere to protocol requirements for hepatitis B serology tests, the option to submit samples for analysis to

the central laboratory is available. Laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle.

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

- Hematology (hemoglobin, hematocrit, RBC count, WBC count, platelet count, and percent or absolute differential [neutrophils, bands, lymphocytes, eosinophils, basophils, and monocytes])
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN/urea, creatinine, calcium, magnesium, phosphorus, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, uric acid/urate, hemoglobin A_{1c} (HbA_{1c}), amylase, and lipase. At screening, all samples for laboratory test will be obtained in a fasting state for all patients according to local guidelines. Subsequent laboratory tests can be non-fasting. HbA_{1c} will be measured only at screening and at Cycle 4, Day 1 and can be obtained in a non-fasting state. Only at screening, obtain β-2 microglobulin.
- Coagulation: INR or PT, and PTT or aPTT
- Viral serology:
  - Hepatitis B surface antibody (HBsAb), HBsAg, and total HBcAb
  - HBV-DNA by PCR if the patient is HBcAb positive
  - HCV antibody
  - HCV RNA by PCR if the patient is HCV antibody positive
- Quantitative immunogloblulins: IgG, IgA, and IgM
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test within 7 days before Cycle 1, Day 1 of study treatment. In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed prior to study treatment on Day 1 of each subsequent cycle of study treatment (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.
- Bone marrow biopsy and aspirate

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

Central Laboratory Assessments

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

- Lymphocyte subsets

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

- PK assessments (see Appendix 2)
  - Immunogenicity assessment (see Appendix 2)
  - Plasma and serum samples for anti-polatuzumab vedotin antibody
  - Plasma and serum samples for anti-obinutuzumab antibody

    Serum samples collected for PK and ADA analysis which may be used for additional method development, including but not limited to, assay validation and characterization, will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

- Central pathology review for confirmation of diagnosis

  Central review of pathology reports and tissue samples will be performed to confirm diagnosis for all DLBCL patients in the study. For DLBCL patients that are in the main study, additional slides may be requested. Refer to the laboratory manual for more details.

- Required samples for exploratory biomarker research are as follows:

  Tumor tissue sample is required at baseline (archival tissue or fresh pre-treatment biopsy is acceptable). Biopsy at the time of progression/transformation is optional. Tumor blocks are preferred. If a tumor block is not available, a minimum of 15 serial freshly cut, unstained slides and a punch biopsy of the tumor block are required. Tumor block or punch biopsy is required for construction of a tissue microarray. The remainders of the tissue blocks will be returned to local pathology according to country-specific procedures.

  A peripheral blood sample for MRD analysis is required for all patients at screening, between Cycle 3, Day 15, and Cycle 4, Day 1, and at the Primary Response Assessment Visit.

  A whole blood and plasma sample will be collected for the analysis of prognostic factors.

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

Patients enrolled in the NF Cohort (Arm G), receiving polatuzumab vedotin (lyophilized) plus BR, will be exempt from exploratory biomarker research samples.

Optional Exploratory Biomarkers for Roche Clinical Repository (see Section 4.5.11)

- Patients may give consent to the acquisition blood samples by signing the Optional Research ICF. Optional samples for exploratory biomarker research are as follows:

  Residual tumor tissue specimens from biopsy samples at baseline and at progression.

  Leftover blood samples from MRD analysis and exploratory whole blood and plasma samples

  If patients consent to participate in the optional exploratory biomarker research, residual blood, plasma, tissue samples, and their derivatives (e.g., including but not limited to RNA, DNA, tissue microarrays, unstained sections, etc.) will be stored in the RCR for up to 15 years after the date of final closure of the associated clinical database to enable future research.

4.5.9 Electrocardiograms

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

4.5.10 Patient-Reported Outcomes

The TINAS is an 11-item questionnaire focused on symptoms of neuropathy related to treatment that is 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 asking 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.

The TINAS will be completed weekly over the course of study treatment, either while on site or at home. Additionally, to collect information about the reversibility of peripheral neuropathy following treatment completion, the TINAS will be completed once a week for the first 2 months following treatment, then once a month for the next 10 months.

The TINAS, 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) or on a device provided to the patient for the purpose of this study to allow for the secure access and transmission of the questionnaire. The eDiary software and

instructions for completing the TINAS electronically will be provided by the Investigator Staff. All measures are to be completed in their entirety by the patient. The data will be transmitted automatically via Web or wireless to a centralized database at the ePRO vendor. To ensure instrument validity and that data standards meet health authority requirements, the TINAS should be completed prior to the completion of other study assessments and the administration of study treatment.

Patients enrolled in the NF Cohort (Arm G and Arm H), receiving polatuzumab vedotin (lyophilized) plus BR, will be exempt from completing the TINAS.

4.5.11 Samples for Roche Clinical Repository

4.5.11.1 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:

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

4.5.11.2 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 ICF by each site's Institutional Review Board or Ethics Committee (IRB/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 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be collected at specific timepoints (see Table 5) for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers:

Residual tumor samples from collection site lymph node biopsy may be submitted at the

screening visit or at disease progression for DNA, RNA, or protein extraction.

- Whole blood and plasma samples for DNA, RNA, or protein extraction will be drawn at the baseline visit and at the end of treatment.
- Residual samples of peripheral blood from MRD analysis.

Table 5 Sample Collection

Sample	Timepoint
Residual whole blood and plasma and their derivatives (e.g., DNA, RNA, protein, etc.)	• Baseline • Primary Response Assessment
Residual tissue (i.e., unstained sections, progression tissue blocks, tissue microarrays), and tissue derivatives (e.g., tumor RNA and DNA)	• Baseline • Progression/transformation
Residual plasma and DNA extracted from samples of peripheral blood (remaining DNA after analysis of [minimal residual disease])	• Baseline between Cycle 3, Day 15 and Cycle 4, Day 1 • Primary Response Assessment (peripheral blood)

Dates of consent should be recorded on the associated RCR page of the eCRF. See the laboratory manual for sampling procedures, storage conditions, and shipment instructions.

Roche Clinical Repository 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 ICF 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.

4.5.11.4 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 the Legal Department at Roche, 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 ICF (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.

4.5.11.5 Consent to Participate in the Roche Clinical Repository

The ICF 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.

A separate, specific signature is not required for the mandatory RCR blood samples collected at baseline.

4.5.11.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their *consent* at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RCR samples have been tested prior to withdrawal of consent, results from those tests will*

remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her *RCR samples during the study*, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the *appropriate* RCR Subject Withdrawal Form and must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. *If a patient wishes to withdraw consent to the testing of his or her RCR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:*

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study GO29365 does not, by itself, constitute withdrawal of *content for testing of RCR samples*. Likewise, a patient's withdrawal *of consent for testing of* RCR *samples* does not constitute withdrawal from Study GO29365.

4.5.11.7 Monitoring and Oversight

Roche Clinical Repository 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 ICF. 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.

4.5.12 Timing of Study Assessments

4.5.12.1 Screening and Pretreatment Assessments

A signed ICF for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

Screening and pretreatment tests and evaluations will be performed within 28 days before first dose, unless otherwise specified. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before first dose may be used; such tests do not need to be repeated for screening. 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.

See Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.12.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments

scheduled on the day of study treatment administration should be performed before administration of study treatment, unless otherwise noted in the schedule of assessments.

See Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.12.3 Follow-Up Assessments

Month 0 in follow-up is considered to be the treatment completion visit.

Treatment Completion Visit

Patients who complete the study treatment period (defined as completion of six cycles of study treatment) or discontinue from the study treatment early (e.g., if they terminated treatment early because of an adverse event) will be asked to return to the clinic within 30 days (±5 days) after the last dose of study treatment for a treatment completion visit. The visit at which response assessment shows progressive disease may be used as the treatment completion visit.

See Appendix 1 for the schedule of assessments performed at the treatment completion visit.

Primary Response Assessment Visit

All patients will be asked to return to the clinic for the primary response assessment visit. This visit is to take place between 6 and 8 weeks after the last dose of study treatment.

For patients with disease progression occurring prior to the anticipated date of the Primary Response Assessment visit, the visit date with the response assessment showing PD may be used in replacement of the Primary Response Assessment Visit.

See Appendix 1 for the schedule of assessments performed at the primary response assessment visit.

Every 3–Month Visit or Every 6-Month Visit until End of Study

For patients without disease progression, assessments will be performed every 3 months ±14 days after the treatment completion visit, until Month 24 and then every 6 months (±14 days) thereafter until the end of study (i.e., the last patient in completes follow-up of 2 years), patient withdraws consent or Sponsor closes the study. Other assessments are indicated in Appendix 1.

Disease Progression and No New Treatment

If response assessment shows PD during the follow-up period, subsequent visits will have assessments limited to recording of any new anti-lymphoma therapy, the occurrence of adverse events (per Section 5.3 and Section 5.4), and survival. 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 new anti-lymphoma

therapy. If no new treatment is started, the subject will be followed per the usual follow-up schedule described above.

Disease Progression and New Treatment

After a patient has PD during follow-up and starts a new anti-lymphoma therapy, contact will be made with patients by telephone on at least an annual basis for survival.

No Disease Progression and New Treatment

Patients who discontinue study treatment early because of adverse event and start a new anti-lymphoma therapy in the absence of PD should be followed according to the protocol schedule, including the response assessments and the reporting of adverse events until 90 days after the last dose of study drug (see Section 5.3 and Section 5.4) unless they withdraw consent.

See the schedule of assessments provided in Appendix 1 for specified follow-up assessments.

4.5.12.4 Assessments at Unplanned Visits

See Appendix 1 for assessments that are required in the event of an unplanned visit.

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

A patient must discontinue study treatment permanently if any of the following occurs:

- Grade 4 IRR: The patient should be withdrawn from study treatment immediately and rituximab or obinutuzumab and bendamustine treatment should be permanently discontinued.

- Recurrence of Grade 3 IRR at re-challenge: Treatment should be permanently discontinued.
- Patients with infusion-related Grade ≥3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study drug on the first occurrence.
- Grade ≥3 toxicity that does not resolve to Grade ≤2 or baseline value within 3 weeks after last dose and that has a reasonable possibility of being related to the administration of polatuzumab vedotin, rituximab, or obinutuzumab, and/or bendamustine
- Recurrent Grade 4 neutropenia with infection, despite G-CSF support
- Grade 4 neurotoxicity including peripheral neuropathy (polatuzumab vedotin only)
- Grade 3 neurotoxicity that leads to a treatment delay of 14 days or more and does not improve to Grade ≤2 within 14 days
- Disease progression
- Any dose delay of ≥4 weeks
- Pregnancy

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

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

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

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

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference for Harmonisation (ICH) guideline for GCP

- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Polatuzumab vedotin is *approved by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other health authority regulatory agencies for use in patients with transplant-ineligible R/R DLBCL.* 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 adverse events, from Cycle 1, Day 1, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug. After this period, the Sponsor should be notified of any post-study serious adverse events or non-serious adverse events of special interest, regardless of attribution (see Section 5.3.1 for reporting details).
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs and physical findings on clinical physical examinations

5.1.1 Risks Associated with Polatuzumab Vedotin

The clinical safety profile of polatuzumab vedotin is based on clinical data obtained in ongoing and *completed* studies. This profile is summarized in Section 1.2.1. On the basis of clinical data to date, the known and suspected risks are described below. Polatuzumab vedotin (170 mg/vial lyophilized) is currently in use in other clinical trials with an observed safety profile that is consistent with the known safety profile. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.5. Refer also to the *current* Investigator's Brochure for complete and updated details.

