

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

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STATISTICAL ANALYSIS PLAN

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF POLATUZUMAB VEDOTIN IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB COMPARED WITH BENDAMUSTINE AND RITUXIMAB ALONE IN CHINESE PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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PLAN PREPARED BY: [REDACTED] Ph.D.
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Date and Time(UTC) **STATISTICAL ANALYSIS PLAN APPROVAL**

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study YO41543 (Polarose), a Phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of polatuzumab vedotin in combination with bendamustine and rituximab (BR) compared with BR alone in Chinese patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

This document is based on the statistical section of the study protocol and will provide more details to the planned statistical analyses.

The detailed background information for the study can be found in the study protocol.

2. STUDY DESIGN

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

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

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

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

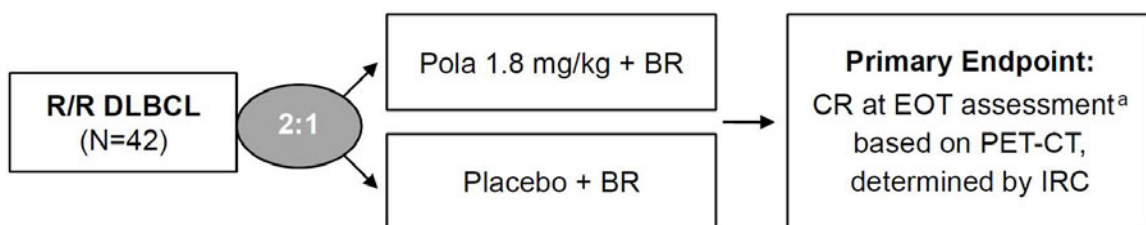
- Duration of response (DOR) to most recent prior therapy: ≤ 12 months versus > 12 months
- Number of prior lines of therapies (1 versus ≥ 2)

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

[Figure 1](#) presents an overview of the study design. A schedule of activities is provided in [Appendix 2](#).

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

Figure 1 Study Schema



Notes: The screening period is from Days -28 to -1. Study treatment will be administered every 21 days for 6 cycles.

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

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

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments in [Appendix 2](#).

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

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

2.2.2 Secondary Efficacy Endpoints

- CR at the end of treatment assessment based on PET-CT, as determined by the investigator according to the Lugano Response Criteria
- Objective response (OR), defined as CR or partial response (PR), at the end of treatment assessment based on PET-CT, as determined by the investigator and IRC according to the Lugano Response Criteria
- CR at the end of treatment assessment based on computed tomography (CT) only, as determined by the investigator and IRC according to the Lugano Response Criteria
- OR, defined as CR or PR, at the end of treatment assessment based on CT only, as determined by the investigator and IRC according to the Lugano Response Criteria
- Best objective response (BOR), defined as CR or PR, while on study based on PET-CT or CT only, as determined by the investigator and IRC according to the Lugano Response Criteria

- DOR, defined as the time from the initial CR or PR until the first occurrence of disease progression or relapse based on PET-CT or CT only as determined by the investigator and IRC according to the Lugano Response Criteria or death from any cause, whichever occurs first
- Progression-free survival (PFS), defined as the time from date of randomization until the first occurrence of disease progression or relapse based on PET-CT or CT only as determined by the investigator and IRC according to the Lugano Response Criteria or death from any cause, whichever occurs first
- Event-free survival (EFS), defined as the time from date of randomization until the first occurrence of disease progression or relapse based on PET-CT or CT only as determined by the investigator according to the Lugano Response Criteria, initiation of new anti-lymphoma treatment (NALT) or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from date of randomization until the date of death from any cause

2.2.3 Safety Endpoints

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence and nature of study drug discontinuation, dose reduction, and dose delay due to adverse events
- Change from baseline in peripheral neuropathy as assessed through use of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX)

2.2.4 Pharmacokinetic Endpoints

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

2.2.5 Immunogenicity Endpoints

- Prevalence of anti-drug antibodies (ADAs) for polatuzumab vedotin at baseline and incidence of ADAs during the study
- Potential relationship between ADA status for polatuzumab vedotin and efficacy, safety, or pharmacokinetic (PK) endpoints

2.2.6 Biomarker Endpoints

- CR at the end of treatment assessment based on PET-CT, as determined by the IRC according to the Lugano Response Criteria in populations of activated B cell diffuse large B-cell lymphoma (ABC-DLBCL), germinal center B cell DLBCL (GCB-DLBCL), double-expressor lymphoma (DEL), and expression of CD79b