5.1.1.1 Known Risks

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

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

Neutropenia, neutropenia-associated events*, thrombocytopenia, and anemia,* including *serious and severe cases,* have been *reported* in *patients receiving polatuzumab vedotin*. Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Study treatment for hematologic toxicities may be delayed or modified as described in Section 5.1.5. The use of G-CSF for neutropenia is described in Section 4.4.1.1. G-CSF primary prophylaxis is required for neutropenia. The decision not to administer G-CSF as primary prophylaxis should be made in consultation with and following the approval of the Medical Monitor. *Transfusion support for anemia and thrombocytopenia is permitted at the discretion of the investigator.*

Peripheral Neuropathy

Patients receiving polatuzumab vedotin may develop peripheral neuropathy, including peripheral sensory and/or motor neuropathy. These events have generally been reversible to varying degrees as much as available, but it is not known if full reversibility can be expected or predicted. Patients in clinical trials with polatuzumab vedotin should be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require a dose delay, change in dose, or discontinuation of treatment and should be managed according to the protocol. Monitoring will include the use of the Total Neuropathy Score (TNS) except in the NF Cohort, which will be monitored by the standard clinical evaluation per investigator's discretion.

Study treatment dose and schedule modifications for peripheral neuropathy are described in Section 5.1.5.

Infections

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

Given the risk of infections associated with bendamustine and the potential added risk with polatuzumab vedotin, antiviral (coverage for HSV and VZV), and

anti-pneumocystis prophylaxis are required beginning at the initiation of study treatment and continuing for at least 6 months after the completion of study treatment. If clinically indicated, anti–infective prophylaxis for other infectious agents is permitted.

Infusion-Related Reactions

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

Premedication and monitoring procedures for polatuzumab vedotin infusion administration are outlined in Section 4.3.2.4.

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

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

5.1.1.2 Potential Risks

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

5.1.1.2.1 Effects on the Relative-Dose Intensity of BR or BG

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

5.1.1.2.2 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a risk if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, tumor lysis prophylaxis measures will be taken. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/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 orally or a suitable alternative treatment [according to institutional practice] starting 12–24 hours before study treatment) and must be well hydrated before the initiation of study treatment at Cycle 1, Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion, as deemed appropriate by the investigator.

5.1.1.2.3 Immunogenicity *(Anti-Drug 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 ADAs before, during, and after the treatment with polatuzumab vedotin. Given the historically low immunogenicity rate of rituximab in patients with NHL, ADAs against rituximab will not be monitored in this study.

5.1.1.2.4 Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of polatuzumab vedotin given the mechanism of action of MMAE. Standard exclusion criteria are used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

5.1.1.2.5 Hyperglycemia

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

5.1.1.2.6 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.

Transient elevations of transaminases have been reported in patients receiving polatuzumab vedotin and have ranged in intensity from Grade 1 to Grade 2. These have been reversible with and without dose modification. Two patients treated with polatuzumab vedotin have experienced serious adverse events, including fatty infiltration of the liver (steatosis) in one patient and hepatic cytolysis in the other. Both were deemed “related” to polatuzumab vedotin and both patients fully recovered following discontinuation of the polatuzumab vedotin. The relationship between polatuzumab vedotin and these two events is not known.

5.1.1.2.7 *Carcinogenicity*

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

5.1.2 Risks Associated with Rituximab Therapy

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

5.1.2.1 Infusion-Related Reactions

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

5.1.2.2 Tumor Lysis Syndrome

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

5.1.2.3 Hepatitis B Reactivation

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

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

5.1.2.4 Progressive Multifocal Leukoencephalopathy

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

hematopoietic SCT. Most cases of PML were diagnosed within 12 months of the patient's last infusion of rituximab.

5.1.2.5 Cardiac Toxicity

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

5.1.2.6 Infection

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, Varicella zoster virus, West Nile virus, and hepatitis B and C viruses.

5.1.2.7 Severe Mucocutaneous Reactions

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

5.1.2.8 Bowel Obstruction and Perforation

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

5.1.3 Risks Associated with Bendamustine

Please see the United Kingdom Summary of Product Characteristics for Bendamustine for full information.

5.1.3.1 Myelosuppression

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

5.1.3.2 Infection

Infection, including pneumonia and sepsis, has been reported. Patients with myelosuppression after treatment with bendamustine are more susceptible to infections. The study physician will treat patients with clinical evidence of infection appropriately. See Section 5.1.5 for monitoring plans and Table 7 for instructions for dose delay and modification of bendamustine. Antiviral (coverage for HSV, VZV) and anti-pneumocystis prophylaxis are required beginning at the initiation of study treatment and continuing for at least 6 months after the completion of study treatment. Opportunistic infections have occurred with treatment of bendamustine. Evaluation for opportunistic infections is recommended in cases of unexplained and prolonged fever, unexplained transaminitis, or unexplained/ongoing symptoms such as diarrhea, nausea, and neurological changes.

5.1.3.3 *Hepatitis B Reactivation*

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received bendamustine hydrochloride. Some cases resulted in acute hepatic failure or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with bendamustine hydrochloride. Carriers of HBV who require treatment with bendamustine hydrochloride should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

5.1.3.4 Infusion-Related Reactions and Anaphylaxis

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

5.1.3.5 Tumor Lysis Syndrome

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

5.1.3.6 Skin Reactions

A number of skin reactions have been reported with bendamustine treatment, including rash, toxic skin reactions, and bullous exanthema. In a study of bendamustine in combination with rituximab, one case of TEN occurred. TEN has been reported for rituximab. Cases of Stevens-Johnson syndrome*, TEN* and *Drug Reaction with Eosinophila and Systemic Symptoms (DRESS),* some fatal, have been reported *with the*

use of bendamustine. Patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine should be withheld.

5.1.3.7 Long-Term Stem-Cell Toxicity

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

5.1.3.8 Extravasation of Bendamustine

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

5.1.3.9 Transfusion-Associated Graft versus Host Disease

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

5.1.3.10 Drug Interactions

Certain medications may interact with bendamustine. Caution should be used or alternative treatments should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed. CYP1A2 inhibitors and inducers are not contraindicated. During treatment with bendamustine, patients will be provided with a card to keep with them that provides notification to other health care providers that the patient is taking bendamustine as a participant in a clinical study (see Appendix 9).

5.1.4 Risks Associated with Obinutuzumab

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

5.1.4.1 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. Patients with pre-existing cardiac conditions may experience worsening of their cardiac disease.

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.

Hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g., serum sickness) have been reported in patients treated with obinutuzumab.

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

5.1.4.2 Tumor Lysis Syndrome

TLS has been reported with obinutuzumab administration. 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. All patients with peripheral blood lymphocyte counts of $\geq 25 \times 10^9$/L or bulky adenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration, consisting of fluid intake of approximately 3 L/day, starting 1−2 days prior to the first dose of obinutuzumab, and administration of allopurinol (300 mg/day orally) or a suitable alternative (i.e., rasburicase) treatment, starting at 12−24 hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts $\geq 25 \times 10^9$/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. For further details please refer to the label of Gazyva.

5.1.4.3 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 required. The decision not to administer G-CSF as primary prophylaxis should be made in consultation with and following the approval of the Medical Monitor.

5.1.4.4 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.

5.1.4.5 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, including some fatal infections, have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

In the FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in maintenance. 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. Particular attention should be given to patients who have previously received significant immunosuppressive treatment, such as high-dose chemotherapy and SCT.

JC viral infections (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.

5.1.4.6 *Impaired* Immunization *Response*

The safety of immunization with live virus vaccines following obinutuzumab therapy has not been studied. Thus, vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

5.1.4.7 Worsening of Preexisting Cardiac Condition

In patients with underlying cardiac disease and treated with obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias, including atrial fibrillation and tachyarrhythmia, have been observed. 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 to prevent a potential fluid overload.

5.1.4.8 Gastrointestinal Perforation

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

5.1.5 Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 7. Additional guidelines are provided in the subsections below.

5.1.5.1 Dose Delays and Dose Modifications

Patients should be assessed clinically for toxicity before each dose using NCI CTCAE v4.03 unless otherwise stated. These guidelines pertain to dose delays and modifications based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable. Dose delays and dose modifications due to adverse events not specified in this section should proceed on the principle of maintaining the dose intensity of bendamustine. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment in consultation with the Medical Monitor and with the approval of the Medical Monitor.

5.1.5.2 Dose Modifications

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

Bendamustine and polatuzumab vedotin doses may be reduced (per the guidelines outlined in Table 8) with the approval of the Medical Monitor.

5.1.5.3 Dose Delay

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

For guidelines for dose delay for obinutuzumab for febrile neutropenia or neutropenia with infection or thrombocytopenia at Cycle 1, Day 8, and Cycle 1, Day 15, see Table 8.

5.1.5.4 Schedule Modifications

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

5.1.5.5 Non-Hematologic Toxicities

5.1.5.5.1 Infusion-Related Reactions and Anaphylaxis

Medications including epinephrine for SC injections, corticosteroids, diphenhydramine hydrochloride for IV injection, and resuscitation equipment should be available for immediate use. Management of infusion-related symptoms for both rituximab and obinutuzumab are summarized in Table 6 according to the administration rates in Section 4.3.2.5 and Section 4.3.2.6. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, rituximab or obinutuzumab should be discontinued and no additional drug should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment. See Appendix 6 for recommended management of anaphylaxis.

Patients who experience rituximab- or obinutuzumab-associated infusion-related temperature elevations of $>38.5°C$ or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol (500–1000 mg) and/or H_1- and H_2- histamine receptor antagonists (e.g., diphenhydramine hydrochloride) and ranitidine. Serious infusion-related events, manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress, should be managed with additional supportive therapies (e.g., supplemental oxygen, β_2-agonists, epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice. See Appendix 6 for recommended management of anaphylaxis.

Guidelines for the management of IRRs and anaphylaxis are detailed in Table 6.

Table 6 Management of Infusion-Related Symptoms

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

IV = intravenous; NCI CTCAE v4.03 = National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Refer to the NCI-CTCAE v4.03 scale for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text following this table.

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

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

Table 7 Guidelines for Dose Delay or Modification of Polatuzumab Vedotin, Rituximab, Obinutuzumab, or Bendamustine

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia on Day 1 of any Cycle with or without infection or fever [a] First delay	• Delay all study treatment. Treatment cannot be delayed for more than 2 weeks. • Administer growth factors as appropriate; (e.g., G-CSF for neutropenia as indicated and for all subsequent cycles). • If ANC recovers to >1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of polatuzumab vedotin, bendamustine, and rituximab or obinutuzumab. • If ANC recovers to >1000/μL on or after Day 8 of the scheduled date for the next cycle, reduce the dose of bendamustine to 70 mg/m^2. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of bendamustine. Decisions must be made in consultation with and with approval of the Medical Monitor.

Recurrent Grade 3 or 4 neutropenia on Day 1 of any Cycle	• Delay doses of all study treatment. Treatment cannot be delayed for more than 2 weeks.
	• If ANC recovers to >1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of study treatment.
	• If ANC recovers to >1000/μL on or after Day 8 of the scheduled date for the next cycle, then:
	  • If the dose of polatuzumab vedotin is 1.8 mg/kg, then reduce bendamustine to the next lowest dose level of 70 mg/m^2 (1st dose reduction) and maintain polatuzumab vedotin dose of 1.8 mg/kg. If there was a prior dose reduction, then reduce bendamustine to the next lowest dose level of 50 mg/m^2 (2nd dose reduction) and maintain polatuzumab vedotin dose at 1.8 mg/kg.
	  • No dose reductions of polatuzumab vedotin for neutropenia are allowed.
	  • No more than 2 dose reductions of bendamustine are allowed. If patient develops persistent Grade 3 or 4 neutropenia despite growth factor support and after bendamustine dose reductions, permanently discontinue all study treatment.

Severe thrombocytopenia (platelets <10,000/μL) and/or symptomatic bleeding in patients who are 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. For guidelines for dose delay for obinutuzumab on Cycle 1, Day 8 and Cycle 1, Day 15, see Table 8.

Event(s)	Dose Delay or Modification
Thrombocytopenia with platelets $<$20,000/μL and/or symptomatic bleeding in patients who are 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. For guidelines for dose delay for obinutuzumab on Cycle 1, Day 8, and Cycle 1, Day 15, see Table 8. • 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]
Grade 3 or 4 thrombocytopenia on Day 1 of any cycle, first episode	• Delay doses of all study treatment. • If platelet count recovers to $>$75,000/μL by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment. • If platelet count recovers to $>$75,000/μL on or after Day 8 of the scheduled date of the next cycle, reduce the dose of bendamustine to the next (lowest) dose level (70 mg/m^2). Full dose of BR may be given to patients on Arm B and Arm D (BR only arms). • If the patient had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of bendamustine.

Recurrent Grade 3 or 4 thrombocytopenia	• Delay doses of all study treatment.
	• If platelet count recovers to $>$75,000/μL by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment
	• If platelet count recovers to $>$75,000/μL on or after Day 8 of the scheduled date of the next cycle, then:
	  • If the dose of polatuzumab vedotin is 1.8 mg/kg, then reduce bendamustine to the next lowest dose level of 70 mg/m^2 (1st dose reduction) and maintain polatuzumab vedotin dose of 1.8 mg/kg. If there was a prior dose reduction, then reduce bendamustine to the next lowest dose level of 50 mg/m^2 (2nd dose reduction) and maintain polatuzumab vedotin dose at 1.8 mg/kg.
	  • No more than 2 dose reductions of bendamustine are allowed.
	  • If patient develops Grade 4 thrombocytopenia following polatuzumab vedotin and bendamustine dose reductions, discontinue all study treatment permanently.

Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay

Event(s)	Dose Delay or Modification
Grade 2 or 3 peripheral neuropathy (including its signs and symptoms)	• Delay all study treatment • If recovered to Grade ≤ 1 within ≤ 14 days of the scheduled date of the next cycle: • If the dose of polatuzumab vedotin is 1.8 mg/kg, then reduce polatuzumab vedotin to 1.4 mg/kg (permanent dose reduction). BR or BG may be administered at their full doses. • If there was a prior dose reduction of polatuzumab vedotin to 1.4 mg/kg for Grade 2 or 3 neurotoxicity, all study treatment must be permanently discontinued. • If not recovered to Grade ≤ 1 until > 14 days or after the scheduled date for the next cycle, all study treatment must be permanently discontinued.
Grade 4 peripheral neuropathy (including its signs and symptoms)	• Discontinue polatuzumab vedotin permanently and discontinue all other treatment.
Total Bilirubin > 3.0 mg/dL	• Delay treatment until resolution to ≤ 1.5 mg/dL within ≤ 14 days. Evaluate for causality. • Any case involving an increase in hepatic transaminase $> 3 \times$ 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 DILI, and drug should be discontinued.
Grade 3 or 4 tumor lysis syndrome	• Hold all study treatment. The patient's next dose may be delayed for up to 14 days. • Following complete resolution TLS, study treatment may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy.
Grade 3 or 4 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	• Delay study treatment for a maximum of 14 days • If improvement to Grade ≤ 1 or baseline, continue study therapy at full dose, or dose reduce at the discretion of the investigator per site's standard after discussion with the Medical Monitor.
Grade 2 non-hematologic toxicity	• Delay study treatment for a maximum of 14 days. • If improvement to Grade ≤ 1 or baseline, administer previous doses of study treatment.
Grade 1 non-hematologic toxicity	• No dose reduction or delay

Event(s)	Dose Delay or Modification
Hepatitis B reactivation (as noted by new detectable HBV-DNA levels)	• HBV-DNA levels between WHO-recommended range of 29 and 100 IU/mL: Re-test within 2 weeks. If still positive, hold all study treatment and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. • HBV-DNA levels at WHO-recommended cutoff of $>$100 IU/mL: hold all study treatment and treat the patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. • Rising HBV-DNA viral load (exceeding 100 IU/mL) while on an appropriate anti-viral therapy: Discontinue all study treatment immediately.

ANC = absolute neutrophil count; BG = bendamustine and obinutuzumab; BR = bendamustine and rituximab; DILI = drug-induced liver injury; G-CSF = granulocyte colony stimulating factor; HBV = hepatitis B virus; LMWH = low molecular-weight heparin; R = rituximab; ULN = upper limit of normal; WHO = World Health Organization.

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

[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 8 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 + bendamustine 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 + bendamustine and polatuzumab vedotin as scheduled (if symptomatic bleeding has resolved)

5.1.5.5.2 Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity because it is an expected outcome of therapy. See Table 4 for specific guidance.

5.1.5.5.3 Dose Discontinuation

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

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

Patients who discontinue all study treatment for adverse events should remain in the study and continue to have disease assessments until progression and standard follow up per Section 4.5.

5.1.5.6 Treatment Discontinuation Criteria

5.1.5.6.1 Polatuzumab Vedotin

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

- Grade 4 peripheral neuropathy
- Grade 3 peripheral neuropathy that leads to a treatment delay of 14 days or more and does not improve to Grade ≤1 within 14 days
- Recurrence of a Grade ≥2 peripheral neuropathy at the reduced dose

5.1.5.6.2 Rituximab or Obinutuzumab

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

- Grade 4 infusion-related symptom or anaphylaxis. The patient should be withdrawn from study treatment immediately and supportive treatment given.
- Recurrence of Grade 3 infusion-related symptoms at re-challenge, regardless of timing (e.g., within same session or at the next session)
- If patient has Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence.

5.1.5.6.3 BR, Polatuzumab Vedotin Plus BR, or Polatuzumab Vedotin plus BG

A patient should permanently discontinue BR, polatuzumab vedotin+BR, or polatuzumab vedotin +BG if any of the following occur:

- Grade 3 or 4 hematologic toxicity that does not resolve to Grade ≤2 and delays treatment by >14 days despite administration of growth factors

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, measurement of protocol-specified safety 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 guideline 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 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- 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 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- 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 AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria) (see Section 5.3.3); the event itself may be of relatively minor medical significance (e.g., severe headache without any further findings).

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

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

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

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

- Potential DILI that includes an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

Adverse events that meet the definition of a safety event during the safety run-in observation period (see Section 3.1.1.2) will be recorded on the Adverse Event eCRF and reported immediately to the Medical Monitor as described in Section 3.1.1.2. If a

safety event also meets the definition of an SAE, the event will also qualify for expedited reporting to the Sponsor (see Section 5.4.2 for reporting instructions).

Real time safety monitoring will be employed for safety run-in assessment and dose expansion decisions.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events or adverse events of special interest, regardless of attribution (see Section 5.6). Secondary malignancies will be recorded indefinitely (even if the study has ended) for all enrolled subjects.

5.3.2 Eliciting Adverse Event Information

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

How have you felt since your last clinic visit?

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.03) will be used for assessing adverse event severity. Table 9 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 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 (v4.03), 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 an serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether 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 Table 10):

- 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 10 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 rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

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

5.3.5.2 Diagnosis versus Signs and Symptoms

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

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. For more information regarding the reporting requirements for persistent or recurrent adverse events, please refer to the eCRF Completion Guidelines document.

5.3.5.5 Abnormal Laboratory Values

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

- 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 (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating 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.

5.3.5.6 Abnormal Vital Sign Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- 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.

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of 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 5.4.2). The IMC will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of 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 Revised Response Criteria for Malignant Lymphoma and Modified Lugano Response Criteria (see Appendix 4). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., 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)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 *Reporting Requirements for Cases of Accidental Overdose or Medication Error*

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event assocatied with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For polatuzumab vedotin, rituximab, and obinutuzumab, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

5.3.5.13 Patient-Reported Outcome Data

The PRO measurements are described in Section 4.5.10. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events *(defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)*
- Any death not due to progression of lymphoma, regardless of relationship to study drug
- Adverse events of special interest *(defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)*
- Pregnancies *(see Section 5.4.3 for details on reporting requirements)*

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.

5.4.1 *Medical Monitors and* Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], *Pharm.D.*

Mobile Telephone No.: [redacted]

Emergency Medical Contact: [redacted], *M.D.*

Mobile 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 Monitor, 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 the Medical Monitor contact information will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche 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.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug with the exception of second malignancies. Second malignancies will be recorded indefinitely (even if the study has ended) and irrespective of new anti-lymphoma treatment (NALT) for all enrolled subjects. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche 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. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting poststudy adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 1 year after the last dose of study treatment. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. 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 the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see Protocol Administrative and Contact Information and List of Investigators). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. 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. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. 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.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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 provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious 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, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The investigator is not required to actively monitor patients for serious 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, regardless of causality. Second malignancies will be recorded indefinitely (even if the study has ended) and irrespective of NALT for all enrolled subjects.