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

2.3 DETERMINATION OF SAMPLE SIZE

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

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

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

2.4 ANALYSIS TIMING

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

3. STUDY CONDUCT

3.1 RANDOMIZATION

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

- DOR to most recent prior therapy (≤ 12 months vs. > 12 months)
- Number of prior lines of therapies (1 vs. ≥ 2)

3.2 INDEPENDENT REVIEW COMMITTEE

An IRC composed of certified radiologists and a hematologist or oncologist with experience in malignant lymphoma will assess all patients for response through use of the 2014 Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) on the basis of imaging results and biopsy results that are performed related to efficacy evaluation. Decisions will be guided by a Charter specific to the independent review.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intention-to-treat (ITT) population is defined as all patients randomized, whether or not the patients received the assigned treatment. The ITT patients will be analyzed according to the treatment assigned at randomization by the interactive web-based response system (IxRS).

4.1.2 Safety Population

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received. Specifically, a patient will be included in the polatuzumab vedotin plus BR arm in safety analyses if the patient receives any amount of polatuzumab vedotin, regardless of the initial treatment assignment by IxRS.

4.1.3 Pharmacokinetic-Evaluable Population

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

4.1.4 Immunogenicity-Evaluable Population

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

4.1.5 Biomarker-Evaluable Population

For each biomarker to be analyzed, the corresponding biomarker-evaluable population will include all randomized patients who have a valid baseline assessment for that specific biomarker. Biomarker-evaluable population will be used for biomarker subgroup analyses.

4.2 ANALYSIS OF STUDY CONDUCT

The enrollment, major protocol deviations, and reasons for discontinuation from the study will be summarized by treatment arm for the ITT population. Study treatment

administration and reasons for discontinuation from study treatment will be summarized by actual treatment arm for the safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, and duration of malignancy) will be summarized by treatment group for the ITT population. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum and maximum. Descriptive summaries of discrete data will include frequencies and percentages.

4.4 EFFICACY ANALYSIS

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is CR at end of treatment assessment (6-8 weeks after Cycle 6 Day 1 or the final dose of study treatment) based on PET-CT, as determined by the IRC. The analysis population for this CR analysis will be the ITT population. Patients without the end-of-treatment tumor assessments or if their response at end of treatment is not evaluable, will be considered non-CR patients. The CR rate, defined as the percentage of patients with CR, will be estimated and the corresponding Clopper-Pearson exact 95% CI will be constructed for each treatment arm. The difference in CR rates between polatuzumab vedotin plus BR and placebo plus BR randomized arms will be estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution.

4.4.2 Secondary Efficacy Endpoints

Response rate is defined as the percentage of patients with CR, OR, or BOR as described below:

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

For the endpoint of CR and OR at end of treatment (EOT), patients without the end-of-treatment tumor assessments or if their response at end of treatment is not evaluable,

will be considered non-CR and non-OR patients. For the endpoint of BOR, patients without a post-baseline tumor assessment will be considered non-responders. The analysis population for CR at EOT, OR at EOT, and BOR as described above will be the ITT population. Analyses of these endpoints will be identical to those described above for the primary efficacy endpoint of CR rate measured by PET-CT scan and determined by the IRC.

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

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

EFS, as determined by the investigator, is defined as the time from date of randomization to any treatment failure including disease progression, relapse, initiation of NALT, or death, whichever occurs first. The analysis population for this EFS analysis will be the ITT population. 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.

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

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

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

4.4.3 Biomarker Analyses

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

4.5 SAFETY ANALYSES

Unless specified otherwise, safety analysis will be performed for the safety population, with patients grouped according to the study treatment they actually received.

4.5.1 Exposure of Study Medication

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

4.5.2 Adverse Events

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

4.5.3 Peripheral Neuropathy

Peripheral neuropathy will be assessed through use of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX).

Visit summary and change from baseline analyses will be performed for the FACT/GOG-NTX. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of score and score change from baseline to each time point will be presented by treatment arm.

4.5.4 Laboratory Data

Laboratory data will be summarized by treatment arm. Values outside the normal ranges will be summarized by treatment arm. In addition, selected laboratory data will be summarized by treatment arm and NCI CTCAE grade. In addition, shift tables describing changes from baseline will be presented using the NCI CTCAE grading scale.

4.5.5 Vital Signs

Changes in vital signs will be summarized by treatment arm.

Electrocardiograms (ECGs) will also be summarized by treatment arm.

4.6 PHARMACOKINETIC ANALYSES

The PK analysis will be performed in the PK-evaluable population.