The investigator should report these events directly to Roche Safety Risk Management via telephone or via fax machine using the Serious Adverse Event Reporting Form and fax cover sheet.

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

The Sponsor will promptly evaluate all serious adverse events and non-serious 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
- Summary of Product Characteristics *(United Kingdom)* for bendamustine

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The Phase Ib part of this study is designed to assess the safety and tolerability of the combination of polatuzumab vedotin with BR or BG in patients with R/R FL or R/R DLBCL. Once the safety and tolerability of polatuzumab vedotin in combination with BR or BG is confirmed, the Phase II part of the study will begin.

The Phase II part of the study has a randomized component that is designed to assess the safety and efficacy of the combination of polatuzumab vedotin with BR compared with that of BR alone in patients with R/R FL or R/R DLBCL. In addition, the Phase II part of the study has a non-randomized component that is designed to assess the safety and efficacy of the RP2D of polatuzumab vedotin with BG in each of two independent cohorts of patients, one enrolling patients with R/R FL and the other enrolling patients with R/R DLBCL.

Furthermore, the Phase II part of the study has an additional two non-randomized arms within the NF Cohort (Arms G and H). Arm G was designed primarily to assess the pharmacokinetics and safety of the new formulation in patients with R/R DLBCL, which uses the new lyophilized formulation of polatuzumab vedotin plus BR. Arm H was designed to further assess the clinical efficacy and safety of using the new lyophilized formulation of polatuzumab vedotin in combination with BR in patients with R/R DLBCL.

The safety and efficacy data from each phase will be summarized separately by treatment arm. Safety analyses will include all treated patients (i.e., patients who received any amount of study medication) according to actual treatment received.

Efficacy analyses for the randomized component of the Phase II will be conducted in accordance with the intent-to-treat principle (i.e., according to randomized treatment assignment) and separately for each histology. Efficacy analyses for the non-randomized component of the Phase II will be done separately for each histological cohort (i.e., FL or DLBCL), including the arms in the NF Cohort. Additionally, efficacy analyses for Arm G and Arm H in the NF Cohort will be summarized individually and in a pooled fashion (see Section 6.4).

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to evaluate the safety, tolerability, and efficacy of polatuzumab vedotin in combination with BR or BG.

6.1.1 Phase Ib: Safety Run-In Stage

In this study, approximately 24 patients will be enrolled during the safety run-in portion of the study (see Section 3.1). This corresponds to treating a minimum 6 FL and 6 DLBCL patients with polatuzumab vedotin in combination with BR and 6 FL and 6 DLBCL patients with polatuzumab vedotin in combination with BG. A combination will be deemed safe for the purpose of moving to the Phase II part of the study as long as <2 safety events are observed in a given 6-patient cohort as this is consistent with requirements for identification of a candidate RP2D based upon a standard 3+3 design.

6.1.2 Phase II: Randomized and Expansion Stage

A total of 200 patients will be enrolled in Phase II (40 patients for each treatment arm and histology in the rituximab-containing regimens and 20 patients for each histology group in the obinutuzumab-containing regimen). In total, enrollment of approximately

224 patients is planned in order to evaluate the safety and efficacy of polatuzumab vedotin when combined with BR or BG. The expected enrollment duration is approximately 25 months and the total study duration is anticipated to be approximately 50 months.

The primary efficacy endpoint is CR rate as determined by PET-CT scan at the primary response assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study medication) as assessed by IRC. The primary analysis will be estimation of treatment-specific PET-CT CR rates as well as the difference in PET-CT CR rates between patients randomized to treatment with polatuzumab vedotin in combination with BR and those randomized to treatment with BR alone for each histological subtype.

With 40 patients per arm, 95% exact Clopper-Pearson CIs (Clopper and Pearson 1934) for estimation of the true CR rate for would have a margin of error not exceeding±17%. Table 11 and Table 12 show Clopper-Pearson exact 95% CIs corresponding to observed CR rates ranging from 60% to 80% based on sample sizes of 40 and 20, respectively. With 40 patients and an observed CR rate of at least 60%, a true CR rate below 43% can be ruled out with 95% confidence. With 20 patients and an observed CR rate of at least 60%, a true CR rate below 36% can be ruled out with 95% confidence. In addition, with 40 patients in each arm, assuming a 40% CR rate in the BR arm, and a 25% increase in CR rate when polatuzumab vedotin is added to BR, the 95% CI for the difference in CR rates is (3.8%, 46.2%).

Table 11 Clopper-Pearson Exact 95% Confidence Intervals for Assumed Observed CR Rates based on Sample Size of 40 Patients

Polatuzumab Vedotin+BR CR rate	No. of Patients with CR (95% CI for rate)
80%	32 (64%, 91%)
75%	30 (59%, 87%)
70%	28 (53%, 83%)
65%	26 (48%, 79%)
60%	24 (43%, 75%)

BR = bendamustine + rituximab; CR = complete response.

Table 12 Clopper-Pearson Exact 95% Confidence Intervals for Assumed Observed CR Rates based on Sample Size of 20 Patients

Polatuzumab Vedotin+BG CR rate	No. of Patients with CR (95% CI for rate)
80%	16 (56%, 94%)
75%	15 (51%, 91%)
70%	14 (46%, 88%)
65%	13 (41%, 85%)
60%	12 (36%, 81%)

BG=bendamustine + obinutuzumab; CR=complete response.

With respect to assessment of safety based on a sample size of 20 in each of the BG arms, the chance of observing at least one adverse event with true incidence of ≥10% is at least 88%. With 40 patients in each of the BR arms, there is at least an 87% chance of observing at least one adverse event with true incidence of ≥5%.

6.1.3 Phase II: New Formulation Cohort

6.1.3.1 Arm G

For the NF Cohort (Arm G), the original sample size was approximately 20–30 patients. The objective of this cohort is to gain clinical PK experience with polatuzumab vedotin (lyophilized) in combination with BR in R/R DLBCL patients. The currently proposed PK sampling scheme (see Appendix 2) is considered sufficient to characterize the pharmacokinetics of polatuzumab vedotin related analytes by using the population PK analysis approach. PK and safety outcomes will be descriptive. Safety will be analyzed as described for the other cohorts.

The sample size for Arm G was initally planned to be approximately 20–30 patients with the goal of obtaining 20 PK-evaluable patients. PK evaluable is defined as the patient having at minimum PK data of all three analytes collected from Cycle 1 until Cycle 2, Day 1 after dosing of polatuzumab vedotin. Since this evaluation is not a comparison of two randomized arms, it is not appropriate to prespecify the criteria of PK comparability. However, when compared to the available data for patients that received Phase I/II material, 20 patients would achieve >80% power to obtain a 90% confidence interval for the geometric mean ratio (GMR) that falls within the 80%–125% range, assuming that the true GMR equals 1.05 and the inter-individual variability of acMMAE AUC equals 20%.

In order to provide confirmatory support of the efficacy observed in the polatuzumab vedotin + BR arm in the randomized cohort, an additional 10 patients with one prior line of therapy will be enrolled into this NF Cohort to achieve similar representation of patients by lines of therapy.

The total sample size of 40 (30 + 10) patients from Arm G would provide at least 87% power to detect PET CR of 40% under the hypotheses below, with one-sided $\alpha = 2.5\%$ for exact binomial one-sample test:

$$H0: \text{PET CR rate} \leq 17.5\%, H_1: \text{PET CR rate} > 17.5\%$$

6.1.3.2 Arm H

In order to further evaluate the clinical efficacy among patients with R/R DLBCL who are ineligible for transplant who received the new lyophilized formulation of polutuzumab vedotin in combination with BR, an additional arm (Arm H) has been added to the NF Cohort, which includes approximately an additional 60 patients with R/R DLBCL. Under the assumption of 40% PET-assessed CR rate at Primary Response Assessment, combining the 40 patients in Arm G of the NF Cohort with the 60 patients in Arm H (100 patients [40+60]) will provide a more precise 95% CI (Clopper-Pearson exact CI) of (30%, 50%) (see Table 13). Furthermore, this 95% CI completely excludes the 95% CI [17.5% (11%, 26%)] of the CR rate observed in the randomized BR arm with an assumed number of 100 patients.

Table 13 Estimated Polatuzumab Vedotin plus BR Complete Response Rate in R/R DLBCL

	n = 40		n = 60		n = 100	
CR Rate	No. of Patients with CRs	95% CI of Rate	No. of Patients with CRs	95% CI of Rate	No. of Patients with CRs	95% CI of Rate
60%	24	(43%, 75%)	36	(47%, 72%)	60	(50%, 70%)
55%	22	(38%, 71%)	33	(42%, 68%)	55	(45%, 65%)
50%	20	(34%, 66%)	30	(37%, 63%)	50	(40%, 60%)
45%	18	(29%, 62%)	27	(32%, 58%)	45	(35%, 55%)
40%	16	(25%, 57%)	24	(28%, 53%)	40	(30%, 50%)
35%	14	(21%, 52%)	21	(23%, 48%)	35	(26%, 45%)
30%	12	(17%, 47%)	18	(19%, 43%)	30	(21%, 40%)

BR = bendamustine and rituximab; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; R/R = relapsed or refractory.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations, and discontinuations from the study will be summarized separately by treatment arm. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated by treatment arm. Major protocol violations, including violations of inclusion/exclusion criteria, will be summarized by treatment arm.

Study drug administration data will be listed by dose level and any dose modifications will be flagged. The number of doses, treatment cycles, and average dose received for each study drug for the schedule/treatment arm will be summarized using means, SDs, medians, and ranges by treatment arms.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race, and duration of malignancy, will be summarized using means, SDs, medians, and ranges for continuous variables by treatment arms. For discrete data, descriptive summaries as frequencies and percentages by treatment arms will be presented.

6.4 EFFICACY ANALYSES

The efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization (Phase II polatuzumab vedotin plus BR and BR alone). For the Phase II expansion, patients assigned to polatuzumab vedotin plus BG will be grouped by histology (i.e., FL or DLBCL). The efficacy analyses will also include the Phase II non-randomized NF cohort in patients with R/R DLBCL.

NF Cohort: Pooled Efficacy Analysis

In addition to the efficacy analyses as outlined in the objectives (see Section 2.3) for the individual arms of the NF Cohort, efficacy analysis will also be pooled for the following endpoints:

- Primary efficacy endpoint: CR at the Primary Response Assessment based on PET-CT, as determined by the IRC
- Secondary efficacy endpoints:
  - CR at the Primary Response Assessment based on PET-CT, as determined by the investigator
  - OR (CR or PR) at the Primary Response Assessment based on PET-CT, as determined by the investigator and IRC
  - BOR (CR or PR) while on study either by PET-CT or CT only, as determined by the investigator and IRC
  - DOR based on PET-CT or CT only, as determined by the investigator and IRC
  - PFS based on PET-CT or CT only, as determined by the investigator and IRC
  - EFS based on PET-CT or CT only, as determined by the investigator
  - OS

6.4.1 Primary Efficacy Endpoint

CR at Primary Response Assessment (6–8 weeks after Cycle 6, Day 1 or last dose of study drug) as measured by PET-CT scan and as determined by an IRC will be used as the primary efficacy endpoint. This primary efficacy endpoint applies to the Phase II randomized cohorts treated with polatuzumab vedotin plus BR versus BR, as well as Arm H of the NF Cohort (individually and together with Arm G). The CR rate, defined as the percentage of patients with CR, will be estimated and the corresponding Clopper-Pearson exact 95% CI will be constructed for each treatment arm. The difference in CR rates between the combination of polatuzumab vedotin + BR and BR randomized arms will be estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution. An exploratory comparison of CR rates for the BR-containing regimens will be conducted using the Cochran Mantel Haenszel χ^2 test adjusted for randomization stratification factors (Agresti 2002).

Response assessment is determined using the Modified Lugano Response Criteria (Cheson et al. 2014) specified in Appendix 4.

6.4.2 Secondary Efficacy Endpoints

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

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

- CR at Primary Response Assessment based on PET-CT, as determined by the investigator
- CR at Primary Response Assessment based on PET-CT, as determined by IRC (for Phase II expansion (polatuzumab vedotin plus BG cohorts) and NF Cohort (Arm G only)
- OR (CR or PR) at Primary Response Assessment based on PET-CT, as determined by the investigator and IRC
- CR at Primary Response Assessment based on CT only, as determined by the investigator and IRC
- OR (CR or PR) at Primary Response Assessment based on CT only, as determined by the investigator and IRC
- BOR (CR or PR) while on study based on PET-CT or CT only, as determined by the investigator
- DLBCL cohorts only: BOR, DOR and PFS based on PET-CT or CT only, as determined by IRC and investigator (see Section 6.4.3 for a description of DOR and PFS determination)
- NF cohort only: OS and EFS based on PET-CT or CT only, as determined by the investigator

6.4.3 Exploratory Efficacy Endpoints

Among patients with a best overall response of CR or PR, DOR will be defined as the time from the initial CR or PR to the time of disease progression, relapsed or death from any cause, whichever occurs first. If a patient does not experience death or disease progression before the end of the study, DOR will be censored on the date of the last tumor assessment. DOR will be summarized descriptively with use of the Kaplan-Meier method (Kaplan and Meier 1958). If analytically possible, median DOR will be estimated, along with the corresponding 95% CI using the method of Brookmeyer and Crowley (1982). No formal comparisons of DOR across treatment arms will be conducted.

PFS is defined as the period from the date of randomization or first treatment for non-randomized arms until the date of disease progression, relapse, or death from any cause, whichever occurs first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of last tumor assessment. If no tumor assessments were performed after the Screening Visit, PFS will be censored at the date of randomization/first treatment. The distribution of times for PFS will be

summarized descriptively using the Kaplan-Meier method (Kaplan and Meier 1958) to estimate median (if analytically possible), 1-year, and 2-year PFS and 95% CIs using Greenwood's formula.

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

OS is defined as the time from date of randomization or first treatment for non-randomized arms until the date of death from any cause. Patients who have not died will be censored at the last date known to be alive.

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

Duration of follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).

6.5 SAFETY ANALYSES

Safety will be assessed through summaries of adverse events, summaries of changes from screening assessments in laboratory test results, ECGs, and changes in vital signs.

All collected adverse event data will be summarized by phase of the study, treatment arm, and histological subtype. All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.03 toxicity grade. All serious adverse events will be listed separately and summarized.

Deaths reported during the study treatment period and those reported during follow-up after treatment discontinuation will be listed.

Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, pulse oximetry, and blood pressure) data will be displayed by time, with NCI CTCAE v4.03 Grade 3 and 4 values identified where appropriate.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum and plasma concentrations of polatuzumab vedotin, bendamustine, rituximab, and obinutuzumab versus time data will be tabulated and plotted. Summary statistics of concentration data will be computed for each scheduled sampling time for each analyte. PK parameters, such as AUC, C_{max}, systemic CL, and V_{ss} may be estimated (as appropriate for the data collected). Estimates for these

parameters will be tabulated and summarized (mean and SD). PK parameters will be determined using the appropriate technique based on available data. Non-compartmental analysis and/or population PK analysis method may be applied for PK parameter estimation. Potential drug interactions may be assessed by comparison of PK in the current study with historical data. Potential correlations between PK variability and demographic and pathophysiological covariates may be explored by population PK analysis. Potential correlations between PK variability and pharmacodynamic, efficacy, and safety outcome may be explored by exploratory graphical analysis and PK-pharmacodynamic modeling. The assessment of PK parameters and related analysis will be performed per Sponsor's discretion, based on the appropriateness of the PK data collected, the trial outcome, and the future development path for polatuzumab vedotin.

6.7 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.

Patients enrolled in the NF Cohort (Arm G and Arm H), receiving polatuzumab vedotin (lyophilized) plus BR, will be exempt from completing the TINAS.

6.8 EXPLORATORY ANALYSES

Exploratory analyses of biomarkers (see Section 2.2.5) related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab or obinutuzumab will be conducted. Analyses will assess prognostic and/or predictive value of candidate biomarkers separately for each histological subtype and both investigator and IRC assessed outcomes. Specifically, the association between candidate biomarkers and PET-CT CR rate and OR rate and potentially other measures of efficacy and safety, independent of treatment, will be explored to assess potential prognostic value. In addition, the potential effect modification of treatment effect on PET-CT CR rate and OR rate and potentially other measures of efficacy and safety, by biomarker status, will be explored to assess potential predictive value.

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) to ensure the secure collection and transmission of the data. 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 ePRO device to capture PRO data. This device will be the patient's own electronic devices (i.e., mobile phone, tablet, or home computer) to ensure the secure collection and transmission of the data. The data will be transmitted via Web or wireless automatically to a centralized database at the ePRO vendor.

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly 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 health 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 the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

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

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, 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 ICFs 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 ICF 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 ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs 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 ICFs must be provided to the Sponsor for health authority submission purposes.

*If the consent forms are revised (through an amendment or an addendum) while a patient is participating in the study, the p*atient *or a legally authorized representative* must re-consent *by signing the* most current version of the ICFs or to *the* addendum*,* in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, 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 ICFs for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the

local health authority and IRB/EC. Investigators may receive written 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 ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the

course of the study and for 1 year after completion of the study (i.e., last patient last visit [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, ICF, 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

In the United States, this trial will be sponsored and managed by Genentech, Inc. F. Hoffmann-La Roche Ltd will sponsor this trial outside of the United States, with management responsibilities shared by Genentech and Roche. Genentech and Roche have authorized Roche Registrations Ltd, a company formed under the laws of England, to act as their legally authorized representative for the purposes of Article 19 of Directive 2001/20/EC relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use. Reference to Sponsor in this protocol will mean Genentech for the United States and F. Hoffmann-La Roche Ltd for countries outside of the United States.

Electronic data capture will be used 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 4.5.8; otherwise, local laboratories will be used. A central

independent review facility will be used to collect CT and PET-CT scans, and the IRC will perform independent assessments of response for all patients enrolled in the study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 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).

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Appendix 1
Schedule of Activities

Cycle of Treatment Period	Screening (Days −28 to −1)	Treatment													Unplanned Visit [c]	Treatment Completion Visit (30 (±5) days after last dose of study treatment) [d]	Primary Response Assessment (after Cycle 6 Day1 or last study treatment +6–8 weeks) [ii]	Follow-Up Period (< 2 years: every 3 months; > 2 years: every 6 months; ±14 days) [e]	Study Completion/Discontinuation [f]
		C1	C1	C1	C1	C1	C1	C2	C2	C3	C3	C3	C4–6	C4–6					
Day[a] (Window)		D1[b]	D2	D3	D8 (±1)	D15 (±2)	D22 (±2)	D1 (±2)	D2 (±2)	D1 (±2)	D2 (±2)	D15 (±2)	D1 (±2)	D2 (±2)					
Informed consent [g]	x																		
Demographic data	x																		
General medical history and baseline conditions	x																		
Concomitant medications [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Adverse events [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG PS	x															x	x	x	x
FLIPI, FLIPI2 (for FL) and IPI (for DLBCL)	x																		
Complete physical exam [j]	x																		
Targeted physical examination [k]		x						x		x			x		x	x	x	x	x
Total neuropathy score clinical assessment [l]		x			x	x		x		x		x	x		x	x	x	x	x
Vital signs [m]	x	x	x	x	(x)	(x)		x		x			x		x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Cycle of Treatment Period	Screening (Days −28 to −1)	Treatment													Unplanned Visit [c]	Treatment Completion Visit (30 (± 5) days after last dose of study treatment) [d]	Primary Response Assessment (after Cycle 6 Day1 or last study treatment + 6–8 weeks) [jj]	Follow-Up Period (< 2 years: every 3 months; > 2 years: every 6 months; ± 14 days) [e]	Study Completion/Discontinuation [f]
		C1	C1	C1	C1	C1	C1	C2	C2	C3	C3	C3	C4 – 6	C4 – 6					
Day [a] (Window)		D1[b]	D2	D3	D8 (±1)	D15 (±2)	D22 (±2)	D1 (±2)	D2 (±2)	D1 (±2)	D2 (±2)	D15 (±2)	D1 (±2)	D2 (±2)					
Height, weight, and BSA [n]	x	x						x		x			x						
12-lead ECG	x									x						x			
Patient-reported outcomes using TINAS [o]		Weekly at the same time each day during study treatment period.														Once per week for the first 2 months, then once per month for the next 10 months			
Clinical response assessment [p]	x							x		x		x	x		(x)	x	x	x	x
PET-CT scan [q]	x [r]											x			(x)		x	(x) [s]	(x) [t]
Rituximab [u]		x						x		x			x						
Obinutuzumab [v]		x			x	x		x		x			x						
Polatuzumab vedotin [w]			x					x		x			x						

Appendix 1
Schedule of Activities (cont.)