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

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

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

4.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis will be performed in the immunogenicity-evaluable population and reported within the Integrated Summary of Immunogenicity (ISI).

The ISI will include an immunogenicity risk assessment, assay strategy, and summary of immunogenicity results. The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer

unit greater than the titer of the baseline sample (treatment unaffected). Samples that confirm positive for ADA will be further characterized by titer determination and domain specificity.

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

4.8 MISSING DATA

See Sections [4.4](#) and [4.5](#) for methods for handling missing data for the primary and secondary endpoints.

4.9 INTERIM ANALYSES

No efficacy interim analyses are planned.

5. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics* 1982;38:29–41.

Cheson B, Fisher R, Barrington S, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;32:1–9.

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Controlled Clinical Trial* 1996;17:343–6.

Appendix 1

Protocol Synopsis

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

Objectives and Endpoints

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

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

Efficacy Objectives

Primary Efficacy Objective

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

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

Secondary Efficacy Objective

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

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

Safety Objectives

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

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

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

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

Pharmacokinetic Objectives

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

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

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

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

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

Immunogenicity Objectives

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

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

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

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

Biomarker Objective

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

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

Study Design

Description of Study

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

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

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

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

- DOR to most recent prior therapy: ≤ 12 months versus > 12 months
- Number of prior therapies (1 vs. ≥ 2)

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

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

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

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

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

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

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

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

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

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

Disease Progression and Follow Up

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

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

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

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

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

Study Treatment Regimen

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

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

Schedule for Cycle 1

Cycle 1 Day 1

- Rituximab 375 mg/m² IV infusion

Cycle 1 Day 2

- Polatuzumab vedotin/placebo IV infusion
- Bendamustine 90 mg/m² IV infusion

Cycle 1 Day 3

- Bendamustine 90 mg/m² IV infusion

Schedule for Cycles 2–6

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

Cycles 2–6 Day 1

- Rituximab 375 mg/m² IV infusion
- Polatuzumab vedotin/placebo IV infusion
- Bendamustine 90 mg/m² IV infusion

Cycles 2–6 Day 2

- Bendamustine 90 mg/m² IV infusion

Independent Review Committee

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

Number of Patients

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

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form Age ≥18 years at time of signing Informed Consent Form
- Able to comply with the study protocol and procedures, in the investigator's judgment
- Transplant ineligible patients with R/R DLBCL, classified as below:
 - Patients who are ineligible for second-line stem cell transplantation (SCT), with progressive disease or no response (stable disease [SD]) < 6 months from start of initial therapy (second-line refractory)
 - Patients who are ineligible for second-line SCT, with disease relapse after initial response ≥ 6 months from start of initial therapy (second-line relapsed)
 - Patients who are ineligible for third-line (or beyond) SCT, with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line or beyond refractory)
 - Patients who are ineligible for third-line (or beyond) SCT with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line or beyond relapsed)
- *Confirmed DLBCL diagnosis as:*
 - DLBCL, not otherwise specified (NOS) (including both GCB and ABC)
 - T-cell/histiocyte-rich large B-cell lymphoma
 - High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
 - High grade B-cell lymphoma, NOS
 - Primary mediastinal (thymic) large B-cell lymphoma
 - Epstein-Barr virus positive DLBCL, NOS
- For patients who have received prior bendamustine, a response duration > 1 year (for patients who have relapsed disease after a prior regimen)
- At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension as measured by CT or magnetic resonance imaging
- Availability of archival or freshly collected tumor tissue before study enrollment
 - Formalin-fixed, paraffin-embedded tissue blocks are preferred.
 - If a tissue block is not available, at least 11 unstained slides or freshly cut serial sections (3–5 μm in thickness), will be accepted.

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

- Life expectancy of at least 24 weeks
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Adequate hematologic function unless inadequate function is due to underlying disease, such as extensive bone marrow involvement or hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator. Adequate hematologic function is defined as follows:
 - Hemoglobin ≥ 9 g/dL
 - ANC $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 75 \times 10^9/L$

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

Women must remain abstinent or use single highly effective or combined contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for ≥ 12 months after the final dose study treatment. Women must refrain from donating eggs during this same period.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of highly effective contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $< 1\%$ per year. Barrier methods must always be supplemented with the use of a spermicide.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

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

With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of study treatment to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- Residence in the People's Republic of China

Exclusion Criteria

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

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

All acute, clinically significant treatment-related toxicity from prior therapy, except for alopecia, must have resolved to Grade ≤ 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 ≤ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy (Cycle 1 Day 1).

Ongoing corticosteroid usage is permitted for the purpose of lymphoma symptom control. For further details refer to the protocol.