Cycle of Treatment Period	Screening (Days −28 to −1)	Treatment													Unplanned Visit [c]	Treatment Completion Visit (30 (±5) days after last dose of study treatment) [d]	Primary Response Assessment (after Cycle 6 Day1 or last study treatment+6–8 weeks) [jj]	Follow-Up Period (<2 years: every 3 months; >2 years: every 6 months; ±14 days) [e]	Study Completion/Discontinuation [f]
		C1	C1	C1	C1	C1	C1	C2	C2	C3	C3	C3	C4 – 6	C4 – 6					
Day [a] (Window)		D1 [b]	D2	D3	D8 (±1)	D15 (±2)	D22 (±2)	D1 (±2)	D2 (±2)	D1 (±2)	D2 (±2)	D15 (±2)	D1 (±2)	D2 (±2)					
Bendamustine [x]			x	x				x	x	x	x		x	x					
Hematology [y]	x	x			x	x	x	x		x			x		x	x	x	x	x
Serum chemistry [z]	x	x			x	x	x	x		x			x		x	x	x	x	x
Coagulation panel [aa]	x																		
Viral serology [bb]	x																		
Serum IgA, IgG, and IgM	x															x	x	x	
Pregnancy test [cc]	x							x		x			x			x			
Bone marrow biopsy and aspirate [dd]	x															(x)	(x)	(x)	
Tumor tissue sample for exploratory biomarker studies [ee]	x																		(x)
Tissue sample and pathology report for central pathology review [ii]	x																		
MRD biomarker studies (whole blood) [ff]		x						x				x					x		

Appendix 1
Schedule of Activities (cont.)

Cycle of Treatment Period	Screening (Days −28 to −1)	Treatment													Unplanned Visit [c]	Treatment Completion Visit (30 (± 5) days after last dose of study treatment) [d]	Primary Response Assessment (after Cycle 6 Day1 or last study treatment+6–8 weeks) [jj]	Follow-Up Period (<2 years: every 3 months; >2 years: every 6 months; ±14 days) [e]	Study Completion/Discontinuation [f]
		C1	C1	C1	C1	C1	C1	C2	C2	C3	C3	C3	C4 – 6	C4 – 6					
Day [a] (Window)		D1[b]	D2	D3	D8 (±1)	D15 (±2)	D22 (±2)	D1 (±2)	D2 (±2)	D1 (±2)	D2 (±2)	D15 (±2)	D1 (±2)	D2 (±2)					
Exploratory biomarker studies (6-mL each of whole blood and plasma prior to treatment and treatment completion)		x															x		
Lymphocyte subsets [gg]		x															x	x (every 6 months)	x
Anti-drug antibody (polatuzumab vedotin and obinutuzumab)	See Appendix 2																		
PK assessment	See Appendix 2																		
Survival follow-up/status [hh]																x	x	x	x

Appendix 1
Schedule of Activities (cont.)

BG = bendamustine + obinutuzumab; BR = bendamustine + rituximab; BSA = body surface area; C = cycle; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = electronic Case Report Form; FLIPI = Follicular Lymphoma International Prognostic Index; FU = follow-up; IPI = International Prognostic Index; MRD = minimal residual disease; NA = not applicable; NF = new formulation; PET-CT = positron emission tomography/computed tomography; PK = pharmacokinetic; R/R = relapsed or refractory; TINAS = Therapy-Induced Neuropathy Assessment Scale; (x) = conditional/optional (refer to footnote).

Notes: Assessments shaded in gray should be performed as scheduled for patients with FL on Cycle 1, Day 22 because treatment is administered on a 28-day cycle. Patients with DLBCL will not need the Cycle 1, Day 22 assessment because treatment is administered on a 21-day cycle. With consent to optional research, residual tissue and blood samples will be stored in the RCR (see Section 4.5.11). Arm G = NF Cohort of R/R DLBCL treated with lyophilized polatuzumab vedotin plus BR. Arm H = NF Cohort of R/R DLBCL treated with lyophilized polatuzumab vedotin plus BR.

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

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

[c] Visit not specified by the protocol. Assessments (possibly including hematology and/or chemistry sample collection) should be performed as clinically indicated.

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

[e] Following completion of treatment, patients who have not progressed will be followed clinically every 3 months (±14 days) until the end of Year 2 from treatment completion visit. Patients will then be followed every 6 months until disease progression, study withdrawal, end of study, or death, whichever comes first. Follow-up visit intervals should be determined from treatment completion visit.

[f] If the study completion/discontinuation visit is simultaneous with other visits in the schedule of assessments, do not duplicate assessments that are common in both of the visits. These assessments should be entered in the study completion or early discontinuation visit only.

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

[h] Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study treatment completion visit, which is 30 (±5) days after the last dose of study treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Please see Section 4.4.1.

Appendix 1
Schedule of Activities (cont.)

[i] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study drug. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events or non-serious adverse events of special interest (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

[k] Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment [lymph nodes, liver, and spleen]). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] All patients, except those in Arm G and Arm H, should undergo a Total Neuropathy Score Clinical Assessment (to include subjective sensory symptoms, motor symptoms, autonomic symptoms; to include objective pinprick sensitivity, vibration sensitivity, strength testing and deep tendon reflex testing) to determine their total neuropathy score on all indicated visits prior to administration of study treatment.

[m] Vital signs to include respiratory rate, pulse rate, pulse oximetry, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. On polatuzumab vedotin infusion days, vital signs should be assessed before the start of the infusion, every 15 ($\pm$5) minutes during the infusion, at the end of the infusion and every 30 ($\pm$10) minutes for 90 minutes following completion of dosing at Cycle 1 and 30 ($\pm$10) minutes following completion of dosing in subsequent cycles. On rituximab infusion days, vital signs should be obtained before the infusion of rituximab and at the end of the rituximab infusion. Additional vital signs measurements are to be obtained as per each institution's standard of care and as clinically indicated. On obinutuzumab infusion days, vital signs are to be obtained before infusion of obinutuzumab, then after the start of the infusion approximately every 15 ($\pm$5) minutes for 90 minutes, then every 30 ($\pm$10) minutes until 1 hour after the end of the infusion for Cycle 1. During administration of obinutuzumab in subsequent cycles, vital signs are to be obtained before infusion of obinutuzumab, then after the start of the infusion, approximately every 30 minutes ($\pm$10) minutes until 1 hour after the end of infusion.

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

Appendix 1
Schedule of Activities (cont.)

[o] The Therapy-Induced Neuropathy Assessment Scale (TINAS) is the patient-reported outcomes instrument. TINAS should be completed weekly 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. Patients in Arm G and Arm H will be exempt.

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

[q] Imaging should be PET-CT at screening, Interim Response Assessment (between Cycle 3, Day 15 and Cycle 4, Day 1) and Primary Response Assessment Visit. All other imaging may be CT only. Response assessment will be performed using the Revised Response Criteria for Malignant Lymphoma and Modified Lugano Response Criteria (see Appendix 4).

[r] Screening PET-CT must not be obtained more than 35 days prior to Cycle 1, Day 1.

[s] Scan (CT or PET-CT) should be performed during follow up every 6 months for 2 years or until study end or at any time that progression is suspected via clinical response assessment.

[t] Scan not necessary if patient has already had a scan within the last 30 days.

[u] For patients who will receive either polatuzumab vedotin+BR or BR alone, rituximab 375 mg/m^2 will be administered on Day 1 of each cycle. Rituximab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine.

[v] For patients who will receive polatuzumab vedotin+BG, obinutuzumab 1000 mg will be administered on Days 1, 8, and 15 of Cycle 1, then on Day 1 of each subsequent cycle. Obinutuzumab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine.

[w] Polatuzumab vedotin will be administered on Day 2 of Cycle 1. If well tolerated, then all study treatment may be administered on the same day (Day 1 of subsequent cycles) during subsequent cycles.

[x] Bendamustine 90 mg/m^2 will administered on Days 2 and 3 of Cycle 1, then on Days 1 and 2 of each subsequent cycle.

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

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

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

Appendix 1
Schedule of Activities (cont.)

[bb] Hepatitis B (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], and total hepatitis B core antibody [HBcAb]) and hepatitis C virus (HCV) antibody serology required. Patients with positive [HBcAb and negative HBsAg) must undergo monthly HBV-DNA testing by polymerase chain reaction (PCR) on day 1 of each cycle during study treatment and for at least 12 months after the study treatment completion. If the patient is HCV-antibody positive, then HCV RNA by PCR is required. HIV testing will be performed at screening if required by the health authority overseeing the study site.

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

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

[ee] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. For construction of a tissue microarray, tumor block or punch biopsy of the tumor block are required. Fresh tissue sections will be generated from tissue microarrays to study proteins that have limited stability in tissue sections. Remainders of archival tissue blocks will be returned to sites upon request according to country-specific procedures. Tumor tissue biopsy at disease progression is optional. See Section 4.1.3. Patients in Arm G will be exempt.

[ff] 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 Primary Response Assessment Visit. Patients in Arm G and Arm H will be exempt.

[gg] Lymphocyte subsets at baseline, Primary Response Assessment Visit, and every 6 months (counting from the treatment completion visit) until the end of study or patient discontinuation.

[hh] During the follow-up period (i.e., after treatment completion): For patients who have progressive disease and have not started new anti-lymphoma therapy, follow-up should consist of recording of first new anti-lymphoma therapy, adverse events, and survival and continue to follow the above schedule. For patients who have progressive disease and started a new anti-lymphoma therapy, contact will be made by telephone on at least an annual basis for survival. For patients who started a new anti-lymphoma therapy but do not have progressive disease, assessments should be followed according to schedule. See Section 4.5.11.3.

Appendix 1
Schedule of Activities (cont.)

[ii] Tissue sample applies only to Arm G and Arm H, and will be submited prior to starting Cycle 1, Day 1. Central pathology review of pathology reports and previously collected tissue samples will be performed for all DLBCL patients. If needed, additional slides may be requested for patients in the main study.

[jj] For patients who progress prior to the anticipated Primary Response Assessment visit, the visit at which response assessment shows progressive disease may be used as the Primary Response Assessment.

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule

Table 1 Phase Ib Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for Patients Treated with Polatuzumab Vedotin plus BR

The pharmacokinetic (PK) sampling schedule below is applicable to patients who receive the rituximab-containing regimen in the Phase Ib portion of the study. Per the sampling schedule (see below), 21 PK samples will be collected from each patient treated with polatuzumab vedotin plus bendamustine and rituximab (BR). Ideally, all PK samples and anti-drug antibody 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 sample flushing.

Study Visit	Sample Timepoint	Samples [a]
Cycle 1, Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of 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-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 4, Day 1	Pre-polatuzumab vedotin dose	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Post-treatment (Follow-up visit at Months 3, 6, 12, 18, and 24)	Random sample	Polatuzumab vedotin ADA (serum) Polatuzumab vedotin concentration (serum)

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

ADA = anti-drug antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Notes: Pre-infusion samples should be drawn 0–4 hours before the start of infusion. End-of-infusion samples should be drawn 30 minutes (±15 minutes) unless otherwise specified.

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

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

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Table 2 Phase Ib Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for Patients Treated with Polatuzumab Vedotin plus BG

The pharmacokinetic (PK) sampling schedule below is applicable to patients who receive the obinutuzumab-containing regimen in the Phase Ib portion of the study. Per the sampling schedule (see below), 37 samples will be collected from each patient treated with polatuzumab vedotin plus bendamustine and obinutuzumab (BG). Ideally, all PK samples and anti-drug antibody 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 sample flushing.

Study Visit	Sample Timepoint	Samples [a]
Cycle 1, Day 1	Pre-obinutuzumab infusion	Obinutuzumab ADA (serum), Obinutuzumab concentration (serum)
Cycle 1, Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of 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 ADA (serum), Obinutuzumab concentration (serum)
	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 4, Day 1	Pre-obinutuzumab infusion	Obinutuzumab ADA (serum), Obinutuzumab concentration (serum)

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Study Visit	Sample Timepoint	Samples [a]
	Pre-polatuzumab vedotin dose	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Post-treatment (Follow-up visit at Months 3, 6, 12, 18, and 24)	Random sample	Obinutuzumab ADA (serum), Obinutuzumab concentration sample (serum), Polatuzumab vedotin ADA (serum), Polatuzumab vedotin concentration sample (serum)

ADA = anti-drug antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Notes: Pre-infusion samples should be drawn 0–4 hours before the start of infusion. End-of-infusion samples should be drawn 30 minutes (± 15 minutes) unless otherwise specified.

[a] Up to 19-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 ADA, polatuzumab vedotin concentration, obinutuzumab ADA, and obinutuzumab concentration at each specified timepoint with separate tubes for plasma or serum samples.

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

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Table 3 Phase II Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for Patients Treated with Polatuzumab Vedotin plus BR

The pharmacokinetic (PK) sampling schedule below is applicable to all patients who receive polatuzumab vedotin plus BR in the Phase II randomized portion of the study. Approximately 30 samples will be collected per patient treated with polatuzumab vedotin plus BR during Phase II. Ideally, all PK samples and anti-drug antibody 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 sample flushing.

Study Visit	Sample Timepoint	Samples [a]
Cycle 1, Day 1	Pre-rituximab infusion	Rituximab PK (serum) [b]
	End of rituximab infusion	Rituximab PK (serum) [b]
Cycle 1, Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
	Pre-bendamustine infusion	Bendamustine PK (plasma)
	Immediately after end of bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	1 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	2 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	3 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	4 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Study Visit	Sample Timepoint	Samples [a]
Cycle 2, Day 1	Pre-rituximab infusion	Rituximab PK (serum) [b]
	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 4, Day 1	Pre-rituximab dose	Rituximab PK (serum)
	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Treatment Completion Visit	Approximately 15–30 days after last infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
Post-treatment (Follow-up visit at Months 3, 6, 12, 18, and 24)	Random sample	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin concentration (serum)

ADA = anti-drug antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.
Notes: Pre-infusion samples should be drawn 0-4 hours before the start of infusion. End-of-infusion samples should be drawn 30 minutes (± 15 minutes) unless otherwise specified.

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

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

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Table 4 Phase II Pharmacokinetic Sampling Schedule for Patient Treated with BR Alone

The pharmacokinetic (PK) sampling schedule below is applicable to all patients who receive BR in the Phase II randomized portion of the study. Approximately 10 samples will be collected per patient treated with BR during Phase II. Ideally, all PK samples and anti-drug antibody 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 sample flushing.

Study Visit	Sample Timepoint	Samples [a]
Cycle 1, Day 1	Pre-rituximab infusion	Rituximab PK (serum)
	End of rituximab infusion	Rituximab PK (serum)
Cycle 1, Day 2	Pre-bendamustine infusion	Bendamustine PK (plasma)
	Immediately after end of bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	1 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	2 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	3 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	4 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
Cycle 2, Day 1	Pre-rituximab infusion	Rituximab PK (serum)
Cycle 4, Day 1	Pre-rituximab dose	Rituximab PK (serum)

PK = pharmacokinetic.

Notes: Pre-infusion samples should be drawn 0–4 hours before the start of infusion. End of infusion samples should be drawn 30 minutes (±15 minutes) unless otherwise specified.

Up to 5-mL whole-blood samples will be taken for rituximab PK and bendamustine PK at each specified timepoint with separate tubes for plasma or serum sample

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Table 5 Phase II Pharmacokinetic Sampling and Anti-Drug Antibody Schedule for Patients Treated with Polatuzumab Vedotin plus BG

The pharmacokinetic (PK) sampling schedule below is applicable to all patients who receive polatuzumab vedotin plus BG in the Phase II expansion portion of the study. Approximately 46 samples will be collected per patient treated with polatuzumab vedotin plus BG during Phase II. Ideally, all PK samples and anti-drug antibody 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 sample flushing.

Study Visit	Sample Timepoint	Samples [a]
Cycle 1, Day 1	Pre-obinutuzumab infusion	Obinutuzumab ADA (serum), Obinutuzumab PK (serum) [b]
	End of obinutuzumab infusion	Obinutuzumab PK (serum) [b]
Cycle 1, Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
	Pre-bendamustine infusion	Bendamustine PK (plasma)
	Immediately after end of bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	1 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	2 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	3 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)
	4 hour post-bendamustine infusion (±5 minutes)	Bendamustine PK (plasma)

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Study Visit	Sample Timepoint	Samples [a]
Cycle 2, Day 1	Pre-obinutuzumab infusion	Obinutuzumab ADA (serum), Obinutuzumab PK (serum) [b]
	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
Cycle 4, Day 1	Pre-obinutuzumab infusion	Obinutuzumab ADA (serum), Obinutuzumab PK (serum) [b]
	End of obinutuzumab infusion	Obinutuzumab PK (serum) [b]
	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) [b]
Treatment Completion Visit	Approximately 15–30 days after last infusion	Obinutuzumab ADA (serum), Obinutuzumab PK (serum), [b] Polatuzumab vedotin ADA (serum), Polatuzumab vedotin PK (serum and plasma) [b]
Post-treatment (Follow-up visit at Months 3, 6, 12, 18, and 24)	Random sample	Obinutuzumab ADA (serum), Obinutuzumab concentration (serum), Polatuzumab vedotin ADA (serum), Polatuzumab vedotin concentration (serum)

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

ADA = anti-drug antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Notes: Pre-infusion samples should be drawn 0–4 hours before the start of infusion. End of infusion samples should be drawn 30 minutes (± 15 minutes) unless otherwise specified.

[a] Up to 19-mL whole-blood samples will be taken for obinutuzumab PK, obinutuzumab ATA, obinutuzumab concentration, polatuzumab vedotin PK (polatuzumab vedotin total antibody, unconjugated MMAE and conjugate [evaluated as antibody-conjugated MMAE]), polatuzumab vedotin ATA, polatuzumab vedotin concentration, bendamustine PK at each specified point with separate tubes for plasma or serum samples.

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

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Table 6 Phase II Pharmacokinetic Sampling and Anti-Drug Antibody Schedule for the NF Cohort (Arm G) for Patients Treated with Polatuzumab Vedotin (Lyophilized) plus BR

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

ADA = anti-drug antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

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

[b] Up to11-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 ADA, and polatuzumab vedotin concentration sample at each specified timepoint with separate tubes for plasma or serum samples.

[c] Polatuzumab vedotin PK, including serum PK samples for total antibody and plasma PK samples for conjugate (evaluated as antibody-conjugated MMAE and unconjugated MMAE). The pharmacokinetic (PK) and anti-drug antibody (ADA) sampling schedule below is applicable to patients with R/R DLBCL who are participating in Arm G of the NF cohort treated with polatuzumab vedotin (lyophilized) plus BR. Per the sampling schedule above, approximately 12 PK sampling points will be pre-specified from each patient treated with polatuzumab vedotin plus bendamustine and rituximab (BR) up to Cycle 4, Day 1, and additional PK sampling points will be at treatment completion/termination visit and follow-up visits. All PK samples and anti-drug antibody samples should be drawn from the arm opposite from the infusion arm. In patients with indwelling catheters, a PK sample may be drawn from the catheter after sample flushing.

Appendix 2
Pharmacokinetic and Anti-Drug Antibody Sampling Schedule (cont.)

Table 7 Phase II Pharmacokinetic Sampling and Anti-Drug Antibody Schedule for the NF Cohort (Arm H) for Patients Treated with Polatuzumab Vedotin (Lyophilized) plus BR

Study Visit	Sample Timepoint a	Samples b
Cycle 1, Day 2	Pre-polatuzumab vedotin infusion	Polatuzumab vedotin ADA (serum) Polatuzumab vedotin PK (serum and plasma) c
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) c
Cycle 2, Day 1	Pre-polatuzumab vedotin dose	Polatuzumab vedotin ADA (serum) Polatuzumab vedotin PK (serum and plasma) c
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) c
Cycle 4, Day 1	Pre-polatuzumab vedotin dose	Polatuzumab vedotin ADA (serum) Polatuzumab vedotin PK (serum and plasma) c
	End of polatuzumab vedotin infusion	Polatuzumab vedotin PK (serum and plasma) c
Treatment Completion/Early Termination Visit	Approximately 30 days ± 5 after last infusion	Polatuzumab vedotin ADA (serum) Polatuzumab vedotin PK (serum)
Post-treatment (Follow-up visit at Month 3)	Random sample	Polatuzumab vedotin ADA (serum) Polatuzumab vedotin PK (serum)

ADA= anti-drug antibody; BR=bendamustine + rituximab; MMAE= monomethyl auristatin E; NF= new formulation; PK= pharmacokinetic.

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

[b] Up to11-mL whole-blood samples will be taken for polatuzumab vedotin PK (polatuzumab vedotin total antibody, conjugate [evaluated as antibody-conjugated MMAE], and unconjugated MMAE), polatuzumab vedotin ADA, and polatuzumab vedotin concentration sample at each specified timepoint with separate tubes for plasma or serum samples.

[c] All PK samples and anti-drug antibody samples should be drawn from the arm opposite the infusion arm. In patients with indwelling catheters, a PK sample may be drawn from the catheter after sample flushing.

Appendix 3
Response Criteria for Malignant Lymphoma

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. Assessment of the PET scan should follow the criteria described by Juweid et al. 2007, which is presented in the table below.

COMPLETE REMISSION

- Complete disappearance of all detectable clinical evidence of disease and disease related symptoms if present before therapy
- 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 ($\leq$ 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 $\leq$ 1.0 cm in their short axis after treatment.
- The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or computed tomography (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 (with a goal of $>$ 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 that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a complete response (CR) until data become available demonstrating a clear difference in patient outcome.

Appendix 3
Response Criteria for Malignant Lymphoma (cont.)