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

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

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

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

- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)

- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Patients with suspected or latent tuberculosis
 - Latent tuberculosis should be confirmed according to local testing requirements.
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)
 - Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing *monthly* (or on Day 1 of every cycle) *during the study* and for at least 12 months after the last cycle of study treatment. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.
- Positive test results for hepatitis C virus (HCV) antibody
 - Patients who are positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Known history of HIV seropositive status
 - For patients with unknown HIV status, HIV testing will be performed at screening.
- Known infection human T-cell leukemia virus 1 virus
- Vaccination with a live vaccine within 28 days prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Pregnant or breastfeeding or intending to become pregnant during the study or within 12 months after the final dose of study treatment
 - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
 - Serum creatinine clearance < 40 mL/min (using Cockcroft-Gault formula)
 - AST or ALT $> 2.5 \times$ upper limit of normal (ULN)
 - Total bilirubin $\geq 1.5 \times$ ULN
 - Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq 3 \times$ ULN.
 - INR or PT $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation
 - PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

Criteria for Lymph Node Biopsy Tissue

Patients must meet following criteria for lymph node biopsy tissue:

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

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

Refer to the laboratory manual for additional details.

End of Study

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

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

Length of Study

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

Investigational Medicinal Products

Polatuzumab Vedotin and Placebo

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

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

Rituximab

Rituximab (MabThera[®]/Rituxan[®]) will be supplied by the Sponsor. For information on the formulation, packaging, and handling of rituximab, see the pharmacy manual and the Rituximab Investigator's Brochure.

Rituximab (375 mg/m²) will be administered by IV infusion on Day 1 of Cycles 1–6.

Bendamustine

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

Bendamustine (90 mg/m²) will be administered by IV infusion over 30–60 minutes on 2 consecutive days of each cycle (Days 2 and 3 in Cycle 1 and then Days 1 and 2 in Cycles 2–6).

Statistical Methods

Primary Analysis

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

Determination of Sample Size

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

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

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

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

Appendix 2 Schedule of Assessments

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

Appendix 2 Schedule of Assessments (cont.)

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

Appendix 2 Schedule of Assessments (cont.)

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

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

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

Appendix 2 Schedule of Assessments (cont.)

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- ^b Screening and pretreatment tests and evaluations will be performed within 28 days before first dose, unless otherwise specified. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before first dose may be used; such tests do not need to be repeated for screening. *Bone marrow biopsies* collected within 90 days prior to Day 1 of study treatment are acceptable. Samples obtained more than 90 days prior to Day 1 require prior approval by the Medical Monitor before the patient can be randomized.
 - ^c Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding Cycle 1 Day 1 administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.
 - ^d Patients who complete the study treatment period will return to the clinic for a treatment completion visit 30 (± 5) days after the final dose of study treatment (Cycle 6 Day 1). Patients who discontinue study treatment prematurely will return to the clinic for a treatment discontinuation visit 30 (± 5) days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.
 - ^e All patients will be asked to return to the clinic for the end of treatment assessment. This visit is to take place between 6 and 8 weeks after Cycle 6 Day 1 or the final dose of study treatment. For patients with disease progression occurring prior to the anticipated date of the end of treatment assessment, the visit date with the response assessment showing progressive disease may be used in replacement of the end of treatment assessment.
 - ^f Following completion of treatment, patients who have not progressed will be followed clinically every 3 months (± 14 days). Follow-up visit intervals should be determined from treatment completion visit.
 - ^g Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained no more than 28 days before initiation of study treatment.
 - ^h Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.
 - ⁱ After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the final dose of study drug. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events or non-serious adverse events of special interest. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 2 Schedule of Assessments (cont.)

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- ^j Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly (clinical response assessment), which will be recorded on the appropriate Tumor Assessment eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed (targeted) physical examinations should be performed.
- ^k Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment [lymph nodes, liver, and spleen]). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^l Vital signs include respiratory rate, pulse rate, pulse oximetry, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. During the administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 15 (\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. During rituximab administration visits, vital signs are to be measured prior to the start of the infusion of rituximab as well as at the end of the rituximab infusion. Additional vital sign measurements that are obtained as per the institution's standard of care are to be recorded on the eCRF.
- ^m Height is required at screening only. BSA is required at screening only unless there has been > 10% change in body weight since the last BSA assessment, in which case BSA should be recalculated and documented on the eCRF. It is recommended that the Mosteller BSA formula (Mosteller et al.1987) be used; however, BSA may be calculated using the investigator's preferred formula.
- ⁿ The FACT/GOG-NTX will be administered on Day 1 of every cycle, at treatment completion/discontinuation, and at specified planned post-treatment visits thereafter until the close of the study (every 3 months after the treatment completion visit). Paper versions of the FACT/GOG-NTX scale will be self-administered or interviewer administered (as appropriate) before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. The data from the questionnaires will be entered into the EDC system by site staff.
- ^o Clinical response assessment of tumor conducted via physical examination.
- ^p *CT scans and* PET-CT scans are required at screening, the interim response assessment (between Cycle 3 Day 15 and Cycle 4 Day 1), and the end of treatment assessment (6–8 weeks after Cycle 6 Day 1 or the final dose of study treatment). *Diagnostic contrast enhanced CT scans obtained as part of a PET-CT may be used in lieu of dedicated CT scans.* All other imaging may be CT only. The Lugano Response Criteria will be used to assess overall response to study treatment.
- ^q Screening PET-CT must be obtained within 35 days of Cycle 1 Day 1.

Appendix 2 Schedule of Assessments (cont.)

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- ^r CT (preferred) or PET-CT scans should be performed during follow-up every 6 months after end of treatment assessment until disease progression, study withdrawal, end of study, or death, whichever comes first; or at any time that progression is suspected via clinical response assessment.
- ^s Rituximab (375 mg/m²) will be administered by IV infusion on Day 1 of Cycles 1–6. No dose modifications of rituximab are allowed. Rituximab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine.
- ^t Polatuzumab vedotin (1.8 mg/kg) or placebo will be administered by IV infusion on Day 2 of Cycle 1 then Day 1 of Cycles 2–6.
- ^u Bendamustine (90 mg/m²) will be administered by IV infusion over 30–60 minutes on 2 consecutive days of each cycle (Days 2 and 3 in Cycle 1, then Days 1 and 2 in Cycles 2–6).
- ^v Hematology includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, and percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes). Results should be obtained within 3 days before study treatment administration.
- ^w Serum chemistry includes sodium, potassium, glucose, BUN or urea, creatinine, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, ALP, LDH, uric acid/urate, HbA_{1c}, amylase, and lipase. At screening, samples will be obtained in a fasting state for all patients. HbA_{1c} will only be measured at screening and at Cycle 4 Day 1 and can be obtained in a non-fasting state. Only at screening, obtain β-2 microglobulin. Results should be obtained within 3 days before study treatment administration.
- ^x INR or, PT, and PTT or aPTT. Results should be obtained within 3 days before study treatment administration.
- ^y At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed at screening and monthly (*or* on Day 1 of each cycle) during the study treatment period, and for at least 12 months after the completion of study treatment to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- ^z All women of childbearing potential will have a serum pregnancy test at screening within 7 days before Cycle 1 Day 1. In addition, a serum or urine pregnancy test must be performed prior to study treatment on Day 1 of each subsequent cycle (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.
- ^{aa} Bone marrow biopsy and aspirate are mandatory in all patients at screening and should include biopsy for morphology. The bone marrow assessment must be performed within 3 months of the Cycle 1 Day 1. For patients with bone marrow involvement (presence of lymphoma) at screening, a repeat bone marrow biopsy and aspirate should be repeated at the end of treatment assessment in patients who achieve radiologic CR or if there is clinical suspicion of progressive disease in the bone marrow in the absence of progressive disease as demonstrated by radiographic imaging. Bone marrow assessments will be performed locally.

Appendix 2 Schedule of Assessments (cont.)

- ^{bb} *Pretreatment tumor* tissue sample is required (archival tissue or fresh pre-treatment biopsy is acceptable) *and to be submitted according to local regulations*. Tumor blocks are preferred. If a tumor block is not available, a minimum of 11 serial freshly cut, unstained slides are required. Remaining archival tissue blocks will be returned to local pathology according to country-specific procedures.
- ^{cc} *Whole* blood samples will be collected at screening, end of treatment assessment, and every 6 months (from the treatment completion visit) until the end of study or patient discontinuation.
- ^{dd} *During* the follow-up period (i.e., after treatment completion): For patients who have disease progression and have not started new anti-lymphoma therapy, follow-up should consist of recording of first new anti-lymphoma therapy, adverse events, and survival and continue to follow the above schedule. *In the case where a patient experiences disease progression, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death (unless the patient withdraws consent or the Sponsor terminates the study)*. For patients who started a new anti-lymphoma therapy but do not have disease progression, assessments should be followed according to the schedule of activities, including response assessments and adverse events.