PARTIAL REMISSION

- At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least two perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver, or spleen.
- Splenic and hepatic nodules must regress by $\geq$50% in their SPD or, for single nodules, in the greatest transverse diameter (GTD).
- 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 partial response (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 CR by the above criteria but who have persistent morphologic bone marrow involvement will be considered partial responders. If the bone marrow was involved before therapy and a clinical CR is achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed.
- Typically FDG-avid lymphoma: for patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET 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, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by more than 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

Appendix 3
Response Criteria for Malignant Lymphoma (cont.)

STABLE DISEASE

- A patient is considered to have stable disease when that patient fails to attain the criteria needed for a CR or PR but does not fulfill those for progressive disease (PD) (see Relapsed Disease [after Complete Remission] or PD [after Partial Remission or Stable Disease]).
- Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
- 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 (AFTER COMPLETE REMISSION) OR PROGRESSIVE DISEASE (AFTER PARTIAL REMISSION OR STABLE DISEASE)

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

- 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 PD, a lymph node with a diameter of the short axis < 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.

Appendix 3
Response Criteria for Malignant Lymphoma (cont.)

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.

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 IHC; 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 positron emission tomography; IHC = immunohistochemistry; PD = progressive disease; PET = positron emission tomography; PR = partial response; SD = stable disease; SPD = sum of product diameters.

Appendix 4
Revised Criteria for Response Assessment: Modified 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)/CT (computed tomography) scan will be performed 6–8 weeks after Cycle 6 Day 1 as assessed by IRC and by investigator. Assessment of the PET-CT scan should follow the criteria described by Cheson BD 2014 presented below.

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

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

Appendix 4
Revised Criteria for Response Assessment: Modified Lugano Classification (cont.)

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 4
Revised Criteria for Response Assessment: Modified Lugano Classification (cont.)

Response	Site	PET-CT-based Response	CT-based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow Normal by morphology; if indeterminate, IHC negative	Normal by morphology; if indeterminate, IHC negative
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extralymphatic sites	Score of 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size at interim, these findings suggest responding disease at end of treatment, these findings indicate residual disease	$\geq 50\%$ decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm $\times$ 5 mm as the default value When no longer visible, 0 $\times$ 0 mm For a node $>$ 5 mm $\times$ 5 mm, but smaller than normal, use actual measurement for calculation

Appendix 4
Revised Criteria for Response Assessment: Modified Lugano Classification (cont.)

Response	Site	PET-CT–based Response	CT-based Response
Partial (cont.)	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by $>50\%$ in length beyond normal
	New lesions	None	None
	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 or Stable Disease		**No metabolic response**	**Stable disease**
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	$<50\%$ decrease from baseline in SPD 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 4
Revised Criteria for Response Assessment: Modified Lugano Classification (cont.)

Response	Site	PET-CT–based Response	CT-based Response
Progressive Disease		**Progressive metabolic disease**	**Progressive disease (requires at least 1 of the following)**
	Individual target nodes/nodal lesions Extranodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.	PPD progression: An individual node/lesion must be abnormal with: • LDi > 1.5 cm AND • Increase by ≥ 50% from PPD nadir AND • An increase in LDi or SDi from nadir • 0.5 cm for lesions ≤ 2 cm • 1.0 cm for lesions > 2 cm
	Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
	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 4
Revised Criteria for Response Assessment: 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] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

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

Appendix 5
Recommendations for the Use of White Blood Cell Growth Factors

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

Primary prophylaxis with growth-colony stimulating factor (G-CSF) is required. The decision not to administer G-CSF as primary prophylaxis should be made in consultation with and following the approval of the Medical Monitor.

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

Source: Smith et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

Appendix 6
Recommended Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry
- Oxygen and masks for oxygen delivery
- Airway management devices per standard of care
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H_1 and H_2 blockers)
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Maintain an adequate airway.
- Provide oxygen
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 7
Total Neuropathy Score Clinical Assessment

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
TNSn	0	1	2	3	4

Sources:

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 8
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 SK, Mendoza TR, Vichaya EG, et al. Validation of the chemotherapy-induced neuropathy scale. J Clin Oncol 2012;30(15 suppl):9140.

Appendix 9
Commonly Used CYP1A2 Inhibitors and Inducers (Drugs, Foods, Over the Counter Medications, and Supplements)

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

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

Appendix 9
Commonly Used CYP1A2 Inhibitors and Inducers (Drugs, Foods, Over the Counter Medications, and Supplements) (cont.)

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

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

Appendix 9
Commonly Used CYP1A2 Inhibitors and Inducers (Drugs, Foods, Over the Counter Medications, and Supplements) (cont.)

Sample card to be handed to patients in the GO29365 study. This card may be adapted to comply with local guidelines.

During this clinical study, I am receiving a drug called bendamustine. This drug is approved for the treatment of lymphoma in the United States of America and a number of the European Union member states. The following medications and substances are examples of drugs and substances that may alter blood levels of bendamustine:

Fluvoxamine

Ciprofloxacin

Omeprazole

Smoking

Caution must be used or alternative treatments be considered if treatment with one of these listed drugs or substances or another CYP1A2 inhibitor or inducer is needed. If you have further questions, please contact the study doctor whose name and contact number are indicated on the other side of this card.

Appendix 10
Follicular Lymphoma International Prognostic Index and International Prognostic Index

Follicular Lymphoma International Prognostic Index (FLIPI)	
Risk Factors	
Ann-Arbor Stage III or IV	
Age > 60 years	
Serum LDH > 1 × ULN	
Anemia (hemoglobin < 120 g/L)	
Involved nodal areas > 4	
FLIPI Risk Group	Number of FLIPI Risk Factors
Low	0 or 1
Intermediate	2
High	3–5

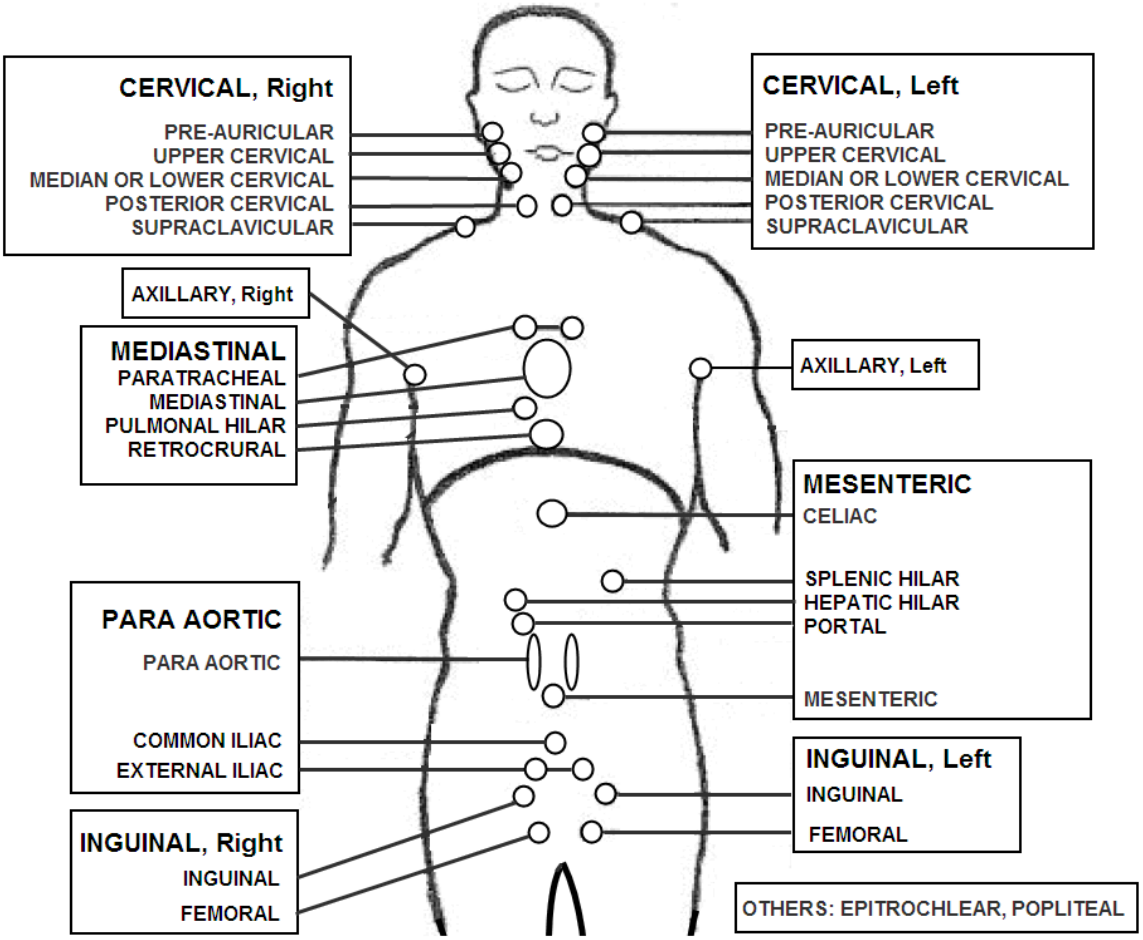
FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactate dehydrogenase; ULN = upper limit of normal.

The results of FDG-PET should not be taken into account for calculation of FLIPI as this prognostic score was established without FDG-PET.

Adapted from: Solal-Celigny P, Roy P, Colombat P, et al. Follicular Lymphoma International Prognostic Index. Blood 2004;104:1258–64

Appendix 10
Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

Follicular Lymphoma International Prognostic Index (FLIPI) Nodal Areas



Reference modified from: Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–64.

Appendix 10
Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

Follicular Lymphoma International Prognostic Index (FLIPI) 2	
Risk Factors	
Bone marrow involvement	
Age $>$ 60 years	
β_2 microglobulin $>$ 1 $\times$ ULN	
Anemia (hemoglobin $<$ 120 g/L)	
Longest diameter of largest involved node $>$ 6 cm	
FLIPI2 Risk Group	Number of FLIPI2 Risk Factors
Low	0
Intermediate	1 or 2
High	3–5

FLIPI2 = Follicular Lymphoma International Prognostic Index 2; LDH = lactate dehydrogenase; ULN = upper limit of normal.

The results of FDG-PET should not be taken into account for calculation of FLIPI2 as this prognostic score was established without FDG-PET.

Adapted from: Federico M, Bellei M, Marcheselli L, et al. Follicular Lymphoma International Prognostic Index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009;27:4555–62.

Appendix 10
Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

International Prognostic Index (IPI)	
Risk Factors	
Ann-Arbor Stage III or IV	
Age $>$ 60 years	
Serum LDH $>$ 1 $\times$ ULN	
ECOG Performance Status $\geq$ 2	
Extranodal involvement $\geq$ 2	
IPI Risk Group	Number of IPI Risk Factors
Low	0 or 1
Low-intermediate	2
High-intermediate	3
High	4 or 5

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; 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 MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive Non-Hodgkin's Lymphoma. N Engl J Med 1993;329:987–94.